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When Ideas Are Not Free: The Impact of Patents on Scientific Research

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Executive Summary

This chapter describes the impact of formal intellectual property rights on the production and diffusion of "dual knowledge"—ideas that are simultaneously of value as a scientific discovery and as a useful, inventive construct. We argue that a great deal of knowledge generated in academia, particularly in the life sciences, falls into this category (sometimes referred to as Pasteur's Quadrant). The production and diffusion of dual purpose knowledge challenges the premise of most science policy analysis, which is implicitly based on a clear separation between basic scientific knowledge and applied knowledge useful in the development of new technology. Instead, dual knowledge simultaneously makes both a basic and an applied contribution. We review qualitative and quantitative evidence relating to the policy challenges raised by the production and dissemination of dual knowledge, highlighting three broad findings. First, rather than facing a fundamental tradeoff between applied research and more fundamental scientific knowledge, research agencies can and do invest in dual purpose knowledge. Indeed, the dual purpose knowledge framework suggests a distinct rationale for public sector involvement in the funding and conduct of research: the social impact of a given piece of knowledge may be enhanced when knowledge is produced and disclosed in accordance with the norms of the scientific research community (particularly compared to secrecy). Second, we suggest that, within Pasteur's Quadrant, the increased use of formal IPR seems to be significantly shaping the structure, conduct and performance of both university and industry researchers. On the one hand, from the perspective of individual researchers, patenting does not seem to come at the expense of scientific publication, and both respond to the process of scientific discovery. There is some evidence, however, that patent grant may reduce the extent of use of knowledge: the citation rate to a scientific article describing a dual-purpose discovery experiences a modest decline after patent rights are granted over that knowledge. Finally, the impact of patents may be indirect; rather than directly impacting behavior through patent enforcement, scientific conduct may be affected through related mechanisms such as material transfer agreements. Not simply a legal document within a seamless web of cooperation, nor a bludgeon to stop scientific progress in its tracks, patents seem to be changing the "rules of the game" for scientific exchange, cooperation, and credit.

I. Introduction

In the early 1980s, Professor Phil Leder, recently recruited to head the new Genetics department at the Harvard Medical School, developed one of the first genetically engineered mice, dubbed the Oncomouse. Leder and his post-doc Tim Stewart had used novel transgenic techniques to insert an oncogene into a mouse embryo; the result was a mouse that was highly susceptible to cancer (Stewart et al. 1984). Using the mouse to examine the importance of genes in the onset of cancer, Leder came to recognize that "it could serve a variety of different purposes, some purely scientific others highly practical" (Kevles 2002, p. 83). This research was published in *Cell* in 1984, and, in 1988 a broad patent for the Oncomouse was granted by the U.S. Patent Office (USPTO). The Oncomouse patent was more controversial than most; not only was the Oncomouse the first living mammal to be patented, but Harvard's licensee DuPont aggressively enforced the property rights. They made demands for "reach-through" rights on inventions that were made using the Oncomouse, requested early review of publications that used the Oncomouse in further scientific research, and prohibited scientists from freely sharing their mice.

The generation of scientific ideas like the Oncomouse—ideas that are simultaneously of value as a scientific discovery and as a useful, inventive construct—is not a new phenomenon.

Stokes described them as lying in Pasteur's Quadrant (Stokes 1997). Louis Pasteur's research on fermentation simultaneously offered fundamental insights that led to the germ theory of disease and was of immediate practical significance for the French beer and wine industry. The production of "dual purpose" knowledge, particularly in the disciplines that underpin modern biotechnology, raises important new challenges for policymakers.

The discovery and exploitation of the Oncomouse offers a rather different perspective on the relationship between science and technology—and the university-industry divide—than traditional policy models. By and large, most policy analysis assumes that science is an important *input* into the process of technological innovation, and that instrumentation and measurement technologies (such as the computer) can provide important feedbacks (in the form of tools) into scientific discovery itself. In contrast, the Oncomouse highlights the possibility that a *single* discovery can simultaneously serve as a scientific discovery and a technological innovation. This insight raises questions about how researchers (and those who fund them) manage the collision between the norms of "open science" and the proprietary incentives of commercialization, and the role played by formal intellectual property rights in the development and diffusion of dual-purpose knowledge.

The "dual purpose" knowledge perspective reframes a range of policy debates about the role of universities in innovation and growth, the Federal commitment to "basic" research, and the ongoing relationship between university and industry. On the one hand, governments are increasingly focused on investing in university research which has tangible benefits in terms of commercialization and regional economic growth. At the same time, universities have come under increasing attack by commentators claiming that the "purity" of academic research is undermined by corporate funding and a focus on commercialization (Krimsky 2003; Blumenthal 1996; Etzkowitz 1998). Dual purpose knowledge has the potential to advance both scientific understanding and technological know-how. To the extent that research investments have a simultaneous impact on science and technology, the incentives for that research (and the incentive to disclose results, make material available, etc.) will be simultaneously influenced by both the scientific reward system and the incentives arising from commercial exploitation.

The entangled relationship between the norms of science and commercial incentives is particularly striking when dual knowledge is disclosed through scientific publication and protected (and again disclosed) through formal intellectual property rights (IPR). The increased use of IPR over research which had traditionally been disclosed only through scientific publication has sparked a vigorous academic and policy debate over the "anti-commons effect." At its core, the anti-commons debate is an argument over whether such expansion of IPR (in the form of patents and/or copyrights) is "privatizing" the scientific commons, and reducing the benefits from scientific progress (Heller and Eisenberg 1998; Argyres and Liebskind 1998; David 2001). Specifically, the anti-commons hypothesis states that (a) IPR may inhibit the free flow and diffusion of scientific knowledge and the ability of researchers to cumulatively build on each other's discoveries, and (b) to the extent that IPR is narrow in scope and highly dispersed across individuals and institutions, fragmentation can impose a further tax in the form of significant transaction costs (Eisenberg 1996; Heller and Eisenberg 1998; Shapiro 2001; David 2000, 2003; Lessig 2002).

On the other hand, a significant amount of research has highlighted the benefits of IPR (Kitch 1977; Arora, Forsfuri, and Gambardella

2001). Recent empirical research on commercial discoveries suggests that IPR may facilitate the creation of a market for ideas, encourage further investment in ideas with commercial potential, and mitigate disincentives to disclose and exchange knowledge which might otherwise remain secret (Merges and Nelson 1990, 1994; Arora, Fosfuri, and Gambardella 2001; Gans and Stern 2000). Indeed, within the context of university research (particularly publicly-funded university research), it has been suggested that IPR offers important incentives to move nascent discoveries out of the "ivory tower" and into commercial practice (Mowery et al. 2004). In other words, from the perspective of an individual discovery, IPR may enhance the ability to realize its commercial and social benefits (Kitch 1977; Hellman 2006).

The objective of this essay is to begin to unpack the policy issues raised by dual purpose research; in particular we focus on issues that arise when patents are granted over knowledge traditionally maintained in the public domain. In section II, we begin with a review of traditional models of the science-technology relationship. We then build on the conceptual framework developed in Donald Stokes' *Pasteur's Quadrant: Basic Science and Technological Innovation* to draw out how research incentives and practice might change when knowledge has both scientific and commercial applications, paying particular attention to identifying the impact of IPR on incentives, research strategy, and knowledge diffusion. In section III, we then turn to an approach we have used in several recent papers to investigate the "paper trail" of dual purpose scientific discoveries that are themselves covered by formal IPR. Specifically, we define and evaluate patent-paper pairs—knowledge which is disclosed first in the form of a scientific publication and then again in the form of a patent grant (Murray 2002; Ducor 2000; Murray and Stern 2006). Patent-paper pairs link scientific articles and individual patents that disclose the same underlying "piece" of knowledge. They are thus more than simply a reflection of the rise in patenting in academia of knowledge unrelated (or only tangentially related) to scientific research. Rather, by embedding the same piece of knowledge in two distinct institutional regimes, they embody the coverage of formal IPR over knowledge that was traditionally disclosed solely through scientific publication.

We use this strategy to offer a qualitative and quantitative portrait of the impact of formal IPR on the production and diffusion of dual-purpose knowledge. First, in section IV, we consider two cases—the discovery of HIV (and the development of the HIV blood test) and a more detailed examination of the Oncomouse. Our analysis highlights the subtle (and often surprising) roles played by formal IPR in the context of Pasteur's Quadrant. For example, while patents do serve to reinforce the commercial incentives of researchers, they also influence negotiations among university researchers over access to research materials and the allocation of scientific credit.

Section V then synthesizes a range of more systematic empirical evidence about the relationship between dual knowledge production and IPR. First, we review a number of studies that have attempted to document whether patents by academics substitute or complement contributions and activity in the scientific realm. While the empirical evidence is not unanimous in this area, the most sophisticated empirical research seems to suggest that patenting behavior by academic researchers is associated with a "flurry" of publications in the scientific literature. In other words, in Pasteur's Quadrant, patenting may be an indicator of a significant scientific breakthrough, rather than a retreat from more fundamental research. Interestingly, the propensity to patent is strongly influenced not only by factors such as academic rank but also by demographics, most notably gender. Though women have made significant strides in participating in the life sciences research community, female academics remain less likely to participate in both scientific research (publishing) and commercial exploitation.

We then summarize the results of our own ongoing joint research in this area. Our statistical approach exploits the fact that patents are granted with a substantial lag, often many years after the knowledge is initially disclosed through paper publication. The knowledge associated with a patent-paper pair therefore diffuses within two distinct intellectual property environments—one associated with the pre-grant period and another after formal IP rights are granted. By evaluating how the citations to a scientific research article *change* after a patent is granted over the knowledge disclosed in that article, we provide a direct test of the overall impact of IPR on the diffusion of scientific knowledge. Our evidence points to a modest but systematic decline in the citation rate after patent grant, a decline which becomes more pronounced with the number of years elapsed since the date of the patent grant.

Finally, we turn to the mechanisms by which IPR and other proprietary research practices impact the ability of scientific researchers to access and build upon each other's discoveries. Recent survey evidence evaluates the role of patents (as well as other formal instruments such as material transfer agreements) on scientific practice. A striking finding from these surveys is that, while many academic researchers in the life sciences have been involved in seeking IP for their own discoveries, the vast majority do not actively evaluate patents *per se* when they choose research projects. At the same time, a sizable fraction of researchers report significant delays in research due to the need to obtain and negotiate materials transfer agreements (MTAs). In other words, recent empirical evidence points to the presence of a "licensing thicket": the proliferation of both patents and contractual mechanisms such as MTAs limiting the exchange and diffusion of scientific research materials and knowledge.

Overall, it is important to emphasize that each of these pieces of empirical evidence should be treated with considerable caution: tracing out the impact of policy and institutions on the creation and diffusion of knowledge is a formidable task. This research is recent and a great deal of further theoretical and empirical work remains to be done. With these important caveats in mind, the empirical evidence to date does seem to suggest that IPR and related institutions have real impacts on the conduct and nature of research in Pasteur's Quadrant, and offers a novel perspective on innovation policy, particularly in the life sciences. Three key issues stand out:

- Rather than facing a fundamental tradeoff between applied research and more fundamental scientific knowledge, research agencies can and do invest in dual purpose knowledge. Moreover, the dual purpose knowledge framework suggests a distinct rationale for public sector involvement in the funding and conduct of research: the social impact of a given piece of knowledge may be enhanced when knowledge is produced and disclosed in accordance with the norms of the scientific research community.
- Within Pasteur's Quadrant, the increased use of formal IPR seems to be significantly shaping the structure, conduct and performance of both university and industry researchers.
- The impact of patents and commercialization incentives is more subtle than traditional policy frameworks would have us believe. Not simply a legal document within a seamless web of cooperation, nor a bludgeon to stop scientific progress in its tracks, patents seem to be changing the "rules of the game" for scientific exchange, cooperation, and credit.

II. Pasteur's Quadrant

The Linear Model

The traditional model of the relationship between science and technology makes a clear distinction between the different types of knowledge produced and the distinctive motives of researchers in each domain of knowledge production. While scientific research is focused on questions of *why*, technology and invention are focused on questions of *how*. While basic research focuses on questions of fundamental scientific interest (without regard to commercial application); applied research is premised on potential commercial application (Bush 1945; Brooks 1993; Stokes 1997). While science is disclosed through peer-reviewed academic publications, technology is maintained through trade secrecy or disclosed through the patent system.

Over the past decade, drawing on classical approaches in the sociology of science (Merton 1973), economists have made significant progress in clarifying the distinctive incentives offered by two alternative domains of knowledge production (David and Dasgupta 1994; Aghion, Dewatripont, and Stein 2005). Each is characterized as having its own unique reward system: Under the Public Rights regime ("science"), researchers have a distinctive set of economic incentives for cumulative knowledge production, including the adoption of norms that facilitate full disclosure and diffusion of knowledge. This system includes the recognition of scientific priority and a system of public (or coordinated) expenditures to reward those who contribute to cumulative knowledge production over the long term (Merton 1973; Dasgupta and David 1994). By premising career rewards (such as tenure) on disclosure through publication, Open Science leverages the public goods nature of basic research and therefore promotes cumulative innovation and "standing on the shoulders of giants."[1] The counterpoint to science is founded on the incentives that govern private property rights. In this "private" regime, the basis of a researcher's ultimate impact on follow-on research receives little attention. Instead, incentives depend on the degree to which a researcher can generate an invention (according to the legal definition) from which he can *exclude* others and in doing so appropriate some of the value created by the knowledge through the commercialization of new technology (Nelson 1959; Arrow 1962; Levin et al. 1987; Kremer 1997; Scotchmer 1996).

Of course, though governed by separate incentive systems, policy analysis has always emphasized the linkage between science and technology (Bush 1945; Rosenberg 1974; Adams 1990; Brooks 1993; Romer 1990). In the canonical linear model, basic scientific research serves as a foundation for subsequent technological innovation and economic growth. Scientific research is not only a source of new knowledge and new tools, but also offers new sources of research practice and instrumentation, as well as a training ground for future industrial researchers. In some cases, scientific research identifies the social and environmental impact of technology. In others, it offers guidance about the most efficient way to develop new technology (Brooks 1993). While the simple linear model is certainly consistent with many classic stories of innovation, economists and other social scientists have long been critical of the linear approach. They argue that complex feedback mechanisms between science and technology are ignored (Kline and Rosenberg 1986). At the very least, the development of new technology can raise new scientific questions or provide new instrumentation and tools that scientists exploit in the context of their own research.

Consider the case of *Thermus Acquaticus*—an example of a linear relationship between science and technology, with significant "feedback" loops (Rabinow 1996). *Thermus Acquaticus* was initially discovered by Thomas Brock and Hudson Freeze in 1967 in the Great Fountain thermal pools region of Yellowstone National Park (Brock and Freeze 1969). It is an extremely unusual bacterium from a scientific perspective, with the capacity to withstand the extreme temperature variations associated with existence in a geothermal vent. While these unique properties were of fundamental scientific interest, any potential commercial applications of *Thermus Aquaticus* were unknown at the time of scientific discovery. To ensure access for follow-on researchers, Brock deposited the material with the American Type Culture Collection, a biological resource center that provides certified biological materials to both scientific and commercial researchers (Stern 2004). In 1976, researchers isolated the DNA polymerase of *Thermus Acquaticus*, and this enzyme (called *Taq*) became a useful restriction enzyme in the emerging field of biotechnology (Chien, Edgar, and Trela 1976). Some time later, Kary Mullis, a researcher at Cetus Corporation, was attempting to solve a key bottleneck in biotechnology—the rate of reproduction of DNA material. He conceived of a general approach to this problem, called polymerase chain reaction (PCR), in which strands of DNA could be isolated and then amplified through rapid heating and cooling in the presence of

DNA polymerase primers. In other words, Mullis recognized that DNA could be amplified by exploiting the innate replicability of DNA material. However at the time, he did not know how to translate his idea into a practical technology. To do so he had to identify a DNA polymerase that would maintain its enzymatic properties during extremes of heating and cooling.

Cetus researchers eventually evaluated the pure scientific research which had been conducted on the enzymatic properties of exteremophiles such as *Thermus Acquaticus* (Saiki et al. 1985, 1988). Amazingly, the *Taq* polymerase was ideally suited for the rapid heating and cooling required of PCR. In combination, Mullis' "idea" and *Taq* resulted in perhaps the single most powerful research tool in modern biotechnology, with applications ranging from genomic sequencing to genetic fingerprinting. Mullis' new technology radically shifted research productivity in biotechnology. Shortly after the unveiling of *Taq*-enabled PCR in 1985, academic scientists also recognized that they had a new and powerful tool for genetics research, and scientists started to shift their research priorities to take advantage of the new method. In recognition of the impact of PCR on both the commercial and academic worlds, *Taq* was declared as "Molecule of the Year" in 1989, and Mullis was awarded the Nobel Prize in 1993.

Technology histories similar to PCR abound, and it is therefore not surprising that the linear model of science and technology continues to pervade innovation policy analysis, in spite of widespread criticism. Research funding agencies often point to unexpected commercial applications of basic scientific research when justifying further scientific investment. There is certainly an important empirical basis for this assumption, grounded in more systematic statistical work (such as Adams 1990); industry-level productivity growth can be linked to basic research investments in scientific and engineering disciplines that are knowledge inputs into industry-specific technological innovation. Nonetheless, the underlying assumptions of the linear model are not without consequences for innovation policy analysis or investment.

More specifically, when policy analysis is founded on a model that makes a clear distinction between science and technology, at least three important implications follow:

1. The measurement of research investment can be divided neatly into basic and applied research, on the assumption that research investments can be categorized one way or the other.

2. Science and technology are distinct (though linked) spheres of knowledge production which are not in joint supply. Thus, the increased prevalence of commercialization activities in academic settings (as measured by rising patents, spin-outs, etc.) is assumed to substitute for continued basic research.

3. Moreover, the incentives for science are assumed to be weaker than those for technology. Indeed in his treatise on scientific funding, *Science: The Endless Frontier*, Vannevar Bush commented that "under pressure for immediate results, and unless deliberate policies are set up to guard against it, applied science invariably drives out pure" (Bush 1945).

Pasteur's Quadrant

While concise in its formulation, the linear analytical framework we have just described fails when knowledge has *both* basic and applied value. By highlighting the potential *duality* of some research projects, Stokes (1997) reformulated this traditional distinction; a single discovery could simultaneously possess both applied and basic characteristics. Figure 2.1 illustrates this essential insight. Stokes' formulation allows for "use-inspired basic research," as exemplified by the research activities of scientists such as Pasteur (hence the term Pasteur's Quadrant).

Qualitative studies of scientific research have increasingly emphasized the importance of dual-use research (Rosenberg 1974; Stokes 1997; Murray 2002, 2006; Murray and Stern 2006). Stokes, in particular,

		Consideration of Use?	
		No	Yes
Quest for Fundamental Understanding?	No		Pure Applied Research (Edison)
	Yes	Pure Basic Research (Bohr)	Use-inspired / translational Basic research (Pasteur)

Figure 2.1
The stokes model.

highlighted the potential for dual-use knowledge by proposing two dimensions along which research might be organized (rather than the more traditional approach of a single linear dimension from basic to applied). One dimension pertained to whether knowledge was produced for fundamental scientific interest. The second was whether knowledge was produced for commercial gain (or in response to practical problems). Two "traditional" quadrants were identified: knowledge produced *only* for scientific interest ("Bohr's Quadrant"), and knowledge produced primarily for commercial gain ("Edison's Quadrant"). Stokes suggested that a significant share of all scientific research *combined* the two motives, resulting in a third type of knowledge production "Pasteur's Quadrant."

Pasteur's fundamental insights into microbiology had practical applications for cholera and rabies and served as a foundation for the germ theory of disease (Geison 1995; Stokes 1997). While Pasteur might have been in the minority (of biologists) in the late 1800s when he contributed knowledge with both scientific and commercial interest, today's life scientists increasingly engage in knowledge production in Pasteur's Quadrant. This has come about, at least in part, because academics in the disciplines that underpin biotechnology were quick to recognize that their discoveries could potentially lead to commercial products (Panem 1984). They found themselves in possession of dual-use knowledge that could at once make a major scientific contribution and interest investors (Kenney 1986; Murray 2002). The exciting new directions ushered in by the discovery of the tools of molecular biology, combined with the willingness of private investors and public markets to make risky investments (through firms like Genentech) provided significant inducement to scientists to produce knowledge in Pasteur's Quadrant.

The dual knowledge framework challenges one of the core assumptions of the linear model: Science and technology are not necessarily substitutes but can be jointly produced in a single research project. Moreover, commercial incentives (such as property rights) may not erode the incentives for basic research—in fact, they have the potential to shift research towards Pasteur's Quadrant and the production of dual knowledge, with implications for scientists, research organizations, and policymakers:

1. Knowledge generated in Pasteur's Quadrant presents scientists with a choice: In which institutional regime (Open Science versus Private Property) will they participate? Ideas are no longer automatically

within the Open Science system because they make a contribution to fundamental knowledge or the Private Property regime because they are of commercial interest. Instead, there are institutional choices to be made which call into question the traditional role of universities and of corporations in the production of knowledge. The disclosure choice is particularly critical. It includes publication in scientific journals, application for protection through formal IPR, and of course secrecy. Moreover, at least patenting and publication decisions are *not* mutually exclusive—a given piece of dual knowledge can both be disclosed through scientific publication *and* be protected by IPR. When and if ideas are published and patented, we observe a phenomenon we have dubbed "patent-paper pairs"—a particular feature of Pasteur's Quadrant that we discuss in more detail in the next section.

2. Dual knowledge may have multiple impacts; a piece of dual knowledge can influence fundamental scientific inquiry while at the same time having a substantial commercial impact. However, the extent and nature of this impact will rest on the complex institutional choices made by a scientist. If a piece of dual knowledge is not patented, but is published, it may have a different impact on innovation and commercialization than if it is patented. Similarly, if dual knowledge is maintained as a secret, fundamental research may suffer as a result.

3. When individuals engage in multiple institutional regimes, there is the potential for serious collisions and conflicts (Murray 2006). With a proliferation of choices about how to disclose and maintain rights over research findings and materials, the role of institutions in shaping individual choices in terms of disclosure and access becomes increasingly salient.

III. Tracing the Paper Trail in Pasteur's Quadrant: Patent-Paper Pairs

At least in part, the difficulty in evaluating the impact of policy and institutions on research that is being conducted in Pasteur's Quadrant is practical—traditional measures of scientific research and technological innovation do not track the prevalence of dual purpose knowledge. While it is feasible to evaluate individual cases and research projects (which we do below), it is harder to measure the share of research activities that are dual purpose by discipline or field, or evaluate how that share has changed over time in individual research areas.

Over the last several years, by focusing on life sciences research (a key sphere for dual purpose research), we have begun to take advantage of a particular window into Pasteur's Quadrant by exploiting the existence and nature of patent-paper pairs (Murray 2002, 2006; Murray and Stern 2005). To more fully illustrate the concept of patent-paper pairs consider the following example of research undertaken in the biology department at the Massachusetts Institute of Technology in the field of bacterial genetics:

"A method has been developed for control of molecular weight and molecular weight dispersity during production of polyhydroxyalkanoates in genetically engineered organisms by control of the level and time of expression of one or more PHA synthases in the organisms. The method was demonstrated by constructing a synthetic operon for PHA production in E. coli ...Modulation of the total level of PHA synthase activity in the host cell by varying the concentration of the inducer...was found to effect the molecular weight of the polymer produced in the cell." (Snell; Kristi D. (Belmont, MA); Hogan; Scott A. (Troy, MI); Sim; Sang Jun (Seoul, KR); Sinskey; Anthony J. (Boston, MA); Rha; Chokyun (Boston, MA) 1998, Patent No. 5,811,272)

"A synthetic operon for polyhydroxyalkanoate (PHA) biosynthesis designed to yield high levels of PHA synthase activity in vivo was constructed ...by positioning a genetic fragment ... behind a modified synthase gene containing an Escherichia coli promoter and ribosome binding site. Plasmids containing the synthetic operon ...were transformed into E. coli DH5 alpha and analyzed for polyhydroxybutyrate production... Comparison of the enzyme activity levels of PHA biosynthetic enzymes in a strain encoding the native operon with a strain possessing the synthetic operon indicates that the amount of polyhydroxyalkanoate synthase in a host organism plays a key role in controlling the molecular weight and the polydispersity of polymer." (Sim SJ, Snell KD, Hogan SA, Stubbe J, Rha CK, Sinskey AJ, Nature Biotechnology 1997)

The first excerpt is taken from a patent and the second from a publication in a leading academic journal. They provide a striking illustration of how research—in this case an investigation into a specific genetic modification of a bacterium (E. Coli) designed to control the chemicals it would ordinarily produce—can lead to dual purpose knowledge disclosed in a publication and a patent. From the scientific perspective, the publication emphasizes that these experiments deepen our understanding of the genes that regulate particular chemical pathways in bacteria. However, as highlighted in the patent, they also provide practical techniques for the manipulation of bacteria and the optimization of their use as a source of useful biomaterials.

Patent-paper pairs are likely an imperfect indicator of the scope and prevalence of Pasteur's Quadrant across fields and over time: only a small share of all dual purpose knowledge is likely to be disclosed through both publication and patenting. However, patent-paper pairs offer a particularly useful perspective on research at the intersection between the modern life sciences and biotechnology, because they have become an increasingly important mode of disclosure in this arena as the result of two important developments.

1. For those generating dual propose knowledge in academia, policy shifts encouraged them to actually file patents over their dual-use knowledge. Prior to this time, patent applications filed by universities on behalf of investigators required often cumbersome case-by-case negotiations with Federal funding agencies. The 1980 Bayh-Dole Act standardized practice by assigning all patents generated with Federal funding to Universities who were also charged with a duty to license and generally facilitate their translation and commercialization (Mowery et al. 2001, 2004).

2. A critical Supreme Court decision was reached in 1980 when the *Diamond v. Chakrabarty* case confirmed that modified organisms could be patented. This decision expanded the scope of patent law to cover genetically modified organisms and (later) genetically modified mammals.

Together, these changes set the stage for a boom in life science patenting, particularly in academia. While well-defined patent-paper pairs are rare in some fields (e.g., most of the commercially important computer science discoveries are not patented), patent-paper pairs are increasingly the norm rather than the exception in life sciences research. In fact, many of the key scientific milestones in the field, but for noted exceptions, have been disclosed as patent-paper pairs:[2]

- The techniques of recombinant DNA provided insights into the cellular machinery of the cell but also laid the foundation for the production of recombinant therapeutic proteins (Cohen et al. 1973),
- The Oncomouse simultaneously provided insight into cancer while becoming a model for investigating cancer therapies (Stewart et al. 1984),
- The discovery of RNA interference represented a further step towards explaining DNA replication but also the foundation of a potentially new therapeutic category (Zamore et al. 2000),

• Embryonic stem cells teach us how cells develop but also have the potential to serve as novel therapeutics or the foundations for organ replacement (Thomson et al. 1998).

Patent-paper pairs are not limited to path-breaking discoveries. In a recent analysis of the patenting of the human genome, Jensen and Murray (2005) showed that almost 20 percent of human genes (identified in the National Center for Biotechnology Information (NCBI)) are claimed in U.S. patents (which include claims for the use of specific sequences in therapeutics, diagnostics, or as research probes). Of the 4,270 patents, over 30 percent are assigned to academic institutions. Between 1989 and 1999 U.S. research universities received over 6,000 life science patents (Owen-Smith and Powell 2003), and, for over 4,000 U.S. academic life scientists who received their PhDs between 1967 and 1995, over 20 percent are listed as inventors on one or more U.S. patent (Ding, Murray, and Stuart 2006a).

IV. Working in Pasteur's Quadrant

The prevalence of patent-paper pairs provides a fruitful approach to tracing out the "paper trail" of dual purpose discoveries, both through individual case histories and through more systematic empirical research (as in the next section). We exploit the patent-paper pairs approach to frame our qualitative analysis of case histories from dual purpose research. Such cases provide a useful window into the process and approaches that researchers take in disclosing their dual purpose ideas, shaping their impact in different spheres, and managing the collision between the publication-oriented norms of open science and the proprietary imperatives associated with commercialization.

HIV and the AIDS Blood Test[3]

The search for the cause of AIDS in the early 1980s led to intense scientific competition between, among others, French researchers headed by Luc Montagnier at the Virology Oncology Unit in the Institut Pasteur and Robert Gallo's lab at the National Cancer Institute (NCI). At the time of the emergence of AIDS, Gallo was the leading researcher in this area, and had recently been awarded the Lasker Medal for his discovery of the linkage between human retroviruses and cancer (he had isolated the first human retrovirus (see Gallo et al. 1983)). With the appearance of AIDS, interest in retroviruses increased dramatically. In 1982, Gallo was placed in charge of the newly created AIDS Task Force at the NCI, giving him wide-reaching control over the allocation of funding and access to critical materials for scientific research.

In 1983, the Institut Pasteur team isolated a human retrovirus from the lymph nodes of AIDS patients that they termed *LAV* (Barré-Sinoussi et al. 1983). As part of the process of certifying and replicating that result (a long-standing scientific norm, particularly in an area where contamination problems are common), Montagnier's lab provided Gallo and the NCI with cell samples containing the *LAV* virus. Shortly thereafter, Gallo announced the discovery of what his team claimed as a related virus, *HTLV 3B*. Gallo's findings simultaneously linked the human retrovirus to AIDS, and also provided a direct application in the form of a simple and commercially viable blood test for viral infection (Popovic et al. 1984; Gallo et al. 1984; Schupbach et al. 1984; Sarngadharan et al. 1984).

The French and the U.S. results were published in the leading journal *Science* (and recognized as key scientific and medical discoveries). The French and U.S. governments both filed for patent rights over the AIDS blood test. When the USPTO issued a patent to the NCI in 1985 but took no action on the French application, the French government sued to have the NCI patent declared invalid (including both a suit in Federal Court and through a re-examination process at the USPTO). In their dispute over the AIDS blood test, the Institut Pasteur team explicitly claimed that the NCI patent should be invalidated because the Gallo team had received cell samples from the French researchers that included *LAV* in the course of establishing the validity of their discovery, and had not disclosed this prior work to the patent examiner.

The patent dispute took almost two years to resolve, resulting in extensive delay for AIDS research and delay clarifying the nature of the AIDS virus (for a long time, the teams disagreed about whether they had identified one or two different retroviruses during their research). The patent settlement, mediated in part by Jonas Salk (the discoverer of the polio vaccine (which he did not patent)), reflects the distinctive nature of research and discovery in Pasteur's Quadrant:

- The simultaneous adjudication of scientific priority and commercial credit including explicit sharing of *scientific credit* for the discovery of the cause of AIDS
- A royalty sharing agreement between U.S. and French health agencies

• An agreement to have the AIDS virus renamed by an international scientific committee (giving it the current name—HIV).

The settlement of the patent dispute did not end the controversy over this discovery. In particular, further studies concluded that Gallo's initial research results were based exclusively on samples from Pasteur (potentially stripping Gallo of his codiscoverer status and raising questions of scientific integrity), although it remains unclear whether this error was intentional or inadvertent (due to contamination). More importantly, this case highlights the central tension that arises when the norms of science collide with the protection afforded by IPR: the allocation of *credit* for the discovery of the AIDS virus was inextricably tangled with the allocation of *rents* arising from the discovery of the AIDS blood test.

Transgenic Discoveries and the Oncomouse[4]

The cancer prone transgenic mouse—the Oncomouse—described above, like the developments in HIV, is typical of knowledge produced in Pasteur's Quadrant. Leder's laboratory had been studying the role of genes in cancer for a number of years. He was particularly interested in the recently discovered oncogenes that were often found to be mutated in cases of cancer. But as Leder was later to write in the introduction to his academic publication, while oncogenes had been analyzed in cells "their action in a living organism is, at best, incomplete" (Stewart et al. 1984, p. 627). Using the recently developed techniques of "building" a transgenic mouse, Leder incorporated an oncogene into mouse eggs which were then fertilized and developed into so-called Oncomice.

The new knowledge produced by Leder provided those in mouse genetics, in cancer biology and beyond with an important scientific discovery which was recognized when Leder won the Lasker Medal in 1989. But the Oncomouse was also a powerful tool with potential commercial applications in the screening of cancer drugs. This potential, together with the terms of a grant that Leder had received from DuPont prompted him to approach Harvard's new technology licensing office. In 1984, some months before submitting the manuscript for peer-review, Harvard filed a patent. In the four years before the patent was granted (1984–1988) academics made considerable scientific progress, building on the Oncomouse and working together according to traditional scientific norms. For example, some scientists attempted to replicate Leder's work, others built oncomice with different oncogenes, and a few worked collaboratively with Leder to develop these ideas and technologies further. As the transgenic techniques were stabilized and the mice became more robust and useful for breeding, they were gradually shared among scientific colleagues.

In 1988, the Oncomouse patent was granted to Harvard and exclusively licensed to DuPont (who had right of first refusal to license discoveries from Leder's lab during the period of their funding). They quickly sought to enforce their property rights to control the use of the Oncomouse (mice they sold directly to scientists and those that were developed in a laboratory according to the methods Leder outlined in his paper). DuPont interpreted their IPR broadly to encompass the introduction of any oncogene to produce a transgenic animal. They chose to enforce their property rights on academic and commercial scientists, with terms more commonly found in the commercial community:

- A high price per mouse although researchers had long-standing norms about freely exchanging mice.
- Restrictions on breeding programs, although this was considered a scientist's prerogative.
- Publication oversight, although scientists were loath to share such information with outsiders.
- A share of any commercial breakthroughs made using the Oncomouse in the form of "reach through rights" to follow-on inventions.

These conditions outraged many academics and exemplify the challenges associated with Pasteur's Quadrant. When knowledge is part of Academia but also subject to IPR, commercial practices can encroach upon academic scientists. Conversely, knowledge that was once freely shared by industry scientists is now available to them only on commercial terms. These issues lie at the heart of the expansion of IPR over knowledge traditionally placed solely in the public sphere, and must be balanced with the important incentives for further investment and commercialization provided by IPR (the traditional justification for the Bayh-Dole Act 1980). Moreover, they highlight the importance of licensing practices in shaping the impact of IPR.

In the decade following the granting of the Oncomouse patent, the mouse community strongly resisted DuPont's claims. However they did not use traditional legal means—for example attempting to narrow or invalidate the patent. Instead they turned to Harold Varmus, a leading biologist and discoverer of oncogenes, who had recently taken over as head of the National Institutes of Health (NIH). By 1999, he negotiated changes in the licensing terms with DuPont for academic scientists using the Oncomouse. However, DuPont still required academics to sign a license (albeit a simple one) when they bought an Oncomouse. They also required scientists to execute a Materials Transfer Agreement (MTA) when they shared mice with colleagues at other institutions. The more widespread use of MTAs among academic institutions and between academic and industry is in large part a reflection of the challenge posed by knowledge production in Pasteur's Quadrant. It is a reflection of the increasing awareness of the commercial value of materials and methods developed in academia.

Another transformation exemplified by the Oncomouse story is the rapid rise in academic patenting. While most of the academic scientists in the mouse genetics community were troubled by DuPont's licensing terms, they started to embrace patenting of their own work. This behavior might seem hypocritical, but it reflects the tensions and challenges associated with Pasteur's Quadrant. Among academics, patents are not used to enforce stringent licensing conditions or extract high profits. Rather scientists have decided for themselves how to use patents. In their hands, they have new functions:

- A way of shaping relationships with industry, including involving industry in making tools and techniques more robust and more widely accessible to academic colleagues,
- A signal of commercial expertise to potential industrial sponsors or collaborators,
- A mechanism to shape collaboration with fellow academics—another bargaining chip in the "market for scientific credit,"
- A tool to protect the "public commons"—when incorporated as part of a defensive patenting strategy, and
- A new source of prestige and satisfaction as they reflect the usefulness and real-world relevance of ideas.

Overall, these short case histories highlight the nature of research activity in Pasteur's Quadrant, and the impact of patents and other levers of innovation policy on the production and diffusion of dual purpose knowledge. Four key issues stand out. First, the case studies suggest that patents do seem to matter to the incentives and conduct of science, at least in some key research areas. Patents helped determine the collaborative patterns of different researchers in their access to the Oncomouse, and the patent settlement over the AIDS blood test specifically determined the formal allocation of scientific credit for a key discovery. Second, patents do seem to have placed a cost on the academic system. In the case of the Oncomouse, the licensing terms were arduous and impeded rapid standardization of an important scientific research tool by limiting easy exchange and access to materials for replication. The patent debacle also slowed the pursuit of academic research in HIV. Third, while patents do matter, academic scientists have not simply foregone science in pursuit of profit; instead, patents have become incorporated and co-opted into science and have become a source of value without changing the underlying logic of the scientific system. Simply put, patents have become part of every day scientific life. Finally, patents have changed the nature of the relationship between academia and industry. Scientists no longer only publish their results and always allow them to "spill over" freely into technology (as the linear model would suggest). Today they are more active participants in building commercial strategies around patents, licenses, and start-ups even while they continue to publish in prestigious scientific journals.

V. The Role of Patents in Scientific Research

The issues raised by our case studies are relevant to policy analysis; however, they require a more systematic assessment of the prevalence and impact of IPR on academic research. While we cannot yet make definitive statements about the long-run impact of IPR, considerable progress has been made in empirical research over the last several years. Specifically, a growing literature traces out the impact of patents (and other associated institutional mechanisms such as MTAs) on the process of scientific research. At least in part, this explosion in empirical studies is due to the increasing availability of data that allow researchers to link publications and patents to individuals throughout their careers (Hall, Jaffe, and Trajtenberg 2001; Azoulay and Zivin 2005). Citation data to both publications and patents also allows for a more careful assessment of the diffusion and impact of individual research studies—or pieces of knowledge (Cronin 2001). Equally importantly, researchers have a growing interest in adapting methods from the program evaluation literature in economics to identify the causal impact of policies and institutions on the scientific research process. Taken together, these studies offer a novel perspective on the impact of patents on the process of scientific research, with implications for policy analysis that we highlight in section VI.

Are Patents and Publications Substitutes or Complements?

The impact of patenting on scientific research depends, in the first instance, on whether researchers are in fact seeking IP protection over their discoveries. While universities increasingly encourage faculty members to engage in patenting (and to facilitate licensing, Jensen and Thursby 2001), each individual is ultimately responsible for the decision to make disclosures that result in academic patents, and must cooperate with technology transfer office staff (and lawyers) in the prosecution of those patent applications. The potential involvement of faculty members in the patenting process raises key questions:

- How prevalent is patenting behavior among academic researchers?
- What are the characteristics of those academic researchers with higher rates of patenting?
- Does patenting activity come at the expense of traditional publication behavior, or do patenting and publication go hand in hand?

Agrawal and Henderson (2002) were among the first to address these questions in a systematic way—through an in-depth examination of the total patenting and publication behavior of two (particularly influential) academic departments at the Massachusetts Institute of Technology (Mechanical Engineering and Electrical Engineering). Relying on in-depth interviews with faculty members and careful statistical analysis, they find that although nearly half of all faculty members file patents at some point in their career, patenting is a relatively minor activity for most faculty in most years. In any given year, less than 20 percent of individual faculty patent and, among those who do patent, the average patenting rate is about one patent every four years (compared to two publications per year). Moreover, there is little evidence that patenting significantly substitutes for publication activity (particularly when one accounts for the citation-weighted impact of those publications).

These insights have been extended and refined in several ways in recent years. For example, Fabrizio and Diminim (2005) examine a diverse group of university researchers over a longer period and find that patenting and publication seem to be complementary to each other, except perhaps for a small "fringe" of especially patent-intensive researchers, and Stephan et al. (2006) document significant variation across field and types of work in the propensity to patent. Ding, Murray, and Stuart (2006a) show that, among life science academics, the patenting rates rise for individuals at highly prestigious schools, with high numbers of industry collaborators, and broad academic networks. Across generations of scientists, they also find that with each new generation of faculty, patenting is taking place earlier in the career and for a greater proportion of each generation. Perhaps not surprisingly, all of these studies find that patenting behavior is more likely after academic researchers achieve career milestones (most notably tenure). Azoulay, Ding, and Stuart (2006) further disentangle the patenting-publication relationship by documenting a systematic pattern: patenting applications by academic life scientists tends to be preceded by a *flurry* of publications in the scientific literature. In other words, it seems that when academic researchers make an important discovery in their lab, this leads to an increase in their rate of publication (relative to their career average) and a higher propensity to engage in patenting activity.

This apparent complementarity between patenting and publication may not be present for all researchers. In a study focused on life sciences faculty, Ding, Murray, and Stuart (2006a,b) find that even when factors such as age, publication productivity, and institutional prestige are accounted for, women are up to three times less likely to engage in the commercially oriented aspects of dual purpose research, with significantly lower rates of patenting, licensing, and participation on scientific advisory boards. Such patterns are particularly worrisome in light of our case study evidence that IPR may be impacting scientific norms, and so the lack of patenting by women may influence the evaluation of *scientific* impact (e.g., in hiring or promotion decisions), drive funding opportunities (e.g., if there is a shift towards industry funding), or shape the allocation of credit provided for scientific discoveries (e.g., if control over IPR allows a researcher to bargain for coauthorship on a paper).

Do Patents Impact the Use and Diffusion of Scientific Knowledge?

To date, most empirical evaluations of the impact of academic patenting on scientific research focus on the potential tradeoff between patenting and publishing from the perspective of individual scientists. In contrast, the "anti-commons" perspective taken by Heller and Eisenberg

(1998) suggests that granting IPR over knowledge traditionally placed in the public domain might impede scientific progress itself (Heller and Eisenberg 1998; Shapiro 2001). In other words the overall rate of scientific progress across the academic community might be stifled by IPR.

Scientific research productivity depends on the ability of independent follow-on researchers to replicate and extend findings. The efficiency of this activity rests upon whether researchers can gain access to scientific materials and resources (including tools, databases, and even organisms such as cell lines or animal models). While most policy analysis simply assumes that scientific research materials and data are freely available and of high fidelity, in fact the mere production of knowledge does not guarantee that others will be able to exploit it (Mokyr 2002). Rather, the ability of scientific researchers to continually "stand on the shoulders of giants" depends not only on the amount of knowledge generated, but on the quality of mechanisms for storing knowledge, certifying and maintaining the fidelity of knowledge, and the costs of accessing that knowledge (Furman and Stern 2006). To the extent that IPR provides a legal means by which to change access costs—for example by charging for access (as in the case of the Oncomouse), or to exclude potential follow-on researchers, it is possible that researchers (or universities and companies, as the owners of the actual IP) are using their rights in a way that places a significant tax on follow-on research, slowing down the process of scientific discovery.

Murray and Stern (2006) investigate this possibility empirically using citation data that traces out the impact of scientific articles (at least in terms of their use in other published research). Our approach is to compare patterns of scientific citations to scientific articles that are part of patent-paper pairs, relative to citation patterns for articles that are *not* part of patent-paper pairs (but are similar along other dimensions). This allows us to evaluate several key hypotheses at the center of the anti-commons debate. First, we evaluate whether citation patterns are different for scientific research which is ultimately also patented. In other words, to what extent does published scientific knowledge disclosed as a patent-paper pair differ in its future cumulative impact on public domain research (as measured by forward citations to the publication) to papers that are similar in topic, published in the same journal in the same time period, but never receive IPR? Second, we take advantage of *patent grant delay*. While publication lags are usually modest (on the order of a few months), patent grant delays are substantial (in most cases IPR is granted two to four years after initial application).

Consequently, scientific knowledge associated with a patent-paper pair diffuses under two distinctive institutional environments—a pre-grant period where no IP rights are present and a post-grant period in which specific property rights have been granted. To the extent that patent grant comes as a "surprise" to at least some potential follow-on researchers, this difference allows us to ask: how does the *grant* of formal patent rights over such knowledge influence the trajectory of forward citations and therefore the impact of the scientific research findings in the public domain?

The "experiment" afforded by the combination of patent-paper pairs and patent grant delay allows for a set of precise tests motivated by the anti-commons perspective: if the grant of intellectual property hinders the ability of researchers to build (in the public domain) on a given piece of knowledge, and the patent grant itself is "news" to the broader scientific community, then the citation rate to the scientific publication disclosing that knowledge should be lower than for scientific publications with no IP and should fall after formal property rights are granted. Of course, such an analysis must control for the fact that citation patterns vary with the underlying quality of the article and with the time elapsed since publication. Our use of patent grant delay allows us to do so. Specifically, by observing a *given* piece of knowledge in two different institutional environments, we are able to evaluate how differences in the institutional environment affect the diffusion of a given piece of knowledge, including a fixed effect for each article in our sample. To evaluate the anti-commons hypothesis, we examine how the grant of IPR *changes* the citation rate to scientific articles, accounting for fixed differences in citation rates across articles and relative to the trend in citation rates for articles with similar characteristics.[5]

Our sample is composed of 340 peer-reviewed scientific articles appearing between 1997 and 1999 in *Nature Biotechnology*, a high-quality scientific publication and perhaps the leading publication for research exhibiting knowledge duality in the life sciences. The incidence of patent-paper pairs is quite high within this sample: For just under 50 percent of the scientific articles in our sample, a U.S. patent has been granted over the knowledge covered in that publication. As well, for those articles which ultimately receive a patent, there is a significant lag between scientific publication and patent grant (on average, more than three years). We exploit these data to establish three core findings. First, published articles also associated with formal IP are more highly cited than those whose authors choose not to file for patents; however, most of this boot is accounted for by observed characteristics such as author location and number of authors on the article. Second, there is robust evidence for a quantitatively modest but statistically significant anti-commons effect; across different specifications, the article citation rate declines by between 10 and 20 percent after a patent grant (see table 2.1), and the estimated impact is increasing in the years elapsed since patent grant (see figure 2.2). Thirdly, the anti-commons effect is particularly salient for articles with public sector coauthors.

We would like to be cautious in our interpretation. On the one hand, though the size of the effect is modest, the approach and results do seem to provide empirical evidence consistent with the anti-commons effect. With that said, the use of citation data is only a noisy indicator of the impact of any given piece of research, and our approach does not separately identify any potentially positive impact of IPR on research

Table 2.1
The impact of patent grant: differences-in-differences estimates (drawn from Murray and Stern, 2006)

	NEGATIVE BINOMIAL Dep Var = FORWARD CITATIONS *Coefs reported as incident rate ratios* (Robust standard errors in parentheses)	
PATENTED	1.195 (0.068)	
PATENTED, POST-GRANT	0.817 (0.099)	0.893 (0.056)
Author and Article Controls	Y	
Article Fixed Effects		Y
Publication Age Fixed Effects	Y	Y
Citation Year Fixed Effect	Y	Y

Table 2.1 reports the results from two of the key specifications from Murray and Stern (2006). Each negative binomial regression is based on a regression of the annual *forward citations* for each of the 340 research articles published in *Nature Biotechnology* from 1997 to 1999 through the end of 2002 (yielding 1688 total citation-years). In the first specification, a number of control variables are included, while the second specification includes a fixed effect for each of the 340 articles. Both specifications include a full set of fixed effects for the age of each publication (CITATION YEAR – PUBLICATION YEAR) as well as a full set of Citation Year fixed effects. As well, each specification includes an (unreported) dummy for the "window" year in which the patent is granted. The results are reported in terms of incident rate ratios, and so can be interpreted relative to a baseline rate of 1.00. For complete details, see Murray and Stern (2006).

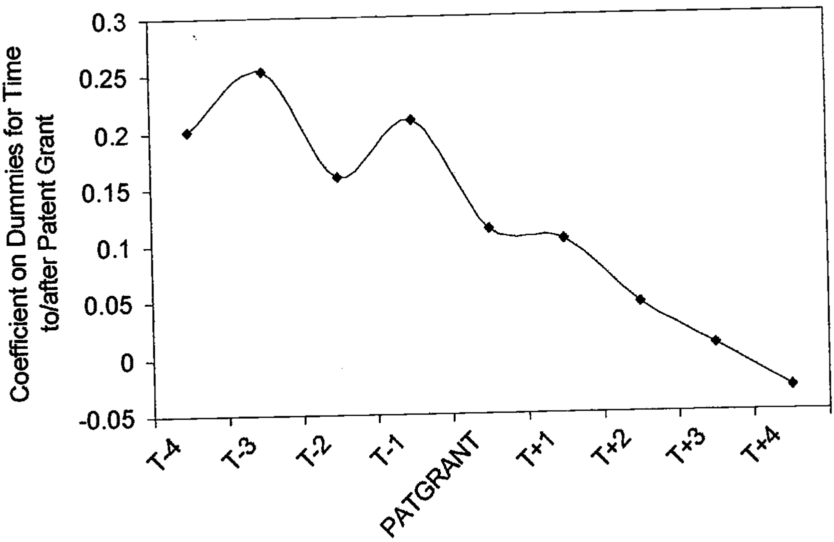

Figure 2.2
Impact of patent grant on forward citations, by year before and after patent grant (negative binomial with article FEs).
Source: Murray and Stern, 2005.

Figure 2.2 describes the coefficient estimates from a negative binominal regression that extends the analysis in table 2.1. The specification is a fixed effects negative binomial regression of the annual *forward citations* for each of the 340 research articles published in *Nature Biotechnology* from 1997 to 1999 through the end of 2002 (yielding 1,688 total citation-years). A separate dummy variable has been included for the number of years before or after the patent grant date (from four years prior to patent grant to four years after patent grant). The results are reported in terms of incident rate ratios, and so can be interpreted relative to a baseline rate of 1.00. For complete details, see Figure D in Murray and Stern (2006).

incentives (from the perspective of the original inventor). Moreover, as we discuss in more detail below, we have not identified the specific institutional mechanism by which patent grant both surprises and influences researcher behavior. With these caveats in mind, these estimates do provide evidence that IPR influences patterns of scientific citation. Simply put, the use of a given piece of scientific research (as measured by its citation rate) on subsequent scientific research declines after IP rights are granted. Taken at face value, the results suggests that, after IPR are granted, between one in ten and one in six researchers (or publications) who might otherwise build on a given paper may forego a specific research project (or a particular research approach) that would necessitate citation to the article in that patent-paper pair. While benign interpretations are also possible (e.g., it is possible that researchers have good substitutes available or are simply engaged in strategic citation), our evidence suggests that, at a broad level, the negative impact of IPR on scientific research seems to have a sound empirical basis, although the absolute size of the effect may be modest.

The Impact of Propriety Research Practices on Scientific Exchange: Mechanisms

The citation methodology described above does not allow us to identify the precise causal mechanisms by which patenting matters. And it cannot reveal how follow-on research scientists find out about and are influenced by the IPR status of specific tools, research methods, or compounds. In a series of detailed and careful survey-based studies, Wes Cohen and John Walsh (together with coauthors) have evaluated the impact of proprietary research practices on scientific exchange and project selection (Walsh et al. 2002, 2003, 2005).

Their findings suggest that the ways in which patents matter may be somewhat indirect. In their most recent survey of 414 academic life scientists, more than 22 percent had themselves been involved in seeking IP over their discoveries in the two years prior to the survey, suggesting that many in this group are actively involved in research in Pasteur's Quadrant. Despite this research orientation, only a small fraction (five percent) report actively monitoring grants of IPR in their research field (on knowledge inputs to their research projects) and only eight percent believe that they have used research inputs covered by others' IPR. However, a more sizeable (although still a minority) group of researchers (one in six) reports that specific projects have been delayed or diverted because their most recent request for materials had been declined or delayed whiled they negotiate access via MTAs with other universities and academics. Consistent with the qualitative evidence from the Oncomouse case (Murray 2006), almost one third of these MTAs included publishing restrictions, and reach-through royalties.

While the survey results suggest that MTAs over *patented* materials are not of particular concern (relative to those MTAs over unpatented materials), these results seem to be consistent with the magnitude of the effects on academic research that we described above in our patent-paper pair research. Furthermore, when taken together with case studies (Murray 2006) and other recent survey evidence (Blumenthal 1996; Campbell 2000, 2002), they provide a more nuanced picture of the ways in which propriety research practices impact scientific research behavior. Specifically while academic scientists may not be directly engaged in evaluating the IPR status of research they seek to build upon, the use of proprietary research practices of a variety of types (patents, licenses, MTAs, data withholding, secrecy) imposes a tax on specific research paths. They essentially slow research in that area by providing incentives for teams to adapt or modify their project to reduce the burden of these practices. While those familiar with the high levels of strategic behavior in science might argue that such practices have always been widespread (Biagioli and Galenson 2002), we would argue that the expansion of IPR and the growing use of more formal contractual devices such as MTAs in the place of informal academic norms may have exacerbated underlying frictions in the process of step-by-step scientific discovery.

VI. Policy Analysis

Taken together, recent empirical evidence on the impact of patenting on academic science offers a novel perspective on key innovation policy issues. These range from the rules that govern the funding, governance and reporting of federally-funded academic research, to intellectual property policy over research materials and tools developed in the context of academic science, to the role of Federal agencies in developing institutional structures that encourage cooperative, efficient multilateral agreements for sharing of resources among researchers.

From the perspective of the research documented in this paper, it is useful to emphasize at the outset what we have *not* found in our research. The qualitative and quantitative evidence brought to bear on the impact of academic patenting on academic science fails to support the strongest critique of academic patenting—that it has somehow fatally undermined the scientific system (Krimsky 2003). While patents (and other institutional mechanisms such as MTAs) do seem to matter in academia, current empirical evidence suggests that patents place a modest and manageable tax on follow-on scientific research. While there are individual circumstances in which patenting has been used to actually foreclose access to research materials or resources, such cases are clearly the exception rather than the norm. While the anti-commons perspective does earn some empirical support (in the sense that patents do seem to impose a burden on follow-on researchers), patents do not seem to be associated with systematic foreclosure over the intellectual commons.

On the other hand, while academic patenting does not seem to be having a decisive impact on the viability of academic science, its rapid rise does seem to be changing the structure, conduct, and performance of the academic research enterprise. While IPR (and related rights of access) has emerged as a new form of currency in the scientific exchange system, the allocation of these rights is quite uneven across different researchers. Certain demographic groups that have traditionally been in weak bargaining positions, including postdoctoral researchers, junior faculty, and women at all stages of their careers, may be further disadvantaged by their lack of IPR. Simply put, the rise of academic patenting may have reinforced the highly stratified power structure of academic science. Moreover, rights owners seem to be using their IP not only to earn a direct commercial advantage but also to enhance their bargaining power with other research scientists. Just as the AIDS blood test patent agreement included a sharing of scientific credit for the discovery of HIV, it is possible that rights owners are attempting to leverage their IPR by demanding collaborator status on follow-on projects. This is particularly likely when universities demand that external researchers negotiate an MTA unless they participate in the collaboration "network" of the initial inventor. In other words, the rise of IPR over scientific knowledge may be transforming the rules and norms over the allocation of scientific credit.

Moreover, our empirical evidence points to real (though modest) performance consequences from academic patenting. Consistent with the anti-commons perspective, the granting of IPR is associated with a reduction in the exploitation of knowledge by follow-on scientific researchers, an effect which may be exacerbated when the rights over various research inputs are distributed across many researchers (i.e., in the presence of a patent thicket). Ultimately, even if academic patenting does not foreclose further scientific progress, it is likely placing a tax on that progress. It is also consistent with our findings that academic patenting by one scientist may foreclose the commercial opportunities of another and in doing so lead them to shift their research in other directions.

Perhaps of broader significance, traditional policy models and evaluation methods may fundamentally misstate the nature of research. Traditional models of the relationship between science and innovation either assume a linear form, with academic research leading to unanticipated technology spillovers, or focus on complex interactions between the distinct realms of science and technology. In contrast, the dual knowledge framework of Pasteur's Quadrant suggests that a *single* research investment can simultaneously yield scientific knowledge as well as new technology. Accounting for the benefits from such an investment must therefore incorporate both the scientific and technological impact of that research. At the simplest level, the social returns from dual purpose research can be amplified through the impact of the research on both science and technology. Of course, it is also possible that institutional choices made to enhance the commercialization prospects for a given discovery (e.g., through patenting or secrecy) may come at the expense of that knowledge having its maximal impact on the scientific community (and vice versa).

The dual impact of knowledge production in Pasteur's Quadrant suggests that rather than focusing on the potential for feedbacks or spillovers *per se*, policy should focus on evaluating the interactions and inter-relationships between institutional mechanisms that allow that knowledge to be diffused and exploited by both the scientific and technological communities. This reorientation has several consequences for the design and evaluation of innovation policy:

- It suggests that the impact of publicly funded investment depends on the rules and institutions governing how that knowledge is disclosed to the scientific community and whether follow-on researchers are able to effectively access and build upon discoveries. While individual researchers may have incentives to limit disclosure and access, overall scientific productivity is enhanced when researchers can build upon each other's discoveries. Both our case studies and the quantitative evidence suggest that, in most cases, the costs of intellectual property do not arise because of patents *per se* but in the way in which property rights are enforced. The governance of scientific research can therefore be used to ensure adequate disclosure and offer protection against the most aggressive types of IP licensing. For example, recent initiatives such as NIH rules specifying the rules governing access to data and organisms (whether they are patented or not) provide a governance framework in which specific rules for scientific research outputs coexist with the proliferation of intellectual property rights covering those research outputs. In other words, Federal agencies can use their roles as primary funders of research to facilitate the sharing and exchange of scientific ideas and resources that arise from their funding activities.

- The classical justification for public funding of research investments is premised on the idea that the private sector will not fund some types of knowledge production that is nonetheless of high social value. In contrast, the dual purpose knowledge framework suggests a separate rationale for public funding; that the social impact of a given piece of knowledge will be enhanced when it is funded by public investment and disclosed in accordance with public norms and governance expectations. In other words, even if the private sector is willing to fund a specific project, the social returns may be higher if the findings of that project are disclosed in a timely and accessible manner to the scientific community, and if intellectual property is realized through patenting (and its disclosure requirements) rather than secrecy. While these issues have come to the fore in specific cases such as the rules and governance of the Human Genome Project, most policy analysis is still premised on the traditional rationale of public research funding.
- Ultimately, the ability to design and implement policies research in Pasteur's Quadrant depends on having an effective system for measuring (a) the amount and type of research being conducted in this sphere, and (b) the scientific and technological outputs of that research. Under the linear model, the traditional measures of basic and applied research are useful constructs for dividing investments into categories that reflect the underlying research motivation. While the incentives for commercialization are present for research in Pasteur's Quadrant (and so that research would be classified as applied according to the traditional NSF research definition), an applied classification can be misleading. For example, as life sciences research has come to account for the majority of all Federal research funding (nearly 60 percent in recent years) a very significant fraction is classified as applied research. However, to the extent that this research is in Pasteur's Quadrant, should we infer that the Federal commitment to basic fundamental research has somehow been compromised?

More broadly, it seems as if the potential for life sciences research in the heart of Pasteur's Quadrant is extraordinary, yielding fundamental insights into biology, key discoveries with implications for public health and welfare, and providing tools and resources with broad commercial application. Whether this promise is realized may depend less on criteria of fundamental scientific and technical merit, but rather on the ability to translate that potential into usable knowledge. To support a process of cumulative scientific discovery and cumulative technological inventiveness, the institutions underpinning the life sciences research infrastructure must be resilient and adaptable to accommodate the production and diffusion of knowledge which has both scientific and commercial application.

Endnotes

1. While closely associated with university research, Open Science is also feasible (and profitably adopted) by private firms, including many within industries dependent on the life sciences (Cockburn and Henderson 1998; Zucker et al. 1998; Stern 2004; Murray 2002).

2. Perhaps the most interesting exception to this pattern concerns the Nobel Prize-winning work on the development of hybridomas that allowed understanding of the immune systems and also allowed the creation of monoclonal antibodies (Kohler and Milstein 1975). As Kohler and Milstein submitted their groundbreaking findings to *Nature*, they also submitted the manuscript to their funding agency (the Medical Research Council) with a proposal to file for a patent. However, the request was refused, on the basis that "It is certainly difficult for us to identify any immediate practical applications which could be pursued as a commercial venture, even assuming that publication had not already occurred" (http://www.path.cam.ac.uk/~mrc7/mab25yrs/index.html last accessed March 14, 2005).

3. This well-studied case has been the subject of a number of (often-conflicting) books and reports, including, among others, Shilts (1993), Gallo (1993), Subcommittee on Oversight and Investigations (1995), and National Institutes of Health (2002).

4. This case is discussed in much greater detail, and with more complete references, in Murray (2006).

5. The analysis employs two distinct (and complementary) approaches to the identification of the impact of patent grant on scientific citation. In the bulk of the analysis in Murray and Stern (2006), we evaluate how the citation rate changes after patent grant, controlling for the trend in citation identified by articles that do not receive IPR (these are the results presented in table 2.1). As well, to address the potential for selection of articles into patenting, we also explore a more nuanced empirical strategy that exploits the variation among patented articles in patent grant delay. Specifically, we examine the impact of patent grant on scientific citation relying exclusively on differences across patented articles in the time it takes to receive a patent. Overall, our approach employs a differences-in-differences estimator to evaluate the impact of IPR on the diffusion of scientific knowledge.

References

Adams, J. 1990. "Fundamental Stocks of Knowledge and Productivity Growth." *Journal of Political Economy* 98: 673–702.

Aghion, Philippe, Matthieus Dewatrapoint, and Jeremy Stein. 2005. "Academic Freedom, Private-Sector Focus and the Process of Innovation." NBER Working Paper. Cambridge, MA: National Bureau of Economic Research.

Agrawal, Ajay, and Rebecca M. Henderson. 2002. "Putting Patents in Context: Exploring Knowledge Transfer from MIT." *Management Science* 48(1): 44–60.

Argyres, Nicholas S., and Julia Porter Liebskind. 1998. "Privatizing the Intellectual Commons: Universities and the Commercialization of Biotechnology." *Journal of Economic Behavior and Organization* 35(4): 427–454.

Arora, Ashish, Andrea Fosfuri, and Alfonso Gambardella. 2001. "Markets for Technology: Economics of Innovation and Corporate Strategy." Cambridge, MA: MIT Press.

Arrow, Kenneth. 1962. "Economic Welfare and the Allocation of Resources for Invention." In Richard R. Nelson, (ed.), *The Rate and Direction of Inventive Activity*, 609–625. Princeton, NJ: Princeton University Press.

Azoulay, Pierre, Waverly Ding, and Toby Stuart. 2006. "The Impact of Academic Patenting on (Public) Research Output." Forthcoming, *Journal of Economic Behavior and Organization.*

Azoulay, Pierre, and Joshua Zivin. 2005. "Peer Effects in the Workplace: Evidence from Professional Transitions for the Superstars of Medicine." Working paper. Accessed from <http://www.rotman.utoronto.ca/~baum/workshop/Azoulay_workshop.pdf>.

Barre-Sinoussi F., J. C. Chermann, et al. 1983. Isolation of a T-Lymphotrophic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)." *Science* 220: 868–871.

Biagioli, Mario, and Peter Galison. 2002. *Scientific Authorship: Credit and Intellectual Property in Science.* New York: Routledge.

Blumenthal, David, Nancy Causino, Eric Campbell, and Karen Seashore Louis. 1996. "Relationships between Academic Institutions and Industry in the Life Sciences — An Industry Survey." *New England Journal of Medicine* 334: 368–374.

Brock, Thomas, and Hudson Freeze. 1969. "*Thermus Aquaticus* gen. n. and sp. n., a Nonsporulating Extreme Thermophile." *J. Bacteriology* 98(1): 289–297.

Bush, V. 1945. *Science: The Endless Frontier, A Report to the President.* Washington, D.C.: U.S. Government Printing Office.

Campbell E. G., J. S. Weissman, N. Causino, and D. Blumenthal. 2000. "Data-Withholding in Academic Medicine: Characteristics of Faculty Denied Access to Research Results and Biomaterials." *Research Policy* 29: 303–312.

Campbell, Eric G., Brian R. Clarridge, Manjusha Gokhale, Lauren Birenbaum, Stephen Hilgartner, Neil A. Holtzman, and David Blumenthal. 2002. "Data Withholding in Academic Genetics: Evidence from a National Survey." *Journal of the American Medical Association* 287(4): 473–479.

Chien, A., D. B. Edgar, and J. M. Trela. 1976. "Deoxyribonucleic Acid Polymerase from the Extreme Thermophile Thermus Aquaticus." *Journal of Bacteriology* 127(3): 1550–1557.

Cockburn, Iain, and Rebecca Henderson. 1998. "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery." *Journal of Industrial Economics* 46(2): 157–182.

Cohen, S., A. Chang, H. Boyer, and R. Helling. 1973. "Construction of Biologically Functional Bacterial Plasmids *In Vitro*." *Proc. Natl. Acad. Sci. USA* 70: 3240–3244.

Cronin, B. 2001. "Bibliometrics and Beyond: Some Thoughts on Web-Based Citation Analysis." *Journal of Information Science* 27(1): 1–27.

Dasgupta, Partha, and Paul David. 1994. "Towards a New Economics of Science." *Research Policy* (23): 487–521.

David, Paul. 2000. "The Digital Technology Boomerang: New Intellectual Property Rights Threaten Global "Open Science."" Stanford: Stanford Working Paper no. 00-016.

David, Paul. 2001. "From Keeping 'Nature's Secrets' to the Institutionalization of 'Open Science'." Stanford: Stanford Working Paper no. 01-006.

David, Paul. 2003. "Can 'Open Science' be Protected from the Evolving Regime of IPR Protections?" Stanford: Stanford Working Paper no. 03-011.

Ding, Waverly, Fiona Murray, and Toby Stuart. 2006a. "An Empirical Study of Gender Differences in Patenting in the Academic Life Sciences." *Science* 313: 665–667.

Ding, Waverly, Fiona Murray, and Toby Stuart. 2006b. "Commercial Science: An Opportunity for Gender Stratification." Working Paper. Available from <http://web.mit.edu/fmurray/www/>.

Ducor P., 2000. "Intellectual Property. Coauthorship and Coinventorship." *Science* 289(5481): 873–875.

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

Etzkowitz, H. 1998. "The Norms of Entrepreneurial Science: Cognitive Effects of the New University-Industry Linkages." *Research Policy* 27: 823–833.

Fabrizio, Kira, and Alberto DiMinin. 2005. "Commercializing the Laboratory: The Relationship between Faculty Patenting and Publishing." Working Paper. Available at <http://mgt.gatech.edu/news_room/news/2005/reer/files/sat_commercializing.pdf>.

Furman, Jeff, and Scott Stern. 2006. "Climbing Atop the Shoulders of Giants: The Impact of Institutions on Cumulative Knowledge Production." Working paper. Available at <http://people.bu.edu/furman/>.

Gallo, R. C. (1993). *Virus Hunting: AIDS, Cancer and the Human Retrovirus: A Story of Scientific Discovery*. New York: Basic Books.

Gallo R. C., S. Z. Salahuddin, M. Popovic, et al. 1984. "Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS." *Science* 224: 500–502.

Gallo R. C., P. S. Sarin, E. P. Gelmann, et al. 1983. Isolation of Human T- Cell Leukemia Virus in Acquired Immune Deficiency Syndrome (AIDS)." *Science* 220: 865–867.

Gans, J., and S. Stern. 2000. "Incumbency and R&D Incentives: Licensing the Gale of Creative Destruction." *Journal of Economics and Management Strategy* 9(4): 485–511.

Geison, G. L. 1995. *The Private Science of Louis Pasteur*. Princeton, NJ: Princeton University Press.

Hall, B., A. Jaffe, and M. Trajtenberg. 2001. "The NBER Patent Citation Data File: Lessons, Insights and Methodological Tools." NBER Working Paper no. 8498. Cambridge, MA: National Bureau of Economic Research.

Heller, M., and R. Eisenberg. 1998. "Can Patents Deter Innovation? The Anticommons in Biomedical Research." *Science* 280(5364): 698–701.

Hellman, Thomas. 2006. "The Role of Patents for Bridging the Science to Market Gap," *Journal of Economic Behavior and Organization* (forthcoming).

Jensen, K., and F. Murray. 2005. "The Intellectual Property Landscape of the Human Genome." *Science* 310(14): 239–240.

Jensen, Richard, and Marie C. Thursby. 2001. "Proofs and Prototypes for Sale: The Licensing of University Inventions." *American Economic Review* 91(1): 240–259.

Kevles, D. J. 2002. "Of Mice & Money: The Story of the World's First Animal Patent." *Daedalus* 131(2): 78.

Kenney M. 1986. *Biotechnology: The University-Industrial Complex*. New Haven: Yale University Press.

Kline S., and Nathan Rosenberg. 1986. "An Overview of Innovation." In R. Landau and N. Rosenberg, (eds.), *The Positive Sum Strategy: Harnessing Technology for Economic Growth*. Washington, D.C.: National Academy Press.

Köhler, G., and Milstein, C. 1975. "Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity." *Nature* 256: 495–497.

Kremer, M. 1997. "Patent Buy-Outs: A Mechanism for Encouraging Innovation." NBER Working Paper no. 6304. Cambridge, MA: National Bureau of Economic Research.

Krimsky, Sheldon. 2003. *Science and the Private Interest*. Lanham, MD: Rowman-Littlefield Publishing Co.

Lessig, L. 2002. *The Future of Ideas: The Fate of the Commons in a Connected World*. Random House Vintage Books, New York.

Levin, R., A. Klevorick, R. Nelson, and S. Winter. 1987. "Appropriating the Returns from Industrial R&D." *Brookings Papers in Economic Activity* 3: 783–831.

Merges, R. P., and R. R. Nelson. 1990. "On the Complex Economics of Patent Scope." *Columbia Law Review* 90(4): 839–916.

Merges, R. P., and R. R. Nelson. 1994. "On Limiting or Encouraging Rivalry in Technical Progress: The Effect of Patent Scope Decisions." *Journal of Economic Behavior and Organization* 25(1): 1–24.

Merton, R. 1973. *The Sociology of Science: Theoretical and Empirical Investigations*. Chicago: University of Chicago Press.

Mokyr, Joel. 2002. *The Gifts of Athena: Historical Origins of the Knowledge Economy*. Princeton: Princeton University Press.

Mowery, David, Richard Nelson, Bhaven Sampat, and Arvids 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.

Mowery, David C., et al. 2004. *Ivory Tower and Industrial Innovation: University–Industry Technolgy Transfer Before and After the Bayh-Dole Act*. Stanford, CA: Stanford University Press.

Murray, Fiona. 2002. "Innovation as Overlapping Scientific and Technological Trajectories: Exploring Tissue Engineering." *Research Policy* 31(8–9): 1389–1403.

Murray, Fiona. 2006. "The Oncomouse that Roared: Resistance and Accommodation to Patenting in Academic Science." Sloan School of Management Working Paper. Cambridge, MA: MIT Sloan School of Management.

Murray, Fiona, and S. Stern. 2005. "Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? An Empirical Test of the Anti-Commons Hypothesis." NBER Working Paper no. 11465. Cambridge, MA: National Bureau of Economic Research.

Murray, F., and S. Stern. 2006. "Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? An Empirical Test of the Anti-Commons Hypothesis." Forthcoming, *Journal of Economic Behavior and Organization.*

National Institutes of Health. 2002. *In Their Own Words: NIH Researchers Recall the Early Years of AIDS*. Office of NIH History.

Nelson, R. R. 1959. "The Simple Economics of Basic Scientific Research." *Journal of Political Economy* 67(3): 297–306.

Owen-Smith, Jason, and Walter W. Powell. 2003. "The Expanding Role of University Patenting in the Life Sciences: Assessing the Importance of Experience and Connectivity." *Research Policy* 32(9): 1695–1711.

Panem, Sandra. 1984. "The Interferon Crusade." Washington, D.C.: Brookings Institution Press.

Popovic M., M. G. Sarngadharan, E. Read, et al. 1984. "Detection, Isolation, and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS." *Science* 224: 497–500.

Rabinow, Paul. 1996. *Making PCR: A Story of Biotechnology*. Chicago: University of Chicago Press.

Romer, Paul M. 1990. "Endogenous Technological Change." *Journal of Political Economy* 98(5): S71–102. October.

Rosenberg, N. 1974. "Science, Invention, and Economic Growth." *The Economic Journal* 84(333): 90–108.

Saiki R. K., D. H. Gelfand, S. Stoffel, S. J. Scharf, R. Higuchi, G. T. Horn, K. B. Mullis, and H. A. Erlich. 1988. "Primer-Directed Enzymatic Amplification of DNA with a Thermostable DNA Polymerase." *Science* 239: 487–491.

Saiki R. K., S. Scharf, F. Faloona, K. B. Mullis, G. T. Horn, H. A. Erlich, and N. Arnheim. 1985. "Enzymatic Amplification of Beta-Globin Genomic Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anemia." 230 (4732): 1350–1354.

Sarngadharan M. G., M. Popovic, L. Bruch, et al. 1984. Antibodies Reactive to Human T-Lymphotrophic Retroviruses (HTLV-III) in the Serum of Patients with AIDS." *Science* 224: 506–508.

Schupbach J., M. Popovic, R. V. Gilden, et al. 1984. Serological Analysis of a Subgroup of Human T-Lymphotrophic Retroviruses (HTLV-III) Associated with AIDS." *Science* 224: 503–505.

Scotchmer, S. 1996. "Protecting Early Innovators: Should Second-Generation Products be Patentable?" *The Rand Journal of Economics* 27 Summer 1996: 322–331.

Shapiro, C. 2001. "Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting." In A.B. Jaffe, J. Lerner, and S. Stern (eds.), *Innovation Policy and the Economy*, Vol. 1.

Shilts, Randy. 1993. *And the Band Played On: Politics, People and the AIDS Epidemic*. New York: St. Martin's Press.

Stephan, P., S. Gurmu, A. J. Sumell, and G. Black. 2006. "Who's Patenting in the University? Evidence from a Survey of Doctoral Recipients." Forthcoming, *Economics of Innovation and New Technology*.

Stern, Scott. 2004. "Do Scientists Pay to be Scientists." *Management Science* 50(6): 835–853.

Stewart, T. A., P. K. Pattengale, and P. Leder. 1984. "Spontaneous Mammary Adenocarcinomas in Transgenic Mice that Carry and Express MTV/myc Fusion Genes." *Cell* 38: 627–637.

Stokes, Donald. 1997. "Pasteur's Quadrant: Basic Science and Technological Innovation." Washington D.C.: The Brookings Institution.

Subcommittee on Oversight and Investigations, U.S. House of Representatives. 1995. "Gallo Report: Investigation of the Institutional Response to the HIV Blood Test Patent Dispute and Related Matters." Washington, D.C.: Government Printing Office.

Thomson, J. A., et al. 1998. *Science* 282: 1145–1147.

Walsh, John P., Wesley M. Cohen, and Ashish Arora. 2003. "Patenting and Licensing of Research Tools and Biomedical Innovation." In *Patents in the Knowledge-Based Economy*, edited by W. M. Cohen and S. Merrill, 285–340. Washington, D.C.: The National Acadamies Press.

Walsh, John, Ashish Arora, and Wesley Cohen. 2003. "Science and the Law: Working Through the Patent Problem." *Science* 299 (5609): 1021.

Walsh, John, Charlene Cho, and Wesley Cohen. 2005. "View from the Bench: Patents and Material Transfers." *Science* 309 (5743): 23.

Zamore, P. D., T. Tuschl, P. A. Sharp, and D. P. Bartel. 2000. "RNAi: Double-Stranded RNA Directs the ATP-Dependent cleavage of mRNA." *Cell* 101(1): 25–33.

Zucker, L., M. Darby, and M. Brewer. 1998. "Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises." *American Economic Review* 88: 290–306.