Exhibit 17

OVERALL CONCLUSIONS

The committee found that the number of projects abandoned or delayed as a result of technology access difficulties is reported to be small, as is the number of occasions in which investigators revise their protocols to avoid intellectual property complications or pay high costs to obtain access to intellectual property. Thus, for the time being, it appears that access to patents or information inputs into biomedical research rarely imposes a significant burden for academic biomedical researchers. However, for a number of reasons, the committee concluded that the patent landscape, which already is burgeoning in areas such as gene expression and protein-protein interactions, could become considerably more complex and burdensome over time.

There are reasons to be concerned about the future. First, the lack of substantial evidence for a patent thicket or a patent blocking problem clearly is linked to a general lack of awareness or concern among academic investigators about existing intellectual property. That could change dramatically and possibly even abruptly in two circumstances. Institutions, aware that they enjoy no protection from legal liability, may become more concerned about their potential patent infringement liability and take more active steps to raise researchers' awareness or even to try to regulate their behavior. The latter could be both burdensome on research *and* largely ineffective because of researchers' autonomy and their ignorance or at best uncertainty about what intellectual property applies in what circumstances. Alternatively, patent holders, equally aware that universities are not shielded from liability by a research exception, could take more active steps to assert their patents against them. This may not lead to more patent suits against universities—indeed, established companies are usually reluctant to pursue litigation against research universities—but it could involve more demands for licensing fees, grant-back rights, and other terms that are burdensome to research. Certainly, some holders of gene-based diagnostic patents are currently active in asserting their intellectual property rights. Even if neither of these scenarios materializes, researchers and institutions that unknowingly and with impunity infringe on others' intellectual property could later encounter difficulties in commercializing their inventions.

Finally, as scientists increasingly use the high-throughput tools of genomics and proteomics to study the properties of many genes or proteins simultaneously, the burden on the investigator to obtain rights to the intellectual property covering these genes or proteins could become insupportable, depending on how broad the scope of claims is and how patent holders respond to potential infringers. The large number of issued and pending patents relating to gene-expression profiling and protein-protein interactions contributes to this concern.

More immediately, the survey data revealed substantial evidence of another, potentially remediable burden on private as well as public research stemming from difficulties in accessing proprietary research materials, whether patented or

Exhibit 18

Final Report to the National Academy of Sciences' Committee Intellectual Property Rights in Genomic and Protein-Related Inventions

Patents, Material Transfers and Access to Research Inputs in Biomedical Research

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September 20, 2005

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ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial support of the Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions of the National Academies' Board on Science, Technology, and Economic Policy and Program on Science, Technology and Law. We also thank Stephen Merrill (Executive Director of the Board on Science, Technology, and Economic Policy), the members of the Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions, Eric Campbell, Robert Cook-Deegan, Robert Kneller and Patrick Reid for their guidance and comments. We also thank Mujuan Jiang for research assistance.

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EXECUTIVE SUMMARY

Concern over the impact of patenting and licensing on biomedical research has grown since the CAFC's 2002 *Madey v. Duke* decision, which visibly affirmed the absence of any research exemption shielding universities from patent infringement liability. This paper examines the impact of patents and licensing on access to research inputs for academic biomedical research through a survey of 1125 academic researchers (including university, non-profits and government labs) and 563 industry researchers (1688 total). To highlight the impact of patents on research related to proteomics, and to focus on a research area with high scientific and commercial interest, we also surveyed 299 researchers from academia and industry who were conducting research on one of three signaling proteins (CTLA-4, EGF and NF-kB). We received a total 655 responses across the sampled groups (unadjusted response rate of 33%). Our results focus on the academic respondents, with the industry respondents used to provide a point of comparison.

We find substantial commercial activity among our academic respondents (although not reflecting much of a change over the last five years). Nineteen percent currently receive industry funding for their research (accounting for 4% of their total research funding). Forty-three percent have applied for a patent at least once over the course of their career, with 22% having applied in the last two years. The average number of patent applications over the last two years was 0.37 per academic respondent. About 30% of academics have engaged in negotiations over rights to their inventions; 11% have at least begun developing a business plan or other groundwork for starting a firm; 8% report actually having started a firm and 13% report the commercialization of a product or process on the basis of one of their inventions. Eighteen percent of academics had some licensing income, and about 5% received more than $50,000 in total. More than half of academic respondents had one or more of the above.

Only 1% of our random sample of 398 academic respondents report suffering a project delay of more than a month due to patents on knowledge inputs necessary for their research. None of our random sample of academics had stopped a project due to the existence of third party patents on research inputs. An apparent reason for the negligible effect overall of patents on research is that respondents tend not to be aware of relevant patents. Only 5% check regularly for patents on research inputs. Although 22% of respondents report having received a notice from their institutions warning them to respect patent rights (compared to 15% from five years ago), receiving such a memo does not change the likelihood of checking for patents. Thus, while institutional awareness of the importance of attending to third party patents may have increased recently, bench-level scientists are still largely proceeding without checking for freedom to operate.

In contrast to the effects of access to intellectual property, access to tangible property in the form of material transfers is more likely to impede research. According to our data, 19% of our respondents did not receive materials in response to their last

request. A comparison with an earlier study suggests that this number has increased since the late 1990s. The major stated reasons for academics not sharing materials is the time and cost of providing those materials and scientific competition, not patents nor concern over commercial returns. Industry researchers, not surprisingly, are more likely to note commercial interests as a reason to not share research materials. Regression results (reported elsewhere) suggest that, for academic scientists, refusing to share research inputs is associated with scientific competition, commercial activity (though not industry funding) and the effort associated with compliance.

About 40% of the time academics make a request they are asked to sign an MTA. About one-quarter of the MTAs take more than one month to negotiate. Thus, overall, only 10% of requests led to a protracted (greater than one month) negotiation. However, 8% of requests for a research input lead to the research having to stop for more than one month (compared to 1% of cases where only a patent is involved). Patented inputs are not more likely to be denied. Research inputs that can be used as drugs are the most difficult to obtain. Overall, as a result of failed requests between academic researchers, we find an average of 0.68 projects delayed per researcher per two year period, and 0.22 projects abandoned.

Those working on the signaling proteins EGF and NF-kB show higher rates of commercial activity, while CTLA-4 researchers are much closer to the norm. While adverse effects from patents are still infrequent, they are somewhat more common for these researchers than for the random sample. Material transfers, on the other hand, have much higher rates of adverse effects for those working on EGF and NF-kB (less so for CTLA-4).

Our data from industry scientists suggests that access to material research inputs is even more difficult for these researchers. For example, 30% of industry scientists said that their last request was not fulfilled (compared to 19% for academic scientists). Industry scientists are also more likely to be faced with restrictive terms for access to research inputs, and to face research delays while the terms are negotiated. Similarly, they are more likely to refuse others' requests, to insist on protecting the commercial value of their own research tools and insisting on terms of exchange that ensure their interests are protected. Finally, they are more likely to check for patents, to find them, and to experience some adverse effects from others' patents, although some of these adverse effects may be due to the fact that they may be competing in the market with the owner of the patent.

Thus, our results suggest that commercial activity is widespread among academic researchers. However, patenting does not seem to limit research activity significantly, particularly among those doing basic research. Access to tangible research inputs from others is somewhat more problematic. Yet, scientific competition and the costs and effort involved seemed to dominate as the main reasons for not fulfilling such requests. A key reason for the negligible impact of patents on the conduct of academic biomedical research is that researchers largely ignore them. While such disregard for IP may, for the time being, minimize the social costs that might otherwise emerge due to restricted access

(Walsh, Arora, and Cohen 2003a), it is still important that the institutional environment maintain a free space for academic research. Furthermore, the importance of scientific competition, transaction costs and commercial interests for limiting access to material research inputs suggests that policymakers should devote their attention to alleviating these causes of friction in the flow of needed research materials.

1. Introduction

As patenting of both the inputs and outputs of scientific research have become more common, policymakers are faced with the question of whether introducing patenting into the system of scientific rewards is hurting or helping the causes of scientific and technological progress. The impact of patent protection on the research conducted in public research institutions—namely universities, government labs and nonprofits—is not well understood. This issue has taken on increasing importance since the combined events of: the passage of the Bayh-Dole Amendment in 1980 and related legislation encouraging institutions to patent findings from research supported by public funds; the 1981 *Diamond v. Chakrabarty* court decision affirming the patentability of life forms; and the revolution in molecular biology, combinatorial chemistry, bioinformatics and related fields that has spawned discoveries of enormous commercial value since the 1970's.

Scholars have recently argued that patents may now impose significant costs upon upstream, noncommercial research. Heller and Eisenberg (Heller and Eisenberg 1998) suggest that the patentability of a broad range of the inputs that researchers need to do their work may give rise to an "anti-commons" or "patent thicket" that may make the acquisition of licenses and other rights too burdensome to permit the pursuit of what should otherwise be scientifically and socially worthwhile research (cf. Shapiro 2000). Merges and Nelson (Merges and Nelson 1990) and Scotchmer (Scotchmer 1991) highlight the related possibility that, in some domains, the assertion of patents on only one or two key upstream, foundational discoveries may significantly restrict follow-on research. A further concern is that the prospect of realizing financial gain from upstream research may increase researchers' reluctance to share information or research materials with one another, thereby impeding the realization of research efficiencies and complementarities. Similarly, researchers may be trading away rights to conduct future research or to freely disseminate their discoveries in exchange for current access to research inputs or financial support (Cohen, Florida, and Goe 1994; Thursby and Thursby 1999). Finally, prospective financial gains from the exploitation of IP may induce researchers to choose research projects on the basis of commercial potential rather than scientific merit.

In an earlier interview-based research study conducted by two of the authors of this paper (Walsh, Arora, and Cohen 2003a; Walsh, Arora, and Cohen 2003b), we considered some of these concerns. On the basis of 70 interviews on the effects of the patenting and licensing of research tools on biomedical innovation, we found that the patent landscape has indeed become more complex, with more patents on upstream discoveries. We also found, however, that few of the frictions that had been anticipated had materialized. In addition to the typical solutions of contracting and licensing, we found that researchers in the field have implemented a variety of "working solutions" that commonly included the disregard—often unknowing—of patents on research tools. Even when our respondents were aware of the possibility that they were using someone else's intellectual property, they claimed to be protected by what they believed to be a "research exemption" shielding non-commercial research from infringement liability. Such disregard of others' IP was especially manifest among academic researchers.[1] Thus, it appeared that patents on research tools did not impede biomedical research as had been feared. Our interview-based study was, however, limited. Our 70 interviewees included, for example, 10 academic researchers, and 7 industry researchers, with the balance of our interviews conducted with university technology transfer officers, intellectual property officers, attorneys and others, making it difficult to generalize the findings.

Shortly after the fieldwork for this earlier study was completed, the *Madey v. Duke* decision of 2002 clarified what many had argued had long been the case—that there was no research exemption shielding academic researchers in biomedicine from infringement liability (Eisenberg 2003). This highly visible decision raised the question whether academics would continue to disregard IP on research tools.

This study probes in greater depth and with greater generality some of the questions considered in our prior work. We also address new questions, including the impact of intellectual property on incentives, knowledge flows and material transfers among bench scientists working in upstream biomedical research. Apart from the impact of IP per se, we also examine the willingness of researchers to share materials and data with one another, the associated terms of exchange, and the factors that might condition

[1] There was evidence of such behavior among researchers employed by firms as well, although for these respondents, there was no claim of protection by a research exemption.

such exchanges, including IP. Finally, we examine the extent to which researchers have become more concerned with IP since the *Madey v. Duke* decision.[2]

This study focuses upon bench scientists, who are the respondents to our survey. Our feeling was that, notwithstanding what university administrators, managers or patent attorneys might report and however important such statements are, it is ultimately the impact of IP at the level of the bench scientist that best reveals the effects of patents on biomedical research.

The paper is divided into six main sections. In Section II, we describe our data. Section III describes the commercial activities of our randomly drawn academic respondents. Section IV considers the impact of patenting on research for the random academic sample, as distinct from sample of respondents working on three signaling proteins (discussed below) and the sample of industry respondents. Section V examines material transfers, also for the random academic sample. Sections VI and VII consider patenting and material transfers for the respondents from, respectively, the signaling proteins and industry samples.

II. Data

We conducted a post-mail survey of biomedical researchers in academia, industry, government and non-profit sectors.[3] We use the term "industry" to refer to scientists

[2] We are not, however, probing one important issue that we had addressed in the prior study. Having confined our survey largely to those involved in more upstream work, and with a focus on bench scientists, we have only limited data to address the question posed by Heller and Eisenberg's (1998) "anti-commons" argument that it now takes the pulling together of too many patent rights to move ahead with the development and commercialization of drugs and other therapeutics. For that question, probably the most informed vantage point is that of the directors of projects or programs, or IP counsels in firms.

[3] The theoretical population is all currently active biomedical researchers in leading public and private research organizations who are doing research related to genomics or proteomics. The survey population was operationalized as current members of relevant professional societies. Our sample was drawn from the membership lists of the American Society of Cell Biology, the Genetics Society of America, the American Crystallographers Association (biological macromolecules SIG) and the following FASEB societies: American Society for Biochemistry and Molecular Biology, American Society for Pharmacology and Experimental Therapeutics, American Association of Immunologists, Biophysical Society, Protein Society, American Society for Clinical Investigation, American Society of Human Genetics, and American Peptide Society. To create the sampling frame, we combined all regular (non-student, non-emeritus) members, and removed duplicates from the list. We excluded from our sampling frame academic or non-profit members belonging to institutions that were not among the top-70 recipients of NIH research awards. For government or industry researchers, we included all of those in the frame. We stratified our sample by

working for firms and "academic" to refer to those working in universities, non-profit research institutes, hospitals and government labs. We drew a sample of 1125 academic researchers. We also drew a sample of 563 industry scientists. Finally, responding to the request of the National Academies' Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions, we added a sample of 299 researchers working on three signaling protein fields to supplement our random sample of academics (see below).[4] Thus, the final sample included 1987 scientists, with about 30% from industry. Sections III, IV and V of this paper focus on the respondents drawn from the random "academic" (i.e., those from universities, government or non-profit research institutions) sample. Sections VI and VII present the results from, respectively, the signaling protein and industry samples.

We mailed out questionnaires during the fall of 2004 to the 1987 researchers. We included in the survey packet a cover letter and an endorsement letter written by Prof. Shirley Tilghman, President of Princeton University, and Chair of the National Academy of Sciences Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions. We also sent a follow-up postcard about two weeks later, a second mailing (including the full packet) to non-respondents about two weeks after that, and a final mailing about six weeks after the second mailing (Dillman 1978). We received a total of 414 responses from our random sample of academic scientists (37% response rate). We also learned that 92 cases were ineligible, retired, deceased or undelivered. Thus, our response rate, adjusting for those who were not part of the effective sample, is 40%. Characteristics of the signaling protein and industry samples are described in Sections VI and VII below.

Because of the modest response rate, we were concerned about non-response bias. Using archival data from the USPTO database and the PubMed database, we compared a sample of respondents and non-respondents in terms of patents and publications to see if our respondents represent a biased subset of our population with respect to these two key variables (reflecting commercial and scientific activities, respectively). We drew a sub-

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sector (academic, non-profit, government, industry), and then drew a systematic random sample from each sector, with a sampling rate designed to produce one-third industry and two-thirds non-industry respondents, which entailed oversampling industry respondents.

[4] We thank the staff of the National Academies' Board on Science, Technology and Economic Policy for constructing this supplemental sample.

sample of 200 of our original sample of 1987 and compared the patenting and publication activity of respondents and the non-respondents in this subset in terms of patents (searching for patents by full name in the USPTO database of issued patents from 1976 to the present and for publications by last name and initials in PubMed from 2003 and 2004). We find that the respondents and the non-respondents have similar numbers of patents and publications, giving us some confidence that our results will not be unduly affected by response bias. For example, among our random sample of academics, respondents averaged 4.9 PubMed publications in the last two years and 0.5 patents in their lifetime, with 16% having at least one issued patent. For our non-respondents the figures are 5.6 publications, 0.5 patents and 21% with at least one patent. Thus we find that respondents and non-respondents are the same in terms of patent counts, but that non-respondents have about 10% more publications, and are somewhat more likely to have had at least one patent.

The survey questionnaire consisted of 159 items (11 pages) covering research topics and research group characteristics, requests for research inputs (including questions about MTAs), responses to such requests, reasons for choosing research projects, patenting and licensing, publishing, collaboration, and demographic items.[5] In order to increase the reliability of self-reported measures, we limited the time-frame to the prior two years, and, whenever possible, focused on specific instances (such as the most recent case) of what are, based on our pre-test interviews, important and often non-routine events, such as starting or abandoning a research project, applying for a patent, receiving an infringement notice or negotiating a request for a research material.

Given the modest response rate, caution is warranted in making any claims of generality beyond our sample. Also, possible biases associated with self-reported data should be considered when interpreting our findings. To limit these biases, we focus our

[5] The survey questionnaire is available from the authors upon request. The survey instrument was pre-tested through interviews with members of the population who had completed the draft instrument, as well as through consultations with expert members of the National Academy of Sciences Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions, who held a closed-door meeting to discuss the instrument and provided extensive feedback on earlier drafts. The instrument was also evaluated by the University of Illinois Survey Research Laboratory's in-house Quality Assurance Committee and corrected to improve the clarity and flow of the questions.

analyses on (self-reported) objective measures and multivariate methods whenever the data will permit such.

Our random sample of academic respondents is 72% male (Table 1.1). Academic respondents spend an average of 46 hours per week on research, 7 on teaching and 2 on clinical practice, have published a mean of 7 papers in the prior two years (with a standard deviation of 6), and participate in a research group with a mean size of 6 researchers. We see that the bulk of the research groups cluster around this mean, with about 70% of the groups having between 3 and 10 researchers. About 20% of the research groups consist of one or two people. And, just under 10% of our academic respondents belong to large groups of more than 10 researchers (what some might characterize as "big science" teams).[6] While the unit of analysis is the individual researcher, the sample can contain multiple respondents from the same institutions, especially in the case of large universities or government labs. In our random sample of academic researchers, excluding NIH (with 34 respondents), each of 5 institutions had from ten to twelve respondents in our sample, accounting for a total of 54 respondents, or 13% of our sample. Sixty-six institutions had from two to nine respondents, accounting for 380 total, or 58% of our sample. And 36 institutions had exactly 1 respondent (account for 9% of the total).[7]

The average respondent received his degree in about 1984, and has been at his current institution for about 14 years. Sixty nine percent of our "academic" respondents work in universities, 11% in hospitals (including university hospitals) and 19% in government labs or non-profit research institutions.

Table 1.2 breaks down the sample by research area, and shows that the preponderance of our academic sample works in genomics or proteomics. Table 1.3 reports on the distribution of respondents by research goal. Here, we see that over 75% of academics report doing basic research, most of these in genomics or proteomics. About 10% of the academics work on drug discovery, diagnostic test development or clinical testing. The remaining respondents are doing research to develop research tools or are engaged in other research activities. Two-thirds of our industry respondents work

[6] The distribution of group size for industry respondents is similar.
[7] Because we have multiple respondents from the same institutions, future analysis will also check for institutional effects, in addition to individual-level effects reported here.

on drug discovery. We will distinguish between respondents conducting basic research versus those engaged in more downstream drug discovery, development of other therapeutics and diagnostic test development (which we will combine under the rubric of "drug discovery").

III. Commercial Activity of Academic Sector

There is strong evidence that over the past 25 years academic scientists have become increasingly focused on commercial activity (Mowery, Nelson, Sampat, and Ziedonis 2001; National Science Board 2002; National Science Board 2004). However, non-commercial activity still constitutes the bulk of academic effort. For example, while industry funding of university research increased significantly during the 1970s and 1980s (rising from 2.7% in 1970 to 6.9% in 1990), it still only accounts for about 7% of total university research funding (National Science Board 2004).[8] The trend in industry funding has been largely flat through the 1990s and the early part of this decade, suggesting that industry funding may have largely settled at its current level.

In our survey, we collected information on the extent to which our respondents were engaged in commercial activity, and the extent to which this has changed over the last five years. This section characterizes the commercial activity for our random academic sample. We begin with a measure of cross-sector collaboration. We asked our respondents if they currently have a research tie, broadly defined (including joint research, contract research, personnel exchanges, paid consulting, etc.), with researchers from other organizations. We also asked if they had such ties five years ago. Figure 1 shows little change in university-industry links over the last five years. Just fewer than 30% of our academic respondents have some research tie with small or medium sized enterprises (SMEs), and about 20% of academics have a tie with a large firm. On the other hand, over 80% of our academic respondents have ties to researchers in universities (for academics, researchers in universities other than their own), and about half have ties to government or non-profit researchers. Thirty-six percent have ties to researchers in hospitals (including university hospitals). Ties to SMEs have increased only modestly

[8] In fact, the latest data, from 2001, show a decline to 6.8%, down from a peak of 7.4% in 1999. Preliminary data from 2002 suggests this downward trend is continuing (NSB 2004).

over the last five years (27% v. 22%, t=2.58, p<.05), and there is little change in ties with large firms.

We also asked academic respondents about industry funding and time spent on commercial activity. Table 2 presents the results for our 414 academic respondents. About 19% of our academic respondents received funding from industry, a slight decline since five years ago when about 23% reported receiving industry funding, a result that is consistent with aggregate data showing a recent decline in industry funding of academic research (cf., NSB 2004). This figure is also very close to the 23%-28% figure found by Bekelman, et al. (Bekelman, Li, and Gross 2003) in their review of the literature on biomedical researcher's ties to industry. The average percent of academic respondents' research budgets supported by industry is 4.0%, down from 5.6% five years ago.[9] The average academic respondent spends about 3% of his time on commercial activity (including time spent working for a new venture based on his invention, time spent in paid consulting, and time spent negotiating rights to his inventions).[10]

Finally, we asked about respondents' participation in several more explicitly commercial activities, including negotiating over rights to their inventions, preparatory efforts to start a firm (for example, by presenting a business plan to potential investors), actually creating a start-up, having a product or process in the market, and receiving licensing revenue. Just over 40% of our academic respondents had applied for a patent at some point, with about 22% having applied in the last two years. The average number of patent applications over the last two years was 0.37 per academic respondent. About 30% of academics have been involved in negotiations over rights to their inventions; 11% had begun developing a business plan or other groundwork for starting a firm; 8% had a startup based on their invention; and 13% had a product or process in the market. Eighteen percent of academics had some licensing income, and about 5% received more than $50,000 in total. Half of academic respondents had one or more of the above. Compared to those engaged in basic research, respondents doing drug discovery, clinical testing or diagnostics had more industry funding (p<.0001), patent more (p<.05), engaged

[9] These numbers are below the overall average for total university funding from industry (across all field) (NSB 2004).

[10] The answer categories were None, 1-25%, 26-50%, 51-75%, 76-100%. We used mid-point means to calculate the average.

in more business-related activity ($p<.10$), and received more licensing income ($p<.25$). These results suggest, not surprisingly, that commercial activity is greater among those scientists whose research is closer to the market.

Thus, our results indicate that a significant portion of researchers engage in commercial activity of some form, although the overall amount of commercial activity has not increased substantially in the last five years, nor does this activity appear to occupy much of the average researcher's time.

IV. Patents and access to knowledge in upstream biomedical research

This section considers the impact of patents on academic researchers' incentives, and on their access to research tools and other inputs into the research process. Because science advances cumulatively, one researcher's discovery is another's necessary research input. For this reason, much of this section focuses on whether patents restrict biomedical researchers' access to the findings of others upon which they wish to build.

Patents and Project Choice and Abandonment

One important concern is whether patenting and commercial gain are driving project choice (Heller and Eisenberg 1998; Thursby and Thursby 2003). That is, will scientists be especially drawn to projects that are patentable? Or, alternatively, does the prospect of having to deal with numerous patents on research inputs (i.e., a "patent thicket") dissuade them from pursuing a project?

To consider these questions, we asked our academic respondents to indicate the importance of different reasons for choosing their research projects on a five point scale, where a score of "1" signified a reason was "not at all important" for selecting research projects, and a score of "5" signified a reason was "very important." For each reason listed, Table 3 reports the percentage of respondents scoring "4" or "5", suggesting the reason was more than "moderately important." Clearly, the most pervasive reasons for selecting research projects are scientific importance (97%), interest (95%), feasibility (88%) and access to funding (80%). The patentability of the research results is reported

to be more than moderately important for only 7% of the respondents, and consideration of the number of patents on research inputs is more than moderately important for only 7% of our respondents. Even commercial potential of research results figures importantly for only 8% of our respondents. These results are consistent with the findings reported by Thursby and Thursby (2003) that suggested that increasing commercial activity was not associated with a shift in research priorities. The 37 academic respondents conducting research on drugs and other therapies, however, depart from these overall results. Patentability ($t=2.06$, $p<.05$), commercial potential ($t=2.13$, $p<.05$) and a lack of patents on research inputs ($t=1.91$, $p<.10$) all figure more prominently in the project choices of those doing research on drugs or other therapies, with each of these business-related reasons considered important for guiding project choice by about 20% of the respondents.

Heller and Eisenberg (1998) raise the prospect that, due to the challenges associated with negotiating access to numerous patents held by different parties, worthwhile projects might not be undertaken. It is difficult to assess the frequency with which something of this sort might occur because one would need to know something about projects that are stopped or even never observed. Nonetheless, to arrive at some sense of such an effect, we asked our academic respondent to "Please think about the most recent case where you seriously considered initiating a major research project and decided not to pursue it at that time." We then asked the respondents to evaluate the importance of reasons that may have dissuaded them from moving ahead with the project, on a scale from "1" ("not at all important") to "5" ("very important"). For each reason listed, Table 4 reports the percentage of respondents scoring a given reason as "4" or "5", indicating more than moderate importance. The results clearly show that the most pervasive reasons why projects end up not being pursued are lack of funding (62%), a respondent's decision that he was too busy (60%), or judgments that the project was infeasible (46%), not scientifically important (40%) or uninteresting (35%). The relative importance of these reasons holds across research areas. After this group of reasons, the next most pervasive reason, with a score of 29%, was the intensity of scientific competition or, specifically, that there were too many groups pursuing similar projects. Technology control rights, such as terms demanded for access to needed research inputs

(10%) and patents covering needed research inputs (3%) were reported to be relatively unimportant. For those 28 respondents involved in research on drugs and therapies, however, 21% indicated that unreasonable terms demanded for research inputs were an important reason for them not to pursue a project ($t=1.56$, $p<.15$).

Thus, we see that patents seem to provide academics little impetus to choose projects, suggesting they are not an important incentive driving the research (Scherer 2002). Nor do patents seem to dissuade scientists from pursuing projects. For those doing drug discovery, the effect of patents is somewhat stronger, although still secondary to funding, scientific importance and scientific competition.

Patents and knowledge flows

In the course of their research, how often do bench scientists believe they need information or knowledge covered by someone else's patent? Of our 381 academic respondents who answered this question, 8%, or 32, indicated that sometime in the prior two years they conducted research where they believed they were using information or knowledge covered by someone else's patent (Table 5). An additional 19% reported that they did not know, and the balance, 73% reported that they did not require access to someone else's IP to conduct their research. How can we explain the low number of respondents reporting that they required access to someone else's IP in light of the proliferation of patents on research tools over the past decade? One has to distinguish between actually using someone else's IP and a scientist believing that he is. To probe this, we asked our respondents whether they regularly check for patents on tangible or knowledge inputs into their research, and learned that only 5% of our academic respondents do so (Table 5). We also see that over half of those who check (9 of 17) started checking for patents more than two years ago, with eight starting within the last 2 years. Thus, it appears that the *Madey v. Duke* decision had only a modest effect on the sensitivity of academic bench scientists to the use of others' intellectual property, since only 2% of our academic respondents have started looking for patents since that decision. Aside from their own checking, respondents may learn of a patent through a notification

letter sent either to them or their institution. As shown in Table 5, 5% of our academic respondents had been made aware of such a notification. This is not much different from the 3% of our respondents who report having received such notification five years ago, prior to the *Madey v. Duke* decision. It is interesting to note that these numbers remain quite small.

The institutions that house academic researchers appear to be more concerned with avoiding patent infringement than the researchers themselves, and this institution-level concern appears to be growing. Table 5 shows that 22% of our academic respondents were notified by their institutions to be careful with respect to patents on research inputs, up from 15% of our respondents who recalled receiving such a notice five years ago ($t=2.34$, $p<.05$). Notably, there was little difference in the behavior of those academics who had received such notification from their institution from those who had not, with 5.9% of the former and 4.5% of the latter regularly checking for patents. These results reflect the autonomy of academics with respect to their administrations and suggest that institutions simply urging faculty to consider the IP rights of others may be insufficient to elicit a response.

Of the 32 respondents who believed they needed to use an input covered by someone else's patents, 23 (i.e., 72% of the 32 or 6% of the total academic respondent sample) reported only 1-2 instances in the prior two years. Another 7 indicated there had been 3-5 such cases, and two respondents indicated there had been six or more cases.[11] Thus, the preponderance of respondents indicating awareness of IP on needed research inputs reported only one or two instances of such in the prior two years, again suggesting that patent thickets are rare in our respondents' experiences: less than 3% of respondents report coming across more than two relevant patents over the last two years, across all their research projects.

Of considerable importance is how the 32 academic respondents who believed that they needed an input covered by someone's patents responded to the existence of that IP. Twenty-four, or 75% of the 32, contacted the IP owner to receive permission to use

[11] Of the 32 respondents believing that they needed access to a patented input into their research, nine reported that they planned to use the patented technology as a compound with potential therapeutic use; two reported they planned to use it as a diagnostic technique, and 19 reported that they planned to use it as a research tool.

the IP. Another five reported that they proceeded with their research without contacting the IP owner, and one modified his project to avoid use of the patented input. No one reported stopping the research project in order to avoid the patented technology. For obvious reasons, the number of those reporting that they proceeded without contacting the IP owner may underestimate the true figure.

Of the 24 respondents who sought permission to use the IP, seven (29%) reported that they did not receive permission within one month. While there was little variation across research goals, there were differences across the technologies requested. Of those who were trying to gain access to a potential drug 43% (3 of 7) said they faced delays, compared to 25% (4 of 16) of those who intended to use it as a research tool. Although it is difficult to infer much from such small numbers (and it is important to note a key point: that few scientists consider research input patents), it appears that frictions are more apparent around technologies that have therapeutic potential. In both the basic research and drug development cases, the vast majority of agreements are settled in under one month.

Of the 24 respondents who were faced with a patent relevant to their research, none reported that they abandoned a promising line of research as a consequence of delay or inability to receive permission. Four reported having to change research approaches to complete the study, and five delayed completion of the experiment by more than one month. Thus, of 381 academic scientists, even including the 10% who claimed to be doing drug development or related downstream work, none were stopped by the existence of third party patents. Even modifications or delays are rare, each affecting around 1% of our sample. Even relative to the small number of respondents (i.e., the 32) who were aware of a patent related to their research, the figures are modest, with 13% modifying their project, 16% having a delay of more than one month, and none stopping a project due to someone else's patent on a research input. In addition, 22 of 23 respondents to our question about costs and licensing fees reported that there was no fee requested for the patented technology, and the 23rd respondent said the cost was in the range of $1-$100. Thus, not only are barriers or delays rare, but costs of access for research purposes are negligible.

Thus, it would appear that, at least for the time being, access to patents on knowledge or information inputs into biomedical research rarely imposes a significant burden for academic biomedical researchers.

V. Sharing Research Materials

In addition to examining the ease with which scientists can gain access to others' *intellectual* property that they may require in their research, we are also interested in the extent to which scientists can access *tangible* research materials created by other labs. Thus, one might think of our analysis in the prior section as an examination of the effects of "pure intellectual property" on biomedical research, while, in this section, we examine the effects of the tangible property represented by research materials.

There is a long and active tradition among biomedical researchers of sharing research materials (Campbell, et al. 2002; Ceci 1988). In addition, recent NIH guidelines have highlighted the need for publicly funded researchers to make the results of their research available to others (Department of Health and Human Services 1999). The norm in biomedical researcher is that publishing implies a quid pro quo to make research materials available (National Research Council 2003). However, while such norms of sharing research materials are well accepted, they are not always practiced (Campbell et al. 2002).

Because access to another scientist's research materials can be critical for the success of a research project, this topic is especially important for understanding how the flow of technology might affect biomedical research. The greater commercial activity of academic scientists, and a greater awareness among commercial scientists of the potential value of IP associated with research, has raised concerns that this flow of research materials may be slowing down (Campbell et al. 2002; Eisenberg 2001). In addition, scientific competition may also interfere with the flow of information and technologies across rival labs (Hagstrom 1974; Merton 1973; Walsh and Hong 2003). Finally, there is concern that the exchange of research materials has been impeded by disputes and delays over the terms of formal material transfer agreements (MTAs) associated with the growth

of university technology transfer offices and the associated rise in bureaucratization that they represent (Eisenberg 2001; Walsh, Arora, and Cohen 2003a).

In order to explore the extent to which technology flows may be being impeded, we asked a series of questions about whether respondents had either made or received requests for research inputs and then explored the outcomes of such requests.

Requests for Research Inputs and Responses

We asked our respondents if, during the past two years, they had requested a research input (including, for example, unpublished information, cloned gene, drug, protein or software) from either an academic or industry researcher. We also asked if they had received a request for a research input from an academic or industry researcher. Table 6 presents the results for the whole sample, and for the sample broken down by the research goals of drug development, basic research or other. First, requests for materials are widespread, although of moderate frequency. Seventy five percent of our academic respondents made at least one request in the last two years and 69% had received such requests. The number making and receiving requests is about the same for those doing basic research and those doing drug discovery. On average, academics made about 7 requests to other academics and 2 to industry labs in the last two years, and received 14 requests from academics and 2 from industry labs. Most importantly, our results suggest that between 7% (suppliers' estimate) and 18% (consumers' estimate) of requests are denied. We also asked if they had received the most recently requested research input (Table 6). For the academic respondents, 81% received their most recently requested material. These results suggest that the vast majority of such requests are fulfilled, but that a non-trivial number are not (almost 20% according to the consumers). [12] Non-compliance rates are very similar (as measured by whether or not the most recent request was fulfilled) between those doing drug development and those doing basic research.

[12] Regression analyses reported elsewhere (Walsh, Cho and Cohen 2005) show that scientists with more publications tend to be more likely to deny requests for research materials. Thus, to the extent that our sample average of papers published is under the population mean, we are likely to be somewhat underestimating the mean rate of refusals of research material requests.

To consider whether non-compliance may have changed over time, we compare our results with those from Campbell and colleagues' (2002) earlier survey.[13] Campbell reports that, among genomics researchers, about 10% of requests were denied in the three years, 1997-1999. Among the genomics researchers in our sample, the comparable number for 2003-2004 is 18% (95% confidence interval:+/-3.7%),[14] suggesting that scientists may now be less willing to share research materials than just four to seven years ago.

Does Sharing of Research Inputs Vary by Technology Requested?

We also asked respondents to report the outcomes of their requests for materials broken down by type of research material. We classified research materials into the following categories: 1.) unpublished information or findings; 2.) cloned gene, plasmid, cell line, tissue, organism; 3.) drug or potential drug; 4.) protein; and 5.) database or software. We also asked respondents to report outcomes separately for requests to academics versus requests to industrial researchers, and to report whether all, some or none of their requests were fulfilled. Note that this is a very strict measure of compliance since even one request denied, no matter the number of requests, or the conditions under which a request was made, counts as a compliance failure (cf. Campbell et al. 2002).

Overall, these results echo those of the prior section. As shown in Table 7, being denied at least some requests for research inputs is common across different types of research materials and different sectors. Typically around half of respondents have had at

[13] To make the two samples comparable, we limited our estimate to those doing genomics research in universities or hospitals (including university hospitals). One distinction between the Campbell survey and ours is that they specifically limited their question to after-publication requests, while our survey did not specify the publication status of the research input. While we assume most such requests are related to published research results, we suspected that at least some requests are for not yet published inputs (as a result of a meeting presentation, for example) and hence these might possibly have a higher rate of non-compliance. In order to check this, we phoned over 60% of respondents with one or more denied requests to find out if any of their requests were for unpublished research inputs and if the denials were disproportionately due to requests for unpublished inputs. We found that 11% of requests were for inputs that had not yet been published. However, refusal rates for unpublished research inputs were no higher (in fact were lower) than for published inputs. Therefore, we feel confident that the growth in non-compliance is not due to differences in question wording.

[14] The average number of requests in genomics is 7.61, and average number denied is 1.36.

least one request denied over a two year period. Using a very strict measure of compliance (receiving every requested research input), drugs or potential drugs are the most difficult material to obtain. There is also no apparent difference between trying to acquire genes or organisms versus proteins.[15]

The Effect of Not Receiving Requested Research Inputs

We also asked respondents to tell us about the impact on their research of not receiving requested research materials or data. When other parties are the only source of essential research inputs such as materials or data, research may cease if those parties do not provide the requested material or data. In contrast, research may proceed without taking a license to another's IP, or in the absence of knowing whether such a license is needed. For this reason, availability of material inputs (which is presumably tied to permission to use them) may have a greater effect on the conduct of research than that of "pure IP" (Walsh, Arora, and Cohen 2003a).

We inquired, separately for academic and industry suppliers to academic respondents about the frequency **over a two year period** of the following four outcomes: delayed completion of the experiment by more than one month; having to change research approaches; abandonment of a promising line of research; and having to develop the research input in their own lab.[16] The results are shown in Table 8.1.

For our random sample of academics, the average number of delays per person over a two-year period that result from failing to receive a material requested from

[15] Table 7 reports the percent of consumers who received all of what they requested, by technology requested, supplier sector, and the consumer's research goal Requests for drugs or potential drugs are generally the most likely to be refused, with only 54% of academic scientists receiving all drugs requested from other academics and 35% receiving all such requested drugs from industry. Compliance rates for other materials tend to be above 60% for academic sources and above 30% from industry sources. Compared to researchers engaged in drug discovery, academic consumers engaged in basic research almost always report higher rates of compliance with their requests to academic suppliers. For industry suppliers, the results are more mixed.

[16] The response categories were 0, 1-2, 3-5, 6-10, more than 10 times. We estimated the average of each type of result, using mid-point means (with >10 set to 16), and with those who received all of their requests set to zero for these events. Thus, we are estimating the total number of such events per person (where one person may have had many such events, contributing each such event to the numerator of the overall average, but only one case to the denominator). These events are not exclusive, so that we cannot add the results across items to compute an aggregate figure (of, for example, "either delays or abandonments").

another academic was 0.68, and, from an industry researcher, it was 0.40. Projects abandoned were 0.22 per person over two years due to academics not supplying materials, and 0.27 due to industry researchers not supplying materials. Having to develop the materials in house or change research approaches also happened less than one time per person per two-year period. We also observe that delays or having to making requested materials in-house are somewhat more common for those academics doing drug discovery compared to those engaged in basic research (though the differences are not statistically significant). Abandoning a research project is much less common for those doing drug discovery ($t=2.23$, $p<.05$).

Table 8.2 analyzes the same data by inquiring about the number of respondents that have had one or more such experiences. Thus, rather than measuring the average incidence of each outcome, we are measuring how widespread the phenomenon is. We observe that, over a two year period, 35% of academic consumers have had a project delayed by more than one month as a result of failing to receive a requested research input from academic suppliers. Fourteen percent of academic consumers have had to abandon at least one project over the last two years. Thus, in an average year, one in fourteen academics abandoned a project due to an inability to access research inputs. By contrast, as noted above, no one reported abandoning a project due to disembodied "pure IP". In comparison to those engaged in basic research, those doing drug discovery are somewhat more likely to make materials in house ($t=1.49$, $p<.15$) or to change research approaches (n.s.), but are less likely to abandon a project ($t=2.12$, $p<.05$).

Are these adverse outcomes of concern from a social welfare perspective? For example, is one in fourteen researchers abandoning a promising line of research in a given year worrisome? To the extent that such redirection of a scientist's research effort or reallocation across investigators significantly reduces the chance of scientific progress, this is a cause for concern. On the other hand, even while the loss may be perceived as substantial by the affected individual, if this is a case of less duplicative research, the overall social welfare loss may be minimal (Cole and Cole 1972). Moreover, there may even be a net gain as a greater variety of projects are pursued by the scientific community (Dasgupta and Maskin 1987). We have no way of testing these rival interpretations of these findings.

The Process of Acquiring Research Inputs: MTAs, Terms, Negotiations

Finally, we asked a series of detailed questions regarding whether respondents, having requested a material, were asked to sign a material transfer agreement, and, if so, to describe the terms of that agreement. Possible terms included a requirement to give the supplier co-authorship; restrictions on publication or dissemination of research results; clauses providing suppliers reach-through or grant-back rights; and royalty payments on future sales of products related to the research input. We also asked if there were negotiations over the terms of the agreement, the involvement of their institution's technology transfer office or patent counsel, the duration of any negotiations over terms, and associated delays, breakdowns and costs. Although the NIH and the National Academy of Sciences recommend that MTAs should not impose claims on future inventions, nor restrictions on the dissemination of findings (Department of Health and Human Services 1999), it is also recognized that, under some circumstances, as when the research input itself has commercial potential, restrictions may be legitimately imposed.[17]

Table 9 summarizes the results. The first thing we can see is that less than half (42%) of the requests for a research input required an MTA. Furthermore, only 40% of MTAs required any negotiation, and only 26% of the MTAs required a negotiation lasting more than one month. While there has been substantial concern about the effect of MTAs on academic researchers (Eisenberg 2001), only 11% (.42 X .26) of requests for research inputs resulted in an MTA negotiation taking more than one month. Eight percent of academic researchers, however, reported having to stop their research for more than one month while negotiating terms. Although modest, this number is larger than the zero cases where "pure IP" stopped the research ($t=3.34$, $p<.001$). Among the academic consumers, those asking for a drug are more likely than average to be presented with an MTA (64% of requests: $t=2.68$, $p<.01$). However, they were only slightly more likely to be in an extended negotiation or to have their research stopped.

[17] Eisenberg (2001) argues that it is uncertainty about the circumstances that might justify restrictions that may lead to extended negotiations and failures to acquire requested inputs.

Are requests for MTAs in general interfering with the transfer of materials? This does not appear to be the case. Of the 40 % of the requests where a prospective supplier of a material asked for an MTA to be signed, 12% ended up being denied. Of the 60% of requests where a prospective supplier did not ask for an MTA to be signed, 23% ended up being denied. These figures suggest that the presence or absence of an MTA is not central to whether materials are shared, and, if anything, suggest that a process involving an MTA is more likely to be associated with compliance. A regression analysis (available from the authors) shows that drugs are especially difficult to acquire. We also see that being asked to sign an MTA is associated with a greater chance of receiving the material, probably because such a request signals that the owner is at least willing to consider sharing. Whether the patented material is itself patented has no significant effect on the likelihood of receiving the material, controlling for the owner and whether it is a drug that is being requested. Scientific competition, on the other hand, has a strong negative effect on receiving the requested material, suggesting that in fields where many scientists are chasing the same research results, they may be less willing to share materials with potential rivals (Hagstrom 1974; Merton 1973; Walsh and Hong 2003).[18]

The next question, however, what are the costs for acquiring these materials? Reach-through claims are fairly common, while royalty payments are less so. The supplier asked for a reach-through claim for 38% of MTAs, and demanded a royalty for 17% of MTAs.[19] Requests for drugs are most likely to generate such reach through claims (70%), with requests for proteins also often including such terms (64%). Publication restrictions were also common, with 30% of MTAs presented to academic scientists imposing such restrictions (Cohen, Florida, and Goe 1994; Thursby and Thursby 1999). Requests for drugs were the most likely to have such a restriction, with 70% of agreements to transfer drugs to academics including some restriction on publication of the research results using those drugs ($t=4.15$, $p<.0001$). On the other hand, only 34% of MTAs accompanying proteins and only 16% of those for biomaterials had such restrictions.

[18] Another interpretation of this result may be that those fields with more competitors are those where you are less likely to know your rivals personally, and hence more likely to refuse the request.
[19] The final agreements are less likely to contain such terms, although we still observe that about 29% of the agreements have reach through claims and 16% have royalty terms.

Academics' requests to industry suppliers are much more likely to result in an MTA than are requests to academic suppliers (70% of research input requests to industry suppliers v. 35% for academic suppliers, $t=4.49$, $p<.0001$). Industry suppliers' MTAs are also much more likely to include in their initial terms a publication restriction (58% of industry MTAs v. 18% of academic MTAs, $t=4.52$, $p<.0001$), a reach through claim (63% of industry MTAs v. 29% of academic MTAs, $t=3.51$, $p<.001$) or a royalty (32% v. 12%, $t=2.10$, $p<.05$). Interestingly, there was little difference in the likelihood of asking for a co-authorship (15% of industry MTAs v. 12% of academic MTAs, $t=0.37$, $p>.70$). Perhaps contrary to expectations, negotiations over terms with industry are more likely to take longer than a month than are negotiations with universities (35% of negotiations with industry suppliers lasted over one month v. 21% of negotiations with university suppliers, 1.61, $p<.15$). Requests to industry are also somewhat more likely to result in the research being stopped for more than one month (16% of requests to industry suppliers resulted in the consumer having to stop for the project for more than one month v. 6% of requests to academic suppliers, $t=1.65$, $p<.15$).

We also inquired about fees and other charges associated with material transfers. For research inputs received from other academics, 93% entailed no charge. Only 4 out of 243 requests (less than 2%) required an upfront payment of over $1000. Even requests to firms were largely supplied without a charge (85% of the time industry suppliers did not demand a fee for the research input). Only 3 out of 41 requested inputs (7%) came with a demand for a fee of over $1000.

Thus, we see that academic to academic transfers are less problematic. However, when making requests to firms for research inputs, academics are more likely to be faced with demands for reach through claims or other restrictions, and the resulting negotiations can be time consuming. While the research generally proceeds unimpeded (over 90% of the time when making requests to other academics, and over 80% of the time when making requests to industry), a notable minority (about 16%) of requests to industry result in significant delays to the research and involve demands for downstream rights or payments. Such transfers are generally free to academics, although there are occasional demands for up front fees.

Although our results suggest that MTA's may contain controversial licensing terms, including reach through claims and publication restrictions, it is hard to know what the social welfare implications of these terms are without a closer look at their specific content and the motivations for their inclusion. For example, one common reason for demanding restrictions on publication, such as the right to review papers before publication, or simply the right of advance notification of a pending publication, is to protect the supplier's ability to file patent claims on his own technology without fear that the consumer's publication will place the technology in the public domain. A modest delay in publication in exchange for access to the technology may be seen as a reasonable payment by the consuming scientist. On the other hand, social welfare losses may be realized if such publication restrictions include the right to withhold publication of results entirely in order to achieve a competitive advantage through secrecy, or, even worse, to ensure that unfavorable research results (such as adverse effects in clinical trials) are never disclosed.[20]

Patents and Other Limits to Making Research Inputs In-House

It is apparent that requests for materials can occasionally impose significant burdens on the researcher making the request. So, why does the researcher not simply avoid making the request by making the research input himself? We considered three possible reasons: the time or cost involved; their lab lacking the capability to make the material; or patents. They were asked to rate each on a 5-point Likert scale ranging from not important ("1") to very important ("5"). Table 10 gives the average scores for each type of research input. The most important reason for not making the material in-house is the time or cost involved (a mean score of 4.3 out of 5.0). Inability to make it in-house

[20] Similarly, reach through claims may be more or less problematic. A claim to give the supplier a non-exclusive right to practice any improvements to the supplied technology may be an important means of ensuring freedom to operate for the supplying organization. Firms supplying a research input may also often want a right of first refusal to a non-exclusive, or even exclusive, license to any derivative inventions, either to ensure freedom to operate (i.e., prevent a blocking patent from going to a rival), or to maintain an option of developing a technology trajectory that they have already started on, and such claims may have beneficial social welfare impacts. On the other hand, an attempt by the supplier to leverage her technology to gain exclusive ownership over any research results that eventuate may be an unreasonable extension of any monopoly right that might be conferred through a patent on the original technology.

(mean=3.1) is the second most important reason. Patents (mean=1.6) score much lower as an impediment to producing the research input in-house ($p<.0001$). Drug inputs are more likely to be seen as limited by patents (3.2; $t=4.41$, $p<.001$), although even here, other reasons rank as more important. Thus, with the exception of drug inputs, respondents do not consider patents the major impediment to producing needed research inputs themselves. Instead, potential time and cost savings motivate them to try to obtain the inputs from another lab.[21]

Why are materials not being shared?

Although the vast majority of requests for research inputs are honored, we still observe a significant number of cases where the requests are not fulfilled. We now examine what might be driving such behavior. Based on prior work, and the findings above, we consider three main motives: commercial concerns (including patents); effort involved; and scientific competition.

For the most recent case where they decided to deny a request for a research input, we asked our respondents how important were each of the following reasons for that decision: a need to protect my research group's ability to publish; a need to protect the commercial value of the results; a need to honor the requirements of a research sponsor; having had their own requests for inputs denied; the cost or effort required to product the research input; a concern that sharing the research input might make them liable for patent infringement; a refusal by the person making the request to accept the respondent's terms for the material transfer or license; sending the research input would violate the terms of other agreements. The answers were on a 5-point Likert scale ranging from not important ("1") to very important ("5").

Figure 2 shows the percentage of respondents who scored each choice as more than moderately important ("4" or "5"), among the 51 academic respondents who denied at least one request. We can see that for academics, the most pervasive reasons for not fulfilling a request were the effort involved and the need to protect publications (with just

[21] For proteins, on the other hand, patents do not seem to be an impediment to making it in-house (rated at 1.5). Proteins and biomaterial requests are primarily motivated by time or costs savings.

under half of academics rating each reason as more than moderately important). Control-rights-related reasons ranked significantly below these reasons ($p<.05$). For example, an unwillingness to accept the supplier's terms was reported to be more than moderately important by 22% of academic suppliers, and concern over violating terms that the supplier signed ranked "high" by 18% of academic suppliers. Commercial concerns were rated as an important reason by only 8% of academic respondents. These results are very similar to Campbell, et al. (2002), who found that effort was seen as the most important reason, and need to protect publications as second and commercial value as the least important reason. There may be some response bias on this item, given that commercial motives may be seen as less legitimate reasons for failing to fulfill one's collegial obligations than are excessive demands or scientific competition. Thus, while these results are suggestive, they may suffer from a socially desirable response effect. Because of the concerns about "socially desirable response" effects, and to further explore the independent effects of these predictors of not sharing, we ran a negative binomial regression predicting the number of requests denied (Walsh, Cho, and Cohen 2005). We find that commercial activity has a negative effect on scientists' willingness to share research inputs. We also see that scientific competition is an important, independent predictor of failure to comply with requests. These findings both confirm earlier regression results by Campbell, et al. (2002), and add to them by showing that scientific competition is a significant predictor for failing to share. The burden associated with the effort involved also apparently limits sharing.[22]

VI. Patenting and Three Signaling Proteins

The results above suggest that patents only rarely interfere with academic research, and even material transfers are largely processed without incident. Yet, even an infrequent problem can have important impacts on scientific and medical advance if the technology is sufficiently important. Thus, in this section, at the suggestion of the

[22] In a logistic regression of the predictors of receiving the most recently requested material, we find that scientific competition and asking for a drug or potential drug reduce the likelihood of receiving the requested material, while the presence of an MTA is associated with greater chance of receiving the drug, and patent status has no independent effect. We also tested the effect of particular terms for MTAs and find that material transfers that involve terms granting publication review or reach through royalties are less likely to be completed (results available from the contact author).

National Academies' Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions, we complement our analysis of the random academic sample by focusing on domains that are medically important and where the preconditions for restricted access or anti-commons are especially apparent—that is, characterized by numerous patents, patents on fundamental, upstream discoveries, and strong commercial interest. A finding of patent-induced problems in such research areas would suggest that research may be vulnerable to important frictions due to IP, if not in general, at least in some important instances. On the other hand, a finding of relatively few problems would importantly reinforce the conclusion from our analysis of the random sample that, despite conditions that are expected to generate anti-commons or access problems, intellectual property is not a key impediment to biomedical research.

For this more focused component of our study, we focus on researchers working on three cellular proteins: **EGF** (Epidermal Growth Factor), **NF-kB** (Nuclear Factor-kappa B) and **CTLA-4** (Cytotoxic T-Lymphocyte Associated Protein-4). These proteins mediate signals along key molecular pathways involved in normal and diseased cellular processes. Stimulation of cells with EGF, for example, has been shown to induce cell division (Cohen 1983), an event that, if left unchecked, can lead to cancerous growth (Kastan and Bartek 2004). The CTLA-4 receptor is involved in regulating T cell proliferation (Oosterwegel, Greenwald, Mandelbrot, Lorsbach, and Sharpe 1999), and its loss of function is believed to contribute to auto-immune diseases such as rheumatoid arthritis, multiple sclerosis and lupus (Kristiansen, Larsen, and Pociot 2000). NF-kB also has been implicated in rheumatoid arthritis, as well as asthma, septic shock and cancer (Yamamoto and Gaynor 2001), and its role in the proper development and function of the immune system is supported by numerous studies of NF-kB knockout and transgenic mice (Baeuerle and Baltimore 1996). These proteins have generated substantial academic interest. For example, foundational papers on EGF (Cohen 1962) and NF-kB (Sen and Baltimore 1986) have each been cited over 1500 times, while the more recent discovery of the functions of CTLA-4 (Linsley, et al. 1991) has been cited over 900 times.

Patenting is also extensive in these areas. Since 1995, the USPTO has granted over 60 CTLA-4-related patents, over 90 NF-kB-related patents and over 760 EGF-related patents (National Research Council 2005). The major patent owners include large

pharmaceutical firms, biotech firms, universities and the Federal government. Such heterogeneity of ownership is one of the conditions that are likely to generate problems of access and licensing (Heller and Eisenberg 1998). These proteins and drugs that act on them also have significant commercial potential, as indicated by the number and types of therapeutic products targeted against these proteins.[23]

There is some concern that the proliferation of patents on such fundamental biological processes may impede research and/or the development of new treatments in these areas, suggesting that they merit further scrutiny. The case of NF-kB is a prime example. On June 25, 2002, the Massachusetts Institute of Technology, Harvard University and the Whitehead Institute were granted a US patent covering broad claims on NF-kB (the Baltimore, et al. patent, US Patent No. 6,410,516). Soon after securing an exclusive license to the patent (and other related patents) Ariad Pharmaceuticals sued Eli Lilly claiming that two of Lilly's drugs on the market, Xigris®, which is used to combat sepsis, and Evista®, which is used in the treatment of osteoporosis, violated the claims of the Baltimore patent by acting on the NF-kB pathway. Ariad also has licensed the patent to Bristol-Myers Squibb, a pharmaceutical firm, and to DiscoveRx, a research tool developer (to develop screening assays). Interestingly, however, Ariad has publicly stated that it has no intention of pressing claims against academic or non-profit researchers. Ariad CEO Harvey Berger has said, "We entirely encourage noncommercial use without a license" (Brickley 2003). A ruling in Ariad's favor could provide those holding patents over such fundamental biological processes with substantial leverage to demand licensing fees or stop research for a broad range of potential projects.

No matter how the case is finally decided, there is concern that the existence of such patents might discourage research, if only because the threat of infringement suits exists. As one test of this conjecture, we examined the case of NF-kB to see if the issuance of these patents has been associated with reduced research activity in this area. We searched PubMed for papers with "NF-kappaB" (or variants)[24] in the title or abstract,

[23] Both Erbitux® (ImClone/Bristol-Myers Squibb) and Iressa® (AstraZeneca) are used for the treatment of cancers associated with EGF receptor expression. CTLA4-Ig® (Repligen) and Abatacept® (Bristol-Myers Squibb) currently are in clinical trials for the treatment of multiple sclerosis and rheumatoid arthritis, respectively.

[24] We used the following search terms: "NF-kappaB" or "NF-kB" or "nuclear factor-kappaB" or ("nuclear factor" AND immunoglobulin) or "NF-.kappa.B" or "nuclear factor-.kappa.B" or "nuclear factor.kappa.B".

and published since 1986, when the Baltimore group published the first papers in this area (cf.(Marx 2002) for a similar analysis for telomerase). Figure 3 gives the results. We can see a steady increase in interest in this area, especially since 1996. The key patents issued in 1998 (No. 5,804,374), 2000 (No. 6,150,090), and 2002 (No. 6,410,516) and the Ariad license and Lilly lawsuit date from 2002. The trend line shows little reaction to either the patents or the lawsuit, with a fairly steady upward trend from 1995 onward, suggesting that the patents and their licensing have not adversely affected biomedical research in this field.[25]

Thus, these three proteins each have significant numbers of patents, commercial activity, and also represent fundamental biological research areas, making these areas especially fertile ground for adverse effects of patents and transfer frictions.

To study the effects of patents in these chosen areas, staff of the National Academies' Science, Technology and Economic Policy Board drew a supplemental sample of researchers working on one of the three signaling proteins: CTLA4, EGF, or NF-kB, drawing 100 researchers from each field (one duplicate was eliminated), which included a total of 29 (out of 299) from industry.[26] We then administered the same questionnaire as provided to the random sample, allowing us to compare the answers from these three fields to the general population analyzed above. We received a total of 93 responses from academic scientists working in these three areas. Due to the modest sample size (about 30 for each protein), we have only limited statistical power for comparisons, and estimates of group means are not very precise and should be interpreted with some caution.

As shown in Table 2, EGF and NF-kB are characterized by an especially high level of commercial activity, while CTLA-4 is much closer to the norm for biomedical research. Compared to the overall sample, academics working in these areas are somewhat more likely to have industry funding, with: NF-kB most likely to have industry

[25] While we see a continuous, absolute increase, it is still possible that we might be observing less of an increase than expected in the absence of patents (Murray and Stern 2004; Sampat 2004).

[26] The sampling frame for the pathways was constructed by combining scientists (and eliminating duplicates) who received NIH funding related to the pathway (top 50 grantees with permanent positions, i.e., assistant, associate or full professor), who received NSF or HHMI funding in that area (all names), who published in that area (using the PubMed database, choosing the first 50 publications each year for 2002, 2003, 2004), or who patented in this area (top 10 patent holders in each area).

funding and reporting the highest percent of industry funding (14%, difference from norm, p<.05); EGF somewhat less; and CTLA4 having the lowest among the three (with CTLA-4 being just below the norm). Over the last two years, NF-kB researchers filed the most patent applications (an average of .89 per respondent, p<.01), followed by EGF (.74, p<.05), with CTLA-4 also above the norm (.63, n.s.). EGF scientists are the most likely to receive licensing revenue (p<.05), and the most likely to generate significant licensing income (with 19% of the respondents reporting more than $50,000 in licensing income, p<.10), with NF-kB and CTLA-4 also above average, at about 9% (n.s.).[27] Thus, it seems that researchers working on EGF and NF-kB are especially commercially active, while those studying CTLA-4 are not much different from the overall average, although somewhat more active on some measures.

For all three fields, respondents choose their projects predominantly due to scientific importance, interest, feasibility and funding. However, EGF researchers are somewhat more likely to cite personal income (11% v. 2% for random sample, n.s.) or the chance to start a new firm (7% v. 1% for random sample, n.s.) as additional reasons to choose projects. Those conducting research on NF-kB were somewhat above average in citing unreasonable terms for access to research inputs as a reason to avoid pursuing a project (19% v. 10% for the norm, n.s.). In general, researchers in these areas choose and reject projects on largely the same bases as other scientists. In particularly, none of the three groups of researchers was more likely than average to rate "too many patents" on inputs as an important reason not to pursue a project.

An examination of the effects of IP on the research itself suggests that, while adverse effects are still infrequent, they are more common for these researchers than for the random sample. Respondents across all three signaling proteins are much more likely to say that they needed access to a patent for their research, with between 15% (EGF, n.s.) and 24% (NF-kB, p<.05) acknowledging a related third-party patent, as compared to 8% for the random sample. Three or four people from each research field contacted the patent owner to obtain permission. Although the numbers are small, and therefore provide little statistical power, we see a slightly higher incidence of adverse

[27] Because EGF was discovered before NF-kB, it is not surprising that licensing revenue and business activity is more common in this field. However, the data on recent patents suggests that NF-kB may be catching up to EGF in terms of commercializing the potential of this discovery.

consequences. Among CTLA-4 researchers, one person abandoned a project (4% of the sample, or 20% of those who faced a patent), but there were no delays or modified projects. Among EGF researchers, two abandoned a project (7% of the sample, or half of those who faced a patent), one modified a project and three delayed their projects, with three people overall having one or more adverse effects (11% of the total, or 75% of those who faced a patent). No one in the NF-kB field (out of 33) abandoned a project. There were three NF-kB cases of delaying and three of modifying (four cases had one or the other), representing 9% of the sample, or about half of those who faced a patent. Thus, we see that, even in fields characterized by considerable patenting and commercial activity, adverse effects from pure IP are uncommon (less than 15% of the sample), though more prevalent than in the general population. In particular, abandoning a project due to inability to access IP is still rare, but non-zero (3 out of 93 respondents, across the three fields, about 3%). These results suggest that pure IP can occasionally delay or even stop a project, but that, even for populations that should have a high incidence of such problems, they are still infrequent, in part for the same reasons as stated previously: scientists do not regularly check for patents.

Our analysis of researchers who study these three important signaling proteins reinforces the conclusion that access to material research inputs may be more problematic than access to "pure IP." Such problems are especially evident among those working on NF-kB and EGF. Relative to the random sample, the number of requests for materials is ten to twenty percent higher in these fields. More importantly, while 81% of the random sample received their last requested input, between 68% (NF-kB, $p<.10$) and 74% (EGF, n.s.) of those working on these signaling proteins were successful in their last request. Similarly, 30% (CTLA-4) to 44% (EGF) of requests to academic suppliers were denied, compared to 19% for the random sample.

Researchers working on NF-kB and EGF also report greater frequency of negative effects from not receiving research materials (Table 8.1). For example, NF-kB researchers report 0.62 cases of projects abandoned ($p<.10$) and 2.85 cases of projects delayed ($p<.05$) as a result of inability to access requested research inputs. These results

are 3-4 times higher than the norm. The gap for EGF is smaller, in the range of 1.5-2 times the norm (n.s.). CTLA-4 is generally close to the norm.[28]

Thus, while pure IP has a small impact on researchers in these patent intensive, commercially active research domains, researchers in these areas are more likely to be stymied by difficulties in accessing needed research inputs, particularly those working on NF-kB.

VII. Industry Scientists' Experiences with Material Transfers and Patents

While we have shown that patents per se have minimal impact on the research activities of academic scientists (including those at government labs and non-profit institutions), there is also concern that patents may limit the ability of industry scientists to develop the leads generated by academic science. This translational research is key to drug development. It also plays an important role in scientific advance, both by testing the implications of basic research and by producing empirical findings that inspire further research into the underlying biology.

In fact, many of the arguments related to the anti-commons and restrictions on access are specifically addressing the problem of for-profit firms gaining access to the technologies necessary for the early stages of the drug development process. To further probe the impact of patents on research inputs, as well as the incidence and effects of failing to receive requested research inputs from other scientists in industry and academia, we collected a random sample of industry scientists from the same sampling frame used to draw the random academic sample. Because industry scientists are relatively scarce in this frame (representing about 10% of the total), we over-sampled industry scientists, yielding a sample of 563 industry scientists. We received 144 industry respondents, for an unadjusted response rate of 26%. After excluding the 105 cases that were ineligible, we had an adjusted response rate of 32%. A non-response bias analysis (n=59) shows that those who responded were very similar to non-respondents on

[28] However, the percent having had a project stopped for more than one month is not much higher in the pathways than in the overall population, with the exception of EGF, where 15% of respondents had their research stopped for more than one month due to failure to acquire a research input.

publications (2.4 v. 2.3), number of patents (1.1 v. 1.7) and likelihood of having any patents (20% v. 32%) (all differences insignificant, $p > 0.40$).

We begin with our data on sharing of research inputs (Table 6). We see that industry scientists are less likely to make such requests (60% v. 75% for academic scientists, $t=3.30$, $p<.01$) or to receive such requests (41% v. 69%, $t=6.02$, $p<.001$). They are also somewhat less likely to get their requests fulfilled. For example, 30% of industry scientists did not receive their last requested research input, compared to 19% for academic scientists ($t=2.22$, $p<.05$). Similarly, they were more likely to refuse requests, with 41% refusing at least one request, compared to 19% for academic scientists ($t=3.22$, $p<.01$). When we compare across specific technologies, we see that industry consumers were less likely than academic consumers to obtain requested biomaterials ($t=1.40$, $p<.20$), proteins ($t=1.52$, $p<.15$) and drugs ($t=2.59$, $p<.05$) from academic suppliers (Table 7). Failing to receive requested inputs has a similar effect on industry scientists as it does on academic scientists. We see that unfulfilled requests to academic suppliers result in 0.39 abandoned projects per person per two-year period (compared to 0.22 for academic consumers) and unfulfilled requests to industry suppliers result in 0.32 abandoned projects (compared to 0.27 for academic consumers). Other adverse effects are also largely the same across the two populations.

When we examine the process of acquiring research inputs, we find some important differences in the experiences of academic and industry scientists (Table 9). Industry consumers are more likely to be presented with an MTA ($t=1.60$, $p<.15$), to have the MTA contain restrictive terms (all $p<.05$), particularly reach through royalties (44% v. 17%, $t=3.24$, $p<.01$), to have a negotiation that lasts more than one month ($t= 3.89$, $p<.0001$), and to have their research stopped for more than one month (16% v. 8%, $p<.10$). Interestingly, if we compare the incidence of protracted negotiations across the two sectors, we find that about 20% of academic to academic transfers took more than one month to negotiate. By contrast, if an industry representative is on either side of the table, the transfer takes longer, suggesting that universities may have an undeserved reputation for being slow moving in negotiations. For example, 45% of industry to industry transfers took more than one month to negotiate. The most problematic case was industry consumers dealing with academic suppliers, where 60% of transfers took more

than one month to negotiate. In fact, it may be this experience that has engendered the complaint about universities being slow. Industry scientists are also more likely to report that patents prevented them from making the research input in-house (2.59 v. 1.63, t=4.68, p<.0001) (Table 10). Interestingly, there was no difference between the two populations with regard to patents on drugs preventing making the research input in-house.

When we asked industry suppliers why they refused requests from other scientists, we see some important, though perhaps unsurprising differences compared to academic suppliers (Figure 2). While academics highlighted the cost and/or effort involved and their need to protect their own ability to publish, industry scientists emphasized protecting the commercial value of the research input and the terms of the transaction (both sector differences, p<.01), with publication a secondary consideration.

We did not explicitly survey our industry respondents about their reactions to "pure IP". [29] However, we did receive a small number (n=17) of responses to these items from industry respondents. While these responses should not be considered representative of industry as a whole, they do provide some insight into the existence (or not) of problems for industrial scientists resulting from others' patents on pure knowledge inputs. We find that industry respondents regularly check for patents related to their research, with over 60% saying they regularly check for patents (compared to 5% for academics). Industry scientists are also more likely to say they needed access to someone else's patent, with 35% reporting that there was a relevant third party patent (compared to 8% for academics). Two out of 17 respondents had to stop a project (12%) and four (24%) had any adverse effect (abandon, delay, or modify). These numbers are substantially greater than the 0-2% for academics, although we might still consider them modest considering that some of these adverse effects may be due to cases where the patented technology and the firm's technology objective were rival in use (cf. Walsh, Arora and Cohen, 2002b). For example, one of the two stopped cases was due to a patent on a drug, leaving only one case in 17 of a research tool patent stopping a research project.

[29] We had a skip-logic in the questionnaire so that industry respondents would not be asked questions about their (possibly infringing) use of other's patented technologies.

Thus, we see that industry scientists are somewhat more likely to have difficulties accessing research inputs from other scientists. They may not be fully included in the community of "gift exchange" that characterizes academic scientists, although they are not fully excluded either (National Research Council 2003). They are also more likely to be faced with restrictive terms, and to face research delays while the terms are negotiated. Similarly, they are more likely to insist on protecting the commercial value of their own research tools and insisting on terms of exchange that ensure their interests are protected. Finally, they are more likely to check for patents, to find them, and to experience some adverse effects from others' patents, although some of these adverse effects may be due to the fact that they may be competing in the market with the owner of the patent.

VI. Conclusions

Our results indicate that academic biomedical researchers are engaged in a significant amount of commercial activity, including patenting and licensing. Patents in biomedical research, while common, do not seem to be having a substantial impact upon academic research in the "pure IP" case. In particular, none of our random sample of academics reported stopping a research project due to another's patent on a research input, and only about 1% of the random sample of academics reported experiencing a delay or modification in their research due to patents. Even among researchers working on signaling proteins associated with important molecular pathways, fields that should have been particularly susceptible to IP-induced frictions, we observed relatively few adverse effects. One important reason is that, notwithstanding the 2002 *Madey v. Duke* decision, academic researchers remain largely unaware of patents relevant to their research and typically proceed without considering them. In other words, the mere existence of patents on intangible knowledge inputs does not impinge substantially on the conduct of academic research. While such disregard for IP may for the time being minimize the social costs that might otherwise emerge due to restricted access (Walsh, Arora, and Cohen 2003a), it remains, however, an open question whether such disregard is sustainable.

In contrast to the case of "pure IP," requests for tangible research inputs from other scientists, while honored in a timely fashion in the majority of cases, are not fulfilled in a significant minority of cases. Almost 20% of our respondents report that their last request for a material was not fulfilled. The refusal rate is even higher for those working on the signaling proteins. Moreover, the incidence of non-compliance appears to be increasing. Furthermore, we find that such non-compliance adversely affects the research programs of individual researchers. For example, one in fourteen researchers abandons a promising line of research in a given year because he did not receive a requested material. The source of this noncompliance has little to do, however, with patent policy, but appears to reflect the impact of commercial incentives on the part of academics, scientific competition, the time and effort required to satisfy requests, and whether the material in question is a drug. Notwithstanding the source, however, without more research, we cannot conclude that adverse consequences of denied requests for individual researchers raise a concern for social welfare. To the extent that redirection of a scientist's research effort or reallocation across investigators impedes scientific progress, this is a cause for concern. On the other hand, if such redirection reduces duplicative research, the social welfare loss may be minimal (Cole and Cole 1972). There may even be a net welfare gain if redirection increases the variety of projects pursued (Dasgupta and Maskin 1987).

Aside from the welfare consequences of stopped or redirected projects, it does appear that there are considerable frictions and costs associated with material transfers. Although MTAs are not universally required, about 40% of such requests require an MTA, and these MTAs (especially those from industry suppliers) frequently include demands for some form of reach-through rights. They also often include terms that put restrictions on publication of research results using these inputs. These MTAs tend to be negotiated quickly, although about 10% of all requests lead to a negotiation lasting more than one month. In a minority of cases (8% of requests), delays in accessing research inputs can stop the research for more than one month, which can represent an important delay in a rapidly evolving research field. Regression analyses suggest that scientific competition, commercial activity, and the cost and/or effort involved, all play an important role in limiting sharing of research inputs. Patents and MTAs, on the other hand, do not seem to be an impediment. Policy efforts that focus on reducing the

transaction costs of such transfers may be the most effective way to improve researchers' timely access to necessary research inputs.[30]

Our data from industry scientists suggests that access to research inputs is even more difficult for these researchers. For example, 30% of industry scientists said that their last request was not fulfilled (compared to 19% for academic scientists). Industry scientists are also more likely to be faced with restrictive terms for access to research inputs, and to face research delays while the terms are negotiated. Similarly, they are more likely to refuse others' requests, to insist on protecting the commercial value of their own research tools and insist on terms of exchange that ensure their interests are protected. Finally, (although this sample is opportunistic and non-representative), those industry respondents who answered questions about access pure IP said that they are more likely to check for patents, to find them, and to experience some adverse effects from others' patents. However, some of these adverse effects may be due to the fact that they may be competing in the market with the owner of the patent.

Based on the data at hand, our results suggest that there is reason for concern about access to tangible research inputs. There is, however, little evidence that patent policy is the cause of restricted access to tangible research inputs (as opposed, for example, to scientific competition or business activity). Furthermore, the impact on scientific progress of this restricted access to research inputs is also not straightforward.

In conclusion, debates that focus on the effects on research of the patenting of upstream biomedical discoveries may not be addressing the most pressing policy question. Instead, scientific progress in biomedicine may be more effectively supported by addressing the transaction costs, competitive pressures and commercial interests that are now impeding the sharing of material research inputs.

[30] For example, mandating that NIH funded research tools be deposited in a central repository (and providing a funding mechanism for maintaining such a core facility) is one solution. In addition, having such repositories provide materials to the research community under standard MTAs that include an exemption from patents for non-commercial research use would alleviate many concerns about patents restricting access in the future. We should note, however, that, as yet, such concerns have not been realized. And, we should also be aware that any such requirements might perhaps undermine the incentives to develop such research tools.

Table 1.1 Basic Demographics.

	Academic	Signal Proteins			Industry
Basic Demographics	Random Sample	CTLA4	EGF	NF-kB	Sample
Male (%Yes)	72	73	80	86	73
Year received highest degree	1984	1979	1983	1986	1987
Years at current institution	14	14	13	11	8
Research group size	6	6	7	11	7
Hours per week spent on research	46	42	42	49	56
Hours per week spent teaching	7	7	7	6	1
Hours per week spent on clinical practice	2	13	5	2	4
Publications (2years)	7	11	13	12	3
N	414	30	30	37	144

Table 1.2 Distribution of Responses by Research Activity,
Random Sample of Academic Respondents.

	Frequency	Percent	Cumulative Freq.	Cumulative %
Genomics	172	42.36	172	42.36
Protein	151	37.19	323	79.56
Drug/Clinical	10	2.46	333	82.02
Other	73	17.98	406	100

Table 1.3 Distribution of Respondents by Research Goal.

	Academia				Industry			
Research Goal	Frequency	Percent	Cumulative Freq.	Cumulative %	Frequency	Percent	Cumulative Freq.	Cumulative %
Drug Discovery	40	9.66	40	9.66	95	65.97	95	65.97
Basic Research	322	77.78	362	87.44	10	6.94	105	72.92
Other	52	12.56	414	100	39	27.08	144	100

Table 2. Commercial Activity for Academic Researchers, Pathways Comparison.

		Random	Research Goal			Signal Proteins		
Measure		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB
Industry Money-Now	% yes	19	54	15	14	30	29	39
Industry Money-5 years ago	% yes	23	44	21	15	38	37	33
%Industry Funding-Now	Mean	4	13	3	5	3	6	14
%Industry Funding-5 years ago	Mean	6	15	4	6	4	9	10
%Time on Commercial Activity	Mean	3	6	3	2	6	7	4
Patent Application	% yes	43	57	42	32	65	82	70
Patent App. last 2 years	% yes	22	50	19	22	41	41	50
#Patent Applications	Mean	0.37	0.76	0.32	0.37	0.63	0.74	0.89
Negotiation	% yes	30	47	29	18	48	50	36
Pre-Startup	% yes	11	17	9	14	26	21	24
Create Firm	% yes	8	14	7	9	13	11	15
Product or Process in Market	% yes	13	28	11	16	22	18	18
License Income	% yes	18	31	17	11	17	33	30
Licensing income>$50k	% yes	5	11	4	2	9	19	9
Any Commercial Activity	% yes	50	70	50	34	70	86	76
Total	N	414	40	322	52	29	29	35

Table 3. Reasons for Choosing Projects, by Research Goal and for Signal Proteins.

		Random	Research Goal			Signal Proteins		
		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB
Scientific Importance	%High	97	97	97	93	96	96	100
Interest	%High	95	95	95	95	100	96	100
Feasibility	%High	88	89	88	91	96	93	88
Sufficient Funding	%High	80	86	80	73	87	86	88
Health Benefit	%High	59	89	54	67	83	59	79
Promotion/Job	%High	24	22	24	30	4	14	15
Commercial Potential	%High	8	22	6	14	13	11	9
Patent Free	%High	7	19	5	11	9	4	3
Patentable	%High	7	19	4	11	22	11	6
Personal Income	%High	2	3	2	2	4	11	0
NewFirm	%High	1	0	1	0	4	7	3
Respondents	N	382	37	301	44	23	28	33

Table 4. Reasons for Not Pursuing Projects, by Research Goal and for Pathways.

		Random	Research Goal			Signal Proteins		
		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB
No Funding	%High	62	86	60	58	63	54	82
Too Busy	%High	60	55	60	59	53	58	48
Not Feasible	%High	46	41	46	47	33	55	53
Not Scientifically Important	%High	40	24	41	45	40	36	50
Not Interesting	%High	35	24	36	33	20	30	29
Too Much Competition	%High	29	21	32	21	27	29	29
Little Social Benefit	%High	15	21	14	15	13	5	22
Unreasonable Terms	%High	10	21	9	6	7	9	19
Not Help w/ Promotion/Job	%High	10	21	7	15	0	13	5
Too Many Patents	%High	3	3	2	3	0	4	0
New Firm Unlikely	%High	3	3	2	3	0	4	0
Little Commercial Potential	%High	2	3	2	3	0	4	0
Little Income Potential	%High	1	3	1	3	0	4	0
Not Patentable	%High	1	3	1	3	0	4	0
Respondents	N	274	28	213	33	16	24	22

Table 5. Check for Patents Regularly or Not, by Research Goal and for Signal Proteins.

		Random	Research Goal			Signal Proteins		
		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB
Needed Patent	%Yes	8	14	8	9	22	15	24
Check for patent	%Yes	5	11	4	2	0	4	9
Warning-Now	%Yes	5	5	6	2	9	4	9
Warning-5 year ago	%Yes	3	3	4	0	9	7	0
Inst. Memo-Now	%Yes	22	30	22	18	9	23	22
Inst. Memo-5 year ago	%Yes	15	8	16	12	18	12	16
Respondents	N	381	37	300	44	23	27	33

Table 6. Sharing Research Inputs, Academic Respondents,
by Research Goal and for Signal Proteins; and Industry Respondents.

		Random	Research Goal			Signal Proteins			Industry
		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB	Respondents
As Consumer									
Request Research Inputs	%yes	75	75	79	56	86	93	94	60
Requests to Academia Unfulfilled	Mean	1.3	1.68	1.28	1.12	1.91	2.63	3.89	1.38
Total Requests to Academia	Mean	7.34	6.88	7.42	7.04	6.39	8.46	13.25	5.49
Requests to Industry Unfulfilled	Mean	0.69	0.95	0.52	1.7	1.16	1.14	0.88	0.86
Total Requests to Industry	Mean	2.15	3.86	1.62	4.3	2.37	2.45	1.84	3.97
Last Request Fulfilled	%yes	81	77	80	93	70	74	68	70
As Supplier									
Received Requests	%yes	69	68	73	43	71	83	91	41
Requests from Academia Unfulfilled	Mean	0.92	0.83	0.84	1.85	2.75	1.45	3.25	2.98
Total Requests from Acadmia	Mean	13.93	7.43	14.24	18.1	11.3	18.5	22.96	7.9
Requests from Industry Unfulfilled	Mean	0.45	0.42	0.37	1.45	1.57	0.94	0.95	0.58
Total Requests from Industry	Mean	1.64	3.05	1.29	3.18	3.71	2.44	2.19	2.52
At Least One Request Not Fulfilled	%yes	19	19	19	18	20	29	22	41
Respondents	N	411	40	319	52	29	29	35	143

Table 7. Likelihood of Receiving All Requested Research Inputs, Academic Respondents, by Research Goal and for Signal Proteins; and Industry Respondents.

		Random	Research Goal			Signal Proteins			Industry
		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB	Respondents
Academic Source									
Unpublished Information	% yes	69	63	70	67	40	33	50	50
Gene, Organism, etc	% yes	63	68	63	53	45	50	50	52
Drug	% yes	54	43	53	100	57	0	20	35
Protein	% yes	62	56	62	83	53	50	52	38
Database/Software	% yes	56	33	58	60	44	29	75	37
Industry Source									
Unpublished Information	% yes	56	63	57	33	17	20	0	57
Gene, Organism, etc	% yes	54	43	56	50	44	17	33	53
Drug	% yes	44	44	43	50	44	21	27	57
Protein	% yes	53	67	51	50	38	20	29	50
Database/Software	% yes	55	60	50	50	0	0	50	65
Respondents	N	152	16	124	12	10	18	12	52

Table 8.1. Average Number of Adverse Effects from Not Receiving Research Inputs over Last Two Years, Academic Respondents, by Research Goal and for Signal Proteins; and Industry Respondents.

		Random	Research Goal			Signal Proteins			Industry
		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB	Respondents
Academic Supplier									
Delay>1 month	Mean	0.68	0.98	0.69	0.33	0.83	1.19	2.85	0.78
Change Research Approach	Mean	0.56	0.89	0.54	0.3	0.45	0.74	2.24	0.68
Abandon	Mean	0.22	0.07	0.24	0.21	0.27	0.2	0.62	0.39
Make In-house	Mean	0.67	0.88	0.65	0.59	0.93	1.23	2.29	1.01
Industry Supplier									
Delay>1 month	Mean	0.4	0.75	0.39	0.18	1.02	1.08	0.87	0.35
Change Research Approach	Mean	0.46	0.66	0.42	0.56	0.68	0.69	1.66	0.49
Abandon	Mean	0.27	0.08	0.3	0.26	0.58	0.86	0.28	0.32
Make In-house	Mean	0.31	0.44	0.28	0.47	0.69	0.78	0.71	0.33
Respondents	N	242	24	195	23	21	24	26	62

Table 8.2 Percent Experiencing Each Adverse Effect at Least Once, Academic Respondents by Research Goal and for Signal Proteins; and Industry Respondents.

		Random	Research Goal			Signal Proteins			Industry
		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB	Respondents
Academic Supplier									
Delay>1 month	% yes	35	38	36	22	48	54	73	37
Change Research Approach	% yes	33	41	33	20	30	30	65	35
Abandon	% yes	14	4	15	14	18	14	33	17
Make In-house	% yes	34	46	32	32	38	54	69	38
Industry Supplier									
Delay>1 month	% yes	16	22	16	12	52	44	47	20
Change Research Approach	% yes	18	26	16	28	37	28	50	33
Abandon	% yes	12	6	12	18	30	39	19	18
Make In-house	% yes	13	11	12	22	28	33	47	19
Respondents	N	242	24	195	23	21	24	26	62

Table 9. MTA, Terms and Negotiation, Academic Respondents, by Research Goal, Technology Requested, and for Signal Proteins; and Industry Respondents.

		Random	Research Goal			Technology Requested						Signal Proteins			Industry
		Sample	DrugDisc	BasicRsrch	Other	UnpInfo	Gene,Cell,etc	Drug	Protein	Data, Soft	Other	CTLA4	EGF	NF-kB	Respondents
MTA	%Yes	42	55	40	44	13	45	64	30	54	50	50	41	45	52
Initial Terms (% of MTAs)															
Co-Author	%Yes	13	27	11	11	52	8	14	19	17	15	25	18	8	34
Publication Review	%Yes	30	50	26	32	52	16	70	34	29	34	34	55	36	55
Reach Through	%Yes	38	61	35	32	29	32	70	64	17	25	44	55	52	56
Royalty	%Yes	17	14	16	32	2	13	26	38	1	21	11	22	31	44
Final Terms (% of MTAs)															
Co-Author	%Yes	13	22	12	13	27	7	15	18	20	22	40	20	11	40
Publication Review	%Yes	26	43	24	24	52	10	70	42	0	32	51	50	21	65
Reach Through	%Yes	29	36	29	14	29	25	52	37	0	23	42	51	22	41
Royalty	%Yes	16	1	16	32	2	10	33	19	0	21	22	24	12	31
Negotiation (% of MTAs)	%Yes	40	50	40	20	0	39	53	58	0	43	58	82	50	70
TTO (% of MTAs)	%Yes	39	50	39	20	0	39	53	58	0	38	50	73	43	69
Negotiation > 1 month (% of MTAs)	%Yes	26	31	25	20	0	22	29	58	0	29	42	64	29	57
Stop Research (% of Requests)	%Yes	10	14	10	7	0	10	21	11	0	14	12	19	15	20
Stop > 1 month (% of Requests)	%Yes	8	10	8	4	0	8	14	9	0	12	8	15	9	16
Respondents	N	304	29	249	27	31	146	28	44	13	42	24	27	31	83

Table 10. Reasons for Not Creating Research Input In-house, Academic Respondents, by Technology Requested and for Signal Proteins; and Industry Respondents.

		Random	Technology Requested						Signal Proteins			Industry
		Sample	UnpInfo	Gene,Cell,etc	Drug	Protein	Data, Soft	Other	CTLA4	EGF	NF-kB	Respondents
Time/Cost	Mean	4.34	3.96	4.64	3.46	4.51	4.31	3.98	4.09	4.48	4.58	3.87
Lack Capabilities	Mean	3.06	3.62	2.68	3.93	3.14	3.77	3.03	3.55	3.31	3.37	3.61
Patent	Mean	1.63	1.54	1.39	3.16	1.53	1.56	1.61	1.79	1.43	1.77	2.59
Respondents	N	295	27	143	26	43	13	43	23	27	33	79

Figure 1. Academics' Research Ties, with Industry and Academic Sectors, Now and Five Years Ago

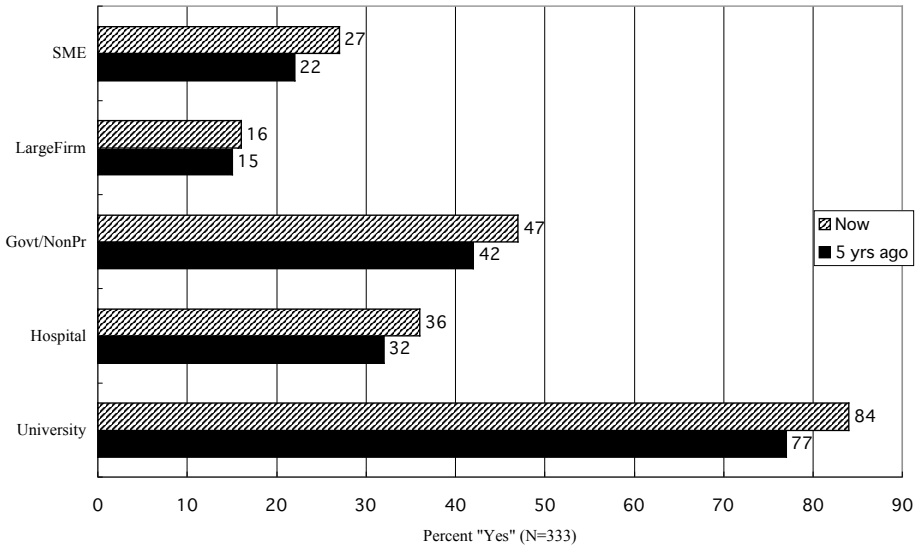

Figure 2. Reasons to Not Fulfill Requests for Research Input

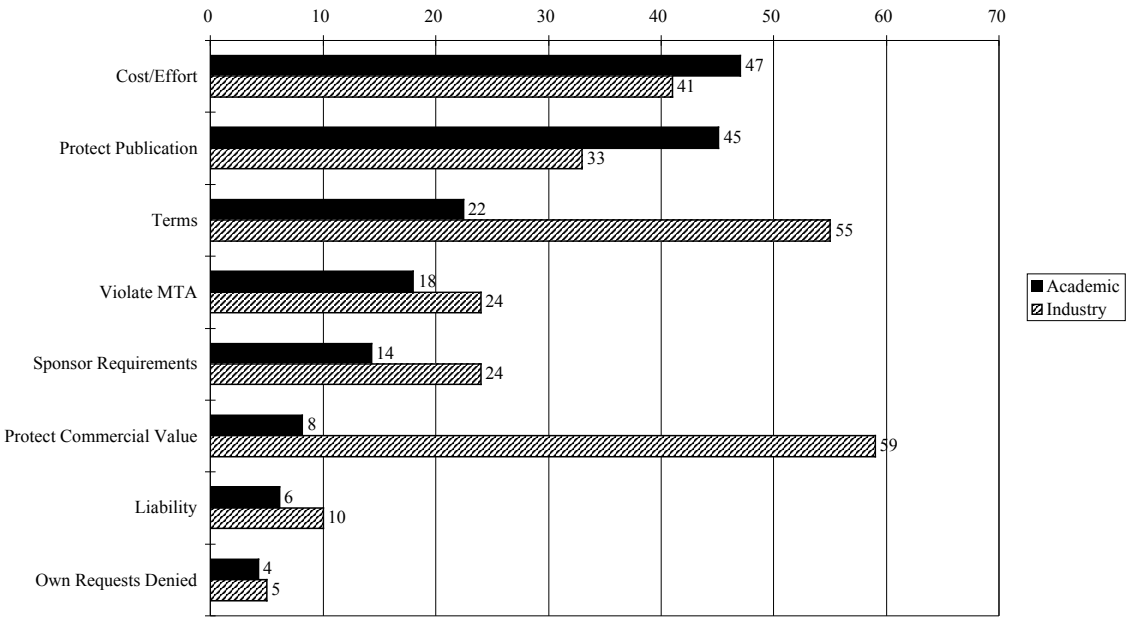

Figure 3. Annual Number of Publications Citing NF-kappaB, 1986-2004

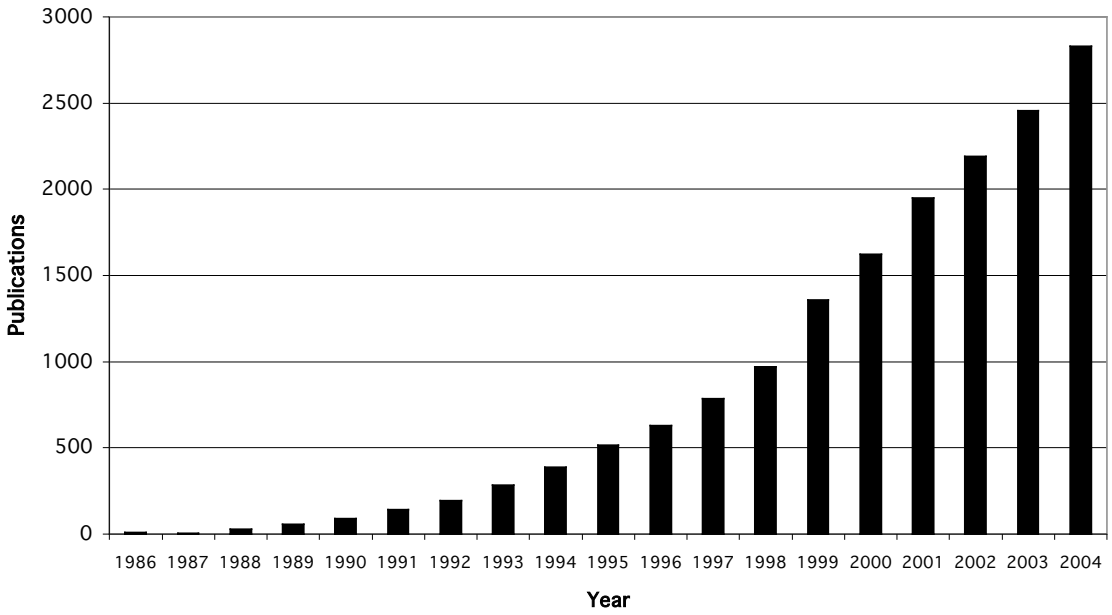

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Exhibit 19

Correspondence

Commercialization, patenting and genomics: researcher perspectives

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Published: 19 February 2009

Genome Medicine 2009, **1**:22 (doi:10.1186/gm22)

The electronic version of this article is the complete one and can be found online at http://genomemedicine.com/content/1/2/22

Abstract

The impact of commercialization and patenting pressure on genomics research is still a topic of considerable debate in academic, policy and popular literature. We interviewed genomic researchers to see if their perspectives offered fresh insights. Regional Genome Canada centers provided us with relevant researcher contact information, and in-depth structured interviews were conducted. Researcher perspectives were sharply divided, with both support and concern for commercialization regimes surfacing in interviews. Data withholding and publication delays were commonly reported, but the aggressive enforcement of patents was not. There are parallels to the Stem Cell community in Canada in these respects. Genomic researchers, as individuals directly implicated in the field of controversy, have developed varied and often novel insights which should be incorporated into the ongoing debates surrounding commercialization and patenting. Many researchers continue to raise concerns, particularly in relation to data withholding, thus emphasizing the need for a continued exploration of the complex issues associated with commercialization and patenting.

Background

Concern about the impact of commercialization pressure on the research environment can be found in both the academic and popular literature [1-4] - and for good reason. For example, there is evidence that commercial influences can increase the rate of information withholding among researchers [5-8] and encourage selective reporting of research outcomes unfavorable to industry [7,9-13]. In addition, close links with industry can erode public trust in both the research being done and the individuals who are doing it ([14]; for an extended discussion of the political and scientific importance of public trust, see [15]).

There is also concern about commercialization in genetics, particularly in the context of patenting. Gene patents have come under intense criticism in the media [16-18] and in the academic community [19-22], and they have been the subject of numerous policy reports [23-25]. Surveys of the public indicate that popular opinion is also largely negative [26]. Although recent research has reduced some of the concerns associated with gene patents [27-29], concerns remain and have, in fact, motivated calls for policy reform [25].

Here, we seek to provide further insights regarding the perceptions of a key group of stakeholders: genomic researchers. Building on the relevant survey work that has been done in other jurisdictions [28,29] and in other related areas of research [30], we conducted a series of in-depth structured interviews with leading Canadian genomics scientists on the topic of commercialization and gene patenting with the hope that their perspectives would provide fresh insights to help advance a debate that has sometimes fallen into stock arguments.

Approach

We contacted regional Genome Canada centers (Genome Alberta, Genome BC, the Ontario Genomics Institute, Genome Quebec and Genome Atlantic) and asked them to provide contact information for all principal investigators, co-investigators and collaborators. Key researchers were then selected from each center on the basis of seniority and success, in approximate proportion to the relative population of the area in question. Some referrals and substitutions were made to ensure that the contacted sample was appropriately representative.

Interviews were conducted by phone and responses were transcribed. A series of structured items analogous to a questionnaire were administered in order to provide a basic understanding of the demographic landscape of our sample (Additional data file 1). These items had been developed in tandem with a more traditional survey instrument on the topic of commercialization administered separately to the Stem Cell Network [30], which, as shown below, provides new comparative insights when paired with this study. Interspersed with these structured items were more open-ended, qualitative items, which allowed the researchers interviewed to speak at length about their outlooks on the interview topics. Although the structure guided the course of the interviews, a dialog approach was used throughout to emphasize individual perspectives.

In total, 70 researchers were contacted for interview and 20 interviews (28.6%) were conducted. Of these, 14 interviews were with Genome Canada principal investigators, four with co-investigators, and two with collaborators. Respondents most frequently identified their Genome Canada-related research efforts as pertaining to human genomics (15, 75%), followed by genomics and non-human model species (five, 25%), and genomics and agriculture (three, 15%). When provided with a selection of descriptive epithets, researchers most often described their work as 'basic' (11, 55%), followed by 'translational' (eight, 40%) and 'applied' (seven, 35%). Respondents often do their work in multiple contexts, the most popular of these being university laboratories (14, 70%), followed closely by academic medical centers (12, 60%).

Although it involves a relatively small sample, the goal of this study was not to provide exhaustive scope, but rather to focus in depth on a key group of stakeholders in order to survey perspectives and elicit novel insights that will help move the ongoing debate surrounding commercialization forwards. The existence of Genome Canada, as a major funder of large-scale genomic research, provided a unique opportunity to locate and engage this relatively small group. Moreover, because Genome Canada has a strong knowledge translation mandate [30], many of these researchers had considered these issues before they were interviewed, and had well-developed, unorthodox perspectives that emerged in their responses.

Results

Almost all the researchers surveyed stated that the most important factors motivating their research careers were high quality of research, the ability to obtain research funding, and academic integrity. Publication record and peer recognition were rated very high on the scale of importance, whereas factors such as monetary gain and the development of inventions or a patenting record were rated moderately important or not important at all.

The largest group of researchers (nine, 45%) found patents to have an overall neutral impact on the research environment, seven felt that they had an overall negative impact, and four felt they had an overall positive impact (Figure 1). Driving the sentiment that patents had a negative impact was the claim that researchers may be unable to obtain permission to use patented technologies (all seven found this important or very important). Researchers were even occasionally sympathetic to the criticisms found in media coverage of the gene patent controversy; one researcher commented: "The problem with patenting biological information is that discovered mutations are patented, not just created mutations."

Among the reasons for endorsing the use of patents, however, the reason most cited was the claim that patents facilitate development of technologies for use by society (all four of the researchers who maintained patents had a positive impact found it important or very important). One researcher suggested that patents, contrary to public opinion, might in fact have a role in the public accountability of scientists: "There are very few cases that an academic has ever seen anything in financial terms [from a patent], but if you see them as having a responsibility in their use of public funds, then patenting is crucially important for it to reach full commercial potential."

Nevertheless, patenting and commercial expectation did seem to have some adverse effects. The potential to patent was perceived to have caused a delay of research results for eight researchers (40%), whereas it was said to have caused the withholding of research information for 11 researchers (55%). Respondents referred to "vague and unspecific" conference abstracts or web updates as instances of data withholding - the implication being that concern about patentability caused the withholding of more detailed information. Of those for whom it delayed publication, the most common delay was by 1-6 months (50%). This pattern did not surprise one researcher, who found the question somewhat redundant: "[Patenting] has to [cause withholding] by definition: if you go out and talk about it, it's not

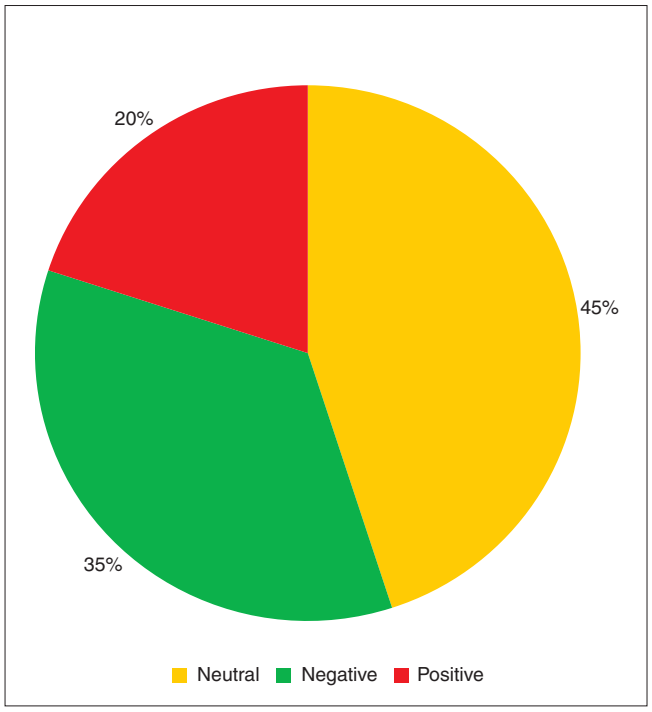

Figure 1
Pie chart showing the opinions of the researchers interviewed on the overall impact of patents on the research environment.

patentable." This is, of course, the reason that there is a concern about publication delays.

Although publication delays and data withholding were acknowledged by researchers, only one researcher had refused to license patented technology to someone who approached them with a request for a license (5%), citing as a reason for refusal that "the technology would not be well used by the recipient". Similarly, only one researcher had been refused a license to a patented technology they needed for research themselves; in response, they worked around the patented technology by using alternative methods and approaches. None had ever been served a 'cease and desist' letter informing them that they had infringed a third party's intellectual property and instructing them to stop all infringing activities or face legal action. We can infer from these results that the researchers' research work itself had never been delayed much by another's patent.

This was certainly not because their particular type of work did not involve patents: most researchers surveyed were involved in commercialization activities. Some 65% of researchers had, at some point, needed to access patented technology from another party, and exactly half of the researchers interviewed had themselves been named as inventor on granted patents or on pending patent applications. All of those who had been named on a granted patent (including pending patent applications) had negotiated license agreements to permit others to use their technology, most often with private companies.

Overall, 13 researchers maintained that the pressure that they are currently under to commercialize is reasonable, and five held that it is unreasonable. Two researchers declined to respond. One said: "It is reasonable under the circumstances but I don't like the circumstances." Another respondent insisted that commercialization pressure helps to boost researcher morale, providing as it does a "real application" for the research that is being done, and thus improving work.

When researchers were given the opportunity to speak openly on the issue of commercialization, interesting and fresh perspectives consistently emerged. It might be, volunteered one researcher, that popular concern is not so much over commercialization *per se* as it is over commercial timelines: "The discovery horizon is much further beyond the commercial horizon. The commercial horizon is to make money within 3-5 years, but the discovery horizon is 8-10. So [the goal should be to make] pressure for commercialization more commensurate with the discovery horizon." Similarly, a different researcher speculated that many of the problems people supposedly have with commercialization are in fact problems with inefficient technology transfer offices (TTOs). "If you could promise a week turnaround time from a TTO, you would find that virtually no-one was complaining about delays."

An older researcher, however, claimed that, despite all reports of a paradigm shift, things have not changed much in the past few decades: "All money comes with strings, whether it's a requirement to succeed scientifically or [to help produce] commercial success." Both requirements from this perspective could arguably produce problems.

Another respondent suggested that there is still a disconnect between the rhetoric surrounding commercialization and its actual implementation in the laboratory setting, reflected in the fact that hiring standards are still overwhelmingly focused on publication record: "The academic ideal has always been not to pay attention to commercialization." A different respondent complained that trying to teach students to be good scientists in today's environment is difficult, because idealistic lessons in scientific integrity are always contrasted with the realities of the commercial world, where one finds "exactly the opposite". Still another argued that, whether pressures were currently seen as reasonable or unreasonable, commercialization is here to stay, and the laboratory had best adapt to it, contending that it would be "mythological to think that we will have a large body of new knowledge that will be freely available."

Discussion

It is clear that the opinions of researchers on this topic are sharply divided, and our interviews were a fruitful exploration of these perspectives. Significantly, aside from evidence of data withholding and delayed publication, the interviews uncovered few concrete negative experiences or anecdotes caused by commercialization. This finding is in keeping with much of the most recent research on the topic [28,29] and is also remarkably similar to the results of a similarly structured survey we administered to the broad membership of the Stem Cell Network [30]. The stem-cell community and the genomics research community, though both working in the face of controversy surrounding emerging technologies, face very different issues, and it is not at all clear that results from the two communities on similar issues would be similar. The fact that they are similar is noteworthy.

In our study and other recent research [28-30], much concern is expressed about commercialization and patents, but little is said to suggest that the progress of research itself is in fact being seriously hindered. Likewise, there is little evidence that gene patents are being aggressively enforced - as evidenced by the fact that this group of very active researchers has had almost no exposure to the enforcement of patent rights (again, this is consistent with other literature [31]). The area of data withholding deserves further investigation, as this has been consistently identified as an issue [1,6] and our research provides some tentative support for its existence. However, other research has found that other factors, such as academic competitiveness, may be a more pronounced source of data withholding behavior [28].

These interviews are exploratory in nature and, of course, the approach has limitations. Interviews of this nature are measurements only of perspective, and even then only of a small sample size. But the window they provide into these often neglected outlooks is valuable. It should also be noted that because Genome Canada has a strong interest in knowledge translation through commercialization [32], this group of researchers, by holding a Genome Canada grant, might be viewed (correctly or incorrectly) as having a bias toward a commercialization ethos. Although this should be considered in the interpretation of our results, it is worth noting that despite this potential bias, we still found a remarkably diverse spectrum of views.

The commercialization of the research environment continues to stir debate. The degree to which commercial interests influence outcomes, reporting, the teaching environment and scientific integrity in the area of genomic research thus deserves further scrutiny. As one respondent suggested, the apparent lack of pejorative data on commercialization might reflect more the structure and timing of the research itself than the landscape of genomics research: "Most researchers don't think about the questions that you're asking until they try to move the technology into the private sector. Universities are developing commercialization offices and want researchers to do this. The results of [these kind of investigations] are going to make it look like everything is hunky-dory when in fact it isn't."

Additional data files

The following additional data is available. Additional data file 1 contains the structured interview instrument, which was administered to all respondents.

Competing interests

The authors received funding for this project from Genome Alberta.

Authors' contributions

CM participated in the design and coordination of the study, conducted the interviews, performed the statistical analysis and helped to draft the manuscript. TC conceived the study, participated in its design and coordination and helped to draft the manuscript. Both authors read and approved the final manuscript.

Acknowledgements

We thank Robyn Hyde-Lay and Lori Sheremeta for help in the early stages of this study and Genome Alberta for support.

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Exhibit 20

GENETICS

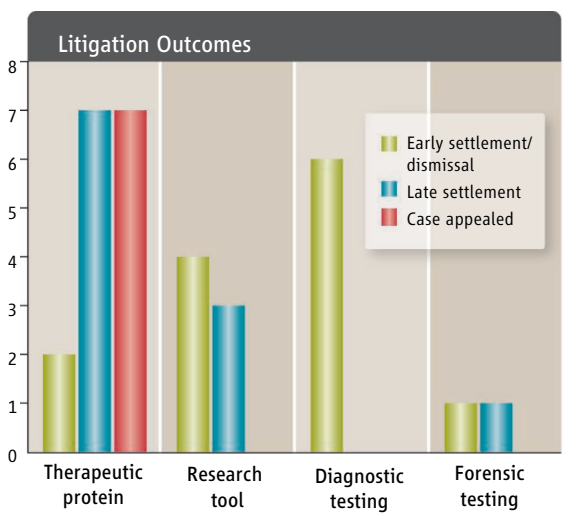
Trends in Human Gene Patent Litigation

Fears surrounding human gene patents have, for the most part, yet to manifest themselves in patent litigation.

Christopher M. Holman

Critics have long warned that patents claiming human genes pose a substantial threat to public health and the progress of science (*1*–*3*). Much of the focus has been on the alleged detrimental impact of gene patents on the development and availability of diagnostic testing (*1*, *3*, *4*). Some have postulated that a "thicket" of patents will impede basic biomedical research and will stifle development and utilization of technologies that involve the use of multiple genetic sequences; DNA microarrays are a prime example (*5*, *6*). Others claim that gene patents are uniquely difficult to design around and, thus, fundamentally more restrictive of follow-on developments than "traditional" patents (*6*).

In response to the perceived threat of gene patents, Congress is considering legislation that would prospectively ban the patenting of not only human genes, but any "nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies" (*7*). Nevertheless, some argue that the problem of human gene patents and the alleged patent thicket have been overstated (*1*, *8*), because there is little empirical evidence that these patents have had a substantial negative impact on research or the availability of diagnostic testing (*1*).



Outcomes for the 31 identified human gene patent litigations (*24*). One of the appealed cases is still pending, the others were pursued to final judicial decisions.

In 2004, Jensen and Murray identified 4270 U.S. patents claiming at least one human gene and concluded that one-fifth of known human genes were claimed in a patent (*9*). This figure raised concerns in the minds of many and was cited as justification for the proposed bill to ban the patenting of DNA (*10*). Other researchers have conducted surveys to gauge the chilling effect of biomedical and human gene patents on research (*11*) or diagnostic testing (*3*).

However, research on judicial enforcement is lacking. Few human gene patents have ever been asserted in court, so any chilling effect arises primarily from a perception of risk that may not comport with reality. A patent generally has no legal effect until successfully asserted in court, and attempts at judicial enforcement often fail.

To address this gap, I conducted a study to identify all instances in which a human gene patent was asserted in an infringement lawsuit and to track the results of these litigations (*12*–*14*). The foundation of this study was a search of Lexis and Westlaw databases for any U.S. patent satisfying two criteria: (i) the patent includes the canonical term "SEQ ID NO." in its claims, or includes within its claims or abstract any one of the terms used to identify a patent for inclusion in the Georgetown DNA Patent Database; and (ii) a notice of litigation has been filed indicating that the patent has been the subject of a lawsuit. Alternate search strategies were also used, including a search for any reported judicial decision involving an allegation of patent infringement and containing one of the Georgetown database terms (*13*). Asserted patents, complaints, and other documents generated by each lawsuit were analyzed to assess whether it involved an allegation of infringement of a human gene patent (*14*).

Frequency of Litigation

I identified 31 human gene patent litigations, dating back to 1987 (*13, 14*) (see chart, left). Considering the large number of human gene patents (*9*), the substantial amount of patent litigation that has taken place involving biotechnology patents other than human gene patents (*15*), and the high level of concern that has been expressed with respect to the negative impact of human gene patents, 31 seems a relatively small number. For example, since 2000 at least 1294 lawsuits have been filed asserting drug patents, and 278 involving molecular biology or microbiology patents (*16*). Furthermore, rather than increasing, the number of human gene patent litigations pending at any given point in time has fallen off in recent years (see chart, page 199). This decline corresponds to reports of a similar marked decline in the filing (*17*) and issuance (*18*) of DNA patents in the United States since 2001.

Only 7 of the 31 lawsuits I identified involved patents identified by Murray and Jensen, indicating that their automated search strategy actually missed many human gene patents (*13*). However, what is most striking is that not one of the 4270 patents in their data set has ever resulted in a decision favoring the patent holder (*13*). Five of the cases settled before any substantive judicial decision (i.e., prior to any decision addressing the merits of the case), one was dismissed by the court, and in one litigation, the accused infringer prevailed.

Litigation Outcomes

Litigation outcome tends to vary depending on the nature of the alleged infringement (see chart, left). The vast majority of human gene patent litigations (as is the case with patent litigations in general) are dismissed before a final court decision, often as the result of the parties' reaching a settlement agreement. Six of the 16 therapeutic protein cases were litigated to a final, unappealable judicial decision (a seventh is currently on appeal), with the patentee prevailing in two cases and losing in the other four. In contrast, the litigations that did not involve a therapeutic protein all either settled or were dismissed before the case could be appealed to a higher court. Overall, lawsuits involving therapeutic proteins rarely settled before at least one substantive judicial decision. In marked contrast, five of the six of the diagnostic testing cases settled before any substantive judicial decision, and the sixth was dismissed soon after

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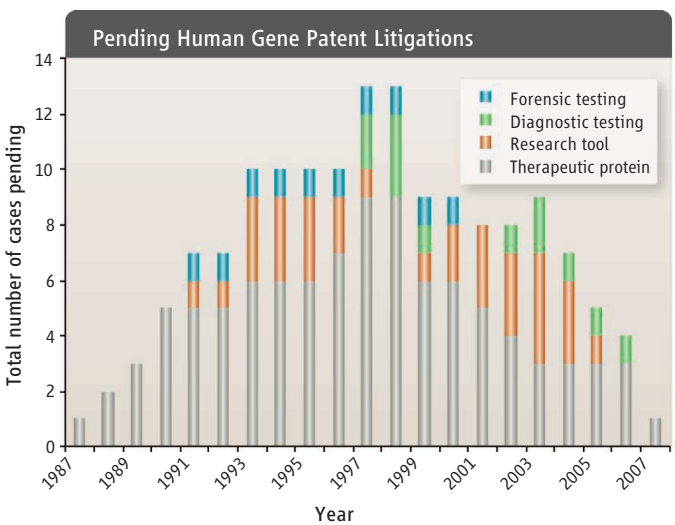
Published by AAAS

the lawsuit was filed because the plaintiff lacked sufficient ownership interest.

Litigations involving protein therapeutics also tend to remain active longer than other human gene patent litigations (*13*). The time from filing to resolution ranged from 23 to 112 months for therapeutic protein litigations, resulting in an average pendency of 63 months (*19*). Cases involving genetic diagnostic testing were all settled or dismissed within 2 to 17 months of filing, resulting in an average pendency of only 8 months.

Implications

Patents can have an impact, even when they are not asserted in court (*1*, *3*, *11*, *13*). However, for the most part, fears expressed concerning human gene patents have not been manifested overtly in patent litigation. Human gene patent litigation invariably has involved an alleged infringer engaged in substantial commercial activities focused specifically on the single gene that is the subject of the asserted patent, the antithesis of a patent thicket scenario (*14*). Some have speculated that DNA microarray technology is particularly at risk of becoming entangled in a thicket (*6*). However, I found no instance in which a human gene patent was asserted against the manufacturer or user of microarray technology, although microarray companies have experienced substantial patent litigation involving nongene patents since the mid-1990s.



Pending human gene patent litigations in each year starting in 1987 and extending to June of 2007. Two lawsuits resolved in the first part of 2007 are not included in the 2007 tally.

Many gene patents only claim some limited use of a gene and, thus, do not preclude use of the gene in a different system or context (*14*). For example, one of the patents characterized by Jensen and Murray as "claiming a human gene" only covers the use of a mammalian cell culture system to express and secrete the product of an exogenous, recombinant human α-galactosidase A gene (*20*). Transkaryotic Therapies designed around the patent by expressing the endogenous gene in cultured human cells (*14*). Gene patents can also be avoided by taking research off shore. For example, in the research tool context, a contract research organization (CRO) based in the United States successfully avoided patents' claiming the use of certain human genes in cell-based assays by performing the assays in Taiwan and importing the data back to the United States (*14*). Likewise, genetic diagnostic testing service could be taken off-shore if patents prove a substantial impediment to access in the United States.

In four cases, an academic research institution was sued for infringement, but invariably the institution was involved in some substantial commercial enterprise focused on the patented human genes. For example, Myriad Genetics asserted its BRCA1 patents against the University of Pennsylvania for providing commercial BRCA1 genetic testing services, in direct competition with Myriad (*14*). Yet, the human gene patents that have been asserted quite often arose out of academic research (*13*, *14*). For example, all but one of the human gene patent litigations that have been brought against a provider of genetic diagnostic testing services has involved an academic patent (*13*).

Most of the litigations have been brought in the context of therapeutic proteins, with the patents serving a function analogous to that of drug patents in the traditional pharmaceutical industry. Thus, these patents maintain companies' incentive to develop biotech drugs despite the expense and risk. My results provide little empirical support for a legislative bar to the patenting of genes or DNA.

If any legislative reform is deemed necessary, its scope would more appropriately be limited to some form of exemption from infringement liability for research and/or diagnostic testing uses of naturally occurring genetic sequences (*21*). Such an approach preserves the patentability of gene-based innovations, while curtailing some of the more problematic enforcement activities. Alternatively, Congress could act to encourage funding agencies to exercise the march-in rights provided by the Bayh-Dole Act (*22*) in cases where a patent resulting from government funded research substantially impedes biomedical research or the availability of diagnostic testing. This approach was proposed by witnesses at a recent congressional hearing focused on gene patents (*23*).

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21. See, e.g., Genomic Research and Diagnostic Accessibility Act of 2002, H.R. 3967, 107th Congress (2002).
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24. Early settlement or dismissal—the parties either agreed to settle the case before any substantive judicial decision or the case was dismissed by the court; Late settlement—the parties agreed to settle the case subsequent to one or more substantive judicial decisions, but before appealing the decision to a higher court; Case appealed—the district court's decision was appealed to a higher court.

25. I thank L. Andrews, J. Carbone, R. Feldman, T. Holbrook, F. S. Kieff, A. Lara, N. Levit, C. Mason, G. Pulsinelli, M. Lemley, R. Cook-Deegan, A. Rai, K. Jensen and participants of the 2007 Intellectual Property Scholars Conference (9 to 10 August, Chicago, IL) for commentary, and K. Jensen and F. Murray for sharing their database of human gene patents.

Supporting Online Material

www.sciencemag.org/cgi/content/full/322/5899/198/DC1

10.1126/science.1160687

Exhibit 21

DNA-based patents: an empirical analysis

Ann E Mills & Patti Tereskerz

The perception of rising litigation rates is driving the push for patent reform.

The Patent Reform Act of 2007 (S.1145, H.R.1908) was introduced in the US Congress in April 2007, and it includes major patent reform measures, which if enacted may have a considerable impact on the country's patent system. Among the controversial reforms included in the proposed legislation is the initiation of post-grant opposition proceedings[1]. Some reform measures contained in S.1145 are controversial because they will affect dissimilar industries differently. For example, in younger industries such as biotechnology where patents are among the primary, if not only, assets, there is fear that a new post-grant opposition proceeding would call into question a patent's validity. This uncertainty would likely discourage future investment by venture capitalists who help support the industry and, in turn, may hinder future innovation and successful commercialization[2,3]. While rising energy costs, a melt-down in the financial sector and a slowing economy have temporarily diverted the attention of the House and Senate, the American Academy for the Advancement of Science indicates in its Research and Development Report for fiscal year 2009 that patent reform is considered to be a vital issue for "competitiveness and innovation," and Congress expects to continue to discuss patent reform[4]. The bill now remains in the Senate. Moreover, at least one of the Presidential candidates, Sen. Barack Obama, considers patent reform to be an important issue and has discussed his position on the reform of the current patent system[5].

One reason advocates of S.1145 justify the need for reform is because they are convinced that the rate of litigation is rising[6]. The perception of rising rates of litigation derives from three reports warning of dire consequences if industry is unable to innovate and successfully commercialize new products[7–9]. Costs associated with litigation are thought to hamper innovation and successful commercialization because they may divert resources away from innovative activities. And there are costs associated with the strategies followed by companies to protect them from the risk of litigation. Such strategies may include defensive patenting by enlarging a firm's portfolio of patents to influence settlement terms or foregoing otherwise valuable research because of the risk of litigation[10].

Although there is anecdotal evidence supporting the perception that the rate of litigation is rising, there is little empirical evidence supporting this[7–9]. And what evidence there is seems to point in a different direction. For example, Lanjouw and Schankerman[11] point out that growth in patent litigation, particularly over the 1990s, encouraged the perception that research companies are burdened by growing enforcement costs. They argued that at that time, the growth in patenting was comparable to the growth in litigation, with the rate of suit filings remaining about constant over two decades[11].

Because some of the reform measures contained in S.1145 are controversial and because there is little objective empirical data supporting the notion that litigation rates are rising, we undertook a small empirical study of DNA-based litigated patents to determine whether or not rates of litigation on DNA-based patents are actually increasing.

Methods

We collected data on lawsuits from the LitAlert database, which contains records for patent lawsuits filed in the 94 US District Courts and reported to the Commissioner of the US Patent and Trademark Office (USPTO), and is updated weekly. In addition, records for thousands of lawsuits filed since the early 1970s that have not been reported in the *Official Gazette* are included in this database. We collected data on lawsuits, rather than patents, to avoid over-counting because one lawsuit may involve multiple patents. We collected the data on lawsuits on April 18, 2008.

To collect the data, we used a slightly modified version of the algorithm that had

Table 1 Litigated cases by patent issue date on DNA-based patents in the biotechnology industry

Date	Number of cases	Total patents issued	Rate
1982	2	72	0.027778
1983	2	86	0.023256
1984	4	105	0.038095
1985	3	96	0.03125
1986	1	134	0.007463
1987	3	219	0.013699
1988	11	280	0.039286
1989	11	373	0.029491
1990	3	375	0.008
1991	5	491	0.010183
1992	1	597	0.001675
1993	16	783	0.020434
1994	38	819	0.046398
1995	6	955	0.006283
1996	21	1,588	0.013224
1997	24	2,556	0.00939
1998	14	3,788	0.003696
1999	12	4,106	0.002923
2000	14	3,827	0.003658
2001	7	4,463	0.001568
2002	6	3,872	0.00155
2003	5	3,536	0.001414
2004	1	3,055	0.000327
2005	1	2,772	0.000361
Total	211		

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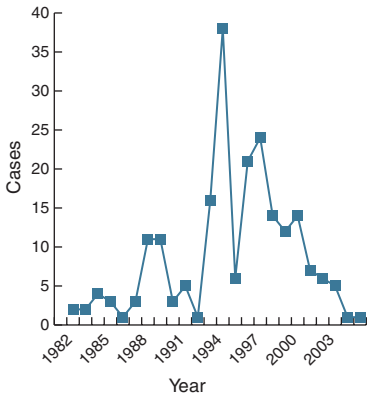

Figure 1 The number of lawsuits involving DNA-based patents occurring in each year between 1982 and 2005.

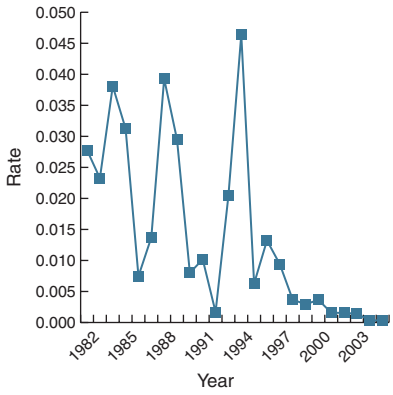

Figure 2 The rate of cases involving DNA-based patents to total number of DNA-based issued patents between 1982 and 2005.

been used to develop the DNA Patent database (http://dnapatents.georgetown.edu/), a publicly available database containing all DNA-based issued patents since 1971 and all DNA-based patent applications since 2001. Our search employed the same algorithm as that used to develop the DNA database with one small modification. The algorithm used to develop the DNA database searches patent 536/subclasses 22 through 23.1 (nucleic acids, genes, etc., but not peptides or proteins) and subclasses 24 and 25 (various nucleic acids, variants, and related methods). LitAlert does not allow searching subclasses. So in LitAlert we searched all of class 536. Therefore, we searched the LitAlert database for US Patent classes 047 (plant husbandry), 119 (animal husbandry), 260 (organic chemistry), 426 (food), 435 (molecular biology and microbiology), 514 (drug, bio-affecting and body treating compositions), class 536 and class 800 (multicellular organisms). And, within these classes we searched for one or more of the following terms in their claims: Antisense, cDNA, centromere, deoxyoligonucleotide, deoxyribonucleic, deoxyribonucleotide, DNA (with or without following letters, such as DNAs), exon, gene or genes (exact match only), genetic, genome, genomic, genotype, haplotype, intron, mtDNA (with or without following letters such as mtDNAs)-exact case match only, nucleic, nucleotide, oligonucleotide, oligodeoxynucleotide, oligoribonucleotide, plasmid, polymorphism, polynucleotide, polyribonucleotide, ribonucleotide, ribonucleic, recombinant DNA (exact match for case and words only), RNA (all upper case only, with or without following letters such as RNAs), mRNA (exact case match only, with or without following letters such as mRNAs), rRNA (exact case match only, with or without following letters such as rRNAs), siRNA (exact case match only, with or without following letters such as siRNAs), snRNA (exact case match only, with or without following letters such as snRNAs), tRNA (exact case match only, with or without following letters such as tRNAs), ribonucleoprotein, hnRNP (exact case match only, with or without following letters such as hnRNPs), snRNP (exact case match only, with or without following letters such as snRNPs) or SNP (exact case match only, with or without following letters such as SNPs).

Because we searched all of class 536 and in order to validate that the cases we identified involved DNA based patents, we cross-referenced the patent numbers involved in the cases we identified to the DNA Patent Database and discarded the case if the patent was not listed in the DNA Patent Database. We then eliminated duplicate cases. (When a subsequent action is taken, LitAlert adds another record instead of updating existing record.)

Six patents were not in the DNA database, and as they were not defined as DNA-based patents, we discarded from our dataset the cases associated with them. We also eliminated one case because LitAlert did not include the date when the case was filed. We then cross-referenced the patents we identified to the USPTO database to obtain issue dates for the patents (LitAlert does not include issue dates of patents). We collected the patent issue dates on April 22–23, 2008.

Because we were only concerned with litigation associated with DNA-based patents, we used the DNA Patent database (rather then the USPTO database) to ascertain the total number of issued patents by year. We collected the data on the total numbers of issued DNA-based patents on April 23, 2008.

We copied and pasted the data we obtained from LitAlert, the DNA Patent and the USPTO databases to eliminate as much as possible the risk of error in building our database. Our dataset contained 211 litigated cases on DNA-based patents issued between 1982 and 2005.

We define litigation rate as the number of cases filed divided by the total number of DNA patents issued in a year. We used Fisher's Exact Test, a 2-tailed test at the 95% confidence level to test for significance.

Results

We did not find any lawsuits for patents issued in 2006, 2007 or 2008. This is not surprising because we calculated the mean time in our dataset between patent issue date and a lawsuit being filed for the patents we studied to be 56.17 months. In **Table 1** and **Figure 1** we show lawsuits by patent issue date on DNA-based patents in the biotechnology industry. For instance, in 1982 a total of 72 patents were issued. Of these 72 patents, there were two lawsuits, which may or may not have involved other patents. Comparing by issue dates allows for the calculation of a true rate of litigation. Moreover, the great majority of lawsuits had a complaint filed with no further action taken. Only 48 of the total cases (211) during the time period studied (23%) had some further action taken on the case. This could mean, for example, the case was settled, there was a jury verdict, summary judgment, or the case was dismissed. For the remaining cases, a complaint was filed with no further action taken.

Additionally, the rate of litigation in the genetic and genomic sector studied has decreased in recent years (**Fig. 2**). Between 2000 and 2005, the rate of patent litigation for the patent classifications studied dropped significantly from 14/3,827 to 1/2,772 ($P < 0.0006$).

Discussion and conclusions

The empirical analysis we undertook shows that the overall number of litigated cases for the classifications studied is declining for the indicated time periods. There are, however, limitations to this study. First, there is considerable lag time between the filing of a lawsuit in a district court and this information being reported to and entered into the LitAlert database used in this study. In addition, these findings are limited to the patent classifications studied. The results of this study cannot be extended to draw conclusions regarding overall litigation rates or litigation rates in other patent classifications.

Notwithstanding these limitations, the results of this small study should call into question whether the perception of rising litigation rates is valid for some industries and whether this argument can continue to be used to justify patent reform without additional research. Our results point to the need for additional empirical research before reform initiatives are implemented. This is important when passage of such legislation may be accompanied by introducing uncertainty as to patent validity, which may in turn discourage investment in younger industries and ultimately stifle innovation and commercialization.

Moreover, future empirical studies should take into account that various industry sectors are different and have different business models. It is possible that empirical data may yield different results for different industry sectors. It is time to step back and reflect upon the adequacy of current evidence to support those reform measures that have the potential to adversely impact commercialization in some industry sectors.

COMPETING INTERESTS STATEMENT
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/

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