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Where excludability matters: Material versus intellectual property in academic biomedical research

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Abstract

On the basis of survey responses from 507 academic biomedical researchers, we examine the impact of patents on access to the knowledge and material inputs that are used in subsequent research. We observe that access to knowledge inputs is largely unaffected by patents. Accessing other researchers' materials and/or data, such as cell lines, reagents, or unpublished information is, however, more problematic. The main factors associated with restricted access to materials and/or data include scientific competition, the cost of providing materials, a history of commercial activity on the part of the prospective supplier, and whether the material in question is itself a drug.

Keywords: Patents; Biomedical research; Research tools; Material transfers; Excludability

1. Introduction

The patenting activity of American universities has grown almost an order of magnitude in 20 years, from 434 patents issued to universities in 1983 to 3259 in 2003. Nelson (2006, 2004) and Dasgupta and David (1994), among others, argue that this growing "privatization of the scientific commons" may jeopardize scientific and technological progress, particularly by restricting access to upstream discoveries and understandings that are essential inputs to subsequent advance. Such restrictions come in the form of licensing fees, terms of exclusivity and other conditions of use, infringement liability, and transactions costs that potentially impose a significant burden on researchers.[1] In addition to permitting the imposition of such restrictions, patents may also confer the incentive to do so by enabling academics to seek financial gain at the expense of the sharing of knowledge, data and materials (Blumenthal et al., 1997; Campbell et al., 2002; Walsh and Hong, 2003).[2] This concern over

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[1] Merges and Nelson (1990) and Scotchmer (1991) highlight the possibility that, in some domains, the assertion of patents on only one or two key upstream, foundational discoveries may significantly restrict follow-on research. Similarly, while their focus is largely on commercial projects, Heller and Eisenberg (1998) and Shapiro (2000) suggest that the patentability of a broad range of research tools that researchers need to do their work has spawned "patent thickets" 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 (the "anticommons" problem).

[2] Similarly, to gain access to industry funding, researchers may trade away rights to conduct future research or freely disseminate their research results (Cohen et al., 1994).

the impact of patenting on the free flow of knowledge in academic science remains of paramount concern even while numerous scholars acknowledge that academic patenting may strengthen firms' incentives to invest in the downstream activities and resources necessary to commercialize discoveries of academic origin.

This paper examines the impact of patent rights on academic researchers' access to the knowledge and material inputs upon which their research depends—what are broadly termed, "research tools." On the basis of a survey of 507 academic researchers in genomics and proteomics, we probe the determinants of project choice, and examine the question of access to research knowledge and material inputs, which is the main focus of our study. Our analysis relies on two samples of academic respondents. The first is a random sample of 414 academic researchers (including those in universities, non-profits or government labs). We also collected data from a second sample of 93 academic scientists who are conducting research on one of three important signaling proteins (CTLA-4, EGF and NF-kB), fields that were chosen because they all are the subject of extensive patenting activity by numerous actors and offer the promise of significant commercial gain; that is, they are characterized by conditions that are likely to spawn problems of research input access. The rationale for this more focused sample is that even if one finds little problem of access in a random sample, social welfare impacts could still be great if access is impeded in just one or two particularly important areas of research.

This paper builds upon the authors' prior work. Based on interviews with a limited number of biomedical researchers,[3] Walsh et al. (2003) found that, despite numerous patents on upstream discoveries, researchers have been readily able to access knowledge inputs. In addition to the typical solutions of contracting and licensing, biomedical researchers have implemented a variety of "working solutions" that commonly included the disregard – often unknowing – of patents on research tools. When questioned about possible infringement of research tool patents, academic researchers commonly suggested that they were protected by a "research exemption" from infringement liability.

The *Madey v. Duke* decision of 2002 raised anew, however, the question of the impact of research tool patents on academic biomedical research by clarifying what many had argued had long been the case—that there was no general research exemption shielding academic researchers in biomedicine or any other field from infringement liability (Eisenberg, 2003). This very visible decision, sample limitations on our prior work, and continuing concerns that the ever-growing number of patents may be impeding academic science prompted the current effort. While Walsh et al. (2005a,b) presents a brief summary of our findings, the current paper examines more thoroughly the impact on academic biomedical research of patents and limits on access to tangible research inputs. For example, we consider whether the *Madey v. Duke* decision has affected access to patented discoveries, and also whether such restricted access causes delays, increased costs, or the redirection of research. We also examine: restrictions on access to material inputs broken down by type of input requested; the terms and impacts of material transfer agreements; and the extent to which patenting affects the ability to create the material input oneself. To the extent that we observe restricted access to either intellectual property or materials, we probe not only the role played by IP, but also the roles played by commercial incentives, burden of compliance, and scientific competition (Hagstrom, 1974; Walsh and Hong, 2003). Indeed, the policy implications attendant upon any social costs associated with restricted access will depend importantly on its source.

To prefigure our main findings, we observe that access to knowledge inputs is largely unaffected by patents, even in our more focused sample. More problematic is access to materials and/or data possessed by other researchers, such as cell lines, reagents, genetically modified animals, unpublished information, etc. Restrictions on access, however, do not appear to turn on whether the material is itself patented. Rather, such restrictions are more closely associated with scientific competition, the cost of providing materials, a history of commercial activity on the part of the prospective supplier, and whether the material in question is itself a drug.

2. Data

We conducted a post-mail survey of biomedical researchers in universities, government labs and non-profits, which we will refer to as "academic" researchers.[4] We drew a sample of 1125 academic researchers. Our questionnaires were mailed during the

[3] We interviewed 10 academic researchers and 7 industry researchers with the balance of the 70 interviews conducted with university technology transfer officers, intellectual property officers, attorneys and others.

[4] The goal of our sampling strategy was to create a sampling

fall of 2004.[5] We received 414 responses from our random sample of academic scientists. Adjusting for 92 cases who were either ineligible, retired, deceased or undelivered, our response rate was 40%.[6] For what we call our "signal proteins sample," we also added 270 academic researchers working in three specific signaling protein fields, from which we received 93 responses (see below).

Our random sample of academic respondents published a mean of seven papers in the prior 2 years. The mean research group size was six researchers, with about 20% of respondents working by themselves or with one other person, and with just under 10% belonging to groups of more than 10 researchers. 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. Over 75% of the academic respondents report doing basic research, most of these in genomics or proteomics. About 10% are doing drug discovery, diagnostic test development or clinical testing. The remaining respondents conduct research to develop research tools or are engaged in other research activities. In selected analyses below, we distinguish between respondents who conduct basic research versus those engaged in more downstream drug discovery,

frame that included both academic and non-academic researchers, that broadly represented those doing genomic or proteomic-related research, and to not select on either patenting or publication. Because there is no extant list representing this population, we had to create a frame based on membership lists from several professional societies that span the diversity of genomic and proteomic-related biomedical researchers. 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. We chose these professional associations in consultation with the NAS Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions, an expert panel chosen to represent the relevant scientific perspectives. To create the sampling frame, we combined all regular (non-student, non-emeritus) members, and removed duplicates from the list. In order to increase the chances that our respondents were research active, and hence at risk to publish, patent and request research materials, 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. These top-70 institutions accounted for 67% of total NIH awards in fiscal year 2004. For government or industry researchers, we included all of those in the frame. Industry researchers represented about 10% of the sampling frame. As a cross-check on the coverage of our frame, we compared the faculty lists from the department of genetics (or a similar department) from 10 randomly-selected institutions from the list of the top-70 NIH grant recipient institutions against our membership lists. We find that 66% of the faculty in the chosen departments were members of at least one of the societies, and hence in our sampling frame. Thus, our sampling frame has broad coverage of academic researchers, with the added advantage of including those in non-profit or government labs (as well as industry scientists).

We stratified our sample by sector (academic, non-profit, government, industry), and then drew a systematic random sample from each sector. To increase the sample size from industry to facilitate cross-sector comparisons, we over-sampled industry respondents in order to generate a sample of approximately one-third industry and two-thirds non-industry respondents. In addition to the 1125 academics and 299 pathways researchers (see below), we also drew a sample of 563 industry scientists. Thus, the final sample included 1987 scientists, with about 30% from industry. We report the results from our industry respondents elsewhere (Walsh et al., 2005a).

[5] The survey questionnaire is available from the authors upon request.

[6] 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-sample of 200 from our original sample of 1987 researchers and compared the patenting and publication activity of respondents and the non-respondents in this subset by 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 (see Table A1). 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 (66 non-respondents and 44 respondents), respondents averaged 4.9 PubMed publications in the last 2 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. Using data from the membership directories (which gives us data on our full sample), we also compared respondents and non-respondents in terms of highest degree (Ph.D., M.D., or Ph.D./M.D.) and institutions (public university, private university, non-profit research institute or government) (see Table A1). Respondents and non-respondents have very similar institutional distributions, with 45% of each group in public universities, about one third in private universities, just under 10% in non-profit research institutes and about 15% in government labs. Respondents were more likely than non-respondents to have Ph.D. degrees (78% versus 66%, $t = 3.87$, $p < .001$) and less likely to have M.D. degrees (12% versus 21%, $t = 3.16$, $p < .01$). Thus, our sample closely represents the population in terms of institutions, but over-represents Ph.D. and under-represents M.D. scientists. However, respondent's degree (M.D. versus Ph.D.) was not associated with willingness to share research materials (results available from the contact author).

Table 1
Commercial activity for academic researchers, by research goal and for signal proteins samples

Measure		Random sample	Research goal			Signal proteins samples		
			Drug discovery	Basic research	Other	CTLA-4	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
%Funding from industry—now	Mean	4	13	3	5	3	6	14
%Funding from industry—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
Business activity								
Negotiation	%Yes	30	47	29	18	48	50	36
Pre-startup	%Yes	11	17	9	14	26	21	24
Created firm	%Yes	8	14	7	9	13	11	15
Product or process in market	%Yes	13	28	11	16	22	18	18
Licensing income	%Yes	18	31	17	11	17	33	30
Licensing income > $50,000	%Yes	5	11	4	2	9	19	9
Any business activity	%Yes	35	50	34	30	57	57	52
Total	*N*	414	40	322	52	29	29	35

development of other therapeutics and diagnostic test development—areas which we refer to in aggregate as simply "drug discovery."

3. Commercial activity of academic sector

Table 1 presents our findings on the commercial activities of our academic respondents, and distinguishes between our random academic sample and our signal proteins sample. For our random sample,[7] about 19% reported receipt of funding from industry, a slight decline since 5 years ago when about 23% reported such funding.[8] The average percent of academic respondents' research budgets supported by industry is 4.0%, down from 5.6% reported for 5 years ago.[9] Just over 40% of our academic respondents had applied for a patent at some point, with about 22% having applied in the last 2 years. The average number of patent applications over the last 2 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; and over one third had one or more of these business activities. Thus, a significant portion of academic biomedical researchers engages in commercial activity of some form.

4. Patents, project choice and access to knowledge in upstream biomedical research

In addition to concerns over the impact of patenting on knowledge flows among academic researchers, Dasgupta and David (1994) also suggest that the financial incentives that may be linked to patents, and commercial ties more generally, may also encourage academics to select research projects on the basis of commercial rather than scientific merit, to the detriment of the conduct of more basic, foundational research. In this section, we consider the different reasons why researchers may select or abandon projects, including commercial motives, the expectation of patent protection of discoveries, researcher interest and scientific importance, among other factors. Given that science advances cumulatively and thus one researcher's discovery is another's research input, we also consider the role that access to knowledge inputs might play

[7] We discuss the results for our signal proteins sample below in Section 7.

[8] This second figure is close to the 23–28% figure found by Bekelman et al. (2003) in their review of the literature on biomedical researcher's ties to industry.

[9] Our numbers correspond well with the patterns from NSF's *Science and Engineering Indicators*, which also show a recent decline in industry funding, although the means in our data are below the overall average for total university funding from industry computed across all fields (National Science Board, 2004).

Table 2
Reasons for choosing projects, by research goal and for signal proteins samples

		Random sample	Research goal			Signal proteins samples		
			Drug discovery	Basic Research	Other	CTLA-4	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
Inputs patent free	%High	7	19	5	11	9	4	3
Results patentable	%High	7	19	4	11	22	11	6
Personal income	%High	2	3	2	2	4	11	0
New firm	%High	1	0	1	0	4	7	3
Respondents	*N*	382	37	301	44	23	28	33

Note: "%High" is the percent answering "4" or "5" on a five point scale ranging from "1: not at all important" to "5: very important".

in choosing or abandoning projects, and particularly if patents on knowledge inputs play any role.

4.1. Patents and project choice and abandonment

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

Table 2 reports the percentage of respondents rating a given reason for choosing a recent major project as more than "moderately important."[10] The most pervasive reasons reported for selecting research projects are scientific importance (97%), interest (95%), feasibility (88%) and access to funding (80%). Patentability of research results and consideration of the number of patents on research inputs are much less likely to be mentioned, with each reported to be more than moderately important for about 7% of the respondents. Similarly, commercial potential figures importantly for 8% of our respondents. 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 project choice, with each considered important for guiding project choice by about 20% of the respondents who are doing drug discovery.

Eisenberg (2003) suggests that the growth of patenting of upstream discoveries by universities and firms may now impede follow-on academic and other research, particularly since the *Madey v. Duke* decision, which made quite clear that academic research does not confer any shield against infringement liability. Similarly, Andrews et al. (2006) argue that the recent Supreme Court ruling in the *LabCorp v. Metabolite* case shows that basic facts of nature are patentable and that such patents will impede scientists' ability to conduct their research. To assess whether restricted access to intellectual property dissuades academic researchers from undertaking scientifically worthwhile research, we asked respondents to evaluate the importance of reasons that may have dissuaded them from moving ahead with the most recent project that they had seriously considered but had not pursued.[11] Presented in Table 3, the results show that the most pervasively reported reasons why projects are not pursued include 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 next most

[10] The question was: "Please think about your most recently initiated major project. By "major" we mean the project on which you spend the bulk of your time. When choosing that research, how important were each of the following considerations? Please answer on a scale from 1 to 5, where 1 is not at all important and 5 is very important." Note that this is not a forced-choice scale, so all reasons can score high or all can score low.

[11] The question was: "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. How important were each of the following in dissuading you from pursuing that project? Please answer on a scale from 1 to 5, where 1 is not at all important and 5 is very important."

Table 3
Reasons for not pursuing projects, by research goal and for signal proteins samples

		Random sample	Research goal			Signal proteins samples		
			Drug discovery	Basic research	Other	CTLA-4	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

Note: "%High" is the percent answering "4" or "5" on a five point scale ranging from "1: not at all important" to "5: very important".

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 much less likely to be included ($t = 6.40$, $p < .0001$).[12] Respondents doing research on drugs and therapies, however, were somewhat more likely to indicate that unreasonable terms demanded for research inputs were an important reason for them not to pursue a project (21% versus 9% for those doing basic research, $t = 1.56$, $p < .15$). These latter results are broadly consistent with the Sampat (2004) and particularly Murray and Stern (2005) findings of a decrease in citations to a paper (on the order of 10% of expected citations) after the published result is patented.[13]

Thus, compared to other factors influencing project choice, the prospect of patenting discoveries appear to provide academics little impetus to choose projects, suggesting they confer little incentive effect. Nor do patents on inputs seem to dissuade scientists from pursuing projects, except for a small minority of our respondents (3%). For those doing drug discovery, the effect of patents is, however, stronger, although still secondary to funding, scientific importance and scientific competition. Since these results are based on self-reports, one qualification is that academics who are exposed to strong norms that they should be doing their work for reasons of intrinsic interest and scientific importance may be reluctant to acknowledge the importance of commercial motives or the prospect of a patent right as an important incentive, and so these means may be biased downward (Rynes et al., 2004).

4.2. Patents and knowledge flows

One reason why patents on research inputs may have little effect on the academics' conduct of research is that the researchers may not even be aware of such patents. Accordingly, we inquired how often bench scientists believe they need information or knowledge covered by someone else's patent (i.e. "pure IP"). Of the 381 academic respondents who answered this question, 8%, or 32, indicated that sometime in the prior 2 years they conducted research where they believed they were using information or knowledge covered by someone else's patent. 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. One reason for the low number of academic respondents who know of patents related to their research

[12] We might consider the meaning of the difference between the 7% who report that a research domain is patent free as a reason to choose a project to begin with, and the 3% who report too many patents as reason to desist from pursuing a project ($p < .01$). One possibility is that once a researcher has chosen a project for scientific and funding reasons (the most cited reasons), he is less likely to abandon it in the face of too many patents, although an expectation of many patents may still have modestly influenced the decision to pick project A over project B.

[13] Stern and Murray's study focused on articles drawn from *Nature Biotech*, which tends to publish articles from more downstream, commercially applicable research.

is that only 5% report that they regularly check for patents on knowledge or tangible inputs related to their research. Furthermore, only 2% (i.e., 9) have begun checking for patents in the 2 years since *Madey v. Duke*, suggesting only a modest influence of the court decision on the sensitivity of academic scientists to the use of others' intellectual property. Five percent of our academic respondents had also been made aware of IP relevant to their research through a notification letter sent either to them or their institution. This also does not differ much from the 3% of our respondents who report having received such notification 5 years ago, prior to the *Madey v. Duke* decision.

Academics' institutions are more concerned about avoiding patent infringement than the researchers themselves, and this institutional concern appears to be growing. Of our academic respondents, 22% 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 5 years prior ($t = 2.34$, $p < .05$).[14] Interestingly, there was little difference, however, 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 ($t = 0.54$, $p > .50$), suggesting that institutions' simply urging faculty to consider the IP rights of others may be insufficient to elicit a response from effectively autonomous research scientists.

While university policies seem to have little influence on whether faculty check for patents, faculty who have engaged in business activity are more likely to check, and more likely to acknowledge that they need access to third party patents. For example, those who ever applied for a patent were more likely to feel they needed someone else's patent (13%) than were those who had never applied (5%) ($t = 2.57$; $p < 0.05$). Similarly, those who have considered creating a new firm are more likely to feel they needed access to someone else's patent (20% versus 7%; $t = 1.99$; $p < 0.06$) and those who have actually created a new firm are even more likely to feel they needed access to someone else's patent (23% versus 7%; $t = 2.05$; $p < 0.05$). We also find higher rates of patent awareness for those: who have negotiated with a firm over the use of their invention, with a commercial product or process in the market, who have received licensing income, or who have engaged in commercial activity (all differences, $p < .05$). Ties to large firms (17% versus 8%, $p < .10$) or to SMEs (14% versus 8%, $t = 1.87$; $p < .11$) are also associated with more awareness of others' patents. Those doing drug discovery are also somewhat more likely to be aware of others' patents, compared to those doing basic research, although the difference is not statistically significant (14% versus 8%, $t = 0.91$, $p > .30$). Commercially active researchers are also more likely to search for patents, although those who are engaged in business activities such as a startup or having a product in the market are only moderately likely to check, with about 10% of such commercially engaged researchers saying they check for patents on research inputs. Thus, those who are more involved in business activity are more likely to check for patents, and more likely to be aware of third party patents (possibly because they are more likely to be engaged in research that uses patented research inputs), although both the rates of checking for patents (about 10%) or awareness of third party patents (about 20%) for such commercially active researchers are still modest.[15]

Of the 32 academic respondents who believed that they needed an input covered by someone's patents, 75% (24) contacted the IP owner to receive permission to use the IP. Due to difficulties in obtaining access, four reported having to change research approaches to complete the study, and five delayed completion of the experiment by more than 1 month. No one reported abandoning a line of research. Thus, of 381 academic scientists – even including the 10% who claimed to be doing drug discovery or related downstream work – none reported having to stop their research due to the existence of third party patents. Modifications or delays of research activity were reported by about 1% of our sample. Expressed as a percentage of the 32 respondents who were aware of a patent related to their research, we find that 13% modified their project, 16% experienced a delay of more than 1 month, and none stopping a project due to someone else's patent on a research input.[16] In addition, 22 of the 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 to IP for research purposes are negligible.

[14] Hansen et al. (2005) surveyed university officials at about the same time as our survey of bench scientists and found that 14% of universities had policies cautioning faculty about using others' IP.

[15] Data from a non-representative sample of *industry* respondents shows higher rates of checking for patents (60%) and of awareness of third party patents (35%) (Walsh et al., 2005a).

[16] As noted above, we also find that 10% reported unreasonable terms (for possibly patented research inputs) and 3% reported too many patents as reasons to not begin a project.

Thus, it would appear that, at least for the time being, access to patents on knowledge or information inputs into biomedical research (i.e., "pure IP") rarely imposes a significant burden for academic biomedical researchers. One key reason for this finding appears to be that academics are simply unaware of the existence of patents on knowledge inputs into their research.

5. Sharing research materials: summary statistics

Campbell et al. (2002), Eisenberg (2001), and the National Research Council (2003) suggest that academics' greater commercial activity and awareness of the potential value of IP may be impeding the sharing of research materials, and, in turn, the advance of biomedical research that often depends upon material transfers across scientists. Thus, in addition to examining the ease with which scientists can gain access to others' *intellectual* property, we consider the extent to which scientists can access the *tangible* research materials and data created by other labs.

To examine material transfers, we queried respondents about both their requests for materials or data, and how they responded when they themselves were asked for materials or data. We analyze the extent of transfers, and the effects and determinants of non-compliance from both perspectives because some information is available only from the prospective acquirer's (i.e., "consumers") perspective, while other information is available only from the supplier's perspective. For example, acquirers typically do not know characteristics of suppliers that may be associated with refusals to supply a material. Similarly, a prospective supplier will typically not know the impact of a refusal on the research program of the scientist making the request. Below, we first present our findings from the consumer's perspective, and then examine sources of supplier non-compliance.

5.1. Requests for research inputs, responses and effects

In contrast to the 6% of our academic respondents who sought permission to use another's IP, about 75% made at least one request for a material in the last 2 years. On average, academics made about seven requests for materials to other academics and two requests to industry labs in the prior 2 years. Eighty-one percent received their most recently requested material. In their role as prospective consumers of material transfers (i.e., those making the requests), our respondents report that 18% of their material requests to other academics were not fulfilled, and 33% of their requests to industry researchers were not fulfilled ($p < .001$). In their role as prospective "suppliers" (i.e., those who were receiving requests for materials or data) our respondents report that they did not fulfill 6% of requests from other academics (and 31% of requests from industry, $p < .001$). Thus the vast majority of such requests are fulfilled, but many are not.[17] Although non-compliance rates, as measured by whether or not the most recent request was fulfilled, are very similar between those *doing* drug development and those doing basic research, materials that are drugs or potential drugs are the most difficult to obtain.[18]

To consider whether non-compliance may have changed over time, we compare our results with Campbell et al.'s (2002) who report that, among genomics researchers, about 10% of requests were denied in the 3 years, 1997–1999.[19] Among the genomics researchers in our sample, the comparable number for 2003–2004 is 18% (95% confidence interval:

[17] Because of this difference in the reported rates according to whether we ask the respondent to address the question of compliance from their vantage point as, alternatively, consumer or the supplier, we must be careful about reports that rely simply on one side, as they may over- (or under-)estimate the true rate. We use multiple indicators to bound the likely correct rate. Similarly, by asking about a discrete, recent event (your last request), we can reduce the biases associated with recalling many events over longer time periods.

[18] 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 44% receiving *all* such requested drugs from industry. For other materials, the probabilities for receiving *all* requests tend to be above 60% from academic sources and above 50% from industry sources.

[19] To make the two samples comparable, we limited our estimate to those doing genomics research in universities or hospitals, including university hospitals (Campbell's population). 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 are confident that the growth in non-compliance is not due to differences in question wording. Also, to make the measures comparable, we are comparing the percent of all requests over a fixed time period for each of the surveys (last 2 years in our survey and last 3 years in the Campbell survey).

±3.7%),[20] suggesting recent growth in non-compliance with research input requests.

To identify the effects of not receiving requested inputs, we inquire about the frequency over a 2 year period of three possible effects: delayed completion of the experiment by more than 1 month; having to change research approaches; and abandonment of a promising line of research. The average reported number of delays per person over a 2-year period that result from not receiving a material requested from another academic was 0.68, and, from an industry researcher, it was 0.40. Projects abandoned were 0.22 per person over 2 years due to academics not supplying materials, and 0.27 due to industry scientists not supplying materials. Thus, each year, because of unfulfilled requests to another academic, there is an average of one project abandoned for every nine researchers.

5.2. What is requested and why not make it in-house?

We asked respondents to tell us about their most recent request for a research input. The first question was, what type of input was it? We received 307 responses to this question. The most commonly requested inputs, accounting for 48% of requests, were biomaterials: a gene, plasmid, cell line, tissue, organism, etc. An additional 15% of requests were for proteins. Unpublished information or findings (such as genetic sequences, protein structures, phenotypic information or lab techniques) account for 10% of requests. Drugs or potential drugs were 9% of requests. Databases and software were 4% of the requests, and 14% of requests were for other types of inputs. Thus, the typical request was for a biomaterial, although unpublished information, proteins and drugs are also important research inputs that are shared among biomedical scientists. We will use the term *tangible* research inputs (or, "materials") to refer to these requests, although we should remember that information, data and software are included and represent about 15% of requests.

We then asked respondents why they did not make the requested input in-house. In particular, we wanted to see the extent to which patents may be preventing scientists from making the input in-house, which would be another manifestation of pure IP restricting research. We asked respondents to tell us, for their most recent request, how important were each of the following in preventing them from making the research input themselves: the time or cost required to produce the input; their does not having the capabilities (i.e., equipment, information, or expertise) to produce the research input; and patents preventing replication of the research input. Respondents were asked to rate each reason on a five-point Likert scale ranging from not important ("1") to very important ("5"). Table 4 presents the average scores for each type of research input, for the random sample overall, and broken out by type of input requested. 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, difference from "not having capabilities," $t = 10.0$, $p < 0001$). Inability to make the research input in-house (due to lack of equipment, information or expertise) was the second most common reason, with a mean score of 3.1. Patents (mean = 1.6) were rated much lower as an impediment to producing the research input in-house (in comparison to lack of capabilities, $t = 12.4$, $p < .0001$). Drug inputs are more likely than other research inputs to be seen as limited by patents (mean = 3.2, comparison to other inputs, $t = 4.4$, $p < .001$). Thus, with the important exception of drugs (as research tools), respondents do not consider patents to be a major impediment to producing needed research inputs themselves. Instead, potential time and costs savings and the benefit of access to others' capabilities motivate them to try to obtain research inputs from another lab. In other words, when they make a request for an input, it is typically not because it is patent protected, but because it is difficult or expensive to make it themselves.

5.3. Acquiring research Inputs: MTAs, terms, negotiations

We also collected information on the transfer process triggered by a request for a research input. Here we asked the scientist about his recollections of the MTA, its terms, and the negotiation process triggered by his most recent request for a research input.[21] We find that

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

[21] Here, we are asking the scientist about his recollections of the terms presented (which may differ from those of an official from the technology transfer office). The question was "As a condition of fulfilling the request, did the sender ask you to sign a licensing agreement or Material Transfer Agreement (MTA)?". If the answer was "yes," then we asked, "Please indicate which of the following terms were requested in the initial version of the agreement. Also please indicate which were included in the final version at the end of the negotiations (when you either signed the agreement or abandoned the request). If you do not know if a particular term was requested, please check 'DK' for 'don't know'." We included a "don't know" option in the original survey instrument, as we suspected that the researcher may not have

Table 4
Reasons for not creating research input in-house, by technology requested

		Random sample	Technology requested					
			Unpublished information	Gene, Cell, etc.	Drug	Protein	Data, soft	Other
Time/cost	Mean	4.34	3.96	464	3.46	4.51	4.31	3.98
Lack capabilities	Mean	3.06	3.62	2.68	3.93	3.14	3.77	3.03
Patent	Mean	1.63	1.54	1.39	3.16	1.53	1.56	1.61
Respondents	*N*	295	27	143	26	43	13	43

fewer than half of the requests (42%) elicited a demand for an MTA (cf. Mowery and Ziedonis, 2007, for a similar result). Only 40% of MTAs required any negotiation, and only 26% of the MTAs required a negotiation lasting more than 1 month. While there has been substantial concern about the effect of MTAs on academic researchers (cf. Eisenberg, 2001), only 11% (.42 × .26) of requests for research inputs entailed an MTA negotiation taking more than 1 month. Eight percent of those who requested a research input reported, however, having to stop their research for more than 1 month while negotiating terms. Although modest, this number is greater than the 1% who were delayed for more than 1 month because of a patent ($t = 3.34$, $p < .001$).[22] Among academic consumers, those asking for a drug are more likely than average to be presented with an MTA (64% of requests; $t = 2.68$, $p < .01$).

Although the NIH and the National Academy of Sciences recommend that MTAs generally should not impose claims on future inventions, nor restrictions on the dissemination of findings (Department of Health and Human Services, 1999; National Research Council, 2003), it is recognized that, under some circumstances, such as when the research input itself has commercial potential, restrictions may be legitimately imposed.[23] Our survey examines the extent of MTA-related terms and constraints on access by asking about respondents' experiences with MTAs associated with their most recent requests. We find that reach-through rights are common (such as the right to an exclusive or non-exclusive license on any improvements, the right to license, or to ownership of, any inventions made using the material, etc.), while royalty payments tied to sales of the product of the research are less so. Suppliers asked for reach-through rights for 38% of MTAs, and demanded a royalty for 17% of MTAs.[24] Even for transfers from one academic institution to another, where NIH guidelines are likely to apply, 29% of MTAs included a reach-through right and 12% included a request for a royalty. Requests for drugs are most likely to generate such reach-through rights (70%), with requests for proteins also often including such terms (64%). Publication restrictions were also common, with 30% of MTAs imposing such restrictions. Requests for drugs were the most likely to yield 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.

Prospective industry suppliers were more likely than university suppliers to ask for an MTA (70% versus 35%), and were more likely to ask for reach through rights (63% versus 29%), royalties (32% versus 12%) and publication restrictions (58% versus 18%) (all differences significant, $p < .05$). Also, negotiations over terms with industry are somewhat more likely to take longer than a month than are negotiations with universities (35% of negotiations with industry suppliers lasted over 1 month versus 21% of negotiations with university suppliers, $t = 1.61$, $p < .15$).[25] Requests to industry are also

been aware of the details of the terms. For each term we asked about, less than 10% of respondents chose "don't know", suggesting respondents generally felt they knew the terms of the MTA. Furthermore, if our interest is in the effects of the terms on the scientists, the scientists' perceptions are important. This is particularly true since only 39% of MTAs included an official from the requesting institution in the negotiations, suggesting that in the vast majority of cases, it is the scientist who is making the decision to accept the MTA terms.

[22] Recognize that this comparison understates the incidence of delay associated with access to materials versus patented pure knowledge inputs in that, per our regression analysis below, the greatest frictions associated with requests for materials occur when the recipient of a request for materials does not request an MTA, which likely signals that the prospective supplier is simply not willing to comply with the request under any circumstances.

[23] 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.

[24] 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.

[25] In fact, even industry to industry transactions (with 45% taking over 1 month) are more likely to be protracted than university to university (21%) ($t = 1.55$, $p < .15$). However, transactions between academics

somewhat more likely to result in a research delay (16% of requests to industry suppliers resulted in the consumer having to stop for the project for more than 1 month versus 6% of requests to academic suppliers, $t = 1.65$, $p < .15$). Interestingly, there was little difference in the behavior of prospective academic versus industry suppliers in the likelihood of asking for a co-authorship (15% of industry MTAs versus 12% of academic MTAs, $t = 0.37$, $p > .70$).

Finally, we examined responses for those prospective consumers of materials who included their organizations' technology transfer office or patent counsel in the negotiations. Of the requests where the consumer was asked to sign an MTA, 39% included a licensing professional from the receiving institution in the negotiations over the transfer. In other words, even if there is a request for an MTA, the vast majority scientists (61%) are not consulting their TTO or patent counsel. Involvement of the prospective consumer's TTO or counsel is more likely if the request is being made to industry (52% of MTAs involving industry included the TTO or counsel) than to another academic (34%, $t = 1.76$, $p < .10$). For requests for drugs, the prospective consumer's TTO or counsel were more likely to be involved in the negotiations (53% if it is a drug requested versus 37% if it is not), although the difference is not statistically significant. The TTO or counsel is also more likely to be involved if the proposed MTA includes requests for royalty (63% versus 34%); reach-through rights (59% versus 26%) or publication restrictions (56% versus 32%, all differences are significant, $p < .05$). Where the proposed MTA includes requests for co-authorship, the TTO or counsel, is more likely to be involved, though not significantly so. (47% versus 37%, n.s.). Finally, if the prospective consumer's TTO or counsel is involved, the chances of the request not being fulfilled is higher. Conditioned on being presented with an MTA, only 6% of requests are not received if the TTO/counsel is not involved. However, if the TTO/counsel is involved, 23% of requests are not fulfilled ($t = 2.60$, $p < .05$). Similarly, for MTAs where the TTO/counsel is involved in the negotiations, 65% lasted over 1 month, while if the TTO or counsel was not involved, none of the negotiations lasted over a month ($t = 9.51$, $p < .0001$). We do not know if the TTO/counsel is impeding the transfer, or if it is simply that the TTO/counsel tends to be involved in the more complicated and difficult transfers.

For research inputs received from other academics, 93% entailed no fee. Only 4 out of 243 requests (less than 2%) required an upfront payment of over $1000. Even firms typically provided materials 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%) from industry suppliers came with a demand for a fee of over $1000.

6. Regression analyses of the determinants of material exchanges

In this section, we employ regression analyses to probe the reasons for noncompliance with requests for materials. In the first set of regressions, we consider factors conditioning whether a respondent's most recent materials request was satisfied. We then conduct an analysis of the determinants of the number of times a respondent denied requests for materials. The reason for running analyses distinguished by the respondent's role as a prospective consumer versus supplier is because, depending on the vantage point, we will know different things. For example, a prospective supplier will not necessarily know whether the potential consumer has industry funding or has previously commercialized his research results, and a perspective consumer will not necessarily know how many other requests the potential supplier has received.

6.1. What makes a research input difficult to acquire?

To examine the relationship between the features of a research inputs and the likelihood that an associated request is fulfilled, we ran a logistic regression of whether the respondent's most recent request was fulfilled against: (i) whether the input was owned by an academic; (ii) whether it was patented, not patented, or the respondent did not know the patent status; (iii) if the material requested was a drug or potential drug; (iv) how competitive the field is; (v) whether an MTA was required and (vi) if the prospective consumer's technology transfer office (TTO) or patent counsel was involved. Table A2 shows the correlation matrix.

Presented in the first column of Table 5,the results show that drugs are especially difficult to acquire (odds-ratio = 0.08), suggesting that a drug request is about

and those from industry tend to take longer than within-sector transaction (47% versus 24%, $t = 3.24$, $p < .01$). The most time-consuming transactions are industry consumers asking for research inputs from universities, with 60% taking over 1 month.

Table 5
Logistic regressions for receiving most recently requested material research input

Variable	Model 1 estimate (S.E.)	Model 2 estimate (S.E.)	Model 3 estimate (S.E.)
Drug material requested	−2.4981*** (0.7466)	−2.8259** (0.8744)	−3.9936** (1.5218)
Number of competing labs	−0.0582 (0.0297)	−0.0624* (0.0311)	0.0183 (0.0713)
Academic suppliers	0.00463 (0.00539)	0.00638 (0.00564)	0.00406 (0.0102)
MTA	0.0204** (0.00627)	−0.00692 (0.00732)	
Patented	0.00673 (0.00523)	−0.0109 (0.00977)	0.0393* (0.0183)
Patent status unknown	−0.00523 (0.00376)	−0.00881* (0.00431)	−0.00042 (0.00841)
TTO/counsel involved	−0.0161* (0.00682)	−0.0153* (0.00680)	
MTA × patent		0.000406** (0.000141)	
MTA × don't know		0.000179* (0.000086)	
MTA co-authorship			−0.00990 (0.0119)
MTA publication review			−0.0171† (0.00941)
MTA reach through right			−0.00468 (0.00859)
MTA royalty			−0.0165† (0.00945)
Intercept	1.5791* (0.6185)	1.6992* (0.6588)	3.4925** (1.2322)
N	273	273	230
χ^2	40.77	51.48	38.62
d.f.	7	9	9
$p > \chi^2$	<.0001	<.0001	<.0001

Note: Standard errors in parentheses.
* $p < .05$.
** $p < .01$.
*** $p < .001$.
† $p < .10$.

one-twelfth as likely as other requests to be fulfilled.[26] We also see that being asked to sign an MTA is associated with a 2% greater chance of receiving the material (odds-ratio = 1.02), probably because such a request signals that the owner is at least willing to consider sharing. Including the TTO or patent counsel is associated with a 2% lower probability of receiving the requested material (odds-ratio = .98), even controlling for whether the owner is an academic or from industry, and whether it is a drug requested. Patent status per se has no significant effect on the likelihood of receiving the material, controlling for the owner's sector (academic versus industry), scientific competition and whether it is a drug that is being requested. Scientific competition, on the other hand, has a negative effect ($p = .051$) on receiving the requested material (odds-ratio = .94), such that one additional competing lab reduces the chance of receiving the material by about 6%, 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).[27] We also interact patent status and MTA request. The results presented in the second column of Table 5 show that patented materials, if accompanied by an MTA, are more likely to be supplied (compared to unpatented, no-MTA, materials), as are those where the patent status is unknown (although the effect sizes are small, with odds ratios very close to 1.0). If, on the other hand, there is no MTA, and the patent status is unknown, the odds of receiving the input decline, possibly because there was no response to the request at all.[28] Finally, we tested the impact of particular terms in the MTA (co-authorship, publication restrictions, reach through rights, and royalties). Shown in Model 3 of Table 5, the results suggest that (controlling for the other terms in the MTA and for academic ownership, scien-

[26] We also tested whether "information inputs" (unpublished information or databases/software) were easier or more difficult to acquire. Neither had significant predictive value, nor did a variable combining them (i.e., "any information input"). Results available from the contact author.

[27] 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.

[28] Following Campbell et al. (2002), we also ran a version of the model which includes characteristics of the scientist making the request, including papers published, commercial activity, gender and whether the respondent was engaged in drug discovery. Adding these characteristics has no substantial effect on the coefficient estimates of the other independent variables, and no characteristic has a significant effect, which is not surprising, since the supplier does not necessarily know the details of the acquirer's background (results available from the contact author).

tific competition, patent status and whether the request was a drug) proposed imposition of publication restrictions or demands for royalty payments are both likely to reduce the chances of receiving the requested material by about 2% ($p < .10$, odds-ratios each = .98), while requests for co-authorship or for reach through rights do not have a significant independent effect.[29] One feature of the Model 3 results is that the existence of a patent on the material now appears to increase the likelihood of compliance with the request. In our view, patent status here is simply picking up the effect of whether there is a request for an MTA to begin with which, in turn, signals a willingness to deal on the part of the prospective supplier.

6.2. *Why do scientists not provide materials?*

We consider three factors that may be associated with non-compliance: commercial incentives; the effort involved in compliance; and scientific competition. Although Campbell et al. (2002) have highlighted the first two motives, the impact of scientific competition, while long considered an important driver of scientists' behavior (Hagstrom, 1974; Merton, 1973; Walsh and Hong, 2003), has not been empirically tested as a possible explanation of non-compliance with requests for materials.

Our respondents received an average of 14 requests from other academics in the last 2 years, although several received over 100 requests. The mean number of requests not fulfilled was 1. We ran a multivariate model predicting the number of requests denied (i.e., a positive coefficient means more non-compliance) by our academic suppliers (i.e., academic scientists who had received requests for their research inputs) as a function of: (i) whether the supplier had engaged in any "business activity" (i.e., had been involved in negotiations over rights to their inventions; had begun developing a business plan or laying other groundwork for starting a firm; had a startup based on their invention; had a product or process in the market; or had some licensing income); (ii) whether he had received any industry money in the last year (another measure of commercial ties); (iii) the number of labs that are competing with the supplier's lab for publication priority (a measure of scientific competition); (iv) the number of requests received per $100,000 in lab funding (as a measure of the overall burden and as a control); (v) the overall lab budget (as a measure of scale economies); (vi) and the number of scientific publications (as a measure of the opportunity cost of complying with a request and/or the academic prestige of the supplier).[30] We also control for gender (Campbell et al., 2002). Table A2 shows the correlation matrix. We estimate the model using a negative binomial regression, which accommodates count variables, as well as corrects for the overdispersion in the counts (Hausman et al., 1984). Presented in Table 6, the results show – consistent with Campbell et al. (2002) – that business activity is associated with a greater number of refusals. Those with a history of business activity are likely to deny 1% more requests than are those who are not business active (exp(.0104) = 1.01). Scientific competition is also an important predictor of refusals, consistent with the sociology of science literature. An increase of one competing lab is associated with an 8% increase in denials (exp(.0776) = 1.08). Number of requests per funding dollar has a significant, positive effect on the number of refusals, suggesting that the overall burden of responding may be an important reason why scientists do not respond to requests.[31] An increase of one request per $100,000 in lab budget is associated with a 4% increase in denials (exp(.0383) = 1.04). However, the overall budget does not have an independent effect, suggesting that it is the relative burden that is driving these refusals. The number of publications also has a substantial effect, with those who publish more likely to refuse requests, suggesting that as the opportunity cost of compliance increases (i.e., the expected loss from taking time away from research to fulfill requests), the likelihood of fulfilling requests decline, or, perhaps, that more eminent

[29] Collinearity problems prevented including both the presence of an MTA and the terms of an MTA in the same regressions (see Table A2). Similarly, TTO/counsel was also excluded from this model due to collinearity. If we include TTO/counsel in Model 3, it continues to have a negative relationship with the odds of receiving the requested material, while publication review and royalty requests continue to have a negative relationship, but at weaker significance levels ($p < .25$).

[30] Our survey, and the Campbell et al. (2002) survey, also simply asked respondents who did not satisfy another scientist's request why they did not comply. The major reason reported was the cost/effort involved (which we are measuring in the regression as requests per dollar). An additional factor highlighted in these responses but not in our regression, and consistent with Campbell et al. (2002) results, was the protection of the respondent's ability to publish. Respondents also reported that commercial concerns played little role in this decision. We feature our regression results rather than rely on these direct responses, however, due to a bias where individuals tend to exaggerate the importance of socially desirable incentives (e.g., intellectual challenge, improving society) as distinct from pecuniary ones (Rynes et al., 2004).

Also, for these supplier questions, we did not ask about the terms of the transfer (MTA) or whether the TTO/counsel is involved.

[31] Indeed, according to our respondents, and to Campbell et al.'s findings, the most important stated reasons for not fulfilling requests are the cost/effort involved (Campbell et al., 2002; Walsh et al., 2005a,b).

Table 6
Negative binomial regression for number of times respondent does not fulfill research input requests

Variable	Model 1 Estimate (S.E.)	Model 2 Estimate (S.E.)
Business activity	0.0104* (0.0042)	0.0101* (0.0042)
#Competing labs	0.0776* (0.0399)	0.0735† (0.0406)
#Publications	0.0750* (0.0367)	0.0754* (0.0366)
#Requests received per $100,000 funding	0.0383* (0.0186)	0.0341† (0.0195)
Total funding ($100,000)	0.0083 (0.0419)	−0.0017 (0.0460)
Industry funding	0.0058 (0.0051)	0.0056 (0.0052)
Drug discovery	0.0000 (0.0073)	0.0002 (0.0073)
Male	−0.0077† (0.0044)	−0.0076† (0.0044)
# Requests		0.0041 (0.0077)
Intercept	−2.3391** (0.5112)	−2.2800** (0.5211)
Dispersion	4.0491 (1.0038)	4.0451 (1.0011)
N	202	202
χ^2	148.94	150.76
d.f.	193	192
Value/d.f.	0.772	0.785

Note: Standard errors in parentheses.
* $p < .05$.
** $p < .01$.
† $p < .10$.

scientists are less likely to respond to requests. One additional publication is associated with an 8% increase in denials (exp(.0750) = 1.08). Women are somewhat more likely to refuse requests than are men ($p < .10$).[32] Industry funding also has no significant effect on compliance with requests (although the effect is positive, $p < .25$). Finally, academics doing drug discovery were no more likely to refuse requests for research inputs than those engaged in basic and other research. Column 2 shows the same model, adding a control for number of requests received, in addition to requests per $100,000 in research budget. The results are qualitatively similar, although significance levels change slightly for scientific competition (number of competing labs) and for requests per $100,000 in funding. Number of requests has no independent effect. Because of the high collinearity between number of requests and requests per dollar ($r = .52$), and the weak independent effect of the raw number of requests, we feature the simpler model.

Thus, these results suggest that a history of commercial activity may have a negative effect on scientists' willingness to share research inputs. We also see that scientific competition may be an important, independent predictor of failure to comply with requests. Finally, the effort involved is also an important reason why labs may not respond to requests for research inputs. These findings both confirm earlier regression results by Campbell et al., and add to them by showing that scientific competition is a significant predictor for failing to share. We should note, however, that although these effects are statistically significant, all the magnitudes of these effects imply that a one unit change produces less than a 10% change in the number of refusals, for which the mean frequency is about 1 refusal every 2 years (out of an average of 14 requests).

7. Patenting and three signaling proteins

The results above suggest that patents rarely interfere with 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, we complement our analysis of the random academic sample by focusing on domains that are scientifically and medically important and where the preconditions for restricted access or anticommons frictions are especially apparent—that is, fields characterized by: numerous patents held by different kinds of institutions, patents on fundamental, upstream discoveries, and strong commercial interest. A finding of patent-induced problems in such 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 in such domains where preconditions lend themselves to such frictions would reinforce the conclusion from our analysis of the random sample that intellectual property is not a key impediment to biomedical research.

For this analysis, 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).[33] These proteins mediate signals along key molecular pathways involved in normal and diseased cellular processes. Stimulation of cells with EGF, for example,

[32] Campbell et al. (7) report that men are more likely to deny requests, $p < .10$.

[33] These three subfields were chosen after extensive consultation with the NAS Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions. The goal was to find proteomics and genomics researchers working in fields that were scientifically important, and where there was enough patenting and commercial interest that there would be a risk of patents interfering with research, without selecting on fields that were known to be having problems.

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 et al., 1999), and its loss of function is believed to contribute to auto-immune diseases such as rheumatoid arthritis, multiple sclerosis and lupus (Kristiansen et al., 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, seminal 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 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) to large pharmaceutical and biotech firms, universities and the Federal government. These proteins and the drugs that act on them also have significant commercial potential, as indicated by the number and types of therapeutic products targeted against these proteins.[34]

Thus, these three proteins are each associated with significant numbers of patents held by different types of institutions, commercial activity, and also represent fundamental biological research areas, making these areas especially fertile terrain for finding adverse effects of patents. To study the effects of patents in these chosen areas, we drew a supplemental sample of researchers working on one of the three signaling proteins: CTLA-4, EGF and NF-kB. We drew 100 researchers for each protein (one duplicate was eliminated), which included a total of 29 (out of 299) from industry.[35] We then administered the same questionnaire as provided to the random sample, which allows us to compare the answers from these three signaling proteins 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 field), we have only limited statistical power for comparisons, and estimates of group means should be interpreted with caution.

As shown in Table 1, EGF and NF-kB are associated with especially high levels of commercial activity, while CTLA-4 is much closer to the norm (i.e., random sample average) for biomedical research. Compared to the overall sample, academics working in these areas are somewhat more likely to have industry funding. NF-kB researchers are most likely to have industry funding (39% saying they have industry funding, difference from norm, $p < .05$) and report the highest percent of industry funding (14% of total research funds, difference from norm, $p < .05$); EGF researchers report somewhat less; and CTLA-4 researchers report the lowest levels of commercial activity (with CTLA-4 being just below the norm). Over the last 2 years, NF-kB researchers filed the most patent applications per respondent (an average of .89, $p < .01$), 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.).[36] Thus, it seems that EGF and NF-kB are especially commercially active, while CTLA-4 is not much different from the overall average, although somewhat more active on some measures.

As shown in Tables 2 and 3, researchers in these areas choose and reject projects for largely the same reasons as other scientists. EGF researchers are, however, more likely to cite personal income (11% versus 2% for random sample, n.s.) or the chance to start a new firm (7% versus 1% for random sample, n.s.) as additional reasons to choose projects. Those in NF-kB were above the random sample average in citing unreasonable terms for research inputs as a reason to decide against pursuing a project (19% versus 10% for the norm, n.s.). For all three

[34] 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), based on CTLA-4, currently are in clinical trials for the treatment of multiple sclerosis and rheumatoid arthritis, respectively. Eli Lilly's drugs Xigris (for sepsis) and Evista (for osteoporosis) work through NF-kB-regulated pathways.

[35] The sampling frame for the fields 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 that area (top 10 patent holders in each area).

[36] 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.

proteins, respondents choose their projects predominantly due to scientific importance, interest, feasibility and funding. In none of the three areas are respondents more likely than the random sample 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 consequences. Among CTLA-4 researchers, one person abandoned a project (4% of the sample, or 20% of those who knowingly 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), and one modified 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 the 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 random sample. In particular, abandoning a project due to inability to access IP is still rare (3% of researchers across the three proteins), but non-zero. 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, such adverse outcomes are still infrequent, and probably, at least in part, for the same reasons highlighted for the random sample: scientists do not regularly check for patents.[37]

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 much higher in these two research fields. While 19% of the random sample did not receive their last requested input, between 32% (NF-kB, $p < .10$) and 26% (EGF, n.s.) of those working on these two signaling proteins had their most recent request denied.

Researchers working on NF-kB and EGF also report a greater frequency of negative effects from not receiving research materials. For example, in a two-year period, NF-kB researchers report 0.62 cases of projects abandoned and 2.85 cases of projects delayed as a result of inability to access requested research inputs. These results are three to four times higher than the norm. Those studying EGF are also above the norm, although the gap is smaller, in the range of 1.5–2 times the norm. CTLA-4 is generally close to the norm.[38]

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

8. Conclusions

Our results suggest that academic biomedical researchers are engaged in a significant amount of commercial activity, including patenting and licensing. The results also suggest that patents in this field, while common, do not regularly prevent academic scientists from gaining access to the knowledge inputs that biomedical scientists require. None of our random sample of academics reported stopping a research project due to another's patent on a research input, and relatively few (1% of sample) reported delays or the redirection of their research, although some (3–10% depending on the question) did report that patents had a significant influence on their project choices. For researchers working on signaling proteins associated with important metabolic molecular pathways in areas that the literature suggests should be particularly susceptible to IP-induced frictions, we observe a slightly higher incidence of adverse effects (3% abandoning a project and 15% having some adverse effect).

[37] For the NF-kB sample, 9% report regularly checking for patents; for EGF, 7%; and for CTLA-4, no one reported regularly checking.

[38] However, the percent of respondents who had a project stopped for more than 1 month is not much higher in the signaling protein fields than in the overall population, with the exception of EGF, where 15% of respondents had their research stopped for more than 1 month due to failure to acquire a research input.

One important reason that the rates of adverse outcomes associated with intellectual property are not higher (given the large number of patents in this area) 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; only 8% of our random sample respondents reported awareness of using information or knowledge covered by a third party patent sometime in the prior 2 years. We do find, however, that those who are more engaged in commercial activity are more aware of third party patents, although, even for this group, only about 20% report knowing of relevant third party patents. We have no way of knowing what the true base rate is for the percentage of respondents who use others' intellectual property. Given, however, the large number of biotech patents issued since 1990, we suspect that the number of academic researchers who are using others' patented technology exceeds 8% of the total.

Although such apparent disregard for IP may for the moment minimize the social costs that might otherwise emerge due to restricted access (Walsh et al., 2003), it remains an open question whether such disregard is sustainable. Indeed, an important question is why academic researchers seemingly disregard the possibility that the knowledge inputs they use may be patent protected. Is it just a matter of habit born of a time, not long ago, when upstream biomedical discoveries were not patented? Or, is it a matter of community norms and organizational and career incentives that place the highest value on getting the work of science done, without paying much attention to anything that might slow the work down? Or is it that, given the low likelihood thus far of academics' being sued for patent infringement, the researchers have little incentive to change their behavior. There is the additional consideration that academic biomedical researchers are also not generally trained in how to conduct effective patent searches, so that the time spent searching the patent databases would unlikely allow the comprehensive identification of relevant patents, suggesting not searching may be the more rational strategy. No matter the explanation, however, our finding underscores Ellickson (1991) observation that the "law on the books" need not be the same as "law in action," particularly if the law on the books contravenes a community's norms and interests.

In contrast to the case of intellectual property, requests for tangible research inputs from other scientists are not fulfilled in a significant minority of cases. Almost 20% of our respondents report that their last request for a material or data was not fulfilled. Moreover, the incidence of non-compliance appears to be increasing. We also find that such non-compliance affects the research programs of individual researchers. For example, one in nine researchers report abandoning a promising line of research in a given year because he did not receive requested materials or data. This noncompliance with others' requests for research inputs does not appear to be associated with a patent on the material, but is rather associated with a history of business activity by academics, scientific competition, the time and effort required to satisfy requests, and whether the material in question is a drug. But even if patents on a material do not affect compliance with a request, perhaps the fact that a material is patented affects whether a request is made to begin with. When asked why researchers do not make the research input themselves, we find, however, that patents are much less important than the cost/time involved or the lack of necessary capabilities in one's lab, suggesting that the likelihood of a request being made is not affected importantly by associated patents.

Notwithstanding the reasons why a material is not shared, without more research, we cannot conclude that less sharing actually imposes a social welfare cost. Denied requests surely impose costs for individual researchers. And, social welfare is diminished to the extent that redirection of a scientist's research effort or reallocation across investigators impedes scientific progress. 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 modified 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. Negotiating these MTAs can be time consuming, although only about 10% of all requests for research inputs led to a negotiation lasting more than 1 month, and in almost all cases there is no fee for the material. However, in a minority of cases (8% of requests), delays in accessing research inputs can stop the research for more than 1 month, which can represent a substantial delay in a fast moving research field.

We find that MTAs (especially from industry suppliers) frequently include demands for reach-through rights of some form. They also often include terms that put restrictions on publication of research results. It is hard to know, however, 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, even under NIH guidelines (Department of Health and Human Services, 1999). 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 to ensure that unfavorable research results (such as adverse effects in clinical trials) are never disclosed.[39]

Given the modest response rate and the limitations of self-report data, we should be cautious in interpreting our findings. However, 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 direct cause of restricted access to tangible research inputs (as opposed, for example, to scientific competition or prior 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 academic research of the patenting of upstream biomedical discoveries may not be addressing the most pressing policy question. Although the patenting of knowledge inputs into academic biomedical research may impose significant social welfare costs in the future, academic biomedical research may for now be more effectively supported by addressing the transaction costs, competitive pressures and commercial interests that are impeding the sharing of data and material research inputs.

[39] 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 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.

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Appendix A

See Tables A1 and A2.

Table A1
Comparing respondents and non-respondents

Measure	Respondents	Non-respondents	Sig.
PubMed papers (mean)	4.9	5.6	n.s.
Patents (mean)	0.5	0.5	n.s.
Any patent (%yes)	16	21	n.s.
Ph.D. (%yes)	78	66	<.001
M.D. (%yes)	12	21	<.01
Public university (%yes)	45	45	n.s.
Private university (%yes)	34	32	n.s.
Non-profit (%yes)	7	9	n.s.
Government (%yes)	14	15	n.s.

Note: For publications and patents, respondent $n = 44$, non-respondent $n = 66$; for degree and institution, respondent $n = 407$, non-respondent $n = 706$.

Table A2
Correlation matrix for regression variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
(1) Requests not fulfilled	–																			
(2) Requests received	**0.18**	–																		
(3) Business activity	**0.19**	**0.13**	–																	
(4) Competing labs	**0.20**	**0.13**	0.08	–																
(5) Publications	**0.30**	0.10	**0.28**	**0.12**	–															
(6) Requests per $100,000 funding	**0.14**	**0.52**	-0.03	0.06	−0.07	–														
(7) Total funding ($100,000)	0.06	**0.17**	**0.13**	0.05	**0.28**	**−0.23**	–													
(8) Industry funding (yes/no)	**0.21**	−0.04	**0.23**	−0.01	**0.19**	−0.12	**0.15**	–												
(9) Drug discovery	−0.01	−0.06	0.10	**−0.11**	**0.15**	−0.08	0.02	**0.30**	–											
(10) Male	0.00	0.06	**0.11**	0.08	**0.15**	0.06	0.06	0.01	0.04	–										
(11) Received last request	0.03	0.05	0.03	**−0.18**	0.01	0.10	−0.04	−0.04	−0.04	0.01	–									
(12) Drug material requested	0.00	−0.06	0.07	0.09	**0.13**	−0.05	0.00	0.03	**0.13**	−0.04	**−0.26**	–								
(13) Academic supplier	0.00	0.09	**−0.15**	−0.05	**−0.15**	0.08	−0.09	−0.15	**−0.17**	0.02	**0.15**	**−0.51**	–							
(14) MTA	0.12	0.07	0.13	−0.02	0.09	−0.07	**0.16**	0.02	0.09	0.06	**0.14**	**0.14**	**−0.25**	–						
(15) Patented material—yes	0.00	−0.02	0.01	0.00	**0.15**	−0.08	0.06	0.04	**0.23**	−0.04	−0.05	**0.49**	**−0.42**	**0.26**	–					
(16) Patented material—don't know	0.10	0.08	**0.17**	**0.19**	0.00	−0.07	**0.12**	**0.14**	−0.02	0.03	−0.07	−0.08	0.02	**0.15**	**−0.27**	–				
(17) MTA: co-authorship	−0.02	−0.04	0.00	−.10	0.05	−0.03	0.06	0.09	**0.15**	0.04	**−0.23**	0.06	−0.10	**0.26**	0.01	**0.17**	–			
(18) MTA: publication review	0.13	0.01	**0.16**	−0.03	**0.23**	−0.03	0.09	0.11	**0.17**	0.06	**−0.30**	**0.37**	**−0.42**	**0.42**	**0.29**	−0.03	**0.25**	–		
(19) MTA: reach through	**0.23**	0.13	0.08	0.06	**0.20**	−0.10	**0.16**	0.05	**0.17**	0.05	**−0.25**	**0.32**	**−0.38**	**0.48**	**0.26**	0.03	**0.15**	**0.49**	–	
(20) MTA: royalty	0.00	0.01	0.01	0.05	0.09	−0.06	−0.01	−0.05	0.01	0.07	**−0.33**	**0.15**	**−0.29**	**0.30**	0.04	0.03	**0.18**	**0.20**	**0.47**	–
(21) TTO involved	0.18	0.01	**0.17**	0.08	**0.21**	0.05	**0.16**	0.02	0.10	0.05	−0.05	**0.15**	**−0.24**	**0.52**	**0.18**	0.03	**0.18**	**0.38**	**0.48**	**0.33**

Note: Bold faced correlations, $p < .05$.

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