Roadblocks to Accessing Biomedical Research Tools

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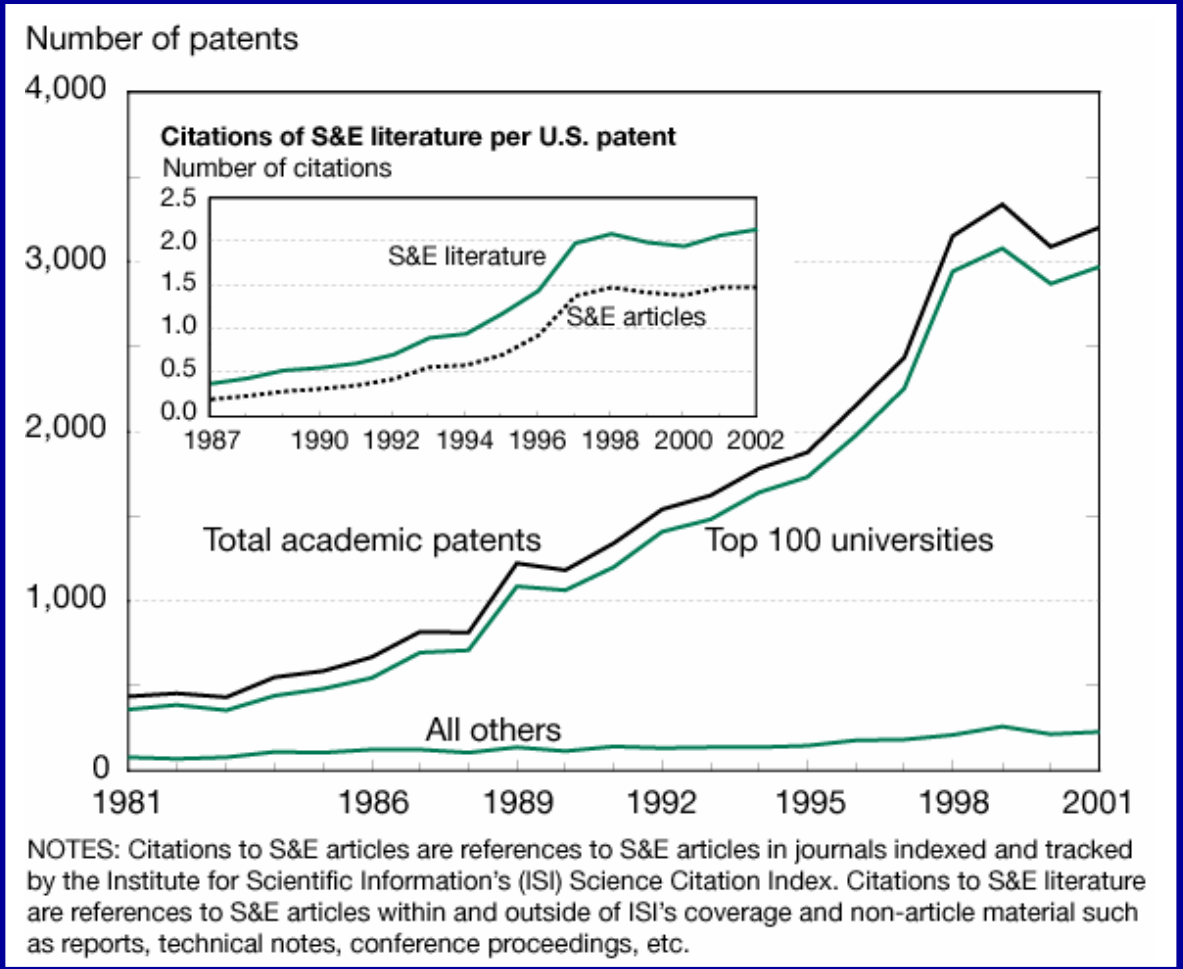
Changing Context of Academic Biomedical Research

- Patents provide important incentives for downstream biomedical innovation, but…
- Technological change
  - Molecular biology revolution
  - Sequencing and bioinformatics
  - Combinatorial chemistry and HTP screening
- Policy change
  - Bayh-Dole and related legislation
- Patentability of life forms
  - *Diamond v. Chakrabarty*

Changing Context of Academic Biomedical Research

- Increasing commercialization of environment for academic biomedical research
- More commercial activity by universities
- More patents on inputs to university research

Patents granted to U.S. universities and colleges: 1981–2001

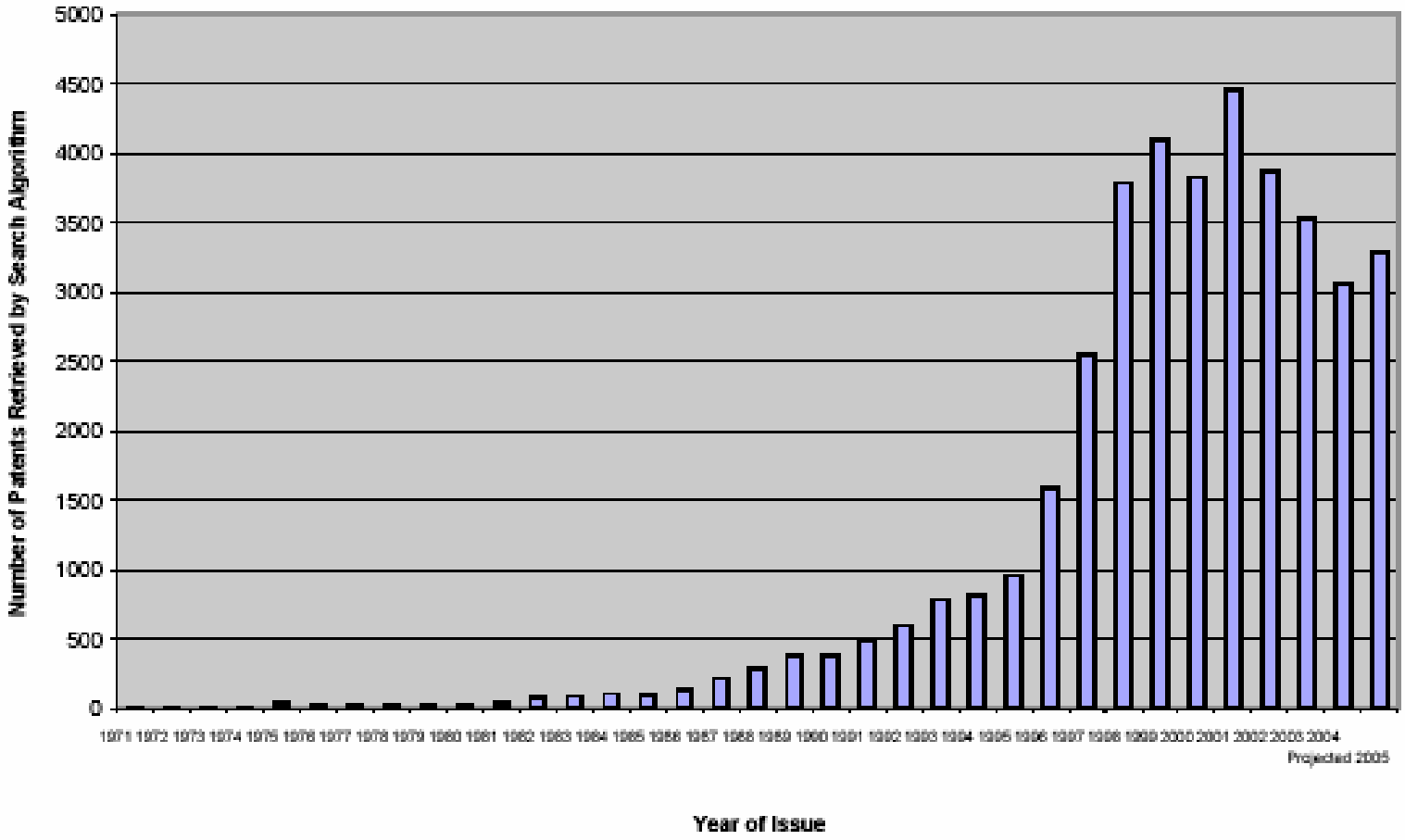


NOTES: Citations to S&E articles are references to S&E articles in journals indexed and tracked by the Institute for Scientific Information's (ISI) Science Citation Index. Citations to S&E literature are references to S&E articles within and outside of ISI's coverage and non-article material such as reports, technical notes, conference proceedings, etc.

SOURCE: National Science Board, Science and Engineering Indicators, 2004

Source: AUTM, 2003

Number of DNA-based US patents, per year, 1970-2005



Source: NAS, 2006

Concerns Raised

- Anti-commons:
  - Demands of numerous claimants may lead to excessive licensing burden, the cessation of otherwise worthwhile projects and the loss of collective surplus, impeding development and commercialization of drugs and therapies, and possibly even basic research
- Access:
  - Limitations on subsequent discovery and improvements imposed by assertion of patents on upstream, foundational discoveries
- Erosion of the norms of open science, possibly undercutting research productivity
  - Restrictions on the sharing of research materials and publication delay

Research Questions

- For **academic** research, is access to research inputs restricted and what are causes and effects of restricted access? :
  - "Disembodied" knowledge research inputs?
  - Tangible research material inputs?
- How do these impacts vary by research goal (basic versus drug development)
- Changes, especially since *Madey v. Duke*
- Goals:
  - Policy implications
  - Understanding how economic incentives, institutional contexts, and occupational norms affect innovative activity, at level of academic bench scientist

Prior Interview-Based Study

- Walsh, Arora and Cohen (2003) reported results of interview-based study of impact of research tool patents on biomedical research
  - 70 interviews, including 17 bench scientists
- Patent landscape more complex
- But, little anti-commons breakdown, and even restricted access generally overcome, due to "working solutions"
  - Especially, though not only, disregard of IP and rational forbearance of such infringement
  - Supported by interdependent system of incentives and constraints

Academics' infringing: The Informal "Research Exemption"

- Faculty feel free to use technologies for "research"
- Firms generally refrain from asserting against universities
  - Little to gain and reputation to lose
  - University research adds value
- Community:
  - Repeated game with information sharing
  - Norms of research: collegiality and open access
  - Outsiders misbehave (e.g., duPont)
- Most noncommercial uses OK
- **Exception**: universities' use of diagnostics using patented genes that are integral to research *and* used commercially
  - Myriad and BRCA1

Limitations on Prior Interview-Based Study

- Could still see problems in future
  - CAFC decision in *Madey v. Duke (2002)*, by publicly removing already narrow research exemption, may undermine use of informal research exemption and chill academic research
- Generality of prior study limited

Current Study

Data and Method

- Post-mail survey: 1,987 biomed researchers
- University, non-profits, government, industry
- Sample frames
  - Professional societies
  - Researchers associated with cell signal proteins: CTLA-4, EGF, NF-kB
- 414 responses from random academic sample, reflecting 40% (adj.) response rate
  - 654 responses in total, including industry and signal protein researchers samples
- Focus on the random "academic" sample, which includes scientists working in universities, non-profit and gov't labs

Academics' Commercial Activities

- Substantial commercial activity
  - Industry funding: 19% have some industry funding
  - Patenting (in last 2 years): 22%
  - Business activity (e.g., startup, negotiations, licensing, commercialization of discovery) : 35%
- More for those doing "drug discovery"

Patenting and Its Impact on Research

- Patents and project choice
- Respondents' awareness of patent protection on intangible (knowledge) research inputs
- Effects of inability to access "pure IP"

"Pure IP" and Academic Research

- Does the existence of disembodied "pure IP" impede academic research?
- Awareness of patents on knowledge inputs?
- Effects?
  - Delay
  - Modify research approach
  - Abandon project

Awareness of Patents on Research Inputs

- 8%, or 32 of 381 respondents, believed they needed knowledge or information covered by patents
- Given burst in research tool patents, why so few?
  - Only 5% check regularly for patents on knowledge or material inputs (little change since *Madey*)
- 22% received instruction from institution (v. 15% 5 years ago)
  - AAAS study: 14% of universities give instructions
  - BUT, instruction does not change behavior (6% v 4%)

Impact of "Pure IP"

- Cost of access?
  - Nearly always (22/23) no cost
- How often does a patent affect academic research?
- How often when the respondent knows there is a relevant patent?

Impact of "Pure IP"

Effect	N	% All Academics (N=381)	% Those Faced w/ Patent (N=32)
Delay (> 1 month)	5	1%	16%
Modify	4	1%	13%
Abandon	0	0%	0%

Access to Tangible Research Inputs

Sharing Material Research Inputs

- Where others' tangible inputs necessary for research activity itself, may have different impact from pure IP
- Examples
  - Cloned gene, organism, cell line, protein, drug, unpublished information, etc.
- About 75% of our academic respondents requested materials in the prior two years
- Average # of requests (last 2 years)
  - 7 to other academics and 2 to industry

Arcane stuff?

"…Scientists demand bigger role in research; setback for vaccine?"

- "China's efforts to maintain control over samples of avian flu taken on its soil…have put it at odds with international health officials trying to defeat the disease." (***WSJ*, 2/24/06, pp. A1, A6)**

Just China?

– "Flu researchers slam US agency [CDC] for hoarding data." (*Nature (22 Sept 2005)*)

Difficulties in Accessing Tangible Research Inputs

- 19% did not receive last requested research input
- Change over time?
  - For academic to academic exchanges in genomics, percent of requests not received:
    - 2003-04 (Walsh, et al): **18**% (+/-3.7%)
    - 1997-99 (Campbell, et al): **10**%
- So, appears to be some increase in recent years
- **Delay research (>1 month): at least 8% of requests (v. 1% for pure IP)**

Why Do Scientists not Provide Materials?

Why Do Scientists not Provide Materials? (multivariate regression)

- Concern about SDR bias in self-report data: use multivariate regression
- From point of view of academic supplier:
  - Commercial orientation (business activity)
  - Industry funding
  - Scientific competition (# competing labs)
  - Burden (requests/lab dollar)
  - Total budget
  - Publications
  - Drug discovery
  - Male

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)
Number of competing labs	0.0776* (0.0399)	0.0735† (0.0406)
#Publications	0.0750* (0.0367)	0.0754* (0.0366)
#Requests Received per $100K Funding	0.0383* (0.0186)	0.0341† (0.0195)
Total Funding ($100K)	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)	4.0415 (1.0011)
N=	202	202
Chi-square	148.94	150.76
df	193	192
Value/DF	0.772	0.785

Why Do Scientists not Provide Materials?

- Main predictors
  - **Scientific competition** (# competing labs)
  - Prior business activity
  - Burden (requests/lab dollar)
  - # Publications (Eminence or opportunity cost?)
- Insignificant
  - Industry funding (modest pos. effect)
  - Drug discovery

Case Studies: At Risk Fields

- Prior results provide base-rate data
- But, even rare result might have major social welfare impacts if it affects important technology
- To probe this, we collected data from researchers in three fields that have high scientific importance, and varying levels of patenting and commercial activity
- EGF, NF-kB, CTLA-4
  - Lots of research activity (foundational paper had over 1500 cites for first two, around 900 for CTLA-4)
  - Many patents (760, 90, 60, respectively)
  - Drugs in market or clinical trials

Case Studies: At Risk Fields

- Pure IP: Adverse affects rare, although slightly more common than base rate
  - More likely to know about patents
  - 3% had abandoned a project (v. 0% for random sample)
- Access to materials even more problematic
  - 26-32% did not receive last request (v. 19% for overall)
  - NF-kB and EGF well above norm in terms of projects abandoned or delayed due to not receiving requested inputs (CTLA-4 near norm)
- Thus, even in high risk areas, the impact of pure IP is small, while the impact of withholding tangible property is even greater than the base rate

Conclusions

- Commercial activity by academics is substantial, but little growth
- Little evidence project choice affected by commercial incentives or anti-commons
  - But beware of SDR bias

Conclusions: Impact of "Pure IP"

- Few are aware
- **Even if aware**, has little impact on research
  - Even in high risk fields (EGF, NF-kB, CTLA-4) minimal impact (3% abandoned a project in last 2 yrs)
- Few academic institutions have policy of notifying faculty
- And, even if notified, does not seem to change behavior
- Earlier qualitative study: similar result
- **"Law on the books" is not the same as "law in action"**

Conclusions: Tangible Inputs

- Access to **tangible** research inputs more problematic than access to pure IP
  - About 10-20% of Ac-Ac requests not fulfilled
  - Refusals increasing
- Adverse affects due to scientific competition (and cost/effort of compliance), as well as commercial incentives
- But, social welfare impacts of denials and MTA terms ambiguous

Conclusions

- **So, if there is a problem, it's one of access to *tangible*—not *intellectual*—property, and the constraints on access turn more on cost/effort, scientific competition and commercial activity than on IP per se**
  - Culprit may not be IP on materials, but Bayh-Dole and IP-related legislation that fosters commercial activity among academics more generally
  - But need to weight benefits of such legislation against any costs
- Solutions should be tied to problems
  - Changing patentability rules may not address problem
  - Facilitating tangible input sharing (to reduce cost/effort) may be key

Questions, Comments, Suggestions?

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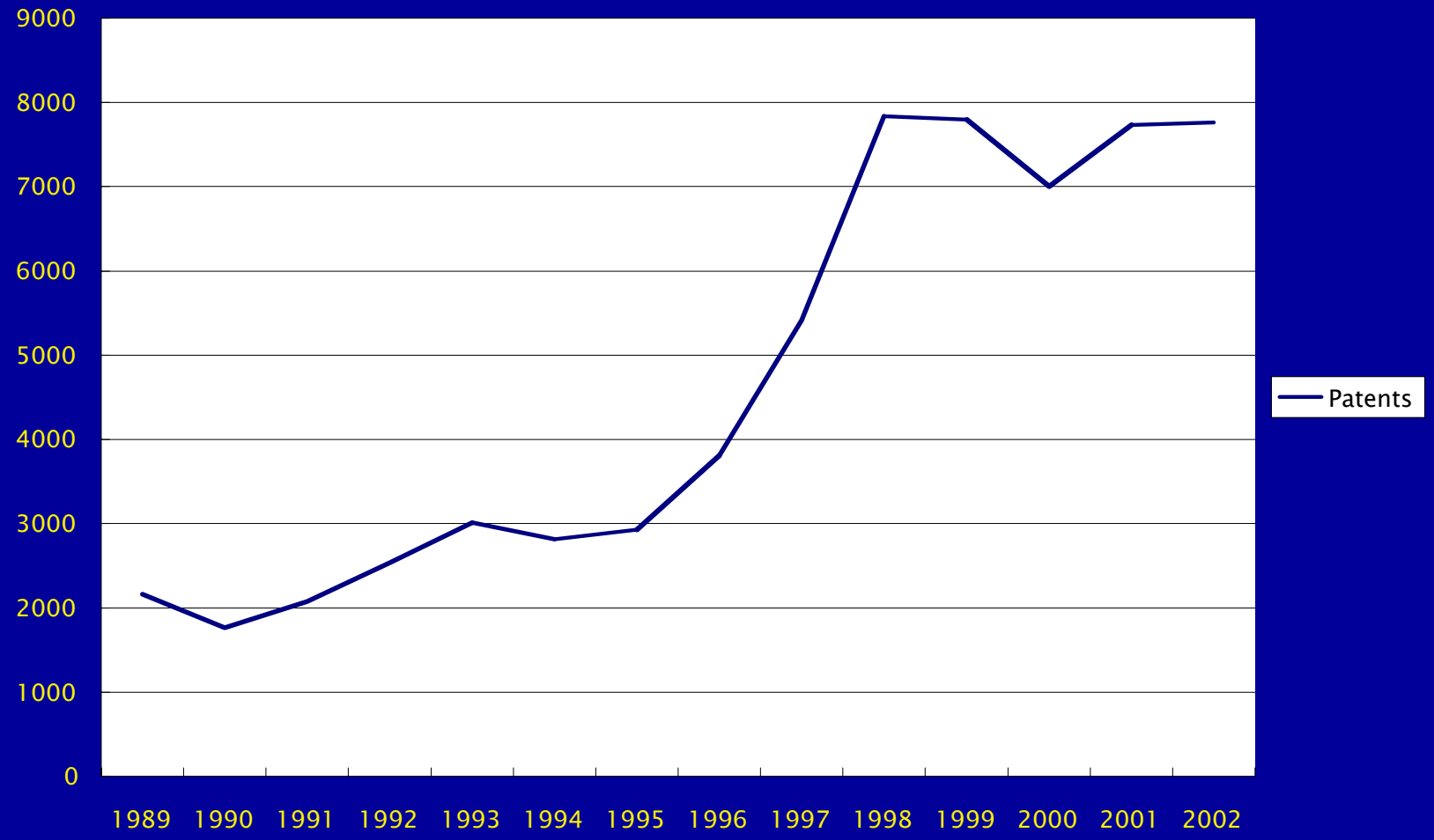
Appendix

Total Biotechnology Patents Granted per Year



Source: BIO

Working Solutions: Firms' Infringing

- Hard to detect
- About one third mention using this strategy; most say others do this
- Some claim research exemption, or that patent scope very narrow
- May take license later if target proves useful
- If need be, can challenge in court, invalidate

Table 1.1 Basic Demographics.

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

Table 1.3 Distribution of Responses by Institutional Affiliation, Random Sample.

Institution	Frequency	Percent	Cumulative Freq.	Cumulative %
University	265	69%	265	69%
Hospital	44	11%	309	81%
Govt/NonProf	74	19%	383	100%

Table 1.5 Distribution of Responsed by Research Goal.

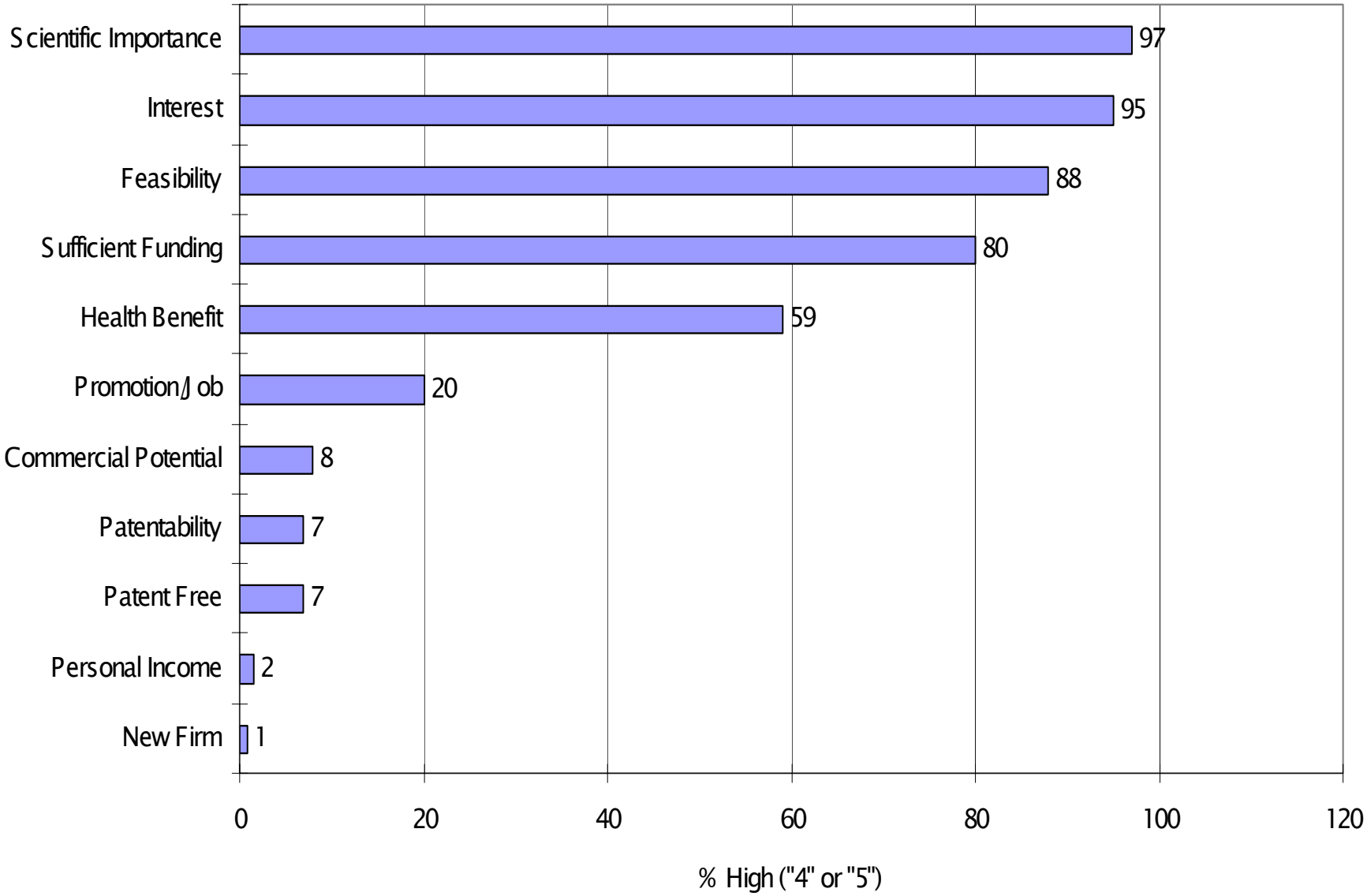
	Academia			
Research Goal	Frequency	Percent	Cumulative Freq.	Cumulative %
Drug Discovery	40	9.66	40	9.66
Basic Research	322	77.78	362	87.44
Other	52	12.56	414	100

Table 1. Commercial Activity for Academic Researchers, Pathways Comparison.

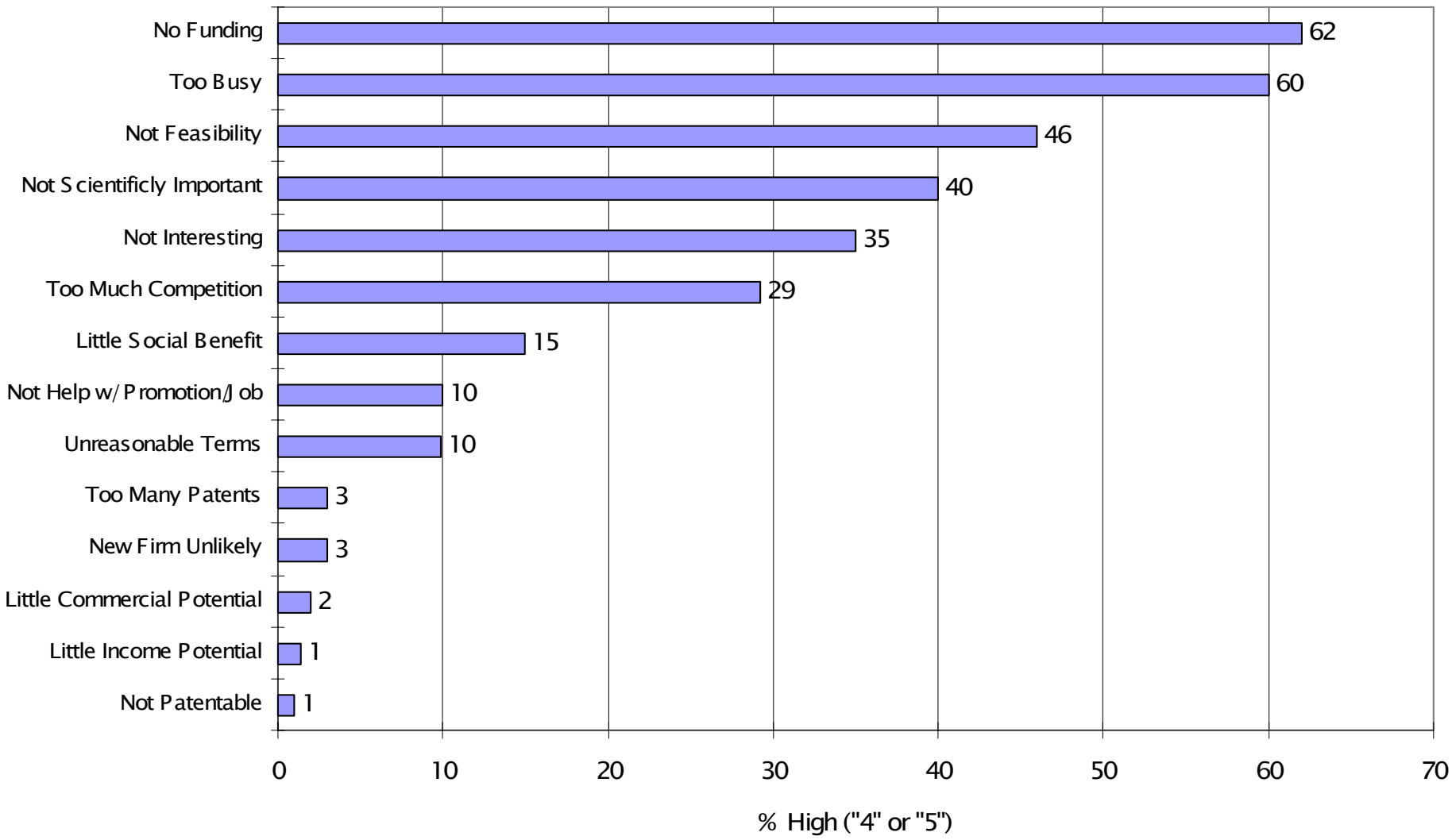
		Random	Research Goal			Pathways		
Measure		Sample	DrugDisc	BasicRsrch	Other	CTLA4	EGF	NF-kB
Industry Money-Now	% yes	19	54	15	14	30	29	39
Industry Money-5 years ago	% yes	23	44	21	15	38	37	33
%Industry Funding-Now	Mean	4	13	3	5	3	6	14
%Industry Funding-5 years ago	Mean	6	15	4	6	4	9	10
%Time on Commercial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

Patents and Project Choice

Reasons for Choosing Projects, Academic Respondents



Reasons for Not Pursuing Projects



Patents and Project Choice

- Project choice driven primarily by scientific objectives, interest and access to funding
- Scientific competition can also redirect projects
- Prospect of patent on research output or commercial potential have little impact (though higher (~20%) for drug discovery)
  - Redirection does not seem to be a problem for basic research
  - Potential SDR bias

Roads not Taken

- Main reasons: Over 40% of respondents rate funding, time constraints, infeasibility, and scientific importance as more than moderately important
- Patent-related reasons
  - Too many patents on tools and other inputs: 3%
    - No different for those involved in drug discovery
  - Terms associated with rights to inputs, including materials: 10%
    - 21% for those involved in drug discovery
- “Patent thicket” on inputs has little impact on decisions to choose, or not pursue projects
  - anti-commons does not seem to be a problem

Impact of Not Receiving Research Inputs (Academic to Academic)

Adverse effect	Annual % of academics who made requests (N=242)
Delay (> 1 month)	18%
Modify a project	16%
Abandon a project	7%

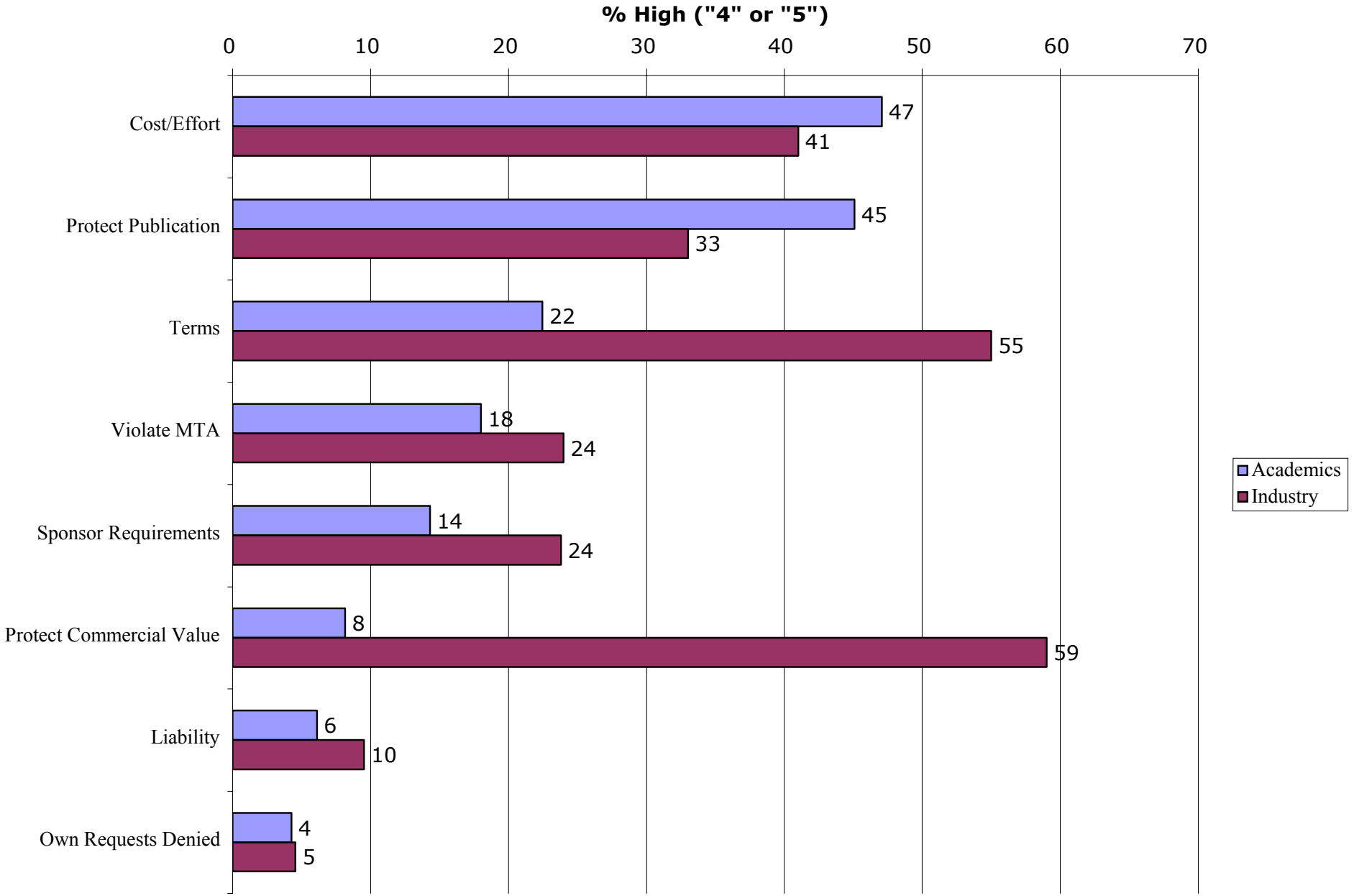
MTA Terms, Negotiations

- About 40% of transfers require MTA
  - More common if request drugs (64%)
- Fees
  - 93% from academic, no charge, < 2% over $1000
  - 85% from industry, no charge, 7% over $1000
- Terms (requested)
  - Reach through-38%
  - Royalties-17%
  - Manuscript review-30%
    - Drugs to Academics: 70% of final agreements

MTA Terms, Negotiations

- Except for royalties, academic respondents doing drug discovery tend to be more subject to restrictive terms than those doing basic research
- Industry suppliers tend to impose more restrictive conditions than academic suppliers
- 26% of MTAs (11% of requests) take more than one month to negotiate

Figure 13. Reasons for not Fulfilling Requests, Academic and Industry Respondents



Reasons for not Fulfilling Request (self-report)

- Academic Suppliers
  - Cost/Effort
  - Scientific Competition
  - Commercial value rarely chosen (<10%)
- Industry Suppliers
  - License Terms
  - Commercial Value
  - Cost/Effort
- Violate MTA in middle

What makes an input hard to acquire?

- Drug or potential drug
- Scientific competition (# competing labs)
- Academic owner
- MTA
- Patented, not patented, don’t know

Table 4. Logistic Regressions for Receiving Most Recently Requested Material Research Input

Variable	Estimate (s.e.)	Estimate (s.e.)
Drug material requested	-2.2169**	-2.4983**
	(0.6825)	(0.7634)
Number of competing labs	-0.0577*	-0.0637*
	(0.0292)	(0.0308)
Academic suppliers	0.00651	0.00804
	(0.00516)	(0.00539)
MTA	0.0124**	-0.00075
	(0.00420)	(0.00547)
Patented	0.00496	-0.0116
	(0.00720)	(0.00951)
Patent status unknown	-0.00423	-0.00864*
	(0.00373)	(0.00430)
MTA*Patent		0.000380**
		(0.000133)
MTA*Don't know		0.000199*
		(0.000084)
Intercept	1.3605*	1.5436*
	(0.5934)	(0.6321)
N=	276	276
Chi-Square	33.72	44.95
df	6	8
p>Chi-square	<.0001	<.0001

What makes an input hard to acquire?

- Drugs are especially difficult to acquire
- MTA associated with a greater chance of receiving
  - probably because signals owner willing to consider sharing
- Patent status no significant effect
- Scientific competition has negative effect
  - Or, may be more competitors means R is less likely to know rivals personally, and hence more likely to refuse
- Because tangible inputs can be withheld, provides leverage, and potential revenue (and source of delays) independent of patents

What makes an input hard to acquire?

- We also interact patent status and MTA request.
- Patented materials, if accompanied by an MTA, are more likely to be supplied (compared to unpatented, no-MTA, materials)
- Also true where the patent status is unknown.
- 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 at all.

What makes an input hard to acquire?

- We also tested the impact of particular terms (reach through, royalty, publication restriction and co-authorship), and found that demanding publication review or royalties reduces the likelihood of completing the transfer