Dual knowledge in the life science:

Scientific and commercial progress in Pasteur's Quadrant

Dr. Fiona Murray
Assistant Professor
MIT Sloan School of Management

& Sloan Foundation Fellow in Biotechnology

Presentation to Sloan Foundation Conference
December, 2005

Agenda

- CONTEXT - rise of “dual scientific knowledge” fueled the development of the biotech industry & brought about a transformation in the intersection of “Science” & “Technology” – e.g. increase in the patent coverage of knowledge once largely in the public domain
- IMPLICATIONS & DEBATE - for scientific & commercial progress and the nature of cumulative innovation?
- EVIDENCE – exploration of the theoretical debate & recent empirical evidence
- DISCUSSION – academic and industry relevant issues

CONTEXT

Dual Scientific Knowledge

Emerging trend exemplified by Harvard's Oncomouse

Leder & Stewart, Harvard 1984 develop the transgenic "Oncomouse"

- First mouse with specific (*myc*) genes inserted that predispose the mouse to cancer
- A significant advance along two dimensions:
  - A tool for advancing *basic research* into the role of genes in cancer
  - An input into *applied research* focused on cancer therapies

Example of the growing category of "dual" scientific knowledge that is in Pasteur's Quadrant – its simultaneously valuable to

- On-going scientific discovery AND
- Translation, innovation & economic growth

Source: Murray 2005

CONTEXT

Dual knowledge lies at the heart of Biotechnology industry

8/10 blockbusters based ideas generated in academia

Table 1 Principal university and pharmaceutical company partners associated with the top ten biotechnology products in 2002

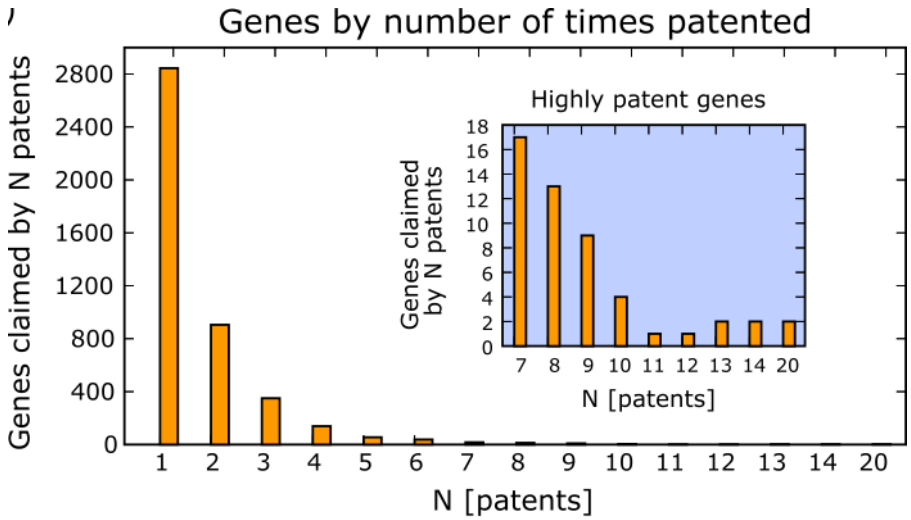
Product (biotechnology company)	2002 sales ($ billion)	University licensor	Pharmaceutical licensee(s)
Procrit (Amgen, Thousand Oaks, CA, USA)	$4.3	University of Chicago (Chicago, IL, USA)	Johnson & Johnson (New Brunswick, NJ, USA)
Epogen (Amgen)	$2.3	University of Chicago (Chicago, IL, USA)	Kirin (Tokyo, Japan)
Neupogen (Amgen)	$1.4	Memorial Sloan Kettering (New York, NY, USA)	Kirin & Hoffmann-La Roche (Nutley, NJ, USA)
Remicade (Centocor, Malvern, PA, USA)	$1.3	University of Munich (Munich, Germany)	Schering-Plough (Kenilworth, NJ, USA) & Tanabe (Osaka, Japan)
Rituxan (IDEC, San Diego, CA, USA)	$1.2	Stanford University (Stanford, CA, USA)	Genentech andZenyaku Kogyo (Tokyo, Japan)
Avonex (Biogen, Cambridge, MA, USA)	$1.0	None	Schering-Plough (terminated)
Humulin (Genentech, S. San Francisco, CA, USA)	$1.0	University of California (San Francisco, CA, USA)	Eli Lilly (Indianapolis, IN, USA)
Combivir (Biochem Pharma, now Shire Pharmaceuticals, Newport, KY, USA)	$0.9	None	GlaxoSmithKline (Brentford, UK)
Betaseron (Chiron, Emeryville, CA, USA)	$0.8	Stanford University	Schering AG (Berlin, Germany) and Berlex (Richmond, CA, USA)

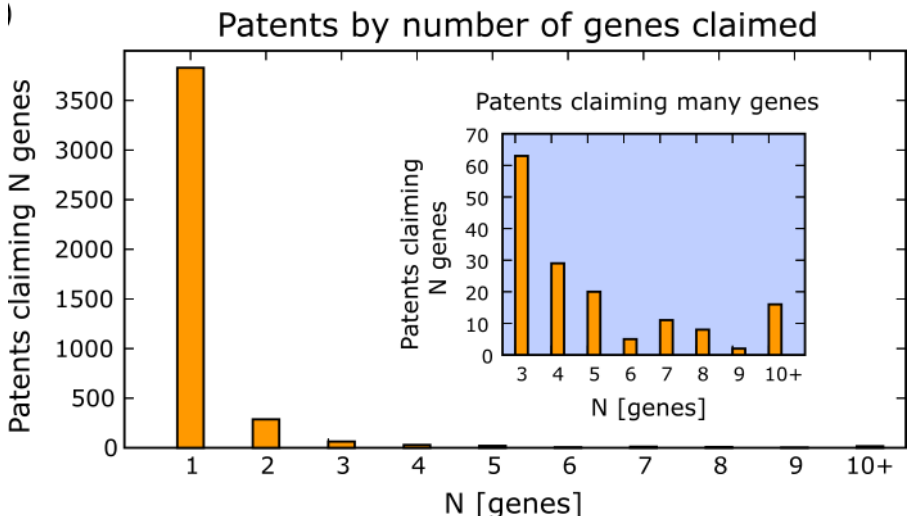
Source: J. Van Brunt, Product sales soar, *Signals Magazine*, (2003).

Source: Edwards, Murray & Yu, 2003

Dual knowledge has extended to the human genome…

- Recent analysis show that 4,382 of the 23,688 genes in the human genome are claimed in granted U.S. patents (Murray & Jensen, 2005)
- At least 30% are owned by academic institutions – the largest academic owner being the U of C system





Research Agenda
Implications of dual knowledge

Organizational

- (Re)-Organization of dual research – in academic & industry & between these two domains

Institutional

- Dual institutions - Conflict in the institutional arrangements for innovation - ideas (and their developers) often captured in two distinctive (& often conflicting) institutions - discovery and invention

Individual

- Dual careers – academic scientist & entrepreneur – who can do this, how are labs structured? Or industry scientist (who continues to publish) – who is successful?

IMPLICATIONS

Traditional Disclosure of Knowledge

Choice of institutional regime (publish or patent) was exogenous

Academia = "Science" contributions to basic knowledge undertaken in academia & published

- Research communities adopt a set of *norms* that require full disclosure
- *Quid pro Quo*: Disclosure of findings (and data) via publication allows for "standing on shoulders of giants" & peer review in return for resources, prestige & job security

Industry = "Technology/Applied Science" contributions to solving useful problems in industry & patented or maintained as secret

- The patent system designed to minimize duplication & facilitate cumulativeness (overcome incentives for secrecy)
- *Quid pro quo*, exchanging limited monopoly rights for public disclosure which provides a base for follow-on researchers

But….what happens when an individual "piece" of knowledge <u>simultaneously</u> holds scientific and commercial interest?

IMPLICATIONS

Dual Knowledge

Expansion of knowledge that simultaneously holds scientific and commercial interest….implications?

		Consideration of Use?	
		NO	**YES**
Quest for Fundamental Understanding?	**NO**		**Pure Applied Research (Edison)**
	YES	**Pure Basic Research (Bohr)**	**Use-Inspired Basic Research (Pasteur)**

Source: Stokes, *Pasteur's Quadrant* 1996

Disclosure of dual knowledge

Disclosure decision becomes endogenous with several choices simultaneously available

Strategic disclosure timeline

Choice I ("Science")	Idea generation	Publish		
Choice II ("Technology")	Idea generation	Patent Application (or secrecy)		Patent Grant (or secrecy)
Choice III ("Duality")	Idea generation	Publication	Patent Application (< 6 months)	Patent Grant

e.g. Oncomouse published in *Science* & Harvard patents - 4,736,866 (first transgenic animal patent)

Debate over IP

What is the impact of patents & specifically patent-paper pairs on progress?

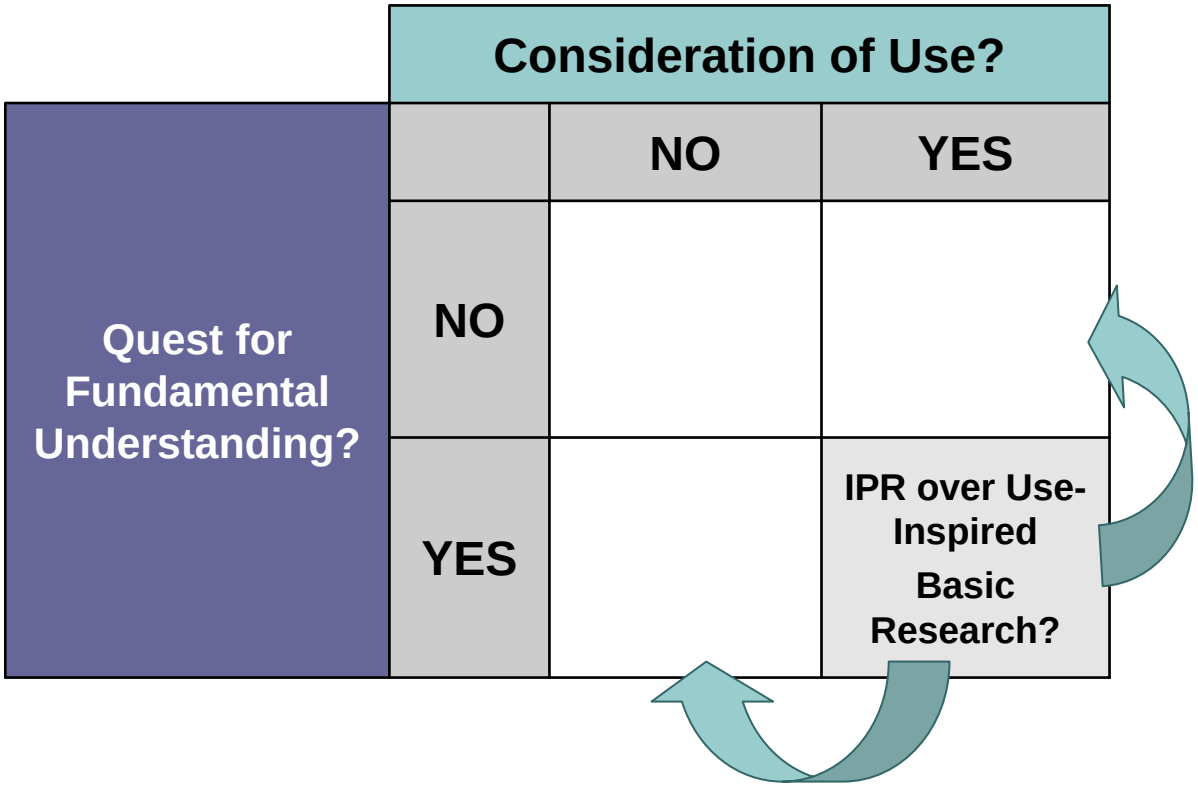
TWO KEY DIMENSIONS

- Impact of patents on **scientific progress**
  - Impact on scientists – rate of progress, research direction or productivity
  - Impact on the institutions of “Open Science” & practice of scientists

- Impact of patents on **commercial progress**
  - Traditionally IP thought to be essential to commercialization but…
  - Impact on academic-industry relationships

DEBATE

The Anti-Commons Debate: What is the impact of IP over knowledge which has traditionally been maintained in the public domain?



IPR can stifle downstream commercial exploitation as the result of a patent thicket and associated hold-up and transaction costs (Heller and Eisenberg, 1997; Shapiro, 2002)

IPR stifles further scientific progress through transaction costs and hold-up (Heller and Eiseberg, 1997), rent-seeking (David, 2002), shifting research agendas (Thursby & Thursby 2003)

Empirical Evidence

Evidence for impact of patents on Scientific Progress

Negative impact of IP

- IP may stifle research but to date main evidence is in the area of genetic testing (Merz et al. 2004)
- Rise in secrecy among academics (Campbell et al. 2002) – but focuses on industry-funded research
- Weak evidence for decline in productivity – hard to observe because those who patent are also often "stars" (Azoulay et al. 2004; Lowe 2004; Lissoni 2005)

Positive/Neutral Impact of IP

- Anecdotal & new survey evidence of IP infringement by academics who suggest they are unaffected by IP (Walsh et al. 2003, 2005)

EVIDENCE

New Empirical Evidence

Single “case” of a scientific community’s collaborative behavior before & after patenting of key new resource

- **The Question: How does scientific collaboration & exchange *change* after patents start to be granted?**
  - This pre- and post- approach overcomes some “selection” issues and captures the impact of IP grant on the exchange and use of knowledge by follow-on researchers
- **The Case: Mouse genetics community before and after the patenting of the Oncomouse**
- **Pre- and post- patent grant**
  - Focus on strategies and tactics of those who developed the Oncomouse as well as follow-on researchers
  - Nature of collaborative arrangements, scope of collaboration, response to patenting, impact on individual researchers

EVIDENCE

Changing Scientist Behavior

Patent initially used to extract “rents” from commercial & academic scientists – reach-through rights, publication review, breeding restrictions.

- Response
  - Outrage among the scientific community over intrusion into “Open Science” institutions – “Revolt” at Cold Spring Harbor meeting
  - Push-back against DuPont through Varmus at NIH to reshape terms

- Response
  - Rise in the rate of patenting by mouse geneticists “will the patentors please stand up”…
  - Patenting as a strategic asset in collaboration
  - Patenting as a defensive mechanism
  - Patenting as a source of control – rent extraction

EVIDENCE

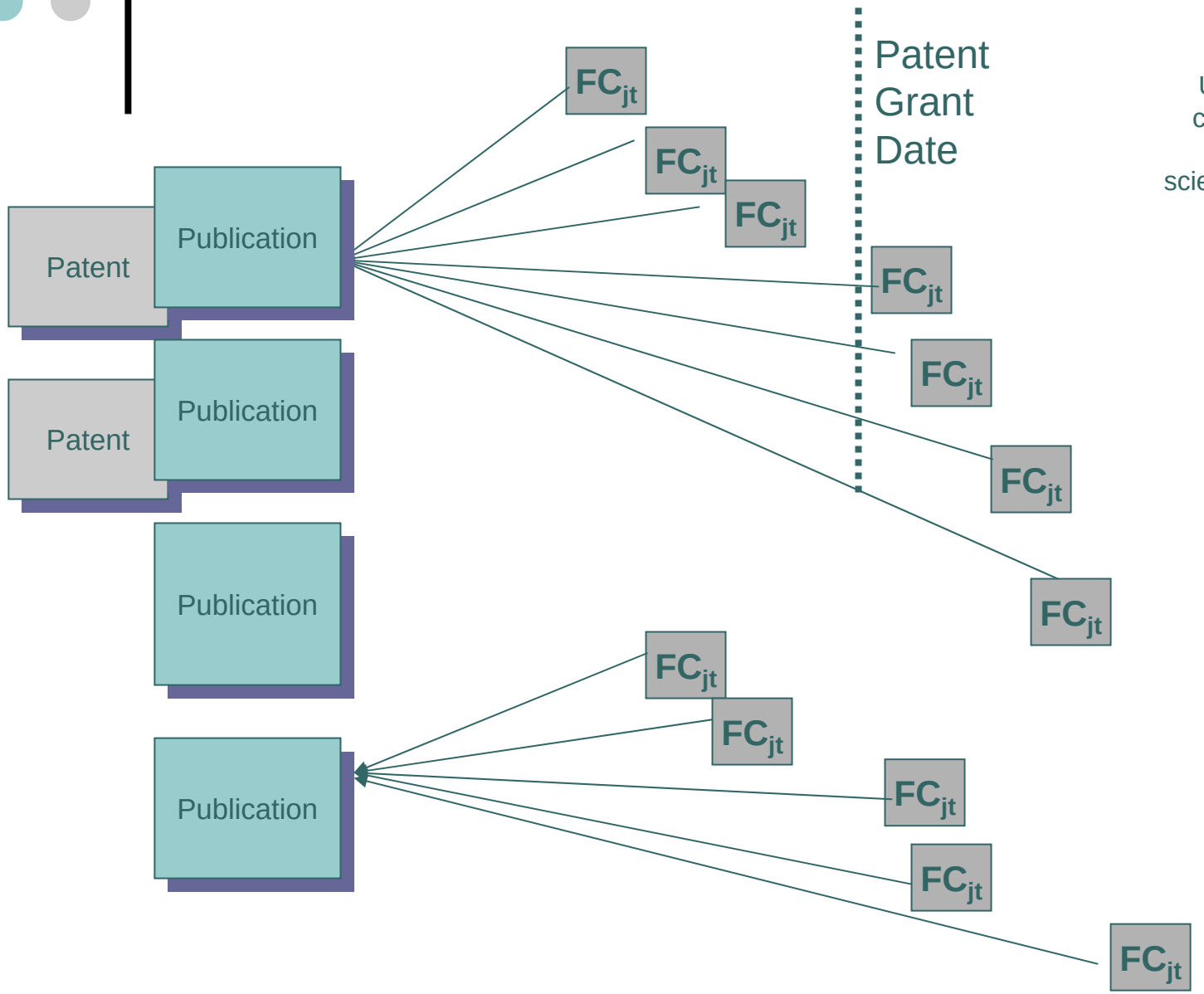
New Large-Scale Empirical Evidence

Joint w/ Prof. Scott Stern, Northwestern University

- **Collect a sample of research articles that are *at risk* for patenting**
  - All Research Articles From A Single Journal with a “dual” focus
- **Patent-paper pairs vs. non pairs**
  - Since not all articles are associated with pairs, we are able to contrast a treatment (“patented”) and control (“non-patented”) group
- **Patent Grant Delay**
  - Scientific publication is rapid (~ 3-6 months), patent grant delay is substantial (>2 yrs)
  - Prior to March, 2001, applications are secret until granted
  - Rights are uncertain until approval & no legal mechanism to enforce rights pre-grant & no damages for use (particularly in research) in pre-grant period
- **Identification**
  - Measure the citation rate by follow-on articles to each sample article
  - Assumption: For some follow-on researchers, patent grant is “news”
    - Also can rely exclusively on variation in patent grant delay itself

EVIDENCE

Empirical Strategy



Use forward citations as a measure of scientific progress

Empirical Setting

Unique sample of publications and the associated patent-paper pairs

Publications in *Nature Biotechnology*

- Raw sample population is composed of *all* research articles published in *Nature Biotechnology* – the leading outlet for "dual type" life sciences research– from 1997-1999
- Of 340 initial papers, 169 are associated with a specific patent, involving matching on name/institution and a content evaluation
- For each article (and patent), we then collected:
  - "Forward" Citations to each paper by Year
  - Publication Characteristics (# Authors, Affiliations, etc)
  - Patent Characteristics (# Inventors, Affiliations, etc)

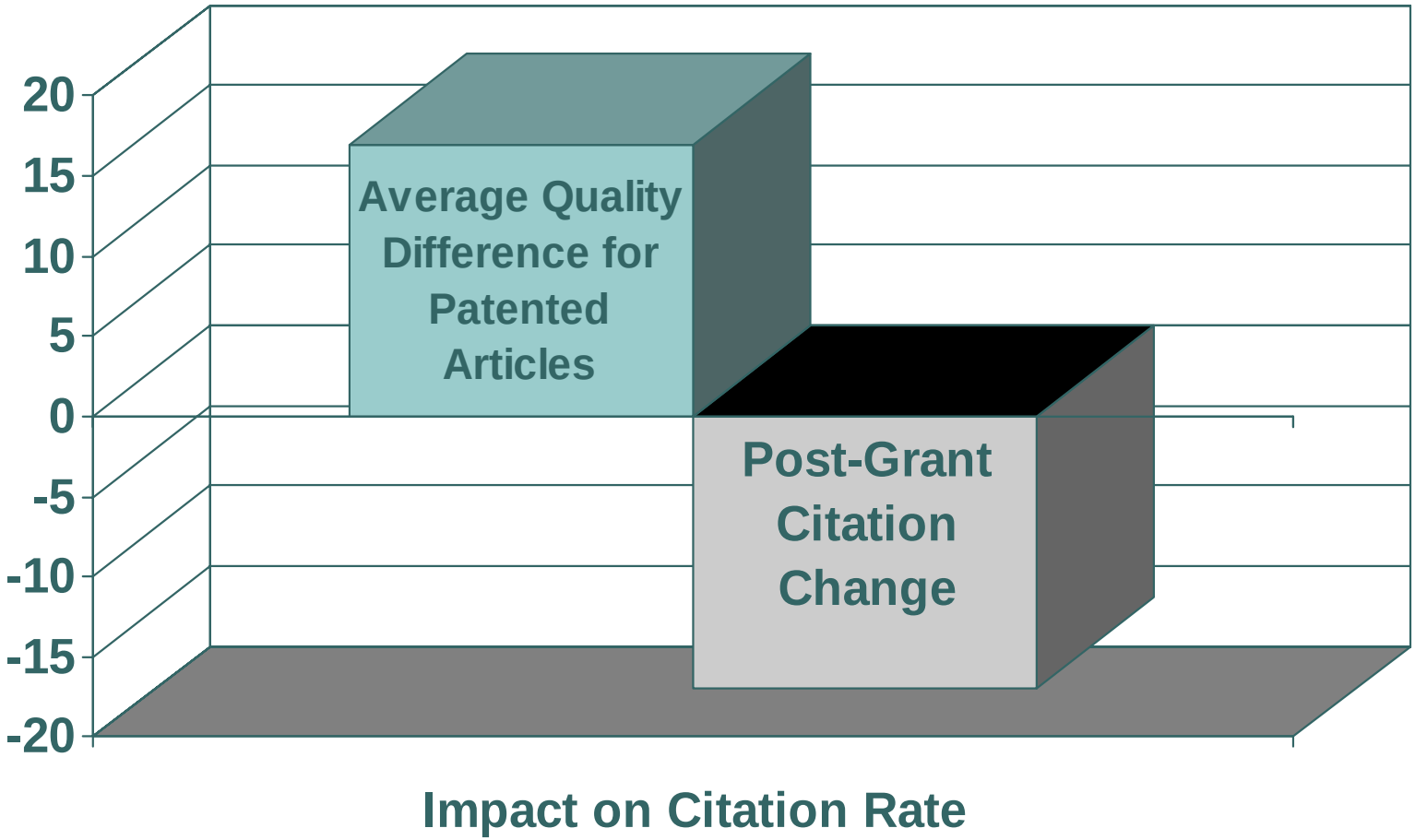
EVIDENCE

Patented Articles have a modestly higher citation rate, tend to be US based, & are more likely to include a private sector author

	NO PATENT	PATENTED
# Publications	171	169
FORWARD CITATIONS (per year)	8.96	10.04
# AUTHORS	5.76	6.03
US AUTHOR	**0.53**	**0.65**
PUBLIC SECTOR AUTHOR	**0.93**	**0.86**
PRIVATE SECTOR AUTHOR	0.25	0.38

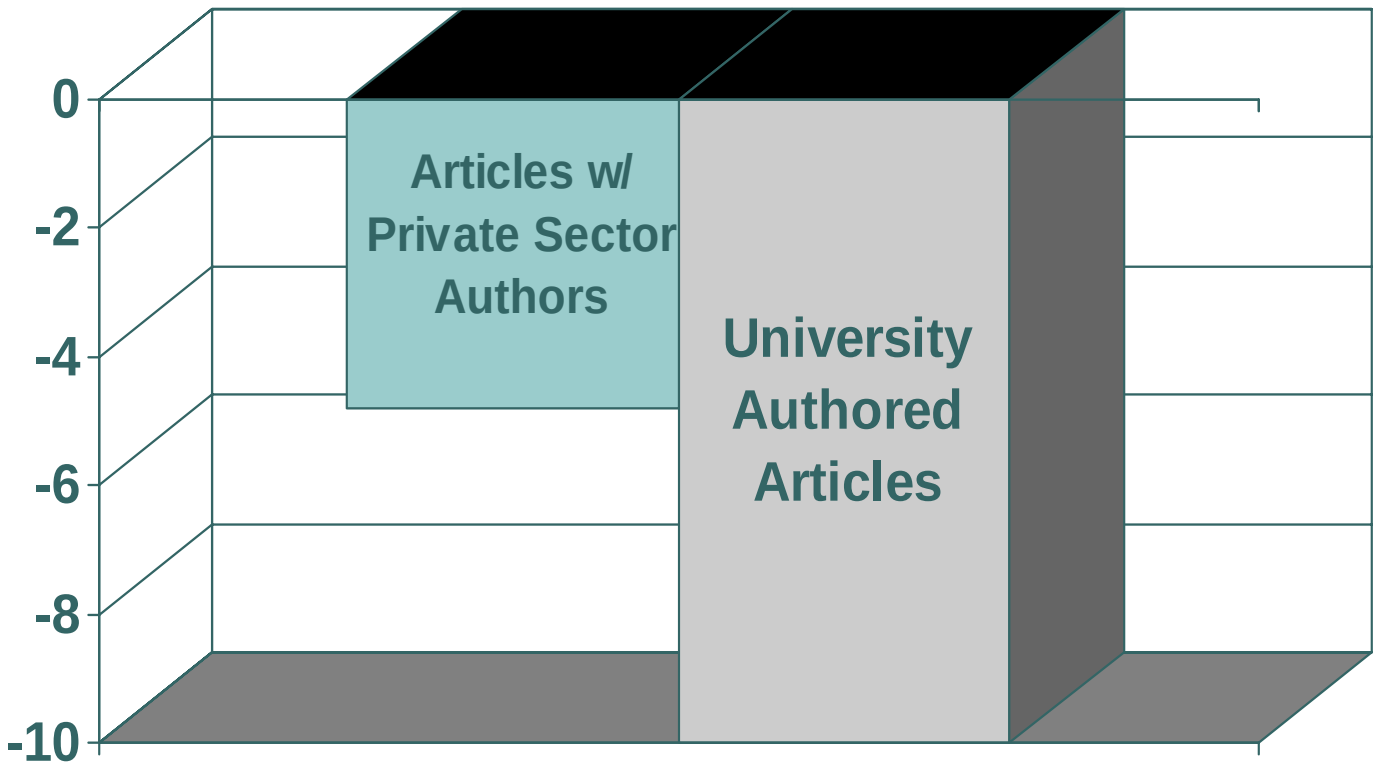
EVIDENCE

Patent Grant reduces the citation rate for the “paired” scientific article by 17%



EVIDENCE

Patent Grant impact is much higher for papers written by university researchers – patent grant is a surprise…



Citation Impact of Patent Grant, by Author Affiliation

Results Summary

- Small but robust anti-commons effect - 9%-17% decline - first systematic empirical evidence that IP “stifles scientific progress” (forward citations)
- Implies that about 1 in 6 cumulative research projects are stopped (or never started) due to IP – modest relative to the strongest claims that IP has a “devastating” impact
- Decline in forward citations suggests NOT that there is less research overall, but that scientists choose alternative (next best) projects

- Contradictory to Walsh et al. 2003, 2005? Perhaps not – effects may be subtle, shifts in agenda, collaboration, small “taxes” on the system…taken for granted

EVIDENCE

Who Stops Citing? Public versus Private Authors

Negative Binomial Specifications	Dep Var = FORWARD CITATIONS (Coeffs reported as incident rate ratios)	
PATENTED	**Public Sector Citations**	**Private Sector Citations**
PATENTED, POST-GRANT	**0.879 (0.058)**	1.045 (0.150)
Article FE	Y	Y
Age FE	Y	Y
Citation-Year FE	Y	Y

The Anti-commons effect is primarily the result of a citation decline associated with publications in which there is *at least one* public sector author....

EVIDENCE

Who Stops Citing? Where in the quality distribution

Negative Binomial Specifications	Dep Var = FORWARD CITATIONS (Coeffs reported as incident rate ratios)	
PATENTED	**TIER1 Citations**	**Lower Tier Citations**
PATENTED, POST-GRANT	**0.627 (0.158)**	0.937 (0.068)
Article FE	Y	Y
Age FE	Y	Y
Citation-Year FE	Y	Y

The Anti-commons effect seems to be mostly the result of a reduction in follow-on work at the most prestigious journals...

DISCUSSION

But what about the potential benefits – what are the effects of IP for commercial progress rather than scientific progress?

Formal IP protection provides incentives to disclose knowledge, relative to a "secrecy" regime **BUT**…growing industry perception that IP over traditionally open ideas may be problematic

FORECLOSURE - COST & CONTROL OF IP

- "they want too much for ideas that are too early stage"
- "if we know there is IP out there but we don't have access then we try and invent around – we know there will be a start-up who gets control"

TRANSACTION COSTS - COST TO NEGOTIATE IP

- "impossible to structure a contract to get follow-on IP – they want to own anything new even when we are directing the experiments"
- "it takes 14-person months to negotiate some academic contracts"
- "we have started to do collaborations with no funding – with well-funded investigators – and hope that we can develop joint IP and negotiate later"

DISCUSSION

Concluding Thoughts

- Rather than facing a tradeoff between basic v. applied research, much “scientific” research has dual application
- Encouraging dual knowledge production may be one mechanism for nurturing university & commercial research
- Patent-paper pairs helps us to understand some of the tradeoffs and rent-seeking associated with intellectual property rights

A Final Thought: Are the costs of intellectual property rights due to patents *per se*, or the *way* that patent rights are used in specific circumstances???

- Key managerial implications – how to use IP & publishing
- Key policy implications – how to optimize patenting in complex research areas e.g. stem cells