Real Impediments to Academic Biomedical Research

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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
Privatization of the biomedical “scientific commons”

- The conventional question:
  - Is the patenting of upstream discoveries conferring upon academics and their institutions both the means and incentive to exclude other academics from using research and material inputs to subsequent research?
Suggestions

- Broaden the object of analysis beyond patent-protected knowledge
- Consider the flows of research inputs more generally
- And consider the private costs and benefits of exclusionary behavior, and what drives those costs and benefits
What Flows Should We Be Talking About?

- Inputs from other researchers are essential to the process of advancing biomedical science
  - Published findings, some of which are patented
  - Unpublished data, knowledge and know-how
  - Materials
- Which of these inputs are historically “public”?
  - Published findings
    - And perhaps the rub is that published findings are now more likely to be patented
- Other inputs largely private, though there is a norm of sharing
- But ready access to all of these inputs contribute to subsequent research and the advance of science
Our questions

- Where do we see restricted access?
- And what drives such restrictions?

Consider the effect of IP in the broader context of the range of factors that might condition access to knowledge and other key inputs to biomedical research.

- So, look at full range of inputs
- And comprehensively assess role of factors—not just IP—affecting the associated flows
Starting point: A priority-based recognition-reward system

- Academics’ quests for priority of discovery and recognition for such are argued to advance dissemination of knowledge, reconciling private and public interests.
- However, reputation due to priority of discovery, as well as many of the inputs upon which such discovery builds, are private, not public goods.
- Recognition-based reward system can produce non-cooperative behaviors similar to those attributed to IP, reflecting a range of academic “appropriability strategies”.
- But what drives the decision to restrict access, and the choice of what appropriability strategies employed?
To understand what might drive restrictions on the flow of research inputs, consider the determinants of the costs and benefits of excluding others from the use of such inputs.
Private benefits of excluding

- Assuming that exclusion strengthens prospects for priority of discovery (especially follow-on discovery), benefits are:
  - Self-reinforcing academic rewards (cf. Merton, Hagstrom)
    - Reputation, status and prizes
    - Grants, students, etc.
    - Positions and income
  - Commercial rewards
    - Commercial rewards to reputation, as well as to the IP itself, can supplement academic benefits (Zucker and Darby)
Private costs of excluding

- Depends on input in question
  - IP on a published discovery
    - Hard to detect infringement and costly to enforce
  - Materials and data: Easy to exclude, and sometimes costly to provide access

- Consequences (for holder) of excluding can be costly
  - Granting agency strictures
  - Social opprobrium in a repeat game with mutual dependence
  - Dampening of complementarities associated with reciprocity of knowledge exchange
  - Loss of recognition (Furman & Stern)
Data

- 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
Have patents been used to exclude academics from using prior discoveries?

Rarely
Do academics seek permission?

- Rarely
- Only 8%, or 32 of 381 academic respondents, even 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 reported since Madey v. Duke)
  - Not related to receiving guidance from institution
- Suggesting lack of concern
  - Per interviews (Walsh et al., 2003), they just want to get their work done
Impact of “Pure IP”

- Cost of access?
  - When they do seek permission, 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”

<table>
<thead>
<tr>
<th>Effect</th>
<th>N</th>
<th>% of all respondents (N=381)</th>
<th>% of those knowingly faced w/ patent (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay (&gt; 1 month)</td>
<td>5</td>
<td>1%</td>
<td>16%</td>
</tr>
<tr>
<td>Modify</td>
<td>4</td>
<td>1%</td>
<td>13%</td>
</tr>
<tr>
<td>Abandon</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Effects of Patents

- Patents rarely lead to delays or abandoning research
- These findings have been replicated in Japan (Nagaoka, Walsh and Huang, 2007), Australia (Nicol and Nielson) and other US studies (Walsh, et al., 2003; Walsh and Huang, 2007)
- Patents on diagnostics an exception (Cho, Merz)
Why so little impact?

- Limits on practical excludability
  - Often hard for IP holder to detect others’ use
  - Even if detected, enforcement often not cost-effective, even for firms
    - Litigation expensive
    - Payoff low (injunction against others’ completing research and reasonable royalties on small-scale use)
    - Loss of added value from infringing academics’ exploring the possibilities of the technology is another cost of excluding
      - Lost access to future cooperation, which may be main cost of exclusion
- Thus, cost of excluding others from using IP on research inputs high
Contrast: Materials/Data where excludability is readily achieved
Background on “Material” Research Inputs

- Examples
  - Cloned gene, organism (mouse), cell line, protein, drug, unpublished information, etc.
- About 75% of our academic respondents requested materials in the prior two years (v. 6% for pure IP)
- Average # of requests (last 2 years)
  - 7 to other academics and 2 to industry
And why not make it yourself?

We asked: How important were each of the following in preventing you from producing the input yourself? (5-pt scale)

- Time/cost 4.34
- Lack Capabilities 3.06
- Patent 1.63 (3.2 for drug request)

Patents (other than if requesting a drug) not a major impediment to making in-house, though time or capabilities may be
Table 10. Reasons for Not Creating Research Input In-house, Academic Respondents, by Technology Requested and for Signal Proteins; and Industry Respondents.

<table>
<thead>
<tr>
<th></th>
<th>Random</th>
<th>Technology Requested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample</td>
<td>UnpInfo</td>
</tr>
<tr>
<td>Time/Cost</td>
<td>Mean</td>
<td>4.34</td>
</tr>
<tr>
<td>Lack Capabilities</td>
<td>Mean</td>
<td>3.06</td>
</tr>
<tr>
<td>Patent</td>
<td>Mean</td>
<td>1.63</td>
</tr>
<tr>
<td>Respondents</td>
<td>N</td>
<td>295</td>
</tr>
</tbody>
</table>
Excludability

- Use of others’ materials requires owner’s permission and effort, sometimes considerable.
- Consequently, excluding others from use of your materials not as costly as in case of pure IP
  - Indeed, can often be achieved passively by not responding to a request
MTA Terms, Negotiations

- Terms (requested)
  - Reach through-38%
  - Royalties-17%
  - Manuscript review-30%

- 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
MTA Terms, Negotiations

- About 40% of transfers require MTA
  - More common if request drugs (64%)
- 26% of MTAs (11% of requests) take more than one month to negotiate

- Fees
  - 93% from academic, no charge, < 2% over $1000
  - 85% from industry, no charge, 7% over $1000

- One in nine each year abandon project due to unfulfilled request
Difficulties in Accessing Tangible Research Inputs

- 19% did not receive last requested research input
- Apparent increase in recent years
  - 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%
- Delayed research (>1 month): at least 8% of requests (v. 1% for pure IP)
  - Conservative comparison since most refusals are associated with no MTA requests or negotiation
- One in nine scientists each year abandon a project due to unfulfilled request
Summary:
What input flows are restricted?

- Patent-protected published findings: Rarely
  - But, see Murray, et al., showing NIH-DuPont MOUs increased amount and diversity of follow-on research

- Materials and data: 10x

- Thus, it is flow of difficult-to-replicate, privately held property—not “pure” intellectual property—that is much more likely to be restricted.
Why Do Scientists not Provide/Receive Materials?

Can understand again in term of costs and benefits to the scientist
Costs to Excluding/Providing?

- Provision costs
  - *Response burden*
  - *Prospect of losing priority race*
    - Scientific competition

- Exclusion costs
  - *Practical excludability*
    - High costs for IP, low costs for materials
  - Social and institutional disapproval
    - Example: Non-compliance with NIH guidelines
    - Not yet examined
  - Diminished reciprocal flows and associated complementarities and reduced recognition
    - Also not examined
Benefits from Excluding Others

- Greater likelihood of commercial gain (though offset to extent that such activity detracts from academic advance)*
  - IP may play indirect role
- Additional publications (PI, students, other "insiders")
  - Not yet examined
- Grants and research support
  - For example, did the rise in NIH support through the 90’s possibly contribute to the observed increase in exclusionary practices in genomics?
    - Not yet examined
Figure 13. Reasons for not Fulfilling Requests, Academic and Industry Respondents

<table>
<thead>
<tr>
<th>Reason</th>
<th>Academics</th>
<th>Industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/Effort</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>Protect Publication</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Terms</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>Violate MTA</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Sponsor Requirements</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Protect Commercial Value</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>Liability</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Own Requests Denied</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

% High ("4" or "5")
Regressions on supplying and receiving materials
### Negative Binomial Regression for Number of Times Respondent Does Not Fulfill Research Input Requests

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 Estimate (s.e.)</th>
<th>Model 2 Estimate (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Business activity</td>
<td>0.0104* (0.0042)</td>
<td>0.0101* (0.0042)</td>
</tr>
<tr>
<td>Number of competing labs</td>
<td>0.0776* (0.0399)</td>
<td>0.0735† (0.0406)</td>
</tr>
<tr>
<td>#Publications</td>
<td>0.0750* (0.0367)</td>
<td>0.0754* (0.0366)</td>
</tr>
<tr>
<td>#Requests Received per $100K Funding</td>
<td>0.0383* (0.0186)</td>
<td>0.0341† (0.0195)</td>
</tr>
<tr>
<td>Total Funding ($100K)</td>
<td>0.0083 (0.0419)</td>
<td>-0.0017 (0.0460)</td>
</tr>
<tr>
<td>Industry funding</td>
<td>0.0058 (0.0051)</td>
<td>0.0056 (0.0052)</td>
</tr>
<tr>
<td>Drug discovery</td>
<td>0.0000 (0.0073)</td>
<td>0.0002 (0.0073)</td>
</tr>
<tr>
<td>Male</td>
<td>-0.0077† (0.0044)</td>
<td>-0.0076† (0.0044)</td>
</tr>
<tr>
<td>#Requests</td>
<td></td>
<td>0.0041 (0.0077)</td>
</tr>
<tr>
<td>Intercept</td>
<td>-2.3391** (0.5112)</td>
<td>-2.2800 (0.5211)</td>
</tr>
<tr>
<td>Dispersion</td>
<td>4.0491 (1.0038)</td>
<td>4.0415 (1.0011)</td>
</tr>
<tr>
<td>N=</td>
<td>202</td>
<td>202</td>
</tr>
<tr>
<td>Chi-square</td>
<td>148.94</td>
<td>150.76</td>
</tr>
<tr>
<td>df</td>
<td>193</td>
<td>192</td>
</tr>
<tr>
<td>Value/DF</td>
<td>0.772</td>
<td>0.785</td>
</tr>
</tbody>
</table>
### Table 4. Logistic Regressions for Receiving Most Recently Requested Material Research Input

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (s.e.)</th>
<th>Estimate (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug material requested</td>
<td>-2.2169** (0.6825)</td>
<td>-2.4983** (0.7634)</td>
</tr>
<tr>
<td>Number of competing labs</td>
<td>-0.0577* (0.0292)</td>
<td>-0.0637* (0.0308)</td>
</tr>
<tr>
<td>Academic suppliers</td>
<td>0.00651 (0.00516)</td>
<td>0.00804 (0.00539)</td>
</tr>
<tr>
<td>MTA</td>
<td>0.0124** (0.00420)</td>
<td>-0.00075 (0.00547)</td>
</tr>
<tr>
<td>Patented</td>
<td>0.00496 (0.00720)</td>
<td>-0.0116 (0.00951)</td>
</tr>
<tr>
<td>Patent status unknown</td>
<td>-0.00423 (0.00373)</td>
<td>-0.00864* (0.00430)</td>
</tr>
<tr>
<td>MTA*Patent</td>
<td></td>
<td>0.000380** (0.000133)</td>
</tr>
<tr>
<td>MTA*Don't know</td>
<td></td>
<td>0.000199* (0.000084)</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.3605* (0.5934)</td>
<td>1.5436* (0.6321)</td>
</tr>
</tbody>
</table>

N= 276 276
Chi-Square 33.72 44.95
df 6 8
p>Chi-square <.0001 <.0001
Why Do Scientists Not Provide/Receive Materials?

- Main predictors
  - **Scientific competition (# competing labs)**
  - Prior business activity
  - Burden (requests/lab dollar)
  - # Publications (eminence or opportunity cost?)
  - Whether material is a drug

- Insignificant
  - Industry funding (modest pos. effect)
  - Drug discovery
  - Patent on material
Why Do Scientists Not Provide/Receive Materials?

- 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.
Case Studies: When infrequent events may have large effects

- Even a rare result can have major social welfare impact if the technology is important enough (e.g., aviation)
- => Collected data from researchers in three fields with high scientific importance and varying levels of patenting and commercial activity
- EGF, NF-κB, CTLA-4
  - Proteins that mediate signals along pathways
  - Lots of research activity
    - Foundational paper 1500 cites for first two, around 900 for CTLA-4
  - Two are prime candidates for adverse outcomes
  - Many patents (760, 90, 60, respectively)
  - Drugs in market or clinical trials
Case Study Results

- Pure IP: Adverse effects rare, though slightly more common than base rate
  - More likely to know about patents
  - 3% had abandoned a project
- Access to materials even more problematic
  - 26-32% did not receive last request (v. 19% for overall)
  - NF-κB 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
Social welfare effects of exclusion?

- We do not know if exclusionary behavior impedes scientific advance
- Though costly for individuals who suffer from exclusion, collective impact unclear
Social welfare effects of exclusion?

- For example, may stimulate scientific diversity, offsetting diminishing returns from additional researchers working on a problem
- Ability to exclude, and increased prospect of priority, may stimulate research activity to begin with
- Cost [time, curation resources] of compliance may overwhelm benefit
  - This may be especially true in the case of mandatory pre-compliance [depositing “well-characterized” materials as condition of publication] since most materials are low value
Conclusion: Impact of “pure IP”

- Pure IP—Little impact on academic research
- “Law on the books” isn’t the same as “law in action”
  - Few are aware of patents, no less ask permission
  - Even when notified by institution to pay attention, they don’t
- Why so little attention to patents?
  - Habit formed when patents not so common?
  - Community norms and org/career incentives that value getting the science done, without paying much attention to anything that might slow it down?
  - Or, low likelihood of being sued, so no incentive to change behavior
Conclusions

- 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
  - But Bayh-Dole and IP-related legislation that fosters commercial activity among academics plays role
  - But need to weight benefits of such legislation against costs

- Consider the full range of inputs, and the range of factors affecting the costs and benefits of associated flows
  - Niu-opportunity costs of compliance, costs of sanctions/benefits
Norms of exchange

- But norms are powerful; indeed, it is surprising that there is as much exchange of materials, data, etc. as there is
  - 80-90% of requests fulfilled (depending on who you ask)
  - Over 90% of academics did not delay or limit publications even once in two years
- These “norms” may simply reflect perception of reciprocal benefits associated with exchange
Norms of exchange

- Thus, norms of exchange and the quest for priority of discovery, and recognition for such, may advance dissemination (at least via publication)—but only to a point.
- And that point changes over time and varies across fields.
- Thus, left with question of how to get a commitment of the community to new, more open and more collective, norms—and does the community really want this change in behavior?
- Redefine what counts as proper scientific results.
- Remember, we are they.
Open Questions

- What are the economic and social factors that condition the costs and benefits of sharing and exclusion of various inputs.
- And don’t lose sight of appropriability incentive effects
  - To the extent that rules regarding exchange, such as those of NIH, are enforced what are the effects on incentives to do research to begin with?
  - If we make sharing requirements too onerous, shift research away from tool production and toward exploiting others’ well-documented tools?
- What are impacts of exclusion on the pace of science?
Thank you
Appendix
Publication-related Secrecy

- Publication-related secrecy is only modestly present, with over 90% of scientists publishing fully and promptly
  - However, much more common among some groups of scientists
- Commercial activities, research ties with small firms and industry funding increase scientists’ withholding behavior, especially among senior scientists
  - Large firms may be more willing to participate in open science (see also AUTM data)
Publication-related Secrecy

- Commercial activities also have stronger impact for those doing basic research
  - This may be particular cause for concern
  - Undermining open science

- Scientific competition for priority has weak and mixed effects, sometimes decreasing secrecy and sometimes (as in case of excluding information) increasing it
Publication-related Secrecy

- Also, institutional context is important.
- Those in more entrepreneurial universities engage in less secrecy
- May be responding more to changing incentives than to shifting norms
- Suggests that a better-developed TTO can help reduce negative effects of commercial activity on open science
Table 7. Likelihood of Receiving All Requested Research Inputs, Academic Respondents, by Research Goal and for Signal Proteins; and Industry Respondents.

<table>
<thead>
<tr>
<th></th>
<th>Random Sample</th>
<th>Research Goal</th>
<th>Signal Proteins</th>
<th>Industry Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DrugDisc</td>
<td>BasicRsrch</td>
<td>Other</td>
</tr>
<tr>
<td>Academic Source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpublished Information</td>
<td>% yes</td>
<td>69</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>Gene, Organism, etc</td>
<td>% yes</td>
<td>63</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>Drug</td>
<td>% yes</td>
<td>54</td>
<td>43</td>
<td>53</td>
</tr>
<tr>
<td>Protein</td>
<td>% yes</td>
<td>62</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>Database/Software</td>
<td>% yes</td>
<td>56</td>
<td>33</td>
<td>58</td>
</tr>
<tr>
<td>Industry Source</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Unpublished Information</td>
<td>% yes</td>
<td>56</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>Gene, Organism, etc</td>
<td>% yes</td>
<td>54</td>
<td>43</td>
<td>56</td>
</tr>
<tr>
<td>Drug</td>
<td>% yes</td>
<td>44</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>Protein</td>
<td>% yes</td>
<td>53</td>
<td>67</td>
<td>51</td>
</tr>
<tr>
<td>Database/Software</td>
<td>% yes</td>
<td>55</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Respondents</td>
<td>N</td>
<td>152</td>
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