First Monday, Volume 12, Number 6 — 4 June 2007

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PEER-REVIEWED JOURNAL ON THE INTERNET

Knowledge Commons: The Case of the Biopharmaceutical Industry

by Arti K. Rai

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The biotechnology and pharmaceutical industries have long viewed patents as central to their business models. Small biotechnology firms rely on patents, often on technology that is far removed from an end product, for purposes of deterring misappropriation when they market their technology [1]. Patents also help small biotechnology firms negotiate vertical R&D alliances with pharmaceutical firms [2]. For their part, pharmaceutical firms rely on patents on end product drugs for purposes of recouping research and development costs [3]. Recent struggles over patent system reform – in which the biopharmaceutical industry has resisted the attempts of information technology firms to curtail patents – underscore the industry's attachment to patents.

A simple opposition of biopharma to information technology would be misleading, however. While they have resisted legislative reform, pharmaceutical firms have repeatedly engaged in private action to promote commons of various sorts [4]. This article describes, and compares, two types of commons creation in which pharmaceutical firms have recently engaged. In one case, the aim has been to defeat a proliferation of upstream property rights that might threaten an "anti–commons." In the other, the aim is to solve the daunting research problem of predicting drug safety and efficacy *ex ante*, before expensive failures in late–stage clinical trials or after the drug has been marketed.

Defeating the Anti–Commons

In the late 1990s, when a proliferation of property rights over upstream research threatened to create a "tragedy of the anti–commons" [5] by imposing significant licensing and royalty burdens on drug development, pharmaceutical firms promoted a number of projects to defeat these patents. One prominent effort involved single nucleotide polymorphism (SNPs), which are single base variations found in the human genome. Individually, and in inherited combinations known as "haplotypes," SNPs can be used to identify genes important for complex diseases and also to predict responses to therapeutic interventions. Pharmaceutical firms, alarmed by the prospect of biotechnology companies securing large numbers of patents on SNPs, joined together to put SNP information into the public domain. More recently, various pharmaceutical firms and the microarray manufacturer Affymetrix have been involved in patent–defeating data generation projects like the Genome Association Information Network (GAIN). The output of the GAIN project – essentially information about which haplotypes are associated with particular diseases – is being put into the public domain [6].

Solving Research Puzzles

The story of pharmaceutical firm efforts to deploy commons–based strategies in order to avert [7] anti–commons difficulties is relatively familiar. Less familiar are recent commons–type

efforts to address the prominent problem of declining productivity in the pharmaceutical industry. Like the SNP Consortium, these recent efforts involve horizontal collaboration among pharmaceutical firms. Unlike the SNP Consortium, however, the goal of these consortia is not defeating patents.

Declining productivity has been much discussed in the popular press, in scholarly journals, and in government white papers. But the numbers reported, which usually focus the declining number of "new chemical entities," actually understate the magnitude of the problem. A new chemical entity is simply a molecule that is structurally quite different from prior molecules. It may target the same biological/disease pathway as prior molecules (and hence not necessarily represent a significant therapeutic advance over these prior molecules). More important than new chemical entities are drugs that actually target new disease pathways. Here the news is particularly disappointing. According to one recent report, over the last few years, an average of only three drugs against novel biological targets (proteins involved in disease progression) has reached the market in any given year [8]. This compares with an estimated 3,000 druggable targets in the human genome [9].

The productivity problem can be traced in part to ineffective testing of drug safety and efficacy before drugs enter clinical trials. Specifically, the lack of early attention to safety and efficacy–related characteristics of proposed molecules has resulted in growing numbers of pipeline failures, including costly failures at late stages of clinical testing or even after FDA approval for commercial marketing [10]. Firms have sometimes designated a "lead" compound, and assembled a full team around it, solely on the basis of the compound having shown significant activity (affinity and selectivity) in a high–throughput laboratory screen against an assay containing a target protein [11].

In the case of safety and efficacy, pharmaceutical firms are beginning to heed the advice of industry analysts that they "fundamentally review R&D business models." [12] Specifically, in at least two consortia, they have recognized that an optimal level of inquiry into safety may require knowledge not contained within the boundaries of a single firm.

To the extent that pharmaceutical firms can, through collaborative efforts, find standard early biological signs (also known as biomarkers) of a drug's toxicity, this information could be used by all pharmaceutical firms for a variety of cost–reducing functions, including expediting preclinical drug safety evaluation, providing early indicators of clinical safety, and "trouble–shooting" compounds that fail preclinical drug safety testing [13]. Indeed, to the extent that a particular biomarker test were ultimately approved by the Food and Drug Administration as a reliable indicator of safety, such a test might be considered an industry standard around which all competing firms could converge [14].

In one of these consortia, the Toxicogenomic Cross–Validation Consortium (TCC), all of the major pharmaceutical firms have committed to sharing internally developed laboratory methods that predict the safety of new treatments. The TCC agreement sets up a commons that relies heavily on a non–profit trusted intermediary, Critical Path, of which the FDA is a founding member. Critical Path (and/or a Director selected by Critical Path) collects membership fees from pharmaceutical firm participants, coordinates the selection of research projects, and manages the flow of any confidential information. Critical Path also owns patent rights to any intellectual property generated. It is obligated to license these patents to all comers on commercially reasonable terms.

While the TCC focuses on tests for safety, the recently formed Biomarkers Consortium aims to encompass research that identifies good biomarkers of both drug safety and efficacy [15]. Like the TCC, the Biomarkers Consortium includes all of the major pharmaceutical firms. In the case of the Biomarkers Consortium, each participant in a particular research project is entitled to a nonexclusive license to all intellectual property created from that project.

The Impact on Small Firms

Commons that defeat patents look quite different from commons that aim to create standard biomarkers. In both cases, however, the ultimate result is arguably detrimental to small biotechnology firms. In the first case, the explicit aim is undermining the profit niche for these small firms. In the second, undermining small firms is a collateral consequence of the fact that developing standard biomarkers may require horizontal collaboration with a standard–setting component, as opposed to the usual sorts of technology markets and vertical alliances.

Should we worry about undermining the role of small biotechnology firms? Economists often champion small firms and technology markets as more likely to produce innovation than large, vertically integrated firms. However, at least one of the reasons for economists' endorsement of markets is the assumption that such markets will produce relatively unencumbered information flow. If this assumption is incorrect, or if large firms operate in a commons that promotes information flow, the virtues of small firms are not as apparent. In the case of the anti–commons concern, we don't know whether significant impediments to information flow would have emerged absent strenuous efforts by large firms to defeat patents. But it is certainly possible. In the case of horizontal collaboration to create standard biomarkers, we can perhaps be even more sanguine about the commons strategy. The biomarkers problem may be sufficiently intractable that it can only be addressed through sustained collaborative efforts made by large firms over a period of time.

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Notes

1. *See generally* Ashish Arora, Andrea Fosfuri, and Alfonso Gambardella, 2002. *Markets for technology: The economics of innovation and corporate strategy*. Cambridge, Mass.: MIT Press.

2. D. Gordon Smith, *The Exit Structure of Strategic Alliances*, 2005 U.Ill.L.Rev., 303, 307 & n. 29 (noting that in a sample of 125 genomics alliances, 113 involved the licensing of intellectual property by smaller technology firm); *cf.* Joshua Lerner and Robert P. Merges, *The Control of Technological Alliance: An Empirical Analysis of the Biotechnology Industry*, 46 J.Indust. Econ. 125 (1998) (noting that biotechnology firms with more intellectual property rights exercised more control over the alliance).

3. Empirical studies have documented pharmaceutical firms' reliance on patents. *See, e.g.* Wesley Cohen, *et al.*, Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not), NBER Working Paper No. 7552 (2002).

4. For purposes of this article, I define commons as encompassing contexts in which information is available on standard, non–discriminatory terms either to all comers or to the group included within the commons. Thus the scope of the term can include the placement of information in the public domain.

5. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, Science, May 1, 1998, at 698.

6. See http://www.fnih.org/GAIN2/home_new.shtml, accessed 4 June 2007

7. Ajay Agarwal and Lorenzo Garlappi, "Public Sector Science and the Strategy of the Commons," at http://www.rotman.utoronto.ca/Ajay.Agrawal/Documents/Agrawal-Garlappi-SoC.pdf, accessed 7 June 2007

8. BP Zambrowicz and AT Sands, *Knockouts Model: the 100 Best-Selling Drugs – Will They Model the Next 100*? Nature Rev Drug Discov 2003, 2:38–51.

9. AP Russ and S Lampel, *The Druggable Genome: An Update*, 10 Drug Discovery Today 1607 (2005). Under the definition used in this article, druggability is defined by whether the protein is capable of binding a chemical compound that might be absorbed orally. This definition does not address the question of whether the binding will yield a result that is biologically useful.

10. *Ibid.*

11. *See, e.g.*, Konrad H. Bleicher, Hans–Joachmin Bohm, Klaus Muller, and Alexander I. Alanine, 2(5) *Hit and Lead Generation: Beyond High–Throughput Screening*, NATURE REVIEWS DRUG DISCOVERY 369, 370 (2003) ("It was not uncommon for a single [hit] compound to be considered a 'lead' structure.")

12. *See* DATAMONITOR, ADDRESSING PHARMA'S R&D PRODUCTIVITY CRISIS: TECHNOLOGICAL AND STRATEGIC INITIATIVES TO IMPROVE CORE DRUG DISCOVERY CAPABILITIES (2004).

13. *See* Toxicogenomic Cross–Validation Consortium Agreement, Section 2.1 (Statement of Purpose) (agreement on file with authors).

14. For a discussion of the challenges that standard–setting might pose in the pharmaceutical industry, *see* Arti K. Rai, *Collaboration, Innovation, and the Firm* (working paper).

15. The Biomarkers Consortium also plans to identify biomarkers for early disease detection. That research goal is not directly relevant here.

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First Monday, volume 12, number 6 (June 2007),
URL: http://firstmonday.org/issues/issue12_6/rai/index.html