

Blurred Boundaries: Tensions Between Open Scientific Resources and Commercial Exploitation of Knowledge in Biomedical Research^{*}

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Introduction

Biomedical research drives some of the most visible and significant sectors of the “knowledge economy.” High margin, high growth, high wage, knowledge-intensive industries such as pharmaceuticals, diagnostics, and medical devices are supported by a global biomedical research budget that likely now exceeds \$100 billion per year. In pharmaceuticals in particular there have been very handsome social and private returns to R&D and knowledge creation — generous returns to investors have been accompanied by substantial declines in mortality and other health indicators across a wide range of diseases and health problems that correlate with the number of new drugs introduced.¹ But the breathtaking scale of these investments (which after all, have opportunity costs) naturally raises questions about the efficiency with which new biomedical knowledge is created and used. And after decades of building on advances in basic science to create a steady stream of new drugs responsible for remarkable economic and medical gains in the treatment of conditions such as heart disease, stomach ulcers, and depression (and equally remarkable gains for their stockholders), pharmaceutical companies now face a “productivity crisis.”

Against a backdrop of rapid advances in the industry’s science base (marked by major scientific achievements such as completing the sequencing of the human genome) as well as in supporting technologies such as instrumentation and computing, the pipeline of new products appears to be shrinking. In 2002 the FDA approved only 17 new molecular entities for sale in the US — a disappointing fraction of the 15-year high of 56 NMEs approved in 1996, and the lowest since 1983.² In 2003, the FDA approved 21 NMEs, of which only nine were designated as “significant improvements” over existing drugs.

Alarming, this decline occurred despite a substantial increase in R&D: between 1995 and 2002 R&D expenditures by US-based pharmaceutical companies roughly doubled to about \$32 billion.³ Similar trends can be seen in worldwide statistics, where the annual number of New Active Substances approved in major markets fell by 50% during the 1990s while private sector pharmaceutical R&D expenditures tripled to \$47 billion.⁴ Numbers such as these have prompted headlines in the popular press and in trade journals referring to “dry,” “weak,” or “strangled” pipelines, and suggestions that the industry’s historically successful business model is “broken” — with dire consequences for investors, who can expect “permanently lower multiples,” and the

¹ Lichtenberg, F. “The impact of new drug launches on longevity: evidence from longitudinal, disease-level data from 52 countries, 1982-2001.” NBER Working Paper No. 9754, 2003.

² FDA CDER website <http://www.fda.gov/cder/rdmt/pstable.htm>

³ PhRMA “Pharmaceutical Industry Profile, 2002”

⁴ EFPIA “The Pharmaceutical Industry in Figures, 2003 Update”

taxpayers, patients, and insurers who will have to foot an ever-higher bill if they want to maintain the pace of technological progress in the industry.

These concerns about productivity are almost surely overblown: if past experience is any guide, the recent surge in R&D spending should generate a commensurate increase in new drug approvals over the next three to ten.⁵ Underlying trends in “true” research productivity (in the sense of the relationship between current R&D expenditures and the stream of future benefits attributable to them) are very difficult to measure. The long and complex process of drug development and the significant role of un-priced knowledge spillovers make it remarkably difficult to unambiguously attribute specific outputs to specific inputs. Today’s new drugs are the result of R&D expenditures stretching back decades into the past, and undertaken by many different institutions. Conversely, today’s R&D will likely contribute to output far into the future, both directly in the form of new products, and indirectly in the form of more efficient research. Simple comparisons of current output with current inputs are therefore uninformative.

But skepticism about what can be inferred from easily observable statistics should not distract from the imperative to understand underlying productivity trends, and their sensitivity to policy changes. Given the extraordinary level of resources committed to medical research, “bang for the buck” is a serious concern. Notwithstanding impressive advances on many fronts, technological progress has been disappointing in other areas. No new broad-spectrum antibiotics have been marketed in almost 40 years, and many forms of cancer, as well as chronic diseases and disorders such as diabetes, Alzheimer’s, Parkinson’s, and schizophrenia, still lack effective and well-tolerated treatments.⁶ Continuing growth in R&D spending represents investment in overcoming these scientific challenges, but this upwards trajectory will only be sustainable if it can be paid for, and as increased research spending collides with ever-intensifying pressure to contain health care expenditures, the factors driving the efficiency of the drug discovery and development process are being brought into sharp focus. Chief among these are the institutions governing creation and use of biomedical knowledge — intellectual property rights, channels for knowledge transfer, and processes for allocating resources and rewarding effort in the research enterprise. These institutions have undergone substantial transformation and realignment in recent decades, but the long-term consequences for system performance of these changes,

⁵ Record numbers of new drug candidates have entered the pipeline in recent years, with more than 3200 in the period 2001-2003 alone. (PJB Publications “Pharmaprojects Annual Review, May 2003.”)

⁶ Shamefully, very little research has been directed towards tropical diseases such as malaria whose burden falls almost entirely on the populations of the world’s poorest countries. See Lanjouw, J. and Cockburn, I. “New Pills For Poor People? Empirical Evidence After GATT.” *World Development*, 2001, 29(2):265-289.

particularly the blurring of distinctions and boundaries between non-commercial and for-profit research, remain poorly understood.

System performance versus component performance

Biomedical research is conducted by a variety of organizations — for-profit companies, non-profit institutes, government labs, universities, and hospitals — linked together in a complex industry. In thinking about the impact of changes in institutions governing knowledge creation and exchange on social returns to investment in biomedical R&D, it can be helpful to draw a distinction between system performance and component performance — that is, between the efficiency or productivity of specific entities and the efficiency of interactions among them.

In general, the productivity of any organization (whether it be a university lab or a drug company) will be driven by factors such as the quality of inputs to production and the nature of the production activity it is engaged in, as well as managerial factors such as the types of incentives used to motivate its employees, and the processes and organizational structure used to allocate resources. In the case of commercial pharmaceutical research, these factors are reasonably well understood. For drug companies, output of new drugs is a function of “shots on goal,” i.e., the number of lead compounds generated or acquired, and the probability of them making it through pre-clinical and clinical development phases. Studies have shown that, at least in the 1980s, the efficiency of this process was related to the size and diversity of the company’s research effort, its reward systems, and the nature of internal decision-making and distribution of authority.⁷ Less is known about the factors driving the productivity of academic or government research.⁸

For the industry as a whole, however, productivity is a function of both the efficiency of its component institutions and of the industry structure — that is to say, the numbers and types of institutions, the allocation of effort among them, and the nature of relationships between them. During the past 30 years the pharmaceutical industry has seen some profound structural changes,

⁷ Henderson, R. and Cockburn, I. “Measuring Competence: Exploring Firm Effects in Pharmaceutical Research.” *Strategic Management Journal*, 1994, 15, pp. 63-84, and Henderson, R. and Cockburn, I. “Scale, Scope, and Spillovers: Determinants of Research Productivity in the Pharmaceutical Industry.” *RAND Journal of Economics*, 1996, 27(1), pp. 32-59

⁸ Though see, for example: Arora, A. David, P. and A. Gambardella “Returns to Scientific Reputation: Funding of Research Projects by the Italian CNR.” *Annales des Economie et des Statistiques*, 1998, No. 49/50, pp. 164-198; Allison P.D., Long J.S. (1990), “Departmental Effects on Scientific Productivity”, *American Sociological Review* 55, pp. 469-478, Geuna, A. *The Economics of Knowledge Production: Funding and the Structure of University Research*. Cheltenham: Edward Elgar, 1999; and Breschi, S., Lissoni, F. and Montobbio, F. “The Scientific Productivity Of Academic Inventors: New Evidence From Italian Data”, *Economics of Innovation and New Technology*, forthcoming 2005.

that are tightly linked to evolving institutions for creating, managing, and exchanging knowledge. These changes have important implications for system performance.

The changing structure of the pharmaceutical industry

The post-war evolution of the pharmaceutical industry can be characterized as a process of progressive vertical dis-integration and growing complexity.⁹

In the 1960s and 1970s, the industry could be seen as having a fairly simple binary structure with a clear division of effort between upstream not-for-profit institutions, which did curiosity-driven basic research, and downstream for-profit companies that did market-oriented applied research. In the for-profit sector, almost all firms were large and fully integrated, from drug discovery, through clinical development, regulatory affairs, manufacturing, and marketing. Most commercial drug discovery activity was conducted in-house, and at least in the early part of this period was dominated by large scale “random screening” programs with limited requirements for deep knowledge about fundamental physiological processes at the molecular level. Licensing activity was driven largely by downstream concerns: rights to sell drugs that were already approved (or were in the late stages of clinical development) would be acquired in order to maintain efficient levels of utilization of manufacturing or marketing assets, or, in the international context, to take advantage of local knowledge and access to regulators and distribution channels. Upstream technology was largely acquired either “for free” by reading journals and attending conferences, or by purchasing tangible inputs and services, such as instruments or highly skilled graduates.

In this industry structure, pharmaceutical firms appropriated returns from R&D through a combination of extensive patenting of production processes and end products, proprietary know-how, brands, regulatory barriers to entry, and favorable product market conditions. Most of these firms were long lived, mature organizations, tracing their roots back many decades, often to the 19th Century chemical industry. Their large and sustained investments in R&D, marketing assets, and human and organizational capital were largely financed from internal cash flow. Competitive advantage was driven by firms’ ability to effectively manage product market interactions with regulators and end users, and to “fill the pipeline” with a steady succession of internally developed blockbuster drugs. The productivity of R&D performed by these firms appears to have been driven to a great extent by economies of scale and scope in conducting research, efficient

⁹ See, for example, Gambardella, A. *Science and Innovation: The U.S. Pharmaceutical Industry During the 1980s*, Cambridge: Cambridge University Press, 1995; Cockburn, I., Henderson, R., Orsenigo, L. and Pisano, G. “Pharmaceuticals and Biotechnology.” Chapter in D. Mowery (ed.) *U.S. Industry in 2000: Studies in Competitive Performance*, National Research Council, Washington DC, 1999, pp. 363-398;

allocation of resources in internal capital markets, and the ability to capture internally and externally generated knowledge spillovers.

In the upstream not-for-profit sector, taxpayers (and to some extent, philanthropists) supported curiosity-driven research conducted at cottage industry scale inside government labs, universities, research institutes, and teaching hospitals. Legal constraints and a strong set of social norms limited commercial or contractual contacts between the world of open science and pharmaceutical firms in important ways. Resource allocation in the not-for-profit sector was driven by peer-reviewed competition for grants on the basis of scientific merit and the reputation of individual researchers. The importance of establishing priority and reputation drove early and extensive publication of results, and social norms (and requirements of granting agencies) promoted routine sharing of research materials. Not-for-profit researchers concentrated largely on fundamental science and filed very few patents.

This is, of course, a gross oversimplification. Many drug companies invested significant resources in “blue sky” basic research, and specialist for-profit research boutiques generated and sold technology to large firms. Public sector institutions conducted screening programs for drug candidates, and many academic researchers had close financial and contractual links with drug companies through individual consulting arrangements and institutional research grants and contracts.¹⁰ Funding priorities reflected political pressure, intellectual fashions, and the dynamics of the Matthew Effect, as well as pure scientific merit.¹¹ Importantly, the “waterfall” model of vertical knowledge spillovers, with a one-way flow of ideas and information down a gradient running from upstream basic science to downstream applied research and clinical practice, appears to have been only partially true. Nobel-winning work in basic science was done in for-profit labs, and non-profit institutions were an important source of data, techniques, and expertise in late-stage drug development, epidemiology, and post-marketing follow-up. Clear institutional boundaries between academic and commercial science did not prevent significant movement of ideas, candidate molecules, research materials, research results and individuals back and forth across the for-profit/not-for-profit divide.

Notwithstanding these caveats, it is still possible to summarize the vertical structure of the industry in this era as being essentially binary, with a clear distinction drawn between upstream open science, and a downstream commercial sector dominated by large, highly integrated firms. Since the early 1980s, industry structure has become considerably more

¹⁰ These ties have a long history in the pharmaceutical industry, see MacGarvie, M. and Furman, J. “Early Academic Science and the Birth Of Industrial Research Laboratories in the U.S. Pharmaceutical Industry”. Mimeo, Boston University School of Management, 2005.

¹¹ “Unto every one that hath shall be given, and he shall have abundance” Matthew 25:29.

complex. After decades of stability and consolidation, in the late 1970s the for-profit side of the industry began to experience significant entry as an intermediate sector emerged between academic research institutions and Big Pharma. By the mid 1990s several thousand biotechnology ventures had been launched, and several hundred had survived to reach sufficient scale to be an important force in the industry. Existing vertical relationships were disrupted and reformed, with consequences that are still far from clear. These new companies straddled the historical divide between for-profit and not-for-profit research. Though they were, for the most part, overtly profit-oriented, they also had much tighter and more explicit links to non-profit research institutions, with close personal, geographical, cultural, and contractual ties to universities, research institutes, and government labs. Academic scientists played a particularly significant role in the founding of these companies, either moving out of academic employment or participating actively in both worlds.¹²

Many of the smaller pharmaceutical firms have disappeared as leading players have merged and consolidated, and worldwide research activity has gravitated towards a handful of locations.¹³ Relationships between the non-profit and for-profit sectors of the industry have changed dramatically, and a new class of competitors — the biotechnology companies — has entered the industry at the interface between academic and commercial research. Some “product” biotechnology companies have entered the industry as direct horizontal competitors to established firms, intending to realize profits by using their command of new techniques and insights from molecular biology to develop products that will be sold to end users. Other “tool” companies have inserted themselves into the industry value chain at the interface between academic research and the downstream for-profit pharmaceutical firms, with a business model based on licensing or selling leading edge knowledge, research tools, or intellectual property to companies focused on less science-intensive clinical development, manufacturing, and marketing.

By taking over a certain amount of research activity from both upstream and downstream entities, these new entrants have forced some important adjustments in university-industry relations and ushered in a new “partnering” mode of research. Large incumbent firms with marketing, manufacturing, regulatory affairs, and clinical development capabilities now rely heavily on research tools and candidate molecules acquired from upstream sources through

¹² Zucker, L., Darby, M. and Brewer, M. “Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises.” *American Economic Review*. March 1998; 88(1): 290-306

¹³ See Furman, J., Kyle, M., Cockburn, I. and Henderson, R. “Knowledge spillovers, geographic location, & the productivity of pharmaceutical research.” Forthcoming, *Annales d'Economie et de Statistique*. 2005.

complex contracts and collaborative agreements. Between 25% and 40% of Big Pharma's sales are now reported to come from drugs originated in the biotech sector.¹⁴

Factors driving structural change

This vertical dis-integration appears to have been driven by a number of interlinked economic and legal forces. Perhaps the most salient of these are the developments in law and administrative practice that have brought much of molecular biology and the life sciences within the ambit of the patent system. Patents are now routinely awarded on fundamental scientific knowledge such as genetic sequence information, cell receptors, and fundamental metabolic pathways. This extension of exclusion-based intellectual property into the domain of basic science means that market-based competition based on proprietary rights over biomedical knowledge now plays a very significant role in determining the overall rate and direction of technological progress. Pharmaceutical and biotechnology companies have become important participants in basic biomedical research while, in parallel, universities and other non-profit entities have become enthusiastic participants in the patent system.

Interestingly, at the same time that exclusionary property rights have become a significant feature of basic research, aspects of classic "Mertonian" rules and norms governing production and exchange of knowledge in "open science" have diffused into commercial research. Many commercial entities increasingly manage internal and external production and exchange of knowledge in ways that closely resemble academic research, emphasizing collaboration, interaction, peer review, and publication.¹⁵ And as biology has become increasingly focused on computational methods and digital data, the anti-exclusionary mechanisms of open source software development are playing an increasingly important role in the development of databases and software tools used in bioinformatics.

This "creeping propertization" of basic biomedical research is not the only way in which boundaries between for-profit commercial research and academic science have been breached and blurred. A number of other legal and economic changes have played an important role, particularly the passage of the Bayh-Dole Act, the Stevenson-Wydler Act and other legislation enabling and encouraging commercialization of publicly funded research,¹⁶ together with the rise

¹⁴ Source: CMR International, cited in "The Pharmaceutical Industry In Figures" (Brussels: EFPIA, 2000).

¹⁵ Cockburn, I., Henderson, R., and Stern S. "Balancing Incentives: The Tension Between Basic and Applied Research." NBER Working Paper No. 6882, January 1999. Cockburn, I., Henderson, R., and Stern S. "The Diffusion of Science Driven Drug Discovery: Organizational Change in Pharmaceutical Research." NBER Working Paper No.7359, September 1999;

¹⁶ Mowery, D., Nelson, B., Sampat, B., and Ziedonis, A. "The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act", *Research Policy*, 2001, (30): 99-119.

of a venture capital industry (and ultimately a stock market) that was (periodically) willing to provide substantial amounts of capital to inexperienced science-based companies with limited prospects of short term profitability and enormous unresolved technology risk. Venture funding of biotechnology is closely associated with general increases in the supply of venture capital as a result of the relaxation in 1979 of the “prudent man rule” governing pension fund investment decisions, although other developments in the capital markets have contributed to the rise of the biotechnology sector. New financial technologies have been developed for pricing and managing risk, and at least in the US, there appears to have been a significant increase in investors’ tolerance for risk, as evidenced by the falling equity premium imputable from stock market returns.

Equally significant, however, are the organizational and managerial impacts of the changes in the technology of pharmaceutical research that arose from the revolution in life sciences. One important factor was the rapid increase in the cost and scale of basic research projects. Another was that drug discovery became progressively more science-intensive, with increased emphasis on understanding and exploiting deep understanding of physiology and disease states at the molecular level. As “rational drug design” took center stage in the late 1980s, changes in the nature of research activity were accompanied by complementary changes in the internal structure and incentives of commercial R&D organizations. Drug companies began to look more like universities and behave more like universities, with increasing emphasis on publication, and individual collaboration across institutions.¹⁷ These changes in business practice were accompanied by increased willingness to consider acquiring external sources of technology in the form of research projects conducted as joint ventures or strategic partnerships. Thus an environment was created in which specialist research firms could expect if not to prosper, at least to survive. At the same time the growing costs and complexity of academic research projects forced successful scientists to acquire managerial and organizational skills — making them better equipped and more favorably disposed towards business ventures, and looking much more like entrepreneurs and managers to outside investors or business partners. As ever-increasing resource requirements, and growing societal pressure to justify their budgets pushed universities and other government funded institutions to become more tolerant of “just-off-campus” commercial activity, or even to actively encourage it, this rising cadre of scientist-entrepreneurs were well positioned to take advantage of the opportunities created.

¹⁷ Cockburn, I. and Henderson R. “Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery.” *Journal of Industrial Economics*, 1998, 46(2), pp. 157-182.

Consequences for industry research performance

The implications of this new industry structure for long-term research performance are far from clear. Standard economic analysis holds that strong property rights, competition, and the profit motive tend to result in socially optimal allocation of resources. To the extent that vertical dis-integration of pharmaceutical research promotes specialization, competition, and risk-taking, and substitutes market signals for bureaucratic allocation of research funds, there may therefore be very large gains in efficiency. On the other hand, the nature of the research process — and particularly the central role played by creation and exchange of scientific knowledge in the economics of the industry — provides less cause for optimism. Arguments in favor of specialization and market exchange presume a world with perfect information, competitive markets, and no transactions costs. Stepping away from this benchmark, and focusing for the moment on commercial knowledge production, it has long been clear that large vertically integrated firms are an efficient response to a number of real world problems. These include limited ability to diversify risk where capital markets are incomplete or imperfect, the presence of transactions costs when complete contracts cannot be written, problems in capturing spillovers or other externalities, and a variety of familiar difficulties that arise from flaws in markets for knowledge. In fact, there is a strong presumption that vertical integration is the first best solution to economic problems such as those encountered during commercial drug discovery and development, i.e., financing and managing multiple projects that are long-term, risky, complex, costly to monitor, require substantial project-specific unrecoverable investments, and have shared costs and vertically complementary outcomes.¹⁸ Here, problems with transactions costs, pricing, and access to information are minimized by internalizing decisions within the firm and allocating resources through an internal capital market.

Under the old bipartite industry structure, therefore, research performance reflected a world in which most exchanges of scientific knowledge were not explicitly priced, and patents excluded industry participants only from the final product market. In sharp contrast, in today's industry exchange, access, and use of knowledge is governed by an active market for licenses and partnership deals. Prices in this market play an important role in allocation of resources in commercial research, and system performance thus relies critically on the market for upstream research generating the “right” signals for downstream resource allocation and for further investment in upstream knowledge creation.

¹⁸ See Milgrom, P. and Roberts, J. *Economics, Organization & Management*. Englewood Cliffs: Prentice Hall, 1992.

“Transactional optimists” believe that this market works well, arguing that potential distortions arising from informational asymmetries, thin markets, bargaining problems, and other sources of market failure can be minimized by creative use of contractual provisions in license agreements and partnership deals.¹⁹ Markets for knowledge are, however, notoriously inefficient due to the unique properties of knowledge as an economic good, and in the context of vertical agreements in biomedical research there are particularly good grounds for skepticism about the ability of these markets to “get the prices right.”

Consider the stylized case of a small biotech company that holds a valid and enforceable patent on a gene coding for a target, whose claims will be infringed by any attempt by a downstream pharmaceutical company to develop a marketable drug. The pharmaceutical company, in turn, blocks the biotech company’s access to the end-user with its own product or use patents. The two parties are clearly better off if they can agree on a license or partnership deal that divides profits between them.

Bargaining is likely to be easy and efficient when both participants can agree on the payoff, neither has an informational advantage, and both are equally risk averse. However, in this context these assumptions are surely violated, and it is quite likely that the two firms will find it hard to agree. Experience suggests that the biotech company will tend to have over-inflated expectations of the value it brings to the table, while the pharmaceutical company will be in a stronger bargaining position given its greater size, wider range of other opportunities, and potentially a credible threat to invent around the biotech company’s patent — or litigate it to death. Both sides will likely have plenty of private information (the pharmaceutical company will be better informed about market prospects and product development risks, while the tool company will be better informed about its technology) and incentives to act opportunistically on that information, raising the costs of drawing up a contract, or inducing the parties to make defensive investments.

To cap it all, imperfect capital markets mean that biotech company will not infrequently be facing a very real threat of bankruptcy. Outside investors’ interest in biotechnology periodically waxes and wanes, and when the “funding window” is closed, cash-poor companies are easily pressured into entering an agreement on adverse terms: a low fixed fee rather than a high reach-through royalty rate, plus exclusivity provisions that limit its ability to sell its technology elsewhere or exploit it through internal development. Add a little more realism to this

¹⁹ Arora, A. Fosfuri, A. and Gambardella A. *Markets for Technology: Economics of Innovation and Corporate Strategy*. Cambridge, MA: MIT Press, 2001; Gans, J. and Stern, S. “Incumbency and R&D Incentives: Licensing the Gale of Creative Destruction.” *Journal of Economics and Management Strategy*, 2000, 9:485-511.

picture by introducing the costs of coordinating contracts with multiple upstream technology vendors, potential anti-commons problems created by overlapping rights, and uncertainty about the ultimate validity and enforceability of broadly written patents, and it becomes increasingly difficult to be optimistic about efficient outcomes being reached in licensing negotiations.

There are, of course, a number of arguments in favor of vertical specialization supported by strong, broad patents on upstream basic technology. First, basic technologies tend to have broad applicability, often in ways that are very difficult to anticipate. To the extent that markets for upstream stimulate development of commercially relevant tools, and competition forces down their prices, there may be faster and more widespread impacts on downstream product development. Development of tool technologies in secret is undoubtedly socially costly, and therefore the prompt disclosure of early stage tools or platform technologies in patent applications may also promote knowledge spillovers and raise social returns.

Second, relying on incumbent firms to develop tools may result in delayed development. Incumbents may have incentives to slow down technology development to avoid cannibalizing existing products. They may also shelve or abandon new technologies that threaten other sources of quasi-rents. Limiting proprietary rights in early stage technologies can reinforce the competitive position of incumbents. The “Strategy of the Commons” argument suggests, for example, that incumbent firms can deter entry into their markets by putting new technology in the public domain.²⁰ Entrants are thus denied the opportunity to establish patent rights, sharply limiting their ability to raise capital and establish a proprietary market position. The SNP Consortium has been suggested as an example of this dynamic in action. (An interesting variant of this strategy is to sponsor university research, but only on condition that it be licensed non-exclusively.)

Third, while large, vertically integrated firms minimize some costs, they may also raise others. Gains from integration come at the cost of creating internal bureaucracies to coordinate and control activity. These systems are costly to maintain and may cause, rigidity, organizational “slack” and a bias towards conservative decisions — limiting the ability of these firms to respond to new technological opportunities. It is widely believed that new enterprises are faster at recognizing and developing new technologies, and they may also enjoy cost advantages in doing research arising from specialization, flexibility, and “focus.”

Fourth, the prospect of obtaining broad patent rights in early-stage technologies may stimulate socially valuable investment in R&D — and further rapid innovation as second movers

²⁰ Agrawal, A. and Garlappi, L. “Public Sector Science and the Strategy of the Commons (Abridged)” *Best Paper Proceedings, Academy of Management, 2002*

invent around the first round of patents on a new technology. Models of sequential innovation highlight the importance of balancing the division of rents between first movers and second movers for equilibrium levels of R&D, and reluctance to grant patent rights to early innovators may therefore have deleterious effects.

Last, though the “gold rush” and “land grab” metaphors commonly employed to describe upstream patenting raise the specter of socially wasteful rent dissipation, such “racing” behavior may also have beneficial effects. Competitive races finish faster. Falling behind in a protracted race may cause weak competitors to drop out, weeding out bad ideas or poorly conceived enterprises. Indeed, some game theoretic modeling of technology races suggests that in some circumstances social surplus can be raised by awarding patents early rather than late in the development of a technology.²¹

To summarize: vertically dis-aggregated industries are not necessarily inefficient, and specialized research firms can play an important role in the right circumstances.²² One can be optimistic about efficiency being raised by increased vertical specialization in industries where horizontal intra-segment competition is high, where specialization reduces costs, where vertical coordination is relatively unimportant, where prices reached in the market for the upstream technology accurately reflect marginal opportunity costs, and where bargaining and contracting are easy and effective.

Unfortunately, it is far from clear that these conditions prevail in biomedical research. High levels of uncertainty and high transactions costs imply serious contracting problems. Horizontal competition in specific areas of technology is often limited, and price signals from end-users are muted at best. The considerations all suggests limited economic gains from vertically dis-integrating the industry, and if this is indeed the case then further vertical restructuring induced by regulatory or technological change may have adverse effects on social welfare. “More and stronger patents” could make things worse if they induce excess entry upstream, exacerbate contracting problems, or strike the wrong balance between incentives for pioneers and subsequent innovators.²³

²¹ Judd, K., Schmedders, K. and Yeltekin, S. “Optimal Rules for Patent Races”, Northwestern University, Center for Mathematical Studies in Economics and Management Science, Discussion Paper No. 1343, April 2002. Empirical evidence for racing behavior is thin. For the case of pharmaceutical R&D see Cockburn, I. and Henderson, R. “Racing to Invest? The Dynamics of Competition in Ethical Drug Discovery.” *Journal of Economics and Management Strategy*, 1994, 2(3), pp. 481-519.

²² See, for example, the case of specialist engineering firms in the chemicals industry, as documented in Arora, A. and Gambardella, A. “Evolution of Industry Structure in the Chemical Industry” in Arora, A., Landau, R. and Rosenberg, N. (eds.) *Chemicals and Long term Economic Growth*, New York: Wiley, 1998.

²³ Scotchmer, S. “Standing on the Shoulders of Giants: Cumulative Research and the Patent Law”, *Journal of Economic Perspectives*, 1991, 5(1):29-41

Anecdotal evidence and the relatively low stock market returns to biotech tool companies support this pessimistic view. For example, the apparently broad claims of patents on DNA sequences have not yet translated into the ability to extract a significant share of the rents accruing to downstream incumbents.²⁴ In part this reflects the superior bargaining position of the downstream firms, which have largely been able to dictate contractual terms to tool companies. But it also reflects what Richard Nelson called “the simple economics of basic scientific research” — patents or no patents, capturing the value that ultimately derives from fundamental early stage research is extraordinarily difficult for profit-oriented organizations. Those firms that succeeded in doing this have, historically, been large, stable, highly integrated firms, sufficiently diversified in product markets to capture spillovers and financially strong enough to be able to effectively manage risk internally.

The “pure play” biotech tool companies seem unlikely to replicate the success of product winners such as Amgen. Falling stock market valuations may reflect a realization by investors that large portfolios of gene patents are unlikely to confer significant access to blockbuster downstream revenues. In fact, licensing revenues may for the most part be confined to one-time payments or periodic user fees, with any royalties eventually realized from sales of downstream products shared with other tool providers. Many tool companies have therefore changed their business strategies. Some have switched to emphasizing product development, while others have moved towards much closer relationships with downstream firms, emphasizing long term mutual interests, proprietary non-disclosed information, and close coordination, i.e., a “quasi-integration solution.” Tools (and associated patents) that the passage of time reveals to be truly valuable are likely to be acquired by downstream firms — potentially raising fresh issues in the antitrust area about vertical foreclosure.

One thing that upstream patents on basic research do seem have done effectively is the creation of powerful incentives for new entrepreneurial companies to enter the pharmaceutical industry as vertical competitors against the established firms. But it is far from clear that these new entrants have, on net, increased value creation in the industry. In one area — gene sequencing and genomics — the new entrants do appear to have dramatically reduced the costs of finding (and then using) biologically significant sequence information. Competitive pressure appears to have rapidly pushed down the cost of gene sequencing and to have brought the global effort to sequence the human genome to completion much faster. The effort induced by incentives to search for patentable DNA sequences may also have had the benefit of generating spillovers to other technologies. But these achievements must be set against the costs of racing

²⁴ Gura, T. “After the Gold Rush, Genome Firms Reinvent Themselves” *Science* 383:1982-84. 2001.

behavior, whether they be socially wasteful duplicative effort, or simply the opportunity cost of employing extra resources to finish faster.

Other than inducing potentially inefficient levels of entry and investment into the tool sector, the impact of gene patents, at least in the medium term, may be quite small. On the positive side they prompted voluminous disclosure of fundamentally important information — though to some extent this information was being created and published elsewhere. On the negative side, in some highly publicized cases gene patents are apparently being used in ways that limit non-profit research activity or otherwise raise the costs of doing research.²⁵ Relatively low marginal costs of generating some types of applications for gene patents also appears to have had adverse consequences: early in the gene patent “gold rush” the Patent Office was flooded with ultimately fruitless applications on ESTs, straining its resources and likely lowering the quality of examination. Anecdotal reports suggesting that some genomics companies have had “more than 60,000” applications pending do nothing to assuage these concerns: though increased stringency of examination may have resulted in some of these applications being abandoned or consolidated, given the very long pendency period for complex molecular biology patents many of these may still be in the pipeline.

Impact on Academic Science

Aside from any impact on the productivity of commercial biomedical science, the extension of exclusionary property rights into basic biomedical research also has the potential to weaken academic research, a vital but fragile component of the biomedical innovation system. Historically, academic research has been driven by social norms and resource allocation procedures that largely ignored market signals and commercial concerns. Patents and the profit motive are largely antithetical to the governance mechanisms of publicly funded science, and their steady perfusion into academic institutions has generated considerable alarm.²⁶ Open science has relied heavily on priority and reputation-based incentives, investigator-initiated research, peer review, and a “gift economy” of prompt reciprocal sharing of data, materials, and

²⁵ Myriad Genetics’ exclusive licensing of the BRCA1 gene is often claimed to restrict academic research. See Schissel, A, Merz, J, Cho, M. “Survey confirms fears about licensing of genetic tests.” *Nature* 402:118, 1999.

²⁶ See *Keeping Science Open: The Effects of Intellectual Property Policy on the Conduct of Science*, London: The Royal Society, 2003; Krimsky, S. *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research*, Lanham MD: Rowan and Littlefield, 2003; Eisenberg, R. “Property Rights and the Norms of Science in Biotechnology Research” *Yale Law Journal*, 1987, 97:177-223, and Rai, A. “Regulating Scientific Research: Intellectual Property Rights and the Norms of Science,” *Northwestern University Law Review*, 1999, 77:94-129, and the interesting counter-argument of S. Kieff, “Facilitating Scientific Research: Intellectual Property Rights and The Norms Of Science — A Response to Rai And Eisenberg”, *Northwestern University Law Review*, 2000, 95:691

results. These mechanisms may be very difficult to sustain in the face of increasing competition from commercial entities for resources and talented scientists, and the proliferation of patents and proprietary data. Decreased information sharing, increased emphasis on product market potential over scientific merit in funding decisions and agenda-setting, and the corruption of the “truth-finding” mechanisms of scientific communities surely have serious consequences for the future vitality and productivity of fundamental science, and for the academic community’s contributions to non-market social goals.

Evidence on these issues is mixed. Universities have become active participants in patenting discoveries in the life sciences, but have begun to experience a growing “push back” from industry in the form of challenges to patents asserted by universities.²⁷ Major funders of biomedical research have become more insistent that licensing deals made by universities be unrestrictive and focus on public benefits. Some surveys suggest important changes in the behavior of individual academic researchers in biomedical disciplines.²⁸ However, studies of patenting and publishing behavior have typically found that participation in patenting or in startup companies is a complement rather than a substitute for publication,²⁹ and compelling evidence for a large “choking” effect of patents on academic research, or of any significant swing away from basic science towards commercial applications, has yet to emerge.³⁰

Though there is little quantitative evidence thus far of a negative impact of patents on scientific research activity, their qualitative impact on the norms of scientific inquiry and on institutional culture may ultimately prove to be very significant. Unfortunately, these are particularly difficult to observe directly, and drawing conclusions about the incidence of scientific fraud or the influence of commercial considerations in promotion decisions from the few cases

²⁷ “Depth Charges Aimed at Columbia’s Submarine,” *Science*, 2003, 301:448; “Judge Turns Rochester’s Golden Patent Into Lead,” *Science*, 2003, 299:1638:39

²⁸ Blumenthal, D. et al. “Participation of Life-Science Faculty in Research Relationships with Industry.” *New England Journal of Medicine*, 1996, 335:23, pp. 1734-39; Campbell, E. et al. “Data Withholding in Academic Genetics: Evidence from a National Survey.” *JAMA*, 2002, 287:4, pp. 473-80.

²⁹ See Stephan, P. et al. “Who’s patenting in the university? Evidence from a Survey of Doctorate Recipients” Mimeo, Georgia State University, 2004; Thursby, G and Thursby, M. “Patterns of Research and Licensing Activity of Science and Engineering Faculty” Mimeo, Georgia Tech, 2003; Azoulay, P. Ding, W. and Stuart, T. “The Determinants of Faculty Patenting Behavior: Demographics or Opportunities?” Mimeo, Columbia University 2005; Markiewicz, K. and DiMinin, A. “Commercializing the Laboratory.” Mimeo, Boston University 2004.

³⁰ A recent survey of life scientists found little evidence that patents on research tools were hindering academic research: see Walsh, J., Arora, A. and Cohen W. “Research Tool Patenting and Licensing and Biomedical Innovation” in Cohen, W. and Merrill, S. (eds.) *Patents in the Knowledge-Based Economy*. Washington, DC: National Academies Press, 2004. On the other hand, in one interesting study, patents have been shown to negatively affect access to knowledge, as measured by citations. See Murray, F. and Stern S. “Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? An Empirical Test of the Anti-Commons Hypothesis” Mimeo, MIT March 2005.

reported in the media is obviously very hazardous. Nonetheless, many observers remain deeply concerned about the impact of expanding exclusionary intellectual property rights into the domain of academic research.³¹

But in at least one important area of biomedical research, the burgeoning new discipline of computational biology or bioinformatics, open science appears to be alive and well. Here, academic researchers appear (thus far) to have effectively limited the incursion of exclusionary IP through aggressive use of the public domain and open source licensing.³² *In silico* biology relies on software algorithms, huge collections of digital data on genetic sequences, molecular structures and disease epidemiology, and interfaces and linkages among them. Situated at the interface of molecular biology and software — two of the most troublesome and controversial areas of IP law and practice — the potential for poor outcomes from widespread acquisition and assertion of exclusionary rights in these types of knowledge would appear to be very high. Yet, with the conspicuous exception of DNA arrays and other hardware technologies, there has been relatively little patenting of bioinformatics. Limited patenting has been accompanied by very few legal disputes, and a conspicuous absence of outrage in the trade press over IP issues.

One reason for this may be that there are large costs to all participants in bioinformatics from fragmentation of data sources and restrictions on access — here the value of the whole is clearly much greater than the sum of its parts. But it also seems clear that lessons learned from the struggle over the human genome sequence have been effectively applied by public sector researchers. Important software tools such as ENSEMBL or BLAST are either public domain or “copylefted” and constitute an important source of prior art against attempts to obtain patents on fundamental algorithms and data structures. New large-scale data gathering initiatives such as the International HapMap Project have also at times used “click-wrap” licenses to enforce open access policies, or even GPL-type requirements for users to make their improvements or additions to the database available to the community of users.

³¹ David, P. “Can ‘Open Science’ Be Protected From the Evolving Regime of IPR Protections?” Stanford Department of Economics Working Paper #03-011, 2003; Editorial “Is the University-Industry Complex Out of Control?” *Nature*, 409(6817):119, 11 Jan 2001; Shorett, P. et al. “The Changing Norms of the Life Sciences” *Science* 21:123, 2003; Angell, M. “Is Academic Medicine for Sale?” *NEJM* 342(20):1516-18, 2000; Lexchin et al. “Pharmaceutical Industry Sponsorship and Research Outcome and Quality: A Systematic Review” *British Medical Journal*, 326(7400):1167-70, 2003; Shulman, S. “Trouble on the ‘Endless Frontier’: Science, Invention and the Erosion of the Research Commons” Washington DC: New America Foundation, 2002; Eisenberg, R. and Nelson, R. “Public vs. Proprietary Science: A Fruitful Tension?” *Daedalus* 131(2):89-101, 2002.

³² Cockburn, I. “State Street Meets the Human Genome Project: Intellectual Property and Bioinformatics” in R. Hahn (ed.) *Intellectual Property Rights in Frontier Industries: Biotechnology and Software*, Washington DC: AEI-Brookings Press, 2005.

These developments suggest an expanded role for collaborative, open, and inclusive structures governing creation and access to biomedical knowledge in the future. But the long-term viability of such structures is questionable, and much work needs to be done to develop robust legal frameworks and business models that can support the investments required to bring the results of this research to market. It is also important to recognize that limiting patenting may encourage data sharing and collaboration, but at a cost. Patents force disclosure, and in bioinformatics, for example, vigorous extension of the public domain may have shifted some commercial actors towards greater use of trade secrets, with important tools and data hidden from sight and priced beyond the reach of most academic users. Agreements to act collectively are also very vulnerable to defection and opportunistic behavior, as has been seen in software and communications industries where consortia convened to facilitate co-ordination through common standards are under constant threat of being “hijacked” by unanticipated patents.

Conclusions

The promise of biomedical research to relieve human suffering and create wealth has never been higher. But the ability of the system to deliver on this promise depends critically on its ability to efficiently create, manage, and exchange knowledge. The patent system is perhaps the most important piece of institutional infrastructure that enables these activities, and the evolution of patent law has played a very significant role in restructuring the pharmaceutical industry. The extension of exclusionary intellectual property rights into basic research has unleashed a surge of entrepreneurial energy and risk taking in commercial science, with potentially very significant benefits to society once the technology reaches end-users. But these benefits carry with them substantial costs: the patent-driven vertical struggle for rents within the biomedical innovation system may have generated important inefficiencies, waste, and misallocation of resources, and drawing universities more deeply into the patent system may prove costly in the long run.

Arguably, some reassessment of the appropriate domain of patents is in order. Restrictions on access to research tools and data are likely to prove very costly in the long run, and stronger protection of the public domain may be a prerequisite for the future health of basic biomedical science. Reforms to patent law and practice suggested by the FTC and the National Academies may go some way towards limiting, if not reversing, decades of patent “creep” into the process of scientific discovery. Statutory protection for research may be necessary, along with more weight given to the implications of university patenting for the conduct of science. The experience of other industries suggests a larger role in biomedical research for collaborative

pre-competitive research, as well as new mechanisms such as open source development for coordinating and rewarding effort within large-scale research projects. Developing such institutions for the unique technological and economic environment of biomedical research presents an interesting challenge.