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Small-Firm Strategic Research Partnerships: The Case of Biotechnology

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ABSTRACT *This paper provides an overview of the theoretical motivation and the empirical literature on small firm strategic alliances in biotechnology, an industry where these alliances have proliferated. We begin by examining the alliance strategy for knowledge-based small firms in general and then turn our attention to the case of biotech.*

> The drug industry, powered by the huge profits of the 1980s, had lately embraced the concept of 'strategic alliances'. Fervently in vogue, they were thought to solve a common problem: in a fractionated marketplace spanning countless diseases, an explosion in knowledge, and thousands of laboratories, no big company was big enough and no small one clever enough to go it alone.
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> Berry Werth, *The Billion Dollar Molecule* (New York, Simon Schuster, 1994), p. 69.

Introduction

Until recently, small firms were invisible in the analysis of innovative activity. Most empirical analyses of innovation focused solely on large corporations,[1] reflecting a theoretical framework that applied to innovation in large corporations.[2] Only within the last 15 years has the vast degree of innovative activity contributed by small enterprises been uncovered.[3] Systematic, comprehensive empirical studies have provided compelling evidence that small firms generate a significant amount of innovative activity, especially in new and emerging industries.[4]

There is, however, very little systematic evidence about the role that strategic research partnerships play in small firms. Part of the reason for this paucity is theoretical. As was the case for the innovation literature only several years ago, the theoretical frameworks to analyze joint research partnerships are predominately oriented towards large corporate partners. Measurement provides even greater challenges. Small firms have systematically lower rates of survival. In high-technology industries, small-firm survival rates are still lower. At the same time, startup rates are higher. This makes it difficult to even identify firms and track them over time. In addition, small firms are notorious for forsaking formal research and development (R&D) for informal research, which typically defies measurement.[5] Measuring the effect of research partnerships between firms that report no formal research expenditures is even more challenging.

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At the same time, however difficult they are to measure, the importance of research linkages and partners to small firms is undeniable. While it may not make sense for firms that are new and most likely transitory to formalize strategic research partnerships with other firms and institutions, such linkages are clearly at the heart of some small-firm strategies.

Biotech research is a sector where the growth of strategic research alliances has been truly dramatic: 20 000 alliances formed since 1988 with an annual average growth rate of 25%.[6] Hagedoorn[7] finds that biotech yields the most prolific rate of alliance formation of any sector. These alliances run the gamut from small biotechnology startups, alternatively known as New Biotech Firms (NBFs), partnering with larger firms, small startups forming alliances between themselves, large established companies joining forces, both large and small firms forming alliances with universities, or three-way relationships involving the combination of large companies, NBFs and universities.

Until the early 1980s, product development in drugs, chemicals and agriculture followed the classic in-house vertically integrated approach although academic research figured prominently in the initial stages of product development.[8] The advent of biotechnology, the commercial application of recombinant DNA and molecular genetics technology was a marked departure from the chemically based expertise of the large firms and created the need for new collaborative research, joint ventures and new forms of cooperative.

By its nature, biotech is a knowledge-intensive activity and its development requires complementary assets that reside in different types of organizations. Universities are the source of basic scientific knowledge and new breakthroughs. New biotech startups are characteristically the commercial application of university knowledge and are very specialized in the types of products and applications they pursue. Established large companies have experience in large-scale production, marketing and distribution. Most importantly they have expertise relevant to the regulatory process required to bring products to the market, and have the substantial resources required to complete the process. Strategic research alliances are formed to bring these complementary competencies together.

The purpose of this paper is to analyze the role that strategic research alliances play in biotechnology. In the second section of this paper, we identify theoretical reasons why small firms in general would rely on strategic alliances. These theories are then applied to the specific case of biotechnology in the third section. Finally, in the last section, a summary and conclusions are presented. In particular, while there is compelling evidence supporting the theoretical reasons why strategic research alliances play an important role in biotechnology, there is very little known about the informal linkages.

The Alliance Strategy for Knowledge-Based Small Firms

According to Kogut,[9] a joint venture occurs when two or more firms pool a portion of their resources within a common legal organization. Conceptually, a joint venture is a selection among alternative modes by which multiple firms can transact. Gomes-Casseres[10] defines alliances more broadly as 'an administrative arrangement to govern an incomplete contract between separate firms in which each partner has limited control'.

Gomes-Casseres[11] suggests that three factors shape the formation of alliances—capabilities, control and context. Capabilities refer to the set of tangible and intangible assets making it feasible for a firm to develop, produce and sell goods and services. Control refers to the authority of the firm to deploy those capabilities. The context refers to the external environment within which the firm operates.

Kogut[12] emphasizes that if all three of these elements—capabilities, control and context—are present within the firm, there will be no need to seek an externally strategic alliance. However, if one of these elements is lacking or weak, the firm has an incentive to seek an external partner or set of partners. If an alliance is formed, the set of capabilities required by the firm shapes the structure of control in the organization. The structure of control similarly shapes the manner in which the capabilities are managed, and the nature of investments made to upgrade the capabilities over time.

Gomes-Casseres[13] points out that in a context where size bestows a competitive advantage—because of economies of scale or scope—large enterprises will tend to have the competitive advantage. To compensate for this size-inherent cost disadvantage, small firms then have a clear incentive to engage in a strategic alliance to increase their scale and scope.

An implication of the aforementioned framework is that not all small firms are at a competitive disadvantage, *per se*, even if larger enterprises exist in the same industry. As long as no size-inherent cost disadvantages exist, there will be no compelling reason to participate in a strategic alliance.

In addition, occupying a strategic niche provides small firms with an opportunity for viability when either no scale economies exist, or there are even modest diseconomies of scale. According to Penrose,[14] 'The productive opportunities of small firms are composed of those interstices left open by the large firms which the small firms see and believe they can take advantage of. The nature of the interstices is determined by the kind of activity in which the larger firms specialize, leaving other opportunities open'. Caves and Porter[15] and Newman[16] provided compelling empirical evidence for the existence of such strategic niches.

By contrast, when a small firm is at a competitive disadvantage, *vis-à-vis* larger competitors, developing a strategic partnership or alliance is a mechanism to compensate for size-inherent disadvantages. Gomes-Casseres[17] provides an example of how a strategic alliance generates compensating competitiveness for small firms. A relatively small computer firm, MIPS Computer Systems, operated in the same market as IBM and Hewlett-Packard. Production scale economies and market penetration determined commercial success. MIPS produced reduced instruction-set computing (RISC) processors, which required large-scale production. Because of these scale economies, it was clear that only a few of the producers in the market ultimately would survive. This also meant that those designs with the greatest market penetration were likely to be among the survivors. Thus, it was crucial for MIPS to obtain a large market share and influence the industry standard. MIPS created an alliance including semiconductor partners and a number of systems vendors. These partners contributed production capacity, market presence, technological competencies and finance. MIPS contributed a highly specialized and unique semiconductor design. Along with Sun Microsystems, one of its partners, the smaller company was able to attain the scale, scope and market impact that otherwise would have been unimaginable.

Through the strategic alliance, MIPS succeeded in leveraging its small size to a larger unit of competitiveness. Gomes-Casseres[18] observed, 'Increasingly, the talk in the industry became one of how the MIPS "camp" was faring versus the camps centered around other firms'.

A different factor motivating compensating strategic research partnerships for small firms is the need for finance. As Lerner and Merges[19] note, 'Young firms with novel technologies frequently lack the financial resources to effectively introduce a new product and may find it difficult to raise equity or debt caused by the informational asymmetries surrounding the project. In many cases, young firms lack complementary assets such as sales forces and manufacturing know-how, which may take many years to develop. As a result, small, research-intensive firms frequently rely on alliances with larger corporations.'

In reviewing the role of financial constraints on investment behavior, Chirinko[20] observed, 'The investment literature has been schizophrenic concerning the role of financial structure and liquidity constraints'. That is, the financial structure of a firm does not play an important role in investment decisions, since the firm can substitute without cost external funds for internal capital. Under the assumption of perfect capital markets, then, firm-specific investment decisions are generally independent of the financial condition of that firm.

The assumption of perfect capital markets has, of course, been rigorously challenged. Once it is no longer assumed that capital markets are perfect, it also can no longer be assumed that external capital is a costless substitute for internal capital. An implication of this view is that the availability of internal finance, access to new debt or equity finance, and other financial factors may shape firm investment decisions.

Which view is correct? According to Fazzari *et al.*,[21] 'Conventional representative firm models in which financial structure is irrelevant to the investment decision may well apply to mature companies with well-known prospects. For other firms, however, financial factors appear to matter in the sense that external capital is not a perfect substitute for internal funds, particularly in the short run.'

There are compelling reasons why liquidity constraints become more severe as firm size decreases. Stiglitz and Weiss[22] pointed out that, unlike most markets, the market for credit is exceptional in that the price of the good—the rate of interest—is not necessarily at a level that equilibrates the market. They attribute this to the fact that interest rates influence not only demand for capital but also the risk inherent in different classes of borrowers. As the rate of interest rises, so does the riskiness of borrowers, leading suppliers of capital to decide to limit the quantity of loans they make at any particular interest rate. The amount of information about an enterprise is generally not neutral with respect to size. Rather, as Petersen and Rajan[23] observe, 'Small and young firms are most likely to face this kind of credit rationing. Most potential lenders have little information on the managerial capabilities or investment opportunities of such firms and are unlikely to be able to screen out poor credit risks or to have control over a borrower's investments.' If lenders are unable to identify the quality of the investment or the degree of risk associated with particular borrowers, Jaffe and Russell[24] show that credit rationing will occur. This phenomenon is analogous to the lemons argument advanced by Akerloff.[25] The existence of asymmetric information prevents the suppliers of capital from engaging in price discrimination between riskier and less risky borrowers. However, as Diamond[26] argues, the risk associated with any particular loan is also not neutral with respect to the duration of the relationship. This is because information about the underlying risk inherent in any particular customer is transmitted over time. With experience, a lender will condition the risk associated with any class of customers by characteristics associated with the individual customer.

Strategic Alliances in Biotechnology

The problems of uncertainty, asymmetric information and high transactions cost are exacerbated in innovative small firms highly reliant upon research. Biotechnology is a new industry that is knowledge based and relies on new startups and small firms. The industry is characterized by the type of incomplete contracting described by Grossman and Hart,[27] Hart and Moore,[28] Hart[29] as well as Aghion and Tirole.[30] The knowledge conditions underlying the biotechnology industry—high uncertainty, asymmetries and high transactions costs—result in, 'Redefining the work when the unexpected happens, as it invariably will. Research is by its very nature an interactive process, requiring constant reassessment depending on its findings. If there is a low risk of unexpected findings requiring program reassessment, then it is probably not much of a research program.'[31]

The relatively small scale of most biotechnology firms may be attributable to the diseconomies of scale inherent in the 'bureaucratic process which inhibits both innovative activity and the speed with which new inventions move through the corporate system towards the market'.[32] Zucker *et al.*[33] provide considerable evidence suggesting that the timing and location of new biotechnology firms is 'primarily explained by the presence at a particular time and place of scientists who are actively contributing to the basic science'.

Strategic research partnerships are particularly important in the biotechnology industry. These strategic research partnerships and linkages occur between entrepreneurial firms, between the scientists involved with the firms, between the firms and universities, and between corporations and biotech firms.

Strategic research alliances have many purposes[34] and Hagedoorn[35] concludes that biotech alliances encompass most or all of these motivations simultaneously. To the extent that strategic alliances in biotech represents a new system for commercializing science that may become a dominant model for other technically complex emerging sectors, understanding the motivations, incentives and barriers to the formation and operation of biotech strategic alliances informs restructuring towards this formation.[36]

NBFs are new entrants that serve as intermediate organizations between universities and large pharmaceutical firms. They typically form around licensees of university intellectual property and involve university researchers as either founders, members of the scientific advisory board, employees or consultants.[37] While industry-university collaborations are often strained because of different objectives and time constraints, NBFs are able to license university technology and work with university researchers while being more attuned to commercial pressures.[38] Thus, NBFs may facilitate the commercialization of academic science and the realization of increased efficiencies. Of course, universities receive licensing fees, royalties and even equity from NBFs in exchange for their intellectual property yet we do not have a good understanding of how these returns are distributed, if this is an efficient way to organize science or provide incentives for the generation and use of knowledge. We do not know how scientists' financial interest in companies may limit the flows of knowledge that are typically unrestricted from universities. Potentially profitable research findings may be kept confidential, remain unpublished, or be significantly delayed in order to secure proprietary rights.

The literature has documented the types of alliances that accompany biotech research. In general, studies focus on firms as the unit of analysis or focus on alliance agreements. While the academic literature has used existing and many time proprietary databases, there is typically an emphasis on augmenting the data with data from other sources or conducting complementary case studies to add understanding to the results.

The consensus is that firms form thick networks that involve multiple partners in a variety of alliances in order to move research forward. Studies have also either focused on alliance characteristics and the effects on participants or alternatively have looked at firm performance to assess how alliance participation affects firm outcomes such as initial public offerings or market valuation. Each of these deserves mention.

The literature generally accepts that alliances are beneficial for the participants: there appear to be great synergies between the research alliance participants that allow firms to take advantage of their competitive assets, prevent duplication of efforts and promote economic efficiencies. Specifically, NBFs gain much needed revenue and access to specialized resources. Large companies are able to fill their product development pipeline, which also helps them in the capital markets. Galambos and Sturchio[39] find that large pharmaceutical firms are able to establish significant capabilities in new fields because of alliances with NBFs. Interestingly, Bower and Whittaker[40] find that NBF partnerships may increase knowledge spillover potential by acting as a knowledge conduit indirectly connecting large companies.

Strategic research alliances provide pathways for knowledge spillovers; however, it is difficult to measure the benefits in terms of knowledge generation and refinement. Two important indicators are the rate of innovation and the rate of growth of the participants, measured by market valuation, revenue or employment. Evaluating the economic consequences of biotech strategic research partnerships is more difficult because of the short time frame these alliances have been in existence, the rapid changes in NBF ownership and the general volatility of the market. Some notable results include:

- Powell *et al.* find that companies which formed alliances experienced higher growth rates.[41]
- Stuart *et al.* find that strategic research alliances send a market signal that increases success of the firm's initial public offering. Alliances with well-known larger companies send an endorsement signal to the stock market.[42]
- Zucker *et al.* find that the number of publications in these bench-level working relationships predicted higher subsequent firm productivity in terms of products in development, products on the market and employment growth in the firm. Firms with access to leading edge scientists performed better than enterprises lacking such access.[43]

Although the consensus in the literature is that alliances are mutually beneficial, some policy issues warrant discussion. First is the relative absence of research on alliances outside of human therapeutics and diagnostics. Most notably, research alliances in agricultural biotech appear to be different because of a market structure with fewer NBFs and greater market concentration. Second, there are concerns that NBFs may enter into partnerships owing to a lack of capital—not because it is the most appropriate strategy. Third, strategic alliances that limit NBFs to be research boutiques may not be the best strategy for the long-term growth of knowledge in the industry. Fourth, there are growing concerns about the distribution of profits from research largely funded by taxpayers. Finally, we may question the degree to which the strategic research alliances in biotech represents a new model of commercializing university science that may extend to other emerging technology-intensive sectors.

Most research on biotech strategic alliances has focused on medical applications, in large part caused by Wall Street investment interests, which in turn, influenced the types of data that are readily available. This focus ignores the importance of biotechnology to the other applications such as agricultural (see Kalaizandonakes and Bjornson[44] for an exception). Biotechnology is already beginning to improve crop yields, provide better pest control and new agricultural products thus reducing farm input costs, and benefiting the environment.[45] Advances in agricultural biotechnology have potential to increase agricultural self-sufficiency and economic stability in developing countries. The USA currently leads the world in agricultural biotechnology; however, other countries have aggressively moved into this application.

Agricultural biotech alliances appear to be different from the human drug and therapeutics market. First, there are relatively fewer NBFs relative to the size of the market. Most of the research alliances appear to involve large firms with universities. Second, the Institute for Biotechnology Information reports that the agricultural-sector has had a relatively large percentage of legal actions (18%) when compared to the pharmaceutical sector (6%).

Greis *et al.*[46] find that contractual or certain barriers to innovation, notably a lack of capital, motivate partnering arrangements among biotech start-ups. One policy concern is the degree to which small firms are forced into alliances by a lack of capital, external funding opportunities or stock market volatility.[47] This may place the NBF in a disadvantaged bargaining position. Lerner and Merges[48] find that the allocation of control rights in an alliance increased with the firm's financial resources, thus financially weak firms may be relatively disadvantaged. As a point of reference, biotech alliances are a major source of revenue, generating US $1.35 billion revenues in 1997 for the top 100 NBFs ranked by number of agreements, for a compound annual growth rate of 33%.[49]

One important question raised by Pisano[50] is that strategic alliances in which the NBF produces the idea and the larger firm undertakes scale-up or large-scale production may or may not be the best long-run strategy because of the specific and specialized nature of the production processes. With an unproven new product, manufacturing process innovation may be critical for developing competence and long-term advantage. In contrast to strategic research partnerships that limit the scope of the NBF, the alternative strategy of becoming a fully integrated operation may be a source of commercially valuable knowledge. Gray and Parker[51] find that the manufacturing of biotech products has occurred in geographic regions where the pharmaceutical industry has excess capacity—not near the locations where the technology was developed and where the knowledge to increase process productivity, improve product quality and augment the specialized knowledge base resides.[52] Thus, strategic alliances may undermine the long-term growth potential of the biotech industry.

There are concerns that strategic alliances with universities allow drug companies to profit from research supported by taxpayers.[53] Although the consensus among economists is that the system of innovation is efficient and that private companies need profit incentives in order to develop commercial products from basic university knowledge,[54] the allocation of the return from products developed from research that was publicly funded appears to be developing into a contentious public policy issue.

The most relevant question we may ask is if this model represents a new system for commercializing science that will become dominant for other technically complex emerging sectors. While strategic alliances have proven difficult to manage, their numbers and persistence indicate that the participants must gain. Yet we still have a limited understanding of the most efficient governance structures, contractual terms and monitoring procedures. Increasingly the literature recognizes that the benefits of contracting and outsourcing depend on specific attributes of the technology and the inherent costs of external partnering.[55] When transaction costs are high, firms pursue in-house research rather than strategic alliances. Biotech start-ups' concerns about the loss of appropriability of intellectual property can limit the firm's willingness to participate in external partnerships.[56] Less is known about the contractual relationships that protect the intellectual property interests of the NBFs and universities reduce moral hazard concerns and minimize transactions costs.[57]

Strategic research partnerships and linkages in biotechnology occur between entrepreneurial firms, between the scientists involved with the firms, between the firms and universities, and between corporations and biotech firms. Strategic research partnerships between large corporations and biotechnology companies have been particularly important for biotech companies specializing in therapeutics. This is because the cost of developing a new drug, complying with the various layers of regulation, manufacturing the product and then marketing the product, have required a level of finance that far exceeds the budgets of most small firms. Cullen and Dibner[58] estimate that the cost of bringing a therapeutic drug to market is around US $250 million. At the same time, the average budget for research and development of a biotech firm is US $12.5 million. To close this gap, biotech firms have engaged in a broad range of marketing and licensing agreements. Under these agreements, the biotech firm provides access to innovative technology in exchange for an infusion of capital from their corporate partners.

In documenting the evolution of strategic alliances in biotechnology, Cullen and Dibner[59] conclude, 'The primary strategic goal of small and medium-sized biotechnological companies was to develop products to be marketed by their partners and their primary concern was finding and developing alliances'. The obvious advantages to such strategic research partnerships is that they enable a small, new company to concentrate on its core mission—moving from basic research to commercialization through technological innovation. The strategic alliances also enable the biotech company to reduce financial risks as well as operating costs. In addition, the biotech firm is better able to offset the major liabilities associated with biotech startups—acquiring manufacturing capabilities, marketing and sales.

The established firms are generally quite positive and supportive towards biotechnology firms. This is because of the strong complementary nature between biotechnology firms and established firms, particularly in the pharmaceutical industry. There are a number of reasons why such a complementary relationship has evolved between established and biotechnology firms. The first is that the former have recognized that it may be a more efficient structure to engage in an arm's length market relationship to obtain new biotechnology products than to produce them internally. The market exchange is apparently more efficient than the internal transaction. The reason for this involves agency problems in undertaking research that is highly uncertain and asymmetric. In addition, the exposure to legal liabilities resulting from biotechnology research is reduced when that research is undertaken at a small firm with limited assets rather than in a large corporation with massive assets.

Sharp[60] identifies three main phases in the relationship between established firms and biotechnology companies. The first phase involved the formation and incipiency of the biotechnology industries. Sharp[61] reports that 'most of the established pharmaceutical companies were uncertain what to make of the new technology and especially of the hype surrounding its development that grew with the small firm sector in the US'. This uncertainty combined with a considerable degree of skepticism resulted in most established pharmaceutical companies distancing themselves from the fledgling biotechnology industry in this initial phase. At the same time, Sharp points out that most established company invested in sufficient scientific expertise to enable them to keep abreast of developments in biotechnology and monitor the industry.

The second phase began in the mid 1980s, when the period of watching and waiting ended. The established pharmaceutical companies recognized that, in fact, biotechnology had a valuable market potential. While strategies pursued by the established enterprises varied, most devised and implemented a strategic biotechnology policy. One common strategy that all companies pursued was to invest heavily to develop an in-house competence in biotechnology. How this was done varied considerably across companies. In some companies, scientific teams were assembled. Other pharmaceutical companies acquired such competence through the acquisition of biotechnology firms or, in some cases through mergers. Another strategy was to engage in external linkages with biotechnology companies. As Cullen and Dibner[62] document, strategic alliances between biotechnology firms and established enterprises exploded in the mid 1980s.

The third phase, which started around a decade ago, involves the commercialization of biotechnology products. The first successful biotechnology products reached the market in the early 1990s. As Juergen Drews, head of R&D at Hoffman LaRoche observed in 1993,

While there are some redundancies among the 150 or so novel proteins in development, about 100 represent truly novel substances that have no precedent in medical therapy. Not all of these proteins will reach the market, but it is fair to assume that their attrition rate will be lower than that for small chemical entities because they should cause few unmanageable toxicological problems. A conservative estimate would expect 30–40 of the recombinant proteins now under development to become successfully marketed products over the next 5–6 years. This means that an average of 5–8 novel proteins should become available each year . . . If we assume an average sales volume for the forthcoming recombinant proteins equal to the average revenues generated by today's recombinant drugs, the portfolio of recombinant proteins now in clinical trials should amount to $10–20 billion.

In this third phase, the large established companies take the products developed by biotechnology companies and move them forward to become large-scale marketed products. For example, Intron A, developed by Biogen but marketed by Schering-Plough, had sales of US $572 million of sales in 1993; Humulin, developed by Genetech was marketed by Eli Lilly, with US $560 million of sales in 1993; Engerix-B was developed by Genetech but marketed by SmithKline Beecham for US $480 million in sales; RecombiNAK HB was developed by Chiron but marketed by Merck for US $245 million.[63]

In addition, this third phase has experienced a shift by the established companies away from the broad learning strategies of phase two and increasingly towards a more focused approach, targeting specific technologies. For example, Ciba Geigy reduced its portfolio of interests in biopharmaceuticals in 1989 in order to focus more narrowly on the development of just several targeted products. Ciba Geigy subsequently increased its investment in those targeted areas and engaged in a number of research and licensing agreements with biotechnology companies. Similarly, Bayer reduced its biotechnology research in agro-chemicals while concentrating its focus on pharmaceuticals. Hoffman LaRoche similarly pulled out of agro-biotechnology to concentrate its focus on pharmaceuticals.[64]

Lerner and Merges[65] use a novel database identifying biotechnology research alliances complied by Recombinant Capital, a San Francisco-based consulting firms specializing since 1988 in tracking the biotechnology industry. As of December 1998, Recombinant Capital had identified over 7000 alliances between private biotechnology firms by examining the US Securities and Exchange Commission (SEC) and state filings, the news media and press releases.[66] Lerner and Merges[67] drew a random sample of 200 of the alliances to encode.

Lerner and Merges[68] use this sample of strategic research alliances between small biotechnology companies and large pharmaceutical companies to examine the determinants of the control rights in the alliances. The control rights consist of:

- Management of clinical trials
- Control of the initial manufacturing process
- Control of manufacturing after product approval
- Creation of exclusive territory for the biotechnology (small research) firm
- Creation of co-marketing rights for the biotechnology (small research) firm.

The empirical evidence suggests that the assignment of control rights between the large pharmaceutical corporation and the small biotechnology company is done in a manner that maximizes innovative output. The exception involves those strategic alliances where the small biotech firm has few resources and little external financing is available.

In a subsequent paper, Lerner and Tsai[69] use the same data set to address two additional questions: (1) Whether success rates differ in agreements that are (i) signed in periods with little external equity financing availability and (ii) cede the bulk of the control to the financing firm; and (2) Whether the less attractive agreements are renegotiated. They find that contracts for strategic research alliances that are signed at times when biotechnology firms are raising little external financing and that assign the most control rights to the large corporation perform significantly worse. These agreements are also more likely to be renegotiated if financial market conditions improve.

Audretsch and Stephan[70] document the strong research partnerships that exist among universities and biotech firms. These partnerships are crucial because biotechnology companies are strongly defined by their scientists. Many of these scientists, particularly senior scientists with strong reputations, do not work for the biotechnology company full time, but instead are members of university faculties.

For example, Audretsch and Stephan[71] show that, of 101 founders of new biotechnology firms in the early 1990s, nearly half (50) are from universities. Of these 50, 35 remain associated with their universities on a part-time basis, while the remaining 15 founders left the university to work full-time for their biotech firm.

These university-based scientists fulfill a variety of roles within biotechnology companies. Some are founders; others serve as members of scientific advisory boards (SABs), while still others serve as directors. The degree of knowledge provided by university-based scientists varies according to the role played by the scientist. Scientific founders seek out venture capitalists in order to transform technical knowledge into economic knowledge. Scientific advisors provide links between scientific founders and other researchers doing work in the area. They, along with founders, also provide the possibility of outsourcing research into university laboratories staffed by graduate students and post-docs. The concept of scientific advisory boards also provides the firm the option of having, at minimal cost, a full roster of the key players doing research in the firm's area of expertise.

In addition to providing knowledge to newly formed biotechnology companies, university-based scientists also provide a signal of firm quality to the scientific and financial communities. An effective way to recruit young scientists is to have a scientific advisory board composed of the leading scientists in the field. George B. Rathman, president and Chief Executive Officer of Amgen, attributes much of the company's success to an SAB of 'great credibility' whose 'members were willing to share the task of interviewing the candidates for scientific positions'. Rathman goes on to say that the young scientists that Amgen recruited would not have come 'without the knowledge that an outstanding scientific advisory board took Amgen seriously'.[72]

Certain roles, such as being a founder of a biotechnology firm, are more likely to dictate geographic proximity between the firm and the scientist than are other roles that scientists play. This is because the transmission of the knowledge specific to the scientist and firm dictates geographic proximity. Presumably, scientists start new biotechnology companies because their knowledge is not transferable to other firms for the expected economic value of that knowledge. If this were not the case, there would be no incentive to start a new and independent company. Because the firm is knowledge-based, the cost of transferring that knowledge will tend to be the lowest when the firm is located close to the university where the new knowledge is being produced. In addition, the cost of monitoring the firm will tend to be minimized if the new biotechnology startup is located close to the founder.

By contrast, the role of scientific advisor to a biotechnology company does not require constant monitoring or even necessarily specialized knowledge. Thus, the inputs of scientific advisors are less likely to be geographically constrained. Furthermore, geographic proximity of all major researchers in a particular scientific field is unlikely given the opportunity cost that universities face in buying into a single research agenda. Thus, if firms are to have access to the technical knowledge embodied in the top scientists in a field, they will be forced to establish links with researchers outside of their geographic area. Scientists whose primary function is to signal quality are also less likely to be local than are scientists who provide essential knowledge to the firm. Their quality signal is produced by lending prestige to a venture they have presumably reviewed—a task that can be accomplished with credibility from a distance.

To identify the links between knowledge sources, the incentives confronting individual scientists, and where the knowledge is commercialized, Audretsch and Stephan[73] rely upon a database collected from the prospectuses of biotechnology companies that prepared an initial public offering (IPO) in the USA between March 1990 and November 1992. This includes 54 firms that were affiliated with 445 university-based scientists during this period. By carefully reading the prospectuses, it was possible to identify the names of university-based scientists affiliated with each firm, the role that each scientist plays in the firm, and the name and location of their home institutions. Universities and firms were then grouped into regions, which are generally larger than a single city but considerably smaller than a state. Certain areas, for example, metropolitan New York, cross several state lines.

Only 138 of the 445 links observed between scientists and biotechnology companies are local in that the scientist and firm are located in the same region. This suggests that geographic proximity does not play an important role for links between biotechnology companies and scientists in general. However, the geographic link between the scientist and the founder is influenced by the particular role played by the scientist in working with the firm. Most strikingly, 57.8% of the scientist-firm links were local when the scientist was a founder of the firm; 42.1% were non-local. By contrast, when the scientist served as a member on the SAB, only 31.8% of the links were local, while 68.2% were non-local. This disparity suggests that the nature of the knowledge transmitted between the university and the biotechnology firm may be different between scientists serving as founders and those serving on a SAB. Presumably, it is a difference in the nature of the knowledge being transferred from the university that dictates a higher propensity for local proximity in the case of the founders.

The consensus from the literature is that firms that are active in biotech have multiple partnerships that cover the range of partnership types. Early studies of biotech alliances were based on case studies of a few companies. More recent work has relied on one of three industry specific data sources: BioScan, Recombinant Capital's Biotech Alliance Database (ReCap), or the Institute for Biotechnology Information (IBI), or has used general alliance data such as MERIT-Cooperative Agreements and Technological Indicators (CATI) maintained by John Hagedoorn. Each of the industry databases will be described in turn. Hagedorn *et al.* provide a description of the MERIT-(CATI) data as well as the US CORE database.[74]

BioScan is perhaps the data source most used to investigate strategic research partnerships in the literature. The database is maintained by American Health Consultants and provides profiles of approximately 1500 US and foreign companies actively involved in biotechnology research and development. The profiles contain information on strategic alliances, mergers, product acquisitions, new products in development, licensing and R&D agreements, principal investors, financial information and key personnel. Information available includes address, personnel, history, facilities, financial information, research interests and products in development. This is proprietary data intended primarily for generating targeted mailing lists, locating business prospects and researching potential partners, and determining industry agreement details.[75]

Research using BioScan typically augments the data with other sources. For example, Powell *et al.*[76] built an augmented database that filled in missing information from other industry directories and published company information and industry publications such as *Genetic Engineering News*, which tracks alliance announcements. It is interesting to note that despite this diligence, Powell *et al.*[77] found that the reaction of the CEO of Centocor to the list of his firm's formal agreements was 'the tip of the iceberg—it excludes dozens of handshake deals and informal collaborations, as well as probably hundreds of collaborations by our company's scientists with colleagues everywhere'.

The Institute for Biotechnology Information (IBI) maintains a proprietary database of strategic activities, including alliances, related to the biotechnology industry. Prevezer and Toker[78] provide an example of a study using this source. For the year 1996, IBI entered 1368 actions into the database, ranging from marketing and licensing agreements between companies, to regulatory approvals and public offerings of individual companies. IBI defines a biotechnology action in most cases as an activity that involves an organization working with genetic engineering or other biotechnologies in their R&D or manufacturing activities. IBI notes the participants involved in the action as well as the type of technology and stage of development involved. Feldman and Ronzio[79] use this data to examine regional specialization in biotech product applications.

Perhaps the most promising existing publicly available database to investigate biotech research alliances is Recombinant Capital's Biotech Alliance Database (ReCap). The database focuses specifically on alliances and contains summaries of more than 7900 alliances in biotech that have been formed since 1978. The material is gathered from the SEC filings of biotechnology companies, as well as from press releases and other literature and company presentations made at investment conferences and other public meetings. The Alliance Database is principally concerned with biotechnology alliances—where a biotechnology company collaborates with a major drug company (drug/biotech), with a university (university/biotech), or with another biotechnology company. In addition, the Database contains many, although by no means all, summaries of alliances of non-biotechnology alliances in the life sciences, although there appears to be limited coverage on agricultural biotech. The Alliance Database is full-text indexed and searchable by company name. Lerner and Merges[80] have analyzed these data.[81]

A related database maintained by the same company is rDNA.com. This is a very comprehensive proprietary database of alliances that offers an alliance summary (including deal press releases), the full text of the actual contract as filed with the SEC (for deals that have been filed) and contract analyses based on a synthesis of the terms of the alliance. This database would be useful for understanding the terms of the contract, the balance of power between the collaborators and ways in which agreement terms have evolved and adapted to market changes.

In order to understand biotech research alliances, researchers have used co-authorship bibliographic citations to discern the degree of collaboration.[82] McMillan *et al.*[83] use patent citations. The literature is developing rapidly. Our understanding of the policy issues may be facilitated with greater integration of the proprietary alliance databases with other sources of company and university data.

While research has made considerable progress into analyzing strategic research partnerships, a number of key hypotheses remain yet to be tested. These include:

- How does the role of strategic research partnerships vary over the life cycle of both the small research oriented biotechnology firm as well as larger, more established partners?

- Are partnerships influenced by the origins of the biotechnology founders, that is their career background and experiences?
- How are strategic research partnerships influenced by the regulatory environment and intellectual property rights regime?
- How do strategic research partnerships vary across countries?
- How are strategic research partnerships formed and how do they evolve over time?
- How do strategic research partnerships vary over specific types of biotechnology or are they the same?

Conclusions

If strategic research partnerships are important to large corporations, they are even more important to small firms. This is because a small enterprise is more likely to be lack a key component involving control, capabilities and context. Consequently, small firms may be more dependent upon strategic research partnerships as a mechanism to compensate for size-inherent competitive disadvantages.

Unfortunately, if measurement of strategic research partnerships is challenging for large corporations, it is even more of a problem for small firms. Just as small firms are a more heterogeneous population than large corporations are, strategic research partnerships may take on forms that are more heterogeneous with small firms than with their larger counterparts. Very little comprehensive and systematic empirical evidence exists about the role that strategic research partnerships play for small firms. Just as scholars were slow to measure the innovative activity of small firms, they have been equally slow to measure and analyze the role that strategic research partnerships play for small firms.

While formal agreements clearly play a role in biotechnology, this may be less true in other industries. A virtue of the Recombinant Capital database is the objectivity in measurement—strategic research alliances are measured externally and reflect contractual agreements. Of course, a cost of that objectivity is the omission of informal research alliances. Just as informal R&D is more important for small firms than for large corporations,[84] informal research partnerships may also be of greater significance for small enterprises. These informal research partnerships clearly involve scientists from different firms and institutions working together, scientist mobility, as well as informal linkages among firms. This might suggest that future research should focus on developing measures of these informal research alliances as well as the formal research partnerships.

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