Small entrepreneurial firms and large companies in inter-firm R & D networks

CHAPTER ELEVEN

Small Entrepreneurial Firms and Large Companies in Inter-Firm R&D Networks – the International Biotechnology Industry

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Introduction

This chapter studies the role played by small entrepreneurial firms and large companies in the international biotechnology industry. The biotechnology industry is one of the main examples of current industries that are characterized by "hypercompetition" (D'Aveni, 1994), with a high degree of uncertainty about the combined effects of both new technologies and new market structures. It is an example of an industry with Schumpeterian competition where revolutionary changes in technology and innovative new products and processes have the potential to threaten the position of existing market leaders and their product-market positions (Liebeskind et al., 1996). It is also a sector where we find a large number of R&D alliances, in particular between large and small companies (Hagedoorn, 1996a; Kenney, 1986; Powell, 1996).

Throughout this chapter we will refer to the biotechnology "industry" although, given the above-mentioned characteristics, this is probably an incorrect term as its status as a separate industrial sector is still somewhat unclear. Strictly taken, biotechnology is not yet a regular industrial sector but a hybrid form of an "industry" with established companies, e.g., from the pharmaceutical sector, and a wide range of new biotechnology companies that are science based and technology driven but still with relatively few regular products and limited manufacturing capabilities (Powell, Koput, and Smith-Doerr, 1996). In other words, when we use the term industry in the following analysis, we recognize that we are mainly analyzing a group of companies that are engaged in R&D, innovation, and the manufacturing of products and processes that can be labeled as biotechnological activities.

Our contribution concentrates on the analysis of inter-firm networks of R&D partnerships and the role played by different groups of companies. This analysis of the role of different groups of companies and the structure of networks in the biotechnology industry follows the suggestion made by Hitt and Ireland (2000) and Shan, Walker, and Kogut (1994) that the study of network structures and the role played by different groups of companies is of importance to understanding emerging sectors such as the biotechnology industry. Within these eminent networks we will pay special attention to the role of small entrepreneurial firms that are known to play such an important role in this industry (Kenney, 1986; Powell et al., 1996).

We have chosen the period from 1985 to 1995 because this period is expected to encompass the end of the first period of the growth of the biotechnology industry with the emergence of a large number of small biotechnology companies during the 1980s and a first phase of some maturation where the commercialization of biotechnology is becoming more important (Arora and Gambardella, 1990; Galambos and Sturchio, 1998). This period also covers the years in which inter-firm partnering has risen rapidly, in this sector as well as in many other fields of technology and sectors of industry (Hagedoorn, 1996a).

In the following, we will first discuss the different roles that large companies and small entrepreneurial firms play in generating innovative output and major technological changes. The perspective that is chosen in our contribution is clearly influenced by the Schumpeterian tradition in the study of innovation. We also pay attention to the complementarities of large and small firms in the networks of R&D partnerships that have become so important in the biotechnology industry. These sections lead us to a set of three research questions that will guide the empirical analysis of this chapter. These research questions focus on the general structure of the inter-firm network of R&D partnerships, changes in the position of small entrepreneurial biotechnology firms, and the role of large pharmaceutical companies. After a description of some methodological issues and an explanation of the data used in our analysis, the second part of the chapter is devoted to an empirical analysis that concentrates on the main issues introduced with the research questions. We first analyse some basic trends in R&D partnerships since the mid-1980s. This is followed by an in-depth analysis of the changes in the inter-firm R&D networks, where attention is paid to groups of companies as well as to the nodal players in the different networks that emerge over time. In the final section of this chapter we discuss our main findings and draw some major conclusions from our contribution.

Innovation – the Role of Both Large Companies and Small Entrepreneurial Firms

Our understanding of the importance of innovation and our perception of the role played by different categories of companies, such as large companies and relatively small entrepreneurial firms, can be clearly placed within the Schumpeterian tradition. We follow Schumpeter (1934) where innovation is described in the context of "new combinations" that replace existing products and markets. As suggested by Hagedoorn (1996b) and others, we understand these Schumpeterian new combinations as "tech-

nical" innovations in terms of new products or new quality of products, new methods of production, or new sources of supply of raw materials. These technical innovations have to be distinguished from "market or organizational" innovations which are new combinations in terms of new markets or new industry structures.

For the pharmaceutical industry, modern biotechnology is a clear example of a set of new combinations with new technologies and state-of-the-art scientific understanding that creates a technological discontinuity. In the context of this technological discontinuity, innovations not only affect the introduction of new products and new processes but these technical innovations also come with new "players," i.e., companies that restructure parts of the pharmaceutical industry that has gradually become mature (Powell, 1996; Powell et al., 1996). These new scientific and technical innovations from biotechnology, that are currently introduced, are largely based on immunology and molecular biology, including recombinant DNA technology, whereas the "traditional" pharmaceutical industry and its innovations are largely based on organic chemistry. Some observers understand these changes to be so fundamental that they describe the technological discontinuity in the pharmaceutical industry, as caused by modern biotechnology, as a clear shift in the existing technological paradigm (Orsenigo, 1989; Della Valle and Gambardella, 1993; Walsh and Galimberti, 1993).

When we consider the innovative role played by both large companies and smaller entrepreneurial firms, there is also a strong Schumpeterian flavor to our understanding of the contribution of these different categories of companies. The importance of the entrepreneurial company as a major generator of new innovations is most clearly stressed in the "early" Schumpeter (1934). In this early work, entrepreneurial companies are small, independent companies that act as major agents of change within new industries. These entrepreneurial companies are innovators that successfully introduce new products whose development is expected to be largely financed through external sources and not so much through internal financial resources (cash flow). In modern strategic management terminology: this Schumpeterian entrepreneurship is based on proactive strategies that capitalize on firm-specific advantages and innovative capabilities, financed through bank loans and venture capital. The Schumpeterian entrepreneur is not necessarily a strictly rational, economically maximizing agent, a risk taker or a capitalist, as in the "classical" theories of entrepreneurship by Knight and Say (Marco, 1985), but primarily an agent of change who is searching for new opportunities (Santarelli and Pesciarelli, 1990; Hagedoorn, 1996b).

Many elements of these Schumpeterian entrepreneurial firms are clearly present in the biotechnology industry. In fact both Kenney (1986) and Powell et al. (1996) depict small biotechnology firms as an ideal type of modern entrepreneurial company. As mentioned by Arora and Gambardella (1990), Pisano (1991), Barley, Freeman, and Hybels (1992), and Powell et al. (1996), small new biotechnology companies are frequently financed through venture capital or loans and equity participation of large companies. Originally based on university research that led to major scientific and technological changes, nearly all of the small biotechnology companies also started as new entrants to the pharmaceutical industry (Kenney, 1986; Pisano, 1990; Powell, 1996).

In terms of their organizational setting and their organizational culture, most of the small biotechnology companies are quite different from the "standard" company that

one finds in traditional industries. New biotechnology companies seem to be driven by scientific discoveries and innovative performance and not only by regular profit-seeking (Lumerman and Liebeskind, 1997). Also, the "academic culture" within these innovation-driven and loosely organized companies, with their informal, non-hierarchical structures, sets them apart from many other "traditional" companies (Pisano, 1991; Powell, 1996).

If we look at the role of large companies in Schumpeter, we have to understand that there also is an important role for these large companies in many publications by Schumpeter. Specifically the "older" Schumpeter (1942) pictures a world of "modern, trustified capitalism" where large science-based companies dominate the innovative environment and where innovation has become routinized in large research laboratories and R&D departments. It is this particular perspective on the role of large companies that for a long period, during the 1950s, 1960s, and 1970s, dominated the understanding of the role of large companies as the main source of innovation (see Kamien and Schwartz, 1982; Scherer, 1984).

In the combined biotechnology and pharmaceutical industry the role of large companies is most clearly found in the dominant role that these companies play in the more traditional pharmaceutical sub-sectors (Arora and Gambardella, 1990). Large companies, with their extensive R&D activities and their long-term experience with time-consuming clinical trials, have come to dominate the innovation process in the traditional pharmaceutical industry. This dominance is based on their leading role in incremental innovation, exploiting their current organic chemical knowledge base and their ability to expand existing portfolios of pharmaceutical products.

Mutual dependence of large and small companies

Some authors (Hakansson, Kjellberg, and Lundgren, 1993; Kenney, 1986; Rothaermel, 2000) stress the importance of complementarity between small, entrepreneurial firms and large companies, in particular in high-tech industries. The basis for this complementarity is to be found in the variety of resources, capabilities, and complementary innovative expertise such as those described in the above.

During the 1980s, when new biotechnology became relevant to the pharmaceutical industry, a certain degree of mutual dependence developed almost instantaneously between large pharmaceutical companies and a group of relatively small new biotechnology firms (Arora and Gambardella, 1990; Pisano, 1991; Powell, 1996). These small biotechnology companies, most of them US-based, have developed a reputation for their R&D capabilities and applied laboratory research in advanced biotechnology at the scientific and technological frontier. Large pharmaceutical companies were already known for their vast body of engineering know-how necessary for scaling up from a laboratory setting to the actual manufacturing process of new pharmaceutical products. They also have the "deep pockets" that are necessary for the extensive and costly clinical testing required as part of the government regulatory process for new diagnostic products and new therapeutic drugs. Furthermore, large companies are known for their financial resources which enable them to deal with the costs of the final stage of commercialization and the successful worldwide market introduction and distribution of safe and effective pharmaceutical products.

The obvious complementarities between both groups of companies during the early period of modern biotechnology led to a mutual dependence as companies started to collaborate on various projects (Laamanen and Autio, 1996; Slowinski, Seelig, and Hull, 1996). This mutual dependence in cooperative projects consisted of financial support and regulatory know-how provided by large pharmaceutical companies to small entrepreneurial biotechnology companies, in return for which large companies acquired access to the research skills of these small biotechnology companies (Arora and Gambardella, 1990; Pisano, 1991; Barley et al., 1992; Shan et al., 1994; Powell, 1996). With the increasing number of new products based on pharmaceutical biotechnology, collaboration between small entrepreneurial firms and large companies also provides the first group with access to new markets and distribution facilities.

Networks as the locus of innovation

The mutual dependence of large pharmaceutical companies and small entrepreneurial biotechnology firms also meant that the locus of innovation in the pharmaceutical industry has gradually changed. Collaboration by these different companies is part of a broader trend in many industries and technologies where the interdisciplinarity of fields of science and technology, the dependence on a substantial stock of knowledge, and the costs of R&D force even the largest companies to collaborate with others (Hagedoorn, 1993). In the biotechnology industry these general developments, together with sector-specific scientific and technological developments, have led to a situation where large pharmaceutical companies are no longer the sole locus of innovation (Arora and Gambardella, 1990). As in so many other industries and fields of technology, extensive collaboration in this sector has led to rather dense networks of companies that enter into all sorts of alliances with a large number of other companies (Hagedoorn, 1990, 1993; Powell et al., 1996). In the biotechnology industry this mutual knowledge resource dependency between groups of large and small companies has led to dense networks of R&D collaboration between a variety of companies, where small firms play an important role in this new locus of innovation.

Some authors (e.g., Arora and Gambardella, 1990; Oakey, 1993; Saviotti, 1998) mention that the network-like structure of this locus of innovation, with both intensive inter-firm collaboration in general and specific cooperation between large companies and small entrepreneurial firms, could be a temporary phenomenon that coincides with the immaturity of biotechnology as a new technological paradigm developed during the 1980s. As the industry matures, small entrepreneurial companies could be taken over or their services could become redundant. Large companies could become more important for the new biotechnology-based pharmaceutical industry as such, as well as for the inter-firm R&D networks that have developed over time. Others (e.g., Pisano, 1991; Segers, 1992; Powell, 1996; Powell et al., 1996; Senker and Sharp, 1997), however, seem to expect that these networks of R&D collaboration in the biotechnology industry are of a more long-term nature because functionally specialized companies can easily maintain various relations with each other through distinctive transactions. In particular, the "nodal" role of small biotechnology companies, both in terms of their critical role as carriers of new scientific knowledge and in their role as major network players with multiple partnerships, is expected to be a long-term affair that will affect the

continuation of a network-like structure of innovation in the biotechnology industry for decades (Powell, 1996; Senker and Sharp, 1997; Galambos and Sturchio, 1998).

Research Questions

As the biotechnology industry gradually became somewhat more mature, some phenomena and patterns, discussed above, that characterized the R&D networks of the 1980s might successively have become less significant during the 1990s while new patterns were emerging. In that context one has to consider in particular the density of networks that followed the growth in R&D cooperation and the role of different groups of companies in these networks. The literature discussed in the above clearly suggests a number of specific research questions that will guide our empirical investigation in the following sections. These research questions are:

- Are inter-firm networks in the biotechnology industry becoming less dense or is their density increasing?
- Is the well-established role of small biotechnology firms as nodal players in these inter-firm networks decreasing over time?
- Are R&D partnerships between large pharmaceutical companies becoming a more important element in these networks of innovation?

Research methodology and data

The core of this chapter is found in the empirical analysis of the evolution of the structure of inter-firm alliance networks in biotechnology and the role played by different categories of cooperating firms. Most attention is paid to measuring variation in network density over time and analyzing the extent to which small entrepreneurial biotechnology firms and/or large pharmaceutical companies play a central role in these networks.

Based on our first research question, which refers to increasing or decreasing density of inter-firm networks, we expect that an increasing or decreasing network density will show up in a growing or declining average number of alliances per firm. To study this aspect of network structure, we calculated the ratio of the total number of R&D alliances between firms to the number of participating companies for each year. The total number of alliances for each year was obtained by counting the number of dyads (relations between two firms) at the level of cooperating firms.

In the present context we do not consider the calculation of standard network density indices as a meaningful alternative to the density indicator that we propose. A standard network density index is defined as the ratio of the actual number of alliances between firms to the possible number of links. Comparing these indices from one year to the next year requires that the calculations be based on a constant number of network participants over time (Barley et al., 1992). One option is to compute density indices on the basis of a constant subset of the most active players. Many small biotechnology firms in our population have engaged in only one alliance during the period of investigation. If we based our analysis on a constant subset of the most active

players, many small firms would disappear from the population, which is not a desired outcome in light of our research objectives.

Our second research question considers the role of small entrepreneurial biotechnology firms as major network participants. In that context we compare the partnering behaviour of small firms to large companies. To evaluate these alliance activities, we calculated the number of R&D alliances per employee for both groups of firms. We first classified each of the firms in our population into one of three distinct size categories, based on their number of employees during the period of study. Firms with less than or equal to 500 employees are regarded as small and those having between 501 and 5,000 employees are considered as medium-sized companies. Firms with over 5,001 employees are classified as large companies. We created a separate category for academic or governmental institutions. Due to the small size and/or private status of some firms we could only obtain information on their size for a few years. We classified these firms into one of the three categories on the basis of the available information.

For small entrepreneurial biotechnology firms and large pharmaceutical companies we calculated, for both categories, the ratio of the total number of R&D alliances between companies to the number of cooperating firms for each year. The total number of alliances for each year was obtained by counting the number of dyads at the level of cooperating firms. For both small and large firms, we divided the results obtained by the means of the appropriate employee categories to control for any size effects on alliance activity. We transformed the mean numbers of employees into a logarithmic scale (natural logarithm) to account for size differentials, which are unrelated to technological activities of companies. Small biotechnology firms typically employ mainly R&D specialists and therefore they have, compared to large pharmaceutical firms, lower numbers of employees in many other functional areas, such as production, marketing, sales, etc.

For our third research question, which looks at the role of R&D alliances among large pharmaceutical firms, we examine the distribution of alliances between firms of similar and different size classes. If large firms have come to play a more central role in alliances than small entrepreneurial firms, we expect the number of alliances between large firms to have increased as well. An intensification of R&D partnering between large and small firms would point at ongoing complementarity between both categories of cooperating firms. For each year we calculated the total numbers of dyads between large firms, small firms, and between large and small companies as percentages of the overall numbers of dyads in that year. These overall numbers also include R&D partnerships involving medium-sized firms. However, given the limited role of medium-sized companies (about 10 percent of the population) and the emphasis in our research questions on large and small companies, the group of medium-sized firms receives little or no attention in the following.

In order to provide some further details about the evolution of networks and the role played by small biotechnology firms and large pharmaceutical companies, we will represent these networks using a non-metric multidimensional scaling (MDS) technique. MDS is a data reduction procedure somewhat comparable to principal component analysis and other factor-analytical methods. One of the main advantages of MDS is that it can usually, but not necessarily, fit an appropriate model in two-dimensional pictures. More specifically, MDS offers a scaling of similarity data into points lying in

an X-dimensional space. The purpose of this method is to provide coordinates for these points in such a way that distances between pairs of points fit as closely as possible to the observed similarities. In order to facilitate interpretation the solution is given in two dimensions, provided that the fit of the model is acceptable. A stress value indicates the goodness-of-fit of the configuration as this measures the proportion of the variance of the disparities that is accounted for by the MDS model, implying that lower values indicate a better goodness of fit (Hair et al., 1994).

Our analysis is restricted to periods of three years, since it is technically impossible to picture all firms in the network when more than three years of data are added. MDS plots are presented for the periods 1985–7, 1989–91, and 1993–5. Comparing these three periods allows us to add a dynamic perspective to our analysis. To improve the interpretation of the pictures, it is useful to draw lines of different styles and thickness between companies, indicating different degrees of cooperation intensity.

For our analyses we make use of two types of data: firm size data and data on R&D alliances. To describe network participants in terms of their size we collected information on the number of employees of each firm from various sources such as the Institute for Biotechnology Information, the US Securities and Exchange Commission, World Scope Global Researcher, Amadeus, and Dun and Bradstreet's Linkages.

The data on R&D alliances is taken from the MERIT–Cooperative Agreements and Technology Indicators (CATI) information system (see Hagedoorn, 1993). This databank contains information on nearly 10,000 cooperative agreements in various sectors, ranging from high-technology sectors such as IT and biotechnology to less technology-intensive sectors such as chemicals and heavy electrical equipment. Cooperative agreements are defined as mutual interests between independent industrial partners that are not linked through majority ownership. In the CATI database, only those agreements are being recorded that involve either a technology transfer or some form of jointly undertaken R&D. Information is also collected on joint ventures in which new technology is received from at least one of the partners, or on joint ventures having some R&D program. Other types of agreements such as production and marketing alliances are not included. Agreements formed between companies and governmental or academic institutions are generally not included in the database unless they involve at least two commercial companies.

Our present study focuses on those alliances that were established in the period 1985–95. In the CATI databank a total of 720 global R&D agreements involving 475 biotechnology and pharmaceutical companies were recorded during this time frame. Our data includes equity agreements, which comprise joint ventures and minority holdings, as well as non-equity alliances that consist of joint R&D agreements and R&D contracts. The data excludes agreements that are established within the context of national and international, government-sponsored, R&D cost-sharing programs. Our population of 475 participating firms comprises 111 large companies, 308 small ones, and 53 firms of medium size. We include three academic or governmental institutions. For our purpose, the most relevant information for each alliance is the number of companies involved, their names as well as the year in which the agreement was established.

This sample is representative for the biotechnology industry during the period 1985–95. Various sources indicate that during this period there are about 100 large pharmaceutical companies with a clear interest in biotechnology (OECD, 1993; OTA, 1988;

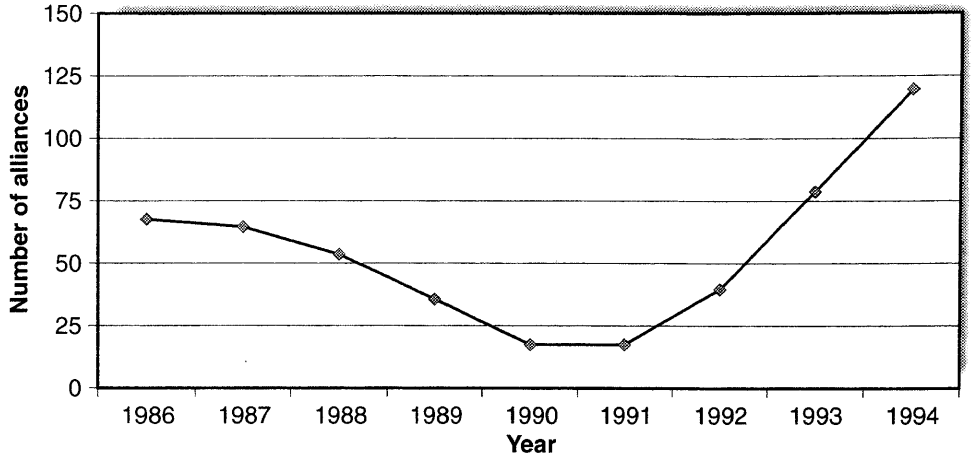


Figure 11.1 Number of newly established R&D alliances, biotechnology, three-year moving averages, 1985–95. *Source*: MERIT-CATI

Walsh and Galimberti, 1993). About two-thirds of the industry during this period consists of small and relatively young firms (Pisano, Shan, and Teece, 1988; Van Vliet, 1998; Walsh, Niosi, and Mustar, 1995).

Trends in R&D partnerships during the period 1985–95

Some general background to the more detailed analysis of the R&D networks in the biotechnology industry is given in figures 11.1 and 11.2. Figure 11.1 demonstrates the importance of pharmaceutical biotechnology in R&D partnering. Over 65 percent of all the biotechnology R&D alliances in the MERIT-CATI database are related to pharmaceutical biotechnology. In the most recent years that we analyze, pharmaceutical biotechnology even reaches a share of over 70 percent of all biotechnology alliances. The dominance of this particular sub-sector in the biotechnology industry, with so few alliances found in other biotechnology sectors, is one of the main reasons why our contribution focuses on the pharmaceutical biotechnology industry.

Figure 11.2 presents the trend in the growth of newly made R&D alliances in pharmaceutical biotechnology during the period 1985–95, as found in the MERIT-CATI database. This development can be characterized as a flattened U-shaped growth pattern. The growth in the number of new R&D alliances drops from about 70 partnerships made annually, as found for the mid-1980s, to about 20 alliances during the early 1990s, after which the growth pattern is restored with a steep increase up to over 100 newly established R&D partnerships during the mid-1990s. This particular growth pattern is quite identical to the pattern found for other industries (Hagedoorn, 1996a). However, to the best of our knowledge, there is no solid explanation in the literature for the specific pattern in the newly established alliances during the period 1985–95.

As a first step in the analysis of the inter-firm R&D networks, and also to assess the

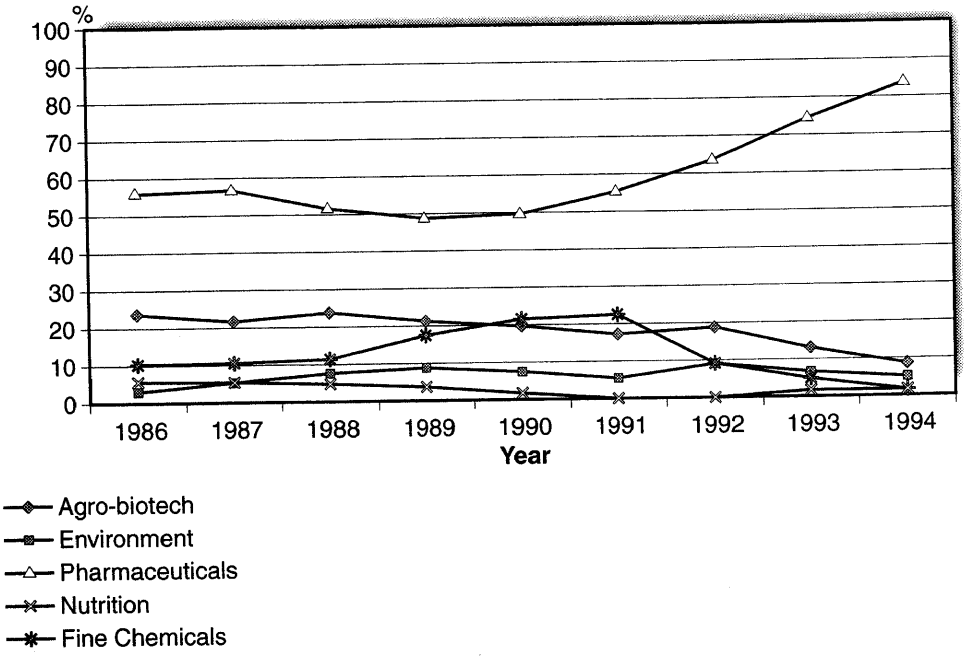


Figure 11.2 Distribution of newly established R&D alliances in various biotechnology-based sectors, three-year moving averages, 1985–95. *Source*: MERIT-CATI

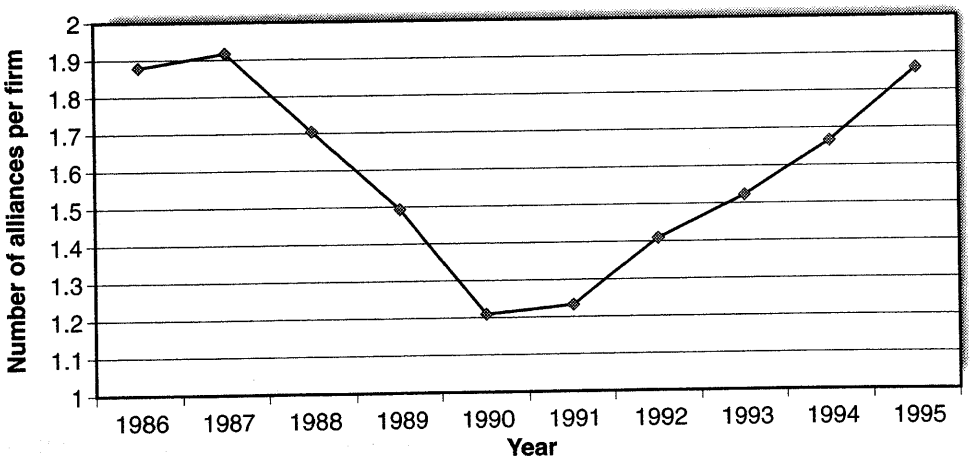


Figure 11.3 Number of newly established R&D alliances per firm, biotechnology, three-year moving averages, 1985–95. *Source*: MERIT-CATI

Table 11.1 Number of newly established R&D alliances and participating firms, biotechnology, 1985–95. *Source*: MERIT-CATI

Year	Alliances	Firms
1985	164	85
1986	158	79
1987	128	75
1988	172	84
1989	76	56
1990	14	13
1991	18	15
1992	78	55
1993	170	106
1994	250	163
1995	332	179

evolution of the network density, we calculated the number of annually, newly made R&D partnerships per firm as they appear in the CATI databank. Information on these numbers of new R&D alliances and participating firms is given in table 11.1. Figure 11.3 shows the total number of newly established alliances per firm in the biotechnology industry for the period 1985–95. These numbers are calculated as three-year moving averages to present the overall trend in the data while correcting for yearly fluctuations. For 1995 we added the actual value to the graph to be able to visualize the strong growth in alliance activity in the last three years of observation.

Figure 11.3 pictures a U-shaped pattern in the average number of newly made R&D partnerships per firm. It demonstrates that, apart from a small increase in 1987, the final years of the 1980s are characterized by a sharp decrease in the number of alliances per firm from 1.9 in 1986 to 1.5 in 1989. The first years of the 1990s show a further decline in the average number of R&D partnerships per firm to a level of 1.2 in 1990. This is followed by a short period of stabilization, which is continued by a sharp rise of new partnerships per firm from 1992 onwards. In 1995 the steep upward trend arrives at a level of 1.85 new alliances per firm.

As an indicator of the magnitude of R&D alliance activities of both small biotechnology firms and large pharmaceutical companies, we computed the number of annually, newly established R&D alliances per employee (logarithmic scale) for both categories of cooperating companies. Figure 11.4 shows the specific trend for the number of new R&D partnerships for these groups of companies. The data in this graph are also shown as three-year moving averages, with the exception of 1995 for which we present the actual values of that year.

We notice that for small firms the average number of new R&D alliances decreased gradually during the final years of the 1980s from about 0.7 in 1986 to fewer than 0.55 in 1989 and this number declined even further to about 0.5 in 1990. In 1991 the number of new R&D alliances was still at a level of around 0.5. From 1992 onwards this number steadily increases and reaches the value of about 0.6 in 1995.

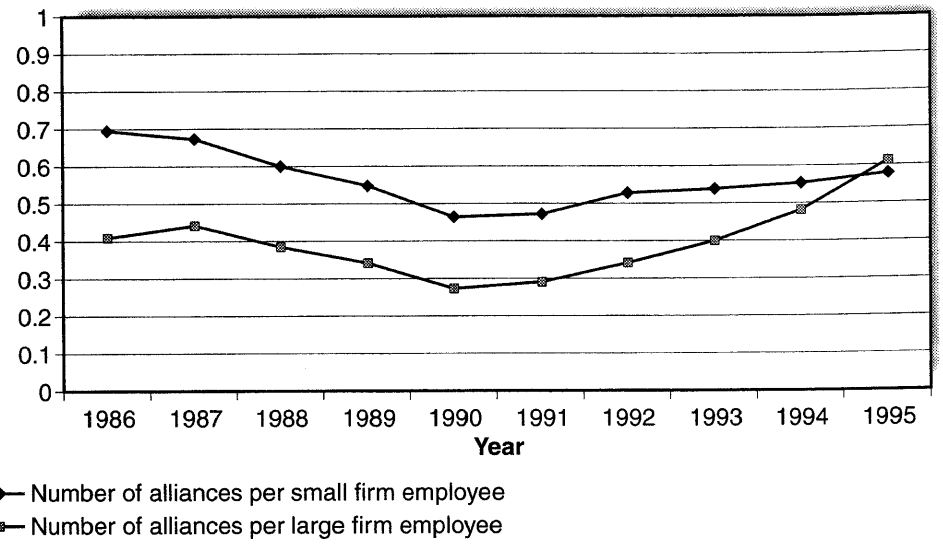


Figure 11.4 Number of newly established biotechnology R&D alliances per employee for small and large firms, mean numbers of employees are log values, three-year moving averages, 1985–95. *Source*: MERIT-CATI

The same pattern of decline in the average number of R&D partnerships during the second half of the 1980s is also found for large firms, albeit at a slightly lower level. Apart from a small increase in 1987, the final years of the 1980s are characterized by a gradual decrease in the average number of alliances from 0.4 in 1986 to fewer than 0.35 in 1989. After a further decline in 1990 to around 0.3 agreements, the number of newly made R&D partnerships took off again during the first half of the 1990s, which is characterized by a rather steep increase to 0.6 in 1995. This number is somewhat higher than the value that we found for small firms in the same year.

To evaluate the importance and magnitude of R&D alliances within and between different categories of companies, we calculated the number of annually, newly established R&D partnerships for large companies, small firms, and combinations of both. Figure 11.5 shows the evolution of the number of newly made alliances between firms of similar and different sizes. All numbers are calculated as three-year moving averages and expressed as percentages of the total number of annually, newly established R&D alliances.

If we consider the specific trend for the share of R&D partnerships between large pharmaceutical firms, we see that during the second half of the 1980s there is a gradual decline from an average share of more than 23 percent in the mid-1980s to around 15 percent in 1989. During the first years of the 1990s the share of R&D partnerships between large firms decreased even further to a level of less than 5 percent in 1992; in 1993 this share reached nearly 7 percent. After this small increase, the downward trend set in again until it arrived at a small share of less than 6 percent in 1994.

During the final years of the 1980s the share of alliances between small biotechnol-

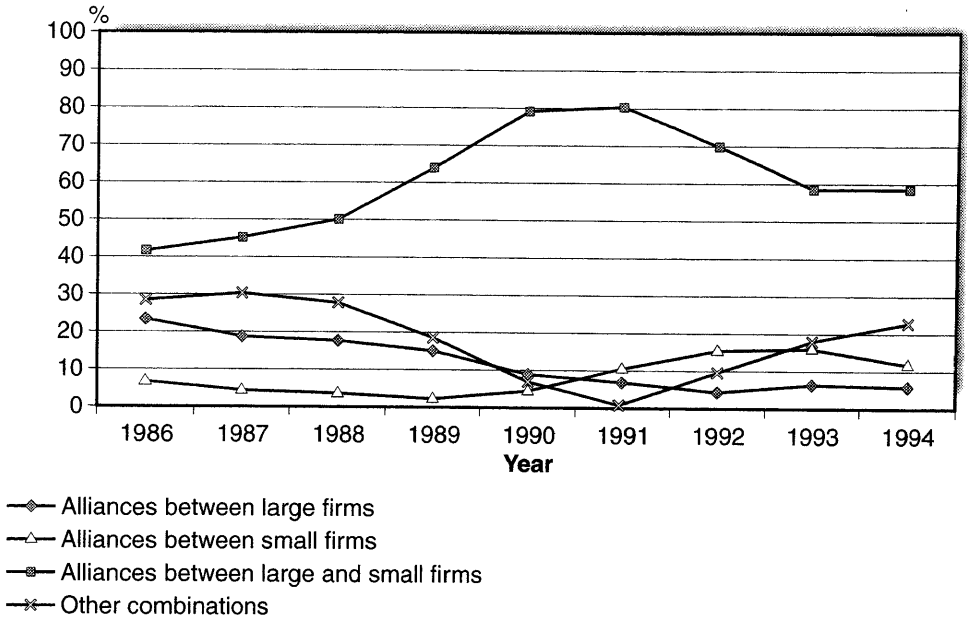


Figure 11.5 Distribution of newly established R&D alliances between firms of similar and different sizes, biotechnology, three-year moving averages, 1985–95. *Source*: MERIT-CATI

ogy firms in all R&D alliances steadily declined from an average of slightly less than 7 percent in 1986 to around 2 percent in 1989. This share reached nearly 5 percent in 1990 after which the upward trend continued until it arrived at a level of more than 16 percent in 1993. In 1994 the share decreased again to slightly more than 12 percent.

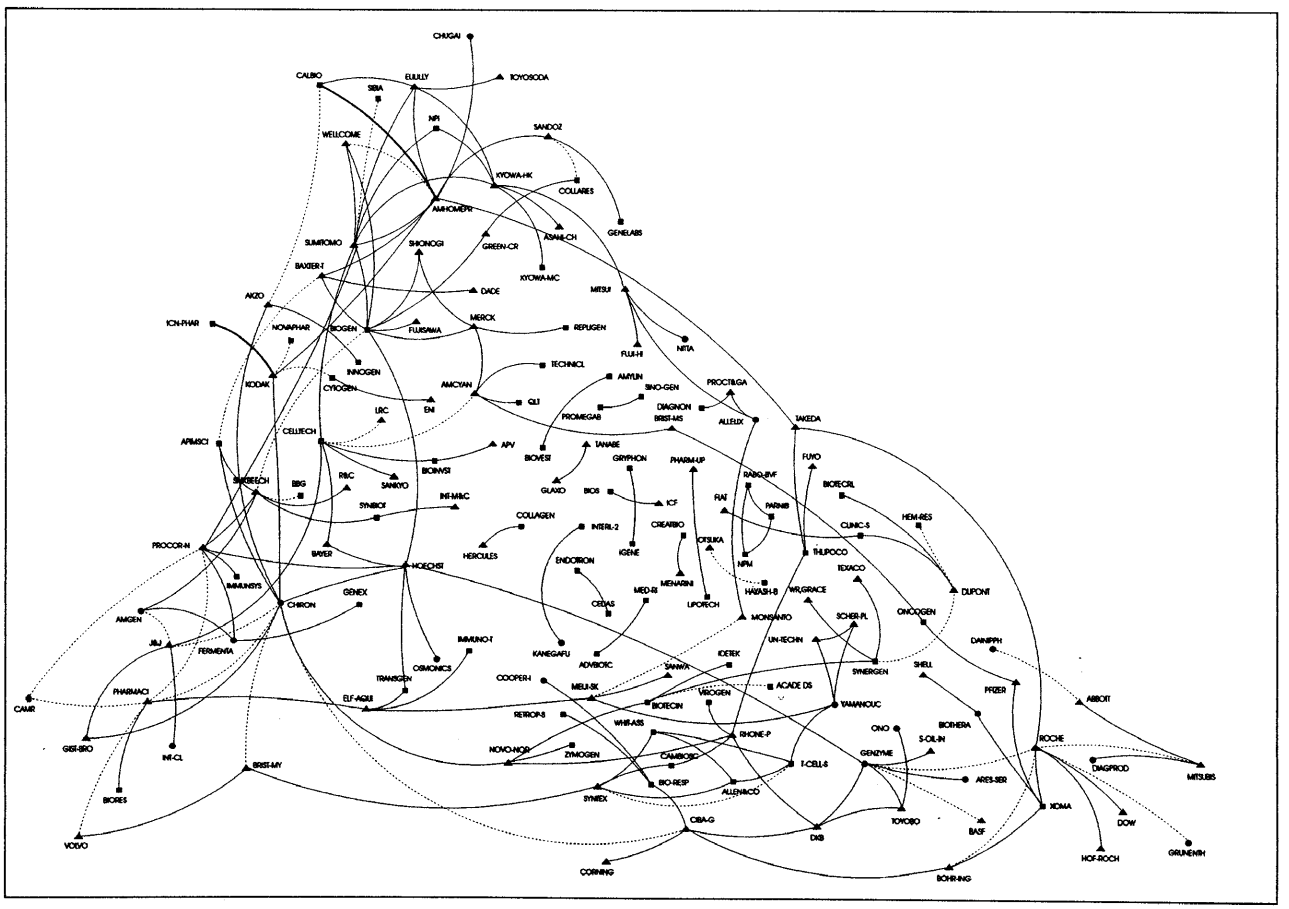
Examining the particular trend for the share of R&D alliances between large pharmaceutical firms and small biotechnology companies, we see that during the late 1980s there is a sharp increase from an average share of slightly more than 41 percent in the mid-1980s to nearly 64 percent in 1989. During the first years of the 1990s the average share of R&D alliances between large and small firms stabilized at a level of around 80 percent. After this short period of stabilization in the early 1990s, a sharp downward trend set in from 1992 onwards. It reached a level of less than 59 percent in 1993 and 1994.

The structure of inter-firm R&D networks

After having identified the basic trends in R&D partnering, we now turn to the particular evolution of R&D networks. We examine networks of R&D alliances at two distinct levels. First, we describe the basic characteristics of the overall network, mainly focusing on density in order to evaluate changes in the intensity of alliances between firms. We then evaluate the importance of particular players for the overall structure of the networks by examining the role of the most intense cooperating firms in biotechnology.

Table 11.2 Number of R&D alliances of the 25 most active network participants, 1985–7, 1989–91, and 1993–5. *Source*: MERIT-CATI

1985–7			1989–91			1993–5		
Chiron Corp	Medium	15	Roche Holding Ag	Large	7	Chiron Corp	Medium	19
Roche Holding Ag	Large	14	Smithkline Beecham Plc	Large	5	Smithkline Beecham Plc	Large	19
American Home Products Corp	Large	13	T Cell Sciences Inc	Small	4	Pfizer	Large	16
Eastman Kodak Co	Large	10	Merck and Co Inc	Large	4	Ciba Geigy Ag	Large	14
Pharmacia Ab	Large	10	Sandoz Ag	Large	4	Rhone Poulenc Sa	Large	13
Biogen Inc	Small	10	Glaxo Holdings Plc	Large	3	Hoechst Ag	Large	11
Sumitomo Corp	Large	10	Chiron Corp	Medium	2	Eli Lilly and Co	Large	11
Smithkline Beecham Plc	Large	9	American Home Products Corp	Large	2	Roche Holding Ag	Large	10
Johnson and Johnson	Large	9	Celltech Group Plc	Small	2	Glaxo Holdings Plc	Large	10
Celltech Group Plc	Small	9	Dupont Ei De Nemours and Co	Large	2	Johnson and Johnson	Large	9
Genzyme Corp	Medium	9	Dai Ichi Kangyo Bank Group	Large	2	Merck and Co Inc	Large	9
Procordia Nova Ab	Large	9	Repligen Corp	Small	2	Glaxo Wellcome Plc	Large	9
Hoechst Ag	Large	7	Dow Chemical Co	Large	2	American Home Products Corp	Large	8
Dupont Ei De Nemours and Co	Large	7	Cytel Corp	Small	2	Ligand Pharma-ceuticals Inc	Small	8
California Biotechnology Inc	Small	7	Biochem Pharma Inc	Small	2	Warner Lambert Co	Large	8
Ciba Geigy Ag	Large	6	Xenova Group Plc	Small	2	Bristol Myers Squibb Co Inc	Large	7
American Cyanamid Co Inc	Large	6	Solvay and Cie Sa	Large	2	Novo Nordisk As	Large	6
Syntex Corp	Large	6	Telios Pharmaceuticals Inc	Small	2	Allelix Bio-pharmaceuticals Inc	Medium	6
Kyowa Hakko Kogyo Co Ltd	Large	6	Biogen Inc	Small	1	Schering Plough Corp	Large	6
Biotechnology Investments Ltd	Small	6	Sumitomo Corp	Large	1	Pharmacia and Upjohn Inc	Large	6
Centre Applied Microbiology and Research	Ac/gov institution	6	Genzyme Corp	Medium	1	Astra Ab	Large	6
Rhone Poulenc Sa	Large	5	Procordia Nova Ab	Large	1	Corange Ltd	Large	6
Eli Lilly and Co	Large	5	California Biotechnology Inc	Small	1	Zeneca Group Plc	Large	6
Baxter Travenol Labs Inc	Large	5	Ciba Geigy Ag	Large	1	Onyx Pharmaceuticals Inc	Small	6
Amgen Inc	Medium	5	Syntex Corp	Large	1	Eastman Kodak Co	Large	5



▪ **Small companies** ▲ **Large companies** • **Medium-sized companies** • **Academic/governmental institutions**

Figure 11.6 R&D partnerships among cooperating companies in the pharma-biotechnology industry, 1985–7

Figures 11.6–11.8 give us a graphical representation of the R&D alliances in the biotechnology industry in the periods 1985–7, 1989–91, and 1993–5. Solid lines represent one alliance between companies, whereas dotted lines indicate two or three alliances. Thick solid lines indicate four or five alliances. See appendix I for company codes. For all MDS solutions presented in this chapter Kruskal's stress values range from good to very good (Kruskal and Wish, 1978), varying from 0.027 for the period 1985–7 to 0.004 for the period 1989–91.

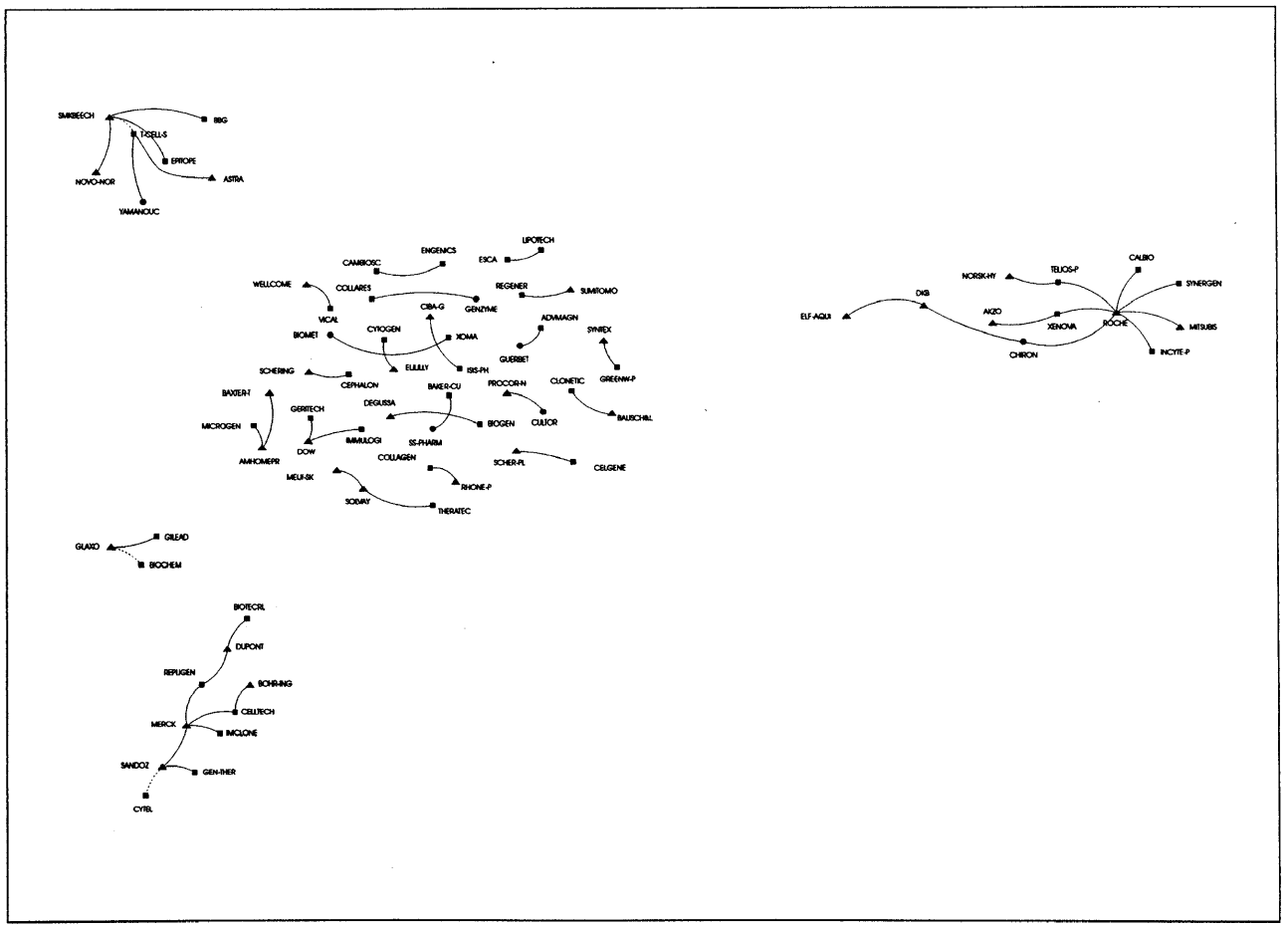
For an evaluation of the importance of small biotechnology firms and large pharmaceutical companies in R&D partnering, we refer to table 11.2. This table lists the 25 network participants with the most R&D alliances in the biotechnology industry during the periods 1985–7, 1989–91, and 1993–5.

The MDS plot for the period 1985–87 (figure 11.6) shows a rather dense network in which cooperation is not concentrated in any particular part of the network and the multitude of lines connects virtually all the companies in the network, either in a direct or indirect way. Although most firms are connected to at least two other partners, we also see quite a few one-on-one links. Many companies have engaged in at least two R&D alliances with one particular firm. This is illustrative for the growth in the number of alliances per firm during that time period.

If we look at the leading companies of the biotechnology network in the period 1985–7, we see that a number of small biotechnology companies such as Biogen, Celltech Group, and California Biotechnology keep very nodal positions in the network (see figure 11.6). These companies also rank high on the list of most intense cooperating companies (table 11.2). Apparently, many small biotechnology firms are attractive partners for large pharmaceutical corporations. Furthermore, the network is characterized by many strongly tied couples of small and large firms. A few important ties: Biogen and Smithkline Beecham, Celltech Group and American Cyanamid, California Biotechnology and American Home Products. Smithkline Beecham is found in the middle of an R&D network with specialized biotechnology companies such as Applied Immune Sciences and British Biotech, as well as a number of large-sized companies such as Procordia Nova. American Home Products, another leading pharmaceutical company, is mainly connected to large partners such as Eastman Kodak and Sumitomo.

Turning to the next period (1989–91) we find a somewhat different pattern (see figure 11.7). The MDS solution shows an extremely sparse network that involves 75 firms of which the vast majority are part of clusters of firms that are all centered around three focal players: Roche, Smithkline Beecham, and Merck. Although some firms are linked to more than one partner, we observe mostly one-on-one alliances. The majority of firms are connected to one specific partner through no more than one R&D alliance.

In the years 1989–91 the group of most partner-intensive companies in the network for the biotechnology industry covers a number of leading pharmaceutical companies as well as many small biotechnology firms (see table 11.2). We notice that the small biotechnology firms that have already been mentioned changed their positions in the rank order of leading R&D partnering firms, while several new small firms such as T Cell Sciences and Repligen entered the top ranking of cooperating companies. It is obvious that in this period R&D partnering has not led to a dense network and we



▪ **Small companies** ▲ **Large companies** • **Medium-sized companies** • **Academic/governmental institutions**

Figure 11.7 R&D partnerships among cooperating companies in the pharma-biotechnology industry, 1989–91

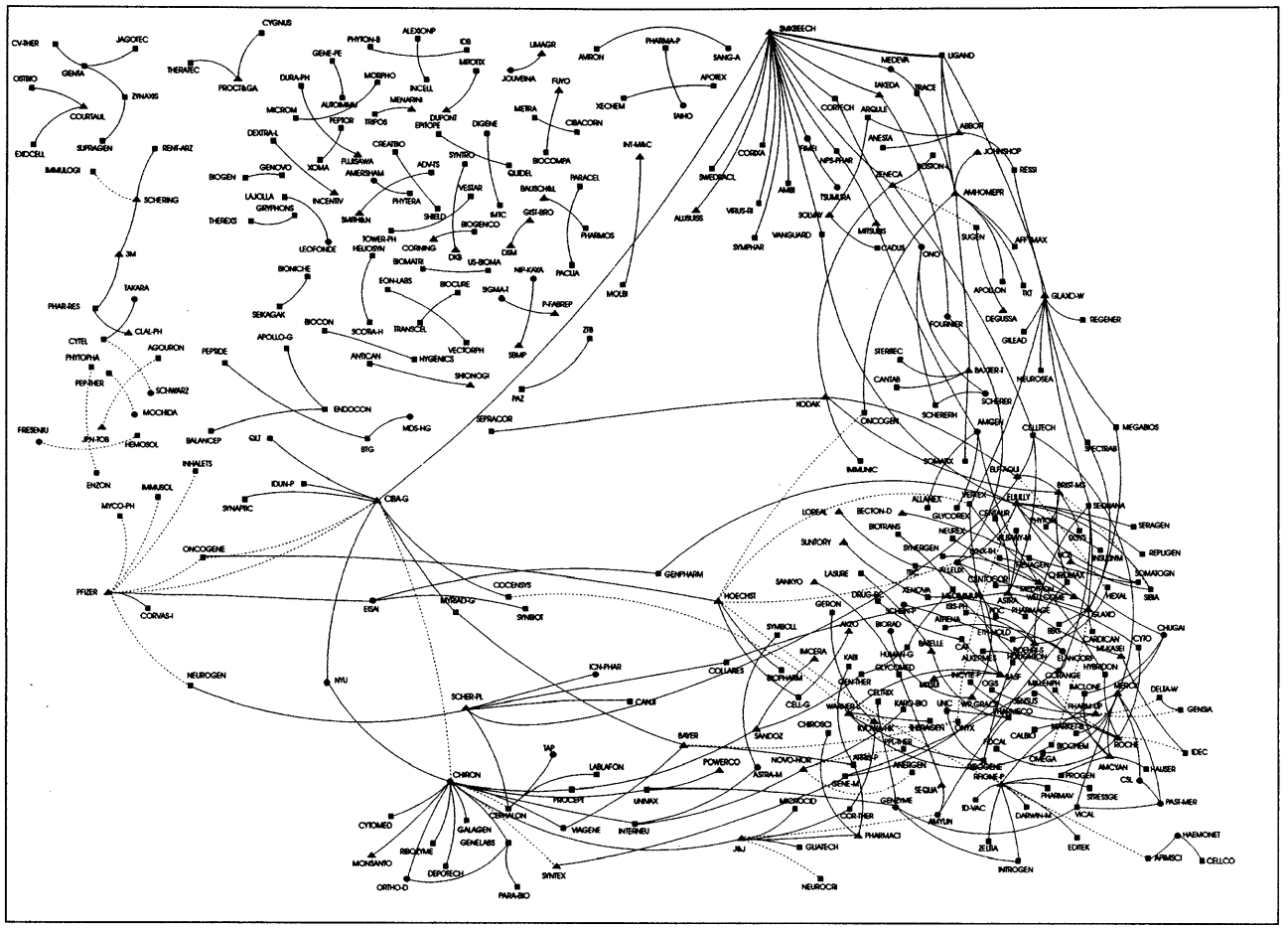


Figure 11.8 R&D partnerships among cooperating companies in the pharma-biotechnology industry, 1993–5

therefore focus on the somewhat denser clusters of cooperating firms that were found (see figure 11.7).

At the top left-hand side of figure 11.7 we can see one cluster involving a number of small and large cooperating companies, which are all centered around the leading pharmaceutical company Smithkline Beecham. A very nodal position in this cluster is held by T Cell Sciences, which is also closely tied to the core of the cluster. Within this cluster, Smithkline Beecham is mainly connected to small biotechnology firms. Glaxo Holdings is found in the middle of a second, somewhat smaller, R&D network with two specialized biotechnology companies, Biochem Pharma and Gilead Sciences. The strong ties between Glaxo Holdings and Biochem Pharma form the core of this cluster.

A third mixed cluster of small biotechnology firms and large pharmaceutical companies is found at the bottom left-hand side of figure 11.7. The core of this cluster is formed by two large pharmaceutical companies, Merck and Sandoz. If we study this particular cluster, we see that these large firms are mainly tied to a number of small biotech firms such as Celltech Group and Repligen that also hold nodal positions in the network. A large cluster of small and large firms is located at the right-hand side. This cluster is basically centered around the large pharmaceutical company Roche which is found in the middle of an R&D network with many specialized biotech companies. Two nodal biotechnology companies, Xenova Group and Telios Pharmaceuticals, hold important positions in this cluster.

The network density in the biotechnology sector shows a substantial increase if one compares the period 1993–5 (see figure 11.8) with 1989–91. During the period 1993–5, the many newly created R&D alliances between biotechnology companies and pharmaceutical firms resulted in a much denser network structure in which cooperation is mainly concentrated at the right-hand side of figure 11.8. Nearly all companies in this dense part of the network are either directly or indirectly connected to each other. However, as indicated by the network pattern at the left-hand side of figure 11.8, there still are a large number of one-on-one links in other parts of the network. Also, the number of firms that are connected to one particular partner through at least two alliances has increased, which is illustrative for the increase in the number of R&D partnerships per firm during this period.

Small firms that held strong positions in the rank order of most intense cooperating firms during the period 1989–91 have left the group of leading cooperating firms for the period 1993–5. Only two new young biotech firms, Ligand and Onyx, have entered this group (see table 11.2). The top of the network for the biotechnology industry during this time period covers only leading pharmaceutical companies such as Smithkline Beecham, Pfizer, and Ciba Geigy, which all hold nodal positions in the network. Ligand is strongly tied to Smithkline Beecham as well as to other large pharmaceutical firms such as Glaxo Wellcome (see figure 11.8). Onyx is tightly related to large companies such as Eli Lilly and Warner Lambert. Apart from R&D alliances with two nodal biotechnology companies, these large pharmaceutical firms are mainly connected to a wide variety of other small partners. In addition to this, some specific partnerships between large companies can be observed, such as the ties between Smithkline Beecham and Ciba Geigy and Warner Lambert and Basf.

Discussion and Conclusions

Our contribution aims at improving the understanding of the specific evolution of R&D partnerships and the related inter-firm networks in the biotechnology industry. In that context we pay extensive attention to the complementary role of small, entrepreneurial firms and large pharmaceutical companies in these R&D networks.

As also found in previous research (Hagedoorn, 1993; Kenney, 1986; Powell et al., 1996), the widespread collaboration between different groups of cooperating firms in the biotechnology industry has led to rather dense network-like structures of joint innovative activities. Small entrepreneurial biotechnology companies play an important role in these R&D networks. This role for small firms can clearly be understood in the light of the Schumpeterian tradition, where entrepreneurial firms are viewed as important generators of innovative change within new industries. In particular during the 1980s, the nodal role of small, new biotechnology firms coincides with major scientific and technological breakthroughs introduced by many of these new entrants in the pharmaceutical industry (Powell, 1996).

However, as the field of biotechnology has gradually matured, entrepreneurial biotechnology firms could have become less important for the newly developed R&D networks while large companies may have become more dominant. This more dominant role for large science-based firms in a more routinized innovative environment is particularly stressed in the later writings of Schumpeter (1942), see also Scherer (1984). Recent contributions (e.g., Senker, and Sharp, 1997) expect, however, that the nodal role of small biotechnology firms, as major players with multiple partnerships in R&D networks, will not decrease as the technology becomes more mature.

Our analysis reveals that during the second half of the 1980s, the R&D partnership-intensity of small firms was higher than for large companies. The more detailed analysis of the periods 1985–7 and 1989–91 shows that numerous entrepreneurial biotechnology firms kept very nodal positions in R&D networks, albeit next to several large pharmaceutical companies that were also well represented.

One of the other major observations in this chapter is the strong increase in the R&D alliance-intensity for large firms during the first half of the 1990s. At the end of the period this alliance-intensity of large firms exceeds the intensity found for small firms. The changing role of large pharmaceutical companies is also found in the analysis of the overall R&D network of the period 1993–5. This analysis shows that only two young biotechnology firms hold strong positions in the rank order of most intense cooperating firms and that the top positions of the network are mainly taken by leading pharmaceutical companies that hold nodal positions in the overall network.

In congruence with "early" Schumpetarian views, these results are indicative of the significant role played by small entrepreneurial biotechnology firms in innovation, particularly during the 1980s when the new biotechnology first became relevant to the pharmaceutical industry. The early 1990s, however, seem to demonstrate a decreasing importance of these small firms in inter-firm R&D networks if compared to the role of large pharmaceutical companies. These large companies developed into more dominant players with multiple partnerships, a change that is clearly more in line with expectations based on the later writings of Schumpeter.

The complementarity of the innovative capabilities of small, entrepreneurial biotechnology firms and large pharmaceutical companies has formed the basis for numerous R&D partnerships between these two groups of firms. An increasingly dominant role of large firms in all sorts of innovative activities might render these complementarities less obvious. The intensity of specific cooperation between groups of small and large companies, as well as of inter-firm collaboration in general, is then likely to drop off (Arora and Gambardella, 1990; Saviotti, 1998). However, others (Powell, 1996; Senker and Sharp, 1997) expect that entrepreneurial firms will continue to play a critical role in R&D networks with large companies and that intensive R&D collaboration in the biotechnology industry will therefore be of a more long-term nature.

Our analysis of the evolution of inter-firm R&D partnerships in the biotechnology industry reveals that during the first half of the 1990s there is an explosive growth in the number of R&D alliances per firm, accompanied by a strong increase in network density. This latter phenomenon is mainly due to an increase in the number of firms that are connected to one particular partner through at least two R&D alliances. In all of this, R&D alliances between two or more large firms played only a minor role and this share of large–large cooperation was even gradually decreasing. Alliances between large firms and small entrepreneurial companies, however, remained important throughout the period. The detailed analysis of the periods 1985–7, 1989–91 and 1993–5 demonstrates that R&D networks in the biotechnology industry are mainly characterized by many strongly tied couples of entrepreneurial biotechnology firms and large companies.

Our findings suggest that the 1990s have introduced a period of intensified R&D cooperation leading to denser inter-firm networks in the biotechnology industry. In these networks, the dominant role of entrepreneurial biotechnology firms as major players with many partnerships seems to be decreasing. However, as large pharmaceutical firms have increasingly become nodal players in R&D networks, their most preferred partners continue to be small biotechnology firms, implying a continuing mutual dependence between these two groups of firms.

Note

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Appendix 1 Network Participants Appearing in the MDS Graphs

Company label	Name of the company	Size	Company label	Name of the company	Size
3M	Minnesota Mining And Manufacturing Co	Large	INNOGEN	Innogenetics Sa	Small
ABBOTT	Abbott Laboratories	Large	INSULINM	Insulin Mimetics Ltd	Small
ACADE DS	Acade Diagnostic Systems	Small	INT-CL	Int Clinical Labs Inc	Medium
ADV-TS	Advanced Tissue Sciences Inc	Small	INT-M&C	Int Mineral and Chemical Corp	Large
ADVBIOTC	Advanced Biotherapy Concepts Inc	Small	INTERL-2	Interleukin 2 Inc	Small
ADVMAGN	Advanced Magnetics Inc	Small	INTERNEU	Interneuron Pharmaceuticals Inc	Small
AFFYMAX	Affymax Nv	Small	INTROGEN	Introgen Therapeutics Inc	Small
AGOURON	Agouron Pharmaceuticals Inc	Small	ISIS-PH	Isis Pharmaceuticals Inc	Small

Company label	Name of the company	Size	Company label	Name of the company	Size
AKZO	Akzo Nobel Nv	Large	IXSYS	Ixsys Inc	Small
ALBANY-M	Albany Molecular Research Inc	Small	J&J	Johnson and Johnson	Large
ALEXIONP	Alexion Pharmaceuticals Inc	Small	JAGOTEC	Jagotec Sa	Small
ALKERMES	Alkermes Inc	Small	JOHNSHOP	Johns Hopkins Health System Corp	Large
ALLANEX	Alanex Corp	Small	JOUVEINA	Jouveinal Sa	Medium
ALLELIX	Allelix Biopharmaceuticals Inc	Medium	JPN-TOB	Japan Tobacco Inc	Large
ALLEN&CO	Allen And Co	Small	KABI	Kabi Pharmacia	Small
ALUSUISS	Swiss Aluminium Ltd	Large	KANEGAFU	Kanegafuchi Chemical Industry Co Ltd	Medium
AMBI	Applied Microbiology Inc	Small	KARO-BIO	Karo Bio	Small
AMCYAN	American Cyanamid Co Inc	Large	KODAK	Eastman Kodak Co	Large
AMERSHAM	Amersham International Plc	Medium	KYOWA-HK	Kyowa Hakko Kogyo Co Ltd	Large
AMGEN	Amgen Inc	Medium	KYOWA-MC	Kyowa Medex Co	Small
AMHOMEPR	American Home Products Corp	Large	L'ORÉAL	L'Oréal Sa	Large
AMYLIN	Amylin Pharmaceuticals Inc	Small	LABLAFON	Laboratoire L Lafon	Small
ANERGEN	Anergen Inc	Small	LAJOLLA	La Jolla Pharmaceutical Com	Small
ANESTA	Anesta Corp	Small	LASURE	Lasure and Crawford	Small
ANTICAN	Anticancer Inc	Small	LEOFONDE	Leo Fondet	Medium
APIMSCI	Applied Immune Sciences Inc	Small	LIGAND	Ligand Pharmaceuticals Inc	Small
APOLLO-G	Apollo Genetics Inc	Small	LIMAGR	Limagrain Group	Large
APOLLON	Apollon Inc	Small	LIPOTECH	Liposome Technology Inc	Small
APOTEX	Apotex Inc	Small	LRC	London Rubber Co Int Plc	Large
APV	Apv Plc	Large	LYNX-TH	Lynx Therapeutics Inc	Small
ARES-SER	Ares Serono Ag	Medium	MARKET-B	Martek Biosciences Corp	Small
ARQULE	Arqule Inc	Small	MDS-HG	Mds Health Group Ltd	Medium
ARRIS-P	Arris Pharmaceutical Corp	Small	MED-RI	Medical Research Int Ltd	Small
ASAHI-CH	Asahi Chemical Industry Co Ltd	Large	MEDEVA	Medeva Plc	Medium
ASTRA	Astra Ab	Large	MEDIMMUN	Medimmune Inc	Small
ASTRA-M	Astra Merck Inc	Medium	MEDTRON	Medtronic Inc	Large
ATHENA	Athena Neurosciences Inc	Small	MEGABIOS	Megabios Corp	Small
AUTOIMMU	Autoimmune Inc	Small	MEIJI-SK	Meiji Seika Kaisha Ltd	Large
AVIRON	Aviron	Small	MENARINI	Menarini Industrie Farmaceutiche	Large
BAKER-CU	Baker Cummins Inc	Small	MERCK	Merck and Co Inc	Large

Company label	Name of the company	Size	Company label	Name of the company	Size
BALANCEP	Balance Pharmaceuticals Inc	Small	METRA	Metra Biosystems Inc	Small
BASF	Basf Ag	Large	MI-KASEI	Mitsubishi Kasei Corp	Large
BATELLE	Battelle Memorial Institute Inc	Large	MICROCID	Microcide Pharmaceuticals Inc	Small
BAUSCH&L	Bausch and Lomb Inc	Large	MICROGEN	Microgen Inc	Small
BAXTER-T	Baxter Travenol Labs Inc	Large	MICROM	Micromet GmbH	Small
BAYER	Bayer Ag	Large	MILLENPH	Millennium Pharmaceuticals Inc	Small
BBG	British Biotech Plc	Small	MITOTIX	Mitotix Inc	Small
BECTON-D	Becton Dickinson and Co Inc	Large	MITSUBIS	Mitsubishi Corp	Large
BIO-RESP	Bio Response Inc	Small	MITSUI	Mitsui Group	Large
BIOCHEM	Biochem Pharma Inc	Small	MOCHIDA	Mochida Pharmaceutical Co Ltd	Medium
BIOCOMPA	Biocompatibles Int Plc	Small	MOLBI	Molecular Biosystems Inc	Small
BIOCON	Biocon Inc	Small	MONSANTO	Monsanto Co	Large
BIOCURE	Biocure Holdings Plc	Small	MORPHO	Morphosys GmbH	Small
BIOGEN	Biogen Inc	Small	MYCO-PH	Myco Pharmaceuticals Inc	Small
BIOGENCO	Biosource Genetics Corp	Small	MYRIAD-G	Myriad Genetics Inc	Small
BIOINVST	Bioinvest	Small	NEUREX	Neurex Corp	Small
BIOMATRI	Biomatrix Inc	Small	NEUROCRI	Neurocrine Biosciences Inc	Small
BIOMET	Biomet Inc	Medium	NEUROGEN	Neurogen Corp	Small
BIONICHE	Bioniche Inc	Small	NEUROSEA	Neurosearch As	Small
BIOPHARM	R Biopharm GmbH	Small	NEXAGEN	Nexagen Inc	Small
BIORAD	Bio Rad Laboratories Inc	Medium	NIP-KAYA	Nippon Kayaku Co Ltd	Medium
BIORES	Biores Bv	Small	NITTA	Nitta Gelatin Inc	Medium
BIOS	Bios Corp	Small	NORSK-HY	Norsk Hydro As	Large
BIOTECIN	Biotechnology Investments Ltd	Small	NOVAPHAR	Nova Pharmaceutical Corp	Small
BIOTECRL	Biotech Research LABS	Small	NOVO-NOR	Novo Nordisk As	Large
BIOTHERA	Biotherapeutics Corp	Small	NPI	Newport Pharmaceuticals Int Inc	Small
BIOTRANS	Biotransplant Inc	Small	NPM	Nederlandse Participatie Maatschappij	Small
BIOVEST	Biovest Partners	Small	NPS-PHAR	Nps Pharmaceuticals Inc	Small
BOEHRI-S	Boehringer Sohn Ch	Large	NYU	State University of New York	Ac/gov institution
BOHR-ING	Boehringer Ingelheim	Large	OGS	Oxford Glycosystems Group Plc	Small
BOSTON-L	Boston Life Sciences Inc	Small	OMEGA	Omega Biologicals Inc	Small

Company label	Name of the company	Size	Company label	Name of the company	Size
BRIST-MS	Bristol Myers Squibb Co Inc	Large	ONCOGEN	Oncogen	Small
BRIST-MY	Bristol Myers Co	Large	ONCOGENE	Oncogene Science Inc	Small
BTG	Btg Plc	Small	ONO	Ono Pharmaceutical Co Ltd	Medium
CADUS	Cadus Pharmaceutical Corp	Small	ONYX	Onyx Pharmaceuticals Inc	Small
CALBIO	California Biotechnology Inc	Small	ORTHO-D	Ortho Clinical Diagnostics Inc	Medium
CAMBIOSC	Cambridge Bioscience Corp	Small	OSMONICS	Osmonics Inc	Medium
CAMR	Centre Applied Microbiology and Research	Ac/gov institution	OSTBIO	Osteometer Biotech	Small
CANJI	Canji Inc	Small	OTSUKA	Otsuka Pharmaceutical Co Ltd	Large
CANTAB	Cantab Pharmaceuticals Plc	Small	P-FABREP	Pierre Fabre Participations	Large
CARDICAN	Cardican	Small	PACLIA	Pacific Liaisons	Small
CAT	Cambridge Antibody Technology Group Plc	Small	PARA-BIO	Pharmadigm Biosciences Inc	Small
CELGENE	Celgene Corp	Small	PARACEL	Paracelsian Inc	Small
CELIAS	Celias	Small	PARNIB	Parnib	Small
CELL-G	Cell Genesys Inc	Small	PAST-MER	Pasteur Merieux Msd	Medium
CELLCO	Cellco Inc	Small	PAZ	Paz GmbH	Small
CELLTECH	Celltech Group Plc	Small	PDC	Pharmaceutical Discovery Corp	Small
CELTRIX	Celtrix Pharmaceuticals Inc	Small	PEP-THER	Peptide Therapeutics	Small
CENTAUR	Centaur Pharmaceuticals Inc	Small	PEPTIDE	Peptide Technology Ltd	Small
CENTOCOR	Centocor Inc	Small	PEPTOR	Peptor Ltd	Small
CEPHALON	Cephalon Inc	Small	PFIZER	Pfizer	Large
CHIRON	Chiron Corp	Medium	PHAR-RES	Pharmaceutical Resources Inc	Small
CHIROSCI	Chiroscience Group Plc	Small	PHARM-UP	Pharmacia and Upjohn Inc	Large
CHROMAX	Chromaxome Corp	Small	PHARMA-P	Pharma Patch Plc	Small
CHUGAI	Chugai Pharmaceutical Co Ltd	Medium	PHARMACI	Pharmacia Ab	Large
CIBA-G	Ciba Geigy Ag	Large	PHARMAGE	Pharmagenics Inc	Small
CIBACORN	Ciba Corning Diagnostics Corp	Small	PHARMAV	Pharmavene Inc	Small
CLAL-PH	Clal Israel Ltd	Large	PHARMECO	Pharm Eco Laboratories Inc	Small
CLINIC-S	Clinical Sciences Inc	Small	PHARMOS	Pharmos Corp	Small
CLONETIC	Clonetics Corp	Small	PHYTERA	Phytera Inc	Small
COCENSYS	Cocensys Inc	Small	PHYTON	Phyton Catalytic Inc	Small
COLLAGEN	Collaborative Genetics Corp	Small	PHYTON-B	Phyton Inc	Small

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COLLARES	Collaborative Research Inc	Small	PHYTOPHA	Phytopharmaceuticals Inc	Small
COOPER-I	The Cooper Companies Inc	Medium	POWERCO	Power Corp of Canada	Large
COR-THER	Cor Therapeutics Inc	Small	PPL-THER	Ppl Therapeutics Plc	Small
CORANGE	Corange Ltd	Large	PROCEPT	Procept Inc	Small
CORIXA	Corixa Corp	Small	PROCOR-N	Procordia Nova AB	Large
CORNING	Corning Glass Works	Large	PROCT&GA	Procter and Gamble Co	Large
CORTECH	Cortech Inc	Small	PROGEN	Progenics Pharmaceuticals Inc	Small
CORVAS-I	Corvas Int Inc	Small	PROMEGAB	Promega Corp	Small
COURTAUL	Courtaulds Plc	Large	QLT	Qlt Phototherapeutics Inc	Small
CREATBIO	Creative Biomolecules Inc	Small	QUIDEL	Quidel Corp	Small
CSL	Csl Ltd	Medium	R&C	Reckitt and Colman Plc	Large
CULTOR	Cultor Oy	Medium	RABO-BVF	Rabobank Biotech Venture Fund	Small
CV-THER	Cv Therapeutics Inc	Small	REGENER	Regeneron Pharmaceuticals Inc	Small
CYGNUS	Cygnus Therapeutic Systems	Small	RENT-ARZ	Dr Rentschler Arzneimittel GmbH and Co.	Small
CYTEL	Cytel Corp	Small	REPLIGEN	Repligen Corp	Small
CYTO	Cytotherapeutics Inc	Small	RESSI	Ressi Group Inc	Small
CYTOGEN	Cytogen Corp	Small	RETROP-S	Retroperfusion Systems Inc	Small
CYTOMED	Cytomed Inc	Small	RHONE-P	Rhone Poulenc SA	Large
DADE	Dade Int Inc	Large	RIBOGENE	Ribogene Inc	Small
DAINIPPH	Dainippon Pharmaceutical Co Ltd	Medium	RIBOZYME	Ribozyme Pharmaceuticals Inc	Small
DARWIN-M	Darwin Molecular Corp	Small	ROCHE	Roche Holding Ag	Large
DEGUSSA	Degussa Ag	Large	S-OIL-N	Amoco Standard Oil of Indiana	Large
DELTA-W	Delta West Pty Ltd	Small	SANDOZ	Sandoz Ag	Large
DEPOTECH	Depotech Corp	Small	SANG-A	Sang A Pharma Co Ltd	Small
DEXTRA-L	Dextra Laboratories	Small	SANKYO	Sankyo Com Ltd	Large
DIAGNON	Diagnon Corp	Small	SANWA	Sanwa Group	Large
DIAGPROD	Diagnostic Products Corp	Medium	SBMP	Snow Brand Milk Products Co Ltd	Large
DIGENE	Digene Corp	Small	SCHEIN-P	Schein Pharmaceutical Inc	Medium
DKB	Dai Ichi Kangyo Bank Group	Large	SCHER-PL	Schering Plough Corp	Large
DOW	Dow Chemical Co	Large	SCHERER	Rp Scherer Corporation	Medium
DRUG-RC	Drug Royalty Corp	Small	SCHERERH	Scherer Healthcare Inc	Small
DSM	Dsm NV	Large	SCHERING	Schering Ag	Large
DUPONT	Dupont E I De Nemours and Co	Large	SCHWARZ	Schwarz Pharma Ag	Medium

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DURA-PH	Dura Pharmaceuticals Inc	Small	SCOTIA-H	Scotia Holdings Plc	Small
EDITEK	Editek Inc	Small	SEIKAGAK	Seikagaku Kogyo Corp	Small
EISAI	Eisai Co Ltd	Medium	SENSUS	Sensus Drug Development Corp	Small
ELANCORP	Elan Corp Plc	Medium	SEPRACOR	Sepracor Inc	Small
ELF-AQUI	Elf Aquitaine Sa	Large	SEQUA	Sequa Corp	Large
ELILILLY	Eli Lilly and Co	Large	SEQUANA	Sequana Therapeutics Inc	Small
ENDOCON	Endocon Inc	Small	SERAGEN	Seragen Inc	Small
ENDOTRON	Endotronics Inc	Small	SHELL	Shell Nv	Large
ENGENICS	Engenics	Small	SHIELD	Shield Diagnostics Ltd	Small
ENI	Eni Group Ente Nazionale Idrocarburi	Large	SHIONOGI	Shionogi and Co Ltd	Large
ENZON	Enzon Inc	Small	SIBIA	Sibia Neurosciences Inc	Small
EON-LABS	Eon Labs	Small	SIGMA-T	Sigma Tau	Medium
EPITOPE	Epitope Inc	Small	SINO-GEN	Sino Genetic	Small
ESCA	Escagenetics Corp	Small	SMITH&N	Smith and Nephew Plc	Large
ETH-HOLD	Ethical Holdings Plc	Small	SMKBEECH	Smithkline Beecham Plc	Large
EXOCELL	Exocell Inc	Small	SOLVAY	Solvay and Cie Sa	Large
FERMENTA	Fermenta Ab	Medium	SOMATIX	Somatix Therapy Corporation	Small
FIAT	Fiat Spa	Large	SOMATOGN	Somatogen Inc	Small
FIMEI	Fimei Finanziaria Industriale Mob. Ed Immob. Spa	Medium	SPECTRAB	Spectra Biomedical Inc	Small
FOCAL	Focal Inc	Small	SS-PHARM	Ss Pharmaceutical Co Ltd	Medium
FOURNIER	Fournier Industrie et Sante	Medium	STERICEC	Steritech Inc	Small
FRESENIU	Fresenius Ag	Medium	STRESSGE	Stressgen Biotechnologies Corp	Small
FUJI-HI	Fuji Heavy Industries Ltd	Large	SUGEN	Sugen Inc	Small
FUJISAWA	Fujisawa Pharmaceutical Co Ltd	Large	SUMITOMO	Sumitomo Corp	Large
FUYO	Fuyo Group	Large	SUNTORY	Suntory	Large
GALAGEN	Galagen Inc	Small	SUPRAGEN	Supragen Inc	Small
GEN-THER	Genetic Therapy Inc	Small	SWEDBACL	Sbl Vaccin Ab	Small
GENE-M	Genemedicine Inc	Small	SYMBOLL	Symbollon Corp	Small
GENE-PE	Gene Pharming Europe Bv	Small	SYMPHAR	Symphar Sa	Small
GENELABS	Genelabs Technologies Inc	Small	SYNAPTIC	Synaptic Pharmaceuticals Corp	Small
GENEX	Genex Corp	Small	SYNBIOT	Synbiotics Corp	Small
GENOVO	Genovo Inc	Small	SYNERGEN	Synergen Inc	Small
GENPHARM	Genpharm Int	Small	SYNTEX	Syntex Corp	Large
GENSIA	Gensia Pharmaceuticals Inc	Small	SYNTRO	Syntro Corp	Small

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GENTA	Genta Inc	Small	T-CELL-S	T Cell Sciences Inc	Small
GENZYME	Genzyme Corp	Medium	TAIHO	Taiho Pharmaceutical Co Ltd	Medium
GERITECH	Geritech Inc	Small	TAKARA	Takara Shuzo Co Ltd	Medium
GERON	Geron Corp	Small	TAKEDA	Takeda Chemical Industries Ltd	Large
GILEAD	Gilead Sciences Inc	Small	TANABE	Tanabe Seiyaku Co Ltd	Large
GIST-BRO	Gist Brocades Nv	Large	TAP	Tap Pharmaceuticals Inc	Medium
GLAXO	Glaxo Holdings plc	Large	TBC	Texas Biotechnology Corp	Small
GLAXO-W	Glaxo Wellcome Plc	Large	TECHNICL	Techniclone International Corp	Small
GLIATECH	Gliatech Inc	Small	TELIOS-P	Telios Pharmaceuticals Inc	Small
GLYCOMED	Glycomed Inc	Small	TEXACO	Texaco Inc	Large
GLYCOREX	Glycorex	Small	THERAGEN	Theragen Inc	Small
GREEN-CR	Green Cross Corp	Large	THERATEC	Theratech Inc	Small
GREENW-P	Greenwich Pharmaceuticals Inc	Small	THEREXS	Therexsys	Small
GRUNENTH	Gruenenthal GmbH	Medium	THLIPOCO	The Liposome Co Inc	Small
GRYPHON	Gryphon Ventures	Small	TKT	Transkaryotic Therapies Inc	Small
GRYPHONS	Gryphon Sciences	Small	TOWER-PH	Towers Phytochemical Ltd	Small
GUERBET	Guerbet Sa	Medium	TOYOBO	Toyo Boseki Co Ltd	Large
HAEMONET	Haemonetics Corporation	Medium	TOYOSODA	Toyo Soda Manufacturing Co Ltd	Large
HAUSER	Hauser Chemical Research Inc	Small	TRACE	Trace Computers Plc	Small
HAYASH-B	Hayashibira Biochemical	Small	TRANSCEL	Transcell Technologies Inc	Small
HELIOSYN	Heliosynthese Sa	Small	TRANSGEN	Transgene	Small
HEM-RES	Hem Research Inc	Small	TRIPOS	Tripos Inc	Small
HEMOSOL	Hemosol Inc	Small	TSUMURA	Tsumura Juntendo Inc	Medium
HERCULES	Hercules Inc	Large	UCB	Union Chemique Belge Sa	Large
HEXAL	Hexal Pharma Ag	Small	UN-TECHN	United Technologies Corp	Large
HOECHST	Hoechst Ag	Large	UNC	University Of North Carolina	Ac/gov institu-tion
HOF-ROCH	Hoffmann La Roche and Do Ag	Large	UNIVAX	Univax Biologics Inc	Small
HOUGHTON	Houghton and Co	Small	US-BIOMA	Usbiomaterials Corp	Small
HUMAN-G	Human Genome Sciences Inc	Small	VANGUARD	Vanguard Medica	Small
HYBRIDON	Hybridon Inc	Small	VECTORPH	Vectorpharma International Corp	Small

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HYGENICS	Hygenics Pharmaceuticals Inc	Small	VERTEX	Vertex Pharmaceuticals Inc	Small
ICF	Icf Inc	Large	VESTAR	Vestar Inc	Small
ICN-PHAR	Icn Pharmaceuticals Inc	Medium	VIAGENE	Viagene Inc	Small
ID-VAC	Id Vaccine Corp	Small	VICAL	Vical Inc	Small
IDB	Idb Holding Spa	Small	VIROGEN	Virogenetics Corp	Small
IDEC	Idec Pharmaceuticals Corp	Small	VIRUS-RI	Virus Research Institute Inc	Small
IDETEK	Idetek Inc	Small	VOLVO	Volvo ab	Large
IDUN-P	Idun Pharmaceuticals Inc	Small	WARNER-L	Warner Lambert Co	Large
IGENE	Igene Biotechnology Inc	Small	WELLCOME	Wellcome Group	Large
IMCERA	Imcera Group Inc	Large	WHIT-ASS	Whitehead Associates	Small
IMCLONE	Imclone Systems Inc	Small	WR.GRACE	Wr Grace and Co	Large
IMMULOGI	Immulogic Pharmaceutical Corp	Small	XECHEM	Xechem International Inc	Small
IMMUNIC	Immunicon Corp	Small	XENOVA	Xenova Group Plc	Small
IMMUNOT	Immunotech Sa	Small	XOMA	Xoma Corp	Small
IMMUNSYS	Immunsystem	Small	YAMANOUC	Yamanouchi Pharmaceutical Co Ltd	Medium
IMMUSOL	Immusol Inc	Small	ZELTIA	Zeltia Sa	Small
IMTC	Imtc Holdings Inc	Small	ZENECA	Zeneca Group Plc	Large
INCELL	Incell Corp	Small	ZTB	Ztb Gmbh	Small
INCENTIV	Incentive Ab	Large	ZYMOGEN	Zymogenetics Inc	Small
INCYTE-P	Incyte Pharmaceuticals Inc	Small	ZYNAXIS	Zynaxis	Small
INHALETS	Inhale Therapeutic Systems Inc	Small			