

Tapping into Public Research.
Why are US Combinatorial Synthesis Firms more Successful than their European Counterparts?

Paper prepared for the EPRIS Conference
London, Great Britain, December 14-15th 2000

First Draft: December 2000 -please do not quote

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Abstract

This paper is primarily concerned with a competence-enhancing discontinuity- this time set off by combinatorial synthesis methods- and the ways in which universities, public and private non-profit research institutions have integrated these research tools into industry. Using ad hoc data from the field, it shows that while the first combinatorial methods had been invented in an Hungarian university and a Dutch public research institute, the greater capacity of US universities, public and private non-profit institutions, most notably the Scripps Research Institute, to absorb, generate and transfer knowledge into industry through network activities and spin-offs could have contributed to reinforce the position of American combinatorial chemistry firms. It therefore focuses on the role of institutional aspects of technological change: on public research, technology transfer mechanisms, and policies affecting the commercialization of public research.

Aldo Geuna from SPRU (GB) has given substantial contributions to the development of this paper.

1. Introduction

In 1996, *The Economist* put combinatorial chemistry on its list of technologies "to watch". Two years later, the scientific journal *Science* (1998) brought further attention to combinatorial synthesis, recognizing it as one of nine discoveries that transform our ideas about the natural world. And yet, social scientists have had little to say about what is perhaps the most exciting technological achievement to happen in the pharmaceutical industry since the first gene splicing experiment by Cohen and Boyer in 1973. There has been no recent empirical work assessing this technology and the firms that have embraced it through the lens of economics of technological change. Nor do we know much the reasons behind the following paradox: the first methods appeared in an Hungarian University and a Dutch public research institute, but the American combichem sector, which encompasses 191 start-ups, appears to be significantly stronger than the European Union-based combichem industry, which comprises 47 firms. The predominance and strengths of the US industry probably owe much to several different interrelated factors, including the existence of sophisticated venture capital system, a highly individualistic entrepreneurial culture, a large biotechnology industry, etc. In this paper, it will be argued, with some caveats, that US universities and scientific institutions are much more involved in the technological transfer of combichem knowledge and innovations into industry than their EU-based counterparts. Specifically, the strengths of the US combichem industry will be interpreted as the logical outcome of the higher levels of public research and diffusion carried out in this country.

The paper is organized in three sections and one annex. The first section briefly looks at the combinatorial synthesis methods. Without wishing to present an exhaustive technical account, a few background facts about the origins, potentials, bottlenecks, and underlying knowledge base of combinatorial chemistry is a useful starting point, as will be shown later, in any discussion about the contributions of academic and public research to industry. The second section describes the "combichem industry". American combichem firms will be compared to EU-based combichem firms and American dedicated biotechnology firms, and each continent contrasted in terms of patent and publication share as well as formal and informal networking activities. In the third section the main question being asked is whether universities, public and private non-profit institutions play an active role in enhancing the competitive standing of the US and the European Union combichem industry. Four technology transfer mechanisms are examined: 1) university-based training; 2) the creation of spin-offs; 3) formal networks; and 4) informal networks. Finally, the annex addresses the question of data collection in the field of combinatorial chemistry.

2. Does the Emergence of Combinatorial Synthesis Methods Introduce a Technological Discontinuity?

Although combinatorial chemistry is often spoken of as a single research tool, the pharmaceutical industry currently exploits dozens of combinatorial synthesis methods, including the portioning-mixing synthesis (Furka 1982), the parallel synthesis method (Geysen et al. 1984), the "tea-bag" technique (Houghten 1985), the cellulose paper disk method (Doerhing 1988), the light-directed synthesis method (Fodor et al. 1991), the "divide-couple-and-recombine" method (Houghten et al. 1991), the split synthesis method (Lam et al. 1991), and the SPOT synthesis method (Frank 1992). The diversity of combinatorial synthesis techniques is further reinforced by the fact that combinatorial drug discovery projects may use different building blocks (from DNA to small chemical molecules), screening strategies (from deconvolution methods to high-throughput screening), automation levels (from simple automated dilution device to complex workstation), etc. Despite these differences, however, it is reasonably safe to say that most combinatorial synthesis techniques have evolved from two different methodological schemes: i) the portioning-mixing synthesis method; and ii) the parallel synthesis method.

The Origins

The portioning-mixing method surfaced in 1982, when Árpád Furka at Eötvös University in Budapest (HU) described the process in an unpublished -albeit notarized- theoretical study. The portioning-mixing method usually involves generating thousands of compounds on solid-support beads in a vessel. The compounds are then split into more vessels and subjected to a different chemical reaction, and then pool again. The mixture-based process can be reiterated several times, leading to an exponential growth of compounds. The method, however, seemed impossible to patent at the time, and the portioning-mixing process only reached wider audience in 1991, when Furka and colleagues published their results in the International Journal of Peptide and Protein Research (Furka et al. 1991). This was done pretty much at the same time as Lam et al. (1991) from Arizona Cancer Center (US) and Houghten et al. (1991) from the Scripps Research Institute (US) announced a similar method in the same issue of Nature. The second methodological scheme, that of parallel synthesis, may cautiously be credited to Mario Geysen, Rob Meloen and Simon Barteling (1984). Geysen, an Australian scientist from Commonwealth Serum Laboratories (CSL; AUS), and Meloen and Barteling from the Central Veterinary Institute in Lelystad in the Netherlands, had discovered a way to synthesize in parallel hundreds of peptides in a reusable format for ELISA assay with antibodies.

The Potentials

The emergence of these two research tools marked a turning point in the history of drug discovery for a simple, powerful reason. Combinatorial synthesis methods produce molecular entities in previously inconceivable quantity and speed, which greatly extent the scope of compounds being screened for biological activity and reduce the cost it takes for launching a new drug to market. The infant combinatorial techniques, suspect experts, could even mean that the time required to develop a drug, which currently takes up to 10 years, could be knocked off by as much as four years (Supplee 1997). An illuminating illustration of these potentials are presented by Thomke, von Hippel and Franke (1998) in what is perhaps the only field study on combinatorial chemistry carried out by economists (see table 1). Using data by the combinatorial synthesis firm Pharmacoopia (NJ, US), one of the most innovative firm in the industry, the authors weighed the development time, cost and experimentation strategies of parallel combinatorial chemistry against those of traditional medicinal chemistry in a drug discovery program aimed at treating glaucoma. In all respects, combinatorial chemistry wins hands down.

Table 1

Comparing the parallel combinatorial chemistry approach with serial traditional medicinal chemistry in the discovery of promising lead compounds for the treatment of glaucoma

Project variable	Combinatorial approach	Traditional approach
(1) Total development time	3.5 months	5 years
(2) No. of chemists needed	4	15
(3) No. of compounds tested	~ 9000	3750
(4) No. of (serial) rounds	1	100 (250 max)
(5) No. of compounds per round	~ 9000	~ 38
(6) Cost of screen per round	US\$10,000	US\$10,000
(7) Total cost (chemists only) million	US\$167,000	US\$18.75
(8) Total cost per compound	US\$ 19	US\$5,000

Source: Thomke et al. (1998)

While combinatorial chemistry has yet to yield a single product, dozens of combinatorial drugs are currently awaiting approval by regulatory agencies (Beeley 2000). The intensity of the activity involved -hundreds of millions of new, diverse compounds are being synthesized and screened for pharmacological potency- has meant that combinatorial synthesis methods had spurred a renaissance of the old screening paradigm. In this connection, the first large collections of molecular compounds, also known as combinatorial libraries, might have been an eye-opener, for the early days of combinatorial chemistry, as with so many other important innovations, had

been characterized by widespread skepticism. Many medicinal chemists, as well as scientific publications and large pharmaceutical companies alike, believed the methods were completely ugly, too empirical, disappointing, not reproducible, not practical, inelegant and unscientific (Service 1998; Lebl 1998). The very persistence and ingenuity of combinatorial chemists, as well as the size of combinatorial libraries, which in exceptional cases can be made of up to 10¹² compounds, may have contributed to turn the modus operandi of medicinal chemists upside-down, forcing them to change, to quote one scientist, "the thinking about numbers of compounds from hundreds to millions and billions" (Lebl 1998:5).
The Bottlenecks

Granted, the initial combinatorial methods had been introduced in a crude form, impaired by several technical shortcomings. Still, there is little doubt that scientists, sensing enormous opportunities in the commercialization of products and services in different markets and even industries, made great strides in enhancing the potentials of these research tools. This is most true when it comes to the quality and performance of drug candidates, where a cluster of incremental innovations in chemistry followed the appearance of combinatorial synthesis methods. To see this, one only has to note that the first combinatorial libraries exclusively consisted of peptides (i.e. small stretches of proteins) and oligonucleotides (i.e. DNA or RNA), which become vulnerable to digestive enzymes when taken orally (Dolle 2000). Judging that libraries made of small molecular weight compounds could be more profitable, Bunin and Ellman (1992) from Berkeley University in California (US) invented a method capable of producing variants of benzodiazepines, which was subsequently extended by "imitators" to other small molecules such as carbohydrate molecules, (-lactams, biphenyls, acylpiperidines and pyrrolidines. Close to these improvements is the number of reactions that have been optimized by solid-phase chemistry, which has been growing substantially ever since the methods became available (Wentworth and Janda 1998). A favorite among combinatorial chemists, solid-phase chemistry allows the reaction to be completed by use of excess of reagents, reducing the risk of losing compounds during the extraction procedures (Williard et al. 1996). Current efforts to discover new solid phase synthesis procedures have therefore taking place across a broad front in the public and private sectors, which should expand further the repertoire of chemical substances.

Given the time consuming nature of having to identify pharmacologically active "needle" in the combinatorial "haystack", and taken into account the cost it takes to bring a new drug to market, it became clear that competitive strengths would not only rest heavily on the ability to create more potent and safer drug candidates. The competitive advantage upon which firms rely would also heavily depend on how rapidly large number of molecules can be synthesized and screened in a given time (Ecker and Crooke 1995). The viewpoint expressed here, then, is that the need to cut the development costs of pharmaceutical drugs and the will to pre-empt rivals are the catalysts that stimulated further research across different disciplines. Provided one accept this idea, one may explain why chemistry -albeit important- could not provide a panacea for all technological problems. The point is best made with three practical examples.

The need to miniaturize and automate scientific equipment. As the time to synthesize and screen compounds is money, instrumentation and a few combichem companies alike have taken steps to miniaturize and automate scientific equipment. On the other hand, miniaturization allows scientists to pack more compounds/vessels into a microtitre plate, which increase the number of compounds being synthesized and screened in a given time. Hence, technological endeavors got underway to introduce 96-well plates in the eighties, 384-well plates in 1994 and, as analysts expect, 1,536-well plates, 6,500-well plates and even 9,600-well plates in the near future (Dove 1999; Kricka 1998; Persidis 1998). On the other hand, automation permits the reduction of time-consuming and labor intensive tasks: the initial formulation of the reactants, labeling, pooling and splitting, cleavage, liquid-liquid extraction, solid-phase extraction and evaporation being but seven obvious

examples (Baum 1996). Parke-Davis (US), which built the first robotic device for parallel synthesis, and Chiron (US), which responded with the first synthesizer for the "portioning-mixing" technique, have recognized these potentials and, in so doing, have caught the interest of dozens of "imitators" (Lebl 1998). While the price of today's synthesizers varies widely, simple, robust and relatively cheap workstations are now available, making the technology accessible to practically every chemist (Calvert et al. 1999).

The need to identify and isolate drug candidates from complex mixtures. As mixture-based combinatorial methods did not allow for direct identification, innovative solutions came from two emerging technological areas: i) deconvolution methods; and ii) tagging technologies. Pioneered by Houghten et al. (1991) from the Scripps Research Institute (US), the deconvolution method involves the creation and screening of sub-libraries in which the building blocks at one position are identified. If a strong pharmacological activity is observed in a particular sub-library, medicinal chemists would i) resynthesize the whole mixture; ii) divide it into even smaller sub-libraries; and iii) retest each one separately. The process is then repeated until the active compound is isolated. The second solution, that of tag-encoding technologies, involves the synthesis of a second compound (i.e. DNA, peptides, etc.) on the bead, each one representing a tag that defines the synthetic history of the compound. The first of these, developed by Brenner and Lerner (1992) from the Scripps Research Institute (US), used biochemical tags made of small stretches of nucleotides, which act a bit like bar codes on products in supermarkets. Another discovery that deserves to be noted is radiofrequency encoding, which has recently been proposed by Prof. K. Nicolaou from the Scripps Research Institute (US) and scientists from the California-based combichem firm Irori (US) (Nicolaou et al. 1995).

The need to manage chemical information. In response to the enormous amount of information needed to be collected, archived, retrieved and processed, ad hoc software programs and databases are being developed by cheminformatics and a few combichem companies alike. In a nutshell, their aim is to provide information on the inventory and commercially available building blocks ("Can starting materials be obtained at reasonable price?"), the related reaction literature ("How can the optimal synthetic route be achieved?"), the existing drugs ("Are there any potentials for infringement?"), the company's own libraries ("How much of this library overlaps with previous ones?"), the availability of bioassays ("Can the newly synthesized compounds be efficiently tested?") and, what is perhaps the latest and most important bottleneck in the field, structure-activity relationships (SAR) data ("Which combinations of physiochemical properties offer the best prospects for improving the drug candidates?") (Krieger 1996; Pavia 1996; Polinsky 1999).

Biotechnology in general and genomics (i.e. search of genes associated with diseases) in particular have also a key place in the development of combinatorial chemistry. Since scientists must determine whether any of newly formed compounds elicit a particular physiological activity, the combinatorial drug discovery process requires that they perform primary screens on a cell- enzyme- or receptor-based assay that is germane to a specific drug research program. The distribution of these assays, however, is heavily skewed, reflecting the opportunism stemming from past medical research experience. Thus, combinatorial libraries can only be screened against about 500 targets cum genetic diseases. On the other hand, the years to come should bring an increase in number of drug therapy targets -estimated to be between 3,000 and 10,000- as a result of the Human Genome Project (Drews and Ryser 1997). This point is particularly noteworthy. The increasing number of drug therapeutic targets demands an increasing number of newly synthesized compounds, thereby unleashing synergetic forces that would most likely result in a stream of new innovations along the trajectories of both combinatorial and biotechnological paradigms.

On Architectural Innovations and Competence-Enhancing Discontinuities

Taken together, the three examples and the contribution of genomics underscore a simple, albeit often overlooked, phenomenon: combinatorial synthesis methods have become much more than a simple subdivision of the chemistry discipline. Rather, combinatorial chemistry has marked the reconfiguration of four technological currents: 1) chemistry; 2) information technologies; 3) scientific instrumentation; and 4) biotechnology. In this respect, combinatorial processes have intrinsic features that accommodate well with both architectural innovations (Henderson and Clark 1990) and competence-enhancing discontinuities (Tushman and Anderson 1986). For one thing, these four technological streams are so tightly intermeshed that the absence of any "component" would have impaired the development and diffusion of combi-chem in industry. As observed by Prof. Fred Fox from University of California, Los Angeles (US): "It is important to look at the whole picture -the chemistry, the screen, the biology that drives the screen, and the informatics that holds these things together. The parts aren't worth much without the whole" (Borman 1999:34). Thus, the combinatorial drug discovery process involves both "component knowledge" -how its components can be effectively tailored to the specific needs of drug discovery; and "architectural knowledge" -how its components can be effectively linked together in a system. For another thing, combi-chem was ripe for development, since public knowledge in chemistry, information technologies, scientific instrumentation and even biotechnology had been around for decades, already known, shared and improved by a large network of scientists, technicians, etc. More importantly, the skills associated with traditional medicinal chemistry had not become obsolete as a result of combinatorial developments; on the contrary, they have been enhanced by the new developments.

3. The Combinatorial Synthesis Industry

In the face of it, the earlier Schumpeter of The Theory of Economic Development (1934) emphasizing the role of small firms more accurately describes the infant combi-chem industry than Schumpeter's later work Capitalism, Socialism and Democracy (1942), which postulated that the large established firms have preempted the role of small firms in innovations. Yet, as will be shown in this section, large firms have come from behind circa 1995, and combi-chem firms, experiencing difficulty in raising the capital they need, have been heavily depending on research contracts from these large corporations as a way to support their research activities. The reasons behind the current mushrooming of formal/informal collaborations in the field, however, extend beyond financial justifications, and the decision to establish a partnerships agreement is also largely motivated by the need, first, to access "missing components", and, second, to accumulate combinatorial-related knowledge and learn new ways of doing things. In the same vein, the establishment of informal linkages provides important learning opportunities, and combi-chem small firms have often used their contacts with scientists from other firms, universities and scientific institutions.

The United States versus the European Union

Insofar as firms tend to diversify into industries that already employ their resources (Teece 1980), the discussion over combinatorial chemistry and its underlying knowledge base provides some strong clues as to the origin of the companies that have adopted these research tools. Specifically, it is possible to distinguish between: i) firms which have historically supplied the pharmaceutical industry with input products and scientific instrumentation (i.e. Advanced Chemtech, Solid Phase Sciences); ii) dedicated biotechnology firms (i.e. Genosys Biotechnologies, Sepracor); iii) firms which had developed capabilities in computational chemistry (i.e. Vertex Pharmaceuticals, 3-Dimensional Pharmaceuticals); and iv) firms which are supplying the pharmaceutical industry with software tools (i.e. Tripos). The heterogeneous nature of these firms makes it difficult to assess the boundaries of the combi-chem industry, and the number of firms that had been operational in different industrial sectors before the techniques became available may be counted by the dozens (see figure 1).

□ EMBED Word.Picture.8 □□□
Source: Compiled by Author

Nevertheless, the potentials of combinatorial synthesis methods have not been lost on entrepreneurs and investors alike, and firms that have been explicitly formed to exploit these research tools may now represent the majority of industrial users. It is therefore the discovery of combinatorial chemistry which activated the foundation of Pharmacoepia (US), Affymax (US), Chemotopix (DE), ComGenex (HU), Cambridge Combinatorial (GB), Oxford Diversity (GB), Auda Pharmaceuticals (DK), Symyx (US), Coselco Mimotopes (AUS), Neokimia (CAN) and over one hundred companies throughout the world. Having said this, the emergence of combinatorial chemistry brought into being, or have been adopted by, approximately 261 small start-up companies, of which 191 were from the United States, 25 from Britain, 11 from Germany and Canada, 6 from Australia, and 3 from France and the Netherlands. Overall, members of the European Union have 47 firms operating in the field (see figure 1). It is instructive to note that, while only 2 firms -Diversomer (US)□ and Redcell (CAN)- have hitherto exited the industry, 59 mergers and acquisitions have been recorded, following the current wave of consolidation in the pharmaceutical industry.

Table 2

Combinatorial EPO-Patents (1985-1996) and Publications (1984-1996),
by geographical location and institution type (Percentage of the total)

□
University□Research Institution□
Small Firm□
Large Firm□
TOTAL□□US Patents□41 (4.6)□67 (7.6)□552 (62.8)□218 (24.8)□878 (100)□□EU patents□7
(2.9)□28 (11.9)□95 (40.6)□104 (44.9)□234 (100)□□US Publications□760 (42.1)□501
(27.7)□285 (15.7)□259 (14.3)□1,805 (100)□□EU Publications□427 (46.7)□373 (40.8)□29
(3.1)□84 (9.2)□913 (100)□□Source: Compiled by Author

The relatively smaller number of innovators in Europe may provide some strong clues as to why it is falling behind the United States in terms of patent and publication share. Looking at table 2, and bearing in mind the usual shortcomings of patent and bibliometric statistics□, it is apparent that the drive to establish core competencies in combinatorial chemistry did not spread equally and simultaneously across countries. In fact, the US displays the strongest overall research capabilities in combinatorial synthesis, with a total of 878 patents and 1,805 publications. (While the patent and scientific publication database comprised 1,165 patents and 2,570 papers, 21 patents and 755 papers had been authored by more than two parties. Hence, the total number of identified authors is higher than the number of patents/publications). Again, it is not difficult to see why: American small firms, with 552 patents, play an important role in tilting the balance in favor of the US, whereas EU-based small firms, with 95 patents, contribute little to reinforce the competitive position of Europe. As a result, the EU places a distant second with 234 patents, which could have been worse without the contribution of large corporations such as Glaxo (GB), Hoechst (DE) and Rhone-Poulenc (FR). On the other hand, the EU fares much better in terms of scientific publications, having published 913 articles by 1996., a high score that may be linked to the strengths of Academic and public research institutes in Europe.

Combichem versus Biotech

As might be expected for an infant industry□, small combichem firms appear to struggle to find the financial support they need to go on. Thus, it appears that most companies have yet to turn a profit□: the average net loss for a small start-up operation in the US amounted to US\$ 19,210,000 in 1998, considerably more than in 1997 -US\$ 14,095,000- and even more so than the therapeutic line of business in the biotechnology industry, which exhibited a net loss of US\$ 6,054,000 on average per firm in 1997 (Ernst & Young 1998) (see table 3).

Table 3

Selected Financial Highlights - Combichem (1997-1998) versus Biotech (1997) in the US

(Average US\$ in thousands)

□ Combichem 1998

(64 firms) □ Combichem 1997

(70 firms) □ Biotech 1997*

(317 firms) □ Sales □ \$ 10,906 □ \$ 6,415 □ \$ 29,882 □ Contract Revenues □ \$ 12,902 □ \$

10,681 □ \$ 6,033 □ Revenues □ \$ 26,916 □ \$ 19,440 □ n.a. □ R&D □ \$ 26,085 □ \$

21,476 □ \$ 21,760 □ Expenses □ \$ 45,965 □ \$ 37,387 □ n.a. □ Net Income (Loss) □ (\$19,210) □ (\$

14,095) □ (\$ 6,054) □ Sources: Compiled by Author; * Ernst & Young 1998.

The lack of profits in the US combichem sector may largely be explained by the absence of any "combinatorial blockbuster" and, most importantly, by the high levels of research expenditures in the field. On the one hand, only 21 public firms out of 64 combichem firms reported sales, estimated at \$US 10,906,000 on average per firm in 1998, up from US\$ 6,412,500 in 1997 and thus much less than in the biotech industry. On the other hand, the combichem firm spent US\$ 26,085,000 and US\$ 21,476,000 on average in R&D in 1998 and 1997 respectively, whereas the average biotech company reported R&D expenditures of US\$ 21,760,000 in 1997. In total, R&D investments from these 64 firms amounted to US\$ 1,669,494,000, slightly less than Merck (US), which spent US\$ 1,821,000,000 in research activities in 1998.

As research intensity is often wrongly confounded with science intensity, a recent scientometric study by Geuna and I on science-technology linkages in combinatorial chemistry provides some additional insights into this emerging research platform (Malo and Geuna 2000). To address this issue, 1,665 citations in 445 combinatorial patents had been retrieved from the 1986-1996 period and categorized according to a classification produced by CHI Research Inc: 1) applied research; 2) engineering and technological sciences; 3) applied research; and 4) basic research. The results revealed a very high level of science intensity: 80.7 percent of citations belong to basic research journals. This somehow came as a surprise, since Collins and Wyatt (1988), who examined 1923 citations from 366 genetics patents in the US patent system that had been granted between 1980-1985, concluded that 80 per cent of genetic citations were in basic research journals. In other words, combinatorial chemistry and biotechnology are essentially similar in terms of basic research intensity. The most interesting feature distinguishing the two technologies, therefore, resides elsewhere: R&D contracts in 1998 and 1997 created a much larger earning stream -US\$ 12,902,000 and US\$ 10,681,000 per firm- than similar arrangements in the biotech line of business, estimated at US \$6,033,000 in 1997 (Ernst & Young 1998).

The Process of Learning through Networks

While it goes unquestioned that these R&D contracts create an important earning stream for the small firms involved, the proliferation of strategic alliances in the field, as demonstrated in table 4, must equally be understood in the light of attempts by firms to fill their "resource gaps" and conduct R&D that would otherwise be prohibitive for any particular firm (Grant 1991; Niosi 1995). Thus, 1,809 co-operative agreements had been signed between 1988 and 1999, involving 3,199 different modes of cooperation and 899 different organizations, which have engaged in approximately 4 co-operative agreements. Hence, the database has unearthed 3,643 "organizations". To the extent that architectural innovations in general and combinatorial chemistry in particular involve the reconfiguration of "components", and given that the core competencies necessary to bring combinatorial projects into fruition are often fragmented, the case for exchanging resources among small firms remains extremely strong. A licensing agreement between Acadia (US) and ArQule (US), enabling the former's R-SAT (receptor selection amplification technology) to screen the latter's mapping array combinatorial chemistry libraries, exemplifies the division of labor between small firms.

Table 4

Formal Network: Increase in number of combichem co-operatives agreements by form of co-operation (absolute number and percentages)

Mode of Cooperation	1988-1994	1995-1999*	TOTAL	Joint Venture	14 (1.2 %)	37 (1.7 %)	51 (1.6 %)	R&D Contract	278 (24.5 %)	827 (40 %)	1105 (34.5 %)	Licensing	598 (52.6 %)	785 (38 %)	1383 (43.2 %)	State Grant	4 (0.3 %)	51 (2.4 %)	55 (1.7 %)	Minority Holding	189 (16.6 %)	204 (9.8 %)	393 (12.2 %)	Merger/Acquisition	19 (1.7 %)	81 (4.7 %)	100 (3.1 %)	Other	34 (3.0 %)	78 (3.9 %)	112 (3.5 %)	TOTAL	1136 (35.0%)	2063 (64.9 %)	3,199 (100 %)	*
																				Data end up in October 1999																

Source: Compiled by Author

This is not to suggest, however, that large pharmaceutical firms sit on the sidelines as far as combichem is concerned. Though the combinatorial commitments of big drug companies only appear when the technology gained credibility with the creation of small molecule libraries by Bunin and Ellman in 1992, the speed at which these firms have adopted these research tools underscores their previous experience in the chemistry discipline, which has been enhanced by the discontinuity, as well as their larger financial resources, giving them with a cost spreading advantage and an ability to buy pretty much what they want (Wernefelt and Karnani 1987; Cohen and Klepper 1994). As a result, these companies had all embedded combichem in their R&D programs by the mid-nineties (Brown 1996). For instance, Eli Lilly (US) uses the process in 75 percent of its pre-clinical drug discovery programs (Glaser 1995), and Merck (US), has recently announced it had synthesized more than 4,500,000 compounds between 1995, the year the firm began using the combinatorial techniques, and 1998. This result reflects nothing short of a dramatic realignment in the way the firm operates its drug discovery programs: it had "only" screened and synthesized 250,000 compounds by traditional methods between 1934 and 1994.

Yet in-house combinatorial efforts did not occur in a vacuum, and these large pharmaceutical companies, taking steps to ensure that they remain dominant over small firms, spent heavily into collaborative agreements. Their approach to the new technology was nevertheless cautious, and these large firms would typically begin by purchasing equity in a combichem firm, a strategy that provided them with a window on the latest technological developments. Prominent examples include the cases of Ciba-Geigy (CH), which took equity stake in Affymax (US) as early as 1991, Smith-Kline Beecham, which purchased equity from COR Therapeutics (US) in 1991 and Mitokor (US) in 1993, and Daiichi Seiyaku (J), which bought shares from Pharmacoepia (US) in 1996. Nevertheless, the relative importance of equity participation shifted towards R&D contracts, some of which heralding a long-term relationships between the large corporations and combichem firms. As a case in point, Sanofi (FR) and Cerep (FR), whose partnerships dates back to 1990, had signed another R&D contract in 1997 and yet another one in 1999. Another case in point is the cardiovascular drug discovery collaboration between Merck (US) and 3-Dimensional Pharmaceuticals (US), which began in 1996 but was further extended in 1998. One must also reckon with the fact that the move towards collaboration has often led to acquisition, which gives the large firm with an instant access to know-how, physical capital as well products and processes that would otherwise be protected under patent laws (Wernefelt 1984). To name the oft-cited examples, Glaxo (GB) acquired Affymax (US) for US\$ 539 million in 1995, Eli Lilly (US) took over Sphinx Pharmaceuticals (US) for US\$ 76 million in 1995, Marrion Merrell Dow (US) absorbed Selectide for US\$ 58 million in 1995, Perkin-Elmer (US) purchased Perspective Biosystems (US) for US\$ 390 million in 1997, Hoechst (DE) bought Ariad Pharmaceutical (US) for US\$ 85 million in 1998 and Dupont (US) took over Combichem (US) for US\$ 95 million in 1999.

Thus far, the discussion may have conveyed the belief that such arrangements have been solely stimulated by the need to fill the financial and resource gaps of small firms and the resource gaps of large firms. Yet this perspective misses an important point: the underlying dynamics of learning opportunities that arise as a by-product of strategic partnering (Nohria 1992). Specifically, it ignores the

possibility for a firm to benefit from membership in a closed set of interdependent actors whose recurring and long term relationships enable the rapid transmission and processing of knowledge (Freeman 1991; Teubal et al. 1991). While a firm would obviously not interact with the whole spectrum of economic agents, the fact that knowledge is neither completely public nor private implies that some elements derived from its R&D department will leak out to enlarge the industry's knowledge pool, thereby benefiting the whole network of innovators (Nelson 1989; Callon 1994; OECD 2000). Thus, knowledge produced by one economic player can spill over to other players, creating synergies forces through interactions that may be conducive to further technological development. In this context, a firm's behavior -and performance- cannot be explained without reference to its relations with collaborators/rivals, suppliers, research institutes, clients, sources of funding, qualified labor and research inputs -the firm's environment (De Bresson and Amesse 1991).

Table 5
 Formal Network: Combichem co-operatives agreements in the United States and the European Union, 1988-1999* (Percentage of the total)

	TOTAL	INTRA	INTER	Alliances	Actors	Alliances	Actors	Alliances	US Actors	EU Actors	Others	US
	1638											
(100)	2789 (76.5)											
(100)	1123											
(68.6)	2,262											
(81.1)	515											
(31.4)	544											
(19.5)	318											
	237											
	EU											
	418											
(100)	549 (15.0)											
(100)	94											
(22.5)	189											
(36.7)	360											
(77.5)	318											
	360											
(63.2)	41 Total											
(World)	1,809 3,643											

* Data end up in October 1999
 Source: Compiled by Author

If one accepts this basic premise, it may be argued that US-based companies have an edge in capturing these spillovers, since the EU network is much smaller than the US network (see table 5). Thus, 2,789 American organizations are present in 1,638 different co-operative arrangements, whereas their EU counterparts, which number 514 in all, had signed 418 strategic alliances. The EU network is also much less compact: 68.6 percent of alliances are between US organizations, but only 22.5 percent between EU-based ones. Thus, EU organizations rely much more on international alliances with US organizations than vice-versa, though their collaborative commitments with organizations outside the US is less significant than US organizations. Only 47 agreements, involving 47 firms and universities from Hungary, Canada, Switzerland and Japan, had been signed with EU-based organizations, whereas the US had established 227 contacts with 237 universities, research institutions and firms from non-EU countries.

Yet formal networks are not the only channels through which scientific and tacit knowledge flow from scientist to scientist and organization to organization (see table 6). Scientists and organizations anxious to acquire combinatorial know-why and know-how have also resorted to informal networking, wherein contacts between scientists with a common interest are established through meeting conferences, telephone conversations, etc. Informal networks are buttressed by shared norms and trustworthy behaviors, rather than competitive pricing or formal

market, allowing valuable knowledge to be traded between professional colleagues in a flexible, low cost fashion (von Hippel 1987; Abramson, et al. 1997). To be sure, informal networks are inherently more difficult to gauge than formal networks, implying that proxies of measures are necessarily imperfect. Nevertheless, Liebeskind et al. (1996), in studying the biotechnology industry, have not only successfully demonstrated that "social networks" can be measured by examining scholarly publications that have been written by 2 or more organizations. They have also shown that informal networks can also contribute to extend the scope of organizational learning and, concomitantly, facilitate the integration of external knowledge by the firm.

Table 6

Informal Network: Combichem papers written by two or more parties in the United States and the European Union, 1984-1996 (Percentage of the total)

TOTAL	INTRA	INTER	Papers	Authors	Papers	Authors	Papers	US authors	EU Authors	Others	US
491											
(100)	944		(54.5)								
(100)	307										
(62.5)	705										
(74.6)	184										
(37.5)	242										
(25.6)	110	118									EU
268	(100)	518	(29.9)								
(100)	156										
(58.2)	370										
(71.4)	112										
(41.8)	110	148									
(28.8)	26	Total (World)	755								
(100)	1,732										
(100)											

Source: Compiled by Author

Bearing this in mind, table 6, which has been constructed on the basis of 755 combinatorial papers on which scientists at two different organizations were named as authors, points to the dominance of American organizations. However, their predominance in informal networks is much less obvious than in formal networks. Whereas 491 papers and 705 authors, representing 54.5 percent of total papers, can be linked to US organizations, 268 papers and 518 authors, representing 29.9 percent of total papers, have been authored by European organizations. Furthermore, the density of the European informal network, where 370 papers (71.4 %) have been written between European parties, is similar to the US one, where 705 (74.6 %) informal collaboration have been written between American organizations. Finally, informal linkages between US organizations and Australian, Hungarian, Japanese and Swiss organizations are 4.5 times more numerous than informal networks between EU-based and other countries. Although the subject is treated more extensively in the following section, it needs to be insisted that such figures hide wide variation in the "quality" of papers; thus, American organizations have been better at establishing contacts with the original inventors.

4. Tapping into Public Research

There is little doubt that combinatorial drugs will spring from industry rather than Academia and public and private non-profit research organizations. A major reason why this is likely to be the case is that only the private sector has the ability to initiate a large, expensive and instrument-intensive research endeavor. As pointed out by scientist Richard Houghton: "The reason [for the predominance of industry] is almost entirely economic. To make 100,00 individual compounds and screen them in a high throughput array format is typically prohibitive for most academic organizations. If you need to look at 100,000 individual data points in triplicate, that will almost short-circuit academic organizations. They just can't get it" (Borman 1998:7). While it is right in presupposing that public research