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EUROPEAN UNIVERSITY INSTITUTE
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This Working Paper has been written in the context of the 2004-2005 European Forum programme on 'The Role of Universities in the Innovation Systems', the overall direction and coordination of which was carried out by Professor Rikard Stankiewicz, EUI, and Dr Aldo Geuna, EUI and SPRU, University of Sussex.

The growing role of universities in the 'knowledge economy' is well known. A dynamic and well-balanced academic system is a key engine of innovation and economic development. Doubts persist however as to whether Europe's universities are fully capable of fulfilling that role. The members of the Forum approached these issues by focusing on the following research themes: (1) Universities and the changing dynamics of knowledge production; (2) Patterns of the division of labour in research and innovation system; (3) The internal organisation of academic systems: tensions and adaptations; and (4) Diversity, innovativeness, and the governance of academic systems.

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Abstract

This paper deals with the effects of publicly-funded research on the process of combinatorial drug discovery. It addresses the following questions, using a combination of databases: Where do public research organizations (PROs) and individual countries stand in terms of combinatorial innovations? How relevant are public research and education to the industrial process of small molecule drug discovery? Does firm size matter in this assessment? Are firms linking with PROs more likely to link with other firms than firms with no linkages with PROs? Has the new synthesis method prompted professors of chemistry to launch new companies? What is the role of PROs in generating useful instruments and methods? Do PROs prefer to license and contract out their research output over traditional means of transfer, such as publications, conferences and informal conversations?

Keywords

Public research organizations, spin-off, networks, knowledge, combinatorial chemistry

1. Introduction*

Early scholars of technological change who have written about universities and other public research organizations (PROs) and their impact on industrial R&D highlighted the benefits stemming from advances in fundamental knowledge (Nelson 1959; Arrow 1962). Their contemporaries later acknowledged and emphasized the importance of other contributions such as the provision of skilled graduates, the stimulation of networks, the formation of new firms and the development of new methodologies and instrumentation (Salter and Martin 2001). And yet nobody who considers the role played by publicly-funded research in national innovation systems can really generalize seriously about its effects. Not only do public research endeavours differ across countries, but the relations between PROs and firms also vary considerably depending on the size of these firms, the industry in which they operate and the technology that they seek to use and/or develop.

One worthwhile technology of research that has received only minimal attention, for example, is combinatorial chemistry—an automated synthesis method capable of creating dozens, if not hundreds and thousands, of different molecules simultaneously for the purpose of discovering and optimizing drugs, new materials, pesticides and so forth. Questions about the effects of publicly-funded research on the process of small molecule drug discovery have thus remained untouched. Among them: Where do PROs and individual countries stand in terms of combinatorial innovations? How relevant are public research and education to the industrial process of small molecule drug discovery? Does firm size matter in this assessment? Are firms linking with PROs more likely to link with other firms than firms with no linkages with PROs? Has the new synthesis method prompted professors of chemistry to launch new companies? What is the role of PROs in generating useful instruments and methods? Do PROs prefer to license and contract out their research output over traditional means of transfer, such as publications, conferences and informal conversations?

This paper will address these questions, using a combination of databases. It is organized as follows: Section 2 begins by briefly examining the literature in relation to the benefits of publicly-funded research for commercial innovations in the pharmaceutical industry. Section 3 provides relevant background information on combinatorial chemistry and the firms that embraced it. Section 4 describes the publication, patent, survey, alliance, company and industry data used throughout the paper. Section 5 follows the insights of Salter and Martin (2001) in exploring some of the most important contributions of PROs to economic growth in greater detail: (1) the advancement of scientific knowledge; (2) the provision of vocational skills; (3) the stimulation of networks; (4) the creation of new firms; and (5) the development of new methodologies and instrumentation. Section 6 goes on to analyse the importance of different channels for learning about public research in small molecule drug discovery, while section 6 closes with a summary of the main findings.

2. Brief overview and limitations of previous empirical studies

Time and again, survey questionnaires indicate that respondents in the majority of industries in the United States (Nelson 1987; Klevorick et al. 1995; Von Hippel 1988; Mansfield 1991, 1998; Cohen et al. 1998; Cohen et al. 2002) and Europe (Arundel et al. 1995; Abramson et al. 1997; Arundel and Geuna 2004; Monjon and Waelbroek 2003) perceive academia and other PROs to be less important as an information source for industrial innovations than suppliers and customers. One of the few exceptions to this rule is the pharmaceutical industry, where universities and other PROs are

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persistently identified as an essential player in the industrial research process. For example, the PACE report indicates that the European Union's largest drug companies listed public research as a better source of information than affiliated firms, customers, suppliers and reverse engineering (Arundel et al. 1995; Arundel and Geuna 2004).

Unlike the PACE report, but supportive of its main conclusions, the Yale survey highlights the close relevance of academic research knowledge in chemistry and biology to industrial innovations in the pharmaceutical industry (Nelson 1987; Klevorick et al. 1995). This relevance is, however, subject to cross-firm variations due to differences in absorptive capacity; as firm size increases, a higher percentage of firms is able to evaluate and incorporate knowledge stemming from publicly funded research (Cohen et al. 2002; Laursen and Salter 2004; Fontana et al. 2004). Case studies, bibliometric analysis and econometric investigation have testified in different ways to the positive influence of public research endeavours on technical advances in therapeutic drug markets. In a case study of 21 drugs deemed by two leading industry experts to 'have the most impact on therapeutic practice', Cockburn and Henderson (2001) reveal that only five did not receive any inputs from the public sector. Using the tools of bibliometrics, Narin et al. (1997) also demonstrate that 79 percent of citations to scientific literature concerning US industry drug and medicine patents come from the public sector. Econometrically, Toole (2000) calculated that a 1 percent increase in public basic research resulted in a 2 percent to 2.4 percent increase in the number of commercially available drugs.

These empirical studies have produced useful insights, but as Salter and Martin (2001) pointedly remarked: 'no simple model of the nature of the economic benefits from [publicly-funded] basic research is possible' (2001:527). If one acknowledges that the production of scientific knowledge is only one of several of the benefits of public research to economic growth, a comprehensive approach that accounts for the provision of skilled graduates, the stimulation of networks, the formation of new firms, and the development of new methodologies and instrumentation is necessary. Each one of these contributions is examined below.

- The provision of skilled graduates cannot be ignored when chartering the effects of public research on commercial innovations, since university graduates bring knowledge and ability into industry to solve complex problems, perform research and develop new ideas (Gibbons and Johnston 1974; Salter and Martin 2001). Apparent cross-firm differences about the value of academic training have nonetheless been found by Schartinger et al. (2001): the demand for highly qualified graduates increases with firm size. These authors hypothesize that such pattern reflects the presence of an R&D department in large firms, though one should also consider the possibility that smaller firms prefer to recruit experienced scientists rather than graduate students, largely because formal training programs involve considerable investments (Black et al. 1999).

- The stimulation of networks by public research organizations is seen as a positive factor behind economic growth, as a result of two closely knitted factors. On the one hand, the learning process characterizing complex innovations demands formal and informal interactions among different types of specialized actors (Lundvall 1992). On the other, membership in this network of innovators is often gained by establishing close linkages with PROs (Callon 1994; Powell et al. 1996). Indeed, as George et al. (2002) demonstrated empirically, biotechnology companies would have a harder time connecting with other companies if they did not forge intimate links with academia. It is also meaningful that the PACE report found that pharmaceutical companies learn a great deal about public research output through informal contacts and conferences (Arundel et al. 1995).

- The creation of public research spin-offs is usually regarded as one of the most effective mechanisms of knowledge transfer in terms of job and wealth creation (Abramson et al. 1997; BankBoston 1997; Rogers et al. 2001). Nothing exemplifies this contribution better than the public research spin-offs in the field of biotechnology. For example, 199 MIT-related

biotechnology companies headquartered in Massachusetts employed 23,900 people in the state and had sales amounting to $US 5.1 billion in 1995 (BankBoston 1997). The case for spawning public research spin-offs is, however, not watertight. There is indeed a consensus that these firms remain very small, with little prospect for growth and survival (Lindholm Dalhstrand 1997; Callan 2001). Scholars are divided on the explanation for this. Some claim that these spin-offs are young research boutiques which occupy fields with long lead times (Callan 2001); others speculate that public researchers often lack the business acumen that is necessary to bring products onto markets (Lindholm Dalhstrand 1997) and the social capital required to secure external financing (Shane and Stuart 2002). These shortcomings notwithstanding, it may be conjectured that public sector research spin-offs can act as important suppliers of technology, thus mediating the interface between PROs and other companies in national innovation systems (Stankiewicz 1994).

- The development of new methodologies and instrumentation often provides the impetus for radical advances in science and technology—a historical observation that is commonly overlooked (Price 1984). Even less widely acknowledged, though highly significant for industrial R&D, is that PROs are an important source of instrumentations (Rosenberg 1992) and methodologies (Salter and Martin 2001) which may later be adapted for commercial requirements (OTA 1995). The Carnegie Mellon survey lends credence to this view, indicating that 35 percent of drug companies considered instruments and techniques developed by PROs as useful for industrial R&D (Cohen et al 2002).

Taken together, these studies have called attention to the essential role played by PROs in the development of therapeutic drug innovations. There are, however, a few specific lessons to be drawn concerning small molecule drug discovery in general and combinatorial chemistry in particular. This paucity of information posits the need to narrow the focus of empirical investigation, by assessing the relative importance of the scientific sub-disciplines and technologies that are used along the value-chain of small molecule drug discovery. Extrapolating the results of past studies to the experience of new entrants with a competence in combinatorial chemistry must also be approached with caution for the reason that these firms occupy a much smaller segment of the pharmaceutical and/or chemical industries. The remainder of the paper can therefore be interpreted as an attempt to remedy the situation by assessing the impact of publicly-funded research in the field of combinatorial chemistry on the innovative capacity of small and medium-sized start-up companies.

3. Industrial and technological background

Combinatorial chemistry was first imported into an industrial setting in 1988, when the renowned entrepreneur Alejandro Zaffaroni launched Affymax in California, and Commonwealth Serum Laboratories spun out Coselco Mimotopes in Australia. From then on, the number of small- and medium-sized firms using the technology has grown to about 520—minus 25 bankruptcies and 86 acquisitions by large biopharmaceutical, pharmaceutical and chemical companies. Despite sharing a competence in combinatorial chemistry, these firms remain highly heterogeneous in relation to their stocks of knowledge assets (i.e. employees, patents), learning based-strategies (i.e. acquisition, alliances) and historical background (i.e. corporate *versus* public research spin-offs). New entrants also target different markets: some are technology-platform firms selling compound libraries to biotechnology and pharmaceutical firms, whereas others can be characterized as drug discovery companies seeking to carve out a niche among large pharmaceutical companies (Thiel 1999; Ratner 1999; Herrera 2002).

Although these large companies showed little interest in combinatorial chemistry in its early days, a seminal paper by Ellman's group at University of California, Berkeley, in 1992, prompted them to start building up their own in-house capability in the field. Combinatorial chemistry started with the synthesis of libraries containing peptides and oligonucleotides—small stretches of proteins that can

usually be administered only through intravenous injections. Ellman and co-workers overcame this limitation by creating analogues similar to the highly successful tranquilizer drug Valium, thus opening the door to the discovery of orally active small molecule drugs. 'It generated a tremendous amount of excitement in the pharmaceutical business,' Ellman says. 'It's not often you publish a paper that causes the major pharma companies to consider changing the way they do business' (Nikolsky and Gotschall 2003: 18). The crucial matching of skills between the old and new screening approach to drug discovery did not, however, turn out to be difficult to achieve. Abbott Laboratories, for example, had set out to master combinatorial chemistry in 1994 but was already employing the method in 80 percent of its drug discovery programs in 1998 (Karet 1998).

All the same, the technology, to be honest, contributed little to increasing drug output in the early stage of diffusion. Carl Dedicco, head of discovery chemistry at Bristol-Myers Squibb, admits that the first years of utilization were a 'nightmare', with many chemists obsessing about synthesizing thousands or millions of compounds for testing without reflecting upon the potentials of these as drug candidates (Landers 2004). Little known to medicinal chemists when combinatorial chemistry was introduced into their labs, the technology was still not at a mature enough stage to be successful. To achieve its full potential, numerous interlocking sets of incremental innovations had to be made along the value chain of small molecule drug discovery—a point substantiated in section 5.5.

As a testament to these improvements, we now find that new entrants, large incumbents and PROs no longer randomly synthesize an almost unlimited number of peptides (most of which are irrelevant) with no particular use in mind—and, in this sense, it can be meaningfully concluded that the huge discovery library model has fallen out of favour. Increasingly, instead, private and public research efforts are concentrated on the preparation of small and moderate-sized collections of complex, drug-like molecules that are focused towards specific protein families, giving rise to a marriage of convenience between combinatorial chemistry and rational drug design: virtual combinatorial library design (Dalemme et al. 1997). Consequently, there is growing evidence that investments made in combinatorial chemistry have started to pay off with a wave of drug candidates that may generate sales growth. According to Golebioswki et al. (2002, 2003), who provided the first reviews of lead compounds derived from combinatorial chemistry, the scientific literature covering the 2000-2003 period describes over 100 active new chemical entities linked to the technology. Soon-to-be commercialized new materials have also been increasingly reported in chemistry journals (Scott 2001; Van Arnum 2004).

4. Method

Sample

For the purposes of simplicity, this paper refers to (1) non-subsidiary, independent firms with a competence in combinatorial chemistry and less than 500 employees as new entrants; (2) firms with more than 500 employees as large companies; and (3) universities, government research laboratories and private, non-profit research organizations as public research organizations (PROs). The OECD definition of public research spin-off used in section 4.4 includes any new entrant (1) which licenses technology from a university or public research organization; (2) which includes a public sector or university employee as a founder; and/or (3) in which a university or national laboratory has made an equity investment (Callan 2001). This definition contrasts with that of corporate spin-offs, which refer to independent entities founded on the basis of a technology *and* human capital originating from a parent company (Lindholm Dalhstrand 1997; Davenport et al. 2002).

As noted, 520 new entrants—either *de novo* entrants, entrants by diversification or entrants by acquisition—have been identified, of which 135 were publicly traded. About 208 new entrants can be regarded as product-oriented, drug discovery firms—the remainder being service-oriented, technology-platform firms (out of business or new subsidiaries of large companies). They were all found in websites dedicated entirely to combinatorial chemistry such as www.5z.com and

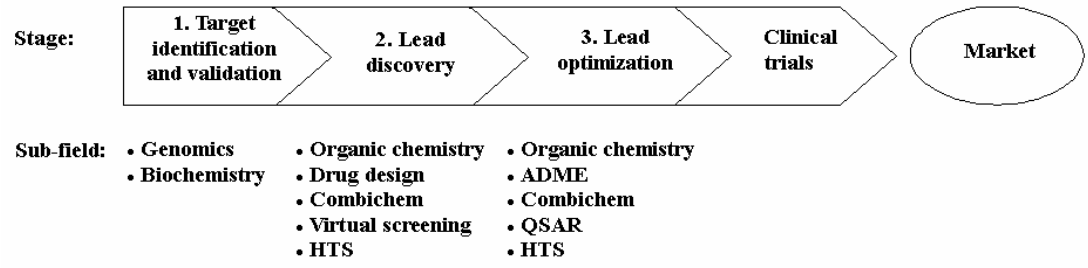
www.combichem.net. The list was extended by examining firms participating in conferences about combinatorial chemistry, patent databases, journals dedicated to the technology, etc.

Data

To gain a more thorough understanding of the contributions of public research to industrial R&D, a survey questionnaire was developed to solicit the views of 'gatekeepers'; experts whose involvement in combinatorial drug discovery—be it chief technical officers, directors of discovery research or combinatorial chemistry, group leaders in medicinal chemistry, senior scientists in chemistry, or vice-presidents for research and product development—place them in a good position to understand the issues at stake. To a large extent, the survey replicates the methodology of studies made by Yale University (Nelson 1987; Klevorick et al. 1995), the Maastricht Economic Research Institute on Innovation and Technology (the Pace report by Arundel et al. 1995), the Fraunhofer Institute for Systems and Innovation Research (Abramson et al. 1997), Carnegie Mellon (Cohen et al. 2000; 2002) and the Massachusetts Institute of Technology (Agrawal and Henderson 2002), where respondents were asked to rate the relevance of public research (i.e. knowledge), academic training (i.e. skills), and different pathways of knowledge flows along a Likert scale.

As with other surveys, the results provide an imperfect picture. Data are biased by the subjective judgment of the respondents. Also, the survey only captures a still shot of the situation and neglects the moving picture; in reality, it is likely to evolve over time. Add to this the caveat that no distinction is made between universities and government laboratories—a fairly major shortcoming considering that these two types of actor have different mind-sets regarding basic research, technology development, publication and technology transfer (Bozeman 2000). However, the survey differentiates from past studies by including a mix of American, British, Canadian, English, French, Hungarian, Italian, Ukrainian and Swiss firms, though the majority of them were clearly based in the United States. Compared to the Yale survey, which dealt with universities, the questionnaire concentrates on the impact of PROs, whenever applicable. It is also distinguishable for providing the first insights into the impact of public research and education on commercial innovations in the sub-field of combinatorial chemistry.

Figure 1: The value chain of small molecule drug discovery



Combinatorial chemistry, however, does not stand alone, as figure 1 illustrates.[1] Hence, the paper focuses on three stages of the value chain of small molecule drug discovery: (1) target identification and validation (e.g. the processes of identifying a molecular target and demonstrating that it is critically involved in a disease process); (2) lead discovery (e.g. the process of identifying active new chemical entities); and (3) lead optimization (e.g. the process of modifying and transforming an active

1 While the figure depicts a linear process, drug discovery does not necessarily start with target identification and validation. The figure also ignores feedback loops from markets, clinical trials and lead optimization.

new chemical entity into a clinically useful drug).[2] Nine scientific subfields and technologies were scored along a scale from 1 (lowest importance) to 7 (highest importance): (1) organic chemistry, (2) genomics (in relation to target identification and validation), (3) biochemistry, (4) drug design, (5) combinatorial chemistry, (6) virtual screening, (7) absorption, distribution, metabolism and excretion (ADME for short), (8) quantitative structure-activity relationships (QSAR for short) and (9) high-throughput screening (HTS for short).

The survey questionnaire was sent to about 250 entrant firms and 25 large companies. Fifty-seven firms returned the survey: 47 new entrants and 10 large pharmaceutical companies; roughly 21 percent of firms responded. Among the new entrants, product-oriented and service-oriented firms are represented almost equally and yielded similar, though slightly different, scores. The difference, however, is not statistically significant, implying that the results presented in the following sections do not reflect any specialization.

The paper also draws on published combinatorial libraries (e.g. collections of diverse molecules that have been reported in the scientific literature) as an indicator of public research knowledge output. They are extracted from the annual surveys of Roland Dolle (1998a, 1998b, 2000, 2001, 2002, 2003; Dolle and Nelson 1999), himself a combinatorial chemist (formerly at Pharmacopeia, now at Adolor). In addition, compounds as an indicator of research output have been drawn from the Biospace database, the websites of new entrants and surveys of lead compounds being derived from combinatorial chemistry by Adam Golebiowski, Sean Klopfenstein and David Portlock (2001, 2003) from Procter & Gamble Pharmaceuticals. Obviously, these bibliometric measures are not perfect; not only one must take into account a 1-2 year time lag between the actual synthesis and publication, but also a statistical discrepancy that may arise from firms wishing to keep their libraries-compounds a trade secret.

The financial, employment and patent data of publicly traded firms will be used to contrast the economic performance of public research spin-offs with that of corporate spin-offs. The financial data here include sales revenues and market capitalization for the fiscal year 2003. The former were gathered from the annual reports and Securities and Exchange Commission filings of 135 public new entrants from Australia, Belgium, Canada, Denmark, Germany, Great Britain, Iceland, Israel, Italy, Sweden, Switzerland and, most of all, the United States, whereas the latter came from the DataStream database. Employment data came from the same sources, while data concerning patent applications were downloaded from the database of the United States Patent Trademark Office (USPTO).

Using the websites of all 520 new entrants, 5,507 alliances were collected; of these alliances, 1,174 connect new entrants with PROs. The data cover the period between 1982 and 2003. In addition to being used to test whether research contracts and R&D consortia with PROs can be used as a ticket of admission to a larger network of industrial innovators, the data have two applications: (1) equity participation to identify many public research spin-offs, and (2) licensing agreements and research contracts to further gauge the significance of formal pathways of information flows relative to knowledge transfers associated with open science.

5. The benefits of public research in Combinatorial chemistry and small molecule drug discovery

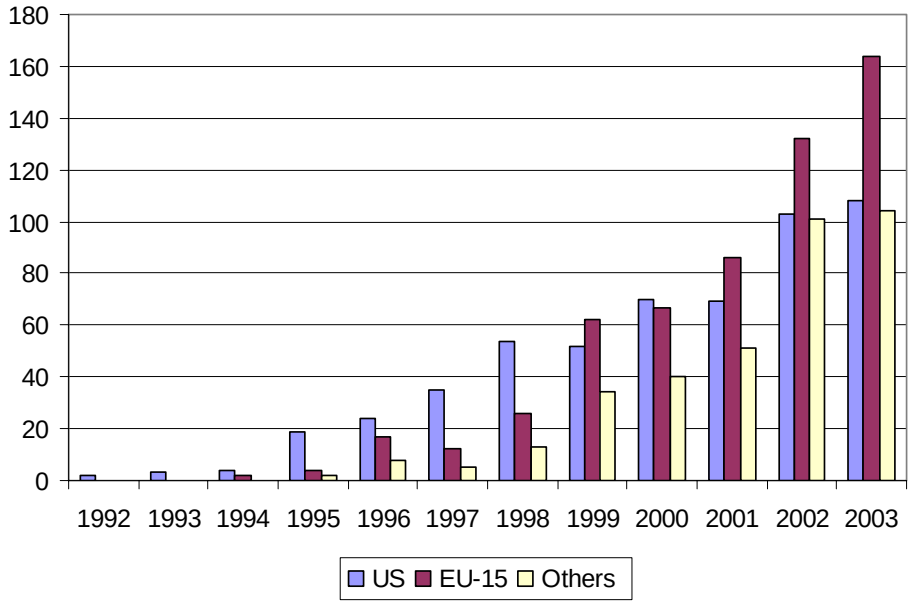
This section examines the importance of public research knowledge in detail and extends the focus of analysis to the provision of skilled graduates, the stimulation of network arrangements, the formation of new firms and the development new methodologies and instrumentation.

2 The stage of clinical trials is overlooked, largely because few, if any, entrants firms possess the necessary skills and financial strength to steer compounds through the entire regulatory process.

5.1 The advancement of scientific knowledge

Before considering in greater detail the economics of public research knowledge in the arena of small molecule drug discovery, it would be useful to examine what constitutes the most obvious visible research outputs of combinatorial chemistry: compound libraries and lead compounds. According to the annual surveys of published combinatorial libraries by Roland Dolle, knowledge created by public research efforts led to the preparation of 1,511 libraries over the period 1992-2003 (see figure 2), as opposed to 821 and 467 libraries, respectively, for large incumbents and new entrants.

Figure 2: Increasing volume of public research in combinatorial chemistry as measured by published libraries -by geographical location (1992-2002)



Source: Extracted from Dolle (1998a, 1998b, 2000, 2001, 2002, 2003, 2004) and Dolle and Nelson (1999).

In his 2003 survey of the literature, Dolle (2003) demonstrates that PROs outpaced industry production by 152 libraries—a reversal of fortune compared to the period 1992-1998, when 63 percent of all published libraries came from the private sector. While it is clear that that number of combinatorial libraries synthesized by the public sector has undergone a very sharp upward trend, the locus of knowledge creation is highly diversified: universities account for 1,126 published combinatorial libraries (74 percent of total), the rest being shared among government laboratories (283 libraries; 19 percent of total) and private, non-profit research organizations (102 libraries; 7 percent of total).

Table 1: Top 20 public research organizations for published libraries (1989-2003)

Name of scientific institution	Country	Number
Scripps Research Institute	US	78
Torrey Pines Institute for Molecular Studies	US	71
University of California -Berkeley	US	58
CNRS	FR	46
University of Cambridge	GB	34
University of Southampton	GB	31
University of California -Davis	US	29
National University of Singapore	SIN	24
Harvard University	US	24
Zhejiang University	CN	22
University of Pittsburgh	US	22
Tübingen University	DE	19
National Dong Hwa University	TW	19
Central Drug Research Institute, Lucknow	IN	17
Indian Institute of Chemical Technology	IN	17
University of Florida	US	16
Tokyo University	JP	16
Shanghai Institute of Organic Chemistry	CN	15
Max Planck Institute	DE	14
University of California -Los Angeles	US	14

Source: Extracted from Dolle (1998a, 1998b, 2000, 2001, 2002, 2003, 2004) and Dolle and Nelson (1999).

Similarly, a country-by-country comparison shows that the drive to spend public monies on combinatorial chemistry did not spread either simultaneously or equally across national innovation systems. As figure 2 demonstrates, the United States occupied the top position for the number of combinatorial libraries being synthesized by PROs until 1998, only to lose it to the European Union as a whole in 1999. While American PROs once again ranked first in 2000, resuming the order observed in 1998, their margin of leadership has been eroded by the EU-15-based PROs since 2001. To date, PROs from the United States have synthesized 542 combinatorial libraries whereas those from EU-15 and other countries have created 598 and 368 libraries, respectively. In the European Union, Great Britain (with 138 libraries) is the most prolific, followed by Germany (131), France (101), Italy (64), Spain (51), Denmark (33) and the Netherlands (29). Another interesting finding is the strong, albeit recent, response of Asian countries. With challengers appearing in countries as diverse as China (with 71 libraries), Japan (71), India (49), Singapore (27), Korea (24) and Taiwan (22), the United States and EU-15 can no longer presume that they are the focal point of innovative activities in the field.

It is also clear that these published combinatorial libraries tend to be concentrated in a few PROs. Table 1 shows the 20 most productive academic, public and private, non-profit research organizations, which account for about 39 percent of all publications. The top PRO is the Scripps Research Institute. Unsurprisingly, perhaps, the synthesis of combinatorial libraries is also high for the Torrey Pines Institute for Molecular Studies, a private, non-profit research organization that spun out from the Scripps Research Institute, since its founder, Richard A. Houghten, was a pioneering combinatorial chemist at the latter before establishing the former in 1988. In the EU-15, the *Centre National de Recherche Scientifique* (CNRS), the University of Cambridge, the University of Southampton, Tübingen University, and the Max Planck Institute are the most productive PROs, as their research output ranges between 14 and 46 libraries. What can also be noticed in table 1 is the significant contributions made by the National University of Singapore (with 24 libraries), Zhejiang University (22) and the Shanghai Institute of Organic Chemistry in China (15), National Dong Hwa University

(19) in Taiwan, the Central Drug Research Institute, Lucknow, the Indian Institute of Chemical Technology (each 17) in India, and the University of Tokyo (16).

Public research motivations for engaging in the synthesis of these combinatorial libraries fall into two categories. The 'classical' motivation is one of open science: developing the types of chemical reactions that small and large companies should look for in their search for new drugs, while the 'business-oriented' motivation is the commercialization of research outputs for financial gains. Indeed, it has also become apparent that public expertise in organic synthesis has become a resource upon which hundreds of combinatorial libraries are being sold or licensed to industrial companies. For example, Aventis, Amersham Pharmacia Biotech, AstraZeneca, GlaxoSmithKline, Eli Lilly, Nycomed Amersham, Organon Laboratories, Pfizer and Roche have invested more than 2.5 million pounds into a research consortium developed by Professor Mark Bradley at the University of Southampton. The University is to develop the methodology to make combinatorial libraries for which industrial partners will have royalty-free licenses (Bradley 2002).

In yet other cases, initiatives to find a drug candidate have been undertaken by PROs. As reported by Golebiowski et al. (2001, 2003), these organizations themselves applied combinatorial means to isolate and identify 17 lead compounds (see table 2). A representative example here is that of a lead compound that promises to treat cocaine abuse. It was discovered *via* virtual and actual screening by Wang and co-workers (2000) from Georgetown and Texas Universities. More often than not, however, these academic, public and private, non-profit research organizations had been generously sponsored by non-academic organizations, primarily by industry and government agencies such as the National Institute of Health. A case in point is the Max Planck Institute and the University of Mainz, whose drug research efforts were supported by the German pharmaceutical giant Bayer. If industrial and governmental sponsorship had been removed from the equation, few if any PROs would have been able to initiate this wide-ranging, expensive and instrument-intensive pre-clinical research endeavour, given the complexity and full costs of lead discovery and lead optimization (Borman 1998).

Table 2: Summary of lead compounds discovered by public research organizations using combinatorial chemistry

Public research organizations	Country	Target
Columbia U, Rockefeller U.	US	VRE
Harvard University	US	Kinesin Eg5
Max Planck Institute, U. of Mainz	DE	PKC
Mayo Clinic	US	FT
Scripps Research Institute	US	Broad application
Scripps Research Institute	US	Anti-infective
Scripps Research Institute	US	Poly [dA]-poly [dT]
Scripps Research Institute	US	HGH
Scripps Research Inst., UC -San Diego, Virginia Polytechnic Institute and State University	US	AChE
Texas University, Georgetown University	US	DAT
UC –Berkeley	US	Anti-infective
UC –Berkeley	US	Human sst
UC –Berkeley	US	Sulfotransferase
UC –San Francisco	US	HGXPRT
University of Amsterdam	NL	BCRP
University of Pittsburgh	US	Cdc25
Yeshiva University, Jefferson University	US	PTP1B

Source: Extracted from Golebiowski et al. (2001, 2003)

Having discussed the economics of public research in combinatorial chemistry *per se*, the next logical step is to compare the relative importance of such research with public endeavours in related sub-fields and technologies. To carry out this comparison, the 'gatekeepers' of new entrants and large incumbents were asked to rank, by scientific sub-disciplines and technological activities, the importance of public research (i.e. knowledge) to their own R&D activities.

The results, albeit interesting, are often predictable. Among new entrants, public research in organic chemistry, with a means score of 5.2, ranked first in importance, closely followed by genomics and biochemistry, as table 3 demonstrates. This observation underscores two important features of the combinatorial approach to small molecule drug discovery. The first is that small molecule drug discovery depends heavily on the underpinning sciences of organic chemistry, genomics and biochemistry. Add to this the restrictions that inadequacies in these scientific subfields can impose on the directions that the search for new drugs can take and the importance of publicly-funded research becomes obvious. Nowhere is this truer than in the area of organic chemistry, where current levels of knowledge are unable to match what is actually needed in order to fruitfully explore the vast realm of molecular diversity. To illustrate this, Eugene Vaisberg, president of ChemBridge, remarks that 'chemistry itself starts to be a key issue and major limiting factor in [the parallel synthesis of novel, chemically complex, structurally diverse and drug-like molecules]' (Borman 1998).

Table 3: The relevance of public research (i.e. knowledge) to small molecule drug discovery

	Mean score (standard deviation)			**% rating public research as important (≥ 5)**	
Sub-field	**New entrant**	**Large incumbent**	**2-tailed t-test (df)**	**New entrant**	**Large incumbent**
Organic chemistry	5.2 (1.7)	6.6 (0.8)	2.03 (37)	81	100
Genomics	5.1 (2.2)	5.2 (2.2)	2.18* (12)	61	60
Biochemistry	4.9 (1.6)	6.2 (0.8)	2.05* (29)	54	90
Drug design	4.2 (1.7)	4 (1.3)	2.06* (25)	34	40
ADME	3.7 (2)	4.5 (1.4)	2.06* 23	32	30
Combinatorial chemistry	3.6 (1.7)	4.3 (1.1)	2.04* (29)	29	40
Virtual screening	3.6 (1.8)	4.6 (1.6)	2.09* (19)	23	40
QSAR	3.5 (1.7)	3.6 (1.3)	2.06* (26)	26	20
HTS	3 (1.7)	3.3 (1.8)	2.11 (16)	13	33

Note: Level of significance:*p <0.05

The respondents placed drug design fourth behind the above-mentioned scientific sub-disciplines. The table also shows that publicly-funded research in chemoinformatics (e.g. virtual screening, ADME, and QSAR) fared even less well, their means score ranging from 3.5 to 3.7. This may indicate that new entrants as users of computational chemistry software, as opposed to developers, see little interest in using public knowledge in the area. In this respect, PROs as a source of commercial technology probably take a back seat to specialized suppliers of chemoinformatics tools. Moving on, the same can be said about high-throughput screening. While HTS has the lowest means score at 3 percent when compared to other sub-disciplines, this ranking does not necessarily indicate that public

knowledge in HTS is unimportant to all innovators. Instead, it probably suggests that public research in this field has a greater and more direct impact on the research productivity of automated instrumentation manufacturers than drug discovery firms, the latter acting as an intermediary between PROs and the former.

Turning to combinatorial chemistry, the table provides the first indication that public knowledge in this area, albeit ranked as important and very important for 29 percent of respondents, is only moderately important for the majority of new entrants. Two plausible reasons could explain this modest ranking. One possibility is that much of the knowledge related to combinatorial chemistry is to a large extent embodied in automated instruments and people rather than, say, in publications. Another line of speculation is that, although combinatorial chemistry still requires the challenging preparation of organic synthetic routes that are safe, high yielding and efficient in minimizing both the number of steps and reagents used (Marsh 2002), the technology itself is no longer considered as a block to better productivity.

Interestingly enough, large and small firms diverge somewhat in their thinking regarding the relevance of public research knowledge. Large incumbents give every sub-discipline and technology, bar drug design, a higher score than new entrants. This variation is difficult to interpret considering that small start-ups are intimately tied to public research by virtue of their public founders and technologies, as will be shown in section 4.4. An important clue to this puzzle can be found in a paper by Cohen et al. (2002), which shows that large pharmaceutical companies are more likely to make effective use of public research outputs than smaller firms, presumably because the latter spend more in R&D and sustain a larger portfolio of research projects than the former.

5.2 The provision of vocational skills

No matter which way new entrants go—toward servicing large incumbents or competing against them in drug markets—the entrepreneurial sector needs skilled labour. It is therefore instructive to note that combinatorial chemistry is now frequently part of the academic curriculum, with the University of Louisville being the first PRO to teach the ABCs of the method in 1996 (Borchardt 2001). Other universities in the United States follow suit, as for example the University of Pittsburgh, Harvard University, the University of Buffalo, the University of Utah, Ohio State University and Cold Spring Harbor University. The lecture course Chemistry 4388 offered by Northeastern University perhaps exemplifies what it is possible to learn as an introduction to the subject. The course covers: (1) peptide chemistry and its application to the discovery of ligands for biological receptors; (2) combinatorial chemistry in drug discovery, materials science and catalysis; (3) methods of solid-phase synthesis; (4) automation in synthesis, analysis, and purification; (5) data handling; (6) design of diverse screening libraries; and (7) drug design (Borchardt 2001).

In EU-15, academic organizations such as Leeds University, the University of Manchester, Cambridge University and Newcastle University in Great Britain, Lund University in Sweden, the Technical University in Denmark, Barcelona University in Spain, Trinity College University in Ireland, Milan University in Italy and Marburg University in Germany are also known to give some form of education in combinatorial chemistry. However, there are grounds for suspecting that the EU-15 responded slowly to training needs in the field. A survey questionnaire regarding postgraduate academic education for medicinal chemistry sent by the International Union of Pure and Applied Chemistry (IUPAC) to faculties in eight countries shows that relatively few medicinal chemistry PhD students attended courses in combinatorial chemistry in European countries in the late nineties, the respective percentages being Germany (11 percent), Japan (12), Spain (17), Italy (20), United Kingdom (31), France (33), Switzerland (50) and the United States (55) (Ganellin et al. 2000).

Will this potential lack of qualified personnel in combinatorial chemistry be detrimental to industrial innovations in the EU-15? After all, making postgraduates active participants in the field, by, for example, engaging them in the construction of libraries, has the potential of fostering problem-

solving abilities that will prove valuable once they reach the labour market. However, while the assertion that well-trained researchers in combinatorial chemistry play an important role in the innovation process is probably correct, it overlooks an important point: companies always prefer scientists endowed with good old-fashioned organic synthetic skills (Gwynne 1999; Brennan 2000; Henry 2001; Dalton 2003).

To substantiate this point, it was clearly appropriate to solicit the industry's opinion once more and to ask firms about the relevance of academic training in combinatorial chemistry and other sub-disciplines cum technologies. Table 4 shows the survey data, which confirms that the provision of skills in combinatorial chemistry is at best considered moderately important. By comparison, a university education in organic chemistry, genomics and biochemistry achieved much higher means scores. This was in fact predictable, for know-how in these three sub-disciplines continues to be a crucial input to the process of finding new drug candidates. Another argument could also be that this know-how is highly tacit, requiring the provision of knowledge that cannot be conveyed in the scientific literature and other pathways of information flows. This might also explain why academic education is generally perceived as more relevant than public research—a point supported by other surveys (i.e. Klevorick et al. 1995; Arundel et al. 1995).

The data also illustrate that new entrants regard training in the computational sub-fields of virtual screening and, unexpectedly, ADME and QSAR as only fairly important. One would have expected higher scores for these skills in view of the fact that 39 percent and 30 percent of clinical failures are attributed, respectively, to poor pharmacokinetic/toxicity characteristics and lack of efficacy (Kennedy 1997). The only explanations that can be given for this are hypothetical. Perhaps software products are more user-friendly than one would have assumed; again, perhaps the perceived needs of new entrants for proficiency in ADME and QSAR investigation are met by organic chemists who have absorbed computational chemistry skills during their graduate studies.

Table 4: The relevance of academic training (i.e. skills) to small molecule drug discovery

	Mean score (standard deviation)			**% rating public research as important (≥ 5)**	
Sub-field	**New entrant**	**Large incumbent**	**2-tailed t-test (df)**	**New entrant**	**Large incumbent**
Organic chemistry	6.2 (1.2)	6.7 (0.5)	2.06* (34)	86	100
Genomics	5.4 (1.9)	4.2 (2.5)	2.16* (13)	50	40
Biochemistry	5.3 (1)	5.5 (1.6)	2.26* (37)	72	50
ADME	4.2 (1.5)	3.3 (1.4)	2.07* (23)	33	30
QSAR	3.4 (1.7)	3 (0.8)	2.05 (26)	23	10
Virtual screening	3.9 (1.6)	4.3 (1.6)	2.09* (19)	29	40
Drug design	3.9 (1.4)	3.9 (1.1)	2.05 (26)	29	30
Combinatorial chemistry	3.3 (1.7)	3.6 (1)	2.03 (31)	19	20
HTS	2.3 (1.1)	1.8 (0.8)	2.11 (13)	10	0

Note: Level of significance:* $p<0.05$

Company size, once again, affected the importance score. Thus an academic training in organic chemistry, biochemistry and combinatorial chemistry was less important for smaller firms. This finding is not, of course, to undermine the significance of a university education in these sub-disciplines, but to highlight an observation often reported in the recruiting pages of chemistry journals: training costs can be a significant burden on small firms' resources. 'We need people who can get in the lab, run displacement reactions, and do it without having to train them for six months' says one director of human resources (Henry 2001:82). As a consequence, new entrants often prefer to hire chemists with experience at a large pharmaceutical company. By contrast, big pharma can afford to recruit relatively 'inexperienced' PhD graduates and to educate them with what they should know about the specific chemical needs of the firm (Gwynne 1999; Brennan 2000; Henry 2001; Dalton 2003). Gerald McMahon, senior vice president of discovery at Sugen, elaborates on the behaviour observed:

> The smaller companies don't have a lot of history with the chemistry that is the mainstay of their company. The larger companies have the accumulated knowledge of chemistry that has and hasn't worked. Therefore, small companies have a greater need than large companies for chemists who can work with a blank sheet of paper and come up with molecules that can be useful and interesting (Henry 2001:82).

On the other hand, survey data indicate that an academic training in genomics, QSAR and ADME is deemed to be slightly more important by new entrants than large incumbents. This finding may seem counter-intuitive, considering that smaller companies are biased towards chemists with some professional experience. This, however, should not obscure the fact that, in recent years, a growing number of new entrants have shifted their business focus from services to products. It follows that smaller firms are often eager to build in-house competences in genomics and computational chemistry; if this fails, attempting to find and turn lead compounds into safe and effective drugs is pointless. Maybe, then, we can conclude that the demand for experienced molecular biologists and computational chemists is such that experience in an academic setting is considered sufficient for industrial purposes.

5.3 The stimulation of networks

If one accepts the premise that the process of small molecule drug discovery requires different actors to interact and share complementary knowledge about the innovation puzzle, one cannot look at the economic effects of publicly-funded research without looking at alliance activities among smaller firms, larger incumbents and PROs. New entrants collaborated 1,992 times with other smaller companies, 3,141 times with large incumbents and 1,174 times with PROs (see table 5). Of the alliances signed between PROs and new entrants, R&D contracts grew most sharply, rising from 143 to 341 over the periods 1984-1995 and 1996-2003. A typical example of a research contract was when Pharmacopeia, seeking to build new competences in chemical genetics, signed a contract with, and had its own scientists conduct research at, Harvard University and its Institute of Chemistry and Cell Biology (ICCB).

It is also interesting to note that 45 new entrants recently decided to participate in R&D consortia, up from nothing in the period 1996-2003. Notable consortia dealing with combinatorial chemistry include the Diversity Biotechnology Consortium launched by the Santa Fe Institute (in New Mexico), the COMBICAT Consortium by the European Union and the Quebec Combinatorial Chemistry Consortium by the Canadian Foundation of Science. Mindful that research centres can facilitate knowledge transfer into industry, governments and public authorities also created combinatorial chemistry research centres in the late 1990s and early 2000s, including the National Institute of Standards and Technology Combinatorial Methods Center (NCMC), Boston University's Center of Excellence in Chemical Methodologies and Library Development, the University of Pittsburgh's Combinatorial Chemistry Center and the Combinatorial Centre at York University, Toronto. This

contribution is clearly illustrated by Dow Chemical's alliance with the NCMC. Chemist Don Patrick of Dow says that:

> We wanted to learn more about the applicability of [NCMC]'s approach to synthesizing and screening combinatorial libraries] to our materials programs. Participating in the center also allows us to network with other companies that have interest in polymer characterization (Dagani 2002:59).

Table 5: Alliances between PROs and new entrants -by mode of cooperation (1984-1995 and 1996-2003) (Absolute number and percent)

Mode of cooperation	1984-1995	1996-2003	TOTAL
Equity Participation	31 (48) (7.6)	34 (52) (4.4)	65 (100) (5.5)
Licensing	229 (41) (57)	329 (59) (43)	558 (100) (47.5)
Consortium	0 (0) (0)	45 (100) (5.8)	45 (100) (3.8)
R&D contract	143 (30) (35.3)	341 (70) (44.3)	484 (100) (41.2)
Others	2 (9) (0.5)	20 (91) (2.6)	22 (100) (1.8)
TOTAL	405 (34.5) (100)	769 (65.5) (100)	1174 (100) (100)

This anecdotal evidence also raises the possibility that PROs-industry collaboration serves as a ticket of admission to a larger network of innovators. The story here is no longer one of unilateral and bilateral knowledge transfer but of multilateral knowledge network—capitalizing on alliances with PROs to forge other ones with third-party organizations. Backing up this assertion is that new entrants with links to PROs are also those that exhibit the highest number of alliances with other firms. As the figures in table 6 show, the firm that establishes one or several research contract and consortia deals with PROs has, on average, three times more collaborative agreements with both small and large firms than the firm that is devoid of any tie with PROs. To be sure, the raw data are bedevilled by the need to control for many factors such as age and size—an exercise that goes beyond the scope of this paper. On the other hand, George et al. (2002:598) find clear indications that a positive relationships exists between academic alliances and business alliance formations, leading them to speculate that '[university] links serve as a magnet that draws technology alliance partners to join alliances with other firms'. There is also the fact that PRO-industry collaboration goes beyond formal network arrangements, involving the informal sharing of knowledge occurring during conversations and conferences. This issue will be dealt with in section 6.

Table 6: Differences in alliances: new entrants with and without research contracts to PROs

Variables	Firms with links to PROs	Firms without links to PROs	Firms without links
Number of firms	124	237	159
Number of links with PROs (average per firm)	722 (5.8)	0 (0)	0
Number of links with SMEs (average per firm)	950 (7.6)	591(2.5)	0
Number of links with large firms (average per firm)	1154 (9.3)	734 (3.1)	0

Note: The total number of links is greater than the sum of R&D contracts and consortia deals because the linkages of subsidiaries and newly merged companies were taken into account

5.4 The creation of new firms

By examining the alliance database and the websites of the sampled population of entrant firms, it was possible to ascertain the existence of 278 spin offs with complete certainty. Of these, 200 can be characterized as public sector research spin offs and 66 as corporate spin-offs. Twelve firms appear to meet the criteria associated with both public sector research and corporate spin-offs. The remaining firms are no longer in business, do not provide enough information on their website and 10-K forms, or do not reply to information requests.

What criteria were used to identify public sector research spin offs? The minority-holding criterion was used to detect 48 companies, although PROs invested funds 65 times, implying that universities and other 'non-profit' organizations took equity in the same spin-off (see table 5 on page 14).[3] This involvement reflects a number of concerns, including reducing graduate unemployment and improving the image of the organization (Callan 2001). These concerns do not rule out the possibility that PROs hold equity in order to see the results of their research exploited. This is exemplified by the equity position taken by Oxford University into Oxford Asymmetry (now Evotec OAI), where the investment was aimed at marketing the chiral chemical synthesis technology developed by Professor Stephen Davies and his research group at the Dyson Perrins Laboratory.

This leads us to the licensed technology criterion. Many spin-offs, often with the help of equity investments made by PROs, have been funded to exploit proprietary technologies licensed from academia and other public research organizations. These technologies range from novel recombinant DNA methods to the laser-heated pedestal-growth technique, though quite a few spin-offs also owe their existence to licensed innovations related to combinatorial chemistry. To name six examples, Auda Pharmaceuticals began with a combinatorial synthesis methodology developed at the Technical University of Denmark; Jerini Bio Tools was launched to exploit the SPOT technology discovered at the German National Research Center for Biotechnology; Pharmacopeia started out with exclusive license agreements with Columbia University and Cold Spring Harbor covering technology related to tagged combinatorial chemical libraries; Avantium Technologies was born out of combinatorial material research carried out at Delft, Eindhoven and Twente Universities in the Netherlands; Ilika uses high-throughput technologies developed by four professors from Southampton University's School of Chemistry; and Fluorous Technologies was spun out of University of Pittsburgh's Combinatorial Chemistry Center to market fluorous chemistry and services.

3 Further analysis indicates that such equity stakes are much more likely to occur in the United States: 52 times, as opposed to 10 in EU-15 and 3 times in non-US, non-EU-15 countries.

Table 7: Spin-offs founded by chemists from the public sector

New entrant (country)		Chemist	PRO (country)	
Acadia Pharmaceuticals	US	Mark R. Brann	U. of Vermont	US
Albachem	GB	R. Ramage	U. of Edinburgh	GB
Ariad Pharmaceuticals	US	Stuart Schreiber	Harvard University	US
Cambridge Combinatorial	GB	Steven Ley	Cambridge University	GB
Cambridge Combinatorial	GB	Alan Fersht	Oxford University	GB
Charnwood Molecular	GB	Philip Page, Steve Allin	Loughborough U.	GB
Coelacanth	US	Barry Sharpless	Scripps Research Inst.	US
Combichem	US	Chi-Huey Wong	Scripps Research Inst	US
Combio	DK	Morten Meldal	Carlsberg Laboratory	DK
CyberChemics	US	David Noever	NASA	US
DDL Drug Discovery Libraries	US	Robert Hodges	University of Alberta	CA
EMC Microcollections	DE	Günther Jung	University of Tubingen	DE
Enzymed	US	Douglas Clark	UC -Berkeley	US
EPIX Medical	US	R.B. Lauffer	Harvard Medical School	US
Gryphon Sciences	US	Stephen Kent	University of Chicago	US
Ilika	GB	M. Bradley, S. Guerin, B. Hayden, M. Hursthouse	University of Southampton	GB
Infinity Pharmaceuticals	US	Stuart Schreiber	Harvard University	US
Kémia	US	T. Bartfai, A. Hamilton, J. Rebek	Scripps Research Inst, Yale University	US
Mixture Sciences	US	Richard Houghten	Torrey Pines Institute	US
Multiple Peptide Systems	US	Richard Houghten	Scripps Research Inst	US
Néokimia	CA	P. Deslongchamps	U. de Sherbrooke	CA
Nuada Pharmaceuticals	US	Mario Geysen	University of Virginia	US
Oxford Asymmetry	GB	Stephen Davis	Oxford University	GB
Pharmacopia	US	Clark Still	Columbia University	US
Prestwick Chemical	FR	Camille Wermuth	Louis Pasteur U.	FR
Probiodrug	DE	Ulrich Demuth	Hans-Knöll Insitute	DE
Semorex	IS	Bernard Green	Hebrew U. of Jerusalem	IS
Signal Pharmaceuticals	US	Michael Karin	UC -San Diego	US
Sunesis Pharmaceuticals	US	Jonathan Ellman	UC -San Francisco	US
Symyx	US	Peter Schultz	UC -Berkeley	US
Syrrx	US	Raymond Stevens	Scripps Research Inst	US
Trega Biosciences	US	Richard Houghten	Torrey Pines Institute	US
Ultrafine	GB	Feodor Scheinmann	Salford University	GB

It is therefore telling that (at least) 33 public research spin-offs were launched by professors, post-doc graduates and other public sector researchers coming from the chemistry discipline, as table 7 testifies. Hence it is tempting to conjecture that the emergence of combinatorial chemistry generated a momentum towards the creation of public sector research spin-offs becoming a phenomenon akin to what has been observed with genetic engineering. The public founder criterion, however, is just as likely to be met by biological-based companies: public sector research spin-offs with a competence in combinatorial chemistry but founded by molecular biologists or biochemists who acted as Schumpeterian entrepreneurs. One example will suffice: Raj Parekh was a post-doctoral biochemist at the University of Oxford before co-founding Oxford GlycoSciences in 1988.

Table 8: Comparison between public sector research and corporate spin-offs

Variable (average)	Public sector research spin-offs (N=93)	Corporate spin-offs (N=35)
Employees	242	312
Sales*	8,971	71,854
Market capitalization*	549,151	1,231,378
Age (years)	12.9	10.1
No. of compounds	11.2	9.3
Patents	65	47
No. of alliances	23	24

*In thousands 2003 $US

Overall, these public sector research spin-offs create considerable economic benefits. Leaving aside private companies, those that are publicly traded together provided the local business community with over 22,000 jobs, generated sales revenues totalling $US 834 million and achieved a market capitalization of $51 billion in 2003. In relative terms, however, public sector research spin-offs fare poorly compared to corporate spin-offs (see table 8). Why this is the case is unclear; presumably, founders coming from academia and other PROs have fewer business skills and are less well connected to venture investors than founders who were previously employed in an industrial company (Lindholm Dalhstrand 1997; Shane and Stuart 2002). One thing is sure, however; the less than impressive economic performance of individual public sector research spin-offs cannot be explained by their youth or service-oriented business model—at least those that are publicly traded. As shown in table 8, these spin-offs are in fact older and have more lead compounds in their pipeline than corporate spin-offs.

In spite of everything, there may be a danger in focusing too narrowly on employees, sales and market capitalization as a barometer of success. In these respects, individual public sector research spin-offs compare unfavourably with corporate spin-offs. With respect to innovations, however, they outperform their corporate counterparts in terms of lead compounds and patented innovations, the latter yielding, on average, 18 more patents than the former. Judging by the number of their alliances with other organizations, it would also seem that both types of spin-offs occupy an important position in the network of innovators. This may suggest that the impact of public sector research spin-offs on regional economic development is more complex and indirect than that of corporate spin-offs. Stankiewicz (1994:105) may therefore be right when he argues that: 'Most academic spin-offs are best seen as a belt of organizations surrounding modern universities and forming a part of the "knowledge industry"'.

5.5 The development of new methodologies and scientific instrumentation

Certainly, most scientists would agree that PROs play an important part in the process of industrial R&D, if only because Árpád Furka (1982) from Eötvös Lorand University in Budapest, Ronald Frank (1983) from the German National Research Center for Biotechnology, Australian Mario Geysen and Dutch colleagues Rob Meloen and Simon Barteling (1984) from the Central Veterinary Institute in the Netherlands, Richard Houghten (1985) from the Scripps Research Institute, Kit Lam and co-workers (1991) from the Arizona Cancer Center and Xiang and colleagues (1995) from the Lawrence Berkeley National Laboratory and University of California, Berkeley, provided the pharmaceutical and chemical industries with the first combinatorial process innovations.

All the same, the impact of these synthesis methods would have been minimal had related techniques and instrumentation not been developed in public laboratories and later adapted by industrial players. Indeed, the emergence of the technology, giving rise to yet other challenging problems along the value chain of small molecule drug discovery, became a focal point of further scientific and technological developments. In some cases, PROs were directly involved in the innovative process, either by inventing a new methodology or by working out the first instrument prototype. In others, they provided the basic knowledge upon which new methods and instruments were developed by manufacturers and suppliers. Here are a few striking examples:

- Lead optimization involves the synthetic modification of a biologically active compound into a clinically useful drug. QSAR methods are very valuable from this point of view. The Hansch analysis established by Corwin Hansch and Toshio Fujita (1964) from Pomona College in California is hard to ignore when considering the historical evolution of the techniques, for it anticipated the development of commercial QSAR and 3-D QSAR software for combinatorial chemistry applications as currently commercialized by Accelrys, Chemical Computing Group and Tripos.

- All too frequently, combinatorial libraries encompass compounds of low purity, thus providing less reliable QSAR data. But manufacturers such as Varian, Biotage, Gilson and Perkin-Elmer have risen to the occasion with a plethora of purification and analytical tools using nuclear magnetic resonance (NMR) and mass spectrometry (MS). These instruments undoubtedly owe much to the pioneering work carried out in the first half of the 20th century by Felix Bloch from Stanford University and Edward Purcell from Harvard University (the fathers of NMR technology) and Sir Joseph John Thomson from the University of Cambridge (the inventor of the first mass spectrometer) (Shapiro and Gounarides, 1999; Papac and Shahrokh 2001).

- Since microwave-assisted combinatorial chemistry speeds up organic reactions from days and hours to minutes and seconds, microwave heating is fast becoming a common technique in industrial laboratories (Santagada et al. 2004). The first organic synthesis promoted by microwave radiation was carried out by Richard Gedye and colleagues (1986) from Laurentian University in Ontario. These scientists relied on domestic microwave ovens, which were later adapted for combinatorial purposes by manufacturers like CEM, Milestone and Personal Chemistry.

- A critical bottleneck for the advance of combinatorial materials sciences is the intrinsic problem of assessing the performance of molecules whose functionalities range from magneto-resistance to luminescence (Koinuma and Takeuchi 2004). In an attempt to remedy this limitation, PROs have been busy modifying old and developing new high-throughput screening methods and instruments, such as, for example, infrared thermography technology (Moates et al. 1996; University of Houston), the resonance-enhanced multiphoton ionization method (Senkan 1998; University of California - Los Angeles), and the x-ray microprobe technique (Isaacs et al. 1998; Lawrence Berkeley National Laboratory).

These limited examples show that publicly-funded basic research yielded substantial contributions to industrial methods and instruments, which, in turn, created very lucrative markets. Numerous

marketing studies prove this point. According to the Freedonia Group (2003), a Cleveland-based industrial market research firm, the US demand for consumables, instruments, software and services for the pharmaceutical and non-pharmaceutical applications of combinatorial chemistry was $US 735 million in 1996 and is expected to increase by over twelve percent annually to nearly $US 4 billion in 2006. On its own, the demand for instrumentation is predicted to grow from $US 288 million in 1996 to $US 1,190 million in 2006. Supporting this study, Kalorama Information estimated that the market for tools and services in combinatorial chemistry approached $US 3 billion in 2003 (as reported in PR Newswire 2004). However, the inherent uncertainty of technological change often led market research institutes to produce a wide variety of estimates. At one extreme one finds Frost & Sullivan, which forecasts global sales of $US 852 million in 2009 (as reported in Business Wire 2004). In the polar opposite case, one finds Technical Insights, which predicts that product sales originating from combinatorial chemistry research will reach as much as $US 115 billion by 2008 (as reported in Drug Discovery/Technology News 1999).

6. The methods of learning about public research in small molecule drug discovery

A central lesson that can be drawn from the previous section is that PROs are becoming more commercially oriented and better at linking research to the needs of the private sector. This sea change in the network of innovators certainly raises an important question: Does science also disseminate through classical channels of information flows such as publications, conferences and informal conversations?

To address this pertinent issue, the survey participants were asked to score the importance of seven different pathways of learning about public research outputs in small molecule drug discovery: (1) publications, (2) research contracts, (3) conferences, (4) consulting, (5) informal conversations, (6) hiring graduates and (7) patents and license. They were also asked to indicate how often these channels of knowledge flows had been used to complete research projects over the last three years. The results of the importance ranking and frequency of use of these pathways of knowledge flows are shown in table 9.

Table 9: Importance of different sources of learning about public research in combinatorial drug discovery

Source	Mean score (SD)			% rating as important (≥5)		Number of use (SD)		
	New entrant	Large incumbent	2-tailed t-test (df)	New entrant	Large incumbent	New entrant	Large incumbent	2-tailed t-test (df)
Publication	6.2 (1.6)	4.7 (1.8)	2.11* (16)	82.4	60	31.9 (81)	19.1 (35.9)	2.02* (40)
Research contract	5.5 (1)	4.1 (1.5)	2.16* (13)	73.8	40	4.6 (2.3)	2.3 (1.8)	2.1* (18)
Conference	5.1 (1.9)	4.6 (0.9)	2.03 (34)	64.7	50	7.7 (6.7)	7.3 (14.5)	2.23* (10)
Consulting	5 (0.84)	4.1 (1)	2.08* (21)	52.9	40	5.5 (1.9)	5.0 (5.6)	2.3* (10)
Conversation	4.9 (1)	4.0 (1.2)	2.09* (19)	52.9	30	13.8 (27.4)	7.6 (14.4)	2.03* (35)
Hiring	4.9 (2.1)	5.3 (1.4)	2.07* (23)	58.8	70	4.7 (5)	4.9 (5.2)	2.13 (15)
Patent & License	4.8 (1.8)	5 (2.2)	2.11* (32)	52.9	60	5.7 (7.4)	2.7 (2.6)	2.01 (47)

Level of significance:* $p<0.05$

While the survey reveals that every pathway of information flow received a relatively high importance score, new entrants put publication first: this classical method of accessing public science received a mean score of 6.2. The result conforms to expectations based on prior surveys (i.e. Arundel et al. 1995; Agrawal and Henderson 2002). It also underscores the value of open science in fast-changing, science-based industries, though one should bear in mind that such channel offers little prospect for face-to-face interactions, which are so important for tacit elements of knowledge to be communicated between PROs and industry.

The combination of these two factors—the presence of a turbulent environment and the need to access tacit know-how embedded in research teams—goes a long way towards explaining why research contracts came in second, with roughly 74 percent of the respondents reporting this learning channel as 'important' or 'very important'. This combination also explains why the number (share) of R&D agreements rose dramatically over the periods 1984-1995 and 1996-2003 (see again table 5). In view of the fact that technology, demand and competition in the field of small molecule drug discovery change rapidly,4 the majority of new entrants has been exploring with new scientific and technological alternatives as part of their strategy of renewing their competences and pre-empting rivals in the generation of innovations within specific therapeutic fields (Gambardella 1995). In addition, these research contracts often, although not always, allow for open-ended learning, enabling new entrants to acquire the tacit elements of technologies (von Hippel 1994). This is, of course, a two-way street: R&D contracts also foster learning opportunities within the PRO itself (Gelijns and Rosenberg 1994).

Interestingly enough, this pathway to knowledge flows was judged only marginally more relevant than conversations and conferences, in part suggesting that informal networking can pave the way for the establishing of more formal networks. Consulting came in fourth position with a means score of 5, which can be interpreted very simply as attesting that new entrants value the solutions provided by public researchers to their specific technical problems. Hiring trained graduates was reported to be less important than consulting. The movement of educated researchers, however, was highly valued by 59 percent of the responding firms, indicating that hiring recent graduates nonetheless plays a significant role in bringing fresh new skills into the industry.

In terms of importance, patents and licensing was the lowest ranked pathway to knowledge flows. However, it cannot be denied that 53 percent of new entrants rated these channels of information flows as greater than 5, nor can one fail to notice from table 5 that 558 licensing agreements have been signed with public research organizations. To explain this, it is appropriate to mention that, according to unpublished survey data, small and large companies alike consider the patent protection of focused libraries and lead compounds discovered by combinatorial means as very effective. This finding is appropriate because firms would be more reluctant to license-in inventions from PROs if their ability to capture the benefits of innovations was undermined by a weak appropriability regime (Shane 2002). The importance of focused libraries and lead compounds notwithstanding, there is little doubt that new entrants have also shown a keen interest in licensing advanced genomics products and technologies, which provide the means to develop screens for specific combinatorial programs. This is undoubtedly what the top management at Senomyx had in mind when the firm entered into licensing transactions involving receptor genes related to taste and olfaction with Rockefeller University, John Hopkins University and the University of California, San Diego in 1999 and 2000.

A final note must be added about the influence of company size on the importance attributed to learning channels. There are two striking differences between the ranking scores of smaller and larger firms. The first is that the recruitment of trained graduates is the most relevant source of learning for large incumbents, as opposed to the sixth position for new entrants. As noted earlier, the reason for this seems to be that new entrants, having less financial resources for training purposes than their

4 The velocity of technological change in combinatorial chemistry is amply confirmed in a recent patent citation analysis, which showed that the peak cited year in combinatorial patents is two years prior to patent grant (Malo and Geuna 2000).

larger counterparts, tend to prefer chemists with some previous experience gained in a major pharmaceutical company (Gwynne 1999; Henry 2001; Dalton 2003). The second difference is that publications, research contracts, conferences, consulting and informal conversations seem to be relatively less important for large pharmaceutical companies than smaller players. One explanation is that new entrants use these channels of knowledge flows more frequently than their large counterparts do, as the middle columns of table 9 attest. A fuller explanation was provided in section 4.4: the majority of new entrants spun-out from PROs, which suggests a close connection with public research.

7. Concluding remarks

In light of the above discussion, a series of observations can be made about the contributions of public research to industrial innovations. First, it has been revealed that small and large companies rely heavily on public research knowledge and, even more so, on education in organic chemistry, genomics and biochemistry. At the same time, it has been shown that the importance granted to organic chemistry overshadows the value of combinatorial chemistry. This, in part, reflects the fact that the research tool has matured and diffused to the point that it is no longer considered a source of enduring competitive advantage.

Yet to leave it there is to understate the influence that public research has already had, and doubtless will continue to exert on the pharmaceutical industry. This leads us to a second series of observations. Publicly-funded research (1) led to the creation of dozens of new companies around the world, (2) provided firms with an access to a larger network of innovators and (3) generated important instruments and methods that are being used throughout the value chain of small molecule drug discovery. It is particularly interesting to note here that public research spin-offs were often launched by chemistry professors. A third series of observations deals with firm size. Echoing Cohen et al. (2002) and others, the effects of public research look different depending on whether one sees them through the prism of larger or smaller firms. New entrants appear to depend more heavily on publicly-funded research than large incumbents. Smaller firms, however, are less likely to value academic skills, in no small measure because training costs can be a major deterrent to hiring new skilled graduates. Large companies, as a result, can be seen as an important source of trained personnel.

The last in this series of observations is that few differences separate the relevance attributed to different pathways of information flows. This, in itself, may suggest that contractual relationships between industry and PROs complement, rather than substitute, channels of knowledge flows that are usually associated with open science. Whether licensing and research contracts hinder publications and informal conversations, however, remains open to question. Further investigation is also necessary if the following questions are to answered: Is the commercialization of combinatorial research outputs by PROs eroding the competitive advantage of new entrants? Are formal and informal networks between the public and private sectors positively affecting firm productivity? Does the supply of trained graduates in various disciplines meet industry requirements? What policy responses are necessary? While these unanswered questions might seem to reduce the usefulness and reliability of this paper, the latter does, all the same, manage to provide some first, clear insights into the impact of public research into combinatorial chemistry innovations.

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