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The contribution of (not so) public research to commercial innovations in the field of combinatorial chemistry

Stéphane Malo*

Grenoble Ecole de Management, 12 rue Pierre Sémard, 38003 Grenoble, France

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ABSTRACT

This paper examines the roles that publicly funded research play in the process of combinatorial drug discovery. It is shown that firms rely heavily on public research knowledge and, even more so, on education in organic chemistry, genomics and biochemistry. Publicly funded research also led to the creation of dozens of chemical-based companies, provided firms with an access to a larger network of innovators and generated important instruments and methods that are being used throughout the value chain of combinatorial drug discovery. The effects of public research, however, often look different depending on whether one sees them through the prism of larger or smaller firms, EU15 countries or the US, universities or other PROs.

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 endeavors differ across countries and organizations, 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 that has received only minimal attention is combinatorial chemistry, which has been defined by the International Union of Pure and Applied Chemistry (IUPAC) as "a process to prepare large sets of organic compounds by combining sets of building blocks" (Wermuth et al., 1998: 1133). The preparation of these sets of compounds, known as combinatorial libraries, represents a sea change from the Woodwardian era of synthesis (Nightingale, 2000). Where under the Woodwardian paradigm a skilled medicinal chemist would have synthesized a single molecule at a cost of about $US 7500, the new paradigm instead provides scientists with the possibility to create compounds en masse at a cost ranging from $US 1 to 10 per unit (Thomke et al., 1998). The desired goal was to explore uncharted chemical space and, it was hoped, increase the odds of finding new drugs that work (Rabinowitz and Shankley, 2006).

Having said that, this paper will address the following questions about the effects of publicly funded research in the field of combinatorial chemistry on commercial innovations, using a combination of databases. How relevant are public research and education to the industrial process of combinatorial drug discovery? 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? Answers to these questions will not only be informative about the general contributions of public research to commercial innovations but also provide valuable insights into the geographical and institutional location of knowledge production, the role of firm size in accessing scientific knowledge *cum* skills, the intertwined relationships between basic and applied research and the impact of computational technologies on university research.

The paper 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

* Tel.: +33 4 76 70 61 45; fax: +33 4 76 70 61 45/+33 4 76 70 65 08(Dir).
E-mail address: stephane.malo@grenoble-em.com.

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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 combinatorial drug discovery, while section 7 closes with a summary of the main findings and policy recommendations.

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, 2002) and Europe (Arundel et al., 1995; Abramson et al., 1997; Arundel and Geuna, 2004; Monjon and Waelbroeck, 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 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 basic research knowledge in chemistry and biology to industrial innovations in the pharmaceutical industry. This is another important distinguishing feature of this industry given that academic applied research is generally considered to be of more direct application to industrial players than is fundamental research (Klevorick et al., 1995).

Case studies, bibliometric analysis and econometric investigation have testified elsewhere in different ways to the positive influence of public research endeavors 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) 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.

But this contribution comes with five caveats. First, the relevance of public knowledge is 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).

Second, there is evidence that countries have not drawn closer together in the relative public production of scientific knowledge (OECD, 2008). The exception to rule are EU-15 countries and the United States, where the former not only narrowed the transatlantic gap but overtook the latter in terms of published scientific output. The overall productivity of EU-15, however, is still considerably lower that of the US when an index for the intensity of university researchers on population is taken into the equation (Dosi et al., 2006). The strong US performance is being attributed to several factors, including large scale government funding of basic research and (as a result) the rapidity with which universities have introduced new fields into the teaching curriculum as soon as their practical utility was demonstrated (Rosenberg and Nelson, 1994; Pavitt, 2001). In principle, EU-15 could "free-ride" on American public research. In theory, understanding and using the outputs of basic research demands considerable investments in institutions, skills, equipment and networks, a point casting doubt on the simple conceptualization of knowledge as mere "information" and pure "public good" (Callon, 1994; Pavitt, 2001).

Third, the patterns of usefulness of university research may be changing due to rapid improvements in computational technologies. As warned by Pavitt (2002), the ensuing decreased in laboratory costs may have increased pressures on university research to capture the financial impact associated with drug discovery, with potential detrimental effects on scientific progress. An expansion of university patenting would be especially detrimental, for a rise of US patents granted to universities has resulted in a rapid increase in "low-quality" patents (Henderson et al., 1998).

Four, as stipulated by Gibbons et al. (1994), a shift may be taking place away from mode 1 of knowledge production, which is disciplinary and investigator-initiated, towards a mode 2 characterized by transdisciplinarity and research focusing on applicability. The authors equally hypothesized that in the new form of knowledge production the role of universities would play second fiddle to government laboratories and other PROs. The later contention, however, has been since been much disputed (Godin and Gingras, 2000).

Last, but not least, the production of scientific knowledge is only one of several benefits of public research to innovation. Key contributions to be considered in a comprehensive approach must also account for 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). 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; Florida, 1999). Such benefits, interestingly, are bound to remain within national boundaries (Pavitt, 2001). It is equally interesting to note that apparent cross-firm differences about the value of academic training have 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 Dahlstrand, 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 Dahlstrand, 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 (De Solla 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 combinatorial drug discovery in general and combinatorial chemistry in particular. No systematic study has yet been conducted on the technology. Yet combinatorial chemistry provides fertile ground for studying the intricate ties that bind public research and industrial innovations, largely because it is a (relatively) new process innovation, is increasingly science-driven, originates in (European) PROs, and relies heavily on computational technologies and, as will be shown, public research in organic chemistry and other scientific disciplines. The remainder of the paper intends to unpack what these ties and characteristics are and assess what this could mean for current policy.

3. Technological and industrial background

Combinatorial chemistry was first imported into 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. 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 (Bunin and Ellman, 1992). 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 coworkers 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. Early problems included the purity of compounds being produced and the deluge of data being analyzed (Rabinowitz and Shankley, 2006). Another bottleneck, yet to be adequately solved, is the vastness of chemical space, which is evaluated at 10^{180} potential drugs (Nightingale, 1998). To this, one can only say that even if a company were to synthesize and screen randomly 100 million compounds, the sampling would still be hopelessly inadequate (Valler and Green, 2000).

Those problems have made the technology suspect in the eyes of many (Landers, 2004), but researchers have been moving ahead in generating libraries of complex, drug-like molecules that are focused towards specific drug targets, giving rise to a marriage of convenience between combinatorial chemistry and the computational tools associated with rational drug design: virtual combinatorial library design (Dalemme et al., 1997). Virtual screening methods are thus increasingly being applied to drug discovery, with the accompanying strengthening of the links between science and technology (Malo and Geuna, 2000). It also follows that library size has been declining with the passage of time. The publication of libraries containing more than 1000 members went down from 57 to 15 percent of total between the period 1992–2003 (Dolle, 2000, 2004). Of the libraries published in 2003, 79 percent were under 500 members (Dolle, 2004). In the words of Herbert Waldmann, a professor at the Max Planck Institute of Molecular Physiology:

> What one clearly can see in the past two or three years is that the first generation of combichem... is now being translated into a second generation. In this second generation, there's more emphasis on quality than on quantity (Borman, 2004:38).

While there is ground for suspecting that the impact of combinatorial chemistry on drug discovery is nowhere near as great as one thought it might have been (Landers, 2004; Rabinowitz and Shankley, 2006), there is equally evidence that investments in R&D involving incremental innovations have started to pay off with a wave of drug candidates that may generate sales growth. According to Golebiowski et al. (2001, 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

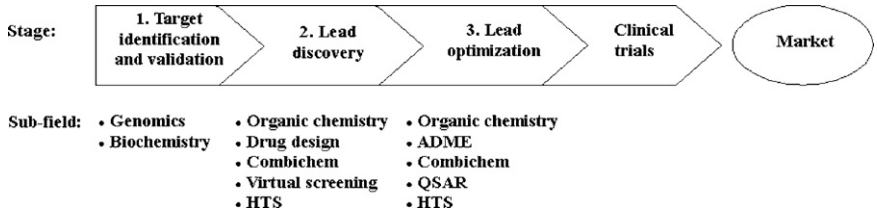

Fig. 1. The value chain of combinatorial drug discovery.

reported in chemistry journals (Scott, 2001; Van Arnum, 2004; Messeguer and Cortès, 2007).

4. Method

4.1. 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 SMEs; (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.

The 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).[1] 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 Dahlstrand, 1997; Davenport et al., 2002).

As noted, 520 SMEs – either de novo entrants, entrants by diversification or entrants by acquisition – have been identified, of which 130 were publicly traded. 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.

Of course, these firms remain highly heterogeneous in relation to their competences: some only possess combinatorial synthesis skills, whereas others combine abilities in combinatorial chemistry, genomics, etc. In the same vein, they may 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). Yet despite this seeming heterogeneity, there is a common thread that binds these firms together. That is, each and every one of the small- and medium-sized firm discussed in this paper, at various degree, uses combinatorial chemistry.

4.2. Data

4.2.1. Survey 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. (The complete text of the initial questionnaire is given in the Appendix A; each data source is summarized in Table 1).

Table 1
Sources of data.

Data	Source
Survey data	"Gatekeepers" of 57 companies
Published combinatorial libraries	Annual surveys of (Dolle, 1998a,b, 2000, 2001, 2002, 2003, 2004; Dolle and Nelson, 1999)
Sales revenues	Annual reports and Securities and Exchange Commission filings
Market capitalization	DataStream
Patent	United States Patent Trademark Office
Alliance	Websites of 520 SMEs

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.

Combinatorial chemistry, however, does not stand alone, as Fig. 1 illustrates.[2] Hence, the paper focuses on three stages of the value chain of combinatorial 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

[1] It is important to acknowledge that there exists no standard definition of public research spin-off. Various definitions have been proposed using more or less restrictive criteria (Callan, 2001).

[2] 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.

and transforming an active new chemical entity into a clinically useful drug).[3] 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 during January and February 2005. Fifty-seven firms returned the survey: 47 new entrants and 10 large pharmaceutical companies; roughly 21 percent of firms responded.[4] 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.

4.2.2. Publication data

The paper also draws on published combinatorial libraries (i.e. 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,b, 2000, 2001, 2002, 2003, 2004; 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 surveys of lead compounds being derived from combinatorial chemistry by Golebiowski et al. (2001, 2003). Obviously, these bibliometric measures are not perfect; one must take into account a 1–2 year time lag between the actual synthesis and publication and a statistical discrepancy may arise from firms wishing to keep their libraries-compounds a trade secret. It is also worth pointing out that while published combinatorial libraries may vary widely in economic and technical importance as well as in size, the growing popularity of focused libraries indicates that libraries are more likely to contain a smaller number of compounds and exhibit a higher probability for activity than those synthesized in the eighties (Dolle, 2004; Rabinowitz and Shankley, 2006).

4.2.3. Financial, employment and patent data

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 130 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).

4.2.4. Alliance data

Using the websites of all 520 new entrants, 5507 alliances were collected; of these alliances, 1174 connect new entrants with PROs. The data cover the period between 1982 and 2003 and include alliances for combinatorial chemistry, HTS and other technology. 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 combinatorial 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.

5.1. The advancement of scientific knowledge

Before considering in greater detail the economics of public research knowledge in the arena of combinatorial drug discovery, it would be useful to examine what constitutes the most obvious visible research outputs of combinatorial chemistry: combinatorial 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 1511 libraries over the period 1992–2003 (see Fig. 2), as opposed to 821 and 467 libraries, respectively, for large incumbents and new entrants.

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, that adds weight to the argument of Pavitt (2002) that computational technologies have been reducing the costs of pharmaceutical research to a level affordable in public laboratories.

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). Regardless of this diversity, however, universities remain at the core of

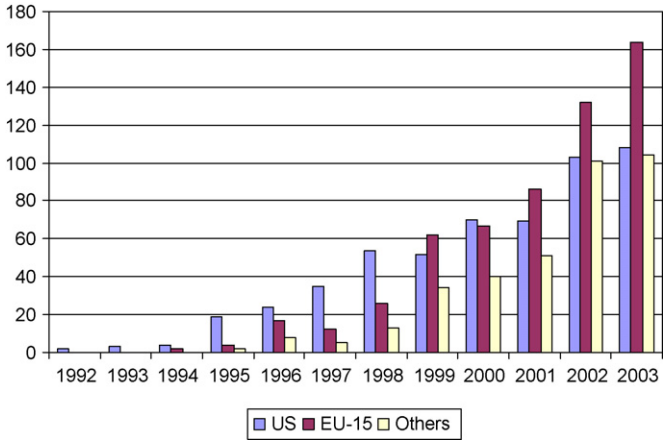

Fig. 2. Increasing volume of public research in combinatorial chemistry as measured by published libraries—by geographical location (1992–2003). *Source*: Extracted from Dolle (1998a,b, 2000, 2001, 2002, 2003, 2004) and Dolle and Nelson (1999).

[3] 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.

[4] The survey response rate may seem low, which is not unusual for the pharmaceutical industry.

Table 2
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 Pittsburg	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).

the system of knowledge production, thus contradicting the thesis advocated by Gibbons et al. (1994) and confirming that of Godin and Gingras (2000).

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 Fig. 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. However, if one takes into consideration the fact that the number of US university researchers is about 23 percent lower than that of EU-15 countries, the overall EU scientific productivity remains below that of the US.[5]

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 whereas others libraries tend to be concentrated in a few PROs. Table 2 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. This should come as no surprise. The Institute has been involved in combinatorial research since its inception, with top scientists such as Nobel Laureate Barry Sharpless, K.C. Nicolaou, Dale L. Boger, Peter G. Schultz and Richard Lerner working at developing new, or improving old, synthetic methodologies and pathways. It was also the No. 1 recipient of grant money from the National Institutes of Health in 2003.

[5] The calculation is based on numbers of university researchers per population reported by Dosi et al. (2006).

Public research motivations for engaging in the synthesis of these combinatorial libraries fall into two categories: the "classical" and "business-oriented" motivations. The "classical" motivation is one of open science: developing the types of chemical reactions that the industry should look for in their search for new drugs—something small and large companies are often not able to achieve. As pointed out by John Porco, assistant professor of chemistry and director of Boston University:

> [In an academic setting] we have greater liberty to take more time to develop the types of new chemical reactions that we do. In a pharmaceutical company, you're up against a deadline to get a drug or a candidate or some compound out the door" (McGee, 2005:44).

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 one thing, the propensity to patent combinatorial innovations among PROs is significant. This is illustrated by a recent, and perhaps only, study of combinatorial chemistry patenting, which reveals that the University of California, the Scripps Research Institute, Stanford University and Columbia University were among the top 20 patent holders in the field in the United States in 1998 (Mulligan and Steele, 1999). For another, PROs often contract out their services in exchange for fees. 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 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 3).

Table 3
Summary of lead compounds discovered from combinatorial libraries by public research organizations.

Public research organizations	Country	Targeted disease area
Columbia U, Rockefeller U.	US	Infections and infectious diseases
Harvard University	US	Cancer
Max Planck Institute, U. of Mainz	DE	Cancer
Mayo Clinic	US	Lung cancer
Scripps Research Institute	US	Cancer, hormonal disorders, etc.
Scripps Research Institute	US	Infections and infectious diseases
Scripps Research Institute	US	Prostate cancer
Scripps Research Institute	US	Hormonal disorders
Scripps Research Inst., UC—San Diego, Virginia Polytechnic Institute and State University	US	Neuromuscular and cognitive disorders
Texas University, Georgetown University	US	Cocaine abuse
UC –Berkeley	US	Infections and infectious diseases
UC –Berkeley	US	Skin disorders
UC –Berkeley	US	Inflammatory disorders
UC –San Francisco	US	Malaria
University of Amsterdam	NL	Breast cancer
University of Pittsburgh	US	Cancer
Yeshiva University, Jefferson University	US	Diabetes

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

Table 4
The relevance of public research (i.e. knowledge) to combinatorial drug discovery.

Sub-field	Mean score (standard deviation)		Chi square	% rating public research as important (≥5)	
	New entrant	Large incumbent		New entrant	Large incumbent
Organic chemistry	5.2 (1.7)	6.6 (0.8)	5.3	81	100
Genomics	5.1 (2.2)	5.2 (2.2)	9.6	61	60
Biochemistry	4.9 (1.6)	6.2 (0.8)	10.5*	54	90
Drug design	4.2 (1.7)	4 (1.3)	7.3	34	40
ADME	3.7 (2)	4.5 (1.4)	6.8	32	30
Combinatorial chemistry	3.6 (1.7)	4.3 (1.1)	9.9*	29	40
Virtual screening	3.6 (1.8)	4.6 (1.6)	8.7	23	40
QSAR	3.5 (1.7)	3.6 (1.3)	8	26	20
HTS	3 (1.7)	3.3 (1.8)	6.5	13	33

Level of significance: $^{*}p < 0.05$.

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 endeavors 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 basic research in organic chemistry, with a means score of 5.2, ranked first in importance, closely followed by genomics and biochemistry, as Table 4 demonstrates. This observation underscores two important features of the combinatorial approach to drug discovery. The first is that combinatorial 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 basic 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:

> [C]hemistry 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).

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.

Turning to combinatorial chemistry, the table provides the first indication that public applied research 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 biochemistry and combinatorial chemistry a higher means score than new entrants. A chi-square test reveals that the means are significantly different. Concomitantly, more large firms consider these sub-disciplines and technologies as important. 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 5.4. 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 labor. 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 (e.g. University of Pittsburgh, Harvard University) and EU-15 (e.g. Cambridge University, Milan University) follow suit.

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 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). This suggests, in accordance with Nelson and Rosenberg (1994) and Pavitt (2001), that the American university system, thanks to large scale government funding, has been able to identify new fields faster than its European counterparts.

Will this head start 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 labor 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).

Table 5
The relevance of academic training (i.e. skills) to combinatorial drug discovery.

Sub-field	Mean score (standard deviation)		Chi square	% rating public research as important (≥5)	
	New entrant	Large incumbent		New entrant	Large incumbent
Organic chemistry	6.2 (1.2)	6.7 (0.5)	4.7*	86	100
Genomics	5.4 (1.9)	4.2 (2.5)	18.5**	50	40
Biochemistry	5.3 (1)	5.5 (1.6)	13.3**	72	50
ADME	4.2 (1.5)	3.3 (1.4)	6.8	33	30
QSAR	3.4 (1.7)	3 (0.8)	8	23	10
Virtual screening	3.9 (1.6)	4.3 (1.6)	8.7	29	40
Drug design	3.9 (1.4)	3.9 (1.1)	8.8	29	30
Combinatorial chemistry	3.3 (1.7)	3.6 (1)	9.9**	19	20
HTS	2.3 (1.1)	1.8 (0.8)	8.7	10	0

Level of significance: $^{*}p < 0.05$, $^{**}p < 0.01$.

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 5 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 involves high levels of tacitness, requiring the provision of knowledge that cannot be conveyed in the scientific literature and other pathways of information flows.[6] 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.

Company size, once again, affected the importance score. Thus an academic training in organic chemistry 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 two 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). Adds a R&D manager at another SME: "For many small companies, experience is a commodity they cannot take time to grow. So the approach is to steal it away from big pharma" (Brennan, 2000: 39). 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).[7]

On the other hand, survey data indicate that an academic training in genomics 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; 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 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 combinatorial 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, 3141 times with large incumbents and 1174 times with PROs (see Table 6). Roughly one third of all alliances concern combinatorial chemistry, the rest involving other technologies along the value chain of drug discovery. 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 1984–1995. 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 centers can facilitate knowledge transfer into industry, governments and public authorities also created combina-

[6] These points can be summed up by citing Rabinowitz and Shankley: "...the notion that academia of the future routinely training chemists in the preparation of hundreds of thousands of compounds in a week has been tempered by the realization that chemical careers in industry are made by the ability to solve problems rather than simply training for the skills of a given technology" (Rabinowitz and Shankley, 2006: 74).

[7] Gerald McMahon, senior vice president of discovery at Sugen, elaborates on the behavior 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).

Table 6
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)

Table 7
Spin-offs that use combinatorial chemistry founded (or co-founded) by chemists from the public sector.

New entrant (country)		Chemist	PRO (country)	
Acadia Pharmaceuticals	US	Mark R. Brann	University of Vermont	US
Albachem	GB	R. Ramage	University 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 University	GB
Coelacanth	US	Barry Sharpless	Scripps Research Institute	US
Combichem	US	Chi-Huey Wong	Scripps Research Institute	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 Institute, Yale University	US
Mixture Sciences	US	Richard Houghten	Torrey Pines Institute	US
Multiple Peptide Systems	US	Richard Houghten	Scripps Research Institute	US
Néokimia	CA	P. Deslongchamps	University 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 University	FR
Probiodrug	DE	Ulrich Demuth	Hans-Knöll Institute	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 Institute	US
Trega Biosciences	US	Richard Houghten	Torrey Pines Institute	US
Ultrafine	GB	Feodor Scheinmann	Salford University	GB

torial chemistry research centers 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 Center 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).

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.

5.4. The creation of new firms

By examining the alliance database and the websites of the sampled population of entrant firms with a competence in combinatorial chemistry, 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 start-ups 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 7).[8] This involvement reflects a number of concerns, including 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.

[8] 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 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*	8971	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 $US 2003.

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.[9]

It is also noteworthy 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. 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.

As for economic benefits, based on 93 public sector research spin-offs for which data are available, the following picture emerges: these 93 spin-offs together provided the local business community with over 22,000 jobs, generated sales revenues totaling $US 834 million and achieved a market capitalization of $US 51 billion in 2003. In relative terms, however, these spin-offs fare poorly compared to corporate spin-offs (see Table 8). Why this is the case is unclear. 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 unfavorably with corporate spin-offs. With respect to research output, however, they surpass their corporate counterparts in terms of lead compounds and patented inventions, 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 public researchers in Hungary, Germany and the Netherlands, themselves building upon the work of Bruce Merrifield (1963) on the synthesis of peptides, provided the pharmaceutical and chemical industries with the first combinatorial process innovations.[10] 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 combinatorial 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:

- Most people associate combinatorial chemistry with automation. In fact, combinatorial synthesis was carried out manually until 1988, when Holm and Myrdal (1989), two chemists from the Carlsberg Laboratory in Denmark, developed the first multiple-column synthesizer. Synthesizers for combinatorial purposes only became commercially available in the nineties, sold by manufacturers such as Advanced ChemTech, Argonaut Technologies, Gilson, Mettler Toledo and Tecan.
- 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

[9] 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.

[10] These inventors are 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.

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

Source	Mean score (SD)		Chi square	%Rating as important (≥5)	
	New entrant	Large incumbent		New entrant	Large incumbent
Publication	6.2 (1.6)	4.7 (1.8)	23.9***	82.4	60
Research contract	5.5 (1)	4.1 (1.5)	17.9**	73.8	40
Conference	5.1 (1.9)	4.6 (0.9)	12.8* (34)	64.7	50
Consulting	5 (0.84)	4.1 (1)	7.9	52.9	40
Conversation	4.9 (1)	4.0 (1.2)	5.4	52.9	30
Hiring	4.9 (2.1)	5.3 (1.4)	3.3	58.8	70
Patent & License	4.8 (1.8)	5 (2.2)	5.9	52.9	60

Level of significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

industrial laboratories (Santagada et al., 2004). The first organic synthesis promoted by microwave radiation was carried out by Gedye et al. (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).

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

A central lesson that can be drawn from the previous section is that PROs have been increasingly performing research activities in the field of combinatorial chemistry and have become more commercially oriented by virtue of their patenting and licensing activities. 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 combinatorial 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.

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 6). In view of the fact that technology, demand and competition in the field of combinatorial drug discovery change rapidly,[11] 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 6 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 is a striking difference between the ranking scores of smaller and larger firms. The difference is that publications, research contracts and attendance to conference seem to be relatively less important for large pharmaceutical companies than smaller players. (Consulting and conversation are also deemed less important, though differences are not statistically significant.) One explanation was

[11] 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).

provided in Section 5.4: 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, and confirming previous findings (Dosi et al., 2006), EU15 countries account for the largest proportion of published combinatorial libraries being synthesized by PROs, though their leadership is somewhat eroded when adjusting for population. In addition, the contribution of public research to the production of libraries has increased steadily to the point that PROs are now more productive than small and large firms. Contradicting the predictions of Gibbons et al. (1994), the role of universities has particularly and steadily increased in importance. One of the most plausible explanations of this outcome was posited by Pavitt (2002), who argued that improvements in computational technologies are reducing the costs of virtual experimentation to a level affordable in university laboratories, and in so doing, is significantly transforming the very nature pharmaceutical research. However, in accordance with Klevorick et al. (1996), small and large companies tap more heavily on basic research than applied research. In fact, the industry ranks the underpinning sciences of organic chemistry, genomics and biochemistry far ahead of combinatorial chemistry. This finding reflects, in part, 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 and, in part, the fact that efforts to discover new drugs via combinatorial chemistry endeavors will come to naught unless scientists possess the ability to discover new chemical pathways, understand the chemical processes associated with living cells and access putative targets.

For policy makers, especially those from EU15 countries, the lessons are clear. It may seem contrary to what common sense would suggest, considering the tendency to expect public funding of university research to generate more concrete and direct returns (Florida, 1999; Geuna, 2001), but the best way to support advances in combinatorial drug discovery is to resist the temptation to emphasize public applied research in combinatorial chemistry *per se* and instead increase government funding in academic basic research in organic chemistry, genomics and biochemistry. Yet the best rationalization for this comes elsewhere. Person-embodied knowledge generated by academic basic research figures predominantly on the list of important contributions.

This is not to say that combinatorial chemistry should be removed from the academic curriculum. Indeed, basic and applied research often co-evolve, interacting in a complex and iterative manner for the benefit of both (David et al., 1992). Consequently, the interaction between fundamental research in organic chemistry, genomics and biochemistry and applied research in combinatorial chemistry is likely to increase the productivity of each type of research. Moreover, combinatorial chemistry has been integrated into the everyday work of industrial chemists. As pointed out by Samuel Gerritz, group leader for lead synthesis at Bristol-Myers Squibb: "Today employers expect that you are familiar with the concepts of combinatorial chemistry. It's becoming part of the natural skill set for synthetic chemists in industry" (Gilman, 2004: 40).

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 combinatorial drug discovery. It is perhaps interesting to note here that many public research spin-offs were launched by chemistry professors and post doc researchers. In view of this finding, one may justifiably argue that promoting public research would allow for easier transfer of research findings to industry as chemists may take their knowledge to work in industry.

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. This, in turn, represents an important policy rationale for government action in the form of subsidies to SMEs for business training activities.

The last in this series of observations is that few differences separate the relevance attributed to different pathways of information flows. Virtually all sources of learning are considered to be important for combinatorial drug discovery. This rule applies no matter the size of the firm. Whether patenting, 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 be answered: What are the effects on university patenting on combinatorial chemists' publication activity and patent quality? Are formal and informal networks between the public and private sectors positively affecting firm productivity? Is the quality of combinatorial chemistry research in EU15 countries comparable to that of the US? Does the supply of trained graduates in various disciplines meet industry requirements? 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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Appendix A

Survey questions

1. What is the relevance of public research (i.e. knowledge) in the following sub-disciplines-technologies to combinatorial drug discovery along a seven point Likert scale where 1 = highly irrelevant and 7 = highly relevant.
2. What is the relevance of academic training (i.e. skills) in the following sub-disciplines-technologies along a seven point Likert scale where 1 = highly irrelevant and 7 = highly relevant.
3. What is the relevance of the different pathways of knowledge flows to combinatorial drug discovery along a seven point Likert scale where 1 = highly irrelevant and 7 = highly relevant.

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