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Survey of Current Trends in DNA Synthesis Core Facilities

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The Nucleic Acids Research Group of the Association of Biomolecular Resource Facilities (ABRF) last surveyed DNA synthesis core facilities in April 1995. Because of the introduction of new technologies and dramatic changes in the market, we sought to update survey information and to determine how academic facilities responded to the challenge presented by commercial counterparts. The online survey was opened in January 1999 by notifying members and subscribers to the ABRF electronic discussion group. The survey consisted of five parts: general facility information, oligonucleotide production profile, oligonucleotide charges, synthesis protocols, and trends in DNA synthesis (including individual comments). All submitted data were anonymously coded. Respondents from DNA synthesis facilities were primarily from the academic category and were established between 1984 and 1991. Typically, a facility provides additional services such as DNA sequencing and has upgraded to electronic ordering. There is stability in staffing profiles for these facilities in that the total number of employees is relatively unchanged, the tenure for staff averages 5.9 years, and experience is extensive. On average, academic facilities annually produce approximately 1/16 the number of oligonucleotides produced by the average commercial facilities, but all facilities report an increase in demand. Charges for standard oligonucleotides from academic facilities are relatively higher than from commercial companies; however, the opposite is true for modified phosphoramidites. Subsidized facilities charge less than nonsubsidized facilities. Synthesis protocols and reagents are standard across the categories. Most facilities offer typical modifications such as biotinylation. Despite the competition by large commercial facilities that have reduced costs dramatically, academic facilities remain a stable entity. Academic facilities enhance the quality of service by focusing on nonstandard oligonucleotides and valuable services such as personal consultations, electronic ordering, and diversifying into other services. (J Biomol Tech 1999;10:187–193)

KEY WORDS: core facility, oligonucleotide synthesis, multiple synthesizers.

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DNA synthesis as a core service first appeared in the academic setting in the late 1970s and continued to grow throughout the 1980s and the early 1990s.[1] During the past several years, advancements in chemistry and technology have had a great impact on the field of DNA synthesis. The most notable of these is the development of high-throughput instrumentation for the rapid synthesis and, in some cases, purification of large numbers of oligonucleotides, which were not in existence during previous surveys[2–4] until after 1997.[5,6] Concomitant with the improvements in chemistry, reagents, and instrumentation, there has been a steady increase in the number of commercial sources for synthetic DNA. These developments prompted the Nucleic Acids Research Group (NARG) of the Association of Biomolecular Research Facilities (ABRF) to survey the membership to assess the current state of DNA synthesis in the core setting with the aim of assessing the future of oligonucleotide production in academic, pharmaceutical, and commercial settings. To this end, the NARG developed an anonymous, web-based survey that was divided into five sections: general facility background information, oligonucleotide production profile, oligonucleotide charges, synthesis

protocols, and trends in DNA synthesis facilities. The ABRF membership and subscribers to its electronic discussion group were asked to participate in the survey, when appropriate. Information about the survey and how to access the web forms was posted on the ABRF electronic discussion group in January 1999, and reminders were posted at intervals until early March 1999, when the survey was closed. In this report, the results of the survey are presented, and an outlook for the future for DNA synthesis is projected.

METHODS

Survey topics and specific questions were determined by consensus of NARG members. Claris Homepage 3.0 (Filemaker, Inc., Santa Clara, CA, USA) was used to develop the web format for presentation of the survey in Internet browsers. The survey was hosted on a server with Webstar 2.0 (StarNine Technologies, Inc.), and the submitted data were processed by Netforms 2.5 (Maxum Development Corp.). Participants were identified with a four-digit code to maintain anonymity.

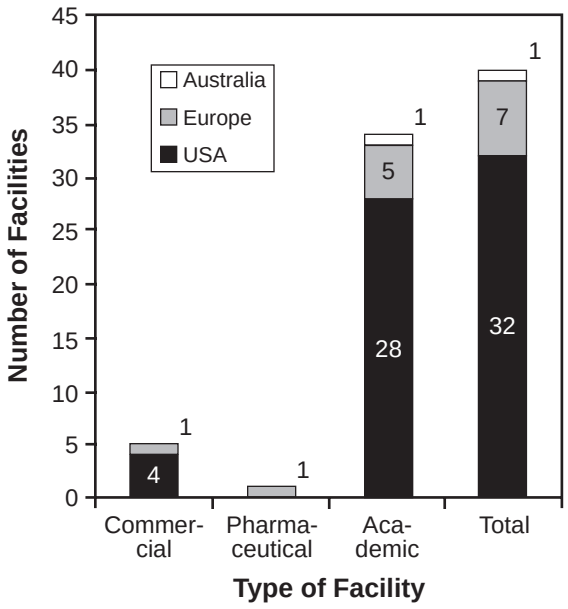

FIGURE 1

Types and locations of DNA synthesis facilities participating in the survey.

RESULTS

General Facility Background Information

During the period of the survey, 40 responses were received, which included participants from the academic (35), pharmaceutical (1), and commercial (4) sectors located in the United States, Europe, and Australia (Fig. 1). One government facility participated in the survey but was classified as academic in this survey. Most of these facilities were established between 1984 and 1991 (Fig. 2). A variety of DNA synthesis instrumentation was represented within core facilities, with the most common unit being the Perkin Elmer/Applied Biosystems (PE/AB) 394 DNA synthesizer in academic settings (Fig. 3). The commercial respondents commonly used the PE/AB 391 model in contrast to the prevalence of "big DNA houses" with proprietary, high-throughput instrumentation. Seventy-five percent of the participants maintained their instruments under service contracts.

Most facilities offered some form of electronic ordering such as web forms or email communication. This probably reflects a customer-service enhancement and reduction of errors during manual transcription of DNA orders. An interesting comment from a commercial vendor pointed out the critical role information technology has played in enhancing the profit stance of his enterprise. It has allowed the concern to concentrate more on enhancing technology and less on sorting through paper trails. Another enhancement is providing services besides DNA synthesis (89% of the facilities), such as DNA sequencing. Some facilities also offered peptide or protein services, indicating that DNA synthesis facilities were nested within other service facilities in their respective institutions. Seventy-five percent of the respondents provide synthetic DNA for users outside of their institutions. Of these, 96% provided DNA products to other academic institutions, 41% to clients in the pharmaceutical industry, and 30% to commercial DNA synthesis companies.

The survey included questions about the staffing profile of facilities, and the responses are summarized in Table 1. A relatively low number of staff members operates the facilities compared with the throughput of oligonucleotides experienced in most settings. The average length of tenure for staff in DNA synthesis facilities is 5.9 years, in contrast to the common belief that facilities experience high turnover rates. The facility staff typically is highly qualified, with significant relevant experience.

Oligonucleotide Production Profile

When comparing academic and commercial facilities with respect to the yearly average number of oligonucleotides prepared, it is not surprising that commercial

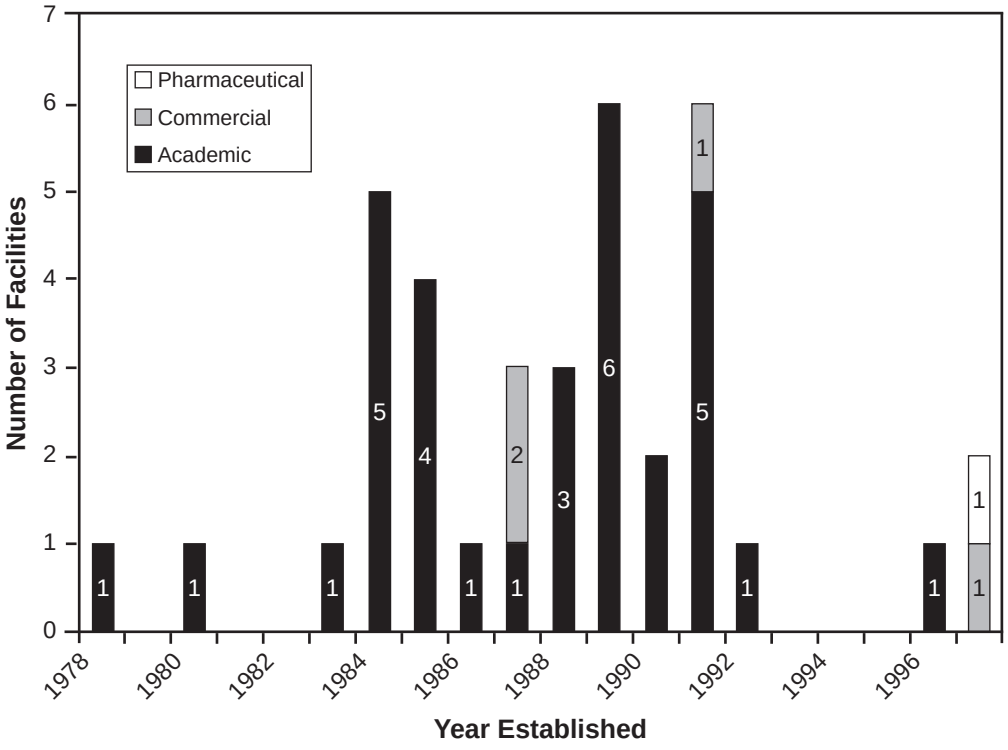

FIGURE 2

Dates of establishment of participating DNA synthesis facilities.

facilities prepare approximately 16-fold more oligonucleotides per year than their academic counterparts (Table 2). In both cases, there is a rather wide range in the number of oligonucleotides synthesized per facility: 250 to 28,000 for academic facilities and 3,000 to 150,000 for commercial facilities. Most facilities have experienced an increase in demand for standard oligonucleotides and modified oligonucleotides (eg, biotinylated, phosphothioates). Five academic and one commercial facility indicated that they outsource a portion of their syntheses.

Oligonucleotide Charges

Thirty-three participants responded to questions regarding their charges for standard 40-nmol and 200-nmol syntheses along with the charge for the same syntheses with an oligonucleotide purification cartridge (OPC) or gel purification. As listed in Table 3, the average cost for a 25-mer at the 40-nmol scale was $23.56 in academic facilities and $21.00 in commercial facilities. The same synthesis at the 200-nmol scale was $37.82 in academic facilities and $31.00 in

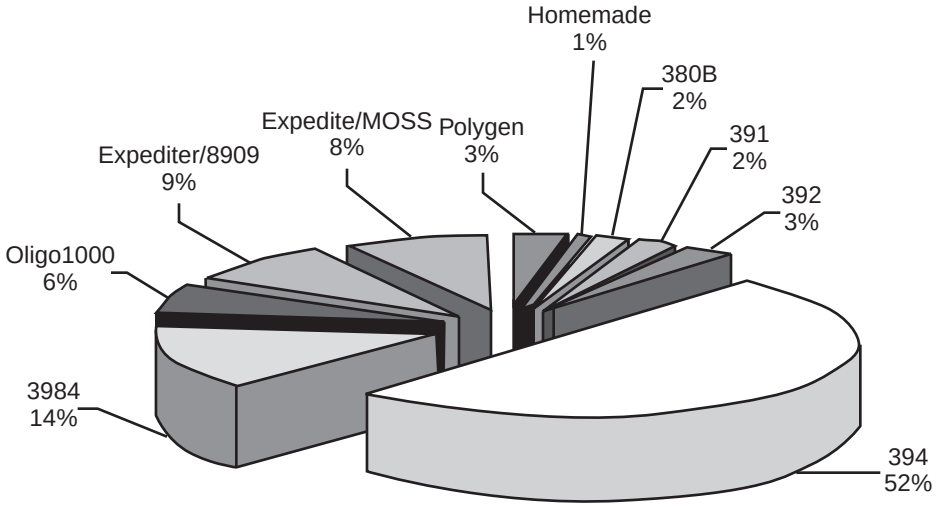

FIGURE 3

Instruments in use in academic facilities.

TABLE 1

Staffing Profile of Academic DNA Synthesis Facilities

Average number of full-time staff	1.4
Average number of part-time staff	0.5
Experience of managers	9.6 years
Experience of technical staff	4.6 years
Facility staffing changes over past 2 years	11% reporting increase 8% reporting decrease 81% no change
Average length of stay in facility position	5.9 years
Percent staff who are ABRF members	50%

commercial facilities. The range in charges for the syntheses was significantly greater for academic facilities compared with that for commercial facilities. This charge differential probably reflects the various levels of subsidy academic facilities receive, which varies from 4% to 100%. As expected, purification of the oligonucleotide by OPC or gel electrophoresis significantly increased the price of the product, particularly those produced in the academic facilities.

Seventeen of the 28 responding facilities reported that they received a subsidy from their home institution or other sources. Nearly all of the nonsubsidized facilities reported that they perform some form of quality control on their DNA synthesis products, whereas subsidized facilities reported an overall lower frequency of quality control for their products. Regardless of the frequency or type of quality control performed commonly by yield analysis or trityl monitoring, the consensus is that most facilities are consistently producing research-quality products, because only 1% to 2% of the oligonucleotides are deemed unacceptable by end users. Subsidized facilities have larger throughput and charged less for their products than the nonsubsidized facilities. For example, the average charge for a 25-mer synthesized at the 40-nmol scale and the 200-nmol scale was $20.00 and $29.89, respectively, for subsidized facilities, compared with $26.30 and $40.55 for nonsubsidized facilities.

Participants were asked about charges for modified oligonucleotides. Shown in Table III are the average costs for 5' phosphorylated, biotinylated, and fluorescently labeled oligonucleotides. Contrary to the finding for the standard syntheses, the academic facilities provided modified oligonucleotides at significantly lower costs than the commercial vendors. Superficially, this may reflect the likelihood that commercial facilities are better suited for the high-throughput production of standard oligonucleotides and that the academic facilities can more readily handle the synthesis of modified or custom oligonucleotides.

Synthesis Protocols

Most facilities offered the three standard synthesis scales: 40 nmol, 200 nmol, and 1.0 μmol. That the 40-nmol scale was by far the most common probably

TABLE 2

Response to Questions Regarding DNA Synthesis

Question	Academic Facilities	Commercial Facilities
Average yearly oligo production	4,940 (n = 35) Range, 250–28,000	77,667 (n = 3) Range, 3,000–150,00
Typical synthesis scale	40 nmol	40 nmol
Average percent of facilities reporting an increase in demand	37% (n = 26)	42% (n = 3)
Average percent of facilities reporting a decrease in demand	28% (n = 2)	
Yearly average number of oligos that are purified	44 (n = 33) Range, 5–100	67 (n = 3) Range, 50–80
Trends in nonstandard oligo production	63% report increase 11% report decrease 26% no change	100% report increase
Facilities reporting that they outsource oligos	5	1
Range of number of oligos outsourced	1–300	

TABLE 3

Charge Comparisons from Academic and Commercial Facilities.

Product	Academic Facilities			Commercial Facilities		
	Average Charge ($)	Range ($)	n	Average Charge ($)	Range ($)	n
Standard Oligonucleotides (25-mer)						
40 nmol, crude prep	23.56	13.00–36.00	23	21.00	17.00–25.00	2
40 nmol, OPC purified	29.77	12.50–53.75	18	31.00	25.00–37.00	2
40 nmol, gel purified	50.50	30.00–93.75	4	43.00		1
200 nmol, crude prep	37.82	25.00–70.00	27	30.50	26.00–35.00	2
200 nmol, OPC purified	47.99	25.00–72.50	16	35.00	30.00–40.00	2
200 nmol, gel purified	84.62	50.00–112.50	6	48.00		1
Modified Oligonucleotides (25-mer)						
40 nmol, crude prep, 5' phosphorylated	43.63	21.25–74.75	19	63.50	47.00–80.00	2
200 nmol, crude prep, 5' phosphorylated	64.66	35.00–137.50	24	72.33	50.00–90.00	3
40 nmol, crude prep, biotinylated	73.70	30.00–174.75	18	103.75	82.50–125.00	2
200 nmol, crude prep, biotinylated	93.74	42.50–239.75	22	115.00	95.00–130.00	3
40 nmol, crude prep, fluorescent dye conjugation	86.42	35.00–174.75	17	146.67	70.00–280.00	3
200 nmol, crude prep, fluorescent dye conjugation	113.29	45.00–282.50	21	170.00	75.00–300.00	3

reflects the needs of most investigators for only very small amounts of product. A few facilities offered any custom scale, as large as 300 μg for specialized applications such as crystallography. Purification options varied among the facilities; however, the most common methods were OPC, ion-exchange or reversed-phase high-performance liquid chromatography (HPLC), and gel electrophoresis. Only protocols recommended by the instrument manufacturers are used.

The average turnaround time for standard oligonucleotides is 1.8 days for academic facilities and 2.5 days for commercial facilities. For consumables, the controlled-pore glass (CPG) columns are used predominantly, and facilities prefer to use standard phosphoramidites despite the availability of "fast amidites," which requires a significantly shorter incubation period for cleavage or deprotection. Most facilities provide a variety of modified phosphoramidites such as biotin, 5' phosphorylation, and several fluorescent labels; however, only 50% offered 5' phosphorylated oligonucleotides chemically modified for OPC purification, 46% offered synthesis of RNA products, and 6% of the facilities synthesized peptide nucleic acids, because most antisense oligonucleotides are synthesized as phosphorothioates.

TRENDS IN DNA SYNTHESIS AND PARTICIPANTS' COMMENTS

Table 4 lists the survey questions devised to map trends in DNA synthesis. Overall, the future appears encouraging for both academic and commercial DNA synthesis facilities. The addition of DNA sequencing services along with previous purchases of high-throughput DNA synthesizers has increased the demand for DNA synthesis in most academic and commercial facilities. This is reflected in the fact that nearly half of the academic facilities and most commercial facilities plan to hire more employees. Only 4 of the 32 academic respondents indicated they would be discontinuing DNA synthesis services, despite the widespread availability of low-cost oligonucleotides from commercial facilities.

Several participants from academic facilities suggested that, although their charges were sometimes greater than those of commercial facilities, they felt

TABLE 4

Trends in DNA Synthesis Facilities

Question	Combined Academic (n = 31) and Pharmaceutical (n = 1) Facilities (Total = 32)	Commercial Facilities (Total = 3)
Will your facility discontinue DNA synthesis within the next year?	Yes (4/32 responses)	No (3/3 responses)
Will your facility be hiring more employees within the next year?	Yes (13/32 responses)	Yes (2/3 responses)
Will your facility purchase a multiple synthesizer within the next year?	Yes (8/32 responses)	Yes (2/3 responses)
Has the previous purchase of a multiple synthesizer increased volume?	Yes (16/17 responses)	Yes (3/3 responses)
If you have added DNA sequencing as a service, did that increase your DNA synthesis volume?	Yes (14/17 responses)	Yes (3/3 responses)
Has your facility reduced prices to match competitors?	Yes (19/32 responses)	Yes (3/3 responses)
Has your facility expanded services beyond DNA synthesis?	Yes (21/32 responses)	Yes (3/3 responses)
Is facility staff cross-trained in other technologies?	Yes (22/32 responses)	Yes (2/3 responses)
Do you have plans to merge small facilities into larger, regional facilities?	Yes (7/32 responses)	Yes (2/3 responses)

that they were offering important value-added services to the institution. For example, many academic facilities provide direct, face-to-face technical consultation for oligonucleotide design and selection and maintain a responsive attitude when dealing with investigators who have difficulties with oligonucleotide products. In doing so, the facility's overall importance to the investigators and the institution is enhanced.

CONCLUSIONS

The state of DNA synthesis in academic and commercial settings appears to be stable, with both sectors having found appropriate market niches. In general, commercial facilities have played an important role in decreasing the prices for oligonucleotides, especially standard oligonucleotide products, throughout the market. There appears to be a trend for academic facilities to focus on nonstandard oligonucleotides and value-added services, which will continue to strengthen their roles in the general research enterprise of their institution. From a technical viewpoint, new chemistries will continue to be developed for use in high-throughput instruments with faster synthesis times. Access to this technology will be critical if academic facilities are to remain competitive with the commercial sector. Meanwhile, it is safe to state that commercial facilities will continue to devise effective measures to increase throughput while lowering costs. Although there is overlap in the services provided by academic and commercial facilities, there may be a place in the research world for both types of facilities, particularly if they concentrate on their individual strengths.

The demand for synthetic DNA is likely to remain strong for the foreseeable future. Although some may consider oligonucleotides a mere commodity, trivial to prepare and use, the variety of options for synthetic DNA products strengthens the field by requiring specialized knowledge, and core facilities therefore can ensure that the research community will have access to the best tools for their studies. Because of continuing changes in the field of DNA synthesis, academic and commercial facilities must maintain a flexible posture if they wish to successfully meet the current and future needs of clientele.

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