



The Scientist 16[12]:43, Jun. 10, 2002

[Previous](#) [Issue Content](#) [Next](#)

PROFILE



**E-mail
article**

The Core of DNA Synthesis

As the prices of commercial oligonucleotides plummet, academic core facilities struggle to justify offering competing services

By Sarah Goforth

Editor's note: This is the second of a three-part series on tools for core facilities. The last installment in the series, on peptide synthesizers, will appear in the Sept. 16 issue.

As the biotech revolution has exploded, so too has the market for oligonucleotides. And as the number of labs in need of these tools has grown, so has the science of their synthesis. In response, oligonucleotides, which are short, synthetic RNA or DNA sequences, have gone from luxury item status to that of a standard reagent. Now researchers use oligonucleotides for PCR, RNA interference, DNA sequencing and mutagenesis, and

myriad other applications. Though a number of sophisticated instruments exist to perform oligonucleotide synthesis chemistry, researchers in need of oligonucleotides don't have to make them themselves; most universities have core facilities dedicated to DNA synthesis.

Marlene Viola

But some core facilities are now questioning whether offering DNA synthesis services still makes good economic sense. These facilities must compete with large, custom DNA-synthesis facilities, which can generally produce oligos less expensively. Maintenance costs for core facilities are high, and without a client volume large enough to justify the expense, some universities have opted to shut down these particular services. Yet core facility operators contend they have a role to play in the biotech market, saying that their higher prices are offset by better service and quality control.

The Synthesis of an Idea

In 1968, scientists at the University of Wisconsin, Madison, created the first chemically synthesized polynucleotide, a transfer RNA for alanine. At that time, there were no known uses for the technique, but by the 1980s, researchers found applications aplenty in the emerging field of molecular biology.

Today's DNA synthesizers are essentially sophisticated fluid-handling devices that make a complicated chemical process as simple as entering the desired sequence into a central workstation. Since 1984, researchers have used solid-phase synthesis to manufacture oligonucleotides, a technique similar to the one they use to create polypeptides. This method begins with a primary residue (the 3'-most nucleotide) anchored to a solid support. Each additional nucleotide is then added in the desired order to assemble the nucleotide chain, but unlike enzymatic methods, chemical DNA synthesis proceeds in the 3'-to-5' direction. (reviewed in ref. 1)

The first oligonucleotide devices were high-throughput and very expensive. Research facilities and individual laboratories specializing in the development of recombinant techniques were eager to purchase these synthesizers, which could originally manufacture up to 15 micromoles of four individually programmed DNA or RNA sequences. By the early 1990s, many companies offered smaller, user-friendly DNA synthesizers for individual laboratories.²

But that market dried up quickly. More than two-thirds of life science researchers were using synthetic

oligonucleotides by 1995, but instead of buying synthesizers, they purchased them from outside sources. Synthesizer sales to individual labs slipped, while the market for phosphoramidites and custom oligonucleotides boomed.

The Core Dilemma

Today, the chemistry and instrumentation of DNA synthesis are so extensively optimized, and the synthesis of short probes and primers is so routine, almost any lab member can use these systems. Yet many researchers cannot afford a DNA synthesizer or its maintenance. In the mid-1980s, institutions with several such labs recognized the potential money and timesaving value of creating central facilities through which individual labs could purchase oligonucleotides without having to go to a third-party source.

Most core facility operators agree that the best source of oligonucleotides for a given researcher will depend on his or her particular needs. **Mark Lively**, professor of biochemistry at Wake Forest University School of Medicine and president of the Association of Biomolecular Resource Facilities (ABRF), concedes there are both advantages and disadvantages to using a core facility to obtain custom oligonucleotides, but one significant advantage is that "as a core facility, we're not here to make money; we're here to service clients."

A recent survey released by the ABRF Nucleic Acids Research Group found that, on average, academic facilities annually produce about one-sixteenth the number of oligonucleotides produced by commercial facilities.⁴ According to the report, charges for standard oligonucleotides from academic facilities are somewhat higher than from commercial sources, whereas the opposite is true for modified phosphoramidites, for which the core facilities have a slight cost advantage.

The oligonucleotide has become "an item of commerce," says Lively, and custom DNA houses can undercut the price of any core facility in the manufacturing of what he calls plain vanilla, or unmodified, oligonucleotides. But core facilities may still provide a cost advantage when producing oligonucleotides with special chemistries or modifications, the so-called boutique oligonucleotides.

More Than Money

Courtesy of Amersham Biosciences



Amersham Biosciences' OligoProcess DNA synthesizer

Cost is only one factor worth considering in choosing a source for oligonucleotides. Academic facilities are more likely to provide face-to-face consultations, electronic ordering, and better quality control, says **Anthony T. Yeung**, chair of the ABRF Nucleic Acids Research Group and director of the Fannie E. Rippel Biochemistry and Biotechnology Facility at the Fox Chase Cancer Center in Philadelphia. "It's just as important to consider reliability," he says. The custom synthesis companies with the greatest demand on performance may not be as reliable as a core facility that tests each custom oligonucleotide for purity. "If there is a 5% failure rate, then 95% of the customers are satisfied and the other 5% can be redone," Yeung says. "On the other hand, if you're in that 5%, and you can't always be guaranteed that an entire experiment will run effectively, it can be very expensive in the long run." Here, Yeung says, is where core facilities have the advantage, as they often provide a number of purity and quality checks on every synthetic oligonucleotide, whereas commercial

suppliers often rely on batch quality control.

In addition, the reliability of specially modified oligonucleotides is much improved in the hands of highly trained specialists, says Yeung, which will be more common in core laboratories than at oligo synthesis companies. "We have people on the cutting edge and everything well-tested," Yeung says of his core facility, noting that a 24-hour turnaround is commonplace in academic institutions but rare among the commercial suppliers. "DNA synthesis is not rocket science," Yeung explains, "but it requires high maintenance and constant attention."

The Struggle to Survive

With the proliferation of custom oligonucleotide suppliers,^{5,6} core facilities must continually justify their oligonucleotide synthesis services. Developments in automation, reagent chemistry, and information technology have allowed custom houses to flourish. Even the most heavily subsidized core labs are left wondering whether they still have a place in the oligonucleotide market.

In light of recent advances in oligonucleotide production chemistry and information technology, **Roger Bumgarner**, research professor of microbiology at the University of Washington, says that many core lab facilities may no longer choose to offer oligonucleotide synthesis. "Oligo synthesis has turned commercial," Bumgarner says. Synthesizers function properly only when used regularly, so if an institution's demand for custom oligonucleotides is fairly low, the cost to maintain the instruments and purchase reagents may outweigh the advantage of staying local. Bumgarner sold his core facility's last remaining synthesizer six years ago. This center now focuses solely on services such as DNA arrays that are more difficult or more expensive for researchers to find commercially.

In 1999, **Lawrence Washington**, director of the core facility at Indiana University's Molecular Biology Institute, found himself in a similar situation. His institute purchased its first oligonucleotide synthesizer in 1984. "It was the guts of the core lab for many years," he says, "used by 40 different labs with the early molecular engineers." The core facility stepped in where the commercial houses fell behind—mostly in the fast, efficient synthesis of primers for PCR experiments. "In the first few years, it was cheaper, quicker, and more reliable to do it yourself. The commercial suppliers didn't do a very good job and were more expensive," Washington says. But when the commercial entities caught up, the lab was left far behind.

Jeffrey Engler, professor of biochemistry and molecular genetics at the University of Alabama, Birmingham, agrees that it has become more difficult for a core lab to justify maintaining its own synthesis equipment. His institution has run a core facility since 1984, and has steadily upgraded its synthesis equipment. The biggest advantage to seeking oligonucleotides from a core lab, Engler says, is quality control. "We focus on a fast turnaround and high throughput, and we've tried to keep abreast of the latest state of the art with ABRF."

In the face of shifting economic pressures, Yeung remains optimistic. "We're trying to shift the core facilities paradigm," he says, to make facilities proactive members of the research community. He adds that the success of core facilities will hinge on their ability to provide a team-based approach to a variety of molecular biology services, oligonucleotide synthesis among them. Though core facilities may not always have the economic advantage outright, the quality of customer service, synthesizer maintenance, and technical support offered by DNA synthesis core facilities may ultimately shift the tide in their favor.

Sarah Goforth (sarahgoforth@hotmail.com) is a freelance writer in Madison, Wis.

References

1. Chemistry of oligonucleotide synthesis explained: www.idtdna.com/program/techbulletins/chemistry_of_oligonucleotide_synthesis.asp
2. C. Gan, "Compact synthesizers let small labs make their own genes," *The Scientist*, 4[6]:30, March 19, 1990.
3. 1995/1996 MSPPSA report on synthetic oligonucleotides, available online at www.phortech.com.
4. K.M. Hager et al., "Survey of current trends in DNA synthesis core facilities," *Journal of Biomolecular Techniques*, 10:187-93, 1999.
5. J. Kling, "Oligos to go!: Purveyors of custom oligonucleotides," *The Scientist*, 12[7]:18, March 30, 1998.
6. L. DeFrancesco, "Special needs: Custom houses that provide specialized oligos," *The Scientist*, 12[9]:21, April 27, 1998.

DNA Synthesizers IN FOCUS | Sarah Goforth

Courtesy of Bioautomation



Bioautomation's MerMade IV DNA synthesizer

Last year, the US DNA synthesis instrumentation market was \$31.2 million (US), according to **Brad Peters**, a senior industry analyst at San Antonio, Texas-based **Frost & Sullivan**. The two biggest players in the market are Foster City, Calif.-based **Applied Biosystems** (50%) and Piscataway, NJ-based **Amersham Biosciences** (40%). Other manufacturers include San Carlos, Calif.-based **Gene Machines**, and Plano, Texas-based **Bioautomation**.

Using flow-through reactor technology, Amersham's pump-driven ÄKTA oligopilot™ scales up synthesis capacity from 1 μ mol to 4 mmol. This technology also reduces the amount of amidite and reagent for additional savings. Amersham reports a synthesis capacity of 1.5 molar equivalents at a coupling efficiency greater than 98%. The cycle time for a 3-mmol synthesis of a 25-mer is about 30 minutes. Amersham's Unicorn software allows for online monitoring, sequence editing, simultaneous local control of as many as four separate synthesis systems, and easy scale-up from lab to production levels. For labs with more customized large-scale needs, Amersham also offers the OligoProcess™, a custom-designed

system that allows operation scales of at least 10-1,000 mmol.

Applied Biosystems' ABI 3900 is designed and marketed for production-level environments, where the need for throughput and flexibility is high, and bench space is limited. It is capable of synthesizing up to 288 primer-length oligonucleotides in less than 10 hours at the 40- and 200-nmol scales. Producing high-quality oligos with low reagent consumption and low operating costs, the ABI 3900 can synthesize labeled and unlabeled primers at scales of 40, 200, and 1,000 nmol. PC software with full-cycle editing and sequence-import functionality simplifies the task of controlling the instrument.

Bioautomation offers the MerMade IV DNA Synthesizer, which was developed at the University of Texas Southwestern Medical Center to support the Human Genome Project. The instrument synthesizes two standard 96-well plates of oligonucleotides in each run using phosphoramidite chemistry. The system, which has a run time of about eight hours for two plates of 20-mers, is designed to operate with a reaction scale of 5-100 nmol. The MerMade is most suitable for use in microarray experiments, PCR reactions, and hybridization experiments. Bioautomation reports a 99% coupling efficiency.

GeneMachines also offers a 96-channel oligonucleotide synthesizer. Its PolyPlex® synthesizer can generate a 96-well plate of 20-mer oligonucleotides in less than three hours, with low reagent consumption. And, because of its refined synthesis steps, the PolyPlex can operate at a cost of less than \$0.10 per base.

The Scientist 16[12]:43, Jun. 10, 2002

[Previous](#) | [Issue Content](#) | [Next](#)

© Copyright 2002, *The Scientist*, Inc. All rights reserved.

We welcome your opinion. If you would like to comment on this article, please write us at editorial@the-scientist.com

[News](#) | [Opinions & Letters](#) | [Research](#) | [Hot Papers](#)
[LabConsumer](#) | [Profession](#) | [About The Scientist](#) | [Jobs](#)
[Classified](#) | [Web Registration](#) | [Print Subscriptions](#) | [Advertiser Information](#)