JDS Uniphase (formerly Uniphase Corporation)

The BioLaser: A Compact Blue Laser for DNA Diagnostics

In 1994, scientists and researchers were attempting to capitalize on the building successes of the "genetic revolution" and move DNA analysis instruments into more laboratories in the United States and around the globe. At the time, U.S.-based companies, such as Perkin-Elmer's Applied Biosystems Division, already had DNA analysis instruments on the market. However, these instruments were expensive and required large power supplies and significant levels of maintenance by factory-trained technicians. The price, life-cycle costs, and infrastructure requirements kept DNA analysis out-of-reach for many laboratories in the United States and for many more laboratories worldwide.

Uniphase Corporation and Perkin-Elmer responded to the Advanced Technology Program's (ATP) 1994 focused competition, "Tools for DNA Analysis," with a joint venture proposal to focus industry attention and resources on a problem with existing DNA analysis tools: the size and power requirements of internal lasers. Lasers were typical components of the automated DNA analysis machines. They were used to signal computers that a particular DNA sequence of interest was present in a sample. Uniphase and Perkin-Elmer proposed a research program that would result in the BioLaser, a solid-state, blue-light laser hoped to be half the cost, 10 times smaller, and 250 times more efficient than existing lasers used in DNA analysis machinery.

At the close of the ATP-funded research project in late 1997, technical barriers prevented Uniphase and Perkin-Elmer from developing the BioLaser at a cost that was commercially viable. However, two ancillary products were created, one for the bioscience industry and one for the digital photo-finishing industry.

COMPOSITE PERFORMANCE SCORE
(based on a four star rating)
* *

Research and data for Status Report 94-05-0004 were collected during September - October 2003.

Lasers for DNA Detection Require Improvements

Machines used in 1994 for automated DNA analysis, such as Perkin-Elmer/Applied Biosystems Division's Model 373, were large and expensive. They also consumed substantial electrical power and required costly maintenance, which raised the total life-cycle costs well above the machine's initial $100,000 price. Moreover, the laser used to identify target DNA sequences did not work with the existing DNA analysis machines. The argon-based lasers were expensive; they constituted one of the most costly components of the entire DNA analysis system. Also, the large size of both the laser head (the portion of the laser that creates the light needed for the machine to function) and the power supply was a problem. These argon-based lasers also wore out quickly, requiring additional expenses for field visits by a trained service representative to replace the laser.

Uniphase and Perkin-Elmer Propose to Address the Laser Problem

Uniphase Corporation and the Applied Biosystems Division of the Perkin-Elmer Corporation jointly proposed to develop the BioLaser, a compact, inexpensive source of blue laser light for instruments intended for DNA analysis. The BioLaser would address industry concerns about DNA analysis machine power, size, initial price, and life-cycle costs.

In 1994, laser-based DNA analysis instruments relied on fluorescent dyes that linked to specific genetic regions of interest for analysis. Lasers were used to excite the dyes so that a computer-linked optical device could identify the dyes and analyze the genetic regions that were bound to the dyes.

The lasers used in 1994 were argon-based, blue-light lasers. The argon gas made the lasers bulky, expensive, and relatively inefficient compared with the envisioned laser that could move DNA-based analysis toward commercial acceptance. The physical limitations of the argon-based lasers also presented substantial roadblocks to developing diagnostic instruments with the low cost, small size, and convenience required for rapid, widespread domestic and international adoption. Uniphase's proposed solid-state laser (as opposed to the argon-based lasers), which would be manufactured using novel methods adapted from other industries, could be smaller, more efficient, longer lived, and half the cost of argon-based lasers.

Technical Barriers to BioLaser Development

Uniphase's proposed solid-state laser would work by directing infrared laser light originating in a semiconductor diode laser through a waveguide (material that amplifies and alters the laser light to a useful frequency) made of nonlinear optical materials (materials used to significantly increase the frequency of the laser light). These optical materials would double the diode's original light to a specific frequency for blue light. Reliably doubling this particular light frequency with a waveguide represented the most significant technical challenge that Uniphase and Perkin-Elmer sought to overcome. Other technical challenges identified by the companies included the following:

- Reliably fabricating the waveguides
- Maintaining the laser light within a narrow frequency band at high power
- Coupling the infrared light to the waveguide material with minimal loss of intensity and power

Project Success Would Benefit the U.S. Economy

In 1994, a typical instrument for the acquisition of genetic information was the Perkin-Elmer/Applied Biosystems Model 373 genetic detection and analysis system. The Model 373 used an expensive argon laser-based fluorescence detection system. Uniphase and Perkin-Elmer proposed to greatly reduce the cost and to increase the efficiency of the laser excitation and detection systems. They envisioned that their successful BioLaser would be half as expensive, 10 times smaller, 250 times more efficient, and 5 times longer lived than lasers used in existing instruments.

The laser used to identify target DNA sequences did not work with the existing DNA analysis machines.

If Uniphase and Perkin-Elmer had succeeded in creating their proposed BioLaser, industry experts projected that the market for automated DNA research projects could have grown as more laboratories in the United States and overseas could have purchased the lower cost, easier-to-maintain machines.

ATP Funding Essential to Gaining Industry Attention

ATP's 1994 "Tools for DNA Analysis" focused competition invited applications for ATP funding from industry participants with proposals to address roadblocks in the DNA analysis industry. Uniphase and Perkin-Elmer responded to that competition.

Their successful BioLaser would be half as expensive, 10 times smaller, 250 times more efficient, and 5 times longer lived.

A partnership of industry powerhouses like these two companies was not common in 1994. The DNA analysis industry was not yet mature, and trade associations and other sources of funding for pre-competitive research did not have enough capital to galvanize the industry to solve specific technical problems. ATP funding facilitated parallel research at multiple companies by numerous scientists and helped DNA analysis research. ATP awarded Uniphase and Perkin-Elmer $1.36 million to conduct initial research into the BioLaser.

Research Team Well Equipped to Tackle Technical Challenges

Affymetrix and Molecular Dynamics joined Uniphase and Perkin-Elmer as informal collaborators on the project. The Uniphase and Perkin-Elmer team also brought in New Focus, Inc. as a subcontractor who would develop specialty antireflection coatings for the photonic (light-directing) components of the BioLaser.

The team assembled by Uniphase and Perkin-Elmer had substantial experience in lasers and bioscience. The team aggregated this expertise and focused on solving the technical challenges posed by solid-state, blue-light lasers in DNA analysis applications. Highlights of the companies' expertise include the following:

Uniphase. This San Jose, California public company had significant experience with optical technologies. Uniphase also maintained a growing position in the marketplace for optical technologies for biomedical applications. Through a series of mergers and acquisitions, Uniphase later became JDS Uniphase.

Applied Biosystems Division of Perkin-Elmer. This division of the Wellesley, Massachusetts public company was focused on the following markets: basic research; commercial research (pharmaceutical and biotechnology); and standardized testing, including forensic human identification, HIV genotyping, and food testing. This division spun off into a separate California-based public company and was later acquired by the Connecticut-based Applera Corporation.

Affymetrix. This Santa Clara, California public company offers an expanding portfolio of integrated products and services, including its integrated GeneChip platform, to address growing markets focused on understanding the relationship between genes and human health. The company's customers include pharmaceutical, biotechnology, agrichemical, diagnostics, and consumer products companies, as well as academic, government, and other nonprofit research institutes. Affymetrix completed an initial public offering in 1996 during this ATP-funded project.

Molecular Dynamics. Molecular Dynamics, a private company based in Cambridge, Massachusetts, focused on genetic sequencing and discovery. The company's flagship products were a series of DNA microarrays that consisted of thousands of DNA samples deposited in small spots on the surface of a slide. Molecular Dynamics worked with Uniphase and Perkin-Elmer to improve the method of analyzing these DNA microarrays using solid-state, blue-light lasers. The company was acquired in 1998 by what later became Amersham Biosciences.

New Focus, Inc. New Focus is a Sunnyvale, California private company that is a leading supplier of photonics research tools. Their product lines include tunable lasers, high-performance photodetectors and receivers, laser modulators, mechanical positioners, and optical components. The proposed blue laser for biotechnology applications required state-of-the-art antireflective coatings for the laser diode, waveguide frequency doubler, and fiber to eliminate distortion. Because New Focus maintained a fully equipped optical coating facility within a short drive from Uniphase, New Focus was hired as a subcontractor to handle all antireflective coating work for the project. New Focus completed an initial public offering in 2000.

Technical Barriers Remain, Yet Products Resulted

All members of the joint venture worked diligently during the three-year project to find a way to manage blue-light, solid-state lasers. The team constructed a prototype laser in the laboratory for testing and further development. During the project, however, technical barriers proved insurmountable, and innovations in DNA analysis methodologies made the BioLaser concept obsolete for DNA analysis applications.

Technical barriers proved insurmountable, and innovations in DNA analysis methodologies made the BioLaser concept obsolete.

The most significant technical barrier Uniphase and Perkin-Elmer faced was in developing new fluorophore labels for light generated by anything other than argon ions in the traditional gas-based laser. (Fluorophore labels create fluorescent light when excited by a laser to signal a DNA match that can then be read by a computer.) Because the fluorophore labels bind directly to the DNA that the diagnostic machine is analyzing, the labels must be compatible with the enzymes used to cut the DNA; must be chemically stable so as not to interfere with the method used to separate the DNA; and must be able to absorb large amounts of laser-generated light before fluorescing.

Before the end of the ATP-funded project, the joint venture participants were able to generate fluorophore labels for blue-light, solid-state lasers. The labels and laser modifications, however, were still expensive. The expected overall cost reduction from the prototype BioLaser generated during the course of the ATP-funded project would have been only 9 percent; a 50-percent reduction was required for commercial acceptance.

After the close of the project, Uniphase continued research into diode-based, red-light lasers as a possible solution for a DNA analysis machine. However, in the late 1990s, shortly after the end of the project, a new method of DNA separation and analysis was introduced, which eliminated the need for relatively high-powered lasers such as the blue and red lasers that Uniphase and Perkin-Elmer sought to create. The new method, polymerase chain reaction (PCR), also used laser-induced fluorescence. With PCR, the fluorescence would occur on DNA probes. Higher powered lasers, however, would destroy the reactions on the DNA probes and ruin the PCR output.

Unrelated to the automated DNA analysis marketplace, Uniphase created two new products flowing from innovations discovered during the ATP-funded project. The first, a Blue Laser Module, was a stripped-down, inexpensive blue laser for tabletop applications within the biotechnology industry. The product represented an adaptation of an existing technique to meet cost pressures. It entered the marketplace in 1999 and sales ranged between $50,000 and $500,000 annually from 1999 to 2002. The second product was a specialized, low-noise blue laser for digital photo-finishing. This new product enhanced digital photo-finishing capabilities above and beyond other commercially available techniques. Uniphase introduced the product in 2000 and earned between $250,000 and $1 million annually from 2000 to 2002. The product made photo-finishing easier and cheaper than was previously possible.

Conclusion

In 1994, a joint venture led by Uniphase and Perkin-Elmer's Applied Biosystems Division sought to reduce the size, cost, and power requirements for the lasers used in DNA analysis. One goal of this ATP-funded project was to make DNA analysis machines accessible to more laboratories in the United States and abroad. The joint venture partners worked diligently for three years, but the expected cost savings on lasers for DNA analysis were not realized. However, the technical developments led JDS Uniphase to unanticipated new products, as well as a patent application, and led Perkin-Elmer to publish an article about the technology.

PROJECT HIGHLIGHTS
JDS Uniphase (formerly Uniphase Corporation)

Project Title: The BioLaser: A Compact Blue Laser for DNA Diagnostics

Project: To develop a compact, efficient, and cheaper source of blue light for fluorescence-based diagnostic instruments and techniques for physicians and biomedical researchers.

Duration: 1/1/1995-12/31/1997
ATP Number: 94-05-0004

Funding (in thousands):

ATP Final Cost	$1,361	50%
Participant Final Cost	1,369	50%
Total	$2,729	

Accomplishments: Although the Uniphase/Perkin-Elmer team achieved partial technical success, they did not succeed in reducing the cost of lasers for DNA analysis applications enough to earn commercial acceptance. The companies did not pursue their research after the close of the ATP-funded project because a new DNA identification technology entered the field, the polymerase chain reaction. However, the following ancillary new products or product improvements resulted from the ATP-funded project:

- The Blue Laser Module, an inexpensive blue-light laser for tabletop applications in the bioscience industry (a new product for Uniphase)
- The MicroBlue SLM, a specialized laser for the digital photo-finishing marketplace (a new product for Uniphase)

The ATP-funded project also resulted in one patent application by Uniphase, as well as the following publication by Perkin-Elmer:

- O'Neill, Michael D. "Sequencers Benefit from Solid State Detectors." Laser Focus World, October 1995: p. 135.

Commercialization Status: The commercialization status is positive for the two ancillary products developed by JDS Uniphase. The Blue Laser Module reached the market in 1999 and has achieved sales as high as $500,000 per year. The MicroBlue SLM was first marketed in 2000 and generated $1 million in annual sales.

Outlook: The outlook for the two ancillary products flowing from the ATP-funded research is good. However, the outlook is poor for the blue-light, solid-state BioLaser that was the initial focus of the project.

Composite Performance Score: * *

Focused Program: Tools for DNA Analysis, 1994

Company:
JDS Uniphase Corporation
1768 Automation Parkway
San Jose, CA 95131

Contact: Dr. Kevin Kalkhoven
Phone: (408) 434-1800

Applied Biosystems Division (formerly a division of Perkin-Elmer)
850 Lincoln Centre Drive
Foster City, CA 94404

Subcontractors:

- Affymetrix
  Santa Clara, CA
- Molecular Dynamics
  Cambridge, MA
- New Focus, Inc.
  Sunnyvale, CA

Research and data for Status Report 94-05-0004 were collected during September-October 2003.