Affymetrix–GE Healthcare (formerly Molecular Dynamics)

Helping to Decode the Genome

DNA sequencing on a large scale began in the 1980s, and by the 1990s researchers were uncovering significant links between genes and disease. To advance knowledge of the body's genetic makeup, the National Institutes of Health and the Department of Energy launched the Human Genome Project (HGP) in 1990 to map the human genome, thought to consist of up to 100,000 genes and 3 billion base pairs. As researchers delved into gene structure, they found that their diagnostic tools were too cumbersome to enable the breakthrough discoveries expected.

To develop better tools, the Advanced Technology Program (ATP) established the "Tools for DNA Diagnostics" focused program in 1994. Among the first successful applicants were Affymetrix and Molecular Dynamics, in a joint venture to develop a miniaturized integrated nucleotide diagnostic device. This would be a handheld device built on microchip technology that extracts DNA from a blood sample and amplifies and analyzes it. Affymetrix had developed the industry's first microarray, based on GeneChip[1] technology, by adapting miniaturization and production techniques from the computer chip industry to enable chemical analysis of clinical samples. Molecular Dynamics, an engineering company, would build instrumentation surrounding Affymetrix's microarray.

As the project proceeded, market research showed little support for point-of-care devices. The companies instead developed a series of tools to enable other genetic testing technologies. Affymetrix produced denser array chips, developed array technologies and instrumentation, and refined its software to handle the vast amount of data generated by the arrays. Their methodologies for gene expression are used extensively in drug discovery and diagnostics. Affymetrix remains the largest and most prominent producer in the "lab-on-a-chip" market.

Molecular Dynamics produced MegaBACE[2], the first high-throughput DNA sequencer. MegaBACE could simultaneously analyze 96 DNA fragments at very high speed, replacing the slow and error-prone slab gel method in use at the time. HGP was able to accelerate its timetable, in part because Molecular Dynamics raised the bar for sequencers' performance. Molecular Dynamics, now a component of GE Healthcare, estimates that MegaBACE 1000 mapped about 30 percent of the human genome. This project produced widespread benefits through its products and its knowledge transferred through patents, publications, and presentations.

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

Research and data for Status Report 94-05-0016 were collected during December 2005 – March 2006.

Biotech Research Needs Better Tools

Large-scale DNA sequencing began in the 1980s and quickly yielded evidence of the genetic basis of many diseases. But a decade later, the industry still lacked the tools to efficiently sequence DNA. Clinicians and researchers were limited to identifying individual genes in a slow and often discontinuous process.

[1]Gene Chip is a registered trademark of Affymetrix. Inc.
[2]MegaBACE is a registered trademark of GE Healthcare

Sample preparation and amplification were cumbersome, expensive, and inexact. In 1990, the U.S. Department of Energy and the National Institutes of Health established the U.S. Human Genome Project (HGP) to determine the sequence of human DNA, estimated to contain 100,000 genes and 3 billion base pairs. The project also expected to transfer sequencing and informatics technologies to the private sector. As HGP's work progressed, the need for new, more efficient, less expensive diagnostic procedures, instruments, and tools became ever more pressing.

Nearly 50 companies and research institutions submitted white papers to ATP on the biotechnology industry, citing diagnostic tools as a critical need. As a result, ATP established the "Tools for DNA Diagnostics" focused program. The program's aim was to hasten the development of cost-effective and efficient technologies for sequencing, storing, and interpreting DNA.

Clinicians and researchers were limited to identifying individual genes in a slow and often discontinuous process.

Scientists at Affymax, a biotechnology company, had adapted a photolithographic technique used in semiconductors to produce GeneChip arrays, the world's first microarray. This was a miniaturized chemical reaction on a glass wafer the size of a postage stamp. The wafer embedded fragments of DNA, called probes, on its surface. By introducing a prepared blood sample to the chip, researchers could analyze matches between the sample and the probes. This meant that medical researchers could, for the first time, see how cells responded to disease and to drug treatments on a large scale. The work was described in *Science* magazine and won the Intellectual Property Owners Association's Distinguished Inventor award in 1993.

That same year, Affymax formed a new company, Affymetrix, to commercialize GeneChip technology and use it to accelerate drug development, to capitalize on the demand for point-of-care tools, and to create an instrument system. As a small start-up company, Affymetrix attracted venture capital, but was devoting its research and development budget to near-term opportunities.

Affymetrix had a long-term goal of shrinking the GeneChip array and combining it with a desktop reader to form a handheld unit, called a miniaturized integrated nucleotide diagnostic (MIND) device. The company needed help with the front and back ends of the process: shrinking the sample before introducing it to the chip and generating a readout on a handheld unit. Affymetrix approached Molecular Dynamics, a small engineering company founded in 1988 to develop and produce high-resolution scanners for bioanalysis. Molecular Dynamics built Affymetrix's first scanner.

In 1994, the two companies submitted a proposal to ATP under the "Tools for DNA Diagnostics" focused program to develop MIND. In October, ATP awarded the two companies cost-shared funding. The five-year project, one of ATP's largest joint ventures, began in February 1995.

The project's primary focus was the core science and components of the MIND unit, developing systems to extract, purify, amplify, and analyze DNA samples. Ultimately, the companies wanted to find a quick, inexpensive method of analyzing DNA, which they proposed to accomplish by hybridizing probe arrays and by using a new kind of electrophoresis that would be quicker and less error-prone.

In probe arrays, a DNA molecule with a known sequence is labeled to find and mark DNA sequences with the probes on the chip. GeneChip technology would expand the capacity of DNA probe arrays so that it could contain thousands of sequences. In addition, they needed to tackle the challenge of processing samples using microfluidics (fluids at volumes thousands of times smaller than a droplet). In miniaturizing sample preparation, the sample volume can become so small that gene expression may not be readable. The project would also develop the software and hardware to do the assays and interpret the results with minimal human intervention. Most of these challenges had been addressed before, but not in the integrated fashion that the MIND unit warranted.

During the first two years of the project, Affymetrix improved its photolithographic process so that it could be scaled up to industrial production levels. As Affymetrix increased the density of its arrays, the amount of data from the chip readout increased exponentially. To cope with increased information,

Affymetrix improved the software that enabled computation and data analysis.

Figure 1.GeneChip Probe Array

In 1996, Affymetrix began limited marketing of a GeneChip system, which consisted of the chip, instruments to process the probe arrays, and software to analyze the information. The company sold nine systems to research laboratories that year and signed agreements with several companies for projects in drug discovery, linking genetic variations to disease, and disease management. These partnerships were outside the scope of the award, but they boosted the chances of rapid commercialization of the technology that ATP was funding. In addition, the agreements allowed the companies to raise capital for continuing research and development (R&D). Affymetrix also entered into an agreement with bioMérieux to use the arrays to detect microbial contamination in food and cosmetic products, a transfer of technology from biomedical research to other industries.

Molecular Dynamics' High-Throughput Sequencer Advances Race

Meanwhile, Molecular Dynamics had been working on a sequencer using capillary array electrophoresis (CAE) to achieve high throughput. The prevailing method of sequencing was slab gel electrophoresis, which could not handle large volumes because gel preparation required careful handling and was prone to errors. In CAE, gel-filled capillary tubes separate DNA fragments, and electrophoresis distinguishes individual molecules in a mixture by passing electric current through the capillary tubes; each kind of molecule travels at a different rate, depending on its electrical charge and size. Molecular Dynamics contracted with a chemistry professor at the University of California Berkeley who had developed a method for reading fluorescently labeled DNA using laser beams inside capillaries. During the ATP-funded project, Molecular Dynamics miniaturized capillaries and integrated chemical processes with electrical engineering. The capillaries' small diameter allowed higher electric fields to pass through them.

Molecular Dynamics' CAE machine, called the MegaBACE 1000, had 96 capillary tubes; a laser and scoring system read the samples. The company developed the first high-throughput sequencer for DNA, defined as those that sequence 1 million base pairs per day. The sequencer could read longer DNA fragments with greater accuracy and speed than those developed up to that time. Before MegaBACE, sequencing each DNA fragment on a gel took several days; now, 96 could be done simultaneously. In June 1997, Molecular Dynamics began testing MegaBACE at three sites. By the end of the year, they had delivered 11 systems and sold dozens more.

Figure 2. MegaBACE 1000 DNA Sequencer (Image courtesy of GE Healthcare)

Molecular Dynamics' introduction of the MegaBACE 1000 induced the company's chief competitor, Applied Biosystems Inc. (ABI), to speed up development of its CAE sequencer, which it brought to market much sooner than planned. By the end of 1997, Molecular Dynamics had sold 40 systems and was expecting other large orders. In mid-1998, Perkin-Elmer (PE) and Celera Genomics announced that they were planning to sequence the human genome in three years, in direct competition with HGP. This accelerated timetable was possible in large part because high-throughput sequencers were available. The PE-Celera team chose ABI's sequencer, but other operating arms of HGP ordered MegaBACE to keep up with the challengers' genome sequencing.

In January 1998, Affymetrix had requested that the project's strategy, timing, and scope be changed. Point-of-care devices such as the MIND device did not seem economically viable in the near term. Insurance companies would not reimburse claims for their use, and doctors were reluctant to cede the ability to make diagnoses to a machine, even an accurate and comprehensive machine. Manufacturers found they had to provide so much technical assistance to buyers that it was difficult to make a profit. Instead, Affymetrix and Molecular Dynamics found that the precursor technologies they were working on could benefit HGP and benefit from the research emanating from the project.

The project's primary focus was developing systems to extract, purify, amplify, and analyze DNA samples.

In July 1998, Affymetrix and Molecular Dynamics launched the Genetic Analysis Technology Consortium to create standards for read-out, data formats, and reagents to process arrays from multiple sources. A standardized and accessible platform would make array technology available to the community of genomics researchers and would be less expensive and duplicative than the current competing and incompatible systems.

Under a nonexclusive licensing agreement, Molecular Dynamics had rights to some of Affymetrix's array technology but was developing its own array technology for gene expression and analysis. Seeing this technology as direct competition for GeneChip technology, the companies scaled back their collaboration to prevent the disclosure of competitive information. Instead of meeting quarterly, they reduced their meetings to twice a year and limited the exchange of information to ATP's minimum reporting requirements, even as they continued to work on their parts of the project. In September 1998, Amersham Pharmacia Biotech acquired Molecular Dynamics.

In August 1998, Affymetrix entered into an agreement with Beckman Coulter to develop and commercialize GeneChip and other DNA probe arrays and anticipated giving other companies and research laboratories access to the technology through cooperative agreements. The company formed a partnership with Sybase to develop databases and reached an agreement with Amersham Pharmacia Biotech to distribute arrays in some countries outside the United States. Affymetrix entered into agreements with OncorMed to use GeneChip arrays to analyze genes associated with cancer. Under a separate alliance, Hewlett-Packard was to develop and supply a next-generation scanner and its software. Affymetrix also collaborated on the selection of specific genes and probes with the Genetics Institute, Roche Molecular Systems, and Incyte Pharmaceuticals.

That same month, Affymetrix introduced the GeneChip HuSNP assay, the first in a line of products to support applications in genotyping. The company was collaborating with the Whitehead/MIT Institute Center for Genome Research and the Stanford Human Genome Center to discover and map many of the gene variations.

Affymetrix and Amersham took advantage of market opportunities to introduce products, while continuing to develop other technologies for sequencing and analytical devices that would lay the groundwork for the MIND device in particular and point-of-care devices in general. ATP continued its commitment to the project, assessing the subsidiary project outcomes and technologies against overall project criteria.

In addition to significant publicity in the biotechnology and business press, newspapers and magazines such as *Popular Science* ran feature articles about the new products. By 1999, between them Affymetrix and Amersham had marketed 5 initial products, signed more than 12 agreements with collaborators and customers, and had attracted substantial additional investment funds. Amersham announced that 20 additional partners had joined the Microarray Technology Access Program, which included 30 drug and biotechnology companies, institutes, and universities. This program provided access to proprietary technology.

Development Continues after ATP Funding

ATP funding ended in 2000, the same year that HGP and the PE-Celera team announced that the mapping of the human genome was essentially complete.

Amersham reported that, "MegaBACE is now established as the major force behind many public- and private-sector genome sequencing operations," and said it had installed more than 400 systems around the world.

By September 2001, the majority of the top pharmaceutical companies, more than a dozen biotechnology firms, and more than 1,000 academic institutions were using GeneChip and other Affymetrix technologies. According to an economic impact analysis[3] in January 2007, "The ATP award had a significant influence on Affymetrix as a company and on the biotechnology industry as a whole…Receiving the award helped Affymetrix secure additional funding from venture capitalists and increased interest in Affymetrix's initial public offering (IPO) by validating the company's efforts. Affymetrix believes the award and the project's success also invigorated investor interest in the biotechnology sector."

The research from the project was the subject of numerous publications and presentations and generated 29 patents. The two companies had myriad technical accomplishments supported in part by the ATP-funded research. Both companies developed software for DNA analysis used for sequencing and diagnosis. They also developed methodologies for gene expression, used extensively in drug discovery and diagnostics.

Affymetrix:

- Produced DNA arrays for a variety of uses
- Developed a prototype disposable cartridge for complete analysis
- Developed technologies for dense arrays using photolithographic techniques

Amersham:

- Developed array technologies for arrays of long oligonucleotides such as cDNA
- Developed instrumentation to fabricate these arrays
- Demonstrated electrophoresis in chip format with multiple lanes and unit base resolution out to 450 bases and beyond

Amersham invested about $20 million in industrial design and had obtained research funding from other Federal agencies. It collaborated with other companies, but was no longer working with Affymetrix. In 2004, the GE Healthcare division of the General Electric Company acquired Amersham. By then, 1,530 MegaBACE systems had been sold, bringing in $20 million in revenue, including new models that had been developed to accommodate larger- and smaller-scale sequencing.

The Molecular Dynamics team estimated that MegaBACE sequencers were responsible for mapping about 30 percent of the human genome. The new sequencer lowered per-unit operating costs, eliminated many time-consuming manual processes, and enhanced the quality of data output. The use of high-throughput sequencers was estimated to have advanced the sequencing of HGP by three years. Molecular Dynamics said it would not have begun the research that led to MegaBACE without the ATP award.

The Molecular Dynamics team estimated that MegaBACE sequencers were responsible for mapping about 30 percent of the human genome.

The handheld device that was the original goal of the project was never produced, but the ATP-funded project contributed to the core science, best practices, processes, and methodologies that could make such a device possible. The products emanating from the ATP award have become pre-eminent tools in the diagnostics industry. DNA chips now enable medical research, which previously took months or was not possible at all, in HIV, cancer, cystic fibrosis, and sudden threats such as SARS and avian flu. As in the semiconductor industry, costs are expected to fall even though features are increasing. In the long term, doctors and other clinicians will use microarray technologies to help determine the benefits of drug

[3]O'Connor, Alan et al. *Economic Impact of ATP's Contributions to DNA Diagnostics Technologies*. NIST Advanced Technology Program, GCR 06-898, January 2007.

therapies for patients given their genetic makeup. Researchers use DNA-chip technology to advance the capability of DNA-based treatments.

The ATP award accelerated Affymetrix's microarray technology and the protocols, assays, and software that enable its practical application. Affymetrix halved the size of DNA probe features from 50 to 25 microns and developed the information technology infrastructure for working with the high volume of data output by DNA microarrays, manufacturing techniques for producing DNA microarrays, proofs of concept, and new analytical methods. These achievements improved the quality and ease of the end-use experience and hastened the introduction of better and faster analysis for the same approximate price.

The introduction of high-throughput sequencers was a milestone that accelerated HGP and the scientific discoveries that emanated from sequencing the genome. Both companies attribute their growth to the ATP-sponsored project. Affymetrix had 66 staff members at the project outset, grew ninefold to 519 by the end of ATP funding, and numbered 1,101 in mid-2006. Affymetrix had 82 percent of the DNA microarray market. Molecular Dynamics, also a small company at the project outset, was acquired by progressively larger companies and is now a component of GE Healthcare.

Conclusion

In 1990, two Federal agencies announced a 15-year program to sequence the human genome, known as the Human Genome Project (HGP). In addition to the knowledge that would be gained by knowing the entire sequence, the project envisioned accelerating the technologies that were needed to undertake the task. Before 1994, scientists used $100 blood tests and other diagnostic procedures to identify individual genes. That year, Affymax introduced the first GeneChip array, which allowed the sequencing of several DNA fragments simultaneously. Affymax subsequently spun off Affymetrix to improve and commercialize the technology. Soon thereafter, Affymetrix joined with Molecular Dynamics to propose a highly sophisticated handheld diagnostic device for use in medical offices and clinics. The companies applied for and received an ATP cost-shared award for a five-year project that began in 1995.

Affymetrix improved its photolithographic process for industrial production and increased the capacity of GeneChip arrays by increasing the probe density. It also improved the software used to work with the ever more copious data readouts generated by GeneChip technology. By 1996, Affymetrix began limited marketing of a GeneChip system that included instruments to process the probe arrays, software, and the chip itself. As the project proceeded, Affymetrix continued to improve and vary the chip's capabilities.

Molecular Dynamics began work on a sequencer that it called MegaBACE. Using a capillary array technique combined with electrophoresis, MegaBACE speeded up sequencing nearly a hundredfold, leading other companies to speed the development of their sequencers. In 1998, Perkin-Elmer and Celera announced plans to sequence the human genome in three years, in direct competition with HGP. Although the rivals would use a different sequencer, laboratories sequencing the genome for HGP ordered many MegaBACE 1000s to meet the challenge.

This project accelerated the use of the DNA chip as a robust method of molecular analysis. Both Affymetrix and Molecular Dynamics, now part of GE Healthcare, have become leaders in the diagnostic device field. As of 2006, Affymetrix had 82 percent of the DNA microarray market and had established a licensing program to stimulate the broad commercialization of genome analysis technologies. The research from the project resulted in several thousand publications and presentations and 29 patents.

PROJECT HIGHLIGHTS
Affymetrix-GE Healthcare (formerly Molecular Dynamics)

Project Title: Helping to Decode the Genome (Miniaturized Integrated Nucleic Acid Diagnostic (MIND) Development)

Project: To develop a miniaturized integrated nucleic acid diagnostic (MIND) device suitable for use in hospitals, clinics, or doctors' offices, which could provide the rapid, accurate diagnosis of a wide variety of diseases.

Duration: 2/1/1995 - 1/31/2000
ATP Number: 94-05-0016

Funding (in thousands):

ATP Final Cost	$28,779	47.8%
Participant Final Cost	31,487	52.2%
Total	$60,266	

Accomplishments: With ATP funding both companies developed software for DNA analysis used for both sequencing and diagnosis, and developed methodologies for gene expression, used extensively in drug discovery and diagnostics. In addition Affymetrix:

- Produced and marketed DNA array chips for a variety of uses
- Developed a prototype disposable cartridge for complete analysis
- Developed array technologies for dense arrays, with short oligonucleotide probes, using photolithographic techniques

Molecular Dynamics (now a component of GE Healthcare) developed the MegaBACE 1000, a capillary array electrophoresis sequencer that scans and detects DNA in human samples. It was used by the Human Genome Project (HGP) to determine the sequence of about 30 percent of the human genome. In addition, the company:

- Developed array technologies for arrays using long oligonucleotides such as cDNA
- Developed instrumentation to fabricate these arrays
- Demonstrated electrophoresis in chip format with multiple lanes and unit base resolution out to 450 bases and beyond

The following patents for technologies related to the ATP-funded project were granted:

Assigned to Molecular Dynamics:

- "Denaturing separation matrix having hydroxyethyl cellulose for nucleic acid electrophoresis" (No. 5,534,123: filed July 10, 1995, granted July 19, 1996)
- "Aminosilane/carbodiimide coupling of DNA to glass substrate" (No. 5,760,130: filed May 13, 1997, granted June 2, 1998)

Assigned to Affymetrix:

- "Computer-aided probability base calling for arrays of nucleic acid probes on chips" (No. 5,733,729: filed September 14, 1995, granted March 31, 1998)
- "Integrated nucleic acid diagnostic device" (No 5,856,174: filed January 19, 1996, granted January 5, 1999)
- "Synthesis of oligonucleotide arrays using photocleavable protecting groups" (No. 6,022, 963: filed April 10, 1996, granted February 8, 2000)
- "Integrated nucleic acid diagnostic device" (No. 5,922,591: filed June 27, 1996, granted July 13, 1999)
- "Photocleavable protecting groups and methods for their use" (No. 6,147,205: filed March 5, 1997, granted November 14, 2000)
- "Computer-aided techniques for analyzing biological sequences" (No. 6,600,996: filed March 28, 1997, granted July 29, 2003)
- "Computer-aided probability base calling for arrays of nucleic acid probes on chips" (No. 6,066,454: filed October 10, 1997, granted May 23, 2000)
- "Miniaturized genetic analysis systems and methods" (No. 6,168,948: filed January 12, 1998, granted January 2, 2001)

PROJECT HIGHLIGHTS
Affymetrix-GE Healthcare (formerly Molecular Dynamics)

- "Process for microfabrication of an integrated PCR-CE device and products produced by the same" (No. 6,261,431: filed December 28, 1998, granted July 17, 2001)
- "Techniques for identifying confirming mapping and categorizing nucleic acids" (No. 7,099,777: filed January 11, 1999, granted August 29, 2006)
- "Integrated nucleic acid diagnostic device" (No. 6,197,595: filed April 19, 1999, granted March 6, 2001)
- "Systems and methods for high performance scanning" (No. 6,545,264: filed August 26, 1999, granted April 8, 2003)
- "Products and methods for analyzing nucleic acids including identification of substitutions, insertions and deletions" (No. 6,699,659; filed December 21, 1999, granted March 2, 2004)
- "System and method for self-calibrating measurement" (No. 6,612,737: filed December 29, 1999, granted September 2, 2003)
- "Computer-aided probability base calling for arrays of nucleic acid probes on chips" (No. 6,228,593: filed January 14, 2000, granted May 8, 2001)
- "Method of manipulating a gas bubble in a microfluidic device" (No. 6,326,211: filed March 10, 2000, granted December 4, 2001)
- "Photocleavable protecting groups and methods for their use" (No. 6,566,515: filed March 14, 2000, granted May 20, 2003)
- "Capillary array electrophoresis scanner" (No. 6,554,986: filed May 25, 2000, granted April 29, 2003)
- "Integrated nucleic acid diagnostic device" (No. 6,830,936: filed December 31, 2000, granted December 14, 2004)
- "Nucleic acid labeling compounds" (No. 6,596,856: filed February 9, 2001, granted July 22, 2003)
- "Computer-aided probability base calling for arrays of nucleic acid probes on chips" (No. 6,546,340: filed March 20, 2001, granted April 8, 2003)
- "Nucleic acid labeling compounds" (No. 6,965,020: filed September 11, 2001, granted November 15, 2005)
- "Capillary array electrophoresis scanner" (No. 7,090,758: filed October 31, 2002, granted August 15, 2006)
- "Biotin containing C-glycoside nucleic acid labeling compounds" (No. 6,864,059: filed December 5, 2002, granted March 8, 2005)
- "Photocleavable protecting groups and methods for their use" (No. 6,881,836: filed January 22, 2003, granted April 19, 2005)
- "Computer-aided probability base calling for arrays of nucleic acid probes on chips" (No. 6,957,149: filed April 1, 2003, granted October 18, 2005)
- "Nucleic acid labeling compounds" (No. 6,844,433: filed June 2, 2003, granted January 18, 2005)

Commercialization Status: Although MIND was never developed, ATP funding for this project brought about Molecular Dynamics' MegaBACE 1000 sequencer, which achieved sales of 1,530 instruments, amounting to more than $200 million in revenue. Several successor models allowed both larger and smaller scale sequencing. GE Healthcare continues to manufacture MegaBACE systems. It substantially improved Affymetrix's GeneChip system, most notably the software that allowed efficient handling of the enormous data output of GeneChip arrays. Further developments stemming from the ATP-funded technology are the GeneChip HuSNP System, which sequenced and analyzed human DNA, the GeneChip p53 array, and the GeneChip CYP450 array.

Outlook: Molecular Dynamics' MegaBACE sequencer contributed significantly to the HGP. Successors to the MegaBACE offer sequencing on both larger and smaller scales and have enjoyed steady sales. Although the product originally envisioned, the MIND device, has not been developed, the two companies developed and marketed supporting

PROJECT HIGHLIGHTS
Affymetrix-GE Healthcare (formerly Molecular Dynamics)

technologies. The products based on these technologies are selling well and are likely to remain on the market for several years to come.

Composite Performance Score: * * * *

Number of Employees: 99 at project start; 1,101 as of March 2006 (Affymetrix).

Focused Program: Tools for DNA Diagnostics, 1994

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- Scientific Generics
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  Berkeley, CA 94720
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Publications: Of the several hundred articles about the ATP-funded technology, the following are a sample.

- Bashkin, et al. “DNA Sequencing by Capillary Electrophoresis with a Hydoxyethylcellulose Sieving Buffer.” *Applied and Therapeutic Electrophoresis*, Vol. 6, pp. 23-28, 1996.
- Mansfield, et al. “Sensitivity, Reproducibility, and Accuracy in Short Tandem Repeat Genotyping Using Capillary Array Electrophoresis.” *Genome Research*, Vol. 6, pp. 893-903, 1996.
- Madabhushi, Vainer, Dolnik, Enad, Barker, Harris, and Mansfield. “Versatile Low-Viscosity Sieving Matrices for Nondenaturing DNA Separations Using Capillary Array Electrophoresis.” *Electrophoresis*, Vol. 18, pp. 140-111, 1997.
- Mansfield, Vainer, Harris, Gasparini, Estivill, Surrey, and Fortina. “Rapid Sizing of Polymorphic Microsatellite Markers by Capillary Array Electrophoresis.” *Journal of Chrom*,, Vol. 781, pp. 295-305, 1997.
- Vainer, Enad, Dolnik, Xu, Bashkin, Marsh, Tu, Barker, and Mansfield. “Short Tandem Repeat Typing by Capillary Array Electrophoresis: Comparison of Sizing Accuracy and Precision Using Different Buffer Systems.” *Genomics*, Vol. 41, pp. 1-9, 1997.
- Dolnik, Xu, Yadav, Bashkin, Marsh, Tu, Mansfield, Vainer, Madabhushi, Barker, and Harris, “Wall Coating for DNA Sequencing and Fragment Analysis by Capillary Electrophoresis.” *Journal of Microcolumn*, Vol. 10, pp. 175-184, September 1998.
- Tu, Knott, Marsh, Bechtol, Harris, Barker, and Bashkin. “The Influence of Fluorescent Dye Structure of the Electrophoretic Mobility of End-Labeled DNA.” *NAR*, Vol. 26, pp. 2797-2802, 1998.

PROJECT HIGHLIGHTS
Affymetrix-GE Healthcare (formerly Molecular Dynamics)

- O'Connor et al. *Economic Impact of ATP's Contributions to DNA Diagnostics Technologies*. NIST Advanced Technology Program, GCR 06-898, January 2007.

Presentations:

- Barker, D., IBC Meeting on Microarray Technology, Baltimore, MD, October 1997.
- Barker, D., International Rice Genome Conference, Tskuba, Japan, January 1998.
- Barker, D., CHI Meeting: Commercial Implications of the Human Genome Project, San Francisco, CA, February 1998.
- Barker, D., Satellite Symposium of the HUGO Meeting, Sestri Levanti, Italy, March 1998.
- Barker, D., CHI Meeting on Gene Quantification, San Diego, CA, March 1998.
- Barker, D., First International Workshop on Advanced Genomics, Tokyo, Japan, April 1998.