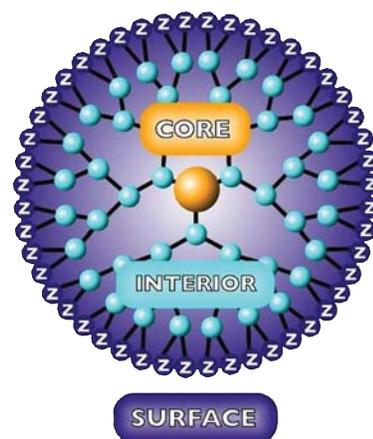
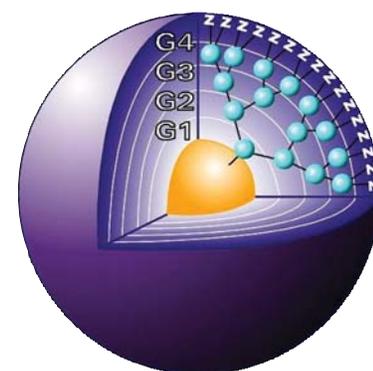
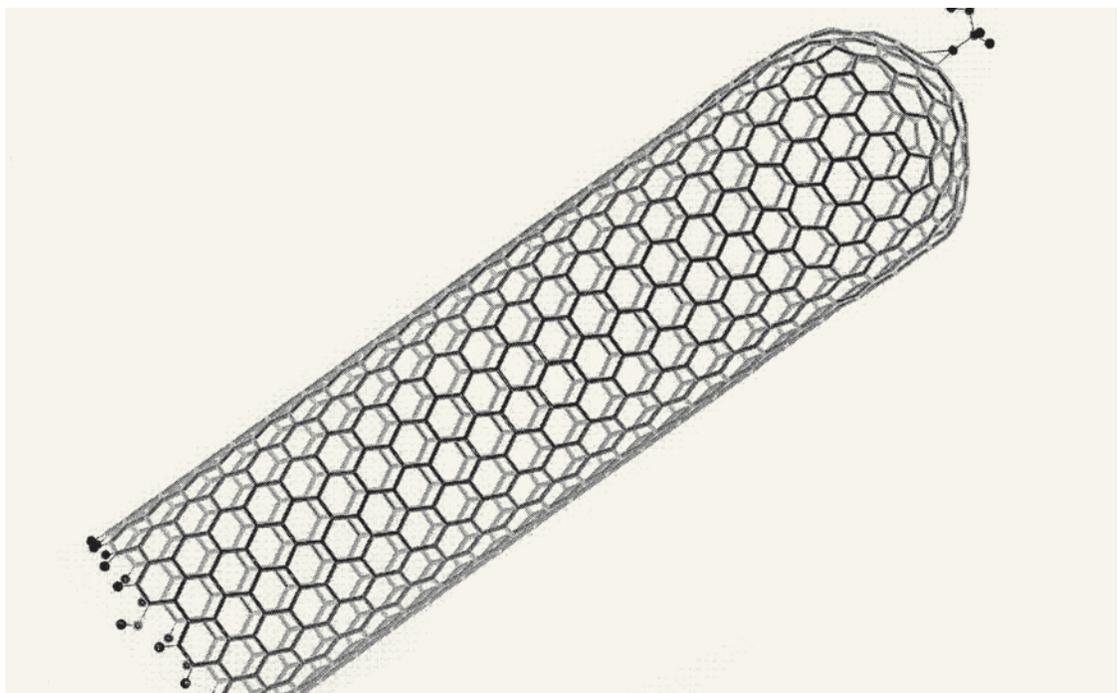


Center for
Contemporary
History and Policy

Studies in Materials Innovation

The Integrated Circuit for Bioinformatics:
The DNA Chip and Materials Innovation
at Affymetrix

Doogab Yi



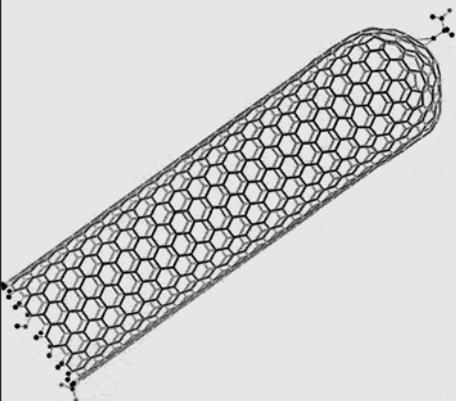
Center for
Contemporary
History and Policy

Studies in Materials Innovation

The Integrated Circuit for Bioinformatics: The DNA Chip and Materials Innovation at Affymetrix

Doogab Yi

C h e m i c a l H e r i t a g e F o u n d a t i o n



© 2010 by the Chemical Heritage Foundation. All rights reserved. No part of this publication may be reproduced in any form by any means (electronic, mechanical, xerographic, or other) or held in any information storage or retrieval system without written permission from the publisher.

Printed in the United States of America.

For information about the Chemical Heritage Foundation, its Center for Contemporary History and Policy, and its publications, write

Chemical Heritage Foundation
315 Chestnut Street
Philadelphia, PA 19106-2702, USA
Fax: (215) 925-1954
www.chemheritage.org

Design by Willie•Fetchko Graphic Design

Cover: Buckytube and buckyball images, gift of Richard E. Smalley, Chemical Heritage Foundation Collections.
Dendrimer images courtesy of Dendritic Nanotechnologies, Inc.

STUDIES IN MATERIALS INNOVATION SERIES

1. **Patterning the World: The Rise of Chemically Amplified Photoresists**
David C. Brock
2. **Sun & Earth and the “Green Economy”:** A Case Study in Small-Business Innovation
Kristoffer Whitney
3. **Innovation and Regulation on the Open Seas:** The Development of Sea-Nine Marine Antifouling Paint
Jody A. Roberts
4. **Co-Innovation of Materials, Standards, and Markets:** BASF’s Development of Ecoflex
Arthur Daemmrich
5. **The Integrated Circuit for Bioinformatics:** The DNA Chip and Materials Innovation at Affymetrix
Doogab Yi
6. **Toward Quantification of the Role of Materials Innovation in Overall Technological Development**
Christopher L. Magee
7. **Institutions as Stepping-Stones:** Rick Smalley and the Commercialization of Nanotubes
Cyrus C. M. Mody

CONTENTS

- I. Executive Summary | 5**
- II. Materials Innovation in the Biotech Industry | 7**
- III. VLSI (Very Large-Scale Integration) for the Biomedical Materials Bank: Affymax | 9**
- IV. The DNA Chip for Bioinformatics: The Spin-Off of Affymetrix | 13**
- V. Affymetrix's GeneChip System | 15**
- VI. Bioinformatics and Genetic Medicine | 17**
- VII. Findings | 19**
- VIII. Appendixes | 21**
 - 1. References
 - 2. About the Robert W. Gore Materials Innovation Project

I. EXECUTIVE SUMMARY

The second generation of biotech firms, established in the 1990s, has expanded its business scope into chemical, materials, and research infrastructure for biomedical research and pharmaceutical development. A few start-up companies, such as Affymetrix, Celera, and Human Genome Sciences, exhibited this broader shift in their business toward materials and research after the first biotech boom of the 1980s subsided. This essay analyzes one such case in materials innovation in the biotech industry—Affymetrix’s DNA chip, which ignited the confluence of information technology and biotechnology. This case study illuminates the evolution of business strategies of the second generation of biotech firms, analyzes the reconfiguration of biotech firms’ strategic alliances with academic research communities and pharmaceutical companies in the 1990s, and examines the hybridization of discrete technological components in the development of bioinformatics. Through its innovative materials and managerial innovations, Affymetrix’s DNA-chip systems have provided one of the core technologies in the development of genomics and genetic medicine.

II. MATERIALS INNOVATION IN THE BIOTECH INDUSTRY

Historians of biotechnology have focused on the impact of such disruptive innovative technologies as recombinant DNA, hybridomas, and polymerase chain reaction on the emergence of the biotech industry and on its economic and legal consequences.¹ This case study shifts the focus from the first generation of innovative biomedical technologies to a broader set of materials, organizational, and business innovations in the biotech industry. The study examines the evolution and diversification of biotech firms from their initial establishment in the 1980s.

The first generation of biotech firms, such as Amgen, Genentech, and Genzyme, was directly involved in drug research and development with a new set of molecular technologies.² Proponents of biotechnology claimed that new innovative molecular technologies were about to revolutionize traditional drug-development processes based on compounds-screening methods. By enabling unprecedented control over genetic and molecular processes of life, for example, these proponents claimed that the new era of rational drug design would obliterate big pharmaceutical companies. The first generation of biotech firms developed a set of drugs using recombinant-DNA technologies.³

In their pursuit of innovative drugs, however, these first-generation companies faced mounting problems in drug development. Critics of biotech companies warned that the whole process of drug development requires more than mere scientific discoveries: potential drug targets would have to go through a prolonged period of production development, clinical trials, and regulatory approvals. Unlike big pharmaceutical companies, start-up biotech firms often had difficulty raising the massive amount of capital necessary for this long-term developmental process.⁴ The result was the survival of only a few first-generation biotech companies, such as Amgen and Genentech, that chose to arrange a business deal with big pharmaceutical companies.

¹ Martin Kenney, *Biotechnology: The University-Industrial Complex* (New Haven, CT: Yale University Press, 1986); Sally S. Hughes, "Making Dollars out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974–1980," *Isis* 92 (2001), 541–575; Alberto Cambrosio and Peter Keating, *Exquisite Specificity: The Monoclonal Antibody Revolution* (Oxford: Oxford University Press, 1995); and Paul Rabinow, *Making PCR: A Story of Biotechnology* (Chicago: University of Chicago Press, 1996).

² Stephen S. Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene* (New York: Atlantic Monthly Press, 1987).

³ Cynthia Robbins-Roth, *From Alchemy to IPO: The Business of Biotechnology* (Cambridge, MA: Perseus Publishing, 2000).

⁴ For Merck's successful adoption of molecular biotechnologies, see P. Roy Vagelos and Louis Galambos, *Medicine, Science, and Merck* (Cambridge: Cambridge University Press, 2004).

The second generation of biotech firms, established in the 1990s, contentiously decided to avoid costly investment in drug development.⁵ Instead, these companies have expanded their business reach into chemical, materials, and research infrastructure for biomedical research and pharmaceutical development—another huge market for the biotech industry. A few of these start-up biotech firms, such as Affymetrix, Celera, and Human Genome Sciences, exhibited this broader shift in the business of biotechnology toward materials and research infrastructure after the first biotech boom of the 1980s subsided.

This paper analyzes one such case in materials innovation—Affymetrix’s DNA chip—and aims to illuminate the evolution of business strategies of the second generation of biotech firms. More specifically, it examines one case of materials innovation that ignited the confluence of information technology and biotechnology. Through this case study we can also observe the reconfiguration in the 1990s of biotech firms’ strategic alliances with academic research communities and pharmaceutical companies.

⁵ Gary P. Pisano, *Science Business: The Promise, the Reality, and the Future of Biotech* (Cambridge, MA: Harvard Business School Press, 2006).

III. VLSI (VERY LARGE-SCALE INTEGRATION) FOR THE BIOMEDICAL MATERIALS BANK: AFFYMAX

Affymetrix is a spin-off from Affymax, a biotech company founded in 1988 by entrepreneur Alejandro Zaffaroni and Stanford biochemist Lubert Stryer. At the beginning of the biotech boom in the late 1970s and early 1980s, Zaffaroni launched DNAX Research Institute with some Stanford University and Harvard University molecular biologists.⁶ Zaffaroni's initial business strategy was to accelerate the drug-discovery process using new molecular technologies. The traditional approach to drug discovery had largely been based on organic chemistry: chemically synthesizing or discovering new candidate drugs and then testing their clinical efficacy. Though Zaffaroni assembled a stellar group of scientists at DNAX, the company failed to attract more venture capital after a few years of "burning" its initial capital. DNAX was later acquired by a pharmaceutical giant, Schering-Plough.

At the beginning of the first biotech boom, pharmaceutical companies tried to acquire new molecular biotechnologies through merger and acquisition instead of building in-house technological and organizational capabilities.⁷ Schering-Plough's acquisition of DNAX exemplified this business strategy. By the late 1970s pharmaceutical firms were faced with the limitations of the traditional screening approach to drug discovery. Because the approach had become increasingly expensive and cumbersome, speeding it up or automating it was of substantial interest to the companies. Affymax was initially established to overcome the disadvantages of traditional drug-screening discovery. The firm aimed to develop technologies to synthesize and screen a massive amount of chemicals for drug candidates.

Affymax Research Institutes, a venture biotech firm in Palo Alto, California, was formed when biochemists and molecular biologists at Stanford originated the concept of peptide microarrays for drug synthesis in the late 1980s. Alex Zaffaroni was behind the founding of Affymax. As a renowned chemist and successful businessman, Zaffaroni was leading a profitable company, ALAZA, which mainly developed drug-delivery systems. In the late 1970s and early 1980s Zaffaroni had founded a few biotech firms, such as DNAX, with Stanford biochemists, and he was well aware of the technological and business potential of such new molecular technologies as recombinant DNA and hybridomas.⁸

⁶ Arthur Kornberg, *The Golden Helix: Inside Biotech Ventures* (Sausalito, CA: University Science Books, 1995).

⁷ Alfred D. Chandler, Jr., *Shaping the Industrial Century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries* (Cambridge, MA: Harvard University Press, 2005).

⁸ Paul Berg, interview with the author, Beckman Center, Stanford University School of Medicine, September 2008.

As other big pharmaceutical companies in the early 1980s recognized, it became increasingly difficult to find a new drug candidate through traditional (organic) chemical synthesis and screening methods. New molecular technologies emerged as a promising source of innovation in drug discovery, and big pharmaceutical companies tried to learn new biotechnological capabilities by acquiring start-up biotech companies in the early 1980s. Likewise, Zaffaroni wanted to develop new tools for drug discovery by using new technologies in molecular biology and genetic chemistry.

Zaffaroni wanted to find ways to go beyond the traditional drug-discovery approach. In order to facilitate the flow of knowledge and technology from cutting-edge research in molecular biology, Zaffaroni appointed Stanford biochemist Lubert Stryer as the chief scientific officer of Affymax. Zaffaroni also assembled a scientific advisory board consisting of Stanford biochemists, chemists, and pharmacologists, such as Paul Berg, Carl Djerassi, Mark Davis, Avram Goldstein, and Michael Pirrung. In 1989 Stryer took a leave of absence from Stanford in order to set up Affymax's business plan for drug discovery.⁹

In the early stages of debate over Affymax's scientific and business strategies, the advisory board decided it was critical to find innovative ways to multiply molecular diversity in order to find potentially useful biomedical materials. They discussed several methods of generating diverse (bio)chemical molecules that could lead to drug target candidates. Goldstein, a Stanford pharmacologist, advocated peptide-synthesis methods as a promising new approach to generate large peptide libraries. He claimed that by combining multiple sequences of amino acids in assembly-line fashion, one could synthesize proteins of diverse molecular composite.¹⁰

In their search for technologies for constructing the library of novel biomedical materials, a young member of the scientific board, a photochemist, Pirrung, suggested that light-controlled synthesis of polymers might be a productive and inexpensive way to create diverse sets of random chemical molecules. Through coupling and decoupling of molecules using photochemical reactions on a solid plate, Pirrung indicated, an efficient system for the generation of chemical diversity could be developed. Together with Leighton Read, Pirrung drew an analogy with the production of silicon chips using photolithography, in which beams of light lay out an intricate circuit on a silicon wafer. Following an innovative technology used in the semiconductor industry, VLSI (very large-scale integration), they decided to develop a VLSIPS (very large-scale immobilized polymer synthesis).¹¹

Using this technological platform to generate chemical diversity for drug targets—a library of synthesized compounds—seemed promising. By synthesizing chemical compounds on chips, this platform in turn would enable scientists to test easily the therapeutic potential of a large quantity of biochemical materials on chips. “The theory behind their work was revolutionary—a notion that semiconductor manufacturing techniques

⁹ Timothy Lenoir and Eric Giannella, “The Emergence and Diffusion of DNA Microarray Technology,” *Journal of Biomedical Discovery and Collaboration* 1:11 (2006), 1–39.

¹⁰ Ibid.

¹¹ Ibid.

could be united with advances in combinatorial chemistry to build vast amounts of biological data on a small glass chip.”¹² Affymax had developed both a photolithographic synthesis system and an advanced screening technology by early 1989.

¹² Affymetrix, *Pioneering an Industry* (Affymetrix, 2004), p. 4, available at www.affymetrix.com/support/technical/other/pioneer_brochure.pdf.

IV. THE DNA CHIP FOR BIOINFORMATICS: THE SPIN-OFF OF AFFYMETRIX

Once the members of Affymax’s scientific advisory board decided to proceed with light-directed chemical synthesis using a VLSIPS platform, they began searching for a scientific leader for the project. Unfortunately, Pirrung had taken a position as a professor of biochemistry at Duke University. Stryer recruited a postdoctoral fellow from the National Institutes of Health, Stephen Fodor, to lead the development of a VLSIPS technology platform using an array manufactured by a photolithographic process. Fodor’s aim was to create very dense arrays of biomolecules (mostly proteins and nucleic acids) by combining photolithographic methods with traditional chemical techniques. As Fodor saw it, by packing biomolecules in dense arrays it was possible to study a large number of molecules.

In 1990 Fodor and Stryer recruited Fabian Pease, an expert on electron-beam lithography and a professor of electrical engineering at Stanford, to be a consultant on Fodor’s photolithographic synthesis system.¹³ Fodor mounted his effort to build a peptide-synthesis system by lithography. In 1991, after eighteen months of experimentation at Affymax, Fodor developed a procedure to generate a diverse peptide array. Published in 1991 in *Science*, “Light-Directed, Spatially Addressable Parallel Chemical Synthesis” by Fodor and colleagues described a new technological platform that could generate chemical diversity for a drug candidate. As was proclaimed in the article, Fodor’s photolithographic method of chemical synthesis has one distinctive advantage: the biochemical materials produced by the application of light-directed synthesis exhibited the rich diversity and a high degree of density:

The revolution in microelectronics has been made possible by photolithography, a process in which light is used to spatially direct the simultaneous formation of many electrical circuits. We report a method that uses light to direct the simultaneous synthesis of many different chemical compounds . . . a high degree of miniaturization is possible because the density of synthesis sites is bounded only by physical limitations of spatial addressability, in this case the diffraction of light.¹⁴

The chemical diversity and miniaturization achieved by photolithography, Fodor envisioned, could significantly help accelerate the production and screening of potential drug candidates. Advances in molecular biology increasingly help pharmaceutical researchers

¹³ Lenoir and Giannella, “Emergence and Diffusion of DNA Microarray Technology.” For the development of photolithography see David C. Brock, “Patterning the World: The Rise of Chemically Amplified Photoresists,” *Studies in Materials Innovation, Center for Contemporary History and Policy*, Chemical Heritage Foundation (Philadelphia: Chemical Heritage Foundation, 2009).

¹⁴ Stephen P. A. Fodor et al., “Light-Directed, Spatially Addressable Parallel Chemical Synthesis,” *Science* 251 (1991), 767–773, on p. 767.

illuminate the ways in which chemical drugs produce therapeutic effects. The multiple and dense peptide arrays could be fruitfully used for drug discovery as the detailed drug pathways inside a human body, especially the ways in which receptors and enzymes interact with specific ligands have been elucidated. As Fodor emphasized, “High-density arrays formed by light-directed synthesis are potentially rich sources of chemical diversity for discovering new ligands that bind to biological receptors and for elucidating principles governing molecular interactions.”¹⁵ Peptide arrays that hold thousands of molecules could provide viable drug candidates that enhance their therapeutic efficacy through precise molecular reactions.

Fodor in turn needed to develop a screening system for his peptide arrays. A company called Automated Visual Inspection, founded by a former employee of Fairchild Semiconductor, Peter Fiekowsky, helped build a laser screening system for the analysis of peptide sequences on a silicon wafer or a glass chip.¹⁶ Researchers adopted a hybridization method to probe for potential drug candidates in a huge number of peptides directly synthesized on a silicon chip. By adding target molecules labeled with fluorescent dye, one can identify molecules that bind with the target.

Fodor’s team developed a computerized screening system that can examine the degree of hybridization between target molecules and drug candidates by a laser-beam scan. With a prototype peptide array and computer scanner, Fodor had produced by the early 1990s the complete peptide-array platform. This system indeed formed the core of Affymetrix’s technology. In 1993 Affymax’s team that guided the development of the peptide-array system—Fodor, Pirrung, Read, and Stryer—won the Intellectual Property Owners Association’s Distinguished Inventor award.

¹⁵ *Ibid.*, p. 767.

¹⁶ Lenoir and Giannella, “Emergence and Diffusion of DNA Microarray Technology.”

V. AFFYMETRIX'S GENECHIP SYSTEM

The establishment of Affymetrix reflects the biotech industry's business-diversification strategy, one that moved away from risky and costly drug development toward creating a broad array of research and materials technologies. As the first wave of the biotech boom waned in the late 1980s, biotech entrepreneurs needed to find ways to minimize the financial, regulatory, and scientific risks involved in drug development. Though Affymax's ambitious project demonstrated the feasibility of a peptide-array system for drug development, its scientific board and Fodor recognized that microarray technologies could be directed toward better and less risky projects like a DNA chip.

As early as 1990 Fodor began to consider a DNA array as a more technically feasible project than complex peptide-array systems. At first the DNA-chip idea was not enthusiastically endorsed. It was commercially unattractive: it seemed the final product could contribute to research in molecular biology, such as DNA sequence analysis, but genomics was not a big science in the early 1990s. Fodor, however, insisted that he could develop a DNA chip (as opposed to a peptide-array system) much cheaper, faster, and more reliably from a technical point of view. As he noted, in terms of molecular complexity DNA is much simpler to synthesize and analyze, especially compared with proteins (DNA consists of four kinds of nucleic acids, and proteins consist of twenty kinds of amino acids).

The onset of the Human Genome Project in the early 1990s changed the commercial prospect of a DNA chip, which could meet the technological demand for this large-scale project in the production and analysis of genetic data. In 1993 Fodor and his collaborators at Affymax formed a new company, Affymetrix (Affinity Matrix), to concentrate on building a DNA-microarray system instead of the more technically demanding peptide-array system. The DNA-chip platform would be able to read and analyze genetic data from a DNA microarray with an automated screening system.

Fodor modified his peptide-synthesis technology for the production of a DNA chip. The core elements of this DNA-chip innovation were drawn from his peptide-synthesis system. First, he perfected light-directed combinatorial chemistry for DNA. This technology could synthesize a large number of discrete molecules at high resolution in precise locations on a silicon wafer. As with his peptide arrays, Fodor used photolithography and solid-phase synthesis to produce DNA molecules on a glass substrate. The DNA chip, or DNA microarray, is a tiny glass chip dotted with thousands of DNA fragments of known sequences. It can be used to measure activity of genes or identify genetic variations in people, thereby opening a way to analyze the medical implications of genetic variation.

Fodor's team then modified his previous laser confocal fluorescence-scanning method for a DNA array. In building a DNA microarray-scanning system he used a core technology from his peptide-scanning system, the fluorescence hybridization technique. Affymetrix's DNA microarray-scanning system can examine the degree of hybridization through base pairing of DNA sequences on the array by measuring the intensity of the fluorescent light generated in the process. For this, Affymetrix developed a computer system with software that can analyze DNA hybridization data generated by laser scanning.

Before the advent of the DNA chip it took one or more doctoral-dissertation projects to elucidate the function of one gene. This so-called one gene–one experiment concept characterized the difficulties and enormous efforts required for the study of a gene at the molecular level. The DNA chip, with its thousands of DNA fragments on a silicon wafer, enables scientists to run thousands of samples simultaneously in a single experiment. It became one of the key technologies in the genomic era. In his 1997 article “Massively Parallel Genomics,” Fodor claimed that his DNA-chip technology, with its high degree of miniaturization of DNA information inside the chip, would “move genetic sequence analysis away from serial gel-based methods to a massively parallel screening format.”¹⁷ In Fodor's vision DNA chips could make available enormous amounts of gene-expression data.

Indeed, Affymetrix developed its GeneChip system as a platform for acquiring, analyzing, and managing genetic information. In addition to the production of a DNA microarray Affymetrix developed software tools and genetic databases. With these tools the DNA chip, a new integrated circuit for molecular biology, became one of the core technologies for bioinformatics. Affymetrix, with its DNA-microarray platform, went public in 1996 with a valuation of \$300 million. Its success in the equity market heralded the confluence of information technology and biotechnology in the age of genomics.

¹⁷ Stephen P. A. Fodor, “Massively Parallel Genomics,” *Science* 277 (1997), 393–395.

VI. BIOINFORMATICS AND GENETIC MEDICINE

By moving from a complex peptide array into a tightly integrated technological platform for a simpler DNA chip, Affymetrix was able to produce a viable prototype research technology very quickly. In retooling his research-and-development strategy for Affymetrix, Fodor tried to reduce financial as well as technical risk by building on his previous innovations with Affymax's peptide-array system. Moreover, when Affymetrix put its first commercial product, the GeneChip system, on the market in 1996, Fodor presented it as a technological platform that encompasses DNA chips, computerized scanners, and software to analyze genetic data.

Though its utility as a research technology was well recognized in the field of genomics, its initial commercial potential was largely unknown. When the GeneChip system went on sale, Affymetrix sold it mostly as a research technology in genomics. Fodor in turn diversified his business into one of data management. For this, he acquired firms like Neomorphic to develop software programs to analyze genetic information. As a company, Affymetrix pioneered bioinformatics based on a DNA-chip technology platform, introducing the GeneChip system for various research needs for pharmaceutical and biotechnology companies, academic research groups, private foundations, and clinical laboratories.

During its first decade Affymetrix enhanced the resolution of a DNA chip through miniaturization. More significantly, to analyze and manage a massive amount of genetic data, Affymetrix developed a software system. By the early 2000s Affymetrix's GeneChip system had become one of the most advanced commercial-research technologies for the investigation of gene expression. "Genome projects give you, in a sense, a list of the words in the genomes' vocabulary," says Stanford biochemist Patrick Brown. "A way of seeing how genes express themselves will be the most widely used application of [DNA] arrays."¹⁸

Moreover, the GeneChip system heralds a new era of genetic medicine, as it can be used for the molecular diagnosis and monitoring of a set of diseases.¹⁹ After the conclusion of the Human Genome Project, advances in bioinformatics have helped elucidate the complexities of the genome and its individual variability. The understanding of genetic variability—or single nucleotide polymorphisms—can bring about a profound revolution in understanding diseases at the genetic level and in pharmacogenomics. Affymetrix's GeneChip platform has contributed to the analysis of genetic variability in human diseases. Further exploration of these genetic data could reveal the causes of disease and help identify new, more precise strategies to diagnose and cure disease at the molecular level.

¹⁸ "DNA Chips and Microarrays Part 1," Product Articles, *Science* (4 May 2001).

¹⁹ For a historical discussion about the development of genetic medicine see Susan Lindee, *Moments of Truth in Genetic Medicine* (Baltimore: Johns Hopkins University Press, 2005).

VII. FINDINGS

1. RISK AND REWARDS: BIOMEDICAL MATERIALS PRODUCT STRATEGY AT AFFYMETRIX

Affymetrix's DNA chip highlights the significance of materials innovation in biotechnology and the evolution and diversification of the biotech industry in the 1990s toward research materials market and research infrastructure. More important, the story of the DNA chip illustrates how innovations in the biotech industry depended on "scarce" venture capital in its development of new drugs. The imperative to reduce business risk after the first burst of the biotech boom waned in the 1980s profoundly shaped the strategy of the second generation of biotech firms. The origins of Affymetrix's DNA chip can be traced back to Affymax's peptide-array system, which sought to generate chemical diversity for drug discovery. Innovation was initially driven by this need for greater diversity. Though Fodor and his team at Affymax developed a prototype peptide-array system, they tried to eschew the huge financial, regulatory, and scientific risk involved in drug development. Fodor insisted on a simpler, technically feasible DNA-microarray system instead of investing further in a costly and risky drug-development peptide system. Like other second-generation biotech firms (e.g., Celera and Human Genome Sciences), Fodor established a spin-off company, Affymetrix, in order to expand business into chemical, materials, and research infrastructure for biomedical research and pharmaceutical development—another huge market for the biotech industry. Fodor's team instead focused on a DNA chip as a way to commercialize a broad array of research and materials technologies in genomic analysis.

2. THE NETWORK OF INNOVATORS: SOURCES OF INNOVATION IN THE BIOTECH INDUSTRY

Affymetrix's close interaction with academic research communities through its scientific advisory board signified the reconfiguration of biotech firms' strategic alliance with those communities in the 1990s. Indeed, both Affymax's and Affymetrix's scientific advisory boards functioned as a central node of the network of innovators that shaped the technical and commercial trajectories of the DNA chip. The network of academic and industrial scientists at Affymetrix fostered the exchange of scientific ideas and technological know-how, and was based on the recognition that the first generation of biotech firms' heavy reliance on patenting and technology licensing hindered technical exchange. Indeed, by the late 1980s small biotech firms had difficulty in attracting venture-capital funds, and a broad array of patented (research) technologies seemed to put additional financial burden on small firms. Instead, Affymetrix, while aggressively pursuing patents on its DNA-microarray technologies, cultivated long-term consultant and collaborative

relationships for the development of the GeneChip system. Through its scientific advisory board Fodor's team solicited technical advice and tried to promote the circulation of technical knowledge through its research network. Rather than maintaining a secretive environment for patent protection, Fodor's team collaborated with academic and industrial researchers for the development of the GeneChip system. For example, Fabian Pease at Stanford's electrical engineering department and Peter Fiekowsky at Automated Visual Inspection played a critical role in the production of both peptide and DNA-microarray platforms.²⁰ This strategic collaboration with research communities in turn provided critical resources for Affymetrix's foray into the research-technologies market when the Human Genome Project launched. Fodor's DNA-chip innovation reflected Affymetrix's appreciation of potential sources of innovation (either at academic or industrial laboratories, or both) and its prudent effort to make creative connections between them. With the Human Genome Project, Fodor's DNA chip found the right market.

3. HYBRIDIZATION AND SYSTEMS BUILDING IN MATERIALS INNOVATION

The materials innovation in the DNA chip exhibits the hybridization of discrete technological components. Affymetrix creatively used instruments from the semiconductor industry for the production of DNA microarrays. Affymetrix in turn mobilized information technologies in analyzing and managing the enormous amount of data generated by the DNA chip. The chip, with its high degree of density and miniaturization, in turn transformed molecular biology. The hybridization of information technology and biotechnology in the DNA chip reshaped molecular biology as information science. At another level the advent of the GeneChip system, especially its software platform for data processing, underlines the significance of a system building that connects heterogeneous components in materials innovation. The GeneChip system, with DNA chip and computerized database, resulted in a new research system through which molecular biologists and pharmaceutical researchers can investigate the genetic basis of human disease. The study of the human genome and its genetic organization and regulation—genomics and bioinformatics—has become one of the most intensively pursued subjects in biomedical research. Through the combination of information technology and biotechnology, Affymetrix's DNA-chip systems have provided one of the core technologies in the development of genomics and genetic medicine.

²⁰ Lenoir and Giannella, "Emergence and Diffusion of DNA Microarray Technology."

VIII. APPENDIXES

1. REFERENCES

- Affymetrix. *Pioneering an Industry*. Affymetrix, 2004. Available at www.affymetrix.com/support/technical/other/pioneer_brochure.pdf.
- Berg, Paul. Interview with the author. Beckman Center, Stanford University School of Medicine, September 2008.
- Brock, David C. "Patterning the World: The Rise of Chemically Amplified Photoresists," *Studies in Materials Innovation*, Center for Contemporary History and Policy, Chemical Heritage Foundation. Philadelphia: Chemical Heritage Foundation, 2009.
- Cambrosio, Alberto, and Peter Keating. *Exquisite Specificity: The Monoclonal Antibody Revolution*. Oxford: Oxford University Press, 1995.
- Chandler, Alfred D., Jr. *Shaping the Industrial Century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries*. Cambridge, MA: Harvard University Press, 2005.
- Fodor, Stephen P. A. "Massively Parallel Genomics." *Science* 277 (1997), 393–395.
- Fodor, Stephen P. A., et al. "Light-Directed, Spatially Addressable Parallel Chemical Synthesis." *Science* 251 (1991), 767–773.
- Hall, Stephen S. *Invisible Frontiers: The Race to Synthesize a Human Gene*. 1st ed. New York: Atlantic Monthly Press, 1987.
- Hughes, Sally S. "Making Dollars out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974–1980." *Isis* 92 (2001), 541–575.
- Kenney, Martin. *Biotechnology: The University-Industrial Complex*. New Haven, CT: Yale University Press, 1986.
- Kornberg, Arthur. *The Golden Helix: Inside Biotech Ventures*. Sausalito, CA: University Science Books, 1995.
- Lenoir, Timothy, and Eric Giannella. "The Emergence and Diffusion of DNA Microarray Technology." *Journal of Biomedical Discovery and Collaboration* 1:11 (2006), 1–39.
- Lindee, Susan. *Moments of Truth in Genetic Medicine*. Baltimore: Johns Hopkins University Press, 2005.
- Pisano, Gary P. *Science Business: The Promise, the Reality, and the Future of Biotech*. Cambridge, MA: Harvard Business School Press, 2006.
- Rabinow, Paul. *Making PCR: A Story of Biotechnology*. Chicago: University of Chicago Press, 1996.
- Robbins-Roth, Cynthia. *From Alchemy to IPO: The Business of Biotechnology*. Cambridge, MA: Perseus Publishing, 2000.
- Science*, Product Articles, 4 May 2001, "DNA Chips and Microarrays Part 1."
- Vagelos, P. Roy, and Louis Galambos. *Medicine, Science, and Merck*. Cambridge: Cambridge University Press, 2004.

2. ABOUT THE ROBERT W. GORE MATERIALS INNOVATION PROJECT

Begun in 2006, the Robert W. Gore Materials Innovation Project, conducted by the Chemical Heritage Foundation's Center for Contemporary History and Policy, aims to illuminate the diverse contributions of materials innovation within the broader process of technological development in the contemporary age. Conceived as a three-year project, it documents, analyzes, and makes known the immense benefits of materials innovation through its white paper series, *Studies in Materials Innovation*, and public symposia.

The Gore Innovation Project is made possible by the generous financial contribution of Robert W. Gore, chairman of W. L. Gore & Associates.

Many staff members within the Chemical Heritage Foundation made the project possible. In particular, Arthur Daemmrigh and Arnold Thackray were instrumental in conceptualizing the project. Thanks to Ron Reynolds and Jody Roberts, for providing intellectual support, and to Chi Chan, for the excellent and much-needed administrative skills that sustained the project. Special thanks are accorded to the scholars who contributed research and writing expertise for the case studies in the series.

Finally, we were fortunate to establish a partnership with the Center for Nanotechnology in Society, University of California, Santa Barbara (CNS-UCSB), which is supported by the National Science Foundation cooperative agreement #SES-0531184. Barbara Herr Harthorn, director of CNS-UCSB, generously offered to provide assistance in distributing the completed case studies through the CNS network. The Chemical Heritage Foundation is grateful for this unique opportunity that allows us to spread the results of our project more broadly.

HYUNGSUB CHOI

MANAGER OF INNOVATION AND EMERGING TECHNOLOGIES
CENTER FOR CONTEMPORARY HISTORY AND POLICY
CHEMICAL HERITAGE FOUNDATION

About the Chemical Heritage Foundation

The Chemical Heritage Foundation (CHF) fosters an understanding of chemistry's impact on society. An independent nonprofit organization, we strive to

- Inspire a passion for chemistry;
- Highlight chemistry's role in meeting current social challenges; and
- Preserve the story of chemistry across centuries.

CHF maintains major collections of instruments, fine art, photographs, papers, and books. We host conferences and lectures, support research, offer fellowships, and produce educational materials. Our museum and public programs explore subjects ranging from alchemy to nanotechnology.

About CHF's Center for Contemporary History and Policy

The Center for Contemporary History and Policy offers historically grounded perspectives on issues related to the molecular sciences and technologies. The center's programmatic initiatives draw on diverse historical and contemporary source materials to provide knowledge, perspective, and advice to stakeholders from industry, academia, government, and citizen groups.

About the series

Studies in Materials Innovation examines the dynamic process of conception, development, manufacturing, marketing, and regulation of new materials innovations in the contemporary world. Each case study in the series will focus on a particular materials innovation based on in-depth research, making explicit the lessons for researchers, research managers, and policy makers.

About the author

Doogab Yi is a Stetten Fellow at the Office of History, National Institutes of Health. He is working on a book on the history of recombinant-DNA research and technology at Stanford University. His research interests include the history of biomedical sciences and technologies and the commercialization of science in the latter half of the 20th century.



Chemical Heritage Foundation

LIBRARY • MUSEUM • CENTER FOR SCHOLARS

315 Chestnut Street • Philadelphia, PA 19106-2702

We tell the story of chemistry.