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History of the Polymerase Chain Reaction
Videohistory Collection, 1992-1993

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Collection Overview

Repository:	Smithsonian Institution Archives, Washington, D.C., osiaref@si.edu
Title:	History of the Polymerase Chain Reaction Videohistory Collection
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Administrative Information

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Historical Note

The Polymerase Chain Reaction (PCR) technique, invented in 1985 by Kary B. Mullis, allowed scientists to make millions of copies of a scarce sample of DNA. The technique has revolutionized many aspects of current research, including the diagnosis of genetic defects and the detection of the AIDS virus in human cells. The technique is also used by criminologists to link specific persons to samples of blood or hair via DNA comparison. PCR also affected evolutionary studies because large quantities of DNA can be manufactured from fossils containing but trace amounts.

Kary Mullis invented the PCR technique in 1985 while working as a chemist at the Cetus Corporation, a biotechnology firm in Emeryville, California. The procedure requires placing a small amount of the DNA containing the desired gene into a test tube. A large batch of loose nucleotides, which link into exact copies of the original gene, is also added to the tube. A pair of synthesized short DNA segments, that match segments on each side of the desired gene, is added. These "primers" find the right portion of the DNA, and serve as starting points for DNA copying. When the enzyme Taq DNA Polymerase from the bacterium, *Thermus aquaticus* is added, the loose nucleotides lock into a DNA sequence dictated by the sequence of that target gene located between the two primers.

The test tube is heated, and the DNA's double helix separates into two strands. The DNA sequence of each strand of the helix is thus exposed and as the temperature is lowered the primers automatically bind to their complementary portions of the DNA sample. At the same time, the enzyme links the loose nucleotides to the primer and to each of the separated DNA strands in the appropriate sequence. The complete reaction, which takes approximately five minutes, results in two double helices containing the desired portion of the original. The heating and cooling is repeated, doubling the number of DNA copies. After thirty to forty cycles are completed a single copy of a piece of DNA can be multiplied to hundreds of millions.

When completed manually, Mullis' PCR technique was slow and labor-intensive. Therefore, Cetus scientists began looking for ways in which to automate the process. Before the discovery of the thermostable Taq enzyme, scientists needed to add fresh enzyme to each cycle. The first thermocycling machine, "Mr. Cycle" was developed by Cetus engineers to address that need to add fresh enzyme to each test tube after the heating and cooling process. Purification of the Taq polymerase then resulted in the need for a machine to cycle more rapidly among different temperatures. In 1985, Cetus formed a joint venture with the Perkin-Elmer Corporation in Norwalk, Connecticut, and introduced the DNA Thermal Cycler. By 1988, Cetus was receiving numerous inquiries about licensing to perform PCR for commercial diagnostic purposes. On January 15, 1989, Cetus announced an agreement to collaborate with Hoffman-LaRoche on the development and commercialization of in vitro human diagnostic products and services based on PCR technology. Roche Molecular Systems eventually bought the PCR patent and associated technology from Cetus for \$300,000,000.

Interviewees included scientists, engineers, and managers from Cetus Corporation, Roche Molecular Systems, and Perkin-Elmer Corporation. Norman Arnheim first became interested in the study of medicine in high school, as the result of a summer spent working at a hospital. He received his B.A. (1960) and M.A. (1962) from the University of Rochester, and his Ph.D. (1966) in *Drosophila* genetics from the University of California, Berkeley. A professor of molecular biology at the University of Southern California, Arnheim formerly worked at Cetus Corporation on PCR. John G. Atwood came to Perkin-Elmer Corporation in November 1948 with a masters' degree in electrical engineering from Columbia University (1948), and served as senior scientist for the biotechnology instrument group.

Peter Barrett received a B.S. in Chemistry from Lowell Technological Institute and a Ph.D. in Analytical Chemistry from Northeastern University. He joined Perkin-Elmer in 1970 as product specialist in the Instrument Division, was promoted to manager of the Applications Laboratory in 1982, and director of the Laboratory Robotics Department in 1985. In 1988, Barrett was named director of European Marketing and relocated to Italy. In 1989, he moved to Germany to set up the European Sales and Service Center. He returned to the U.S. in 1990 to serve as Division Vice-President of Instruments and was named Vice-President of the Life Sciences Division in 1991. In 1993, in conjunction with the merger with Applied Biosystems Incorporated, he moved to California to become Executive Vice-President, Applied Biosystems Division.

Joseph L. DiCesare received his Ph.D. in Biochemistry from the University of Rhode Island. In 1976, he accepted the position of Assistant Product Line Manager at Perkin-Elmer Corporation and was appointed Product Line Manager of the Gas Chromatography Division in 1983. In 1987, he was promoted to the position of Research and Development Applications Manager of the Biotechnology Division. Henry Anthony Erlich received his B.A. in biochemical sciences from Harvard University in 1965 and his Ph.D. in genetics from University of Washington in 1972. He served as a postdoctoral fellow in the Department of Biology at Princeton University from 1972 to 1975 and in the Department of Medicine at Stanford University from 1975 to 1979. He joined the Cetus Corporation in 1979 and was appointed Senior Scientist and Director of Human Genetics in 1981. After the dissolution of Cetus in 1991, Erlich transferred to Roche Molecular Systems to serve as director of Human Genetics.

A few years after graduating from high school, Fred Faloona began working as a research assistant under Kary B. Mullis at the Cetus Corporation, c. 1983. He assisted Mullis with the initial development and application of PCR. He followed Mullis to Xytronyx Incorporated in 1986 where he served as a Research associate working on DNA and RNA sequencing and further applications of PCR. In 1988, he returned to Cetus as a research assistant where he worked on the application of PCR to the discovery of new retroviruses and he further refined PCR detection techniques. In 1991, Faloona and a partner began Saddle Point System, a small company designing computer hardware and software.

David H. Gelfand completed his B.A. in Biology at Brandeis University in 1966. After receiving a Ph.D. in Biology from the University of California, San Diego in 1970, he began work as an assistant research biochemist at the University of California in San Francisco. He was offered the position of Director of Recombinant Molecular Research at Cetus in 1976 and was promoted to Vice-President of that division in

1979. He later accepted positions as Vice-President of Scientific Affairs and Director of Core Technology, PCR Division, in 1981 and 1988. In 1991, Gelfand also transferred to Roche Molecular Systems to serve as Director for the Program in Core Research.

Lawrence Allen Haff received his B.S. in Biochemistry from Michigan State University in 1969. After completing his Ph.D. in Biochemistry from Cornell University in 1974, Haff served as a research fellow in the biological laboratories of Harvard University. In 1976, he accepted the position of Senior Research Scientist at Pharmacia. He transferred to Millipore Corporation in 1982 to serve as Technical Research Manager developing and supporting high performance separation techniques. He joined the Perkin-Elmer Corporation in 1985 as principal scientist and research manager to help develop the DNA Thermal Cycler.

After receiving his B.S. in mechanical engineering from the University of California-Davis in 1978, David C. Jones worked as a stress engineer for the Boeing Commercial Aircraft Company. In 1980, he joined the Bio-Rad Laboratories designing and developing chromatography instruments. He accepted the position of Mechanical Engineer at Cetus Corporation in 1986 to work on thermocycling instrumentation. He also completed an M.B.A. in management from Golden State University in 1988.

Elena D. Katz was awarded her M.S. degree in Chemistry from Moscow University, Russia. From 1969 to 1972, she studied in the Ph.D. program at the Institute of Physical Chemistry of the Academy of Sciences in Moscow. In 1973, she was appointed Associate Researcher in the physical chemistry department of Moscow University. After moving to the United States, Katz became Senior Staff Scientist at Perkin-Elmer in 1977 working on various multidisciplinary projects utilizing liquid and gas chromatography. After 1985, Katz concurrently pursued a Ph.D. in Chemistry from the University of London. Shirley Kwok began her career as a research associate with the Assay Department of Cetus Corporation after graduating from the University of California, Berkeley, with a degree in microbiology. Kwok was part of a group of researchers devoted to the use of PCR to detect HIV in human cells, and held the position of Research Investigator for Hoffman-La Roche at Roche Molecular Systems.

Richard Leath started with Cetus in 1980, after receiving a masters' degree in electrical engineering from Purdue University in 1974. Leath spent a decade developing machines like Mr. Cycle, and later worked as Senior Engineer at Maxwell Labs, Richmond, California, a firm which developed particle accelerators.

Kary B. Mullis received his B.S. in Chemistry from the Georgia Institute of Technology in 1966 and his Ph.D. in Biochemistry from the University of California-Berkeley in 1972. In 1973, he was awarded a post-doctoral fellowship in pediatric cardiology at the University of Kansas Medical School. He returned to California in 1977 and was awarded another fellowship in pharmaceutical chemistry from the University of California, San Francisco to research endorphins and the opiate receptor. He accepted the position of Scientist at Cetus in 1979 to work in the chemistry department researching oligonucleotide synthesis and chemistry. He transferred to the Department of Human Genetics in 1984 to conduct research on DNA technology. In 1986, Mullis accepted the position of Director of Molecular Biology at Xytronyx, Inc. researching DNA technology, photochemistry, and photobiology. He left Xytronyx in 1988 and then served as a private consultant to a variety of companies in the field of nucleic chemistry. Mullis won the Nobel Prize in chemistry in 1993 for his invention of the PCR technique.

Lynn H. Pasahow graduated from Stanford University in 1969 and received his law degree from the University of California at Berkeley School of Law in 1972. He joined the firm of McCutchen, Doyle, Brown, and Enersen in 1973, where he chaired the firm's intellectual property group. He had advised clients and handled complex litigation involving patent, copyright, trademark, trade secret, licensing, export-import, noncompetition, and trade regulation disputes, most involving biotechnology, computer hardware and software and other advanced technology products. He led the group of lawyers which successfully obtained a jury verdict upholding Cetus' landmark polymerase chain reaction patents against the Dupont Company challenge. Enrico Picozza began work with Perkin-Elmer in June 1985, shortly after receiving his degree from the University of Connecticut. He was a Senior Technical Specialist, devoted to specifying, developing, testing and evaluating instrumentation primarily for the PCR market.

Riccardo Pigliucci earned his degree in chemistry in Milan, Italy and graduated from the Management Program at the Northeastern University. He joined Perkin-Elmer in 1966 and held numerous management positions in analytical instrument operations in Europe as well as in the U.S. He was appointed General Manager of the U.S. Instrument Division in 1989 after serving as director of Worldwide Instrument Marketing since 1985. In 1988, Pigliucci was appointed a sector Vice-President in Connecticut Operations. The following year, he was elected corporate Vice-President of Perkin-Elmer Instruments. He became President of the Instrument Group in 1991 and was named Senior Vice-President of Perkin-Elmer Corporation in 1992. In 1993, he was elected President and Chief Operating Officer and also served as a Director of the Corporation.

After receiving his bachelors degree in Chemistry and Biology from the University of Washington in 1978, Randall K. Saiki served one year as a laboratory technician in their Department of Microbiology. In 1979, he transferred to Washington University to serve as a lab technician in the Biology Department. He joined the Cetus Corporation in late 1979 as a research assistant in the Recombinant DNA Group. In 1981, he was promoted to Research Associate in the Department of Human Genetics and was named Scientist in that department in 1989. Saiki transferred to Roche Molecular Systems in 1991 to serve as Research Investigator in the Department of Human Genetics. Stephen Scharf received a degree in bacteriology from University of California, Davis. He worked there as a biochemist for four and a half years until 1980, when he came to Cetus. Scharf was a Research Associate in the Department of Human Genetics at Cetus at the time PCR was developed and later served as Senior Scientist at Roche Molecular Systems.

Donna Marie Seyfried graduated from Lehigh University with a B.S. in Microbiology. Her professional career began as a microbiologist for the E.I. Dupont de Nemours Company. Seyfried joined Perkin-Elmer in 1985. From 1990 to 1993, she served as Business Director for Biotechnology Instrument Systems. In 1994, she was appointed Director of Corporate Business Development and Strategic Planning. She was responsible for managing the development, commercialization, and marketing of the PCR business as part of the Perkin-Elmer Cetus JointVenture, and the subsequent strategic alliance with Hoffman-LaRoche. She was also instrumental in the Perkin-Elmer Applied Biosystems merger.

After receiving his B.S. from Bates College in 1972 and his Ph.D. from Purdue University in 1976, John J. Sninsky accepted a postdoctoral fellowship from the Departments of Genetics and Medicine at the Stanford University School of Medicine. In 1981, he accepted an assistant professorship at the Albert Einstein College of Medicine. He joined the Cetus Corporation in 1984 as a Senior Scientist in the Department of Microbial Genetics. In 1985, he was appointed Director of the Diagnostics Program and of the Department of Infectious Diseases. In 1988, he was promoted to Senior Director of both of those departments. Sninsky transferred to Roche Molecular Systems in 1991 to serve as Senior Director for Research. Robert Watson, who joined Cetus in 1977, was a Research Investigator with Roche Molecular Systems, working on nucleic acid-based diagnostics.

Thomas J. White graduated from John Hopkins University in 1967 with a B.A. in Chemistry. After serving for four years as a Peace Corps volunteer in Liberia, he received his Ph.D. in Biochemistry from the University of California, Berkeley in 1976. In 1978, he joined the Cetus Corporation as a scientist, and was promoted to Director of Molecular and Biological Research and Associate Director of Research and Development in 1981. He was appointed Vice-President of Research in 1984. He transferred to Roche Diagnostics Research in 1989 to serve as Senior Director and in 1991 was appointed Vice-President of Research and Development of Roche Molecular Systems and Associate Vice-President of Hoffman-LaRoche, Incorporated. Joseph Widunas, who graduated from the University of Illinois with a degree in engineering in 1975, came to Cetus in 1981 as a sound engineer. Later, as Director of new product development for Colestech Corporation, Hayward, California, he was instrumental in the development of the second Mr. Cycle prototype, "Son of Mr. Cycle."

Timothy M. Woudenberg received his B.S. in Chemistry from Purdue University in 1980. He worked as an electronics design engineer for Mulab Incorporated from 1980 to 1982. He served as a teaching and research assistant at Tufts University from 1982 to 1987 and there completed his Ph.D. in Physical

Chemistry in 1988. He joined Perkin-Elmer in 1987 as an engineer in the Instrument Division of the Biotechnology Department.

Also interviewed were Perkin-Elmer's Robert P. Regusa, biotechnology systems engineering manager for the biotechnology group responsible for the development of the thermocycler instrumentation; Robert L. Grossman, an engineer at Perkin-Elmer, involved with the design and manufacture of the thermocycler line; Senior Marketing Specialist Leslie S. Kelley; as well as Cetus' Senior Scientist, Richard Respass.

Introduction

The Smithsonian Videohistory Program, funded by the Alfred P. Sloan Foundation from 1986 until 1992, used video in historical research. Additional collections have been added since the grant project ended. Videohistory uses the video camera as a historical research tool to record moving visual information. Video works best in historical research when recording people at work in environments, explaining artifacts, demonstrating process, or in group discussion. The experimental program recorded projects that reflected the Institution's concern with the conduct of contemporary science and technology.

Smithsonian historians participated in the program to document visual aspects of their on-going historical research. Projects covered topics in the physical and biological sciences as well as in technological design and manufacture. To capture site, process, and interaction most effectively, projects were taped in offices, factories, quarries, laboratories, observatories, and museums. Resulting footage was duplicated, transcribed, and deposited in the Smithsonian Institution Archives for scholarship, education, and exhibition. The collection is open to qualified researchers.

Descriptive Entry

Ramunas Kondratas, curator at the Smithsonian's National Museum of American History (NMAH), documented the discovery, development, commercialization, and applications of PCR technology. Three sessions were recorded May 14 and May 15, 1992 at Emeryville, California; September 25, 1992 at Alameda, California; and February 25, 1993 at Norwalk, Connecticut.

This collection consists of three interview sessions, totalling approximately 19:00 hours of recordings and 346 pages of transcript.

Several participants were also interviewed on audiotape. The audiotapes and transcripts complement the videotape sessions and are available through the Division of Medical Science, National Museum of American History.

Names and Subject Terms

This collection is indexed in the online catalog of the Smithsonian Institution under the following terms:

Subjects:

- Bioengineering
- Biotechnology
- DNA thermal cycler
- Interviews

Molecular biology
Oral history
Patents
Polymerase chain reaction
Science -- History
Scientific apparatus and instruments
Technology -- History

Types of Materials:

Transcripts
Videotapes

Names:

Arnheim, Norman
Atwood, John G.
Barrett, Peter
Cetus Corporation
DiCesare, Joseph L.
Erlich, Henry Anthony
Faloona, Fred
Gefland, David H.
Grossman, Robert L.
Haff, Lawrence Allen
Hoffman-La Roche Corporation
Jones, David C.
Katz, Elena D.
Kelley, Lesley S.
Kondratas, Ramunas A., interviewer
Kwok, Shirley
Leath, Richard
Mullis, Kary B.
Pasahow, Lynn H.
Perkin-Elmer Corporation
Picozza, Enrico
Pigliucci, Riccardo
Regusa, Robert P.
Roche Molecular Systems
Saiki, Randall K.
Scharf, Stephen
Seyfried, Donna Marie
Sninsky, John J.
Watson, Robert
White, Thomas J.
Widunas, Joseph
Woudenberg, Timothy M.

Container Listing

Interviews

Interviews

Session 1: May 14-15, 1992

Interviews

Was recorded at Cetus Corporation, Emeryville, California. Kwok, Sninsky, Saiki, Scharf, Leath, Widunas, Jones, Watson, Respass, Erlich, Gelfand, Mullis and Faloona discussed the invention of the PCR technique, early applications, and development of technologies for automating the process, c. 1980-1992, including: Participants' biographical data; application of the PCR technique to the diagnosis and study of HIV and AIDS; invention of the PCR technique; introduction of the thermostable enzyme Taq DNA Polymerase from the bacterium *Thermus aquaticus* to the PCR technique; design and engineering of automated thermocycling machines; publicizing the invention of PCR; use of PCR for genetics research; development of commercial thermocycling instruments; Cetus' work environment; sale of PCR patent to Hoffman-LaRoche; use of PCR in forensics; and patenting PCR. Visual documentation included: Operations of Mr. Cycle, the first generation cycling machine; peltier device; demonstrations of the second- and third-generation thermocycling machines; Perkin-Elmer TC 4800 and 9600 thermocyclers; demonstration of the gel electrophoresis process using the TPCR 9600; Mullis diagramming the PCR process; gel from first successful experiment; Mullis' PCR lecture slides; and Cetus mural.

Interviews

Transcript, pp 1-156, of videotape recording, 8 hours.

Interviews

Video Recordings of Interviews: Total Recording Time: 8.0 hours

Note:

- Original Masters: 16 Beta videotapes
- Preservation Masters: 16 Motion jpeg 2000 and 16 mpeg digital files
- Dubbing Masters: 8 U-Matic videotapes
- Reference Copies: 4 VHS videotapes, 8 Windows Media Video and 8 Real Media digital files

Interviews

Session 2: September 25, 1992

Interviews

Was recorded at Roche Molecular Systems, Alameda, California. White, Arnheim, Erlich, and Pasahow discussed the invention of PCR, patent rights, the development of PCR at Cetus, and PCR applications, c. 1980-1992, including: Participants' biographical data; transition of PCR technology from Cetus to Roche Molecular Systems; invention and validation of the PCR technique; diagnostic applications; participants' working relationship with Kary Mullis; laboratory culture at Cetus; and litigation between Cetus and Dupont Company. Visual documentation included: PCR publications; exterior of Roche Molecular Systems facility.

- Interviews Transcript, pp 1-96, of videotape recording, 5 hours.
- Interviews Video Recordings of Interviews: Total Recording Time: 5.0 hours
Note:
- Original Masters: 10 Beta videotapes
 - Preservation Masters: 10 Motion jpeg 2000 and 10 mpeg digital files
 - Dubbing Masters: 5 U-Matic videotapes
 - Reference Copies: 3 VHS videotapes, 5 Windows Media Video and 5 Real Media digital files
- Interviews **Session 3: February 25, 1993**
- Interviews Was recorded at Perkin-Elmer Corporation, Norwalk, Connecticut. Picozza, Haff, DiCesare, Katz, Seyfried, Barrett, Atwood, Pigliucci, Regusa, Grossman, and Woudenberg discussed the joint venture with Cetus, the design and engineering of commercial thermocyclers, marketing, and future applications, c. 1980-1993, including: Participants' biographical data; thermocycler development to the current 9600 model; military and forensic use of PCR; current research on new developments in PCR including high performance chromatography and electrochemiluminescence; hardware and software development for PCR instruments; and design and machinery of PCR instrumentation. Visual documentation included: Tour of Biotech Engineering and Biotech Chemistry laboratories; shipping facility and distribution warehouse; various PCR advertising campaigns, Perkin-Elmer newsletter, and *PCR Journal*; demonstration of the parts of the TC Model 4800 and 9600; and tour of the manufacturing areas including machining center, printed circuit assembly area, electronic test area, sheet metal area, and paint area.
- Interviews Transcript, pp 1-94, of videotape recording, 6 hours.
- Interviews Video Recordings of Interviews: Total Recording Time: 6 hours
Note:
- Original Masters: 12 Beta videotapes
 - Preservation Masters: 12 Motion jpeg 2000 and 12 mpeg digital files
 - Dubbing Masters: 6 U-Matic videotapes
 - Reference Copies: 4 VHS videotapes, 6 Windows Media Video and 6 Real Media digital files