

Paul Berg

Genetic Engineering Pioneer Passes Away

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Paul Berg (1926–2023)



Paul Berg with his wife Mildred Levy at Pennsylvania State University

Genetic engineering is today associated with every facet of human life. Be it the food we consume, the medicine we take or even in the production of gene-edited plants and animals, including humans. Many medicines including insulin and vaccines available in the market are products of genetic engineering.

Genetic engineering is the process of modifying an organism's DNA or genetic material to introduce new traits or characteristics. This is usually done through various techniques, such as inserting, deleting, or altering specific genes within an organism's genome. And this became possible because of a landmark discovery by Paul Berg, a Nobel Prize-winning biochemist who ushered in a new era of genetic engineering in 1971.

The breakthrough discovery was the first in a series of breakthroughs that have led to the genetic engineering of

novel therapeutic therapies for diseases and vaccinations, such as the messenger RNA versions used to combat the virus that causes Covid-19.

Paul Berg was born on 30 June 1926, in New York City, United States. He grew up in Brooklyn and was the son of Harry Berg and Sarah Brodsky — Jewish immigrants from Eastern Europe. Berg's father was a printer also involved in the labour movement, while his mother was a housewife. Berg was the youngest of three children and attended the Abraham Lincoln High School in Brooklyn.

As a child, Berg was interested in science and liked to read books about nature and animals. He was also good at music and played the clarinet in the marching band in his school. By the time he was in junior high school, he had a strong desire to become a scientist.

Arrowsmith by Sinclair Lewis and *Microbe Hunters* by Paul DeKruif, two books he read, helped fuel this desire. In his Nobel autobiography, he credited Sophie Wolfe, the lab technician at the Abraham Lincoln High School, with firing his passion for discovery. She ran a popular after-school biology club. “Rather than answering questions we asked, she encouraged us to seek solutions for ourselves, which most often turned into mini research projects. Sometimes that involved experiments in the small lab she kept, but sometimes it meant going to the library to find the answers.

“The satisfaction derived from solving a problem with an experiment was a very heady experience, almost addicting,” he continues. “Looking back, I realise that nurturing curiosity and the instinct to seek solutions are perhaps the most important contributions education can make. With time, many of the facts I learned were forgotten, but I never lost the excitement of discovery.”

Two others who attended the school in the same decade also won Nobel prizes: Berg’s mentor and colleague Arthur Kornberg, and crystallographer Jerome Karle.

Berg joined the US Navy after high school, during World War II. In 1947, Berg married his friend Mildred Levy, a nurse, amateur musician and supporter of nature conservation, and a year later their son, John Alexander, was born. While he was waiting for his Navy training, he was able to take biochemistry lessons at Penn State University.

After the war, Berg went back to Penn State and got a degree in biology in 1948. Then, he went to graduate school



Arthur Kornberg (left) and Paul Berg (right)

at Western Reserve University, now called Case Western Reserve University, in Cleveland, Ohio. In 1952, under the guidance of Prof. Harland Wood, he earned a PhD in biochemistry. He did his undergrad work on enzymes. He made a big step forward when he found out that vitamin B12 and folic acid are needed for a process called “one-carbon metabolism” which happens in mitochondria and cytoplasm and makes it possible for cells to do many things.

After PhD, he spent his postdoc years first with Herman Kalckar at the Institute of Cytophysiology in Copenhagen, Denmark, and then with Arthur Kornberg at the National Institutes of Health (NIH) in Bethesda, Maryland.

In 1959, he joined the burgeoning biochemistry department at Stanford University, which served as his primary research base for the remainder of his career. He held numerous positions at the university, including department chairman for five years in the early 1970s and director of the Beckman Centre for Molecular and Genetic Medicine from 1985 to 2000, until he retired as the emeritus professor.

Paul shifted his focus from pure biochemistry to mammalian virology in the 1960s. He spent his sabbatical at the Salk Institute in the virology laboratory of Renato Dulbecco, where he learned cell culture techniques from Marguerite Vogt. Together, he and his longstanding research assistant Marianne Dieckmann learned how to work with simian virus 40 (SV40), which contains DNA and causes cancer. As the enzymology of DNA manipulation became available in the early 1970s, Paul recognised that the DNA of SV40 and the DNA of bacteria or bacterial viruses could be combined to produce hybrids or chimeric molecules, subsequently referred to as recombinant molecules.

Berg’s 1971 seminal gene-splicing experiment involved splicing a portion of the DNA of the lambda bacterial virus into the DNA of the monkey-hosting simian virus SV40.



Harland Wood (left) and Paul Berg (right)



Both of these viruses' DNA consist of closed loops. In the first phase of Berg's experiment, each loop was cut at a single location by the enzyme EcoRI. In order to reconnect the ends of these now-linear molecules, they were modified by two additional enzymes using a technique devised by Stanford colleagues. Then, the two forms of DNA were combined where they joined into loops, creating new loops that contained DNA from both sources. This work was published in the *Proceedings of the National Academy of Sciences* journal in 1972.

Berg's gene-splicing operation produced the first human-made recombinant DNA (rDNA), which was previously thought to exist only in science fiction. Recombinant DNA methods rapidly spread throughout biology, creating a new revolution in biological science. The techniques became the basis of the biotechnology industry, marking the beginning of genetic engineering.

In 1980, Berg was awarded one-half of the Nobel Prize in Chemistry, along with Walter Gilbert and Frederick Sanger, "for his fundamental studies of the biochemistry of nucleic acids, with a focus on recombinant DNA".

Berg did not immediately introduce the rDNA into another organism due to the controversy surrounding the possible hazards of such an experiment. Medical ethicists questioned whether Dr Berg's creation of what became known as recombinant DNA constituted interference with the natural order.

Officials in the field of public health and others pondered whether exchanging DNA could create new diseases or unleash environmental disasters. It was feared that rDNA carrying a dreaded gene, such as the one responsible for the formation of cancerous tumours, could escape the laboratory in common bacteria and proliferate worldwide.

Even Dr Berg was concerned. He stopped working with SV40 and *E. coli* because he felt worried about splicing the DNA of a disease-causing virus with a common intestinal bacteria. In a 1974 letter co-signed by Dr Berg and 10 other researchers and published in science, they expressed "serious concern that some of these artificial recombinant DNA molecules could prove biologically hazardous". Scientists from around the world were urged to get together in the open letter to "deal with the potential biohazards of recombinant DNA molecules".

The Asilomar Conference on Recombinant DNA was held as a direct result of this in 1975 in California. Over 140 scientists from all around the globe attended the meeting. Limits on the sorts of genes utilised and protections to keep recombinant DNA contained in laboratories were part of the overarching principles to which they agreed. The National Institutes of Health and other international health regulatory agencies approved the Asilomar Conference Centre recommendations in 1976. These restrictions have been loosened over time as it has become clear that the risks are significantly lower than initially thought.

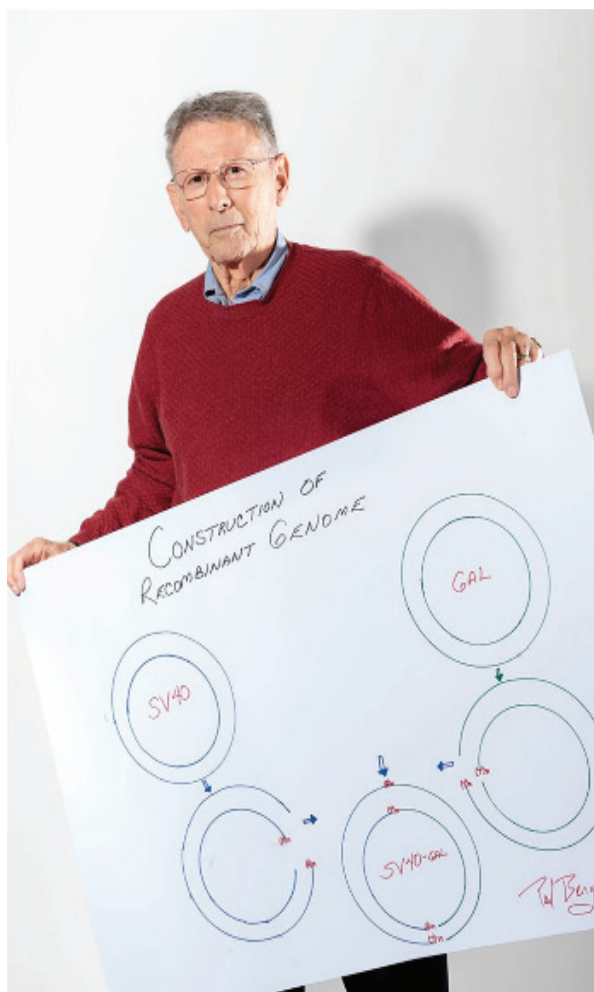
Like many other geneticists, Berg established linkages between academic and industrial researchers. In 1980, he co-founded DNAX, a biotechnology research institute



Asilomar Conference on Recombinant DNA. (Left to right) Maxine Singer, Norton Zinder, Sydney Brenner, and Paul Berg
(Photo credit: National Academy of Sciences)

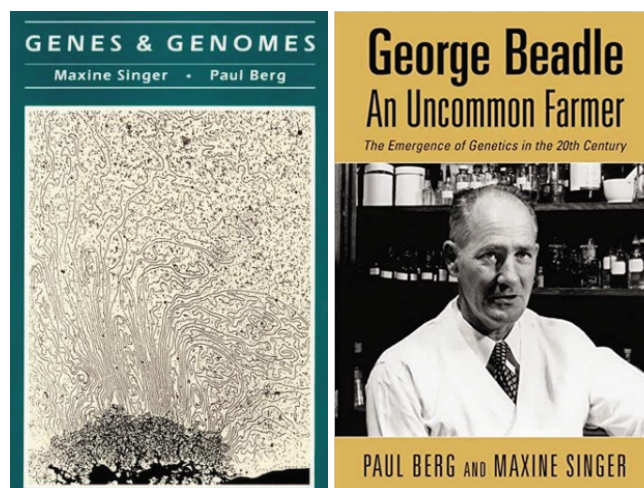
with Arthur Kornberg and Charles Yanofsky. The initial focus of DNAX's research was to design immunoglobulins (immune system antibodies) with unique properties using rDNA. After Schering-Plough acquired the institute, research shifted to producing interleukins (immune system components that are not antibodies) using an expressive cloning system devised in Berg's laboratory. Since its founding, DNAX has become one of the foremost immunology research institutions.

In addition to the 1980 Nobel Prize, Berg received Eli Lilly Award in Biological Chemistry in 1959, Albert Lasker Basic Medical Research Award in 1980 and the National Medal of Science in 1983. In addition, he was



Paul Berg with his "Sketch of Science"

elected to the National Academy of Sciences in 1966, the American Philosophical Society in 1983, the Royal Society in 1992, and received four honorary doctorates. A gifted teacher, he also received the Stanford University School of Medicine's Henry J Kaiser award in 1969 and again in 1973.



Dr Berg has published over 200 scientific articles, and with molecular biologist Maxine Singer, has written several popular science books on genetics like *Genes and Genome* (1991); *Dealing With Genes: The Language of Heredity* (1992); and *George Beadle: An Uncommon Farmer* (2003).

Berg always argued that scientists should talk about the role of science in society more. He was a consistent proponent of the function of basic science in medical student education. He instructed students and postdoctoral associates, all of whom remained loyal to him. Berg's open mind kept him in touch with his students. If students came up with ideas that seemed unjustified at first, he would ask them to investigate further, allowing them to achieve scientific independence. He was confident they would succeed if there was a creative spark.

At Stanford, he founded and directed the Beckman Centre for Molecular and Genetic Medicine, for which he raised substantial funds. He resided in a house on campus and enthusiastically participated in university life.

Berg was always dedicated to sharing research space as well as scientific findings. He refused to patent his discoveries and provided information ahead of publication, which is unusual in an often-secretive area. Berg described himself as a science purist, noting that in his formative years, "you did science because you loved it".

He followed his passion and explored new areas that no one had touched. With Paul's death, science has lost one of its strongest, most humane, and most accomplished scientist and a teacher.

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