Arthur Kornberg's Discovery of DNA Polymerase I

Enzymatic Synthesis of Deoxyribonucleic Acid. I. Preparation of Substrates and Partial Purification of an Enzyme from *Escherichia coli*

Enzymatic Synthesis of Deoxyribonucleic Acid. II. General Properties of the Reaction

Arthur Kornberg was born in Brooklyn, New York in 1918 and was educated in its public schools. He received his undergraduate degree in science from the City College of New York in 1937 and an M.D. degree from the University of Rochester in 1941. After a 1-year internship in internal medicine, he served as a commissioned officer in the U. S. Public Health Service. He was first assigned to the Navy as a ship’s doctor and then as a research scientist at the National Institutes of Health (NIH) in Bethesda, Maryland, from 1942 to 1953. He obtained training in enzymology with Severo Ochoa at New York University School of Medicine in 1946 and with Carl Cori at Washington University School of Medicine in 1947. Both Ochoa and Cori were authors of *Journal of Biological Chemistry* (JBC) Classics (1, 2), and additional information on Kornberg’s research in these laboratories can be found in his JBC Reflections (3).

Upon returning to Bethesda, Kornberg organized and directed the Enzyme Section at the NIH. He resigned in 1953 with the rank of Medical Director to assume the chairmanship of the Department of Microbiology at the Washington University School of Medicine in St. Louis, Missouri. In 1959, he organized the Department of Biochemistry at the Stanford University School of Medicine, serving as its chairman until 1969 and thereafter as professor. He accepted the title of Professor Emeritus in 1988 and has been on active status to the present.

From his early studies of the mechanisms of the enzymatic synthesis of coenzymes and inorganic pyrophosphate, Kornberg extended his interest to the biosynthesis of the nucleic acids, particularly DNA. After elucidating key steps in the pathways of pyrimidine and purine nucleotide synthesis, including the discovery of 5’-phosphoribosyl-1-pyrophosphate (PRPP) as an intermediate, he found the enzyme that assembles the building blocks into DNA, named DNA polymerase. This is the subject of the two JBC Classics reprinted here. Earlier, Kornberg’s group had discovered an enzyme system in *Escherichia coli* extracts that catalyzed the incorporation of deoxyribonucleotides into DNA. Joined by two postdoctoral fellows, Maurice J. Bessman and Robert I. Lehman, and his technician, Ernest S. Simms, Kornberg set about purifying the active enzyme from the extracts and elucidating the properties of the DNA synthesis system. In the first Classic, Kornberg and his colleagues describe the purification of DNA polymerase from *E. coli*. In the second Classic, they report that polymerized DNA, Mg$^{2+}$, and all four deoxynucleoside triphosphates (adenine, guanine, cytosine, and thymine) are needed for DNA synthesis to occur. From these requirements, they hypothesized that the polymerized DNA was serving as a template to guide the formation of new DNA.

These two Classics were declined by the JBC when submitted in the fall of 1957. Among the critical comments were: “It is very doubtful that the authors are entitled to speak of the enzymatic synthesis of DNA”; “Polymerase is a poor name”; “Perhaps as important as the elimination of certain banalities . . .” etc. Through the fortunate intervention of John Edsall,
who had just assumed the position of Editor-in-Chief in May 1958, the two papers were eventually accepted and appeared in the July 1958 issue. A more in-depth account of the discovery of DNA polymerase can be found in Lehman’s JBC Reflections (4). One year after these Classics were published, Kornberg was awarded the Nobel Prize in Physiology or Medicine with Ochoa “for their discovery of the mechanisms in the biological synthesis of ribonucleic acid and deoxyribonucleic acid.”

Continuing his work on DNA synthesis, Kornberg was eventually able to get DNA polymerase to assemble a 5000-nucleotide DNA chain with the identical form, composition, and genetic activity as DNA from a natural virus. This successful synthesis of the biologically active φX174 virus in 1967 was the first time a biochemist produced an active virus in the lab. Kornberg’s additional work concerning DNA synthesis includes the elucidation of the proof-reading and editing functions of DNA polymerase and the discovery of single-strand binding protein, primase, and DNA polymerase III holoenzyme. Later, Kornberg switched his research focus from DNA replication to inorganic polyphosphate (poly(P)), a polymer of phosphates that likely participated in prebiotic evolution and is now found in every bacterial, plant, and animal cell. Kornberg has found a variety of significant functions for poly(P), once neglected and long regarded a molecular fossil, that include responses to stresses and stringencies and factors responsible for motility and virulence in some of the major pathogens.


In his academic career, Kornberg has served as departmental chairman, on the committees of the Medical School and university, as president of the American Society of Biological Chemistry (1965), and on the advisory boards and councils of numerous university, governmental, and industrial research institutes. He is a founder of the DNAX Research Institute of Molecular and Cellular Biology (a Division of Schering-Plough, Inc.) and a member of its Policy and Scientific Advisory Boards. He serves on the Scientific Advisory Boards of Regeneron.
Among Kornberg’s honors are memberships in the National Academy of Sciences, the Royal Society, American Philosophical Society, a number of honorary degrees, the Nobel Prize in Physiology or Medicine (1959), the National Medal of Science (1979), the Cosmos Club Award (1995), and other medals and awards.\(^1\)

The other authors of the two Classics, Lehman and Bessman, have also had distinguished research careers and remain active in research today. Lehman is currently Hume Professor Emeritus at the Stanford School of Medicine, Department of Biochemistry. He studies the enzymology of eukaryotic DNA replication and is an Associate Editor for the JBC. Some of his work will be featured in an upcoming JBC Classic. Bessman is at Johns Hopkins University where he is currently studying the Nudix hydrolase family of enzymes.

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REFERENCES


\(^1\) Biographical information on Arthur Kornberg was taken from Ref. 5.