TIMELINE

The eureka enzyme: the discovery of DNA polymerase

Errol C. Friedberg

Abstract | The identification and partial purification by Arthur Kornberg and his colleagues in 1956 of an enzyme — DNA polymerase I of *Escherichia coli* — that catalysed the stable incorporation of deoxyribonucleotides into DNA *in vitro* came as a surprise. At the time, most scientists in the field believed that DNA synthesis was too complicated to be accurately reflected outside the living cell.

The first DNA polymerase was discovered 50 years ago this year, just 3 years after the elucidation of the DNA structure by Watson and Crick. This finding was remarkable for many reasons, not least because many believed that it would not be possible to duplicate the exquisite genetic specificity that is required for DNA replication outside the intact cell. Here, I summarize events that led to the 'eureka' discovery of the enzyme DNA polymerase (TIMELINE), and how this finding opened the door for the discovery of many more such enzymes. With this historical bias in mind, this article focuses primarily on the initial detection, by Arthur Kornberg (FIG. 1) and his colleagues, of what became known as DNA polymerase I of *Escherichia coli*, and on some of the seminal events in Kornberg's scientific career that led to this discovery.

Arthur Kornberg — the early years

Few fundamental scientific discoveries revolved so entirely around the efforts of a single investigative team than that of the discovery of DNA polymerase by Arthur Kornberg and his colleagues. When he entered the University of Rochester Medical School in 1937, Kornberg had no explicit intention of becoming a biochemist. But, similar to many successful scientists, Kornberg was endowed with an essential characteristic that is fundamental to the pursuit of knowledge — a burning intellectual curiosity. When, during his introduction to pathology, he noted that his eyes were slightly jaundiced, Kornberg examined his classmates systematically and measured their (and his own) bilirubin levels, performing analyses "…on a borrowed bench, late at night and at weekends"[1]. In due course, he published his first contribution to the biomedical literature, documenting latent liver disease in medical students[2].

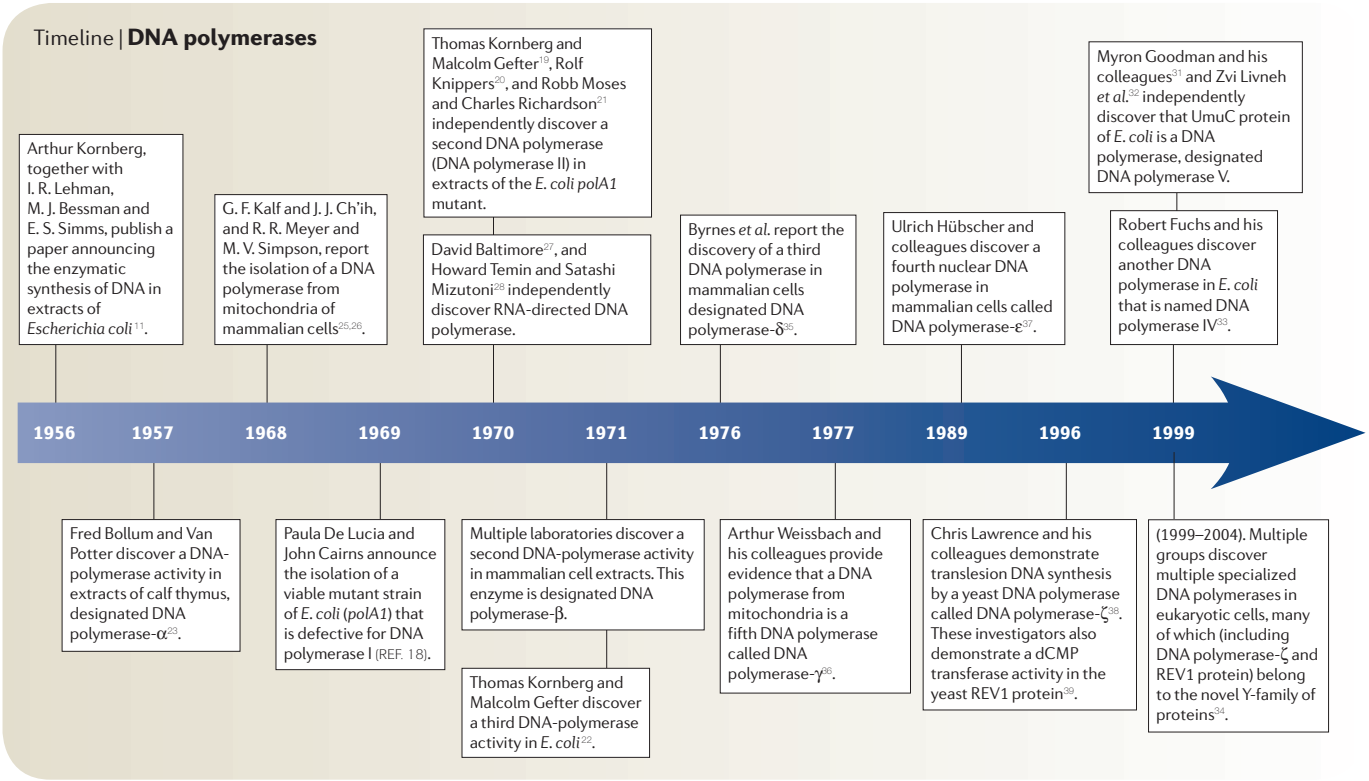
This initial foray into investigative medicine was to have far-reaching consequences for Kornberg's career. World War II was raging and jaundice among American troops who were inoculated against yellow fever was a matter of concern to the US Armed Forces. Shortly after he enlisted in the navy in August 1942, Kornberg's small study came to the attention of the Director of the National Institute of Health (NIH) and he was summarily transferred from sea duty to a research commission in Henry Sebrell's Nutrition Laboratory at the NIH. Now fully engaged as a bench scientist, Kornberg's intellectual horizons broadened to the point that he switched to Bernard Horecker's biochemistry laboratory to explore how ATP is generated during the oxidation of pyruvic acid. It was here that he began to hone his skills as an enzymologist — and to seek a career as a biochemist.

Kornberg soon became aware of the work of the young Spanish-born biochemist Severo Ochoa at New York University, who was "…doing the very kind of thing I hoped to do…"[1] He organized a one-year period of postdoctoral training with Ochoa, followed by an additional six months under the tutelage of Carl and Gerty Cori at Washington University, the 'father' and 'mother' of an entire generation of outstanding American biochemists. Following what Kornberg describes as perhaps the most memorable 18 months of his career, he returned to the NIH where Sebrell appointed him to a staff position and promoted the establishment of an Enzyme Section in the Nutrition Division at the NIH under the direction of Kornberg, Horecker and Leon Heppel[1,3].

Synthesizing nucleic acids *in vitro*

Watson and Crick's model of the structure of DNA and the celebrated concluding sentence in their 1953 *Nature* paper, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material,"[4] did not immediately take the scientific world by storm. Many in the scientific community remained unconvinced that DNA was the hereditary material in cells, and at least as many viewed Watson and Crick's model as nothing more than that — a model. But Kornberg was not among the sceptics. He was aware of the experiments by the famous phage group led by Max Delbrück and Salvador Luria, and of the challenging questions prompted by the observation that within a short time after infection of a bacterium with a single bacteriophage, hundreds of new phages, replete with new genomes, were released. With his new-found appreciation of the importance of enzymes in biosynthetic processes, Kornberg "…hoped eventually to find an enzyme that assembles the building blocks of DNA and RNA into nucleic acid chains"[1]. In 1950, he began investigating the biosynthesis of the nucleotide precursors for DNA synthesis, his formal entrée into nucleic-acid biochemistry.

In 1954, when he was just 35 years old, Kornberg was appointed chairman of the Department of Microbiology at Washington University in St Louis, Missouri, USA. It was here that he began a serious search for enzymes that catalyse the assembly of polynucleotide chains. Enzymatic biosynthesis had been demonstrated for other polymeric molecules, such as starch and lipids. Despite the prevailing view that the biosynthesis of DNA was beyond the pale of *in vitro* biochemistry[5], Kornberg held unrelenting faith in the fidelity with which biochemical



reactions in the living cells can be mirrored *in vitro*. "It always seemed to me", he wrote, "that a biochemist devoted to enzymes could, if persistent, reconstitute any metabolic event as well as the cell does it. In fact, better!"[1]

Together with postdoctoral fellow Uri Littauer, Kornberg observed that following the addition of radiolabelled ATP to extracts of *E. coli*, significant amounts of radioactivity were incorporated into acid-precipitable material, presumably RNA. Excitement reigned and efforts were quickly extended to include the biosynthesis of DNA. The latter studies were conspicuously promoted by the availability of radiolabelled thymidine from Morris Friedkin in the Department of Pharmacology at Washington University. Friedkin had discovered the reverse reaction of thymidine phosphorylase, which catalyses the phosphorolysis of thymidine and other pyrimidine 2′ deoxyribosides, therefore enabling the conversion of thymine to thymidine and inorganic phosphate in the presence of deoxyribose-1-phosphate. Friedkin was trying to demonstrate the incorporation of ^{14}C-thymidine into DNA in extracts of chick embryos, and was not at all motivated to donate his precious reagent for experiments with *E. coli* extracts. However, he offered Kornberg residual supernatants from his studies. Initial results were disappointing. Only about 0.01% of the total radioactivity in the incubations (yielding a mere 50 scintillation counts above the background) was transferred to acid-precipitable material, presumably DNA.

The discovery of DNA polymerase

While labouring to improve the robustness of this assay, Kornberg and Littauer learned that Marian Grunberg-Manago (then a postdoctoral fellow in Ochoa's laboratory) had stumbled onto the enzymatic synthesis of RNA in extracts of a nitrogen-fixing bacterium. This reaction, catalysed by an enzyme that Ochoa dubbed "polynucleotide phosphorylase"[6], used ADP rather than ATP as a substrate. Spurred to redouble their efforts on RNA synthesis in extracts of *E. coli*, Kornberg and Littauer switched to using radiolabelled ADP instead of ATP. In so doing, they merely confirmed the existence of polynucleotide phosphorylase in another microorganism. Had they continued using ATP as a substrate, they almost certainly would have discovered RNA polymerase — an enzyme not formally discovered until 1959 (REF. 7).

This diversion postponed further attempts at the enzymatic synthesis of DNA. But when these experiments were resurrected in late 1955, the results were as inconclusive as those of the original trials. Nonetheless, the radiolabelled thymidine used in the second round of experiments was about three times 'hotter', and Kornberg took faint heart at the observation that the radioactivity recovered in the acid-insoluble fraction increased correspondingly. More reassuring was the finding that the radioactivity was lost following incubation of the acid-precipitable material with pancreatic DNase. Kornberg later described how he felt.

> "Without the encouragement that the diagnostic action of DNase gave me, I wonder whether I would have had the will to pursue such a feeble light."[1]

On learning about Kornberg's return to *in vitro* DNA synthesis, I. Robert (Bob) Lehman, who had recently joined the Kornberg laboratory as a postdoctoral fellow, discovered that thymidine monophosphate was a better precursor for DNA synthesis than thymidine. Later, Lehman showed that thymidine triphosphate worked even better[8]. From the outset, the *in vitro* assay included the addition of *E. coli* DNA. Kornberg deployed this experimental nuance for several cogent reasons. Primarily, he hoped that the DNA would function as a primer for extended DNA synthesis, much in the fashion that carbohydrate chains had been shown by Carl and Gerty Cori to be extended by glycogen phosphorylase. Additionally, cognizant of the potent nucleases in *E. coli* extracts, Kornberg reasoned that

adding exogenous DNA might alleviate the degradation of newly synthesized DNA by sequestering the nuclease activity. Assisted by Lehman, Maurice J. Tessman and Ernest S. Simms, Kornberg began to enrich the protein fraction that catalysed the synthesis of new DNA. "Through this tiny crack we tried to drive a wedge, and the hammer was enzyme purification."[5]

The initial results of these studies were announced at the 1956 annual meeting of the Federation of American Societies for Experimental Biology (FASEB) in Atlantic City, New Jersey, USA[9], and at the 1956 McCollum-Pratt Symposium entitled The Chemical Basis of Heredity, in Baltimore, Maryland, USA[10]. In the same year, Kornberg, Lehmann, Bessman and Simms published a brief report[11] (the 50th anniversary of which we celebrate this year), which clearly revealed Kornberg's reservations that the DNA that was being synthesized in this *in vitro* reaction was probably not derived from the template-directed process that determines the fidelity of DNA replication in living cells. He and his co-authors referred to the addition of *E. coli* DNA as "…'primer' for the crude enzyme fraction", and did not entertain the notion of a template-directed process until later, when key observations by Lehman prompted them to do so. In fact, the authors were initially aware of the possibility that the DNA that was being synthesized in their reaction might not reflect the genetic fidelity of DNA replication in living cells.

> "Further investigations with phage-infected *E. coli* and studies with biologically active DNA may begin to clarify the question of how genetically specific DNA is assembled."[11]

In his own recent reflections on the DNA-polymerase story, Lehman commented on the imperatives for considering a template-directed process.

> "The requirement for all four dNTPs was puzzling. If the DNA that we added was simply serving as a primer, why would all four dNTPs be needed? Was it possible that the DNA polymerase was performing the template-directed replication proposed by Watson and Crick for their double-stranded structure of DNA… To test this idea we used DNAs with AT/GC ratios ranging from 0.5 to 1.9 as 'primers.' The result was stunning … Clearly, the added DNA was serving as a template to direct the polymerase as it synthesized new DNA chains…"[8]

Two definitive papers on the enzyme DNA polymerase were published in the *Journal of Biological Chemistry* in July 1958 (REFS 12,13). Sceptical that the enzymatic reaction might not reflect bona fide DNA synthesis, the reviewers suggested that the authors use the term 'polydeoxyribonucleotide' rather than 'DNA' to identify the product of the reaction. But reason prevailed when the authors appealed to the Editor-in-Chief, John Edsall.

Cells have multiple DNA polymerases

Kornberg and his colleagues reasonably assumed that the DNA polymerase they discovered supported semi-conservative replication of the *E. coli* genome, and that it was the only DNA polymerase in these cells. But John Cairns (then Director of the Cold Spring Harbor Laboratory) was not convinced that the Kornberg enzyme could catalyse the copying of DNA rapidly enough to account for the *in vivo* rate of DNA replication in *E. coli*, or that *E. coli* possessed enough enzyme to accommodate the rate of DNA replication.

Cairns was also aware of studies on an *E. coli* mutant that undergoes aberrant cell division near one pole, resulting in the generation of small enucleate cells known as minicells[14]. Minicells were known to contain RNA and protein, but were essentially devoid of DNA, despite the fact that the specific activity of DNA polymerase in minicell extracts was essentially the same as in normal cells[15,16]. "This said to me", Cairns later related, "that the 400 molecules of DNA polymerase were not busily replicating DNA. They were just floating around. Instantly the thought came to me that they were not there to replicate DNA …"[17]

Cairns decided to attempt the isolation of a mutant of *E. coli* defective in DNA polymerase activity. If such a mutant was viable, the Kornberg enzyme was clearly not the polymerase that replicated DNA semi-conservatively. Cairns set his laboratory assistant Paula De Lucia the daunting task of propagating thousands of individual *E. coli* colonies, making cell-free extracts of each, and assaying them for DNA-polymerase activity. De Lucia struck gold with clone number 3478 and identified the *polA1* mutant[18] (so-named because of the agreeable alliteration of 'polA' with 'Paula' [De Lucia] whom Cairns wanted to credit.[17])

These studies naturally begged the question, which DNA polymerase replicates the *E. coli* chromosome? Answers to this came quickly. And, remarkably, they came first

Figure 1 | **Arthur Kornberg, circa 1956 — the year that he announced the discovery of DNA polymerase.** Photograph courtesy of A. Kornberg.

from the efforts of Thomas Kornberg, one of Arthur Kornberg's three sons (FIG. 2). In 1970, the younger Kornberg, then a graduate student with Malcolm Gefter at Columbia University, reported the identification of what became known as DNA polymerase II of *E. coli*[19]. Similar observations were independently reported at about the same time by Rolf Knippers[20] and by Robb Moses and his mentor Charles Richardson[21]. The following year, Thomas Kornberg and Gefter reported the identification of what became DNA polymerase III of *E. coli*[22], the true replicative polymerase. The enzyme discovered by Arthur Kornberg is now known as DNA polymerase I.

Yet more DNA polymerases

The discovery of DNA polymerase in eukaryotes did not lag far behind Kornberg's pioneering efforts. By 1957, radiolabelled thymidine was commercially available and Fred Bollum announced the identification of what eventually came to be called DNA polymerase-α in rat liver homogenates[23]. It took years of effort by multiple investigators to sort out the plethora of DNA polymerases in mammalian cell extracts, to define the multiprotein composition of many of these enzymes and to distinguish each as independent DNA polymerases[24]. We now recognize the existence of four such enzymes, designated DNA polymerase-α, -β, -δ and -ε (TABLE 1). In the late 1960s, two groups reported the identification of DNA-polymerase activity in extracts of rat liver mitochondria[25,26], and additional

Figure 2 | **Arthur Kornberg with his sons Roger (left), Kenneth (next to his mother Sylvia) and Thomas (next to his father), circa 1959.** Photograph courtesy of A. Kornberg.

studies in the 1970s led to the remarkable observation that mitochondria contain a dedicated DNA polymerase (DNA polymerase-γ; TABLE 1) encoded by the mitochondrial genome. In 1970, David Baltimore[27] and Howard Temin[28] independently discovered a viral RNA-dependent DNA polymerase (now known as reverse transcriptase), efforts that won them the Nobel Prize in 1975. Such scientific recognition was also accorded to Kary Mullis in 1983 for his application of DNA polymerases to the polymerase chain reaction (PCR), an innovation that prompted the discovery of thermostable archaeal DNA polymerases.

Still more DNA polymerases laid in wait, and, once again, bacteria paved the way. Genetic studies on ultraviolet (UV)-radiation-induced mutagenesis in *E. coli* prompted the hypothesis that mutations in *E. coli* cells that were exposed to UV light were generated (at least in part) by inaccurate DNA replication directly across photoproducts in the template strand by the replicative machinery, a process known as translesion DNA synthesis (TLS)[29]. It was initially speculated that TLS in *E. coli* was effected by the replicative enzyme DNA polymerase III, the fidelity of which was relaxed by interaction with the products of the *umuC* (and *umuD*) gene that are obligatory for UV-radiation-induced mutagenesis[30]. But several studies subsequently demonstrated that the UmuC protein is itself a DNA polymerase with novel properties[31,32]. At about the same time, it was shown that DinB, an *E. coli* protein that shares extensive structural homology with the UmuC protein, is also a DNA polymerase[33]. DinB is now designated DNA polymerase IV (TABLE 1) and UmuC acquired the formal name of DNA polymerase V (TABLE 1).

By the late 1990s, the availability of the nucleotide sequences of several eukaryotic organisms facilitated the identification of an astonishing array of DinB and UmuC homologues in eukaryotes[34], leading to the discovery of a plethora of new DNA polymerases (TABLE 1). It is now established that vertebrate cells contain no less than 14 distinct DNA polymerases that belong to the A, B, X and Y families.

Table 1 | **DNA polymerases in prokaryotes, lower eukaryotes and mammalian cells**

E. coli	*S. cerevisiae*	*H. sapiens*	Polymerase family
Pol I	–	–	A
Pol II	–	–	B
Pol III	–	–	C
Pol V	–	–	Y
Pol IV	–	Pol κ	Y
–	–	Pol β	X
–	Pol α	Pol α	B
–	Pol δ	Pol δ	B
–	Pol ε	Pol ε	B
–	Pol γ	Pol γ	A
–	Pol IV	Pol λ	X
–	Rev1	Rev1	Y
–	Pol η	Pol η	Y
–	Pol ζ	Pol ζ	A
–	–	Pol ι	Y
–	–	Pol μ	X
–	–	Pol θ	A
–	–	Pol ν	A

E. coli, *Escherichia coli*; *H. sapiens*, *Homo sapiens*; *S. cerevisiae*, *Saccharomyces cerevisiae*; Pol, DNA polymerase.

Concluding remarks

Following his discovery of DNA polymerase I of *E. coli* (for which Kornberg was acknowledged with a Nobel Prize in 1959), he devoted most of his career to deciphering the mechanism of DNA replication in *E. coli*, a challenging problem that is far more complex than the simple deployment of DNA polymerases. Indeed, many questions about DNA replication, especially in eukaryotes, remain unanswered to this day and conferences on DNA replication continue to abound. As for Arthur Kornberg, at the age of 87 he has returned full cycle to an early love affair with polyphosphate biochemistry and continues to manage an active laboratory at Stanford University with undiminished curiosity — and with a timeless 'love of enzymes'.

Errol C. Friedberg is at the Laboratory of Molecular Pathology, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas 79503-9072, USA.
e-mail: errol.friedberg@utsouthwestern.edu

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Competing interests statement

The author declares no competing financial interests.

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OPINION

Not so divided: the common basis of plant and animal cell division

Clive Lloyd and Jordi Chan

Abstract | Plant cells do not have centrioles and their mitosis is frequently likened to the chromosome-based mechanism seen in acentriolar animal cells. However, this is a false analogy. Although plants can use this mechanism, they generally divide by a method that uses bipolar mitotic caps, which is more similar to the canonical centrosome-based method of animals.

As plants evolved from an aquatic to a land environment, their gametes became transmitted through the air by insects or wind and they lost the ability to make the flagella that are used by animals and lower plants to propel their gametes through water. As a consequence, higher land plants no longer possess the basal body from which flagellar (or ciliary) microtubules grow[1]. However, virtually all vertebrate cells contain basal bodies, which are composed of a ring of nine specialized microtubules. Even those animal cells that do not form cilia or flagella retain basal bodies in the form of structurally identical centrioles that are found in the middle of the centrosome or microtubule-organizing centre (MTOC). Although they are vestigial, in the sense that they no longer function as flagellar templates, the centrioles do provide a focal point for gathering the amorphous microtubule-nucleating material. A centriole pair focuses the MTOC during interphase and, when duplicated, also defines the spindle poles of animal cells during mitosis. It is the loss of the centriole or basal body that is thought to be responsible for the dispersion of the MTOC and the more diffuse spindle poles in higher plant cells.

However, here we argue that the loss of the centriole as an organizing entity has been consistently overemphasized, and has diverted attention away from the true manner in which plant cells divide. In terms of mitosis, plants are usually lumped together with those animal cells that also lack centrioles (for example, germ-line cells), and it is commonly assumed that all such cells must divide by a non-canonical method that lacks strong input from the spindle poles. We stress that plants do possess a pole-based mitotic mechanism, which has been overlooked in the discussions about centrioles.