Preface

Maintenance of the information embedded in the genomic DNA sequence is crucial for the survival of any living species. DNA polymerases play pivotal roles in this complex process since they are involved in all DNA synthesis events occurring in nature. Besides their essential tasks *in vivo*, DNA polymerases are now the workhorses in numerous important molecular biological and medical core technologies such as the widely applied polymerase chain reaction (PCR), cDNA cloning, genome sequencing, nucleic acids–based diagnostics and in techniques to analyze ancient and otherwise damaged DNA.

The history of DNA polymerases goes back over 53 years to the mid-1950s. With the discovery of a DNA polymerase (now known as DNA polymerase I) in the bacterium *Escherichia coli* by Arthur Kornberg and his colleagues, it was for the first time possible to synthesize the genetic material, the DNA, in the test tube. A manuscript reporting the discovery submitted to the *Journal of Biological Chemistry* was rejected with comments such as "the researchers were incompetent" and DNA polymerase was "a poor name" for this enzyme. What a terrible judgment by an incompetent editor! The observation by Kornberg and collaborators that a DNA polymerase synthesizes DNA according to the Watson–Crick base pair rule (A–T and G–C), needs activated bases (dNTPs), a template, a primer and $MgCl_2$ is still true today for most DNA polymerases in all organisms tested.

Bruce Alberts in a feature article in *Nature* stated in 2003[1]: "Knowledge of the structure of DNA enabled scientists to undertake the difficult task of deciphering the detailed molecular mechanisms of two dynamic processes that are central to life: the copying of the genetic information by DNA replication, and its reassortment and repair by DNA recombination. Despite dramatic advances towards this goal over the past five decades, many challenges remain for the next generation of molecular biologists."

A comprehensive book focusing on DNA polymerases appeared in 1986 and covered exclusively animal DNA polymerases.[2] At that time the animal DNA polymerase family was still small. Only three DNA polymerases, α, β and γ were known in detail and the scientific community just started to believe in a fourth DNA polymerase, called DNA polymerase δ. In the last 23 years, due to the analysis of various genomes, including the one from humans, we have witnessed the discovery of an abundance of novel DNA polymerases in the three kingdoms of life (bacteria, archaea and eukaryotes) with specialized properties whose physiological functions are only beginning to be understood. For several decades the dogma was widely accepted that very accurate DNA polymerases guarantee the faithful duplication of DNA, while their limited capacity of making mistakes might be one of the drivers for evolution and a cause of disease. When in 1999 the human genome was sequenced, nine newly discovered DNA polymerases appeared within three years in the literature (1999–2002). Many of these DNA polymerases appear to have distinct functions in translesion synthesis, in different DNA repair events or in immunoglobulin V(D)J recombination.

This book starts by presenting the history of the discovery of DNA and DNA polymerases, including the polymerase chain reaction (PCR) (Chapter 1), followed by the presentation of DNA polymerases from the three kingdoms of life: bacteria, archaea and eukaryotes (Chapter 2). Next, the structural and functional aspects of the different DNA polymerase families are described in prokaryotes (Chapter 3) and in eukaryotes (Chapter 4). Preventing genetic instability is of great importance in life. Temporal and spatial regulation of DNA polymerases is of paramount interest for the organism. This might occur via regulation of their expression, their stability and their localization. Many posttranslational modifications contribute to these properties. DNA polymerases are not autistic enzymes but rather work in a broader context within a cell and they can replace one another under certain physiological and even pathological situations (Chapter 5: Global functions of DNA polymerases). Many fundamental mechanistic properties have been elucidated, thanks to the study of DNA polymerases from bacterial and animal cells viruses. The most relevant ones will be described in Chapter 6. A recent field of Chemical Biology has developed techniques that allow the evolution of DNA polymerases in the test tube and thus a variety of novel applications may be ahead of us in the near future (Chapter 7). Many diseases have been correlated with malregulations and malfunctions of DNA polymerases (Chapter 8) and DNA polymerase inhibitors are used as chemotherapeutic agents (Chapter 9). The chapters are written so that they can be read and understood in their own and this will necessarily bring a certain redundancy. We have also made cross-references where appropriate. In summary, this book provides the arguments and evidence that characterize DNA polymerases as enzymes essential to life and also place them among the most important tools in modern chemistry, biology and medicine.

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