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, next-generation sequencing, nucleic acids–based diagnostics and in techniques to analyze ancient and otherwise damaged DNA (e.g. for forensic applications).

The history of DNA polymerases goes back 60 years to the mid-fifties in the last century. 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 $MgCl_2$ (or a divalent cation) is still true today for most DNA polymerases in all organisms tested.

Bruce Alberts in a feature article in *Nature* stated in 2003 (Alberts B. 2003. *Nature* 421: 431–435): "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 30 years and covered exclusively animal DNA polymerases (Fry M., Loeb L.A. 1986 *Animal Cell DNA polymerases*, CRC Press, Inc. Baton Rota, Florida). 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 30 years, due to biochemical work, as well as 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 by the end of last century the human DNA 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, which is entitled *Human DNA Polymerases: Biology, Medicine and Biotechnology*, is an updated version of our book *DNA Polymerases: Discovery, Characterization and Functions in Cellular DNA Transactions* by U. Hubscher, S. Spadari, G. Villani and G. Maga

(World Scientific Publishing, 2010, ISBN-13: 978-981-4299-16-9). In three sections we describe first, the biology of DNA polymerases (Chapters 1 to 4), second the medical applications of DNA polymerases (Chapters 5 and 6) and third, the biotechnical applications of DNA polymerases (Chapters 7–9).

Chapter 1 summarizes the history of DNA polymerases. General aspects of DNA polymerases are outlined in Chapter 2. Next the structural and functional aspects of the different DNA polymerase families are described (Chapter 3) and Chapter 4 discusses different DNA transactions of DNA polymerases. In the last few years DNA polymerases came also in the focus of human diseases (Chapter 5) and as targets for therapy by chemicals (Chapter 6).

With the discovery of the polymerase chain reaction (PCR) and the use of heat-stable DNA polymerases a door with an enormous potential opened to the scientific community. The history and the potential of evolved DNA polymerases are briefly introduced in Chapter 7. The 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 were developed in the last ten years. This current status is summarized in Chapter 8. The final Chapter 9 is devoted to the billion USD market for evolved DNA polymerases in routine and medical applications.

In summary this book provides the arguments and evidence that characterized DNA polymerases as enzymes essential to life and also placed them among the most important tools in modern chemistry, biology, biotechnology, and medicine.

The chapters are written so that they can be read and understood individually. A certain redundancy of information was therefore done intentionally or references to other Chapters were made.

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