PREFACE

The field of DNA repair has been the subject of increasing interest at both the genetic and biochemical levels, leading to impressive progress in this area. DNA repair and its associated regulatory mechanisms lie at the heart of almost every fundamental aspect of cell biology, including transcription, cell cycle, apoptosis, and development. Thanks to the fascinating investigations of the inherent gene defects of specific components of DNA repair pathways found in rare human syndromes (e.g., xeroderma pigmentosum), we have been provided with the framework for subsequent studies on the translational aspects of DNA repair. Several genes have been cloned, and the crystal structures of some proteins are now reported. Polymorphisms in certain of the DNA repair genes are being identified in human populations. Furthermore, increased research efforts highlight the involvement of DNA repair mechanisms in the maintenance of genomic stability, mutagenesis and carcinogenesis, and resistance to endogenous and exogenous genotoxic stress.

In preparing *DNA Repair in Cancer Therapy*, we have been concerned with those practicing oncologists who are dealing on a daily basis with the hallmark "relapse" or "drug resistance" phenomena. Among the multifactorial mechanisms described so far, there is increasing evidence that impaired expression/activity of at least some of the DNA repair proteins can account for tumor cell resistance to a particular therapeutic agent. Further interest has been stimulated by the demonstration that DNA repair is coupled to cell cycle checkpoint controls which, when impaired, could account for clinical drug resistance. Surprisingly, there have been relatively few comprehensive review articles and, as far as we know, no complete volume dedicated to the translational aspect of DNA repair in the clinic. This fostered the need to organize a set of timely, in-depth reviews covering the latest developments having potential for translational and clinical applications.

Chapter 1 by Dr. Leyland-Jones on the clinical implications of resistance to anticancer agents, including those whose primary mechanisms of cell death can be affected by DNA repair, introduces the important role that alterations in DNA repair play in limiting the therapeutic index of anticancer therapy. Experts in the field subsequently review the various mechanisms involved and their implications. Although the application of DNA repair pathways in therapeutics is still at the embryological stage, some inhibitors of DNA repair mechanisms (e.g., O^6-methylguanine-DNA methyltransferase [MGMT]) that would increase sensitivity/selectivity to kill tumor cells in a particular molecular context have reached

the clinical stage, and the results will be discussed in the light of the clinical impact. Furthermore, inhibitors of other DNA repair enzymes, such as PARP and DNA-PK, are being developed, and clinical trials with such inhibitors alone or in combination with anticancer therapy (drugs and/or radiotherapy) should be completed in the foreseeable future. Thus, prospects are exciting, and the translation of bench research to the clinic is on the horizon. Some chapters deal with overlapping subjects, although from different experimental and personal perspectives; this reflects the complexity of a topic wherein there are sometimes conflicting data, but it also ensures that most of the current views are represented. We believe that *DNA Repair in Cancer Therapy* will prove to be valuable reading for a broad audience of clinicians, pharmacologists, medicinal chemists, and basic scientists.

We would like to thank the authors who have spent their valuable time in contributing to *DNA Repair in Cancer Therapy*. Their cooperation and expertise was crucial in obtaining this comprehensive, state-of-the-art synopsis of a complex area.

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