Chemotherapeutic Targets in Parasites

Contemporary Strategies

Parasitic infections are the most prevalent of human diseases. Parasites' effective evasion of their hosts' immune defenses and their complex physiology and life cycles make them especially resistant to attack by chemotherapeutic agents. Researchers continue to face the challenge of designing drugs to successfully counteract them.

Chemotherapeutic Targets in Parasites analyzes the critical metabolic reactions and structural features essential for parasite survival and advocates the latest molecular and biochemical strategies with which to identify effective antiparasitic agents. An introduction to the early development of parasite chemotherapy is followed by an overview of biophysical techniques and genomic and proteomic analyses. Several chapters are devoted to specific types of chemotherapeutic agents and their targets in malaria, trypanosomes, leishmania, and amitochondrial protists. Chapters on helminths include metabolic, neuromuscular, microtubular, and tegumental targets. Emphasized throughout is the design of drugs that are more selective and less toxic than those used in the past.

A comprehensive discussion of selective targets in parasites for new drugs is long overdue. This up-to-date book will be especially relevant to medical and clinical researchers and to graduate students in parasitology, pharmacology, medicine, microbiology, and biochemistry.

Tag E. Mansour is Professor Emeritus in the Department of Molecular Pharmacology at the Stanford University School of Medicine. His research on biochemical and molecular parasitology and the action of antiparasitic agents has been published extensively.

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Tag E. Mansour

with the assistance of

Joan MacKinnon Mansour

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Preface

I became intrigued with parasites when I started my research career as a graduate student in England. I was rightly told that the field of parasites has a great future for a starting biochemist/pharmacologist. The field of parasite research was not crowded and therefore was designated as a neglected area of research. Subsequently, a large number of talented and highly sophisticated young scientists were attracted by the urgent need for modern studies on parasites and antiparasitic agents. The fields of parasite biology and biochemistry accumulated a large volume of information that led to the possibility of rational design of antiparasitic agents. There is renewed hope for discovery of more selective and less toxic drugs against parasites.

At the present time infections by parasites, both protozoal and helminthic, constitute the most prevalent diseases in the world. The World Health Organization estimates that there are at least 3 billion people in the world who are infected with parasites. Many of these harbor more than one infection. The prevalence of these infections, especially in developing countries, is not only a cause of untold human suffering and mortality but a growing impediment to better local and global economies.

The prime aim of this book is to discuss critical metabolic reactions and cellular structural features that are essential for survival of parasites, particularly those that differ from those of the host. A comprehensive discussion of selective targets in parasites for old and new drugs is long overdue. The term selective targets may not apply to targets of older antiparasitic agents. Most of these early drugs were not discovered by a rational procedure.

Chapter 1 includes a discussion of the development of parasite chemotherapy from Paul Ehrlich's time to our new era when the search for antiparasitic agents has been influenced by the impact of modern biochemistry and biology. Animal models and *in vitro* cultures for screening are discussed. Traditional ways of designing antiparasitic chemicals to inhibit the functioning of specific targets, the

more modern use of relationships between chemical structure and biological activity to design new drugs, and the latest techniques of combinatorial chemistry to prepare hundreds of thousands of new molecules are included.

In Chapter 2 I introduce several recently successful biophysical techniques with which to analyze drug–target interactions. Nuclear magnetic resonance is now used to carry out noninvasive experiments on the energy metabolism of intact parasites. Some aspects of DNA technology are discussed generally, but not in detail, because specialized laboratory manuals are readily available. Mention is made of the latest information about genomic analysis of major parasite groups. Structural genomics is a growing field that promises to have a major impact on identifying three-dimensional structure and function using DNA sequences. Proteomics is another new area that is rapidly expanding. Some scientists whose major interests are in genes seem to have forgotten that the actions of genes are manifested through proteins. This is particularly important for identification of drug targets in parasites.

In Chapters 3–6 I emphasize those aspects of parasite life in the host that have distinguishing features such as metabolic differences between host and parasite. Also included are discussions of the mechanism of action of some of the current antiparasitic agents against their targets. The concept of "selective toxicity" is emphasized and the most selective drugs are more fully described. A few examples of the value of determining the mechanism of action of both old and new drugs are given. It was in the 1950s that the discoveries of Lederberg, and Park and Strominger drew attention to bacterial cell wall synthesis as a selective target for penicillin and other antibiotics. More research on mechanisms of action will lead to discovery of new targets and new antiparasitic agents.

The subject of parasite resistance to certain antiparasitic agents has been integrated with discussion of the mechanism of action. In many cases studies on resistant strains of parasites gave clues to new drug targets with more details about drug–target interactions. There are some divergent views in the literature about parasite resistance. Information on drug resistance from *in vitro* cultures and from laboratory animals should always be considered in relation to human field studies.

In the Chapters 7 and 8 I discuss topics that have been less studied than parasite metabolism. Motility of parasitic helminths plays an important role in maintenance of their location in the host. Many parasites can be eliminated from the host by drugs acting on the neuromuscular receptors of the parasites. Information is given about neuromuscular receptors, neurotransmitters, and changes in parasite behavior as a result of antiparasitic agents. This is an area that has not been fully exploited in the search for new drug targets. Also included are discussions of the microtubules that are basic to control of the location of

intracellular organelles and how the benzimidazoles owe their anthelmintic activity to blocking of the microtubular matrix. The last chapter is a discussion of the tegument of platyhelminths as a target. Although there are several anthelmintics that affect components of the tegument, there have not been enough studies of the different ways the tegument functions to help the parasites' life in the host. It is generally accepted that the tegument of flatworms plays an essential role in the transport of nutrients from the host and acts as a protective shield. The interaction between antiparasitic agents against the tegument and the host's immune system has a potential synergistic role in therapy.

Some of the chapters include sections titled "Potential Research." These cover areas that require more experimentation and are included for those who are fortunate enough to be able to go to the laboratory to perform experiments.

The life cycles of several typical parasites are briefly given for the sake of clarity in the discussion of targets. These are not intended as a substitute for more detailed descriptions found in parasitology textbooks.

The bibliographies at the end of each chapter are not comprehensive, but they should give the reader indications of where to look for additional information. References to reviews should be useful to readers who wish to have an overview of a particular area. Although I have been careful to refer to both old and new publications, I may have neglected some of great distinction and so offer my apologies to my biochemistry, pharmacology, and parasitology colleagues who may feel overlooked.

Tag E. Mansour
Stanford, California
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