MOLECULAR ASPECTS OF ANTI-CANCER DRUG ACTION

**TOPICS IN MOLECULAR
AND STRUCTURAL BIOLOGY**

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Preface

The idea that understanding the molecular bases of drug action will lead to major advances in medical practice is not new. It has been hallowed by the award of prestigious prizes. It has become enshrined in the thinking of a generation of scientists and physicians. Few people are brave (or foolhardy) enough to doubt the enormous potential of fundamental studies as a guide to drug design. This book represents an attempt to summarise certain areas of endeavour which provide a timely assessment of progress: it is unashamedly wedded to the concept that molecular and structural studies will point the way ahead.

A glance at the list of contents will reveal that it is in no sense comprehensive. On the contrary, in selecting chapter titles and authors we were guided first and foremost by considerations of topicality, particularly as regards molecular interpretations. Even so, it is easy to point to yawning gaps in our coverage of the subject and we hope no-one will feel offended if there is no mention of his or her favourite drug or modality of cancer treatment. With much regret we have tended to avoid discussion of clinical applications/applicability though we are conscious of the vitally important goal of transporting the insights and innovations of the laboratory into the clinic. Perhaps that aspect alone is worthy to form the subject of another volume.

There is an obvious preoccupation with matters concerning drug-nucleic acid interactions, if only because they are so amenable to investigation at the molecular level. But this is not intended to imply that drugs have a single site-specific mode of action or that DNA is the only important receptor for anti-cancer drugs. Indeed, we have deliberately encouraged several authors to adopt the role of "devil's advocate" and to examine critically the possibility of significant effects mediated by antitumour drugs at levels other than that of nucleic acids. It is clear that for many useful compounds the very concept of a primary site of action must be held open to question.

It may appear that the treatment of antimetabolites is particularly deficient, granted their prominent place in various cancer treatment regimes. This is chiefly due to our insistence on limiting attention to topics where a substantial body of information at the molecular level is available for the receptor — realistically a crystal structure from which precise molecular structural data can be derived. Such information is now available for dihydrofolate reductase, which therefore represents the outstanding example of a well-characterised antimetabolite receptor.

Until two or three years ago it was natural to regard the double-helical ten-fold B-form as the final word on DNA structure, and therefore the best-defined receptor for anticancer drug action. However, recent developments outlined in the first two volumes of this series reveal that we must discard the notion that DNA is a monotonously repeating biopolymer. Sequence-dependent variation of the local conformation of DNA is now a serious concept which presents an alluring challenge to those who would seek molecular interpretations of drug action.

Inevitably considerations of space have forced us to neglect a number of interesting areas where molecular insights are currently being applied to develop new drugs with promising clinical potential. We can only hope that the principles which emerge from the existing chapters will prove to be of sufficient generality to serve as pointers to developments in related fields.

Lastly, we hope the book may prove useful to physicians and others whose principal concern is with the use of drugs in the clinic to treat cancer, as well as to the more obvious audience of laboratory research workers. Our underlying belief remains that fundamental studies cannot be neglected in assessing future priorities: indeed we are prepared to argue that they represent the cornerstone of the subject, and this attitude (perhaps better described as an article of faith) is implicit in the message of several contributions. In this claim we make no boast for originality, only a driving concern to make best use of molecular and structural biology in the service of medicine.

Stephen Neidle
Michael Waring