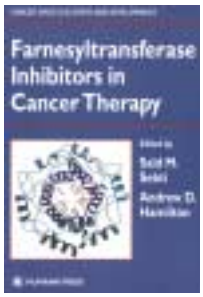

Farnesyl-transferase Inhibitors in Cancer Therapy

Edited by Saïd M. Sebti and Andrew D. Hamilton, Humana Press, 2001. $125.00, 296 pages, hardback, ISBN 0-89603-629-4

Farnesyltransferase inhibitors: preclinical promise to be fulfilled?

This volume forms Part 8 of the series *Cancer Drug Discovery and Development* (series ed. Beverley A. Teicher) and covers in some detail the development of farnesyl- and geranylgeranyl-transferase inhibitors principally as anticancer agents, but also to a lesser extent in cardiovascular and anti-trypanosomal therapy.

Coverage

The book covers a fairly narrow field of research in some detail; in this respect the coverage is fairly comprehensive and I see no obvious omissions. The book begins with a wide-ranging discussion of the cancer problem (which could have found its way into almost any textbook dealing with cancer chemotherapy) and the need for new and innovative therapeutics before moving onto the more specific issue of the Ras protein and intracellular signalling. The biochemistry and structural aspects of the farnesyltransferase enzyme are covered in sufficient detail to set the scene for subsequent chapters dealing with the systematic discovery and early development of inhibitor molecules. This program has produced several lead compounds with a number of interesting and surprising properties.

The question as to the exact mechanism of action of these agents is discussed in several of the later chapters. It is clear from these discussions that key mechanistic questions regarding farnesyltransferase inhibitor (FTI) action remain unresolved. Other wider implications of FTI therapy are also explored, e.g. the role of FTIs as candidates for radiosensitization of tumour cells and the potential utility of trypanosomatid FTIs as anti-parasitic agents.

Finally, the early clinical experience with FTIs, both as single agents and in combination therapies, is described. Despite encouraging preclinical observations, it is still unclear as to whether FTIs can inhibit tumour growth in patients with advanced disease, and many unresolved questions regarding the use of FTIs in the clinic (e.g. optimum schedules and doses) remain.

Analysis

The book consists of a collection of chapters from laboratories involved in the FTI area, edited by prominent researchers in the field, and some duplication of both content and references can be found. The role of Ras and its farnesylation in intracellular signalling pathways, for example, can be found at the beginning of the majority of chapters. The quality and depth of the various chapters is variable, ranging from thought-provoking mechanistic discussions to the some rather bland descriptive accounts of systematic structure–activity relationship studies.

Inhibiting farnesylation is one of several anti-Ras therapeutic strategies that could be considered; others could include inhibition of geranylgeranyltransferase (touched on in this volume), restoring GTPase activity to mutant Ras–GAP complexes and inhibiting Ras–Raf interactions. The issue of whether inhibiting farnesylation represents the best (selective) approach towards developing anti-Ras drugs or simply the most pharmacologically tractable remains a valid concern and one not discussed at length in this book.

Unfortunately, the promise provided by some remarkable preclinical observations has yet to reach clinical fruition. Many unresolved questions remain pertaining to the mechanism of action of these agents and whether they will eventually find their way into the therapeutic armamentarium against cancer. From this viewpoint, the book comes to a rather unsatisfactory conclusion. Considering the number of unanswered questions posed, the timing of this publication seems surprising. In many ways, however, the FTI project has been very successful, representing one of the first cases in which basic research into cancer biology has been translated into a truly novel therapeutic strategy, a message this book puts across well.

Priced at US$125 and with a fairly narrow appeal, this book will probably only find its way onto the shelves of research groups interested in novel approaches to cancer chemotherapy. It certainly provides an intriguing insight into an ongoing saga in anticancer drug discovery and is, for the most part, well written. I would certainly recommend it, albeit to a rather limited audience.

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