Schultz RM. Advances in Targeted Cancer Therapy, Progress in Drug Research. Basel (Switzerland): Birkhäuser Verlag; 2005. 303 pages; ISBN 978-3764371746 price: US$249.00

> doi: 10.3325/cmj.2007.6.889

Field of medicine: Oncology, molecular biology of new anticancer agents.

Format: Hardcover.

Audience: Medical oncologists and radiotherapists, as well as biochemical researchers and other professionals involved in development of new drugs, especially in the exciting field of cancer specific targeted therapy.

Purpose: Insight into new research on tumor biology and pathways that control tumor cell growth and differentiation, which resulted in the development of new selective cancer therapeutics. It is a book that gives hope that eventually new ways of attacking tumor cells will be found and that key molecules and pathways will be identified and used in the battle against cancer.

Content: This book, in its eleven chapters, offers the reviews on various novel specific targeted anticancer agents, along with additional topics like target validation, preclinical models, successes and obstacles in the development of targeted agents, and development of resistance.

In the first chapter, the author gives a brief introduction on chemotherapy development from the use of antifolate drugs and nitrogen mustards in 1940s to targeted anticancer drugs, which interact with a single molecule in the tumor cell. Anticancer therapy is constantly changing; it has entered the postgenomic era, enabling a development of drugs that target cancer cells and do not harm the healthy cells. Specific targets in cancer cells available for potential treatment are presented, with a brief description how these targets can be identified, validated, and used in clinical practice, along with possible mechanisms of resistance to novel agents.

The second chapter presents the obstacles to the development of new anticancer agents, beginning with a selection of valid targets in tumor cells – those that have the key role in tumor cell biology. It continues with the problems of determination of appropriate dose, administration schedule of a new agent, screening for a truly effective agent, selection of target patient population, and combining novel agents with standard chemotherapy regimes.

The third chapter describes a development of preclinical models that accurately mimic human cancer cells and tissues, since human cancer is a difficult disease to model. Two classes of new agents, trastuzumab, monoclonal antibody to HER-2/neu growth factor receptor and inhibitors of epidermal growth factor receptor (EGFR) are more closely described, since they are examples of targeted anticancer therapy that are very potent in their action, although not in all patients. The finding of changed expression of various targets (like HER-2/neu or EGFR) in cancer cells led to the development of diagnostic tests for the selection of patients who have the best chance of responding to a specific therapy.

The fourth chapter gives an insight into mechanism of tumor angiogenesis, its significance in clinical practice, and obstacles that accompany the use of antiangiogenic agents. Several antiangiogenic agents are described – including direct endothelial cell cycle inhibitors, agents that change endothelial cell adhesion, and the most promising ones – agents that attack vascular endothelial growth factor pathway.

The fifth chapter describes epidermal growth factor receptor (EGFR) inhibitors – agents that inhibit the action of family of membrane EGF receptors – like gefitinib, cetuximab, erlotinib. Their antitumor activity in various types of human cancer is presented in many preclinical and clinical trials, showing activity in non-small cell lung cancer, colorectal cancer, and head and neck squamous cell carcinoma.

In the sixth chapter, authors describe the apoptotic pathways of cell and their activation, regulation of programmed cell death, the mechanisms used by cancer cells to avoid apoptosis, and prosurvival genes which are awaken to protect them from apoptosis.

The seventh chapter discusses the role of histone deacetylase inhibition which is (along with histone acetyltransferase) an enzyme important for nucleosome core histone acetylation and, therefore, the regulation of gene transcription. It describes various histone deacetylase inhibitors, their biological properties, and mechanisms of antitumor activity in preclinical and clinical studies.

The eighth chapter describes inhibitors of cyclin-dependent kinase modulators. They are a class of possible potent anticancer agents, since cell cycle is governed by cyclical activation of cyclin dependent kinases which are required for phosphorylation of the substrate involved in cell cycle progression. Cyclins have been proven to be involved in the development of several human tumors. Authors explain how cell cycle can be manipulated through kinase activity by agents such as small-molecule cyclin-dependent kinase modulators flavopiridol or UCN-01.

The ninth chapter deals with the importance of COX-2 inhibitors in cell metabolism and the role of COX-2 in tumor cells and mechanisms of its action and inhibition. COX-2 selective inhibitors, which were initially approved as anti-inflammatory agents, showed interesting function in cancer prevention. Celecoxib was approved by Food and Drug Administration for patients with familial adenomatous polyposis (which if untreated, leads to development of colorectal cancer), in spite of increased cardiovascular toxicity of COX-2 inhibitors (namely of rofecoxib). Increased amounts of COX-2 are detected in premalignant and malignant cells, and some of the standard chemotherapeutics appear to increase the level of COX-2. In vitro and in vivo preclinical trials with COX-2 inhibitors showed anticancer action, synergy with radiotherapy and standard chemotherapy, and a substantial role in cancer prevention.

In the tenth chapter, authors present a brief overview of the use of antisense nucleic acids (namely DNA) in drug discovery and drug development. Antisense nucleic acids are single stranded oligonucleotides that are complementary to a certain sequence of target RNA or DNA. Antisense technology with an RNA silencing activity may be used in the identification of gene function, identification of novel therapeutic targets (in various diseases), in pharmacogenetics and pharmacogenomics, and in the development of new drugs. The first antisense drug was approved for the treatment of patients with cytomegalovirus-induced retinitis, while several others are entered in I-III clinical trials as anticancer drugs. This chapter also includes a valuable table showing which antisense oligonucleotides were entered clinical trials and which in preclinical targeting studies. In this chapter, the role of antisense oligonucleotides is explained in a general manner – they interact with complementary target RNA and block gene expression. Although they are not fully understood, several antisense mechanisms of oligonucleotide interaction are described, as well as their chemistry and delivery into cells. In vitro and in vivo preclinical studies showed their influence on survival, proliferation, and invasiveness of cancer cells. For example, oligonucleotide targeting of mouse double minute 2 sequence (MDM2) increased apoptosis, arrested cells in G1 phase, and made them more sensitive to chemotherapy and gamma irradiation. In clinical phase I trials, oligonucleotides were well tolerated, especially after the introduction of oligonucleotides that avoid nuclease degradation and do not activate immune system. Several examples of antisense anticancer drugs with promising results are described, but future studies are needed to confirm the efficacy of these agents.

The last chapter provides a review of preclinical development of pemetrexed – a novel antifolate agent. Although it primarily acts against thymidylate synthase (TS), it is in fact a multitargeted antifolate. It showed its efficiency in various cancer cell lines, including colon carcinoma, breast carcinoma, leukemia, and lung carcinoma. Lower resistance to pemetrexed than to other antifolates confirms its usefulness and supports the idea of inhibition of several targets. Interesting observations from preclinical studies led to the conclusion that, in resistant cells, pemetrexed shifted from its main target (TS) to another enzyme – dihydrofolate reductase (DHFR), but kept its activity. In combination with other chemotherapeutics, it showed mostly synergistic and additive interactions. Pemetrexed was proven to be a valuable agent in preclinical studies and was introduced in clinical studies, although further biochemical experiments are needed to fully characterize its multitargeted action.

Highlights: The book offers an excellent insight into development of molecular targeted antitumor agents, their benefits and limitations.

Limitations: As changes in this field of medicine are numerous and happen fast, journal articles usually offer more up-to-date information.

Related reading: Page M. Tumor targeting in cancer therapy. Totowa (NJ): Humana Press; 2002. Amiji MM. Nanotechnology for cancer therapy. CRC Press; 2002. Rak JW. Oncogene directed therapies. Totowa (NJ): Humana Press; 2002. Syrigos K, Harrington K. Targeted therapy for cancer. Oxford (UK): Oxford University Press; 2003. El-Deiry WS. Death receptors in cancer therapy. Totowa (NJ): Humana Press; 2004. Los M, Gibson SB. Apoptotic pathways as targets for novel therapies in cancer and other diseases. New York (NY): Springer-Verlag; 2005.

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