PREFACE

Successful cancer chemotherapy relies heavily on the application of various deoxynucleoside analogs. Since the very beginning of modern cancer chemotherapy, a number of antimetabolites have been introduced into the clinic and subsequently applied widely for the treatment of many malignancies, both solid tumors and hematological disorders. In the latter diseases, cytarabine has been the mainstay of treatment of acute myeloid leukemia. Although many novel compounds were synthesized in the 1980s and 1990s, no real improvement was made. However, novel technology is now capable of elucidating the molecular basis of several inborn errors as well as some specific malignancies. This has enabled the synthesis of several deoxynucleoside analogs that could be applied for specific malignancies, such as pentostatin and subsequently chlorodeoxyadenosine (cladribine) for the treatment of hairy cell leukemia. Already in the early stage of deoxynucleoside analog development, it was recognized that several of these compounds were very effective in the treatment of various viral infections, such as for the treatment of herpes infections. This formed the basis initially for the design of azidothymidine and subsequently many other analogs, which are currently successfully used for the treatment of HIV infections. As a spin-off of these research lines, some compounds not eligible for development as antiviral agents appeared to be very potent anticancer agents. The classical example is gemcitabine, now one of the most widely applied deoxynucleoside analogs, used for the (combination) treatment of non-small cell lung cancer, pancreatic cancer, bladder cancer, and ovarian cancer. The knowledge gained with the development of all of these compounds formed the basis for the design of a number of novel analogs currently being used for the treatment of various malignancies or currently in an advanced stage of development. Interestingly, several of the nucleoside analogs are also targeted directly against cell cycle regulatory proteins as well as other protein kinases.

In this volume of the Cancer Drug Discovery and Development series, the current status of development and application of deoxynucleoside analogs has been summarized. A number of scientists well known in their specific area contributed with authoritative up-to-date reviews of their field. Their contributions were not limited to writing, but also included sound advice on structure and topics that was extremely valuable. *Deoxynucleoside Analogs in Cancer Therapy* is organized into several parts: the first part (Chapters 1–5) deals with general aspects of drug uptake and metabolism, the second deals with a number of specific drugs (Chapters 6–12),

while the last part covers pharmacokinetics, prodrugs, and specific applications such as radiosensitization and the use of deoxynucleoside analogs as tracers.

In order to be taken up by the cell, deoxynucleoside analogs require specific transporters, whereas other transporters can mediate efflux of (monophosphorylated) nucleosides. Novel technology enabled a rapid expansion of this field in the last decade (Chapters 1–5). Subsequent phosphorylation of nucleoside analogs is essential for their action and is mediated by a number of specific and less-specific deoxynucleoside kinases; their characteristics and regulation are summarized in Chapters 2 and 3. The role of nucleotidases in resistance to nucleoside analogs is described in Chapter 4. Specific viral deoxynucleoside kinases were recognized to be very suitable for local activation of otherwise inactive deoxynucleoside analogs. The HSV-specific thymidine kinase was therefore extensively used in early gene therapy studies. More active deoxynucleoside kinases with broad substrate specificity seem very suitable for future gene therapy applications, as described in Chapters 3 and 16.

A chapter on cytarabine—the first real deoxynucleoside analog widely used in the clinic—is essential to a complete book (Chapter 6). Various novel deoxynucleoside analogs have been developed in the last decade; several aspects of their mechanism of action and applications have been described throughout the above-mentioned chapters, while several of these analogs are described extensively in specific chapters on gemcitabine (Chapters 11 and 12), troxacitabine (Chapter 9), clofarabine, which was approved recently for acute leukemia (Chapter 7), and ara-G (Chapter 10). Two additional chapters deal with prodrug design (Chapter 15) or the novel class of L-nucleosides (Chapter 8).

Modern drug development tends to focus on specific targets, thereby neglecting that, in order to be effective, a drug needs to be taken up by the body and transported to the malignant tissues. A proper understanding of pharmacokinetics and pharmacodynamics of deoxynucleoside analogs is indispensable to their administration (Chapter 14). Also, pharmacogenomics, specific genetic properties of a tumor or a subject, determines whether a tumor will be sensitive to a drug and whether a patient will tolerate a drug. Proper knowledge of a patient's pharmacogenomics profile enables individualized treatment, as described in chapters on specific drugs.

Deoxynucleoside analogs can be considered ideal compounds to be combined with other drugs, either with classical cytotoxic agents or with novel so-called targeted agents such as cell cycle-directed compounds, various protein kinase inhibitors, and angiogenesis inhibitors. These applications are also described in specific chapters, while a specific chapter is dedicated to the excellent radiosensitizing properties of deoxynucleoside analogs (Chapter 13). The last chapter focuses on a novel application of a deoxynucleoside analog, the use of 3'-deoxy-3'-fluorothymidine as

an active tracer in PET with the potential to replace fluorodeoxyglucose in specific applications (Chapter 17).

Throughout *Deoxynucleoside Analogs in Cancer Therapy,* the focus is on novel aspects of deoxynucleoside analogs in the clinical context, as well as on unexpected targets of these compounds, such as their specific activity against cell cycle-dependent kinases or oncogenes. Modern targeted cancer chemotherapy aims to be more specific than in the past, but it has now been recognized that inhibition of just one target often enables the cell to find another pathway, bypassing this inhibition. Current knowledge of deoxynucleoside analogs has already led to successful combinations with novel targeted agents that prevent inhibition of one target from being bypassed by simultaneous activation of another. Future research in this field should use this knowledge to design rational combinations aimed at inhibiting various cellular signaling pathways, enhancing apoptotic pathways, or combining inhibition of various targets. *Deoxynucleoside Analogs in Cancer Therapy* has been designed specifically to facilitate such an interaction between various fields.

Godefridus J. Peters, PhD

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