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Introduction to Cancer Chemotherapeutics

Cancer, the uncontrolled growth of cells, is a major cause of death throughout the world. In 2007, it killed ~7,900,000 people worldwide, a value that represents ~13% of total deaths. In the U.S., the number of deaths caused by cancer is second only to that from cardiovascular disease. While great strides have been made in the treatment of cancer over the past 50 years, it continues to be a major health concern and, therefore, extensive efforts have been devoted to searching for new therapeutic approaches.

The past century has demonstrated that cancer can be effectively treated with surgery, chemotherapy, and radiotherapy. These treatment strategies, when used either alone or in combination, can significantly impact tumor growth and even produce cures. For many solid tumors, as in colon cancer, improved methods for early diagnosis and combination therapies have had an important impact on survival. However, once the tumor has metastasized, treatment becomes more complicated. Even in such cases, current treatment strategies can relegate cancer to more of a chronic disease. Still, significant challenges remain for specific cancer types, such as glioblastoma, in which a combination of early detection, surgery, chemotherapy, and radiotherapy cannot extend survival beyond 1−2 years.

In this issue of Chemical Reviews, we focus on cancer chemotherapeutics. The development of these agents began in the 1940s. Prior to this time, the only treatment available was surgical removal of the tumor. Initial drugs were based on the nitrogen mustards, an extremely powerful class of alkylating agents. While these highly electrophilic reagents can react with a huge number of cellular nucleophiles, their ability to add alkyl groups onto bases in DNA is the critical lesion that results in death of cancer cells. Thus, one of the scourges of WWI—sulfur mustard gas used as chemical warfare—opened the door to a new way of approaching the cancer problem. Around the same time, a second class of cancer chemotherapeutics arose, the so-called antimetabolites (e.g., aminopterin and amethopterin, which interfere with folate synthesis). Unlike the nitrogen mustards, the antimetabolites do not directly attack the DNA bases but rather interfere with synthesis of and/or mimic DNA precursors, thus either halting replication or causing mistakes during DNA replication, eventually leading to cancer cell death. The success of these initial drugs led to the development of a large number of additional antimetabolites. Since the development of these initial drugs, a large number of additional chemotherapeutics that target DNA replication as well as a variety of other biological targets within the cell—such as microtubules necessary for cell division—have been developed.

Donna Shewach received her bachelor's degree from the University of Michigan in 1976 with a concentration in mathematics. She then completed her Ph.D. degree at the University of Texas Graduate School of Biomedical Sciences in Houston with Dr. William Plunkett, where she studied nucleoside analogue anticancer drugs. In 1981, she began her postdoctoral work at the University of Michigan with Dr. Peter Daddona and later Dr. Beverly Mitchell, studying enzymes involved in nucleoside metabolism, including deoxycytidine kinase and its anticancer substrates. In 1988, she joined the Pharmacology faculty at University of Michigan, where she currently holds the title of Professor. Since 1999 she has also held the position of Associate Director of the Upjohn Center for Clinical Pharmacology. The Shewach laboratory focuses on mechanistic studies of nucleoside analogues to develop novel clinical applications for cancer chemotherapy, cancer gene therapy, or chemoradiotherapy. Her work demonstrating that gemcitabine is one of the most potent radiation sensitizers has stimulated numerous clinical trials.

The idea of combination therapy arrived in the 1960s and resulted in tremendous improvements in patient outcome, especially in leukemias in which combination chemotherapy provided the first cures. The logic behind this approach was remarkably accurate—whereas becoming resistant to a single agent requires just one or a few mutations, becoming resistant to multiple agents that attack different targets will require more mutations. Indeed, tuberculosis treatment follows this strategy and, in a sense, the adaptive immune system also uses this logic—by simultaneously attacking a large number of targets on an invading virus or bacteria, the immune system makes it very difficult for the invading organism to respond via mutagenic change. Currently, nearly all chemotherapeutic regimens involve cocktails of drugs.

"We have met the enemy, and he is us," a quote from the comic strip "Pogo" by Walt Kelly, summarizes the primary difficulty of treating tumors using chemotherapeutics, namely, that cancerous and normal cells are

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remarkably similar. Although cancer cells harbor mutated genes and resultant mutated proteins that affect cell division and/or contribute to oncogenesis, the tumor and normal cells share the same DNA and major metabolic pathways. Thus, traditional chemotherapeutic compounds that attack DNA replication or cell division in a cancer cell can also attack a normal dividing cell, resulting in serious side effects such as bone marrow and gastrointestinal toxicity. One advantage of the newer chemotherapeutics that target specific differences between tumors and normal tissue—such as the angiogenesis inhibitors—is that they do not typically exhibit these toxicities.

In this thematic issue, leading experts in various fields relevant to the development and use of cancer chemotherapeutics provide reviews on topics related to this extremely important class of drugs. First, **Berdis** discusses the mechanisms of DNA polymerases, the enzymes that synthesize all new DNA. While DNA polymerases are rarely the actual, final target for chemotherapeutics, the biological activity of some nucleoside-based drugs absolutely depends upon DNA polymerases to incorporate them into DNA. Furthermore, errors by DNA polymerases are a primary cause of the mutations that give rise to tumors and that allow tumors to become resistant to chemotherapeutics. **Parker** then reviews the purine- and pyrimidine-based nucleoside antimetabolites. These drugs, some of which have been around for several decades, are frontline therapies for a large number of different tumors. Indeed, even though one might think that we have thoroughly explored the potential for this class of relatively simple drugs, the imagination of chemists has continued to produce new nucleoside analogues containing modified sugars and/or bases that show promise as new therapeutics.

DNA topoisomerases are critical for DNA replication because of their ability to unwind DNA and relieve superhelical stress in the DNA; hence, inhibiting this class of enzyme potently kills replicating cells. **Pommier** examines the mechanism and inhibition of type I topoisomerases. IMP dehydrogenase, a key enzyme in cellular guanine nucleotide metabolism and, therefore, an attractive target for new therapeutics, is examined by **Hedstrom**. A wealth of mechanistic information on this enzyme exists, and several inhibitors have been evaluated for a variety of therapeutic applications. IMP dehydrogenase has been targeted successfully for immunosuppressive therapy, with continued development directed toward anticancer therapeutics.

DNA synthesis represents the primary target for a large number of cancer chemotherapeutics, and a common feature of many of these drugs is their ability to either directly or indirectly damage DNA. Since tumor cells have the unfortunate property of not wanting to be killed, their ability to sense and repair this damage can mitigate the effects of the drugs. Cells also contain a series of "checkpoints" that can arrest cell cycle progression in response to detection of DNA damage. Again, how the checkpoint apparatus responds to the DNA damage induced by chemotherapeutics can modulate the toxicity of the drug. **Ljungman** reviews the DNA damage response as a potential target for new chemotherapeutics. **Skladanowski et al.** describe the DNA checkpoints and their role in drug targeting and modulating the response to chemotherapeutics. **Tofilon and Camphausen** examine radiosensitization by attacking appropriate molecular targets, including various kinases, checkpoint control, and the DNA damage response. Radiation is widely used for cancer therapy and targets cells by directly damaging DNA; hence, agents that prevent the tumor cell from appropriately responding to this insult could significantly increase the efficacy of radiation. Export of toxic drugs represents an important mechanism by which tumors become drug-resistant. Indeed, once a tumor cell has learned how to export drugs via expression of a transporter, they often resist virtually all drugs of that class (i.e., multidrug resistance). **Eckford and Sharom** review the impact and mechanism of the ABC efflux pumps on tumor cell resistance.

Natural products have historically provided new drugs against a wide variety of diseases, and cancer is certainly no exception. Indeed, the imagination of nature for developing toxic compounds of unusual structure is second to none. **Newman and co-workers** examine the impact of natural products on development of cancer chemotherapeutics. Then **Phillips and colleagues** review the halichondrins and E7389, an exciting new class of potential drugs. These new compounds interfere with microtubule dynamics, a process that established drugs such as taxol also target. The variolins and related alkaloids are discussed by **Morris and co-workers**. These compounds attack specific cyclin-dependent kinases, a relatively new target for the expanding arsenal of anticancer drugs. The cyclin-dependent kinases are a particularly intriguing target for chemotherapeutics because of the critical roles they play in cell cycle progression, apoptosis, transcription, and other aspects of cellular regulation.

Roberts and co-workers examine signaling processes that relate to angiogenesis. Angiogenesis, the development of new blood vessels, is critical for a tumor to grow beyond a minimal, non-life-threatening size. With the clinical success of antiangiogenic drugs such as bevacizumab, which target vascular endothelial growth factor, exploring chemical inhibition of other angiogenesis pathways is an extremely attractive approach for new drug development. Another novel approach uses oncolytic viruses engineered to specifically attack tumor cells with minimal collateral damage to surrounding normal tissue. To date, however, these targeted oncolytic viruses have had only limited success in treating tumors in patients. **Chiocca and co-workers** discuss the host responses that limit replication of these viruses to subvert their efficacy and highlight pharmacologic agents that could potentially increase the ability of oncolytic viruses to kill tumor cells. **Medina and El-Sayed** then review the use of dendrimers to specifically and potently attack cancer cells. Dendrimers represent one facet of nanotechnology and offer the potential of combining enhanced tumor cell targeting along with high-dose drug delivery for killing cells.

Despite recent improvements in selectively targeting cancer cells, as addressed in these reviews, all anticancer drugs cause adverse effects. An important and debilitating adverse effect for patients is the nausea and vomiting associated with many chemotherapeutics. The molecular mechanisms that cause chemotherapy-induced vomiting and potential mechanisms to overcome this problem are discussed by **Darmani and Ray**.

Finally, **Simeone and co-workers** discuss one of the most controversial and potentially important aspects of cancer—do tumors contain "cancer stem cells"—and the implications for developing new therapeutic strategies.

These various chapters provide reviews of some of the most exciting areas for the development of new chemotherapeutics. Hopefully, they may inspire the development of new compounds or approaches that will help reduce the toll from cancer.

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