Preface

The past three decades have seen significant advances in cancer treatment and early detection. Particularly noteworthy are decreased mortality from childhood leukemia, and increased screening for breast, colon, and prostate cancer, resulting in the detection of smaller, less advanced lesions with concomitant improved treatment and, in some cases, improved outcomes. Nonetheless, during this same period overall cancer incidence has increased; morbidity associated with surgery, radiation, and chemotherapy is still considerable; and disappointingly, overall cancer survival has remained relatively flat (1,2). However, there has been an enormous gain in our understanding of carcinogenesis and cancer progression, owing in large part to the technology allowing exploration of signal transduction pathways, identification of cancer-associated genes, imaging of tissue architecture, and molecular and cellular function.

This knowledge has focused cancer therapeutics on drugs that take advantage of cellular control mechanisms to selectively eradicate cancer cells. Several of these new drugs are now on the market—notably, the monoclonal antibody trazumutab (Herceptin®) and imatinib mesylate (Gleevec®). Trazumutab blocks ligand binding to human epidermal growth factor receptor-2 (HER2; also called ErbB2, Neu) (3). HER2/Neu has tyrosine kinase (TK) activity that activates signal transduction involved in cell growth and development, and is associated with cancer progression and resistance to chemotherapy. Trazumutab is approved for use in treatment of metastatic breast cancer that overexpresses HER-2/Neu. Imatinib mesylate is an oral small molecule inhibitor that targets the bcr-abl TK that results from the Philadelphia (Ph) chromosome, which is found in 95% of chronic myeloid leukemia (CML) (4). The drug is approved for treatment of CML. Imatinib mesylate also inhibits platelet-derived growth factor receptor and c-Kit TKs, and has been approved to treat unresectable or metastatic c-kit-positive gastrointestinal stromal tumors (5).

Most importantly, knowledge of carcinogenesis has provided new and promising opportunities to prevent cancer—that is, to treat precancer or inhibit carcinogenesis (a process often involving 20–30 years in human epithelial cancers) rather than waiting to treat the cancer. Sporn (6) coined the term chemoprevention to describe this discipline in oncology: use of drugs, biologics, or nutrients that can be applied at any time in the process before invasive disease to inhibit, delay, or reverse carcinogenesis. Since that time, remarkable progress has been made in developing chemoprevention strategies, started by Sporn’s (e.g., 6) and Wattenberg’s (e.g., 7,8) research on mechanisms of chemopreventive drugs and assays for evaluating these drugs in animal models, and Hong’s early clinical studies on prevention of head and neck carcinogenesis (9,10). In the early 1980s, the US National Cancer Institute (NCI), recognizing the promise of chemoprevention, established a chemoprevention drug development program that has grown to incorporate and support mechanistic research on potential chemopreventive agents, in vitro and animal efficacy screening, efficacy modeling of human cancers, development of cancer biomarkers as potential surrogate endpoints, preclinical toxicology and pharmacology, clinical safety and pharmacology, and clinical efficacy studies. In the mid-1990s, NCI and FDA scientists worked together to develop guidance for developing and obtaining marketing approval for chemoprevention drugs (11). The chemopreventive agent development program has been complemented by worldwide research efforts in screening and early diagnosis, epidemiology of cancer prevention, mechanisms of carcinogenesis, and agent discovery. The 1990s saw the first fruits of chemopreventive agent development—FDA approvals for tamoxifen in prevention of breast cancer (12) and celecoxib in treatment of colorectal precancers (13).

The general strategy for developing chemopreventive agents, as described in the NCI/FDA guidance (11, see also 14–18), is to first characterize the efficacy of candidate drugs using in vitro transformation modulation, chemoprevention-related mechanistic assays, and animal tumor models of carcinogenesis. As for most other drug indications, the most promising efficacious agents then undergo preclinical toxicity, pharmacokinetics, and pharmacodynamics evaluation. Clinical development is planned and implemented for those agents that meet criteria for acceptable toxicity as well as efficacy. Often, additional efficacy and toxicity testing is done to test alternative routes of agent delivery, dosage regimens, new target tissues, and combinations of agents for increased efficacy and decreased toxicity, and to evaluate toxicities seen in early clinical studies.

Clinical development of chemopreventive agents, as for other pharmaceuticals, is carried out primarily in Phase I, II, and III trials. Phase I clinical trials are safety, pharmacokinetics, and pharmacodynamics studies. These...
trials include single-dose studies in both fasting and nonfasting normal subjects to characterize single-dose pharmacokinetics and acute toxicity. Also, repeated daily-dose studies assess multiple-dose pharmacokinetics and chronic toxicity using multiple-dose levels for a period of 1–3 months in subjects at increased risk of cancer(s) for which the drug demonstrates efficacy in preclinical evaluation. Participation of normal subjects for more than one month is considered based on available information (toxicity, clinical experience, etc.) for each drug on a case-by-case basis. In most cases, the Phase I studies evaluate drug effects as well as serum (and sometimes agent tissue) levels of the agent. Agent effects believed to be potentially associated with chemopreventive activity are measured. For example, in studies of nonsteroidal antiinflammatory drugs (NSAIDs), serum and tissue levels of prostaglandins (e.g., PGE2) would be measured. In studies with the irreversible ornithine decarboxylase (ODC) inhibitor eflornithine, tissue levels of polyamines are measured.

Phase II trials are initial efficacy studies. These randomized, double-blind, placebo-controlled trials emphasize the evaluation of phenotypic and genotypic (molecular) biomarkers that are highly correlated to cancer incidence and may serve as surrogate endpoints for cancer incidence reduction. Phase III studies are randomized, blinded, placebo-controlled clinical efficacy trials. These studies are typically large and have the objectives of demonstrating a significant reduction in incidence or delay in occurrence of cancer, validating surrogate endpoints, further assessing drug toxicity, and further characterizing the relationship of dose and/or pharmacokinetics to efficacy and toxicity.

Cancer Chemoprevention Volume 1 is a comprehensive survey of promising cancer chemopreventive agents, grouped by pharmacological and/or mechanistic classes. The agent classes presented vary widely in terms of stage of development as chemopreventives, ranging from such extensively studied groups as NSAIDs and antiestrogens to drugs with recently identified potential based on mechanistic activity (e.g., protein kinase inhibitors, histone deacetylase inhibitors, and anti-angiogenesis agents), as well as agents yet to be evaluated in chemoprevention settings (e.g., proteasome and chaperone protein inhibitors). Attention is devoted to food-derived agents (such as tea, curcumin, soy isoflavones), vitamins, and minerals because of their high promise for prevention in healthy populations. For each agent class, the discussion addresses considerations for chemopreventive drug discovery and development outlined above as they apply to the class in general and to specific agents within the class. Methods for evaluating chemopreventive activity and strategies for chemoprevention in major cancers are described in detail in the second volume of Cancer Chemoprevention.

Antimutagens (Chapters 1–4) block the activity of carcinogens by preventing carcinogen activation (e.g., modifiers of cytochrome P450s described in Chapters 2 and 4) and promoting carcinogen detoxification (e.g., phase 2 enzyme enhancers described in Chapters 1 and 3). The interest in developing phase 2 enzyme enhancers, particularly glutathione-S-transferase (GST) inducers, is considerable because they are found in foods (e.g., cruciferous vegetables, garlic), may be effective in restoring effects of genes masked by hypermethylation (e.g., GST genes), and have demonstrated preclinical chemopreventive activity in multiple cancer targets (e.g., olitipraz).

Antiinflammatories and their derivatives (Chapters 5–11), particularly NSAIDs (Chapters 5 and 6), may be the best substantiated chemopreventive agents. A wealth of mechanistic, epidemiologic, animal efficacy, and clinical intervention (e.g., celecoxib, sulindac, and aspirin) data support the chemopreventive potential of antiinflammatories, as well as their activities against other diseases of aging. Toxicity presents some problems for antiinflammatories. Gastrointestinal bleeding and ulceration are associated with chronic NSAID use, caused by this interference with cyclooxygenase (COX) products (the primary mechanism of action of NSAIDs is COX inhibition). As described in Chapters 5 and 6, several strategies have been explored to limit this toxicity, including use of agents specific for inhibition of COX-2, the inducible, inflammation-associated form of COX, thus sparing normal cell function mediated by COX-1. Other strategies include topical instead of systemic delivery of drug as described for corticosteroids in Chapter 9.

Steroid hormones and their nuclear receptors are targets for chemoprevention because they exert tissue-specific proliferative effects on cells by modulating transcription. Although some of these effects are associated with carcinogenesis and other toxicities, many can be beneficial (e.g., bone-protecting effects of estrogens). Two strategies have been explored for chemoprevention in hormone-responsive tissues—reducing levels of hormones (by inhibiting steroid aromatase and 5α-reductase) and selectively blocking hormone receptors (Chapters 12–16). Antiestrogens have shown high promise as chemopreventive agents (e.g., tamoxifen), and mechanistic studies have suggested that tissue and receptor-specific activities can be exploited to develop third and fourth generation selective estrogen receptor modulators (SERMs) that maximize beneficial activities (Chapters 12 and 16). Although current androgen receptor antagonists have side effects that limit their use in treating asymptomatic men, selective androgen receptor antagonists (SARA) may have activities in androgen-sensitive tissues similar to SERM activities in estrogen-sensitive tissues (the theoretical basis for SARA is described in Chapter 14). Other members
of the steroid superfamily—vitamin D, retinoids, and dehydroepiandrosterenedione (DHEA)—have shown potent chemopreventive activity, but also have some dose-related safety issues. As for the steroid hormones and receptors, much research has been devoted to strategies that avert toxic side effects. For example, Chapters 17 and 19 describe the design of vitamin D and DHEA analogs with reduced toxicity that retain chemopreventive activity. Many side effects of retinoids (e.g., night blindness and dermatitis) result from vitamin A depletion. Chapter 18 describes the design of retinoids that interact selectively with retinoid receptor isoforms associated with carcinogenesis and its inhibition (and may have less effect on vitamin A activities), as well as study designs that lessen toxicity (e.g., retinoid drug holidays and combinations with other chemopreventive agents).

As noted earlier, cellular control mechanisms are of great interest for cancer therapy, and molecules on signal transduction pathways that mediate these mechanisms are potentially good targets for cancer drugs. Because many of these molecular targets are overexpressed, amplified, or mutated in precancers, signal transduction pathways are also of interest as mechanisms for chemoprevention. Chapters 20–28 outline the rationale and potential strategies for chemoprevention at some of these targets: EGFR, ODC, ras, raf, cyclic GMP phosphodiesterase, Hsp90, and molecules involved in cell cycle control. Because signal transduction pathways are also critical to normal cell function, chemoprevention strategies involving these pathways are designed to minimize effects on normal cells. For example, potential chemopreventive agents inhibit targets expressed or depleted only in rapidly proliferating cells or focus on targets at points on the pathways that allow normal cells to function via alternative routes. A few drugs have shown chemopreventive efficacy at these targets (e.g., EGFR and ras inhibitors); however, side effects resulting from their primary mechanisms of action and correlating with their potency raise concerns about safety and tolerability for long-term use in asymptomatic people. For that reason, food-derived agents that demonstrate pleiotropic inhibitory effects on signal transduction are interesting potential chemopreventives because of their expected relatively low toxicity. Soy isoflavones, which are also antiestrogens (Chapter 24) and monoterpenes (Chapter 25), are examples of food-derived agents that have demonstrated chemopreventive efficacy.

Dietary antioxidants (e.g., tea polyphenols, flavonoids) and modulators of fat metabolism (e.g., 4-3 fatty acids, conjugated linoleic acid), vitamins and their analogs (e.g., carotenoids, vitamin C, folic acid), vitamin antioxidants (e.g., lycopene, vitamin E) and minerals (e.g., calcium and selenium) have demonstrated chemopreventive efficacy in animal and, in some cases, clinical and epidemiological cancer settings (Chapters 29–39). However, the development of chemopreventive agents from these sources is complicated. In some cases, identification and use of a key component in the complex dietary mixture (e.g., epigallocatechin gallate in tea) has proven to be a useful sentinel. In most cases, it has only been possible to demonstrate chemopreventive activity of vitamins in deficiency states, making it difficult to evaluate vitamin agents in a clinical setting. These issues are discussed in Chapters 31–37. Activity with tea (Chapter 30) and other dietary polyphenols presents the issues and strategies for identifying chemopreventive activity of complex dietary mixtures.

Recently, interest has increased in evaluating potential chemopreventive agents that may not work directly on precancer cells, but modify the activity of cellular and tissue machinery (Chapters 40–43). Angiogenesis, which requires stimulation of endothelial tissue and is required for growth of neoplastic tissue, has been a target of chemoprevention in particular (Chapter 40). Also, proteasomes can be involved in cell proliferation by promoting activation of transcription factors (e.g., NIB) and their inhibition may have a role in chemoprevention (Chapter 41). Epigenetic modulation of DNA is another new and potentially very productive mechanism for chemoprevention—e.g., by modulation of DNA methylation (Chapter 42) and inhibition of histone deacetylases (Chapter 43). Proof of principle studies have shown chemopreventive efficacy of the DNA methylating agent, azacytidine, and the histone deacetylase inhibitor SAHA in animal studies. As this volume demonstrates, much progress has been made in discovering and developing of agents that have shown or promise to become chemopreventive drugs. The pace of this progress is increasing because of advances in many scientific disciplines that contribute to our understanding, not least of which is delineation of genetic progression models that define the carcinogenesis process from precancer to invasive disease in both humans and preclinical models. These models provide the information and opportunity to discover and develop agents targeted to the specific molecular abnormalities that define carcinogenesis. Data derived from diverse disciplines continue to prove that disruption of carcinogenesis is always more successful when the intervention is early in the neoplastic process, that is, when genetic lesions are less numerous and dysregulation of key pathways is minimal. Therefore, the promise that chemopreventive drug intervention can reduce the human cancer burden is very great. Limited success in achieving this goal thus far relates more to the difficulty and need of obtaining data that candidate drugs are safe on chronic administration than questions of relative efficacy. The dose relationship of antioxidants becoming prooxidants depending on tissue microenviron-
ments, of antihormones becoming agonists based on tissue-specific context, and of signal transduction inhibitors disturbing normal cell function while successfully inhibiting carcinogenesis, are but a few examples of this phenomenon. The field of chemoprevention drug discovery and development will move forward by access to and recruitment of numerous scientific disciplines that allow incremental developments documenting efficacy/safety and net therapeutic benefit at each stage. Important components of this process include definition of molecular targets, creation of in vitro and in vivo models to evaluate inhibition of the targets, establishing assays for measuring drug effect biomarkers, establishing therapeutic dose and incremental safety, stratifying human subjects for cancer risk and presence of relevant molecular targets, and developing biomarkers that can serve as surrogates of clinical response and clinical benefit—all so that human trials of short duration and limited size can be conducted to establish clear clinical benefit or provide data compelling enough to justify large trials. This volume describes the relevant drug classes, drugs, mechanisms of action, and relevant drug effect markers. Volume 2, Strategies in Chemoprevention, describes exciting methodologies that will help accelerate progress in this field, and includes a comprehensive review of the state of clinical development of chemoprevention in the various human cancer target organs.

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