Meeting Report

Molecular Targets for Cancer Prevention: A Meeting Review of the Third American Cancer Society-Schilling Research Conference

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Abstract
The American Cancer Society-Schilling Research Conference, held at Seascape, California, on October 26–29, 2000, convened over 25 experts in interdisciplinary fields to discuss the prospects for molecular targets of cancer prevention. Promising molecular targets fell into four main classes: (a) genes in which altered expression or activation drives induction of cancer and for which inhibitor drugs are commercially available; (b) genes in which altered expression or activation is shown to be causal in two or more models but for which inhibitor/modulator drugs are not commercially available; (c) molecular targets for which drugs are available but of which the causal significance is unknown; and (d) known and unknown molecular targets of preventive dietary modifications. Recent developments in genomics and proteomics have brought us to the threshold of an extraordinarily promising era in our battle to reduce the burden of cancer. Knowledge of genes that drive or prevent cancer progression and genes that specify cancer susceptibility should bring molecular-targeted interventions to the individuals who will benefit most.

Introduction
Scientists know more than ever about the genetic and cellular events that accelerate or inhibit cancer induction. Yet cancer is still the number one health concern of Americans, and most current treatments have clear limitations. In the last few years, genetic information about cancer has been translated into therapies that target specific molecules, and it should be just as possible to exploit molecular targets for prevention. Interventions can occur at any time during the process of multistage carcinogenesis: preventing the initial mutation; blocking promotion to premalignant tumors; stopping progression from the premalignant state to in situ carcinomas; or preventing invasion or metastasis. As the early stages of tumor promotion and progression are rate limiting, successful targeting of molecular events during these stages can have a high impact on outcomes.

Several promising molecular targets for chemoprevention or dietary interventions were discussed at the third American Cancer Society-Schilling Research Conference held at the Seascape Resort, Aptos, California, in October 2000. Promising molecular targets discussed fell into four main classes: (a) genes in which altered expression or activation drives induction of cancer and for which inhibitor drugs are commercially available; (b) genes in which altered expression or activation has been shown to be causal in two or more models but for which inhibitor/modulator drugs are not commercially available; (c) molecular targets for which drugs are available but of which the causal significance is unknown; and (d) known and unknown molecular targets of preventive dietary modifications. Table I summarizes the major classes of molecular targets, their inhibitors, and the cancers potentially affected.

Class I Targets: Genes with Altered Expression or Activity that Drives or Prevents Cancer Induction; Inhibitors Commercially Available
Cox2-2/Colon Cancer. The chemopreventive agents that are farthest along in development and use are inhibitors of Cox-2, an enzyme of the prostaglandin synthesis pathway. Multiple solid tumors (colon, lung, cervix, breast, skin, esophagus, pancreas, and bladder) are known to overexpress Cox-2 and to produce more PGE2 than healthy tissues from the same sources. Both NSAID treatment and Cox-2 gene deletions inhibit intestinal carcinogenesis in carcinogen-induced and genetically induced animal models (1, 2), making Cox-2 inhibitors particularly appealing as tools for chemoprevention of cancer. Aspirin contains inhibitors of both Cox-1 and Cox-2, but the gastrointestinal side effects of Cox-1 inhibition mitigate against the wholesale application of aspirin or other NSAIDs to healthy people.

Ernest Hawk described how the need for specific Cox-2 inhibitors for the alleviation of arthritic pain led to the development of celecoxib and other drugs that were quickly approved by the FDA for that purpose. A National Cancer Institute-FDA-Searle-Pharmacia program was designed to carry out a placebo-controlled Phase II/b trial of celecoxib in FAP patients, who despite early screening, surgery, and surveillance have a 3-fold elevation in colon cancer death rates over the general population. The entire colon in each of the 77 patients

Received 2/15/02; revised 6/12/02; accepted 7/11/02.
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2 The abbreviations used are: Cox, cyclooxygenase; PGE2, prostaglandin E2; NSAID, nonsteroidal anti-inflammatory drug; FDA, Food and Drug Administration; FAP, familial adenomatous polyposis; UVB, ultraviolet B; TPA, 12-O-tetradecanoylphorbol acetate; AP-1, activator protein 1, ERK, extracelluar signal-related kinase; MAPK, mitogen-activated protein kinase; MEK, MAP/ERK kinase; SMI, small molecule inhibitor; RKI, RAF kinase inhibitor; ILK, integrin-linked kinase; ECM, extracellular matrix; PK, protein kinase; PTK, phosphatase and tensin homologue on chromosome 10; MMP, matrix metalloproteinase; MMPI, MMP inhibitor; APC, adenomatous polyposis coli; Min, multiple intestinal neoplasias; TGF, transforming growth factor; cdk, cyclin-dependent kinase; DER, dietary energy restriction; IGF, insulin-like growth factor; POH, perilyl alcohol; BaP, benzo(a)pyrene; NNK, 4-methyl nitrosamine-1-(3 pyridyl)-1-butanol.
D3, which increases the metabolic breakdown of PGE2 to Cox-2 enhancer binding protein appears to drive expression from the human keratin 14 promoter in skin tumor development (8). Transgenic mice that overexpress Cox-2 but also down-regulate hydroxyprostaglandin dehydrogenase (7). Mouse tumors not expressing a dominant negative Raf kinase RKI (Onyx) or PKCδ (280–320 nm), whereas melanoma results from intense, brief exposure to UVB (8). Transgenic mice that overexpress Cox-2 under control of the human keratin 14 promoter were found to develop tumors at a much lower frequency and size and also increased the length of the latent period. The surprising result clearly indicates that more work is needed to resolve the role of Cox-2 in tumor development.

In a search for more specific inhibitors of UVB-induced Cox-2, Timothy Bowden has examined each of the 13 steps in the metabolic signaling leading to Cox-2 induction. In HaCaT cells, treatment with UVB stimulated the binding of c-Fos to Jun D, with the subsequent activation of AP-1 that depended on phosphorylation of MEK by Raf kinase, John Lyons from Onyx Pharmaceuticals and the Bayer Corporation have signed agreements to develop SMI for these targets. Focusing first on the Raf kinase RKI (Onyx) Pancreas, lung, colorectal and PKCδ Skin Cox-2 NSAIDs, celecoxib Colorectal, skin, esophagus, lung, breast, cervical, pancreas, bladder.

Table 1 Summary of molecular targets and inhibitors for chemoprevention

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was videotaped. In patients given 400 mg/day celecoxib, there was a 28% reduction in the number and size of adenomatous polyps, whereas the reduction was only 4.5% in patients receiving placebo (3). The results of this trial led to FDA approval in December 1999 of celecoxib as an adjunct to the usual care of surveillance and surgery in FAP patients. The success of this trial and strong preclinical data supporting the use of Cox-2 inhibitors in other cancers makes trial extension to esophageal, bladder, skin, prostate, and lung cancers a high priority.

**Cox-2/Skin Cancer.** In addition to the role of Cox-2 in colon carcinogenesis, preclinical data suggest that it plays an important role in UVB-induced skin carcinogenesis (4). Epidemiological studies indicate that basal cell carcinoma and squamous cell carcinoma are caused by continuous exposure to UVB (280–320 nm), whereas melanoma results from intense, brief early events (5). Susan Fischer discussed the sensitive-to-carcinogenesis or SKH hairless mouse models of multistage skin carcinogenesis promoted by either TPA or by UVB. Although most human skin cancers are not chemically induced, the biochemical changes occurring after TPA treatment are the same as those induced by UVB. Cox-2 is induced by topical application of TPA to SKH mice, with the subsequent formation of PGE2 (3). Constitutive Cox-2 expression is seen in developing focal patches of tumor. The δ-isofrom of CCAAT/enhancer binding protein appears to drive expression from the Cox-2 promoter in tumors, perhaps offering an alternative way to target Cox-2 (6). Another possible intervention is vitamin D3, which increases the metabolic breakdown of PGE2 to hydroxyprostaglandin dehydrogenase (7). Mouse tumors not only overexpress Cox-2 but also down-regulate hydroxyprostaglandin dehydrogenase, suggesting that prostaglandins provide a selective growth advantage to the developing tumor. Celecoxib achieved a 90% inhibition of tumor development and size and also increased the length of the latent period. The results using topical indomethacin treatment after every UVB exposure suggest that people exposed to UVB might be able to use indomethacin as a morning-after sunburn treatment.

However, recent data from the Fischer laboratory raises questions regarding the role of Cox-2 and prostaglandin levels in skin tumor development (8). Transgenic mice that overexpress Cox-2 under control of the human keratin 14 promoter were found to develop tumors at a much lower frequency and have significantly reduced tumor burdens in response to an initiation/promotion protocol than their littermate controls. This surprising result clearly indicates that more work is needed to resolve the role of Cox-2 in tumor development.

In a search for more specific inhibitors of UVB-induced Cox-2, Timothy Bowden has examined each of the 13 steps in the metabolic signaling leading to Cox-2 induction. In HaCaT cells, treatment with UVB stimulated the binding of c-Fos to Jun D, with the subsequent activation of AP-1 that depended on phosphorylation of MEK by Raf kinase, John Lyons from Onyx Pharmaceutical and the Bayer Corporation have signed agreements to develop SMI for these targets. Focusing first on the Raf kinase RKI (Onyx) Pancreas, lung, colorectal and PKCδ Skin Cox-2 NSAIDs, celecoxib Colorectal, skin, esophagus, lung, breast, cervical, pancreas, bladder.

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Once the target was validated, a variety of approaches was used to generate many compounds that acted as SMI of Raf. One selective inhibitor, RKI, was active on large established tumors in all of the animal models tested. The effects were reversible in that the tumors regrew when the drug was withdrawn. RKI pretreatment of tumors appeared to elicit a better response to cytotoxic drug-induced apoptosis, indicating that RKI could be used in combination with such drugs. RKI went into Phase I trials overseas last year. Currently, Onyx has no plans to test RKI as a chemopreventive, but if RKI pills can be taken long term without deleterious side effects on the non-Raf part of the Ras signaling pathway, those plans could change.

**ILK.** Both epithelial and endothelial cells depend on their proximity to and interactions with the ECM to survive (17). Various steps in carcinogenesis involve the ECM: loss of adhesion; loss of anchorage; resistance to apoptosis; angiogenesis; invasion; and metastasis. When normal cells are deprived of ECM, they go into a specialized type of apoptosis called anoikis, but cancer cells are resistant to both anoikis and apoptosis (18, 19). Cell contact with the ECM is through integrin proteins, which integrate the ECM with the cellular cytoskeleton. Shoukat Dedhar discussed ILK signaling as a potential target for cancer chemoprevention. To examine the signaling pathways regulated by integrins, changes in gene expression were recorded after plating cells on ECM. ILK is the intermediary between integrin and the anti-apoptotic kinase PKB: the ultimate results of inhibiting ILK are down-regulation of cyclin D1 expression and cell cycle inhibition as well as apoptosis (19).

In cells with an intact tumor suppressor PTEN gene, ILK activity is low, and expression of increased amounts of ILK after gene transfection stimulates PKB phosphorylation and activation (20). Many prostate and other tumors lack a functional PTEN gene. A kinase-negative ILK gene, which acts as dominant negative, was derived and found to suppress phosphorylation of PKB in PTEN-null cells (20). The Dedhar lab is collaborating with pharmaceutical companies to derive inhibitors of various enzymes on this critical carcinogenesis pathway. A recently discovered ILK-selective inhibitor, KPSD1, is active in vitro and inhibits PKB phosphorylation and activation in a dose-dependent manner in vitro. In tumors with missing or mutated PTEN, this inhibitor can be used to induce apoptosis or cell cycle arrest, providing proof of concept that small molecule ILK inhibitors could be a useful strategy for control of this pathway (20). Because ILK is up-regulated in colon polyps in both FAP and sporadic colon cancers, it promises to be an important therapeutic target for the control of cancer progression (21).

**Matriylsin.** Matriylsin is a member of the MMP family, a class of enzymes that has classically been viewed as facilitating tumor invasion and metastasis by degradation of the basement membrane. Additional roles for MMPs have been uncovered in earlier stages of tumor progression, including angiogenesis, tumor growth, and tumor development (22). Matriylsin MMP-7, a stromelysin with multiple substrates, is expressed in the majority of malignant adenocarcinomas and many adenomas, making it an attractive target for cancer treatment and prevention.

Lynn Matrisian described studies using the Min mouse, which carries a mutation in the APC gene, the gene mutated in humans with FAP (23). Min mice developed dozens of primary adenomas and died by 6 months of age. Matrisian is expressed in 88% of the early tumor cells, in contrast to other MMPs, which are seen in the stroma in up to 65% of lesions (24). To determine whether the absence of matriylsin could affect the formation of Min adenomas, a matriylsin-null mouse was generated and mated with the Min mouse (24). The resulting matriylsin-null/Min offspring displayed a 58% reduction in tumor number as well as a reduction in tumor size. Of the adenomas that developed in the matriylsin-null mice, 100% expressed gelatinase in the surrounding stroma, suggesting a survival advantage to tumors in which the stroma expresses gelatinase. Using a broad spectrum MMP inhibitor, it was possible to get a 48% reduction in tumor number in Min mice (25), indicating that MMPs are valid targets for the prevention of benign intestinal adenomas.

Three broad-spectrum MMP inhibitors have been tested in Phase III clinical trials, but the results have been disappointing. These trials were carried out in advanced disease. Douglas Hanahan and his colleagues have examined the effects of MMP inhibition on the progression of hyperplastic lesions to adenomas, the ultimate result of inhibiting ILK is down-regulation of cyclin/cdk and inhibiting cell cycle progression from G1 to S (26). Although it is rare to find mutations of p27 in human tumors, it is expressed in the surrounding stroma, suggesting a survival advantage to tumors in which the stroma expresses gelatinase. Using a broad spectrum MMP inhibitor, it was possible to get a 48% reduction in tumor number in Min mice (25), indicating that MMPs are valid targets for the prevention of benign intestinal adenomas.

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**PKCα.** In the mouse skin carcinogenesis model, activation of Ras produces an autocrine loop through the epidermal growth factor receptor. This, in turn, stimulates TGF-α and other epidermal growth factor receptor ligands, resulting in hyperproliferation (27). Ras activation also produces alterations in PKC isoforms. PKCα increases and produces changes in gene expression through alterations in the AP-1 family of transcription factors. At the same time, PKCβ is inactivated by tyrosine phosphorylation, resulting in defective apoptosis. Stuart Yuspa described the use of a PKCα-expressing adenovirus to show that the active kinase migrates to the mitochondria and induces cell death (28). If tyrosine phosphorylation of PKCβ is blocked, cell differentiation takes place instead. Both events are potential targets for prevention. One can envision combinations of targets, one to restore the differentiation program, and another to cause cell death later in the process.

p27. p27, also called Kip1 and CDKN1b, is a cdk inhibitor that blocks cell cycle progression by binding to the active site in cyclin/cdk and inhibiting cell cycle progression from G1 to S (29). Although it is rare to find mutations of p27 in human tumors, one often observes loss of heterozygosity or copy-number sequestration of the p27 protein. Reduced p27 protein expression is highly predictive of reduced survival in breast, colon, prostate, lung, and Barrett’s esophagus cancer patients, indicating an important role for this protein in tumor formation. The p27 knockout mouse created by James Roberts and Matthew. Fero is larger than normal and is prone to develop benign pituitary adenomas (30). When challenged with carcinogens, p27 knockout mice develop tumors in multiple tissues, including adenocarcinomas of the lung and colon. In contrast to the recessive nature of most tumor suppressor genes, p27 is haploinsufficient (30, 31) in that the lack of a second functional copy of the gene in the heterozygous animal is sufficient to unleash widespread tumor formation.

Because of the unexpected appearance of colon carcino-
mas in p27 knockout mice exposed to carcinogens, Christopher Kemp investigated whether there was an interaction of p27 with either p53, which is mutated in ~50% of human cancers, or the APC gene, mutated in >85% of human colorectal cancers. The Min+/− mouse, which is heterozygous for an APC mutation, and p53 knockout mice were crossed with the p27 knockout mice to examine possible interactions. Min+/− mice are predisposed to tumor development in the intestine and die at 15 weeks, whereas the p27+/−/Min+/− heterozygotes developed tumors at 12 weeks. The process took only 9 weeks in Min/−/+p27-nulls, demonstrating a synergy between p27 and APC in colon cancer formation. Reduction of p27 also accelerated the development of pulmonary adenomas, lymphomas, and sarcomas. Prevention strategies might attempt to restore expression of the p27 protein by inhibiting the ubiquitin pathway that degrades it or to engineer a p27 gene with sequences for transport from cytoplasm to nucleus.

AP-1. AP-1 is a DNA sequence-specific transcriptional activator composed of Jun and Fos subunits. AP-1 activation occurs in response to many external stimuli, resulting in induction of AP-1 target genes for mitogenesis, differentiation, transformation, or inflammation, depending on the stimulus and the tissue. The activity of the AP-1 complex is modulated through translational and posttranslational modifications of Jun and Fos proteins, with a key role in stimulation of AP-1 activity played by various MAPKs.

The first clue that AP-1-dependent gene expression might be important in tumor promotion came from the 1989 observation in the laboratory of Nancy Colburn that transformation-resistant variants of mouse JB6 epidermal cells lacked an AP-1 activation response to tumor promoters (32). The use of a dominant-negative jun transgene established that tumor promoter-induced activation of AP-1 is required for induced transformation in this model of tumor promotion as well as in mouse skin. (33, 34). The inhibition of tumor promotion occurred without effects of transgene expression on epidermal differentiation or on the morphology of any tissue. Moreover, transgene expression did not inhibit the tumor promoter-induced hyperproliferation required for tumor promotion.

The initial microarray search of 588 genes for AP-1 target genes revealed no candidates, even among genes having AP-1 sites in their promoters (34). A larger microarray has disclosed a few candidates. This may reflect different signaling thresholds for activating different genes potentially regulated by AP-1. Identification of the functionally significant AP-1 target genes is expected to reveal candidate genes that might alone or in combinations constitute even more effective molecular targets for cancer prevention, especially for SMI therapy.

AP-1/DER. In one of the most intriguing presentations of the conference, Diane Birt described her studies of cancer prevention through DER, which appears to target AP-1 transactivation. DER mice were fed a diet with a 40% reduction in calories from fat and carbohydrates, with all other nutrients equal between groups. In this model, DER inhibited both skin carcinogenesis and AP-1 DNA binding induced by 7,12-dimethylbenz(a)anthracene/TPA initiation/promotion (35). The inhibition of AP-1 DNA binding by DER was reversed by adrenalectomy, but corticosteroid supplementation restored the effect in adrenalectomized animals, demonstrating that the effects of DER on AP-1 DNA binding and carcinogenesis were mediated in part by corticosteroids (35).

The Birt model confirms the involvement of AP-1 in mouse skin carcinogenesis and adds to the evidence that upstream signaling events leading to AP-1 activation are rate-limiting to tumorigenesis in skin. This study provided important mechanistic information regarding AP-1 activation and MAPK signaling events that are targeted by DER. Humans are not willingly going to reduce their caloric intake by 40% but targeting AP-1 by an appropriately modified version of DER, e.g., a one-day-a-week fast, appears feasible.

Class III Targets: Molecular Targets for Which Drugs Are Available; Causal Significance Unknown

IGF-1. Considerable effort is going into the development of selective estrogen receptor modulators such as tamoxifen and raloxifene for the prevention of breast cancer. However, preventing the action of other hormones such as prolactin or IGF-1 might also be effective. Susan Hankinson reported that high levels of IGF-1 are associated with a 3-fold increase in breast cancer risk in premenopausal women (36, 37). Moreover, increased mammographic density is related to high levels of IGF-1 and IGF binding protein 3 in premenopausal women (38). Because increased levels of IGF-1 are also associated with prostate and colon cancer growth and metastases (39–41), there is an even stronger impetus for research in this area. Companies have developed IGF-1 inhibitors, one of which, octreotide acetate, is currently being used in the clinic to treat acromegaly. One could begin a Phase II study right away because the drug is available, regulatory concerns have been addressed, and cohorts and risk have been identified. Steve Hursting also reported that inhibition of tumorigenesis in p53-null mice by calorie restriction might owe its effectiveness in part to downregulation of IGF-1 (42, 43).

One important caveat in the use of IGF-1 inhibitors for cancer prevention is that IGF-1 has positive effects in heart disease, diabetes, and osteoporosis, and giving IGF-1 to the elderly has been shown to increase their muscle mass and feelings of well-being. The challenge is to weigh the risks and benefits of chemical interventions and determine who would benefit most from them.

Class IV Targets: Known and Unknown Molecular Targets of Preventive Dietary Modifications

Target(s) of Monoterpenes. Monoterpenes (e.g., limonene, POH) are common compounds derived from the essential oils found in fruits and vegetables. They selectively inhibit cell proliferation via a G1 block, inducing apoptosis (44). Limonene reduces N-nitrosomethylurea-induced mammary carcinogenesis from two tumors to less than one-half tumor/animal but is toxic in preventive doses. POH, commonly found in the sushi leaf, has a low-grade GI toxicity even at high dosages. Initial results with POH give encouraging hints of prolonged stable disease in prostate cancer, breast cancer, chronic myelogenous leukemia, and ovarian and rectal cancer. Using the method called subtractive display to identify genes repressed or induced by POH, Michael Gould reported changes found in the expression of genes involved in the TGF-β and TGF pathways, as well as of genes related to calcium metabolism. Administration of POH to mice produces a rapid increase in jun, fos, TGF-β, and SMAD2/3 mRNAs in tumor cells, whereas there is no such effect of POH on normal cells, thus explaining its selective toxicity (44). If treated with a carcinogen followed by POH, animals show increased expression of TGF-β and M6P/IGF2R genes. The downstream protein M6P/IGF2R may thus be a good target for chemoprevention.

A second signaling pathway affected by POH is that of calcium. Terpenes can reduce muscle motility at high doses,
with notable effects on calmodulin levels (44). POH rapidly binds to the L-type calcium channel, ultimately producing a decrease in constitutive nuclear factor κB, creating a permissive state for apoptosis. Adding the calcium pathway to the other activities of POH in cancer cells such as (a) inhibiting G protein isoprenylation, (b) increasing TGF-β synthesis, (c) inhibiting cell proliferation, (d) inhibiting nuclear factor κB signal transduction, and (e) increasing apoptosis, one has a compound that should be useful in both prevention and treatment of cancer.

**Targets of Isothiocyanates.** The cytochrome P450 enzymes constitute a large superfamily of hemeproteins involved in the metabolism and detoxification of foreign compounds, endogenous substrates, and dietary components. Over 30 human P450 isoenzyme systems have been identified, and knowledge of how P450 systems operate is critical to our understanding of drug metabolism and drug interactions. One possible mechanism of chemoprevention by isothiocyanates, naturally occurring constituents of cruciferous vegetables, is inhibition of cytochrome P450 enzymes that metabolically activate carcinogens (45).

The goal of Stephen Hecht’s laboratory is to develop effective chemopreventive agents against lung cancer for current and ex-smokers using the tobacco smoke carcinogens themselves as targets. This approach focuses on inhibition of cytochrome P450-mediated activation, or enhancement of the P450-mediated detoxification, of two of the more than 20 pulmonary carcinogens in tobacco smoke: BaP, a polycyclic aromatic hydrocarbon; and NNK, a tobacco-specific nitrosamine (46, 47). Both of these carcinogens require activation of cytochrome P450 enzymes to form DNA adducts that can be repaired by effective DNA repair systems. If the adducts persist, they can cause miscoding in critical oncogenes or tumor suppressor genes, leading to cancer.

Naturally occurring isothiocyanates such as the phenethyl isothiocyanate found in watercress inhibit the P450 enzymes that lead to activation and DNA adduct formation of NNK, and benzyl isothiocyanate, also found in cruciferous vegetables, inhibits the activation of BaP. Chemopreventive compounds that inhibit later events would be of even greater use to ex-smokers. Isothiocyanates may have some value in this regard because they induce apoptosis, but an even more promising mechanism of chemoprevention by isothiocyanates, naturally occurring constituents of cruciferous vegetables, is inhibition of cytochrome P450 enzymes that metabolically activate carcinogens (48).

The further development of effective chemopreventive agents should be a major priority for those determined to reduce the incidence of lung cancer.

Gary Stoner discussed prevention of N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in male Fischer-344 rats (49). The molecular events in esophageal papilloma development are similar in the human and the rat model. Two experimental protocols were used: one in which an inhibitor was administered simultaneously with the carcinogen to give a complete carcinogenesis assay, and the antipotomoter/progression assay in which the carcinogen was administered alone for several weeks followed by administration of a candidate inhibitor. The latter condition more closely approximates what one would expect in cohorts selected for chemoprevention studies. The primary agents found to be effective in the complete carcinogenesis assay were isothiocyanates such as phenethyl isothiocyanate from cruciferous vegetables and ellagic acid found in various fruits such as strawberries and black raspberries (49, 50). Freeze-dried strawberries and black raspberries inhibited esophageal carcinogenesis in the complete carcinogenesis bioassay and in the antipotomoter/progression assay (51, 52).

**Discussion**

We now have evidence that some types of chemopreventives work, at least in the short term. Dietary intervention to prevent cancer is particularly intriguing; it should be relatively easy to get the public involved in testing the benefits of freeze-dried berries in reducing the risk of colon cancer. For those millions of Americans who don’t eat fruits and vegetables, genetically modified foods or chemical additives could introduce the components into the diet.

The use of genetic tools will lead to more accurate classification of tumors and a better understanding of the natural history of the disease. We will be able to tell which cancers require dramatic therapeutic efforts, which can be considered cured, and which can be better managed as chronic diseases. A goal is to identify the individuals whose risks of cancer justify the risks of administering agents that may be effective but whose long-term effects are unknown. Since tumor development occurs over a long period of time, reducing the rate of tumor progression may reduce the frequency of life-threatening malignancies that develop within a lifetime as effectively as preventing tumor induction (Fig. 1). Prevention trials are critically needed for all modalities of prevention: molecularly targeted behavior and dietary changes; reduction of occupational, environmental, and medical exposures to carcinogens; modifiers of hormonal status; vaccines; and pharmaceutical and nutriceutical agents.

This leads us to consider the question of how to allocate our resources on cancer care versus research or prevention. We currently spend $1.3 trillion each year for medical care, which amounts to $4500 for every person in the United States. The attendees of the Schilling Conference advocated that at least one-fourth of that, or $300 billion, should be spent on prevention or on additional research to achieve prevention. Conflicts arise at several levels: health care providers focus on individuals, not public health; health care professionals stress treatment, not behavioral change and prevention; and for-profit organizations thrive on treating diseases, not preventing them.

If prevention of disease can contribute to the bottom line, then the development of prophylactic interventions would be more appealing to corporate research.

Before another generation has passed, we will have catalogued every gene and protein involved in the expression spec-
trum of every type of cancer. Knowledge of genes that drive or prevent cancer progression and genes that specify cancer susceptibility should bring molecularly targeted interventions to the individuals who will benefit most. Thus, we appear to be at the threshold of an extraordinarily promising era in our effort to reduce the toll of cancer on humanity.

Acknowledgments

We thank Gary Stoner and James Whitlock, cochairs of the American Cancer Society-Schilling Research Conference, for their dedication and assistance in planning the program; David Kaufman for helpful discussion and editorial advice; and all of the participants in the American Cancer Society-Schilling Conference for their contributions to the final report.

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Cancer Epidemiology, Biomarkers & Prevention

Molecular Targets for Cancer Prevention: A Meeting Review of the Third American Cancer Society-Schilling Research Molecular Targets for Cancer Prevention Conference

Dawn B. Willis and Nancy H. Colburn


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