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## Commentary

# American Society of Preventive Oncology Distinguished Career Achievement Lecture 2006—Enjoy the Journey: The Long and Winding Road of Chemoprevention Agent Development

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### The Spring Years: The Early Days

My career in chemoprevention derived from an attempt to find a better treatment for cutaneous malignant melanoma (1). This led me to the exploration of retinoids as therapeutic modalities in a number of malignant conditions with the identification of activity in several epithelial malignancies (2-5), particularly squamous cell carcinoma and preneoplastic lesions of the skin (3, 4), as well as in cutaneous T-cell lymphoma (6). These positive results provided strong clinical support for our own subsequent work in chemoprevention of cervical intraepithelial neoplasia and for those investigators who later undertook chemoprevention trials of retinoids in oral leukoplakia and secondary head and neck cancers (7, 8) as well as for the prevention of squamous cell cutaneous cancers and actinic keratoses (9-11).

In the late 1970s, there was also a lot of interest in the differentiation effects of retinoids on leukemic cells. An interesting trial of high-dose vitamin A in patients with chronic myelogenous leukemia (Southwest Oncology Group 79-84) was started, and in 1994, the results were finally reported. A substantial increase in relapse-free and total survival was evident (12), but more targeted therapy was being developed that eventually led to Imatinib (Gleevec). Whether retinoids and Imatinib should be combined is probably worth pursuing at an investigational level as drug resistance seems to occur in many patients.

In a memorable Gordon conference in 1978, I met Michael Sporn. We had a lengthy conversation, and my interest in chemoprevention was sparked. At that time, the gynecologic group at the University of Arizona was very strong, leading to an interest in the potential prevention of cervical cancer. As we wished to avoid the systemic toxicity of retinoids, and concern about teratogenic effects was high, we decided to develop the retinoid  $\beta$ -*trans*-retinoic acid and to deliver it topically to patients with cervical intraepithelial neoplasia. In series, pilot, pharmacokinetic, phase I and II studies were done and reported (13-15). The results of these investigations encouraged us to submit an NIH application to support a randomized trial; an ironic result of the review process was

that the study section strongly suggested that the elegant markers we proposed be dropped. Of course, after the results of the phase III trial were published in 1994 (16), the most frequent question I received for the next few years was, "When are you going to report the biomarker studies?" Although the results of the phase III trial showed some activity in moderate cervical dysplasia (16), toxicity was not insignificant, and the use of topical retinoic acid in the clinical setting for cervical intraepithelial neoplasia is infrequent.

One final important area with which we were engaged was participation, as a clinical unit, in the CARET trial in which supplementation with retinol or  $\beta$ -carotene was used to try to prevent lung cancer in heavy smokers. As is well known, both this study and the ATBC trial from Europe showed that  $\beta$ -carotene increased rather than decreased lung cancers (17, 18). This was a shocking result that led me to take a sabbatical in a redox laboratory and has led to a whole new area of research, including reconsideration of the factors affecting the pathogenesis of cutaneous melanoma (19), returning full circle to where we had started in 1978 when retinoids had been explored as treatment modalities for melanoma (1).

This sojourn with retinoids and those trials in the early years (the 1980s) as well as the experiences of other investigators led to several important lessons:

- Developing chemoprevention agents is hard work.
- Modest efficacy alone is not enough to engender acceptance in the medical community.
- Even fairly mild toxicity is a deal breaker.
- Biomarkers needed to be developed that inform and hasten the process of developing chemoprevention compounds into drugs (ref. 20 for one of the earliest discussions of this topic).
- The field of chemoprevention was, at that time, in the process of separating into public health (low dose, no toxicity whatsoever) and medical approaches (acceptable dose, toxicity proportionate to risk).
- Again, at that time, intraepithelial neoplasias were being identified as important targets for chemoprevention although the issue did not surface widely until many years later (21).

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The entire power point lecture will be provided upon request as will the lecture given on "new thoughts on the pathogenesis of melanoma" mentioned in this report.

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### The Summer Years: Difluoromethylornithine and Bowman-Birk Inhibitor Concentrate

The lessons learned in the early years coincided with my move from the University of Arizona to the University of California, Irvine in 1989. After much internal debate, I decided to leave the retinoids behind, including two Program

Projects (a moment of temporary insanity). We then set out to develop chemoprevention agents that were nontoxic and efficacious. Our first choice was difluoromethylornithine. This compound was rationally developed as an inhibitor of ornithine decarboxylase, the key enzyme in polyamine synthesis, and showed great promise in *in vitro* therapeutic models. We and others were, however, unable to show significant anticancer activity in the clinical setting (22).

Nevertheless, a series of studies in animal models was done in the 1980s that suggested that difluoromethylornithine was an effective chemoprevention agent, particularly against colon cancer (23, 24). These observations led to a series of clinical chemoprevention studies in concert with my Arizona colleague Gene Gerner (25-27). For all these trials, patients who had had a prior colonic adenoma were our target population. The basic strategy was this: because we knew the highest dose at which the drug would be given in a therapeutic trial, we implemented a dose de-escalation design. In the initial 1-month trial, the goal was to achieve a dose that no longer modulated polyamines in rectal colonic mucosa (25). Based on these results, a 1-year trial using three doses of difluoromethylornithine and a placebo group was conducted in which the goal was to show polyamine modulation and no toxicity. An analysis of the results indicated that a dose of 200 mg/m<sup>2</sup>/d decreased polyamines, and that side effects in the difluoromethylornithine group were no greater than that seen in the placebo arm (26).

At that point, in about 1997, we were faced with a critical decision: How should we do the randomized phase III trial in which change in the number of colon adenomas would be the end point? Should the study be difluoromethylornithine alone versus placebo or should difluoromethylornithine be combined with another agent? If another drug, which? Most likely, a nonsteroidal anti-inflammatory drug. If a nonsteroidal anti-inflammatory drug, then nonspecific or specific? A lot of discussion ensued, and we elected to start a randomized phase IIIb trial in which the combination of low-dose difluoromethylornithine and low-dose sulindac was the active arm. The end point was to be a comparison, between treatment and placebo, of the modulation of colonic polyamine and prostaglandin levels and other markers and recurrence and biology of adenomatous polyps. Accrual has been completed, and all patients passed their 3-year colonoscopy evaluation in October 2005; there are continuing discussions with the Data and Safety Monitoring Board as to whether to report this analysis because this study has been morphed into a larger phase III trial (see below).

In the middle of the phase IIb trial, we made the decision to use the study as a basis for a phase III interventional trial with a 2 × 2 factorial design (difluoromethylornithine, sulindac, difluoromethylornithine + sulindac, placebo); however, two unsuccessful attempts at funding led us to simplify the design (although markers were retained!) to a two-arm trial of difluoromethylornithine plus sulindac versus placebo. Accrual was 80% complete at the time of the first Data and Safety Monitoring Board review in February 2006; the recommendations were made that the study should continue, further accrual was not necessary, and long-term audiology testing was recommended. However, the Data and Safety Monitoring Board recommended that no results should be released at this time. Follow-up is continuing. Those interested in a detailed discussion of the development of polyamines, difluoromethylornithine, and chemoprevention are referred to ref. 28.

My interest in Bowman-Birk inhibitor was initiated by Dr. Ann Kennedy of the University of Pennsylvania at a conference on nutrients in 1988. Bowman-Birk inhibitor is a unique protein that was discovered in 1942; a large amount of preclinical data suggest substantial chemoprevention activity. Among its more prominent properties is that this protein remains intact after oral ingestion, inhibits a wide range of proteases, and has a chymotrypsin active site. The unique properties of this agent and the extensive activity of Bowman-

Birk inhibitor in *in vitro* assays and in animal models are summarized in several reviews (29, 30); most relevant to this current discussion was the demonstration of activity in the hamster oral cheek pouch model in 1986 (31), and in 1992, the demonstration of mucosal proteases in exfoliated oral keratinocytes in humans (32). These data provided the basis for development of Bowman-Birk inhibitor as a drug, which was a formidable task. After an IND was obtained, a phase I trial was conducted (33), and subsequently, a 1-month phase IIa single arm dose-escalation study was completed (34, 35). The drug was well tolerated and produced a 32% complete plus partial response rate with a dose-response effect, and modulation of markers, such as the marker neu in serum and oral keratinocytes, were in the anticipated direction (34, 35). Based on these results, a phase IIb 6-month randomized trial was initiated in patients with oral leukoplakia. Eighty of the projected 140 patients have been accrued; four new sites, in different geographic areas, have been added as subject accrual has been exhausted in the initial sites. We anticipate completing this trial by 2008.

This odyssey over the past 17 years has led to several important realizations:

- The development of chemoprevention agents is very hard, takes a long time, and is not for the faint of heart.
- Trying to develop agents without major pharmaceutical backing is dicey and complex at best.
- Implementation of combination chemoprevention is going to be tough.
- Appropriate markers for drug development may or may not be relevant as surrogates for the disease end point.

### The Autumn Years: New Thoughts and New Directions

We need to take a giant step back and examine what we are trying to accomplish with chemoprevention. A few comments and questions to think about:

1. "Proof of principle" of the effectiveness of chemoprevention has been shown in a number of situations, perhaps most convincingly for breast cancer and colon adenomas. And yet, adoption into medical practice has not occurred. Why not? Is it only a matter of finding a drug with strong efficacy and little toxicity (consider statins for cardiovascular disease); is cancer too diverse in its physiologic/molecular makeup to warrant a drug approach for prevention; or is it something more fundamental?
2. Dietary epidemiologic observations for a number of molecules suggest protection against a number of malignancies. In general, these observations have not been validated in randomized trials. Is the problem solely one of measurement (36) or, as we and others have suggested, is it a more fundamental conundrum (37, 38)?
3. Should we be developing chemoprevention only for high-risk individuals (certainly the approval process is easier; e.g., celecoxib for familial adenomatous polyposis, Bacillus Calmette-Guerin for *in situ* bladder cancer, and diclofenac for actinic keratoses)? Then, is the market large enough for pharmaceutical companies to become involved? Is the risk-benefit ratio worth it?
4. How should oncologists engage other subspecialties? Should chemoprevention even be part of the oncology management portfolio? Will coverage for prevention occur more efficiently and universally if oncologists are not the physician of record?

There are many more issues that need to be explored, especially in the broader context of prevention and health maintenance. Recently, an update of IEN has begun to explore some of these issues (39), but much more needs to be discussed and explored, and a deep examination of the field needs to occur.

In the meantime, we are trying to continue our logical approach on two major fronts: new agents and new ideas. Within the next few months, we will be launching the following early-phase innovative trials:

1. A phase IIa trial testing Erlotinib as an intervention against intraductal pancreatic mucinous neoplasms (S. Lipkin, Protocol PI),
2. A phase IIa dose-finding trial among current smoking patients with prevalent aberrant crypt foci to understand the effects of tobacco carcinogens on normal mucosa and aberrant crypt foci (R. Carroll, Protocol PI),
3. A phase IIb placebo-controlled randomized trial in patients with a prior melanoma to test the efficacy of lovastatin on atypical nevi. (K.Linden, Protocol PI),
4. A phase IIb randomized placebo-controlled trial of the safety and efficacy of S-adenosyl-1-methionine disulfate in reducing serum  $\alpha$ -fetoprotein in patients with hepatitis C cirrhosis and moderately elevated  $\alpha$ -fetoprotein (T. Morgan, Protocol PI).

In all these studies, extensive biomarkers will be measured.

Our other novel contribution involves an experimental and epidemiologic reexamination of the pathogenesis of human melanoma. The background for this adventure is discussed in ref. 40. We have done a large number of studies involving biophysical, chemical, and molecular approaches as well as reexamined the epidemiologic data (19, 41, 42). We have come to the following conclusion: the oxidation of melanin and its conversion from an antioxidant to pro-oxidant early in the pathogenic process of melanoma genesis is a key (? first) epigenetic event in the development of human melanoma. This observation has enormous implications for thinking about the etiology, prevention, and treatment of melanoma (19, 41).

### The Winter Years: Thinking about the Next Generation

A major emphasis in the next decade (my last decade?) will be training the next generation both at home (University of California-Irvine) and abroad. I have also had fun thinking about the future and in the year 2000 gave an "after-dinner" talk ("Cancer Prevention 2025: an Anticipation"), which later warped into my first fiction story (43).

I often have heard the late Ernst Wynder say, "The goal of medicine should be to help us to die young at an old age." Kurzweil argues that in 2050, we should be prepared to live forever as a biochip (see refs. 44, 45). Having just passed age 60 this year, I am not sure which option I would choose but I began writing poetry again a few years ago (46) after a long hiatus. I offer these visions.

#### Cyborg

I.  
*Vision focused by glass  
 Hearing amplified by audio  
 Breasts augmented by silicone  
 Hips, knees, wrists, ankles  
 ...artificially constructed.  
 Hearts paced and voices synthesized  
 and now humungous organs for sale.*

II.  
*At what level does the physical become biology  
 and of religious concern  
 when neural interfaces are already in place  
 that make stiff men walk.*

Frank L. Meyskens, Jr.

#### Cherry Blossom Time

*Nature renews.  
 Why not I?  
 It's as if the universe  
 is quantum Wu Li,  
 and I was Newtonian,  
 Or perhaps, on a good day, Einsteinian.*

*But on earth, Winter's bare limbs  
 become Spring's rapture  
 of white and pink.  
 and I just look more grey.*

*If the past is not permissible  
 and the future is always  
 a possibility, what does that  
 make today?*

*I guess it's the day  
 I noticed that I am no longer young.  
 Though my mind is twenty-five,  
 the body is no longer in sync.*

*Perhaps a personal trainer  
 will do the trick,  
 and I can learn to bloom again,  
 like a cherry blossom tree.*

Frank L. Meyskens, Jr.

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# Cancer Epidemiology, Biomarkers & Prevention



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