Foreword

Cancer deaths in general are increasing in the industrialized world at a rate that cannot be explained by population demographics alone [1]. Based on 1992 statistics, cancer is the second leading cause of death in the United States, accounting for 22.4% of all deaths [1].

Many laboratory studies and most epidemiological data suggest that the majority of cancer deaths, approximately three-fourths, are attributable to so-called lifestyle factors (diet, tobacco, and alcohol use) and occupational exposure. The lung and upper aerodigestive tract (buccal cavity, larynx, pharynx, and esophagus) will harbor an estimated 226,000 new cancer cases in the United States in 1992, despite primary prevention efforts [1]. These data suggest that efforts at secondary prevention, *i.e.*, intervention, strategies including chemoprevention, should be aggressively pursued, as should new and existing primary prevention (avoidance) strategies.

The concept of cancer chemoprevention is based on the long-held model of the cancer process as a continuum. Chemoprevention then, is the intervention with chemicals (drugs) that either abolish or delay the development of those processes which begin with normal-appearing tissues and progress to invasion and metastasis. Methods for testing potential chemopreventive drugs differ substantially from testing methods used for chemotherapeutic drugs. Efficacy testing of chemotherapeutic drugs involves cancer patients as the study population and uses reduction in disease and/or improved mortality as study endpoints. Testing of chemopreventive agents, on the other hand, involves basically healthy individuals who may or may not be at increased risk for cancer, and uses the reduction of cancer incidence as the endpoint. Since an individual cancer may develop over decades, the design of clinical trials requires extremely large study populations, lengthy time frames, and high cost [2,3].

Surrogate endpoints, particularly intermediate biomarkers, may help circumvent the length and expense involved in chemoprevention clinical trials. Intermediate biomarkers are defined as morphological and/or molecular alterations in epithelial tissues associated with a phase of carcinogenesis preceding malignancy and are classified as histological, genetic, proliferation-related, and differentiation-related. Experimental studies on the development of intermediate biomarkers and their modulation by putative chemopreventive agents focuses on the reliability and predictive value of the individual markers as measured by such factors as specificity, sensitivity, and overall correlation with cancer endpoints. One of the benefits of intermediate biomarkers in cancer chemoprevention clinical trials is the reduced time interval necessary for the trial since the study endpoints are correlated with earlier stages in the carcinogenesis process. Efficacy trials will also require smaller study populations. As a direct result of these two considerations, chemoprevention trials should be lower in cost than other clinical trials. Finally, the results of efficacy trials for the modulation of biomarkers may serve as the rationale for performing further clinical trials with cancer incidence as the endpoint.

This special issue of the *Journal of Cellular Biochemistry* is the fourth in a series representing manuscripts presented at conferences sponsored by the National Cancer Institute (NCI). The purpose of these conferences is to bring together basic and clinical research scientists to design clinical trial strategies. The concept of intermediate endpoint biomarkers as surrogate trial endpoints was introduced in Supplement 16G, with the colon as the representative organ. The second issue, Supplement 16H, addressed chemoprevention of prostate cancer, the site of the highest incidence of cancer (22%) and the second highest cause of cancer deaths (12%) in US males. The design of chemoprevention trials for the prostate presents the additional problems of competing mortality in older study populations and the lack of dependable methods for detecting microscopic cancers. For this reason, the concept of biomarkers was expanded to include markers of progression. The third issue, Supplement 16I, addressed the chemoprevention of bladder cancer. Ten percent of the cancer deaths in the United States are attributable to cancers of the urinary tract; over 50,000 new cases of bladder cancer were diagnosed in 1992 [1]. The natural history of transitional cell carcinoma of the bladder presents many opportunities for intervention by chemopreventive agents. Trials designed for chemoprevention of bladder cancers involve all the considerations enumerated previously as well as strong components of lifestyle factors (smoking in particular) and occupational exposures.

The subject of this supplement is the chemoprevention of premalignant lesions of the upper aerodigestive tract, the site of an estimated 226,000 new cases of cancer in 1992. The workshop addressed (1) the identification and detection of premalignant markers, (2) characterization of biomarkers, (3) potential chemopreventive drugs, and (4) strategies for the design of clinical trials using surrogate endpoints.

REFERENCES

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