Chapter Two

NATURAL PRODUCT CANCER CHEMOPREVENTIVE AGENTS

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INTRODUCTION

At the current time, cancer claims the lives of approximately seven million people worldwide on an annual basis. In the United States alone, there are approximately one million new cases diagnosed each year, and approximately one-half
millions succumb to the disease. However, various cancer causes and methods of prevention are now obvious, and this knowledge should be brought to bear by members of an enlightened society. As an example, over 100,000 individuals in the United States die per year due to the manifestations of lung cancer, and a large percentage of these deaths could undoubtedly be negated by abolishing the smoking of cigarettes. In fact, the National Cancer Institute has devised a campaign in which the goal is to reduce the 1985 cancer mortality rate by 50% by the year 2000. The approach to achieving this goal is understandably comprehensive. In addition to primary prevention strategies (e.g., cessation of cigarette smoking, reduction of exposure to chemical carcinogens), elements such as early diagnosis, dietary modification, and cancer training programs will need to be emphasized.

An adjunct approach to reducing the incidence of cancer is chemoprevention. Cancer chemoprevention is a term that was coined by Dr. Michael B. Sporn as part of his classical work dealing with retinoids and cancer prevention. It may be defined in general terms as the prevention of cancer in human populations by ingestion of chemical agents that inhibit the process of carcinogenesis. Various groups of compounds have been classified as cancer chemopreventive agents, largely based on the results of animal studies. Of key importance, of course, is the potential of these agents to affect the incidence of cancer in human populations.

Cancer chemoprevention in humans remains largely speculative. However, epidemiological data have suggested inverse correlations between human cancers and various dietary constituents. Particularly strong epidemiological evidence has been provided suggesting an inverse correlation between lung cancer and consumption of carotene-rich foods among smokers. One study involved over 250,000 subjects, and similar conclusions regarding smoking and carotene consumption have been reached in cohort and case-control studies. These types of observations are not limited to carotenoids in that other epidemiological evidence suggests an inverse correlation between vitamin C and esophageal and stomach cancers, selenium and various types of cancer, vitamin E and lung cancer, protease inhibitors and breast, colon, prostate and oral cancers, and folic acid and cervical dysplasia.

While the health benefits of cancer chemoprevention are now generally recognized with human populations, large-scale rational drug discovery has not been undertaken. Thus, it is reasonable to ask “Can additional cancer chemopreventive agents be discovered that will be useful adjuncts or replacements for the agents in the current armamentarium?” The focus of this manuscript will be to describe our efforts in this area of drug discovery and to briefly overview some recent results.

NATURAL PRODUCT CANCER CHEMOPREVENTIVE DRUG DISCOVERY

Certain aspects of natural product drug discovery programs conducted at the University of Illinois at Chicago have been described in the literature as has the overall philosophical approach of natural product drug discovery. For