Journal of Cellular Biochemistry Supplement 27:vi–vii (1997)

Foreword

Progress in Cancer Chemoprevention: Agents

Collaborative chemoprevention projects between the United States (US), China, Korea, and Japan are desirable because each country contributes significant specialized resources and expertise, making the projects proceed more rapidly than they could in any one country alone. The US offers experience in managing short-term Phase II chemoprevention trials, and experience in quantitative measurement of surrogate endpoint biomarkers, including molecular markers, in tissue and cytologic samples, using computer-assisted image analysis to increase precision and objectivity.

Japan has multiple research activities related to the discovery of new chemopreventive agents, particularly those from food, and a pharmaceutical industry capable of supplying new and innovative drugs in the kilogram amounts required for clinical toxicology testing and clinical trials.

Chinese and Korean research institutes have identified many cohorts with premalignant lesions suitable for chemopreventive intervention. Examples of such cohorts of interest are ductal carcinoma *in situ* of the breast, oral leukoplakia, respiratory metaplasia and dysplasia, colon polyps, low-stage bladder and prostate neoplasms, prostatic intraepithelial neoplasia, and cervical intraepithelial neoplasia.

Evaluation of chemopreventive strategies requires good agents, reliable biomarkers, and suitable cohorts. This volume is concerned with chemopreventive agents (Volume 2 deals primarily with biomarkers and cohorts but also covers a few interesting agents). Although many chemopreventive agents have multiple pharmacologic effects, mainly they can be placed into six categories: antiproliferatives, antioxidants, antiinflammatory agents, antimutagens, proapoptotics, and prodifferentiating agents.

This volume begins with two general papers. K.A. Johnson (Food and Drug Administration, Rockville, MD) discusses protocol designs for clinical testing of chemopreventive agents and R. Han (Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, China) reviews recent progress in cancer chemoprevention research in China and his own work on developing new retinoids for cancer chemoprevention. Several presentations describe chemoprevention with antiproliferatives. Specific inhibitors of *ras* farnesylation, such as manumycin, are covered by F. Tamanoi (UCLA, Los Angeles, CA). Perillyl alcohol, which primarily inhibits isoprenylation of the *ras* molecule and other small G proteins to inhibit proliferation, is discussed by L.E. Lantry (Medical College of Ohio, Toledo, OH). In Volume 2, difluoromethylornithine, an inhibitor of ornithine decarboxylase which blocks synthesis of the histamines necessary for cell replication, is presented by A.J.P. Klein-Szanto (Fox Chase Cancer Center, Philadelphia, PA) as a chemopreventive in mouse skin tumors, and also by M. Mitchell (University of Texas M.D. Anderson Cancer Center, Houston, TX) as a chemopreventive of dysplastic progression in human uterine cervix.

The following antioxidants are presented. The effect of curcumin in suppressing benzo[*a*]pyrene-induced skin tumors in mice is discussed by M.T. Huang (Rutgers University, Piscataway, NJ). The subject of tea catechins is a popular one, whether used as extracts, defined mixtures of catechins, or pure compounds. The chemopreventive effects of defined catechin mixtures and pure epigallocatechin gallate (EGCG) are described by Y. Hara (Mitsui-Norin Co., LTD., Fujieda City, Japan), H. Mukhtar (Case Western Reserve University, Dept. of Dermatology, Cleveland, OH), and I. Lee (Korean FDA, Ministry of Health and Welfare, Seoul, Korea). In Volume 2, polyphenolic flavonoids as inhibitors of protein kinase C, in addition to their antioxidant effects, are discussed by J.K. Lin (National Taiwan University, Taipei, Taiwan).

The antiinflammatory agent aspirin is presented by D. Brenner (University of Michigan Medical School and Veterans Affairs Medical Center, Ann Arbor, MI). The following antimutagenic agents are described. Indole-3-carbinol, which suppresses DNA adduct formation in rats given the heterocyclic

amine PhIP, is discussed by H.A.J. Schut (Medical College of Ohio, Toledo, OH). F-L Chung (American Health Foundation, Valhalla, NY) describes the lung cancer chemopreventive potential of thiol conjugates of isothiocyanates. S. Fukushima (Osaka City University Medical School, Osaka, Japan) discusses cancer prevention by organosulfur compounds from garlic and onion. In Volume 2, dose-range finding studies for indole-3-carbinol applied to human breast cancer chemoprevention are described by G.Y.C. Wong (Strang Cancer Prevention Center, New York, NY), and T.W. Kensler (Johns Hopkins University School of Public Health, Baltimore, MD) presents an oltipraz chemoprevention trial in Qidong, Jiangsu Province, China.

With regard to prodifferentiating agents, H. Nishino (Kyoto Prefectural University School of Medicine, Kyoto, Japan) describes cancer prevention by natural carotenoids, and K. Crist (Medical College of Ohio, Toledo, OH) discusses effects of the retinoid *N*-(4-hydroxyphenyl)retinamide on *N*-methyl-*N*-nitrosourea-induced rat mammary tumorigenesis.

Finally, a variety of chemopreventive agents is described by H. Mori (Gifu University School of Medicine, Gifu, Japan), including the preventive effects of chlorogenic acid and protocatechuic acid on tongue, liver, and colon tumors of rodents, and rat colon carcinogenesis inhibition by *S*-methyl methanethiosulfonate and the oxygenated carotenoids astaxanthin and canthaxanthine.

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