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Wednesday 8 November**10:15–12:00****WORKSHOP 5****Chemoprevention and biomarkers****18**

INVITED

Angiogenesis as a target for chemoprevention

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Angiogenesis is necessary for solid tumor growth and dissemination, a promising target not only in cancer therapy but also in prevention. We have shown that various molecules, such as flavonoids, antioxidants and retinoids, act in the tumor micro-environment inhibiting the recruitment and/or activation of endothelial cells and phagocytes of innate immunity. N-acetyl-cysteine, the green tea flavonoid epigallocatechin-3-gallate (EGCG), and Alpha lipoic acid (ALA) all prevent angiogenesis in the Matrigel sponge angiogenic assay in vivo and inhibit the growth of the highly angiogenic Kaposi's sarcoma tumor cells (KS-Imm) in nude mice. The synthetic retinoid 4-hydroxyfenretinide (4HPR) also showed anti-angiogenic effects. Taken together, these data indicate that angiogenesis is a common and key target of most chemopreventive molecules, where they most likely suppress the angiogenic switch in pre-malignant tumors, a concept we termed "Angioprevention". Functional genomics analyses of gene expression regulation by anti-angiogenic chemoprevention compounds in primary human umbilical endothelial cells (HUVEC) in culture through Affymetrix GeneChip arrays identified overlapping sets of genes regulated by the anti-oxidants. In contrast, the ROS-producing 4HPR induced members of the TGF β -ligand superfamily, which, at least in part, explains its anti-angiogenic activity. NAC and the flavonoids all suppressed the I κ B/NF- κ B signalling pathway even in the presence of NF- κ B stimulation by TNF α , and showed reduced expression of many NF- κ B target genes. A selective apoptotic effect on transformed cells, but not on endothelial cells, of the anti-oxidants may be related to the reduced expression of the NF- κ B dependent survival factors Bcl2 and Birc5/survivin, that are selectively over-expressed in transformed cells, by these factors. Inflammation is increasingly recognized as an angiogenic stimulant in cancer, the repression of the NF- κ B pathway suggests anti-inflammatory effects for the anti-oxidant compounds that may also have an indirect role in angiogenesis inhibition. For example, the green tea flavonoid EGCG inhibits inflammation-associated angiogenesis by targeting inflammatory cells, in particular neutrophils.

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INVITED

"Integrative epidemiology" – from risk assessment to outcome prediction

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We propose an integrative epidemiologic approach to studying the entire cancer spectrum from exposure, to predisposition, early diagnosis and ending with cancer outcome, by applying the principles and perspective of epidemiology to the notable advances in molecular biology. This approach begins with epidemiologic case-control studies in which biologically intensive studies can be carried out usually on surrogate tissues (lymphocytes, plasma or serum). Common genetic variants that modulate behavior (eg CYP2A6) may also modify predisposition through altered metabolism of carcinogenic exposures. Tumor DNA can be isolated from serum or plasma, as a useful source for screening specific transcripts or mutations in mitochondrial or nuclear-DNA sequences. Identification of protein patterns in serum using high throughput proteomics linked to novel bioinformatics approaches can be useful for early detection. As we move along the continuum from surrogate to intermediate and target tissues, the procedures become more invasive, the size of the study more restricted, and we apply the case series approach. Pharmacogenetic profiles can be used to individualize therapy and to understand the functional consequences of chemoprevention, chemotherapy, or radiotherapy response. Again, common genetic variants may affect both risk and outcome, eg, matrix metalloproteases. At this level we can also correlate the genetic and epigenetic spectrum of changes in tumor tissue with epidemiologic

data, and with surrogate tissue phenotype and genotype data. The converse direction also applies in that genes demonstrated to contribute to tumorigenesis provide a rich source of candidates for analysis related to exposure, to predisposition, early diagnosis. For example, polymorphisms in the cyclin D1 protooncogene, which is frequently elevated in tumors, are predictors of risk of development of lung cancer. This allows leveraging of the power of approaches arising from the completion of the human genome project that facilitate analysis of genetic changes in tumors on a global basis. This is a powerful new approach that cannot be successfully accomplished by any discipline independently. Integrating these new approaches requires a combination of the rigor of data and sample collection and validation inherent in epidemiologic research with the ability to perform global, unbiased analysis of genetic aberrations in tumors.

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INVITED

The cancer preventive agent identification and early development program at the NCI

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Increasing knowledge of the molecular biology of cancer and improving methods of screening and early detection provide opportunities to prevent cancer initiation and to reverse or delay premalignant progression. To this end the Chemopreventive Agent Development Program of the Division of Cancer Prevention, U.S. National Cancer Institute has established a systematic research and development program to identify, develop, and qualify potential cancer preventive agents for clinical trials. The preclinical stages of the program encompass processes to identify potential agents and molecular targets, in vitro mechanistic and in vivo efficacy screening assays, in vivo intermediate endpoint and cancer incidence/multiplicity testing, and pharmacology and toxicology assessments. With chemical synthesis, manufacturing, and formulation data, also generated by the program, the preclinical in vitro and in vivo results are assembled into Investigational New Drug applications to the U.S. Food and Drug Administration for clinical studies. Clinical studies are initiated as single and repeat-dose phase 1 safety and pharmacokinetic studies and move forward to phase 2 biomarker modulation and efficacy studies. In this presentation, the processes of agent identification and development will be reviewed, particularly emphasizing newer computational approaches to agent identification using QSAR tools to mine chemical libraries for potential leads, toxicities, and molecular targets and to pharmacological evaluations using systems biology to study combinations of agents. Examples of agents currently in development will be presented to illustrate the challenges presented by complex botanical mixtures, biological peptide vaccines, single chemical entities, and combinations of agents. Experimental data illustrating the established methodologies for efficacy and toxicity assessment will be cited. Whether implemented as medical interventions in high risk subjects, dietary and supplement recommendations to population subsets, or changes in screening algorithms, the continued governmental commitment to cancer prevention promises to reduce significantly the economic and medical burden of cancer.

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INVITED

Development of cancer chemopreventive agents post-coxibs

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The realisation that the long term use of the selective COX-2 inhibitors such as celecoxib can be associated with cardiac complications has led to the re-consideration of the risk-benefit assessment associated with their potential use in cancer chemoprevention. The coxib experience has engendered a subtle re-orientation of cancer chemoprevention drug development activities. There are indications according to which the adverse effects of coxibs are dose-dependent, so pre-clinical drug discovery and development efforts have been increasingly directed at the exploration of combinations of low dose coxibs with other drugs e.g. atorvastatin. An alternative development strategy is based on the expectation that diet-derived agents and age-old herbal remedies may have *a priori* a favorable safety record. Thus the characterisation of mechanisms of action and efficacy of naturally occurring agents with potential cancer chemopreventive properties has gained considerable momentum. Our group explores the chemopreventive efficacy, mechanisms, pharmacokinetics and pharmacodynamics of naturally occurring phytochemicals exemplified by silibinin from milk thistle, anthocyanins contained in fruits and berries and tricin from rice bran in the Apc^{Min+} mouse model of gastrointestinal carcinogenesis. All three agents reduced Apc^{Min+} mouse adenoma multiplicity. Measurement in clinical pilot studies of agent levels and biochemical changes germane to anticarcinogenesis in blood and tissues of humans who ingest these agents helps to ascertain whether the levels achieved in the preclinical