blocking ERK1/2 and p38 MAP kinases (7). [6]-Gingerol, a pungent ingredient present in ginger (*Zingiber officinale* Roscoe, Zingiberaceae), inhibited TPA-induced tumor necrosis factor-alpha production, ornithine decarboxylase activity, and skin tumor promotion in female ICR mice (8). Topically applied [6]-gingerol inhibited TPA-induced phosphorylation of p65 at Ser 536 and its interaction with the coactivator cAMP response element binding protein-binding protein(CBP/p300) in mouse skin, thereby rendering NF-κB transcriptionally inactive (9). The NF-κB inhibitory effects of [6]-gingerol appears to be associated with inhibition of p38 MAP kinase. [6]-Gingerol also inhibited anchorage-independent growth of mouse epidermal JB-6 cells stimulated with epidermal growth factor (10). Capsaicin, a major pungent principle of hot chili pepper (*Capsicum annuum* L., Solanaceae) with potential anti-inflammatory and anti-tumor promoting properties, also suppressed TPA-induced activation of NF-κB in mouse skin in vivo (11). It also induces apoptosis in cancerous cells (12). Resveratrol, a phytoalexin present in grapes and red wine, inhibited TPA-induced phosphorylation of IκBα and subsequent p65 nuclear translocation by blocking IKKα and IKKβ (13). It also blocked the TCDD-induced expression of CYP1A1 and CYP1A2 in MCF10A cells, thereby reducing the formation of catechol estrogens from 17-beta estradiol (14). A recent study from my laboratory has revealed that resveratrol protects against oxidative PC12 cells by inducing Nrf2-driven expression of heme oxygenase-1 (15). The green tea polyphenol EGCG also inhibited activation of NF-κB and AP-1 thereby suppressing the COX-2 induction in mouse skin *in vivo* and/or cultured human mammary epithelial (MCF10A) cells (16). EGCG also upregulated antioxidant enzymes by activating the Nrf2-ARE signaling pathway. Cysteine thiols present in various transcription factors and their regulators are recognized to function as redox sensors involved in fine-tuning of transcriptional regulation of many genes essential for maintaining cellular homeostasis. Thus, oxidation or covalent modification of thiol groups present in redox-sensitive transcription factors and their regulating molecules can provide a unique strategy for molecular target-based chemoprevention and cytoprotection with anti-inflammatory and antioxidant phytochemicals (17,18).

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M11-04 **Chemoprevention, Tue, Sept 4, 10:30 - 12:00**

Lung cancer chemoprevention trials

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Lung cancer has been the most common cancer worldwide since 1985. It is the leading cause of cancer death in the world. Close to 90% of lung cancers are caused by tobacco smoking. Smoking cessation unfortunately does not eliminate the risk of lung cancer. In fact, over 50% of newly diagnosed lung cancers are now found in former smokers. The lack of effective therapy underscores the urgency to explore new frontiers of management, such as chemoprevention. Chemoprevention refers to the use of specific agents to reverse, suppress, or prevent the process of carcinogenesis.

Based on epidemiological or preclinical data, several phase III lung cancer chemoprevention trials involving beta-carotene, vitamin A, E, 13-cis retinoic acid and N-acetylcysteine had been conducted but none had demonstrated beneficial results. To facilitate the evaluation of promising agents, focus is now turning toward phase II studies with assessment of surrogate endpoint biomarkers (SEBM) of lung carcinogenesis. With understanding of important cellular signaling pathways involved in malignant transformation, various agents capable of modulating carcinogenic pathways are currently under active investigation. This presentation summarizes ongoing chemopreventive trials sponsored by the National Cancer Institute, many of which entail modulations of the ecosanoid signaling pathway, with a focus on studies involving COX-2 inhibition.

Eicosanoids are lipid metabolites that derive their names from their common origin, the eicosaenoic acids, which are C20 polyunsaturated

fatty acids. The major precursor Arachidonic acid (all-cis-5,8,11,14-eicosatetraenoic acid) is metabolized to prostaglandins (PG) and prostacyclin (PGI) by the cyclooxygenase (COX) pathway, while leukotrienes are formed via the lipoxygenase (LOX) pathway. These down stream lipid metabolites are thought to be involved in carcinogenesis, and ample preclinical findings support modulations of arachidonic acid pathways for inhibition of carcinogenesis. There are two main isoforms of COX: COX-1 and COX-2. COX-1 exists in most cells and is constitutively active. In contrast, COX-2 is an inducible enzyme that is up-regulated by carcinogens, inflammatory and mitogenic stimuli. COX-2 is primarily responsible for the overproduction of PG in inflamed, as well as neoplastic tissues. Overproduction of PGE2 is associated with a variety of carcinogenic mechanism, including abnormal expression of epithelial growth factors, epithelial and microvascular proliferation, resistance to apoptosis and inhibition of antitumor immunity.

COX-2 expression has been demonstrated in premalignant bronchial tissue and lung cancer. Patients with higher levels of COX-2 expression in their tumors have a poorer prognosis. In murine models, COX-2 inhibition impedes lung tumorigenesis, decreases the rate of growth of lung cancer and number and size of metastasis. Expression of COX-2 has been shown to enhance tumorigenesis by regulation of angiogenesis via CXC chemokines and EGFR, invasion via CD44 and matrix metalloproteinases, apoptosis via survivin and insulin like growth factor, and anti-tumor immunity via IL-10 and IL-12. Several clinical trials addressing the use of Celecoxib for lung cancer prevention are underway. Results of a pilot, phase IIa trial in high-risk smokers performed at UCLA suggest that Celecoxib may modulate SEBM with reduction of PGE2 production, restoration of anti-tumor immunity and reduction of proliferation indices (Ki-67 labeling index). A follow-up larger phase IIb trial focusing on heavy former smokers is evaluating the effect of Celecoxib on cellular and molecular events associated with lung carcinogenesis. Another phase IIb trial of Celecoxib in current and former smokers is being conducted at MD Anderson Cancer Center. Moreover, A multicenter study with the lead center at Mayo Clinic using Sulindac, a nonspecific COX inhibitor, is also recruiting patients.

5-lipooxygenase (LOX) is an enzyme involved in the conversion of arachidonic acid to leukotrienes. Leukotrienes have been implicated to play a prominent inductive role in lung carcinogenesis. This is based on data demonstrating that 5-LOX is expressed in lung cancers and 5-LOX inhibitors reduced the multiplicity and incidence of lung tumors in mice. A Phase II Clinical trial of the 5-LOX inhibitor Zileuton has been conducted at the Karmanos Cancer Institute addressing the effect of Zileuton on bronchial dysplasia and multiple SEBM in at-risk smokers or patients with curatively treated aerodigestive cancers.

Another arachidonic acid metabolite of interest is prostacyclin (PGI). It has been demonstrated that up-regulation of PGI decreased tumorigenicity in mice exposed to carcinogens. A multicenter study with the lead center at the University of Colorado is currently enrolling smokers and ex-smokers with sputum atypia in a phase II randomized clinical trial to evaluate the effectiveness of Iloprost, a synthetic analog of PGI. Endpoints include comparisons of phenotypic modulation of bronchial epithelium between the two groups, as well as evaluation of multiple SEBM.

Numerous clinical studies evaluating promising agents in lung cancer chemoprevention are underway. Important goals for future chemoprevention trials include devising strategies to minimize toxicity, identify and validate appropriate SEBM. To this end, integration of new diagnostic technologies such as fluorescence bronchscopy and spiral CT, molecular profiling of risks, using high-throughput technology such as genomics microarray and proteomics, for therapeutic stratification and monitoring, will collectively facilitate the development of effective paradigms for prevention, early detection and treatment of lung cancer.

Session M12: EGFR/VEGF - Inhibitors in Combination with other Modalities

M12-03 EGFR/VEGF - Inhibitors in Comb. w/o Modalities, Tue, Sept 4, 10:30 - 12:00

Pharmacodynamic separation

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Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) given concurrently with chemotherapy do not improve patient outcomes compared to chemotherapy alone in advanced non-small cell lung cancer (NSCLC). One potential explanation for this lack of benefit is a negative interaction or antagonism between chemotherapy and EGFR TKIs when delivered concomitantly. Support for this line of reasoning is provided by preclinical data demonstrating that EGFR TKIs induce primarily a cytostatic effect resulting from a G1 cell cycle arrest in cell lines with wild type (WT) EGFR, reducing cell cycle phase-dependent activity of chemotherapy, whereas they induce apoptotic cell death in tumors with EGFR activating mutations. Thus, sequence-specific interactions of EGFR TKI-chemotherapy combinations may negatively influence the efficacy of these regimens in patients with NSCLC. Preclinical and clinical rationale for studies examining the concept of pharmacodynamic separation as a means for overcoming hypothesized antagonism of EGFR TKIs and chemotherapy as well as recent clinical trial results will be discussed.

M12-04 EEGFR/VEGF - Inhibitors in Comb. w/o Modalities, Tue, Sept 4, 10:30 - 12:00

EGFR/VEGF Inhibitors in combination with other modalities: Zactima (ZD6474) in combination

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In the last years the identification of a number of molecular targets essential and specific for tumor growth, cell proliferation and metastasis development has produced a new class of anticancer drugs, the molecular targeted therapies.

Molecular biology has clearly identified many different tumoral metabolic pathways which are active and crucial to neoplastic phenotype across different histologic solid tumors. Among these, the HER family receptors and neoangiogenesis have been particularly studied and a number of new drugs that inhibit specific growth factors such as epidermal growth factors (EGF) and vascular endothelial growth factors (VEGF) have been developed through phase I-II-III trials as single agents or in combination with chemotherapy and some have been already registered for the treatment of advanced Non Small Cell Lung Cancer (NSCLC).

Among many factors related in promoting angiogenesis, Vascular Endothelial Growth Factor (VEGF) has a recognized critical rate-limiting role because of its ability to regulate key steps in the angiogenesis