activity in AML cells which endogenously express an activated FLT3 receptor. The selective and potent cytotoxicty of FLT3 PTK inhibitors support a clinical strategy of targeting FLT3 as a new molecular treatment option for patients with FLT3ITD/D835 positive AML.

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Tumour associated cellular and molecular changes induced in endothelial cells

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Tumour angiogenesis is a complex process based upon a sequence of interactions between tumour cells and endothelial cells. To model tumour/endothelial cell interactions, we co-cultured U87 human glioma cells with human umbilical vein endothelial cells (HUVEC). U87 cells induced an "activated" phenotype in HUVEC including an increase in proliferation, migration, tube formation and protection from radiation-induced apoptosis. Activation was observed in co-cultures where cells were in direct contact and physically separated, suggesting an important role for soluble factor(s) in the phenotypic and genotypic changes observed. Expressional profiling of tumour-activated endothelial cells was evaluated using cDNA arrays and confirmed by quantitative PCR. Four major functional groups of genes have been shown to be induced in endothelial cells in the result of their interactions with tumor cells. These groups were 1. growth factors, cytokines and chemokines, 2. receptors of growth factors and cytokines, 3. cell structure/motility/extracellular matrix and 4. DNA repair/recombination. Matching pairs of receptors/ligands were found to be coordinately expressed, including TGFbRII with TGFb3, FGFRII and CRF-1 with FGF7 and FGF12, CCR1, CCR3, CCR5 with RANTES and CGRP type 1 receptor with adrenomedullin. Consistent with cDNA array data immunohistochemical staining of expressed proteins revealed the up-regulation of Tie-2 receptor *in vitro* and *in vivo*. Our data suggest that tumour-induced activation of quiescent endothelial cells involves the expression of angiogenesis-related receptors and the induction of autocrine growth loops. Combination of co-culture system with large scale expressional profiling of both counterparts (tumor cells and endothelial cells) may lead to identification of new molecular targets for tumor therapeutics.

Chemoprevention

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Risk targeting and strategy for chemoprevention of head and neck cancer

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Emerging data indicate a link between genetic instability and up-regulation of cyclooxygenase-2 (COX-2). To see if individuals at high risk of oral cancer are candidates for treatment with selective COX-2 inhibitors (coxibs), levels of COX-2 expression in healthy, premalignant and cancerous oral mucosa were compared to the occurrence of DNA ploidy status as a genetic risk marker of oral cancer. COX-2 gene product was detected immunohistochemically in 30 healthy persons, in 22 patients with dysplastic lesions without previous or concomitant carcinomas, and in 29 patients with oral carcinomas. The immunohistochemical findings were verified by in situ hybridization of COX-2 mRNA and Western blotting. COX-2 expression was correlated to DNA content as a genetic risk marker of oral cancer. COX-2 was up-regulated from healthy to premalignant to cancerous oral mucosa. Thus, COX-2 expression was found in 1 case of healthy oral mucosa (3 percent). All specimens from healthy mucosa had a normal DNA content. In patients with premalignancies. In 29 patients with oral carcinomas, cyclooxygenase-2 expression was observed in 26 (88 percent), and aneuploidy was observed in 25 cases (94 percent, P = 0.04). Notably, Of 22 patients with dysplastic lesions, COX-2 was exclusively expressed in a subgroup of 9 patients (41 percent) identified to be at high risk of cancer by the aberrant DNA content of their lesions. Seven of these patients were followed for 5 years or more. An oral carcinoma developed in 6 of them (85 percent; P=0.02). These findings emphasize the need to determine whether coxibs can reduce the risk of oral cancer in patients with high-risk precancerous lesions.

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A phase II trial of an attenuated adenovirus, ONYX-015, as mouthwash therapy for premalignant dysplastic oral lesions

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Oral leukoplakia and erythroplakia are measurable lesions of the oral mucosa that can progress to carcinoma, especially when harboring histologic characteristics of severe dysplasia. It is estimated that 30-40% of these dysplastic lesions contain inactivating mutations of the p53 gene, while a significant proportion of the remainder are likely to have functional defects in p53 response pathways. Surgery can eradicate these lesions but does not reduce cancer incidence. ONYX-015 is an adenovirus lacking the gene encoding E1B 55kd. Since this protein binds to and inactivates cellular p53, and is necessary for efficient viral replication in cells, ONYX-015 should be selectively cytotoxic against p53 deficient cancerous and precancerous cells. The current study sought to establish the feasibility and activity of ONYX-015, administered topically as a mouthwash, to patients with clinically apparent lesions and histologic dysplasia. The trial endpoint was the degree of histologic improvement. ONYX-015 was administered in three different schedules to consecutive cohorts (TABLE). Biopsies of the involved mucosa were performed to evaluate histologic response and changes in expression of p53, cyclin D1, and Ki-67 by immunohistochemistry. Serology was also performed to measure anti-adenoviral titers. A total of 22 (19 evaluable) patients were enrolled on study from August 1998 to January 2002. Complete histologic resolution of dysplasia was seen in 4 (21%) of 19 patients, while the grade of dysplasia improved in an additional 3 patients. Of the patients who had complete responses, 2 have gone on to develop worsening histological features at the same or a new site. No toxicity greater than grade 2 (febrile episode in one patient) and no increase in anti-adenoviral antibodies were seen. A comprehensive analysis of biologic correlates to clinical and histologic responses will be presented. This approach to cancer prevention is tolerable, feasible, and has demonstrable activity.

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COX189 (PrexigeTM), a novel, selective cyclooxygenase-2 inhibitor, totally inhibits formation of intestinal polyps in C57BL/6J-APCmin mouse model of human adenomatous polyposis coli, and reduces neovascularization *in vivo*

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Levels of cyclooxygenase-2 (COX-2) are elevated in various types of cancers, like adenocarcinomas of the colon, breast and pancreas, and squamous cell carcinomas of the head and neck. Inhibition of COX-2 activity delays growth of tumors in animal models, and inhibits neovascularization. Here we describe the antineoplastic activity of a novel, selective, COX-2 inhibitor, COX189 (PrexigeTM, lumiracoxib). The compound, administered as a dietary admixture at 125 and 250 ppm, totally inhibited formation of intestinal polyps in the C57BL/6J-APCmin mouse model of human adenomatous polyposis coli. At higher doses (500, and 1000 ppm) COX189 also reduced the number of existing polyps without lowering the platelet thromboxane B2 levels, indicating that COX-1 was not inhibited under these conditions. In the mouse corneal micropocket assay the compound administered at 250 ppm caused statistically significant reduction of bFGF-induced neovascularization by 66%. The above results confirm that selective COX-2 inhibition, without inhibiting COX-1 activity, result in a potent antitumor activity, which, in part, may result from the inhibition of neovascularization.