initiate molecular and genetic testing, to refer for genetic counselling and risk assessment, and how to interpret genetic test results.
The table provides a summary of the main inherited syndromes that predispose to gastro intestinal cancer and their associated genes and features.

Inherited syndromes that predispose to GI cancer and their associated genes

Syndromes	Associated genes
Familial Adenomatous Polyposis (FAP), attenuated FAP	APC, MYH (rare)
Hereditary Non-Polyposis Colorectal Cancer (HNPCC)	Mismatch repair genes: MLH1, MSH2, MSH6, PMS2 (rare)
Peutz-Jeghers syndrome	STK11
Juvenile Polyposis	SMAD4, BMPR1A
Cowden's syndrome	PTEN
Familial diffuse gastric cancer	E-cadherin
Familial pancreatic cancer	BRCA2, Mismatch repair genes, STK11, CDKN2A

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Chemoprevention of colorectal cancer: from the bench to the bed-side

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At the dawn of this century preventive medicine is becoming a corner stone in our concept of health. This is especially significant in regard to cancer, as it is predicted to become the leading cause of death, surpassing heart disease, by the end of this decade.
Chemoprevention is an emerging science of the current decade which reflects an alternative approach to reducing mortality from CRC as well as other cancers. Chemoprevention involves the long term use of a variety of oral agents that can delay, prevent or even reverse the development of adenomas in the large bowel or the multi-step progression from adenoma to carcinoma. Recent observations suggest a number of potential targets for chemoprevention. Many agents including folic acid, calcium, estrogen, vitamins, olpitraz, ursodiol and fiber have shown a great deal of promise, but only modest chemopreventive efficacy in clinical trials. There is much evidence suggesting a link between aspirin or NSAIDs consumption and CRC prevention, as supported by results from 100 animal studies and 37 epidemiological studies, 34 of which demonstrated a reduction of colorectal tumor incidence in patients regularly taking NSAIDs. However, NSAIDs consumption is not problem-free, as figures from 1997 showed 107,000 hospitalizations and 16,500 deaths due to NSAIDs consumption in the US alone, equaling the mortality from AIDS or leukemia. Therefore, although chemoprevention of CRC is already possible, drugs that have more acceptable side-effect profiles than the currently available NSAIDs are required.
COX-2-specific inhibitors, which have an improved safety profile, in comparison to traditional NSAIDs that inhibit both the COX-1 and COX-2 enzymes, are an ideal drug candidate for the prevention or treatment of cancer for several reasons. The link between COX-2-specific inhibitors and carcinogenesis is now well established; celecoxib (Celebrex, Pfizer, NY, USA) was shown to inhibit the growth of many cancer cell lines. In my lab, celecoxib was shown to be 3–4 times more efficient in inhibiting the growth of transformed cells than that of normal cells. This growth inhibition was associated with induction of apoptosis through the caspase pathway. It is of interest that rofecoxib (Vioxx, Merck, NJ, USA) does not inhibit cell growth in vitro, but is a potent drug in vivo. In COX-2 knockout mice that have been crossed with *Min* mice, the progeny have demonstrated a marked reduction in the number of intestinal tumors. Celecoxib has chemopreventive activity in the azoxymethane (AOM) rat model, and is very effective when administered during the promotion/progression stage of colon carcinogenesis. In humans, up to 50% of polyps and 85% of colonic tumors over-express COX-2. In a recently conducted double blind, placebo-controlled clinical study, subjects with familial adenomatous polyposis (FAP) received celecoxib (400 mg bid) or placebo for 6 months. Celecoxib was well tolerated and effective in the treatment group. Patients treated with celecoxib had a 28% reduction in polyp number and 30% reduction in polyp burden, as compared with patients who received placebo.
International prospective, randomized, placebo-controlled and multi-center trials in the secondary prevention of CRC were launched in the years 1999 and 2000. The primary end point was to evaluate the efficacy of celecoxib and rofecoxib in the secondary prevention of colorectal polyps. Each study recruited between 1,500 to 2,500 patients from over 100 sites. Celecoxib was evaluated in two of these studies. The NCI study, Adenoma Prevention with Celecoxib (APC) trail, compared two doses of celecoxib, 100 and 400 mg bid, with placebo. In a second study, sponsored by Pfizer, the Prevention of Spontaneous Adenoma Polyps (PreSAP) trail, 400 mg of celecoxib qd was compared to the placebo. In a third study, run by Merck, for rofecoxib in the Adenomatous Polyp Prevention on Vioxx (APPROVe), rofecoxib, 25 mg qd, had been evaluated in comparison to placebo.
There has been concern, however, that selective COX-2 inhibitors may increase the risk of cardiovascular events, possibly by reducing endothelial prostacyclin production while leaving platelet thromboxane A2 generation unopposed. Indeed, in 2001, an analysis of the cardiovascular events in the Vioxx Gastrointestinal Outcome Research (VIGOR) trial revealed a higher rate of myocardial infarction in patients taking rofecoxib (0.4 percent) than in those treated with naproxen (0.1%). Subsequently, large-scale observational studies likewise showed an increased risk of cardiovascular events in individuals taking rofecoxib. On September 30th, 2004, it was reported that a similar risk had been seen in the APPROVe study. Consequently, the manufacturer withdrew rofecoxib from the market.
These findings for rofecoxib plus experimental mechanistic data raised concern about all selective COX-2 inhibitors having a possible "class effect" with respect to cardiovascular risk. This was indicated recently by the APC trail, which showed a dose-related increase in the risk of composite of cardiovascular death, myocardial infarction, stroke, or heart failure in patients randomized to receive 200 or 400 mg of celecoxib twice daily (The APC trial). At the same time, the PreSAP study did not show increase cardio-vascular toxicity.
In the intriguing jigsaw puzzle of cancer prevention, we now have a definite positive answer for the basic question "if", but several other parts of the equation (proper patient selection, ultimate drug, optimal dosage and duration) are missing. The most challenging task is to find the proper place for these interventions in the entire effort of cancer prevention, in subjects at risk for colorectal neoplasia, as well as in those at risk for other tumors. The achievement of this important goal may contribute to the conversion of CRC into a truly preventable disease, in up to 90% of cases.

Scientific Symposium
Loco-regional treatment of breast cancer

70 INVITED

Impact of sentinel node procedures and findings for radiotherapy

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Sentinel node biopsy (SLNB) has became almost universally adopted as a substitute for axillary dissection in women with small node negative breast cancer as part of conserving therapy but also in women who undergo mastectomy. With this technique the lymph nodes that receive lymph from a primary breast cancer are visualized. These sentinel nodes can be found in the axilla and reflect, with high sensitivity, the status of the axillary nodes. Besides the axilla, breast cancer spreads to internal mammary chain, interpectoral, intraparenchymal, supra and infraclavicular lymph nodes. Although studies of SLNB with lymphatic mapping using a radiolabelled isotope report the detection of extra-axillary drainage in up to 27% of patients [1], at the present, extra-axillary nodes are not usually considered in the management of early-stage breast cancer. However, the value of elective radiotherapy to these nodes is the subject of ongoing randomized studies in Europe and in Canada. The results of two recent randomized trials and a meta-analysis have fostered renewed interest in internal-mammary nodes irradiation. The need to dissect axillary nodes in patients with early breast cancer and clinically negative axilla is controversial and axillary radiotherapy seems to protect patients from axillary recurrence almost completely [2,3]. The original objective is to improve survival by maintaining an immunological barrier in the axillary lymph nodes. Treating the axilla with irradiation, the process of dissemination was supposed to be influenced in a positive way. The regional control for patients with proven axillary lymph nodes metastasis by SLNB with axillary radiotherapy is the main objective of the EORTC AMAROS trial 10981 in Europe, in patients with an operable invasive breast cancer less than 3 centimetres without clinically suspect regional lymph nodes. More meticulous pathologic examination of the SLN has upstaged breast cancer patients and an unanswered question is if isolated tumour cells and micrometastases are clinically significant and additional surgery or radiotherapy are justified.

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