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Symposium "Molecular early diagnosis of colorectal cancer"

CRC1
PATHOGENESIS OF COLORECTAL CANCER & SCREENING

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An enormous body of literature exists on colorectal adenoma to carcinoma progression, both related to clinical and biological aspects. Inherently, hardly any longitudinal data on humans exist; reason why most knowledge is extrapolated from cross sectional studies, leaving a substantial number of important unresolved issues.
What has become clear is that colorectal cancer is a heterogeneous and complex disease in terms of underlying molecular biology, etiology and clinical phenotype. Yet, the interactions between these areas we are only starting to unravel. Examples of this dilemma are, the time it takes for adenomas to progress to cancer, the proportion of colorectal cancer actually arising form e.g. flat or serrated adenomas, the best surrogate endpoint for screening studies, and the clinical and biological meaning of CIMP.
Optimal understanding of these aspects is mandatory to arrive to the best strategies for colorectal, especially against the background of new molecular tests for early diagnosis of colorectal cancer coming up.

CRC2
SOMATIC MUTATIONS AS MARKERS FOR EARLY DETECTION AND MONITORING OF PATIENTS WITH COLORECTAL CANCER

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The accumulation of somatic mutations is a major mechanism responsible for the development and progression of human cancer. The importance of mutations in tumorigenesis and their irreversible nature make them uniquely specific tumor markers. It has been shown that trace amounts of tumor-specific mutant DNA can be present in plasma, serum, urine, and stool of patients with colorectal cancer, raising the possibility that mutant DNA can be used for early detection and patient management. However, the detection of mutated DNA requires highly sensitive and specific assays, as the number of mutant molecules is small compared to the number of normal DNA molecules in these sample types. We have recently developed a technology called BEAMing (Beads, Emulsion, Amplification and Magnetics), which provides an extremely high sensitivity and at the same time precisely enumerates the fraction of mutant and normal DNA molecules. In a prospective study, we applied BEAMing for the analysis of mutant DNA in plasma and stool samples collected from patients with colorectal cancer. We found that stool DNA is ideal for early detection whereas plasma DNA can be used to monitor systemic tumor burden during treatment. These non-invasive approaches have the potential to greatly enhance early detection, patient management, and the development of new therapies.

CRC3
DNA COPY NUMBER CHANGES IN COLORECTAL ADENOMA-TO-CARCINOMA PROGRESSION

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Genomic instability occurs, in the majority of colorectal cancers, at the chromosomal level giving rise to aneuploidy. While for a long time these chromosomal aberrations have been regarded random noise, secondary to cancer development, it has now been well established that these DNA copy number changes occur in specific patterns and are associated with different clinical behaviour.
Colorectal cancers develop from pre-malignant lesions, adenomas, however only a small percentage of adenomas are estimated to progress to malignancy.
We showed that some of the copy number aberrations observed in colorectal carcinomas are already present in adenomas, which harbour a focus of carcinoma - progressed adenomas, revealing a role of these aberrations in the progression of these tumours.

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Genome-wide expression analysis pinpointed genes, located in the regions of copy number aberrations, whose expression is altered in carcinomas, when compared to adenomas.
Follow-up of both candidate tumour suppressor genes as well as candidate oncogenes is ongoing with a two-fold aim; on one side understanding the biology behind progression of CRC and on the other hand the possibility of using these genes as biomarkers in molecular screening tests for diagnosis and in prognostic tests, such as response to therapy.

CRC4
SCREENING FOR COLON CANCER 2008: NO TEST IS PERFECT BUT ANY IS BETTER THAN NONE

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Until the early 1990s, no evidence was available to show that screening for colorectal cancer (CRC) by any means actually saved lives. Subsequently, sufficient evidence for the efficacy of fecal occult blood testing (FOBT) and flexible sigmoidoscopy allowed the US Preventive Services Task Force to publish guidelines for CRC screening. Since that time the major organizations in the United States concerned with screening guidelines have recommended a menu of screening test options including FOBT, flexible sigmoidoscopy, flexible sigmoidoscopy plus FOBT, barium enema, and colonoscopy. None, except for the American College of Gastroenterology and the American Society for Gastrointestinal Endoscopy, has designated any one of these options as “preferred.”Nevertheless, the American lay press and many U.S. gastroenterology opinion leaders have encouraged Americans to have only one test”colonoscopy. In this presentation I will discuss the various available test options, the rationale for caution in designating one screening test as “the best”and information on how new technology tests can be used to effectively screen for CRC.

Suggested references: 1. Allison JE and Lawson M. Screening Tests for Colorectal Cancer; 2006 A Menu of Options Remains Relevant Current Oncology Reports 2006, 8:492-498. 2. Allison JE, Sakoda LC, Levin TR, et al. Screening for Colorectal Neoplasms with New Fecal Occult Blood Tests: Update on Performance Characteristics J Natl Cancer Inst 2007;99: 1 – 9. 3. Allison JE. The Role of Fecal Occult Blood Testing in Screening for Colorectal Cancer Practical Gastroenterology June 2007 Vol. XXXI; 20-32.

CRC5
COLORECTAL CANCER EPIGENETICS: FROM BIOLOGY TO BIOMARKER

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Aberrant promoter methylation is involved in transcriptional silencing of tumour suppressor- and DNA repair genes in colorectal cancer and has been proposed as biomarker for early detection of this disease.
In order to identify novel tumor suppressor genes and sensitive and specific methylation markers for detection of colorectal cancer we performed genome-wide epigenetic screens. Since promoter methylation is also associated with aging and chronic inflammation, the selection of methylation markers is crucial for sensitive and specific detection of colorectal cancer. These novel methylation markers have been validated in large, well characterised series of tissue, stool and blood of colorectal cancer cases and controls. Comparison of the efficacy and cost-effectiveness of methylation markers against the current gold standards colonoscopy and FOBT is currently ongoing.
These epigenetic screens provide 1) novel insight in the tumor biology of colorectal cancer and 2) novel methylation markers for the early detection of colorectal cancer.

CRC6
PROTEOMICS TARGETED TO SUB-CELLULAR COMPARTMENTS AND SECRETOMES FOR CANDIDATE BIOMARKER DISCOVERY IN COLORECTAL CANCER

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Recent years have seen great upward leaps in the development of mass spectrometry applied to the field of proteomics, the large scale analysis of protein expression, modications and protein-protein interactions. Today it is possible to take a complex biological sample such as organelles, cells, tissue or a biofluid, diseased or stimulated in some way, and identify and quantitate up to several thousand proteins and determine the level of

relative change. Thereby, proteomics may offer insight into biological and disease mechanisms as well as yield novel candidate biomarkers that are translatable to routine clinical use.
In this lecture, I will highlight the potential of LC-MS/MS-based proteomics of sub-nuclear compartments and tumor secretomes in colorectal cancer for discovery of candidate biomarkers and discuss strategies for candidate validation.

CRC7
SERUM PROTEOMICS FOR EARLY DETECTION OF COLORECTAL CANCER

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Serum proteomic expression profiling generated by mass spectrometry is suggested as a promising approach for detection of early stage colorectal cancer. To this end, pre-operative serum samples obtained from 66 colorectal cancer patients and 50 controls were collected. In a randomized block design these samples were used to generate MALDI-TOF peptide profiles after isolation of peptides using C8 magnetic beads. The spectra were preprocessed and linear discriminant analysis in combination with principal component analysis was used to create a model for discrimination of peptide profiles. This model was assessed using double cross-validation. A total recognition rate (92.6%), sensitivity (95.2%) and specificity (90.0%) for the detection of CRC were established. The area under the curve of the classifier was 97.3%, and demonstrated the high, significant separation power of the classifier. Double cross-validation shows that classification can be attributed to information in the profile. New results suggest that methodological influences (e.g. type of affinitive magnetic beads) on cancer-specific information in the peptide profiles have to be further investigated. However, the high sensitivity and specificity indicate the potential usefulness of serum peptide profiles for the early detection of colorectal cancer.

CRC 8
MEDICAL TECHNOLOGY ASSESSMENT OF MOLECULAR SCREENING FOR COLORECTAL CANCER

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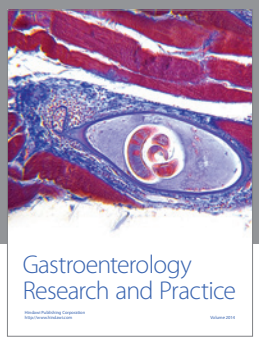
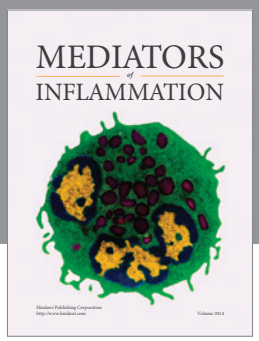
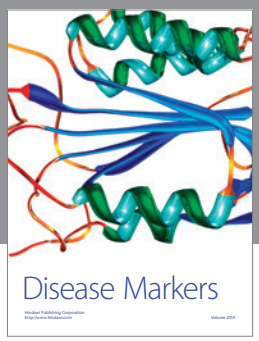
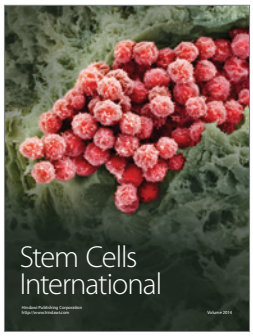
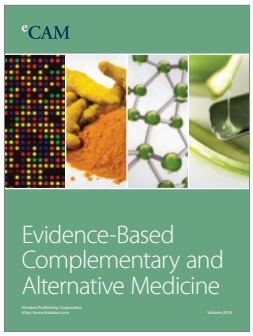
NO ABSTRACT AVAILABLE.

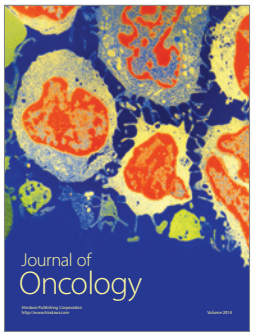


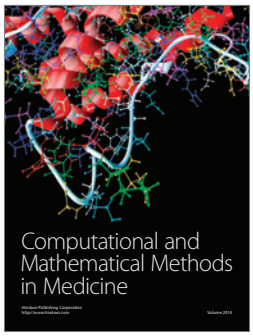


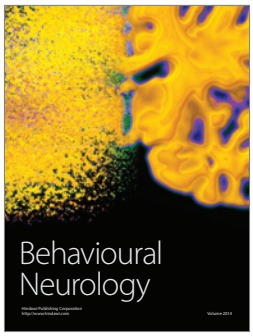


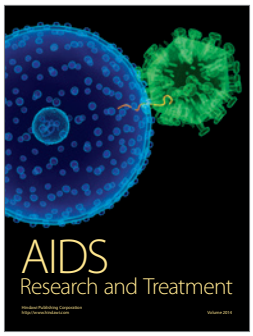


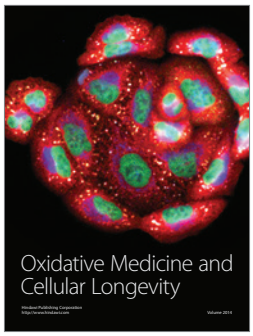












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