80% of the mutations cause a single amino acid change (V599E). We have subsequently shown that BRAF mutations cause activation of the BRAF kinase activity, are transforming in NIH3T3 cells and often (but not always) render the cell independent of signalling through RAS proteins. The patterns of BRAF mutation and their associated biology have revealed new insights into kinase function, pathway function and have generated a plausible new target for drug development. In the future as systematic genome wide mutational screens progress they will reveal insights into global patterns of mutation that differ between individual cancers and cancer types and will provide information on fundamental parameters of human cancers: how many genes are mutated and implicated in the genesis of a single human cancer and how many different cancer genes are there?

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Predicting breast cancer behaviour by genetic analysis

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In the treatment of breast cancer, patient tailored therapy is becoming increasingly important. Decisions on optimal treatment include the choice between mastectomy and breast conserving treatment; dose of radiotherapy; and decisions on adjuvant chemotherapy and hormonal therapy.

Specific DNA alterations, most notably amplification of oncogenes and inactivation of tumour suppressor genes, will have an influence on tumour cell behaviour and may therefore be clinically useful. The assessment of germline alterations in the BRCA1 and BRCA2 genes are already used to identify women with a genetically determined increased risk to develop breast cancer. It has been shown that breast carcinomas with an amplified HER2 gene respond to optimal dosed anthracyclin based therapy and may be less sensitive to tamoxifen. The unravelling of other associations between genetic alterations and tumour behaviour can be expected to impact on the clinical management of breast cancer patients.

Gene expression profiling by micro-array analysis allows the study of the level of expression of large numbers of mRNA's in a single experiment. Gene expression analysis can be used to subclassify tumors on the basis of hierarchical cluster analysis in specific subgroups; supervised cluster analysis can be used to directly link gene expression profiles to clinical characteristics, including prognosis and response to various forms of treatment.

We have used microarray analysis, first on a series of 117 breast carcinomas and more recently on a series of 295 breast carcinomas.

We have defined a gene expression profile of 70 genes that is predictive for a short interval to distant metastases (<5 yrs) in lymph node negative (LN0) patients. We have validated the prognostic value of this gene expression profile in lymph node negative patients; and also in premenopausal lymph node positive patients. The profile outperforms all currently used clinical parameters in predicting outcome of disease.

At present, we are employing gene expression profiling to identify patients at high risk of local recurrence after breast conserving therapy and to predict the responsiveness of primary and metastatic disease to systemic treatment.

As a result, we expect that in the future, gene expression profiling of breast cancer will be used to guide optimal therapy.

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Expression and CGH analysis in soft tissue sarcomas, bladder cancer, and prostate cancer

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We have performed Expression and Comparative Genomic Hybridization studies onto cDNA arrays for a variety of cancer types including sarcomas, prostate cancer and bladder cancer. Expression profiles were obtained for 37 leiomyosarcomas. The dataset was first filtered to select a set of 335 genes whose expression varied most widely between primary and metastatic tumours. Clustering analysis of non-metastatic tumours using this gene set revealed that the tumours could be divided into two distinct groups. The metatstatic potential of primary tumours in the two groups were dramatically different (log-rank test p=0.001). We concluded that expression profile could predict metastatic potential of human sarcomas and that the ability to metastasis was a bulk property of the tumour. Expression studies have also been performed on primary prostate cancer with the objective of identifying new potential prostate markers. In this study we used microarrays randomly selected from a prostate LNCaP cDNA library. Several novel potential prostate cancer markers have been identified. CGH onto Geneset microarrays studies were performed usingh prostate and bladder DNA to identify regions of genetic gain and loss. Several novel classes of genetic alteration have been identified. Acknowledgements: We thank the National Cancer Research Institute, Cancer Research UK and the Medical Research Council for funding this work.

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Proteomic pattern analysis serum for early detection of ovarian cancer

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Diagnosis and management of cancer requires tools with both high sensitivity and specificity. The minimally invasive cervical smear has demonstrated how such a test can change the public health profile of a cancer from deadly to cured. Neither a robust test, nor reliable or specific early symptoms are available for ovarian cancer and other solid tumors. Current approaches testing one protein or gene at a time will not address this expeditiously. New high throughput cost-efficient technologies are needed. These should focus on available patient resources, blood or urine, or minimally invasive approaches such as cervical smears. Proteomics, the study of the expressed proteins and protein fragments, has been applied experimentally to cancer diagnostics. Ovarian cancer is a rare disease with 1:2500 postmenopausal women affected in their lifetime. It is diagnosed in advanced stage in over 70% of women with similar trends for pancreatic, gastric, and other cancers. A specificity of 99.6% on a background of 100% sensitivity is the target requirement for an ovarian cancer biomarker to yield positive predictive value of 10% but is not powered for the detection of early stage cancer, occurring in 15% of ovarian cancer cases. Early detection of ovarian cancer can increase frequency of long term survival to over 90%. The goal of proteomic monitoring is development of a reliable screen to identify stage I/II disease and to allow rapid and optimal patient intervention. We have applied mass spectroscopy (MS)-based proteomic screening of serum with bioinformatic pattern analysis for ovarian cancer biomarker development under the hypothesis that circulating blood contains information from organ-confined disease. Surface-enhanced or matrix-assisted laser desorption and ionization MS has been used to detect low molecular weight proteins, an untapped information reserve. Small serum samples yield datastreams containing over a hundred thousand features. A protein separation on a solid-phase capture matrix directs the view of the proteome. Advanced bioinformatics algorithms mine the MS datastreams for diagnostic patterns of information. The algorithm is trained with data from known samples to define the signature pattern. This pattern is tested with blinded unknowns for validation. The weak cation exchange matrix analysis yielded a experimental diagnostic signature pattern 99-100% sensitive and 99-100% specific when queried with blinded unknown samples (n=250). All 36 early stage cases were correctly identified as cancer. The features comprising the diagnostic pattern can soon be isolated and identified with newer. We are initiating a large scale prospective blinded study to determine the robustness of these early findings and to form the basis for prospective randomized testing. Application of MS coupled with bioinformatic techniques has promise for identification of discriminating protein signature patterns in the blood of organ-confined ovarian and other cancers.

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Early colorectal cancer - treatment choice

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Early colorectal cancer unfortunately is a seldom diagnosis in symptomatic patients. The proportion of 10% however may be increased to 45%, provided that screening for colorectal cancer (CRC) with fecal occult blood test programs are accepted in average risk persons above 50 years of age and positive stool tests are followed by a complete colonoscopy.

The pT-stage may be defined, when the resection margin is free of tumour tissue. Before treatment it is possible to define the T-stage by intraluminal ultrasound examination with a high accuracy; and local excision (endoscopic polypectomy, peranal excision Transanal Endoscopic Microsurgery) of a TI