Chinnaiayan, Arul

Using microarrays to study apoptosis

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TRAIL is a member of the Tumour Necrosis Factor (TNF) Family and a potent inducer of apoptosis in many breast carcinoma cell lines but not in normal human mammary epithelial cells. *In vivo* administration of soluble TRAIL causes regression of breast cancer xenografts without causing measurable toxicity. Combining it with other traditional anti-cancer therapies enhances the efficacy of TRAIL treatment. The basis for the resistance of normal breast epithelial cells to TRAIL-induced apoptosis will be investigated using filter arrays and high-density microarrays. Using a similar approach, the synergy between TRAIL and other cancer therapies will be studied.

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Chuang, Y. Eric

Profiling toxic oxygen related-species–induced gene expression using cDNA microarrays

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Oxidative stress has emerged to encompass a broad variety of biological stresses, some of which have obvious implications for health care. Several modalities used in cancer treatment, including X-rays, phototherapy and some chemotherapy drugs, exert their cytotoxicity by producing oxygen-related free radicals, which imposes an added burden of oxidative stress to normal cellular detoxification systems. Toxic oxygen-related species including superoxide, hydrogen peroxide and hydroxyl radical are produced by diverse initiating agents and both chronic and acute diseases. Thus, it is important to understand the patterns of oxidative stress-induced gene expression, which can provide valuable insight with respect to how oxidative stress influences genetic stability, including the cell cycle, DNA replication and repair, cytotoxicity and mutation. In addition, such information may provide new molecular targets for the development of more effective reagents in cancer treatment. With the invention of microarray technology, we are able to profile gene expression patterns of tens of thousands of genes in a single experiment. In this study, we will use 6.9K cDNA microarrays to investigate the patterns of gene expression following exposure of oxidative stress in human tumour cells (MCF7). We will compare the patterns of gene expression among various toxic oxygen-related species. MCF7 cells will be treated with hydrogen peroxide, menadione or T-butyl hydroperoxide for 1 hour, and then total RNA will be extracted 0, 1, 3, 7 and 24 hours after treatments for cDNA microarrays.

Clarke, Paul A.

Analysis of tumour gene expression following chemotherapeutic treatment of patients with bowel cancer

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Treatment with drugs can alter tumour gene expression. We are interested in using DNA array approaches to examine alterations in the pattern of gene expression following chemotherapeutic treatment and have used this technology to analyse gene expression in tumours before and during treatment with DNA-damaging agents or signal-transduction inhibitors (see accompanying abstract by Workman *et al.*). The aim of this strategy was to profile constitutive gene expression and identify drug-responsive genes that may have potential as surrogate markers for drug action or future targets for drug development. To apply the technology to the clinical situation, tumour biopsies were obtained from patients with inoperable bowel cancer. These patients were enrolled in a clinical study examining the utility of a chemotherapeutic regime to reduce tumour volume sufficiently for surgical resection. This regime consists of a single dose of mitomycin C and a protracted venous infusion (PVI) of 5-fluorouracil (5-FU). On evidence of reduced tumour volume, the patients undergo further treatment and the remaining tumour is removed by surgical resection. Diagnostic tumour biopsies were taken by endoscopy before treatment and subsequent biopsies were taken 6 weeks into the treatment with 5-FU. A small portion of each biopsy was set aside for gene expression analysis. Poly(A)$^+$ mRNA was extracted from the biopsy and radiolabelled by reverse transcription from oligodT primers in the presence of [a^{33}P]dATP. Labelled single-strand cDNA was hybridized to commercially available arrays containing IMAGE/LLNL cDNAs and the data collected by phosphorimaging. Good reproducibility was obtained between experiments and changes in gene expression during treatment were detected. These included increased expression of thymidylate synthetase and uracil DNA glycosylase, consistent with treatment of 5-FU. Additional data profiling constitutive gene expression and expression in response to treatment will be presented.

Corbeil, Jacques

Magnitude and specificity of temporal gene expression during HIV-1 infection of a CD4+ T cell

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We have developed an application called HAPI (High-Density Array Pattern Interpreter), which facilitates the analysis of microarray data by selecting subsets of genes with specific characteristics and displaying them with dynamic links to web-based databases. This allows comparison of subsets of selected genes by determining similarities and common properties of a selected set of genes using a