ly from the tumors. Within the tumor group, the clear-cell and chromophobe carcinomas demonstrated markedly distinct patterns of gene expression. To assess the functional differences between the two types, we selected genes using a twofold change threshold in expression common to both samples of each tumor type and assigned functional classification to each gene where possible. Gene function was divided into 16 different cellular categories using the *Saccharomyces cerevisiae* functional categories of the Munich Information Center for Protein Sequences as a guide. Graphical representations of the numbers of genes from each category indicated that the clear-cell tumors might have different cellular functions than the chromophobes. We will use this database in future work to assess the differences between animal xenografts and human renal tumors.

Gillanders, E. [66]

Use of experimentally constructed haplotypes in gene mapping studies of hereditary cancers

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The technique of conversion provides several advantages for gene mapping projects of complex diseases such as cancer. The approach takes advantage of selective retention of a subset of human chromosomes within somatic cell hybrids, isolating single copies of all desired human chromosome pairs. This strategy functions both to simplify mutation detection, as well as allow unambiguous phase information to be determined. Constructing haplotypes on the basis of conventional genotype and pedigree data is challenging, particularly for late age of onset diseases such as cancer.

Identification of which homolog is retained in a particular hybrid is determined by conventional genotyping of a few markers per chromosome. These 'haploid' hybrids can then be used to increase the sensitivity of traditional mutation analysis as the disease causing chromosome will not be accompanied by the normal wild-type allele. Additionally, haplotypes maybe determined simply by genotyping each haploid hybrid. We have typed DNA from 100 hybrids to examine chromosomal retention patterns, test the feasibility of conversion for whole genome analysis, and evaluate assumptions regarding appropriate experimental design.

We have investigated the theoretical efficiency of using haplotypes compared to conventional genotypes in linkage and linkage disequilibrium studies. In the linkage disequilibrium setting, we determined the Fisher information (with respect to haplotype frequency) provided by unrelated individuals. For two-SNP haplotypes, conversion provides 5–45% more information per subject than standard genotyping, depending on true haplotype frequencies; for five-SNP haplotypes, improvement ranges 20–92%. As Fisher information is inversely related to sample size, conversion requires up to 12.5 times fewer subjects than standard genotyping to obtain the same information. We currently are completing similar calculations in the linkage analysis setting. The extra cost associated with conversion includes hybrid construction and characterization, and duplicate genotyping. However, the increased information per subject reduces overall recruitment and phenotyping costs, which tend to dominate those for genotyping. The efficiency of using conversion to construct haplotypes is likely to increase even further as automated methods of genotyping continue to improve.

Gokgoz, Nalan [67]

Analysis of gene expression patterns in breast cancer by microarray technology

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Although alterations in several specific genes have been implicated in breast cancer progression, greater understanding of the molecular basis of the disease may result from the evaluation of global gene expression patterns using microarray technology. To identify patterns of gene expression of prognostic importance in axillary node–negative breast cancer, we are studying a large cohort of patients with this type of cancer. Before using the limited amount of RNA from these specimens, we performed pilot studies designed to evaluate the feasibility of applying the technology on a larger scale. We studied gene expression in four different breast cancer cell lines (T47D, MDA231, SKBR3 and BT474) using complementary DNA microarrays containing 1,700 and 19,000 sequence-verified human cDNAs produced by the microarray facility at the Ontario Cancer Institute, Toronto (http://www.oci.utoronto.ca/services/microarray). Each hybridization compared Cy5-labeled complementary DNA from one of the cell lines with Cy3-labeled cDNA from a reference sample (MCF12A, a normal breast cell line). We also performed reciprocal labeling with subsequent hybridization to demonstrate the consistency and reproducibilty of the technology. In addition, different amounts of RNA (50 µg, 25 µg and 10 µg) from the same cell lines were labeled to determine the sensitivity of the system. We have been able to devise a system that can now be applied to primary breast tumors. After expression analysis, we will use biostatistical modeling to detect clusters of genes that are coordinately expressed, repressed or both. These clusters are likely to represent common pathways of genes involved in breast carcinogenesis.

Golubic, Mladen [68]

Genetic basis of radiation response in glioblastoma multiforme

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Glioblastoma multiforme (GBM) is an almost uniformly fatal brain tumor; patients have a median survival time of less than one year despite aggressive treatments, including surgery, radiation and chemotherapy. Despite the clear benefits of radiation therapy in prolonging the survival of some patients with GBM, only about one-third of them demonstrate an objective radiographic response. To pinpoint the genetic difference between GBMs that responded well to radiation treatment and those that did not, we analyzed the gene expression profiles of two non-responding (NR) and two responding (R) tumors using Affymetrix Hu6800 oligonucleotide arrays. Comparison between two paired tumor samples (R versus NR) revealed that 423 and 236 genes were differentially expressed (sort score 0.5). Of those, 33 genes showed consistently increased or decreased expression in both R tumors compared with NR tumors. These differentially expressed genes are known to regulate cell motility, cellular responses to DNA damage, cell cycle, angiogenesis and apoptosis. For example, decreased expression of genes known to stimulate tumor cell motility and increased expression of genes that inhibit cell migration was observed in R tumors. We also determined the gene expression of