tumor development in association with data on gene alterations, such as p53 mutations and deletion of the *p16/p14ARF* locus, which are hallmarks of previously defined genetic pathways. Our preliminary results with eight tumors confirm upregulation of some genes already known to be important in the development of glioblastoma and the exclusivity of some genetic pathways (p53 mutations versus *EGFR* overexpression). We have created expression profiles of 120 differentially expressed genes using the Cluster program from Stanford University, and we have grouped tumors according to genetic pathways. We will link patterns of differential gene expression to clinical outcomes to identify subtypes of tumors with distinct clinical behavior.

Helou, Khalil [8]

The *Hgfr/Met* oncogene is the target for gene amplification in DMBA-induced rat sarcomas

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Analysis of chromosome rearrangements in tumors is an important means for revealing genetic pathways underlying tumorigenesis and tumor progression. In a set of 17 rat sarcomas induced by exposure to 7,12-dimethylbenz[*a*]anthracene (DMBA), we had previously found homogeneously staining regions (which are generally accepted as cytogenetic signs of gene amplification) in 5 tumors, using cytogenetic analysis. By employing comparative genomic hybridization, we detected regional increases in DNA copy number of the proximal part of rat chromosome 4 (RNO4) in the tumors harboring homogeneously staining regions. We detected amplification of the *Hgfr/Met* oncogene, located at RNO4q21.2, by fluorescence *in situ* hybridization (FISH) in all five tumors. In four of them, several flanking genes located in the near vicinity of *Hgfr/Met,* including *Cav1* (q21.1), *Wnt2* (q21.2?q21.3) and *Cftr* (q21.3), were also amplified, although amplification was seen in a smaller fraction of the cells than *Hgfr/Met* amplification. In the fifth tumor (BL150T), *Hgfr/Met* was amplified in all cells and was the sole amplified gene of those tested. In addition the *Hgfr/Met* FISH signals in BL150T were tightly clustered and formed compact and intense spots compared with the signals seen in the other four tumors. Application of the free chromatin FISH technique to BL150T showed that the genomic *Hgfr/Met* probe stained the extended chromatin fibers of up to 1.5 megabases with an almost uninterrupted signal, indicating that the BL150T amplicon was build up solely from *Hgfr/Met* gene sequences. Our results indicate that the *Hgfr/Met* oncogene may be the primary target for amplification in a subset of rat DMBA sarcomas.

Hermann, Thomas [9]

Effects of the RXR-specific ligand Targretin on gene expression in carcinogen-induced mammary tumors in the rat

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Targretin (LGD1069), a high-affinity ligand for the retinoid X receptors (RXRa, RXRb and RXRg), is highly effective in the prevention and treatment of carcinogen-induced breast cancer in various rat models. To understand the molecular basis of the tumor response to Targretin, we used microarray analysis to compare the gene expression profiles of tumors regressing in response to Targretin with those of either vehicle-treated tumors or tumors resisting Targretin treatment. The vehicle-treated and Targretin-resistant tumors had very similar profiles, but the tumors responding to Targretin exhibited broad changes in gene expression. These included genes involved in proliferation, markers of differentiation, tumor markers and expressed sequence tags of unknown function. We selected a subset of these genes for further evaluation. Quantitative analysis by real-time polymerase chain reaction confirmed the differential expression for the majority of the selected genes. However, a small fraction was identified as false positives. We evaluated a subset of the confirmed genes, as well as additional genes with related biological activities, by immunohistochemistry and laser capture microdissection of tumor sections, and their regulation in better-defined *in vitro* systems is now under investigation.

Herrmann, John [10]

A genomics approach to therapeutic antibody target discovery

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Functional genomics is expected to bring about significant advances in the discovery and development of new anticancer agents. Genomics-based drug target discovery will revolutionize how cancer is detected and classified, resulting in more finely tailored therapies. The explosion of information generated by large-scale functional genomics technologies has led to an exponential increase in the number of potential genes and proteins available for pharmaceutical and diagnostic research development. In tapping this potential, the primary challenge is to develop a strategy to integrate and extract meaning from the human genomic sequence information generated since the start of the Human Genome Project, relying on pragmatic strategies to sort and triage this information. Using a suite of integrated, high-throughput genomics technologies developed at CuraGen, we have devised streamlined approaches to identify new gene sequences rapidly, link them to specific diseases using reverse biology and finally validate them as effectors of disease progression. Application of these technologies has enabled us to identify 24 antibody drug targets for further evaluation and possible development as anticancer agents. We will discuss the role of some of the targets in cancer progression.

Hester, Susan [11]

Studies of normal gene expression in the rat nasal epithelium using cDNA array technology

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The nasal epithelium is an important target site for chemically induced toxicity and carcinogenicity. Gene expression data are being used increasingly in studies of such conditions. In order to provide normal baseline data for this target organ, we investigated gene expression profiles in nasal transitional and respiratory epitheli-