

# Functional Genomics

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**Activities 2007.** High-throughput technologies are the most powerful tools for attempting holistic approaches in the post-genome era, and are rapidly becoming essential for the discovery and analysis of genetic networks underlying cancer. The use of microarrays to study specific gene expression patterns in cancer model systems is a well established procedure, and has led to the analysis of complex molecular interactions that accompany transformation and tumor progression. More recent technological advancements have rendered microarrays amenable to genotyping, comparative genomic hybridization (CGH), and chromatin immunoprecipitation (ChIP). The concerted use of these techniques, to discover and characterize genes and/or gene families relevant to oncogenesis is one of the current challenges in the field of oncogenomics.

We are using an integrated genomic approach for the analysis of the molecular basis of Acute Myeloid Leukemia (AML) and for the identification of cancer-related genes. We previously characterized global gene expression profiles in diverse models of AML ([link1](#)) and differentiation therapy ([link2](#)) through the use of microarray technology. We are now defining the molecular signature of leukemic stem cells (LSC) derived from mouse models (AML1/ETO and PML/RAR transgenic), and focusing on the identification of specific LSC markers as well as on the molecular changes that accompany AML progression. Furthermore, we are identifying direct transcriptional targets of AML fusion proteins through high-throughput ChIP studies (ChIP-on-chip), with the aim of unraveling the molecular machinery involved in fusion protein-dependent transcriptional regulation. Future challenges include the integration of gene expression data, fusion protein ChIP data, histone modification ChIP data and proteomic analysis of transcriptional complexes containing AML fusion proteins for the understanding of transcriptional networks underlying leukemogenesis.

Two AML-related genes, PRDM3 (MDS1-EV1) and PRDM16, belong to the PRDM gene family, which consists of 17 known members characterized by the presence of the PR



domain (that shares sequence homology with the SET domain of histone methyltransferases). The better characterized members of the family encode for two major isoforms, one containing the PR domain (PR-plus) and one lacking it (PR-minus). PRDM genes seem to have a dual function that follows a similar pattern: the PR-plus isoform behaves as tumor suppressor, while the PR-minus isoform functions as an oncogene. We have initiated a series of investigations aimed at analyzing the role of the PRDM gene family in human cancer.