MOLECULAR SIGNATURES OF IN VITRO DRUG RESPONSE IN LUNG CANCER.

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We are developing in vitro drug response signatures based on profiling of mRNA (Illumina WG6-V3 arrays), DNA mutation (COSMIC and deep sequencing), DNA copy number (Illumina Human1M-Duov3 SNP array) and DNA methylation (Illumina HumanMethylation450) from lung cancer cell lines to predict which drugs a patient's tumor is most likely to respond to. We have generated drug response phenotypes (MTS colorimetric assays) for ~25 standard, targeted, and new chemotherapy agents and combinations for ~100 non-small cell lung cancer (NSCLC) lines. All assays were done in triplicates or more and were very reproducible over time ($r > 0.8$). More than 10,000 MTS assays were generated and we designed a high-throughput database software named DIVISA (Database of In VItro Sensitivity Assays) for the purpose of storing and analyzing these assays. Some drugs showed a wide range of sensitivities (> 10,000-fold in IC50 values) and IC50 clustering indicates that drug response phenotypes can be grouped according to drug types. As part of a joint NCI SPORE, NCI SPECS, and DOD PROSPECT effort we have collected 275 clinically annotated frozen tumors with drug response information including 94 that represent lung cancer resection followed by adjuvant treatment. These specimens have also been profiled on Illumina expression arrays to formally test the clinical relevance of the tumor cell line signatures, and to verify that the signatures predict for response only in the presence of treatment and thus are not prognostic of survival in the absence of treatment. In addition, we have 3 primary tumor datasets totaling 96 specimens with EGFR mutation information, thus providing a validation set for EGFR tyrosine kinase inhibitor signatures. Using a weighted voting classification, cell line signatures predicted drug response in primary tumors with accuracies of ~65% for targeted therapy (EGFR) but with somewhat lower accuracies for platin/taxane therapies suggesting that cell line predictive signatures may be better suited for targeted drugs. To facilitate translation to clinical trials we are working with High Throughput Genomics (HTG) to develop quantitative mRNA profiles that are performed on formalin fixed paraffin embedded (FFPE) material on a platform that can be transferred to a CLIA certified environment. These studies thus provide a preclinical human tumor model platform for systematically testing new drugs and for developing signatures to guide their most efficient use in early clinical tests.