Cancer Target Discovery and Development (CTD^2)

Specific Aims

Institution: University of Texas, Southwestern

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Lung cancer is a major cause of death in the United States and there is a clear need for additional and better therapeutic approaches to its treatment. It is clear that there are multiple oncogenotypes that cause lung cancer and that these different genotypes respond differently to currently approved therapeutics. However, the molecular basis of these differences is not understood completely and a systematic approach to identifying most of the functional differences in cells derived from tumors having different oncogenotypes has not been carried out. The work we propose will provide a systematic study of differential sensitivities of cells with different oncogenic mutations to the loss of function of each human gene, revealing pathways that contain novel drug targets. It will be conducted on a scale large enough to distinguish genetic weaknesses that are specific for a single cell line from potential therapeutic targets that are present in all cells sharing the same set of oncogenic genetic changes. In parallel, we will determine if any of a set of 200,000 compounds, including a subset currently approved for use in humans, has therapeutic benefit in one or more subsets of genetically distinct lung cancer. This will provide a potential fast-track for novel therapies as well as a method for detecting tumor specific vulnerabilities that are resistant to detection by RNAi strategies.

Aim 1. Using high-throughput siRNA technology we will identify the differences in gene expression required for the survival of each individual lung cancer cell line in a large panel of lines that have been grouped by specific gene expression signatures. We will also conduct functional genomic screens for survival of normal human bronchial epithelial cells (HBECs). By comparing the results of these functional genomic screens, we will identify those genes whose expression is required in some cancer genotypes, but not others and not in normal HBECs (a signature "lethal gene" phenotype). We will use gene set enrichment analysis to determine which biological pathways contain differentially sensitive genes. For any pathways that contain targets of known drugs, we will determine if the differential sensitivity to siRNA correlates with a differential sensitivity to the known pathway inhibitor.

Aim 2. Using high-throughput screening of a library of approximately 200,000 drug-like compounds on our panel of cell lines, we will identify those compounds that inhibit growth or kill cancer cells with a specific "lethal gene" phenotype. Drug sensitivity data will be correlated with "lethal gene knockdown" data to identify biological pathways that may contain a drug target. Compounds that inhibit cancer cells in culture will be tested for their ability to inhibit the growth of human tumors explants that have never been in culture and that have the same gene expression signature.