

Cancer Target Discovery and Development (CTD²)

Specific Aims

Institution: Cold Spring Harbor Laboratories

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The overarching goal of our CTD² program is to discover and validate new therapeutic targets by integrating functional and computational analyses of cancer genomes. Our project is based on a long history of collaborations between program investigators who have combined computational and functional genomic approaches to identify and validate over 50 cancer genes in the last five years, several of which are compelling therapeutic targets. We have also produced powerful new RNAi tools and mouse models that enable in depth analysis of relevant gene space using the highest quality reagents available and in vivo validation of drug targets. Additionally, we have developed innovative computational tools that pinpoint sets of genes and networks significantly altered in cancer genomes. We will combine these tools to conduct in-depth, focused screens of gene sets highly relevant to specific cancer genomes to identify those that have properties of genotype-specific cancer targets. Our two major goals are to further optimize these methods for target discovery and validation and to apply these approaches to specific cancer types and gene sets. An additional important goal of our program is to develop these tools and approaches into a blueprint for analyses of other gene sets or cancer types. Our specific aims are:

Aim 1. Optimization of computational and functional genomic approaches for cancer target discovery.

Functional target discovery and validation is a tedious process that can be streamlined through the use of high quality biological tools and approaches that have strong bioinformatic support. Similarly, identification of candidate targets by bioinformatic analyses of cancer genome datasets can be improved by developing computational tools that are tested in functional assays. In this aim, we will continue our efforts to optimize approaches in five areas: (a) computational identification of candidate oncogenic drivers, pathways, and networks (b) increased efficiency and throughput of cDNA screening for oncogenic drivers; (c) increased efficiency and throughput of shRNA screening for tumor cell dependencies; (d) developing polycistronic shRNA combinatorial target discovery; and (e) increased efficiency and throughput of “speedy mouse” technology. This aim is an extension of ongoing method development that has proven successful, and by the development of generally applicable tools, has the potential to impact work beyond the CTD² program.

Aim 2. Target discovery and validation based on cancer driver gene identification.

Studies suggest that many cancers remain dependent on their initiating oncogenic lesions, making the underlying cancer genes (and the pathways they regulate) rational drug

targets. This aim has three components: (a) computational prediction of oncogenic driver genes and pathways in a specific cancer type; (b) functional screening of these candidates using an appropriate mosaic mouse model; and (c) testing validated drivers for human tumor cell dependency using RNAi. In this aim we focus initially on serous ovarian adenocarcinoma, building upon our proven success using this approach to discover and validate new targets in HCC. Our goal is to further develop this proven approach so it can be applied to any cancer type for which there is an appropriate mosaic mouse model and a set of human cancer cell lines that are genetically representative of the alterations found in primary human tumors.

Aim 3. Target discovery and validation based on cancer genotype-specific dependencies.

Certain cancer genotypes create dependencies that can be exploited therapeutically. We will conduct focused shRNA screens using custom-validated shRNA libraries to identify targets based on particular cancer genotypes. Recent studies have illustrated the power of this approach using an epigenetics-focused shRNA set in genetically defined AML models, identifying drug targets whose inhibition targets cancer cells with stem-cell like properties. Here we will extend this approach initially in three cancer types: AML, serous ovarian cancer, and lung adenocarcinomas. In each case, we will screen focused shRNA libraries that are customized by computational prediction of driver genes and altered pathways specific to individual cancer genotypes. The strategies we develop can be applied to other shRNA sets, other cancer genotypes, or other cancer models.

Aim 4. Identification of targets for drug combinations.

Although targeted therapeutic agents have shown promise, most cancers rapidly develop drug resistance owing to mutations in the target, parallel pathways, or feedback mechanisms that compensate for target inhibition. In this aim, the program will develop approaches to systematically identify targets for combination therapies. Our initial focus will be on EGF receptor inhibitors in lung cancer. We will initially focus on identifying partner targets using validated shRNA libraries against predicted synthetic lethal genes based on mutual exclusion with genomic alteration of EGFR in lung cancer and other potential combinatorial targets. Through development of these examples we will produce a blueprint for identifying and validating other combination therapies. Such strategies may be required for the ultimate success of targeted cancer therapy.