Cancer Target Discovery and Development (CTD^2)

Specific Aims

Institution: Columbia University

Specific Aims

The emergence of multidimensional datasets characterizing genetic, epigenetic, and functional properties of large normal and tumor-related samples is creating unique opportunities for the systems-level dissection of mechanisms associated with malignant phenotypes. Coupled with novel high-throughput technologies and systems-biology approaches for the assembly, interrogation, and perturbation of genome-wide regulatory pathways, this will lead to highly efficient approaches for the rapid identification and validation of therapeutic targets, associated biomarkers, and small molecule inhibitors. Columbia University investigators have pioneered systems-biology-based approaches for the dissection of regulatory networks in human malignancies and for their interrogation, using computational, RNAi, and small-molecule approaches, to identify molecular targets for therapeutic intervention. As one of five pilot centers of the ARRA funded Cancer Target Discovery and Development Network (CTD^2), we have applied these approaches to aggressive and drug-resistance tumor subtypes, including the mesenchymal subtype of glioblastoma (MGES-GBM), glucocorticoid resistant T-cell acute lymphoblastic leukemia (GCR-T-ALL), and transformed follicular lymphoma into diffuse large B-cell lymphoma (FL→tDLBCL), with substantial accomplishments, see Track Record section Based on a proven record of accomplishments and on the specific objectives of the CTD^2 RFA, this document outlines the first of two closely integrated proposals for continuation of CTD^2 activities. While these proposals are meant to work optimally together, providing a fully integrated and highly scalable pipeline for cancer target discovery and development, each proposal is also structured to be fully functional in isolation. Each one will address independent and complementary elements of the process, also relevant to the other centers in the CTD^2 network, using proven processes and methodologies for cross-center interaction and collaboration.

In this proposal, we address the rapid discovery and validation of cancer targets, as well as their characterization in terms of synergies, tumor dependency, and ability to modulate drug sensitivity. This will be accomplished by converting the algorithms and approaches successfully tested in the pilot – including multivariate analysis of gene regulatory networks, pooled and targeted RNAi screening, and small-molecule screening – into a robust pipeline for Cancer Target High-throughput Optimized Discovery and Evaluation (CaTHODE). The goal is the discovery and validation of master regulator (MR) modules that implement functional bottlenecks that integrate aberrant signals from multiple genetic and epigenetic alterations and thus constitute natural Achilles' heels for the tumor subtype. These will be characterized in terms of their synergistic behavior, driver genetic alterations, and druggable modulators. This pipeline will allow processing of a novel tumor phenotype every 18 to 24 months, yielding validated individual and synergistic targets that constitute either oncogene or non-oncogene dependencies of the tumor or that

increase sensitivity to existing FDA approved or late-stage development compounds. The output of this pipeline will dovetail into a second pipeline, discussed in a separate proposal, which will address the chemical tractability of these targets. Thus, our specific aims are:

Aim 1: Implementing and disseminating a scalable and robust pipeline for Cancer Target High-throughput Optimized Discovery and Elucidation (CaTHODE), yielding subtype specific targets, associated biomarkers, and small-molecule modulators. This will require implementing tightly coupled sub-processes for:

> ***Sub-Aim 1.a*: Assembling, validating, and interrogating tumor-specific regulatory networks** using expression and genetic/epigenetic profiles. This process will be used to identify master regulator genes constituting either individual or synergistic dependencies of the tumor subtype.
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> ***Sub-Aim 1.b***: **Integrating experimental evidence from pooled, genome-wide RNAi screens** in the prioritization of candidate targets from Sub-Aim 1.a, using machine-learning methods.
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> ***Sub-Aim 1.c***: **Validating inferred targets from Aim 1.b, using high-throughput *in vitro* techniques and *in vivo* analysis** and by defining molecular signatures associated with their RNAi mediated inhibition.
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> ***Sub-Aim 1.d***: **Identifying genetic and epigenetic alterations** activating master regulator genes.
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> ***Sub-Aim 1.e***: **Identifying candidate modulators of master regulator activity** in a library of FDA-approved, experimental, and custom tricyclic indole derivative (TIDs) compounds.

Aim 2: Appling CaTHODE to pediatric neuroblastoma (NBL), using molecular and genetic profile data from the TARGET consortium, to identify actionable targets for pharmacological intervention in different subtype of the tumor, including *N-Myc*^{amp} and *N-Myc*^{wt}, as well as in a new mesenchymal subtype.

Aim 3: **Applying CaTHODE to a new tumor subtype every 18 – 24 months**, based on the prioritization criteria defined in the RFA for the CTD^2 network, and disseminating pipeline components and full pipeline.