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Towards patient-based cancer therapeutics

The Cancer Target Discovery and Development Network#

Abstract

A new approach to the discovery of cancer therapeutics is emerging that begins with the cancer patient. Genomic analysis of primary tumors is providing an unprecedented molecular characterization of the disease. The next step requires relating the genetic features of cancers to acquired gene and pathway dependencies and identifying small-molecule therapeutics that target them.

Introduction

Small-molecule drug discovery was originally a ‘compound-based activity’. The process begins with the discovery of a biologically active compound, often a naturally occurring small molecule. The next step involves the identification of a disease that may benefit from treatment with the compound, followed by optimization and development of the eventual drug (or drugs via synthetic modifications). Penicillin is an original example of a drug that arose from this approach. Despite many advances in drug discovery in the intervening decades, compound-based drug discovery is still common today. Rapamycin, for instance, was discovered as a secondary metabolite of a *Streptomyces* strain and was explored without success as an antifungal agent, before emerging as an effective immunosuppressive agent (sirolimus), with derivatives being approved or investigated as therapeutics in cancer (torisel; afinitor; ridaforolimus) and in other diseases.

The ability of recombinant DNA to provide nearly unlimited access to human proteins resulted in a second approach that is also common today – ‘target-based drug discovery’. Here, therapeutic targets are selected using insights gained most often from biochemistry, cell biology and model organisms. Small molecules are identified that modulate the targets (often by small-molecule screening) followed by optimization and clinical testing. Although

*Address correspondence to this author at stuart_schreiber@harvard.edu.

#**Authors**

Broad Institute of Harvard and MIT: Stuart L. Schreiber*, Alykhan F. Shamji, Paul A. Clemons, Cindy Hon, Angela N. Koehler, Benito Munoz, Michelle Palmer, Andrew M. Stern, Bridget K. Wagner

Cold Spring Harbor Laboratory: Scott Powers, Scott W. Lowe, Xuecui Guo, Alex Krasnitz, Eric T. Sawey, Raffaella Sordella, Lincoln Stein, Lloyd C. Trotman

Columbia University: Andrea Califano, Riccardo Dalla-Favera, Adolfo Ferrando, Antonio Iavarone, Laura Pasqualucci, José Silva, Brent R. Stockwell

Dana Farber Cancer Institute: William C. Hahn, Linda Chin, Ronald A. DePinho, Jesse S. Boehm, Shuba Gopal, Alan Huang, David E. Root, Barbara A. Weir

National Cancer Institute: Daniela S. Gerhard, Jean Claude Zenklusen

University of Texas Southwestern Medical Center, Dallas: Michael G. Roth, Michael A. White, John D. Minna, John B. MacMillan, Bruce A. Posner

this is a robust process, the common failure of candidate drugs in late-stage clinical testing, due to unforeseen toxicity or lack of efficacy, reveals limits in our ability to select targets using these surrogates of human physiology.

Advances in human genetics suggest that a third approach – 'patient-based drug discovery' – may be most productive in the future. Molecular characterization of patient tissues is providing remarkable insights into the root cause of many disorders. As these insights often point to targets and processes that are believed to be especially challenging for small-molecule therapeutics – targets such as transcription factors, regulatory RNAs and processes such as disrupting specific protein/protein interactions – scientists have been innovating in chemistry, cell-culture science, and mechanism-of-action studies, among others. As a consequence, these 'hard to drug' yet key targets and processes are being pursued with new optimism.

Although heritable disorders and infectious diseases are the subject of intensive patient-based drug-discovery efforts, recent insights into the genetics and biology of human cancers have made this family of diseases a prime target for this approach. High-throughput genetic, epigenetic, and proteomic analyses of cancer tissues are providing unprecedented molecular insights into genes and pathways causally related to oncogenesis, tumor progression, and drug sensitivity and resistance. This points to a path entailing the determination of genomic features of patients' tumors and the discovery and development of new types of therapeutics that target the dependencies (i.e., addictions) arising from the specific patterns of (epi)genetic alterations within them1. This path has been validated in a growing number of extraordinary cases2,3. But its generalization is a tall order, one far from the reality of current routine clinical medicine and not without additional challenges for payers, patients and healthcare providers2,4.

An approach to the challenge

To pursue this path *comprehensively* and *prospectively*, the National Cancer Institute created the Cancer Target Discovery and Development (CTD^2) Network (http://ocg.cancer.gov/programs/tddn.asp). The Network currently comprises five interacting Centers (Figure 1). The mission of the CTD^2 Network is to decode cancer genotypes so as to read out acquired pathway and oncogene addictions of the specific tumor subtypes, and to identify small molecules that target these dependencies. The Network builds on the data and insights gained from The Cancer Genome Atlas (TCGA), Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative and other cancer genomic efforts that are systematically cataloguing the genetic and epigenetic alterations of specific cancers (e.g., mutational status and changes in gene expression, DNA methylation, chromosomal segment copy numbers, etc.). The CTD^2 Network is probing the consequences of these alterations on the dependencies or co-dependencies different cancers have on specific oncogenes or their interacting genes ('oncogene addiction' and 'non-oncogene co-dependencies')5. Cataloguing these Achilles' heels and linking them to the causal genetic alterations will be critically important for therapies that are personalized to individual patients, including combination therapies aimed at targeting multiple such dependencies at once. It will also be important for anticipating resistance mechanisms and identifying clinical biomarkers.

The CTD^2 Network is currently taking five integrated approaches to determine the targets and processes upon which defined cancer genotypes become dependent: 1) Techniques that enable the systematic under- or over-expression of selected mRNA transcripts are being used to identify candidate genes. 2) Computational network analyses are being performed on cancer genomic datasets to reveal critical master regulatory hubs in the circuitries of cancers, acting as integrators of the complex spectrum of genetic alterations that determine specific tumor subtypes. 3) A small-molecule probe set has been assembled, having members that modulate the activity of defined proteins and pathways that constitute candidate tumor dependencies. By testing these compounds in many genomically characterized cancer cell lines, the genetic features of the cancer cells are being correlated to small-molecule sensitivities. (In each of these three approaches, the CTD^2 Network measures the fitness of cells having defined cancer genetic features following targeted perturbations.) 4) Simultaneously, probe-development projects are undertaken to yield novel small molecules that modulate the functions of cancer therapeutic targets revealed by these approaches. 5) The consequences of these and other perturbagens are being or will be tested in, for example, mouse models of cancer having genetic alterations that closely mimic the patient-derived cancers (Figure 1).

1. Probing acquired dependencies via RNA

The CTD^2 Network is exploiting the extraordinary advances in modulating gene function using RNAi-based knockdown or RNA overexpression methods. Three examples illustrate the principles behind this approach to identifying acquired somatic genotype-specific dependencies.

The CTD^2 Center at UT Southwestern at Dallas is screening genomic siRNA libraries against a large panel of human tumor-derived non-small cell lung cancer cell (NSCLC) lines to identify siRNAs that are lethal only to cancers that share a similar cancer genotype6 as a particular NSCLC subtype or clade. Clade-specific lethal siRNAs are being used to identify metabolic vulnerabilities that occur in a particular cancer subtype, vulnerabilities that might be exploited for developing genetically matched anti-cancer therapeutics. The CTD^2 Center at the Dana Farber Cancer institute is screening shRNA libraries to identify different types of cancer vulnerabilities. For example, by screening a set of 20 human cancer cell lines, Barbie et al. looked for kinases that were selectively required for the survival of cancer cell lines that depend on oncogenic KRAS and found that, second only to KRAS itself, the non-canonical kinase TBK1 was a synthetic lethal partner with KRAS7. The CTD^2 Center at Columbia is using pooled shRNA libraries to complement the computational analysis of master regulators of high-grade glioma subtypes and of glucocorticoid resistance in T-ALL.

2. Probing acquired dependencies via network analyses

Context-specific regulatory networks of the tumor cell are being assembled and interrogated computationally to reveal otherwise cryptic master regulator proteins whose gain/loss is necessary and sufficient for tumor initiation or progression. These proteins are emerging as master “integrators” of a spectrum of genetic and epigenetic alterations contributing to the malignant phenotype and thus provide promising novel biomarkers as well as targets for therapeutic intervention. For instance, at the CTD^2 Center at Columbia, C/EBP and STAT3

were recently identified as synergistic master regulators of the mesenchymal subtype of glioblastoma by computational analysis of a regulatory network dissected from a large collection of gene expression profiles of human high-grade gliomas8. Validation was achieved by two experimental approaches: 1) shRNA-mediated silencing of these two genes reduced tumor aggressiveness in orthotopic xenografts, and 2) co-ectopic expression reprogrammed murine neural stem cells along an aberrant mesenchymal lineage.

3. Probing acquired dependencies via proteins

The dramatic clinical consequences of linking genetic features of cancers to drug efficacies, including response rates of >80%, are well known, yet these advances today only affect <1% of patients suffering from cancer3. The CTD^2 Centers at the Broad Institute and UT Southwestern in Dallas are relating the genetic features of cancers to small-molecule probe or drug efficacies broadly. The Network is extending earlier efforts9–11 by: 1) assembling and synthesizing highly specific small molecules (currently a collection of 225 probes and drugs) that target a wide range of proteins and that exploit advances in probe discovery12,13; 2) assembling small-molecule screening collections having novel chemical properties; 3) making quantitative cellular measurements in a wide range of human cancer cell lines treated with the compounds; and 4) identifying the genetic features in these cells that correlate with sensitivities of the small-molecule probes or drugs. The CTD^2 Network is studying these novel compounds using cell lines whose genomic features (copy number; mutation; expression) have been richly characterized and parallel many of the changes found in patient cancers14,15 (although not without exception16,17). The CTD^2 Network aims to identify: 1) therapeutic targets of cancers linked to specific cancer genetic features10; 2) combinations of targets that, by using guided combination therapy, yield high rates of durable responses; and 3) potential resistance mechanisms associated with such targets18. The resulting data and resources will be publicly available through the project's web site.

4. Probe-development projects for novel cancer targets

The CTD^2 Network also aims to accelerate the development of genetically matched cancer drugs by discovering novel small-molecule probes of candidate cancer targets not yet modulated by small molecules. The goal is to identify these gaps and to undertake collaborative probe-development projects involving high-throughput screening, follow-up and medicinal chemistry and biology, and mechanism-of-action studies. Advances in the science of probe discovery, especially in fundamental synthetic chemistry, the culturing and co-culturing of cells in more physiological environments, and in small-molecule assay development, have enabled the discovery of compounds that modulate challenging cancer-relevant targets and processes12,13. CTD^2 investigators are especially interested in projects involving targets such as transcription factors and processes such as gene regulation and cellular differentiation. For example, small molecule probe-development projects are underway involving both transcription factors (including STAT3, C/EBP (β and δ)8 and MYC) and chromatin-modifying enzymes (including histone methyltransferases and histone demethylases) that have been identified from genomic studies of cancer.

5. Probing genetic alterations in mouse models of human cancers

Genomic characterization of human cancers has revealed many of genes that are altered. Transgenic or knockout mice that contain germline alterations in the candidate cancer gene can be used to assess oncogenic function. However, their generation and analysis precludes high-throughput evaluation of mutated genes. Transplantable mouse models offer the advantage of speed since genetic lesions are introduced into stem or progenitor cells that are then transplanted into recipient animals. Such models exist for a number of cancer types, including lymphoma, glioblastoma, and carcinomas of the liver19–21. These models can be used to screen large numbers of genes for oncogenicity and acquired dependencies22 and to determine the efficacy of small-molecule probes that have been optimized for animal testing.

The CTD^2 Network was formed by the NCI to serve as a link in the overall effort to discover safe and effective patient-based cancer drugs and to facilitate their clinical development through the identification of the genetic features of human cancers that predict drug efficacy, resistance mechanisms and clinical biomarkers. The Network aims to relate these features to their unique dependencies and to identify small molecules that target them, even when this entails ‘hard to drug’ targets and processes – an empirical path that begins and ends with cancer patients.

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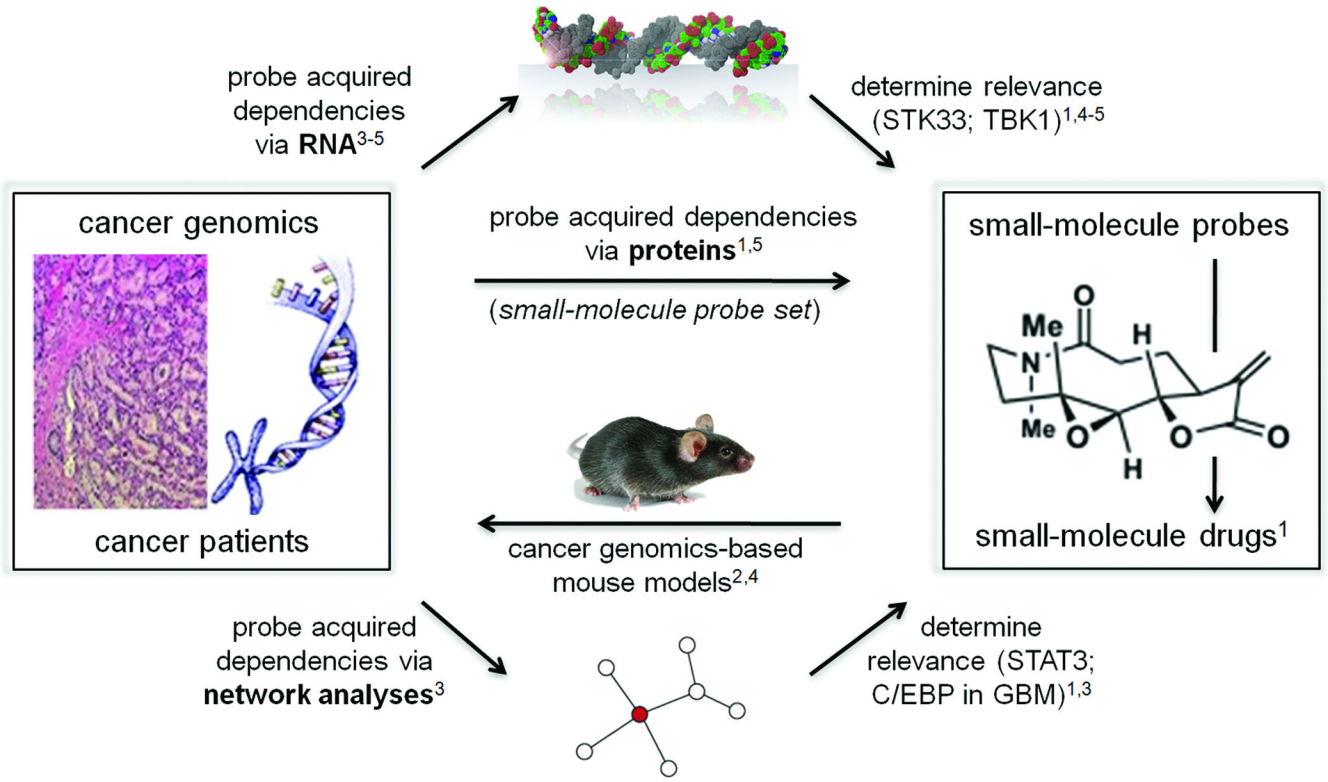

Figure 1.

The Cancer Target Discovery and Development (CTD[2]) Network of the NCI aims to relate the genetic features of cancers to acquired cancer dependencies and to identify small molecules that target the dependencies (superscript numbers refer to: [1]Broad Institute of Harvard and MIT; [2]Cold Spring Harbor Laboratory; [3]Columbia University; [4]Dana Farber Cancer Institute; [5]University of Texas Southwestern Medical Center at Dallas).

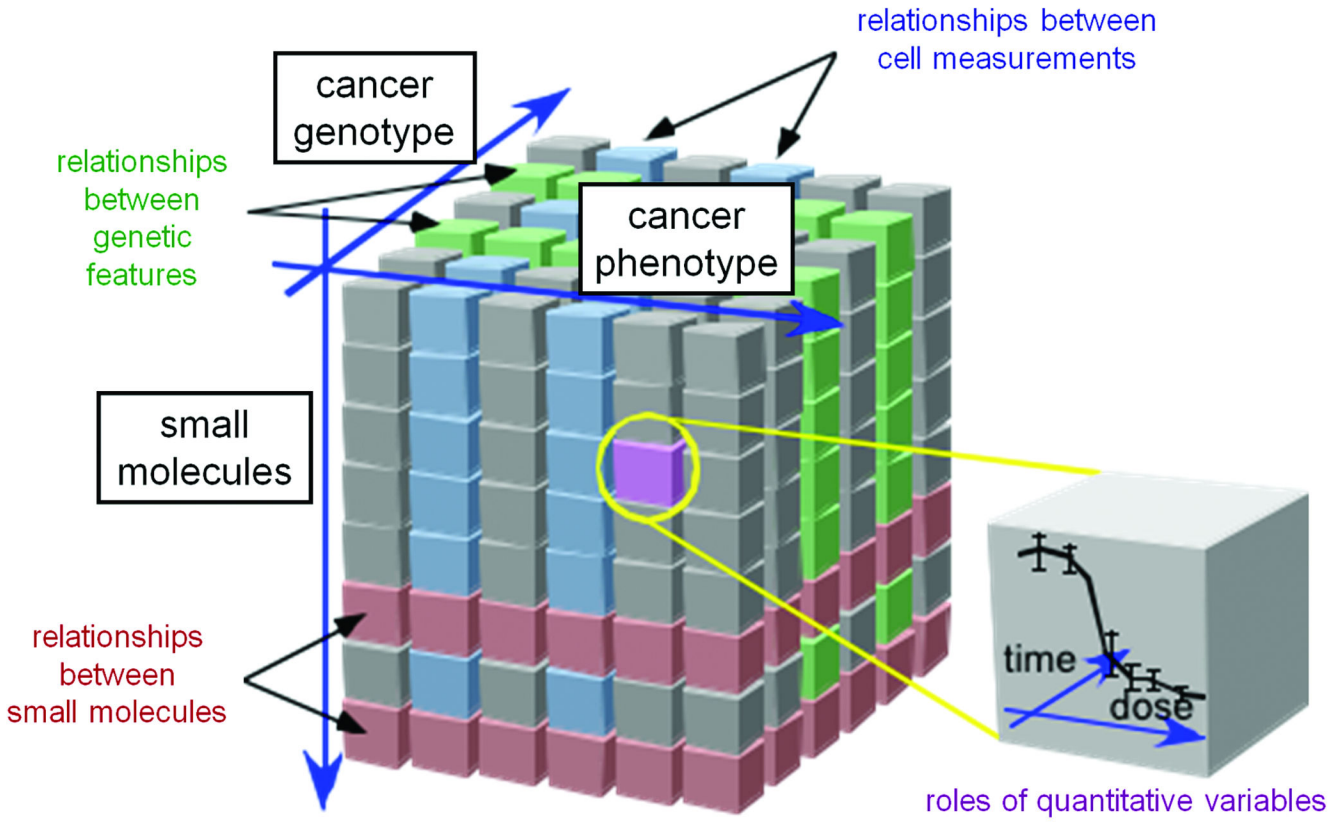

Figure 2.

Conceptual image of a matrix of data relating cancer genotype, cancer phenotype and sensitivity to highly specific small-molecule modulators of cancer-relevant proteins. The CTD^2 Network is performing quantitative cellular measurements using small molecules (both with and without a knowledge or their targets) and genetically characterized cancer cell lines (copy number variation; mutational status; gene expression). Computational analyses are being performed that correlate the pattern of sensitivity with the genetic features of the cancer cell lines9–11. These analyses yield hypotheses for cancer genotype/drug efficacy relationships that can be tested in vitro and in vivo using systems developed within the Network.