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Clinical potential for off-target based drug repositioning

Examples of off-target based drug repositioning

Crizotinib represents a powerful example of the transformative potential of off-target based drug repositioning. Originally developed as a potent inhibitor of MET, it ultimately received approval for treatment of ALK fusion-positive non-small cell lung cancer (NSCLC) in its capacity as an inhibitor of the ALK[1]. Imatinib, which was first rationally developed to inhibit ABL and approved for the treatment of BCR-ABL driven chronic myeloid leukemia, was also approved to treat unresectable KIT-positive gastrointestinal stromal tumors (GIST) due to its potency to inhibit KIT[2]. Recently, in vitro and in vivo studies revealed that ceritinib which is an approved targeted therapy for ALK fusion-positive NSCLC, effectively killed cholangiocarcinoma cells, irrespective of ALK expression or mutation status, or overcame proteasome inhibitors resistance in multiple myeloma by targeting IGF1R/InsR signaling[3][4].

Advantages of drug repositioning

Drug repositioning is the process of utilizing approved or investigational drugs for new therapeutic applications beyond their initially intended indication. If the candidates for repositioning have gone through phase 1 safety studies, the risk for toxicity-associated failure is usually low. Furthermore, since pharmacokinetics and pharmacodynamics profiles, formulations and dosing schedules are at this point well established, it is possible for development teams to skip several steps in the usual drug development process, significantly reducing further costs and development times.

The potential of computational approaches to expand drug repositioning

Recently, with the advancement of next generation high-throughput DNA and RNA sequencing technologies, various computational approaches using bioinformatic techniques have been widely explored to identify new targets for potential therapeutic indications.

As an example, there is a report on a mega-analysis approach in which genes involved in inflammatory bowel disease (IBD) pathogenesis were detected and then potential candidate compounds for IBD therapy were identified using Connectivity Map (CMap), a collection and analysis tool of genome-wide transcriptional expression data responses from human cell lines that have been treated with chemical compounds.

The researchers collected RNA sequencing data from intestinal biopsies of Ulcerative Colitis (UC), Crohn's disease (CD) and non-IBD patient controls which were available on Gene Expression Omnibus (GEO) and ArrayExpress (AE) databases. Using this data, they detected statistically significant, differentially expressed genes (DEGs) and then employed machine learning (ML) techniques, identifying 34 genes whose collective expression effectively distinguishes inflamed biopsies of IBD patients from non-IBD control samples. Most of these genes were upregulated in IBD. Using CMap, they ran an analysis to identify compounds that induced opposing (anti-correlating) expression patterns in intestinal cells to the top significant 300 DEGs, comprising 150 upregulated and 150 downregulated genes within the IBD vs. non-IBD control DEGs. In addition, they performed another query that contained the 34 genes selected in IBD ML analysis, 30 of these were recognized by the CMap tool. As a result, several potential candidate compounds including kinase inhibitors were identified, such as RAF inhibitors (Vemurafenib, AZ-628 and PLX-4720), mTOR inhibitor (WYE-354), SYK inhibitor (Fostamatinib) and MEK inhibitors (PD-0325901). The targets of these compounds were suggested to be potentially associated with IBD[5]. The prediction of potential therapeutic targets using computational approaches opens new treatment strategies, including repositioning compounds which act on these potential targets as off-targets.

The importance of understanding of off-target effects

As remarkable advances in computational approaches in drug discovery are expanding opportunities for

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drug repositioning, it is equally important to deepen our understanding of off-target effects as well as on-target effects. While gene expression-based techniques like the CMap have been shown to be highly useful for target identification, they have limited utility for dissecting off-target effects that are specific for polypharmacology mechanisms where a compound simultaneously acts on multiple molecular targets or biochemical pathways. Recombinant protein binding, or catalytic enzyme screening assay panels, can detect new drug-protein interactions and at the same time provide functional validation of these interactions, which is extremely useful in the understanding of off-target effects[2].

Carna's Profiling Assay Services

Carna Biosciences offers profiling assay services using only internally produced active kinase proteins. These services cover ~350 targets including mutant kinases, and ~300 wild-type kinase targets.

• Activity-based (cell-free) Biochemical Screening/Profiling Assay Services

To celebrate the launch of our MSA profiling service using Sciex BioPhase™ 8800 Capillary Electrophoresis System, we have released (on our website) the kinase profiling data of 60 FDA-approved kinase inhibitors as performed by Carna, as well as the kinome plots that visualize the profiling results (Fig. 1). For more details, please visit **our new page**.

References:

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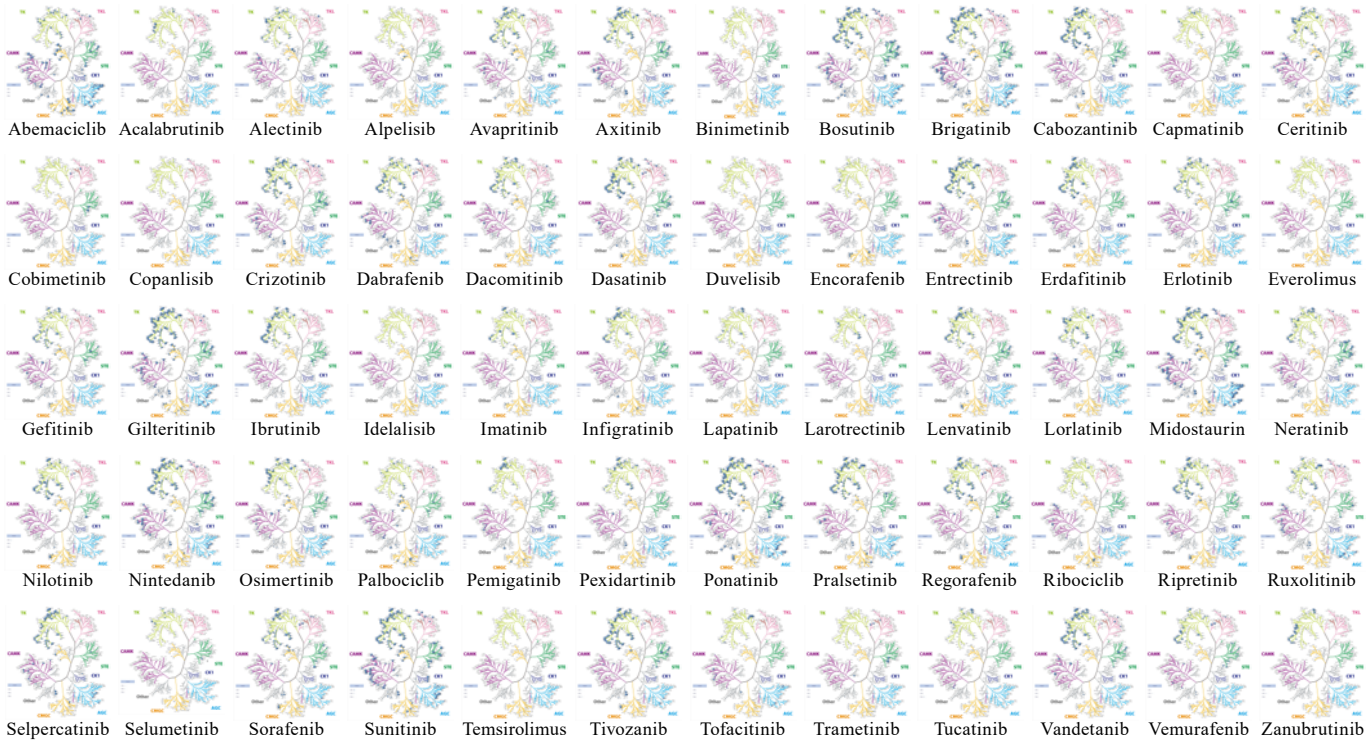

Fig. 1. Plotted % Inhibition at compound conc. of 1μmol/L

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