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Toward better drug repositioning: prioritizing and integrating existing methods into efficient pipelines

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Recycling old drugs, rescuing shelved drugs and extending patents' lives make drug repositioning an attractive form of drug discovery. Drug repositioning accounts for approximately 30% of the newly US Food and Drug Administration (FDA)-approved drugs and vaccines in recent years. The prevalence of drug-repositioning studies has resulted in a variety of innovative computational methods for the identification of new opportunities for the use of old drugs. Questions often arise from customizing or optimizing these methods into efficient drug-repositioning pipelines for alternative applications. It requires a comprehensive understanding of the available methods gained by evaluating both biological and pharmaceutical knowledge and the elucidated mechanism-of-action of drugs. Here, we provide guidance for prioritizing and integrating drug-repositioning methods for specific drug-repositioning pipelines.

A repositioned drug does not need the initial six to nine years typically required for the development of new drugs, but instead goes directly to preclinical testing and clinical trials, thus reducing risk and costs [1]. Repositioning or repurposing drugs has been implemented in several ways. One of the well-known examples is sildenafil citrate (brand name: Viagra), which was repositioned from a common hypertension drug to a therapy for erectile dysfunction [2]. Similarly, off-label use of Food and Drug Administration (FDA)-approved drugs for cancer medical practice is also popular. The National Comprehensive Cancer Network (NCCN) estimates off-label use accounts for 50–75% of drugs or biologic therapies for cancer in the USA [3]. It has been reported that 78% and 75% of patients with breast or lung cancer, respectively received FDA-approved drugs, although 68% and 95% of these drugs, respectively, were used for off-label indications not approved by the FDA [4]. Obviously, these examples were serendipitously identified and these repositioning strategies lack guidance and information to support clinical decision.

Pharmaceutical companies rely on traditional drug discovery methods to seek repositioning opportunities. Among the 75 agents (50 small molecules and 25 biologics) approved between 1999 and 2008, 28 first-in-class small molecules were discovered by phenotypic drug screening and 17 were identified by target-based methods [5,6], accounting for more than 50% of the FDA-approved small molecules and biologics. Phenotypic drug-screening approaches discover drug candidates from libraries serendipitously. Alternatively, target-based methods improve the repositioning process by including known target information into drug-repositioning studies.

Nevertheless, the low knowledge content of elucidated mechanisms for traditional drug-repositioning methods makes it hard to satisfy unmet medical needs by successfully repositioning a large number of existing or shelved drugs. Computational methods are able to alleviate this problem by high-level integration of available knowledge and elucidation of unknown mechanisms. These computational methods significantly improve the discovery process in which new indications for a drug or new drugs for a disease can be identified. They take advantage of the methods and tools available in chemoinformatics [7–9], bioinformatics [10–14], network biology [15–17] and systems biology [18–20] to make full use of known targets, drugs, and disease biomarkers or pathways, thus leading to the development of proof-of-concept methods and the design of clinical studies with accelerated timelines. Accordingly, computational drug-repositioning methods can be classified into

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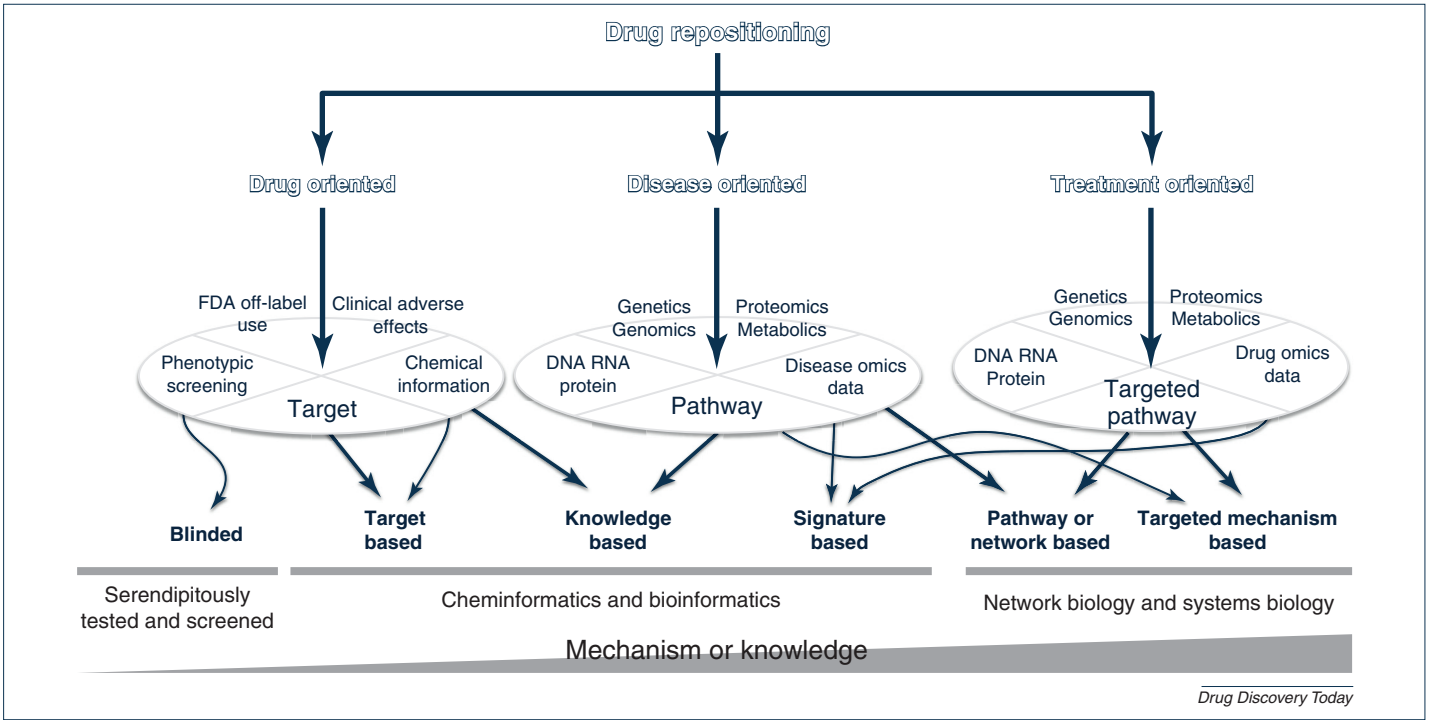

FIGURE 1

Lotus leaves flowchart (LLF) for categorization of existing drug-repositioning methods. Drug repositioning takes advantage of different potential avenues to repurpose drugs for new indications, including drug, disease and treatment oriented. These avenues were developed according to the availability of biological and pharmaceutical knowledge and requirement of understanding the mechanisms of action of drugs. Traditional phenotype-based screening methods do not need prior knowledge, and the repositioned drugs are just serendipitously tested. Targeted-based methods need specific knowledge about the targets, such as 3D protein structures, whereas knowledge-based methods require the knowledge about the drugs or diseases, such as adverse effects, FDA approval labels, records of clinical trials and published disease biomarkers (potential targets) or disease pathways. Signature-based methods mainly make use of gene signatures defined by '-omics' data (for diseases, drug treatments, or both). Pathway- or network-based methods generally use pathway analysis or network biology methods to discover essential pathways from genetic, genomic, proteomic and metabolic data of diseases to find new targets for repositioned drugs. More advanced drug-repositioning methods, such as targeted mechanism-based methods, aim to discover mechanisms of action of drugs by identification of off-targets or targeted pathways of treated drugs using drug omics data (before and after drug treatments). Details of these methods are in Table 1 (main text). Integrated knowledge and elucidated mechanisms of drug actions increases with the complexity of modeling methods.

target-based, knowledge-based, signature-based, pathway- or network-based, and targeted-mechanism-based methods, as shown in Fig. 1. These methods focus on different orientations defined by available information and elucidated mechanisms, such as drug oriented, disease oriented and treatment oriented. These computational drug-repositioning methods enable researchers to examine nearly all drug candidates and test on a relatively large number of diseases within significantly shortened time lines.

In recent years, the number of drug-repositioning methods has dramatically increased. It is essential to better understand these existing methods and prioritize them based on specific studies. Application of an efficient drug-repositioning pipeline to a specific study needs identification of feasible methods based on available information of the drugs or diseases of interest. In this review, we link existing drug-repositioning methods with their integrated biological and pharmaceutical knowledge and discuss how to customize a new drug-repositioning pipeline for specific studies.

Prioritize available drug-repositioning methods

Figure 1 is a top-down flowchart that we developed to better understand orientations, integrated information types, categories and complexities of existing drug-repositioning methods. We call this flowchart a lotus leaves flowchart (LLF). It enables better understanding of repositioning methods from the top down while customizing new repositioning pipelines from the bottom up. As an example, if one wants to reposition drugs for an orphan disease, one needs to identify how much pharmaceutical or biological knowledge is available for this disease and whether understanding the mechanisms of action of repositioned drugs is necessary. There are several options to do such drug repositioning. Option 1: when little information is available for the disease, phenotypic screening or FDA off-label use would be the best option. Option 2: if there exists one protein biomarker for the disease, target-based or knowledge-based methods should be prioritized for the study. Option 3: if there is more disease information available, either knowledge-based or signature-based methods can be deployed to integrate available disease pathways or disease omics data (i.e. omics data generated from diseases) into the drug-repositioning process. Lastly, option 4: if treatment omics data (i.e. omics data generated from drug treatment) are available, it is possible to use signature-based or targeted-mechanism-based methods to elucidate unknown targeted mechanisms, such as off-targets and targeted signaling pathways.

It is easy to see that the development of an efficient drug-repositioning pipeline is a process of tradeoff among purposes, methods and available information. Here, we introduce the repositioning methods shown in the LLF to facilitate understanding the purpose, the integrated information and the complexities of