Computational and Experimental Advances in Drug Repositioning

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Abstract- **Drug repositioning is an important component of therapeutic stratification in the precision medicine paradigm. Molecular profiling and more sophisticated analysis of longitudinal clinical data are refining definitions of human diseases, creating needs and opportunities to re-target or reposition approved drugs for alternative indications. Drug repositioning studies have demonstrated success in complex diseases requiring improved therapeutic interventions as well as orphan diseases without any known treatments. An increasing collection of available computational and experimental methods that leverage molecular and clinical data enable diverse drug repositioning strategies. Integration of translational bioinformatics resources, statistical methods, chemo informatics tools and experimental techniques (including medicinal chemistry techniques) can enable the rapid application of drug repositioning on an increasingly broad scale. Efficient tools are now available for systematic drug-repositioning methods using large repositories of compounds with biological activities. Medicinal chemists along with other translational researchers can play a key role in various aspects of drug repositioning. In this review article, we briefly summarize the history of drug repositioning, explain concepts behind drug repositioning methods, discuss recent computational and experimental advances and highlight available open access resources for effective drug repositioning investigations. We also discuss recent approaches in utilizing electronic health record for outcome assessment of drug repositioning and future avenues of drug repositioning in the light of targeting disease comorbidities, underserved patient communities, individualized medicine and socioeconomic impact.**

INTRODUCTION

Over the past decades, de novo drug discovery has grown to be time-consuming and costly, despite the advances in genomics, life sciences and technology. Investments in pharmaceutical R&D have steadily increased, while the number of new drug approvals has stagnated. Indeed, failures are spread throughout the drug development pipeline, and it takes billions of investment dollars and an average of about 9–12 years to bring a new drug to the market. Improving R&D productivity remains the most important priority for pharmaceutical industry. In light of these challenges, drug repositioning, which concerns the detection and development of new clinical indications for those existing drugs, or for those that are in the development pipeline, has emerged as an increasingly important strategy for the new drug discovery. It could substantially reduce the risks of development and the costs, and shorten the lag between drug discovery and availability. Among the 84 drug products introduced to market in 2013, new indications of existing drugs accounted for 20% . Drug repositioning has played a key role in drug discovery and precision medicine paradigm.

In recent years, drug repositioning is becoming strongly supported by governments, non-trading organizations and academic institutions. For example, both the United States (National Center for

Advancing Translational Sciences) and the United Kingdom (Medical Research Council) have launched large-scale funding programs in this area with a goal to extend molecules that already have undergone significant research and development by the pharmaceutical industry to more new indications. Furthermore, the US Food and Drug Administration (FDA) is also enabling drug repositioning, with the creation of several public databases specifically for computational drug repositioning. There are also substantial economic incentives to reposition marketed drugs for the treatment of orphan and rare disorders. All of these efforts significantly promoted drug repositioning research.
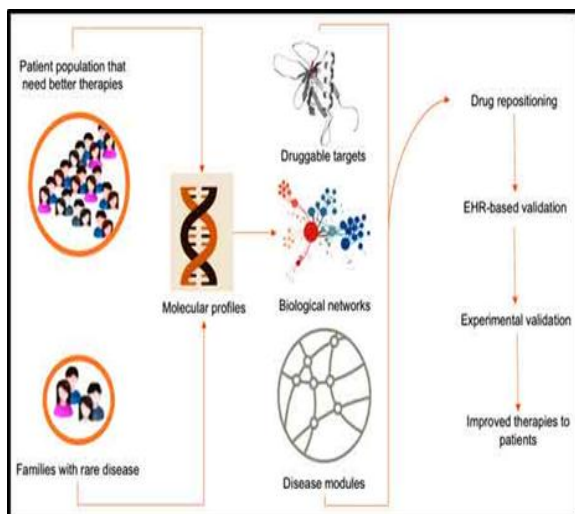
Historically, the discovery of new uses of old drugs is mostly through serendipity or resulted from a better understanding of the drugs' mechanism of action. For example, the monoclonal antibody bevacizumab, originally developed to treat patients with metastatic colon cancer and non-small cell lung cancer by inhibiting angiogenesis, is now being used to slow or reverse abnormal vascularization of the retina in exudative (wet) macular degeneration. With the accumulation of the large volumes of omics data, bioinformatics plays an increasingly important role in the discovery of new drug indications. Depending on where the discovery comes from, these newly proposed computational methods can be categorized as either 'drug based' or 'disease based'. Traditional studies mostly focus on exploring the shared characteristics among drug compounds such as chemical structures and side effects.
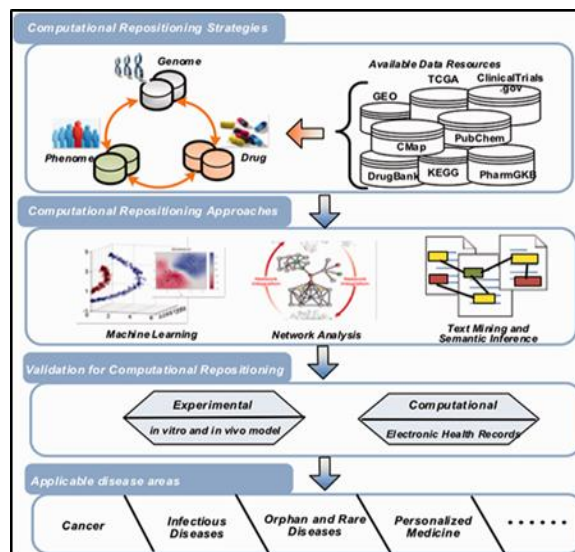
Other methods include rescreening the existing pharmacopeia against new targets to uncover the novel drug indications, looking for similarities of molecular activities, or exploring the relationships between drugs and diseases. With the drug-related data growth and open data initiatives, a set of new repositioning strategies and techniques has emerged with integrating data from various sources, like pharmacological, genetic, chemical or clinical data. These methods can accumulate evidence supporting discovery of new uses or indications of existing drugs. In this review, we summarize recent progress in computational drug repositioning as the following four parts (see Figure 1): repositioning strategies (with available data sets), computational approaches, validation methods and application areas.

DRUG REPOSITIONING

Drug repositioning was defined as systematic or targeted evaluation of pharmaceutical compound libraries or compound to identify new indications for diseases other than the primary diseases for which the drug was originally designed [1-4]. It is a rapidly evolving area in the field of drug discovery at the interface of medicinal chemistry, chemoinformatics, biomedical informatics and pharmacology. Drug repositioning can play a key role in therapeutic stratification for patients with rare, complex or chronic diseases with less effective or no marketed treatment options available .Compounds at all stage of development in drug development cycle, clinical trials or experimental medicine projects can be used

as candidates for drug repositioning followed by toxicity studies to identify new indications. Clinical knowledge from secondary or off-label use and even side effects of approved pharmaceutical compounds can also be used in drug repurposing methods. Longitudinal disease diagnosis and prescription data from electronic health records (EHR) can be abstracted and analyzed. Outcome of drug repositioning based on Pharmacovigilance 2.0 guidelines. Attempts have been made by ourselves and Murterial et al. to conceptually classify and define various modalities and approaches tdrug repositioning. We have provided an overview of definitions for drug repositioning and other related methods that utilize re-use or repositioning of pharmaceutical compounds (Table 1). Concepts of drug reformulation, drug combination, altered dosing, altered mode of delivery, line extension and therapeutic switching are some related concepts, but do not qualify as drug repositioning examples. Although, such compound reuse and reformulation approaches can play an important role in drug repurposing studies, in terms of getting a repurposed compound or formulations to the market. While different terms like drug repositioning, drug repurposing, drug profiling have been used to define similar approaches of using pharmaceutical compounds for new indications, we will be using the term drug repositioning in this review.

BRIEF HISTORY OF DRUG REPOSITIONING

Drug repositioning has been successful in different classes of diseases defined across the International Statistical Classification of Diseases and Related Health Problems (ICD-9)

COMPUTATIONAL AND EXPERIMENTAL METHODS FOR DRUG REPOSITIONING

Drug repositioning methods can be focus around a target (target-based repositioning methods) ,disease (disease-based drug repositioning), expression datasets (signature-based drug repositioning), repositioning investigations aimed broadly at identifying global relationships among drugs, targets, and diseases to identify novel drug repurposing opportunities in a hypothesis-free approach (systematic drug repositioning) or network-scale data

(network-based drug repositioning) . Flowcharts to compare target-driven drug discovery pipeline and computational drug repositioning methods are shown in (Fig. 1). Computational and experimental approaches can be leveraged to implement various modalities of drug repositioning. Both computational screening and experimental screening methods can be utilized for repurposing investigations. In recent years, drug repositioning investigations are performed as hybrid approach where results from computational analyses were validated by experimental assays, followed by clinical trials designed to understand therapeutic efficacy of the new indication.

A METHODOLOGICAL OVERVIEW OF COMPUTATIONAL DRUG REPOSITIONING

Drug repositioning investigations can be performed as workflow based, automated bioinformatics approaches and also as a tailored analysis around the pathophysiology of the disease using information about target molecules or target networks and associated expression data. Various approaches require an array of carefully designed multi-step analyses for candidate compound identification; compound prioritization coupled with well-designed validation experiments. Irrespective of the variations in the drug repositioning study design, drug repositioning study can be broadly classified into a three-step process: primary analyses, secondary analyses and tertiary analyses. Typically a primary analysis can be initiated using data from expression signatures, target biology, protein-protein or protein-small molecule network datasets (co-expression or Bayesian) and generate a list of ranked compounds for further evaluation. Secondary analysis refers to a collection of analyses approaches to filter or prioritize compounds for validation. Finally, tertiary analyses aim to validate the compounds using experimental approaches, pre-clinical models and assess outcomes of the drug repositioning using longitudinal mining of EHR data. Here we are discussing methodological overview using an example of the signature-based drug repositioning method
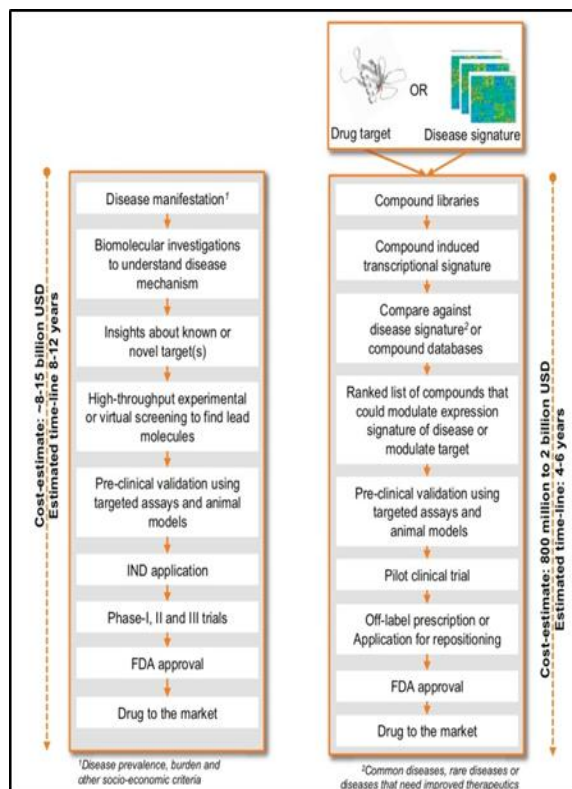
PRIMARY ANALYSES-IDENTIFICATION OF PHARMACEUTICAL COMPOUNDS FOR DRUGREPOSITIONING

Signature-based drug repositioning uses a compendium of transcriptomic signatures derived from RNA expression levels of various cell-lines with and without perturbation of alibrary of small molecules. Publicly available resources like Connectivity Map (cmap http://www.broadinstitute. org/ cmap/) and LINCS (http://www.lincsproject. org/) have generated thousands of drug induced transcriptional profiles representing a diverse range of FDA approved drugs, experimental compounds and research probes. One approach begins with investigators defining a biological state of interest, (which may reflect differential gene expression from an affected tissue in a disease of interest) in the form of "upregulated" and "down regulated" gene identifiers. These identifiers can be used as input to tools like cmap, Genomics of Drug Sensitivity in Cancer (GDSC) or Cancer Cell Line Encyclopedia (CCLE) . Many algorithms are available to process lists with direction of expressions.

SECONDARY ANALYSES–PRIORITIZATION OF PHARMACEUTICAL COMPOUNDS FOR DRUGREPOSITIONING

Once list of compounds are identified using systematic repositioning or target-based repositioning analyses, multiple filtering approaches can be used to prioritize candidate compounds for experimental validation. These approaches are similar to a chemical screening method in medicinal chemistry. Computational methods are available to integrate orthogonal data types to support the interpretation of the list of compounds generated using primary analyses. Compounds can also be prioritized using patent life, toxicity, mechanism of action, routes of delivery and other biological, physiological, chemical or disease specific features. Although these compounds will have certain similarities in their transcriptional or other molecular signature (as implied by a robust relationship to the query state or ligand specificities), the biological interpretation of this is not always clear. To help identify the shared biological underpinnings of the given set of candidate compounds, a series of secondary analyses on this list of compounds can be performed, using a range of biological, pathway and other ontology or rich-annotation databases driven enrichment analyses.

TERTIARY ANALYSES – VALIDATION OF PHARMACEUTICAL COMPOUNDS FOR NEW INDICATION AND PHARMACOVIGILANCE USING EHR

Prioritized compounds from secondary analyses of drug repositioning investigations need rigorous experimental and clinical evaluation before the release as new indications. These steps include validation in animal models, dose evaluations and clinical trials to assess efficacy of new indications. EHR based pharmacovigilance can be also performed as part of tertiary analyses. Tertiary analyses in drug repositioning can be divided as a bimodal approach:

COMPUTATIONAL DRUG REPOSITIONING USING OPEN ACCESS TOOLS
An array of biomedical informatics databases, webservers, software modules and chemoinformatics toolkits are available for computational drug repositioning. Databases of drug-induced

transcriptional signatures, as well as higher-level drug annotations, such as drug-drug interactions, side effects, small molecule libraries, bioactivities, and compound-target binding kinetics datasets are now available. Databases also provide access to various meta-data including drug ability of targets, compounds with regulatory agency approval status, collection of pre-clinical compounds, new molecular entities (NMEs) and experimental biopharmaceuticals repositories. Tools are also available for matching a given disease signature to a database of transcriptomic signatures and computing various properties. A subset of open access databases, webservers and software toolkits for drug repositioning listed.

TARGETING DISEASE COMORBIDITIES

Disease comorbidities are a key component in defining individualized
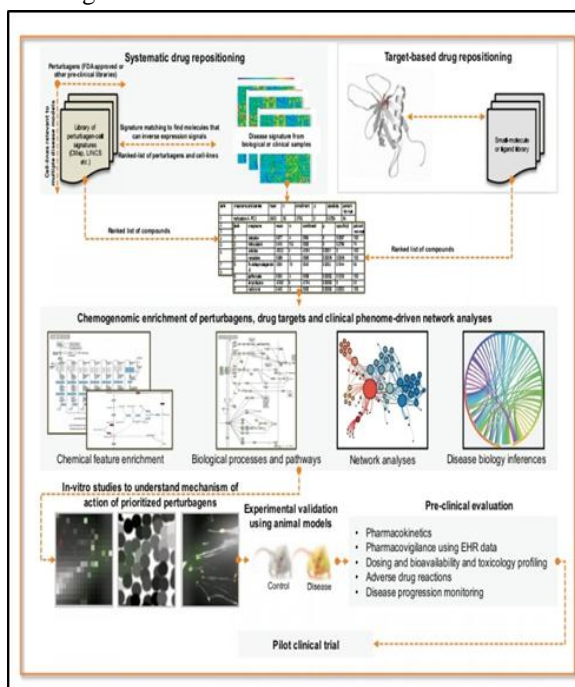
Clinical phonemic profile of patients. Treatment strategies that consider a primary disease and its comorbidities may have a better outcome compared to treating the condition as a singular clinical manifestation. Incorporating the existing knowledge of population specific, age and gender matched disease.

SOCIO-ECONOMIC IMPACT OF DRUG REPOSITIONING

Developing a new drug from the discovery phase to market requires significant investments in time (~15 years) and resources (USD $800- $1 billion) Chemical screening, lead identification [97], biological experimentation by in-vitro and in-vivo validation studies and extensive multi-center clinical trials .Lead molecules are also rigorously assayed to define pharmacological effects, bioavailability, the optimal dosing and formulation, and potential toxicity assessments. Irrespective of the dynamics in pharmaceutical, pre-clinical and drug-development budgets, drugs are often burdened with known and unknown side effects that lead to the recall of the drug(See: http://www.fda.gov/Safety/MedWatch/ and http://www.fda.gov/drugs/guidancecomplianceregula toryinformation/surveillance/adversedrugeffects/ucm 070093.htm). These aspects influence the product development and revenue cycles of pharma companies, which in turn affect the pricing of the drug. United States patent rules can also limit the return of the investment (ROI) for pharmaceutical companies due 20-year patent rule with an additional five years of patent exclusivity based on the Hatch-Waxman act (Public Law 98-417 http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/ STATUTE-98-Pg1585.pdf). In such a scenario patients, care providers or payers have to share the high cost of medications.

TOWARDS GLOBAL CATALOG OF DRUG REPOSITIONING

More than 300 drug-repositioning examples were reported in the literature and a catalog is currently being developed (Manuscript in preparation). A striking observation from the drug repositioning catalog is the importance of different axes of similarity between the disease states and drug groups that are implied by specific drug repositions. For example intra-disease category repositioning (primary and secondary indications are in the same sub or primary category of ICD-9 coding system), inter-disease category repositioning (primary and secondary indications are in different primary category of ICD-9 coding system), comorbid conditions and underlying pathophysiological modules could also drive successful repositioning. A subset of cancer drugs repurposed to another class of diseases in the ICD-9 classification is provided in

(Fig. 3). Analyzing a large number of successful drug repositioning examples would help to design predictive models and gain novel insights to global properties of drug repositioning (Manuscript in preparation).

FUTURE OUTLOOK

Agents that have failed clinical trials due to lack of efficacy or minor adverse profiles can also be used as candidates for drug repositioning as part of a systematic drug repositioning pipeline followed by toxicity studies of the new indications. Drug repositioning offers a cost-effective, accelerated and effective strategy for pharmaceutical companies and discovery driven treatment options for patients. Focused clinical trials may be required to re-validate the use of repurposed indications. Ancillary techniques of repositioning including reformulation strategies (altered dosage, drug combinations, mode of delivery) can help to identify better therapeutic interventions for complex and orphan diseases alike. Repositioning investigations can also reveal serendipitous examples where a prior clinical, comorbidities, shared pathway or other biological evidences does not exist. Such off target or polypharmacology driven results can be further perturbed using controlled experiments to understand shared disease pathways. The future outlook of drug repositioning is promising for patient communities, translational researchers and the pharmaceutical industry. Patient communities will greatly benefit from drug repositioning as it provides accelerated treatment strategies with limited side effects in a short period compared to the traditional drug development life cycle. Understanding clinical representations and their molecular phenotype is key for translational research and enabling precision medicine. Tracking the mechanism of actions for new indications could also help in understanding the molecular basis of genetic, complex, chronic or rare diseases. Pharmaceutical companies could leverage their large repertoires of public and private compound libraries in search of molecules that can provide better secondary indications and primary indications for rare diseases.

CONCLUSION

Increasing growth of the global population along with a growing global disease burden, emergence of new infectious diseases, high rates of drug resistance in cancers and chronic diseases and multi-drug resistant pathological strains call for the immediate requirement of effective therapies to improve global health. Drug repositioning solves an important gap in public health setting by providing alternate therapeutic compounds for complex, chronic or orphan diseases using molecular information derived from a single patient; family members with rare clinical manifestation or case-control cohorts. Several successful use cases of drug repositioning were reported across different therapeutic domains. Designing semi-automated workflows that can handle multi-omic analyses coupled with software modules for drug repositioning and validation using medicinal chemistry experiments would rapidly improve therapeutic stratifications for a wide array of diseases.

ABBREVIATIONS

Cmap = Connectivity map GO = Gene Ontology ICD-9 = International Classification of Disease – version 9 GPCR = G-protein coupled receptor FDA = Federal Drug Administration

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