Drug Repositioning: A Review

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Abstract:

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, chemoinformatics 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.

Keywords: Individualized medicine, Drug repositioning, Network analysis.

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).

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.

DRUG REPOSITIONING

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 to drug 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; ).

Drug repositioning (also known as drug repurposing or drug repprofiling) is the process of redeveloping a compound for use in a different disease (Oprea et al., 2011). This approach capitalizes on the fact that approved drugs and many abandoned compounds have already been tested in humans and detailed information is available on their pharmacology, formulation, dose, and potential toxicity (Ashburn & Thor, 2004). Drug repositioning is underpinned by the fact that common molecular pathways contribute to many different diseases. Drug repositioning has many advantages over traditional de novo drug discovery approaches in that it can significantly reduce the cost and development time and as many compounds have demonstrated safety in humans it often negates the need for phase I clinical trials (Oprea et al., 2011).

Examples of successful drug repositioning using zebrafish chemical screens include the identification of prostaglandin E2 as an activator of blood stem cell production (North et al., 2007) and the discovery that leflunomide, a pyrimidine biosynthesis inhibitor, prevents melanoma growth (White et al., 2011). Both of these compounds have now progressed to human clinical trials. Drug repositioning may use drugs that have already been approved for use in humans, these include libraries of FDA-approved compounds such as the Prestwick Chemical Library or the Enzo Screen-Well FDA-approved drug library.

classification system. The concept of using approved or regulated drugs for new indications can be traced back to the 1950s. The use of reticulose (lipoprotein nucleic acid complex) as a drug for postradiation effects is among the earliest examples of drug repositioning. Later examples include evaluating anti-malarial drugs in systemic lupus erythematosus, rheumatoid arthritis, and connective tissue diseases. More recent commercially successful examples of drug repurposing include the use of thalidomide as an anticancer agent and the use of duloxetine as an experimental drug for urinary tract infection.

**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.

**V 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 a library 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. But in general, algorithms score the input query against the available drug induced signatures, to identify compounds that concordantly modulate the query signature in a direction “towards” or “away” from the query state. A number of statistical approaches can be used to calculate this “connectivity score”, assign statistical significance and control the false discovery rate. These primary analyses produce a ranked list of candidate compounds that may potentially modulate (as within the scope of the assayed cell lines or quantity of replicates) a biological state of interest. Depending on the appropriate validation experiments, for a biological state of interest, there are often many more candidate compounds than would be feasible to escalate to experimental validation, and hence, systematic methods are required to prioritize top ranking compounds for further analyses. Targeted drug repositioning using a protein structure or putative
set of protein targets and search a compound library for pharmaceutical molecules, ligand databases or pharmacophore libraries that can activate, inhibit downstream functional effects, protein-protein interactions or enzymatic reactions. This approach, similar to high-throughput screening using medicinal chemistry platforms provides a set of ligands and statistical metrics to define the binding, activity or functional indications. Detailed account of the methodology to derive ligands sets for target based repositioning were described elsewhere. Irrespective of the study design; primary analyses provide a list of compounds with a ranking and a statistical metric to indicate the significance.

**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. Using an enrichment analysis tests enriched terms associated with the list of candidate compounds can be identified. Careful evaluation of enrichment analyses can help to identify of possible mechanisms of action of relevance to the disease, and can potentially be used as the basis for a further compound queries and prioritization. For example inferences like compound list is enriched for G-protein coupled receptor (GPCR) agonists; compounds were enriched for anticholinergic molecules or targets are encoded with signaling domains as PDZ etc. can be obtained from this step. Integrating this information with pathophysiology of the chronic, common or rare disease also requires extensive biocuration. In summary, secondary analyses steps can help identify the biological themes, which may underlie the shared drug signature of a set of candidate compounds, which can help prioritize compounds for further validation.

**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:

a. **Experimental Validation and Clinical Trials for New Indications**

Based on biomolecule, network driven, or chemogenomic insights gained from secondary analyses, a subset of compounds can be now prioritized for experimental evaluation. The quantity of compounds to be experimentally validated will vary depending on the cost and complexity of the relevant preclinical models. A typical experimental evaluation may involve cell-line based targeted assays; this will be followed by a closely monitored experimental evaluation in disease-relevant animal. This step would include evaluating the compound for both known and unknown side effects,
toxicity, pharmacokinetics and bioavailability testing. Dosing of the compound and its impact on the clinical manifestation of the disease would be assessed at this stage. This preclinical development step combined with data from previous experiments and literature will be helpful for investigators to plan clinical trials for the compound and its new indications. An illustrative summary of the three steps involved in systematic drug repositioning using expression signature is provided in (Fig. 2).

DRUG REPOSITIONING AND RELATED METHODS FOR THERAPEUTIC STRATIFICATION

Therapeutic stratification is an emerging concept of providing precise, personalized and data-driven therapeutic recommendations based on biological insights gained from risk prediction models, molecular profiling of the patient using multi-omics experiments and pharmacogenomics information. Integrating risk-prediction models and molecular profiling data with drug repositioning approaches could help patients to access better treatment in a shorter amount of time. Tumor grade-based treatment to treat cancer patients, recommending medications to lower the risk of adverse cardiovascular outcomes based on risk models and genetic variants from personalized genome scans or using multi-omics (genome, transcriptome or metabolomics) information to capture molecular state of the patient and use it for therapeutic recommendations are some of the recent examples of therapeutic stratifications. With the advent of low-cost, high precision molecular profiling techniques, molecular profiling can be performed at the hospital setting and could aid in therapeutic stratification of patients with complex or rare clinical manifestations.

NEW AVENUES FOR THE APPLICATION OF DRUG REPOSITIONING

Targeting disease comorbidity subgroups, matching drugs to specific patients for individualized medicine, and identifying off-label use of FDA approved drugs for orphan diseases represent areas of high potential for the use of drug repositioning. Comorbidities in drug repurposing pipelines may also help to identify better drug targets and new indications for existing disease based on shared pathophysiology modules of disease [85-89].

DRUG REPOSITIONING FOR ORPHAN DISEASES

Rare diseases (diseases that affect one in 1,500 people in the United States) are now being cataloged in public access resources such as the Orphanet (See: http://www.orpha.net/) and Genetic and RarDiseases Information Center (GARD) http://www.rarediseases.info.nih.gov/gard. These numbers are expected to grow as more and more families with rare disorders can be profiled using next-generation sequencing for identification of underlying genetic variation. Information about disease associated variants and genes from familial or small-cohort sequencing studies will be helpful in

Fig. (2). Computational and experimental outline of drug repositioning approaches.
designing target-driven drug repurposing for rare diseases [90]. Drug repositioning investigations targeting orphan diseases have significant potential in providing faster therapeutic options for patients.

● SOCIO-ECONOMIC IMPACT OF DRUG REPOSITIONING

This targeted re-use and recycling approach helps in reducing the cost of drug discovery pipelines and thus could help to reduce the cost to the patient population, further enabling the patients to access better therapeutics with shorter times for translation of therapies from clinical research to therapeutic interventions. Relicensing a compound for new indications may also help the pharmaceutical companies and experimental investigators expand the patent exclusivity by altering the mode of delivery, dosing or via combination therapy. Due to off-label use, repositioning an off-patent drug in the United States might not be a financially lucrative option for pharma companies, it could help inform policy efforts in other countries to consider drug repositioning strategies as part of drug discovery lifecycle. For example repositioning a cheap and widely available drug for malaria or tuberculosis for a new indication with costly therapeutic options can make the treatment affordable to larger, underserved patient communities. Patents, policies and cost estimate around drug repositioning are evolving in different countries. Unified guidelines to protect drug repositioning based indications and provide affordable therapeutic options based on existing indications in faster turnaround time could ultimately improve therapeutic outcomes.

● 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),

Fig. (3). Drug repositioning of cancer drugs. Nodes are different disease categories based on ICD-9 definitions. Edge labels indicate number of drugs primarily designed to treat a cancer and repurposed for a secondary indication including other types of cancers.
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).

- **Computational repositioning strategies**

**Genome**

Rapid advances in genomics have led to the generation of large volumes of genomic and transcriptomic data for a diverse set of disease samples, normal tissue samples, animal models and cell lines. Much of these data are publicly available. Together with other phenotypic, and clinical database, these data sets provide a unique opportunity to understand disease mechanism, elucidate drug mechanism of actions and identify new use of old drugs. Among those, transcriptomic profiles, such as gene expression data are most widely used, while other genomic and genetic profiles have been explored for drug repositioning as well.

One key source of data behind several repurposing efforts is the Connectivity Map (CMap) project and its extended project Library of Integrated Network-Based Cellular Signatures (LINCS), which produced large-scale gene expression profiles from human cancer cell lines treated with different drug compounds under different conditions. CMap aims to construct a detailed map for functional associations among diseases, genetic perturbations and drug actions. By integrating with other functional genomics databases [e.g. NCBI Gene Expression Omnibus (GEO)], its data have been extensively explored in drug repositioning studies. One approach using these data is to look for inverse drug–disease relationships by comparing drug gene expression profiles and disease gene expression profiles. This approach is also referred as ‘signature reversion’. For example, by systematically comparing gene expression signatures of inflammatory bowel disease (IBD) derived from GEO against a set of drug gene expression signatures comprising 164 drug compounds from CMap, Dudley et al. inferred several new interesting drug–disease pairs and validated one pair in IBD preclinical models. In another case, Jahchan et al. used a similar systematic drug-repositioning bioinformatics approach to query a large compendium of gene expression profiles to identify antidepressant drugs for the treatment of small cell lung cancer.

Recently, noncoding RNAs, especially the microRNA (miRNAs), have been shown in regulating kinds of cell activity, thus becoming promising therapeutic targets for drug repositioning. For example, Liu et al. developed an in silico drug repositioning strategy based on miRNA-TF feed-forward loops (FFLs). miRNAs and transcript factors (TFs) were found to be significantly enriched in cystic fibrosis (CF) associated gene regulations from public available data sources. Then they constructed FFLs in CF by defining specific TFs and miRNAs as two regulatory elements. Forty-eight existing drugs showing ability to influence the expression of miRNA that are part of FFLs were repurposed for the treatment of CF patients. Jiang et al. predicted new indications for existing drugs by constructing small molecule-miRNA network for each cancer. Rukov et al. developed a web server that links miRNA expression and drug function by combining data on miRNA targeting and protein–drug interactions. SM2miR is a database containing manually curated relationships between experimentally validated molecules and miRNA.

In addition to transcriptomic data, other genomic profiles (e.g. genetic mutations) can be applied to drug repositioning. For instance, Garnett et al. carried out a large-scale screening of human cancer cell lines with 130 clinical/preclinical drugs. A multivariate analysis of genetic and gene expression profiles of cancer cell lines showed that a few mutated cancer genes that are associated with drug sensitivity may serve as potential
biomarkers of drug response. To some extent, these mutations reflect the molecular activity of drugs, and can be regarded as drug signatures during the repositioning process. In another case, Okada et al. performed a three-stage genome-wide association study (GWAS) meta-analysis of rheumatoid arthritis (RA) patients and linked the risk loci to known RA drug targets. In their study, logistic regression models assuming additive effects of the allele dosages were used to assess the relationship of the single-nucleotide polymorphisms (SNPs) and RA. In total, 101 RA risk loci were identified (e.g. 42 are novel), and they showed significant overlapping with approved RA drug target genes. Furthermore, several drugs approved for other diseases were connected to RA risk genes, indicating they could be repositioned for RA. In another GWAS, a catalog of disease-associated genes from published genome-wide association studies were further integrated with targets of drugs from pharmaceutical projects. In this way, the drugs with targets mapped to the disease-associated genes from GWAS data may be repositioned.

Phenome

The phenome, defined as the comprehensive collection of phenotypic information, was emerged as a new source for drug repositioning. In recent years, the phenome-wide association study (PheWAS) has become increasingly popular as a systematic approach to identify important genetic associations with human diseases. For instance, Denny et al. performed a large-scale application of the PheWAS using electronic medical records (EMRs), and demonstrated that PheWAS is a useful tool to enhance the analysis of the genomic basis and to detect novel associations between genetic markers and human diseases.

Meanwhile, clinical side effects are shown to be capable of profiling drug-related human phenotypic information and can subsequently help discover new therapeutic uses. For example, Yang et al. used drug side effects as features to predict its indications. Ye et al. identified novel indications based on the hypothesis that similar side-effect profiles may share similar therapeutic properties. Bisgin et al. developed a Latent Dirichlet Allocation model for drug repositioning that adopted the phenome information from the Side Effect Resource (SIDER). Using drug side-effect profiles to suggest its novel indications has shown to be attractive but its practical use would require deep understanding of the underlying molecular/pathological mechanisms.

Finally, the phenome can be incorporated with other kinds of data for drug repositioning. As an example, Hoehndorf et al. developed an integrated system to predict novel drug–disease associations by linking genotype–disease associations with drug–gene associations. In this model, beginning with integrating phenotype ontologies for disease and gene or genotype, they derived a semantic similarity-based score to measure genotype–disease associations. With this approach, most of the known drug–disease associations have been retrieved and the new associations may indicate a new repositioning opportunity. Although some researchers have demonstrated the potential correlations between genome and phenome, there is still an urgent need to understand these correlations better and turn them into disease treatment or personalized health care. For example, the BRCA mutation (mutation in either BRCA1 or BRCA2 genes) was found to be associated with the risk of getting breast cancer for ovarian cancer patients. Because BRCA mutations are clinically significant, a deeper understanding of the relationship between BRCA mutation status and cancer phenotype will be important for making precise treatment decisions for patients.
Drug chemical structures:

The drug chemical structures can also point toward repositioning opportunities. Moreover, publicly available databases of chemical structures, high-throughput screening data and literature-derived biochemical data containing massive amounts of information useful for repositioning. The key insight behind these approaches is that the molecules with similar chemical structures often affect proteins and biological systems in similar ways. Similarity may be measured in many different methods using different structural features, including 2D topological fingerprints or 3D conformations, and is an active area of research. The way to incorporating similarity between chemicals into repositioning inferences is also an active area of research.

For example, Swamidass et al. proposed to use chemical structure to infer which targets modulate disease-relevant phenotype. Knowing which targets modulate disease-relevant phenotypes is a signal that can indicate what other drugs might work to treat the disease.

All three different types of data were integrated to define a kernel function used by a support vector machine (SVM) classifier. This method was further compared with other methods, and showed high efficiency. Similarly, Tan et al. incorporated drug chemical structure similarity and gene semantic similarity to construct a drug similarity network, which was further used to extract novel indications. Ng et al. proposed a novel algorithm called ‘ligENTS’ to define novel drug–target associations by mapping the drug to its global pharmacological space according to its chemical information. Then structural systems biology platform was integrated to reposition approved drugs for malaria. A full review of chemical structure-based approaches to repositioning is beyond our scope, but these studies show a trend toward including chemical structures alongside other types of data.

Drug combinations

As many diseases are driven by complex molecular and environmental interactions, targeting a single component may not be sufficient to disrupt those mechanisms, and interest in early drug discovery stages has increasingly evolved to target multiple molecules using combined drugs or multi-target inhibitors. For example, the activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) is a malignant cancer with poor prognosis. Constitutive activation of the NF-kB by IkB kinase (IKK) has shown to be a key pathogenic factor. Ceribelli et al. screened 466 drugs that have been approved or in early stage for cancer therapy and found that ibrutinib, a kinase inhibitor that can block B-cell receptor signaling pathway to activate IKK, shows a significant synergistic effect with JQ1 in killing ABC DLBCL cells both in vitro and in vivo, suggesting that the combination of JQ1 and ibrutinib might be a new effective therapy.

Other than in silico methods, experimental characterizations of drug efficiency (e.g. library screening and cell viability assays) were also adopted to identify new drug combinations. Kang et al. identified antileukemic drugs that could be combined with imatinib to overcome drug resistance in BCR-ABL+ leukemia. They first used library screening, literature search and correlation analysis to select 11 candidate drugs that might be combined with imatinib. Dose responses for these candidates with/without imatinib were applied in an iterative search algorithm to identify effective combinations that can overcome drug resistance. These predicted combinations were further confirmed in preclinical models.
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 offtarget 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.

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.

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LIST OF 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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