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Review

Drug repurposing: Iron in the fire for older drugs

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ABSTRACT

Repositioning or "repurposing" of existing therapies for indications of alternative disease is an attractive approach that can generate lower costs and require a shorter approval time than developing a de novo drug. The development of experimental drugs is time-consuming, expensive, and limited to a fairly small number of targets. The incorporation of separate and complementary data should be used, as each type of data set exposes a specific feature of organism knowledge Drug repurposing opportunities are often focused on sporadic findings or on time-consuming pre-clinical drug tests which are often not guided by hypothesis. In comparison, repurposing in-silico drugs is a new, hypothesis-driven method that takes advantage of big-data use. Nonetheless, the widespread use of omics technology, enhanced data storage, data sense, machine learning algorithms, and computational modeling all give unparalleled knowledge of the methods of action of biological processes and drugs, providing wide availability, for both disease-related data and drug-related data. This review has taken an in-depth look at the current state, possibilities, and limitations of further progress in the field of drug repositioning.

1. Introduction

DR is often referred to as drug repurposing, drug redirecting, drug retasking, drug reprofiling, and therapeutic switching. (Maryam Lotfi Shahreza,) National center for advancing Translational Sciences (NCATS), an initiative from of national institute of health (NIH) in the united states of America (USA), defined drug repurposing as "studying the drugs that are already approved to treat one disease or condition to see if they are safe and effective for treating other diseases" [1]. In May 2012, NCATS introduced the program "Discovery of New Therapeutic Uses for Existing Molecules" to focus on new therapeutic indications for the existing drugs, drugs currently in clinical development as well as shelved and discontinued drugs [2]. There are, indeed, other barriers to overcome until the drug is accepted on the market, most notably, the long development process of drug discovery, drug development cost, side effect (adverse events) of novel drugs. The total expense of developing a novel drug from start to finish is projected at between $1.8 and 2.6 billion; however, full processes will take between 10-15 year [3,4]. Hence, alternative approaches for drug development is explicitly required. Repurposing drugs or drugs that have expired in human clinical trials due to loss of primary use effectiveness can significantly reduce both times and costs (Fig. 1).

The basic method of most drug repositioning programs is to assemble a list of known drugs — either as actual samples or, in the case of analytical approaches, robust 2D models, and then evaluate them in an acceptable device (either a physical assay or in silico) Fig. 2.

1.1. Advantages

1. The primary benefit of drug repurposing is, of course, linked to time and cost problems, since drug repurposing significantly reduces the risks and costs associated with the development of drugs and shortens the gap between drug discovery and patient availability due to the accessibility of a large amount of pharmacokinetics, pharmacodynamics and clinical data [6,7]
2. Only a few drug development will receive FDA approvals, while over 65% of drug repositioning programs have been completed. [8]
3. Drug repositioning may rekindle some drugs that failed in phases of drug development but may find new applications [8]
4. Drug repositioning will change the usage of such drugs and recommend alternative uses [8] Table 1
5. Drug resistance is one of the key causes for diminishing drug efficacy; DR is a positive solution to overcoming drug resistance, such as the usage of non-antibiotic medicines to counteract resistance to antimicrobial [9]

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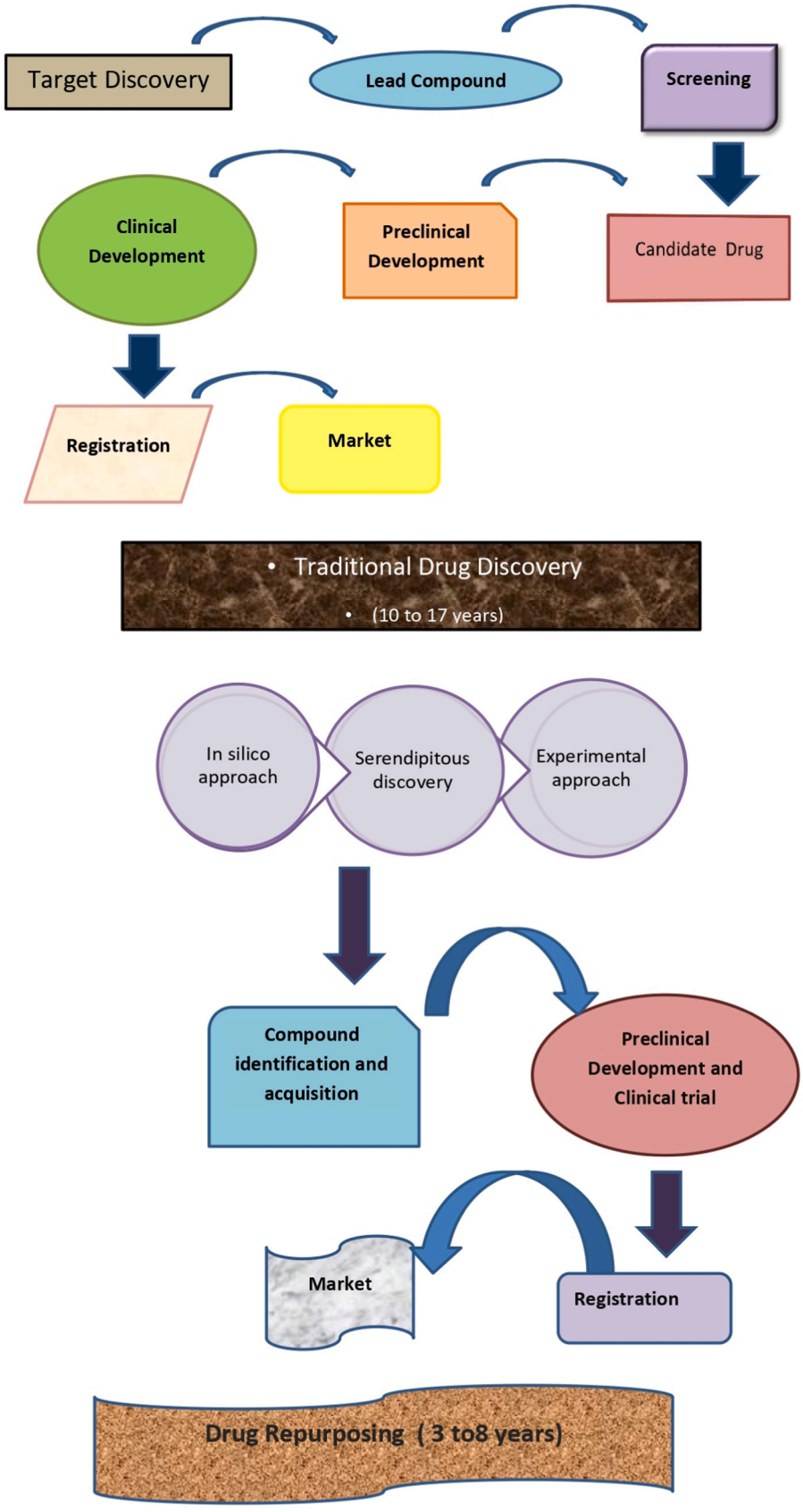

Fig. 1. Schematic representation of the steps involved in traditional drug discovery and drug repurposing strategy.

6. This is an attractive and successful technique, especially in the current decade when deep-data mining tools become available. It is simple to screen with the use of genomics, metabolic, microbiomics, signal transduction pathways details, device biology, safety and adverse reactions from authorized product libraries, and the secondary targets of approved drugs. Technology [10]
7. It gives the conventional de novo drug development a tremendous chance since the effective rate of producing a new molecular entity is just 2.01 percent [3] and the number of approved drugs has decreased since the 1990s [11].
8. The repurposing of drugs is a direct application of polypharmacology describing the ability of drugs to act on multiple targets (genes or proteins) or pathways of disease. Multiple drugs are known to interact with different targets (average 6–13 multiple targets [12].
9. DR is a complex mechanism where good efficiency is not obtained by any particular computational procedure. This motivates the integration of various biological data to enhance the reach and reliability of new DR methods [13] (Table 2).

1.2. Governmental granting agencies

With the creation of the National Center for Advancing Translational Sciences (NCATS), within the National Institutes of Health in 2012 governmental financial support for drug repurposing began in the US. NCATS facilitates technology development to aid in the creation and implementation of novel therapies. Thus, although not explicitly focused on cancer-based projects, NCATS has dedicated resources to drug repositioning efforts.NCATS also provides development grants for different stages of product repositioning, spanning from early silico projections to late-stage clinical trials. There are also external support organizations, such as the National Cancer Institute (US) and the Ontario Center for Cancer Science (Canada); however, such entities do not usually include academic or corporate collaborators with repurposing-centric grants/subsidies.

Besides, two specific grants to support drug repurposing programs were developed by the Canadian Institutes of Health Research (CIHR) in partnership with Muscular Dystrophy Canada: the Joint Translational Call (JTC) E-Rare 3 and the North American Re: Rare NAR: [14].

The JTC provides funding for phase Ib or IIa clinical trials and is co-funded with European partners, while the NAR: R has been developed through partnerships with philanthropic organizations — Cures Within Reach (CWR), the Mindset Foundation, and Mitacs — and provides proof-of-principle funding. Like NCATS, the CIHR has failed to set up financing mechanisms for fundamental science work to repurpose medications, let alone repurpose initiatives for cancer therapies [15].

Table 1
Examples of DR programs that have completed and some started but not completed.

Drug category	Original indication	New indication	Status of development
Amphotericin B (AMB), Anti-fungal antibiotic	Fungal infections	Leishmaniasis	Already developed
Aspirin NSAID	Pain and inflammation	CVDs (Anti-platelet)	Already Developed``
		Prostate cancer	DR Programs not completed
Amantadine, Anti-viral	Influenza	PD	DR programs completed
Astemizole, Anti-histaminic	Allergic illness such as urticaria	Malaria	DR Programs not completed
Avermectin, Anthelmintic	River blindness, Elephantiasis	Tuberculosis	DR Programs not completed

Table 2
Based on scientific evidence classification of drug repurposing [20].

Drug Repositioning level	Quality of Scientific Evidence
0	No evidence include in silico prediction without confirmation
1	In vitro studies with limited value for predicting in vivo / human situation
2	Animal studies with hypothetical relevance in man
3	Incomplete studies in man at the appropriate dose eg proof of concept very cases or inference from medical records some clinical effect observed
4	Well-documented clinical endpoints observed for the repurposed drug at doses within safety limits

1.3. Combination of drug

Throughout the field of drug development, the combination of two or more drug substances with specific modes of action was shown as an effective method for raising the success rate of drug repurposing [16]. Furthermore, for combined therapy, the concurrent usage of metformin and temozolomide in glioblastoma care has been documented to be effective [17]. Advantages of a combination of the drug in DR including i)Deeply better synergic results relative to single-drug treatment ii) Reduced incidence/emergence of mechanisms for drug resistance, iii) Use of far lower concentrations of drugs and therefore trivial adverse reactions, and iv) Higher performance rate of treatment mortality [18].

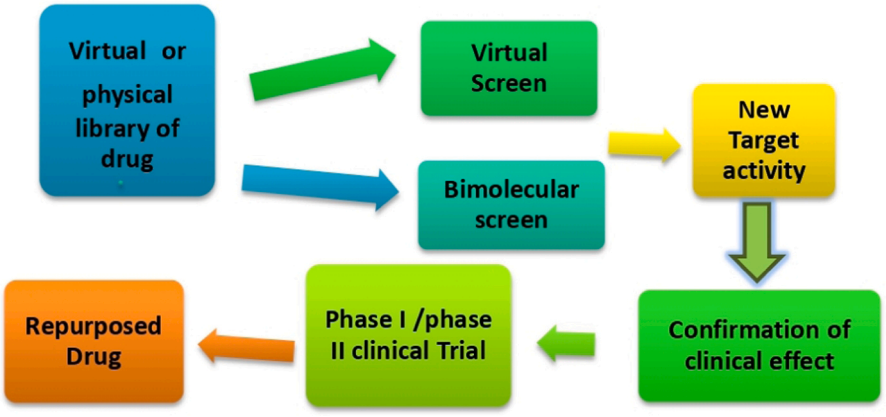

Fig. 2. General-purpose drug repositioning workflow.

1.4. Early-stage repurposing

A common first step in repurposing is to screen libraries of compounds already approved — against a disease-specific biological assay (i.e., one that tests for cell kill). Researchers can select a subset of bioactive compounds from such screens for further questioning in secondary and tertiary assays accessing relevant aspects of disease biology and molecular pathophysiology. The numerous services to promote attempts to repurpose common as well as rare diseases. Besides, scientists at the Center research the development and screening of high-throughput assays, informatics and modeling, and analytical and medicinal chemistry to improve the repurposing process.

1.5. Late-stage repurposing

If a researcher has already detected a promising accepted or current molecule by initial screening and confirmation, they may require assistance in planning the clinical testing agent. Experts assist these researchers by supporting the development of regulatory data packages allowing the drug to enter clinical trials for new disease indication help for these activities by its initiatives Therapeutics for Rare and Neglected Diseases (TRND) and Bridging Interventional Development Gaps (BrIDGs), which include access to funding and experience in drug creation through joint collaborators. Furthermore, the Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) initiative offers reciprocal grants to academic researchers to employ current pharmaceutical industry representatives to carry out repurpose studies [19].

2. Methodology

2.1. Identify the most promising drugs for further clinical investigation

Repurposing programs focus on advanced known molecules either approved or failed with some available knowledge of their safety or MoA, led by in-depth screening and compound libraries of smaller size. Typically approved libraries of compounds containing 500–2000 compounds and a similar number of existing but unapproved compounds are believed to be available [21].

2.2. Binding assays to identify target interactions or Target focused screening

About a specific mechanism is based on a specific compound activity. (Cha Y 2018) Target-based repurposing is based on prior knowledge of the specific molecular or cellular determinant/function target recognized by the drug intended for repurposing. If new research finds that the target plays an important role in a condition or disease other than the original indication, then there is a potential for repurposing. For example, the drug plays the same role as a viral RNA polymerase inhibitor against both influenza and Ebola viruses in the case of the aforementioned favipiravir.

On the other side, the Abelson tyrosine-protein kinase 2 (Abl2), target of the anti-cancer drug imatinib, was found to be needed for efficient fusion and release into the cytoplasm of the infected cell of severe acute respiratory syndrome coronavirus (SARS-CoV) and pseudovirions of the Middle East respiratory syndrome coronavirus (MERS-CoV), a key phase in viral replication [22]. Proteomic techniques such as chromatography of affinity and mass spectrometry were used as approaches to identify binding partners for a growing number of drugs [23]. Analyzes of the product goals and off-targets have been common bedfellows in an age of chemical biology for target confirmation. For example, the Cellular Thermo Stability Assay (CETSA) technique was implemented as a way to model target engagement in cells using biophysical principles that predict the thermal stabilization of targets by drug-like ligands with the correct cell affinity [24].

2.3. Phenotypic screening

This is dependent on cell behavior for example cell growth and cell death with or without the application of the drug. Historically, phenotypical screens have been more effective in producing new drugs than target screening [25,26]. Phenotypic screening may identify compounds in model systems that display disease-relevant results without previous knowledge of the affected target(s) [27]. In the product repurposing sense, whether the compounds being tested are licensed or investigational products, that could mean possibilities for repurposing that can be readily explored. In vitro phenotypic displays usually use a broad variety of cell-based assays in a good size of 96 [28]. A highly effective variation of phenotypic assays is the use of screens that record signals related to the biology of diseases. Nonetheless, the usage of in vitro assays is questioned by its usefulness in the treatment of the human disease condition and an ongoing debate on the use of more specific cell-based models such as human-induced pluripotent stem cell-derived tissues for degenerative diseases is likely to continue [29]. A multicellular model sampling of the cells [e.g. Worms infected with human genes and/or disease-causing defects (Caenorhabditis elegans), fruit flies (Drosophila melanogaster), and larval zebrafish (Danio rerio) also offer a more convincing path to phenotypic screening [30]. While there are certainly drawbacks to the degree to which the human disease phenotype is. completely reflected in such models, they can better recognize and target active molecules early in a repurposing project [31].

2.4. Review drug-related data and bring it to the attention of clinical investigators

Besides developing the database all about repurposing candidates, the project has released peer-reviewed scientific papers on drugs containing extensive evidence to endorse repurposing [32,33].

2.5. Document about how such medications should be combined with exiting or other repurposed drugs

From the literature review, it was noticed that drug combination therapy utilizing two to three compounds with specific action mechanisms will resolve the repurposing challenge The combined usage of drugs may create a synergistic impact if each of the drugs impinges on a particular target or signaling mechanism resulting in a reduction of the necessary doses of drugs for each specific medication. The usage of medication formulations may, however, improve the success rate of product repurposing screens. It can be done in two steps: a product repurposing check for licensed product collections to classify hit compounds, and then a drug combination test with the defined hit compounds to determine successful drug combinations for a specific reason for clinical usage.

Two approaches to detecting synergistic interactions use product repositioning sensor strikes. The first form of synergistic combination deals with the problem of weak compound strength compared to toxicity synergistic influence of a mixture of three medications, however, reduces of increasing human drug concentration to 1/10 of the concentration used in the single drug treatment [34].

3. Classification based on the data type used

Computational methods allow the link of multiple layers of omics-generated data such as transcriptomics, genomics, metabolomics, and proteomics-to decode the biology of old and new cancer targets, together with data on drug mode of action. In silico product repositioning, the potency of targeted controlled treatments may be improved. Docking simulation and deep learning are methods in silico DR.

3.1. Molecular docking methods

Molecular docking approaches aim to model and simulate physical interactions between drugs and targets [35] and are used in structural molecular biology and computer-assisted drug design. Successful docking methods can search high-dimensional conformation spaces efficiently, and rank candidate dockings accurately using a scoring function [36].

3.1.1. Limitation

1. The requirement of a known three-dimensional (3D) structure of chemical ligands and protein targets severely restricts the application of docking because many physiologically important protein structures are not fully resolved [36]
2. The findings of molecular docking have large false-positive levels due to mistakes in the defined protein structure and insufficient simulations of atomic and molecular interactions;[36]

3.2. Machine learning methods

Appear to be more beneficial than docking simulation, because they will review more qualified applicants for more experimental screening [37]machine learning methods can be classified as either drug-based or disease-based methods.

3.3. Drug based methods

Drug-based approaches aim to find possibilities for repositioning by studying the drug or pharmaceutical prospective investigation, If more detailed identification of pharmacological properties is needed, drug-based approaches that require pharmacological or chemical data on drugs may be preferred.

3.4. Disease-based methods

Focus on managing disease, symptomatology, or pathology. Disease-based approaches may be preferred when there is insufficient knowledge of pharmacology. Gonen [38] divided the conventional analytical DR approaches into three groups in another classification.

(i) docking simulations,
(ii) ligand-based approaches and
(iii) literature text mining.

4. Drug repositioning approaches and resources

Network modeling is one of the most widely employed data-driven methods. A network-based technique for determining a drug target first reconstructs and then simulates the interactions. The subsequent relationships of activity between the drug targets can expose possible drug targets [39].

4.1. An overview of the existing approaches to drug repositioning

Detection of unintended side effects, the establishment of drug interaction with different targets, creation of new regulatory networks identifying particular symptoms of illness, recognition of pharmaceutical agents that may influence human phenotypic manifestations. An illness, and the discovery of new relationships by the use of text mining.

Drug Repositioning Approaches divided them into three categories: network-based approaches [40–50], text-mining approaches [51–63], and semantic approaches [66–68].

4.2. Network-based approaches

Network-based methods in the fields of genomics, transcriptomics, proteomics, and system biology will dramatically enhance the drug development cycle and the difference between pharmaceutical production and marketability through the creation and confirmation of suitable disease-related biomarkers signaling pathogenic processes and pharmacological responses to therapeutic drugs [69]. Increasing emphasis is being put on DR due to significant economic opportunities to reposition established medications, particularly for orphan care and rare disorders. Besides, research on DR is beneficial to human health since it can facilitate the discovery of new uses for existing drugs [13]. Two types of network-based approaches are network-based cluster approaches and network-based propagation approaches [70].

4.3. Network-based cluster approaches

Network-based cluster approaches are proposed to discover novel drug-disease relationships or drug-target relationships. These approaches aim to find several modules (also known as subnetworks, groups, or cliques) using cluster algorithms according to the topology structures of networks. These modules include various relationships such as drug-disease, drug-drug, or drug-target relationships. The most common network-based cluster approaches, including DBSCAN [71], CLIQUE [72], STING [73], and OPTICS [74], cannot detect overlapping clusters.

4.4. Network-based propagation approaches

The workflow of these approaches is that all network nodes and some subnetwork nodes are propagated from the source node to the prior knowledge. These approaches can be divided into two types, based on the different ways of propagation: local approaches and global approaches [75].

4.5. Local propagation approaches

This takes the limited information of the network into account and may fail to make correct predictions in some cases [76].

4.6. Global approaches

Global approaches that include knowledge from all over the network do better than local strategies. The majority of current researchers focus on global approaches to deliver outstanding performance. For example, Köhler et al. [77] built a network propagation method to identify novel disease-gene interactions, centered on global network knowledge. The method involved three phases: extracting drug-disease relationships and creating a disease-gene network; (ii) collecting the network's global knowledge using a network algorithm for random walk propagation; and (iii) identifying global metrics to forecast novel disease-gene relationships [78] (Figs. 3 and 4).

4.7. Semantics-based approaches

Semantics-based approaches are widely used in information retrieval, image retrieval, and other fields. Recently, these methods have been applied to drug repositioning. The workflow of these methods mainly includes three steps (Fig. 5). First, biological entity relationships are extracted from prior information in massive medical databases to build the semantic network. Then, semantics networks based on existing ontology networks are constructed by adding the prior information obtained in the previous step. Finally, mining algorithms are designed to predict novel relationships in the semantic network [70].

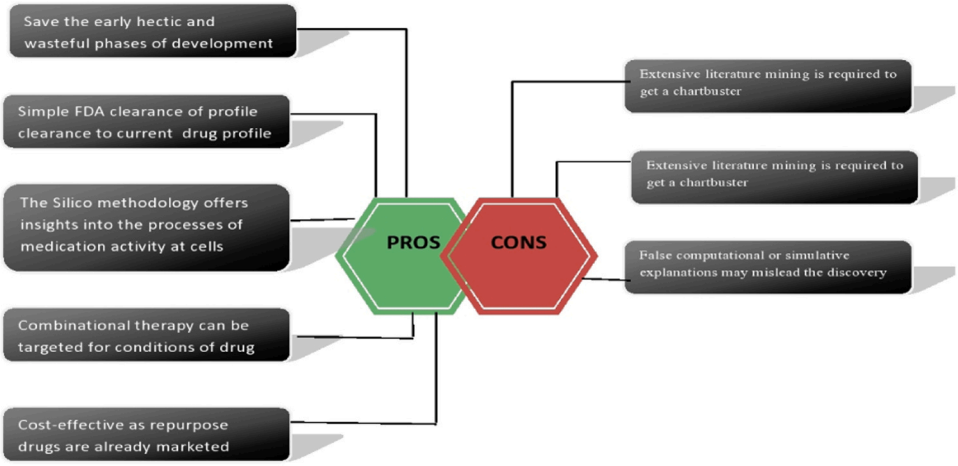

Fig. 3. Pros and Cons of drug repurposing.

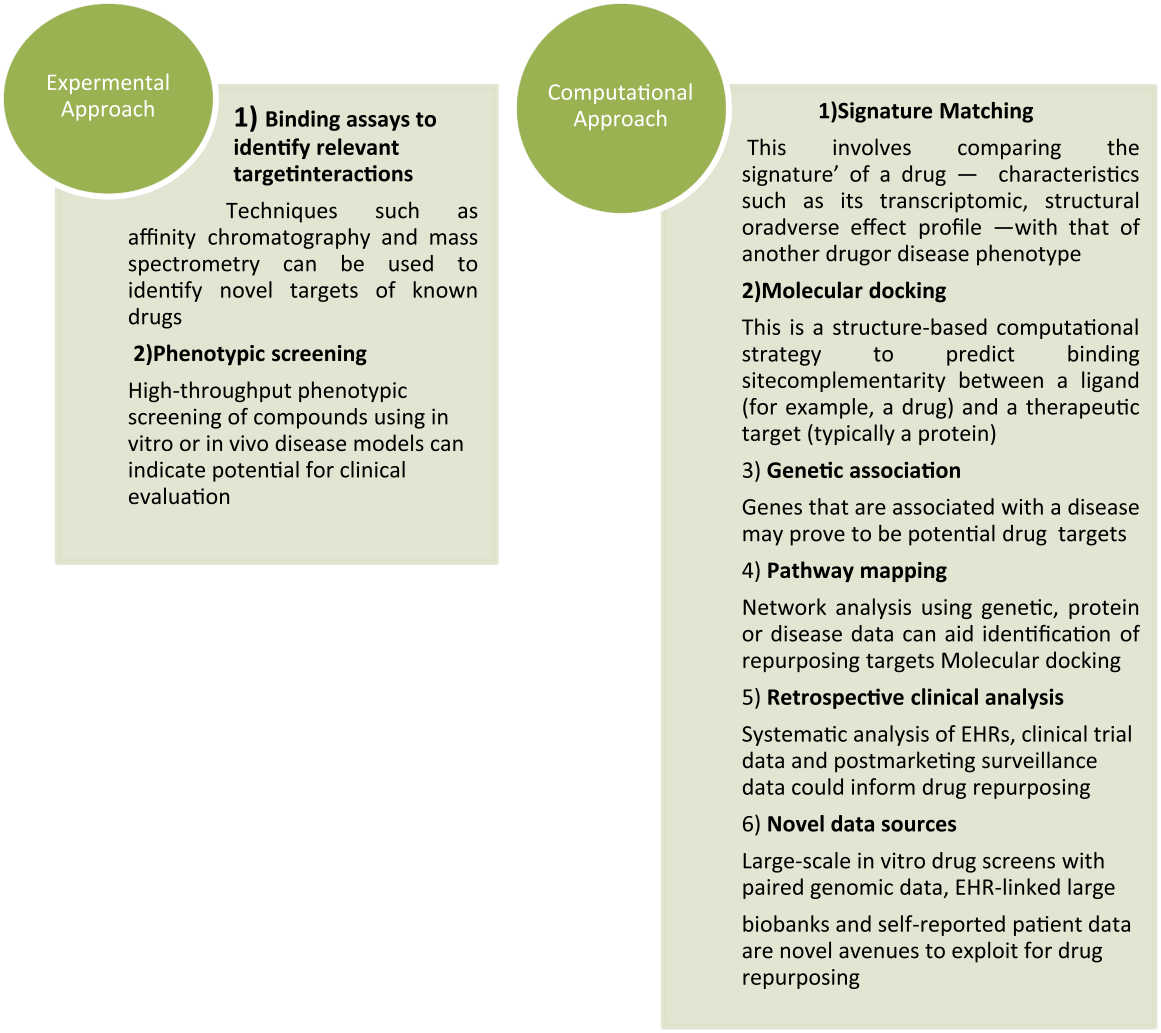

Fig. 4. Experimental approach and computational approach (pushpakom2018).

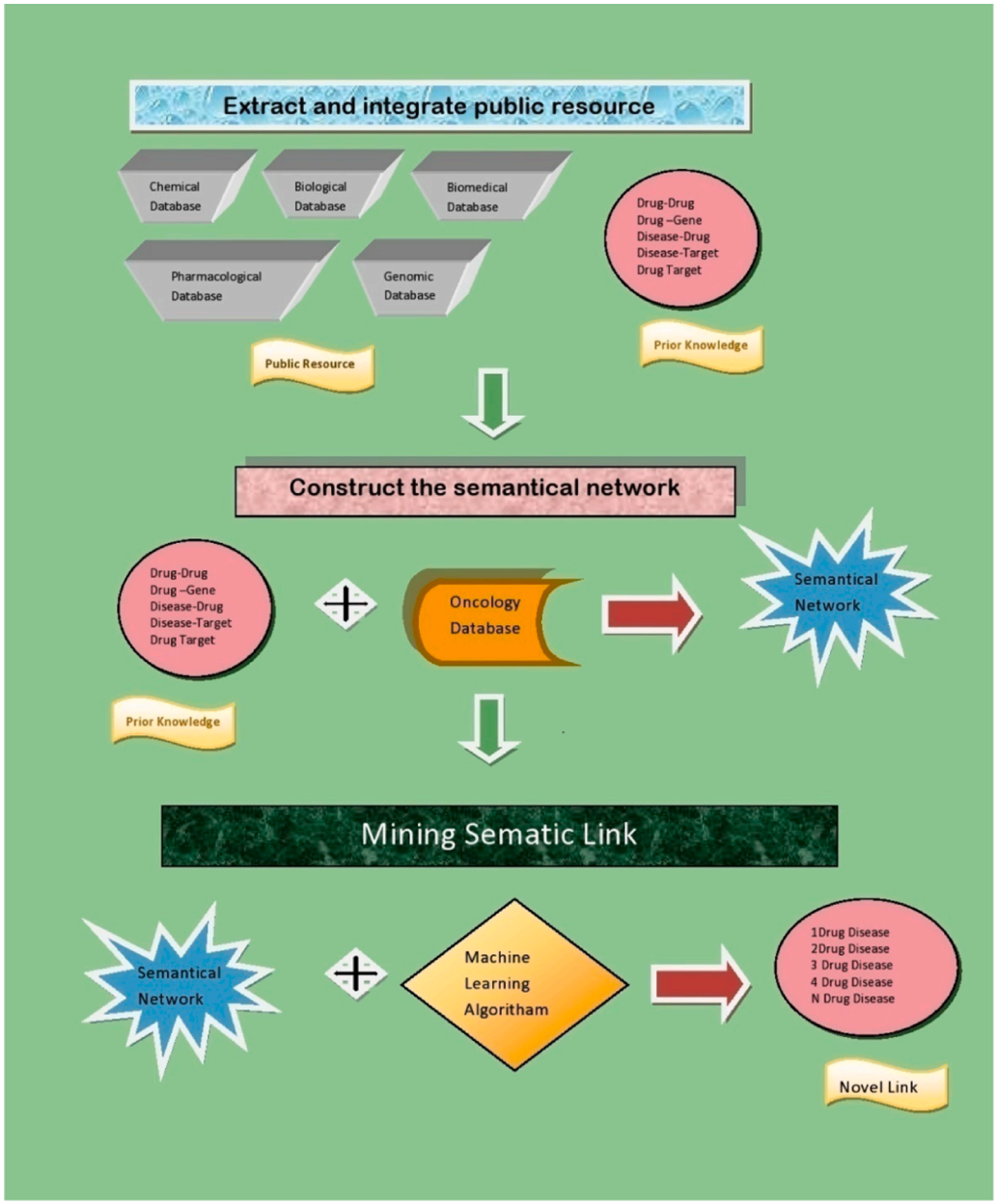

Fig. 5. workflow of semantic network inference.

5. Challenges in the repurposing process

5.1. Optimization of inclusion and exclusion criteria in target population selection

Selecting the treatment groups is the key challenge of determining the drug's desired result. Incorrect collection of subjects contributes to the drugs' catastrophe results rather than the ones predicted. Thalidomide, for example, results in amelia and phocomelia as administered by pregnant women in the first trimester by treating morning sickness. Excluding certain specific population parameters in the screening of topics contributed to the detection of a current program toward multiple myeloma [79] (hemn stre).

5.2. Achievement under time constraints

Repurposing old medication for a new indication requires several factors such as dosing protocol and path of administration to gain the major benefit with the new indication. It is a challenge to refine the formulations without destabilizing the product [80].

1. Drug repositioning targets a particular community of patients with a specific range of medical disorders, and it is important to predict unexpected harmful effects, requiring a thorough analysis of-answer.
2. Repurposing medication formulations require precondition evidence on non-drug interactions, pharmacodynamics, and product pharmacokinetics with a particular focus on the profile of toxicity [81].

6. Conclusion

The identification of novel drug targets is an important task in drug production. Increasing emphasis is being put on DR due to significant economic opportunities to reposition existing medications, particularly for orphan treatment and rare disorders. Also, work on DR is beneficial to public health because it can promote the development of new applications for existing drugs. DR is a complicated process where

satisfactory performance is not obtained by any single computational procedure. This motivates the incorporation of various biological data to enhance the scope and efficiency of modern DR approaches. Because any single data type provides a one-dimensional view of a biological system, it may not be accurate to assess the output of an integrative approach based on one data type.

Conflict of interest statement

No conflict of interest.

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