Network based strategies for Drug repurposing

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Abstract **- Traditional approach of drug discovery process is highly expensive and time -consuming. That's why, Drug repurposing strategy was developed as an alternate approach to accelerate the process of drug discovery. Drug repurposing is the process of finding new therapeutic uses for existing drugs and is very efficient, less expensive, time saving and low risk of failure. It utilizes the mutual effect of experimental and computational approaches to find new drug targets. In this article, different drug repurposing approaches have been discussed. In which, Computational approaches have been known to greatly improve the performance of drug repurposing. This article also provides an overview of progress and efficiency in the field of drug repurposing by network based strategy.**

Index Terms **- Drug discovery, Drug repurposing, Computational approach, Drug target, Computational approach, network-based approach.**

INTRODUCTION

The traditional approach to discover new drugs is a slow, laborious, risky, and expensive process. The total average development expense of a drug ranges from 2-3 billion $ and the total time taken for developing new drugs is usually 13-15 years.[1] Drug repurposing is a novel approach to discover drugs which is based on an assumption that the finding new applications of existing or old drugs will minimize the failure risk at the time of clinical trials and thus lead to faster approval of the drug. Due to fast growth in the field of bioinformatics data and biological data, drug repurposing takes less time and low investment for the drug development process. Researchers usually take 1 to 2 years of time to find a new target for drugs and approx 8 year of time to develop a drug using novel repurposing approach.[2] In traditional drug discovery every year about 90% of drugs failed in 1st phase clinical trials /FDA evaluations. Lack of efficacy and toxicity are two most important causes of drug failures during FDA evaluations.[20] The drug repurposing approach skips many of the tests that are essential for FDA evaluation of newly developed therapeutic compounds. Drug repositioning is primarily applied to identify new therapeutic applications of an existing or old drugs having both preclinical information & clinical profile (pharmacodynamic & pharmacokinetic).[3] In last few years, drug repurposing approach has received a significant boost: about 1/3rd of newly approved drugs are repurposed drugs, that's generate approx 25 percent of the pharmaceutical industry's annual revenue.[4] Drug repurposing approaches can help in finding therapies for new disease at very low cost & in very less time, especially where studies have been already done regarding preclinical safety. Drug repurposing requires a much lower cost & time investment for developing a drug via repurposing approach.[21] Due to this advantage of Drug repurposing, It offers many countries the opportunity to develop medicines with lower investment. Drug repurposing approach is based on the fact that a single drug can act on more than one target. In United States, About 1/3rd of newly developed drugs are repurposed drugs.[1] Some of the best-known examples of drugs that have emerged from drug repositioning are sildenafil, aspirin, thalidomide, valproic acid, methotrexate, etc. The first drug repurposing example was an accidental discovery. Sildenafil, It was originally developed to treat pulmonary hypertension and angina (chest pain due to heart disease) during cardiac clinical trials, the drug was also shown to be effective in inducing an erection.[3,4]

Traditional drug development approach vs drug repositioning:

In comparison with traditional approaches to discover drugs, the drug repurposing approach has many advantages. Drug repurposing has the potential to minimize both time investment & cost investment developing new drug compare to traditional approach of drug development.[9] Drugs Developed by repurposing approach skips initial 6 to 8 years of time

that are required for the developing a new drugs via traditional approach and it directly enter into clinical test Phase 1, Phase 2, and Phase 3 to check safety, thus reducing the overall risk.[2] Traditional drug discovery pipeline from target identification to drug approval takes an average of 10-17 years whereas, drug repurposing takes an average of 3-12 years because it bypasses many steps.[12] The main focus of the traditional approach of drug development is to treat multifactorial diseases or long time persisting disease, while drug repurposing focuses on drug development for fastly emerging disease and recurrent diseases, and neglected diseases.[4] Traditional approaches to discover new drug typically comprises 5 steps: 1. Early drug discovery and development 2. Preclinical development 3. clinical development 4. FDA drug review and 5. FDA drug safety monitoring. However drug repurposing comprises usually 4 stps: 1. Identification of compound 2.acquisition of compound 3. Clinical trials and 4. FDA safety monitoring and registration. [2] In the Traditional approach of drug development, only 11% of drugs investigated in clinical trials are eventually approved. However Drug repurposing approval rates are close to 30%

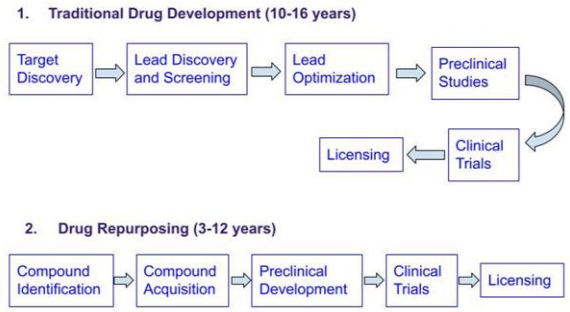

Figure: Traditional Drug Development vs Drug Repurposing

Approaches used for drug repositioning:

One of the main issues in drug repurposing is to find new relationships between drug and disease. To deal with this issue there are several approaches. In which, activity based approach and computational approach are most commonly used.[2] The activity-based/experiment-based approach refers to actual drug screening to identify new application of drug on the basis of experimental analysis. Without taking any information about target structure or conformation, the activity-based approach involves target based protein screening and cell based screening in invitro or invivo model.[4] Computational / in-silico drug repurposing approach utilizes publicly available drug databases or data from compound libraries by using tools of bioinformatics to identify drug-protein target interaction networks. In silico method of drug repurposing has become more successful because of the availability of data related to protein structural information and accumulation of pharmacophores in last few decades along with advancement in the area of bioinformatics and computational science.[5] The computational approach of drug development has become possible by the following two technology trends. 1. Accumulation of data from various sources, such as proteomics source, genomics source, and chemoproteomics source due to which information of drug profiles, disease phenotypes characteristics, and pathways maps also became available for researchers. 2. Advancement in field of computational biology, bioinformatics & data science have made it possible to create repositioning algorithms along with retrospective analysis and database maintenance of experimental data.[1] The drug repurposing approach of drug discovery is used to find drug targets by computational screening of drug data source and also it helps predicting interaction relationship between drug, target and protein using computational method.[4] Identifying the Drug target involves getting a molecular level understanding of drug target function and includes analysis of sequences of gene, structure of protein, and metabolic pathways.[18] The computational methods can be categorized into the three categories: Machine learning approaches, text mining approaches and network based approaches.

Network-based approaches: In this approach, the network nodes represent the database entities (drugs, targets, and side effects), while the edges represent direct or indirect relationships between two nodes. Networks are computationally derived from different sources of data & represent several interactions such as, interactions between drug and target, target and disease, and drug and disease.[1] In computational drug repurposing, network based approaches are the most commonly used method. It has the ability to integrate data from different data sources and analyse those data. This approach predicted the drug-target relationship by its ability to integrate and analyze various data sources.[13] Network-based analysis aso provides primary information of physical

association.[22] Network-based approach aims to organize the relationship between biomolecules in network form to find properties of biomolecules at network level and to find out how cellular systems under different conditions induce biological phenotypes.[6] To predict relationship between drug and target, network based method create a similarity network and after analyzing provide list of interaction between drug and target that can reveal drug target relationships. [3] Using freely available gene expression data of NCBI, Guanghui Hu & Pankaj Agarwal created a disease-similarity network and then integrated it with drugs and target information profile to predict opportunities of drug repurposing and suggest molecular target.[8,17] Sometimes researchers get confused, when making decisions for selecting an appropriate approach.

Name of approach	Method	Network	Key Findings	Description
RRW	Clusters	P&P interaction	complex proteins	This approach is used to find complex protein using P-P interaction network
RNSC	Clusters	P&P interaction	complex proteins	Algorithm to find protein using clusters on P-P interaction
ClusterONE	Clusters	P&P interaction	complex protein	This method outperformed the other approaches on P-P interaction network
	Clusters	Drug, target & disease	(Vismodegib and Basa1 cell carcinoma)= Gorlin	Algorithm is used to find out cluster on network
	Clusters	Drug, protein and disease	(Iloperidone and schizophrenia) = Hypertension	Cluster1 variant to node of clusters on non homogeneous networks
MBiRW	Clusters	Drug & disease	Alzheimer & Migraine	An algorithm based on random walk to find the relationship between drug & disease.
	Clusters	Drug, protein and chemical	Canertinib, Acute lymphoblastic leukemia) → SCLC	cluster based algorithm on non homogeneous networks.
	Propagations	Disease, protein and gene	Some disease-gene relationships	algorithm based on random walk with a diffusion to find relationship between drug and disease
	Propagations	Drug and target	Melanoma predicted	algorithm which integrates 4 approaches to find relationships between drug-disease.
DrugNet	Propagations Disease,drug & protein	Disease & gene	cancer & neuropathic pain	A propagation method to find out different strategies of propagation.
PRINCE	Propagations gene & disease	Disease,drug and protein	Relationship between disease and gene	A propagation algorithm to find relationship between gene and disease

Table: Summary of approaches along network information, key findings & description

There are two types of network-based approaches: network based clustering approaches and network based propagation approaches.

Network based clustering methods- have been proposed for the detection of new relationships between drugs and targets. This method aim to identify

relationships between drug & target, drug and disease, drug & drug using clustering algorithms based on network topology structure.[2]

Network-based cluster algorithms are able to predict accurate relationships between drug and disease in drug & disease networks and interactions between Protein and Protein in protein protein networks. These algorithms are most commonly used for predicting interesting interaction relationships between biomolecular entities. [2]

Network based propagation methods- In this type of network based approach propagation of information takes place from source node to all other network nodes.[9] Network propagation algorithms are sometimes also used to predict relationships between drug & targets, disease & genes and disease & drug. This approach gives accurate predictions and implementation of this approach is easy. This approaches take information from the specific components as well as from expanding components.[2]

RESOURCES

Pharmacological databases are one of the important resources of drug repurposing. These databases comprise data related to drug characteristics and data of interactions between drugs and other biomolecular entities. DrugBank is a unique data resource for drug repositioning. It contains detailed data of drugs as well as detailed information of drug targets. There are several in silico methods, In which network based method was created based on this database that provide accurate results. One of the another important type of data resource is Proteomics databases. This database is important for generating heterogeneous networks. For example: drug, protein and disease networks.[2]

DRUG-TARGET INTERACTION

Prediction of drug target interaction is the basis of drug repurposing process. Experimentally determination of drug target interaction relationship is time taking and expensive. Whereas, a computational method can give necessary information that is required for finding drug-target interaction relationship between drug and target in a specific time and at low cost.[10] There are several Computational approaches that are developed to resolve the problem of determining drug & target interaction.[19] According complex network theory, there are three supervised inference methods For determining interaction between target & drug 1.drug-based similarity inference 2.target-based similarity inference and 3.network-based inference. Out of these three methods, network-based inference performs best.[11] The in silico analysis of drugs–target interaction networks allows new applications to predict relationship between optimal treatments and patient as well as new clinical application of registered drugs. [15] Drugs and target interaction networks comprise pairwise relationships between targets, drugs, adverse events, other gene products and phenotypes. This is based on accumulation of various types of clinical and pharmacologically relevant data .[10] Drugs target network interaction analysis allow us to identify interaction relationship between the patients and specific treatments, and also to determine new clinical application of licensed drugs. [15] To discover the drug & target interactions, there are several computational methods. Researchers have developed several algorithms to resolve issue of drug–target interactions-related predictions such as literature text mining, docking simulations, machine learning, and network information among other. [7]

OPPORTUNITIES AND CHALLENGES

The 1st drug developed via drug repurposing process was an accidental discovery. After a long time of discovery, There are several approaches have been proposed to increase the process of drug repurposing. That's why drug repurposing approaches has more succeed.[16] Due to advancement of high-performance technologies, bioinformatic tools and availability of large amounts of biomedical & life science data. Drug Repurposing method can help in finding new therapies for diseases at low investment and in less time, specially in that case where preclinical study & safety tests has been completed. Since, Traditional methods of drug development are costly, time taking, high failure rate, and risky process. Therefore, drug repurposing approach was developed. which was also a challenging issue because of several factors such as technology, commercial model, investment and market demands. However, there are several database of medical that have been established, selecting the well approach to make full use of huge amounts of data is still a challenge. The most common

challenge in drug repurposing is to discover new drug-targets relationship.

CONCLUSION AND DISCUSSION

Drug repurposing approach reduces the cost and time investment by identifying new indications for registered drugs due to which drug development process has been accelerated. There are many advantages of drug repurposing approach such as extension of existing drug life, reduction of clinical trials time, & reduction of risk of failure due to which importance of this approach of drug development has been increased in last few years.[14] Computational approaches of drug development enable combined analysis of different types of data sources, such as genomic data source, biomedical data source & pharmacological data source that improves the efficiency of drug repurposing. Network based approaches have become most widely used approach for in silico drug repurposing due to Its ability to find interaction relationship between the components that perform certain functionalities. Networks based approach provide an interesting and non-complex structure for combined analysis of large amount of information sources and to represent the qualitative & quantitative interactions relationship between the molecules. There is also a demerit of Network-based approaches. These approaches probably do not make an expected contribution in the area of drug repurposing. Probably because, network-based approaches are based on prior knowledge, and for newly discovered organisms or disease (Covid-19) sufficient critical mass of knowledge is not available.

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