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Review Article

Drug Repurposing: An Overview

Mahendra Saini*, Nikhita Parihar, Shankar Lal Soni, Vandana Sharma

Arya College of Pharmacy, Kukas, Jaipur, Rajasthan – 302028, India

A B S T R A C T

Drug repurposing (also known as drug repositioning) means finding novel indications for currently marketed drugs. This strategy may reduce the costs of new drug development and advance the delivery of new therapeutics to patients with incurable diseases. By specifically regulating multiple targets, more effective drugs can be developed through polypharmacology. Drug repositioning is underpinned by the fact that common molecular pathways contribute to many different diseases. Various data-driven and experimental approaches have been suggested for the identification of repurposable drug candidates; however, there are also major technological and regulatory challenges that need to be addressed. In this Review, we present approaches used for drug repurposing, discuss the challenges faced by the repurposing community and recommend innovative ways by which these challenges could be addressed to help realize the full potential of drug repurposing.

Key Words: Drug repositioning, drug discovery, drug library, multiple targeting, cellular pathways.

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***Address for Correspondence:**

Mahendra Saini, Arya College of Pharmacy, Jaipur, Rajasthan, India

INTRODUCTION

Drug repurposing (also known as drug repositioning, drug reprofiling, indication expansion or indication shift) involves establishing new medical uses for already known drugs, including approved, discontinued, shelved and experimental drugs. Although this strategy is far from new, it has gained considerable momentum in the last decade: about one-third of the approvals in recent years correspond to drug repurposing, and repurposed drugs currently generate around 25% of the annual revenue for the pharmaceutical industry [1]

Drug repositioning refers to the identification of new indications from existing drugs and the application of the newly identified drugs to the treatment of diseases other than the drug's intended disease. A well-known example of drug repositioning is the use of sildenafil (Viagra) in erectile dysfunctions. Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) and was originally developed for the treatment of coronary artery disease by Pfizer in 1980s. The side effect of sildenafil, marked induction of penile erections, was serendipitously found during the Phase I clinical trials for the patients with hypertension and angina pectoris [2]. After sildenafil failed in Phase II clinical trials for the treatment of angina, it was redirected to the treatment of erectile dysfunctions.

Sildenafil received a US-Food and Drug Administration (FDA) approval and entered the US market in 1998, quickly becoming a blockbuster. Another well-known example of drug repositioning is thalidomide. Thalidomide was originally developed as a sedative by the German pharmaceutical company Grünenthal in 1957. It had been used to alleviate morning sickness in pregnant women. Not long after the drug was introduced, it was found to cause serious birth defects. More than 10,000 children in 46 countries were born with malformation of the limbs and other body extremities due to the use of thalidomide, and around half of them died within a few months after birth [3], leading to its withdrawal from the market. In the ensuing

decades, several research groups found that thalidomide possesses anticancer activity. It was found to inhibit angiogenesis in animal models by Robert D'Amato and Judah Folkman [4] and was subsequently shown to have promising therapeutic effect on refractory multiple myeloma and metastatic prostate cancer [5, 6]. In 2006, thalidomide received US-FDA approval for the treatment of multiple myeloma in combination with dexamethasone.

2. Drug repurposing challenges

2.1. Intellectual property and economic considerations

There are some legal aspects that could impair patenting a new medical use and/or the enforcement of patent rights, thus diminishing the incentives for drug repurposing. First, some national legislations impede obtaining a patent for second or further medical uses (although, it is possible to protect a repurposed medical use in most of the major pharmaceutical markets). Second, many potential repurposing uses have already been reported in the specialized literature or are already being exploited in the clinical practice as off-label, non-registered uses [7]. Even if such uses have still not been endorsed by controlled clinical trials, the information is already in the public domain and affects novelty and, consequently, patentability.

For drugs that are off-patent, a patent for the new indication can be obtained but enforceability could become an issue if the new indication makes use of already available strengths and dosage forms. Therefore, whereas using the same strengths than were marketed for the original indication might be useful to exploit some of the advantages of drug repurposing, an ideal situation would be than the new indication required non-marketed strengths (preferably, lower than the previously available ones) or that it required a unique, new formulation [7,8]. Newer derivatives are not a valid option here, since changing the drug molecule implies stepping away from the repurposing strategy.

Regarding exclusivity, the European Union usually provides 8 years of data protection plus 2 years of market exclusivity; if a second indication is developed by the originator during the 8-year data exclusivity period, an additional year of protection may be granted; on their part, the United States grants an initial period of 5 years which might be expanded by 3 years for a new use [9]. Nevertheless, such extra periods might not constitute an appropriate time to make an acceptable return of investment, with additional economic incentives being required to make drug repurposing cost-effective.

2.2. Data and compound availability

Whereas the open-source model is progressively gaining ground within the drug discovery community [10], public access to certain types of (valuable) data (e.g. clinical trials) is still limited. Even if accessibility was not an issue, some types of data are less friendly to data mining, integration and manipulation (e.g. imaging data) or are sometimes offered in a non-standardized manner [7]. Integrating different types of data has also proven computationally demanding as it increases the power of analysis [11].

Despite a shelved drug could be regarded as an idle capital or a missed or postposed opportunity, some pharmaceutical companies are less inclined than others to release their chemical libraries (e.g. failed drugs) to branch the possible applications of their compound collections (or could prove extremely selective at choosing partners), which could pose a fundamental barrier to drug repurposing prospects if a potential repurposed indication falls outside the organization's core disease area.

Even when a big company is willing to engage in crowdsourcing/collaborative efforts with smaller players (e.g. boutique firms or academic groups) it is imperative to facilitate and make more flexible the inherent administrative procedures, especially at the level of material transfer agreement signatories and compound distribution.

Compound availability with generic active pharmaceutical ingredients might occasionally also present some issues, especially if the compound is gone from the international market. Finding a reliable vendor in such circumstances might prove challenging.

2.3. Can the repurposing space be exhausted?

Despite the universe of diseases requiring improved therapeutic solutions (or, plainly, therapeutic solutions) is undoubtedly large, it may be argued that systematic drug repurposing campaigns may rapidly exhaust the drug repurposing prospects for a given disease (after all, the number of repurposing candidates is limited and it expands rather slowly year after year).

For example, several high-throughput screens directed to the identification of trypanocidal repurposed drugs with possible applications as treatments for Chagas disease have been reported throughout the years (see, for example, refs [12–15]), and this without taking into consideration previous low-throughput screens [16,17] and in silico screens or wet screens focused on specific drug targets and comprising experimental validation of the hits (see, for instance, refs [18,19]). A valid question that emerges is how many more repurposed-oriented phenotypic screens focused on *Trypanosoma cruzi* would be justified. By the same token, we could ask if enthusiasm in drug repurposing would decay gradually as successive systematic screens on collections of known drugs are executed.

An immediate answer would be that the strategy could be redirected to unexplored target disorders. The possibilities of drug repurposing may be amplified if instead of potential repurposed monotherapies, drug combinations are examined, a strategy that is already bearing fruit in the field of infectious diseases, as exemplified by the approval of nifurtimox–eflornithine combination therapy for second-stage African trypanosomiasis [20]. Precision and system medicine, each in its own way, also offers a whole new

prospect to expand the scope of drug repurposing, as discussed in the next sections.

At last, target-oriented screens may hold additional value. Once an approved drug has proven its activity on an unsuspected target, the whole set of compounds from a pharmaceutical firm that share the same active scaffold could be explored (typically, hundreds of such compounds are generated and used to build structure–activity relationships during hit-to-lead and lead-optimization programs; the lead compound for one therapeutic goal might not necessarily be the same for another condition).

Multiple Targeting:-

Drug-target interaction prediction in drug repositioning

A precise identification of drug–target interactions allows users to compare different binding behaviours and therefore brings to the generation of novel rational repositioning hypotheses. Experimental identification of binding interactions can be challenging and expensive, therefore computational techniques for drug-target interaction prediction has gained a lot of attention. Computational approaches have been generally classified into ligand-based approaches, target-based approaches and machine learning-based methods[14]. With ligand-based approaches the binding is predicted by comparing the candidate ligand with compounds with known activity on the putative protein target. The performance of ligand-based approaches, such as QSAR and pharmacophore modeling, is related to the number of active ligands available for the protein target [15]. Target-based approaches, such as docking and binding-site similarity, are powerful tools for the identification of protein-ligand interactions based on the 3D structures of the target. Their limitations are related to the scarce availability of target structures, such in the case of GPCRs.[15,16]. Machine learning approaches predict novel drug-target pairs by using similarities among both compounds and targets. Those approaches are generally classified in feature vector-based machine learning and similarity-based machine learning. Similarity-based machine learning methods can be further grouped into three categories: kernel-based approaches, matrix factorization-based approaches and network-based approaches[17]. Compared with time consuming docking and information-demanding QSAR, machine learning methods can be faster and more efficient [18]. However, many limitations are related to the commonly used databases which contain only true-positive interactions and ignore many important aspects of the drug–target interactions, such as their dose-dependence and quantitative affinities.[19].

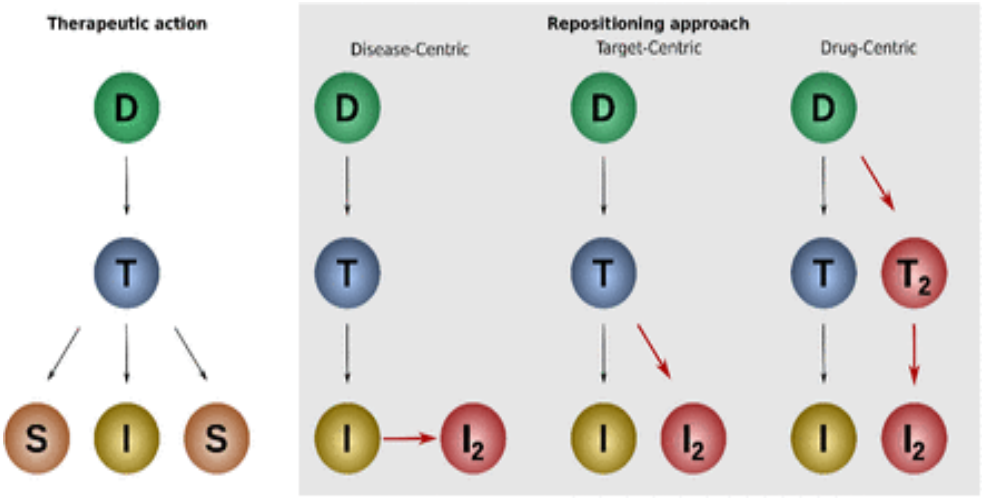
Structure based drug repositioning for new drug-target interactions

Several drug-centric approaches use structural information of the target active site or the complex drug-binding site to infer novel connections between drugs and targets. Many studies showed a correlation between drug-promiscuity and shared binding sites across the drug's multiple targets, demonstrating the potential role of structural analyses of shared binding sites in drug repositioning [20]. Structure-based techniques, such as molecular docking, have been often applied on successful repositioning pipelines to predict new therapeutic candidates. For example, a docking-based approach was used to find novel targets for existing drugs by computationally screening the whole druggable proteome. As a result nilotinib was validated as potent inhibitor of MAPK14, adding potential to his role as antinflammatory drug[21]. A similar strategy was used to repurpose drugs against multi-drug resistant (MDR) and extensively drug resistent (XDR) tuberculosis. As a results, the anti-Parkinson drugs entacapone and tolcapone have been predicted to treat MDR and XDR tuberculosis since the structural and interaction similarity between the original target COMT and the new target InhA[22]. Docking scores have also been fused with other structural information with data integration techniques. For example, the method TMFS combined docking scores, ligand and receptor topology descriptor scores, and ligand-target interaction points, to predict potential new drug-target interactions and provide structural insight about their mechanism of action. In this way two novel drug-target interactions have been predicted and validated: mebendazole-VEGFR2 and celecoxib-CDH11[23]. Also several structure-based non-docking approaches found an extensive application in drug-repositioning in order to overcome the problem related with inefficiency and inaccuracy of docking. For example using information about the active-like state of the serotonin receptor 5-HT2C in complex with ergotamine and the inactive-like state of the same receptor in complex with ritanserin, was possible to suggest the extension of ergotamine pharmacological profile to the delta-opioid receptor[24]. Another non-docking structure-based approach used interactions patterns comparison to identify novel repositioning candidates against the cancer target Hsp27. Analysing the interaction patterns of the Hsp 27 inhibitor brivudine was possible to indicate the approved anti malaria drug amodiquine as a promising anti-cancer agent[25]. Notwithstanding a rich history of successful cases, structure based drug repositioning suffers the limitation due to the scarce availability of structural information, concerning in particular certain classes of drug targets, such as GPCRs.

Pros and cons of disease-, target-, and drug-centric repositioning

At first glance, disease-centric repositioning may appear faster and more direct than target- and drug-centric repositioning. In fact, a disease-centric repositioning hypothesis it's based on a close connection drug-indication which might also avoid the deep knowledge about physicochemial interactions between drug and target. However, if this were the case, one cancer drug would cure all forms of cancer. Disease-centric approaches require a detailed understanding of the disease phenotype and underlying molecular processes to pursue the novel indication. Also, disease-centric approaches are hindered or supported (depending on the point of view) by patents. The drug under consideration and the old indication will be backed by patent claims, which tend to be broader than the old indication. Hence, the commercial exploration of a

disease-centric repositioning needs to be closely coordinated with the relevant patent claims possibly limiting opportunities. Disease-centric approaches are suitable for systematic exploration. E.g. comprehensive, computational comparisons of phenotypes and drug side effects[26,27] or comparisons of gene expression profiles [28] define numeric similarities of diseases, which may drive a disease-centric approach.



Different concepts behind drug repositioning.

Relations among drug (D), targets (T) and siseases/indications(I) according to the different drug repositioning concepts. In disease-centric a drug's application can be expanded from the original to a closely related indication, in target-centric the identification of a new indication is linked to a well established target and in drug-centric a new target is identified linking the drug to a new indication.

In target-centric repositioning, we consider only drugs, for which old and new indication are of different type. Hence, it becomes less likely, that the new indication is already covered by patents of the drug. However, a novel link from target to new indication is a rare finding. And hence, these approaches are limited by the technology to uncover novel target-disease associations. Besides screening methods such as deep sequencing, micro-arrays, RNAi, which can give hints on candidate targets, the target-centric approach needs a deep molecular understanding of the relation of target and disease. The drug-centric pipelines are therefore the most indirect one, as the drug is only linked to the new indication via the discovery of a novel target, which is already established for the indication. Since each repositioning approach shows several pros and cons we performed a retrospective analysis to understand their distribution among the real successful drug-repositioning cases and the role of drug-target interaction prediction on indication switch of known drugs.

Drug repurposing opportunities

3.1. Rare and neglected conditions

Drug repurposing is a particularly attractive approach for rare and neglected conditions, where the economics for developing a drug are unfavorable, explaining why academics and non-for-profit organizations have a predominant role in the drug discovery process for those diseases, and why specific regulatory measures and public policies encourage research into these types of disorders. Such measures include tax waiving, fast-track approval, grants and regulatory fee waivers [7]. Noteworthy, a considerable fraction of the Drug for Neglected Diseases initiative (DNDi)'s portfolio undergoing clinical trials corresponds to repurposed drugs, including fexinidazole, fosravuconazole, Ambisome™, and miltefosine. In fact, fexinidazole is the first oral-only drug, with the potential for treating advanced-stage sleeping sickness, approved in 30 years [33], and DNDi spent only USD 62.5 million in its development, in contrast with the estimated 1 to 3 billion dollars for a *de novo* drug. Interestingly, some of the commercial barriers to drug repurposing (concerns regarding off-patent drugs) are not as important when addressing neglected conditions, since investigations of therapeutic solutions for such disorders are not driven by profit expectancies. What is more, repurposing a low-cost, off-patent drug might even be desired to assure accessibility.

In the case of rare diseases, whose pathophysiology is often poorly characterized, computational techniques for predictive repurposing offer a quick way of identifying testable hypotheses that may be translated into the clinic, with large-scale genome-sequencing initiatives contributing to identify the genetic variation/s responsible for the disorder, and opening up opportunities to rapidly repurpose drugs that target the correspondent protein/s [7].

3.2. Precision medicine

Precision medicine is an emerging approach that considers individual variability in genes, environment, and lifestyle for each person to decide on or pursue an appropriate treatment [34]. It is increasingly clear that some disorders with common traits that in the past were characterized as a single condition actually comprise a spectrum of diseases and that more effective and/or safe medications could be found if

tailored to variations in an individual's genome, transcriptome, proteome, and metabolome, or to specific types of a general condition.

The positive outcome of such approaches is already being realized in the field of oncology. For instance, a recent case report on a patient with metastatic colorectal cancer, treatment-related toxicity, and resistance to chemotherapy and radiation [35] seems particularly relevant in relation to drug repurposing. The patient underwent immunohistochemical analysis for expression of the MMR proteins MSH2, MSH6, PMS2, and MLH1 and the V600E mutant BRAF protein. Whole-genome sequencing was carried out on the pretreatment tumor and blood, and whole-genome sequencing and whole transcriptome sequencing were performed on the metastatic tumor. Whole-genome sequencing identified more than 2000 genomic alterations, including point mutations, insertions, deletions, and copy-number variations. Among the most differentially expressed genes identified through transcriptome analysis, there were the members of two proto-oncogene families, FOS and JUN. These data supported that blocking the renin–angiotensin system could provide therapeutic benefit, which led to the (hard) repurposing of the antihypertensive angiotensin II receptor antagonist irbesartan as an anticancer therapy, resulting in the patient experiencing a radical and persistent response.

3.3. Systems medicine

Systems medicine/network pharmacology offers an integrative perspective on previous (and seemingly colliding) paradigms in drug discovery: phenotypic-oriented and target-oriented, 'rational' drug discovery. Network and metabolic control analysis can be useful tools to design multi-target therapeutics or, alternatively, choose a synergistic drug combination. For instance, nifurtimox–eflornithine combination therapy has been included in World Health Organization's Model List of Essential Medicines to manage advanced stages of the Gambiense form of sleeping sickness. The combination is easier to administer, it has a shorter treatment duration than the eflornithine monotherapy, and it is potentially protective against the emergence of resistant parasites. Interestingly, both drugs in the exemplified combination are repurposed cases: eflornithine was initially developed for cancer treatment in the late 1970s, and nifurtimox was originally approved for the treatment of American trypanosomiasis.

Combination drug repurposing can expand the horizon of drug repurposing, which has so far mostly explored repurposing known drugs as monotherapies: naturally, the combinatory nature of polypharmacy turns the space of potential combination drug repurposing much more difficult to exhaust than that of single-drug therapies.

Furthermore, many newly identified active compounds have low potency, which limits their immediate clinical applications because the tolerated plasma drug concentrations are lower than the effective ones. Synergistic drug combinations are an alternative approach to increase the success rate of drug repositioning, as they may lower the required therapeutic doses in comparison with monotherapies .

3.4. Collaborative models

There is increasing realization that pharmaceutical companies and academics can contribute in a highly complementary manner to the discovery of novel repurposing prospects. Pharmaceutical companies have highly valuable (though often idle) chemical libraries of failed or shelved drug candidates, and they have a first-hand experience on translational research and clinical development. Furthermore, they can provide access to screening technologies that are difficult to acquire and maintain for most of academic institutions. Biotechnology companies and academics possess valuable knowledge on emerging areas of disease biology, which may lay the foundation for highly innovative medications. Non-negligible byproducts of such type of collaborations include human capacity development and exchange [10]. From an intellectual property perspective, some options that can be explored include patent pools, open licensing for drug development targeting neglected or rare diseases and allowing participation of academic institutions and staff into the patent ownership for new medical uses. New collaboration and business models are arising to bridge stakeholders, including new funding models that welcome venture capitals, public funding, and non-for-profit organizations. Such models might greatly impact in certain fields of medicine (e.g. rare disorders) where drug repurposing plays a prominent role.

Applications-

Repurposing Drugs in Oncology (ReDO)

Over 200 non-cancer drugs have shown some evidence of anticancer effects. Of these, 50% are supported by relevant human data and 16% are supported by data from at least one positive clinical trial. In response, the Anticancer Fund, together with Global Cures, launched the ReDO project which aims to:

- Identify the most promising drugs for further clinical investigation;
- Review drug-related data and bring it to the attention of clinical investigators;
- Document how these drugs can be combined with existing therapies or other repurposed drugs;
- Develop clinical trials to provide positive or negative evidence of efficacy;
- Suggest areas where further preclinical work is necessary.

In addition to building the database of over 200 repurposing candidates, the ReDO project has published peer-reviewed journal articles on drugs with significant evidence supporting repurposing. These drugs include diclofenac, propranolol, cimetidine, nitroglycerin, clarithromycin and mebendazole – all common, generic drugs with excellent safety records and a wide range of data sources showing potent anticancer effects.

Repurposing of Drugs: Innovative Revision of Cancer Treatment (ReDIReCT)

The driving force behind the ReDIReCT doctoral thesis, which aims to bridge the gap between clinical research and practice in cancer drug repurposing, is Ciska Verbaanderd, an ACF associate and PhD student at the University of Leuven. The end goal of this thesis is to facilitate the implementation of drug repurposing in standard practice through (1) policy recommendations supporting the use of drug repurposing as a valid anticancer treatment option, and (2) a guidance tool for containing regulatory requirements and incentives, intellectual property right strategies, potential finance models and reimbursement policies in the context of drug repurposing.

The untapped potential of non-cancer drugs

New cancer treatments are being developed by the pharma industry, but the process of bringing these drugs to the market is slow and expensive. A largely untapped, affordable and safe treatment approach is to reuse available licensed non-cancer drugs as new anticancer treatments. Drug repurposing has the potential to make clinically important contributions to oncology, and could offer important economic and societal benefits for more sustainable healthcare systems in the long term.

Our trials in this focus area

ASPIRIN

Aspirin for recurrence and survival in colon cancer
Trial phase: 3
Cancer types: Digestive cancer
Status: Recruiting

Nitroglycerine MAASTRO

Repurposing angina pectoris medication as lung cancer treatment
Trial phase: 2
Cancer types: Lung cancer
Status: Completed

PROSPER

Perioperative use of a β-blocker and an anti-inflammatory drug in pancreatic cancer
Trial phase: 2
Cancer types: Digestive cancer
Status: Recruiting

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