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Drug repurposing

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Abstract
Drug repurposing is the process of finding new therapeutic applications for previously used, available or older medications. Drug repurposing, refers to a set of approaches that aim to adapt the current pharmacological effects to new applications. Repurposing can help uncover new medicines for diseases at a low cost and in less time. Availability of prior knowledge regarding safety, efficacy and the appropriate route of administration significantly reduces the development costs and cuts down the development time resulting in less effort required for successfully bringing a repositioned drug to market. There are three approaches for drug repurposing i.e. disease-centric, target-centric and drug-centric. Knowledge-based drug repurposing utilizes the drug-target related information, including drug-targets network, chemical structures of drug and targets, pathways, adverse effects etc. The approach is called as target repositioning if the new indication is treated by acting with the same target protein as previously determined. Approximately 80% of drug repositioning projects have occurred based on this target based approach. In repurposed drug's the preclinical, pharmacokinetic, Pharmacodynamic and toxicity information are previously known thus minimising the risk of compound creation. Drug repositioning involves multiple factors such as technology, commercial models, patents, investments and market demands. Considering the associated advantage of drug development through repurposing approach it is expected to gain popularity in near future.

Keywords: Drug repurposing, drug re-tasking, drug repositioning, drug re-profiling, drug redirection

Introduction
Drug repurposing is also referred to as drug repositioning, drug re-tasking, drug reprofiling, drug rescuing, drug recycling, drug redirection and therapeutic switching (Lotfi Shahreza *et al*., 2018) [27]. Drug repurposing is the process of finding new therapeutic applications for previously used, available, or older medications. It is a successful method for locating or creating medicinal compounds with novel pharmacological or therapeutic applications (Ng *et al*., 2021) [35]. Drug repurposing, in general, refers to a set of approaches that aim to adapt the current pharmacological effects to new applications. It maximises and increases the therapeutic value of a drug, which consequently increases the success rate. Thus, drug repositioning is an effective alternative approach to the traditional drug discovery process (O'Connor *et al*., 2005) [37].

It can play an important role in the "clinical screening approach" for patients with rare, complex, or chronic diseases that have few or no approved therapy possibilities (Dotolo *et al*., 2021) [14]. Repurposing can help uncover new medicines for diseases at a low cost and in less time, especially when preclinical safety studies have already been performed (De Oliveira *et al*., 2018) [12].

Modern pharmaceutical research faces significant hurdles, including declining drug development productivity and a persisting gap between therapeutic requirements and available treatments. The number of pharmaceuticals approved per dollar spent on R & D is decreasing, with current studies predicting that it takes 15 years and more than $1 billion to bring a new treatment to market. This is partly due to high failure rate; only 10% of drugs that reach phase II clinical trials are subsequently approved, with the majority of failures due to safety concerns or poor efficacy (Hodos *et al*., 2016) [18].

Drug development involves a deep understanding of the mechanisms of action and potential side effects of each drug, and can result in the discovery of new and unexpected uses for drugs, a process known as drug repurposing (Tanoli *et al*., 2021) [51]. Drug repurposing has many drawbacks and challenges, but it also has many benefits, including assisting in overcoming the wastage that is now occurring in the field of innovative drug research (Jourdan *et al*., 2020) [21].

Need for drug repurposing

Drug repurposing has the potential to address unmet medical needs such as neglected diseases, as well as rare and orphan diseases (Bellera *et al*., 2015) [6]. It also has the potential to provide more effective, less expensive alternative treatments as well as drugs with a favourable side effect profile in diseases where the present drugs have a negative side effect profile (Liu *et al*., 2013) [26]. Availability of prior knowledge regarding safety, efficacy and the appropriate administration route significantly reduces the development costs and cuts down the development time resulting in less effort required for successfully bringing a repositioned drug to market (Padhy *et al*., 2011) [38]. Furthermore, the pharmaceutical business is facing revenue losses due to patent expiration as well as competition from generics and off-label prescribing. From an industrial perspective, drug repurposing is said to be less dangerous and more likely to succeed (Ayyar *et al.*, 2022) [4].

Traditional drug discovery vs drug repurposing

The traditional drug development process consists of five stages: development and preclinical study, safety review, clinical trials, federal agency review, and post-market safety monitoring. Drug repositioning, on the other hand, has only four stages: compound identification, compound acquisition, compound development and post-market safety monitoring (Rudrapal *et al.*, 2020) [45].

The major goal of traditional discovery program is to discover medications to treat chronic and complex diseases, whereas the drug repositioning method prioritises drug development for fast emerging and re-emerging infectious, difficult-to-treat, and neglected diseases (NTDs) (Mani *et al*., 2019) [29].

Another important difference between drug discovery and repurposing is the fate of the hits. A compelling hit in a repurposing screen is a drug molecule that is a candidate for further development. This is separate from an HTS (High Throughput Screening) hit in drug discovery that serves as the beginning point for a newly discovered medicinal chemistry programme, which is subsequently continuously evolved. Finally, for drug discovery screens, an efficient assay must be simple and rapid in order to handle the number of possible compounds for review, whereas for repurposing screens, the limited scale allows for a greater range of assay complexity (Cha *et al*., 2018) [10].

Repurposing approaches

Drug repositioning can be approached in three ways: disease-centric, target-centric, and drug-centric. Disease-centric strategies find relationships between an old and new indication. A target-centric strategy connects an existing target and its drug to a new indication. Finally, a drug-centric strategy links a well-known drug to a new target and its underlying application (Parisi *et al*., 2020) [40].

Discovering new indications for an existing drug (drug-centric) and identifying effective treatments for a disease (disease-centric), with the common technique of drug and/or illness similarity assessment. Drug repurposing might be target-based, pathway-based or target mechanism-based (Park, 2019) [41].

The methods for systematic repurposing can be roughly categorised into experimental screening procedures and *in silico* approaches.

(A) Experimental screening approaches

The experiment-based approach, also identified as activity-based repositioning, corresponds to the screening of existing drugs for novel therapeutic indications using experimental assays. It entails protein target-based and cell/organism-based screens in in vitro and/or in vivo disease models, with no requirement for target protein structural information. Several approaches of experimental repositioning are target screening approach, cell assay approach, animal model approach and clinical approach (Lionta *et al*., 2014) [25].

Target screening approach

Target-based drug repurposing begins with high-throughput and/or high-content screening (HTS/HCS) of drug compounds, followed by in silico screening of drug compounds from drug libraries, such as ligand-based screening or docking (Swamidass., 2011) [48]. In comparison to blinded search or screening, which does not employ biological or pharmacological data when screening, target-based repurposing directly links targets with disease pathways, significantly improve the probability of drug discovery. The target-based technique has the benefit of being able to screen practically all drug molecules with known chemical structures. Target-based approaches, on the other hand, cannot identify unknown mechanisms beyond the identified targets (Park., 2019) [41].

Animal model approach

The sequencing of the human genome and that of many animal models, the rapid development of high-throughput phenotyping and genotyping technologies and our ability to create specific mutations in the genomes of model organisms have provided us with a vast amount of information that supports the discovery of meaningful associations between the genotype and phenotype of an organism. This information, in turn, extends our ability to comprehensively characterize the phenotypic manifestations of diseases and generate hypotheses on which the intelligent design of drugs can be built (Morgan *et al*., 2010) [34].

The better we understand an organism's pathophysiology and underlying *in vivo* biology, the more likely we are to benefit from the development of new technologies that enable drug discovery. Animal models, as a result, provide a potent mechanism for drug discovery since they specify the physiological circumstances and intricate interdependencies across different cell types and tissues in which chemical interactions with drug targets may be explored. Animal models such as the mouse, zebrafish, fruit fly, yeast, and worm have been used to provide an in-depth understanding of the biological mechanisms that govern the effect of drug administration, based on the premise of evolutionarily conserved pathogenetic pathways. These advantages place animal models in a prominent position in the drug discovery process (Amberger *et al*., 2011) [3].

Clinical approach

Positive clinical studies are uncommon because the majority of drugs fail during Phase II/III trials. However, many drugs that have already been launched produce distinct results during post-marketing surveillance. Some may exhibit various side effects, while others may treat certain types of disease with no defined indication (Xue *et al.*, 2018) [55]. With the

help of these studies, many drugs have been repurposed. Some examples include apomorphine, which was originally prescribed for Parkinson's disease but was later repurposed for erectile dysfunction; drospirenone, which was originally prescribed as an oral contraceptive but was later repurposed for hypertension, and dapoxetine, which was originally prescribed for analgesia and depression but was later repurposed for hypertension. These are only a few instances of therapeutically repurposed medications; there are many more that have been repurposed with several new indications (Pushpakom *et al*., 2019) [43].

(B) *In silico* repurposing approaches

Using computational biology and bioinformatics/cheminformatics techniques, *in silico* repositioning performs virtual screening of public databases of massive drug/chemical libraries (Talevi. 2018) [50]. Computational techniques are generally data-driven; they require systematic study of any type of data (for example, gene expression, chemical structure, genotyping or proteomic data, or electronic health records), which can then lead to the creation of repurposing hypotheses (Hurle *et al*., 2013) [19].

In silico approaches can be broadly divided into two categories: (I) molecular approaches and (ii) RWD approaches

Molecular approaches: molecular approaches, which are based on understanding of drug activity and disease pathophysiology and are frequently powered by large scale molecular data (i.e.,'omic data') such as genomic, transcriptomic or proteomic data as well as data on drug targets and chemical structure (Cha *et al*., 2018) [10]. Transcriptional data for therapeutic repurposing, which involves finding drugs with opposing transcriptional profiles that target a disease (Khataniar *et al*.,2022) [22].

RWD (‘real world data) approaches: RWD approaches focus on identification of unknown and sometimes unexpected, relationships between drugs and diseases or their symbiosis (Cha *et al*., 2018) [10].

The term 'real world data' (RWD) in the healthcare area refers to data obtained from sources other than traditional clinical trials, such as electronic health records (EHRs), claims and billing data, and registries, among others. RWD includes specific patient information like as disease state, treatment, treatment outcomes, and comorbidities, which are recorded continuously. RWD data provides valuable real-world evidence (RWE) for patient care, safety surveillance, treatment development, outcomes-research, and comparative effectiveness studies (Sherman *et al*.,2016) [47].

Classification of drug repurposing

Knowledge-based repurposing

This repurposing strategy, utilizes the drug-target related information, including drug-targets network, chemical structures of drug and targets, pathways, adverse effects etc. and models are built to predict unknown targets, bio-markers or mechanisms for diseases (Emig *et al*., 2013)[16]. Knowledge-based techniques use available data about a medicine to predict previously unknown processes, such as the availability of previously undiscovered drug targets for older pharmaceutical, unknown drug-drug correlations, and novel biomarkers. Knowledge-based techniques include bioinformatics, cheminformatics, and text analytics. Knowledge-based techniques for drug repurposing enhance prediction confidence by combining a huge amount of data. The most promising repurposing conclusion stems from a combination of biological, chemical, and diagnostic characteristics, which can establish the framework for introducing a powerful target for an already-approved treatment, as well as a detailed understanding of its mechanism of action (Behera *et al*., 2021) [5].

Targets based drug repurposing

The study of a drug candidate with an isolated biological target (i.e., protein, receptor) to identify a biological response is known as target-based screening (Al-Ali *et al*., 2016) [1]. This method determines new indications by linking a drug to a specific disease based on its protein targets. As previously stated, a new indication for a specific medicine might be decided based on the primary target as well as off-target proteins (Masoudi-Sobhanzadeh *et al*.,2020) [30]. If the new indication is treated by interacting with the same target protein as previously determined, the approach is known as target repositioning (Parvathaneni *et al*., 2019) [42]. Approximately 80% of drug repositioning projects have occurred based on this approach. Off-target repositioning occurs when an approved medicine interacts with a secondary target and can treat a new indication (Sekhon.,2013) [46].

Signature-based

To find unknown off-targets or illness processes, employ gene signatures produced from disease omics data (genomic data) with or without treatments. Databases containing genomic data are freely accessible to the public. The benefit of these approaches is that they can be used to investigate previously unknown pharmacological mechanisms of action. Signature-based methods, as opposed to knowledge-based methods, use computational methodologies to examine pharmacological processes at a molecular level, such as changes in gene expression (Dey *et al*., 2019) [12].

Repurposing in rare diseases

Approximately 7000 rare diseases (RDs) have been detected to date. While they are individually uncommon, they affect 300 million people (or 10% of the world's population) with new diseases being described in medical literature on a regular basis (Dawkins *et al*., 2018) [11].

These disorders are frequently poorly described patho-physiologically and there is a lack of understanding of the molecular mechanisms involved in illness progression. Orphan pharmaceuticals are medications used to treat rare diseases. The majority of RD are life-threatening and require immediate treatment (Botella, 2020) [7]. In response to the concerns about the economics of creating a drug for a rare condition, the first of its kind, the Orphan Medication Act (ODA, 1983), was established, because R&D expenses can only be amortised over a long period of time (Pushpakom *et al*., 2019) [43].

When compared to the creation of original orphan medications, the process of repurposing drugs for new indications is a time-saving and cost-effective strategy that result in greater success rates, which can thus dramatically lower the risk of drug development for rare diseases. Although drug repurposing is not new, new ways for doing so in a systematic and sensible manner have emerged in recent

years (Roessler *et al*., 2021) [44]. A noteworthy example is the use of Sildenafil in the treatment of pulmonary arterial hypertension, a rare disease. The medication is a PDE 5(phosphodiesterase 5) inhibitor with a tiny molecule. It was initially approved to treat angina. Because of its favourable impact on vascular biology, it was approved for erectile dysfunction in 1998. The FDA then authorised it for pulmonary arterial hypertension in 2005 (Butler., 2020) [9].

Another example where a drug was repurposed for a rare disease involves Muckle-Wells syndrome (MWS), an autoinflammatory disorder caused by increased interleukin-1 (IL-1) in the body. Canakinumab (Ilaris), a drug originally approved to treat rheumatoid arthritis, is a human IgG1 anti-IL-1 monoclonal antibody that provides selective and sustained blockage of IL-1, neutralising the effect of excess IL-1. Various clinical trials have demonstrated that canakinumab results in long-term disease management and quick remission of related symptoms in MWS patients. In 2009, the FDA and the European Commission approved it for the treatment of MWS patients (Roessler *et al*., 2021) [44].

Significance of drug repurposing

A new medicine must follow severe standards in order to access the market. Identifying and developing a medicine takes enormous investment, owing to the various physicochemical features of the chemical entities and the challenge of scaling up manufacturing. Investigational compounds that fail to demonstrate efficacy for a predetermined indication usually give an excellent starting point for their repurposing (Parvathaneni *et al.,* 2019) [42].

There is a list of successfully repurposed medications, such as aspirin, which had an initial indication of inflammation and pain but now has a new indication of "coagulation and stroke" (Mehndiratta *et al.,* 2016) [32]. Metformin appears to offer weight-stabilizing, Reno protective, neuroprotective, cardioprotective, and antineoplastic properties, as well as the ability to alleviate polycystic ovarian syndrome. Metformin's anti-inflammatory and antioxidant properties appear to qualify it as an adjuvant therapy in the treatment of infectious disorders such as TB, viral hepatitis, and the recently discovered Covid-19 infections (Mbara *et al.,* 2021) [31].

Minoxidil was introduced to the market as a hypotensive agent, however practically all patients had hypertrichosis after using it. This negative effect stimulates the repositioning or repurposing of minoxidil as a topical therapy for hair loss (Al-taie *et al.,* 2022) [2].

Table 1: Examples of Drug Repurposing

Drug	Original indication	New indication	
Allopurinol	Cancer	Gout	(Park, 2019) [41].
Aspirin	Inflammation, Pain	Antiplatelet	
Bromocriptine	Parkinson's disease	Diabetes mellitus	
Bupropion	Depression	Smoking cessation	
Duloxetine	Depression	Stress urinary incontinence	
Finasteride	Benign prostatic hyperplasia	Hair loss	
Gabapentin	Epilepsy	Neuropathic pain	
Gemcitabine	Antiviral	Cancer	
Methotrexate	Cancer	Rheumatoid arthritis	
Propranolol	Hypertension	Migraine headache	
Raloxifene	Osteoporosis	Breast cancer	
Sildenafil	Angina	Erectile dysfunction	
Thalidomide	Sedation, Morning sickness	Leprosy, Multiple myeloma	
Zidovudine	Cancer	AIDS	
Lidocaine	Local anaesthetic	Arrhythmia	
Fingolimod	Transplant rejection	Multiple sclerosis	
Ketoconazole	Fungal infections	Cushing syndrome	
Cyclosporine	Immunosuppressant	Fungal infections	(Bhagat *et al*., 2021) [7].
Itraconazole	Antifungal	Anticancer	
Nelfinavir	Antiviral	Anticancer	
Nitroxoline	Antibiotic	Anticancer	

Tamoxifen (a breast cancer treatment) has been shown to have anti-leishmanial activity, eflornithine (a topical hirsutism treatment) has been shown to be effective for sleeping sickness, and auranofin (a rheumatoid arthritis treatment) has been shown to be effective against lymphatic filariasis and Onchocerca volvulus-induced river blindness. (Klug *et al*., 2016) [24].

Challenges in drug repurposing

Drug repositioning is a complex process involving multiple factors such as technology, commercial models, patents, investment and market demands (Kiriiri *et al.,* 2020) [23].

Although drug repurposing has gained popularity recently, there are fewer applications than anticipated due to several difficulties in proper implementation. Because there are no hard and fast regulatory criteria for repurposing medication candidates, upcoming start-ups face a difficult problem in providing appropriate information to regulatory agencies (Pahud *et al*., 2014) [39].

One of the most significant problems confronting drug repurposing efforts is most likely related to commercial, regulatory or intellectual property issues (non-technical challenges) (Talevi, 2018) [50]. A number of legal and intellectual property barriers exist in the way of drug repurposing (Waring *et al*., 2015) [54]. The difficulties connected with patenting a new repurposed indication and enforcing patent rights are key barriers to motivating medicine repurposing (Talevi *et al.,* 2020) [49], since they have a significant impact on the potential profit expected from the repurposed product (Drucker., 2020) [15].

Advantages of drug repurposing

According to Eroom's Law, the number of new medications approved per billion USD drops dramatically after the year 2000, showing increased spending on research and development with significantly fewer new molecular entities approved per year. Furthermore, numerous pharmaceutical corporations reported up to $20 billion in yearly sales for the repositioning of failed medications in 2012 (Low *et al.*, 2020) [28].

Drug repositioning results in significant reductions in development time and expense, as well as increased revenue and decreased risk (Henriksen *et al.*, 2011) [17]. The drug's preclinical, pharmacokinetic, Pharmacodynamic and toxicity profiles are previously known, minimising the risk of compound creation. As a result, the chemical can move quickly through Phase II and III clinical trials, resulting in a shortened development time (Vanhaelen *et al*., 2017) [53]. Furthermore, demand in therapeutic fields is growing, and traditional drug research cannot keep up with these increased demands. (Mohammad *et al*., 2021) [33].

Limitations of drug repurposing

Although great progress has been achieved in drug repurposing in recent years, regulatory approval is the only aim for a successfully repurposed drug. Many difficulties to achieving this goal can be considered, from the development phase to regulatory approval. Some of the difficulties associated with drug repurposing, like lack of funding to commercialise the product, lack of collaboration between academia and industry, clinical trial feasibility for rare diseases, technical challenges to repurposing drugs, lack of clinical compound repositories, requirement for robust evidence, conducting PoC (Proof of Concept) experiments etc.

Drugs that have been repurposed for reasons other than novel indications, such as new dosage, new formulation or new patient group, must go through clinical studies to demonstrate safety and efficacy, which is similar to the *de novo* drug discovery process (Ayyar *et al.*, 2022) [4].

Aside from that, a lack of participation and a lack of prominent repositioning projects, particularly from large renowned pharmaceutical companies, contribute to a Significant challenge in drug repositioning. This situation is due to a lack of belief in potential projects, the possibility of failure, and a significant time and financial investment in these projects. Surprisingly, companies other than the primary inventor initiated the role of drug repositioning (Janku *et al*., 2010) [20]. Thalidomide, for example, was brought back to life by the company Celgene to treat Multiple Myeloma Nodosum Leprosum and Erythema with the isolation of pregnant women, but not by the inventor company Grünenthal (Low *et al*., 2020) [28].

Conclusion

Drug repurposing is a field of drug research that has grown its importance in recent years due to several advantages, including shortening the clinical trials, extending the life of an old drug by discovering a new therapeutic target, and discovering relationships between seemingly distant diseases. Drug repurposing has gaining popularity among pharmaceutical industry and the public sector/academic community as a faster and less expensive strategy for widening the approved drugs. Economically, the repurposing strategy appeals, especially when weighed against the enormous costs and time involved in new drug discovery. As pharmaceutical companies are becoming avers to new and significant investments in new drug development, the future of drug repurposing is bright.

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