Drug repurposing: a promising tool to accelerate the drug discovery process

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Traditional drug discovery and development involves several stages for the discovery of a new drug and to obtain marketing approval. It is necessary to discover new strategies for reducing the drug discovery time frame. Today, drug repurposing has gained importance in identifying new therapeutic uses for already-available drugs. Typically, repurposing can be achieved serendipitously (unintentional fortunate observations) or through systematic approaches. Numerous strategies to discover new indications for FDA-approved drugs are discussed in this article. Drug repurposing has therefore become a productive approach for drug discovery because it provides a novel way to explore old drugs for new use but encounters several challenges. Some examples of different approaches are reviewed here.

Introduction

The process for a new drug to be approved is expensive and can take 10–15 years [1]. This long discovery process opens the doors for drug repurposing (repositioning) as an alternative approach for cutting down the time required to develop a drug. Repurposing of a drug includes use of drugs approved by regulatory agencies such as the FDA, the European Medicines Agency (EMA), the Medicines and Healthcare Products Regulatory Agency (MHRA), among others, for a new indication. Owing to immense promise of a shortened development cycle, many pharmaceutical companies are currently adopting drug repurposing to redevelop some of their FDA-approved and previously unsuccessful pipeline molecules as novel therapies for diverse disease conditions. The present review gives an overview of approaches currently being used for repurposing and discusses case studies illustrating the power and utility of drug repurposing observed by the substantial decrease in time needed to develop a drug because of availability of all relevant clinical and toxicological data [2]. Different approaches for repurposing and the associated challenges are discussed in this article.

Significance of drug repurposing

For a new drug to enter the market, it needs to abide by stringent regulations. To identify a drug and develop it further requires significant investment, primarily as a result of diverse physicochemical properties of the chemical entities and complexity of scaling up the production [3–5]. This limitation further empowers pharmaceutical companies or academic centers to quickly and efficiently utilize already-approved medications for a new indication, not yet available to the patients with that disease. Investigational molecules that fail to show efficacy for a predetermined indication typically provide a good start for their revival by repurposing. They can be further rediscovered for a new indication(s), ultimately being developed as viable therapies, particularly useful in cases of rare diseases, which present significant challenges in diagnosis, treatment and lack of resources [6–8]. For instance, some autoimmune disorders, bacterial infections and rare cancers are not inherited, thus making it more difficult to treat because they are idiopathic in nature [9]. Drug repurposing, being a less expensive and shorter approach, brings effective therapies to patients compared with cumbersome traditional discovery and development processes. Moreover, this approach helps overcome the inflating costs for drug development, thus lowering out-of-pocket cost for patients, and ultimately reducing the actual cost of therapy [10].

For a new investigational molecule, safety and efficacy data are not yet available, resulting in higher attrition during the drug discovery process leading to the most failures regarding safety or efficacy [11,12]. By contrast, all safety, preclinical and efficacy data

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are readily available for a repurposed molecule, thus enabling the investigator to make an informed decision at each stage of drug development [11,12]. 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 [13].

For example, sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor represents one of the successful repurposing efforts. Sildenafil was originally developed for hypertension treatment but was later identified to have significant benefits in erectile dysfunction and was approved by the FDA for the same. It was later repurposed for treatment of a rare disorder: pulmonary hypertension [14]. With the advent of new technologies as well as availability of computational tools, drug discovery is a much more affordable approach when starting with an already-approved drug [15]. This approach has accounted for ~30% of all newly approved drugs by the FDA in recent years [10]. Drug repositioning offers a great deal of potential for out-licensing as well, because these drugs possess characteristics attractive to potential buyers [16]. Although attractive, it is also important that identification of a new disease target should not cripple the marketing potential of the drug for its original indication [17]. A major area of interest for drug repurposing could be rare disorders, representing a significantly unmet medical need owing to nonavailability of standard therapies and worsening clinical outcomes [18]. Fig. 1 summarizes key differences and benefits of drug repurposing approaches compared with traditional drug discovery approaches.

Challenges for drug repurposing

Although drug repurposing has been gaining attraction lately, there are fewer applications than expected owing to various challenges in proper implementation. Because there are no hard and fast regulatory guidelines for repurposing drug candidates, it is an uphill task for upcoming start-ups to provide relevant information to regulatory bodies. In addition, exclusivity provided by patents and the Orphan Drug Act can be nominally applicable to use a repurposed drug for a new use [19]. However, such exclusivities might not prevent a physician from off-label use of the drug. There are a few drugs like thalidomide and rapamycin that have received additional exclusivity through an abrupt regulatory change allowing patients to access needed therapies at low cost. However, owing to the lack of a clear exclusivity path, it is still a big hurdle in utilizing repurposed drugs [19].

Generally, a repurposing candidate carries a potential time risk, especially if it has failed for a previously intended indication. In this scenario, it is advisable to design a branched development program, in which the lead compound or drug is evaluated for several indications simultaneously. This approach reduces the time risk and possibility of imminent expiration of intellectual property, which would otherwise require reinvestment of significant resources for re-profiling the same molecule [20]. Drug repurposing requires thorough comprehension of biological and molecular pathways that a drug can modulate as well

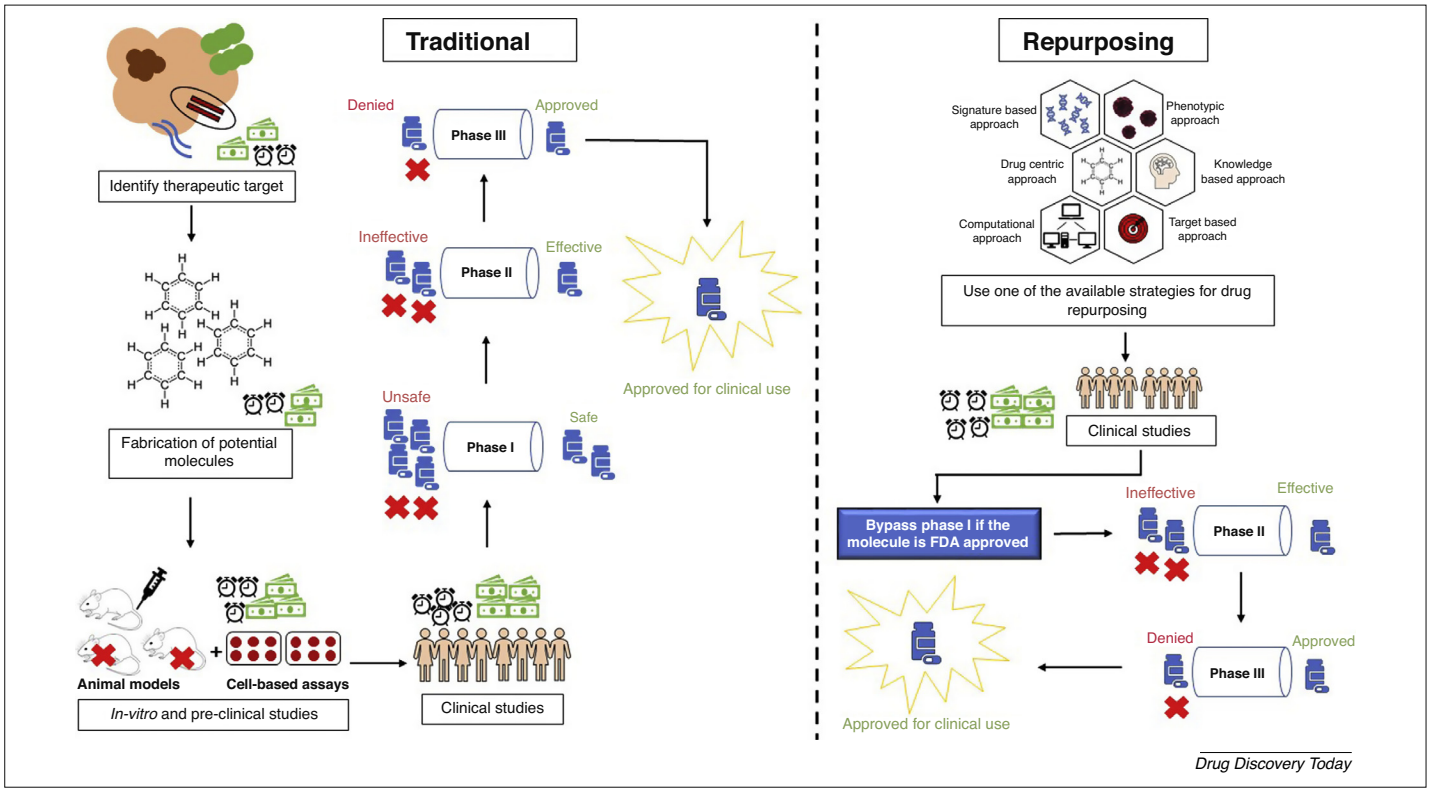

FIGURE 1

A comparison of traditional drug discovery process versus drug repurposing. The traditional drug discovery process is time consuming and involves a large financial burden on the innovators. By repurposing a drug, precious years can be cut down from a typical drug discovery cycle. Repurposing abolishes all the steps needed for FDA approval. Also, once the drug is FDA approved, Phase I of clinical trials can be eliminated, which saves a lot of time, effort and money involved in the studies. A short path can be followed to innovate a new system for clinical use using drug repurposing strategies.

as its interactions with endogenous biomolecules. With comprehensive knowledge of the drug and its impacted pathways, this hypothesis risk can be significantly diminished, resulting in successful repurposing of a drug [21].

Pharmaceutical companies pay significant attention to cost-effective and profitable discovery areas. However, when repurposing a drug for rare and neglected diseases, there is no assurance that the economic returns will be substantial (https://repurposingdrugs101.com). Therefore, it is more feasible for an industry to concentrate on a specialized and more established research directive. Additionally, lack of financial incentive and research funding is another challenge confronted by pharmaceutical companies. For example, there are few incentives available for pharmaceutical companies to invest in research on medications with no assurance of return on investment, as in the cases of rare cancers like pediatric cancers (https://www.anticancerfund.org). This challenge hinders the typical drug discovery process owing to investment-hesitance on the part of pharmaceutical companies and drug developers [22].

There are other potential barriers to cross while conducting clinical trials with a repurposed candidate. Proof-of-concept and preclinical studies might not work to establish scientifically validated efficacy; and a significant monetary investment could be required to start the process from Phase I clinical trials [13]. There could also be concerns associated with limited patient enrollment for large clinical studies required for certain rare diseases owing to scarcity of patients. In addition, product safety must be established in the elderly, and other special patient populations with comorbidities [23]. If the intellectual property rights of a drug or dosage form have expired, identifying a new indication will typically result in minimal return on investment, and could also pose potential legal issues for the developer [24]. There might only be a very small window of opportunity for the developer to retrieve development costs, let alone make a return on investment before generic drugs come onto the market [23]. Based on all these challenges, drug repurposing requires creative strategies and a great deal of persistence on the part of pharmaceutical companies.

TABLE 1

Significance, challenges and approaches of drug repurposing

Significance and challenges of drug repurposing

No.	Significance	Refs	Challenge	Refs
1	Ensures safety	[16]	Lack of knowledge on regulatory requirements	[18]
2	Saves time and money	[13]	Lack of financial motivations	[18]
3	Marketing potential: higher global revenue stream; stimulate market growth	[10,16]	Problems in clinical trials: chance of failure of proof of studies for new indication	[13,23]
4	Out licensing probability: toward a new indication retaining the rights for original indication	[16,17]	Intellectual property related issues hinder the commercialization of repositioned molecule	[13]
5	Address unmet medical needs: identifying the new uses for old drugs to treat rare diseases and to target cancers with non-cancer drugs	[18,69]	Demands market analysis	[20,25]

Brief summary for repurposing approaches

No.	Repurposing approach	Challenges	Significance	Examples
1	Phenotypic *in vitro* assays *In-vivo*-based phenotypic screens	Hit validation and target deconvolution; possible lead compounds with poor pharmacokinetics might not be active in the primary screens [70]	Ability of multiple independent screens to identify similar classes of compound and the potential to advance repurposing hits rapidly into clinical development effectively highlight the potential of repurposing screens; furnish efficacy details	Pimozide and tamoxifen are prescribed to treat psychiatric disorders and breast cancer, respectively. Found to have the ability to kill Toxoplasma through novel pathways [71]
2	Target-based method	Poor productivity	Suboptimal profiles can be rescued and low-affinity hits can be pursued; confirm cellular target engagement and modulation of desired phenotypic biology [70]	L-type calcium channel blockers to treat cryptococcosis [72]
3	Pathway- or network-based methods	Incorporate the cellular context and genetic background into the disease networks to enable more stratified and selective target predictions, as well as how to make the prediction models more realistic for the practical drug discovery and therapeutic applications	Suggest completely unexpected and novel investigational probes for drug development	Potential repositioning of GV1001 as a therapeutic agent for testosteroneinduced benign prostatic hyperplasia [73]
4	Signature-based approaches	Provide data for primary analysis only, further analysis is required	Reveal unknown mechanisms of action of molecules and drugs	New drug candidates for treatment of atypical meningioma [74]

These hurdles can discourage development of a drug for a new indication [25]. The challenges encountered by drug repurposing are summarized in Table 1.

Repurposing approaches

Novel indications for a drug candidate can be identified serendipitously or can be hypothesis-driven through rational approaches. Hypothesis-driven strategies for drug repurposing can include experimental and computational strategies that have enormous potential to establish a better understanding of mechanisms and pathways involved in disease pathogenesis [13,26,27]. Table 1 summarizes significance and challenges to be encountered in the case of several repurposing approaches.

Experimental repurposing approaches include binding assays and phenotypic screening methods that can be used to identify binding interactions of ligands to assay components and to identify lead compounds from large compound libraries, respectively [26,28]. Computational approaches are typically categorized into target-based, knowledge-based, signature-based, pathway- or network-based, and target-mechanism-based approaches. These approaches are proven to be cost-effective and of imminent value in discovering novel therapeutic agents. Most notably, computational methods augment the drug discovery process by effectively utilizing cheminformatics, bioinformatics, network biology and systems biology. More specifically, these methods exploit known targets, drugs, disease biomarkers or pathways to establish novel methods and accelerate the planning of crucial clinical trials [29]. Major repurposing approaches are summarized in Fig. 2.

Experimental approaches

Binding assays

Techniques such as proteomics and mass spectrometry enable the identification of targets for various compounds. For instance, the cellular thermostability assay (CETSA) technique predicts thermal stabilization of target proteins through binding of compounds with highest cellular affinity. Recently, cellular targets for the tyrosine kinase inhibitor (TKI) crizotinib were confirmed [30]; and quinone reductase 2 was detected as an off-target of acetaminophen at the cellular level [31].

Phenotypic approaches

Phenotypic drug-screening methods often discover drug candidates accidentally [29]. New drugs can be identified based on changes in *in-vitro–in-vivo* models or even clinical observations [32]. For instance, it can involve screening a compound library against cell lines to measure cellular response; and finding the compounds that alter the phenotype followed by identification of disease state and mechanism of action [33]. Evaluation of a series of compounds in an array of independent models with the aim of identifying efficacy in one or more of the tested models illustrates the vital prerequisites needed for efficient drug repurposing [34].

In vitro phenotypic screening necessitates consideration of known drugs or drug-like molecules originally in disease-relevant phenotypic assays, to identify and confirm candidates for repositioning [35]. Phenotypic assays are characterized as those representing disease biology in cells or tissues acquired from an experimental species or humans. Robotic screening platforms and highly sensitive detection systems are used to rapidly screen large chemical libraries. Identification of novel functions for approved drugs can save time and resources in drug discovery and development, while reducing the risk of failure in early clinical trials. Using *in vitro* assays to identify repositioning activity, direct knowledge can be gained in relation to a potential new disease setting. Moreover, multiple compounds with distinct mechanisms of action can also be tested to obtain a therapeutic effect over a complete concentration range [35].

Liu *et al.* described new advances in investigation of *in silico* methods for projecting polypharmacology of known drugs and new molecules by means of structure-based methods like molecular docking, binding-site structural resemblance, receptor-based pharmacophore searching and other approaches that have demonstrated a favorable future in facilitating drug repositioning [36]. Recent studies have also pointed toward the utility of induced pluripotent stem cell technology to generate patient-derived cells for high-throughput *in vitro* screening of existing drugs for effects on patient-specific cellular phenotypes [37].

Genome editing technologies such as the CRISPR/Cas-9 system, combined with small animal preclinical studies, have been used to model human diseases and to execute *in vivo* screening of old drugs

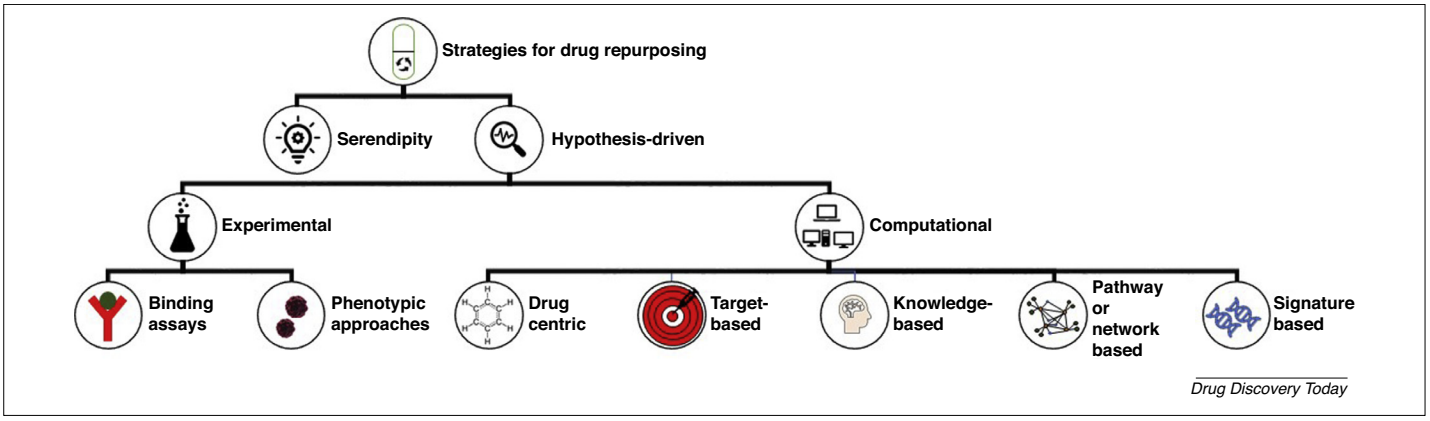

FIGURE 2

A schematic representation of strategies that can be used for repurposing a drug. These strategies can be classified based on whether it is a drug-centric approach, which involves replacement of an existing drug with unwanted effects, or a disease-centric approach, which aims at improving the prognosis of rare, neglected or otherwise difficult-to-treat diseases.

for disease-related phenotypic effects [37]. *In vivo* phenotypic screening systems focus more on high-quality drug candidates or compounds rather than evaluating compound libraries. These models can estimate efficacy as well as general tolerability and safety [38].

Jacquemet *et al.* utilized phenotypic screening to identify FDA-approved calcium channel blockers as potent inhibitors of filopodia formation in cancer cells. They observed the importance of L-type calcium channels in regulating calcium entry and filopodia stabilization by treating cancer cells expressing MYO10-GEP with a library of compounds. From this screen, they identified that L-type calcium channel blockers such as amlodipine besylate, felodipine, manidipine dichloride and cilnidipine were able to inhibit filopodia formation and block cancer cell invasion [39]. Zilbermintz *et al.* also reported an approach for exploring host-oriented therapies by screening an FDA-approved drug library against detrimental effects of multiple pathogens. They found that the effect of amodiaquine, an antimalarial drug, in killing anthrax and Ebola toxins is efficient at protecting host cells against multiple infections [40].

Computational approaches

Drug-centric approaches

Drug-centric repurposing approaches revolve around predicting new indications for previously approved drug molecules. Most of the molecules involved in this approach follow a common theme of potentially interacting with multiple targets (i.e., polypharmacological agents). Although polypharmacological agents are known to produce unwanted side effects, their actions can be exploited because they present potentially new indications for a particular drug [41]. Discovery of a drug for a new indication can be determined through the study of the drug–receptor interactions of its 'off-target' hits.

When searching for a new target for a previously known drug, assessing drug–target binding and interaction is helpful in discovering other structurally similar compounds that might possess binding ability for the same target. Polypharmacological approaches examine how a single drug acts on multiple targets of a unique disease pathway or on multiple targets related to multiple disease pathogenesis. The polypharmacological approach also helps in revealing the unknown off-targets for existing drugs. However, this approach needs to combine all the data derived from methods such as computational modeling, *in-vitro–in-vivo* pharmacological testing and clinical studies [41]. In 2018, Issa *et al.* reported efficiency of a computational method called RepurposeVS in predicting drug–protein target interactions. They quantified the repurposing potential scores, which were found to be higher for antineoplastic drugs [42].

Target-based approaches

Target-based screening is the study of a drug candidate with an isolated biological target (i.e., protein, receptor) to distinguish a biological response [43]. In this approach, new indications are determined by linking a drug to a specific disease based on its protein targets. As discussed earlier, a new indication for a particular drug can be determined based on the primary target and also off-target proteins [44]. If the new indication is treated by interacting with the same target protein as previously determined, the approach is known as target repositioning. Approximately 80% of drug repositioning projects have occurred based on this approach [45]. When the approved drug interacts with a secondary target and can treat a new indication, this kind of approach is known as off-target repositioning [46,47]. In 2014, Galvin *et al.* identified *N*-myristoyltransferase as a new candidate to target filarial nematodes using a targeted repurposing approach [48].

Knowledge-based methods

Although effective, blinded (unintentional, fortuitous discoveries) and target-based approaches are not usable to explore new drug–target interactions. Knowledge-based approaches consolidate known information about a drug to anticipate previously unexplored mechanisms including presence of unidentified drug targets for old drugs, undiscovered drug–drug similarities and new biomarkers. By integrating a considerable amount of information into drug repurposing, knowledge-based methods upgrade the prediction certainty [29]. A combination of biological, chemical and clinical knowledge enables the most encouraging repurposing outcome and can pave the way toward determining a new target for an already-approved drug along with deep vision into its mechanism of action. Recently, Hafeez *et al.* reported ormeloxifene as a suppressor of prostate cancer through knowledge-based studies [49]. As discussed further, knowledge-based approaches can be broken down into three categories: bioinformatics, cheminformatics and text analytics [50].

The importance of bioinformatics and data mining in repurposing is discussed. Traditional drug discovery processes make it challenging to identify multiple uses of a single drug. Conversely, this can be accomplished by drug repurposing through in-depth scientific analysis and/or simple serendipity. Given this perception and availability of large datasets, it is important that methods are in place for investigators to adequately make use of such data. More specifically, utilizing proper experimental design and addition of different biological, chemical and clinical datasets can result in identifying novel and unexplored relationships or targets for a certain drug. These conclusions can result in profound understanding in disease biology, target or compound selection, as well as drug toxicity [50].

In biological data mining (bioinformatics), a drug discovery corporation can either access data achieved internally or obtain publicly sourced information; and implement data mining approaches to discover new inter-relationships and potentially new intellectual property in a particular field of interest. An organization that identifies their inherent biological data for repurposing studies will often investigate against multiple disease states. By contrast, generalist organizations do not focus their endeavors toward a specific disease; instead, they constitute a panel of disease-relevant models, and then screen compounds to be repurposed universally. Specialists lean on their ability and specialization within a particular disease area to screen large numbers of compounds against a targeted set of diseases [50]. There are several different types of protein interaction databases available for data mining, including the Biomolecular Interaction Network Database (BIND), Database of Interacting Proteins (DIP), Search Tool for Interactions of Chemicals (STITCH), The Human Protein Reference Database (HPRD), Search Tool for the Retrieval of Interacting Genes/Proteins (STRING), Kyoto Encyclopedia of Genes and Genomes (KEGG) and Protein–Protein Interaction Predictions (PIPS). These databases were developed by the Proteomic Standard Initiative (PSI) and Human Proteome Organization

(HUPO) [51]. Bioinformatics-based approaches have also successfully been used to discover new relationships between biomedical entities such as genes, biological pathways and diseases in a drug repurposing approach [52]. Using transcriptional data for drug repurposing is another pathway where compounds consisting of opposite transcriptional signatures toward a disease are identified. Despite the underwhelming performance of this method, newer transcription-based methods such as CuGuCtD are providing further understanding and ability to identify whether a compound has the potential to upregulate the genes in the same way as compounds already treating that particular disease [53].

Jahchan *et al.* utilized a bioinformatics-based approach to repurpose FDA-approved tricyclic antidepressants to treat patients with small-cell lung cancer (SCLC). Specifically, they utilized computational methods to compile a list of candidate drugs with predicted efficacy against SCLC. A systematic drug repurposing bioinformatics approach was then employed to explore FDA-approved drugs for SCLC treatment. They also determined that tricyclic antidepressants are potent inducers of cell death in SCLC cells and other neuroendocrine tumors [54].

In chemical data mining (cheminformatics), a demand for drug repurposing can also come after achieving successful Phase I clinical trial outcomes, and subsequent recruitment of an appropriate patient population for Phase II/III trials. Determination of pertinent biomarkers provides validation of a desired mode of action hypothesis. If the drug is a validated hit to the target, a subsequent failure could be due to lack of understanding the target protein's role in pathogenesis and progression of the disease.

To comprehend how to effectively repurpose these safe drug entities to appropriate indications, two vital concepts are required for comprehensive scrutiny. First, any given small-molecule drug candidate can interact with numerous proteins. Second, complex diseases are frequently the result of sophisticated crucial intra- and inter-cellular molecular interactions, which are repeatedly standardized and ordered. Information about drug–protein interactions is frequently inadequate and much of the computational data assessment for repurposing comes from integration of distinct data sources. More specifically, this arises across the boundaries of traditional regulations of clinical medicine, chemistry, biology and toxicology [50].

Pathway- or network-based methods

Pathway- or network-based approaches exploit the disease omics data, which include: pathways through which the drug manifests its efficacy; and drug–target interactions. Therefore, from a large network of different pathways, one can identify a specific network consisting of a few specific targets. A recent study of drug repurposing directed definite signaling mechanisms of metastatic subtypes of breast cancer [55], which was not elucidated in earlier studies [29].

Kotelnikova *et al.* reported a new computational workflow for planning therapy. Two novel computational workflows were proposed to identify drugs effective in glioblastoma treatment. The first workflow consisted of studying different pathogenic pathways by obtaining data in scientific literature, whereas the second workflow analyzed gene expression data by utilizing a unique algorithm developed for Pathway Studio called sub-network enrichment analysis (SNEA). This approach resulted in the discovery of fulvestrant (Faslodex®), an FDA-approved drug for hormone-receptor-positive metastatic breast cancer, demonstrating inhibitory effects on several glioblastoma pathways [56].

In a study by Dönertaş *et al.*, systems-level drug repurposing methodology was used to discover new drugs to target aging. Multiple gene expression datasets from brain tissue of patients of different ages were used and gene expression changes associated with aging were compared to drug-perturbed expression profiles. They identified few drugs that can modulate the lifespan directly or function by improving cognitive outcomes and promoting healthy aging [57]. In another study, Ovalle *et al.* demonstrated the efficacy of verapamil, an antihypertensive calcium-channel blocker, in decreasing the expression of thioredoxin-interacting protein, thus promoting the survival of insulin-producing beta cells [58].

Yu *et al.* proposed an approach for predicting possible drug–disease interrelations that could handle drugs or diseases with or without related genes. This method then correlated a drug's side effects and disease symptoms to identify drug–module and disease–module sets [59]. Network-based drug discovery aims at utilizing the power of networks to shed light on mechanisms of action of existing or new molecules to recognize novel therapeutic treatments [60].

Signature-based approaches

Signature-based drug repurposing approaches rely on gene signatures derived from disease omics data with or without treatment to discover unexplored off-targets or unidentified disease mechanisms. As microarray and next-generation sequencing techniques advance, vast volumes of genomics data pertinent to drug repurposing studies are accumulated, which could be used to identify gene signatures for exploring unknown disease-altering pathways. NCBI-GEO (http://www.ncbi.nlm.nih.gov/geo/), SRA (Sequence Read Archive; http://www.ncbi.nlm.nih.gov/Traces/sra/), CMAP Connectivity Map and CCLE Cancer Cell Line Encyclopedia are a few of the available databases for obtaining genomics data. Because the efficacy of a drug depends on individual gene signatures, a gene signature database is helpful in the repurposing of a drug through computational methods [61]. Signature-based methods reveal unknown mechanisms of action of drug molecules by utilizing mechanistic data at the molecular level, such as an altered gene and subsequent protein expression using methods such as weighted gene co-expression network analysis (WGCNA) to CMap and Library of Integrated Network-Based Cellular Signatures (LINCS) [29]. Dönertaş *et al.* recently identified 24 drugs capable of modulating aging in the human brain through generating a genomics meta-analysis approach with CMap [57].

Other databases and potential tools for drug repurposing

Drug Repurposing Hub, Drug Target Profiler, RepurposeDB, Ligand Expo, ZINC and KEGG DRUG databases consolidate assorted information such as molecular pathways, binding experiments and drug targets. PubChem, one of the largest public databases, contains results from many screens and bioassays and is fundamental to drug repurposing approaches [62]. Off-target databases include ChEMBL and Drug Target Commons.

Recent case studies of repurposed drugs in clinical trials

Because many of the molecules chosen for repurposing are already approved, chances of failure are considerably reduced when identifying new indications. In addition to lowering the drug

TABLE 2

List of approved and under-studied repurposed drugs

No.	Drug name	Original indication	New indication	Mechanism of action	Status of study	Refs
1	Itraconazole	Antifungal	Prostate cancer	Reducing prostate-specific antigen (PSA) levels	Phase II	[75]
2	Metformin	Type II diabetes	Advanced prostate cancer	Inhibition of the mammalian target of rapamycin complex 1 (mTORC1) pathway	Phase II	[76,77]
3	Aspirin	Fever and pains	Melanoma	Stop the growth of tumor cells by blocking some of the enzymes needed for cell growth	Phase II	[78]
4	Sildenafil	Angina pectoris	Erectile dysfunction	Phosphodiesterase type 5 (PDE5) inhibition	Approved	[79]
5	Raloxifene	Osteoporosis	Breast cancer	Estrogen-antagonistic effects	Approved	[80,81]
6	Thalidomide	Morning sickness	Multiple myeloma	Antiangiogenic	Approved	[82]
7	Tamoxifen	Metastatic breast cancer	Bipolar disorder	Anti-estrogenic	Approved	[80]
8	Rapamycin	Prevents organ transplant rejection	Autoimmune lymphoproliferative syndrome (ALPS)	Immunosuppressant	Approved	[80]
9	Minoxidil	Antihypertensive	Hair regrowth	Stimulates follicle movement	Approved	[80]
10	Lomitapide	Hypercholesterolemia	Homozygous familial hypercholesterolemia	Inhibition of the microsomal triglyceride transfer protein (MTP)	Approved	[80]
11	Pentostatin	Chemotherapy for specific types of leukemia T-cell-related	B-cell-related, called hairy cell leukemia	Immunosuppressive action	Approved	[80]
12	Sodium nitrite	Antidote to cyanide poisoning	Chronic leg ulcers associated with sickle cell and other blood disorders	Vasodilation	Recruiting participants for clinical trial	[80]
13	Sodium nitrite	Antidote to cyanide poisoning	Out of hospital cardiac arrest (SNOCAT)	Vasodilation	II/III	[83]
14	MSDC-0160	Type 2 diabetes	Parkinson's disease	Reduced levels of inflammation and less nerve cell death	Phase II completed	[84,85]
15	Tamoxifen	Breast cancer	Antimicrobial activity	Enhance the antibacterial activity of white blood cells	Under clinical trials	[86]
16	Celebrex	Osteoarthritis	Reduce the risk of additional polyp formation in colon cancer	Inhibiting COX-2 receptors	Approved	
17	all-*trans* retinoic acid (ATRA)	Acne	Acute myeloid leukemia (AML) with chemotherapy	Induction of APL cell differentiation and apoptosis	Clinical trial data available	[87]
18	Pioglitazone	Diabetes	Acute myeloid leukemia (AML)	Regulate cell growth and death	Preclinical data	[87]
19	Minocycline	Acne and sexually transmitted infections	Fragile-X syndrome	Inhibition of matrix metalloproteinases (MMPs)	Under study	[88]
20	Dapsone	Leprosy	Malaria	Inhibit bacterial dihydropteroate synthase	Phase III completed	[89,90]
21	Amphotericin	Antifungal	Leishmaniasis	Disruption of parasite membrane	Phase III completed	[90,91]
22	Eflornithine	Cancer	African trypanosomiasis	Inhibition of ornithine decarboxylase (ODC)	Phase III completed	[90,92]
23	Auranofin	Rheumatoid arthritis	Amebiasis	Unknown	Clinical use	[90]
24	Digoxin	Congestive heart failure and arrhythmia	Cancer	Inhibition of Src activity	Phase I completed, recruiting subjects for Phase II	[93,94]
25	Itraconazole	Antifungal	Cancer	Angiogenesis inhibitor	Phase II active	[93,95]
26	Nitroxoline	Urinary-tract infections	Cancer	Angiogenesis inhibitor	Preclinical	[93,96]
27	Riluzole	Amyotrophic lateral sclerosis	Melanoma and other cancers	Downstream glutamatergic signaling	Phase II active	[93,97]
28	Fosmidomycin	Urinary-tract infections	Malaria	Selective toxicity	Phase II completed	[90,98]
29	Paromomycin	Antiamebic	Visceral leishmaniasis	Inhibition of translation	Phase IV completed	[90,99]
30	Fumagillin	Antiamebic	Cancer (angiogenesis inhibitor)	Angiogenesis inhibitor	Preclinical	[90,100]

development costs, repurposing provides an opportunity for rare disease therapy. Many studies have reported new indications for already-approved drugs using repurposing approaches. For example, amyloid-β plays a crucial part in pathogenesis of Alzheimer's disease. AstraZeneca's shelved cancer drug saracatinib, a dual kinase inhibitor, was recently found to target amyloid-β signaling in the brain and to rescue synapse loss in mice [63]. A Phase II trial of saracatinib for Alzheimer's patients is currently underway [64].

A recent study reported that acetazolamide, often used to treat altitude sickness, can also be used in combination with temozolomide (TMZ) to treat glioblastoma. Adding acetazolamide to TMZ therapy enabled mice with glioblastoma to survive longer. Therefore, it was suggested that repurposing acetazolamide along with TMZ as a combination therapy might be an effective treatment strategy in a subgroup of glioblastoma patients with tumors with BCL-3 overexpression [65].

Crvz-Muniz *et al.* recently published a study elucidating the antimicrobial properties of anticancer drug mitomycin-C (MMC). Owing to its general cytotoxic properties, they investigated its effect against bacterial infections, and concluded that MMC can be repurposed to treat persistent bacterial infections from *Acinetobacter baumannii* [66]. Gertis *et al.* examined the effects of the anticancer agent toremifene (Fareston®) against oral bacteria *Porphyromonas gingivalis* and *Streptococcus mutants*. Toremifene was found to be capable of inhibiting pathogen growth as well as preventing biofilm formation. Macromolecular synthesis assays indicated that toremifene did not act through DNA, RNA or protein synthesis pathways but was revealed to have membrane-damaging activity [67]. Costabile *et al.* showed that the anthelmintic drug niclosamide had antivirulence properties and demonstrated its potential therapeutic value against *Pseudomonas aeuruginosa* lung infections. They formulated inhalable nanosuspensions of niclosamide and tested for cytotoxicity. Experimental evidence provided a significant rationale for further development of niclosamide to treat *P. aeruginosa* infections in the lung through inhalable formulations [68]. There are various drugs that have already been repurposed and are approved or under clinical trials. Some of the examples are summarized in Table 2.

Concluding remarks

Drug repurposing has gained significant traction owing to its advantages such as cost effectiveness and shortened timeline for drug development. A systematic application of repurposing approaches improves its feasibility. For instance, retrieving information using phenotypic and computational methods such as the target-based approach will result in high-quality data with unsurpassed drug–target validation. Drug repurposing provides an opportunity to broaden our knowledge without limiting the existing information. Hence, drug repurposing can assist in commercial and scientific drug development in the pharmaceutical industry and for academic researchers. Drug repurposing is a promising field in drug discovery for identifying new uses for old drugs. However, there are existing barriers for application of drug repurposing today; but they can be overcome with advanced technologies.

Conflicts of interest

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drudis.2019.06.014.

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