

# Drug repositioning for orphan diseases

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Submitted: 12th December 2010; Received (in revised form): 18th February 2011

## Abstract

The need and opportunity to discover therapeutics for rare or orphan diseases are enormous. Due to limited prevalence and/or commercial potential, of the approximately 6000 orphan diseases (defined by the FDA Orphan Drug Act as <200 000 US prevalence), only a small fraction (5%) is of interest to the biopharmaceutical industry. The fact that drug development is complicated, time-consuming and expensive with extremely low success rates only adds to the low rate of therapeutics available for orphan diseases. An alternative and efficient strategy to boost the discovery of orphan disease therapeutics is to find connections between an existing drug product and orphan disease. Drug Repositioning or Drug Repurposing—finding a new indication for a drug—is one way to maximize the potential of a drug. The advantages of this approach are manifold, but rational drug repositioning for orphan diseases is not trivial and poses several formidable challenges—pharmacologically and computationally. Most of the repositioned drugs currently in the market are the result of serendipity. One reason the connection between drug candidates and their potential new applications are not identified in an earlier or more systematic fashion is that the underlying mechanism ‘connecting’ them is either very intricate and unknown or indirect or dispersed and buried in an ever-increasing sea of information, much of which is emerging only recently and therefore is not well organized. In this study, we will review some of these issues and the current methodologies adopted or proposed to overcome them and translate chemical and biological discoveries into safe and effective orphan disease therapeutics.

**Keywords:** orphan disease; rare disease; orphan drug; drug repositioning; drug repurposing

## INTRODUCTION

With more than 6000 rare or orphan diseases (ODs) and fewer than 325 of them amenable to treatment, the need and opportunity to discover therapeutics for ODs are enormous. By definition ODs have <200 000 US prevalence. The fact that drug development in general is complicated, time-consuming and expensive with extremely low success rates only makes the situation grimmer. One response to this

productivity gap is ‘Drug Repositioning’ or ‘Drug Repurposing’, namely, the identification and development of new uses for existing or abandoned pharmacotherapies [1]. Since the starting point in drug repositioning is usually approved compounds with known bioavailability and safety profiles, proven formulation and manufacturing routes, and well-characterized pharmacology, this approach can significantly reduce the risks associated with drug

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development and potentially facilitate repositioned drugs to enter clinical phases more rapidly and at a lower cost than novel compounds [2]. It is, therefore, not surprising that of the 51 new medicines that reached their first markets in 2009, repositioned drugs accounted for 30% [3].

Following the FDA Orphan Drug Act (ODA) in 1983, which provided several incentives for pharmaceutical companies manufacturing drugs for rare diseases, there has been a dramatic rise in the new treatment options for rare diseases with approximately 325 drugs now available in the market to treat rare diseases. However, these drugs cover only about 5% of known ODs. Bypassing the traditional drug discovery process, which typically takes as long as 10–12 years, by discovering OD indications for already approved compounds could be a viable strategy to jump-start the orphan drug discovery process. Thus, the premise of finding OD therapeutics at a faster pace is the single best rationale for resorting to drug repositioning for ODs. The recent release of a 235-drug database of approved compounds and products that show promise in ODs by the FDA rationalizes and further strengthens the need for a systematized analysis of approved drugs, both common and orphan, for novel OD indications.

Drug repositioning conceptually is backed by two core scientific principles. The first one is based on the ‘promiscuous’ nature of the drug, i.e. a single drug often interacts with multiple targets or pathways. Growing scientific evidence [1] indeed suggests that any compound found to be safe in humans is likely to have multiple therapeutic uses and most of the repositioned drugs show little explicit connections to their original approved indications. Compounds with significant off-target effects are usually labeled ‘dirty’ because of the adverse events they trigger. However, the undesirable adverse event of a drug in one indication may sometimes prove to be desirable in another indication. Repositioning efforts based upon a compound’s potentially ‘desirable promiscuity’ follow what can be categorized as the ‘known compound–new target’ approach. Two recent reviews [4, 5] discuss the importance of the concept of polypharmacology in the integration of systems biology and drug discovery and how navigating protein–ligand polypharmacology will be a critical component of pharmaceutical research and discovery. The second principle is that targets relevant to a particular disease or pathway or process can

also play critical roles in other biological processes, pathways or phenotypes [6]. Although the links between a target and a disease, and between a target and the compound are often established, those between the compound and the disease are not clear or unavailable or ‘hidden’ in the databases and literature.

So how exactly are the new indications discovered? Ideas for repositioning can be serendipitous (e.g. sildenafil) or based on informed insights (e.g. duloxetine) [7] or can come from systematic analytical platforms established to identify repositioning candidates [e.g. Zalicus’s (formerly CombinatoRx) cHTS or combination high throughput screening system [8]] [1]. While there are clearly several advantages, rational drug repositioning poses formidable challenges, more so in the case of ODs. The molecular basis and the underlying mechanism of OD and drug actions are either unknown, intricate or dispersed and buried in an ever-increasing sea of information and much of which is emerging only recently and therefore is not well-organized. In the following sections, we will review some of these issues and the current methodologies adopted or proposed to overcome them and translate pharmacological and biomedical discoveries into safe and effective OD therapeutics.

## Orphan or rare diseases

In general, an orphan or rare disease is any disease that affects a small percentage of the population. Most of the known rare diseases are genetic, and therefore, are present throughout the entire life of an affected individual. Many appear early in life and about 30% of children with rare diseases die before the age of 5 years. There is no single cut-off number that has been universally agreed upon for which a disease is classified as rare. For instance, in the United States, the Rare Disease Act of 2002 defines a rare disease as any disease or condition that affects less than 200 000 persons in the United States, while in Japan a rare disease is defined as one that affects fewer than 50 000 patients. The European Commission on Public Health, on the other hand, defines rare diseases as those which are life-threatening or chronically debilitating and are of such low prevalence (1 in 2000 people) that special combined efforts are needed to address them. Additionally, a disease considered rare in one part of the world, or in a particular group of people, could be a common disease in

**Table 1:** List of resources relevant to ODs and drugs

| Resource name                           | Description and URL  |
|---|--|
| NIH rare diseases (GARD)                | Genetic and Rare Diseases; <a href="http://rarediseases.info.nih.gov/GARD/">http://rarediseases.info.nih.gov/GARD/</a>   |
| List of the American ODs                | <a href="http://rarediseases.info.nih.gov/RareDiseaseList.aspx">http://rarediseases.info.nih.gov/RareDiseaseList.aspx</a>  |
| Orphanet                                | Portal for rare diseases and orphan drugs; <a href="http://www.orpha.net">http://www.orpha.net</a>   |
| EURODIS                                 | European organization for rare diseases; <a href="http://www.eurordis.org">http://www.eurordis.org</a>   |
| NORD                                    | National Organization for Rare Disorders; <a href="http://www.rarediseases.org">http://www.rarediseases.org</a>  |
| OOPD at FDA                             | Office of Orphan Product Development; <a href="http://www.fda.gov/orphan">http://www.fda.gov/orphan</a>  |
| Orphan drugs at FDA                     | Orphan drug designations and approvals; <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>                    |
| RDRD from FDA                           | Rare Disease Repurposing Database; <a href="http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/">http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/</a> |
| List of marketed orphan drugs in Europe | <a href="http://www.fda.gov/orphan/designat/Approvals.htm">http://www.fda.gov/orphan/designat/Approvals.htm</a>  |
| List of orphan drugs in Australia       | <a href="http://www.tga.gov.au/docs/html/orphand2.htm">http://www.tga.gov.au/docs/html/orphand2.htm</a>  |
| RAMEDIS                                 | Rare Metabolic Disease Database; <a href="http://www.ramedis.de">http://www.ramedis.de</a>   |

another. The incidence of an individual rare disease may be small. However, cumulatively, the 6000 known rare diseases affect about 25 million Americans, or nearly 10% of the US population [9]. Since the definitions of rare diseases refer to treatment availability, resource scarcity and disease severity, rare diseases are now commonly referred to as ODs, especially after the orphan drug movement that began in the United States in 1983. Thus, the United States' Orphan Drug Act (1983) includes both rare diseases and any non-rare diseases for which there is no reasonable expectation that the cost of developing and making available a drug for such a disease in the United States can potentially be recovered from sales of that drug in the United States. About 6000 rare or ODs have been identified, and a list is maintained by the Office of Rare Diseases (ORD) at the National Institutes of Health (NIH). While some of the listed ODs are well-known (e.g. cystic fibrosis, Huntington's disease), a majority are less familiar with several ODs having patient populations of fewer than a hundred. Approximately 250 new ODs and conditions are described each year [10]. The ODA went into effect to encourage the development and marketing of drugs (orphan drugs) to treat ODs and conditions. The ODA evolved in response to the small number of orphan drugs that were approved in the US in the years prior to the approval of the ODA [11]. Unfortunately, the drug development process for ODs is the same as that for any other disease—very expensive and time consuming. Table 1 lists some of the resources related to ODs and drugs.

## Drug repositioning strategies

Drug repositioning is not a new idea. What is new is the ability to do it in a systematized and rational way instead of relying on serendipity. With the value of drug repositioning becoming increasingly evident, a number of companies have developed approaches to make it a systematic exercise. Although unique proprietary approaches and technologies could be applied, drug companies focusing on repositioning tend to deploy one or more of the following possible strategies [12].

### Strategy 1: knowledge-based drug repositioning

This strategy exploits the accumulating pharmacological, genomic, biomedical and chemical data generated by the drug industry and academia. By integrating this information and mining using novel analytical algorithms and approaches, virtual screening is performed to discover unrecognized or non-explicit connections between a drug, target, and disease. Since this approach relies upon interactions that have been previously identified and reported, there is potentially less risk associated with hypotheses derived from it. The focus and resources can therefore be directed toward verifying and optimizing the new 'connections'. Because the information used in this approach is available freely (exceptions are in-house generated proprietary information), anyone with the requisite expertise and tools can make new drug–target and/or drug–disease connections [12]. Knowledge-based drug repositioning [13, 14] also exploits known interactions

between a drug and a target and combine this information with new knowledge about the target's role in a new indication. Iorio *et al.* [15] recently reported an automatic and robust approach based on similarity in gene expression profiles following drug treatment across multiple cell lines and dosages to predict similarities in drug effect and mechanism of action. Using their Mode of Action by Network Analysis (MANTRA) method and leveraging the Connectivity Map assays, the authors discovered that fasudil (a Rho-kinase inhibitor) could be potentially repositioned for treating neurodegenerative disorders.

Knowledge-based approaches can be used not only to identify new therapeutic agents, but also to validate new therapeutic targets. A principal advantage is that any new use will be based on a clearly defined mechanism of action. Additionally, this approach can elucidate new biological information about ODs, which can be potentially used to identify two classes of repositioned drugs: (i) new targets for known compounds and (ii) new indications for known targets. Because it requires an in-depth understanding of a particular disease, this approach can be typically limited to a specific therapeutic area.

### Strategy 2: rescreening the pharmacopeia against new targets

The second strategy takes advantage of the recent and rapid advances in the screening technology that allows a semi-blind approach of re-screening existing compounds against a multitude of targets to identify possible therapeutic benefits or side-effects in an unbiased manner [16]. Putative novel interactions between approved drugs and previously unexplored or incompletely explored targets (e.g. OD causative genes) can be discovered from this target-focused approach. Focusing on neglected parasitic diseases, researchers at the University of Dundee carried out a large scale screening to cover a broad range of potential targets. As part of this, they compiled three different libraries: (i) diverse *in silico* library for virtual screening comprising 222 552 compounds; (ii) diverse screening compound library comprising 57 438 compounds; and (iii) a focused compound library of 1697 compounds for the discovery of kinase inhibitors. Computational and experimental characterization of the general screening library revealed that the selected compounds span a broad range of lead-like space and show a high degree of structural integrity and purity. They also

demonstrated appropriate solubility for the purposes of biochemical screening [17]. In another study, using high-throughput screening, Lee *et al.* discovered the unexpected synergistic combination of an antiparasitic agent (pentamidine) and a phenothiazine antipsychotic (chlorpromazine). The combinatorial (CRx-026) inhibited the growth of tumor cell lines *in vivo* more effectively than either pentamidine or chlorpromazine alone [18]. Thus, screening the known drugs (common and orphan) against OD causative and druggable proteins can not only identify potentially new therapeutic agents for validated targets, but also identify and validate new OD-relevant targets and potential drug combinatorials. Common drug repositioning using the OD target approach can provide a useful strategy for jump-starting OD therapeutic programs with the opportunity to conduct proof-of-concept clinical studies with an existing drug. Additionally, if a novel target is discovered for an existing drug (common or orphan), its chemical scaffold can be used as a good starting point to identify potential new chemical entities with the premise of developing them as drugs for the novel target [12].

### Strategy 3: endpoint screening

In this strategy, starting with a phenotype of interest that may have significant therapeutic impact, the existing drugs are screened to discover both on- and off-target effects of compounds. By focusing on a validated endpoint of interest, this strategy can identify existing drugs that produce an unanticipated, yet desired, phenotypic result. The drawback, however, is that it often provides little or no mechanistic insight and may, therefore, require additional investigations to precisely determine how the existing drug works to achieve the desired effect (on- or off-target). While this is not always easy to do, it may be worth the effort to discover that an existing common drug hits a new target that is either causative or relevant to an OD. By casting the broadest possible net, the endpoint phenotype screening strategy has the potential to generate novel OD indications for the common drugs [12]. For instance, enhancing autophagy is a potentially effective strategy for the treatment of several human disorders. Iorio *et al.* [19] developed a computational approach (based on the Connectivity Map data set) and using 2-deoxy-D-glucose (2DOG), a known inducer of autophagy, generated a list of drugs that were predicted to share a similar mode of action as 2DOG.



The authors were able to reproduce a previously repositioned autophagy inducer (trifluoperazine) apart from identifying a novel autophagy enhancer drug (fasudil). The exact mechanism responsible for enhancement of autophagy by fasudil, however, is not yet known.

### Methods of knowledge integration and mining

Drug repositioning in principle works on existing knowledge. It is based on the hypothesis that by reshuffling what we know about diseases and approved drugs in novel and interesting ways, we can discover potential new indications that could lead to better therapies. The caveat is that since it is based on existing or prior knowledge, it only can be as good as the knowledgebase it is based on, and the OD knowledgebase is incomplete. One of the prerequisites of any knowledge-driven approach is the need to collect, structure and normalize data resources before storing in knowledge bases and mining for knowledge discovery and hypothesis generation. The resources that can go into these knowledge bases are diverse and heterogeneous and can include but are not limited to electronic data, text-mined relations, domain-centric databases, specialized rules and the web in general. The identification and integration of informative features associated with OD, OD-causing mutant genes, pathways and drug entities are critical to uncovering pathophysiological mechanisms and developing or discovering novel OD therapeutic options for existing drugs. There have been relatively few studies which employed a systematic knowledge engineering approach to identify drug repositioning candidates. Keiser *et al.* [20] built a drug–target network based on the respective ligand structural similarities and used it to predict novel targets for known drugs. In two other studies [21, 22], chemical systems biology-based approaches were employed to discover potential new indications for existing drugs. Recently, Eichborn *et al.* [13] developed PROMISCUOUS database, an exhaustive network-focused resource of protein–protein and protein–drug interactions enriched with side-effects and structural information, which can be used as starting point for indication finding and also drug-repositioning. In another recent study, Cockell *et al.* [14] reported Ondex, an integrated data platform to facilitate *in silico* discovery of novel drug repositioning candidates. All these methods,

however, focus on the common or non-ODs. A seemingly promising approach, therefore, is to devise a similar knowledge framework of OD–drug correlations to support the discovery of novel and inferable relationships between known drugs and ODs. A fundamental prerequisite for such an approach is a comprehensive OD knowledgebase that can maximally represent reusable knowledge components across pharmacological and biological domains, enabling scientists to distill insightful hypothesis.

Several new computational approaches exist to facilitate the integration of heterogeneous data [23] including Semantic Web (SW) standards and technologies [24] such as the Ontology Web Language (OWL), Resource Description Framework (RDF) and SPARQL. Together, these approaches can aid the prediction of novel therapeutic applications in drug development by providing a powerful platform to integrate and query various entities including therapeutic compounds, drug targets, genes, pathways, indications and the complex interactions and interdependencies among them. OWL defines the structured vocabulary representing the domain knowledge, and RDF provides the generic framework to describe entity properties, relationships and constraints by forming an acyclic graph (DAG) of multidimensional data sets. SPARQL is a query language and protocol that provides functions and syntax to query by pattern matching of underlying RDF graphs. SW standards mediate data to be modeled as a semi-structured graph in which complex relations can be readily modeled and inferred [25–28]. This is a relatively burgeoning area, and very few attempts have been made in the area of drug repositioning. Qu *et al.*, [27] created a large RDF graph by semantically linking multiple genomic, phenomic and pharmacome databases and querying for molecular mechanisms of existing drugs. To explore the implicit drug–pathway associations, the authors investigated the graph by traversing multiple paths through compounds, targets and shared clinical features and proposed new indications. Their results support the effectiveness of using SW for data integration and the potential to enhance therapeutic knowledge for drug development. Observing the limitations of a combined repository for chemistry and biology data, Chen *et al.* [29] developed a semantic database, Chem2Bio2RDF, by aggregating data from various chemogenomics repositories cross-linked to Bio2RDF [30] and LODD [31].

With the use of this integrated database, several compounds having different chemical structure but sharing multiple targets with marketed drugs were identified. For instance, it was found that the compounds loxapine (antipsychotic drug used to treat the symptoms of schizophrenia) and oxybutynin (anticholinergic medication used to relieve urinary and bladder difficulties) share similar pharmacology with quinacrine, which was previously used as an antimalarial and reported to be effective for treating giardiasis and tapeworm infections.

### Network pharmacology—drug target discovery and repositioning

With the current shift from the predominant ‘one drug, one target, one disease’ paradigm to a poly-pharmacology paradigm, the ‘many-to-many’ relationship between drugs and target proteins can be illustrated by a network view, where most drugs are interconnected by shared targets and most targets are interlinked by related common drugs [32]. Including network topological information and systems-biology models can potentially accelerate and improve the outcomes of virtual drug repositioning techniques. For example, identification of protein targets for a known drug that occupy a relevant position in a cell network associated with an OD can provide useful and testable information regarding a new therapeutic area [6].

In a protein–protein interaction (PPI) network, topologically important proteins, such as hubs and bottlenecks, tend to be essential and may serve as potential drug targets [33, 34]. A recent study by Florez *et al.* [35] predicted a PPI network for the pathogenic trypanosomatid *Leishmania major* and identified 142 hub and bottleneck proteins that have no orthologs in humans as potential drug targets. In addition to selecting important proteins from PPI networks, analyzing metabolic networks, or reactomes, which link metabolites by reactions on a systems level, can also shed light on disease mechanisms and drug target discovery. By applying flux balance analysis on a reconstructed metabolic network of *L. major*, Chavali *et al.* [36] simulated and predicted single- and double-gene deletions. Their study identified 69 (or 12%) single-gene knockouts as lethal, 10% as growth reducing, and 56 genes involved in lethal double deletions, all of which may constitute promising drug targets. Combining important proteins/genes from both the interactome and the reactome of *Mycobacterium tuberculosis*,

Raman *et al.* [37] proposed a drug target identification pipeline, namely targetTB, to predict and refine drug targets for the tuberculosis bacterium. Potential drug targets can be inferred from similar known drug targets. This requires the knowledge of known drug–target relationships, as well as the measures of drug similarity and target similarity. By constructing and mining an Alzheimer’s disease (AD) drug-oriented chemical–protein interactome using a matrix of 10 drug molecules known to treat AD toward 401 human protein pockets, Yang *et al.* [38] were able to recover acetylcholinesterase (validated therapeutic target of AD) apart from several other putative targets. Recently, Zhao and Li combined the measures of drug therapeutic (or phenotypic) similarity and drug chemical structural similarity, and predicted links between drugs and target proteins by a regression model called drugCIPHER, based on known drug–target relationships collected from FDA and DrugBank [39, 40]. For more details on network pharmacology, the emerging paradigm in drug discovery and repositioning, readers are referred to [41–43].

### On-target and off-target interactions

Although designed to target on the therapeutic targets, drug molecules inevitably interact with unexpected proteins (off-targets) [44], their associated biological processes and pathways [45–47], displaying undesired therapeutic effect or adverse reactions. In ‘on-target repositioning’, known pharmacological mechanisms of a drug are applied to a different therapeutic indication from the one for which it was initially developed. Even more innovative is ‘off-target repositioning’, which looks for pharmacological mechanisms that have not yet been described for a known molecule. In other words, the drug repositioning avenue is equally open to both drugs that have been marketed or have been withdrawn (or discontinued) because of their failure during clinical development. A number of computational strategies have been reported to explore the off-target paradigm, including molecular docking [47, 48], protein structure comparison [21, 49], chemical structure comparison [20, 44, 50] and text mining [51, 52], each of which have become a low cost but efficient way of finding drug repositioning candidates.

Several success stories of off-target identification and drug repositioning using docking-based methodology are reported. For example, the antipsychiatric drug haloperidol had been repositioned to the

anti-HIV drug lead by using DOCK [53]. Docking multiple chemicals across protein pocket set with a statistical model has been applied to identify off-targets for anti-Alzheimer drugs [38]. The structural similarity comparison among protein pockets is another way to identify the off-targets. For instance,  $\text{Ca}^{2+}$  ion channel ATPase was found to be the off-target of estrogen receptor modulators because it shares significant structural similarity with an estrogen receptor [49]. By comparing the pocket structure similarities, Comtan (entacapone), a drug for the treatment of Parkinson's disease, was also found to be effective in treating multi-drug and extensively drug resistant tuberculosis [21]. Due to the lack of human protein structures, some methodologies utilize the ligands' structure for off-target fishing. One can 'fish' for the off-targets of a ligand by querying the 2D structures of it across the known ligands of the proteins [54]. A methodology named as the similarity ensemble approach (SEA) utilized the normalized sum of the structure similarity scores of the query molecule towards the ligand sets for each candidate off-target [20, 44] and predicted new targets for existing drugs. Hypothesizing that two drugs tend to share the targets of each other if they share the 2D structure and the side effects of each other, Campillos *et al.* [52] predicted the off-targets for marketed drugs by mining both the 2D structure of the drugs and the side effects on the drug label. These methods were proved to be applicable on some drugs in the wet lab validation.

### Drug repositioning for orphan diseases

The completion of the Human Genome Project and the advent of several high-throughput technologies resulted in acceleration of the identification of the genetic basis for many ODs. Additionally, with the improving availability of gene annotations for both human and model organisms, the newly identified causative genes for many ODs can be checked to see if they share same pathways or biological processes with that of common diseases. For instance, the genes causing each of Neurofibromatosis Type-1, Cowden Disease and Retinoblastoma share common processes and pathways that are highly relevant to several types of cancer. Thus, a drug discovered to be useful in treating the ODs may have potential undiscovered indications for the common diseases (non-ODs). In the following sections, we present several scenarios wherein an approved common or orphan drug was successfully

repositioned (approved or designated) for an OD and vice versa. Some of these examples are based on serendipitous discoveries while others are based on informed insights or label-extensions. We also discuss the potential reviving of discontinued or withdrawn drugs for OD indications.

### Case study 1: common drug repositioning for orphan diseases

Two best examples where a common or non-orphan drug is being developed as a treatment for ODs based on informed insights and not serendipitous observations are tretinoin and sildenafil. Tretinoin, a metabolite of vitamin A commonly used for the topical treatment of acne vulgaris was approved by FDA in 1995 as an orally administered soft gel capsule for induction of remission in acute promyelocytic leukemia (APL), an OD. APL is associated with a specific cytogenetic abnormality wherein a portion of the long arm of chromosome 17 translocates onto the long arm of chromosome 15. Subsequent molecular studies revealed that the DNA rearrangements that clustered in the region of the first intron for the nuclear retinoic acid receptor alpha (RAR- $\alpha$ ) resulting in the expression of abnormal messenger RNA (mRNA) transcripts for RAR- $\alpha$ . RAR- $\alpha$  was previously shown to be involved in the growth and differentiation of certain myeloid cells in vitro and couple of studies from China and France reported that treatment with tretinoin induced complete remission in patients with acute promyelocytic leukemia. All these data suggested a possible molecular link between APL and tretinoin which was confirmed subsequently in a high proportion of patients [55]. Likewise, sildenafil, a blockbuster drug widely used for erectile dysfunction, has recently been approved at a lower dosage for the treatment of the OD pulmonary arterial hypertension (PAH). In May 2009, the US FDA also approved the phosphodiesterase PDE5 inhibitor tadalafil (a compound similar to sildenafil) as an orphan drug for the treatment of PAH, including etiologies such as idiopathic and familial PAH, as well as that associated with scleroderma and congenital heart disease. Another interesting example is ceftriaxone, a  $\beta$ -lactam third-generation cephalosporin antibiotic, which when delivered to animals increased both brain expression of glutamate transporter GLT1 and its biochemical and functional activity. Although glutamate transporters are critical for maintenance of synaptic activity and in preventing

glutamate neurotoxicity, currently there is no drug that can positively modulate this protein. Animal studies show that dysfunction of GLT1 is implicated in acute and chronic neurological disorders including amyotrophic lateral sclerosis (ALS), stroke, brain tumors and epilepsy. Ceftriaxone was found to be neuroprotective *in vitro* when used in models of ischemic injury and motor neuron degeneration, both based in part on glutamate toxicity. When used in an animal model of ALS, the drug delayed loss of neurons and muscle strength and increased mouse survival [56].

### Case study 2: orphan drug repositioning for a common indication

Apart from common drugs repositioned for ODs, there are several examples where an orphan drug was approved for a common indication. Albuterol, designated as an orphan drug for prevention of paralysis due to spinal cord injury, is indicated for the relief of bronchospasm, a common condition. The pharmacologic effects of albuterol, a  $\beta$ -adrenergic agonist, are partly due to stimulation through  $\beta$ -adrenergic receptors (predominant in bronchial smooth muscle cells) of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of ATP to cyclic AMP. Increased cyclic AMP levels are associated with bronchial smooth muscle relaxation and inhibition of release of hypersensitivity mediators from mast cells. Dimethyl sulfoxide (DMSO) is an approved orphan drug in Europe for treating severe closed traumatic brain injury and is designated for several OD indications such as cutaneous manifestations of scleroderma, palmar-plantar erythrodysesthesia syndrome and, in combination with other antimicrobial drugs, the treatment of drug-resistant tuberculosis. At the same time, DMSO is approved for symptomatic relief of patients with interstitial cystitis, a non-OD. Similarly, mifepristone, a designated orphan drug for Cushing syndrome, is used alone or in combination with misoprostol to end an early pregnancy ( $\leq 49$  days).

### Case study 3: orphan drugs with approval for another orphan disease indication

Succimer, an approved orphan drug, is indicated for treatment of lead poisoning in pediatric patients. It is also designated for prevention of cystine kidney stone formation in patients with homozygous cystinuria who are prone to stone development and for treatment of mercury intoxication. Similarly,

riluzole, indicated for treatment of patients with amyotrophic lateral sclerosis, is designated for treatment of Huntington's disease following an open-label trial which is a type of clinical trial where in both the researchers and participants know about the treatment being administered.

### Case study 4: orphan-designated products with marketing approvals for both common and orphan disease indications

In addition to the examples listed above, there are certain orphan-designated drugs that are approved for both common and orphan conditions. Initially developed for cancer treatment in the late 1970s, eflornithine was found to be highly effective in reducing hair growth, as well as in treatment of sleeping sickness (African trypanosomiasis). Eflornithine is a selective irreversible inhibitor of ornithine decarboxylase (ODC), which is a key enzyme in the biosynthesis of polyamines and catalyzes the conversion of ornithine to putrescine, the first and rate-limiting step in the synthesis of putrescine and of the polyamines spermidine and spermine [57]. When applied topically, Eflornithine, by irreversibly inhibiting ODC, catalyzes the conversion of ornithine to putrescine, which plays an important role in cell division and proliferation in the hair follicle [58]. Trypanosomes (*Trypanosoma brucei gambiense*) are more susceptible to the drug than human cells due to the slow turnover of this enzyme in the parasite. Eflornithine can effectively inhibit ODC activity and deplete polyamines in trypanosomes, which bring them into a static state that renders them vulnerable to the host's immune attack [57]. The FDA approved eflornithine for the treatment of gambiense sleeping sickness in 1990. Additionally, eflornithine is designated for treatment of *Pneumocystis carinii* pneumonia in AIDS patients and for treatment of anaplastic glioma.

### Case study 5: reviving withdrawn drugs

While sildenafil is an example of a successfully repositioned drug that was never marketed for its original development, thalidomide is an example of a withdrawn drug successfully revived and repositioned for OD. Introduced first as a sedative drug during the late 1950s and subsequently withdrawn in 1961 for potential human embryotoxicity, thalidomide was revived in 1998 with FDA approval for the treatment of erythema nodosum leprosum (ENL),



a complication of leprosy. In a classic case of serendipity, in 1964 physician Jacob Sheskin at the University Hospital of Marseilles (France) administered thalidomide as a last resort to treat weeks of sleeplessness of a critically ill ENL patient suffering with severe pain. While the patient had a good night's sleep, Sheskin observed that the patient's sores were also healed and the pain was eliminated. Sheskin then conducted a double-blind study on 173 patients in Venezuela and found that 92% were completely relieved of their symptoms following the administration of thalidomide [1, 59]. The potent immunomodulatory properties of thalidomide discovered subsequently are exploited for the treatment of several other conditions, such as oral and genital ulcers, vasculitis, rheumatoid arthritis and chronic graft versus host disease. Thus, thalidomide continues to be a classical example wherein a withdrawn drug has been found to be useful in a multitude of other diseases as an immunomodulatory compound. Additionally, the thalidomide analogs, lenalidomide (CC-5013; Revlimid) and CC-4047 (Actimid), are reported to have enhanced potency as inhibitors of TNF- $\alpha$  and other inflammatory cytokines, as well as greater capacity to promote T-cell activation and suppress angiogenesis. Thus, both thalidomide and lenalidomide are effective in the treatment of multiple myeloma and myelodysplastic syndromes [60]. The drug was subsequently found to be active against the aphthous ulcers of Behcet's syndrome and effective as a substitute for immunosuppressive therapy for graft versus host disease.

### Rare disease repurposing database

Recently, the US FDA's Office of Orphan Products Development has established a new resource: Rare Disease Repurposing Database (RDRD) for drug developers. It is a compilation of drugs that have shown promise for treating ODs and already have FDA approval or designation. It is a database of products that (i) have received orphan status designation (i.e. they have been found 'promising' for treating a rare disease); and (ii) are already market approved for the treatment of some other diseases. Since these compounds already have FDA approval, it is anticipated that repositioning these drugs for a new OD indication will be quick and inexpensive for the developer, and will therefore help patients by getting to market quicker. The data are provided as three downloadable excel files: (i) orphan-designated products with at least one marketing approval for a

common disease indication; (ii) orphan-designated products with at least one marketing approval for a rare disease indication; and (iii) orphan-designated products with marketing approvals for both common and rare disease indication. These lists offer sponsors a new tool and a 'shorter path' for finding special opportunities to develop niche therapies instead of beginning with an untested new therapy compound and obtaining an FDA approval. Additionally, these data sets can be used as a 'positive control' or 'gold standard' for testing or validating high-throughput and computational approaches for drug repositioning for ODs. Table 1 lists some of the resources related to ODs and drugs.

### Faster access to approved orphan drugs—beyond barriers and frontiers

Comparing the orphan drugs (designated or approved) in the United States with those in other countries, we found several drugs that have been approved and available in other countries but not in the United States and vice versa. For example, stiripentol, an orphan drug with an indication exclusively for Dravet Syndrome was approved by the European Medical Association in October 2006 while it received an Orphan designation by the FDA in November 2008. Two studies which compared the European Medicines Agency (EMA) performance metrics with those for FDA in the drug approval found that there was considerably variability between the approval times of the two regulatory bodies. The first study assessing products approved from 2000 through 2005 by both agencies found that nearly three times as many were approved first in the United States (52 versus 19 were first approved in the United States and the European Union, respectively) [61]. The second study [62] which compared the drugs approved during a 12-month period (2008–09) by the European Union's European Medicines Authority (EMA) and the FDA found that of the total 39 new medicines, 15 were approved only by the FDA, 11 were approved only by the EMA and 13 were approved by both regulators. Of the 13 drugs approved by both the FDA and EMA, for 5 drugs the EMA was the first to approve issuing the approvals about 550 days faster than the FDA. Thus, if a drug is approved or designated for OD indication by a regulatory body in a comparable jurisdiction (e.g. the European Union), drug manufacturers should probably be permitted to distribute their medicines to willing doctors and

patients in the United States. Alternately, drug companies in the United States can identify orphan drugs that are already available in Europe and attempt to usher them through US FDA to facilitate an orphan drug get to the market fast. The FDA and EMEA are increasingly collaborating to increase communication between the two agencies and sponsors. To this effect, the EMEA and FDA have jointly signed a Confidentiality Arrangement (18-month pilot program that started in September 2009), which facilitates the sharing of regulatory guidance documents, information related to the authorization and supervision of medicinal products including inspection reports and sites where clinical trials take place.

### Key Points

- Drug repositioning is an alternative and efficient strategy to boost the discovery of OD therapeutics. It is based on the hypothesis that by reshuffling what we know about diseases and approved drugs in novel and interesting ways, we can discover potential new indications that could lead to better therapies.
- For many of the ODs, the causative gene(s) can share pathways or biological processes that are common to genes associated with nonorphan or common diseases.
- RDRD is a compilation of drugs that have shown promise for treating ODs and already have FDA approval or designation.

### Acknowledgements

The authors thank the entire Orphanet team for providing us with the orphan drug data. We thank Ron Bryson for language-editing of the manuscript.

### FUNDING

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, partial.

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