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The drug repurposing landscape from 2012 to 2017: evolution, challenges, and possible solutions

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As the name suggests, drug repurposing is a strategy to identify new therapeutic uses for marketed drugs, discontinued and/or shelved drugs, and drug candidates currently in clinical development. Although not a recent concept, drug repurposing has gained momentum over the past few years and several drugs have been successfully repurposed. Here, we summarize the drug repurposing landscape from 2012 to 2017, with a major focus on repurposed drugs, collaborative opportunities, and funding opportunities specific to drug repurposing projects. Along with success stories, we also highlight the challenges and limitations associated with drug repurposing.

Introduction

Drug repurposing, also known as drug reprofiling or drug repositioning, is an approach used to identify alternate therapeutic uses for compounds that have failed during the developmental stage and to extend the uses of drugs already in use [1,2]. Drug repurposing is considered as a vital strategy, especially for rare genetic diseases, for which the traditional drug discovery approach is time-consuming and expensive because of the rare nature of such diseases, the limited patient population and, therefore, the small market space [3]. Although not a new strategy, drug repurposing, with successes such as thalidomide and sildenafil, has gained momentum over the past few years because of the significant benefits offered by this approach to the pharmaceutical industry, which is facing unprecedented challenges with respect to the product pipeline, and decreased rates of number of new molecular entities (NMEs) approved every year globally [1]. From 1991 to 2000, high attrition rates occurred during Phase II trials, where the efficacy and safety parameters of drug candidates are tested [4]. Hence, to protect and optimise the drug discovery pipeline, many strategies, including acquisitions, collaborations, and advanced technologies were implemented, although with little impact. Given these challenges, drug repurposing has emerged as a promising approach to overcome hurdles during drug research and development [5]. This strategy can be applied to reinvestigate marketed drugs, withdrawn drugs, and drug candidates discontinued during the clinical development phase because of efficacy or commercial reasons, although not because of safety.

Drug repurposing began serendipitously; however, with increasing interest from pharmaceutical companies and the identification of various bioinformatics and cheminformatics methodologies, it has evolved into an innovative, data-driven, cutting-edge strategy (Fig. 1). The identification in 1998 of erectile dysfunction [6,7] and in 2005 of pulmonary arterial hypertension [8] as new indications for sildenafil, and in 1998 of leprosy [9] and in 2006 of multiple myeloma [10] for thalidomide were the results of serendipitous clinical observations. Repurposing imatinib (an ABL kinase inhibitor for systemic mastocytosis, which was originally approved for chronic myelogenous leukemia [11]) is an example of data-driven approach. This strategy also identified a combination partner for imatinib mesylate in treating gastrointestinal stromal tumors [via *in vitro* screening of a US Food and Drug Administration (FDA)-approved drug library] [12]. Another example of systematic drug repurposing that gained FDA approval is topiramate, a sulfamate based anticonvulsant initially approved for epilepsy and migraine prophylaxis. Weight loss as an adverse effect of topiramate was first noticed in a clinical study for migraine prevention and bipolar disorder [13]. Later, many proof-of-concept (PoC) and investigational clinical studies were planned to further assess the effect of topiramate on weight loss [14–16]. However, because topiramate was associated with adverse effects, it was not approved as mono-

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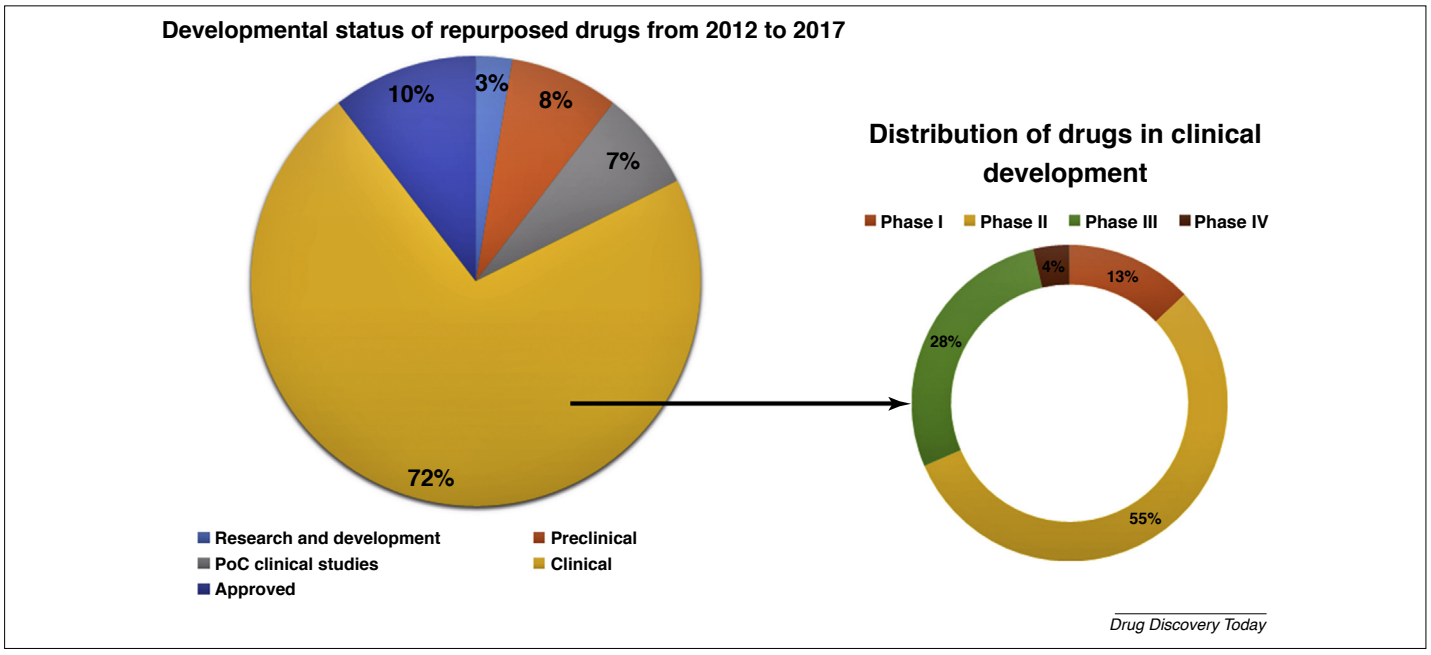

FIGURE 1

The developmental status of repurposed drugs from 2012 to 2017. Abbreviation: PoC, proof of concept.

therapy [17]. However, when combined with phentermine, an antiobesity drug, in low-dosage and controlled release formulations, topiramate was effective in treating obesity [18]. Drug repurposing relies on the facts that: (i) a drug can act on multiple targets; (ii) two diseases can have molecular similarities; and (iii) a target can exhibit pleotropic effects with respect to molecular function. Currently, with existing technologies such as big data analytics, computational methodologies, and screening platforms, hitherto hidden associations among drugs, diseases, and targets can be predicted [19–22].

Computational methods now have a significant role in drug repurposing because these methods provide tools and techniques for cheminformatics, bioinformatics, network biology, and systems biology for integrating available data on drugs, diseases, and targets that can then be used to elucidate unknown or hidden mechanisms in short timelines [23–25]. The number of drug-repurposing articles published monthly has grown rapidly [26,27]. In addition, a dedicated journal, *Drug Repurposing, Rescue, and Repositioning*, has been launched recently, reflecting this increase in publications.

Repurposed drugs accounted for 30% of drugs approved by the FDA in recent years [27,28]. The drug repurposing approach has also been adopted and supported by academic institutions, the corporate sector, nonprofit organizations (NPOs), and government organizations. There has also been a substantial increase in the number of drug repurposing companies created year on year over the past decade [29]. With regard to therapeutic area, drug repurposing has significantly impacted rare and neglected diseases for which effective therapies were not previously available [30]. Here, we review data relating to the number of repurposed drugs approved or having entered clinical development, funds raised for repurposing projects, and collaborations initiated pertaining to drug repurposing from 2012 to 2017. We also shed light on the challenges involved in developmental and regulatory pathways of repurposed drugs, and strategies to overcome these challenges.

Repurposed drugs in the recent past

To understand the recent impact of drug repurposing on drug discovery and development, data on repurposed drugs were collated from Excelra's proprietary drug repurposing portal, news bodies, and social networking sites, and then analyzed to reveal any drug repurposing trends. From 2012 to 2017, almost 170 repurposed drugs entered the drug development pipeline. Currently, these 170 drugs are at different stages of development. Most (72%) are in clinical development, especially Phase II, 7% are in PoC clinical studies, 8% in preclinical stages, 3% in research and development, and 10% have been approved (Fig. 1). For example, OCU300 (brimonidine) was previously marketed by Allergen for the treatment of open-angle glaucoma and is now being developed under FDA's 505(b)(2) regulatory pathway for ocular graft-versus-host disease (GVHD).

Almost 70% of the Phase I and II trials for repurposed drugs were sponsored by academia and 30% by industry. This emphasizes the fact that major research is happening in academic institutions, although collaboration with industry is required to facilitate Phase III studies, regulatory approval, manufacturing and commercialization of the product.

A list of repurposed drugs approved during the past 5 years is provided in Table 1. Three Novartis drugs (canakinumab, difluprednate, and everolimus) gained FDA approval for repurposed indications. For three drugs (bevacizumab, sorafenib, and lenvatinib), the therapeutic area of original indication and repurposed indication was same (i.e., oncology). Pfizer's Rapamune (rapamycin/sirolimus) received breakthrough status in 2015 for use against lymphangioleiomyomatosis (LAM), a rare lung disease affecting women [31,32]. Rapamycin stabilized the lung function, reduced

TABLE 1

Examples of recently approved repurposed drugs

Drug name	Brand name	Original indication	New indication (repurposed)	Company
Aspirin	Durlaza	Inflammation and/or pain	Stroke and/or myocardial infarction	New Haven Pharmaceuticals
Bevacizumab	Avastin	Colorectal cancer	Platinum-sensitive ovarian cancer	Roche
Canakinumab	Ilaris	Cryopyrin-associated periodic syndromes	Tumor necrosis factor receptor-associated periodic syndrome; hyperimmunoglobulin D syndrome; familial Mediterranean fever	Novartis
Coagulation factor VIIa (recombinant)	NovoSeven	Hemophilia	Glanzmann's thrombasthenia	Novo Nordisk Pharmaceuticals
Collagenase clostridium histolyticum	Xiaflex	Dupuytren's contracture	Peyronie's disease	Auxilium Pharmaceuticals
Difluprednate	DUREZOL	Inflammation and pain associated with ocular surgery	Endogenous anterior uveitis	Novartis
Dimethyl fumarate	Tecfidera	Psoriasis	Multiple sclerosis	Biogen
Everolimus	Afinitor	Organ transplant rejection	Neuroendocrine tumors of gastrointestinal or lung origin; HER2-negative breast cancer	Novartis
Lenvatinib	Lenvima	Metastatic, radioactive iodine-refractory differentiated thyroid cancer	Advanced renal cell carcinoma	Eisai
Mifepristone	Korlym	Abortion	Hyperglycemia in Cushing's syndrome	Corcept Therapeutics
Nintedanib	Vargatef	Idiopathic pulmonary fibrosis	Non-small-cell lung cancer	Boehringer Ingelheim
Propranolol	Hemangeol	Hypertension, angina pectoris, tachyarrhythmias, myocardial infarction, tachycardia	Infantile hemangioma	Pierre Fabre
Rapamycin	Rapamune	Organ transplant rejection	Lymphangioleiomyomatosis	Pfizer
Ruxolitinib	Jakafi	Myelofibrosis	Polycythemia vera	Incyte
Sorafenib	Nexavar	Liver and kidney cancers	Thyroid cancer	Bayer Healthcare Pharmaceuticals
Topiramate	Qsymia	Epilepsy	Obesity	Vivus

symptoms, and improved the quality of life of patients with LAM [31,32]. Tecfidera (dimethyl fumarate), an antipsoriatic drug, emerged as a first-line therapy for relapsing-remitting multiple sclerosis, for which it was approved by the FDA in 2013 [33–35]. Propranolol (a β-blocker) gained FDA approval for the treatment of infantile hemangiomas (vascular tumors) in 2014 and remains the only drug approved for this disease [36].

Among the 170 drugs reprofiled from 2012 to 2017, 60% were repurposed for a new indication belonging to different therapeutic category from that of the original indication, whereas for 40% of the drugs, the therapeutic category of new indication was the same as that of the original indication (Fig. 2). The current data emphasize the fact that drug repurposing projects have been more focused on oncological and neurological diseases. In addition, most of these repurposed drugs were both oncology and neurology drugs (Fig. 2), as also reported by a 2004 drug repurposing survey [37]. An oncology drug is most often repurposed for other oncology indication and a neurology drug for another neurology indication. This is justified by the fact that cancers are associated with kinases and neurological diseases are majorly influenced by G-protein-coupled receptors (GPCRs) [38]. Thus, a drug perturbing a particular kinase can also act on other kinases, and it is also the case for drugs acting on GPCRs [37]. However, this promiscuous drug–target interaction is limiting the success of repurposing in oncology and neurology and, therefore, repurposing a non-anticancer drug for oncology indications could be of value [38].

Drug repurposing-specific collaborations

There were almost 40 collaborations pertaining to drug repurposing from 2012 to 2017 (http://drugrepurposingportal.com/index.php?category=Collaborations). Almost 50% of these collaborations were between two industries, with 20% between an industry and a NPO, and 9% between industry and academia (Fig. 3).

Some recent industry–industry collaborations include: (i) a 3-year drug repurposing collaboration between the global pharmaceutical company Teva and technology leader IBM (www.healthcareitnews.com/news/ibm-watson-teva-partnership-create-new-medicines-tackle-chronic-diseases). The main objective of this partnership is to identify correlations between molecules and diseases by using machine-learning and natural language processing technologies; (ii) collaboration between Galapagos and Pharnext to identify effective, low-dose combinations of approved drugs to enhance the efficacy of Galapagos' pipeline prospects (www.fiercebiotech.com/biotech/galapagos-pharnext-join-forces-to-develop-drug-combos); and (iii) BioXcel is in collaboration with Centrexion for the development of therapies for

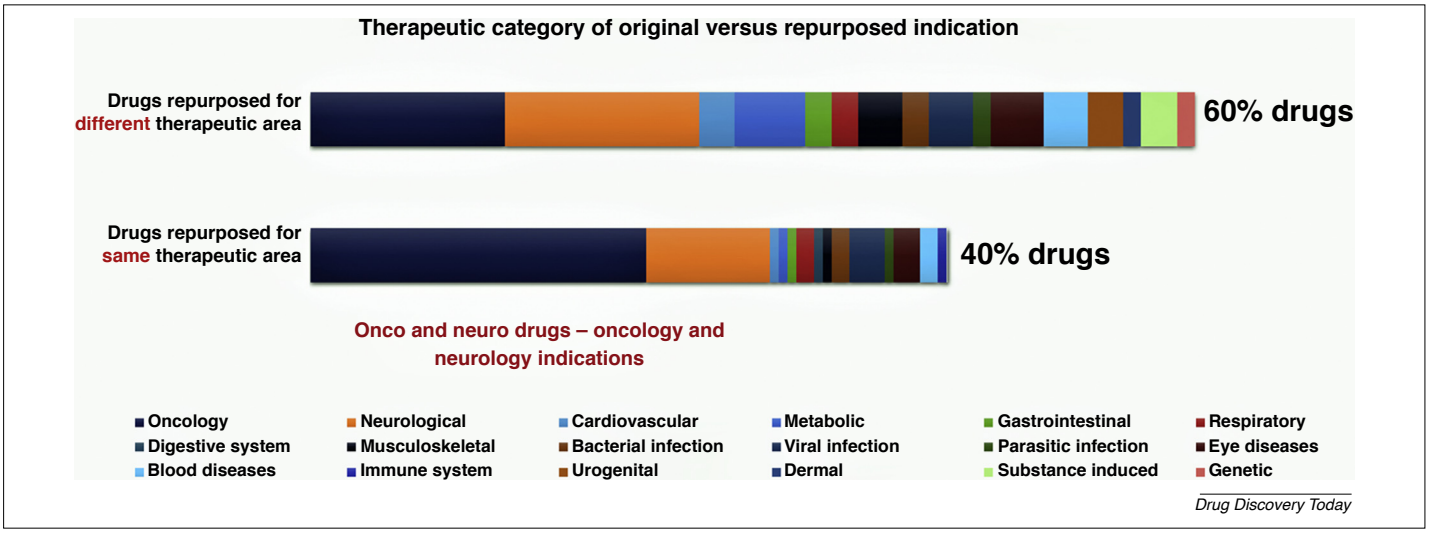

FIGURE 2

Drug repurposing paradigm pertaining to different therapeutic areas from 2012 to 2017.

chronic pain-related diseases (http://globenewswire.com/news-release/2016/01/11/800874/0/en/BioXcel-and-Centrexion-Partner-to-Develop-Novel-Chronic-Pain-Therapies.html). Cures within Reach (CWR), a NPO actively facilitating drug repurposing research, entered into collaboration with Cyclica and Elsevier to identify treatment options for rare diseases from existing drugs. The number of collaborations aiming to identify novel associations between molecular diseases and targets has increased significantly since 2012. The year on year (YoY) trends in drug repurposing-based collaborations are illustrated in Fig. 3. Almost 50% of drug repurposing collaborations have focused on rare diseases, including: chronic fatigue syndrome, Angelman syndrome, Zika viral infection, Niemann–Pick disease type A, Fragile X syndrome, Rett syndrome, familial transthyretin (TTR) amyloidosis, pulmonary arterial hypertension, Dravet syndrome, congenital hyperinsulinism, idiopathic pulmonary fibrosis (IPF), and Duchenne muscular dystrophy.

Funds raised for drug repurposing research projects

To intensify drug repurposing research, many NPOs have come forward to grant funds for research programs. There was a substantial increase in funds raised for drug repurposing projects from 2012 to 2017 (http://drugrepurposingportal.com/index.php?category=Funding). The YoY trends in the number of drug repurposing-related research projects funded and initiated are depicted in Fig. 4. Funds raised for drug repurposing projects increased consistently from 2012 (US$1 million) to 2015 (US$100 million). In 2016, although the funds raised was comparatively low, there were more drug repurposing projects initiated (47 projects). This emphasizes the fact that drug repurposing has gained traction in the recent past.

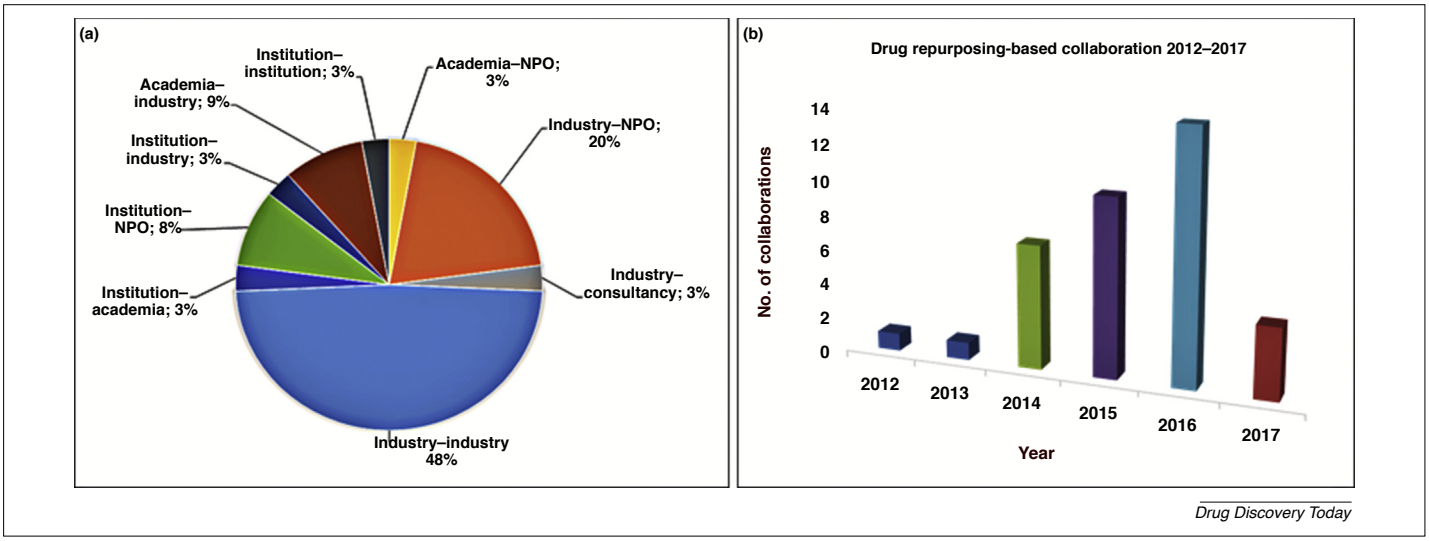

FIGURE 3

Patterns of drug repurposing-based collaborations (a) and year-on-year trends (b) for the number of collaborations from 2012 to 2017. Abbreviation: NPO, nonprofit organization.

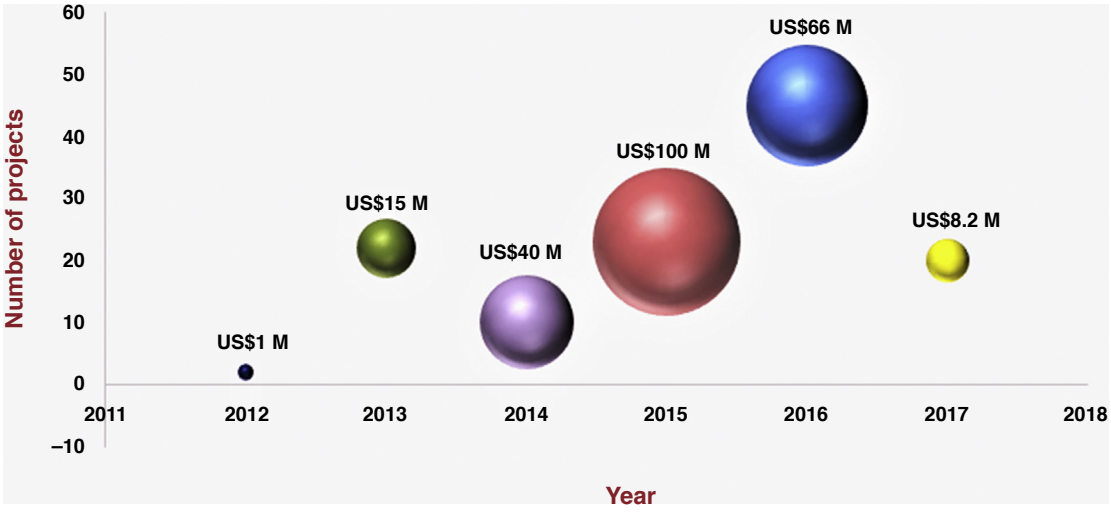

FIGURE 4

Year-on-year trends in funds granted for drug repurposing projects from 2012 to 2017.

Most funding was granted by the National Center for Advancing Translational Sciences (NCATS) and CWR. NCATS, established in 2012 [as a part of the US National Institute of Health (NIH)], has granted a fund value of almost US$20 million for over 25 drug repurposing projects since 2013. CWR granted funds for over 30 drug repurposing projects, of which 13 drugs have advanced to Phase III trials for new therapeutic indications. CWR also launched the Cure Accelerator platform to process drug repurposing-focused research; this also forms a market place for all drug repurposing researchers that enables them to work together and to drive more innovative drug repurposing projects. Disease areas in drug research projects supported by CWR include autism, multiple sclerosis, Alzheimer's disease, lymphoproliferative disease, polycystic kidney disease, childhood epilepsy, myotubular myopathy, and glioblastoma. In addition, the Canadian Institutes of Health Research (CIHR) partnered with Muscular Dystrophy Canada to support two rare disease-focused drug repurposing programs: the E-Rare 3 Joint Translational Call (JTC) and the North American Re:Rare (NAR:R). JTC2016 focuses on clinical trial projects (from preclinical to Phase Ib and IIa trials) and NAR:R focuses on PoC clinical studies (www.cihr-irsc.gc.ca/e/49739.html). Findacure is another organization funding drug repurposing projects, and launched its first grant opportunity in 2017. These agencies funded projects either independently or with other funding agencies. Other funding agencies that have supported drug repurposing projects in the recent past are listed in Box 1.

BOX 1

List of Funding agencies supporting drug repurposing projects

- AKU Society
- Alzheimer's Drug Discovery Foundation (ADDF) and Alzheimer's Society
- Amadeus Capital and investors
- British Heart Foundation
- Cancer Research and Prevention Institute of Texas
- CFIDS Association of America
- Cure Brain Cancer Foundation
- Deep Knowledge Ventures
- EB5 Life Sciences LP
- FRAXA Research Foundation
- Global Cures
- Grassroots foundation
- H.I.G. BioVentures, Adam Street Partners
- Lux Capital and Felicis Ventures
- Mayne Pharma
- Michael J. Fox Foundation
- National Cancer Institute
- National Institutes of Health
- Sante Ventures and New Enterprise Associates co
- Stichting Participatie Atriva and High-Tech Gründerfonds
- TRICON
- U.S. Department of Defense
- U.S. Department of Health and Human Services
- VC giant New Enterprise Associates

Challenges and limitations to the repurposed drug pathway

Although much progress in drug repurposing has been made in recent years, regulatory approval is the only aim for a successfully repurposed drug. Many challenges to meeting this goal can be foreseen, from the developmental phase all the way to regulatory approval.

Lack of funding to commercialize the product

Although there has been an increase in the number of small biotech companies and/or academic institutions working on drug repurposing projects, resulting in and PoC evidence, such institu-

tions fail to commercialize the resulting product because of an inability to find the right commercial partners, and a lack of funds and resources.

Lack of collaboration between academia and industry

In recent years, has been is a mass migration of skilled scientists from industry to academia and, hence, a shift in the amount of drug repurposing research activity from industry to academia. However, as discussed earlier, academia has to partner with big pharma to commercialize the resulting product. Currently, only a few academia–industry collaborations are reported for repurposed drugs (Fig. 4).

Clinical trial feasibility for rare diseases

Although there are almost 7000 rare diseases, only 5% of them have treatment options available, leaving many patients with little hope of clinical support. Compared with the traditional drug discovery strategy, drug repurposing holds the greatest potential for rare diseases, because it offers a chance to provide treatment options rapidly with lower costs. However, the clinical development of drugs for rare diseases is hindered by the fact that the rare disease market is small, and the generation of revenues is low.

Technical challenges to repurposing drugs

During the drug discovery process, a drug undergoes a long optimization process directed towards improving the selectivity and efficacy of the drug. If a new target has been identified for the same drug, the chances of the drug being more potent towards the secondary target is low compared with the primary target. Also, target validations are required even in drug repurposing because the relation between targets on which a drug acts and new indication needs to be validated experimentally.

Lack of clinical compound repositories

Drug repurposing involves the re-investigation and/or reprofiling of marketed drugs or drug candidates that are either in or have been discontinued from clinical development. This requires pharmacodynamic, pharmacokinetic, toxicity, and safety information, and any other relevant information about the drug and/or drug candidate. Currently, several drug repositories are available, but not for drug candidates. Hence repurposing a novel clinical candidate is difficult.

Novelty in repurposing

For a drug that is selective and specific to a target, the chances of it being repositioned for another target is unfeasible given that the potency values for the new targets identified will be lower than for the primary target [39]. Hence, a drug is often repositioned for another target belonging to the same class (e.g., a GPCR to another GPCR because cross-pharmacology among GPCRs is high; Fig. 2). This trend hinders, to some extent, the intellectual property generation and regulatory approval for the drug being repurposed because the 505(b) (2) pathway requires substantial innovation results.

Requirement for robust evidence

Although the repurposed drug and/or drug candidate has already gone through clinical development and regulatory approval for the primary indication, when proposed for new indication, a significant amount of robust, supporting, scientific evidence is needed, because the review process for 505(b) (2) applications is analogous to that of a new drug application (NDA).

Conducting PoC experiments

In the pharmaceutical industry, many drug repurposing-based research projects are more common in contract research organizations (CROs) or small biotech companies. However, few such institutions are ready to take risks in conducting PoC clinical studies, which are expensive [40].

Solutions

How can the drug development community overcome these limitations? Possible solutions include: (i) enhancement of collaborations between academia, biotech start-ups, institutions, and industry. These smaller groups should be able to strike a deal with big pharma and convince them to look back at their pipeline for potential shelved assets and then try to generate value out of those. These types of collaboration will make available the resources and capital required for the development and commercialization of repurposed drugs; (ii) engagement of all the relevant stakeholders (healthcare professionals, regulatory agents, etc.) right from the start of the drug repurposing strategy; and (iii) ensure clinical feasibility, cutting-edge innovation, and the novelty of the repurposed product.

Concluding remarks

Bringing a brand-new drug to market requires significant investment of time, money, and resources. These bottlenecks in the drug discovery and development process can hinder or delay the translation of discovery from bench to bedside. Thus, drug repurposing has been viewed as an attractive strategy commercially because chemical synthesis steps, manufacturing processes, and early clinical developmental phases (Phase I and Phase IIa trials) have already been performed for the candidates of repurposing.

Although the drug repurposing field had surpassed expectations, there are limitations and challenges that hinder its further development. The success of a repurposed drug depends on multiple factors, including the availability and extent of drug-related data, clinical trial feasibility of the identified indication, drug off-target effects, and so on. Nonetheless, consideration of all these factors from beginning of the process, interactions with regulatory groups, collaborations with big pharma, and cutting-edge innovations will pave the way for repurposed drugs to successfully enter the market.

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