Expert Opinion on Drug Discovery

ISSN: 1746-0441 (Print) 1746-045X (Online) Journal homepage: https://www.tandfonline.com/loi/iedc20

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To cite this article: Alan Talevi & Carolina L. Bellera (2020) Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics, Expert Opinion on Drug Discovery, 15:4, 397-401, DOI: 10.1080/17460441.2020.1704729

To link to this article: https://doi.org/10.1080/17460441.2020.1704729

Published online: 17 Dec 2019.

EXPERT OPINION ON DRUG DISCOVERY
2020, VOL. 15, NO. 4, 397–401
https://doi.org/10.1080/17460441.2020.1704729

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EDITORIAL

Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics

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ARTICLE HISTORY Received 25 September 2019; Accepted 11 December 2019

KEYWORDS Drug repurposing; drug repositioning; intellectual property; economics; big data; rare diseases; neglected diseases; crowdsourcing; precision medicine

1. Introduction

Drug repurposing (also known as drug repositioning, drug reprofiling, indication expansion or indication shift) involves establishing new medical uses for already known drugs, including approved, discontinued, shelved and experimental drugs. Although this strategy is far from new, it has gained considerable momentum in the last decade: about one-third of the approvals in recent years correspond to drug repurposing, and repurposed drugs currently generate around 25% of the annual revenue for the pharmaceutical industry [1]. Unsurprisingly, the strategy has thus been integrated in the life cycle management of pharmaceutical products. Public and non-for-profit organizations have released specific programs to promote drug repurposing initiatives (see, for instance, the successful *Discovering New Therapeutic Uses for Existing Molecules* initiative launched by the NIH–National Center for Advancing Translational Sciences in partnership with several pharmaceutical companies [2]). Moreover, a myriad of small, drug repurposing-focused companies have been created in the last 20 years [1,3]. The increasing interest in drug repurposing can be also realized in the evolution of related academic publications (Figure 1).

Since the new indication is built on previous knowledge, such as pharmacokinetic and manufacturing data, the drug development timeline is substantially shortened, as is the required investment. The main advantage of repurposed candidates is that it many cases they have already proven to be sufficiently safe in preclinical models and, at least, at early-stage trials in humans, thus being less likely to fail from a safety point of view in subsequent efficacy trials (unless drug–disease interactions are found). In the case of approved drugs, they have successfully passed clinical trials and regulatory scrutiny, and they have already undergone post-marketing surveillance.

In principle, if dose compatibility is found (i.e. the required strength for the new indication is equal or lower than the one used for the original indication) [4], much of the preclinical testing, safety assessment, and even phase I clinical trials might be bypassed, as only efficacy for the new indication should be now confirmed at preclinical and clinical levels.

Most of the successful and best-known drug repurposing stories (e.g. sildenafil, minoxidil, aspirin, valproic acid) have emerged, if not from serendipitous observations, from unorganized ('field') discovery processes, often relying on the already known pharmacology of a drug (e.g. an off-target adverse effect) to solve a clinical problem from another domain [5,6]. In recent years, though, the drug discovery community has committed to the implementation of organized, systematic, data-driven drug repurposing approaches, which in most cases integrate computational assistance [5,7,8]. Among them, we may mention signature matching of transcriptomic or proteomic data; molecular similarity approximations; structure-based virtual screens and; systematic analysis of electronic health records and clinical trial and post-marketing surveillance data.

Here, we will briefly cover what, from our perspective, are the most significant challenges and opportunities in drug repurposing.

2. Drug repurposing challenges

2.1. Intellectual property and economic considerations

There are some legal aspects that could impair patenting a new medical use and/or the enforcement of patent rights, thus diminishing the incentives for drug repurposing. First, some national legislations impede obtaining a patent for second or further medical uses (although, it is possible to protect a repurposed medical use in most of the major pharmaceutical markets). Second, many potential repurposing uses have already been reported in the specialized literature or are already being exploited in the clinical practice as off-label, non-registered uses [8]. Even if such uses have still not been endorsed by controlled clinical trials, the information is already in the public domain and affects novelty and, consequently, patentability.

For drugs that are off-patent, a patent for the new indication can be obtained but enforceability could become an issue if the new indication makes use of already available strengths and dosage forms. Therefore, whereas using the same strengths than were marketed for the original indication might be useful to exploit some of the advantages of drug repurposing, an ideal situation would be than the new indication required non-marketed strengths (preferably, lower than the previously

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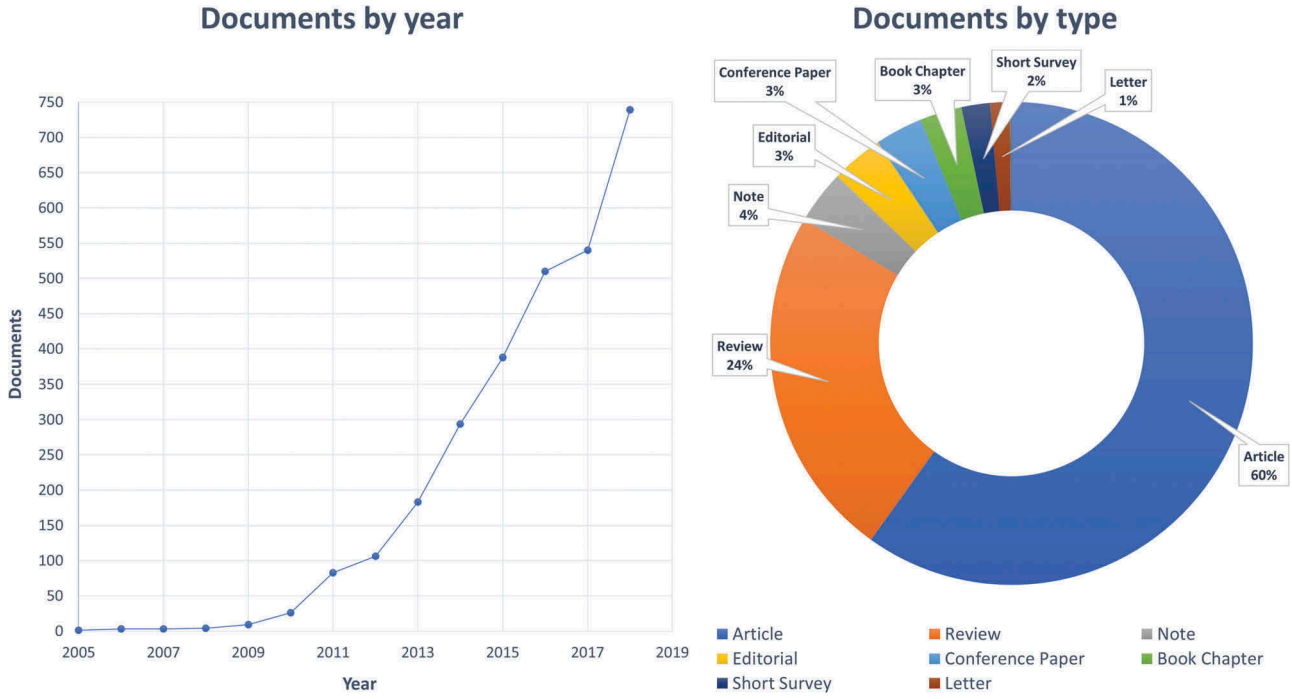

Figure 1. Number of scopus-indexed publications containing the terms 'drug' and 'repurposing' or 'drug' and 'repositioning' in their title, abstract or keywords, versus year of publication. 3.3k publications were retrieved (left). Distribution of the publication types (right). 68% of the retrieved documents correspond to original articles.

available ones) or that it required a unique, new formulation [8,9]. Newer derivatives are not a valid option here, since changing the drug molecule implies stepping away from the repurposing strategy.

Regarding exclusivity, the European Union usually provides 8 years of data protection plus 2 years of market exclusivity; if a second indication is developed by the originator during the 8-year data exclusivity period, an additional year of protection may be granted; on their part, the United States grants an initial period of 5 years which might be expanded by 3 years for a new use [10]. Nevertheless, such extra periods might not constitute an appropriate time to make an acceptable return of investment, with additional economic incentives being required to make drug repurposing cost-effective.

2.2. Data and compound availability

Whereas the open-source model is progressively gaining ground within the drug discovery community [11], public access to certain types of (valuable) data (e.g. clinical trials) is still limited. Even if accessibility was not an issue, some types of data are less friendly to data mining, integration and manipulation (e.g. imaging data) or are sometimes offered in a non-standardized manner [8]. Integrating different types of data has also proven computationally demanding as it increases the power of analysis [12].

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

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

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

2.3. Can the repurposing space be exhausted?

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

For example, several high-throughput screens directed to the identification of trypanocidal repurposed drugs with possible applications as treatments for Chagas disease have been reported throughout the years (see, for example, refs [13–16]), and this without taking into consideration previous low-throughput screens [17,18] and in silico screens or wet screens focused on specific drug targets and comprising experimental validation of the hits (see, for instance, refs [19,20]). A valid

question that emerges is how many more repurposed-oriented phenotypic screens focused on *Trypanosoma cruzi* would be justified. By the same token, we could ask if enthusiasm in drug repurposing would decay gradually as successive systematic screens on collections of known drugs are executed.

An immediate answer would be that the strategy could be redirected to unexplored target disorders. The possibilities of drug repurposing may be amplified if instead of potential repurposed monotherapies, drug combinations are examined, a strategy that is already bearing fruit in the field of infectious diseases, as exemplified by the approval of nifurtimox–eflornithine combination therapy for second-stage African trypanosomiasis [21]. Precision and system medicine, each in its own way, also offers a whole new prospect to expand the scope of drug repurposing, as discussed in the next sections.

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

3. Drug repurposing opportunities

3.1. Rare and neglected conditions

Drug repurposing is a particularly attractive approach for rare and neglected conditions, where the economics for developing a drug are unfavorable, explaining why academics and non-for-profit organizations have a predominant role in the drug discovery process for those diseases, and why specific regulatory measures and public policies encourage research into these types of disorders. Such measures include tax waiving, fast-track approval, grants and regulatory fee waivers [8]. Noteworthy, a considerable fraction of the Drug for Neglected Diseases initiative (DNDi)'s portfolio undergoing clinical trials corresponds to repurposed drugs, including fexinidazole, fosravuconazole, Ambisome™, and miltefosine. In fact, fexinidazole is the first oral-only drug, with the potential for treating advanced-stage sleeping sickness, approved in 30 years [22], and DNDi spent only USD 62.5 million in its development, in contrast with the estimated 1 to 3 billion dollars for a *de novo* drug. Interestingly, some of the commercial barriers to drug repurposing (concerns regarding off-patent drugs) are not as important when addressing neglected conditions, since investigations of therapeutic solutions for such disorders are not driven by profit expectancies. What is more, repurposing a low-cost, off-patent drug might even be desired to assure accessibility.

In the case of rare diseases, whose pathophysiology is often poorly characterized, computational techniques for predictive repurposing offer a quick way of identifying testable hypotheses that may be translated into the clinic, with large-scale genome-sequencing initiatives contributing to identify the genetic variation/s responsible for the disorder, and opening up opportunities to rapidly repurpose drugs that target the correspondent protein/s [8].

3.2. Precision medicine

Precision medicine is an emerging approach that considers individual variability in genes, environment, and lifestyle for each person to decide on or pursue an appropriate treatment [23]. It is increasingly clear that some disorders with common traits that in the past were characterized as a single condition actually comprise a spectrum of diseases and that more effective and/or safe medications could be found if tailored to variations in an individual's genome, transcriptome, proteome, and metabolome, or to specific types of a general condition.

The positive outcome of such approaches is already being realized in the field of oncology. For instance, a recent case report on a patient with metastatic colorectal cancer, treatment-related toxicity, and resistance to chemotherapy and radiation [24] seems particularly relevant in relation to drug repurposing. The patient underwent immunohistochemical analysis for expression of the MMR proteins MSH2, MSH6, PMS2, and MLH1 and the V600E mutant BRAF protein. Whole-genome sequencing was carried out on the pretreatment tumor and blood, and whole-genome sequencing and whole transcriptome sequencing were performed on the metastatic tumor. Whole-genome sequencing identified more than 2000 genomic alterations, including point mutations, insertions, deletions, and copy-number variations. Among the most differentially expressed genes identified through transcriptome analysis, there were the members of two proto-oncogene families, FOS and JUN. These data supported that blocking the renin–angiotensin system could provide therapeutic benefit, which led to the (hard) repurposing of the antihypertensive angiotensin II receptor antagonist irbesartan as an anticancer therapy, resulting in the patient experiencing a radical and persistent response.

3.3. Systems medicine

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

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

Furthermore, many newly identified active compounds have low potency, which limits their immediate clinical applications because the tolerated plasma drug concentrations are lower than the effective ones. Synergistic drug combinations are an alternative approach to increase the success rate of drug repositioning, as they may lower the required therapeutic doses in comparison with monotherapies [25].

3.4. Collaborative models

There is increasing realization that pharmaceutical companies and academics can contribute in a highly complementary manner to the discovery of novel repurposing prospects. Pharmaceutical companies have highly valuable (though often idle) chemical libraries of failed or shelved drug candidates, and they have a first-hand experience on translational research and clinical development. Furthermore, they can provide access to screening technologies that are difficult to acquire and maintain for most of academic institutions. Biotechnology companies and academics possess valuable knowledge on emerging areas of disease biology, which may lay the foundation for highly innovative medications. Non-negligible byproducts of such type of collaborations include human capacity development and exchange [11]. From an intellectual property perspective, some options that can be explored include patent pools, open licensing for drug development targeting neglected or rare diseases and allowing participation of academic institutions and staff into the patent ownership for new medical uses. New collaboration and business models are arising to bridge stakeholders, including new funding models that welcome venture capitals, public funding, and non-for-profit organizations. Such models might greatly impact in certain fields of medicine (e.g. rare disorders) where drug repurposing plays a prominent role.

4. Expert opinion

The relevance of drug repurposing in the pharmaceutical sector has been progressively growing in the recent years, with about one-third of approvals corresponding to repurposed drugs, some of which have even achieved blockbuster status.

The successful drug repurposing stories have paved the way for new models of collaboration between the public and private sectors, a virtuous partnership which, in our opinion, is far from having reached its highest point yet. Government agencies and organizations have the tools to elaborate solutions to overcome some of the legal and commercial barriers faced by drug repurposing projects. On their part, pharmaceutical companies have the invaluable (though sometimes idle or underexploited) capital of their proprietary chemical libraries, including failed and shelved drug candidates which may be rescued to address unmet medical needs (prominently, rare and neglected conditions). Moreover, pharmaceutical sponsors and government agencies and other stakeholders also possess access to restricted, crucial information emerging from clinical trials, which may imply a quality leap for the drug discovery community if allowed into the public domain. Possibly, open collaboration models bridging academy with private partners (non-for-profit organizations and industry) will continue to grow, as drug rescue poses excellent, cost-efficient opportunities to commercially exploit abandoned drug projects and maximize the benefits of pharmaceutical companies' portfolios.

Once and again, drug repurposing has been advocated as an interesting strategy to explore new pharmaceutical solutions for rare and neglected conditions (in fact, many of the available medications for such conditions can be regarded as repurposed drugs). The pursue of pharmaceutical solutions for rare and neglected disorders, whereas maybe not particularly profitable in purely economic terms, does imply other forms of value, such as corporate social responsibility and the consequent increased social awareness/perception of pharmaceutical companies. Social responsibility involves sustaining the equilibrium between economic development and the welfare of the society and environment; one of its goals is, thus, helping to eliminate or reduce barriers such as financial condition. Government organizations, on their part, also have the means to promote such initiatives though different economical incentives: it is, then, essential to gain and generate awareness that economic loss due to rare and neglected conditions greatly exceeds the required investment to develop new therapeutic solutions.

Systems and precision medicine are possibly the two fields that show greater prospects for drug repurposing.

Network pharmacology underlines the possible advantages of polypharmacology to treat complex disorders. The paradigm is also showing promise in the field of infectious diseases. In complement with metabolic control analysis, this holistic approach to drug discovery allows a rational choice of drug target combinations and, therefore, of repurposed drug combinations. Often, hits emerging from systematic screens are only moderately potent (usually, in the low micromolar or sub-micromolar range), which, in the case of drug repurposing, greatly limits the perspectives for repurposed drug candidates: whereas de novo drug discovery can exploit hit-to-lead and lead optimization programs to gain potency and balance pharmaceutically desirable properties, repurposed candidates, by definition, cannot be optimized without losing the repurposing advantages. Synergistic drug combinations of repurposed drugs offer a way to exploit moderately potent repurposed hits for new indications.

On the other hand, as precision medicine will deepen the characterization, understanding, and classification of disease (e.g. uncovering disease subtypes) new drug repurposing prospects will be uncovered, revitalizing the field.

In parallel, technological advances are required to efficiently extract and integrate heterogeneous large-scale data, such as imaging and structural data or clinical trial documentation, electronic health records, etc.

Funding

The authors are supported by the Fondo para la Investigación Científica y Tecnológica (FONCyT), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT).

Declaration of interest

The authors are members of the Argentinean National Council of Scientific and Technical Research Council (CONICET) and researchers at the National

University of La Plata (UNLP). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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