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Drug Repositioning: Concept, Classification, Methodology, and Importance in Rare/Orphans and Neglected Diseases

Emanuel Almeida Moreira de Oliveira[1], Karen Luise Lang[1,2]*

[1]Department of Pharmacy, Federal University of Juiz de Fora – Governador Valadares, MG, Brazil.
[2]Multicenter Program in Biochemistry and Molecular Biology, Federal University of Juiz de Fora – Governador Valadares, MG, Brazil.

ABSTRACT

The development of new drugs is a long and complex process, with extremely high investment and small expectation of success. In recent years, there was a significant decline in the number of new drugs approved for clinical use, notwithstanding powerful tools were developed to support the research and development (R&D) process. Drug Discovery programs are pursuing strategies that optimize the R&D process. Among them, we highlight the drug repositioning as an approach that seeks new therapeutic applications for already approved drugs, different from its initial indication. This strategy is aimed to reduce costs and research time considerably. There is a limited commercial interest in the development of drugs for the treatment of rare/orphans and neglected diseases, due to the onerous nature, the associated risk and low return on investments in R&D. Thus, repositioning is important, due to the advantages over traditional approaches, to an area that has historically suffered from limited resources and an enormous need for effective therapies. Herein, this review discussed recent data about drug repositioning as an important strategy for the development of new therapies for the treatment of rare/orphans and neglected diseases.

INTRODUCTION

The development of a drug is a long and complex process, with extremely high investment and small expectation of success (Kaitin, 2010; Scannell *et al*., 2012). Currently, it is estimated that an average of $1.4 billion will be spent on the entire research and development (R&D) process, in the course of 10 to 17 years, resulting in a registration dossier of up to 300 thousand pages (Lombardino and Lowe, 2004; Alex *et al*., 2016).

The traditional research and drug development process can be simplified into two major steps: (i) preclinical and (ii) clinical. In the first one, the basic research is developed focused mainly on the identification and optimization of molecules, determination, and validation of a specific molecular target and the knowledge of pharmacological and toxicological aspects through *in vitro* tests and *in vivo* models (Lombardino and Lowe, 2004; FDA, 2015). In this step, the main objective is to obtain

a new chemical entity (NCE) - a molecule not yet described in the literature that has an active portion capable of triggering a physiological/pharmacological action (Branch and Agranat, 2014; FDA, 2015). The second major step - the clinic, is subdivided into 4 phases. The first clinical stage is phase I, conducted in volunteers with the aim of assessing the human tolerance of the new drug candidate and measuring their safe dosage (Brunton *et al*., 2012). Phase II consists mainly of evaluating efficacy and safety in the treatment of a specific pathology and it is essential for the continuity of the studies. Likewise, phase III assesses toxicity and safety, however, in a larger number of patients, with a number of volunteers close to the population in which the drug is intended. Furthermore, a comparison is made between the new treatment and the existing standard treatment (Katzung *et al*., 2014; FDA, 2015). In phase IV, also called pharmacovigilance, the new drug is already approved. The objective of this phase is a long-term evaluation of some parameters that, most of the time, are not observed in previous phases, such as adverse reactions, side effects and drug interactions (Brunton, 2012; FDA, 2015).

Despite the high investment and great efforts employed, few molecules achieve promising results. Statistically, in a

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Corresponding Author
Karen Luise Lang, Federal University of Juiz de Fora, Mailing address:
Manoel Byrro, 241, ZIP 35032-620, Governador Valadares, Minas
Gerais, Brazil. E-mail: karenluise @ gmail.com

screening of one million potential drug candidates, only one has a profile to entry in clinical studies, still susceptible to a significant number of failures. Currently, the main developmental failure in the clinical stage occurs in phase II and phase III is associated mainly with safety and efficacy (Arrowsmith, 2011a; Arrowsmith, 2011b; Harrison, 2016).

Over the past 60 years, powerful tools have been developed that directly support the development of new drugs, such as molecular biology, biotechnology, DNA sequencing, databases of three-dimensional protein structures and combinatorial chemistry (Blundell et al., 2002; Lombardino and Lowe, 2004). However, there is a significant decline observed in the number of new drugs approved for clinical use in recent years, showing a discrepancy in the face of scientific advances and R&D investments. In the world's largest pharmaceutical market, the North American, the number of new drugs approved by the Food and Drug Administration (FDA), despite billions of dollars spent on R&D, falls by half every nine years (Scannell et al., 2012).

As a result, Drug Discovery programs are pursuing strategies that optimize the R&D process. Among them, we highlight the drug repositioning (DR) - an approach that seeks new therapeutic applications for already approved drugs, different from its initial indication. This strategy is intended to reduce costs and research time considerably when compared to traditional R&D methods (Ashburn and Thor, 2004; Ekins et al., 2011).

In recent decades there has been a continuous increase in the incidence of chronic diseases, such as diabetes and hypertension, and a greater interest of the pharmaceutical companies in the development of therapies for the treatment of these diseases. Consequently, there is less investment in the development of drugs for the treatment of rare, orphan and neglected diseases because they often have a lower economic return (Robertson and Renslo, 2012; Berenstein et al., 2016). According to the World Health Organization (WHO), approximately 1 billion people are affected by neglected diseases and 420 to 560 million by rare diseases (WHO, 2017a). Some global initiatives such as the WHO special program *Tropical Disease Research* aims to encourage research and innovation in the development of medicines to improve the health and well-being of populations affected by neglected diseases.

This paper provides a non-exhaustive review of recent data about DR as a systematic, safe and effective strategy inside the drug R&D process, aiming to understand concepts, methodologies, advantages, challenges and relevance in the development of new therapies for rare, orphans and neglected diseases.

DRUG REPOSITIONING

DR (or redirection) can be defined as a process of identification and discovery of new therapeutic uses, outside the scope of the original pharmacological indication, for already approved drugs. However, it is common to find difficulties in conceptualizing the DR, since it is a new term and its definition is often ambiguous and unclear (Ashburn and Thor, 2004; Li et al., 2011; Oprea and Mestres, 2012; Langedijk et al., 2015). Some definitions include drug candidates or abandoned drugs, as described by Padhy and Gupta (2011) and Allarakhia (2013) were repositioning have been the search for new therapeutic indications for existing drugs or drug candidates that did not demonstrate efficacy for their particular indication in the phase II or phase III trials, but have a known pharmacological and toxicological profile, including drugs with expiring patents.

In view of the inconsistency of terminologies found in the literature, Murteira et al. (2013) proposed a harmonized nomenclature for DR: (i) repositioning, (ii) reformulation, and (iii) combination. Repositioning is defined as the process of discovering new therapeutic indications for drugs, drugs candidates or abandoned drugs, other than the indication previously approved or intended, considering the 10th version of the International Classification of Diseases (ICD-10), except for the situations in which the new use is similar to the initial indication with different pharmacological targets. The reformulation consists in the development of new formulations for medicinal products by exploiting technological advances towards the release of active substances, pharmaceutical forms, and routes of administration. The latter approach, however, is determined as the combination of one or more drugs previously used as separate pharmaceuticals and is a strategy for recurrent drug reuse in repositioning (Murteira et al., 2013).

Although the methodology has long been known, the use of the term DR, as a strategy in R&D for new therapies could not be found in the literature before 2004 (Langedijk et al., 2015). Nevertheless, it is possible to observe the practice of this strategy in the late 1990s, with the repositioning of thalidomide. This drug was responsible for one of the biggest tragedies of medicine in the 1960s when it was widely used as antiemetic for pregnant women. Thalidomide has a teratogenic form, and as the drug was used in the racemic mixture, the result was the birth of children with congenital deformities, being withdrawn from the market in that same decade (Vianna et al., 2017). However, Sampaio and coworkers (1991) demonstrated that thalidomide plays an essential role in the selective inhibition of tumor necrosis factor (TNF-α), cytosine found in elevated levels in leprosy patients. FDA approved the drug for the treatment of erythema nodosum leprosum, a serious and debilitating condition associated with leprosy, in July 1998 based on these studies (Vianna et al., 2017). Thalidomide was again repositioned for the treatment of refractory multiple myeloma, the use is regulated in Brazil by The Brazilian Health Regulatory Agency (ANVISA), in 2000 (Singhal et al., 2000; Ashburn and Thor, 2004; Brazil, 2000; Brazil, 2011).

Another important example, which also occurred in the 1990s, was the repositioning of sildenafil. The drug entered clinical studies for its potential antianginal effect, but cardiovascular effects were unsatisfactory and several volunteers reported unusually strong and persistent erections during their use. Sildenafil (Viagra®) was approved in the following years and became a blockbuster in the treatment of erectile dysfunction (Boolell et al., 1996; Ashburn and Thor, 2004). In this case, a repositioning of a drug candidate was observed, which at the time was not classified in this way. Currently, sildenafil has been repositioned again, being used as an orphan drug in the therapy of severe pulmonary hypertension (Galiè et al., 2005; Velayati et al., 2016).

ADVANTAGES AND CHALLENGES

Repositioning has several advantages in comparison with traditional approaches to drug development. A repositioned

drug does not need the initial six to nine years typically required for the development of new drugs, but instead goes directly to preclinical testing and clinical trials, thus reducing risk and costs. At the start of a repositioning project, a range of toxicological, pharmacological and clinical safety information is already available, as candidates have now gone through some stages of development such as structural optimization, preclinical and/or clinical trials, in addition to the possibility of the candidate being an approved drug, having its clinical safety already been attested by the time of use (Ashburn and Thor, 2004; Padhy and Gupta, 2011; Oprea and Mestres, 2012; Novac, 2013; Zheng *et al.*, 2017).

In this way, there is a reduction of the risks associated with failures in the early stages of development, which are high in traditional approaches, as well as a significant cost reduction and a possible increase in clinical safety.

When comparing traditional drug discovery programs with others using DR, a significant reduction of the time spent in R&D can be observed. In traditional approaches, it is estimated that 10 to 17 years are spent for the development of a new drug, while in DR the estimated time is between 3 to 12 years (Figure 1) (Ashburn and Thor, 2004; Vora *et al.*, 2016).

Fig. 1: A comparison between traditional approaches *versus* DR for drug discovery and development Ashburn and Thor (2013), adapted.

However, the DR faces some challenges: new preclinical and/or clinical trials may be necessary if the available data are not satisfactory, outdated or do not meet the requirements of regulatory agencies such as ANVISA, FDA or the European Medicines Agency (EMA) (Ashburn and Thor, 2004; Padhy and Gupta, 2011). Another recurrent obstacle is the low potency or high toxicity of the drugs in view of the new therapeutic indications, as the known and tolerated concentrations of the drugs are lower or higher than the required therapeutic concentrations. The use of combinations of two or more drugs with different mechanisms of action is an alternative that can help the success of DR (Sun *et al.*, 2016; Zheng *et al.*, 2017).

The development of a new pharmaceutical is very time consuming, extremely costly and high risk. Therefore, a market exclusivity period is required to achieve a return on investment commensurate with the risks. There are basically two means to achieve market exclusivity: through patents or granted by regulatory agencies (Barratt and Frail, 2012).

Some regulatory and intellectual property/patent barriers make DR difficult. For example, in the United States, where the patent

for a medicinal product is valid for up to 20 years, only the patent owners have the autonomy to change or insert any data in the leaflet, repositioning the drug while it is in force (Smith, 2011; Murteira *et al.*, 2011). Often, potential DR is already known in the scientific literature or in clinical practice with *off-label* use, and even though it has not been approved by regulatory agencies, it can no longer be patented, since there has been widespread public knowledge (Ashburn and Thor, 2004; Smith, 2011; Murteira *et al.*, 2014).

The repositioning of old drugs that do not have patent owners becomes uninteresting for pharmaceutical companies, as they do not promote significant financial returns. Registering a patent source for a repositioning that has generic drugs does not guarantee a period of exclusivity in the market, once these drugs are widely available to many manufacturers. In addition, there is the possibility of an *off-label*, use for an indication other than that authorized by the competent regulatory body, and *skinny-label*, when the applicant for generic medicine requests a marketing authorization and excludes product information relating to indications or pharmaceutical forms protected by patents (Witkowski, 2011; Barratt and Frail, 2012).

However, there are some regulatory strategies that make DR an attractive approach to pharmaceutical companies, as patent extension and regulatory exclusivity period for the new product, protecting its new formulation, indication or methods of use, even when the original product has already lost its protection patent for the active pharmaceutical ingredient, formulation and/or indication (Smith, 2011; Witkowski, 2011; Murteira et al., 2014).

Repositioning a non-orphan drug for an orphan disease is an excellent example of attractive development, with good periods of regulatory exclusivity (7 years in the United States, 10 years in the European Union and Japan), tax credits of 50% in development costs, R&D grants and incentives, FDA's rapid approval profile and dispensing of drug application fees. In Brazil, no information related to repositioning was found on ANVISA website and in the literature, showing the need for updating regarding the regulation of repositioning/repurposing of drugs and medicines in the country (Smith, 2011; Barratt and Frail, 2012).

Pharmaceutical companies specialized in DR often face recurring problems like the lack of specialists in the field, technology and market issues facing large pharmaceutical companies. An example of success was the repositioning of mifepristone for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance, by Corcept Therapeutics, which is specialized in repositioning (Fleseriu and Petersenn, 2012; Novac, 2013).

There is a political, social and economic dimension involved in DR and the discovery of new therapies. Success in the pharmaceutical market does not depend exclusively on efficient or effective therapy, but also on market factors, the intended indication of the drug and the characteristics of the target population (age, socioeconomic condition, access to pharmaceutical and medical care) that directly implicate on the final value of the new therapy. As a result, efficient repositioning does not directly mean a commercially successful drug.

DR PROFILES

The DR has two profiles: *on target* and *off target* (Figure 2). In the first one, the known pharmacological mechanism of a drug or drug candidate is applied to new therapeutic indications, i.e., they are molecules that act on the same biological target in the treatment of different diseases (Barratt and Frail, 2012; Koch et al., 2014). One example is the repositioning of finasteride for the treatment of male pattern baldness (Vora et al., 2016). This drug was originally developed for the treatment of benign prostatic hyperplasia because its mechanism of action leads to a reduction in the bioavailability of dihydrotestosterone - a biologically active metabolite of testosterone, the hormone responsible for normal and abnormal prostate growth - by the inhibition of the 5-α-reductase enzyme. The bioavailability of dihydrotestosterone in the scalp is also reduced with the use of finasteride, leading to inhibition of miniaturization of the hair follicle and helping in the treatment of male pattern baldness (alopecia). In the repositioning of finasteride, an *on-target* profile is observed, since the drug acts on the same target and produces two different therapeutic effects (Ashburn and Thor, 2004; Vora et al., 2016; Würth et al., 2016).
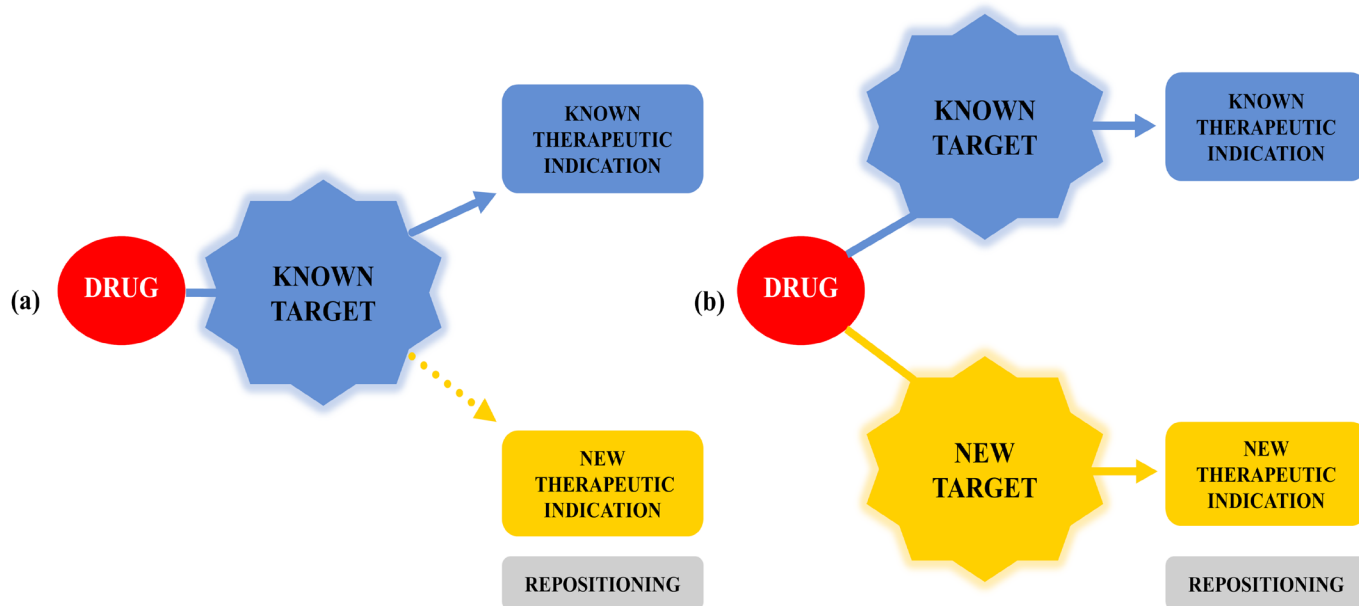

Fig. 2: DR profiles: *On target* (a) profile where a known pharmacological mechanism of a drug or drug candidate is applied to new therapeutic indications and *off target* (b) profile where the pharmacological mechanism is unknown and the drugs act on new targets, out of the original scope, for new therapeutic indications.

In the *off-target* profile, the pharmacological mechanism is unknown. Drugs and drugs candidates act on new targets, out of the original scope, for new therapeutic indications. Therefore, both the targets and the indications are new (Koch et al., 2014; Vora et al., 2016; Würth et al., 2016). These repositioning, in the main, are discovered through the serendipity and several computational strategies using different databases, algorithms, molecular coupling, among

others. Thalidomide, described above, is an excellent example of the *off-target* profile.

MAIN METHODOLOGIES USED FOR REPOSITIONING

The methodologies applied in repositioning can be divided into three groups: (i) drug-oriented, (ii) target-oriented, and (iii) disease/therapy-oriented. The type of guidance in which the methodologies are applied depends mainly on the quantity and quality of the pharmacological, toxicological and biological information (Jin and Wong, 2014).

In the drug-oriented methodologies, the structural characteristics of the molecules, *off-label* use data, adverse effects and phenotypic screening are evaluated (Jin and Wong, 2014). This screening is a strategy for identifying molecules with biological effects in cell/animal assays in order to identify compounds that cause some desirable change in a particular phenotype (Moffat *et al.*, 2017). This type of guidance is based on traditional pharmacology, where little data is available and only after the discovery of activities against phenotypes studies are conducted to determine the biological targets related (Swinney, 2013; Jin and Wong, 2014; Moffat *et al.*, 2017). The greatest DR successes to this date have been obtained with this orientation profile, through serendipity or clinical observation, such as sildenafil, previously discussed. This process can be considered a blind research approach, i.e., the discovery of new indications occurs randomly, especially during clinical R&D trials (Ashburn and Thor, 2004).

Target-based DR methods comprise *in vitro* and *in vivo* high-throughput and/or high-content screening (HTS/HCS) of drugs for a protein or a biomarker of interest and *in silico* screening of drugs or compounds from drug libraries such as ligand-based screening or docking (Kolb *et al.*, 2009; Jin and Wong, 2014; Li *et al.*, 2016; Bellomo *et al.*, 2017). Compared with drug-oriented methods, targeted-based methods significantly improve the likelihood of drug discovery because most targets link directly with the disease mechanisms (Swinney, 2013; Jin and Wong, 2014).

On the other hand, if there is more disease information available, DR can be guided by diseases and/or treatments. This information is given by proteomics, genomics, metabolomics or data concerning how drugs modulate phenotypes in diseases, e.g., knowledge of adverse and side effects with possible *off-target* mechanisms. The main methods applied here are computational such as network and pathway analysis. They consist of construction of specific disease networks, considering key targets, identifying proteins related to cell and metabolic pathways of interest. These methods help to understand the omics data, allowing the discovery of pathways of diseases and their possible pharmacological targets (Liu *et al.*, 2013; Li and Lu, 2013; Jin and Wong, 2014; Jadamba and Shin, 2016; Berenstein *et al.*, 2016; Wu *et al.*, 2017).

The DR methods based on signature genes are disease-driven and use disease-specific genetic data with or without treatments, for the discovery of *off-target* mechanisms or unknown pathological mechanisms. In addition, there are methods based on chemoinformatics and bioinformatics knowledge, integrating a large amount of data available for diseases and drugs such as adverse effects, *off-label* use, target drug networks, drug chemical structures, omics data, among others. These methods include a large amount of known information that can improve the DR

process (Dudley *et al.*, 2011; Iorio *et al.*, 2013; Jin and Wong, 2014; Wu *et al.*, 2017).

It is important to highlight available free databases that provide free access to essential data in repositioning strategies for pharmaceutical companies and academic research centers. Some of these databases focus on neglected diseases, such as the TDR Targets database (http://tdrtargets.org), which explores the availability of genomic and chemical data to facilitate the identification and prioritization of drugs and targets in neglected disease pathogens (Magariños *et al.*, 2012). Another important database is TriTrypDB (http://tritrypdb.org/tritrypdb/) which has a large amount of genomic and functional data integrated for pathogens of the Trypanosomatidae family, including organisms of the genus *Leishmania* and *Trypanosoma*, responsible for leishmaniasis and Chagas disease (Aslett *et al.*, 2010; Silva *et al.*, 2015; TDR, 2017; TritryBD, 2017).

The computational and systematic methodologies offer a robust and logical approach to the discovery of new indications, demonstrating a greater efficiency than the processes based on serendipity. These methodologies offer a rational and exhaustive exploration of all possible repositioning opportunities, taking into consideration improved access to high-quality data, analytical capacity and technological advances.

NEGLECTED TROPICAL DISEASES

Neglected tropical diseases (NTDs) are a diverse group of communicable diseases that prevail in tropical and subtropical conditions affecting more than one billion people. Populations living in poverty, without adequate sanitation and in close contact with infectious vectors and domestic animals and livestock are those worst affected (WHO, 2017b; Peeling *et al.*, 2017).

Available treatments for NTDs have several limitations, such as cost, safety profile and/or efficacy poorly established and possible drug resistance mechanisms. In addition, there is a limited commercial interest in the development of drugs for the treatment of these conditions, due to the onerous nature, the associated risk and the low financial return on investments in R&D (WHO, 2017a; Berenstein *et al.*, 2016).

For this reason, development of therapies for these diseases becomes increasingly necessary. It reaffirms the importance of repositioning in the development of these therapies, mainly because of the advantages over traditional approaches, such as a significant reduction of costs, risks, and an improvement in safety and efficacy profiles for an area that has historically suffered from limited resources and an enormous need for effective therapies (Ashburn and Thor, 2004; Ekins *et al.*, 2011; Berenstein *et al.*, 2016).

There are some successful DR on DTNs. Miltefosine, repositioned for the treatment of visceral leishmaniasis was initially an antineoplastic compound, but during phase II clinical trials, the drug did not show satisfactory activity, being limited to topical treatment of cutaneous metastases (Barratt and Frail, 2012; Verhaar *et al.*, 2014). The antileishmanial activity was described in 1987 and miltefosine was the first effective oral treatment for cutaneous and visceral leishmaniasis (Machado *et al.*, 2010; Padhy and Gupta, 2011; Barratt and Frail, 2012).

Another important DR on DTNs was amphotericin B, a drug used for the treatment of systemic fungal infections and

repositioned for the treatment of visceral leishmaniasis. This approval was supported directly by the Phase IV clinical safety data accumulated by the time of use of amphotericin B as an antifungal (Padhy and Gupta, 2011; Barratt and Frail, 2012).

Another repositioning can also be highlighted as antibacterial (dapsone, sulfadoxine), tetracyclines (doxycycline) and the combination of trimethoprim/sulfamethoxazole and fluoroquinolones in the treatment of malaria and tuberculosis (Nzila et al., 2011; Barratt and Frail, 2012).

Nowadays, several studies have reported promising results regarding repositioning aided by computational tools such as target-based chemogenomics screen in the development of therapies for NTDs, such as schistosomiasis (Neves et al., 2015). Other examples of a potentially promising repositioning for this disease are antineoplastic inhibitors of kinases proteins, e.g. trametinib, vandetanib - and the HMG-CoA reductase inhibitor drugs, e.g. atorvastatin (Rojo-Arreola et al., 2014; Cowan and Keiser, 2015).

Brazil is affected by several NTDs, but a current concern is with viral diseases such as dengue, Zika, and chikungunya. Zika virus, in special, is associated with severe birth defects and Guillain-Barré syndrome (Cao-Lormeau et al., 2016; Miranda-Filho et al., 2016; Mlakar et al., 2016). To date, no antiviral agents have been approved for treating Zika virus infection. However, two recent drug-repurposing studies (Tabata et al., 2016; Xu et al., 2016) demonstrated that screening FDA-approved drugs for antiviral activity is a promising strategy for identifying therapeutics with novel activity against Zika virus infection. Recent works have identified promising activities of sofosbuvir (SOF), currently approved by the FDA for the treatment of hepatitis C. This drug targets viral RNA polymerase, a common protein among Zika virus and hepatitis C virus (Mesci et al., 2018). It has been shown that SOF present protective activity for human neuronal progenitor cells and a reduction of viral load both in vitro and in vivo (Sacramento et al., 2017; Ferreira et al., 2017; Mesci et al., 2018). Besides, the work of Simanjuntak and co-workers (2015) evidences the promising repositioning of prochlorperazine, a dopamine D2 receptor antagonist approved to treat nausea, vomiting, and headache in humans that has potent in vitro and in vivo antiviral activity against dengue virus infection, by targeting viral binding and viral entry.

RARE OR ORPHAN DISEASES

There are an estimated 7000 rare diseases in the world. Considering them individually they reach a small number of people, however together they affect between 6% and 8% of worldwide population. There are many concepts for rare or orphan diseases (RD), but they have one key point in common - a group of diseases that affect a small portion of the population (Ekins et al., 2011; NIH, 2017; Orphanet, 2017).

In the United States, the Orphan Drug Act (1983) defines RD as any disease or condition that affects less than 200.000 people. In Japan, a disease is considered rare when affects less than 50.000 patients (Tambuyzer, 2010; Barratt and Frail, 2012; Richter et al., 2015). The European Commission on Public Health (2016) defines rare diseases as potentially fatal or chronic, mostly hereditary, affecting a small number of people, approximately 1 in 2000. In Brazil, the National Policy of Integral Attention to People with Rare Diseases ordinance was approved, considering

rare those that affects up to 65 people in every 100.000 individuals (Brazil, 2014). This ordinance can be considered a milestone in the health care of patients with rare diseases in the country.

Often the concept of rare diseases is mistaken for that of neglected tropical diseases mainly by the sanitary laws of some countries, which use the term "orphan medicine" to designate treatments of a rare disease as well as the NTD. These drugs are designated as orphans because under normal market conditions, pharmaceutical companies have little interest in development and marketing due to the small number of individuals affected (Ekins et al., 2011).

The development of drugs for the treatment of rare diseases faces major challenges since the low number of individuals affected and the large geographic distribution can make clinical trials invalid or difficult. Another recurring problem is the great heterogeneity among diseases, being mostly influenced by genetic factors. Besides, there is a long period of development, high costs, and extremely low success rates, reaching a group of extremely specific and reduced patients, not bringing a financial return on investments and R&D (Sardana et al., 2011; Augustine et al., 2013; Hee et al., 2017).

In view of this, DR is an interesting strategy, given the possible prior knowledge of safety profiles, bioavailability, tolerance in humans and some pharmaceutical and pharmacodynamic aspects, which can significantly reduce the risks associated with drug development and potentially facilitate the beginning of clinical trials, with reduced investment costs when compared to traditional approaches (Ekins et al., 2011; Barratt and Frail, 2012).

The relevance given to the repositioning of drugs in rare diseases can be observed in the incentives offered by the governmental entities of some countries for the pharmaceutical and biotechnology industries. Influencing R&D of drugs in the treatment of these diseases, providing reductions in fees for regulatory procedures, regulatory assistance, market exclusivity, among other benefits mentioned before (Li and Jones, 2012; Murteira et al., 2014).

CONCLUSION

Repositioning is an approach that has been used for a long time, but the ability to carry it out in a systematic and rational way is an innovation that can meet social and market needs. Despite this, the greatest repositioning successes still being discovered through serendipity.

It is remarkable, however the importance and advantages of DR in the development of new therapies. This approach offers lower R&D costs, greater chances of success, shorter research time and lower investment risk. These advantages are of benefit to patients and pharmaceutical companies, enabling the application of DR in rare and neglected diseases that have several limitations in traditional approaches. Thus DR can be a tool in the development of treatments for diseases that suffer historically from limited resources and a huge need for effective therapies.

FINANCIAL SUPPORT AND SPONSORSHIP

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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