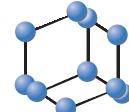


REVIEW ARTICLE

BENTHAM
SCIENCE

Drug Repurposing: An Emerging Tool for Drug Reuse, Recycling and Discovery

Supriya Roy¹, Suneela Dhaneshwar^{1,*} and Bhavya Bhasin²¹*Amity Institute of Pharmacy, Amity University Uttar Pradesh, Lucknow Campus, India;* ²*Poona College of Pharmacy, Bharati Vidyapeeth University, Pune, India*

Abstract: Drug repositioning or repurposing is a revolutionary breakthrough in drug development that focuses on rediscovering new uses for old therapeutic agents. Drug repositioning can be defined more precisely as the process of exploring new indications for an already approved drug while drug repurposing includes overall re-development approaches grounded in the identical chemical structure of the active drug moiety as in the original product. The repositioning approach accelerates the drug development process, curtails the cost and risk inherent to drug development. The strategy focuses on the polypharmacology of drugs to unlocks novel opportunities for logically designing more efficient therapeutic agents for unmet medical disorders. Drug repositioning also expresses certain regulatory challenges that hamper its further utilization. The review outlines the eminent role of drug repositioning in new drug discovery, methods to predict the molecular targets of a drug molecule, advantages that the strategy offers to the pharmaceutical industries, explaining how the industrial collaborations with academics can assist in the discovering more repositioning opportunities. The focus of the review is to highlight the latest applications of drug repositioning in various disorders. The review also includes a comparison of old and new therapeutic uses of repurposed drugs, assessing their novel mechanisms of action and pharmacological effects in the management of various disorders. Various restrictions and challenges that repurposed drugs come across during their development and regulatory phases are also highlighted.

ARTICLE HISTORY

Received: March 29, 2020
Revised: September 07, 2020
Accepted: October 26, 2020

DOI:
10.2174/2589977513666210211163711



CrossMark

Keywords: Drug reprofiling, retargeting, therapeutic switching, drug rescue, drug repositioning, polypharmacology, serological biomarkers, drug target.

1. INTRODUCTION

National Center for Advancing Translational Sciences defines drug repositioning as a novel drug development approach that uses existing scientific or medical knowledge as well as the technology already “approved” for human use in one disease and applying this knowledge to treat or manage another disease condition [1]. Other terms used for drug repositioning are drug re-profiling, repurposing, drug re-tasking, or therapeutic switching. The drug repositioning strategy includes screening the drug libraries currently approved in the market for treating one ailment and reviewing whether it can be used effectively in treating some other ailments. If a drug is effective in treating the disease symptoms outside the range of its traditional use, the information can be communicated further by health professionals to those candidates who may benefit from it [2]. There are thousands of possibilities for drugs already available in the market, which may restrict the need to synthesize, formulate, or screen any new chemical entities. Repositioning may combine an older drug with a newer drug in order to increase the efficacy of

newer drugs or there may be the permutations of available drugs already used in a specific disease but are not currently prescribed together. There may be a combination of existing drugs with a non-drug treatment option, such as radiation [3-6]. The central focus of the drug repositioning approach is on the fact that mutual molecular and pharmacological pathways may contribute to the pathophysiology of many different diseases. As the existing drug has already been tested in humans, its comprehensive information such as dosage, formulation, and pharmacological profile, including possible toxicity, is available. The drug development success rate is augmented by 250%. Also, the cost and time involved during the drug development process are significantly reduced by fifth-sixths and two-third, respectively [7, 8]. The approach towards drug repositioning originated due to two main factors that include: (i) Polypharmacology of drugs due to which they show affinity to more than one targets, eliciting efficacy in new tissues that were not formerly targeted (ii) undiscovered or unknown tissue targets, where drug molecules probably exert supplementary effects by directly activating or inhibiting their target(s) [9-12]. On this basis, drug re-profiling can be of two types:

[a] **On-target drug repositioning approach:** it includes identification of new therapeutic potential or

* Address correspondence to this author at the Amity Institute of Pharmacy, Amity University Uttar Pradesh, Lucknow Campus, India; Tel: +919850125430; Fax: 0522-2399610;
E-mail: s.dhaneshwar1@lko.amity.edu

indications of a drug acting through the originally known target and mechanism. Antidiabetic drug exenatide has been shown to target glucagon-like peptide 1(GLP-1) receptors in the brain to show neuroprotective effects in Parkinson's disease.

- [b] **Off-target drug repositioning approach:** it includes identification of new uses of a drug acting through a novel or unanticipated target. As a drug molecule, on average, may hit about 6 to 13 targets at a time, therefore this approach is largely exploited. Cardiac glycoside induces apoptosis in human tumor cells by activating transcriptional regulation of Fas ligand and inhibition of DNA topoisomerase II [13-15].

1.1. Drug Repositioning as an Emerging Tool for Drug Discovery

More than 14 years can be required for transforming any active molecule into an approved drug. Drug repositioning is an evolving field that offers new possibilities in the area of drug discovery. Drug repositioning is one of the accelerated drug development strategies that suggest the new drug discovery solutions to innumerable problems faced by pharmaceutical companies, thereby aims to reduce costs, efforts, and the long-lasting time frame and improve success rates. The repositioning has emerged during the last few years when pharmaceutical companies faced the problem of extensive drying pipelines of new drugs and nonprofit organizations pursued to develop low-cost drug discoveries. Re-profiling of old to new drugs to treat symptoms and retooling of unsuccessful compounds to focus on different disorders presents a significant approach for treating rare and newer ailments. The need to come up with economical solutions to bring new drugs to the market can be easily understood by current estimations for drug development. A survey of 30 biotechnology and pharmaceutical companies reported that the estimated cost for re-introducing a repurposed drug accounts for about 84 lacs, whereas re-introducing a new formulation of an old drug for its originally known indication costs an average 4.13 crores. As the drug that is to be repurposed must have already passed the substantial amount of safety assessments and been considered safe, the possibility of drug failure due to its side effects is also minimized. It is also reported that repurposed drugs are usually approved in the market in a much shorter time (within 3-12 years) with an approval rate of 30% as compared to new drugs that achieve only 10% of market approval [16-18].

2. CLASSIFICATION OF DRUG REPOSITIONING

Drug repositioning can be divided into three main categories:

- 1) Repositioning with a purpose
- 2) Repositioning with strategy
- 3) Repositioning with confidence

2.1. Repositioning with a Purpose

Disease-centric and drug-centric are two basic approaches to drug repurposing. Drug-centric means identifying new therapeutic indications for an existing drug. The main focus is on marketed drugs that could be repurposed to widen its applications by finding new, more efficacious, safe, and cost-effective therapies for unmet medical needs into a broader population. Disease-centric means identifying effective drugs for disease and repositioning mainly focus on complex and chronic diseases such as cancer, diabetes, inflammatory bowel disease, and AIDS, and rare and neglected diseases like psoriasis that lack long-term treatment and disease stabilization due to limited availability of safe and effective therapies and therefore new approaches need to be discovered [19].

2.2. Repositioning with Strategy

Various bioinformatics and chemoinformatics approaches have been encountered to develop a network between drug therapeutic applications and disease. Nature and Schwartz illustrated a network modeling-based drug repositioning to associate the drug with its known therapeutic indications [20]. It is anticipated that if the drugs have identical therapeutic uses, a drug-based network system can be established between them and if two disorders have allied drug remedy, a disease-based system can also be developed. Drugs that have multiple pharmacological actions and act on numerous molecular targets are more likely to be a candidate for drug repurposing [21].

Repurposing with the strategy can be further divided into two types:

- 1) Target-driven reprofiling
- 2) Genome-wide reprofiling

2.2.1. Target-Driven Reprofiling

A bio-molecular target serves as an immediate link between a disorder and a drug. Association of a drug to multiple bio-molecular targets serves as a key feature of drug reprofiling. Approaches such as molecular dynamics, QSAR modeling, and molecular docking directly aim to identify new uses of an existing drug acting through a new target. Drug-target interaction can be expanded by screening drugs against various types of cultured cells [22]. Another technique to investigate the drug-target interaction for the possible repositioning opportunities for existing drugs includes Similarity Ensemble Approaches (SEA) or *in-silico* modeling. These are utilized to check the target for definite adverse effects, toxicity, or other disorders [23-25].

2.2.2. Genome-Wide Reprofiling

One of the important repositioning approaches is to use human genome-based metrics to determine the resemblance between various disease conditions. Database such as Online Mendelian Inheritance in Man (OMIM) and Gene Expression Omnibus (GEO) enables a systematic review of the association of the genome organization with the diseases.

Protein-protein interactions provide another opportunity for drug repositioning as disease networking pathways may be identified from the protein-protein interaction analysis [26, 27].

2.3. Repositioning with Confidence

Repositioning verdicts are principally reliant on *in-vitro* and *in-vivo* wet-lab experiments along with controlled population studies. There is a persistent need to select credible repositioning drug candidates before the entire experimental endorsement takes place. Drugs of New Indications (DNI) database currently contains data of 240 drugs with original and new therapeutic indications with supplementary chemical and target information that is obtained from the drug repositioning Wiki, extensive literature review [28-31], and the Rare Disease Repurposing Database (RDRD).

3. COMPUTATIONAL TARGET FISHING

The methods to determine the drug targets can be classified into five groups [32-38]:

- 1) Chemical or molecular similarity searching
- 2) Data extraction and machine intellect method
- 3) Analysis of biological activity spectra
- 4) Protein- structure-based methods

3.1. Molecular Similarity Method

“Chemical similarity principle” is one of the simplest methods that states that identical chemical molecules tend to possess the same chemical properties [39, 40]. The molecular targets may be identified by recognizing proteins that bind already acknowledged drug ligands that are extremely analogous to the query drug ligand [41, 42]. The method includes chemical fingerprints of a drug molecule that confirms the presence or absence of specific sub-structures in the ligand. The Tanimoto coefficient can be used to compare the fingerprints of two molecules. The more the two compounds are identical, the closer the Tanimoto coefficient is around 1. Databases like the MDL Drug Data Report database describes the bioactivities of known as well as unknown drug molecules that may be utilized for predicting the molecular targets. Shape-based methods employ software such as USR, ROCS, PARAFIT, Phase Shape, ESHAPE2D that help to compare the 3D shape of the molecules and detect resemblances between the drug molecules having dissimilar atomic structures [43-48].

3.2. Data Extraction and Machine Intellect Methods

It is a chemogenomic approach that utilizes fingerprints and other machine intellect methods like Bayesian classifiers, network classification, or self-organizing maps [49-51] that assist to identify the biological response and association between query molecule substructure and its predicted targets [52-55]. The correlation between chemical substructure and its explicit target binding information is preserved in multiple-target model forms.

3.3. Analysis of Biological Activity Spectra

Biological activities of the chemical molecule like various protein pathways or alteration in gene expression profiles can also be used for target prediction. This method uses the transcriptional profile of the query molecules and presents that data as evidence, which helps to expose novel action mechanism and advanced applications of originally established drugs. Also, drug-prompted changes in genomic expression can be used to describe on-target as well as off-target effects of the drug molecule [56-58].

3.4. Protein Structure-Based Methods

Information about the target protein structure can also be used to predict new bioactivities of a query molecule. Protein, protein-drug interaction fingerprints or pharmacophore examining can be used [59, 60]. The limitation of this method is that the targets with resolved structures can only be utilized to predict the interaction of the query molecule. Ligand-target interactions can be investigated by docking a query molecule to the number of resolved target structures [61-64].

4. THE NOVELTY IN DRUG REPOSITIONING

Some of the most primitive repurposed drugs were discovered serendipitously, such as the cardiovascular advantages of aspirin. Subsequently, several novel and advanced approaches have been proposed and developed for the identification and validation of repurposed targets. These methods are broadly divided into experimental approaches that include target identification by binding assays and phenotypic screening, and computational approaches, that include the genetic link, signature matching, and, pathway-mapping. Even though these methods vary in several ways, incorporation of “omics” is a commonality among them. Omics can be focused on various genes and proteins and are directed towards the entire holistic assessment of every single cell, tissue, or organism in a non-targeted and unbiased manner. Previous validation of drug safety and toxicity by integrating omics has led to amplified success chances of drug repositioning.

Genomics has become an attractive approach in the drug repurposing strategy as it can significantly expand the knowledge about the genetic basis of several multifaceted diseases. Resources like the Drug Gene Interaction database help streamline the process of mapping disease-associated single-nucleotide polymorphisms. Another analytical resource for drug repurposing includes an approach that integrates genome-wide association study with *in silico* pipeline that recently helped in the identification of 42 novel risk loci for rheumatoid arthritis. Other novel resources that support epigenetic drug repurposing are the Database of Epigenetic Modifiers (dbEM) and Human Epigenetics Drug Database that can provide genetic knowledge about more than 150 epigenetic proteins as well as their probable drug targets. Other strategies such as transcriptomics, metabolomics, and proteomics, are yet to contribute as an essential share in the drug repositioning success. Fields such as pregenomics and mi-

crobiomics are still emerging to provide a better insight into drug repurposing processes. The repurposing opportunities are expanding by the incorporation of the “omics” that helps in enhancing several approaches such as deriving hypotheses, defining precision phenotypes, developing more systematic approaches (not serendipitous), uncovering new disease mechanisms, predicting potential drug efficacy and toxicity, improving understanding of pregnant physiology, improving understanding of microbe/drug interactions. These approaches can greatly broaden the depth of knowledge about biological systems. New ways of integration of several omics’ information could help yield powerful novel strategies for illuminating drug actions on the targeted pathogens and aid in the selection of the utmost promising drug candidates for futuristic repurposing research [65].

4.1. Serological Biochemical Markers as an Advanced Methodology

Compounds that are able to modify specific drug receptors like G protein-coupled receptor, nuclear receptor, or alter the activity of an enzyme or an ion channel can be utilized for drug development using the drug repurposing approach. Gigantic high throughput screening of thousands of drug candidates is required for the identification of such compounds. As the drug development expenditures and the number of drugs approved are inversely related, the US Food and Drug Administration (FDA) has started a new initiative that concentrates on focusing biomarkers to escalate the efficacy of the drug. A cluster of serological markers called ‘neoepitopes’ that possess the potential to amend post-translational modifications of proteins has been identified to meet drug development needs. They are routinely measured in serum samples for the prompt evaluation of drugs throughout various stages of drug development. Drugs that have been approved for safety and acceptability in phase I trials may perhaps be probable candidates for therapeutic switching. The chief task in drug reprofiling is to find a new indication. Re-screening of the compound using a variety of new technologies such as cell-based assays, bacteria assays are done to ascertain a new target, mode of action, influence on serological biomarkers, and thereby classifying new therapeutic indications of a query drug [66-68].

Numerous serological biomarkers are known as Alanine Transaminase (ALT) and Aspartate Aminotransferase (AST) but have low sensitivity and disease specificity. Thus, additional explicit approaches are necessary. Neoepitope can be of different types of post-translational modification of a protein that can comprise phosphorylation, oxidation, hydroxylation, glycosylation, glycation, cross-linking nitrosylation, enzymatic cleavages, and isomerization. These processes tend to modify the activity of various target receptors or proteins [69-71]. A biomarker in combination with specific post-translational modification of proteins may develop a high level of specificity for a certain disease. An example of one such biomarker is bone resorption biomarker CTX-I that precisely and selectively monitors the osteoclast bone resorption process and is utilized during drug discovery and for drug reprofiling [72-76].

Serological markers are the markers of whole-tissue pathology. Technologies that focus only on *in vitro* assays involving inhibition or stimulation of single enzymes often do not represent entire tissue pathology, whereas neoepitopes engendered by various proteases may more precisely reveal the entire tissue turnover grade. These finished products of tissue turnover may also identify those enzymes that were not thought to be involved directly, as slight alteration of biological pathways may lead to a shift in tissue phenotype. An example may include the effect of cyclic Adenosine Monophosphate (cAMP) Modulators On Matrix Metalloproteinase (MMP) expression in cartilage. Other examples of neoepitope biomarkers that have been substantially validated are N-Terminal Telopeptide (NTX), Hemoglobin A1c (HbA1c), and Cartilage Degradation marker CTX-II [77-80].

5. ROLE OF DRUG REPOSITIONING IN PHARMACEUTICAL RESEARCH AND DEVELOPMENT (R&D)

The process of drug development is extremely challenging with a predictable success rate of just 2%. Such lower success rate can directly augment the drug discovery cost to US \$2–3 billion. There is a severe decline for the past 6 decades in the number of novel therapeutics developed per billion dollars financed in the pharmaceutical R&D. Consequently, an average investment done to release medicine in the market has amplified to greater than \$2 billion today and the profit returned to the pharmaceutical industry is enormously less as compared to the investment, signifying futuristic decline of the pharmaceutical R&D. Failure of the drug candidate in the various phases of drug development is considered as one of the main reasons for the declined return on investment. The drug repositioning is an alternative time-effective strategy that can offer grounds for some hopefulness for the R&D by removing various hurdles in the drug development process, including cost cut-down, simultaneously meeting the quality standards, reducing the failure rate as well as delivering the medicines at a more affordable range. Drug repurposing assists in gaining in-depth knowledge about the various disease targets and their mechanisms that can help to conquer various market imperfections. The chief factors that can contribute to the commercial appeal of therapeutic drugs. The first factor is the availability of a considerable large patient population for making the drug profitable. However, considering this situation, rare diseases may present certain challenges [81]. The second contributing factor is the collaborations between pharmaceutical industries and academic institutes that can produce synergistic outcomes. Where academic institutes help in delivering extensive insights into the pathological mechanism of the disease and linking them pharmacologically to the specific drug indications, pharmaceutical industries can encourage the drug execution, including its development, manufacturing, regulatory endorsement, and commercialization. Drug repositioning, a strategy that is being adopted by several biopharmaceutical and pharmaceutical companies, has been the symbol for bringing the intensified business escalation. Pharmaceuticals have started focusing on repurposing as they are working

with the drug compounds that have already gone million dollars' worth of clinical or preclinical testing or are already approved. Consequently, the strategy can help market those drugs in a comparable, faster and cheaper way than traditional research and drug development. Additionally, where 25% of the repurposed drugs make their way to market from the Phase II clinical trials and 65% from Phase III trials, the rates for the new molecular drugs are only 10% and 50%, respectively. The drug repurposing approach has escalated the overall market growth from almost \$25 billion in 2015 to approximately \$32 billion by 2020, with an annual growth rate of 5%. Since the drug safety reports have already been recognized, the strategy also permits a rapid regulatory approval to market, thereby declining the cost while augmenting the availability of these much desirable drugs to patients [82].

6. COLLABORATION MODELS

There is an expanding realization that the collaboration of pharmaceutical companies with academics can significantly contribute to the successful development of the potential repurposed drugs and that the advanced novel business strategies are essential for driving the drug repositioning field. Pharmaceutical industries own abundant failed yet valuable libraries of drug candidates and have an immediate experience of clinical research and development. Besides, they also have access to advanced screening methodologies that most academic institutions find difficult to acquire or maintain. On the other hand, academic institutions possess treasured information on evolving disease areas, which can serve as the basis for extremely innovative treatments. The collaborative strategy has been identified as a significant way for drug repurposing and includes the combination of the robustness of pharmaceutical industries with the academic and research institutes, biotechnology companies, and project investors.

The three chief components for the successful drug reprofiling collaborations include:

- [i] Identifying research experts and scientists for encouraging innovative concepts in evolving fields of disease biology,
- [ii] Enthusiastic engagement of all the participated collaborators, and
- [iii] Alternate funding sources

There are unique advantages of executing drug repurposing research in collaboration with an academic institutes:

- [i] Translational research in academia offers direct access to healthcare practitioners and hospitals that can promote the repurposing process by cutting down the huge communication gap between two disciplines.
- [ii] Academic researchers hold exhaustive knowledge about the various disease areas, their mechanisms, process of apoptosis, autophagy, and cell division, thereby eliminating the "activation barriers" and empowering projects to swiftly advance through the early stages.

- [iii] In-depth knowledge about the common inter-dependent cellular and molecular pathways linked with various diseases can lead to the promotion of drug repurposing efforts in those specific ailments that do not have any effective treatments.

There are numerous repurposing collaborations between the pharmaceutical industries, academic scientists, and grant funding organizations that have been recently established for addressing the chief challenges in the drug reprofiling approach. Noteworthy examples are:

- [i] A collaboration among AstraZeneca and Medical Research Council (MRC), known as "Mechanisms for Human Diseases Initiative", and
- [ii] The partnership of National Institutes of Health–National Centre for Advancing Translational Sciences (NIH–NCATS) in association with eight pharmaceutical companies, identified as "Discovering New Therapeutic Uses for Existing Molecules".

The NCATs, in association with various pharmaceutical industries, provide samples of existing compounds and make the scientific data accessible to the academic researchers free of cost for further assessment and evaluation of the molecules to reposition them as novel treatments. Pfizer has set up an open innovation collaborative model called 'Centers for Therapeutic Innovation (CTI)' with various hospitals and universities for identifying the potential of various therapeutics for unmet ailments. Likewise, Astra and Glaxo-SmithKline (GSK) have collaborated with the University of Manchester and launched the 'Manchester Center for Inflamm Res (MCIR)' intending to interpret basic researches into the development of novel or repurposed medications for various inflammatory disorders. Additionally, publishing companies such as Elsevier are involved in the collaboration process with Findacure, allowing them to access the literature information on previously known drug molecules. Although it is too early to definitively assess the success of these pilot government-sponsored programs given the long time frames of drug development, initial indications suggest some positive outcomes. The initial positive outcomes of these collaborations include anticancer drug saracatinib, that is presently being preclinically and clinically explored by MRC and NCATS programs for various indications such as neurodegenerative diseases, psychosis, chronic otitis media, and lymphangiomyomatosis. Another promising example of the AstraZeneca-academic partnership is the investigation of the antagonist of neurokinin 3 receptors for the management of menopausal hot flushes. In 2016, researchers at NIH-NCATS, along with the 'National Institute of Allergy and Infectious Diseases' (NIAID) employed a novel screening method for scrutinizing almost 4000 marketed drugs and identified twenty-five active candidates that were found to be effective against drug-resistant microbes, specifically *Klebsiella pneumonia* strains. In 2017, a grant of \$1.6 million was received by researchers at Purdue University from NIH to explore whether two prevailing drugs auranofin and ebselen can be suitable candidates for repurposing against *Clostridium difficile*.

Collaboration models with academics can help to predominantly discover probable repositioning opportunities for generic marketed drugs for the treatment of rare diseases. Apart from the government organizations, there are public-private partnerships such as the ‘Repurposing Drugs in Oncology (ReDO) project’ and ‘Center for Drug Repurposing’ that involve various industrialists and academic researchers to facilitate drug repurposing activities. The relationships between huge pharmaceutical industries and academic institutes are mounting to alleviate the risk of failed drugs and expand the numbers of successful repurposed drug candidates [83-86].

7. DRUG REPOSITIONING FUNDING INITIATIVES

Drug repositioning offers an economical technique to intensify several treatment opportunities. In the long-term, it could offer vital societal and economic advantages for the advancement of sustainable healthcare systems. However, repositioning research is the link with certain financial hurdles. There is a significant shortage of economic support that leads to a rare interest of the pharmaceutical developers in this field. Researchers from various fields perform several minor research for testing the repurposing hypotheses, but they frequently have deficient funding for further expensive confirmatory trials. The relative discrepancy of funding opportunities for both industrial drug developers and academic researchers replicates the disappointment of the drug repurposing initiatives. Certain financial aids have been provided by the Governmental for accelerating the drug repurposing and escalates the technology development for the discovery of and application of novel therapeutics. The MRC invited research proposals and received more than 100 proposals, from which 15 proposals were accepted and financially supported by the MRC, with a total worth of £7 million. The NIH-NCATS in 2013 also funded 9 research proposals that eventually were funded by an approximate amount of \$12.7 million [87].

7.1. Funding Mechanisms

There are four funding mechanisms for clinical research related to drug repurposing:

- 1) Traditional grant funding
- 2) Crowdfunding
- 3) Public-Private Partnerships (PPP)
- 4) Social Impact Bonds (SIB)

7.1.1. Traditional Grant Funding

It is a donation-based funding process that provides financial support to autonomous clinical studies *via* funding programs. It mainly consists of a funding organization and several applicants from a diverse field of research institutes and academia. The grant can be offered from several organizations such as government foundations, research institutes, universities, pharmaceutical industries, not-for-profit agencies, and philanthropic organizations. The submitted proposed project is accurately scrutinized and examined by the

scientific committees, and the funding is offered when the research project meets all the specified eligibility criteria for the grant.

7.1.2. Crowdfunding

It involves levitating minor contributions and donations from various groups of people through an online portal for funding clinical research. It provides the advantage of raising funds for innovative clinical research projects that have a significant high patient or societal impact but have little profit return. An exclusive example of such funds in drug repurposing project is the “NeoART study”, in which antimalarial drug artesunate is being explored for its probable effectiveness in colorectal cancer, and the fund collected through this mechanism is approximately £54,300. This type of fund mechanism involves public engagement and upsurges their awareness of scientific research needs.

7.1.3. Public-Private Partnerships (PPP)

The PPP is a partnership among the public and private organization with a mutual perspective of the improvement of the healthcare scheme. The foundation may comprise government, pharmaceutical groups, as well as not-for-profit organizations, along with research groups, hospitals, and academic institutes. Their principal focus is to improve the research and attenuate the drug development costs as well as mutual sharing of the drug development financial risk between all the collaborators.

7.1.4. Social Impact Bonds (SIB)

SIB is an innovative mechanism that receives funds through private investments for the development of public health interventions. It is also known as pay-for-success. It involves an official contract amongst an outcome payer that is usually a government or a private company and a service provider that is generally a not-for-profit research organization in quest of financial support for conducting clinical studies. In this mechanism, the outcome payer mentions an anticipated outcome and assures to pay back the funds to the investors if the desired outcome is obtained [88].

7.2. List of Funding Agencies

There are certain funding programs established by philanthropic and governmental organizations that are explicit to fuel up the drug repositioning industry.

- [i] NIH-NCATS
- [ii] National Cancer Institute (US)
- [iii] Ontario Institute for Cancer Research (Canada)
- [iv] Canadian Institutes of Health Research (CIHR)
- [v] University of New Mexico Health Sciences Center (UNM-HSC)
- [vi] Global Cures
- [vii] Joint Translational Call (JTC)
- [viii] Cures Within Reach (CWR)
- [ix] Findacure (FC)
- [x] Stem Cell Network

- [xi] Michael J. Fox Foundation (MJF)
- [xii] LifeArc
- [xiii] Anticancer Fund (ACF)

8. APPLICATIONS OF DRUG REPOSITIONING APPROACH IN VARIOUS PATHOLOGIES

8.1. Central Nervous System (CNS) Disorders

8.1.1. Parkinson's Disease

Niclosamide originally used to cure tapeworm infections can be a probable new drug candidate for patients with Parkinson's disease. Niclosamide is an effective activator of the Parkinson's disease-related protein PINK1 and potently augments the activity of PINK1 that plays a substantial role in halting neurodegeneration and slowing the progression of Parkinson's disease. Drugs like diethylstilbestrol, testosterone, erlotinib, dasatinib, sorafenib, lidocaine, melatonin, nifedipine, and nicardipine are the non-Parkinson's drugs that presented high connections in the Indication-Drug-Target Network (IDTN), as well as their target proteins, showed high topological significance in the PD-Specific Protein-Protein Interaction Network (PPIN). Stimulation of GLP-1 receptors present in the brain has a positive impact on brain cells. Antidiabetic drug bydureon, also known as exenatide, targets these receptors to show neuroprotective effects in Parkinson's, slowing down the persistent impairment of dopamine-producing brain cells, and consequently delaying the worsening of symptoms. Lixisenatide and liraglutide are other longer-acting novel anti-diabetic drugs that target GLP-1 receptors. The cholesterol-lowering drug simvastatin is under the proposed a 2-year clinical trial supported by The Cure Parkinson's Trust may also help protect brain cells in Parkinson's. The proposed mechanism to reduce the risk of developing Parkinson's is by reducing oxidative damage in cells, inhibiting inflammation, reducing the formation of alpha-synuclein bundles in the brain as well as increasing the production of neurotrophic factors [89-91]. Research studies suggested that mitochondrial letdown also has a crucial influence on the loss of brain cells in Parkinson's. Ursodeoxycholic acid (UDCA), which is used to treat liver disease, has shown to exert restorative effects on mitochondria in human dopamine-producing brain cells *in vitro* and animal models of Parkinsonism. Anti-mucolytic drug ambroxol has been shown to act through a novel mechanism by inhibiting another major genetic risk factor, glucocerebrosidase enzyme gene mutation, involved in the development of Parkinson's disease. It increases glucocerebrosidase levels in neuronal cells and disposes off alpha-synuclein protein [92-94].

8.1.2. Major Depressive Disorder (MDD)

It has been reviewed by researchers that Histone Deacetylase (HDA) has been implicated in the pathogenesis of depression. Although no clinical data are available, HDA inhibitors have been testified to present anti-depressant effects in rodent models. HDA inhibitors such as vorinostats and trichostatin A have been identified as the topmost repurposed hits for depression. Additionally, tetrandrine, a calci-

um channel blocker, revealed antidepressant effects in mice using tail suspension and forced swimming tests. It augmented the levels of norepinephrine, 5-hydroxytryptamine (5-HT), as well as a brain-derived neurotrophic factor (BDNF) in mice treated with reserpine or chronic mild stress. Advance research proposed that apart from noradrenaline or 5-HT, cytokines such as tumor necrosis factor (TNF) alpha may also contribute to the pathogenesis of MDD. Inflammation is one of the important factors in the expansion of MDD which is mediated by the action of TNF-alpha. Thus, drugs that can possibly suppress inflammation through inhibition of these mediators may be repurposed for the potential treatment for MDD. Anti-inflammatory drug infliximab is being repurposed for the management of drug-resistant MDD. Infliximab improved depressive symptoms and attenuated C-Reactive Protein level, which was reported to be excellent in patients with drug-resistant depression. Studies also reported that anti-TNF agents such as adalimumab and etanercept may tend to diminish minor depressive symptoms in patients with psoriasis [95-98].

8.1.3. Glioblastoma

Glioblastoma (GBM) is the most aggressive and common brain tumor in adults. The addition of the chemotherapeutic temozolomide (TMZ) to the standard care is the major improvement in the treatment for GBM, however, despite this, about 90% of patients expire within six years after diagnosis. Combining FDA-approved drug hydroxyurea with TMZ for the treatment of GBM could be highly beneficial for these patients, which could lead to an increase in their survival rate. A synthetic analog of the coenzyme Q10, idebenone, is used in the treatment and management of inherited heart disease and Alzheimer's. Now it is being investigated to treat GBM as it interrupts the multiplication, propagation, and migration of GBM cells. Apart from this, it also augments the cellular toxic effects of oxaliplatin and temozolomide [99-101].

8.2. Cardiovascular Diseases (CVD)

The common inflammatory pathway between atherosclerosis and gout is mediated *via* interleukin (IL)-1b. Drugs that may inhibit the IL-1 b, such as colchicine and canakinumab, may be used in the treatment and management of both diseases. Also, metformin is reported to prevent CVD in diabetic patients. UK Prospective Diabetes Study reported that metformin treatment lowered the possibility of myocardial infarction by 39%. It also prevents plaque formation and shows antiatherosclerosis action. It has been reported that metformin induces adenosine monophosphate-activated protein kinase (AMPK) activation and restricts endothelial cell damage caused by excessive reactive oxygen species generation catalyzed by hyperglycemic conditions, thereby promoting endothelial integrity. As metformin counteracts the production of plasminogen activator inhibitor 1 (PAI-1) under the influence of hyperinsulinemia, it has been reported to exhibit anti-thrombotic property also [102-105].

Methotrexate originally used in the treatment of autoimmune disorders and rheumatoid arthritis, has been found to

lessen the risk of CVD in rheumatoid arthritis patients. It probably acts via activating protective AMPK as well as modulating the levels of pro-inflammatory and anti-atherogenic cytokines. Other mechanisms include changes in blood pressure, arterial stiffness, and insulin resistance [106-109].

8.3. Infectious Diseases

8.3.1. Tuberculosis (TB)

Chlorpromazine (CPZ), originally developed as an antipsychotic drug, was found to have anti-mycobacterial action along with other antitubercular drugs. The mechanism of action of phenothiazines was indefinable. It was formerly anticipated that they act as efflux pump inhibitors, but consequent *in-vitro* assays concluded that chlorpromazine target the NADH/menaquinone oxidoreductase pathway essential for the survival of mycobacteria. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have offered the extensive potential for therapeutic switching from the perspective of anti-TB therapy. Various key metabolic pathways have been identified, targeted, and modulated by NSAIDs in *M. tuberculosis*. Apart from specific mycobactericidal properties, many molecules of this family also target endogenous mechanisms of anti-tubercular action, such as inhibition of thymidine integration required for DNA synthesis by diclofenac, inhibition of DNA polymerase III β subunit-DNA replication, and repair by vedaprofen and bromfenac. Also, complexes of tenoxicam, meclofenamic, mefenamic acid, and indomethacin can be excellent repurposed anti-tubercular molecules as they have demonstrated *in vitro* minimum inhibitory concentration of <1 µg/mL against *M. tuberculosis*. The antidiabetic drug, metformin could be used as add-on therapy with other anti-TB drugs to augment their effectiveness in drug-resistant tuberculosis. Metformin acts by promoting the generation of reactive oxygen species in mitochondria and limits ailment immunopathology by inhibiting the growth of mycobacterium intracellularly. The anti-leprotic drug minocycline, is successfully repurposed for the treatment and management of extensively drug-resistant tuberculosis (XDR-TB). Also, a combination of second-line drugs with antibiotics such as linezolid, amoxicillin-clavulanic acid has led to positive results in the treatment of multi-drug-resistant tuberculosis (MDR-TB) [110-113].

8.3.2. Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome (HIV-AIDS)

An anti-rheumatoid drug auranofin is currently being investigated for probable therapeutic benefit in a number of diseases such as bacterial and parasitic infections, neurodegenerative disorders, various cancers, and HIV-AIDS. The drug acts to inhibit the redox enzyme, thioredoxin reductase. The enzyme is crucial for monitoring the levels of reactive oxygen species intracellularly, thereby it prevents proviral HIV-DNA damage in memory T cells. Auranofin act by inhibiting thioredoxin reductase that induces cell death as a result of increased cellular oxidative stress. A lung cancer drug, nivolumab administered to HIV-infected patients showed a drastic decrease in latent HIV reservoirs.

Nivolumab is an inhibitor of programmed death-1 (PD-1) and restores the immune defense mechanism in the early stage of HIV infection by activating CD4+ T cells to fight against the virus. Anticancer drugs such as erlotinib and sunitinib respectively inhibited cyclin G associated kinase (GAK) and adaptor protein 2 (AP2)-associated protein kinase 1 (AAK1). These host kinases regulate intracellular viral trafficking during their entry and assembly. The *in vitro* activity has been demonstrated against dengue and Ebola virus in cultured cells. Alternatively, lapatinib targeted epidermal growth factor receptor (EGFR), another host kinase required by human cytomegalovirus as an entry co-receptor. Adenovirus in order to promote its replication, phosphorylates host cyclin-dependent kinases (CDKs). Inhibition of CDKs can inhibit the activity of various viruses, including HIV and DNA virus [114-116]. Various CDK inhibitors are under preclinical and clinical investigations. Examples include PHA-690509 (CDK2 inhibitor, Phase I), seliciclib (CDK2/5 inhibitor, Phase II), alvocidib (CDK9 inhibitor, Phase II), and dinaciclib (CDK1/2/5/9 inhibitor, Phase III). An anti-alpha-4beta-7 integrin antibody (a4b7), vedolizumab, has been used in the management of inflammatory bowel disease. When HIV localizes to the gastrointestinal tract, it infects T-cells, directly interacts with a4b7, and forms a viral envelope [117]. Vedolizumab tends to reduce the lymphoid masses in the intestine where tenacious replication of the virus occurs. Thus, anti a4b7 therapy could be promising for HIV therapy [118].

8.3.3. Helminth Infection

Praziquantel is the standard treatment against a range of helminth infections such as *Schistosoma mansoni*, *S. haematobium*, *C. sinensis*, *Opisthorchis felineus*, *Opisthorchis viverrini* and intestinal flukes. *Artemisia annua*, commonly known as *qinghao*, has been used for its antimalarial properties. Sesquiterpene lactone ring with characteristic peroxide bridge is the active part of the artemisinin that is responsible for its polypharmacological interactions. Artemether, artesunate, and dihydroartemisinin are the main active artemisinin compounds that represent antischistosomal activity. A recent meta-analysis showed that the multiple low dose administration of artemether or artesunate over a period of 2 weeks results in 65–97% protection against *Schistosomiasis japonicum*. They have also shown great efficacy against *C. sinensis*, *Fasciola* spp., *Schistosoma* spp., *Opisthorchis* spp, liver, and intestinal flukes. Another antimalarial drug mefloquine showed promising results in a clinical trial for antischistosomal activity. The unique characteristic of mefloquine was that it showed activity against both the juvenile and adult stages of all three *Schistosoma* spp. It produced severe morphological damage to the fluke and showed a 95% egg reduction rate (ERR) against *S. haematobium* in children. Oxantel pamoate which was a veterinary drug, revealed significantly higher efficacy at a dose of 20 mg/kg against *T. trichiura* and *T. muris* as compared to standard treatments benzimidazoles or levamisole with 26% cure rates and 93% ERR [119-121].

8.3.4. Nipah Virus (NiV) and Ebola Virus

Kochi State Government along with the World Health Organization (WHO) and some of the leading researchers in the world are trying to find if drug repurposing is possible for treating these viral infections. Though anti-viral molecule ribavirin has been found to be effective against NiV and it has helped to reduce mortality by 30%, at present, there is no drug to cure it. For the Nipah virus, a computational drug repositioning approach is being applied. Gene expression data obtained from endothelial cells treated with NiV is reported by scientists in Malaysia and France that are now applying ‘computational drug repositioning’ to find potential drugs that could be useful against NiV. Amodiaquine is an anti-malarial drug, derivatives of which have promising effects against Ebola infection. Almost 70 derivatives of amodiaquine were tested for anti-Ebola activity and found that amodiaquine derivatives act by amending the alkyl chains lengthening from the aminomethyl group and a halogen attached to the quinoline ring. These amendments may perhaps escalate the selectivity index of the amodiaquine by 10 times approximately [122]. Thus, amodiaquine derivatives could be investigated further to test their efficacy and therapeutic potential against the Ebola infection. Amiodarone, used for treating cardiac arrhythmia, recently has been shown to possess antiviral action against the Ebola virus *in vitro*. Further *in vivo* evaluation is required to confirm the anti-Ebola activity of amiodarone. Antihistaminic drug diphenhydramine also presents an anti-Ebola activity that acts by constraining the entrance of the virus into cells through endosomes [123].

8.3.5. Coronavirus Disease (COVID-19)

COVID-19 is recognized as the pandemic respiratory syndrome by World Health Organization (WHO) in the year 2020. The coronavirus belongs to the family Coronaviridae and is an enveloped, non-segmented positive-sense single-stranded RNA virus broadly dispersed in various mammals and humans [124]. The viral genome translates two main polyproteins-ppla and pplb. A proteinase enzyme called main protease (Mpro) or 3C-like protease (3CLpro) cleaves these polyproteins into various vital and functional viral proteins. Mpro being an important factor for viral polyprotein processing and maturation is considered as a major target for virus inhibition. Research studies have reported that HIV-1 protease inhibitors such as lopinavir, ritonavir, and saquinavir are capable of deactivating Mpro by binding to its specific site and thus these drugs may be regarded as potential anti-corona virus drugs. The viral genome also consists of about 16 non-structural proteins (NSP). RNA polymerase (NSP 12) in association with NSP7 and NSP 8 helps the virus replicate long RNA. Several *in-vitro* cell line study and animal models have demonstrated that antiviral drug remdesivir (originally used against Marburg and Ebola virus) focus on this key target and restricts with viral replication by interfering with the NSP12 polymerase. Favipiravir, another antiviral drug approved for influenza A and B, is an inhibitor of RNA-dependent RNA polymerase and has been repurposed potentially to treat corona symptoms [125-127]. A highly ef-

fective anti-malarial drug chloroquine, is also repurposed for treating COVID-19. The exact mechanism of action is unknown, but numerous probable mechanisms are explored to date. Chloroquine is expected to cause inhibition of pH-dependent viral replication along with its synergistic immunomodulatory actions. Research has also demonstrated that chloroquine potently interrupts the glycosylation of angiotensin-converting enzyme 2 receptors on the human cell that is the main binding site for the virus that causes COVID-19. Chloroquine additionally suppresses the production and release of inflammatory cytokines such as interleukins and tumor necrosis factor-alpha [128].

8.4. Pulmonary Disorders

8.4.1. Lung Fibrosis

Drug-repurposing accounts for approximately 25% of the newly FDA-approved drugs. Fascinatingly, almost 95% of the current FDA-approved compounds for lung fibrosis were initially used for off-label indications and were serendipitously identified. Idiopathic pulmonary fibrosis is the consequence of heightened stimulation of angiogenesis and fibroblast differentiation as a result of the disproportion between tyrosine kinases and phosphatases. Nintedanib is the FDA-approved anti-fibrotic drug that prevented angiogenesis and hyperproliferation was later announced as a therapeutic drug for lung fibrosis [129]. Thyroid hormone prevents the degradation of mitochondria and improves mitochondrial biogenesis in epithelial cells of alveoli and maybe a probable anti-fibrotic candidate. Metformin prevented experimentally induced lung fibrosis by governing cellular bioenergetics and autophagy through activation of AMP-activated protein kinase. The anthelmintic drug, niclosamide has been shown to exert an anti-fibrotic effect and could be repurposed for the treatment of pulmonary fibrosis. Niclosamide acts by preventing fibroblast migration, inhibiting fibrotic signaling pathways, regulating WNT/β-catenin signaling, and decreasing epithelial-mesenchymal transition [130]. Histone deacetylase (HDAC) inhibitors were studied for repurposing in a mouse model of idiopathic pulmonary fibrosis (IPF). The two inhibitors under study were suberanilohydroxamic acid and 4-(dimethylamino)-N-[7-(hydroxyamino)-7-oxoheptyl] benzamide. Both of them significantly interfered with the biosynthesis of leukotriene B4 (LTB4) by inhibiting a vital enzyme leukotriene A4 hydrolase involved in the synthesis. Blocking of LTB4 biosynthesis results in a significant reduction in neutrophilic inflammation in IPF [131].

8.4.2. Chronic Obstructive Pulmonary Disease (COPD)

Currently, there is no cure for COPD, and treatments available help only to prevent the worsening of symptoms. Drug reprofiling strategy opens multiple possibilities to explore new repurposing options using pre-existing drugs for diseases with no known treatment such as antidiabetic medication metformin possesses beneficial effects in patients with COPD. It acts by decreasing oxidative stress, airway inflammation or remodeling, parenchymal fibrosis, and pro-in-

flammatory cytokines, as well as stimulates the production of anti-inflammatory cytokines [132]. Repurposing the bisphosphonate bone drug alendronate relieves symptoms of emphysema associated with COPD by targeting alveolar macrophages. The researchers confirmed that alendronate inhibits the mevalonate pathway in lung cells and prevents apoptosis [133]. Inhaled nebulized unfractionated heparin was used in a research study for determining its efficacy in managing and treating moderate-to-severe COPD. Heparin considerably improved lung functions suppressed labored breathing without any significant side-effects. Heparin also demonstrated to have a mucolytic property and helped to clear mucus from the respiratory passage [134, 135].

8.5. Diabetes Mellitus

During a randomized clinical trial of 12 weeks, an anti-inflammatory and anti-allergic drug amlexanox that is used to treat asthma showed a substantial decrease in blood glucose levels in type 2 diabetic patients. Amlexanox seemed to act through a novel mechanism by inhibiting two enzymes, IKK ϵ and TBK1. Inhibition of these two enzymes led to changes in gene expression in the adipose tissue, increasing oxidation and insulin sensitivity, thereby improving glucose control in patients with fatty liver disease and type-2 diabetes [136, 137]. Amlexanox also significantly reduced Hemoglobin A1c and fructosamine that act as parameters for controlling glycemic levels in obese patients. Due to mitochondrial uncoupling action, niclosamide ethanolamine, an anti-parasitic drug, maintains energy metabolism, improves lipid metabolism, and increases whole-body energy expenditure. The overall result of these effects is a delayed onset of genetic as well as dietary forms of diabetes, signifying that it could be repurposed as a novel hypoglycemic agent. One of the genetic association studies acknowledged a robust link between type 2 diabetic mellitus and gestational diabetes and the range of genes that are targeted by calcium channel blockers (CCBs) such as nifedipine [138-140]. All CCBs are very much effective in lowering fasting glucose and improving glucose tolerance, supporting the fact that CCBs could be promising candidates for drug repurposing in diabetes. The only CCB labeled safe in pregnancy is nifedipine that prevents pancreatic beta-cell apoptosis as well as defends against endoplasmic reticulum stress. Previous preclinical studies demonstrated that increased thioredoxin-interacting protein (TXNIP) has a detrimental influence on pancreatic beta cells. Increased calcium ion inflow into beta cells respond to an elevated level of TXNIP. Further research demonstrated that verapamil having the ability to block calcium channels reduces the levels of TXNIP, and thus prevents the progressive loss of beta cells during a diseased state. Another robust association was seen between genes involved in serotonin synthesis, their receptors such as 5HT-2A, 5HT-3B, and metabolic syndrome [141-143]. *In vitro* study showed that glucose-induced insulin secretion was inhibited by serotonin whereas 5HT-3 antagonist; tropisetron reversed this effect and stimulated the secretion of insulin from insulin-secreting cell lines INS-1 cells. Hyperactivation renin-angiotensin-aldosterone system plays a

vital part in initiating and aggregating various micro- and macrovascular complications associated with diabetes mellitus. Angiotensin-converting enzyme (ACE) inhibitors have shown to exert 'diabetes targeted organ protective' effect. ACE inhibitors block the effects of angiotensin II at both blood and tissue levels and have been testified to improve the functioning of heart and kidney in patients with early diabetes mellitus to a greater extent as compared to that of peripheral neurons and eye [144, 145].

8.6. Cancer

Prostaglandin E2 (PGE2) is dominantly produced in tumor cells from cyclooxygenase (COX)-2 and to a lesser extent from COX-1. PGE2 plays an imperative part in hastening angiogenesis, cell explosion, and tumor development. Several observational studies revealed that aspirin targets both COX-1 and COX-2 isoforms and can significantly reduce the risk of major cancers such as gastric cancer, esophageal cancer, colorectal cancer, prostate cancer, and breast cancer. A low dose of aspirin suppresses upregulated levels of PGE2 colorectal cancer cells. Beta-adrenoreceptors are present in the cell lines of ovarian cancer, pancreatic cancer, breast, and nasopharyngeal cancer. Catecholamine-induced activation of beta-adrenoreceptors also has a crucial part in tumor progression. Chronic stress leads to the upregulation of catecholamines such as epinephrine and norepinephrine that bind to beta-adrenergic receptors. This, in turn, stimulates cAMP-PKA pathway that further hastens tumor growth and invasion as well as stimulates the protein tyrosine kinase 2 (PTK2) pathway that speeds up cancer cell propagation by preventing their apoptosis. Beta-blockers such as propranolol suppress pancreatic tumor proliferation and invasion by suppressing catecholamine to induce distant tissue metastasis through M2 macrophage infiltration. An additional mechanism of action involves inhibiting activator protein 1 (ap-1), protein kinase A (PKA), cyclic adenosine monophosphate response element-binding protein (CREB), transcription factors nuclear factor κ B (NF κ B), and mitogen-activated protein kinase (MAPK) pathways. A recent publication also revealed that bisoprolol in a dose-dependent manner improved cardiac physiology in rats with cancer cachexia, signifying the promising effect of beta-blockers in the fatal phase of cancer [146-148].

Early observational studies have also revealed that cardiac glycoside induces apoptosis in human breast tumor cells. Binding to Na $^+$ -K $^+$ -ATPase, transcriptional upregulation of Fas ligand, suppression of NF κ B, activation of calcineurin, and inhibition of DNA topoisomerase II are the proposed mechanism for the induction of apoptosis in cancerous cells. Metformin also inhibits cysteine-rich 61 (Cyr61)/Akt/Mammalian Target of Rapamycin (mTOR) signaling pathway in ovarian cancerous cells [148]. One of the research studies suggested that the anti-leprotic drug clofazimine could be a favorable contender for repurposing it in triple-negative breast cancer (TNBC), one of the most complicated cancers to treat. Numerous cellular processes such as cell evolution, proliferation, migration, and development are governed by wnt signaling regulatory pathways. Hyper-activation of the

wnt signaling pathway is the basic pathophysiology observed in TNBC. No drug is currently available that can target this pathway other than clofazimine that has anti-cancer influence by inhibiting hyper-activated wnt signaling pathway in TNBC cells as well as by inhibiting tumor growth in mouse xenograft experiments [149-151].

8.7. Kidney Disorders

Levosimendan, a drug initially used for cardiac failure, has shown potent renal protection against ischemia-induced reno-toxicity. The drug reduces renal injury activating nitric oxide (NO) synthase and mitochondrial ATP-sensitive potassium channel leading to increased blood flow, vasodilation, Glomerular Filtration Rate (GFR), and renal oxygenation. Treatment with GLP-1R agonist in the rat model for Type I and II diabetes showed significant renal protection which was mediated by its action on the infiltrating inflammatory cells and glomerular endothelial cells [152]. The GLP-1R also showed an anti-inflammatory effect by activating the cyclic adenosine monophosphate pathway and reducing receptor for advanced glycation end products (RAGE) expression in mesangial cells. Recombinant GLP-1 dominates the angiotensin II actions and reduce proteinuria and renal pathology. Xanthine Oxidase (XO) inhibitors allopurinol and febustat lower serum uric acid and decrease the production of reactive oxygen species by inhibiting the renin-angiotensin system (RAS) [153-155].

8.8. Rare Diseases

Over 6500 rare diseases are documented in medical literature and about 1 in every 17 people is affected by some of the other rare diseases. Unfortunately, less than 5% of approved therapeutic drugs are available for them. Also, rare diseases are often not on the agenda of many pharmaceutical companies for new drug development. However, this economic barrier can be overcome by utilizing a drug repositioning approach that can help rare-disease researchers to create new cures. Rapamycin, due to its immunosuppressant properties, was originally developed as an organ transplant anti-rejection drug. It is now found to be effective in the treatment of pediatric blood disease, Autoimmune Lymphoproliferative Syndrome (ALPS). Sirolimus was also found to ameliorate the symptoms of ALPS as well as presently, it is clinically tested in a number of rare diseases, including autoimmune hemolytic anemia, pediatric lupus, and Evan's disease. Nitrofenone, a drug used in hereditary tyrosinemia type 1 is being tested for the rare disease alkaptunuria. Rare disease late infantile neuronal ceroid lipofuscinosis (LINCL) is a neurodegenerative disorder accompanied by progressive mental deterioration and cognitive disturbances. LINCL is found to be associated with mutations in the Cln2 gene that encodes Tripeptidyl-Tripeptidase I (TPP-I). Cln2 gene mutation leads to failure of TPP-I to remove tripeptides which results in the accumulation of ceroid-lipofuscin and brain cell destruction. The effectiveness of the combination of gemfibrozil and ATRA in upregulating the expression of Cln2 gene via the PPAR α /RXR α pathway is currently being investigated both in cell lines and animal models [156-159].

8.9. Ulcerative Colitis

Quinacrine originally used as an antimalarial, antiprotozoal, and anticancer drug is under investigation to be repurposed for ulcerative colitis (UC). Quinacrine acts by suppressing the levels of inflammatory biomarkers such as ions, Cox-2, p53 *in vitro* and *in vivo*, and clinical disease index (CDI) in dextran-induced mouse models of UC. The additional mechanism involves the blockade of the inflammatory pathway, such as arachidonic acid cascade, phospholipase A2 and formation of prostaglandins. The Janus kinase/ signal transducers and activators of transcription (JAK/STAT) inflammatory pathway has been found to increase the level of pro-inflammatory mediators mainly the interleukins (ILs) and cytokines, expressed by T-helper 17 (Th17) lymphocytes. Tofacitinib is an inhibitor of JAK/STAT inflammatory pathways that target a major candidate gene JAK2 and could be repurposed for ulcerative colitis, as these mediators play a magnificent role in the pathogenesis of UC. A drug used for myelofibrosis ruxolitinib, is an inhibitor of JAK and target candidate gene JAK2. It could also be considered for repurposing in UC. Muromonab is used in patients to avoid acute organ transplant rejection. Preclinical studies have demonstrated that muromonab has an effect on autoimmune reactions, mainly T cell activation. Clinical data also represents that muromonab inhibits Th1 activation and decreases the levels of IL2. A phase II placebo-controlled trial showed the efficacy of this drug in other inflammatory disorders that share the same genetic background as that of UC. Thus, muromonab is a potent candidate that can be repurposed for the treatment and management of IBD. A randomized, double-blinded clinical trial showed the effectiveness of rosiglitazone in UC by reducing colonic inflammation. Rosiglitazone is an agonist for peroxisome proliferator-activated receptors- gamma (PPAR- γ) and acts by increasing the levels of adipophilin and activity of PPAR γ in epithelial cells of exacerbated mucosa. Rosiglitazone also reduced the disease activity score from 9 to 4. A recent study demonstrated that Gamma-Aminobutyric Acid (GABA) plays a significant role in gastrointestinal inflammation. Potent anti-epileptic drug with GABA agonistic property, topiramate has shown to significantly reduced basic clinical manifestations of UC as marked by reduced disease activity score and histopathological reports [160-163].

8.10. Miscellaneous Applications of Drug Repositioning

- [i] Celebrex, a COX-2 inhibitor is widely used for the treatment of osteoarthritis. Recently it presented beneficial effects in colon cancer, reducing the risk of additional polyp formation without negative gastrointestinal effects associated with existing treatments.
- [ii] Nitrocatechols currently used in the treatment of Parkinson's disease were found to significantly inhibit tau-aggregation suggesting that nitrocatechols have the potential to be repurposed as a novel drug in Alzheimer's and other tau pathologies.
- [iii] In recent preclinical experimentation, researchers

found a protein in the endoplasmic reticulum named Sigma-1 Receptor (S1R) that restricts inflammatory reaction in sepsis. Antidepressant drug fluvoxamine acts as an agonist to S1R receptor and limits the activity of stress sensors and decreases the levels of inflammatory cytokines in a mouse model of septic shock.

- [iv] Various cancer studies suggested GSK3 α/β as a novel tumor suppressor pair that disrupts β -catenin and obstructs Wnt signaling pathway in acute myeloid leukemia (AML). A highly specific c-Met tyrosine kinase inhibitor tivantinib targets GSK3 α/β , exhibiting its anticancer activity in AML.
- [v] Antidepressant drug clomipramine may be an attractive treatment option for leishmaniasis. It acts by inducing lipid peroxidation, oxidative stress, plasma membrane permeability, apoptosis and autophagy in *Leishmania amazonensis*.
- [vi] Immunosuppressive drug tacrolimus may also have an efficient application in bone renewing engineering. In an *in vitro* screening, tacrolimus showed extensive osteogenic response within a day. Tacrolimus can be therapeutically switched as a promoter of osteogenesis that may help scheme effective approaches to regenerate, revive, and renew osteogenic tissues.
- [vii] Antidiabetic drug metformin has been shown to reduce the risk of breast cancer in diabetes patients and is being investigated as a treatment for cancer in many clinical trials.
- [viii] *All-trans* retinoic acid has brought remission of acute promyelocytic leukemia in 90% of treated patients which is used as a popular remedy for acne.
- [ix] The antibiotic minocycline, which is used to treat acne and sexually transmitted infections, also decreases the symptoms of patients with Fragile-X syndrome, a genetic disorder that leads to cognitive disabilities. It is being evaluated in clinical trials.
- [x] National Cancer Institute discovered a new indication for drug pentostatin, which was originally used as a chemotherapeutic agent for specific T cell-related leukemia. The drug showed successful efficacy in treating a B-cell related rare leukemia called hairy cell leukemia [164].

9. CHALLENGES AND LIMITATIONS

There have been prominent success stories for the drug repositioning approach (Table 1), yet the strategy does not always flourish. There have been certain drug molecules that failed at the terminal phase III of the repurposing process or even some candidates failed at the late stage of drug development. These failures are not just due to drug safety and toxicity profiles, there can be several reasons that may fail the repositioning. The barriers explicit to drug reprofiling include regulatory aspects, patent considerations, and organizational hurdles.

9.1. Regulatory Aspects of Drug Repositioning

For a drug to be repurposed successfully, regulatory approval is the most essential and crucial step. However, multiple challenges lie between a drug development phase and regulatory approval.

- 1) In order to improve the effectiveness of the drug, it has to pass through a long optimization procedure during repurposing. If a drug acts on more than one target, its affinity, efficacy, and potency have to be compared between primary and secondary targets. Consequently, targets are validated experimentally in order to determine the association between the primary target on which a drug acts and a new secondary target.
- 2) For a target-specific drug, the probabilities of it being repurposed for some other secondary target is often impractical as the efficacy of the drug for the novel target recognized will be lower than for the chief target [39]. Thus 505(b) (2) regulatory process necessitates significant novelty in order to seek the regulatory approval and intellectual property generation of the drug being repositioned.
- 3) No matter whether the repositioned drug has already undergone the robust process of clinical trials and regulatory approval for the primary objectives, whenever a new therapeutic indication has been proposed, a substantial quantum of supportive scientific evidence is always required.
- 4) A drug reprofiling process includes the re-scrutinizing and re-inspecting drugs that are already marketed for some other indication or that have been withdrawn from the market or discontinued from clinical evaluation. This necessitates the evaluation of the safety-toxicity ratio and relevant pharmacodynamic and pharmacokinetic profiles of the drug. Presently, numerous drug depositories' options exist, but repositioning them to a novel drug candidate is still a tough task.
- 5) Lack of association and connection between the pharma industry and academic institutes is another struggling factor that suppresses re-profiling applications.
- 6) Extensive research on drug repositioning projects has been carried out by a number of pharmaceutical and biotechnological companies as well as at the level of academia, but due to lack of resources/capitals and failure to discover the right marketable partners, these institutions fail to advertise and commercialize the positive results of the drug discovery [165, 166].

9.2. Patent Considerations

Therapeutic switching of a molecule is embedded with several intellectual property and legal barriers. Complications allied with patenting a novel repurposed therapeutic indication and imposing patent rights are the main hurdles in motivating the strategy, as it may have a huge influence on the probable profit anticipated from the repositioned drug molecule. There are abundant potential repurposed drug examples specified in the various scientific reports. Even if the clinical efficacy of the molecule is not established with signi-

ificant results, previous scientific information of the repurposed indication could limit the ability to attain patent considerations unless the patentee mentions certain differentiation between patent claims and previously available knowledge in the public domain. For obtaining a patent grant of a novel repurposed therapeutic indication, it is mandatory for the applicant to present entire scientific data in the patent application exhibiting the credible efficacy of the drug for the management of the new disease concerned. For off-patent drugs, there is a separate method-of-use (MOU) patent that can be attained for the novel repurposed application of the original generic drug. However, but if the novel repurposed indication employs the use of previously available dosage forms and formulations of the generic drug, the patent execution may be a major concern. Thus, to maximize the patentability chances, approaches such as development of the new drug preparations, formulations, and dosage forms or the development of advanced derivatives having similar therapeutic actions or by receiving exclusive marketing sanction in other geographical areas.

9.3. Organizational Hurdles in Industry

The potential of drug repositioning strategy is now being recognized by the pharmaceutical companies and are open up for various forms of collaborations with academic institutes and biotech industries. The notable examples of such industries include the AstraZeneca Open Innovation Platform, GlaxoSmithKline, and Centers for Therapeutic Innovation at Pfizer, which encourages external collaborations to augment the research in drug repurposing. However, the pharmaceutical industry can face certain hurdles in the drug repurposing research, specifically, if the novel repositioned indication/disorder does not fall into the core disease criteria of the organization or if the drug molecule has been withdrawn from the further development and therefore no further dedicated support (in form of personnel, resources or funding) to the project within the R&D division for the new therapeutic indication. Utilization of regulatory support, alternate funding sources or use of external drug supply resources, as well as augmenting the choice of the drug compounds are some ways to address these organizational hurdles.

Table 1. List of repurposed drugs.

S. no.	Drug	Original Indication	Repurposed Indication
1.	5-nitro-8-quinolinol	Antimicrobial, anticancer, and anti-inflammatory	Neuroprotection
2.	Aripiprazole	Antipsychotic	Candida infections
3.	Azithromycin,	Pneumonia	Pulmonary Sarcoidosis
4.	Chloroquine	Malaria	T-cell acute lymphoblastic leukemia
5.	Dichlorophen	Antiparasitic	Alveolar echinococcosis
6.	Exenatide	Type-II diabetes	Neurological conditions and idiopathic intracranial hypertension
7.	Felodipine	Anti-hypertensive drug	Neurogenerative diseases
8.	Fluoxetine	Depression	Diabetic foot ulcers
9.	Haloperidol	Antipsychotic drug	Fibrosis
10.	Liraglutide	Type 2 diabetes adults	Type 2 diabetes children and adolescents
11.	Lopinavir/ritonavir	HIV-1 infection	COVID-19 (under clinical trial)
12.	Obinutuzumab	Chronic lymphocytic leukemia	Lupus nephritis
13.	Miconazole	Fungal infection	Breast cancer
14.	Metformin	Type-II diabetes	Schizophrenia
15.	Methotrexate	Anti-cancer	Rheumatoid arthritis
16.	Minocycline	Acne	Arterial calcification
17.	Nifuroxazide	diarrhea	Cancer
18.	Nintedanib	Idiopathic pulmonary fibrosis	Interstitial lung disease
19.	Pantothenamides	Psoriasis	Malarial
20.	Penfluridol	Psychosis	Glioblastomas
21.	Pregabalin	Epilepsy & neuropathic pain	Postherpetic neuralgia and chronic refractory cough
22.	Promethazine	Antihistamine	Schistosomiasis
23.	Ramucirumab	Stomach, lung and colorectal cancer	Hepatocellular carcinoma
24.	Remdesivir	Ebola virus	COVID-19 (under clinical trial)
25.	Ribostamycin sulfate	Sepsis skin infection, chronic pyoderma, osteomyelitis	Chikungunya virus
26.	Sunitinib	Cancer	Brain aneurysms
27.	Tegaserod maleate	Irritable bowel syndrome	Lung, liver, and prostate cancers
28.	Terazosin hydrochloride	Prostatic hyperplasia	Parkinson's disease
29.	Ustekinumab	Plaque psoriasis, psoriatic arthritis	Moderate to severe ulcerative colitis
30.	Verapamil	Tachyarrhythmias	Pediatric ependymoma

9.4. Limitations

Despite massive research in the field of drug repositioning, utilization of reprofiled drugs are limited and face major obstacles related to their safety, mode of delivery and therapeutic dosage. The major concern related to repositioned drugs includes:

- 1) The establishment of the fixed-dose range inside the accepted therapeutic index, as the clinical utility of finding novel drug-target communication within the well-defined safety margins, has rarely been reported.
- 2) The augmented dose of the drug is generally essential to produce the desired efficacy for the new indications, which in turn require a reconsideration of the drug administration route that can further affect the progression of repurposed drugs significantly.
- 3) Safety studies are mandatory to conduct if the desired effective dose falls outside the therapeutic window range. Thus, it is sometimes not feasible to achieve all aspects such as vibrant therapeutic advantages, as well as the discovery of novel drug-target interactions within a specified therapeutic window.
- 4) Although not many clinical trials are necessary for repurposed drugs, the conduction of clinical studies with reference to the efficacy of a molecule against new indication is mandatory. Hence, the chief discrepancy among *de-novo* drug discovery and repositioning is lost while lessening the advantages of drug reprofiling.
- 5) The issues of novel repurposed drugs such as permeability, stability, pharmacokinetics and biodistribution parameters, and solubility may lead to a problem for its utilization.
- 6) The drug release profile of the repurposed candidate dosage form is necessary to be modulated for the establishment of an effective therapeutic action.
- 7) As per the required indication, the repurposed drug must possess certain properties like the ability to permeate through the blood-brain barrier, effective intestinal penetration, cellular permeability, and sustained release profile. Consequently, additional efforts are needed for the successful repositioning of the drug candidates against new indication.
- 8) Reformulation of the repurposed drug or coupling of the formulation with appropriate drug delivery devices is challenging. This may further necessitate the amalgamation of pharmaceutical sciences with toxicological sciences to explore the most safer dose.
- 9) No stringent guidelines and regulations related to drug repurposing have been confirmed by any regulatory agencies counting the FDA that reflects a potent hurdle in the drug reprofiling process [167].

CONCLUSION

Although pharmaceutical companies invest a lot, the development of new drugs has failed to keep up with the increasing incidence of many diseases. Drug repositioning

strategy tries to overcome the blockages frequently encountered with conventional approaches. Drug repositioning accelerates the drug development process by identifying new uses of already approved drugs for the treatment of various ailments. However, there are certain recommendations that need to be considered for realizing the potential of the approach. The process requires further simplification. The access to various industries-formulated clinical and preclinical drugs need major consideration. Enhanced access to these compounds should be allowed to academic researchers as well. Boosted funding opportunities are also essential to support various organizations to carry out drug repurposing research. Since intracellular signaling pathways and molecular mechanisms behind many diseases are still not fully understood, the direct application of polypharmacology and repurposing of drugs becomes difficult. However, extensive research is being carried out to collect information and data regarding the polypharmacology of the drug, the application of which will eventually help in the future of drug development. Moreover, augmented collaboration and partnership between industry and academics is recommended to make the strategy more efficient.

CONSENT FOR PUBLICATION

Not applicable

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Deotarse PP, Jain A, Baile MB. Drug repositioning: a review. *Int J Pharma Res Rev* 2015; 4: 51-8.
- [2] Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. *Nat Rev Drug Discov* 2004; 3(8): 673-83.
[<http://dx.doi.org/10.1038/nrd1468>] [PMID: 15286734]
- [3] Napolitano F, Zhao Y, Moreira VM, et al. Drug repositioning: a machine-learning approach through data integration. *J Cheminform* 2013; 5(1): 30.
[<http://dx.doi.org/10.1186/1758-2946-5-30>] [PMID: 23800010]
- [4] Zou J, Zheng MW, Li G, Su ZG. Advanced systems biology methods in drug discovery and translational biomedicine. *BioMed Res Int* 2013; 2013: 742835.
[<http://dx.doi.org/10.1155/2013/742835>] [PMID: 24171171]
- [5] Swinney DC, Anthony J. How were new medicines discovered? *Nat Rev Drug Discov* 2011; 10(7): 507-19.
[<http://dx.doi.org/10.1038/nrd3480>] [PMID: 21701501]
- [6] Novac N. Challenges and opportunities of drug repositioning. *Trends Pharmacol Sci* 2013; 34(5): 267-72.
[<http://dx.doi.org/10.1016/j.tips.2013.03.004>] [PMID: 23582281]
- [7] Allarakha M. Open-source approaches for the repurposing of existing or failed candidate drugs: learning from and applying the lessons across diseases. *Drug Des Devel Ther* 2013; 7: 753-66.
[<http://dx.doi.org/10.2147/DDDT.S46289>] [PMID: 23966771]
- [8] Swamidass SJ. Mining small-molecule screens to repurpose drugs.

- Brief Bioinform 2011; 12(4): 327-35.
[<http://dx.doi.org/10.1093/bib/bbr028>] [PMID: 21715466]
- [9] Keiser MJ, Setola V, Irwin JJ, et al. Predicting new molecular targets for known drugs. Nature 2009; 462(7270): 175-81.
[<http://dx.doi.org/10.1038/nature08506>] [PMID: 19881490]
- [10] Campillos M, Kuhn M, Gavin AC, Jensen LJ, Bork P. Drug target identification using side-effect similarity. Science 2008; 321(5886): 263-6.
[<http://dx.doi.org/10.1126/science.1158140>] [PMID: 18621671]
- [11] Zhu F, Han B, Kumar P, et al. Update of TTD: Therapeutic Target Database. Nucleic Acids Res 2010; 38(Database issue): D787-91.
[<http://dx.doi.org/10.1093/nar/gkp1014>] [PMID: 19933260]
- [12] Overington JP, Al-Lazikani B, Hopkins AL. How many drug targets are there? Nat Rev Drug Discov 2006; 5(12): 993-6.
[<http://dx.doi.org/10.1038/nrd2199>] [PMID: 17139284]
- [13] Cheng F, Liu C, Jiang J, et al. Prediction of drug-target interactions and drug repositioning via network-based inference. PLOS Comput Biol 2012; 8(5): e1002503.
[<http://dx.doi.org/10.1371/journal.pcbi.1002503>] [PMID: 22589709]
- [14] O'Connor KA, Roth BL. Finding new tricks for old drugs: an efficient route for public-sector drug discovery. Nat Rev Drug Discov 2005; 4(12): 1005-14.
[<http://dx.doi.org/10.1038/nrd1900>] [PMID: 16341065]
- [15] Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov 2011; 10(6): 428-38.
[<http://dx.doi.org/10.1038/nrd3405>] [PMID: 21629293]
- [16] Tobinick EL. The value of drug repositioning in the current pharmaceutical market. Drug News Perspect 2009; 22(2): 119-25.
[<http://dx.doi.org/10.1358/dnp.2009.22.2.1303818>] [PMID: 19330170]
- [17] Sleigh SH, Barton CL. Repurposing strategies for therapeutics. Pharmaceut Med 2010; 24(3): 151-9.
[<http://dx.doi.org/10.1007/BF03256811>]
- [18] Chong CR, Sullivan DJ Jr. New uses for old drugs. Nature 2007; 448(7154): 645-6.
[<http://dx.doi.org/10.1038/448645a>] [PMID: 17687303]
- [19] Kaitin KI. Deconstructing the drug development process: the new face of innovation. Clin Pharmacol Ther 2010; 87(3): 356-61.
[<http://dx.doi.org/10.1038/clpt.2009.293>] [PMID: 20130565]
- [20] Liu Z, Fang H, Reagan K, et al. *In silico* drug repositioning: what we need to know. Drug Discov Today 2013; 18(3-4): 110-5.
[<http://dx.doi.org/10.1016/j.drudis.2012.08.005>] [PMID: 22935104]
- [21] Méndez-Lucio O, Tran J, Medina-Franco JL, Meurice N, Muller M. Toward drug repurposing in epigenetics: olsalazine as a hypermethylating compound active in a cellular context. ChemMedChem 2014; 9(3): 560-5.
[<http://dx.doi.org/10.1002/cmde.201300555>] [PMID: 24482360]
- [22] Keiser MJ, Roth BL, Arnsburger BN, Ernsberger P, Irwin JJ, Shoichet BK. Relating protein pharmacology by ligand chemistry. Nat Biotechnol 2007; 25(2): 197-206.
[<http://dx.doi.org/10.1038/nbt1284>] [PMID: 17287757]
- [23] Kovács D, Simon Z, Hári P, et al. Identification of PPAR γ ligands with one-dimensional drug profile matching. Drug Des Devel Ther 2013; 7: 917-28.
[<http://dx.doi.org/10.2147/DDDT.S47173>] [PMID: 24039401]
- [24] Dudley JT, Sirota M, Shenoy M, et al. Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. Sci Transl Med 2011; 3(96): 96ra76.
[<http://dx.doi.org/10.1126/scitranslmed.3002648>] [PMID: 21849664]
- [25] Nacher JC, Schwartz JM. A global view of drug-therapy interactions. BMC Pharmacol 2008; 8(1): 5.
[<http://dx.doi.org/10.1186/1471-2210-8-5>] [PMID: 18318892]
- [26] Hopkins AL. Drug discovery: predicting promiscuity. Nature 2009; 462(7270): 167-8.
[<http://dx.doi.org/10.1038/462167a>] [PMID: 19907483]
- [27] Andronis C, Sharma A, Virvilis V, Deftereos S, Persidis A. Literature mining, ontologies and information visualization for drug repurposing. Brief Bioinform 2011; 12(4): 357-68.
[<http://dx.doi.org/10.1093/bib/bbr005>] [PMID: 21712342]
- [28] Huang R, Southall N, Wang Y, et al. The NCGC pharmaceutical collection: a comprehensive resource of clinically approved drugs enabling repurposing and chemical genomics. Sci Transl Med 2011; 3(80): 80ps16.
[<http://dx.doi.org/10.1126/scitranslmed.3001862>] [PMID: 21525397]
- [29] Feng BY, Simeonov A, Jadhav A, et al. A high-throughput screen for aggregation-based inhibition in a large compound library. J Med Chem 2007; 50(10): 2385-90.
[<http://dx.doi.org/10.1021/jm061317y>] [PMID: 17447748]
- [30] Yildirim MA, Goh KI, Cusick ME, Barabási AL, Vidal M. Drug-target network. Nat Biotechnol 2007; 25(10): 1119-26.
[<http://dx.doi.org/10.1038/nbt1338>] [PMID: 17921997]
- [31] Iskar M, Zeller G, Blattmann P, et al. Characterization of drug-induced transcriptional modules: towards drug repositioning and functional understanding. Mol Syst Biol 2013; 9: 662.
[<http://dx.doi.org/10.1038/msb.2013.201>] [PMID: 23632384]
- [32] Kolb P, Ferreira RS, Irwin JJ, Shoichet BK. Docking and chemoinformatic screens for new ligands and targets. Curr Opin Biotechnol 2009; 20(4): 429-36.
[<http://dx.doi.org/10.1016/j.copbio.2009.08.003>] [PMID: 19733475]
- [33] Wu Z, Li W, Liu G, Tang Y. Network-based methods for prediction of drug-target interactions. Front Pharmacol 2018; 9: 1134.
[<http://dx.doi.org/10.3389/fphar.2018.01134>] [PMID: 30356768]
- [34] Pantziarka P, André N. Editorial: drug repurposing. Front Med (Lausanne) 2019; 6: 154.
[<http://dx.doi.org/10.3389/fmed.2019.00154>] [PMID: 31334237]
- [35] Reaume AG. Drug repurposing through nonhypothesis driven phenotypic screening. Drug Discov Today Ther Strateg 2011; 8: 85-8.
[<http://dx.doi.org/10.1016/j.ddstr.2011.09.007>]
- [36] Sardana D, Zhu C, Zhang M, Gudivada RC, Yang L, Jegga AG. Drug repositioning for orphan diseases. Brief Bioinform 2011; 12(4): 346-56.
[<http://dx.doi.org/10.1093/bib/bbr021>] [PMID: 21504985]
- [37] Ekins S, Williams AJ, Krasowski MD, Freundlich JS. *In silico* repositioning of approved drugs for rare and neglected diseases. Drug Discov Today 2011; 16(7-8): 298-310.
[<http://dx.doi.org/10.1016/j.drudis.2011.02.016>] [PMID: 21376136]
- [38] Deftereos SN, Andronis C, Friedla EJ, Persidis A, Persidis A. Drug repurposing and adverse event prediction using high-throughput literature analysis. Wiley Interdiscip Rev Syst Biol Med 2011; 3(3): 323-34.
[<http://dx.doi.org/10.1002/wsbm.147>] [PMID: 21416632]
- [39] Dudley JT, Deshpande T, Butte AJ. Exploiting drug-disease relationships for computational drug repositioning. Brief Bioinform 2011; 12(4): 303-11.
[<http://dx.doi.org/10.1093/bib/bbr013>] [PMID: 21690101]
- [40] Loging W, Rodriguez-Esteban R, Hill J, et al. Chemoinformatic/bioinformatic analysis of large corporate databases: Application to drug repurposing. Drug Discov Today Ther Strateg 2011; 8: 109-16.
[<http://dx.doi.org/10.1016/j.ddstr.2011.06.004>]
- [41] Koutsoukas A, Simms B, Kirchmair J, et al. From *in silico* target prediction to multi-target drug design: current databases, methods and applications. J Proteomics 2011; 74(12): 2554-74.
[<http://dx.doi.org/10.1016/j.jprot.2011.05.011>] [PMID: 21621023]
- [42] Wang L, Ma C, Wipf P, Liu H, Su W, Xie XQ. TargetHunter: an *in silico* target identification tool for predicting therapeutic potential of small organic molecules based on chemogenomic database. AAPS J 2013; 15(2): 395-406.
[<http://dx.doi.org/10.1208/s12248-012-9449-z>] [PMID: 23292636]
- [43] Perez-Nueno VI, Souchet M, Karaboga AS, et al. Predicting drug side effects from drug-target relationships. J Chem Inf Model 2012; 52: 1948-61.
[<http://dx.doi.org/10.1021/ci300471k>] [PMID: 22747187]
- [44] Achenbach J, Klingler FM, Hahn S, et al. Fragment-based identification of multi-target ligands by self-organizing map alignment. J Cheminform 2012; 4(1): 57.
[<http://dx.doi.org/10.1186/1758-2946-4-S1-P57>]
- [45] Dunkel M, Günther S, Ahmed J, Wittig B, Preissner R. Super-

- Pred: drug classification and target prediction. *Nucleic Acids Res* 2008; 36(Web Server issue): W55-9.
[\[http://dx.doi.org/10.1093/nar/gkn307\]](http://dx.doi.org/10.1093/nar/gkn307) [PMID: 18499712]
- [46] Allison M. NCATS launches drug repurposing program. *Nat Biotechnol* 2012; 30(7): 571-2.
[\[http://dx.doi.org/10.1038/nbt0712-571a\]](http://dx.doi.org/10.1038/nbt0712-571a) [PMID: 22781662]
- [47] Chen X, Ji ZL, Chen YZ. TTD: Therapeutic target database. *Nucleic Acids Res* 2002; 30(1): 412-5.
[\[http://dx.doi.org/10.1093/nar/30.1.412\]](http://dx.doi.org/10.1093/nar/30.1.412) [PMID: 11752352]
- [48] Pérez-Nueno VI, Karaboga AS, Souchet M, Ritchie DW. GES polypharmacology fingerprints: a novel approach for drug repositioning. *J Chem Inf Model* 2014; 54(3): 720-34.
[\[http://dx.doi.org/10.1021/ci4006723\]](http://dx.doi.org/10.1021/ci4006723) [PMID: 24494653]
- [49] Bender A, Young DW, Jenkins JL, et al. Chemogenomic data analysis: prediction of small-molecule targets and the advent of biological fingerprint. *Comb Chem High Throughput Screen* 2007; 10(8): 719-31.
[\[http://dx.doi.org/10.2174/138620707782507313\]](http://dx.doi.org/10.2174/138620707782507313) [PMID: 18045083]
- [50] Jenkins JL, Bender A, Davies JW. *In silico* target fishing: predicting biological targets from chemical structure. *Drug Discov Today Technol* 2006; 3(4): 413-21.
[\[http://dx.doi.org/10.1016/j.ddtec.2006.12.008\]](http://dx.doi.org/10.1016/j.ddtec.2006.12.008)
- [51] Schomburg KT, Bietz S, Briem H, Henzler AM, Urbaczek S, Rarey M. Facing the challenges of structure-based target prediction by inverse virtual screening. *J Chem Inf Model* 2014; 54(6): 1676-86.
[\[http://dx.doi.org/10.1021/ci500130e\]](http://dx.doi.org/10.1021/ci500130e) [PMID: 24851945]
- [52] Shen C, Ding Y, Tang J, Xu X, Guo F. An ameliorated prediction of drug-target interactions based on multi-scale discrete wavelet transform and network features. *Int J Mol Sci* 2017; 18(8): 1781.
[\[http://dx.doi.org/10.3390/ijms18081781\]](http://dx.doi.org/10.3390/ijms18081781) [PMID: 28813000]
- [53] Adams JC, Keiser MJ, Basuino L, et al. A mapping of drug space from the viewpoint of small molecule metabolism. *PLOS Comput Biol* 2009; 5(8): e1000474.
[\[http://dx.doi.org/10.1371/journal.pcbi.1000474\]](http://dx.doi.org/10.1371/journal.pcbi.1000474) [PMID: 19701464]
- [54] Chen B, McConnell KJ, Wale N, Wild DJ, Gifford EM. Comparing bioassay response and similarity ensemble approaches to probing protein pharmacology. *Bioinformatics* 2011; 27(21): 3044-9.
[\[http://dx.doi.org/10.1093/bioinformatics/btr506\]](http://dx.doi.org/10.1093/bioinformatics/btr506) [PMID: 21903625]
- [55] Wu C, Gudivada RC, Aronow BJ, Jegga AG. Computational drug repositioning through heterogeneous network clustering. *BMC Syst Biol* 2013; 7 (Suppl. 5): S6.
[\[http://dx.doi.org/10.1186/1752-0509-7-S5-S6\]](http://dx.doi.org/10.1186/1752-0509-7-S5-S6) [PMID: 24564976]
- [56] Wang L, Xie XQ. Computational target fishing: what should chemogenomics researchers expect for the future of *in silico* drug design and discovery? *Future Med Chem* 2014; 6(3): 247-9.
[\[http://dx.doi.org/10.4155/fmc.14.5\]](http://dx.doi.org/10.4155/fmc.14.5) [PMID: 24575960]
- [57] Nettles JH, Jenkins JL, Bender A, Deng Z, Davies JW, Glick M. Bridging chemical and biological space: “target fishing” using 2D and 3D molecular descriptors. *J Med Chem* 2006; 49(23): 6802-10.
[\[http://dx.doi.org/10.1021/jm060902w\]](http://dx.doi.org/10.1021/jm060902w) [PMID: 17154510]
- [58] Gfeller D, Grosdidier A, Wirth M, Daina A, Michelin O, Zoete V. SwissTargetPrediction: a web server for target prediction of bioactive small molecules. *Nucleic Acids Res* 2014; 42(Web Server issue): W32-8.
[\[http://dx.doi.org/10.1093/nar/gku293\]](http://dx.doi.org/10.1093/nar/gku293) [PMID: 24792161]
- [59] Hawkins PCD, Skillman AG, Nicholls A. Comparison of shape-matching and docking as virtual screening tools. *J Med Chem* 2007; 50(1): 74-82.
[\[http://dx.doi.org/10.1021/jm0603365\]](http://dx.doi.org/10.1021/jm0603365) [PMID: 17201411]
- [60] Ballester PJ, Richards WG. Ultrafast shape recognition to search compound databases for similar molecular shapes. *J Comput Chem* 2007; 28(10): 1711-23.
[\[http://dx.doi.org/10.1002/jcc.20681\]](http://dx.doi.org/10.1002/jcc.20681) [PMID: 17342716]
- [61] Venkatraman V, Pérez-Nueno VI, Mavridis L, Ritchie DW. Comprehensive comparison of ligand-based virtual screening tools against the DUD data set reveals limitations of current 3D methods. *J Chem Inf Model* 2010; 50(12): 2079-93.
[\[http://dx.doi.org/10.1021/ci100263p\]](http://dx.doi.org/10.1021/ci100263p) [PMID: 21090728]
- [62] Gfeller D, Michelin O, Zoete V. Shaping the interaction landscape of bioactive molecules. *Bioinformatics* 2013; 29(23): 3073-9.
[\[http://dx.doi.org/10.1093/bioinformatics/btt540\]](http://dx.doi.org/10.1093/bioinformatics/btt540) [PMID: 24048355]
- [63] Reker D, Rodrigues T, Schneider P, Schneider G. Identifying the macromolecular targets of *de novo*-designed chemical entities through self-organizing map consensus. *Proc Natl Acad Sci USA* 2014; 111(11): 4067-72.
[\[http://dx.doi.org/10.1073/pnas.1320001111\]](http://dx.doi.org/10.1073/pnas.1320001111) [PMID: 24591595]
- [64] Bender A, Scheiber J, Glick M, et al. Analysis of pharmacology data and the prediction of adverse drug reactions and off-target effects from chemical structure. *ChemMedChem* 2007; 2(6): 861-73.
[\[http://dx.doi.org/10.1002/cmde.200700026\]](http://dx.doi.org/10.1002/cmde.200700026) [PMID: 17477341]
- [65] Pulley JM, Rhoads JP, Jerome RN, et al. Using what we already have: uncovering new drug repurposing strategies in existing omics data. *Annu Rev Pharmacol Toxicol* 2020; 60: 333-52.
[\[http://dx.doi.org/10.1146/annurev-pharmtox-010919-023537\]](http://dx.doi.org/10.1146/annurev-pharmtox-010919-023537) [PMID: 31337270]
- [66] Ptolemy AS, Rifai N. What is a biomarker? Research investments and lack of clinical integration necessitate a review of biomarker terminology and validation schema. *Scand J Clin Lab Invest Suppl* 2010; 242: 6-14.
[\[http://dx.doi.org/10.3109/00365513.2010.493354\]](http://dx.doi.org/10.3109/00365513.2010.493354) [PMID: 20515269]
- [67] Hampel H, Frank R, Broich K, et al. Biomarkers for Alzheimer’s disease: academic, industry and regulatory perspectives. *Nat Rev Drug Discov* 2010; 9(7): 560-74.
[\[http://dx.doi.org/10.1038/nrd3115\]](http://dx.doi.org/10.1038/nrd3115) [PMID: 20592748]
- [68] Ransohoff DF. Proteomics research to discover markers: what can we learn from Netflix? *Clin Chem* 2010; 56(2): 172-6.
[\[http://dx.doi.org/10.1373/clinchem.2009.126698\]](http://dx.doi.org/10.1373/clinchem.2009.126698) [PMID: 20040622]
- [69] Goodsaid FM, Mendrick DL. Translational medicine and the value of biomarker qualification. *Sci Transl Med* 2010; 2(47): 47ps-44.
[\[http://dx.doi.org/10.1126/scitranslmed.3001040\]](http://dx.doi.org/10.1126/scitranslmed.3001040) [PMID: 20811041]
- [70] Anderson NL. The clinical plasma proteome: a survey of clinical assays for proteins in plasma and serum. *Clin Chem* 2010; 56(2): 177-85.
[\[http://dx.doi.org/10.1373/clinchem.2009.126706\]](http://dx.doi.org/10.1373/clinchem.2009.126706) [PMID: 19884488]
- [71] Bauer DC, Hunter DJ, Abramson SB, et al. Osteoarthritis Biomarkers Network. Classification of osteoarthritis biomarkers: a proposed approach. *Osteoarthritis Cartilage* 2006; 14(8): 723-7.
[\[http://dx.doi.org/10.1016/j.joca.2006.04.001\]](http://dx.doi.org/10.1016/j.joca.2006.04.001) [PMID: 16733093]
- [72] Kuo TR, Chen CH. Bone biomarker for the clinical assessment of osteoporosis: recent developments and future perspectives. *Biomark Res* 2017; 5: 18.
[\[http://dx.doi.org/10.1186/s40364-017-0097-4\]](http://dx.doi.org/10.1186/s40364-017-0097-4) [PMID: 28529755]
- [73] Lindström E, Rizoska B, Henderson I, et al. Nonclinical and clinical pharmacological characterization of the potent and selective cathepsin K inhibitor MIV-711. *J Transl Med* 2018; 16(1): 125.
[\[http://dx.doi.org/10.1186/s12967-018-1497-4\]](http://dx.doi.org/10.1186/s12967-018-1497-4) [PMID: 29743078]
- [74] Ferreira A, Alho I, Casimiro S, Costa L. Bone remodeling markers and bone metastases: From cancer research to clinical implications. *Bonekey Rep* 2015; 4: 668.
[\[http://dx.doi.org/10.1038/bonekey.2015.35\]](http://dx.doi.org/10.1038/bonekey.2015.35) [PMID: 25908969]
- [75] Conversano F, Franchini R, Greco A, et al. A novel ultrasound methodology for estimating spine mineral density. *Ultrasound Med Biol* 2015; 41(1): 281-300.
[\[http://dx.doi.org/10.1016/j.ultrasmedbio.2014.08.017\]](http://dx.doi.org/10.1016/j.ultrasmedbio.2014.08.017) [PMID: 25438845]
- [76] Eastell R, Hannon RA. Biomarkers of bone health and osteoporosis risk. *Proc Nutr Soc* 2008; 67(2): 157-62.
[\[http://dx.doi.org/10.1017/S002966510800699X\]](http://dx.doi.org/10.1017/S002966510800699X) [PMID: 18412989]
- [77] Henriksen K, Christiansen C, Karsdal MA. Serological biochemical markers of surrogate efficacy and safety as a novel approach to

- drug repositioning. *Drug Discov Today* 2011; 16(21-22): 967-75. [http://dx.doi.org/10.1016/j.drudis.2011.06.010] [PMID: 21745584]
- [78] Gns HS, Gr S, Murahari M, Krishnamurthy M. An update on Drug Repurposing: Re-written saga of the drug's fate. *Biomed Pharmacother* 2019; 110: 700-16. [http://dx.doi.org/10.1016/j.biopha.2018.11.127] [PMID: 30553197]
- [79] Shankar S, Hosking DJ. Biochemical assessment of Paget's disease of bone. *J Bone Miner Res* 2006; 21 (Suppl. 2): 22-7. [http://dx.doi.org/10.1359/jbmr.06s204] [PMID: 17229003]
- [80] Qvist P, Christgau S, Pedersen BJ, Schlemmer A, Christiansen C. Circadian variation in the serum concentration of C-terminal telopeptide of type I collagen (serum CTx): effects of gender, age, menopausal status, posture, daylight, serum cortisol, and fasting. *Bone* 2002; 31(1): 57-61. [http://dx.doi.org/10.1016/S8756-3282(02)00791-3] [PMID: 12110413]
- [81] Pantziarka P, Pirmohamed M, Mirza N. New uses for old drugs. *BMJ* 2018; 361: k2701. [http://dx.doi.org/10.1136/bmj.k2701] [PMID: 29945952]
- [82] Sachs RE, Ginsburg PB, Goldman DP. Encouraging New Uses for Old Drugs. *JAMA* 2017; 318(24): 2421-2. [http://dx.doi.org/10.1001/jama.2017.17535] [PMID: 29204602]
- [83] Frail DE, Brady M, Escott KJ, et al. Pioneering government-sponsored drug repositioning collaborations: progress and learning. *Nat Rev Drug Discov* 2015; 14(12): 833-41. [http://dx.doi.org/10.1038/nrd4707] [PMID: 26585533]
- [84] Pantziarka P, Bouche G, Meheus L, Sukhatme V, Sukhatme VP, Vikas P. The Repurposing Drugs in Oncology (ReDO) Project. *Ecamericalscience* 2014; 8: 442. [http://dx.doi.org/10.3332/ecancer.2014.485] [PMID: 25075216]
- [85] Prague JK, Roberts RE, Comninos AN, et al. Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; 389(10081): 1809-20. [http://dx.doi.org/10.1016/S0140-6736(17)30823-1] [PMID: 28385352]
- [86] Talevi A, Bellera CL. Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics. *Expert Opin Drug Discov* 2020; 15(4): 397-401. [http://dx.doi.org/10.1080/17460441.2020.1704729] [PMID: 31847616]
- [87] Pushpakom S, Iorio F, Eyer PA, et al. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov* 2019; 18(1): 41-58. [http://dx.doi.org/10.1038/nrd.2018.168] [PMID: 30310233]
- [88] Bloom BE. Creating new economic incentives for repurposing generic drugs for unsolved diseases using social finance. *Assay Drug Dev Technol* 2015; 13(10): 606-11. [http://dx.doi.org/10.1089/adt.2015.29015.bedrrr] [PMID: 26284286]
- [89] Kowal SL, Dall TM, Chakrabarti R, Storm MV, Jain A. The current and projected economic burden of Parkinson's disease in the United States. *Mov Disord* 2013; 28(3): 311-8. [http://dx.doi.org/10.1002/mds.25292] [PMID: 23436720]
- [90] Strittmatter SM. Overcoming drug development bottlenecks with repurposing: old drugs learn new tricks. *Nat Med* 2014; 20(6): 590-1. [http://dx.doi.org/10.1038/nm.3595] [PMID: 24901567]
- [91] Corsello SM, Bittker JA, Liu Z, et al. The Drug Repurposing Hub: a next-generation drug library and information resource. *Nat Med* 2017; 23(4): 405-8. [http://dx.doi.org/10.1038/nm.4306] [PMID: 28388612]
- [92] Meissner WG, Frasier M, Gasser T, et al. Priorities in Parkinson's disease research. *Nat Rev Drug Discov* 2011; 10(5): 377-93. [http://dx.doi.org/10.1038/nrd3430] [PMID: 21532567]
- [93] Rakshit H, Chatterjee P, Roy D. A bidirectional drug repositioning approach for Parkinson's disease through network-based inference. *Biochem Biophys Res Commun* 2015; 457(3): 280-7. [http://dx.doi.org/10.1016/j.bbrc.2014.12.101] [PMID: 25576361]
- [94] Johnston TH, Lacoste AMB, Visanji NP, Lang AE, Fox SH, Brotchie JM. Repurposing drugs to treat l-DOPA-induced dyskinesia in Parkinson's disease. *Neuropharmacology* 2019; 147: 11-27. [http://dx.doi.org/10.1016/j.neuropharm.2018.05.035] [PMID: 29907424]
- [95] Fuchikami M, Yamamoto S, Morinobu S, Okada S, Yamawaki Y, Yamawaki S. The potential use of histone deacetylase inhibitors in the treatment of depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2016; 64: 320-4. [http://dx.doi.org/10.1016/j.pnpbp.2015.03.010] [PMID: 25818247]
- [96] Hobara T, Uchida S, Otsuki K, et al. Molecular mechanisms of the antidepressant actions by histone deacetylase inhibitors. *Neurosci Res* 2010; 68: E316. [http://dx.doi.org/10.1016/j.neures.2010.07.1405]
- [97] Covington HE III, Maze I, LaPlant QC, et al. Antidepressant actions of histone deacetylase inhibitors. *J Neurosci* 2009; 29(37): 11451-60. [http://dx.doi.org/10.1523/JNEUROSCI.1758-09.2009] [PMID: 19759294]
- [98] Gao S, Cui YL, Yu CQ, Wang QS, Zhang Y. Tetrandrine exerts antidepressant-like effects in animal models: role of brain-derived neurotrophic factor. *Behav Brain Res* 2013; 238: 79-85. [http://dx.doi.org/10.1016/j.bbr.2012.10.015] [PMID: 23085478]
- [99] Yang SH, Li S, Lu G, et al. Metformin treatment reduces temozolamide resistance of glioblastoma cells. *Oncotarget* 2016; 7(48): 78787-803. [http://dx.doi.org/10.1863/oncotarget.12859] [PMID: 27791206]
- [100] Wang D, Berglund A, Kenchappa RS, Forsyth PA, Mulé JJ, Etame AB. BIRC3 is a novel driver of therapeutic resistance in Glioblastoma. *Sci Rep* 2016; 6: 21710. [http://dx.doi.org/10.1038/srep21710] [PMID: 26888114]
- [101] Wishart DS, Knox C, Guo AC, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res* 2006; 34(Database issue): D668-72. [http://dx.doi.org/10.1093/nar/gkj067] [PMID: 16381955]
- [102] Lazzeroni D, Bini M, Camaiora U, et al. Serum uric acid level predicts adverse outcomes after myocardial revascularization or cardiac valve surgery. *Eur J Prev Cardiol* 2018; 25(2): 119-26. [http://dx.doi.org/10.1177/2047487317744045] [PMID: 29164926]
- [103] Grassi D, Ferri L, Desideri G, et al. Chronic hyperuricemia, uric acid deposit and cardiovascular risk. *Curr Pharm Des* 2013; 19(13): 2432-8. [http://dx.doi.org/10.2174/1381612811319130011] [PMID: 23173592]
- [104] Taghizadeh N, Vonk JM, Boezen HM. Serum uric acid levels and cancer mortality risk among males in a large general population-based cohort study. *Cancer Causes Control* 2014; 25(8): 1075-80. [http://dx.doi.org/10.1007/s10552-014-0408-0] [PMID: 24906474]
- [105] Bennett DA, Holmes MV. Mendelian randomisation in cardiovascular research: an introduction for clinicians. *Heart* 2017; 103(18): 1400-7. [http://dx.doi.org/10.1136/heartjnl-2016-310605] [PMID: 28596306]
- [106] Satoh K. Development of novel therapies for cardiovascular diseases by clinical application of basic research. *Circ J* 2017; 81(11): 1557-1563. [http://dx.doi.org/10.1253/circj.CJ-17-1029]
- [107] Bhatt MP, Lim YC, Kim YM, Ha KS. C-peptide activates AMPKα and prevents ROS-mediated mitochondrial fission and endothelial apoptosis in diabetes. *Diabetes* 2013; 62(11): 3851-62. [http://dx.doi.org/10.2337/db13-0039] [PMID: 23884890]
- [108] He G, Pedersen SB, Bruun JM, Lihn AS, Richelsen B. Metformin, but not thiazolidinediones, inhibits plasminogen activator inhibitor-1 production in human adipose tissue *in vitro*. *Horm Metab Res* 2003; 35(1): 18-23. [http://dx.doi.org/10.1055/s-2003-38386] [PMID: 12669266]
- [109] Mangoni AA, Zinelli A, Sotgia S, et al. Methotrexate and cardiovascular protection: current evidence and future directions. *Clin Med Insights Ther* 2017; 9: 1179559X1774128. [http://dx.doi.org/10.1177/1179559X17741289]
- [110] Ameen SM, Drancourt M. *In vitro* susceptibility of Mycobacteri-

- um tuberculosis to trimethoprim and sulfonamides in France. *Antimicrob Agents Chemother* 2013; 57(12): 6370-1.
[\[http://dx.doi.org/10.1128/AAC.01683-13\]](http://dx.doi.org/10.1128/AAC.01683-13) [PMID: 24060877]
- [111] Tiberi S, Payen MC, Sotgiu G, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016; 47(4): 1235-43.
[\[http://dx.doi.org/10.1183/13993003.02146-2015\]](http://dx.doi.org/10.1183/13993003.02146-2015) [PMID: 26965290]
- [112] Sotgiu G, Pontali E, Migliori GB. Linezolid to treat MDR-/XDR-tuberculosis: available evidence and future scenarios. *Eur Respir J* 2015; 45(1): 25-9.
[\[http://dx.doi.org/10.1183/09031936.00145014\]](http://dx.doi.org/10.1183/09031936.00145014) [PMID: 25552734]
- [113] Yassin MA, Jaramillo E, Wandwalo E, et al. Investing in a novel shorter treatment regimen for multidrug-resistant tuberculosis: to be repeated. *Eur Respir J* 2017; 49(3): 1700081.
[\[http://dx.doi.org/10.1183/13993003.00081-2017\]](http://dx.doi.org/10.1183/13993003.00081-2017) [PMID: 28331045]
- [114] Banga R, Procopio FA, Noto A, et al. PD-1(+) and follicular helper T cells are responsible for persistent HIV-1 transcription in treated aviremic individuals. *Nat Med* 2016; 22(7): 754-61.
[\[http://dx.doi.org/10.1038/nm.4113\]](http://dx.doi.org/10.1038/nm.4113) [PMID: 27239760]
- [115] Larsson M, Shankar EM, Che KF, et al. Molecular signatures of T-cell inhibition in HIV-1 infection. *Retrovirology* 2013; 10: 31.
[\[http://dx.doi.org/10.1186/1742-4690-10-31\]](http://dx.doi.org/10.1186/1742-4690-10-31) [PMID: 23514593]
- [116] Wightman F, Solomon A, Kumar SS, et al. Effect of ipilimumab on the HIV reservoir in an HIV-infected individual with metastatic melanoma. *AIDS* 2015; 29(4): 504-6.
[\[http://dx.doi.org/10.1097/QAD.0000000000000562\]](http://dx.doi.org/10.1097/QAD.0000000000000562) [PMID: 25628259]
- [117] Schor S, Einav S. Repurposing of kinase inhibitors as broad-spectrum antiviral drugs. *DNA Cell Biol* 2018; 37(2): 63-9.
[\[http://dx.doi.org/10.1089/dna.2017.4033\]](http://dx.doi.org/10.1089/dna.2017.4033) [PMID: 29148875]
- [118] Weller ML, Amornphimoltham P, Schmidt M, Wilson PA, Gutkind JS, Chiorini JA. Epidermal growth factor receptor is a coreceptor for adeno-associated virus serotype 6. *Nat Med* 2010; 16(6): 662-4.
[\[http://dx.doi.org/10.1038/nm.2145\]](http://dx.doi.org/10.1038/nm.2145) [PMID: 20473307]
- [119] Panic G, Duthaler U, Speich B, Keiser J. Repurposing drugs for the treatment and control of helminth infections. *Int J Parasitol Drugs Drug Resist* 2014; 4(3): 185-200.
[\[http://dx.doi.org/10.1016/j.ijpddr.2014.07.002\]](http://dx.doi.org/10.1016/j.ijpddr.2014.07.002) [PMID: 25516827]
- [120] Keiser J, Adelfio R, Vargas M, Odermatt P, Tesana S. Activity of tribendimidine and praziquantel combination therapy against the liver fluke *Opisthorchis viverrini* *in vitro* and *in vivo*. *J Helminthol* 2013; 87(2): 252-6.
[\[http://dx.doi.org/10.1017/S0022149X12000387\]](http://dx.doi.org/10.1017/S0022149X12000387) [PMID: 22892101]
- [121] Knopp S, Steinmann P, Keiser J, Utzinger J. Nematode infections: soil-transmitted helminths and trichinella. *Infect Dis Clin North Am* 2012; 26(2): 341-58.
[\[http://dx.doi.org/10.1016/j.idc.2012.02.006\]](http://dx.doi.org/10.1016/j.idc.2012.02.006) [PMID: 22632643]
- [122] Zhao Z, Martin C, Fan R, Bourne PE, Xie L. Drug repurposing to target Ebola virus replication and virulence using structural systems pharmacology. *BMC Bioinformatics* 2016; 17: 90.
[\[http://dx.doi.org/10.1186/s12859-016-0941-9\]](http://dx.doi.org/10.1186/s12859-016-0941-9) [PMID: 26887654]
- [123] Ng C, Hauptman R, Zhang Y, Bourne PE, Xie L. Anti-infectious drug repurposing using an integrated chemical genomics and structural systems biology approach. *Pac Symp Biocomput* 2014; 19: 136-47.
[\[PMID: 24297541\]](http://dx.doi.org/10.1101/02297541)
- [124] Battegay M, Kuehl R, Tschudin-Sutter S, Hirsch HH, Widmer AF, Neher RA. 2019-novel Coronavirus (2019-nCoV): estimating the case fatality rate - a word of caution. *Swiss Med Wkly* 2020; 150: w20203.
[\[http://dx.doi.org/10.4414/sm.2020.20203\]](http://dx.doi.org/10.4414/sm.2020.20203) [PMID: 32031234]
- [125] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* 2020; 19(3): 149-50.
[\[http://dx.doi.org/10.1038/d41573-020-00016-0\]](http://dx.doi.org/10.1038/d41573-020-00016-0) [PMID: 32127666]
- [126] Dayer MR, Taleb-Gassabi S, Dayer MS. Lopinavir; a potent drug against coronavirus infection: insight from molecular docking study. *Arch Clin Infect Dis* 2017; 12: e13823.
[\[http://dx.doi.org/10.5812/archcid.13823\]](http://dx.doi.org/10.5812/archcid.13823)
- [127] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res* 2020; 30(3): 269-71.
[\[http://dx.doi.org/10.1038/s41422-020-0282-0\]](http://dx.doi.org/10.1038/s41422-020-0282-0) [PMID: 32020029]
- [128] Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J* 2005; 2: 69.
[\[http://dx.doi.org/10.1186/1743-422X-2-69\]](http://dx.doi.org/10.1186/1743-422X-2-69) [PMID: 16115318]
- [129] Park CS, Bang BR, Kwon HS, et al. Metformin reduces airway inflammation and remodeling via activation of AMP-activated protein kinase. *Biochem Pharmacol* 2012; 84(12): 1660-70.
[\[http://dx.doi.org/10.1016/j.bcp.2012.09.025\]](http://dx.doi.org/10.1016/j.bcp.2012.09.025) [PMID: 23041647]
- [130] Gabasa M, Ikemori R, Hilberg F, Reguart N, Alcaraz J. Nintedanib selectively inhibits the activation and tumour-promoting effects of fibroblasts from lung adenocarcinoma patients. *Br J Cancer* 2017; 117(8): 1128-38.
[\[http://dx.doi.org/10.1038/bjc.2017.270\]](http://dx.doi.org/10.1038/bjc.2017.270) [PMID: 28898237]
- [131] Bueno M, Lai YC, Romero Y, et al. PINK1 deficiency impairs mitochondrial homeostasis and promotes lung fibrosis. *J Clin Invest* 2015; 125(2): 521-38.
[\[http://dx.doi.org/10.1172/JCI74942\]](http://dx.doi.org/10.1172/JCI74942) [PMID: 25562319]
- [132] Pryor R, Cabreiro F. Repurposing metformin: an old drug with new tricks in its binding pockets. *Biochem J* 2015; 471(3): 307-22.
[\[http://dx.doi.org/10.1042/BJ20150497\]](http://dx.doi.org/10.1042/BJ20150497) [PMID: 26475449]
- [133] Ito K, Colley T, Mercado N. Geroprotectors as a novel therapeutic strategy for COPD, an accelerating aging disease. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 641-52.
[\[http://dx.doi.org/10.2147/COPD.S28250\]](http://dx.doi.org/10.2147/COPD.S28250) [PMID: 23055713]
- [134] Cameron AR, Morrison VL, Levin D, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. *Circ Res* 2016; 119(5): 652-65.
[\[http://dx.doi.org/10.1161/CIRCRESAHA.116.308445\]](http://dx.doi.org/10.1161/CIRCRESAHA.116.308445) [PMID: 27418629]
- [135] Hyun B, Shin S, Lee A, et al. Metformin down-regulates TNF- α secretion via suppression of scavenger receptors in macrophages. *Immune Netw* 2013; 13(4): 123-32.
[\[http://dx.doi.org/10.4110/in.2013.13.4.123\]](http://dx.doi.org/10.4110/in.2013.13.4.123) [PMID: 24009539]
- [136] Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest* 2011; 121(6): 2111-7.
[\[http://dx.doi.org/10.1172/JCI57132\]](http://dx.doi.org/10.1172/JCI57132) [PMID: 21633179]
- [137] Mowers J, Uhm M, Reilly SM, et al. Inflammation produces catecholamine resistance in obesity via activation of PDE3B by the protein kinases IKK ϵ and TBK1. *eLife* 2013; 2: e01119.
[\[http://dx.doi.org/10.7554/eLife.01119\]](http://dx.doi.org/10.7554/eLife.01119) [PMID: 24368730]
- [138] Glass CK, Olefsky JM. Inflammation and lipid signaling in the etiology of insulin resistance. *Cell Metab* 2012; 15(5): 635-45.
[\[http://dx.doi.org/10.1016/j.cmet.2012.04.001\]](http://dx.doi.org/10.1016/j.cmet.2012.04.001) [PMID: 22560216]
- [139] Karyekar CS, Frederick R, Ravichandran S. Clinically relevant reductions in HbA1c without hypoglycaemia: results across four studies of saxagliptin. *Int J Clin Pract* 2013; 67(8): 759-67.
[\[http://dx.doi.org/10.1111/ijcp.12212\]](http://dx.doi.org/10.1111/ijcp.12212) [PMID: 23795975]
- [140] Xu G, Chen J, Jing G, Shalev A. Preventing β -cell loss and diabetes with calcium channel blockers. *Diabetes* 2012; 61(4): 848-56.
[\[http://dx.doi.org/10.2337/db11-0955\]](http://dx.doi.org/10.2337/db11-0955) [PMID: 22442301]
- [141] Xu G, Chen J, Jing G, Shalev A. Thioredoxin-interacting protein regulates insulin transcription through microRNA-204. *Nat Med* 2013; 19(9): 1141-6.
[\[http://dx.doi.org/10.1038/nm.3287\]](http://dx.doi.org/10.1038/nm.3287) [PMID: 23975026]
- [142] Chen J, Saxena G, Mungre IN, Lusis AJ, Shalev A. Thioredoxin-interacting protein: a critical link between glucose toxicity and beta-cell apoptosis. *Diabetes* 2008; 57(4): 938-44.
[\[http://dx.doi.org/10.2337/db07-0715\]](http://dx.doi.org/10.2337/db07-0715) [PMID: 18171713]
- [143] Yin T, Kuo SC, Chang YY, Chen YT, Wang KK. Verapamil use is associated with reduction of newly diagnosed diabetes mellitus. *J Clin Endocrinol Metab* 2017; 102(7): 2604-10.
[\[http://dx.doi.org/10.1210/jc.2016-3778\]](http://dx.doi.org/10.1210/jc.2016-3778) [PMID: 28368479]
- [144] Khodneva Y, Shalev A, Frank SJ, Carson AP, Safford MM. Calci-

- um channel blocker use is associated with lower fasting serum glucose among adults with diabetes from the REGARDS study. *Diabetes Res Clin Pract* 2016; 115: 115-21.
[\[http://dx.doi.org/10.1016/j.diabres.2016.01.021\]](http://dx.doi.org/10.1016/j.diabres.2016.01.021) [PMID: 26818894]
- [145] Koning SH, Hoogenberg K, Lutgers HL, van den Berg PP, Wolfenbuttel BH. Gestational Diabetes Mellitus: current knowledge and unmet needs. *J Diabetes* 2016; 8(6): 770-81.
[\[http://dx.doi.org/10.1111/1753-0407.12422\]](http://dx.doi.org/10.1111/1753-0407.12422) [PMID: 27121958]
- [146] Flossmann E, Rothwell PM. British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007; 369(9573): 1603-13.
[\[http://dx.doi.org/10.1016/S0140-6736\(07\)60747-8\]](http://dx.doi.org/10.1016/S0140-6736(07)60747-8) [PMID: 17499602]
- [147] González-Pérez A, García Rodríguez LA, López-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. *BMC Cancer* 2003; 3: 28.
[\[http://dx.doi.org/10.1186/1471-2407-3-28\]](http://dx.doi.org/10.1186/1471-2407-3-28) [PMID: 14588079]
- [148] Sloan EK, Priceman SJ, Cox BF, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res* 2010; 70(18): 7042-52.
[\[http://dx.doi.org/10.1158/0008-5472.CAN-10-0522\]](http://dx.doi.org/10.1158/0008-5472.CAN-10-0522) [PMID: 20823155]
- [149] Springer J, Tschirner A, Haghikia A, et al. Prevention of liver cancer cachexia-induced cardiac wasting and heart failure. *Eur Heart J* 2014; 35(14): 932-41.
[\[http://dx.doi.org/10.1093/euroheartj/eht302\]](http://dx.doi.org/10.1093/euroheartj/eht302) [PMID: 23990596]
- [150] Raghavendra PB, Sreenivasan Y, Ramesh GT, Manna SK. Cardiac glycoside induces cell death via FasL by activating calcineurin and NF-AT, but apoptosis initially proceeds through activation of caspases. *Apoptosis* 2007; 12(2): 307-18.
[\[http://dx.doi.org/10.1007/s10495-006-0626-3\]](http://dx.doi.org/10.1007/s10495-006-0626-3) [PMID: 17203245]
- [151] Ishida J, Konishi M, Ebner N, Springer J. Repurposing of approved cardiovascular drugs. *J Transl Med* 2016; 14: 269.
[\[http://dx.doi.org/10.1186/s12967-016-1031-5\]](http://dx.doi.org/10.1186/s12967-016-1031-5) [PMID: 27646033]
- [152] Zoppini G, Targher G, Chonchol M, et al. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. *Diabetes Care* 2012; 35(1): 99-104.
[\[http://dx.doi.org/10.2337/dc11-1346\]](http://dx.doi.org/10.2337/dc11-1346) [PMID: 22028277]
- [153] Kanji T, Gandhi M, Clase CM, Yang R. Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis. *BMC Nephrol* 2015; 16: 58.
[\[http://dx.doi.org/10.1186/s12882-015-0047-z\]](http://dx.doi.org/10.1186/s12882-015-0047-z) [PMID: 25928556]
- [154] Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, et al. Effect of pentoxyfylline on renal function and urinary albumin excretion in patients with diabetic kidney disease: the PREDIAN trial. *J Am Soc Nephrol* 2015; 26(1): 220-9.
[\[http://dx.doi.org/10.1681/ASN.2014010012\]](http://dx.doi.org/10.1681/ASN.2014010012) [PMID: 24970885]
- [155] Liu D, Wang LN, Li HX, Huang P, Qu LB, Chen FY. Pentoxyfylline plus ACEIs/ARBs for proteinuria and kidney function in chronic kidney disease: a meta-analysis. *J Int Med Res* 2017; 45(2): 383-98.
[\[http://dx.doi.org/10.3389/fonc.2017.00273\]](http://dx.doi.org/10.3389/fonc.2017.00273) [PMID: 29184849]
- [156] [http://dx.doi.org/10.1177/0300060516663094]
[\[http://dx.doi.org/10.1177/0300060516663094\]](http://dx.doi.org/10.1177/0300060516663094) [PMID: 28415944]
- [157] Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. *Nat Rev Genet* 2013; 14(10): 681-91.
[\[http://dx.doi.org/10.1038/nrg3555\]](http://dx.doi.org/10.1038/nrg3555) [PMID: 23999272]
- [158] Schumacher KR, Stringer KA, Donohue JE, et al. Social media methods for studying rare diseases. *Pediatrics* 2014; 133(5): e1345-53.
[\[http://dx.doi.org/10.1542/peds.2013-2966\]](http://dx.doi.org/10.1542/peds.2013-2966) [PMID: 24733869]
- [159] Vissers LE, Veltman JA. Standardized phenotyping enhances Mendelian disease gene identification. *Nat Genet* 2015; 47(11): 1222-4.
[\[http://dx.doi.org/10.1038/ng.3425\]](http://dx.doi.org/10.1038/ng.3425) [PMID: 26506899]
- [160] Briggs MD, Bell PA, Wright MJ, Pirog KA. New therapeutic targets in rare genetic skeletal diseases. *Expert Opin Orphan Drugs* 2015; 3(10): 1137-54.
[\[http://dx.doi.org/10.1517/21678707.2015.1083853\]](http://dx.doi.org/10.1517/21678707.2015.1083853) [PMID: 26635999]
- [161] Coskun M, Salem M, Pedersen J, Nielsen OH. Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease. *Pharmacol Res* 2013; 76: 1-8.
[\[http://dx.doi.org/10.1016/j.phrs.2013.06.007\]](http://dx.doi.org/10.1016/j.phrs.2013.06.007) [PMID: 23827161]
- [162] Sandborn WJ, Ghosh S, Panes J, Vranic I, Wang W, Niezychowski W. Study A3921043 Investigators. A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014; 12(9): 1485-93.e2.
[\[http://dx.doi.org/10.1016/j.cgh.2014.01.029\]](http://dx.doi.org/10.1016/j.cgh.2014.01.029) [PMID: 24480677]
- [163] Panés J, Su C, Bushmakina AG, Cappelleri JC, Mamolo C, Healey P. Randomized trial of tofacitinib in active ulcerative colitis: analysis of efficacy based on patient-reported outcomes. *BMC Gastroenterol* 2015; 15: 14.
[\[http://dx.doi.org/10.1186/s12876-015-0239-9\]](http://dx.doi.org/10.1186/s12876-015-0239-9) [PMID: 25651782]
- [164] Dignass A, Van Assche G, Lindsay JO, et al. European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohn's Colitis* 2010; 4(1): 28-62.
[\[http://dx.doi.org/10.1016/j.crohns.2009.12.002\]](http://dx.doi.org/10.1016/j.crohns.2009.12.002) [PMID: 21122489]
- [165] Xue H, Li J, Xie H, Wang Y. Review of drug repositioning approaches and resources. *Int J Biol Sci* 2018; 14(10): 1232-44.
[\[http://dx.doi.org/10.7150/ijbs.24612\]](http://dx.doi.org/10.7150/ijbs.24612) [PMID: 30123072]
- [166] Jin G, Wong STC. Toward better drug repositioning: prioritizing and integrating existing methods into efficient pipelines. *Drug Discov Today* 2014; 19(5): 637-44.
[\[http://dx.doi.org/10.1016/j.drudis.2013.11.005\]](http://dx.doi.org/10.1016/j.drudis.2013.11.005) [PMID: 24239728]
- [167] Bertolini F, Sukhatme VP, Bouche G. Drug repurposing in oncology-patient and health systems opportunities. *Nat Rev Clin Oncol* 2015; 12(12): 732-42.
[\[http://dx.doi.org/10.1038/nrclinonc.2015.169\]](http://dx.doi.org/10.1038/nrclinonc.2015.169) [PMID: 26483297]
- Hernandez JJ, Pryszlak M, Smith L, et al. Giving drugs a second chance: overcoming regulatory and financial hurdles in repurposing approved drugs as cancer therapeutics. *Front Oncol* 2017; 7: 273.
[\[http://dx.doi.org/10.3389/fonc.2017.00273\]](http://dx.doi.org/10.3389/fonc.2017.00273) [PMID: 29184849]