REVIEW ARTICLE

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Drug Repurposing: A Paradigm Shift in Drug Discovery

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ABSTRACT

The traditional methods of drug discovery and drug development are a tedious, complex, and costly process. Target identification, target validation; lead identification; and lead optimization are a lengthy and unreliable process that further complicates the discovery of new drugs. A study of more than 15 years reports that the success rate in the discovery of new drugs in the fields of ophthalmology, cardiovascular, infectious disease, and oncology to be 32.6%, 25.5%, 25.2% and 3.4%, respectively. A tedious and costly process coupled with a very low success rate makes the traditional drug discovery a less attractive option. Therefore, an alternative to traditional drug discovery is drug repurposing, a process in which already existing drugs are repurposed for conditions other than which were originally intended. Typical examples of repurposed drugs are thalidomide, sildenafil, memantine, mirtazapine, mifepristone, etc. In recent times, several databases have been developed to hasten drug repurposing based on the side effect profile, the similarity of chemical structure, and target site. This work reviews the pivotal role of drug repurposing in drug discovery and the databases currently available for drug repurposing.

Keywords: Drug Repurposing; Promiscuous; approaches in drug repurposing; Databases/tools in drug repurposing.

1. INTRODUCTION

The Traditional drug discovery and development process is classified into two phases/stages, these are, 1) The discovery phase (Target identification, lead finding and lead optimization, etc.) and 2) The development phase (Pre-clinical development and clinical trials).[1,2] The entire process of drug discovery takes an average of 13-15 years and usually requires an investment of US$ 1.8 billion to bring a single drug successfully into the therapeutic market.[3,4] The long development process, high cost, toxicity, drug resistance, and a very low success rate[5,6] demonstrates the inevitable role of repurposing old drugs for new uses in the current scenario. Drug repurposing is a strategy used for finding new uses for the existing drugs.[4] It has been used interchangeably with drug repositioning, drug reprofiling, and drug rediscovery, but these terminologies have slightly different meanings. Drug repositioning is defined as the use of existing drugs for new targets. Drug reprofiling is defined as the reuse of existing drugs for new indication by manipulating the therapeutic profiles for reducing the costs and risks associated with a drug. Drug rediscovery is defined as the investigation of currently used drugs for a new indication.[7,8]

Drugs have been discovered in the past as a result of serendipity or a result of intentional repurposing. A few examples of drugs that were discovered serendipitously and repurposed are penicillin (while researching on influenza), chlordiazepoxide (while searching to develop synthetic dyes), and imipramine as an anti-depressant (while searching for a chlorpromazine-like substance for the treatment of schizophrenia), chloral hydrate as a sedative and hypnotic (as a result of an inaccurate idea), lithium for the treatment of manic patients (as a result of an inaccurate idea), lysergic acid diethylamide from uterotonic to psychotomimetic and finally to serotonin inhibitors, chlorpromazine (CPZ) as a patenting agent in general anesthesia to psychiatric use (while research-

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ing for the treatment of protozoal infection), iproniazid which was originally intended as a drug for the treatment of tuberculosis but was later used as an anti-depressant which further led to the discovery of the group, monoamine oxidase (MAO) inhibitors.[9] Sildenafil (Viagra) was originally used to treat angina pectoris but later in the treatment of erectile dysfunction and thalidomide initially for the treatment of morning sickness for pregnant women to multiple myeloma[10,11] are two most important repurposed drugs based on side effect profile.

In 2018, a total of 13 drugs failed in various stages of clinical trials carried out by various leading pharmaceutical companies. Out of 13 failed drug candidates, 5 were anti-Alzheimers, 3 were anticancer and others were for Tourette syndrome, asthma, acne vulgaris, tinnitus and Lewy body dementia.[12] This report highlights the hurdles involved in the traditional drug discovery process and the inevitable role of alternatives in drug discovery. Drug repurposing helps reduce the time and investment, where the pharmacokinetics and pharmacodynamic properties of the drug(s) used have been generated and greatly improve the chances of success.[1] Drug repurposing can play a vital role in bringing back these failed drugs into therapeutics for new indications.

1.1. Why Repurposing?

Sir James Black, Noble Prize winner of the year 1988 in Physiology and Medicine, famously stated that "The most fruitful basis for the discovery of a new drug is to start with an old drug".[13] Steve Felstead, a retired vice president of clinical research at Pfizer, once quoted that "There may be knowledge out there we do not know about, and we do not tend to cover every possible therapeutic indication when we study compounds; perhaps the wider community can facilitate some new clinical or preclinical studies that will give us vital new information".[14] From a financial perspective, the revenue that could potentially be gained by drug repurposing as reported by Business Communications Company (BCC) research in 2015 was $24.4 billion and is expected to reach $31.3 billion by 2020.[15] For instance, thalidomide and sildenafil generated revenues worth US $271 million and the US $1.88 billion in 2003[16] respectively. Similarly, Dimethyl fumarate (DMF), earned a revenue of more than $2.5 billion in 2014 after it was repurposed to treat multiple sclerosis (MS) in 2013.[17]

2. DATABASES/TOOLS USED IN DRUG REPURPOSING

In recent times, numerous databases have been developed to aid the process of drug discovery. Some of the databases used in drug repurposing are discussed below. Table 1 represents the databases used in drug repurposing.

Table 1: Databases used in drug repurposing[13]

Databases	*Type*
Promiscuous	Drug
Adverse Drug Reaction Classification System (ADReCS)	
Comparative Toxicogenomics Database	
Therapeutic Target Database (TTD)	
Toxin and Toxin-Target Database (T3DB)	
Inxight Drugs	
Pharmacogenomics knowledgebase (PharmGKB)	
Open Targets PlatformProject Achilles	
ChEMBL	
Side Efect Resource 4 (SIDER4)	
PubChem	
STITCH	
ChemSpider	
SuperPredare the drug-type database	
Drug Gene Interaction Database (DGIdb)	
Genomics of Drug Sensitivity in Cancer (GDSC)	
DailyMED	
Clue (L1000 Platform)	
DrugBank 5.0	
DrugCentral	
e-Drug3D	
Human Protein Atlas,	Disease and Drug
Kyoto Encyclopedia of Genes and Genomes (KEGG) Medicus	
Search Tool for the Retrieval of Interacting Genes/Proteins (STRING)	
International Cancer Genome Consortium (ICGC),	
Encyclopedia of DNA Elements (ENCODE)	
Gene Expression Omnibus (GEO)	
Allen Brain Atlas	
Database of single nucleotide polymorphisms (dbSNP)	
Catalogue of Somatic Mutations in Cancer (COSMIC)	Disease
ArrayExpress	
Cancer Cell Line Encyclopedia (CCLE)	
Orphadata	
DisGeNET	
Genomics Data Commons	
Human Proteome Map	
International Genome Sample Resource (IGSR)	
Genotype-Tissue Expression (GTex)	
DbVar	
Roadmap Epigenomics	

2.1. Promiscuous

Promiscuous is a database with an exhaustive network-focused resource of 25000 drugs including withdrawn and experimental drugs. Drugs, proteins and side-effects are the three entities that promiscuous contains and these entities are interconnected with one another through drug-target, drug side-effect, protein-protein and drug-drug relationship. It is also considered as a tool used to link various drugs with various diseases.[18,19]

2.2. DrugBank

Drugbank is a database that provides information on drugs regarding their mechanism of action, drug-drug interactions, and their targets. Drugbank 5.0 includes statistics on the influence of hundreds of drugs on gene expression levels (pharmacotranscriptomics), metabolite levels (pharmacometabolomics), and protein expression levels (pharmacoproteomics).[20]

2.3. ChemSpider

ChemSpider is a database that acts as an aggregator of chemical information. It provides access to physical and chemical properties, spectral data, safety information, molecular structures, synthetic methods and nomenclature of 64 million chemical compounds.[13,21]

2.4. PubChem

Pubchem is a database that provides information on chemical substances, their biological activities, spectral and scientific articles mentioning chemicals, information on food and agricultural chemicals, and a brief description of PubChem3D. Substance, Compound, and Bioassay are the three inter-linked databases that PubChem contains.[22,23]

2.5. Side Effect Resource (SIDER)

SIDER is a database that contains 1430 drugs data, 5880 ADRs, and 140064 drug-ADR pairs. It keeps a record of unwanted side effects of drugs and adverse drug reactions (ADRs) that occurred during clinical trials. It automatically extracts adverse drug reactions (ADRs) from Structured Product labels (SPLs) by combining natural language and processing (NLP) and filtering techniques.[24,25]

2.6. Kyoto Encyclopedia of Genes and Genomes (KEGG) Medicus

KEGG is an integrated database resource that deals with genes, genomes, biological pathways, diseases, drugs, and chemical structure. KEGG Medicus was developed by integrating drug labels (package inserts) used in society to understand genome analysis and the scientific basis of diseases and drugs of personal interest. It aims to bring the genomic revolution to society by integrating information resources viz., drugs, diseases, and health-related substances.[26,27]

2.7. Search Tool for the Retrieval of Interacting Genes (STRING)

STRING, a protein-protein interaction database that currently covers 5090 organisms and 24.6 million proteins. Protein-protein interactions association includes direct or physical interactions and indirect or functional interaction. Uploading an entire, genome-wide dataset as input is an important feature of the latest version of STRING (11.0).[28-30]

2.8. Catalog of Somatic Mutations in Cancer (COSMIC)

COSMIC, a comprehensive global database that provides information on human cancer related to somatic mutations. Curated from over 26000 publications, COSMIC latest version (v86) contains almost 6 million coding mutations from 1.4 million tumor samples. It also consists of 20 drugs with wide resistance mutation profiles. Manual curated of mutation is done from a wide range of scientific literature, thereby allowing very precise definitions of patient details and disease types.[31-34]

2.9. Cancer Cell Line Encyclopedia (CCLE):

CCLE is a database of chromosomal copy numbers, gene expression that provides a thorough framework for studying candidate targets, genetic variants, small-molecules, and biological therapeutics as well as in the identification of new cancer markers.[26,35,36]

3. APPROACHES IN DRUG REPURPOSING

Drug repurposing can be carried out by the following approaches (Figure 1)

3.1. Drug-side effect(s) similarity

Drug repurposing using side effect profile of drugs is based on the hypothesis that "If the side-effects associated with a drug D are also induced by many of the drugs

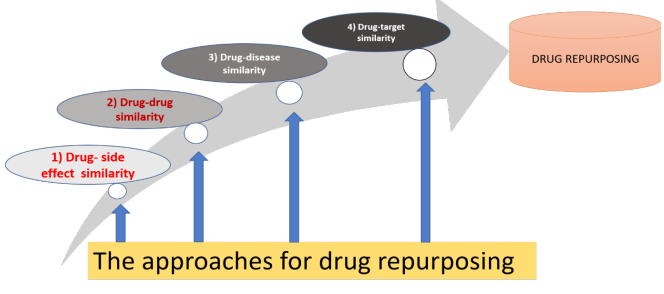

Figure 1: Approaches in drug repurposing

treating disease X, then drug D should be evaluated as a candidate for treating disease X".[37] Drug-side effect(s) similarity profiles can be obtained from Meyler's Side Effects of Drugs. It is a resource that provides information on adverse drug reactions (ADRs) and drug-drug interactions. Side Effects of Drugs Annuals is one more resource that provides information on the side effects of drugs. The side Effects of Drugs Annual was first published in 1977. It has been continually updated and published since then as a yearly update to Meyler's Side Effects of Drugs. Drugs@FDA Database is a database that includes most of the drug products approved by the FDA since 1939. It also provides data on patient information, approval letters, reviews, labels, approval packages, and other information for drug products approved since 1998.[38] Medical Dictionary for Regulatory Activities (MedDRA) is a database with standardized side-effects (SE) terms that can be used for drug repositioning.[39] SIDER (Side Effect Resource) is a database of drugs that stores side effects and a record on ADRs.[24,25,40]

3.2. Drug-drug similarity

Medical Subject Heading Drug-Drug (MeSHDD) is a drug-drug similarity database based on Medical Subject Heading (MeSH) terms. This database includes the complete spectrum of genetic, structural, biomedical evidence, and clinical information. Based on this approach, metformin is linked to cystic fibrosis[41]; thalidomide and its derivative (lenalidomide) for the treatment of multiple myeloma cells.[42] The drug-drug similarity approach can also be carried out based on drug analogs. For instance, from mevinolin, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors were derived; H_2 antagonists derived from cimetidine and the angiotensin-converting enzyme (ACE) inhibitors derived from captopril.[43]

3.3. Drug-disease similarity

Drug repurposing based on similarities between drug and disease is based on an approach called "guilt by association". The hypothesis or idea of this approach is that if two diseases share similar treatments, then the other drugs that are presently used for only one of the two diseases may also be therapeutically used for the other. For example, the use of rivastigmine for the treatment of Parkinson's disease, dementia, and Alzheimer's disease, and bevacizumab for the treatment of nonsquamous nonsmall-cell lung cancer and colorectal cancer. Further, this approach also suggests the use of the drug(s) for the novel disease. For example, Annie P Chang et al. suggest rituximab for the treatment of 107 novel diseases and atorvastatin for 76 novel diseases.[44,45] A resource called Sirius used side effects and pathway data to correlate drugs-diseases relationship based on the assumption that chemicals affecting similar pathways and having similar side effects can cure similar diseases. Examples of drug-disease associations predicted from this study include acitretin, oxaliplatin and cisplatin for cutis laxa disease, etodolac, naproxen, and nabumetone for breast cancer, and triamcinolone, tolmetin, and diflunisal for exostoses disease.[46] The Drug-disease approach is also based on the assumption that drugs tend to have similar target profiles and could be correlated with similar genetic diseases if they have a similar gene expression profile. Based on this approach, H Wang et al., suggest repositioning of angiotensin-converting enzyme inhibitors like ramipril, enalapril and lisinopril to Alzheimer's disease (AD).[47]

3.4. Drug-target Similarity

Drug-target similarity for drug repurposing is based on the hypothesis that if a drug interacts with a target, that drug can probably be used to treat the corresponding disease.[48] Based on this approach, Feixiong Cheng et al reported the potent antiproliferative activities of simvastatin and ketoconazole on MDA-MB 231 cell lines in MTT assays. Similarly, the pharmacological activities of old drugs viz., montelukast on dipeptidyl peptidase-IV, diclofenac on ERα and ERβ, simvastatin on ERβ, ketoconazole on ERβ, and itraconazole on ERα and ERβ was reported.[49] Rabeprazole, an antiulcer drug, has been found to share targets with the drugs acting on the nervous system like pergolide, paroxetine, fluoxetine, and in vitro cell assay studies, rabeprazole has been confirmed to bind to serotonin receptor HTR1D and dopamine receptor DRD3.[50]

4. A FEW EXAMPLES OF REPURPOSED DRUGS

Table 2, Table 3, represents few examples of repurposed drugs.[1] Table 4 represents generic drugs indicated as an anticancer agent based on at least one randomized clinical trial.[51] Drugs that show promising potential for repurposing based on similar side effects profile are listed in Table 5.[38,52] Table 6 are the few examples of drugs has been explored for repurposing based on similar side-effect profile.[53]

5. CHALLENGES IN DRUG REPURPOSING

Pharmaceutical companies are unwilling to invest in drug repurposing, especially in the case of failed drugs. A few examples include floseqinan, darapladib and tredaptive.[51,54] In case of failed drugs, there is confusion and less chance of investment because the drug has to be modified and a different group of patients should

Table 2: A few examples of repositioned anti-depressant drugs

Generic	*Mechanism of action*	*Original indication*	*New indication*	*Comments*
Buproprion	Enhancement of noradrenaline function	Depression	Smoking cessation	Approved as Zyban for smoking cessation in 1997
Dapoxetine	Selective serotonin reuptake inhibitor (SSRI)	Analgesia and depression	Premature ejaculation	Currently in phase III
Duloxetine	Non-selective serotonin reuptake inhibitor (NSRI)	Depression	Stress urinary inconsistence (SUI)	In development for both depression and SUI
Fluoxetine	SSRI	Depression	Premenstrual dysphoria	It was approved on 6 July 2000 in the United States in premenstrual dysphoria disorder
Milnacipran	NSRI	Depression	Fibromyalgia syndrome	Currently in phase III
Sibutramine	NSRI	Depression	Obesity	It was approved on 24 November 1997 in the United States for the management of Obesity

Table 3: Examples of repositioned neurological drugs

Generic	*Mechanism of action*	*Original indication*	*New indication*	*Comments*
Atomoxetine	NSRI	Parkinson's disease	Attention-deficit hyperactivity disorder (ADHD)	Approved by FDA for ADHD in 2002
Chlorpromazine	Dopamine Receptor blocker	Anti-emetic/ antihistamine	Non-sedating tranquilizer	Marketed it by SmithKline as a Non-sedative tranquilizer and became a standard element of psychiatric care.
Galantamine	Acetylcholinesterase inhibitor	Polio, paralysis and anesthesia	Alzheimer's disease	Approved in many countries for Alzheimer's disease (mild to moderate state)
Lidocaine	Sodium channel blocker	Local anesthesia	Oral corticosteroid-dependent asthma	Currently in phase II in the United States and Europe
Ropinirole	Dopamine-2 agonist	Hypertension	Parkinson's disease and idiopathic restless leg syndrome	Currently in phase III for idiopathic restless leg syndrome
Tofisopam	Unclear	Anxiety-related conditions	Irritable bowel syndrome	A phase II trial in irritable syndrome with the R-enantiomer has been done

Table 4: Generic drugs indicated as anticancer agents based on atleast one randomized clinical trial

Generic	*Original indication*	*New Indication*	*Comments*
Aspirin	Painkiller, stroke and coronary events prevention	For early-stage CRC	Reduction of metastasis and risk of new adenomas in patients developing CRC and other cancers.
Pravastatin	Hypercholesterolemia, prevention of coronary events	For advanced-stage hepatocellular carcinoma (HCC)	In the selected Japanese population it was tested as maintenance treatment (single drug)
Verapamil	Hypertension	For metastasis breast cancer	In combination with vindesine and 5-fluorouracil
Arsenic trioxide	Acute promyelocytic leukemia	For patients with HCC	In combination with trans-arterial catheter embolization as well as open-label study in a Chinese population with HCC of viral etiology.
Propranolol and etodolac	Hypertension, rheumatoid and osteoarthritis	For pancreatic cancer and patients with advanced-stage HCC	For pancreatic cancer, it was tested within combination with nab-paclitaxel and gemcitabine whereas for patients with advanced-stage HCC it was tested in combination with sorafenib
Disulfiram	Alcohol dependence	For metastasis breast cancer and metastasis NSCLC	Development was discontinued for metastasis breast cancer after failure in trials for HIV treatment whereas for metastasis NSCLC it was tested in combination with a common first-line regimen (cisplatin/vinorelbine)

Table 5: Drugs repurposed based on similar side effects

Drug	*Developed by*	*Category*	*Shared side effects with*	*New indication*	*Ref*
Dynastat (Parecoxib)	Pfizer	COX-2 selective inhibitor	It displayed similar side effects to 33 RA drugs (examples procofen, actron, antiflog, ethos, calibene, aflexetc)	Rheumatoid arthritis (RA) treatment	38
Tasmar (Tolcapone)	Roche	COMT inhibitor	It displayed a similar side effect to 15 drugs approved for the treatment of anti-depressant (examples amfebutamone, actan, Cipralex, fluoxetine, neripros)	Depression treatment	38
Adamon (Tramadol HCl)	Grunenthal GmbH.	Synthetic opioid analgesic	It displayed a similar side effects to 13 anti-depressant drugs (Examples cipralex, bextra, ecridoxan, cambia, duragesic, eldepryletc)	Depression treatment	38
Rozerem (Ramelteon)	Takeda Pharmaceuticals North America, Inc.	Selective MT_1 and MT_2 agonist	Atypical antipsychotic drug (Ziprasidone)	Bipolar I disorder	52
Vivlodex (Meloxicam)	Iroko Pharmaceuticals, LLC	COX-2 selective inhibitor	Monoclonal antibody against CD20-antigen	Non-Hodgkin lymphoma	52

Table 6: Drugs being explored for repurposing based on similar side-effect profile

Drug	*FDA indication*	*New indication*	*Proposed mechanism*
Telmisartan	Angiotensin II receptor antagonist	Colon cancer	Peroxisome Proliferator-Activated Receptor-Y (PPAR—Y) activation Caspase 3 activation via dose-dependent
Phylloquinone	Vitamin-K dietary supplement	Colon cancer	(↑) Bax/Bcl2-2 ratio and induced apoptosis MAPK/ ERK pathway activation Caspase independent pathway
Aliskiren	Antihypertensive as a Renin inhibitor	Renal cancer	Notch1 and KRT6B-Keratin 6 activating

be recruited for further studies. Further, works carried out by the academic, the regulatory authorities hardly consider non-profit and public involvement in research and development of repurposed drugs.[55] Drug repurposing procedure is required to undergo 505 (b) (2), an application procedure which is similar to that of a new drug application (NDA),[56] making repurposing of old or failed drugs no less different from that of designing and developing a new drug. The next challenge is that available data for old compounds might not meet the current regulatory standards and gaining access to intellectual property rights (IP) is hard.[1] For a drug to be considered as a high-potential target in repurposing, certain criteria have to be met with viz., A drug that is intended for repurposing should be renowned and extensively used clinically, less toxic, a related and presumed mechanism of action, have strong *in vitro, in vivo* and human data, and last but not the least the drug(s) is not present and not commonly used as an active agent in oncology.[57] Further, trials are expensive and a huge risk financially. It costs approximately US $300-400 million to perform a phase 3 trial and the time gets FDA approval for a new indication varies for different categories of drugs. For instance,

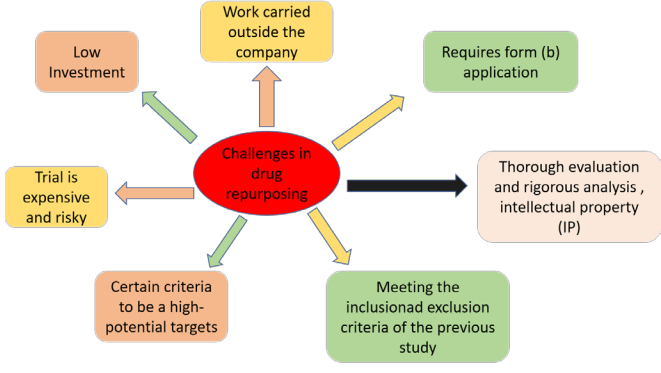

Figure 2: Represents the challenges in drug repurposing

orphan drugs, non-cancer and drugs sponsored by the large companies are more likely to gain FDA approval than the non-orphan, non-cancer and drugs sponsored by smaller companies[58,59] (Figure 2).

6. WAYS TO OVERCOME CHALLENGES IN DRUG REPURPOSING

Relying on the novel Method of Use (MOU) protection which is also known as a 'use code narrative' patent that provides substantial barriers to entry into the market in case if the drug has never been marketed or the drug

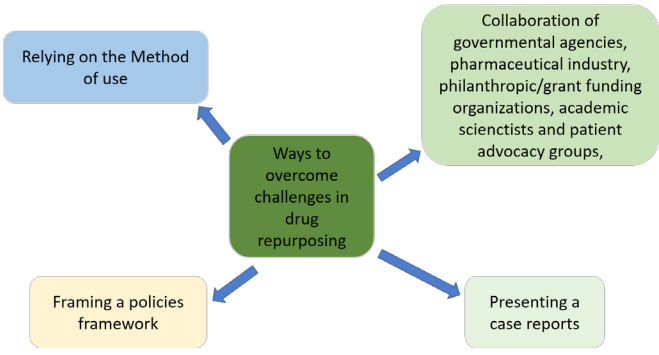

Figure 3: Ways to overcome drug repurposing

is in the development stage. In such case developing drug combinations, new formulations, and new dosage forms might be able to obtain new Composition Of Matter (COM) Intellectual Property (IP): COM, which is one of the four principal categories of patents for any novel inventions by striking a deal to license or acquire that IP.[1] Repurposing initiatives through consortiums/ collaboration of governmental agencies, pharmaceutical industry, philanthropic/grant funding organizations, academic scientists and patient advocacy groups is an effective way to overcome the challenges in drug repurposing. For instance, in 2011, Medical Research Council (MRC) and Astra Zeneca collaborated for the initiative in Mechanism for Human Diseases. In 2012, an initiative from the US National Institute of Health (NIH) National Center for Advancing Translational Sciences (NCATS) was launched. This initiative brings together the eight world's largest pharmaceutical companies (Pfizer, AstraZeneca, Eli Lilly, Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Jansen Pharmaceuticals, and Sanofi) and the academic scientists to find out new uses of abandoned drugs.[14,60] Further, case reports also stand as an important source of evidence for further investigation in repurposing drugs. For example, a study reports that combination treatment of refractory pediatric atypical teratoid rhabdoid tumor based on a backbone of metronomic chemotherapy and the non-steroidal anti-inflammatory drug (NSAID), celecoxib.[61,62] Policy frameworks that incentivize industries to invest in drug repurposing are required to motivate pharmaceutical industries to invest in drug repositioning.[58] (Figure 3)

7. CONCLUSIONS

Drug repurposing can be seen as an important approach towards the health care society Further, looking towards the funding initiative in the field of drug repurposing, example 1) Governmental granting agencies like the National Centre for Advancing Translational Sciences (NCATS) and Canadian Institutes of Health Research (CIHR) 2) Philanthropic organizations like Cure Within Reach (CWR), Belgium-based Anticancer Fund 3) Findacure, which a United Kingdom-based organization 4) Stem Cell Network and Global Cure, where the funding are either independently or co-funds applicants in collaboration with governmental agencies or patient interest group. Steve Felstead, the then vice president of clinical research at Pfizer, New York quotes, "There may be knowledge out there we don't know about" similarly he quotes, "We don't tend to cover every possible therapeutic indication when we study compounds; perhaps the wider community can facilitate some new clinical or pre-clinical studies that will give us vital new information." [14]. Therefore, we can conclude that, with the regulatory and pharmaceutical company paving the way for rediscovery and further exploration of the failed drugs, ongoing patented and off-patent drugs (i.e generic drugs) that act as barriers, drug repurposing can be one of the steps to cope up with the problem facing by the conventional method of drug discovery and development.

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