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Drug Repurposing: An Effective Tool in Modern Drug Discovery

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Abstract—Drug repurposing is using an existing drug for a new treatment that was not indicated before. It has received immense attention during the COVID-19 pandemic emergency. Drug repurposing has become the need of time to fasten the drug discovery process and find quicker solutions to the over-exerted healthcare scenario and drug needs. Drug repurposing involves identifying the drug, evaluating its efficiency using preclinical models, and proceeding to phase II clinical trials. Identification of the drug candidate can be made through computational and experimental approaches. This approach usually utilizes public databases for drugs. Data from primary and translational research, clinical trials, anecdotal reports regarding off-label uses, and other published human data information available are included. Using artificial intelligence algorithms and other bioinformatics tools, investigators systematically try to identify the interaction between drugs and protein targets. It can be combined with genetic data, clinical analysis, structure (molecular docking), pathways, signatures, targets, phenotypes, binding assays, and artificial intelligence to get an optimum outcome in repurposing. This article describes the strategies involved in drug repurposing and enlists a series of repurposed drugs and their indications.

Keywords: drug repurposing, clinical trials, molecular docking, drug discovery, post-market safety

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INTRODUCTION

Drug repurposing is the technique of using an existing drug or drug candidate for a new treatment or medical condition for which it was not indicated before [1]. It was initially developed to treat a different medical condition. It has been described as a serendipitous process that happens unexpectedly. In this process, the undesired side effects of drug molecules can also be a pointer to exploring the possibility of its effectiveness in an entirely different medical condition [2]. Usually, drugs with established safety in humans and tested and developed for efficacy in a particular disease other than the one for which they were developed [3]. This process brings the drugs directly to preclinical and clinical trials, skipping the drug development process, and thus reducing risk and costs [4].

STAGES OF DRUG REPURPOSING

The stages of repurposing are elucidated in Fig. 1 [17].

IMPORTANCE OF DRUG REPURPOSING

Repurposing can identify new compounds based on phenotypic benefits without explicitly defining the mechanism of action. This can be directly tested in preclinical animal models, and these results are more applicable to clinical applications and research. It may progress directly straight to Phase II clinical trials [5]. There is a minimum risk of failure with repurposed drugs [6]. The difference between traditional drug discovery and drug repurposing is described in Table 1.

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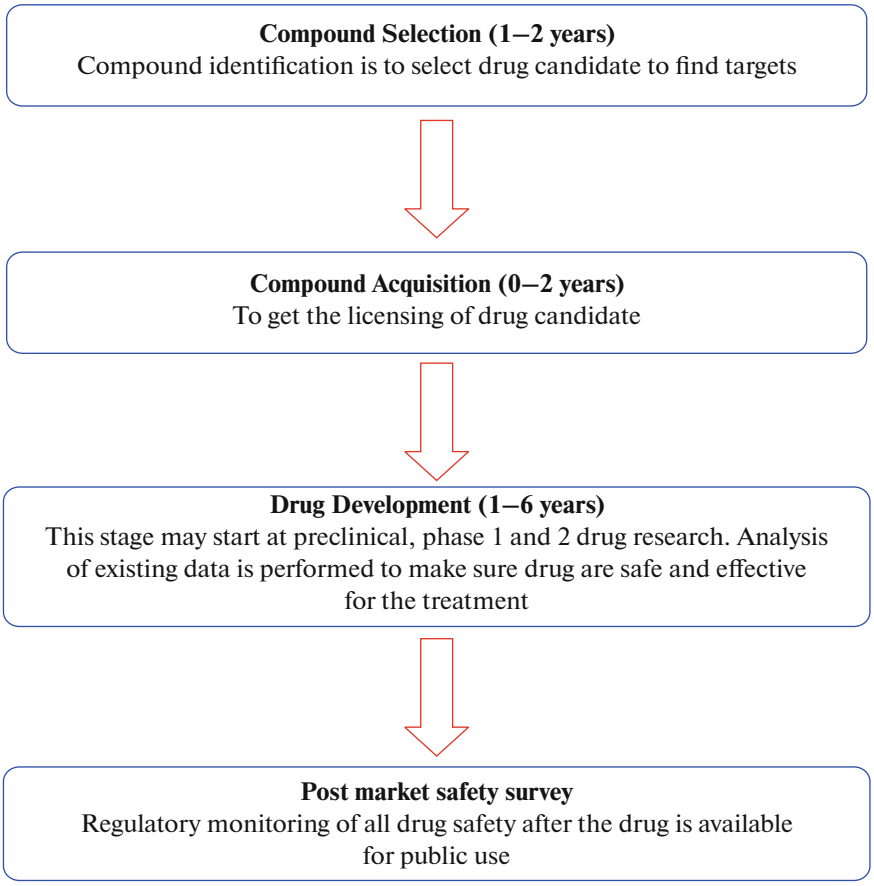

Fig. 1. Stages of Repurposing.

AN IDEAL CANDIDATE FOR REPURPOSING

A drug has undergone clinical drug development and has been marketed as an ideal candidate for repurposing. A drug with well-established safety and toxicity studies in previous clinical trials, approved by the regulatory authorities, can skip clinical trials with sufficient data support and justification. The mechanism of action of the selected drug shall be established [3].

Those drugs that have gone through several stages of clinical development and have been unsuccessful for reasons other than safety are ideal candidates for repurposing. Some drug repurposing has occurred during clinical trials, like the well-known Viagra

Table 1. The main difference between Traditional Drug Discovery System and Drug Repurposing [6–13]

TRADITIONAL DRUG DISCOVERY	DRUG REPURPOSING
Include 5 stages: • Discovery and preclinical • Safety review • Clinical research • FDA review • FDA post-market safety monitoring	**Include 4 stages:** • Compound identification • Compound acquisition • Development • FDA post-market safety monitoring
Generally, more time consuming	Less time consuming
High investment or cost	Lesser investment compared to traditional drug discovery
More risk of failure	Less risk of failure
Clinical efficacy and safety profile should be evaluated	Clinical efficacy and safety profiles already exist

Repurposing drugs have a significant advantage in decreasing the development cost and time to market over standard discovery. Data like pharmacokinetics, toxicology, and safety data from the standard discovery process [14–16].

Table 2. Drug repurposing can be drug-oriented, disease-oriented, and treatment-oriented

Drug-oriented Information of drugs	Disease-oriented	Treatment oriented
Off-label use of drugs	Information on disease pathway	Disease omics data
Phenotypic screening	Disease omics data	All information related to treatment strategies
Target 3D structure of the drug	Genetics data of disease	Genetics genomics
Chemical structure of drugs and ligands	Protein interaction network	Proteomics metabolics
An adverse effect of drugs		

Table 3. Methods of Repurposing [4]

Method	Required knowledge[#]
Blinded search or screening method	Off-label use Phenotypic screening
Target-based methods	Phenotypic screening; Target 3D structure, chemical structure information of drugs and ligands
Knowledge-based methods	Drug–target information, chemical structure information of targets and adverse effects (clinical trial information) Regulatory approval labels and adverse effects Available pathway information of disease
Signature-based methods	Disease omics data; Genetics data; Drug omics data Disease omics and drug omics data
Pathway- or network-based methods	Disease omics data, available pathway information, and protein interaction network; Drug omics data
Targeted mechanism-based methods	Drug omics data, disease pathway and protein interaction network

[#] Repurposing methods require various skills and knowledge of various factors, that is, it may be drug-oriented or disease-oriented, or treatment-oriented [4]

(sildenafil) indicated initially for hypertension and angina. The new role of treating erectile dysfunction was unravelled during the clinical trials.

There are examples of abandoned drugs with their toxicity resurfaced with different indications. Thalidomide, indicated for vomiting, was used to treat nausea in pregnant women and resulted in several congenital disabilities. Due to this tragic effect on fetal development, its use was banned or restricted in several countries. Later, the drug was repurposed for leprosy and multiple myeloma [18]. However, this type of repurposing has met objections from the scientific community [19]. The benefit-to–to-risk ratio can be considered during repurposing cases. A rational decision from the regulatory authorities is essential to address the concern "Is it worth the risk? Or can an existing therapy perform better than the repurposed drug?".

STRATEGIES FOR DRUG REPURPOSING

This approach usually utilizes public databases for drugs. Data from primary and translational research, clinical trials, anecdotal reports regarding off-label uses, and other published human data information available are included. Using artificial intelligence algorithms and other bioinformatics tools, investigators systematically try to identify the interaction between drugs and protein targets. In-silico drug repositioning is a powerful technology with significant advantages, including speed and reduced costs [20]. There are usually three kinds of approaches; computational approach, biological experimental approach, and mixed approach, which are described in Table 2 [17].

Traditional phenotype-based screening methods do not need prior knowledge, and the repositioned drugs are just serendipitously tested. The integrated knowledge and elucidated drug action mechanisms increase with the complexity of modelling methods [4]. These methods are listed in Table 3.

Phenotypic Screening

The phenotypic screening method was used to discover molecules and biologics approved by the regulatory bodies. These methods do not include pharmaceutical or biological information and therefore are less likely to help elucidate any mechanisms of action of drugs. Most depend on serendipitous identification from tests aimed at specific diseases and medicines. The advantage of these methods (off-label use and phenotypic screening) is that they have a high chance of application to many drugs or conditions [4, 21].

Target-Based Methods

This method requires specific knowledge about the targets, such as 3D protein structures. Knowledge-based methods require knowledge about drugs or diseases, such as adverse effects, regulatory approval labels, records of clinical trials, and published disease biomarkers (potential targets) or disease pathways). These methods enable researchers to quickly screen any number of drug molecules with a known chemical structure (e.g., Simplified Molecular Input Line-Entry System SMILES). Target-based drug repositioning methods include.

• In-vitro and in vivo high-throughput and/or high-content screening (HTS/HCS) of drugs for a protein or biomarker of interest and

• In-silico screening of drugs or compounds from drug libraries, such as ligand-based screening or docking.

Compared to blinded methods, targeted-based methods improve the chances of drug discovery as targets are directly linked to the disease mechanism. Integrating target information and drug repurposing increases the possibility of finding therapeutically beneficial compounds [4, 21, 22].

Knowledge-Based Methods

These methods apply bioinformatics or cheminformatics approaches to include the available information of drugs, drug-target networks, chemical structures of targets and drugs, clinical trial information, FDA approval labels, signalling or metabolic pathways, and so on, into drug-repositioning studies. The information content of blinded and target-based methods may not be sufficient to identify new mechanisms beyond the known targets. Knowledge-based methods incorporate known information into predicting unknown mechanisms, such as novel drug targets, obscure drug-drug similarities, and new disease biomarkers. Knowledge-based methods include much-known information into the drug repositioning process to improve prediction accuracy [4, 21].

Signature-Based Methods

Signature-based drug-repurposing methods use gene signatures derived from disease omics data with or without treatment to discover unknown off-target or disease mechanisms. Such genomics data can be assessed through publicly available databases, such as NCBI-GEO (http://www.ncbi.nlm.nih.gov/geo/), SRA Sequence Read Archive (http://www.ncbi.nlm.nih.gov/Traces/sra/), CMAP Connectivity Map and CCLE Cancer Cell Line Encyclopedia. Signature-based methods help uncover unknown mechanisms of action of molecules and drugs. Using computational approaches includes molecular-level mechanisms, such as significantly changed genes [4, 21].

Pathway- or Network-Based Methods

This method utilizes genetic disease data, available signalling or metabolic pathways, and protein interaction networks to reconstruct disease-specific pathways, thereby identifying the key target for repurposing drugs. They help narrow general signalling networks from a large number of proteins down to a specific network with a few proteins (or targets). These methods use pathway analysis or network biology methods to discover essential pathways from diseases' genetic, genomic, proteomic, and metabolic data to find new targets for repositioned drugs. Example: Signalling mechanisms of metastatic subtypes of breast cancer because the subtype signalling mechanisms are hard to elucidate from existing breast cancer pathways or the gene signatures [4, 21].

Targeted Mechanism-Based Methods

These methods integrate treatment omics (genetic) data, available signalling pathway information, and protein interaction networks to delineate the unknown mechanisms of the action of drugs. It aims to discover drug action mechanisms by identifying off-target or targeted pathways of treated drugs using drug omics data (before and after drug treatment). For example, drug resistance is an issue in cancer therapy. Although patients initially respond well to a drug, they often acquire resistance to that drug after a few months of treatment. Hence, successful drug treatment needs additional information about the mechanisms of action of drugs to find better drug targets. However, there are fewer studies on targeted mechanism-based methods that developed elegant computational models to predict the drug effects and related targeted pathways. This is because of the difficulties in deriving effective computational models [4, 21].

Molecular Docking

Molecular docking is a versatile tool used to predict the geometry and to score the interaction of a protein in a complex with a small-molecule ligand. Docking can be performed by docking a known drug into a large set of different target structures or a database of approved medications into one intended target. Molecular docking is a convenient and fast method to screen large libraries of ligands and targets, with a full range of sampling options [23]. 3D structures of the target shall be available through crystallography, nuclear magnetic resonance (NMR), or comparative models to carry out docking. Drawbacks and limitations include approximate scoring function and imperfect binding mode placement algorithms. However, these problems can be overcome by postprocessing docking results with more accurate scoring functions and other criteria [24].

Table 4. Examples of repurposed drugs

S. No.	Drug	Discovered	Repurposed	Ref.
1	Amiloride	Acid-sensing ion channel antagonist	Secondary progressive multiple sclerosis (SPMS)	[26]
2	Anastrazole	Ovulation induction	Breast cancer	[9]
3	Angiotensin-converting enzyme 2 (ACE2) inhibitor, angiotensin receptor blocker (ARB) and statins	Antihypertensives	Effective against SARS-CoV-2 (COVID-19) [Few controversies are seen apart from promising results]	[27]
4	Aripiprazole	Antipsychotic/Antidepressant	Active against fungal biofilms	[28]
5	Artesunate	Anti-infective	Active against fungal biofilms	[28]
6	Aspirin and ibuprofen	Inflammation	Antibacterial and antifungal	[25]
7	Atorvastatin (generic Lipitor)	Hyper-cholesterolaemia	Cavernous angioma	[26]
8	Auranofin	Rheumatoid arthritis	Antibacterial and antifungal	[25]
9	Avermectin B1a	Anti-infective	Active against fungal biofilms	[28]
10	Azathioprine	Crohn's disease	Antibacterial and antifungal	[25]
11	Bacitracin	Anti-infective	Active against fungal biofilms	[28]
12	Benzbromarone	Vasodilator	Active against fungal biofilms	[28]
13	Bithionate disodium	Anti-infective	Active against fungal biofilms	[28]
14	Bleomycin	Antitumor	Active against fungal biofilms	[28]
15	Bromperidol	Antipsychotic/Antidepressant	Active against fungal biofilms	[28]
16	Broxyquinoline	Anti-infective	Active against fungal biofilms	[28]
17	Capecitabine	Colon cancer	Breast cancer	[9]
18	Carboplatin	Antitumor	Active against fungal biofilms	[28]
19	Celecoxib	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
20	Chloroquine	Anti-malarial	Active against fungal biofilms	[28]
21	Cisplatin	Antitumor	Active against fungal biofilms	[28]
22	Clarithromycin	Anti-infective	Active against fungal biofilms	[28]
23	Clarithromycin, pioglitazone, and treosulfan	Antibiotic Antidiabetic	Non-small cell lung cancer	[29]
24	Clomiphene	Fertility	Antibacterial and antifungal	[25]
25	Cyclophosphamide	As immuno-modulator in autoimmune diseases	Breast cancer	[9]
26	Cyclosporine	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
27	Dacarbazine	Antitumor	Active against fungal biofilms	[28]
28	Daunorubicin	Acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and Kaposi's sarcoma	Antibacterial and antifungal	[25]
29	Dexpramipexole	ALS and other neurological diseases: phase 3 trials did not meet the endpoint	Hypereosinophilic syndromes	[26]
30	Diazepam	Antipsychotic/Antidepressant	Active against fungal biofilms	[28]
31	Digoxin	Treatment for cardiac diseases	Anticancer	[30]
32	Dihydroartemisinin	Anti-infective	Active against fungal biofilms	[28]
33	Disulfiram (Antabuse)	Reduces ethanol tolerance in alcoholism	Metastatic breast cancer & Alzheimer's disease	[26]

Table 4. (Contd.)

S. No.	Drug	Discovered	Repurposed	Ref.
34	Docetaxel	Hormone-refractory prostate cancer	Breast cancer and active against fungal biofilms	[9, 28]
35	Doxepin	Antipsychotic/Antidepressant	Active against fungal biofilms	28]
36	Doxorubicin	*Antibiotic from Streptomyces peucetius*bacterium,	Bladder, breast, stomach, lung, ovarian, and thyroid cancers	[9, 25]
37	Ebastine	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
38	Ebselen	Bipolar disorder and ischemic stroke	Antibacterial and antifungal	[25]
39	Edaravone	Neuroprotective agent in acute ischemic stroke and ALS	Multiple sclerosis	[26]
40	Eltrombopag	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
41	Esketamine (S enantiomer of ketamine)	Intravenous anesthetic	Treatment-resistant major depressive disorder (TRD)	[31]
42	Etodolac	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
43	Everolimus (Votubia, Evertor)	Immunosuppressants during organ transplants, wound healing	Breast cancer	[9]
44	Exemestane	Ovulation induction	Breast cancer	[9]
45	Favipiravir	Inhibitors of RNA-dependent RNA polymerase of virus (Antiviral drug)	Effective against SARS-CoV-2 (COVID-19) [More studies ae required]	[27, 34]
46	Fenofibrate	Reduces, triglyceride-rich particles (LDL) in plasma	Reduces macrophage recruitment in abdominal aortic aneurysm	[26]
47	Finasteride	Benign prostatic hyperplasia	Antibacterial and antifungal	[25]
48	Floxuridine	Colorectal cancer	Antibacterial and antifungal	[25]
49	Fluorouracil	Keratoacanthomas, actinic keratosis, and skin warts	Breast cancer	[9]
50	Fluorouracil	Solid tumors	Antibacterial and antifungal	[25]
51	Fluoxetine	Antipsychotic/Antidepressant, Serotonin selective reuptake inhibitor (SSRI)	Active against fungal biofilms, secondary progressive multiple sclerosis (SPMS)	[28, 26]
52	Fluvastatin	Lipid-lowering	Active against fungal biofilms	[28]
53	Fulvestrant	Antiestrogen	Breast cancer	[9]
54	Gallium nitrate	Lymphoma and bladder cancer	Antibacterial and antifungal	[25]
55	Gemcitabine	Anti-viral drug	Breast cancer	[9]
56	Goserelin	Prostate cancer, uterine fibroids, assisted reproduction	Breast cancer	[9]
57	γ-Secretase inhibitors (GSI)	Alzheimer disease: prevent amyloid precursor cleavage	Several inhibitors are being tested against a variety of cancers	[26]
58	Human Albumin	Blood additive	Immuno-restoration	[26]
59	Hydroxychloroquine	Antimalarial	Antiviral drug (HIV, Chicken guinea, dengue, SARS-CoV-2)	[34]
60	Imipramine	Antipsychotic/Antidepressant	Active against fungal biofilms	[28]
61	Iodoquinol	Anti-infective	Active against fungal biofilms	[28]
62	Itraconazole	Antifungal	Anticancer	[30]
63	Ivermectin	Anti-parasitic	Effective against SARS-CoV-2 (COVID-19) [safe in conventional doses]	[27]

Table 4. (Contd.)

S. No.	Drug	Discovered	Repurposed	Ref.
64	Ketoprofen	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
65	Ketorolac	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
66	Letrozole	Ovulation induction	Breast cancer	[9]
67	Lopinavir/ritonavir	Antiviral drug	Effective against SARS-CoV-2 (COVID-19) Drug needs to be further investigated]	[27, 34]
68	Lorazepam	Antipsychotic/Antidepressant	Active against fungal biofilms	[28]
69	Losartan	Blood pressure reduction	Alzheimer disease	[26]
70	Lovastatin	Lipid-lowering	Active against fungal biofilms	[28]
71	Loxapine	Antipsychotic and antischizophrenia	Irritability associated with autism	[26]
72	Mebendazole	Antiparasitic/Helminthiasis/Anti-infective	Brain cancer (i.e., medulloblastoma and glioblastoma)/Antibacterial and antifungal/Active against fungal biofilms	[25, 28, 29]
73	Meloxicam	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
74	Metformin	Diabetes	Anti-nonsmall cell lung cancer, and augmented resistance in aging, Colo rectal cancer	[26, 32]
75	Methotrexate	Leukemia	Breast cancer	[9]
76	Mibefradil (Posicor)	Antihypertensive, calcium channel blocker	Short term use as an adjuvant in cancer therapy	[26]
77	Midazolam	Antipsychotic/Antidepressant	Active against fungal biofilms	[28]
78	Mifepristone	Emergency contraceptive	Cushing's syndrome	[29]
79	Mycophenolic acid	Immunosuppressant	Anticancer	[30]
80	Nelfinavir	HIV protease inhibitor	Solid tumors	[26]
81	Niclosamide	Helminthiasis/Anti-infective	Antibacterial and antifungal and active against fungal biofilms Treats multidrug-resistant leukemia	[25, 28, 33]
82	Nitazoxanide	Antiprotozoal agent	Influenza	[26]
83	Nitroxoline	Anti-infective	Active against fungal biofilms	[28]
84	Nortriptyline	Antipsychotic/Antidepressant	Active against fungal biofilms	[28]
85	Oxyclozanide	Helminthiasis	Antibacterial and antifungal	[25]
86	Paclitaxel	Ovarian cancer, atrial restenosis	Breast cancer	[9]
87	Pentetic acid	Hypocalcaemia	Antibacterial and antifungal	[25]
88	Perhexiline maleate	Anti-anginal	Active against fungal biofilms	[28]
89	Phenobarbitone	Anticonvulsant	Active against fungal biofilms	[28]
90	Pimozide	Severe Tourette's syndrome and schizophrenia	Antibacterial and antifungal	[25]
91	Promethazine	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
92	Propanolol	Antiarrhythmic	Active against fungal biofilms	[28]
93	Pyrvinium pamoate	Anti-infective	Active against fungal biofilms	[28]
94	Quinacrine	Helminthiasis	Antibacterial and antifungal	[25]
95	Raloxifene	Osteoporosis in postmenopausal women	Breast cancer	[9]

Table 4. (Contd.)

S. No.	Drug	Discovered	Repurposed	Ref.
96	Rapamune	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
97	Remdesvir	Inhibitors of RNA-dependent RNA polymerase in virus (Antiviral drug)	Effective against SARS-CoV-2	[27, 34]
98	Ribavirin	Antiviral drug	Effective against SARS-CoV-2(COVID-19)	[27, 34]
99	Rifampicin	Anti-infective	Active against fungal biofilms	[28]
100	Riluzol	Glutamate antagonist	Secondary progressive multiple sclerosis (SPMS)	[26]
101	Saracatinib	Cancer therapy	Mild to moderate Alzheimer disease	[26]
102	Sildenafil (Viagra)	Angina	Erectile dysfunction,	[29]
103	Silymarin	Anti-hepatotoxic	Active against fungal biofilms	[28]
104	Simvastatin	Hyper-cholesterolemia (Lipid-lowering)	Antibacterial and antifungal	[25, 28]
105	Sirolimus and Zoledronic acid	Prophylaxis of organ rejection, Osteoporosis respectively	Osteosarcoma (combined with Metzolimos, metronomic cyclophosphamide, methotrexate)	[29]
106	Statins	Hyper-cholesterolaemia	Oncology	[26]
107	Streptozotocin	Pancreatic islet cell cancer	Antibacterial and antifungal	[25]
108	Sulfadiazine	Anti-infective	Active against fungal biofilms	[28]
109	Sulfadimethoxine	Anti-infective	Active against fungal biofilms	[28]
110	Sulfamethoxazole	Anti-infective	Active against fungal biofilms	[28]
111	Sulfamethoxy-pyridazine	Anti-infective	Active against fungal biofilms	[28]
112	Tacrolimus	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[28]
113	Tamoxifen	Breast cancer, Albright syndrome, ovulation induction	Antibacterial and antifungal	[9, 25]
114	Teicoplanin	Antibacterial	Antiviral, potentially repurposable for COVID-19 treatment	[27]
115	Telmisartan	Blood pressure reduction	Abdominal aortic aneurysm	[26]
116	Thalidomide	Antiemetic	Hanson's disease, Leprosy	[26]
117	Thiotepa	Immunosuppressant	Breast cancer	[9]
118	Tigecycline	Anti-infective	Active against fungal biofilms	[28]
119	Tocilizumab	Immunosuppressive drug for cytokine release syndrome	Severe COVID-19 infection	[27, 34]
120	Toremifene	Infertility with an ovulatory disorder	Breast cancer	[9]
121	Valproic acid	Anticonvulsant	Active against fungal biofilms	[28]
122.	Verapamil	Antiarrhythmic	Active against fungal biofilms	[28]
123.	Vinblastine	Hodgkin lymphoma, non-Hodgkin's lymphoma, histiocytosis	Breast cancer	[9]
124.	Yohimbine hydrochloride	Vasodilator	Active against fungal Biofilms	[28]

Application of Drug Repurposing in Drug Discovery

Besides developing new treatment options (such as immunotherapy and host-directed therapies), scientists worldwide are working to repurpose existing drugs against SARS-CoV-2 [27]. Table 2 gives a detailed list of repurposed drugs, and a few are repurposed for the treatment of COVID-19. Another example is metformin, an antidiabetic drug that shows anticancer effects by decreasing the incidence of different cancers and inhibiting the proliferation and migration of cancer cells, activating apoptosis, and reducing EMT (epithelial-mesenchymal transition) and metastasis. Repurposing helps overcome antibiotic resistance. For

example, TB strains resistant to currently used drug combinations are found in all parts of the world. The product antibiotic, pyridomycin, discovered in the 1950s, is repurposed to treat TB, which takes the place of isoniazid [25, 26]. Table 4 contains a detailed list of repurposed drugs with their initial indication and repurposed use.

Challenges

Although screening efforts are relatively inexpensive, approved drug clinical trials are expensive. The advantage of drug repurposing is that the early stages of clinical development are complete; hence, the drugs can proceed to clinical studies. However, doing clinical studies directly without preclinical studies is a risk. Inaccurate identification of drugs may prove to have no significant impact on therapy or mortality rates, and it may result in a loss in terms of treatment and expense.

Identifying a new therapeutic indication for an existing drug is a significant challenge. Choosing the right therapeutic area for the drug under investigation, evaluating the clinical trials with respect to the new therapeutic use, and deciding which stage of the clinical study or preclinical study shall be restarted are a few challenges repurposing. New preclinical and clinical trials may be required to be carried out if the available data are not satisfactory and do not comply with the requirements of regulatory agencies.

Another critical issue is patent application and intellectual property rights (IPR). Patents or IPR can prevent some repurposed drugs from entering the market, and IP protection for drug repurposing is minimal. Hence, the regulatory constraints and the risk of abandoning repurposing projects due to unsatisfactory results can discourage the investment of money or resources towards drug repurposing. A spike in market demand can be an excellent motivator to shift researchers and investors into action.

CONCLUSIONS

There are numerous diseases for which good therapeutic options have not been developed. The concept of repurposing a drug enables exploring the hidden potential of many molecules and better utilization of therapeutic agents. For better drug repositioning, more in-depth understanding along with integrated approaches between computational and experimental methods may be required to ensure high success rates of repositioned drugs.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest.

This article does not contain any studies involving human participants performed by any of the authors and does not contain any studies involving animals performed by any of the authors.

REFERENCES

1. Oprea, T.I. and Mestres. J., *AAPS J.*, 2012, vol. 14, pp. 759–763. https://doi.org/10.1208/s12248-012-9390-1
2. Strittmatter, S.M., *Nat Med.*, 2014, vol. 20, pp. 590–591. https://doi.org/10.1038/nm.3595
3. Dinić, J., Efferth, T., García-Sosa, A.T., Grahovac, J., Padrón, J.M., Pajeva, I., Rizzolio, F., Saponara, S., Spengler, G., and Tsakovska, I., *Drug Resist. Updates*, 2020, vol. 52, p. 100713. https://doi.org/10.1016/j.drup.2020.100713
4. Jin, G. and Wong, S.T.C., *Drug Discovery Today*, 2014, vol. 19, pp. 637–644. https://doi.org/10.1016/j.drudis.2013.11.005
5. Turner, N., Zeng, X.Y., Osborne, B., Rogers, S., and Ye, J.M., *Trends Pharmacol. Sci.*, 2016, vol. 37, pp. 379–389. https://doi.org/10.1016/j.tips.2016.01.007
6. Rudrapal, M., Khairnar, S.J., and Jadhav, A.G., *Drug Repurposing (DR): An Emerging Approach in Drug Discovery*, 2020. https://doi.org/10.5772/intechopen.93193
7. Hughes, J.P., Rees, S., Kalindjian, S.B., and Philpott, K.L., *Br. J. Pharmacol.*, 2011, vol. 162, pp. 1239–1249. https://doi.org/10.1111/j.1476-5381.2010.01127.x
8. Kalita, J., Chetia, D., and Rudrapal, M., *Med. Chem.*, 2020, vol. 16, pp. 928–937. https://doi.org/10.2174/1573406415666190806154722
9. Aggarwal, S., Verma, S.S., Aggarwal, S., and Gupta, S.C., *Semin. Cancer Biol.*, 2020, vol. 68, pp. 8–20. https://doi.org/10.1016/j.semcancer.2019.09.012
10. Cha, Y., Erez, T., Reynolds, I.J., Kumar, D., Ross, J., Koytiger, G., Kusko, R., Zeskind, B., Risso, S., Kagan, E., Papapetropoulos, S., Grossman, I., and Laifenfeld, D., *Br. J. Pharmacol.*, 2018, vol. 175, no. 2, pp. 168–180. https://doi.org/10.1111/bph.13798
11. Agrawal, P., *J. Pharmacovigil.*, 2018, vol. 6, pp. 1–2. https://doi.org/10.1016/j.drudis.2020.10.010
12. Allarakhia, M., *Drug Des. Dev. Ther.*, 2013, vol. 7, pp. 753–766. https://doi.org/10.2147/DDDT.S46289
13. Parvathaneni, V., Kulkarni, N.S., Muth, A., and Gupta, V., *Drug Discovery Today*, 2019, vol. 24, pp. 2076–2085. https://doi.org/10.1016/j.drudis.2019.06.014
14. Padhy, B.M. and Gupta, Y.K., *J. Postgrad. Med.*, 2011, vol. 57, p. 153. https://doi.org/10.4103/0022-3859.81870
15. Agrawal, P., *J. Pharmacovigil.*, 2015, vol. 2, pp. 1–2. https://doi.org/10.4172/2329-6887.S2-e002
16. Pantziarka, P., Bouche, G., Meheus, L., Sukhatme, V., Sukhatme, V.P., and Vikas, P., *Ecancermedicalscience*, 2014, vol. 8, p. 442. https://doi.org/10.3332/ecancer.2014.442

17. Xue, H., Li, J., Xie, H., and Wang, Y., *Int. J. Biol. Sci.*, 2018, vol. 14, pp. 1232–1244. https://doi.org/10.7150/ijbs.24612
18. Kim, J.H. and Scialli, A.R., *Toxicol. Sci.*, 2011, vol. 122, pp. 1–6. https://doi.org/10.1093/toxsci/kfr088
19. Pannikar, V., *Lepr. Rev.*, 2003, vol. 74, pp. 286-288.
20. Abbruzzese, C., Matteoni, S., Signore, M., Cardone, L, Nath, K., Glickson, J.D., and Paggi, M.G., *J. Exp. Clin. Cancer Res.*, 2017, vol. 36, p. 169. https://doi.org/10.1186/s13046-017-0642-x
21. March-Vila, E., Pinzi, L., Sturm, N., Tinivella, A., Engkvist, O., Chen, H., and Rastelli, G., *Front. Pharmacol.*, 2017, vol. 8, p. 298. https://doi.org/10.3389/fphar.2017.00298
22. Napolitano, F., Zhao, Y., Moreira, V.M., Tagliaferri, R., Kere, J., D'mato, M., and Greco, D., *J. Cheminform.*, 2013, vol. 5, p. 30. https://doi.org/10.1186/1758-2946-5-30
23. Kitchen, D.B., Decornez, H., Furr, J.R., and Bajorath, J., *Nat. Rev. Drug Discovery*, 2004, vol. 3, pp. 935–949. https://doi.org/10.1038/nrd1549
24. Sgobba, M., Caporuscio, F., Anighoro, A., Portioli, C., and Rastelli, G., *Eur. J. Med. Chem.*, 2012, vol. 58, pp. 431–440. https://doi.org/10.1016/j.ejmech.2012.10.024
25. Miró-Canturri A., Ayerbe-Algaba, R., and Smani, Y., *Front. Microbiol.*, 2019, vol. 10, p. 41. https://doi.org/10.3389/fmicb.2019.00041
26. Schein, C.H., *Med. Res. Rev.*, 2020, vol. 40, pp. 586–605. https://doi.org/10.1002/med.21627
27. Jean, S.S. and Hsueh, P.R., *Expert Rev. Anti Infect. Ther.*, 2020, vol. 18, pp. 843–847. https://doi.org/10.1080/14787210.2020.1771181
28. de Mello, T.P., Silva, L.N., Ramos, L.S., Frota, H.F., Branquinha, M.H., and dos Santos, A.L.S., *Curr. Top. Med. Chem.*, 2020, vol. 20, pp. 509–516. https://doi.org/10.2174/1568026620072003161426 26
29. Hernandez, J.J., Pryszlak, M., Smith, L., Yanchus, C., Kurji, N., Shahani, V.M., and Molinski, S.V., *Front. Oncol.*, 2017, vol. 7, p. 273. https://doi.org/10.3389/fonc.2017.00273
30. Shim, J.S. and Liu, J.O., *Int. J. Biol. Sci.*, 2014, vol. 10, pp. 654–663. https://doi.org/10.7150/ijbs.9224
31. Das, J., *J. Med. Chem.*, 2020, vol. 63, pp. 13514–13525. https://doi.org/10.1021/acs.jmedchem.0c01193
32. Sang, J., Tang, R., Yang, M., and Sun, Q., *Biomed. Res. Int.*, 2020, pp. 1–9. https://doi.org/10.1155/2020/9312149
33. Hamdoun, S., Jung, P., and Efferth, T., *Front. Pharmacol.*, 2017, vol. 8, pp. 1–11. https://doi.org/10.3389/fphar.2017.00110
34. Ng, Y.L., Salim, C.K., and Chu, J.J.H., *Pharmacol. Ther.*, 2021, vol. 228, pp. 1–14. https://doi.org/10.1016/j.pharmthera.2021.107930