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Review Article

Repurposing – second life for drugs

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Abstract

Drug repurposing refers to finding new indications for existing drugs. The paradigm shift from traditional drug discovery to drug repurposing is driven by the fact that new drug pipelines are getting dried up because of mounting Research & Development (R&D) costs, long timeline for new drug development, low success rate for new molecular entities, regulatory hurdles coupled with revenue loss from patent expiry and competition from generics. Anaemic drug pipelines along with increasing demand for newer effective, cheaper, safer drugs and unmet medical needs call for new strategies of drug discovery and, drug repurposing seems to be a promising avenue for such endeavours. Drug repurposing strategies have progressed over years from simple serendipitous observations to more complex computational methods in parallel with our ever-growing knowledge on drugs, diseases, protein targets and signalling pathways but still the knowledge is far from complete. Repurposed drugs too have to face many obstacles, although lesser than new drugs, before being successful.

Keywords

Indication switch, *In silico* method, Use patent, Re-profiling

Introduction

"*The real voyage of discovery consists not in seeking new landscapes but in having new eyes*"
Marcel Proust

In brief, drug repurposing refers to finding new indications for existing drugs which may be either approved and marketed or in clinical trials or shelved due to reasons other than safety. A repurposed drug may also include new dosage, new formulation, and new method of use or new patient population. Drug re-profiling, drug re-tasking, drug rescue, indication expansion or indication switching are other terms used for drug repurposing(Bellera et al. 2015). A new drug discovery begins with target identification for a disease of interest which may be an abnormal protein, a signalling pathway or a gene mutation related to the disease of concern. This is followed by high-throughput screening to identify 'hits' against the target. Those hits with maximum activity form the lead compounds which are then validated through assays and undergo optimisation to characterise the structure-activity relationship (SAR) and to enhance favourable pharmacokinetic properties of the compounds. Lead optimisation is then followed by preclinical and clinical studies(Zheng et al. 2013). Such a process is labour intensive, time consuming and too costly with no guarantee of success. In drug repurposing, the major difference from new drug discovery is that the lead compounds identified have established safety and large literature corpus which allows for accelerated drug development, reduced time consumption, lower cost and less risks (Fig. 1)(Bellera et al. 2015). Chlorpromazine, originally synthesized as an antimalarial

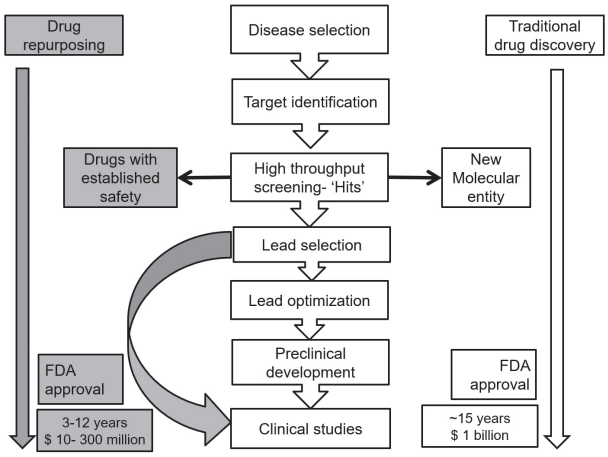

Figure 1. Drug repurposing concept in drug development.

was found to have sedative-anxiolytic effects in patients before surgery by a surgeon-anaesthesiologist in 1950 and later used successfully in acute mania as adjunct to barbiturates(Baker et al. 2018). These discoveries were made without knowing the precise mechanism underlying these effects. However, with the advent of advanced technologies, current repurposing strategies are evidence based demonstrating a degree of plausibility before the repurposed drugs enter clinical trials. In May 2012, the National Centre for Advancing Translational Sciences (NCATS), a component of National Institute of Health (NIH), launched "Discovery of New Therapeutic Uses for Existing Molecules" initiative to aid repurposing marketed drugs or new chemical entities in development and offer financial support(Gns et al. 2019).

Need for drug repurposing

From the medical community-patient perspective, drug repurposing has the ability to meet unmet medical needs- neglected diseases and, rare and orphan diseases(Bellera et al. 2015). It also has the potential to provide more effective treatment, cheaper alternative drugs, and drugs with favourable side effect profile in diseases where the available drugs have adverse side effect profile(Liu et al. 2013). It can also play a significant role in the development of personalised medicine(Naylor and Schonfeld 2014). New drug discovery faces the challenges of increasing Research & Development (R&D) costs, long timeline for drug development, low success rate and regulatory hurdles. In addition, pharmaceutical industry is also confronted with revenue loss from patent expiry and competition from generics and off-label prescription. Drug repurposing is claimed to be less costly, less time consuming, less risky and increased chance of success from the industrial perspective (Reaume 2011; R Flower 2013). The above-mentioned factors call for novel strategies for drug discovery and drug repurposing may provide an answer to the question.

Drug repurposing approaches

Drug repurposing strategies could be either drug oriented or disease oriented(Chen et al. 2015). In drug-oriented approach, repurposing efforts begin from the chemical or drug perspective. This method is preferred when extensive data regarding the drug is available. In disease-oriented approach, repurposing efforts begin with the symptoms, pathophysiology, or mechanism of disease. This method is preferred when a specific disease is under focus or if data on drug is inadequate. Successful drug repurposing more often incorporates both approaches(Dudley et al. 2011).

Drug oriented repurposing could be either on-target or off-target repurposing (Fig. 2). In on-target repurposing, the known target of a drug is associated with diseases different from the drug's original indication (example – sildenafil originally developed for angina repurposed for erectile dysfunction – molecular target in both is phosphodiesterase-5). Off-target repurposing is based on drug promiscuity or more aptly polypharmacology i.e., a drug can act on multiple targets and the secondary targets can be used for a new indication (example- cimetidine, a peptic ulcer drug repurposed for lung cancer). While off-target repurposing is significantly cost and labour intensive than on-target strategy, it is more innovative than the latter(Mucke 2010; Jin et al. 2012; Tari et al. 2012).

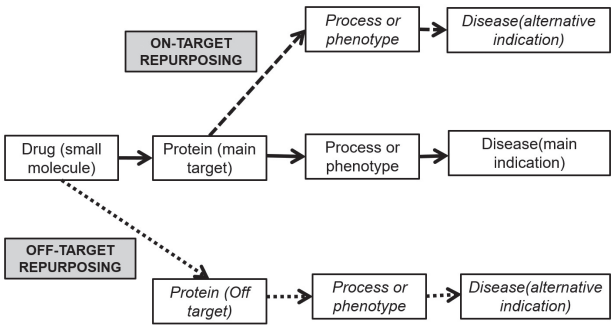

Figure 2. On-target and Off-target drug repurposing.

Methods of drug repurposing

Drug repurposing methods can be broadly classified into either activity based or *in silico* methods. Activity based methods include *in vivo* (living organisms) and *in vitro* high-throughput screening methods where the drug/chemical of interest is used for screening(Pihan et al. 2012; Shim and Liu 2014). In *in-silico* or computational or virtual screening methods, hits are identified in a systematic way from information gathered from various databases and involve tools to identify drug-target interactions. Activity based methods, though time and labour intensive in contrast to computational methods, are characterised by lower false positive hits and easy validation of screening hits than computational methods(Shim and Liu 2014).

Phenotypic screening based approach

Phenotypic screening using *in vivo* and *in vitro* cell based assays have been central to the discovery of new drugs where chemical libraries are screened to identify 'hits'(Zheng et al. 2013). This method can also be used to repurpose drugs by screening a library of existing drugs to identify new activities(Reaume 2011). Extensive knowledge on mechanism of action and target is not necessary. This method is also more physiological, as intact cells and organisms are used as opposed to *in silico* methods and the chances of success for the repurposed drug to move to clinical trials is high(Zheng et al. 2013). However, the method has relatively low throughput and costly compared to *in silico* methods. Astemizole and its metabolite desmethylastemizole were identified as inhibitors of *Plasmodium falciparum* growth through this strategy(Reaume 2011).

Literature based approach

Novel hypotheses can be generated by linking seemingly unrelated scientific facts or indirect associations between them by analysing extensive volumes of data to identify correlations. Based on Swanson's ABC model-two islands of knowledge A and C may be related to each other if they share a common intermediate link B(Andronis et al. 2011). The methods based on this approach include co-occurrence method which associates terms with each other when appearing in the same text but more prone for false positives and does not indicate the nature of relationship, and natural language processing-based methods which is more sophisticated and provides details about concepts and relationship(Lekka et al. 2011; Bellera et al. 2015). Fish oil use for Raynaud's syndrome was based on Swanson's model (Fig. 3A). Diltiazem and quinidine were identified as candidate drugs for Alzheimer's disease by combining text mining and molecular interaction network mining(Lekka et al. 2011).

Chemical similarity based approach

Similar property principle i.e., similar drugs with similar structures lead to similar biological effects, forms the base for this approach (Keiser et al. 2009). This principle is rooted in known quantitative relationships between chemical structures and biochemical activity (quantitative structural activity relationship). But, chemical structures from databases may contain errors or may be with-held as proprietary information. Some drugs undergo transformation inside the body before being active and also that physiological effects cannot be predicted on the basis of structural properties alone(Dudley et al. 2011). Mebhydrolin (Fabahistin) which binds to histamine H1 receptor was found to be chemically similar to serotonin and subsequently was found to have 5-HT5A binding affinity more than H1 receptor.

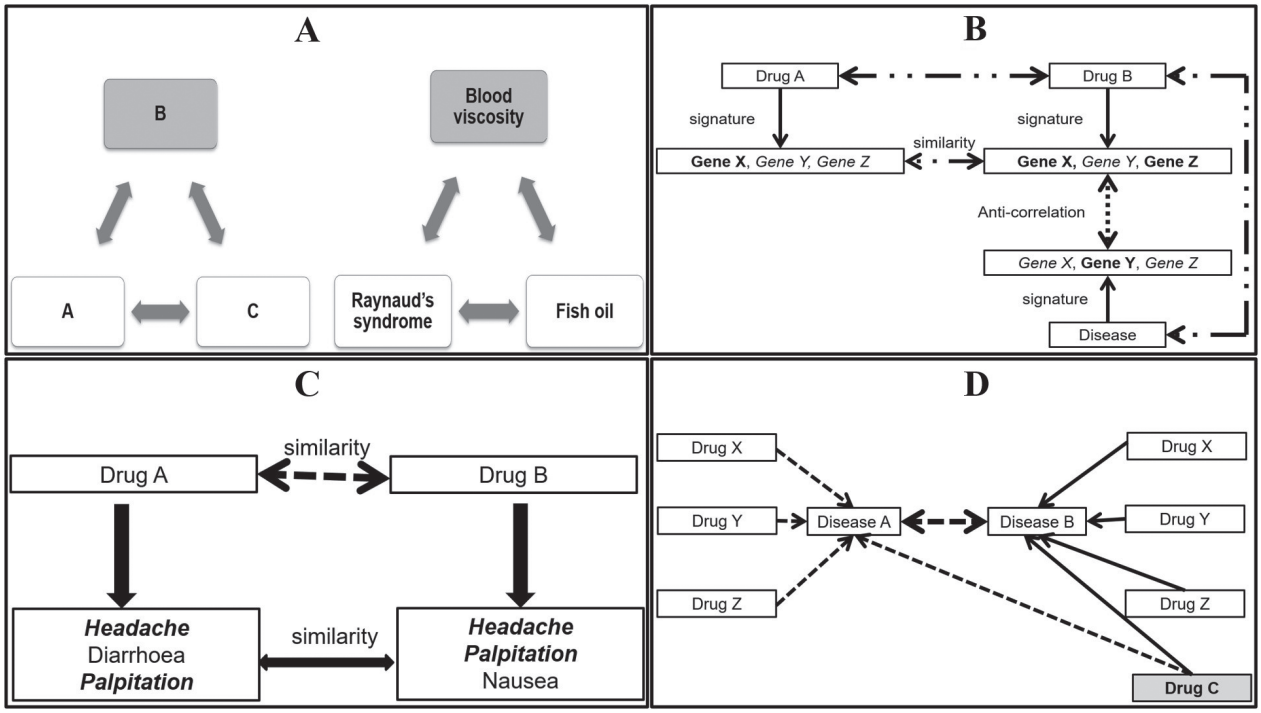

Figure 3. A) Swanson's ABC model B) Signature similarity approach – Drug B has inverse signature similarity with the disease against which it is effective and drug A with similar signature to drug B can be potentially repurposed for the same disease C) Side effect similarity approach D) Associative indication transfer approach.

Molecular similarity/signature based approach

Administration of a pharmacologically active compound into a biological system causes perturbation of the biological system owing to the drug's action and it is possible to construct a 'signature' of the molecular activity of the drug using high throughput molecular measurement techniques, such as gene expression microarrays even though the precise mechanism of action is not known. The molecular 'signatures' of a drug can then be compared with that of the disease to establish drug-disease relationship by anti-correlational transcriptional effects or inverse signature method(Hu and Agarwal 2009; Dudley et al. 2011; Sirota et al. 2011; Jin and Wong 2014). In a similar way, the signatures of different drugs can be compared by correlating their transcriptional effects to establish drug-drug relationship(Lamb et al. 2006; Iorio et al. 2010). The molecular activity profiles are created by exposing the drug compound to various cancer cell lines, which may not reflect the biological activity of the drug *in vivo*. Many drugs undergo chemical transformations when they are metabolized, and these changes are neglected in the creation of the profiles. Since many diseases affect multiple tissues and organ systems, it is difficult to represent them as single molecular activity profiles. Cimetidine, a peptic ulcer drug was repurposed for lung cancer by inverse similarity signature approach.

Connectivity map project

Connectivity map (CMap) project contains gene expression profiles for 1309 compounds by exposing these compounds to a few cancer cell lines and measuring the genome wide transcriptional response. Based on similarities in molecular activity shown in their CMap profiles, drugs can be connected to either drugs or diseases through pattern matching algorithms. If a disease is used as a query signature then drugs with inverse similarity signature can be used as treatment. In case of drug effect used as a query, the drug effect signatures stored in CMap Project similar to the query will have similar effects (Fig. 3B)(Lamb et al. 2006; Bellera et al. 2015). Dexamethasone resistance in acute lymphoblastic leukemia was overcome with concomitant use of sirolimus using the gene signature of dexamethasone resistance and sensitivity as query signatures in connectivity map profile. A high correlation was identified between the genes downregulated by sirolimus and the genes upregulated in dexamethasone resistant cells(Gns et al. 2019).

Protein structure and molecular docking – target based approach

Molecular docking involves simulation and modelling of drug-target interactions, as most small molecules exert their effect by binding to proteins or targets. A drug can be repurposed for a new disease if it is shown to interact with a protein target known to be involved in the pathogenesis of the disease. Inverse docking refers to the investigation of binding of a drug against a panel of known therapeutic targets to identify 'off-target' binding of the drug in question allowing for repurposing opportunities(Dudley et al. 2011; Bellera et al. 2015). However, 3-dimensional (3D) structure of ligand and protein target which are essential prerequisite for docking, are not fully resolved even for physiologically important proteins and high false-positive rates are common due to errors in protein structures(Dudley et al. 2011). Entacapone, a catechol-O-methyl transferase inhibitor used in the treatment for Parkinson's disease is repurposed for multidrug resistant tuberculosis by identifying off-target affinity for the protein enoyl-acyl carrier protein reductase (InhA), which is involved in synthesis of the bacterial cell wall(Kinnings et al. 2009).

Genetic variation based approach

Genome-Wide Association Study (GWAS), a database developed by the National Human Genome Research Institute (NHGRI) consist of reported Single Nucleotide Polymorphisms (SNP) and their associated genetic trait expressions(Gns et al. 2019). GWAS involves sequencing of DNA of individuals and identification of common gene mutations associated with a phenotypic trait and is typically used to relate a single nucleotide polymorphism (SNP) to a disease. Diseases having different phenotype may be similar at the molecular level (share same SNPs) and by integrating drug-target interactions, a drug can be repurposed if its gene target is associated with another disease different from its original indication(Grover et al. 2014). However, gene-disease relation is more complex and, GWAS does not provide information regarding the direction of the pharmacological effect, and it is difficult to determine whether an agonist or antagonist should be used to treat the disease. Pirenzepine, a peptic ulcer drug acts on *CHRM1* gene product and *CHRM1* gene is a candidate gene and novel therapeutic target for Type 2 diabetes mellitus (T2DM). Pirenzepine could be potentially repurposed for T2DM(Grover et al. 2014).

Side effect similarity approach

Drugs with similar target binding profiles cause similar side-effects - this provides the basis to relate drugs to other drugs or diseases by side effect profiles, even in cases where the precise pharmacological mechanism facilitating the side effect is unknown (Fig. 3C) (Campillos et al. 2008). The disadvantages of this approach are well characterised side effect profile of drugs is not completely available for most drugs and drugs sharing a similar side effect may cause the side effect by altogether different mechanisms. Many drugs used in transplant medicine for immunosuppression have Cytomegalovirus (CMV) infection as a side effect. Based on side effect similarity approach, it can be hy-

pothesized that drugs associated with increased CMV infection risk may also be drugs for transplant rejection which may not be true always.

Associative indication transfer approach

'Guilt by association' – diseases are considered similar if they shared significant number of drugs. A drug can be repurposed, if it is indicated for only one disease of a pair, for the other disease of the pair (Fig. 3D)(Chiang and Butte 2009). However, applying a drug indicated for a particular disease condition, based on varied and complex drug-disease relationship, to a different disease may not prove efficacious.

Network based method

A network is constructed with drugs, diseases and targets as nodes and edges on the basis of connectivity established through known relationship (experimental data) or through predicted associations from data derived from cheminformatics, bioinformatics, literature-based connections and other data. In short, data from almost all methods are combined holistically, and drug repurposing is done by constructing new edges based on the topology of the network. Extensive knowledge on the drug, disease, target proteins and mode of action is necessary for construction of a network and to draw inferences from it(Yildirim et al. 2007; Liu et al. 2013; Bellera et al. 2015). The network-based approach can be divided into two types. In the network-based clustering approach, novel drug-disease/target interactions are identified by finding modules using cluster algorithms according to the networks' topology. Vismodegib, a drug for basal cell carcinoma was predicted using the clustering method for Gorlin syndrome. In the network-based propagation strategy, prior information propagates from the source node to all network nodes and some subnetwork nodes(Xue et al. 2018).Anticonvulsant property of artificial sweeteners (saccharin, cyclamate, acesulfame) could be established through this model. They are linked with glutamate through action at T1R3 receptor which is shared by both glutamate and artificial sweeteners(Bellera et al. 2015).

Regulatory issues

A repurposed drug's commercial success depends on attaining effective market exclusivity through a combination of intellectual property protection and regulatory exclusivity(Smith 2011).

Patent exclusivity

A repurposed drug can be protected by composition of matter and/or use patent. A comparison between the modes of patent protection is shown in Table 1.

Table 1. Comparison between composition of matter patent and method of use patent.

Feature	Composition of matter patent	Method of use patent
Applies to	New patentable API or formulation or delivery mechanism or combination of API	New method of dosing or use for a specific indication
Level of protection	Strong	Weak

*API – Active Pharmacological Ingredient.

Regulatory exclusivity

This can be used for product protection in the absence of patent protection. Regulatory exclusivity differs between new chemical entities and new use/formulation (Table 2). In addition to regulatory exclusivity, we also have orphan drug exclusivity (7-year product exclusivity) and paediatric exclusivity for additional 6 months(Murteira et al. 2014). Strategic combination of new composition of matter and use patent together with a formulation and/or new use protected from generics provides strongest market exclusivity and thereby maximises the returns from the repurposed drug product(Smith 2011; Rai and Rice 2014).

Table 2. Comparison between new chemical entity exclusivity and new use/formulation exclusivity in drugs that are being repurposed.

Feature		New chemical entity exclusivity	New use/formulation exclusivity
Applies to		API not approved as marketed drug product	Addition of new indication, dose, formulation, delivery method or patient population
Duration		5 years from approval	3 years from approval
ANDA for generic version or 505(b)(2) new drug application for a modified version of the reference drug	Waiting period to file application	First 4 years of exclusivity period	None
	Approval	Not before exclusivity period	Not before exclusivity period
Patent challenge from ANDA or 505(b)(2) to be filed along with application		After the waiting period – 4 years	None
Patent infringement suit from the owner of reference listed drug		Additional 30 month stay	Additional 30 month stay

*API – Active Pharmacological Ingredient, ANDA -Abbreviated New Drug Application

Drug repurposing for Corona virus disease 19 (Covid-19)

The Covid-19 pandemic undoubtedly brought the world to a standstill but set the wheels in motion for the research community in search for a drug effective against the dreaded severe acute respiratory syndrome-coronovirus-2 (SARS-CoV2). While, conducting methodical drug trials was fraught with logistic and scientific challenges and with no vaccine in sight in the near future during the initial phase of the raging pandemic, drug repurposing offered probably the only hope of finding 'hits' potentially useful against Covid-19(Sultana et al. 2020). The drugs initially chosen to repurpose against Covid-19 were those which have shown *in vitro* efficacy or those that were used prior for severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS)(Martinez 2021). However, with the computational

repurposing approaches hundreds of drug candidates have been repurposed thanks to the resolution of 3D structure of viral proteins and viral genomic sequencing. As of October 2020, about 500 structures of the viral proteins with or without their associated ligands or target receptors have been made public to the research community which triggered off the explosion of repurposable hits. The major computational strategies employed for repurposing against Covid-19 included network-based approach, structure-based approach, and artificial intelligence-based approach. Molecular docking based on 3D viral structure augmented by molecular dynamic simulations and other methods are the main structure-based approach for repurposing. Drug repurposing strategies for Covid-19 based on artificial intelligence algorithms are few. Among the various methods, majority of the drugs were repurposed based on molecular docking method(Dotolo et al. 2020). The *in silico* approach facilitated drugs such as amiodarone, bromhexine and others being tested against the virus. The repurposed drugs with their potential targets and proposed mechanism(s) of action are tabulated in Table 3 (Parvathaneni and Gupta 2020; Senanayake 2020; Singh et al. 2020; Sultana et al. 2020; Kifle et al. 2021; Taneja 2021). A detailed discussion on the individual drugs is outside the scope of this review. Drug repurposing made possible for drugs getting approved under accelerated regulatory process by the major drug approval agencies across the globe.

Table 3. Drugs repurposed for Covid-19.

Therapeutic effect	Drug	Proposed mechanism of action
Viral entry inhibitors	Estradiol	ACE2 receptor downregulation preventing interaction of spike protein with cellular ACE2 receptor
	Spironolactone	
	Isotretinoin/retinoic acid	
	Bicalutamide	TMPRSS2 inhibition
	Nafamostat	
	Camostat mesilate	
	Umifenovir	Inhibit spike glycoprotein trimerisation
	Nelfinavir	Interferes with membrane fusion
	Chloroquine/hydroxychloroquine	ACE2 receptor glycosylation; reducing pH of endosomes
	Amiodarone	Reducing pH of endosomes
	Chlorpromazine	Inhibit clathrin mediated endocytosis
	Verapamil	Blocking ion channels
	Linagliptin, sitagliptin	DPP4 inhibitor
	Baricitinib	Reduces endocytosis by affinity for AP2 associated protein kinase 1
	Imatinib	Lysosomal accumulation
	Arbidol	Hemagglutinin fusion machinery, spike glycoprotein
	Bictegravir	Interferes with viral protein dimer formation
Viral replication inhibitors	Remdesivir	Inhibit RdRp
	Favipiravir	
	Galidesivir	
	Tenofovir alefanamide	
	Clevudine	
	Ribavirin	Reduces intracellular GTP inhibiting RdRp indirectly
	Elbasvir	Inhibit RdRp, papain like proteinase and helicase
	Famotidine	Inhibit papain like proteinase
	Emtricitabine	RNA synthesis nucleoside analogue
	Lopinavir-ritonavir	Inhibit main protease
	Darunavir	
	Atazanavir	
	Danoprevir	
	Tegobuvir	
	Cepharanthine	Inhibit RdRp, main protease
	Sofosbuvir	RdRp chain termination
	Oseltamivir	Inhibit viral replication
	Plitidepsin	
	Selinexor	
	Atorvastatin	
Dampen cytokine release/inflammation	Dexamethasone	Inhibit various cytokine synthesis and effect
	Methyl prednisolone/prednisolone	
	Doxycycline	IL-6 inhibition; interference with cell fusion and viral replication through MMP chelation
	Tocilizumab	Anti-IL-6 receptor mab
	Sarilumab	
	Clazakizumab	Anti-IL-6 mab
	Olokizumab	
	Canakinumab	Anti-IL-1β mab
	Ravulizumab	Anti-C5 mab
	Anakinra	Recombinant IL-1 receptor antagonist
	Infliximab	Anti-TNF-α mab
	Baricitinib	JAK 1/2 inhibitor
	Ruxolitinib	
	Abivertinib	EGFR kinase inhibitor
	Acalabrutinib	Bruton tyrosine kinase inhibitor
	Ibrutinib	
	Zanubrutinib	
Dampen cytokine release/inflammation	Ozanimod	Sphingosine-1-phosphate receptor modulator
	Leronlimab	Anti-CCR5 receptor mab
	Emapalumab	Anti-IFN-γ mab
	Duvelisib	Inhibits PI3K
	Conestat alpha	Inhibit complement activation
	Crizanlizumab	Anti-P-selectin mab
	Dornase alpha	Degrades DNA of NET
	Montelukast	Inhibit NF-κB signalling
	Pentoxifylline	Inhibit proinflammatory cytokine synthesis
	Fluoxetine	
	Fluvoxamine	
	Pyridostigmine	
	Etoposide	
	Melphalan	
	Thalidomide	
	Fingolimod	
	Methotrexate	
	Colchicine	
	Cholecalciferol	
	Naltrexone	
	N-acetyl cysteine	
	Ulinastatin	
	Prazosin	
Miscellaneous	Ivermectin	Inhibit nuclear transport
	Pegylated IFN α-2b	Enhanced antiviral host response through IFNAR1 signalling
	Nitazoxanide	Increase phosphorylated factor 2-α
	Calcineurin inhibitors	Inhibit viral replication and cytokine transcription
	Sirolimus	
	Daclatasvir	Target different viral proteins
	Dapagliflozin	Reduces lactate and tissue oxygen consumption
	Aspirin	Antiplatelet and inhibit viral replication
	Isoflurane/sevoflurane	Decrease ARDS severity
	Alteplase/rtPA	Fibrinolytic
	Bevacizumab	Anti-VEGF mab
	Iloprost	PGI2 analogue
	Ibudilast	PDE4 inhibitor
	Lucinactant/poractant α	Surfactant
	Aviptadil	Synthetic VIP
	Sargramostim	Recombinant GM-CSF
	Sildenafil citrate	Inhibit nitric oxide synthase
	Pirfenidone	Inhibit apoptosis, reduce ACE2 receptor expression, antioxidant
	ARB/ACE inhibitors	Increase lung ACE2 receptor expression
	2-deoxy-D-glucose	Inhibit glycolysis in virus-infected human cells, reduces inflammation and interferes with viral replication

*ACE - Angiotensin Converting Enzyme, ARB - Angiotensin receptor I blockers, ARDS – Acute Respiratory Distress Syndrome, AP2 associated protein kinase 1 - Adaptor-associated protein kinase 1, C5 – Complement factor 5, CCR5 – C-C chemokine Receptor type 5, DNA – DeoxyriboNucleic Acid, DPP4 – DiPeptidyl Peptidase 4, EGFR – Epidermal Growth Factor Receptor, GM-CSF – Granulocyte-Macrophage-Colony Stimulating Factor, GTP – Guanosine Tri Phosphate, IFNγ – InterFeroNγ, IFNAR1 – InetrFeroN α/β Receptor alpha chain, IL – InterLeukin, JAK 1/2 – JAnus Kinase 1/2, NET – Neutrophil Extracellular Trap, NF-κB – Nuclear Factor Kappa light chain enhancer of activated B cells, PDE4 – PhosphoDiEsterase4, PGI2-ProstaGlandin I2, PI3K – PhosphotidylInositol 3-Kinase, RdRp - RNA-dependent RNA polymerase, RNA – RiboNucleic Acid, rtPA – recombinant tissue Plasminogen Activator, TMPRSS2 - TransMembrane Serine Protease-2, TNFα – Tumour Necrosis Factor α, VEGF – Vascular Endothelial Growth Factor, VIP – Vasoactive Intestinal Peptide.

Limitations of drug repurposing

Drugs repurposed for reasons in addition to novel indication such as new dosage, new formulation or new patient population have to undergo clinical trials to demonstrate safety and efficacy which is almost similar to *de novo* drug discovery process. Even for drugs entering late phase clinical trials, the cost involved in bringing the drug to market is still in millions and the drug can still fail during clinical trials or post-marketing, though the failure rate is low compared to new drug discovery(Naylor and Schonfeld 2014). *In-silico* methods suffer from incomplete knowledge about complex biological systems(Thayer 2012). Drugs that could potentially be repurposed are growing in number due to upsurge in the academic enthusiasm in drug repurposing which lowers the credibility of *in-silico* methods, since most of these drugs are unlikely to pass validation and proceed through clinical trials to regulatory approval and making to the market(Oprea and Mestres 2012).

Selected examples

Selected drugs which had a big bang, thanks to drug repurposing are cited in Table 4.

Table 4. Top mini-blockbuster and blockbuster repurposed drugs.

Drug	Original indication	New indication (year)
Gemcitabine	Anti-viral	Various Cancers (Various)
Raloxifene	Osteoporosis	Invasive Breast Cancer (2007)
Finasteride	Hypertension	Benign prostatic hyperplasia (1992)
		Male Pattern Baldness (1997)
Thalidomide	Anti-Nausea	Erythema Nodosum Leprosum (1998)
		Multiple Myeloma (2006)
Sildenafil	Angina	Erectile Dysfunction (1998)
		Pulmonary artery Hypertension (2005)
Rituximab	Various Cancers	Rheumatoid Arthritis (2004)
Dimethyl fumarate	Psoriasis	Multiple Sclerosis (2013)

Failed repurposed drugs

Though repurposing appears to be an attractive strategy, several challenges exist for the drugs identified to be repurposed before making it to the market. These include, but not limited to, low potency, dose adjustments, new safety signals and route of administration(Parvathaneni and Gupta 2020). Data available from *in vitro* and animal studies may not be generalisable to humans. With regard to computational approaches such as molecular docking, because of the diversity of the protein database and differences in the algorithm used for docking, there is differing agreements on drugs converging on same targets(Dotolo et al. 2020). There is an estimated 65% attrition rate for repurposed drugs(DCAT value insights 2021).

Chloroquine/hydroxychloroquine touted to be the game changer in the battle against Covid-19 fizzled out in a matter of few months. The Food and Drug Administration (FDA) agency revoked emergency use authorisation (EUA) granted to these antimalarials for lack of efficacy and cardiac adverse events within 3 months of initial approval(Parvathaneni and Gupta 2020). Remdesivir, a drug initially developed for hepatitis C, was repurposed against Ebola virus but failed to show efficacy and later found to be effective against MERS in animal studies also received EUA for Covid-19(Borowiec 2020; Parvathaneni and Gupta 2020). However, the interim results of WHO Solidarity trial failed to show benefits in terms of mortality, ventilation initiation and hospital stay in Covid-19 hospitalised patients with remdesivir. Hydroxychloroquine, lopinavir and interferon regimens were also found to be ineffective in this large randomised controlled trial (RCT) of more than 11000 patients(WHO solidarity trial consortium 2020). Another large RCT, the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial of over 20000 hospitalised Covid-19 patients demonstrated the lack of efficacy for azithromycin, aspirin, colchicine, hydroxychloroquine, and lopinavir-ritonavir against the virus(RECOVERY Collaborative group 2020a, 2020b, 2021; Iacobucci 2021; RECOVERY collaborative group 2021). With the failure of initially promising drugs, current repurposing research is focussing on multiple targets of the viral structure such as spike protein and main protease or virus-host targets such as spike protein-angiotensin converting enzyme-2 (ACE2) receptor interface and main protease, or transmembrane serine protease-2 (TMPRSS2) and main protease using drug combinations(Dotolo et al. 2020; Martinez 2021).

Bupropion, a norepinephrine and dopamine reuptake inhibitor in combination with naltrexone, a pure opioid antagonist was approved as an adjunct for weight management in adults by FDA in December 2010(Plodkowski et al. 2009; The San Diego Union-Tribune 2014). Within 3 months of approval, FDA rejected the drug for need of studies on cardiovascular safety of the drug. However, FDA approved the combination for marketing in September 2014 with studies pending on safety. The product labelling contains a boxed warning regarding suicidal intentions and a note that cardiovascular safety has not been established as a limitation of use(Center for Drug Evaluation and Research 2019).

Bevacizumab, a humanised anti-VEGF monoclonal IgG1 antibody has been approved for treatment of advanced colorectal carcinoma, advanced non-small cell lung carcinoma, metastatic breast carcinoma and advanced renal cell carcinoma in addition to chemotherapy(Kazazi-Hyseni et al. 2010). The drug failed to meet the primary end point of improvement in overall survival of advanced gastric carcinoma patients in addition to capecitabine and cisplatin in a phase III trial despite having a preclinical and phase II study evidence(Kang et al. 2010).

Conclusion

Drug repurposing – a second life for failed drugs and drug candidates, and expanding successful ones, appears to offer some real solution to the problem the pharma-

ceutical industry is facing by turning the tables on pipeline erosion and also offers the prospect of identifying treatment for unmet medical needs, finding safer, efficacious and cheaper drugs to the community. Drug repurposing strategies have their own pros and cons and selection of a combination of strategies tailored to the need is essential for a repurposed drug to make it to the market and be successful.

"Although a bit of an exaggeration, there is a lot of truth in the saying that we do not need to find new drugs; rather we need to find the patients who can benefit from existing drugs" - Christopher Lipinski.

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