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Chapter

In Silico Drug Repurposing: An Effective Tool to Accelerate the Drug Discovery Process

Kareti Srinivasa Rao and P. Subash

Abstract

Repurposing "old" drugs to treat both common and rare diseases is increasingly emerging as an attractive proposition due to the use of de-risked compounds, with potential for lower overall development costs and shorter development timelines. This is due to the high attrition rates, significant costs, and slow pace of new drug discovery and development. Drug repurposing is the process of finding new, more efficient uses for already-available medications. Numerous computational drug repurposing techniques exist, there are three main types of computational drug-repositioning methods used on COVID-19 are network-based models, structure-based methods and artificial intelligence (AI) methods used to discover novel drug–target relationships useful for new therapies. In order to assess how a chemical molecule can interact with its biological counterpart and try to find new uses for medicines already on the market, structure-based techniques made it possible to identify small chemical compounds capable of binding macromolecular targets. In this chapter, we explain strategies for drug repurposing, discuss about difficulties encountered by the repurposing community, and suggest reported drugs through the drug repurposing. Moreover, metabolic and drug discovery network resources, tools for network construction, analysis and protein–protein interaction analysis to enable drug repurposing to reach its full potential.

Keywords: drug repurposing, protein–protein interaction, drug discovery, COVID-19

1. Introduction

Drug repurposing, also known as drug repositioning, is a strategy for speeding up the medicine discovery process by identifying a new therapeutic usage for an already-approved drug for a different indication. One of the outcomes of polypharmacology is the increased success and applicability of drug repurposing, which is a manifestation of the transition from a single to multitarget paradigm in drug discovery [1]. COVID-19 has now been labelled a pandemic, necessitating the development of novel medicines as we move beyond containment. It is unrealistic to meet the current global crisis by developing new pharmaceuticals from the ground up because it is a lengthy

procedure. Drug repurposing is a new method in which current drugs that have been proven safe in humans are repurposed to treat diseases that are difficult to cure. While taking these repurposed medications alone may not provide a meaningful clinical advantage, strategically combining them into a cocktail could be quite useful [2].

Repositioning previously approved medications is a promising practice since it lowers the cost and length of the drug development pipeline while also lowering the risk of unexpected side effects. The ability to quickly screen candidates in silico and limit the number of prospective repositioning candidates makes computational repositioning particularly interesting. What is not obvious is how effective such strategies are at generating clinically useful repositioning hypotheses is represented in **Figure 1** [3]. The SARS-CoV-2 virus causes a respiratory infection that can lead to pneumonia. COVID-19 has a mortality rate of 2–3.5%, which rises with age and the presence of comorbidities (e.g., hypertension, cardiac insufficiency, diabetes, and asthma). By April 15, 2020, the new coronavirus has infected 2,033,406 people worldwide and killed over 130,000 people [4]. COVID-19 has depleted health systems around the world, leading countries to take drastic measures such as closing land borders and instituting social distancing regulations to halt the disease's spread [5].

The new coronavirus (SARS-CoV-2), which causes COVID-19, has swiftly become a global danger to public health and the economy [5, 6]. SARS-CoV-2, according to recent clinical reports, produces both mild, self-limiting respiratory tract infection and severe progressive pneumonia, which can lead to multiorgan failure and death. Despite the severity of some cases, no pathogen-specific antivirals are currently available to treat this infection. As a result, several studies have looked at the anti-SARS-CoV-2 activity of currently available medicines [7].

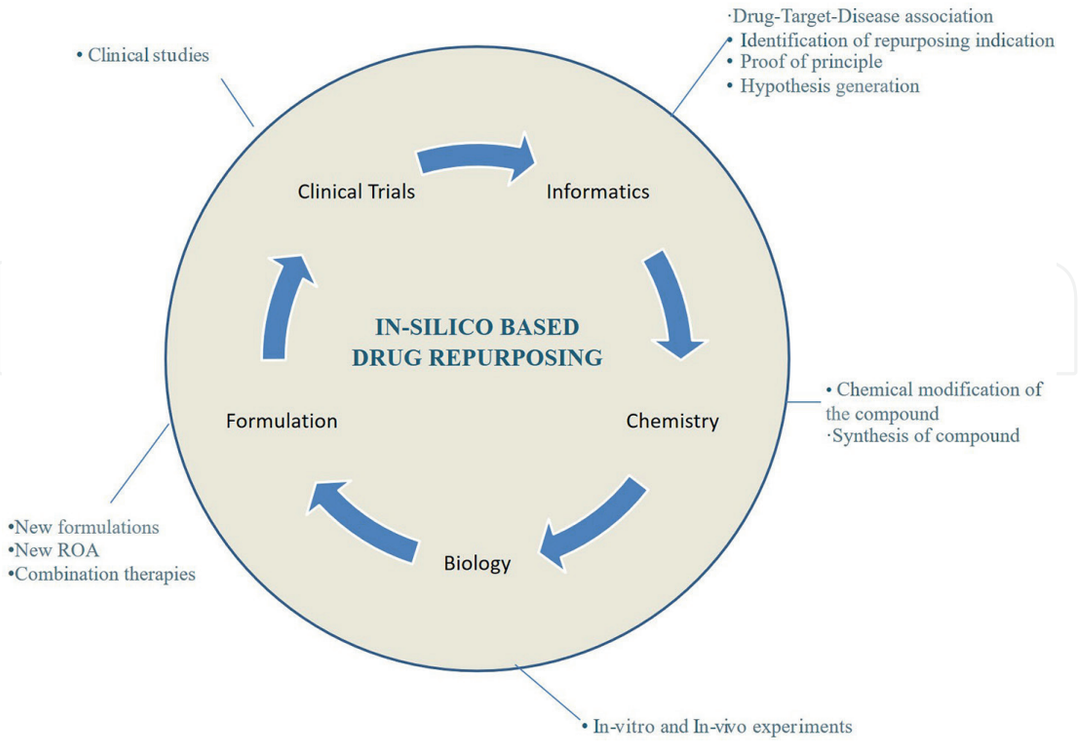

Figure 1.
In silico-based drug repurposing.

2. Faster development times and reduced risks

Attempts to speed up the development of a medication are typically accompanied by an increase in risk. Drug repositioning, on the other hand, offers a solution to the problem. Repositioning candidates have generally gone through numerous phases of clinical development and hence have well-known safety and pharmacokinetic properties, which reduces development risk. Shorter paths to the clinic are also possible because *in vitro* and *in vivo* screening, chemical optimization, toxicity, bulk production, formulation development, and even early clinical development have all been achieved in many situations. In summary, these considerations allow for the reduction of many years from the path to market, as well as major risks and costs (**Figure 2**). As a result, repositioning may provide a superior risk-to-reward ratio than other medication development tactics. These benefits have not gone unnoticed by venture capital firms looking for high value exits for their companies in the near future. Because of the strong response such firms have had from the public equity markets, it is nearly impossible for venture capitalists to invest in a therapeutics company without drug prospects in or approaching clinical trials in 2004. Indeed, repositioning allows for the rapid creation of such a pipeline, and repositioning firms are having little issue with getting venture capital.

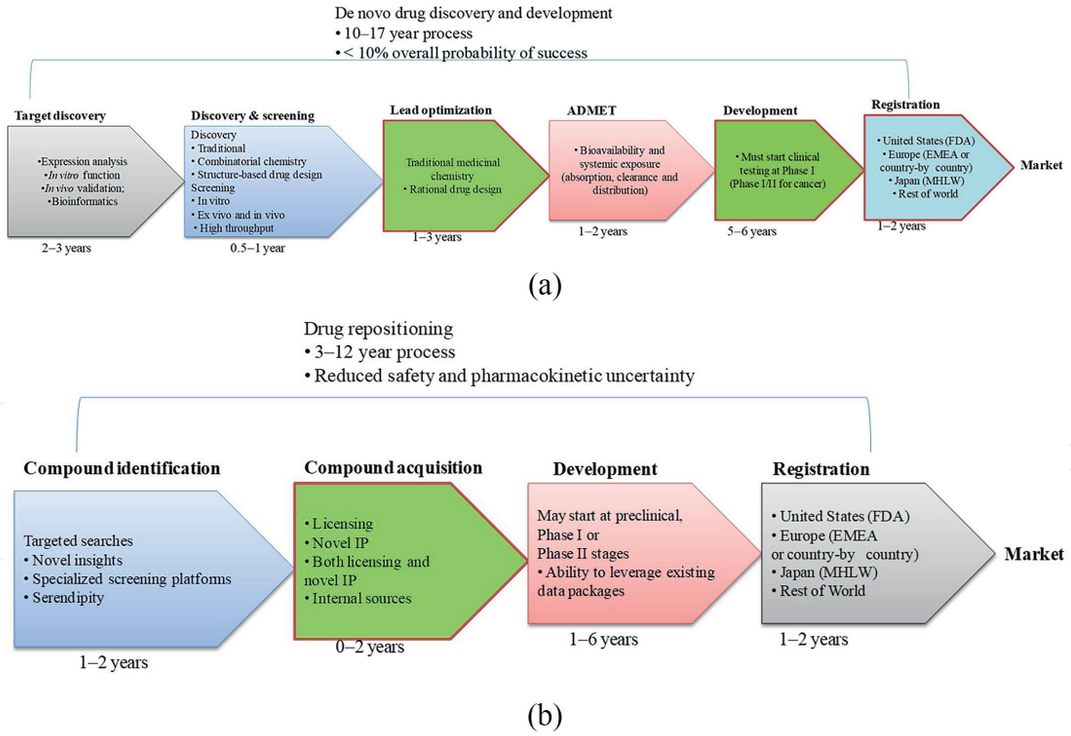

Figure 2.
A comparison of traditional de novo drug discovery and development versus drug repositioning. (a) It is well known that from concept to marketable medicine, de novo drug research and development takes 10–17 years [8]. The probability of success is lower than 10% [9]. (b) because repositioning candidates have frequently gone through numerous phases of development for their initial indication, several phases common to de novo drug discovery and development can be avoided, allowing for a reduction in time and risk. ADMET is an abbreviation for absorption, distribution, metabolism, excretion, and toxicity; EMEA is an abbreviation for European medicines agency; FDA is an abbreviation for Food and Drug Administration; IP is an abbreviation for intellectual property; and MHLW is an abbreviation for Ministry of Health, labour, and welfare.

3. Drug repositioning opportunities

Drug repositioning is a potential approach that is gaining traction among governments and pharmaceutical corporations due to its critical role in decreasing time, cost, and risk in the development of treatments for cancer and other terminal diseases. As this technique became more widely known, multidisciplinary teams of researchers and scientists attempted, with varying degrees of efficiency and success, to computationally study the potential of repositioning drugs to treat other diseases and identify alternative indications, regardless of whether the drug in question was approved, withdrawn, in clinical trials, or failed. Despite the fact that drug repositioning is a relatively new technique, the traditional, costly, and risky de novo drug development process is still necessary for discovering and testing new drugs; however, incorporating some computational drug repositioning models into this process can help to move drugs forward in the development pipeline and ultimately improve drug efficiencies in clinical trials. The potential for drug repositioning to help create the critical medications needed to combat the present coronavirus outbreak cannot be overstated [10].

4. Challenges and opportunities

Traditional drug development strategies are risky, expensive, and prone to failure. As a result, drug repositioning has recently gained attention, and it expedites the release of medications for clinical usage. Drug repositioning, on the other hand, is a complicated process involving a variety of aspects, including technology, business models, patents, investment, and market demands. Despite the fact that many medical databases have been built, determining the best strategy to fully utilise huge volumes of medical data remains a challenge. New techniques for drug repositioning are urgently needed. Another problem that needs to be addressed is intellectual property (IP). IP protection for repositioning medications is minimal [11]. Some novel drug-targeted-disease connections discovered by repositioning researchers, for example, were corroborated by papers or online databases; yet, according to the law, it is difficult to seek IP protection for such associations. Some repositioned medications are unable to enter the market due to intellectual property issues. Furthermore, some repositioning attempts have to be abandoned, wasting both time and money [12]. Because the existing commercial model is serial and produces overlapping investment concerns, it is required to develop a new commercial model. Challenges accompany opportunities. An unintentional finding in the 1920s was the first example of medication repositioning. More ways of speeding up the process of drug repositioning have been proposed after nearly a century of development. As a result, medication repositioning has made significant progress. **Table 1** contains 75 examples of pharmacological repositioning culled from the extensive literature. To increase the performance of drug repositioning in this circumstance, massive machine learning techniques were applied. Experimental procedures, such as target screening approaches, have been developed in addition to computational approaches to provide direct proof of correlations between medications and diseases [11, 12, 24].

5. Drug-based computational approaches

The structure and chemical characteristics of a medicinal compound are clearly linked to its final therapeutic effectiveness. As a result, repositioning options

Drug name	New indication	Origin indication	Mining Approaches	References
Atomoxetine	ADHD	Parkinson's disease	Network Approach	[13, 14]
Allopurinol	Gout	Tumour lysis syndrome	Experiment	[13]
Amphetamine	Hyperkinesis in children (attention deficit hyperactivity disorder, ADHD)	Stimulant	Semantic Approach	[13, 15]
Apomorphine	Erectile dysfunction	Parkinson's disease	Experiment	[16]
Aspirin	Colorectal cancer	Analgesic, antipyretic	Experiment	[16]
Budesonide	Colitis, Ulcerative	Asthma	Computational Approach	[17, 18]
Bupropion	Smoking cessation	Depression	Experiment	[13, 19]
Celecoxib	Colon, colorectal, lung, and breast cancer are all linked to familial adenomatous polyposis.	Osteoarthritis and adult rheumatoid, arthritis	Computational Approach	[17, 20]
Chlorpromazine	Non-sedating tranquillizer	Antiemetic/ antihistamine	Experiment	[17]
Crizotinib	NSCLC	Clinical trials for anaplastic large-cell lymphoma	Experiment	[21]
Cymbalta	Diabetic peripheral neuropathy	Depression	Experiment	[13]
Dapoxetine	Premature ejaculation	Analgesia and depression	Experiment	[13]
Doxepin	Insomnia antipruritic	Antidepressant	Experiment	[19]
Drospirenone	Hypertension	Oral contraceptive	Experiment	[22]
Duloxetine	Stress urinary incontinence, fibromyalgia,	Depression	Computational Approach	[19]
Duloxetine	chronic, musculoskeletal pain, shoulder pain, back pain, osteoa-arthritis knee	Diabetic Neuropathies	Experiment	[17]
Eflornithine	Reduction of unwanted facial hair in women	Anti-infective	Experiment	[17]
Etanercept	Asthma	Rheumatoid arthritis	Network Approach	[22]
Everolimus	Pancreatic neuroendocrine tumours	Immunosuppressant	Text-mining Approach	[21]
Finasteride	Hair loss	Benign prostatic hyperplasia	Experiment	[13, 17]
Fludrocortisone	Hypertension	Cerebral salt wasting syndrome	Experiment	[22]

Drug name	New indication	Origin indication	Mining Approaches	References
Fluoxetine	Premenstrual dysphoric disorder	Depression	Network Propagation	[13]
Furosemide	Bartter syndrome	Edema associated with congestive heart failure	Experiment	[22]
Galantamine	Alzheimer's disease	Polio, paralysis and anaesthesia	Network Approach	[17]
Gemcitabine	Anticancer agent	Antiviral	Experiment	[16]
Hydroxychloroquine	Anti-arthritic systemic lupus erythematosus	Antiparasitic	Experiment	[19]
Imatinib	GIST	BCR-ABL	Experiment	[21]
Imidapril	Cancer cachexia	Hypertension	Experiment	[19]
Infliximab	Different arthritis forms; Alzheimer's disease	Crohn's disease	Experiment	[19]
Leflunomide	Prostate cancer	Rheumatoid arthritis	Network Approach	[16]
Lidocaine	Oral corticosteroid dependent asthma, arrhythmia	Local anaesthesia	Experiment	[13]
Lumigan	Hypotrichosis simplex	Glaucoma	Experiment	[13]
Mecamylamine	ADHD	Moderately severe to severe essential hypertension and uncomplicated cases of malignant hypertension	Experiment	[17]
Metformin	Breast, adenocarcinoma, prostate, colorectal cancer	Diabetes mellitus	Experiment	[16]
Methotrexate	Osteosarcoma, breast cancer, Hodgkin lymphoma	Acute leukaemia	Network Approach	[13]
Methotrexate	Rheumatoid arthritis	Cancer	Experiment	[16]
Mifepristone	Psychotic major depression, Cushing's syndrome	Pregnancy termination	Experiment	[13]
Milnacipran	Fibromyalgia	Depression	Experiment	[13]
Miltefosine	Visceral and cutaneous leishmaniosis	Breast cancer	Experiment	[19]
Minocycline	Ovarian cancer, glioma	Acne	Experiment	[16]
Monoxide	Hair loss	Hypertension	Experiment	[13]
Mycophenolate mofetil	Renal symptoms of systemic lupus erythematosus	Transplanted organ rejection	Experiment	[19]

Drug name	New indication	Origin indication	Mining Approaches	References
Naltrexone	Alcohol withdrawal	Opioid addiction	Experiment	[19]
Nelfinavir	In clinical trials for multiple cancer	AIDS	Network Approach	[21]
Nitroxoline	Bladder, breast cancer	Antibiotic	Experiment	[16]
Noscapine	Multiple cancer types	Antitussive,antimalarial,analgesic	Experiment	[16]
Paclitaxel	Restenosis	Cancer	Network Approach	[13]
Pegvisomant	Hypercholesterolemia	Acromegaly	Experiment	[22]
Perindopril	Alzheimer's disease	Hypertension	Network Approach	[22]
Phentolamine	Impaired night vision, dental anaesthesia reversal agent	Hypertension	Network Approach	[13]
Pioglitazone	Nonalcoholic steatohepatitis	Type 2 diabetes mellitus	Experiment	[23]
Raloxifene	Osteoporosis	Breast and prostate cancer	Experiment	[19]
Rapamycin	Colorectal cancer, lymphoma, leukaemia	Immunosuppressant	Computational Approach	[16]
Requip	Restless legs	Parkinson's disease	Experiment	[13]
Retinoic acid	Acute promyelocytic leukaemia	Acne	Experiment	[19]
Ropinerole	Parkinson's, restless legs syndrome	Hypertension	Experiment	[17]
Sibutramine	Obesity	Depression	Experiment	[13, 16]
Sildenafil citrate	Erectile dysfunction (approved)	Hypertension, angina	Experiment	[13, 19]
Statins	Cancer, leukaemia	Myocardial infarction	Network Approach	[16]
Sunitinib	Pancreatic tumours/ Gastrointestinal Tumour	GIST, renal cell carcinoma	Network Approach	[21]
Tadalafil	Male erectile dysfunction	Inflammation and cardiovascular disease,	Experiment	[17]
Tadalafil	Prostate cancer, hypertension, pulmonary hyperplasia and prostatic hyperplasia	Impotence	Network Approach	[17]
Thalidomide	Moderate to severe erythema nodosum leprosum cutaneous symptoms in leprosy and multiple myeloma	Sedation, nausea and insomnia	Experiment	[17]

Drug name	New indication	Origin indication	Mining Approaches	References
Thalidomide	Leprosy, multiple myeloma	Morning sickness	Network Approach	[13]
Thalidomide	Erythema nodosum leprosum	Anti-emetic	Experiment	[19]
Thiocolchicoside	Leukaemia, multiple myeloma	Muscle relaxant	Network Approach	[16]
Tofisopam	Irritable bowel syndrome	Anxiety-related conditions	Experiment	[17]
Topiramate	Migraine,bu1imia	Epilepsy	Experiment	[13]
Trastuzumab	HER2-positive metastatic gastric cancer	HER2-positive breast cancer	Network Approach	[21]
Valproic acid	Solid tumours, Leukaemia	Antiepileptic	Experiment	[16]
Vesnarinone	Oral cancer, leukaemia, lymphoma	Cardioprotective	Experiment	[16]
Wortmannin	Leukaemia	Antifungal	Experiment	[16]
Zidovudine	HIV/AIDS	Cancer	Experiment	[13]
Zoledronic acid	Multiple myeloma, prostate cancer, breast cancer	Anti-bone resorption	Experiment	[16]

Table 1.
Pharmacological repositioning culled from the extensive literature.

for medicinal molecules can be investigated based on chemical similarities. The rationale for this method is based on quantitative connections between chemical structures and biological activity that are well-known (QSAR). Although identical structures in biological systems do not always act the same, computational techniques for drug repositioning can take use of the degrees of resemblance that exist. Chemical similarity techniques work by extracting a set of chemical properties for each drug in a group of medications, then clustering or creating networks based on the recovered features to relate the drugs directly to one another [25]. Simple chemical associations or looking for specific biological traits, such as known drug targets, enriched in the resulting correlations can subsequently be used to infer therapeutic repositioning prospects.

Chemical systems biology is being used to identify new drugs in a network. A unique method of modelling and predicting drug–target interactions is statistical modelling of similarities in chemical structure between medicines and possible ligands [26, 27]. Before and after modelling with chemical drug – ligand interactions, network mapping of a wide range of drugs to protein targets enabled the prediction of new targets, including primary sites of action and off-target proteins as explanations for well-known side effects, with new and unexpected drug binding revealed across major categories of proteins unrelated by sequence or structure. A number of modelling predictions were validated using binding assays, proving the method's

efficacy [28]. A generated network of chemogenomic space exhibited a high level of interaction between gene families, giving tractable drug combinations the ability to act on projected targets, by integrating structure – activity data for predicted multiple target binding compounds [29]. This demonstrates how networks can be used as templates for statistical and computational modelling predictions of drug–ligand interactions, and it adds to our understanding of polypharmacology, or the particular binding of a molecule to two or more biological targets [27]. Computational tools for drug discovery are represented in **Table 2**.

Databases	**Functions**	**URL**
BIND	Portal for biomolecular interaction networks	http://bond.unleashedinformatics.com/
BioGRID	A database of physical and genetic interactions of many organisms	http://thebiogrid.org
DIP	A database for experimentally determined protein interactions	http://dip.doe-mbi.ucla.edu/dip/Main.cgi
GWAS	Resource of genome-wide association studies	http://gwas.nih.gov
HPRD	Human proteome database HPID	www.hprd.org/
HPID	A human-protein interaction database	http://wilab.inha.ac.kr/hpid/
IntAct	Open source analysis tools for molecular interaction data	http://www.ebi.ac.uk/intact/
MINT	Database of curated molecular interactions	http://160.80.34.4/mint/
MIPS	Database of mammalian protein–protein interactions that has been manually curated.	http://mips.helmholtz-muenchen.de/proj/ppi/
OMIM	A repository of human genes and genetic diseases.	http://www.ncbi.nlm.nih.gov/omim
STRING	Known and predicted protein–protein interactions database	http://string-db.org/
Metabolic network resources		
BRENDA	A comprehensive enzyme database	www.brenda-enzymes.info/
KEGG	A comprehensive database on metabolic pathways, diseases, drugs, and other topics.	http://www.genome.jp/kegg/
REACTOME	Open access curated pathway database	http://www.reactome.org/ReactomeGWT/entrypoint.html
Drug Discovery Network resources		
CPNM	Context-specific Protein Network Miner	http://www.biotextminer.com/CPNM/index.html
Drug bank	Information on drugs and their targets	http://www.drugbank.ca/
PROMISCUOUS	Resource of drugs, proteins and side effects	http://bioinformatics.charite.de/promiscuous/
STITCH	A database of known and projected drug-protein interactions	http://stitch.embl.de/
ZINC	Chemical compounds that are commercially available are stored in a database	http://zinc.docking.org/

Databases	Functions	URL
Tools for network construction		
Cobweb	A tool for visualising and exploring networks.	http://bioinformatics.charite.de/cobweb/
Cytoscape	Tool for network visualisation and data integration. Many plugins are available for various types of analysis.	http://www.cytoscape.org/
NAViGaTOR	Network visualisation tool	http://ophid.utoronto.ca/navigator/
Tools for network analysis		
Pajek	A large network visualisation and analysis tool	http://vlado.fmf.uni-lj.si/pub/networks/pajek/
Gephi	A dynamic network visualisation tool that also allows for specialising, filtering, navigating, altering, and clustering of network data.	https://gephi.org/
BIANA	Automated network data integration and analysis using other tools such as Cytoscape	http://sbi.imim.es/web/index.php/research/servers/biana?
POINeT	PPI searching, analysis and visualisation tool	http://poinet.bioinformatics.tw/
Network analyser	Plugin for analysing and visualising molecular interaction networks, as well as computing specific network topological metrics.	http://med.bioinf.mpi-inf.mpg.de/netanalyzer/

Table 2.
Tools for protein–protein interaction analysis.

6. Applications of personalised medicine and drug repositioning

The utilisation of personalised medicine methodologies to investigate particular diseases and reposition medications for these diseases has far-reaching diagnostic and therapy implications. Both of these approaches are particularly useful for rare diseases or disease subtypes that are difficult to investigate and conduct clinical trials for due to their rarity [30]. They're also important for patients who are resistant to or have developed resistance to medicines and do not have any other options for treatment. We'll look at how customised medicine and drug repositioning methods can help in these two cases in this section.

7. Orphan or rare diseases

Any disease that affects a small percentage of the population is classified as an orphan or uncommon disease. The majority of known uncommon diseases are genetic in nature, and so they affect people for the rest of their lives. Many manifest early in life, and approximately 30% of children with rare diseases die before reaching the age of five. There is no commonly agreed-upon cut-off figure for determining whether or not a disease is rare. The Rare Disease Act of 2002, for example, defines a rare sickness as any disease or condition that affects fewer than 200,000 people in the United States, whereas in Japan, a rare disease is defined as one that affects fewer than 50,000 people. Rare diseases, on the other hand, are defined by the European Commission on Public Health as those that are life-threatening or chronically

debilitating and have such a low prevalence (1 in 2000 individuals) that they require special coordinated efforts to combat. Furthermore, a sickness that is rare in one part of the world or among a specific group of people may be widespread in another. An individual uncommon disease may have a low incidence. However, the 6000 identified rare diseases collectively impact around 25 million Americans, or about 10% of the total [31]. Because rare diseases are defined by therapy availability, resource scarcity, and disease severity, they are now referred to as orphan diseases (ODs), especially since the orphan drug movement began in the United States in 1983. As a result, the United States Orphan Medication Act (1983) covers both rare and non-rare diseases for which there is no reasonable expectation that the cost of developing and commercialising a drug for such a disease in the United States will be recouped via drug sales in the United States. About 6000 rare or OD diseases have been recognised, and the National Institutes of Health's Office of Rare Diseases (ORD) keeps track of them (NIH). While some of the mentioned ODs are well-known (e.g., cystic fibrosis, Huntington's disease), the majority of people are unaware of numerous ODs with patient numbers of less than a hundred. Each year, about 250 new ODs and diseases are characterised [32]. The ODA was created to support the research and marketing of medications (orphan pharmaceuticals) for the treatment of ODs and other disorders. The ODA arose in response to the modest number of orphan medications approved in the United States in the years leading up to the ODA's approval [33]. Unfortunately, the drug research process for ODs is the same as it is for any other disease: it is extremely costly and time-consuming.

8. Discussion and conclusion

After looking at the various ways that computational drug repositioning strategies and models have been used to identify novel therapeutic interactions, we can conclude that each strategy and approach has its own set of benefits and drawbacks, and that combining different strategies and approaches often results in a higher success rate. Despite the fact that we have some excellent computational drug repositioning models, establishing robust models is still a difficult endeavour. Because of the intricacy of mapping such theoretical approaches to imitate actual organisms behaviour, as well as other difficulties such as missing, skewed, and erroneous data, one of the key challenges is bringing theoretical computing ideas into action. For example, reliable gene expression signature profiles may be difficult to define due to a variety of factors, including differences in experimental conditions (e.g., environment variables and patient age) between experiments, which can lead to data discrepancies in gene expression signatures, contributing to biased data. Furthermore, when these genes are employed as medication targets, there may not always be large changes in gene expression, which might lead to erroneous results. Furthermore, when using the chemical structure and molecular information technique, the dearth of high-resolution structural data for drug targets makes it difficult to detect potential drug-target interactions. Another issue that computational drug repositioning models face is the absence of reliable gold-standard datasets with which to evaluate their efficacy.

We offer a brief overview of the subject of computational drug repositioning, with a focus on analytically validating such methods. We cover the three methods of validation that are currently in use, as well as the challenges with consistency and essential assumptions that each of them makes. Finally, we offer an approach for increasing the validity of computational repositioning validation.

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References

[1] Medina-Franco JL, Giulianotti MA, Welmaker GS, Houghten RA. Shifting from the single to the multitarget paradigm in drug discovery. Drug Discovery Today. 2013;**18**(9-10):495-501

[2] Senanayake SL. Drug repurposing strategies for COVID-19. Future Drug Discovery. 2020;**2**(2):689-706

[3] Brown AS, Patel CJ. A review of validation strategies for computational drug repositioning. Briefings in Bioinformatics. 2018;**19**(1):174-177

[4] Coronavirus E. 13,968 Cases and 223 Deaths: Available from: https://www.worldometers.info/coronavirus/country/ethiopia. Accessed: 2020;27.

[5] Lima WG, Brito JC, Overhage J, Nizer WS. The potential of drug repositioning as a short-term strategy for the control and treatment of COVID-19 (SARS-CoV-2): A systematic review. Archives of Virology. 2020;**165**(8):1729-1737

[6] Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Medicine and Infectious Disease. 2020;**34**:101623

[7] Qu YM, Kang EM, Cong HY. Positive result of Sars-Cov-2 in sputum from a cured patient with COVID-19. Travel Medicine and Infectious Disease. 2020;**34**:101619

[8] Reichert JM. Trends in development and approval times for new therapeutics in the United States. Nature Reviews. Drug Discovery. 2003;**2**(9):695-702

[9] Gilbert J, Henske P, Singh A. Rebuilding big pharma's business model. In vivo-New York then Norwalk. 2003;**21**(10):73-80

[10] Carvalho T, Krammer F, Iwasaki A. The first 12 months of COVID-19: A timeline of immunological insights. Nature Reviews Immunology. 2021;**21**(4):245-256

[11] Oprea TI, Bauman JE, Bologa CG, Buranda T, Chigaev A, Edwards BS, et al. Drug repurposing from an academic perspective. Drug Discovery Today: Therapeutic Strategies. 2011;**8**(3-4):61-69

[12] Roin BN. Unpatentable drugs and the standards of patentability. Texas Law Review. 2008;**87**:503

[13] Novac N. Challenges and opportunities of drug repositioning. Trends in Pharmacological Sciences. 2013;**34**(5):267-272

[14] Yeu Y, Yoon Y, Park S. Protein localization vector propagation: A method for improving the accuracy of drug repositioning. Molecular BioSystems. 2015;**11**(7):2096-2102

[15] Mullen J, Cockell SJ, Tipney H, Woollard PM, Wipat A. Mining integrated semantic networks for drug repositioning opportunities. PeerJ. 2016;**4**:e1558

[16] Gupta SC, Sung B, Prasad S, Webb LJ, Aggarwal BB. Cancer drug discovery by repurposing: Teaching new tricks to old dogs. Trends in Pharmacological Sciences. 2013;**34**(9):508-517

[17] Ashburn TT, Thor KB. Drug repositioning: Identifying and developing new uses for existing drugs.

Nature Reviews. Drug Discovery. 2004;**3**(8):673-683

[18] Ross MK, Yoon J, van der Schaar A, van der Schaar M. Discovering pediatric asthma phenotypes on the basis of response to controller medication using machine learning. Annals of The American Thoracic Society. 2018;**15**(1):49-58

[19] Henriksen K, Christiansen C, Karsdal MA. Serological biochemical markers of surrogate efficacy and safety as a novel approach to drug repositioning. Drug Discovery Today. 2011;**16**(21-22):967-975

[20] Nagaraj AB, Wang QQ, Joseph P, Zheng C, Chen Y, Kovalenko O, et al. Using a novel computational drug-repositioning approach (DrugPredict) to rapidly identify potent drug candidates for cancer treatment. Oncogene. 2018;**37**(3):403-414

[21] Deotarse PP, Jain AS, Baile MB, Kolhe NS, Kulkarni AA. Drug repositioning: A review. International Journal of Pharmacy Research and Review. 2015;**4**:51-58

[22] Wang ZY, Zhang HY. Rational drug repositioning by medical genetics. Nature Biotechnology. 2013;**31**(12):1080-1082

[23] Wang ZY, Quan Y, Zhang HY. Medical genetic inspirations for anticancer drug repurposing. Trends in Pharmacological Sciences. 2014;**35**(1):1-3

[24] Swinney DC, Anthony J. How were new medicines discovered? Nature Reviews. Drug Discovery. 2011;**10**(7):507-519

[25] Eckert H, Bajorath J. Molecular similarity analysis in virtual screening: Foundations, limitations and novel approaches. Drug Discovery Today. 2007;**12**(5-6):225-233

[26] Keiser MJ, Roth BL, Armbruster BN, Ernsberger P, Irwin JJ, Shoichet BK. Relating protein pharmacology by ligand chemistry. Nature Biotechnology. 2007;**25**(2):197-206

[27] Hopkins AL. Network pharmacology: The next paradigm in drug discovery. Nature Chemical Biology. 2008;**4**(11):682-690

[28] Keiser MJ, Setola V, Irwin JJ, Laggner C, Abbas AI, Hufeisen SJ, et al. Predicting new molecular targets for known drugs. Nature. 2009;**462**(7270):175-181

[29] Paolini GV, Shapland RH, van Hoorn WP, Mason JS, Hopkins AL. Global mapping of pharmacological space. Nature Biotechnology. 2006;**24**(7):805-815

[30] Li YY, Jones SJ. Drug repositioning for personalized medicine. Genome Medicine. Mar 2012;**4**(3):1-4

[31] Rados C. Orphan products: Hope for people with rare diseases. FDA Consumer. 2003;**11**:10-15

[32] Wästfelt M, Fadeel B, Henter JI. A journey of hope: Lessons learned from studies on rare diseases and orphan drugs. Journal of Internal Medicine. Jul 2006;**260**(1):1-10

[33] Levitt JA, Kelsey JV. The orphan drug regulations and related issues. Food & Drug LJ. 1993;**48**:525