

Evolution of the Drug Repurposing Paradigm

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ABSTRACT

The appearance of novel diseases like COVID-19, as well as the resistance of severe diseases to existing medications, have caused a need for new drugs to be developed quickly. The concept of drug repurposing has been offered to increase efficiency and minimise time and financial costs associated with drug development. Repurposing is a strategy for discovering new medical applications for already approved drugs. The study covers recent computational and experimental approaches for finding drug candidates for repurposing, as well as the challenges that arise along the way.

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The resistance of hazardous diseases to existing drugs and the emergence of new diseases such as COVID-19 have generated a need for the prompt development of new pharmaceuticals. However, conventional approaches to drug discovery and development have proven inadequate in addressing this demand, as they require an average duration of 13-15 years and \$2-\$3 billion, and do not guarantee against high drug attrition rates [1-3]. A classic "where there's demand, there's supply" scenario led to the concept of drug repurposing which was introduced in 2004 and aimed to increase efficiency, decrease time and financial costs for drug development [4]. Repurposing is a method by which previously approved drugs can be identified for use in novel medical indications [5].

The appeal of repurposing lies in the fact that the drug being repurposed has previously completed the preclinical research phase and phase I clinical trials, allowing for the elimination of these phases and direct progression to phase II. As a result, the financial costs and drug development timelines can be decreased, and the risk of side effects and drug attrition can be minimised due to the medicine's established safety [6].

In 2010, Justin Thomas of the University of Oxford provided an inspiring motivation for drug repurposing. In experiments on bacteria and mice, Thomas found that the drug ebselen, intended for people who have had a stroke, hinders the activity of enzymes associated with bipolar disorder [7,8]. Following that, clinical trials of ebselen for bipolar disorder were promptly initiated, starting with phase II to assess its effectiveness.

The repurposing concept received additional inspiration from the classic success story with sildenafil. Sildenafil, developed in 1989 to treat hypertension and angina, was repurposed by Pfizer

into an effective drug called Viagra for the treatment of erectile dysfunction.

The benefits of repurposing have had a significant impact on the academic community and the pharmaceutical industry. In 2021, 993 publications on this topic were published, which is 20 times the number of articles prior to 2011 [9]. It was not surprising to see that in recent years, 90% of papers have devoted to the extremely hazardous SARS-CoV-2 virus [9]. Since there was no time to develop a new drug against the virus, the strategy of repurposing existing drugs was adopted to rapidly identify a therapy for COVID-19.

The pharmaceutical industry has provided several examples of the triumph of drug repurposing. Repurposed hydroxychloroquine, originally developed as an antimalarial drug, has been proposed as a therapy for SARS-CoV-2 [10]. In another example, rifampicin, an anti-tuberculosis drug, and metformin, developed to treat diabetes, were repurposed as analgesics, eculizumab, originally indicated for uremia, was used to treat myasthenia gravis, and finally, paclitaxel, a drug for the treatment of arterial stenosis, became effective against tumours [5,11].

Drug combinations may increase repurposing success through synergistic effects and reduced cytotoxicity. For example, a combination of prednisolone and perphenazine, a 6-thiourea, began to be prescribed for histiocytosis [12]. Thalidomide and methotrexate, used as antiemetics and folic acid substitutes, have been repurposed for the treatment of autoimmune diseases [9].

The field of repurposing has also expanded to encompass active compounds that have failed clinical trials due to toxicity or low efficacy [13]. For example, azidothymidine, a failed chemotherapy medication, was repurposed for the treatment of HIV [14].

Repurposing has enabled the development of drugs at lower costs and faster return on investment. Thus, the average cost of drug repurposing is expected to be \$300 million and takes 6.5 years, compared to \$2-3 billion and 13-15 years for a new drug [15].

Approaches to the Search of Drug Candidates for Repurposing

Historically, as soon as an off-target effect of a drug was accidentally identified, it was attempted to be used for new indications. Thoughtful physicians noticed an off-target impact of the previously described antihypertensive medication sildenafil. A retrospective analysis of sildenafil's clinical effect led to its application in the treatment of erectile dysfunction. Another example. Thalidomide, a sedative, was recalled in 1957 because of its association with skeletal birth abnormalities in infants born to mothers who used the drug during pregnancy. However, it was unintentionally discovered that it could be effective in myeloma [16].

Following a few successful drug repurposings, a simple concept emerged: if randomly discovered repurposing candidates produce such good results in terms of disease treatment and cost reduction, why not shift to a science-based, systematic search for drug repurposing? As a result, serendipity, which is responsible for the discovery of novel uses for old drugs, has increasingly given way to a systematic approach. To be fair, precisely random search methods based on 1. screening of generic drugs, 2. analysis of physicians' observations of interesting/new effects of drugs, and 3. analysis of failed drugs that did not pass clinical trials served as the "progenitor" of the systematic approach.

The first random search method involves generic drug screening. This method considers drugs that have been available in the market for a long time and are readily accessible for clinical trials because their patents have expired. If, during the process of repurposing such a drug, new formulations or administration routes are developed, they have the potential to be eligible for patent protection. As a result, pharmaceutical corporations continue to find them appealing targets. Some companies thoroughly evaluate various sources of information pertaining to generic pharmaceuticals, ranging from scientific literature to data on potential side effects. In particular, Biovista determined that the generic antidepressant pirlindole developed in Russia has the potential to be used as a treatment for multiple sclerosis. The drug successfully passed clinical trials in patients diagnosed with multiple sclerosis, and the company received a patent for a novel application of pirlindole [17].

The second approach is a random search, wherein physicians start using a well-known medication for a new indication in addition to its direct use after analyzing what they observe in the clinic and based on their expertise. Therefore, a more or less systematic survey of practicing physicians can help in finding a candidate for repurposing. For instance, aspirin was first prescribed as an analgesic, but subsequently researchers and doctors unintentionally found that aspirin also has antiplatelet characteristics [18]. And again, sildenafil is an excellent example [19].

A third random search strategy involves looking at failed medications that have passed phase I trials but did not advance to phase II because they do not have a desired specific activity. Nonetheless, these medications exhibit some biological activity and are safe for humans. So it made sense to look for a disease that was "suitable" for them. The example above was azidothymidine,

which failed clinical trials as a chemotherapeutic medication but was eventually used to treat HIV [14].

In these methods of random candidate search for repurposing, a growing number of researchers have begun to employ network analysis [20-22]. Shahreza, et al. predicted the feasibility of drug repurposing through the analysis of various databases and use of software to generate metabolic and molecular networks, gene regulatory networks, and protein interaction networks [23-26]. Thus, a systematic search for potential repurposing candidates emerged, which was more effective than a random search.

Modern drug repurposing consists of three steps that precede the advanced phases of clinical trials. These are: 1. identifying a candidate drug for a specific medical indication - hypothesis generation; 2. assessing the drug's effect on preclinical models; and 3. evaluating efficacy in phase II trials, provided that safety data are available from phase I studies conducted as part of the drug's original development. Step one is crucial. This is where systematic approaches to hypothesis generation can be most beneficial. System analysis is based on computational and experimental methods.

Computational Approaches

Computational approaches rely on an analysis of gene expression, cell morphology, chemical structure, proteome, or electronic health record (EHR) data. The analysis can aid in the development of a hypothesis and enhance the efficacy of drug repurposing. Here are the most important computational methods.

Signatures Matching

"Signature matching" is the process of comparing a drug's unique characteristics, known as its "signature," to those of other medications or conditions [27]. The drug signature can be derived from data on the transcriptome, cell morphology, chemical structures, and side effects.

The Transcriptomic Signature

The transcriptomic signature of a drug is acquired by analyzing gene expression in a biomaterial, such as a cell or tissue, before and after the drug's effect. The resulting drug signature can then be matched to the disease's transcriptome profile. If signature matching reveals that genes activated in a disease are suppressed by a drug and vice versa, it is possible that the drug could be repurposed to treat the condition [28]. Mapping drug-disease transcriptomic signatures has contributed to drug repurposing success for metabolic disorders [29].

Comparing the transcriptomic signatures of two drugs aims to uncover shared mechanisms of action amongst pharmaceuticals from different classes with differing structures. Such comparisons help in identifying unknown drug targets and off-target effects that can be used in the clinic [27]. The matching transcriptome profile of two drugs may indicate that they have similar therapeutic applications, despite differences in their chemical structures.

Morphological Signature

The morphological signature (profile) of a cell is a set of a large number (more than 1000) quantitative morphological features (including size, shape, intensity, texture, correlation, and several others) extracted from color images of cells stained with six fluorescent dyes that label eight cellular components or organelles [30]. Image-based morphological profiling (Cell Painting assay) is

conceptually similar to transcriptional profiling but significantly cheaper and has already been used in a variety of applications. Many approved drugs have distinct morphological profiles that can be used as a query to retrieve information from specialised databases [31].

Chemical Signature

Chemical signature comparison allows us to assess whether drugs from different classes have chemical similarities, which might indicate common therapeutic activity [32]. If the two drugs have the same chemical structures/properties and the therapeutic targets of one are known, a chemoinformatics algorithm can predict the interaction with the identical targets of the other drug. Keiser et al. used chemical signature matching to find 23 new drug-target associations after analyzing 878 FDA-approved small molecule drugs and 2787 pharmaceutical compounds [27]. As a result, 23 candidates for repurposing appeared. However, the chemical similarity technique has its pitfalls. These are physiological consequences that go beyond structural correlations. For example, the therapeutic molecule could be a metabolite of the parent drug with a different chemical structure [33].

Side Effect Signature

Finally, each drug has a distinct side effect profile. The identification of drug candidates for repurposing by matching the side effect profiles of two drugs is based on the premise that two drugs that generate the same side effects may act on the same target or signalling pathway, resulting in a similar therapeutic effect [33]. The challenge with this technique is the difficulty in obtaining information about pharmacological adverse effects [33]. However, artificial intelligence technology can help overcome these restrictions.

Computational Molecular Docking

Computational molecular docking is a computer technique that uses knowledge of drug structures and potential therapeutic targets to predict drug binding to a target, such as a disease-specific receptor [34]. The rationale behind molecular docking-based strategy is that the more a pharmacological molecule interacts with a receptor involved in a disease or pathological molecule, the more likely it is to be repurposed. Another advantage of molecular docking is that it can reveal whether a protein to which a drug can bind is additionally involved in the development of another disease. Everolimus, previously used to prevent organ transplant rejection, was repurposed for cancer treatment after it was discovered that the protein it targets is also implicated in cancer development [35]. Dakshanamurthy, S. et al. used molecular docking and high performance computing to calculate 3671 FDA-approved drugs and discovered that mebendazole, an antiparasitic treatment, has the ability to inhibit vascular endothelial growth factor receptor 2, an angiogenesis mediator [36].

However, molecular docking has issues. For example, 3D structures of certain protein targets of interest may not be available. Furthermore, molecular docking algorithms' ability to predict binding affinity is far from perfect [37].

Genome-Wide Association Studies (GWAS)

GWAS aims to find genes associated with diseases. These genes could be potential drug targets. The logic behind GWAS is as follows. If disease A is treated with drug A and shares a gene or group of genes with disease B, why not try repurposing drug A to treat disease B [38]? This is one way to predict a candidate for

repurposing. Another theory is that genes associated with disease traits encode proteins that are "druggable" or "biopharmaceutical," that is, potential drug targets [38]. This allows researchers to test many different drugs that target the protein products of these genes for new medical applications. Grover et al. employed bioinformatics to link target genes identified for coronary artery disease with pharmacological information from three databases (DrugBank, Therapeutic Target Database, and PharmGKB), successfully identifying candidates for repurposing [39].

However, there are certain concerns with using GWAS for drug repurposing. For example, interpreting GWAS data requires pathophysiological information that is frequently unavailable. It should also be noted that our current understanding of the human genome is incomplete, and many new genes may be identified.

Pathway or network Mapping

Network analysis of multiple links in multicomponent systems (cell, tissue, organ, organism) using data on genes, proteins, or diseases can aid in identifying candidates for repurposing [40]. Network analysis reveals not only the gene(s) implicated in drug action or pathology, but also the signalling routes that lead to gene activation, signalling pathways activated by the gene, and protein interactions within this network. This improves the chances of drug repurposing success. Greene et al. found that combining gene information from GWAS with metabolite-macromolecule interaction networks from network-wide association studies (NetWAS) resulted in more accurate disease-gene connections than using GWAS data alone. Greene et al. used this approach to study hypertension and found that NetWAS gave more reliable information on antihypertensive drug targets than GWAS [41].

In yet another study, network analysis of gene expression data collected during human respiratory virus infection revealed 67 shared biological pathways implicated in viral infections [40]. Drugs with potential impacts on viral targets were found by an examination of these pathways in the DrugBank database. These include pranlukast, a leukotriene receptor 1 antagonist used in asthma, and amrinone, a phosphodiesterase inhibitor used to treat heart failure. Both of these drugs could be repurposed to treat viral infections.

Retrospective Clinical Evaluation

EHRs, post-marketing surveillance data, and clinical trial data can all be used to get retrospective clinical information. EHRs contain both organised and unstructured data, including pathology and laboratory data, clinical descriptions of patient symptoms, and imaging data. All of this data can help determine whether drugs could be repurposed for a new indication. Paik et al. conducted a systematic analysis of clinical data from EHRs over 13 years, including 9.4 million laboratory tests from half a million patients, as well as various genomic signatures, and identified the anti-asthma drug terbutaline sulfate as a candidate for repurposing for the treatment of amyotrophic lateral sclerosis [42].

There are databases containing data about patients, diseases, and drugs that, following computational analysis and the use of machine learning and artificial intelligence algorithms, may suggest a drug repurposing strategy. These are The UK Clinical Practice Research Datalink, the Yellow Card scheme of the Medicines and Healthcare Products Regulatory Agency, the FDA Adverse Event Reporting System and the World Health Organization global database for adverse drug reactions. However, there are

ethical and legal constraints to accessing and utilizing these and EHR data.

Post-marketing monitoring data and clinical trial data are also useful for hypothesizing drug repurposing, but their availability may be limited due to commercial or confidentiality concerns. However, in 2016, the EMA began to make clinical trial data available (<https://clinicaldata.ema.europa.eu/web/cdp/home>), which can be used to identify candidates for repurposing.

New Data Sources for Predicting Candidates for Repurposing
High-throughput drug screening in disease models, large DNA biobanks, and online patient data are being considered as new sources for identifying drug candidates for repurposing.

So, Huang and Weinstein screened hundreds of compounds to determine their effect on CCL cancer cells. The results were compared to CCL genomic data [43,44]. This allowed researchers to find links between the molecular characteristics of tumor cells and their response to the treatment. The identification of such paired genomic and pharmacological data on CCL resulted in the establishment of a new resource for recognizing repurposing candidates. A drug that lowered CCL viability while being inversely linked with the CCL genomic signature, i.e. suppressed genes activated in CCL or activated genes silent in CCL, was considered a candidate for repurposing as an anticancer drug.

Biobanks of human DNA linked to EHR data could be another source for evaluating the potential efficacy of drug repurposing. Following the failure of phase III trials of darapladib (an inhibitor of the PLA2G7 gene product Lp-PLA2) in coronary heart disease and acute coronary syndrome, GlaxoSmithKline used the China Kadoorie Biobank, which contained DNA and EHR data from half a million people, to investigate the role of PLA2G7 gene variants in vascular diseases [45]. PLA2G7 gene variations were not associated with vascular disease, validating the phase III findings. Although the biobank was used to validate the ineffectiveness of a drug, the same method might be used to confirm gene targets for a repurposed drug. In this way, computational analysis of biobank data and EHRs can reveal therapeutic targets for drug development as well as repurposing existing drugs.

Finally, online self-reported patient data has been proposed as another new source to justify drug repurposing [46]. However, this approach has risks of bias and patient safety.

Experimental Approaches

Binding Analysis to Identify Target Interactions

Affinity chromatography and mass spectrometry have made it possible to identify biomolecules to which drugs can bind and the Cellular ThermoStability Assay method has mapped cell targets by predicting the stability of target proteins with drug-like ligands [47,48]. Experiments with affinity matrices encompassing various protein kinases identified novel off-targets for known drugs [49]. This method was used to repurpose the BCR-ABL inhibitor imatinib as a therapy for gastrointestinal cancers [50]. Experimental studies have established the cellular targets of crizotinib, a tyrosine kinase inhibitor, and identified quinone reductase 2 (NQO2) as an acetaminophen off-target [51,52]. Experimental approaches have overcome the problem of promiscuity of protein kinase inhibitors, revealing drugs that act selectively on one or more protein kinases involved in the disease [53]. It is crucial to recognize that a drug's capacity to inhibit a

pathologically active protein kinase in vitro does not necessarily imply therapeutic efficacy in vivo. When tested on cells, certain protein kinase inhibitors unexpectedly activated protein kinases [54]. This could cause malignancies in patients [55].

To further understand the complexities of protein kinase inhibitor drug effects, Karaman et al. assessed the in vitro binding of 38 kinase inhibitors to a panel of 317 different human protein kinases. The analysis found 3175 bindings [56]. Interestingly, the kinase inhibitors sorafenib and dasatinib had a higher affinity for secondary kinase targets than for their known primary targets. The non-kinase targets of protein kinase inhibitors have opened up new opportunities for repurposing these drugs and their use in the treatment of cancer and Zika virus [57,58].

Phenotypic Screening

Phenotypic screening can identify compounds with disease-relevant effects in model systems without prior knowledge of the targets [59]. In vitro phenotypic screening is often performed using a variety of cell-based assays in a 96-well format. Iljin et al. performed a cell-based screening of 4910 drug-like compounds in four prostate cancer cell lines and two non-malignant prostate epithelial cell lines. They identified disulfiram, an alcohol addiction drug, as a selective anticancer agent, which was then verified using GWAS [60].

Morphological cell profiling described above is a phenotype-based assay widely used for drug repurposing. In 2021, a Cell Painting-based quantitative high-throughput screen to identify efficacious agents against SARS-CoV-2 was developed [61]. Seventeen hits from a library of 1,425 FDA-approved compounds and clinical candidates that inhibited SARS-CoV-2 infection were identified and their antiviral activity in LNCaP cells and a physiologically relevant model of alveolar epithelial type 2 cells was tested. It has been found that lactoferrin, a glycoprotein found in secretory fluids like mammalian milk, inhibits SARS-CoV-2 infection in all cell models at nanomolar levels by blocking virus attachment to cellular heparansulfate and boosting interferon responses. Lactoferrin is a safe, easily translated treatment for the management of COVID-19.

Whole-body phenotypic assays are also used for drug repurposing. So Cousin et al. used zebrafish to test 39 drugs approved by the FDA for tobacco dependency and found that apomorphine and topiramate altered nicotine- and ethanol-induced behavior in the fish [62].

Problems on the Path of Drug Reporting

Although drug repurposing has obvious advantages, it also has certain drawbacks [2].

One issue is the difficulty of patenting repurposed drugs, particularly when the drug's trademark has already been registered. This could make it harder for pharmaceutical companies to return their investment in drug development and reduce motivation for research in this field [63].

Another problem is that developing drugs for new indications still requires a large investment and does not guarantee complete success. Repurposed drugs must still undergo phase II and III clinical trials for their new indication, which may reject 70% and 40% of compounds, respectively, for a variety of reasons.

The third issue is that side effects that may be acceptable in a life-threatening condition may not be acceptable in a chronic one. And the traditional business rationale for repurposing - lowering costs because safety testing have already been passed - is only applicable if the dose and route of administration remain unchanged. If a new condition requires a larger dose, the drug must go through Phase I trials again. After all, the cost of repurposing may be comparable to that of a new molecule [64].

All of these issues may dampen drug companies' enthusiasm for drug repurposing. However, three to four drug repurposing firms are presently being established each year, and, according to some estimates, the number of drugs with modified indications for use is increasing, potentially accounting for up to 30% of all drugs approved for use annually [65].

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