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Drug Repurposing: Engineering New Uses for Existing Medications

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ABSTRACT

Drug repurposing, also known as drug repositioning, is the process of identifying new therapeutic uses for existing drugs. This approach offers a cost-effective and time-efficient alternative to traditional drug development, which is often hindered by high failure rates, long timelines, and prohibitive costs. The repurposing of drugs leverages existing pharmacokinetic and pharmacodynamic data, allowing researchers to bypass early-stage safety trials and accelerate clinical application. Advances in computational biology, artificial intelligence, and high-throughput screening have enhanced the ability to predict novel drug-disease interactions. This paper examines the historical context, methodologies, regulatory considerations, challenges, and success stories in drug repurposing. Additionally, emerging technologies such as AI-driven modeling, genomic data integration, and personalized medicine approaches are discussed as transformative tools that will shape the future of drug repurposing. Despite regulatory hurdles and intellectual property challenges, drug repurposing remains a promising strategy for addressing unmet medical needs, improving patient outcomes, and enhancing global healthcare access.

Keywords: Drug repurposing, drug repositioning, computational drug discovery, high-throughput screening, pharmacokinetics, pharmacodynamics.

INTRODUCTION

One of the most fascinating and occasionally frustrating aspects of medicine is the broad range of ways in which biology and chemistry can interact. Of the millions of putative therapeutic compounds in existence, relatively few agents have demonstrated efficacy across multiple disease states. Drug repurposing (or repositioning) is the investigation of existing drugs for novel therapeutic purposes beyond their initial formula indication. This is accomplished through several different mechanisms of action. Up to 70% of a drug's targets can be off-target, meaning that many agents have a complex, unknown mechanism of action. As a corollary, this also implies that other drugs interacting with those off-targets can have beneficial properties. However, repurposing is not limited to single therapeutic agents, distinct harmaceuticals can be combined to produce synergistic effects for a new indication. Additionally, approved drugs can be tested for new indications so long as they share some mechanism of action with compounds under investigation. Repurposing advocates also highlight its economic advantages. The median cost of drug development has skyrocketed to over $1B in recent years, with some companies suggesting development costs of almost $3B. In contrast, targeted efforts repurposing established medications are estimated to cost roughly $40M in preclinical studies. After a drug has passed toxicity screening and is ready for clinical trials, estimates suggest a mean cost of $50M to repurpose. Therefore, it is substantially less expensive in many cases to determine a new indication for an already established medication. As healthcare costs continue to rise, payers such as insurers and governments have found difficulty justifying more expensive novel treatments. There are five times as many Americans with Alzheimer's disease as HIV, yet until the recent approval of a potentially largely ineffective second-line

agent, no drugs specifically addressing the underlying biology of the disease were approved from 2003 to 2021 [1, 2].

Definition and Significance

Repositioning, also known as repurposing, reprofiling, or rediscovery, is a practice in which an existing medication is developed for a different medical indication than it was initially tested or intended. Drug repurposing is beneficial as an applied process rather than basic knowledge. Medications are often tested for an uncovered indication, with ineffective treatments to date often opening up a new area of drug discovery. The testing often occurs in clinical practice and patient centers, and the released data often needs to be transformed to be usable. Drug repurposing is financially beneficial as well, with the process being considerably less expensive and risky compared with developing a new drug. This inexpensive, low-risk, and rapid effect strategy, based on previous clinical or preclinical studies, has been used to expand medication uses concentrating on new molecular targets, therapeutic benefits, and relevant unmet needs. The same drugs or drug candidates are under inspection alone or in combinations for multiple therapeutic applications or biological effects, with the possibility of synthesis, design, or preparation in new forms. Finally, drug eligibility may also concern the stage of the patient, such as design for preventive intervention or as an add-on medication for combination therapy [3, 4].

Historical Background

The average cost to develop a new drug is 2.7 billion U.S. dollars and typically takes 10-15 years. Many drugs fail during testing, with only a few making it to the market, leading to increased pressure for high-throughput screening of genetic and proteomic data to discover new molecules. Searching through thousands of existing drugs can aid those in need globally. However, methods like computer-assisted drug design (CADD) are expensive for large-scale use. Thus, drug repurposing has emerged as a viable strategy, utilizing existing drugs for different ailments. Initially, this approach involved accidental discoveries, but advancements in bioinformatics and centralized databases have reinforced its application. Analyzing existing drug records allows for tracking therapeutic equivalences, facilitating swift transitions into preclinical and clinical trials, which lowers costs and risks. Progress is observed in drug development, evaluation, and post-marketing monitoring. The FDA's Orange Book lists generic drug equivalents, and standardized vocabularies help in identifying therapeutic links. The STRICT program harmonizes data outputs related to drug consumption. An analysis of 651 FDA-approved molecules shows that 11% of diseases can find therapeutic alternatives. Drug repurposing helps reduce the occurrence of medical accidents in over 18 million invasive operations in the U.S [5, 6].

Drug Repurposing Approaches

Repurposing drugs is a notable alternative to the lengthy and high-risk conventional method of new drug development with high rates of failure. The emergence of novel diseases has necessitated drug repurposing efforts. Drug repurposing, often known as drug repositioning or rediscovery, is the discovery of new therapeutic applications for currently utilized or earlier underdeveloped medications. This method is substantially faster and more cost-effective than traditional drug development, significantly mitigating risks since repurposed medications already have pharmacokinetics and pharmacodynamics data and known safety profiles. Besides, they are already approved by regulatory agencies worldwide. Moreover, emerging tools, datasets, and the increasing connectivity of the scientific community are pushing new limits on what it is feasible to comprehend and achieve. Consequently, the present situation is a golden period for observing new applications for approved drugs. Modern technologies and methodologies are henceforth needed to find the best way to take advantage of this wealth. Technological advances have allowed extensive biomedical data to be produced for the first time on a vast scale. This data can be leveraged for mass drug screening for new indications. Among others, genetic perturbation, expression, and compound knockout profiles have been useful in investigating the biological basis of drug actions. Medication data include annotations of a wide variety of drug properties, most notably drug sensitivity profiles. Drug repurposing is, therefore, a clear match for the wealth of omic data as it leverages predicted and observed off-target effects of medications and matches these predictions to the disease-perturbed gene from the patient data. Efforts in drug repurposing stop at data curation and therapeutic application predictions by comparing the scaffold or target similarity between the new indication and the original indication of the drug. Drug repurposing prediction is aided by computational models to determine the relevance of the drug's target. High-throughput drug screenings exploit combinatorial compound libraries, RNAi or CRISPR libraries, and organoids or genetically modified disease models for a particular disease of interest to identify the best drug candidates for repurposing. Recent work on drug repurposing

has utilized a combination of computational and experimental strategies, yet works have generally neglected to use the same drugs, diseases, and predictions in a fully interconnected way. This work delineates a method for fully interconnected analyses of high-throughput screening, compound screening, medication response profile analysis, and patient data. It is demonstrated that the prediction–discovery–validation cycle parameterizes the repurposing process distinct naturally, instead of dividing it artificially. Finally, the method is validated on the emergence of a drug repurposed medication candidate in the context of a novel disease [7, 8].

In Silico Methods

Drug repurposing refers to the process of finding new therapeutic applications for drugs already on the market or in development that are outside of the indications for which they were originally approved. In recent years, researchers have taken advantage of the vast amount of biological and chemical data that has been made publicly available to develop computational methods for identifying potential repurposing candidates, which include bioinformatics and cheminformatics techniques. Two broad classes of in silico repurposing techniques are explored: those that analyze drug-related data and those that analyze disease-related data. Network pharmacology is highlighted as an example of a class of methods to repurpose existing medication that leverage drug networks to predict drug-target interactions and new indications; virtual screening is also presented as a particularly popular technique for drug repositioning involving high-throughput in silico docking calculations between drugs and target proteins. In this paper, in silico methods are the focus, as those methods compute, predict, or analyze interactomes, candidate set enrichments, and other drug-related results, the methods that analyze bioinformatics or cheminformatics data processing are described briefly to place in context the assessment of potential drug reposition candidates before revisiting these method classes. The in-silico methods hold particular advantages about their ability to swiftly investigate and analyze vast amounts of molecular data, especially when integrated with large-scale public bioinformatics or cheminformatics data platforms, and because of their cost efficiency compared to large-scale lab or clinic-based experiments. Nonetheless, false positives are still a critical limitation that should be confirmed experimentally, and the broadly known problems with bias and limited evidence quality affecting many public bioinformatics and cheminformatics data resources are also evident throughout this reporting on actual drug repurposing results. Subsequently, some case studies are reviewed to demonstrate the role of in silico computation in identifying drug reposition candidates, the consistent need for in silico predictions to be experimentally validated, and touch upon some of the key issues still need to be resolved [7, 9].

High-Throughput Screening

Inside the growing field of drug repurposing, high-throughput screening (HTS) has garnered significant interest. HTS is a rapid drug discovery method for testing numerous chemical compounds against specific biological targets. It is common in many laboratories and promoted by various companies. The drug discovery pipeline encompasses target selection, validation, HTS, secondary screening, lead optimization, and drug candidate identification. Libraries of natural products and small molecules are screened to discover new drug entities. HTS is also applied in target-based screening of gene-encoding products. Initial biological screening tests are conducted, often assessing therapeutic potential, which guides developmental toxicological screening. Neuroteratogenicity is a key type of developmental neurotoxicity (DNT), with many compounds exhibiting known DNT effects. This work aims to adapt high-throughput developmental toxicological screening tests to new chemicals for hazard indication. UCB and LU designed a microfluidic, microelectrode analytical device in a 96-well format. Its potential was evaluated in vitro for 9 days with various standard DNT test compounds, leading to a proposed high-throughput microanalytical screening test for acute DNT effects. HTS interrogates large compound libraries using scalable, automated technologies, generating around 10,000 data points weekly. Over the last decade, HTS has evolved into a sophisticated method, utilizing advanced robotics, microfluidics, and information technology. Screening formats vary, encompassing cells, tissues, blood, and membranes. HTS is also integral to agnostic research, although it often results in false positives that require validation. Despite its limitations, HTS has unexpectedly revealed new functions for existing therapeutic agents. In such instances, repositioning does not fit standard drug discovery definitions, highlighting the importance of incorporating HTS in broader drug repurposing initiatives [10, 11].

Clinical Trials and Regulatory Considerations

While the population of repurposed drugs as cancer therapeutics is growing, a significant factor contributing to those activities, patient and healthcare systems will not be able to predict their future.

Repurposing approved non-oncology drugs as cancer therapeutics represents a viable alternative to traditional drug discovery and development and provides numerous advantages over conventional new drug development. In the US, there are three separate regulatory approval pathways for drugs, although only one, Section 505(b)(2), is relevant to drug repurposing. In the EU, a similar process is regulated by the EMA under Article 10 of Directive 2001/83/EC. However, in contrast to section 505(b)(2), Article 10 does not provide a legal basis for the use of non-proprietary studies, patients, and otherwise confidential facts. To understand the challenges facing those attempting to repurpose approved drugs, it is important to first understand the regulatory and economic frameworks governing the approval of a new drug and then describe how these hurdles are overcome by those attempting to repurpose approved drugs as therapeutics. At each step of the bench-to-bedside research process, there is a complex interplay between the discovery research data generation, clinical research data interpretation, and the practical regulatory guidelines meant to protect patient safety. Oncologists, translational researchers, clinical trialists, pharmaceutical companies, and regulatory agencies all have different, often constraining, mandates related to the same data and, on occasion, these mandates may appear to be in direct opposition. The goal of all this part is to take the little-understood landscape of how therapeutic interventions progress through the stages of preclinical to clinical research, through regulatory review and finally conventional practice, and articulate the median priorities, goals, and hurdles faced by each of the aforementioned stakeholders, thereby uniting disparate data to inform and guide fundamental and translational research efforts [12, 13].

Success Stories in Drug Repurposing

One of the most notable stories in drug repurposing is aspirin, which has been used for over 100 years as an anti-inflammatory, analgesic, and antipyretic. Primarily recognized in cardiovascular medicine, aspirin has reduced the risk of recurrent heart attacks or strokes in patients with cardiovascular diseases since the 1980s, fundamentally changing treatment approaches. Similarly, antipsychotics have transformed their therapeutic indications, with recent research exploring their potential in neuro-oncology, specifically glioblastoma treatment. Antipsychotics exhibit various anti-cancer properties, making them promising candidates. However, their development faces challenges, particularly the severe metabolic side effects that can compromise glioblastoma outcomes. The growing focus on drug repurposing in academic and policy discussions highlights the collaboration among international researchers and an increase in investment in this field. Addressing complex healthcare concerns has recently attracted significant attention, promoting multi-faceted approaches yielding safe, effective treatments. Drug repurposing success stories enhance patient outcomes and improve healthcare access. Recent research applications across disciplines showcase methodological specifics for designing new drugs, emphasizing innovative clinical trial methodologies for greater success in drug development [14, 15].

Challenges and Limitations of Drug Repurposing

There has been a rapidly expanding interest in drug repurposing. An estimated 20% of marketed drugs can be repurposed, and yet it is apparent that many existing drugs, especially older drugs, are underutilized and under investigated in terms of their full potential therapeutic uses. Defining the intellectual property-related conditions that shape the environment for drug repurposing is needed to develop an inventory of the suggested research models, including traditional drug development, the 'learn and confirm' model used in clinical research, the so-called benchmarking model, and the so-called VA and DOD models. Drug repurposing, also known as drug repositioning, finds new uses for existing drugs, including their off-label uses, i.e., uses besides the carefully tested and prescribed indications. Interest in drug repurposing has grown markedly in recent years. Consequent to these legislative changes, additional research has been published about drug repurposing, some of which implicitly prompted consideration of the patent protection of new uses of existing drugs. Repurposing even involves the discovery or identification of new methods of use for existing compounds over which their sponsors can obtain market exclusivity. Despite this mandatory change in the law, which began to be implemented in 2012, the literature and commentary on drug repurposing have only tacitly developed in this area. As is the case with 'new chemical entities' (NCEs), the new uses or potential new uses of existing drugs must meet the same regulatory requirements. These requirements include the demonstration of 'safety and effectiveness' through 'adequate and well-controlled investigations.' As of direct relevance to patents, to meet these regulatory requirements for potential new uses of existing drugs, sponsors must also generate 'high quality' preclinical and clinical results. This so-called 'patent provision' is challenging and has often slowed down the repurposing effort [16, 17].

Future Directions and Emerging Technologies

As recent scientific advancements continue to underscore the potential power and utility of drug repurposing as a research approach, future directions and proposed technologies will likely influence the trajectory of efforts going forward. In a broad overview, advancements in artificial intelligence and machine learning are noted as promising technologies poised to usher in a revolution in how repurposing candidates are identified and validated as more and more pharmaceutical and patient data are generated and made accessible. Complementarily, it is suggested that genomic data and personalized medicine will come to play an increasingly important role in suggesting more tailored approaches to repurposing—both at the level of identifying patient populations that will best respond to a given drug and in proposing precise drug combination strategies. Socially, the growing recognition of the importance of partnerships between academia and industry is expected to lead to innovative protocols combining multiple drugs to treat unmet needs and novel clinical trial designs to speed drugs to market. In terms of the regulatory environment, ongoing shifts are observed that will create more accommodating conditions for repurposed drugs to achieve fast-track approval via mechanisms such as applications or expedited review pathways. By the same token, as the benefits of these emerging technologies become more widely harvested, it is acknowledged that they may also generate new challenges, such as concerns over the over-interpretation of large-scale data or the disincentivizing of personal collaboration among scientists. To this end, it is urged that these powerful tools be rigorously applied to leverage their benefits without creating adverse downstream effects [18, 19].

CONCLUSION

Drug repurposing represents a pivotal strategy in modern pharmacology, offering an efficient pathway to discovering new treatments for various diseases. By leveraging existing drug data and utilizing advanced computational techniques, repurposing reduces development costs, minimizes risks, and accelerates time to market. While challenges such as regulatory barriers and intellectual property rights persist, ongoing advancements in artificial intelligence, bioinformatics, and personalized medicine continue to refine and optimize this approach. As the pharmaceutical industry and regulatory agencies adapt to these innovations, drug repurposing will likely play a crucial role in addressing complex health challenges, improving patient outcomes, and shaping the future of drug discovery.

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