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Popular Article

DRUG REPURPOSING –New targets old drugs

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Introduction

The progressing of technology and our understanding of human disease is improving day by day but the translation of these advantages into therapeutic advancements has occurred at a much slower pace than anticipated. The global pharmaceutical industry faces diverse challenges, including high attrition rates, extended timelines for introducing new drugs in certain therapeutic areas and evolving regulatory demands which together contributes to higher costs. The increasing cost and time commitments associated with developing new medications have led to estimates suggesting that the average return on investment for each dollar allocated to research and development (R&D) is under a dollar. This trend may render the pharmaceutical industry a less attractive option for investors. Drug repurposing (also known as drug repositioning, reprofiling, or re-tasking) refers to a strategy aimed at finding new applications for approval of investigational drugs that fall outside their original medical indications. This approach has several benefits over new drug discovery. First, and most crucially, the likelihood of failure is reduced because the repurposed drug has already been found to be sufficiently safe in preclinical models and humans. Secondly, the duration of the drug development process can be shortened, as majority of preclinical testing, safety evaluations, and formulation development have already been done. Third, the required investment is lower, but it depends significantly on the stage and development process of the repurposing candidate. While the costs associated with regulation and phase III for a repurposed drug may be comparable to those of a new drug targeting the same indication, significant savings could still be realized in preclinical and phase I and II expenses. These benefits could lead to a less risky and quicker return on investment in repurposed drug development, with lower

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average costs after factoring in failures (the estimated average cost of bringing a repurposed drug to market is US$300 million, while the cost for a new chemical entity is estimated to be ~$2–3 billion). Ultimately, repurposed medications might uncover novel targets and pathways for further exploitation. Historically, drug repurposing has been mostly opportunistic and serendipitous; after a drug was recognized as having an off-target effect or a newly acknowledged on-target effect, it was promoted for commercial use. Till date, the most successful cases of drug repurposing have actually not used a systematic approach like sildenafil citrate's repurposing for erectile dysfunction relied on retrospective clinical experience, whereas thalidomide's repurposing for erythema nodosum leprosum (ENL) and multiple myeloma occurred by chance. Sildenafil was initially used to treat high blood pressure, but when Pfizer repositioned it as a treatment for erectile dysfunction and branded it as Viagra, it captured 47% of the erectile dysfunction drug market in 2012, with global sales reaching $2.05 billion. Thalidomide, a sedative that was first marketed in some countries in 1957, was withdrawn within four years due to its notorious association with severe skeletal birth defects in children whose mothers had taken the drug during the first trimester of pregnancy. Nonetheless, it was discovered by chance to be effective for the treatment of erythema nodosum leprosum (ENL1) in 1964 and, many years later, for multiple myeloma in 1999. It has achieved considerable commercial success in the context of multiple myeloma and has also resulted in the creation and endorsement of derivatives that are even more successful, like lenalidomide, which recorded global sales of $8.2 billion in 2017. These successes have fostered the creation of more systematic methods for identifying compounds that can be repurposed and have led to the discovery of several promising candidate drugs, some of which are undergoing advanced clinical trials, and have potential for treating both common and rare diseases.

Approaches for repurposing drugs

Before considering a candidate drug further along the development pipeline, a drug repurposing strategy usually entails three main steps: finding a candidate molecule for a particular indication (generating hypotheses); evaluating the drug's efficacy in phase II clinical trials (assuming there is adequate safety data from phase I studies conducted as part of the original indication); and assessing the drug's effect mechanistically in preclinical models. The most crucial of these three phases is step 1 i.e. choosing the appropriate drug for an indication of interest with a high degree of certainty. This is where contemporary methods for developing hypotheses could be most helpful. These methodical techniques can be further separated into experimental and computational techniques, which are increasingly being applied in tandem. These two major categories include drug repurposing based on clinical evidence. The Table 1 shows few drugs that are repurposed successfully and are already available in market.

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Drugs	Original Indication	Repurposed Indication	Mechanism of Action
Thalidomide	Morning sickness	Multiple myeloma, leprosy	Immunomodulatory; inhibits TNF-α and angiogenesis.
Topiramate	Epilepsy	Migraine prevention & weight loss	Modulates sodium channels, enhances GABA activity.
Aspirin	Pain and fever	Cardiovascular disease & cancer prevention	COX inhibitor; anti-inflammatory and antiplatelet properties.
Chloroquine	Malaria	Rheumatoid arthritis & lupus	Immunomodulatory; interferes with cytokine release.
Gabapentin	Epilepsy	Neuropathic pain & hot flashes	Modulates calcium channels; affects neurotransmitter release.
Sildenafil	Angina (chest pain)	Erectile dysfunction & pulmonary hypertension	PDE5 inhibitor; increases cGMP leading to smooth muscle relaxation.
Amantadine	Influenza A	Parkinson's disease & multiple sclerosis fatigue	Increases dopamine release; NMDA receptor antagonist.

Computational approaches

A key component of contemporary drug repurposing is computational (*in silico*) methods, which enable scientists to methodically examine enormous datasets and forecast possible novel applications for already approved medications. These techniques can significantly cut down on the time required to find best drug candidates and are scalable and reasonably priced. The primary computational techniques used for contemporary drug repurposing include:

1. Transcriptomic Profiling / Signature Matching

In drug repurposing, transcriptomic profiling also referred to as signature matching is a potent computational technique that compares gene expression patterns in drug treated cells or tissues with those in diseased cells. The basic premise is that medications can also produce particular changes in gene expression, known as drug signatures, while diseases already create distinctive changes in gene expression, known as disease signatures. It is thought that a drug may have therapeutic promise against a disease if it causes a gene expression profile that is contrary to or counteracts the disease signature (i.e., it downregulates suppressed genes and reverses elevated ones). This method is very helpful for finding medications that, despite having unrelated initial indications may alter disease pathways. The library of integrated network based cellular signatures (LINCS) project, connectivity map (Cmap) and its updated version, which offer extensive gene expression profiles from human cells exposed to hundreds of small compounds, are a key resource for this strategy. Using methods such as gene set enrichment analysis (GSEA), researchers utilize these databases to calculate similarity or anti similarity scores between medication and disease markers. The discovery of topiramate, an anti-epileptic medication, reverses the gene expression profile of inflammatory bowel disease, making it a promising treatment for the condition, is a well-known illustration of this methodology.

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2. Molecular Docking & Virtual Screening

The two important computational methods in drug discovery and repurposing are molecular docking and virtual screening, which attempt to forecast the physical interactions between tiny molecules (drugs) and biological targets like proteins or enzymes. By simulating a drug candidate's binding to a target protein's active site, molecular docking estimates the drug's binding posture, or how it is oriented within the binding pocket, as well as its binding affinity, or how strongly it binds. Finding substances that can successfully alter the way disease related proteins function is the aim. Docking algorithms score compounds according to their expected interactions, such as electrostatic forces, hydrophobic effects, and hydrogen bonds, using scoring functions. Virtual screening, on the other hand, is the high-throughput application of docking techniques to quickly screen huge libraries of compounds sometimes millions for the ability to bind a particular target. The two primary forms of virtual screening are ligand-based, which infers possible activity by comparing novel compounds to known active molecules, and structure based, which makes use of the target protein's three-dimensional structure (often acquired via X-ray crystallography or cryo-EM). When authorized medications like remdesivir, lopinavir, and favipiravir were docked against viral proteins (including the SARS-CoV-2 primary protease) during the COVID-19 pandemic to assess their potential as antiviral medicines, molecular docking was crucial to the repurposing process.

4. Network based approaches

It works by examining the intricate connections between genes, proteins, medications, and illnesses, network-based approaches to drug repurposing take use of the interconnectedness of biological systems to find novel therapeutic applications for already-approved medications. According to these approaches, biological and pharmacological entities are represented as nodes in a network, and their interactions such as those between drugs and their targets, proteins, genes, or diseases are represented as edges. Researchers can deduce possible new therapeutic indications by looking at the topology and proximity of nodes inside these networks. This is done by analyzing the nodes' positions and relationships. For instance, a medicine may have therapeutic significance for a disease if it is linked to a protein that is closely related to a disease-associated protein (via interactions or pathways). Building heterogeneous networks (hetnets) that combine several data types like molecular functions, side effects, genetic pathways, and clinical outcomes into a single framework is one popular tactic. Hetionet, a large-scale integrative network that assisted in forecasting that the antipsychotic perphenazine would be repurposed for the treatment of glioblastoma, is a notable example. These

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methods are especially effective at identifying off-target effects that could have therapeutic value and capturing polypharmacology, or pharmaceuticals that act on numerous targets.

5. Pathway and systems biology analysis

A potent strategy for drug repurposing is pathway and systems biology analysis, which focuses on comprehending how illnesses and medications impact intricate biological pathways and cellular networks rather than single genes or proteins. This approach entails determining which molecular pathways such as metabolic, regulatory, or signaling pathways are dysregulated in a certain illness and then locating medications that are currently on the market that are known to alter those same pathways. The fundamental idea is that a medication may have therapeutic efficacy even if it was initially created for a different reason if it helps correct the imbalance of a disturbed route. To map genes or proteins linked to disease onto established biological pathways, researchers commonly utilize databases like KEGG, Reactome, BioCarta, and Gene Ontology. Ingenuity Pathway Analysis (IPA) and Gene Set Enrichment Analysis (GSEA) are two tools that can be used to prioritize medications that affect significantly disrupted pathways. A mechanism-based repurposing strategy is made possible by this method, in which medications are chosen not only for their initial targets but also for their capacity to alter whole networks implicated in the pathophysiology of disease. For instance, medications like rapamycin, which were first licensed for immunosuppression, may be effective in treating tumors with overactive PI3K/AKT/mTOR signaling. This comprehensive approach is especially useful for complicated or multifactorial disorders because it enables researchers to forecast off-target effects, medication synergies, and context-specific activity. The requirement for biological validation, high-quality route annotations, and the possibility of cell type and illness stage-specific variations in pathway activity are obstacles, though.

6. Similarity-Based Approaches

The idea behind similarity-based methods to drug repurposing is that similar things, such as medications, illnesses, targets, or side effects, frequently have similar therapeutic or functional qualities. By comparing current medications to other medications or illnesses based on a variety of similarities, such as chemical structure, target profiles, gene expression, phenotypic results, or side effect patterns, these techniques seek to discover novel applications for already-approved medications. For instance, a medication may also be beneficial against a certain disease if its molecular makeup or mode of action is comparable to that of another medication used to treat that condition. Chemical similarity is frequently measured using tools like the Tanimoto coefficient and fingerprint-based

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similarity measures, while medications can be matched using the Similarity Ensemble Approach (SEA) and ChemMapper based on shared biological targets or three-dimensional molecular characteristics. Off-target effects that overlap with symptoms of other diseases can also be found by comparing side effect profiles (as listed in resources such as SIDER), which may indicate potential for repurposing. One prominent instance is the identification of sildenafil's (originally created for angina) potential for treating pulmonary hypertension and erectile dysfunction due to its resemblance to medications that impact smooth muscle relaxation. These techniques are appealing for preliminary screening since they are quick and reasonably simple to use.

7. Text Mining and Literature-Based Discovery (LBD)

Research articles, clinical trial reports, patents, and electronic health records are just a few examples of the vast amounts of unstructured biomedical literature from which text mining and literature-based discovery (LBD) in drug repurposing use computational techniques to extract meaningful patterns, relationships, and hypotheses. The basic thesis is that because of the sheer amount and fragmentation of information, important drug-disease connections may be hidden in published literature but go unnoticed. Natural language processing (NLP) methods are used in text mining to find and connect important biomedical elements in hundreds of papers, including genes, biological processes, disease phrases, and medicine names. By tying together ideas that are logically related across several sources but not directly connected in any one publication, literature-based discovery goes one step further. The work of Don Swanson, who deduced a possible benefit of fish oil for Raynaud's illness by observing distinct, unrelated references to fish oil lowering blood viscosity and high blood viscosity being a contributing factor in Raynaud's, is a famous example. Using machine learning and semantic reasoning, contemporary LBD systems, such Semantic MEDLINE and BioBERT, can automatically extract, rank, and show these hidden associations. These methods are particularly helpful for generating hypotheses, identifying untapped therapeutic potential, and ranking candidates for experimental validation.

Experimental approaches

In order to find new therapeutic uses for existing medications, experimental approaches to drug repurposing entail direct laboratory or clinical testing. By examining real medication effects in vitro (in test tubes), in vivo (in animal models), or in clinical settings, these techniques offer evidence that is both physiologically and therapeutically meaningful. Experimental procedures verify drug efficacy

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and mechanism of action under controlled conditions, in contrast to computational methods that produce hypotheses.

1. Phenotypic screening

Without needing to know the drug's molecular target beforehand, phenotypic screening is a crucial experimental strategy in drug repurposing that tests current medications on biological models, such as cells, organoids, or animal systems, to detect quantifiable changes in disease-related phenotypes. By using a target-agnostic approach, scientists can find substances that have the intended therapeutic effect for example, stopping the development of cancer cells, lowering inflammation, or fixing a biological flaw based only on actual results rather than hypothesized mechanisms. Phenotypic screening is particularly useful for complex or poorly understood diseases since it can reveal off-target or previously unidentified mechanisms of action, which is one of its key advantages. Phenotypic effects seen in unrelated trials have historically been used to identify a number of medications, such as thalidomide (repurposed for multiple myeloma) and chlorpromazine (repurposed for glioblastoma). The accuracy and applicability of phenotypic screenings have been significantly improved by developments in high-content imaging, 3D cell culture techniques, and disease-specific tests, such as patient-derived organoids or CRISPR-modified cell lines.

2. Target-based screening

A targeted experimental strategy for drug repurposing is target-based screening, which compares established medications or compound libraries to particular, well-characterized biological targets like enzymes, receptors, or ion channels that are linked to a disease. Target-based screening depends on prior understanding of disease mechanisms and molecular biology to find therapy options, in contrast to phenotypic screening, which is outcome driven and target-agnostic. Assays that test how well a drug binds to or modifies the activity of the target, like blocking a kinase or activating a receptor, are usually biochemical or cell-based. The anticancer medication imatinib, for instance, was first created to block BCR-ABL in chronic myeloid leukemia. However, it was later discovered to block other pertinent tyrosine kinases involved in fibrosis and vascular remodeling, leading to its repurposing for conditions such as systemic sclerosis and pulmonary arterial hypertension. When the target is druggable and the disease biology is well understood, this strategy is especially beneficial because it allows for mechanism-specific repurposing. Additionally, it makes logical drug design and optimization easier. Target-based screening, however, may not detect complex, system-level reactions observed in living things and may overlook medications that have indirect or multi-target effects.

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3. High-throughput screening (HTS)

In drug repurposing, high-throughput screening (HTS) is a potent experimental method that quickly assesses the biological activity of thousands to millions of currently available drugs against a particular disease target or model. To screen huge drug libraries quickly and affordably, HTS uses automation, robotics, and miniature assays. By monitoring their effects on disease-relevant targets (such as enzymes or receptors) or cellular phenotypes, HTS is frequently used in drug repurposing to test authorized medications, shelved compounds, or clinical prospects for novel therapeutic applications. For instance, by testing current medications against SARS-CoV-2 targets or infected cell models, HTS could quickly uncover antiviral options such as remdesivir and hydroxychloroquine during the COVID-19 pandemic. By testing current medications against SARS-CoV-2 targets or infected cell models, HTS played a key role in quickly finding antiviral options such as hydroxychloroquine and remdesivir. HTS assays can be cell-based, evaluating more general biological outcomes like cytotoxicity, changes in gene expression, or pathway activation, or biochemical, measuring particular molecular interactions like enzyme inhibition. HTS's speed and scalability are two of its key advantages since they enable objective screening over large chemical regions.

4. Binding Assays / Target Engagement Studies

In drug repurposing, binding assays and target engagement studies are essential experimental techniques that seek to verify if a medication physically interacts with a particular biological target linked to a disease. These techniques offer concrete proof of a medication's mode of action, supporting the validation of existing therapeutic applications or revealing novel ones. Researchers use methods like surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), fluorescence polarization, or radioligand binding to assess a drug's affinity and specificity for a target protein in binding experiments. By determining if an existing medication binds to a novel target, these tests can assist the drug's possible repurposing for disorders involving that target. By proving that the medication binds to its target in a physiologically significant setting, like inside living cells or tissues, target engagement studies go one step further. This interaction is evaluated under physiological settings using techniques such as drug affinity responsive target stability (DARTS) and cellular thermal shift assay (CETSA).

5. Animal models and *in vivo* studies

Drug repurposing relies heavily on animal models and *in vivo* research, which offer crucial preclinical data on a medication's safety, pharmacokinetics, efficacy, and overall biological impact in

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a living thing. Researchers can evaluate therapeutic effects in the context of complicated, systemic biology by testing repurposed medications in disease-relevant animal models, such as mice, rats, or zebrafish, that closely resemble human pathological circumstances. By demonstrating how a drug behaves in terms of absorption, distribution, metabolism, and excretion (ADME) and identifying potential toxicities or off-target effects, in vivo investigations aid in bridging the gap between in vitro or computational discoveries and human clinical applications. For example, fluoxetine, an antidepressant, was studied for multiple sclerosis after it shown encouraging neuroprotective and anti-inflammatory benefits in mice models of the condition. Similar to this, medications that were first created to treat infectious or cancerous diseases have been modified to treat autoimmune or neurodegenerative diseases in response to findings from animal experiments.

6. Clinical and observational studies

By using real-world human data to find novel therapeutic applications for already-approved medications, clinical and observational studies are essential to drug repurposing. In order to find correlations between medication exposure and favorable health outcomes in conditions outside than a medicine's original indication, these studies systematically analyze data from clinical trials, off-label drug use, electronic health records (EHRs), insurance claims, and patient registries. These strategies provide direct evidence from human participants, which increases the possibility of successful clinical translation in contrast to preclinical procedures. Retrospective cohort studies, case-control studies, and cross-sectional analyses are examples of observational research that can show unanticipated advantages or a lower incidence of disease in patients using a particular drug. One well-known example is the identification of metformin's possible anti-aging and anti-cancer effects, which were demonstrated by decreased cancer rates in diabetes individuals receiving the medication.

Recommendations for drug repurposing

The suggestions to assist and achieve the full potential of drug repurposing, keeping in mind the opportunities and difficulties include improved data analysis and integrative platforms. Large data has several advantages, and it can help find chances for repurposing. Data integration and access, especially for clinical data (such as clinician notes in patient case records), continue to be a bottleneck. More sophisticated technical solutions are required to lessen the requirement for manual curation and assist in integrating various omics data types so that more "non-experts" can modify and analyze subsequent analyses in easily understandable formats. There has to be better access to pre-clinical and clinical substances produced by the industry. The more information from phase II–IV clinical a trial

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financed by the industry has to be made available. This would enable other researchers to search the data for fresh insights that might lead to prospects for repurposing, especially for programs that have been stopped. The research should be done on the more recent safety risks associated with repurposed medications. Finding any additional safety issues related to repurposed medications is an ongoing necessity. These could emerge from different dose schedules (e.g., chronic rather than intermittent dosing), use in new demographics, or new interactions between the medicine and the condition for which it is repurposed. Additionally, novel funding sources like crowd sourcing and parent entrepreneurs are required for drug repurposing projects, particularly in uncommon diseases. Last but not least, steps must be taken to encourage drug repurposing, especially to remove the previously mentioned patent and regulatory obstacles. To guarantee that there is ample opportunity to recover investment in medicine repurposing programs; such steps could include royalty agreements with generic companies, improved data exclusivity periods for repurposed indications, or other legislative reforms.

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