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Repurposing Clinically Approved Drugs: Mechanistic Insights, Therapeutic Opportunities, and Regulatory Challenges

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ABSTRACT

Drug repurposing or drug repositioning is becoming a cheaper and more time-saving option to traditional drug discovery that finds new therapeutic uses for already clinically approved medicines. Contrary to the classical de novo development route that requires more than a decade of research and billions of dollars invested, repurposing takes advantage of known pharmacokinetic, pharmacodynamic, and safety profiles, cutting down on attrition rates. Mechanistically, repurposing takes advantage of varied rationales such as conserved molecular targets between diseases, common signaling pathways, polypharmacology, and host-directed therapeutic strategies. Computational advances in machine learning, network pharmacology, computational biology, and large-scale data integration have boosted the identification of opportunities for repositioning, and phenotypic screening and real-world evidence through electronic health records further enhance translational capability. Many success stories, e.g., sildenafil for erectile dysfunction, thalidomide for multiple myeloma, and dexamethasone for severe COVID-19, highlight the clinical and societal importance of this strategy. However, problems remain, such as optimization of doses, safety assessment in new patient populations, and failures in translational efforts due to pharmacokinetic mismatches. In addition, regulatory and commercial hurdles such as intellectual property limitations, constraints in financial incentives for off-patent medicines, and heterogeneity worldwide in routes of approval make broad application difficult. In spite of such challenges, drug repurposing is highly promising for filling unmet medical demands, particularly in oncology, infectious diseases, neurodegenerative disorders, and rare diseases. Precision repurposing based on biomarkers, AI-based prediction platforms, and innovative regulatory schemes that harmonize safety with faster access are the directions ahead. Together, repurposing is a strong paradigm for enriching therapeutic spaces, leveraging scientific investments, and providing affordable and effective interventions to patient populations across the globe.

Keywords: Drug repurposing; drug repositioning; polypharmacology; computational pharmacology; phenotypic screening; network medicine; regulatory challenges; translational pharmacology; precision medicine.

INTRODUCTION

Drug discovery and development are among the most intricate, resource-demanding, and risk-prone activities within contemporary biomedical science. Conventional pipelines take 10-15 years with continuous research and investments usually amounting to over 1.5 to 2 billion USD, but failure is too high. Even once compounds reach clinical trials, only approximately 10% of those that enter Phase I will finally reach regulatory approval. Attrition is often the result of problems like unexpected toxicity, poor pharmacokinetics, reduced efficacy, or lack of differentiation from current drugs. This inefficacy not only restrains innovation but also postpones the release of life-saving drugs, leaving essential therapeutic gaps unclosed. In this context, drug repurposing or drug repositioning is now a valuable strategy for promoting faster therapeutic innovation. Repurposing entails the discovery of new disease indications for existing approved, postponed, or investigational drugs. The essence of this technique is in the utilization of the already acquired safety, pharmacology, and manufacturing information of such drugs, significantly lowering development expenses and times. Since repurposed medications have already been subjected to stringent toxicological and pharmacokinetic assessment, they are less likely to fail on the basis of safety issues, allowing for accelerated translation from bench to bedside. The history of contemporary medicine is filled with instances where medications originally developed for one purpose discovered breakthrough success in another. Sildenafil, which was first created for angina, was a blockbuster for erectile dysfunction and, subsequently, for pulmonary hypertension. Minoxidil, as an antihypertensive, discovered new purpose as a topical therapy for alopecia. Thalidomide, in spite of its catastrophic past, was remanufactured as an immunomodulatory drug for multiple myeloma and leprosy. More recently, dexamethasone appeared in the COVID-19 pandemic as an essential, low-cost treatment to decrease mortality for severe cases, highlighting the role of repurposing in emergency public health emergencies. These instances illustrate two of the large-scale ways in which opportunities for repurposing occur: through accidental clinical observations and through

methodical mechanistic or computational discovery. Mechanistically, drug repurposing is underpinned by increased understanding of polypharmacology the capacity of a single drug to interact with several molecular targets and signaling pathways. Better understanding of genomics, transcriptomics, proteomics, and metabolomics has uncovered complex disease networks, whereby drugs initially targeted for a specific purpose can modulate surprising but therapeutically significant pathways. For example, kinases-targeted anticancer drugs have shown promise in inflammatory and autoimmune disease because the signaling cascades overlap. Likewise, psychotropic drugs that act in the central nervous system have been found promising in oncology through the modulation of apoptosis and cell survival pathways. These examples illustrate how repurposing is not opportunistic but rather reflects deeply the systems biology of human disease.

Advances in technology have further extended the scope of repurposing. Artificial intelligence (AI), machine learning, and network pharmacology software are now able to search enormous biomedical databases to discover drug-disease relationships that were not detectable by human scientists. Computational drug repurposing combines data from clinical history, adverse event reports, molecular docking, and gene expression signatures to forecast new therapeutic pairings. Those predictions can then be tested and confirmed in preclinical models, greatly reducing the cycle of discovery. Concurrently, high-throughput screening platforms enable systematic testing of available drug libraries against multiple disease-relevant assays at an accelerated pace, thus speeding up the discovery of repositioning candidates. Aside from its scientific justification, drug repurposing has deep societal and economic importance. Repurposed drugs tend to be cheaper since their production processes, formulations, and distribution channels are already in place. This makes them exceptionally useful in low- and middle-income nations, where healthcare expenditures are limited but the prevalence of infectious and chronic illness is inordinately high. Further, repurposing has provided windows for rare diseases and orphans, where conventional drug development proves financially impossible because patient numbers are too low. By assigning new functions to existing molecules, scientists are able to bring therapy to under-resourced populations, filling gaps in health equity around the world. While promising, repurposing is not without its problems. Translational challenges include dose optimization, pharmacokinetic mismatch, and drug–drug interaction when a compound is used in a new therapeutic environment. Regulatory approaches for repurposed drugs, although potentially fast-tracked, are still multifaceted and sometimes jurisdiction-dependent. Intellectual property rights are another constraint; firms have no incentive to fund clinical trials for off-patent medicines, reducing commercial potential. In a few instances, lack of definable ownership or exclusivity prevents investment, despite sound scientific reasoning. Despite these challenges, alignment of scientific discovery, technological progress, and urgent clinical need has driven drug repurposing into mainstream of contemporary pharmacology. It is increasingly seen not only as a stopgap measure, but as a pillar of precision medicine, allowing for the repurposing of mature drugs to new patient populations on the basis of molecular, genetic, and phenotypic understanding. As healthcare systems across the globe struggle to cope with the twin threats of escalating costs and unmet medical needs, drug repurposing presents a pragmatic and visionary solution a solution that saves resources while opening up new therapeutic possibilities.

2. Drug Repurposing Mechanistic Fundamentals

The scientific basis of drug repurposing is rooted in the conserved biological principles that direct disease processes. Most drugs, although first created with a limited range of indications, have pharmacological activities beyond their original therapeutic applications. With the help of molecular conservation, pathway overlap, polypharmacology, and pharmacokinetic plasticity, scientists can discover new uses for known compounds. What follows is a description of mechanistic rationales that support drug repurposing.

2.1 Target-Based Rationales

Central to repurposing is that of common molecular targets between diseases. For any two or more conditions, if they are mediated by a common protein or enzyme, drugs for one condition might be effective for another. One of the best examples is imatinib, which was first discovered as a BCR-ABL tyrosine kinase inhibitor for chronic myeloid leukemia (CML). Outside of CML, imatinib proved effective in gastrointestinal stromal tumors (GIST) by inhibiting the KIT receptor tyrosine kinase and in hypereosinophilic syndrome through PDGFR inhibition. This shows how one drug can be used to treat several diseases by targeting conserved oncogenic drivers. Another example is rituximab, an anti-CD20 monoclonal antibody used for the treatment of B-cell lymphomas, which was subsequently repurposed for autoimmune diseases like rheumatoid arthritis and multiple sclerosis, wherein B-cell depletion is beneficial. These examples illustrate the utility of profound molecular insight in promoting rational repurposing.

2.2 Pathway and Network-Level Overlap

Clinically different diseases frequently have convergent signaling pathways, a concept that has provided therapeutic redirection opportunities. For example, inappropriate NF-κB pathway activation underlies both oncogenesis and inflammatory and autoimmune diseases. Agents that affect this pathway, originally explored in cancer, have then proven useful in chronic inflammation. Pirfenidone,

initially explored as an anticancer drug, was subsequently repurposed for idiopathic pulmonary fibrosis (IPF) because of its property to inhibit TGF-β-mediated fibrotic signaling. Likewise, drugs acting against oxidative stress responses or angiogenic processes have had cross-disease utilities. Network pharmacology also solidifies this strategy, demonstrating that apparently disparate diseases have molecular nodes that are targetable pharmacologically. This overlap establishes a systems-level justification for repositioning.

2.3 Polypharmacology

Unlike the "one drug-one target" dogma, a majority of drugs exhibit polypharmacology-the ability to bind multiple targets. Such off-target effects, previously viewed as unwanted, are responsible for emerging therapeutic actions. Duloxetine, a SNRI antidepressant, was discovered to regulate pain descending spinal pathways, allowing it to be repurposed for neuropathic pain and fibromyalgia. Similarly, valproic acid, originally an antiepileptic, showed histone deacetylase (HDAC) inhibition, which has led to investigation in oncology and neurodegenerative disorders. Kinase inhibitors like sunitinib and sorafenib are examples of polypharmacology that act on various kinases involved in various cancers as well as in non-oncological diseases. Hence, polypharmacology not only accounts for side effects but also offers therapeutic potential beyond the primary indication.

2.4 Host-Directed Therapy in Infectious Diseases

Drug repurposing in infectious diseases tends to mean targeting host-cell functions instead of the pathogen itself. This is more useful in the battle against resistance, as pathogens are less likely to become resistant to host-directed treatments. One high-profile example includes the assessment of chloroquine and hydroxychloroquine, which modulate endosomal pH and disrupt viral entry mechanisms. Whereas findings in viral diseases such as COVID-19 were non-conclusive, host response modulation remains an active approach. Statins too, initially discovered for hyperlipidemia, have been promising in the infectious environment by virtue of their immunomodulatory and anti-inflammatory activity, such as sepsis mortality reduction. Host-directed repurposing shows the promise to extend the therapeutic armamentarium in the fight against infection, particularly in the context of increasing antimicrobial resistance.

2.5 Pharmacokinetic and Formulation Relevance

Effective repurposing is frequently dependent on whether a drug is able to reach therapeutically relevant concentrations in new target tissues, or whether formulation adjustments can release new uses. Methotrexate is a prime example: at high dose, it acts as an antimetabolite chemotherapy, whereas at low dose it has immunomodulatory activity and is thus useful in rheumatoid arthritis and psoriasis. This dose-dependent dichotomy illustrates the pharmacodynamic versatility of some agents. In addition, reformulation can improve repurposing opportunity. Corticosteroids, for instance, previously being mainly systemic drugs, were reformulated effectively as inhaled drugs for asthma and chronic obstructive pulmonary disease (COPD) so as to provide local delivery with less systemic toxicity. Topical and transdermal reformulations of systemic drugs have also widened therapeutic applications by facilitating tissue-specific targeting.

3. Strategies for Identifying Repurposing Opportunities

Identifying new therapeutic uses for existing drugs requires a combination of experimental, computational, and clinical approaches. Over the past two decades, advances in high-throughput technologies, bioinformatics, and real-world data analytics have expanded the toolkit available for systematic drug repurposing. The following strategies exemplify the diverse methodologies being applied.

3.1 Phenotypic Screening

One of the oldest and most empirically effective approaches is phenotypic screening, by which libraries of drugs that are already approved or under investigation are tested systematically in cell-based, organoid, or animal models for disease-relevant phenotypes. In contrast to target-based methods, phenotypic screening does not entail a mechanistic hypothesis but rather depends on monitoring functional effects. For instance, high-throughput screening of FDA-approved molecules against the Ebola virus revealed compounds like selective estrogen receptor modulators (SERMs) and ion channel blockers with novel antiviral activity. Likewise, phenotypic screens have revealed anticancer repurposing opportunities in oncology, as drugs initially developed to treat infectious or metabolic illnesses showed anti-proliferative activity against cancer cell lines. This unbiased approach is especially useful for difficult or poorly characterized diseases in which defined molecular targets might not be known.

3.2 Target-Based Screening

Target-based screening, by contrast, seeks to find compounds that specifically interact with disease-related proteins or enzymes. High-throughput in vitro binding assays enable the rapid testing of thousands of compounds for binding affinity to a defined target,

making it possible to discover novel drug-target interactions. Computational methods like molecular docking and virtual screening augment this strategy by forecasting interactions between drugs and new binding sites at the structural level. For example, oncology-directed kinase inhibitors have been retrospectively screened against a wide range of kinases involved in inflammation, fibrosis, and neurodegeneration and have shown potential for cross-disease repositioning. This approach offers mechanistic insight, albeit at the need for good quality structural or biochemical knowledge of the target.

3.3 Computational Approaches

Advances in systems biology and computational analysis have made drug repurposing a data-driven science:

Connectivity Mapping (CMap): CMap is a technique that cross-references drug-treated gene expression signatures with disease-specific transcriptomic profiles. Candidates are identified in drugs that are able to reverse pathological expression patterns. CMap has been used to suggest antidepressants and antiepileptics for use in oncology.

Network Pharmacology: By building drug-gene-disease interaction networks, researchers can find common molecular hubs that are points for intervention. This is particularly potent in overlapping pathophysiology diseases, like cancer and inflammation.

Machine Learning: Structural similarity-trained algorithms, side effect clinical data, or omics datasets-trained algorithms can predict new drug–disease associations. For instance, machine learning models have been used to predict repurposing potential for statins in autoimmune diseases.

AI-based Platforms: Future-generation platforms like BenevolentAI, Insilico Medicine, and AlphaFold-powered applications of DeepMind combine big data, protein structure prediction, and clinical results for speeding up repurposing breakthroughs. AI-based pipelines were quickly scaled up during the COVID-19 pandemic to screen host- and virus-targeting drugs to emerge as trial candidates like baricitinib.

Collectively, these computational approaches broaden the vista of repurposing beyond serendipity, allowing systematic and scalable probing of therapeutic space.

3.4 Real-World Evidence

Increased availability of electronic health records (EHRs), standardized insurance claims databases, and retrospective cohort research offers a rich source of real-world data for repurposing. Observational signals have the potential to identify unforeseen benefits or harms of medicines in various populations. Retrospective analyses, for example, showed that patients treated with statins exhibited reduced incidence of cancer and enhanced survival in certain situations, leading to clinical trials exploring their anticancer properties. Likewise, EHR mining has also found correlations between antidiabetic medications (e.g., metformin) and decreased risk of some malignancies. Although these results must be tightly validated, real-world evidence provides an inexpensive, population-level means of generating hypotheses.

3.5 Adaptive Trial Platforms

Final validation of repurposing candidates must occur through prospective clinical testing, and adaptive trial platforms are a new paradigm. In contrast to the traditional trials where a single treatment is tested at a time, adaptive platforms permit the simultaneous or sequential testing of several interventions within a single design. The UK's RECOVERY trial for COVID-19 exemplified this efficiency through the testing of dexamethasone, hydroxychloroquine, lopinavir/ritonavir, azithromycin, and remdesivir within a single trial scheme. This design not only hastens discovery but also facilitates quick decision-making regarding efficacy and futility, thereby making adaptive platforms ideal for emerging infectious diseases and global health crises.

4. Case Studies in Drug Repurposing

The utility of drug repurposing is best described by shining examples where older drugs were given a new lease of life by mechanistic insights or clinical observations.

4.1 Sildenafil (Viagra®)

Initial use: It was originally developed as an anti-anginal and pulmonary hypertension drug.

Repurposed use: Initially licensed for erectile dysfunction; subsequently for pulmonary arterial hypertension (PAH).

Mechanism: Phosphodiesterase-5 inhibition enhances cyclic GMP, causing smooth muscle relaxation and vasodilatation of penile and pulmonary vasculature. This repurposing turned sildenafil into one of the most financially successful repurposed medicines.

4.2 Thalidomide

Initial use: Sold as a sedative and anti-nausea medication in the 1950s, withdrawn following disastrous teratogenicity.

Repurposing use: Rediscovered as an immunomodulator and anti-angiogenic factor; currently a staple in multiple myeloma and employed in erythema nodosum leprosum.

Mechanism: Tumor necrosis factor-α (TNF-α) inhibition, cytokine production modulation, and angiogenesis suppression underlie its therapeutic effects.

4.3 Minoxidil

Original use: Introduced as an oral antihypertensive vasodilator.

Repurposing use: Formulated as a topical solution for alopecia (hair loss).

Mechanism: Activates ATP-sensitive potassium channels in vascular smooth muscle, increasing blood supply to hair follicles and promoting hair growth.

4.4 Metformin

Original indication: Oral first-line treatment for type 2 diabetes mellitus, enhancing glycemic control via decreased hepatic glucose output and increased insulin sensitivity.

Repurposed research: Thoroughly investigated for cancer prevention, polycystic ovary syndrome (PCOS), cardiovascular protection, and age-associated diseases.

Mechanism: Activates AMP-activated protein kinase (AMPK), suppresses mTOR signaling, and induces systemic metabolic reprogramming effects, which can inhibit cancer growth and prolong healthspan.

4.5 Dexamethasone and Remdesivir in COVID-19

Dexamethasone

Original indication: Broad-spectrum corticosteroid in inflammatory and autoimmune disorders.

Repurposed indication: Shown to decrease mortality in hospitalized patients with severe COVID-19 on oxygen or ventilation (RECOVERY trial).

Mechanism: Suppresses cytokine storm and systemic inflammation, preventing acute respiratory distress syndrome (ARDS).

Remdesivir

Original purpose: Created to treat Ebola virus but having limited effectiveness.

Repurposed purpose: One of the initial antivirals to get emergency use authorization for COVID-19.

Action: A nucleoside analog prodrug that impedes viral RNA-dependent RNA polymerase, hence inhibiting SARS-CoV-2 replication.

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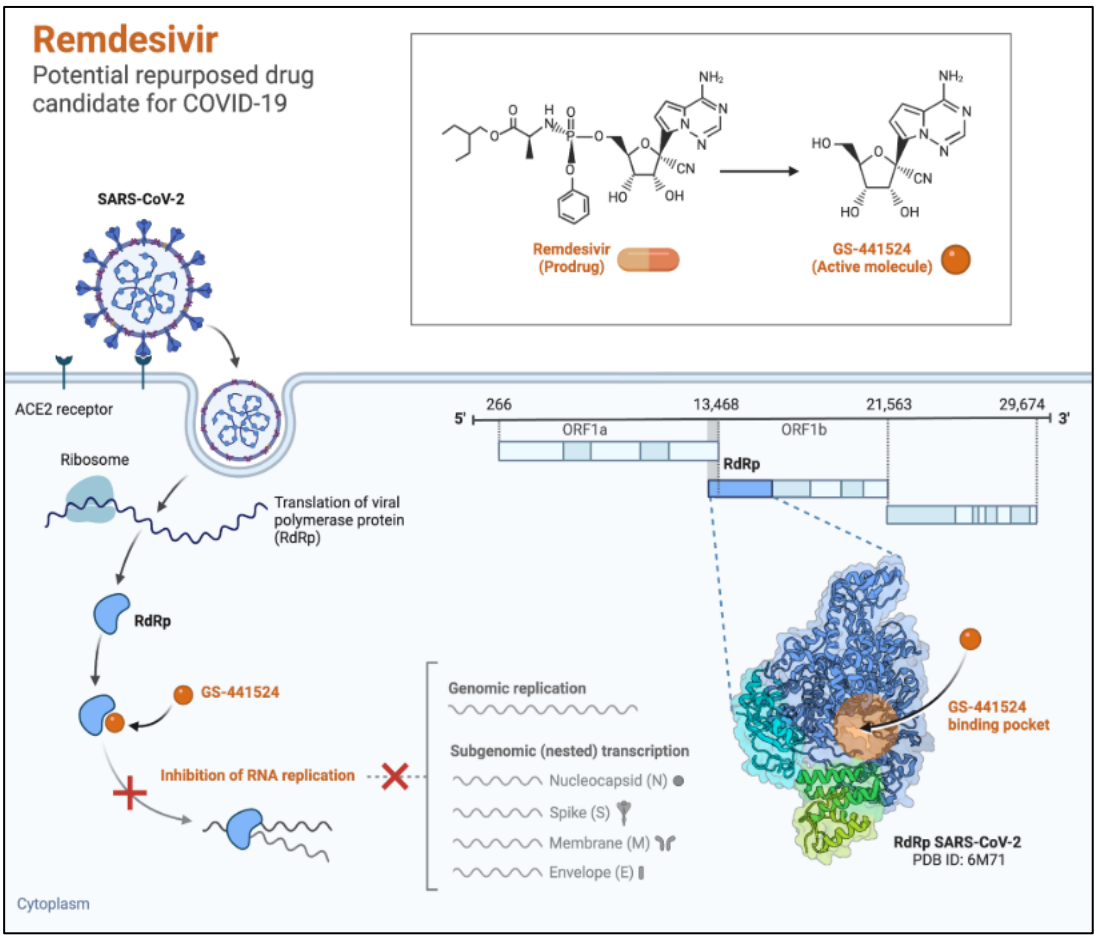

5. Translational Considerations

The journey from identifying a repurposing opportunity to establishing clinical utility is rarely straightforward. Translational hurdles often dictate whether a promising candidate ultimately reaches patients.

Dose Bridging:

The best dose of a drug can differ quite dramatically between the drug's initial and revised indication. For instance, methotrexate is administered in gram doses in oncology but milligram doses in autoimmune disease. Aspirin is also given at high doses in analgesia but low doses in antiplatelet actions. Bridging doses involves detailed pharmacokinetic (PK) and pharmacodynamic (PD) modeling to bridge efficacy without imparting new toxicities.

Biomarkers:

Biomarker development and validation are key to generating proof-of-concept within repurposing. Biomarkers may monitor biological activity (pharmacodynamic markers), forecast clinical outcomes (prognostic markers), or stratify individuals (predictive markers). For instance, decreases in C-reactive protein (CRP) levels are an anti-inflammatory efficacy biomarker, whereas viral load quantification was pivotal in showing antiviral activity during COVID-19 repurposing trials. The use of biomarker-driven endpoints accelerates assessment and decreases trial size.

Patient Subsets

Not every patient will gain equally from an off-target drug. Stratification by genomic, proteomic, or metabolomic profiles makes precision repurposing possible. The best example is treatment with PARP inhibitors in BRCA-mutated cancer, where pre-existing defects in DNA repair make the tumors extremely sensitive. Likewise, subsets of patients with certain inflammatory cytokine signatures may respond preferentially to immunomodulatory drugs.

Safety Re-evaluation:

Repurposing does not eliminate safety issues. Administration of a drug in novel populations, at varied doses, or over prolonged periods will expose underlying toxicities. Thalidomide, for instance, though successful in myeloma, needs tight vigilance for safety because of teratogenicity. Similarly, fluoroquinolones, early on viewed as safe antimicrobials, later became known to carry risks of tendon rupture and neuropathy with prolonged exposure. Safety re-evaluation is hence critical, especially in progression from acute to chronic use or use extension to susceptible populations like children or pregnant women.

6. Regulatory Environment and Challenges

The regulatory environment will play a central function in making drug repurposing feasible and commercially viable. There are mechanisms in place to enable approval, yet challenges remain.

United States (FDA):

The 505(b)(2) process delivers a streamlined course for repurposing with applicants being able to draw partially on current safety and efficacy data, supported by bridging studies. This decreases redundancy and speeds up approval times. The need for new clinical evidence can still pose cost barriers, particularly with off-patent medications.

Europe (EMA):

The European Medicines Agency provides hybrid applications under Directive 2001/83/EC, which similarly allow partial reliance on previously submitted dossiers while requiring new information for the new indication. Although harmonized at the EU level, individual national regulatory agencies may require additional requirements, complicating the process.

Orphan Drug Designation:

Repositioning has had greatest success in orphan diseases because of incentive structures. The US Orphan Drug Act and its EU counterparts offer market exclusivity, waiver of fees, and tax credits. The repositioning of thalidomide in the treatment of multiple myeloma shows that orphan designation can make an economically unappealing drug become a valid treatment.

Intellectual Property (IP) Issues

Off-patent medicines are of huge commercial concern. In the absence of exclusivity, firms might not have financial incentives to sponsor expensive clinical trials. Innovative approaches like new-use patents, reformulation patents, and fixed-dose combinations can stretch IP protection, but these usually offer few revenue opportunities in comparison to innovative medicines. Innovative business models, such as public-private partnerships and philanthropic support, become increasingly vital to overcome these hurdles.

Ethical Considerations

One of the chronic challenges is the balance between off-label prescribing and official regulatory approval. On the one hand, off-label utilization guarantees swift patient access but departs without systematic scrutiny, risking inappropriate use and unequal access. Official approval guarantees uniform dosing, safety surveillance, and payment but takes time and expenditure. The balance of patient necessity and regulatory stringency continues to be a challenge.

7. Opportunities and Future Perspectives

In spite of obstacles, drug repurposing is well-poised to emerge as a keystone of 21st-century therapeutics, supported by technological advancement, precision medicine, and collaborative structures.

AI and Multi-Omics Integration

The intersection of artificial intelligence, machine learning, and multi-omics data sets (genomics, proteomics, metabolomics, and transcriptomics) is revolutionizing repurposing. AI-powered platforms like BenevolentAI and Insilico Medicine are able to forecast drug-disease matches with unprecedented precision. The combination of omics data further allows for the discovery of disease signatures that can be reversed using existing drugs.

Combination Repurposing

Instead of single drugs, repurposed drug combinations provide synergies. This is particularly valuable in oncology and infectious disease, where multi-pathway action can break resistance. For instance, combination of repurposed agents like metformin and immune checkpoint inhibitors is being explored in cancer trials.

Precision Repurposing:

As personalized medicine continues to evolve, repurposing is becoming more and more genomic-guided. PARP inhibitors in BRCA-mutated cancers and ivacaftor in G551D mutation-positive cystic fibrosis are examples of how genetic knowledge facilitates targeted repurposing of therapies. Precision repurposing holds the promise of delivering maximum benefit with a minimum of unnecessary exposure.

Public-Private Partnerships:

Collaborative frameworks are critical to the maintenance of repurposing. Programs such as the NIH National Center for Advancing Translational Sciences (NCATS) and international collaborations have led the way in establishing models wherein academia, industry, regulators, and patient organizations cooperate in investigating repurposing options together. Collaborations share risk, confirm data sharing, and increase access.

Repurposing for Rare Diseases:

Arguably the most revolutionary potential is in rare and orphan diseases, where conventional development is not commercially feasible. Repurposing leverages existing pharmacological information to bring new hope to patient populations otherwise left behind. Examples include drugs like sirolimus (mTOR inhibitor) in lymphangioleiomyomatosis. In the future, drug repurposing will transition from a reactive, serendipitous activity to a proactive, precision-medicine discipline. Through the intersection of advanced computational resources with clinical expertise and regulatory creativity, the discipline can provide cost-effective, safe, and effective treatments beyond the traditional drug discovery models.

Conclusion

Drug repurposing has emerged as a transformative paradigm in modern drug development, offering a pragmatic solution to the rising costs, high attrition rates, and lengthy timelines that plague conventional discovery pipelines. By leveraging the established safety, pharmacokinetic, and pharmacodynamic profiles of existing drugs, repurposing accelerates the translation of therapeutic candidates from bench to bedside. Success stories, ranging from thalidomide in multiple myeloma to sildenafil in pulmonary hypertension, illustrate the profound clinical and societal impact of this strategy. Mechanistic insights remain central to successful repositioning. Advances in systems biology, molecular docking, network pharmacology, and omics-driven approaches have deepened our understanding of drug-disease relationships, enabling rational repurposing. Nonetheless, translation is often complicated by challenges in dose optimization, biomarker development, patient stratification, and safety re-evaluation in new populations. These factors underscore the necessity of rigorous preclinical and clinical validation. Regulatory frameworks in the United States and Europe have introduced streamlined pathways such as the FDA's 505(b)(2) and the EMA's hybrid application, yet barriers remain in terms of intellectual property protection, commercial incentives, and ethical considerations. Off-label prescribing may provide immediate patient benefit but falls short of ensuring consistent safety, efficacy, and equitable access without formal regulatory approval. Looking forward, the integration of artificial intelligence, machine learning, and multi-omics technologies will expand the frontiers of precision repurposing. Collaborative models particularly public private partnerships are essential to overcome financial and infrastructural hurdles, while orphan drug incentives open avenues for addressing unmet needs in rare diseases. Ultimately, drug repurposing is poised to shift from opportunistic discovery toward a deliberate, data-driven discipline that complements traditional pipelines, enhances therapeutic innovation, and ensures more efficient delivery of affordable medicines worldwide.

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