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Review

Drug Repurposing in the Modern Era: Focus on Newly Approved and Investigational Therapeutic Applications

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Abstract

Drug repurposing has emerged as a pivotal strategy in modern therapeutics, offering cost-effective and accelerated pathways to identify new indications for existing drugs. In the post-genomic era, the field has shifted from serendipitous observations to data-driven, mechanism-guided repositioning, leveraging computational intelligence, multi-omics integration, and network pharmacology. Advances in artificial intelligence, machine learning, and CRISPR-based functional genomics have enabled systematic identification of drug–disease interactions, while translational approaches including adaptive clinical trials and biomarker-guided patient stratification ensure rapid validation and clinical applicability. Recent successes, such as the repurposing of remdesivir for COVID-19, ketamine/esketamine for treatment-resistant depression, and colchicine for cardiovascular inflammation, underscore the impact of these strategies. Emerging pipelines targeting oncology, neurodegenerative diseases, and regenerative medicine highlight the potential of repurposing to address unmet medical needs, including rare and orphan diseases. This review synthesizes the current landscape of drug repurposing, emphasizing novel mechanisms, AI-guided discovery, and translational outcomes, and outlines future directions for sustainable, patient-centered innovation in therapeutics.

Keywords: Drug repositioning, AI in drug discovery, Omics integration, Network pharmacology, Translational therapeutics.

1. INTRODUCTION

1.1 The Evolution of Drug Repurposing: From Chance Findings to Algorithmic Precision

Drug repurposing, also referred to as drug repositioning, involves identifying new therapeutic indications for existing or previously approved pharmaceutical agents. Historically, several repurposing discoveries were made through serendipity rather than deliberate design. Classic examples include sildenafil, initially investigated for angina but later repurposed for erectile dysfunction, and thalidomide, transformed from a sedative to a treatment for multiple myeloma and leprosy[1]. Over time, advancements in bioinformatics, high-throughput screening, and systems pharmacology have converted drug repurposing from an observational process into a data-driven scientific strategy[2].

The post-genomic era has accelerated this transformation, enabling researchers to map disease–gene–drug interactions using network biology, machine learning, and artificial intelligence (AI) tools. This paradigm shift allows not only for the prediction of potential therapeutic targets but also for the rational selection of candidates with established safety profiles[3]. Such algorithmic precision has drastically reduced both the cost and duration of drug development, thereby addressing a critical bottleneck in pharmaceutical innovation.

1.2 Current Unmet Medical Needs Driving Repurposing Innovation

Despite remarkable progress in modern drug discovery, numerous diseases remain without effective or affordable therapies. The escalating burden of cancer, neurodegenerative, metabolic, and rare diseases continues to challenge global healthcare systems[4]. Traditional de novo drug development is resource-intensive, often exceeding a decade and costing billions of dollars, with a high attrition rate during clinical trials. Consequently, drug repurposing provides a pragmatic solution by exploiting the pharmacokinetic, pharmacodynamic, and toxicological data of known compounds[5].

Additionally, public health emergencies such as the COVID-19 pandemic have underscored the urgency of rapid therapeutic deployment. Repurposed drugs like remdesivir, dexamethasone, and colchicine demonstrated how pre-existing agents can be adapted to novel conditions within a compressed timeframe[6]. This real-world success has catalyzed global investment in repurposing pipelines, fostering collaboration between academia, industry, and regulatory agencies to accelerate translational outcomes.

1.3 Comparison Between Traditional Repurposing and Precision-Guided Repositioning

Traditional repurposing approaches relied largely on clinical observation, off-label use, or accidental discovery, with limited mechanistic understanding. While effective in some instances, such approaches lacked scalability and reproducibility. In contrast, precision-guided repositioning integrates computational biology, multi-omics analysis, and AI-driven predictions to identify drug–disease relationships based on molecular signatures[7].

This modern framework leverages big data from genomic, proteomic, and transcriptomic studies to uncover previously unrecognized therapeutic opportunities. By combining experimental validation with computational insight, researchers can predict and test hypotheses with far greater efficiency. As a result, precision-guided repurposing not only enhances success rates but also aligns with the broader goals of personalized and precision medicine, where treatment is tailored to the patient's molecular and clinical profile[3].

1.4 Objective and Novelty of This Review

This review aims to provide a comprehensive and forward-looking analysis of drug repurposing in the modern biomedical landscape. Unlike traditional reviews that primarily catalog repurposed agents, this paper emphasizes the convergence of mechanistic insights, artificial intelligence, and translational science in shaping next-generation repositioning strategies. It also highlights recent newly approved and investigational drugs (2018–2025) to illustrate how multi-omics integration and computational precision are revolutionizing therapeutic discovery.

The novelty of this review lies in its systems-oriented perspective, connecting molecular network biology, regulatory frameworks, and AI-driven analytics to propose a roadmap for future repurposing research and clinical translation. Through this approach, it underscores drug repurposing not merely as a shortcut in drug development, but as a strategic pillar of modern pharmacology and global healthcare innovation[2 5 7].

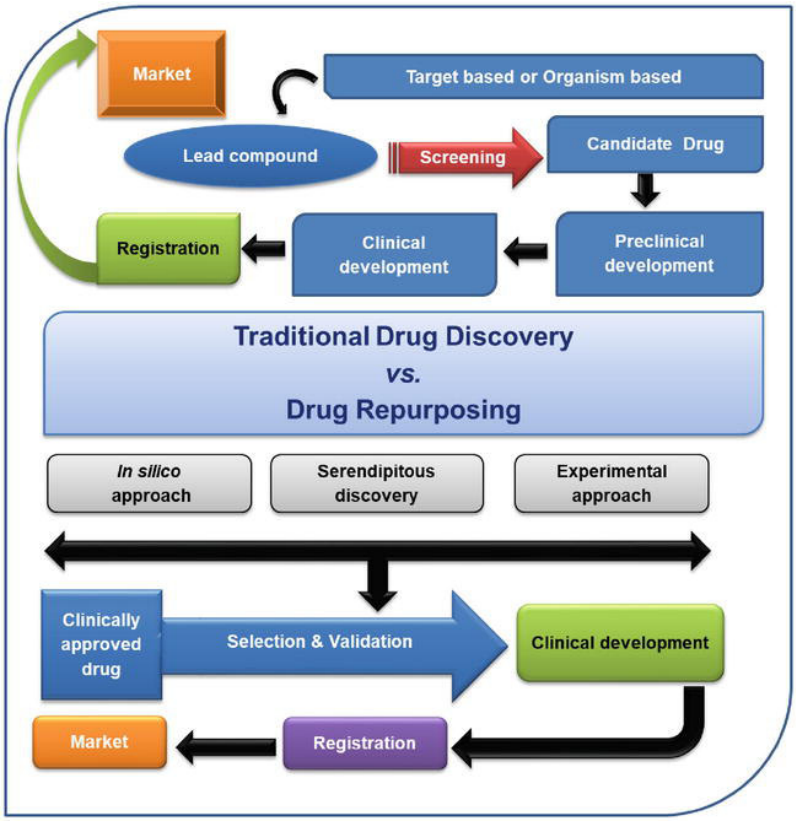

Fig 1: Traditional drug discovery vs. drug repurposing.

2. Rethinking the Paradigm: From Serendipity to Systems Medicine

2.1 Limitations of Traditional De Novo Drug Development

Conventional drug discovery follows a linear and time-intensive pipeline beginning with target identification, progressing through preclinical and clinical evaluation, and culminating in regulatory approval. Despite technological progress, this model remains inefficient and high-risk, with an estimated success rate of less than 10% for molecules entering clinical trials[8]. The average cost of bringing a single new drug to market can exceed USD 2.6 billion, reflecting both research expenditures and the high attrition rates associated with efficacy or safety failures[9].

Furthermore, traditional drug development is hindered by target redundancy, poor translatability of animal models, and unforeseen adverse effects emerging in late-stage trials. These issues contribute to extended timelines often more than a decade from discovery to approval and limit accessibility in low-resource settings[10]. In contrast, drug repurposing leverages existing pharmacological and toxicological data, effectively bypassing early developmental barriers. This efficiency is increasingly vital in an era demanding rapid responses to emerging diseases and evolving clinical challenges[11].

2.2 Emergence of Systems Pharmacology in Redefining Therapeutic Landscapes

The limitations of reductionist approaches have catalyzed the rise of systems pharmacology, a discipline integrating pharmacology with systems biology, computational modeling, and network theory to view the body as a complex, interconnected system rather than a collection of isolated targets[12]. Instead of focusing solely on "one drug–one target–one disease," systems pharmacology investigates multi-target interactions, pathway crosstalk, and feedback loops within cellular and molecular networks.

This integrative perspective has redefined therapeutic discovery by enabling prediction of off-target effects, identifying synergistic drug combinations, and revealing new intervention points for existing molecules. Importantly, systems pharmacology supports the concept of polypharmacology, where drugs exert beneficial effects through modulation of multiple pathways a principle central to successful drug repurposing[13]. Such approaches have led to renewed clinical interest in older agents that influence broad signaling cascades, such as statins, metformin, and nonsteroidal anti-inflammatory drugs (NSAIDs), for conditions beyond their original use.

2.3 The Network Concept: Disease Modules and Drug–Target Interactomes

In the context of systems medicine, diseases are viewed as disruptions within biological networks, where clusters of genes, proteins, or metabolites form distinct disease modules. These modules represent interconnected functional units within the cellular interactome, and therapeutic interventions are most effective when they target key nodes or hubs that regulate disease dynamics[14].

The drug–target interactome a comprehensive map linking drugs to their molecular targets—serves as the foundation for network pharmacology. By overlaying disease modules with drug–target networks, researchers can identify repurposing opportunities based on shared or adjacent nodes. For example, network-based proximity analysis has been employed to predict new indications for cardiovascular drugs in oncology and inflammatory disorders[12]. This approach provides a mechanistic rationale for repositioning, grounded in systems-level connectivity rather than empirical observation.

Computational frameworks now allow the integration of diverse datasets, including protein–protein interactions, signaling pathways, and metabolic flux maps, to predict how perturbing one target influences others within a disease network. This holistic model enhances both the precision and reliability of repurposing predictions, guiding experimental validation with greater efficiency.

2.4 Integration of Multi-Omics Data (Genomics, Proteomics, Transcriptomics, Metabolomics) for Hypothesis Generation

The expansion of multi-omics technologies has provided unprecedented insights into disease mechanisms and drug responses. Integration of genomic, proteomic, transcriptomic, and metabolomic data enables a comprehensive understanding of biological complexity and variability among patients[13]. For instance, genomic profiling can reveal mutations that make certain pathways druggable, while transcriptomic data identify gene expression patterns correlating with drug sensitivity or resistance.

Proteomics further enriches this understanding by quantifying protein–protein interactions and post-translational modifications, while metabolomics elucidates the downstream biochemical changes associated with drug action. When analyzed collectively using computational models, these datasets facilitate hypothesis generation for drug repurposing, allowing identification of drugs that modulate similar molecular signatures across diseases.

Recent advances in machine learning and AI-driven data fusion have made it possible to correlate multi-omics fingerprints of diseases with known drug action profiles, leading to systematic identification of repositioning candidates[14]. This integrative paradigm marks a departure from trial-and-error discovery and ushers in a predictive, systems-level era of drug repurposing, capable of transforming both research and clinical practice.

3. Mechanistic Repurposing: Rediscovering Drugs through Biology

3.1 Molecular Crosstalk and Shared Disease Pathways

Modern repurposing strategies increasingly rely on understanding the molecular convergence among distinct disease entities. Many disorders that appear unrelated clinically often share overlapping pathophysiological networks, such as inflammation, oxidative stress, or mitochondrial dysfunction[15]. For instance, the link between chronic inflammatory signaling and oncogenic transformation has unveiled opportunities to reposition anti-inflammatory and psychotropic drugs for cancer management. Through the analysis of molecular crosstalk, researchers can uncover how existing drugs affect upstream signaling cascades, such as the NF-κB or PI3K–AKT–mTOR pathways, which are implicated in multiple disease phenotypes[16]. This approach enhances the rational identification of secondary drug benefits beyond their original indication.

3.2 Polypharmacology and Multi-Target Drugs

Unlike the traditional “one-drug–one-target” paradigm, polypharmacology emphasizes that a single molecule may exert therapeutic effects via multiple molecular interactions. This concept has reshaped the modern repurposing framework by recognizing that drug promiscuity can be therapeutically beneficial rather than undesirable[17]. Many FDA-approved drugs, such as imatinib and metformin, exhibit multi-target engagement that influences metabolic and signaling pathways relevant to various diseases. Computational modeling and binding affinity profiling now allow the prediction of secondary targets within cellular networks, accelerating hypothesis-driven repositioning efforts[18]. Moreover, the exploitation of polypharmacological profiles is particularly valuable in multifactorial diseases like Alzheimer’s and systemic autoimmune disorders, where modulation of multiple pathways is necessary for efficacy.

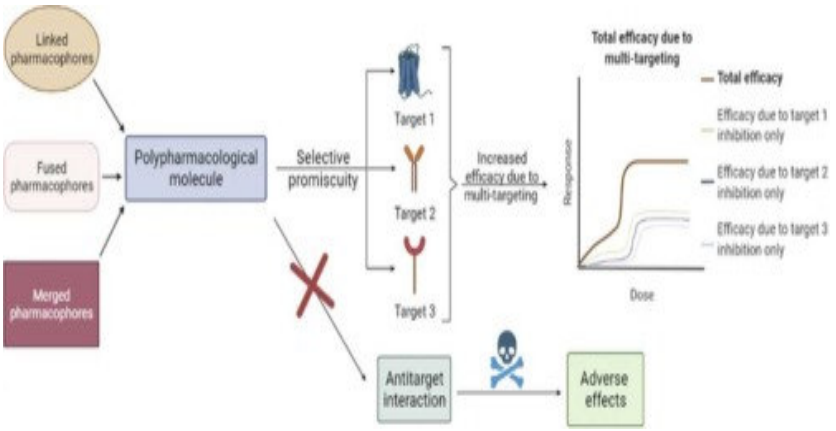

Fig 2: Polypharmacological design showing multi-target efficacy with potential adverse interactions.

3.3 Network-Based Clustering of Disease-Drug Associations

Network pharmacology provides a graph-theoretical framework for mapping the interactions between drugs, targets, and disease modules. By clustering these interactions into functional modules, it becomes possible to visualize therapeutic clusters that reveal unrecognized links between drug action and disease mechanisms[19]. Network-based approaches integrate heterogeneous data sources such as protein–protein interactions, transcriptomic signatures, and clinical phenotypes to identify clusters of compounds with shared mechanistic profiles. These models have successfully predicted novel indications for cardiovascular and neuropsychiatric drugs, validating the role of systems-level connectivity in drug discovery[20].

3.4 Novel Case Studies

3.4.1 Antidepressants Modulating Inflammation in Oncology

Several antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), have demonstrated anti-inflammatory and antiproliferative properties in tumor models[20]. Their ability to modulate cytokine production, induce apoptosis, and interfere with cell cycle regulators supports their repositioning as adjunctive agents in cancer therapy. Fluoxetine, for instance, was observed to inhibit tumor cell viability through the suppression of NF-κB activation and reactive oxygen species regulation in preclinical studies[21].

3.4.2 Statins in Neurodegenerative and Immune Disorders

Beyond their cholesterol-lowering effects, statins modulate key neuroinflammatory and immunological pathways, making them promising candidates in neurodegenerative and autoimmune conditions. Statins exert pleiotropic effects via downregulation of microglial activation, improvement of endothelial nitric oxide bioavailability, and suppression of T-cell proliferation[20]. Clinical trials exploring their role in multiple sclerosis, Alzheimer's disease, and rheumatoid arthritis have demonstrated partial efficacy, highlighting the need for precise dosing and biomarker-guided application[21].

3.4.3 Antiviral Repositioning in Oncology and Autoimmune Diseases

The global focus on antiviral drug development has generated compounds with broad immunomodulatory potential. Agents such as ribavirin and remdesivir have exhibited secondary effects on cell proliferation and immune checkpoint regulation, suggesting oncological and autoimmune applications. Recent in silico and in vitro analyses indicate that viral polymerase inhibitors may interfere with aberrant DNA repair and interferon signaling pathways, presenting novel therapeutic opportunities in malignant and inflammatory diseases[19].

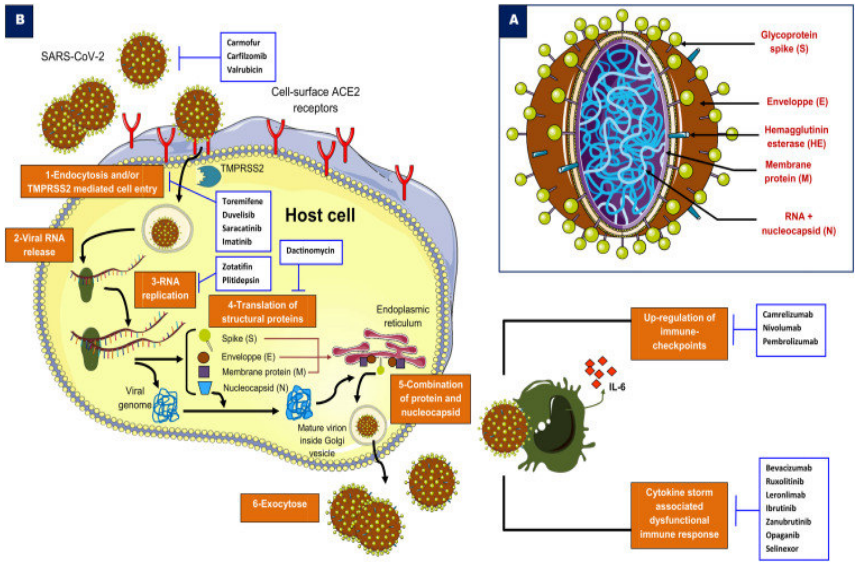

Fig 3: SARS-CoV-2 structure, life cycle, and key therapeutic intervention targets.

4. Artificial Intelligence and Computational Intelligence in Repurposing

4.1 Transition from "Trial and Error" to "Predict and Validate"

The integration of artificial intelligence (AI) has redefined the trajectory of drug repurposing, moving it from the empirical "trial and error" model to a predictive and hypothesis-driven paradigm. Instead of relying solely on chance observations or clinical coincidences, modern AI frameworks employ pattern recognition, molecular similarity analyses, and predictive analytics to generate evidence-based hypotheses[21]. This transition allows researchers to virtually test thousands of compounds against diverse disease signatures, significantly reducing both time and cost associated with experimental screening[22]. The iterative "predict and validate" cycle ensures that computational insights are experimentally corroborated, creating a self-learning ecosystem that enhances accuracy and translational relevance.

4.2 Machine Learning and Deep Learning Models for Drug–Disease Mapping

Machine learning (ML) and deep learning (DL) algorithms have become the core engines of computational repurposing. These systems integrate vast datasets xzsuch as chemical structures, omics profiles, and clinical outcomes to uncover hidden relationships between drugs and diseases. For example, convolutional neural networks (CNNs) and graph convolutional networks (GCNs) can model molecular interactions in multidimensional space, enabling accurate prediction of binding affinities and phenotypic outcomes[23]. Similarly, random forest classifiers and support vector machines (SVMs) are extensively used to prioritize candidate drugs for specific disease clusters based on feature similarity. The integration of multi-modal data, including transcriptomic responses and adverse event profiles, allows these models to simulate biological systems with unprecedented precision[24].

4.3 Knowledge Graphs and Natural Language Processing (NLP) in Literature Mining

Knowledge graphs and natural language processing (NLP) algorithms have revolutionized how information is extracted from biomedical literature. By linking entities such as drugs, targets, pathways, and diseases—AI-driven knowledge graphs can infer novel mechanistic connections overlooked by traditional manual curation[24]. NLP models, particularly those trained on large biomedical corpora (e.g., BioBERT, PubMedBERT), can parse complex scientific narratives, detect semantic associations, and prioritize candidate drugs for repurposing[25]. For instance, mining millions of abstracts enables the identification of shared mechanistic terms (e.g., "inflammation," "oxidative stress," or "angiogenesis") that connect disparate therapeutic areas. These tools thus transform unstructured biomedical knowledge into actionable insights for repositioning.

4.4 AI-Driven Clinical Trial Design and Virtual Screening Platforms

AI is also transforming clinical trial design through adaptive algorithms that predict patient stratification, optimize dosing schedules, and identify potential responders. Virtual screening platforms powered by deep learning can simulate ligand–target interactions at atomic resolution, dramatically improving hit identification rates[25]. Platforms such as DeepChem, AtomNet, and AlphaFold-based models have enabled the evaluation of repurposing candidates in silico, supporting early-stage validation. Furthermore, AI-based trial simulations allow

dynamic adjustment of inclusion criteria and endpoint definitions, thereby reducing attrition rates and enhancing reproducibility[26].

4.5 Validation Challenges and Data Bias Concerns in AI Pipelines

Despite significant promise, the use of AI in drug repurposing faces critical validation and ethical challenges. Model accuracy depends heavily on the quality, diversity, and representativeness of training datasets. Data derived from specific populations or experimental systems may introduce biases that limit generalizability[26]. Moreover, the "black-box" nature of some deep learning models hinders mechanistic interpretability, complicating regulatory acceptance. Addressing these issues requires transparent model architectures, independent validation datasets, and integration with experimental pharmacology to ensure that computational predictions translate effectively into clinical outcomes.

Table 1. Summary of AI-driven approaches in drug repurposing.

Aspect	AI Approach	Key Role	Advantages	Challenges
4.1 Predict and Validate	Predictive modeling, molecular similarity	Shifts from empirical to data-driven discovery	Faster, cost-effective screening	Needs reliable data validation
4.2 ML/DL Models	CNNs, GCNs, SVMs, Random Forests	Map drug–disease relationships	Accurate target prediction	Overfitting, low interpretability
4.3 Knowledge Graphs & NLP	BioBERT, PubMedBERT, graph mining	Extract and link biomedical entities	Finds hidden mechanistic links	Dependent on text quality
4.4 Virtual Screening & Trials	DeepChem, AtomNet, adaptive algorithms	Simulate interactions, optimize trials	Improves hit rates, stratification	Computational and biological limits
4.5 Validation & Bias	Explainable AI, bias correction	Ensure reliability and ethics	Builds regulatory trust	Data bias, lack of transparency

5. Translational and Clinical Repurposing: Bridging the Gap

5.1 Real-World Evidence and Pharmacovigilance Databases as Discovery Tools

The translation of repurposing hypotheses into clinical practice is increasingly supported by real-world evidence (RWE) and pharmacovigilance databases. These large-scale repositories such as the FDA Adverse Event Reporting System (FAERS), VigiBase, and EHR-linked databases enable researchers to identify unexpected therapeutic benefits or adverse effect trends associated with existing drugs[27]. For example, retrospective mining of adverse event data has revealed off-target benefits of antiepileptic and antihypertensive drugs in neurodegenerative disorders. RWE studies also help evaluate dose–response relationships and demographic variations, providing translational insights that guide clinical trial prioritization. This data-driven approach enhances post-marketing surveillance and identifies candidates suitable for rational repositioning rather than empirical trial-and-error screening[28].

5.2 Adaptive Clinical Trial Frameworks for Repurposed Candidates

Conventional randomized controlled trials (RCTs) often fail to capture the dynamic potential of repurposed drugs, especially in emerging diseases or rare conditions. Adaptive clinical trial designs which allow for protocol modifications based on interim results offer a pragmatic pathway for rapid validation of repurposed candidates[28]. Examples include platform trials like the RECOVERY and SOLIDARITY studies, which successfully assessed multiple repurposed therapeutics during the COVID-19 pandemic. Adaptive methodologies employ Bayesian inference models to adjust sample sizes, treatment arms, and endpoints in real time, thus optimizing trial efficiency while maintaining statistical rigor[29]. This flexibility significantly accelerates the translational journey from computational prediction to clinical implementation.

5.3 Regulatory Repositioning: Emerging Global Models (FDA, EMA, CDSCO)

The regulatory landscape for drug repurposing is evolving, with agencies like the U.S. FDA, European Medicines Agency (EMA), and Central Drugs Standard Control Organization (CDSCO) in India formulating frameworks to facilitate the repositioning of approved drugs[30]. The FDA's 505(b)(2) pathway allows developers to reference existing safety and efficacy data, minimizing redundant testing. Similarly, the EMA's Adaptive Pathways and India's New Drugs and Clinical Trials Rules (2019) provide accelerated mechanisms for repurposed candidates addressing unmet medical needs. However, disparities in data exclusivity, labeling, and intellectual property protection remain challenges that necessitate global harmonization. Collaborative regulatory models are

being explored to streamline approval processes for repositioned molecules, particularly for orphan and neglected diseases[30].

5.4 Economic Feasibility and the Rise of "Repurposing Consortia"

Drug repurposing presents a cost-effective alternative to traditional drug discovery, with development timelines often reduced from 10–15 years to less than 5[31]. The growing recognition of its economic potential has led to the formation of public–private partnerships and repurposing consortia, such as the Cures Within Reach, REPO-TRIAL, and Open Targets initiatives. These consortia facilitate data sharing, high-throughput screening, and coordinated regulatory engagement, thus bridging the translational gap between academia and industry. By pooling resources and expertise, they reduce redundancy and enable collective prioritization of high-value repurposing opportunities. Furthermore, the economic sustainability of repurposing is reinforced by reduced attrition rates and favorable cost-to-benefit ratios in late-stage development[31].

5.5 Compassionate Use and Ethical Perspectives in Off-Label Transitions

The ethical dimensions of drug repurposing emerge prominently in off-label and compassionate use contexts. While off-label prescribing can offer early access to promising therapies, it raises issues related to informed consent, liability, and evidence quality[32]. Ethical frameworks emphasize transparent communication of risk–benefit ratios and rigorous post-use monitoring. Compassionate use programs, particularly during pandemics or terminal illnesses, highlight the balance between urgency and scientific validity. Global regulatory agencies are increasingly adopting adaptive ethics models that allow controlled access while ensuring robust data collection for future approval pathways. As drug repurposing becomes more systematized, ethical governance remains integral to maintaining public trust and safeguarding patient welfare[32].

The post-pandemic landscape demands sustainable, preemptive repurposing infrastructures capable of addressing future outbreaks with agility. Key components include integrated global databases, AI-enabled drug libraries, and cross-sectoral coordination between public health agencies and private entities[38]. Establishing permanent consortia to maintain repurposing pipelines ensures that validated molecules remain accessible for rapid redeployment. Ethical frameworks must also balance speed and safety, ensuring that emergency use authorizations are backed by transparent data sharing and adaptive regulation. Additionally, embedding repurposing strategies within One Health and global biosecurity policies could enhance resilience against zoonotic and emerging pathogens. Ultimately, sustainable repurposing demands a synergy of technology, governance, and scientific collaboration, transforming reactive discovery into proactive preparedness[38].

6. Novel Case Compendium: Recently Approved and High-Impact Candidates (2018–2025)

In recent years, drug repurposing has produced several high-impact therapeutic candidates. Thalidomide, historically a sedative, is now approved for multiple myeloma and erythema nodosum leprosum due to its immunomodulatory and anti-angiogenic properties[139]. Remdesivir, originally developed for Ebola, gained approval for COVID-19 by inhibiting viral RNA polymerase[40]. Ketamine and esketamine, previously anesthetics, have been repurposed for treatment-resistant depression through NMDA receptor antagonism, producing rapid antidepressant effects[41]. Cardiovascular repurposing examples include colchicine, which reduces coronary inflammation via NLRP3 inflammasome inhibition[42], and sildenafil, initially developed for angina but now widely used for erectile dysfunction and pulmonary arterial hypertension via PDE5 inhibition[44].

Metabolic and aging-related repositioning includes metformin, which activates AMPK and modulates mTOR/IGF pathways, making it a candidate in oncology, PCOS, and aging-related interventions[43]. Propranolol, a beta-blocker for hypertension and arrhythmia, became a first-line therapy for infantile hemangioma by inducing apoptosis in vascular endothelial cells[45]. Minoxidil, initially an antihypertensive, is now applied topically for androgenetic alopecia through hair follicle K^+ channel activation[46]. Investigational oncology candidates include ribavirin (inhibiting eIF4E-mediated mRNA translation)[47], nelfinavir (inhibiting PI3K/Akt/mTOR signaling)[49], and disulfiram (copper-mediated oxidative stress and proteasome inhibition)[51]. Additionally, statins are being explored in neurodegenerative and immune disorders due to anti-inflammatory and pleiotropic effects[48], and low-dose aspirin is evaluated for chemoprevention in colorectal cancer through antiplatelet and COX inhibition[50].

These examples highlight how repurposing strategies combine mechanistic rationale, computational prediction, and clinical evidence to expand the utility of established drugs across multiple therapeutic domains, accelerating clinical translation while leveraging known safety profiles.

Table 2: Examples of repurposed drugs with new indications, mechanisms, and current status

Drug	Original Indication	New / Investigational Use	Mechanistic Rationale	Status
Thalidomide	Sedative	Multiple myeloma, leprosy	TNF-α modulation, anti-angiogenesis	Approved

Remdesivir	Ebola antiviral	COVID-19	Viral RNA polymerase inhibition	Approved
Ketamine / Esketamine	Anesthetic	Treatment-resistant depression	NMDA receptor antagonism	Approved
Colchicine	Gout	Coronary inflammation	NLRP3 inflammasome inhibition	Investigational
Metformin	Diabetes	Cancer, aging, PCOS	AMPK activation, mTOR modulation	Ongoing trials
Sildenafil	Angina	Erectile dysfunction, PAH	PDE5 inhibition	Approved
Propranolol	Hypertension / arrhythmia	Infantile hemangioma	Endothelial apoptosis via β-blockade	Approved
Minoxidil	Antihypertensive	Hair loss (alopecia)	Hair follicle K^+ channel activation	Approved
Ribavirin	Antiviral	AML / oncology	eIF4E inhibition	Early-phase trials
Statins	Hyperlipidemia	Neurodegenerative / immune disorders	Anti-inflammatory, pleiotropic	Investigational
Nelfinavir	HIV PI	Oncology	PI3K/Akt/mTOR inhibition	Early-phase trials
Aspirin	Analgesic / antiplatelet	Colorectal cancer prevention	Anti-inflammatory, antiplatelet	Investigational
Disulfiram	Alcohol-use disorder	Oncology	Copper-mediated oxidative stress, proteasome inhibition	Early-phase trials

7. The Next Frontier: Repurposing Beyond Conventional Boundaries

7.1 Repurposing in Rare and Orphan Diseases: A Socio-Economic Lifeline

Rare and orphan diseases present a unique therapeutic challenge due to small patient populations, high drug development costs, and limited commercial incentives. Drug repurposing offers a cost-effective and accelerated pathway for these conditions, enabling clinicians and researchers to leverage existing safety and pharmacokinetic data for new indications. For example, several repurposed oncology and metabolic drugs have gained orphan drug designations, offering patients early access to therapies while reducing economic barriers for developers[52]. This strategy not only addresses unmet medical needs but also promotes equitable healthcare access.

7.2 AI + CRISPR Synergy for Target Discovery

The integration of artificial intelligence (AI) with CRISPR-based functional genomics is transforming the discovery of repurposing targets. High-throughput CRISPR screens identify essential disease genes and pathways, while AI algorithms prioritize candidates for repositioning based on predicted efficacy, safety, and network connectivity[53]. This synergy allows for mechanism-driven repurposing, reduces false positives, and accelerates the transition from computational prediction to experimental validation. Early applications have identified novel drug–gene interactions in cancer, metabolic disorders, and viral infections.

7.3 Multi-Omics Biomarkers for Patient Stratification

Modern repurposing increasingly relies on multi-omics profiling (genomics, transcriptomics, proteomics, metabolomics) to stratify patients who are most likely to benefit from existing drugs. By integrating molecular signatures with drug-target databases, researchers can tailor therapies to specific disease subtypes or patient cohorts, enhancing both efficacy and safety[54]. This approach also facilitates adaptive clinical trial designs, enabling the repurposing of agents in genetically defined populations rather than broad, heterogeneous groups.

7.4 Predictive Repurposing in Personalized and Regenerative Medicine

Drug repurposing is poised to play a central role in personalized and regenerative medicine. Computational models now predict cell-type-specific and tissue-specific drug responses, allowing interventions to be tailored at the individual level[55]. In regenerative medicine, repurposed small molecules and biologics are explored for stem cell modulation, tissue repair, and anti-aging applications, offering alternatives to conventional, expensive biologic therapies. These predictive frameworks reduce trial-and-error approaches and enhance translational efficiency.

7.5 Green Repurposing: Sustainability and Environmental Pharmacology

Sustainability considerations are increasingly shaping the repurposing landscape. **Green repurposing** focuses on minimizing environmental impact by utilizing drugs with established manufacturing processes, reducing waste, and promoting eco-friendly pharmacology[56]. Additionally, repurposed drugs with improved metabolic stability or biodegradable formulations contribute to reduced environmental contamination and lower carbon footprints, aligning drug development with global sustainability goals. This emerging paradigm reflects a holistic approach where human health and environmental stewardship intersect.

Collectively, these frontiers underscore a multidimensional evolution of drug repurposing, where technological integration, patient-centric strategies, and sustainability converge to redefine therapeutic innovation[57].

8. Challenges and Future Directions

8.1 Scientific Reproducibility and Validation Gaps

Despite significant advances in drug repurposing, scientific reproducibility remains a major challenge. Many computational predictions and preclinical findings fail to translate into clinical efficacy, often due to heterogeneity in experimental design, insufficient validation, or limited mechanistic understanding[58]. Bridging this gap requires standardized protocols, rigorous cross-validation across multiple datasets, and transparent reporting of negative results. The adoption of integrated in vitro–in silico–in vivo pipelines may enhance reproducibility and facilitate more reliable identification of clinically relevant repurposing candidates.

8.2 Balancing Open Access with Intellectual Property Rights

Drug repurposing often depends on access to existing molecular, clinical, and regulatory data, but open access is frequently limited by intellectual property (IP) protections and commercial interests[59]. Balancing IP rights with the need for rapid innovation is critical, particularly in pandemic scenarios or for rare diseases. Strategies such as time-limited licensing, public-private partnerships, and data-sharing consortia can help align commercial incentives with public health priorities while maintaining innovation pipelines.

8.3 Global Data-Sharing Initiatives and Collaborative Ecosystems

The emergence of global data-sharing platforms and collaborative ecosystems has been instrumental in accelerating drug repurposing. Initiatives like CORD-19, Open Targets, and Project Score enable cross-institutional integration of molecular, clinical, and pharmacological data[60]. Such collaborative infrastructures enhance network pharmacology, AI-driven prediction, and meta-analysis, enabling rapid identification of candidate drugs for diverse indications. However, challenges remain in ensuring data quality, interoperability, and equitable access across countries and institutions.

8.4 The Vision for Next-Generation Repurposing: From Molecules to Mechanisms

The future of repurposing is moving beyond simple molecule-centric approaches toward mechanistic, patient-specific strategies[61]. Integration of systems pharmacology, multi-omics profiling, AI-driven prediction, and CRISPR-based functional validation allows the identification of drug-disease-mechanism triads that can be personalized for individual patients. Additionally, repurposing pipelines are increasingly incorporating predictive toxicology, biomarker-guided stratification, and adaptive clinical trial frameworks, ensuring that candidate drugs are both effective and safe across diverse populations. This vision emphasizes precision, efficiency, and sustainability, transforming repurposing from a supplementary strategy into a cornerstone of modern therapeutics[62],[63].

9. CONCLUSION

Drug repurposing has undergone a remarkable transformation, evolving from a largely serendipitous and reactive practice into a proactive, mechanism-driven science. Initially reliant on chance observations or anecdotal clinical effects, modern repurposing now leverages computational intelligence, multi-omics data, and network pharmacology to systematically identify new indications for existing drugs. The integration of artificial intelligence, machine learning, and deep learning frameworks with systems biology enables precise mapping of drug–disease interactions, accelerating the discovery pipeline while minimizing risk and cost.

Furthermore, translational pharmacology has become central to bridging computational predictions with clinical reality. By incorporating adaptive trial designs, real-world evidence, biomarker-guided patient stratification, and post-marketing surveillance, repurposing efforts can achieve robust clinical validation and ensure patient safety. Emerging paradigms such as repurposing for rare diseases, regenerative medicine, and environmentally sustainable pharmacology highlight the breadth and societal relevance of modern repositioning strategies.

Ultimately, sustaining innovation in drug repurposing requires interdisciplinary frameworks that combine computational modeling, molecular biology, clinical pharmacology, regulatory science, and ethical stewardship. By fostering global collaboration, open-access data sharing, and mechanistic precision, the next generation of repurposed therapies promises to deliver timely, cost-effective, and personalized solutions for a wide spectrum of unmet medical needs, redefining the landscape of modern therapeutics.

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