Drug repositioning: transforming pharmacoscience and biomedical research.

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Introduction

Drug Repositioning—also known as drug repurposing—involves identifying new therapeutic uses for existing approved or investigational agents. This strategy accelerates the drug development process by leveraging established safety profiles, known pharmacokinetics, and existing manufacturing pipelines. In the realms of phamas scine and biomedile, repositioning efforts have yielded impactful treatments for diverse pathologies, from oncology to neurodegenerative disorders. By integrating computational screening, high-throughput assays, and real-world clinical data, researchers can systematically uncover novel indications for established compounds, thereby reducing cost, time, and attrition rates associated with conventional de novo drug discovery. Rationale for Drug Repositioning in Phamas Scine and Biomedile [1].

Traditional drug discovery pipelines often span over a decade and cost upwards of a billion dollars from target validation to market approval. An estimated 90 percent of candidate molecules fail during clinical development—largely due to safety issues or insufficient efficacy. Drug repositioning bypasses early-stage toxicity studies and safety pharmacology, since repositioned agents have already demonstrated acceptable tolerability in humans. Key advantages include: Shortened Development Timelines: Preclinical toxicology, ADME (absorption, distribution, metabolism, excretion), and Phase I trials can often be abbreviated or skipped, given prior human exposure data. Reduced Financial Risk: By building on known compounds, pharmaceutical companies and academic investigators require fewer resources compared to synthesizing novel chemical entities. Expanded Therapeutic Utility: One molecule can address multiple disease pathways—especially valuable in complex, multifactorial conditions such as Alzheimer's disease or autoimmune disorders [2].

Advances in bioinformatics and chemoinformatics underpin modern repositioning pipelines. Principal strategies include: Transcriptomic Connectivity Maps: By comparing gene-expression profiles induced by approved drugs against disease-specific expression signatures, researchers identify compounds capable of reversing pathological gene sets. For example, the Connectivity Map (CMap) database allows high-throughput matching of drug-induced mRNA changes to disease profiles. A notable success involved repositioning topiramate—originally an anticonvulsant to treat alcohol dependency based on shared gene-signature patterns [3].

Proteomic Interaction Networks: Protein–protein interaction (PPI) networks, integrated with drug–target databases, reveal "off-target" effects amenable to therapeutic repurposing. When an approved kinase inhibitor exhibits strong binding affinity to a second protein implicated in fibrotic pathways, it becomes a candidate for repositioning in fibrotic diseases [4].

Chemical Structure–Based Models: Machine-learning algorithms—random forests, support vector machines, and deep neural networks—train on existing drug datasets to predict novel target–ligand interactions. For instance, AI models identified sildenafil's potential as an antitumor agent by recognizing structural features shared with known cyclooxygenase inhibitors. Clinical Data Mining: Natural language processing applied to electronic health records (EHRs) and adverse event reporting systems can reveal unexpected therapeutic benefits or adverse outcomes. A retrospective analysis noted that patients on metformin exhibited lower cancer incidence, prompting multiple clinical trials of metformin as an adjunct therapy in oncology [5].

Polypharmacology Frameworks: Complex diseases often involve multiple pathways. Network pharmacology models map drug–target–disease relationships, identifying existing drugs that simultaneously modulate nodes across a disease network. This has guided the repositioning of drugs like thalidomide—originally developed as a sedative but withdrawn due to teratogenicity—toward multiple myeloma treatment via TNFα and VEGF pathway modulation [6].

Cell-Based Phenotypic Screens: Libraries of FDA-approved drugs (e.g., the Prestwick Chemical Library) are tested against disease-relevant cell lines to measure phenotypic endpoints—cell viability, reporter gene activation, or metabolic shifts. In one study, HTS identified nilotinib (a BCR-ABL kinase inhibitor) as a candidate for treating Parkinson's disease by enhancing autophagic clearance of α-synuclein aggregates. Biochemical Enzyme Assays: When a candidate drug is predicted to inhibit a specific enzyme mutated in a genetic disorder, in vitro enzyme kinetics confirm binding affinity (K_d) and inhibitory potency (IC_{50}), guiding subsequent medicinal chemistry optimization [7].

Rodent Models of Disease: After initial in vitro confirmation, repositioned candidates are evaluated for in vivo efficacy.

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For example, itraconazole—an antifungal with known safety—demonstrated improved survival in a mouse model of non-small cell lung cancer by inhibiting the Hedgehog signaling pathway. Even when a drug is FDA-approved, its PK profile may differ in new indications requiring altered dosing. PK studies in healthy and disease-model animals assess parameters such as C_max, T_max, half-life, and tissue distribution to refine dosing regimens. When repositioning for a rare disease, companies often initiate small, single-arm Phase II studies to demonstrate clinical benefit. For instance, hydroxychloroquine—long used in malaria—was repositioned for systemic lupus erythematosus (SLE) after Phase II data showed reductions in disease flares, leading to widespread off-label use prior to formal approval. Seamless Phase I/II trials leverage Bayesian statistics to adjust dosing cohorts in real time, accelerating timelines for repositioned drugs with strong preclinical rationale [8].

Originally developed as a sedative, thalidomide's severe teratogenicity led to its market withdrawal in the 1960s. Decades later, its anti-angiogenic and immunomodulatory properties prompted investigations in multiple myeloma. Phase II trials revealed significant activity, leading to FDA approval in combination with dexamethasone in 2006. This repositioning underscores the power of revisiting shelved compounds with new mechanistic insights. As a first-line therapy for type 2 diabetes, metformin's impact on AMPK signaling and reduced insulin/IGF-1 levels suggested anticancer potential. Retrospective epidemiological studies associated metformin use with lower cancer incidence, prompting over 80 clinical trials across breast, prostate, and colorectal cancers. Recent Phase III trials explore metformin combined with standard chemotherapy regimens, aiming to harness its metabolic effects in tumor microenvironments [9].

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor initially approved for mantle cell lymphoma, demonstrated unexpected efficacy in B-cell–mediated cGVHD. Early Phase II data showed high overall response rates in steroid-refractory patients; in 2017, the FDA granted accelerated approval for cGVHD—expanding its therapeutic scope beyond hematologic malignancies. Patents for repositioned compounds often have expired or near expiration, reducing exclusivity and diminishing profit margins. To incentivize investment, stakeholders may pursue method-of-use patents or orphan drug designations for rare indications.

Even an established safety profile may not extend to new patient populations. For example, a drug safe in young cancer patients might exhibit unexpected cardiotoxicity in elderly individuals with comorbidities. Rigorous Phase I/II safety assessments remain essential. Agencies like the FDA and EMA offer streamlined "505(b)(2)" and "hybrid" pathways for repositioned drugs. However, demonstrating adequate evidence of efficacy in the new indication—often via randomized trials—can be resource-intensive. Payers may resist covering repositioned drugs if new indication trials are small or lack robust cost-effectiveness data. Clear evidence of clinical benefit and pharmacoeconomic analyses support market uptake.

Combining genomics, transcriptomics, proteomics, and metabolomics from patient cohorts will reveal subtle disease signatures, guiding more rational repositioning. For instance, proteomic profiling of cerebrospinal fluid in Alzheimer's patients may highlight unexpected associations with kinase pathways—suggesting kinase inhibitors as repositioning candidates. Deep learning models trained on heterogeneous datasets (EHRs, omics, chemical libraries) will outperform traditional QSAR approaches, offering higher accuracy in predicting off-target benefits. Cloud-based AI platforms will democratize access for academic researchers with limited computational infrastructure.

Precompetitive collaborations uniting academia, industry, and nonprofit organizations—aim to pool resources, share negative data, and launch coordinated repositioning efforts. Initiatives like the Cures Acceleration Network (CAN) and the Center for Leading Innovation & Collaboration (CLIC) exemplify this trend. Wearable devices and mobile health apps can capture longitudinal patient-reported outcomes, feeding real-time data into pharmacovigilance systems. Such real-world evidence will inform ongoing repositioning studies—identifying off-label benefits earlier than traditional clinical trial endpoints [10].

Conclusion

Drug Repositioning stands as a powerful paradigm in phamas scine and biomedile, enabling the expedited discovery of new therapeutic uses for existing compounds. By leveraging computational modeling, high-throughput screening, and real-world clinical data, researchers can rapidly identify candidates with strong efficacy and safety profiles. While intellectual property challenges and regulatory hurdles persist, innovative funding mechanisms, AI-driven predictive tools, and collaborative networks promise to overcome these barriers. As multidimensional data integration and personalized medicine become mainstream, drug repositioning will continue to play a pivotal role—transforming how we develop treatments and leading to more efficient, cost-effective, and patient-centric healthcare solutions.

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