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Perspective

Drug Repositioning Strategies: A Rational Approach to Accelerate Therapeutic Discovery

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ABOUT THE STUDY

Drug repositioning, also known as drug repurposing, represents a strategic and cost-effective approach to therapeutic discovery by identifying new uses for existing drugs. Unlike de novo drug development, which typically requires more than a decade and billions of dollars in investment, drug repositioning leverages compounds with established safety profiles, expediting their path to clinical application. This paradigm has gained significant traction in recent years due to its potential to rapidly deliver treatments for both common and rare diseases, especially in scenarios where urgent therapeutic needs arise, such as global pandemics or emerging diseases. The COVID-19 pandemic notably highlighted the importance of this approach, with drugs like remdesivir and dexamethasone being evaluated and deployed swiftly based on existing clinical data.

The fundamental advantage of drug repositioning lies in its ability to bypass the early and most resource-intensive phases of drug development, including discovery, preclinical toxicity testing, and early pharmacokinetics studies. Since repurposed drugs have often already undergone extensive animal and human testing, they enter clinical trials with well-documented safety and dosing information, which reduces the risk of failure and accelerates the regulatory approval process. This makes drug repositioning particularly attractive for low-resource healthcare systems and for treating diseases that are not traditionally prioritized by the pharmaceutical industry, such as neglected tropical diseases or rare genetic disorders.

The success of drug repositioning is underpinned by a rational approach that combines computational modeling, data mining, and systems biology. One widely used strategy involves analyzing gene expression profiles to match drugs with diseases exhibiting similar molecular signatures. This "signature reversion" approach assumes that a drug capable of reversing the gene expression pattern of a disease may have therapeutic potential. Tools such as the Connectivity Map (CMap) have enabled researchers to match disease states with compounds capable of counteracting them. Similarly, network pharmacology approaches map out the complex interactions between drugs, targets, and disease pathways to identify potential repositioning opportunities.

In addition to bioinformatics-driven methods, phenotypic screening plays a pivotal role in uncovering new uses for approved drugs. High-throughput screening of drug libraries against disease-relevant models can identify compounds that produce desired therapeutic effects, even if their mechanisms of action are not fully understood. This empirical approach complements target-based strategies, especially in complex diseases like cancer or neurodegenerative disorders, where multiple pathways may be involved. Moreover, the integration of artificial intelligence and machine learning is revolutionizing drug repositioning by analyzing vast biomedical datasets to detect patterns and predict drug-disease associations with greater accuracy and speed.

A notable example of successful drug repositioning is sildenafil, originally developed for hypertension and angina, but later approved for erectile dysfunction and pulmonary arterial hypertension. Similarly, thalidomide, once withdrawn for its teratogenic effects, was repositioned as a treatment for multiple myeloma and leprosy. These examples illustrate how even drugs with controversial histories can be reevaluated and adapted for new therapeutic contexts when supported by robust scientific evidence. Another promising case includes metformin, a decades-old antidiabetic drug currently under investigation for its anticancer and anti-aging properties, driven by its effects on cellular metabolism and the AMPK pathway.

Despite its advantages, drug repositioning is not without challenges. Intellectual property concerns can limit commercial incentives, as many repurposed drugs are off-patent and may not offer exclusivity to pharmaceutical companies. Furthermore, the mechanistic basis for a drug's effect in a new indication is not always clear, which can complicate regulatory approval and clinical adoption. In some cases, altered dosing regimens or new delivery methods may be necessary, requiring further development and testing. Nevertheless, collaborative efforts among academia, government, and industry are beginning to overcome these barriers through public-private partnerships, open-access drug libraries, and innovative licensing models.

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Drug repositioning also holds significant promise in precision medicine, where patient stratification based on genetic or molecular profiles can help identify those most likely to benefit from a repurposed therapy. By matching specific biomarkers or pathway signatures with known drug actions, clinicians can personalize treatments more effectively. This approach is especially relevant in oncology, where molecular heterogeneity often limits the efficacy of one-size-fits-all treatments. As genomic databases and patient registries continue to grow, they will provide an increasingly rich resource for guiding repositioning efforts with greater precision and impact.

In conclusion, drug repositioning is a powerful and pragmatic strategy that capitalizes on existing pharmacological knowledge to accelerate the discovery and development of new therapies. It offers a more efficient route to clinical benefit, particularly when guided by molecular insights and supported by computational tools. As biomedical research continues to advance, drug repositioning will likely remain a cornerstone of innovation in pharmaceutical development, especially for complex and urgent medical challenges.