

Medicinal Chemistry Approaches to Drug Repurposing for the Treatment of Rare Genetic Diseases

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Introduction

Rare genetic diseases are often associated with significant morbidity and mortality and they typically present considerable challenges for both diagnosis and treatment. These conditions, which affect a relatively small number of individuals, are generally caused by mutations in a single gene that disrupts normal biological processes. While each rare genetic disease is unique, many share common challenges, such as the limited availability of effective therapies and the complexity of finding treatments that can address the underlying genetic causes. Traditional drug discovery for rare diseases can be time-consuming, costly and labor-intensive, often requiring the development of entirely new therapeutic agents. However, drug repurposing finding new uses for existing drugs has emerged as a promising strategy for tackling rare genetic diseases more efficiently and rapidly. By repurposing drugs that have already been approved for other indications, medicinal chemists can bypass many of the early-stage drug discovery hurdles, such as safety testing and toxicity evaluations, thereby accelerating the time to market for rare disease treatments. Drug repurposing offers several key advantages over the development of novel drugs for rare genetic diseases. First, repurposed drugs have already undergone significant clinical testing, so their safety profiles are well-established, reducing the risk of unforeseen adverse effects. Additionally, repurposed drugs are often already formulated for oral administration, which simplifies the development process and improves patient compliance [1].

Description

The repurposing of existing drugs for rare genetic diseases is increasingly facilitated by advances in genomics, High-Throughput Screening (HTS) and computational techniques. Whole-genome sequencing and other genomic tools have allowed researchers to identify specific genetic mutations that drive rare diseases, opening the door to targeted drug repurposing efforts. By understanding the genetic underpinnings of these conditions, medicinal chemists can more precisely identify drugs that are already known to interact with the pathways or proteins involved in disease mechanisms. High-throughput screening of drug libraries against disease models can also quickly identify candidate compounds that might be repurposed for treating rare genetic diseases. These approaches are rapidly becoming integral components of drug repurposing strategies, enabling the efficient identification of novel therapies for rare genetic conditions. One of the primary challenges in drug repurposing for rare genetic diseases is the need for drugs to reach the site of action in sufficient concentrations and with the proper pharmacokinetic and pharmacodynamic properties. As such, medicinal chemists play a critical role in optimizing these repurposed compounds to better suit the needs of patients with rare genetic diseases. Chemical modifications to improve the drug's

solubility, stability and bioavailability, as well as the use of drug delivery systems (e.g., nanoparticles, liposomes, or prodrugs), are important strategies to enhance the therapeutic potential of repurposed drugs. Furthermore, efforts to optimize the drug's specificity and reduce off-target effects are crucial to ensuring that repurposed drugs achieve maximal efficacy while minimizing toxicity [2].

In some cases, the repurposing of existing drugs for rare genetic diseases requires the development of combination therapies. Since rare genetic diseases often involve complex molecular pathways, single-drug treatments may not be sufficient to address all aspects of the disease. By combining repurposed drugs with other existing therapies or novel agents, medicinal chemists can create more effective treatment regimens that target multiple disease pathways simultaneously. For example, combination therapies might include a repurposed drug that modulates a specific mutated protein in conjunction with another compound that corrects downstream cellular dysfunction. Drug combinations can also help overcome drug resistance, a common issue in the treatment of many diseases, by targeting different mechanisms of action. Cystic fibrosis, caused by mutations in the CFTR gene, leads to severe pulmonary and digestive problems due to defective chloride ion transport across epithelial membranes. Research revealed that Ertugliflozin could help reduce the harmful effects of CFTR mutations by improving the function of the CFTR protein. Through this repurposing approach, the drug has shown potential in managing CF symptoms and improving the quality of life for patients. Such examples of successful repurposing underscore the potential of this approach to address rare genetic diseases with existing therapeutic agents [3].

Drug repurposing has also proven to be invaluable in the development of therapies for diseases caused by mitochondrial dysfunction, which are a group of rare genetic disorders that affect cellular energy production. Drugs such as EPI-743 (a repurposed drug) have been explored for their potential to modulate mitochondrial activity, protect against oxidative stress and improve overall cellular function in conditions like Leber's Hereditary Optic Neuropathy (LHON). This approach offers hope for diseases that have limited therapeutic options and it highlights the importance of medicinal chemistry in repurposing existing compounds for new indications. The concept of drug repurposing holds tremendous promise for the treatment of rare genetic diseases, providing a faster, cost-effective alternative to the traditional drug development pipeline. By leveraging the wealth of information already available on approved drugs, medicinal chemists can identify novel therapeutic applications that were previously unexplored. In addition to genomic and computational advancements, the role of regulatory agencies in facilitating the repurposing process is critical. Streamlined regulatory pathways for repurposed drugs can expedite their approval for rare diseases, ensuring that patients benefit from new therapies more quickly [3].

In addition to the advantages of repurposing existing drugs for rare genetic diseases, the increasing availability of patient-reported data and real-world evidence is providing invaluable insights that can guide drug repurposing efforts. Patient registries, healthcare databases and patient advocacy groups are playing a crucial role in generating real-world data on the progression of rare diseases, as well as the outcomes of existing treatments. This data can help identify previously overlooked therapeutic opportunities and guide researchers in selecting the most promising drug candidates for repurposing. The integration of AI and Machine Learning (ML) technologies into drug

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repurposing efforts is also poised to accelerate the discovery of new therapies for rare genetic diseases. Machine learning algorithms can analyze vast datasets, including molecular profiles, patient demographics and clinical outcomes, to predict which existing drugs might be effective for specific rare diseases. These models can uncover hidden patterns in the data that may not be immediately obvious, enabling researchers to identify drug candidates with a higher likelihood of success. By combining traditional medicinal chemistry approaches with advanced AI and ML techniques, the process of drug repurposing can be made more efficient, precise and tailored to the unique needs of rare disease patients [4].

Moreover, the regulatory landscape for drug repurposing is evolving in response to the growing recognition of its potential to address unmet medical needs. Regulatory agencies, such as the US Food and Drug Administration (FDA), have established pathways like the Orphan Drug Designation to incentivize the development of therapies for rare diseases, including repurposed drugs. The FDA's 21st Century Cures Act and similar regulatory frameworks in other countries have further streamlined the approval process for drugs with new indications, including repurposed drugs for rare diseases. These regulatory incentives, coupled with the increasing support from governmental and non-governmental organizations, are likely to continue to drive innovation in drug repurposing. By providing financial incentives and expedited review processes, regulatory agencies are helping to overcome some of the challenges associated with developing treatments for rare genetic conditions, ultimately accelerating the delivery of life-saving therapies to patients [5].

Conclusion

In conclusion, medicinal chemistry approaches to drug repurposing offer significant advantages for the treatment of rare genetic diseases, which often lack effective therapies due to the challenges associated with traditional drug discovery. By optimizing existing drugs, understanding disease mechanisms at the molecular level and utilizing computational tools, researchers are uncovering new uses for drugs that can improve the quality of life for patients with rare genetic conditions. Although challenges remain in terms of pharmacokinetic optimization, drug delivery and combination therapy design, drug repurposing represents an exciting and efficient strategy to meet the unmet medical needs of individuals with rare genetic diseases. Through continued research and collaboration, repurposed drugs may become pivotal in transforming the treatment landscape for these often-overlooked conditions, offering hope and therapeutic options to patients worldwide.

Acknowledgment

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Conflict of Interest

None.

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