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Drug Repurposing for Orphan Disease

Author(s): [1]Hemant Kumar, [2]Hema Rani, [2]Ruhit Ashraf*

[1]B Pharm (Student), S. Lal Singh Memorial College of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab, India
[2]Associate Professor, S. Lal Singh Memorial College of Pharmacy, Desh Bhagat University, Mandi Gobindgarh Punjab, India

Corresponding Author*
Mr. Ruhit Ashraf
Associate Professor
Orcid id: - 0000-0001-6697-0761
Email: ruwaidashraf1819@gmail.com

Abstract

There are a great need and opportunity to find treatments for orphan or rare diseases. Of the roughly 6000 orphan diseases, some have little commercial prospects and/or low prevalence. Many chemicals have the potential to be reprofiled in a new indication, even if only a small number of compounds have been licensed for new indications in the field of metabolic diseases. In general, there are three categories into which reprofiled medications for metabolic diseases can be divided. Drug repurposing is the term used to describe the current change in focus to alternative uses for costly new medications. The discovery of novel therapeutic uses for already available or experimental medications is known as drug repurposing or reprofiling. Numerous potentially fatal illnesses, including some types of cancer, neurological problems, immunological disorders, and rare infectious diseases, may benefit from this idea and innovative treatment methods. Numerous potentially fatal illnesses, including some types of cancer, neurological problems, immunological disorders, and rare infectious diseases, may benefit from this idea and innovative treatment methods.

Keywords: Repurposing Orphan drugs, reprofiling, neurodegenerative

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Introduction

Drug repurposing is a tactic that uses compounds that have been given a marketing authorization (MA) for particular therapeutic indications and, as a result, have a safety profile that is well-known to scientific and regulatory communities. Because it involves finding a new clinical use for pharmacological ingredients, the conventional drug discovery process is accelerated in this instance. This strategy offers the benefit of reducing the expenses needed for preclinical research and phase I and II clinical trials, while other expenses, such as regulatory and phase III clinical trials, typically stay on pace with those of new pharmaceuticals.[1] Orphan diseases are uncommon illnesses that only a tiny percentage of people have. They are referred regarded as "orphan" diseases since researchers and pharmaceutical companies frequently overlook them because their revenue is insufficient to cover the expense of creating treatment plans. An estimated 350 million people worldwide are afflicted by more than 7,000 orphan illnesses. Between 6,000 and 8,000 uncommon disorders have been found thus far, with 80% of them being brought on by mutations in many genes. [2]. To present, about 7000 RIDs have been found, impacting an estimated 300 million people globally. These illnesses can significantly lower a patient's quality of life and result in potentially fatal situations throughout their lifetime. New medications are created and marketed for RIDs far more slowly than for diseases that afflict a large number of people, despite the fact that there are significant unmet medical needs.[3]. It has been suggested that the pharmacology of many substances is likely to change for a new indication that involves a different target, tissue, or dosage schedule. One Repurposing cellular assays, such as phenotypic and through-put screening assays, are often susceptible to undesired bioactivity mechanisms or assay interference.[4].

Drug repurposing in rare diseases

Repurposing drugs could be especially appealing for the creation of uncommon disease remedies.There are about 350 million people affected by nearly 8000 uncommon diseases worldwide. However, just 5 percent obtain a particular licensed or authorized treatment. In July 2017, there were only 112 orphan medications on the European market, with over half of these being for rare cancer conditions, while over 450 are currently being developed. [5].

Significance of drug repurposing

A new medication must adhere to strict standards in order to be released onto the market. Because of the various physicochemical characteristics of the chemical entities and the difficulty of scaling up production, it takes a substantial investment to identify a medicine and subsequently develop it.[6].

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Challenges for drug repurposing

Drug repurposing has been more popular recently; however fewer applications exist than anticipated because of a number of implementation-related issues. Future start-ups have a difficult time supplying regulatory agencies with pertinent information because there are no strict regulations around the repurposing of medicinal prospects. Furthermore, the Orphan Drug Act and patent exclusivity may be ostensibly applicable to the use of a repurposed medication for a novel purpose. [7]

Table1: Challenges and Regulatory Issues in Drug Repurposing

Aspect	Description	Impact on Drug Repurposing	References
Rising Popularity	Drug repurposing has gained significant attention in recent years due to its cost-effectiveness and reduced development time.	Encourages research and innovation, but expectations exceed actual implementation.	[8]
Limited Applications	Despite popularity, the number of successfully repurposed drugs is lower than anticipated.	Indicates practical and translational challenges in real-world application.	[9]
Regulatory Challenges	Lack of well-defined and strict regulatory guidelines for repurposed drugs.	Creates uncertainty and delays in approval processes.	[10]
Data Submission Issues	Start-ups face difficulty in providing adequate and relevant data to regulatory agencies.	Hinders drug approval and commercialization.	[11]
Orphan Drug Act	May apply to repurposed drugs targeting rare diseases.	Provides incentives like market exclusivity but applicability can be complex.	[12]
Patent & Exclusivity Issues	Existing patents and exclusivity rights may or may not extend to new indications.	Creates legal ambiguity and discourages investment.	[13]

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Nitishnone for Alkaptonuria

A pioneering physician from Oxford, Professor Sir Archibald Gerrard, coined the term "alkaptonuria" to describe inherited metabolic diseases. He linked the simple observation of dark urine in patients who presented with skin pigmentation and chronic knee pain (ochronosis) to a lack of an enzyme required for the breakdown of homogentisic acid. This rare illness is closely linked to disorders of tyrosine and phenylalanine metabolism.[Figure 1] [14].

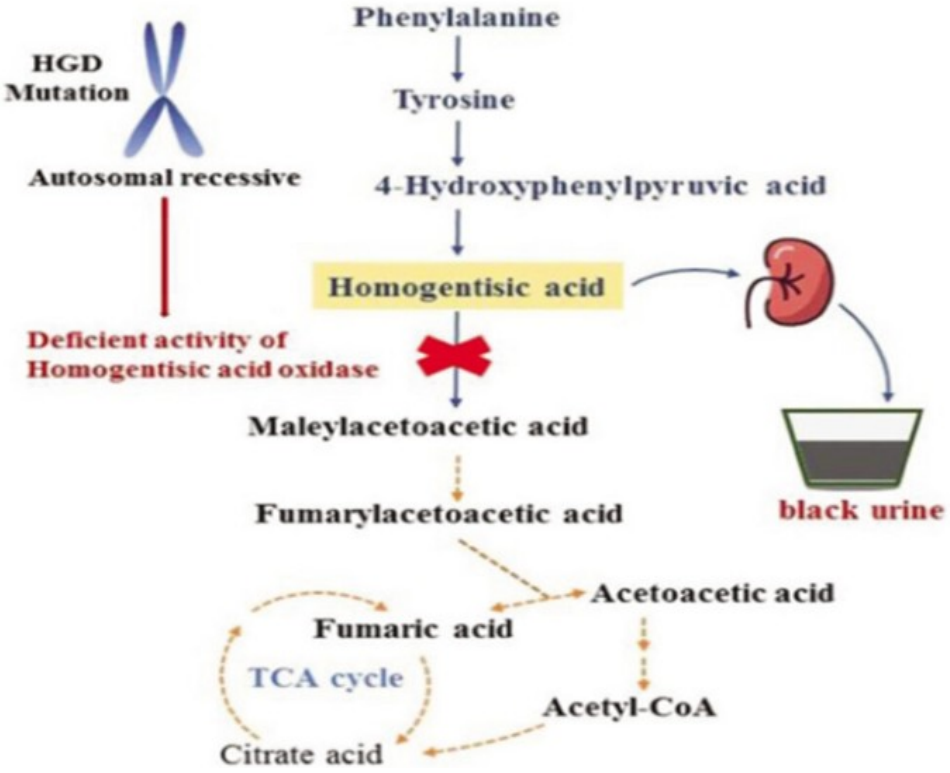

Figure 1: Deficient activity of homogentisic acid oxidase (HGD) in alkaptonuria

A novel medication called nitisinone, a well-known herbicide, has been approved to treat tyrosinemia type 1. Later, this medication was used to treat alkaptonuria. Clinical trials in the United States, however, failed. Nitisinone was later licensed for the treatment of alkaptonuria after a sizable worldwide clinical trial was carried out by the UK-based Alkaptonuria Society and produced encouraging results [15].

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mTOR Inhibitor (Everolimus) for Tuberous Sclerosis

Numerous clinically diverse rare illnesses, such as cancer familial syndromes, are linked to a variety of distinct protein kinase (PK) molecules. The majority of PKs participate in several signaling pathways that are linked to cell division, autophagy, and apoptosis. The final endpoint of the mTOR (mammalian target of rapamycin) signaling pathway receptors (mTORC1 and mTORC2) is intimately related to the molecular mechanisms of various PKs [Figure 2]. The mTOR signaling pathway is well supported by the data. linked to a number of common and complex disorders, including osteoporosis, insulin resistance, cancer, and arthritis [16]. The hunt for mTOR inhibitors for anti-tumor therapy has been the subject of numerous clinical investigations. Clinical trials using the recently identified mTOR inhibitors sirolimus and everolimus have demonstrated impressive advantages in the treatment of tuberous sclerosis complex (TSC0) (Figure 2) [17].

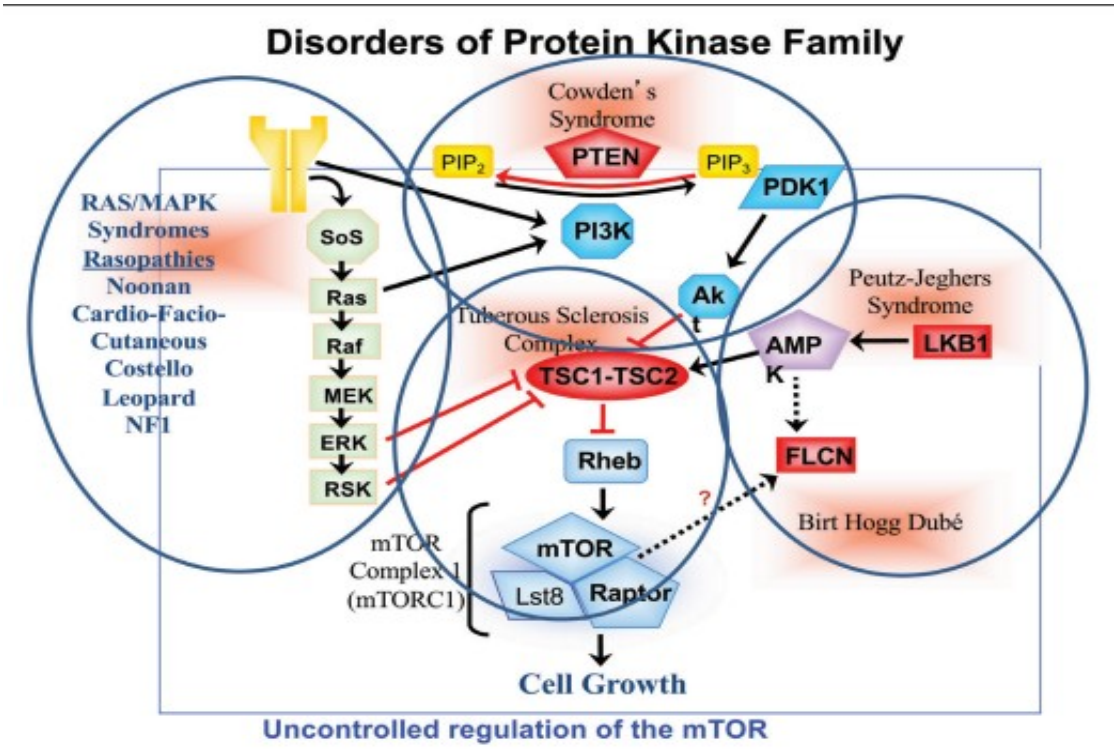

Figure 2: RAS/MAPK/mTOR signaling pathway

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DRUG REPURPOSING FOR RARE NEURODEGENERATIVE DISEASES

Huntington's disease Clinical Signs and Genetic Origin in the Caucasian population, the frequency of Huntington's disease (HD), the most prevalent uncommon neurological illness, is believed to be between 1/20,000 and 1/10,000. George Huntington made the discovery in 1872. A trio of motor, cognitive, and mental symptoms define the illness (Ghosh and Tabrizi, 2018). Involuntary choreatic movements, stiffness, and dystonia are examples of motor characteristics; behavioral and mental illnesses include depression, anxiety, apathy, irritability aggression, and dementia among others [18]. The clinical manifestations usually appear during the third decade of life and become fatal after 15–20 years due to progressive neuronal dysfunction and ultimate neuronal death (Ghosh and Tabrizi, 2018). The diagnosis of this disease is usually performed by molecular genetic testing followed by computerized tomography scanning, magnetic resonance imaging (MRI), and electroencephalography. HD is an autosomal dominant disorder caused by an unstable.fig.3 [19].

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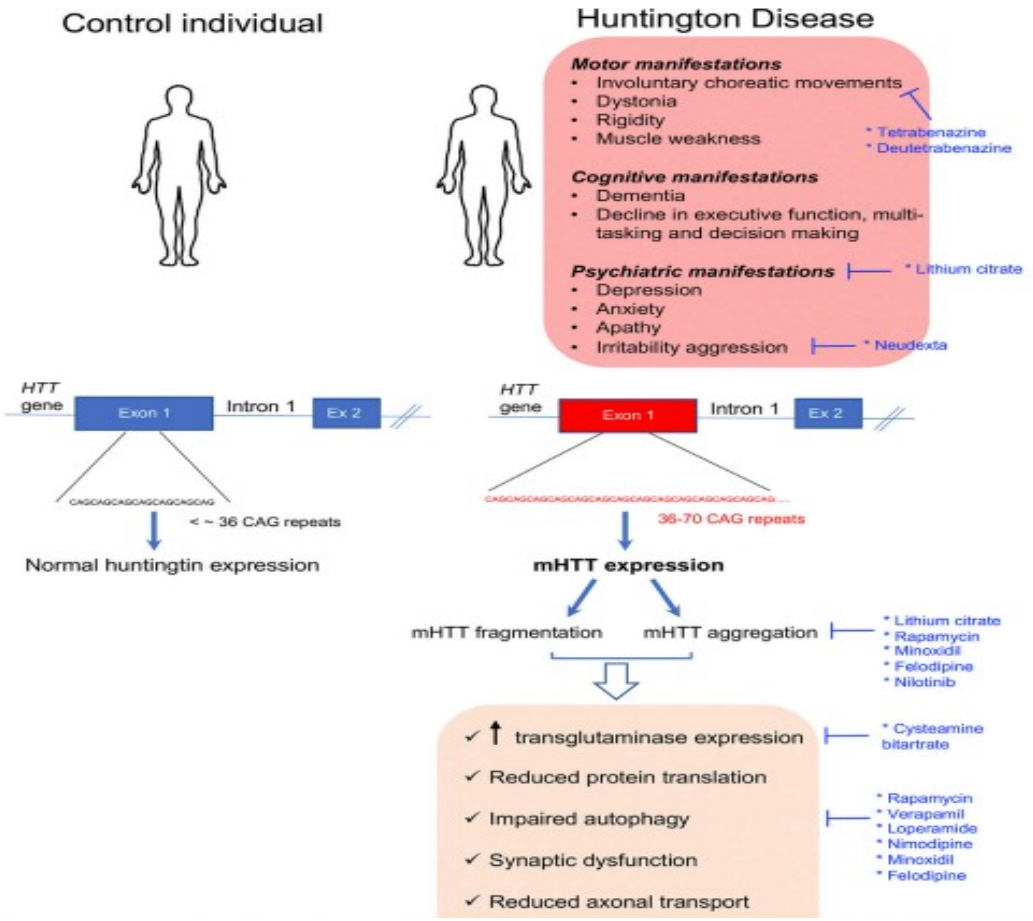

FIGURE 3 | Clinical manifestations and molecular disease mechanisms in Friedreich's ataxia. This pathology is caused by GAA repeat expansions in the first intron of the FXN gene. This results in reduced frataxin protein expression which causes a wide variety of cellular alterations leading to cell dysfunction and death. Repurposed drugs with and without orphan designation for Friedreich's ataxia are highlighted in blue along with the cellular dysfunctions or clinical manifestations that they tackle. Ex: exon

Machine Learning and Artificial Intelligence for Drug Repurposing

The breadth and applications of machine learning (ML) and artificial intelligence (AI) are covered in a number of recent publications on pharmacological repurposing or repositioning.[20] Using cutting-edge computational techniques like machine learning and artificial intelligence (ML) has made it easier for researchers to sift through massive databases, spot trends, and create fictitious medication repurposing models. For choosing particular targets, the drug in question, and disease phenotypes, the traditional in silico methods are most widely used.[21] In essence, there are three

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basic methods: matrix factorization, molecular target categorization, and the network(s). Methodology specifics are outside the purview of this piece. The KUALA framework, which enables the identification of kinase active ligands and the prioritization of multi-target compounds for therapeutic repurposing, is by far the greatest example. In over 80% of cases, the KUALA project uses 12 distinct machine learning techniques for classification in order to assign closely related kinase inhibitors in clinical trials. medication repurposing research for medication repositioning on similar targets has widely accepted this strategy. [22]

Conclusions

Without a doubt, the best strategy to maximize the effectiveness and efficiency of costly new medications in the treatment of rare diseases is through pharmacological repurposing or repositioning. Compared to the initial licensing agreement, very few medications are currently approved for new or different indications. However, a number of obstacles stand in the way of this significant endeavor reaching its intended objectives. The availability and utilization of compound databases, multi-partner partnerships, and the required financial incentives are all urgently needed. It goes without saying that the treatment of uncommon diseases in LMICs with fewer resources would be greatly impacted by the economical and effective repurposing of current medications.

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