REVOLUTIONIZING MEDICINE: EXPLORING THE REMARKABLE ADVANCEMENTS IN DRUG REPURPOSING

Sonal Sharma[1], Sonia Dhiman[2*], Teenu Sharma[3]

Abstract

The traditional drug discovery and development process encompasses multiple stages to discover new drugs and obtain marketing approval. It is crucial to explore innovative approaches that can reduce the time required for drug discovery. Drug repurposing involves investigating alternative medical uses for existing drugs, including those that have already been approved, discontinued, shelved, or are still under investigation. This strategy is increasingly being employed to discover novel medications, leveraging previous investments while minimizing risks associated with clinical activities. Repurposing can occur serendipitously, through unintentional fortunate observations or systematic approaches. This article explores numerous strategies for discovering new indications for FDA-approved drugs. The appeal of this approach lies in addressing significant gaps in the drug-target interaction matrix and leveraging safety and efficacy data accumulated during clinical studies. The development of experimental drugs is a time-consuming and expensive process that is limited to a relatively small number of targets. In contrast, drug repurposing takes advantage of existing safety, pharmacokinetic, and manufacturing data, enabling the expedited development of innovative medications. This approach has gained particular interest in the fields of rare and neglected conditions. Recent advancements in drug repurposing have led to the emergence of novel treatments, and this overview highlights these developments. The review examines recent efforts to identify new medical uses for existing drugs and delves into the challenges, opportunities, and success stories associated with drug repurposing. Furthermore, it provides insights into recent applications and regulatory approaches in this field.

Keywords: Advancements, Drug Repurposing, New Trends, Regulatory Perspective, Strategies,

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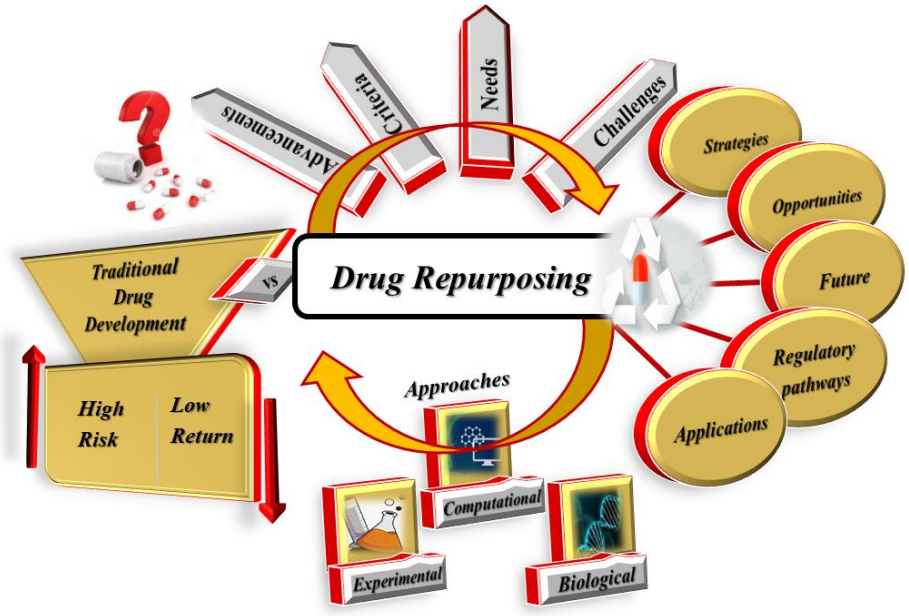

Figure 1. Graphical Abstract

Introduction

The procedure of recognizing, developing, and commercializing a present therapeutic drug for one new disease sign is called drug repurposing (DR). It is the use of previously permitted drugs and composites to treat a diverse disease. Re-evaluating currently available medications that were rejected for a new therapeutic use is recognized as drug repositioning. Some other terms like "Drug reformulating" are same as drug repurposing. Drug reprofiling provides a lowered risk and cost of drug development while benefiting from the fact that the drug has previously undertaken preclinical and clinical tests [1] [2]. "Drug reformulating" refers to the process of modifying a preparation to permit a drug to enter the market. The benefit of DR is that it is low-cost, riskless, and highly efficient. The procedure to approve a novel drug is costly and might take a long time. These numerous discoveries of drug repositioning and drug reprofiling open new opportunities for drug repurposing as a substitute for reducing the time spent on drug development. The reusing of used medications is deemed safe by regulatory bodies, such as corresponding to the FDA (Food Drug & Administration), EMA (European Medicinal Agency), and the Medicines Healthcare Products Regulatory Agency (MHRA) for fresh indication, among others [3]. Repurposed prospect's key benefit is that, in many cases, they have already demonstrated that they are enough secure in preclinical representations and, at the very lowest, at early-period human trials, making them less like to be unsuccessful from a safety opinion of view in later effectiveness trials. In theory, lots of safety assessments, preclinical testing and even clinical trials (phase I) may be skipped if compatibility of doses is discovered (i.e., the strength mandatory for the novel sign is the same as or less than the strength required for the first indication.) Only potency should be examined in preclinical and clinical settings for the new indication. The majority of most well-known and successful drug repurposing stories (SAR CoV2 treatments that have been repurposed such as dexamethasone and tocilizumab) have come from unplanned discovery processes, typically addressing a clinical problem from a different sector by using the drug's already-understood pharmacology (such as an off-target side effect) [4]. Historically, drug repurposing has been mostly exploitative and serendipitous In fact, the most successful drug repurposing cases to date have not followed a systematic process; Instead, thalidomide for multiple myeloma and erythema nodosum leaprosum was repurposed as a consequence of serendipity, while sildenafil citrate for erectile dysfunction was repurposed based on retrospective clinical experience. [5]. The drug sildenafil, which was first developed as an antihypertensive, was repurposed by Pfizer for the treatment of erectile dysfunction and sold as Viagra. In 2012, sildenafil held a market-leading 47% share of the erectile dysfunction drug market with global sales of $2.05 billion. [6]. The largest manufacturers of Repurposed Drugs worldwide are Tevaa Novartis, Myllan, Johnson & Johnson, Pfizer, Bausch Health, GSK, Glenmark, ChemRar Group, Fujiifilm, Dr.. Reddy, R-Pharma [7].

Key Benefits

Drug discovery is a long, expensive, and tough task. Drug repurposing has the potential to address unmet medical needs, neglected diseases, uncommon and orphan diseases, and patients' needs from the medical community and patient perspectives [8]. In disorders where the currently available medications have unfavourable side effect profiles, it may also be able to offer more effective therapy, less expensive alternatives, and medications with acceptable side effects profiles [9]. According to Naylor and Schonfeld (2014), it can have a substantial impact on the advancement of personalised medicine. Research & Development (R&D) expenses are rising, medication development takes a long time, there is a poor success rate, and there are regulatory barriers to overcome. The pharmaceutical sector must also contend with generic drug competition, off-label prescribing, and income loss due to patent expiration. From an industrial standpoint, drug repurposing is said to be slighter expensive, minimum time-consuming, lesser dangerous, and more likely to succeed [10] [11]. The aforementioned elements demand fresh approaches to drug making, and drug repurposing could provide the solution.

Drug Candidates Accessible Bioinformatics Databases

Drug repositioning has a wide range of options since it allows scientists to identify new drugs that recognise certain targets based on earlier findings without needing to do extensive studies. This is possible due to the ever-growing bioinformatics and cheminformatics databases, which supply the requisite chemical and gene structures for the applicable candidate screening. Proteomic databases (UniProt), genomic databases (Entrez-Gene), and pharmaceutical databases (Drug Central/DrugBank/PubChem) are a few examples of these databases [12] . For example, tricyclic antidepressants were discovered using these databases to treat renal carcinomas in addition to

small-cell lung cancers [13]. Massive volumes of data created by different web technologies, data mining tools and including PubMed Boolean-type online searching engines, which make information retrieval more accessible, are the driving force behind these unusual in-silico tactics for medication repositioning [14].

Criteria for selection of repurposed drug

i. Drugs that have previously received regulatory agency approval for a specific indication from the US FDA or EMA
ii. Drugs whose initial use was rejected due to a lack of effectiveness, but whose safety had previously been shown in preliminary clinical studies. Giving these medications a second opportunity is similar to that. This tactic is referred to as drug rescue [15].
iii. Medications that have been withdrawn from circulation subsequent to receiving approval and entering the market.

Approaches for drug repurposing

Finding alternative drug-disease correlations is the major challenge in drug repositioning. To solve this problem various methodologies are developed and frequently employed for the repurposing of drugs which is Biological experimental approaches, combined approaches, and computational approaches [16].

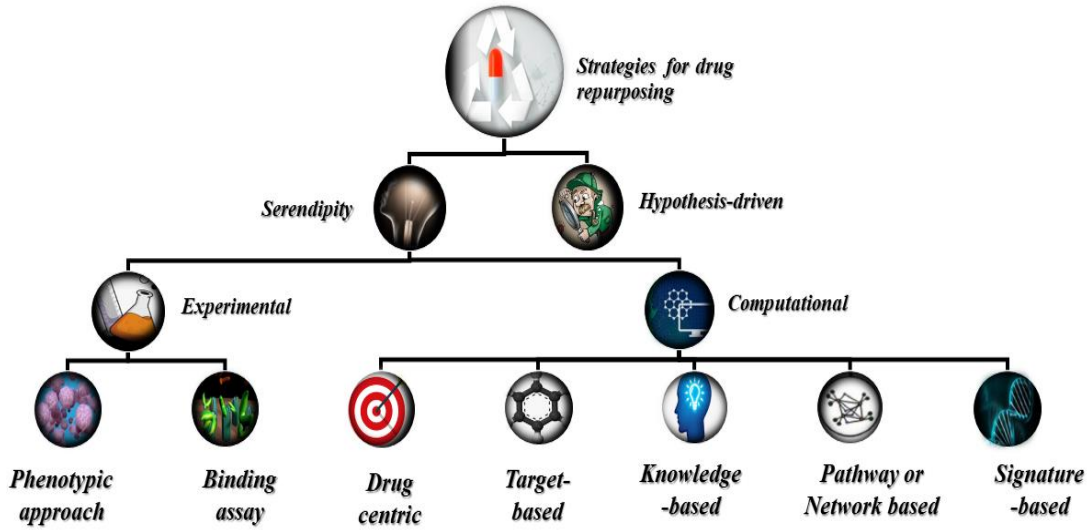

Figure 2. Strategies for Drug Repurposing

Computational Approaches

Numerous pharmacological and disease knowledge databases, including ChemBank9, KEGG11, OMIM10, DrugBank8, and Pubmed12, as well as sizable genomic databases, including MIPS13, PDB 14, MIPS13, MIPS13, and GenBank 16, have all emerged due to the quick development of biology microarray techniques. This information and data accelerated the creation of several revolutionary computing techniques. The costs and barriers of computational approaches are significantly lower than those of biological experimental approaches (Oprea and Overington 2015) [18] This computational approach refers to 'In silico drug repurposing. [19] *In silico* drug, repurposing is divided into two categories: finding new uses for existing drugs (drug-centric- Drug-centric approaches focus on the drug to be repurposed to another target/disease.) and finding actual drugs for diseases (disease-centric- Disease-centric approaches identify close relationships between an old and a new indication.). Both of these approaches share the technique of comparing drugs to diseases or vice versa [20]. Due to the following two technical developments, in silico drug repurposing was created and is now widely used. The first trend is the accumulation of high-throughput data from various sources, including proteomics, phenomics, chemo-proteomics, and genomics. Consequently, there is now access to comprehensive information encompassing disease characteristics, drug profiles, and detailed pathway maps. Moreover, advancements in computational and data sciences have enabled the development of repurposing algorithms, retrospective analysis, and effective database organization for experimental data. [21].

Data Analysis

Because there is so much knowledge about genes, data mining is now required for researchers to find the vast quantity of information that is buried in the literature due to the medications, diseases, and available literature that has grown up due to the rapid increase in the amount of biological,

pharmaceutical studies and biomedical [22]. Text analysis techniques are used in the vast majority of studies that take a data mining approach.

Text Analysis

The co-occurrence of relevant entities or information from the returned data is frequently used to classify relevant entities or information when text analysis is used to address the drug repositioning problem, as well as normal verbal processing. For example, if drug R is related to gene G and gene G is linked to disease D, there may be a new relationship between the two. NER (New entity recognition), knowledge discovery, IE (information extraction), and IR (Information retrieval) are traditionally the four text mining operations (KD) [23].

Cheng et al. [24] completed this research to recognize, highpoint, and rank useful abstracts, passages, or sentences He created a web-based data mining structure to extract relations between biological terms like diseases, genes, tissues, drugs, and proteins. They achieved this by applying various text mining and info retrieval systems to a wide range of current biological databases.

Semantic technologies

Combining data from various sources has become easier with the help of semantic technologies, enabling the prediction of therapeutic possibilities and new applications for existing medications. By utilizing semantically annotated data from multiple publicly accessible sources, such as protein-protein interactions, drug side effects, and drug-drug relationships, it is now possible to forecast connections between drugs and targets within a connected and diverse network. [25].

Noor and Assiri (2021) Concluded this study in which they utilized advanced technology like Drug prediction using semantic web related to rare diseases like SLE (Systematic Lupus Erythematosus). The framework of this research produced four pathways with potential associations with ten diseases and ten drugs with potential beneficial or detrimental effects on SLE. This novel strategy creates opportunities for anticipating new suggestions for currently available drugs while lowering the risky effect of drug-induced illness [26].

Machine learning

Machine learning devices such as random forest,support vector machines, neural network, and deep learning have been used for drug repurposing. Through logistic regression, EXPECT, a similarity-based machine learning foundation has been presented to forecast comparable drugs for similar diseases. The similarities between drugs and diseases were combined to produce integrated similarity values [27].

"Wang *et al*." developed the SVM model, which takes into account molecular activity, drug chemical structure, and side effects. The kernel function of the SVM classifier was then built using three different types of data, and their approach demonstrated greater efficiency than other approaches [28].

Network-Based

Network nodes represent diseases, in these designs, nodes signify drugs and gene products, whereas edges represent node interactions and linkages. Networks include a variety of connections, with interactions between drugs, between drugs and their targets, between diseases, between diseases and genes, and between proteins, as well as transcriptional and signaling networks. Networks can be computationally or knowledge-based inferred from many data sources [29]. The process can find undiscovered or unseen drug-disease profile by integrating heterogeneous data, which is based on the guilt-by-association principle. This idea suggests that medications with similar transcriptional responses may function in similar ways [30]. “Wu et al” (2013). They recognized closely related parts of drugs and disorders to collect data on potential medication-disease couples applicants for drug repositioning [31]. “Jin et al”.(2012) by utilizing possible off-target properties on tumor cell signaling pathways, he developed an approach for repurposing cancer medicines [32].

Drug-centric

This approach examines a drug's mode of action for possible activity in contrast with other diseases after selecting a drug with identified activity against a specific disease [33]. The drug thalidomide, which was suggested to pregnant women to treat morning sickness, was recalled after five years because it was linked to birth malformations [34]. Unfortunately, it was only much later that it was discovered that thalidomide's potent anti-angiogenic effects may be used to treat multiple myeloma [5]. Remdesivir is repurposed by this approach, It works by attaching to the viral RdRP and inserting itself into the developing RNA chain, which causes the RNA chain to prematurely end and prevents viral RNA replication [35].

Target-based

The ability of a drug to prohibit a single target important for the development of the disease—naturally a protein or a gene—is used to assess the drug's efficacy in target-based screening [36]. The action's mechanism, in this case, is well established. Target identification, the first phase, identifies the paths or cellular procedures essential for the progression of the disease. Target validation is the next step, which verifies the significance of the target to the disease. The following phase is assaying growth, which *invivo* modelling the target-disease relationship and often uses a cell-free required assessment to enable drug screening. The next step is hit identification, which involves testing and comparing different medications based on how well they inhibit the specified target. The final phase is to chemically change the hit to increase its efficiency, safety, and stability [37]. For instance, the medication repurposing strategy proposed by "Xia et al." targets the spike glycoprotein of SARS-CoV-2, which promotes cell-cell formation or makes it easier for the virus to enter the host cell. [38].

Knowledge-based

Knowledge-based techniques make use of knowledge currently available about medicine to predict potentially undiscovered processes, such as the existence of unidentified pharmacological targets for olden medications, unidentified Drug-Drug similarities, and novel biomarkers. Knowledge-based methods improve the prediction confidence of anti-neoplastic medications by incorporating a significant quantity of knowledge about drug repurposing [39].

Structure-based

Structure-based showing studies for SARS-CoV-2 inhibitors have received significant attention from numerous research groups around the world due to powerful computing capabilities and the accessibility of 3D structures of drug and receptor targets, making them one of the most commonly used drug repurposing approaches in the COVID-19 disease [40]. As an example, to establish the effectiveness of toremifene in suppressing the activity of NSP14 and SARS-CoV-2 spike glycoprotein at the time of live illness progression, the molecular docking study utilizing toremifene carried out by Cheng and Martin which is required to be verified by them [41].

Pathway-based

Throughout epidemic, pathway mapping has proven to be a critical foundation for therapeutic repurposing [42]. Because the prospective gene targets discovered by GWAS may not be completely suitable as drug targets, this method is an important supplement to GWAS data. In these cases, pathway analysis of genes upriver or downriver of a GWAS-related target may be used to recognize potential drug-repurposing candidates. The process of developing drug and disease networks in order to identify the primary targets for drug repurposing based on common molecular devices is known as pathway mapping. In this process, information from gene expression data, metabolic pathways, and protein interactions is used [43]. Zhou and colleagues recognized sixteen candidate repurposable drugs in the interaction by conducting network proximity studies among drug targets and HCoV-host (Human coronavirus host) interactions, including sirolimus, irbesartan, and melatonin [44].

Experimental Approaches

Binding Assays

Proteomics and mass spectrometry are two approaches that enable the recognition of targets for many compounds. By binding constituents with the uppermost cellular affinities, the cellular thermostability assay (CETSA) tactic, forecasts the thermal stabilization of target proteins. The tyrosine kinase inhibitor (TKI) crizotinib's cellular targets were recently verified, while quinone reductase 2 was shown to be acetaminophen off-target in cells [45].

Phenotype approach

Drug candidates are frequently accidentally found using phenotypic drug-screening techniques [39]. Variations in in-vitro-in-vivo replicas or even clinical remarks can be used to find new drugs [46]. For occurrence, it can contain screening a library of drugs in contrast to cell lines to assess cellular response, recognizing the compounds that affect phenotypic, then determining the disease state and mechanism of action [47]. By using structure-based techniques like molecular docking, receptor-based pharmacophore searching, binding-site structural resemblance, and other techniques that have shown promise in terms of facilitating drug repositioning, “Liu *et al*”. defined new developments in the study of *in silico* approaches for prominent poly pharmacology of identified drugs and novel molecules [48].

Drug Repurposing vs. Traditional Drug Design

The traditional drug advancement method, which contains 5 stages—discovery and preclinical, clinical test, Food and drug administration review, safety review, and FDA, post-market safety

monitoring—includes de novo detection of new molecular entities as one of its components. These approaches are expensive, time-consuming method with a high failure rate Whereas, the repurposing of drugs has only 4 steps: compound identification, compound acquisition, FDA post-market safety monitoring, and growth. The development of cheminformatics and bioinformatics technologies, as well as the availability of enormous structural and biological databases, have significantly reduced the amount of time, money, and chances of failure of the drug development process [49].

Advancements in Drug Repurposing

As far back as the 1970s, drug repurposing had a remarkable success. There are vast number of drugs which has been repurposed for different sort of diseases and had nailed as an excellent example in repurposing the drug.

Repurposed Drug in Infectious Disease

A.) A ribonucleoside prodrug of N-hydroxycytidine is **molnupiravir**. A prescribed antiviral medicine. The **SARS-CoV-2 virus**' RdRp is blocked by this new antiviral drug, which prevents viral genome transcription and replication. According to a publication, molnupiravir cleaves in the plasma to produce -D-N4-hydroxycytidine. NHC is subsequently transported throughout the liver cells and converted into NHC triphosphate, which serves as the substrate for RdRp. With the aid of RdRp, NHC modifies the viral RNA and alters the genome sequence, preventing SARS-CoV-2 genome transcription and replication.

B.) A significant barrier to the treatment of cancer and **infectious disorders** is multidrug resistance. The overexpression of **efflux pumps**, which are in charge of ejecting antibacterial and anticancer drugs, is one of the leading mechanisms of multidrug resistance. The growth of bacterial infections and the development of cancer may be aided by the extra detoxifying functions of efflux pumps. The efflux pump may thus be a promising target for the procurement of cancer and bacterial infections [50].

C.) Emricasan is the first caspase inhibitor tested on humans, and works to prevent **liver cells from undergoing excessive apoptosis**. Emricasan inhibits the action of caspase-3, which is triggered by ZIKV (Zika Virus), and lessens neuronal cell death to produce antiviral effects. The same target serves as the foundation for the repurposing technique, which is then used to various disease scenarios [51].

D.) Favipiravir (T-705) is an anti-influenza drug that has been repurposed for "**COVID-19**" patents. This Japanese-developed medication was licensed to treat influenza in 2014. The viral RNA-dependent RNA polymerase is inhibited by this medication (RdRp) [52]. The discovery that favipiravir has demonstrated positive clinical activity against COVID-19 was initially made in China. But Chen et al. reported no conclusive data about its benefit to COVID-19 patients. [53] Favipiravir and other substances like marboxil and baloxavir were examined in a recent study at the School of Medicine, Zhejiang University. Researchers found no further use of favipiravir in a sufferer with "COVID-19" at the study doses [54] [55].

Repurposed Drug in Neurological Disease

A.) Patients with **dysphagia** frequently take many medications. Drugs that are often taken may affect swallowing function, either enhancing it or impairing it. In order to investigate the possibilities of medication repurposing for the treatment of dysphagia, the authors of this study employ a systematic review and real-world data analysis to investigate the potential impacts of three classes of commonly prescribed medications on dysphagia pneumonia from aspiration. In order to enhance swallowing function and lower the risk of aspiration pneumonia, their study examines the potential pharmacological repurposing of **ACEi, DPP-4i and beta-blockers,** in neurological patients with dysphagia [56].

B.) Niclosamide, which was first sold as Yomesan for human use in 1962, has been used as an anti-helminthic medication for more than 50 years with a high level of safety and is on the WHO list of requisite medicines. Niclosamide is a pharmacologic drug that belongs to the salicylanilide class and has the aryl -hydroxy-carbonyl pharmacophore motif that is often seen in many biological natural products. This tiny molecule has pleiotropic properties and the ability to interact with a variety of biological targets because to the pharmacophore motif. The translocation of protons across the mitochondrial membrane, which causes a little uncoupling of the mitochondria, is its first known activity. Although typically well tolerated by human cells, this action is sufficient to kill tapeworms in the gastrointestinal system. In addition, niclosamide alters the activity of the Wnt/-catenin, signal transducer and activator of transcription, nuclear factor kappa B, mammalian target of rapamycin, transmembrane protein 16, and Notch signalling pathways [57]. Given that these molecules

regulate the transcription of several genes, it is conceivable that their direct or indirect impacts on various signalling pathways account for the compound's wide-ranging biological action. Preclinical validation shown that niclosamide is effective against **solid tumours, rheumatoid arthritis, and fibrotic diseases.** A phase II–III clinical study for metastatic colorectal cancer, prostate cancer is presently underway [58].

C.) Tamibarotene is synthestic retinoid and traditionally investigated ad given in the treatment of leukemia. Tamibarotene is now also being used to treat **Alzheimer's disease** and proposed mechanism was that it significantly reduce the insoluble Aβ levels [59].

D.) A neurodevelopmental condition with a significantly rising incidence rate is autism spectrum disorder. It is distinguished by repeated behaviour, learning challenges, and deficiencies in social interaction and communication. Although there is no known cure for this ailment, several drugs, nutritional supplements, and behavioural therapies have been suggested for therapy. Sodium-glucose cotransporter 2 (SGLT2) shows potential effect for autism spectrum disorder. Due to their capacity to lower free radical production and upregulate antioxidant systems like glutathione and superoxide dismutase while crossing the blood brain barrier, SGLT2 inhibitors have also been shown to have the potential to have antioxidant effects. The neurologic results of several experimental illness models, including brain oxidative stress in diabetes mellitus and ischemic stroke, Alzheimer's disease, Parkinson's disease, and epilepsy, have significantly improved as a result of these features. These illnesses have biomarkers with autism spectrum disorder, which may be a connection to close a gap in the research looking at the possibility of repurposing SGLT2 inhibitors for treating autism spectrum disorder symptoms [60].

Repurposed Drug in Rare Disease

A.) An uncommon and deadly kind of brain tumour called a **glioblastoma** arises from oligodendrocyte and astrocyte cells [61]. The most aggressive and common malignant first brain tumour, glioblastoma accounts for 54% of all gliomas and 16% of all primary brain tumours. [62]. In many nations, the incidence of glioblastoma is increasing and varies from 0.59 to 5 per 100,000 people [63]. The typical survival time for individuals with glioblastoma is only 15 months, and less than 5% of them survive five years following diagnosis. Glioblastoma presently has no known treatment [61] For grades 3 or 4 high-grade gliomas, including grade 4 glioblastoma, the standard of care at the moment is radiation therapy, temozolomide, and maximally safe surgical excision. Stupp et al. have demonstrated that patients who get radiation in addition to temozolomide treatment have a two-year survival rate of just 26.5 percent, despite the fact that this standard of care has extended the median survival duration of glioblastoma patients [64]. Furthermore, Stupp et al. showed that 7 percent of patients who had concurrent radiation and temozolomide experienced grade 3 or 4 hematologic adverse effects. By April 2022, the FDA had authorised lomustine, [65] intravenous carmustine, [66] carmustine implants, [67] bevacizumab, [68] and tumour treatment fields in addition to TMZ and one device for the treatment of high-grade gliomas [69].

B.) The diagnosis and treatment of **conjunctival melanoma**, an uncommon and lethal malignant eye tumour, are weak. Here, we describe a unique use for the FDA-approved antiarrhythmic drug **propafenone**, which has been shown to be effective in reducing the vitality and homologous recombination pathway of conjunctival melanoma cells. D34, one of the derivatives with the most promising structure-activity connections, significantly reduced Conjunctival melanoma cells' viability, migration, and roliferation migration, and proliferation of Conjunctival melanoma cells at sub micromolar concentrations. By inhibiting the homologous recombination process and its components, namely the complex of D34, MRE11-RAD50-NBS1 has the ability to mechanically increase -H2AX nuclear foci and exacerbate DNA damage. D34 reduced the endonuclease activity of the human recombinant MRE11 protein by binding to it. D34 dihydrochloride also dramatically reduced tumour development in the CRMM1 NCG xenograft model without showing any clear adverse effects [70].

C.) The major symptoms of skeletal muscle ion channelopathies are **myotonia** (muscle stiffness) or periodic paralysis (muscle weakening). The treatment options for **periodic paralyses and non-dystrophic myotonias** which mostly include medication repositioning to address stiffness or weakening episodes. **Mexiletine** for non-dystrophic myotonias and **dichlorphenamide** for periodic paralyses were designated as orphan drugs and given marketing authorizations following successful randomised clinical studies and empirical usage. However, neither the genetic

origin of the disorders nor the individual variation in medication response are taken into account by these therapies. Thus, continuing research strives to find repurposed medications that can replace mexiletine and dichlorphenamide in order to enable therapy customisation.

D.) Dercum disease is an uncommon disorder marked by several uncomfortable fatty tumours located all throughout the body. The quality of life for many individuals with Dercum disease is severely impacted by the lack of US FDA - approved medicines and the ineffectiveness of the treatments that have been tested. **Deoxycholic acid**, a treatment authorised for the adipolysis of submental fat, was used to treat three individuals with Dercum disease who were identified with the condition in a case series presented by Silence et al. Radiographic data shows that the tumours shrank in size, and the patients' symptoms subsided significantly [71].

Repurposed Drug in Cancer

A.) Over 40 years ago, **Prazosin** received clinical approval for the therapy of hypertension. Prazosin is now being used to cure a variety of clinical problems, including **congestive heart failure, Raynaud's illness and benign prostatic hyperplasia**. According to pharmacological studies, prazosin can block the 2B-adrenergic receptor while being a non-selective inhibitor of the 1-adrenergic receptor. Prazosin has been suggested as a therapy for pheochromocytoma because it may have anticancer properties.

B.) Prostate cancer has been shown to be resistant to the anti-proliferative and anti-cancer actions of **metformin**, an oral biguanide used as the first-line therapy for type 2 diabetes mellitus. Metformin has been proposed to have direct anti-cancer effects by activation of liver kinase B1 and adenosine monophosphate-activated protein kinase, suppression of protein synthesis, promotion of apoptosis and autophagy through p53 and p21, and lowered blood insulin levels. The development and progression of prostate cancer have been linked to the metabolic syndrome and its elements, according to research. Therefore, the lower incidence of prostate cancer and greater quality of life may be attributed to the medication's direct anti-cancer mechanisms or the adverse consequences of metformin users' increased survival [72].

C.) Different types of **thalidomide** derivatives are used in contemporary **cancer treatment**. A person who abruptly awoke from a 60-year nap would be astounded to learn that this notorious medicine is still in utilization today. The clinical tragedy connected to its first launch serves as a lesson to everyone working in the drug development industry. Thalidomide was initially created to treat morning sickness and was made available over-the-counter to expectant mothers in Germany in the (1950s), with dosages ranging from 300 to 500 mg. The drug's approval in the USA was halted by adverse effects such peripheral neuropathy. However, thalidomide wasn't completely banned until 1962 after it was discovered to cause serious birth abnormalities. Thalidomide was still being used in clinical settings to treat Hansen disease (leprosy) even after its discontinuation. Thalidomide and its derivatives were primarily used for immunomodulatory purposes for many years. There are currently a number of thalidomide-related substances to pick from that have been particularly created to modulate various immune cell route. This medication family's very affordable therapy options allow it to contribute to a variety of cancer therapies through both its ability to limit tumour development and its anti-inflammatory properties [73].

D.) Celecoxib is a COX-2 selective inhibitor that is an NSAID and has chemopreventive qualities against cancers including **colorectal and breast cancer** [74] . Repeated celecoxib usage was observed to lower the risk of breast cancer incidence and progression. Breast cancer, , gastric cancer, oesophageal cancer and liver cancer all showed elevated COX-2 expression [75]. Additionally, the amount of PGE2 rose in the tumour location, which finally sparked the growth of cancer cells. According to reports, COX-2/PGE2 also encourages Akt phosphorylation and aids in lowering cancer cell death. Unrelated side Through the activation of the -catenin signalling pathway, PGE2 promotes cell mitosis and metastasis [76].

E.) Recent studies have shown that the FDA-approved medication Mebendazole has **anticancer** characteristics. This artificial **benzimidazole** was successful in treating a variety of intestinal Helminthiasis. By targeting signalling pathways involved in cell proliferation, apoptosis, invasion, or migration, mebendazole, which can cross the blood-brain barrier, has been shown to slow the malignant spread of gliomas. It has also been shown to make glioma cells more susceptible to conventional chemotherapy and radiotherapy. Acute myeloid leukaemia, brain cancer, breast cancer, gastrointestinal cancer, adrenocortical carcinoma, oropharyngeal squamous cell

carcinoma, lung carcinoma, and head and neck cancer, prostate cancer are just a few of the cancers for which Mebendazole is being tested in preclinical models and ongoing clinical trials [77].

Emerging Technologies and Trends

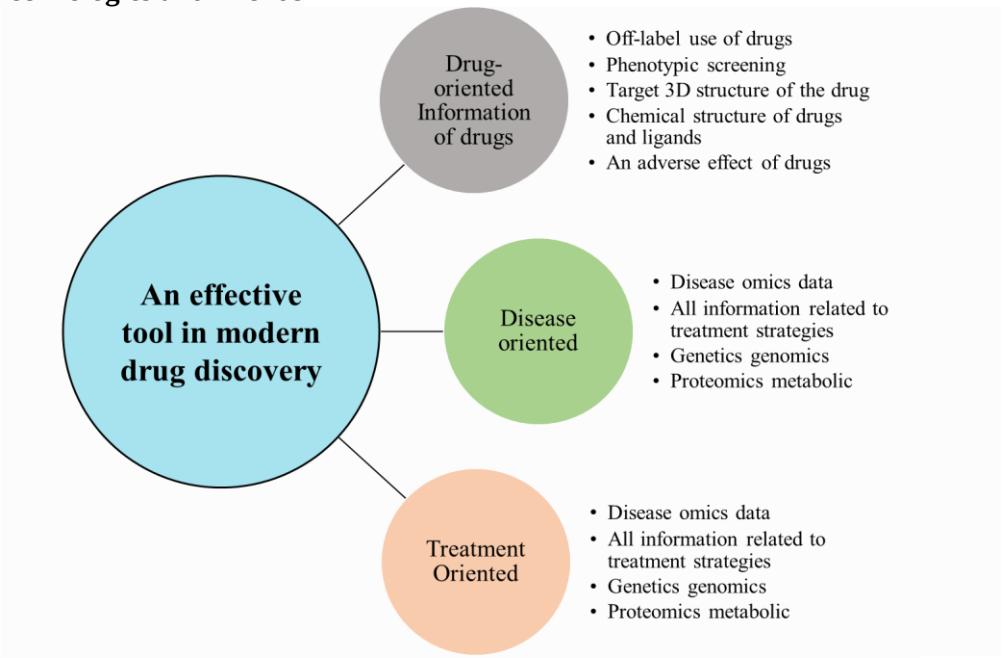

Figure 3. Drug Repurposing: An Effective Tool in Modern Drug Discovery

Genomics and Precision Medicines

The term "rare disease" lacks a precise meaning since local authorities define the requirements in a variety of ways, ranging from the European Union's definition of less than 5 occurrences per 10,000 people to the global average of 40 cases per 100,000 people [78]. According to various criteria, there are typically 7000 orphan illnesses that have been identified [2] . Despite their enormous prevalence and diversity, RD share challenges such as (i) delayed diagnosis and a protracted patient odyssey; (ii) a lack or rarity of disease biomarkers that might provide light on the pathophysiology; and (iii) problematic medication discovery and therapy [79] [80]. However, the development of Whole Exome Sequencing and Whole Genome Sequencing during the past ten years, employing a next-generation sequencing technology, has revolutionised the approach to rare disease and led to the identification of previously unknown diagnoses and genes in 25–50% of individuals with unresolved cases [5].The first publication utilising WES for Miller syndrome diagnosis in 2010 [81] was a game-changer in the evolution of the RD method. Preclinical investigations on mouse and human induced pluripotent stem cell in vitro models and genome editing have revealed promising therapeutic possibilities. As a small group of rare disease patients' genetic information was deemed to potentially pave the way for developing treatments for others with common illnesses, precision medicine therapy became more approachable [8].

Drug Repurposing Platforms and Databases

Due to imperfect understanding of medication activities across organs and species, clinical trials have had a high failure rate, which has impeded the discovery of new drugs. To better understand treatment effectiveness, possible side effects, and interspecies variations, it is important to understand how species- and tissue-specific pharmacological functionalities work. PharmOmics, a pharmacological knowledgebase and analysis tool maintained on an interactive web server. A gene-network-based strategy for medication repositioning is implemented using species-specific, tissue-specific and mouse, transcriptome data from human, and rat that have been collected from various sources. PharmOmics' ability to find well-known therapeutic medications and recognise drugs with tissue toxicity utilising in silico performance assessment is demonstrated. PharmOmics is a useful auxiliary tool for network-based medicine and drug characterisation [82]

Integration of Multi-Omics Data

In silico drug prescribing and multi-omics data integration can enhance individualised precision medicine by providing medications tailored to specific molecular profiles, facilitating improved patient stratification that results in more accurate diagnoses and treatments, and identifying novel

biomarkers for drug response [83]. PanDrugs2 is a flexible in silico medication prescription tool that combines and evaluates several forms of omics data, such as minor variations, CNVs, and transcriptomics. It was developed by Harbeck et al. This novel technique broadens the therapy options by taking into account a larger range of molecular modifications than the conventional one-size-fits-all strategy [84].

Machine Learning and Artificial Intelligence Applications

It has been shown via past research that artificial intelligence is capable of learning new data and transforming it into knowledge. Artificial intelligence and machine learning have demonstrated to be future activities in the health and biological sciences. Therefore, the goal in the field of pharmacology is to use this technology, which is also economical, to produce innovative and more effective vaccines. Predicting the molecular mechanism and structure will boost the probability of discovering novel medicines. Drug research can benefit from using clinical, electronic, and high-resolution imaging databases as inputs. A therapeutic molecule has also been repurposed using comprehensive target activity, providing a new indication, by extending pharmacological target profiles to include off-targets with therapeutic potential [85].

Challenges and Limitations

Regulatory Hurdles

So, what hinders the motivation to develop a currently inexpensive generic drug (whose patent protection has expired) for a new purpose or repurpose an approved drug (or investigational compound) with limited remaining patent life? In essence, the answer lies in the significant amount of high-risk investment required to develop a new use for an existing drug. Unless the investor has the opportunity to recover their expenses and generate profit, they are generally unwilling to undertake the necessary work and associated risks [86]. A substantial portion of this risk resembles that faced when developing any new drug: the possibility that the repurposed drug may not demonstrate a favourable benefit-to-risk profile in clinical trials, which is necessary for regulatory approval of the new indication. Even if the safety profile of the drug is already well-known, such as in the case of long-standing market presence, differences in benefits for the new indication could impact the overall benefit-to-risk profile. Additionally, there are other factors to consider that may limit the potential advantages of existing knowledge about the drug's clinical characteristics. Firstly, selecting the appropriate dosage is crucial to achieve optimal therapeutic response for any medicine in any indication. In a medicine with multiple uses, the appropriate dosage may differ between the two indications. Therefore, further studies to establish the dose-response relationship in the new indication may need to be conducted before initiating trials to support approval for the new indication. Secondly, as regulatory science standards progressively improve, previous data, such as preclinical toxicology, may no longer meet the requirements for a new indication, necessitating repetition of earlier tests. Both of these factors increase the overall development costs, making the project less attractive. Finally, gaining market access for the new indication depends not only on regulatory evidence of quality, efficacy, and safety but also on health technology assessments based on comparative clinical efficacy and cost-effectiveness. Currently, many countries have regulatory and legal systems that offer exclusivity regimes aiming to encourage businesses to invest resources in researching and developing further uses for existing drugs. However, these regimes are often inadequate in many aspects and fail to provide a framework for drug developers to recoup their investments, especially for drugs that already have generic versions available [87].

Intellectual Property Issues

Drug repurposing is hindered by a countless legal and intellectual property issues [5] . The primary challenges in promoting the repurposing of medicines are associated with obtaining patents for new indications and protecting patent rights, as they significantly affect the expected profitability of the repurposed product. In most of the main pharmaceutical markets, a newly repurposed medicinal application of an existing therapeutic molecule may be protected as long as it is novel and innovative (i.e., not apparent) [88]. But a lot of the potential repurposing applications are already widely employed in the scientific or medical domains. Even though they might not have completed clinical testing to prove their usefulness, prior scientific understanding of the repurposed application may make it more difficult to secure patent protection. This is accurate unless the patentee can somehow discriminate between the knowledge that already exists in the public domain and the patent claims. The patentee must additionally include evidence in the patent application proving that the medicine is a successful therapy for the new indication in issue in order to be granted patents for a newly repurposed medicinal use [89].

Table 3. Application of Drug Repurposing

S.no.	Chemical name	Original indication	Repurposed for	Mechanism	References
1.	Fluoxetine	Antidepressant	non-small-cell lung cancers	inhibits cell proliferation.	[90]
2.	Posiphen	neurodegenerative diseases	Alzheimer's disease (HTT)	Posiphen has been shown to reduce HTT levels significantly by binding to the atypical iron response element of mRNA and inhibiting HTT mRNA translation.	[91]
3.	Retinoic acid	psoriasis	Alzheimer's disease (ADAM10)	Retinoic acid, through its action on ADAM10, can activate the nonamyloidogenic pathway	[92]
4.	Gemcitabine	Gemzar	Antiviral drug	Thymidine	[93]
5.	Methotrexate	Trexall	Leukemia	production	[94]
6.	Duloxetine	Anti-depressants	Diabetic Naturopathy	Inhibition of serotonin and norepinephrine reuptake	[95]
8.	Naringenin	Antioxidant, anti-inflammatory, and anti-cancer properties	Alzheimer's disease (AMPK/ULK1)	Naringenin may improve approval by inducing autophagy via the AMPK/ULK1 axis.	[96]
9.	Pregabalin	Anticonvulsants	Diabetic Naturopathy	Inhibits calcium and potassium channels, decrease	[97]
10.	Cyclophosphamide	Autoimmune disease	Breast cancer	Inhibits DNA	[98]

Table 4. List of drugs that are approved for drug repurposing or under clinical trials

Drug name	Original indication	New Indication	Mechanism of Action	Study Status	References
Itracoanazole	Anti-fungal	Prostate cancer	prostate-specific antigen reduction	Phase II	[96]
Minocycline	Sexually transmitted disease and acne	Fragile-X syndrome	Inhibition of matrix metalloproteinases (MMPs)	Under study"	[99]
Aspirin	Pain and Fever	Maelanoma	Stop tumor cell development	Phase II	[3]
Metformin	Type 2 diabetes	prostate cancer	mTORC1 (mammalian target of rapamycin complex 1) pathway inhibition	Phase II	[100]
Sildenafil	Angina pectoris	Erectile-dysfunction	Inhibition of phosphodies terase type 5 (PDE5)	Approved	[101]
Riluzole	Amyotrophic lateral sclerosis	Melanoma and other cancers	Downstream glutamatergic signaling	Phase II active	[102]
Minoxidil	Anti-hypertensive	Hair regrowth	Stimulates follicle movement	Approved	[103]
Eflornithine	Cancer	African trypanosomiasis	Inhibition of ornithine decarboxylase (ODC)	Phase III completed	[104]
Auranofin	Arthritis rheumatoid	Amebiasis	Unknown	Clinical use	[104]
Digoxin	Congestive heart failure and arrhythmia	Cancer	Sarcoma activity inhibition	Phase I is complete, and subjects are being sought for Phase II.	[20]

Opportunities and Future Directions

Opportunities for more quickly and efficiently creating repositioned medicines are provided by the mixed approach of drug repurposing. The term mixed methods refer to the modern practice of combining computational and experimental methods to find new applications for established medications. With greater access to databases and technical advancements, the mixed methods to repurposing provides a logical and thorough examination of all potential repurposing options. Additionally, compared to traditional drug development, drug repositioning requires less R&D effort. As a result, medication repositioning gives many pharmaceutical companies the chance to create treatments with smaller investments [105]. According to the market, many illnesses require novel drugs to be treated in order to fulfil potential market demand and economic implications. For instance, there is a

sizable potential market to investigate drugs developed to treat uncommon or neglected diseases. Therefore, there is a chance for medication repurposing to treat uncommon, untreated, orphan diseases or diseases that are challenging to cure. Over 6000 uncommon diseases are untreated because they are so rare. 5% of them are being studied. There is a sizable market to be explored for rare diseases. Repurposing existing drugs to treat both common and unusual diseases is rapidly growing as an intriguing area of study due to the utilisation of pharmacological molecules with reduced development costs, failure rates, and time frames. This results in a sluggish rate of medication discovery and growth, high attrition rates, and large costs [15].

While the manufacturing of repurposed medications has until now mostly depended on random discoveries, new OMICS technology coupled with systems biology and high-throughput drug screens enables a more methodical approach. The combination of these resources would ideally result in a flexible and uniquely individualized therapy approach for each patient. In a single-arm clinical study (NCT02060890), Byron et al. investigated the viability of this method [106]. The development of platforms where intellectual, technological, and financial resources are combined is another strategy to facilitate and accelerate effective drug repurposing. Such a coordinated effort should ideally involve university researchers, pharmaceutical firms, and financing sources, among others. Such a collaborative environment would make it simpler for pharmaceutical companies to exchange their intellectual property, including the disclosure of failed drug development efforts or incompletely developed and deprioritized compounds and supporting information. Discovering New Therapeutic Uses for Existing Molecules program, a partnership between the NIH National Centre for Advancing Translational Sciences (NCATS) and pharmaceutical firms like Astra Zeneca, Janssen Research and Development, LLC, and Pfizer Inc., is one such initiative that has recently been launched [107].

Conclusion

Drug repurposing has become popular due to its benefits like cost-effectiveness and faster drug development. Phenotypic and computational information retrieval techniques for example, such as the target-based strategy, will produce high-quality data with unrivalled drug-target validation. Drug repurposing allows you to expand your information without limiting what you already know. Therefore, drug repurposing can help the pharmaceutical sector, as well as research organizations, produce new scientifically based drugs. Finding new uses for outdated medications through drug repurposing is a useful drug development approach.

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