REVIEW ARTICLE

CHALLENGES AND OPPORTUNITIES WITH DRUG REPURPOSING: AN EMERGING TECHNIQUE IN DRUGS DISCOVERY

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ABSTRACT

The term "drug repurposing" refers to the practice of identifying unmet medical needs and developing innovative solutions using already available drugs. It's a useful strategy for identifying or developing new medicinal molecules with untapped therapeutic potential. Some of the computational drugs repurposing methods currently in use have been employed in the fight against the 2019 coronavirus illness (COVID-19) pandemic. Many currently used medications are being repurposed, thanks to advances in computational approaches and a fundamental understanding of viral etiology and pharmacological pharmacodynamics. The objective of this work is to highlight the utilization of repurposed medicines for COVID-19, bacterial infections and cancer therapy. The drug repurposing method is fast-growing in both business and academia, since it focuses on the initial knowledge and investment that brought the product to market in the first place. Recently, medication repositioning has been included in the drug R&D plans of several pharmaceutical companies, aiming to create new therapies in response to the identification of novel biological targets. In addition to being highly efficient, the drug repurposing method also saves money and the pharmacological profiles are generally known.

Keywords: Drug repurposing, COVID-19, computational techniques, methodology

ABBREVIATIONS

IND: Investigational new drug, NDA: New drug application, NME: New molecular entity, vHTS: Virtual high-throughput screening, GIST: Gastrointestinal stromal tumor, DR: Drug repurposing

INTRODUCTION

The worldwide coronavirus disease (COVID-19) outbreak, which began in China, has given the drug repositioning strategy a new sense of urgency. Finding a new purpose for an existing medicine is known as drug repurposing[1]. Alternative terms for therapeutic switching include drug repositioning, drug re-tasking, drug reprofiling, drug recycling, drug redirection and drug repurposing. The process of introducing a brand-new drug is complex, difficult, time-consuming, and financially prohibitive[2]. Drug repositioning promises profit-sharing with decreased risk since these repurposed medications have recently been evaluated as safe in humans, and have passed all research trials. Nowadays, drug repurposing has emerged as a promising approach in the drug discovery process due to its high applicability and lower expenses[3-14]. As a result, analyzing the repurposing of an existing medicine for a new therapeutic purpose is quick and easy[15]. Pharmaceutical companies have shown increasing interdisciplinary interest in finding new uses for existing drugs. This method is effective, time-saving, and cost-effective, which may maximize the success rate. Some examples of repurposed drugs have been depicted in Table I.

Traditional drug delivery Vs drug repurposing

The gold standard for drug discovery is the *de novo* assessment and selection of new molecular entities (NME), which consists of five stages: discovery and preclinical, safety assessment, clinical research, FDA review, and FDA

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Table I: Examples of repurposed drugs[1,2,6,15]

Drug	Original indication	New indication
Sildenafil	Hypertension/ angina	Erectile dysfunction
Zidovudine	Cancer	HIV/AIDS
Cycloserine	Urinary tract infection	Tuberculosis
Finasteride	Benign prostatic hyperplasia	Hair loss
Tamoxifen	Breast cancer	Anti-bacterial activity
Amantidine	Anti-viral	Parkinson's disease
Topiramate	Epilepsy	Obesity
Phentolamine	Hypertension	Impaired night vision
Tadalafil	Inflammation and CVS disease	Male erectile dysfunction
Thalidomide	Sedative	Leprosy

post-market safety monitoring. This is laborious method with a high potential for errors. Drug repositioning involves simply four processes: compound discovery, compound procurement, development, and FDA post-market quality control. Traditional drug research and development is a lengthy process that begins with the discovery of a new treatment and ends with regulatory approval for its commercial launch. It is important to develop modern strategies to reduce the time it takes to manufacture a drug. Recently, the COVID-19 outbreak has severely impacted the entire healthcare system, leading the attention of many scientists toward the repurposing approach as well as herbal alternatives[16-28]. Drug repurposing has become increasingly important in discovering new therapeutic applications for medicines that are currently on the market[29]. Repurposing is often accomplished through accidental (unintentional fortunate observations) or systematic methods. This article discusses several methods for discovering new indications for FDA-approved medicines. Drug repurposing has thus become a fruitful approach to drug discovery, as it provides a novel way to explore existing medicines for new applications, even though it is highly challenging[30].

The time required to produce a new medicine is expected to be 10–17 years, while the time needed to develop a new drug through drug repurposing (DR) is estimated to range between 3 and 12 years. A repurposed medication does not require the initial 6–9 years typically needed for the development of new drugs. Instead, it bypasses the laboratory phase and proceeds directly to clinical trials, which saves development time and money, and reduces risk[15,31,32]. Fig. 1 illustrates the comparison of processes in traditional drug discovery and drug repurposing.

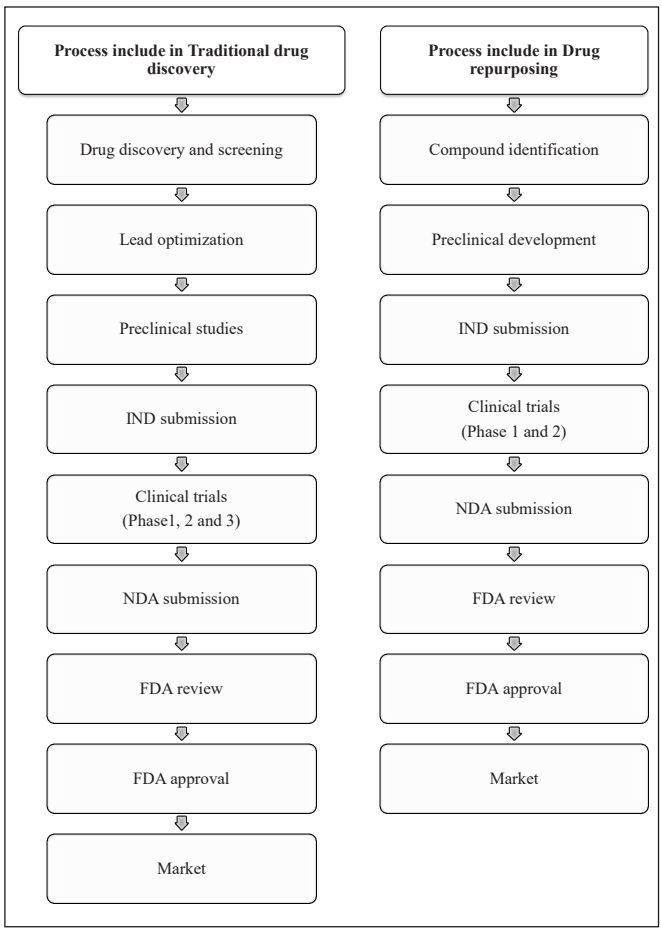

Fig. 1: Traditional drug delivery Vs drug repurposing[31]

STRATEGIES

There are mainly two strategies:

A. On-target

B. Off-target

On-target and off-target DR are the two basic DR techniques. On-target DR involves the use of a drug's known pharmacological effect in a different clinical setting. In this method, the therapeutic molecule's biological target remains the same even when the ailment being treated varies. The pharmacological mechanism is unknown in

the off-target profile. On the other hand, novel therapeutic indications are being addressed by medications and drug candidates that act on new targets outside of their initial scope. As a result, the objective and indicators are both new[15].

APPROACHES

Various pharmacological and disease information databases, like Drug Bank, ChemBank, OMIM, KEGG, and PubMed, have emerged as a result of the rapid development of biological microarray methods, and huge genomic databases, such as MIPS, PDB, GEO, and GenBank, have been established[33-36].

The rapid development of a range of innovative computing techniques was aided by this information and data. Most present computational methods either combine various sources of data on disease-drug relationships that may be divided into distinct categories, or use the gene expression response of cell lines following therapy as their basis. Network-based techniques are commonly utilized for drug repositioning thanks to their flexibility in incorporating a wide variety of data sources[34].

These techniques have been presented over several decades and have been in a focus, in the last ten years. DBSCAN, CLIQUE, STING, and OPTICS are among the most popular network-based cluster methods[33]. The experimental technique and the *in silico* approach are two complementary but distinct methods[37-38].

Experiment-based approach

Using experimental assays, traditional medicines may be screened for novel pharmacological indications, a process called experiment-based method or activity-based repositioning. Included are *in vitro* and/or *in vivo* disease models based on protein targets and cells or organs; target protein structural information is not necessary for these models.

In silico based approach

In contrast, *in silico* repositioning performs virtual screening of public databases of massive drug and chemical libraries using computational biology and bioinformatics / chemoinformatics technologies. This strategy, which relies on the pharmacophoric interaction between the therapeutic chemical and the protein target, allows for the identification of putative bioactive compounds. Moreover, extensive use of *in silico* platforms for drug repurposing has been reported for various disease conditions[39-51]. Computational and experimental approaches to drug repositioning can be broadly differentiated. These techniques are sometimes coupled to make use of the advantages of both computational approaches and experimental screens. Data is critical in predicting novel indications for current medications using systematic drug-target-disease connection pairings, on which computational techniques strongly depend[52].

DRUG REPURPOSING APPROACH TO FIGHT COVID-19

COVID-19, spread all over the world, pays critical attention to save human beings through effective treatments, which are urgently needed. The discovery of new molecules may be time-consuming and cost-effective compared to repurposed, available drugs. Several approaches have been developed that may encounter the complexity of new drug applications and drug discovery processes[53-60]. Recently, a strategy for rapidly identifying repurposable medicines against SARS-CoV-2 using integrative network-based systems pharmacology has been published. With this method, we can assess how the human protein-protein interaction network connects to therapeutic targets in the context of coronavirus infection. Research employing this method identified 30 medicines with untapped potential for other applications[61-62].

Remdesivir is being explored as a potential repurposed medication option for COVID-19. In a 14-day study with 1059 patients (538 of whom received remdesivir and 521 of whom received a placebo), the death rate was 7.1% with remdesivir and 11.9% with a placebo. The study was conducted across 60 primary locations and 13 secondary ones worldwide. In a randomized, double-blind, placebo-controlled experiment involving 237 patients, 158 received remdesivir, and 79 (one withdrew) received a placebo. The duration of symptoms was statistically significantly shorter and (10 days or less) in patients receiving remdesivir compared to patients receiving a placebo. In a different remdesivir clinical study involving patients with severe COVID-19 who did not require mechanical ventilation at any stage during therapy, there was no statistically significant difference between the 5-day and 10-day treatment regimens. On day 14, 64% of patients in the 5-day group and 54% in the 10-day group showed clinical improvements of two points or more on a scale of 1 to 7. The medications favipiravir, ribavirin, the lopinavir-ritonavir combination, arbidol, and tocilizumab have shown assurance in clinical trials conducted based on compassionate use to save the lives of COVID-19 patients. Consequently, these medications might represent viable pharmacological therapies against this devastating illness in the future[63-66].

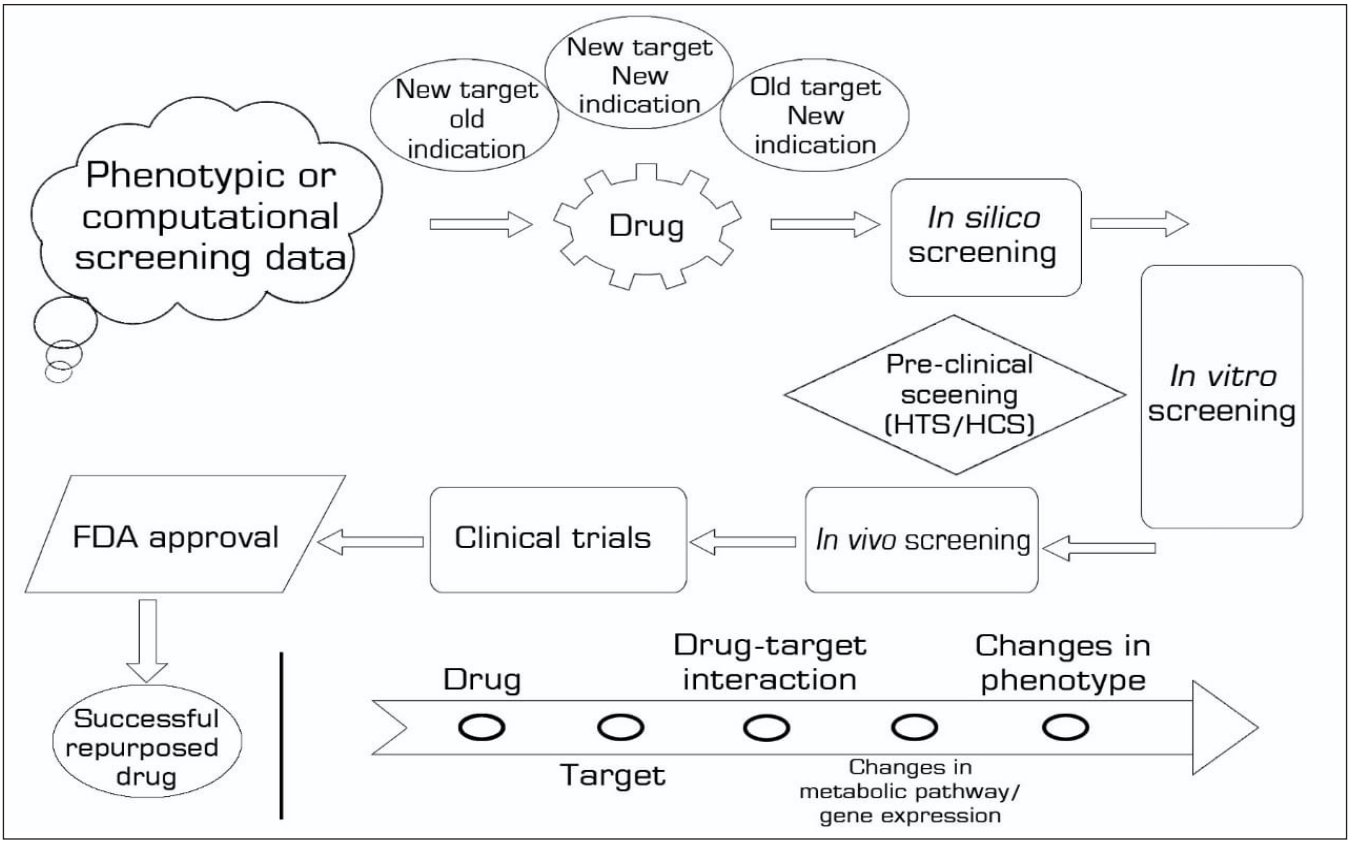

Fig. 2: Steps involved in drug repurposing[15]

METHODOLOGY

Based on the quantity and quality of pharmacological, toxicological, and biological activity data, drug repurposing techniques can be categorized into three classes, primarily focusing on (i) drugs, (ii) targets, and (iii) treatments and diseases. Drug-oriented research examines how drugs function from various perspectives, including their molecular structure, biological action, and potential for harm. This approach relies on studies in cells and animals to identify chemicals with biological effects. It is based on established principles of pharmacology and drug development, where trials are conducted to determine the biological effectiveness of pharmacological compounds before identifying their biological targets. Large-scale developments in drug repurposing with this drug-centered profile, such as the discovery of sildenafil, have occured by chance or as a result of clinical observations[67].

A target-based technique involves drug screening (HTS/HCS) with high throughput and/or high content *in vivo*, as opposed to a particular protein molecule or biomarker of interest. This is an example of *in silico* or virtual high-throughput screening (vHTS) of pharmaceuticals or compounds from drug libraries or compound data sets. It includes methods like ligand-based screening or molecular docking, followed by *in vitro* testing. Compared to drug-oriented research, this procedure has a significantly higher success rate because most biological targets are direct representations of disease pathways and mechanisms, making it a valuable strategy in drug discovery[68].

As data on the disease model accumulates, the illness/therapy-oriented approach to drug repurposing (DR) will become increasingly important. In this scenario, disease-specific data from disciplines like proteomics (disease-specific target proteins), genomics (disease-specific genetic data), metabolomics (disease-specific metabolic pathways/profile), and phenotypic data can be utilized to guide DR. This includes adverse and side effects, off-target mechanisms, pharmacological targets, illness pathways, pathologic states, and more. Disease-specific networks must be developed, genetic expression must be recognized, essential targets must be considered, and protein molecules involved in cellular and metabolic processes must be identified.

Medication repositioning is presented alongside the various methods and steps required. More than half of the small medication molecules and biologics currently

authorized by the FDA are the result of phenotypic screening and target-based procedures using drugs. Drug candidates can be discovered through phenotypic screening procedures, but this method relies on random observations to sift through large libraries of small molecules.

Methodologies and steps involved in drug repositioning

More than half of the small medication compounds and biologics authorized by the FDA were discovered using phenotypic screening or target-based approaches. In phenotypic drug screening, therapeutic candidates are identified from small molecule libraries based on unexpected discoveries. Drugs are discovered using target-based approaches because their target molecules are already known. Fig. 2 illustrates the steps involved in drug repurposing. Therapeutic or treatment-based repositioning is analogous to disease-based repositioning[69].

We provide a comprehensive breakdown of the numerous approaches used in medication repositioning, accompanied by concrete examples. Various methodologies employed in drug repurposing are depicted in Table II.

Table II: Various methodologies employed in drug repurposing[15,33,34,61,62,69]

Drug	Usual drug	Repurposed to treat
Nilotinib	Leukemia	Parkinson's disease
Metformin	Anti-diabetic	Pancreatic cancer stem cell
Aspirin	Pain killer	Heart attack
Ibuprofen	Anti-inflammatory	Anti-microbial
Sildenafil	Hypertension and angina	Erectile dysfunction
Amantadine	Anti-viral	Parkinson's disease
Cyclosporine	Rheumatoid arthritis and Psoriasis	Transplant rejection

The following is a concise description of the various repositioning options:

Screening method

The reliance on serendipity through biological tests/ experimental screens targeted at specific disease models and therapies is a significant component of blinded search or screening procedures. These approaches tend to be more flexible when it comes to screening a wide variety of medications or conditions.

Target-based method

In vivo and *in vitro* high-throughput and/or high-content screening (HTS/HCS) of drug molecules for a protein target or a biomarker of interest are examples of target-based methods. In contrast, target-independent methods include *in silico* screening of compounds or drugs from large ligand-based screening or molecular docking. Compared to blinded search approaches, these offer a better chance of uncovering potentially helpful pharmaceuticals or drug leads. The entire screening process can be completed in a shorter amount of time.

Knowledge-based methods

Utilized bioinformatics or chemoinformatics methods to compile information such as drug profiles, target and drug chemical structures, drug-target networks, and data from clinical trials. Knowledge-based techniques are more comprehensive in terms of information content compared to blinded and target-based approaches. The ability to make predictions based on available data also allows for its application in forward planning, anticipating new mechanisms, such as unidentified medication targets.

Signature-based method

This method utilizes gene profiles obtained from disease omics data, with or without therapies, to identify off-target effects or disease processes. One source for obtaining genomics data is a publicly available database. Adopting these methods has the potential advantage of allowing researchers to investigate pharmaceutical mechanisms of action that are yet to be discovered. Signature-based strategies use computational tools to examine pharmacological processes at the molecular level, such as alterations in gene expression, as opposed to the knowledge-based approach. Data from disease omics are commonly used in pathway- or network-based approaches.

Pathway- or network-based

Methods are developed using omics data on the disease, existing signaling or metabolic pathways, and protein interaction networks to recreate disease circuits that are essential targets for repositioning medications. The use of such methods has the potential to simplify complex signaling networks by reducing the number of proteins involved (or target molecules).

Targeted mechanism-based method

Targeted mechanism-based techniques can characterize the mechanisms of action of medications about which little is known by integrating treatment omics data with existing signaling circuit knowledge and protein interaction networks. The benefit of these techniques is that they are used not only to decipher disease mechanisms or medications but also to identify those directly related to therapeutic therapies for certain diseases[69-71].

Challenges with repurposing of drugs

Despite its numerous advantages, the economic viability of repurposed therapies is limited. Clinical trial repurposing is expensive, as is demonstrating safety, establishing efficacy, securing patent protection, and achieving commercialization[72]. Despite benefits such as lower costs and a shorter time to market, financial support for medication repurposing initiatives has been lacking[73]. Additionally, the FDA only grants a three-year exclusivity period for a new application of a previously used drugs for a range of purposes, giving pharmaceutical firms limited time to recover their investment and avoid a loss[74]. Drug repurposing may have its roots in the medicalization of previously unrecognized physiological diseases; sildenafil, originally developed as an antihypertensive, is now used to treat erectile dysfunction. A medication that has previously failed due to toxicity issues, as per Ringel, cannot be repurposed for a new indication[75]. He also proposed that by having a thorough grasp of the illness target and mechanisms, market obstacles hindering repurposing can be overcome. Some businesses have attempted to provide a platform for creating disease matrices and chemicals that can be used to treat specific diseases[76].

Furthermore, not all repurposed medications are effective. Bevacizumab, a kinase inhibitor that has been repurposed to treat various types of cancer, was unsuccessful in phase III studies for gastric cancer[77]. Clinical studies using the multikinase inhibitor sunitinib, which had been authorized for the treatment of renal carcinomas, pancreatic neuroendocrine tumors, and gastrointestinal stromal tumors (GISTs), were ineffective for these diseases[78]. Because the medicine has previously been used for another purpose, there is also the potential for it to have unwanted side effects when applied to new situations. Rigorous clinical studies are required before repurposed drugs can be used. To effectively treat a new indication, clinical studies will need to be conducted to determine the optimal dose and delivery schedule.

INTELLECTUAL PROPERTY AND ECONOMIC CONSIDERATIONS

Certain legal challenges may complicate the process of patenting a new medical use and/or enforcing patent rights, potentially reducing the incentives for drug repurposing. For instance, in some countries, obtaining a patent for a product intended for secondary or tertiary medical applications can be challenging. However, most major pharmaceutical markets do offer protection for repurposed medicinal uses. Another consideration is that many potential repurposed uses have either been documented in specialized literature or are currently being employed off-label in clinical practice. Despite the absence of confirmed results from regulated clinical research, this can impact both innovation and patent eligibility.

Pharmaceuticals that currently lack patents may still have the opportunity to obtain one for a new use, although enforcing it can be problematic if the new indication involves readily available dosages and dosage forms. While it is possible to reap some of the benefits of repurposing by using the same strength that was originally marketed, it is preferable if the new indication requires an unmarketed strength (preferably lower than those previously available) or an entirely new formulation. Changing the medication molecule would mean departing from the repurposing approach, making newer derivatives an impractical alternative.

The need for pharmaceutical repurposing is influenced by real factors that may affect the patenting of new medical uses and the utilization of patent rights. Firstly, in certain national laws, obtaining a patent for a drug's second or subsequent medical use can be challenging, although this is not the case in most of the world's major pharmaceutical markets. Secondly, several off-label, unregistered applications are currently in use in clinical practice or have been documented in specialized literature. The implications for novelty and patentability are recognized, even though controlled clinical studies have not yet been conducted to validate such usage.

A patent for a new medical use can be obtained after the original patent has expired. However, if the new indication involves a drug that is available on the market in the appropriate dose and strength forms, it can pose challenges. As a result, while using the same strengths that were advertised for the original indication may yield some therapeutic benefits, it would be ideal, if the new indication called for either not-commercially available strengths (preferably ones that were lower than those that were previously available) or a special, innovative formulation. Due to the fact that modifying the medication

molecule would imply abandoning the repurposing process, new derivatives cannot be considered.

Data and compound availability

Gradually, the drug development industry is embracing the open-source model. However, there are still barriers to public access to certain critically important data, such as clinical trials. Some data, like imaging data, can be challenging to extract, combine, and manage due to its non-standard format or complexity, even when access is not an issue. Additionally, integrating diverse forms of data has been demonstrated to be computationally intensive.

A significant hurdle to medication repurposing may arise when a potential new indication falls outside the scope of an organization, and the pharmaceutical company is reluctant to disclose its chemical library for exploring future uses of its compound collections. Even when a major institution is open to crowdsourcing or collaborating with smaller businesses, the underlying administrative processes, particularly those related to who can sign material transfer agreements and how compounds are distributed, should be streamlined and made more flexible, including boutique firms or academic groups.

Generic versions of active pharmaceutical compounds may also face supply challenges at times, especially, if the original chemical has been withdrawn from foreign markets. In such situations, finding a reliable vendor can be challenging[79-81].

CAN THE REPURPOSING SPACE BE EXHAUSTED?

Although, there are undoubtedly many diseases in need of improved therapeutic approaches or novel treatments, the potential for medication repurposing for specific diseases may be quickly exhausted due to extensive drug repurposing efforts. Over the years, numerous high-throughput screens have been conducted in an attempt to identify repurposed medicines effective against trypanosomiasis, such as Chagas disease. Alongside these, several low-throughput screens, both *in silico* and wet screens, have effectively targeted specific therapeutic targets, and included experimental confirmation of the results.

For example, one might question the necessity for further phenotypic screening specifically focused on *Trypanosoma cruzi*, a parasite that occurs naturally. Similarly, one might wonder if the interest in medication repurposing will decline over a time as successive systematic screenings of known drugs are carried out[79-85].

EXAMPLES OF REPURPOSING DRUGS

Aspirin

Acetylsalicylic acid is undoubtedly one of the oldest examples of drug repurposing. Aspirin was initially introduced as an analgesic by Bayer in 1899. Later, in the 1980s, it was repurposed as an antidepressant, but only at low doses. It is a drug that prevents platelets from aggregating[86]. It is still in widespread use today, primarily as a preventive measure against heart attacks and strokes. For his work, which earned him the Nobel Prize in Medicine in 1982, Dr. J. R. Vane's research played a crucial role[87]. Dr. Lawrence Craven, a general practitioner at California's Glendale Memorial Hospital, observed that aspirin can lead to increased bleeding when administered to patients undergoing tonsillectomy as an analgesic. Thromboxin A2 is a potent activator of platelet aggregation, and the enzyme platelet cyclooxygenase 1 (COX-1) is responsible for its production from the prostaglandin precursor leukotriene B4. To prevent platelet aggregation, aspirin continuously blocks the cyclooxygenase-1 enzyme.

Aspirin's analgesic and anti-inflammatory effects result from its ability to inhibit cyclooxygenase 2 (COX-2), particularly vascular COX-2, an enzyme crucial in the production of prostaglandins that cause pain and prevent platelet aggregation. Aspirin exhibits limited selectivity for COX-1 at low dosages (300 mg day^{-1}), and exerts its antiplatelet aggregation effect, which is overridden at

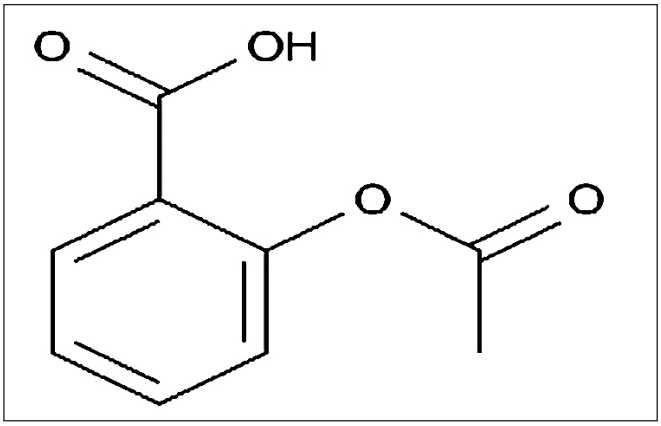

Fig. 3: Structure of aspirin[87]

higher levels due to concurrent COX-2 inhibition. Aspirin's anti-inflammatory benefits are attributed to COX-1's involvement in producing prostaglandins responsible for cytoprotection. However, this is also the reason for the drug's adverse effects on the digestive system, which are unrelated to the dosage. In the near future, aspirin could assume a different role in cancer prevention. Research indicates that taking aspirin daily for at least

Table III: Repurposed drugs for treating bacterial infections[91,92,93,94]

Drug	Initial use	New use
Amlodipine	Anti-hypertensive agents	Anti-bacterial, antileishmanial and antitrypanosomial
Chlorpromazine	Dopamine antagonist to treat schizophrenia	Anti-amoebic, anti-bacterial agent
Ebselen	Anti-atherosclerotic, anti-inflammatory and anti-oxidative	Anti-microbial activity
Dicyclomine	Anti-spasmodic agent	Anti-bacterial agent
Phenothiazine prototype methdilazine	Skin allergy	Anti-bacterial agent
Oxyfedrine hydrochloride	Used in the treatment of cardiovascular disorder like angina pectoris as vasodilators	Anti-bacterial agent
Edaravone	Treatment of brain ischemia and myocardial ischemia	Anti-bacterial agent

five years can reduce the risk of developing various types of cancer, including colorectal cancer[88]. The anticancer action of aspirin is believed to result from its inhibition of COX-2, which counteracts COX-2's antiapoptotic effect in cancer cells and promotes apoptotic cell death[89]. Fig. 3 demonstrates the structure of aspirin.

Thalidomide

In 1962, the World Health Organization (WHO) banned thalidomide due to its serious teratogenic effects, which resulted in the deaths of thousands of people worldwide and continued to affect a second generation, largely due to its use as an antiemetic for pregnant women. However, in 1964, Dr. Jacob Sheskin of Jerusalem's Hadassah University demonstrated its exceptional effectiveness against erythema nodosum leprosum, an autoimmune complication of leprosy. In 1998, Celgene reclassified thalidomide as an orphan drug for the treatment of leprosy sequelae because of its ability to inhibit the production of the proinflammatory cytokine tumor necrosis factor-alpha (TNF-a)[90]. Certainly, its use must be coupled with strict contraceptive measures to ensure that pregnant women and children are not exposed to the medication. These case studies illustrate that a medication's toxicity profile does not necessarily need to be ideal for it to be repurposed, especially if the new indication is for a rare condition.

In the field of cancer, thalidomide has undergone a similar repositioning process as aspirin. Research into the mechanism of thalidomide's teratogenicity led to the discovery of the drug's antiangiogenic activity, which is responsible for the limb development abnormalities observed after in utero exposure. Subsequently, it underwent another repositioning, this time as a frontline therapy for multiple myeloma, following initial studies suggesting its effectiveness in blocking or destroying blood vessels that supply malignant tumors. Concerns are widely shared, and in Europe, the prescription and distribution of thalidomide are closely regulated. The structure of thalidomide is depicted in Fig. 4.

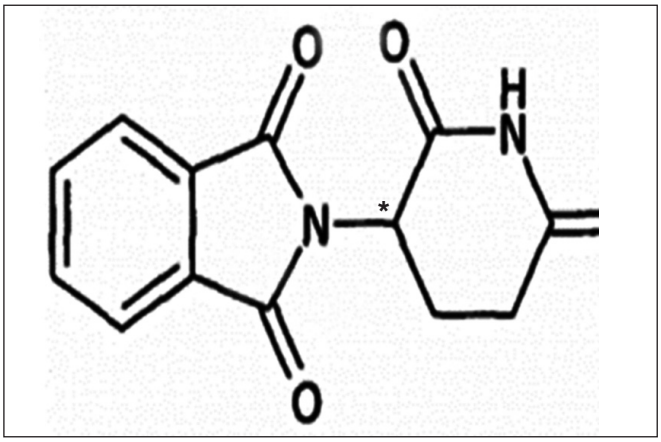

Fig. 4: Structure of thalidomide[90]

Potential for repurposing medications in treating bacterial infections

These days, bacterial infections are one of the leading causes of death worldwide, posing a significant security risk for humanity as a whole. The emergence of drug-resistant bacteria is a threat to public health due to the overuse and improper use of antibiotics, as well as the lack of new antibiotics[91]. In the critical care unit, multidrug-resistant bacterial infections can be a significant cause of mortality and disability[92].

Bacterial multidrug resistance is caused by two mechanisms:

(i) The accumulation of many R plasmids within a single cell, each of which encodes resistance to a different drug class.

(ii) Multidrug efflux pump activity, where a single pump can expel a wide variety of drugs.

Examples of drug-resistant microbes include:

- Cephalosporin- and fluoroquinolone-resistant *E. coli*
- Multidrug-resistant *Klebsiella pneumoniae*
- Antibiotic-resistant *Staphylococcus aureus*
- Penicillin-resistant *Streptococcus pneumoniae*
- Fluoroquinolone-resistant non-typhoidal *Salmonella*
- Cephalosporin-resistant *Neisseria gonorrhoeae*
- MDR-TB, caused by *Mycobacterium tuberculosis* that has developed resistance to at least one of the three main drugs used to treat it: rifampin, isoniazid, and fluoroquinolones[94].

New antibiotics are being developed, but researchers are primarily focusing on those that meet specific criteria:

(i) Giving greater attention to novel targets and mechanisms, such as the cell-cell communication between bacteria that up-regulates virulence.

(ii) Exploring alternative antimicrobials, such as bacteriophages.

(iii) The development of multidrug efflux pump blockers[95] is one type of bacterial resistance inhibitor that has been explored. The concept of "new applications for existing pharmaceuticals" is a popular topic in pharmaceutics, rivaling the development of newer antibiotics in terms of interest. Clinical survey data suggests that approximately 50% of already available medications are being reconsidered for potential new therapies[96].

Here are a few examples of FDA-approved drugs that have been modified to treat bacterial infections. Repurposed drugs for treating bacterial infections are shown in Table III.

Opportunities of repurposed drugs in cancer treatment

Cancer has become a significant threat to the community in recent years. Only 5-10% of cancer cases are caused by genetic abnormalities, while the remaining 90%-95% are attributed to environmental and lifestyle factors[97]. Therapeutic options may include surgery, chemotherapy, or radiation therapy. Examples of unconventional therapies include targeted radionuclide therapies, targeted immunotherapies, apoptosis regulation therapies, anti-angiogenesis therapies, differentiation therapies, transmission therapies, and nucleic acid-based therapies. Additionally, a significant challenge nowadays is the development of tumor resistance to anticancer medicines[98].

Since the 1990s, the number of FDA-approved cancer treatments has decreased. Due to the shortage of medications, a novel idea was developed: the repurposing of FDA-approved non-cancer treatments[99]. Existing non-cancer pharmaceuticals were examined for their anticancer efficacy because only around 5% of novel cancer treatments reach phase I clinical trials and are regularly used for cancer therapy[100]. Previous studies have shown that treating cancer with a single medicine is less successful than treating it with a combination of drugs because cancer leads to more DNA alterations. Therefore, preclinically and clinically tested drugs originally intended for other conditions may be useful in treating cancer through repurposing[101]. Some of the FDA-approved cancer treatments are shown in Table IV.

However, there have been few reported cases of effective medication repurposing for cancer therapy. Therefore, there is a substantial need for the repurposing of pharmaceuticals for cancer therapies, providing researchers with ample opportunities to investigate FDA-approved non-cancer drugs for cancer treatments[101].

Table IV: Repurposed drugs for treating cancer[97-101]

Drug	Initial use	New use
Cimetidine	Gastric or duodenal ulcer	Colorectal cancer
Thalidomide	Nausea	Bone marrow cancer
Raloxifene	Osteoporosis	Breast cancer
Chloroquine	Anti-malarial	Suppress growth of tumor cells
Aspirin	Stroke	Colorectal cancer
Mebendazole	Anti-helminthic	Lung cancer
Metformin	Diabetes	Breast cancer

CONCLUSION

Drug repositioning is a potential method gaining attraction among governments and pharmaceutical firms due to its critical role in reducing time, cost, and risk in the development of medicines. The future of contemporary medicine lies in drug repurposing. Proper strategies and methodologies can aid in the revolutionization of drug repositioning to meet/unmet customer demands. In recent months, there has been significant progress in this area of study, driven by the urgent need for drugs to address the COVID-19 outbreak. In the era of precision medicine, the drug repositioning technique has been crucial for understanding how drugs work by studying innovative disease, metabolic, and signaling pathways, off-targets, target-specific processes, as well as genomic expression profiles for genetic illnesses.

REFERENCES

1. Dey G., Jyothi R. and Girish K.: An overview of drug repurposing: Review article, **J. Med. Sci. Clin. Res.,** 2019, 7, 55-56.
2. Sindhu S. and Murugan S.: Challenges and opportunities in repurposing of drugs: Mini Review, **Bangladesh J. Medical Sci.,** 2020, 19, 365-371.
3. Kaitin K. I.: Deconstructing the drug development process: the new face of innovation, **Clin. Pharmacol. Therapeut.,** 2010, 87, 356–361.
4. Tobinick E.: The value of drug repositioning in the current pharmaceutical market, **Drug News Perspect.,** 2009, 22, 53.
5. Sleigh S. H. and Barton C.L.: Repurposing strategies for therapeutics, **Pharmaceut. Med.,** 2010, 24, 151–159.
6. Novac Natalia.: Challenges and opportunities of drug repositioning, **Trends Pharmacol. Sci.,** 2013, 34, 267–272.
7. Clout A. E., Della P. O., Hanna M.G., Orlu M. and Pitceathly R.D.S.: Drug repurposing in neurological diseases: an integrated approach to reduce trial and error, **J. Neurol. Neurosurg. Psychiatry,** 2019, 90, 1270.
8. Drouin E. and Drouin G.: The first report of Alzheimer's disease, **Lancet Neurol.,** 2017, 16, 687.
9. Qu L. and Tang X.: Bexarotene: a promising anticancer agent, **Cancer Chemother. Pharmacol.,** 2010, 65, 201–205.
10. Baccarani M., Saglio G., Goldman J., Hochhaus A. and Hehlmann R.: Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet, **Blood,** 2007, 108,1809–1820.
11. Ben A. E. and Demetri G. D.: A safety evaluation of imatinib mesylate in the treatment of gastrointestinal stromal tumor, **Expet. Opin. Drug Saf.,** 2016, 15, 571–578.
12. Wang J., Ho L., Chen L., Zhao Z., Wei Z., Qian X., Humala N., Seror I., Bartholomew S. and Rosendorff C.: Valsartan lowers brain β-amyloid protein levels and improves spatial learning in a mouse model of alzheimer disease, **J. Clin. Invest.,** 2007, 117, 3393–3402.
13. Bachmeier C., Beaulieu-Abdelahad D., Mullan M. and Paris D.: Selective dihydropyiridine compounds facilitate the clearance of β-amyloid across the blood-brain barrier, **Eur. J. Pharmacol.,** 2011, 659, 124–129.
14. Vanhanen H., Fa Gard R., Tuomilehto J., Birkenhäger W., Seux M. L., Staessen J. A., Babeanu S., Webster J., Yodfat Y. and Forette F.: The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study, **Arch. Intern. Med.,** 2003, 12, 32–33.
15. Rudrapal M., Khairnar S. J. and Jadhav A. G.: Drug Repurposing (DR): An emerging approach in drug discovery, in: Drug Repurposing - Hypothesis, molecular aspects and therapeutic applications, London, IntechOpen, 2020, 99193.
16. Zhang R., Hristovski D., Schutte D., Kastrin A., Fiszman M. and Kilicoglu H.: Drug repurposing for COVID-19 via knowledge graph completion, **J. Biomed. Inform.,** 2021, 115, 103696.
17. Dotolo S., Marabotti A., Facchiano A. and Tagliaferri R.: A review on drug repurposing applicable to COVID-19, **Brief. Bioinform.,** 2021, 22, 726–741.
18. Oliveira EAM and Lang K. L.: Drug repositioning: concept, classification, methodology, and importance in rare/orphans and neglected diseases, **J. Appl. Pharm. Sci.,** 2018, 8, 157–165.
19. Herrmann I. K., Wood M. J. A. and Fuhrmann G.: Extracellular vesicles as a next-generation drug delivery platform, **Nat. Nanotechnol.,** 2021, 16, 748–759.
20. Cusinato J., Cau Y., Calvani A. M. and Mori M.: Repurposing drugs for the management of COVID-19, **Expert Opin. Ther. Patents,** 2021, 31, 295–307.
21. Singh T. U., Parida S., Lingaraju M. C., Kesavan M., Kumar D. and Singh R. K.: Drug repurposing approach to fight COVID-19, **Pharmacol. Rep.,** 2020, 72, 1479–1508.
22. Parvathaneni V. and Gupta V.: Utilizing drug repurposing against COVID-19–Efficacy, limitations, and challenges. **Life Sci.,** 2020, 259, 118275.
23. Lu H.: Drug treatment options for the 2019-new coronavirus (2019-nCoV), **Biosci. Trends,** 2020, 14, 69–71.
24. Liu S., Zheng Q. and Wang Z.: Potential covalent drugs targeting the main protease of the SARS-CoV-2 coronavirus, **Bioinform.,** 2020, 36, 3295–3298.
25. Altay O., Mohammadi E., Lam S., Turkez H., Boren J., Nielsen J, Uhlen M. and Mardinoglu A.: Current status of COVID-19 therapies and drug repositioning applications, **iScience,** 2020, 23, 101303.
26. Galindez G., Matschinske J., Rose T. D., Sadegh S., Salgado-Albarrán M., Späth J. and Pauling J. K.: Lessons from the COVID-19 pandemic for advancing computational drug repurposing strategies, **Nat. Comput. Sci.,** 2021, 1, 33–41.
27. Chatre C., Roubille F., Vernhet H., Jorgensen C. and Pers Y. M.: Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature, **Drug Saf.,** 2018, 41, 919–931.
28. Liu J., Du C., Pu L., Xiang P., Xiong H., Xie W. and Li A.: Comparative therapeutic efficacy of interferon alfa-2b and combination lopinavir/ritonavir plus interferon alfa-2b against SARS-CoV-2; **BMC Infect. Dis.,** 2021, 21, 1–8.
29. Ashburn T. T. and Thor K. B.: Drug repositioning, identifying and developing new uses for existing drugs, **Nat. Rev. Drug Discov.,** 2004, 3, 673-683.
30. Berdigaliyev N. and Aljofan M.: An overview of drug discovery and development, **Future Med. Chem.,** 2020, 12, 939-947.
31. Parvathaneni V., Kulkarni N. S., Muth A. and Gupta V.: Drug repurposing: a promising tool to accelerate the drug discovery process, **Drug Discov. Today,** 2019, 24, 2076-2085.
32. Maya A. F. and Eric D. B.: Drug repurposing for antimicrobial discovery, **Nat. Microbiol.,** 2019, 4, 565-577.
33. Hanqing X., Jie L., Haozhe X. and Yadong W.: Review of drug repositioning approaches and resources, **Int. J. Biol. Sci.,** 2018, 14, 1232-1244.

34. Tamer N. J., Jon G. R. and Reda A.: A review of computational drug repositioning: strategies, approaches, opportunities, challenges, and directions, **J. Cheminformatics,** 2020, 12, 46.
35. Hamosh A., Scott A. F., Amberger J. S., Bocchini C. A. and Mckusick V. A.: Online Mendelian Inheritance in Man (OMIM), a knowledge base of human genes and genetic disorders, **Nucleic Acids**, 2005, 33, D514-517.
36. Ogata H., Goto S., Sato K., Fujibuchi W., Bono H. and Kanehisa M.: KEGG: Kyoto Encyclopedia of Genes and Genomes, **Nucleic Acids, Res.,** 1999, 27, 29-34.
37. Luo H., Wang J., Li M., Luo J., Peng X., Wu F. X. and Pan Y.: Drug repositioning based on comprehensive similarity measures and Bi-Random walk algorithm, **Bioinform.,** 2016, 32, 2664-2271.
38. Oprea T. I. and Overington J. P.: Computational and practical aspects of drug repositioning, **Assay Drug Dev. Technol.,** 2015, 13, 299-306.
39. Mali D. P. and Bhatia N. M.: Hetero-tricyclic lead scaffold as novel PDE5A inhibitor for antihypertensive activity: *In silico* docking studies, **Curr. Comput. Aided Drug Des.,** 2019, 15, 318-333.
40. Mali D. P. and Bhatia N. M.: Discovery of two novel hetero-tricyclic lead scaffolds as PDE5A inhibitor: virtual screening, molecular docking and pharmacophore modeling approach, **Nat. Prod. Res.,** 2021, 35, 92-98.
41. Alexander P. and Jean D.: New advances in the molecular biology of hepatitis C virus infection: towards the identification of new treatment targets, **Gut,** 2012, 61, i25–i35.
42. Indu P., Ragavan R. M., Narasingam A. and Al-Dhabi N. A. and Ignacimuthu S.: Raltegravir, Indinavir, Tipranavir, Dolutegravir, and Etravirine against main protease and RNA-dependent RNA polymerase of SARS-CoV-2: a molecular docking and drug repurposing approach, **J. Infection Public Health,** 2020, 13, 1856-1861.
43. Chen Y. W., Yiu C. and Wong K. Y.: Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CLpro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates, **F1000Res.,** 2020, 9, 129.
44. Lo M. K., Jordan R., Arvey A., Sudhamsu J., Shrivastava-Ranjan P., Hotard A. L., Flint M., Mcmullan L. K., Siegel D. and Clarke M. O et. al.: GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. **Sci. Rep.,** 2017, 7, 43395.
45. Mothay D. and Ramesh K.V.: Binding site analysis of potential protease inhibitors of COVID-19 using AutoDock, **VirusDisease,** 2020, 31, 194–199.
46. Berger N. A., Besson V. C., Boulares A. H., Bürkle A., Chiarugi A., Clark R. S., Curtin N. J., Cuzzocrea S., Dawson T. M., Dawson V. L., Haskó G., Liaudet L., Moroni F., Pacher P., Radermacher P., Salzman A. L., Snyder S. H., Soriano F. G., Strosznajder R. P., Sümegi B., Swanson R. A. and Szabo C.: Opportunities for the repurposing of PARP inhibitors for the therapy of non-oncological diseases, **Br. J. Pharmacol.,** 2018, 175, 192–222.
47. Lin S. Y., Liu C. L., Chang Y. M., Zhao J., Perlman S. and Hou M. H.: Structural basis for the identification of the *N*-terminal domain of coronavirus nucleocapsid protein as an antiviral target, **J. Med. Chem.,** 2014, 57, 2247.
48. Sekhar T.: Molecular docking and virtual screening based prediction of drugs for COVID-19, **Comb. Chem. High Throughput Screen.,** 2021, 24, 716–728.
49. Hall D. C. and Ji H.-F.: A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease, **Trav. Med. Infect. Dis.,** 2020, 35, 101646.
50. Hsieh S. C., Wu Y. C., Zou G., Nerurkar V. R., Shi P. Y. and Wang W. K.: Highly conserved residues in the helical domain of dengue virus type 1 precursor membrane protein are involved in assembly, precursor membrane (prM) protein cleavage, and entry, **J. Biol. Chem.,** 2014, 289, 33149.
51. Kashour Z., Riaz M., Garbati M. A., AlDosary O., Tlayjeh H., Gerberi D., Murad M. H., Sohail M. R., Kashour T. and Tleyjeh I. M.: Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis, **J. Antimicrob. Chemother.,** 2020, 76, 30–42.
52. Zhou Y., Hou Y., Shen J., Huang Y., Martin W. and Cheng F.: Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2, **Cell Discov.,** 2020, 6, 14.
53. Yadav R., Chaudhary J. K., Jain N., Chaudhary P. K., Khanra S., Dhamija P., Sharma A., Kumar A. and Handu S.: Role of structural and non-structural proteins and therapeutic targets of SARS-CoV-2 for COVID-19, **Cells,** 2021, 10, 821.
54. Serafin M. B., Bottega A., Foletto V. S., da Rosa T. F., Hörner A. and Hörner R.: Drug repositioning is an alternative for the treatment of coronavirus COVID-19, **Int. J. Antimicrob. Agents,** 2020, 55, 105969.
55. Zheng W., Sun W. and Simeonov A.: Drug repurposing screens and synergistic drug-combinations for infectious diseases, **Br. J. Pharmacol.,** 2017, 175, 181–191.
56. Wang M. Y., Zhao R., Gao L. J., Gao X. F., Wang D. P. and Cao J. M.: SARS-CoV-2: Structure, biology, and structure-based therapeutics development, **Front. Cell Infect. Microbiol.,** 2020, 10, 587269.
57. Walls A. C., Park Y. J., Tortorici M. A., Wall A., McGuire A. T. and Veesler D.: Structure, function, and antigenicity of the SARS-CoV-2 Spike Glycoprotein, **Cell,** 2020, 181, 281–292.
58. Rahman M. S., Hoque M. N., Islam M. R., Islam I., Mishu I. D., Rahaman M. M., Sultana M. and Hossain M. A.: Mutational insights into the envelope protein of SARS-CoV-2, **Gene Rep.,** 2021, 22, 100997.
59. O'Leary V. B., Dolly O. J., Höschl C., Černa M. and Ovsepian S. V.: Unpacking pandora from its box: Deciphering the molecular basis of the SARS-CoV-2 coronavirus, **Int. J. Mol. Sci.,** 2020, 22, 386.
60. Zeng W., Liu G., Ma H., Zhao D., Yang Y., Liu M., Mohammed A., Zhao C., Yun Y., Xie J., Ding C., Ma X., Weng J., Gao Y., He H. and Jin T.: Biochemical characterization of SARS-CoV-2 nucleocapsid protein, **Biochem. Biophys. Res. Commun.,** 2020, 527, 618–623.
61. Li X., Yu J., Zhang Z., Ren J., Peluffo A. E. and Zhang W.: Network bioinformatics analysis provides insight into drug repurposing for COVID-2019, **Med. Drug Discov.,** 2021, 10, 100090.
62. Nicastri E., Petrosillo N., Ascoli B. T., Lepore L., Mondi A., Palmieri F., D'Offizi G., Marchioni L., Murachelli S., Ippolito G. and Antinori A.: National Institute for the Infectious Diseases "L. Spallanzani", IRCCS, Recommendations for COVID-19 clinical management, **Infect. Dis. Rep.,** 2020, 12, 8543.
63. Grein J., Ohmagari N., Shin D., Diaz G., Asperges E. and Castagna A.: Compassionate use of remdesivir for patients with severe Covid-19, **N. Engl. J. Med.,** 2020, 382, 2327–2336.
64. Beigel J. H., Tomashek K. M., Dodd L. E., Mehta A. K., Zingman B. S., Kalil A. C., Hohmann E., Chu H. Y., Luetkemeyer A., Kline S., Lopez C. D., Finberg R. W., Dierberg K., Tapson V., Hsieh L., Patterson T. F., Paredes R., Sweeney D. A., Short W. R., Touloumi G., Lye D. C., Ohmagari N., Oh M. D., Ruiz-Palacios G. M., Benfield T., Fätkenheuer G., Kortepeter M. G., Atmar R. L., Creech C. B., Lundgren J., Babiker A. G., Pett S., Neaton J. D., Burgess T. H., Bonnett T., Green M., Makowski M., Osinusi A., Nayak S. and Lane H. C.; Remdesivir for the Treatment of

Covid-19 - Final Report, **N. Engl. J. Med.,** 2020, 383, 1813-1826.

65. Goldman J. D., Lye D. C. B., Hui D. S., Marks K. M., Bruno R. and Montejano R.: Remdesivir for 5 or 10 days in patients with severe Covid-19, **N. Engl. J. Med.,** 2020, 383, 1827-1837.
66. Koch U., Hamacher M. and Nussbaumer P.: Cheminformatics at the interface of medicinal chemistry and proteomics, **Biochem. Biophys. Acta,** 2014, 1844, 156-161.
67. Napolitano F., Zhao Y. and Moreira V. M.: Drug repositioning, A machine-learning approach through data integration, **J. Cheminformatics,** 2013, 5, 30.
68. Chong C. R., Chen X., Shi L., Liu J. O. and Sullivan D. J.: A clinical drug library screen identifies astemizole as an antimalarial agent, **Nat. Chem. Biol.,** 2006, 2, 415-416.
69. Apple by B. S. and Cummings J. L.: Discovering new treatments for Alzheimer's disease by repurposing approved medications, **Curr. Top. Med. Chem.,** 2013, 13, 2306-2327.
70. Shah B., Modi P. and Sagar S. R.: *In silico* studies on therapeutic agents for COVID-19, Drug repurposing approach, **Life Sci.,** 2020, 20, 117652.
71. Shineman D. W., Alam J., Anderson M., Black S. E., Cerman A. J., Cummings J. L., Dacks P. A., Dudley J. T., Frail D. E., Green A., Lane R. F., Lappin D., Simuni T., Stefanacci R. G., Sherer T. and Fillit H. M.: Overcoming obstacles to repurposing for neurodegenerative disease, **Ann. Clin. Transl. Neurol.,** 2014, 1, 512-518.
72. Guangxu J. and Stephen T. C. W.: Toward better drug repositioning: prioritizing and integrating existing methods into efficient pipelines, **Drug Discov. Today,** 2014, 19, 637-644.
73. Chong C. R. and Sullivan D. R.: New uses for old drug, **Nature,** 2007, 448, 645-646.
74. Rahman S. Z., Gupta V., Sukhlecha A. and Khunte Y.: Lifestyle drugs: Concept and impact on society, **Indian J. Pharm. Sci.,** 2010,72, 409-413.
75. Eftychia L., Spyros N., Deftereos, Aris P., Andreas P. and Christos A.: Literature analysis for systematic drug repurposing: a case study from Biovista, **Drug Discov. Today Ther. Strateg.,** 2011, 8, 103-108.
76. Li Y. Y. and Jones S. J.: Drug repositioning for personalized medicine, **Genome Med.,** 2012, 4, 27.
77. Kim S., Ding W., Zhang L., Tian W. and Chen S.: Clinical response to sunitinib as a multitargeted tyrosine-kinase inhibitor(TKI) in solid cancers: a review of clinical trials, **Onco. Targets Ther.,** 2014, 7, 719-728.
78. Alan T. and Carolina L. B.: Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics, **Expert Opin. Drug Discov.,** 2020, 15, 397-401.
79. Pushpakom S., Iorio F. and Eyers P. A.: Drug repurposing: progress, challenges and recommendations, **Nat. Rev. Drug Discov.,** 2019, 18, 41-58.
80. Breckenridge A. and Jacob R.: Overcoming the legal and regulatory barriers to drug repurposing, **Nat. Rev. Drug Discov.,** 2019, 18, 1-2.
81. Allarakhia M.: Open-source approaches for the repurposing of existing or failed candidate drug: learning from and applying the lessons across diseases, **Drug Des. Devel. Ther.,** 2013, 7, 753-766.
82. Ritchie M. D., Holzinger E. R. and Li R.: Methods of integrating data to uncover genotype-phenotype interactions, **Nat. Rev. Genet.,** 2015, 16, 85-97.
83. Engel J. C., Ang K. K. H. and Chen S.: Image-based high-throughput drug screening targeting the intracellular stage of Trypanosoma cruzi, the agent of Chaga's disease, **Antimicrob. Agents Chemother.,** 2010, 54, 3326-3334.
84. Alirol E., Schrumpf D. and Amici Heradi J.: Nifurtimox-eflornithine combination therapy for second-stage gambiense human African trypanosomiasis, Medicines Sans Frontieres experience in the Democratic Republic of the Congo, **Clin. Infect. Disease,** 2013, 56, 195-203.
85. Monneret C. and Bohuon C.: Fabuleuxhasards: historie de la decouverte de medicament. Paris: EDP, 2009.
86. Vane J. R.: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs, **Nat. New Biol.,** 1971, 231, 232-235.
87. Rothwell P. M.: Effect of daily aspirin on long-term risk of death due to cancer: Analysis of individual patient data from randomized trials, **Lancet,** 2011, 377, 31-41.
88. Ruscoff J., Wallinger S., Dietmaier W., Bocker T., Brockhoff G., Hofstädter F. and Fishel R.: Aspirin suppresses the mutator phenotype associated with hereditary nonpolyposis colorectal cancer by genetic selection. **Proc. Natl. Acad. Sci. U S A.,** 1998, 95, 11301-6.
89. Raje N. and Anderson K.: Thalidomide a revival story, **N. J. Med.,** 1999, 341, 1606-1609.
90. Lau Q. Y., Tan Y. Y., Goh V. C., Lee D. J., Ng F. M., Ong E. H., Hill J. and Chia C.S. An FDA-Drug library screen for compounds with bioactivities against Meticillin-Resistant *Staphylococcus aureus* (MRSA), **Antibiotics (Basel),** 2015, 4, 424-34.
91. Maviglia R., Nestorini R. and Pennisi M.: Role of old antibiotics in multidrug resistant bacterial infections, **Curr. Drug Targets,** 2009, 10, 895-905.
92. Nikaido H.: Multidrug resistance in bacteria, **Ann. Rev. Biochem.,** 2009, 78, 119-146.
93. Jyoti T., Shrayanee D., Zeeshan F. and Saif H.: Multidrug resistance: an emerging crisis. **Interdiscip. Perspect. Infect. Dis.,** 2014, 541340.
94. Rangel-Vega A., Bernstein L. R., Mandujano-Tinoco E. A., García-Contreras S. J. and García-Contreras R.: Drug repurposing as an alternative for the treatment of recalcitrant bacterial infections, **Front. Microbiol.,** 2015, 6, 282.
95. Allarakhia M.: Open-source approaches for the repurposing of existing or failed candidate drugs: learning from and applying the lessons across diseases, **Drug Des. Devel. Ther.,** 2013, 7, 753-766.
96. Anand P., Kunnumakara A. B., Sundaram C., Harikumar K. B., Tharakan S. T., Lai O. S., Sung B. and Aggarwal B. B.: Cancer is a preventable disease that requires major lifestyle changes, **Pharm. Res.,** 2008, 5, 209-216.
97. Ke X. and Shen L.: Molecular targeted therapy of cancer: the progress and future prospect, **Front. Laboratory Medicine,** 2017, 1, 69-75.
98. Sleire L., Forde-Tislevoll H. E., Netland I. A., Leiss L., Skeie B. S. and Enger P. O.: Drug repurposing in cancer, **Pharmacol. Res.,** 2017, 124, 74-91.
99. Kato S., Moulder S. L., Ueno N. T., Jennifer J. W., Meric-Bernstam F., Razelle K. and Janku F.: Challenges and perspective of drug repurposing strategies in early phase clinical trials, **Oncoscience,** 2015, 2, 576-580.
100. Bertolini F., Sukhatme V. P. and Bouche G.: Drug repurposing in oncology-patient and health systems opportunities. **Nat. Rev. Clin. Oncol.,** 2015, 12, 732-742.
101. Sindhu S. and Murugan S.: Challenges and opportunities in repurposing of drugs: Mini Review, **Bangladesh J. Medical Sci.,** 2020, 19, 365-371.