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Drug Repurposing; A Cumulative Study On A Multi-Faceted Alternative To De Novo Synthesis

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Abstract

Challenges faced by the pharmaceutical industry when it comes to treating various diseases are ever growing. There is a need to find out alternatives to supplement the growth of research and development segment in a cost-effectivemanner in order to increase the pace of delivery of medications to patients in need. One of these ways is drug repurposing which essentially is an approach tofind new therapeutic uses of a drug than the one it was originally used for. This approach circumvents various safety and toxicity trials that generally take up a lot of time when it comes to development since the data is already available.

Various approaches towards drug repurposing are already available or are underdevelopment. This review covers various approaches towards drug repurposing while delving deeper into 5 major drug categories and examples of few drugs along with rare diseases and drugs repurposed for them. We have also emphasized on the prospect of drug repurposing approach in the coming years while taking a look at the past when it comes to various drugs that were initiallyused for certain indications but were later repurposed to provide therapeutic value for indications that were different from the original ones.

Introduction

In the current global scenario, the pharmaceutical industry faces the challenge of slow conversion of knowledge to treat human diseases into medicinal benefits despite the amelioration of technology (Pushpakom et al., 2018a). The development of new drug is a strenuous process, influenced by the high monetary value, time required. A timeline of 10-15 years along with infusion offunds ranging from $500 million to $2 billion is what the process of the currentdrug development requires (Deftereos et al., 2011). In order to subdue these challenges a strategy of Drug repurposing has been widely adopted by various pharmaceuticals.

Drug repurposing can be defined as an approach for figuring out new therapeutic uses of an accepted drug that vary from the original medicinal effects for which the medical indication initially was used. It is also known as drug reprofiling or drug repositioning (Gil & Martinez, 2021; Pushpakom et al., 2018). The drug molecules that have been dropped due to certain reasons during the trial phase or the development phase can also be repurposed. (Mehta & Dhapte- Pawar, 2021a) The 3 basic elements of Drug Repurposing are given in fig 1.

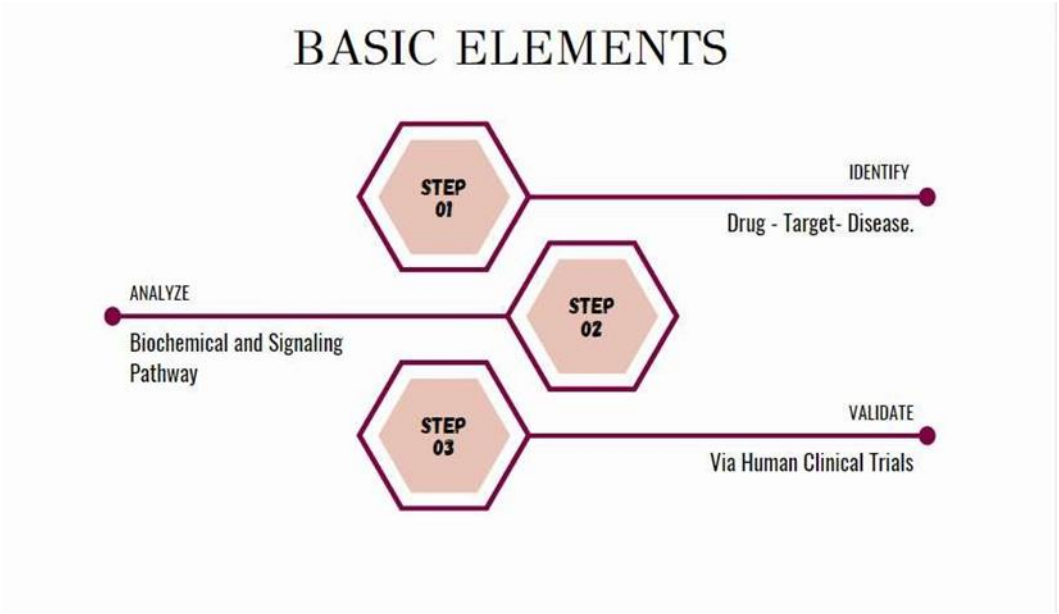


Fig -1 (Mehta & Dhapte-Pawar, 2021a)

Step 1 of the process involves the correct identification ofDrug, its target and the disease it affects which is followed up with the analysis of the biochemical and signaling pathway. This final process involves validation of the drug via human clinical trials. All these being the vital steps aid in drug repurposing process.

The advantages of this strategy include the 1) reassurance of safety due to the existence of data on previously conducted preclinical studies, safety trials if they have been completed and efficacy trials. In such instance phase II clinical studies can be directly be approached bypassing phase I clinical trials. 2) The investment cost is lowered 3) The timeline of the process can be shortened and up to 5-7 years can be saved due to the presence of pre-existing data on studies, assessment, manufacturing processes and in certain cases formulation development if it has been completed. (Cha et al., 2018a; Gil & Martinez, 2021a; Pushpakom et al., 2018a).

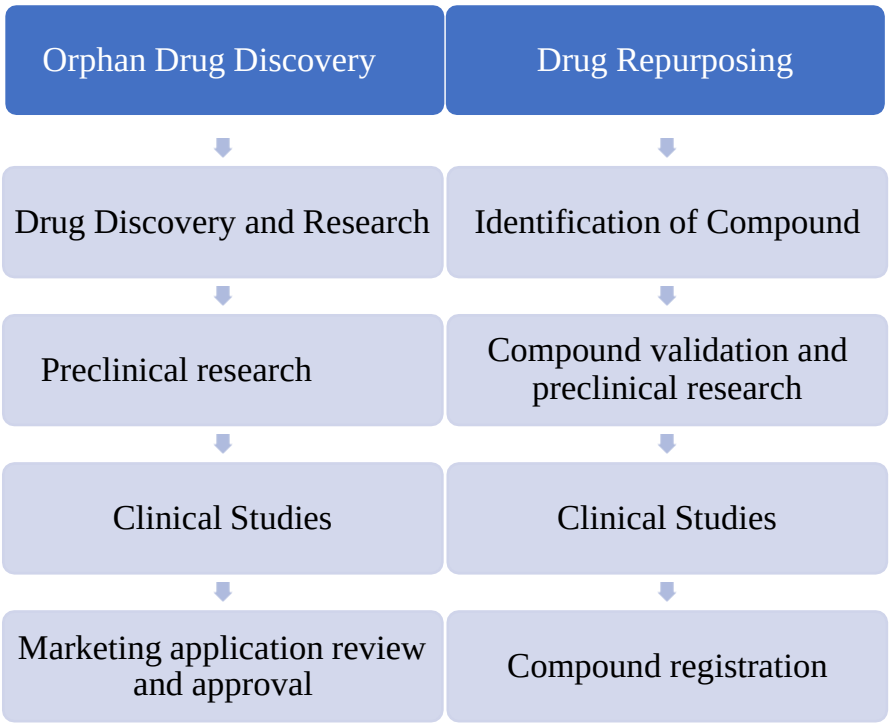


Fig 2 - Advantages over traditional way of orphan development

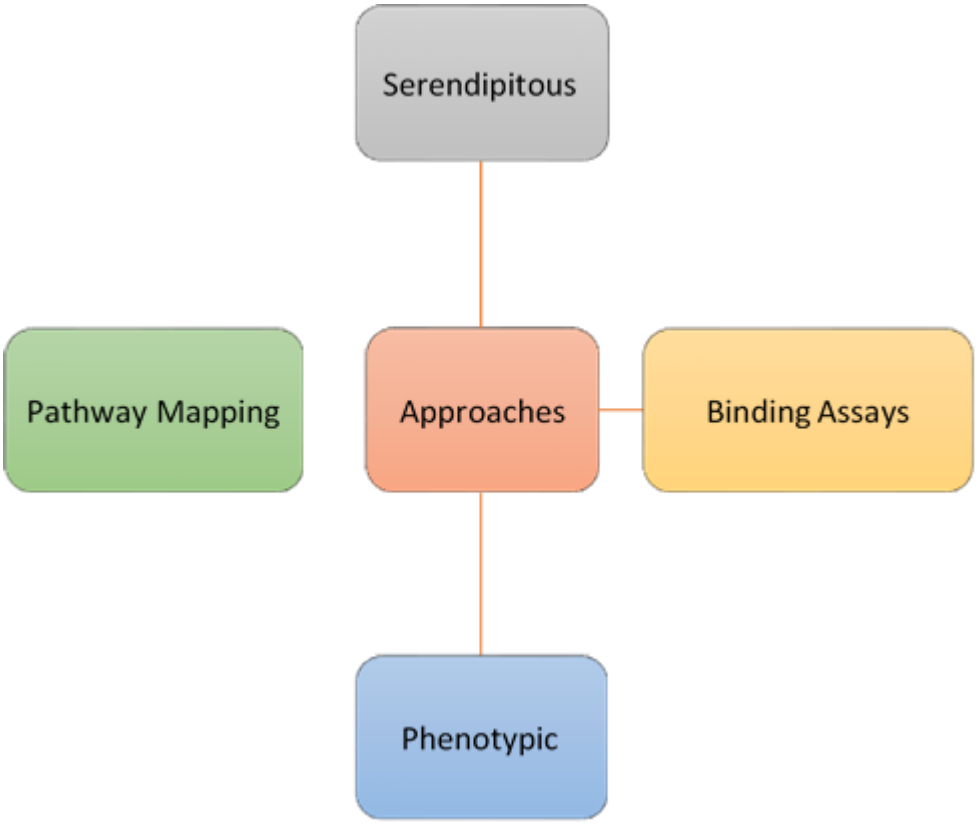
The advent of Drug repositioning started with Aspirin (Acetylsalicylic Acid) in 1980s. Currently used as an antiplatelet aggregation drug at lower doses, aspirinwas marketed as an analgesic in 1899 by Bayer prior to its repositioning.

Some of the notable examples of repurposed drugs include Sildenafil, Celecoxib. Sildenafil was repurposed by Pfizer. Originally developed as an antihypertensive, Sildenafil was repurposed and was finally marketed as Viagra used in the treatment of erectile dysfunction, while 53% market share was held by other marketed drugs during the drug market in 2012 the rest was held by Viagra with the sales up to $2.05 billion. Celecoxib's original indication was for Pain and inflammation but was repurposed for Familial adenomatous polyps using pharmacological analysis as the repurposing approach. It was repurposed by Pfizer at the latter half of 2014. Such opportunistic accomplishments have encouraged newer strategies and techniques for the development and identification of newer chemical entity that could be repurposed. (Pushpakom etal., 2018a)

In this review we will highlight various approaches, methodologies, categoriesof drugs, their computational data, challenges and solutions with respect to Drug Repurposing.

We will also be looking at the currently approved repurposed drugs and certaindrugs on which studies are underway to find out possible repurposing scope ofsuch drugs.

Drug repurposing approaches



Serendipitous approach –

Observations recorded in a serendipitous manner during pre/post clinical trials have provided a fruitful result in identifying potential treatment approaches.

(Ashburn & Thor, 2004)

Example – Sildenafil

Prior to its launch as an antihypertensive, side effects on erectile dysfunction were observed and ended up in an approval to be commercialised as such under the commercial name of Viagra®. Recently, under the commercial name of Revatio®, Sildenafil is being used for the treatment of pulmonary hypertension.(Ghofrani et al., 2006)

Example- Thalidomide

Initially introduced as an anti-nausea for pregnant women but was removed from the market because of its teratogenic effect. It was then repurposed for treatment of multiple myeloma and leprosy. (Rehman et al., 2011)

Phenotypic screening-

The method of phenotypic screening is based on the identification through high- throughput screening of compounds using in vitro or in vivo disease models.

These compounds exhibit disease pertinent effects in the model system. Use of wide range cell-based assays is common consisting of a 96-well format.(Pushpakom et al., 2018b). The major limitation of target-based drug repurposing is the fact that it is dependent on the prior scientific knowledge of a particular disease/drug. Unless and until the data surrounding the drug molecular and cellular target is known the true potential of drug repurposing cannot be antedated. Phenotypic screening approach overcomes this limitation and hence is used widely. The target-based approaches fell short when compared to high throughput screening of first-in class small molecule drug discovery. (Pizzorno et al., 2019)

For example, (Cousin et al., 2014) evaluated the domain of tobacco dependent medications. They used the zebrafish model to evaluate 39 FDA-approved medications and observed that nicotine induced behaviour and ethanol induced behaviour were modified by apomorphine and topiramate in this model.

Binding assays for identification of target interactions –

Method of mass spectrometry and affinity chromatography is used for the identification of novel targets of already known drugs. Such methods are known as Proteomic techniques. The principle of Cellular Thermo Stability Assay is based on mapping target engagement in cells using biophysical principles. Such principles are involved in predicting thermal stabilization of target protein using ligands possessing cellular affinity.

Cellular targets for tyrosine kinase inhibitor crizotinib were successfully confirmed (Alshareef et al., 2016)

There has been an increase in efforts in order to develop probe compounds thatprove to be better for preclinical research which informs clinical drug development and the drug repurposing using an audit trail in cells.(Blagg & Workman, 2017) The unbiased affinity approaches adopted in the early stages are useful to comprehend the common effects of compound in cells, including the activation of paradoxical kinase by inhibitors. (Hall-Jackson' et al., n.d.)

Example, incubation of HeLa cell lysate extracts was carried out by Brehmerand colleagues with a matrix the consisted of covalently attached gefitinib.

More than 20 protein kinases as putative gefitinib targets that differed from each other were identified through the mass spectrometry of the resultant elutes. (Pushpakom et al., 2018b)

(Karaman et al., 2008) followed the method of in vitro competition binding assay and evaluated 38 kinase inhibitors against a panel containing 317 distinctprotein kinases. Upon their analysis, a total of 3,175 binding interactions were identified. Notably sorafenib and dasatinib exhibited higher affinity to secondary kinase targets than their known primary target. This potentially invalidated their use in the patient populations.

In the kinase field, originally designed to inhibit protein kinases, the non-kinasetargets of small molecules are being recognized(Munoz, 2017) and are providing repurposing opportunity in cancer (Hsieh et al., 2016), as Zika virus modulator.(Xu, Lee, Wen, Cheng, Huang, Qian, Tcw, et al., 2016) and also as potential agents for the treatment of antibiotic-resistance microorganisms. (Sun et al., 2016)

Network or pathway mapping-

Pathway based approaches provides information about the genes with respect to Genome-wide association studies. The genes may be upstream or downstream and could provide to be useful for the purpose of repurposing.

On the basis of gene expression patterns, pathology of the disease, Genome- wide association studies data the disease networks are constructed under Network analysis. This is done to help in identifying potential repurposing candidates.

Analysis of gene expression data sets among studies involving respiratory viruses in human host infection models lead to identification of 67 common biological pathways.(Smith et al., 2012)

When these pathways were compared with the database of Drug Bank several drugs with a potential effect against host-viral targets were identified.

Example – Pranlukast which is a leukotriene receptor 1 antagonist used in asthma and amrinone which is a phosphodiesterase inhibitor used in treatment of CHF. Both of these drugs could prove to be potential drugs to be repurposedin treating viral infection because of their potential ability to alter immune response. (Pushpakom et al., 2018b)

Drugs repurposing for Antitubercular activity –

There has been an increase in the number of Tuberculosis infections that are resistant to most of the effective marketed drugs in the past decade. According to the data, drug resistant tuberculosis cases reached 4, 84,000 in the year 2018.(An et al., 2020)

In order to prevent loss of time and resources it becomes necessary to identify lead compounds that prove to be valuable as potential anti-tubercular agents. Such potential candidates should be further analysed for their safety in administration and distribution characteristics in humans. Such distribution characters must be

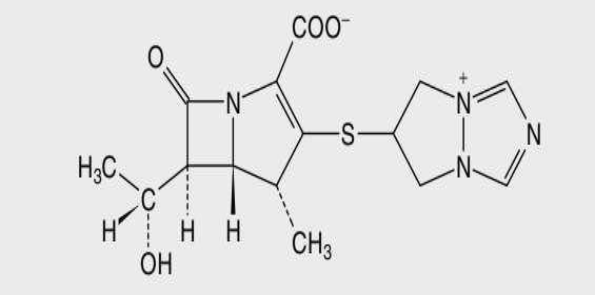
characterized and for this purpose necessary tests shall be carried out. In order to minimize the loss of time and resources that include time and subjects willing to be exposed to the trials repurposed drugs are employed, since for them the detailed safety trials have already been carried out and data for such exists. (An et al., 2020)

Drugs –

1) Biapenem

Biapenem is a carbapenem antibiotic. The effectiveness of carbapenems against Mycobacterium tuberculosis was evaluated by (Kaushik et al., 2015). The resultshowed that biapenem showcases in vitro bactericidal activity against the H37Rv strain having 90% MIC_{90} (Minimum Inhibitory Concentration) of 2.5–5 µg/mL. When clavulanic acid an inhibitor of beta-lactamase enzyme was addedit caused a 4 – times decrease in the MIC_{90}. (An et al., 2020).

Bianchet et al., 2017 observed the complexation of Biapenem and the co-crystal structure of Mycobacterium tuberculosis Ldt_{mt2} which indicated that the outer cavity of Ldt_{mt2} gets bounded to biapenem (Bianchet et al., 2017). Hence Biapenem may be used in the clinical treatment of tuberculosis.

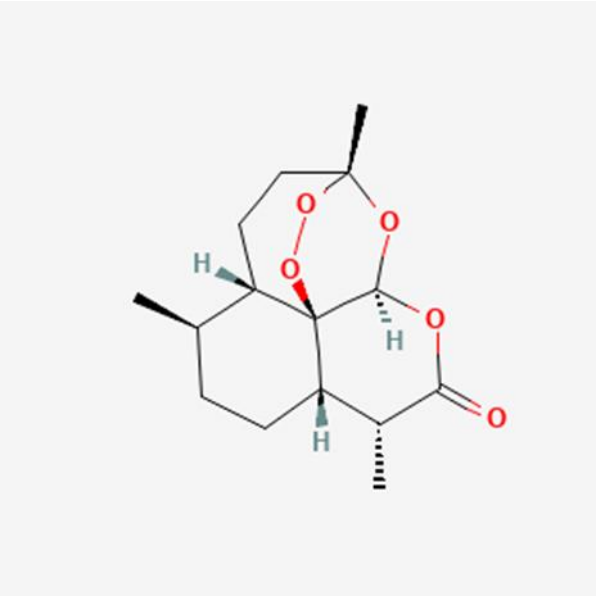


Biapenem Structure (Perry & Ibbotson, 2002)

2) Artemisinin

It is a sesquiterpenoid containing peroxy group. Artemisinin has an antimalarial activity. Choi, 2017 in the year 2016 hypothesized use of Artemisinin to inhibit proliferation of Mycobacterium tuberculosis. They found in-vitro anti- tubercular activity using different anti-tubercular indicator assays for example resazurin microtiter test. (Choi, 2017) Thus the potential use of artemisinin as an effective anti-tubercular drug was highlighted.

Zheng et al., 2017, screened ~5,40,000 compound small molecule library using a DosRST dependent fluorescent Mycobacterium tuberculosis reporter strain. The results showed that artemisinin was a novel inhibitor of the DosRST regulon, which inhibited persistence-associated physiological processes of Mycobacterium tuberculosis. Artemisinin directly targeted heme sensor which were carried by DosS and DosT histidine kinases and using this mechanism Artemisinin modulated DosRST signalling pathway. (Zheng et al., 2017)

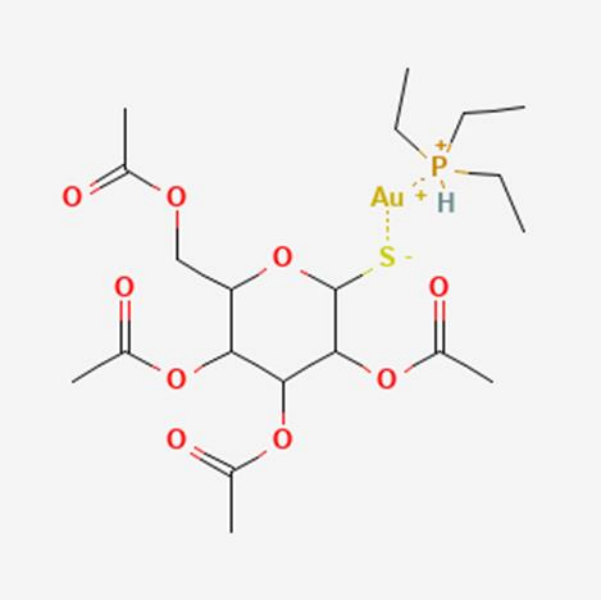


National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 68827, Artemisinin. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Artemisinin.

3) Auranofin

Originally developed for rheumatoid arthritis as an oral therapy. In a cell-based screening by Harbut et al., 2015 auranofin demonstrated efficacy against Mycobacterium tuberculosis with Minimum inhibitory concentration of 0.5 µg/mL which resulted in thiol-redox depletion further compromising defence against oxidative

stress.



National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 6333901, Auranofin. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Auranofin.

Drugs repurposing for Anti-Fungal activity –

Ant-Microbial resistance is a causative factor that is accountable for more than 7,00,000 casualties over a period of year, which is predicted to cross over 10 million mark by the year 2050, involving a total expenditure of $100 trillion.

There should be appropriate augmentation in the efforts for the discovery andutilization of newer novel antimicrobials drugs, owing to the undeniable needfor newer and better treatment options (Farha & Brown, 2019a).

Over more than 1.5 million deaths are caused by fungal mycoses and related Infections, majority of which have occurred in patients who have administeredimmunosuppressive agents as they have undergone transplant surgeries, chemoradiotherapy or haemodialysis (Deaguero et al., 2020) (Drgona et al.,2014).

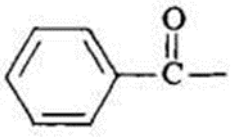
The pharma industry has enormously increased the research which favour getting better and stronger investmental developments and research in the past few years, thus leading towards decreasing investments cost and time required potentially by emphasizing more on Drug Repurposing. Drug repurposing is also referred to as Accelerated Drug Development Process (Farha & Brown, 2019a).

The first discovered molecule griseofulvin with anti-mycotic properties was discovered in 1939. Generally, drugs from Anti-bacterial, Immunosuppressants, Statins, NSAIDs, Anti-Depressants and Anti-Arrhythmic Category (Zhang et al., n.d.).

Drugs:

1) Mebendazole

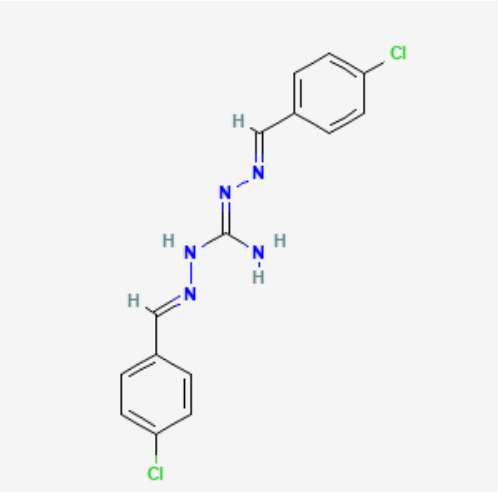
Used as an Anthelminthic primarily, it has now found to be useful in anti-fungalactivity against phagocytized *C. neoformans*, affecting biofilm formation and reducing capsular dimensions (Joffe et al., 2017).



Mebendazole Structure (van den Bossche et al., 1982)

2) Robenidine

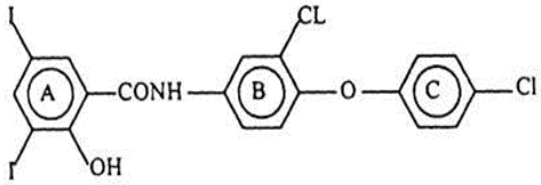
It has recently found to be useful in causing the inhibition of yeast cell growth,filamentation and reducing biofilm formation. This drug has been repurposed from treating debilitating infections in poultry to effectively fighting against *A. fumigatus, C. albicans, C. neoformans, S. cerevisiae* (Mei et al., 2020).



National Center for Biotechnology Information (2022). PubChem CompoundSummary for CID 9570438, Robenidine. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Robenidine.

3) Halogenated Salicylianilide

They are recognized for anti-parasitic properties has shown activity like antifilamentation and antibiofilm activities against *C. albicans* and *C. auris*(Garcia et al., 2018).



Halogenated Salicylianilide (e.g., Rafoxanide) (Swan, 1999)

Drugs repurposing for Anti-Cancer activity –

Cancer consists of a highly complicated diseases grouped together which is globally a major clinical burden that has resulted and still leading to millions ofdeaths and being the second-most death causing disease globally (Malik et al., 2022).

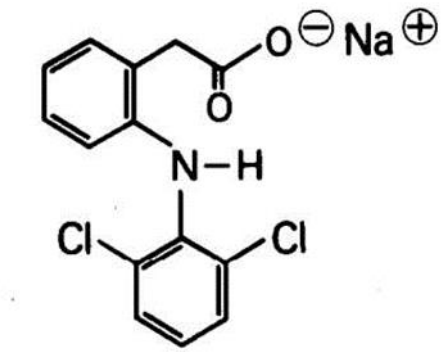
More than 14 million individuals were diagnosed with cancer, out of which 8.2suffered death in the year 2012. It is expected for cancer patients to rise more than 20 million by the year 2025 (Sleire et al., 2017).

Standard drug development process is already very expensive and time- consuming process, and to add to this Anti-Cancer agents are even more costly due to the higher failure rate of as much as 90% which has given rise to the crises of innovation gap, and its R&D procedure requires even more time due tothe necessary safety evaluations and toxicity tests that are required to perform (Chung et al., 2014). The total capital investments range vary from 161 to 1800 million dollars per drug, and only 5% of these drugs are approved for phase I clinical trials. FDA approved 45 more Anti-Cancer drugs in the year 2015 followed by 22 in the year 2016 (Sleire et al., 2017).

Drugs-

1) Diclofenac (DCF)

It was first developed by Ciba-Geigy (Today known as Novartis after merging with Sandoz) is commonly used as Non-Steroidal Anti-Inflammatory Drug (NSAID) for the treatment of pain during Rheumatoid Arthritis and other Musculoskeletal conditions. It can also be used topically in gel form for localized pain relief. It is common available OTC in gel format and is known by the names Voltarol, Cataflam, Cambia, Zipsor and Zorvolex. DCF has been established for its oncological role in topical treatment of pre-Cancerous lesions known as Actinic Keratosis. As of 21st September, four clinical trials are currently being conducted (Pantziarka et al., 2016).



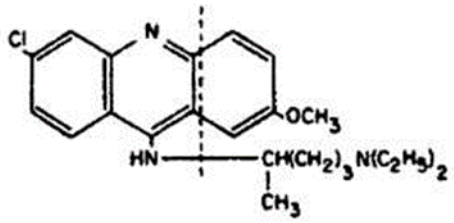
Structure of Diclofenac (Sallmann, 1986)

2. Quinacrine

An acridine derivative discovered in the 1920s used for its anti-malarial properties as a prophylactic and for treatment and for its anti-microbial properties for giardiasis. It is available as 4-N-(6-chloro-2-methoxyacridin-9- yl)-1-N,1-N-diethylpentane-1,4-diamine [Quinacrine dihydrochloride] for oraladministration (Oien et al., 2021).

Quinacrine exhibit cancer cell cytotoxicity through different mechanisms andhence found

useful as an Anti-Cancer agent, it has shown to intercalate into DNA, impact nuclear proteins, arachidonic pathways, induce p53 and inhibit NF**K**B signalling (Oien et al., 2021).

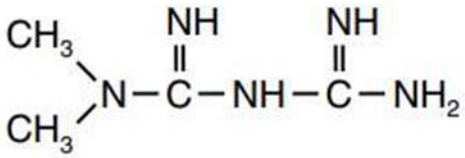


Structure of Quinacrine (Tanenbaum, 1980)

3. Metformin

Originally used for Type-2 Diabetes, has been found to be useful in the effectivetreatment of Renal Cell Carcinoma (RCC) or Metastatic Renal Cell Carcinoma (mRCC) based on 7 studies performed including a total of 6623 patients. The drug targets localized and mRCC by the mechanism of Inhibition of gluconeogenesis and glycogenolysis (Ari Hakimi et al., 2013; Hamieh et al., 2017; Keizman et al., 2016; Li et al., 2017; Nayan et al., 2016, 2017; Psutka et

al., 2015).



Structure of Metformin (Bailey & Turner, 1996)

Drugs repurposing for Antiviral activity –

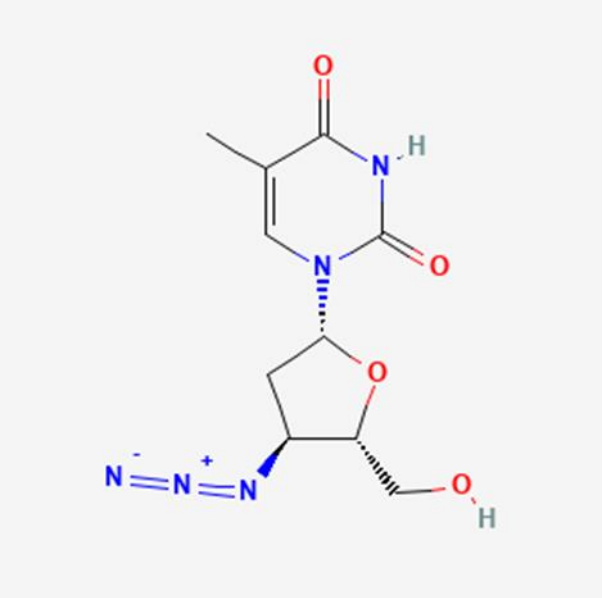
Viruses are large family of pathogens causing severe infections all over the globe including animals as well as plants. Only 12 new antiviral medications have been approved by FDA for public use in the years 2012 to 2017. Out of the total 12 molecules, 8 drugs are meant for treatment against Hepatitis C and 2 drug combinations are introduced against HIV (Mani et al., 2019).

In spite of the numerous improvisations in the field of sciences and thereby controlling number of viral pathogens, specific treatment and effective treatment for majority of the viral infections has not yet been discovered or achieved. It is a major medical crisis, where specific treatment against viral infections hasn't been successfully accomplished, and is still a major field ofdiscovery (Mercorelli et al., 2018).

Drugs:

1) Zidovudine

Zidovudine was used as Anti-Cancer agent in the 1960s until its discovery as the first Anti-HIV medication in 1987. It has been approved by FDA and now itis commonly utilized for its anti-viral properties against AIDS and AIDS related complexes and easily available in the market (Yarchoan et al., 1986).

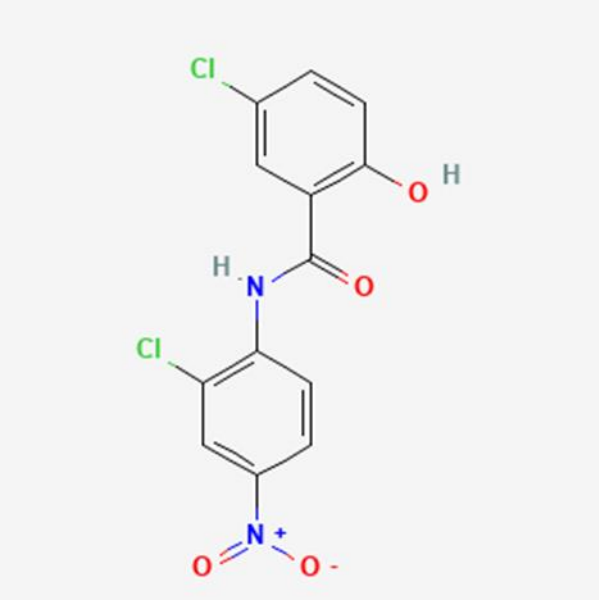


National Center for Biotechnology Information (2022). PubChem Compound Summary forCID 35370, Zidovudine. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Zidovudine.

2) Niclosamide

Currently in the world is used for its anthelminthic properties has been discovered for its Antiviral and Antibacterial properties (Imperi et al., 2013; Xu,Lee, Wen, Cheng, Huang, Qian,

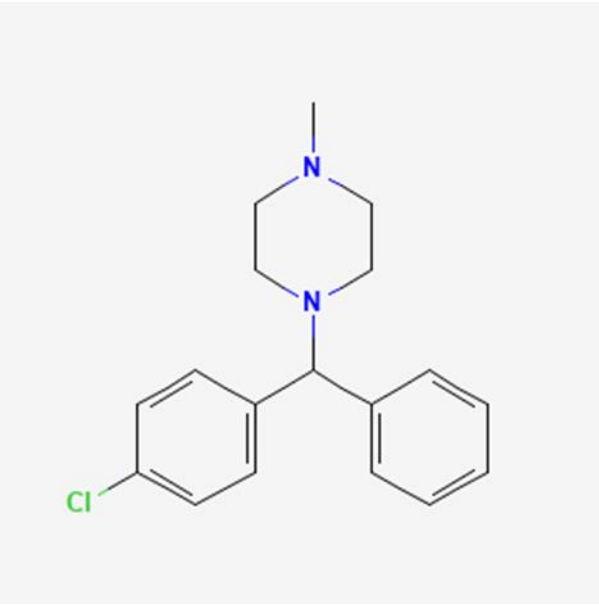
TCW, et al., 2016).



National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 4477, Niclosamide. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Niclosamide.

3) Chlorcyclizine

A drug initially used for the its activity against allergy has been found to usefulas an Anti-Viral Agent against Hepatitis C and has currently completed phase Itrials (He et al., 2015).



National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 4477, Niclosamide. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Niclosamide.

Drug repurposing for Antidepressant activity –

Depression is one of the most widespread mood disorders that has affectedmillions of people at an all-encompassing level. (Sadeghi et al., 2021)

According to the World Health Organisation's updated report issued in June 2022, under pre-pandemic conditions it stated that about 280 million people were living with depressive disorders. In 2020, the numbers rose significantlydue to the COVID-19 pandemic.

Major depressive disorder (MDD) is a serious and in some severe cases, a lethaldisorder.

Plenty antidepressant drugs are on the market, yet effective management ofMDD is still a cause of concern.(Jaronczyk & Walory, 2022) Even though extensive research has been done, the information regarding the pathophysiology, mechanisms and the pathways underlying MDD also remain limited.(Azam etal., 2020)

Drugs:

1. Scopolamine

Scopolamine is a non-selective muscarinic acetylcholine receptor (M-AChR) antagonist drug (Liu et al., 2021), approved for motion sickness, that produces a rapid antidepressant effect in depressed patients suffering from MDD or Bipolar Disorder (BD). (Furey & Drevets, 2006) It is able to penetrate the Blood Brain Barrier (BBB) more easily as compared to other anticholinergics, since it has a rather large unionised presence due to the epoxide group and weaker base strength.(Jaffe et al., 2013) Scopolamine exerts rapid antidepressant effects by promoting the brain-derived neurotrophic factor (BDNF) and glutamate. (Liu et al., 2021)The responses to scopolamine were evaluated with the changes in MADRS and HAM-A scores. It produced improvement in the severity of depression, the rapidity of the antidepressant activity was equivalent. By the end of the study, the extent of response was

greater in females as compared to maleswhich led to the conclusion that the influence of gonadal steroids on serotonin, dopamine and catecholamines, which interact with acetylcholine, contributes as well.(Furey et al., 2010) It is an effective treatment for unipolar and bipolar depression.(Jaffe et al., 2013)

2. Ketamine

A non-competitive antagonist at Glutamate N-methyl-D-aspartate (NMDA) receptors, Ketamine (Matveychuk et al., 2020), clinically used as a non- dissociative intravenous anaesthetic drug and an off-label antidepressant (Potter & Choudhury, 2014), as well as an analgesic and for addiction.(*5 Kronenberg RH. Ketamine as an Analgesic Parenteral, Oral, Rectal, Subcutaneous, Transdermal and Intranasal Administratio*, n.d.; Carboni et al., 2021) Its bioavailability differs with route of administration.(Matveychuk et al., 2020) Ketamine is extensively metabolised via CYP2B6- and CYP3A4-mediated N-demethylation to Norketamine which further undergoes catabolism to hydroxynorketamine (HNKs) and dehydronorketamine. (Zanos et al., 2018) In low doses, Ketamine was found to be rapid acting and hence, useful for treating resistant depression (Salvadore & Singh, 2013) and also induces anti-anhedonic effect.(Zanos et al., 2018) It exerts anaesthetic action through non-competitive blockage of N- methyl-D-aspartate glutamate receptors. (Aroni et al., 2009)

3. Nimodipine

Originally approved by the FDA for cerebrovascular complications, Nimodipineis a calcium channel blocker. It improved therapeutic effect in old patients suffering from vascular depression, and were being administered antidepressants.(Taragano et al., 2001) Nimodipine enhanced depression remission rate in fluoxetine treated patients who were also diagnosed with vascular depression.(Taragano et al., 2005) The clinical use of Nimodipine is limited due to its low solubility in gastrointestinal fluids and high first pass effect, which ultimately leads to low bioavailability after oral administration. (Moreno et al., 2016) Since it is lipophilic in nature, it can easily cross the BBB.(Taragano et al., 2005)

Rare Diseases

When a small percentage of the population due to a certain disease, it is termedas a Rare Disease (RDs) (Roessler et al., 2021). Recently, rare diseases have increasingly become a public threat having an effect range of 3.5% to 5.9% globally, shown by Epidemiological data (Nguengang Wakap et al., 2020).

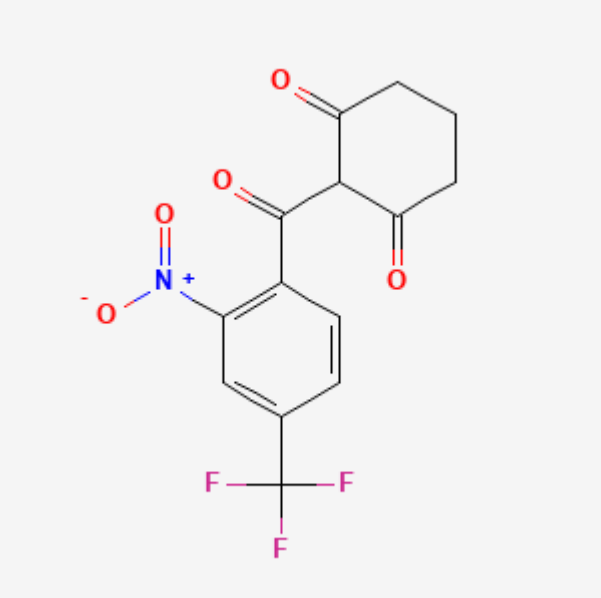
Finding newer drugs is restricted to limited interest by the large number of heterogeneities in rare diseases, leading to drug repurposing to come up with aneffect solution (Bellomo et al., 2021).

In order to diagnose these rare diseases, identification of the RD- Associated genes and its variants is of utmost importance for diagnosis and disease prognosis. The number of genes identified has grown tremendously due to advancement in the DNA sequences technologies and due to advancement in data analysis, this has been a transformative step in the overall treatment of RDs(Gonzaga-Jauregui et al., 2012).

Drugs:

1) Nitisinone

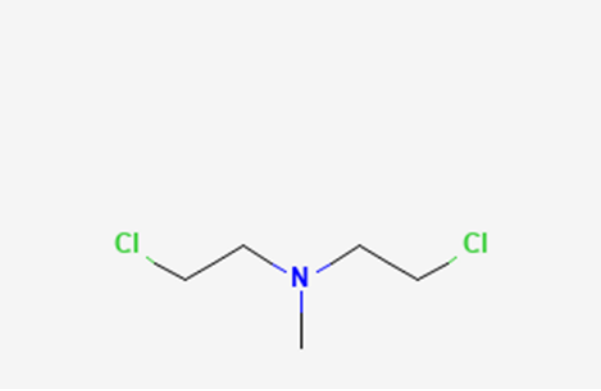
A drug primarily used in the treatment of a rare disease called Hereditary Tyrosinemia type I, have also found to be first effective in potential treatment ofanother rare disease Alkaptonuria (AKU). AKU is a condition where the patients cannot metabolically break down toxic acid called Homogentisic acid and leads to build up this acid in the body due to lack of enzyme homogentisic dioxygenase. Currently, it is only licensed for Hereditary Tyrosinemia type I and not against AKU (Ranganath et al., 2016).



National Center for Biotechnology Information (2022). PubChem Compound Summary forCID 115355, Nitisinone. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Nitisinone.

2) Chlormethine

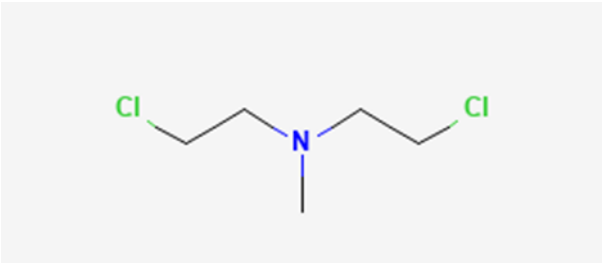
A drug under the category L-Antineoplastic and immunomodulating agents, currently known for its therapeutic value for against cutaneous Mycosis fungoides T-cell Lymphoma has been found to be useful in treatment of certainrare disease (Lessin et al., 2013).



National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 4033, Mechlorethamine. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Mechlorethamine.

3) Abatacept

Abatacept for Cytotoxic T-Lymphocyte Antigen 4 Haploinsufficiency: Currently marketed as Orencia® Subcutaneous injection, it was registered in 2007 in Europe for Rheumatoid Arthritis Treatment as an immune modulator acting as a barrier to T-cell activation. For many years, it is used off-label for the treatment of rare disease CTLA-$ haploinsufficiency which causes SevereImmune Dysregulation (Kuehn et al., 2014; Lapides & McDonald, 2020).



National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 4033, Mechlorethamine. Retrieved August 1, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Mechlorethamine.

Future Prospects:

It is an alternative way to introduce a new drug, rather a new purpose of the already existing drug that has been already accepted and passed the Pre-Clinicaland Phase I trials. It doesn't have to go through all the stringent regulations all over again, which drastically reduces the time required for a new drug to introduce in the market. This method also helps overcome the expensive and tedious method of drug development. Due to prior knowledge about a drug safety, efficacy and the most opportune administration route reduces the cost and time requirements drastically, thus reducing the overall effort and time required for successfully repurposing a drug in an already fda.gov (Padhy & Gupta, 2011; Parvathaneni et al., 2019; Vaidya et al., 2019) (Kulkarni et al., 2019; The Lancet Diabetes & Endocrinology, 2019).

Repurposing lowers the initiation cost for discovery of therapies considerably for rare diseases. It has also drastically decreased the time duration required from a range of 10-15

years to almost 5-7 years (Gil & Martinez, 2021b).

The typical drug discovery happens in a specified sequence or stages: Discovery and growth, preclinical testing and clinical trials. All this is followed by FDA who performs a review and conducts post-marketing monitoring. The best way to find a safe and efficient treatment choice is to repurpose an already approved FDA-approved therapeutic (Khare & Dr. Raychaudhuri P. S., 2021).

During the pandemic of COVID-19, repurposing served as a major backbone ofthe pharma industry, where hydroxy chloroquinoline which originally an anti-malarial was now used for primarily level treatment for patients diagnosed withCovid-19.

A wide spread awareness along with efforts from the public and private partnerships, non-profit organizations, academic researchers and companies isrequired to successfully investigate and approve drugs for other indications

(Farha & Brown, 2019b).

There are some hurdles that has been seen so far, one of them being the lack of proper patent protection for the newly discovered use as patents are drug basedand not activity based. More market exclusivity and precise regulations is required in order to successfully utilize repurposing as a tool to find new drug uses unanimously (Farha & Brown, 2019b).

Drugs	Initially used for	Repurposed for	Status
Auranofin	Rheumatoid arthritis	Amoebic Dysentery	Orphan Drug Status
Doxycycline	Antibacterial	Malaria	Off-label use
Zidovudine	Anticancer	Antiviral	Approved
Biapenem			
Metformin	Oral hypoglycaemic agent – Type 2 Diabetes	AMPK pathway regulation for treatment of IPF	Approved
Raloxifene	Osteoporosis in postmenopausal women	Breast cancer treatment	Approved
Galantamine	Polio, Paralysis	Alzheimer's Disease	Approved
Lidocaine	Local anaesthetic	Oral corticosteroid asthma – dependent asthma	Approved
Tofisopam	Anxiety related conditions	Irritable bowel syndrome	Approved
Minoxidil	Hypertension	Hair loss	Approved
Topiramate	Epilepsy	Obesity	Approved

Fig – Table contains drugs along with their initial indication, the disease theywere repurposed for and their status. (Farha & Brown, 2019a) (Ashburn & Thor, 2004) (Mehta & Dhapte-Pawar, 2021b) (Malik et al., 2022)

Conclusion –

The piqued interest in the area of drug repurposing is due to the high failure rate and extensive financial issues faced by the company when adopting the conventional method of drug

development. The driving force behind the success of drug repurposing technique is the availability of pre-existing data on safety and toxicity trials. The scientific landscape for research and drug development is still undergoingchanges but the process is expected to pick up pace in the upcoming years.

Drug repurposing is an efficient strategy to treat various diseases and from an economic point of view it is a very lucrative alternative as well. The ability of this alternative to branch out further and cover almost all diseases including the rare onesis what makes it valuable and the need in current times, where the cost of the processis directly proportional to the cost of medicines and the time taken to provide medication for certain diseases to the public is often more and occasionally may be too late.

We hope that this article highlighted the importance and potential of drug repurposingin the field of research and development. The approaches and various categories of drugs discussed in this article were mere tip of the iceberg. This technique is ever growing and involves various new approaches some which are still under development or awaiting approval. In these coming years, repurposed drugs awaiting approval from regulatory authorities could rise and account for about 20-30% of all the drugs approved every year according to different estimations. (Cha et al., 2018b; Davies et al., 2017)

Reference

[1] 5 Kronenberg RH. Ketamine as an analgesic parenteral, oral, rectal, subcutaneous, transdermal and intranasal administratio. (n.d.).

[2] Alshareef, A., Zhang, H. F., Huang, Y. H., Wu, C., Zhang, J. D., Wang, P., El-Sehemy, A., Fares, M., & Lai, R. (2016). The use of cellular thermal shift assay (CETSA) to study Crizotinib resistance in ALK-expressing human cancers. Scientific Reports, 6. https://doi.org/10.1038/srep33710

[3] An, Q., Li, C., Chen, Y., Deng, Y., Yang, T., & Luo, Y. (2020). Repurposed drug candidates for antituberculosis therapy. EuropeanJournal of Medicinal Chemistry, 192. https://doi.org/10.1016/j.ejmech.2020.112175

[4] Ari Hakimi, A., Chen, L., Kim, P. H., Sjoberg, D., Glickman, L., Walker, M. R., & Russo, P. (2013). The impact of metformin use on recurrence and cancer-specific survival in clinically localized high-risk renal cell carcinoma. Canadian Urological Association Journal = Journal de l'Association Des Urologues Du Canada, 7(11–12). https://doi.org/10.5489/CUAJ.1447

[5] Aroni, F., Iacovidou, N., Dontas, I., Pourzitaki, C., & Xanthos, T. (2009). Pharmacological aspects and potential new clinical applications of ketamine: Reevaluation of an old drug. In Journal of Clinical Pharmacology (Vol. 49, Issue 8, pp. 957–964). https://doi.org/10.1177/0091270009337941

[6] Ashburn, T. T., & Thor, K. B. (2004). Drug repositioning: Identifying and developing new uses for existing drugs. In Nature Reviews Drug Discovery (Vol. 3, Issue 8, pp. 673–683). Nature Publishing Group. https://doi.org/10.1038/nrd1468

[7] Azam, S., Haque, M. E., Jakaria, M., Jo, S. H., Kim, I. S., & Choi, D. K. (2020). G-Protein-Coupled Receptors in CNS: A Potential Therapeutic Target for Intervention in Neurodegenerative Disorders and Associated Cognitive Deficits. In Cells (Vol. 9, Issue 2). NLM (Medline). https://doi.org/10.3390/cells9020506

[8] Bailey, C. J., & Turner, R. C. (1996). Metformin. New England Journal of Medicine, 334(9), 574–579. https://doi.org/10.1056/NEJM199602293340906

[9] Bellomo, F., de Leo, E., Taranta, A., Giaquinto, L., di Giovamberardino, G., Montefusco, S., Rega, L. R., Pastore, A., Medina, D. L., di Bernardo, D., de Matteis, M. A., & Emma, F. (2021). Drug Repurposing in Rare Diseases: An Integrative Study of Drug Screening and Transcriptomic Analysis in Nephropathic Cystinosis. International Journal of Molecular Sciences, 22(23), 12829. https://doi.org/10.3390/ijms222312829

[10] Bianchet, M. A., Pan, Y. H., Basta, L. A. B., Saavedra, H., Lloyd, E.P., Kumar, P., Mattoo, R., Townsend, C. A., & Lamichhane, G. (2017). Structural insight

into the inactivation of Mycobacterium tuberculosis non-classical transpeptidase LdtMt2 by biapenem and tebipenem. BMC Biochemistry, 18(1), 8. https://doi.org/10.1186/s12858-017-0082-4

[11] Blagg, J., & Workman, P. (2017). Choose and Use Your Chemical Probe Wisely to Explore Cancer Biology. In Cancer Cell (Vol. 32, Issue 1, pp. 9–25). Cell Press. https://doi.org/10.1016/j.ccell.2017.06.005

[12] Carboni, E., Carta, A. R., Carboni, E., & Novelli, A. (2021). Repurposing Ketamine in Depression and Related Disorders: Can This Enigmatic Drug Achieve Success? In Frontiers in Neuroscience (Vol. 15). Frontiers Media S.A. https://doi.org/10.3389/fnins.2021.657714

[13] Cha, Y., Erez, T., Reynolds, I. J., Kumar, D., Ross, J., Koytiger, G., Kusko, R., Zeskind, B., Risso, S., Kagan, E., Papapetropoulos, S., Grossman, I., & Laifenfeld, D. (2018a). Drug repurposing from the perspective of pharmaceutical companies. In British Journal of Pharmacology (Vol. 175, Issue 2, pp. 168–180). John Wiley and Sons Inc. https://doi.org/10.1111/bph.13798

[14] Cha, Y., Erez, T., Reynolds, I. J., Kumar, D., Ross, J., Koytiger, G., Kusko, R., Zeskind, B., Risso, S., Kagan, E., Papapetropoulos, S., Grossman, I., & Laifenfeld, D. (2018b). Drug repurposing from the perspective of pharmaceutical companies. In British Journal of Pharmacology (Vol. 175, Issue 2, pp. 168–180). John Wiley and Sons Inc. https://doi.org/10.1111/bph.13798

[15] Choi, W. H. (2017). Novel pharmacological activity of artesunate and artemisinin: Their potential as anti-tubercular agents. Journal of Clinical Medicine, 6(3). https://doi.org/10.3390/jcm6030030

[16] Chung, F. H., Chiang, Y. R., Tseng, A. L., Sung, Y. C., Lu, J., Huang, M. C., Ma, N., & Lee, H. C. (2014). Functional Module Connectivity Map (FMCM): A framework for searching repurposed drug compounds for systems treatment of cancer and an application to colorectal adenocarcinoma. PLoS ONE, 9(1). https://doi.org/10.1371/journal.pone.0086299

[17] Cousin, M. A., Ebbert, J. O., Wiinamaki, A. R., Urban, M. D., Argue, D. P., Ekker, S. C., & Klee, E. W. (2014). Larval zebrafish model for FDA-approved drug repositioning for tobacco dependence treatment. PLoS ONE, 9(3). https://doi.org/10.1371/journal.pone.0090467

[18] Davies, E. H., Fulton, E., Brook, D., & Hughes, D. A. (2017). Affordable orphan drugs: a role for not-for-profit organizations. British Journal of Clinical Pharmacology, 83(7), 1595–1601. https://doi.org/10.1111/bcp.13240

[19] Deaguero, I. G., Huda, M. N., Rodriguez, V., Zicari, J., Al-Hilal, T.A., Badruddoza, A. Z. M., & Nurunnabi, M. (2020). Nano-Vesicle Based Anti-Fungal Formulation Shows Higher Stability, Skin Diffusion, Biosafety and Anti-Fungal Efficacy In Vitro. Pharmaceutics, 12(6), 516. https://doi.org/10.3390/pharmaceutics12060516

A. Deftereos, S. N., Andronis, C., Friedla, E. J., Persidis, A., & Persidis, (2011). Drug repurposing and adverse event prediction usinghigh-throughput literature analysis. In Wiley Interdisciplinary Reviews: Systems Biology and Medicine (Vol. 3, Issue 3, pp. 323– 334). https://doi.org/10.1002/wsbm.147

[20] Drgona, L., Khachatryan, A., Stephens, J., Charbonneau, C., Kantecki, M., Haider, S., & Barnes, R. (2014). Clinical and economic burden of invasive fungal diseases in Europe: focus on pre-emptive and empirical treatment of Aspergillus and Candida species. European Journal of Clinical Microbiology & Infectious Diseases, 33(1), 7–21. https://doi.org/10.1007/s10096-013-1944-3

[21] Farha, M. A., & Brown, E. D. (2019a). Drug repurposing for antimicrobial discovery. In Nature Microbiology (Vol. 4, Issue 4, pp. 565–577). Nature Publishing Group. https://doi.org/10.1038/s41564-019-0357-1

[22] Farha, M. A., & Brown, E. D. (2019b). Drug repurposing for antimicrobial discovery. In Nature Microbiology (Vol. 4, Issue 4, pp. 565–577). Nature Publishing Group. https://doi.org/10.1038/s41564-019-0357-1

[23] Furey, M. L., & Drevets, W. C. (2006). Antidepressant efficacy of the

antimuscarinic drug scopolamine: A randomized, placebo- controlled clinical trial. Archives of General Psychiatry, 63(10), 1121–1129. https://doi.org/10.1001/archpsyc.63.10.1121

[24] Furey, M. L., Khanna, A., Hoffman, E. M., & Drevets, W. C. (2010). Scopolamine produces larger antidepressant and antianxiety effectsin women than in men. Neuropsychopharmacology, 35(12), 2479–2488. https://doi.org/10.1038/npp.2010.131

A. Garcia, C., Burgain, A., Chaillot, J., Pic, É., Khemiri, I., & Sellam, (2018). A phenotypic small-molecule screen identifies halogenated salicylanilides as inhibitors of fungal morphogenesis, biofilm formation and host cell invasion. Scientific Reports 2018 8:1, 8(1), 1–15. https://doi.org/10.1038/s41598-018-29973-8

[25] Ghofrani, H. A., Osterloh, I. H., & Grimminger, F. (2006). Sildenafil: From angina to erectile dysfunction to pulmonary hypertension and beyond. In Nature Reviews Drug Discovery (Vol. 5, Issue 8, pp. 689– 702). https://doi.org/10.1038/nrd2030

[26] Gil, C., & Martinez, A. (2021a). Is drug repurposing really the future of drug discovery or is new innovation truly the way forward? In Expert Opinion on Drug Discovery (Vol. 16, Issue 8, pp. 829–831). Taylor and Francis Ltd. https://doi.org/10.1080/17460441.2021.1912733

[27] Gil, C., & Martinez, A. (2021b). Is drug repurposing really the future of drug discovery or is new innovation truly the way forward? In Expert Opinion on Drug Discovery (Vol. 16, Issue 8, pp. 829–831). Taylor and Francis Ltd. https://doi.org/10.1080/17460441.2021.1912733

[28] Gonzaga-Jauregui, C., Lupski, J. R., & Gibbs, R. A. (2012). Human genome sequencing in health and disease. In Annual Review of Medicine (Vol. 63, pp. 35–61). https://doi.org/10.1146/annurev-med-051010-162644

[29] Hall-Jackson', C. A., Eyersl, P. A., Cohen', P., Goedert, M., Boyle3, T., Hewitt3, N., Plant3, H., & Hedge3, P. (n.d.). Paradoxical activation of Raf by a novel Raf inhibitor. http://biomednet.com/elecref/1074552100600559

[30] Hamieh, L., McKay, R. R., Lin, X., Moreira, R. B., Simantov, R., &Choueiri, T. K. (2017). Effect of Metformin Use on Survival Outcomes in Patients With Metastatic Renal Cell Carcinoma. Clinical Genitourinary Cancer, 15(2), 221–229. https://doi.org/10.1016/j.clgc.2016.06.017

[31] Harbut, M. B., Vilchèze, C., Luo, X., Hensler, M. E., Guo, H., Yang, B., Chatterjee, A. K., Nizet, V., Jacobs, W. R., Schultz, P. G., & Wang, F. (2015). Auranofin exerts broad-spectrum bactericidal activities by targeting thiol-redox homeostasis. Proceedings of the National Academy of Sciences of the United States of America, 112(14), 4453–4458. https://doi.org/10.1073/pnas.1504022112

[32] He, S., Lin, B., Chu, V., Hu, Z., Hu, X., Xiao, J., Wang, A. Q., Schweitzer, C. J., Li, Q., Imamura, M., Hiraga, N., Southall, N., Ferrer, M., Zheng, W., Chayama, K., Marugan, J. J., & Liang, T. J. (2015). Repurposing of the antihistamine chlorcyclizine and related compounds for treatment of hepatitis C virus infection. Science Translational Medicine, 7(282). https://doi.org/10.1126/scitranslmed.3010286

[33] Hsieh, Y. Y., Chou, C. J., Lo, H. L., & Yang, P. M. (2016). Repositioning of a cyclin-dependent kinase inhibitor GW8510 as aribonucleotide reductase M2 inhibitor to treat human colorectal cancer. Cell Death Discovery, 2(1). https://doi.org/10.1038/cddiscovery.2016.27

[34] Imperi, F., Massai, F., Ramachandran Pillai, C., Longo, F., Zennaro, E., Rampioni, G., Visca, P., & Leoni, L. (2013). New Life for an Old Drug: the Anthelmintic Drug Niclosamide Inhibits Pseudomonas aeruginosa Quorum Sensing. Antimicrobial Agents and Chemotherapy, 57(2), 996–1005. https://doi.org/10.1128/AAC.01952-12

[35] Jaffe, R. J., Novakovic, V., & Peselow, E. D. (2013). Scopolamine as an antidepressant: A systematic review. In Clinical Neuropharmacology (Vol. 36, Issue 1, pp. 24–26). https://doi.org/10.1097/WNF.0b013e3182

78b703
[36] Jaronczyk, M., & Walory, J. (2022). Novel molecular targets of antidepressants. In Molecules (Vol. 27, Issue 2). MDPI. https://doi.org/10.3390/molecules27020533
[37] Joffe, L. S., Schneider, R., Lopes, W., Azevedo, R., Staats, C. C., Kmetzsch, L., Schrank, A., Poeta, M. del, Vainstein, M. H., & Rodrigues, M. L. (2017). The Anti-helminthic Compound Mebendazole Has Multiple Antifungal Effects against Cryptococcus neoformans. Frontiers in Microbiology, 8(MAR). https://doi.org/10.3389/FMICB.2017.00535
[38] Karaman, M. W., Herrgard, S., Treiber, D. K., Gallant, P., Atteridge, C. E., Campbell, B. T., Chan, K. W., Ciceri, P., Davis, M. I., Edeen, P. T., Faraoni, R., Floyd, M., Hunt, J. P., Lockhart, D. J., Milanov, Z. v., Morrison, M. J., Pallares, G., Patel, H. K., Pritchard, S., … Zarrinkar, P. P. (2008). A quantitative analysis of kinase inhibitor selectivity. Nature Biotechnology, 26(1), 127–132. https://doi.org/10.1038/nbt1358
[39] Kaushik, A., Makkar, N., Pandey, P., Parrish, N., Singh, U., & Lamichhane, G. (2015). Carbapenems and Rifampin Exhibit Synergy against Mycobacterium tuberculosis and Mycobacterium abscessus. Antimicrobial Agents and Chemotherapy, 59(10), 6561–6567. https://doi.org/10.1128/AAC.01158-15
[40] Keizman, D., Ish-Shalom, M., Sella, A., Gottfried, M., Maimon, N., Peer, A., Hammers, H., Eisenberger, M. A., Sinibaldi, V., Neiman, V., Rosenbaum, E., Sarid, D., Mermershtain, W., Rouvinov, K., Berger, R., & Carducci, M. A. (2016). Metformin Use and Outcomeof Sunitinib Treatment in Patients With Diabetes and Metastatic Renal Cell Carcinoma. Clinical Genitourinary Cancer, 14(5), 420– 425. https://doi.org/10.1016/j.clgc.2016.04.012
[41] Khare, S., & Dr. Raychaudhuri P. S. (2021). CHALLENGES AND OPPORTUNITIES OF DRUG REPURPOSING: A COST- EFFECTIVE STRATEGY FOR PRODUCT DEVELOPMENT AND NEW MARKET DEMAND. www.pbme.in
[42] Kuehn, H. S., Ouyang, W., Lo, B., Deenick, E. K., Niemela, J. E., Avery, D. T., Schickel, J.-N., Tran, D. Q., Stoddard, J., Zhang, Y., Frucht, D. M., Dumitriu, B., Scheinberg, P., Folio, L. R., Frein, C. A., Price, S., Koh, C., Heller, T., Seroogy, C. M., … Uzel, G. (2014). Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science, 345(6204), 1623–1627. https://doi.org/10.1126/science.1255904
[43] Kulkarni, N. S., Parvathaneni, V., Shukla, S. K., Barasa, L., Perron, J. C., Yoganathan, S., Muth, A., & Gupta, V. (2019). Tyrosine kinase inhibitor conjugated quantum dots for non-small cell lung cancer (NSCLC) treatment. European Journal of Pharmaceutical Sciences, 133, 145–159. https://doi.org/10.1016/j.ejps.2019.03.026
[44] Lapides, D. A., & McDonald, M. M. (2020). Inflammatory Manifestations of Systemic Diseases in the Central Nervous System. Current Treatment Options in Neurology, 22(9), 26. https://doi.org/10.1007/s11940-020-00636-2
[45] Lessin, S. R., Duvic, M., Guitart, J., Pandya, A. G., Strober, B. E., Olsen, E. A., Hull, C. M., Knobler, E. H., Rook, A. H., Kim, E. J., Naylor, M. F., Adelson, D. M., Kimball, A. B., Wood, G. S., Sundram, U., Wu, H., & Kim, Y. H. (2013). Topical Chemotherapy in Cutaneous T-cell Lymphoma. JAMA Dermatology, 149(1), 25. https://doi.org/10.1001/2013.jamadermatol.541
[46] Li, Y., Hu, L., Xia, Q., Yuan, Y., & Mi, Y. (2017). The impact of metformin use on survival in kidney cancer patients with diabetes: a meta-analysis. International Urology and Nephrology, 49(6), 975. https://doi.org/10.1007/S11255-017-1548-4
[47] Liu, S., Shi, D., Sun, Z., He, Y., Yang, J., & Wang, G. (2021). M2- AChR Mediates Rapid Antidepressant Effects of Scopolamine Through Activating the mTORC1-BDNF Signaling Pathway in the Medial Prefrontal Cortex. Frontiers in Psychiatry, 12. https://doi.org/10.3389/fpsyt.2021.601985
[48] Malik, J. A., Ahmed, S., Jan, B., Bender, O., al Hagbani, T., Alqarni,A., & Anwar, S. (2022). Drugs repurposed: An advanced step towards the treatment of breast cancer and associated challenges. In Biomedicine

and Pharmacotherapy (Vol. 145). Elsevier Masson s.r.l. https://doi.org/10.1016/j.biopha.2021.112375

[49] Mani, D., Wadhwani, A., & Krishnamurthy, P. T. (2019). Drug Repurposing in Antiviral Research: A Current Scenario. Journal of Young Pharmacists, 11(2), 117–121. https://doi.org/10.5530/jyp.2019.11.26

[50] Matveychuk, D., Thomas, R. K., Swainson, J., Khullar, A., MacKay,M.-A., Baker, G. B., & Dursun, S. M. (2020). Ketamine as an antidepressant: overview of its mechanisms of action and potential predictive biomarkers. Therapeutic Advances in Psychopharmacology, 10, 204512532091665. https://doi.org/10.1177/2045125320916657

[51] Mehta, P. P., & Dhapte-Pawar, V. S. (2021a). Repurposing drug molecules for new pulmonary therapeutic interventions. In Drug Delivery and Translational Research (Vol. 11, Issue 5, pp. 1829–1848). Springer. https://doi.org/10.1007/s13346-020-00874-6

[52] Mehta, P. P., & Dhapte-Pawar, V. S. (2021b). Repurposing drug molecules for new pulmonary therapeutic interventions. In Drug Delivery and Translational Research (Vol. 11, Issue 5, pp. 1829–1848). Springer. https://doi.org/10.1007/s13346-020-00874-6

[53] Mei, Y., Jiang, T., Zou, Y., Wang, Y., Zhou, J., Li, J., Liu, L., Tan, J., Wei, L., Li, J., Dai, H., Peng, Y., Zhang, L., Lopez-Ribot, J. L., Shapiro, R. S., Chen, C., Liu, N.-N., & Wang, H. (2020). FDAApproved Drug Library Screening Identifies Robenidine as a Repositionable Antifungal. Frontiers in Microbiology, 11. https://doi.org/10.3389/fmicb.2020.00996

[54] Mercorelli, B., Palù, G., & Loregian, A. (2018). Drug Repurposing for Viral Infectious Diseases: How Far Are We? Trends in Microbiology, 26(10), 865–876. https://doi.org/10.1016/J.TIM.2018.04.004

[55] Moreno, L. C. G. E. A. I., Rolim, H. M. L., Freitas, R. M., & Santos-Magalhães, N. S. (2016). Antidepressant-like activity of liposomal formulation containing nimodipine treatment in the tail suspension test, forced swim test and MAOB activity in mice. Brain Research, 1646, 235–240. https://doi.org/10.1016/j.brainres.2016.06.004

[56] Munoz, L. (2017). Non-kinase targets of protein kinase inhibitors. In Nature Reviews Drug Discovery (Vol. 16, Issue 6, pp. 424–440). Nature Publishing Group. https://doi.org/10.1038/nrd.2016.266

[57] Nayan, M., Finelli, A., Jewett, M. A. S., Juurlink, D. N., Austin, P.C., Kulkarni, G. S., & Hamilton, R. J. (2017). Metformin Use and Kidney Cancer Outcomes in Patients With Diabetes: A PropensityScore Analysis. Clinical Genitourinary Cancer, 15(2), 300–305. https://doi.org/10.1016/j.clgc.2016.06.008

[58] Nayan, M., Macdonald, E. M., Juurlink, D. N., Austin, P. C., Finelli,A., Kulkarni, G. S., & Hamilton, R. J. (2016). Medication use and survival in diabetic patients with kidney cancer: A population-basedcohort study. Pharmacological Research, 113, 468–474. https://doi.org/10.1016/j.phrs.2016.09.027

[59] Nguengang Wakap, S., Lambert, D. M., Olry, A., Rodwell, C., Gueydan, C., Lanneau, V., Murphy, D., le Cam, Y., & Rath, A. (2020). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. European Journal of Human Genetics, 28(2), 165–173. https://doi.org/10.1038/s41431-019-0508-0

[60] Oien, D. B., Pathoulas, C. L., Ray, U., Thirusangu, P., Kalogera, E.,& Shridhar, V. (2021). Repurposing quinacrine for treatment- refractory cancer. In Seminars in Cancer Biology (Vol. 68, pp. 21– 30). Academic Press. https://doi.org/10.1016/j.semcancer.2019.09.021

[61] Padhy, B., & Gupta, Y. (2011). Drug repositioning: Re-investigating existing drugs for new therapeutic indications. Journal of Postgraduate Medicine, 57(2), 153. https://doi.org/10.4103/0022-3859.81870

[62] Pantziarka, P., Sukhatme, V., Bouche, G., Melhuis, L., & Sukhatme, V. P. (2016). Repurposing Drugs in Oncology (ReDO)—diclofenac as an anti-cancer agent. Ecancermedicalscience, 10. https://doi.org/10.3332/ecancer.2016.610

[63] Parvathaneni, V., Kulkarni, N. S., Muth,

A., & Gupta, V. (2019). Drug repurposing: a promising tool to accelerate the drug discovery process. In Drug Discovery Today (Vol. 24, Issue 10, pp. 2076– 2085). Elsevier Ltd. https://doi.org/10.1016/j.drudis.2019.06.014

[64] Perry, C. M., & Ibbotson, T. (2002). Biapenem. Drugs, 62(15), 2221–2234. https://doi.org/10.2165/00003495-200262150-00005

[65] Pizzorno, A., Padey, B., Terrier, O., & Rosa-Calatrava, M. (2019). Drug repurposing approaches for the treatment of influenza viral infection: Reviving old drugs to fight against a long-lived enemy. InFrontiers in Immunology (Vol. 10, Issue MAR). Frontiers Media S.A. https://doi.org/10.3389/fimmu.2019.00531

[66] Potter, D. E., & Choudhury, M. (2014). Ketamine: Repurposing and redefining a multifaceted drug. In Drug Discovery Today (Vol. 19, Issue 12, pp. 1848–1854). Elsevier Ltd. https://doi.org/10.1016/j.drudis.2014.08.017

[67] Psutka, S. P., Boorjian, S. A., Lohse, C. M., Stewart, S. B., Tollefson, M. K., Cheville, J. C., Leibovich, B. C., & Thompson, R. H. (2015).The association between metformin use and oncologic outcomes among surgically treated diabetic patients with localized renal cell carcinoma. Urologic Oncology: Seminars and Original Investigations, 33(2), 67.e15-67.e23. https://doi.org/10.1016/j.urolonc.2014.07.008

[68] Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., Doig, A., Guilliams, T., Latimer, J., McNamee, C., Norris,A., Sanseau, P., Cavalla, D., & Pirmohamed, M. (2018a). Drug repurposing: Progress, challenges and recommendations. In Nature Reviews Drug Discovery (Vol. 18, Issue 1, pp. 41–58). Nature Publishing Group. https://doi.org/10.1038/nrd.2018.168

[69] Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., Doig, A., Guilliams, T., Latimer, J., McNamee, C., Norris,A., Sanseau, P., Cavalla, D., & Pirmohamed, M. (2018b). Drug repurposing: Progress, challenges and recommendations. In Nature Reviews Drug Discovery (Vol. 18, Issue 1, pp. 41–58). Nature Publishing Group. https://doi.org/10.1038/nrd.2018.168

[70] Ranganath, L. R., Milan, A. M., Hughes, A. T., Dutton, J. J., Fitzgerald, R., Briggs, M. C., Bygott, H., Psarelli, E. E., Cox, T. F., Gallagher, J. A., Jarvis, J. C., van Kan, C., Hall, A. K., Laan, D., Olsson, B., Szamosi, J., Rudebeck, M., Kullenberg, T., Cronlund, A., … Rovensky, J. (2016). Suitability Of Nitisinone In Alkaptonuria 1 (SONIA 1): an international, multicentre, randomised, open-label, no-treatment controlled, parallel-group, dose-response study to investigate the effect of once daily nitisinone on 24-h urinary homogentisic acid excretion in patients with alkaptonuria after 4 weeks of treatment. Annals of the Rheumatic Diseases, 75(2), 362– 367. https://doi.org/10.1136/annrheumdis-2014-206033

[71] Rehman, W., Arfons, L. M., & Lazarus, H. M. (2011). The rise, fall and subsequent triumph of thalidomide: Lessons learned in drug development. In Therapeutic Advances in Hematology (Vol. 2, Issue5, pp. 291–308). https://doi.org/10.1177/2040620711413165

[72] Roessler, H. I., Knoers, N. V. A. M., van Haelst, M. M., & van Haaften, G. (2021). Drug Repurposing for Rare Diseases. In Trendsin Pharmacological Sciences (Vol. 42, Issue 4, pp. 255–267). Elsevier Ltd. https://doi.org/10.1016/j.tips.2021.01.00375.Sadeghi, H. M., Adeli, I., Mousavi, T., Daniali, M., Nikfar, S., & Abdollahi, M. (2021). Drug repurposing for the management ofdepression: Where do we stand currently? Life, 11(8). https://doi.org/10.3390/life11080774

[73] Sallmann, A. R. (1986). The history of diclofenac. The American Journal of Medicine, 80(4), 29–33. https://doi.org/10.1016/0002-9343(86)90076-8

[74] Salvadore, G., & Singh, J. B. (2013). Ketamine as a Fast Acting Antidepressant: Current Knowledge and Open Questions. In CNS Neuroscience and Therapeutics (Vol. 19, Issue 6, pp. 428–436). https://doi.org/10.1111/cns.12103

[75] Sleire, L., Førde, H. E., Netland, I. A., Leiss, L., Skeie, B. S., & Enger, P. Ø. (2017). Drug repurposing in cancer. Pharmacological Research, 124, 74–91.

https://doi.org/10.1016/j.phrs.2017.07.013

[76] Smith, S. B., Dampier, W., Tozeren, A., Brown, J. R., & Magid-Slav, M. (2012). Identification of common biological pathways and drug targets across multiple respiratory viruses based on human host geneexpression analysis. PLoS ONE, 7(3). https://doi.org/10.1371/journal.pone.0033174

[77] Sun, W., Weingarten, R. A., Xu, M., Southall, N., Dai, S., Shinn, P.,Sanderson, P. E., Williamson, P. R., Frank, K. M., & Zheng, W. (2016). Rapid antimicrobial susceptibility test for identification of new therapeutics and drug combinations against multidrug-resistant bacteria. Emerging Microbes and Infections, 5(11). https://doi.org/10.1038/emi.2016.123

[78] Swan, G. E. (1999). The pharmacology of halogenated salicylanilides and their anthelmintic use in animals : review article. Journal of the South African Veterinary Association, 70(2), 61–70. https://doi.org/10.4102/jsava.v70i2.756

[79] Tanenbaum, L. (1980). Antimalarial Agents. Archives ofDermatology, 116(5), 587. https://doi.org/10.1001/archderm.1980.01640290097026

[80] Taragano, F. E., Allegri, R., Vicario, A., Bagnatti, P., & Lyketsos, C. G. (2001). A double blind, randomized clinical trial assessing the efficacy and safety of augmenting standard antidepressant therapywith nimodipine in the treatment of "vascular depression." International Journal of Geriatric Psychiatry, 16(3), 254–260. https://doi.org/10.1002/gps.340

[81] Taragano, F. E., Bagnatti, P., & Allegri, R. F. (2005). A double- blind, randomized clinical trial to assess the augmentation with nimodipine of antidepressant therapy in the treatment of "vasculardepression." International Psychogeriatrics, 17(3), 487–498. https://doi.org/10.1017/S1041610205001493

[82] The Lancet Diabetes & Endocrinology. (2019). Spotlight on rare diseases. The Lancet Diabetes & Endocrinology, 7(2), 75. https://doi.org/10.1016/S2213-8587(19)30006-3

[83] Vaidya, B., Parvathaneni, V., Kulkarni, N. S., Shukla, S. K., Damon, J. K., Sarode, A., Kanabar, D., Garcia, J. v., Mitragotri, S., Muth, A.,& Gupta, V. (2019). Cyclodextrin modified erlotinib loaded PLGA nanoparticles for improved therapeutic efficacy against non-smallcell lung cancer. International Journal of Biological Macromolecules, 122, 338–347. https://doi.org/10.1016/j.ijbiomac.2018.10.181

[84] van den Bossche, H., Rochette, F., & Hörig, C. (1982). Mebendazoleand Related Anthelmintics (pp. 67–128). https://doi.org/10.1016/S1054-3589(08)60021-6

[85] Xu, M., Lee, E. M., Wen, Z., Cheng, Y., Huang, W. K., Qian, X., Tcw, J., Kouznetsova, J., Ogden, S. C., Hammack, C., Jacob, F., Nguyen, H. N., Itkin, M., Hanna, C., Shinn, P., Allen, C., Michael, S. G., Simeonov, A., Huang, W., … Tang, H. (2016). Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. Nature Medicine, 22(10), 1101–1107. https://doi.org/10.1038/nm.4184