Drug Repurposing in Antiviral Research: A Review

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Abstract **- Drug discovery and development are long, huge costly and time-consuming processes. On an average it takes at least 10 years and cost 2.6 billion USD for successful drug discovery and approval for clinical use. Drug repurposing is a promising, fast and cost-effective method that can overcome traditional de novo drug discovery and development challenges of targeting various diseases. Drug repurposing is a process of identifying new therapeutic use for old and existing drugs. It is highly efficient strategy in the developing drug molecules with new pharmacological and therapeutic indications. In recent years, many pharmaceutical companies are developing new drugs with the discovery of novel biological targets by applying the drug repositioning strategy in drug discovery and the development processes. This strategy is an effective, time saving, low-cost and minimum risk of failure. It increases the therapeutic value of a drug and hence it increases the success rate. Thus, drug repositioning is an efficacious, successful and alternative approach to traditional drug discovery process. The repurposing approach has given many promising drug candidates for various viral infectious diseases like Ebola, Influenza, ZIKA, dengue, HIV infections and various other viral infectious diseases. The emergence of resistance to existing antiviral drugs and re-emerging viral infections are the biggest challenges in antiviral drug discovery process. The drug repurposing approach is an assuring strategy in finding new antiviral agents within a short period of time to overcome the challenges in antiviral therapy. In this review, we describe the most promising results of the drug repurposing approach in the treatment of various viral infectious diseases.**

Index Terms **- Drug repurposing, antiviral, drug discovery, viral infection.**

INTRODUCTION

Drug repurposing is also known as drug repositioning, drug re-tasking, drug recycling, drug rescuing, drug profiling, drug redirection, and therapeutic switching. It can be defined as a process of identification of new pharmacological indications from old, existing, investigational/already marketed, FDA approved drugs/pro-drugs, and the application of the newly developed drugs to the treatment of diseases other than the drug's original/intended therapeutic use. Drug repurposing uses the already available clinical trials data for toxicity and adverse effects, at the same time explores the drug's therapeutic potential for a different disease. It includes establishing new therapeutic uses for already known drugs, including approved, discontinued, abandoned and experimental drugs. Traditional drug discovery is a very time-consuming, laborious, expensive and high-risk process. Novel approach of the drug repositioning has the potential to be employed over traditional drug discovery program by reducing the high monetary cost, longer duration of development and increased risk of failure. It confers reduced risk of failure where a failure rate of ~45% is associated due to safety or toxicity issues in the traditional drug discovery with additional benefit of saving up to 5–7 years in average drug development time. In recent years, the drug repositioning strategy has obtained considerable momentum with about one-third of the new drug approvals correspond to the repurposed drugs which currently generate around 25% of the annual revenue for the pharmaceutical industry. It has been accounted that approximately 30% of the US Food and Drug Administration (FDA) approved drugs and biologics (vaccines) are the repositioned drugs. According to recent estimates, pharmaceutical industries have significantly placed the market for repurposed drugs at $24.4 billion in

2015 year with projected growth up to $31.3 billion in 2020.

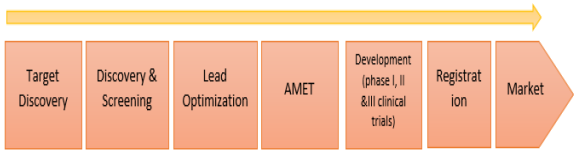
History of drug repurposing:

The oldest example of drug repositioning is acetylsalicylic acid .It is initially marketed by Bayer in 1899 as an analgesic, aspirin was first repositioned in the 1980s, at low doses only, as antiplatelet aggregation drug. It is still widely used today in this second indication to prevent cardiovascular events, based on the work of Vane, for which he was awarded the Nobel Prize in Medicine in 1982.Some most successful and best-known drugs that have been emerged out of the drug repositioning approach are sildenafil, minoxidil, aspirin, valproic acid, methotrexate etc. For example, in mid 2000s sildenafil originally developed for the treatment of hypertension and angina pectoris has currently been used to treat erectile dysfunction and thalidomide for morning sickness was repositioned to multiple myeloma. Few examples involve chlor-promazine synthesized in 1950 that was indicated for use in controlling mental disorders and as a preoperative medication which was later tried for the various diseases like treating whooping cough and symptoms developed in radiation therapy for cancer patient's in1972. Chloroquine was a well-known antimalarial compound synthesized in the year 1934 and was later targeted towards the many other diseases including parasitic diseases (before 1960), fever, and lupus skin rashes.

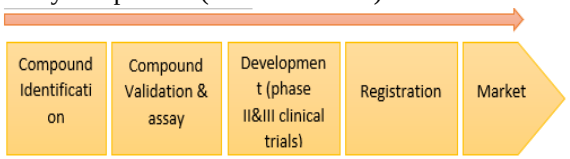
Why is drug repurposing required?

Drug repurposing or drug repositioning is fast, highly efficient, time saving, cost effective and minimum risk of failure method. It maximizes the therapeutic value of a drug. Thus, drug repositioning is an effective alternative approach to traditional drug discovery process. Finding new molecular entities by de novo approach of drug discovery is a lengthy, time consuming and expensive venture. Drug repurposing or repositioning utilizes the combined efforts of experimental based and in silico-based approaches to develop the new uses of drug molecules on a rational basis. It is, therefore, believed to be an emerging strategy where the existing medicines, having already been tested safe in humans, are redirected based on a valid target molecule to combat particularly, rare, difficult to treat diseases and the neglected diseases.

Traditional Drug Discovery Method:
10-17 years process (use 2.6 billion)



Drug Repurposing:
3-12 years process (use 0.35 billion)



Strategies of drug repositioning:

There are two main strategies-

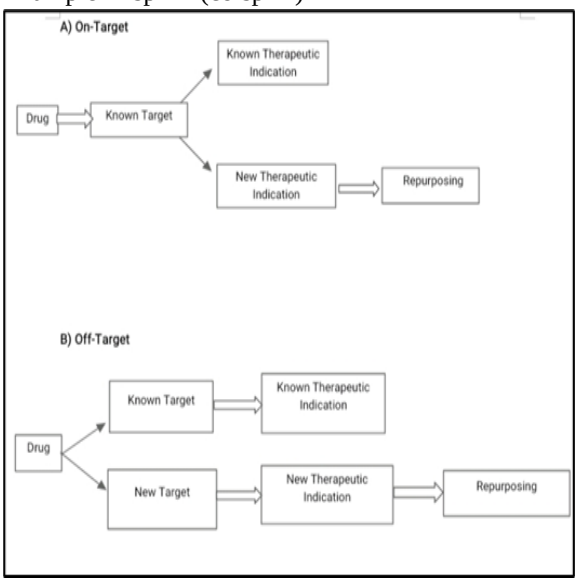
- On-target
- Off-target

In on-target drug repositioning the known pharmacological mechanism of a drug molecule is applied to a new therapeutic indication. In this strategy, the biological target of a drug molecule is same, but the disease is different.

Example- Minoxidil (Rogain)

In off-target drug repositionig the pharmacological mechanism is unknown. Drugs and drugs candidates act on the new targets, out of the original scope, for the new therapeutic indications. Therefore, both the targets and indications are new.

Example- Aspirin (colsprin)



Drug Repositioning in various viral infectious diseases:

1)Drug repurposing in Ebola virus infection

Ebola is also known as Ebola virus disease (EVD) or Ebola Haemorrhagic Fever (EHF) that causes severe bleeding, organ failure and can lead to death. Ebola virus is filo virus responsible for the several outbreaks since it's discovery in the late 1970s, but the last one, in 2014-2016,was the most alarming due it's size and spread. Due to the urgent need for an effective Ebola virus treatment, there were additional efforts to study the existing drugs as potential antiebola virus disease therapeutic agent which is called as drug repositioing. The study of favipiravir against the Ebola virus has shown good results both in vitro and in vivo. The ability of chloroquine to inhibit Ebola virus has shown promising outcomes in different in vitro studies with various cell lines. Toremiphene and clomiphene are widely available selective estrogen reuptake modulators Approved for the treatment of breast cancer and infertility. These drugs were found to have antiviral activity by inhibiting Ebola virus entry in vitro by more than 90%. Amiodarone is a well-established and commonly used multi-iron channel blocker, for the treatment of atrial fibrillation and the ventricular tachycardia arrhythmias. It has been reported as a potent inhibitor of Ebola virus in various cell lines. Among several drugs investigated for anti-ebola virus activity in vitro and in vivo, azithromycin was found to be the potent in vitro inhibitor of the ebola virus. A targeted drug combination approach resulted in identification of the several combinations of drugs which can act synergistically in blocking the ebola virus entry.

2)Drug Repurposing in ZIKA virus infection

Zika virus (ZIKV) is a mosquito-borne flavivirus transmitted primarily by Aedes mosquitos. Zika virus infection during the pregnancy can cause infants to be born with microcephaly and other congenital malformations, known as congenital Zika syndrome. Infection with the Zika virus is also associated with other complications of pregnancy including preterm birth and miscarriage. Increased risk of neurologic complications is associated with Zika virus infection in adults and children, including Guillain-Barré syndrome, neuropathy and myelitis.

Nanchangmycin, a polyether of bacterial origin, blocked Zika virus infection in different cell lines and in ex vivo midbrain neuron– glia mixed cultures from embryonic mice. Chloroquine is a commonly used anti-inflammatory, antimalarial agent shows antiviral activity against a number of viruses. It also exhibits antiviral activity against ZIKV in Vero, human brain micro vascular endothelial and in neural stem cells. Chloroquine decreases virus production, the number of infected cells and cell death promoted by ZIKV infection without any cytotoxic effect. Sofosbuvir has an antiviral activity against ZIKV. Ni-closamide and Azithromycin are the most commonly used drugs used in ZIKV treatment in pregnant women and their effective concentration is easily achievable in human plasma. A natural compound Hippeastrine hydrobromide is reported to be a potent inhibitor of ZIKV infection and microcephaly- related effects. Combining drug–target network analysis and functional validation will help in identifying new genes and pathways to develop new antiviral drug molecules for ZIKV infection. Developing new high-throughput, drug-repurposing assays and leveraging existing functional genomics tools against viral replication pathways, is a promising path in the discovery of effective antiviral therapies against ZIKV and other infectious agents.

3)Drug repurposing in influenza virus infection

Influenza is viral infection that attacks respiratory system. It is commonly called as Flu, belong to the family orthomyxoviridae and is a pathogen of global public health importence as it caused pandemic disease outbreaks. Drug repurposing compaigns identified some drugs which are already approved or under clinical evaluation with anti-influencer activities such as BAY 81-8781, dapivirine, naproxen and the antibiotic clarithromycin. Three drug combinations of Clarythromycin and naproxen along with oseltamivir showed efficacy in the treatment of influenza virus disease. Nalidixic acid and dorzolamide showed efficacy against oseltamivir resistant Influenza virus by an in-silico screening specially targeting mutant viral neuraminidase and, the most advanced example of drug repurposing is the case of the anti-parasitic drug nitazoxanide, currently being Reaper positive for the treatment of influenza. The kindness inhibitors namely dinaciclib, flavopiridol and PIK-75 were reported to be highly effective against the H7 N 9 virus with the less toxicity. These drugs were also found to

be effective against representative strains from the two circulating IAV subtypes, the PdmH1N1 and H3N2.

4)Drug repurposing in Dengue virus infection

Dengue is a mosquito borne single positive stranded RNA viral disease of the family falviviridae caused by four antigenically distinct serotypes of dengue virus namely DENV-1, DENV-2, DENV-3, DENV-4. Dengue virus is currently the most important arthropod born viral disease in the world. With the rapid spreading of the Dengue virus and the long time required for bringing a new drug in the market, the repurposing of existing seems to be an attractive approach for rapid therapeutic intervention. Nelfinavir and other viral proteins inhibitors like lopinavir and ritonavir were repurposed against dengue virus infection by computer aided drug design. As a result of many studies involving chloroquine in many drug repositioning studies for the dengue virus infection, It was proved to be able to inhibit dengue virus Type2 replication in Vero cells at a dose of 5μg/ml by plaque assay and qRT-PCR(Quantitative Real Time – Polymerase chain Reaction).

Castanospermine is a natural alkaloid is active in vitro against influenza virus, cytomegalovirus,HIV-1 and DENV-1 and in Vivo against Herpes simplex virus and Rauscher Murine leukaemia virus. Dasatinb bortezomib and AZD053, prochlorperazine (antipsychotic agent),ivermectin, suramin, nitazoxanide (Antiparasitic drugs), Dexamethasone, Prednisolone (Steroids),Geneticin, narasin and Minocyclin(Antibiotics) were found to be effective against DENV.

5)Drug repurposing in HIV and coronavirus infection

Human immunodeficiency virus (HIV) Infection is a viral infection that attacks cells in the immune system. If HIV is not treated it can lead to a acquired immunodeficiency syndrome (AIDS).According to World Health Organisation 26 million people have died since 1981 and 1.6 million in 2012 alone. In several studies the HIV 1 replication was found to be inhibited by the chloroquine and its hydroxyl analogue hydroxychloroquine.

A novel corona virus disease infection has come out which causes pneumonia explores first in the Wuhan region of China and now days with high transmission efficiency spreading worldwide. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). The most recently discovered coronavirus causes coronavirus disease COVID-19 and having a death rate approximate about 2% to 2.5%, increasing with age and the exciting with underlying diseases. Coronaviruses are named for the crown-like spikes on their surface. There are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta.

The seven coronaviruses that can infect the humans are

Human coronaviruses:

1. 229E (alpha Coronaviruse)
2. NL63(alpha Coronavirus)
3. OC43(beta Coronavirus)
4. HKU1(beta Coronavirus)
5. MERS-CoV(the beta Coronavirus that causes Middle East Respiratory Syndrome)
6. SARS-CoV(the beta Coronavirus that causes Serve Acute Respiratory Syndrome)
7. SARS-CoV-2(the novel Coronavirus that causes Coronavirus disease 2019 or COVID-19)

Previously, chloroquine derivatives had been tested on the coronaviruses and demonstrated a potential antiviral effect in-vitro, which were further supported by the recent findings where the Hydroxy chloroquine (HCQ) was demonstrated to inhibit the COVID-19 replication in vitro. Initially, HCQ demonstrated promising antiviral effects in the patients suffering from severe acute pneumonia infected with SARS-CoV-2, which led to the fast-track approval of HCQ for COVID-19 patients by the USFDA. However, subsequent reports of moderate or no effect of Hydroxychloroquine questioned its use in COVID-19 patients and eventually its retraction after two pioneering studies demonstrated reduced antiviral but more adverse effects of HCQ in patients raising alarming signals over the effectiveness of HCQ against COVID-19 disease. Further, the use of intravenous immunoglobulins for their ability to produce anti-inflammatory and immunomodulatory effects is being evaluated in the patients suffering from the pneumonia caused by COIVD-19 . Subsequently, HIV-1 protease inhibitors have gained a popularity in the scientific community for their inhibitory potential against COVID-19. Several of the HIV-1 reverse

transcriptase inhibitors including remdesivir , umifenovir are being evaluated either individually or in different combination in the patients suffering from Corona virus disease. Additionally, other gold-standard medications such as Thalidomide as well as vitamin-C are being investigated actively in patients suffering from severe Coronavirus disease. Furthermore, other pharmacologically active molecules such as methylprednisolone, pirfenidone , bromhexine hydrochloride , bevacizumab , fingolimod have occupied a prominent place as potential therapeutic candidates in patients suffering from critical illness due to the COVID-19 disease associated complications . These studies collectively validated the fact that the utilization of the drug repurposing approach will not only considerably reduce the recourse consumption, but also help to drastically reduce the failure rate.

CONCLUSION

Drug repositioning or Drug repurposing (DR) is a field of drug research whose importance has been increasing in the past years, due to the several advantages, such as the possibility to shorten the clinical trials, the extension of the life of an old drug by finding a new therapeutic target and the discovery of often-unknown relationships among probably distant diseases. Drug repurposing approach offers significant reduction in Research & Development costs, greater chances of success, shorter research time and the lower investment risk, it has gained increasing market demands. Because these advantages are beneficial for the discovery scientists, drug researchers, consumers, and the pharmaceutical companies, enabling the application of novel approaches of repositioning strategy in the drug discovery program for almost all human diseases. Drug repositioning can be successfully utilized in the discovery and the development of new drugs with novel and effective therapeutic indications for human diseases.

REFERENCES

[1] F. Lopez-Mu noz, C. Alamo, E. Cuenca, W.W. Shen, P. Clervoy, G. Rubio, His- ~tory of the discovery and clinical introduction of chlorpromazine, Ann. Clin. Psychiatr. 17 (3) (2005) 113e135.

[2] F.R. Frankenburg, R.J. Baldessarini, Neurosyphilis, malaria, and the discoveryof antipsychotic agents, Harv. Rev. Psychiatry 16 (5) (2008) 299e307.

[3] R.A. Gordon, M. Campbell, The use of chlorpromazine in intractable painassociated with terminal carcinoma, Can. Med. Assoc. J. 75 (5) (1956) 420.

[4] M. Schlitzer, Malaria chemotherapeutics part I: history of antimalarial drugdevelopment, currently used therapeutics, and drugs in clinical development, ChemMedChem 2 (7) (2007) 944e986.

[5] D.J. Wallace, The history of antimalarials, Lupus 5 (1_suppl) (1996) 2e3.

[6] Sweiti H, Ekwunife O, Jaschinski T, Lhachimi SK. Repurposed Therapeutic Agents Targeting the Ebola Virus: A Systematic Review. Curr Ther Res Clin Exp. 2017;84:10-21.1

[7] Dowall SD, Bosworth A, Watson R, Bewley K, Taylor I, Rayner E, et al. Chloroquine inhibited Ebola virus replication in vitro but failed to protect against infection and disease in the in vivo guinea pig model. J Gen Virol. 2015;96(12):3484-92.

[8] Madrid PB, Chopra S, Manger ID, Gillian L, Keepers TR, Shurtleff AC, et al. A systematic screen of FDA-approved drugs for inhibitors of biological threat agents. PLoS One. 2013;8(4):e60579.

[9] Salata C, Baritussio A, Munegato D, Calistri A, Ha HR, Bigler L, et al. Amiodarone and metabolite MDEA inhibit Ebola virus infection by interfering with the viral entry process. Pathog Dis. 2015;73(5):ftv032.

[10] Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J. 2010;36(3):646-54.

[11] Michael SK, Eric P. An analysis of FDA-approved drugs for infectious disease: HIV/AIDS drugs. Drug Discover Today. 2014;19(10):1510-3.

[12] Michael SK, Eric P. An analysis of FDA-approved drugs for infectious disease: HIV/AIDS drugs. Drug Discover Today. 2014;19(10):1510-3.

[13] Savarino A, Shytaj IL. Chloroquine and beyond: exploring anti-rheumatic drugs to reduce immune

hyperactivation in HIV/AIDS. Retrovirology. 2015;12(1):51.

[14] Hung IFN, To KKW, Chan JFW, Cheng VCC, Liu KSH, Tam A, et al. Efficacy of Clarithromycin-Naproxen-Oseltamivir Combination in the Treatment of Patients Hospitalized for Influenzas A (H3N2) Infection: An Open-label Randomized, Controlled, Phase IIb/III Trial. Chest. 2017;151(5):1069-80.

[15] Bao J, Marathe B, Govorkova EA, Zheng JJ. Drug Repurposing Identifies Inhibitors of Oseltamivir-Resistant Influenzas Viruses. Angew Chem Int Ed Engl. 2016;55(10):3438-41.