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A Review on Drug Repurposing: A Perspective for COVID

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ABSTRACT: Drug Repurposing or Drug Repositioning or Drug Cycling has become a new approach to overcome the problems faced in drug discovery and development of new drug molecule via identifying a new therapeutic value of the existing drug. Drug Discovery process is time consuming and have several steps for finding a lead molecule. With the serendipitous effect of Sildenafil which was a repurposed drug, the Drug Repurposing came with a newer dimension of drug development. There are wide varieties of computational methods which enables systematic repurposing of drugs, through experimental and in silico approaches. As the World is suffering from Pandemic disease COVID-19, drug repurposing approach has become popular as the specific drug and vaccine is still not available for the treatment. Some repurposed drugs used in different diseases as well as for COVID-19 are highlighted with the emerging trends of new indication to drug development.

KEYWORDS: Repurposing, COVID, in silico, SARS, MERS

I. INTRODUCTION

The time was running by its pace. All the countries of the world were engaged in uplifting their economy. Nobody was aware of what will happen the next. Suddenly a breakthrough came, when many people of Wuhan (China), came with the respiratory problems, Pneumonia like symptoms to the doctor in early December 2019. The disease was later identified as a viral disease similar to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[1,2] By the onset of corona virus and the disease has not much similarity with that of the previous epidemic, World Health Organization named it as Novel (new) Corona virus or COVID-19 on 11 February 2020. The disease has crossed all its barrier and became Pandemic. [3]

About the Virus

Corona viruses are relatively large viruses containing a single stranded positive- sense RNA genome encapsulated within a membrane envelope. The viral membrane has glycoprotein spikes that give coronavirus, crown like appearance. The coronavirus infects animals and humans, certain types animals like bats being the hosts of the virus are immune to coronavirus- induced illness. According to the International Committee on Taxonomy of viruses, Coronaviruses are class of Nidovirales, family Coronaviridae, subfamily Coronavirinae which is then further classified as genus alphacoronavirus, betacoronavirus, gammacoronavirus and deltacoronavirus. The SARS CoV belonged to lineage B of betacoronavirus and MERS CoV belonged to Lineage C of betacoronavirus. [4, 5, 6] World Health Organization(WHO) has classified COVID-19 as from betacoronavirus group 2B.[7] Also known as SARS CoV-2. The researchers found that the genetic sequence of COVID-19 showed more than 80% identity to SARS-CoV and 50% to the MERS-CoV. [8] As SARS-CoV and MERS-CoV, SARS CoV-2 attacks the lower respiratory tract causing viral pneumonia , but it may also affect gastrointestinal system, heart, kidney, liver and central nervous system which may lead to multiple organ failure. The disease more transmissible and contagious.[9] The coronavirus genome encodes several structural proteins including glycosylated spike (S) protein that acts as a major inducer of host immune responses. This S-protein mediates the binding of SARS CoV and SARS CoV2 to the host cell, there by binding with the host receptor protein present on the surface membrane which is known as Angiotensin Converting Enzyme 2. [10] Some studies also revealed that the invasion process requires S protein priming which is facilitated by the host cell serine protease TMPRSS2 (transmembrane protease serine2). Also the viral genome encodes several non- structural proteins like RNA dependent RNA polymerase (RdRp), Corona virus main protease (3CL pro) and papain like protease(PL pro).Upon entrance to the

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host cells, the viral genome is released as a single stranded positive RNA. Further it is translated into viral polyproteins using host cell protein translation, which then cleaves to effector proteins 3CL pro and PL pro. [11, 12] The PL pro behaves as a deubiquitinase which deubiquitinate certain host cell proteins, including interferon factor 3 and NF-κB, leading to immune suppression. The RdRp also synthesizes a full length negative strand RNA template used by RdRp to make more viral genomic RNA.

The interaction between the S-protein and ACE-2 on the host cell surface is of great interest as it initiates the infection process. The study done by Cryo-EM Structure analysis showed that the binding affinity of SARS CoV-2 S protein to ACE2 is 10-20 times higher than the SARS CoV S protein. This may be the reason of contagious and transmissible nature of SARS CoV-2. [9] The highly conserved proteins associated with SARS- CoV and SARS- CoV-2 is perspective for future drug targeting.

II. DRUG REPURPOSING

Drug Discovery is the basis for the generation of new drug or new chemical entity. Drug discovery process started with random screening of crude plants like opium, rauwolfia and many more which has given rise to drug industry, leading to the advancement in the industries in our society. [11] Drug Repurposing or Drug Repositioning or Drug cycling has become a new approach to overcome the problems faced in drug discovery and development of new drug molecule via identifying a new therapeutic value of the existing drug. As we know, that the new drug molecule has to go through many phases before coming into the market like formulation, manufacturing methods, pharmacokinetic parameters, adverse effects, clinical trial information and post-marketing surveillance safety data; here the repurposed drug can have all these basic established data. Drug Repurposing came into existence by the very well known example of Sildenafil which was originally produced to be use for coronary artery disease but became failure in phase 2 trials, having side effect of inducing penile erections and became popular for the treatment of erectile dysfunction. Many other drugs like thalidomide, nelfinavir, minoxidil has been used effectively another indication for which they have been intended. [13, 14, 15]

Aspects of Clinical Drug Development For Drug Repurposing

Clinical development for drug repurposing should be adopted as that of the clinical development of New Chemical Entity (NCE), but there may be some elements in the process which can be omitted as due to existing knowledge of the drug. The clinical testing of the drug is based on the three pillars of survival which are: the integrated understanding of the pharmacodynamic and pharmacokinetic principles at the site of action, target binding and manifestation of pharamcological activity. [26] For drug repurposing Process, Some factors are interpretated like early risk, cost and time . The strategy is based on the approved drug to be examined for a new indication at similar or low doses than the maximum dose already approved by the regulatory agencies to target via same mechanism in a different patient population.

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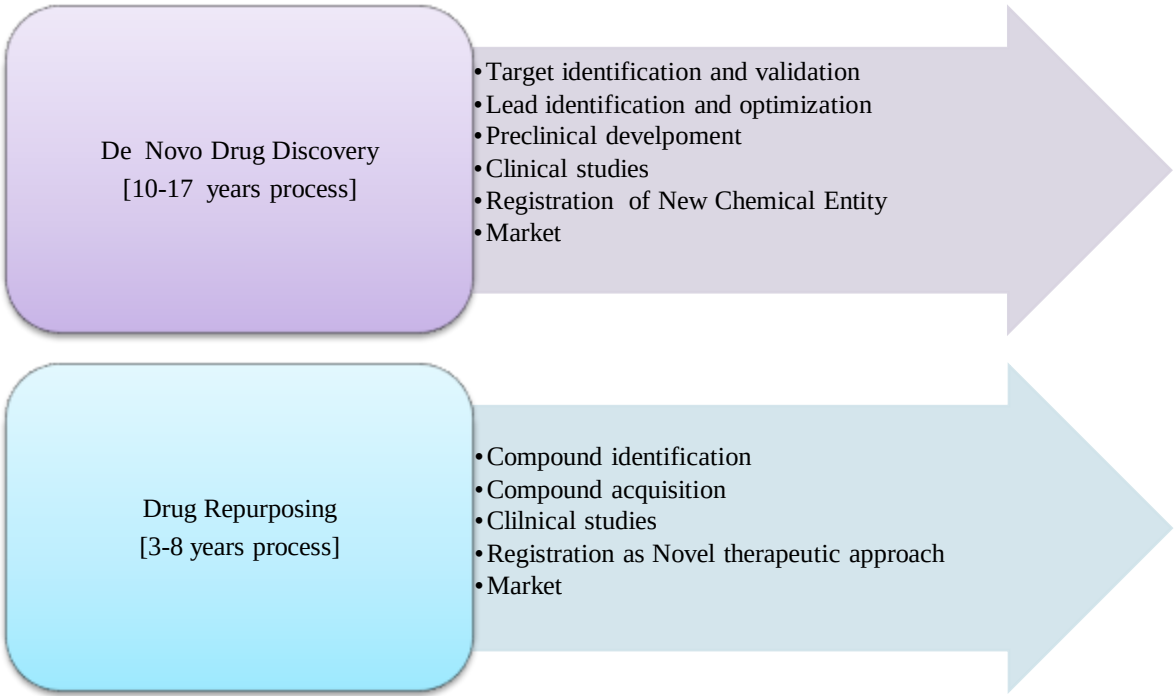

Fig: Drug Discovery and Drug Repurposing Process

Some examples of Repurposed Drug with disease – drug - new indication are given in table: [27]

S.No.	Disease	Drug	New indication
1.	Hypertension	Minoxidil	Alopecia
2.	Benign Prostatic Hyperplasia	Finasteride	Alopecia
3.	Glaucoma	Lumigan(Bimatoprost)	Hypotrichosis simplex
4.	Hypertension	Phentolamine	Dental anaesthesia reversal agent
5.	Prostate and breast cancer	Raloxifene	Oesteoporosis
6.	Depressive disorder	Doxepine	Antipruritic
7.	Asthma	Zileuton	Acne
8	Leprosy	Dapsone	Malaria
9.	Antifungal	Amphotericin	Leishmaniasis
10.	Parkinson disease	Apomorphine	Erectile dysfunction
11	Parkinson disease	Bromocriptine	Diabetes
12	Type-2 Diabetes Mellitus	Pioglitazone	Non-alcoholic steatohepatitis
13	Depression	Nortryptyline	Neuropathic pain
14	Depression	Sibutramine	Obesity
15	Asthma	Budesonide	Ulcerative colitis
16	Hypertension	Propranolol	Migraine prophylaxis
17	Cancer	Methotrexate	Rheumatoid Arthritis
18	Cancer	Zidovudine	HIV/AIDS
19	Antiepileptic	Valproic acid	Leukemia
20	Immunosuppresant	Rapamycin	Lymphoma, leukemia
21	Alcoholism	Disulfiram	Melanoma
22	Morning sickness	Thalidomide	Multiple myeloma
23	Local Anaesthetic	Lignocaine	Arrythmia

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24	Hypertension	Perindopril	Alzheimer's disease
25	Influenza	Amantadine	Parkinson's disease
26	Pregnancy termination	Mifepristone	Psychotic depression
27	Epilepsy	Gabapentin	Neuropathic pain
28	Myocardial Infaraction	Statins	Leukemia, Cancer
29	Gout	Colchicine	Recurrent pericarditis
30	Angina	Sildenafil	Erectile dysfunction
31	AIDS	Nelfinavir	Clinical trial of multiple cancer

Systematically Combined Drug Repurposing Approach

To identify potential new drug- disease relation, systematic repurposing approach is based on:

1. Experimental screening approach.
2. In- silico approach.

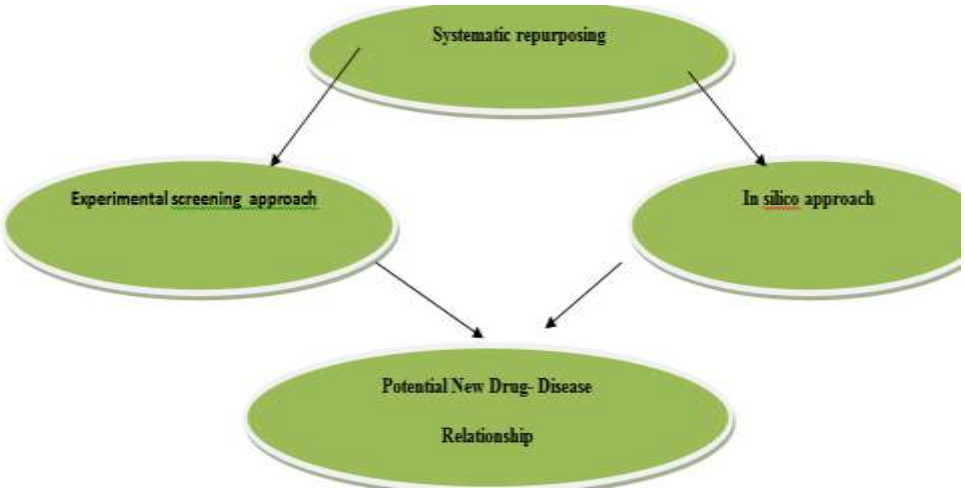

Fig: Approaches of Drug Repurposing

1. Experimental Screening approaches:-

Experimental Screening approaches are basically used for identifying lead in both drug discovery and drug repurposing process. As drug discovery process starts with de novo molecule through High Throughput Screening, which requires highly specialized facilities, large compound libraries. On the contrary, repurposing is a advanced one having the knowledge of their efficacy and safety. The hit produced in the drug discovery has to go through various screening process to become a potential drug while repurposed drug has many advancement in itself. [16] For all these processes to be achieved, compound libraries plays a very important role. Some of which are:-

A. The Drug Repurposing Hub:-

The Drug Repurposing Hub is a curated and annotated collection of FDA approved drugs, clinical trial drugs, and preclinical tool compounds with a companion information resource.

B. FDA approved drug library:-

The drug library has enzyme inhibitors, natural products, Active Pharmaceutical Ingredients, Natural products, Antibiotics, Antibody drug conjugates, Dyes, hydrotropic agents and many more compilations.

C. LOPAC®[1280] :-

LOPAC®[1280] – The Library of Pharmacologically Active Compound. This biologically annotated collection of inhibitors, receptor ligands, pharma developed tools and approved drugs impacts, most signaling pathways and covers all major target classes.

D. The Microsource spectrum collection: International Drug Collection: Compounds marketed in Europe and or/Asia.

E. Chem Div: The Chemistry of cure:-

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It helps in finding synthetic chemistry, hit findings, Integrated drug discovery, Virology, Drug Development, Disease based models.

The hit produced in the High Throughput Screen drug discovery (initial stage), has to go through various barriers of medicinal chemistry which are further screened to get the potential drug .High Throughput Screens are of three types:

1. **Cell free or cell based** depends on specific compound activity in relation to a specific mechanism.
2. **Target- focused screens**, based on cell behavior (growth and death).
3. **Phenotypical screening**, it is the screening with multicellular organism model (ex: worms,fruit flies,zebrafish) introduced with human genes and /or disease causing mutation provides approach for phenotypical screening. [17]

The case study o repurposing potential through screening approach is provided by the efforts of various laboratories in search to promote myelin repair. Myelin repair involves: (a). enhancing the differentiation of oligodendrocyte precursor cells (OPC's) into oligodendrocytes and (b) the promotion of axon remyelination.

A phenotypical screen using rat optic nerves OPC's identified **benzotropine**, a muscarinic antagonistbasically used in the treatment of Parkinson Disease, also penetrates Blood Brain Barrier (BBB) which is a requirement for myelin repair. **Clemastine,** having muscarinic and histamine antagonistic activity is another brain penetrant showed OPC differentiation into cells that form myelin. **Quetiapine** another muscarinic antagonist showed relation to remyelination in primary rat OPC differentiation assay. These drugs found advantage in case of multiple sclerosis. Thus, the potential of repurposing screens to identify hits rapidly into clinical development through the ability of multiple independent screens has been successful.[18, 19,20,21,22]

2. In silico repurposing approaches

In silico drug repurposing approaches are highly sophisticated methods for identifying new potential of drug from the existing data with the relationship between drug and disease. They are categorized into Molecular approach and RWD approach. [23]

1. **Molecular approach –** Based on large scale molecular data i.e. 'omic data' which means genomic, transcriptomic or proteomic data. The molecular approach is based on understanding the drug activity and pathophysiology of disease.

In molecular approach, transcriptomics and genomics are widelyused for drug repurposing because of the availability of combination of datasets of drugs and diseases. [24] Trancriptomics is measuring the expression levels of thousands of genes, by quantification of RNA – sequencing or gene expression microarray. The combination of transcriptomics and genomic has been used for identification of potential repurposing candidates for Alzheimers disease.

2. **RWD approach –** RWD means Real World Data focuses on identification of unknown. It is based on relationships between drug and diseases or their symptoms.RWD has basics of individual's health, habits and behavior based purely on data collection methodologies. It is based on observational (non-interventional) data on individual activities, and health. Database of millions of patients often containing several years of data which is from electronic medical records (EMR's) or hospital data or administrative data, health, surveys or adverse event, these types of data helps in the development of new drug to support health of the society. EMR data, demonstrated that metformin, a common oral medication for type-2 diabetes was associated with decrease mortality of cancer patients compared to non-diabetic cancer patients, not on metformin. [25]

Some of the **Drug Database** are: Pubchem, ChEMBL, LINCS, CMAP, Project Achilles, CTRP, Pharm GKB, Daily MED, Imm Port.

Some of the **Disease Databases** are: Multiomic level, Genomic, Transcriptomic, Proteomic, Epigenetic.

Some of the **Omics Tools** are: ksRepo, GoPredict, PREDICT, RE:fine drugs, RANKS, COGENA, DR.PRODIS, GIFT, NF Finder, PROMISCUOUS, MANTRA, DSigDB.

Drug Data Access

Drug Data Access simply means how to approach for drug to be repurposed. Three sources are under:

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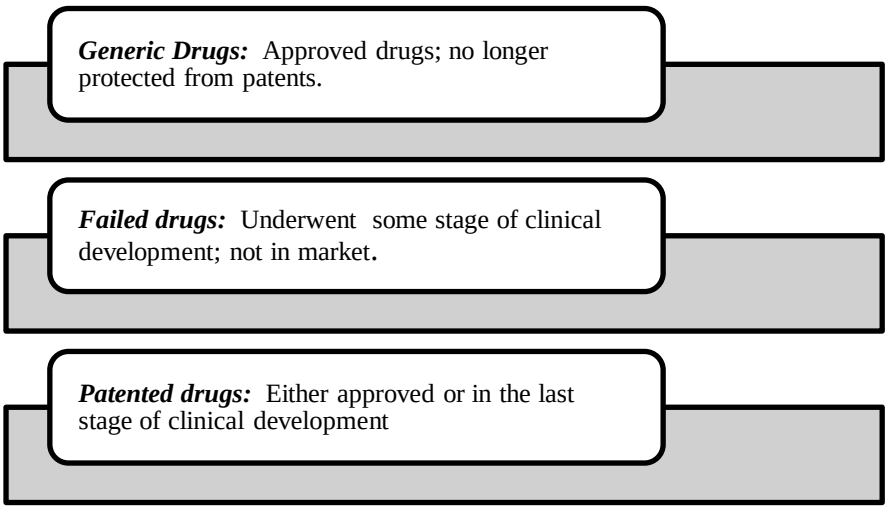

Fig: Drug Data Access

REPURPOSED DRUGS FOR COVID-19

With the emergence of SARS- CoV-2, a novel disease, there is no cure or any specific drug for the treatment of disease. So an economic and efficient strategy is to repurpose the existing drug. It is based on the genomic sequence information and the protein structure modeling. Some of the suggested examples with therapeutic potential of COVID-19 are: [2, 28, 29]

1. Lopinavir and Ritonavir, targeting viral proteases, approved drug combination for HIV infection.
2. Remdesivir, is a nucleotide analogue that may block viral nucleotide synthesis to stop viral replication, used for Ebola.
3. Ribavirin, indicated in hepatitis C, some viral hemorrhagic fever.
4. Arbidol, targeting ACE2/S protein which is an inhibitor that may disrupt the binding of viral envelope protein to host cells and prevent viral entry to the target cell, used as influenza antiviral drug.
5. Chloroquine and hydroxychloroquine are 4–aminoquinoline, which are antimalarial drugs,inhibits infection of cells by SARS CoV-2, the mechanism is not clearly known but changes the pH of endosomes and beleved to pprevent viral entry, transport and post entry events.
6. Azithromycin, a macrolide broad spectrum antibiotic blocks autophagosome clearance in human cells and replication of Zika virus and influenza virus in human cells in vitro.
7. Camostat mesilate is a protease inhibitor , blocks viral maturation and entry to cells, may be effective for SARS CoV-2.
8. Darunavir/ Cobicistat is a protease inhibitors, blocks viral cellular entry. Established drug in the treatment of HIV.
9. Favipiravir, is RNA polymerase inhibitor, act by inhibiting viral RNA dependent polymerase. Used as a broad spectrum anti viral against influenza, arenavirus, bunyavirus and filovirus.
10. Umifenovir is a fusion inhibitor, that inhibits fusion between viral and cellular membrane. It is an antiviral agent against other coronaviruses.
11. SARS CoV-2 specific antibodies are the antibodies that bind to virus and blocks infection.

III. FUTURE PERSPECTIVES OF DRUG REPURPOSING

The Drug repurposing strategy is widely used as an alternative approach to drug development since it lowers the risk of safety and toxicity and at the same time is economical to pharmaceutical R&D. Many drugs have been repositioned and registered for use in alternate indications and many more repurposed drugs are currently at the phase II and III clinical trials. The Drug repositioning approach is thus a simple yet powerful strategy to fuel pharmaceutical research and a novel approach for drug discovery process. As the epidemics and Pandemics situations are present and in the future also, what type of condition will arise, it's not known, so we have to be prepared and by applying smart tools in Research, we can surely cope up with the situation.

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