DRUG RE-PURPOSING: A RAPID RESPONSE MECHANISM TO COMBAT COVID-19 PANDEMIC

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COVID-19, a viral disease caused by the SARS-CoV-2 virus, has affected a large population across the whole world. On 11th March 2020, WHO declared this viral outbreak a pandemic. The affected individuals may show multiple symptoms or may even be asymptomatic. It is a novel and highly contagious disease with no specific treatment available. Since then, the whole world has started working together to develop an effective vaccine to curb the pandemic. In addition, the entire scientific community is trying to develop alternative treatment methods to save lives and reduce disease transmission. Drug re-purposing is one of them which is being employed to manage this present emergency. This article gives a step-wise comparison of drug re-purposing to the traditional drug development process and its benefits. There is a brief description of SARS-CoV-2 with its mechanism of replication and possible drug targets. Some of the important on-going clinical trials for drug re-purposing using different drug targets in the coronavirus replication cycle have been discussed. A global initiative taken by the WHO named 'SOLIDARITY' to rapidly perform multiple clinical trials in collaboration with many different countries has been mentioned. In the end, an attempt has been made to draw attention to the broader perspectives of drug re-purposing, such as ethical issues for emergency use. Some of the ethical considerations regarding reliable data collection, accuracy and integrity of clinical trials, maintenance of randomized evidence, and voluntary consent of the participants need unbiased monitoring.

Keywords: Drug re-purposing, SARS-CoV-2, solidarity.

COVID-19 pandemic spread throughout the world by a novel SARS-CoV-2 virus for which there is no available cure as of now. Countries have started developing the vaccine against this virus, with many of them entering the clinical trials within few months. However, till the vaccine is developed and labelled for its safety and efficacy, the existing therapeutics are the saviours. The whole scientific community—the scientists, medical professionals, and pharmaceuticals from many countries, including India, in collaboration with international labs, have started large-scale pre-clinical and clinical trials to identify potential drug candidates individually or in combination with the existing approved drugs.

Drug Re-purposing or Repositioning is a strategy to use the existing licensed drugs for new therapeutic purposes. It is an approach to reuse the already approved (de-risked) drugs used to treat other similar kinds of infections or diseases, thus reducing the overall time and cost of development (Singh, et al., 2020). The Emergency Use Authorization (EUA), an authority of FDA, US allows the use of unapproved medical products, or unapproved uses of approved medical products, to diagnose, treat, or prevent serious or life-threatening diseases when certain criteria are met in the absence of adequate, approved, and available alternatives during a public health emergency. In India, the Drug Controller General of India (DCGI) has the

authority to approve such drugs amidst an emergency like a pandemic.

Stages in Drug Development—A Comparison between Traditional Process and Re-purposing

The US Food and Drug Administration (FDA) lays down five major steps in the Traditional Drug Development process as described in figure 1.

Step 1: Discovery and Development: Involves Target Discovery, Target Validation (Elimination of wrong targets), Lead Generation, and Refinement to generate candidate molecules.

Step 2: Pre-clinical Research: Conducting *"in vitro"* and *"in vivo"* studies using computational and biological experiments.

Step 3: Clinical Research: Determination of effective dosage, single and multiple dosage studies, combined dosage studies. This stage is further divided into three different phases (Table 1).

Step 4: FDA drug review, approval, and registration

Step 5: FDA post-market drug-safety monitoring.

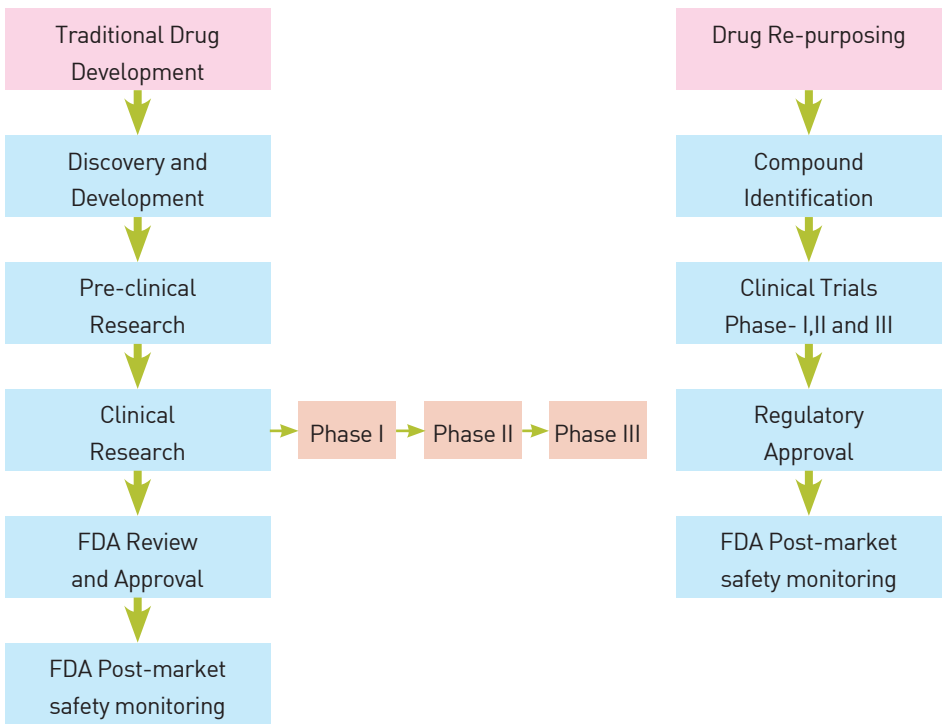

Fig. 1. Different stages in Traditional Drug Development and Drug Re-purposing Processes

Table 1- Phases of Clinical Trials for Drug Development

Phase	Study Participants	No. of Participants	Length of Study	Purpose
I	Healthy volunteers	Less than 100	Several months	Safety and dosage
II	Volunteers with disease	Several hundred	Months to 2 years	Efficacy and side effects
III	Volunteers with disease	Several thousand	1 to 4 years	Efficacy and monitoring of adverse reactions

Thus, it takes a minimum of 7-10 years to develop a new safe and effective drug. Drug re-purposing saves this time and money to address the diseases quickly since the drug is already approved and available for human use. Also, their safety is established, and the side effects profile is known.

Drug Repositioning

Step 1: Identification of a suitable licensed drug candidate. For a microbial infection, we require detailed information about the causative agent such as its phylogeny, morphological characteristics, genome organization, replication cycle, pathogenesis, and any other specific information about that organism.

Step 2: Testing the drug candidate for the proposed treatment using various data-driven and experimental approaches. To accomplish this, multiple batches of experiments are conducted for standardization of formulation, dosage, combination, and delivery of the drug candidate for different test groups. Data is collected and carefully analyzed for its safety, efficacy, and side effects, if any.

Step 3: A standard protocol of testing the drug safety and efficacy for various study groups is developed, modified from time to time as per the need to generate reliable data about the clinical, laboratory, and safety outcomes.

Step 4: The re-purposed drug undergoes various technological and regulatory approvals before commercialization.

Step 5: Once the drug is approved for public use, it is still under FDA post-market surveillance. The purpose being safety monitoring, effectiveness among the varied population, ensuring drug quality control and assurance (Fig.1).

SARS-CoV-2—Causative agent of COVID-19 pandemic

Viruses are primarily classified based on their structure, chemical composition of nucleic acid, and replication site. Morphologically they may have helical symmetry, icosahedral symmetry, or are complex structured. The viral genome is composed of viral nucleic acid, which contains genetic information. The nucleic acid may be DNA or RNA, both single-stranded or double-stranded, linear or circular. The nucleic acid may exist as a

single molecule or be divided into different segments. Viruses can either replicate in the host cytoplasm or enter the host cell nucleus for its multiplication.

Coronavirus belongs to the family of Corona viridae of order Nidovirales (Phadke, et al., 2020). There are four coronaviruses: alpha and beta coronaviruses infect mammals, gamma coronaviruses infect birds, delta coronaviruses infect both birds and mammals. SARS-CoV-2 is a beta coronavirus. It has a large (27–32 kb) positive single-stranded RNA genome, the largest group of RNA viruses. The virus is enveloped with its genome packed inside a helical capsid. The virus has four structural proteins: membrane protein (M), an envelope protein (E), spike protein (S), and nucleocapsid protein (N). The spike (S) protein forms large protrusions on the viral surface, giving it a crown-like appearance and hence, the name corona. S protein has S1 and S2 subunits. S1 subunit has a large receptor-binding domain (RBD) and can combine with host cell receptor ACE2 while S2 forms the stalk of the spike. It is a critical determinant of viral host range and tissue tropism and a major inducer of host immune response. ACE2 enzyme acts as a cellular doorway for SARS-CoV-2 virus. It plays a vital role in the breakdown of Angiotensin I to Angiotensin II. Angiotensin II causes damage to the epithelium by vaso-constriction, inflammation, fibrosis, haemorrhage, and leaky vessels leading to oxidative stress.

The treatment options for drug re-purposing can target the following stages in the coronavirus replication cycle:

1. Attachment

Spike (S) protein binds to the host cellular receptor angiotensin-converting enzyme 2 (ACE2). ACE2 is on the alveolar cell membrane, and itself acts as a receptor for SARS-CoV-2 and allows it to infect cells.

2. Penetration

The host cell protease primes the S protein, which is then recognized by the cellular receptor. The human serine protease TMPRSS2 is responsible for priming the S protein of both SARS-CoV and SARS-CoV-2. This leads to a conformational change in the S protein and facilitates viral envelope fusion with the cell membrane through the endosomal pathway.

3. Uncoating

SARS-CoV-2 releases its RNA into the host cell.

4. Translation and RNA Replication

Coronaviruses have a positive single-stranded RNA genome, which can directly produce proteins and more RNA strands in the host cytoplasm. The virus synthesizes its own RNA-dependent RNA polymerase. Using this enzyme and the positive single-stranded RNA as a template, the negative strand of RNA is synthesized. This negative-strand helps in further replication of new positive-strand RNA. It also serves as a template to transcribe smaller sub-genomic RNA (guide RNA), which is used to synthesize structural proteins and non-structural proteins.

5. Assembly and Release

Viral proteins and RNA genome are subsequently assembled into virions in the ER and Golgi. These are then transported via vesicles to the cell membrane and released out of the cell.

Experimental Treatments by Targetting Different Stages in the Coronavirus Replication Cycle

Presently there are two broad categories of therapies being used. The first one directly targets the viral entry and replication process (Fig. 2). The other approach is to activate the innate and adaptive immune response against these viruses. Drugs designed for modulation of the human immune response, such as preventing cytokine storm, will inhibit the inflammatory responses causing lung injury. In March 2020, the World Health Organisation launched an international clinical trial called 'SOLIDARITY' across the globe to find a drug or drug combination as an effective treatment for COVID-19 (WHO, 2020).The strategy was to compare four experimental therapies against the standard of care to assess their relative effectiveness against COVID-19. Solidarity being a global initiative, aimed to conduct multi-country trials to rapidly identify whether any of the existing drugs or drug combinations slow down the disease progression or reduce the fatality, and also, other drugs to be added based on emerging evidence through laboratory animal, and clinical studies.

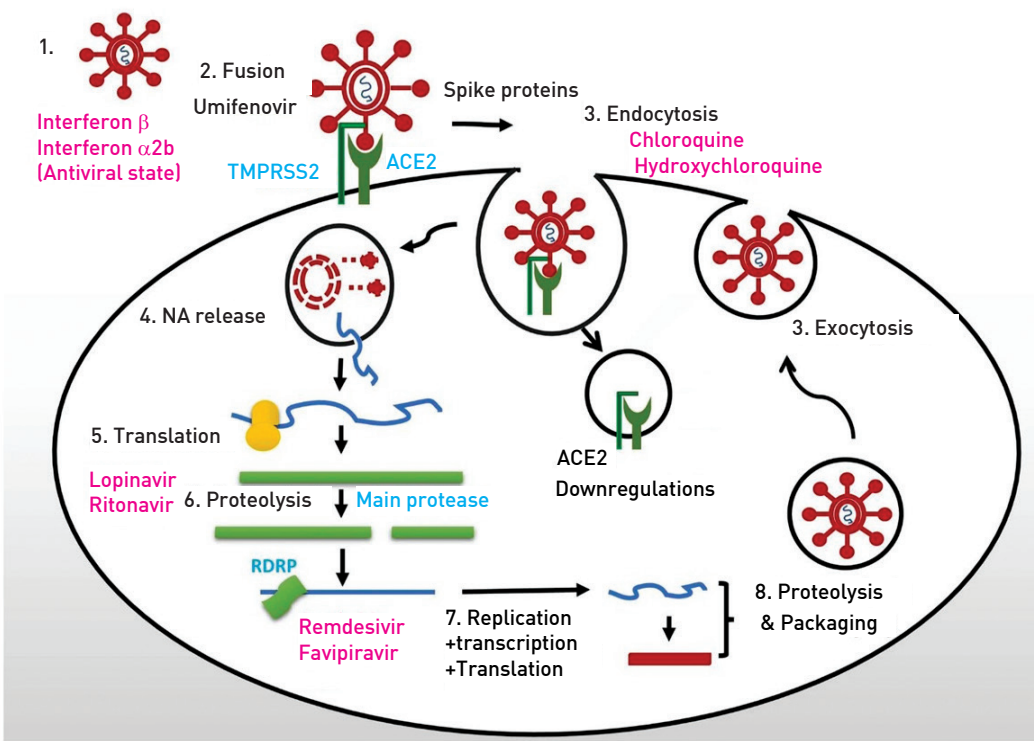

Fig. 2. Therapeutic targets of the currently considered drugs for re-purposing against COVID-19

Some on-going Clinical Trials

Remdesivir

Remdesivir is an antiviral drug originally developed by Gilead Sciences against the Ebola virus. Although it did not show its effectiveness against Ebola in trials but proved safe for humans; thus, it was immediately allowed to enter clinical trial since COVID emergency. Remdesivir is a pro drug with a structural resemblance to adenosine (Tu, et al., 2020). This enables it to incorporate into nascent viral RNA and further inhibit the RNA-dependent RNA polymerase leading to premature termination of the viral RNA chain. The replication of the viral genome is then shut down. In the past, it has also shown good results both in *in vitro* and *in vivo* studies for Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV), thereby making it a favourable drug candidate for trials (Guy, et al., 2020).

Favipiravir

It is a modified pyrazine initially approved for its antiviral activity against the influenza virus. Favipiravir has a structural resemblance to endogenous guanine, by which it competitively inhibits the RNA-dependent RNA polymerase enzyme of the virus (Tu, et al., 2020). This greatly interferes with the viral replication machinery. This drug was discovered by a Japanese chemical manufacturing company called Toyoma Chemical Co. Ltd. Many countries, including India, are conducting clinical trials on its effectiveness against SARS-CoV-2. In June 2020, the Drug Controller General of India approved the emergency use of favipiravir only in patients with mild to moderate COVID-19 infections.

Umifenovir

It is an antiviral drug against influenza viruses and arboviruses. When administered orally, it targets the hemagglutinin (HA), a surface glycoprotein on the influenza virus, and inhibits its fusion with the host cell membrane (Tu, et al., 2020). This prevents endocytosis of the virus into the host cell. Thus, both the viral infection and replication are suppressed. In India, the CSIR-CDRI (Council of Scientific and Industrial Research-Central Drug Research Institute (CDRI) got the approval to carry out Phase- III clinical trials of Umifenovir for COVID-19 treatment.

Chloroquine and Hydroxychloroquine

These are well-known anti-malarial drugs that increase the endosomal pH in the host cell. Endosomes are the cellular compartments that ingest outside material, paving the way for viral entry into the host cell. An increase in pH inhibits membrane fusion between the virus and host cell endosome blocking the viral infection (Tu, et al., 2020).Though these anti-malarial drugs have shown some activity against SARS-CoV-2 in non-randomized cell culture studies, they demonstrated high doses with serious toxicities in clinical trials (Guy, et al., 2020). Lack of larger randomised studies, in sufficient evidence, high dose, and toxicities; the WHO discontinued this arm of Solidarity trial.

Ritonavir/Lopinavir

This drug combination is used for the treatment of HIV infections. Lopinavir specifically inhibits the protease of HIV, which is an enzyme that cleaves a long chain of polypeptides into short peptides during the virus assembly (Tu, et al., 2020). Lopinavir is

susceptible to our proteases; therefore, it is combined with low levels of Ritonavir, another protease inhibitor that increases the stability of Lopinavir. This combination of the antiviral drug is a protease inhibitor of coronaviruses. The combination showed its effectiveness against SARS and MERS in several in vitro, animal, and clinical studies. However, little benefit was observed when clinical trials were performed against SARS-CoV-2 in patients having mild to moderate symptoms. No benefits were observed in patients with severe COVID-19 infections beyond the standard care. Thus, the Solidarity trials for this drug combination were interrupted in July 2020 with immediate effect.

Ethical Considerations while Re-purposing of Drugs

Drug re-purposing has recently become a popular strategy to find the treatment of diseases within a short time frame reducing the preliminary stages of traditional drug development. The entire process is economical and possesses lower risk as compared to a novel drug. Three broad approaches used are—computational, biological experimental, and mixed approaches. A mixed approach which is the combination of the other two is widely used wherein the initial results of the computational approach are validated by biological experimentation and clinical trials. This leads to rapid and effective drug repositioning in times of emergency. Overall, this process proves to be advantageous over the traditional drug development process in terms of time, safety, cost, and labour involved. However, it is important to address some ethical issues that may occur during this process. Compound identification by a virtual or computational screening of drug candidates forms the first step in drug re-purposing. One must analyze the available data regarding its target, mechanism of action, safety, effectiveness, and side effects over a large sample population. The drug candidate must pass through an adequate number of pre clinical and clinical trials for the purposed disease before its approval. Even in case of emergency, the tests must follow proper standard protocols. It is important to carry out multiple tests or studies to understand the drug's kinetics and dynamics in humans. This step should comprise extensive data collection, close monitoring of all the test samples or participants, and complete data analysis. These must be performed carefully to attain accurate and reliable information regarding the test drug candidate's safety, efficacy, and possible side effects. During emergencies, ethical issues such as maintaining proper evidence level and integrity of the clinical research performed need proper attention (Ino, et al., 2020). For the rapid accumulation of ethically and scientifically valid evidence, both quality and quantity of data are of utmost importance. This can be achieved through global collaborations for data and resource sharing.

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