

# Drug Discovery and Development Strategies for COVID-19

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## ABSTRACT

### COVID-19 Special Issue

Coronavirus Disease 2019 (COVID-19) has emerged as a global threat. Scientists and clinicians are endeavoring to find effective drugs and vaccines for this disease. This special issue of the Europasian Journal of Medical Sciences (EJMS) aims to cover the problems, solutions, and challenges of COVID-19 around the world. In this Editorial, EJMS Editors Aarajana Shrestha and Tara Man Kadayat highlight the processes of drug discovery and development and a brief overview of the current drug development strategies against COVID-19.

**Keywords:** COVID-19, Drug Discovery and Development, Drug Repurposing

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## Article Info

**Received:** 1 May 2020; **Accepted:** 10 June 2020; **Published Online:** 10 June 2020

### How to cite this article in Vancouver Style? [8/10]

Shrestha A, Kadayat TM. Drug Discovery and Development Strategies for COVID-19. *Europasian J Med Sci.*2020;2(Covid-19 Special Issue):1-5. <https://doi.org/10.46405/ejms.v2i2.89>

### Disclaimer

Conflict of Interest: None Declared;

Source of Support: Nil

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### Publisher's Note

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## BACKGROUND

World Health Organization (WHO) has declared novel coronavirus disease 2019 (COVID-19) as a pandemic disease. As of June 10, 2020, globally 7,127,753 COVID-19 cases have been confirmed, including 407,159 confirmed deaths.<sup>1</sup>

There is unmet need to develop and produce new drugs and vaccines against COVID-19. Scientists from all over the world are investigating to develop therapeutic prescription drug or preventive vaccine against COVID-19. In a virtual press briefing with

global biopharma top executives, Director General of International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) recently noted that it will take at least 12 to 18 months for a COVID-19 vaccine to be available in the market.<sup>2</sup> Meanwhile several research programs have been initiated for the development of drugs against this global public health crisis. Recently, in the previous issue Sajed and Amgain<sup>3</sup> reported about COVID-19 outbreak and general strategy for prevention. Our objective for this special issue is to broaden the knowledge through original research papers, review articles, or short communication about brief introduction, modes of transmission, safety recommendation, combating strategies for COVID-19, and global status, challenges and efforts for the prevention of COVID-19. In this editorial, we provide a general overview of the processes of drug discovery and development, and a brief overview of the current drug development strategies against COVID-19.

### Overview on Drug Discovery and Development Process

New medicines have saved millions of lives as well as improved the quality of life of human. Pharmaceutical scientists and healthcare workers have great contributions to discover and develop a safe and effective medicine. The drug discovery and development (DDD) process is a complete process to develop a new medicine and bring it to the market. The DDD process is costly, lengthy, risky, challenging and there are hundreds to thousands of people including, molecular biologist, medicinal chemist and clinician to bring some hope to patients.<sup>4</sup> The DDD proceeds from a concept to clinic and takes average 10 years (Figure 1).

The first step of Drug Discovery Process is the appropriate target selection. Target could be a protein (such as enzyme, receptors) in patient's body or protein in microorganism (such as bacteria, virus, parasite) that cause the disease. Then, hit molecules that can interact with the fully validated target are identified using diverse library of potential compounds. From the hit molecule, a promising molecule called lead compound is identified which is tested for pharmacokinetic studies (compound's absorption, distribution, metabolism, excretion and toxicological (ADME/Tox properties) to assess preliminary safety and efficacy of the compound.<sup>5</sup> Then medicinal Chemist plays important role to optimize the lead compound by modifying

compound's structure and physicochemical properties so that the compound could be safer and more effective with reduced adverse effects. The optimized lead compound is considered as the candidate drug and scientists make clear plan and idea for the drug's formulation, dosage form, and large-scale production.

Drug development process includes scientific studies on animals, clinical trials and ultimately regulatory approval.<sup>6,7</sup> In order to ensure safety and efficacy of the drug, preclinical development study in animals is compulsory and very important to reduce the risk of drug's toxicity during clinical development stages. Before initiating clinical development studies, regulatory authority such as US Food and Drug Administration must approve Investigational New Drug (IND) application by reviewing results of the preclinical work and detailed plan for conducting the clinical development studies.

Clinical development process is very expensive and time consuming. It mainly consists of three phases of clinical trials, each of which is focused to evaluate safety and efficacy of the drug. In phase 1 clinical trial the candidate drug is usually tested in 20 to 100 healthy volunteers to determine its safety, pharmacokinetics and safe dosing range. Phase 2 clinical trial is conducted in a group of about 100 to 500 patients with the disease to evaluate efficacy and to determine the side effects, optimal dose, safety, frequency of the drug for improving the condition. Phase 3 clinical trial includes large number of patients (usually 1,000 to 5,000 patients) to monitor and confirm the safety and side effects in diverse group of patients in different part of the world. If the drug passes the phase 3 clinical trial, the new drug is registered for New Drug Application (NDA) by the health authority. The NDA is customized with different regions and countries in the world to meet the requirement of health authorities so that the drug can be sold in different part of the world. Phase 4 Trials (Post-marketing safety monitoring) is continued even after approval to evaluate long long-term safety of the new medicine in different group of patients.

### Strategies for Developing Drugs Against COVID-19

Since the drug development process is long and multistep process, the World Health Organization along with the regulatory authorities such as

US FDA, the Chinese National Medical Product Administration (NMPA), European Medicines Agency (EMA), and drug manufacturers are coordinating pharmaceutical scientists and physicians to speed up COVID-19 drug development.<sup>8</sup> There are two COVID-19 drug development strategies that are focused to overcome this pandemic: 1. Conventional Drug Discovery and Development Strategy, and 2. Drug Repurposing Strategy (Figure 1).

### 1. Conventional Drug Discovery and Development Strategy

Several universities, research institutes and industries are searching for novel drug for the treatment of COVID-19. Although this conventional strategy is lengthy process, it will provide not only valuable information to target various aspects of the viral life cycle and exaggerated host immune response, but also provide knowledge and experience to develop new drugs for implementation if another coronavirus outbreak occurs. The high-throughput screening of diverse compound libraries is ongoing in different research institutes to discover novel drugs that inhibits viral entry and replication. Effort to identify broad spectrum antiviral agents with or without combined antiviral agent is an important strategy to minimize emergence of secondary resistance and to improve efficacy of the COVID-19 therapy.<sup>9</sup> The world-renowned scientists at Scripps Research Institute have joined forces to understand and overcome the novel coronavirus and help in discovery and development of medicines for COVID-19.<sup>10</sup>

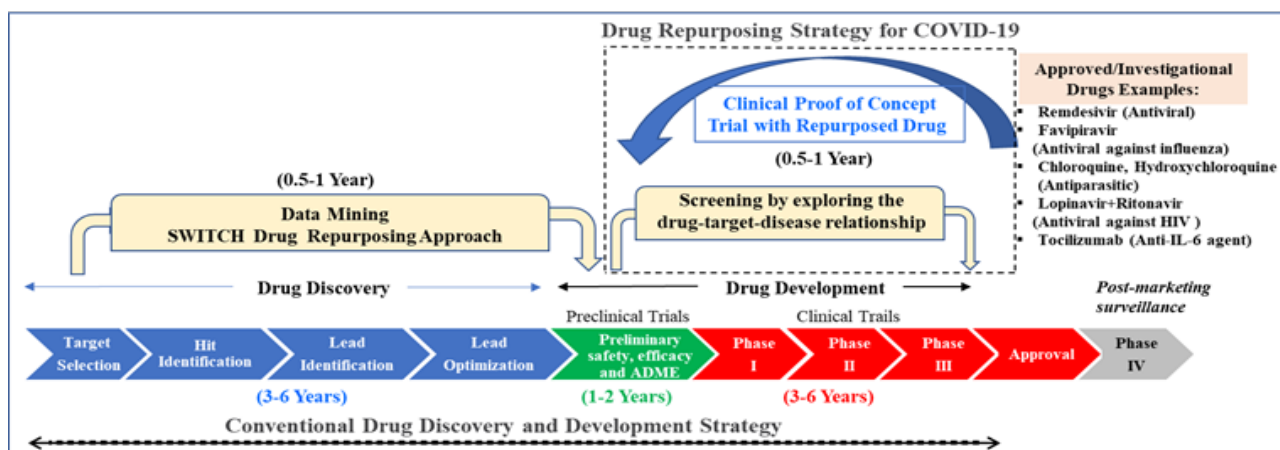
### 2. Drug Repurposing Strategy for COVID-19

Drug repurposing (also known as drug repositioning,

reprofiling or therapeutic switching) is a promising strategy for identifying new and safer drug for a different disease from approved or investigational drugs.<sup>9</sup> To overcome the immediate global COVID-19 challenge, drug repurposing studies are ongoing to develop treatments for COVID-19 from already approved or under investigation drug for another disease or conditions. Since the drug is already tested in humans, safety profile of the drug is well established. The major advantages of developing COVID-19 drugs using drug repurposing strategy are reduced development time, comparatively less amount of investment and less chance of failure due to safety reasons.

It is very important to explore the role and mechanism of action of repurposed drugs for COVID-19 and to get regulatory approval in order to face this immediate global emergency. There are two major approaches for developing therapies for COVID-19. One is directly acting on coronavirus, either by blocking viral entry to human cells, or by inhibiting viral enzyme responsible for the genome responsible. The other approach is to modulate the human immune system by boosting the immune response or by inhibiting the lung inflammation.<sup>11</sup> Based on preclinical and clinical data, several drugs have been repurposed for clinical trials to develop drug against COVID-19. Remdesivir, favipiravir, chloroquine/hydroxychloroquine, lopinavir/ritonavir, and tocilizumab are some of the repurposed drugs selected for clinical development based on their antiviral, immune-modulatory and/or anti-inflammatory actions (Figure 1).

Remdesivir, an antiviral agent, is a repurposed drug that has been recently authorized for emergency



**Figure 1.** Schematic representation of drug development strategies for COVID-19.

use in the USA, Japan and India to treat COVID-19 patients.<sup>12</sup> Remdesivir was originally developed to treat hepatitis C and Ebola virus disease by the American company Gilead Sciences.<sup>13</sup> Another antiviral drug favipiravir developed by the Japanese company Toyama Chemical was used to treat severe influenza virus infection. In March 2020, Favipiravir was approved by the Chinese NMPA as the first COVID-19 drug in China.<sup>11</sup> A generic version of Favipiravir (Avifavir) was also approved by Russian Health Ministry on May 30, 2020 as Russia's first anti-COVID-19 drug.<sup>14</sup> Two well-known antimalarial and anti-autoimmune drugs chloroquine and hydroxychloroquine were labelled as "miracle cure" and US FDA issued an Emergency Use Authorization in the USA to treat COVID-19. Latest study showed that there are no beneficial effects of these drugs in COVID-19 patients, and therefore recently the WHO temporarily stopped enrolling COVID-19 patients for clinical trial. Lopinavir and ritonavir are approved anti-HIV retroviral combination therapy. Based on the beneficial results of preclinical and clinical studies conducted on SARS and MERS, this combination therapy was under clinical trial for COVID-19 patients (ClinicalTrials.gov identifier NCT04252885). However, studies showed little or no benefits of lopinavir/ritonavir therapy for COVID-19.<sup>15</sup> Tocilizumab, a monoclonal antibody that modulates inflammatory pathways through inhibition of human interleukin-6 receptors, was mainly developed for rheumatoid arthritis. The Swiss pharmaceutical company Roche Pharma has initiated clinical trial with Tocilizumab for the treatment of COVID-19 (ClinicalTrials.gov identifier NCT04335041).

In conclusion, the conventional approach for COVID-19 drug development will take long time and therefore may not be considered as the best strategy to overcome this emergency. Several clinical trials using drug repurposing strategy is currently underway as the best option to face this pandemic. Variety of promising drugs seems to allow immediate development of drug against COVID-19 through rapid repurposing of drugs.

### Author's Biography

**Dr. Aarajana Shrestha<sup>1</sup>** obtained her bachelor's degree in Pharmaceutical Sciences with honors from Pokhara University-affiliated Central Institute of Science and Technology (CIST) College Kathmandu in Nepal. She then received her Master's and Ph.D.

degrees in Pharmacy from Yeungnam University College of Pharmacy in South Korea, where she is currently pursuing her postdoctoral research work. In her Ph.D., she designed and synthesized several heterocyclic small molecules for breast cancer and inflammatory bowel disease. She has published over 25 papers in various drug discovery related journals. Her research interests include the synthesis of biologically active molecules for cardiovascular-metabolic diseases and cancer.

**Dr. Tara Man Kadayat<sup>2</sup>** is a registered pharmacist who graduated with honors from Pokhara University, Nepal. From 2009 to 2010, he worked as a pharmacology instructor at Nepalgunj Medical College. He was awarded a Korean Government Scholarship to pursue his graduate studies in Korea. In 2016, he received his Ph.D. in Pharmacy from College of Pharmacy Yeungnam University under the guidance of Professor Eung-Seok Lee. Afterward, he joined the Medicinal Chemistry department of the Daegu-Gyeongbuk Medical Innovation Foundation's (DGMIF) New Drug Development Center. As a principal researcher of a national grant funded by the National Research Foundation of Korea, he is currently focused on discovering novel epigenetic inhibitors for brain cancer.

### Acknowledgement:

We sincerely thank to Dr. Ganesh Bist and Dr. Dipendra Khadka from Khas Health Group for providing technical support and useful feedback for this editorial.

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