Review Article

Promising Therapeutic Targets to halt the Global Pandemic of SARS CoV-2

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Abstract

The global coronavirus pandemic has posed serious challenges to entire world especially to the healthcare community. The widespread distribution of this virus has led to a major public health concern globally. In response to this crisis we have very rare specific tools to control the growing epidemic and treat those who are sick. We rely on quarantine, isolation, and infection-control measures to prevent disease spread and on supportive care for those who become ill. Now the race is to find viable strategies to discover potential candidate drugs to improve the immune system of patients to win the fight against SARS CoV-2, but at present no specific antiviral treatments or vaccines have been confirmed effective. In current situation while the whole mankind is eagerly waiting for a suitable vaccine, drugs presently being used to treat other diseases can be scrutinized as treatment option for COVID-19 pandemic. Although researchers all over the world are working to investigate the key features, pathogenesis and treatment options, it is deemed necessary to focus on existing competitive therapeutic options and cross-resistance of other viral drugs or vaccines. Here we summarized various promising candidates which are currently being used to treat other illnesses but can be a game changer in case of SARS CoV-2 virus to tackle this emergency. This review on recent updates will surely downsize the translational gap between preclinical testing results and clinical outcomes, which is a notable problem in the rapid development of an effective treatment options to fight this global crises.

Key Words: Coronavirus; SARS-CoV-2; COVID-19; Drug repurposing; Vaccine

Introduction

Research team around the world are working on potential treatments and vaccines for the new coronavirus disease known as COVID-19. Various efforts for the development of suitable vaccines are underway, but according to WHO, it is estimated that potential vaccine for COVID-19 will take about 18 months to be available. Even so a suitable vaccine is likely to take more than a year prior it can used to tackle the outbreak because there is not a single magic bullet, but it demands various drugs in our ordnance depot and we will be needed to be used in amalgamation with others. So there is an urgent need to move quickly to point out the existing drugs that are effectual in clinical trials so that we can start medicating patients as rapidly as possible to tackle this global pandemic. Moreover the drugs that can be evaluated and perceive about the targets, the more likely we are to acquire something which is worthwhile. According to Rismanbaf 2020, in inclusion to the drugs currently advised to treat COVID-19, repurposing of existing medicines can also be cast off due to their consequences reported in clinical studies [1]. Lei *et al*. reported that the medicament of 51 COVID-19 patients with traditional Chinese medicine, interferon, Lopinavir, Ritonavir and short-term (3 to 5 days) corticosteroids was fortunate and resulted in betterment and discharge of 50 patients as well [2]. According to rheumatologically point of view, except for respiratory failure, the critical COVID-19 patients have common features like -1) sudden deterioration of disease around one to two weeks after onset; 2) much lower level of lymphocytes, especially natural killer (NK) cells in peripheral blood; 3) extremely high inflammatory parameters, including C reactive protein (CRP) and pro-inflammatory cytokines (IL-6, TNFα, IL-8, et al); 4) destroyed immune system revealed by atrophy of spleen and lymph nodes, along with reduced lymphocytes in lymphoid organs; 5) the majority of infiltrated immune cells in lung lesion are monocytes and macrophages, but minimal lymphocytes infiltration; 6) mimicry of vasculitis, hypercoagulability and multiple organs damage [3], Based on the above characteristics of COVID-19, in this review we compiled the possible drug targets against this emergency. Various targets for direct-acting antivirals are being look over to manage this viral infections [4, 5]. According to Agostini *et al*. One grade of antiviral compounds, nucleoside analogues, imitates naturally occurring nucleosides to obstruct viral replication [6]. While these compounds have been victorious therapeutics for diverse viral infections, mutagenic nucleoside analogues, such as ribavirin and 5-fluorouracil, have been ineffective in combating SARS CoV-2. Wang *et al*. revealed that remdesivir in combination with chloroquine which is a cheap and safe drug are highly effective in the control of coronavirus infection in vitro [7]. Chloroquine is extensively assigned in the whole body, together with lung, following oral administration. The EC_{90} value of chloroquine against SARS CoV-2 in Vero E6 cells was 6.90 μM, which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration; therefore, it is much clinically applicable against the global epidemic. His report also suggested that EC_{90} value of remdesivir against COVID-19 in Vero E6 cells was 1.76 μM, suggesting its working concentration is likely to be achieved in NHP so it might be a successful candidate to inhibit viral infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to SARS CoV-2 viral infection. The drug which is very effective

against zika as well ebola virus -Azithromycin (a macrolide antibacterial) and hydroxychloroquine combination were also reported to treat COVID-19 patients [8]. These molecules may decrease the inflammatory responses and production of excessive cytokine accompanying viral infections. The immunomodulatory mechanisms may be due to decreasing chemotaxis of neutrophils to lungs by inhibiting cytokines and formation of reactive oxygen species. According to Wu *et al*. 2020, the above described drugs and therapeutic agents include antiviral agents like oseltamivir and supporting agents like Ascorbic acid, Azithromycin, Corticosteroids, Nitric oxide, IL-6 antagonists etc might play a vital role in prevention and control of COVID-19 patients until the approval of vaccines and specific drugs targeting SARS-CoV-2 [9]. Apart from this several Ayurveda medicines are also included in the list of possible drugs to combat this epidemic such as Shadanga Paniya, Agastya Harityaki and Samshamani Vati [10]. These drugs were also recommended by Ministry of Ayush, Shadanga Paniya is a herbal formulation that mainly comprises *Cyperus rotundus*, *Fumaria indica*, *Vetiveria zizanioides*, *Pterocarpus santalinus*, *Pavonia odorata*, and *Zingiber officinale*. This herbal combination is mainly recommended for the treatment of symptoms such as high fever, shivering, muscle aches, headache, loss of appetite, dehydration, fatigue, restlessness, excessive thirst, irritability, and burning sensation. Agastya Harityaki is a potent polyherbal Ayurverdic medicine mainly advised for respiratory problems such as asthma, pneumonia, and chronic bronchitis. The medicine is reported to have antiviral, antibacterial, antifungal, antioxidant, anticarcinogenic, antiaging, antidiabetic, antiulcer, cardioprotective, hepatoprotective, and wound healing properties. Samshamani Vati have tremendous role in the treatment of acute to chronic fever and anemia (500 mg twice a day). *Tinospora cordifolia* is the main ingredient and responsible for anti-inflammatory and antipyretic properties of Samshamani Vati. Including this Pratimarsha Nasya (Anu taila/sesame oil) has immune booster as well as curative aspect for the challange of Nasobronchial diseases and enhances the respiratory immunity. The compositions present in sesame oil are well known for anti-inflammatory, antipyretic, and antibacterial proprieties. Another potential agents which comprises Trikatu (Pippali, Marich, and Shunthi) and Tulasi is also given green flag by the Ministry of Ayush for the prevention and control of coronavirus infection in India [10]. Khalili *et al* reported that several antiviral drugs like ribavirin may have potential role in confronting the challenge of the outbreak of SARS CoV-2. Ribavirin, that has an existing inventory and reliable supply chain may be a priority recommendation for therapies developed for the COVID-19 pandemic [11].

In this emergency our country also have plenty of options for repurposing most effective drugs along with antibiotics to treat COVID-19 and our health workers desperately need these information (as summarized in table 1) to limit the current mortality rate. This repurposed strategy might be the basic reason for moderate death ratio in India (0.04 deaths/ 1milion people) as compared to other countries like US & Italy (178 deaths/ 1milion people).

Table 1: Possible candidates for covid-19

Serial no	Drug/Compounds	Originally Stand for	Mode of Action	Effect on Coronavirus	Reference
1.	Remdesivir	Ebola and related Viruses.	Inhibits viral RNA polymerases.	It can inhibit the coronaviruses that cause SARS and MERS.	Grein *et al.* 2020 & Jiang *et al.* 2019 [12&13]
2.	Anakinra	Rheumatoid arthritis	IL-1 pathway blocking peptide.	Anti-inflammatory action might be use for current outbreak.	Faccenda 2020 [14]
3.	Baricitinib	Rheumatoid arthritis	JAK1/2 inhibitor & inhibition of AAK1 which is an important regulator of clathrin-mediated endocytosis.	It inhibit viral invasion and inflammation.	Jiang *et al.* 2019 [13]
4.	Ruxolitinib	Myelofibrosis or polycythemia vera	Anti-inflammatory JAK1/2/TYK2 inhibitor.	Under clinical evaluation for Covid-19.	Faccenda 2020 [14].
5.	Tocilizumab / Actemra	Rheumatoid arthritis (RA) / Juvenile Idiopathic Arthritis (PJIA) or Systemic Juvenile Idiopathic Arthritis (SJIA)	Anti- inflammatry Approved immunosuppressive anti-IL-6 receptor mAb.	Phase 2 trial of COVID-19 is underway in Italy.	Abd El *et al.* 2020 & Faccenda 2020 [15, 14]
6.	Darunavir	HIV	Anti-retroviral HIV-1 protease inhibitor.	Inhibited SARS-CoV-2 replication & under phase 3 trial for COVID-19.	Abd El *et al.* 2020 [15]
7.	Imatinib	Cancer	Inhibits the fusion of virions with the endosomal membrane.	It Could be a viable strategy against COVID-19. Likely to be most effective during the early stage of infection.	Dong *et al.* 2020 [16]

8.	Ivermectin	Parasite infestations.	Binds with high affinity to glutamate-gated chloride channels & block neurotransmitters.	Inhibit SARS-CoV-2 replication.	Abd El *et al*. 2020 [15]
9.	Favipiravir	Against RNA viruses	Viral RNA polymerase inhibitor & nucleoside analogue.	It can be used for prevention and treatment of COVID-19. Two clinical studies are registered on ClinicalTrials.gov.	Dong *et al.* 2020 [16]
10.	Arbidol/Umifenovir	Influenza infection	Inhibit viral entry/stimulate immune response.	Under clinical trial.	Haviernik *et al*. 2018 [17]
11.	Hydroxychloroquine	An existing antimalarial drug	Anti-inflammatory and antiviral.	In vitro activity against SARS-CoV2.	Geleris *et al.* 2020 [18]
12.	Chloroquine	Antimalarial drug	Anti-inflammatory and antiviral.	Inhibit SARS Cov-2 replication.	Touret *et al.* 2020 [19]
13.	Renin–angiotensin–aldosterone system (RAAS)	Hypertension, improving diabetic nephropathy and other forms of chronic kidney disease.	ACE inhibitors and angiotensin-receptor blockers.	Under clinical evaluation for Covid-19.	Vaduganathan *et al*. 2020 [20]
14.	LPV/RTV-IFN-β	Multiple sclerosis	Key modulator of immune defence against viruses.	Anti-viral immune response to SARS-CoV-2 & 50% reduction in viral replication.	Sheahan *et al*. 2020 [21]
15.	Zanamivir, Indinavir, Saquinavir	HIV	$3CL^{PRO}$ main proteinase inhibitors.	Inhibit SARS COV-2 replication.	Hall *et al.* 2020 [22]
16.	Carfilzomib	Multiple myeloma	Proteasome inhibitors.	Under clinical investigation against COVID-19.	Al Saleh *et al*. 2020 [23]
17.	Atazanavir	Treatment of HIV	Protease inhibitors.	Decrease the risk of spreading	Dong *et al.* 2020 [16]

		infection		virus in the blood.	
18.	Apilimod	Treatment of autoimmune conditions.	Inhibitor of the type III phosphoinostol kinase.	Anti-SARS-CoV-2 activity in vitro.	Faccenda. 2020 [14]
19.	ASC09F	HIV	Viral protease inhibitor.	Being repurposed for COVID-19.	Lythgoe *et al.* 2020 [24]
20.	Brensocatib	Treatment of chronic obstructive pulmonary disease (COPD).	Inhibits activation of neutrophil elastase via direct inhibition of dipeptidyl peptidase 1, that is being investigated as a treatment for neutrophilic lung inflammation.	Clinical trial.	Faccenda 2020 [14]
21.	β-D-N4-hydroxycytidine	Several viral infections	Broad-spectrum ribonucleoside analogue.	Exhibits broad spectrum antiviral activity against SARS-CoV-2, MERS-CoV, SARS-CoV, and related zoonotic group 2b or 2c Bat-CoVs.	Agostini *et al*. 2019 [6]
22.	Bevacizumab	Anti-cancer	Approved anti-VEGFA mAb.	Reduce pulmonary edema in patients with severe/critical COVID-19.	Faccenda 2020 [14]
23.	Thalidomide	To treat various cancer	Immunosuppressive action of thalidomide with the anti-inflammatory actions of glucocorticoids and COX inhibition.	Being evaluated for clinical efficacy in patients with severe COVID-19.	Rismanbaf 2020 [1]
24.	Sirolimus	Autoimmune conditions	Immunosuppressive drug.	Inhibits MERS-CoV infection of	Zhou *et al*. 2020 [25]

				human liver cells in vitro; may be applicable to SARS-CoV-2 infection.	
25.	Ruxolitinib	Myelofibrosis	Anti-inflammatory JAK1/2/TYK2 inhibitor.	Under clinical evaluation for Covid-19	Zhang *et al.* 2020 [3]
26.	Sarilumab	To treat severely active rheumatoid arthritis (RA)	Immunosuppressive anti-IL-6 receptor mAb.	Under clinical trial.	Lu *et al.* 2020 [26]
27.	Relacatib	To treat bone disease	Cathepsin K inhibitor.	Potential to block SARS-Cov-2 entry into host cells.	Faccenda 2020 [14]
28.	REGN3051 and REGN3048	MERS-CoV	Target the spike protein of MERS-CoV	Phase 1 anti-coronavirus clinical trial.	Faccenda 2020 [14]
29.	Galidesivir	Several viral infections	Viral RNA-dependent RNA polymerase inhibitor.	Under clinical investigation.	Elfiky 2020 [27]
30.	Fingolimod	Multiple sclerosis	Immunomodulators / S1P1 receptor inhibitor.	Clinical trial.	Barzegar *et al.* 2020 [28]
31.	lopinavir–ritonavir	HIV infection	Direct inhibitor of viral replication (anti 3CL protease)	Suppress viral replication.	Baden *et al.* 2020 [29]
32.	Teicoplanin	Antibiotic	Inhibits low pH cleavage of microbial protein by cathepsin L in the late endosomes.	Resist the genomic viral RNA release & inhibit viral replication.	Pawar 2020 [8]
33.	Nitazoxanide and ivermectin	parasitic infections	Selectively blocks the viral hemagglutinin intracellular trafficking and insertion of this protein into the host plasma membrane.	Effective in treating a wide range of viruses including human coronaviruses in vitro at very low concentrations.	Şimşek *et al.* 2020 & Pawar 2020 [30, 8]

Other Possible Drugs- Apart from the above mentioned repurpose drugs there are other drugs which gained less access against coronavirus outbreak but may be a possible game changer if applicable for investigation. These includes various antiviral such as tipranavir, fosamprenavir, enzaplatovir, presatovir, abacavir, bortezomib, elvitegravir, maribavir, raltegravir, montelukast, deoxyrhapontin, polydatin, chalcone, disulfiram, carmofur, shikonin, ebselen, tideglusib, PX12, TDZD-8, cyclosporin A, and cinanserin as reported by joint research team of the Shanghai Institute of Materia Medica and Shanghai Tech University. The team also claimed several herbal medicines such as Rhizoma Polygoni Cuspidati and Radix Sophorae Tonkinensis to be effective against SARS-COV-2 [16]. In addition to this Pawar 2020 also demonstrated that other glycopeptide antibiotics like Oritavancin, Dalbavancin, Bafilomycin A1, Ascorbic acid (Vitamin C) and Telavancin may be exploited against SARS-CoV, Ebola virus and MERS-CoV transcription and replication-competent virus-like particles [8].

Vaccines Targets- The coronavirus emergency may be an inevitable fact of mankind, but there are many strategies available which help to protect ourselves from infection and to treat the disease when it has been developed. At present clinical management includes infection prevention, control measures and supportive care including supplementary oxygen and mechanical ventilation when indicated. The FDA has approved the using of blood plasma from patients who have recovered from COVID-19 with a high neutralizing antibody titer and they may be a valuable donor source of convalescent plasma (CP) (chen *et al.* 2020) [31, 32]. While many countries across the world are working toward a vaccine against SARS-CoV-2, with much successful clinical trial. According to Praveen Duddu's article (titled- Coronavirus treatment: Vaccines/drugs in the pipeline for COVID-19) various vaccines are under ways and passed many significant trial to counter this epidemic. Here we also cumulated the current status of vaccine development which shed a positive hope to overcome from this standstill situation of mankind and for which the whole life is eagerly waiting.

Table 2: Current status of vaccine development

Serial no.	Name	Type of vaccine	Mechanism	Function	Stage	Organisation
1.	Fusogenix	DNA vaccine	An optimised payload containing multiple protein epitopes derived from SARS-COV-2 proteins.	It stimulates an immune response in the body to prevent COVID-19 infection.	Clinical investigation.	Entos pharmaceticals.
2.	Gimsilumab	Human monoclonal antibody	The drug targets granulocyte-macrophage colony stimulating factor (GM-CSF), which is a pro-inflammatory cytokine found in high levels in the serum of COVID-19 patients.	Targeting GM-CSF is expected to reduce lung damage and reduce mortality rate in COVID-19 patients.	Clinical-stage.	Roivant Sciences
3.	TZLS-501	Monoclonal antibody	Human anti-interleukin-6 receptor (IL-6R), which helps in preventing lung damage and elevated levels of IL-6.	The drug works by binding to IL-6R and depleting the amount of IL-6 circulating in the body thereby reducing chronic lung inflammation.	Preclinical	Tiziana Life Sciences
4.	TNX-1800	Modified horsepox virus	Immunomodulator.	To express a protein derived from the virus that causes the coronavirus infection.		Tonix Pharmaceuticals has partnered with Southern Research
5.	Brilacidin	Defensin mimetic drug	Immunomodulator	Shown antibacterial, anti-inflammatory and	Clinical trials.	Innovation Pharmaceuticals

				immunomodulatory properties.		
6.	Recombinant subunit vaccine	Subunit vaccine	Immunomodulator	Trimeric S protein (S-Trimer) of the COVID-19 coronavirus, which is responsible for binding with the host cell and causing a viral infection.	Pre-clinical studies.	Clover Biopharmaceuticals
7.	VAAST	Recombinant vaccine	Immunomodulator	Mucosal and systemic immune responses.	Pre-clinical models.	Vaxart
8.	leronlimab (PRO 140)	CCR5 antagonist	Immunomodulator	Treatment for HIV	Phase two clinical trials	CytoDyn
9.	Linear DNA vaccine	DNA vaccine	Immunomodulator.	Based on the entire spike gene of the coronavirus, while the remaining is designed based on the antigenic portions of the protein.	Under investigation.	Applied DNA Sciences' subsidiary LineaRx and Takis Biotech
10.	BX-25	Drug	Oxygen supplement	The drug can help in supplying oxygen to the vital organs and enable the patient to recover and survive.	Under clinical investigation.	BIOXYTRAN
11.	BPI-002	Drug	Immune booster	Activate CD4+ helper T cells and CD8+ cytotoxic T cells and generating an immune response in the body.	Filed US patent.	Beyond Spring

12.	NP-120 (Ifenprodil)	Drug	Ifenprodil is an N-methyl-d-aspartate (NDMA) receptor glutamate receptor antagonist sold under the brand name Cerocal.	It has demonstrated efficacy in improving survivability in mice infected with H5N1.	Preclinical.	Algernon Pharmaceuticals
13.	AT-100	Human recombinant protein	Reducing inflammation and infection in the lungs.	It generates an immune response against various respiratory diseases.	Preclinical studies.	Airway Therapeutics
14.	AdCOVID Altimmune	COVID Vaccine	Immune booster	It generates an immune response against SARS CoV-2 & various respiratory diseases.	Preclinical animal studies and phase one clinical trial in the third quarter of 2020.	University of Alabama at Birmingham (UAB)
15.	TJM2	Neutralising antibody	Targets the human granulocyte-macrophage colony-stimulating factor (GM-CSF), which is responsible for acute and chronic inflammation.	It generates an immune response against various respiratory diseases.	Pre-clinical studies	I-Mab Biopharma
16.	INO-4800	Target vaccine	Immune booster	--	Human clinical trials.	Novio Pharmaceuticals has collaborated with Beijing Advaccine Biotechnology
17.	APN01	Protein vaccine	Immune booster	Target ACE2 protein the main receptor for the SARS	Phase one pilot trial	University of British Columbia & APEIRON

				virus.		Biologics
18.	Mrna-1273	Protein vaccine	Immune booster	Targets the Spike (S) protein of the coronavirus.	Phase one human clinical trial.	Moderna and the Vaccine Research Center,
19.	Infectious Bronchitis Virus (IBV)	Target vaccine	Immune booster	-----	Pre-clinical trials.	MIGAL Research Institute in Israel
20.	Virus-Like Particles (VLP) of the coronavirus	Antibodies against SARS CoV-2	Immune booster	-----	Preclinical studies.	Medicago in collaboration with Laval University's Infectious Disease Research Centre to develop antibodies against SARS-CoV-2.
21.	OYA1	Target vaccine	Immune booster	Inhibits SARS-CoV-2 from replicating.	Preclinical studies.	---

Discussion

China and rest of the world have faced an outbreak of a novel Corona virus which became a global pandemic with high morbidity and mortality rate. Researchers around the world pushing forward with several attempts to manufacture suitable vaccines and treatments to decelerate the emergency situation and lessen the disease's damage. An effective and scalable vaccine is likely to take over a year before it can used to tackle the global pandemic. While waiting for suitable vaccine or drugs Repurposing the already existed drugs may create a possible hope to combat COVID-19 emergency. In this emergency situation we need to move quickly to identify existing drugs that are effective in clinical trials so that the world can begin treating patients as rapidly as possible .In this study, we presented a recent updates on all putative repurposable drugs for effective clinical trials and current status of related vaccines stages for potential treatment of 2019-nCoV/SARS-CoV-2. The mysterious coronavirus outbreak comes with a usual symptom of pneumonia and acute respiratory distress syndrome; we have several ways or potential drugs to treat these symptoms with promising approaches to reduce the effect. These promising candidates are summarized above (Table 1) which are currently being used to treat other illnesses but can be investigated as treatments for COVID-19 to halt the emergency situation. The pandemic has rally the development of novel coronavirus vaccines across the world in this report we summarized the current updates of the coronavirus vaccines in various stages of development, across the world (Table-2). Possible target of these drugs were also described in the figure-1. Even after a new vaccine candidate has been shown to offer immunity against the coronavirus in humans, it needs to be tested in larger numbers of people to ensure it is safe to use. Manufacturing and distributing a vaccine at the scale needed to tackle this pandemic will also present significant challenges. This study will surely downsize the translational gap between preclinical testing results and clinical outcomes, which is a notable problem in the rapid development of an effective treatment options to fight this global crises. From a translational perspective, if broadly applied, the above updates will helpful in speed up the potential vaccine development which hopefully provides a greater degree of protection, not just against the COVID-19 virus, but also against the next viral threat. Likewise, it is mandatory to follow the WHO guidelines to limit the spread of COVID-19 until applicable drugs and vaccines have been developed.

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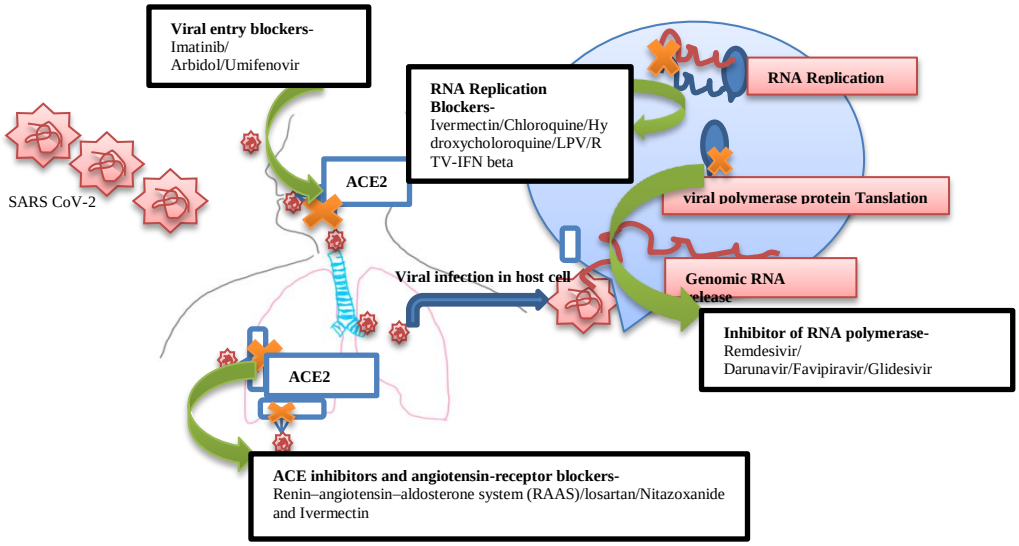

Figure1: Possible targets of repurposing drugs to tackle SARSCoV-2 infection at different viral life cycle.

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