Potential targets and plausible drugs of Coronavirus infection caused by 2019-nCoV

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Abstract

The world is confronting a dire situation due to the recent pandemic of the novel coronavirus disease (2019-nCoV) with so far mortality cases of 100,000 all over the world. Currently, there are no effective enough treatment options for this previously unknown virus. The current drugs in pipline and some plausible drug are overviewed in this paper. The potential molecular targets of each steps of the 2019-nCoV drug life cycle is discussed and highlights here. Although different types of anti-viral targets are applicable for 2019-nCoV drug screenings, the more promising targets can be considered as protease and RNA polymerase. Based on the results from antiviral agents repurposing and clinical studies, the remdesivir could be an encouraging drug in the frontline to be administrated for 2019-nCoV. Much progress in understanding the 2019-nCoV the molecular details of its life cycle followed by the identification of therapeutic targets seems to be an efficient approach in discovering potential drugs.

Hypothetical targets and plausible drugs of Coronavirus infection caused by 2019-nCoV

Running Title: Drugs targets of 2019 novel coronavirus

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Summary

The world is confronting a dire situation due to the recent pandemic of the novel coronavirus disease (2019-nCoV) with the mortality rate passed over 150,000. Attaining efficient drugs evolve in parallel to the understanding of the 2019-nCoV pathogenesis. The current drugs in the pipeline and some plausible drugs are overviewed in this paper. Although different types of antiviral targets are applicable for 2019-nCoV drug screenings, the more promising targets can be considered as 3cl protease and RNA polymerase. The remdesivir could be considered the closest bifunctional drug to be provisional clinical administration for 2019-nCoV. The known molecular targets of the 2019-nCoV include fourteen targets while four molecules of ACE2, cathepsin L, 3cL protease and RdRp are suggessted as more promising potential targets. Accordingly, dual acting drugs as an encouraging solution in drug discovery is suggested. Emphasizing on the potential route of 2019-nCov infection and virus entry related factors like Integrins, cathepsin and ACE2 seems valuable. The potential molecular targets of each step of the 2019-nCoV life cycle are discussed and highlighted in this paper. Much progress in understanding the 2019-nCoV the molecular details of its life cycle followed by the

identification of new therapeutic targets needed to lead us to an efficient approach in anti-2019-nCoV drug discovery.

Keywords: Antivirals, Drug repurposing, Molecular targets, Novel coronavirus, 2019-nCoV, Proteases

1 Introduction

1.1 Life cycle of the Coronavirus

Coronaviruses (CoVs) are zoonotic, spherical (diameters of approximately 60-140 nm), positive-sense enveloped RNA viruses, belonging to the*Coronaviridae* family, including four genera of*Alphacoronavirus* , *Betacoronavirus* ,*Deltacoronavirus* , and *Gammacoronavirus* (Cascella et al., 2020; Li et al., 2019).

The *betacoronavirus* genome including 2019-nCoV comprises of the 5'-untranslated region (5'-UTR), 3'-untranslated region (3'-UTR), open reading frame (ORF) 1a/b, structural proteins and accessory proteins. Sixteen non-structural proteins (nsp 1-16) are encoded through proteolytic processing (3CL and PL proteases) of the replicase polyproteins (pp1a and pp1ab) encoded by the ORF1a/b. Nsps progress the formation of the replication-transcription complex and indirect escape from the host immune system (Chan et al., 2020).

The ~30,000 Nucleotide viral genome also, express four main structural proteins of spike (S), membrane (M), envelope (E), and nucleocapsid (N) encoded from the 3' end of the viral genome (Figure 1). The attachment of 2019-nCoV via the interaction of its S protein with angiotensin converting enzyme receptor on the host cell is the primary step in its life cycle and followed by proteolytic cleavage of S protein, the virus enters the cytosol. The second step is the expression of replicase proteins. Following replication and RNA synthesis (Third step) and assembly (last step), virions are released from the cell surface by exocytosis (Figure 2) (Fehr and Perlman, 2015).

2. Current plausible drugs of 2019-nCoV

2.1 Potential drug compounds

There are three lines of drug discovery approach to develop the novel drug for 2019-nCoV. These three approaches leading to the potential treatment options include drug repurposing, screening molecular databases using drug design tools and screening compound libraries in antiviral assays. By the time required to randomly screen the natural or chemical compound libraries, the third option is not compatible with the rapid rate of 2019-nCoV transmission in the community. Therefore, drug repurposing and computational docking analysis are the two main current approaches to find potential drugs for the treatment of 2019-nCoV.

The efficiency of seven antiviral drugs (ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine (CQ) remdesivir (RDV, GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV are so far evaluated in the wet lab. These drugs have previously exhibited broad-spectrum antiviral activity against a diverse panel of RNA viruses such as SARS-CoV, MERS-CoV and Ebola virus (EBOV) (García-Serradilla et al., 2019). The recently investigated potential anti-2019-nCoV described in repurposing programs are summarized in Table 1. The cell culture investigations showed that the compounds chloroquine (CQ) and remdesivir (RDV) potently blocked virus infection at low-micromolar concentration with a high selectivity index (SI) (Wang et al., 2020).

2.2 Potential drug candidates in clinical trials

Remdesivir (GS-5734) is an adenosine analogue that has completed the phase III clinical trial for the treatment of Ebola virus infection. The antiviral drug remdesivir (GS-5734) is entered to the phase III clinical trials in Asian countries to assess the use of antiviral drug candidate for the potential treatment of coronavirus by Gilead Sciences. All reported potential drug candidates in clinical trials and their status are presented in Table 2. Moreover, multiple parallel attempts are in progress to develop 2019-nCoV vaccine. Currently 18 vaccine candidates are in preclinical phases and five candidates are in clinical phases (Table 3).

3. Molecular targets of 2019-nCoV drug discovery

3.1 Host attachment and entry

3.1.1 Modification of host cell serine protease

Despite the possibility of surface alteration of RNA viruses, blocking the viral receptor protein on the host cell surface, thereby inhibiting the virus entry, can be a proper option in the drug discovery process. Transmembrane Serine Protease 2 (TMPRSS2) that mediate the entry by distinct mechanisms. One is cleavage and activation of the spike glycoproteins of coronaviruses (like HCoV-229E and HCoV-EMC) which facilitates the virus-cell membrane entry. Conformational flexibility of S protein which is needed for fusion is facilitated by proteolytic cleavages (Bosch et al., 2003) which is catalyzed by TMPRSS2 as the most relevant cellular proteases in this process. Another mechanism is the proteolytic cleavage of angiotensin-converting enzyme 2 (ACE2), which might activate the coronavirus spike glycoprotein for cathepsin L-independent host cell entry.

3.1.2 Angiotensin-converting enzyme 2 (ACE2)

Angiotensin converting enzyme 2 (ACE2) is a type I membrane zinc metalloprotease mainly expressed in lung alveolar epithelial cells, enterocytes of the small intestine and arterial cells. ACE2 is able to hydrolyze angiotensin I to produce angiotensin (1–9) (Donoghue et al., 2000). The enzyme was known for its function as the virus receptor of SARS-CoV (Kuba et al., 2005) which was proved as the cellular receptor of 2019-nCov by Zhou et al (Zhou et al., 2020). Blocking the entrance of 2019-nCoV through this protein intervention seems to be a possible target for antiviral drug discovery.

3.1.3 Integrins

Recently, Sigrist et al suggested that 2019-nCoV may also use integrins as cell receptors in host cells, binding to them through a conserved RGD (403–405: Arg-Gly-Asp) motif in receptor-binding domain of S protein that is absent from other coronaviruses (Sigrist et al., 2020). The conformational changes due to ACE2 binding expose the RGD containing region. Different viruses like Ebola virus (Schornberg et al., 2009), human papillomavirus (Yoon et al., 2001), HIV-1 (Monini et al., 2012) and EBV (Tugizov et al., 2003) use integrins for cell attachment or entry. The antibody natalizumab ($\alpha4\beta1/\beta7$ integrin antagonist) for the treatment of multiple sclerosis/Crohn's disease and the small molecule tirofiban ($\alpha IIb\beta3$ inhibitor) for the treatment of acute coronary syndrome are the known inhibitors of integrin (Ley et al., 2016). These studies confirm that inhibiting the integrin scan impede some coronaviruses from entering the host cells is considered as a prolific target for antiviral drug discovery.

3.1.4 Host tyrosine kinase receptor

Receptor tyrosine kinases (RTKs) are a group of growth factor receptors that are autophosphorylated after ligand binding (Lemmon and Schlessinger, 2010). Dong et al introduced an RTK inhibitor named (A9) as a robust inhibitor of transmissible gastroenteritis virus (TGEV) infection belong to Alphacoronavirus genera as a surrogate model for CoV in cell-based assays (Dong et al., 2020). The specific RTK inhibitors (RTKIs), known as AG879 and tyrphostin A9 (A9), are also reported as strong antiviral activity against the influenza A virus (Kumar et al., 2011). It was shown that blocking the receptor kinase activity by approved inhibitors broadly impair infection by all major HCV genotypes and viral escape variants in cell culture and in a human liver chimeric mouse model (Jilg and Chung, 2012). The tyrosine kinase inhibitor such as genistein can block the replication of HIV-1, herpes simplex virus type 1 (HSV-1) and Arenavirus (Vela et al., 2008). These findings suggest a potentially promising host-centered approach like RTKs to treat the 2019-nCoV.

3.1.5 Viral spike protein

The trimeric S glycoprotein responsible for the coronaviruses crown-like appearance, mediates attachment to the host receptor (Ou et al., 2020). Despite spike protein sequence similarity above 72% with SARS-CoV, a peculiar furin-like cleavage site at the S1/S2 position in the S-protein sequence of the 2019-nCoV was identified, lacking in the other SARS-like CoV (Coutard et al., 2020). Following the host cell attachment, entry is mediated by S protein priming by cellular protease. In some cases, the S protein is cleaved by a

host cell furin-like protease. Blocking S protein attachment or furin-like cleavage sites are promising targets in drug discovery. Recently, Xia et al introduced a lipopeptide named EK1C4 effectively block 2019-nCoV infection at the cellular level in a dose-dependent manner with IC50 of 36.5 nM (Xia et al., 2020). The presence of three vaccine candidates in clinical phases accentuates the importance of this protein in the process of drug development (Thanh et al., 2020).

3.2 Inhibition of genome uncoating

The cessation of the capsid disintegration by viral or host enzymes/proteins is a drug target used against the influenza virus, rhinoviruses, hepatitis A, poliovirus and enteroviruses (Yamauchi and Greber, 2016). In accordance with this approach, rimantadine disintegrates the viral capsid by blocking the ion channel in the influenza virus (Balgi et al., 2013). Maoto, a traditional Japanese herbal medicine also shows inhibitory activity on influenza virus A (PR8) presumed by inhibition of genome release (Masui et al., 2017).

No effort on blockage of uncoating step in the 2019-nCoV life cycle as a drug discovery target is reported so far. However, the S-protein-based vaccines can induce antibodies that block the genome uncoating besides the viral receptor blockage. Furthermore, it is still not determined whether the uncoating of 2019-nCoV can occurs in both acidic and neutral conditions similar to IBV or it is uncoating can be suppressed by the neutralization of the acidic condition of endosomes and its subsequent fusion.

3.3 Inhibition of Replicase Protein Expression

Following the uncoating step, the replicase gene of the viral genome encodes two large polyproteins (pp1a and pp1ab) (Chan et al., 2020). Then, viral proteinases perform post-translational modification on the polyproteins yielding proteins that mediate the formation of viral replication complexes. The protease activities for all coronaviruses include both papain-like proteinase (PLP) and cornavirus 3C-like proteinase activities that are encoded within the replicase polyproteins and mediate cleavage events. Because of their unique and essential function in processing the viral polyprotein, these proteases are appropriate targets for the development of 2019-nCoV drugs.

3.3.1. Protease

3.3.1.1 Papain-like proteinase (PLpro)

PLproteinase or nsp3 releases proteins is involved in both processes of coronavirus replication and infection of the host. Some studies have highlighted the importance of these protease inhibitors in other Coronaviruses. Ratia et al identified a compound, GRL0617, with an EC50 of 15 μM that inhibits SARS-CoV viral replication in Vero E6 cells (Ratia et al., 2008). PLpro inhibitors against MERS-CoV (Kilianski et al., 2013), HEV (Saraswat et al., 2020), etc have also been reported. Disulfiram, an approved drug to treat alcohol dependence, has been reported to inhibit the papain-like protease of MERS and SARS in cell cultures, but clinical approval of its effectiveness is lacking (Li and De Clercq, 2020). The inhibition of Pl pro can be considered as a promising target in the development of coronavirus drug discovery.

3.3.1.2 3C-like main protease (3CLpro)

3CLprotease (which is the main protease (Mpro)) or nsp5 directly mediates the processing of the viral polyprotein and maturation of viral nonstructural proteins (nsps), which are essential in the life cycle of the virus. Initiation of viral RNA synthesis and switching translation to RNA replication are other functions of this protein. 3CLpro is among the most attractive target for anti-coronavirus drug development. Based on a computational drug repurposing study performed by Junmei Wang (Wang, 2020), five drugs, namely, Carfilzomib, Eravacycline, Valrubicin, Lopinavir and Elbasvir, are identified to have inhibitory activities on 3Cl pro of 2019-nCoV. According to another computational study performed by Nguyen et al., Bortezomib, Flurazepam, Ponatinib, Sorafenib, Dasatinib, are five potent potential inhibitors of 3CL pro for 2019-nCoV (Nguyen et al., 2020).

Due to the similar active-site architecture of the 3C protease in coronaviruses and enteroviruses, Zhang et al designed peptidomimetic α-ketoamides as suitable targets for the development of broad-spectrum antiviral

drugs. They introduced a compound (11r) expecting to exhibit excellent antiviral activity against 2019-nCoV (Li and De Clercq, 2020; Zhang et al., 2020b)

3.4 Replication of the CoV-19 genome

3.4.1 RNA-dependent RNA polymerase (RdRp)

The most important conserved protein in the coronavirus replication/transcription complex is RNA-dependent RNA polymerase (RdRp) (nsp12) or RNA replicase (Gao et al., 2020). Genome multiplication is critical in the viral life cycle and can be an attractive target for the intervention in the infection progress.

The antiviral agents of remdesivir, favipiravir, penciclovir can inhibit the RNA-dependent RNA polymerase (RdRp) of many RNA viruses, specially the influenza virus. Wang et al. determined the efficiency of these agents on infected Vero E6 cells with 2019-nCoVBetaCoV (Li and De Clercq, 2020; Wang et al., 2020; Zhang et al., 2020b). The high concentrations of penciclovir (EC50 = 95.96 μM) and favipiravir (EC50 = 61.88 μM) were required to reduce the viral infection while remdesivir (EC50 = 0.77 μM) potently blocked the virus infection at low-micromolar concentration.

3.4.2 Helicase

Helicase (nsp13) is a critical multi-functional protein required for virus replication containing two main domains; N-terminal metal binding domain (MBD) and a conserved helicase domain at the C-terminus (Hel). In positive-sense RNA viruses, the enzyme separates nucleic acid and unfold the highly stable secondary structures within the genomic RNA to increase the efficiency of its translation (Adedeji et al., 2012a). Despite the essential function of helicase in virus multiplication, a few potential inhibitors of nsp13 have been reported so far (Adedeji et al., 2012b; Shum and Tanner, 2008).

A 1,2,4-triazole derivative, SSYA10-001, has shown inhibition effect on both helicase of SARS-and MERS-CoVs with EC50 values of 25 μM and 7 μM, respectively (Adedeji et al., 2014). In another study, Yu et al demonstrated that myricetin and scutellarein can inhibit the SARS-CoV helicase protein by affecting the ATPase activity (Yu et al., 2012). The potent inhibition of the helicase activities and replication of SARS coronavirus with EC50 of less than 10 μM is also reported by the Adamantane-derived Bananins (Tanner et al., 2005).

3.4.3 The peptidyl/prolyl isomerases (PPIases)

The 18-kDa cytosolic cyclophilin A is an essential cellular molecule required for replication of RNA viruses including HIV (Luban et al., 1993), HCV (Watashi et al., 2005), influenza A (Liu et al., 2012) and also coronavirus. Cyclophilins (Cyps), belonging to the family of peptidyl-prolyl isomerases (PPIases), catalyze the rate-limiting cis/trans isomerization step of proline-preceding peptide bonds during the protein folding. The PPIase activity is blocked by cyclosporin A and its different non-immunosuppressive analogs (de Wilde et al., 2018) such as Alisporivir (ALV; or Debio-025) (Landrieu et al., 2010), NIM811 (Ciechomska et al., 2005) and SCY-635 (Hopkins et al., 2010).

There are various reports indicating the effect of Cyps (de Wilde et al., 2011; Pfefferle et al., 2011) and its derivatives (Carbajo-Lozoya et al., 2014; de Wilde et al., 2017) on different genera of coronaviruses mainly MERS-CoV, HCoV-229E, HCoV-NL63 and SARS-CoV in cell culture.

3.4.4 Nucleoside analog inhibitors

Nucleoside analogs are dNTPs or rNTPs that lack 3'-OH group resulting in chain termination. They are widely used as a treatment for HBV, HCV, HIV-1, and HSV. Compared to the other RNA viruses, the proofreading activity of RdRp by the capability of 3' to 5' exoribonuclease (nsp14), leads up to 20-folds increase in accuracy of replication. The inhibitors enzyme of coronavirus is highly resistant to many nucleoside analogs including fabiravir (guanine analog), ribavirin (guanosine analog) and 5-fluorouracil (pyrimidine analog) (Harrison, 2020).

Remdesivir, (adenosine analog) as a potent phosphoramidate prodrug is effective against filoviruses, pneumoviruses, and paramyxoviruses with two suggested mechanisms of action (Lo et al., 2017). One is being as nucleoside analog and the second is acting on viral RdRp. Accordingly, Peters et al evaluated the efficiency of a series of doubly flexible nucleoside analogues suggesting that compound 2 with EC50 $<$ 10 μM was promising against HCoV-NL63 (Peters et al., 2015). The combinations of nucleotide analoges can mitigate the resistance mediated by mutations in the viral RdRp, perhaps by additive or synergistic interactions effect (Pruijssers and Denison, 2019). Despite the proofreading activity, identifying nucleoside analog inhibitors hold promise for the treatment of 2019-nCoV.

3.5 Viral protein assembly

Capsid proteins have a pivotal function in the assembly of the virus, and interfering with the structure or function of these key proteins can be a solid antiviral strategy. Coronaviruses are distinct from other enveloped viruses in that they assemble at the intracellular membranes in the endoplasmic reticulum and golgi intermediate compartment (ERGIC) and transported out of the cell by exocytosis (Schoeman and Fielding, 2019). Envelope proteins (E) are clearly important for coronaviruses assembly, but their exact mechanistic role(s) is still not yet fully described (Schoeman and Fielding, 2019). Although E protein is abundantly expressed inside the infected cell, only a small portion is incorporated into the virion envelope and the major part is localized in intracellular trafficking, and participates in coronavirus assembly. The envelope protein (E) of coronaviruses (HCoV-229E, MHV, IBV) mediates viral assembly and form cation-selective ion channels that their function is not clear (Wilson et al., 2004). Involvement of E protein in critical aspects of the viral life cycle, make 2019-nCoVs lacking E protein, a promising vaccine candidate. Pharmacological blockage of its assembly with acylguanidine, cinnamoylguanidine reduced the SARS-CoV and MHV viral titer by 76 and 88% at a concentration of 10 μM, respectively (Gage et al., 2007).

Qin et al. designed siRNAs that inhibit M protein expression through degradation of M mRNA in SARS-associated coronavirus, which provides an approach for studies on the functions of M protein and for the development of novel therapeutic agents for CoV infection (Qin et al., 2007)

Application of viral assemble inhibitors for different types of viruses including Mo-MLV (McNally et al., 2010), CSFV (Zhou et al., 2008), HIV-2 (Wu et al., 1995), HIV-1 (Li et al., 2009), DENV2 (Qin et al., 2005), HBV (Seo et al., 2019) and influenza A (Liu et al., 2014) is investigated. However, no drug candidate disparting the 2019-nCoV assembly is in the trial or is reported so far.

3.6 Cell release of the virus

Prevention of the release of the viruses from infected cells as the last step of the viral cycle, is an attractive strategy to limit the spread of the virus especially in pandemics. Drugs like zanamivir, oseltamivir, laninamivir octanoate and peramivir inhibit this step by targeting viral neuraminidase to block the release of Influenza virus (De Clercq and Li, 2016). Tetherin (bone marrow stromal cell antigen 2—BST-2, CD317) was discovered as the factor responsible for the defect in virion release of HIV-1 mutants lacking the accessory gene vpu (Van Damme et al., 2008).

One of the coronavirus virulence factors is ORF7a that inhibits the bone marrow matrix antigen 2 (BST-2) (Taylor et al., 2015) related to its escape from the innate immune system by host mRNA degradation and interferon production inhibition. Bone marrow matrix antigen 2 (BST-2), also known as tetherin or CD 317, is a host protein constitutively expressed in mature B cells, plasma cells and plasmacytoid dendritic cells, that can inhibit the release of newly-assembled coronavirus from host cells. The evidence suggests that ORF7a may be a potential target for antiviral drug discovery of 2019-nCoV.

4 Concluding remarks

In the past twenty years, two new coronaviruses have been emerged mainly causing the acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) responsible for the epidemics in 2002 and 2012, respectively (World Health Organization, 2003; World Health

Organization, 2013). Since the pandemic outbreak of novel coronavirus (2019-nCoV) and the rapidly increasing number of patients by minutes (155175 Deaths by April 18, 2020), the focus has been on the assessments to of recruite the existing antiviral compounds which must be complemented by the new drug discovery programs in the future. Nevertheless, the current urgent demand is addressing by the clinical trials of 30 drugs to approve the effectiveness of the existing antiviral drugs on 2019-nCoV.

The potential molecular targets in anti 2019-nCoV drug discovery is surveyed in the paper that can be employed in HTS programs for systematic drug discovery for 2019-nCoV infection. Little is currently known about the biology of 2019-nCoV specially, viral protein synthesis and assembly and most of what we know have been for the last 4 months. Due to the high virus transmission and the global spread of coronavirus, the foremost controversial issue is the mitigation of its pathogenicity using the existing anti-viral compounds. Therefore, *in silico* or practical screening of molecular targets are being conducted on structural information obtained from all major variants of the virus. Although, the ongoing clinical trials are evaluating the potential treatments of more than 30 drugs, there are currently no specifically certified drugs or vaccines for 2019-nCoV. In addition to the above approach, detailed studying the viral life cycle can lead to assigning some even more effective drug targets. In this direction, some drug targets based on bioinformatics analysis and relative similarities of this new virus with other members of its family like host cell receptors, spike glycoproteins, papain-like and 3C-like protease, RdRp have been documented so far. However, an approximate half of the potent drug candidates and nearly one-third of the drugs registered on the www.clinicaltrials.gov webpage, solely inhibit proteases affecting the replicase protein expression step in the viral life cycle.

While full-length S proteins of 2019-nCoV and SARS-CoV share up to 76% identities in amino acid sequences, the N terminal domain that binds to the receptor show only 53.5% of homology reflecting its ability to bind different sugars. Therefore, emphasizing on other virus entry related factors like cathepsin seems valuable for 2019-nCoV drug discovery. Based on a recent report (Walls et al., 2020), host proteases cathepsin L and TMPRSS2 prepare the 2019-nCoV S protein for cell entry. Considering the results of repurposing strategies and clinical tests until now, remdesivir seems a promising drug. Nevertheless, HIV protease inhibitors (ritonavir/lopinavir/ASC09), favipiravir and chloroquine need further investigations.

5 Future directions

As we proceed with the current molecular docking studies and presuming the effectiveness of the existing antiviral compounds, the de novo drug discovery will join to evaluate the modulation of the new molecular targets of 2019-nCoV in bioassay platforms which were discussed above and not only limited to 3cl pro and RdRpin. To accelerate the long, costly and rigorous process of drug discovery, high throughput methods and high content screening methods can be employed. However, by the immediate global need for drugs to control the COVID-19 infection drug search is currently pursued by the repurposing approach. Accordingly, the critical viral life cycle steps like entry, genome and protein synthesis reflect the multiple drug target groups that can be addressed by the conventional de novo strategy of drug discovery. Assembly and release inhibitors are less considered steps in 2019-nCov life cycle for its drug discovery. While most of the drug cases for 2019-nCoV are registered for the control purpose rather than prophylaxis; S protein, integrins and ACE2 targets are of value for drug repurposing or discovery programs to hinder the viral entry and fusion process. Considering the fact that the primary goal of all viruses is to deliver and replicate their genome to the competent host cells, blocking angiotensin-converting enzyme 2 (ACE2), cathepsin L, 3cL protease and RdRp are suggested to be promising targets for anti-2019-nCoV drug discovery.

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Table 1. Potential repurposing candidates with effectiveness on novel coronavirus 2019 (2019-n CoV). ND: Not Determined

Drug candidate	Target	Antiviral mechanism of action	References
Remdesivir	RNA polymerase	Prodrug of an adenine analog that incorporates into nascent viral RNA chains and results in pre-mature termination	(Wang et al., 2020)
Baloxavir marboxil	RNA polymerase	Cap-dependent endonuclease inhibitor	(Harrison, 2020)
Triazavirin	RNA polymerase	A guanosine nucleotide analog that inhibits RNA synthesis	(Loginova et al., 2011)
Favipiravir (Avigan)	RNA polymerase	Inhibits RNA-dependent RNA polymerase (RdRp)	(Wang et al., 2020)
Ribavirin	RNA polymerase	Inhibits viral RNA synthesis and mRNA capping	(Khalili et al., 2020)
Penciclovir	RNA polymerase	Inhibits RNA-dependent RNA polymerase (RdRp)	(Wang et al., 2020)
Acyclovir fleximer analogue	RNA polymerase	Inhibits RNA-dependent RNA polymerase (RdRp)	(Li and De Clercq, 2020)

Drug candidate	Target	Antiviral mechanism of action	References
Galidesivir	RNA polymerase	Inhibits viral RNA polymerase function by terminating non obligate RNA chain	(Li and De Clercq, 2020)
Ritonavir	Protease	Inhibits 3CLpro	(Stower, 2020)
ASC09F	Protease	A combination drug containing ASC09 (HIV protease inhibitor) + ritonavir/ Oseltamivir	(Li and De Clercq, 2020)
Camostat	Protease	Serine protease inhibitor with activity against the host TMPRSS2 protease that is exploited on 2019-nCoV	(Li and De Clercq, 2020)
Danoprevir	Protease	A potent HCV protease (NS3/4A) inhibitor	(Shah et al., 2020)
Nelfinavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Xu et al., 2020)
Colistin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Liu and Wang, 2020)
Valrubicin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Liu and Wang, 2020)
Icatibant	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Liu and Wang, 2020)
Bepotastine	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Liu and Wang, 2020)
Epirubicin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Liu and Wang, 2020)
Epoprostenol	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Liu and Wang, 2020)
Vapreotide	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Liu and Wang, 2020)
Rupintrivir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Liu and Wang, 2020)
Lopinavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Stower, 2020)

Drug candidate	Target	Antiviral mechanism of action	References
Ebselen	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Jin et al., 2020)
Cinanserin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Zhang and Liu, 2020)
Flavonoids	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Zhang and Liu, 2020)
Beclabuvir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Talluri, 2020)
Saquinavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Talluri, 2020)
α- ketoamide	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Zhang et al., 2020b)
Hesperidin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Adem et al., 2020)
Angiotensin II human acetate	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Contini, 2020)
GHRP-2	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Contini, 2020)
Indinavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Contini, 2020)
Cobicistat	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Contini, 2020)
Atazanavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	(Contini, 2020)
Mycophenolic acid	Protease	Inhibits papain-like protease (PLpro)	(Elfiky and Ibrahim, 2020)
Grazoprevir	Protease	Inhibits papain-like protease (PLpro)	(Elfiky and Ibrahim, 2020)
Formoterol	Protease	Inhibits papain-like protease (PLpro)	(Arya et al., 2020)
Telaprevir	Protease	Inhibits papain-like protease (PLpro)	(Elfiky and Ibrahim, 2020)
Diarylheptanoids	Protease	Inhibits papain-like protease (PLpro)	(Zhang and Liu, 2020)

Drug candidate	Target	Antiviral mechanism of action	References
Darunavir/cobicistat alone or with lopinavir/ritonavir	Protease	An HIV-1 protease and cytochrome P450 (CYP)3A enzyme inhibitors	(Zhai et al., 2020)
Ikarugamycin	ACE2	ACE2 inhibitors that block the site of viral spike protein interaction	(Yang et al., 2020)
Molsidomine	ACE2	Effective on the genes co-expressed with ACE2	(Yang et al., 2020)
Eriodictyol	ACE2	Binding potency to viral S-protein at its host receptor or to the S protein-human ACE2 interface	(Smith and Smith, 2020)
Nitrofurantoin	ACE2	Binding potency to viral S-protein at its host receptor or to the S protein-human ACE2 interface	(Smith and Smith, 2020)
Cepharanthine	ACE2	Binding potency to viral S-protein at its host receptor or to the S protein-human ACE2 interface	(Smith and Smith, 2020)
Baricitinib	Kinase	Janus-associated kinase (JAK) inhibitor which is an important regulator of clathrin-mediated endocytosis.	(Richardson et al., 2020)
Ruxolitinib	Kinase	Janus-associated kinase (JAK) inhibitor blocking ACE2-mediated endocytosis	(Stebbing et al., 2020)
Nitazoxanide	Interferon response	Induces the host innate immune response to produce interferons	(Wang et al., 2020)
Nafamostat	Spike glycoprotein	Inhibits membrane fusion	(Wang et al., 2020)
Teicoplanin	Cathepsin L	Antibiotic inhibiting the low-pH cleavage of the viral spike protein by cathepsin L in the late endosomes	(Zhang et al., 2020a)

Drug candidate	Target	Antiviral mechanism of action	References
Ciclesonide	Endoribonuclease	An approved corticosteroid that inhibit replication via inhibition of viral nsp15	(Matsuyama et al., 2020)
Camrelizumab	Programmed cell death 1 (PD-1)	A humanized monoclonal antibody (mAb) targeting PD-1	(AminJafari and Ghasemi, 2020)
Emtricitabine	Reverse transcriptase	Non-nucleoside reverse transcriptase inhibitor	(Harrison, 2020)
Tenofovir	Reverse transcriptase	Nucleotide reverse transcriptase inhibitor	(Harrison, 2020)
Azvudine	Reverse transcriptase	Experimental reverse transcriptase inhibitor drug against HIV-1/AIDS	(Harrison, 2020)
Methylprednisolone	Nuclear receptors	Synthetic corticosteroid that binds to nuclear receptors to dampen proinflammatory cytokines	(Harrison, 2020)
IFN alpha-1b	Immunomodulation	Bind to cellular surfaces' receptors and initiate JAK-STAT signaling cascades	(Harrison, 2020)
Interferon alfa-2a	Immunomodulation	Interferon alfa-2b is a recombinant cytokine with antiviral properties; ribavirin is a guanine derivative	(Li and De Clercq, 2020)
Tocilizumab	IL-6 receptor	Approved immunosuppressive anti-IL-6 receptor mAb	(Harrison, 2020)
Thalidomide	ND	Regulating immunity, inhibiting the inflammatory cytokine surge	(Dastan et al., 2020)
Umifenovir (Arbidol)	ND	Membrane fusion inhibitor targeting viral entry	(Li and De Clercq, 2020)

Drug candidate	Target	Antiviral mechanism of action	References
Chloroquine/ hydroxychloroquine	ND	1. Elevate the pH of acidic intracellular organelles, such as endosomes/lysosomes, essential for membrane fusion 2.Inhibit the entry through changing the glycosylation of ACE2 receptor and spike protein	(Touret and de Lamballerie, 2020)
Fingolimod	ND	Sphingosine-1-phosphate receptor regulator	(Rosa and Santos, 2020)
Dipyridamole		Adenosine deaminase and phosphodiesterase inhibitor	(Aly, 2020)

Table 2. Potential drug candidates for 2019-nCoV in clinical trials and their status in April 2020 based on clinicaltrials.gov database.

ClinicalTrials.gov Identifier	Intervention
NCT04321096	Camostat Mesilate
NCT04324996	Biological: NK cells,IL15-NK cells,NKG2D CAR-NK cells,ACE2 CAR-NK cells,...
NCT04276688	Lopinavir/ritonavir; Ribavirin ; Interferon Beta-1B
NCT04280588	Fingolimod
NCT04273529	Thalidomide
NCT04288102	Biological: MScs
NCT04317092	Tocilizumab
NCT04321993	Lopinavir/ritonavir; Hydroxychloroquine sulfate; Baricitinib (janus kinase inhibitor) ; Sarilum
NCT04313023	PUL-042 Inhalation Solution
NCT04275245	Meplazumab
NCT04279197	Acetylcysteine
NCT04311177	Losartan
NCT04292899	Remdesivir
NCT04325633	Naproxen
NCT04304313	Sildenafil citrate
NCT04320615	Tocilizumab (TCZ)
NCT04315896	Hydroxychloroquine
NCT04317040	CD24Fc
NCT04261270	ASC09F+Oseltamivir; Ritonavir+Oseltamivir ; Oseltamivir
NCT04321616	Hydroxychloroquine; Remdesivir
NCT04315298	Sarilumab
NCT04324021	Emapalumab
NCT04252274	Darunavir and cobicistat
NCT04308317	Tetrandrine
NCT04286503	Carrimycin
NCT04254874	Arbidol Hydrochloride combined with Interferon atomization
NCT04263402	Methylprednisolone

ClinicalTrials.gov Identifier	Intervention
NCT04252885	Umifenovir (Arbidol)
NCT04255017	Umifenovir (Arbidol); Oseltamivir; Lopinavir/ritonavir
NCT04291729	Drug: Ganovo (Danoprevir)+ritonavir+/-Interferon nebulization

Table 3. Vaccine candidates for 2019- nCoV in clinical trials and their current status in April 2020 based on clinicaltrials.gov database.

ClinicalTrials.gov Identifier	ClinicalTrials.gov Identifier	Interventions	Mechanism of action
NCT04283461	mRNA-1273	mRNA-1273	Novel lipid nanoparticle (LNP)-encap
NCT04313127	Ad5-nCoV	Ad5-nCoV	Adenovirus type 5 vector that expres
NCT04336410	NO-4800	NO-4800	DNA plasmid encoding S protein deli
NCT04276896	LV-SMENP-DC	LV-SMENP-DC	Lentiviral vector system (NHP/TYF)
NCT04299724	Pathogen-specific aAPC	Pathogen-specific aAPC	aAPCs modified with lentiviral vecto

Table 4. Principle molecular targets of 2019-nCoV for drug discovery or design. ND: Not determined.

Viral cycle	Target	Antiviral drug
Host attachment and entry	Host cell serine protease receptor	Eriodictyol, Cepharanthine, Ergoloid, Nitrofurantoin
	Host tyrosine kinase receptor	ND
	ACE2	ND
	Integrins	ND
	Spike protein	EK1C4
Uncoating	Ion channel proteins	ND
Replicase Protein Expression	Papain-like proteinase (PLpro)	Mycophenolic acid, Grazoprevir, Formoterol, Telaprevir, Diarylheptanoids, etc
	3C-like main protease (3CLpro)	Ritonavir, Nelfinavir, Lopinavir, Ebselen, Cinanserin, Ketoamide, Atazanavir,
Replication of viral genome	RNA-dependent RNA polymerase (RdRp)	Remdesivir, Baloxavir marboxil, Triazavirin, Favipiravir (Avigan), Ribavirin, Penciclovir, Acyclovir fleximer analogue, Galidesivir
	Helicase	ND
	The peptidyl/prolyl isomerases (PPIases)	ND
	Nucleoside analogs	Remdesivir, Favipiravir, ribavirin, 5-fluorouracil
Viral protein assembly	Envelope protein (E protein)	ND
Cell release of the virus	ORF7a	ND

Figure legends

Figure 1

The schematic diagram (left) (original in this paper) and the scanning electron micrograph (right) (Source: NIAID-RML) of the 2019-nCoV surface proteins

Figure 2

2019-n CoV cell cycle in host cells. The virus enters the target cells through direct membrane fusion (A) or a clathrin-mediated endosomal pathway (B). Binding of the surface unit of the S protein (S1) to angiotensin-converting enzyme 2 (ACE2) facilitates the viral attachment. Viral fusion is primed by TMPRSS2 and the active spike protein of 2019-nCoV acquire an RGD motif known to bind integrins. Spike glycoprotein RGD lies in the receptor-binding domain. Binding to integrin may play a supplemental role to ACE2 binding, like facilitating endocytosis by signaling through the integrin. This motif is absent in other coronaviruses. The viral RNA is unveiled by the effect of endosomal cathepsins at low pH. Following, the replicase gene of the viral genome is translated into large polyproteins which are cleaved by the proteases to yield 16 non-structural proteins (nsps). In consequence ofreplication, transcription and translation, viral nucleocapsids are assembled with genomic RNA and N protein in the cytoplasm, followed by budding into golgi intermediate compartment. Then, virions are released from the infected cell through exocytosis.