Repurposing approved drugs to target SARS-CoV-2

CURRENT TREATMENTS

As of April 2020, there are no specific therapies approved for the treatment of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). One of the strategies for the treatment of COVID-19 is to repurpose approved drugs, known to act on different stages of both the infection and host response. The use of these drugs fast-tracks a treatment plan for COVID-19 as they have known favorable safety profiles for patients.

TREATMENT TARGETS IN SARS-CoV-2 INFECTION

Therapeutic targets against COVID-19 exist at various stages of the infection and disease progression:

- **Viral attachment and entry**

SARS-CoV-2 binds to two host surface-expressed proteins, ACE2 and the serine protease, TMPRSS2, through its Spike (S) protein. The viral S protein is cleaved into two functional subunits, S1 which interacts with ACE2, and S2 that is further cleaved and activated by TMPRSS2. Together, these actions result in viral-host membrane fusion [1]. These high-affinity interactions are essential in viral entry and are therefore prime targets in the treatment of COVID-19. Chloroquine has formerly been shown to interfere with the terminal glycosylation of ACE2, and thus negatively influences the virus-receptor binding in SARS-CoV infection [2]. Additionally, Camostat and Nafamostat are both clinically proven inhibitors of TMPRSS2 that have shown effectiveness against coronaviruses (e.g. MERS-CoV) [1, 3].
The β-coronaviruses, SARS-CoV and MERS-CoV, have been shown to enter the host cell by endocytosis [4]. During endocytosis, the virion is surrounded by the cell membrane, internalized, and then a vesicle buds off inside the cell (endosome). In order for the virus to infect host cells, endosomal acidification is required. The role of endocytosis is not yet elucidated in SARS-CoV-2 infection [5]. Nevertheless, it is a possible target through the repurposing of Imatinib, an Abelson (Abl) kinase inhibitor, that has been shown to block endocytic entry of other β-coronaviruses [6]. Furthermore, endosomal acidification may be inhibited with Chloroquine [2] or its more potent chemical derivate Hydroxychloroquine [7, 8], which have shown promise in testing with SARS-CoV-2 in vitro.

- **Viral proteolysis**

Upon the release of viral RNA into the host cytoplasm, the host machinery is used to translate the essential viral polyproteins (pp1a and pp1ab), which include the proteases 3CLpro and PLpro. These viral proteases are responsible for the proteolysis of the polyproteins into effector proteases [4]. 3CLpro is an important protease for a number of viruses such as HIV and thus has been previously targeted for drug development. The fixed-dose combination of Lopinavir & Ritonavir (sold under the name Kaletra), is known to inhibit the activity of 3CLpro and is approved for the treatment of HIV/AIDS [9]. Preliminary clinical trials using Kaletra for the treatment of SARS-CoV-2 have been disappointing [10], however, it is currently being evaluated in combination with other antiviral drugs. Additionally, a clinically available alcohol-averse drug, Disulfiram, has been shown to inhibit PLpro in both MERS-CoV and SARS-CoV [11].

- **Viral replication**

Viral replication requires the ‘replication-transcription complex’ consisting of a number of components including the viral RNA-Dependent RNA polymerase (RdRp) and helicase [4]. It has been reported that the most promising antiviral agent against COVID-19 is Remdesivir, an adenosine analog, developed to combat other viruses (e.g. Ebola virus) [12]. It has proven to be highly effective against SARS-CoV-2 in vitro, with its active form able to incorporate into nascent viral RNA by RdRp and ultimately, causing RNA synthesis arrest [13, 14]. Additionally, the antiviral Favipiravir, approved for the treatment of Influenza in China, is recognized as a substrate by viral RdRp and thereby inhibits its activity. It has also been shown to be effective against a number of viruses [9].

**Cyclosporin A** is an approved immunosuppressant drug for a number of conditions such as Crohn’s disease. Importantly, Cyclosporin A has shown effectiveness against a wide range of viruses in vitro, including coronaviruses, by interfering with protein interactions and thereby affecting viral replication [15]. Therefore, its effect in the treatment of COVID-19 may be two-fold, against both the virus and the hyper-inflammation response.

- **Host cytokine response**

A coordinated, controlled, and balanced cytokine response is essential for the host immune response to SARS-CoV-2. Therefore, a dysregulated response may lead to a hyperinflammatory condition in some patients. It has been shown that severe cases of COVID-19 have higher levels of pro-inflammatory cytokines (such as IL-6) in their plasma compared to others [16, 17]. Monoclonal antibodies (mAbs) against the IL-6 receptor, Sarilumab & Tocilizumab, are emerging as possible treatments for COVID-19 patients with a higher risk of developing cytokine storms [18]. Furthermore, preliminary in vitro data suggest that SARS-CoV-2 is more susceptible to type I interferon (e.g. Interferon-β) treatment than SARS-CoV [19].

**ONGOING CLINICAL TRIALS AND OTHER LINES OF RESEARCH**

Drug repurposing for the treatment of COVID-19 is being evaluated in a constantly increasing number of clinical trials. Importantly, the first data are expected in the coming weeks. Additionally, scientists are exploring other strategies to develop safe and effective COVID-19 therapeutics. These include the screening of large chemical libraries and the development of novel molecules based on artificial intelligence (AI) simulations of SARS-CoV-2 and its interaction with the host.

REFERENCES: