Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Target Virus or Target Ourselves for COVID-19 Drugs Discovery?—Lessons learned from anti-influenza virus therapies

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ABSTRACT

The COVID-19 pandemic, after it was reported in December 2019, is a highly contagious and now spreading to over 190 countries, causing a severe public health burden. Currently, there is no vaccine or specific drug to treat COVID-19, which is caused by a novel coronavirus, SARS-2-CoV. For this emergency, the FDA has approved Remdesivir and Hydroxychloroquine for treatment of COVID-19 as Emergency Use Authorization. However, even after this pandemic, COVID-19 may still have a chance to come back. Therefore, we need to come out with new strategies for drug discovery for combating COVID-19 in the future.

The pandemic of COVID-19 (Coronavirus Disease-2019) is a highly contagious respiratory disease resulting from a life-threatening novel coronavirus, SARS-CoV-2. Since its outbreak in December 2019, it has reported causing 837,104 infections, 41,249 deaths worldwide, and quickly spread out to over 190 countries [1–3]. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA betacoronavirus of the family *Coronaviridae*. In the last two decades, two viruses from the same family, SARS-CoV in 2002 to 2003 and MERS-CoV in 2012, have also caused two out of four outbreaks in the 21st century, and the other two are influenza virus H1N1 in 2009 and Ebola in 2014 [4]. Two drugs, Remdesvir and Chloroquine, developed for treating Ebola virus and Malaria, respectively, have been approved by the FDA to treat COVID-19 as Emergency Use Authorization, although no formal clinical trial has been finished [5,6]. So far, there is no effective vaccine for COVID-19. Several vaccines are in the process or clinical trail [7]. Recent advancements in mRNA vaccines, mRNA-1273, targeting the Spike protein of the coronavirus, has started for SAEs-CoV-2 patients in Phase 1 clinical trial. However, from lessons learned from anti-influenzas virus therapy in the past, we believe that therapeutics targeting the host-virus interactions could potentially present more effective and broad-spectrum treatment modalities for COVID-19. The strategy of targeting host factors is arguably less mutational resistance with more broad anti-virus spectrum potential.

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1. Target viruses

In the past, the therapeutic strategy for anti-microbial pathogens primarily targets pathogen genes and proteins. This strategy works well for anti-bacterial in most of the cases. Still, it has much less success in anti-viruses' therapy as the viral genes have the intrinsic nature to mutate very frequently to become resistant to vaccine and drugs due to the less error correction activity of their nucleotide polymerases in virus replication, as well as multiple sub-families with small different target genes. Although the flu vaccines have been widely distributed, it is estimated that the efficacy of flu vaccines against both influenza A and B viruses is estimated to be 40% [8]. On the other hand, viruses can become resistant to antiviral drugs. In the US, three neuraminidase inhibitors (NAI) are recommended by the CDC: oseltamivir, zanamivir, and peramivir. Most of the recently circulating influenza viruses have been susceptible to the NAI antiviral medications, but recent virus isolates from patients show significant drug resistance, even in the same year of the drug lauched [9–13]. There is another class of influenza antiviral drugs (amantadine and rimantadine) that are not recommended for use in the US because about half flu A viruses are resistant to these drugs and they are not effective against influenza B virus. Besides, the antiviral agents must be used within 48 h of the onset of influenza symptoms to be effective. But most of the time, when severe symptoms occur, it already passes the timeline and is at a very late stage. As a consequence of the current anti-influenza virus strategy, although broad vaccines and drugs targeting virus proteins have been developed in

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the last decade, the influenza virus is still a highly life-threatening disease. In the 2014–2015 flu season, the Centers for Disease Control and Prevention (CDC) estimates, 34 million Americans were infected by the infected, 710,000 were hospitalized, and approximately 56,000 died, making this year as one of the most significant outbreak years recently. In the most recent 2018–2019 season, there has already been 34,157 death caused by the flu up to now [8]. This severity of influenza virus gives a very high burden to the health of people in the whole world. However, the current pipeline of anti-influenza drug discovery is still mainly focusing on virus proteins [14].

2. Target the host

New strategies to control emerging viruses, including their drug-resistant mutants, such as SARS-CoV-2, are utmost needed. A new approach of targeting host factors for anti-pathogens emerged recently [15]. We have been working on this topic for more than a decade, mainly focusing on SUMOylation and other Ubiquitylation-like pathways because they both regulate cytokine signaling and viral proteins stabilities [16–19]. Discovery and characterization of cellular factors or pathways that are critical for pathogen life cycle in a host or regulate pathogenesis hold great promise for revealing new strategies for anti-infections. There may be several benefits by targeting host factors. First, the viral genomes, particularly ssRNA viruses, such as SARS-CoV-2 virus and Hepatitis C virus (HCV), have a very high mutation rate (10^{-3}–10^{-6} substitutions/bp/cell infection) mainly due to the lack of proofreading activities of RNA-dependent RNA Polymerase (RdRP), RNA-dependent DNA Polymerase (RdDP) or Reverse Transcriptase (RTase), and other cellular enzymes that modify the nucleotides, although a recent study shows that SARS-CoV open reading frame 14 (nsp14) may encode a 3′-to-5′ exoribonuclease activity (exoN) [20–22]. In contrast, viral hosts are most multicellular organisms, including human, and mutation rate of DNA polymerases are much lower (10^{-9}–10^{-10} substitutions/bp/cell division), mostly due to both proofreading activity of DNA polymerase and mismatch repair pathways of host cells [20,21]. Second, targeting host factors may have a broader anti-virus spectrum. For example, both SARS-CoV-2 and SARS-CoV use Ace2 as their receptors to enter cells, and if any agents that can block the virus-Ace2 interaction may be effective for both viruses. Third, both COVID-19 and SARS have cytokine storms resulting in severe pneumonia, causing the death of patients. The control of the cytokine storm is also a very desirable treatment approach for patients in serious conditions for virus infection-induced pneumonia, such as COVID-19.

Besides, the viruses utilize cellular machineries for their replication, and those cellular machineries can be drug targets too. Recently, an old drug, Nitazoxanide(NTZ), developed initially as an antiprotozoal agent, has been identified as broad anti-influenza A and B viruses and drug-resistant mutants [23]. The results from phase II/III clinical trial are very suspicious. NTZ depletes ATP-sensitive intracellular Ca^{2+} stores as well as alteration of viral protein N-linked glycosylation and trafficking [24]. The long-term efficacy and potential side effect(s) need to be evaluated in the future. There is no approved antiviral therapy available for multiple viruses or multiple drug-resistant viruses that cause serious diseases. Therefore, targeting host factors can be a plausible approach for developing COVID-19 therapeutics or other emerging viruses in the future.

Conflict of Interest

The authors declare no conflict of interest.

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