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May we target double membrane vesicles and oxysterol-binding protein to combat SARS-CoV-2 infection?

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Dear Editor,

Since the first human infection of SARS-CoV-2 was reported in the Hubei (Wuhan) province of China, the world has been facing a relentless degree of socioeconomic and medical crisis. The disease of SARS-CoV-2 infection which is now called the COVID-19 pandemic has spread to several countries across the globe (Nicastri et al., 2020). The symptoms of SARS-CoV-2 are similar with flu and usually include fever, cough, shortness of breath, and muscle ache (Huang et al., 2020). Although several drugs have been identified to be effective in SARS-CoV-2 infection *in vitro* and some anecdotal evidences presented for a handful of repurposed drugs, an effective treatment for COVID-19 has not yet been introduced (Yang et al., 2020). From those tried so far, concomitant use of

antiviral and anti-inflammatory drugs as supportive therapy has been suggested to be effective in reducing the severity of SARS-CoV-2 (Stebbing et al., 2020). The various approaches for suppressing SARS-CoV-2 infection and/or COVID-19 therapy include: inhibiting the RNA-dependent RNA polymerase, inhibiting the viral protease, blocking virus–cell membrane fusion, enhancing the innate immune system, attenuating the inflammatory response, symptomatic control, vaccine, and pathogen-specific artificial antigen-presenting cells (Tu et al., 2020). Considering the lengthy process of novel drug discovery programs, and the unprecedented level of human and economic cost of the disease, repurposing the FDA-approved medications appear to be the best available option at this very moment. In this regard, reviewing the lesson learned from the pathogenicity and therapeutic options for other related viruses is critical.

Coronavirus replication involves formation of double-membrane vesicles (DMVs) derived from endoplasmic reticulum (ER) in which the replication-transcription complexes (RTCs) composed of nonstructural proteins (nsp3, 4 and 6) are anchored (Angelini et al., 2013). Inhibition of DMV formation

at an early step of the viral life cycle can prevent viral infection by impairing viral RNA synthesis. One such compound identified is K22, which suppresses both animal and human coronaviruses replication by interacting with nsp6, the membrane spanning integral component of RTC, present in DMV (Lundin et al., 2014). Nsp6 mutants display K22 resistance suggesting the inhibitory role of K22 in viral RNA synthesis. K22 has been found to have virucidal effect against diverse lineages of *Nidoviruses* and members of *Flaviviridae*, suggesting its involvement in a critical and conserved step during viral replication (Rappe et al., 2018). More studies should be conducted on inhibitors of DMVs as they can be used as broad-spectrum antivirals.

Another target can be oxysterol-binding protein (OSBP), a lipid-binding protein found in all eukaryotes with high affinity for 25-hydroxycholesterol and other oxysterols (Pietrangelo and Ridgway, 2018). Among the various known cellular functions of OSBP is a transfer of cholestrol in contact with membranes sites (MCS) from ER to Golgi, while counter-transporting phosphosphoinositide-4-phosphate (PI4P) back to the ER (Mesmin et al., 2017).

Some studies show that OSBP has essential role in the proliferation of RNA viruses (Albulescu et al., 2015). For example, its critical role in enterovirus replication has been well-established and while the protein ligand (OSW-1) inhibits viral replication in nanomolar concentration range, overexpression of OSBP appears to rescue viral pathogenicity (Nchoutmboube et al., 2015). Interestingly, the enteroviruses (family Picornaviridae) are positive-strand RNA viruses just like the coronaviruses and their genomic replication is dependent on remodeling of intracellular membranes (Dorobantu et al., 2015), as well as alteration of organelles/lipids function (Belov and van Kuppeveld, 2012). More importantly, picornavirus infection has been shown to be inhibited by targeting OSBP and some of the identified leads include: OSW-1 (Roberts et al., 2018), itraconazole (Bauer et al., 2018), T-00127-HEV-2, and TTP-8307 (Arita, 2014). Based on their prophylactic activity against *Enterovirus* replication *in vitro*, the structure-activity relationship of various OSBP targeting compounds (OSW-1, itraconazole, T-00127-HEV2 and TTP-8307) has also been established (Roberts et al, 2019). To date, however, neither the role of OSBP in coronavirus infection nor

the efficacy of therapeutic agents targeting OSBP in COVID-19 has been studied. In view of the broad range of available OSBP targeting compounds and their established antiviral potential, studies on coronaviruses therapy via OSBP modulation are highly encouraged.

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Figure 1. Inhibitors of double membrane vesicles and oxysterol-binding protein for COVID-19