the figure). In regions where there are no cables, particularly the southern oceans, efforts to develop long-term autonomous seafloor seismometers (*9*), operate floating sensors (*10*), and deploy strategically placed arrays of temporary seismometers (*11*) are critical for improving the resolution of seismic images of the Earth's structure and the completeness of global earthquake catalogs. Where cables do cross ocean basins, they could transform academic seismology by providing new observations in regions that are presently poorly observed. Subduction zones are costly to instrument offshore with dedicated warning systems (*12*), but many of the most hazardous coincide with regions where telecommunication cables land. Here, distributed acoustic sensing could be supported by repurposing decommissioned commercial cables and by adding spare fibers to the nearshore portions of new installations. Polarization monitoring and ultrastable laser interferometry could extend observations further offshore using cables that run both perpendicular and parallel to coastlines. Incorporating fiber-sensing technologies into effective earthquake and tsunami warning systems will require that the signals are accurately quantified through extensive co-sited observations with conventional seismic and pressure sensors. Obviously, this can be most comprehensively achieved by making the new cables "SMART" with these sensors incorporated along their path where they would also contribute to warning. Given that SMART cables will also provide observations to constrain how climate change is affecting the temperature of the deep ocean, ocean circulation, and sea-level rise (*7*), it is time for cable suppliers and technology companies to step forward and work with scientists and governments to make them a reality. ■

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CORONAVIRUS

SARS-CoV-2 dependence on host pathways

A drug that inhibits host protein synthesis shows antiviral activity against SARS-CoV-2

By **Jason P. Wong**[1,2] and **Blossom Damania**[1,2]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in 2019, and its high pathogenicity, infectivity, and transmissibility have led to a global pandemic. Although several vaccines have been approved in different countries, most of the global population currently remains unvaccinated because of disparities in vaccine distribution and limited manufacturing capabilities (*1*). Owing to a lack of treatment options (particularly in low- and middle-income countries), the slow progression of vaccination, and the emergence of SARS-CoV-2 variants that elicit reduced responses to vaccines, there is an urgent need to identify therapeutics to reduce COVID-19 morbidity and mortality. On page 926 of this issue, White *et al.* (*2*) demonstrate that the small-molecule drug, plitidepsin, which is approved to treat relapsed and refractory multiple myeloma, possesses antiviral activity against SARS-CoV-2 and may be a promising drug candidate for treating COVID-19.

In broad terms, treatments for viral infections can target the virus, host, or underlying symptoms of infection. Antiviral treatments work by disrupting the viral life cycle. For SARS-CoV-2, the life cycle can be divided into three stages: host cell entry and trafficking, replication of the viral genome, and packaging and egress of new virions (*3*) (see the figure). Entry of SARS-CoV-2 into host cells occurs through receptor-mediated endocytosis or virion fusion with the cell membrane. Once in the cell, two polyproteins, pp1a and pp1ab, are translated from the RNA genome. These polyproteins are cleaved to generate nonstructural protein 1 (nsp1) to nsp16. The Nsps form the replication and transcription complex (RTC), which transcribes the viral genomic and subgenomic RNA (sgRNA). The sgRNAs encode structural and accessory proteins. Structural proteins traffic through the endoplasmic reticulum–to–Golgi secretory pathway, where viral genomes are packaged to form budding vesicles, which are then released as new virions by exocytosis.

A common class of antivirals being tested in clinical trials against SARS-CoV-2 is nucleoside and nucleotide analogs, which inhibit viral replication when incorporated into the RNA by the RTC (*3*–*5*). Remdesivir is a nucleotide analog that is presently the only U.S. Food and Drug Administration (FDA)–approved antiviral for COVID-19 treatment and is recommended for use in patients requiring oxygen that is administered in a noninvasive manner (*6*). However, like other antivirals, it is most effective when administered early during infection, when individuals exhibit mild-to-moderate disease symptoms. Currently, remdesivir is given as an intravenous infusion, restricting its use to clinical settings. Hence, new antivirals with oral bioavailability, which are readily available and accessible to the general public, are needed to shorten the infectious phase and prevent further spread. Nucleotide or nucleoside analogs that can be administered orally, such as sofosbuvir (combined with either daclatasvir or ledipasvir), ribavirin, and favipiravir are being tested in clinical trials for treating COVID-19. Favipiravir has shown promise in a few open-label clinical trials for COVID-19, but more studies are needed to confirm its efficacy (*3*). Another way to disrupt viral genome replication is to prevent cleavage of the polyproteins that generate the RTC. Many clinical trials are examining if lopinavir and/or ritonavir, which target the SARS-CoV-2 3C–like protease that is responsible for cleaving the polyproteins (*6*), are effective. Other inhibitors in clinical trials include those that target viral entry and trafficking such as camostat mesilate and baricitinib (*6*).

An alternative antiviral approach is to target host cell pathways that are essential for virus replication, such as protein synthesis. Viruses are completely dependent on the host for translation and have evolved a variety of ways to exploit this machinery for their use (*7*). In human cells, translation can be divided into four phases: initiation, elongation, termination, and recycling of the ribosome. Translation is initiated by binding of the 5′ cap on messenger RNA (mRNA) by the 43*S* preinitiation complex. This complex scans

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the mRNA for the start codon and recruits the 60*S* ribosomal subunit to complete the assembly of the ribosome and begin elongation. Viruses can mimic host mRNAs, which contain a 5′ cap, 3′ polyadenylated tail, and untranslated regions (UTRs) flanking the 5′ and 3′ end, to utilize the host translation machinery (*7, 8*). The SARS-CoV-2 proteins, nsp10, nsp13, nsp14, and nsp16, cap the 5′ end of viral RNA (*3*). Coronaviruses are known to down-regulate global host mRNA translation (*8*). SARS-CoV-2 nsp1 blocks entry of mRNAs into the ribosome, thereby preventing translation (*9–11*). Currently, it is unclear whether viral mRNAs are completely able to avoid suppression by nsp1 (*10, 11*). However, a reporter gene encoding a viral 5′ UTR demonstrated a fivefold increase in gene expression in comparison to one encoding a host cell 5′ UTR (*10*). Thus, SARS-CoV-2 commandeers the host translational machinery and is highly dependent on it to make its own viral proteins.

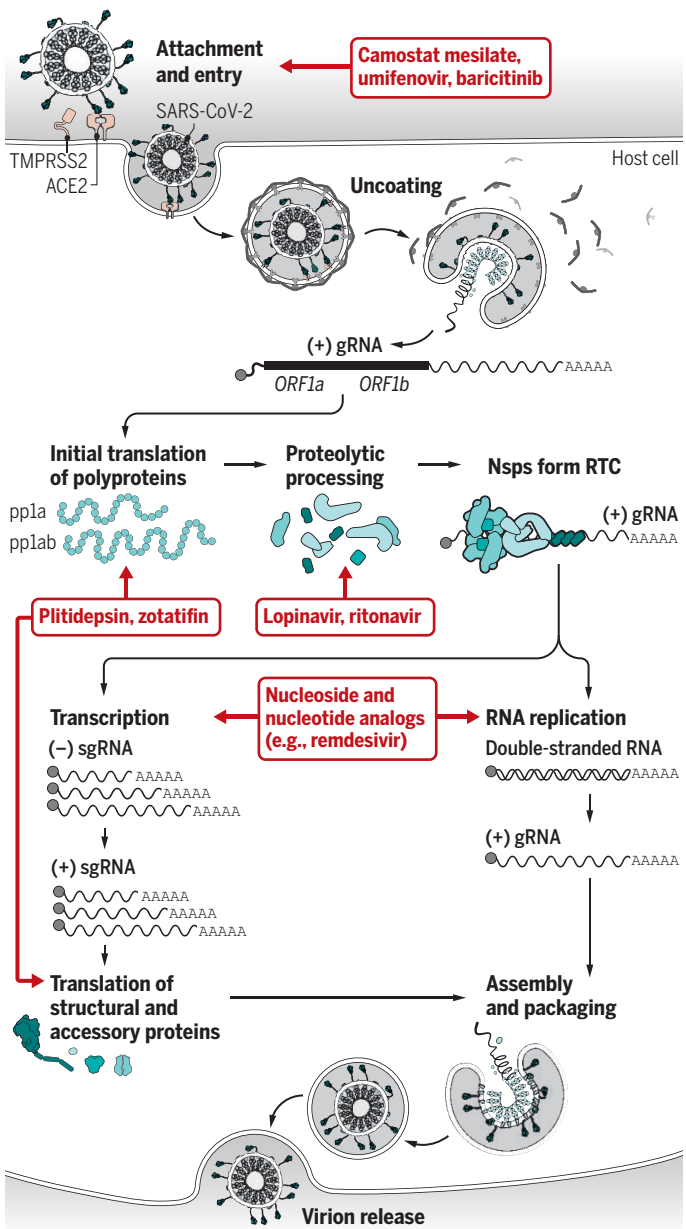
White *et al.* convincingly demonstrate that plitidepsin, which targets the host eukaryotic translation elongation factor 1α (eEF1A), possesses antiviral activity against SARS-CoV-2. Treatment of mice with plitidepsin reduced viral lung titers and lung pathology upon infection to a similar degree as remdesivir. Expression of the structural protein, N, was also lower in plitidepsin-treated cells compared to remdesivir-treated cells despite similar amounts of N sgRNA in both cells. This is likely due to the inhibition of translation of N by plitidepsin. A concern and limitation of translation inhibitors are the potential toxicities arising from the systemic inhibition of host translation. However, the safety profile of plitidepsin is well studied as it has been tested in many cancer clinical trials (*2*). An open-label proof-of-concept clinical trial of plitidepsin, given intravenously, to treat COVID-19 has been completed (NCT04382066), and another translation inhibitor, zotatifin, is in clinical trials as an intravenous treatment for COVID-19 (NCT04632381). Zotatifin inhibits the eukaryotic translation initiation factor 4A (eIF4A) (*2*). Both phase 1 clinical trials aim to evaluate the safety of these inhibitors for use in patients with mild or moderate COVID-19.

Another small molecule that modulates host translation is rapamycin, which is an orally administered drug that regulates kinases involved in host protein synthesis (*12*). Multiple clinical trials are underway to examine the efficacy of rapamycin in patients with mild to moderate COVID-19. The study of White *et. al.* suggests that translation inhibitors may have promise in treating patients with mild or moderate COVID-19. There are discernable advantages to targeting the host, which include creating a higher bar for viruses to develop resistance and a broader protection against diverse viral strains.

Despite the rollout of vaccines in several countries, discovering antivirals to treat SARS-CoV-2 continues to be important. There are already concerns about the emergence of SARS-CoV-2 variants that may be less susceptible to the current vaccines. Moreover, new antivirals are needed if remdesivir-resistant SARS-CoV-2 strains emerge. Recent data indicate that plitidepsin maintains potent antiviral activity against the B.1.1.7 SARS-CoV-2 variant (*13*). Furthermore, many viruses rely on similar host pathways for propagation, leading to some antivirals having a broad spectrum of activity against multiple viruses (*3*, *6*). Remdesivir was originally identified for treating hepatitis C and respiratory syncytial virus, but was ineffective. It was repurposed for use against Ebola virus, and now against SARS-CoV-2. This suggests that antivirals discovered in the race to treat COVID-19 may be useful for future epidemics. ■

Targeting the viral life cycle

The SARS-CoV-2 life cycle begins with entry into the host cell, followed by generation of the RTC derived from pp1a translated from *ORF1a*, and pp1ab translated by ribosomal frameshifting to *ORF1b*. Then, the viral genome is replicated and packaged into new virions. Inhibitors (red) targeting viral and host factors that are important in the viral life cycle could prevent the spread of infection.



ACE2, angiotensin-converting enzyme 2; gRNA, genomic RNA; Nsps, nonstructural proteins; *ORF1*, open reading frame 1; pp1a, polyprotein 1a; RTC, replication and transcription complex; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sgRNA, subgenomic RNA; TMPRSS2, transmembrane protease serine 2.

GRAPHIC: V. ALTOUNIAN/*SCIENCE*

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