viral S protein such that it is proteolytically cleaved and activated by cathepsins and TMPRSS2 (cell-surface transmembrane protease serine subfamily member 2), furin and trypsin. With the aim of stopping SARS-CoV-2 at this stage, Stefan Pöhlmann and colleagues at the University of Göttingen and Leibniz Institute for Primate Research [recently reported](#) that a generic TMPRSS2 blocker, camostat mesilate (indicated for pancreatitis), effectively blocks SARS-CoV-2 infection in cultures of human Caco-2 and simian Vero E6 cells. At least [five](#) clinical trials of the drug are underway in COVID-19, yet TMPRSS2 might prove to be an overly specific target. “There’s the potential for a whole family of back-up proteases that could take over the role of TMPRSS2 in human airway or lung,” says Gary Whittaker at the Department of Microbiology & Immunology, Cornell University College of Veterinary Medicine, New York. Another [publication](#) has reported that a related generic compound targeting TMPRSS2, nafamostat mesilate, also inhibits SARS-CoV-2 infection of Vero cells; the drug is set to enter a [clinical trial](#) for COVID-19.

The most widely discussed compounds in the context of blocking viral entry — via inhibition of ACE-2 glycosylation, proteolytic processing and endosomal acidification — are the generics chloroquine and hydroxychloroquine sulfate. At the end of April, hydroxychloroquine — which is indicated for malaria and prescribed off-label in systemic lupus erythematosus and rheumatoid arthritis — received an [Emergency Use Authorization \(EUA\)](#) from the US Food and Drug Administration, reflecting its wide use in combination with the generic antibiotic azithromycin in [small-scale trials](#). Although assessment of its efficacy against COVID-19 remains an area of active investigation, its [serious cardiac side effects](#) (associated with QT interval prolongation on electrocardiograms) and neurotoxicity are well known; as a result, many clinical centers no longer consider it a baseline therapy.

Pinpoint Therapeutics, a Philadelphia-based biotech startup built around the work of Ravi Amaravadi at the University of Pennsylvania, raised \$1 million from Kairos Ventures in February. The company is developing a dimeric version of chloroquine that can be used at much lower doses, doesn’t cross the blood–brain barrier (and hence has lower toxicity) and [targets](#) palmitoyl-protein thioesterase 1 (PPT1), a modulator of autophagy. Last month, the startup announced it was starting in vitro infectivity assays of dimeric chloroquine against SARS-CoV-2.

Although viral entry inhibitors have produced several leads for drug developers, several other groups of host proteins are also attracting interest. The recent *Nature* paper by Krogan and colleagues describes a comprehensive study of interactions between SARS-CoV-2 proteins and human proteins: Krogan’s team cloned, tagged and expressed 26 of the 29 SARS-CoV-2 proteins in human cells, identifying interactions between the betacoronavirus’s proteins and human proteins using affinity-purification mass spectrometry (MS).

After applying computational tools (SAINTexpress and MiST) to screen the MS results for high-confidence protein–protein interactions, the researchers used chemoinformatics and human expertise to match 66 druggable human proteins or host factors as targets of 69 different compounds (29 of which have been approved by the US Food and Drug Administration, 12 of which are experimental molecules in clinical testing, and 28 of which are experimental molecules in preclinical testing). In vitro infectivity assays in Vero 6 cells carried out at Mount Sinai Medical Center in New York (37 drugs tested) and at the Pasteur Institute in Paris (44 drugs tested) then highlighted sigma receptors in the endoplasmic reticulum, proteins involved in cap-dependent mRNA translation, and stress granules that sequester mRNA and RNA-binding proteins as particularly promising drug targets.

Sigma 1 receptors and sigma 2 receptors are hijacked by SARS-CoV-2’s Nsp6 and ORF9c, respectively. The sigma 1 receptor carries out Ca²⁺ signaling in the endoplasmic reticulum’s mitochondria-associated membrane and is known to promote cell survival, activate the unfolded protein response, mediate lipid remodeling and influence [autophagosome–lysosome](#) fusion. Three generics — hydroxychloroquine, the antipsychotic haloperidol and the antihistamine clemastine — effectively inhibited SARS-CoV-2 in vitro through this mechanism.

Coronaviruses are also known to rely on cap-dependent mRNA translation through the host translation machinery. SARS-CoV-2 Nsp9 was found in the Krogan MS screen to interact with eukaryotic initiation factor 4H (eIF4H), which partners with eIF4A. The team observed a strong antiviral effect with eFFECTOR Therapeutics’ experimental therapy zotatifin, a small-molecule inhibitor of eIF4A in phase 1/2 testing for the treatment of advanced solid tumors. The authors point out that another eIF4A inhibitor, Madrid-based PharmaMar’s Aplidin (plitidepsin), was approved in April by the Spanish Agency of Medicines

Dyno advances AI-powered gene therapy

Dyno Therapeutics stepped out of the shadows in May, announcing partnerships with Novartis and Sarepta to use its AI-driven platform to design adeno-associated virus (AAV) vectors for use in gene therapies. The deal with Novartis is centered on eye diseases and the collaboration with Sarepta focuses on muscle disease. For Dyno, which was founded in 2018 with a \$9 million venture round from Polaris and CRV, the deals could be worth over \$2 billion.

The company is one of 16 startups [cofounded in 2018](#) by George Church, who is based at the Wyss Institute and Harvard Medical School. Dyno drew attention late in 2019 with a [publication](#) in *Science* that demonstrated a machine-guided approach to engineering AAV vector capsids with improved tissue tropism and manufacturability. Several biotechs — including 4DMT, Adverum Biotechnologies, Taysha Gene Therapies and Asklepios BioPharmaceutical — screen large libraries to identify capsids with improved qualities over naturally occurring ones for delivering gene therapies. But Church’s group, which includes Dyno CEO Eric Kelsic and cofounder Sam Sinai, systematically engineered the AAV genome with single codon substitutions, insertions and deletions in the AAV2 capsid followed by high-throughput testing in cells and mice to select the best resulting capsid variants. Machine learning analyzed the capsid libraries optimized for different properties, such as the ability to target the liver or the central nervous system.

In the Novartis collaboration, Dyno will use its platform to develop novel capsids. If drug candidates are developed, Novartis will conduct preclinical and clinical testing of any resulting drug candidates.

Under the Sarepta deal, Dyno will be similarly responsible for generating capsids with improved targeting capabilities in muscles.

In March, Affinia Therapeutics raised \$60 million in series A financing to advance its AAV platform, and in April, the company forged a deal with Vertex to engineer new AAV capsids to treat Duchenne muscular dystrophy, myotonic dystrophy type 1 and cystic fibrosis.

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