LITERATURE REVIEW

COVID-19 Therapeutic Drug Discovery

Current Approaches to Identify Possible COVID-19 Therapeutics

In the midst of the current COVID-19 pandemic, multiple approaches to identify potential therapeutics, including drug repurposing studies, large-scale phenotypic screening of compound libraries, and target-based drug discovery, are being pursued to help develop medicines targeting SARS-CoV-2 infection. Currently, over 300 therapeutics are at various phases of development – either new medicines or repurposed therapeutics that were previously approved to treat other diseases.[1]

Most of the treatments in development fall into one of three categories: antivirals (designed to inhibit SARS-CoV-2 replication), antibodies (designed to bind the virus for inhibition or neutralization), or protein-protein interaction inhibitors (designed to inhibit essential virus protein interactions with human proteins, thereby inhibiting the viral life cycle). Alternative approaches, including treating the symptoms of COVID-19 rather than the virus infection itself, are also being explored.

This review provides an overview of each therapeutic approach and highlights some of the innovative work going on in the field of COVID-19 therapeutic drug discovery.

PerkinElmer®
For the Better

Antiviral Research

Antivirals are a class of drugs used for treating viral infections. Most antivirals target specific viruses, but some are effective against a number of viruses. These drugs either prevent the virus from replicating, entering host cells, or releasing viral particles. One of the challenges when developing antivirals is that viruses use host cells to reproduce; therefore, an effective treatment must selectively target the virus without injury to the infected host cells. Therapy for viral diseases is further complicated by the narrow window of time that an antiviral will likely prove effective.

Since the outbreak of the COVID-19 pandemic, researchers have strived to find an antiviral that can effectively treat SARS-CoV-2 infection, with little success thus far. Only remdesivir, which was approved by the FDA for treating hospitalized patients with COVID-19 in October 2020,[2] has shown some potential; however, questions have since been raised relating to the drug's effectiveness.[3] In June 2021, the Biden Administration announced it was investing more than $3 billion to accelerate the discovery, development, and manufacturing of antiviral medicines as part of its strategy to develop the next-generation of COVID-19 treatments.[4]

At the start of the pandemic, one factor that hampered the rapid identification of potential antiviral compounds was the lack of suitable assays and reagents for detecting live virus infection and replication in host cells.[5] Prompted by this urgent need, Kirill Gorshkov and Wei Zheng, from the National Center for Advancing Translational Sciences (NCATS) in the US, led a team to develop and optimize a high-throughput AlphaLISA® screening assay for the identification of the SARS-CoV-2 nucleocapsid protein (NP) – one of the four main structural proteins of the virus.[5] The researchers were able to detect the NP with high sensitivity, suggesting the assay could be useful for future high-throughput screening approaches.

The exploration of libraries of molecules already approved for human use, and well characterized in terms of human metabolism, is an attractive approach for the identification of potential antivirals against SARS-CoV-2. For example, a team of Italian-based researchers recently identified the antipsychotic drug lurasidone and antiviral drug elbasvir as potential SARS-CoV-2 inhibitors using a combined *in silico* and *in vitro* approach.[6] The team first analyzed a public database of approved/investigational drugs targeting a wide region around the active site of SARS-CoV-1 RdRp – a highly conserved region that plays a crucial role in the CoV replication cycle. They then tested the *in vitro* viral activity of 13 selected compounds using cell-based assays and high-content imaging to establish their antiviral activity (Figure 1). "Our approach allowed the identification of lead drugs for further *in vitro* and clinical investigation to contain the present outbreak," the researchers concluded in their paper published in *Antiviral Research*.

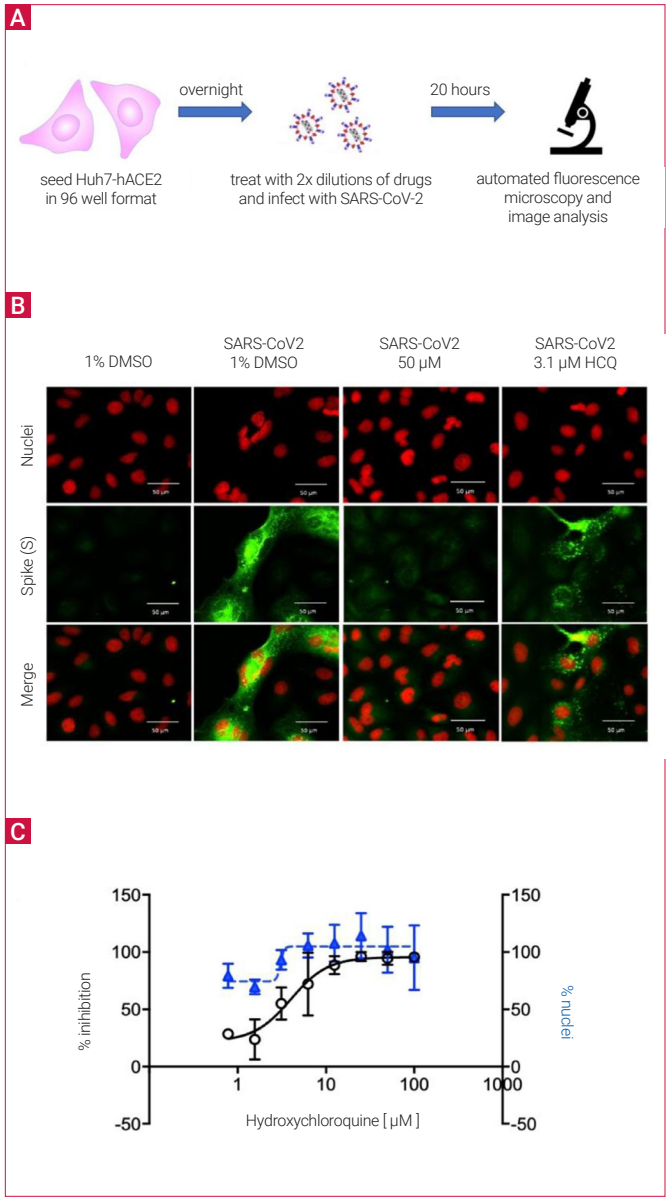


*Figure 1: High content screening assay for SARS-CoV2. **(A)** Scheme of SARS-CoV2 HCA. Huh7-hACE2 were seeded onto 96-well plates, after 24 h cells were treated with the drugs in two-fold dilutions and immediately infected with SARS-CoV2 (MOI 0.1). 20 h after infection, cells were fixed, stained, and analyzed. **(B)** Representative images of the HCA with the control drug hydroxychloroquine (HCQ). Nuclei are stained by DAPI (red) and Spike (S) is stained with the mSPI-3022 antibody (green), scale bar corresponds to 50 µm. **(C)** Dose response of the positive control hydroxychloroquine. White dots represent the percentage of normalized % of inhibition. Blue triangles represent the % of nuclei compared to the average % of non-infected cells. Error bars represent the standard deviation (SD) of two independent experiments.*[6]

Scientists from Mahidol University in Thailand also utilized high-content imaging, coupled with a plaque reduction assay, to identify anti-SARS-CoV-2 agents from the Thai medicinal plant library.[7] A total of 122 extracts and purified compounds derived from Thai medicinal plants were screened and results showed that *Boesenbergia rotunda* extract and its phytochemical compound, panduratin A, exhibited potent anti-SARS-CoV-2 activity. Another study conducted by Kim et al.[8] used a high-content screening system to assess the antiviral activity of a naturally existing sulfated polysaccharide, lambda-carrageenan (λ-CGN), against SARS-CoV-2. The team observed that λ-CGN inhibits SARS-CoV-2 by targeting the virus' entry process, suggesting it could be a promising antiviral agent for preventing infection.

Yang et al.[9] focused on identifying leads that target the main protease (M^{pro}) of SARS-CoV-2, which mediates viral replication and transcription. Through a combination of structure-based virtual and high-throughput screening the team assayed more than 10,000 compounds – including approved drugs, drug candidates in clinical trials, and other pharmacologically active compounds – as inhibitors of M^{pro}. Using this approach, they identified six inhibitory compounds, one of which (ebselen) exhibited promising antiviral activity in cell-based assays.

Another group has developed an approach known as biological activity-based modeling (BABM), which builds on the hypothesis that compounds showing similar activity patterns tend to share similar targets or mechanisms of action.[10] In the study, BABM identified over 300 compounds with potential activity against SARS-CoV-2. When tested in a cell culture live virus assay, approximately one third had confirmed antiviral activity. According to the researchers, most of the confirmed compounds, which were found to be viral entry inhibitors and/or autophagy modulators, have the potential to be further developed into anti-SARS-CoV-2 therapies.

Scientists from Oregon State University in the US have suggested that mRNA-based nanotherapeutics in combination with antiviral therapies could emerge as a treatment option against SARS-CoV-2 infection. For their study, the team engineered synthetic mRNA to encode a soluble form of human angiotensin-converting enzyme 2 (hsACE2) to prevent SARS-CoV-2 infection.[11] Novel lipid nanoparticles (LNPs) were used to package mRNA and transfect mammalian cells, and *in vivo* imaging revealed this resulted in enhanced production of secreted hsACE2 protein (Figure 2). Results further showed that mRNA-generated hsACE2 was able to bind with the receptor binding domain (RBD) of the SARS-CoV-2 spike (S) protein and strongly inhibited SARS-CoV-2 infection.

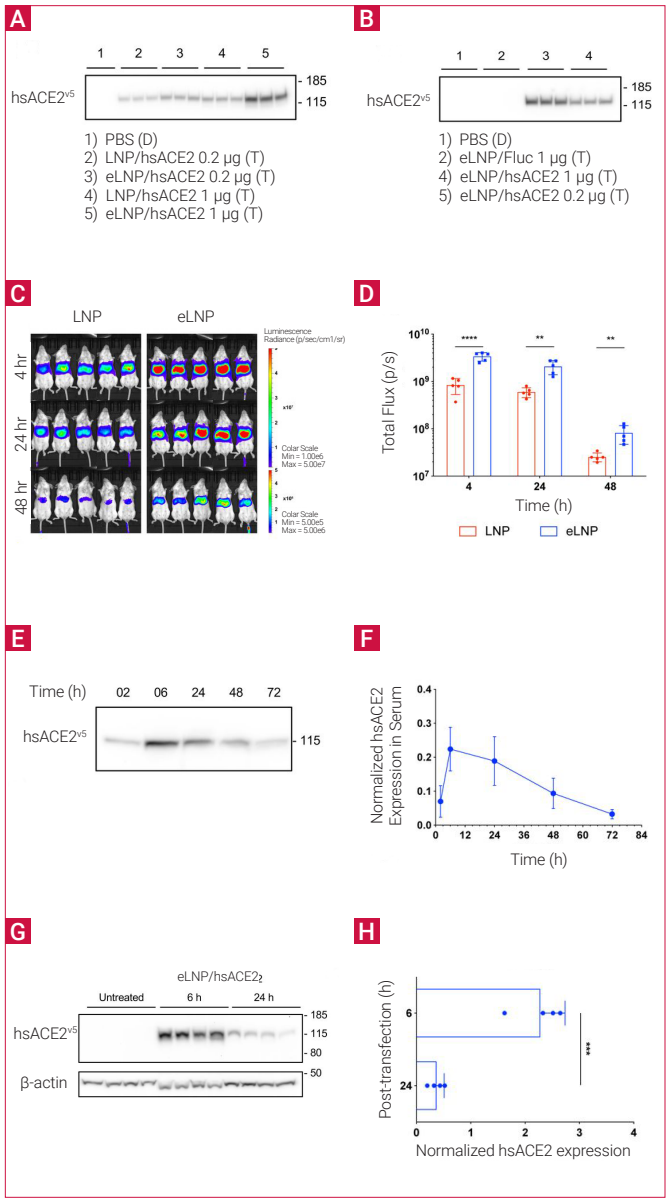


*Figure 2: hsACE2 mRNA transfection results in rapid production of the circulatory hsACE2 protein. **(A,B)** Western blot of cell-free conditioned media from **(A)** 293T and **(B)** Hep G2 cell culture after mRNA transfection using various LNPs. Treatment and mRNA dose are described under each blot (Duplicate (D): n=2, Triplicate (T): n=3). **(C)** In vivo bioluminescent images of BALB/c mice after treatment of 0.05 mg/kg mRNA delivered through IV injection of LNP/Fluc or eLNP/Fluc (n = 5). **(D)** Quantification of bioluminescent signals from IVIS images. Region of interest kept constant in all images (n = 5). **(E)** A representative image of western blot with mouse sera collected with predetermined time intervals after IV injection of 0.15 mg/kg eLNP/hsACE2. **(F)** Densitometric quantitation of temporal levels of the circulatory hsACE2 protein in mouse sera after IV injection of eLNP/hsACE2 (n = 5). Expression of hsACE2 protein was normalized to the total amount of protein in each lane. All data were expressed as the mean ± S.D. **(G)** Western blot of liver homogenates collected from BALB/c mice after IV injection of 0.15 mg/kg eLNP/hsACE2. (h) Expression of hsACE2 protein in mouse liver homogenates after IV injection of eLNP/hsACE2 (n = 4). Densitometric analysis of hsACE2 protein expression normalized to β-actin levels. Statistical analysis was performed using Student's t test. **p < 0.01, ***p < 0.001, ****p < 0.0001. All data were expressed as the mean ± S.D.[11]*

One FDA-approved drug that has recently gained attention as a potential antiviral against SARS-CoV-2 is famotidine – which is approved in the US for the treatment of gastroesophageal reflux disease (GERD) and gastric ulcers. In a recent study, a group of US-based researchers, led by Mohsan Saeed from Boston University School of Medicine and Ali H. Munawar from Bisect Therapeutics, analyzed the effect of famotidine on SARS-CoV-2 proteases and explored whether it inhibits virus replication in cultured cells.[12] Leveraging a series of biophysical and enzymatic assays, the researchers found that famotidine neither bound or inhibited the functions of two SARS-CoV-2 proteases, $3CL^{pro}$ or PL^{pro}. Similarly, no direct antiviral activity of famotidine was observed when tested against SARS-CoV-2 in two different cell lines, including a human cell line originating from the lungs. Although these results rule out famotidine as a direct-acting inhibitor of SARS-CoV-2 replication, they highlight the importance of *in vitro* studies in addition to *in silico* predictive approaches to identify antivirals for COVID-19.

Antibody Research

Monoclonal antibodies (mAbs) that can bind to and neutralize a virus in infected patients are a novel class of antiviral intervention. Known as neutralizing mAbs, these recombinant proteins can be derived from the B cells of recovering patients or humanized mice. By utilizing high-throughput screening approaches, researchers can identify antibodies that bind the virus and block viral entry, minimizing its virulence.

The discovery and development of SARS-CoV-2-neutralizing mAbs is one approach to potentially treat or prevent COVID-19 infection. In the US, several mAb therapies have been granted emergency use authorization (EUA) for the treatment of non-hospitalized patients with mild-to-moderate COVID-19. These include bamlanivimab monotherapy,[13] and combination therapies of bamlanivimab together with etesevimab,[14] or casirivimab with imdevimab.[15] Meanwhile, other potential therapeutics are currently under investigation by researchers.

The primary target for SARS-CoV-2-neutralizing mAbs is the viral S protein, which is responsible for binding of the virus to the ACE2 receptor on the host cell. In a recent study, researchers used neutralization assays and epitope mapping to identify a collection of diverse and potent neutralizing mAbs against multiple epitopes on the SARS-CoV-2 S protein.[16] Writing in *Nature*, the authors suggest that several of these mAbs are promising candidates for future clinical development. Another group at Regeneron Pharmaceuticals used both humanized mice and recovering patients to generate a large panel of antibodies against the S protein.[17] From this panel they identified several pairs of highly potent antibodies that simultaneously bind the RBD of the S protein. The researchers say these pairs could prove to be ideal partners for a therapeutic antibody cocktail, which could decrease the potential for virus escape mutants that arise as pressure is put on the virus to survive.

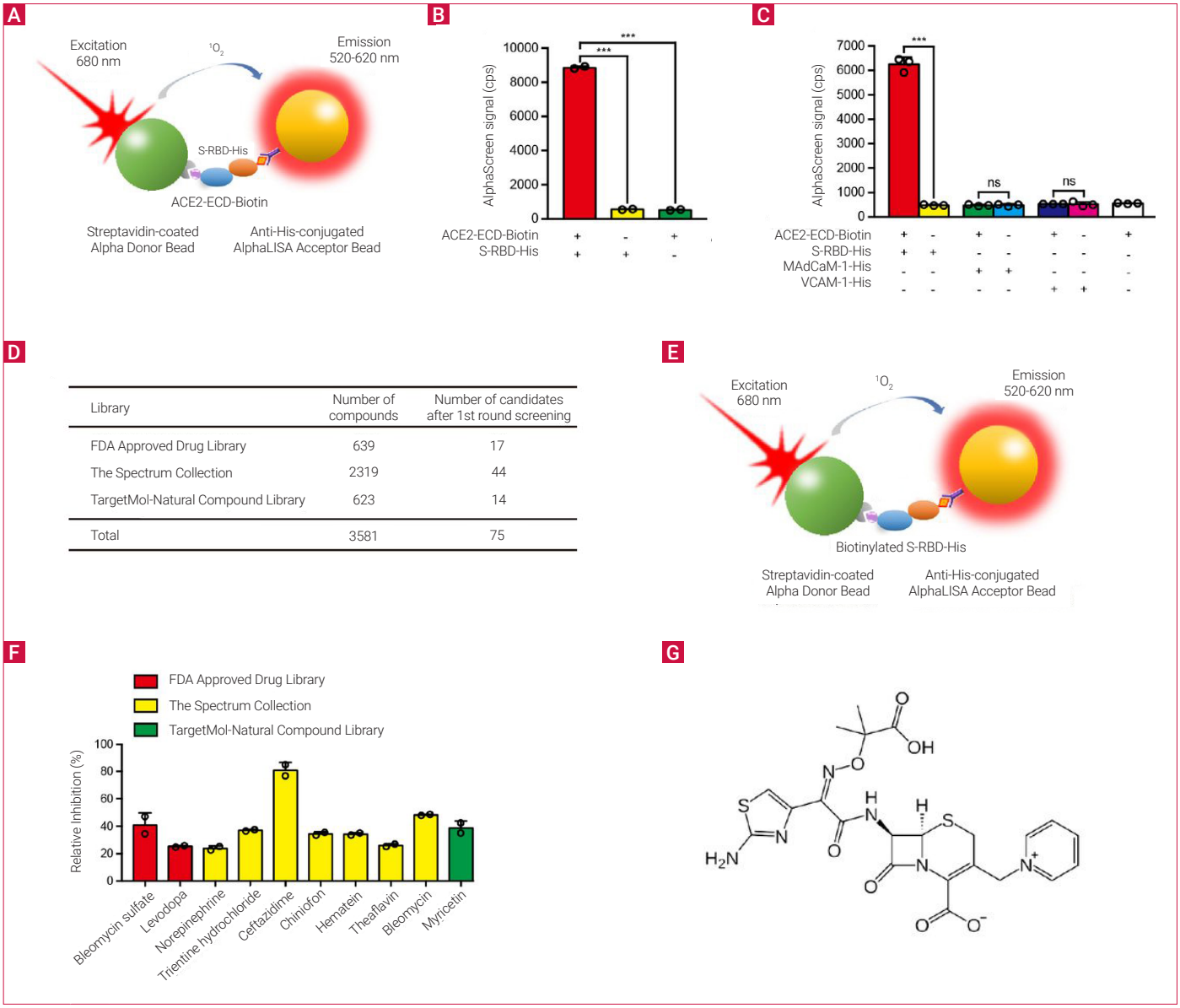
In the case of SARS-CoV-2, escape mutations may cause changes in the S protein that could interfere with the effectiveness of currently available vaccines and antibody therapeutics. It is therefore critical for researchers to understand whether and how SARS-CoV-2 may evolve to evade antibody-dependent immunity. The receptor-binding motif (RBM) is a highly variable region of the SARS-CoV-2 S protein and in a recent study, Gyorgy Snell of Vir Biotechnology and colleagues investigated the various impacts of the RBM mutation N439K, which has emerged independently in multiple lineages.[18] The researchers demonstrated that N439K increased the S protein's binding affinity to the ACE2 receptor, but viral fitness and disease were similar compared to viruses with the wild-type N439 residue. Interestingly, they report that the N439K mutation conferred resistance against several neutralizing mAbs, including one authorized for emergency use by the FDA, and resulted in immune escape from polyclonal sera from a proportion of recovered individuals. The team concluded: "N439K provides a sentinel example of immune escape, indicating that RBM variants must be evaluated when considering vaccines and the therapeutic or prophylactic use of mAbs."

Another group of researchers based at the Institut Pasteur in France have also been investigating the risk posed by emerging SARS-CoV-2 variants. They utilized a rapid neutralization assay to examine the sensitivity of two variants, B.1.1.7 and B.1.351, to neutralizing mAbs.[19] Analysis revealed that the D614G reference virus and B.1.1.7 strain were similarly sensitive to sera. However, for B1.351 the neutralization titers were significantly decreased when compared with the D614G and B.1.1.7 strains. According to the researchers, these findings show that the B.1.351 variant is therefore potentially more problematic as it is less sensitive or even insensitive to sera from immunized individuals. Taken together, the findings of these studies and others highlight the importance of monitoring the evolution of SARS-CoV-2 for escape mutants.

Protein-Protein Interaction Inhibitors

As mentioned earlier, entry of SARS-CoV-2 into host cells is mediated by the early interaction between the viral S protein and the host ACE2 receptor. This protein-protein interaction has attracted attention from researchers as a potential therapeutic target for treating COVID-19. A group from the University of Chinese Academy of Sciences has been investigating whether repurposing drugs that inhibit

this complex could facilitate the development of an effective COVID-19 therapy. Using an AlphaScreen®-based high-throughput system (Figure 3) the team recently identified ceftazidime, which has been approved for the treatment of pneumonia, as a potential drug to inhibit SARS-CoV-2 infection.[20] In another study, Parissi et al.[21] used a combination of *in silico*, *in vitro*, and *in cellulo* approaches to monitor the S protein-ACE2 association. In particular, AlphaLISA technology was used to detect the interaction between both proteins. Writing in *Viruses*, the researchers concluded that their combined approach could help determine the effects of drugs on this specific mode of viral entry.



Library	Number of compounds	Number of candidates after 1st round screening
FDA Approved Drug Library	639	17
The Spectrum Collection	2319	44
TargetMol-Natural Compound Library	623	14
Total	3581	75

Figure 3: Screening of small molecule compounds that specifically block the interaction between S-RBD and ACE2. ***(A)*** *Schematic diagram of AlphaScreen system to detect the interaction between S-RBD and ACE2-ECD. The donor and acceptor beads are coated with streptavidin and anti-His monoclonal antibody, respectively.* ***(B)*** *The interaction between S-RBD and ACE2-ECD was monitored using AlphaScreen system.* ***(C)*** *Comparison of the AlphaScreen signal of S-RBD-His, MAdCAM-1-His and VCAM-1-His proteins in the presence or not of ACE2-ECD-Biotin in AlphaScreen system.* ***(D)*** *Libraries used in AlphaScreen-based high-throughput system and 75 candidates were identified from 3581 compounds in positive selection. The inhibition rate was calculated by the decrease of AlphaScreen signal of each compound compared with that of DMSO vehicle control group.* ***(E)*** *Schematic diagram of negative selection using AlphaScreen system. Biotinylated S-RBD-His simultaneously links streptavidin-coated donor bead and anti-His-conjugated acceptor bead together to generate AlphaScreen signal directly.* ***(F)*** *Relative inhibition of 10 candidate compounds on S-RBD–ACE2 interaction using AlphaScreen system. The relative inhibition rate was calculated by subtracting the inhibition rate in negative selection from that in positive selection.* ***(G)*** *Molecular structure of ceftazidime. Data represent the mean ± SEM (n ≥ 2) in b, c and f. *** p < 0.001, ns: not significant (Student's t test).*[20]

NCATS researchers have also utilized AlphaLISA technology to measure the binding of the SARS-CoV-2 S protein to ACE2. The team developed a proximity-based assay, which was used for a drug-repurposing screen of over 3,000 compounds.[22] Although the study yielded no actionable therapeutic candidates, the researchers say their assay can be leveraged for future studies evaluating compounds that can perturb this interaction.

Alternative Pharmacological Approaches

In addition to targeting the virus itself, some research groups are looking at ways to treat the symptoms of SARS-CoV-2 infection. For example, based on evidence suggesting that the complement pathway plays a pathogenic role in COVID-19, a group of Austrian researchers used a human primary 3D tissue model to analyze the impact of SARS-CoV-2 infection on complement component 3 (C3) activation.[23] High-content imaging revealed that intracellular C3 levels significantly increased following infection, leading the researchers to suggest that complement inhibitors could be a potential strategy to prevent excessive inflammatory responses in high-risk patients during the early stage of disease. Results of another study suggest that apabetalone, a bromodomain and extraterminal domain (BET) protein inhibitor, can suppress the hyperimmune processes that lead to acute respiratory distress syndrome (ARDS) and mortality in COVID-19 infections.[24] BETs are epigenetic regulators of gene transcription and inhibitors of BET proteins have been reported to modulate SARS-CoV-2 infection. Using high-content imaging the researchers demonstrated that apabetalone downregulates expression of viral uptake receptors and reduces SARS-CoV-2 infection *in vitro*.

Another molecule predictive of ARDS and acute lung injury (ALI) is Mucin-1 (MUC1), a membrane-bound molecule expressed on the apical surfaces of most mucosal epithelial cells. In an attempt to identify compounds that reduce levels of MUC1, Greka et al. performed a high-content screen of over 3,500 compounds at different stages of clinical development.[25] The screen identified Fostamatinib, an inhibitor of spleen tyrosine kinase (SYK) approved for the treatment of chronic immune thrombocytopenia, as a potential repurposing candidate for the treatment of ALI. Further *in vivo* analysis revealed that Fostamatinib reduced MUC1 abundance in lung epithelial cells in a mouse model of ALI.

The link between cardiovascular comorbidities and worse outcomes in patients with COVID-19 prompted Stevens Rehen, from the Federal University of Rio de Janeiro in Brazil, and colleagues to investigate the role of the Sigma-1 receptor (S1R), which has been proposed as a potential SARS-CoV-2 therapeutic target, in viral infection in the heart.[26] Using human cardiomyocytes derived from induced pluripotent stem cells (hiPSC-CM) as an experimental model along with high-content imaging, the team demonstrated that S1R inhibition reduced SARS-CoV-2 infection and replication, preventing infection-associated cell death and cytokine release. "Our *in vitro* results suggest that the inhibition of S1R as a therapeutic strategy against COVID-19 should be further investigated," concluded the researchers.

Conclusion

Scientists around the world are working at unprecedented speed to find the best ways to treat and prevent SARS-CoV-2 infection. However, in contrast to the rapid development of effective vaccines, treatments for COVID-19 remain somewhat elusive. Here, we have highlighted various approaches that researchers have adopted to identify potential new therapeutics and the challenges they face keeping up with the latest viral variants. It is hoped these, and other studies, will help identify possible therapeutic candidates to ultimately treat the disease.

References

1. COVID-19 TREATMENT AND VACCINE TRACKER [Internet]. Covid-19tracker.milkeninstitute.org. 2021 [cited 1 July 2021]. Available from: https://covid-19tracker.milkeninstitute.org/

2. FDA Approves First Treatment for COVID-19 [Internet]. U.S. Food and Drug Administration. 2021 [cited 1 July 2021]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

3. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. *New England Journal of Medicine*. 2021;384(6):497-511.

4. Biden Administration to Invest $3 Billion from American Rescue Plan as Part of COVID-19 Antiviral Development Strategy [Internet]. HHS.gov. 2021 [cited 1 July 2021]. Available from: https://www.hhs.gov/about/news/2021/06/17/biden-administration-invest-3-billion-american-rescue-plan-as-part-covid-19-antiviral-development-strategy.html

5. Gorshkov K, Chen C, Xu M, Carlos de la Torre J, Martinez-Sobrido L, Moran T *et al*. Development of a High-Throughput Homogeneous AlphaLISA Drug Screening Assay for the Detection of SARS-CoV-2 Nucleocapsid. *ACS Pharmacology & Translational Science*. 2020;3(6):1233-1241.

6. Milani M, Donalisio M, Bonotto R, Schneider E, Arduino I, Boni F *et al*. Combined in silico and in vitro approaches identified the antipsychotic drug lurasidone and the antiviral drug elbasvir as SARS-CoV2 and HCoV-OC43 inhibitors. *Antiviral Research*. 2021;189:105055.

7. Kanjanasirirat P, Suksatu A, Manopwisedjaroen S, Munyoo B, Tuchinda P, Jearawuttanakul K *et al*. High-content screening

of Thai medicinal plants reveals Boesenbergia rotunda extract and its component Panduratin A as anti-SARS-CoV-2 agents. *Scientific Reports*. 2020;10(1).

8. Jang Y, Shin H, Lee M, Kwon O, Shin J, Kim Y *et al*. Antiviral activity of lambda-carrageenan against influenza viruses and severe acute respiratory syndrome coronavirus 2. *Scientific Reports*. 2021;11(1).

9. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y *et al*. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature*. 2020;582(7811):289-293.

10. Huang R, Xu M, Zhu H, Chen C, Zhu W, Lee E *et al*. Biological activity-based modeling identifies antiviral leads against SARS-CoV-2. *Nature Biotechnology*. 2021;39(6):747-753.

11. Kim J, Mukherjee A, Nelson D, Jozic A, Sahay G. Rapid generation of circulating and mucosal decoy ACE2 using mRNA nanotherapeutics for the potential treatment of SARS-CoV-2. 2020.

12. Loffredo M, Lucero H, Chen D, O'Connell A, Bergqvist S, Munawar A *et al*. The *in-vitro* effect of famotidine on SARS-CoV-2 proteases and virus replication. *Scientific Reports*. 2021;11(1).

13. Fact sheet for health care providers emergency use authorization (EUA) Of Bamlanivimab [Internet]. Fda.gov. 2021 [cited 1 July 2021]. Available from: https://www.fda.gov/media/143603/download

14. Fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab and etesevimab [Internet]. Fda.gov. 2021 [cited 1 July 2021]. Available from: https://www.fda.gov/media/145802/download

15. Fact sheet for health care providers emergency use authorization (EUA) of REGEN-COV (casirivimab and imdevimab) [Internet]. Regeneron.com. 2021 [cited 1 July 2021]. Available from: https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf

16. Liu L, Wang P, Nair M, Yu J, Rapp M, Wang Q *et al*. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. *Nature*. 2020;584(7821):450-456.

17. Hansen J, Baum A, Pascal K, Russo V, Giordano S, Wloga E *et al*. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science*. 2020;369(6506):1010-1014.

18. Thomson E, Rosen L, Shepherd J, Spreafico R, da Silva Filipe A, Wojcechowskyj J *et al*. Circulating SARS-CoV-2 spike N439K variants maintain fitness while evading antibody-mediated immunity. *Cell*. 2021;184(5):1171-1187.e20.

19. Planas D, Bruel T, Grzelak L, Guivel-Benhassine F, Staropoli I, Porrot F *et al*. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. *Nature Medicine*. 2021;27(5):917-924.

20. Lin C, Li Y, Zhang Y, Liu Z, Mu X, Gu C *et al*. Ceftazidime is a potential drug to inhibit SARS-CoV-2 infection *in vitro* by blocking spike protein–ACE2 interaction. *Signal Transduction and Targeted Therapy*. 2021;6(1).

21. Lapaillerie D, Charlier C, Fernandes H, Sousa S, Lesbats P, Weigel P *et al*. *In Silico*, *In Vitro* and *In Cellulo* Models for Monitoring SARS-CoV-2 Spike/Human ACE2 Complex, Viral Entry and Cell Fusion. *Viruses*. 2021;13(3):365.

22. Hanson Q, Wilson K, Shen M, Itkin Z, Eastman R, Shinn P *et al*. Targeting ACE2–RBD Interaction as a Platf orm for COVID-19 Therapeutics: Development and Drug-Repurposing Screen of an AlphaLISA Proximity Assay. *ACS Pharmacology & Translational Science*. 2020;3(6):1352-1360.

23. Posch W, Vosper J, Noureen A, Zaderer V, Witting C, Bertacchi G *et al*. C5aR inhibition of nonimmune cells suppresses inflammation and maintains epithelial integrity in SARS-CoV-2–infected primary human airway epithelia. *Journal of Allergy and Clinical Immunology*. 2021;147(6):2083-2097.e6.

24. Gilham D, Smith A, Fu L, Moore D, Muralidharan A, Reid S *et al*. Bromodomain and extraterminal protein inhibitor, apabetalone (RVX-208), reduces ACE2 expression and attenuates SARS-CoV-2 infection *in vitro*. 2021.

25. Kost-Alimova M, Sidhom E, Satyam A, Chamberlain B, Dvela-Levitt M, Melanson M et al. A High-Content Screen for Mucin-1-Reducing Compounds Identifies Fostamatinib as a Candidate for Rapid Repurposing for Acute Lung Injury. *Cell Reports Medicine*. 2020;1(8):100137.

26. Salerno J, Torquato T, Temerozo J, Goto-Silva L, Mendes M, Sacramento C *et al*. Inhibition of SARS-CoV-2 infection in human cardiomyocytes by targeting the Sigma-1 receptor disrupts cytoskeleton architecture and contractility. 2021.

PerkinElmer, Inc.
940 Winter Street
Waltham, MA 02451 USA
P: (800) 762-4000 or
(+1) 203-925-4602
www.perkinelmer.com

PerkinElmer®

235691 PKI