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Viewpoint

Early Returns on Small Molecule Therapeutics for SARS-CoV-2

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ABSTRACT: The COVID-19 pandemic has generated an unprecedented response within the scientific community. Extraordinary efforts have been undertaken to identify potential new therapeutics to treat SARS-CoV-2 infection spanning traditional medicinal chemistry, repurposing, and computational approaches. The breadth of the effort and rapid progression of many small molecules to clinical testing provide an opportunity to determine what chemical and testing approaches have been the most efficient in identifying potential treatments and how this may inform preparation for future pandemics.

INTRODUCTION

The COVID-19 pandemic is the most significant public health emergency in over a century. The outbreak rallied an unprecedented response from the global research community in both public and private sectors. One such effort was the Massachusetts Consortium on Pathogen Readiness (MassCPR), a 17 institution consortium incorporating the major research universities and medical schools in Massachusetts, as well as industry partners.[1] This Viewpoint focuses on emerging lessons from small molecule antiviral research on COVID-19, both from the MassCPR and a more general perspective. Specifically, how effective were early efforts to search for small molecule antivirals to treat COVID-19?

REPURPOSING AS A STARTING POINT FOR SMALL MOLECULE ANTIVIRALS FOR COVID-19 TREATMENT

At the outset of the pandemic, innumerable empirical and computational efforts were launched to determine if existing therapeutics could be useful in the treatment of COVID-19 (for reviews, see refs 2−5). The first empirical approaches focused on *in vitro* screening, using Vero E6 cells (monkey kidney), which are a viable substrate for infection. An initial small-scale screen focused on a handful of molecules with known antiviral properties. This study identified remdesivir, favipiravir, and chloroquine as having *in vitro* activity against SARS-CoV-2.[6]

Larger screens followed, expanding the molecules and mechanisms interrogated, most notably the screening of drug-like molecules from the 14000 compound RePHRAME library.[7] A handful of additional active molecules and mechanisms were identified, acting through both host and viral targets.

The most promising and consistent host target classes to emerge involve endosomal trafficking and viral entry. The FYVE-type zinc finger containing phosphoinositide kinase (PIKfyve) inhibitor apilimod has been reproducibly identified as a promising inhibitor of viral infection across numerous laboratories and testing systems.[7,8] The target was further supported by the efficacy of additional chemically distinct PIKfyve inhibitors and target deletion screens identifying both the target and the pathway as critical for viral replication.[9−11] Both apilimod[12] and PIKfyve inhibitors from Verge genomics[13] have proceeded to clinical trials.

A second class of molecules to emerge were cysteine protease inhibitors aimed at a number of targets (cathepsin B and K, calpain).[7] Mechanistic studies demonstrated that these molecules could function as antivirals, both as viral entry inhibitors via host protease inhibition and through direct inhibition of the viral main protease, M^{pro}. Characterization of the entry inhibitors suggested that multiple proteases can facilitate spike processing and viral entry.[14] The level of compound efficacy was cell line dependent, and combinations of inhibitors were required to completely suppressed replication.[7,14,15] This is an exemplar of the partial inhibition of replication commonly observed in repurposing screens, suggesting a target is involved in replication but is not essential.

PROTEASE INHIBITORS AS BROAD-SPECTRUM ANTIVIRALS

Protease inhibitors with appropriate inhibitory mechanisms also provided starting points for targeting the viral protease M^{pro}, a cysteine protease required for viral replication and assembly[16,17] (Figure 1). For example, the proteasome inhibitor MG-132 and calpain inhibitor calpeptin were demonstrated to be micromolar inhibitors of SARS-CoV-2 M^{pro}.[16] Serine protease inhibitors that employ an electrophilic warhead have also provided viable starting points for optimization. An example is the HCV NS3/4A inhibitor boceprevir.[16,18] The common feature for these molecules is less the initial viral or host target but rather that they are tri- or tetrapeptide mimetics containing an electrophile capable of interacting with the catalytic cysteine.

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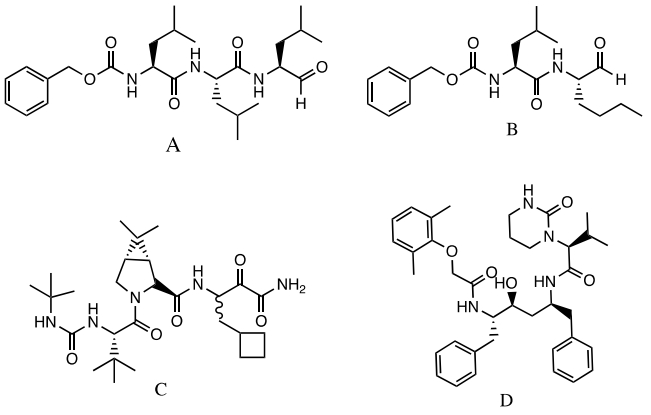

Figure 1. Comparison of structures of cysteine and serine protease inhibitors that have displayed cross reactivity with the SARS-CoV-2 M^{pro} with the HIV protease inhibitor lopinavir. (A) Proteasome inhibitor MG-132. (B) Calpain inhibitor calpeptin. (C) HCV NS3/4A inhibitor boceprivir. (D) HIV protease inhibitor lopinavir. All of the molecules are tri- or tetrapeptide mimetics, but lopinavir's "warhead" is the statin hydroxyl, a common hallmark of aspartyl protease inhibitors, and it lacks an aldehyde or diketoamide warhead seen in the other effective inhibitors.

The cleavage sites for the viral protease M^{pro} are highly conserved across coronaviruses, with a strong preference for A/VXLQS/A from P4−P1′.[19−21] This would argue that peptidomimetics based on the shared cleavage sequence could possess a spectrum of action across coronaviruses.[20] Emerging data suggest that this is indeed the case. The M^{pro} inhibitor GC-376, which was initially developed for treatment of feline coronavirus, demonstrated potent inhibition of the SARS-CoV-2 M^{pro} and activity against viral replication[16,22,23] (Figure 2). PF-

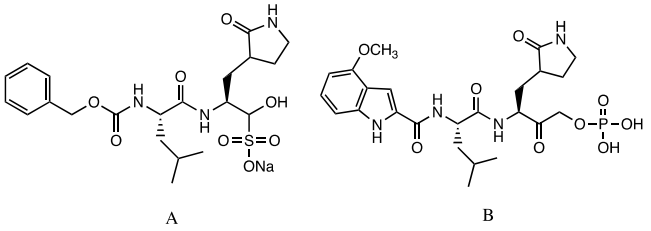

Figure 2. M^{pro} inhibitors that have displayed potent *in vitro* activity and proceeded toward clinical development: (A) GC-376; (B) PF-07304814. Both molecules are pro-drugged tripeptide aldehydes with demonstrated spectrum of action across other coronavirus encoded M^{pro} enzymes.

07304814, a molecule initially designed for treatment of SARS, also demonstrated potent activity against SARS-CoV-2[24] (Figure 2). Both molecules have progressed to clinical development and support the principle of designing molecules with broader antiviral activity by substrate mimicry.

NUCLEOSIDES AS BROAD-SPECTRUM ANTIVIRALS

Nucleoside analogues also employ this strategy and to date are the most promising therapeutic class of antivirals for treating COVID-19.[25−27] These molecules function as substrates for the viral polymerase, where their incorporation into the viral RNA strand can either lead to chain termination or drive accumulation of mutations in the viral genome, leaving replication inviable.[28−30] A number of nucleotide analogues have entered clinical trials for COVID-19 including remdesivir,[31] favipiravir,[32] molnupiravir,[33] sofosbivir,[23,34] azivudine,[35] and galidesivir[36] (Figure 3). Remdesivir is the first antiviral approved for treatment of SARS-CoV-2,[37] and well controlled studies suggest favipiravir may also be clinically active.[32] Similar to protease inhibitors, these molecules were originally designed for a variety of different viruses; hence the observed spectrum is derived from the substrate-like properties of the molecule, rather than the initial target virus. These data again support the value of molecules based on substrate mimicry and designed for broad viral spectrum in the face of a new viral outbreak.

LESSONS FROM THE EARLY EFFORT

The cumulative effort on small molecule discovery for SARS-CoV-2 provides a number of suggestions that will help facilitate rapid advancement of small molecule discovery for the current and future pandemics. In summary, they support the need to improve and diversify our *in vitro* testing capability as well as the chemical matter we screen.

Benchmarking of *in vitro* data is important for assessing a compound's viability for clinical development, in particular for repurposing.

- *In vitro* data are often reported as IC_{50} or EC_{50} for viral replication and CC_{50} (a dose 50% toxic to cells). It is likely that more complete suppression of viral replication (IC_{90} or greater) will be required for efficacy. Comparison of an IC_{90} to CC_{50} would provide a more relevant standard for addressing efficacy and *in vitro* tolerability.
- For repurposed molecules, *in vitro* potency should also be benchmarked against clinical exposure at the approved dose. This provides a better assessment of clinical viability. Quoted cellular potencies often far exceed achievable clinical exposures.[38] Reciprocally, favipiravir has a relatively weak 62 μM IC_{50} in Vero E6,[6] but multiples of this exposure can be achieved clinically.[39]
- Another important factor is compound efficacy: how completely does a molecule inhibit replication of SARS CoV-2. Partial inhibition is commonly observed and can serve as a first indication that the drug target is involved in supporting viral replication but not essential. The ability to achieve complete inhibition of replication is also a critical factor in compound viability.

Potency and efficacy vary by assay system and cell type.[7,40] Hence demonstration of potent, complete inhibition across several viral replication systems is an important step to ensure that activity is not cell line specific and that the molecule is more likely to be effective *in vivo*. This is a particular issue with host cell targeting and nucleoside analogues (which require host cell activation for efficacy). For example, remdesivir shows an IC_{90} of 3.5 μM in Vero E6 cells but 0.09 μM in Huh 7 cells.[27] Concerns have also been noted in the use of computational approaches to repurposing without supportive empirical data,[3] again arguing the need for broader access to well validated screening systems.

It is also clear that screening of molecules with a mechanistic rationale for functioning as antivirals has been the more efficient strategy for finding new molecules to target SARS-CoV-2 over random screening or broad repurposing screens.[41] Molecules designed to exploit common substrate characteristics for critical viral targets are fertile starting points to attack the next coronavirus and to date have been the only molecules with convincing clinical efficacy against SARS-CoV-2. Continuing to advance molecules against targets like M^{pro}, PL^{pro}, and the RNA-dependent RNA polymerase of SARS-CoV-2 with a spectrum of

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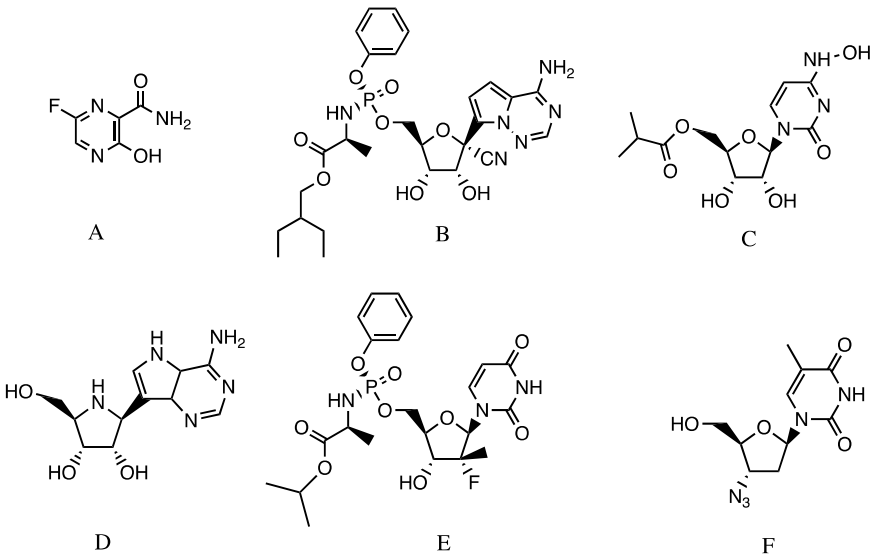

Figure 3. Nucleotide analogs that have proceeded to clinical trials or that have been approved for treatment of COVID-19. Structures of (A) favipiravir, (B) remdesivir, (C) molnupiravir (EIDD2801), (D) galidesivir, (E) sobosbivir, and (F) azivudine. While all of the molecules show *in vitro* activity, each requires different levels of cellular conversion to the active triphosphate. Remdesivir and sobosbivir are prodrugged monophosphates, molunpiravir is a prodrugged nucleoside, azivudine is a non-prodrugged nucleoside, and favipiravir is a modified pyrimidine base. Differences in the rate of conversion to the triphosphate by the host cell can lead to variability in antiviral potency of molecules depending on the cell line.

activity for other coronaviruses may be the most effective chemical strategy for future coronavirus outbreaks and a worthy investment in preparation for future outbreaks.

The MassCPR consortium aided early progress in COVID-19 research and provided some valuable lessons. Dedicated core resources (both enzyme and viral infection screening, expression of reagents such as high-quality spike protein, a system for sharing of clinical samples, a diagnostics accelerator to compare different emerging technologies) allowed multiple laboratories and companies to vet their approaches and more easily compare data between laboratories. Weekly calls across the 6 working groups (pathogenesis, diagnostics, vaccines, epidemiology, therapeutics, and clinical outcomes) encouraged an unprecedented level of collaboration and exchange of reagents, molecules, and approaches between multiple laboratories. Integration of industry partners working with or within the consortium also played a critical role in accelerating the pace and scope of discovery allowing for a number of venues for fundamental research to rapidly progress into development and fostered collaborative efforts in diagnostics, vaccines, and therapeutics. The crisis of COVID-19 would not allow business as usual, and a lesson for the future would be to employ the collaborative and business frameworks developed for COVID-19 at any future time where a crisis requires a unified scientific response.

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Notes

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