Editorial

Are there any Therapeutic Options Currently Available for Wuhan Coronavirus?

Coronaviruses (CoVs) of zoonotic origin are enveloped, positive-sense, single-stranded RNA viruses belonging to Coronaviridae. They are the causative agents of pandemics of respiratory infectious diseases with high mortality such as severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and, recently, the sadly famous viral pneumonia outbreak (labelled 2019-nCoV by The World Health Organization). This last pathogen has been fully genomically sequenced and share a high homology to SARS-CoV Tor2 and bat SARS-like coronavirus WIV1 [1]. It causes a severe respiratory illness like SARS and MERS, although it is considered clinically less pathogenic. The transmissibility of 2019-nCoV is still debated, but its human-to-human transmission has been demonstrated [2].

Since its spreading from Wuhan and other cities in China at the end of 2019, WHO established strict and sudden emergency procedures to limit the mortality rate and avoid the development of a global threat. Meanwhile, scientists enlarged their knowledge of 2019-nCoV pathogenicity and transmissibility starting from the sequencing of patient samples from bronchoalveolar lavage fluid and cultured isolates [3], analyzing these genomes phylogenetically and studying the likely receptor-binding properties of this "unknown" virus by homology modelling. Remarkably, homology modelling studies highlighted that 2019-nCoV possessed a receptor-binding domain structure similar to SARS-CoV, being varied by only some crucial, and it was also able to bind to the angiotensin converting enzyme 2 (ACE2) receptor such as SARS-CoV14. This protein could be used as a cellular entry receptor in humans, whereas other well-recognized coronavirus receptors (aminopeptidase N and dipeptidylpeptidase 4) were not involved in this mechanism [4]. More in detail, dipeptidylpeptidase 4 (DPP-4) has often been the main target of several inhibitors to prevent or treat human diseases [5].

This situation opened new scenarios in the field of Medicinal Chemistry as happened for Ebola and Zika viruses spread. Anti-viral agents, and in particular anti-influenza drugs, usually have specific biological stages or targets such as virus entry and uncoating, genetic material production and new viruses release from the infected cell. Considering the high infection rate and urgency to limit this diffusion, the first approach was based on testing the existing antiviral drugs effective in treating related viral infections or evaluating drugs approved for other pathologies (drug repositioning). One of the first studies explored the anti-viral efficacy of ribavirin, interferon, lopinavir-ritonavir, corticosteroids (used also against SARS or MERS), but the results were controversial. Successively, Wang et al. tested *in vitro* seven FDA-approved drugs (ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, remdesivir and favipiravir) against a clinical isolate of 2019-nCoV in order to assess virus yield and infection rates in infected Vero cells and against Vero E6 cells for determining the cytotoxic effect using CCK8 assay. In Table **1**, we collected all the information published on the concentrations useful to reduce the viral infection.

The best results were obtained with remdesivir and chloroquine. The former was shown to function as a stage post virus entry blocker, in agreement with its antiviral mechanism, inhibiting virus infection efficiently in human liver cancer Huh-7 cells, which are sensitive to 2019-nCoV. The latter is also known to limit virus infection by enhancing endosomal pH useful for virus-cell fusion and blocking the cellular receptor glycosylation in SARS-CoV. Chloroquine acted as both entry and post-entry stages blocker of infection in Vero E6 cells. These encouraging results in vitro, along with the knowledge of their pharmacokinetic/safety properties, must be developed in the design of related active compounds [6].

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Table 1. Drugs (small molecules) tested against a clinical isolate of 2019-nCoV.

Drug Candidate	Drug Classification	EC_{50}	CC_{50}	Selectivity Index (SI)	Further Information
Ribavirin	Nucleoside analog	109.50 μM	>400 μM	>3.65	
Penciclovir	Nucleoside analog	95.96 μM	>400 μM	>4.17	
Favipiravir	Nucleoside analog	61.88 μM	>400 μM	>6.46	Effective in protecting mice against *Ebola* virus
Nafamostat	Membrane fusion blocker	22.50 μM	>100 μM	>4.44	Potent inhibitor of MERS-CoV
Nitazoxanide	Antiprotozoal agent	2.12 μM	>35.53 μM	>16.76	Wide antiviral potential against viruses including human and animal coronaviruses
Remdesivir	Adenosine analogue	0.77 μM (EC_{90} = 1.76 μM)	>100 μM	>129.87	Promising antiviral drug against RNA viruses (including SARS/MERS-CoV5 and Ebola) in cultured cells, mice and non-human primate models
Chloroquine	Antimalarial agent	1.13 μM (EC_{90} = 6.90 μM)	>100 μM	>88.50	Has an immune-modulating activity

Moreover, another research group designed and produced a pan-CoV fusion inhibitor, namely EK1 peptide, capable of blocking the infection of five human coronaviruses (SARS-CoV and MERS-CoV, and three bat-SL-CoVs) after intranasal administration before or after viral challenge. This result could pave the way to a potential prophylactic and therapeutic effect also against 2019-nCoV. On the other hand, there is no specific antiviral treatment or vaccine based on biotechnologically produced macromolecules. The first tentative, to boost up the vaccine development, took advantage of the relatively high homology of receptor binding domain (RBD) in 2019-nCoV and SARS-CoV. Researchers exploited the putative cross-reactivity exerted by CR3022, a SARS-CoV-specific human monoclonal antibody, able to bind to 2019-nCoV RBD. Interestingly, its epitope did not overlap with the ACE2 binding site within 2019-nCoV RBD (S1 subunit of S protein), because other potent SARS-CoV-specific antibodies targeting the ACE2 binding site of SARS-CoV, failed to bind to 2019-nCoV spike protein [7]. Therefore, the 2019-nCoV S-RBD must be considered a key target for developing 2019-nCoV neutralizing mAbs, keeping in mind that neutralizing mAbs targeting non-RBD regions (such as NTD and S2 of SARS-CoV and MERS-CoV) have minor neutralizing potency than that of RBD-specific mAbs [8].

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