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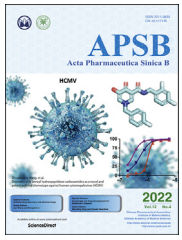

Editorial of Special Column on Antiviral Drug Discovery and Pharmacology

The COVID-19 pandemic is an overdue reminder of the urgent need for antivirals. Development of antiviral drugs has been historically neglected compared to those for other diseases, including cancer, neurodegeneration diseases, inflammatory diseases and others. Retrospectively, if the 2003 SARS-CoV-1 had raised the alarm of the need for vaccines and antivirals against coronaviruses, we would have been in a much better position fighting against the SARS-CoV-2. Current FDA-approved antivirals only target a small number of viruses that are known to infect human[1]. Unfortunately, there is currently no vaccines or antivirals for many viruses that have pandemic potential or are known to cause severe diseases, such as enterovirus A71 and D68, Zika virus (ZIKV), Nipah virus, Ebola, Marburg, and Lassa Fever virus. Furthermore, viruses continuously mutate either naturally or under drug selection pressure. As such, newer generation of antivirals with novel mechanisms of action are also needed to combat drug resistance. The therapeutic benefits of antivirals have been undoubtably demonstrated by HIV antivirals, which turned a once terminal disease into a chronic yet manageable disease[2], and by the SARS-CoV-2 antivirals including remdesivir, molnupiravir, and PAXLOVID, which have proven effective in preventing severe symptoms and reducing mortality rates[3-6].

The special column of "Antiviral Drug Discovery and Pharmacology" is organized with the aim of attracting public attention on small molecule antivirals. This issue covers some of the most significant viruses including SARS-CoV-2[7-10], enterovirus A71[11], ZIKV[12], human cytomegalovirus (HCMV)[13], and human immunodeficiency virus (HIV)[14]. Xiang et al.[7] presented a comprehensive review of the current landscape of the SARS-CoV-2 antivirals against virus fusion, against essential viral enzymes such as main protease, papain-like protease, RNA-dependent RNA polymerase (RdRp), and helicase, and against the host factors including ACE2, TMPRSS2, and cathepsins. Zhou et al.[8] reported the optimization of fusion inhibitors targeting the SARS-CoV-2 spike protein. The dePEGylated lipopeptide, EKL1C, had potent activity against SARS-CoV-2 and its variants. Significantly, EKL1C was effective in reducing the SARS-CoV-2 viral titers in the infected hACE2-Tg mice when dosed either before or after viral infection. Aliyari et al.[10] identified a pro-viral host factor of SARS-CoV-2, the fatty acid synthase (FASN). FASN is involved in lipid metabolism. Overexpression of FASN increased viral replication while down-regulation by knockdown or knockout of FASN reduced infection, suggesting FASN might be a host antiviral drug target. Indeed, FASN inhibitors such as C75 (4-methylene-2-octyl-5-oxotetra-hydrofuran-3-carboxylic acid) inhibited a number of viruses, including SARS-CoV-2 and its variants. Ma et al.[9] conducted a systematic validation of the reported main protease inhibitors using a consortium of biochemical and cell-based assays including the Flip-GFP, Protease-Glo, FRET, and thermal shift assays. The main protease is a validated drug target; and structurally disparate compounds have been reported as main protease inhibitors[15]. However, their mechanisms of action remain debatable. Moreover, there is a lack of understanding of their target specificity in cellular engagement[16−19]. The results presented by Ma et al. are expected to clarify the confusion within the scientific community, so that medicinal chemists can focus their efforts on the hits with translational potential. Enteroviruses A71 and D68 are common viruses that mainly infect children and cause respiratory diseases[20,21]. However, contemporary EV-A71 and EV-D68 have both been reported to cause neurological complications such as acute flaccid myelitis. Despite many years of intensive research, there is no vaccine or antiviral for these viruses. To mitigate that deficiency, Wang et al.[11] summarized the current landscape of antiviral drug discovery targeting EV-A71 and discussed the knowledge gaps that need to be filled to advance the drug candidates to clinic. ZIKA virus is a known neurotropic pathogen for which there is no vaccine or antiviral. Following their previous discovery of erythrosine B as a ZIKV NS2B−NS3 serine protease inhibitor[22], Li et al.[12] reported the *in vivo* antiviral efficacy of erythrosine B against ZIKV infection in mice when given by oral gavage. Erythrosine B is an FDA-approved food additive, so the demonstration of its *in vivo* antiviral efficacy is significant. To address the toxicity and drug resistance issues of current HCMV antivirals, Senaweera et al.[13] reported the lead optimization of a series of *N*-benzyl hydroxypyridone carboxamide analogues as HCMV antivirals, and several leads were identified with sub-micromolar potency and favorable absorption, distribution, metabolism and excretion (ADME) properties. Lastly, Li et al.[14] summarized the development of HIV reverse transcriptase inhibitors in the past decade and

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shared the insights of the requirements of the next generation of antiretroviral inhibitors.

This special column comprises reviews, research articles on lead optimization of small molecules and peptide-based drugs, pharmacokinetic optimization, assay developments, hit validation, and *in vivo* animal model studies. The results presented represent significant advancement in the field. We sincerely appreciate the contributions from participating research groups, reviewers, and journal editors.

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