Technology Offer

Ref.-No. M09/21

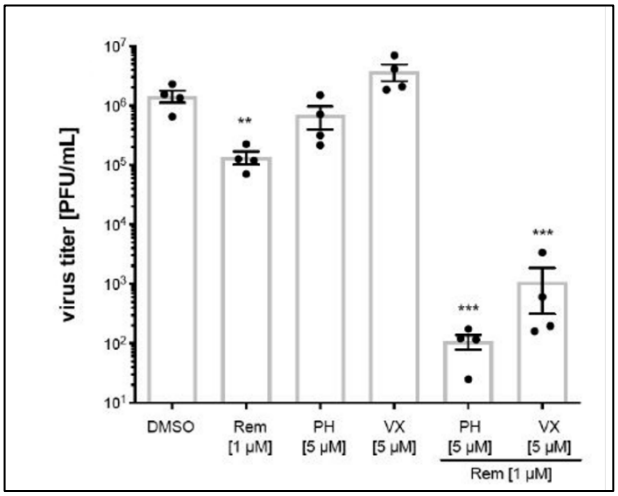
p38-inhibitors for the treatment of coronavirus infections and/or COVID-19 cytokine storm

Introduction

The newly emerged pandemic SARS-CoV-2 virus is the etiological agent of COVID-19, a severe respiratory disease accompanied by pneumonia and systemic inflammation. So far, SARS-CoV-2 has infected more than 750 million individuals worldwide and caused more than 6.8 million deaths (WHO, February 2023). Despite the recent availability of efficient SARS-CoV-2 vaccines, the number of viral infections and individuals requiring intensive clinical care remains high, which leads to an extraordinary burden of the national health care systems.
The development of new therapeutic options and identification of repurposed drugs that reduce the disease burden and high lethality of COVID-19 by inhibiting viral replication and rebalancing of the dysregulated immune response is of highest priority.

Invention

We provide a p38 inhibitor for the treatment of COVID-19, which is administered in combination with a ribonucleoside analog, preferably selected from the group consisting of Remdesivir (GS-5734), GS-441524 monophosphate, GS-441524 triphosphate, Sofosbuvir, Ribavirin, Favipiravir or Molnupiravir. Surprisingly, it was found that the combination of the p38 inhibitors with Remdesivir reduced SARS-CoV-2 viral titers 100-fold more efficiently *in vitro* compared to the treatment with Remdesivir alone. This was unexpected as p38 inhibitors alone do not significantly reduce the viral load. In addition, there is evidence that p38 inhibitors are able to decrease inflammatory cytokine expression, which plays a significant role in the COVID-19 cytokine storm and the transition from Stage II to Stage III COVID-19 disease severity.



To assess the degree of drug synergism between p38 inhibitor PH-797804 and Remdesivir to reduce viral titers of SARS-CoV-2 a titration matrix using the drug concentrations shown in Figure 1 (Remdesivir (Rem), PH-797804 (PH), VX-702 (VX) and a combination of Remdesivir (Rem) with PH-797804 (PH) or VX-702 (VX)) was performed and titers were determined by plaque assay.

Advantages of the invention

- the dual mechanism provided by p38 inhibition and viral inhibition through the synergistic effect with a ribonucleoside analog can prevent progressing into Stage III and therefore decrease severe disease outcome and mortality.

Patent situation

A PCT patent application has been filed.

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