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Zapnometinib – A MEK1/2-inhibitor with broad anti-SARS-CoV-2 activity, synergistic potential and a reduced risk of resistance introduction

Inhalt

Infections with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause coronavirus disease 2019 (COVID-19) with devastating consequences especially for high-risk patients. We could show that SARS-CoV-2 transiently activates the Raf/MEK/ERK pathway in the very early phase of the infection. Specific inhibition of the MEK1/2 kinases with the inhibitor ATR-002, now designated as Zapnometinib (ZMN), in single treatment scenarios as well as in combination with direct-acting antiviral drugs (DAAs), such as the nucleoside inhibitors Remdesivir, Molnupiravir, and the 3C-like protease inhibitors Nirmatrelvir and Ritonavir (Paxlovid), led to significantly reduced SARS-CoV-2 titers in different cell culture models and showed synergistic effects during the combinatory treatment. Additionally, ZMN diminished SARS-CoV-2-induced expression of pro-inflammatory cytokines, which is associated with hyperinflammation during COVID-19 progression. Serial passaging of the virus in the presents of ZMN or DAAs to force reduced drug susceptibilities showed no effect on ZMN passaged viruses, while the DAAs forced the virus to develop resistance introducing mutations. These data suggested the Raf/MEK/ERK signaling cascade as a druggable target for an anti-SARS-CoV-2 therapy and ZMN as a suitable drug for single and combinational treatment strategies with a very low risk of resistances.

Keywords

Raf/MEK/ERK; SARS-CoV-2; Zapnometinib; Drug synergy; Drug resistance

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No, I am not a Junior Scientist.

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