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# Synergistically targeting pyrimidine metabolism and RNA integrity for the treatment of respiratory diseases caused by zoonotic influenza A viruses

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The zoonotic potential of this virus has been highlighted by recent transmission events of avian influenza viruses (AIV) circulating in wild and domestic birds to different mammalian species, and sporadic transmissions of swine influenza viruses (SIV) to humans. High mutation rates and reassortment of the segmented influenza viruses require yearly updates of human vaccines. In addition, rising levels of viral resistance affect therapeutic efforts for humans suffering from severe respiratory symptoms. To counteract this pathogen, we are exploiting antiviral drug combinations that not only rely on viral targets, but also on host factors. We have therefore combined a nucleoside analogue, N4-hydroxycytidine (NHC; active compound of Molnupiravir), with a pyrimidine synthesis inhibitor targeting the enzyme dihydroorotate dehydrogenase (DHODH), to achieve exquisite synergy against virus propagation. AIVs of H5 subtypes as well as different SIVs have been tested in vitro for their sensitivity against different drug combinations. So far, we found all tested strains to be sensitive to drug treatments at varying degrees. To further analyze this drug efficiency in vivo, animal trials in the ferret and swine model are planned. In conclusion, our approach may lead to the development of drugs that are effective against influenza A viruses with a low susceptibility to the development of viral resistance, and are therefore encouraging in terms of preparedness for future influenza pandemics.

## Keywords

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## Professional Status of the Speaker

Postdoc

## Junior Scientist Status

No, I am not a Junior Scientist.

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