Inhibitors of viral macrodomains as new broad-spectrum antiviral drugs (MACROVIR)

Initiative: Innovative Ansätze in der antiviralen Wirkstoffentwicklung

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Human innate defense mechanisms against viruses include poly-ADP-ribose polymerases (PARPs) that covalently attach ADP-ribose to virus proteins, inactivating them and thus preventing viral replication. Several RNA virus families (including Hepeviridae, Irinoviridae, Coronaviridae and others) possess conserved macrodomain proteins that have evolved to evade this human innate immune response: They carry an enzymatic activity that removes ADP-ribose from proteins and can prevent the infected cells' "call for help". The goal of the project is to discover and optimize orally available antiviral compounds that target the catalytic activity of viral macrodomains to strengthen human innate antiviral immunity. The project team will generate a "plug-and-play" assay platform for a broad range of macrodomains. It is planned to expand and further optimize existing lead series of SARS-CoV-2 nsp3 macrodomain inhibitors to target other viral macrodomains such as those of HEV and selected alphaviruses. Furthermore, additional chemotypes targeting HEV and alphaviruses will be explored using a combination of chemoinformatics and screening approaches. Compounds will be characterized in established in vitro and in vivo viral infection models. Importantly, macrodomain inhibition is expected to be complementary to known antiviral mechanisms such as viral protease or polymerase inhibition, allowing combination therapy to strengthen efficacy and avoid mutational escape.

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