

Conserved RNA elements as novel drug targets for antiviral therapy (Target-RNAantiV)

Initiative: Innovative Ansätze in der antiviralen Wirkstoffentwicklung

Bewilligung: 21.06.2021

Laufzeit:

The aim of this project is to develop novel low molecular weight inhibitors targeting essential regulatory RNA elements in the genome of SARS-CoV-2. Based on preliminary work, with all 15 RNA regulatory elements made available, their NMR spectra assigned, NMR-based fragment screens against all 15 RNAs performed, and biological assays (including S3 conditions) established, the project team will first focus on targeting the RNA pseudoknot element that induces -1 ribosomal frameshifting to toggle between expression of ORF1a and ORF1b. The researchers identified three lead compounds that bind the pseudoknot and inhibited frameshifting with μM affinities and efficacies, and determined their binding epitope by NMR spectroscopy. This approach will be extended to target the attenuator sequence adjacent to the pseudoknot and also selected RNA elements from the 5'-untranslated region particularly involved in regulation of translation of viral proteins. Further development of initial lead compounds relies on convergent synthesis strategies, their testing in biological assays and use as benchmark compounds in sophisticated 3D in vitro models of the human lung. Promising drug candidates will be tested in these assays and drug-loaded aerosol formulations will be developed, allowing potential translation for therapy development. Progress in the project is published immediately on www.covid19-nmr.de, including available resources, primary data, and publications.

Projektbeteiligte

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1H, 13C and 15N assignment of stem-loop SL1 from the 5'-UTR of SARS-CoV-2