Investigating the druggability of SARS-CoV-2 nucleocapsid protein RNA interactions

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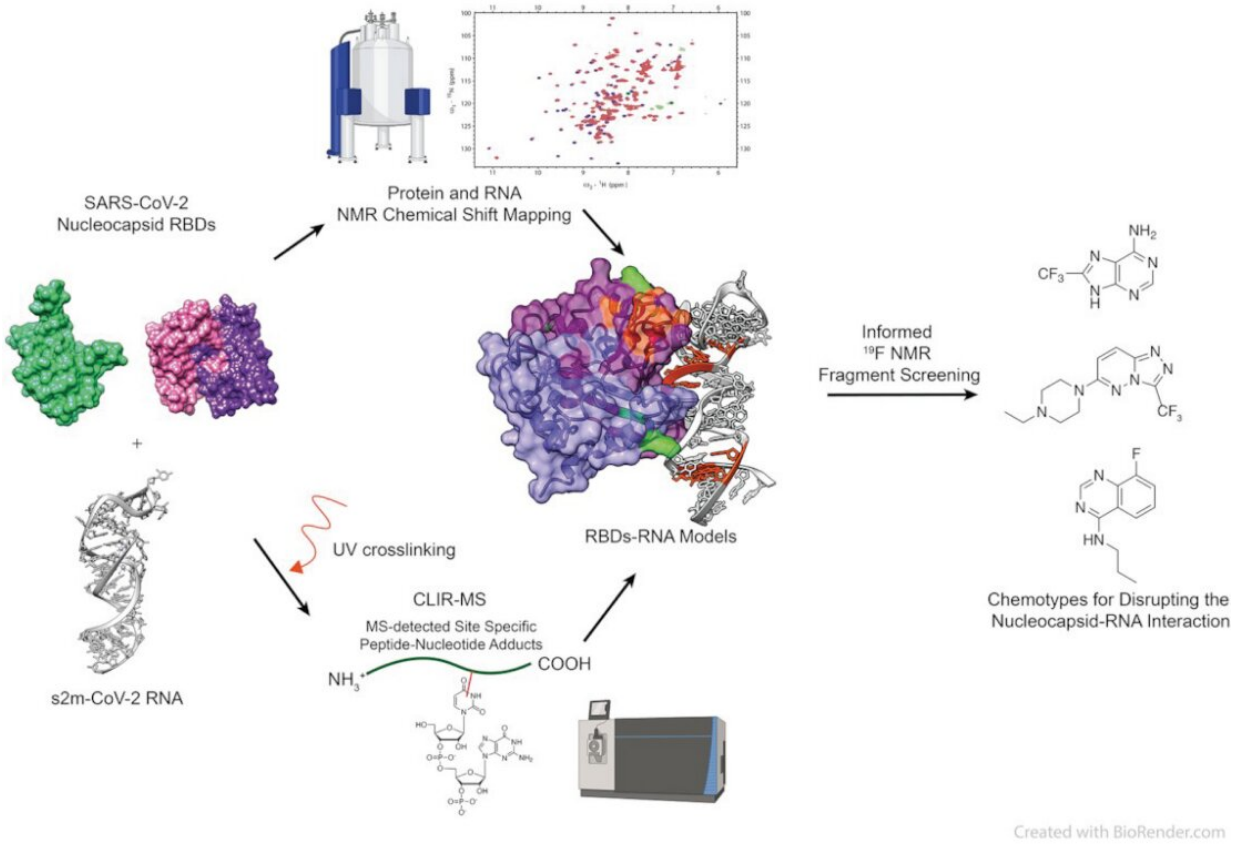

A hybrid structure determination approach elucidates the interaction between the RNA binding domains of SARS-CoV-2 nucleocapsid and RNA, and informs a fragment screening to identify promising molecular scaffolds for drug development. Credit: *Nucleic Acids Research* (2023). DOI: 10.1093/nar/gkad195

The Allain (IBC), Gossert (BNSP) and Leitner (IMSB) groups investigated the druggability of the SARS-CoV-2 Nucleocapsid protein RNA interactions by a hybrid structure determination approach, which led to the identification of primary fragment hits. Their findings were published in *Nucleic Acids Research*.

Besides effective vaccines, antiviral compounds represent a fundamental approach to combat viral diseases. The D-BIOL groups led by Frédéric Allain, Alvar Gossert and Alexander Leitner investigated whether the interactions between the SARS-CoV-2 nucleocapsid protein, which possesses two known RNA binding domains, and the sm2 RNA located in the 3'UTR of the SARS-CoV-2 RNA could be druggable.

They opted for a hybrid structural approach based on solution NMR experiments and crosslinking MS to obtain structural information on these complexes rapidly. This information was then used to generate restraints to build models of the complexes of the sm2 RNA and the two RNA binding domains of the nucleocapsid protein, for which the unbound structures were solved previously. This approach resulted in the first model of how one of the RNA binding domains interacts with RNA and expanded the knowledge on the other RNA binding domain.

Then an NMR-based fragments screen was used to identify compounds binding to either one of the two protein domains or the RNA in isolation. From these compounds, the ones were selected that bind to the interaction interface of the respective molecules, which were known from the hybrid structural approach models. Overall, the experiments revealed that these protein RNA interactions seem druggable. Therefore, the identified compounds provide the basis to develop more potent molecules inhibiting these protein-RNA interactions.

More information: Giacomo Padroni et al, A hybrid structure determination approach to investigate the druggability of the

nucleocapsid protein of SARS-CoV-2, *Nucleic Acids Research* (2023). DOI: 10.1093/nar/gkad195

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