Targeting Non-native Protein–protein Interactions of Nucleocapsid Proteins for Drug Discovery Against Coronavirus

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Abstract

The COVID-19 pandemic has afflicted over 31 million people and caused the death of about 1 million individuals worldwide. Our group has recently found a novel non-native protein-protein interaction (PPI) between nucleocapsid (N) protein dimers of MERS-CoV. Formation of the PPI inactivates the N protein by occluding its essential RNA-binding site but requires the presence of a "glue" molecule to stabilize the non-native contacts. The shape of the non-native PPI interface is highly conserved among other coronaviruses, making it a potential target for broad-spectrum antiviral screening that may also be effective against SARS-CoV-2. We identified 5-benzyloxygramine (P3) as a new N protein PPI orthosteric stabilizer that displays both antiviral and N protein-stabilizing activities. X-ray crystallography and small-angle X-ray scattering showed that P3 stabilizes the N-NTD dimers through simultaneous hydrophobic interactions with both partners, resulting in atypical N protein oligomerization that was further confirmed in the cell. Preliminary in vitro studies showed that P3 was effective across MERS-CoV, SARS-CoV and mouse hepatitis virus, and early studies assessing its efficacy against SARS-CoV-2 appear to yield promising results. Elucidation of other non-native PPIs among coronaviral proteins may contribute additional non-canonical targets for drug development.

Keywords –coronavirus, drug discovery, non-native PPI, PPI orthosteric stabilizer

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