NSP14/10 Complex Inhibitors for the Treatment of SARS-CoV-2 and Pan-Coronavirus Infections

Innovative and efficacious therapeutic to treat current and future pan-coronavirus infections

Technology Overview

This invention pertains to novel, small-molecule NSP14/10 complex inhibitors for the treatment of SARS-CoV-2 and pan-coronavirus infections. As described in *Rona et al. Nature CDD 2021*, the inventors designed and leveraged an innovative screening assay using fluorescent FRET oligonucleotide pairs (patent-pending tech) to identify small molecules capable of inhibiting NSP14 ExoN activity *in vitro*. The identified HIT candidates (10 compounds) displayed potent inhibition of NSP14 EXoN activity (low micromolar IC_{50} values) and showed synergistic neutralization of SARS-CoV-2 (in combination with Remesdivir) in A549 cells expressing ACE2. A similar synergistic antiviral effect was also observed in the Coronavirus homolog HCoV-OC43, demonstrating the broad applicability of these NSP14 ExoN inhibitors as pan-CoV antivirals.

Background

NSP14 is a strictly conserved protein among Coronaviruses (and other Nidoviruses) that harbors proofreading ExoN activity. NSP14 binds to NSP10, an allosteric activator that greatly enhances its activity. NSP14 is required for viral genome integrity by functioning to offset the relatively low fidelity of viral RNA-dependent RNA-polymerase (RdRP) enzymes. Mutations in the ExoN catalytic site of NSP14 generally result in lowered viral viability (SARS-CoV) or complete loss of viral replication (MERS-CoV), depending on the strain. Additionally, loss of NSP14 catalytic activity sensitizes the virus toward inhibitory base analogues or their prodrugs. Therefore, small molecule inhibitors of the NSP14-NSP10 complex are expected to be efficacious pan-CoV therapeutics, either alone, or in combination with RNA base analogs or prodrugs.

Application

Treatment of SARS-CoV-2 infections, as well as other viral infections caused by Coronaviruses and Nidoviruses

Advantages

- **Strictly-conserved target**: NSP14 is strictly-conserved across Coronaviruses and other Nidoviruses.
- **Lead compounds are potent exonuclease inhibitors:** Identified HIT compounds inhibit NSP14 exonuclease activity with low micromolar IC_{50} values.
- **Lead compounds show synergistic pan-COV antiviral activity with Remdesivir** (FDA-approved nucleoside base analog).

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Category

COVID-19

Life Sciences/Biochemicals & Small Molecules

Life Sciences/Therapeutics/Infectious Disease/Coronavirus

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Intellectual Property

A US non-provisional patent application has been filed covering the screen methodology, the identified NSP14 inhibitors, and the method of using such inhibitors.

References

1. Michele Pagano, MD, et al. , https://pubmed.ncbi.nlm.nih.gov/34862481/