Cleveland Clinic Innovations

Antisense Oligonucleotide Therapy Targeting SARS/Sarbecovirus Conserved Viral Motif

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PRODUCT
Peptide-conjugated phosphorodiamidate morpholine oligonucleotide (PPMO) for antiviral treatment

INDICATION
Sarbecovirus infections including SARS, MERS, and related viruses

VALUE PROPOSITION
- PPMOs target a novel, non-coding RNA region that is critical for viral replication
- The targeted "SPEAR" element is conserved across all coronaviruses
- Treatment option ready "off-the-shelf" for emerging pandemics
- Pending patent claims both methods and compositions for SPEAR inhibition

DEVELOPMENT STAGE
Proof-of-concept *in vitro*; *in vivo* studies underway

INTELLECTUAL PROPERTY
Provisional patent filed

RELATED PUBLICATIONS
Khan D. *et al*., *Nat. Com.* 2023, Jun 9;14(1): 3385. PMID: 37296097.

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UNMET NEED
Both the COVID19-causing virus SARS-CoV-2 and the near-pandemic virus SARS-CoV-1 are highly transmissible and deadly ssRNA coronaviruses from the sarbecovirus sub-genus. The discovery of effective vaccines and small molecule antivirals has greatly reduced the burden of SARS-CoV-2—however, the emergence of treatment resistant SARS-CoV-2 variants and/or novel sarbecoviruses remains an ever-present danger. Developing new therapeutics against unique molecular targets, especially those conserved across all sarbecoviruses, reduces the risk of future pandemics and allows "off-the-shelf" weapons to neutralize emerging threats.

SOLUTION
Researchers at Cleveland Clinic have identified a previously uncharacterized, non-coding "SPEAR" (EPRS1-binding sarbecoviral pan-end activating RNA) motif located at the 3' end of the genome of all sarbecoviruses that co-opts a defined host protein complex to enhance viral fitness. Researchers have developed two different cell-penetrating anti-sense oligos (PPMOs) that silence the SARS-CoV-2 SPEAR motif, reduce viral titers, slow viral replication kinetics, and decrease viral RNA levels *in vitro* (Figure 1). Research in the Fox lab suggests that the SPEAR element defines a novel, non-protein therapeutic target that is conserved across sarbecoviruses and likely acts as a generic viral transcriptional regulator, opening the possibility for pan-sarbecovirus therapeutic efficacy with SPEAR inhibitors. Our 3'-conjugated PPMOs, which are conceptually like siRNA but do not require nanoparticle encapsulation for cell entry, is one of the first reported proof-of-concept therapeutic approach that targets this unique viral vulnerability.

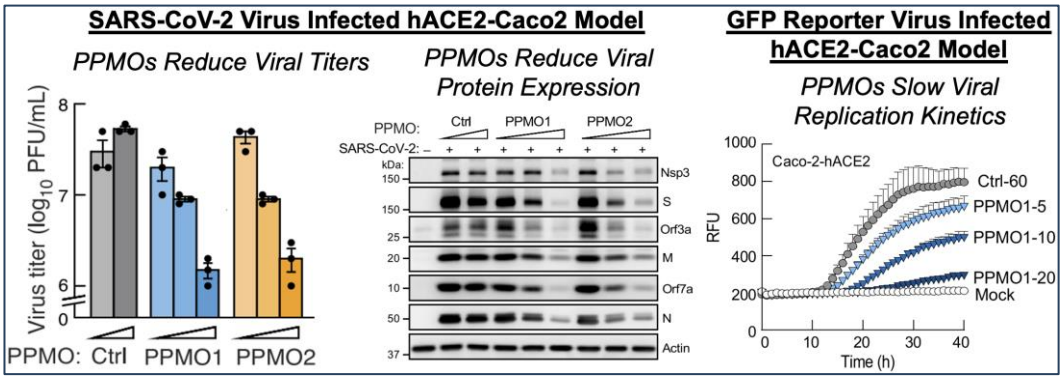

Fig 1: Proof-of-concept data validating PPMO efficacy