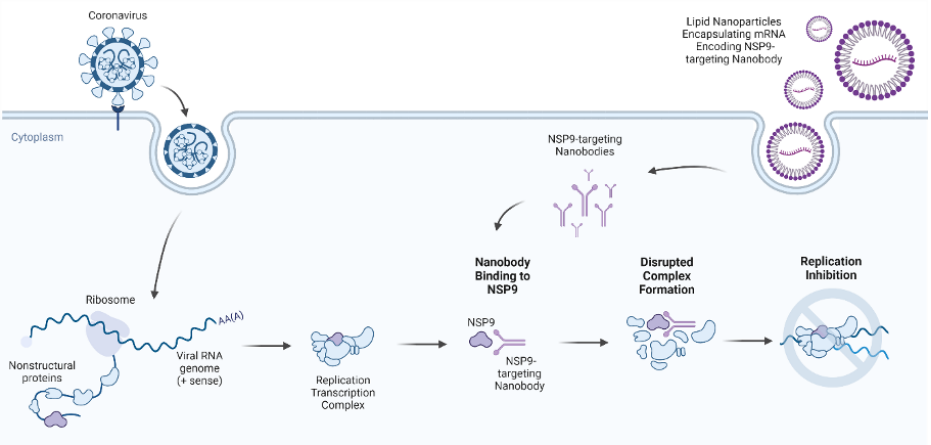
Nanobodies Targeting SARS-CoV-2 NSP9 for COVID Treatment



Technology ID

PER03-04

Category

Life Sciences/Therapeutics/Infectious Disease/Coronavirus

Doug Brawley

Authors

Piergiorgio Percipalle, PhD

Learn more

Unmet Need

Innovative and efficacious pan-coronavirus antiviral treatments.

Technology

The Percipalle Lab at NYU Abu Dhabi have generated and characterized nanobodies that specifically target SARS-CoV-2 nonstructural protein 9 (NSP9) for the treatment and prevention of COVID (see schematic). As described in Esposito et. al., Advanced Biology 2021, two lead nanobody clones were selected from an initial panel of 136 clones generated from a camelid immunization series using recombinant SARS-CoV-2 NSP9. In proof-of-concept studies these clones were demonstrated to effectively bind to (1) purified recombinant NSP9 and (2) endogenous NSP9 from SARS-CoV-2 positive patient saliva samples. Additionally, structural studies using nuclear magnetic resonance (NMR) spectroscopy revealed the interaction interface between the lead nanobody clones and NSP9, and showed that these nanobodies stabilize a tetrameric form of NSP9 preventing it from forming a functional viral replication transcription complex (RTC). Further, in new unpublished work, one of the lead clones was found to block NSP9-mediated SARS-CoV-2 replication when delivered in nucleotide format (mRNA) using lipid nanoparticles (LNPs). Lastly, using LNP-mediated mRNA delivery, this clone was able to inhibit replication of multiple SARS-CoV-2 variants (Wuhan, Omicron, B1-621, B1-617, and UK strains) suggesting applicability as a pan-coronavirus therapeutic.

Background

Coronaviruses are well regarded as pandemic-potential pathogens, which has been exemplified by the current COVID-19 pandemic. While vaccines and antiviral treatments are now available for SARS-CoV-2, the occurrence of viral variants which are resistant to these treatments has

highlighted the need for more robust and diversified therapeutic options. Antiviral therapeutics which can universally target all coronavirus strains are of great importance as they may confer protection against future coronavirus variants. Targeting of the SARS-CoV-2 NSP9 protein, which is highly conserved among all coronaviruses and is critical for RTC-mediated viral replication, is an attractive pan-coronavirus antiviral therapeutic approach. Nanobodies, which are recombinant variable domains of heavy-chain-only antibodies, possess many unique properties (small size, excellent solubility, superior stability) making them a particularly attractive therapeutic modalities for targeting NSP9.

Advantages

- Targets a critical pan-coronavirus replication mechanism: NSP9 is strictly conserved across coronaviruses.
- Well-characterized target: The structure and function of NSP9 is known.
- Antibody-based therapeutic: Nanobodies possess many favorable attributes, such as affinity, specificity, and modes of delivery.
- Cell penetrant: Lipid nanoparticles (LNPs) can deliver anti-NSP9 nanobody mRNA into cells for expression.
- Potential synergy with other approved coronavirus antivirals in a combined therapy
- Prophylactic administration: Anti-NSP9 nanobodies (or LNPs containing mRNA encoding such) could be given to at-risk individuals prior to infection.

Application

Passive and prophylactic treatment of SARS-CoV-2 infections, as well as other viral infections caused by coronavirus variants.

Proof-of-Concept Studies

NMR-Based Analysis of Nanobodies to SARSCoV- 2 NSP9 Reveals a Possible Antiviral Strategy Against COVID-19

https://pubmed.ncbi.nlm.nih.gov/34705339/

IP Status

NYU has filed a PCT application covering composition and method of use.

References

1. Percipalle, et al. , https://pubmed.ncbi.nlm.nih.gov/34705339/