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# COVID-19 treatment through RNA interference

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## Introduction

Small interfering or short interfering RNA (siRNA), also known as silencing RNA, are double stranded non-coding ribonucleic acid molecules. siRNA is about 20-25 base pairs in length; hence termed as short/ small interfering RNA [1]. siRNAs are responsible for gene silencing, and follows the phenomenon of RNAi. Various Cancers, viral and genetic diseases have previously been treated with siRNA-based therapeutics [2]. An enzyme called Dicer, cleaves siRNA that leads to the formation of a complex called RISCs resulting into sense and anti –sense strand. The sense strand is cleaved by Argonaute 2 protein while the antisense strand is guided by RISCs complementary toward target mRNA, causing downregulation of target gene (destruction of target mRNA) [3]. Novel corona virus (nCoV-19), also called severe acute respiratory syndrome viruse-2 (SARS-CoV-2) was first originated from Wuhan (China) in December 2019. The city was lock downed and the entire world was alarmed about the novel health consequences of the virus [4]. The world health organization (WHO) declared the nCoV-19 as a global and public health emergency on 30th of January, 2020 [5]. The latest situation shown by world health organization on 25 May 2020, revealed the existence of more than 5304772 confirmed and 342029 death cases across the globe, while 84536 confirmed and 4645 death cases in China [6]. In this situation, several drugs such as antiviral (remdesivir, lopinavir, ritonavir and favipiravir), antimalarial i.e., hydroxychloroquine and anticancer agents like interferon -alpha 2b are under clinical trials. These drug candidates are expected to prove their full pledge efficacy [7]. However, based on previous performance in combating SARS and MERS, siRNA-based treatment can be the effective one against COVID-19 [8]. Among all the RNA viruses, SARS-CoV-2 has the largest size of viral genome about 29 kb. The identified small interfering RNAs in case of SARS has successfully targeted the nucleotide sequence of amino acid for viral RNA- polymerases, helicases, nucleoprotein N, and proteolytic enzymes. It resulted in the termination of the viral mRNA and a subsequent decrease in viral load of 50, 70, 90 and 95%, respectively for polymerase, helicase, proteolytic enzymes and nucleoprotein N [9]. The genomic composition of the COVID-19 shows that, two largest open reading frames (ORFs) at 5′ UTR exists i.e. ORF1a and ORF1b (Figure 1). These frames are further translated by ribosomes into a single large polyprotein following a frame shift event.

**Keywords:** Covid-19, siRNA, SARS-CoV-2 , proteolytic enzymes, open reading frames, viral RNA-polymerases.

The ORF1a is of prime importance and is further composed of 3-chymotripsin like protease (nsp5) and nsp3 (papain like protease). Within the viral proteases the sequence encoded for nsp3 is less conserved while the sequence coded for nsp5 appears to be more conserved [7, 10]. Until now, protease has been found to be a key drug target side for clinical trials, in the same way for the sequence coding nsp5 (highly conserved site) can be considered an effective target for the siRNA-based therapeutics. Apart from it, the ORF1b is composed of Rd-Rp (RNA dependent RNA polymerase), lies between 13 to 16kbp within viral genome and then stretch downward up to 18kbp being identified the coding site for helicase. These two sites were found highly conserved in case of SARS and MERS [11]. It is obvious that due to similarity in viral genome of COVID-19 with previous version of viruses, these two sites are considered to be the potential targets for the RNA interferences and ultimately siRNA-based therapeutics.

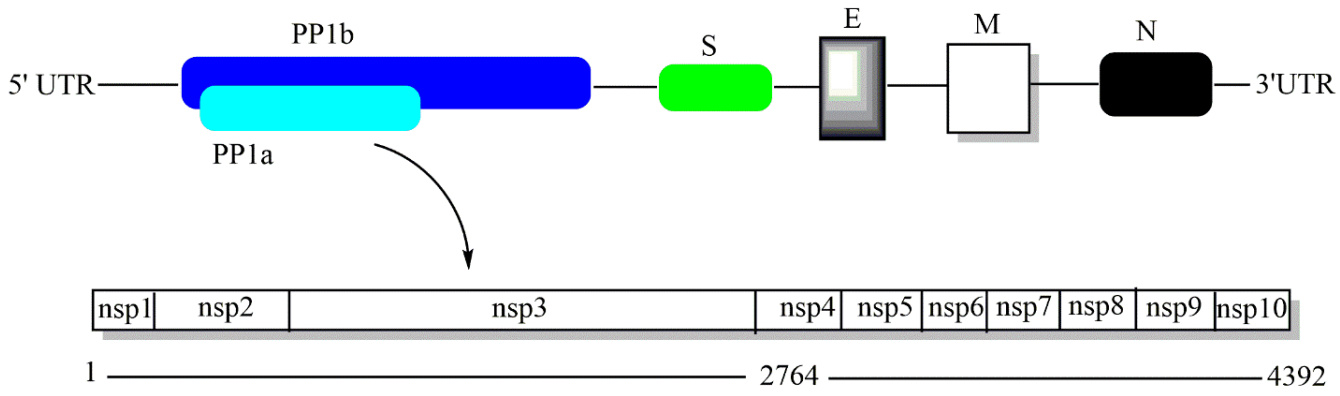


Figure 1: Schematic representation of SARS genome with conserved sites

Up till now, siRNA have been targeted using Nano carrier and vector system. Sirnaomics, Inc. (USA) in 2003 developed siRNA-based therapeutics for the SARS pandemic and H5N1 influenza virus. Similarly, in 2017 Alnylam Pharmaceuticals, USA developed six siRNA for infectious diseases and more than 350 siRNA targeting conserved regions of SARS were synthesized [12]. However, partial delivery of cargos to the target site and improper payloads for carriers has restricted its use. More effective carriers are required to deliver the desired quantity of cargo to the target side.

Human lungs are composed of ciliated cells, these cells are primary sites for viral infection of SARS CoV-2 and are transmitted through saliva droplets or fomites from the infected person. In such case, targeting the lung epithelial cells are desired, which will help in timely and effective targeting of the virus. Dendrimer based nanocarrier for the siRNA is suitable option in this condition because of its high stability and low antigenicity [13]. Embedding the siRNA in nanocarrier will help to protect it from degradation, the dendrimer will promote its permeability across the pleural mucosae and converting the resultant blend into aerosol formulation which will deposit the cargo in to the deep desired target within the lung atmosphere [14].

## CONCLUSION

Currently no treatment is available and the transmission is rising exponentially. Therefore, it is necessary to develop siRNA-based therapeutics for COVID-19, that may target the conserved region of the virus RNA ultimately silencing the genes (mRNA). This measure could emphasis on a productive way to control the health threats and obtain better treatment goals globally.

## CONFLICT OF INTEREST

The author declares no conflict of interest.

## AUTHOR CONTRIBUTION

N/A

## FINDING SOURCE

N/A

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