Antiviral Group

Special isirv-AVG Virtual Conference on "Therapeutics for COVID-19"

EXPLORING ANTIVIRAL STRATEGIES AGAINST A BROAD RANGE OF BETA-COVS: **SPIKE AND POLYMERASE PROTEINS AS PROMISING ANTI-COV TARGETS.**

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Introduction

Since December 2019, over **30 000 000 cases** of COVID-19 and 1 million deaths have been reported by WHO (1).

Currently, there are no prophylactic or therapeutic agents specific for SARS-CoV-2 infection (2).

Giving the enormous impact of the COVID-19 pandemic on society and economy and on human health and well-being, there is an urgent need for new antiviral therapies.

The important role that **Spike** (S) and **Polymerase** (Pol) proteins have in viral infection and pathogenesis highlights their promising role as potential anti-CoV targets.

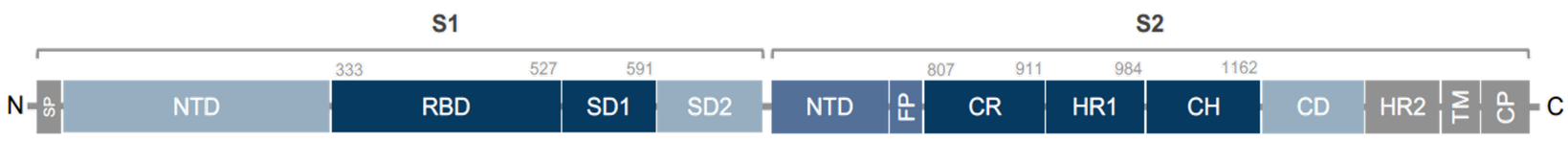


Fig. 1. Schematic illustration of SARS-CoV-2 **S** protein. Adapted from (3).

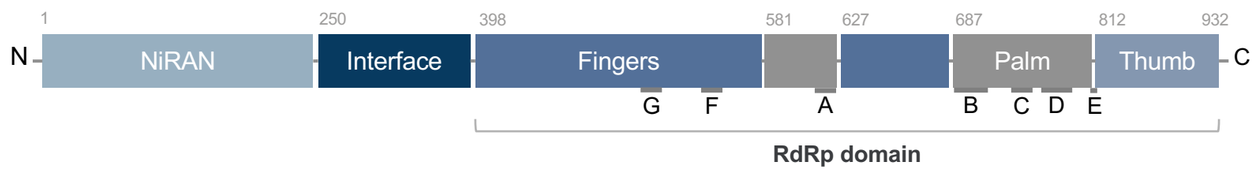


Fig. 2. Domain structure of the main subunit (nsp12) of **Pol** protein.

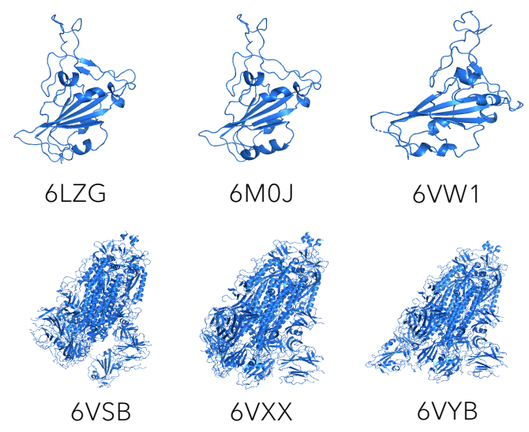
Objective: explore conserved druggable regions in SARS-CoV-2 S and Pol protein structures and identify druggable hot spots for the development of new therapies against beta-CoVs (SARS-CoV-2, SARS-CoV and MERS-CoV).

Materials and Methods

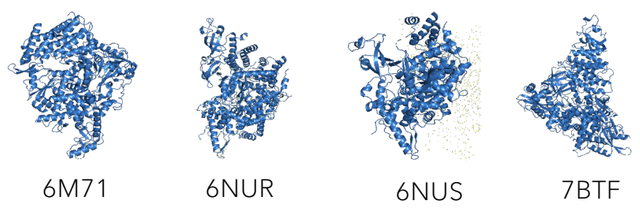
Sequence datasets: **1,065** (S) and **1106** (Pol) sequences (SARS-CoV-2, SARS-CoV and MERS-CoV) from all continents, retrieved from public databases.

Amino acid (aa) **conservation** was calculated and **druggability** was predicted using computational methods (4-6).

S structures



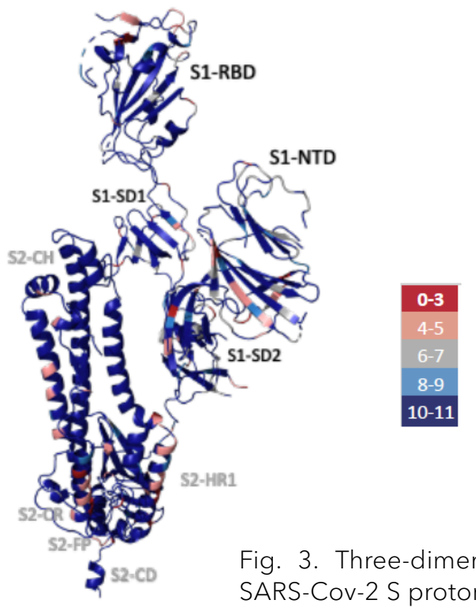
Pol structures



Source: Protein Data Bank (7)

Results and Discussion

SPIKE (S)



S1 subunit exhibits higher conservation (**99.8%**) when compared to S2 (**95.6%**) in SARS-CoV-2. But, in SARS-CoV and MERS-CoV, S2 presents an higher conservation.

Fig. 3. Three-dimensional sequence conservation of SARS-CoV and SARS-Cov-2 S protomer. Adapted from (3).

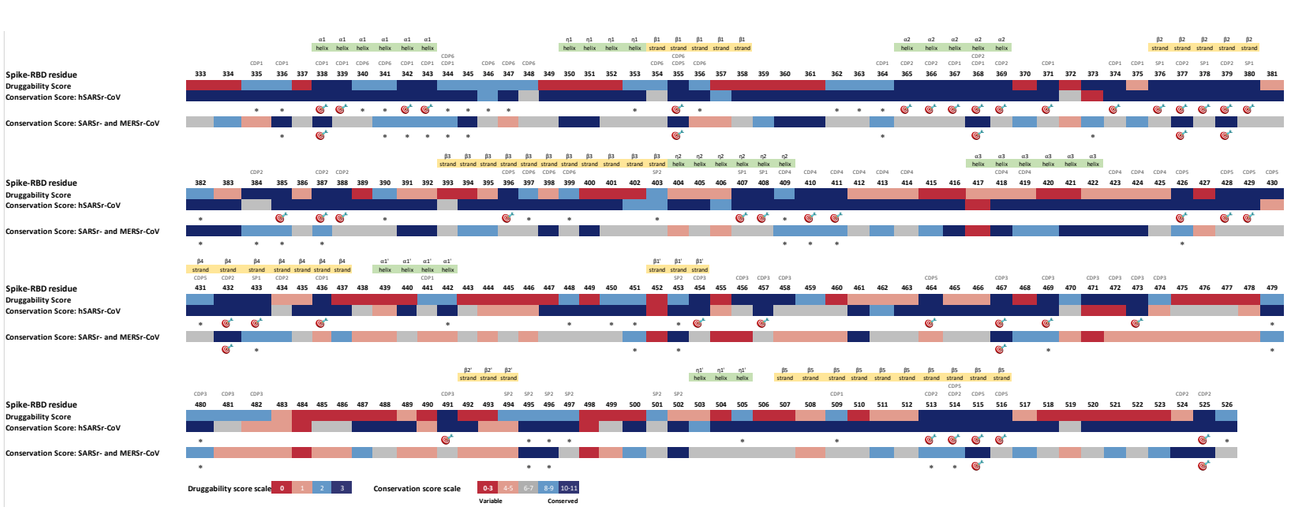


Fig. 4. Overall alignment of S-RBD druggability and conservation scores for each residue position.

We identified **181 new potential hot spot residues** for the human SARS-CoV-2 and **72** new hot spot residues for the SARS-CoV, SARS-CoV-2 and MERS-CoV S protein.

S1-RBD and **-SD1**; and **S2-CR**, **-HR1** and **–CH** domains are the most promising druggable S regions.

POLYMERASE (Pol)

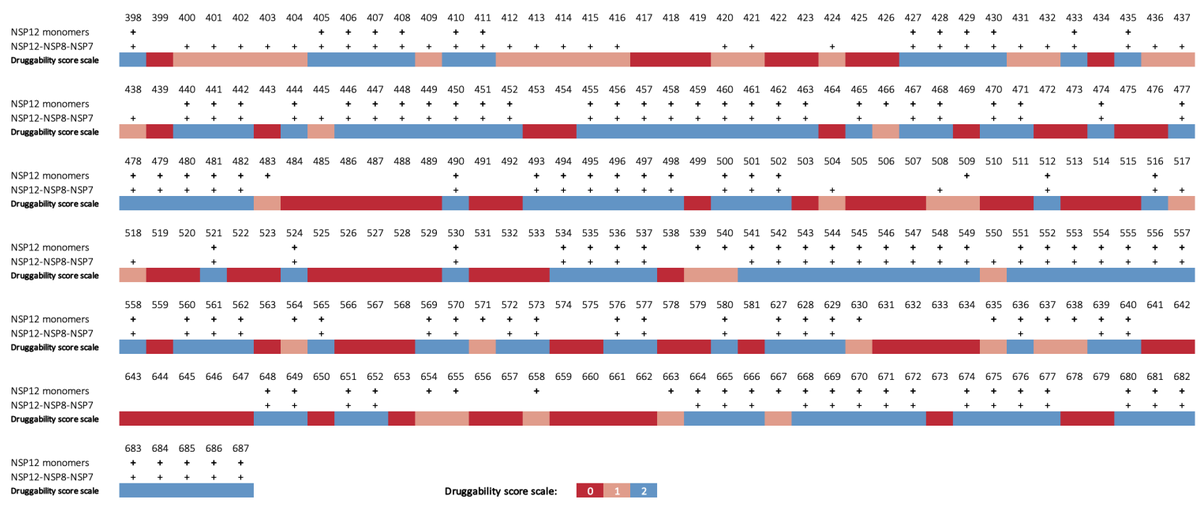


Fig. 5. Nsp12-subunit druggable sites and respective scores.

327 residues were ranked with the maximum druggability score in both monomeric and tetrameric conformations of SARS-CoV-2 Pol.

Fingers subdomain (aa 398-580; 627-686) - which is highly conserved across SARS-CoV-2, SARS-CoV and MERS-CoV - is the most promising region.

This subdomain is close to the putative binding site of remdesivir.

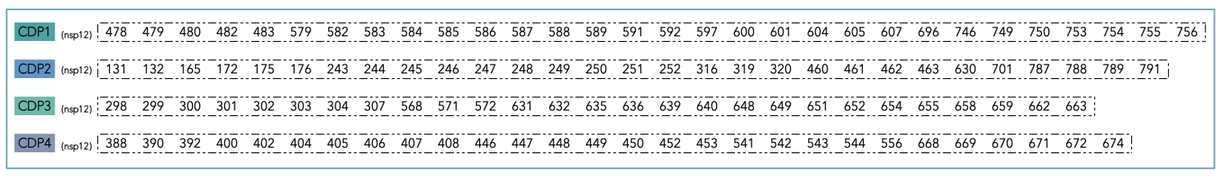


Fig. 6. Top four larger consensus druggable pockets (CDP) of SARS-CoV-2 Pol, common to both conformations.

We discovered **15 consensus druggable pockets,** that can act as antiviral targets for the development of new therapeutic strategies against SARS-CoV-2.

Conclusions

Potential binding pockets can be found in highly conserved regions either in SARS-CoV-2, SARS-CoV and MERS-CoV S and Pol proteins, underpinning their **promising role as antiviral targets.**

The disclosed hot spots represent **attractive targets** for structure-function studies and pharmacological modulation.

This study lays the basis for structure-based design of **antiviral molecules** against a broad spectrum of Beta-CoV.

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