

Elucidating Interactions Between SARS-CoV-2 Trimeric Spike Protein and ACE2 Using Homology Modeling and Molecular Dynamics Simulations

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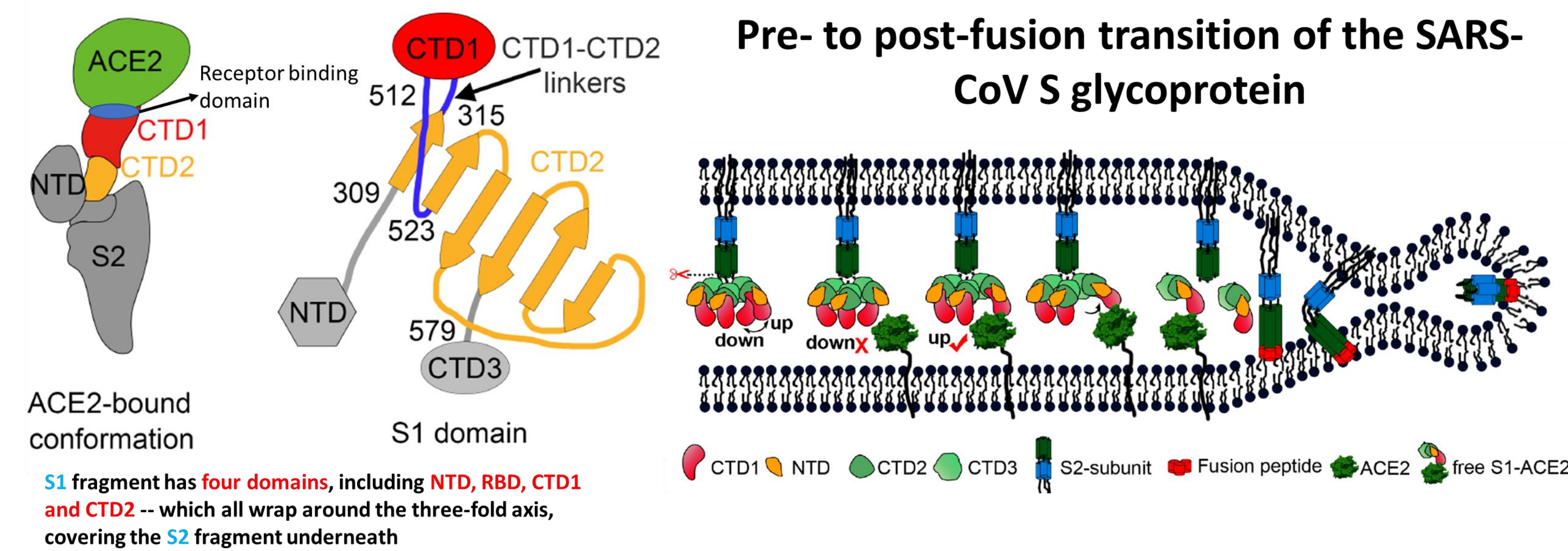
Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a respiratory illness known as COVID-19. As of 26th August 2020, more than 24 million confirmed cases and more than 8 lakhs of deaths are reported around the world. SARS-CoV-2 spike protein presents on the outer surface of the virion and binds human ACE2 protein on the host cell, playing a key role in the virus infection. Therefore, understanding interactions between the spike protein and ACE2 protein would facilitate development of drugs for the treatment of COVID-19. Many crystal structures have been experimentally determined for various regions of the spike protein. Recent studies uncovered that ACE2 protein binds the trimeric spike protein through multiple conformational poses, for which experimentally determined structure is not available. Hence, we generated a trimeric form of spike bound with ACE using homology modeling. The best modeled spike-ACE2 complex was subjected to MD simulations to elucidate the dynamic interaction between the spike protein and ACE2 protein. Clustering analysis was used to select distinct conformation of the trimeric spike protein complex with ACE2. Our results provide valuable structural details that could facilitate development of drugs to combat covid-19.

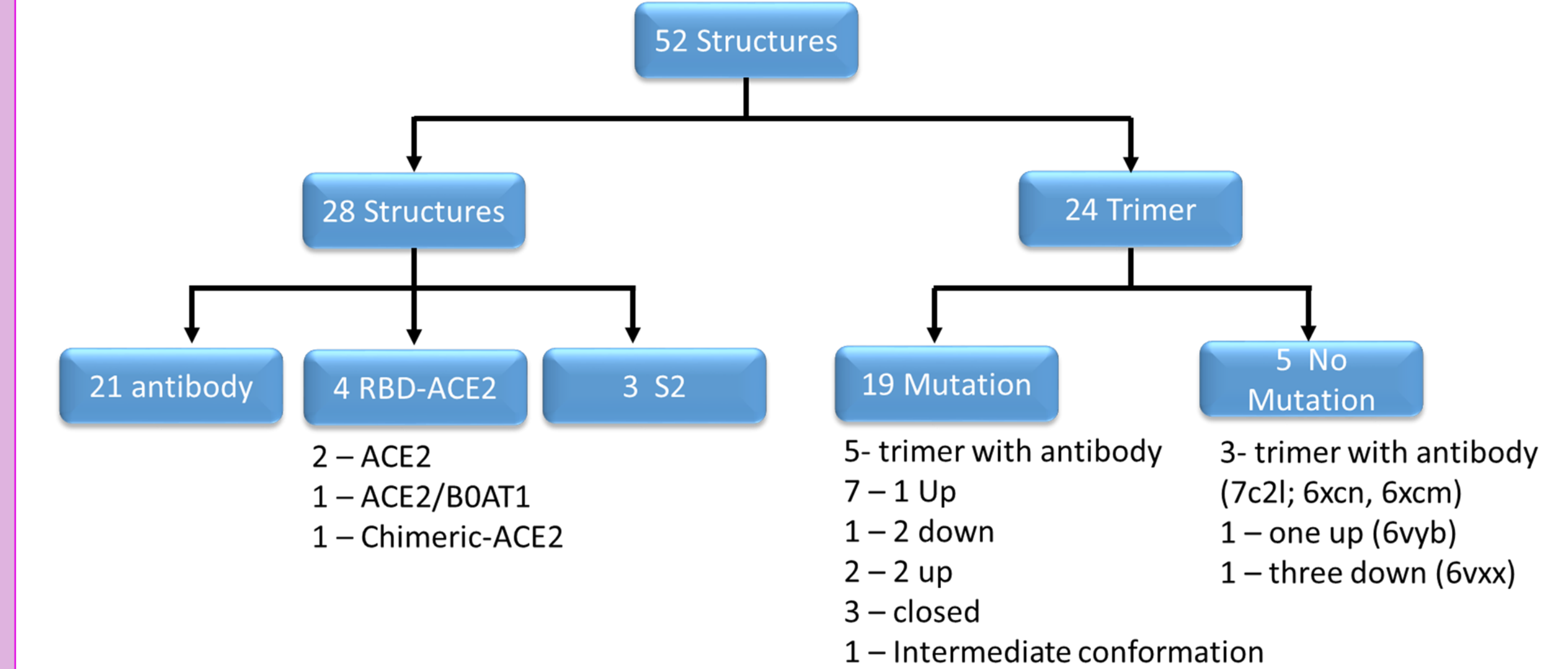
Introduction

- COVID-19 pandemic is caused by SARS-CoV-2
- As of 26th August 2020, more than 24 million confirmed cases and more than 8 lakhs of deaths are reported around the world
- Like other corona virus, SARS-CoV-2 is composed of 4 structural proteins, 16 non-structural proteins and 9 accessory proteins
- Spike protein presents in the outer surface of the virion and plays a major role in the viral infection
- Spike protein binds with ACE2 receptor of the host cells for the RNA to enter host cells
- Understanding interactions between the trimeric form of the spike protein and ACE2 could facilitate discovery of drugs that inhibit the binding of SARS-CoV-2 to ACE2

Structural Details of Spike Protein



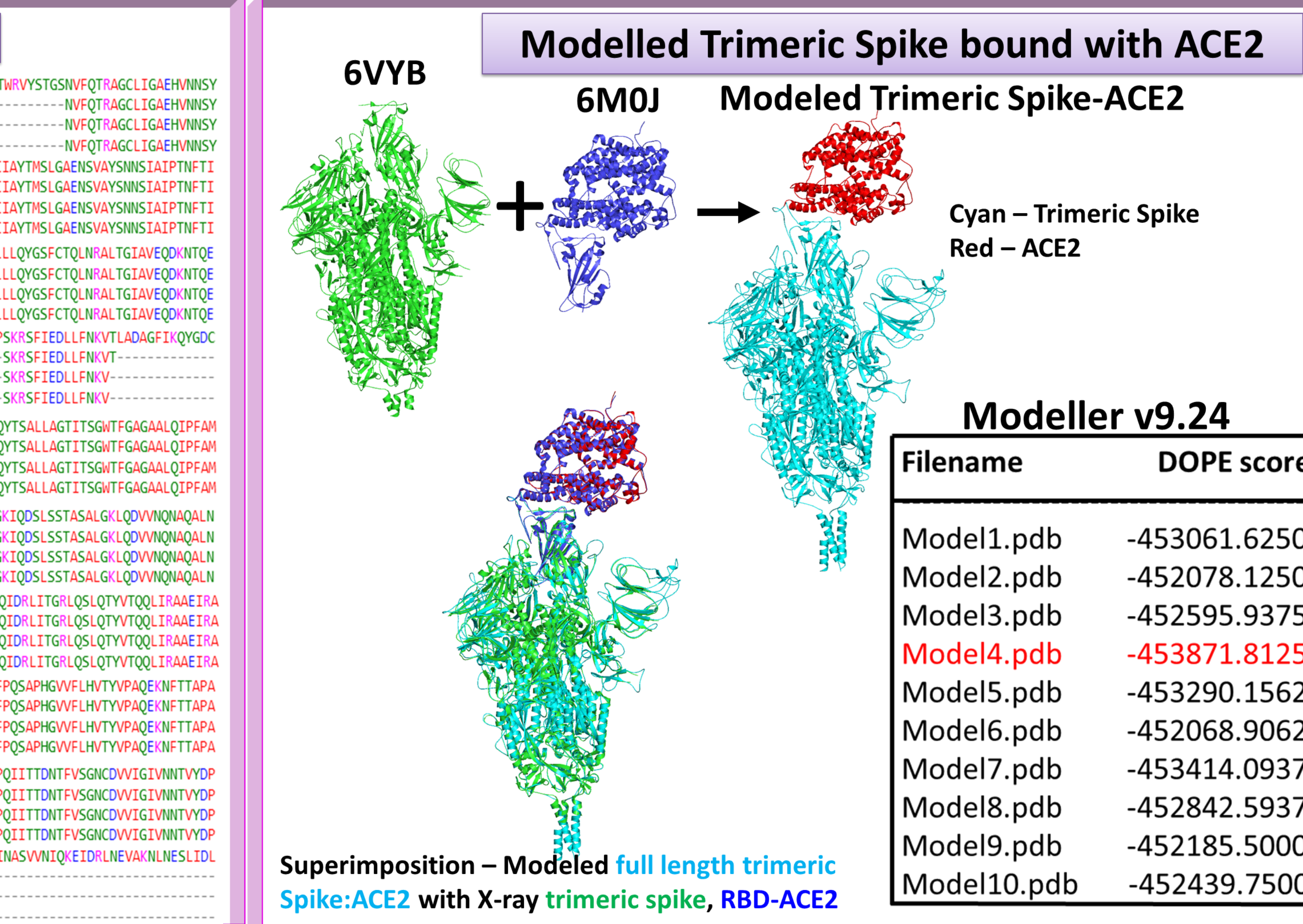
PDB Details – Spike Protein



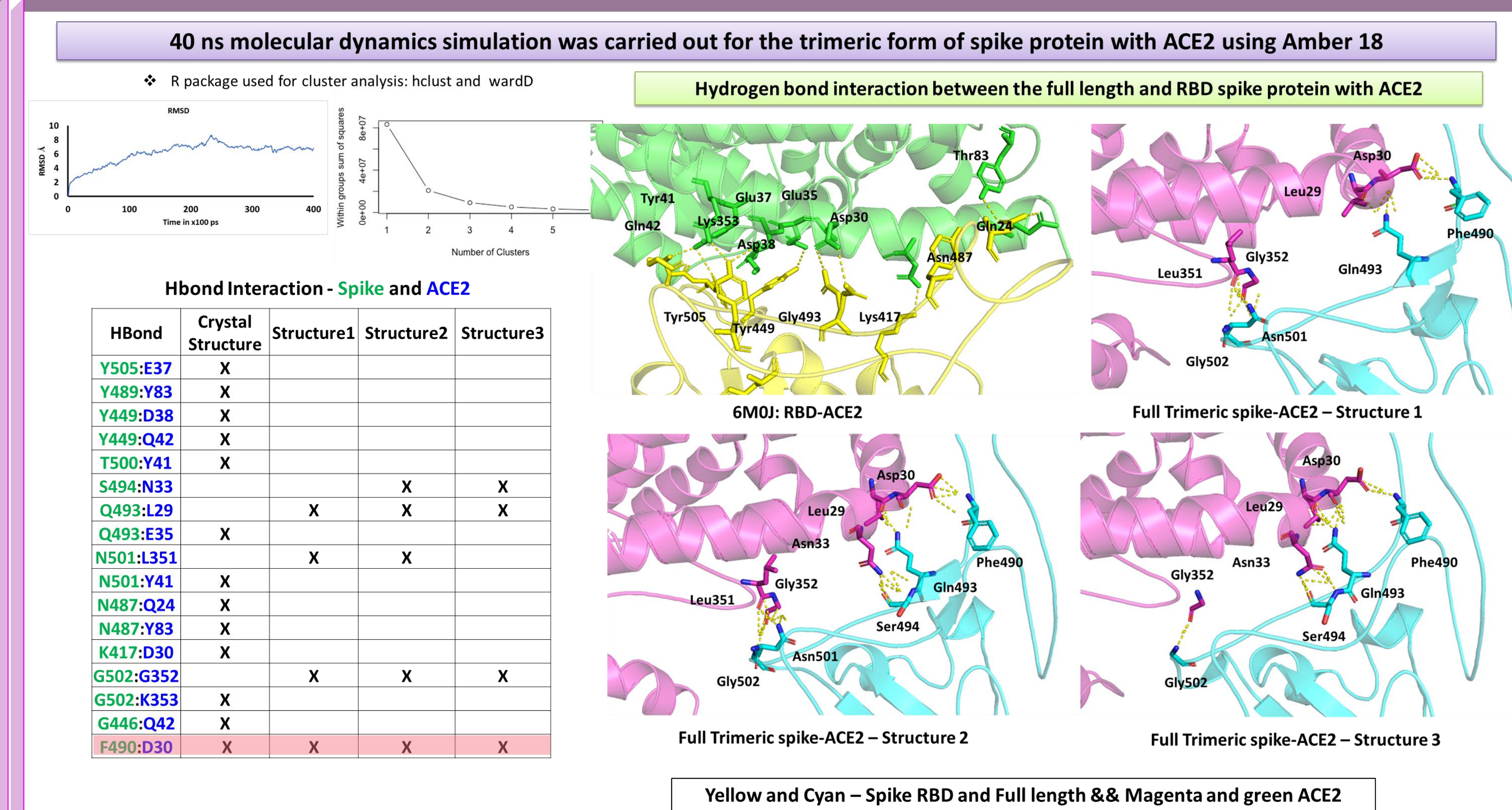
Homology Modeling

Sequence Alignment – Clustal Omega

PB0TC2	MFVFLVLLPSSQSNLITLTPAPPYNSFTGIVYDQVRFVSSVHSTQQLPFFES	PB0TC2	GTNITSQVAVLYQVICTEVVAVTHAQDLTPPTVYVSTGSHVQTRAGCLIGHEINISY
6VYB_AAYNSFTGIVYDQVRFVSSVHSTQQLPFFES	6VYB_BINVTQTRAGCLIGHEINISY
6VYB_BAYNSFTGIVYDQVRFVSSVHSTQQLPFFES	6VYB_CINVTQTRAGCLIGHEINISY
6VYB_CAYNSFTGIVYDQVRFVSSVHSTQQLPFFES	6VYB_AGTNITSQVAVLYQVICTEVVAVTHAQDLTPPTVYVSTGSHVQTRAGCLIGHEINISY
PB0TC2	NVTFVHAIHNSGTFKRFNPLPFDGQVYFASSTENIITGIGFTGLDLSIQSLLEV	PB0TC2	ECDPIGTGAGCAGVQTSNPRASVASQSIATVYHSLGAEVSVAVSNISIAIPFTNFI
6VYB_BPVLPPDQVYFASSTENIITGIGFTGLDLSIQSLLEV	6VYB_BSOSIAIVYHSLGAEVSVAVSNISIAIPFTNFI
6VYB_APVLPPDQVYFASSTENIITGIGFTGLDLSIQSLLEV	6VYB_ASOSIAIVYHSLGAEVSVAVSNISIAIPFTNFI
6VYB_CPVLPPDQVYFASSTENIITGIGFTGLDLSIQSLLEV	6VYB_CSOSIAIVYHSLGAEVSVAVSNISIAIPFTNFI
PB0TC2	NNATNVIKICEFQFCIDPFLGVYHNNISMSPEFVYSSANNKTFEYVSPDFLDLE	PB0TC2	SVTTEILPVSHITVYDCTHYVCGGSSCTESNLLIQVGSFCTQINRALTGAJEGQINTQE
6VYB_BNCTFEYV	6VYB_ASVTTEILPVSHITVYDCTHYVCGGSSCTESNLLIQVGSFCTQINRALTGAJEGQINTQE
6VYB_ANCTFEYV	6VYB_BSVTTEILPVSHITVYDCTHYVCGGSSCTESNLLIQVGSFCTQINRALTGAJEGQINTQE
6VYB_CNCTFEYV	6VYB_CSVTTEILPVSHITVYDCTHYVCGGSSCTESNLLIQVGSFCTQINRALTGAJEGQINTQE
PB0TC2	GQGFQINLIEFVFNIDQYFVYNSHTPNNLVDLPQGSALPELVLPDPIGINTFRQQT	PB0TC2	VFAQVQVYKTPPIKDFGGFNFSQQLPDPKSKIKSIEDLLENINVTADAGFETQYQDC
6VYB_BSFLNIEFVFNIDQYFVYNSHTPNNLVDLPQGSALPELVLPDPIGINTFRQQT	6VYB_BVFAQVQVYKTPPIKDFGGFNFSQQLPDPKSKIKSIEDLLENINVTADAGFETQYQDC
6VYB_ASFLNIEFVFNIDQYFVYNSHTPNNLVDLPQGSALPELVLPDPIGINTFRQQT	6VYB_AVFAQVQVYKTPPIKDFGGFNFSQQLPDPKSKIKSIEDLLENINVTADAGFETQYQDC
6VYB_CSFLNIEFVFNIDQYFVYNSHTPNNLVDLPQGSALPELVLPDPIGINTFRQQT	6VYB_CVFAQVQVYKTPPIKDFGGFNFSQQLPDPKSKIKSIEDLLENINVTADAGFETQYQDC
PB0TC2	LLAHLHSYLPDSSSSGDTAGAAAYVQYQPTFLLYIENGTITDVAOCALDPLSETK	PB0TC2	LVGIIAARDLCAQFNGILVLPPLLDENIAYTSALLAGITTSQWTFGAGAAIQTFEAM
6VYB_BAAVYVQYQPTFLLYIENGTITDVAOCALDPLSETK	6VYB_BKFNGLVLPPLLDENIAYTSALLAGITTSQWTFGAGAAIQTFEAM
6VYB_AAAVYVQYQPTFLLYIENGTITDVAOCALDPLSETK	6VYB_AKFNGLVLPPLLDENIAYTSALLAGITTSQWTFGAGAAIQTFEAM
6VYB_CAAVYVQYQPTFLLYIENGTITDVAOCALDPLSETK	6VYB_CKFNGLVLPPLLDENIAYTSALLAGITTSQWTFGAGAAIQTFEAM
PB0TC2	CTLSFVTEIGVYQTSNIFQVPTSEVFPFNTLCPFGGEVFNATFASVYAMNKRISN	PB0TC2	QVAYYFNGITGVYVYENQVLIANQVNSAIGIQDLSSTASALGILQVVMQVQALN
6VYB_BCTLSFVTEIGVYQTSNIFQVPTSEVFPFNTLCPFGGEVFNATFASVYAMNKRISN	6VYB_BQVAYYFNGITGVYVYENQVLIANQVNSAIGIQDLSSTASALGILQVVMQVQALN
6VYB_ACTLSFVTEIGVYQTSNIFQVPTSEVFPFNTLCPFGGEVFNATFASVYAMNKRISN	6VYB_AQVAYYFNGITGVYVYENQVLIANQVNSAIGIQDLSSTASALGILQVVMQVQALN
6VYB_CCTLSFVTEIGVYQTSNIFQVPTSEVFPFNTLCPFGGEVFNATFASVYAMNKRISN	6VYB_CQVAYYFNGITGVYVYENQVLIANQVNSAIGIQDLSSTASALGILQVVMQVQALN
PB0TC2	CVADYSVLYNSASSTFKCVGSPFLINDLCTFNAYADSVFVIGDEVQVQAPQGTQZAD	PB0TC2	TLVYQSSNIFGASSVINDLSLIDPPEAEVQDRLITGLQSLQVYVYQQLIAAEETRA
6VYB_BCVADYSVLYNSASSTFKCVGSPFLINDLCTFNAYADSVFVIGDEVQVQAPQGTQZAD	6VYB_BTLVYQSSNIFGASSVINDLSLIDPPEAEVQDRLITGLQSLQVYVYQQLIAAEETRA
6VYB_ACVADYSVLYNSASSTFKCVGSPFLINDLCTFNAYADSVFVIGDEVQVQAPQGTQZAD	6VYB_ATLVYQSSNIFGASSVINDLSLIDPPEAEVQDRLITGLQSLQVYVYQQLIAAEETRA
6VYB_CCVADYSVLYNSASSTFKCVGSPFLINDLCTFNAYADSVFVIGDEVQVQAPQGTQZAD	6VYB_CTLVYQSSNIFGASSVINDLSLIDPPEAEVQDRLITGLQSLQVYVYQQLIAAEETRA
PB0TC2	WYVLPDQVYFASSTENIITGIGFTGLDLSIQSLLEV	PB0TC2	SANLAATVSECVLQGSVDFCGGQVHLVSPFQSAHPGHVHTVYVPAQENFTTAPA
6VYB_BWYVLPDQVYFASSTENIITGIGFTGLDLSIQSLLEV	6VYB_BSANLAATVSECVLQGSVDFCGGQVHLVSPFQSAHPGHVHTVYVPAQENFTTAPA
6VYB_AWYVLPDQVYFASSTENIITGIGFTGLDLSIQSLLEV	6VYB_ASANLAATVSECVLQGSVDFCGGQVHLVSPFQSAHPGHVHTVYVPAQENFTTAPA
6VYB_CWYVLPDQVYFASSTENIITGIGFTGLDLSIQSLLEV	6VYB_CSANLAATVSECVLQGSVDFCGGQVHLVSPFQSAHPGHVHTVYVPAQENFTTAPA
PB0TC2	NGVEGNCYLPQSYGQFTNGVQVYVYVFLFELHAPATVCGPKKSTNLVNICVNI	PB0TC2	ICHQGHAFPRGQVYVSGNTHAVFTQVNFYEQEITLITNTFVSGKCDVIGVMVYVDP
6VYB_BATVCGPKKSTNLVNICVNI	6VYB_BICHQGHAFPRGQVYVSGNTHAVFTQVNFYEQEITLITNTFVSGKCDVIGVMVYVDP
6VYB_AATVCGPKKSTNLVNICVNI	6VYB_AICHQGHAFPRGQVYVSGNTHAVFTQVNFYEQEITLITNTFVSGKCDVIGVMVYVDP
6VYB_CATVCGPKKSTNLVNICVNI	6VYB_CICHQGHAFPRGQVYVSGNTHAVFTQVNFYEQEITLITNTFVSGKCDVIGVMVYVDP
PB0TC2	FNHGLTGTGLVYTESNKKFLPQGGGIDQADTDAVDQPTLELDTFCFSGGVSITP	PB0TC2	LQPELDS
6VYB_BFNHGLTGTGLVYTESNKKFLPQGGGIDQADTDAVDQPTLELDTFCFSGGVSITP	6VYB_BLQPELDS
6VYB_AFNHGLTGTGLVYTESNKKFLPQGGGIDQADTDAVDQPTLELDTFCFSGGVSITP	6VYB_ALQPELDS
6VYB_CFNHGLTGTGLVYTESNKKFLPQGGGIDQADTDAVDQPTLELDTFCFSGGVSITP	6VYB_CLQPELDS



Molecular Dynamics Simulations



Conclusions

- We constructed the structure of trimeric full length SARA-CoV-2 spike protein bound with ACE2 using homology modeling and molecular dynamics simulations;
- The interactions between the spike protein and ACE2 identified in our structure are different from those reported in the crystal structure of monomeric receptor binding domain (RBD) of the spike protein bound with ACE2, indicating the RBD monomer may not represent the trimer of full length spike protein in the body;
- Our findings shed lights on understanding the mechanism on entrance of the virus into the host and could assist development of drugs to treat COVID-19.

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