

Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2

Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., & Zhou, Q. (2020). Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science, 367(6485), 1444-1448. doi: 10.1126/science.abb2762

Journal Club Presentation by Carolyn Egekeze, Jack Menzagopian, and Karina Vescio

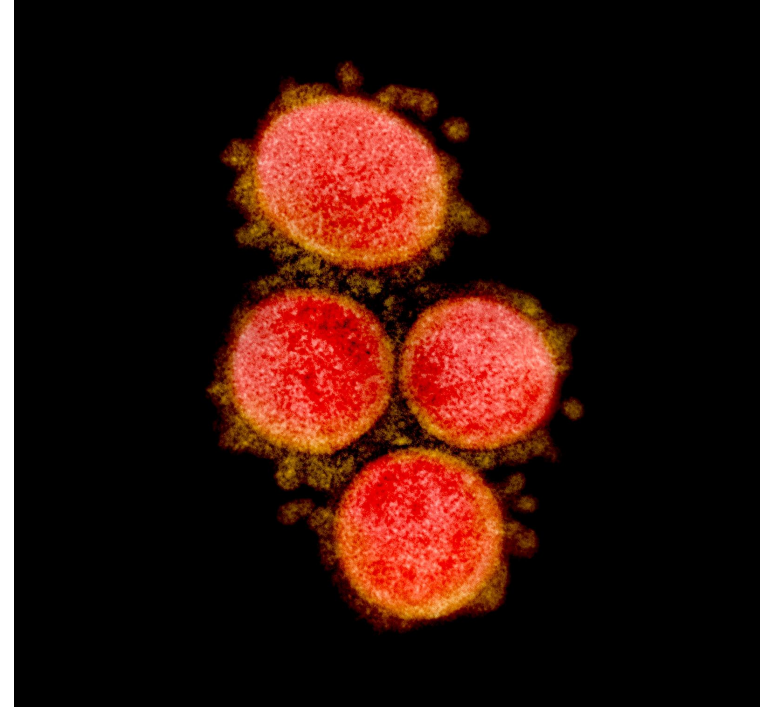
**BIOL 368: Bioinformatics Laboratory
April 16, 2020**

Outline

- I. SARS-CoV-2 is a novel virus**
- II. SARS-CoV-2 infects the host by interacting with ACE2**
- III. The purpose of the Yang et al. (2020) study is to provide a full-length sequence of human ACE2 to better understand the structure-function relationship between the enzyme and virus**
- IV. The main results of the study are:**
 - A. PD influences conformational change and dimerization in ACE2**
 - B. RBD-SARS-CoV-2 interacts with ACE-PD**
 - C. Variation in residues changes strength of interaction**
- V. The study provides a base for exploring structure-function relationship but is limited by its ignorance of cofactors**

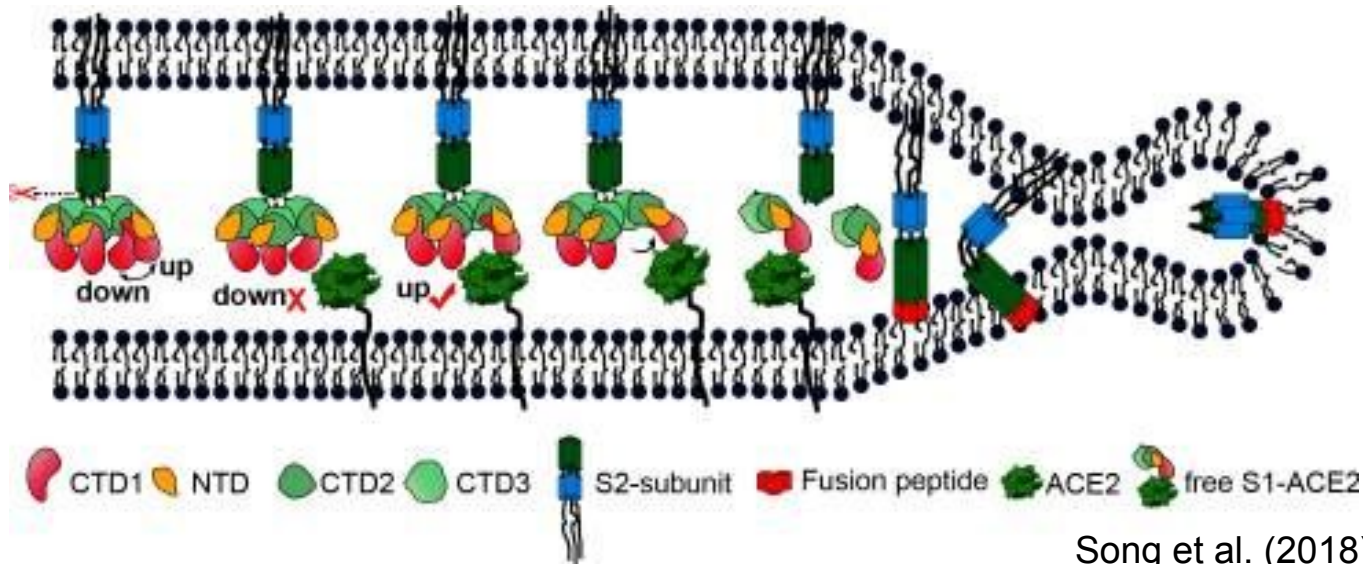
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus

- SARS-CoV-2 is a positive RNA virus (Yan et. al., 2020)
- Causes coronavirus disease 2019 (COVID-19), which has become a global pandemic
 - As of April 15, 2020: 2,064,815 confirmed cases (Dong et. al., 2020)
- Shares 80% of its sequence with SARS-CoV, another coronavirus (Yan et. al., 2020)



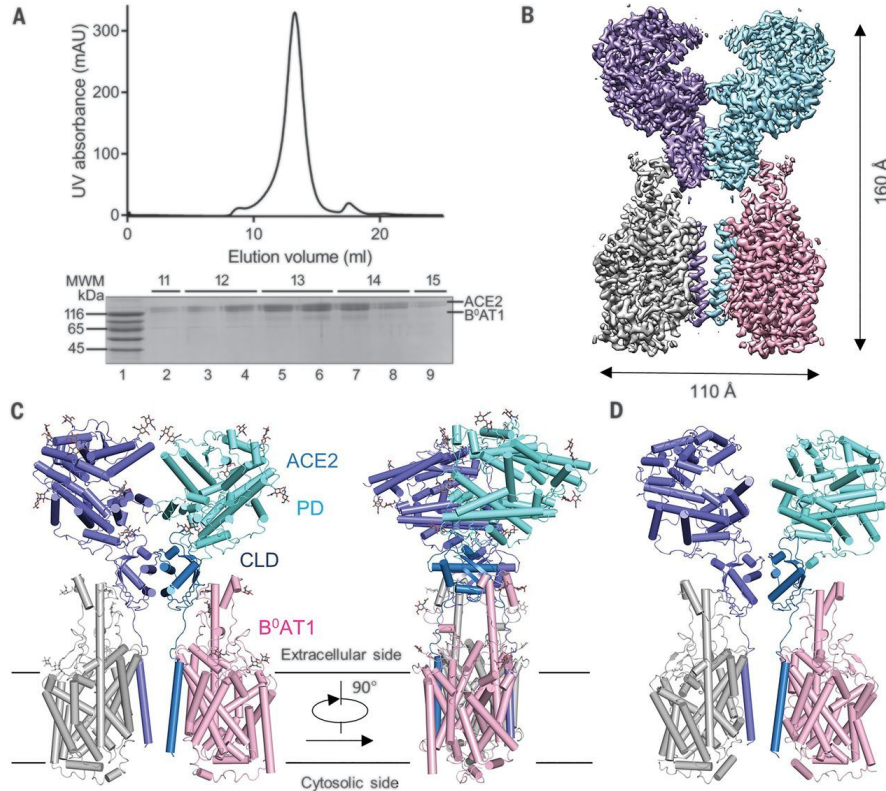
SARS-CoV-2 particles isolated from a patient
Source: NIAID IRF (2020)

S protein of SARS-CoV interacts with human ACE2 during viral infection



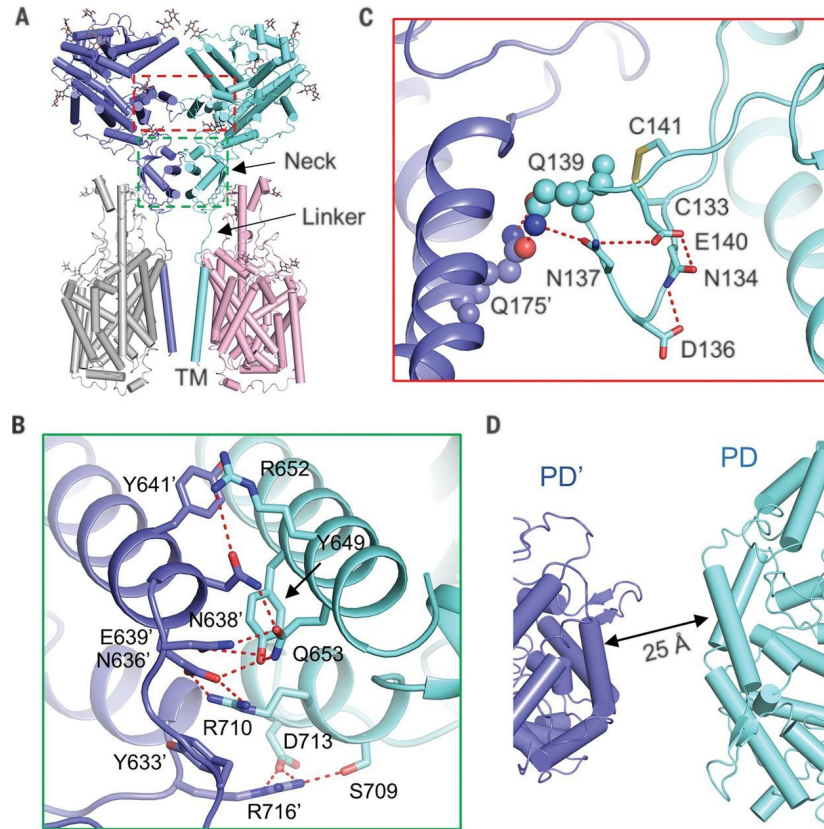
- S protein is cleaved into two subunits
 - RBD of S1 binds to ACE2-PD and S1-ACE2 complex dissociates
 - S2 begins membrane fusion after S1-ACE2 complex dissociates

Two conformations for ACE2-B⁰AT1 complex that differ in rotation of PD

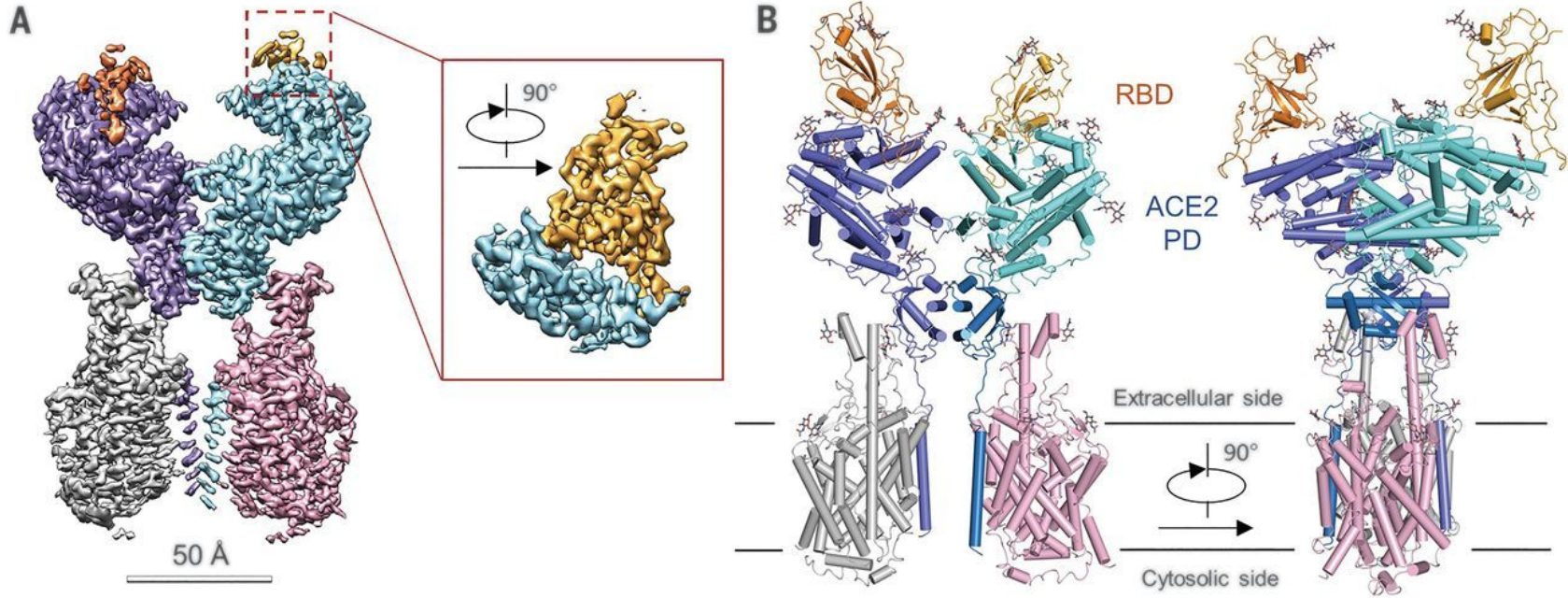


- CLD in blue
- PD in cyan
- B⁰AT1 promoters shown in grey and pink

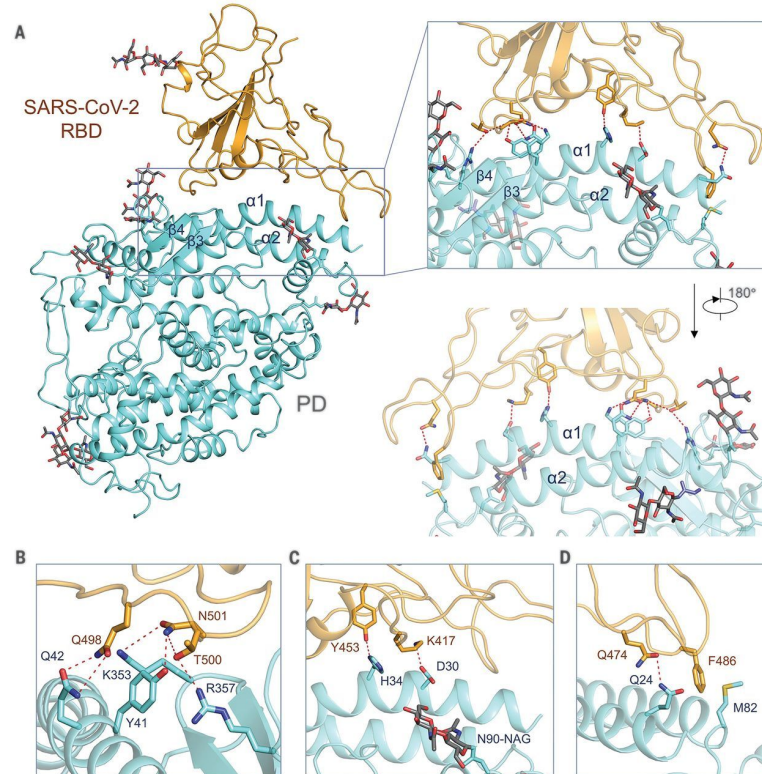
Dimerization of ACE2 is mediated by the neck region and PD



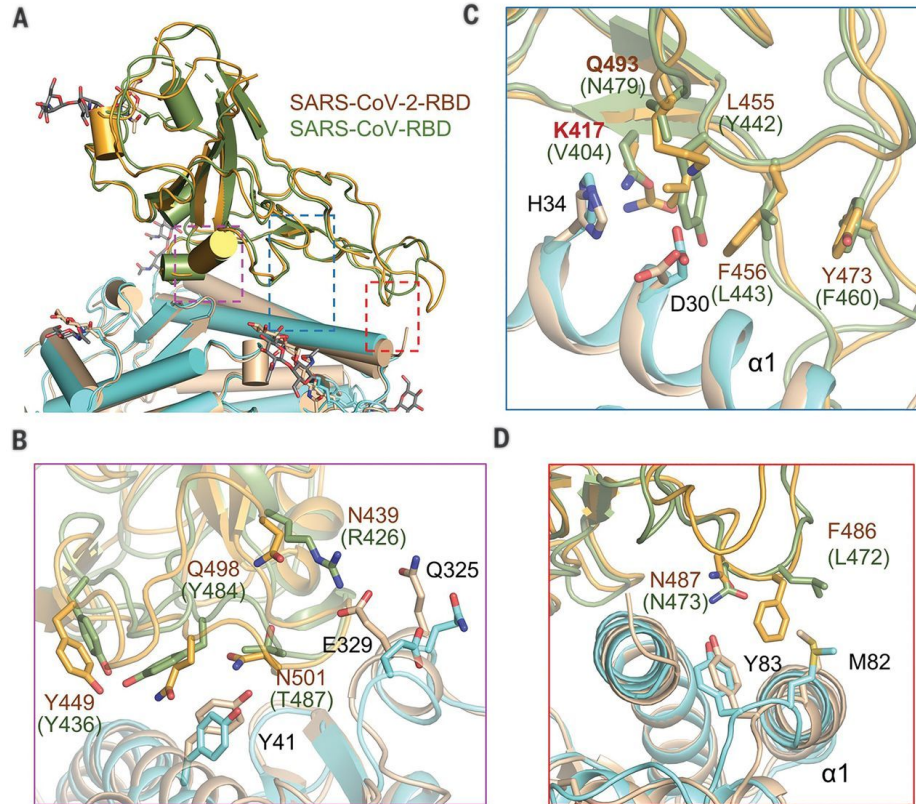
Addition of RBD from SARS-CoV-2 produced only closed conformation



Contact between RBD and ACE2 can be seen in three clusters of polar interactions



RBD in SARS-CoV-2 and SARS-CoV show variation in residues interacting with ACE2



Discussion

- Overall, study shows neck and PD domains in ACE2 structure allow for homodimer formation
- Study also shows that SARS-CoV-2 binds to ACE2 in a similar to SARS-CoV
 - Residues variation may determine if SARS-CoV-2 binds more strongly to ACE2
- A previous study showed the S protein in SARS-CoV-2 had a trimeric structure
 - This study confirms that the RDB of the virus can only bind to ACE2 in the up conformation
- One limitation of the study is that effect of cofactors on binding is not examined
- In the future, researchers can use the structure of ACE2 and SARS-CoV-2 to determine what ligands may be able to block the interaction

Summary

- **SARS-CoV-2 is a novel coronavirus that causes COVID-19**
- **Cryo-EM structures of ACE2-B0AT1 complex show full-length structure of ACE2 homodimer**
- **Polar interactions stabilize binding between the RBD in SARS-CoV-2 and PD in ACE2**
- **Sequence variation in SARS-CoV and SARS-CoV-2 affects binding affinity between the RBD in each virus and ACE2**
- **Structural information can be used to help design molecules that inhibit binding between SARS-Cov-2 and ACE2**

Acknowledgements

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References

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