Molecular Dynamics Studies on the Interactions between SARS-CoV-2 Spike Protein and hACE2 or mAbs

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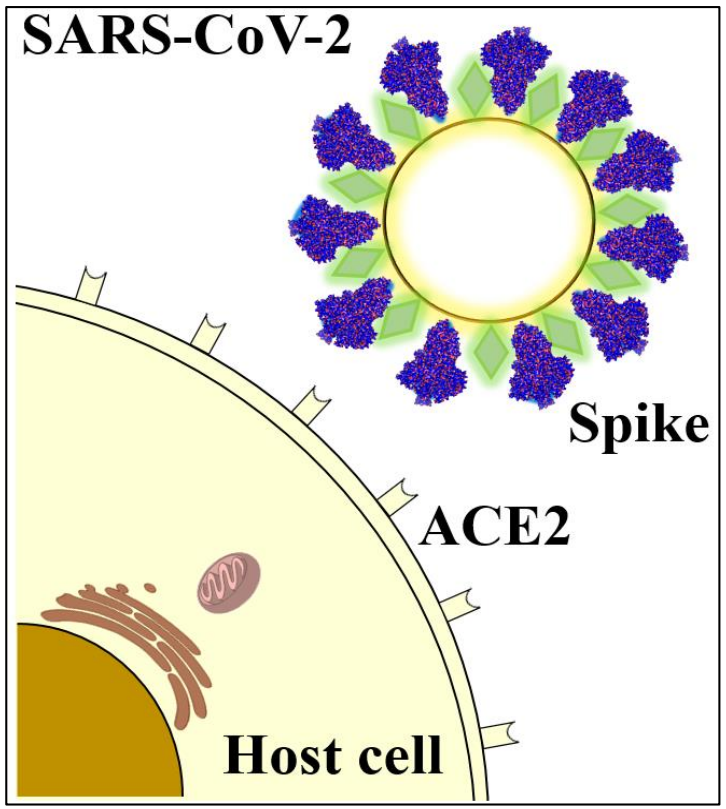
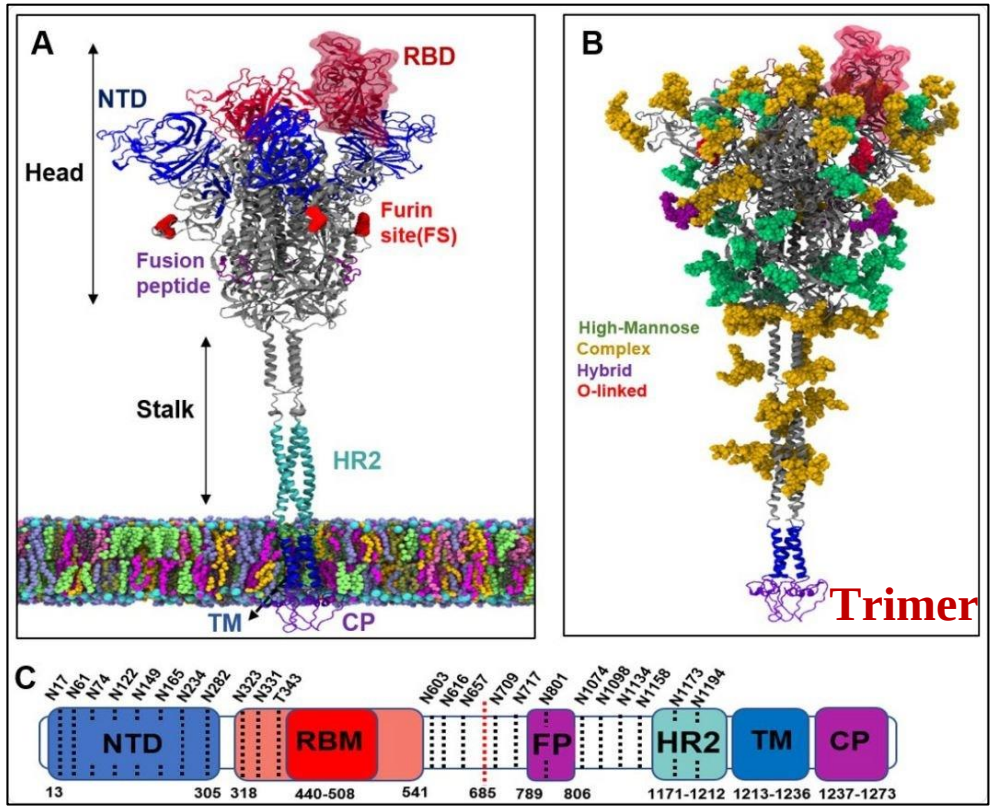
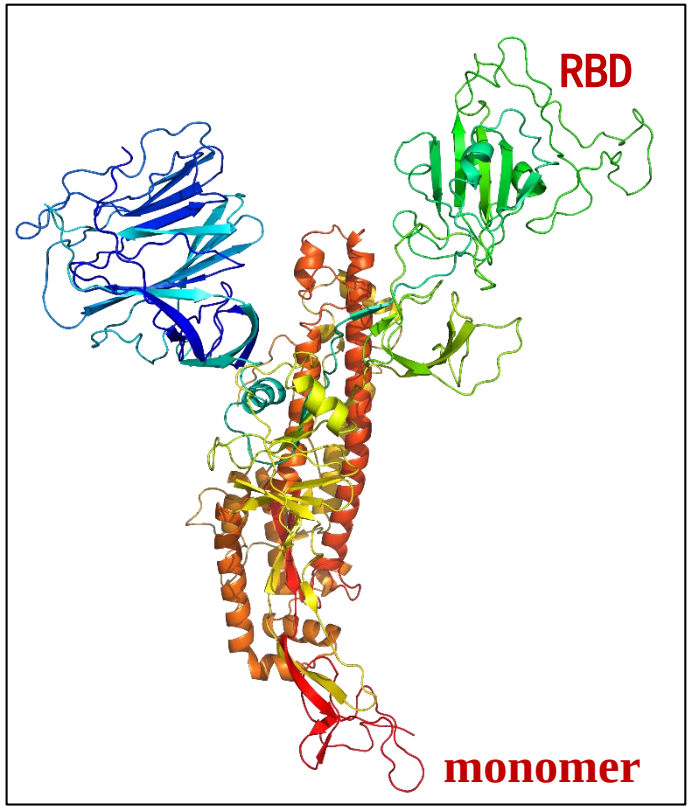
Spike protein and viral infection







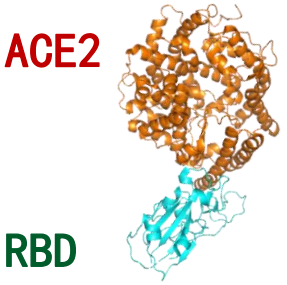
Cell, 183, 730-738, (2020)

- **The first step of SARS-2 infection is the binding of its spike protein to human ACE2.**
- **The spike protein on the surface of the virus particle is in a state of a trimer.**
- **The domain to interact with ACE2 is called RBD, which has up- and down- conformations.**

Experiments showed contradictory binding affinities

- ACE2-RBD Binding Affinity

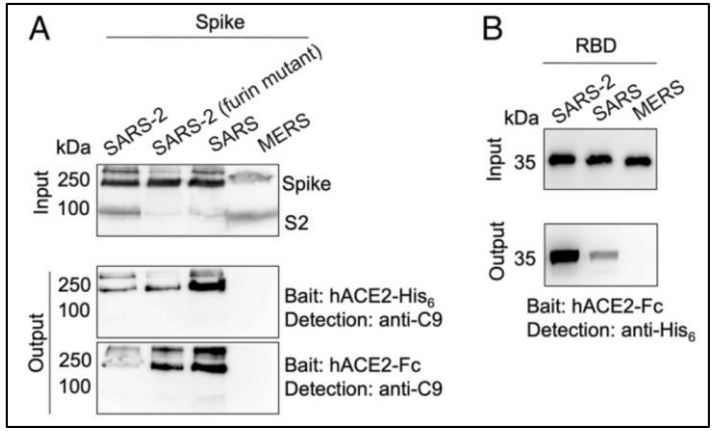
Protein coated	K_d (M)	Method
SARS-CoV-RBD-His tag	1.85×10^{-7}	SPR
SARS-CoV-2-RBD-His tag	4.42×10^{-8}	SPR

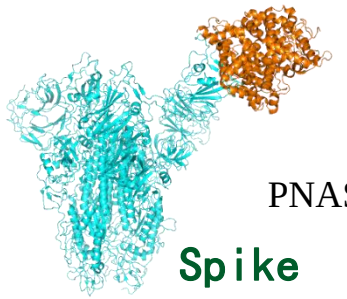


Nature, 581, 221–224 (2020)

- The binding of the RBD of SARS-2 spike to ACE2 is **stronger** than that of SARS

- ACE2-Spike Binding Affinity



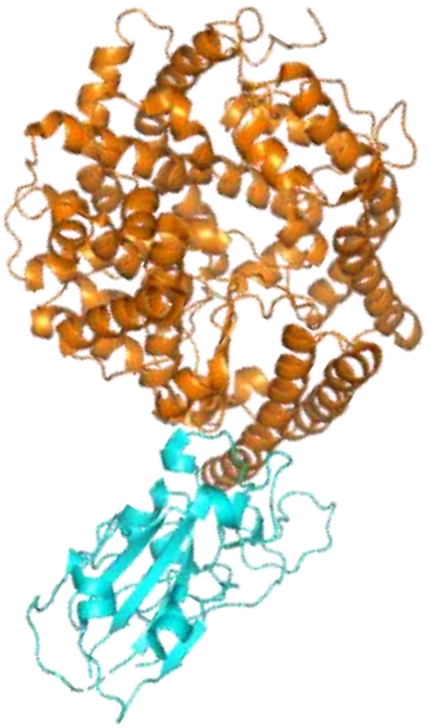


PNAS, 117, 11729–11734 (2020)

- The binding of the full length spike of SARS-2 to ACE2 is **weaker** than SARS

- **The ACE2 binding affinities of RBD and full length spike are contradictory;**
- **Why?**

RBD-ACE2 binding affinity simulated by MD simulation



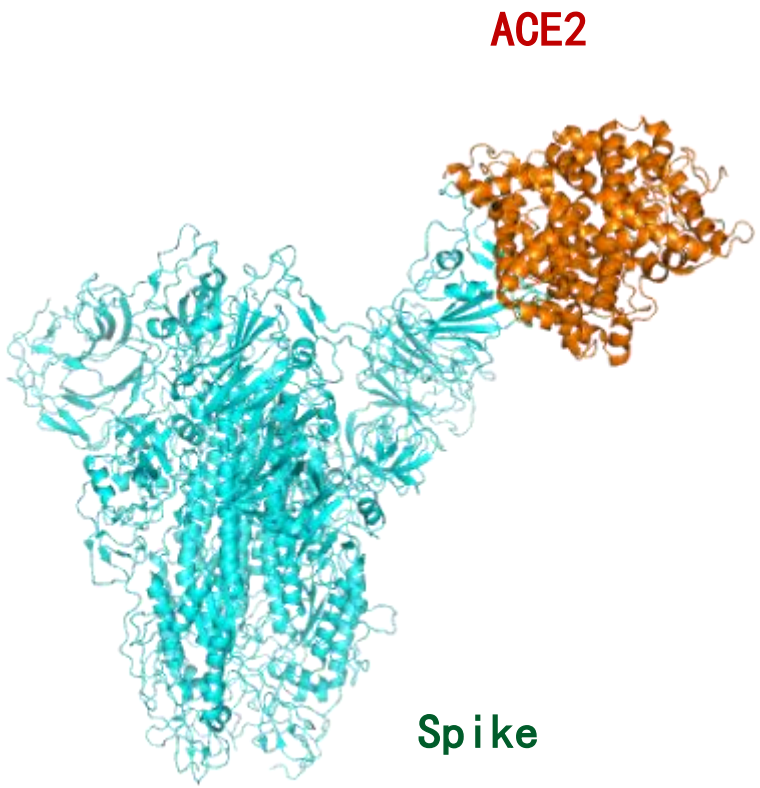
ΔG calculated by MM/GBSA with 100 ns MD simulation

Energy term	CoV-2-S RBD	CoV-S RBD
E_{vdw}	-86.91±0.06	-80.73±0.07
E_{ele}	-697.07±0.56	-742.78±0.71
E_{gb}	760.94±0.51	812.86±0.67
E_{np}	-12.05±0.06	-10.34±0.10
ΔH	-35.10±0.62	-20.98±0.64
$-T\Delta S$	-10.24±0.56	-10.94±0.69
ΔG	-24.86±0.59	-10.04±0.66

Methods: Amber16, Amber ff03, 100 ns MD simulation, 50-100 ns trajectory for MM/GBSA calculation
Temperate: 2AJF and 6M0J (SARS RBD-ACE2)

- The binding of ACE2 to RBD of SARS-2 is calculated to be stronger than SARS, which is in well agreement with the experimental results.

Spike-ACE2 binding affinity simulated by MD



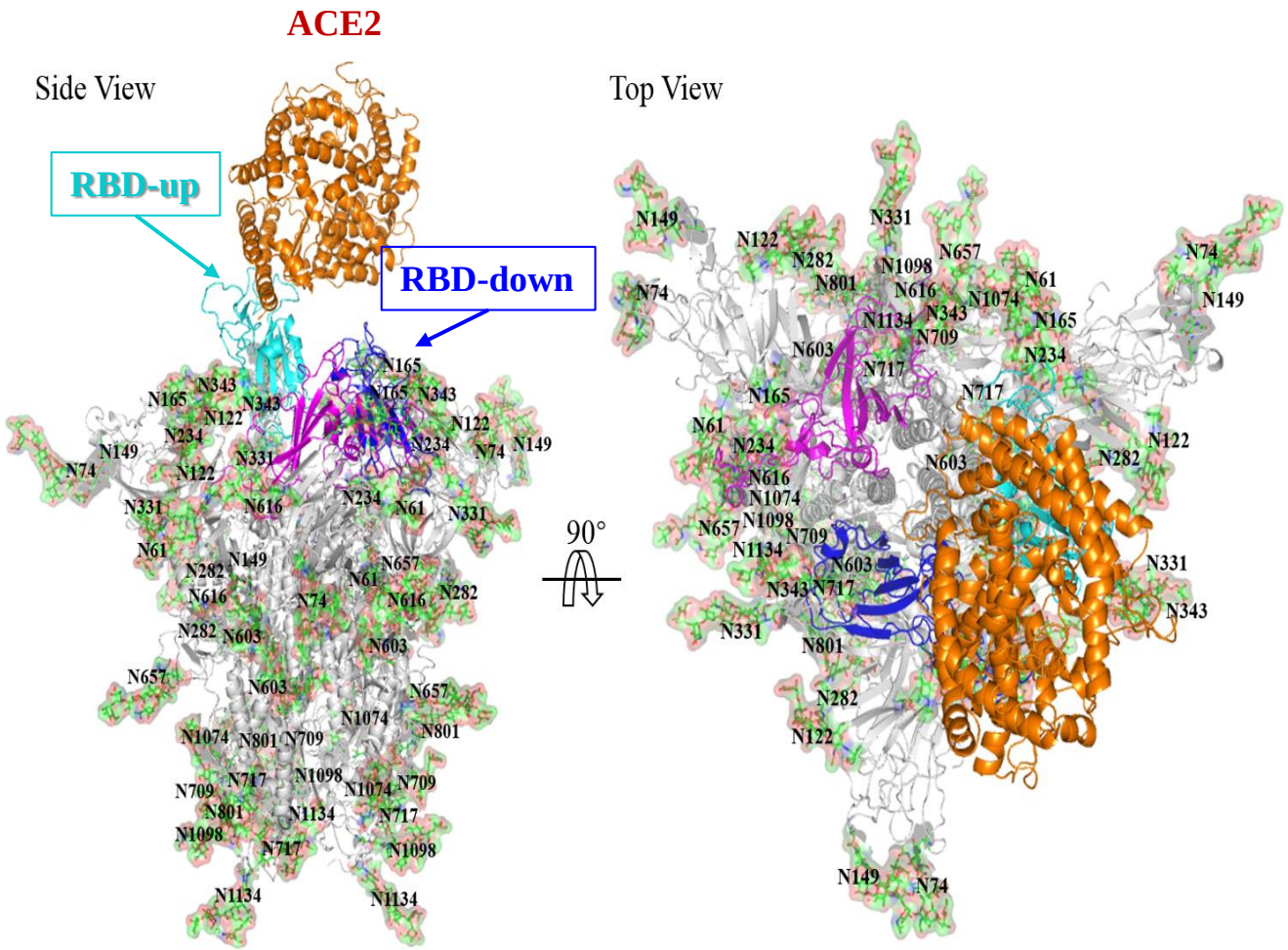
ΔG calculated by MM/GBSA with 100 ns MD simulation

	6ACG	6ACJ	6CS2	6ACK
SARS-CoV-2				
E_{vdw}	-81.34±0.47	-95.90±0.53	-100.86±0.72	-106.25±0.56
E_{ele}	-816.09±0.59	-796.20±2.59	-763.73±3.59	-763.10±2.86
E_{gb}	875.10±0.52	866.54±2.59	830.25±3.43	828.67±2.66
E_{np}	-11.14±0.07	-13.98±0.06	-14.61±0.08	-15.21±0.05
ΔH	-33.47±0.71	-39.55±0.56	-48.95±0.95	-55.89±0.56
-TΔS	-15.47±0.98	-14.45±0.81	-16.55±0.78	-16.37±0.66
ΔG	-18.00±0.84	-25.10±0.68	-32.40±0.86	-39.52±0.61
SARS-CoV				
E_{vdw}	-74.67±0.60	-84.99±0.54	-81.48±0.69	-86.15±0.47
E_{ele}	18.69±0.66	-53.59±0.56	-109.67±3.05	-120.10±3.29
E_{gb}	34.91±0.82	122.73±0.68	173.18±3.09	182.77±3.26
E_{np}	-9.72±0.08	-11.10±0.07	-10.42±0.10	-12.04±0.06
ΔH	-24.79±0.61	-26.96±0.56	-28.39±0.70	-35.52±0.54
-TΔS	-14.20±0.62	-14.57±0.80	-16.85±0.74	-14.89±0.67
ΔG	-10.59±0.62	-12.39±0.68	-11.54±0.72	-20.63±0.60

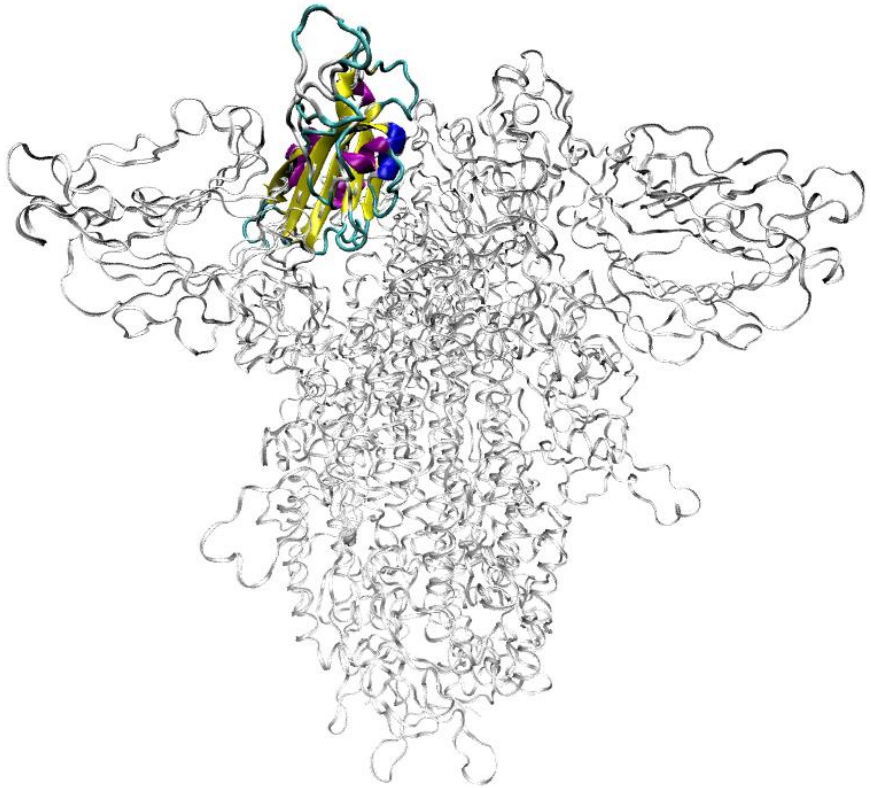
Methods: Amber16, Amber ff03, 100 ns MD simulation, 50-100 ns trajectory for MM/GBSA calculation

- The calculated **Δ*G*** of ACE2 to spike of CoV-2 with different models are always stronger than SARS, which are contradictory to experimental results.
- **Different models have different conformation, implying that conformation matters?**

Do the RBD-up and –down conformations matter?



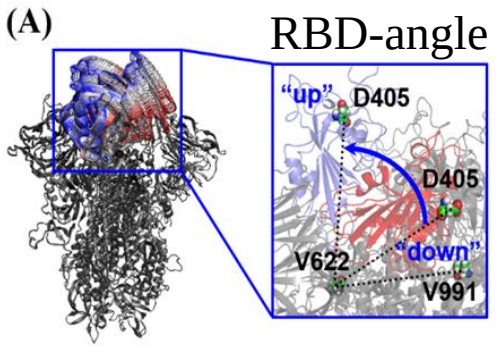
NUMD simulation for transition pathway

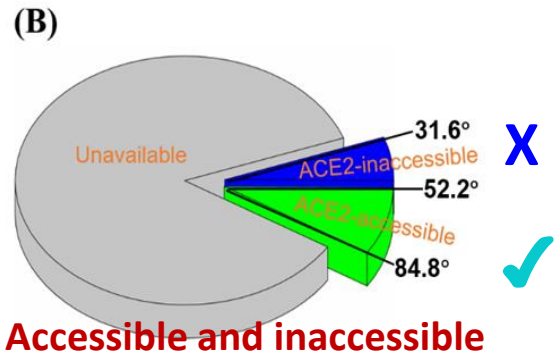


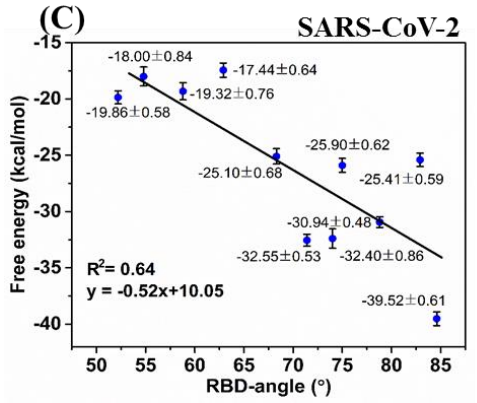
RBD-down → RBD-up

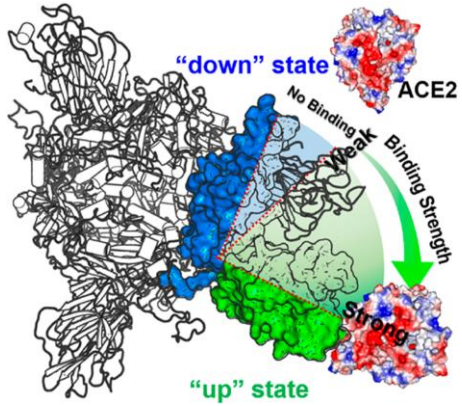
Method: *J. Wang, et al., W. Zhu, J. Phys. Chem. B*, **2014**, *118*, 134

Accessible and inaccessible conformations for spike binding ACE2









RBD-angle	54.8 °	68.3 °	74.0 °	84.6 °
	6ACG	6ACJ	6CS2	6ACK
SARS-CoV-2				
E_{vdw}	-81.34±0.47	-95.90±0.53	-100.86±0.72	-106.25±0.56
E_{ele}	-816.09±0.59	-796.20±2.59	-763.73±3.59	-763.10±2.86
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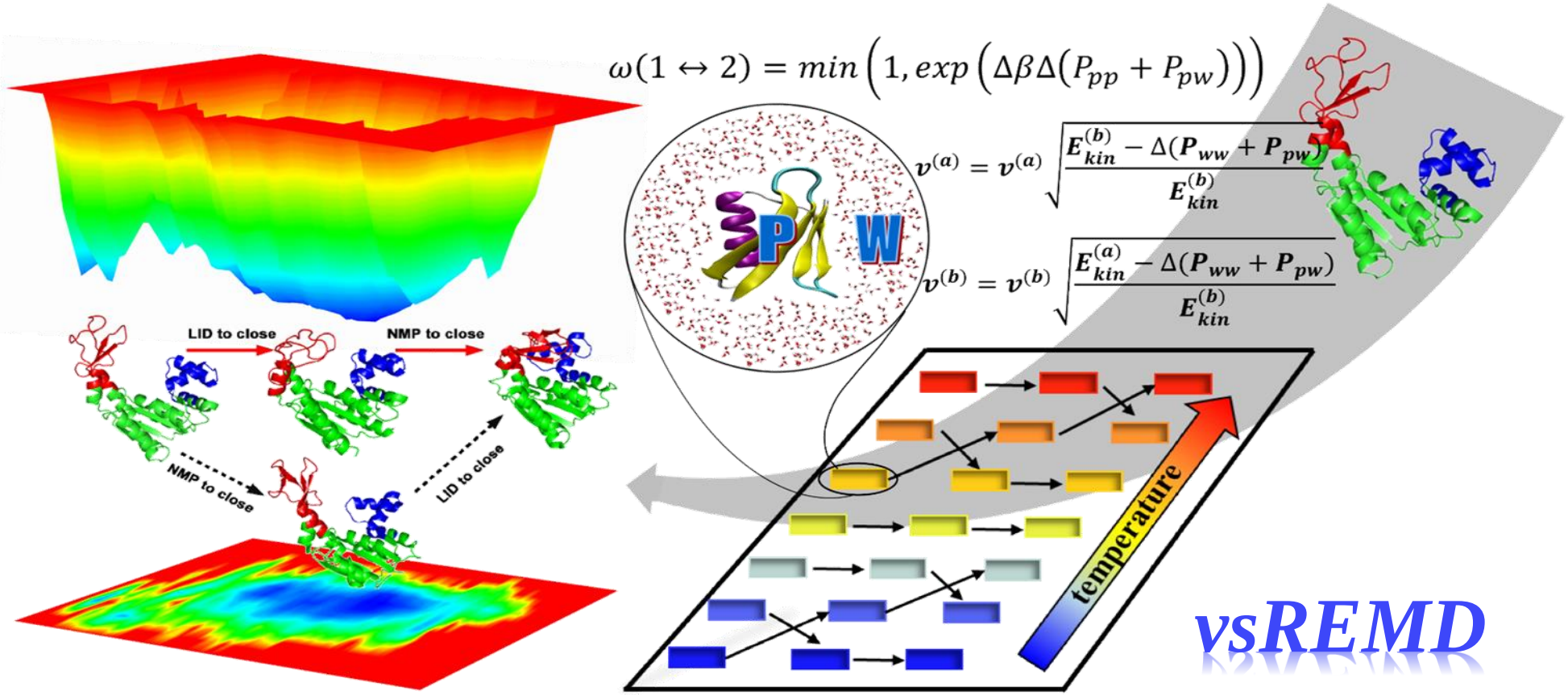
E_{np}	-11.14±0.07	-13.98±0.06	-14.61±0.08	-15.21±0.05
ΔH	-33.47±0.71	-39.55±0.56	-48.95±0.95	-55.89±0.56
-TΔS	-15.47±0.98	-14.45±0.81	-16.55±0.78	-16.37±0.66
ΔG	-18.00±0.84	-25.10±0.68	-32.40±0.86	-39.52±0.61
SARS-CoV				
E_{vdw}	-74.67±0.60	-84.99±0.54	-81.48±0.69	-86.15±0.47
E_{ele}	18.69±0.66	-53.59±0.56	-109.67±3.05	-120.10±3.29
E_{gb}	34.91±0.82	122.73±0.68	173.18±3.09	182.77±3.26
E_{np}	-9.72±0.08	-11.10±0.07	-10.42±0.10	-12.04±0.06
ΔH	-24.79±0.61	-26.96±0.56	-28.39±0.70	-35.52±0.54
-TΔS	-14.20±0.62	-14.57±0.80	-16.85±0.74	-14.89±0.67
ΔG	-10.59±0.62	-12.39±0.68	-11.54±0.72	-20.63±0.60

- RBD-angle was defined to be ∠D405-V633-V991.
- ACE2 was docked to the conformations with different RBD-angles.
- RBD-angle of ≥ 52.2º is required for binding ACE2, the larger the stronger.
- The experimentally observed weaker SARS2 spike-ACE2 binding can not be interpreted.
- Any other reason affecting the binding of the spike to ACE2? Accessible conformation distribution?

Method for conformation sampling



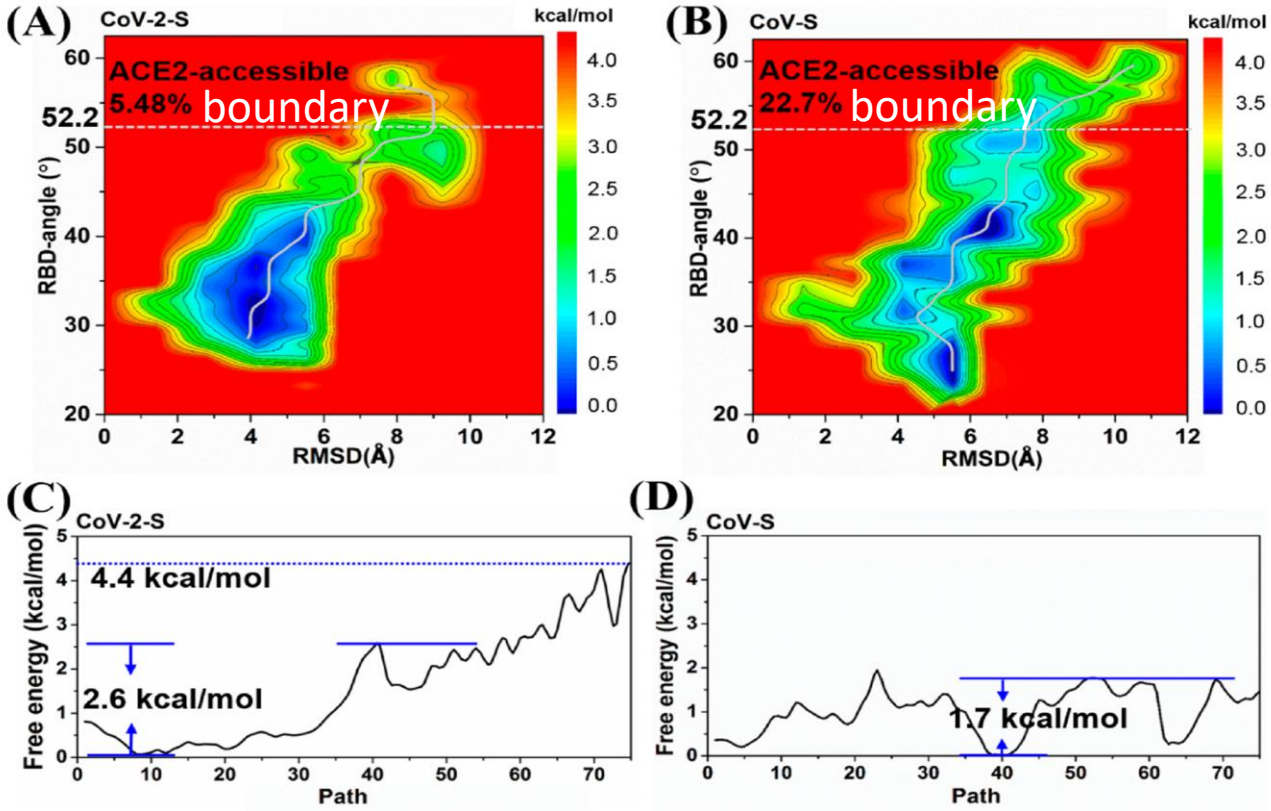
Method:

- **Trimers of the SARS and SARS-2 spikes**
- **48 replica for each systems**
- **100 ns vsREMD simulation with Gromacs5.1.4**

J. Wang, et al., Z. Xu, W. Zhu, *Biophysical Journal*, **2020**, *118*, 1009

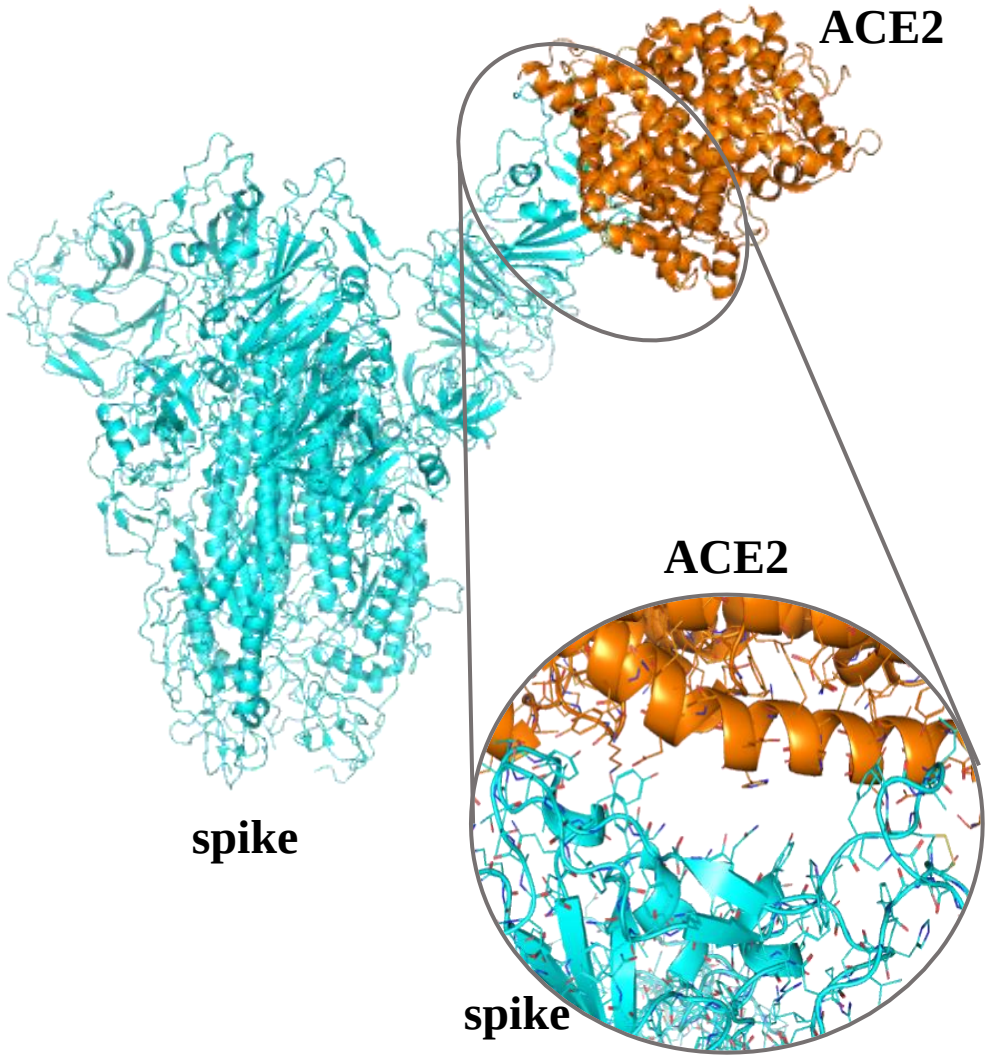
Significantly different conformation distributions

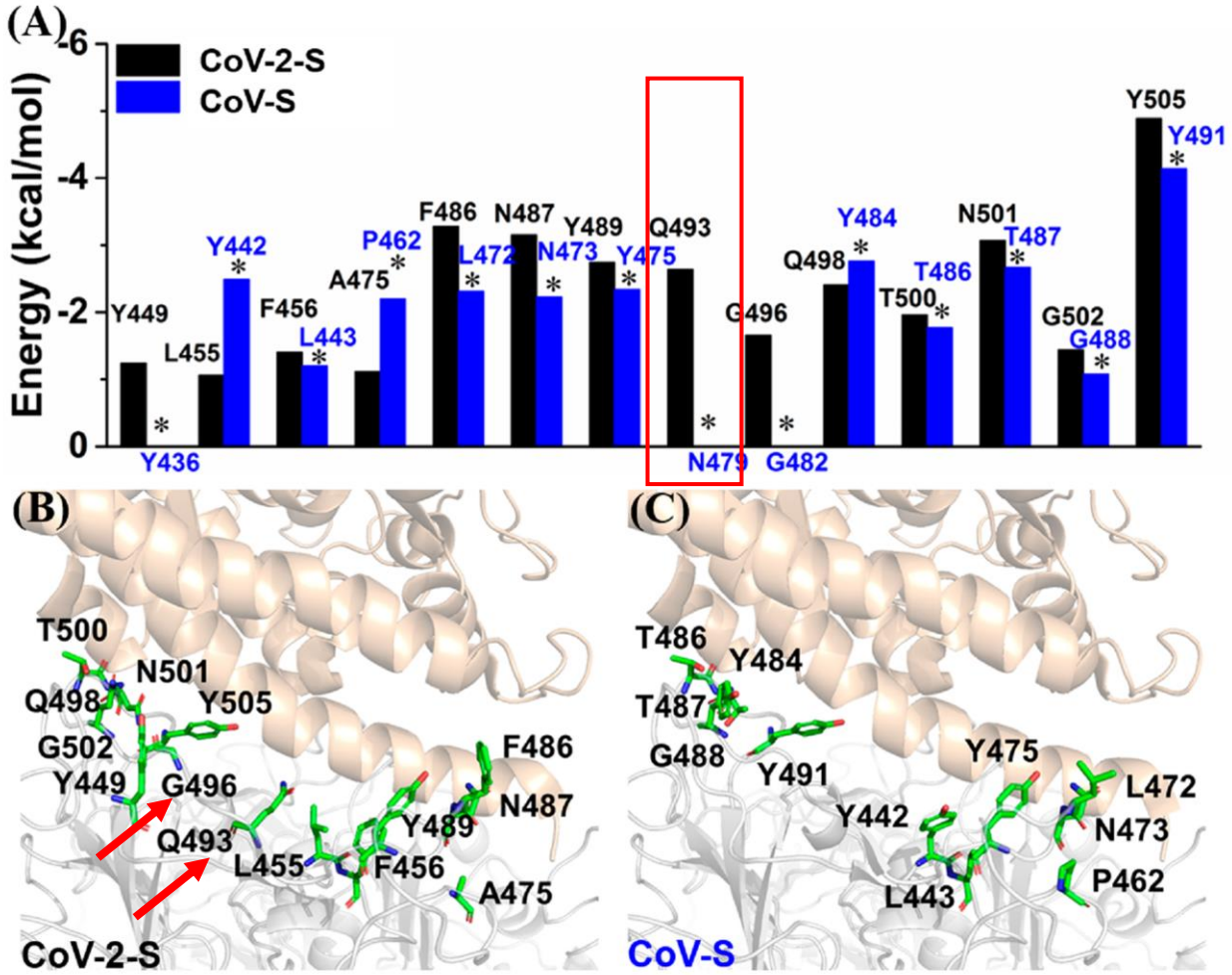
- The accessible conformations of SARS-2 is 5.5% while that of SARS is 22.7%.
- Transition from inaccessible to accessible conformation of SARS-2 has higher barrier (2.6-4.4 kcal/mol) than that of SARS (1.7 kcal/mol).
- Remarkably, the SARS spike has evenly distributed conformation space, while the SARS-2 are mainly located at inaccessible ones.



- Although the SARS-2 spike RBD has stronger binding affinity to ACE2, the SARS-2 spike has much less accessible conformation and higher transition barrier, making the SARS-2 spike difficult to bind ACE2.
- **In terms of infectiousness of SARS-2, human being is quite lucky this time.**
- **Why does the SARS-2 RBD bind to ACE2 stronger?**

The origin of the stronger binding affinity of SARS2 RBD-ACE2



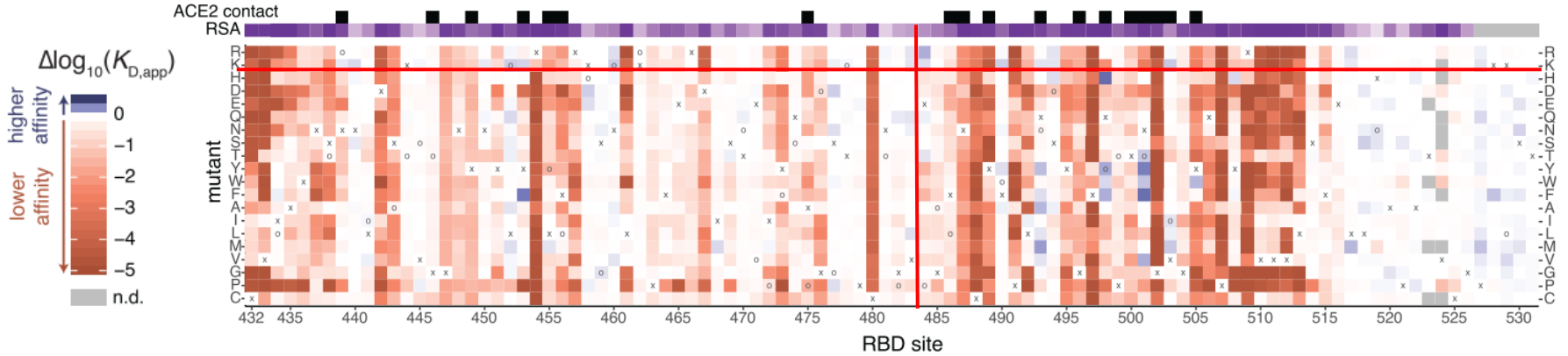


- **In comparison with SARS, some mutation enhanced the spike-ACE2 binding of SARS-2.**
- **Could mutations significantly affect the spike binding mAbs?**

C. Peng, W. Zhu, *et al.*, *J. Phys. Chem. Lett.* **2020**, *11*, 10482−10488

New variants, new risks?

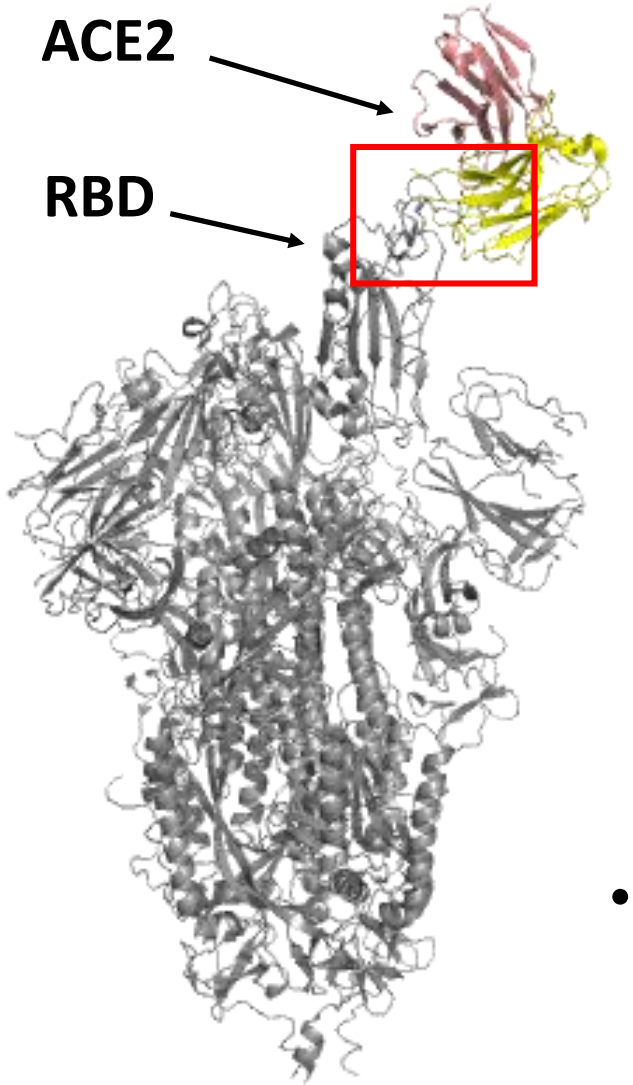
- A variant harbored a E484K mutation (B.1.351) was first sequenced on 15/12/2020.
- The variant may have stronger binding to ACE2, indicating potential severe infectiousness.
- The neutralization by some mAbs against the variant was weakened, indicating potential immune evasion risk.

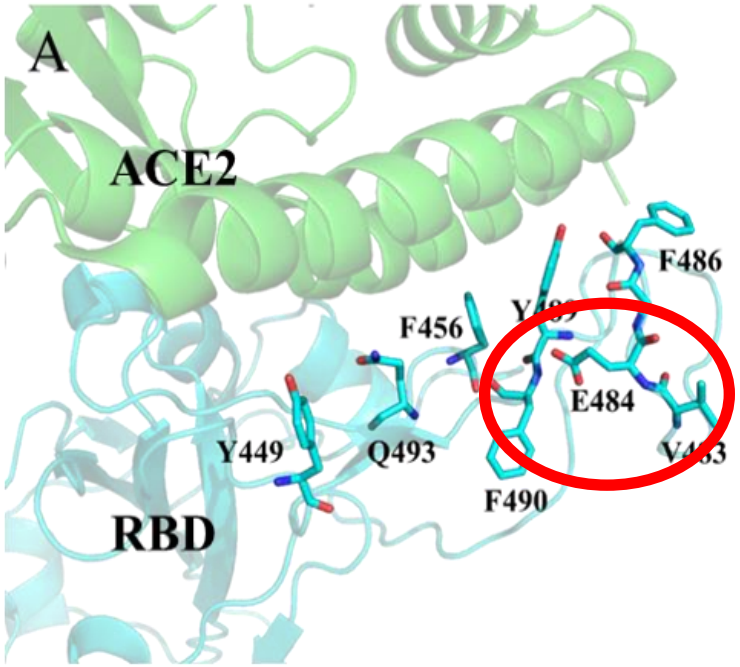


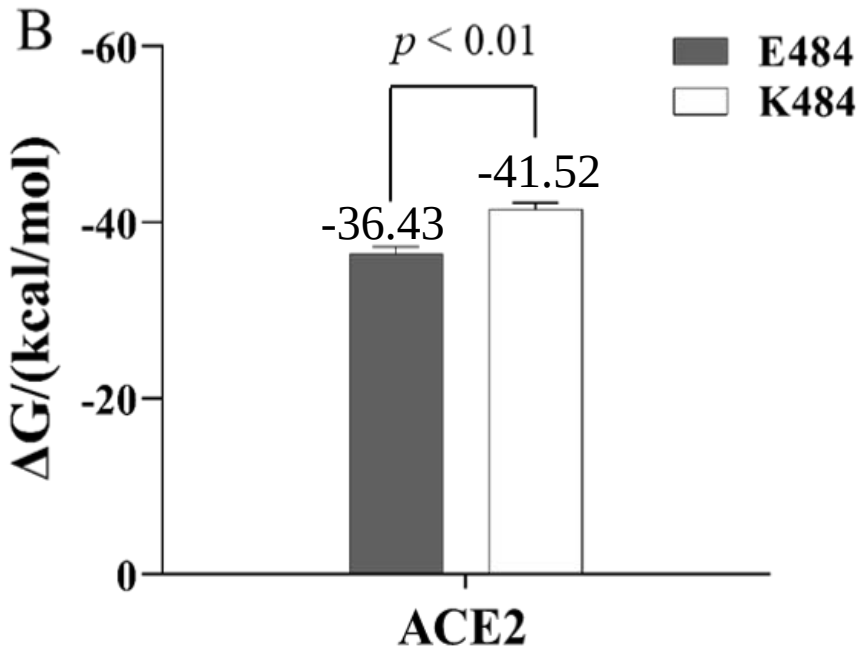
Starr, T. N., *et al*. *Cell.* **2020**

- What is the reason of the high infectiousness and diminished neutralization?

Calculated binding affinity of ACE2-RBD harbored E484K mutation



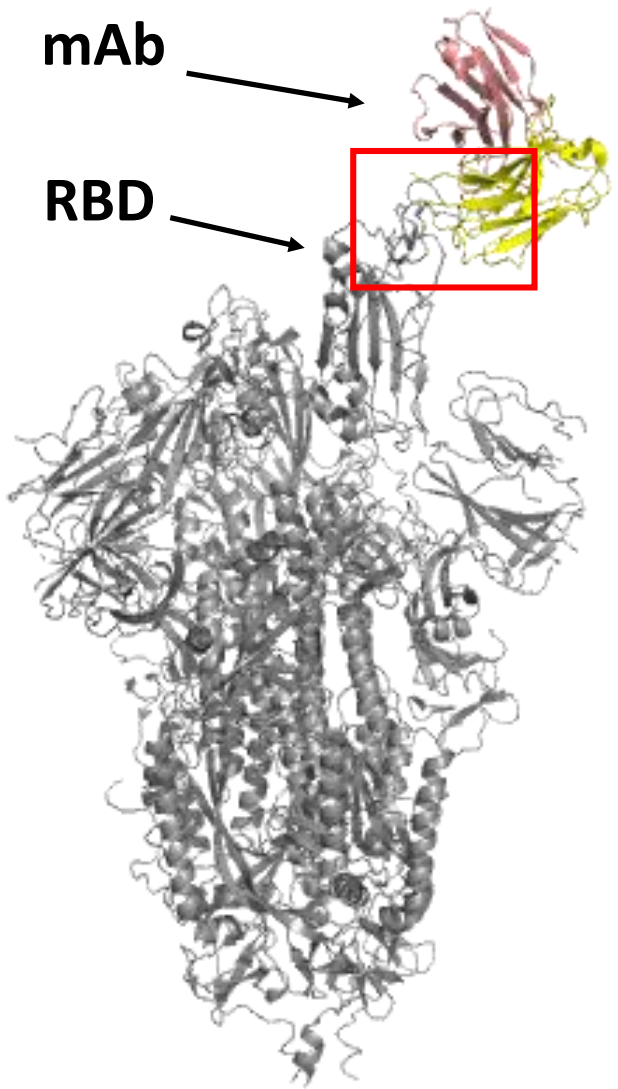


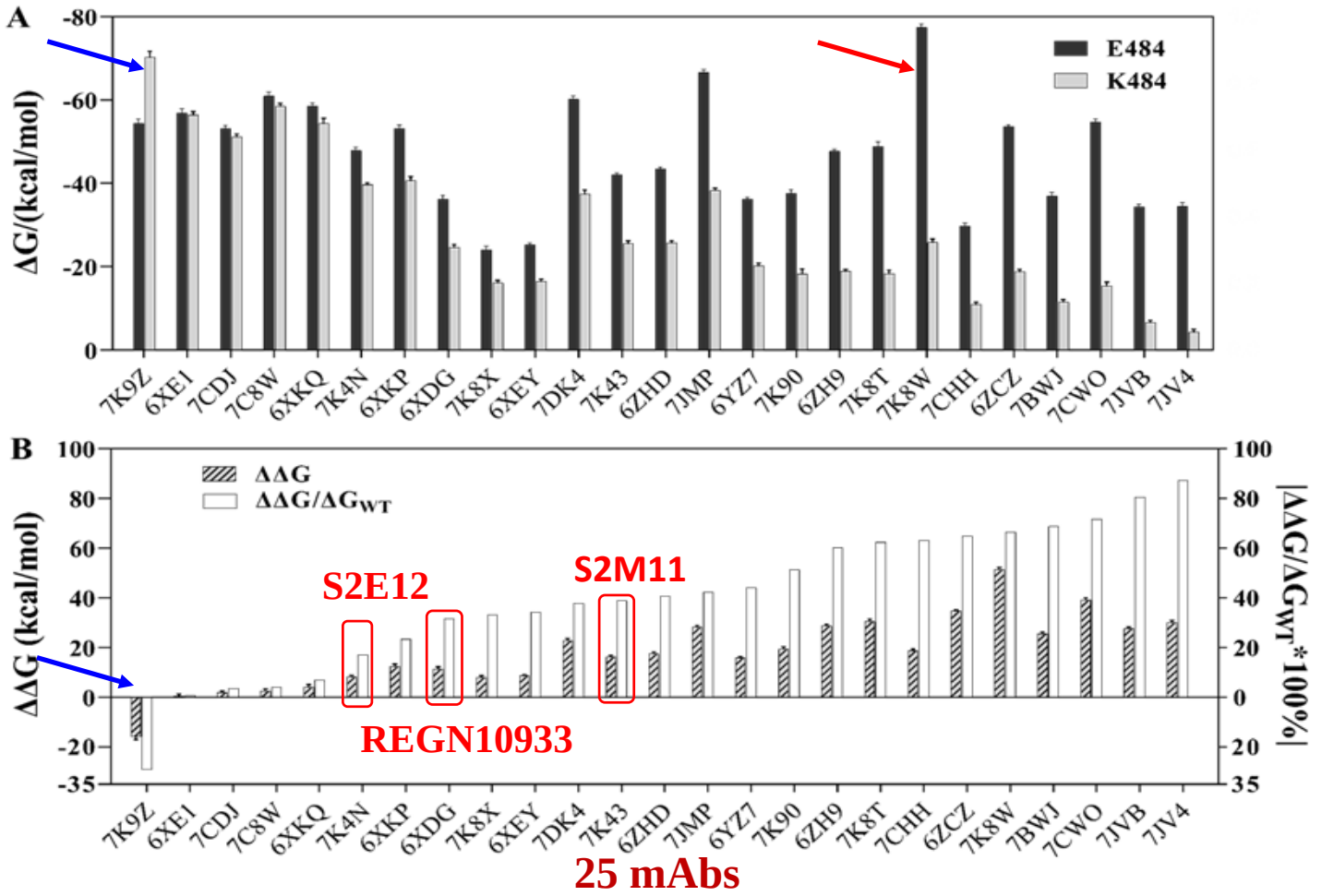


Methods: Amber18, Amber ff14SB, 4-20 ns MD simulation trajectory for MM/GBSA calculation

- The E484K mutation of the spike resulted in a strong binding to ACE2 than WT, indicating high infectiousness of the new variant.
- Any changes in binding mAbs?

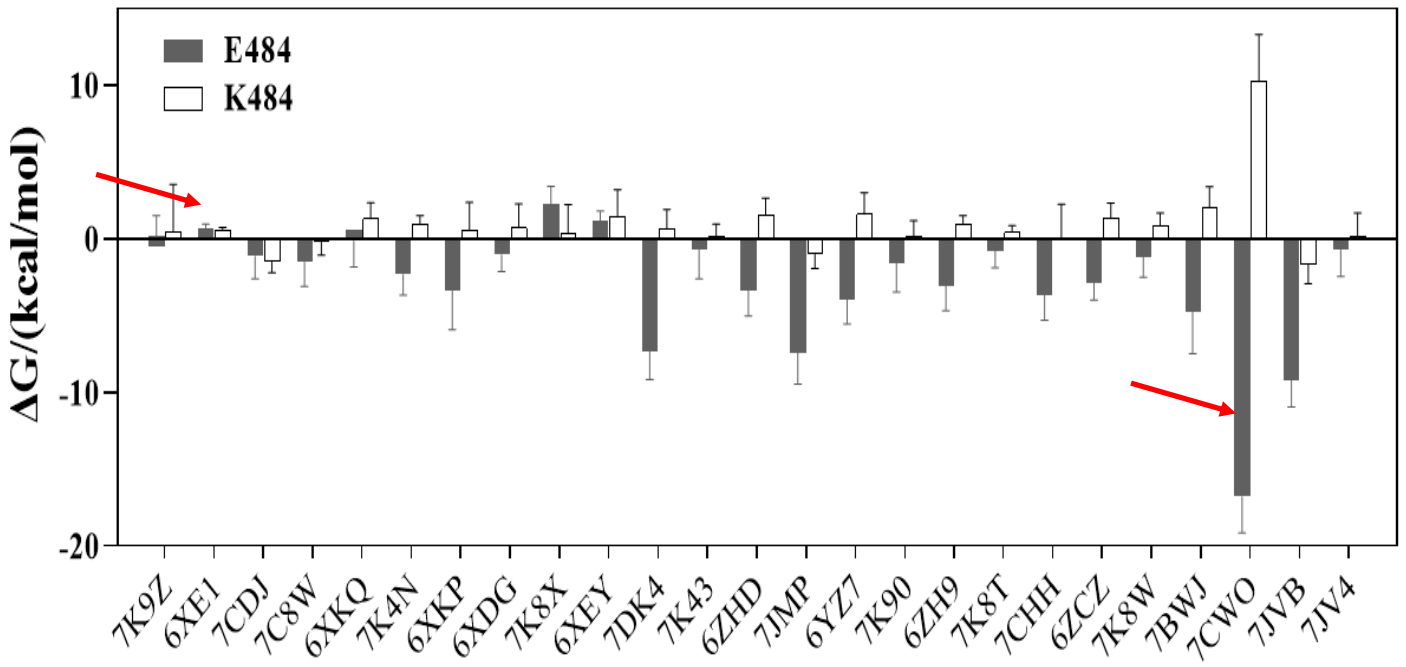
Predicted binding affinity of the variant RBD to 25 mAbs

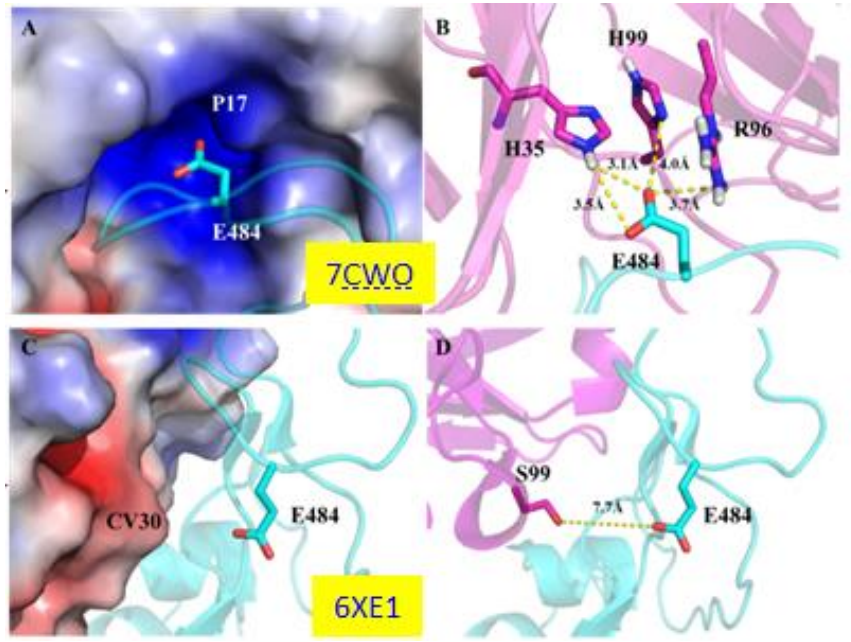




- 22/25 mAbs (88%) showed decreased binding affinity to the E484K mutated RBD;
- Only 7K9Z (4%) showed increased binding affinity;
- Indeed, 3 of them were reported having decreased affinity.

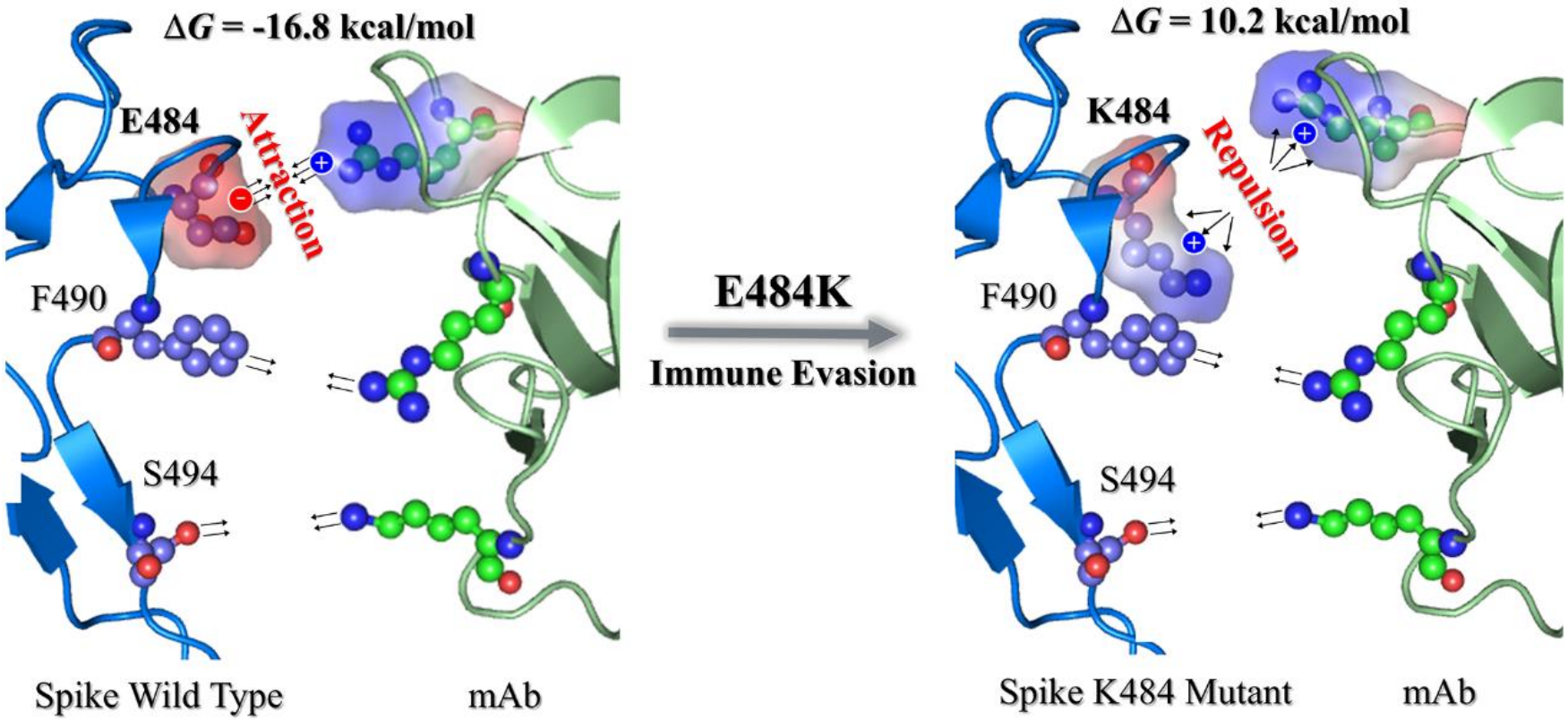
Contribution of the residue E484/K484 to ΔG





- E484 is favorable to binding ACE2 in 21/25 (86%) systems, while K484 is only in 3/25 (12%) (7CWO);
- The negative E484 is attractive to the mAb 7CWO, while the K484 is repulsive to;
- 7 systems have ΔG weakened by ≥5 kcal/mol, indicating high immune evasion risk.

Effect of E484K mutation on the spike-ACE2 binding



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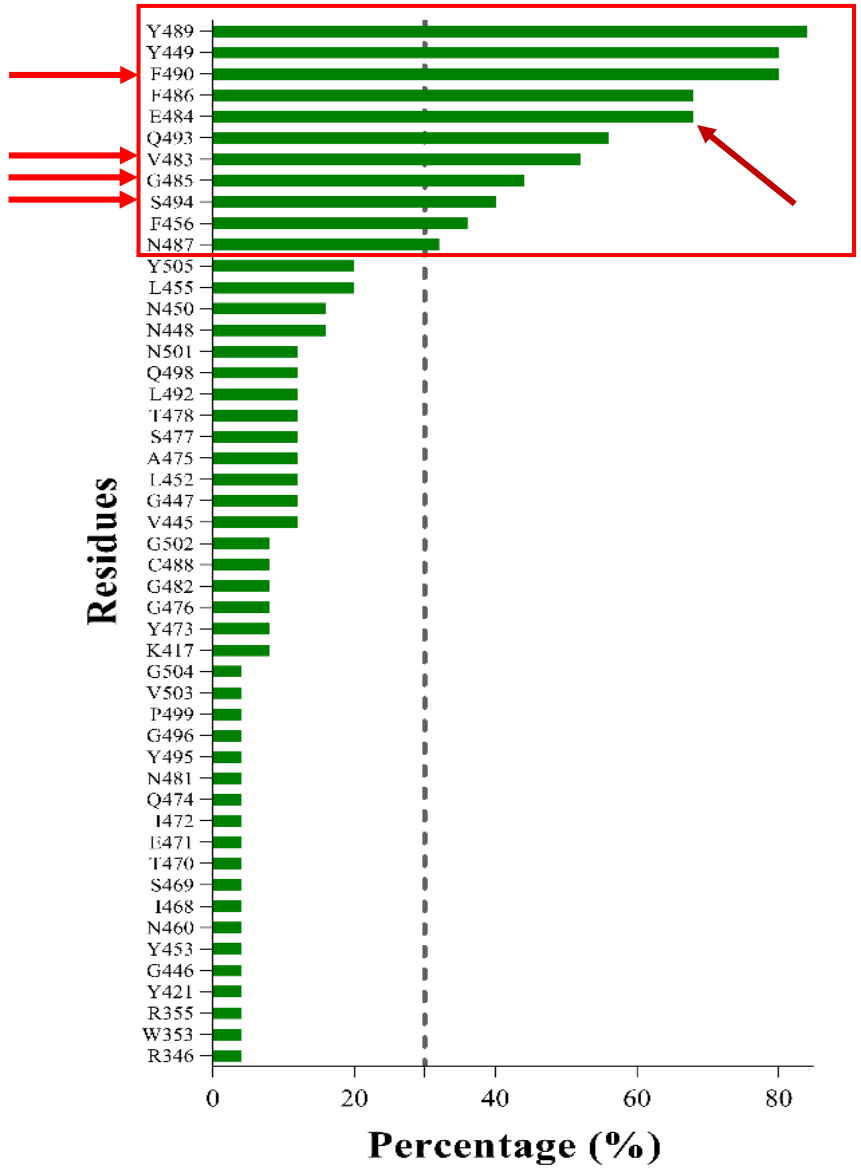
Other potential mutation with immune evasion risk predicted

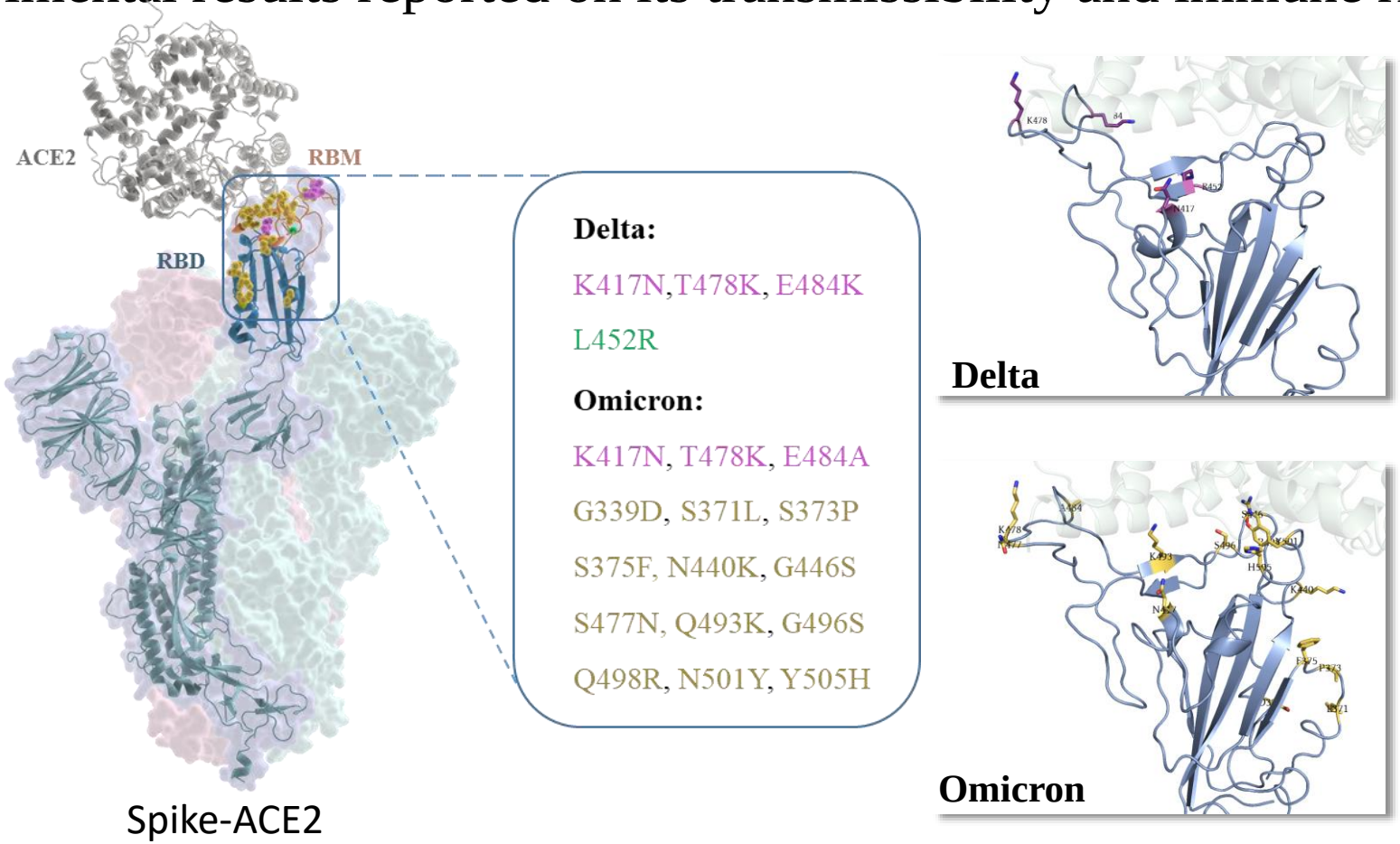


mAb-Spike interaction:

- Besides E484, there are additional 10 residues that are important to binding mAbs (>30% mAbs);
- Among them, Y489, Y449, F486, Q493, F456 and N487 are important to binding ACE2, their mutations may result in weaker infectiousness;
- But, the mutations of F490, V483, G485 and S494 might be highly risk to infectiousness and immune evasion.

Infectiousness of Omicron *vs* Delta

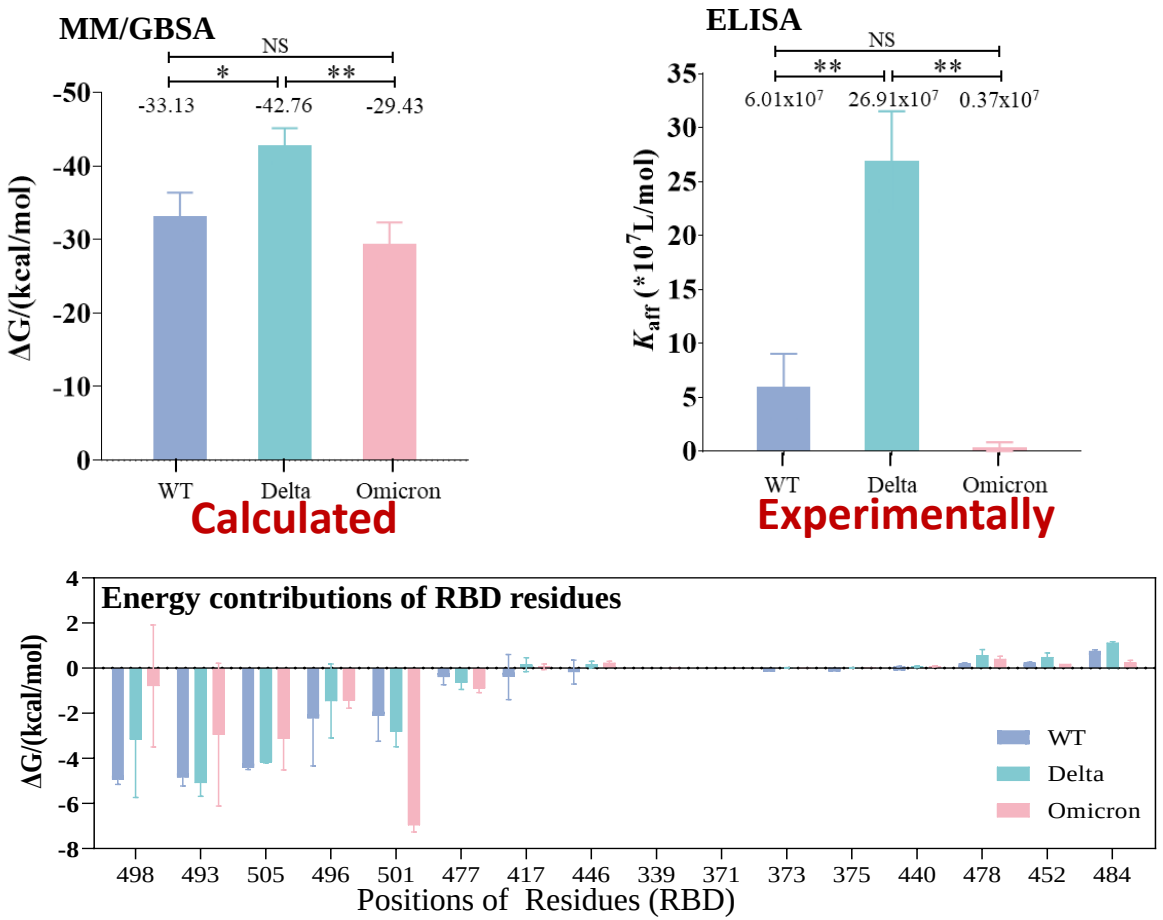
- Omicron variant (B.1.1.529) was first reported to WHO on 24/11/2021;
- No experimental results reported on its transmissibility and immune risk;



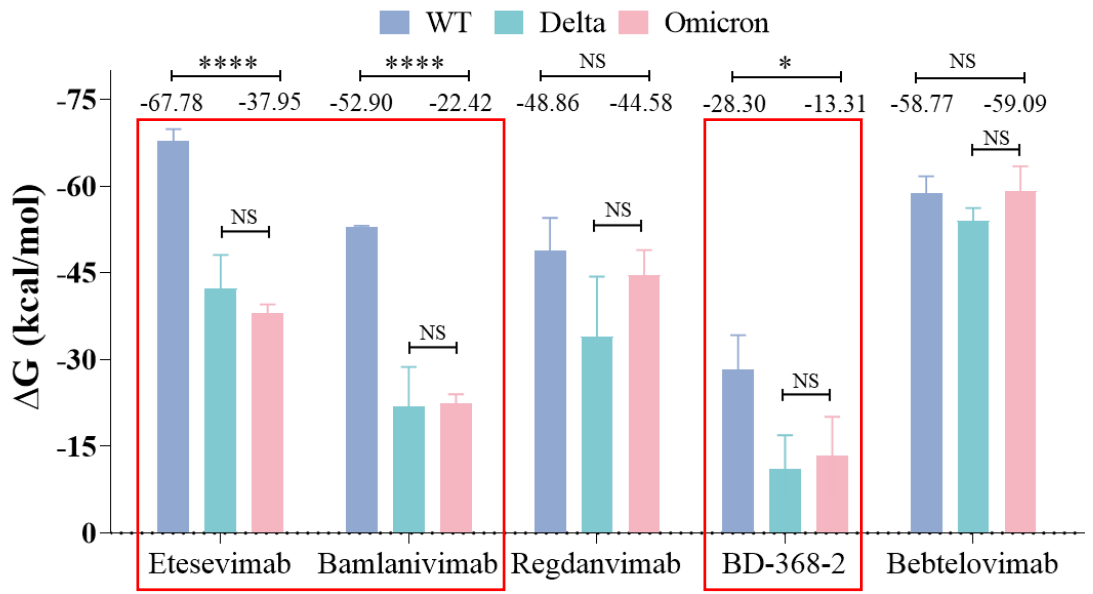
Omicron has 15 mutations on RBD, while Delta has 4.

Calculated and Experimentally Determined Binding Affinity

Binding affinity of RBD-ACE2



Binding affinity of RBD-mAbs



- $RBD_{Omicron}$ possesses much **weaker binding affinity** to ACE2 than RBD_{Delta}
- Omicron variant has high risk of **immune evasion**

Methods: Gromacs2020.2, Amber ff14SB, 50-200 ns MD simulation trajectory for MM/GBSA calculation

L Wu, W Zhu, *et al.*, *Signal Transduction and Targeted Therapy* **2022,** *7* (1), 8

Summary

1. The RBD of SARS-2 spike has stronger binding affinity to ACE2 than SARS, but the accessible conformation of the SARS-2 spike is significantly less than SARS spike, which should be one of the reasons why SARS-2 spike has weaker binding affinity.
2. E484K mutant has weaker binding affinity to most mAbs due to the weakened electrostatic interaction or the increased electrostatic repulsion, possibly leading to high risk of immune evasion.
3. Omicron RBD has lower binding affinity than Delta RBD to ACE2, but has great potential risk of immune evasion to most mAbs.

Publications

1. Leyun Wu[1], Liping Zhou[1], Mengxia Mo[1], Tingting Liu[1], Chengkun Wu[1], Chunye Gong, Kai Lu, Likun Gong[*], Weiliang Zhu[*], Zhijian Xu[*], SARS-2 Omicron RBD shows weaker binding affinity than the currently dominant Delta variant to human ACE2. *Signal Transduction and Targeted Therapy* **2022,** *7* (1), 8.

2. Leyun Wu[1], Cheng Peng[1], Yanqing Yang, Yulong Shi, Liping Zhou, Zhijian Xu[*], Weiliang Zhu[*], Exploring the immune evasion of SARS-2 variant harboring E484K by molecular dynamics simulations. *Briefings in Bioinformatics* **2022**, *23* (1), bbab383, DOI: https://doi.org/10.1093/bib/bbab383

3. Cheng Peng,# Zhengdan Zhu,# Yulong Shi, Xiaoyu Wang, Kaijie Mu, Yanqing Yang, Xinben Zhang, Zhijian Xu,* and Weiliang Zhu*, Computational Insights into the Conformational Accessibility and Binding Strength of SARS-2 Spike Protein to Human Angiotensin-Converting Enzyme 2, *J. Phys. Chem. Lett.* **2020**, *11*, 10482−10488

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- Miss Mengxia Mo

Thank You for Your Attention