Cocktail of REGN Antibodies Binds More Strongly to SARS-CoV-2 Than Its Components, But The Omicron Variant Reduces Its Neutralizing Ability

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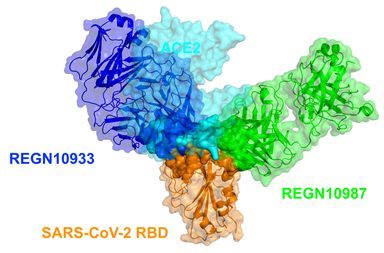
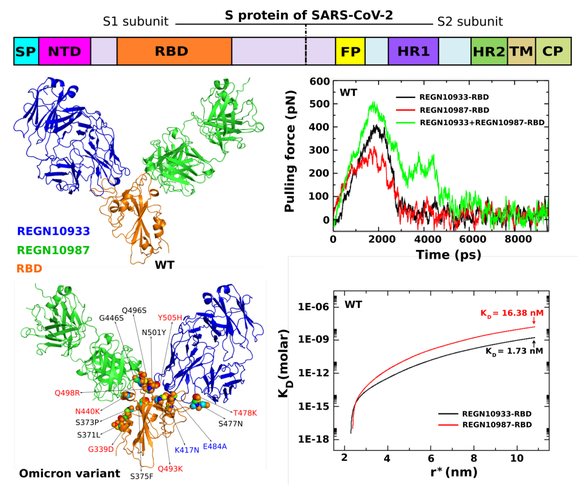


Introduction

Recently, a cocktail of REGN10987 and REGN10933 antibodies was shown to be an excellent candidate for the treatment of Covid-19. Here, using all-atom steered molecular dynamics and coarse-grain umbrella sampling we examine the interactions of the receptor binding domain (RBD) of the SARS-CoV-2 spike protein with REGN10987 and REGN10933 separately as well as together. Both computational methods show that REGN10933 binds to RBD more strongly than REGN10987. Importantly, the cocktail binds to RBD (simultaneous binding) more strongly than its components. The dissociation constants of REGN10987-RBD and REGN10933-RBD complexes calculated from the coarse-grained simulations are in good agreement with the experimental data. Thus, REGN10933 is probably a better candidate for treating Covid-19 than REGN10987, although the cocktail appears to neutralize the virus more efficiently than REGN10933 or REGN10987 alone. We also studied the effectiveness of these antibodies on the two most dangerous variants Delta and Omicron. Consistent with recent experimental reports, our results confirmed that the Omicron variant reduces the neutralizing activity of REGN10933, REGN10987, and REGN10933+REGN10987 while the Delta variant slightly changes their activity.



Materials and Simulation Methods

Cα coarse-grained model: each amino acid is represented by a single interaction site centered on the Cα atom position.

Configuration potential energy:

$$E = \sum_i k_b(r_i - r_0)^2 + \sum_i \frac{-1}{\gamma} ln\left\{exp[-\gamma(k_\alpha(\theta_i - \theta_\alpha)^2 + \varepsilon_\alpha)] + exp\left[-\gamma k_\beta(\theta_i - \theta_\beta)^2\right]\right\} + \sum_{ij} k_{\varphi,ij}[1 + cos(j\varphi_i - \delta_{ij})] + \sum_{ij} \frac{q_i q_j e^2}{4\pi\varepsilon_0\varepsilon_r r_{ij}} exp\left[\frac{-r_{ij}}{l_D}\right] + \sum_{ij\in\{NC\}} \eta\varepsilon_{ij}^{NC}\left[13\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - 18\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{10} + 4\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_{ij\notin\{NC\}} \varepsilon_{ij}^{NN}\left[13\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - 18\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{10} + 4\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] \quad (1)$$

Calculations of Dissociation constant K_D

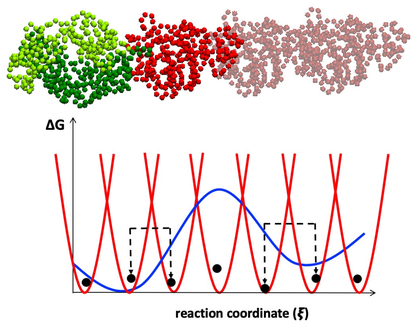
$$K_D = \frac{[monomer][monomer]}{[complex]} \quad (2)$$

Fraction of the bound state complex,

$$P_b = \frac{[complex]}{[monomer]+[complex]} \quad (3)$$

Fraction of unbound state, $P_u = 1 - P_b$ (4)

Replica exchange umbrella sampling MD simulation



Criterion for replica exchange in REX-US

$$P(1 \leftrightarrow 2) = e^{-\Delta}$$

$$\Delta = \beta[U_2(X_1) + U_1(X_2) - U_1(X_1) - U_2(X_2)]$$

$$P_b = \frac{\int_0^{r_b} 4\pi r^2 e^{-\beta G(r)} dr}{\int_0^{r^*} 4\pi r^2 e^{-\beta G(r)} dr} \quad (5)$$

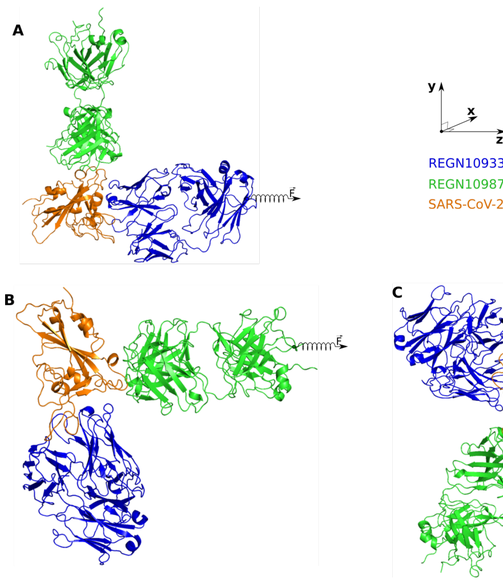
$$[monomer] = \frac{P_u}{V(r^*)} C_0 \quad (6)$$

So, $K_D = \frac{P_u}{P_b}[monomer]$ (7)

All-atom steered molecular dynamics simulation

The force experienced by the pulled atom is measured according to the following equation: $F = k(\Delta z - vt)$. The spring constant k=600 kJ/(mol*nm2) (~1020 pN/nm), which is a typical value used in atomic force microscope (AM) experiments. pulling speed v = 0.5 nm/ns.

Estimation of pulling work, unbinding free energy:



The extended Jarzynski's equation:

$$\exp\left(\frac{-\Delta G}{k_B T}\right) = \left\langle \exp\left(\frac{W(t) - \frac{1}{2}k(z_t - vt)^2}{k_B T}\right)\right\rangle_N \quad (8)$$

The pulling work:

$$W = \int F dx = \sum_{i=1}^{N} \frac{F_{i+1} + F_i}{2}(x_{i+1} - x_i) \quad (9)$$

Figure 1: Structure of the REGN10933+REGN10987-RBD complex, retrieved from PDB with ID 6XDG. RBD is shown in orange while green and blue describe REGN10987 and REGN10933. The external force is applied to (A) REGN10933, (B) REGN10987 and (C) RBD (REGN10933+REGN10987). The pulling direction in SMD simulations is shown with a spring along the *z*-axis.

Results and Conclusions

Coarse-grained simulation results

REGN10933 binds to wide type RBD more stronger than REGN19876

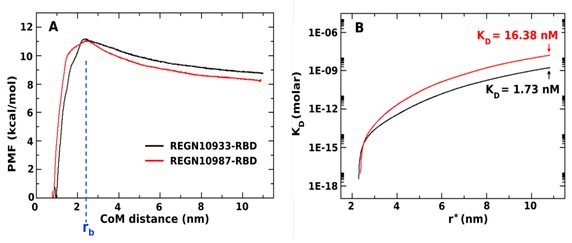


Figure 2: (Left) one-dimensional potential of mean force of REGN10933-RBD (black curve) and REGN10987-RBD (red curve). (Right) K_D curves as a function of r* corresponding to the change in the total free monomer concentration

	REGN10933	REGN10987	REGN10933 + REGN10987
Experiment Hansen, J.; et al. Science **2020**, 369, 1010-1014.	3.37	45.2	//
Our Simulation	1.37	16.38	//
PRODIGY Xue, L. C.; et al. Bioinformatics **2016**, 32, 3676-3678.	31 ± 8.96	69 ± 25.33	0.056 ± 0.027

Figure 3: The K_D (nM) of REGN-COV2 antibodies bound to RBD for the WT case was estimated from the experimental and computational results

Steered molecular dynamics simulation results

Ranking of binding affinities of REGN-COV2 antibodies to RBD: REGN10987 < REGN10933 < REGN10933+REGN10987

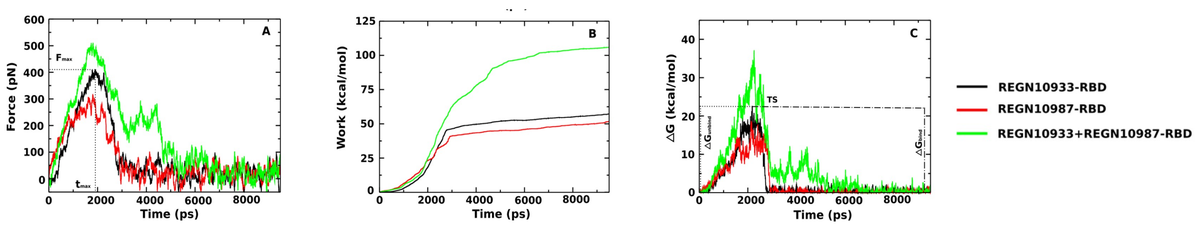


Figure 4: Time dependence of (A) the force, (B) pulling work, and (C) non-equilibrium free energy of the REGN10933-RBD, REGN1097-RBD and REGN10933+REGN10987-RBD complexes. The results were averaged over five independent SMD runs

The stability of REGN10933-RBD and REGN10933+REGN10987-RBD is driven by electrostatics interaction while the stability of REGN10987-RBD is controlled by vdW interaction

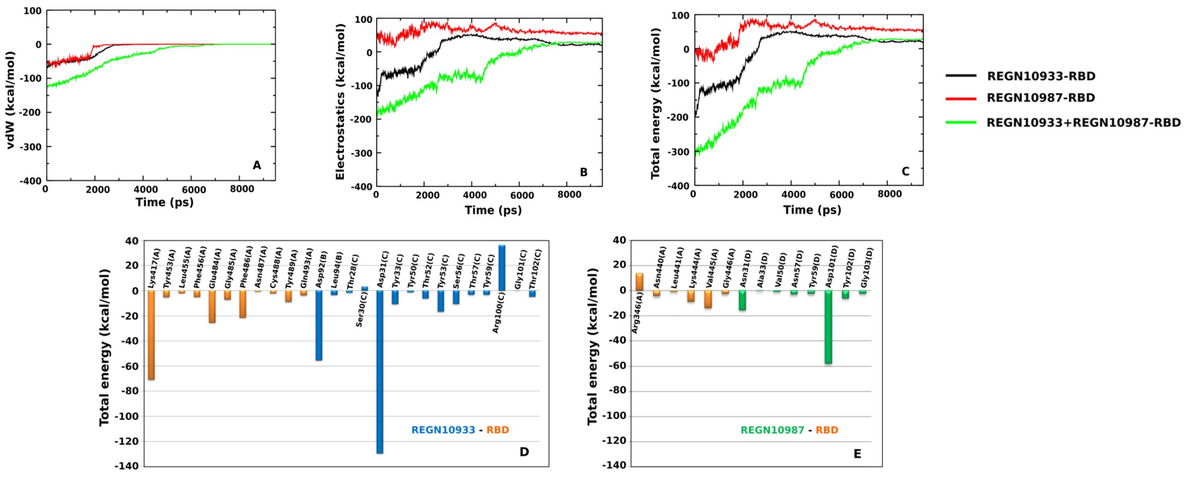


Figure 5: Time dependence of (A) the force, (B) pulling work, and (C) non-equilibrium free energy of the REGN10933-RBD, REGN1097-RBD and REGN10933+REGN10987-RBD complexes. The results were averaged over five independent SMD runs

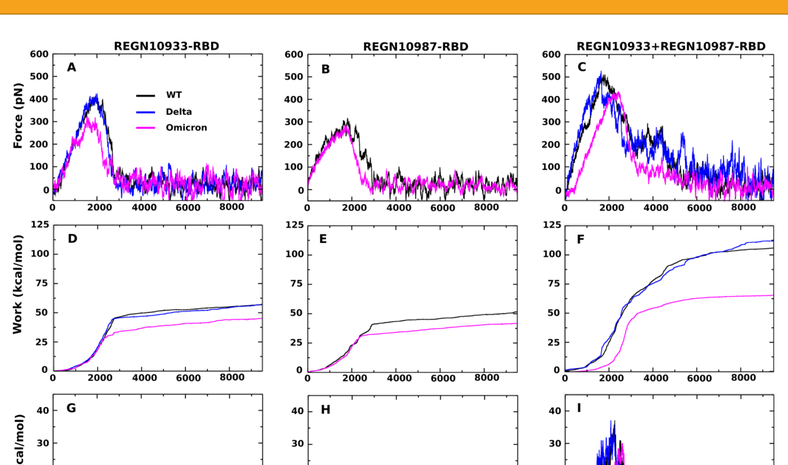
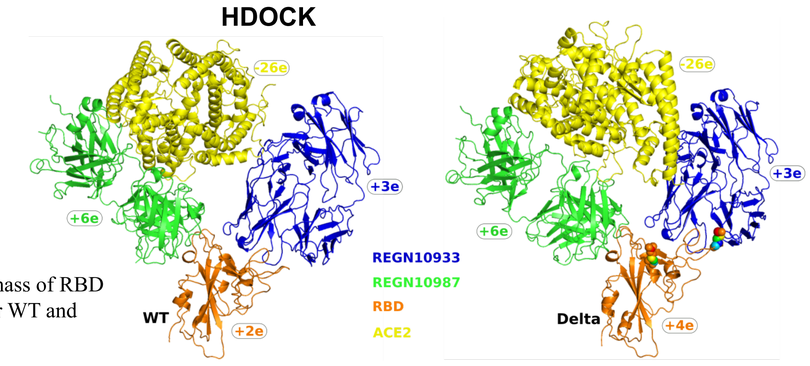


Figure 6: Time dependence of (A to C) pulling force, (D to F) pulling work, and (G to I) non-equilibrium free energy of the complexes. These results averaged over five independent SMD runs for WT and the variants.

Mutation points on RBD		
WT	Delta	Omicron
G339: -0.1		D339: -2.5
S371: 0.03		L371: 0.1
S373: -0.2		P373: -0.1
S375: -0.03		F375: -0.04
K417: -71.1		N417: -5.0
N440: 0.1		K440: 6.4
G446: 0.02		S446: -0.8
L452: -0.5	R452: 0.4	
S477: -9.9		N477: -8.8
T478: -3.4	K478: -3.5	K478: -5.5
E484: -25.7		A484: -1.9
Q493: -3.9		K493: -8.5
G496: -0.3		S496: -2.1
Q498: 1.6		R498: 16.7
N501: -2.1		Y501: -1.2
Y505: -0.02		H505: 1.3

Table: Total Interaction Energies (kcal/mol) of the Important Residues of RBD to REGN10933 (Casirivimab) and REGN10987 (Imdevimab) for the WT and variants.

Cocktail shows a stronger neutralizing activity against Delta than against WT.



The distance between the centers of mass of RBD and ACE2 is 2.37 nm and 2.19 nm for WT and Delta, respectively.

Conclusions

- ***REGN10933 binds to RBD more strongly than REGN10987. The SMD results is consistent with the result calculated from coarse-grained REX-US.***
- ***SMD results showed that REGN10933 and REGN10933+REGN10987 seem to have a similar activity for the Delta variant and WT.***
- ***Mutations K417N, N440K, E484A, and Q498R play a key role in reducing the effectiveness of REGN-COV2 antibodies against the Omicron variant.***

Acknowledgments

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References

Nguyen, H., Lan, P. D., Nissley, D. A., O'Brien, E. P., & Li, M. S. (2022). Cocktail of REGN antibodies binds more strongly to SARS-CoV-2 than its components, but the Omicron variant reduces its neutralizing ability. The Journal of Physical Chemistry B, 126(15), 2812-2823.