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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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A promising approach to combat Covid-19 infections is the development of effective antiviral antibodies that target the SARS-CoV-2 spike protein. Understanding the structures and molecular mechanisms underlying the binding of antibodies to SARS-CoV-2 can contribute to quickly achieving this goal. 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. REGN10987's association with RBD is driven by van der

Waals interactions, while the electrostatic interactions dominate in the case of REGN10933 and the cocktail. 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 with the K417N, N440K, L484A, and Q498R mutations playing a decisive role, while the Delta variant slightly changes their activity.

Keywords: SARS-CoV-2, RBD, Covid-19, REGN-COV2, REGN10933, REGN10987, antibody cocktail, SMD simulation, Coarse-grained simulation, Delta variant, Omicron variant.