DOI 10.18699/SBB-2022-178

Structure and dynamics of REGN10987 Fab interaction with S-proteins of Delta and Omicron SARS-CoV-2 variants

Shenkarev Z.O.[1]*, Pichkur E.[2], Nolde D.E.[1], Varizhuk A.[3], Kocharovskaya M.V.[1, 4], Kirpichnikov M.P.[1, 5], Lyukmanova E.N.[1, 5]

[1] *Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry, RAS, Moscow, Russia*

[2] *National Research Center "Kurchatov Institute", Moscow, Russia*

[3] *Federal Research and Clinical Center of Physical-Chemical Medicine, FMBA, Moscow, Russia*

[4] *Phystech School of Biological and Medical Physics, Moscow Institute of Physics and Technology, Dolgoprudny, Moscow Region, Russia*

[5] *Interdisciplinary Scientific and Educational School of Moscow University "Molecular Technologies of the Living Systems and Synthetic Biology", Biological Faculty, Lomonosov Moscow State University, Moscow, Russia*

** zakhar-shenkarev@yandex.ru*

Key words: coronavirus; neutralizing antibodies; RBD; ACE-2; cryo-EM

Knowledge how neutralizing antibodies recognize various SARS-CoV-2 variants is critical for design of vaccines and antibody-based therapeutics. Here, we reported 2.3 Å cryo-EM structure of full-length trimeric S-protein of the SARS-CoV-2 Delta variant in a complex with recombinant analogue of REGN10987 antibody's Fab (Fig. 1).

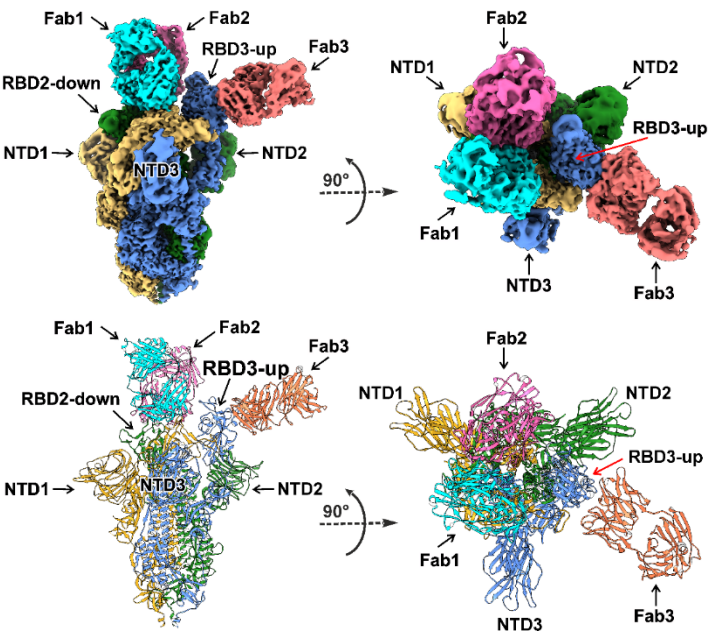

Fig. 1. Cryo-EM structure of the full-length Delta SARS-CoV-2 spike protein in a complex with REGN10987 Fab. Cryo-EM map of the S-protein/Fab complex refined to 2.3Å resolution and pseudoatomic model of the complex after local refinement of RBD/Fab regions. NTD – N-terminal domain; RBD – receptor-binding domain; Three protomers (1, 2, and 3) of S-protein are colored by yellow, green, and blue respectively. Corresponding Fabs are colored by cyan, magenta, and coral. RBD1/Fab1 and RBD2/Fab2 complexes are in 'down' conformation, while RBD3/Fab3 – in 'up'

Receptor-binding domain (RBD)/Fab regions were locally refined to 3.2–3.4 Å. Two RBDs were in the ‘down’ state, while third RBD adopted the ‘up’ conformation. Fab interacted with RBDs in both conformations occupying a fragment of the receptor-binding motif and blocking ACE2 recognition. 3D variability analysis revealed high mobility of the RBD/Fab regions. Molecular dynamics simulations explained the differences observed in the Fab interaction with Delta and Omicron RBDs. Our study provides a structural insight into the role of all known to date significant RBD mutations of the Omicron and other SARS-CoV-2 variants in the REGN10987 evasion. Data obtained will be useful for development of new therapeutic antibodies.

Acknowledgements: This work was supported by the Russian Science Foundation (the project No. 19-74-30014).