Commentary

iMedPub Journals
http://www.imedpub.com

Archives of Clinical Microbiology
ISSN 1989-8436

2021
Vol. 12 No. 5:175

Fast Restoration of a Cross-Reactive SARS-CoV Therapeutic Antibody

Sara Zhang, Mike Young and Jason J Pan*

Department of NovoAb Bioanalytics, Structural Characterization Division, Victoria, British Columbia, Canada V8P 2L5

*Corresponding author: Pan JJ,

Department of NovoAb Bioanalytics, Structural Characterization Division, Victoria, British Columbia, Canada V8P 2L5,

jpan@novoab.com

Citation: Zhang S, Young M, Pan JJ (2021) Fast Restoration of a Cross-Reactive SARS-Cov Therapeutic Antibody for SARS-Cov-2. Arch Clin Microbiol Vol.12 No.5: 175.

Received: September 15, 2021; Accepted: September 29, 2021; Published: October 07, 2021

Description

The rapid spread of SARS-Cov-2 remains a major threat for public health and global economy, both preventative and therapeutic solutions are therefore urgently needed. Through the use of Epitope-Guided Antibody Design (EGAD), we successfully restored a cross-reactive SARS-CoV antibody for SARS-CoV-2. Compared to the precursor antibody CR3022, the newly designed antibody NOVOAB-20 binds to SARS-CoV-2. Receptor Binding Domain (RBD) with a more than an order of magnitude higher affinity. Because this antibody targets a highly conserved epitope and the mutations on SARS-CoV-2 known so far are all not in this region, it also has the potential to block future SARS-CoV-2 mutants. As a fully humanized antibody, NOVOAB-20 is a promising candidate to be developed as potential therapeutics for SARS-CoV-2, either as monotherapy or in combination with other neutralizing antibodies targetingdifferent epitopes (e.g. the ACE2 binding site). This fast antibody restoration rationale may also be useful for designing drugs for other pandemic-causing viruses.

Effective therapeutics against SARS-CoV-2 is urgently needed to contain the ongoing global COVID-19 pandemic. Aside from vaccine development, therapeutic Monoclonal AntiBody (mAb) is considered one ofthe most promising alternative approaches as it potentially can not only prevent but also treat the disease, and may work better for the elderly or people who are immune compromised. SARS-CoV-2 uses its Receptor Binding Domain (RBD) on the S protein to engage the host receptor ACE2 for viral entry. RBD-targeting antibodies that blocks ACE2 binding could neutralize the virus. Many such mAbs have been discovered so far, with most of them from the blood of recovered COVID-19 patients. However, since the ACE2 binding site (epitope) on RBD mutates rather quickly, mAbs targeting this site may easilylose activity for new viral mutants. This was actually what happened for SARS-CoV 17 years ago-all of the effective mAbs developed for SARS-CoV lost their neutralizing ability on SARS-CoV-2. When developing a mAb drug against rapidly mutating viruses like SARS-CoV-2, it is desirable if the drug works not only for the original virus, but also for its mutated variants. This is the focus of the current work.

CR3022 is a unique broadly neutralizing antibody discovered for SARS-CoV, and it targets a highly conserved cryptic epitope on RBD. It completely blocked all mutant escapes of CR3014, a mAb that targets ACE2 interaction site on SARS-CoV RBD. However, CR3022 lost neutralization ability for SARS-CoVv-2, although it still binds to the viral RBD. Considering the extremely high similarities between SARS-CoV and SARS-CoV-2 (almost identical 3D structure of their RBDs and Spike proteins; both viruses use the same receptor ACE2 for cell entry; and the binding modes between the two RBDs and ACE2 are nearly identical), we reasoned that the diminished neutralization of CR3022 could be due to its more than 10-fold lowered binding affinity to SARS-CoV-2 RBD compared to SARS-CoV. This motivated us to design a cross-reactive antibody for SARS-CoV-2 based on CR3022 and its epitope.

Multiple factors are considered in our EGAD program to optimize the interaction of new antibody candidates with the SARS-CoV-2 RBD antigen. These include amino acid hydrophobic interactions, electrostatic interactions, aromatic-aromatic interactions, hydrogen bonding of both main chain and side chain, backbone-dependent bond angles, potential new salt bridges, and side chain-solvent interactions. When we perform in silico amino acid mutation in the precursor antibody, CR3022 in this case, the potential effect on the conformational dynamics of the corresponding antibody-antigen complex is also taken into account based on our extensive experience in antibody epitope mapping. Here we take epitope residue H519 as an example. In the crystal structure of CR3022-RBD (SARS-CoV-2) complex.

Conclusion

In summary, we successfully designed and generated a fully humanized IgG antibody against SARS-CoV-2 RBD by using epitope-guided antibody design. It has a high binding affinity comparable to the binding between mAb CR3022 and SARS-CoV RBD, which resulted in complete neutralization of the SARS-CoV virus. We expect NOVOAB-20 to work similarly on the current SARS-Cov-2 virus. Since it targets a highly conserved cryptic epitope, it should also work for SARS-CoV-2 mutants. It is worth noting that the mutations on SARS-Cov-2 known so far are all not in the epitope of this mAb. In addition, CR3022 was reported to exhibit a superior synergy effect when used in combination with CR3014, a mAb targeting the ACE2 binding site on SARS-CoV. The combination enhanced the potency of both mAbs by 5 and 20 times, respectively. As antibody drugs are usually very expensive because of their high production cost, the dramatically (>10 ×) reduced dosage may be an important factor to consider if antibody drugs are going to be used for COVID-19 patients. It would be also interesting to screen the antibody pools isolated from recovered COVID-19 patients or vaccinated animals through trageted epitope mapping towards this highly conserved epitope, in the hope of discovering more cross-reactive mAbs like NOVOAB-20. Compared to the effective but time and labour-intensive single B cell sorting method, the fast antibody restoration rationale presented in this work may also be useful for designing drugs for other viruses, especially during a pandemic.