Antibody cocktail effective against variants of SARS-CoV-2

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an RNA virus with a high mutation rate. Importantly, several currently circulating SARS-CoV-2 variants are associated with loss of efficacy for both vaccines and neutralizing antibodies.

Methods: We analyzed the binding activity of six highly potent antibodies to the spike proteins of SARS-CoV-2 variants, assessed their neutralizing abilities with pseudovirus and authentic SARS-CoV-2 variants and evaluate efficacy of antibody cocktail in Delta SARS-CoV-2-infected hamster models as prophylactic and post-infection treatments.

Results: The tested RBD-chAbs, except RBD-chAb-25, maintained binding ability to spike proteins from SARS-CoV-2 variants. However, only RBD-chAb-45 and -51 retained neutralizing activities; RBD-chAb-1, -15, -25 and -28 exhibited diminished neutralization for all SARS-CoV-2 variants. Notably, several cocktails of our antibodies showed low IC50 values (3.35–27.06 ng/ml) against the SARS-CoV-2 variant pseudoviruses including United Kingdom variant B.1.1.7 (Alpha), South Africa variant B.1.351 (Beta), Brazil variant P1 (Gamma), California variant B.1.429 (Epsilon), New York variant B.1.526 (Iota), and India variants, B.1.617.1 (Kappa) and B.1.617.2 (Delta). RBD-chAb-45, and -51 showed PRNT50 values 4.93–37.54 ng/ml when used as single treatments or in combination with RBD-chAb-15 or -28, according to plaque assays with authentic Alpha, Gamma and Delta SARS-CoV-2 variants. Furthermore, the antibody cocktail of RBD-chAb-15 and -45 exhibited potent prophylactic and therapeutic effects in Delta SARS-CoV-2 variant-infected hamsters.

Conclusions: The cocktail of RBD-chAbs exhibited potent neutralizing activities against SARS-CoV-2 variants. These antibody cocktails are highly promising candidate tools for controlling new SARS-CoV-2 variants, including Delta.

Keywords: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Receptor-binding domain (RBD), Neutralizing antibody, Cocktail therapy

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic, with more than 255 million confirmed cases and 5.14 million deaths as of November 2021. In response to the pandemic, major efforts have been devoted to identifying neutralizing antibodies (Abs) from COVID-19 convalescent patient sera [1–8]. In parallel, mouse immunization and phage display have been utilized to identify other potential therapeutic Abs against SARS-CoV-2 [9–12]. In order to optimize the efficacy of antibody treatments, it may be desirable to develop cocktails of neutralizing Abs that can simultaneously bind different sites of the spike (S) protein receptor binding domain (RBD) and synergistically neutralize SARS-CoV-2 [8, 13]. The emergency use authorizations...
(EUA)s and rapid deployment of antibody-based prevention and therapeutic agents for COVID-19—such as neutralizing Abs, COVID-19 convalescent sera, messenger RNA vaccines, inactivated vaccines, and viral-vector vaccines—have greatly improved clinical outcomes and helped to prevent progression of infected individuals to intensive care and mortality.

During the evolution of SARS-CoV-2 in humans, variants containing the D614G substitution in the S protein have become dominant due to their increased infectivity and high transmission [14, 15]. Compared to the original SARS-CoV-2 S protein, the D614G mutants are more stable and have a reduced tendency for premature conformation change [16, 17]. However, it widely is accepted that the D614G mutation itself does not increase the severity of disease. More recently, further genetic variants of SARS-CoV-2 have emerged and begun circulating around the world. Among the variants, four that were first identified in the United Kingdom (Alpha, B.1.1.7), South Africa (Beta, B.1.351), Brazil (Gamma, P1) and India (Delta, B.1.617.2) are classified as variants of concern (VOCs). These VOCs have been shown to exhibit increased infectivity, cause more severe disease, reduce the neutralization ability of antibodies generated by previous infection or vaccination, and impair the effectiveness of current therapeutic monoclonal antibodies or vaccines [18–20]. Thus, the VOCs are clinically associated with enhanced transmissibility, increased disease severity, higher risk of death and decreased therapeutic and vaccine effectiveness [21–24]. In particular, Alpha (B.1.1.7), Beta (B.1.351) and Gamma (P1) contain an N501Y mutation in the RBD, which has been shown to increase ACE2 receptor affinity and virulence in mice [25–27]. In addition to N501Y, Beta (B.1.351) and Gamma (P1) include K417N/T and E484K mutations in the RBD, which may also cause important conformational changes. Notably, the binding and neutralization effects of many SARS-CoV-2-neutralizing Abs can be abolished by the K417N and/or E484K mutations [20, 26, 28]. The fourth VOC, Delta (B.1.617.2), harbors L452R and T478K mutations in the RBD and is even more highly transmissible than the other three [29]. In the past several months, the Delta (B.1.617.2) variant has accounted for more than 90% of new cases worldwide. The L452R mutation enhances S protein stability, viral fusogenicity and infectivity, while the T478 mutation likely increases the affinity to ACE2 and impacts the neutralization abilities of monoclonal antibodies and convalescent serum [30, 31]. It has been shown that Delta (B.1.617.2) can fully or partially escape neutralization by antibodies targeting the RBD or N-terminal domain of SARS-CoV-2 S protein [18, 31]. The L452R and E484K/Q mutations are also present in several variants of interest (VOIs), including Epsilon (B.1.427/429) and Iota (B.1.526), which were identified in the United States, and Kappa (B.1.617.1), which was identified in India. These VOIs are predicted to have different transmission, diagnostic, therapeutic, or immune escape profiles than other strains [19]. As the emergence of variant lineages is a major challenge preventing effective control of the COVID-19 pandemic, next-generation vaccines and therapeutic Abs must target variant epitopes, especially those with a high possibility to alter transmission or infectivity. With regard to the efficacies of antibody therapies or vaccines, it will be crucial to understand the implications of antigenic variation on agents for clinical use.

Studies with authentic virus or pseudovirus suggest that neutralization by some antibodies and immune sera may be diminished for variants expressing mutated S protein [18, 20, 28, 32–37]. In our previous study, we generated six neutralizing chimeric Abs (chAbs) against the RBD of SARS-CoV-2 S protein, all of which exhibited potent neutralizing capabilities in vitro and in vivo. Furthermore, the prophylactic and therapeutic efficacies of these chAbs or antibody cocktails were confirmed in SARS-CoV-2-infected mouse and hamster models [38, 39]. Variants of SARS-CoV-2 that carry mutations in the RBD could affect the binding and neutralizing abilities of our antibodies. Therefore, we sought to evaluate the neutralizing activities of our chAbs with pseudotyped virus of SARS-CoV-2 variants, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P1), Epsilon (B.1.427/429), Iota (B.1.526) and Kappa (B.1.617.1) and Delta (B.1.617.2). Our data showed that most of the chAbs maintain neutralizing ability against these variants, which correlated with the abilities of the chAbs to bind full S protein. Moreover, a cocktail of therapeutic chAbs targeting separate epitopes on the receptor binding motif (RBM) of SARS-CoV-2 S protein may increase therapeutic efficacy and decrease the potential for emergence of virus escape mutants. The prophylactic and therapeutic potentials of these antibodies and their combinations were confirmed in SARS-CoV-2 hamster infection models, wherein injection of the therapeutic chAb cocktail markedly reduced the virus titers, underscoring their potential for use in prevention and treatment of COVID-19. Thus, cocktails of our chAbs may provide effective tools to tackle the emergence of new variants harboring multiple S protein mutations.

**Materials and methods**

**Antibody binding to SARS-CoV-2 S protein variants by ELISA**

ELISA plates were coated with 0.5 μg/ml SARS-CoV-2 variant S-His protein or EpEX-His protein (negative control) in 0.1 M NaHCO₃ (pH 8.6) buffer at 4 °C overnight,
followed by blocking with PBS containing 1% bovine serum albumin (BSA) at RT for 2 h. After blocking, the wells were washed twice with PBS; then, the plates were stored at −20 °C. RBD-chAb or rabbit anti-His Ab was added at a concentration of 30 ng/ml in each well, and the plate was incubated for 1 h at room temperature. The plates were washed with PBS containing 0.1% Tween-20 (PBST) three times and then incubated for 1 h with Peroxidase AffiniPure Goat Anti-human IgG (H+L) (Jackson ImmunoResearch) (1:4000 dilution) or Peroxidase AffiniPure Goat Anti-rabbit IgG (H+L) (Jackson ImmunoResearch) (1:10,000 dilution), as appropriate. After three washes with PBST, signal was produced.

The SARS-CoV-2 variants used in this study, i.e., Alpha (hCoV-19/Taiwan/792/2020), Gamma (hCoV-19/Taiwan/906/2021) and Delta (hCoV-19/Taiwan/1144/2021), were obtained from Taiwan Centers for Disease Control (CDC). The PRNT assay was performed at the BSL-3 facility in the Institute of Biomedical Sciences, Academia Sinica.

In vivo prophylactic and therapeutic assays for SARS-CoV-2 infection

Hamster models of SARS-CoV-2 infection were used to evaluate the potency of neutralizing chAbs against SARS-CoV-2 RBD in vivo. Each hamster was first intraperitoneally administered RBD-chAb antibody or normal human IgG as a control. Twenty-four hours later, each hamster was intranasally inoculated with 10^4 PFU SARS-CoV-2 (strain: TCDC#4). At day 3 after virus challenge, the hamsters were sacrificed to harvest lung tissues to quantify the viral load. Lung tissues were weighed and homogenized for two cycles of 2 min in the Speed-Mill PLUS equipment (Analytik Jena AG) or RLT buffer (RNeasy mini kit, Qiagen). After tissue homogenization, the supernatant was collected for the TCID_{50} assay or RNA extraction. Homogenates were serial tenfold dilutions and applied to a Vero-E6 cell monolayer in 1% FBS/DMEM for 4 days. The plates were observed for cytopathic effects and used to calculate TCID_{50} the amount of virus causing cytopathic effects in 50% of inoculated cells.

The therapeutic activities of chAbs cocktails in hamsters were evaluated after intranasal inoculation with 10^4 PFU virus. Mixtures of RBD-chAb-15 and -45 were intraperitoneally injected into hamsters at day 2 after SARS-CoV-2 inoculation. The hamsters were sacrificed to collect lung tissue at day 3 post-challenge. All animal studies were carried out in accordance with the established guidelines for the ethical use and care of animals provided by the Institutional Animal Care and Use Committee (IACUC) at Academia Sinica, Taiwan. All experiments involving animals were approved by the IACUC (protocol 20–05–147). The SARS-CoV-2 strains used in this study are clinical isolates of the WT strain (hCoV-19/Taiwan/4/2020) and Delta variant (hCoV-19/
Taiwan/1144/2021) and were obtained from the Taiwan CDC.

Real-time RT-PCR for SARS-CoV-2 RNA quantification
SARS-CoV-2 viral burden in the lung tissues was measured by Taqman quantitative real-time RT-PCR with primers designed to target the envelope (E) gene of SARS-CoV-2 genome, as previously described [40]. Forward primer E-Sarbeco-F1 (5’-ACAGGTACGTATA GTAAAGCCTG-3’) and reverse primer E-Sarbeco-R2 (5’-ATATTGCACGTACGCACA-3’), in addition to the probe E-Sarbeco-P1 (5’-FAM-ACA CTA GCC CTG CTT CG-BBQ-3’) were used. RNA was extracted from lung homogenate supernatants using RNeasy Mini Kit (QIAGEN, Germany) according to the manufacturer’s instructions. The RNA sample (5 μL) was added in a total 25 μL mixture using Superscript III one-step RT-PCR system with Platinum Taq Polymerase (Thermo Fisher Scientific, USA). The final reaction mix contained 400 nM forward and reverse primers, 200 nM probe, 1.6 mM of deoxy-ribonucleoside triphosphate (dNTP), 4 mM magnesium sulphate, 50 nM ROX reference dye and 1 μL of enzyme mixture from the kit. The cycling conditions were performed with a one-step PCR protocol: 55 °C for 10 min for cDNA synthesis, followed by 3 min at 94 °C and 45 amplification cycles at 94 °C for 15 s and 58 °C for 30 s. Data were collected and calculated with the Applied Biosystems 7500 Real-Time PCR System (Thermo Fisher Scientific, USA). To establish a qPCR standard curve, a synthetic 113-bp oligonucleotide fragment was used to estimate numbers of viral genome.

Results
Binding and neutralizing abilities of anti-RBD chAbs
VOCs contain common mutations, such as K417N/T, L452R, T478K, E484K, in their RBD domains; therefore, we first used ELISA to examine the binding ability of our RBD-chAbs to recombinant S protein of SARS-CoV-2 variants. The results showed that most of the RBD-chAbs maintained binding ability to S protein from SARS-CoV-2 variants, with PRNT50 values ranging from 50 to 94 ng/ml (Fig. 1C). In line with the antibody recognition sites identified in our previous study, only the binding of RBD-chAb-25 was significantly diminished when tested against the S proteins of Alpha, Beta, and Gamma variants containing the N501Y mutation. This result suggested that besides RBD-chAb-25, most of our neutralizing Abs might retain activity against these VOCs. Our previous work showed that RBD-chAb-25 and -45 could simultaneously bind to the RBD of SARS-CoV-2 S protein using cryo-EM, and the combination exhibited a synergistic effect compared to single chAbs when used as a prophylactic treatment [39]. Therefore, we further examined the neutralizing abilities of our six most potent RBD-chAbs toward several SARS-CoV-2 variant pseudoviruses. Pseudovirus neutralization assays revealed that RBD-chAb-25 exhibited poor neutralizing abilities for the United Kingdom variant B.1.1.7 (Alpha), South African variant B.1.351 (Beta) and Brazil variant P1 (Gamma), all of which contain the N501Y mutation (Fig. 1B). However, the rest of the RBD-chAbs retained their abilities to neutralize several common variants, including the United Kingdom variant B.1.1.7 (Alpha), South African variant B.1.351 (Beta), Brazil variant P1 (Gamma), California variant B.1.429 (Epsilon), New York variant B.1.526 (Iota) and India variants B.1.617.1 (Kappa) and B.1.617.2 (Delta) (Fig. 1B). RBD-chAb-45 and -51 exhibited lower IC50 values and better neutralizing activities than the other four RBD-chAbs for all variants (Table 1). Additionally, we evaluated the neutralization potentials of the RBD-chAbs by conducting the in vitro plaque reduction neutralization test (PRNT). RBD-chAb-45 and -51 could effectively block infection with authentic SARS-CoV-2 Alpha, Gamma and Delta variants, with PRNT50 values of less than 18 ng/ml; RBD-chAb-15 and -28 were worse at neutralizing the authentic SARS-CoV-2 Alpha and Gamma variants, with PRNT50 values ranging from 50 to 94 ng/ml (Fig. 1C).

Neutralizing abilities of anti-RBD chAbs in combination
Previously, we found that RBD-chAb-45 and -51 share overlapping epitopes according to an ELISA-based competition-binding assay [39]. In addition, RBD-chAb-15 and -28 have highly similar epitopes, and RBD-chAb-25 has an epitope that partially overlaps with those of RBD-chAb-15 and -28. However, only RBD-chAb-25 loses its neutralizing ability against SARS-CoV-2 variant pseudoviruses with the N501Y mutation [39]. To evaluate the neutralizing abilities of cocktails containing RBD-chAbs with different epitopes, we performed neutralization tests using SARS-CoV-2 variant pseudoviruses. Combinations...
**Fig. 1** (See legend on previous page.)
of RBD-chAb-15 or -28 with RBD-chAb-45 or -51 exhibited high neutralizing activities toward different SARS-CoV-2 pseudoviruses, including Alpha, Beta, Gamma, Epsilon, Iota, Kappa and Delta variants (Fig. 2A). The RBD-chAb cocktails showed low IC50 values ranging from 3 to 27 ng/ml (Table 2). To evaluate the RBD-chAbs cocktail neutralization potential against the authentic SARS-CoV-2 Alpha, Gamma and Delta variants, we performed the PRNT and showed that RBD-chAb-15 or -28 combined with RBD-chAb-45 or -51 displayed the high potencies against the authentic virus; the PRNT50 values were less than 38 ng/ml (Fig. 2B).

Prophylactic effect of RBD-chAb in SARS-CoV-2-infected hamsters

Next, we studied our antibodies in a hamster model of mild human SARS-CoV-2 infection that has been utilized in the development of therapies [41]. We examined the efficacies of two low-dose RBD-chAbs (RBD-chAb-15 and -45) individually and as a cocktail in the hamsters (Fig. 3). Single intraperitoneal injections of one RBD-chAb alone (3 mg/kg) or RBD-chAb-15 and -45 in combination (1.5 mg/kg each) were made one day prior to WT SARS-CoV-2 infection and conferred dramatic protection; infectious SARS-CoV-2 titers were determined from the lung tissue at the third day post-infection. The viral genome RNA (as measured by RT-qPCR) could still be detected at the end of the experiment (Fig. 3A). Nevertheless, the infectious SARS-CoV-2 titers were just above the limit of detection (LOD, 1 × 10^2 TCID50/ml) for almost all hamsters in the RBD-chAb cocktail-treated group (1.5 mg/kg of each RBD-chAb-15 and -45) at 3 days post-infection (Fig. 3B).

Therapeutic effect of RBD-chAb cocktail in SARS-CoV-2-infected hamsters

We next tested the therapeutic effects of the antibody cocktail administered after SARS-CoV-2 infection in the hamster model (Fig. 4). We treated hamsters with RBD-chAb-15 or -28 combined with RBD-chAb-45 at one day post-inoculation with WT (Fig. 4A, B) or Delta (Fig. 4C, D) SARS-CoV-2 (intranasal). The infectious...
Fig. 2 (See legend on previous page.)
SARS-CoV-2 titers were then determined from lung tissue at the third day post-infection. The levels of viral genome RNA were measured by RT-qPCR at the end of the experiment (Fig. 4A, C). Similar to the results of the antibody prophylaxis experiments, the infectious SARS-CoV-2 titers were close to the limit of detection (LOD, $1 \times 10^2$ TCID$_{50}$/ml) for all hamsters receiving RBD-chAb cocktail treatments (1.5 mg/kg each of RBD-chAb-15 and -45 for WT SARS-CoV-2; 3 mg/kg each of either RBD-chAb-15 or -28 combined with RBD-chAb-45 for Delta SARS-CoV-2) at 3 days post-infection (Fig. 4B, D). Collectively, these data demonstrated remarkable prophylactic and therapeutic effects of combined RBD-chAb-15 and -45 in SARS-CoV-2-infected hamsters.

**Discussion**

SARS-CoV-2 is an RNA virus with a high mutation rate, which results in the rapid emergence of variants. Identified variants with high transmissibility or that cause increased rates of severe disease or death are classified as VOCs and include: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) [42]. A major public health concern is that new SARS-CoV-2 variants may be
resistant to neutralizing antibodies induced by infection or vaccination, as well as therapeutic antibodies developed against original SARS-CoV-2. Here, we report that our previously identified antibodies, RBD-chAb-45 and -51, retain high binding ability for all tested SARS-CoV-2 variant pseudoviruses, including four VOCs (Fig. 1). Because the epitope for RBD-chAb-25 includes N501 in the S protein, the antibody had reduced binding ability toward variants with the N501Y mutation [including B.1.1.7 (Alpha), B.1.351 (Beta) and P1 (Gamma)] (Fig. 1). However, RBD-chAb-25 still retained the ability to recognize other variants (Fig. 1). Combinations of RBD-chAbs showed neutralization ability for all tested SARS-CoV-2 variants in the pseudovirus neutralization assay (Fig. 2).

Therefore, our six RBD-chAbs can be used strategically to create cocktail therapies against various SARS-CoV-2 mutant strains. The prophylactic and therapeutic potentials of a cocktail including RBD-chAb-15 and -45 were verified in SARS-CoV-2-infected hamster animal models (Figs. 3, 4).

Up to now, hundreds of mutations have been identified in the S protein of SARS-CoV-2. Some of these mutations might confer resistance to vaccines and neutralizing Abs due to local or global changes in protein conformation [20, 42]. For example, bamlanivimab (LY-CoV555), a human IgG1 targeting the RBD of S protein, was discovered by Eli-Lilly and AbCellera from single antigen-specific B cells of a COVID-19 convalescent patient [43].
Bamlanivimab received an EUA from the U.S. FDA to treat mild to moderate COVID-19 in adults and pediatric patients on November 9, 2020 [44], and it exhibits high neutralization potency against the B.1.1.7 (Alpha) variant strain. However, bamlanivimab is unable to block B.1.351 (Beta), P.1 (Gamma), B.1.429 (Epsilon), B.1.526 (Iota) and B.1.617.1 (Kappa) variants, due to the presence of E484K/Q or L452R mutations [20, 27, 28, 45]. Because many of the common circulating SARS-CoV-2 viral variants are resistant to the drug, the U.S. FDA revoked the EUA for use of bamlanivimab alone to treat COVID-19 on April 9, 2021.

Etesevimab (LY-CoV016) is a human IgG targeting the RBD of S protein that was identified from single B cells from a COVID-19 convalescent patient [7]. The combination of bamlanivimab and etesevimab received an EUA from the U.S. FDA, as it can neutralize B.1.1.7 (Alpha); however, B.1.351 (Beta) and P.1 (Gamma) variants with the K417N/T mutation are resistant to the cocktail of etesevimab and bamlanivimab [20, 28]. Notably, the B.1.351 (Beta) and P.1 (Gamma) variants are also resistant to casirivimab [20, 28]. In contrast, all of our potent neutralizing RBD-chAbs except RBD-chAb-25 could effectively block B.1.351 (Beta) and P.1 (Gamma) variants in the pseudovirus neutralization assay.

The SARS-CoV-2 B.1.617.2 variant, also known as Delta, was first identified in October 2020 in India and became the dominant strain around the world by July 2021 [18]. The B.1.617.2 (Delta) variant is up to 60% more transmissible than the B.1.1.7 (Alpha) variant, with an R_0 estimated at 5–7 [29]. Planas et al. reported that sera from people who had received one dose of Pfizer or AstraZeneca vaccines barely inhibited variant B.1.617.2 (Delta). Furthermore, the levels of neutralizing antibodies in people with two vaccine doses were 3–5-fold lower when tested against B.1.617.2 (Delta) compared to B.1.1.7 (Alpha) [18]. Additionally, bamlanivimab does not have appreciable antiviral activity against B.1.617.2 (Delta) due to the L452R mutation, but etesevimab retains neutralization ability against the variant [18, 45]. Our potent neutralizing antibodies, RBD-chAb-1, -15, -25 and -28, also exhibited partially reduced neutralizing ability against the B.1.617.2 (Delta) variant. However, according to the pseudovirus neutralization assay, RBD-chAb-45 and -51 retained high neutralizing capabilities toward the B.1.617.2 (Delta) variant, with IC_{50} values of about 8–15 ng/ml for single RBD-chAb treatments and 10–25 ng/ml for combination treatments.

According to cryo-EM structures of the UK (Alpha) variant S protein in combination with RBD-chAb-15 and -45, the two antibodies have non-overlapping epitopes and can simultaneously bind to the same upward pointing RBD. Further, three each of the RBD-chAb-15 and -45 molecules can bind to the three RBDs in a SARS-CoV-2 UK variant S protein trimer [38]. This cryo-EM structure of RBD-chAbs and S protein suggested that RBD-chAb-15 and -45 could be useful as a cocktail therapy for COVID-19, and we demonstrated that the cocktail of RBD-chAbs exhibited good neutralizing capability with low IC_{50} values in SARS-CoV-2 variant pseudovirus neutralizing experiments. Furthermore, the antibody cocktail of RBD-chAb-15 and -45 exhibited prophylactic and therapeutic effects in SARS-CoV-2-infected hamsters. Therefore, we predict that RBD-chAb-15 and -45 may be used strategically to create cocktail therapies against multiple SARS-CoV-2 variants.

**Conclusions**

COVID-19 is caused by SARS-CoV-2, and several currently circulating SARS-CoV-2 variants are associated with loss of efficacy for both vaccines and neutralizing antibodies. Here, we analyzed the binding of six highly chAbs to the spike proteins of SARS-CoV-2 variants with ELISA, and assessed their neutralizing abilities with pseudovirus and authentic SARS-CoV-2 variants. Notably, several cocktails of our antibodies showed low IC_{50} and PRNT_{50} values against the pseudovirus and authentic SARS-CoV-2 variants, respectively. Furthermore, the antibody cocktail of RBD-chAb-15 and -45 exhibited potent prophylactic and therapeutic effects in WT and Delta SARS-CoV-2 variant-infected hamsters. Thus, these antibody cocktails are highly promising candidate tools for controlling new SARS-CoV-2 variants.

**Abbreviations**

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; S: Spike; RBD: Receptor-binding domain; RBM: Receptor binding motif; VOC: Variant of concern; VOI: Variant of interest; chAbs: Chimeric antibodies; PRNT: Plaque reduction neutralization test; IC_{50}: Half maximal inhibitory concentration; CDC: Centers for disease control; PFU: Plaque-forming units; LOD: Limit of detection; EUA: Emergency use authorization.

**Acknowledgements**

We are indebted to Taiwan Centers for Disease Control for providing SARS-CoV-2infected hamsters. We thank the National RNAi Core Facility at the Academia Sinica in Taiwan for providing the SARS‑CoV‑2 pseudovirus. RML, YLL, MHT and JTJ performed the PRNT and animal experiments, HTL and WYC performed neutralizing Abs expression. YCC prepared pseudovirus and wrote paper. SHK performed in vitro neutralization by pseudovirus. KHL performed in vitro neutralization by pseudovirus and wrote paper. PYC performed ELISA binding assay of antibodies, in vitro neutralization by pseudovirus and wrote paper. SKH performed in vitro neutralization by pseudovirus. HTL and WYC performed neutralizing Abs expression. YCC prepared pseudovirus. RML, YLL, MHT and JTJ performed the PRNT and animal experiments, and revised the paper. HCW conceived the experiments, obtained funding, wrote and revised the paper, and provided overall direction for the study. All authors read and approved the final manuscript.

**Funding**

This research was supported by the funding supports from Academia Sinica, the Emerging Infectious and Major Disease Research Program [AS-KPQ-110-EIMD], and the Ministry of Science and Technology.
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