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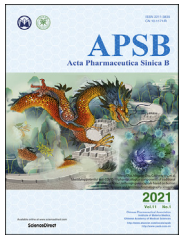

LETTER TO THE EDITOR

Letter to the editor: Neutralizing antibodies for the treatment of COVID-19

KEY WORDS

SARS-CoV-2;
Neutralizing antibody therapy;
COVID-19

To the Editor:

Coronavirus disease 2019 (COVID-19) is a global epidemic caused by the infection of severe acute respiratory coronavirus 2 (SARS-CoV-2) and its mortality rate was up to 20 times higher than that of influenza. The virus is infectious, strange and variable. The treatment of it must be urgent and targeted. It is not enough to wait for a vaccine available to contain and prevent its spreading, we need to take all kinds of feasible measures to deal with the severe challenge from the virus transmission and mutation.

Using convalescent plasma to treat COVID-19 patients is an emergency plan in an early stage of the outbreak. Up to date, more evidences have been provided that COVID-19 convalescent plasma contains neutralizing antibodies against the virus infection, so the “plasma therapy” has been already applied in some countries and has achieved promising outcomes. A Chinese research team treated 5 COVID-19 critical illness patients with the convalescent plasma and achieved an effective treatment indicating the neutralizing antibody has played a therapeutic role.

Although the plasma antibody therapy has demonstrated its efficacy, it has the limitations as: 1) the consent of the convalescent must be obtained before a blood donation; 2) the amount of the plasma is difficult to meet the clinical needs; 3) the plasma must undergo strict blood biosafety test and inactivation of the virus; 4) the endogenous non-specific antibodies in the plasma may cause the antibody dependent enhancement (ADE).

However, using modern bioengineering technologies to develop the neutralizing antibodies for the treatment of COVID-19 could make up for the defects of the plasma treatment scheme to a great extent.

Currently, a number of pharmaceutical and academic teams have explored multiple optional techniques, including but not limited to single B cell sorting, phage display, humanized animals, and high throughput sequencing (HTS), etc. A typical development process is provided in the paper[1]. Those technologies have the following advantages: 1) the antibody with extremely high affinity and superior neutralizing function can be selected from a huge pool; 2) the selected antibodies can be engineered to remove or change the sites related to potential side effect; 3) the selected antibodies can be constructed into multivalent or multi-specific neutralizing antibodies, aiming at improving affinity or avidity, and competing with the endogenous antibodies or the naïve receptors of the virus; 4) the selected antibodies can be produced massively to meet their great clinic demands. The updates of the development of the neutralizing antibodies by means of the above technologies are summarized in Table 1 and more clinical applications can be found in published article[2].

Based on the above updates, the humanized antibody drugs have been tested in the animal studies and clinical trials and demonstrated promising therapeutic potentials, and no significant side effects found yet. The following points of view are presented for discussions:

1. The neutralizing antibodies have great potentials to be developed to the drug for the therapy against COVID-19

As mentioned in Table 1, a number of R&D teams have proved the therapeutic potential by the cell-based assays and animal models. Also, they have provided strong evidence from preclinical studies

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Table 1 Clinical status of SARS-CoV-2 neutralizing antibodies.

Antibody name	Organization, country	Antibody target	Technique	Biological resource	Clinical phase	Start date
LY-CoV555	AbCellera, Canada	S protein	Single B cell sorting	Convalescent patients	I	May 28, 2020
	Eli Lilly, US				II	Jun 17, 2020
	P3, DARPA, US				III	Aug 2, 2020
					III	Aug 4, 2020
					II/III	Aug 19, 2020
REGN-CoV2	Regeneron, US	S protein	Humanized mouse;	Mouse; convalescent patients	I/II	Jun 16, 2020
	Roche, US		single B cell sorting		1/II	Jun 10, 2020
					III	Jul 13, 2020
VIR-7831	Vir Biotechnology, US	SARS-CoV-2	Functional genomics; computational	Convalescent patients	II/III	NA
VIR-7832	GlaxoSmithKline, UK		biology; machine learning		II	NA
JS-016	Institute of Microbiology, CAS, China	RBD	Single B cell sorting	Convalescent patients	I	Jun 5, 2020
	Junshi Biosciences, China				II	Jun 17, 2020
	Eli Lilly, US					
AZD7442	AstraZeneca, UK	SARS-CoV-2	Immunology of humanized mouse;	Humanized mouse; convalescent patients	I	Aug 18, 2020
	Vanderbilt U, US		phage display			
BRII-196	Tsinghua U, China	SARS-CoV-2	Single B cell sorting	Convalescent patients	I	Jul 12, 2020
BRII-198	Brii Biosciences, China				I	Jul 13, 2020
SCTA01	Sinocelltech, China	SARS-CoV-2	NA	NA	I	Jul 24, 2020
TY027	Tychan, Singapore	S protein	Convergent analysis	NA	I	Jun 9, 2020
CT-P59	Celltrion, South Korea	SARS-CoV-2	NA	NA	I	Jul 18, 2020
STI-1499	Sorrento Therapeutics, US	S1 subunit	NA	Convalescent patients; human libraries	I	Sep, 2020
SAB-185	Sab biotherapeutics, US	SARS-CoV-2	Genetically engineered bovine	Bovine	I	Jul 18, 2020
	BARDA, US				I	Aug 5, 2020

NA, not available.

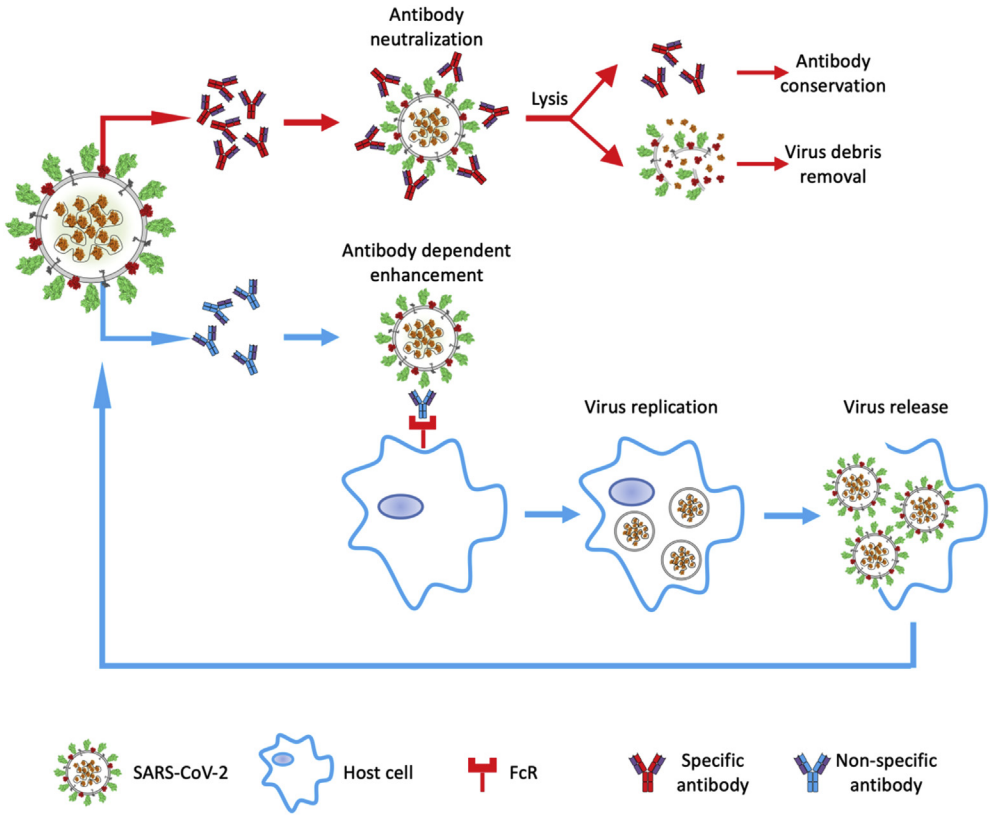

Figure 1 Action of neutralizing antibodies to SARS-CoV-2.

and clinical trials in supporting the neutralizing antibody drugs possessing their great potentials to successfully develop to the therapeutics. A US team reported the nano-bodies derived from *Llamas* could neutralize the SARS-CoV-1/2 virus. Their results demonstrated that the antibody culture medium showed the binding of nano-body to the S protein RBD of the virus to prevent it from infecting human host cells. This is also recently reconfirmed in the laboratory tests by a UK researcher team that the nano-bodies from *Llamas* could bind tightly to the S protein of the virus and avoid the virus infection[3].

It has been shown that the recently published nano-bodies were bound to those unique epitopes on the S protein RBD to block the interactions of ACE2 or non-neutralizing antibody. This implies further evidence in support of the possibility for the neutralizing antibody drug to block the binding site of the endogenous antibodies.

In general, after the human body is infected by the virus, it elicits a large quantity of the neutralizing antibodies and nonspecific endogenous ones. Once the specific neutralizing antibodies are identified, their affinity competition analysis needs to be done for screening the specific neutralizing antibodies with the affinity constants [K_D] between 5 and 39 nmol/L[4]. Those antibodies with a high affinity and/or avidity could block the interference of the endogenous antibodies. Furthermore, a US team reported that the naïve *Llamas* single-domain antibody library-derived neutralizing nano-bodies blocked the interactions of S protein RBD with ACE2, indicating the antibodies could neutralize the virus. Additionally, they used cryo-EM to reveal that nano-bodies bind to all of three S protein RBDs. The crystal structures of the nano-body−RBD complex showed how both nano-bodies recognized the same epitope, which partly overlapped with the ACE2 binding sites, and blocked RBD−ACE2 interaction[4].

2. The superior neutralizing antibodies are effective against the virus

Once the neutralizing antibody is developed, preclinical research should be performed before the clinical study. This has been illustrated by the following work[3]: 1) the *in vitro* neutralization ability of CA1 and CB6 against SARS-CoV-2 was investigated using pseudovirus and the live virus; 2) CB6 *in vivo* was tested in a *Rhesus macaque* model of SARS-CoV-2 infection in both prophylactic and treatment settings, and a strong protection effect of the antibody was observed.

3. The authors believe the possibility of antibody drugs can block the binding site of endogenous antibody

During the process of selecting the high affinity antibody, the rare antibody recognizing the epitope of interest can be picked up and functionally assayed. Endogenous antibodies are polyclonal antibodies that can recognize either neutralizing or non-neutralizing antibodies with a binding affinity at the different levels. The antibody recognizing non-neutralizing epitopes or with a low or an ordinary affinity does not have a neutralizing function. The

specific neutralizing antibodies with a high affinity or avidity work well by competing with ACE2 or the endogenous antibodies at the same epitopes or recognizing the unique different epitopes. This process provides an alternative route to developing therapeutic neutralizing antibody drugs.

4. The clinical application is feasible

As presented in Table 1 and the detailed applications demonstrated in Ref. 2, a total of 13 SARS-CoV-2 neutralizing antibodies have entered different clinical trial stages at 21 different sites, including 13 of them have entered phase I/II, 2 of them phase II/III, and 3 of them phase III. The promising data summarized above could support the clinically trialed neutralizing antibodies are feasible for the use in the clinical application. The more detailed supporting evidence can be found in the published article.[2] In addition, based on the current progress in the development of the neutralizing antibody, humanized antibody drugs could be safely used without a significant side effect.

Regarding the ADE effect, the bio-engineering technologies can be used to change the Fc molecular conformation of the neutralizing antibody, and avoid its combining with FcR complex, then remove ADE effect before the clinical use (Fig. 1). For example, the LALA mutation of CB6 monoclonal antibody could lower the risk of Fc-mediated acute lung injury. It is a key to develop the neutralizing antibodies with the high affinity and avidity. They can be promisingly used for the treatment of COVID-19[5].

The novel SARS-CoV-2 is more transmissible than the previous virus and causes more serious illness than influenza. In addition, the virus mutates rapidly. One of the vigorous approaches is to develop those antibodies with a high affinity and avidity to treat COVID-19 by using bioengineering technologies.

In conclusion, we have the confidence that it is feasible to use the neutralizing antibodies for clinical application in the treatment of COVID-19. The evidences have shown that they are safe, effective and no significant allergy. Several teams in the world have been developing a number of candidates of the neutralizing antibody drugs which have entered the preclinical studies and clinical trials. It is expected the some of them could be launched for the therapy of COVID-19 in the near future.

Author contributions

Zeqi Zhou was responsible for writing the letter. Xiangbin Wang, Yankai Fu and Xuqing Zhang provided the data. Changxiao Liu reviewed the letter.

Conflicts of interest

There are no conflicts of interest.

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