Human neutralizing antibodies to SARS-CoV-2: views and perspectives from Professor Linqi Zhang at Tsinghua University

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Statement of Significance:

Professor Linqi Zhang’s laboratory has uncovered the structure of SARS-CoV-2 spike receptor-binding domain binding with cell receptor angiotensin converting enzyme 2, and isolated more than 200 receptor-binding domain-specific monoclonal antibodies against SARS-CoV-2. The top SARS-CoV-2 neutralizing antibodies are now under development with partnership in pharmaceutical industry.

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Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has become a global pandemic since December 2019 [1]. As of June 2, 2020, COVID-19 has caused 6,325,303 of infections and 377,460 of deaths worldwide [2]. To fight against the COVID-19 pandemic, academic institutions, pharmaceutical industries, and government agencies have launched numerous urgently needed therapeutics development and clinical studies. Antibody-based therapy is one of the most viable treatment options. According to the “Biopharma products in development for COVID19” released by Bioworld, 59 antibody-therapeutics of 226 therapeutics and 87 vaccines are under development at different stages as of April 22, 2020. Among them, 20 therapeutics are neutralizing antibodies targeting SARS-CoV-2 at early preclinical stages [3,4].
As an enveloped single strand RNA virus, SARS-CoV-2 enters into cells through its spike (S) protein binding to the cell receptor angiotensin converting enzyme 2 (ACE2). In order to discover and develop effective neutralizing antibodies to SARS-CoV-2, the structure of the SARS-CoV-2 spike receptor-binding domain (RBD) bound to ACE2 is very important [5]. This crystal structure was firstly published in *Nature* by the laboratory of Dr. Linqi Zhang, Professor & Department Chair of Center for Global Health and Infectious Diseases, Comprehensive AIDS Research Center at School of Medicine, Tsinghua University in February 2020 [6]. His lab not only confirmed that the identified residues in the SARS-CoV-2 RBD are critical for ACE2 binding; but also isolated and analyzed numerous RBD-specific monoclonal antibodies (mAbs) derived from single B cells of SARS-CoV-2 infected individuals, identified potent neutralizing antibodies as promising candidates for prophylactic and therapeutic SARS-CoV-2 interventions [7]. These findings that were newly published online in *Nature* collectively not only helped to better understand the initial step of infection at an atomic level, but also contributed to the fast development of highly potent neutralizing antibodies to SARS-CoV-2.

Chinese Antibody Society, the sponsor of *Antibody Therapeutics*, invited Prof. Zhang to give a webinar on May 2, 2020 entitled as “Human neutralizing antibodies to SARS-CoV-2: The Path Towards Clinical Interventions”. In this talk, Prof. Zhang systematically presented the progress and status of SARS-CoV-2 study from structural basis to antibody discovery in his lab. Started with brief introduction of coronavirus background, he elicited that up conformation of RBD on SARS-CoV spike trimer is
critical for its binding to ACE2. His lab further studied interaction between RBD of SARS-CoV-2 spike and ACE2. Surprisingly, although the sequence and structure of SARS-CoV-2 RBD are highly similar to these of SARS-CoV RBD, the residues in the interface for ACE2 binding still have 50% difference. This might explain why the current neutralizing antibodies to SARS-CoV have less effect on SARS-CoV-2. Thus, it’s necessary and urgent to discover and develop effective neutralizing antibodies against SARS-CoV-2.

To isolate potent neutralizing antibodies against SARS-CoV-2, his lab firstly collaborated with Prof. Xinquan Wang in Tsinghua University and Prof. Zheng Zhang’s group in Shenzhen Third People’s Hospital to explore plasma cross reactivity in SARS-CoV-2 infected patients and recovered individuals. They found although plasma derived from recovered SARS-CoV-2 infected individuals showed binding ability with trimeric spike proteins of SARS-CoV-2, SARS-CoV, and MERS-CoV, it could only specifically bind with SARS-CoV-2 RBD but not SARS-CoV or MERS-CoV RBD. These findings suggested that antibody response to RBDs is viral species-specific.

Then, they directly isolated RBD-specific single B cells from eight SARS-CoV-2 infected patients, and finally collected 206 RBD-specific mAbs derived from these single B cells. Genetic divergence analysis of these 206 mAbs showed that these mAbs coming from diverse families of antibody heavy and light chains without apparent enrichment for particular families in the repertoire. Germline and germline divergent clones coexisted in further analysis of mAbs from one patient. These mAbs
with potent neutralizing activity against pseudovirus and live SARS-CoV-2 had no cross-activity with RBDs from SARS-CoV or MERS-CoV. Among them, two clones with high competing capacity against ACE2 receptor showed abilities to block 98%-99% viral entry [7,8]. Structural basis for interaction of one human neutralizing antibody to SARS-CoV-2, SARS-CoV-2 RBD, and ACE2 showed that this neutralizing antibody could block interaction between SARS-CoV-2 RBD and ACE2 through binding to both up conformation and down conformation of RBD.

Next, Prof. Zhang presented the current ongoing studies regarding human neutralizing antibodies against SARS-CoV-2: 1) isolating and characterizing more mAbs to SARS-CoV-2; 2) collaborating with Brii Biosciences to co-develop the neutralizing mAbs. The first in human clinical trial for the neutralizing mAbs may be initiated as early as this summer.

In addition, he briefly introduced structure-based vaccine against COVID-19. Chimpanzee adenovirus-based vaccine and mRNA vaccine designed and developed based on the structure of interaction between RBD of SARS-CoV-2 spike and ACE2 have shown powerful abilities to trigger neutralizing antibodies against SARS-CoV-2 in vivo. Prof. Zhang is now seeking for partners to co-develop these SARS-CoV-2 vaccines for clinical use. He may be available at zhanglinqi@tsinghua.edu.cn upon the collaboration opportunities.

At the end of his talk, Prof. Zhang discussed the current status of developing other targeting non-RBD anti-SARS-CoV-2 antibodies, especially for neutralizing mAbs to spike S2 subunit of SARS-CoV-2. Although in theory it’s possible to develop
broad-spectrum neutralizing Abs, their neutralizing abilities still need to be further explored. As a result, broad-spectrum neutralizing Abs development has a long way to go, Prof. Zhang commented. In contrast, developing viral-species specific neutralizing Abs is one of the most feasible solutions. Meanwhile, it’s necessary to develop more different neutralizing mAbs to fight against SARS-CoV-2 mutation even though there’s no mutation of RBD motif residues for ACE2 binding now. Antibody-dependent enhancement (ADE) has become big concern during vaccine and antibody development, while it’s difficult to evaluate ADE from *in vitro to in vivo* under molecular level. Prof. Zhang further commented, although currently there’s no ADE report for RBD-specific neutralizing mAbs, especially for those with high ACE2 binding abilities, it’s also possible to overcome potential ADE through modifying Fc domain or developing nanobodies.

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