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Bivalent binding of a fully human IgG to the SARS-CoV-2 spike proteins reveals mechanisms of potent neutralization

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ABSTRACT

In vitro **antibody selection against pathogens from naïve combinatorial libraries can yield various classes of antigen-specific binders that are distinct from those evolved from natural infection. Also, rapid neutralizing antibody discovery can be made possible by a strategy that selects for those interfering with pathogen and host interaction. Here we report the discovery of antibodies that neutralize SARS-CoV-2, the virus responsible for the COVID-19 pandemic, from a highly diverse naïve human Fab library. Lead antibody 5A6 blocks the receptor binding domain (RBD) of the viral spike from binding to the host receptor angiotensin converting enzyme 2 (ACE2), neutralizes SARS-CoV-2 infection of Vero E6 cells, and reduces viral replication in reconstituted human nasal and bronchial epithelium models. 5A6 has a high occupancy on the viral surface and exerts its neutralization activity via a bivalent binding mode to the tip of two neighbouring RBDs at the ACE2 interaction interface, one in the "up" and the other in the "down" position, explaining its superior neutralization capacity. Furthermore, 5A6 is insensitive to several spike mutations identified in clinical isolates, including the D614G mutant that has become dominant worldwide. Our results suggest that 5A6 could be an effective prophylactic and therapeutic treatment of COVID-19.**

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KEYWORDS

SARS-CoV-2, COVID-19, SARS-CoV, coronavirus, spike protein, monoclonal antibody, phage display

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