

## **Potent Neutralizing Monoclonal Antibodies Directed to Multiple Epitopes on the SARS-CoV-2 Spike.**

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The SARS-CoV-2 pandemic rages on with devastating consequences on human lives and the global economy. The discovery and development of virus-neutralizing monoclonal antibodies could be one approach to treat or prevent infection by this novel coronavirus. Here we report the isolation of 61 SARS-CoV-2-neutralizing monoclonal antibodies from 5 infected patients hospitalized with severe disease. Among these are 19 antibodies that potently neutralized the authentic SARS-CoV-2 in vitro, 9 of which exhibited exquisite potency, with 50% virus-inhibitory concentrations of 0.7 to 9 ng/mL. Epitope mapping showed this collection of 19 antibodies to be about equally divided between those directed to the receptor-binding domain (RBD) and those to the N-terminal domain (NTD), indicating that both of these regions at the top of the viral spike are quite immunogenic. In addition, two other powerful neutralizing antibodies recognized quaternary epitopes that are overlapping with the domains at the top of the spike. Cryo-electron microscopy structures of one antibody targeting RBD, a second targeting NTD, and a third bridging two RBDs revealed recognition of the closed, “all RBD-down” conformation of the spike. Several of these monoclonal antibodies are promising candidates for clinical development as potential therapeutic and/or prophylactic agents against SARS-CoV-2.