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ARTICLE OPEN

ACE2-targeting monoclonal antibody as potent and broad-spectrum coronavirus blocker

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The evolution of coronaviruses, such as SARS-CoV-2, makes broad-spectrum coronavirus preventional or therapeutical strategies highly sought after. Here we report a human angiotensin-converting enzyme 2 (ACE2)-targeting monoclonal antibody, 3E8, blocked the S1-subunits and pseudo-typed virus constructs from multiple coronaviruses including SARS-CoV-2, SARS-CoV-2 mutant variants (SARS-CoV-2-D614G, B.1.1.7, B.1.351, B.1.617.1, and P.1), SARS-CoV and HCoV-NL63, without markedly affecting the physiological activities of ACE2 or causing severe toxicity in *ACE2* "knock-in" mice. 3E8 also blocked live SARS-CoV-2 infection in vitro and in a prophylactic mouse model of COVID-19. Cryo-EM and "alanine walk" studies revealed the key binding residues on ACE2 interacting with the CDR3 domain of 3E8 heavy chain. Although full evaluation of safety in non-human primates is necessary before clinical development of 3E8, we provided a potentially potent and "broad-spectrum" management strategy against all coronaviruses that utilize ACE2 as entry receptors and disclosed an anti-coronavirus epitope on human ACE2.

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INTRODUCTION

In the last 20 years, coronaviruses have caused three major transmissible disease outbreaks in human, including severe acute respiratory syndrome (SARS),[1] Middle East respiratory syndrome (MERS)[2], and coronavirus disease 2019 (COVID-19).[3,4]

One of the challenges to control coronaviruses is that they evolve constantly, even though slower than HIV and influenza.[5] Analyses of over 28,000 gene sequences of SARS-CoV-2 spike protein (S-protein) in May 2020 revealed a D614G amino acid substitution (SARS-CoV-2-D614G) that was rare before March 2020, but increased greatly in frequency as the pandemic spread worldwide, reaching over 74% of all published sequences by June 2020[6] and 81% by May 2021 (GISAID). Evolution of coronaviruses renders them ability to evade virus-specific medications.[7,8] Recently, the emergence of multiple mutant variants of SARS-CoV-2, including B.1.1.7 (UK), B.1.351 (South Africa), P.1 (Brazil)[9], and B.1.617[10] (India) manifests such challenge. In fact, a monoclonal antibody against SARS-CoV-2, bamlanivimab, has been revoked Emergency Use Authorization for expected poor performance against variants currently popular in the US (FDA news). In theory, broad-spectrum coronavirus therapeutics can withstand viral mutations and be potentially utilized in future campaigns against different coronavirus outbreaks.

The key to developing broad-spectrum coronavirus therapeutics is to identify broad-spectrum anti-viral targets. Although RNA polymerase is a broad anti-RNA virus target, it suffers from low specificity and efficacy.[11,12] By employing a multi-dimensional approach, Gordon et al. proposed a set of potential "pan" viral target for coronaviruses, but the druggability of these targets are yet to be evaluated.[13] ACE2 fusion proteins can act as decoy receptors to trap SARS-CoV-2,[14,15] but the affinity and developability of these proteins are generally less than antibodies. Recently, Rappazzo et al. generated a set of monoclonal antibodies that bound to a large panel of coronaviruses, but their neutralizing abilities have not been tested yet.[16]

The infection of SARS-CoV-2 is triggered by binding of their envelope spike glycoproteins (S-protein) to angiotensin-converting enzyme 2 (ACE2) molecules expressed on host cells.[17,18] The S-protein consists of two subunits: (1) S1-subunit (also called S1-protein) at N-terminal, containing the receptor-binding domain (RBD) responsible for ACE2 binding; (2) S2-subunit at C-terminal responsible for membrane fusion.[18] The RBD of SARS-CoV-2 has been heavily targeted by antibodies as well as small molecule approaches,[19–23] but the RBD-targeting approaches are prone to drug resistance caused by viral evolution and are not broad-spectrum.

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