NEWS FLASH

An Update on Novel Soluble ACE2 Therapeutics to Treat SARS-CoV-2: Insights from a Preclinical Study

By Andrew M. South and Matthew A. Sparks

Novel therapeutics remain urgently needed to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19), including associated acute kidney injury. Angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 spike protein-binding site, is expressed in numerous tissues, including the lungs and kidneys. Soluble ACE2 is a potential *therapeutic* with dual roles: 1) binding SARS-CoV-2 to attenuate infection and replication and 2) shifting the renin-angiotensin system away from the pro-inflammatory angiotensin II and bradykinin pathways. There is precedent for using recombinant soluble ACE2 clinically. A pilot randomized clinical trial in 44 patients with acute respiratory distress syndrome (pre-COVID-19 pandemic) demonstrated that human recombinant ACE2 was well tolerated (1). A case report of compassionate use of human recombinant ACE2 in a patient with COVID-19 also demonstrated tolerability (2). However, major limitations to the soluble ACE2 therapeutic potential in humans remain, including short duration of action and susceptibility to degradation, unclear optimal dosing timing (e.g., early- vs. late-stage infection), and potentially limited viral affinity.

Emerging preclinical models using engineered human tissues have begun to shed light on mitigating these limitations. Monteil et al. (3) demonstrated that full-length (amino acids 1–740) soluble human recombinant ACE2 inhibited SARS-CoV-2 infection in human blood vessel and kidney organoids. In a recent *JASN* article, Wysocki et al. (4) investigated the effect of two short-length soluble ACE2 variants on SARS-CoV-2 infectivity using human kidney organoids and assessed their enzymatic activity in vitro and in vivo. They generated a human recombinant ACE2 of 618 amino acids (ACE2 1–618) and one fused to a small (5-kD) albumin-binding domain protein (ACE2 1–618-ABD) to improve stability. They generated human kidney organoids to create proximal tubules that expressed cell membrane ACE2 and transmembrane protease, serine 2 (TMPRSS2), to assess viral replication neutralization. Three days after infection, ACE2 1–618-ABD and ACE2 1–618 markedly reduced viral replication in the organoid cells to the same extent as native ACE2 1–740. They also found that ACE2 1–618-ABD had a greater peak and duration of enzymatic activity and ability to blunt the blood pressure response to angiotensin II compared to ACE2 1–618 and native ACE2 1–740 (Figure 1).

Soluble ACE2 1–618-ABD is an important step toward ACE2-based therapeutics, which include full-length ACE2 and ACE2 fused with a crystallizable fragment (1, 2, 5). However, several caveats remain. Similar studies in human lung organoids will be crucial to developing these therapies. It is unknown if soluble ACE2 penetrates into tissues (lung, kidney) to bind SARS-CoV-2 or if soluble ACE2 in circulation requires sufficient viremia to be efficacious. Although theoretically, soluble ACE2 should retain sufficient enzymatic activity upon binding the spike protein, this has not been determined in vivo. It remains to be seen if soluble ACE2-SARS-CoV-2 binding is transient or sustained and how and to what extent the ACE2-SARS-CoV-2 complex is cleared. Whereas short-fragment soluble ACE2 likely undergoes glomerular filtration to reach the proximal tubular lumen and thus may be beneficial in COVID-19–associated acute kidney injury, it is unclear if ACE2 1–618-ABD bound to albumin possesses this ability. Moreover, these preclinical studies must be appropriately translated into adequately designed and powered clinical trials. Several groups are currently working on various delivery approaches to enhance SARS-CoV-2 binding (6), and clinical trials treating patients with COVID-19 are ongoing (ClinicalTrials.gov: NCT04335136). Thus, further investigations to answer these questions are critical next steps. ■

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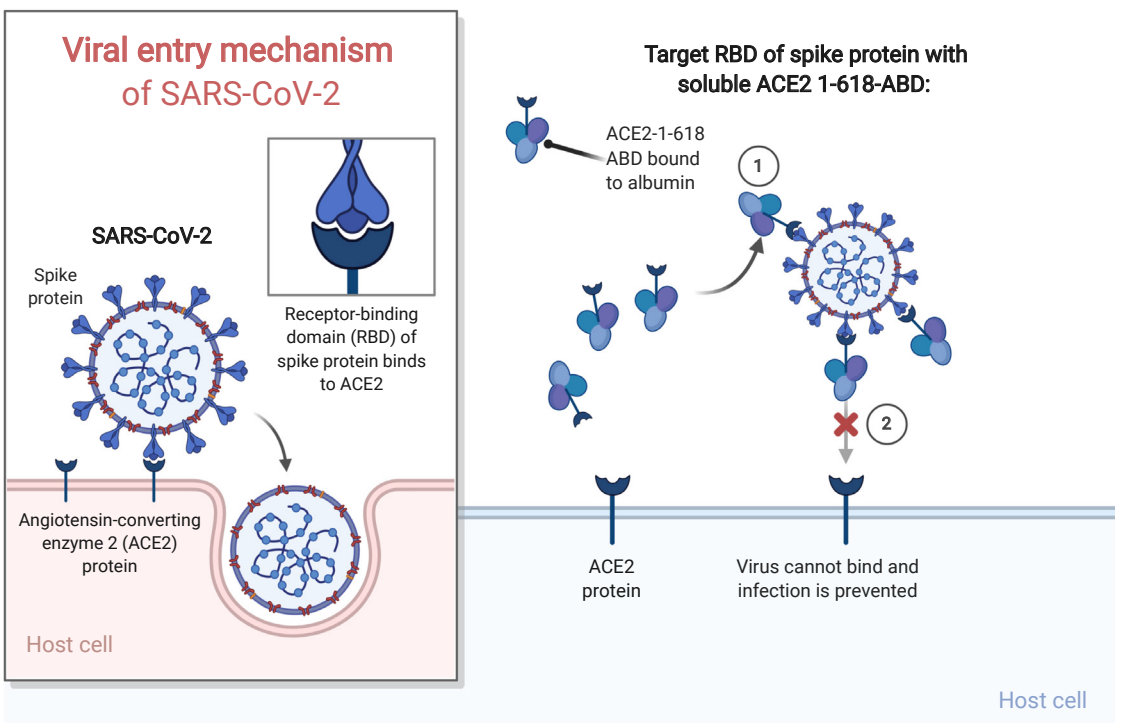
Figure 1. Mechanism for how soluble ACE2 1–618-ABD neutralizes SARS-CoV-2



(Left) Entry mechanisms for SARS-CoV-2 depend on the recognition and binding of the spike protein receptor-binding domain (RBD) to ACE2. (Right) 1. Amino acids 1–618 of ACE2 with the addition of ABD (a 5-kD albumin-binding domain) bind to albumin in the circulation and recognize the RBD of the SARS-CoV-2 spike protein, resulting in 2. the inability of SARS-CoV-2 to bind to ACE2, preventing infection. Made with BioRender.