Medical Xpress

New monoclonal antibodies targeting ACE2 receptor could treat the next waves of SARS-CoV-2

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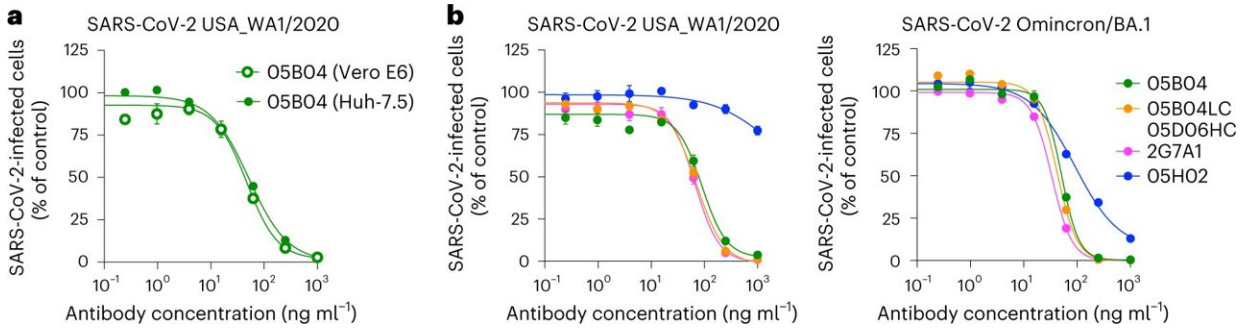

Inhibition of authentic SARS-CoV-2 infection by human anti-hACE2 mAbs. a,b, Anti-hACE2 mAbs (2G7A1, 05H02, 05B04 and the hybrid antibody 05B04LC/05D06HC) were serially diluted and incubated with Vero E6 and Huh-7.5 target cells (a) or Vero E6 target cells only (b). Thereafter, cells were infected with authentic SARS-CoV-2 (WA1/2020) (a and b) or SARS-CoV-2 Omicron BA.1 variants (b). Infected cells were quantified by immunostaining and plotted as a percentage of the number of cells infected in the absence of anti-hACE2 mAbs. Mean and range of three independent titrations is plotted. Credit: *Nature Microbiology* (2023). DOI: 10.1038/s41564-023-01389-9

Research led by Rockefeller University in New York investigated alternate targets for monoclonal antibodies to combat SARS-CoV-2 infections.

In the paper "Pan-sarbecovirus prophylaxis with human anti-ACE2 monoclonal antibodies," published in *Nature Microbiology*, the authors warn that therapeutic monoclonal antibodies (mAbs) used against SARS-CoV-2 infection have been rendered obsolete by the emergence of mAb-resistant virus variants.

Monoclonal antibodies have been used to treat COVID-19 by targeting the viral spike protein to prevent the virus from binding to the ACE2 receptor, blocking its entry into cells. As the spike proteins mutate between variants of the virus, different mAbs have been required, occasionally being developed just as the spike protein of the virus mutates.

Looking for a different approach, the researchers developed a set of six human mAbs that bind the human angiotensin-converting enzyme-2 (hACE2) receptor in patients instead of the SARS-CoV-2 spike protein on the virus.

In experiments with modified mice, these antibodies were selected after showing efficacy by preventing binding by all hACE2 binding viruses tested, including SARS-CoV-2 ancestral, delta and omicron variants. The highly specific targeting of an hACE2 epitope, the precise location that binds to the SARS-CoV-2 spike, allows hACE2 to maintain normal function. The mAbs did not inhibit hACE2 enzymatic activity or induce cell-surface depletion.

Crucially, by acting on the target and not the virus, the new treatment method is much less likely to be overcome by genetic mutation-driven resistance in future variants. The authors suggest their approach could treat current SARS-CoV-2 variants and any hACE2-binding viruses that emerge in the future.

Before any treatments can occur, further safety testing is required.

Unlike the previous methods, which targeted a protein on the virus, this one targets the human host receptors. One potential obstacle to getting approval quickly is that governments are no longer on a fast-tracked pandemic response footing. Like declaring victory over winter in the spring, that footing may only last a few seasons.

More information: Fengwen Zhang et al, Pan-sarbecovirus prophylaxis with human anti-ACE2 monoclonal antibodies, *Nature Microbiology* (2023). DOI: 10.1038/s41564-023-01389-9