Molecular makeover makes wimpy antibody a SARS-CoV-2 tackler

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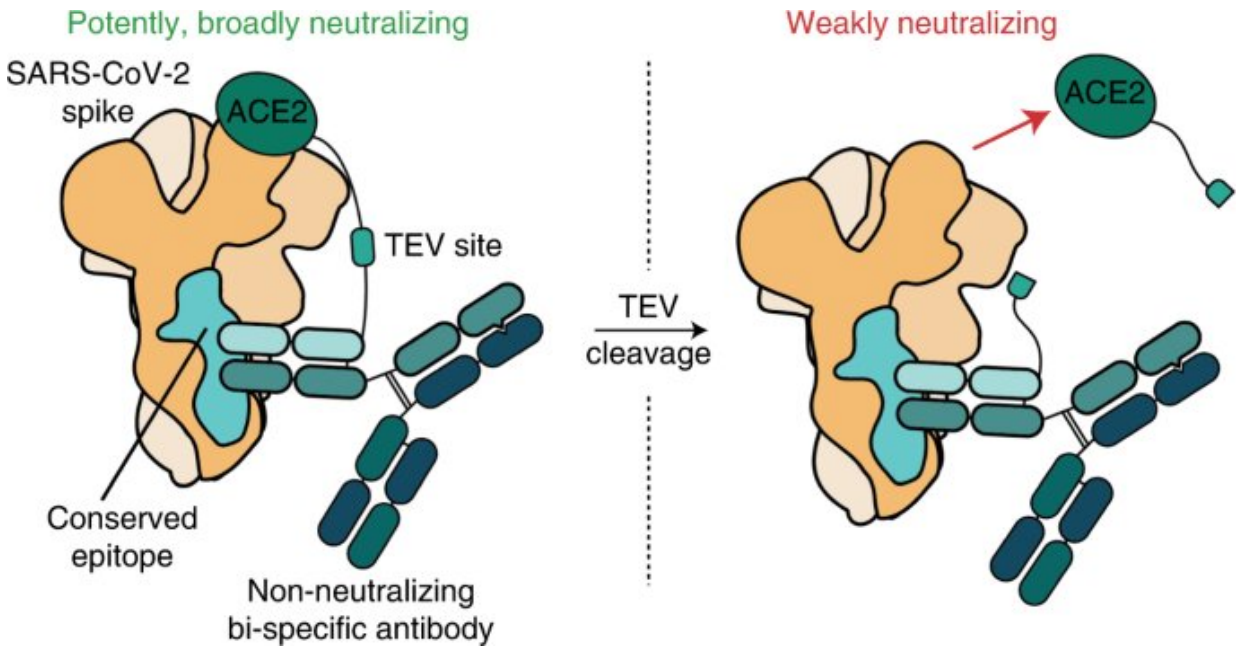

Graphical abstract. Credit: *Nature Chemical Biology* (2022). DOI: 10.1038/s41589-022-01140-1

Like the Roadrunner outwitting Wile E. Coyote, SARS-CoV-2 (the infectious virus responsible for COVID-19) keeps mutating, generating new variants that can slip from the grip of a well-trained immune system or a well-aimed drug or vaccine.

Now, Stanford Medicine scientists have found a way to imbue immune

molecules once thought useless with the ability to put SARS-CoV-2 in a therapeutic headlock it can't wriggle out of. Their method is described in a paper published Sept. 8 in *Nature Chemical Biology*. The study was led by biologist and vaccinologist Peter Kim, Ph.D.

Two things about the study stand out. First, although it's not ready yet for use in humans, it's a solid step toward the development of broadly effective drugs that don't stop working just because a nasty virus has thought up a new trick. And second, a key component of the new therapy was a molecule that had been routinely getting tossed in the trash.

To fully appreciate Kim's team's discovery, let's step back to ask: What exactly happens when a virus infects our bodies? And what does the immune system do about it?

The basics of infection

To cause infection, a virus must first get inside a cell. Cells' outer membranes are normally tough to penetrate without a special pass. But these little safe-crackers have figured how to tease open a lock on the cell's surface, climb in, hijack the cell's replication machinery, make a bazillion copies of themselves and bust out to spread to other cells.

The lock SARS-CoV-2 knows how to pick is ACE2, that appears on the surface of cells in the throat, lungs, heart, kidney, intestines and blood-vessel linings. ACE2 is famous for, among other things, helping keep our blood pressure low. But SARS-CoV-2 doesn't care what ACE2 does for a living. Any cell bearing ACE2 is vulnerable to SARS-CoV-2 infection.

Our immune system has ways of dealing with such intruders. Upon recognizing a pathogen's presence, B cells, which help make up our immune system, pump out a broad assortment of antibodies aimed at the

invader. These are molecules uniquely suited to glom onto pathogens like matching jigsaw-puzzle pieces and—when they glom onto just the right places and the fit is good—put them out of commission.

Antibodies that excel at grabbing on to some feature crucial to the pathogen's cellular safe-cracking success are declared to be "neutralizing": They prevent the pathogen from infecting cells. The best of these neutralizing antibodies can then be made into drugs.

For instance, patients hospitalized with COVID-19 often receive a dose of monoclonal antibodies: multiple copies of the same powerfully neutralizing antibody. The trouble is, SARS-CoV-2 is adept at tweaking the shapes of its vulnerable features by mutating, so a once-neutralizing monoclonal antibody loses its grip and can no longer squelch the new variant. The COVID-19 pandemic has been a parade of one immune-escape artist after another.

Souped-up antibody

"It's whack-a-mole," said Kim, who spent a chunk of his career working in the pharmaceutical industry. "You go to all that trouble of developing these monoclonal antibodies, shepherding them through clinical trials, setting up manufacturing operations and getting an emergency use authorization from the FDA. Then, months later, the virus morphs and the monoclonal antibody's no good anymore."

Of the more than a half-dozen SARS-CoV-2-targeting monoclonal antibodies that have received an emergency use authorization, only one is still in use.

But Kim's lab has a souped-up antibody that may take on all comers.

All of the monoclonal antibodies the FDA has approved so far stick to

SARS-CoV-2's receptor-binding domain, or RBD. That's the "business end" of the virus's infamous spike protein, the viral protuberance that fiddles with ACE2 to gain admittance to cells. By spinning off new variants with mutated RBDs, the virus keeps shaking off successive monoclonal antibodies' grip.

But the SARS-CoV-2 spike protein contains other regions that are, for all practical purposes, unchanging. These regions are said to be highly evolutionarily conserved, meaning it hasn't changed over time even among viral strains that differ elsewhere.

So, why not come up with a monoclonal antibody that goes after one of those conserved regions? Wouldn't that solve the escape artist problem?

Yes, said Kim, who is the Virginia and D. K. Ludwig Professor in Biochemistry. "But so far, nobody has found an antibody to a conserved region on SARS-CoV-2 that's not a wimp." In other words, it seems none of these antibodies are potent neutralizing antibodies—they glom on and just sit there, riding along with the virus but not stopping it from infecting cells.

Wimp no longer

Kim credits Payton Weidenbacher, Ph.D., a former graduate student in his lab, with a flash of ingenuity that sparked the advent of what they've called "ReconnAbs" (short for "receptor-blocking conserved non-neutralizing antibodies").

Weidenbacher's idea: Take another molecule that could neutralize SARS-CoV-2 and tie it to one of these wimpy-but-clingy antibodies that binds to a well-conserved site on the viral spike protein.

"Lots of other researchers were just throwing these antibodies in the

garbage pail, and so were we," said Weidenbacher.

They found an antibody that targeted a part of SARS-CoV2's spike protein that never seems to change, no matter what new variant pops up. Using a flexible protein snippet as a leash, they tethered this antibody to the piece of ACE2 that sticks out from the cell surface—the part the virus latches onto.

"There's no way SARS-CoV-2 can mutate its way out of its dependence on ACE2," Weidenbacher said.

In a lab dish, the tethered construct proved able to block SARS-CoV-2 infection of human cells normally susceptible to the virus. It's worked on all SARS-CoV-2 strains tested up through BA.2.

The next step is to test ReconnAbs on animals.

Looking beyond the current pandemic, Kim envisions ReconnAbs serving as a modular mix-and-match "parts kit" that could quickly be put into action when the next pandemic hits to stall off the virus from the get-go while awaiting the hoped-for development of even better drugs.

Such a kit would contain three parts: antibodies known to cling tightly to strongly conserved regions of whatever well-studied virus (a coronavirus or influenza virus, for example) comes along; whatever cell-surface "lock" that virus knows how to pick to get inside our cells; and little leashes to hook them together.

"It was a stroke of creativity," Kim said. "Payton figuratively reached into the garbage pail, pulled out these lemons and turned them into lemonade."

More information: Payton A.-B. Weidenbacher et al, Converting non-

neutralizing SARS-CoV-2 antibodies into broad-spectrum inhibitors, *Nature Chemical Biology* (2022). DOI: 10.1038/s41589-022-01140-1