Medical Xpress

The new antibody that may be able to stay 'one step ahead' of coronavirus mutations

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An antibody (CoV-X2) was constructed by the ATAC team from two potent monoclonal antibody candidates derived from humans, chosen from a shortlist of over 100 antibodies. Credit: Louis Reed / Unsplash

A new antibody that can mount a double attack on the SARS-CoV-2

virus by binding to two different sites on the spike protein is starting human trials, leading to hopes of an antibody therapy that can maintain its effectiveness even against new variants of coronavirus.

A virus is constantly mutating. Staying ahead of the evolutionary game is key in the fight against an infectious virus—especially one like the SARS-CoV-2 coronavirus, which has its genetic material encoded in RNA rather than the more stable DNA. Even the smallest change in its surface spike proteins can make it unrecognisable to the host's immune system, meaning a drug that's effective on the original virus may have little impact on its successors. That's why researchers are working against the clock to develop treatments and vaccines to tackle troublesome variants of the coronavirus, of which there are currently three of concern, with more likely to come.

Many groups are putting their money on antibody cocktails to treat the symptoms of a COVID-19 infection. "The idea is that one antibody in the cocktail will bind to a particular spike protein on the virus and another antibody will bind to another," said Professor Qiang Pan-Hammarström from Sweden's Karolinska Institute. "That way, the cocktail still works even when one of the spike proteins mutates."

The international project known as ATAC, however, is taking a radically different approach. Its researchers developed a single antibody that can mount a double attack on the coronavirus, rather than two antibodies working in tandem. The group's 'bispecific' antibody binds to two separate sites on the spike protein on the virus' surface, therefore remaining potent even if one of the two sites undergoes a significant mutation.

"Experiments—both in-vitro and using animal models—show this antibody binds well to all variants of the virus," said Prof. Pan-Hammarström, who is the coordinator of the ATAC consortium. "Our

two-in-one model seems to prevent the virus from escaping the immune response."

Double attack

Late last year, a two-antibody cocktail created by biotech company Regeneron brought hope for coronavirus patients – studies showed it boosted the body's defence against COVID-19, reducing hospitalisations and deaths. It was authorised for emergency use in the US. In February, a second cocktail—this one produced by Eli Lilly—was given similar US approval, and shortly after, the European Medicines Agency (EMA) expressed a positive opinion of Lilly's cocktail. But less than a month on, new studies suggest the treatment is being outwitted by a constantly evolving virus, with new variants of the disease showing resistance to the monoclonal, or lab-made, antibodies.

"The coronavirus is mutating, and it will continue to mutate, so we need treatments that can keep up with these changes and work effectively on all variants of the virus," said Prof. Pan-Hammarström. "In other words, we need solutions that save lives now and also prepare us for the future."

Though bispecific antibodies, such as the one emerging from the ATAC consortium, are gaining popularity in the treatment of certain cancers (where one part of an antibody might bind to a tumour cell and the other to an immune cell), the ATAC researchers are the first to produce a bispecific antibody against SARS-CoV-2, according to Prof. Pan-Hammarström.

"This antibody means we can stay one step ahead of the virus," said Prof. Pan-Hammarström. A paper describing their findings has been published in the scientific journal Nature.

The ATAC antibody (CoV-X2) was constructed by the team from two

potent monoclonal antibody candidates derived from humans, chosen from a shortlist of over 100 antibodies. It is now being prepared for Phase 1 clinical trials, during which it will be tested on healthy volunteers. The trials will take place in Italy, the locus of Europe's first brutal outbreak of COVID-19 and home to an ATAC partner. Prof. Pan-Hammarström is hopeful that these trials will have been launched by the summer, and that a new, variant-resistant antibody could be on the market within six to eight months.

"We have some good vaccines for COVID and I'm sure there will soon be vaccines for variants of the virus too, but infected patients are still getting very sick from this disease and they will continue to do so until we have some really good therapies available for them," said Prof. Pan-Hammarström. "Thus far, only two therapies have been found to work in large-scale randomised clinical trials—steroids (dexamethasone), which are used to reduce inflammation, and … medicine(s) used to treat for rheumatoid arthritis (drugs that block the interleukin-6 receptor), which is also immunomodulatory (modifies the response of the immune system).

"This is very disappointing—we definitely need to find new drugs to treat this illness."

She added: "We are confident that our antibody could be one of the treatments clinicians and patients have been waiting for."

Complementary

Since the onset of the pandemic, hundreds of projects have sprung up around the world to develop monoclonal antibodies to treat COVID-19 patients. These antibodies work in a similar way to vaccines, first recognising and then neutralising a virus, though they are regarded as complementary to, not replacements for, regular vaccines.

When a person receives a vaccination, their immune system is triggered into producing infection-fighting antibodies and it can take several weeks for immunity to set in. By contrast, monoclonal antibodies (generated from natural antibodies that have undergone modifications) enter the bloodstream through a drip and are ready for action straight away. But though these antibodies mimic the infection-fighting work of the immune system, they don't last forever—typically, a monoclonal antibody will stick around for a number of weeks or months.

"Why do we need antibody therapies when there are now good vaccines against COVID? Because some people are immunocompromised and don't respond to a vaccine, plus of course it will take several years for the whole world to be vaccinated against COVID-19, so there will be an ongoing need for medicines that can temperately protect us or treat the disease," explained Prof. Pan-Hammarström.

The hope is to find an effective antibody treatment that can be mass produced and distributed at speed to hospitals around the world, though cost is a factor to be considered—antibodies are notoriously expensive to produce (to give an idea, the average annual price of monoclonal antibody cancer treatment in the US exceeds €80,000 per person). However, Prof. Pan-Hammarström says ATAC's double-whammy antibody goes some way to addressing this problem as a single antibody is a lot cheaper to produce than a cocktail of two, such as the ones created by Regeneron and Eli Lilly.

"I'm not saying it will be half the cost, but it will be more cost effective," she said.

Professor Luis Serrano from the Centre for Genomic Regulation (CRG) in Spain, who was involved in COVID-19-related research nearer the start of the pandemic but is not involved in ATAC, welcomes research into bispecific antibodies but stresses the importance of 'very, very high

affinity' between the antibody and both sites. "Otherwise non-binding to one site could result in the antibody binding weakly to the other, and not being effective," he said.

Models

Being prepared for the next pandemic—or for a catastrophic twist to the current one—through large-scale international collaborations is a major theme in today's research community.

"It's difficult to make predictions on whether a more dangerous variant will emerge in the future, but we can prepare for it," said Prof. Pan-Hammarström. She is among those calling for greater links between scientists and industry, where researchers are invited to float and test new ideas, and banks of antibodies are established well in advance of a new infection taking root.

"If we can prove the concept of our bispecific antibody, we can use computer and animal models to predict what a virus might do next, and to come up with solutions before there's an actual problem," she said.

"Our consortium is already starting to work on this idea with scientists from around the world, including China. They have identified sequences for viruses from animals that don't yet infect humans, but one day might mutate and do just that. We could prepare ourselves by making antibodies against these viruses already now. We could create a pool of antibodies to dip into the moment a new infection emerges. We could stop the next pandemic before a single person has died."

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