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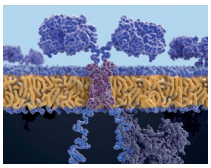

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T-cell vaccines could top up immunity to COVID, as variants loom large

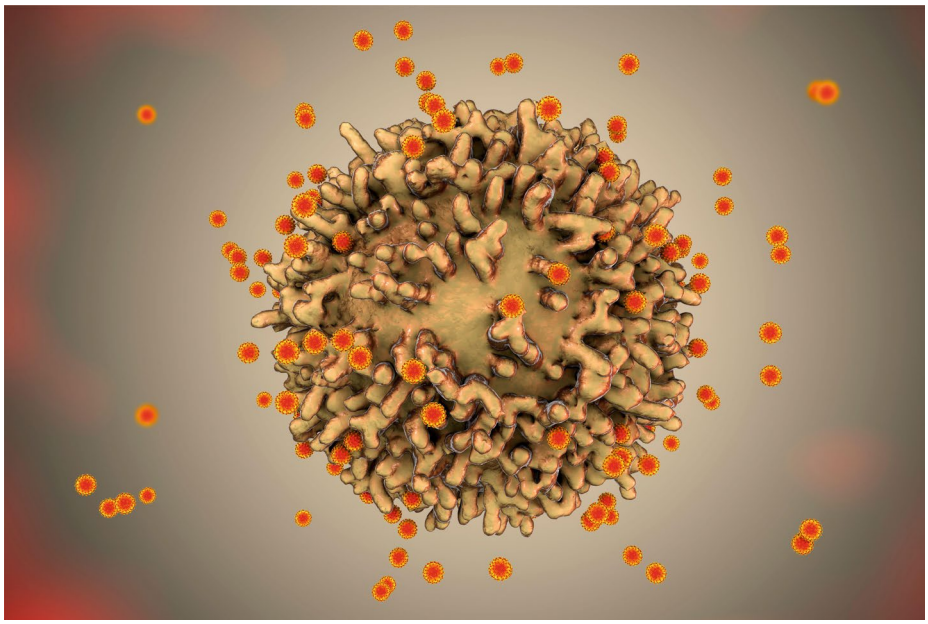
Peptide jabs targeting T cells could be especially useful for people with compromised immune systems, as backups for spike-based vaccines, or against Omicron and other emerging variants.

The first peptide vaccine designed to elicit T-cell immunity against SARS-CoV-2, rather than antibody responses, appears to be safe and broadly protective against a range of worrisome viral variants, including Omicron.

Such a vaccine, if clinically validated in larger trials, could offer a much-needed immunization option for patients with B-cell deficiencies who don't mount sufficiently strong immune defenses after inoculation with existing COVID-19 shots. If used as a booster in the general population, it could also strengthen the types of cellular immune responses that help clear infections and keep people from developing severe disease or dying.

The six-peptide vaccine contains human leukocyte antigen DR (HLA-DR)-restricted fragments of five SARS-CoV-2 proteins (spike, nucleocapsid, membrane, envelope and open reading frame (ORF)-8) that get picked up by antigen-presenting cells and recognized by T-cell receptors. Phase 1 data reported in late November by Juliane Walz and her colleagues at the University Hospital Tübingen in Germany showed that a single dose of the vaccine, termed CoVac-1, was tolerable and triggered multifunctional $CD4^+$ and $CD8^+$ T-cell responses at a magnitude that well exceeded those brought about by natural infections or other vaccine technologies.

Every participant in the 36-person trial developed a hardened nodule around the injection site, an expected consequence of the vaccine being formulated with a synthetic peptide called XS15, which binds to and activates Toll-like receptors (TLR) 1 and 2, emulsified in Montanide, a mixture of surfactant and mineral oil — an adjuvant combo that creates a depot for prolonged antigen release. That side effect was generally well tolerated. And



T cells primed by a peptide vaccine could tackle different fragments of coronavirus proteins. Credit: Science Photo Library / Alamy Stock Photo

vaccine-induced T cells maintained their ability to recognize viral variants and destroy infected cells, regardless of mutations found in Delta, Omicron or any other widely circulating form of SARS-CoV-2.

"It's very encouraging," says Alessandro Sette, a T-cell immunologist at the La Jolla Institute for Immunology in California who was not involved in the vaccine's development. "The current spike-based vaccines have worked very well, and hopefully will continue to work very well with a booster." But if available vaccine options — nearly all of which are built solely around the spike protein — turn out to be hobbled by viral escape mutations like those found in the Omicron variant, it will be important to have backup designs that promote immunity against a wide range of proteins, structural and non-structural alike. "A larger breadth of response would be desirable," Sette says. With the right peptide designs, T-cell vaccines might even offer 'abortive' immune protection, helping to rapidly clear SARS-CoV-2 before people even know they are infected with the virus, notes Mala Maini, an immunologist from University College London. In November, she and her colleagues described a population of memory T cells directed against a cluster of non-structural viral proteins called the replication–transcription complex (RTC) that seemed

FDA go-ahead for myasthenia gravis agent

The US Food and Drug administration has approved a new drug to treat the autoimmune condition myasthenia gravis. Vyvgart (efgartigimod alfa-fcab) is a human IgG1 antibody fragment developed by argenx, a global biotech headquartered in the Netherlands. The myasthenia gravis treatment is designed to reduce the pathogenic circulating antibodies that drive the disease. It does so by blocking the neonatal Fc receptor (FcRn) and is the first agent to tackle this pathway. In myasthenia gravis, antibodies against the acetylcholine receptor (AChR) bind to the postsynaptic membrane at the neuromuscular junction. This causes fluctuating muscle weakness — ocular, bulbar, limb and respiratory — as the main clinical manifestations of the disease. Argenx's Vyvgart blocks FcRn, involved in rescuing IgG antibodies from degradation, an intervention that lowers pathogenic antibodies in plasma.

In the phase 3 ADAPT trial, 68% of patients with generalized myasthenia gravis who were positive for antibodies to AChR responded when treated with Vyvgart, as measured on the Myasthenia Gravis Activities of Daily Living (MG-ADL) score, compared with 30% of patients on placebo. The first reports from this trial were published in July 2021. The drug is indicated for adult patients with generalized myasthenia gravis who are AChR antibody positive (85% of the patient population). Brussels-based UCB is also developing an FcRn-targeting treatment for myasthenia gravis; its antibody rozanolixizumab is in phase 3 trials. The company revealed in October that, in a phase 3 study testing the antibody in adults with generalized myasthenia gravis, the trial met its primary endpoint. Soliris (eculizumab), developed by Alexion, was the first approved myasthenia gravis drug in US and European Union markets. This monoclonal antibody targets the C5 complement cascade and has been available since 2017 for patients with AChR antibodies. Standard treatments for myasthenia gravis involve anticholinesterase agents, thymectomy and immunosuppression.

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to prevent SARS-CoV-2 from gaining a foothold inside the body. If some of those same RTC-specific reactions were induced through vaccination, "you could potentially stop [the virus] in its tracks," Maini says.

Walz and her colleagues are now evaluating CoVac-1 in patients who either because of genetics (X-linked agammaglobulinemia), cancer (leukemia or lymphoma) or some treatment regimen (anti-CD20 drugs or CAR-T cell therapies) cannot mount B-cell–mediated antibody responses against standard vaccines targeting spike-based antigens. Preliminary data on the first 14 trial participants — most of whom had received mRNA jabs but did not develop neutralizing antibodies — revealed potent T-cell responses in all but one.

"We really see our vaccine as an additional T-cell booster for this high-risk group," says Walz, a hematologist and cancer immunologist by training.

Others, including immunologist Eui-Cheol Shin from the Korea Advanced Institute of Science and Technology in Daejeon, South Korea, see a broader clinical need for such a T-cell-oriented strategy. "COVID-19 will be an endemic disease ultimately," he points out. And as booster campaign efforts shift away from their current focus on stopping viral spread and begin to focus more on prevention of severe disease and death — with the possible added benefit of early virus control through abortive immune responses — Shin predicts that public health officials will increasingly look to T-cell vaccines as a preferred source of top-up immunity, particularly as there are indications that T-cell immunity to SARS-CoV-2 persists longer than antibody-mediated defenses.

"I expect that CoVac-1 can be a booster vaccine for general populations," he says.

The same may hold true of other T-cell-priming peptide jabs that are now moving their way through early clinic testing. Emergex Vaccines, for example, is slated to begin human trials in early 2022 of its nanoparticle-based vaccine, which contains gold atoms that shield the attached peptides from degradation. The experimental jab contains nine protein fragments selected on the basis of their sequence conservation between SARS-CoV-2 and the related coronavirus responsible for the 2003 global outbreak of severe acute respiratory syndrome (SARS).

According to co-founder and CEO Thomas Rademachers, this focus on shared viral epitopes recognized by T cells, including those that have undergone long-term selection in people who recovered from SARS infections in 2003, should yield a vaccine that offers broad and long-lasting protection against the entire sarbecovirus lineage of SARS-like coronaviruses — thereby offering a "way out of the never-ending boosters [with spike-based vaccines] that, in any event, will diminish in effectiveness with time or no longer recognize new variants," he says.

"Shin predicts that public health officials will increasingly look to T-cell vaccines as a preferred source of top-up immunity, particularly as there are indications that T-cell immunity to SARS-CoV-2 persists longer than antibody-mediated defenses."

OSE Immunotherapeutics likewise has in phase 1 testing a 12-peptide vaccine geared toward T-cell activation. The company selected peptides that $CD8^+$ T cells recognize from among fragments of three viral structural proteins (spike, nucleocapsid and membrane), the accessory factor ORF3A and seven non-structural proteins. The vaccine also contains a 'universal' 13-amino-acid pan-HLA-DR peptide epitope (PADRE) to activate $CD4^+$ T cells, all emulsified in Montanide. Preliminary results from the first eight trial participants revealed strong virus-specific T-cell responses six weeks after injection.

According to CSO Nicolas Poirier, the company is now waiting for six-month immunogenicity data — and watching to see how authorized spike-based vaccines fare against SARS-CoV-2 variants — before deciding on next steps for its T-cell vaccine candidate. Trials in immunocompromised patients are under consideration, as are booster studies. But, says Poirier, in such a fast-changing pandemic world, "it's very difficult to anticipate if there is still a commercial path for such a strategy in the global population." ❐

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