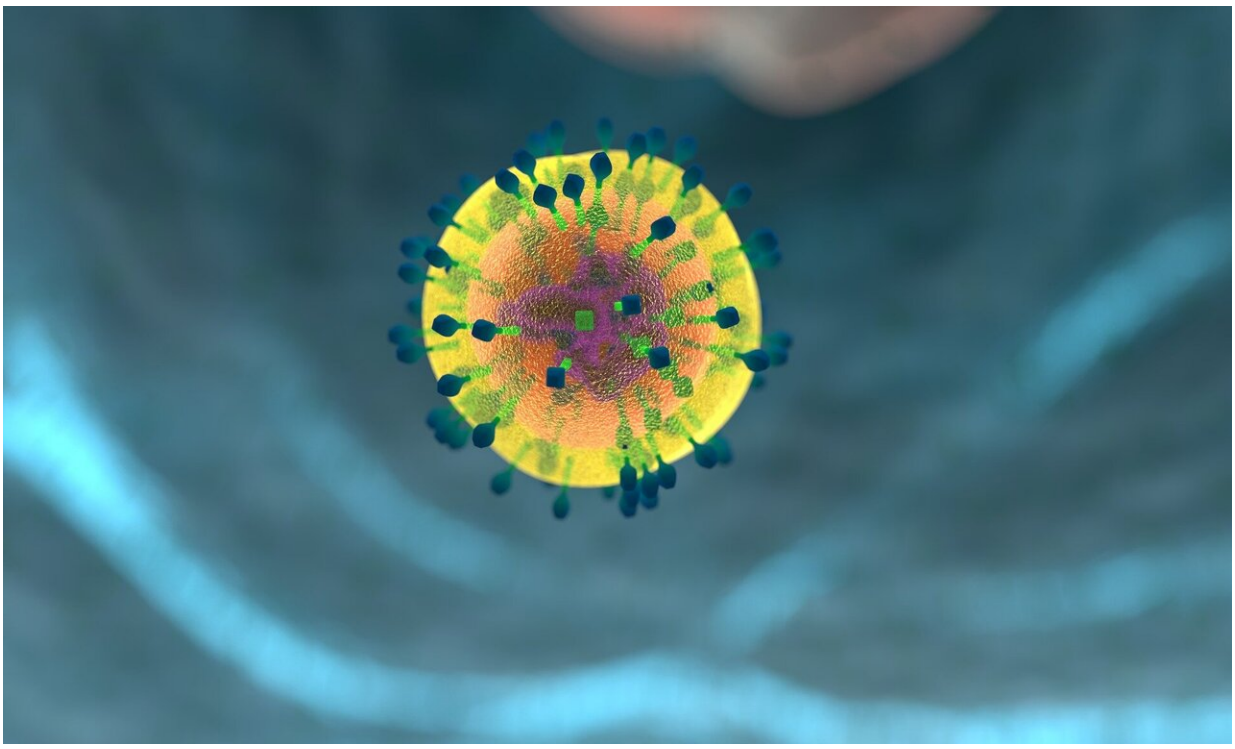
New strategy against autoimmune disease demonstrates safety and efficacy in preclinical animal models

September 21 2020, by Alex Gardner



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Researchers at the Perelman School of Medicine at the University of Pennsylvania found that a powerful new potential treatment for the autoimmune disease mucosal pemphigus vulgaris (PV) appeared safe

and effective in preclinical studies in animal models. The researchers designed and developed this new targeted cell therapy approach based on the learnings from a cutting-edge anticancer strategy called chimeric antigen receptor (CAR) T-cell therapy, a technique that modifies patients' own T cells to attack cancer cells. Similar modifications directed T cells to selectively destroy the autoreactive B cells that cause PV. The findings, including cell cultures, animal experiments, and very telling tests called high-throughput membrane proteome arrays, have paved the way for initiation of a clinical study and have established a preclinical testing paradigm for potentially developing new cell-based therapies for autoimmune diseases. The study was published in the *Journal of Clinical Investigation*.

"Based on these studies, the FDA cleared an Investigational New Drug application enabling a first-in-human clinical trial to test the safety and tolerability of this new therapy for patients with mucosal-dominant PV," said study co-senior author Aimee Payne, MD, Ph.D., a professor of Dermatology at Penn.

Mucosal PV, which affects a little more than 4,000 people in the United States, is caused when the immune system mistakenly interprets one of the body's own proteins as "foreign," and mounts an antibody attack on it. The protein, desmoglein 3 (DSG3), is found in the lining of the mouth and other orifices, and patients experience blistering of the mouth and other mucosal sites, with potentially fatal complications. Although current treatments, which include steroids and other broadly immune-suppressing agents, can be effective, they require chronic use and have significant side effects, including an increased vulnerability to dangerous infections.

Payne and her colleagues sought a safer, more targeted treatment approach that would knock out only the cells making antibodies against DSG3, while leaving the rest of the immune system intact.

To achieve this, they used a modified version of CAR T cell therapy. Multiple CAR T cell therapies have been successfully developed over the past decade into new, approved treatment options for patients with certain B-cell leukemias and lymphomas.

In the standard CAR T-cell approach, doctors harvest T cells from the blood of patients, modify the T cells to attack B cells, grow and expand the altered T cells in the lab, and then reinfuse these CAR T-cells into patients to seek and destroy all B cells in the body, including both lymphoma-causing and normal B cells.

B cells are the immune cells that make antibodies, including antibodies against DSG3 in PV patients. But instead of using the CAR T cell strategy to wipe out all B cells in PV patients, the research team adapted the strategy to be more precise—; the idea is to modify PV patients' T cells using DSG3 as part of a decoy receptor on the surface of modified T cells, programming them to attack and kill only the anti-DSG3 antibody producing B cells.

This "surgical strike" approach would, in principle, only destroy the specific B-cells giving rise to the antibodies that cause PV, while leaving the rest of the immune system intact—thus avoiding the increased infection risk to the patient that comes from broad immune suppression.

In their paper, the researchers reported a panoply of successful preclinical tests of this new strategy, known as desmoglein 3 chimeric autoantibody receptor T cells (DSG3-CAART). Among their findings:

- In lab cell culture tests with B cells from PV patients, DSG3-CAART cells killed nearly all anti-DSG3 B cells while sparing other B cells.
- In both a passive transfer hybridoma cell line and active immune mouse model of PV, DSG3-CAART treatment improved blister-

like disease signs and reduced the levels of anti-DSG3 antibodies, without apparent toxicity.
- In ex vivo cultures of human cells and high-throughput membrane proteome arrays, DSG3-CAART cells appeared to have no relevant interactions with targets other than the intended targets: B cells targeting DSG3.
- DSG3-CAART manufacturing from cells collected from PV patients on immune suppressive therapy was as good as cells collected from healthy donors, except for a small subset of patients on high doses of more than one immune suppressive drug; however, cell product was achieved in all cases.

Based on promising preclinical experimentation, including experimental data published in the recent JCI article, the FDA recently cleared an Investigational New Drug application for a Phase 1 clinical trial of DSG3-CAART, which began recruiting patients in July.

Payne states that in principle, a similar, highly targeted strategy, using T cells to destroy errant populations of B cells producing harmful antibodies, could be adapted against other autoimmune conditions.

"The preclinical data we have presented here provide a foundation that may help inform the future development of CAART therapies for other antibody-mediated diseases," Payne said.

More information: Jinmin Lee et al. Antigen-specific B-cell depletion for precision therapy of mucosal pemphigus vulgaris, *Journal of Clinical Investigation* (2020). DOI: 10.1172/JCI138416

Provided by Perelman School of Medicine at the University of Pennsylvania