A COVID-19 vaccine strategy to give the body 'border protection'

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A simple addition to injected COVID-19 vaccines could enhance their effectiveness and provide "border protection" immunity in areas like the nose and mouth to supplement antibodies in the bloodstream, new

research suggests.

The strategy involves dampening the activity of an enzyme produced by some white blood cells when they're responding to the vaccine challenge. When highly active, this enzyme breaks down not just the pathogen—its job—but also degrades pieces of cells that participate in the immune response.

Research in mice showed that an experimental COVID-19 vaccine containing a compound to inhibit the enzyme stimulated a robust antibody response that included immunity in the nose and mouth, ultimately providing extra protection for airways and the gastrointestinal tract.

"Our approach is to improve 'border control.' The benefits are broad because in addition to providing protection in the bloodstream like most vaccines do, we also have excellent protection in the doors and windows of the body that communicate with the outside," said senior study author Prosper Boyaka, professor and chair of the Department of Veterinary Biosciences at The Ohio State University.

"If we protect the mucosal area where the pathogen enters, then even if you don't reach total immunity there, you limit the amount of pathogen that enters the body so the antibodies inside are more efficient at clearing the infection."

The experimental vaccine was produced by packaging a segment of the SARS-CoV-2 (the virus that causes COVID-19) spike protein as an antigen with the common vaccine ingredient aluminum salts and an enzyme inhibitor. The findings suggest this affordable design could be particularly helpful in developing countries, where cold storage needed for existing vaccines is a challenge, said Boyaka, also an investigator and program director in Ohio State's Infectious Diseases Institute.

The study was published online Aug. 5 in *Proceedings of the National Academy of Sciences*.

There is an irony to the use of aluminum salts (also known as alum) in about 70% of the world's vaccines: While alum's presence actually enhances the immune response, it also recruits the white blood cells that secrete the enzyme, called elastase.

Alum is inexpensive to obtain or produce and can be stored at room temperature, and is effective at promoting development of a bloodstream-based antibody response to vaccination. But it doesn't do much for cell-mediated immunity that improves protection against viruses and bacteria that use cells to reproduce, and can't generate a useful number of antibodies in the body's portals of entry for most pathogens: the nose, mouth and genitourinary tract.

The researchers found that suppressing elastase in a vaccine containing alum had the dual benefits of broadening and speeding up the antibody response in the bloodstream and triggering the specific types of antibodies needed for immune protection of mucous membranes.

"We found a way to have the cells come and help the immune response to develop and the enzyme to break down the pathogen, but we don't want that response to be so high that it goes out of control. So we're just putting a brake on the activity those enzymes would have," Boyaka said. "And we found if you apply that strategy, you can induce a response in the airways even if the vaccine is not given through the airway."

The experimental vaccine enhanced the magnitude of mouse antibodies, which reacted to the same section of the spike protein in the vaccine that antibodies in plasma from COVID-19 patients attach to, as well as generating antibodies in mucosal areas. Immunized mice lacking the gene for the enzyme developed high-affinity antibodies as well.

To further test the concept, the researchers found the enzyme-suppressing compound used in the study triggered production of specialized inflammation-regulating cells in cultures of human immune cells and pig spleen cells, showing that this strategy could improve vaccine immune responses in other species—including people.

Boyaka's team envisions that a future injected vaccine containing an elastase inhibitor could expand SARS-CoV-2 vaccination availability across the world and even be used to boost existing vaccines.

"COVID will stay with us for some time, unfortunately, with the new variants," he said. "What we need to do is have a portfolio of options that we could use depending on the health environment.

"Reprogramming the immune response induced by an injected vaccine containing alum is a way to make the vaccine more efficient for what we need. This could be a cheap and simple approach that can benefit people in developing countries."

More information: Eunsoo Kim et al, Inhibition of elastase enhances the adjuvanticity of alum and promotes anti–SARS-CoV-2 systemic and mucosal immunity, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2102435118

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