Researchers develop a nasal vaccine that prevents COVID-19 in preclinical studies

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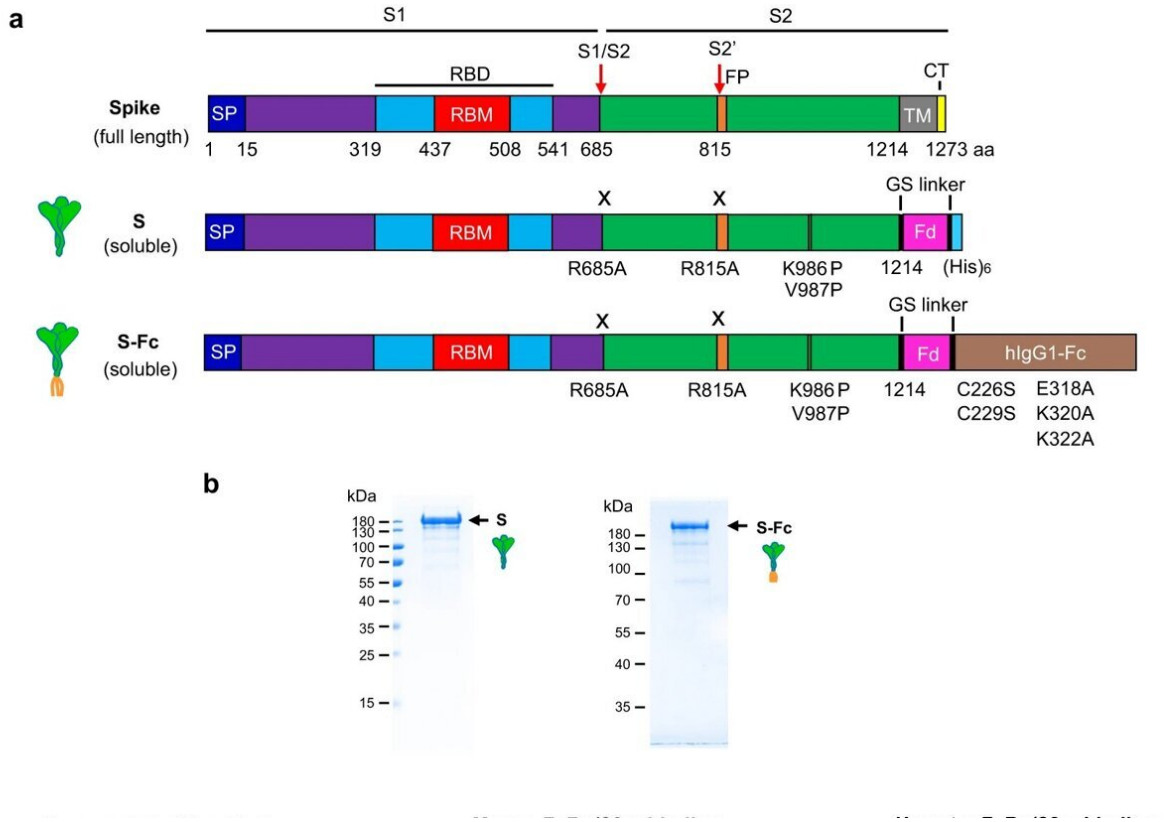

Expression and characterization of the Spike and prefusion Spike-Fc (S-Fc) protein. **a** Schematic illustration of the full-length protein sequence of SARS-CoV-2 Spike. SP: signal peptide; RBD: receptor binding domain; TM: transmembrane domain; CT: cytoplasmic tail. Graphic design of the fusion of SARS-CoV-2 Spike with the T4 fibritin foldon domain (Fd) to create a soluble, prefusion-stabilized, and trimeric Spike protein. Mutations were made in the SARS-CoV-2 (strain USA/WA1/2020) spike by replacing Arg 685 and Arg 815, respectively, with an Ala residue to remove the cleavage site and replacing Lys

986 and Val 987, respectively, with a Pro residue to create a prefusion-stabilized form. The diagram demonstrates the fusion of a SARS-CoV-2 Spike with the T4 fibritin foldon domain and human Fcγ1 to create a prefusion-stabilized and trimeric S-Fc fusion protein. Mutations were also made in the Fcγ1 fragment by replacing Cys 226 and Cys 229, respectively, with a Ser residue to abolish Fc dimerization, and replacing Glu 318 Lys 320 Lys 322 with Ala residues to remove the complement C1q binding site. **b** The S and S-Fc fusion proteins were purified from the stable CHO cell lines. The soluble S and S-Fc proteins were purified by anti-His and Protein A affinity chromatography, respectively, subjected to SDS-PAGE gel electrophoresis under reducing conditions and visualized with Coomassie blue staining. The figure is a representative result from three independently-repeated experiments. **c–f** Test of the S-Fc binding to human, mouse, or hamster FcRn/β2m; human, mouse, or hamster FcγRI; human ACE2; and human or mouse C1q. The ELISA determined the specific binding. The purified S protein was used as a positive control for ACE2 binding and a negative control for FcRn/β2m or FcγRI binding. Respiratory syncytial virus (RSV) protein F alone or Fc-fused F proteins were used as a negative control. Mouse IgG, human IgG1, hamster IgG2, and a mAb (D25) against RSV F protein were used as the positive control, respectively. Source data are provided as a Source data file. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-42796-0

A team of University of Maryland researchers developed a nasal spray vaccine that delivers the SARS-CoV-2 spike protein into cells of the airway in mice and hamsters, triggering an immune response that significantly reduced infection and spread of COVID-19. The technology can be adapted to induce immunity to other respiratory illnesses, such as influenza and respiratory syncytial virus (RSV) infections.

A nasal vaccine for respiratory viruses would be a significant improvement over intramuscular shots, because they are less invasive and stop viral particle replication in the airway, before a virus can enter

the bloodstream. This could improve the rate of vaccination and reduce the spread of disease.

The development was described in a research paper published in *Nature Communications*.

"We continue to hear about new variants, and new waves of COVID-19, and to prevent this, we need a vaccine that is easy to administer and can prevent transmission," said Xiaoping Zhu, professor of veterinary medicine at UMD and lead author of the study. "This nasal vaccine prevents virus transmission and can be easily adapted for new variants."

The virus that causes COVID-19 enters the body through the nose or mouth and replicates within epithelial cells, the protective cells that separate the inside body from the outside world. Vaccines that rely on a shot mainly create immunity in the bloodstream, which means the virus must enter the body and replicate in the blood before being detected by the body's immune system. The new nasal vaccine produces immunity in the cells that line the nose, mouth, and throat, preventing the virus from getting that far.

Zhu and his team developed a technology that leverages the body's natural mechanism to transport the COVID-19 spike protein into the cells of the airway, where the local immune system can learn to recognize the virus.

The mechanism they tapped into uses a protein called neonatal Fc receptor (FcRn) to carry antibodies across epithelial cells. The researchers developed and patented a technology to bind their chosen human antibody to FcRn. Then, they attached the spike protein from SARS-CoV-2 to FcRn and sprayed it into the noses of mice.

The team then exposed the mice to ancient SARS-CoV-2, delta, and

omicron variants of COVID-19. All unvaccinated mice exposed to the Delta variant died, while most vaccinated mice (83-100%) survived. Although mice exposed to major omicron variants survived, the researchers found significantly reduced inflammation and virus loads in vaccinated mice compared to unvaccinated mice.

Comparing results in mice that had the Spike protein delivered by nasal vaccine, versus injection, the researchers found that the nasal vaccine triggered a significantly more potent immune response in the airway and lungs. Consequently, the researchers also found that the nasal vaccine, but not the intramuscular vaccine, dramatically reduced SARS-CoV-2 airborne transmission.

This result is essential as inhalation represents a major transmission route for COVID-19, and airborne virus particles have the potential to linger in the air for up to 9 to 12 hours.

Due to the emergence of new variants, COVID-19 cases and hospitalizations are now ticking up again. While the updated mRNA vaccines remain effective at preventing severe illness and death, they may not be as effective in reducing infection and transmission over time. To overcome this gap, the U.S. government initiative called Project NextGen seeks to develop an effective and safe nasal vaccine for controlling the spread of variants. According to Zhu, the nasal vaccine he and his team developed meets all the criteria of Project NextGen.

More information: Weizhong Li et al, An FcRn-targeted mucosal vaccine against SARS-CoV-2 infection and transmission, *Nature Communications* (2023). DOI: 10.1038/s41467-023-42796-0

Provided by University of Maryland