Nanobodies from alpacas could steer immune attacks on influenza

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While conventional flu vaccines are designed to anticipate the influenza strains projected to dominate in the next flu season, they're only partially effective. And while antiviral drugs are available to treat active flu cases,

the body quickly clears them, requiring high, frequent doses.

Coupling one existing flu drug with a special ingredient from alpacas, the lab of Hidde Ploegh, Ph.D., now demonstrates a potent approach that could both treat and prevent influenza.

Ploegh, a scientist in the Program in Cellular and Molecular Medicine at Boston Children's Hospital, believes the technique could also apply to SARS-CoV-2, HIV, and other infections. He and his colleagues describe it in *Science Immunology*.

Constructing a potent flu fighter

The researchers, led by Xin Liu, Ph.D., and Thomas Balligand, MD, Ph.D., in Ploegh's lab, started with the flu drug zanamivir, which inhibits the viral enzyme neuraminidase and targets cells carrying the flu virus. To the drug, they attached a nanobody made from alpacas' unusual heavy-chain-only antibodies.

The nanobodies' small size enables them to penetrate deeply into tissues. But just as important, they recognize and draw in so-called polyclonal immunoglobulins, an all-purpose mixture of antibodies that circulate abundantly in people's blood.

Once on location at an influenza-infected cell, the immunoglobulins mount a broad range of immune attacks, activating complement proteins, attracting natural killer cells, and more.

"We used zanamivir not so much to block the activity of the neuraminidase enzyme, but as an entity that seeks out virus particles and virus-infected cells," explains Ploegh. "The polyclonal immunoglobulins have multiple classes with different properties, enabling many components of the immune system to immediately engage. This

approach directs them to a target we'd like to eliminate."

Given beforehand as a prophylactic, a single injection of the zanamivir-nanobody construct protected mice against influenza A and B. Given as a treatment several days after infection, it protected the mice even after a normally lethal dose of flu virus. Because the construct targets neuraminidase, an enzyme that influenza needs to replicate, drug resistance would be unlikely to develop, Ploegh says.

As a prophylactic, Ploegh thinks a similar approach in humans would be protective about four weeks, potentially making it useful if given once or twice before and during the flu season. He also thinks that a single shot, given as a treatment, could have longer-term vaccine-like effects.

"That's something we're exploring now," he says. "Destroying influenza-infected cells releases components of the virus, making them available for immune recognition."

Other potential applications

Ploegh thinks a variety of compounds could be swapped in for zanamivir to target other infections. He has patented the technology, and a company he cofounded, Cerberus Therapeutics, will pursue its further development.

In the meantime, Ploegh and colleagues continue to refine the technology and adapt it for other viral infections like HIV and SARS-CoV-2. They've shown preliminary efficacy for these, as well as for Ebola. The lab is also investigating their use in cancer and malaria.

More information: Xin Liu et al, An armed anti-immunoglobulin light chain nanobody protects mice against influenza A and B infections, *Science Immunology* (2023). DOI: 10.1126/sciimmunol.adg9459

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