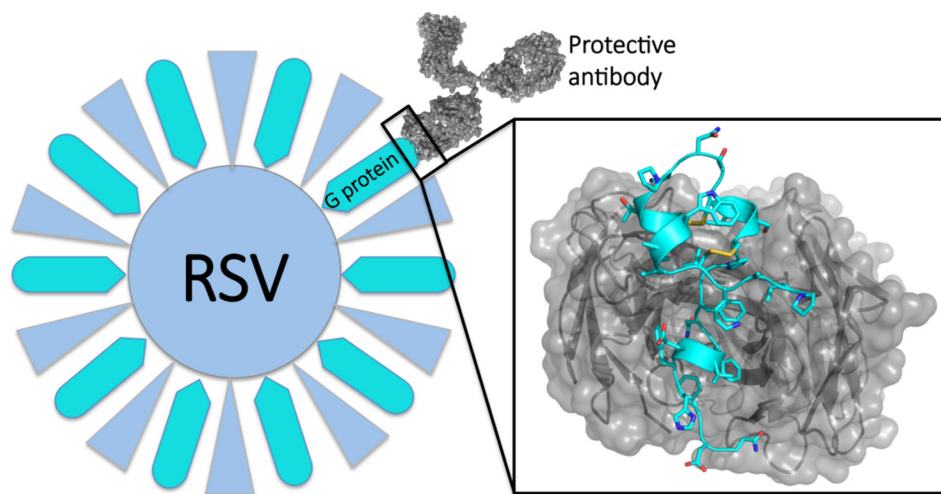
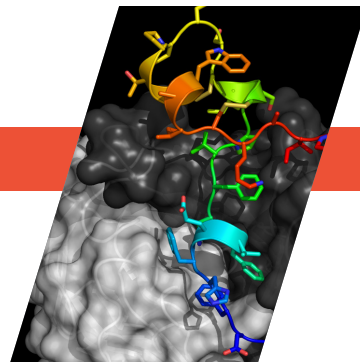


Respiratory Virus Study Points to Vaccine Target



Structure of a protective human antibody bound to the RSV G protein. The antibody binds to a three-dimensional, twisted site on the RSV G protein.

Vaccine failures prompt new approach

Respiratory syncytial (sin-SISH-uhl) virus (RSV) causes 118,000 deaths in young children each year worldwide and 57,000 hospitalizations of children each year in the United States alone. Attempts to develop a vaccine—at first based on inoculations with inactivated virus, and then targeting a key viral surface protein (RSV F)—have failed. Recent studies, however, suggest that a second viral surface protein (RSV G) is a promising target.

In one earlier study, elevated concentrations of antibodies targeting both RSV F and RSV G were associated with lower clinical disease severity scores, despite a substantially lower absolute abundance of anti-G antibodies. Another study found that higher levels of maternal anti-G antibodies correlated with less severe disease in infants (up to 4–6 months of age), even

though anti-G antibodies were again found in lower concentrations.

While the RSV F surface protein allows the virus to enter a host cell, RSV G is what allows the virus to stick to lung cells and distort immune responses. This disruption of the immune response by RSV G might explain why vaccines based on RSV F have failed. Thus, a protective antibody response that blocks RSV G activity could be more effective, but scientists didn't know how antibodies target RSV G at the molecular level.

Reverse vaccinology

In this work, the researchers took a "reverse vaccinology" approach: they are first studying where and how the antibodies bind to the virus, so that they can reverse engineer a vaccine antigen (a substance that induces an immune response upon vaccination).

Scientific Achievement

The molecular structures of human antibodies bound to a respiratory syncytial virus (RSV) surface protein reveal potential targets for antiviral therapies.

Significance and Impact

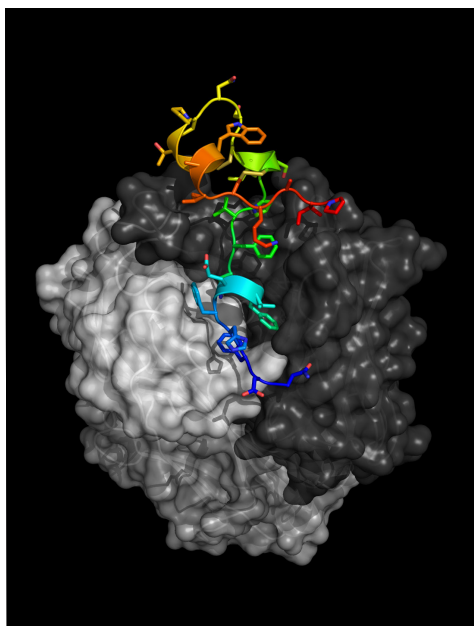
The work provides a promising route for designing a vaccine effective against a broad range of RSV strains, which cause serious respiratory disease in infants and older adults.

Collaborators at Trellis Bioscience, a biotechnology company in Menlo Park, California, successfully isolated anti-G antibodies from patients recently infected with RSV. The research team then co-crystallized the protective antibodies with RSV G protein, producing submillimeter-sized crystals.

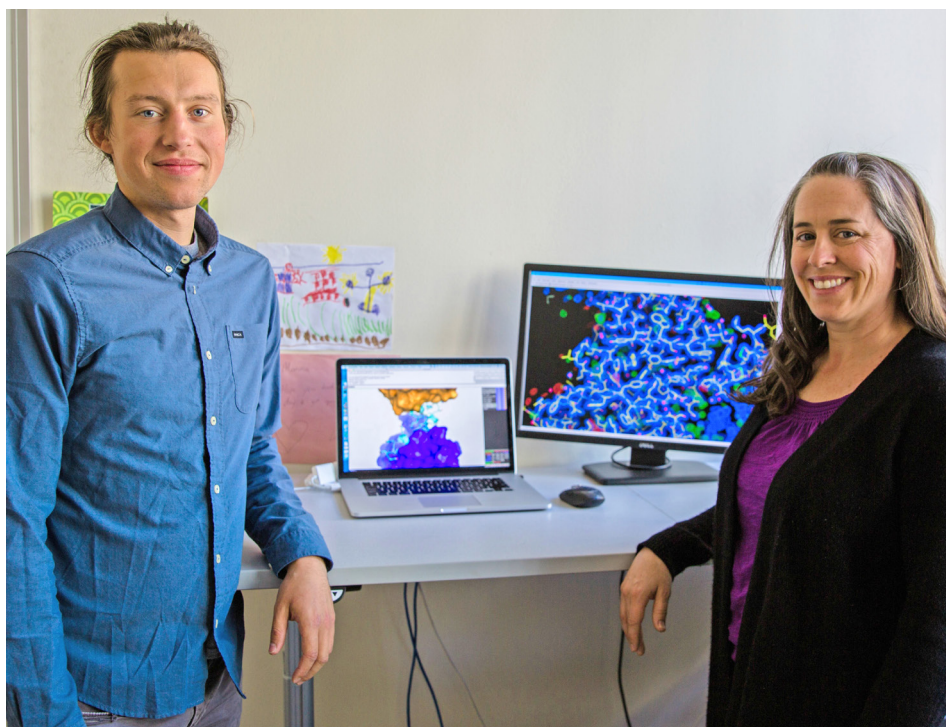
X-ray crystallography of the samples at ALS Beamline 8.3.1 was used to determine the high-resolution molecular structures, allowing the researchers to pinpoint the exact sites on the virus targeted by the anti-G antibodies.

Region of vulnerability

The structures revealed that the anti-G antibodies bind with high affinity to a three-dimensional, twisted sequence of amino acids called the central conserved domain (CCD)—a region of vulnerability on the RSV G protein. Because this domain is



A protective human antibody (dark and light gray surface) sticks to a folded part of the RSV G protein (rainbow colored blue-to-red). (Credit: R. DuBois/UC Santa Cruz)



Stanislav Fedechkin and Rebecca DuBois. (Credit: C. Lagattuta/UC Santa Cruz)

the same in all strains of the virus, the protective antibodies are broadly neutralizing: exactly the type of antibodies that are the desirable products of successful vaccination.

The study also revealed that the protective antibodies block the ability of RSV G to bind and induce signaling in a receptor (CX3CR1) that's involved in attaching the virus to lung cells and distorting the immune response. Thus, the antibodies have the dual protective functions of blocking virus infection as well as blocking virus manipulation of human

immune responses.

Based on these results, Trellis Bioscience is currently developing an antiviral antibody therapy heading toward clinical trials. Going forward, the researchers will

be studying how other protective human antibodies bind to RSV G in order to design novel vaccine antigens, with the long-term goal of creating the first effective RSV vaccine.

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