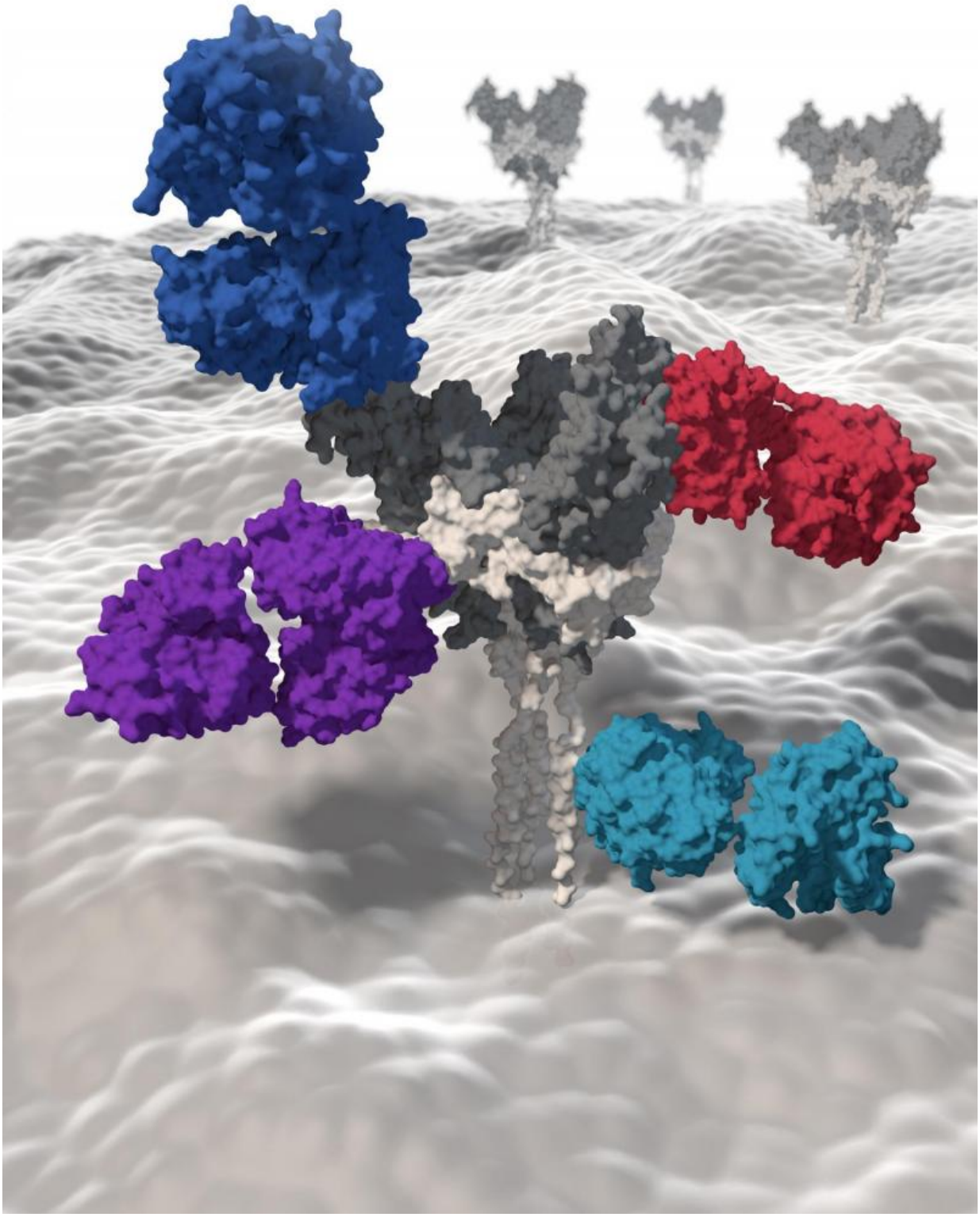
Researchers discover new Ebola-fighting antibodies in blood of outbreak survivor (Update)

February 18 2016



Ebola virus trimer bound by neutralizing antibodies. Credit: Christina Corbaci

A research team that included scientists from The Scripps Research Institute (TSRI) has identified a new group of powerful antibodies to fight Ebola virus.

The antibodies, isolated from the blood of a survivor of the 2014 Ebola outbreak and the largest panel reported to date, could guide the development of a vaccine or therapeutic against Ebola. The new study also revealed a previously unknown site of vulnerability in the structure of the deadly virus.

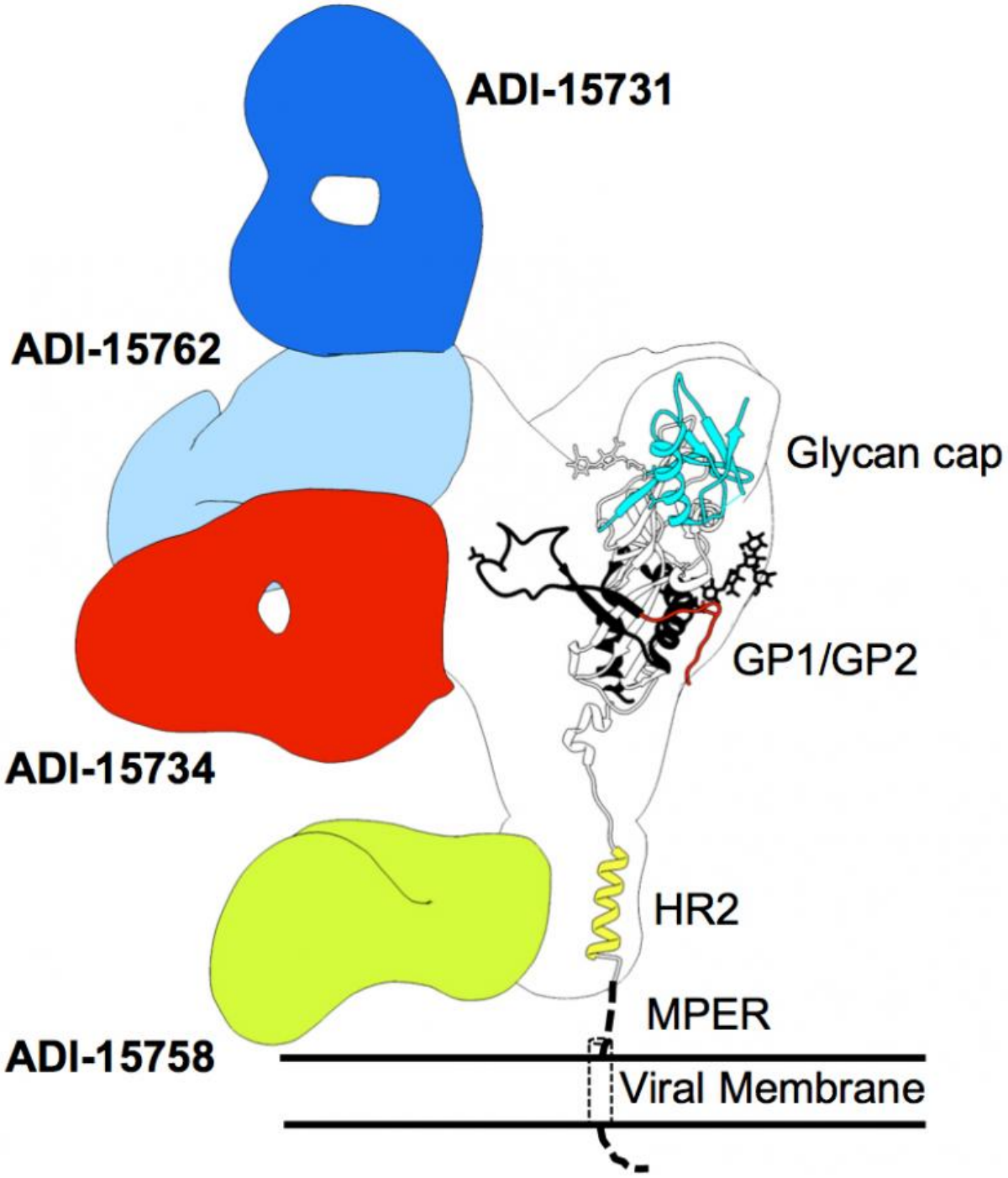
"Our *Science* paper describes the first in-depth view into the human antibody response to Ebola virus," said team leader Laura Walker, senior scientist at Adimab, LLC, and an alumna of TSRI's PhD program. "Within weeks of receiving a blood sample from a survivor of the 2014 Ebola outbreak, we were able to isolate and characterize over 300 monoclonal antibodies that reacted with the Ebola virus surface glycoprotein."

Co-authors of the paper included TSRI lab heads Professor Erica Ollmann Saphire (also co-director of the Global Virus Network Center of Excellence at TSRI); Associate Professor Andrew Ward; and Professor Dennis Burton (also scientific director of the International AIDS Vaccine Initiative's (IAVI) Neutralizing Antibody Center and the National Institutes of Health (NIH)-sponsored Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID), both at TSRI).

The study was published February 18, 2016, in the journal *Science.*

Searching for Powerful Antibodies

Studies at TSRI and other institutions have shown that Ebola virus has several weak points in its structure where antibodies can target and neutralize the virus. However, the immune system typically needs a long period of trial and error to produce the right antibodies against these sites, so researchers have been working with only a small library of anti-Ebola options.



This image shows a key Ebola virus protein and vulnerable sites where antibodies (in color) can bind and neutralize it. Credit: Hannah Turner and Daniel Murin, The Scripps Research Institute.

Despite this limited library, researchers have had some success in designing antibody "cocktails" that target several weak points at once. One treatment in development, Mapp Biopharmaceutical Inc.'s ZMapp, is a cocktail of three mouse antibodies modified to resemble human antibodies. This treatment was successful in primate trials and used as an experimental human treatment in the 2014 outbreak.

With ZMapp showing promise, researchers are searching for additional antibodies to fight Ebola.

"These types of antibodies could be developed into different types of antibody cocktails or therapeutics, in addition to advancing vaccine design," said Ward.

Bringing New Technologies Together

The new study took advantage of a recently launched single B cell isolation platform from Adimab, which researchers used to quickly find more than 300 antibodies that reacted with the Ebola virus surface glycoprotein—the viral structure that fuses with host cells.

Researchers at TSRI and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) then performed an in-depth analysis of the therapeutic potential of these antibodies. Crucial to this effort was the TSRI development of antigens—molecules that can "fish" for antibodies in blood serum.

"That's where our expertise came into play," said the study's first author Zachary Bornholdt, an assistant professor in the Ollmann Saphire lab at the time of the study and current associate director of antibody discovery at Mapp Biopharmaceutical.

Remarkably, 77 percent of the antibodies in the new study showed the potential to neutralize Ebola virus, and several antibodies demonstrated significant protection against the virus in mouse models. "We identified three highly protective antibodies that each targeted a different site—or epitope—on the Ebola virus glycoprotein," Bornholdt said.

Because these are human antibodies, not modified mouse antibodies, researchers potentially could quickly use them to design a treatment. Furthermore, with these new antibodies available, researchers might be able to design secondary treatments in case the Ebola virus mutates to escape other treatments.

Next, the researchers used an imaging technique, called electron microscopy, to investigate exactly where the antibodies were binding with Ebola virus. The imaging, led by the Ward lab at TSRI, revealed a previously unknown Achilles heel on the virus: a spot at the base of the Ebola virus surface glycoprotein.

While Ebola virus mutates rapidly, this site is part of the virus's larger machinery and tends to stay the same. This means targeting this spot could neutralize many strains of Ebola.

To encourage further studies, the researchers have made the genetic sequences of these antibodies available to the research community.

Stopping Emerging Diseases

The researchers believe the techniques in this study could be used to find treatments for other emerging diseases, such as Zika virus.

Bornholdt thinks of the new study as a test case. In just over a year, the combination of Adimab and TSRI methods led to the discovery of promising antibodies—and future experiments should move even more

quickly now that researchers have experience with these tools.

"With other outbreaks, we could take blood samples from the first wave of survivors and potentially produce a therapeutic rapidly," said Bornholdt. "That's the long-term goal."

More information: Isolation of potent neutralizing antibodies from a survivor of the 2014 Ebola virus outbreak, *Science*, DOI: 10.1126/science.aad5788

Provided by The Scripps Research Institute