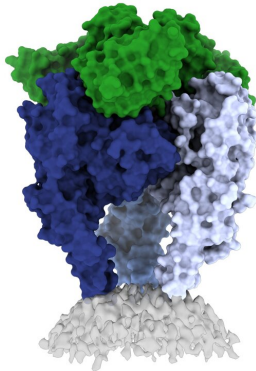


Researchers capture new high-resolution view of rabies virus, revealing potential vaccine targets

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Scientists from La Jolla Institute for Immunology and the Institut Pasteur have shed light on the structure of the rabies virus glycoprotein, seen here. Credit: Heather Callaway, Ph.D., LJI

Rabies virus kills a shocking 59,000 people each year, many of them children. Some victims, especially kids, don't realize they've been exposed until it is too late. For others, the intense rabies treatment regimen is out of the question: treatment is not widely available and the average \$3,800 expense poses unthinkable economic burden for most people around the world.

Rabies vaccines, rather than treatments, are much more affordable and easier to administer. But those vaccines also come with a massive downside:

"Rabies vaccines don't provide lifelong protection. You have to get your pets boosted every year to three years," says LJI Professor Erica Ollmann Saphire, Ph.D. "Right now, rabies vaccines for humans and [domestic animals](#) are made from killed virus. But this inactivation process can cause the molecules to become misshapen—so these

vaccines aren't showing the right form to the [immune system](#). If we made a better shaped, better structured vaccine, would immunity last longer?"

Saphire and her team, in collaboration with a team led by Hervé Bourhy, Ph.D., at the Institut Pasteur, may have discovered the path to better vaccine design. In a new study, published in *Science Advances*, the researchers share one of the first high-resolution looks at the [rabies virus](#) glycoprotein in its vulnerable "trimeric" form.

"The rabies glycoprotein is the only protein that rabies expresses on its surface, which means it is going to be the major target of neutralizing antibodies during an infection," says LJI Postdoctoral Fellow Heather Callaway, Ph.D., who serves as the study's first author.

"Rabies is the most lethal virus we know. It is so much a part of our history—we've lived with its specter for hundreds of years," adds Saphire, who also serves as LJI's President and CEO. "Yet scientists have never observed the organization of its surface molecule. It is important to understand that structure to make more effective vaccines and treatments—and to understand how rabies and other viruses like it enter cells."

Rabies the shapeshifter

Scientists don't know exactly why rabies vaccines don't provide long-term protection, but they do know that its shape-shifting proteins are a problem.

Like a Swiss Army knife, the rabies glycoprotein has sequences that unfold and flip upward when needed. The glycoprotein can shift back and forth between pre-fusion (before fusing with a host cell) and post-fusion forms. It can also fall apart, changing from a trimer structure (where three

copies come together in a bundle) to a monomer (one copy by itself).

This shapeshifting gives rabies a kind of invisibility cloak. Human antibodies are built to recognize a single site on a protein. They can't follow along when a protein transforms to hide or move those sites.

The new study gives scientists a critical picture of the correct glycoprotein form to target for antibody protection.

Capturing the glycoprotein at last

Over the course of three years, Callaway worked to stabilize and freeze the rabies glycoprotein in its trimeric form. This "pre-fusion" form is the shape the glycoprotein takes before it infects human cells.

Callaway paired the glycoprotein with a human antibody, which helped her pinpoint one site where the viral structure is vulnerable to antibody attacks. The researchers then captured a 3D image of the glycoprotein using cutting-edge cryo-electron microscope equipment at LJI.

The new 3D structure highlights several key features researchers hadn't seen before. Importantly, the structure shows two key pieces of the virus structure, called the fusion peptides, the way they appear in real life. These two sequences link the bottom of the glycoprotein to the viral membrane, but project into the target cell during infection. It is very hard to get a stable image of these sequences. In fact, other rabies researchers have had to cut them off to try to get images of the glycoprotein.

Callaway solved this problem by capturing the rabies [glycoprotein](#) in detergent molecules. "That let us see how the fusion sequences are attached before they snap upward during infection," says Sapphire.

Now that scientists have a clear view of this viral structure, they can better design vaccines that tell the body how to make antibodies to target the virus.

"Instead of being exposed to four-plus different

protein shapes, your immune system should really just see one—the right one," says Callaway. "This could lead to a better vaccine."

Preventing a family of viruses

Sapphire hopes stronger, broader immunity could help people in regular contact with animals, such as veterinarians and wildlife workers, as well as the billions of people who may accidentally come in contact with a rabid animal. Rabies is endemic across every continent except Antarctica and infects numerous species including dogs, racoons, bats, and skunks.

This new work may also open the door to a vaccine to protect against the whole lyssavirus genus, which includes rabies and similar viruses that can spread between humans and other mammals.

The next step in this work is to capture more images of rabies virus and its relatives together with neutralizing antibodies. Callaway says scientists are working on solving several of these structures, which could reveal antibody targets that lyssaviruses have in common.

"Because we didn't have these structures of the rabies [virus](#) in this conformational state before, it's been hard to design a broad-spectrum [vaccine](#)," says Callaway.

More information: Heather M. Callaway et al, Structure of the rabies virus glycoprotein trimer bound to a prefusion-specific neutralizing antibody, *Science Advances* (2022). [DOI: 10.1126/sciadv.abp9151](https://doi.org/10.1126/sciadv.abp9151). www.science.org/doi/10.1126/sciadv.abp9151

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