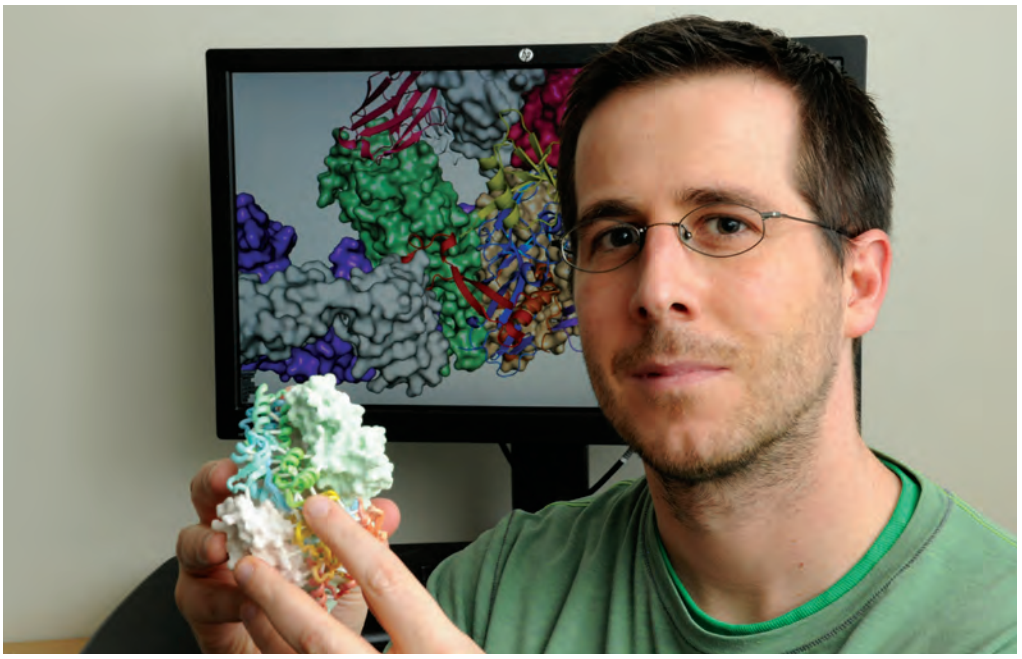
Jon Gilbert Fox



FUNCTION FOLLOWS FORM – REVEALING THE MOLECULAR MECHANISMS OF VIRUSES

WHEN VISITING THE OFFICE OF JASON MCLELLAN, PHD, an assistant professor of biochemistry at the Geisel School of Medicine, your eyes are drawn to two 3D-printed models on his desk that he often uses to help people visualize the work of his lab. McLellan's groundbreaking research with viral proteins is providing new insights into deadly outbreaks such as Ebola and MERS-CoV (Middle East Respiratory Syndrome coronavirus).

Intrigued, you pick up the models, which have similar looking colors and patterns but are quite different in shape. McLellan explains that you're holding two different conformations or forms of the same protein—the fusion (F) glycoprotein from the respiratory syncytial virus (RSV).

"The F glycoprotein starts off on the viral surface in a compact, pre-fusion conformation, then undergoes a dramatic rearrangement into an elongated, post-fusion conformation," he says, giving you an appreciation for how dynamic and complex the molecular workings of viruses can be. "This facilitates fusion of the viral membrane with the host-cell membrane and allows the viral RNA to enter the host cell and begin replicating."

In his work as a structural biologist, McLellan is particularly interested in a type of protein known as class I fusion glycoproteins (proteins decorated with sugars) that viruses need to gain entry into host cells.

Using a technique called X-ray crystallography—where crystals of proteins are grown in the lab, frozen, and then exposed to X-rays—he and his colleagues are able to determine the three-dimensional protein structures in atomic-level detail.

"Once we know a protein's structure, it gives us insight into its function," says McLellan, explaining that the work is highly collaborative, involving domestic and international investigators from academia, government, and industry. "Our ultimate goal is to translate the structural and mechanistic information that we obtain into the development of products like vaccines, antibodies, and small molecules that can prevent viruses from causing severe illness and death."

One such virus is RSV, an extremely common and highly contagious respiratory pathogen that is globally responsible for about 7 percent of deaths among infants between one month and one year of age. In the US, the virus hospitalizes more than 100,000 children and infants each year, and is a leading cause of respiratory infections in the elderly.

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During his post-doctoral training at the National Institute of Health's (NIH) Vaccine Research Center in Bethesda, MD, McLellan determined the pre- and post-fusion structures of the RSV F glycoprotein. He and his colleagues then used this structural information to rationally design an immunogen (a key ingredient in vaccines), which elicited a highly protective response in animal studies and has helped accelerate efforts to develop a vaccine for RSV.

Called one of the top 10 scientific breakthroughs in 2013 by the journal *Science*, their efforts helped validate the effectiveness of structure-based vaccine design. Researchers are now applying lessons learned from this research to other viruses such as HIV, which has proved resistant to effective therapies because of its rapid mutations.

"Traditionally, the approach has been more random and empirical, which has worked very well in many cases," he explains. "However, we want to provide a very logical basis for making changes and alterations that can either lead to new therapies or optimize current ones."

These successful collaborations have led to some recent high-profile projects with other research groups—giving McLellan and his team at Geisel the opportunity to apply their structure-based approach to some important viruses that contain the same class of glycoproteins as RSV.

In one study, published recently in the journal *Nature*, they worked with colleagues at The Scripps Research Institute (TSRI) and the

NIH to solve the structure of a coronavirus spike (S) protein in its pre-fusion conformation. This protein is found in a coronavirus known as HKU1, which is closely related to more potent and deadly coronaviruses such as SARS-CoV (Severe Acute Respiratory Syndrome) and MERS-CoV.

"It's thought there will continue to be epidemics with coronaviruses, since they have large animal reservoirs that are increasingly being encroached on by human populations, and they're able to cross species barriers pretty easily," says McLellan.

The different groups of this virus share the same fusion machinery used to enter host cells, he explains. Working with colleague Andrew Ward from TSRI—who uses a complementary technique called cryo-EM (electron microscopy), which freezes proteins and then images them with an electron beam—they were able to map the spike protein in 3D.

"Solving this long-awaited structure of the spike protein sets the stage for structure-based vaccine design efforts, which we are embarking on now, that can elicit broadly protective vaccines against coronaviruses, such as SARS and MERS," he says.

Another recent study, published in the journal *Science*, details how McLellan and his team collaborated with scientists from the National Institute of Allergy and Infectious Disease and other colleagues to characterize an antibody that shows great promise as a potential treatment for Ebola. There is still no cure or specific treatment for the virus, which killed more than 11,000 people during its 2014-15 outbreak in West Africa.

"We studied antibodies that were obtained from blood samples from an Ebola survivor in Africa, and discovered how one particular antibody, mAb114, binds to the Ebola glycoprotein (GP), blocking its interaction with host cells," McLellan explains. "By determining the structure of the antibody and how it worked, we identified novel targets on GP for antibody therapeutics and vaccine design."

The antibody had proved to be highly protective in animal studies, even when administered five days after Ebola infection. "It was the first time a single antibody showed the ability to protect macaques against Ebola virus," he says. "Now it can be tested in human clinical trials."

Meanwhile, McLellan and his team are continuing to work on various aspects of RSV, particularly in the areas of small molecule and antibody development, as part of their efforts to gain a greater understanding of how the virus infects host cells and how it can be more effectively neutralized.

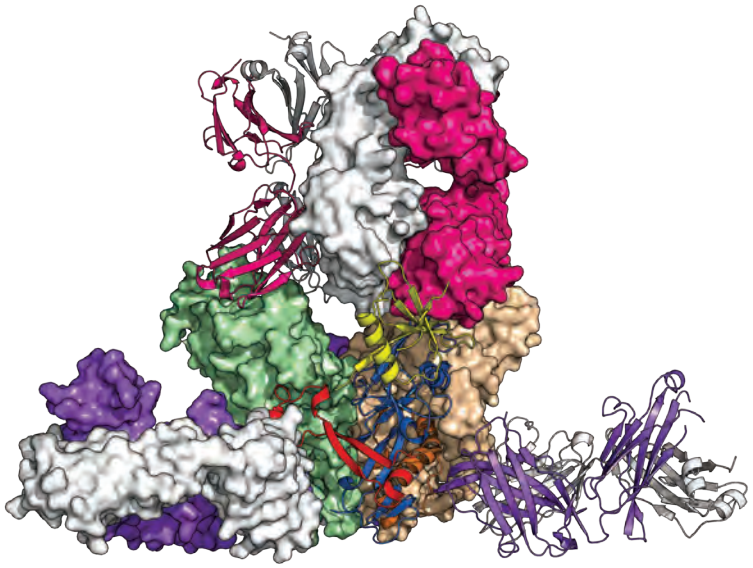
A recent study involving small molecules, published as the cover story in the journal *Nature Chemical Biology*, reveals new details about the role that small-molecule inhibitors play in disrupting the function of the F glycoprotein.

"We were able to show that these small molecules bind in the center of this protein and prevent it from converting into the post-fusion conformation," says McLellan. "The structure revealed some key properties for next-generation compounds that we're working with Janssen Pharmaceuticals (owned by Johnson and Johnson) and others to develop."

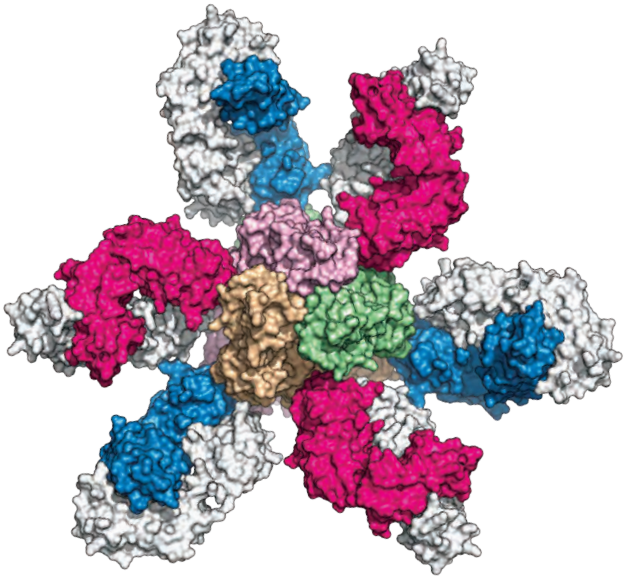
McLellan and his lab are also collaborating with the Neonatal Intensive Care Unit at Dartmouth-Hitchcock. "They've drawn blood samples from RSV-infected babies and we're using those blood samples to isolate antibodies to learn more about how best to make a vaccine to protect them from severe RSV disease," he explains.

"It's an exciting time to be in structural biology," says McLellan. "Our work provides a nice interplay between basic science and translational science. And the advances being made in equipment and computational power are allowing us to illuminate and determine structures of important targets. Hopefully, this will lead to new interventions that will have a big impact on human health."

TIM DEAN



Antibodies 114 (pink & white) and 100 (purple & white) bound to the trimeric prefusion Ebola glycoprotein, viewed along the viral membrane. (Image: McLellan Lab, Science 18 Mar 2016: Vol. 351, Issue 6279, pp. 1343-1346, DOI: 10.1126/science.aad6117)



Antibodies AM14 (blue & white) and motavizumab (pink & white) bound to the trimeric prefusion RSV F protein, viewed looking down toward the viral membrane. (Image: Morgan Gilman, Vol. 11(7) July 2015. PLoS Pathog 11(7): ev11.i07. doi:10.1371/image.ppat.v11.i07. Creative Commons)