

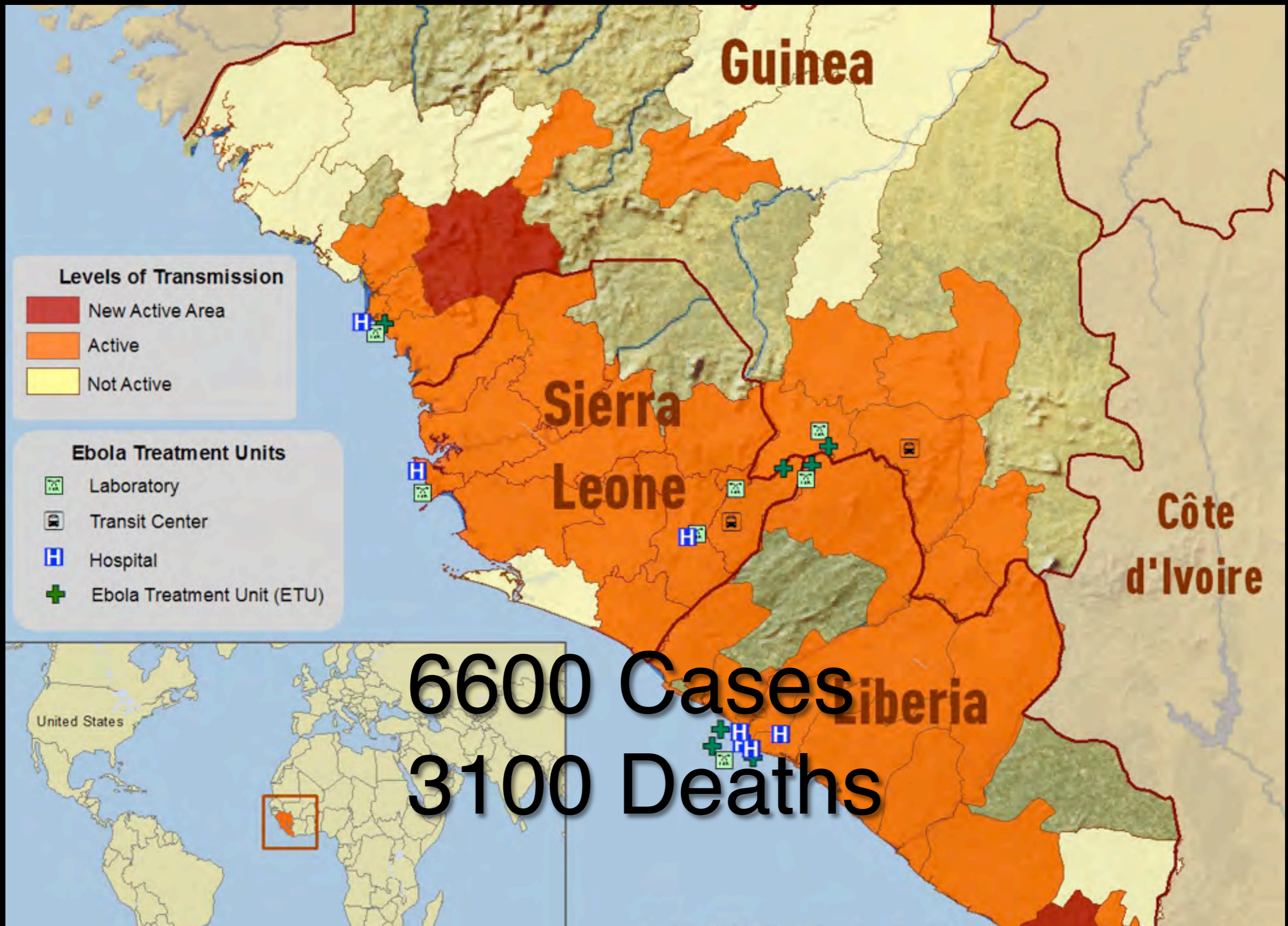
Ebola Entry and the ZMapp Cocktail

Erica Ollmann Saphire, Ph.D.
Immunology & Microbial Science
The Scripps Research Institute

Ebola virus



50-90% lethal



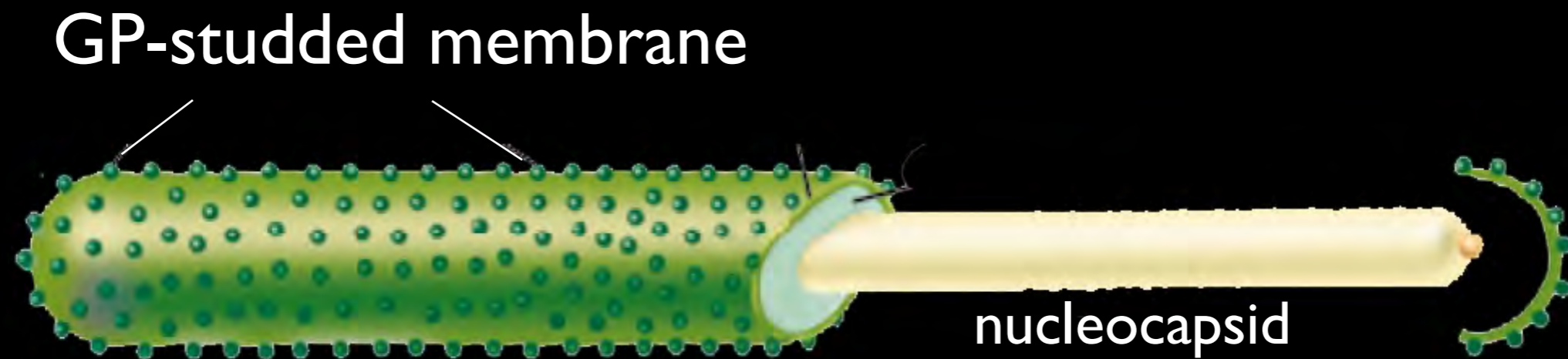
Ebola virus has one molecule that it uses to enter cells

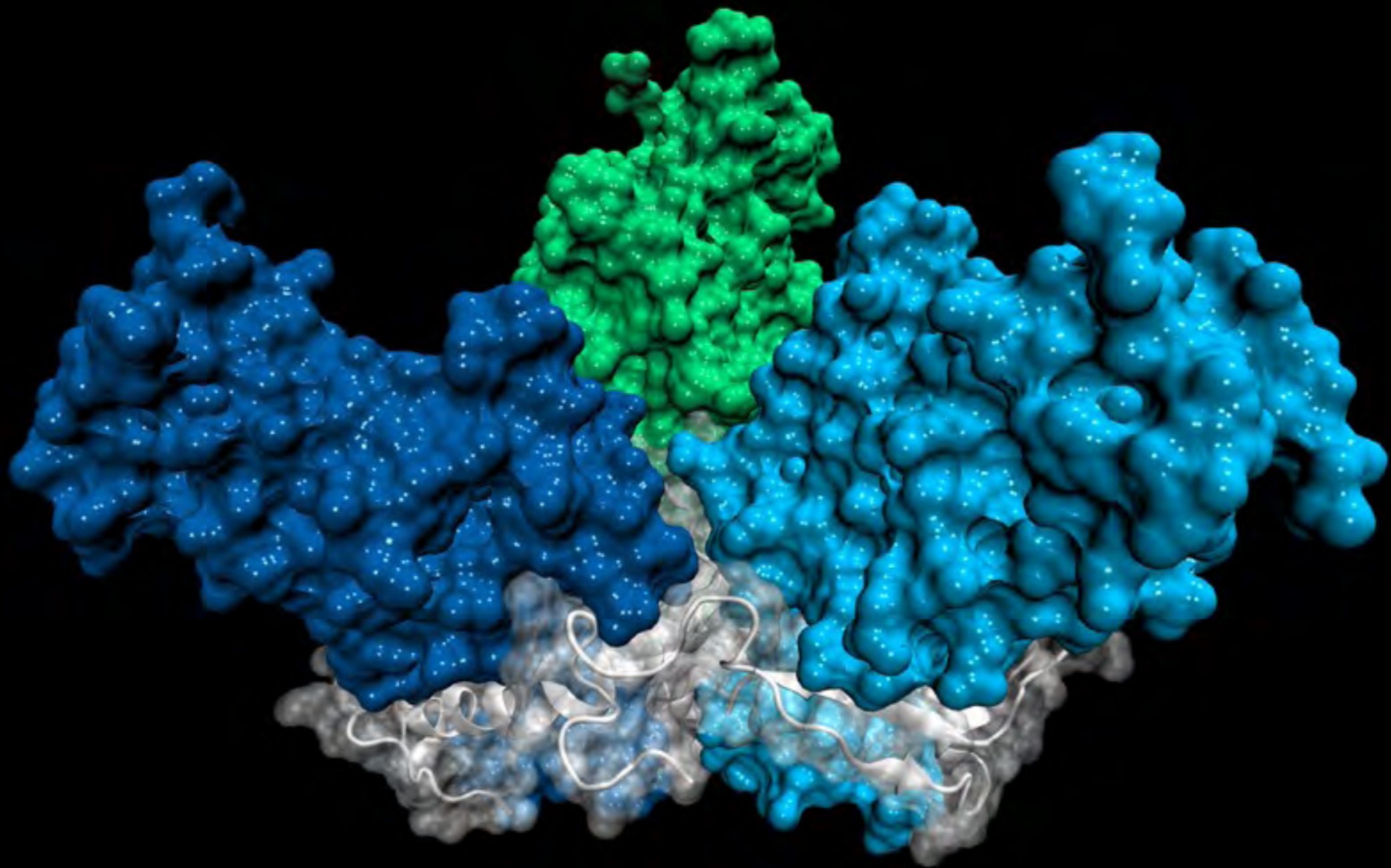
Ebola virus has one molecule that it uses to enter cells

“GP” for GlycoProtein

Ebola virus has one molecule that it uses to enter cells

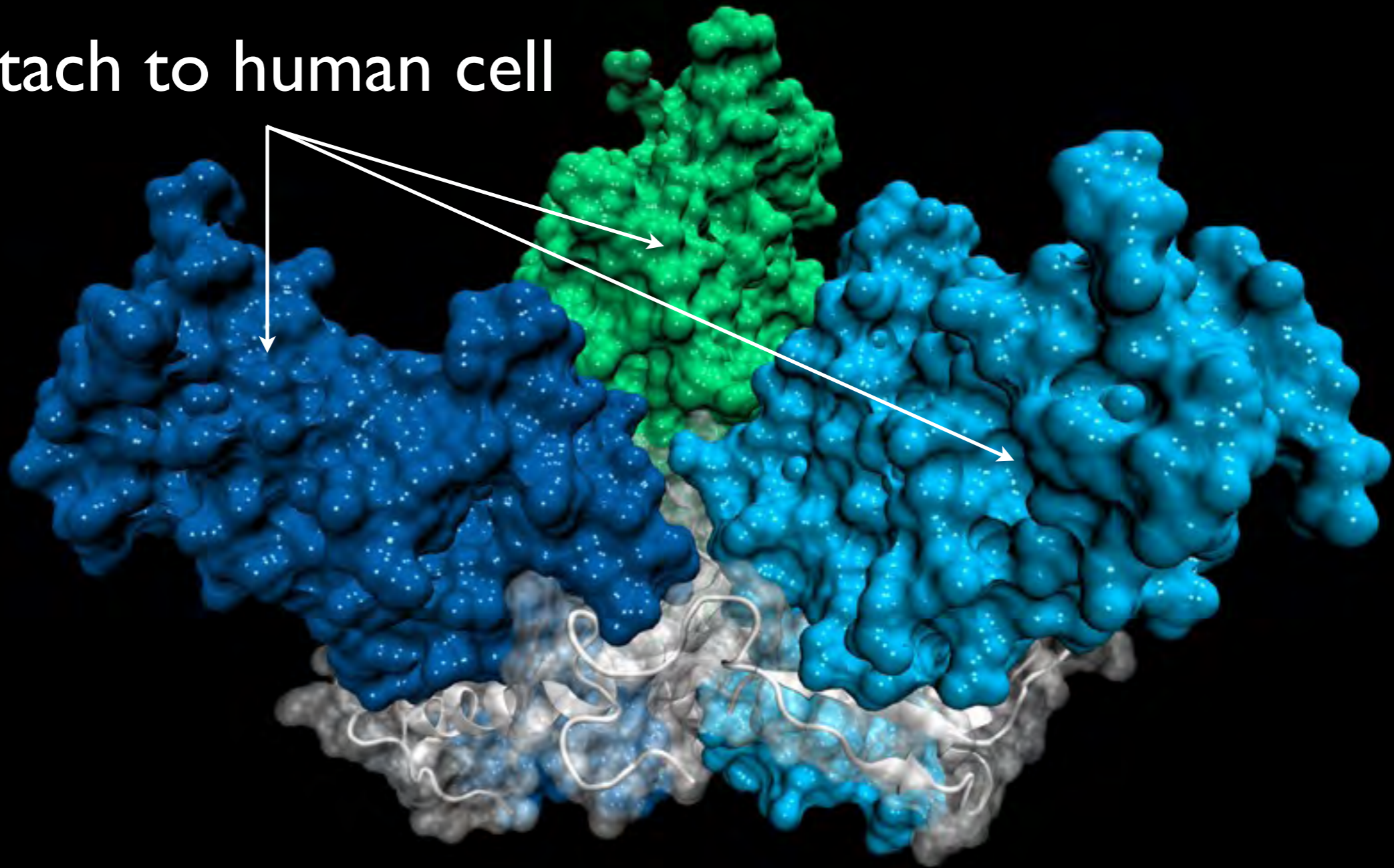
“GP” for GlycoProtein





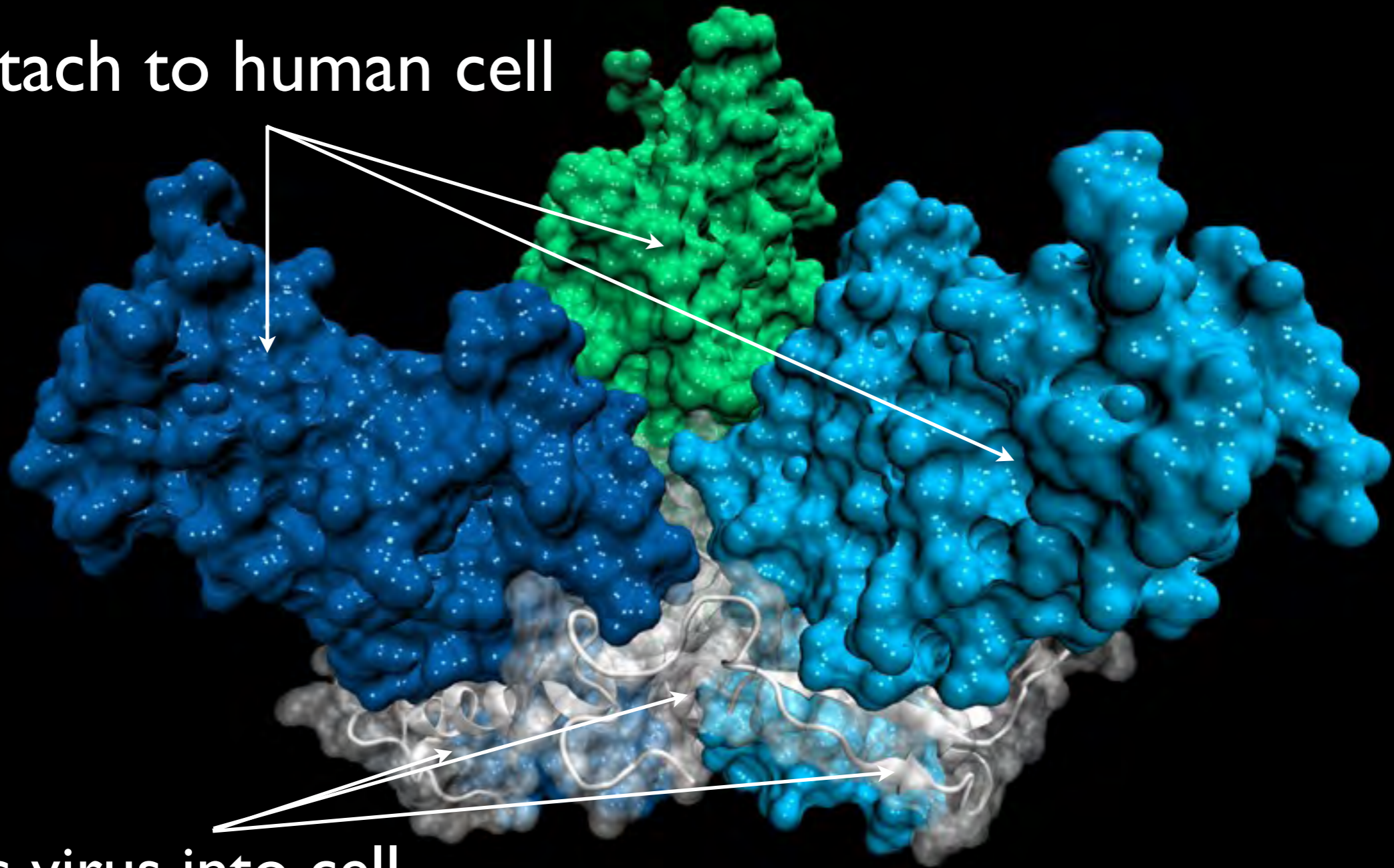
Ebola virus GP

attach to human cell



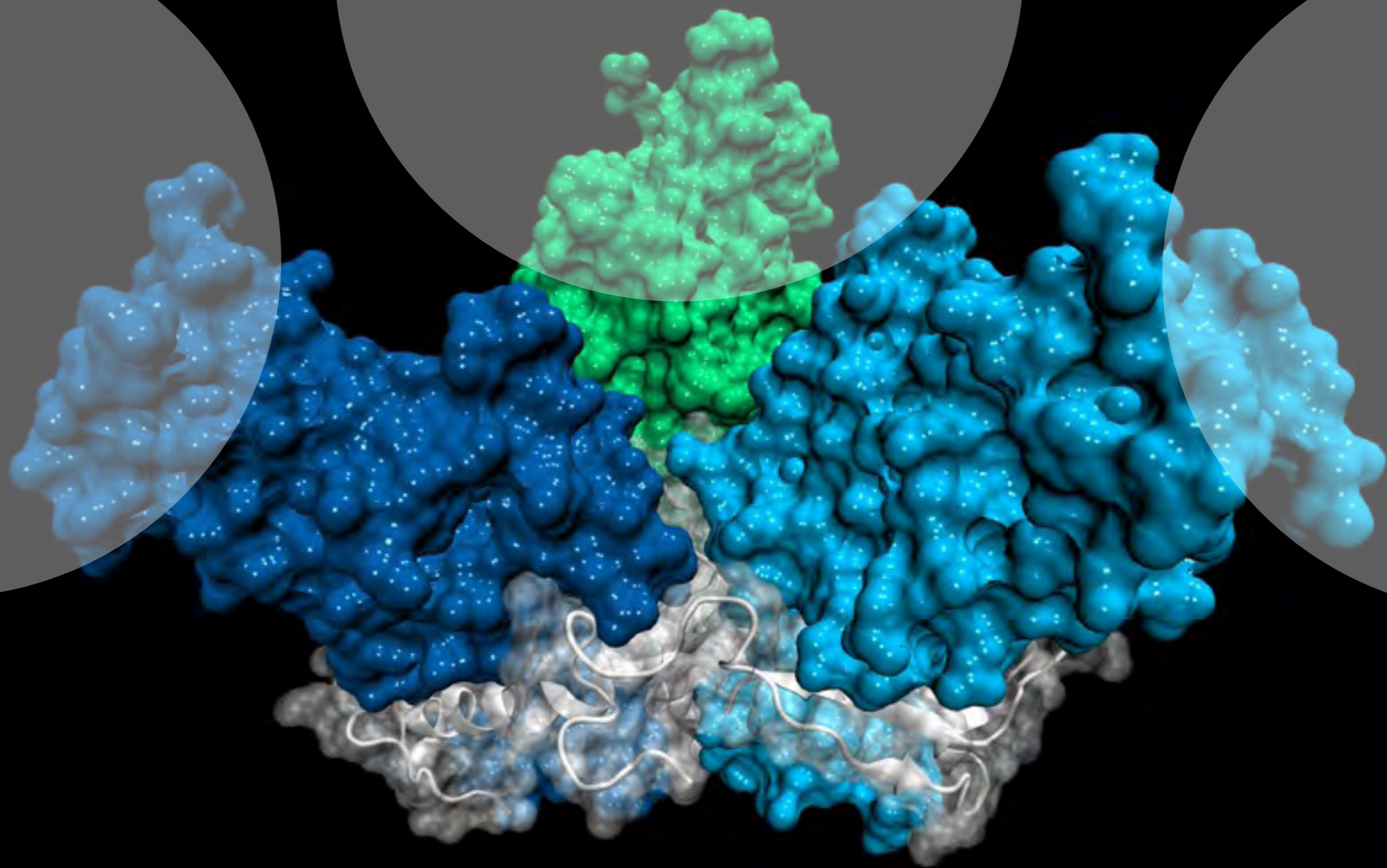
Ebola virus GP

attach to human cell

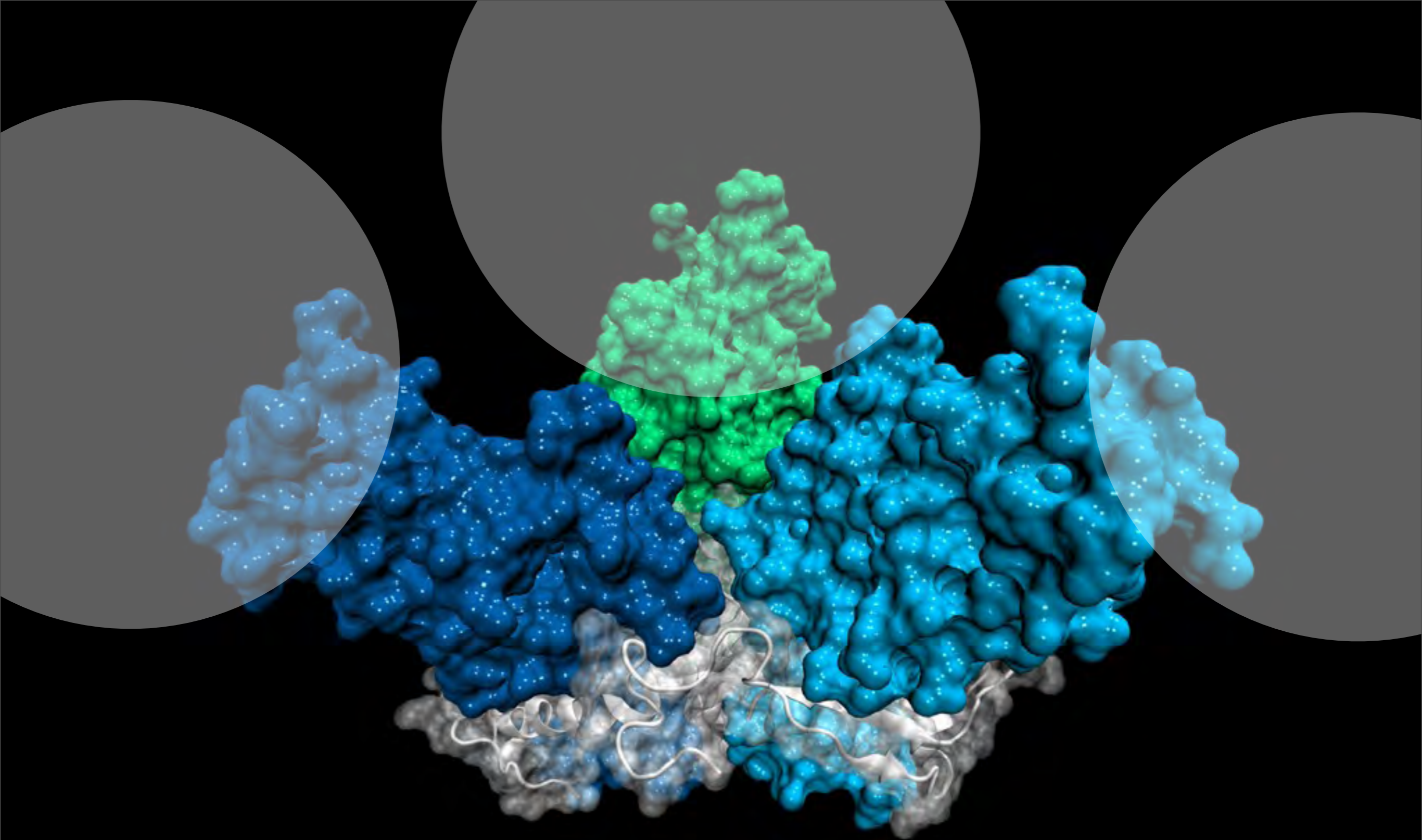


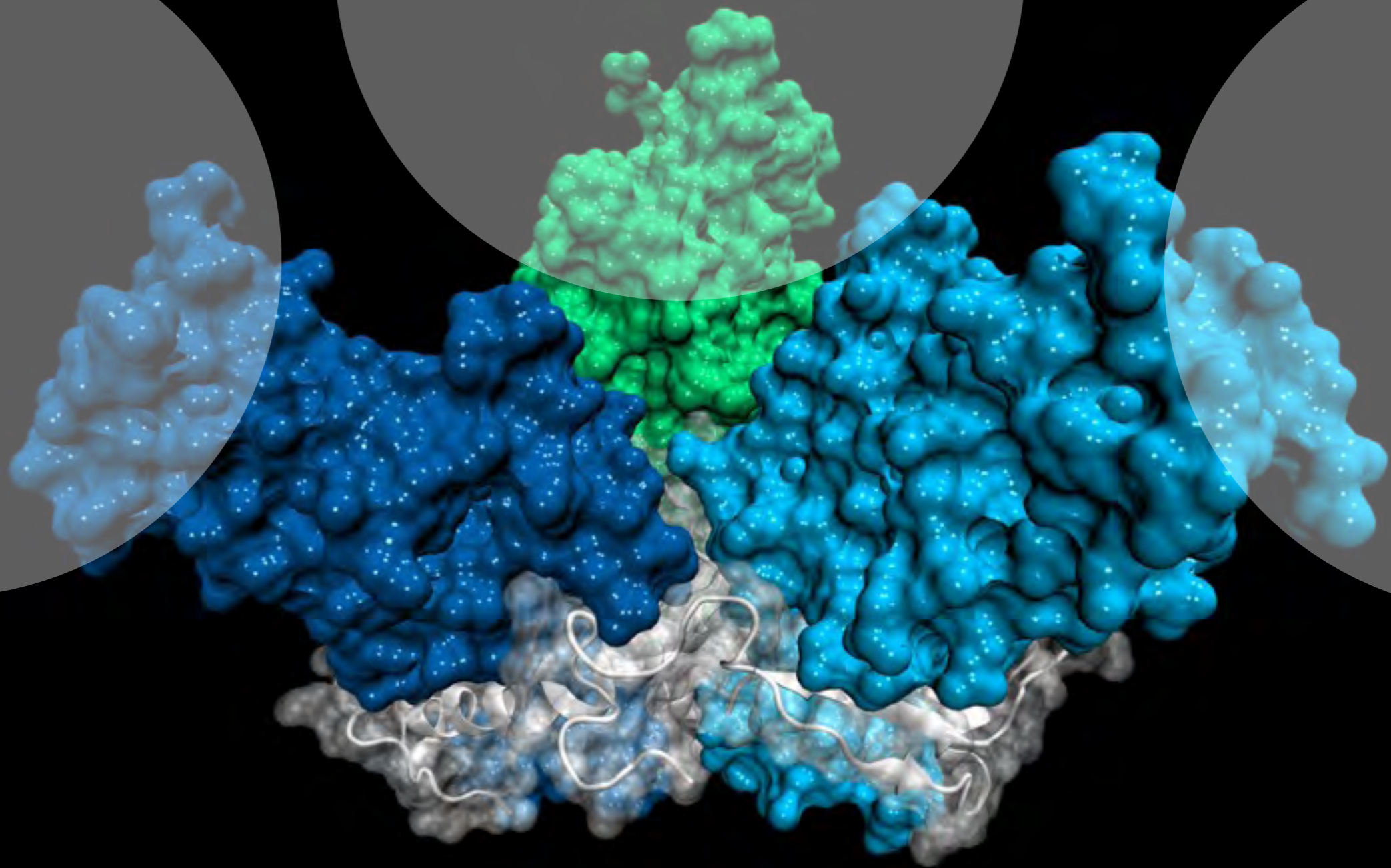
drives virus into cell

Ebola virus GP

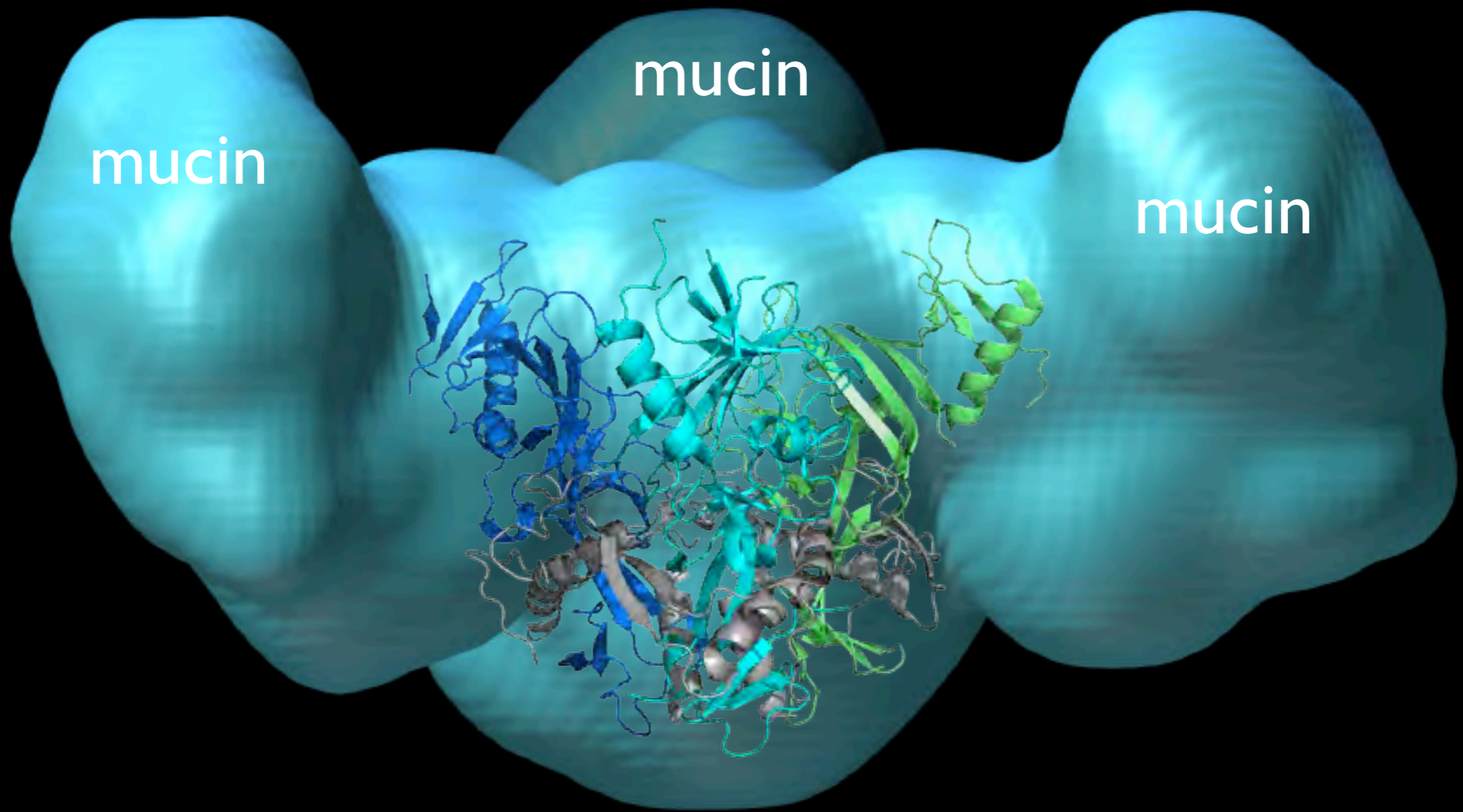


Sugar-rich mucin domains attached at top





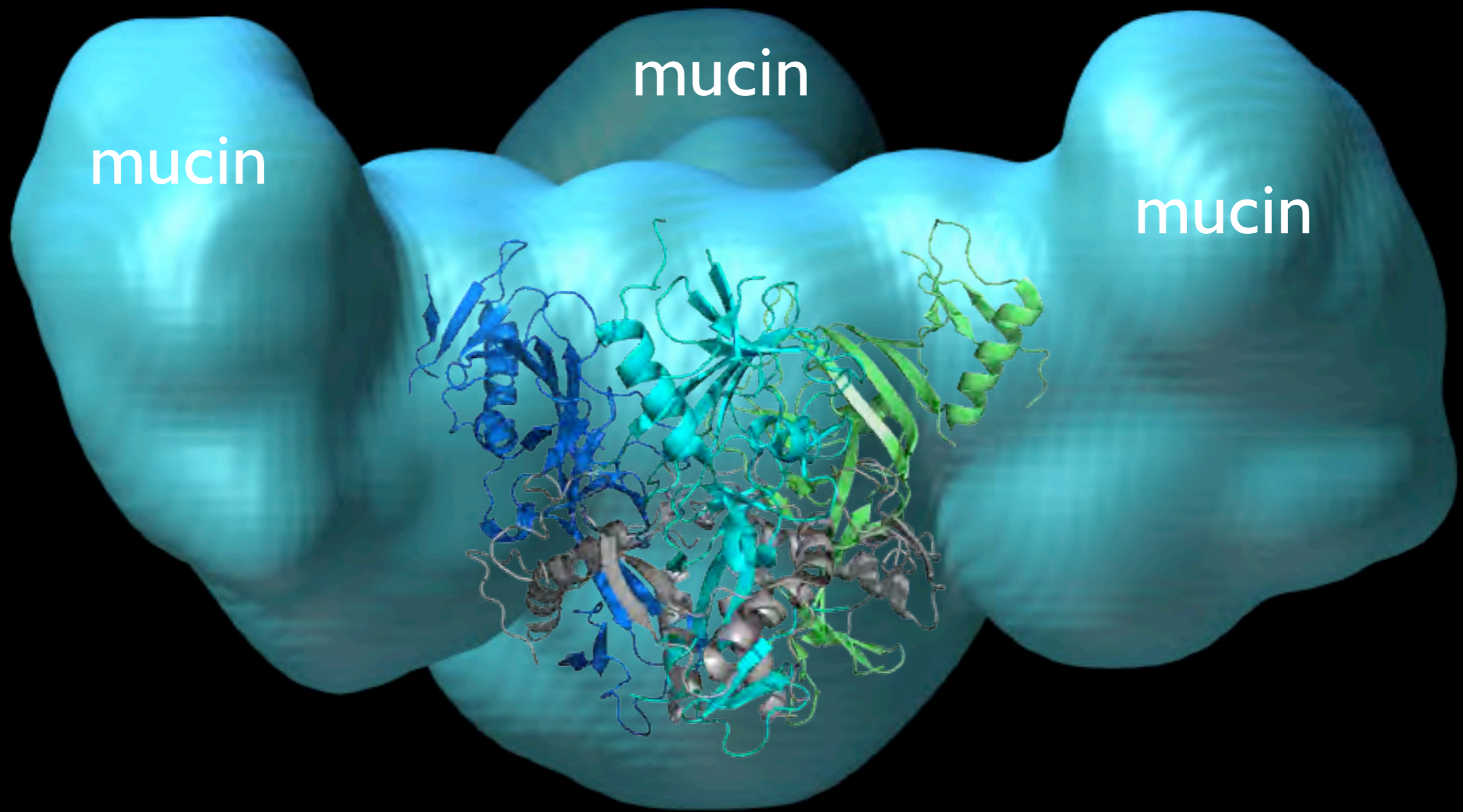
What does the complete Ebola molecule look like?



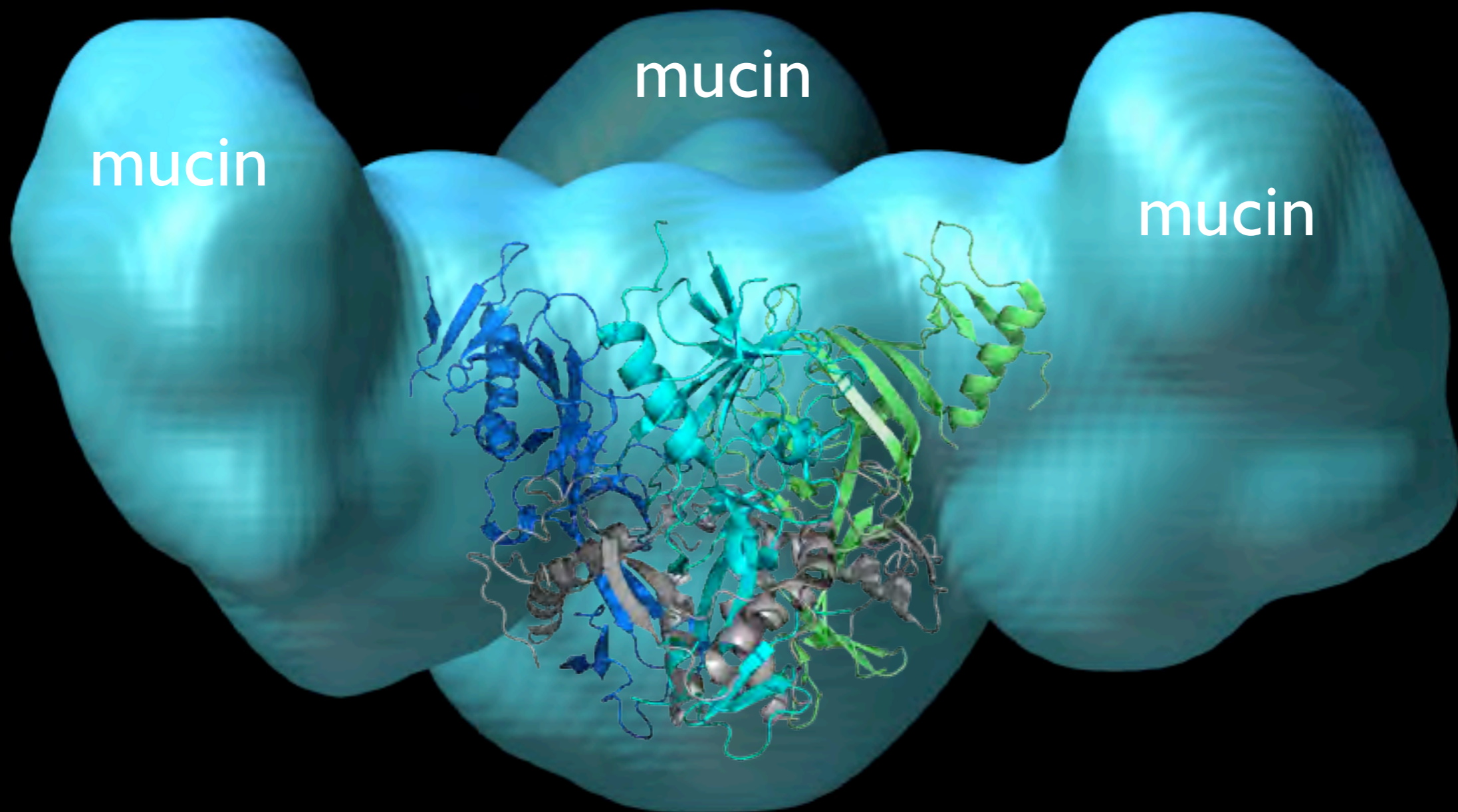
mucin

mucin

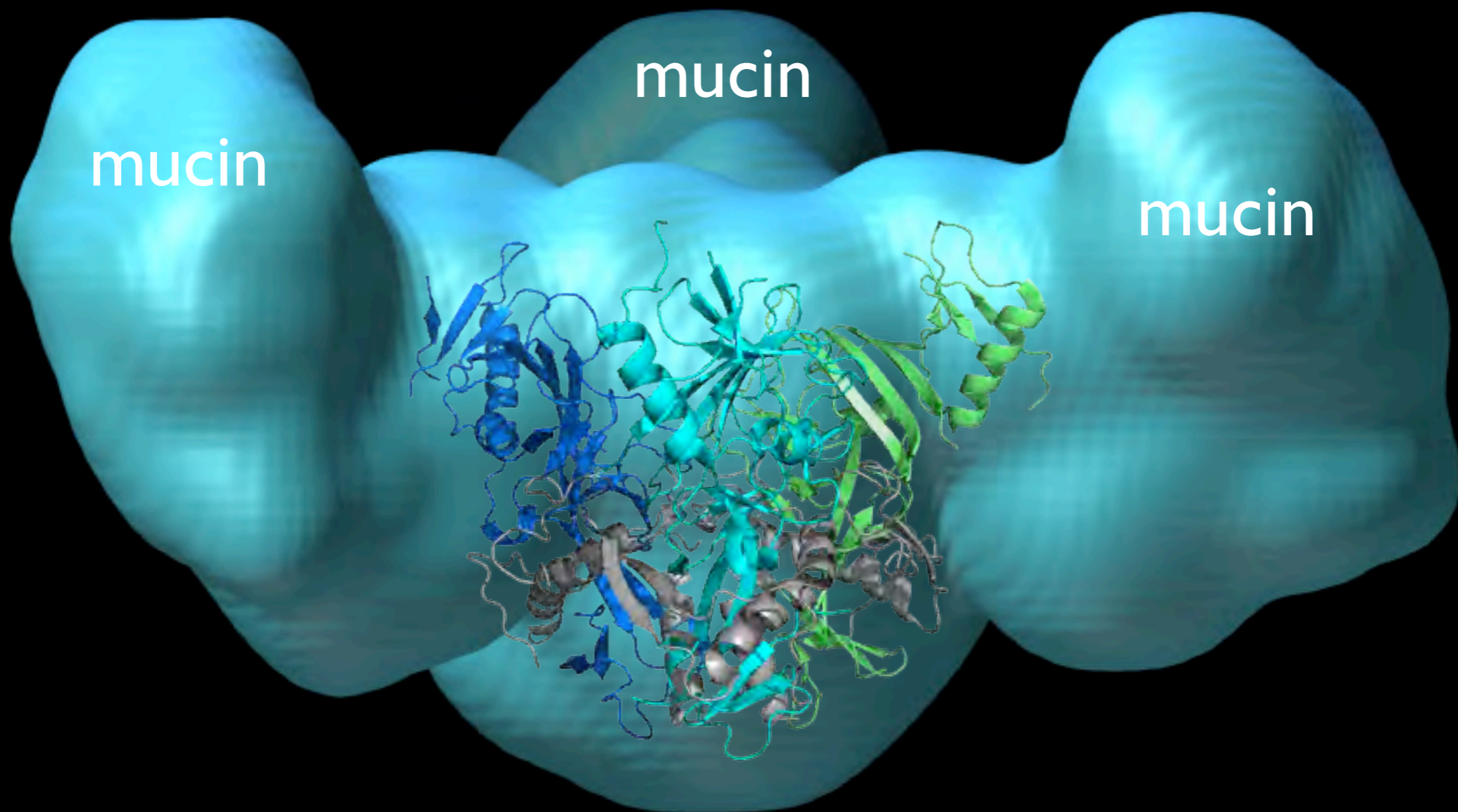
mucin



Mucin domains triple its size

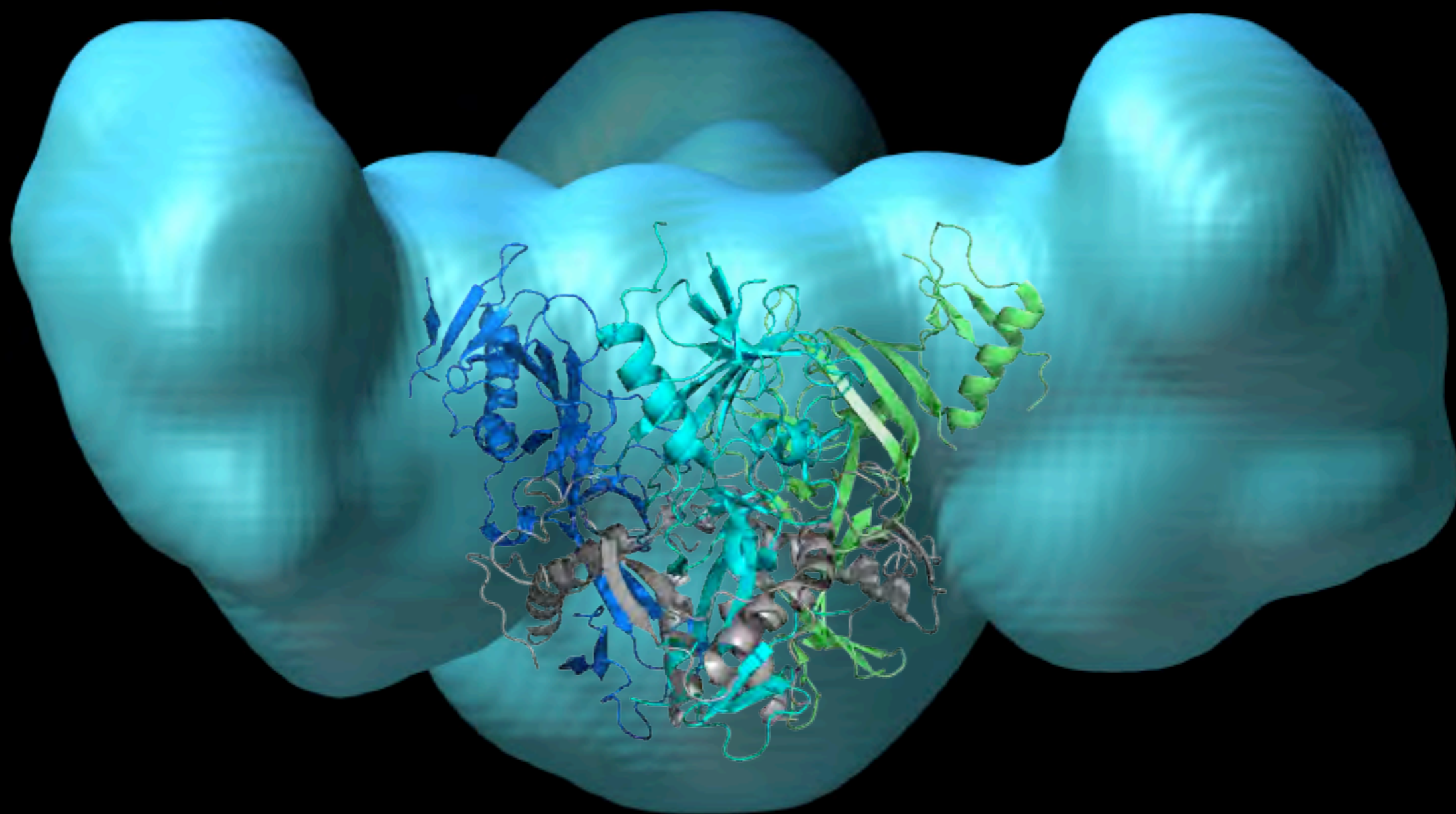


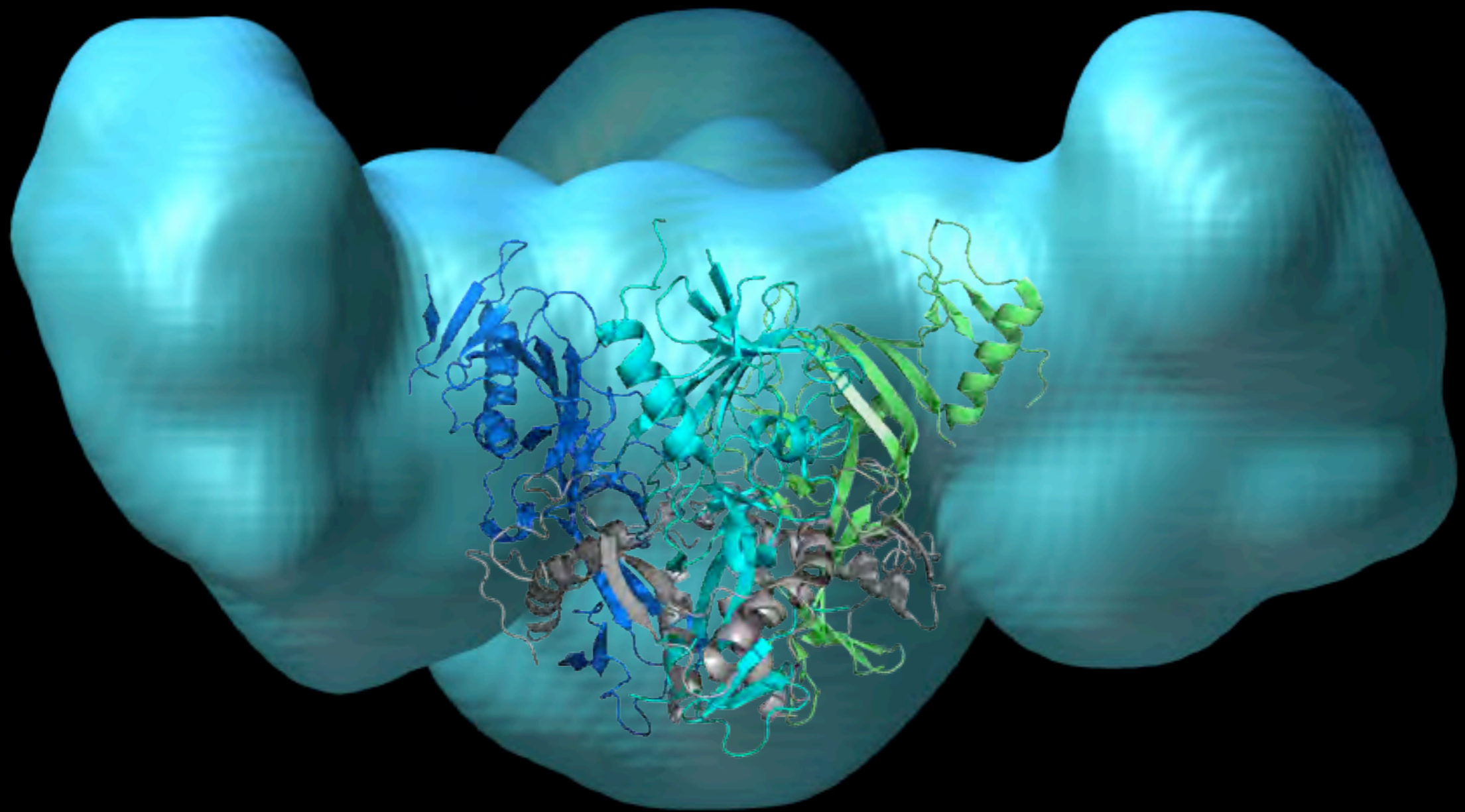
**Mucin domains triple its size
(a wolf in sheep's clothing)**



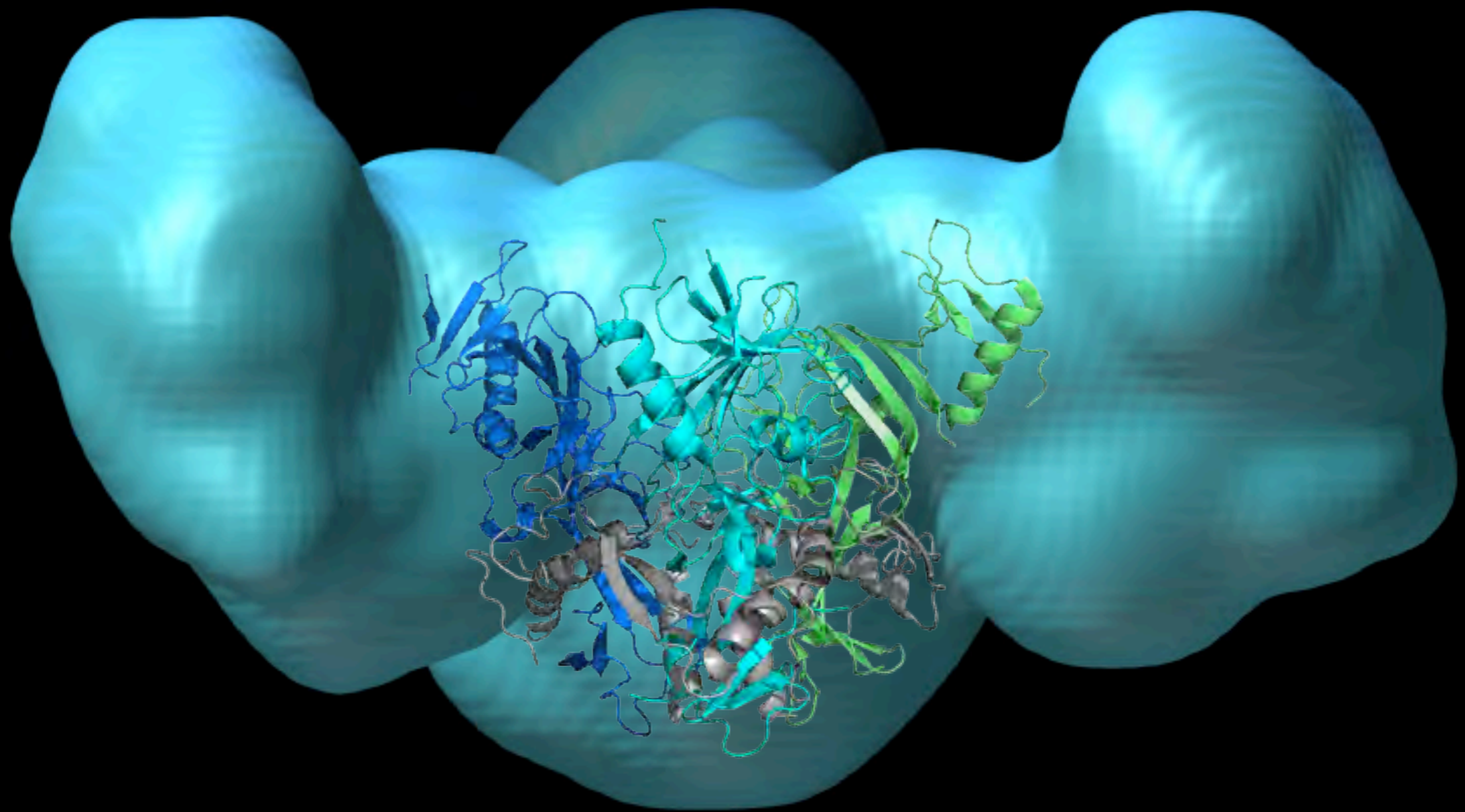
Mucin domains triple its size
(a wolf in sheep's clothing)

also tricky in another way...



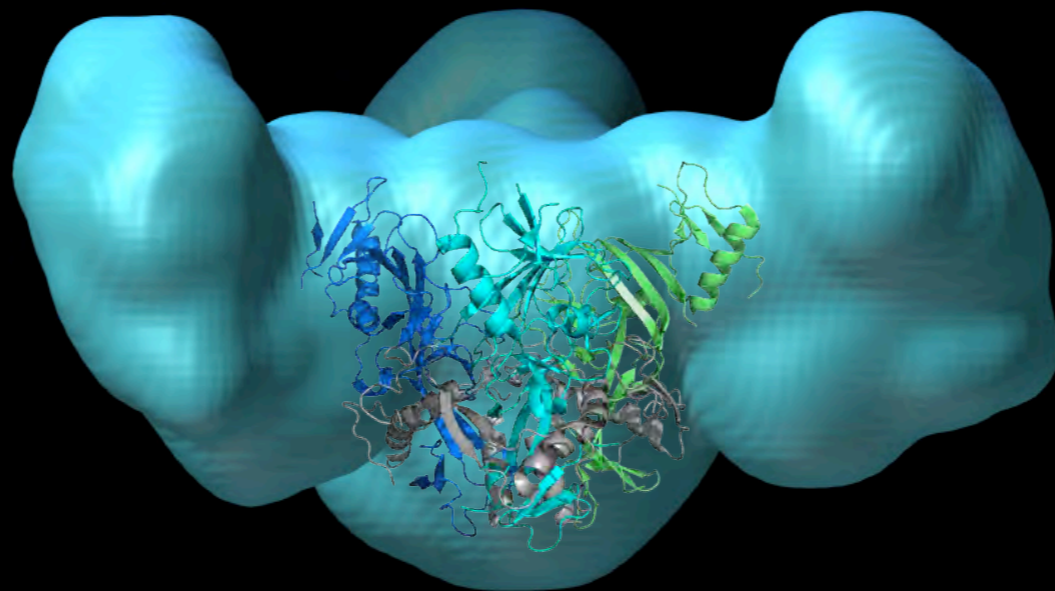


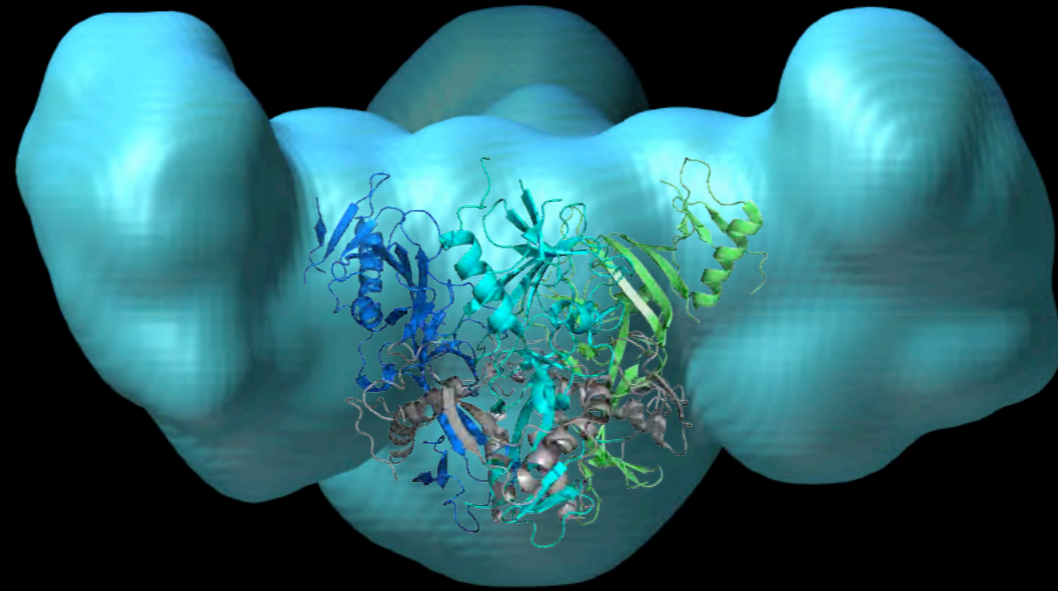
Reshapes itself as it enters the cell.



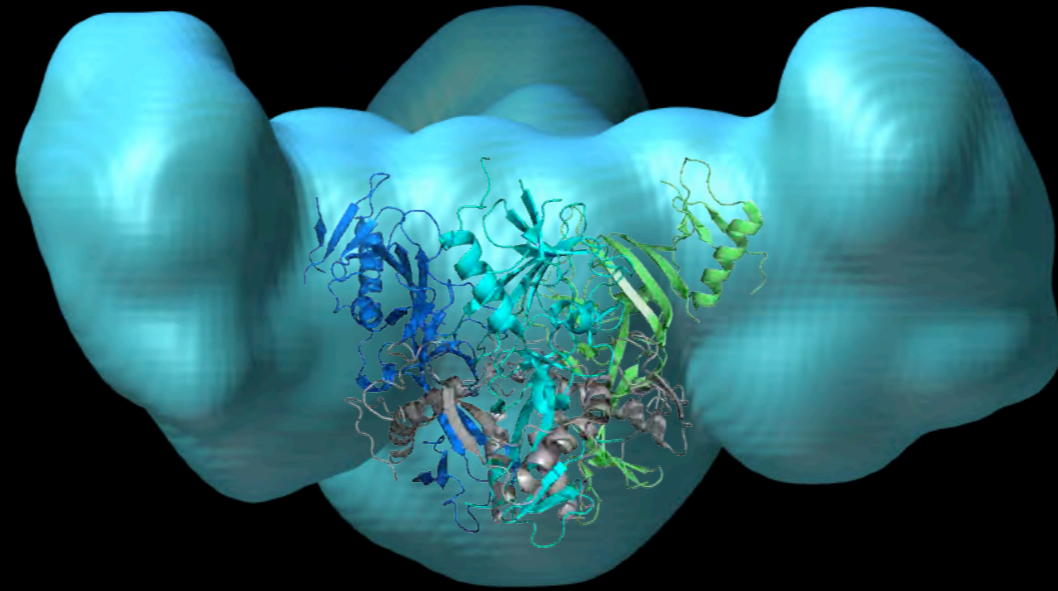
Reshapes itself as it enters the cell.

This is what happens:

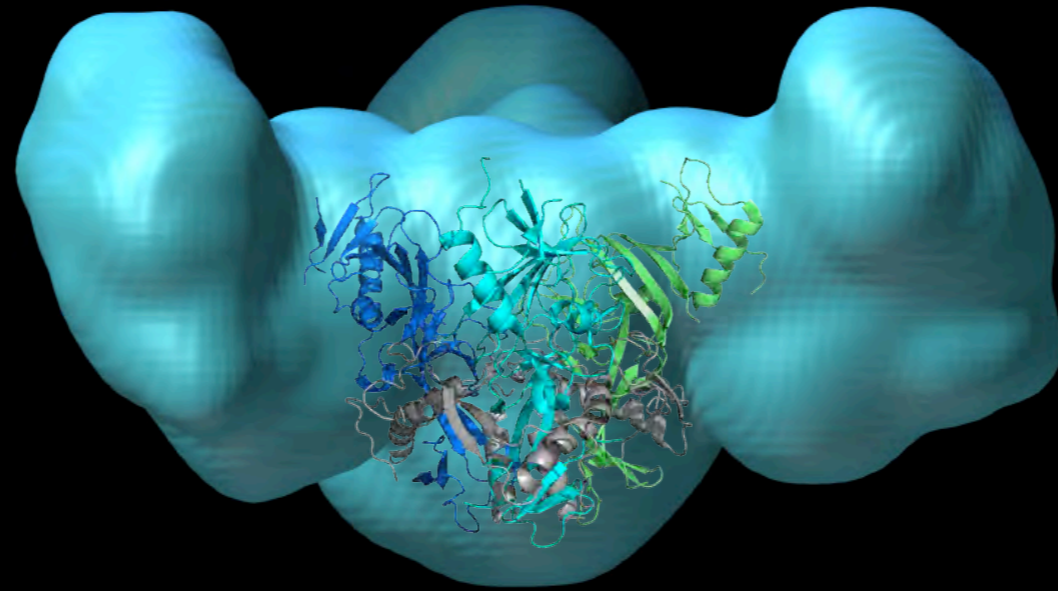




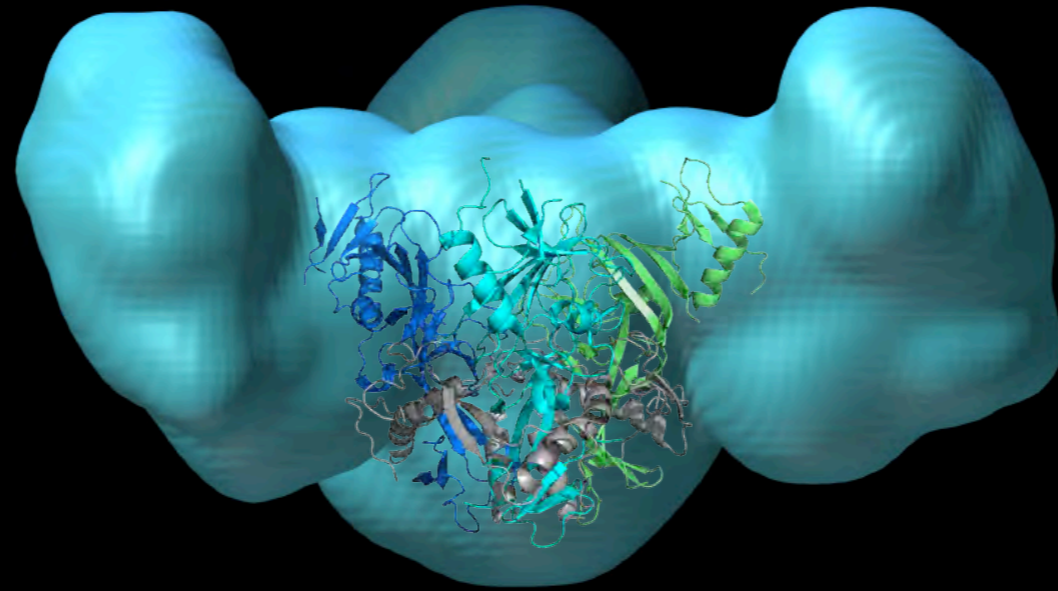
Cell swallows virus by macropinocytosis...



Cell swallows virus by macropinocytosis...
Once virus is in the endosome,

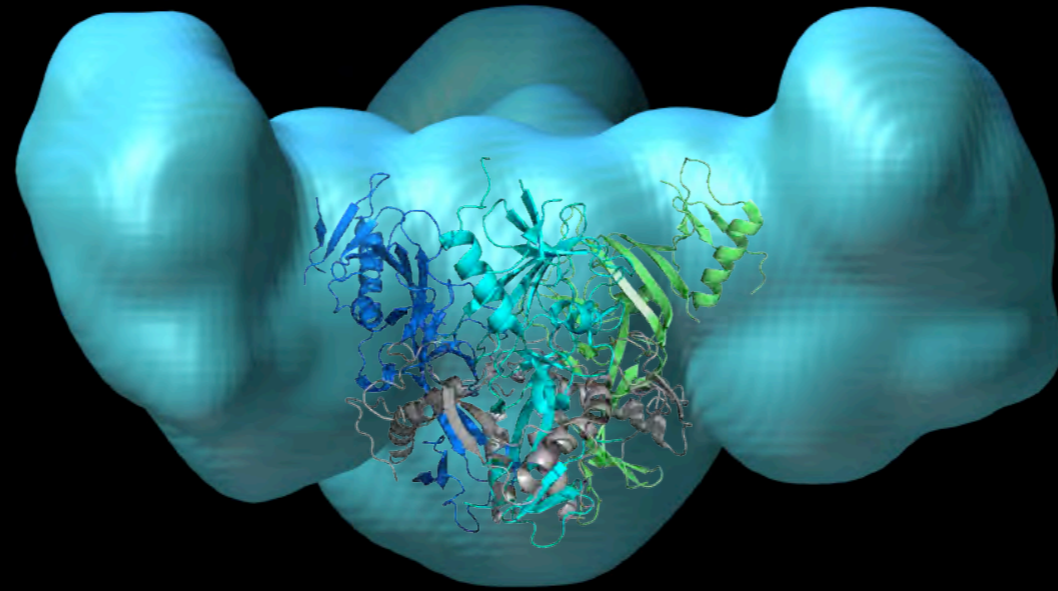


Cell swallows virus by macropinocytosis...
Once virus is in the endosome,
human enzymes cleave cloak from GP.

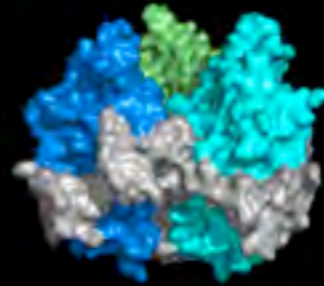


before cleavage

Cell swallows virus by macropinocytosis...
Once virus is in the endosome,
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Cell swallows virus by macropinocytosis...
Once virus is in the endosome,
human enzymes cleave cloak from GP.



after cleavage

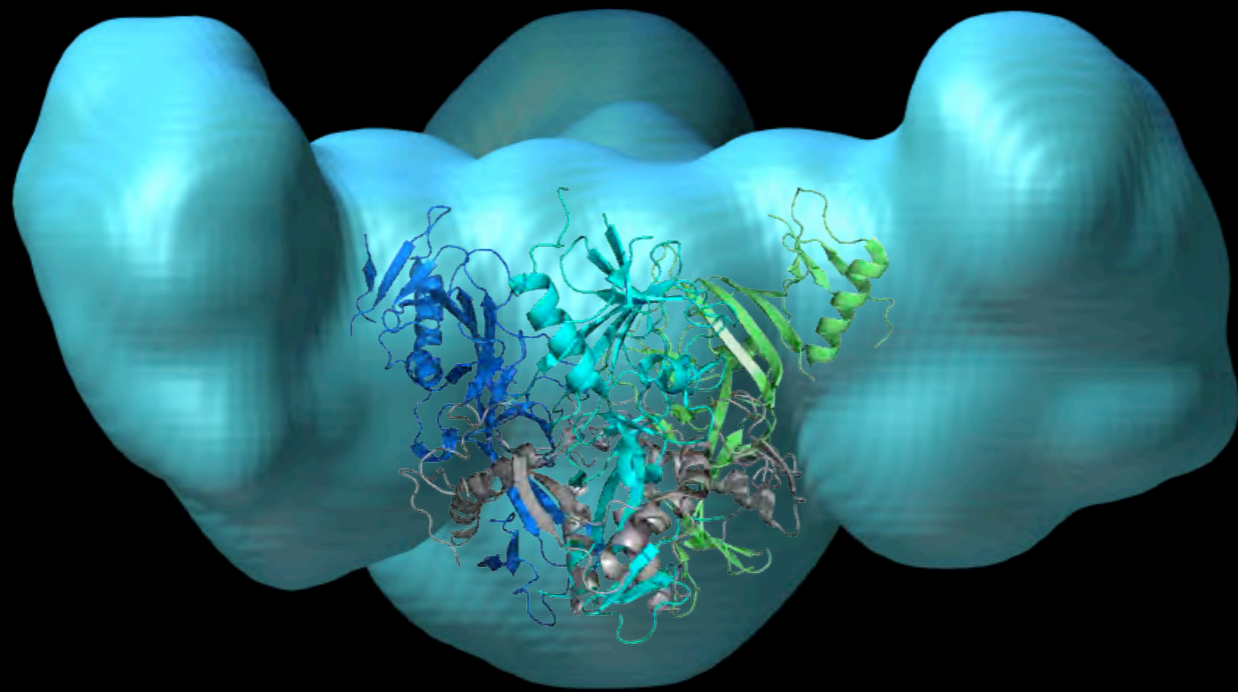
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after cleavage

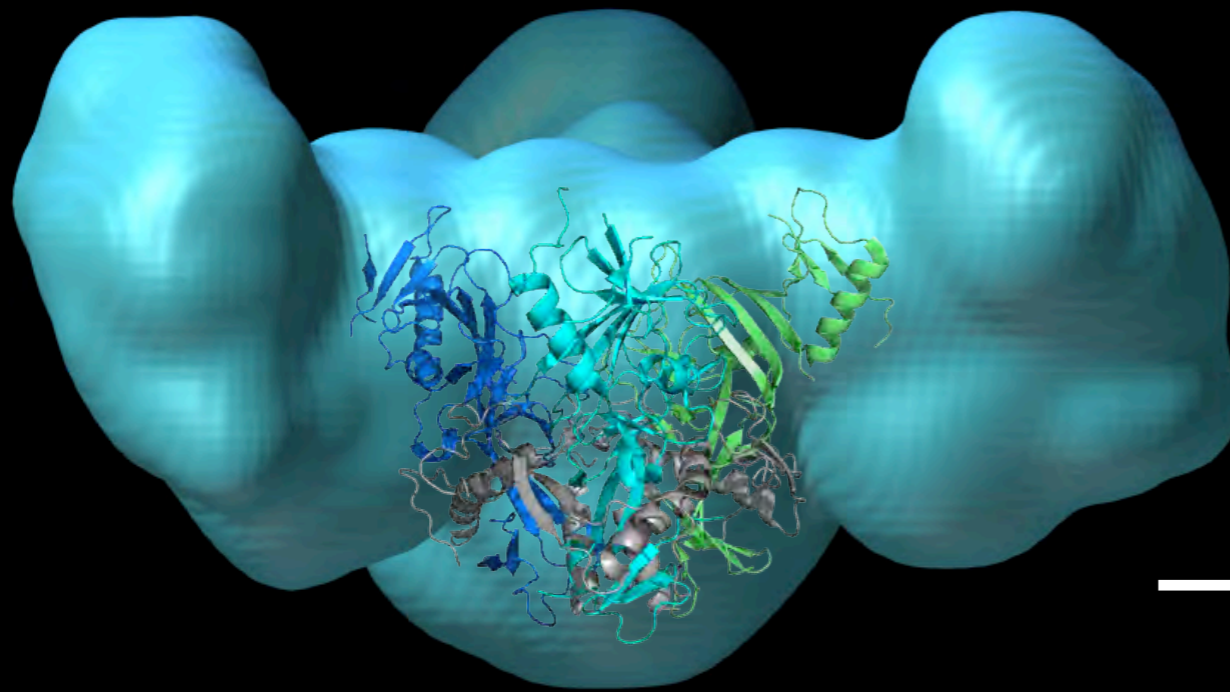
Cell swallows virus by macropinocytosis...
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Two forms of Ebola surface molecule.

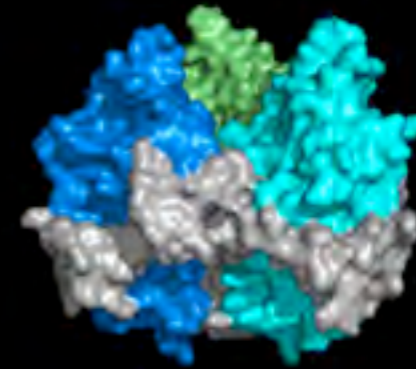


subject to
immune surveillance

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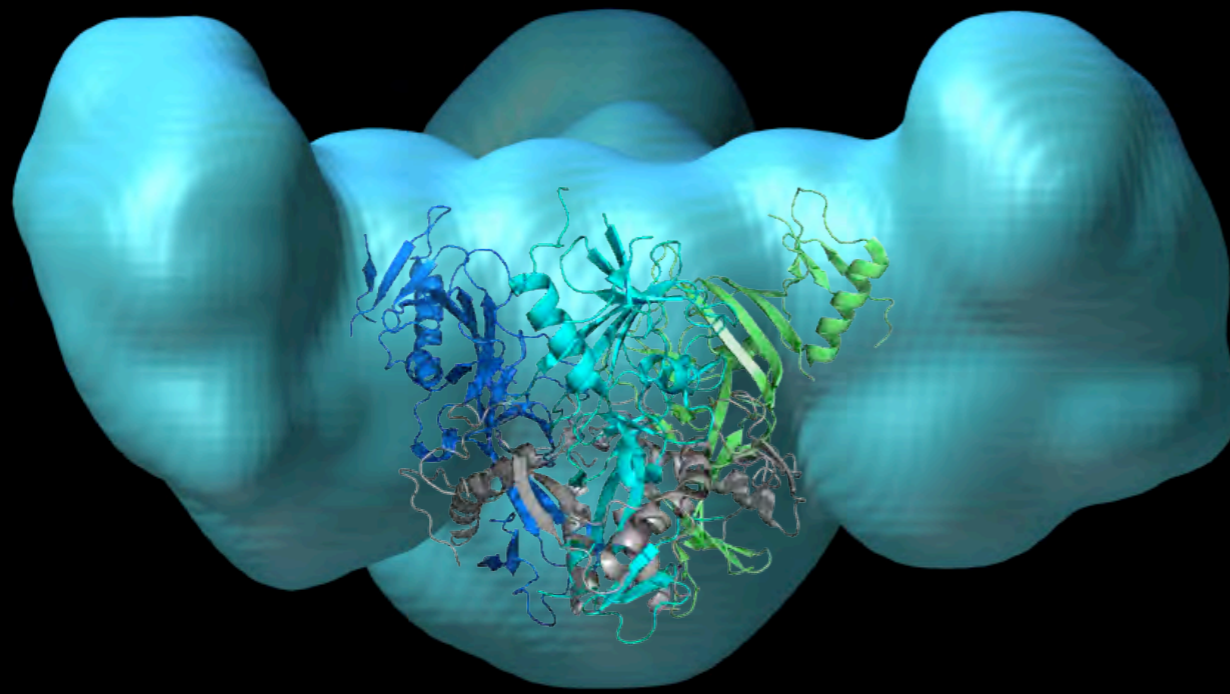


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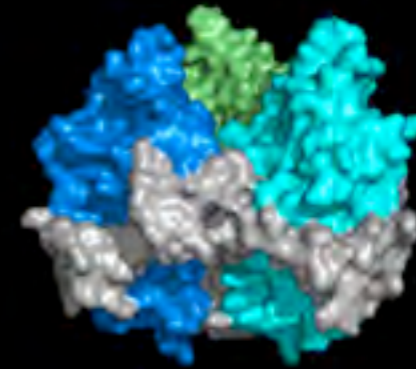


competent for
receptor binding

Two forms of Ebola surface molecule.

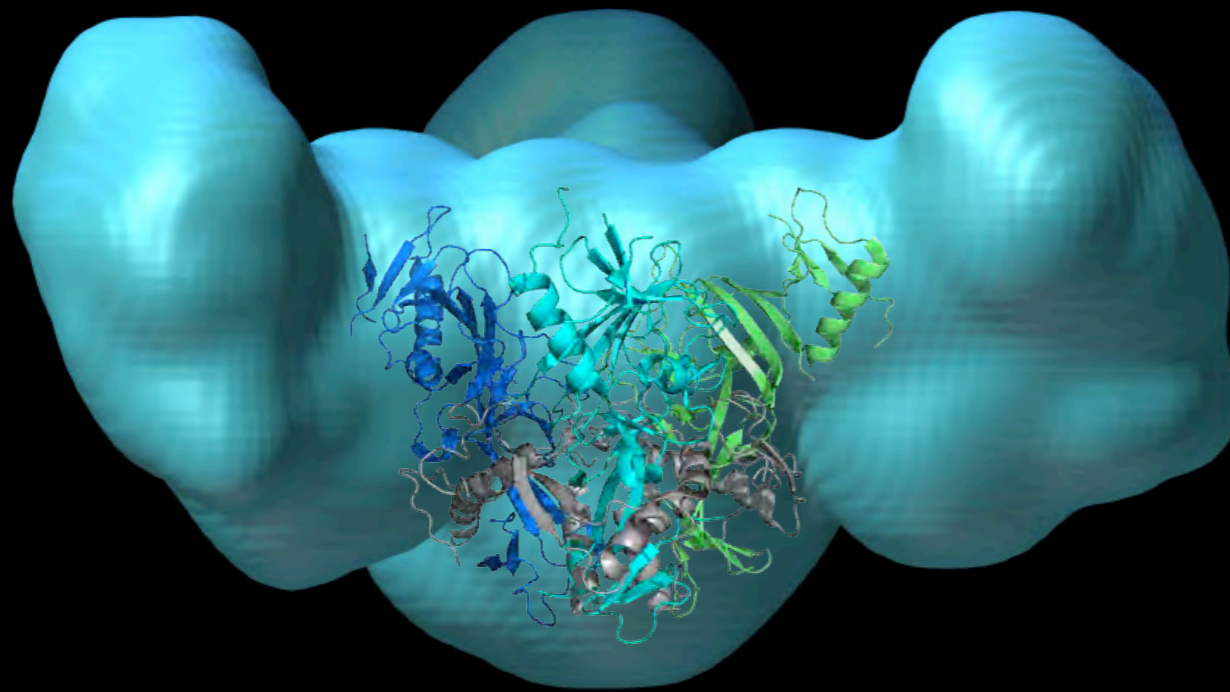


hiding

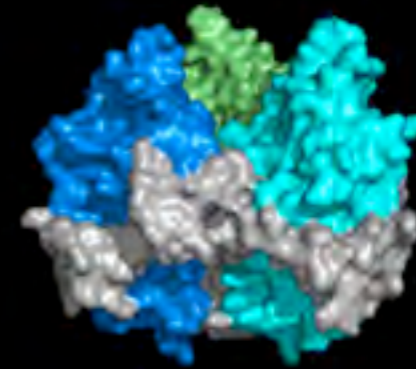


infecting

What does this mean for the immune response?



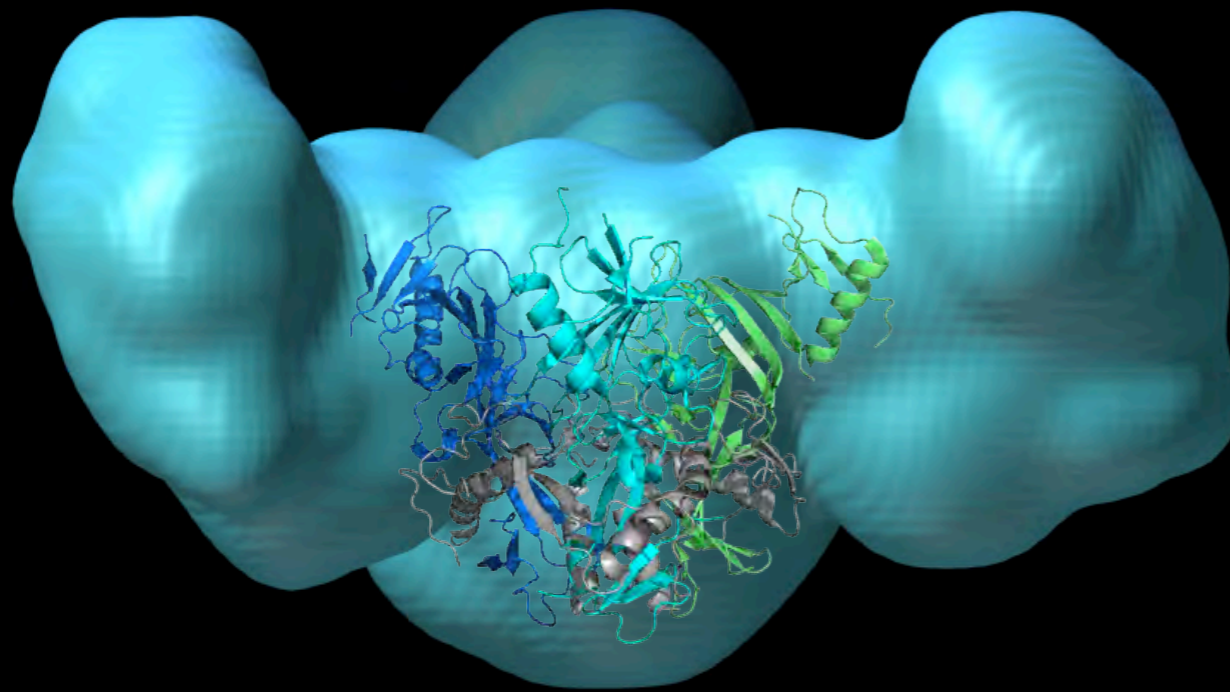
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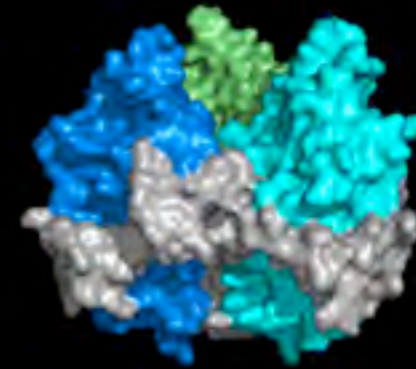
infecting

What does this mean for the immune response?

Many target sites are lost.



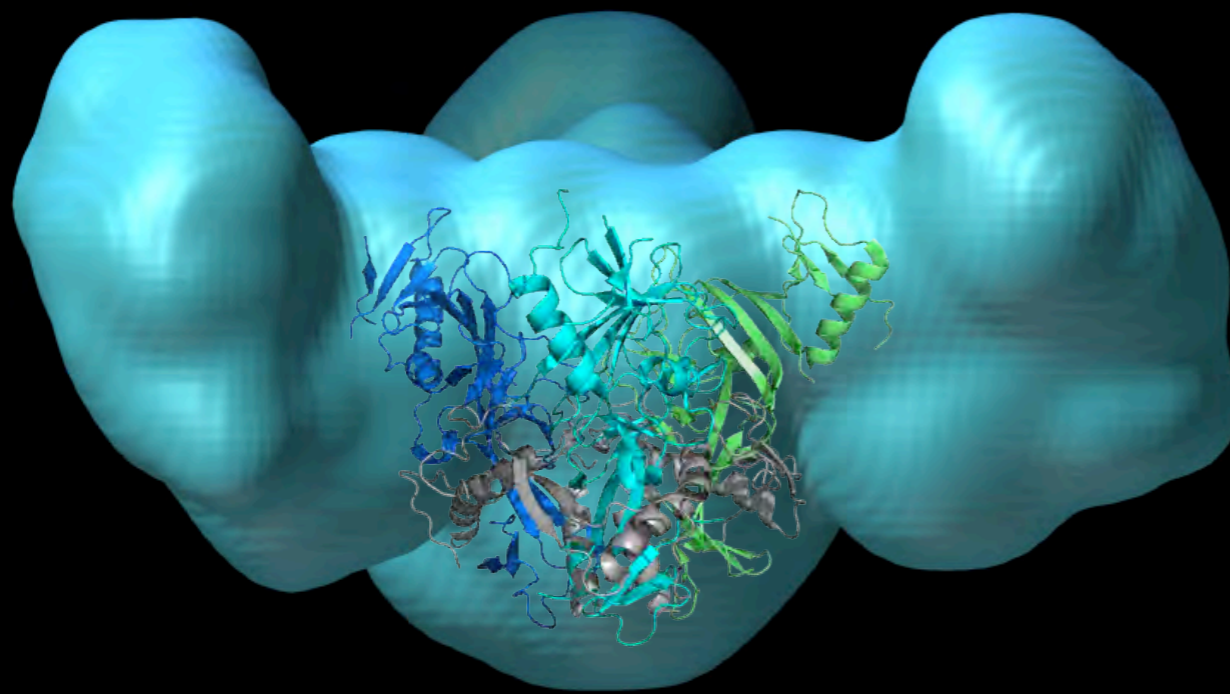
hiding



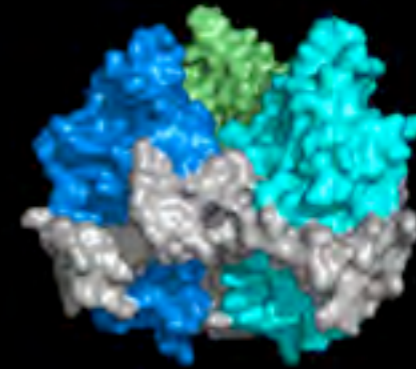
infecting

What does this mean for the immune response?

Many target sites are lost.
Other sites are hidden.



hiding



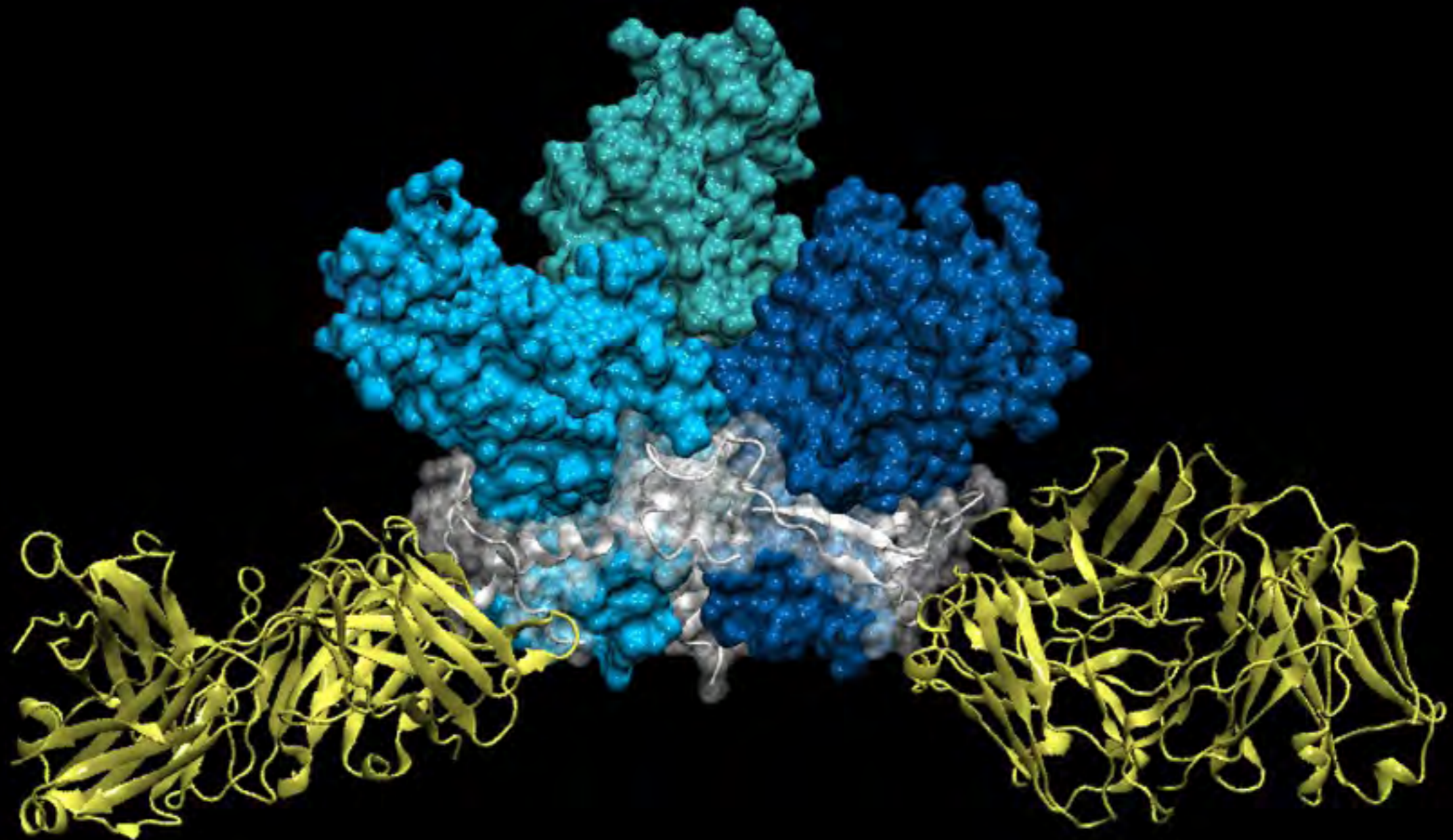
infecting

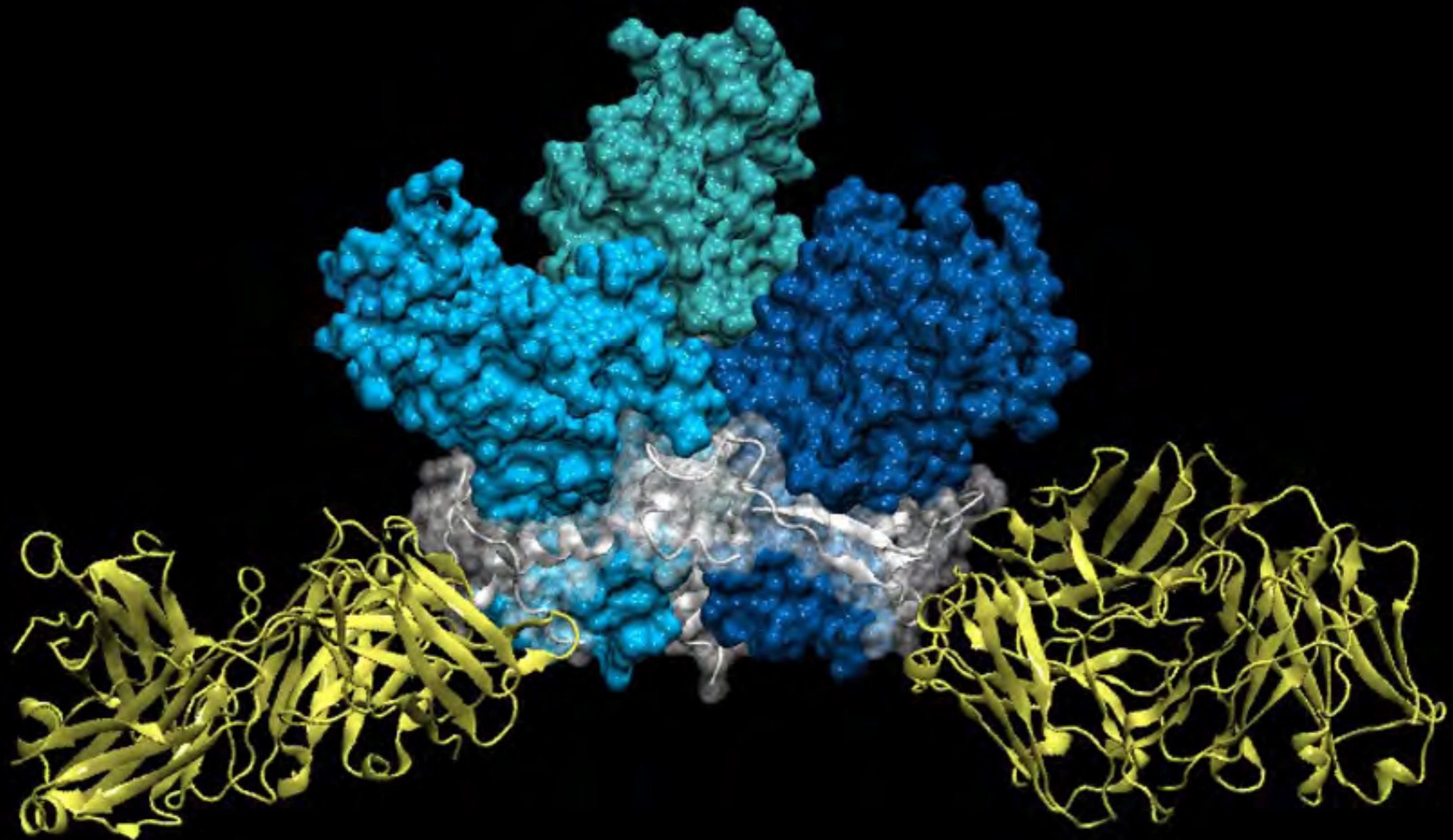
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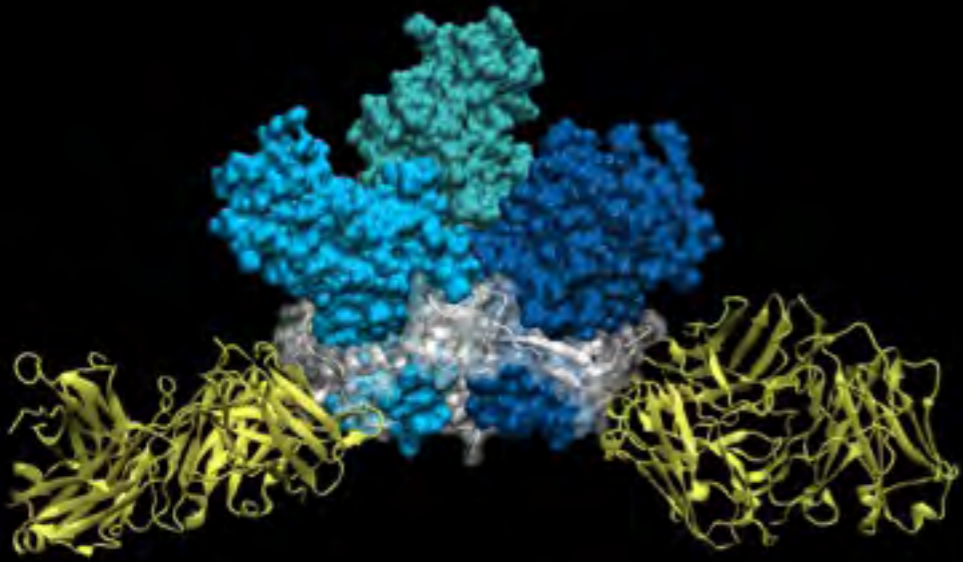
Other sites are hidden.

What works? What “neutralizes” the virus?

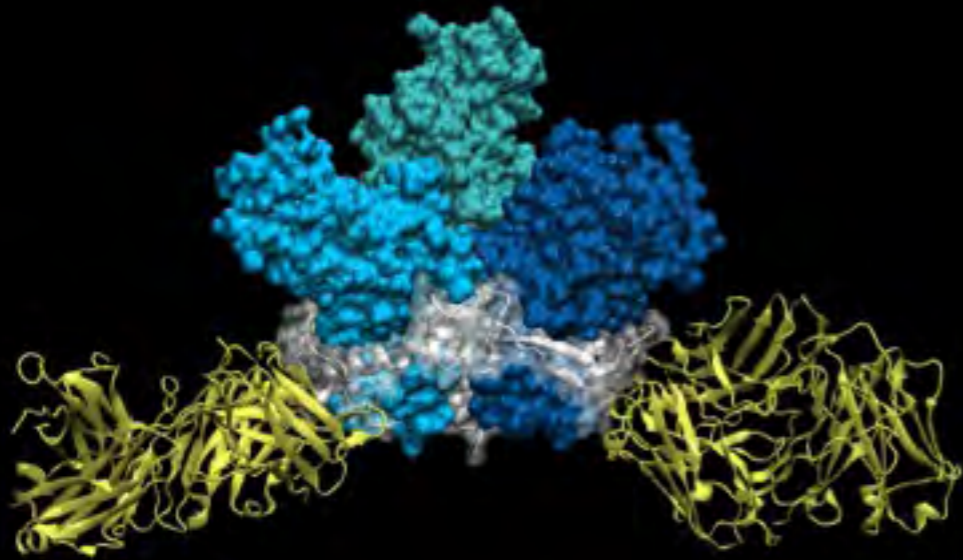




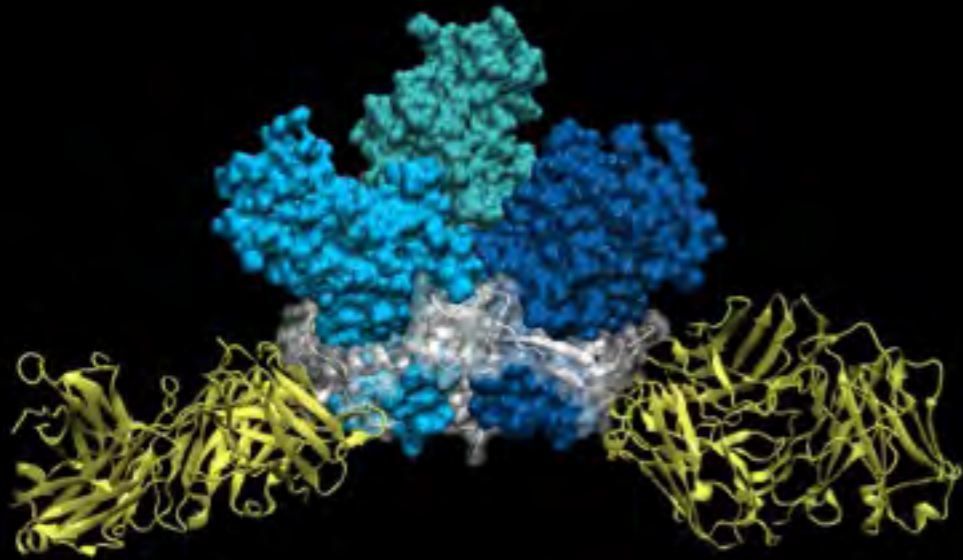
Human antibody, from 1995 survivor
called KZ52



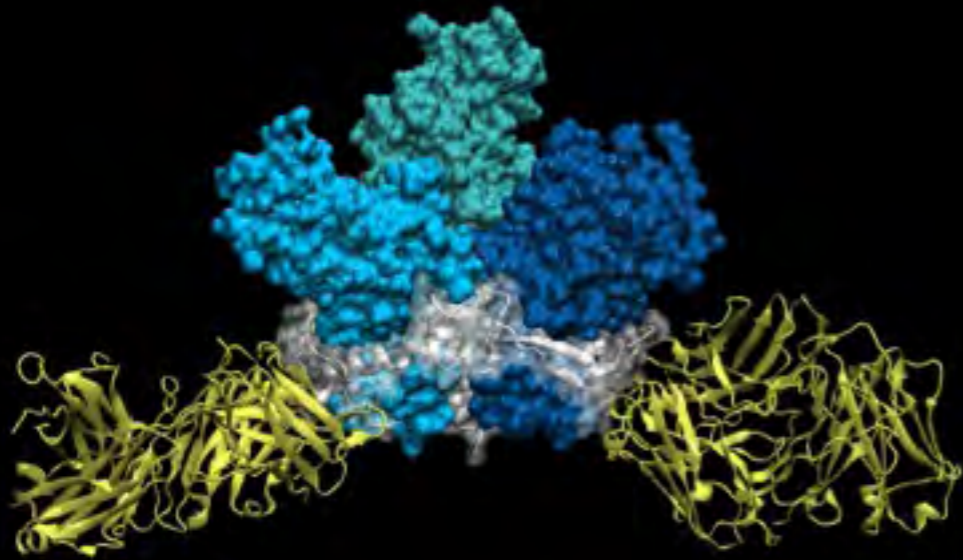
Antibody KZ52:



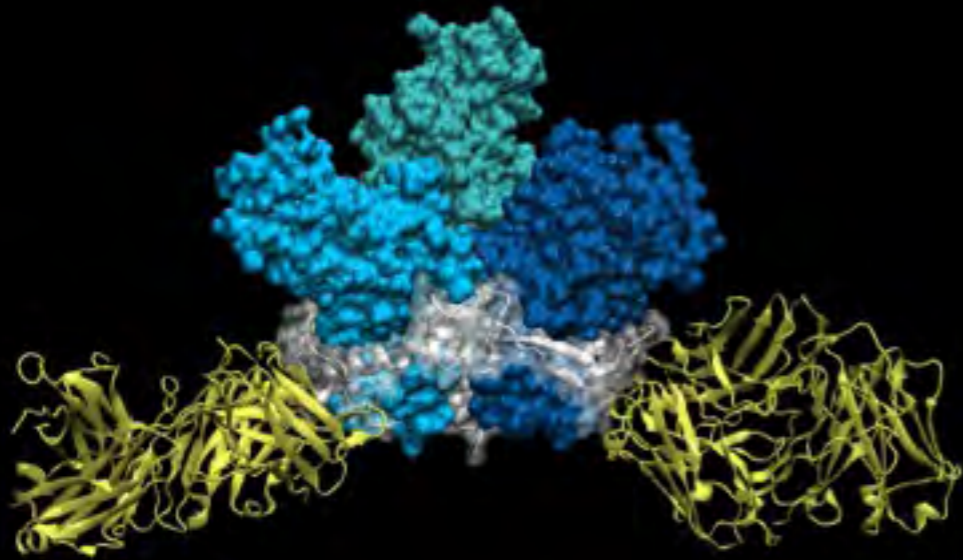
Antibody KZ52: Works in test tubes.



**Antibody KZ52:
Works in test tubes.
Works in mice.**



Antibody KZ52:
Works in test tubes.
Works in mice.
Works in guinea pigs.



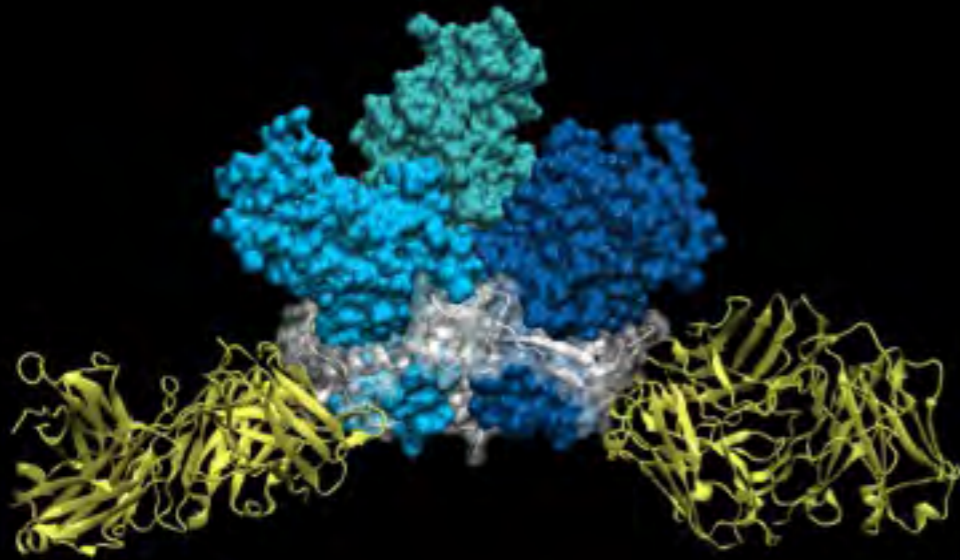
Antibody KZ52:

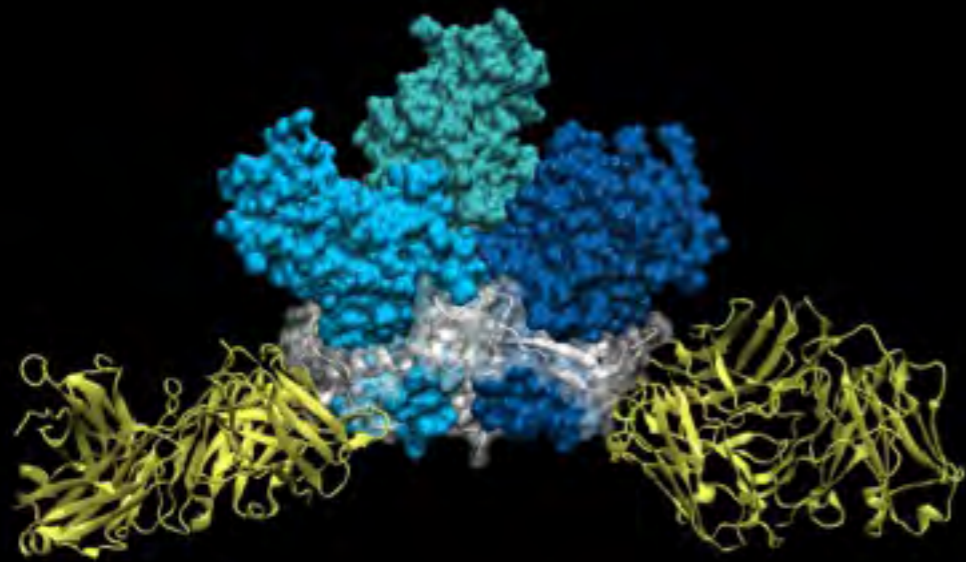
Works in test tubes.

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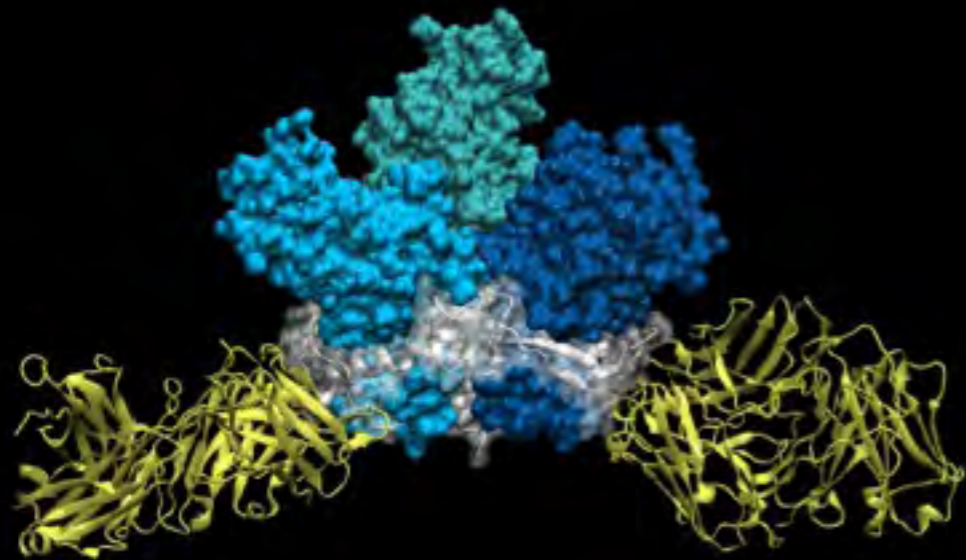
Does not save monkeys.





Antibody KZ52:
Works in test tubes.
Works in mice.
Works in guinea pigs.
Does not save monkeys.

KZ52 was the best antibody we had against Ebola.



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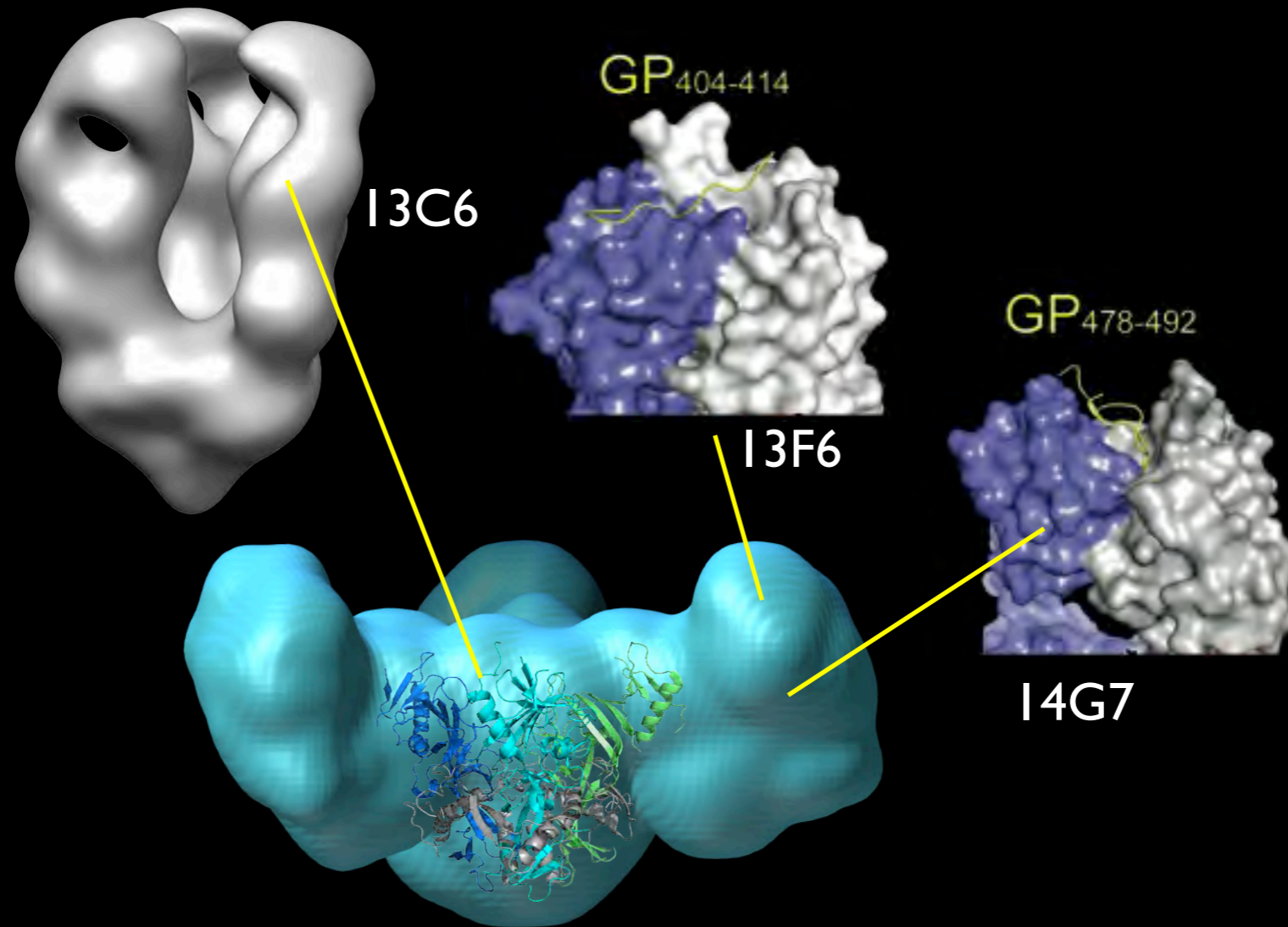
Does this mean antibodies will not work against Ebola?

No - Mixtures of antibodies cure infection!
even after severe disease has developed

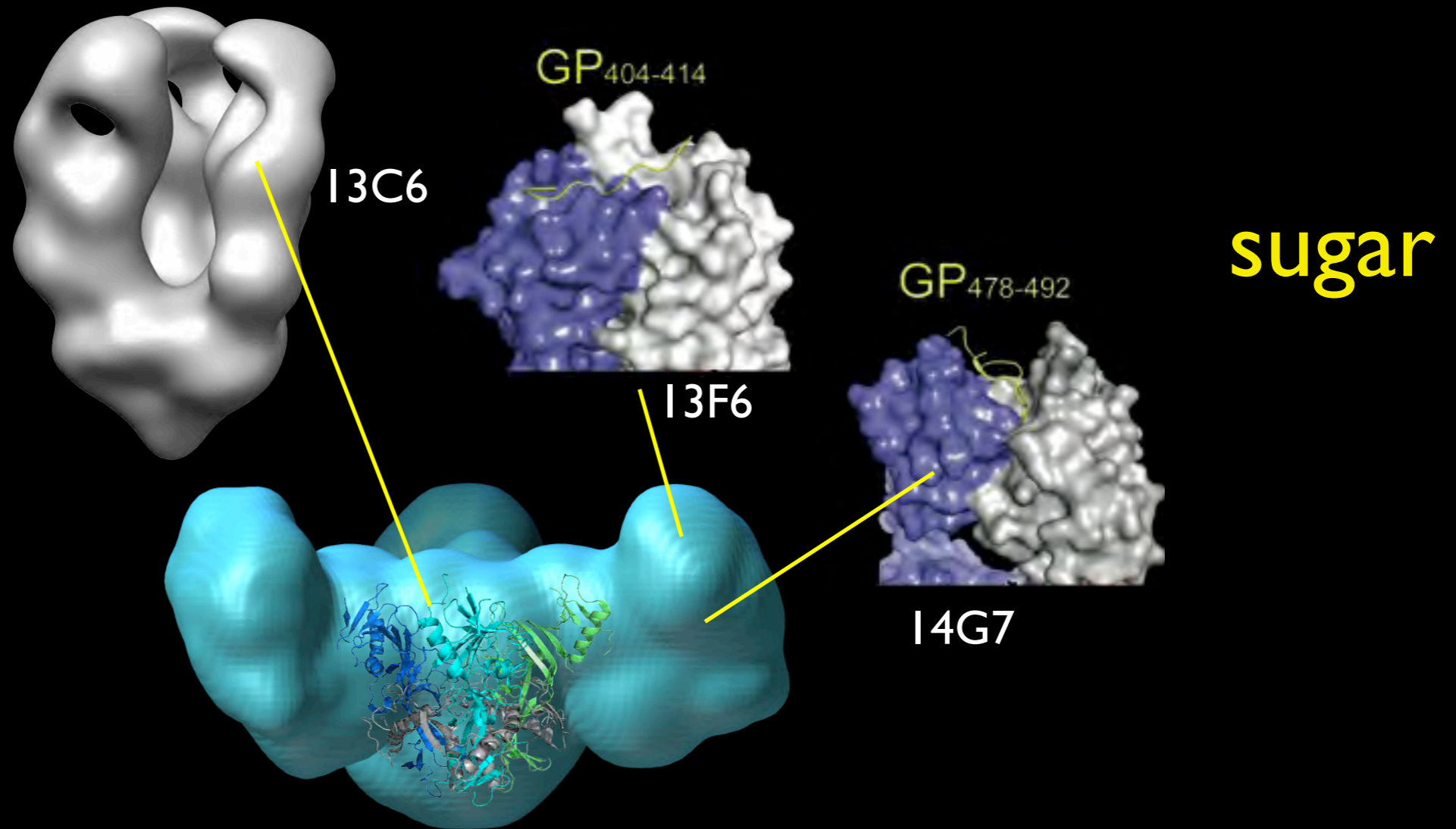
No - Mixtures of antibodies cure infection!
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What are these Ebola-curing antibodies?

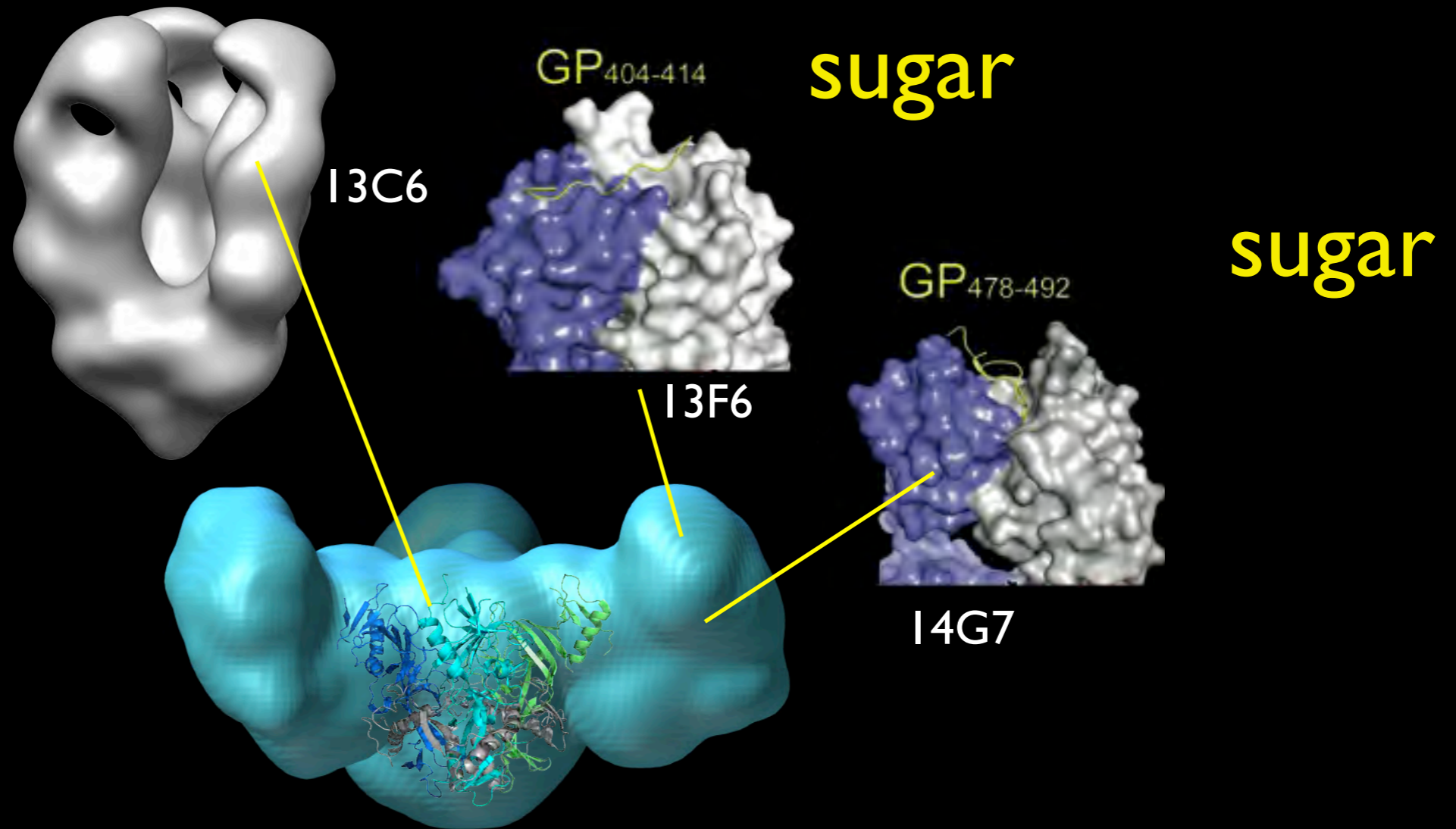
This is the US Army's mixture of three antibodies.



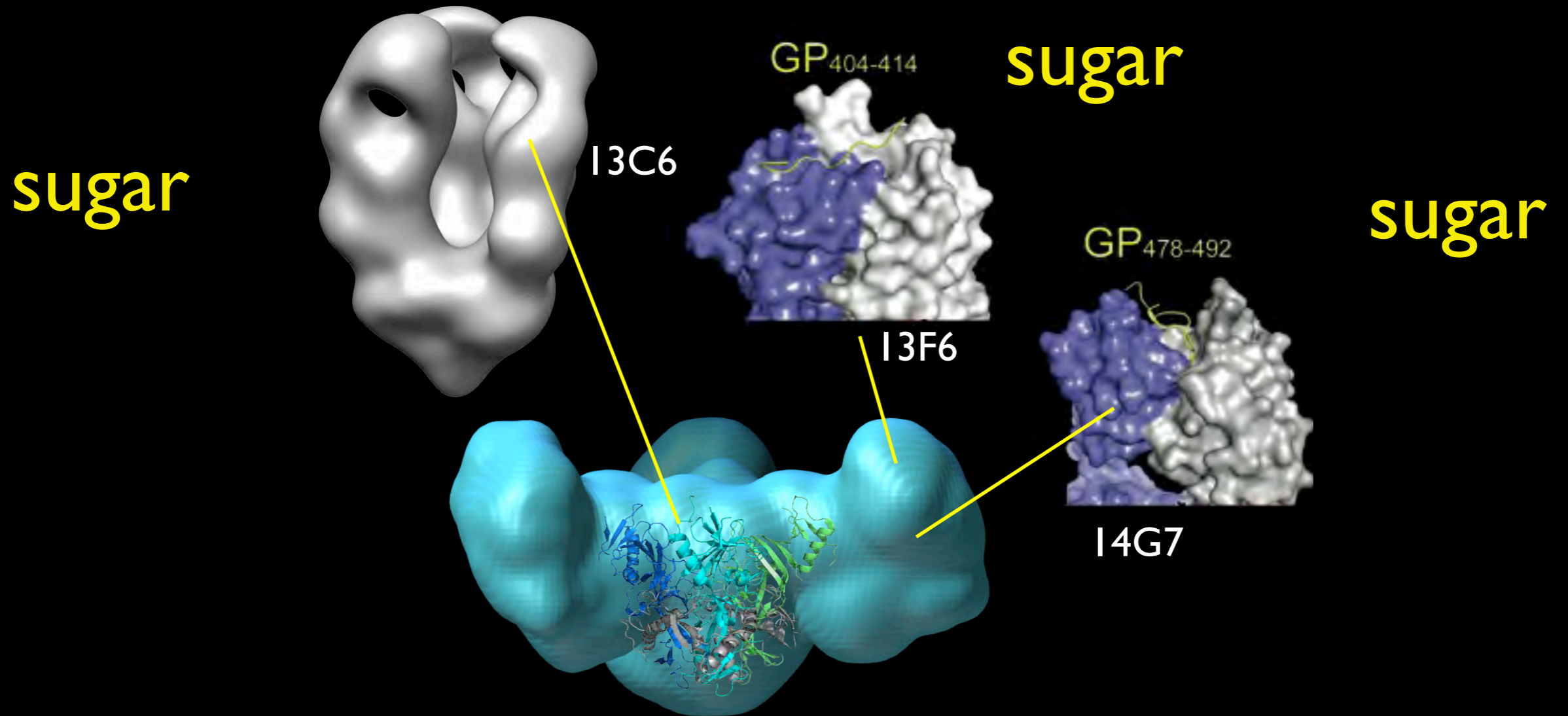
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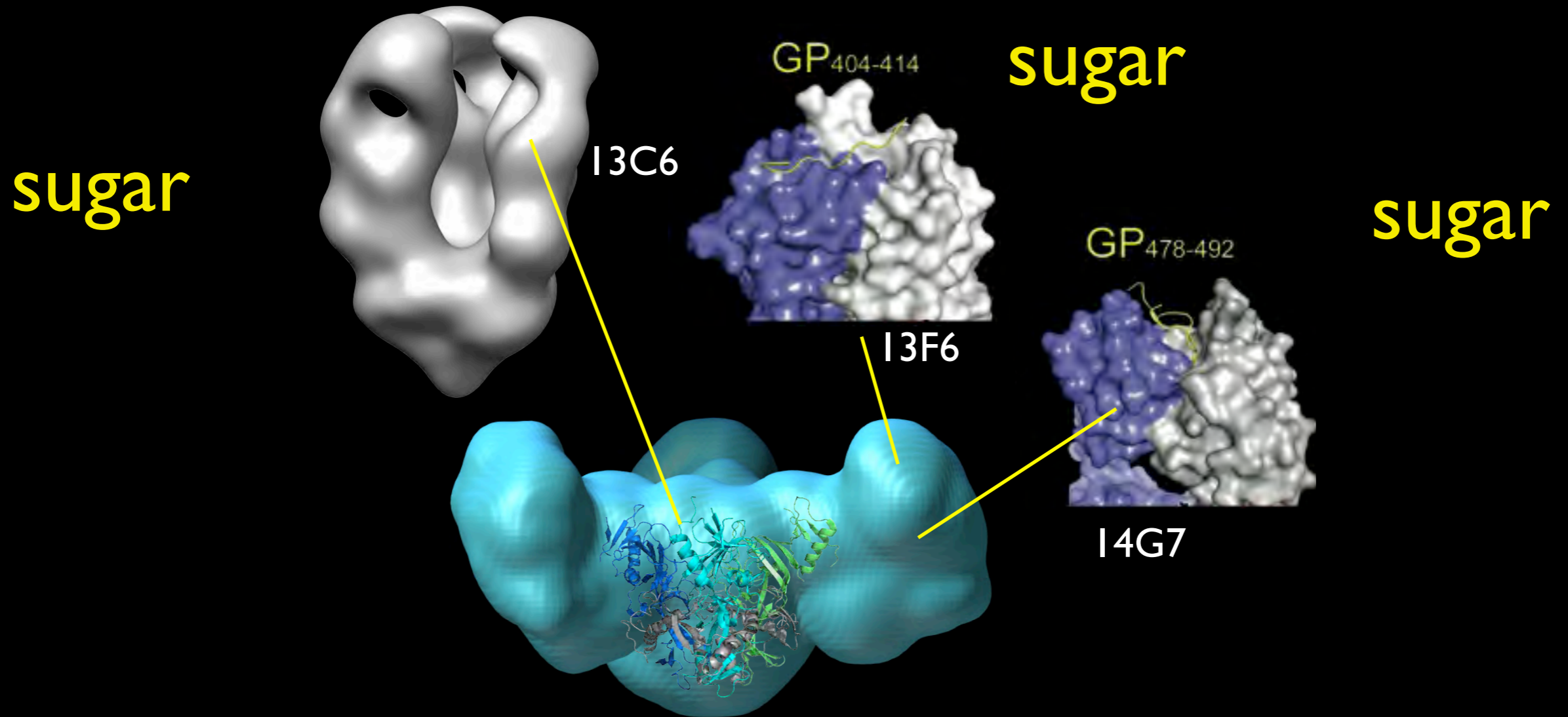
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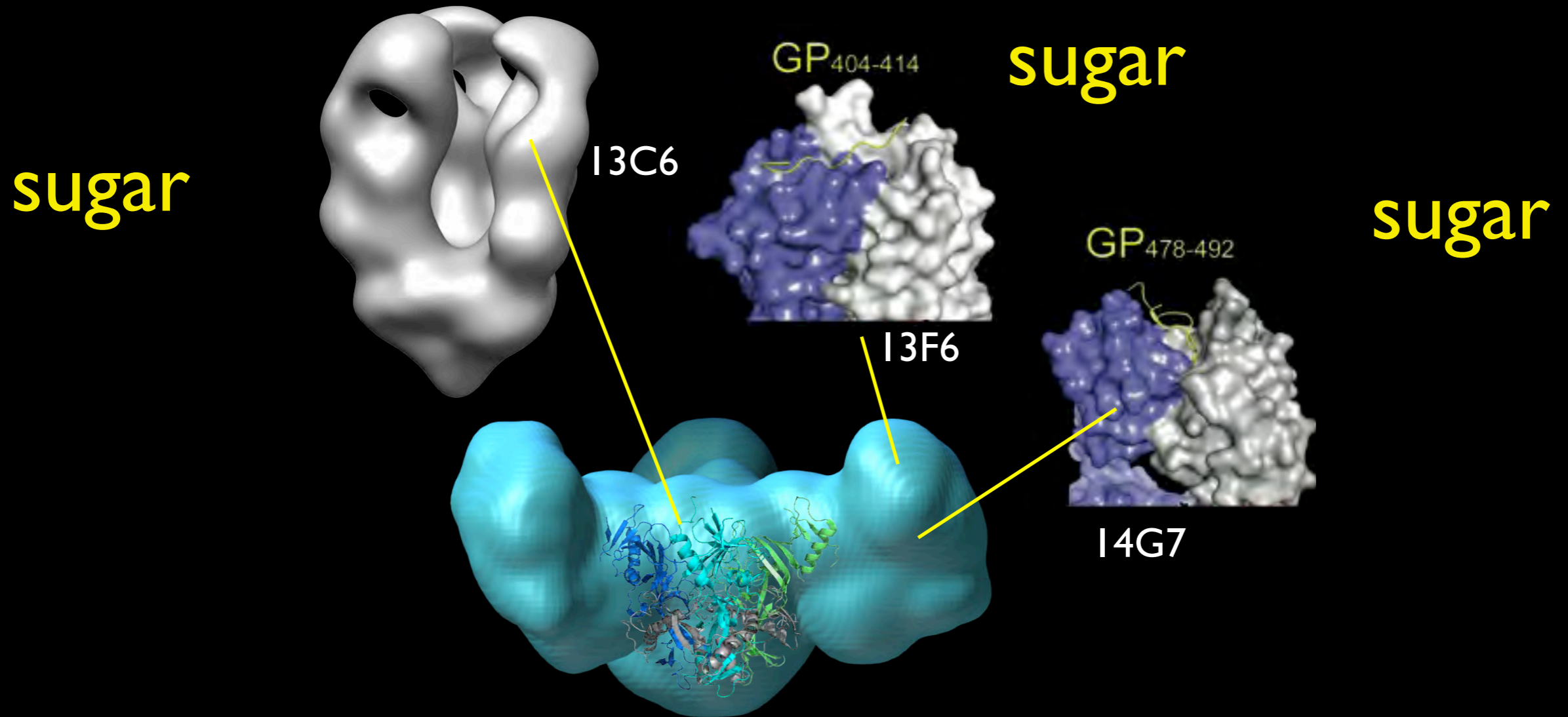


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These don't work in test tubes...

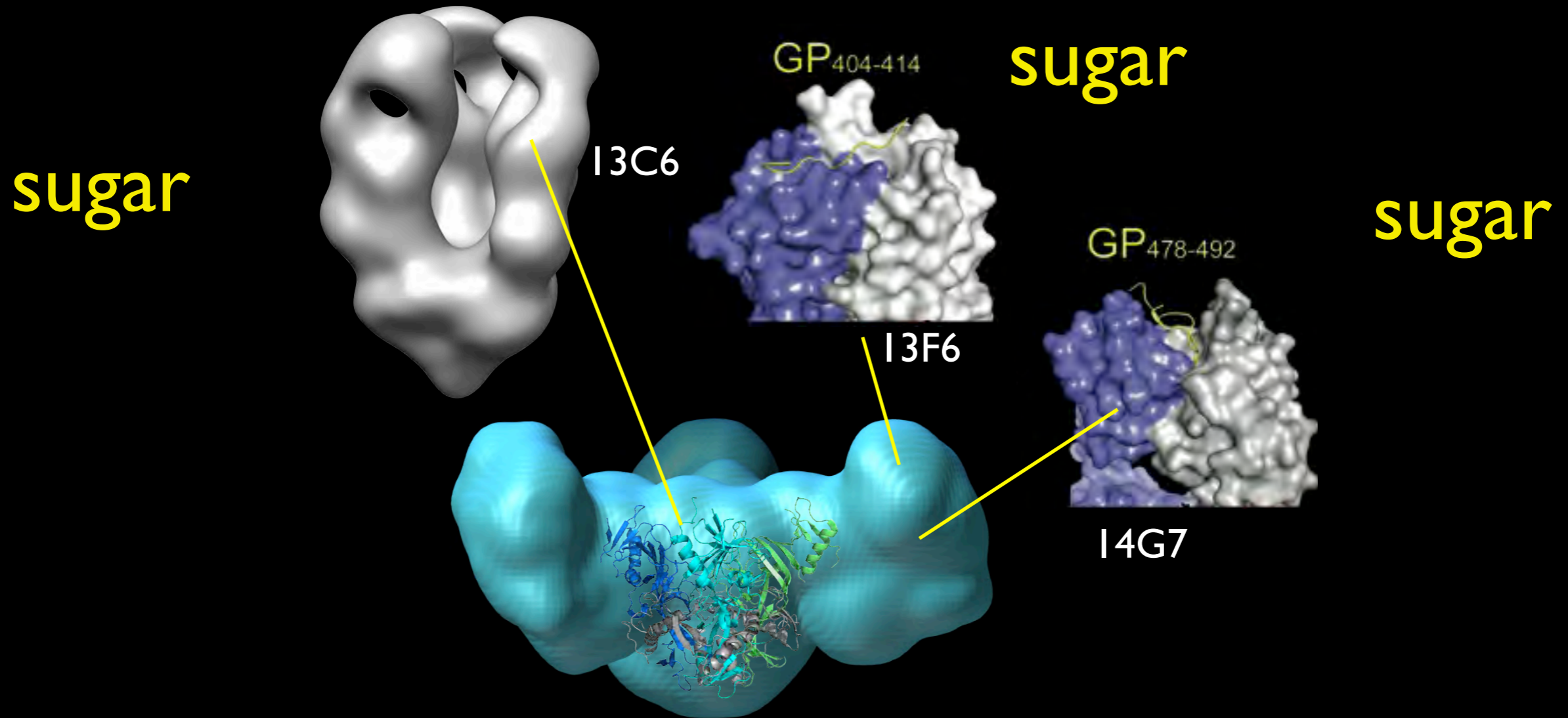
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These don't work in test tubes...

Yet, they save the lives of infected animals.

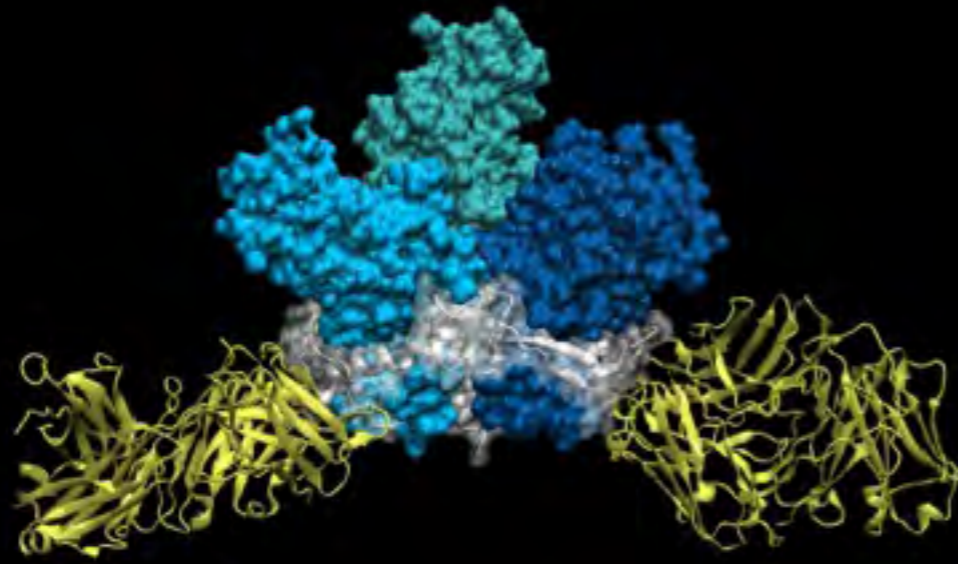
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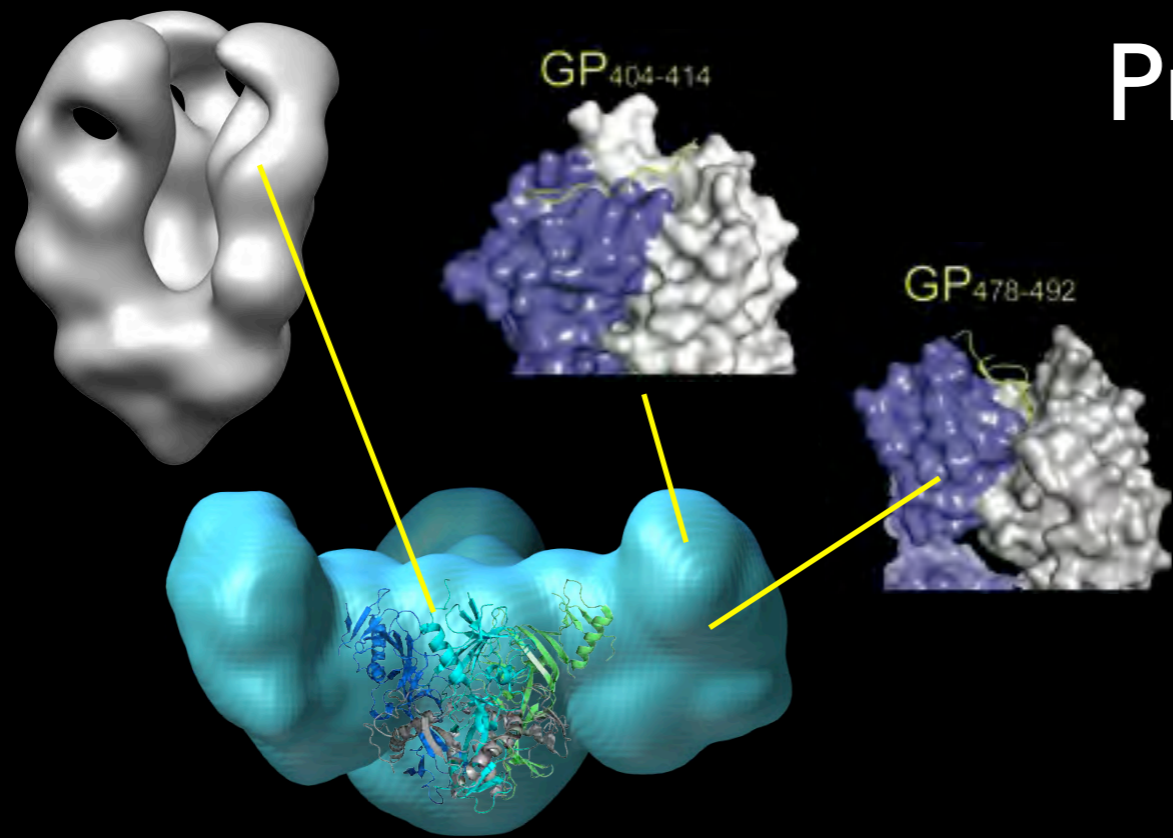




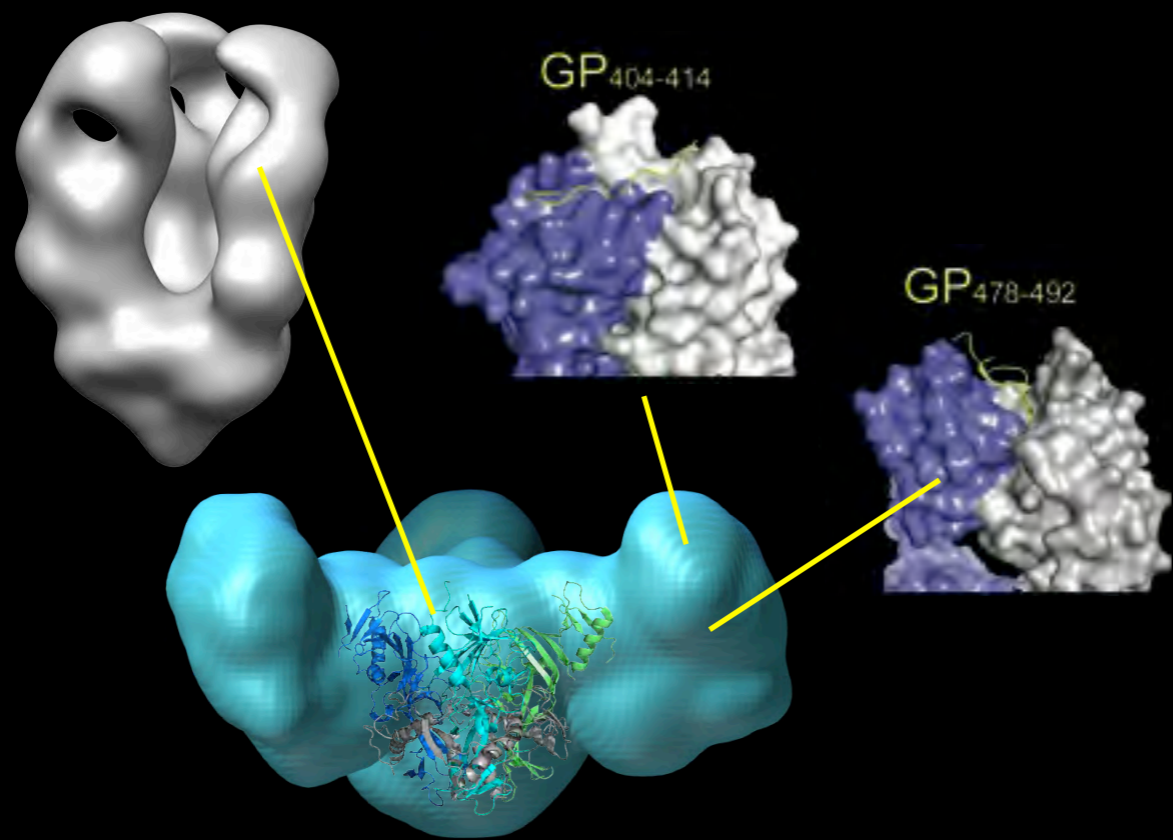
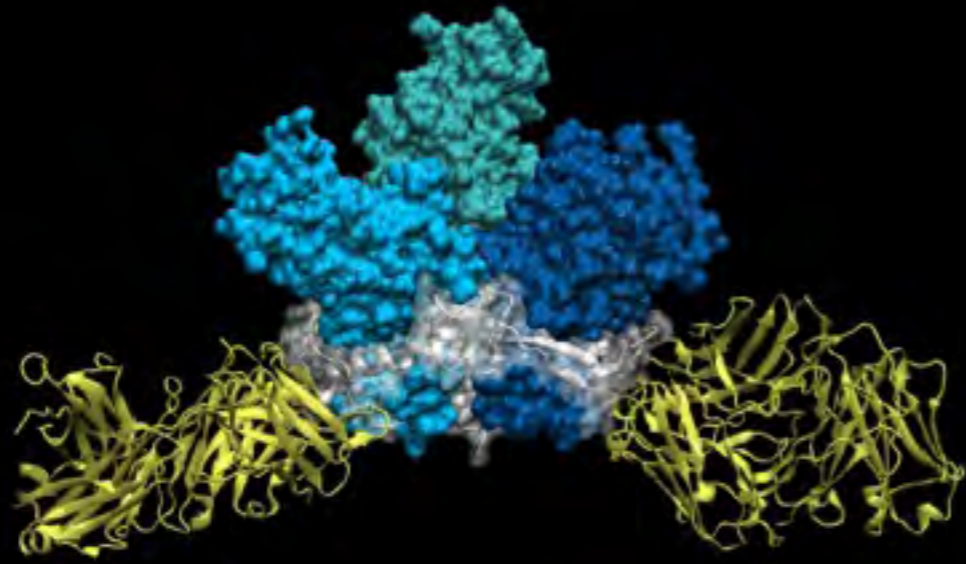
Does not protect

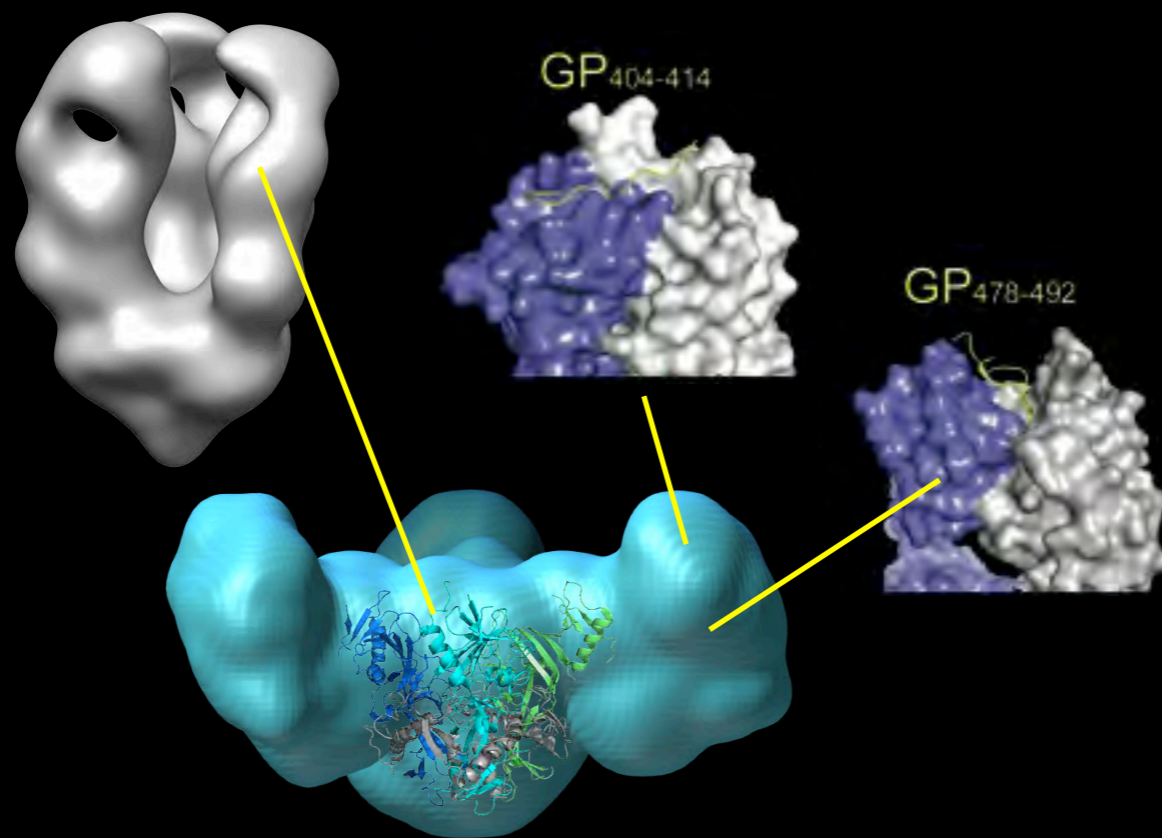
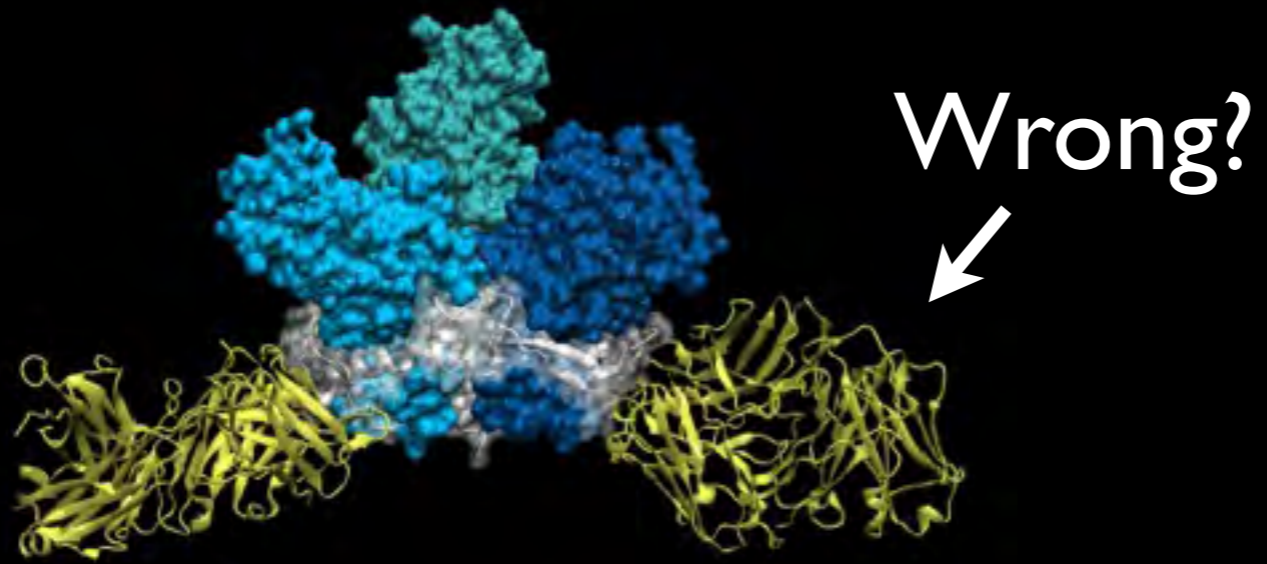


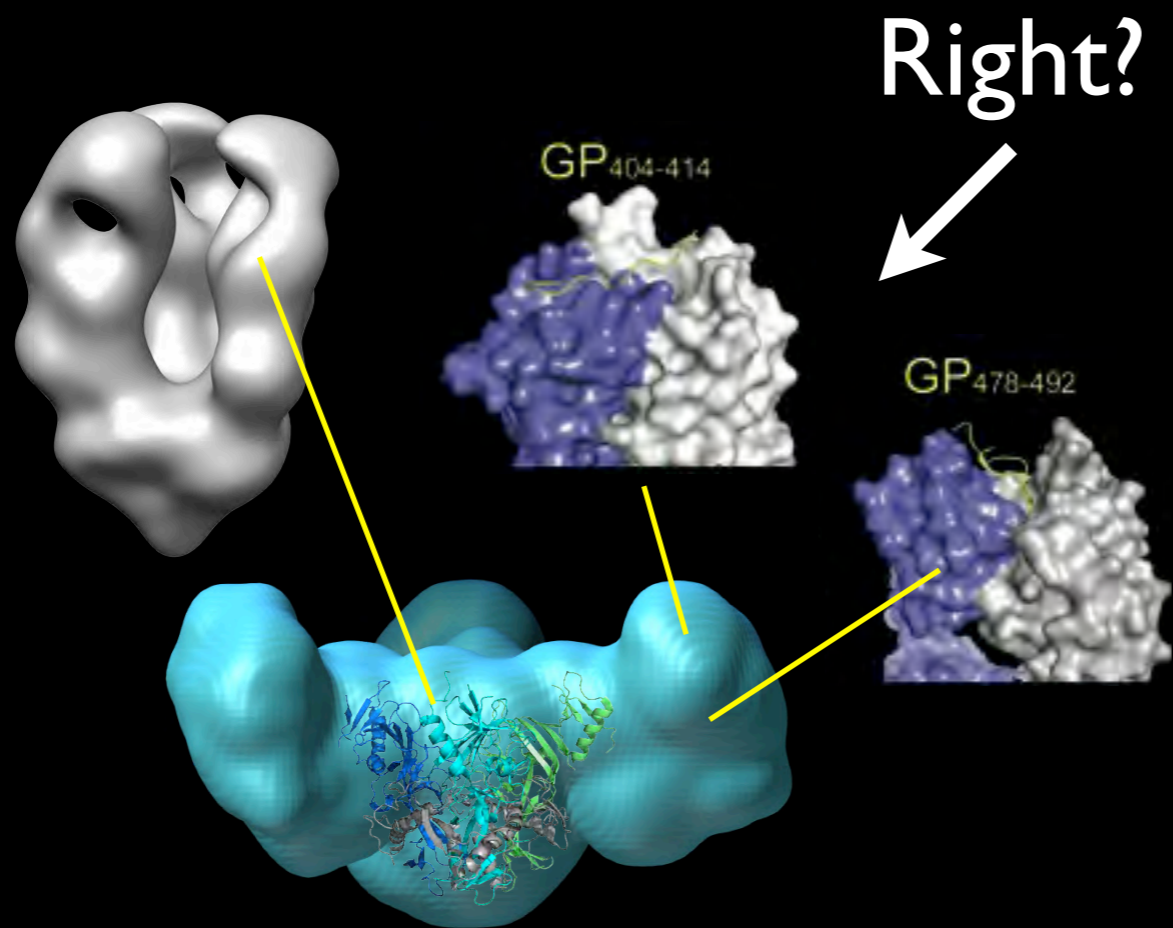
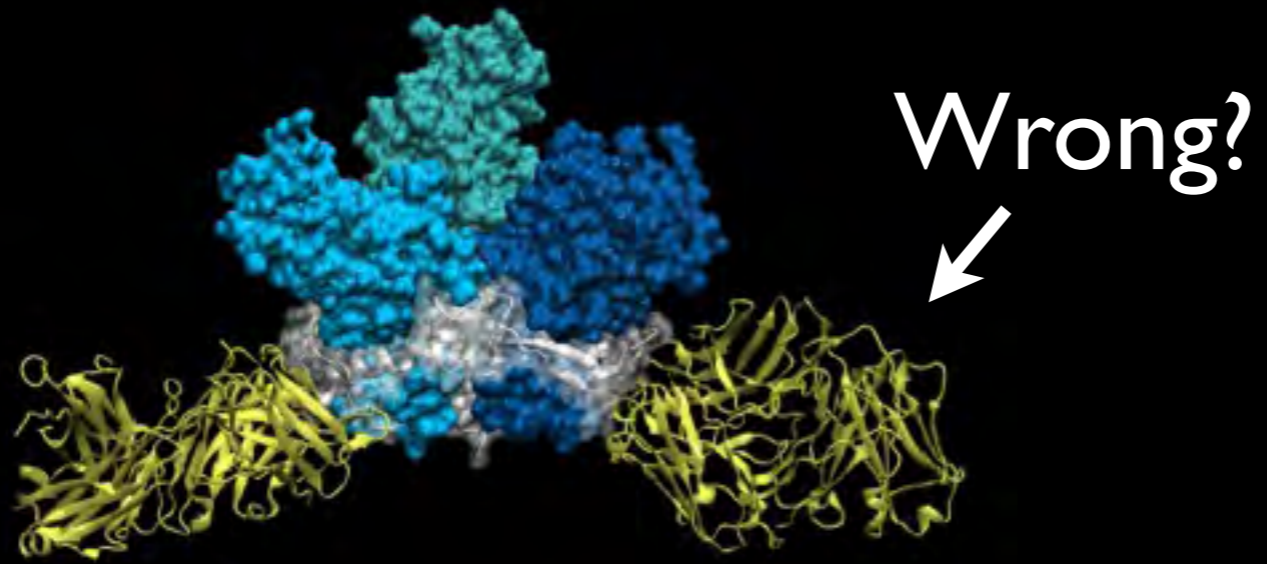
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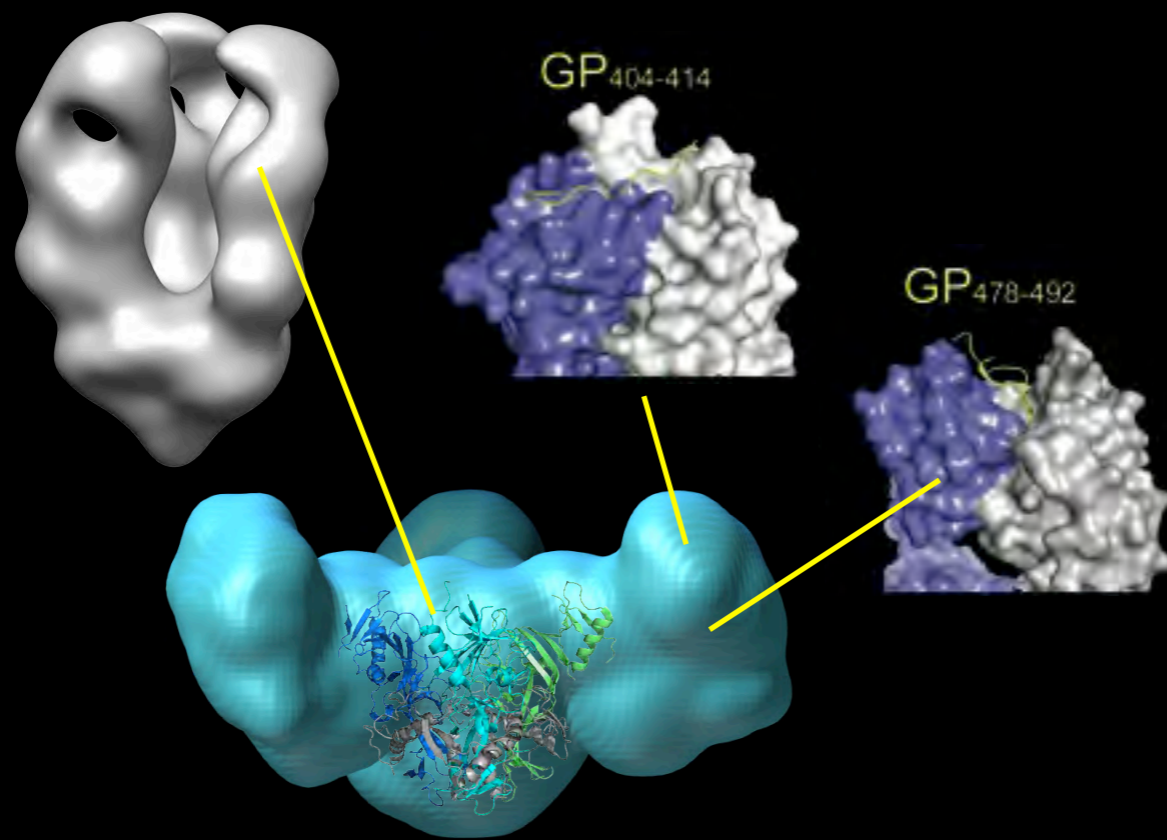
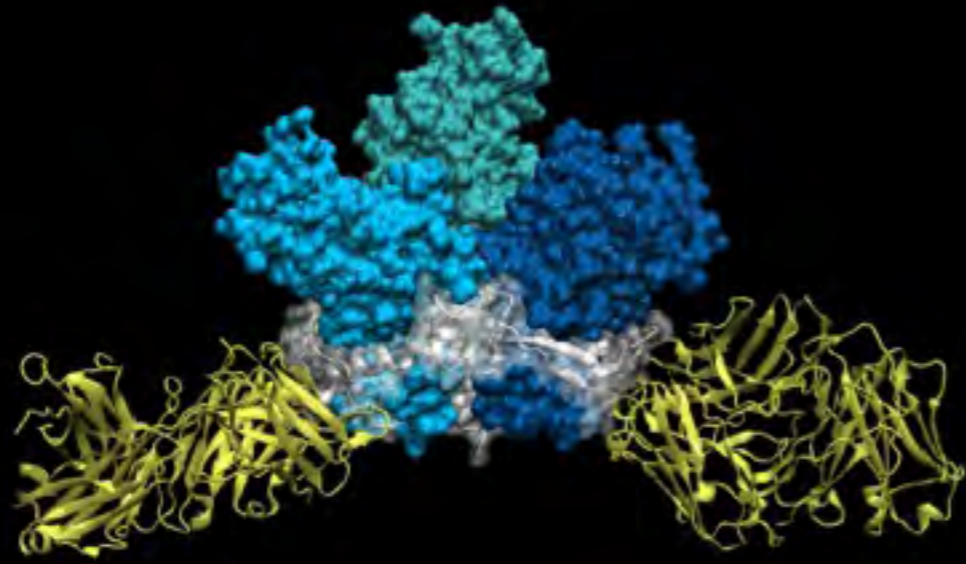


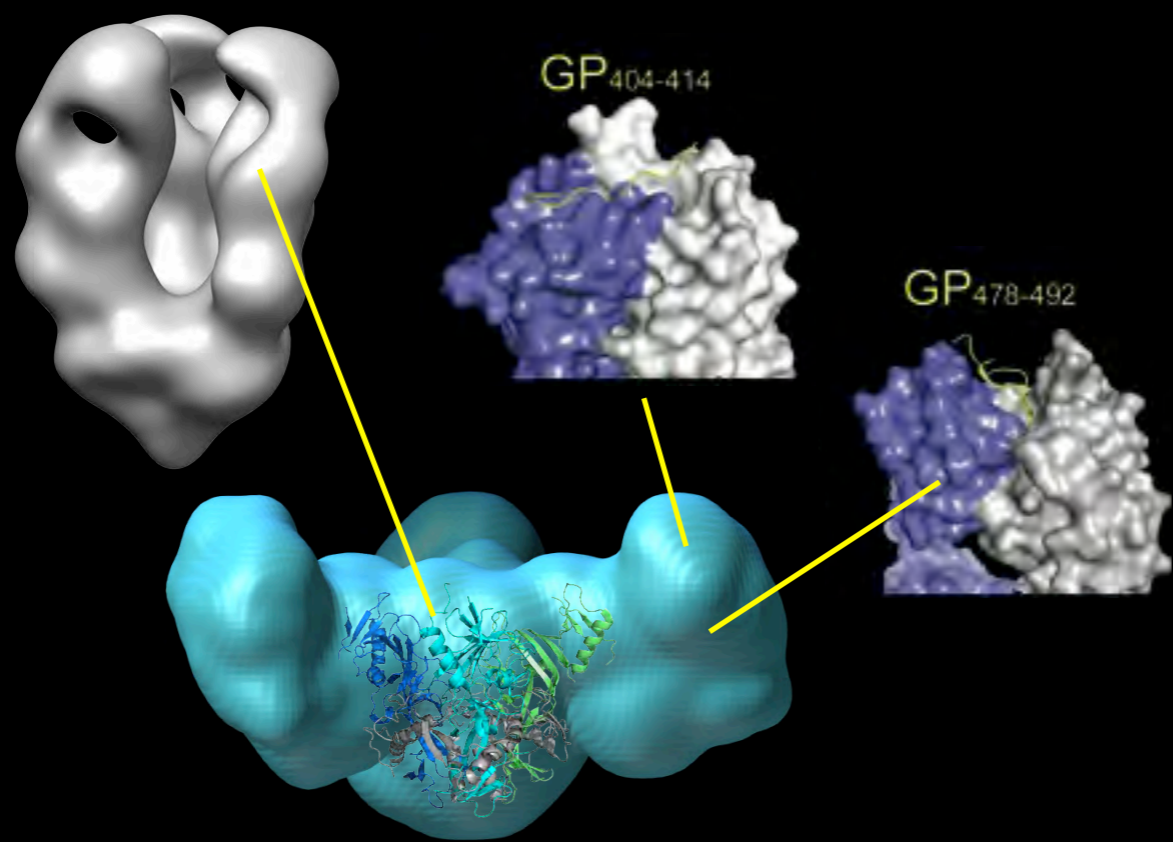
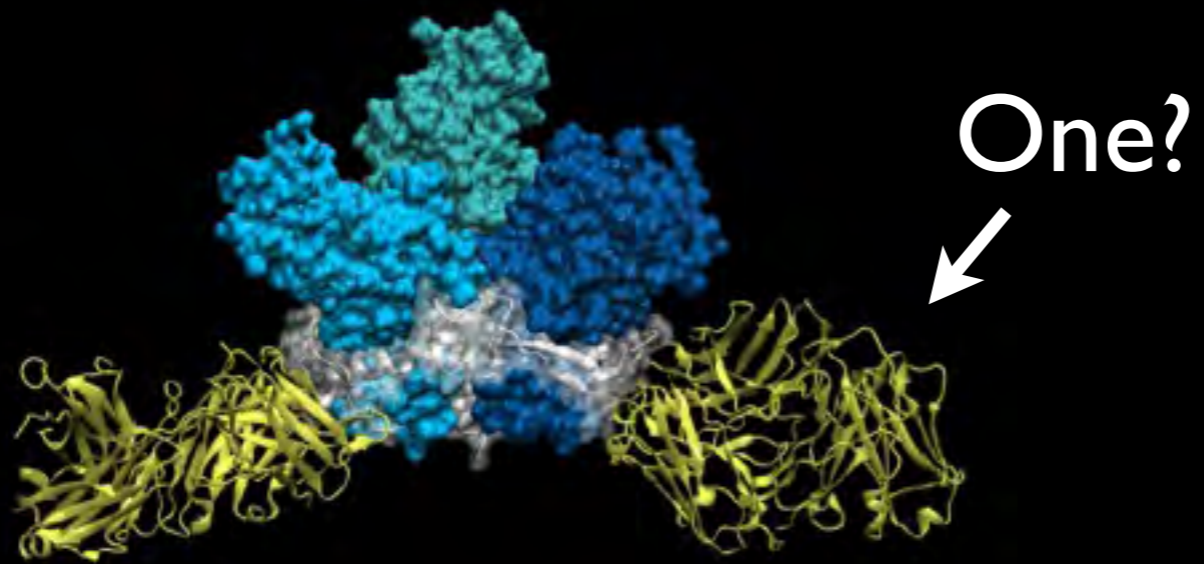
Protects

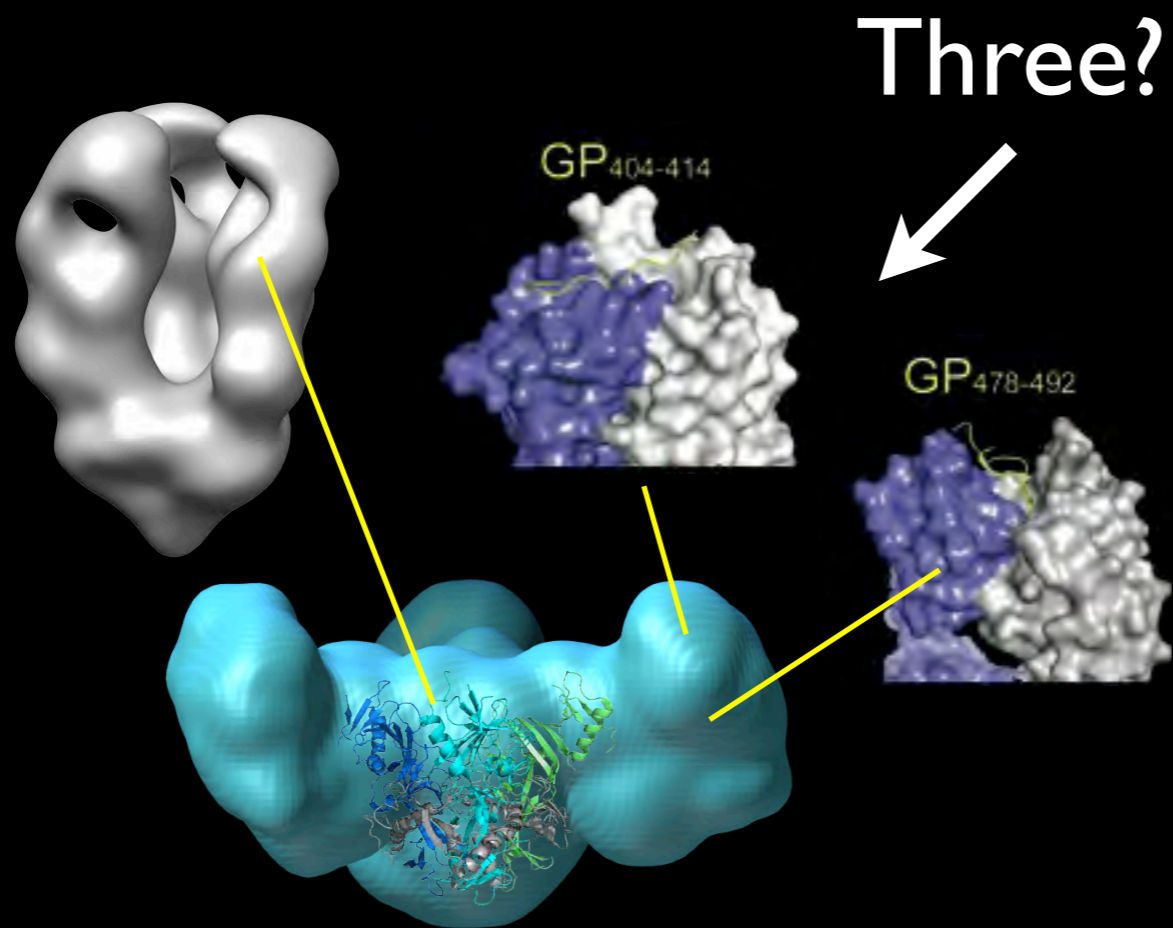
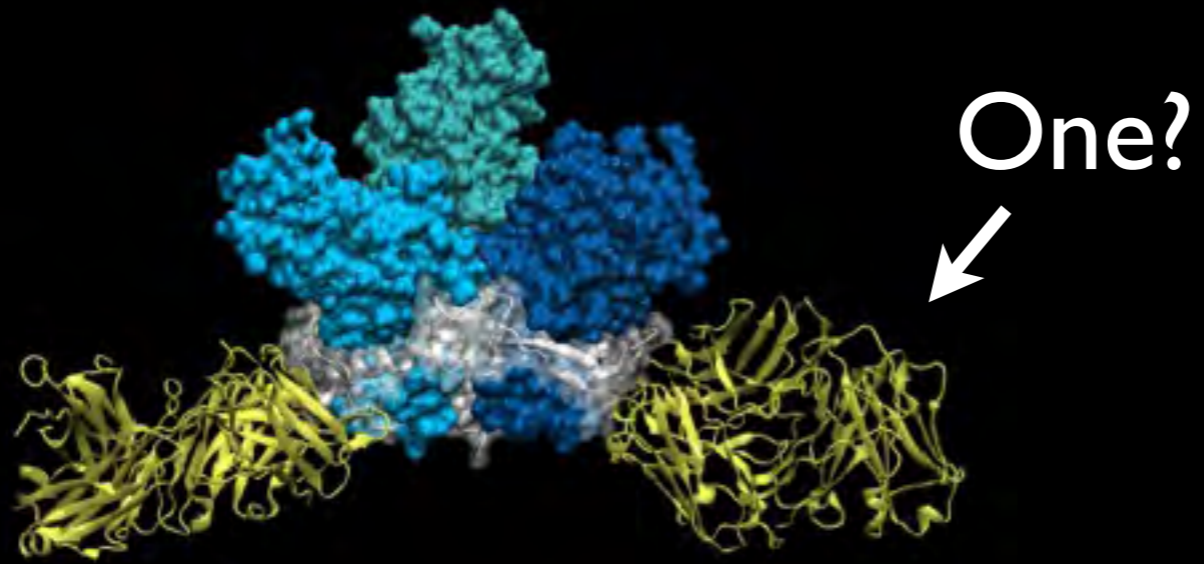












One year ago:

One year ago:
we have >150 anti-Ebola antibodies...

One year ago:
we have >150 anti-Ebola antibodies...
Which are best?

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Which are best?
How would we know?

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Which do we combine?

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We need to cure this virus.

Viral Hemorrhagic Fever Immunotherapeutic Consortium

Site Search

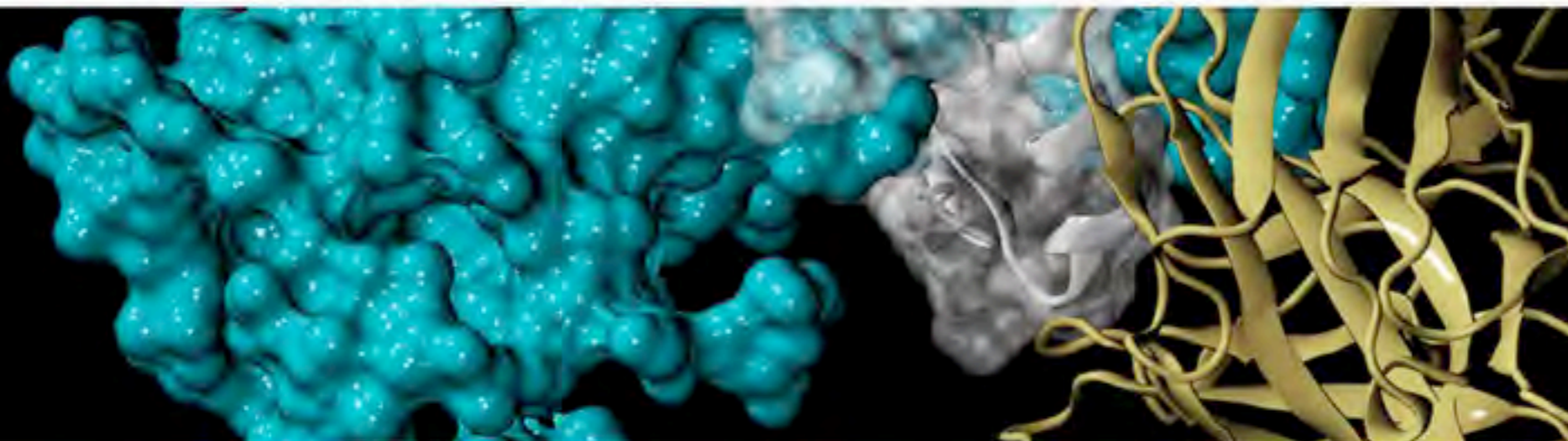


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Welcome to the Viral Hemorrhagic Fever Immunotherapeutic Consortium

Objectives

Development and provision of highly effective post-exposure immunotherapeutics against the Ebola, Marburg, Sudan, Lassa, Lujo, Machupo and Junin viruses that cause hemorrhagic fever.

Collaboration

We are an open, non-profit, 20+ investigator research consortium that spans four continents. We invite samples, input, and collaboration from researchers, NGOs and governmental bodies to help bring these emergency treatments to the clinic.

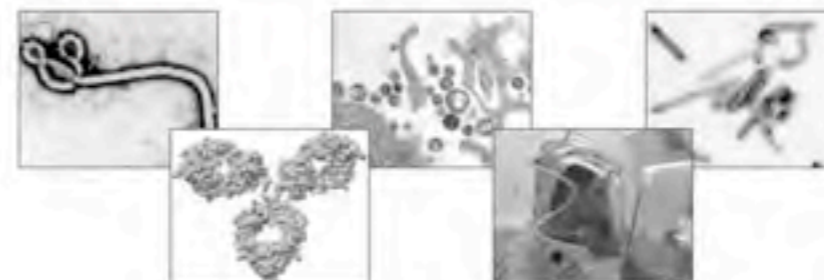
LATEST NEWS

Lassa virus antibodies from human survivors confer 100% post-exposure protection.

International commercial partnership between Mapp Biopharmaceutical and Defyrus Inc. to advance Ebola virus immunotherapeutic to clinic.

Structure of Marburg virus GP - receptor complex provides new direction for antiviral development.

Novel antibodies against Marburg virus confer protection via a variety of mechanisms.



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\$28 million TSRI-led global collaboration: Find best treatment from all available in the world

Viral Hemorrhagic Fever Immunotherapeutic Consortium Site Search

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1st stage of this collaboration = ZMapp
“mash-up” of MB-003 and ZMAb cocktails

Mapp Bio
USAMRIID

Public Health Agency of Canada

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Mapp Bio
USAMRIID
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ZMapp identified ~February 2014

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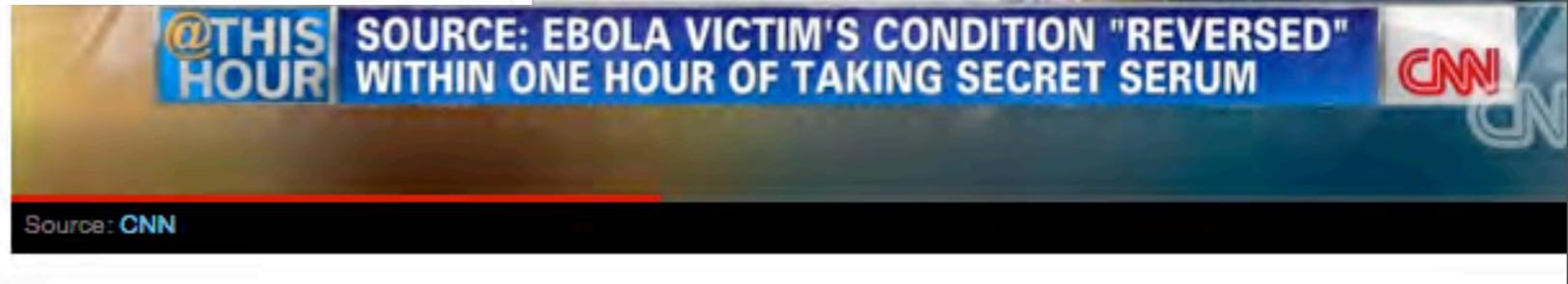
Public Health Agency of Canada

ZMapp identified ~February 2014
Ebola outbreak started Dec. 2013,
exploded July-August 2014

Experimental drug likely saved Ebola patients

By Dr. Sanjay Gupta and Danielle Dellorto, CNN

updated 8:22 PM EDT, Tue August 5, 2014

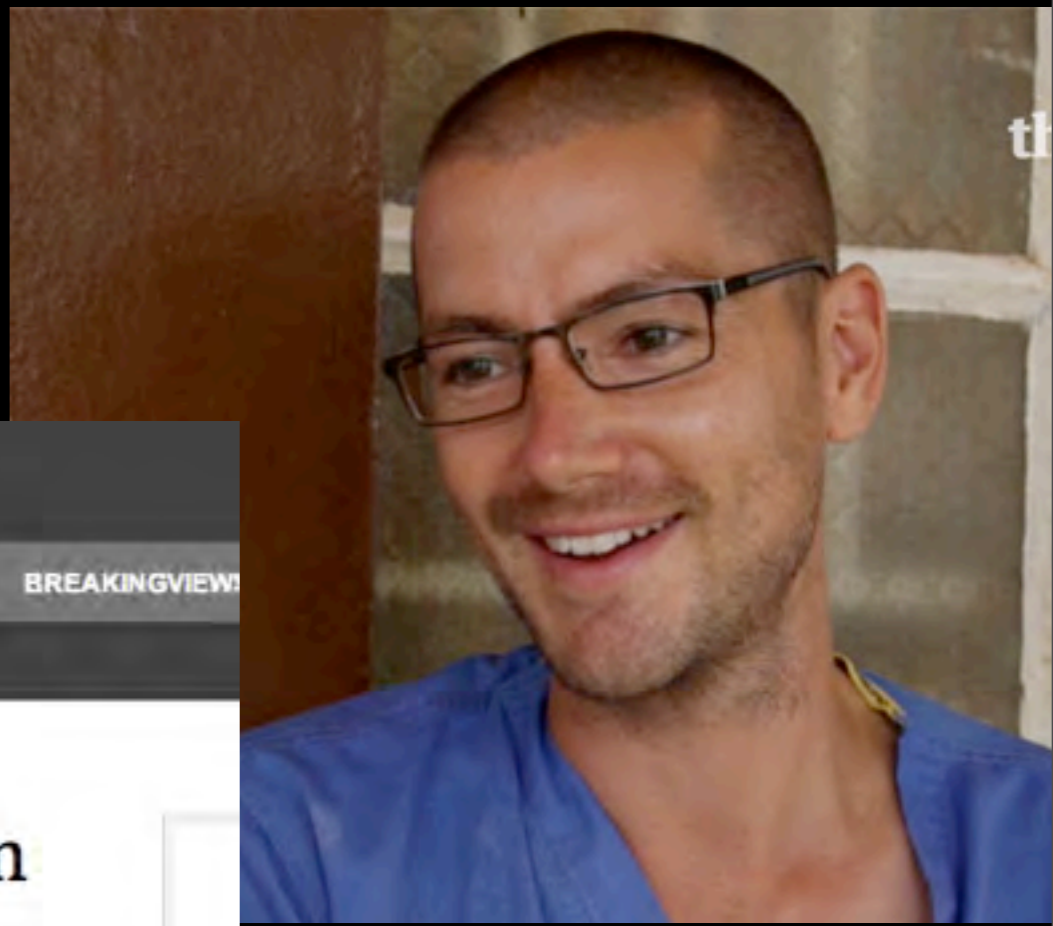


August 2014



DAVID MORRISON/SAMARITANS PURSE

Dr. Kent Brantly leaves Emory University Hospital on Thursday, August 21, after being declared no longer infectious from the Ebola virus. Brantly was one of two American missionaries brought to Emory for treatment of the deadly virus, which has killed more than 1,350 people in West Africa since March, according to the World Health Organization.



REUTERS EDITION: UK ▾

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VIDEO

British Ebola patient discharged from hospital after ZMapp treatment

LONDON | Wed Sep 3, 2014 3:50pm BST

Two Liberian medical workers discharged after recovering from Ebola

By Nima Elbagir and Joshua Berlinger, CNN

updated 5:16 PM EDT, Sat August 30, 2014



The 53-year-old surgeon feels even more certain that ZMapp was crucial in saving a Liberian health worker, Kyndy Kobbah, who was in a coma in critical condition when she received it. "If it wasn't for ZMapp, she wouldn't have made it," he said.

"Everybody was amazed. Nobody gave her a chance to survive. She got her recovery because of ZMapp. If they can expedite the production of it, they should try, because we really need it."

HEALTH



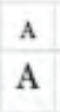
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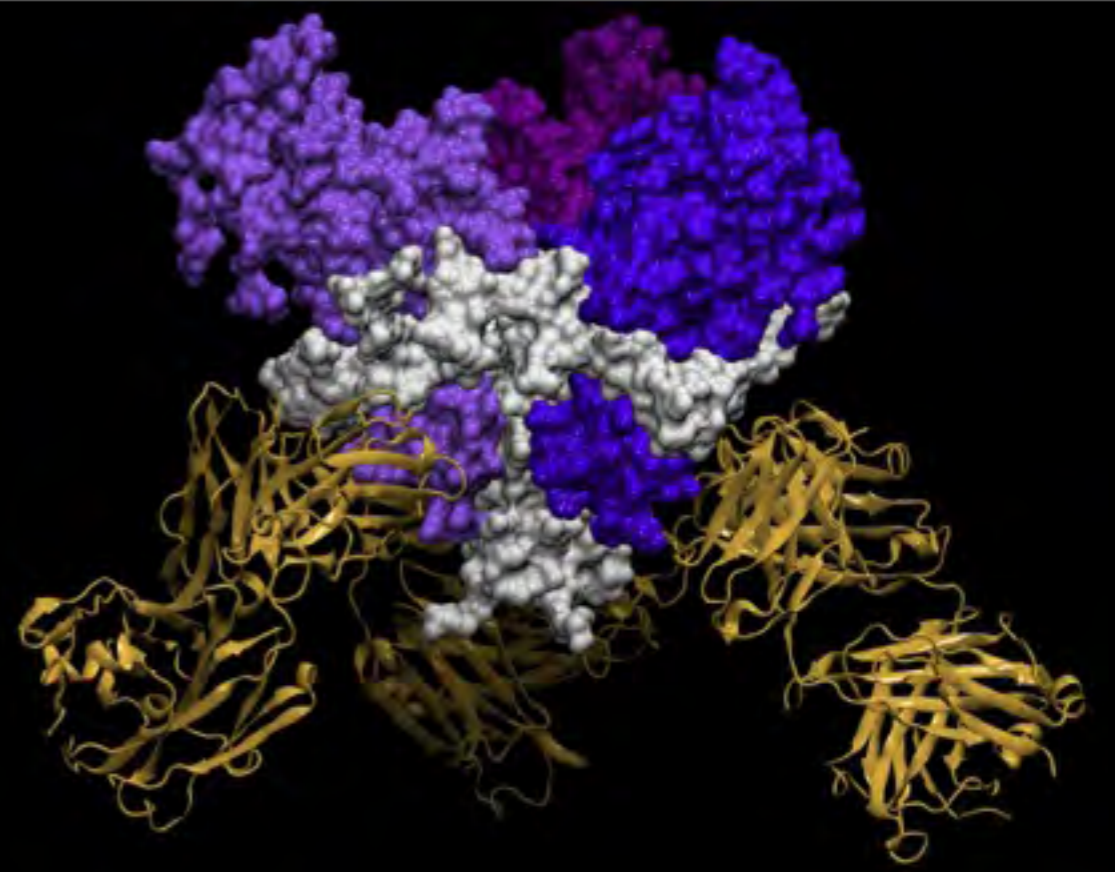
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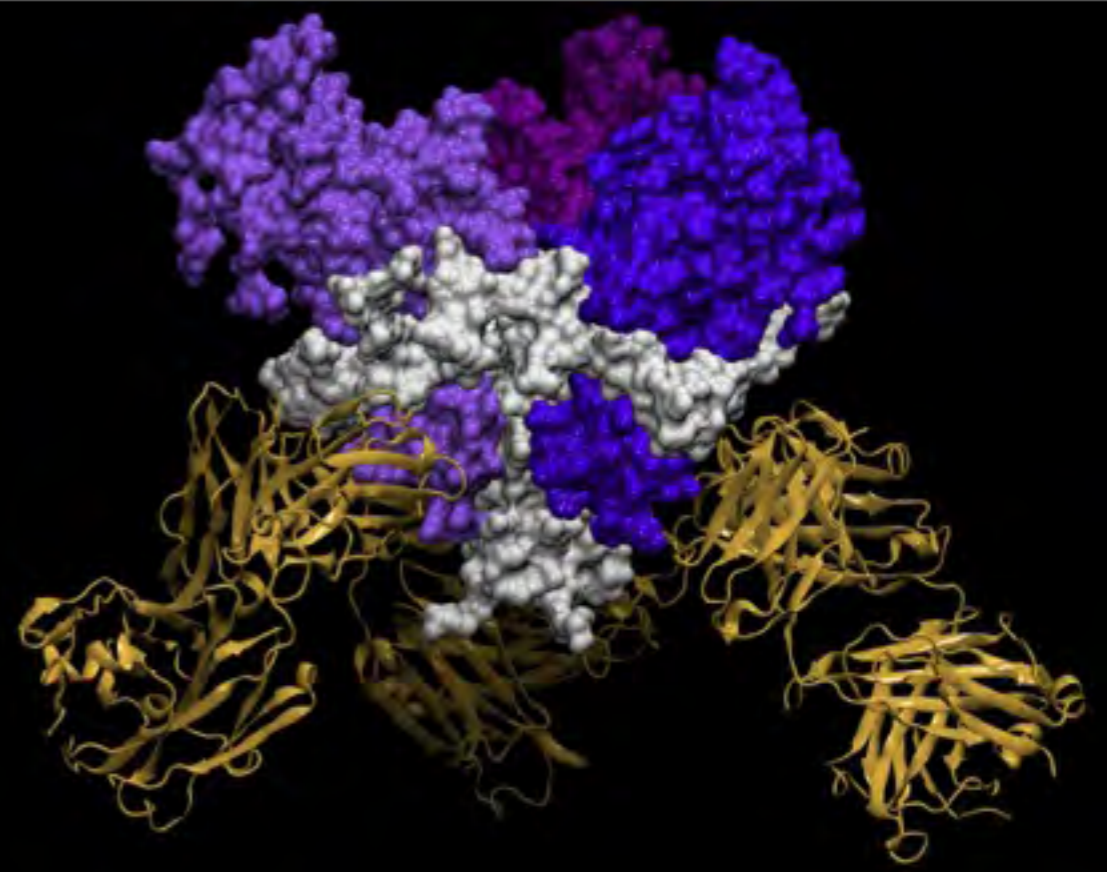


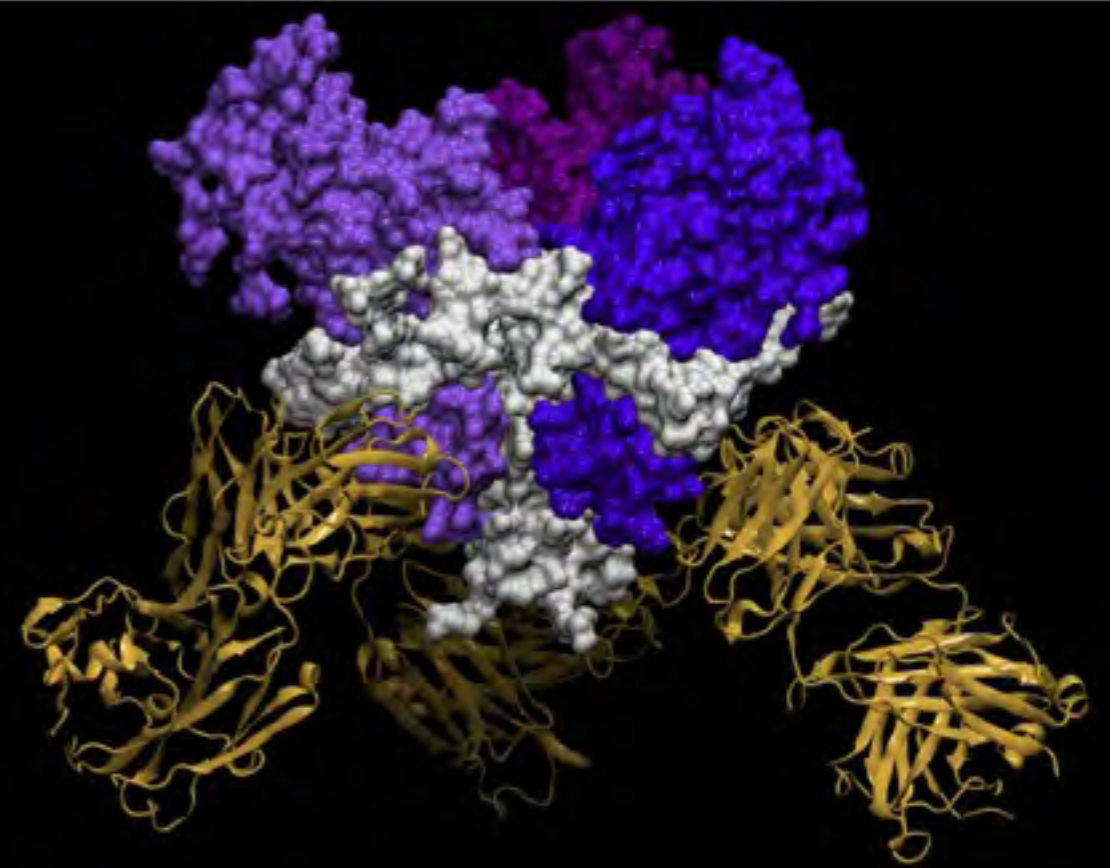
By **MATT MOFFETT** [CONNECT](#)

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My lab at The Scripps Research Institute



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