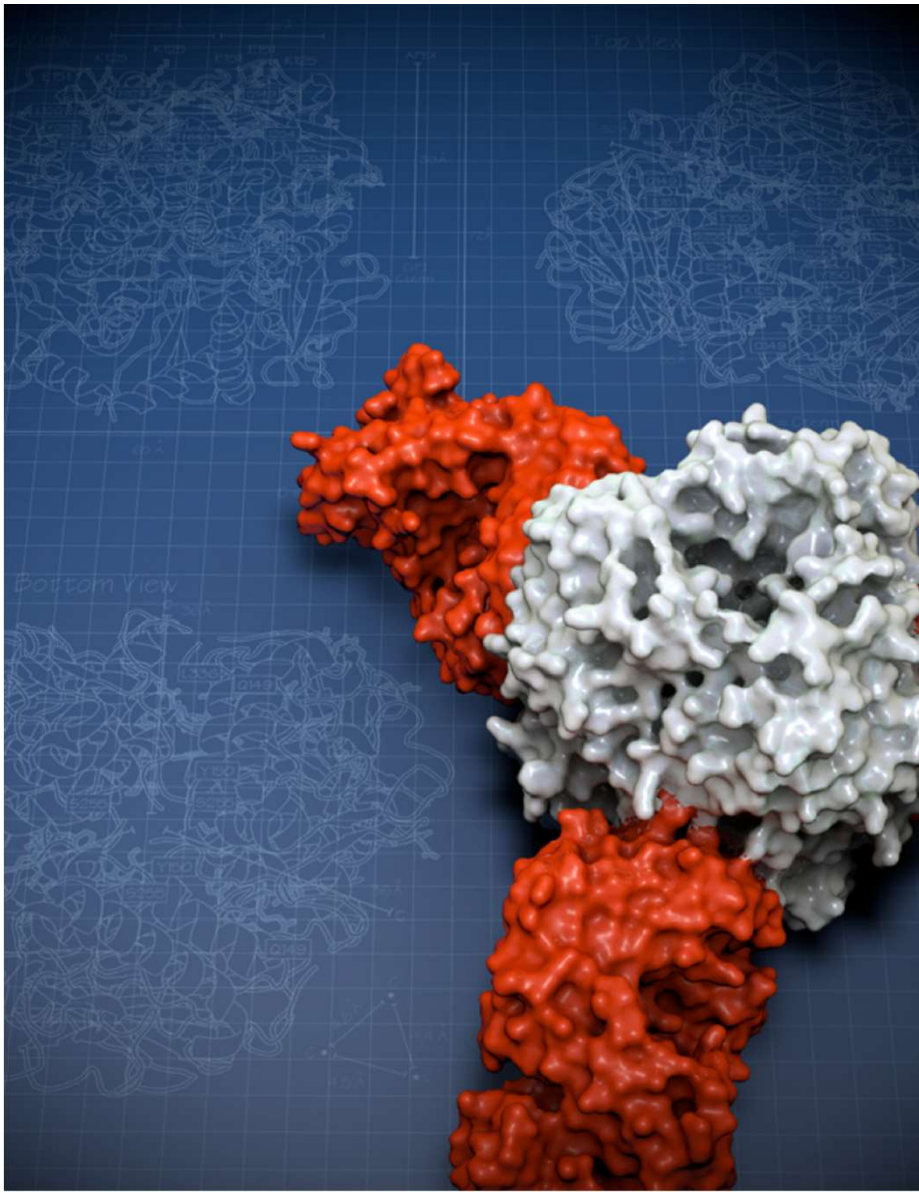
Neutralizing epitopes on Lassa GPC and novel immunogens that present them



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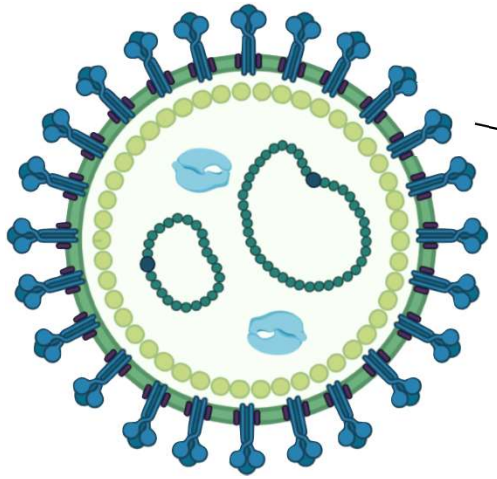
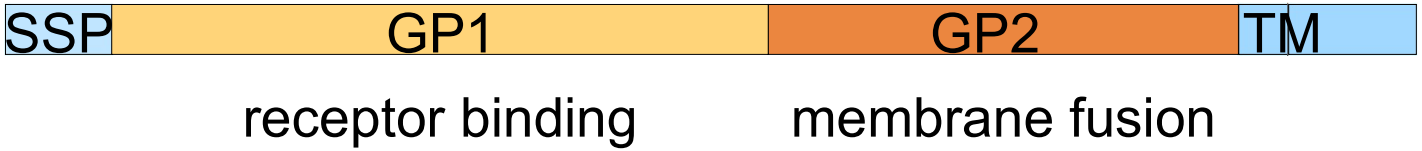
Erica Ollmann Saphire, Ph.D. MBA
Kathryn Hastie, Ph.D.
Haoyang Li, Ph.D.



Arenaviruses express one protein on surface, glycoprotein GPC



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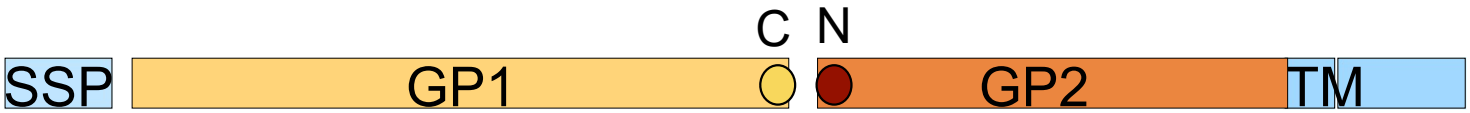
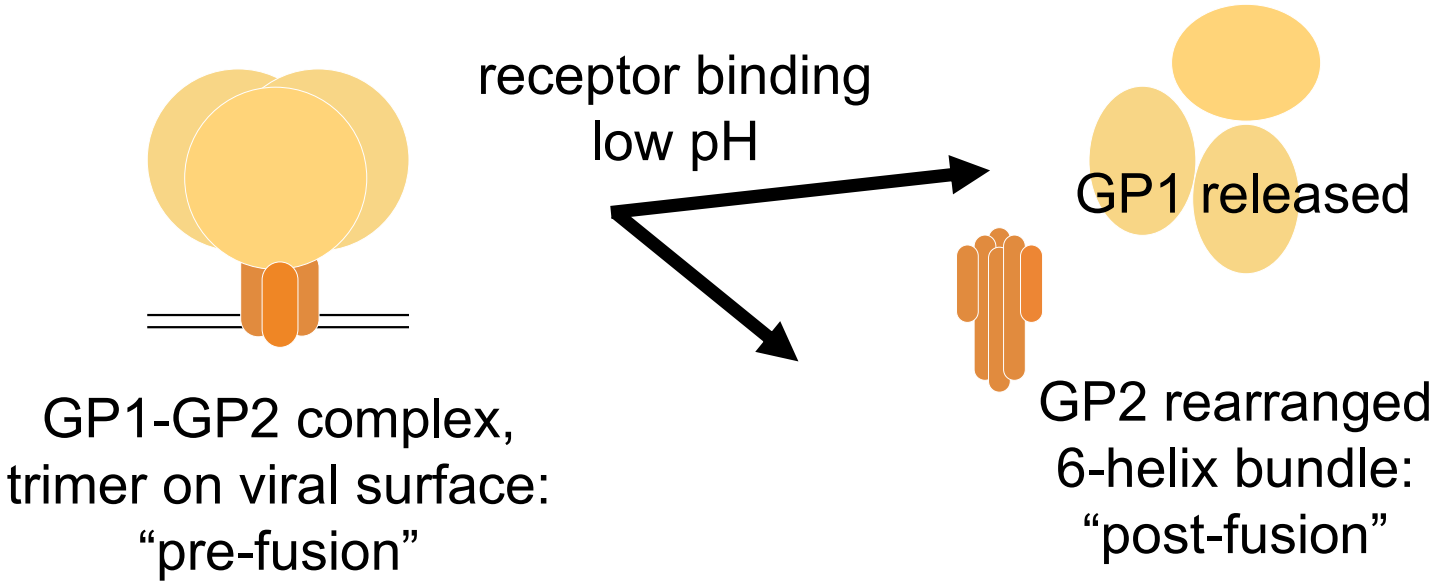
Arenavirus GPC





Prevailing thought had been: neut. Abs didn’t exist for Lassa
The right tools to find them just hadn’t been available yet

Need the right bait to catch the right fish

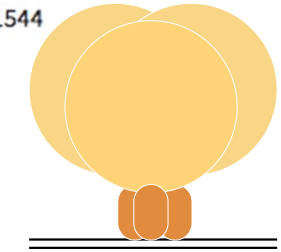
nature COMMUNICATIONS

Most neutralizing human monoclonal antibodies target novel epitopes requiring both Lassa virus glycoprotein subunits

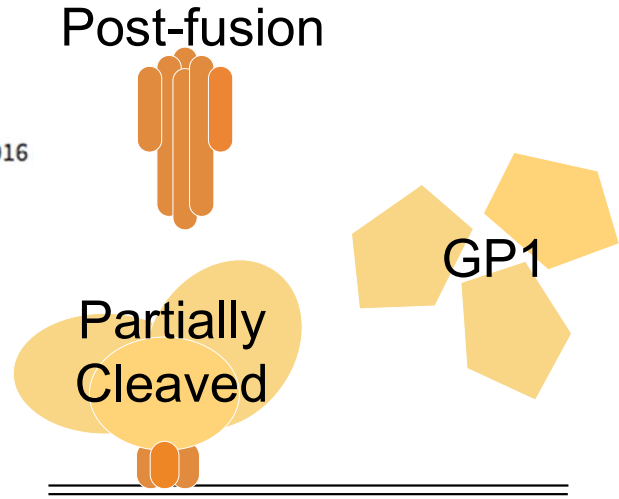
James E. Robinson ✉, Kathryn M. Hastie […] Robert F. Garry

Nature Communications **7**,
Article number: 11544 (2016)
doi:10.1038/ncomms11544

Received: 15 March 2016
Accepted: 07 April 2016
Published online: 10 May 2016

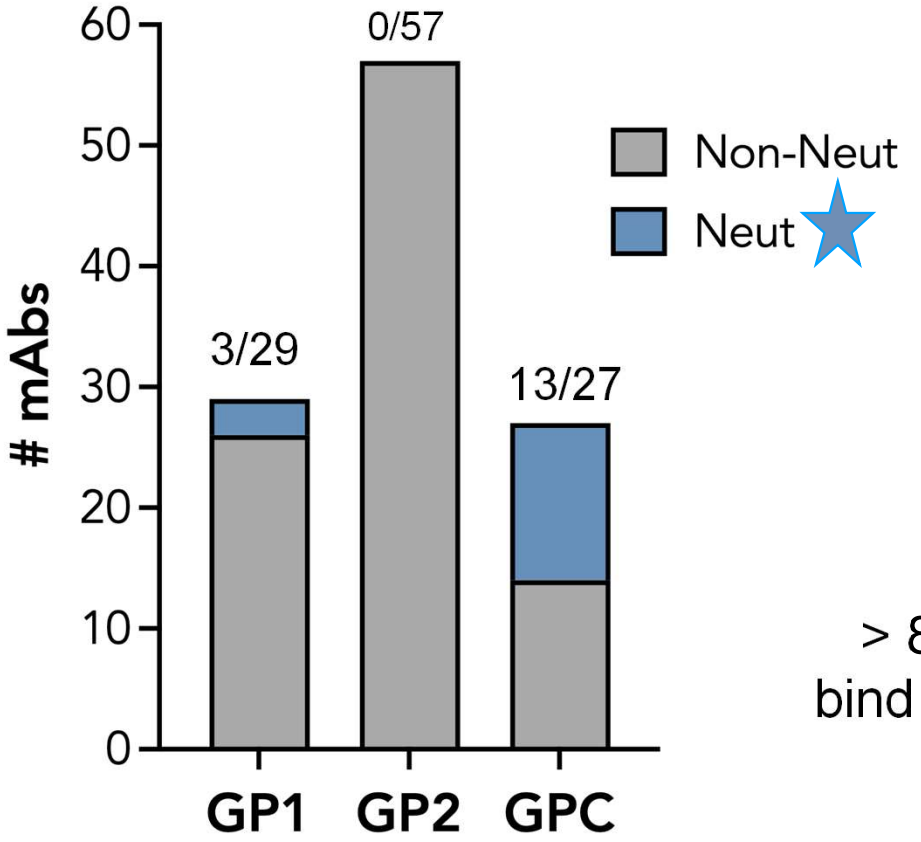


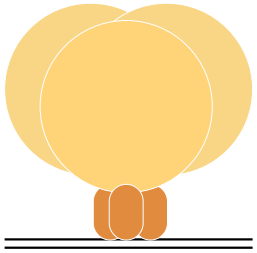
The best antibodies bind fully condensed pre-fusion trimer



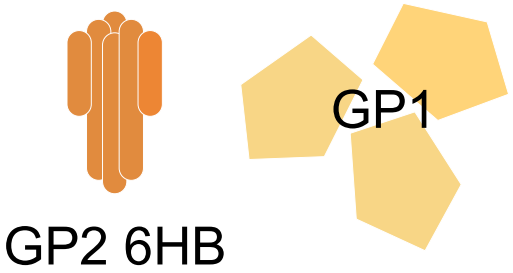
…not these

>100 antibodies isolated from Sierra Leonean and Nigerian survivors of Lassa Fever

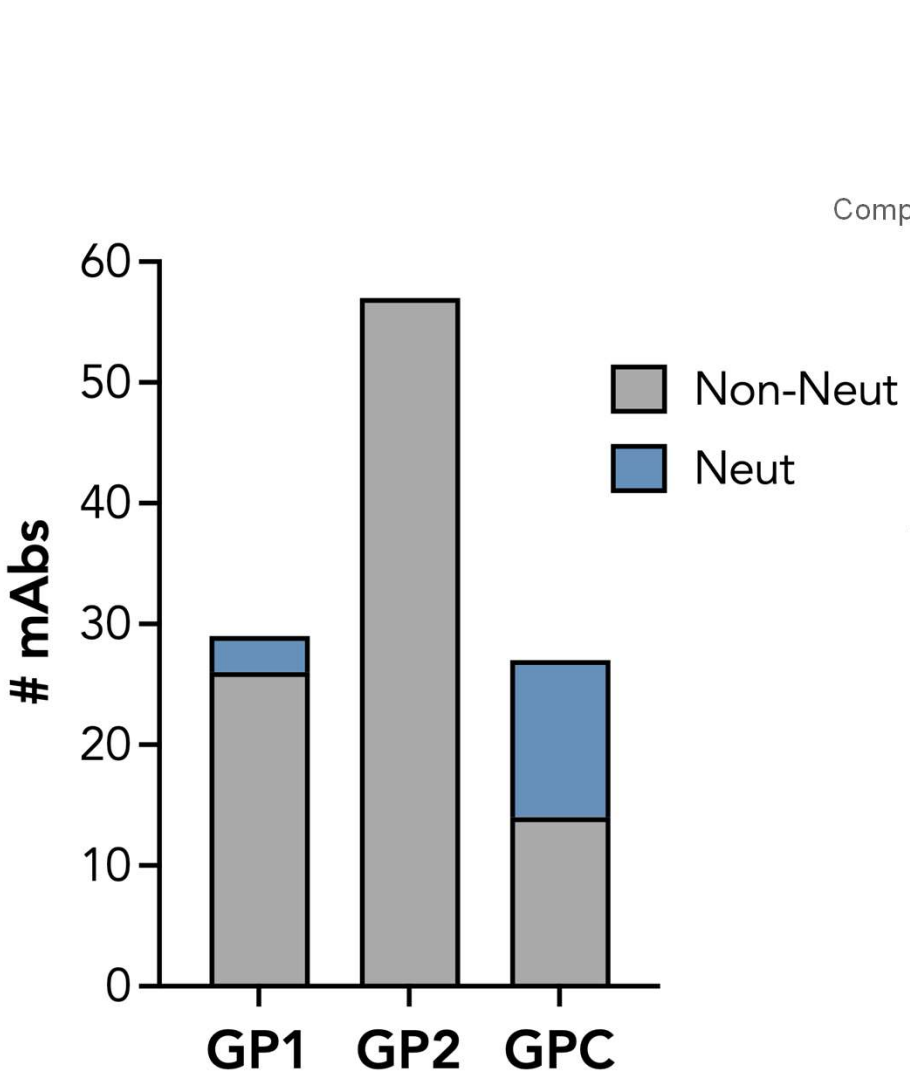


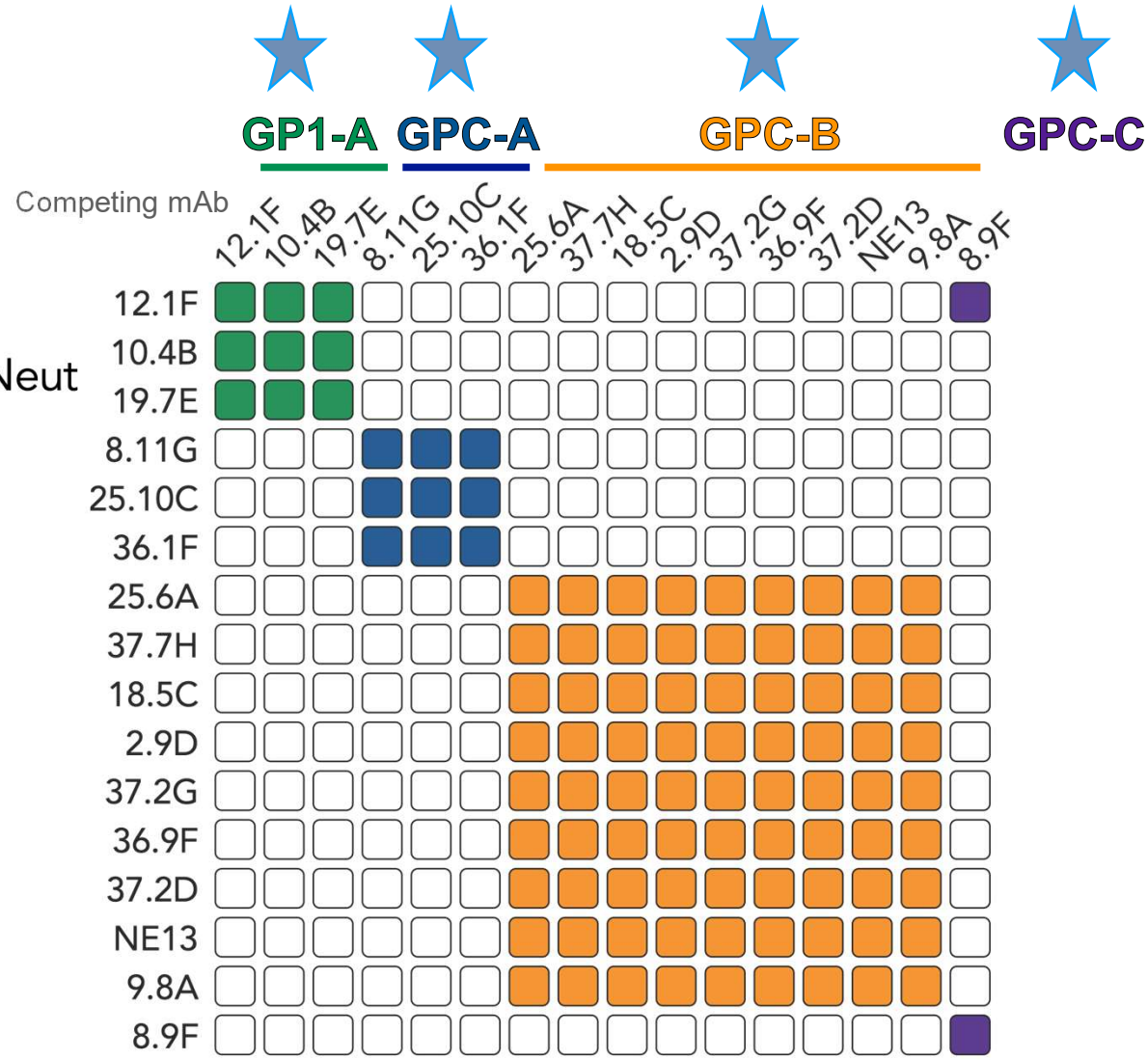


> 80% antibodies bind pre-fusion trimer



Not the subunits in post-fusion conformations


mAbs
60
50
40
30
20
10
0
GP1
GP2
GPC
Non-Neut
Neut


GP1-A
GPC-A
GPC-B
GPC-C
Competing mAb
12.1F
10.4B
19.7E
8.11G
25.10C
36.1F
25.6A
37.7H
18.5C
2.9D
37.2G
36.9F
37.2D
NE13
9.8A
8.9F

Most nAbs target prefusion GPC

Where do they bind and how can we elicit them?

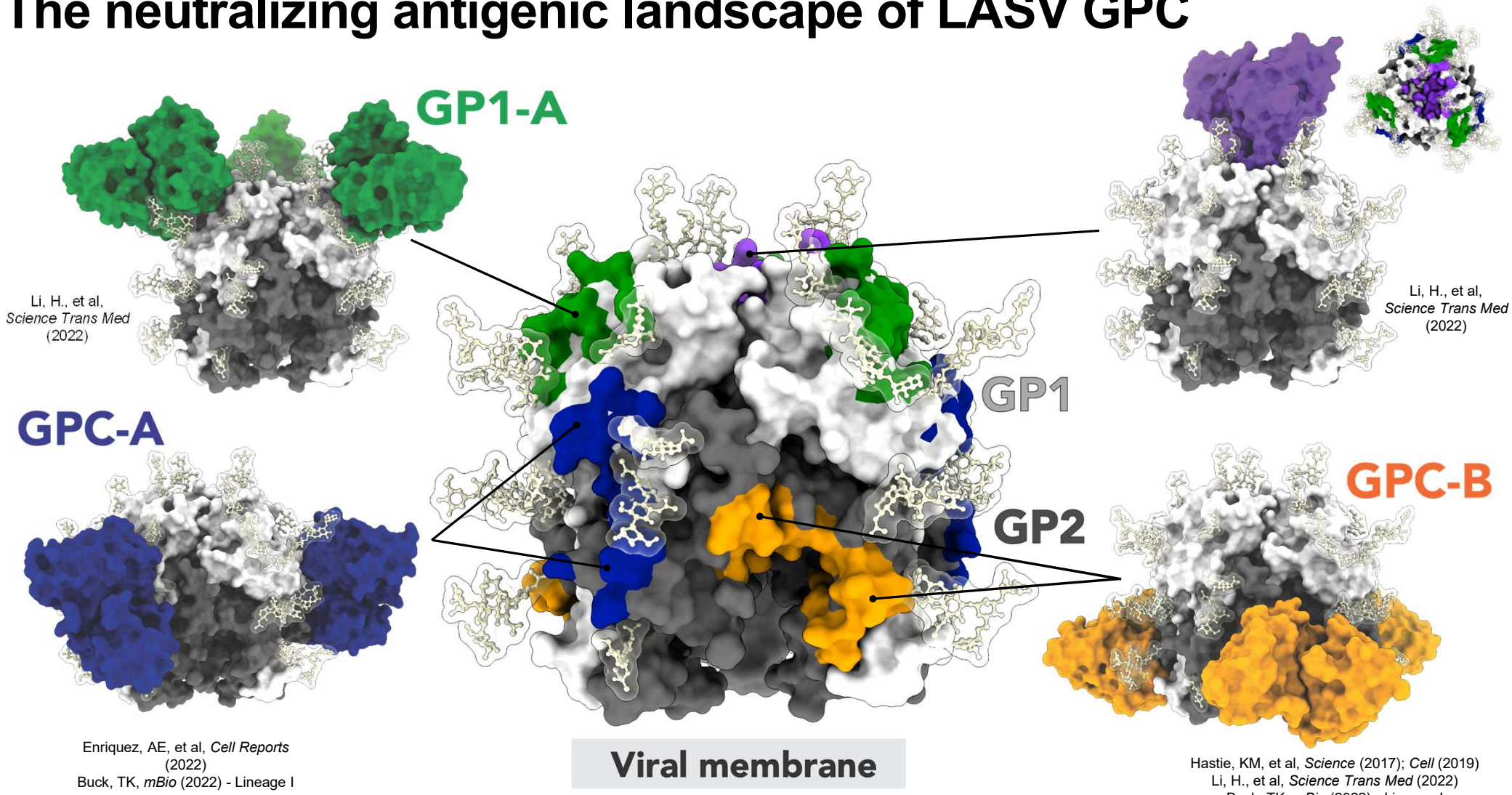
The challenges for structure determination are the same for nAb elicitation and detection

GPC is metastable

GPC is heavily glycosylated

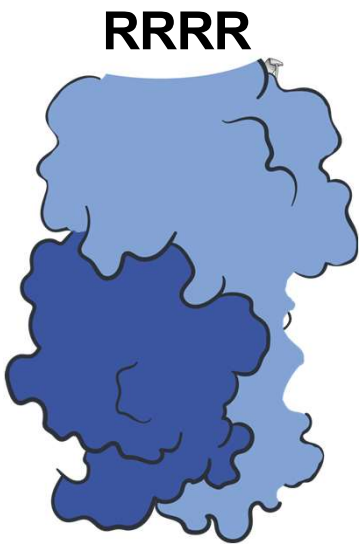
Proper GP1-GP2 processing required for trimerization

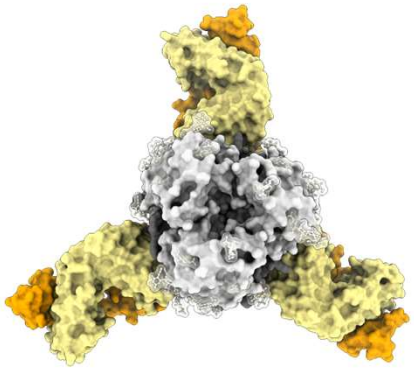
The neutralizing antigenic landscape of LASV GPC

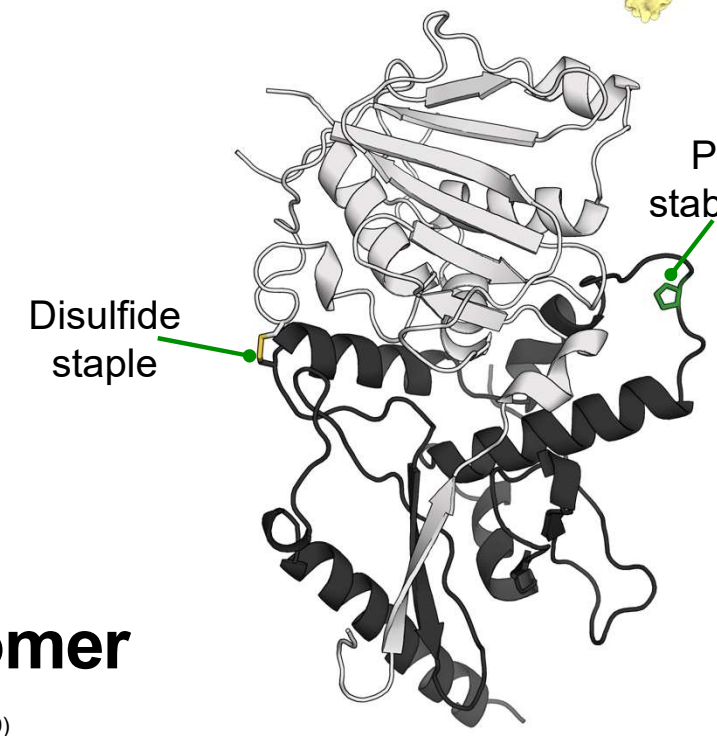


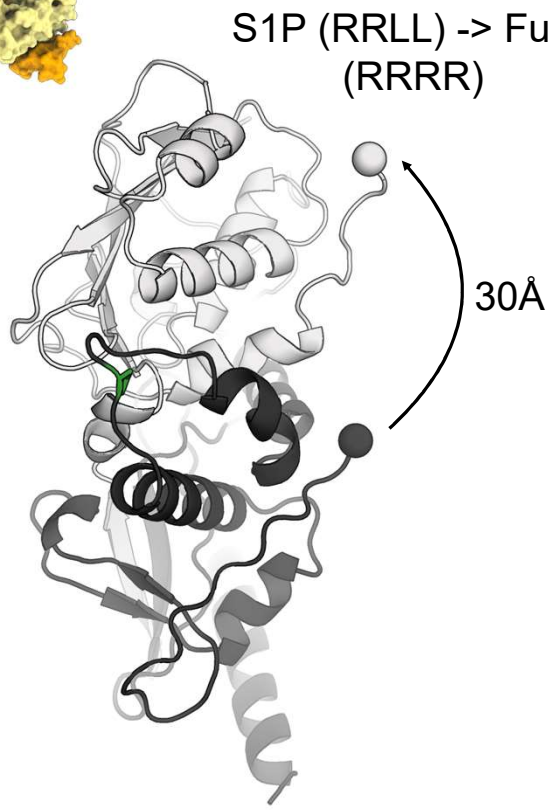
>15 years of protein engineering:

Dominant GPC-B epitope defined
Immunofocusing target identified







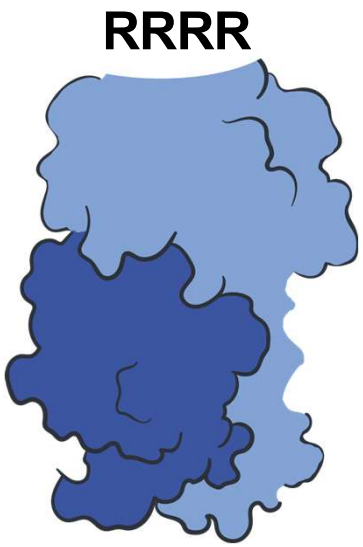


Version 1
Prefusion monomer

Hastie, *Science* (2017); *Cell* (2019)
Formed trimer in crystal packing

>15 years of protein engineering:

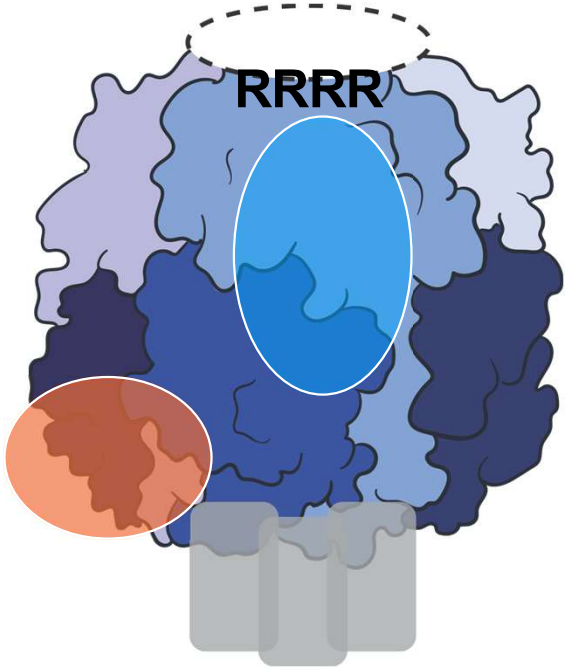
GPC-B epitope defined



Version 1
Prefusion monomer

Hastie, *Science* (2017); *Cell* (2019)
Formed trimer in crystal packing

GPC-A epitope defined



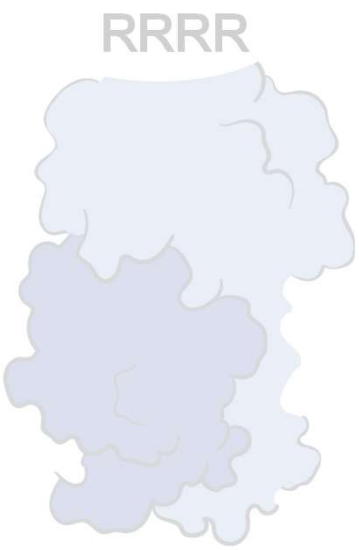
Version 2
Prefusion trimer

Enriquez, *Cell Reports* (2022)
Buck, *mBio* (2022) - Lineage I

Pros:
Now have a pre-fusion trimer
Can get GPC-B and GPC-A epitopes

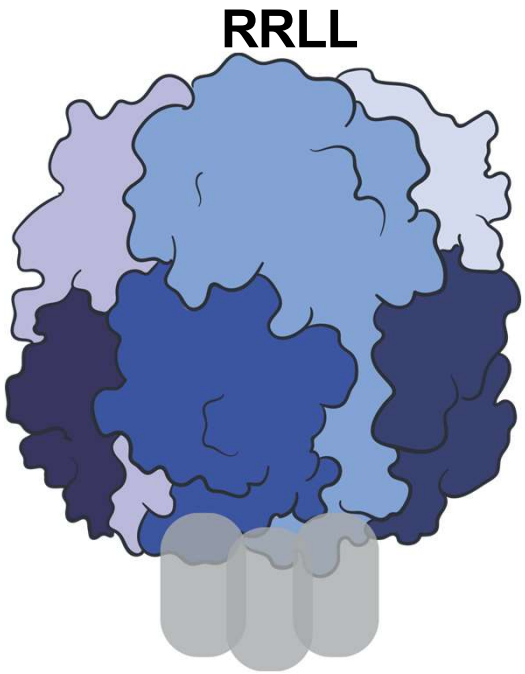
Cons:
Cleavage site still is not native (it was furin)
Can't get GP1-A well
or GPC-C at all

>15 years of protein engineering:



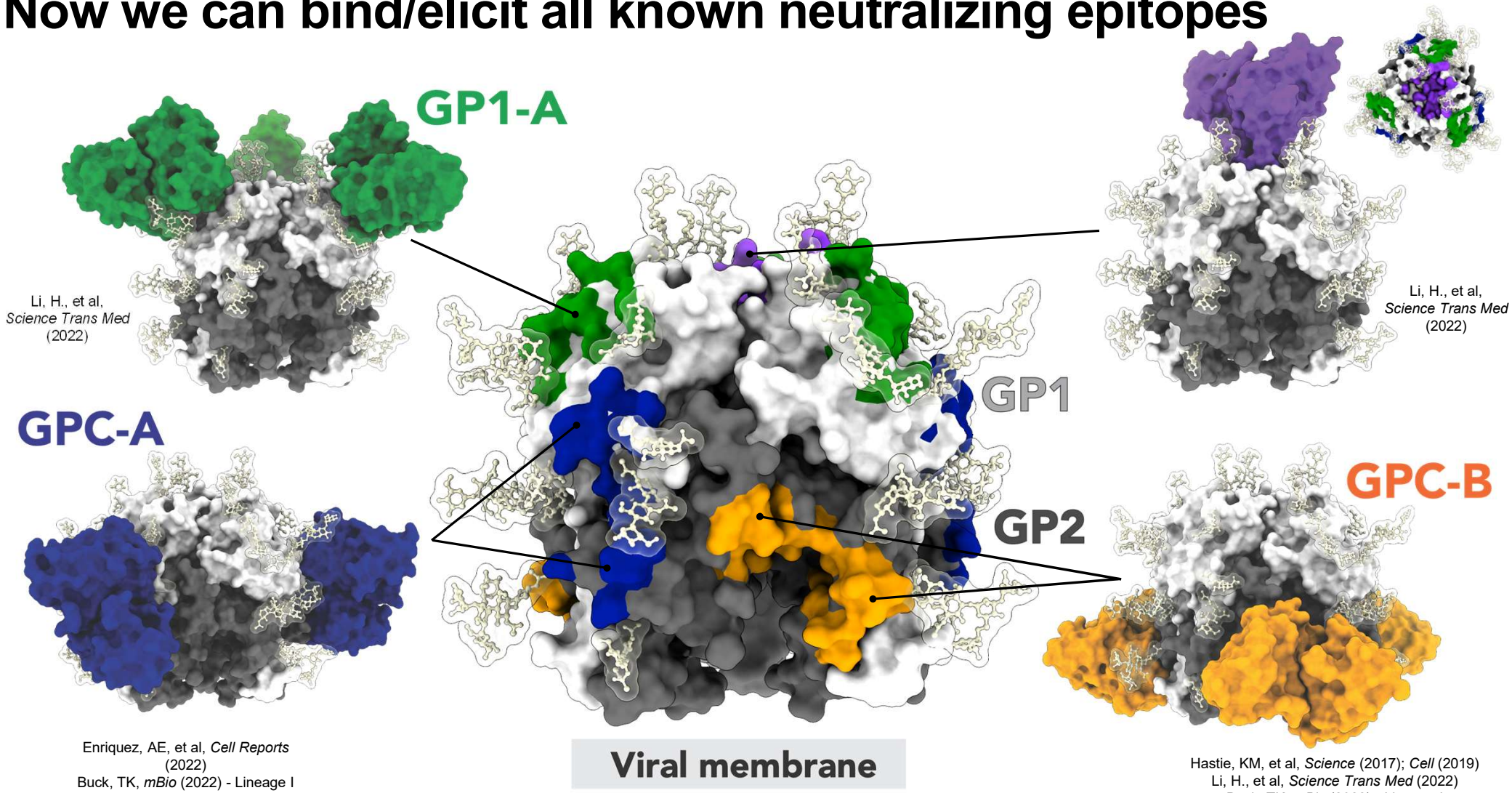
Version 1
Prefusion monomer

Version 2
Prefusion trimer



Version 3
Native-like
trimers

Now we can bind/elicit all known neutralizing epitopes

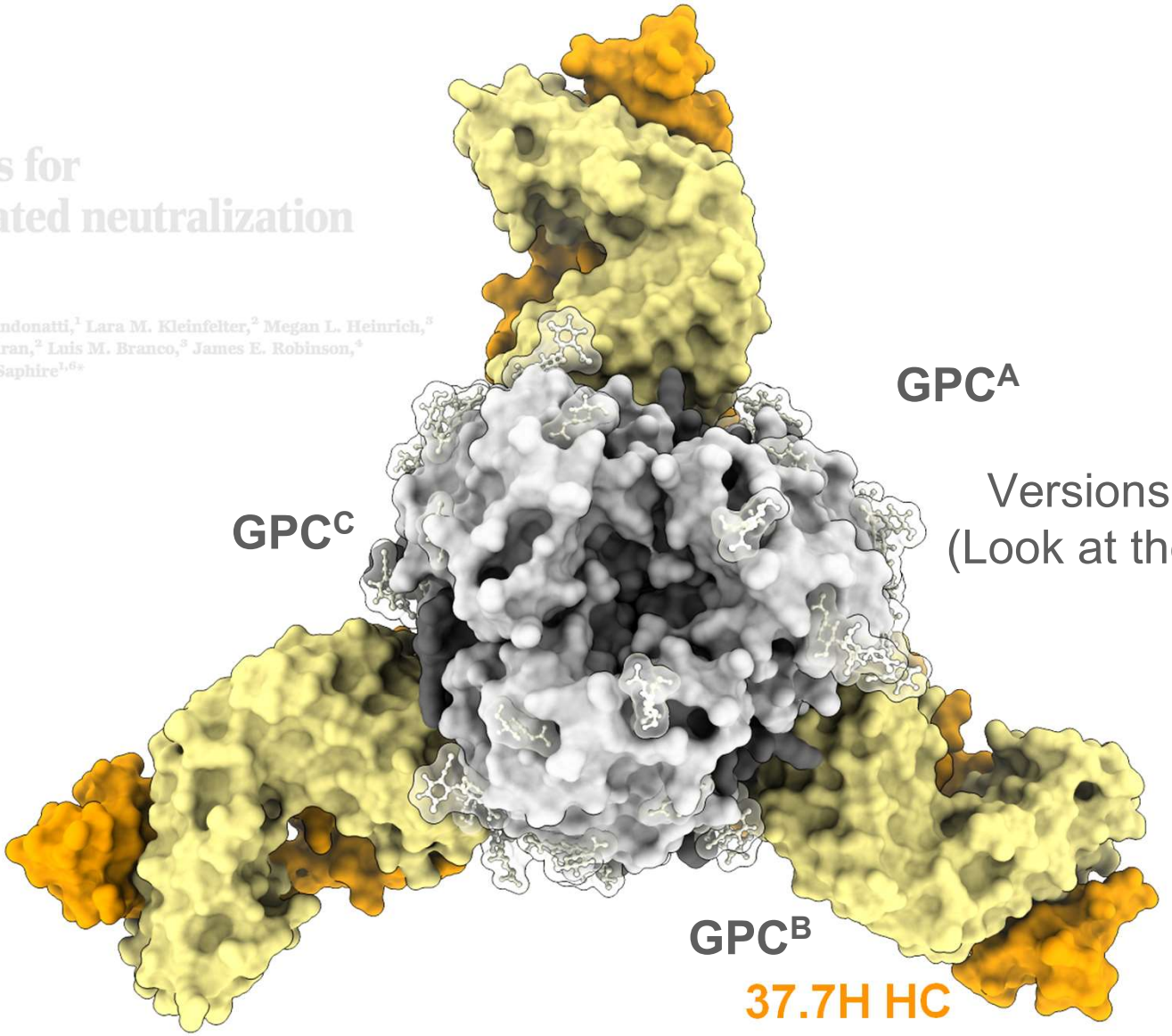


RESEARCH ARTICLE

STRUCTURAL BIOLOGY

Structural basis for antibody-mediated neutralization of Lassa virus

Kathryn M. Hastie,[1] Michelle A. Zandonatti,[1] Lara M. Kleinfelter,[2] Megan L. Heinrich,[3] Megan M. Rowland,[3] Kartik Chandran,[2] Luis M. Branco,[3] James E. Robinson,[4] Robert F. Garry,[3,5] Erica Ollmann Saphire[1,6]*



Versions 1,2
(Look at the top)

37.7H LC

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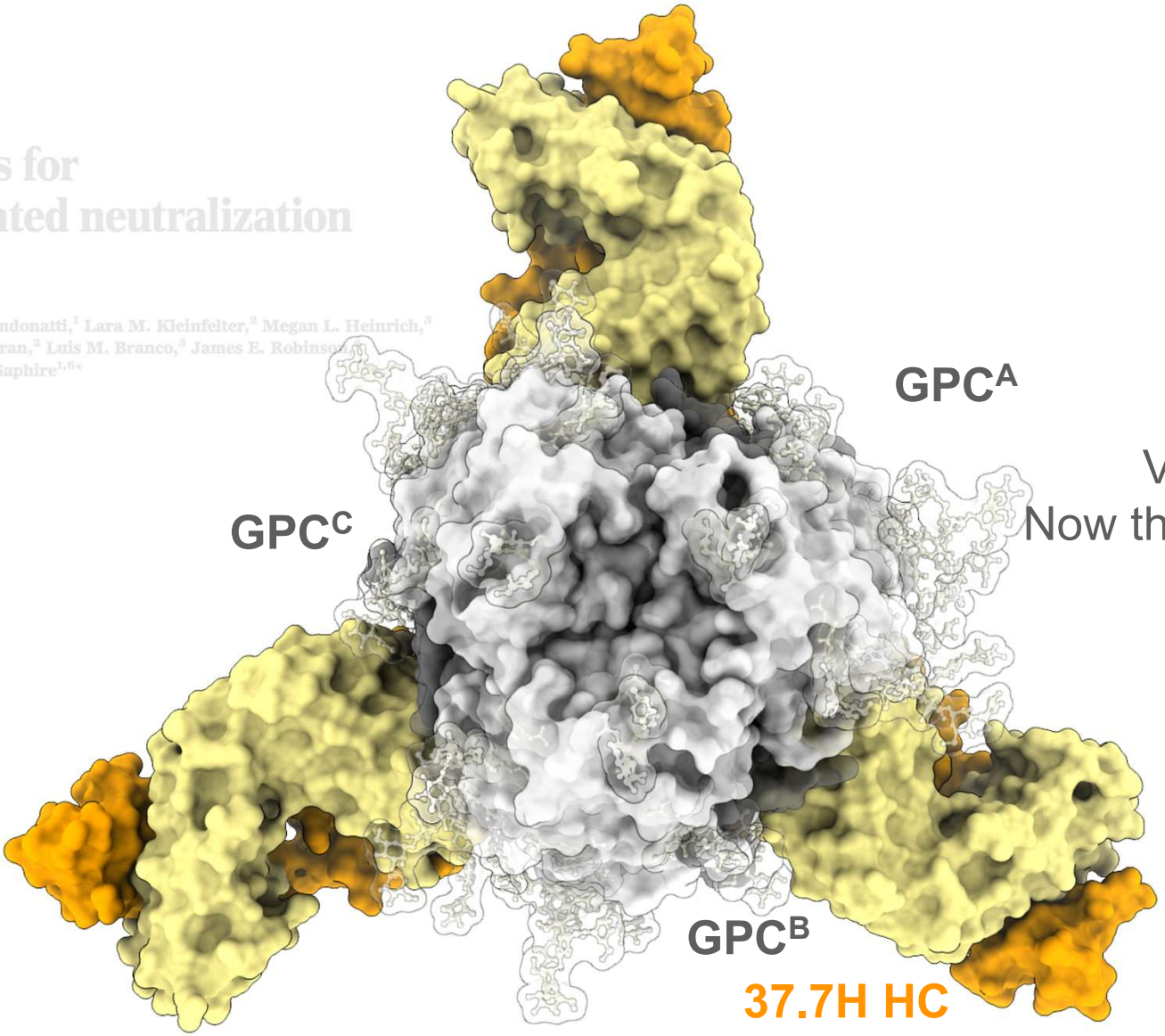

Version 3
Now the top is native

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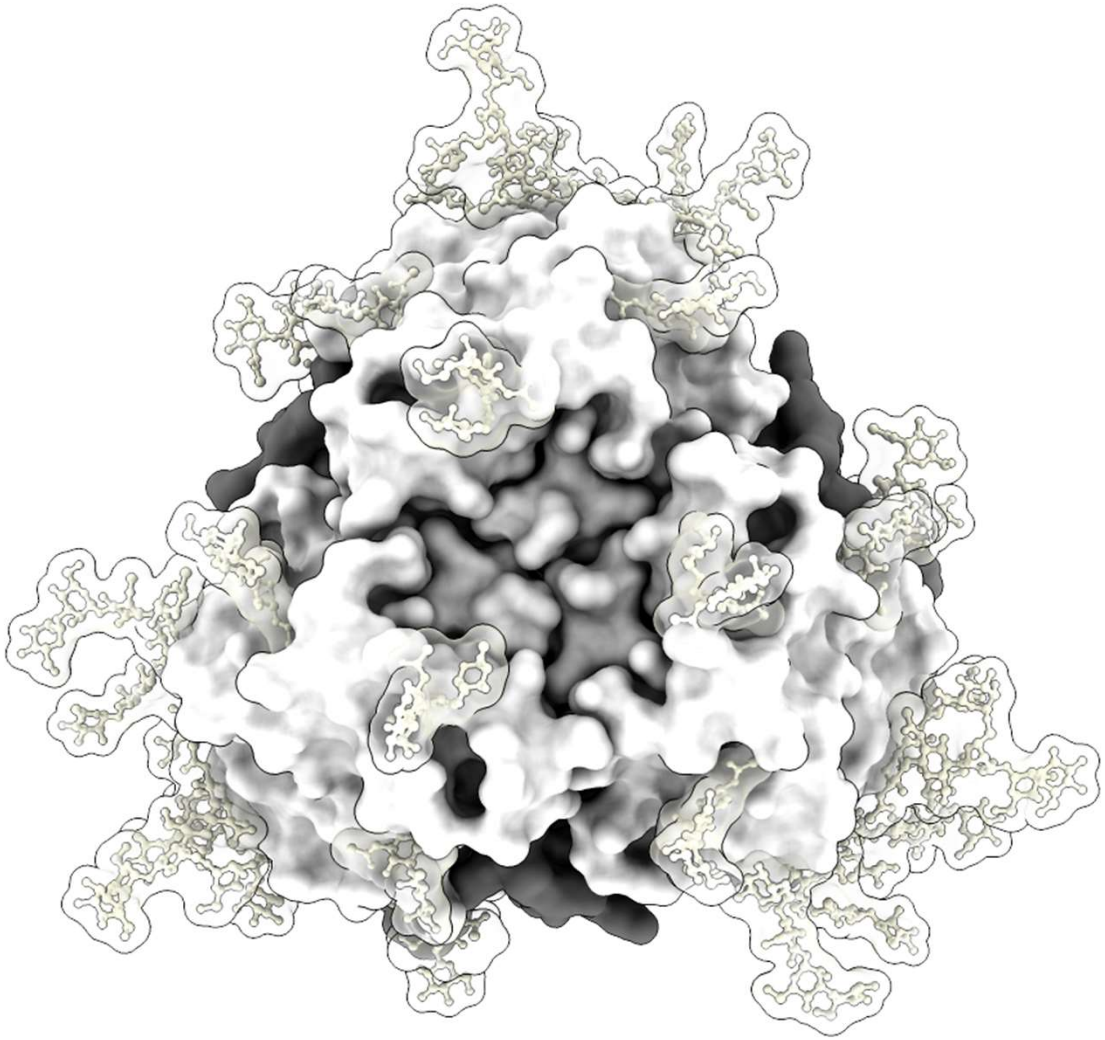
Native cleavage site stabilizes trimer apex



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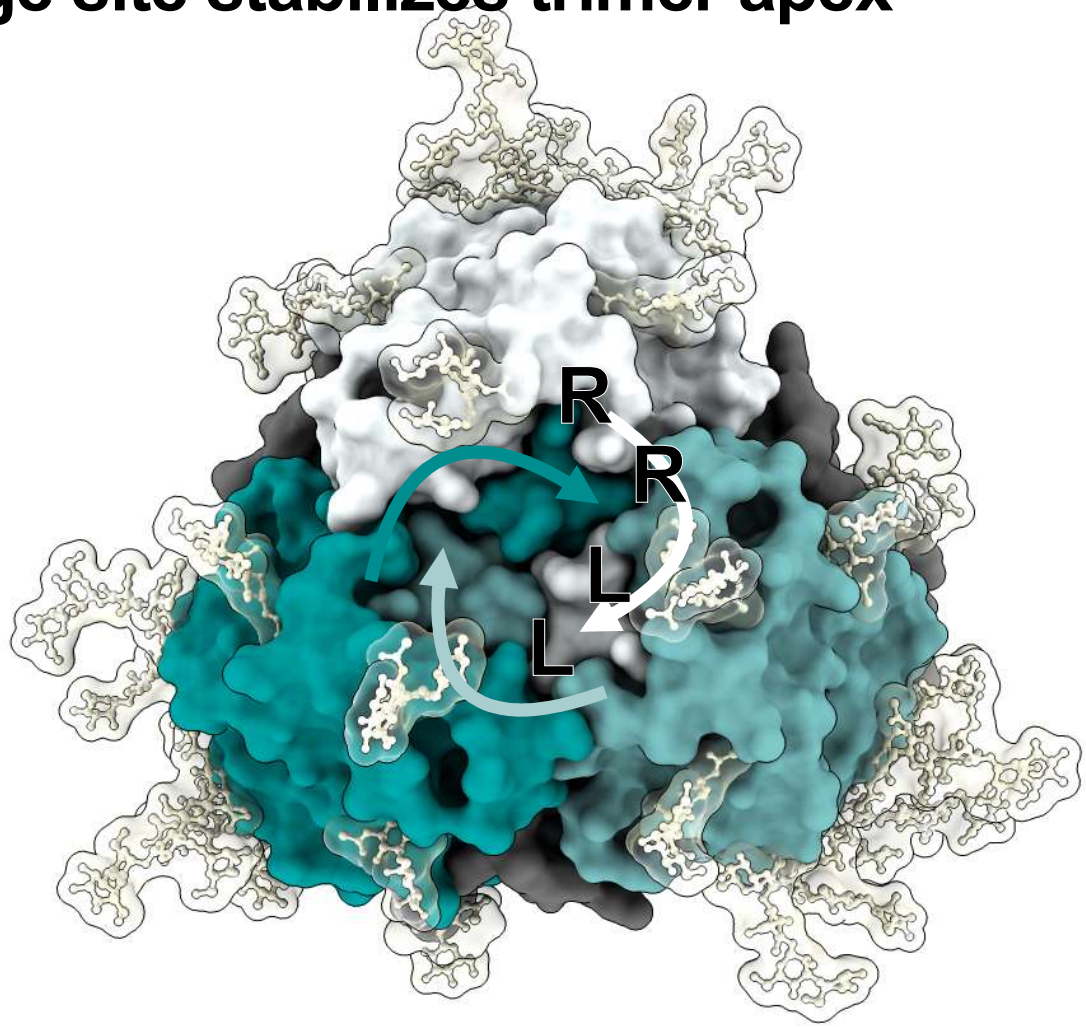
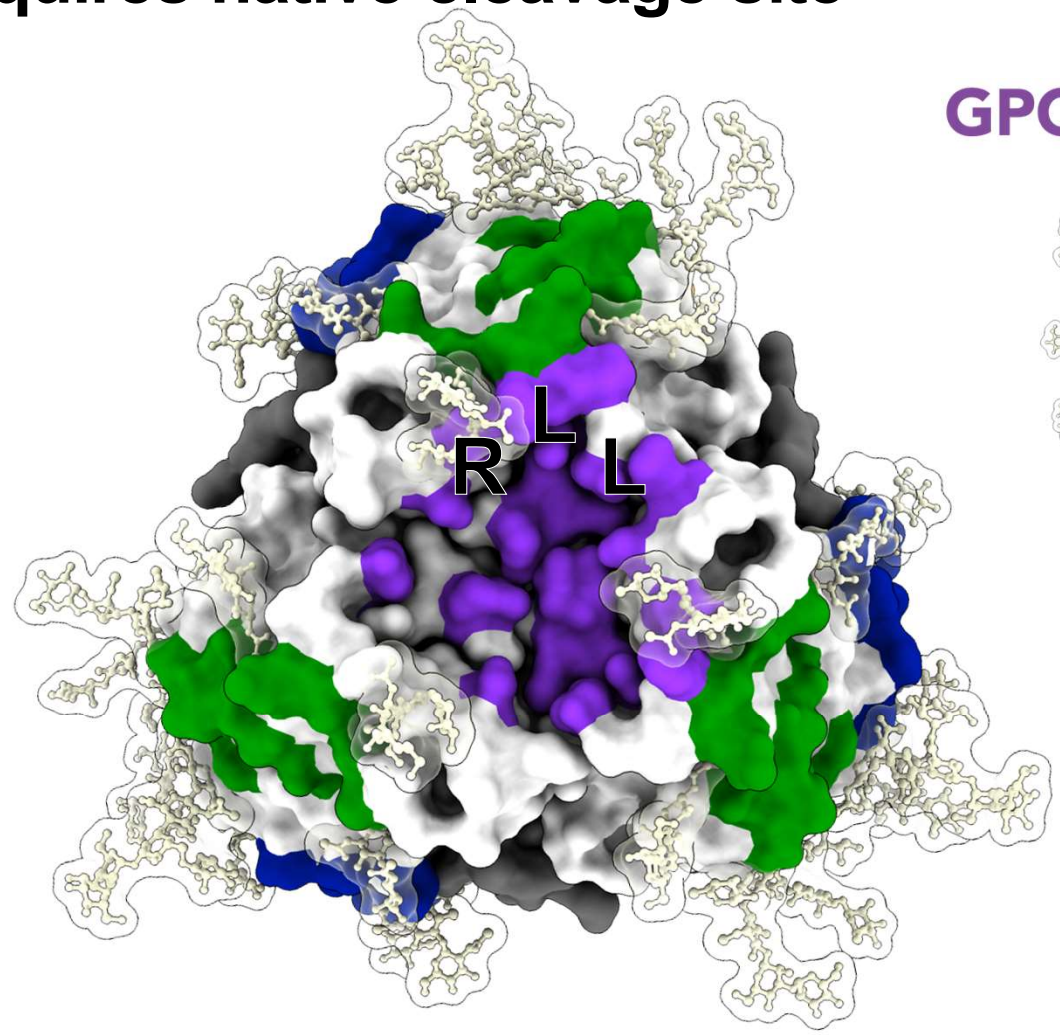
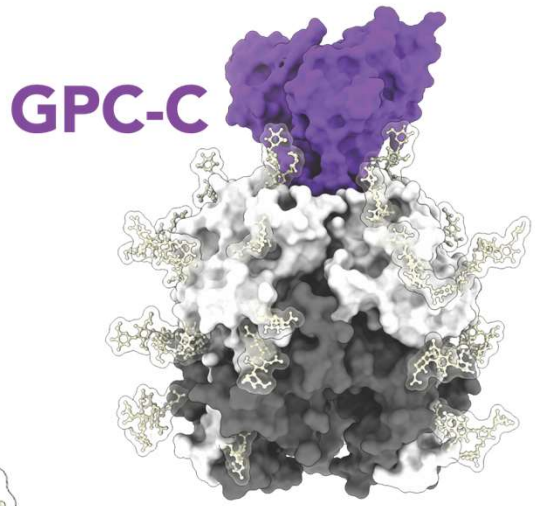
Native cleavage site stabilizes trimer apex



GPC-C nAb requires native cleavage site





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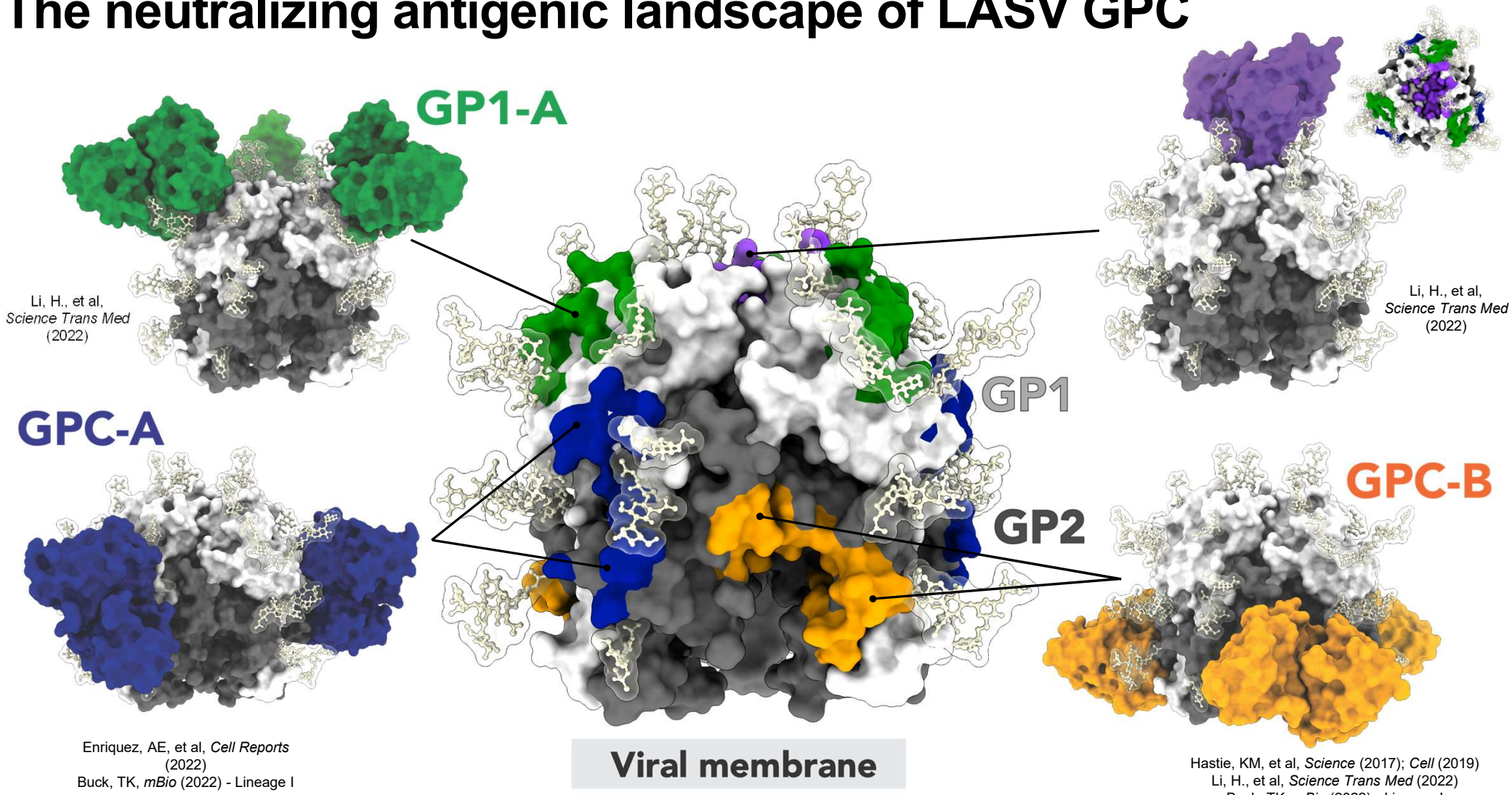
The neutralizing antigenic landscape of LASV GPC



How to elicit broadly neutralizing mAbs through vaccination?

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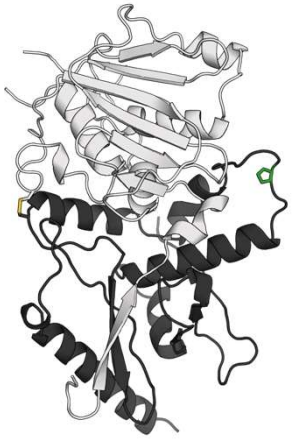
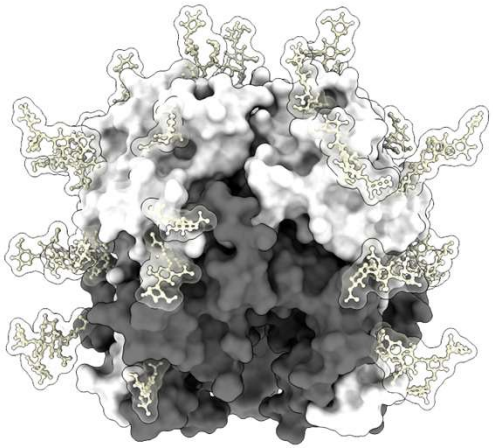
Lessons learned from 15 years of LASV GPC engineering and antibody analysis

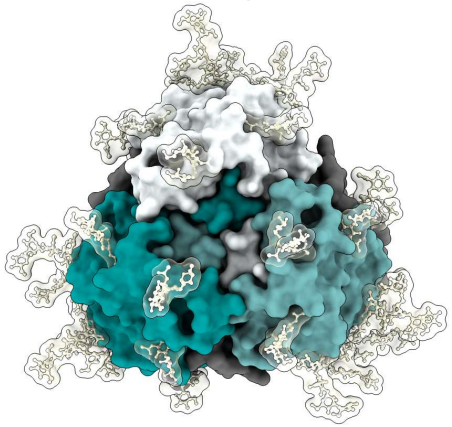
Stabilization of pre-fusion conformation



Trimerization and mammalian glycosylation



Native cleavage site



Version 3 GPC can now bind all known nAbs

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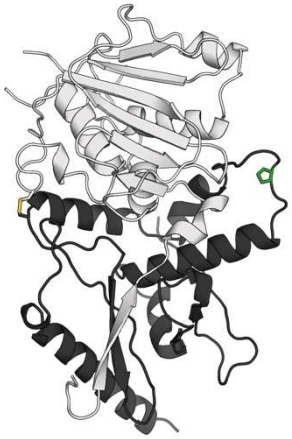
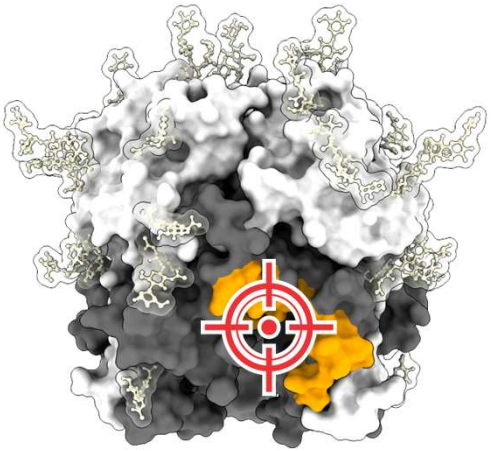
Lessons learned from 15 years of LASV GPC engineering and antibody analysis

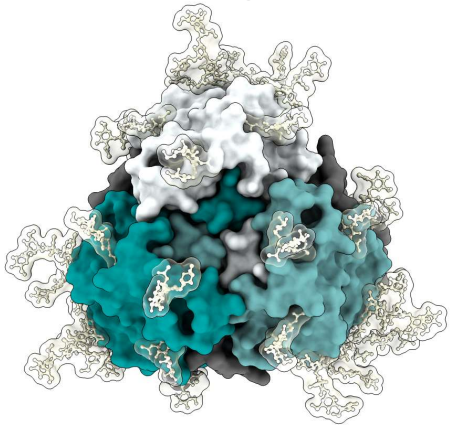
Stabilization of pre-fusion conformation



GPC-B epitope immunofocusing



Native cleavage site



Version 3 GPC can now bind all known nAbs

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Although protection is *possible*
without strong neutralizing antibody, by T cells alone…

Neutralizing antibodies, when present, are stunningly protective.
Plus, they are the only thing that could prevent an infection.

We now have an antigen to elicit them.

Adding neutralizing antibody on top of T cell is the best approach.

Essentially all approved vaccines for other viruses
have neutralizing antibody as their primary correlate of protection.

Current Lassa vax candidates: weak or non-neutralizing antibody.

We can improve all of these with the right-shaped GPC.

La Jolla Institute for Immunology
Erica Ollmann Saphire, Ph.D. MBA. **erica@lji.org**
Kathryn Hastie, Ph.D. **kmhastie@lji.org**
Haoyang Li, Ph.D. **haoyangli@lji.org**

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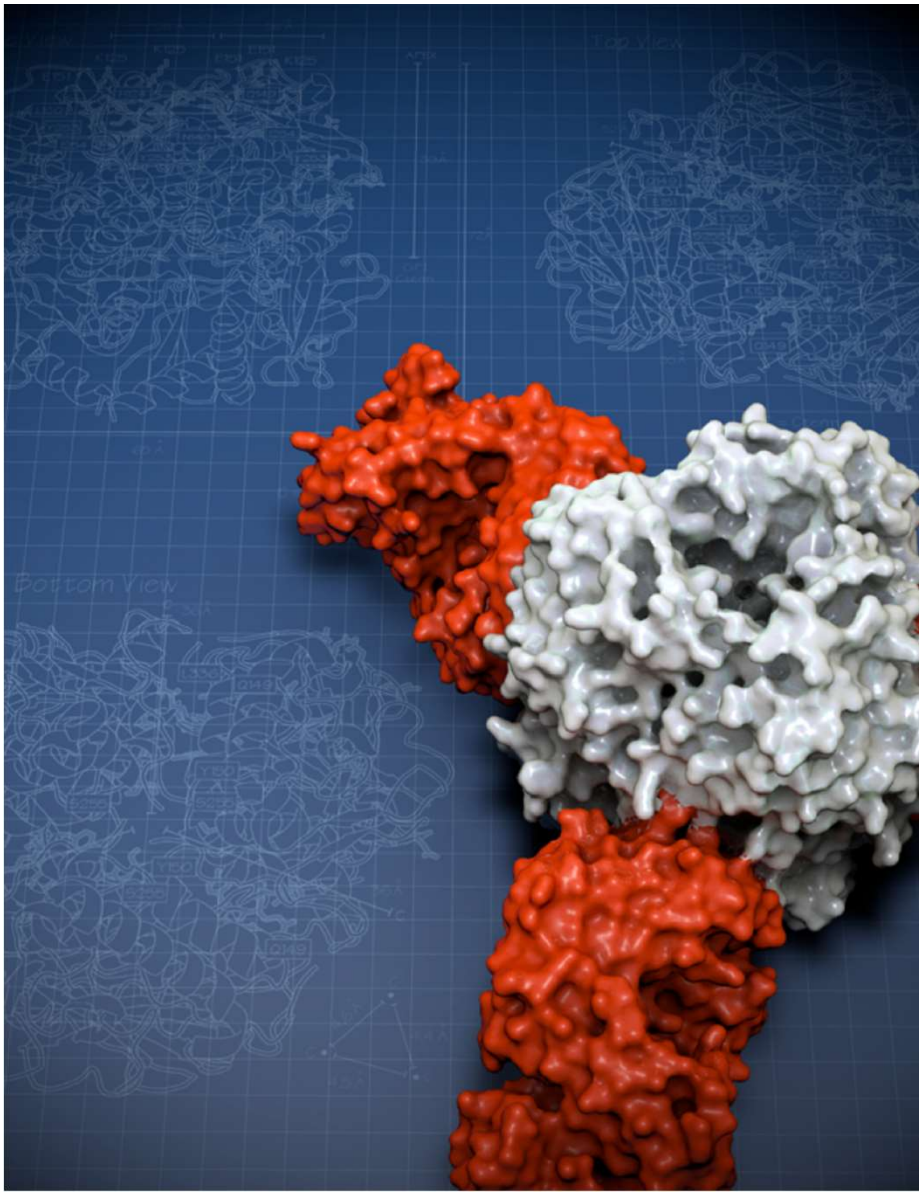

With thanks

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James Robinson

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Luis Branco
Anatoliy Koval
Megan Rowland
Megan Heinrich

Kenema Government Hospital

VIRAL HEMORRHAGIC FEVER CONSORTIUM

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