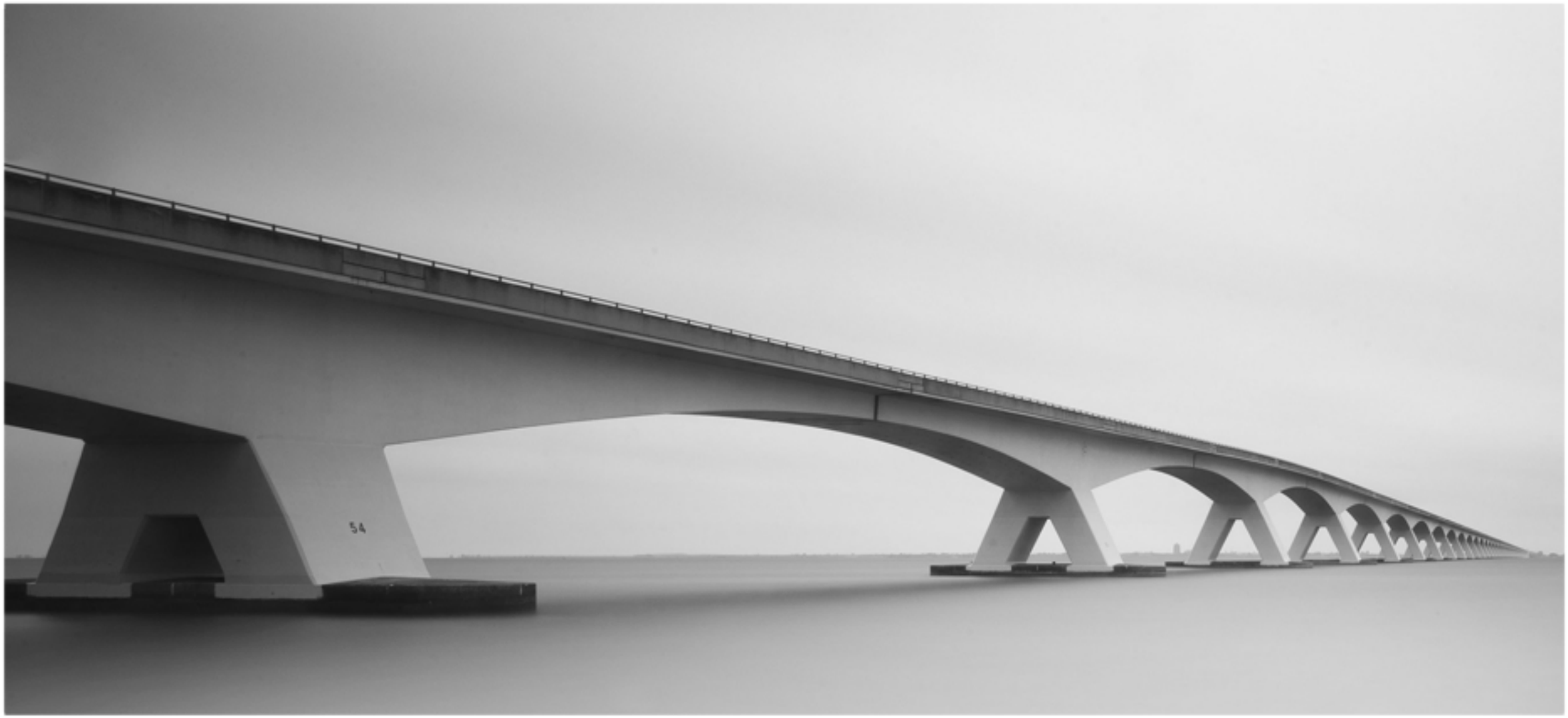

Zika virus NS1: association with virus infection and immune system

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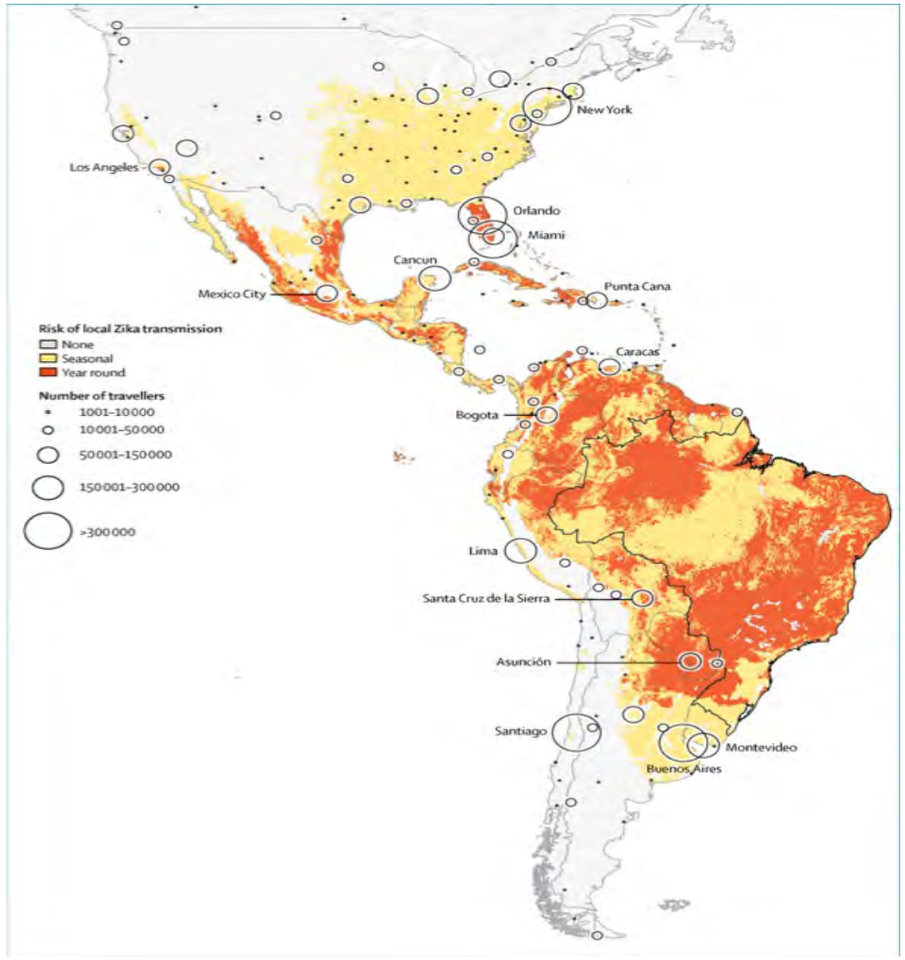
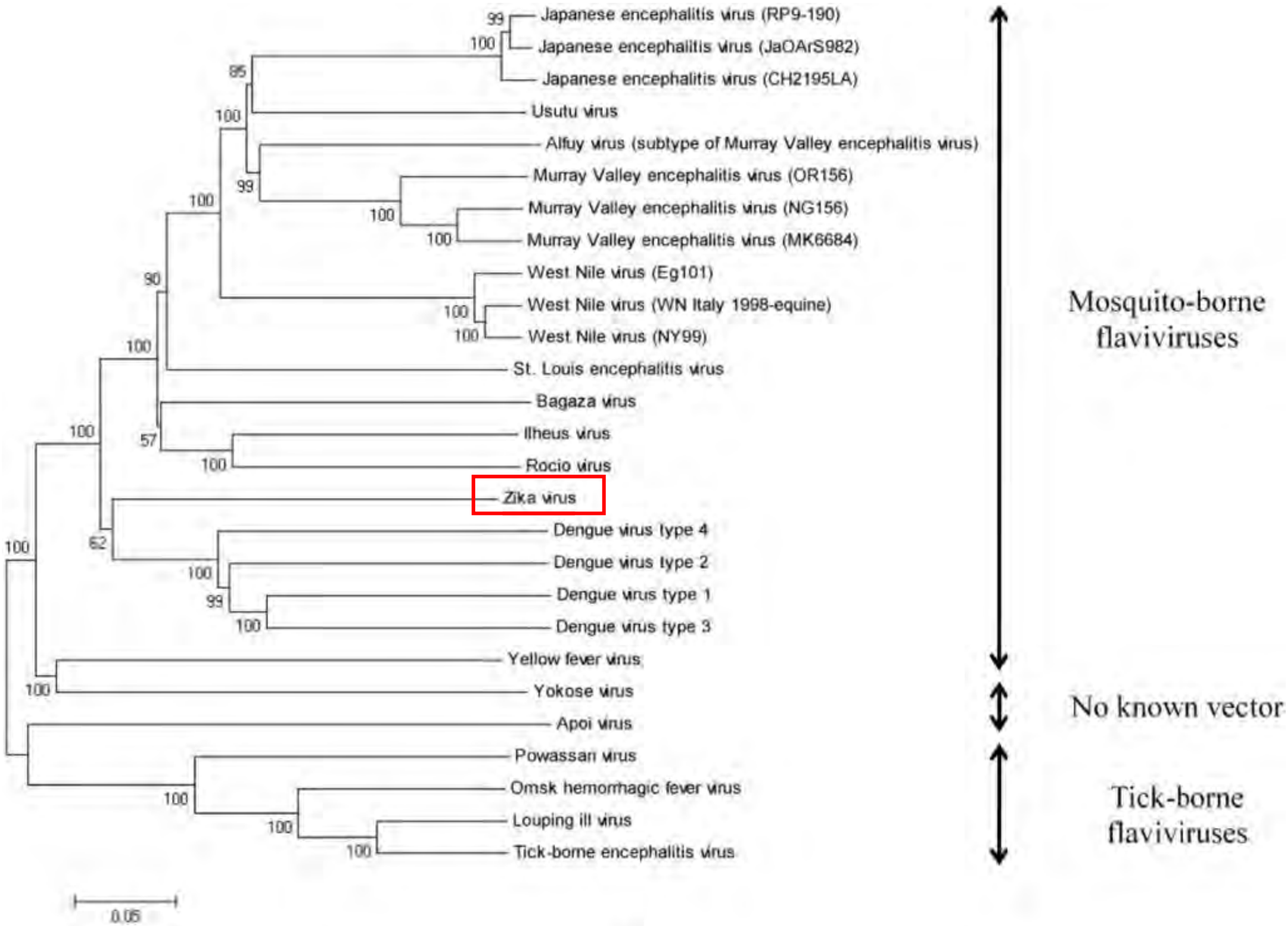
What is Zika virus?

- **Zika virus belongs to flavivirus family**
- **Transmission mainly by Aedes aegypti**
- **Clinical syndrome: fever, maculopapular rash, conjunctivitis, joint pain**
- **Classified into African and Asian genotypes by phylogenetic analysis**



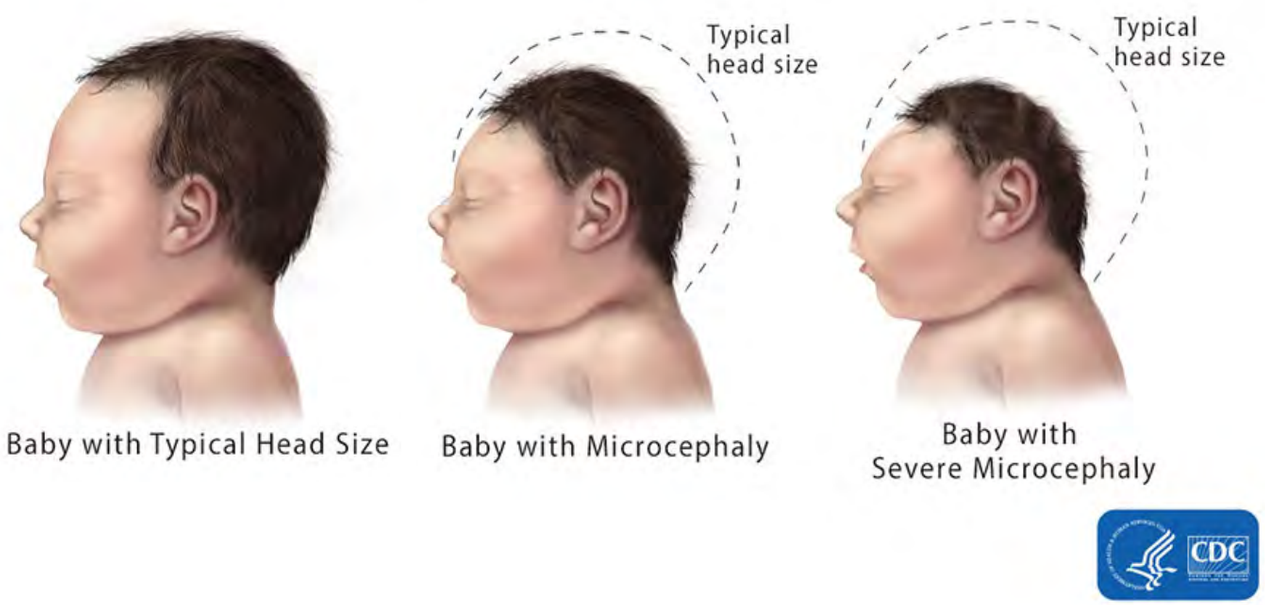
Zika virus -- “brother” of dengue virus



ZIKV infection

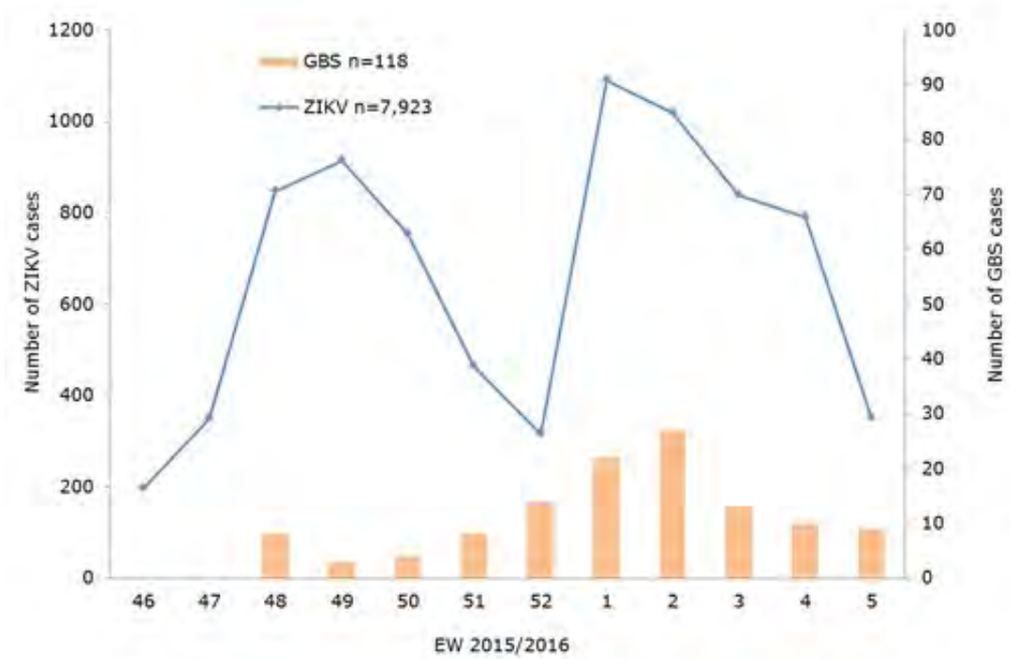
Microcephaly

Guillian-Barre Syndrome (GBS)



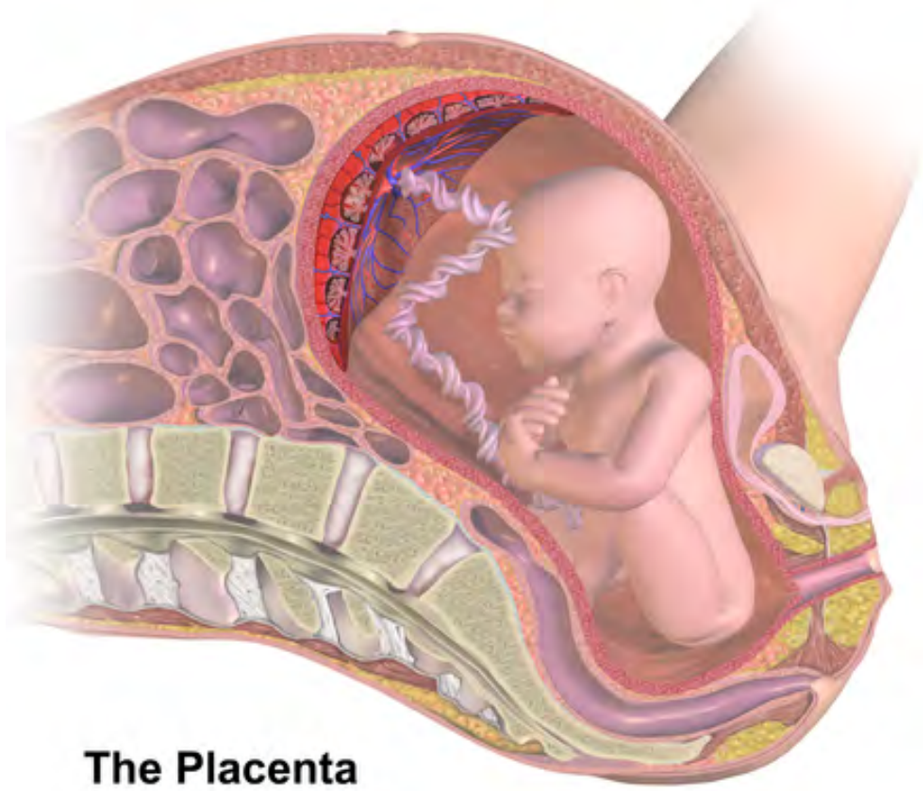
Cases of ZIKV and GBS, Colombia. EW 40/2015- 4/2016
(from Ministry of Health of Colombia)

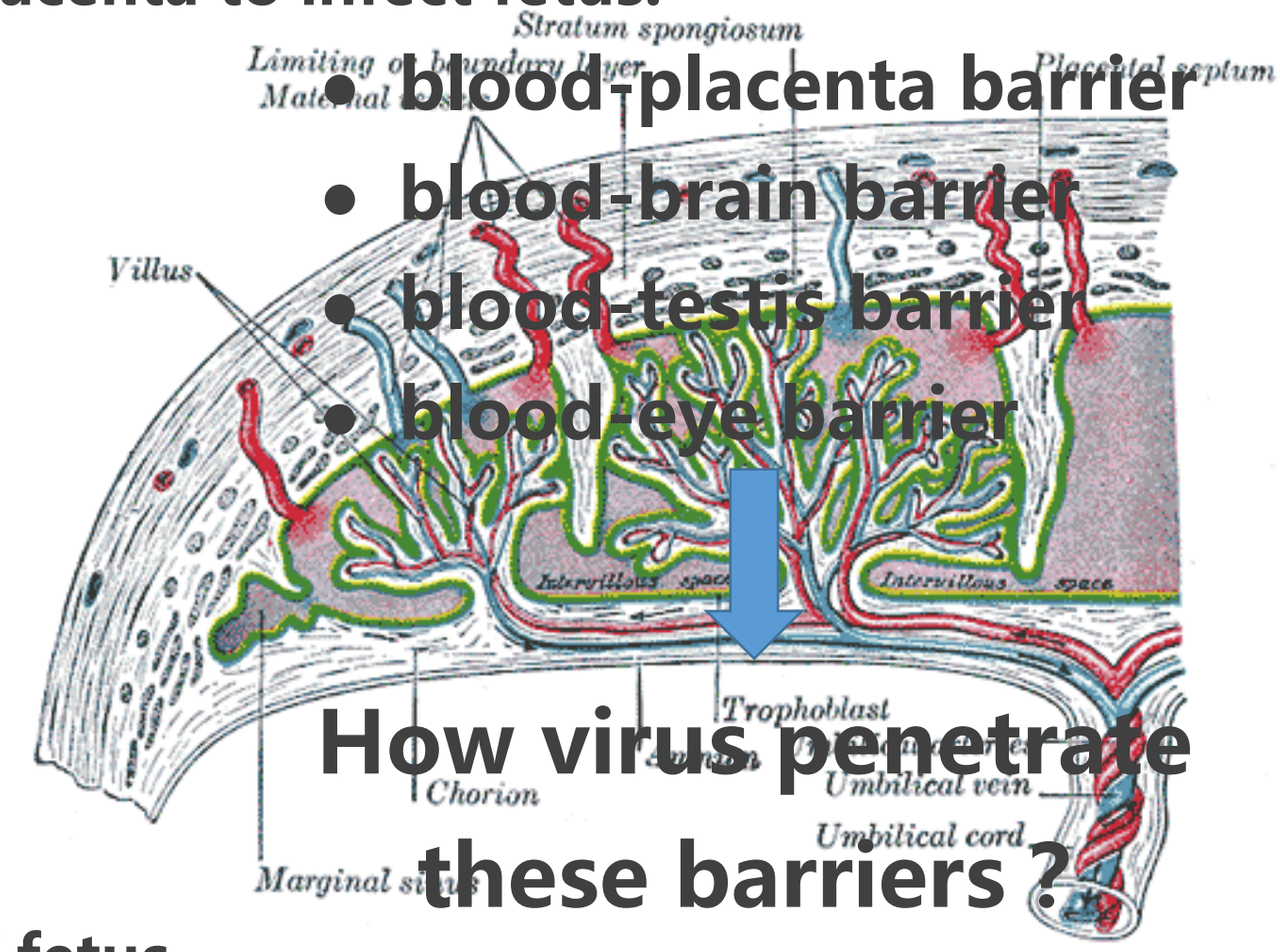
Cases of ZIKV and GBS, El Salvador. EW 48/2015- 5/2016
(from Ministry of Health of El Salvador)



Zika virus exists in immune-tolerant regions

- **The structure of placenta determines that the material exchange between mother and fetus is indirect.**
- **Zika virus must penetrate the placenta to infect fetus.**

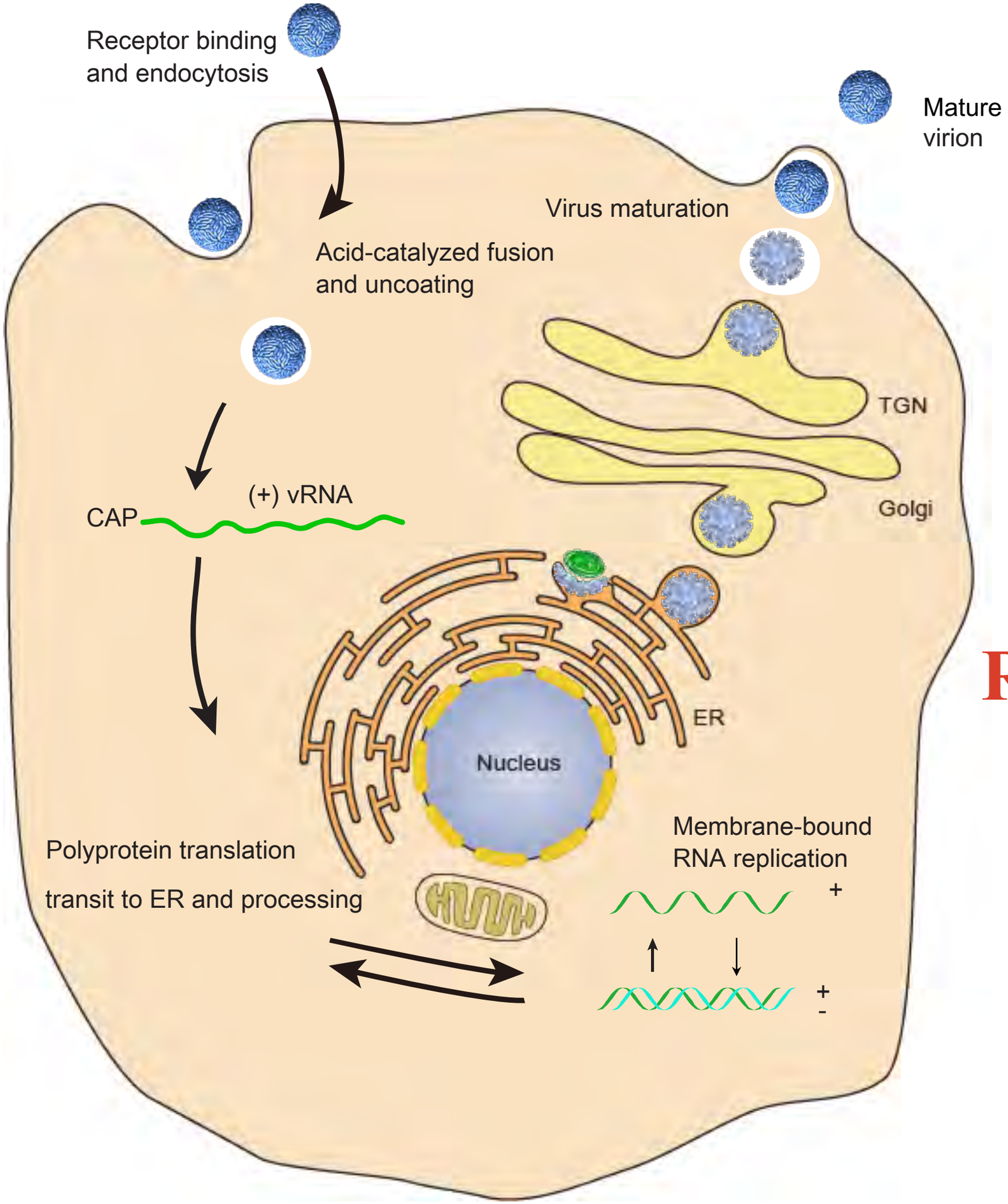




- **blood-placenta barrier**
- **blood-brain barrier**
- **blood-testis barrier**
- **blood-eye barrier**

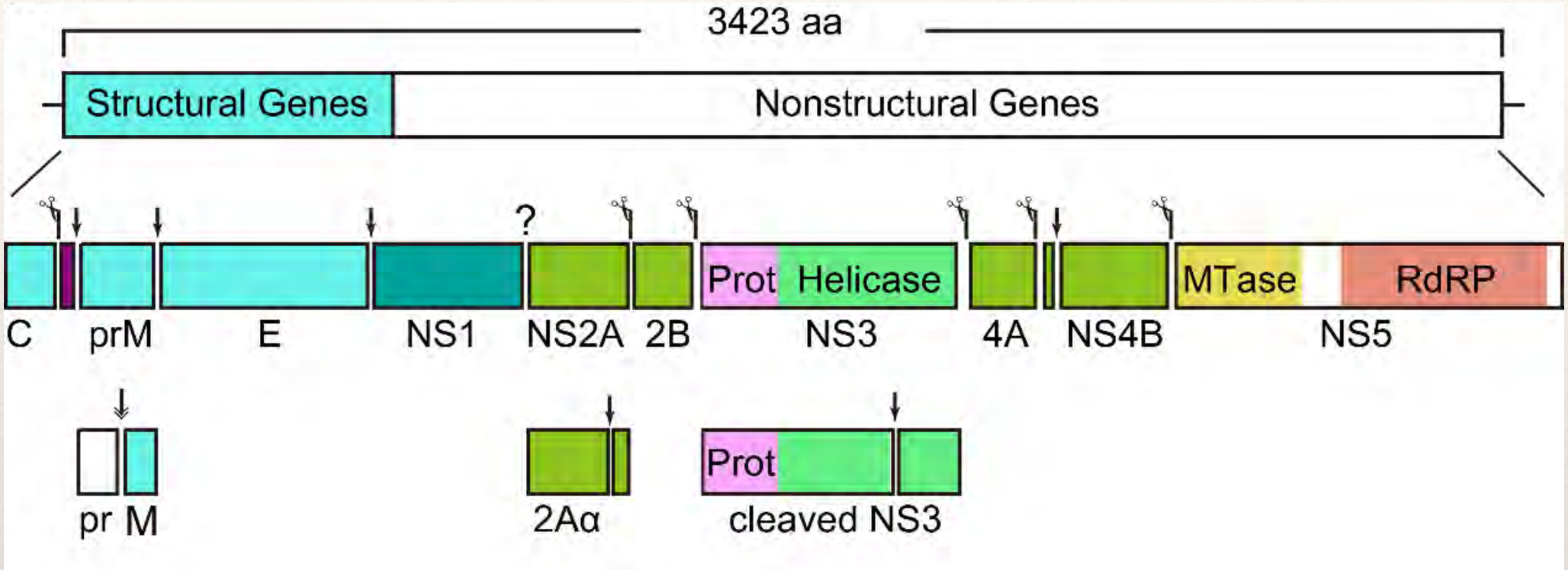
How virus penetrate these barriers ?

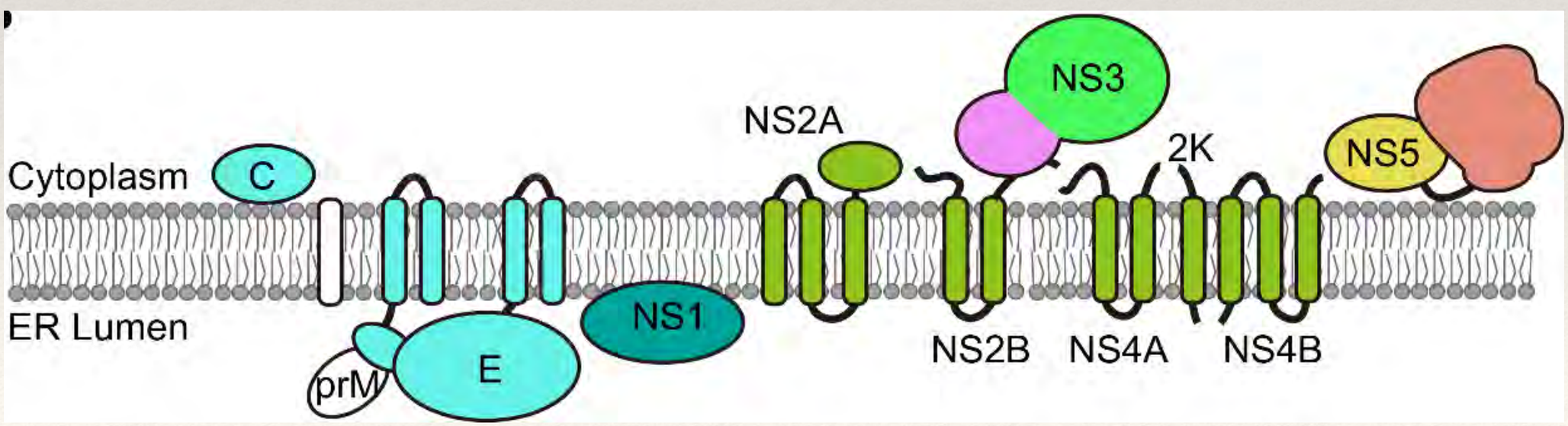
- **Zika virus was found in the brain of fetus.**
- **Zika virus was also found in semen, lasting for a long time, and also in eyes.**



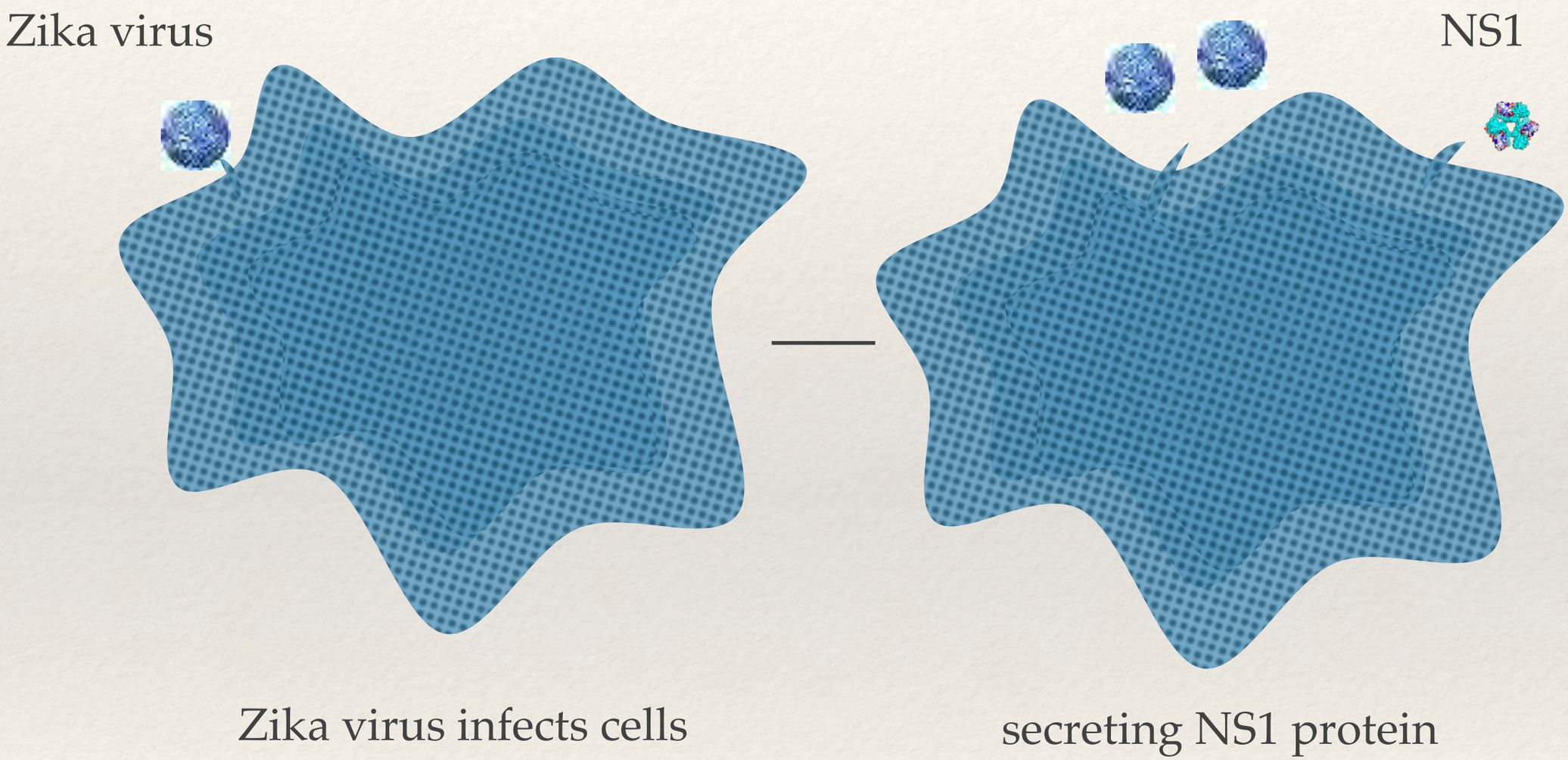
Replication cycle of flavivirus

Genome and polyprotein of Zika virus

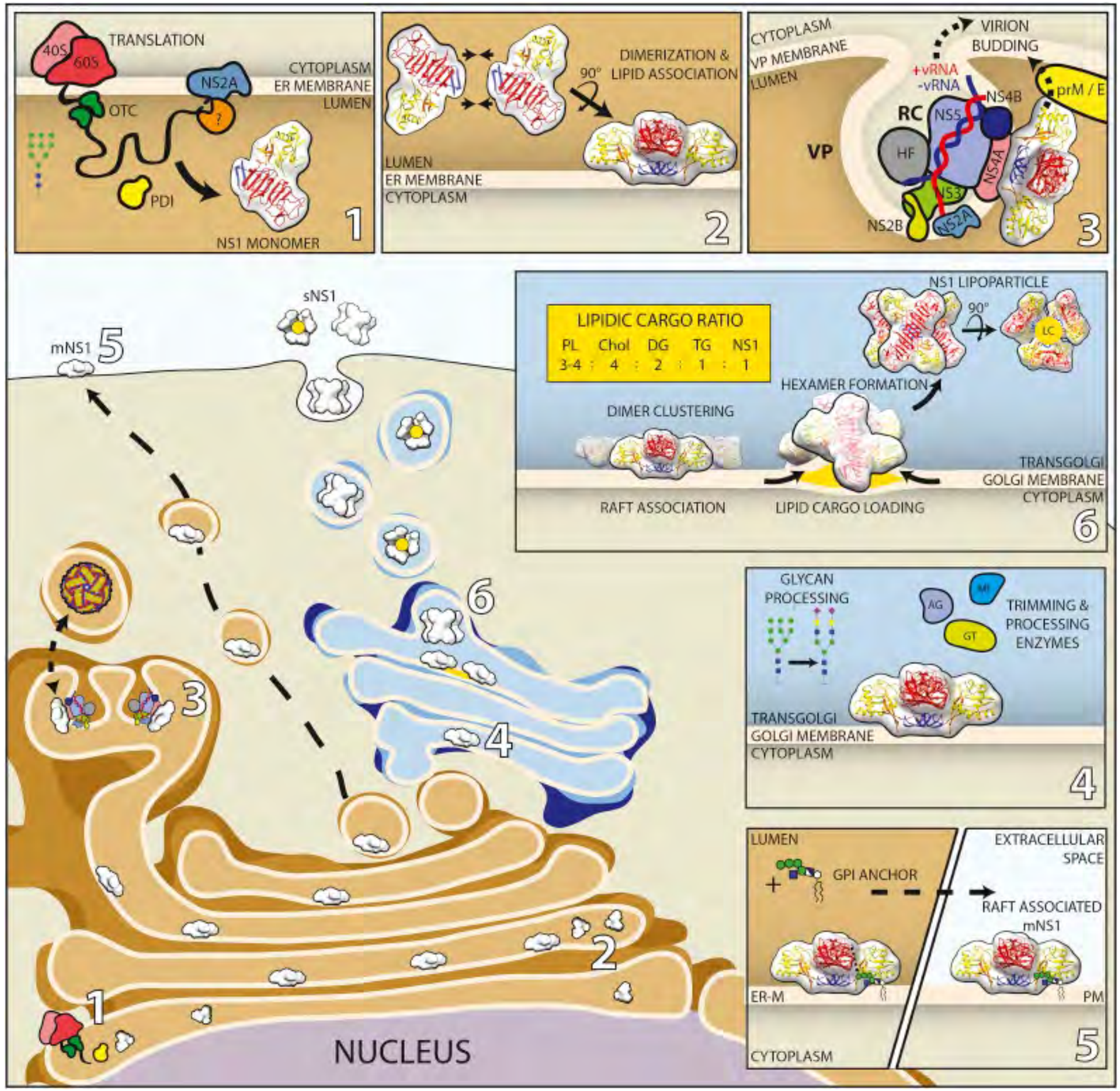




Zika virus NS1 protein and disease pathogenesis



NS1 within the infected cell



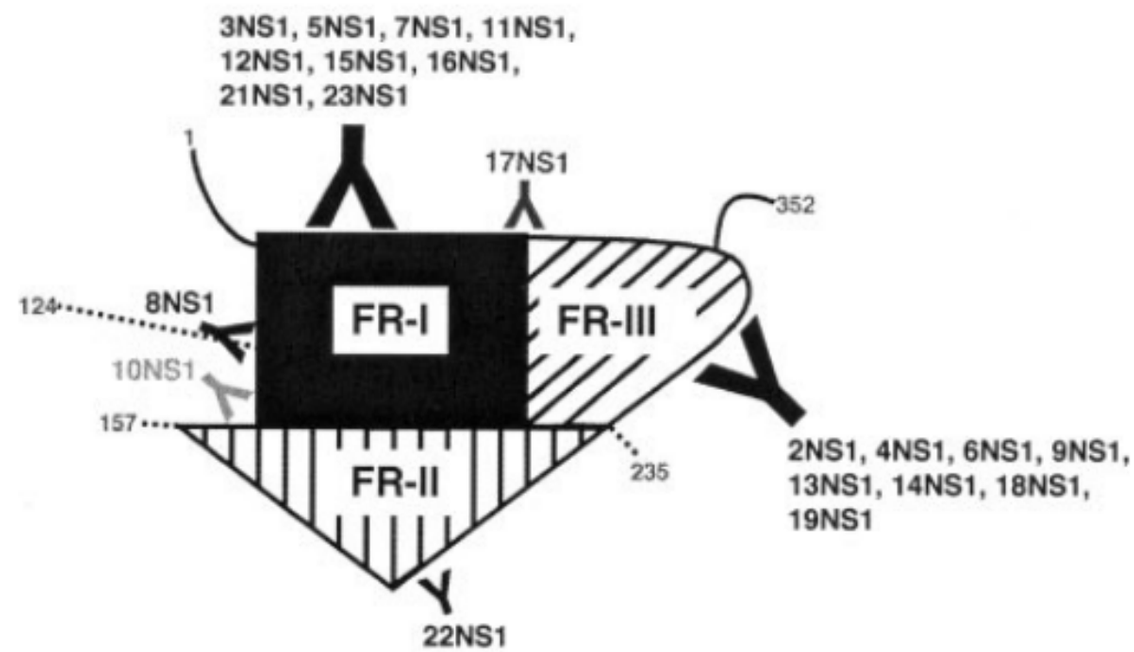
Watterson, D., N. Modhiran, and P.R. Young, *The many faces of the flavivirus NS1 protein offer a multitude of options for inhibitor design. Antiviral Res, 2016.* ***130: p. 7-18.***

Protective anti-NS1 mAbs to WNV infection

Protective activity of anti-NS1 MAbs

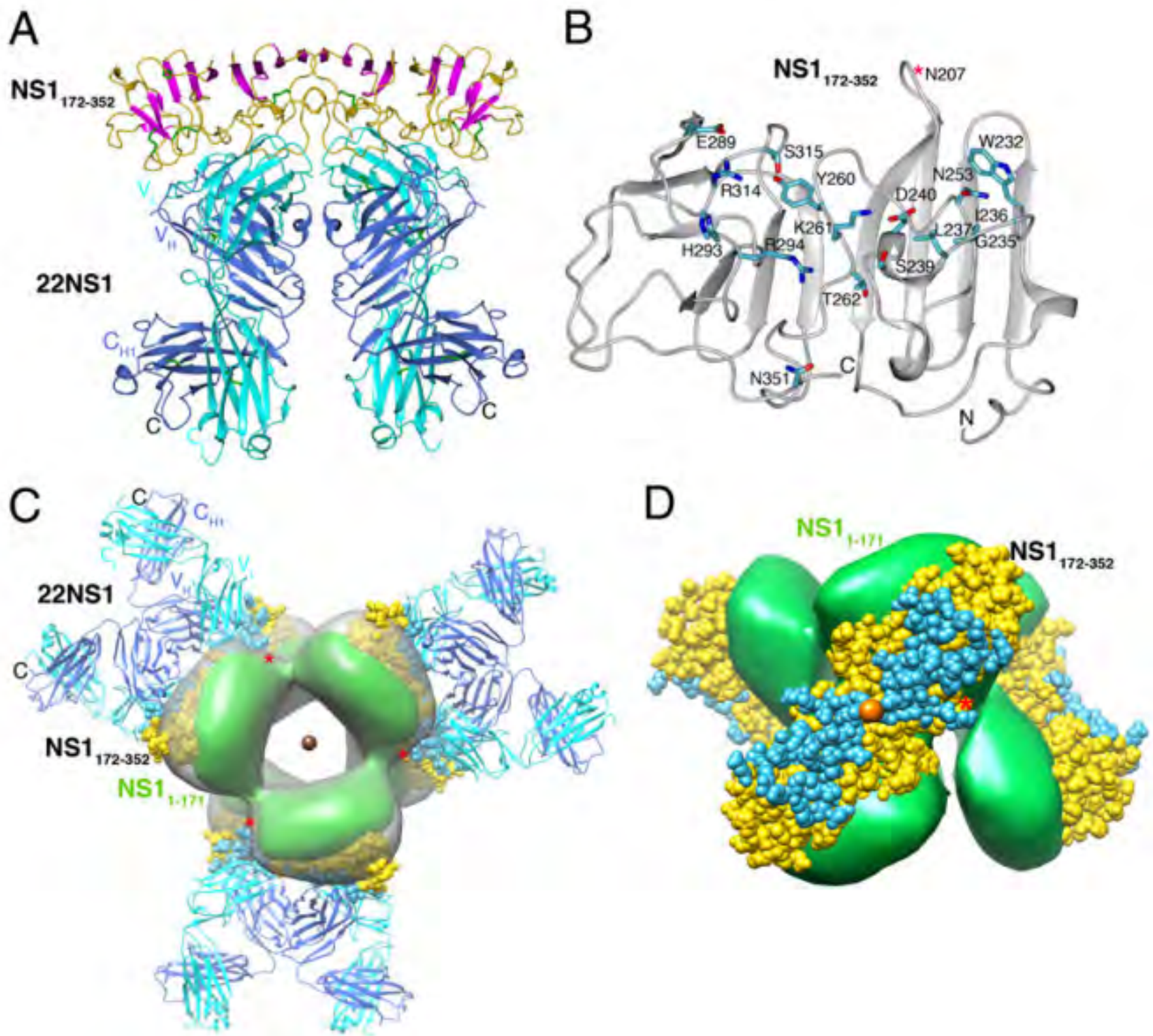
Antibody or control	% Surviving mice	No. of mice	*P* value	Antibody source
PBS	17	60		
1NS1	25	20	0.29	PUR
2NS1	40	10	0.09	ASC
3NS1	50	10	0.02*	PUR
4NS1	50	10	0.02*	PUR
5NS1	40	10	0.10	ASC
6NS1	20	10	0.93	ASC
7NS1	0	10	0.66	ASC
8NS1	20	10	0.50	ASC
9NS1	40	10	0.15	ASC
10NS1	75	20	0.0001*	ASC/PUR
11NS1	50	10	0.04*	ASC
12NS1	10	10	0.95	ASC
13NS1	30	10	0.30	ASC
14NS1	95	40	<0.0001*	ASC/PUR
15NS1	0	10	0.74	ASC
16NS1	90	10	0.0001*	ASC
17NS1	75	20	<0.0001*	PUR
18NS1	10	10	0.14	ASC
19NS1	20	10	0.36	ASC
21NS1	40	10	0.27	ASC
22NS1	70	10	0.004*	ASC
23NS1	0	10	0.21	ASC

The topography of WNV NS1 and antibody binding sites



Chung, K.M., et al., *Antibodies against West Nile virus nonstructural protein NS1 prevent lethal infection through Fc gamma receptor-dependent and -independent mechanisms. Journal of Virology, 2006.* ***80(3): p. 1340-1351.***

Structure of WNV NS1$_{172–352}$ in complex with 22NS1 Fab

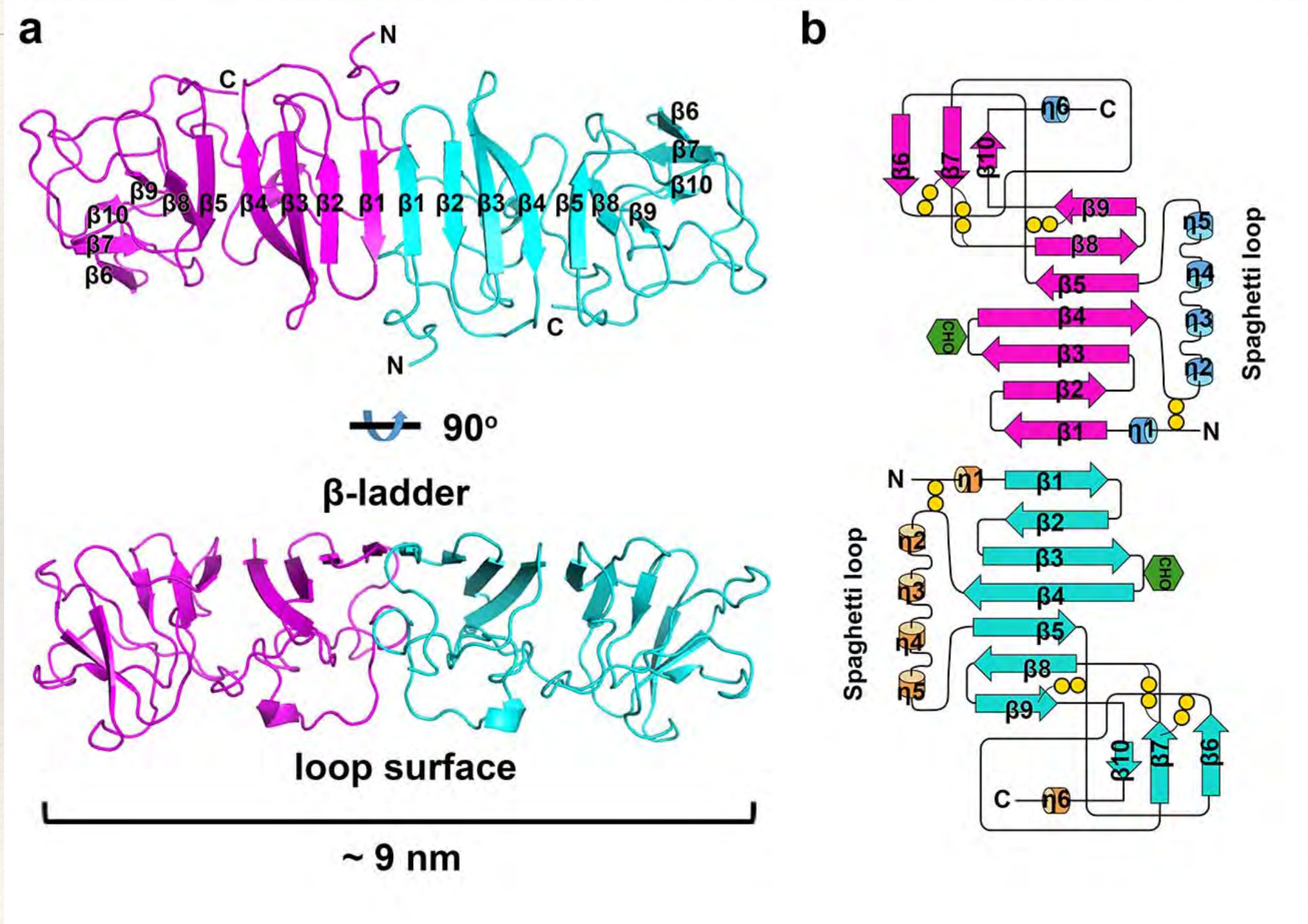


Edeling, M.A., M.S. Diamond, and D.H. Fremont, *Structural basis of Flavivirus NS1 assembly and antibody recognition. PNAS, 2014.* ***111(11): p. 4285-90.***

What can ZIKV NS1 structure tell us?

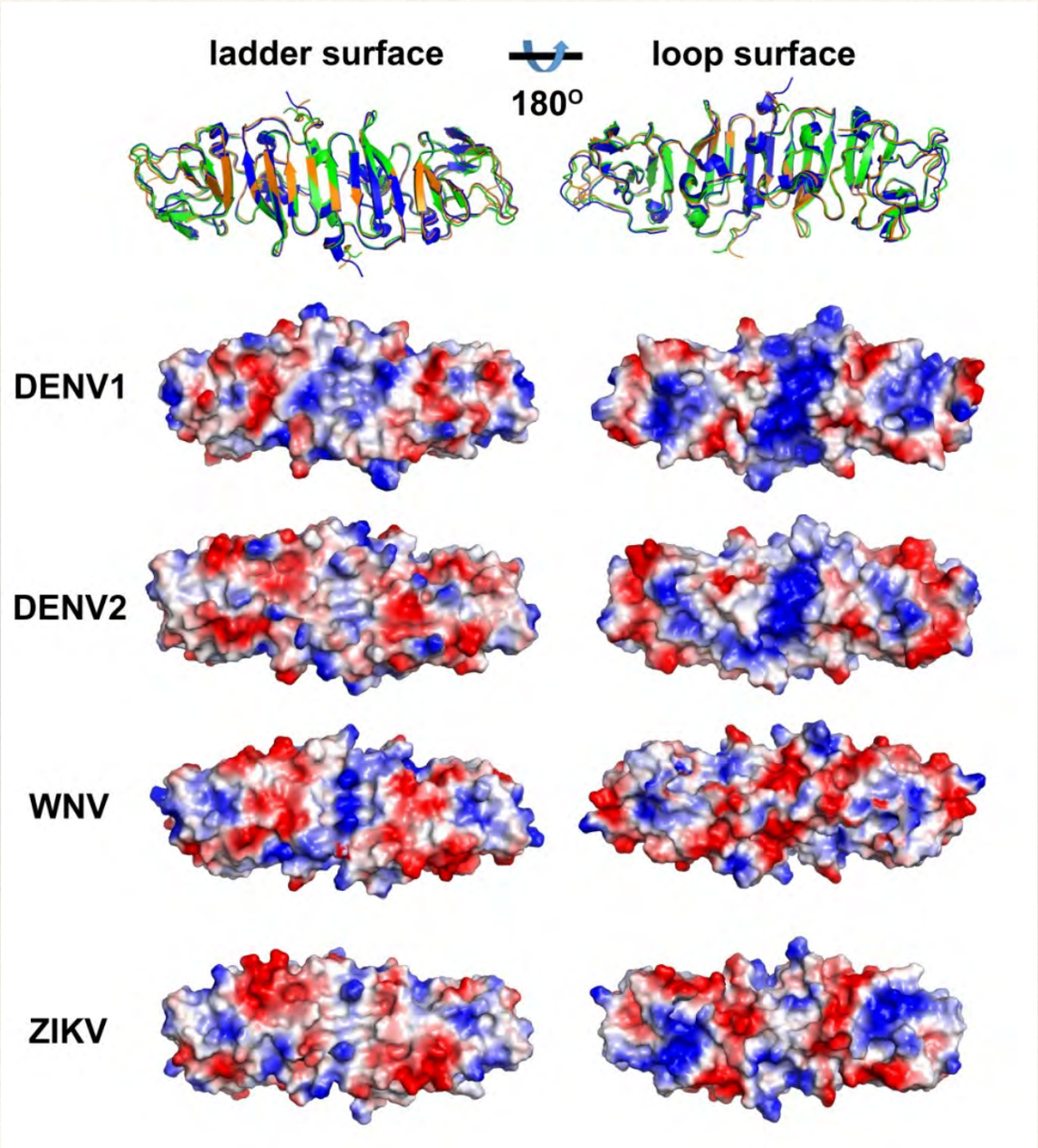
- Electrostatic potential map: affect the host interaction
- Membrane association site
- Vulnerable sites for development of diagnostic tools

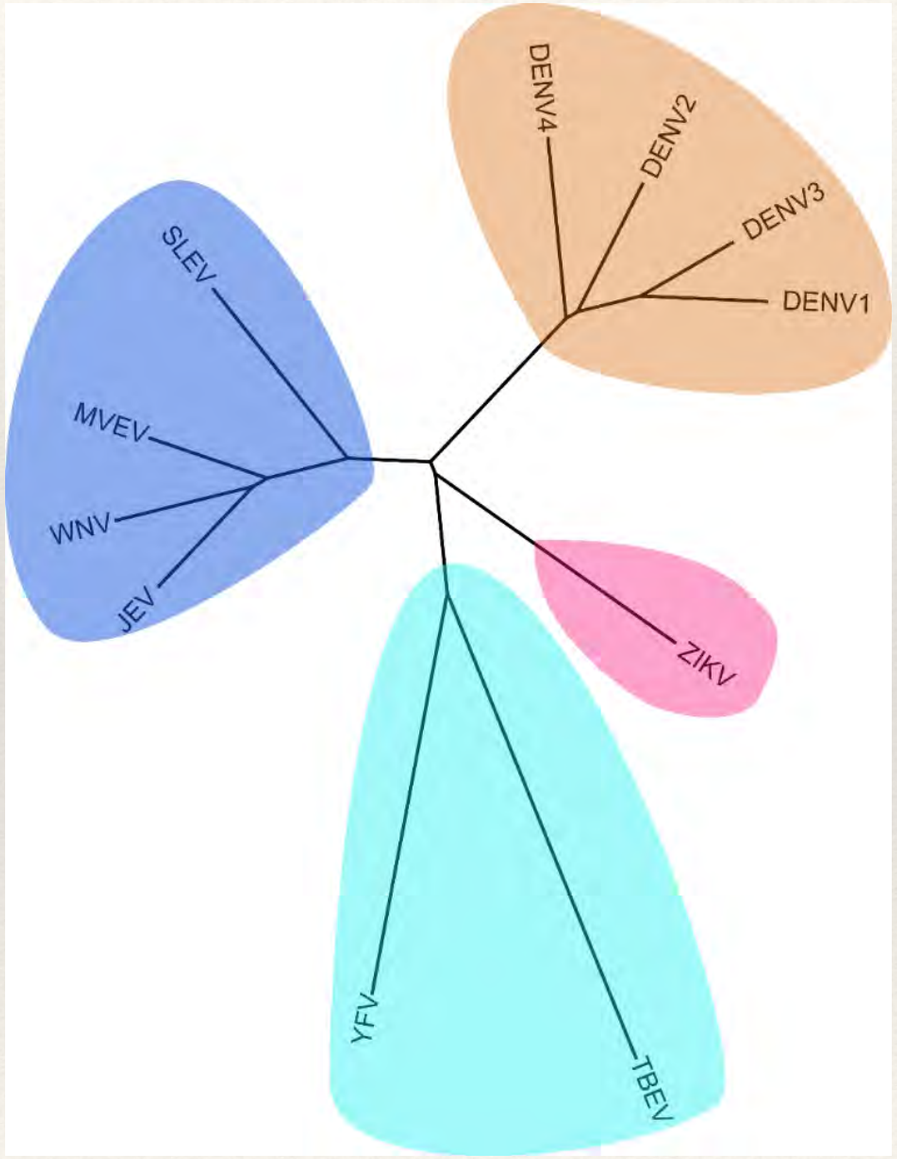
Crystal structure of Zika NS1(172-352)



Nature Structural & Molecular Biology. 2016

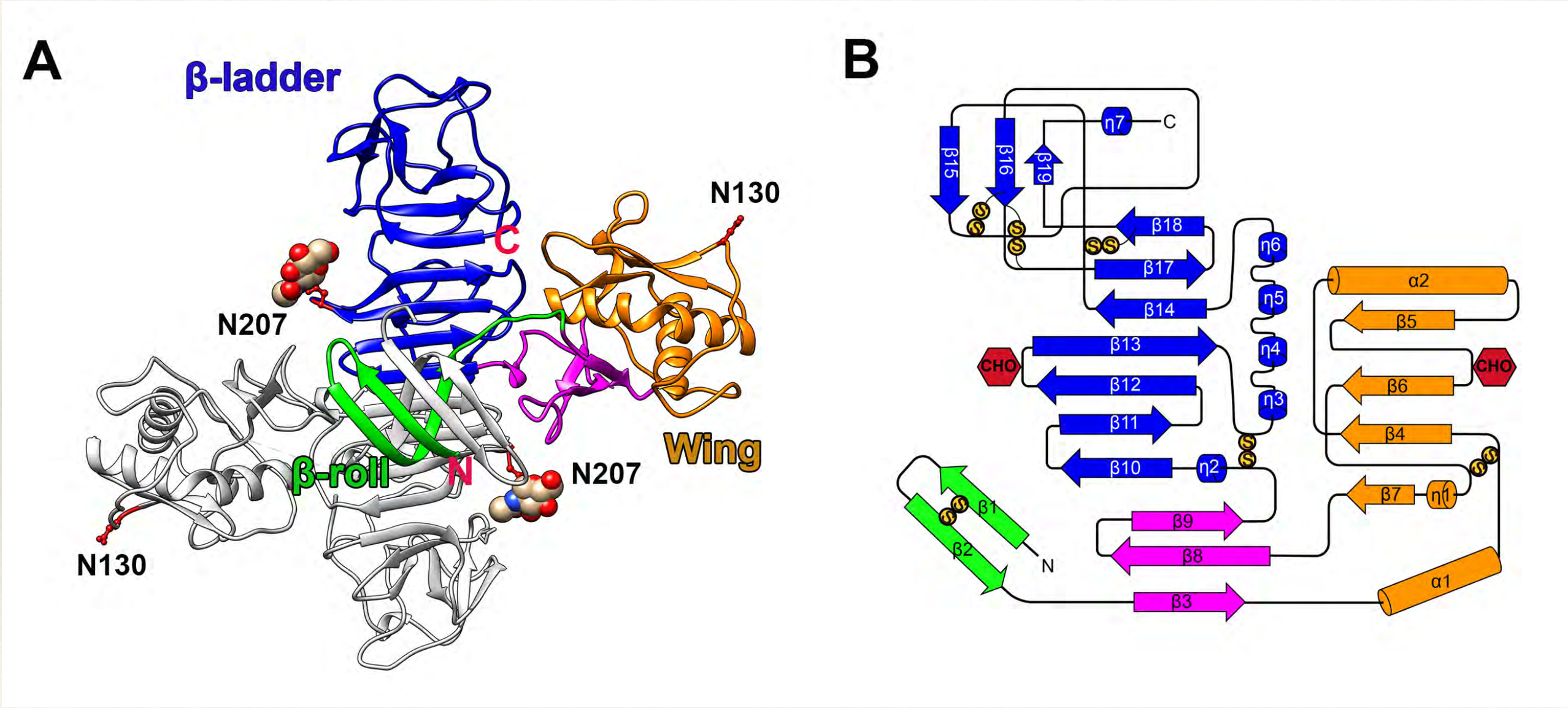
Diverse electrostatic potential on host-interaction interface of different flaviviruses





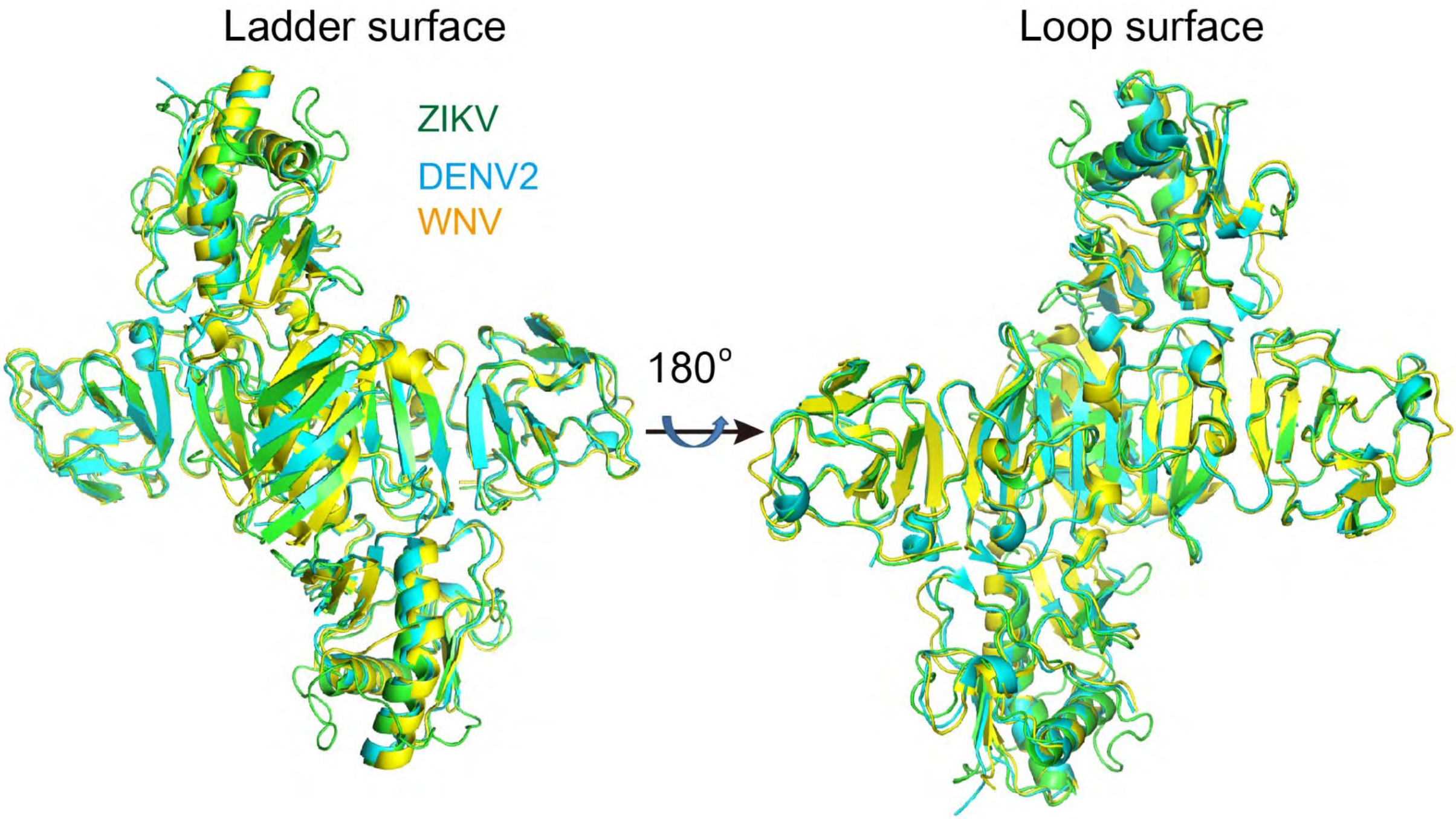
Nature Structural & Molecular Biology. 2016

Full-length Zika NS1 structure

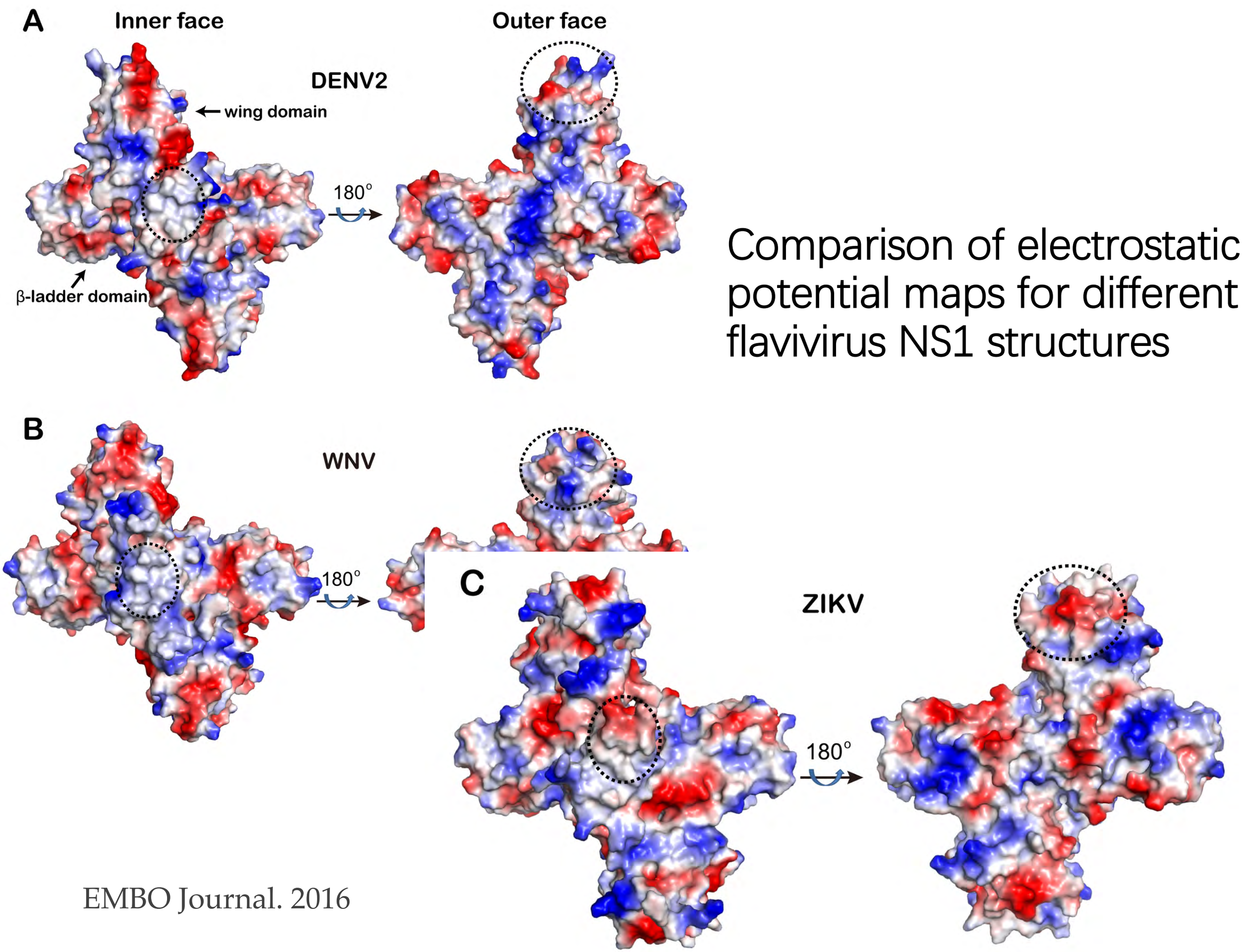


EMBO Journal. 2016

Comparison of flavivirus NS1 structures



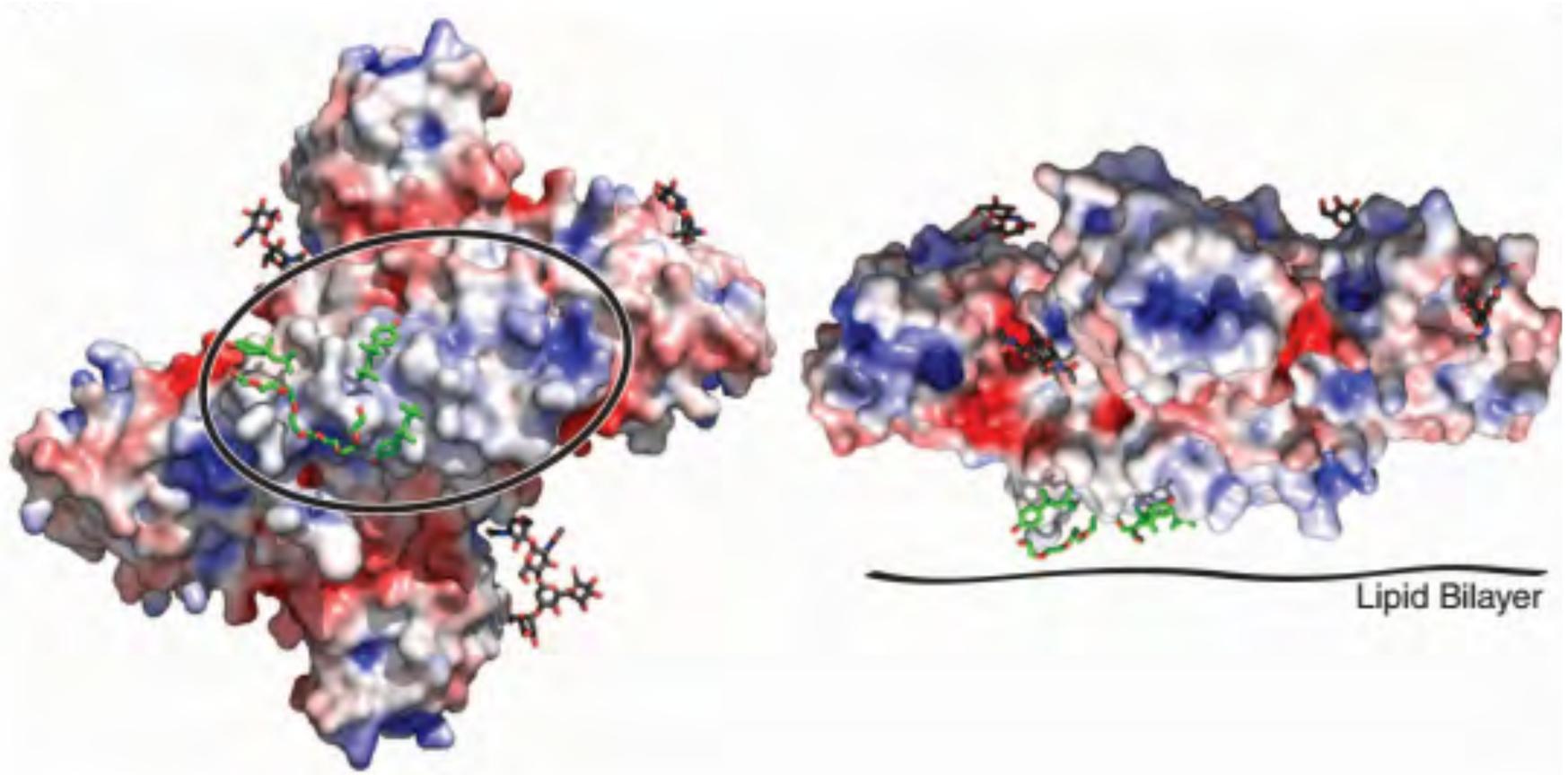
EMBO Journal. 2016

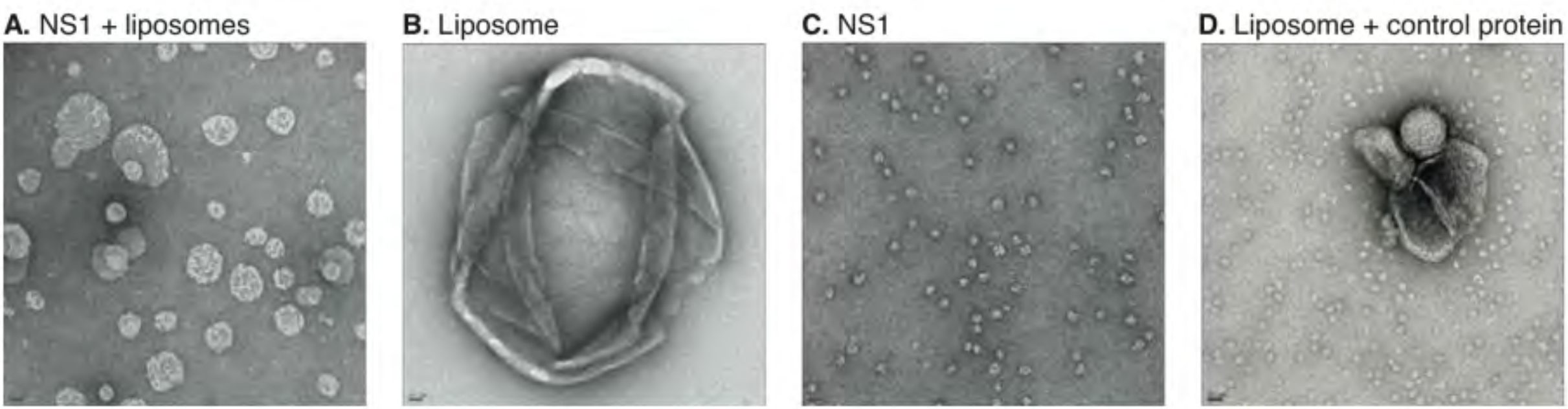


Comparison of electrostatic potential maps for different flavivirus NS1 structures

EMBO Journal. 2016

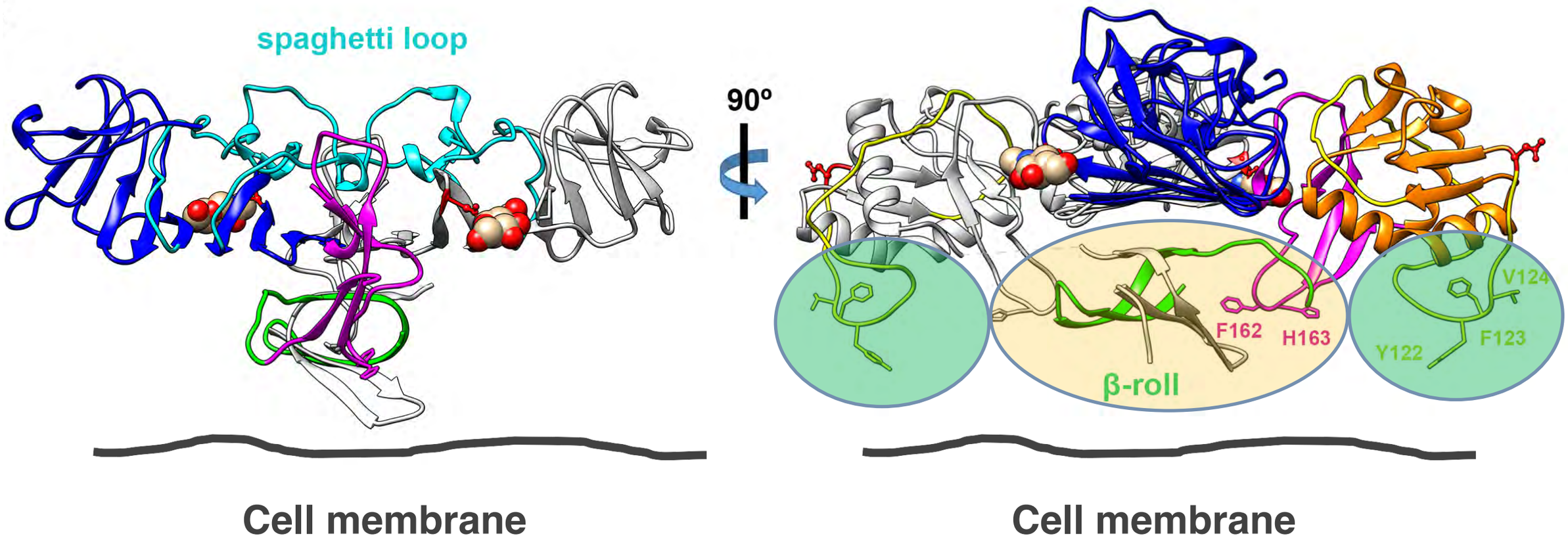
Hydrophobic protrusion for membrane interaction





Akey, D.L., et al., *Flavivirus NS1 structures reveal surfaces for associations with membranes and the immune system. Science, 2014.* ***343(6173): p. 881-5.***

A hydrophobic ’spike’ observed in ZIKV structure



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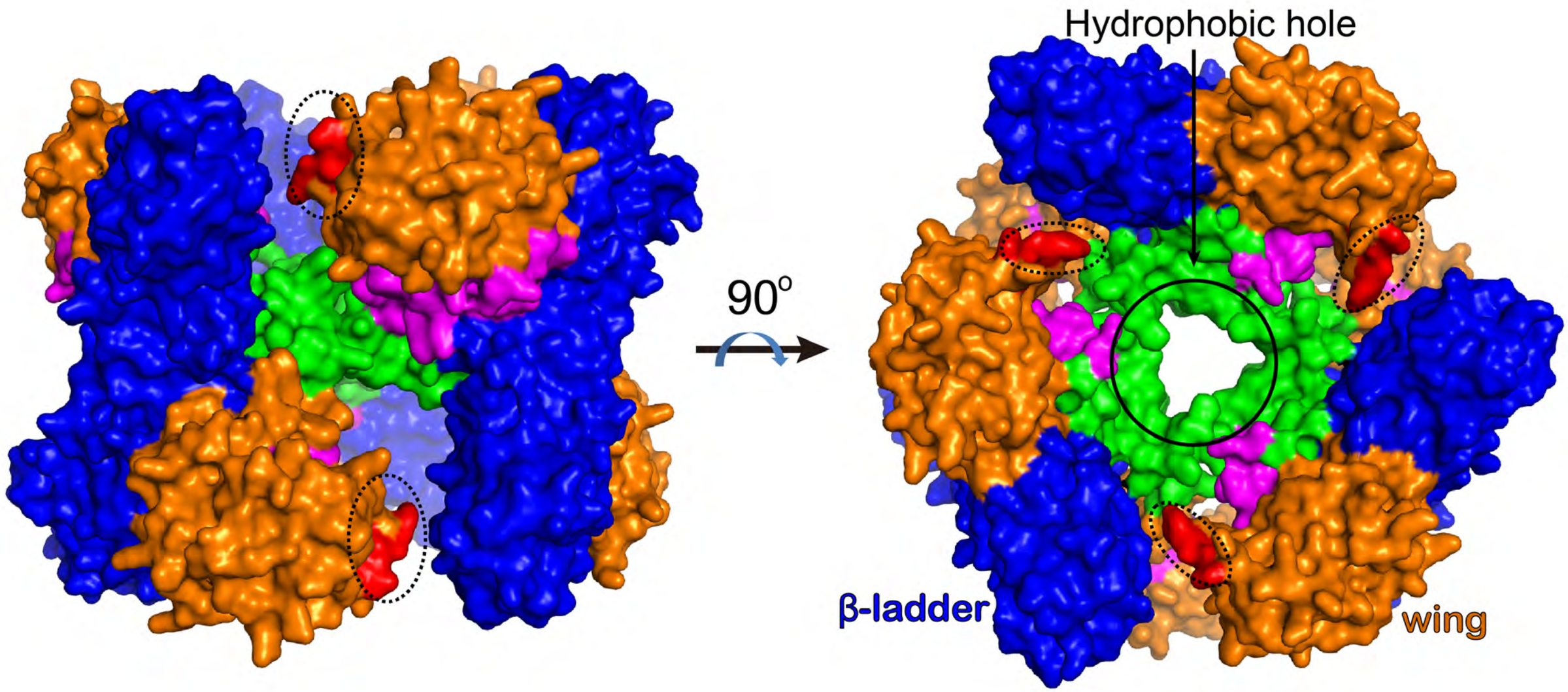
Hydrophobic “spike” can contribute to the hexamer formation



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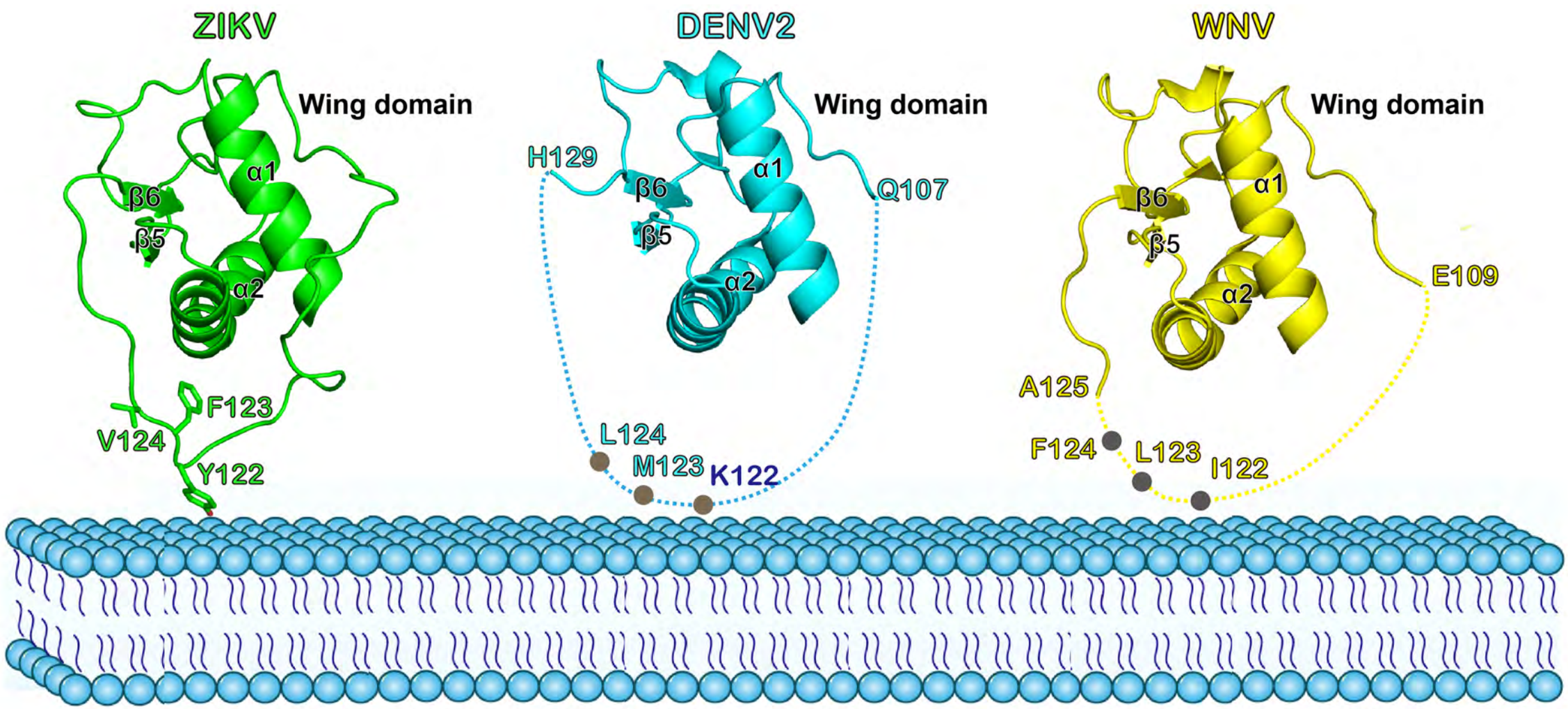
Hydrophobic “spike” can be involved in membrane association



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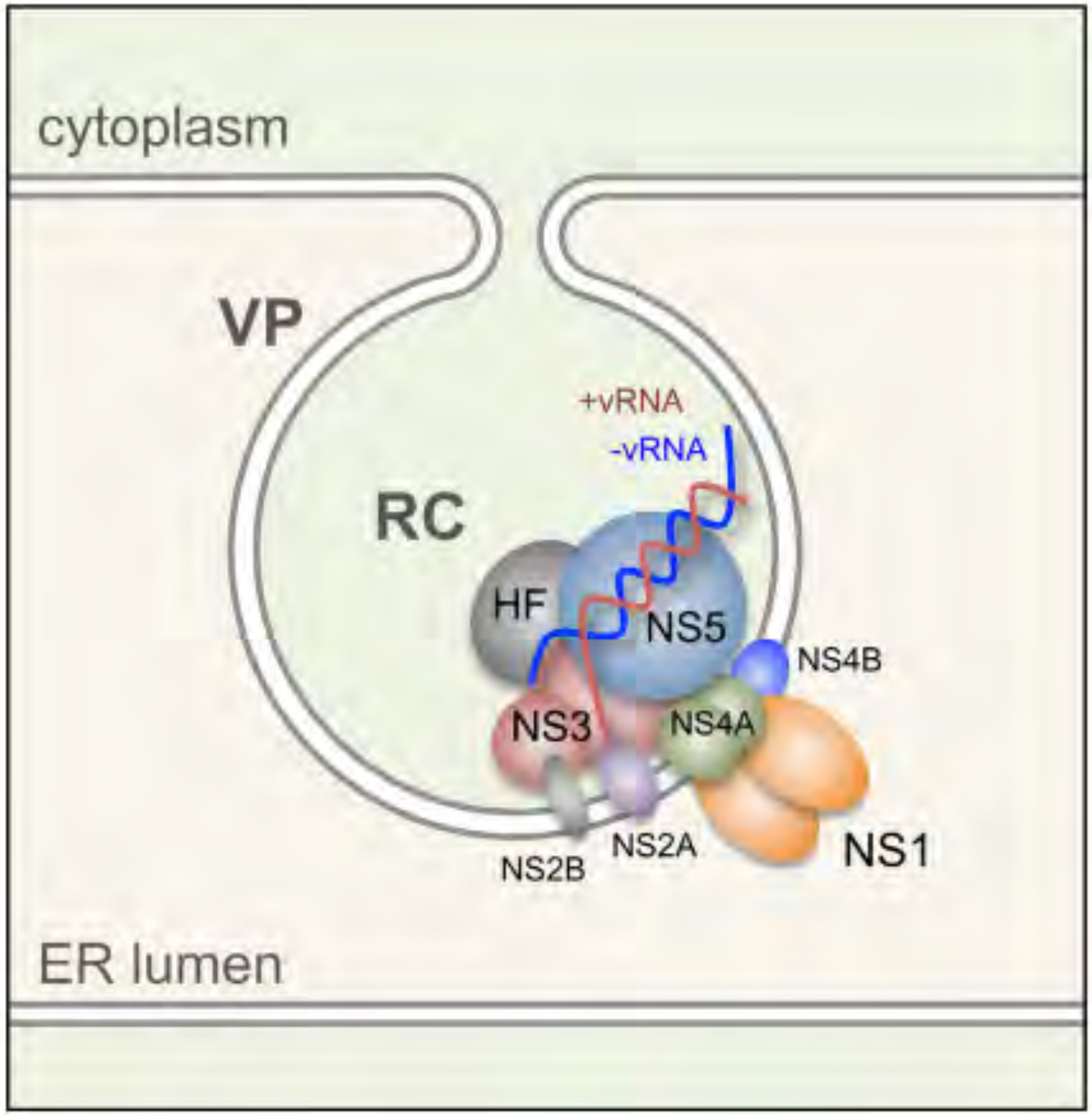
Spike region is predicted to be involved in replication process

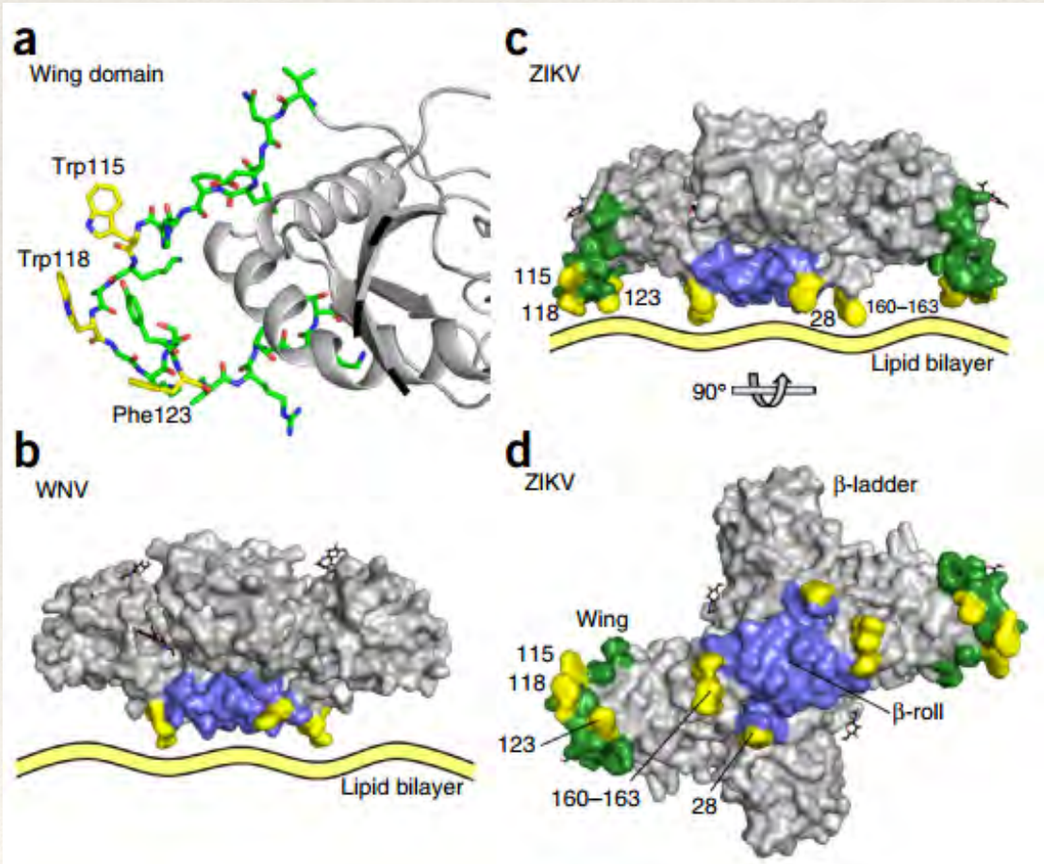


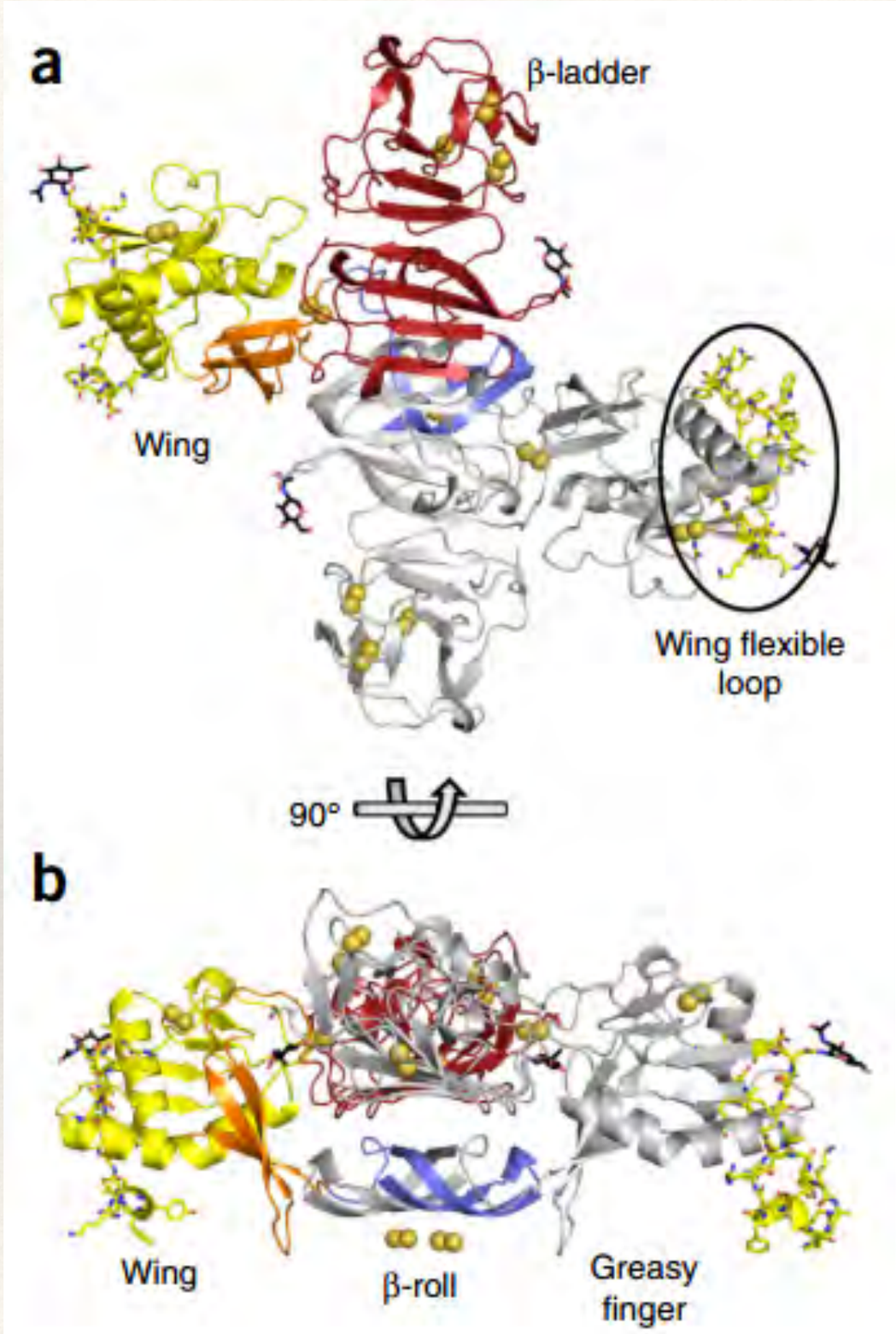
nature structural & molecular biology

Zika strain MR766, the original 1947 Ugandan strain

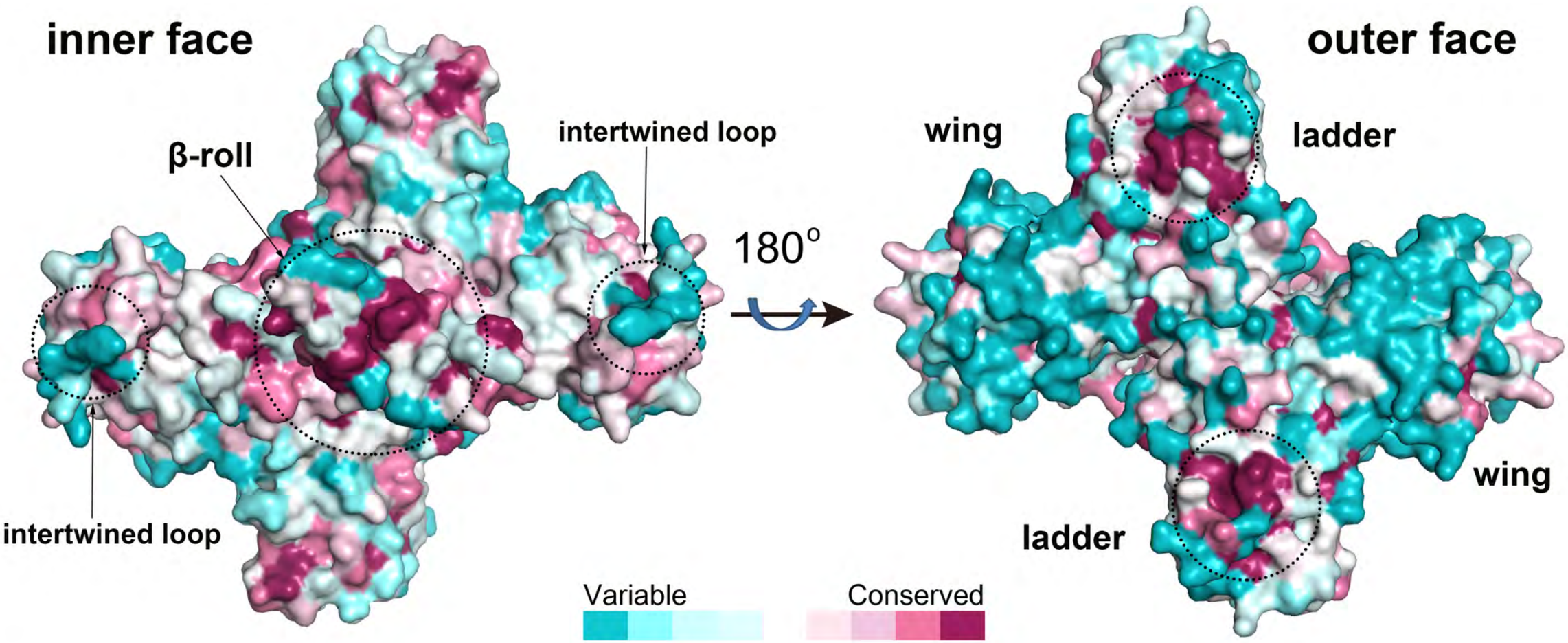
Extended surface for membrane association in Zika virus NS1 structure

W Clay Brown[1,5], David L Akey[1,5], Jamie R Konwerski[1], Jeffrey T Tarrasch[1], Georgios Skiniotis[1,2], Richard J Kuhn[3,4] & Janet L Smith[1,2]



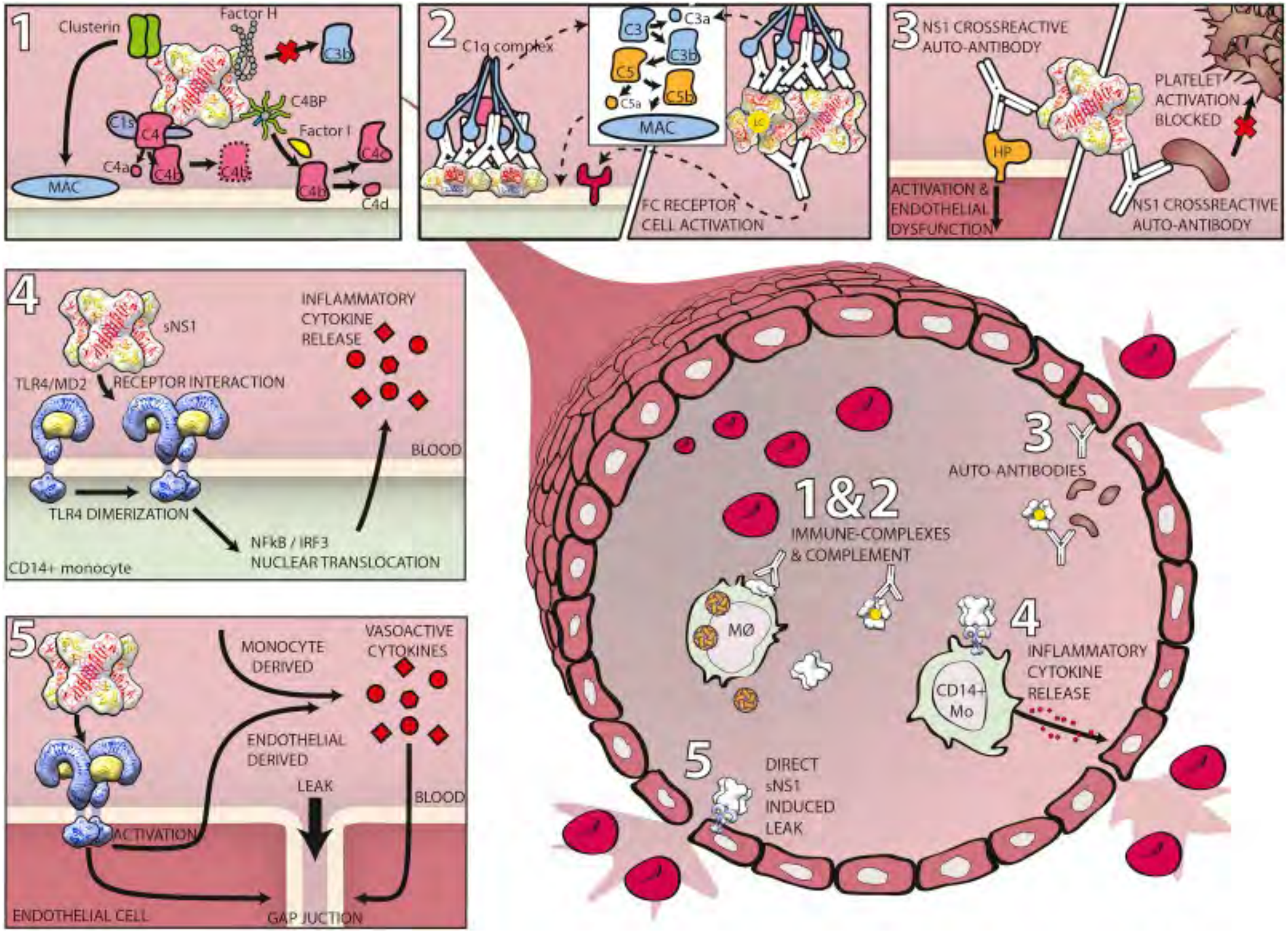


Conserved regions of flavivirus NS1



EMBO Journal. 2016

The many functions for extracellular sNS1



Watterson, D., N. Modhiran, and P.R. Young, *The many faces of the flavivirus NS1 protein offer a multitude of options for inhibitor design. Antiviral Res, 2016.* ***130: p. 7-18.***

Unsolved key questions

Could Zika NS1 help virus to penetrate the blood-placenta barrier, blood-brain barrier, blood-eye barrier and blood-testis barrier?

Can antiviral intervention targeting NS1 prevent the virus to infect fetus?

Acknowledgment

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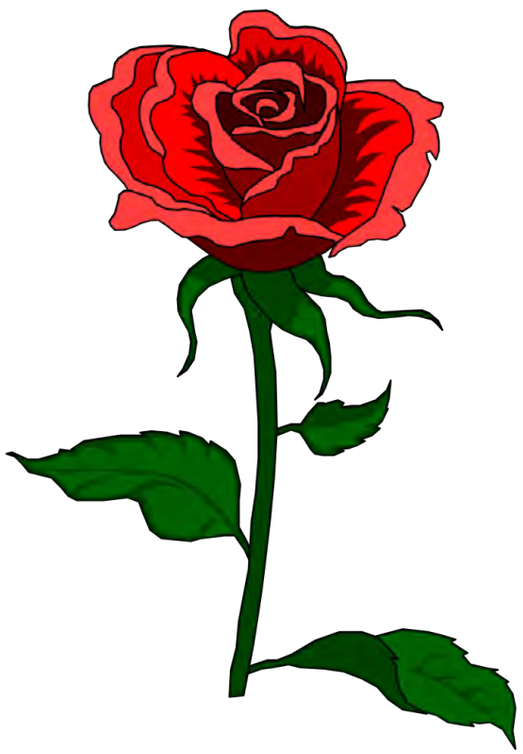
Chao Su



Thanks for your attention!