

# **Crystal Structures of HIV Neutralizing Antibody 2557 in Complex with V3 Peptides**

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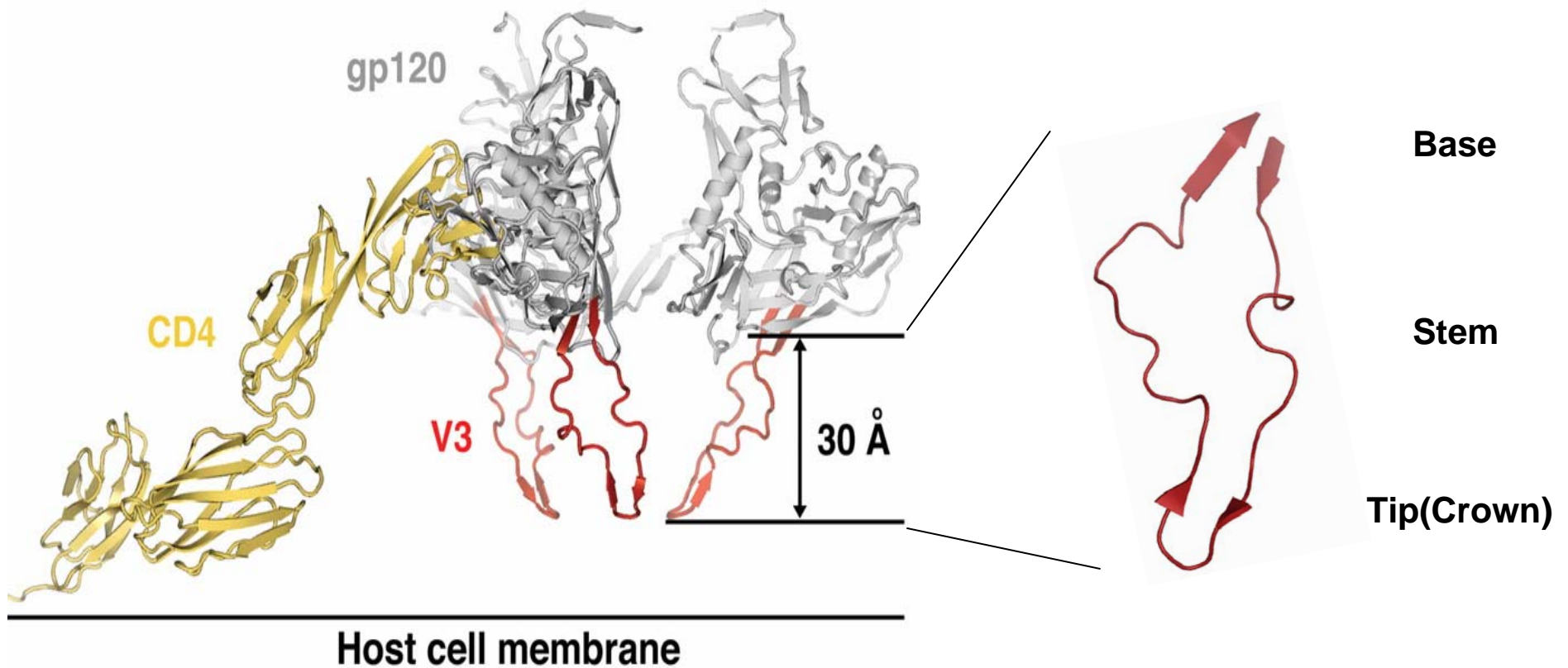
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## The third variable loop (V3) of GP120

- ~35 amino acids, disulfide linked loop
- Highly flexible
- Highly immunogenic
- Abs target the ~14 amino acids at the crown

# Orientation of V3 loop in GP120



Huang, CC, *et. al.* 2005. *Science*. 310(5750):1025-1028.

# Human anti-V3 MAb 2557

- **MAb 2557 was derived from a CRF02\_AG HIV-1 infected patient from Cameroon.**
- **MAb 2557 reacts strongly with subtype A, B, and C V3 loops expressed as fusion proteins. It is one of the best cross-reactive anti-V3 antibodies.**
- **MAb 2557 neutralizes several viruses from clade A, B, and C.**

# Summary

- **Four different V3 peptides with distinct sequences were shown to bind to 2557 in a conserved conformation.**
- **The V3 crown can be divided into 3 regions.**

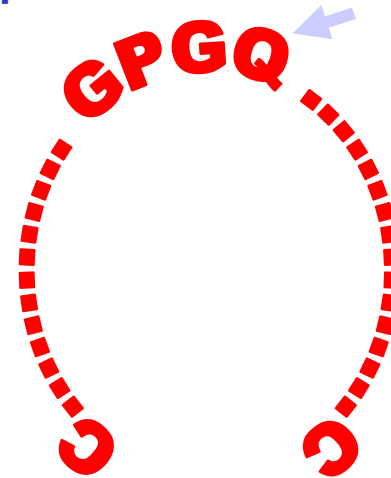
# Fab2557/V3 Crystal Structures

V3 peptide in complex	V3 peptide sequences	Resolution
UG1033 ( clade A )	NNTRKSIHL <b>GPGR</b> AFYATGDIIG	2.5 Å
NY5 ( clade B )	NNTKKGIAI <b>GPGR</b> TLYREK	1.8 Å
NOF ( clade C )	NNTRKRIRV <b>GPGQ</b> YVYATNA	2.5 Å
ZAM18 ( clade C )	NNTRKSIRI <b>GPGQ</b> AFYATGGIIG	2.8 Å

Predominant Motifs at the Tip  
of the V3 Loop

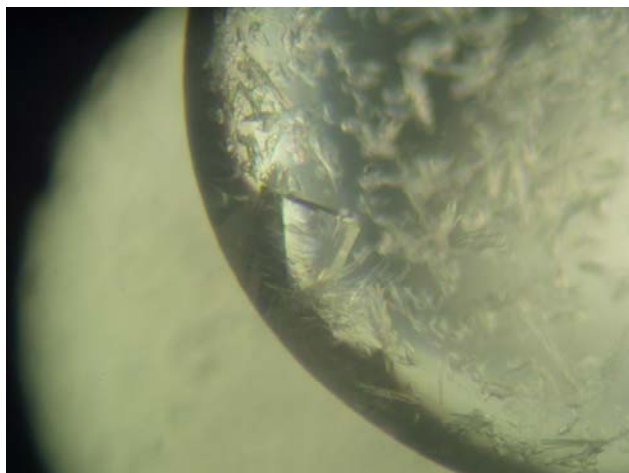


Mostly clade B



Mostly non-B clade

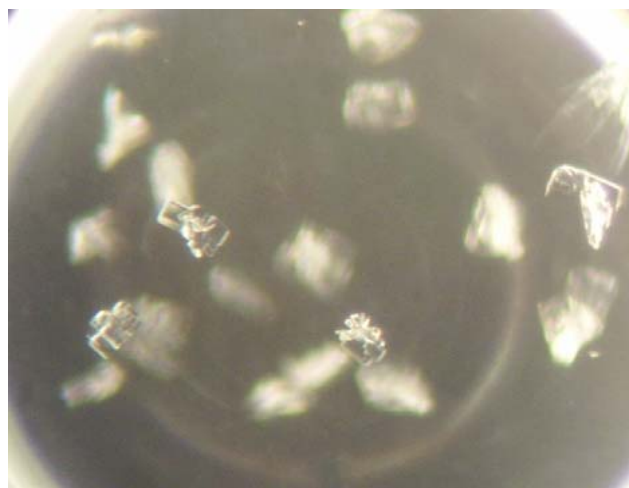
# Fab2557/V3 Crystals



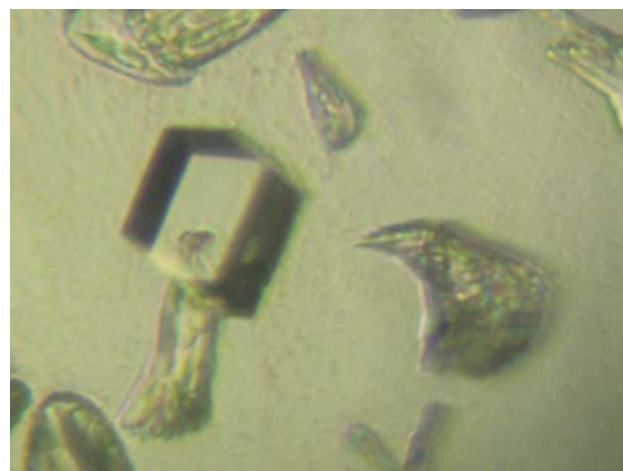
**2557/UG1033**



**2557/NY5**

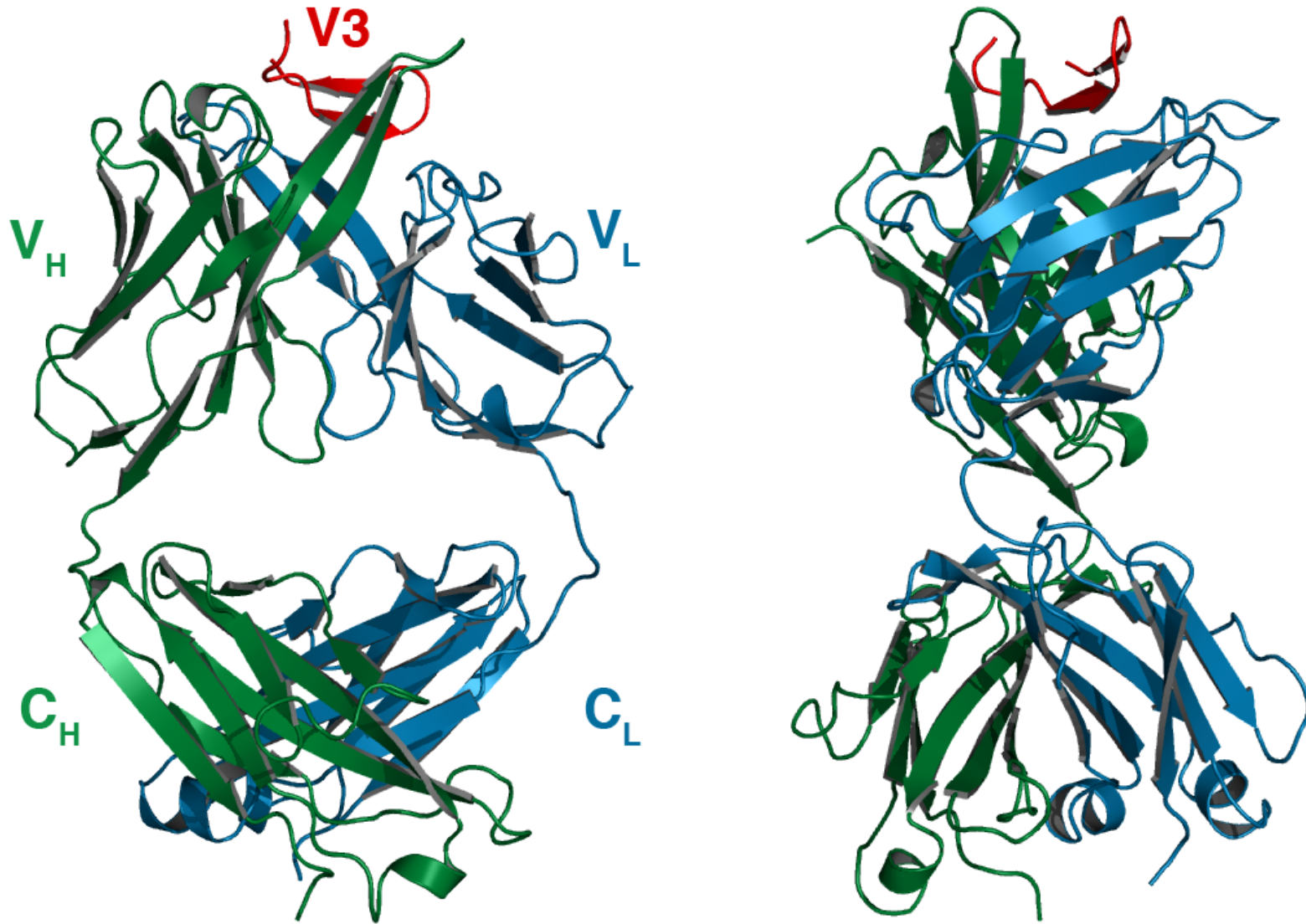


**2557/NOF**

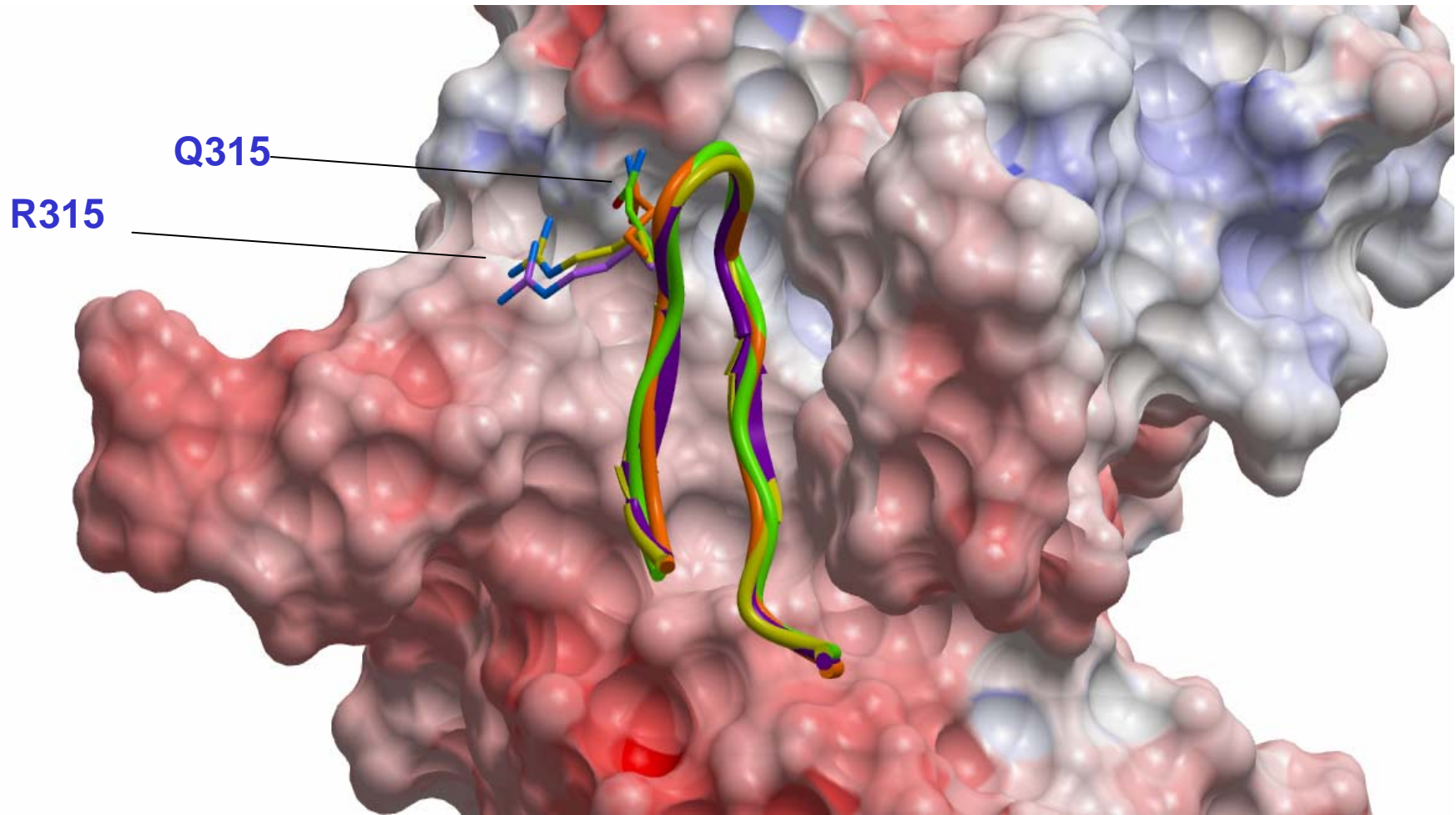


**2557/ZAM18**

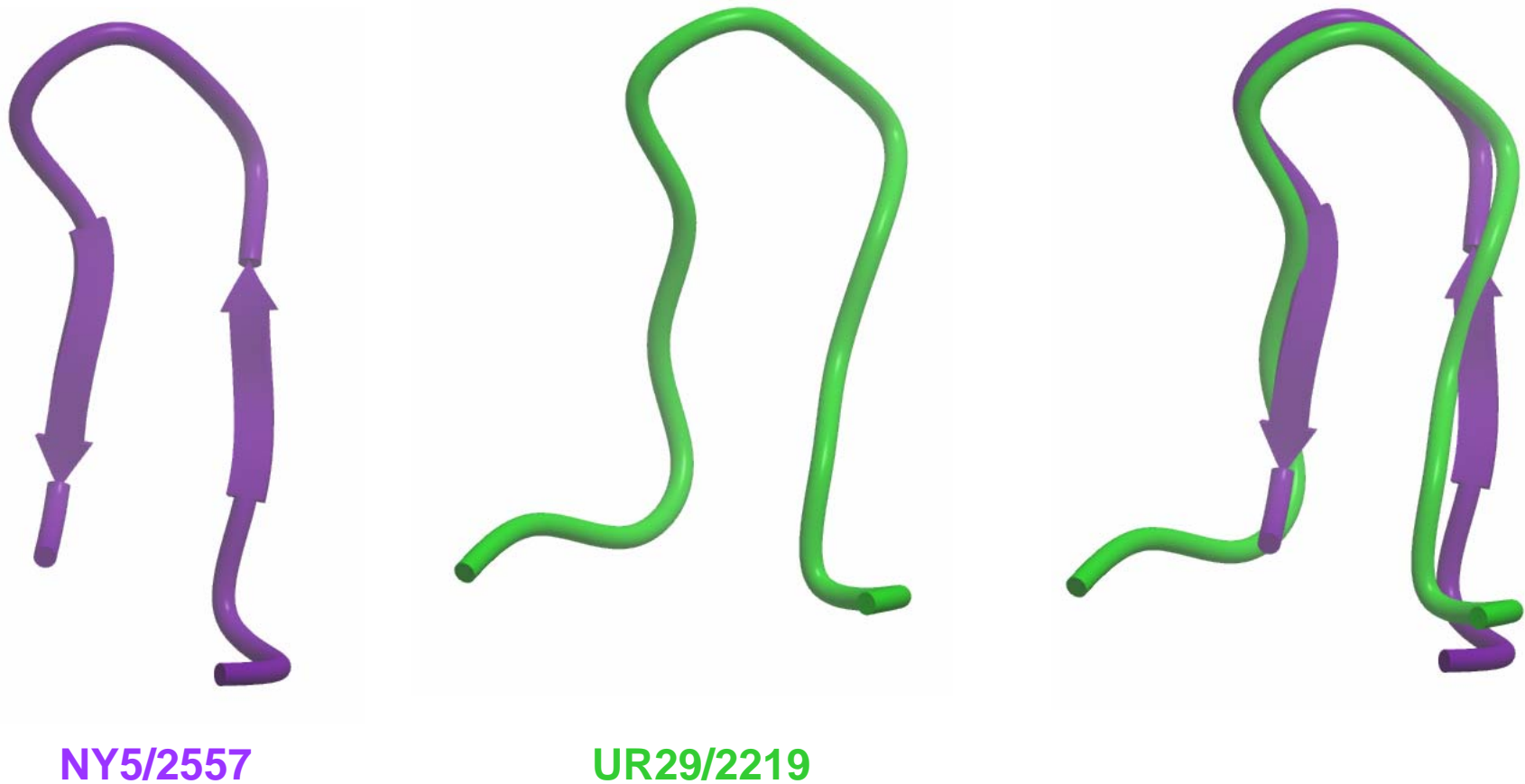
# Overall structure of Fab 2557/NY5



# Surface presentation of mAb 2557 complexed with V3 peptides UG1033, NY5, NOF, ZAM18



# Comparison of V3 peptides complexed with mAb 2557 (from clade AG patient) and mAb 2219 (from clade B patient)



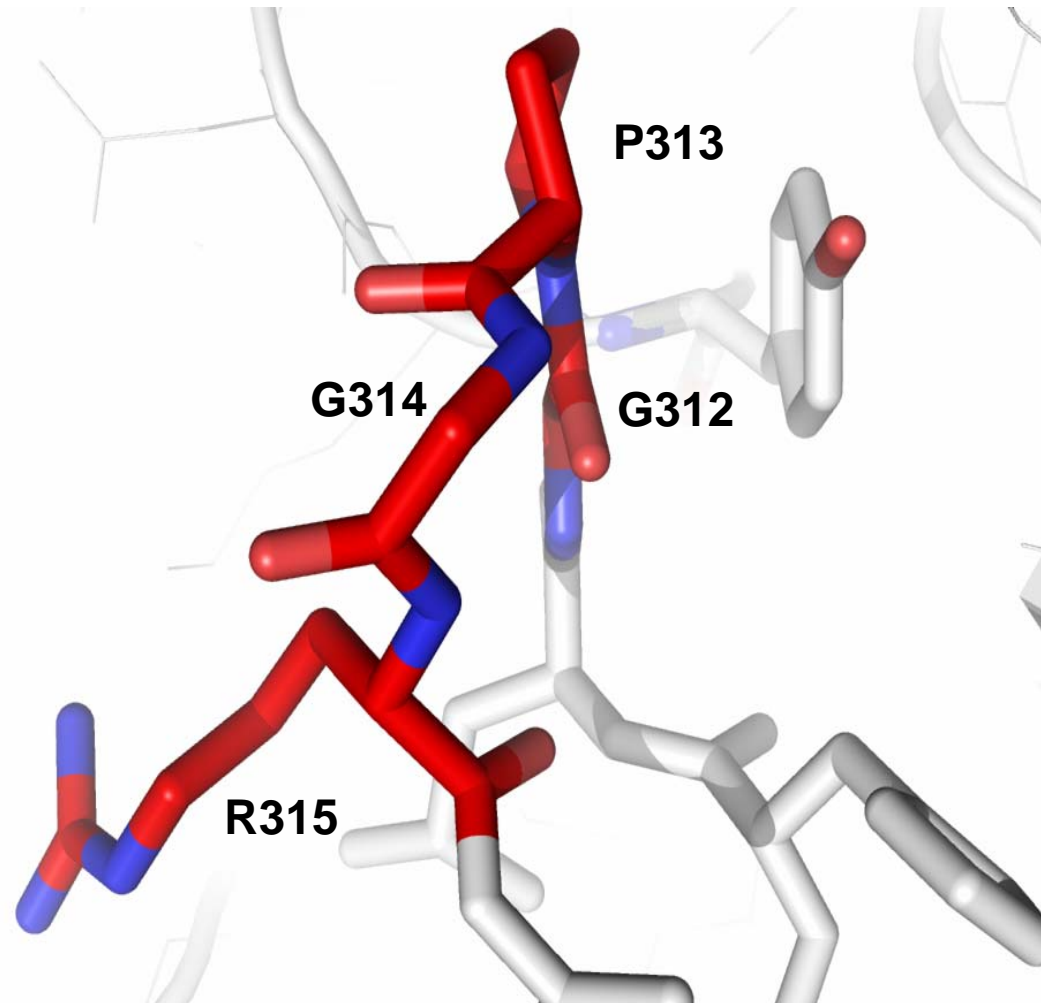
Stanfield, R.L., *et. al.* 2006. *J.Virol.* 80(12):6093-6105.

# How to divide the (V3) Crown



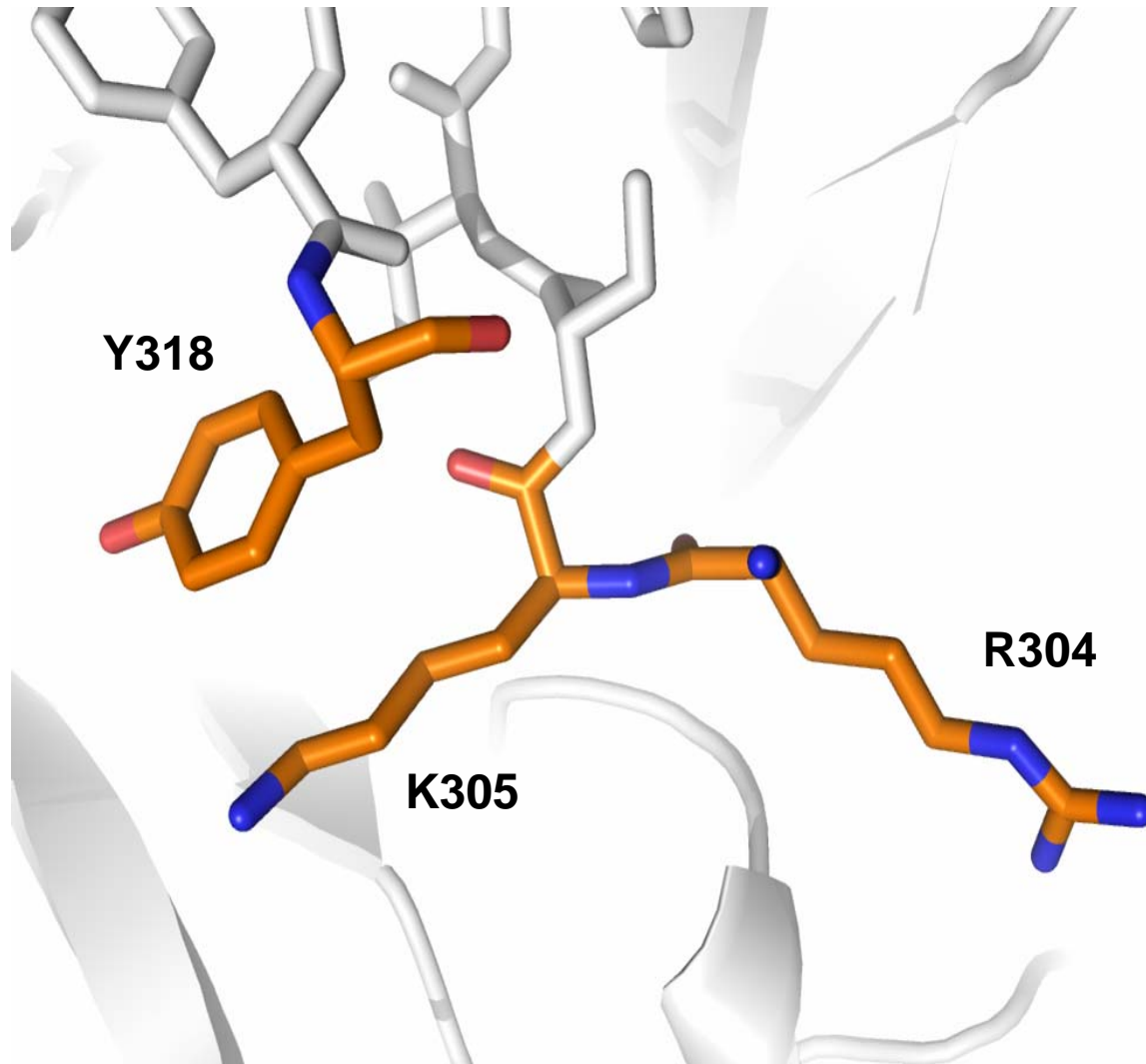
As per Ronald Allison, former Press Secretary to Queen Elizabeth II

# Arch

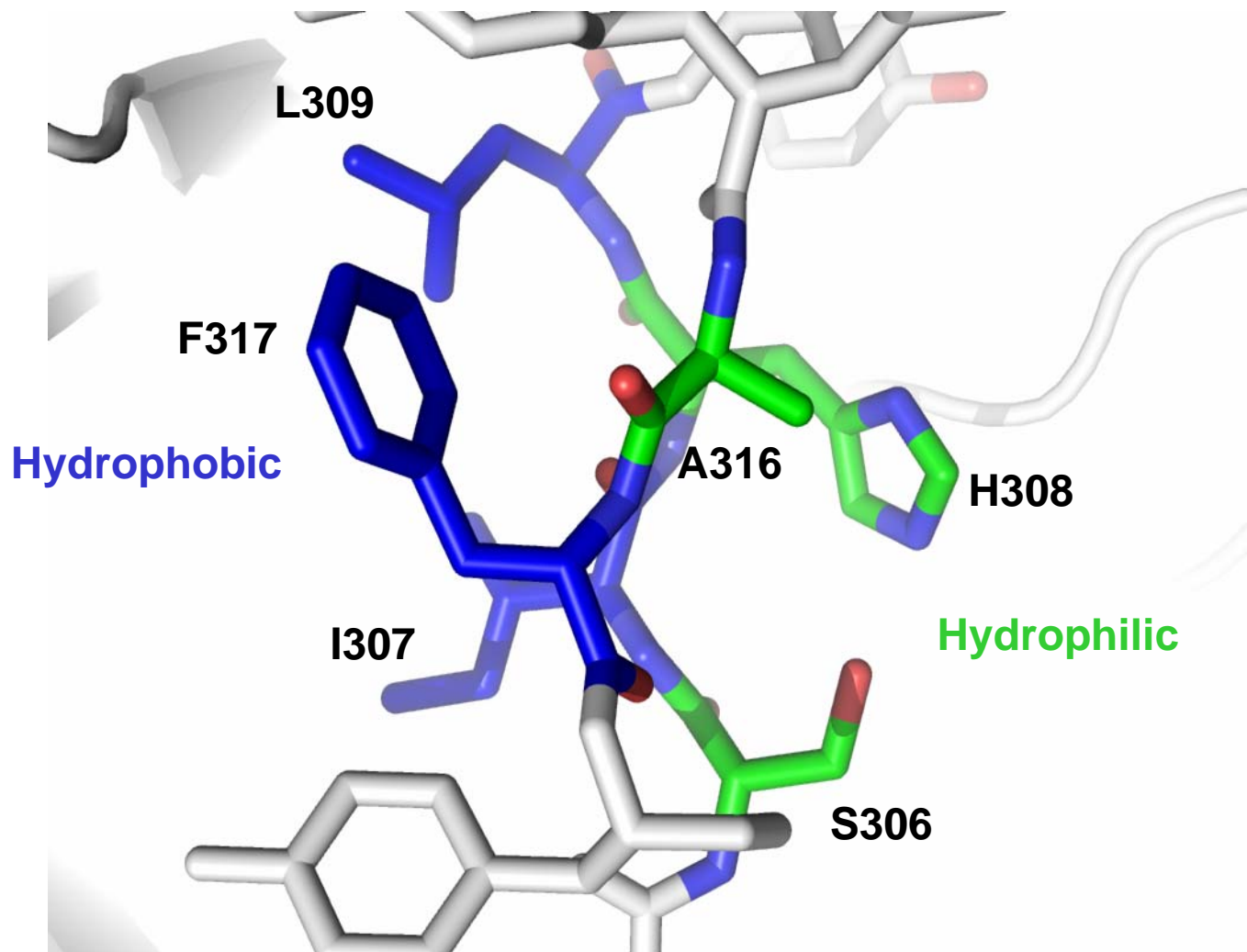




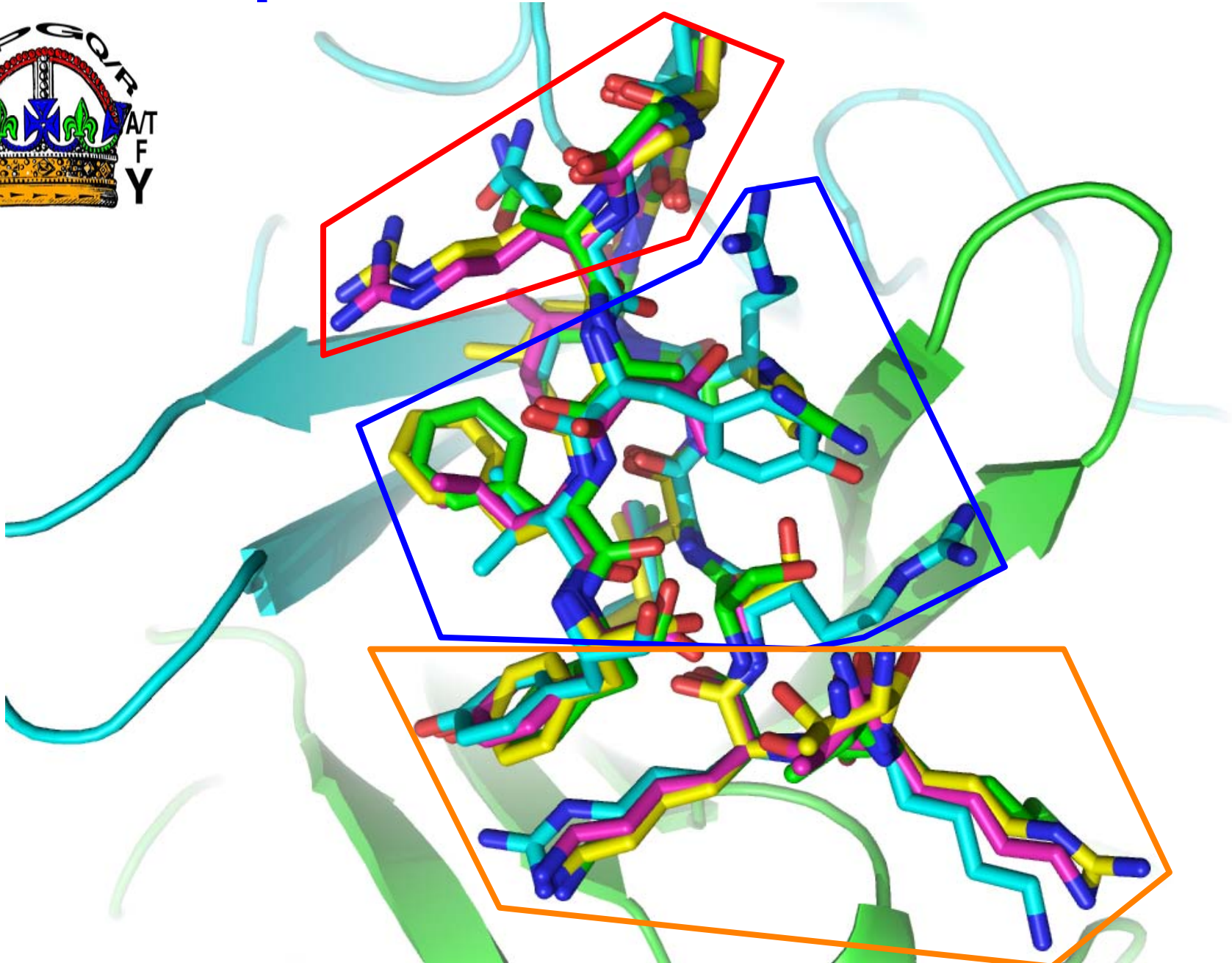
# Band



# Circlet



# Peptides in the 4 structures



# Conclusions

- We have crystallized Fab 2557 in complex with four different V3 peptides.
- Four different peptides with distinct sequences were shown to bind to 2557 in a conserved conformation.
- V3 complexed with 2557 (from clade AG) and mAb 2219 (from clade B) shares similar structures.
- The crown can be divided into 3 regions: Arch, Circlet, Band
  - The Arch and the Band have highly conserved sequences while the Circlet is more variable.
  - The Circlet has a hydrophilic and a hydrophobic face.
- The R/Q residue in the Arch does not form a major contact with the Ab, allowing mAb 2557 to react with both V3 motifs.

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