

Structures of anti-HIV mAbs and AIDS vaccine discovery

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**X6A NSLS
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HIV-1 is a wimpy virus

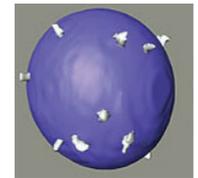
High rate of mutation

Varied post translational modification

Variable loops

Functional fitness

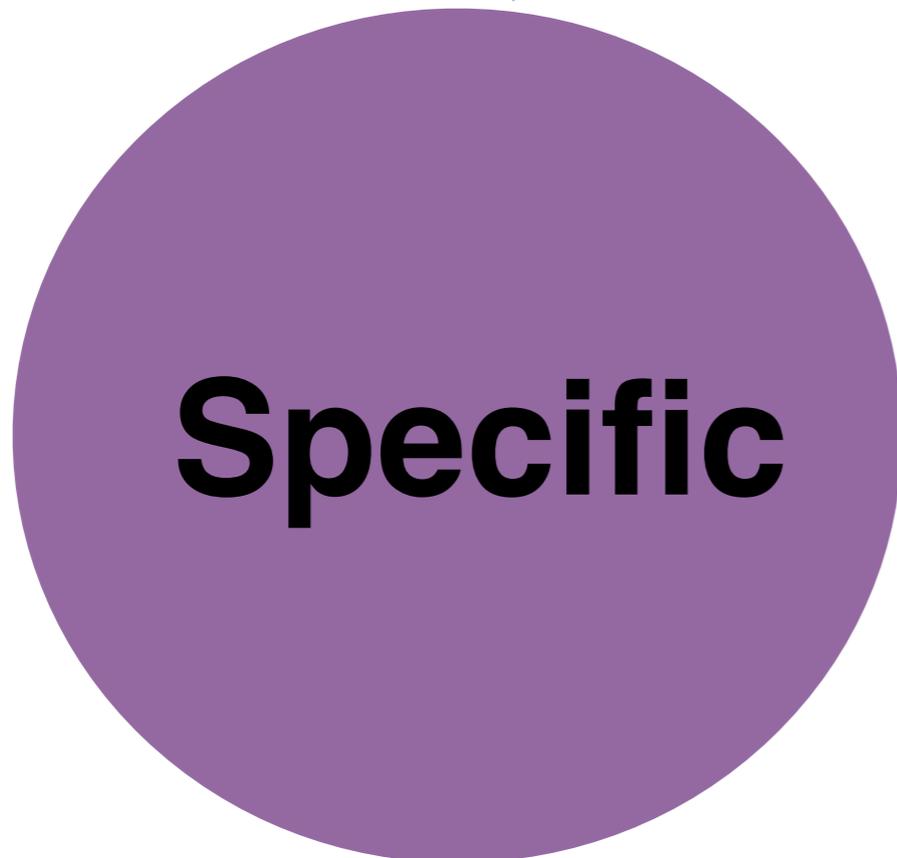
Poor assembly

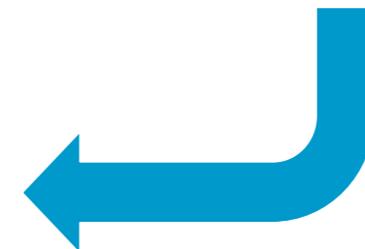
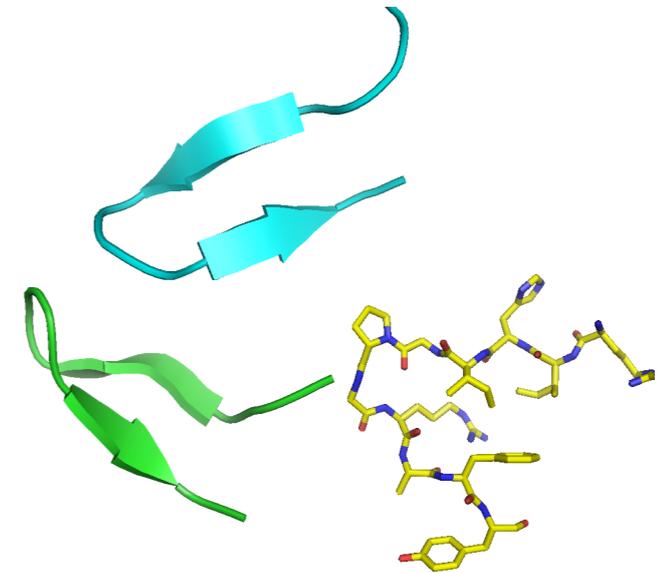
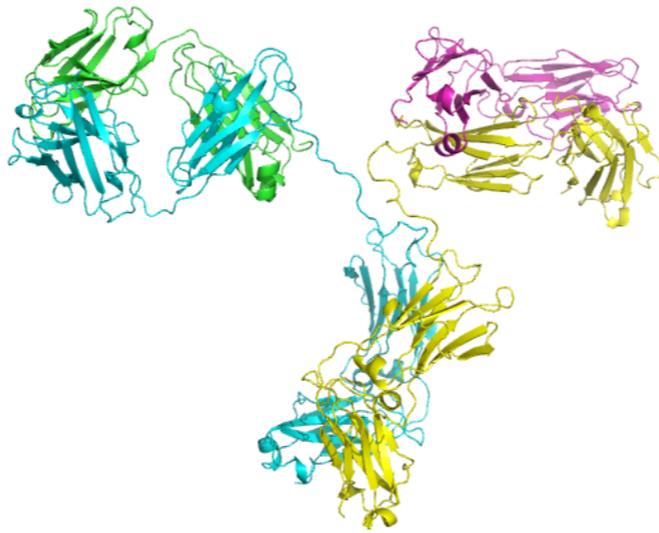
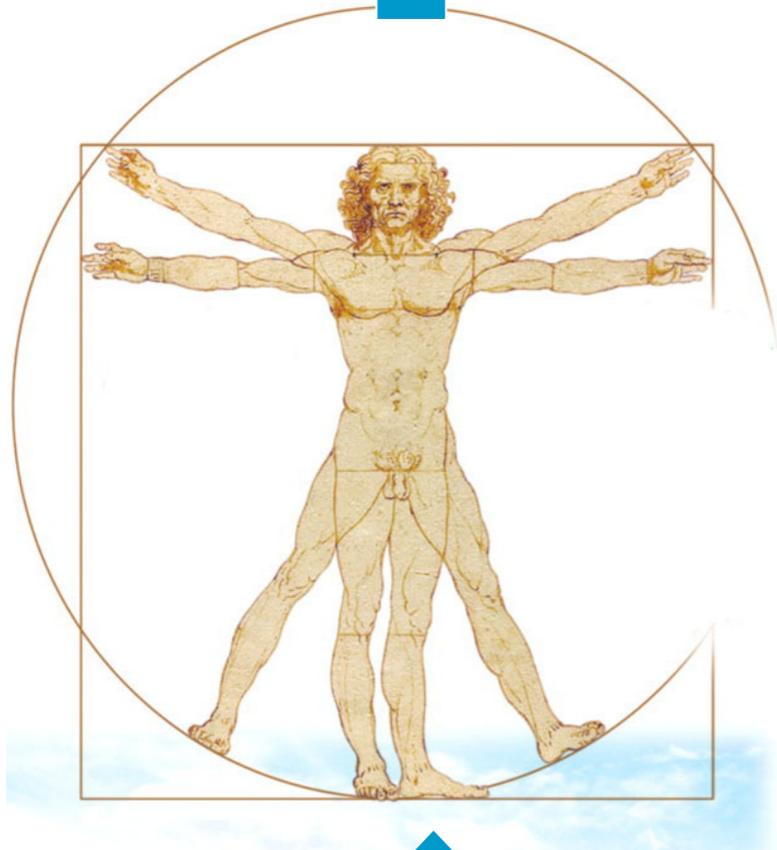


Zhu et al, Nature 2006

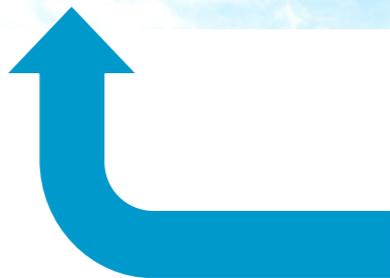
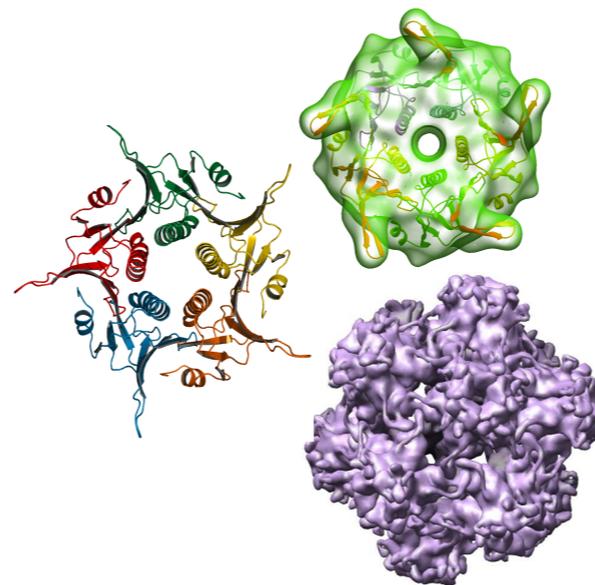
Laozi: 天下之至柔，馳騁天下之至堅。

Humoral immune response

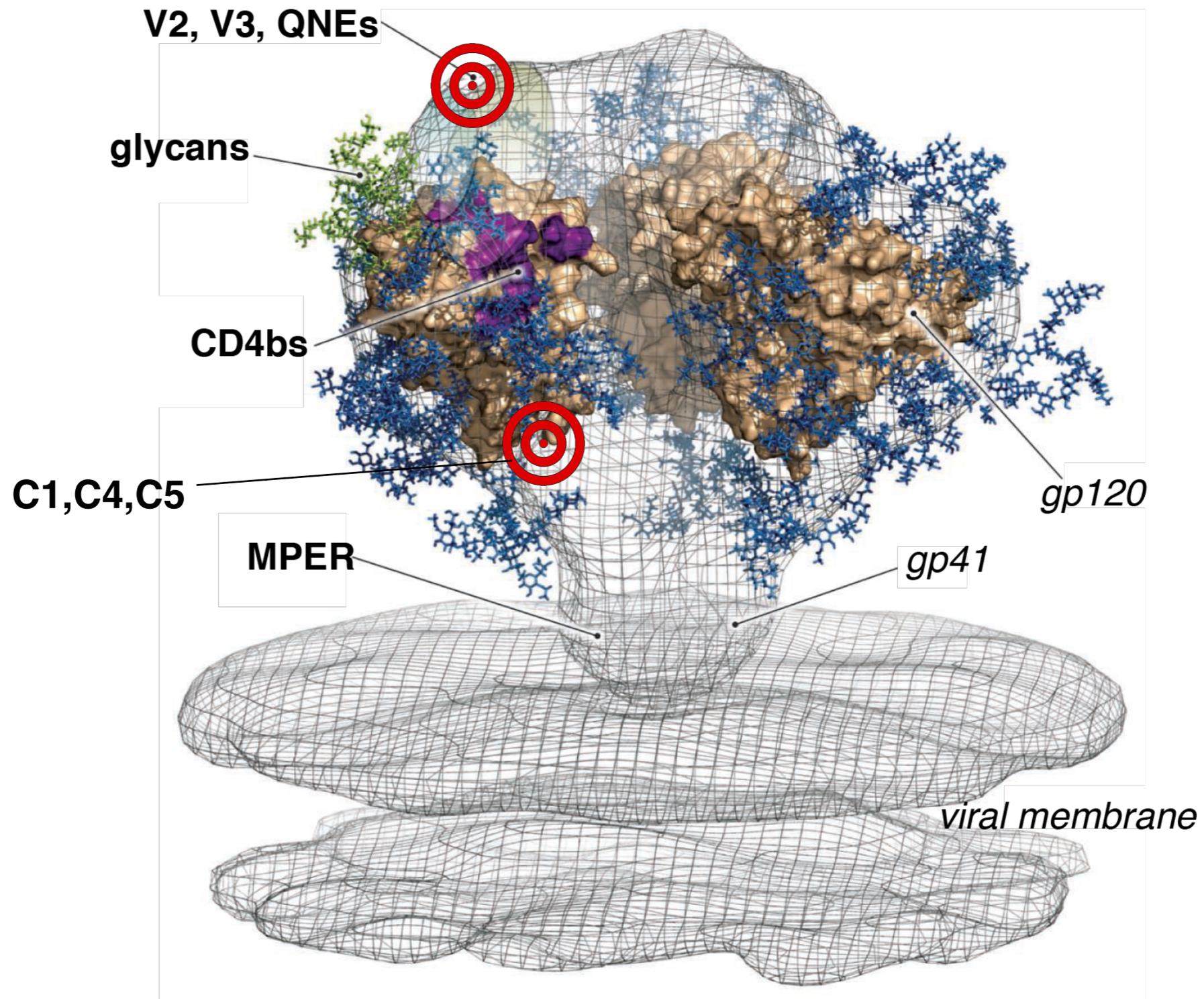




Reverse Vaccinology



Epitope, Epitope, Epitope

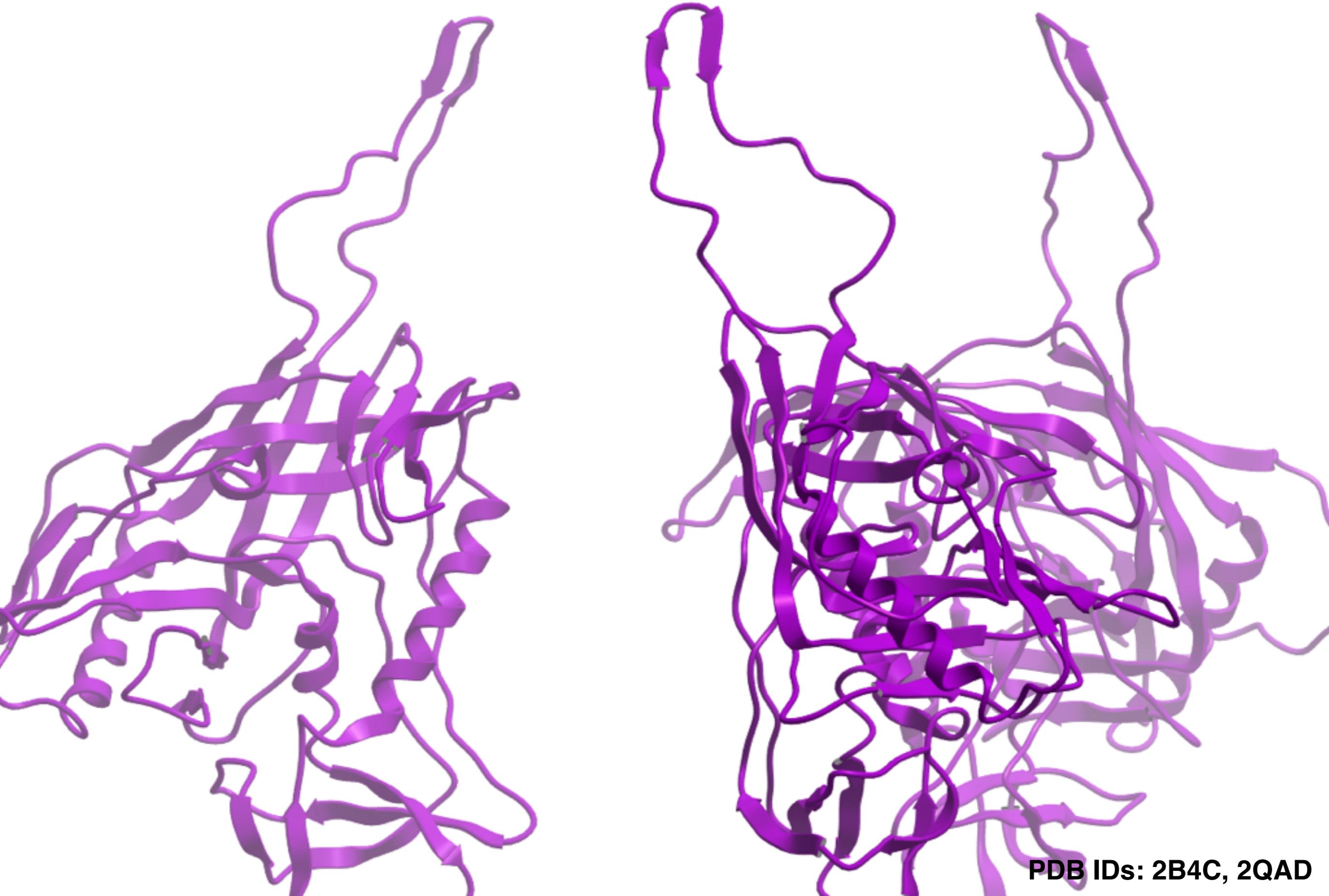


Adapted from Burton and Weiss, *Science* 329, 770-773 (2010)

>30 structures
many of them from X6A

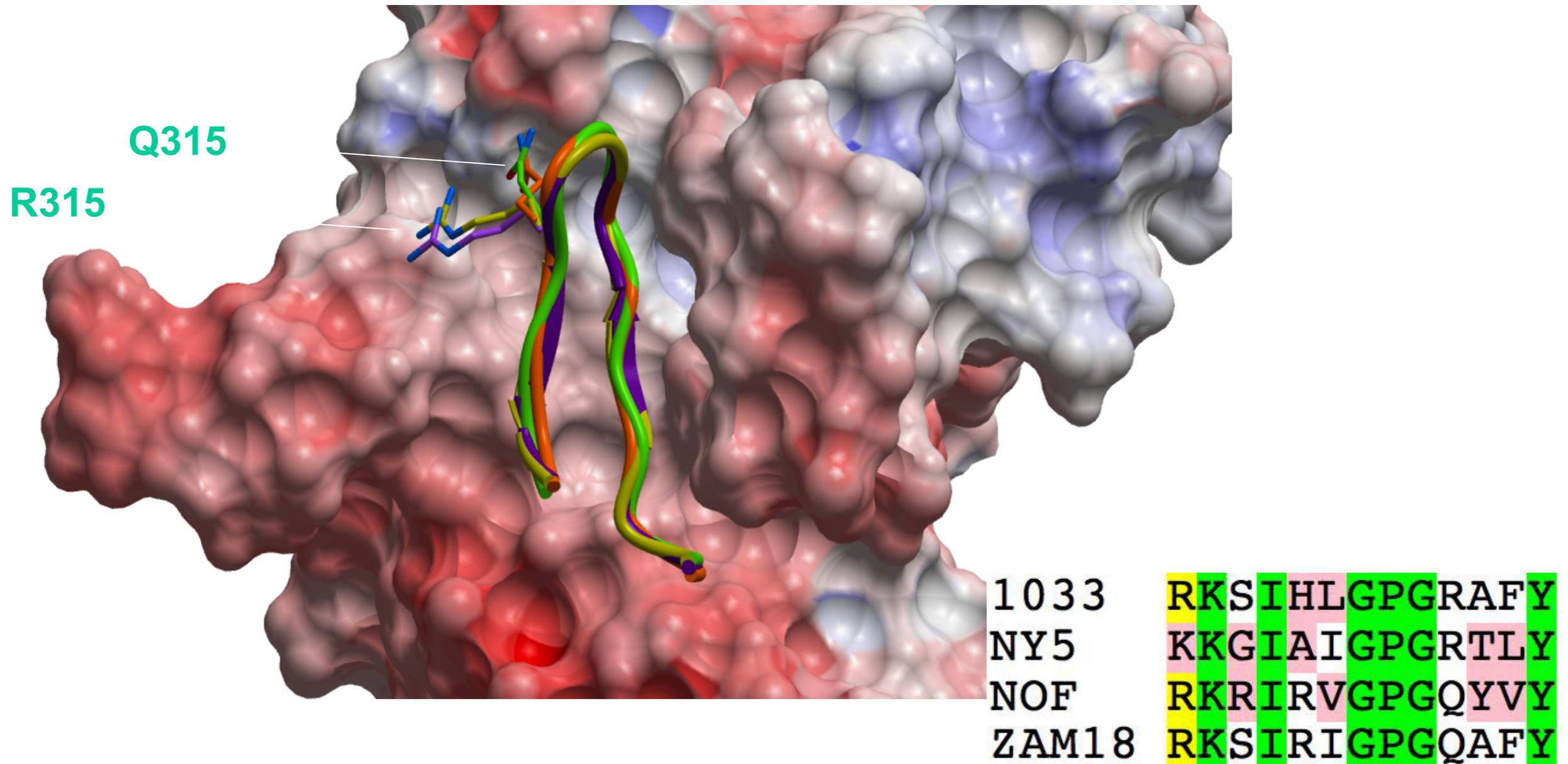
Conserved structural elements of V3 crown

Location of V3

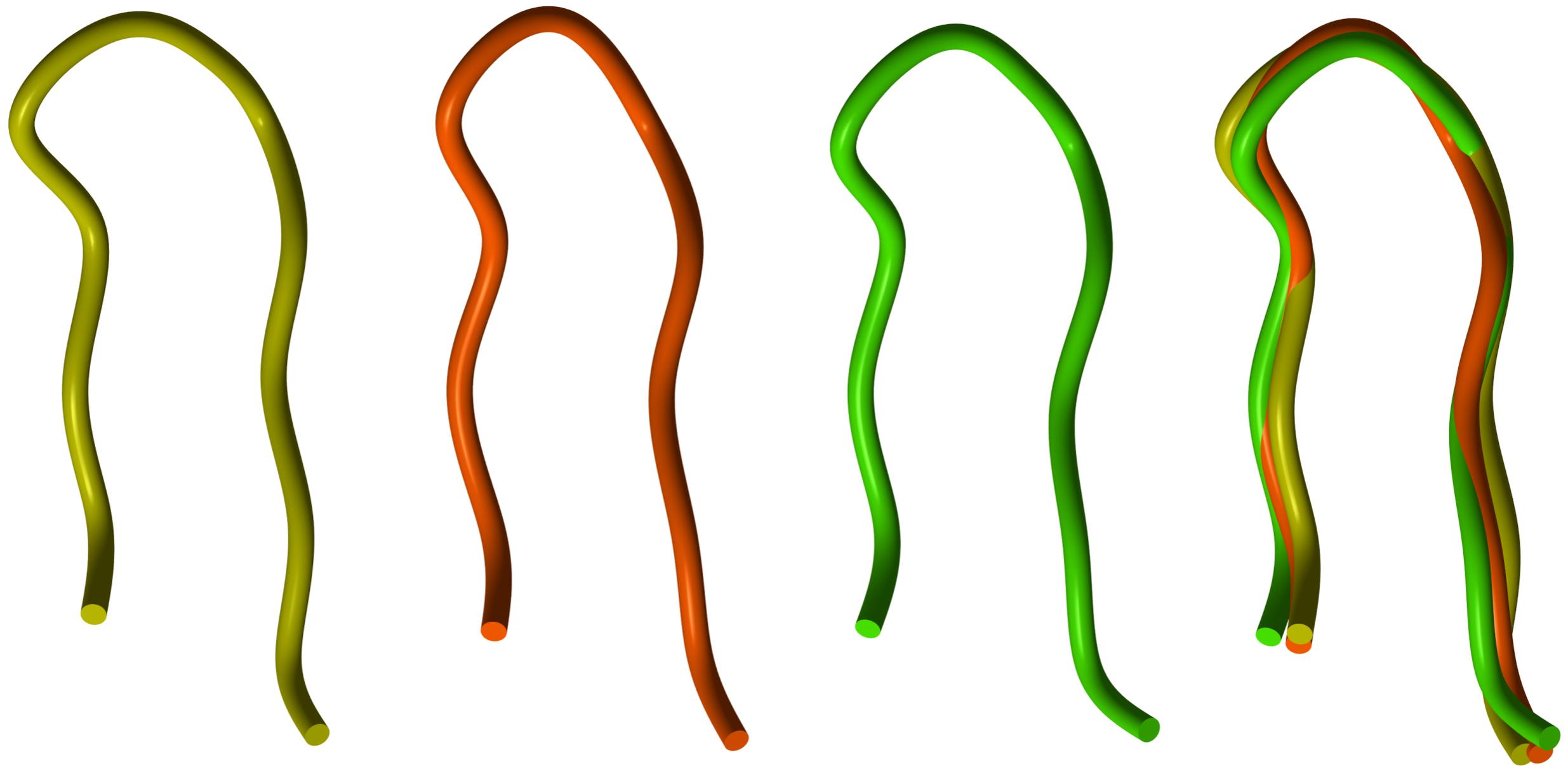


PDB IDs: 2B4C, 2QAD

2557 in complex with V3s of NY5(B), NOF(C), 1033(A) and ZAM18(C)

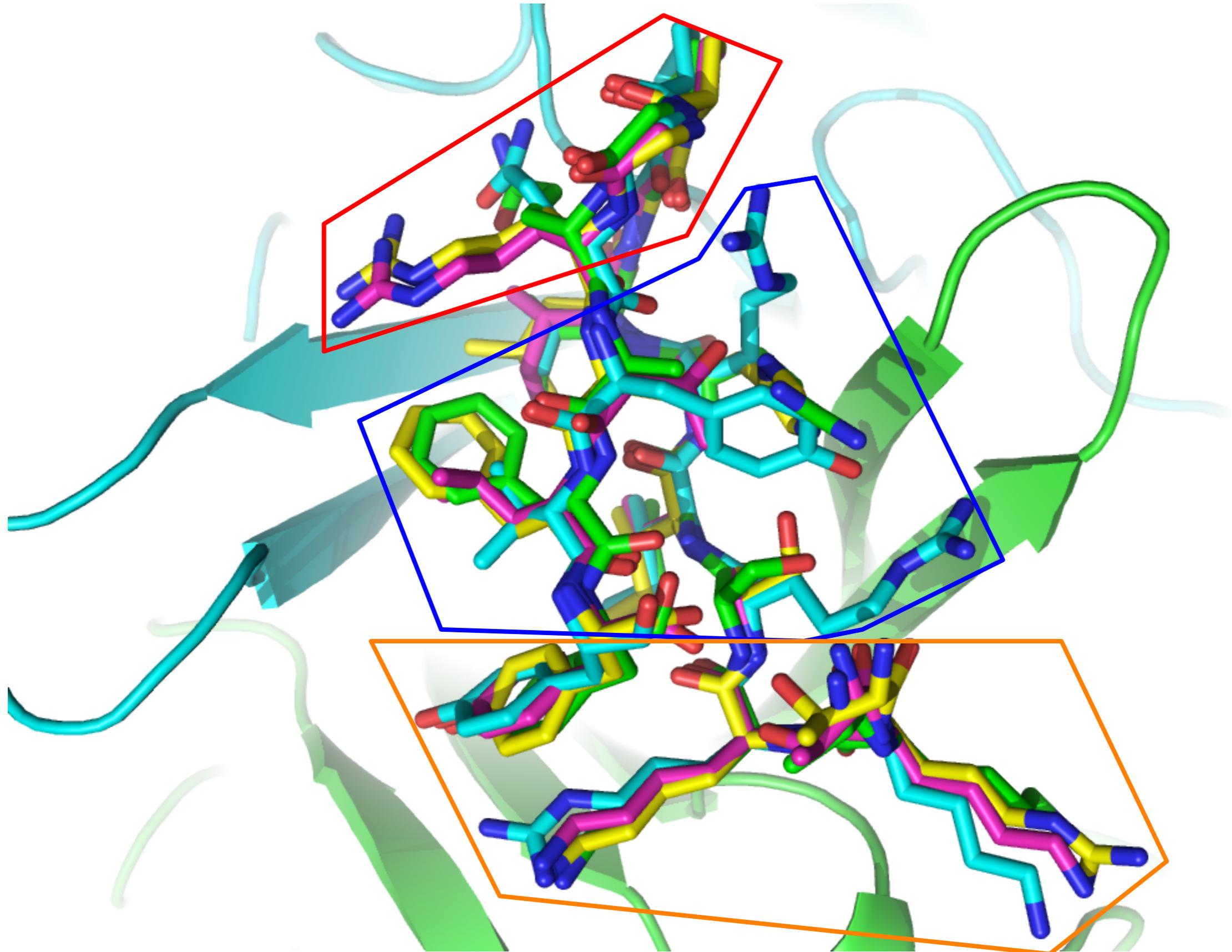


Comparison of V3 crowns complexed with human mAbs 2557 (clade AG) & 2219 (B) & 1006 (B)



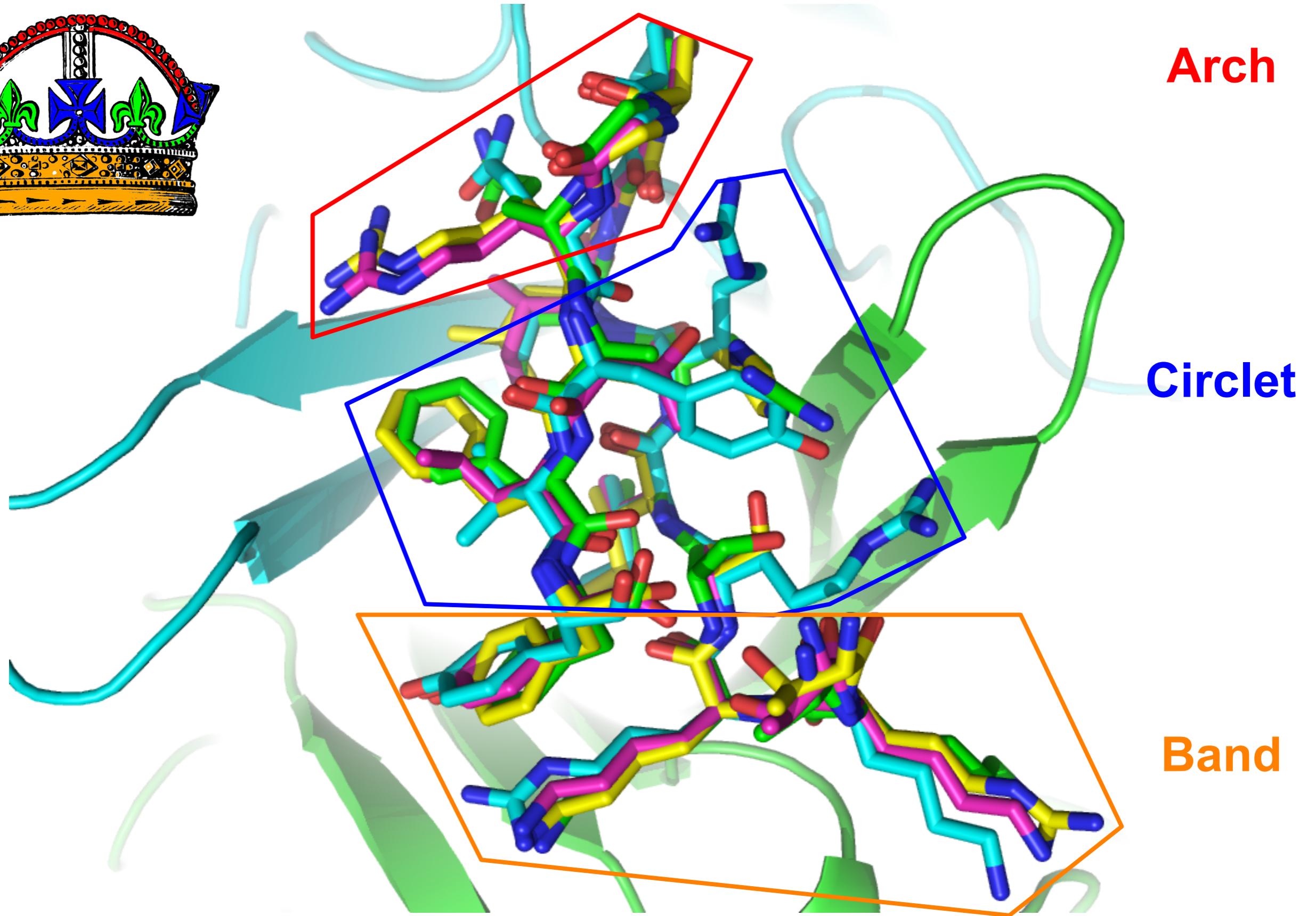
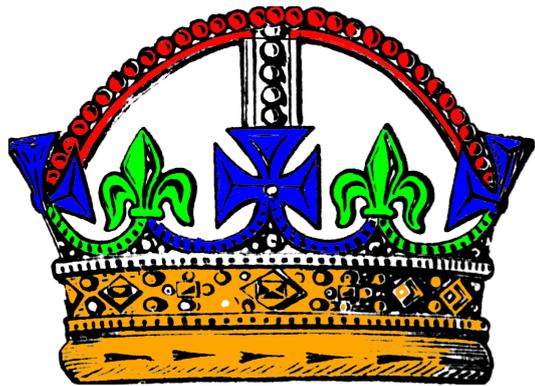
2219 is from Stanfield et al. (2006)

Four peptides in complex with 2557: 3 regions of the V3 crown



Four peptides in complex with 2557:

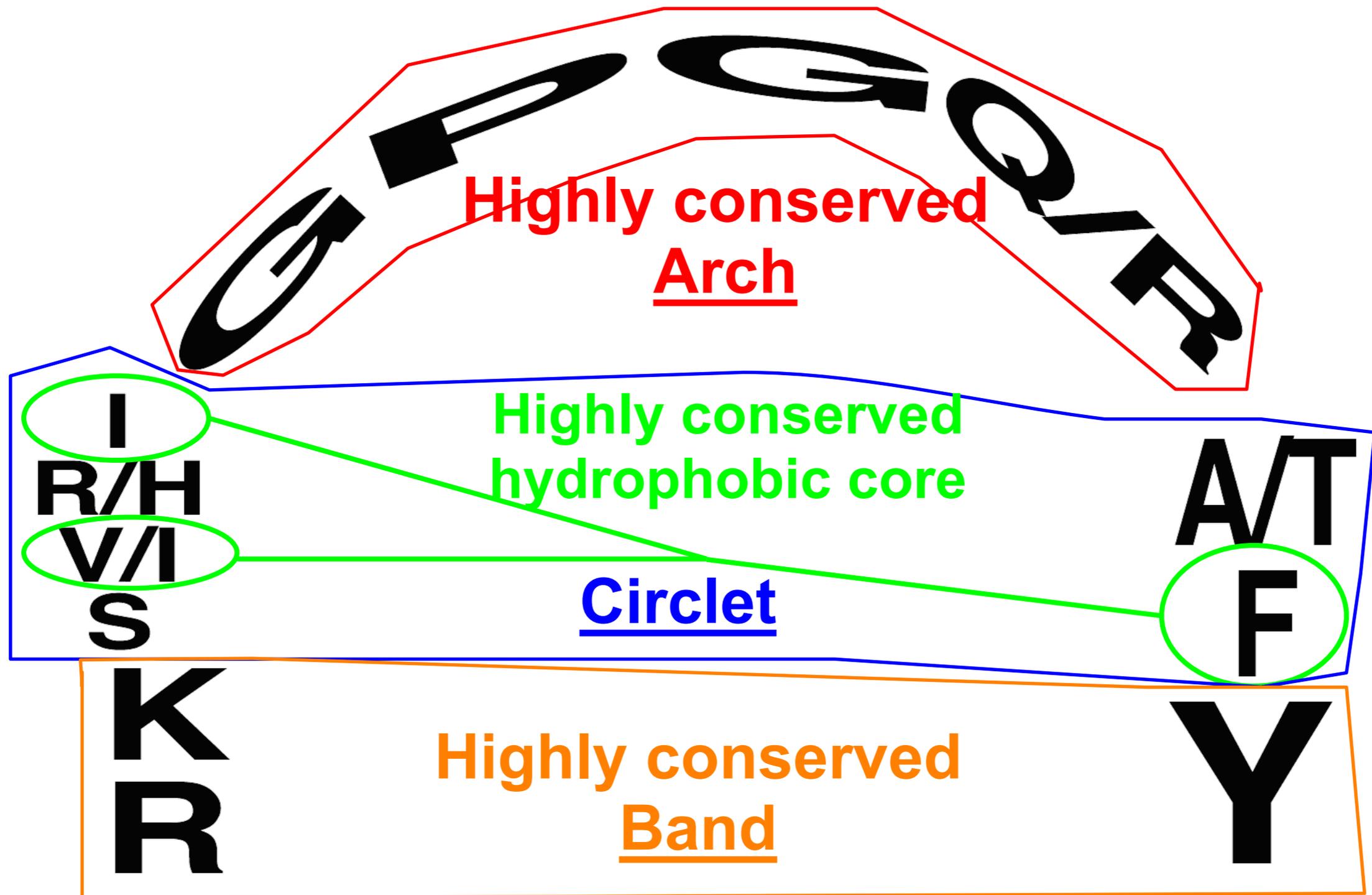
3 regions of the V3 crown



Three regions of the V3 Crown



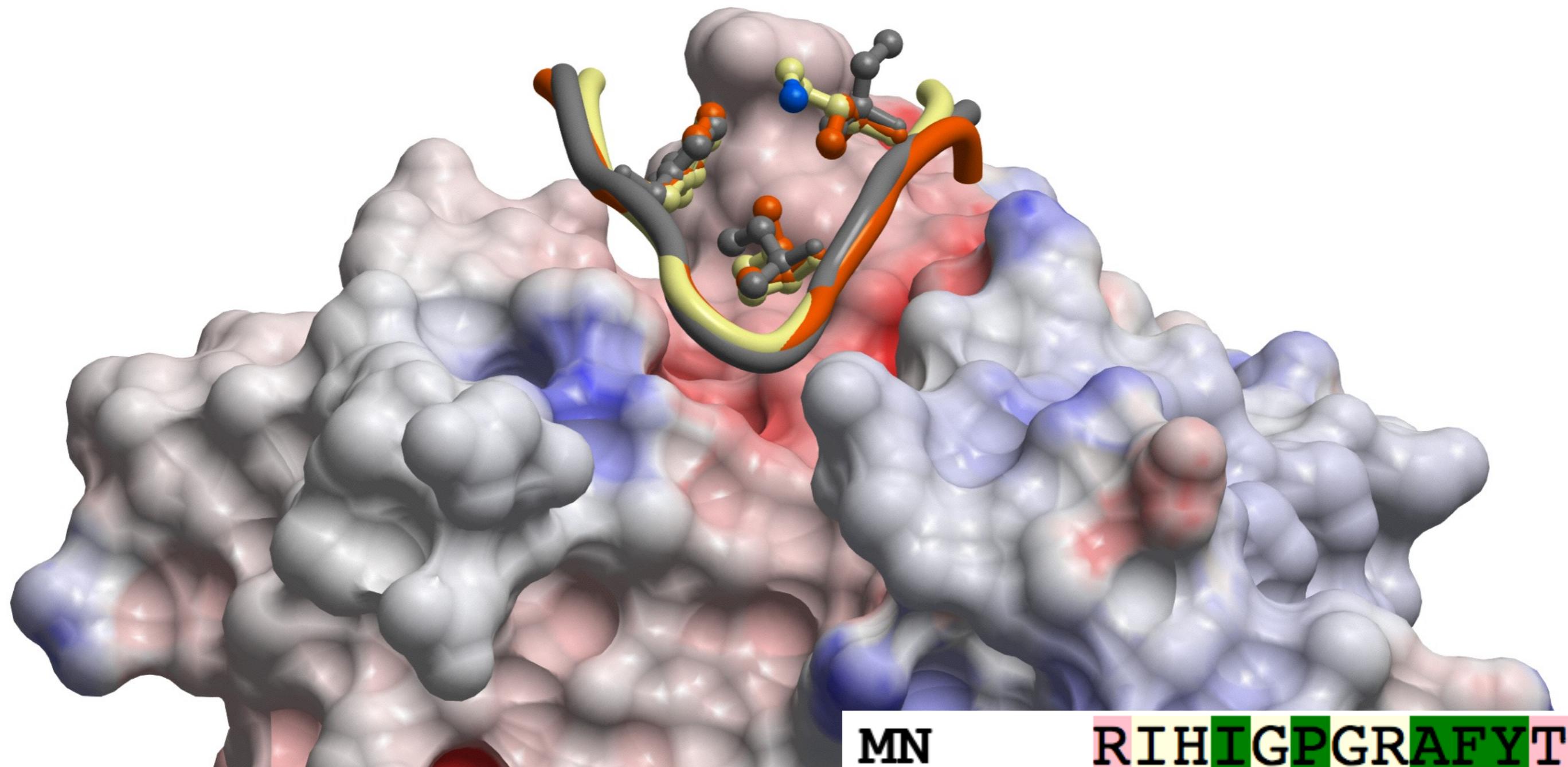
Three regions of the V3 Crown



3074 in complex with V3s of

MN(B), VI191(A) & UG29(C)

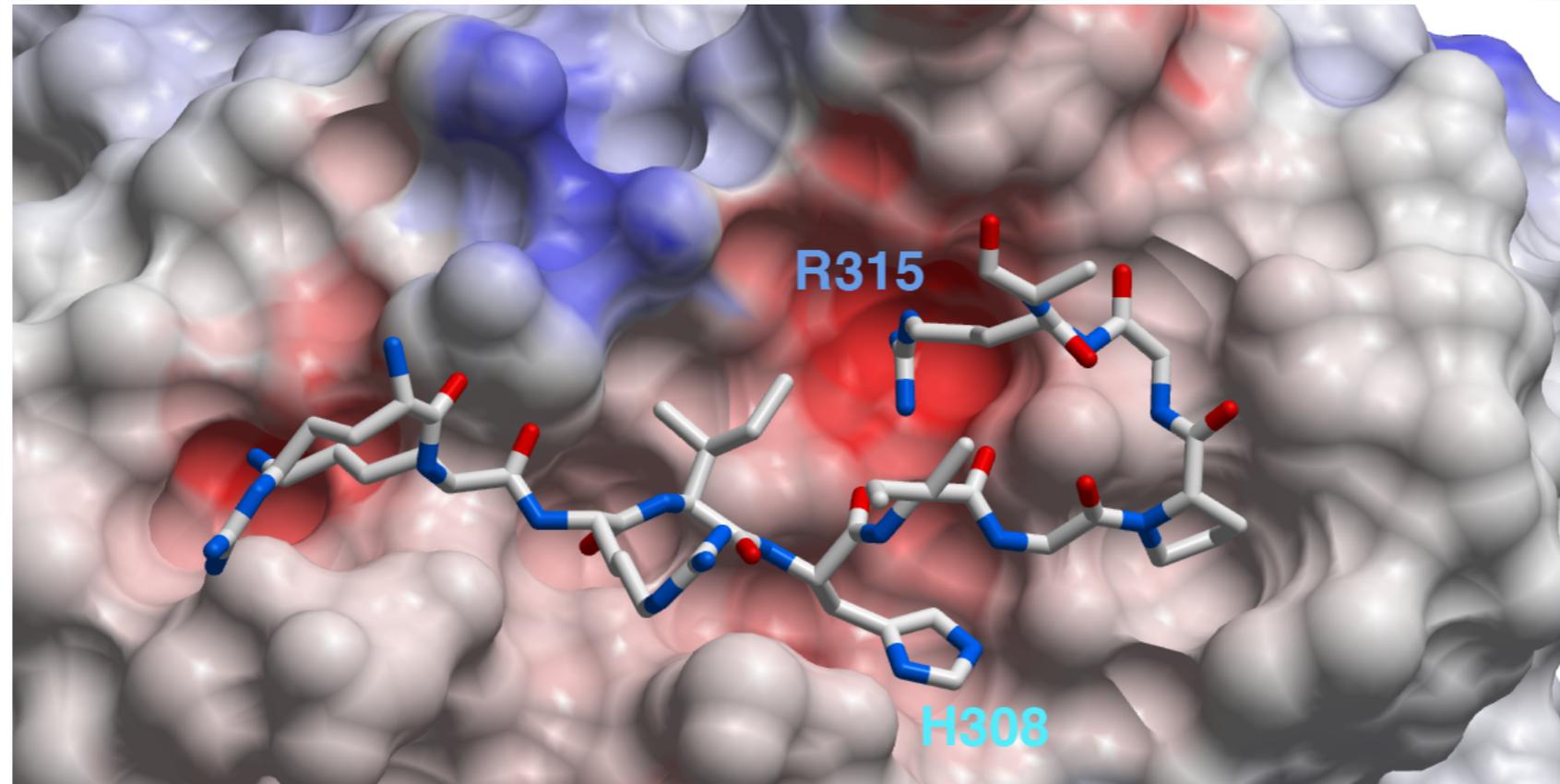
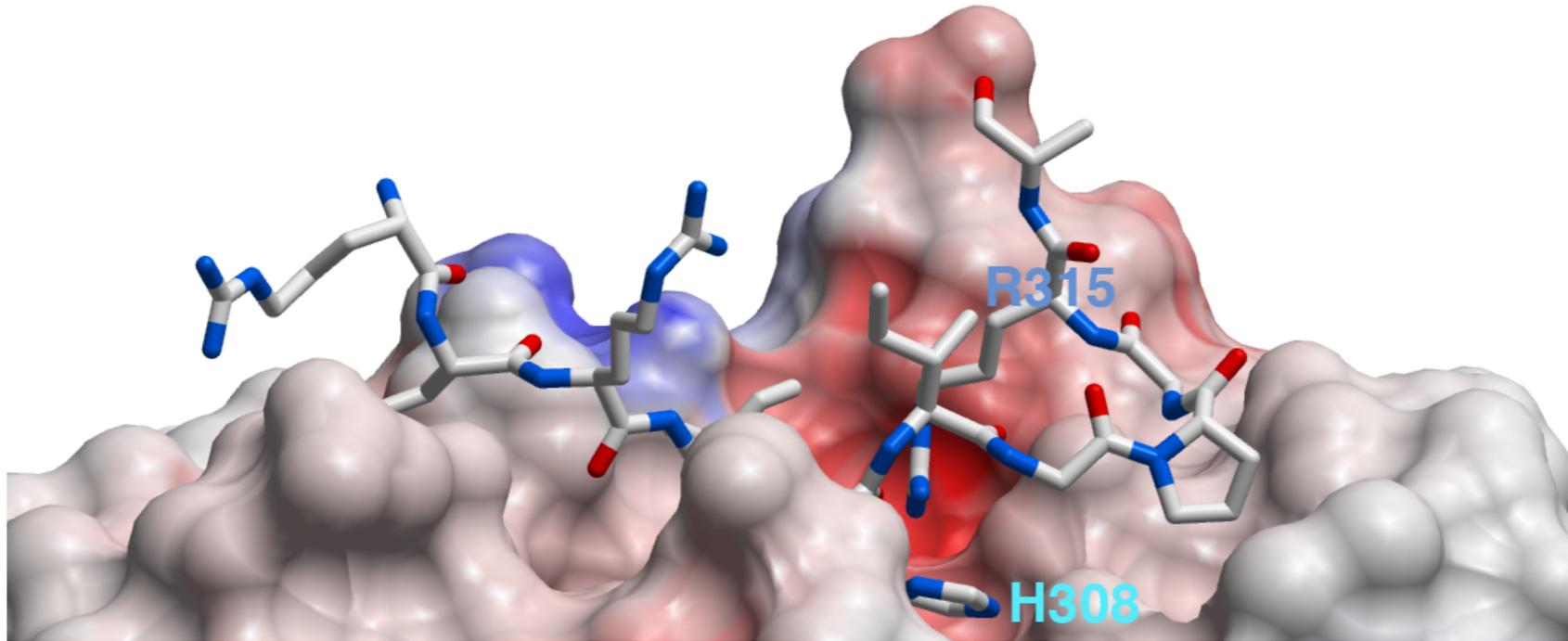
Binding the hydrophobic core



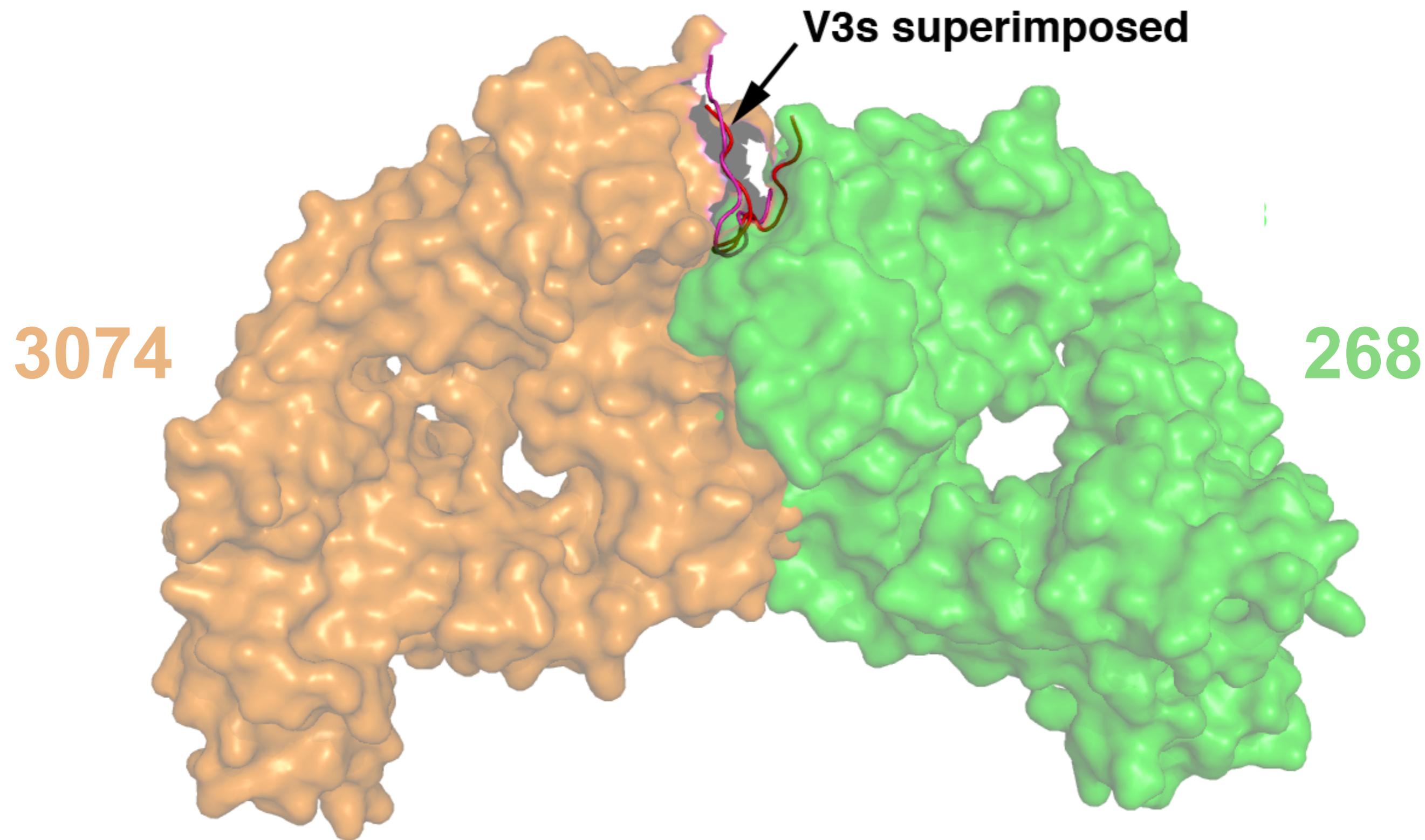
MN	RIHIGPGR	AFYT
VI191	GIHIGPGR	AFYA
UG29	SKRIRPRQ	AFYA

268/MN

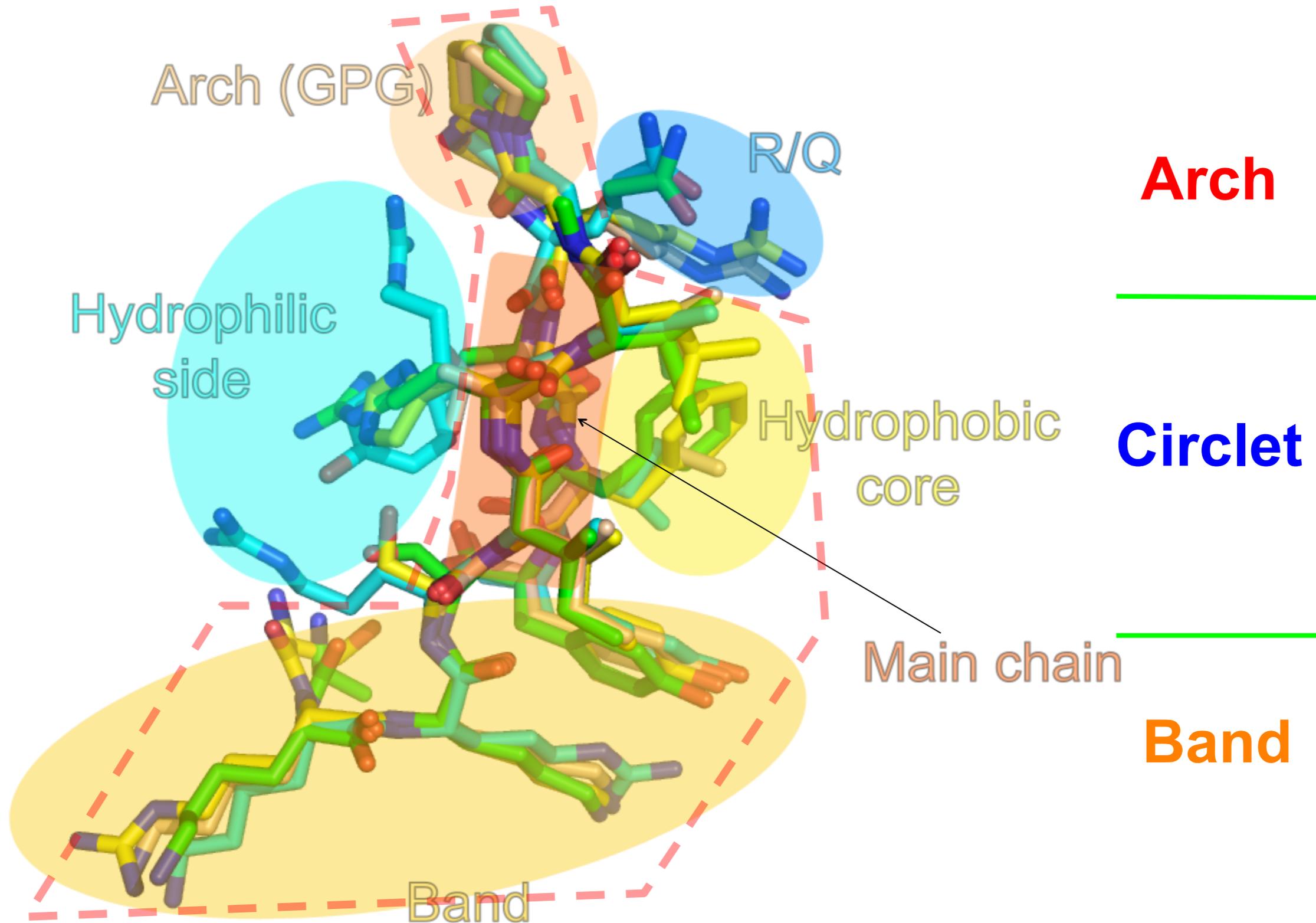
Binding the hydrophilic face



3074 and 268 bind different sides of V3 crown

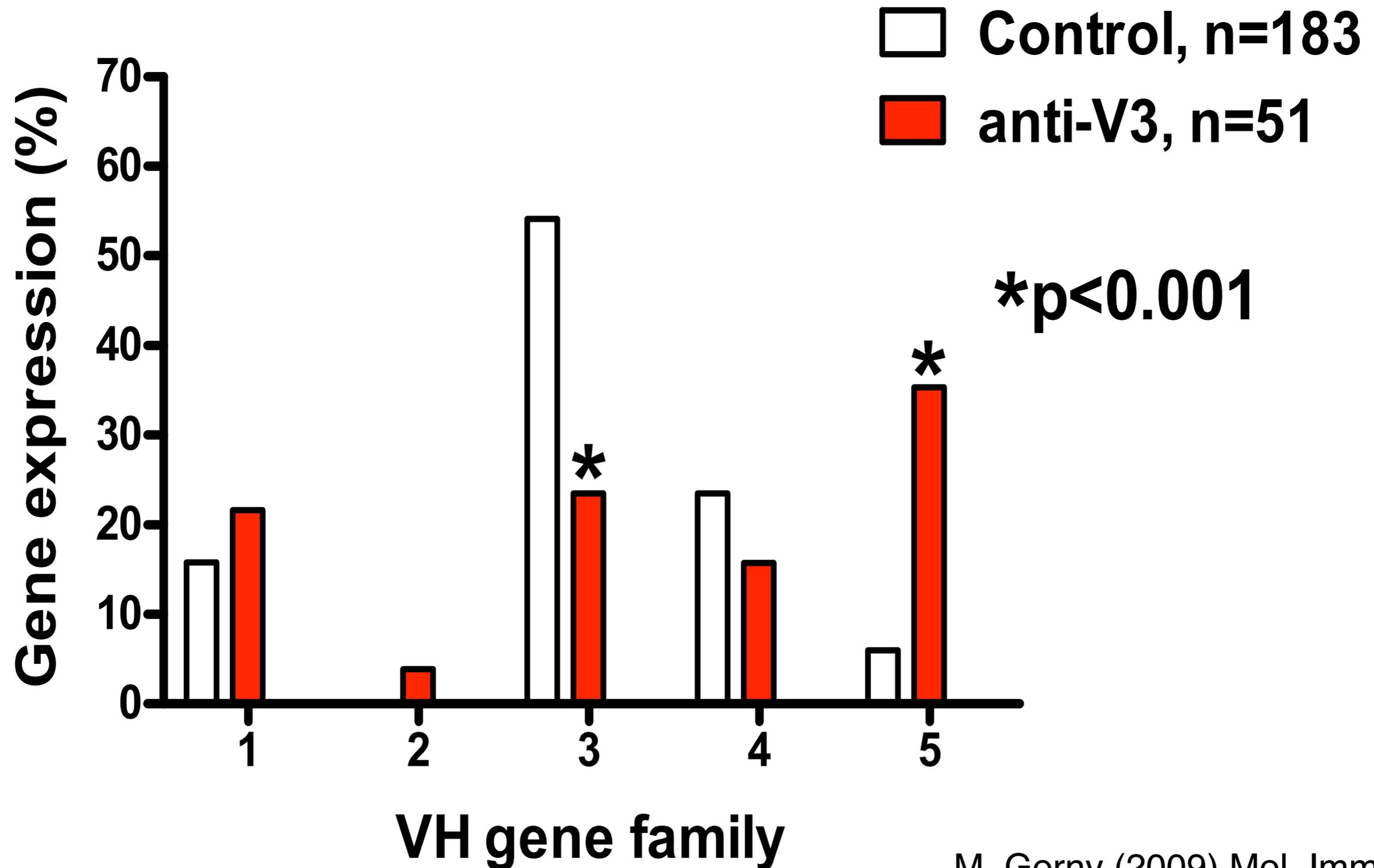


Structural elements in V3

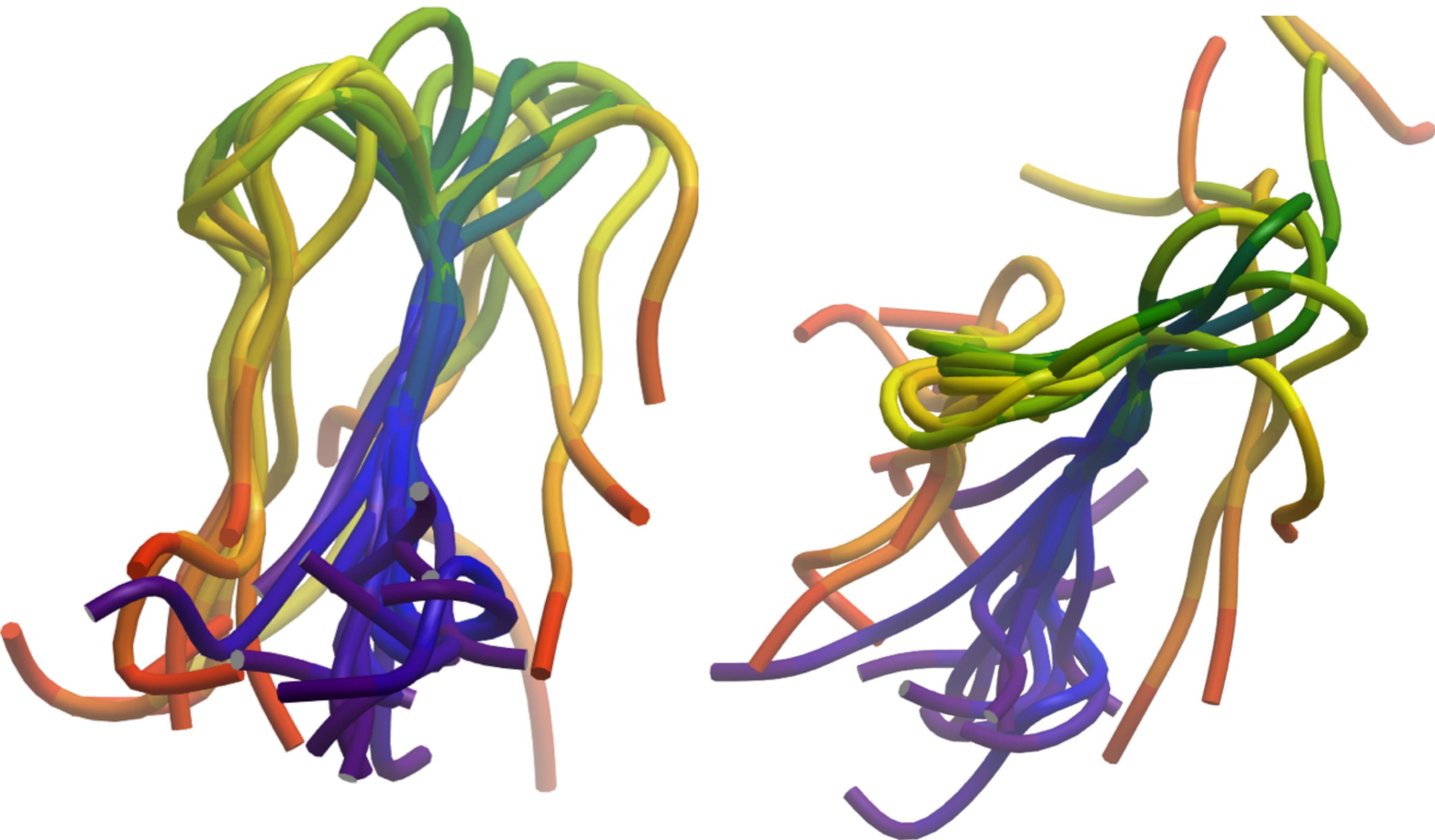


Structure and gene usage of anti-V3 human mAbs

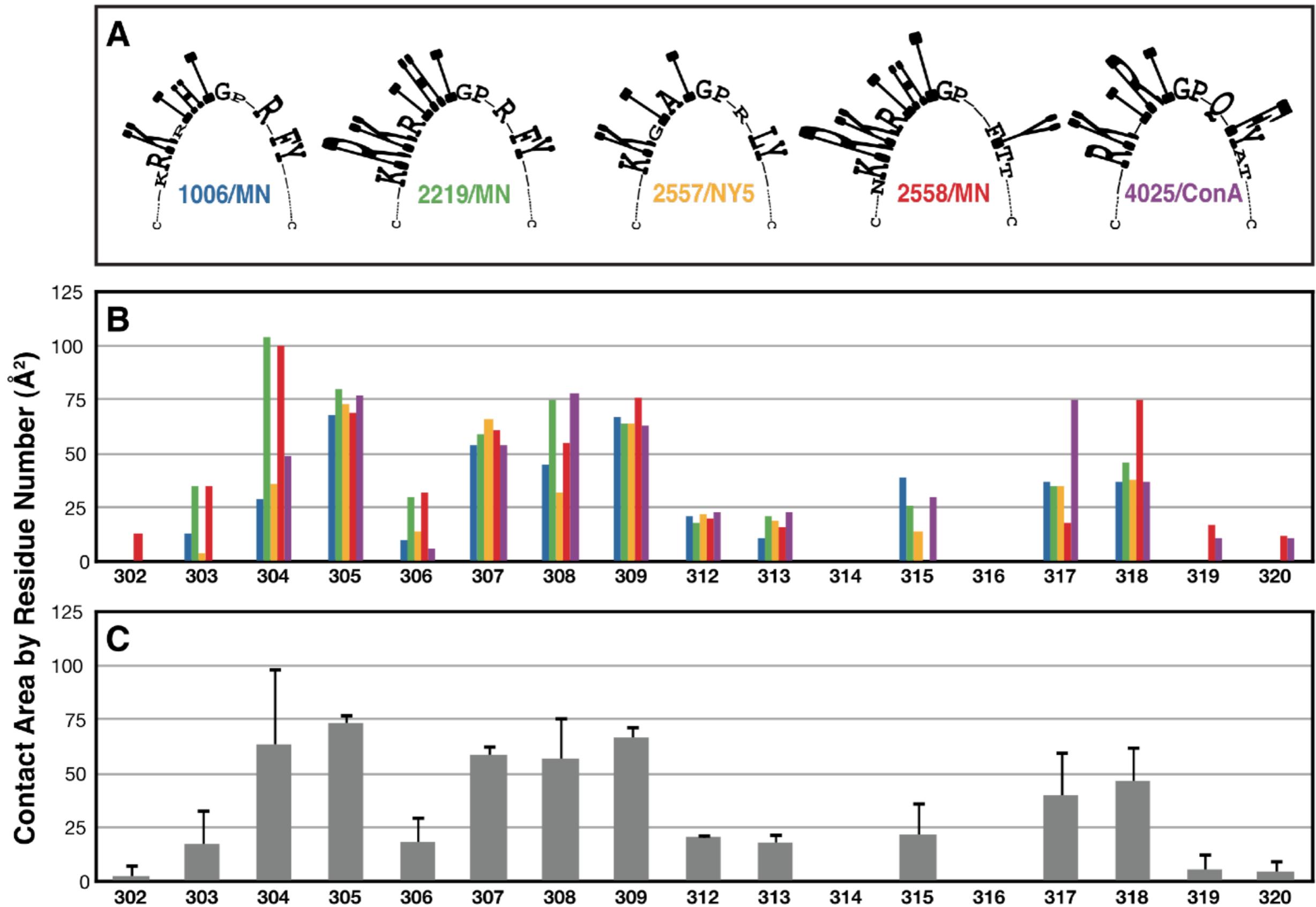
Preferential gene usage of anti-V3 human mAbs



Superimposition of 15 V3 epitopes



Five VH5-51 anti-V3 mAbs in complex with V3 peptides.

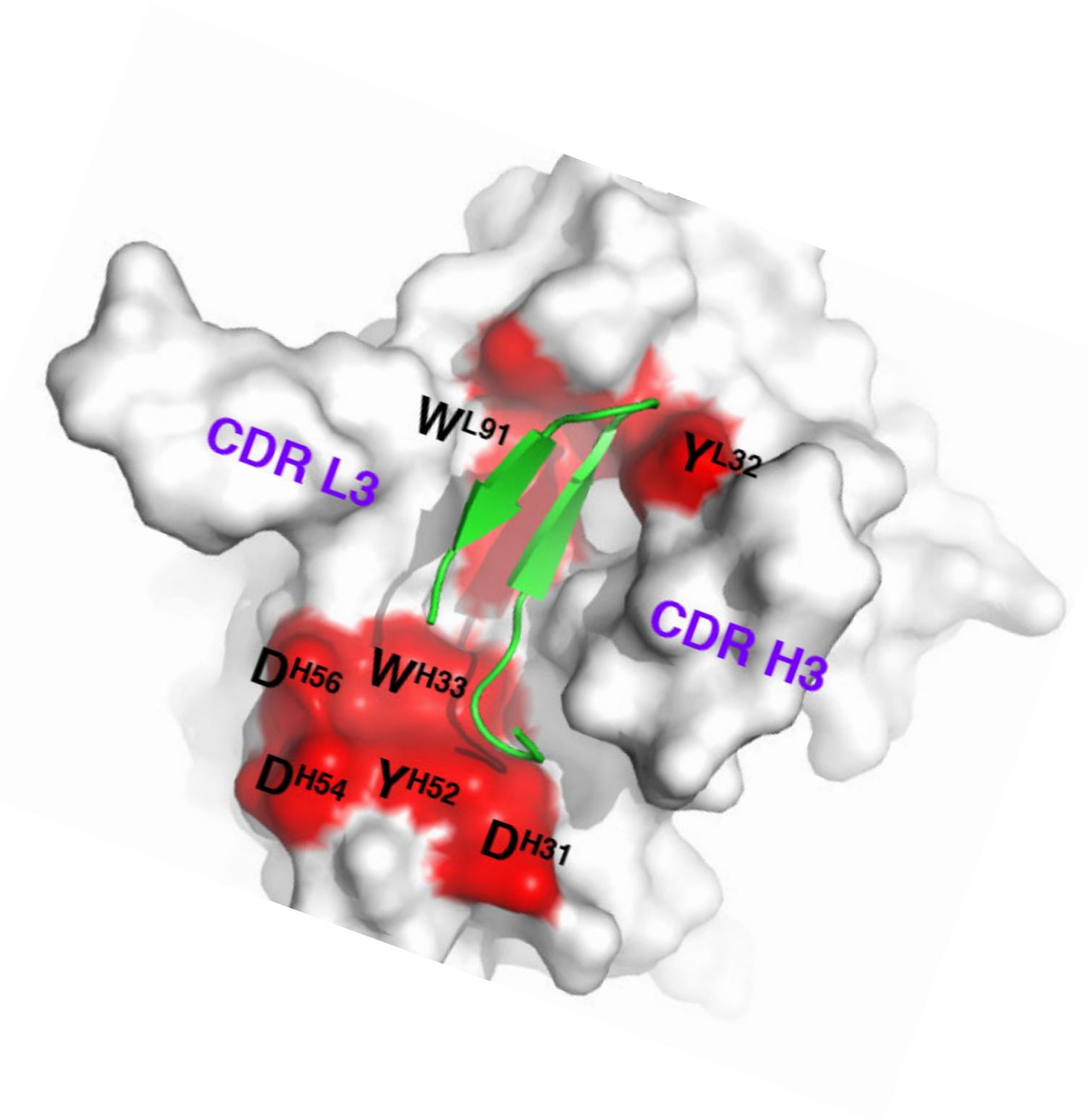
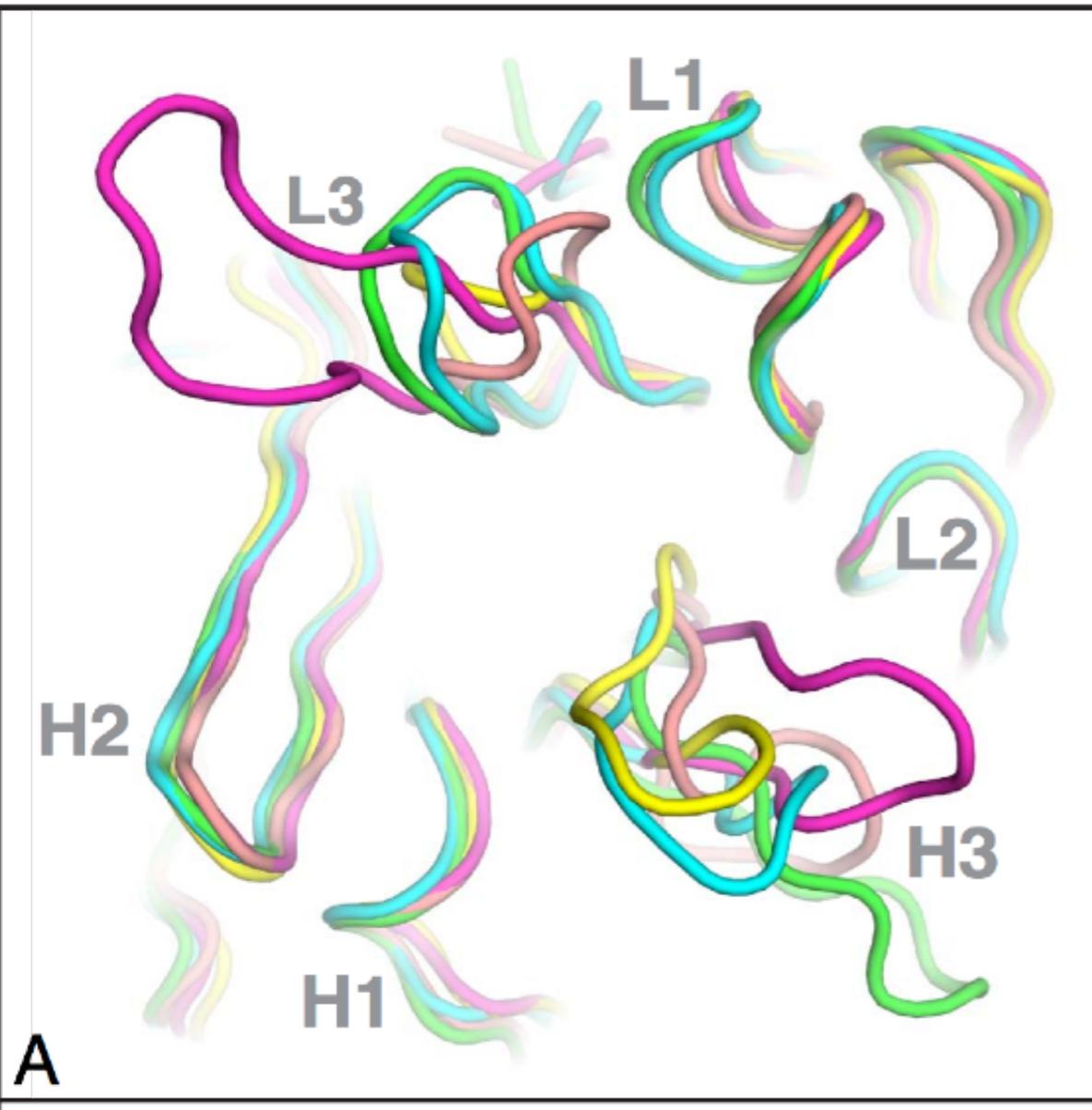


Germline residues comprise the paratopes

mAb (peptide)	CDR H1	CDR H2	CDR H3
	GYSFTSYW	IYPGSDT	AR
1006-15 (NY5)	GYTFTDHW	IYPGSDT	ARLHYSDRSGSYFNDVFHM
2219 (MN)	GYSFSDYW	FYPGSDS	ARLGGDYEDSGADAFDF
2557 (MN)	GYNFLDSW	IYPDDSDA	TRLYLFEGAQSSNAFDL
2558 (MN)	GYSFSNYW	VYPDDSDS	ARLGFEGDYSGSFFDY
4025 (conA)	GYSFSSYW	IYPADSDT	AILGFWGANRGGGGMDV

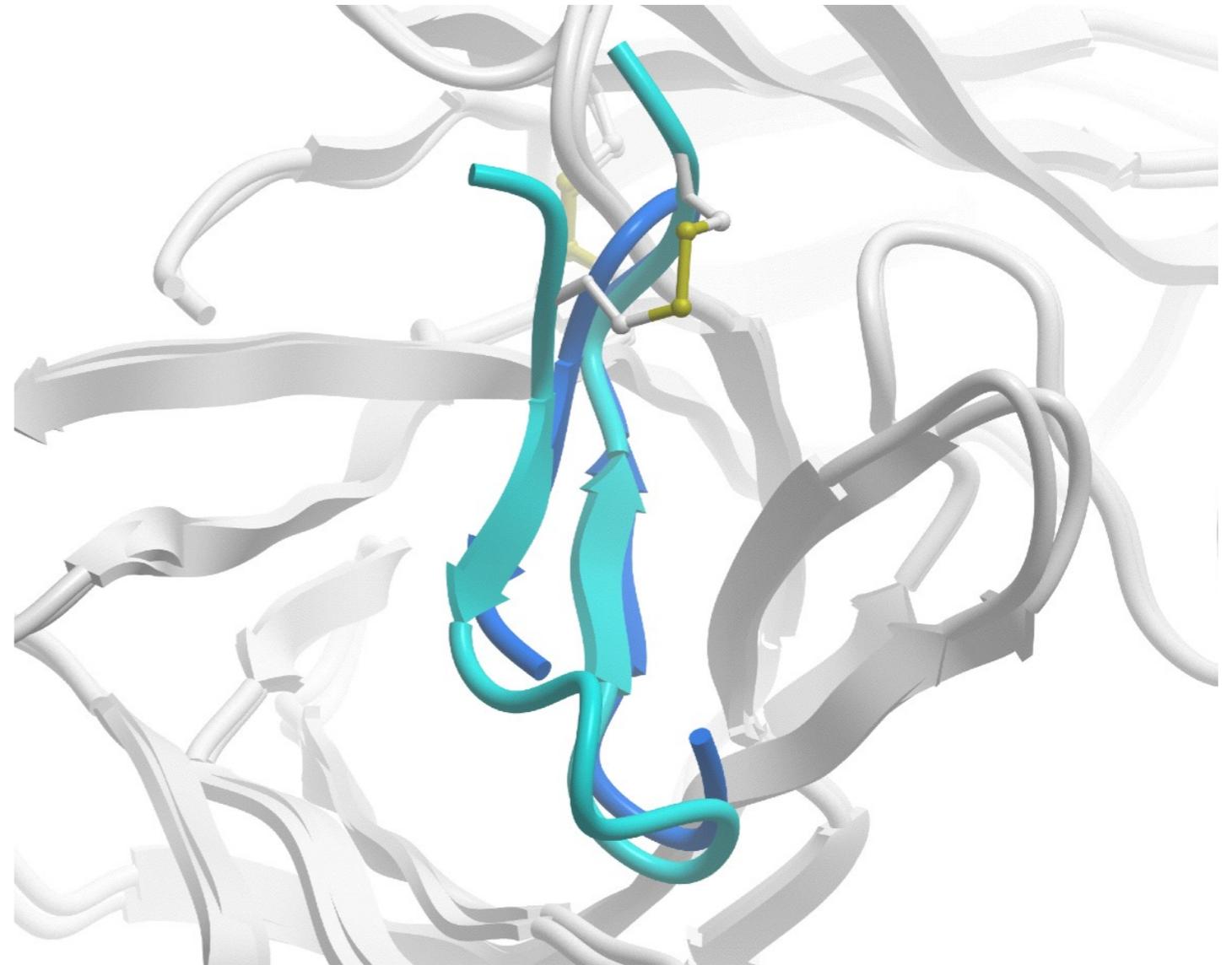
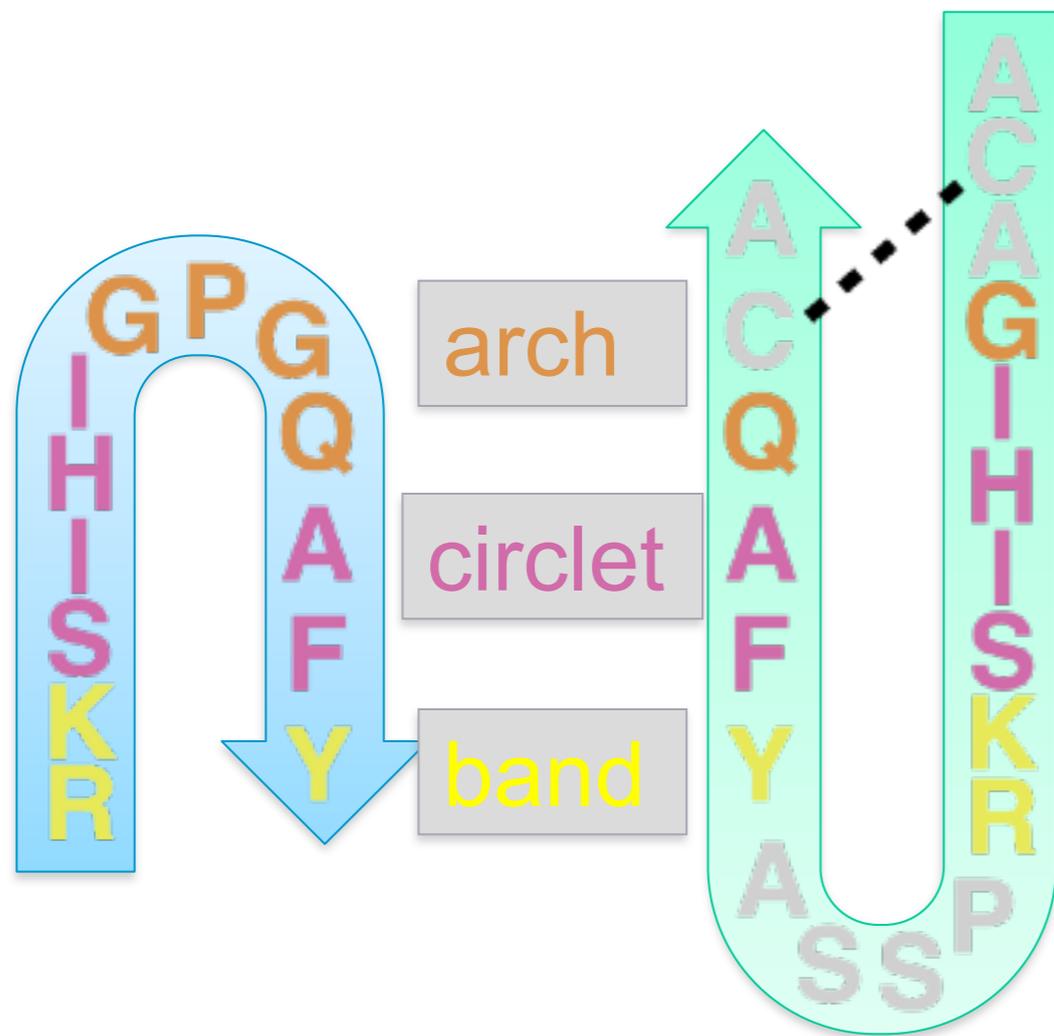
Germline	mAb (peptide)	CDR L1	CDR L2	CDR L3
VL1-47		SSNIGSNY	RNN	AAWDDSLSG
	1006-15 (MN)	SSNIENNY	RDD	ASWDDSRGGPDYV
	2219 (MN)	SSNVENNY	RND	AAWDDSRGGPDWV
VL3-1		KLGDKY	QDS	QAWDSSSTA
	2557 (NY5)	KLDDKY	QDF	QAWDASTGV
	2558 (MN)	ILGDKY	EDT	QAWDSTLGVV
VL3-10		ALPKKY	EDS	YSTDSSGNH
	4025 (conA)	ALPEKY	EDS	YSTNSGGTFFV

Antigen-binding site of VH5-51 mAbs



A mimotope targeting the VH5-51 gene usage

Crystal structure at 2.5Å resolution



**Using X6A for teaching a structural biology course for
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Acknowledgments

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Max Totrov

Tulane University

James Robinson

X6A

X4A & X4C

GM/CA



**BILL & MELINDA
GATES foundation**