

Survivors of HIV infection produce potent, broadly neutralizing IgAs directed to the superantigenic region of the gp120 CD4 binding site

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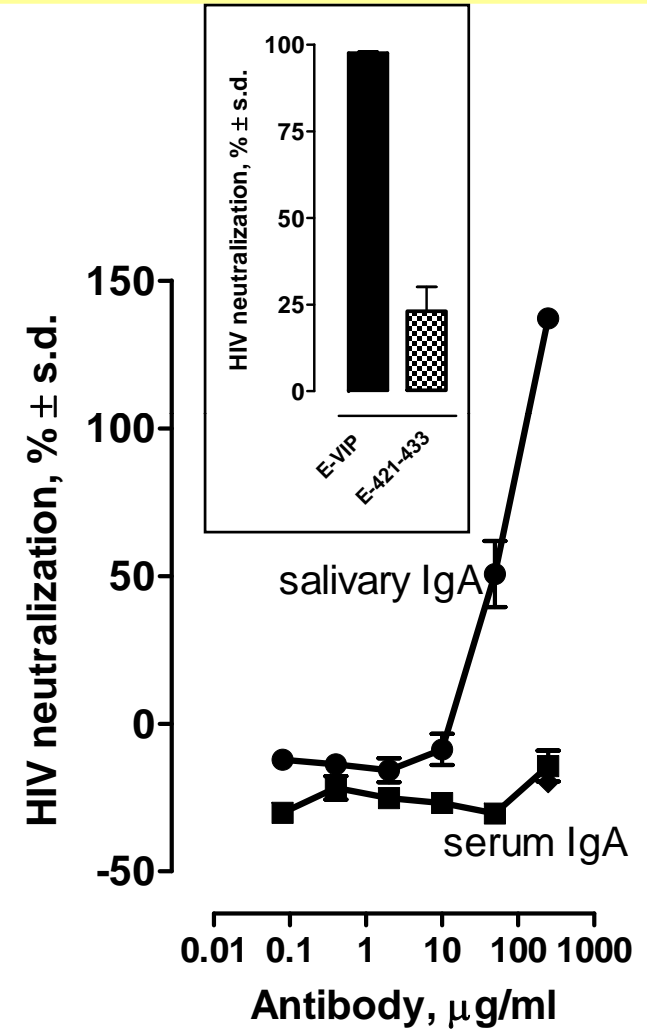
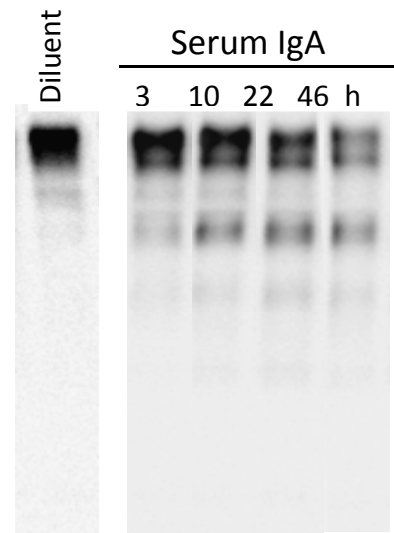
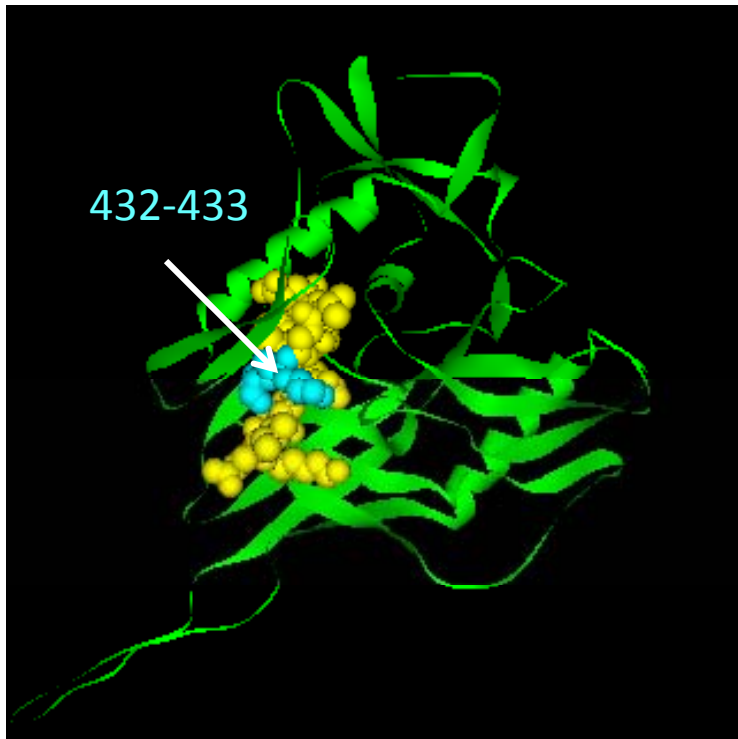
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Preimmune anti-gp120 IgA in noninfected individuals

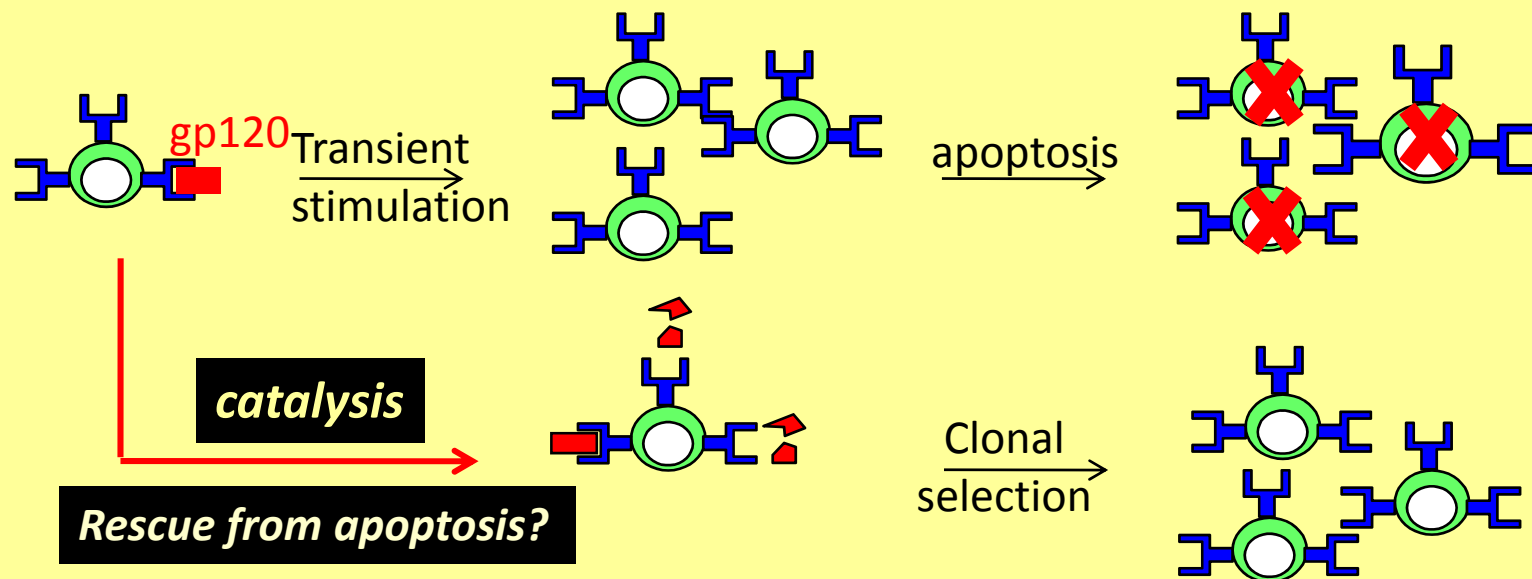


Does HIV infection induce adaptive production of broadly neutralizing anti-CD4bs-SAg IgAs?

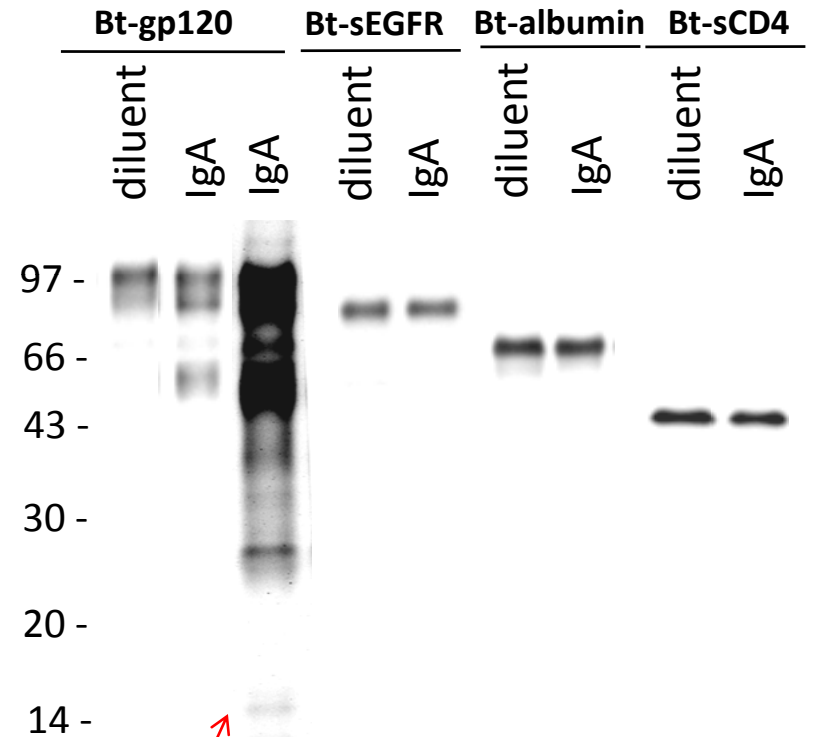
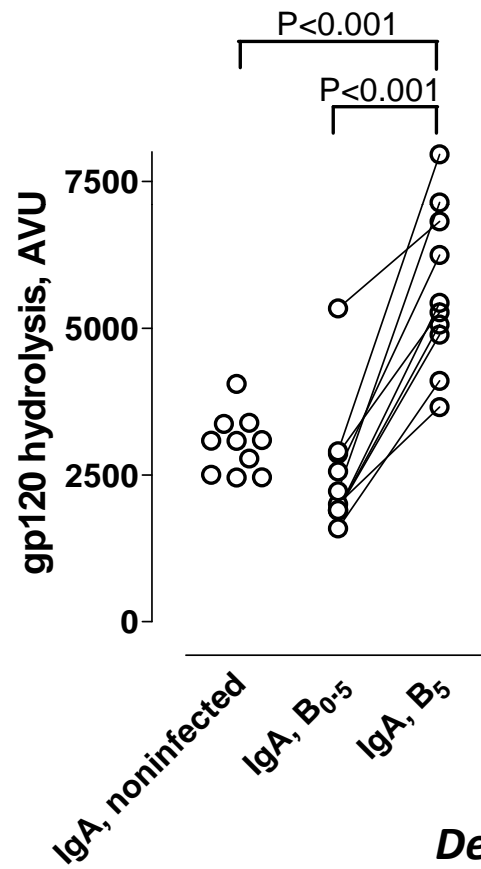
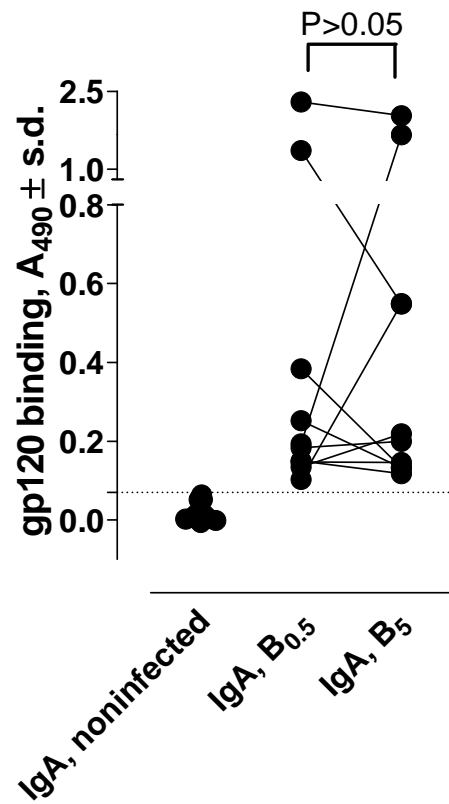
SAg character, B cells must escape apoptosis to make the Abs

Braun group, Blood. 1991, 78:175-179

Zouali group, Faseb J, 1998. 12:1473-1480

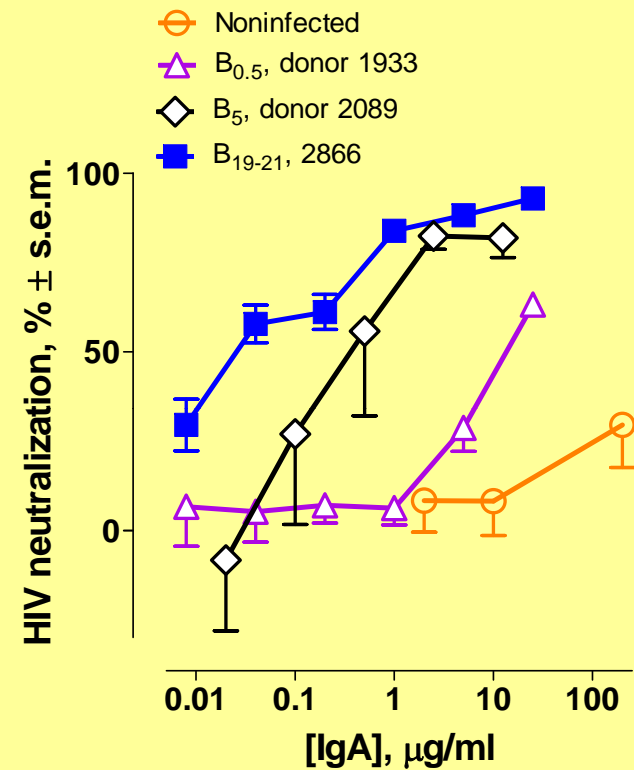
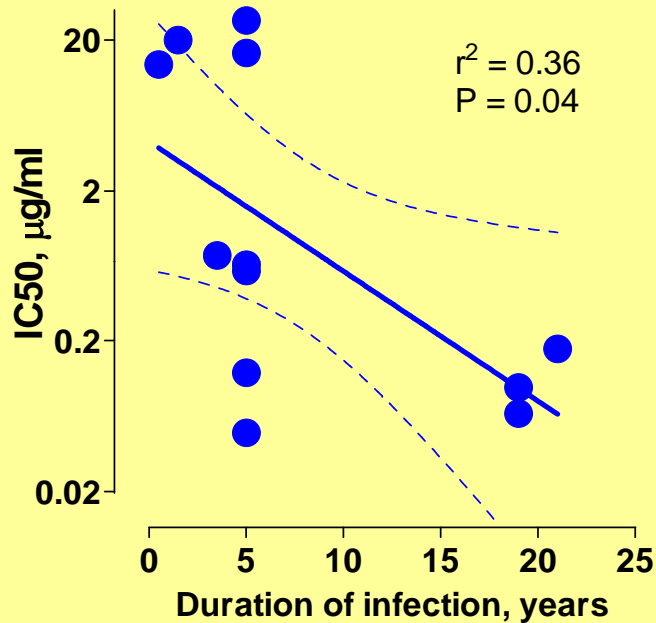


Induction of gp120ase IgAs by prolonged infection



Deduced cleavage site, $K^{432}-A^{433}$

Prolonged clade B infection induces increased neutralization of a heterologous clade C strain



LPSRI-416-433 epitope:

Consensus, clade B

Autologous, clade B

Heterologous, clade C 97ZA009

LPCRIKQIINMWQEVGKA

.....

.....R.

296-331 V3 loop:

Consensus, clade B

Autologous, clade B

Heterologous, clade C 97ZA009

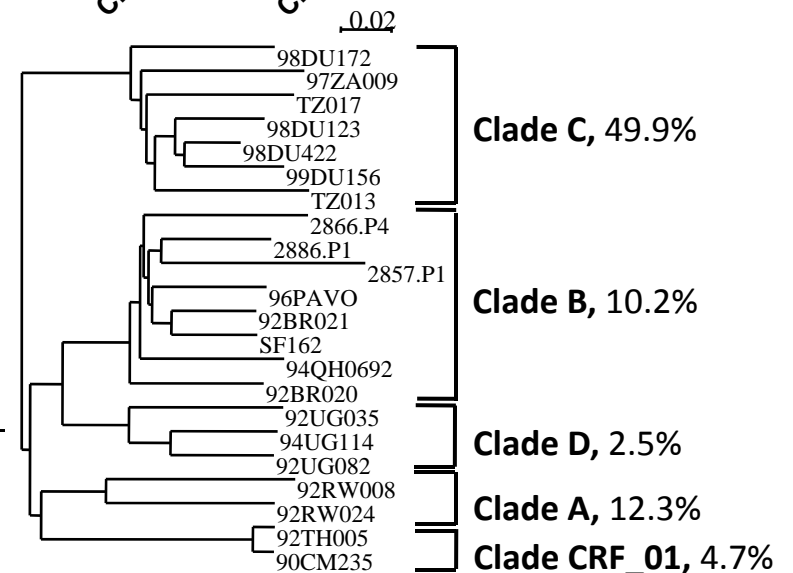
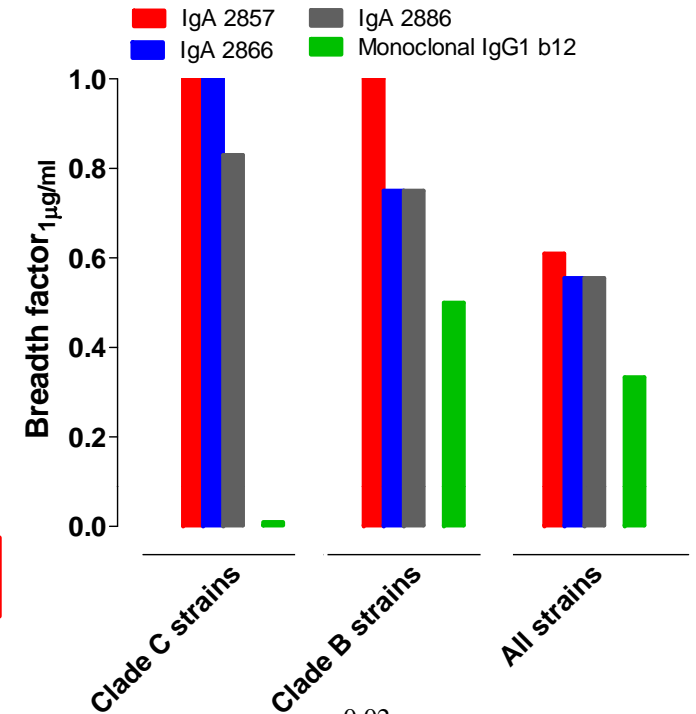
CTRPNNNTRKSIHIGPGRFYTTGEIIGDIRQAHC

.I.....R.V.....S.....N.....

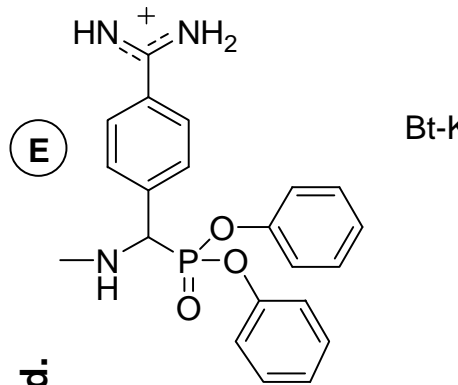
..G.....MR....QV..A.NG.....

Broad IgA neutralization of R5-dependent strains

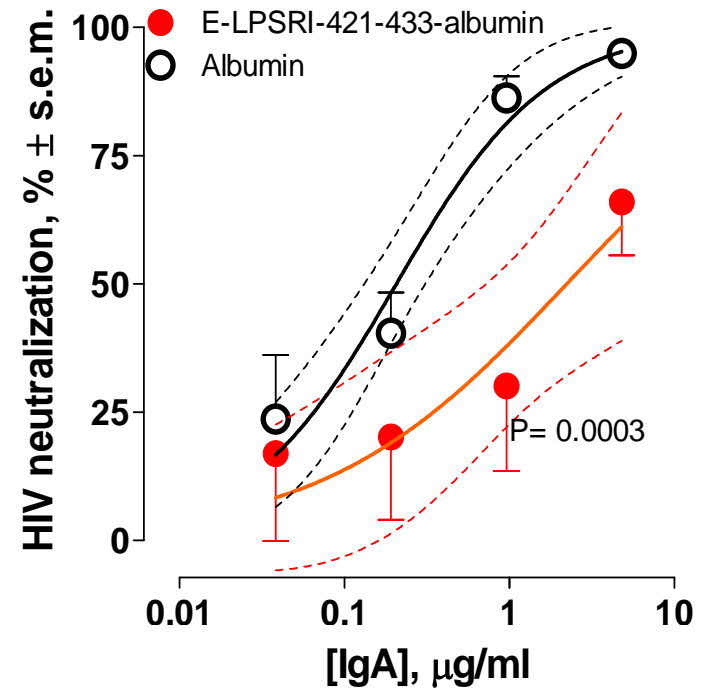
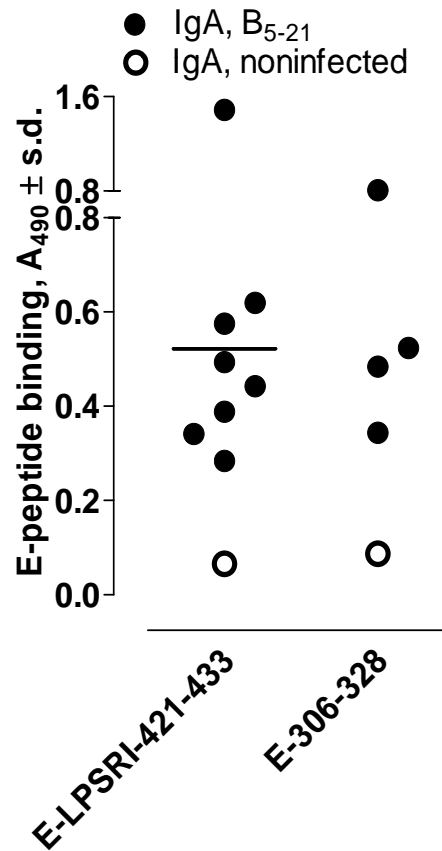
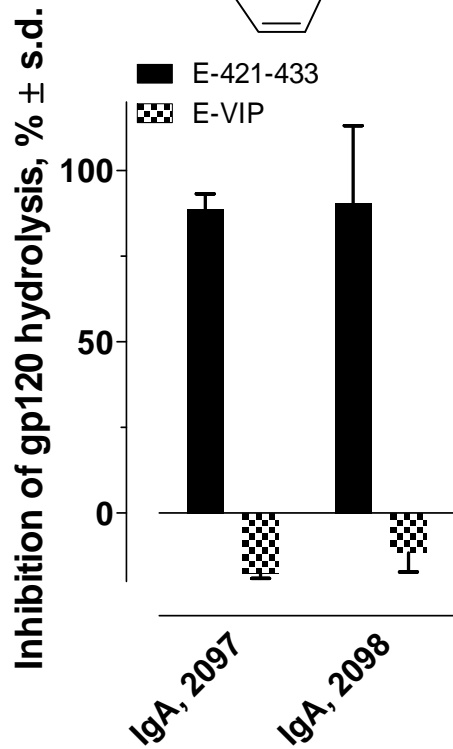
Clade	Coreceptor	Strain	IC50, $\mu\text{g/ml}$			
			IgA, 2857	IgA, 2866	IgA, 2886	IgG, b12
C	R5	98Du123	0.086 (>25)	0.053 (>25)	0.39 (>25)	>100 (1.6)
	R5	99Du156	0.16 (>25)	0.04 (>25)	0.39 (>25)	>100 (1.7)
	R5	98Du172	0.0025	0.0037	0.066	9.93
	R5	98Du422	0.026	0.023	0.19	3.62
	R5	98TZ017	0.1	0.044	1.67	82
	R5	97ZA009	0.067	0.18	0.11	>100
	Geometric mean			0.042	0.033	0.219
B	R5	92BR021	0.38	2.43	1.85	0.57
	R5	SF162	0.16	0.18	0.0044	0.72
	R5	96PAVO	0.002 (>25)	0.034 (>25)	0.2 (>25)	29.7
	R5	94QHO692	0.83 (>25)	0.094 (>25)	0.52 (>25)	1.32 (1.30)
	Geometric mean			0.100	0.194	0.171
A	R5	92RW008	0.41	12.97	0.016	0.14
	R5	92RW024	1.36	0.13	1.26	0.023
	R5	97USSN54	6.15	10.4	4.44	0.26
D	R5	93UG082	6.45	13.74	3.75	4.83
	R5	94UG114	4.87	1.9	0.91	2.36
	R5	92UG035	6.65	2.7	0.96	4.83
CRF_01	R5	CM235	10.39	26.05	5.71	2.44
	R5	92TH005	15.54	9.9	10.98	0.73



Evidence for CD4bs-SAg epitope recognition by neutralizing IgAs

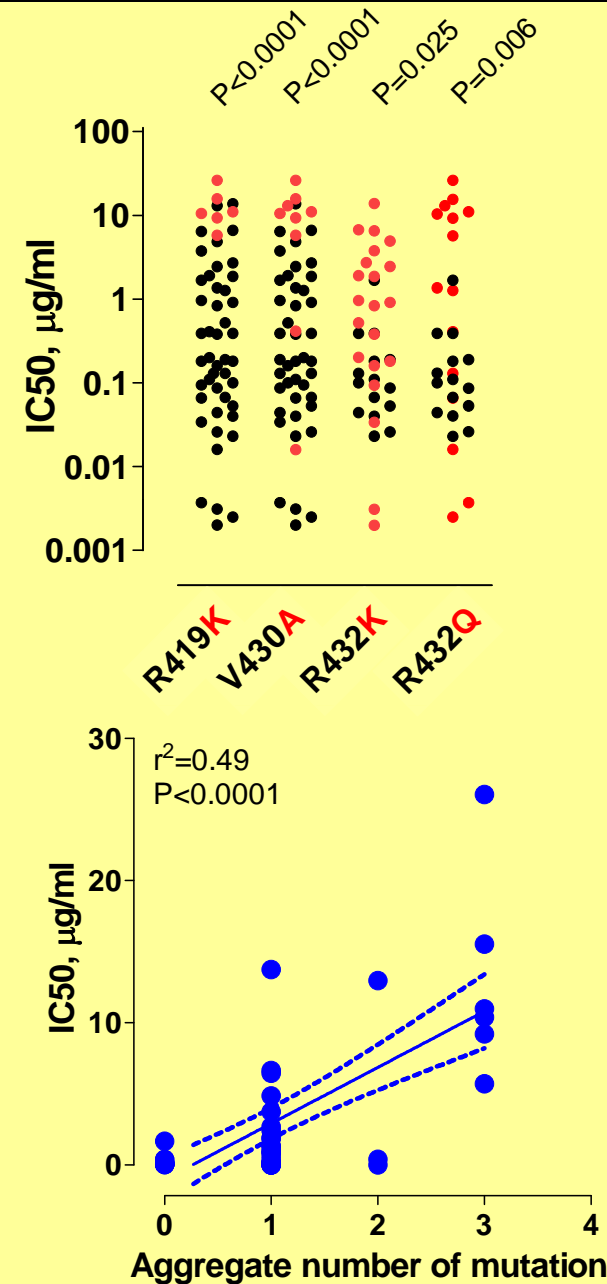


Bt-KQIINMWQEVG-**(E)**
E-421-433



Sequence-neutralization potency relationships for CD4bs-SAg epitope

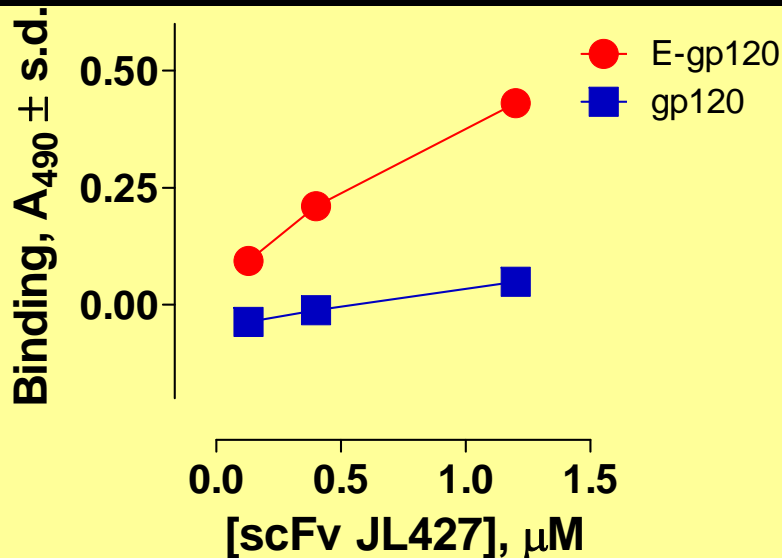
Coreceptor	Clade	strain	LPSRI-421-433
			* * *
CCR5/CXCR4	C	Consensus	LPCRIKQIINMWQEVGRA
CCR5	C	98Du123	LPCRIKQIVNMWQGVGRA
CCR5	C	99Du156	IPCRIKQIINMWQGVGRA
CCR5	C	98Du172	LQCRIKQIIRMWQGVGQA
CCR5	C	98Du422	LPCRIKQIINMWQEVGRA
CCR5	C	98TZ017	LQCRIKQIINMWQEVGRA
CCR5	C	97ZA009	LPCRIKQIINMWQEVGRA
CCR5	B	92BR021	LPXRIKXII XMWQEVGKA
CCR5	B	SF162	LPCRIKQIINRWQEVGKA
CCR5	B	96PAVO	LPCRIKQIVNMWQEVGKA
CCR5	B	94QHO692	LPCRIKQIVNMWQEVGKA
CCR5	A	92RW008	LQCRIKQIINMWQRAGQA
CCR5	A	92RW024	LQCRIKQIINMWQRVGQA
CCR5	D	93UG082	LPCRIKQIINMWQEVGKA
CCR5	D	94UG114	LQCRIKQIINMWQEVGKA
CCR5	D	92UG035	LPCRIKQIINMWQGVGKA
CCR5	AE	90CM235	LPCIKQIINMWQGAGQA
CCR5	AE	92TH005	LPCIKQIINMWQGAGQA
		▼	
CCR5/CXCR4	B	Consensus	LPCRIKQIINMWQEVGKA
CCR5	B	Autologous, 2857	LPCRIKQIINMWQEVGKA
CCR5	B	Autologous, 2866	LPCRIKQIVNMWQEVGKA
CCR5	B	Autologous, 2886	LPCRIKQIINMWQEVGKA



Poor IgA neutralization of X4-dependent strains

Clade	Coreceptor	Strain	IC50, $\mu\text{g/ml}$			
			IgA, 2857	IgA, 2866	IgA, 2886	IgG, b12
A	X4	92USNG017	>100	>100	>100	>100
B	X4	92HT599	>100	>100	>100	0.11
	X4	BZ167	>100	>100	1.54	0.26
	X4	IIIB	1.5	0.96	2.08	<0.080
D	X4	92UG001	17.24	28.47	12.73	0.15
	X4	92UG024	>100	>100	7.27	NT
	X4	92UG046	6.22	0.11	19.75	1.63
	X4	90UG266	>100	>100	>100	NT

Epitope occlusion may limit contact with B cells

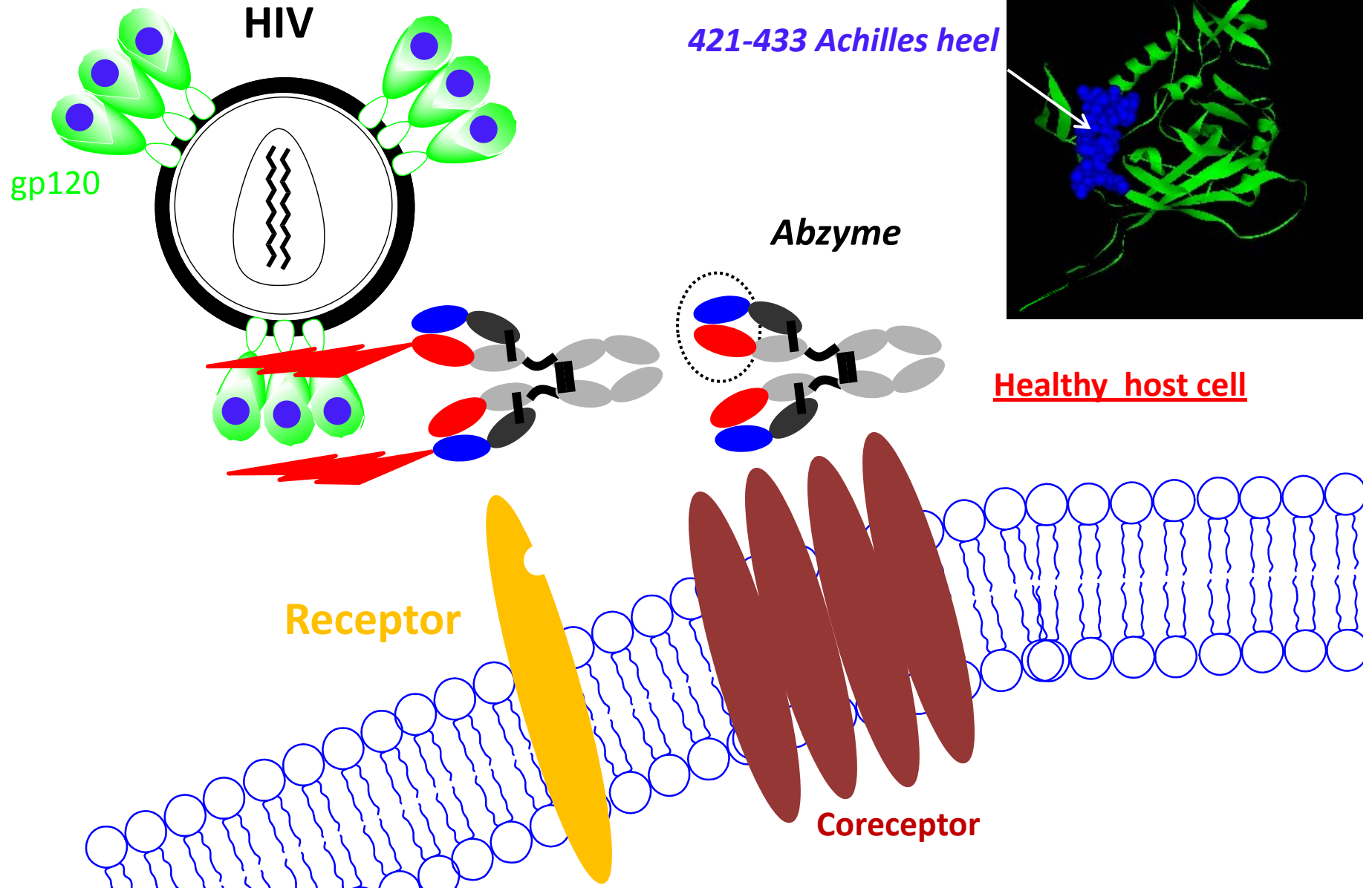


2B4C CD4-bound
 2NY7 B12-bound
 1GC1 CD4-bound
 2BF1 Unbound (SIV)



E-gp120 contains dimers and trimers (Paul et al JBC 2003) that expose the CD4bs-SAg epitope. For details of epitope 421-433 specificity of sc Fv JL427 see poster#LBPE1134

Prolonged HIV infection induces catalytic IgAs with broadly neutralizing activity directed to the CD4bs-SAg epitope.



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