Identification of Broadly Neutralizing Antibodies From SHIV Infected Chinese Macaques

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BACKGROUND

Broadly neutralizing antibodies (bnAbs) have been obtained from HIV-1-infected individuals after 2-4 years of infection. However, bnAbs with similar breadth and potency have not been isolated from SHIV-infected rhesus macaques. Understanding how bnAbs develop in SHIV-infected non-human primates (NHPs) will have important implications in use of rhesus macaques to study efficacy of HIV-1 vaccines.

METHODS

Single memory B cells were sorted with a pair of HIV-1 Env V2 differentiating baits from an $SHIV_{1157ipd3N4}$-infected rhesus macaque with broad neutralization activity in plasma after 6 years of infection. Paired variable heavy and light chains were amplified from the single memory B cells. Neutralization activity was determined using recombinant antibodies against autologous and heterologous tier 1 and tier 2 viruses on TZM-bl cells.

RESULTS

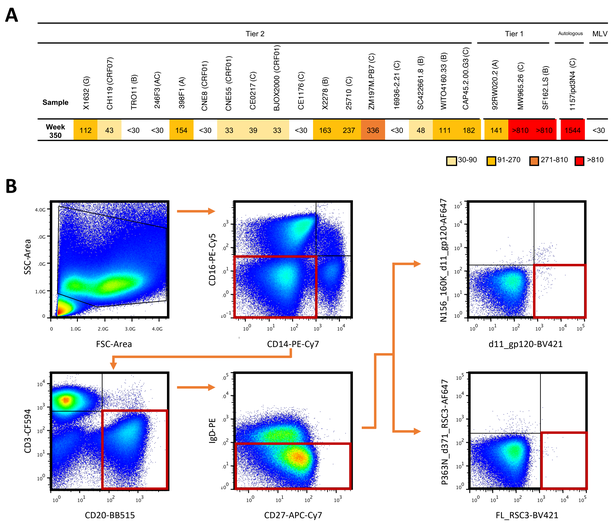

Figure 1. Isolation of antigen-specific mAbs. Epitope-specific memory B cells were sorted with a pair of differentiating baits with V1V2 bnAb specificity from PBMC collected at week 350 from G1015R, in which the broadly neutralizing activity was elicited.

Table 1. Neutralization activity of mAbs isolated from G1015R

	Tier 2																	Tier 1			Autologous	MLV
mAb ID	X1632 (G)	CH119 (CRF07)	TRO11 (B)	246F3 (AC)	398F1 (A)	CNE8 (CRF01)	CNE55 (CRF01)	CE0217 (C)	BJOX2000 (CRF01)	CE1176 (C)	X2278 (B)	25710 (C)	ZM197M.PB7 (C)	16936-2.21 (C)	SC422661.8 (B)	WITO4160.33 (B)	CAP45.2.00.G3 (C)	92RW020.2 (A)	MW965.26 (C)	SF162.LS (B)	1157ipd3N4 (C)	
J007	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	1.25	>50	0.98	>50
J013	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	8.16	>50
J024	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>20	>50	>50	>20	0.4	0.64	0.62	>50
J029	>50	>50	43.48	>50	>50	>50	29.41	4.44	>50	>50	1.25	0.81	>50	>50	4.73	0.28	0.14	>50	0.102	>50	0.077	>50
J031	>50	>50	37.03	>50	>50	>50	47.61	>50	>50	>50	0.78	15.42	>50	>50	9.71	6.67	2.99	>50	0.055	>50	0.155	>50
J032	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	27	>50	>50	>50	>50	>50	>50	0.005	0.172	0.96	>50
J033	>50	>50	18.05	20.59	21.43	38.46	>50	15.00	5.14	14.85	>50	1.78	1.56	>50	>50	20.83	0.19	0.23	>50	0.307	>50	0.031	>50
J037	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	0.195	0.731	0.39	>50
J038	41.67	29.90	13.80	25.42	29.41	>50	20.83	5.54	26.32	>50	1.28	0.87	>50	>50	37.50	0.76	0.48	>50	0.11	>50	0.023	>50
J039	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	0.213	>50	4.97	>50
J040	>50	>50	>50	>50	>50	>50	48.29	4.35	>50	>50	2.27	1.72	>50	>50	>50	0.61	0.25	>50	0.043	>50	0.24	>50
J044	>50	>50	>50	>50	>50	>50	44.12	>50	>50	>50	3.75	9.47	>50	>50	>50	27.78	>50	>50	0.96	>50	<0.06	>50

50-10 ug/ml 10-2 ug/ml 2-0.2 ug/ml <0.2ug/ml

Neutralization activity of 12 mAbs isolated from G1015R were determined against 17 tier 2 viruses, 3 tier 1 viruses and 2 autologous viruses.

Table 2. Gene family analysis of rhesus monoclonal antibodies

	Heavy chain					Light chain			
mAb	IGHV	IGHJ	IGHD	CDR3 (aa)	SHM (%)	IGKV/LV	IGKJ/LJ	CDR3 (aa)	SHM (%)
J024	4-2*01 F	5-1*01 F	2-1*01 F	18	11.31	K1S15*01 F	K1*01 F	9	13.26
J029	4-2*01 F	4*01 F	3-1*01 ORF	18	16.22	K1-20*01 F	K4*01 F	9	19.57
J031	4-2*01 F	4*01 F	3-1*01 ORF	18	20.48	K1-20*01 F	K4*01 F	9	16.3
J033	4-2*01 F	4*01 F	3-1*01 ORF	18	20.6	K1-20*01 F	K4*01 F	9	19.25
J038	4-2*01 F	4*01 F	3-1*01 ORF	18	21.35	K1-20*01 F	K4*01 F	9	17.7
J040	4-2*01 F	4*01 F	3-1*01 ORF	18	21.62	K1-20*01 F	K4*01 F	9	16.77
J044	4-2*01 F	4*01 F	3-1*01 ORF	18	11.02	K1-20*01 F	K4*01 F	9	12.73
J039	4-2*01 F	4*01 F	3-3*01 F	18	9.67	K3S1*01 F	K1*01 F	10	9.32
J007	3-21*01 F	5-2*01 F	3-3*01 F	22	13.99	L8-1*01 F	L6*01 F	10	1.9
J013	3-7*01 F	5-1*01 F	2-4*01 F	19	5.76	K3S11*01 F	K2*01 F	9	8.86
J032	3-11*01 F	5-1*01 F	1-1*01 F	22	9.01	K3-1*01 F	K2*01 F	9	4.14
J037	3-7*01 F	5-1*01 F	1-8*01 F	22	16.47	K1-20*01 F	K2*01 F	9	4.76

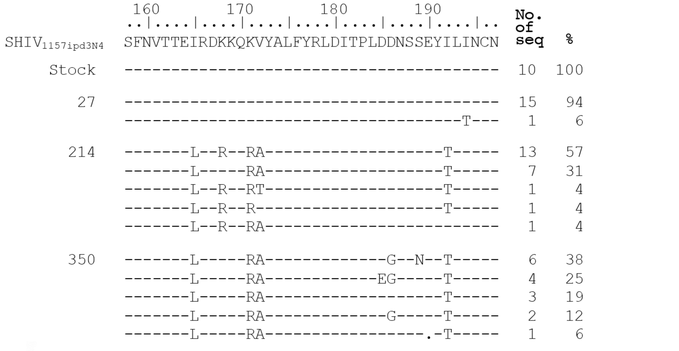

Figure 2. Identification of neutralization escape mutations in V2 region in G1015R. Amino acid sequences of V2 region from the viral stock and weeks 27, 214 and 350 post infection were compared to the $SHIV_{1157ipd3N4}$ reference sequence.

Table 3. Neutralization susceptibility of autologous escape mutants

Virus	J029		J031		J033		J038		J040		J044	
	IC_{50}	Fold change	IC_{50}	Fold change	IC_{50}	Fold change	IC_{50}	Fold change	IC_{50}	Fold change	IC_{50}	Fold change
wt 1157	0.08	1	0.16	1	0.09	1	0.05	1	0.15	1	0.12	1
I165L	0.26	3.38	2.81	18.13	0.21	2.5	0.12	2.6	0.38	2.53	1.29	10.8
K171R	0.34	4.39	0.89	5.74	0.35	4.1	0.27	5.9	0.99	6.6	0.23	1.9
V172A	0.18	2.36	1.02	6.58	0.15	1.8	0.11	2.5	0.29	1.93	0.17	1.43
I192T	0.06	0.77	0.31	1.97	0.07	0.87	0.05	1	0.08	0.53	0.09	0.76
Trimut	0.96	12.47	>10	>65	0.67	7.9	1.44	31.3	1.81	12.07	0.82	6.88

Neutralization sensitivity of wild type $SHIV_{1157ipd3N4}$ and its V2 mutants was determined by the J029-lineage antibodies.

CONCLUSIONS

- J038 and J033 isolated from SHIV-infected Chinese rhesus macaques can neutralize 70% of tier 2 viruses.
- All nAbs are from the same lineage.
- This lineage Abs target V2 region of HIV-1 Env and select escape mutants in vivo.
- BnAbs with similar neutralization potency and breadth similar to those in humans can be elicited in rhesus macaques after long term SHIV-infection.

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