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ELITE NEUTRALIZATION AND UNIQUE EPITOPE SPECIFICITY OF A VIREMIC NON-PROGRESSOR

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BACKGROUND

In HIV infection, only 10-30% of the individuals are able to generate broadly neutralizing antibody response (bnAbs)[1].Development of bnAb response was significantly associated with duration of infection, high viral load and low CD4 counts among typical progressors. Conversely, HIV-1 viremic non-progressors are individuals who maintain higher CD4 counts with moderate viral load without any symptoms for > 7 yrs of infection[2]. However, bnAb responses have not been described among HIV-1 viremic non-progressors.

METHODS

In this study, plasma samples from a cohort of 90 ART-Naïve HIV-1infected individuals with various stages of disease progression were tested against Tier-2 global virus panel (n=11) which includes subtype A, B C, G, AC, BC & AE. The cohort includes viremic controllers, viremic non-progressors and typical progressors. The Epitope mapping was carried out by ELISA, neutralization assay with point mutants (V2 Region-N160A &R166A &V3 Region -N301A &N332A) and protein competition neutralization assay by using MPER &RSC3 antigens. Samples that are able to neutralize >50% of virus with ID50 >100 (moderate neutralization), were then tested against an extended virus panel (n=19) to find Elite neutralization. Elite neutralizers are those able to neutralize >75% of viruses tested with ID50 >100 and geometric mean ID50 > 500.

RESULTS

Through screening of 90 plasma samples we observed moderate neutralization among 28 samples (Table: 1). Neutralization potency among viremic non-progressors were significantly higher than typical progressors (p=0.043). Remarkably, we were able to identify 4 elite neutralizers with geometric mean ID50 titer between 500 and 700 and three of them were viremic non-progressors. Epitope mapping of those elite neutralizers were not specific to known targets like V2, V3, CD4bs and MPER region. Interestingly, the top most elite neutralizer has neutralized N301A mutant virus with 2.0 fold greater than the wild type. When assessed its CD4bs neutralization activity by treating with RSC3 protein, there was 1.5 fold drop in the ID50 titer to the untreated plasma.

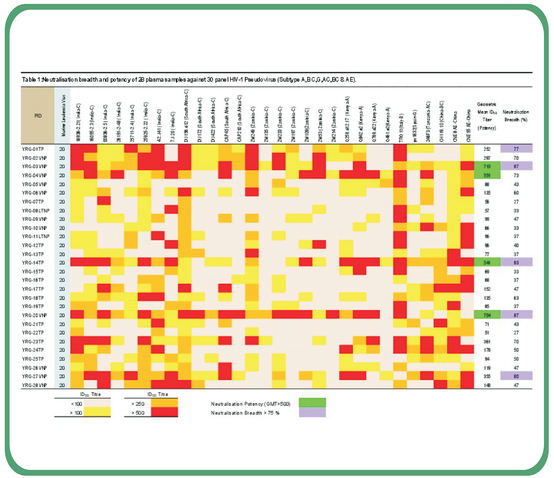

Table 1:Neutralisation breadth and potency of 28 plasma samples against 30 panel HIV-1 Pseudo virus (Subtype A,B,C,D,AC,BC & AE).

PID	Number of positives (n=30)	BR08-2-22 (Tier2-C)	BR08-2-23 (Tier2-C)	BR08-2-28 (Tier2-C)	2010-10-2-16 (Tier2-C)	2010-6-2-22 (Tier2-C)	42-A11 (Tier2-C)	7-1231 (Tier2-C)	DU156.12 (South Africa-C)	DU172.17 (South Africa-C)	DU422.1 (South Africa-C)	CAP45.2.00.G3 (South Africa-C)	CAP210.2.00.E8 (South Africa-C)	25710.2.43 (Zambia-C)	25711.11.39 (Zambia-C)	25710.2.10 (Zambia-C)	25711.2.29 (Zambia-C)	25711.10.03 (Zambia-C)	25710.2.43 (Zambia-C)	6535.3.4.17 (Tier2-AE)	16055.2.3 (Tier2-AE)	6240.08.1.F3 (Tier2-AE)	6040.18.1.A.G1 (Tier2-AE)	6094.2.1.B.C1 (Tier2-AE)	6094.2.1.B.C2 (Tier2-AE)	6094.2.1.B.C3 (Tier2-AE)	6094.2.1.B.C4 (Tier2-AE)	6094.2.1.B.C5 (Tier2-AE)	6094.2.1.B.C6 (Tier2-AE)	6094.2.1.B.C7 (Tier2-AE)	6094.2.1.B.C8 (Tier2-AE)	Geometric Mean ID_{50} Titer (Potency)	Neutralization Breadth (%)
YRG-04TP	20																																252	77
YRG-02VNP	20																																267	70
YRG-03VNP	20																																318	87
YRG-04VNP	20																																335	73
YRG-05VNP	20																																88	43
YRG-06VNP	20																																102	60
YRG-07TP	20																																19	27
YRG-08LTNP	20																																57	33
YRG-09VNP	20																																66	47
YRG-10VNP	20																																66	33
YRG-11LTNP	20																																16	37
YRG-12TP	20																																16	40
YRG-13TP	20																																77	37
YRG-14TP	20																																318	83
YRG-15TP	20																																88	33
YRG-16TP	20																																88	37
YRG-17TP	20																																102	47
YRG-18TP	20																																135	63
YRG-19TP	20																																40	37
YRG-20VNP	20																																704	67
YRG-21TP	20																																71	43
YRG-22TP	20																																51	27
YRG-23TP	20																																381	70
YRG-24TP	20																																178	50
YRG-25TP	20																																94	50
YRG-26VNP	20																																116	47
YRG-27VNP	20																																335	60
YRG-28VNP	20																																148	47

ID_{50} Titre: > 100; > 100

ID_{50} Titre: > 250; > 500

Neutralisation Potency (GMT>500)

Neutralisation Breadth > 75 %

CONCLUSIONS

These results demonstrate that viremic non-progressors develop bnAb response and it suggests that provision of CD4 helper T cells is critical for the formation of functional germinal centre. This bnAb response was associated with the presence of CD4bs Abs and it is due to viral escape in N301 glycan of V3 region which may expose occluded conserved epitope that facilitating the development of breath among elite neutralizers.

International AIDS Vaccine Initiative

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