ENHANCED COMPLEMENT ACTIVITY DOES NOT IMPROVE PROTECTION IN SHIV-CHALLENGED MACAQUES

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David A. Spencer[1], Benjamin Goldberg[2], Jérémy Dufloo[3], Timothée Bruel[3], Olivier Schwartz[3], Margaret E. Ackerman[2] and Ann J. Hessell[1]

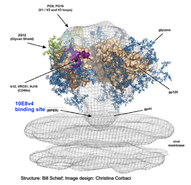
[1]Oregon Health & Science University, Oregon National Primate Research Center, Beaverton, OR. [2]Thayer School of Engineering at Dartmouth College, Hanover, NH. [3]Pasteur Institute, Paris, France.

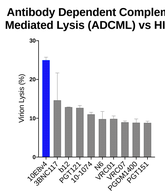
BACKGROUND

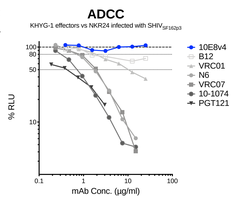
Fc-modified broadly neutralizing antibodies (bnAbs) are being advanced as next generation HIV therapeutics. Modifications to extend half-life have progressed to clinical trials.

The impact of Fc-mediated complement activity during HIV infection is largely uncharacterized**. We hypothesized that enhanced antibody mediated complement activity would improve viral outcomes.**

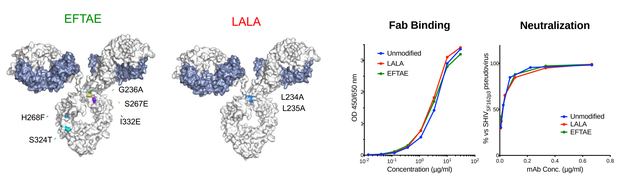
10E8v4, an MPER targeting bnAb with no ADCC activity, was selected for improving complement activation.

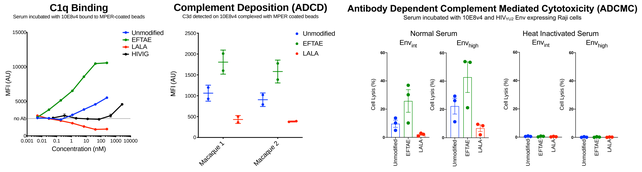




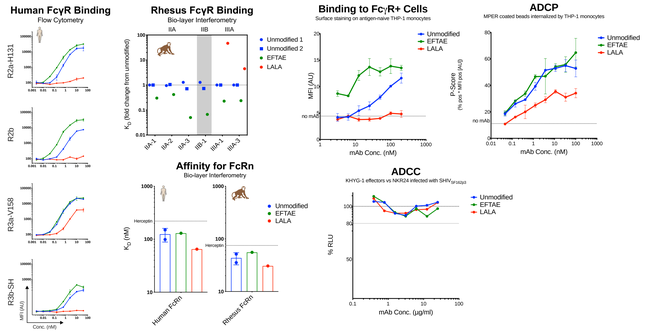


10E8v4 EFTAE has enhanced Fc-mediated complement activity.





10E8v4 EFTAE displays unaltered ADCP and ADCC activity but does possess a modified FcγR binding profile.

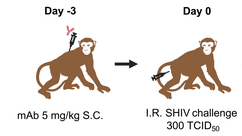


METHODS

Adult rhesus macaques were pre-treated with a sub-protective dose of unmodified and Fc variants of 10E8v4 followed by a single high dose SHIV$_{SF162p3}$ mucosal challenge.

Groups (n=6)

10E8v4
10E8v4-EFTAE
10E8v4-LALA
Control mAb

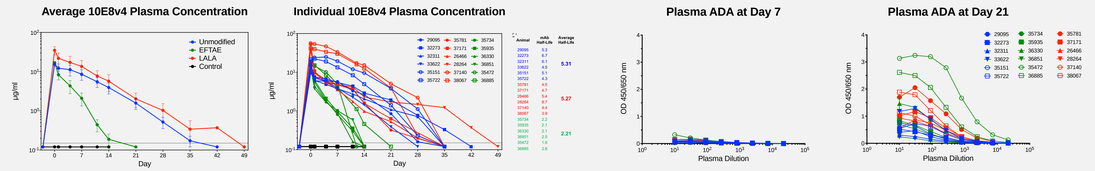


Tissue sampling

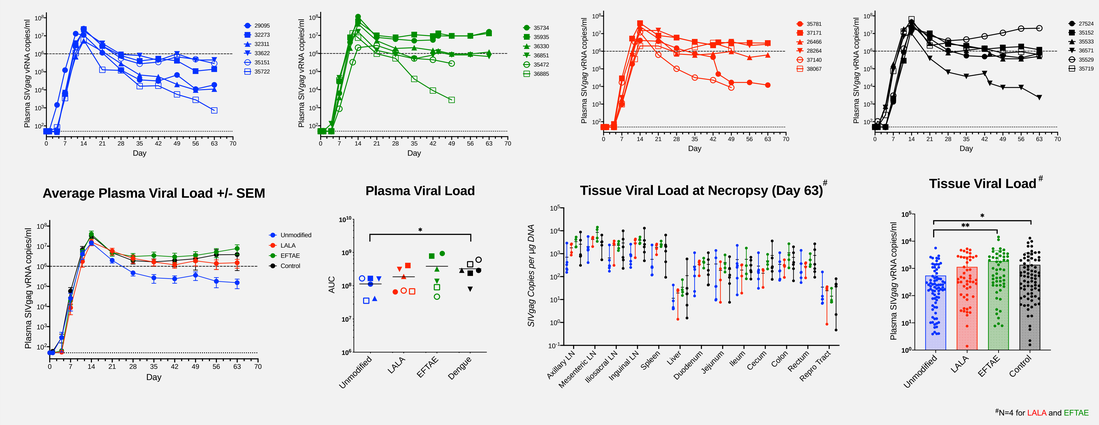
Plasma and PBMCs throughout
Day 1: Vaginal biopsies
Day 5: Rectal biopsies
Day 14: Inguinal lymph node biopsies
Wk. 9: Necropsy and tissue collection

CENTRAL FINDINGS

1. 10E8v4 EFTAE has a shorter plasma half-life. Anti-drug responses were induced in 2/6 of these macaques.



2. Pre-treatment with unmodified 10E8v4, but not 10E8v4 EFTAE or LALA, reduced viremia compared to controls.



#N=4 for LALA and EFTAE

SUMMARY OF RESULTS

10E8v4 EFTAE displays

- enhanced C1q binding, C3d deposition, and antibody dependent complement mediated lysis
- increased affinity to FcγRs, particularly FcγRIIb, but not to FcRn

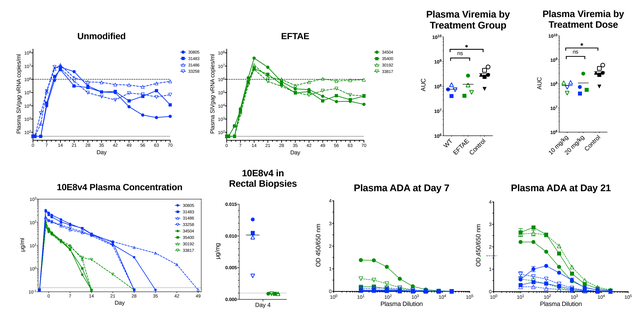
Pre-treatment with a sub-protective dose of unmodified 10E8v4 resulted in significantly lower viremia than controls. Notably, this was not observed in the Fc functional knockout (LALA) or Fc complement enhanced (EFTAE) groups.

The possible elevated viremia after pre-treatment with 5 mg/kg 10E8v4 EFTAE was not observed with higher doses, likely due to mitigated effector contributions with higher neutralization titers. However, *in vitro* assays with primary splenocytes indicate that in the absence of MAC formation, pre-treatment with 10E8v4 EFTAE can enhance infection in a complement dependent manner.

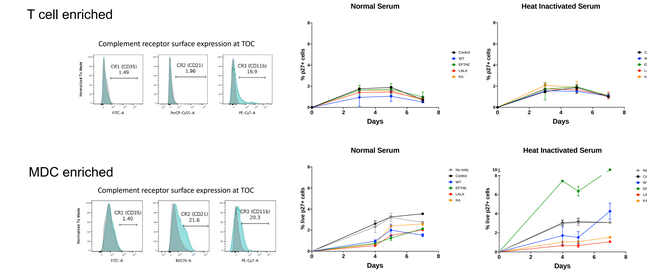
ADDITIONAL RESULTS

Pre-treatment with higher doses of 10E8v4 or 10E8v4 EFTAE mitigates viremic differences between treatment groups.

10E8v4 doses are shown as: 10 mg/kg (dashed lines) or 20 mg/kg (solid lines)



10E8v4 EFTAE enhances infection of primary splenocytes in the absence of MAC formation.



CONCLUSIONS

Fc mediated effector functions contributed to reduced viremia after pre-treatment with low doses of unmodified 10E8v4.

Enhanced Fc mediated complement activity combined with increased affinity for FcγRs worsened viral outcomes with 10E8v4.

HIV/SHIV may exploit antibody mediated complement deposition to traffic to target cells through transient linkage with CR2/CR3 on antigen presenting cells.

These results are consistent with the hypothesis that biophysical conditions at infection influence viral persistence.

Further studies examining the interplay of pro- and anti-viral contributions of antibody mediated complement activity are warranted.

National Institute of Allergy and Infectious Diseases

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