LS-variant anti-CCR5 monoclonal antibody provides long-lasting protection against intrarectal SHIV acquisition in rhesus macaques

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ABSTRACT

Background: Development of pre-exposure prophylaxis (PrEP) agents that provide long-acting, effective protection from HIV acquisition is a promising approach to bolster PrEP usage and adherence and slow the HIV epidemic. Anti-CCR5 monoclonal antibody Leronlimab blocks CCR5-mediated HIV entry, and has previously been shown to be an effective agent for HIV suppression in PLWH and for SHIV suppression and PrEP when administered to rhesus macaques weekly or biweekly. Here, we tested the ability of a long-acting variant of anti-CCR5 blocking antibody Leronlimab to protect against intrarectal SHIV acquisition in rhesus macaques.

Methods: A macaque-ized, long-acting, Fc-silenced, and heavy-chain-stabilized version of anti-CCR5 monoclonal antibody Leronlimab, termed "macLS Leronlimab", was developed by exchanging the human IgG4 Fc portion for rhesus IgG4 Fc and adding M428L and N434S (LS), L234A and L235A (LALA), and S131C (SC) mutations. Rhesus macaques received either a single (n=6) or double (n=6) 10 mg/kg subcutaneous dose of macLS Leronlimab, or served as untreated controls (n=10). One week after the last macLS dosing, all 22 macaques underwent weekly intrarectal SHIVsf162p3 challenges until infection was confirmed in all study animals. Macaques were monitored for Leronlimab CCR5 receptor occupancy on blood CD4+ T cells, Leronlimab concentrations in plasma, Leronlimab-directed antibody drug antibodies (ADAs), and SHIV plasma viral loads.

Results: Three macLS-dosed macaques (2/6 single-dosed, 1/6 double-dosed) developed Leronlimab-directed ADAs, resulting in incomplete CCR5 occupancy on blood CD4+ T cells, clearance of plasma Leronlimab, and subsequent SHIV acquisition. The remaining 9 macLS-dosed macaques retained complete blood CD4+ T cell CCR5 blockade for 12-18 weeks and detectable plasma Leronlimab for 10-22 weeks after dosing. SHIV acquisition was significantly delayed for macLS Leronlimab-dosed macaques (p=0.0142, log-rank test), with a median of 11 weekly challenges until viral acquisition in dosed macaques compared to 2.5 weekly challenges in control macaques. While there was a trend toward enhanced protection in the double-dosed versus single-dosed macLS Leronlimab groups (median 13 versus 7.5 weekly challenges), this did not reach statistical significance (p=0.5641, log-rank test).

Conclusions: These data demonstrate the ability of LS-variant Leronlimab to provide long-term protection against intrarectal SHIV acquisition and support development of long-acting CCR5 blockade for HIV PrEP.

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Figure 1. macLS Leronlimab binds rhesus macaque CCR5 and blocks SHIVsf162p3 spreading *in vitro*

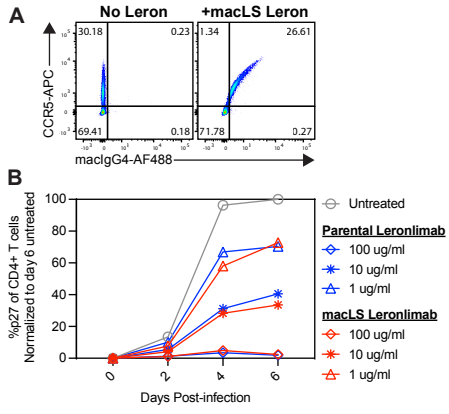

Figure 1. (A) Representative flow cytometry plot showing co-staining of macLS Leronlimab and surface CCR5. Plots gated on live, CD4+ T cells. **(B)** Activated rhesus macaque CD4+ T cells were left untreated or treated with either parental (human IgG4) Leronlimab (blue) or macLS Leronlimab (red), then infected with SHIVsf162p3. Infection levels were measured longitudinally by flow cytometry staining for intracellular gag p27. Graphs shows data normalized to p27+ frequencies at day 6 in untreated, infected wells.

Figure 2. macLS Leronlimab PrEP study

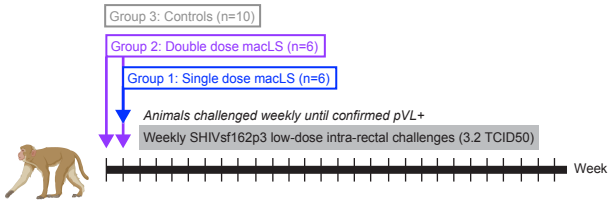

Figure 1. Timeline of macLS Leronlimab PrEP study in rhesus macaques.

Figure 3. Single dose macLS Leronlimab (Group 1)

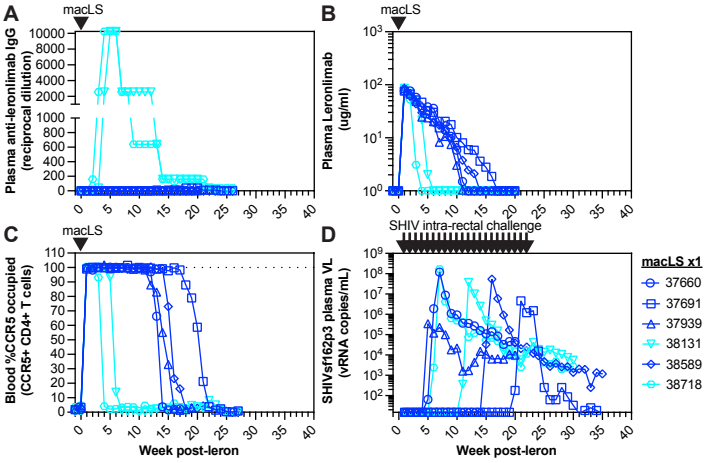

Figure 3. (A) Plasma anti-drug antibody levels. **(B)** Plasma macLS Leronlimab concentrations. **(C)** CCR5 receptor occupancy (RO) on blood CD4+ T cells. **(D)** SHIV plasma viral loads. Undetectable pVLs graphed at the LOQ (15 copies/mL). Macaques with ADA-mediated macLS Leronlimab clearance indicated in bright blue.

Figure 4. Double dose macLS Leronlimab (Group 2)

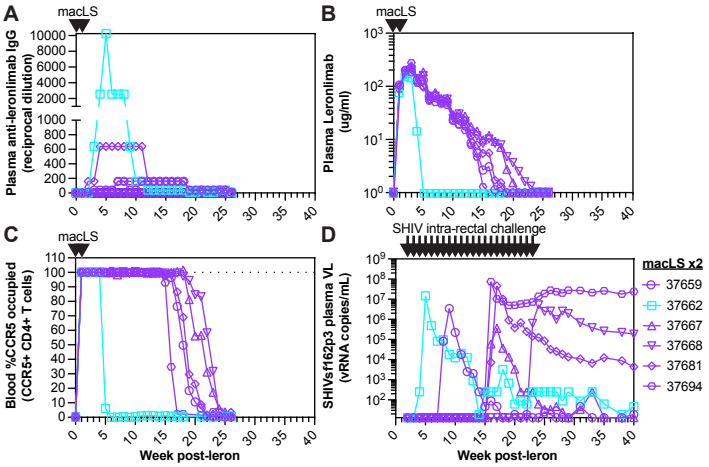

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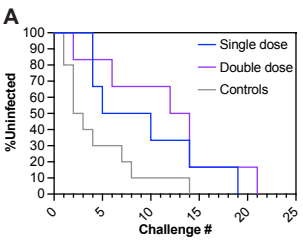
Figure 5. macLS Leronlimab delays SHIV acquisition



	n	Median challenge #
Single dose macLS	6	7.5
Double dose macLS	6	13
Combined macLS	*12*	*11*
Controls	10	2.5

Figure 5. (A) Kaplan-Meier survival curve of macLS Leronlimab-treated macaques and controls. **(B)** Summary of SHIV acquisition in PrEP studies. Asterisks denote significant differences (*p<0.05 by log-rank test), ns = not significant by log-rank test.

Future Directions

-Determine factors leading to ADA development in ~25% of macLS Leronlimab-dosed macaques

-Determine mechanism of breakthrough SHIV acquisition despite complete CCR5 blockade in ~25% of dosed macaques

-Test solid-phase formulation of macLS Leronlimab administered in <1mL volume