Delivery and long-term expression of CCR5-blocking monoclonal antibody Leronlimab with AAV for ART-free remission from SHIV viremia

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Abstract

CCR5 blockade represents a scalable non-transplantation approach for long-term ART-free HIV remission. Here, we tested if AAV vectors could induce long-term expression of CCR5-blocking monoclonal antibody Leronlimab in a SHIV-infected rhesus macaques (RMs). Four SHIV-infected RMs received AAV9 encoding macaque Fc Leronlimab with stabilizing, silencing, and half-life extending mutations (AAV9-MacLSLeron). Animals were monitored longitudinally for CCR5 receptor occupancy (RO), plasma Leronlimab concentrations, antidrug antibodies (ADAs), and SHIV plasma viral loads. All four AAV9-MacLSLeron-treated RMs reached 100% CCR5 RO on blood CD4+ T cells within 1 week and plasma Leronlimab was detected (>1ug/ml) within 2 weeks of AAV administration. In two of the RMs, SHIV viremia declined and reached undetectable levels between 10-40 weeks post-AAV, and those levels have remained undetectable through 70 weeks post-AAV. The remaining two RMs developed ADAs within 5-15 weeks post-AAV resulting in complete clearance of Leronlimab from plasma as well as a rapid decline in CCR5 RO. Spontaneous reemergence of CCR5 RO by Leronlimab was observed approximately 1 year post-AAV. One of the two animals has had full and sustained CCR5 RO, detectable plasma Leronlimab, and undetectable SHIV RNA in plasma for over 1 year post-reexpression. The second re-expressing animal has achieved and maintained 100% CCR5 RO for about 10 weeks, has detectable plasma Leronlimab, and has declined plasma viremia. While further investigation is needed to develop AAV vectors and/or regimens that reduce the incidence of ADAs, the transgene reexpression phenomenon we have observed highlights the need to further investigate the interplay between AAV establishment and the development of ADAs. Overall, these data demonstrate the potential of AAV vectors for sustained antibody-based CCR5 blockade as a gene therapy approach for long-term ART-free HIV remission.

Figure 1. CCR5 Receptor Occupancy – Long-term expressors

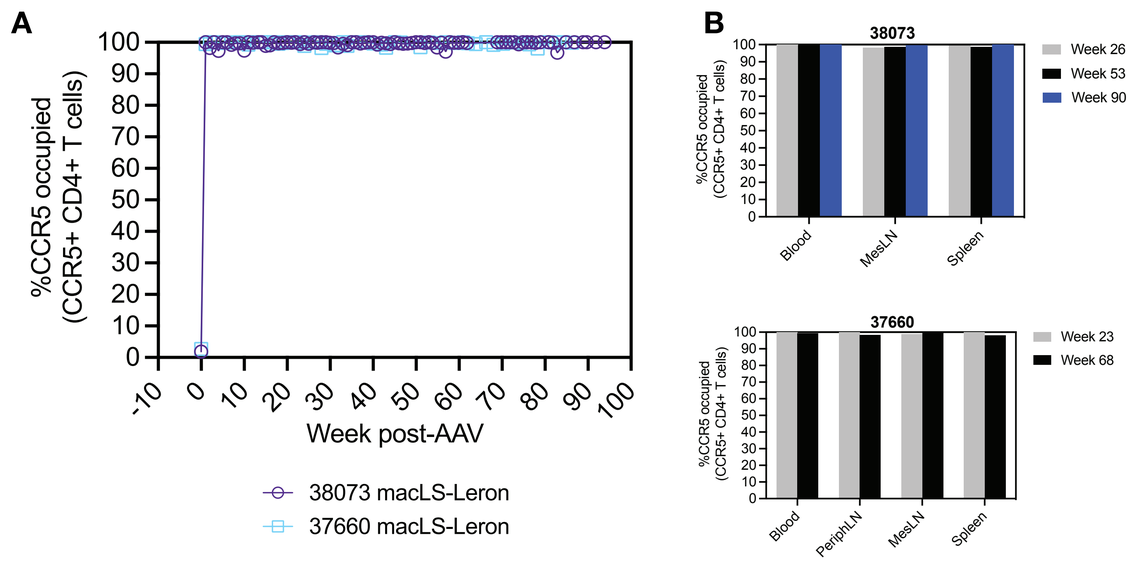

Figure 1: (A) Longitudinal CCR5 receptor occupancy by leronlimab on blood CD4+ T cells. **(B)** CCR5 receptor occupancy by leronlimab on blood, mesenteric lymph node (mesLN), peripheral lymph node (periphLN), and spleen CD4+ T cells from 38073 and 37660 at timepoints post-AAV administration.

Figure 2. Anti-drug antibodies – Long-term expressors

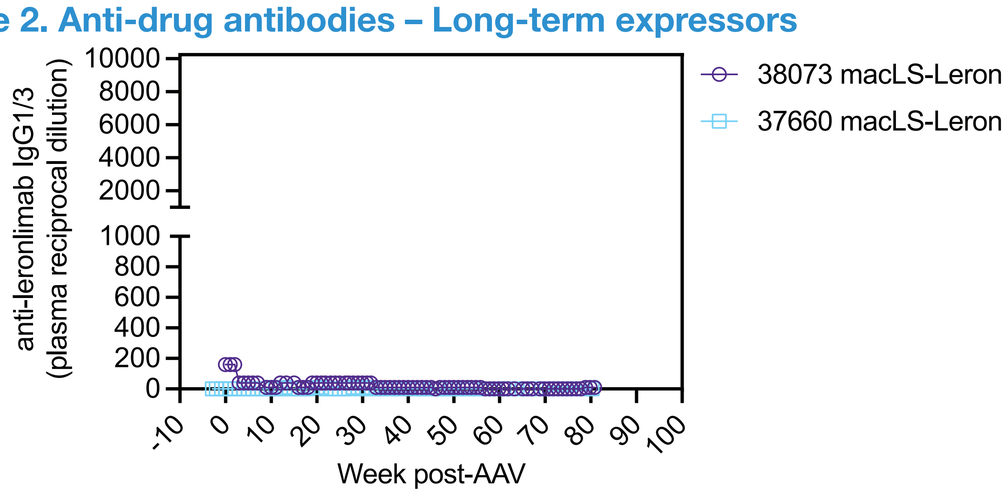

Figure 2: Longitudinal anti-leronlimab rhesus IgG levels in plasma.

Figure 3. Plasma leronlimab concentration – Long-term expressors

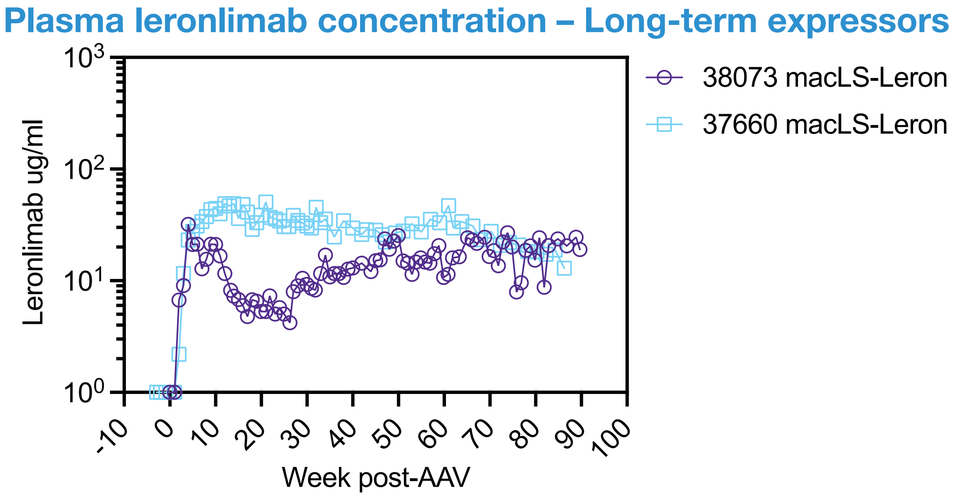

Figure 3: Longitudinal leronlimab concentrations in plasma.

Figure 4. SHIV plasma viral loads – Long-term expressors

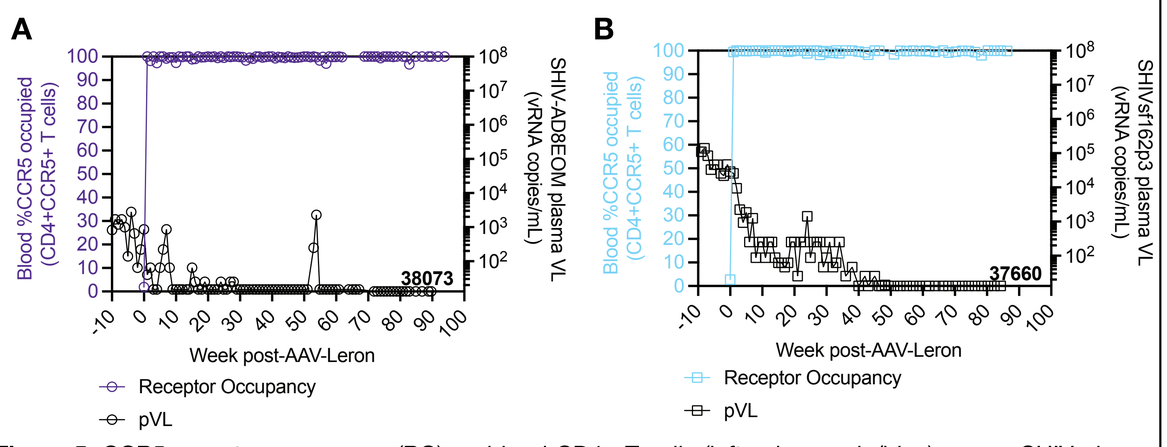

Figure 5: CCR5 receptor occupancy (RO) on blood CD4+ T cells (left axis, purple/blue) versus SHIV plasma viral load (right axis, black) in **(A)** 38073 (SHIV-AD8EOM) and **(B)** 37660 (SHIVsf162p3). Undetectable SHIV pVLs graphed at the limit of quantification (LOQ) of 50 copies/ml.

Summary & Future Directions

Three distinct outcomes of AAV9-leronlimab are described here:

1. 38073 and 37660: Sustained leronlimab expression indicated by detectable leronlimab in plasma as well as complete occupancy of CCR5 receptors in blood and tissue of CD4+ T cells for over 80 weeks.

2. 35784: Transient leronlimab expression and receptor occupancy followed by rapid development of antidrug antibodies leading to clearance of leronlimab and elimination of RO. Nearly 1 year post-AAV and after full clearance of leronlimab, a reemergence of leronlimab expression is detected in plasma and reflected in receptor occupancy. SHIV viral loads have remained near or below the limit of quantification for over 1 year post-reexpression.

3. 35788: Another example of leronlimab rexpression 1 year after full clearance from plasma and CCR5 on blood CD4+ T cells. SHIV viral loads have decreased since leronlimab reexpression, but remain ~10^4 copies/ml for reasons unknown.

AAV9 vectors can be successfully used for long-term antibody delivery, but further investigation is needed to develop regimens that do not induce ADA, such as modifying AAV promoters or reducing the immunogenicity of encoded antibodies. The mechanism behind reexpression of an AAV-delivered transgene is also unknown and warrents further exploration. **The complete receptor occupancy and subsequent control of CCR5-tropic SHIV replication observed in 38073 and 37660 supports the investigation of CCR5 blockade as a promising approach for long-term ART-free HIV remission.**

Figure 5. CCR5 Receptor Occupancy – Re-expressors

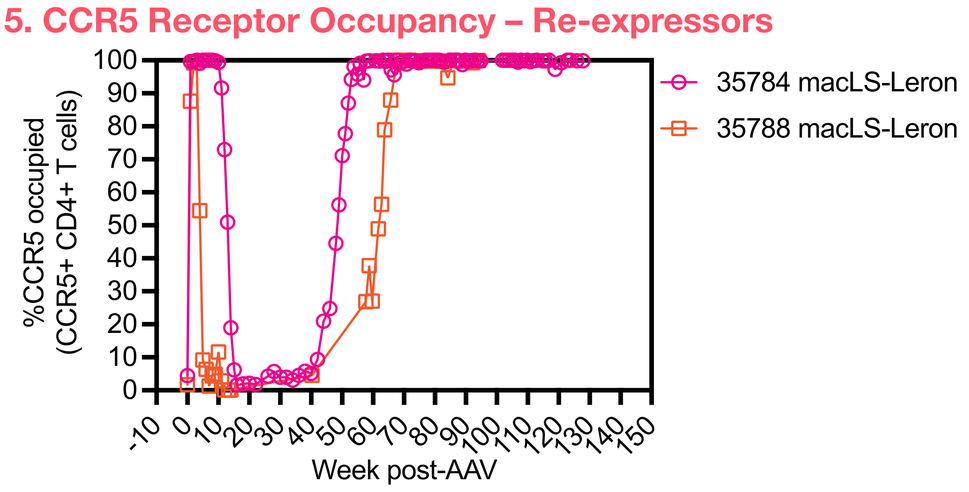

Figure 5: Longitudinal CCR5 receptor occupancy by leronlimab on blood CD4+ T cells.

Figure 6. Anti-drug antibodies – Re-expressors

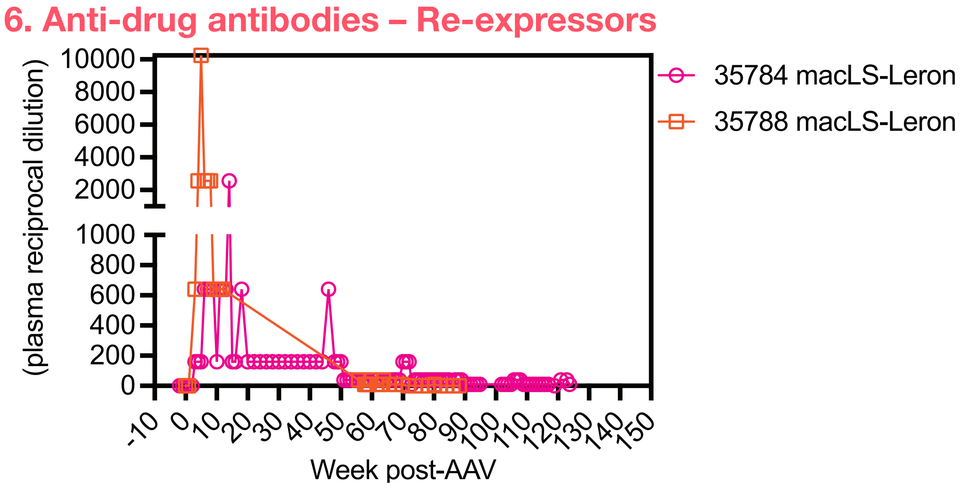

Figure 6: Longitudinal anti-leronlimab rhesus IgG levels in plasma.

Figure 7. Plasma leronlimab concentration – Re-expressors

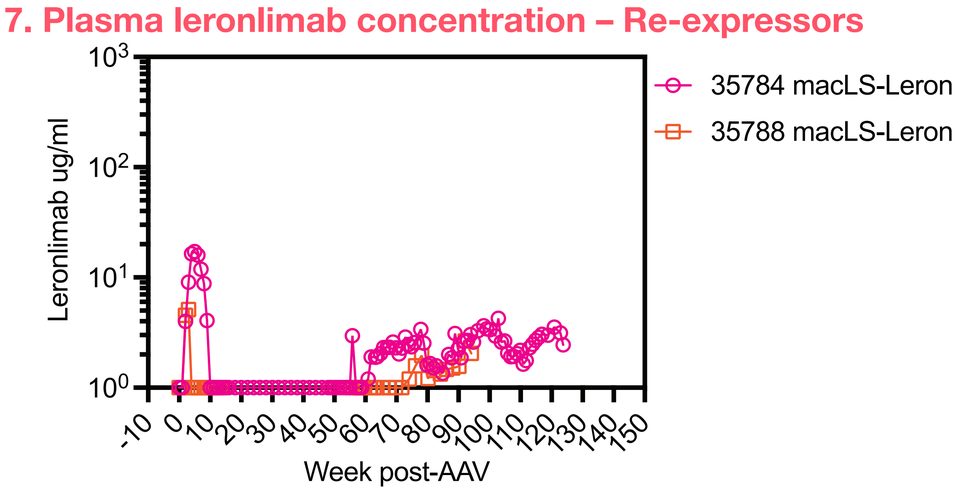

Figure 7: Longitudinal leronlimab concentrations in plasma.

Figure 8. SHIV plasma viral loads – Re-expressors

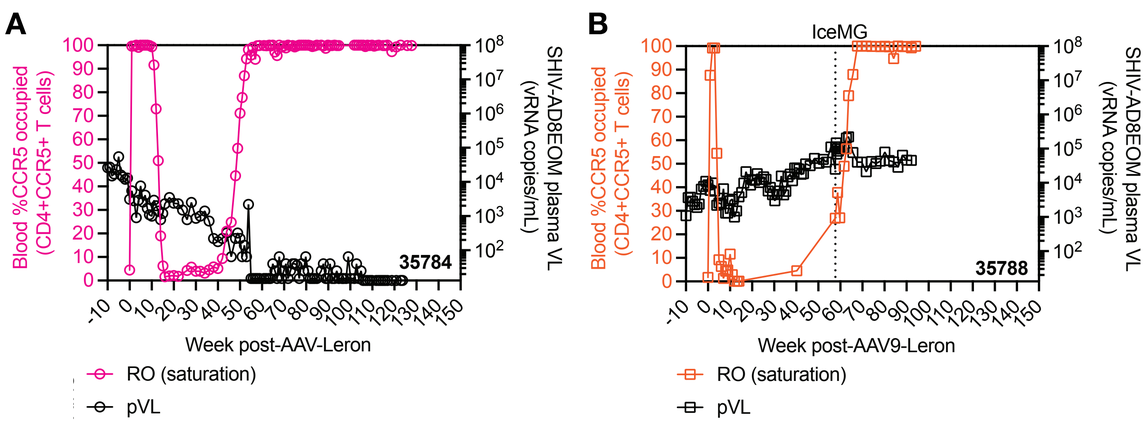

Figure 8: CCR5 receptor occupancy (RO) on blood CD4+ T cells (left axis, pink/orange) versus SHIV-AD8EOM plasma viral load (right axis, black) in **(A)** 35784 and **(B)** 35788. Undetectable SHIV pVLs graphed at the limit of quantification (LOQ) of 50 copies/ml.

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