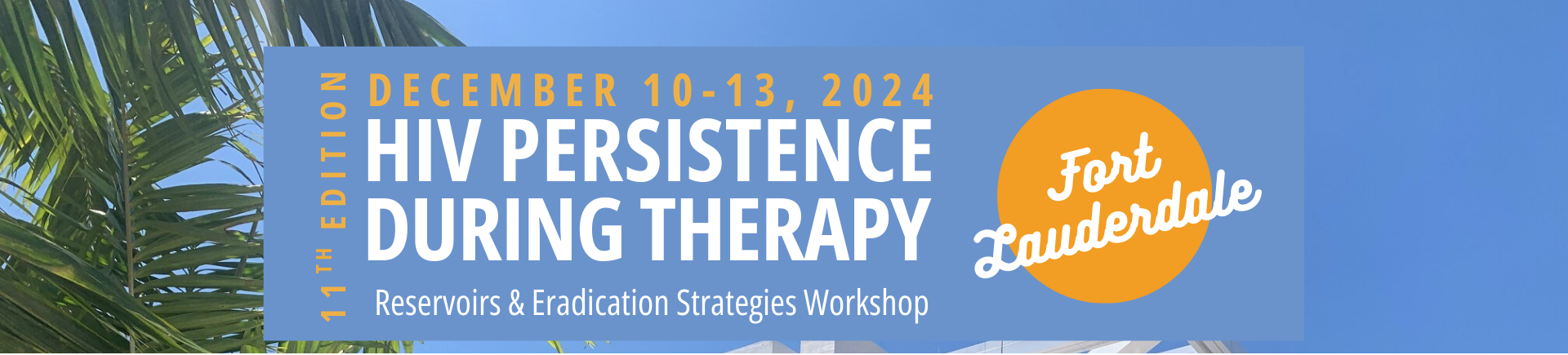


AAV Delivery of the CCR5-blocking monoclonal antibody Leronlimab yields long-term expression and ART-free remission from SHIV viremia

Helen L. Wu
Jonah B. Sacha Laboratory
Division of Pathobiology & Immunology
Oregon National Primate Research Center

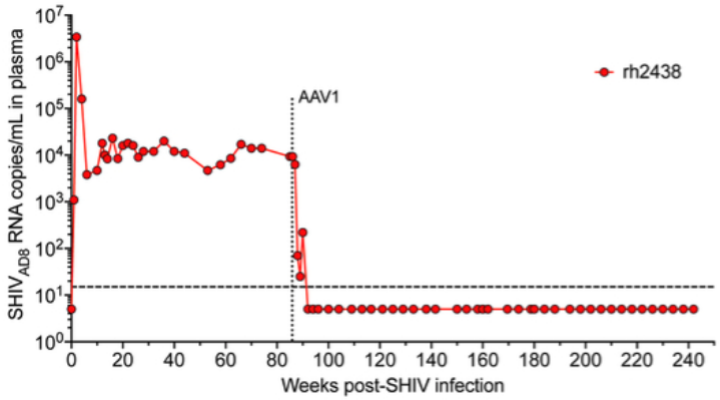
CONFLICTS OF INTEREST

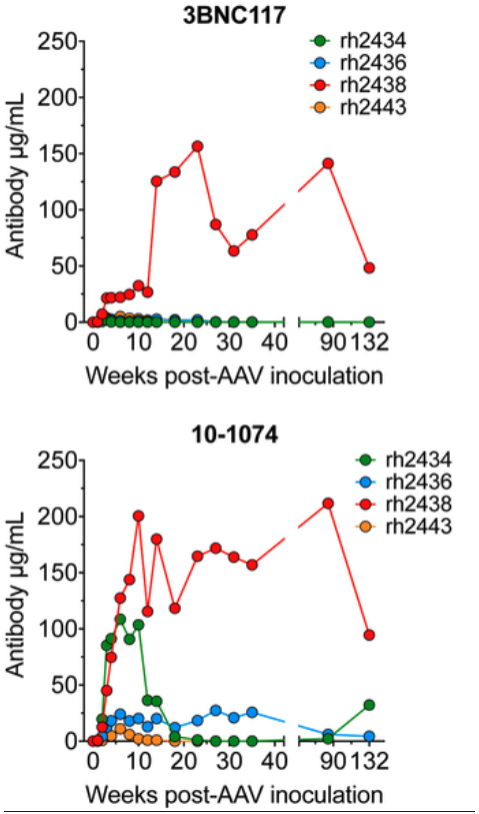
No conflicts to declare

Currently FDA approved AAV therapies

Name	Company	Disease	Approval date	AAV serotype	Transgene
Luxturna	Spark Therapeutics	Retinal dystrophy	2017	AAV2	RPE65
Zolgensma	Novartis	Spinal muscular atrophy	2019	AAV9	SMN1
Hemgenix	CSL Behring	Hemophilia B	2022	AAV5	Factor IX
Elevidys	Serepta Therapeutics	Duchenne muscular dystrophy	2023	AAVrh47	Micro-dystrophin
Roctavian	BioMarin	Hemophilia	2023	AAV5	Factor VIII

AAV-mediated delivery of antibodies for HIV suppression



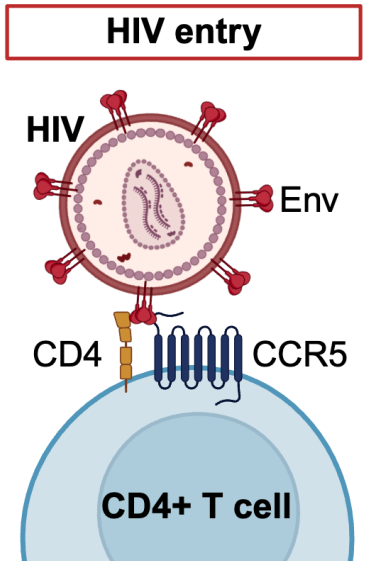


Martinez-Navio *et al.*, Immunity, 2019

AAV-mediated delivery of CCR5-blocking antibody

Why target CCR5?

- CCR5 is the main coreceptor required for HIV entry into cells
- Vast majority of sexually transmitted HIV strains utilize CCR5 as an entry co-receptor (CCR5-tropic)
- CCR5Δ32-homozgyous individuals possess high level of resistance to HIV infection



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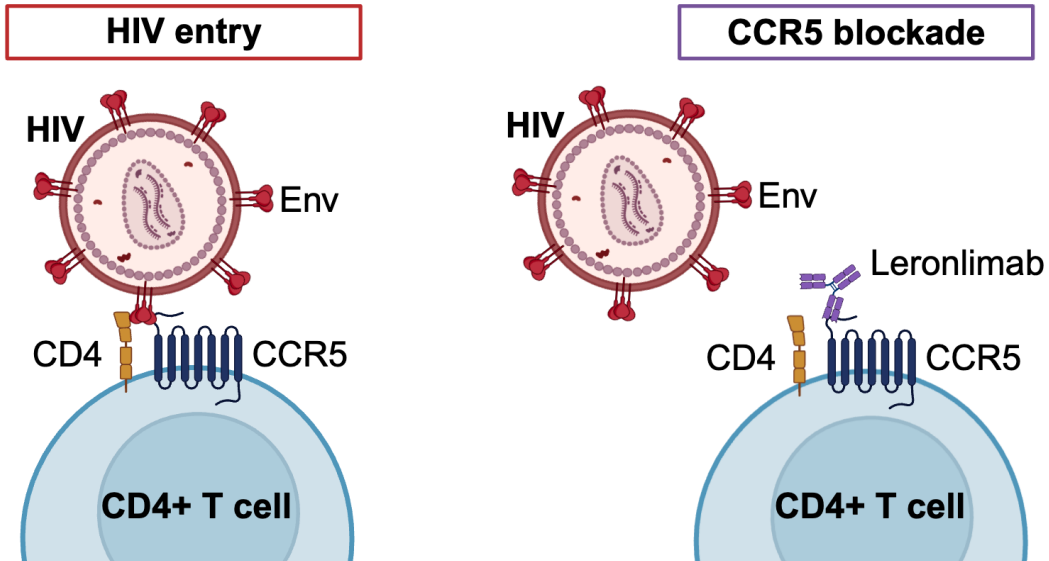
AAV-mediated delivery of CCR5-blocking antibody

Leronlimab CytoDyn

- Anti-CCR5 humanized IgG4
- Binds to the same CCR5 extracellular loop-2 and N-terminus domains as HIV Env



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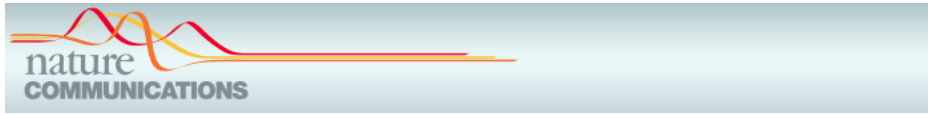
AAV-mediated delivery of CCR5-blocking antibody

Leronlimab CytoDyn

- Anti-CCR5 humanized IgG4
- Binds to the same CCR5 extracellular loop-2 and N-terminus domains as HIV Env
- Administered to >1,600 individuals with no serious adverse events, side-effects, toxicity, drug-drug interactions reported



Antibody-based CCR5 blockade protects Macaques from mucosal SHIV transmission

Xiao L. Chang[1,2,10], Gabriela M. Webb[1,2,10], Helen L. Wu[1,2], Justin M. Greene[1], Shaheed Abdulhaqq[1], Katherine B. Bateman[1], Jason S. Reed[1], Cleiton Pessoa[1], Whitney C. Weber[1], Nicholas Maier[1], Glen M. Chew[3], Roxanne M. Gilbride[1], Lina Gao[2], Rebecca Agnor[2], Travis Giobbi[2], Jeffrey Torgerson[2], Don Siess[2], Nicole Burnett[2], Miranda Fischer[2], Oriene Shiel[2], Cassandra Moats[2], Bruce Patterson[4], Kush Dhody[5], Scott Kelly[6], Nader Pourhassan[6], Diogo M. Magnani[7], Jeremy Smedley[2], Benjamin N. Bimber[1,2], Nancy L. Haigwood[1], Scott G. Hansen[1], Timothy R. Brown[8], Lishomwa C. Ndhlovu[9,11✉] & Jonah B. Sacha[1,2,11✉]

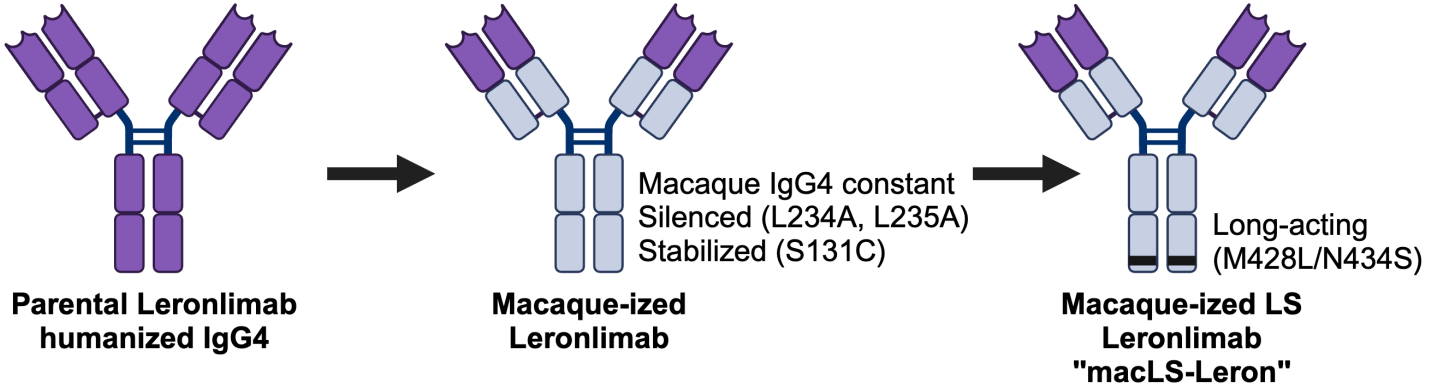
RESEARCH ARTICLE

Suppression of human and simian immunodeficiency virus replication with the CCR5-specific antibody Leronlimab in two species

Xiao L. Chang[1,2], Jason S. Reed[1], Gabriela M. Webb[1], Helen L. Wu[1], Jimmy Le[3], Katherine B. Bateman[1], Justin M. Greene[1], Cleiton Pessoa[1], Courtney Waytashek[1], Whitney C. Weber[1], Joseph Hwang[1], Miranda Fischer[2], Cassandra Moats[2‡], Oriene Shiel[2], Rachele M. Bochart[2], Hugh Crank[2], Don Siess[2], Travis Giobbi[2], Jeffrey Torgerson[2], Rebecca Agnor[2], Lina Gao[2], Kush Dhody[4‡], Jacob P. Lalezari[3], Ivo Sah Bandar[5], Alnor M. Carnate[5], Alina S. Pang[5], Michael J. Corley[5], Scott Kelly[6], Nader Pourhassan[6‡], Jeremy Smedley[2], Benjamin N. Bimber[1,2], Scott G. Hansen[1], Lishomwa C. Ndhlovu[5], Jonah B. Sacha[1,2*]

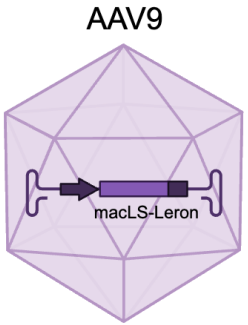
A long-acting, stabilized, macaque-ized Leronlimab

“macLS-Leronlimab”- macaque IgG4 Leronlimab, silenced, stabilized, half-life extended



“AAV9-macLS-Leron”- AAV9 vector encoding macLS-Leronlimab transgene

- Serotype: AAV9
- Promoter: CMV
- Transgene: macLS-Leronlimab
- Linker: P2A



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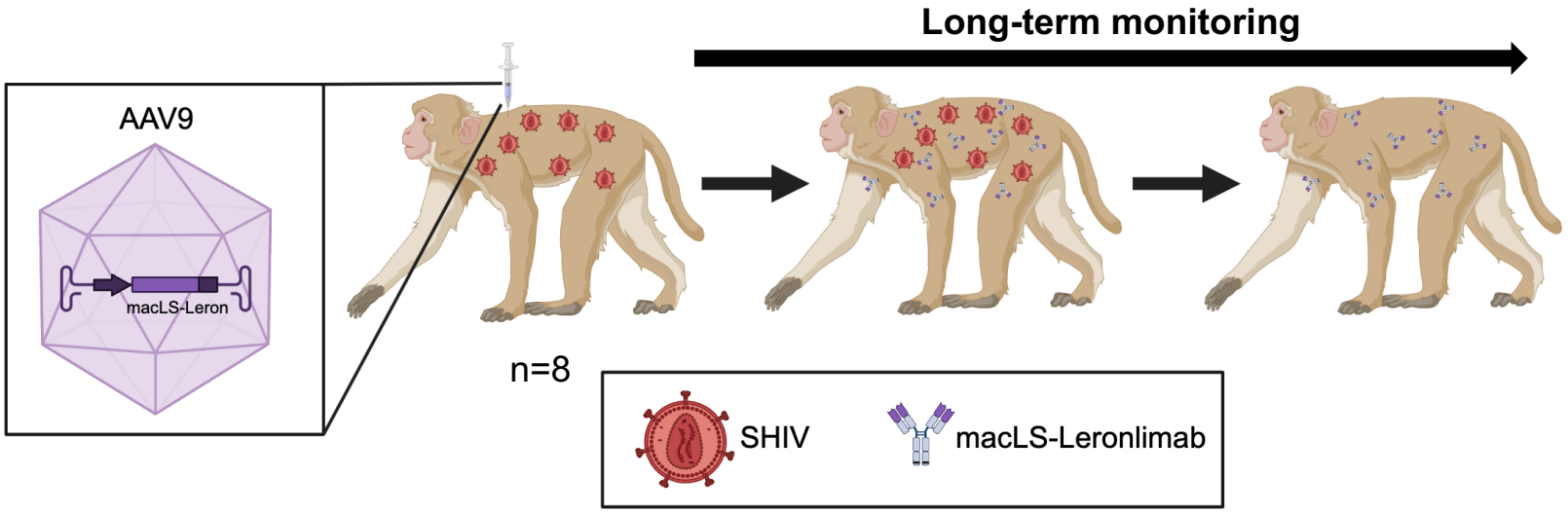
Study: AAV9-macLS-Leronlimab in rhesus macaques

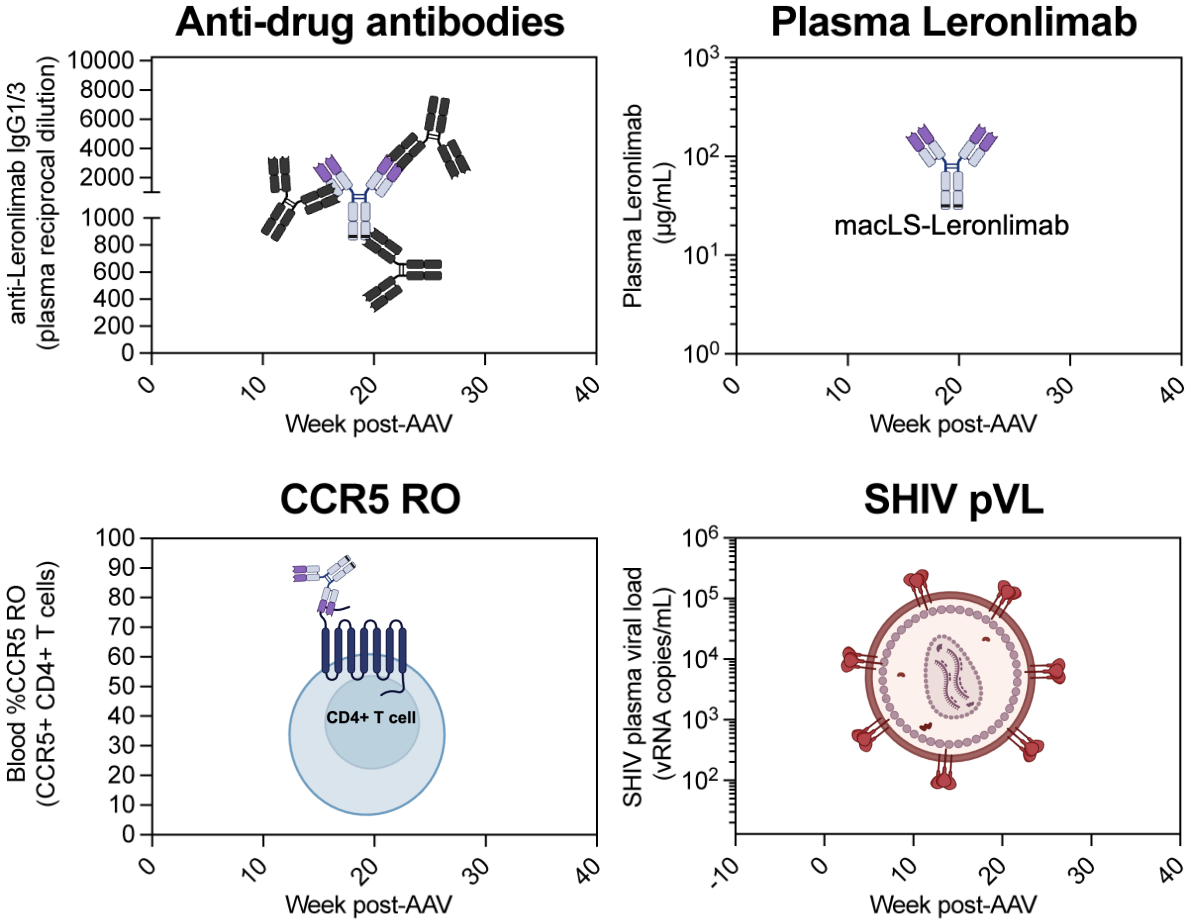
- Chronically infected with CCR5-tropic SHIVs: SHIVsf162p3 or SHIV-AD8EOM
- AAV9 NAb ID50 titers <400 prior to dosing



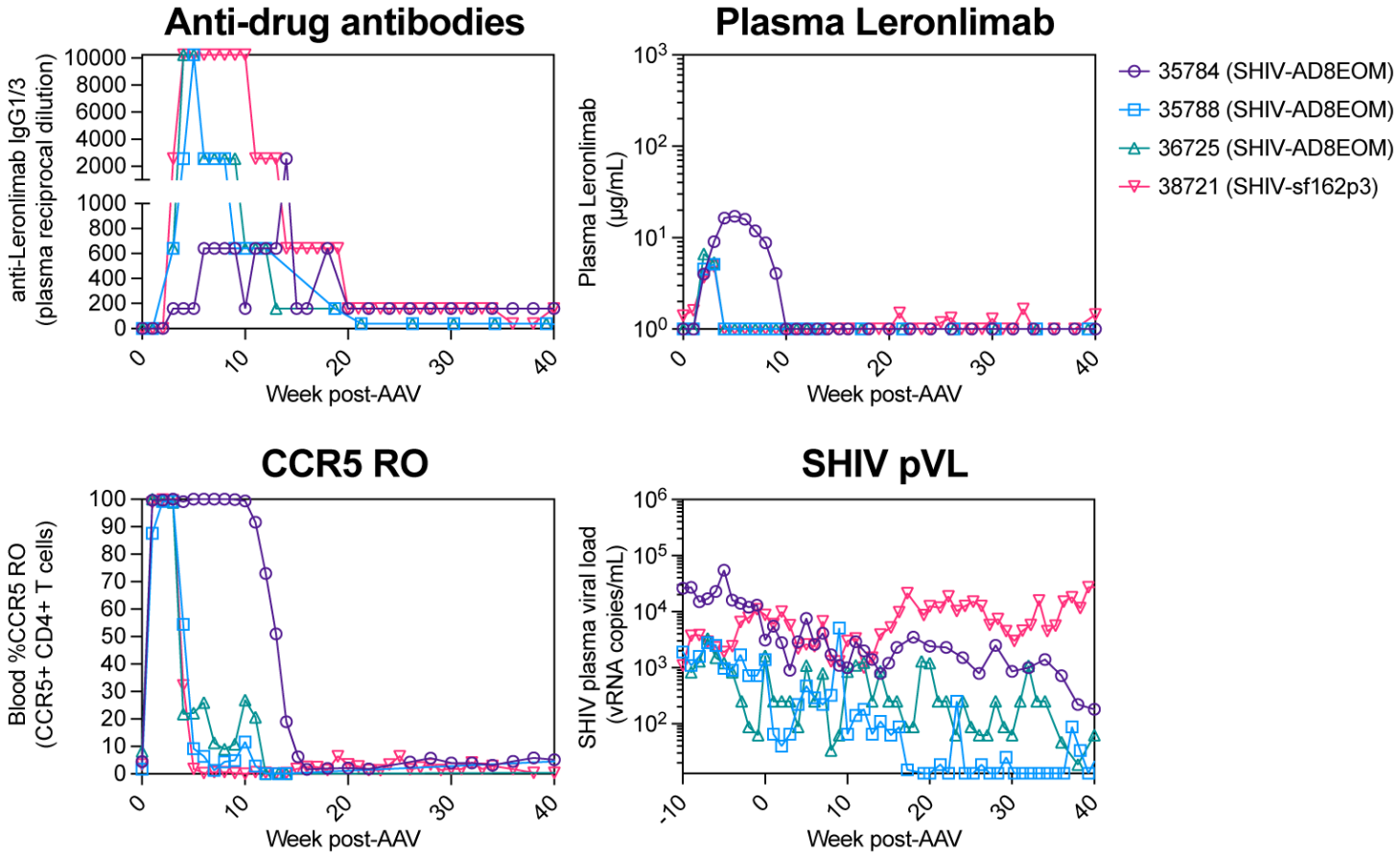
Can a single dose of AAV9-macLS-Leron mediate long-term SHIV suppression thru CCR5 blockade?

Created with Biorender

Readouts


Anti-drug antibodies
anti-Leronlimab IgG1/3 (plasma reciprocal dilution)
10000
8000
6000
4000
2000
1000
800
600
400
200
0
0
10
20
30
40
Week post-AAV
Plasma Leronlimab
Plasma Leronlimab (µg/mL)
10^3
10^2
10^1
10^0
macLS-Leronlimab
0
10
20
30
40
Week post-AAV
CCR5 RO
Blood %CCR5 RO (CCR5+ CD4+ T cells)
100
90
80
70
60
50
40
30
20
10
0
CD4+ T cell
0
10
20
30
40
Week post-AAV
SHIV pVL
SHIV plasma viral load (vRNA copies/mL)
10^6
10^5
10^4
10^3
10^2
-10
0
10
20
30
40
Week post-AAV

50% of macaques develop ADA and clear Leronlimab



4/8 macaques

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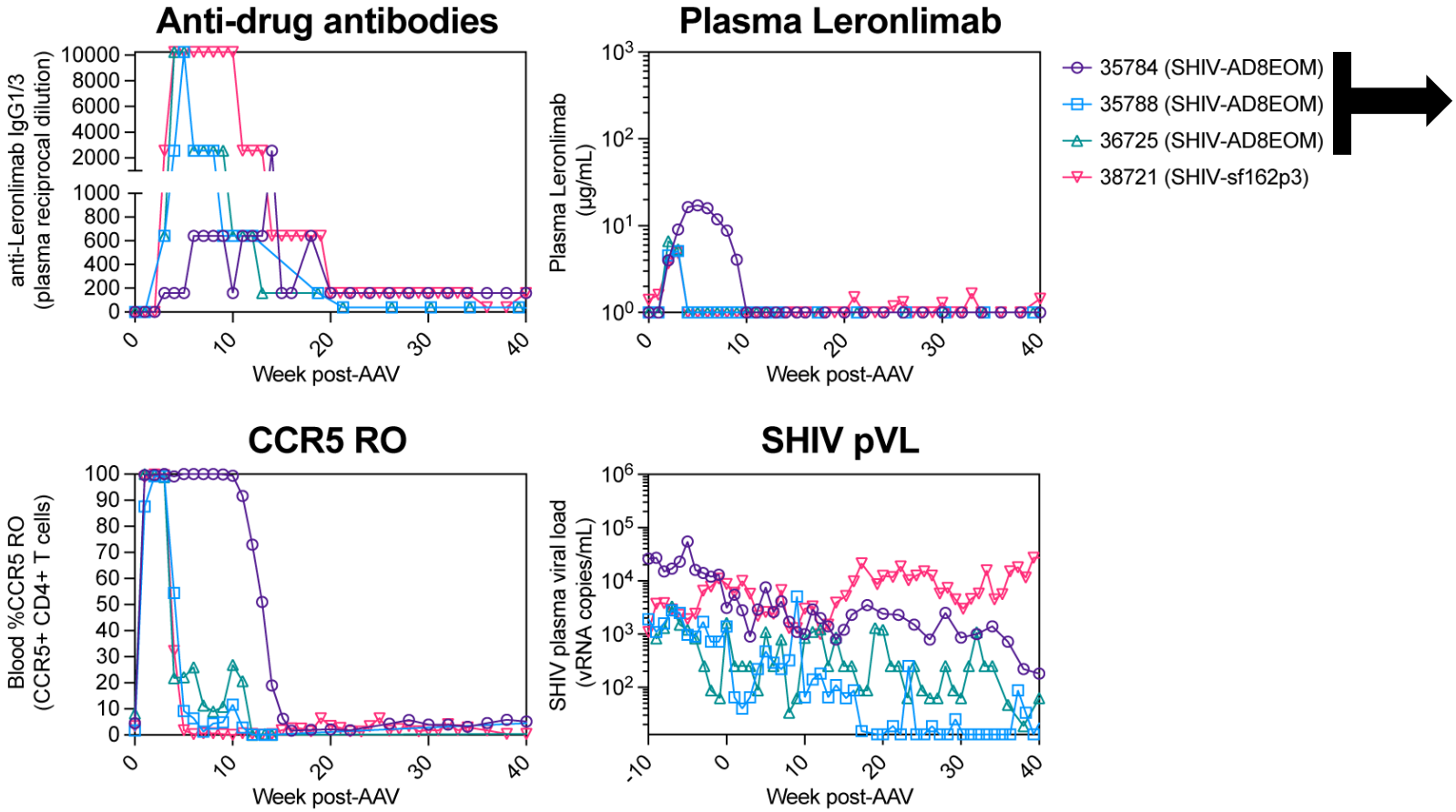
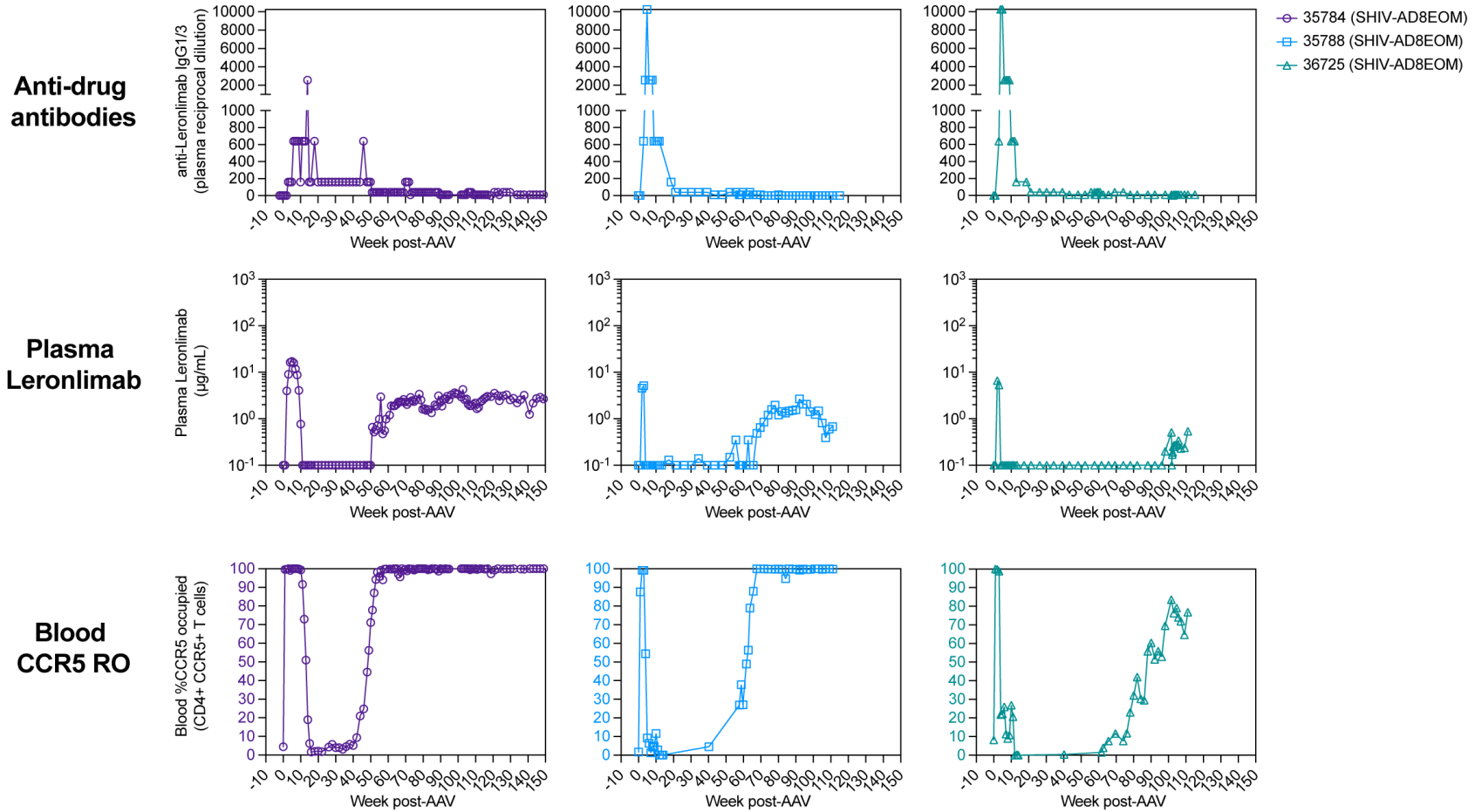
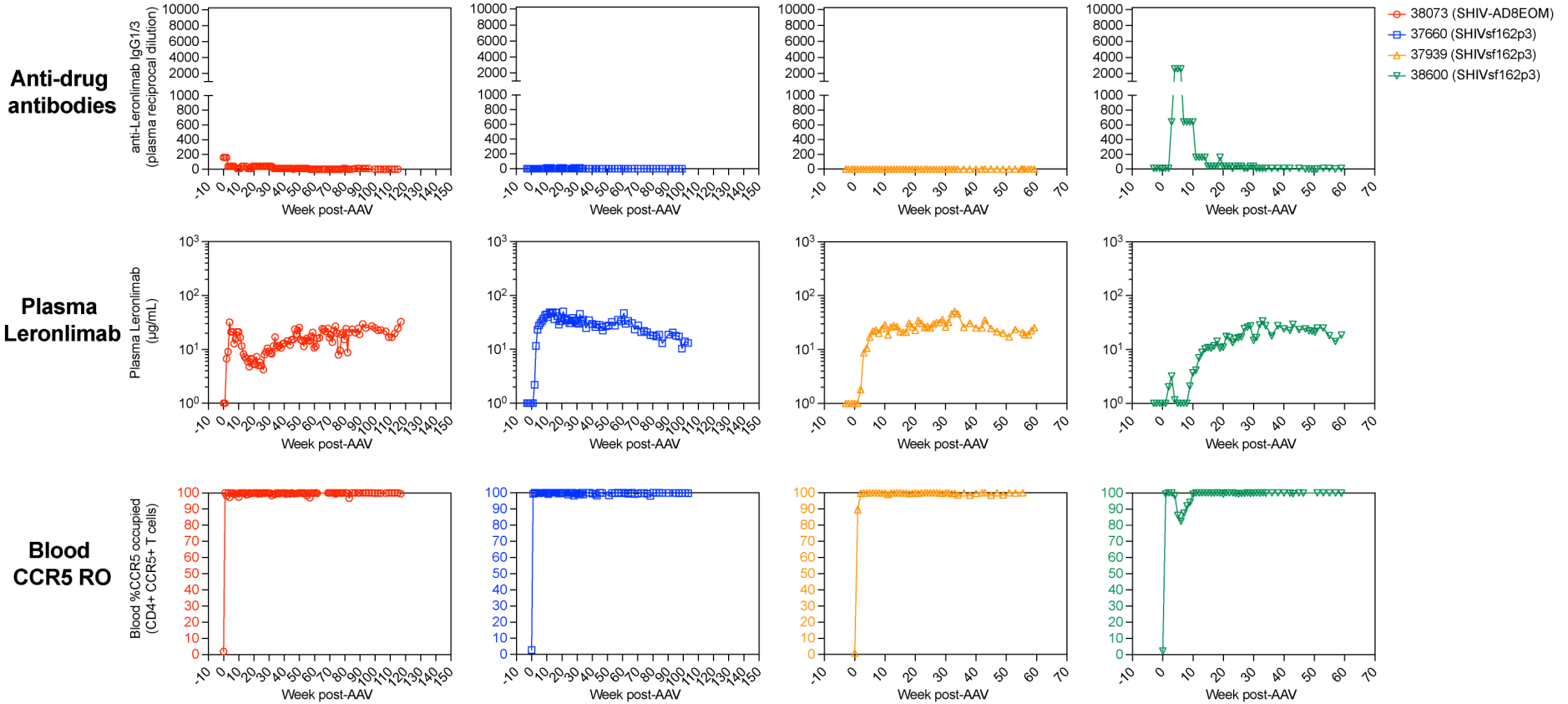


4/8 macaques

But transgene can re-emerge >40 wks post-AAV

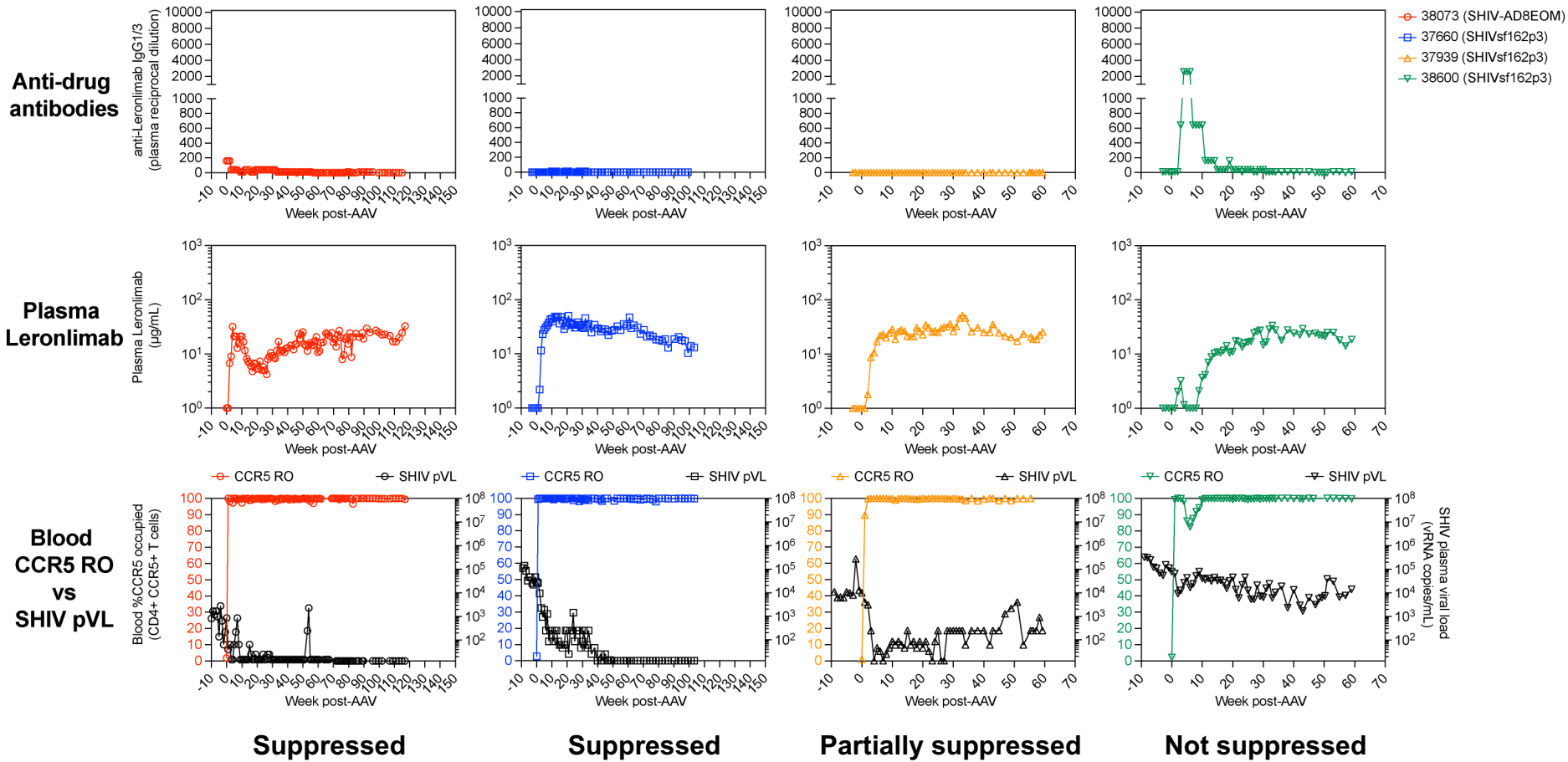


Other 50% of animals exhibit minimal ADA and long-term transgene expression



4/8 macaques

Variable AAV-Leronlimab-mediated SHIV suppression



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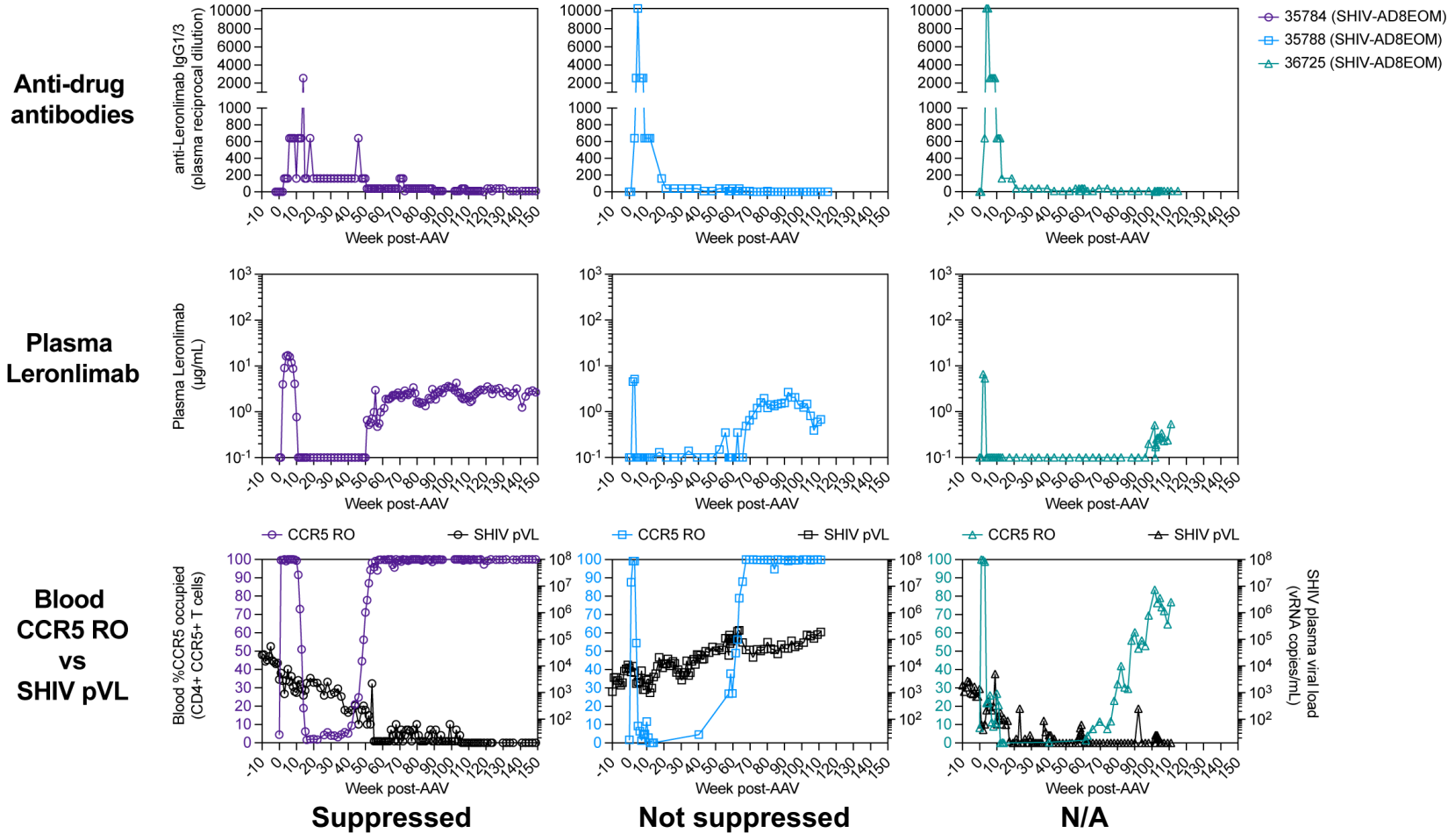
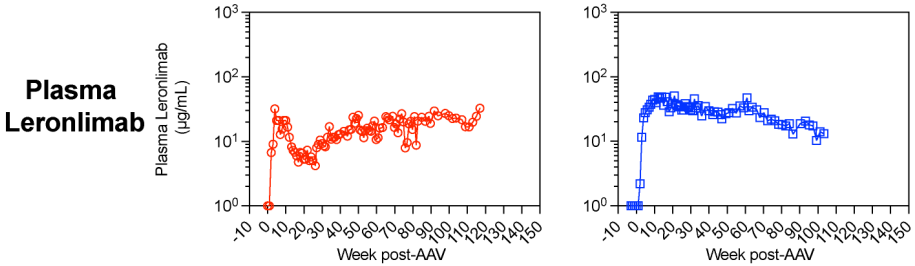


Summary

- A single dose of AAV-Leronlimab can lead to long-term Leronlimab production (>2 years)



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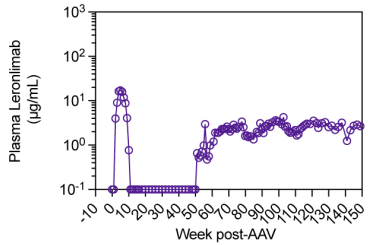
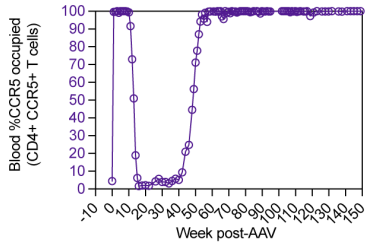
Plasma Leronlimab



Blood CCR5 RO



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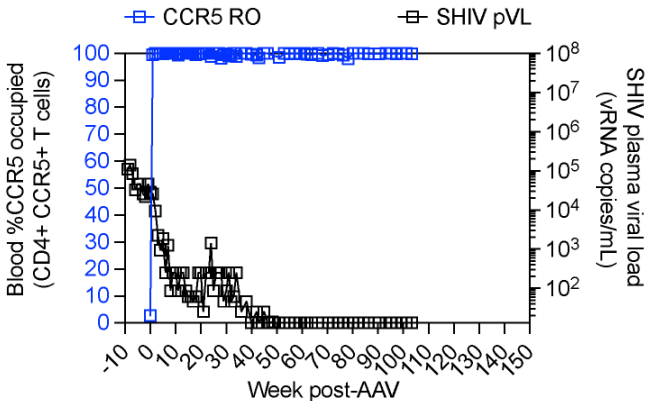

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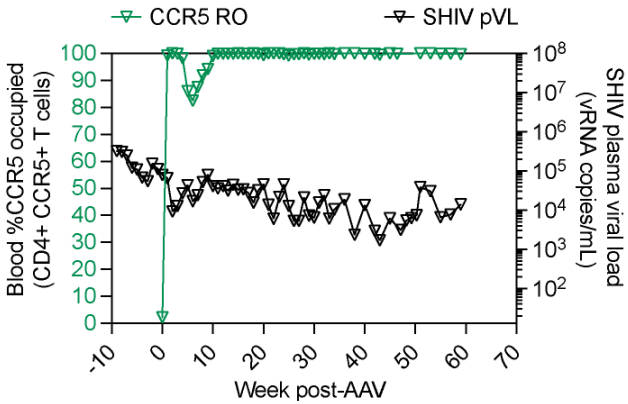
  - But can also fail to control viremia in other cases…



Hypotheses behind persistent viremia

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- CCR5 sequence differences among animals? → Sequence CCR5

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Jeremy Smedley
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Kim Chun
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Riely White
Aaron Barber-Axthelm

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Jeff Torgerson

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NHP Reagent Resource
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Joanna Zikos

University of Miami
Sebastian Fuchs
Ron Desrosiers

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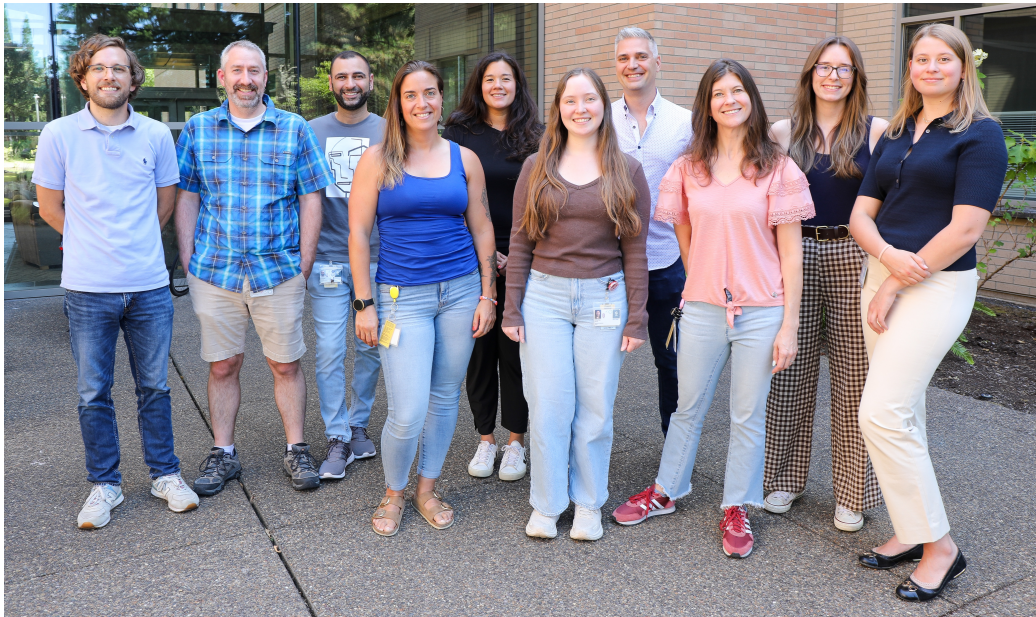
R01 AI154559



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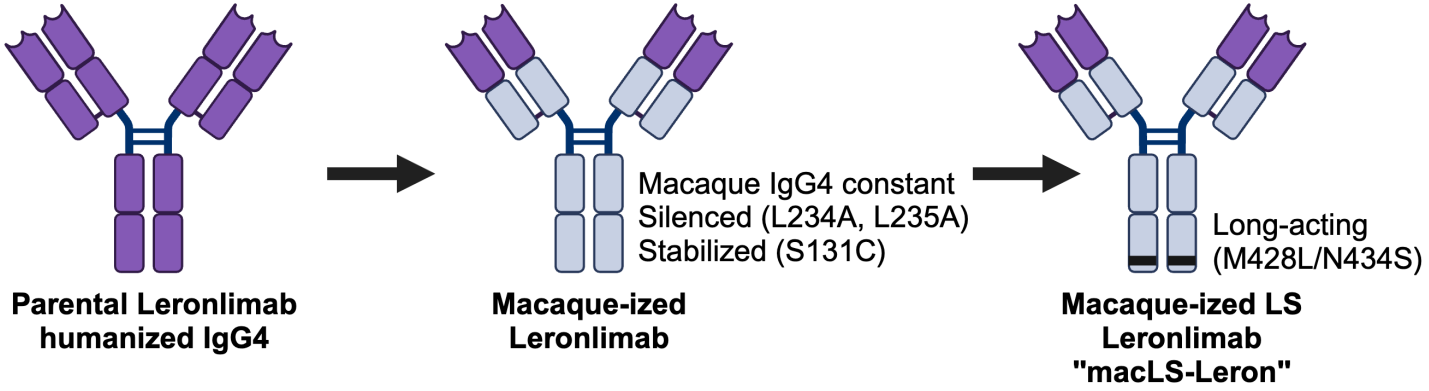
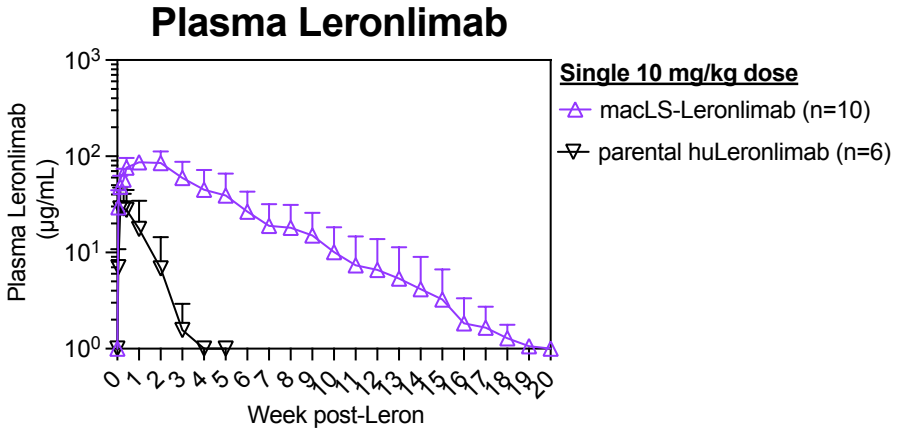
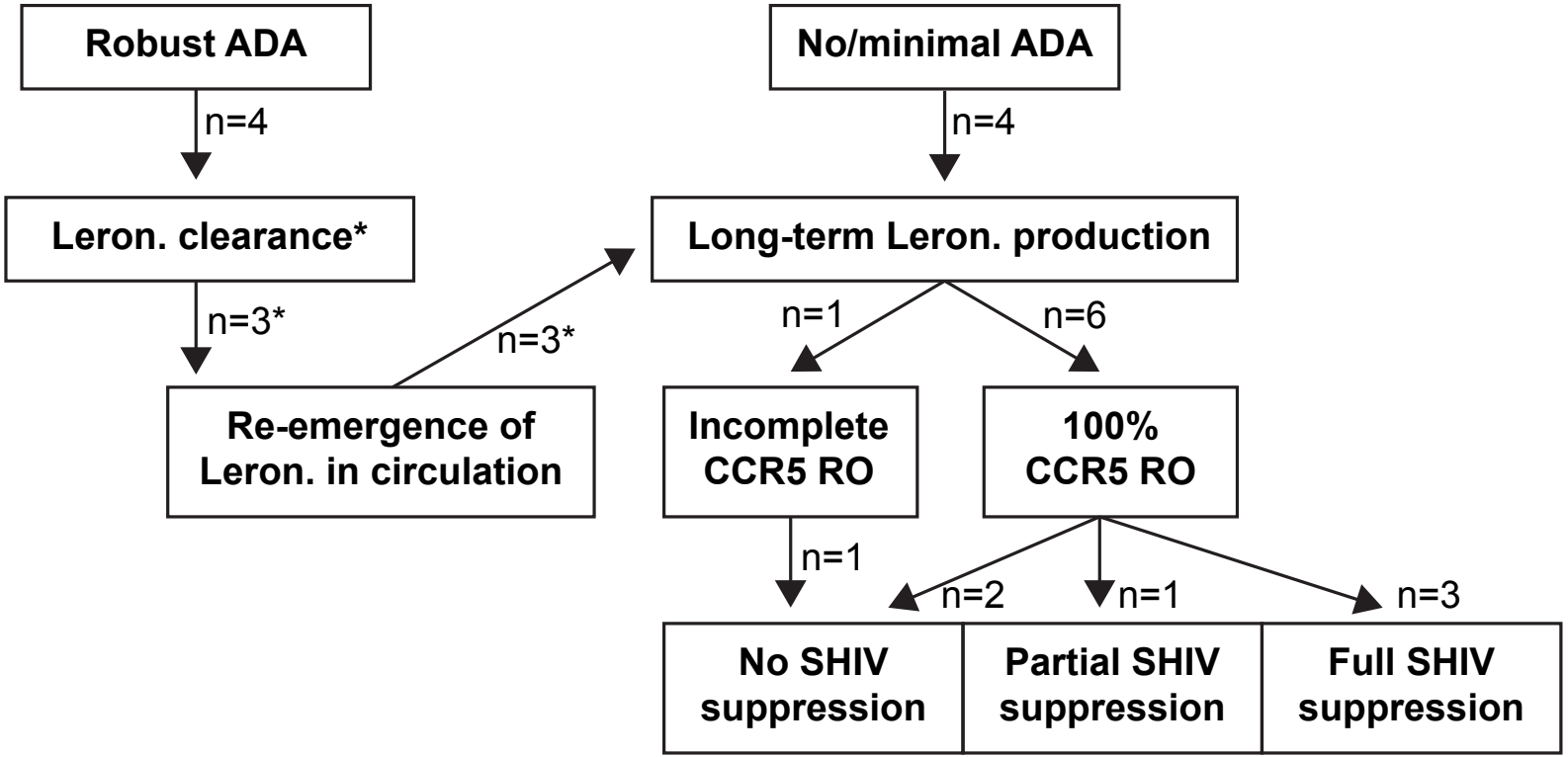




AAV-Leronlimab: Outcomes



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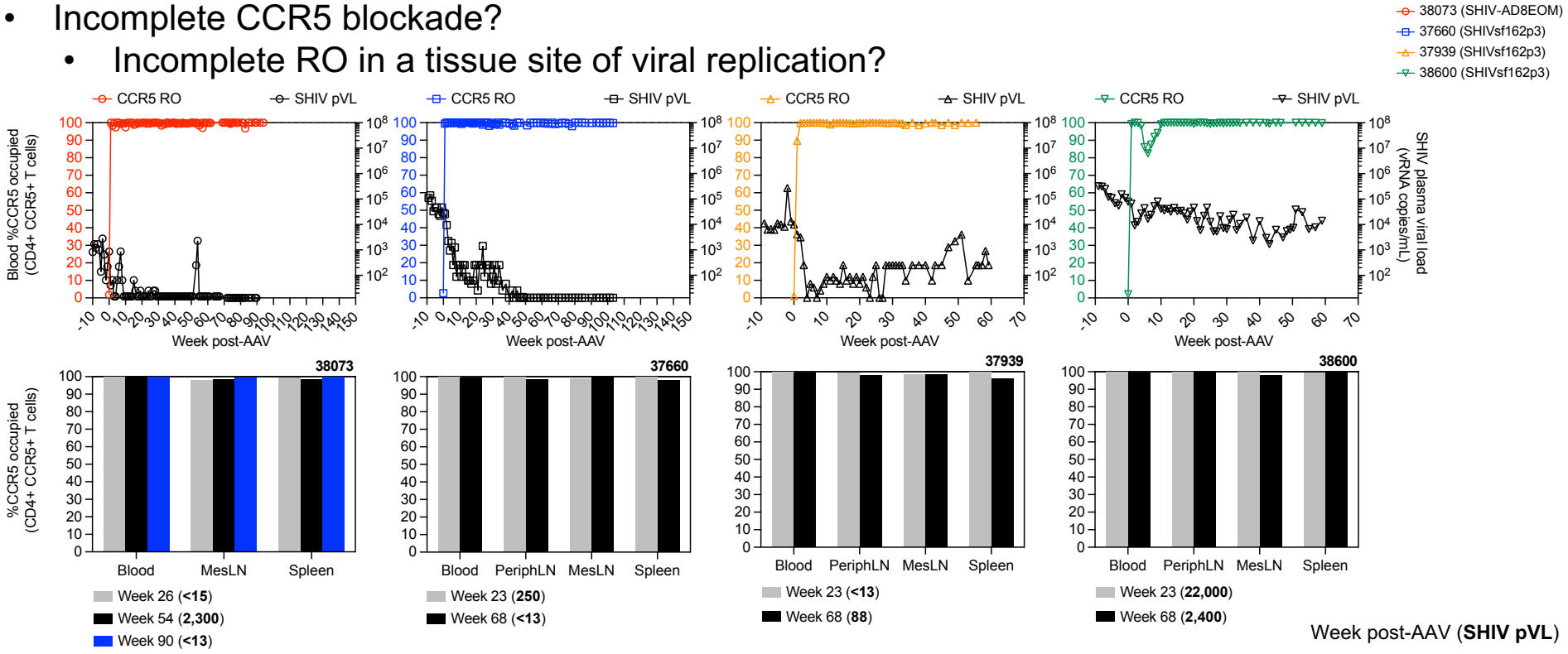

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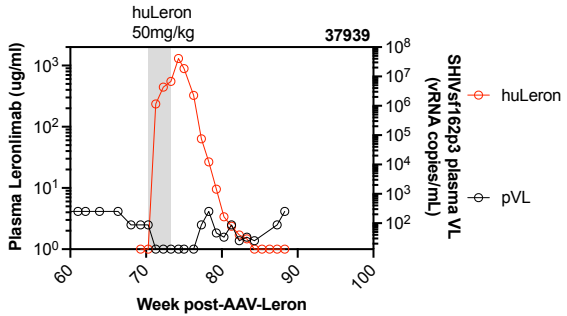
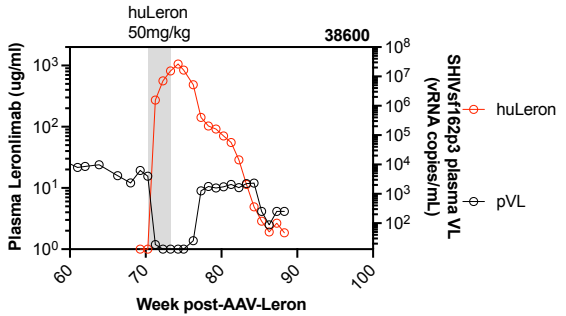
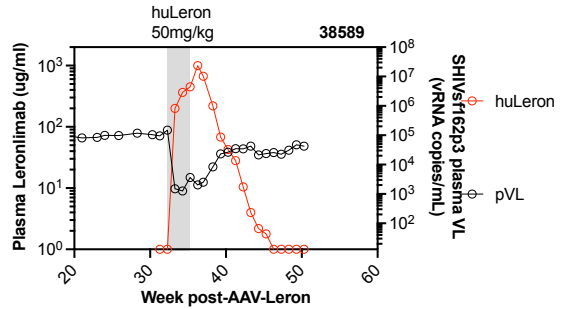
AAV9-macLS-Leron macaques with 100% CCR5 RO but incomplete SHIV suppression >> treated with exogenous Leron:







Exogenous CCR5 blockade sufficient to suppress	Exogenous CCR5 blockade **NOT** sufficient to suppress

But transgene can re-emerge >40 wks post-AAV