

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

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EDITION
10TH

HIV PERSISTENCE DURING THERAPY™

Reservoirs & Eradication
Strategies Workshop



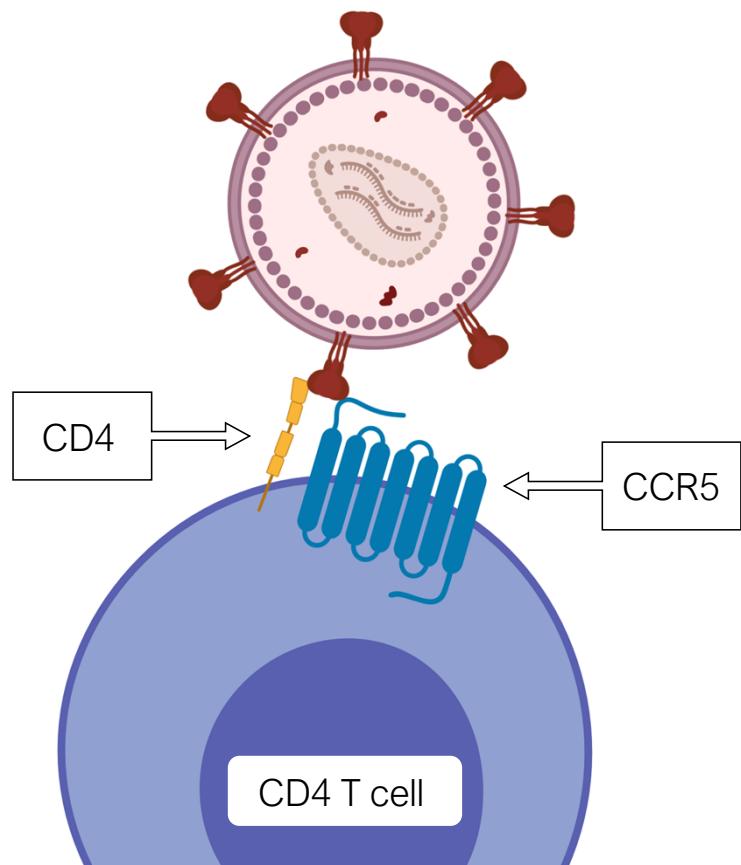
DECEMBER 13-16, 2022
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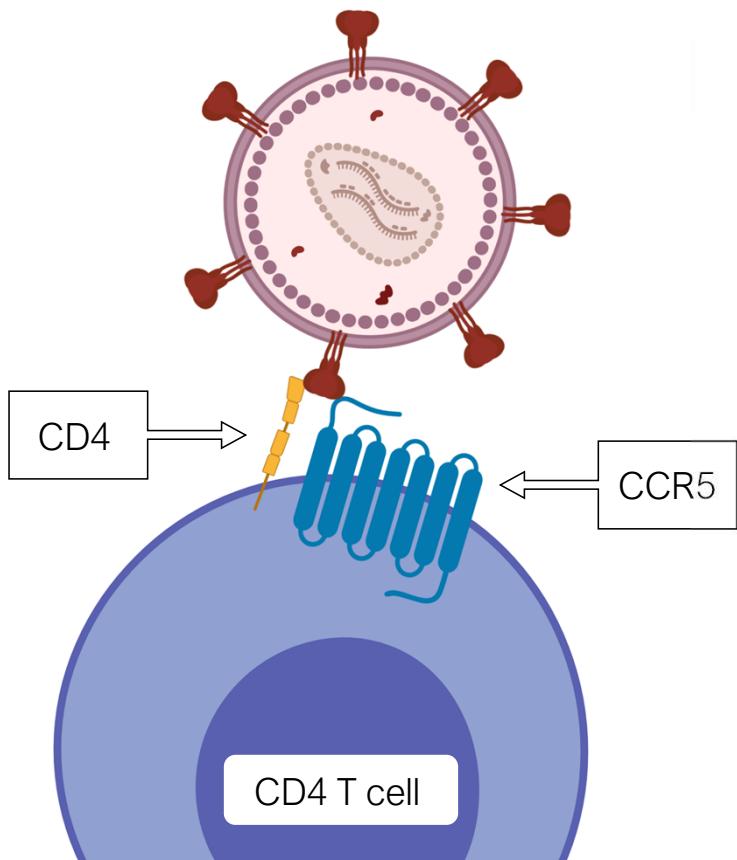
CONFLICTS OF INTEREST

Dr. Webb has a financial interest in CytoDyn, Inc., a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU.

CCR5 is critical in sexual transmission of HIV



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LETTERS TO NATURE

Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene

Michel Samson*, Frédéric Libert*, Benjamin J. Doranz†, Joseph Rucker‡, Corinne Liesnard‡, Claire-Michèle Farber§, Sento Saragosti||, Claudine Lapouméroulie¶, Jacqueline Cogniaux#, Christine Forceille#, Gaetan Muyldermans#, Chris Verhofstede#, Guy Burtonboy#, Michel Georges☆, Tsuneo Imai*, Shalini Rana††, Yanji Yi††, Robert J. Smyth††, Ronald G. Collman††, Robert W. Doms†, Gilbert Vassart†† & Marc Parmentier*

Cell

ARTICLE | VOLUME 86, ISSUE 3, P367-377, AUGUST 09, 1996

Homozygous Defect in HIV-1 Coreceptor Accounts for Resistance of Some Multiply-Exposed Individuals to HIV-1 Infection

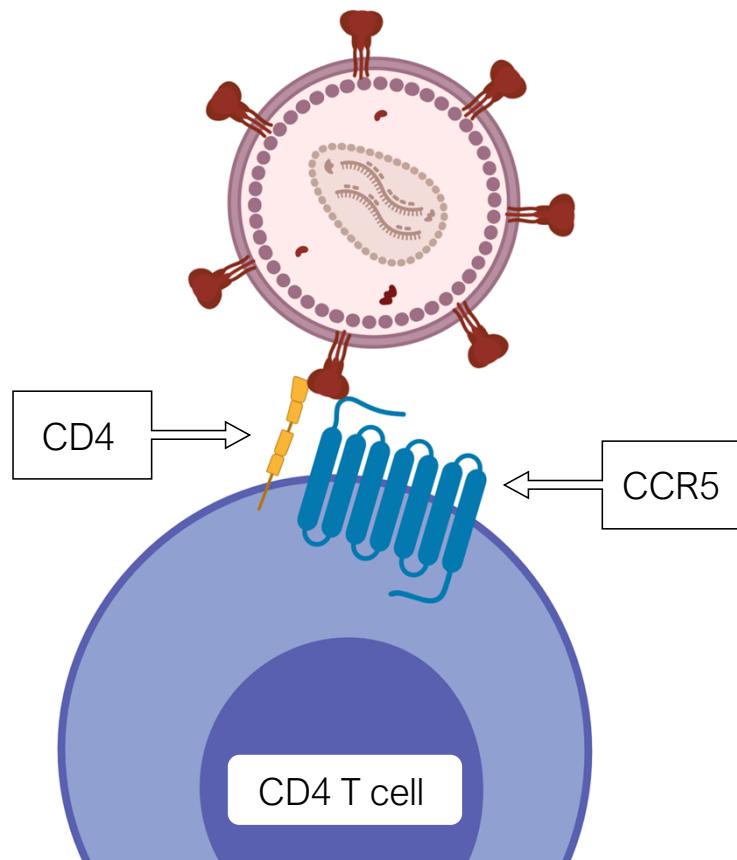
REPORTS

Genetic Restriction of HIV-1 Infection and Progression to AIDS by a Deletion Allele of the CCR5 Structural Gene

Michael Dean*, Mary Carrington*, Cheryl Winkler, Gavin A. Huttley, Michael W. Smith, Rando Allikmets, James J. Goedert, ...

Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Franci:

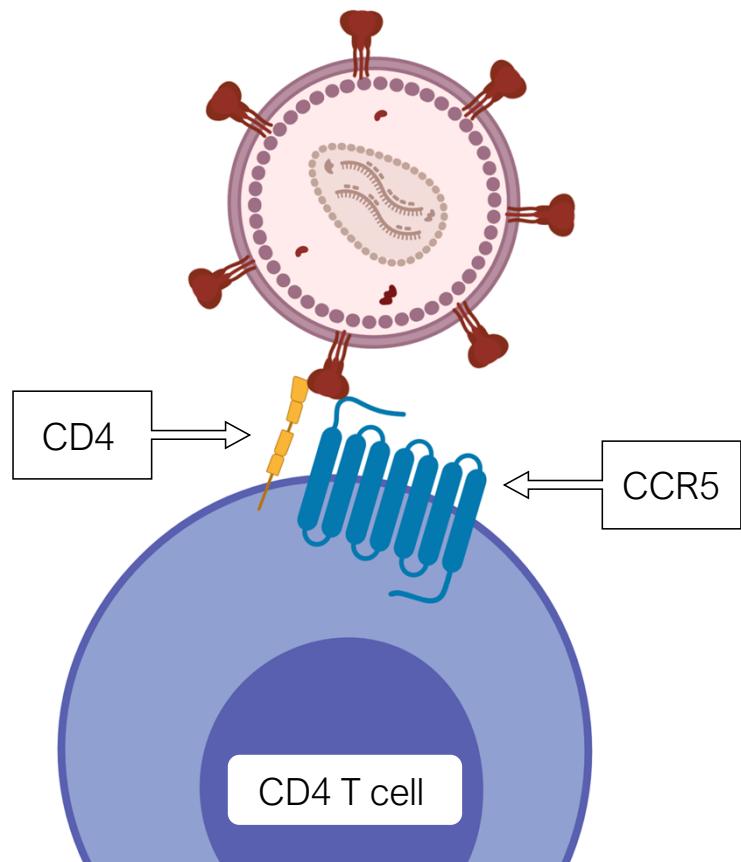
CCR5 is critical in sexual transmission of HIV



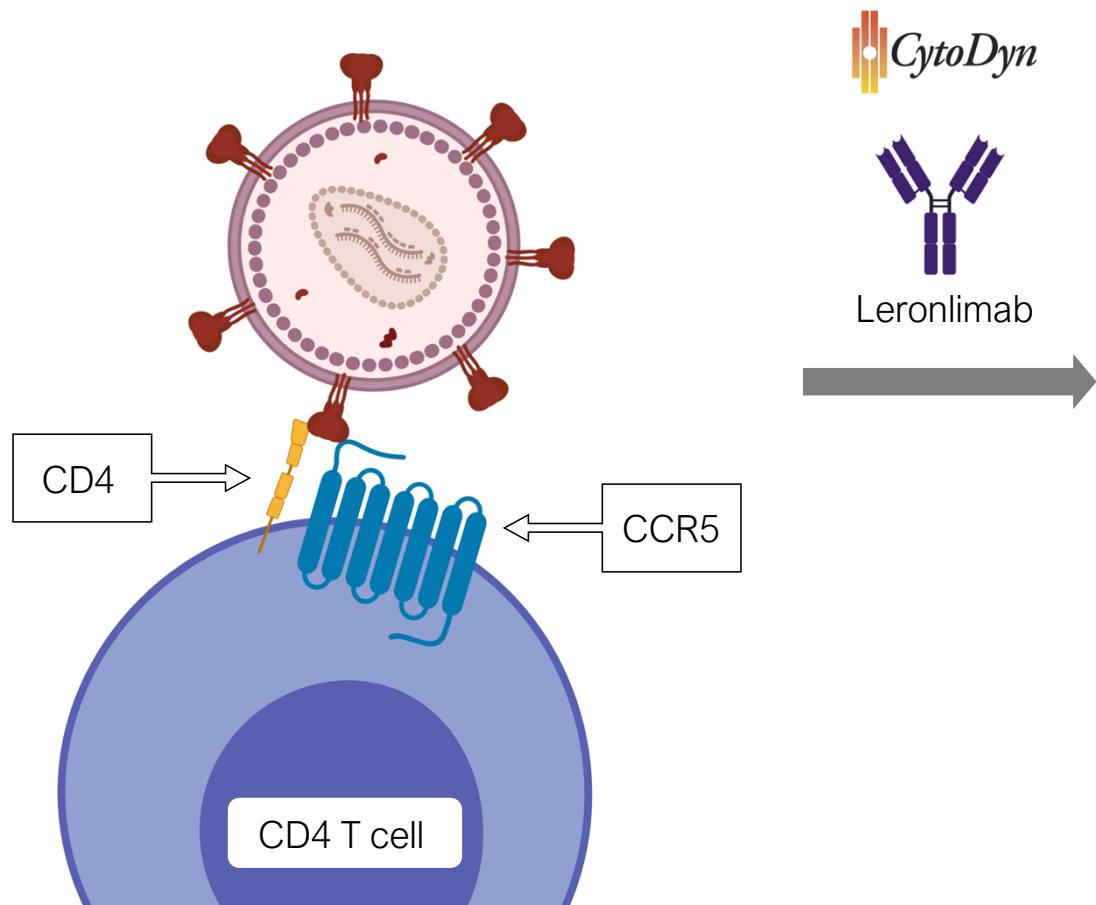
IMPAACT P1107 Team Presents First Known Case of a Woman with HIV Remission


IMPAACT
International Maternal Pediatric Adolescent
AIDS Clinical Trials Network

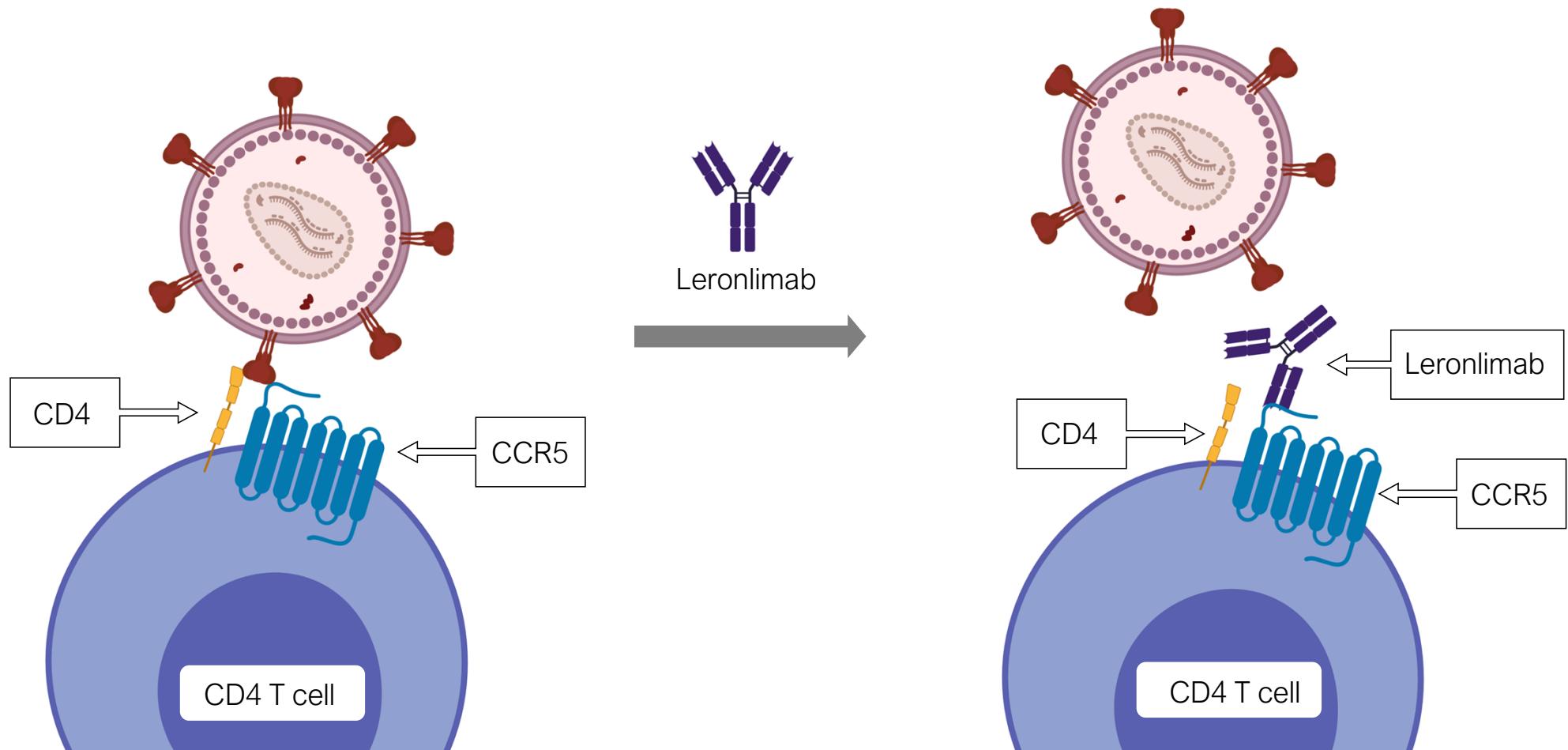
Can we mimic CCR5 $^{\Delta 32/\Delta 32}$ phenotype?



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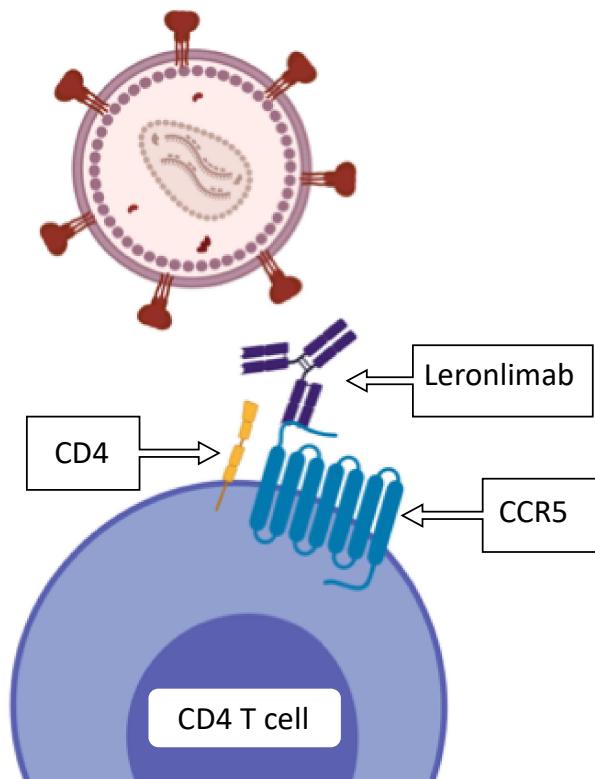


Can we mimic CCR5 $^{\Delta 32/\Delta 32}$ phenotype?



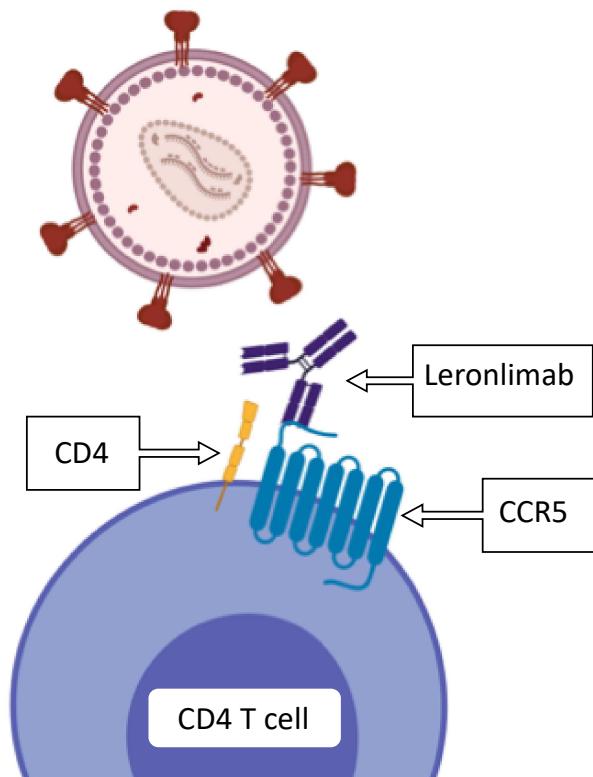
Leronlimab (formerly PRO140)

- Humanized monoclonal IgG4 antibody (PA14 clone)



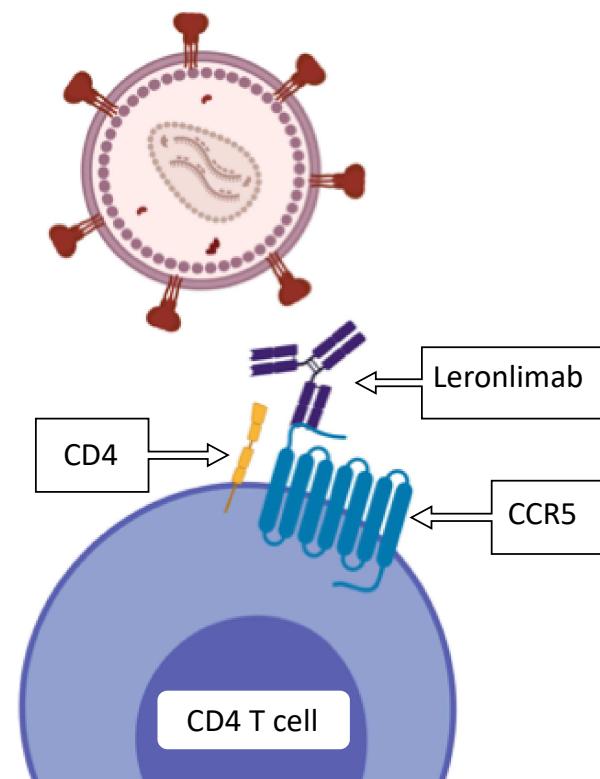
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Leronlimab (formerly PRO140)

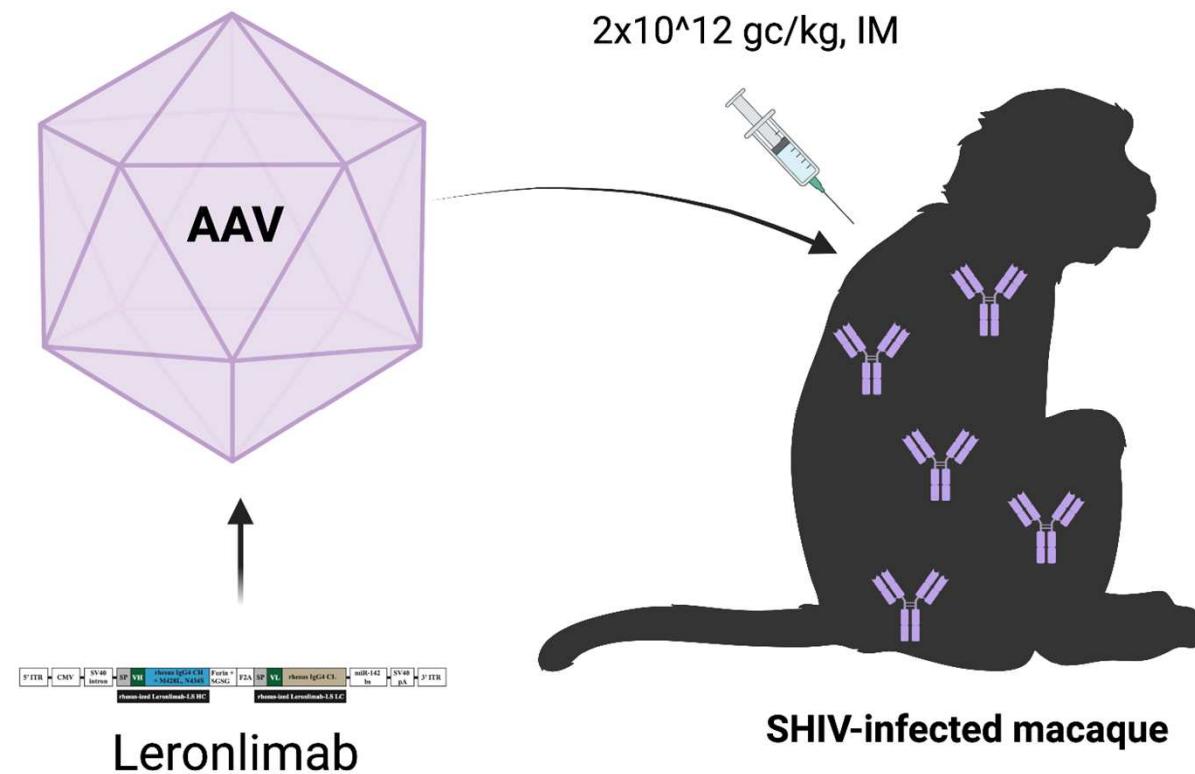
- Humanized monoclonal IgG4 antibody (PA14 clone)
- Binds to N-terminus and ECL2 of CCR5
- In multiple clinical trials
 - High safety profile - tested in over 1,000 volunteers living with HIV
 - Once-weekly, at home subcutaneous injection



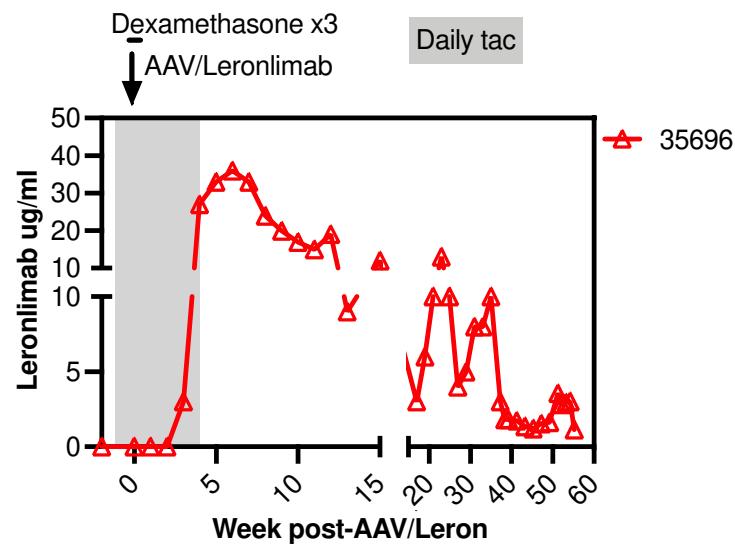
AAV-delivered Leronlimab for functional cure?



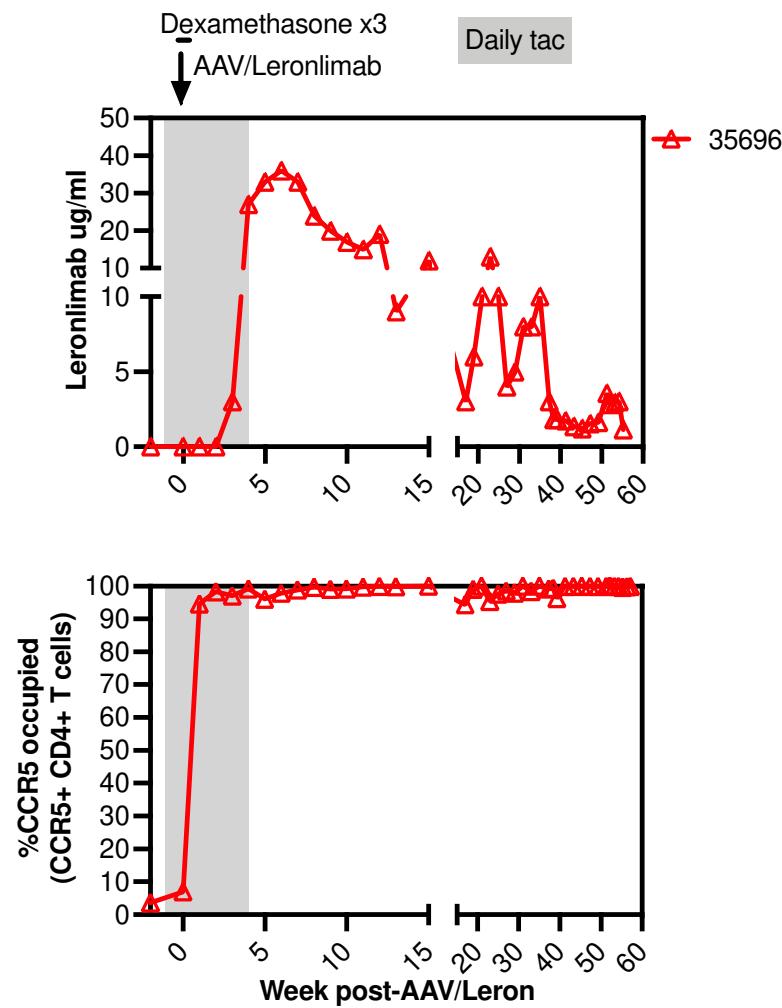
AAV-Leronlimab: A tale of two monkeys



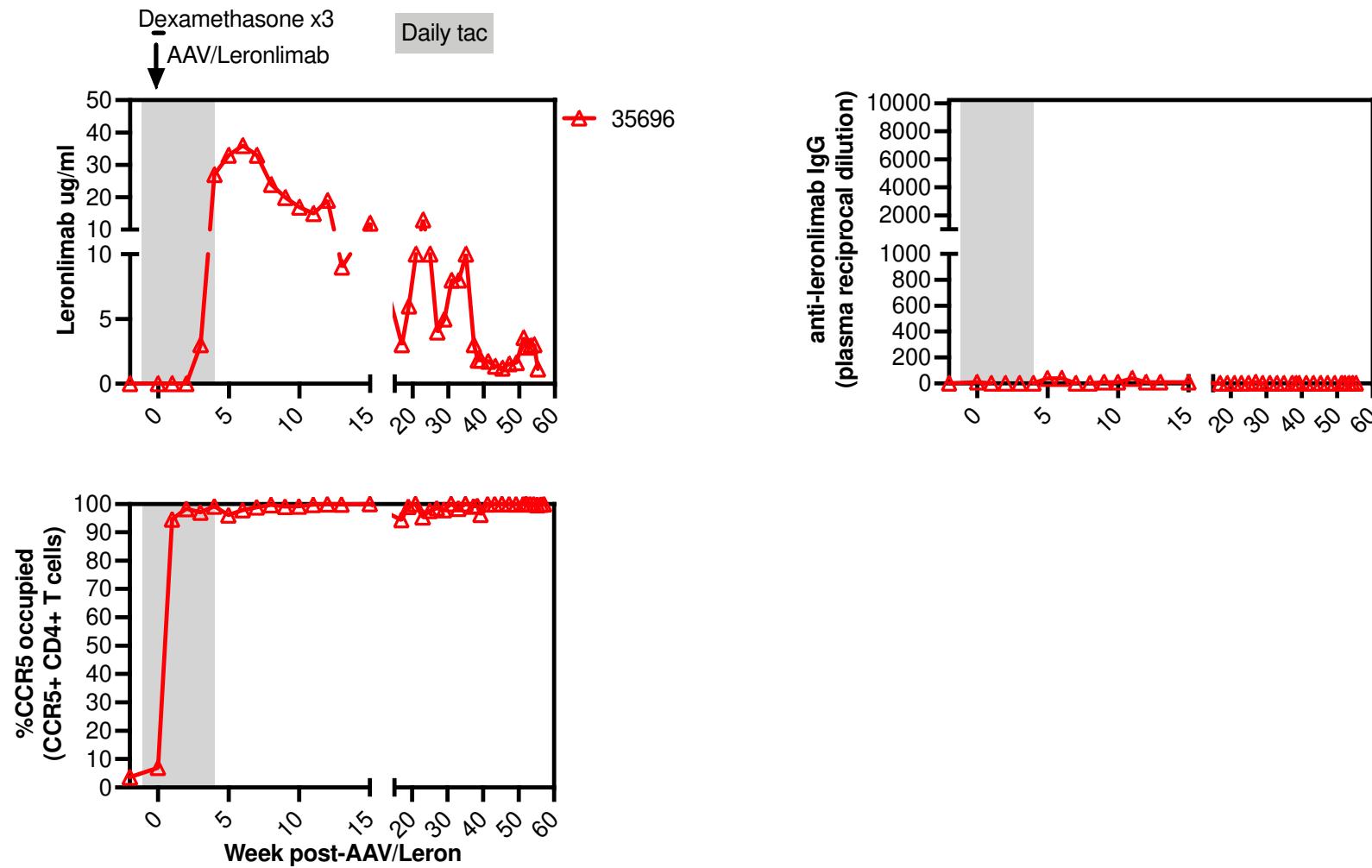
Case #1: AAV-Leronlimab + immunosuppression



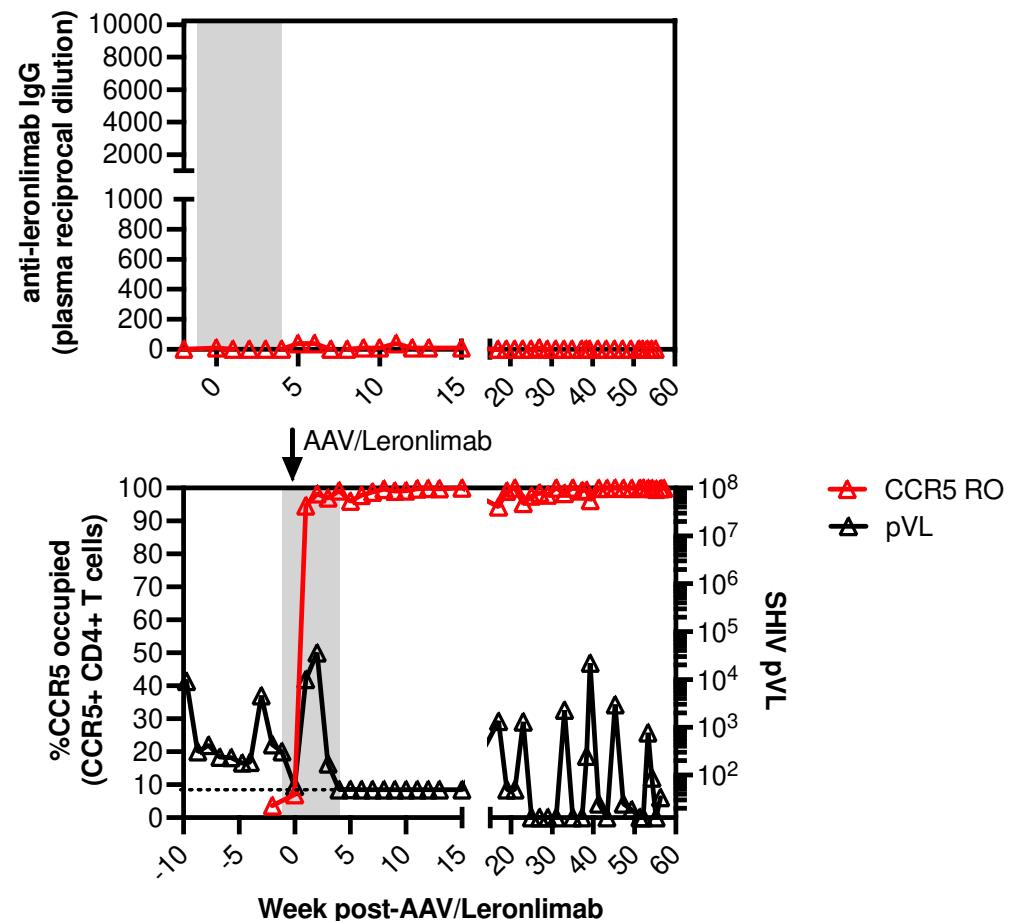
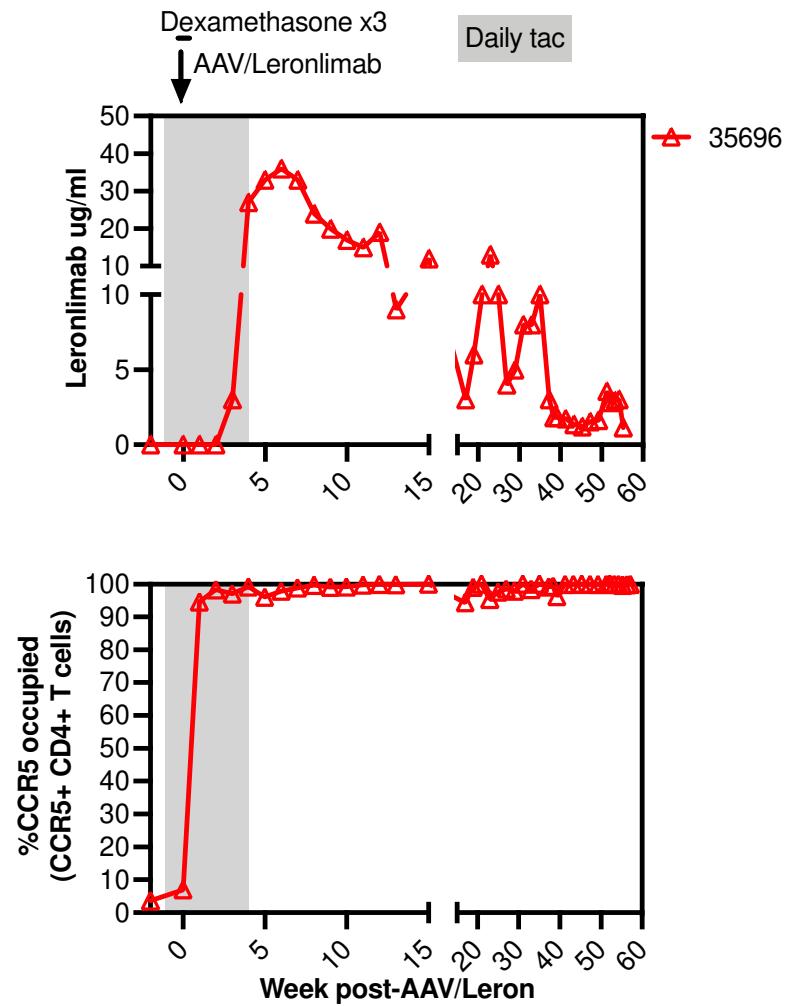
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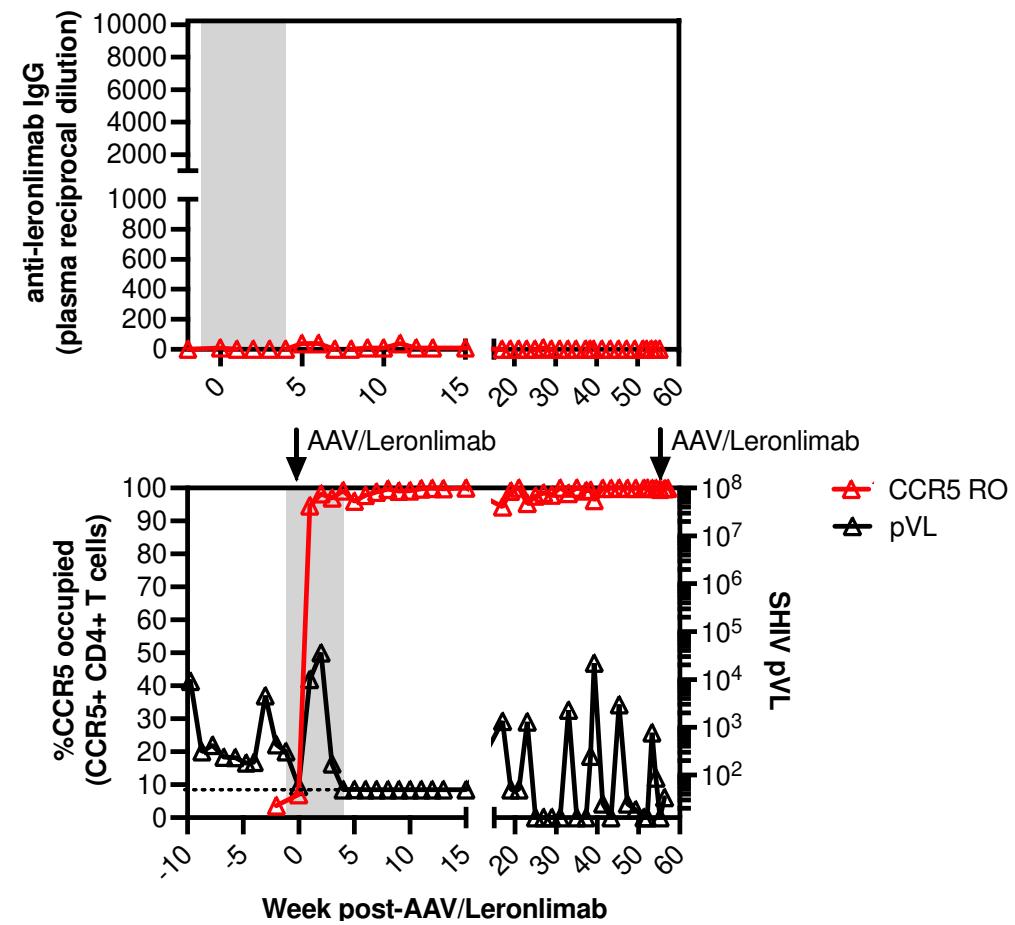
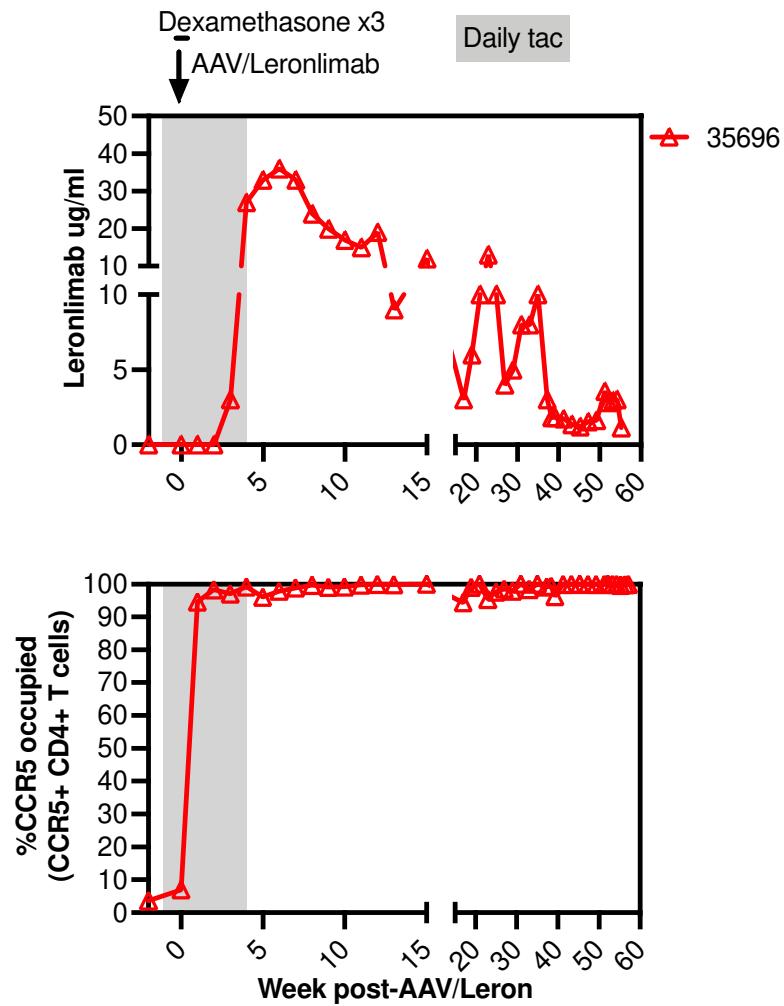
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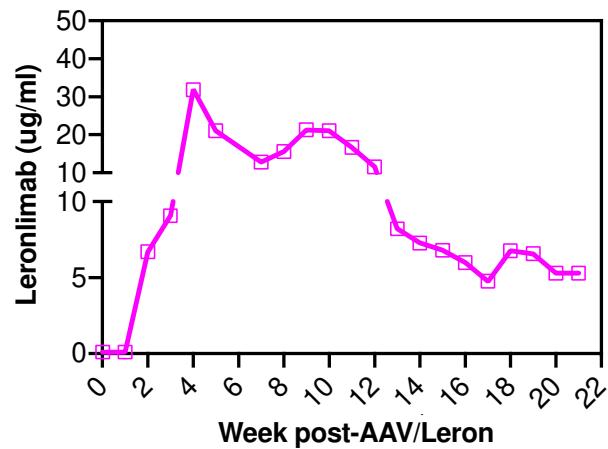
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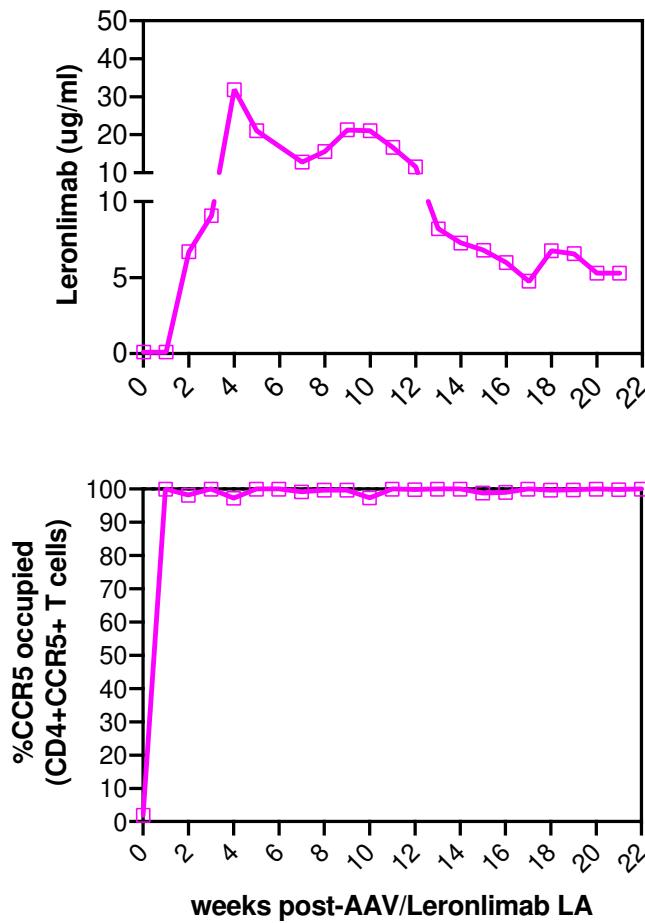
Case #2: AAV-Leronlimab (long-acting)

Animal ID	SHIV strain	Immunosuppression	Leronlimab
35696	sf162p3	Dex/tacrolimus	human
38073	AD8EOM	-	macaque LS

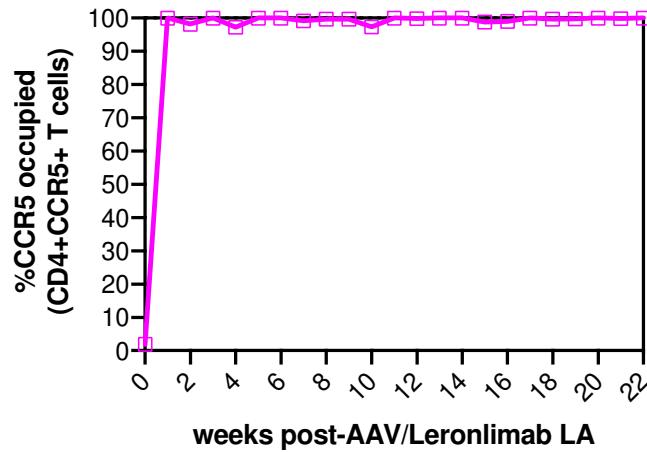
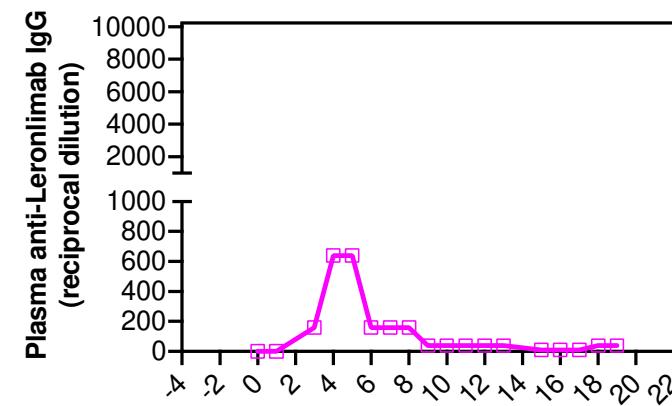
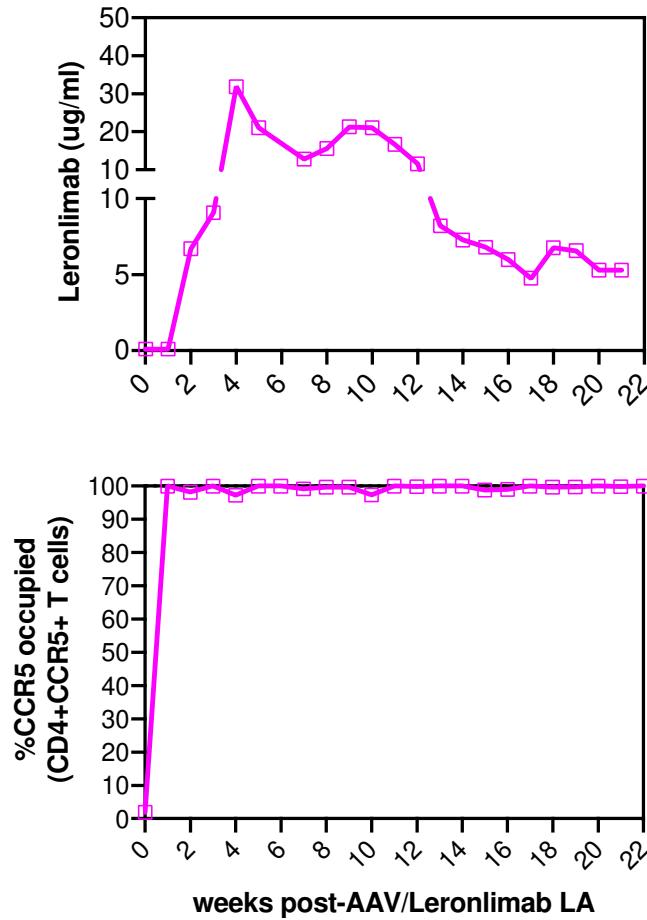
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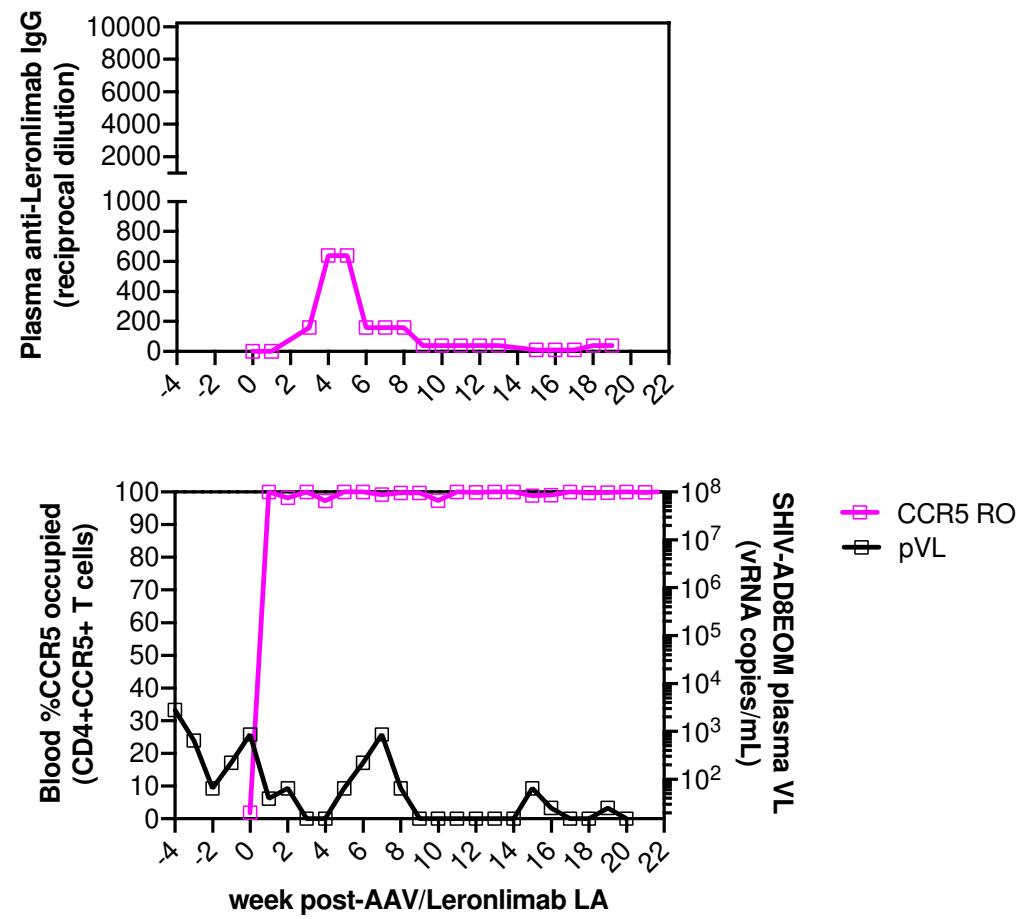
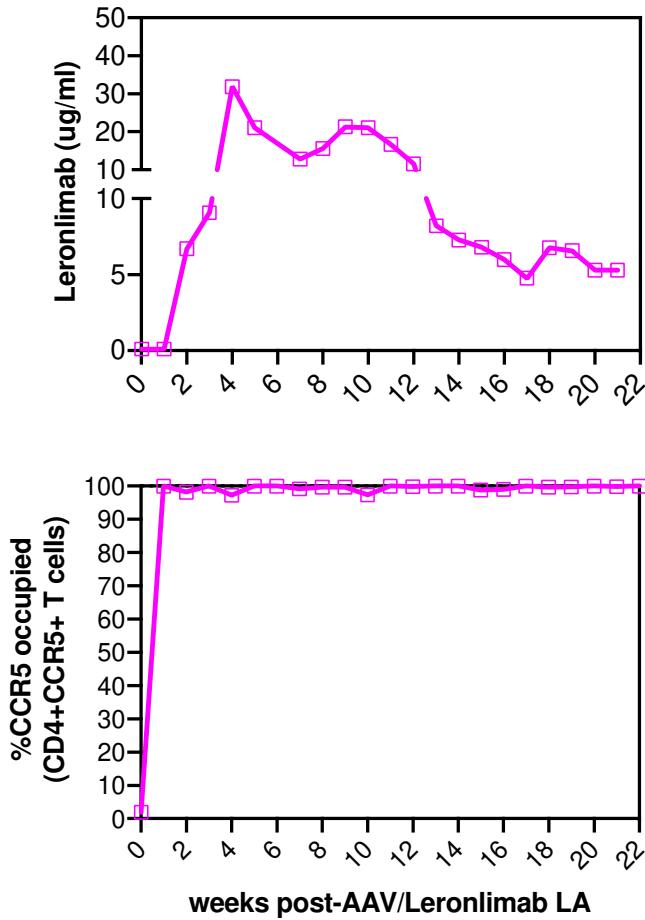
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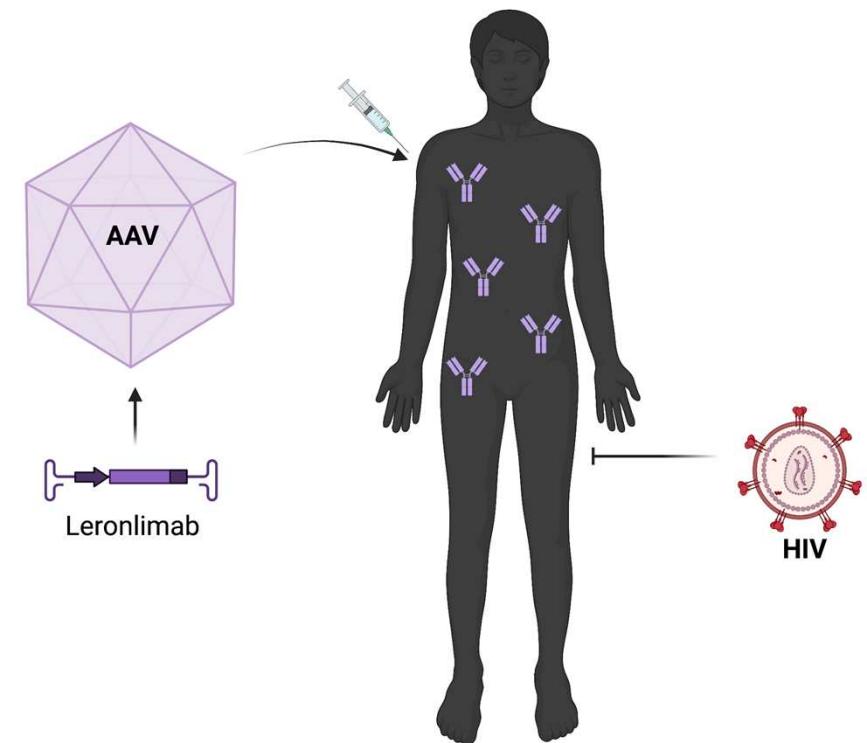
Summary

Animal ID	SHIV strain	Immunosuppression	Leronlimab	Current time post-AAV
35696	sf162p3	Dex/tacrolimus	human	>1 year *AAV boost at 1 year
38073	AD8EOM	-	macaque LS	23 weeks

Future Directions

How can we consistently achieve long-term Leronlimab expression through AAV delivery?

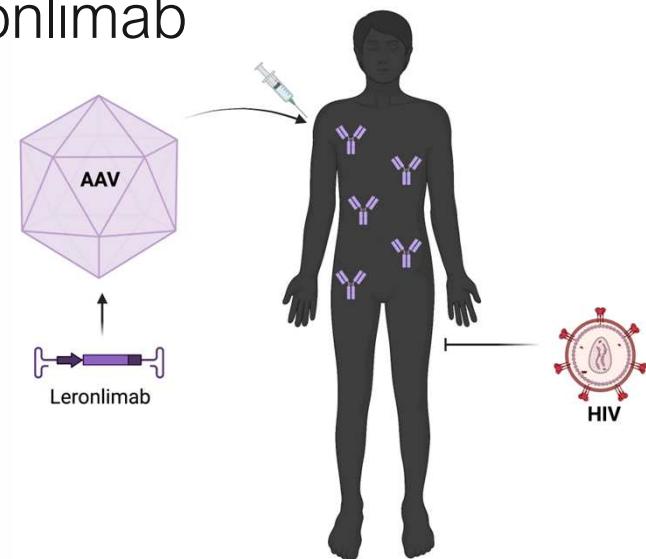
- Reduce ADA
- Reduce ADA
- Reduce ADA
- Increase Leronlimab expression
- Alternate AAV capsids





COMMUNITY SUMMARY

- Key question: Can an AAV-delivered CCR5-specific monoclonal antibody lead to HIV remission in macaques?
- Key finding: Two proof-of-concept cases of long-term transgene expression and suppressed viremia from a single shot of AAV-Leronlimab
- Next steps
 - Reduce antidrug antibodies
 - Reduce AAV immunogenicity
 - Increase transgene production



Acknowledgements

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