Viral Suppression in SHIV-infected Rhesus Macaques following AAV-mediated Delivery of Closer-to-germline Monoclonal Antibodies

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- **Background:** Delivery of potent and broadly neutralizing antibodies by means of a viral vector (adeno-associated virus or AAV) is a promising approach for both, the prevention and treatment of HIV infection. However, when the AAV-delivered antibodies are seen as 'non-self', unwanted host antibodies are raised against them, which can compromise their efficacy by reducing their concentration and functionality.

- **Key question:** Can we overcome this critical issue by using 'more-self' antibodies?

- **Key finding:** The use of naturally 'more-self' antibodies may be a viable strategy for overcoming the 'foreignness' problem and make the AAV-mediated delivery of antibodies more consistent.

Adeno-Associated Virus (AAV) as a delivery vehicle of broadly neutralizing antibodies against HIV

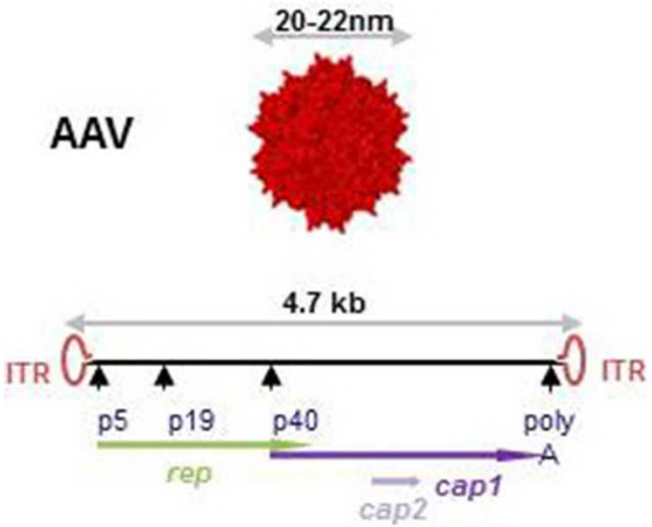
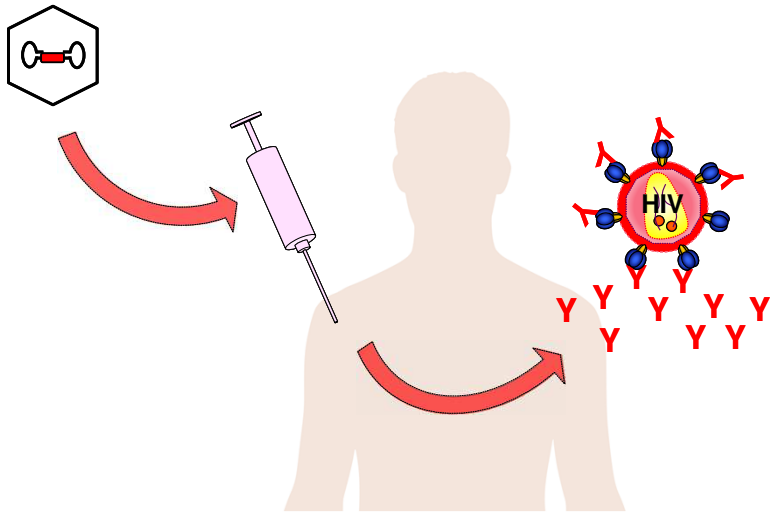


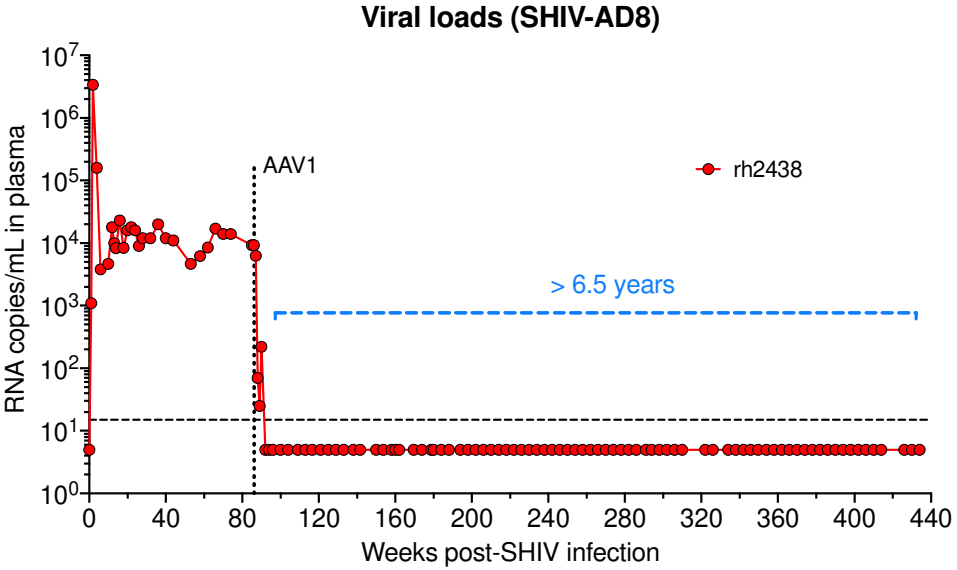
Image credit: CIRI / Nucleovir

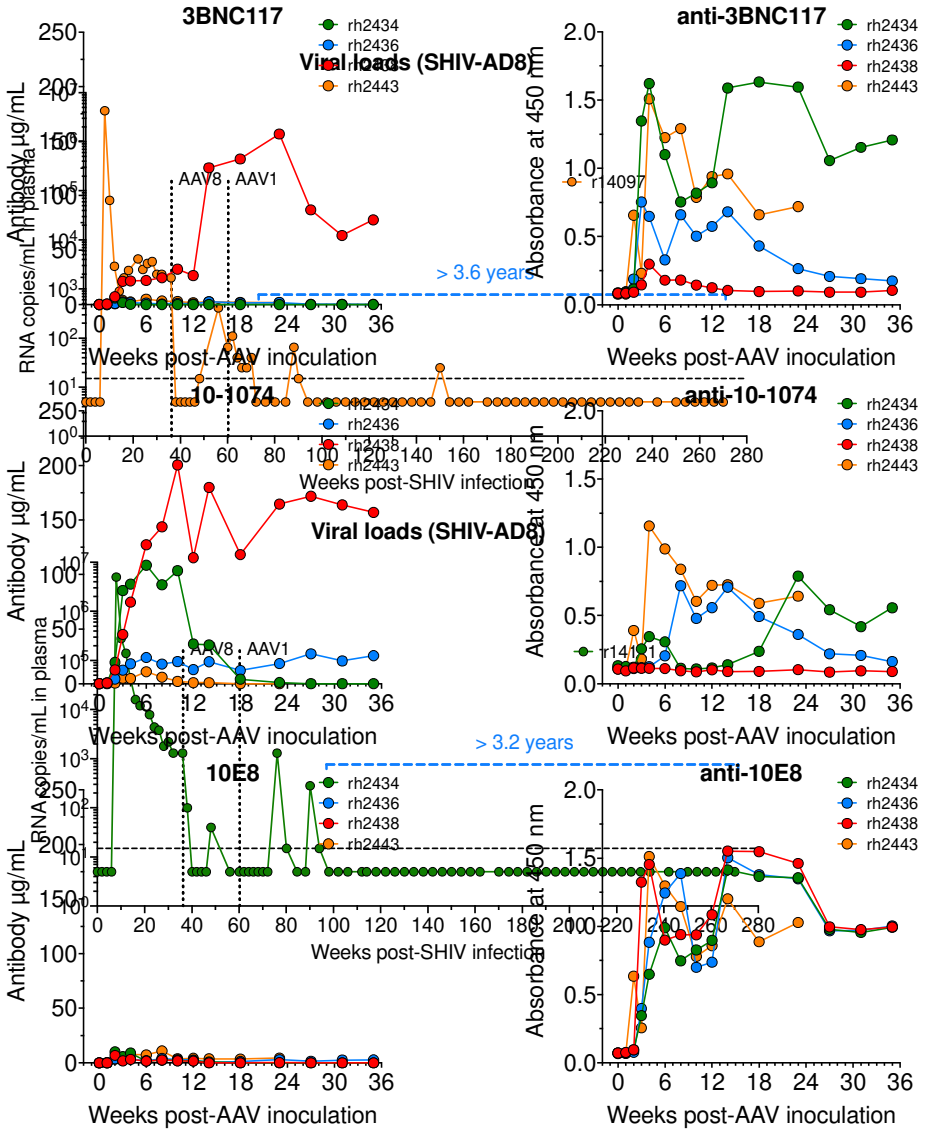
AAV is a small virus which infects humans and other animals. AAV is not currently known to cause disease and is being exploited for gene therapy.



1. **Circumvents the difficulties of generating a successful immunogen or vaccine.**
2. **Well characterized, broad and potent antibodies.**
3. **No need to produce large amounts of pharmaceutical grade antibody.**
4. **No need for repeated inoculations.**
5. **One administration could account for years of antibody expression.**
6. **Delivery of neutralizing antibodies with AAV is a promising approach for the prevention and treatment of HIV infection.**

Therapeutic use of AAV-delivered antibodies: promise & problems





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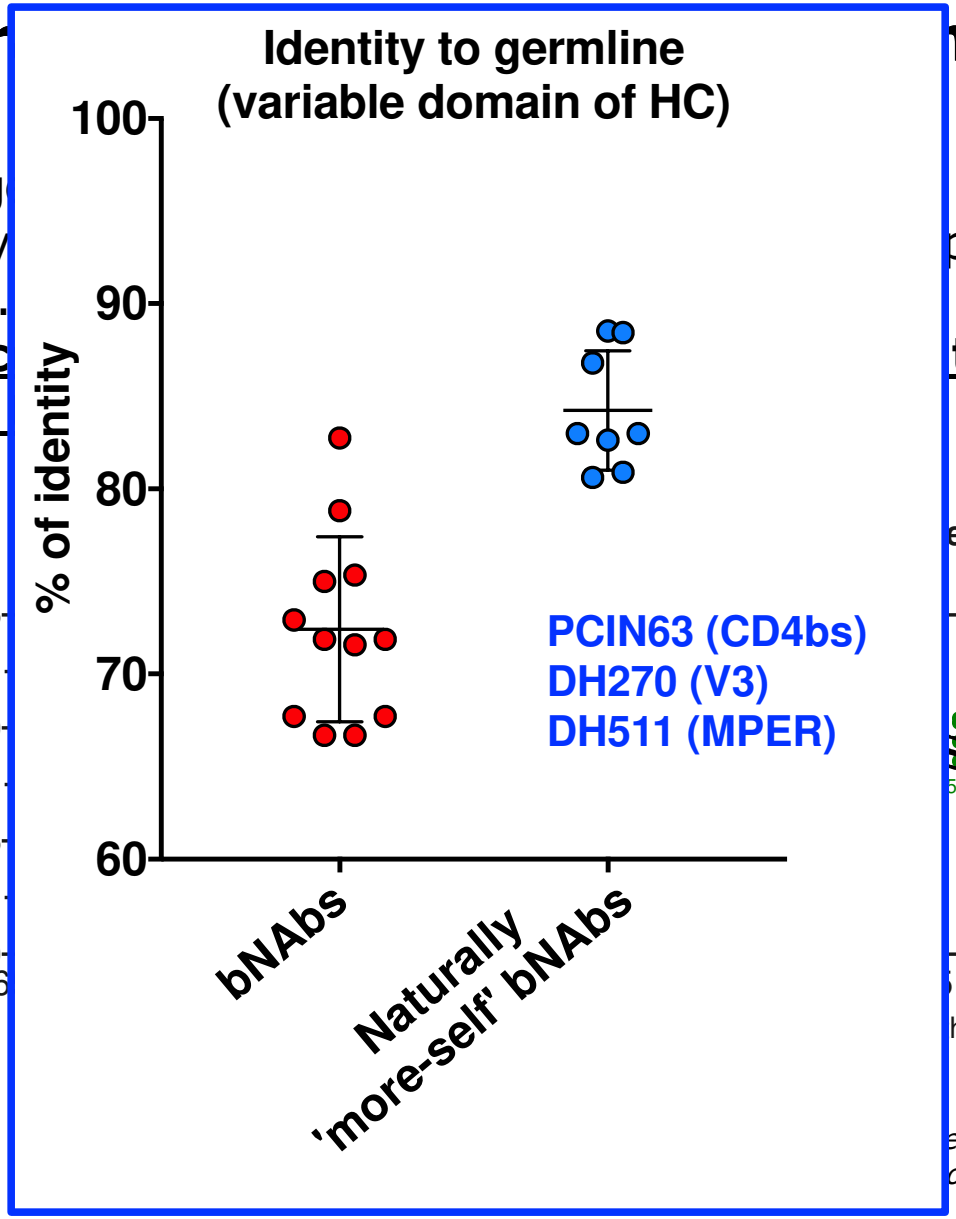
Martinez-Navio & Fuchs et al. Immunity 2019
& Manuscript in preparation

Char…nses:

1. ADAs mostly targ…
2. CDR-H3 reactivity …ptides covering the variable domains.
3. **<u>Levels of ADA c… the more divergent from germline,</u>**



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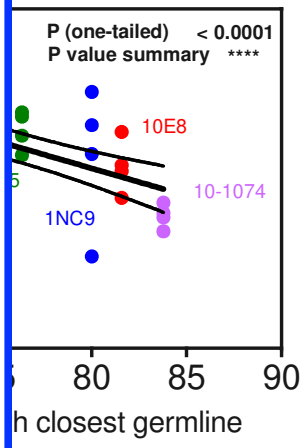

…h closest germline

…erapy 2016
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Potency and breadth:

	IC50 µg/mL (SHIV-AD8)	Breadth
PCIN63 (CD4bs)		
DH270 (V3)		
DH511 (MPER)		

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Immunity
Article

CellPress

Rapid and Focused Maturation of a VRC01-Class HIV Broadly Neutralizing Antibody Lineage Involves Both Binding and Accommodation of the N276-Glycan

Jeffrey Umotoy,[1,2] Bernard S. Bagaya,[3,4] Collin Joyce,[5] Torben Schiffner,[5,6] Sergey Menis,[1,2] Karen L. Saye-Francisco,[5] Trevor Biddle,[5] Sanjay Mohan,[7] Thomas Vollbrecht,[7] Oleksander Kalyuzhniy,[1,2] Sharon Madzorera,[8] Dale Kitchin,[8] Bronwen Lambson,[9] Molati Nonyane,[9] William Kilembe,[9] The IAVI Protocol C Investigators and The IAVI African HIV Research Network, Pascal Poignard,[1,5,10] William R. Schief,[1,5,6] Dennis R. Burton,[1,5,6,11] Ben Murrell,[7,12] Penny L. Moore,[8,13,14] Bryan Briney,[5,6] Devin Sok,[1,2,5,6,*] and Elise Landais[1,2,5,15,*]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

Staged induction of HIV-1 glycan–dependent broadly neutralizing antibodies

Mattia Bonsignori,[1,2*†] Edward F. Kreider,[3†] Daniela Fera,[4†] R. Ryan Meyerhoff,[1,2†] Todd Bradley,[1,2†] Kevin Wiehe,[1,2] S. Munir Alam,[1,2] Baptiste Aussedat,[5] William E. Walkowicz,[5] Kwan-Ki Hwang,[2] Kevin O. Saunders,[2,6] Ruijun Zhang,[2] Morgan A. Gladden,[2] Anthony Monroe,[2] Amit Kumar,[2] Shi-Mao Xia,[2] Melissa Cooper,[2] Mark K. Louder,[7] Krisha McKee,[7] Robert T. Bailer,[7] Brendan W. Pier,[4] Claudia A. Jette,[4] Garnett Kelsoe,[2,8] Wilton B. Williams,[1,2] Lynn Morris,[9] John Kappes,[10] Kshitij Wagh,[11] Gift Kamanga,[12‡] Myron S. Cohen,[13] Peter T. Hraber,[11] David C. Montefiori,[2,6] Ashley Trama,[2] Hua-Xin Liao,[1,2] Thomas B. Kepler,[14] M. Anthony Moody,[2,8,15] Feng Gao,[1,2] Samuel J. Danishefsky,[5] John R. Mascola,[7] George M. Shaw,[3] Beatrice H. Hahn,[3] Stephen C. Harrison,[4] Bette T. Korber,[11*†] Barton F. Haynes[1,2*†]

Sci Immunol. 2017 January 27; 2(7): . doi:10.1126/sciimmunol.aal2200.

Potent and broad HIV-neutralizing antibodies in memory B cells and plasma

LaTonya D. Williams[1,*], Gilad Ofek[2,*], Sebastian Schätzle[3,*], Jonathan R. McDaniel[3,*], Xiaozhi Lu[1,*], Nathan I. Nicely[1], Liming Wu[2], Caleb S. Lougheed[2], Todd Bradley[1,4], Mark K. Louder[5], Krisha McKee[5], Robert T. Bailer[5], Sijy O'Dell[5], Ivelin S. Georgiev[6], Michael S. Seaman[7], Robert J. Parks[1], Dawn J. Marshall[1], Kara Anasti[1], Guang Yang[1], Xiaoyan Nie[1], Nancy L. Tumba[8,9], Kevin Wiehe[1,4], Kshitij Wagh[10], Bette Korber[10], Thomas B. Kepler[11], S. Munir Alam[1,4,12], Lynn Morris[8,9], Gift Kamanga[13], Myron S. Cohen[14], Mattia Bonsignori[1,4], Shi-Mao Xia[1], David C. Montefiori[1,15], Garnett Kelsoe[1,16], Feng Gao[1,4], John R. Mascola[5], M. Anthony Moody[1,16,17], Kevin O. Saunders[1,15], Hua-Xin Liao[1,4], Georgia D. Tomaras[1,15,16,18], George Georgiou[3,19,†], and Barton F. Haynes[1,4,16,†]

Sequence and Structural Convergence of Broad and Potent HIV Antibodies That Mimic CD4 Binding

Johannes F. Scheid,[1,2] Hugo Mouquet,[1*] Beatrix Ueberheide,[3*] Ron Diskin,[4*] Florian Klein,[1] Thiago Y. K. Oliveira,[1] John Pietzsch,[1,5] David Fenyo,[3] Alexander Abadir,[1] Klara Velinzon,[1] Arlene Hurley,[6] Sunnie Myung,[3] Farid Boulad,[7] Pascal Poignard,[8,9] Dennis R. Burton,[8,10] Florencia Pereyra,[10,11] David D. Ho,[12] Bruce D. Walker,[10,11,12] Michael S. Seaman,[14] Pamela J. Bjorkman,[4,12] Brian T. Chait,[3] Michel C. Nussenzweig[1,12†]

SCIENCE VOL 333 16 SEPTEMBER 2011

Rational Design of Envelope Identifies Broadly Neutralizing Human Monoclonal Antibodies to HIV-1

Xueling Wu,[1*] Zhi-Yong Yang,[1*] Yuxing Li,[1*] Carl-Magnus Hogerkorp,[1†] William R. Schief,[4] Michael S. Seaman,[5] Tongqing Zhou,[1] Stephen D. Schmidt,[1] Lan Wu,[1] Ling Xu,[1] Nancy S. Longo,[1] Krisha McKee,[1] Sijy O'Dell,[1] Mark K. Louder,[1] Diane L. Wycuff,[1] Yu Feng,[1‡] Martha Nason,[2] Nicole Doria-Rose,[3] Mark Connors,[3] Peter D. Kwong,[1] Mario Roederer,[1] Richard T. Wyatt,[1‡] Gary J. Nabel,[1§] John R. Mascola[1§]

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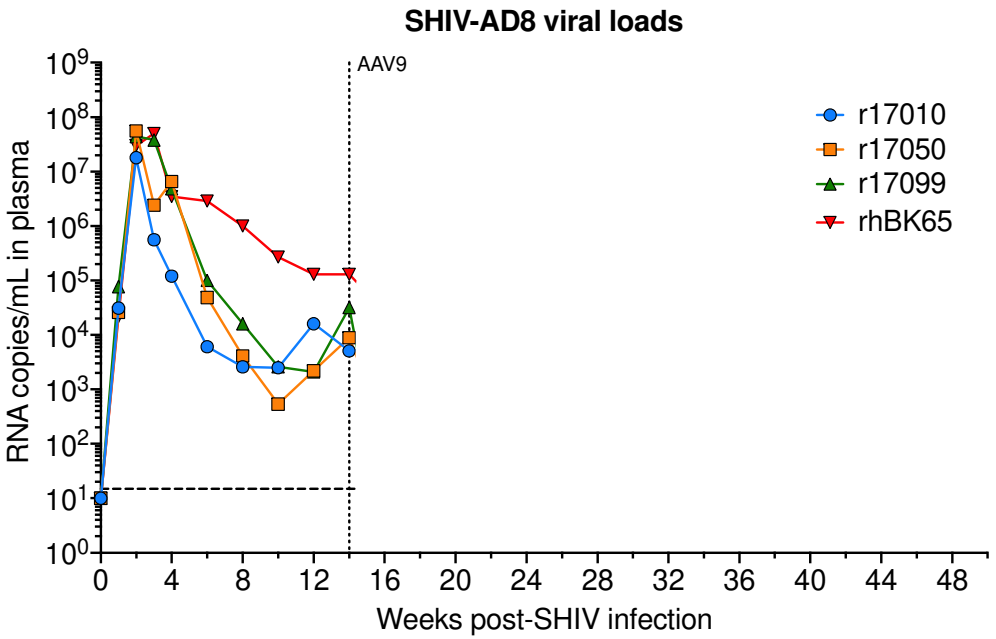
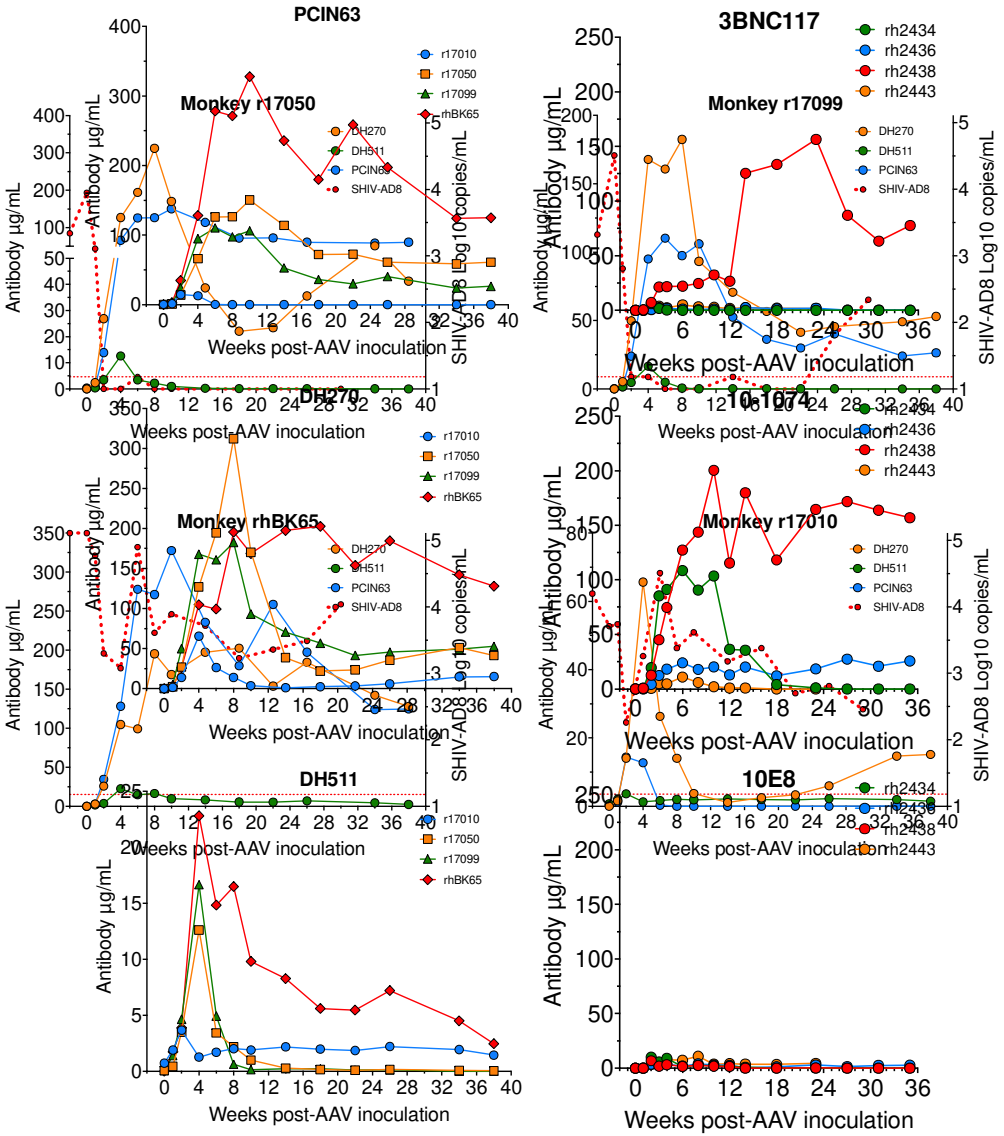
Therapeutic use of AAV-delivered antibodies: promise & problems





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Conclusions

1. **The use of closer-to-germline bNAbs may be a viable strategy for avoiding ADAs following gene therapy with AAV-bNAb vectors.**

2. **Our data support the potential for long-term suppression of viral loads with the AAV-antibody approach but also highlight the difficulties associated with achieving such long-term suppression.**

3. **Eradicating or minimizing ADA responses is crucial to make the AAV-delivery of antibodies a consistent and reliable approach against HIV.**

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Acknowledgements

University of Miami:

- **Ron Desrosiers**
- **Sebastian Fuchs**
- **Desiree Mendes**
- **Claudia Muniz**
- **Leydi Machado**
- Shara Pantry
- Andy Lauer
- Natasha Duggan
- James Termini
- Danielle Gill
- Brandon Rosen
- Paula Mondragon

UMass: Gao Lab

NCI at Frederick:

- Jeffrey Lifson

Wisconsin National Primate Center:

- Eva Rakasz
- Kim Weisgrau
- Jessica Furlott
- Eric Alexander
- Joe Kurian
- Saverio Capuano
- Nancy Schultz-Darken
- Wendy Newton

SHIV-AD8:

- Malcolm Martin

Thank you!

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