Vacunas

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14 Marzo 2023

IrsiCaixa Institut de Recerca de la Sida
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UVIC UNIVERSITAT DE VIC UNIVERSITAT CENTRAL DE CATALUNYA

Orals

General

Sunday March 3rd
OPENING

Modern Vaccinology: A Legacy of HIV Research
Barney S. Graham

Monday 4th
PLENARY

What's New in HIV Vaccines: Vaccine-Induced Immune Responses
Juliana M. McElrath

HIV prevention

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Therapeutic Vaccines

Wednesday 6th

OA - HIV Reservoir and Cure Strategies (All in SIV)

AAV-Expressed HIV IgG Biologics Enable Durable ART-Free Viral Control in Infant Macaques
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A T Cell-Targeting mRNA SIV Vaccine Extends Time to Rebound and Enhances Post-ART Viral Control
Benjamin Varco-Merth

IL-15/IL-15RA Cytokine Therapy Enhances Control of Viral Rebound in SIV-Infected Macaques
Vijayakumar Ve

STI

Orals

Tuesday 5th

OA - STI

Final Results of ANRS 174 DOXYVAC: A Randomized Trial to Prevent STI in MSM on PrEP
Jean-Michel G. Molina

Tuesday 5th

Symposium New Frontiers in Hepatitis B

Advances in HBV Immunotherapy: The Beginning of the End?
Adam Gehring

Wed 6th

Special session O-LB

HepB-CpG Vaccine Is Superior to HepB-alum in People With HIV and Prior Vaccine Nonresponse: A5379
Kristen Marks

Posters

379 - Sex-Based Differences in Antibody Responses Induced by a Native-Like HIV-1 Envelope Trimer Vaccine

383 - Mucosal HIV Vaccine Targeting Host Epithelial Stem Cells for Long-Term Immunity

414 -Targeting HIV-Infected Cells for Immunotherapy Through HLA-E

529 - Vaccination Combined With PD-1 Blockade Provides Sustained SIV Suppression in Mamu-A01(+) Macaques

506 - Immune Profile During ATI in AELIX-002 HTI Vaccine Trial and Its Role in Post-Intervention Control

446 - Post-Intervention HIV Control Linked to Early In Vivo CD8+ T-Cell Proliferative Response to Rebound

407 - Characterizing New and Boosted HIV-Specific T-Cell Responses Elicited by an HIV Therapeutic Vaccine (PENNVAX)

General

Sunday March 3rd
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Modern Vaccinology: A Legacy of HIV Research
Barney S. Graham

HIV PRIMARY ISOLATES WHERE NOT NEUTRALIZED BY SERUM AB FROM PWH

Recognizing when old paradigms don't work

Nature volume 369, issue 6476, 12 May 1994

COMMENTARY

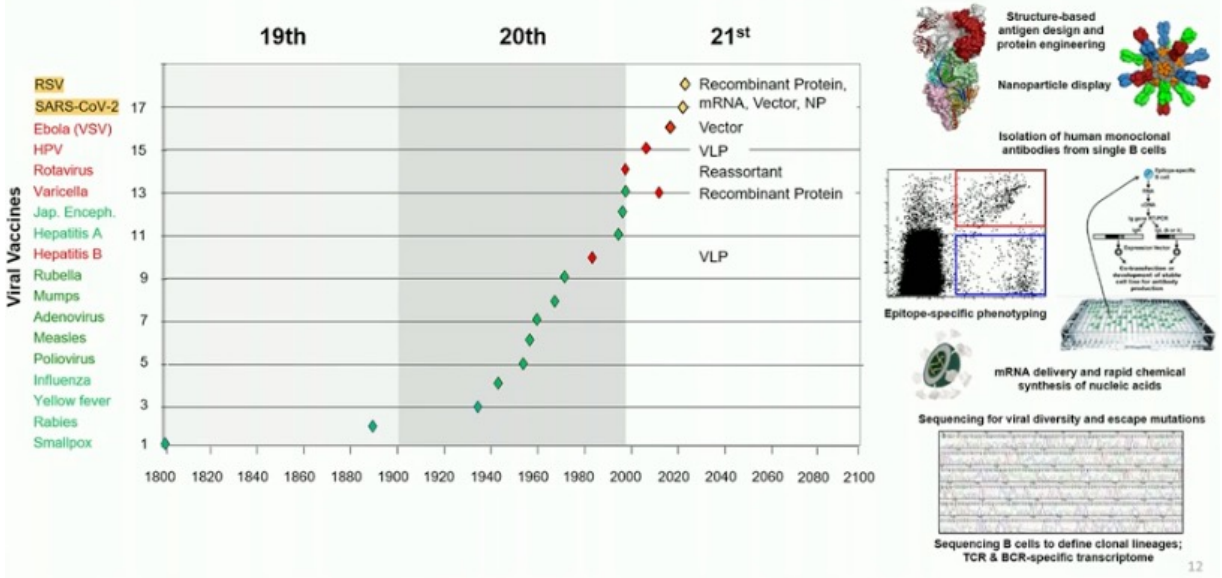
AIDS: time to turn to basic science

Bernard N. Fields

Success in controlling the AIDS epidemic is as likely to arise from unrelated areas of research as from AIDS-directed programmes.

VACCINOLOGY EVOLUTION

21st Century Vaccinology



Modern Vaccinology: Progress in Vaccine Science

20th Century

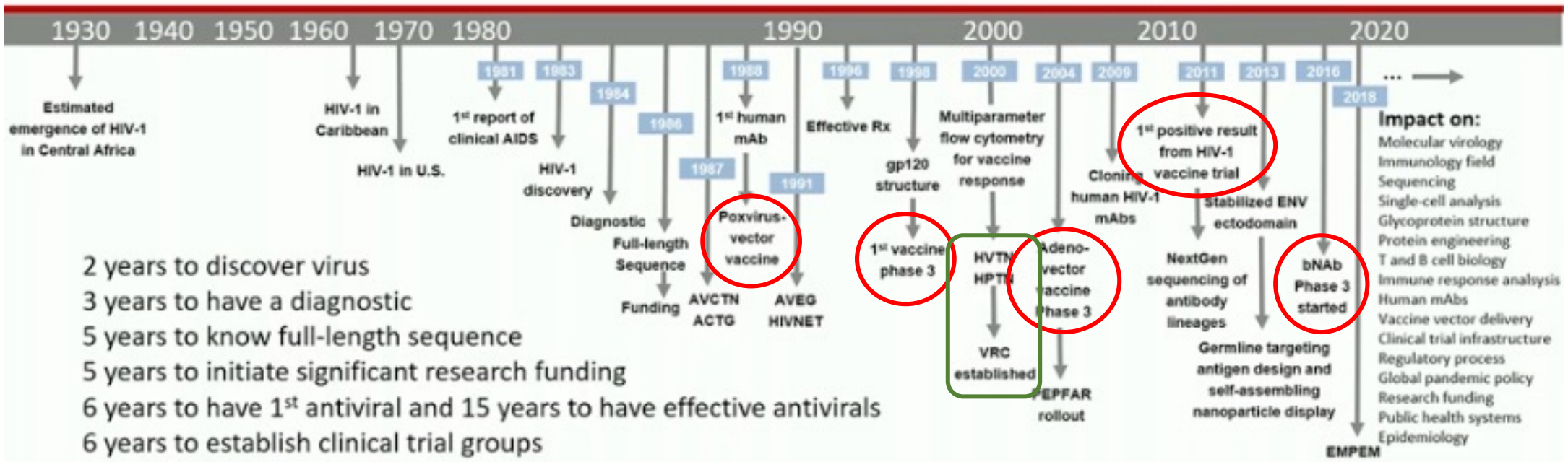
Live-attenuated
Whole-inactivated
Virus-like particles

Trial & error	Precision engineering
Cell culture →	Chemical synthesis
Individual products	Platform technologies
Decades	Months-Years

21st Century

Structure-based antigen design
Protein engineering
Nanoparticle display
High throughput sequencing
Rapid gene synthesis
Single cell analysis including B cell lineages
Human mAb isolation
B cell and lymph node biology
Custom animal models
Lipid biochemistry
Glycobiology
Formulation and manufacturing science
Data management & regulatory processes
Bioinformatics
Artificial intelligence

EMERGENCE AND RESPONSE TO HIV AND AIDS



2 years to discover virus
3 years to have a diagnostic
5 years to know full-length sequence
5 years to initiate significant research funding
6 years to have 1st antiviral and 15 years to have effective antivirals
6 years to establish clinical trial groups
7 years after effective ARVs to deploy internationally
7 years to isolate 1st human mAb
17 years to known gp120 core structure
17 years to initiate 1st phase 3 vaccine trial
27 years to clone broad, potent human mAbs
35 years to initiate 1st phase 3 study of passive antibody

~559,000 HIV/AIDS publications in PubMed

General

Monday 4th
PLENARY

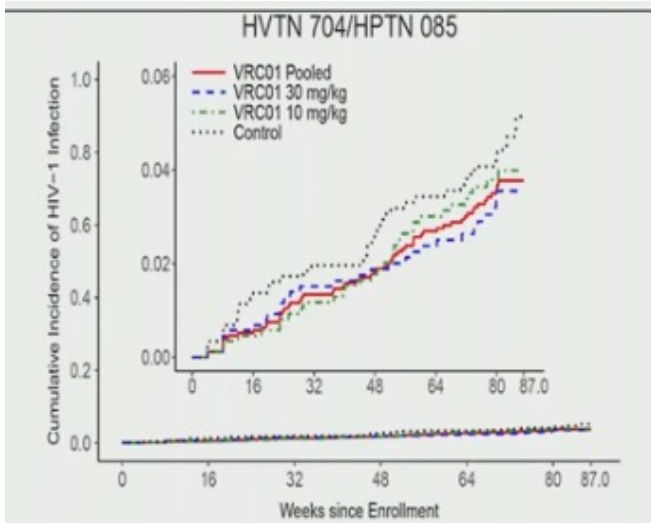
What's New in HIV Vaccines: Vaccine-Induced Immune Responses
Juliana M. McElrath

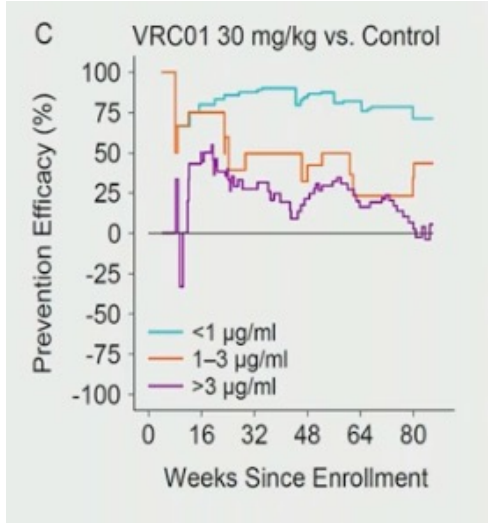
Collective knowledge from 10 HIV vaccine efficacy trials

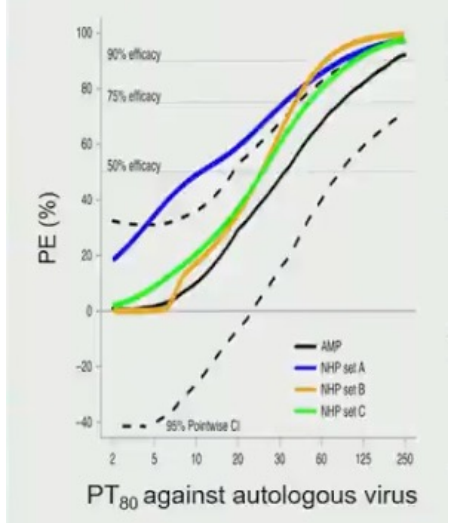
Phase 2b/3 Vaccine Trials	VE	Knowledge Gained
Vax003: bivalent clade E/B gp120 in alum **Vax004:** bivalent clade B/B gp120 in alum	no	Strain-specific Abs alone are not protective
HVTN 502 Step, HVTN 503 Phambili: Ad5 clade B gag/pol/nef	no	Increased infection in vaccinees; reduced viremia post-HIV with higher Gag-specific T cell magnitude
RV144: ALVAC gag/pro/Env + bivalent clade **AE/B** gp120 **in alum**	31.1%	Lower risk: higher V1V2 IgG3, polyfunctional CD4+ T cells. Higher risk: higher anti-Env IgA
HVTN 505: DNA + Ad5 clade B gag/pol/nef + clade A,B,C Envs	no	Ab Fc effector function, anti-Env IgG3, Env-specific CD8+ T cell functionality related to lower HIV risk
HVTN 702 Uhambo: clade C ALVAC gag/pol/Env + bivalent **clade C** gp120 in **MF59**	no	Interactions with high IgG V1V2 antibody and vaccine-matched CD4+ T cells related to lower HIV acquisition
HVTN 705 Imbokodo: Ad26 4-valent mosaic genes + clade C gp140 **HVTN 706 Mosaico:** Ad26 4-valent mosaic genes + bivalent clade C gp140/ mosaic gp140	no	Correlates analyses in progress
PrEP**VACC**: DNA-HIV-PT123 + AIDSVAX B/E DNA-MVA + CN54gp140 in MPLA + MVA-CMDR	no	Recent outcome

See Haynes BF et al, Nat Rev Immunol 2022 and references within

AMP example (Ab Mediated Prevention) trials, VCR01 (aCD4bs)
Corey, Gilbert, NEJM 2021





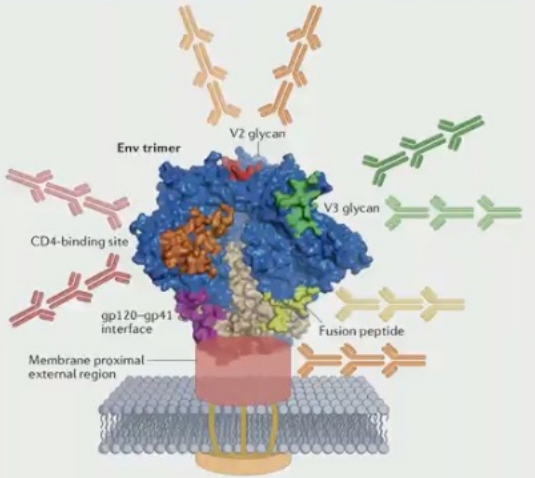


PT_{80} = 200 as biomarker/benchmark for candidate BnAb-inducing vaccines
Gilbert P, Nat Med 2022

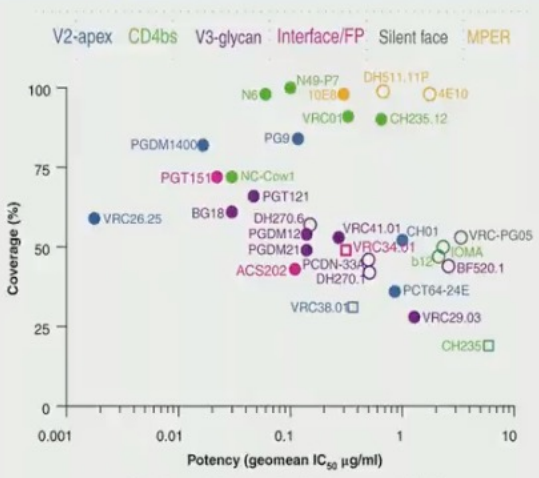
Current strategies to develop an HIV vaccine

Approach	Clinical Trials	Status
1. Induce broad neutralizing antibodies, ideally targeting 2-3 epitope regions	Phase 1 discovery medicine trials with novel Env immunogens, including new platforms and adjuvants	14+ trials underway or planned 2024 using bnAb-inducing vaccines targeting CD4bs, V3 glycan, MPER, or fusion peptide
2. Induce CD8+ T cells with broad coverage and antiviral function	Phase 1 trials with viral vectors: attenuated HCMV gorilla adenovirus networked epitope	HVTN 142 phase 1 trial: attenuated HCMV-HIV vaccine (VIR-1388) underway Gorilla adenovirus-vectored HIV networked epitope T cell vaccine in planning
3. Administer HIV bn-mAbs for immunoprophylaxis and to inform vaccine design	Combination bn-mAbs	Ongoing

Overall Goal: Design a vaccine regimen that can induce bnAbs targeting 2-3 Env epitope regions



Haynes B et al, Nat Rev Immunol 2022



Sok D and Burton D, Nat Immunol 2019

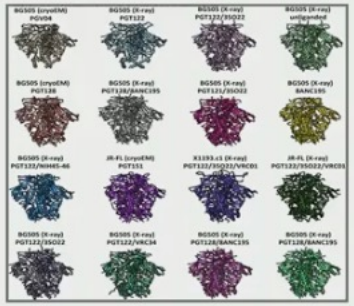
bNAb – inducing Vaccines

2012
Stabilized HIV envelope trimers
BG505 SOSIP
John Moore, Rogier Sanders

Negative stain EM

Binley JM, Sanders RW, Moore JP, J Virol 2000
Sanders RW and Moore JP Immunol Rev 2017

2013
Identification of bn-mAb interactions with Env epitope regions
Ian Wilson, Andrew Ward



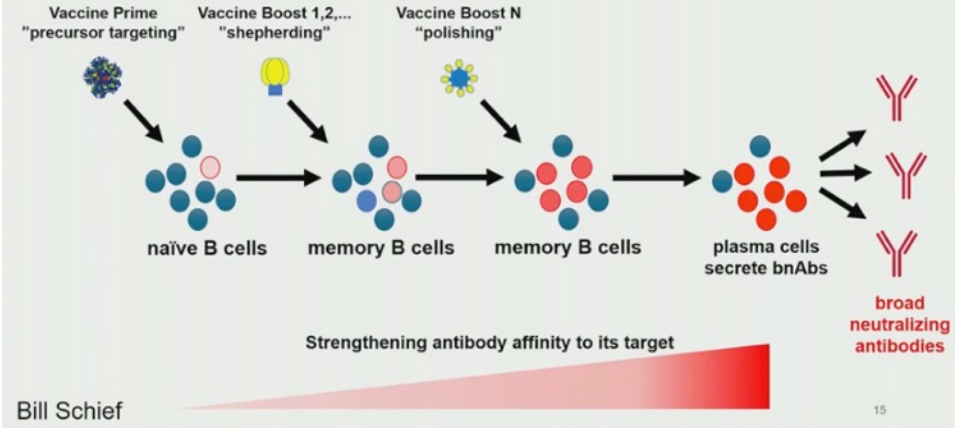
Lymkis D et al, Science 2013
Julien et al, Science 2013

2019
First in human testing initiated
BG505 SOSIP.664 trimer immunogen

3 trials:
1. Trimer 4571 with alum,
2. BG505 SOSIP.664 with AS01b
3. BG505 SOSIP.664 with multiple adjuvants

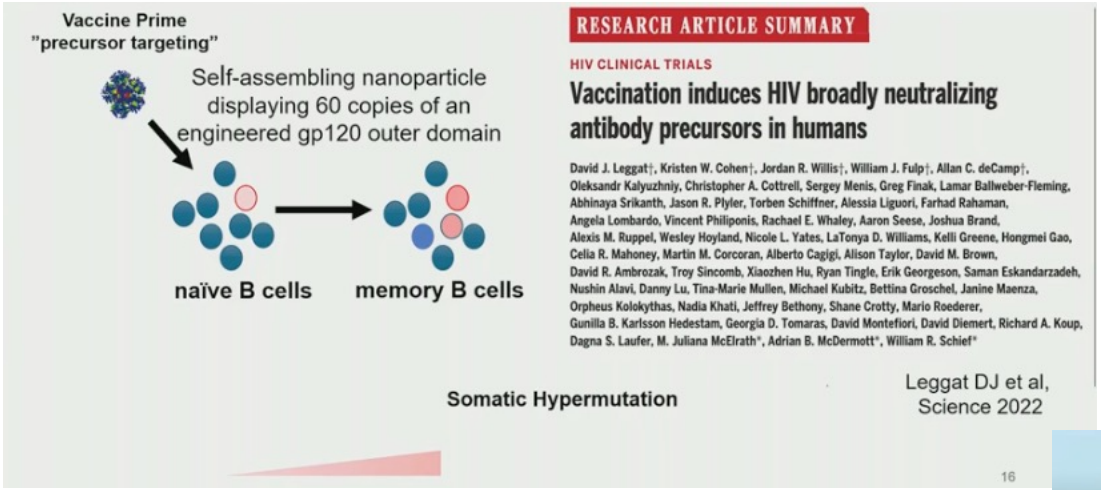
Houser KV et al eClin Med2022

Sequential vaccination: train naïve B cells to mature and produce antibodies that recognize their specific target bnAb epitope



eOD-GT860mer

1st step for VRC01-class bNAb



RESEARCH ARTICLE SUMMARY

HIV CLINICAL TRIALS

Vaccination induces HIV broadly neutralizing antibody precursors in humans

David J. Leggat†, Kristen W. Cohen†, Jordan R. Willis†, William J. Fulp†, Allan C. deCamp†, Oleksandr Kalyuzhniy, Christopher A. Cottrell, Sergey Menis, Greg Finak, Lamar Ballweber-Fleming, Abhinaya Srikanth, Jason R. Plyler, Torben Schiffner, Alessia Liguori, Farhad Rahaman, Angela Lombardo, Vincent Philiponis, Rachael E. Whaley, Aaron Seese, Joshua Brand, Alexis M. Ruppel, Wesley Hoyland, Nicole L. Yates, LaTonya D. Williams, Kelli Greene, Hongmei Gao, Celia R. Mahoney, Martin M. Corcoran, Alberto Cagigi, Alison Taylor, David M. Brown, David R. Ambrozak, Troy Sincomb, Xiaozhen Hu, Ryan Tingle, Erik Georgeson, Saman Eskandarzadeh, Nushin Alavi, Danny Lu, Tina-Marie Mullen, Michael Kubitz, Bettina Groschel, Janine Maenza, Orpheus Kolokythas, Nadia Khati, Jeffrey Bethony, Shane Crotty, Mario Roederer, Gunilla B. Karlsson Hedestam, Georgia D. Tomaras, David Montefiori, David Diemert, Richard A. Koup, Dagna S. Laufer, M. Juliana McElrath*, Adrian B. McDermott*, William R. Schief*

Leggat DJ et al, Science 2022

16

SCIENCEINSIDER | HEALTH

Puzzling skin side effects stymie advance of promising HIV vaccine

Strategy of multiple, Moderna-made mRNA shots to hone powerful antibodies hits a pothole

1 MAR 2024 · 5:55 PM ET · BY JON COHEN

iavi

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Home / Features / IAVI statement on mRNA HIV vaccine candidate trials

March 2, 2024

IAVI statement on mRNA HIV vaccine candidate trials

Response to Science news article

CD4 binding Site VRC01 class bnAbs

eOD-GT8-60mer nanoparticle (Bill Schief, Scripps CHAVD, IAVI)

- High response rates of VRC01 precursors in IAVI G001
- Recently evaluated using mRNA platform (Moderna), and responses similar to greater (G002, G003)
- Boosting immunogen Core-g28v2 60mer mRNA under evaluation in G002 and G003 underway

426c.Mod.Core-C4B nanoparticle (Leo Stamatatos, HVTN 301)

- VRC01-class and CD4bs precursor responses induced, analysis in progress
- Serum autologous neutralizing antibodies induced
- Fractionated escalating dose delivery looks promising for increased responses with one dose in comparison to the bolus delivery
- Heterologous boosting studies soon
- Collaborations underway to evaluate in people with HIV who are ART-suppressed and +/- ATI.

GT1.1 (Rogier Sanders, BMGF)

- BG505 SOSIP.664.v4.1-GT1.1 germline targeting immunogen

CD4bs CH505 M5 N179D trimer (Bart Haynes, Duke CHAVD, HVTN 309)

- Lineage pathway, Clade C TF modified, testing protein and mRNA
- Starting April 2024

HIV prevention

Orals

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Safety Profile and Immunogenicity of a Phase I Clinical Trial Using Germline Targeting Trimer GT1.1

Karlijn van der Straten

Vaccine Combining Slow-Delivery and Follicle-Targeting Improve Humoral and Germinal Center Responses

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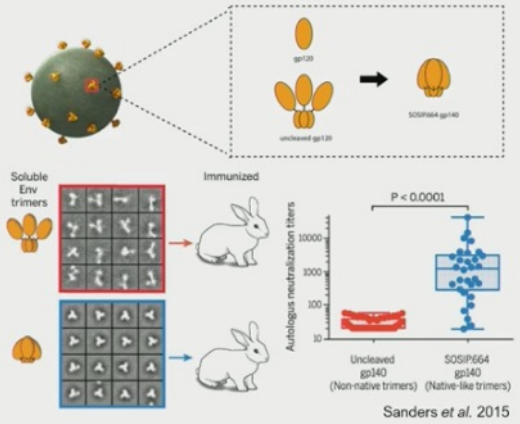
Darrell Irvine

Phase I Clinical Trial Using Germline-Targeting Trimer GT1.1 : IAVI-C101 trial -> IAVI-C107 trial

- Stabilization (SOSIP) of Env results in a more native-like appearance and higher neutralizing antibody titers after vaccination



Sanders *et al.* 2015

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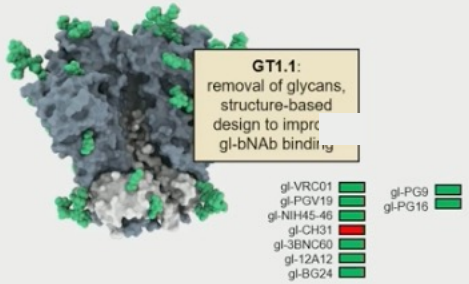
IAVI-C101 trial

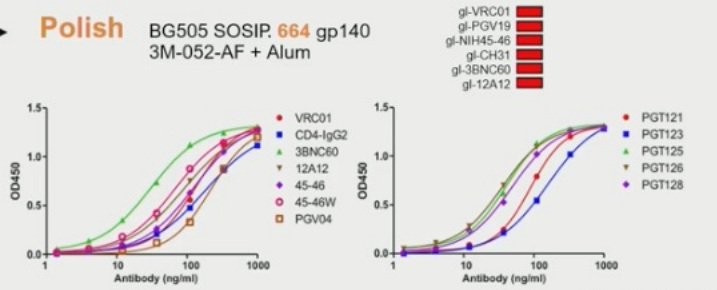
Prime BG505 SOSIP.GT1.1 gp140 $AS01_B$*

- BG505 SOSIP.664 GT1.1 is specifically designed as priming immunogen to elicit CD4bs and apex-directed antibodies
- GT1.1 primes VRC01-class precursor B cells in pre-clinical studies (manuscript in revision)



IAVI-C107 trial

Polish BG505 SOSIP. 664 gp140 3M-052-AF + Alum



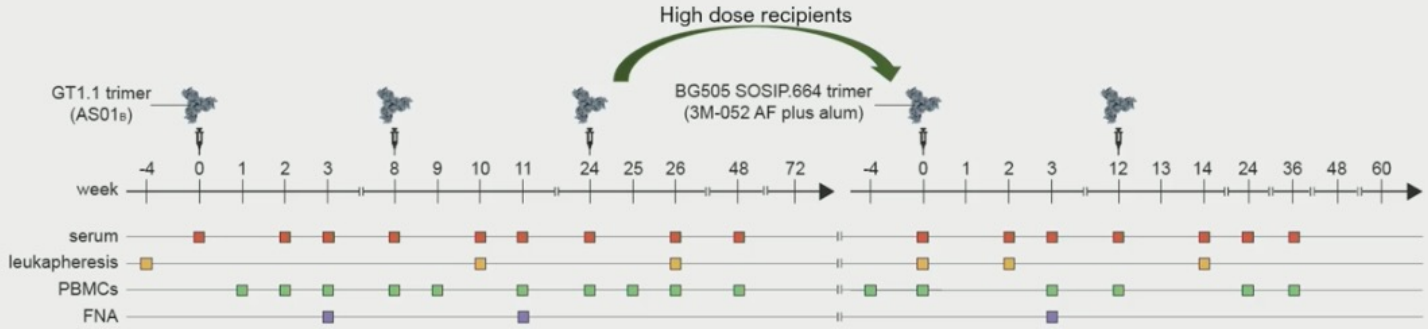
Lyumkis *et al.* 2013
Sanders *et al.* 2013
Sanders *et al.* 2015

- No GMP-produced "shaping" immunogen available
- In-human experience with BG505 SOSIP.664, adjuvanted
- GT1.1 priming and BG505 SOSIP.664 boosting elicited CD4bs-directed neutralizing antibodies in NHPs (manuscript submitted)

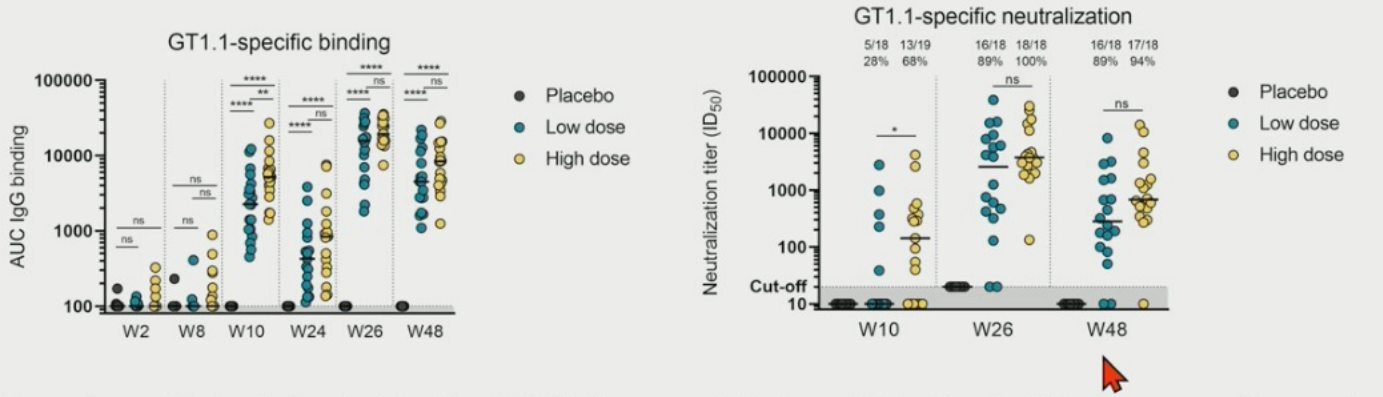
Multicenter, double-blinded, placebo-controlled (1:5), dose-escalating

- Rockefeller University (dr. Caskey, PI), George Washington University (dr. Diemert), Amsterdam UMC (dr. de Bree)

- High dose recipients of C101 trial were asked to enrol in IAVI-C107
- Median time since last C101 IP administration is 18 months (15 to 21 months); 6 months after LPLV



Phase I Clinical Trial Using Germline-Targeting Trimer GT1.1 : IAVI-C101 trial -> IAVI-C107 trial

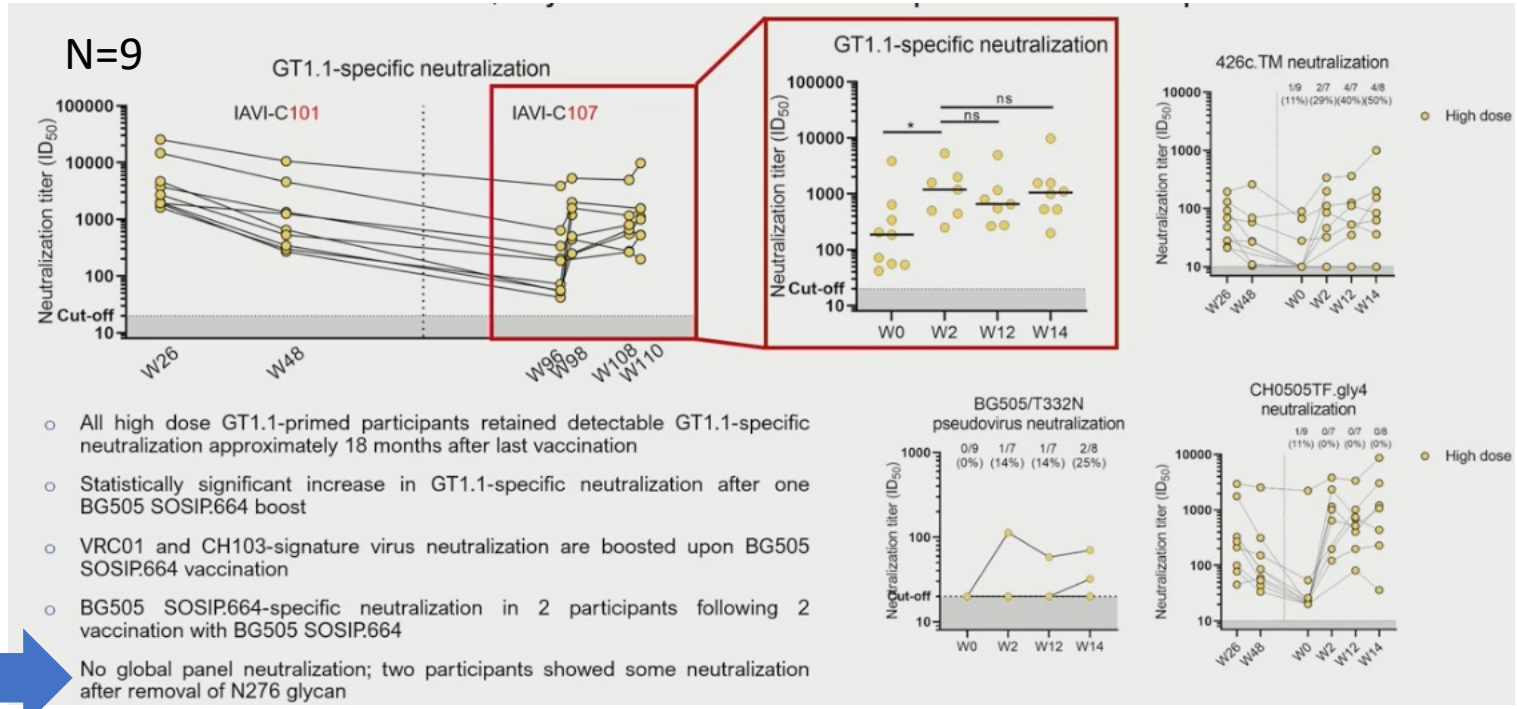


All vaccine recipients developed detectable GT1.1-binding antibodies after two vaccinations (W10)

No statistically significant differences in titers between dose groups after W10

- High dose recipients showed a higher response rate after second vaccination (W10) compared to low dose recipients
- 89% of LD and 94% of HD participants retained detectable GT1.1-specific neutralization 6 months after last vaccination (W48)

- The proportion of participants with CD4bs-directed serum antibodies increase with time and vaccinations
- **CD4bs-directed antibodies** were found in 72% of W26 sera of high dose group recipients using EMPEM
- Neutralization of VRC01 signature virus with N279K KO in majority of participants at W26



- All high dose GT1.1-primed participants retained detectable GT1.1-specific neutralization approximately 18 months after last vaccination
- Statistically significant increase in GT1.1-specific neutralization after one BG505 SOSIP.664 boost
- VRC01 and CH103-signature virus neutralization are boosted upon BG505 SOSIP.664 vaccination
- BG505 SOSIP.664-specific neutralization in 2 participants following 2 vaccination with BG505 SOSIP.664
- No global panel neutralization; two participants showed some neutralization after removal of N276 glycan

HIV prevention

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Safety Profile and Immunogenicity of a Phase I Clinical Trial Using Germline Targeting Trimer GT1.1

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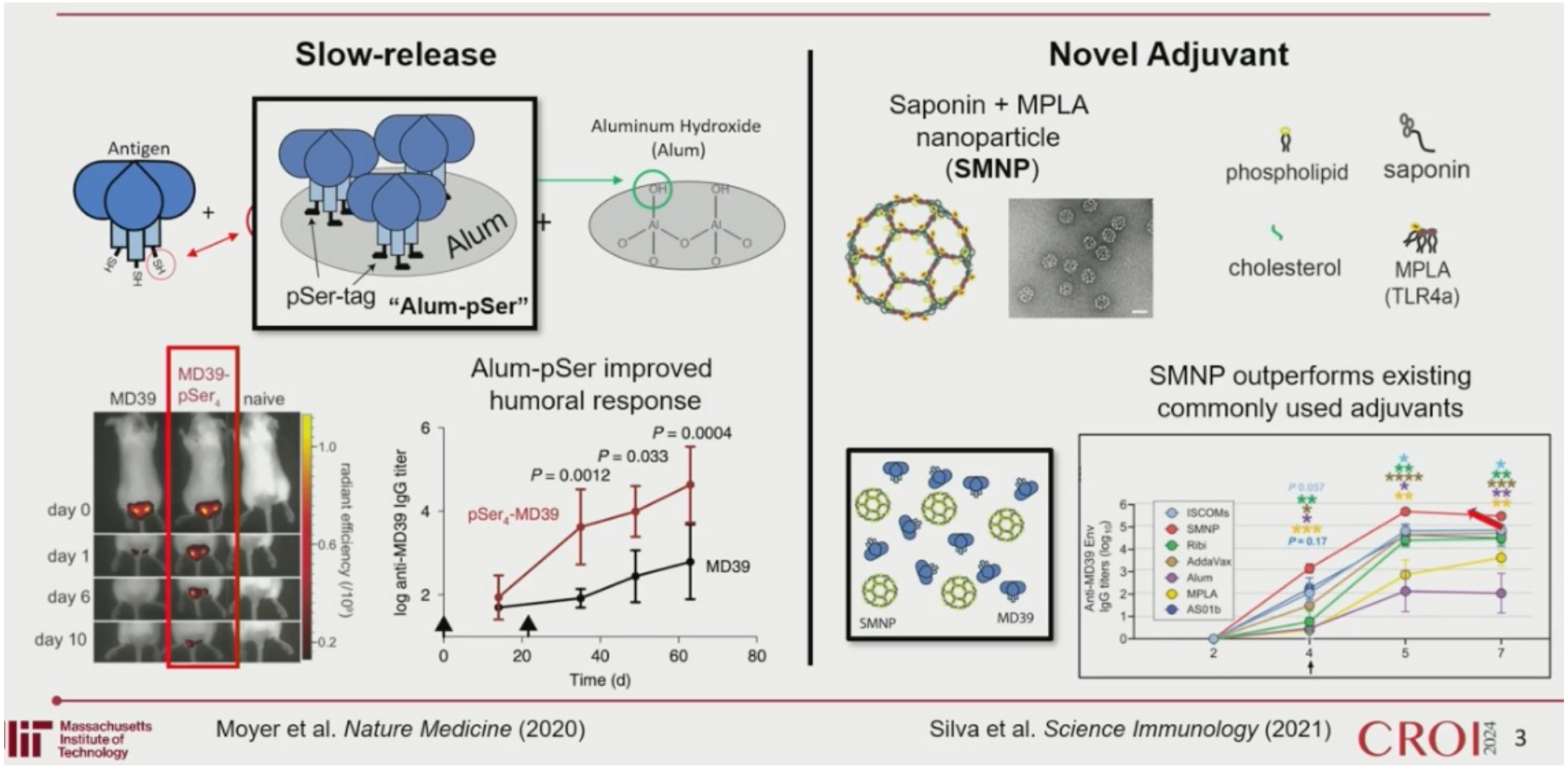
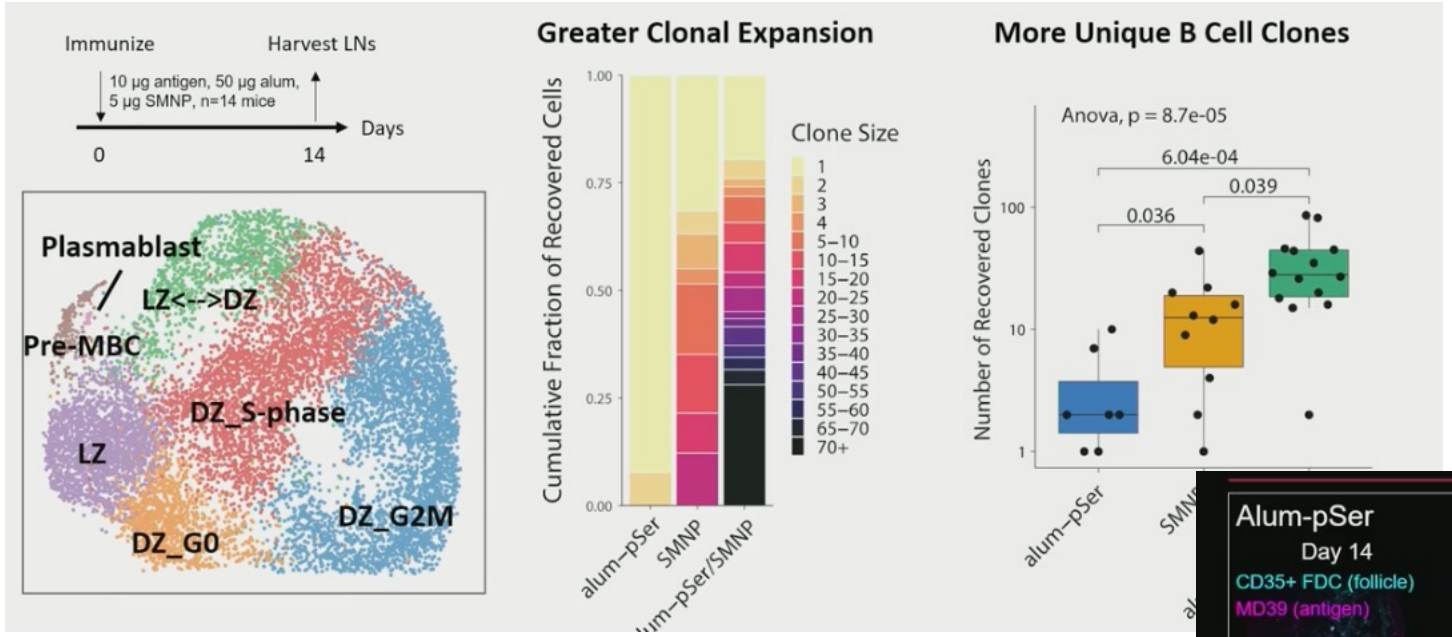
'Adjuvants' to improve sustained Ag delivery & Follicle targeting (MIT): Alum.pSer/SMNP

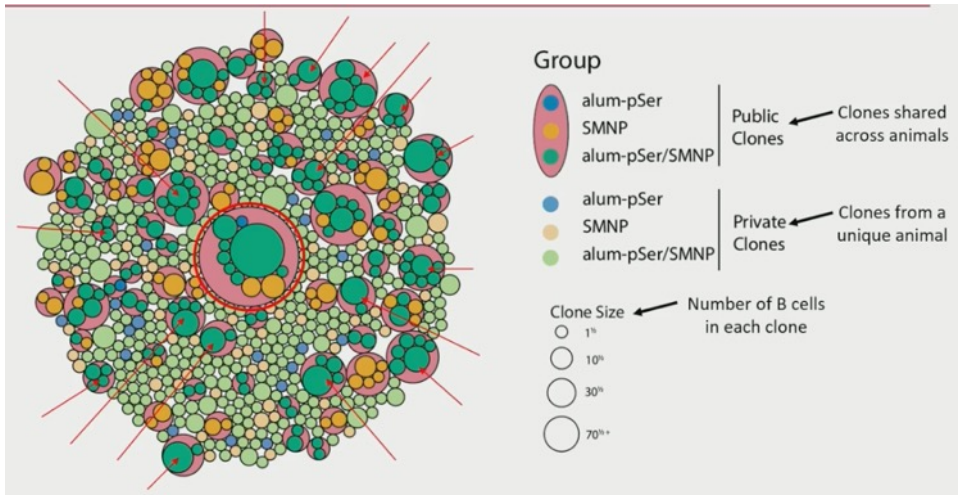


Combination of both into Alum-pSer/SMNP → MoA?

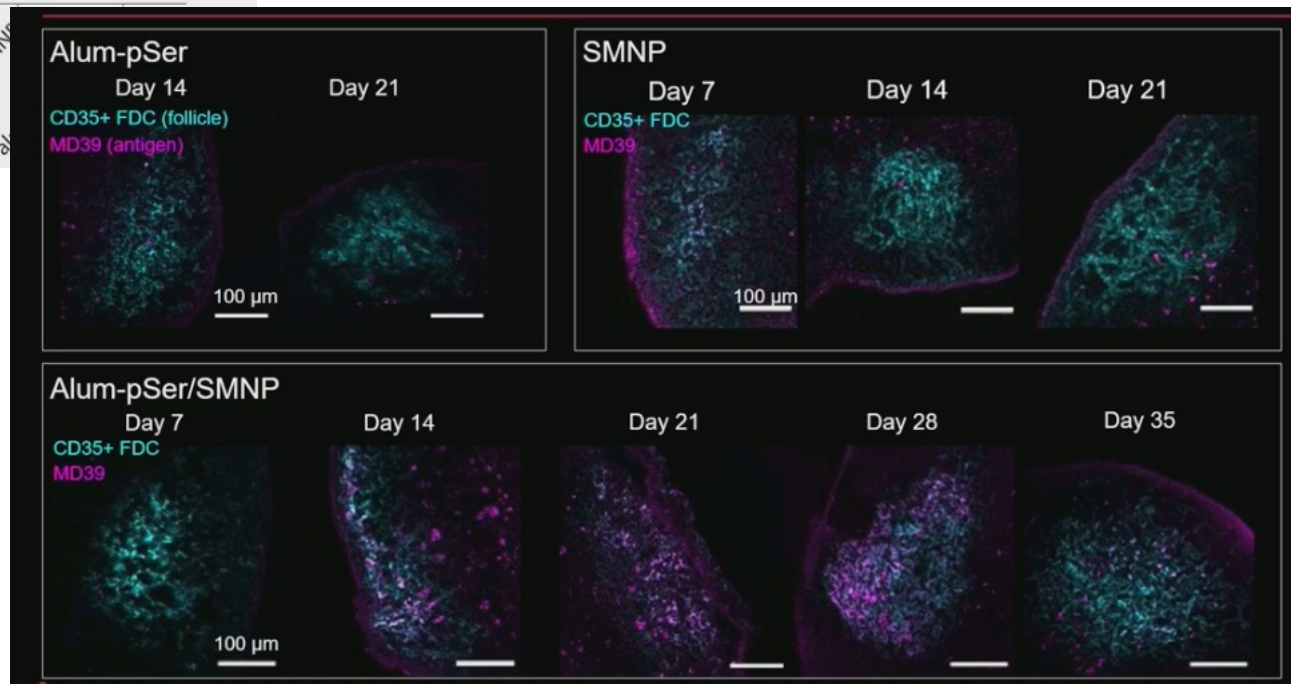
'Adjuvants' to improve sustained Ag delivery & Follicle targeting (MIT): Alum.pSer/SMNP

Increased BCR repertoire breadht



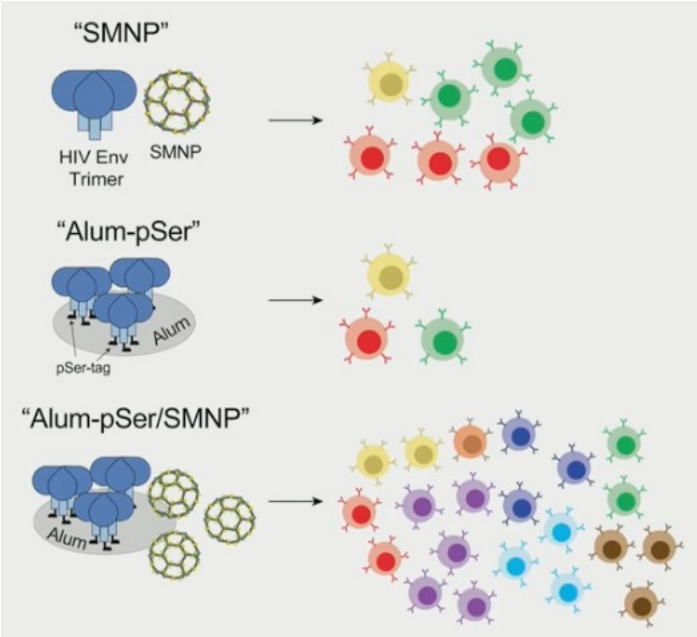


Enhanced Ag accumulation in B cell follicles

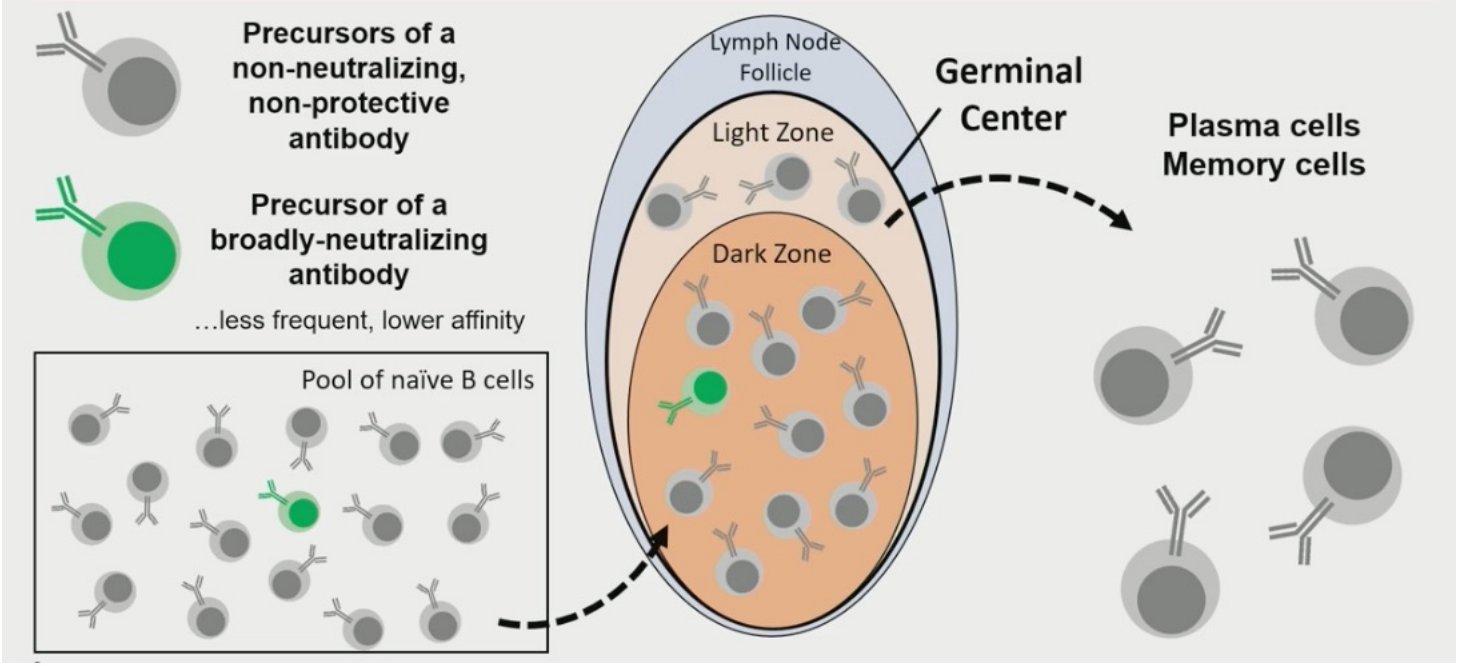


'Adjuvants' to improve sustained Ag delivery & Follicle targeting (MIT)

→ Promoting trafficking of immunogens to the follicles
→ Enhanced B cell clonal expansion, diversity and repertoire breadht



Relevance for the HIV vaccine field:
bNAb precursors are rare and prone to be outcompeted in GCs



Therapeutic Vaccines

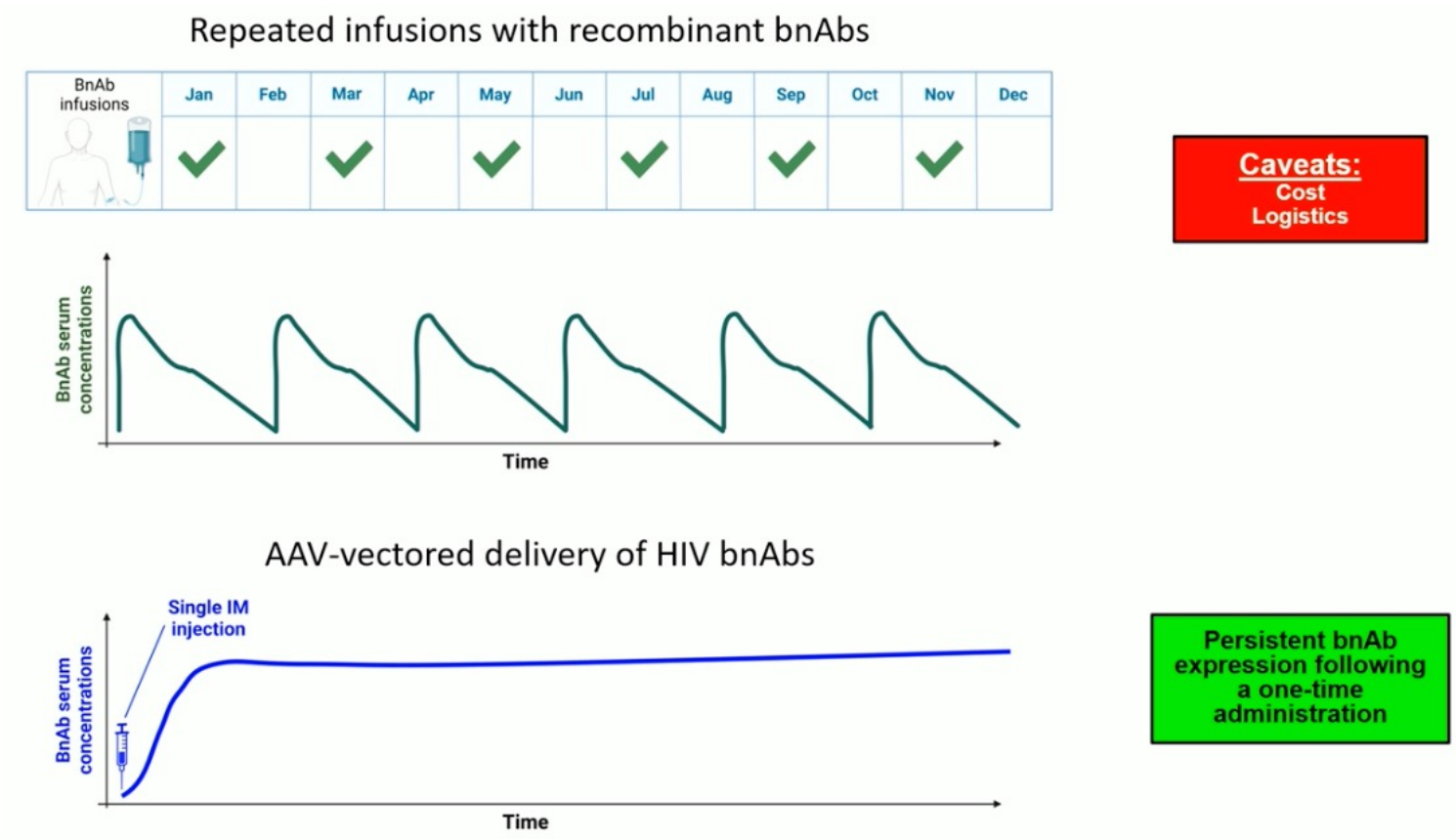
Wednesday 6th

OA - HIV Reservoir and Cure Strategies (All in SIV)

AAV-Expressed HIV IgG Biologics Enable Durable ART-Free Viral Control in Infant Macaques
Mauricio A. Martins

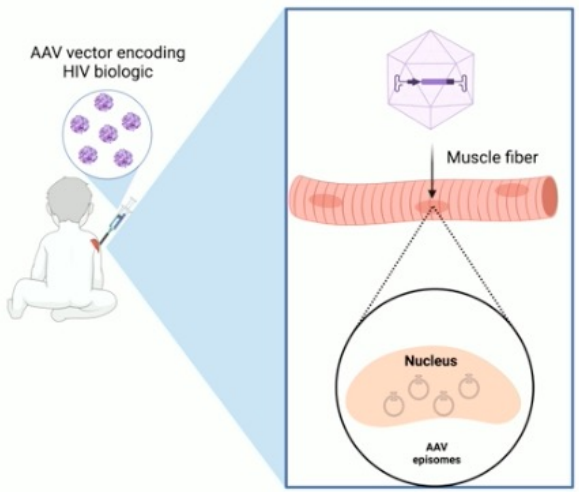
A T Cell-Targeting mRNA SIV Vaccine Extends Time to Rebound and Enhances Post-ART Viral Control
Benjamin Varco-Merth

IL-15/IL-15RA Cytokine Therapy Enhances Control of Viral Rebound in SIV-Infected Macaques
Vijayakumar Ve



Caveats:
Cost
Logistics

Persistent bnAb expression following a one-time administration



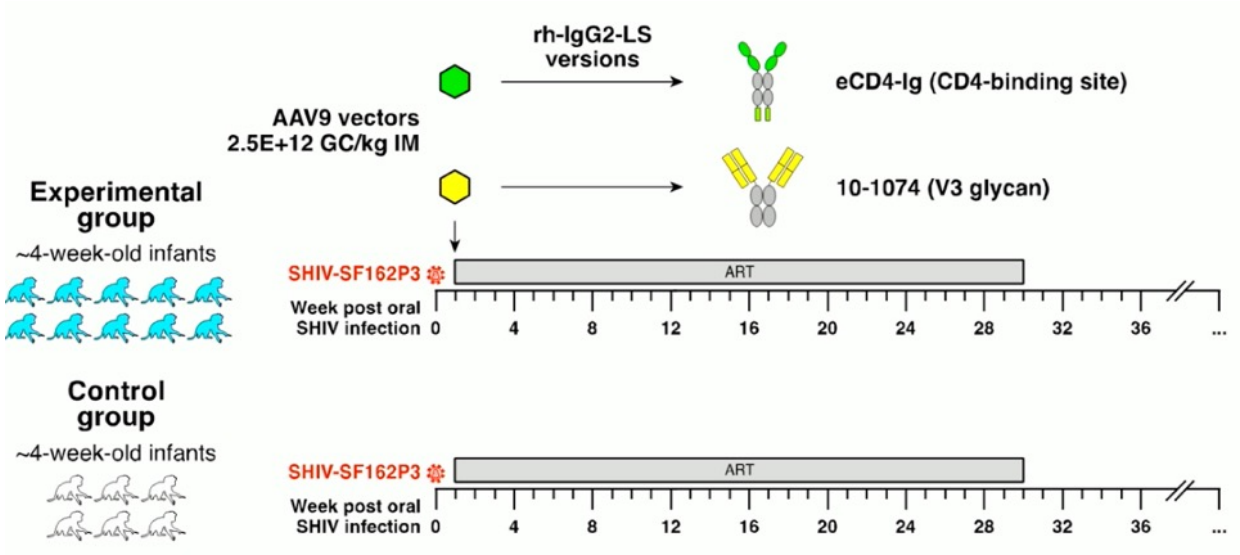
- AAV vector persists in the cell nucleus as extrachromosomal episomes

→ Persistent transgene expresion (for the lifespan of the transduced cell)

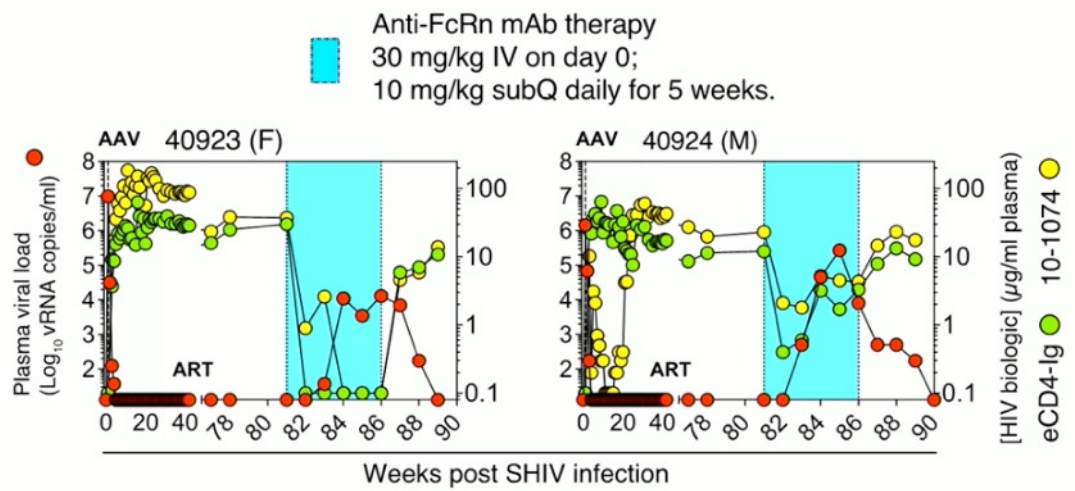
Skeletal muscle

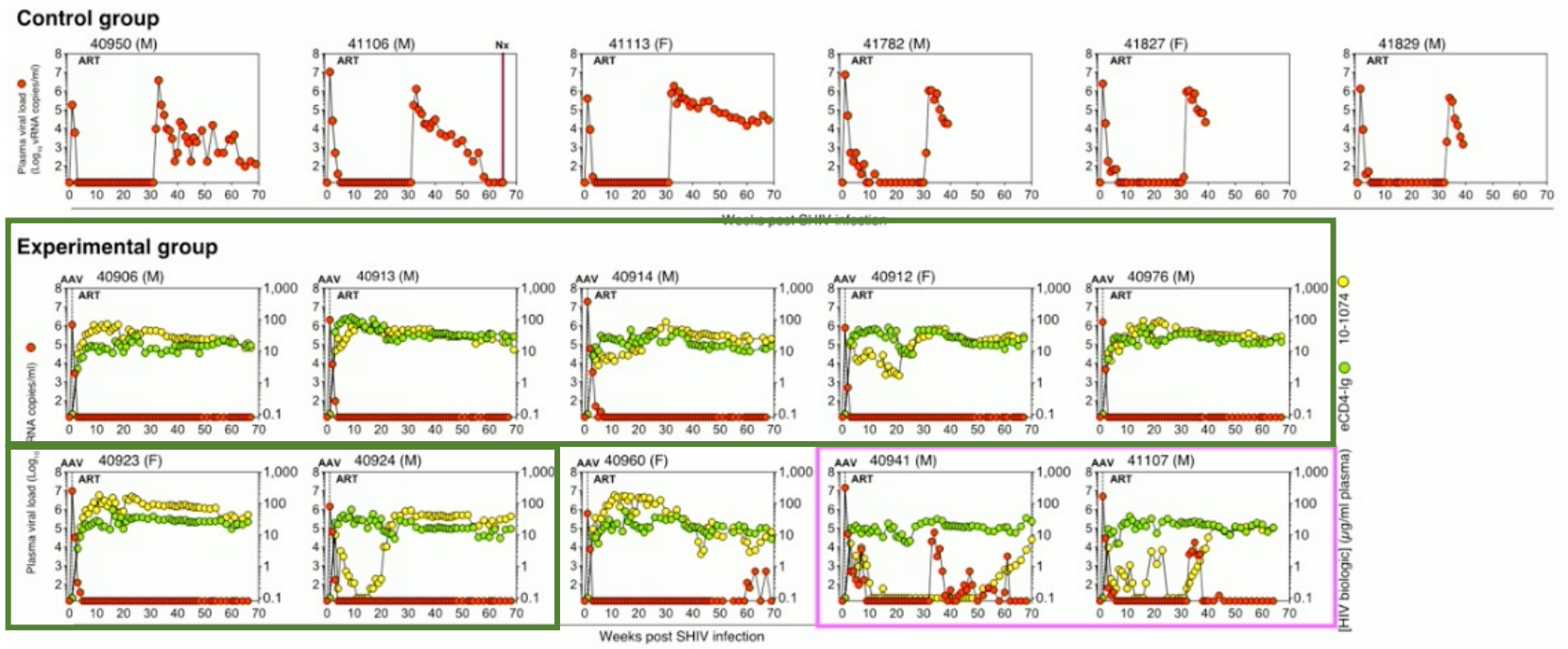
- long lifespan
- abundant
- easy acces

SHIV model (acute ART)



Transient los of control upon depletion of Ab





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Benjamin Varco-Merth

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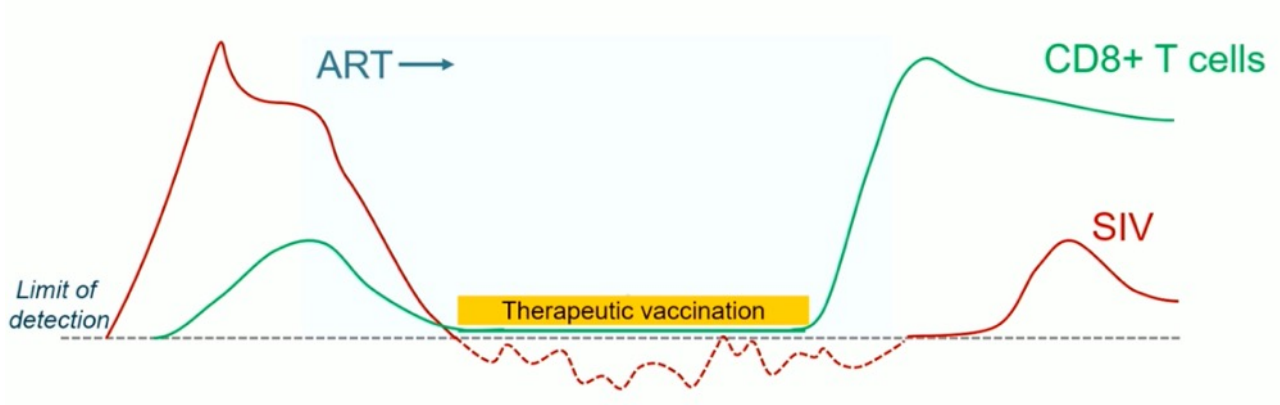
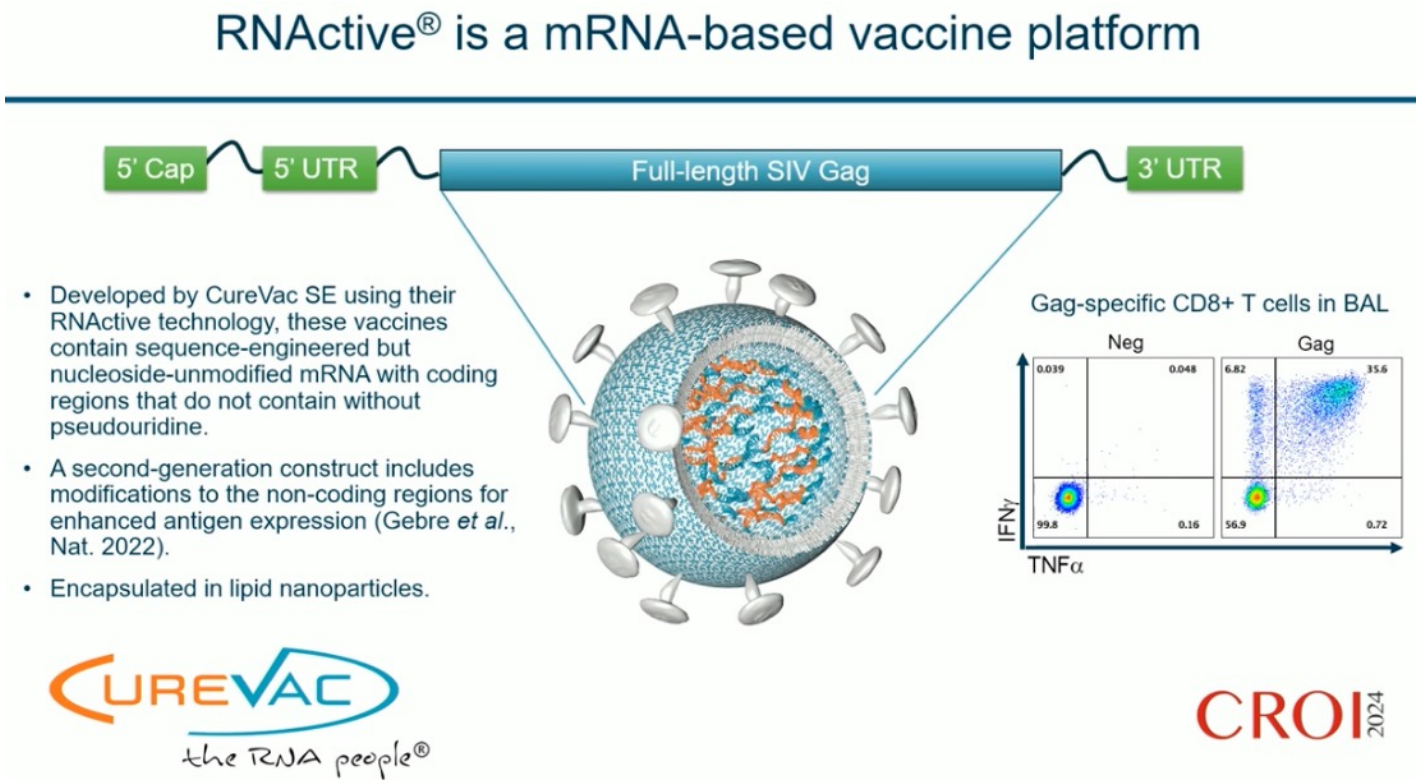
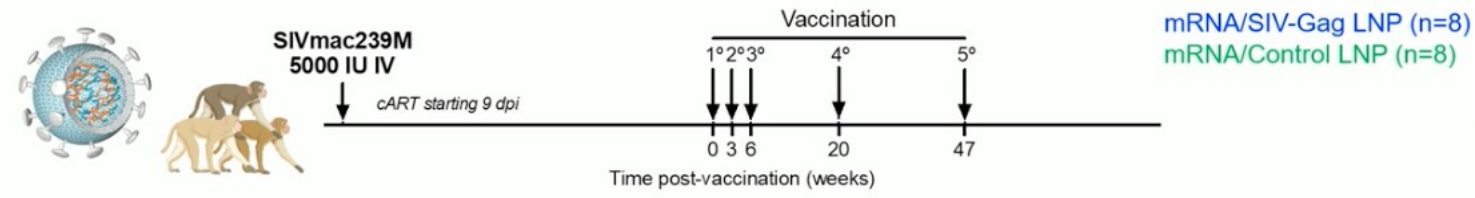
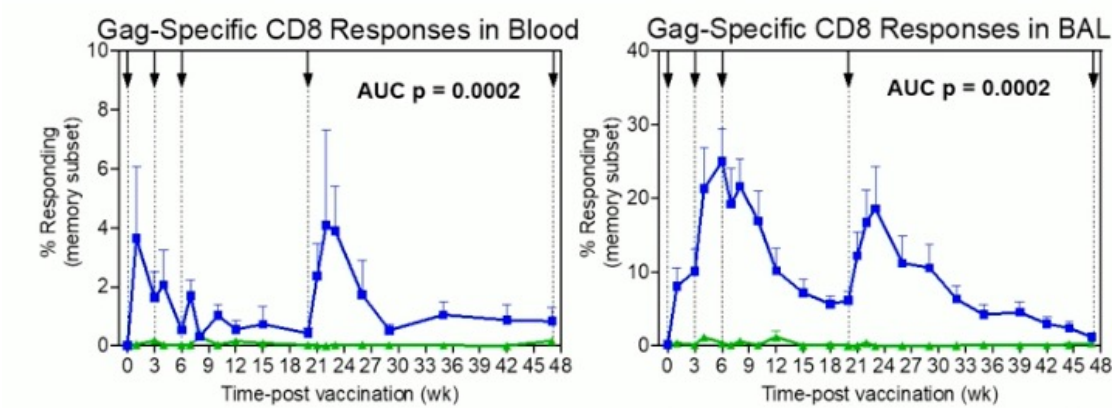
Vijayakumar Ve

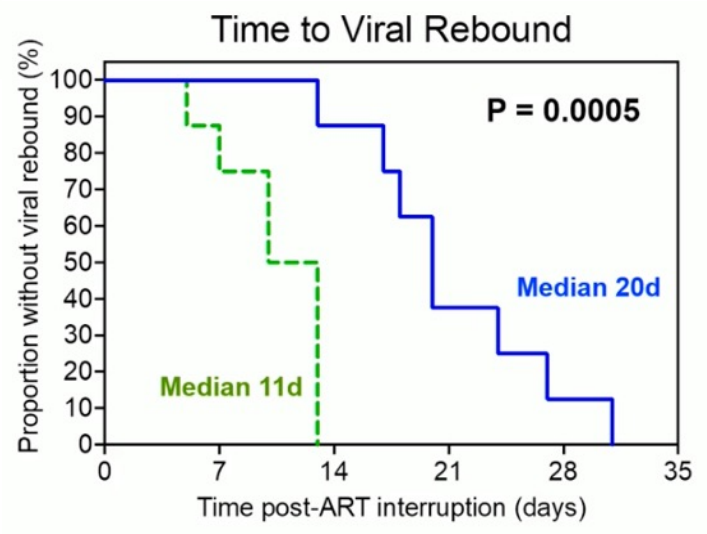


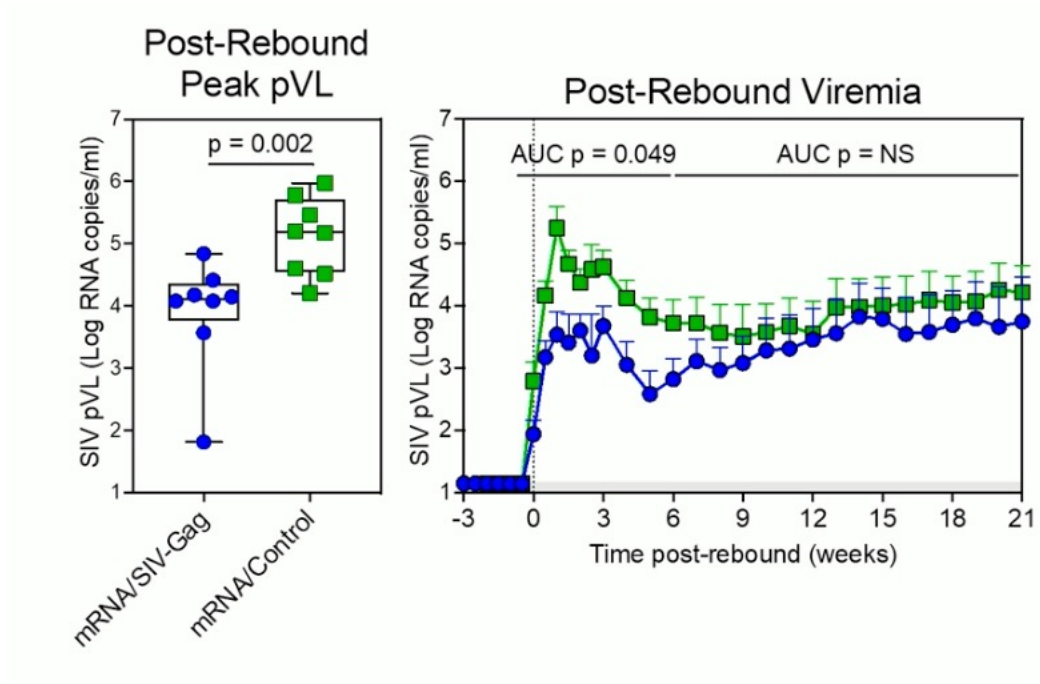




mRNA/SIV-Gag LNP (n=8)
mRNA/Control LNP (n=8)







Therapeutic Vaccines

Wednesday 6th

OA - HIV Reservoir and Cure Strategies (All in SIV)

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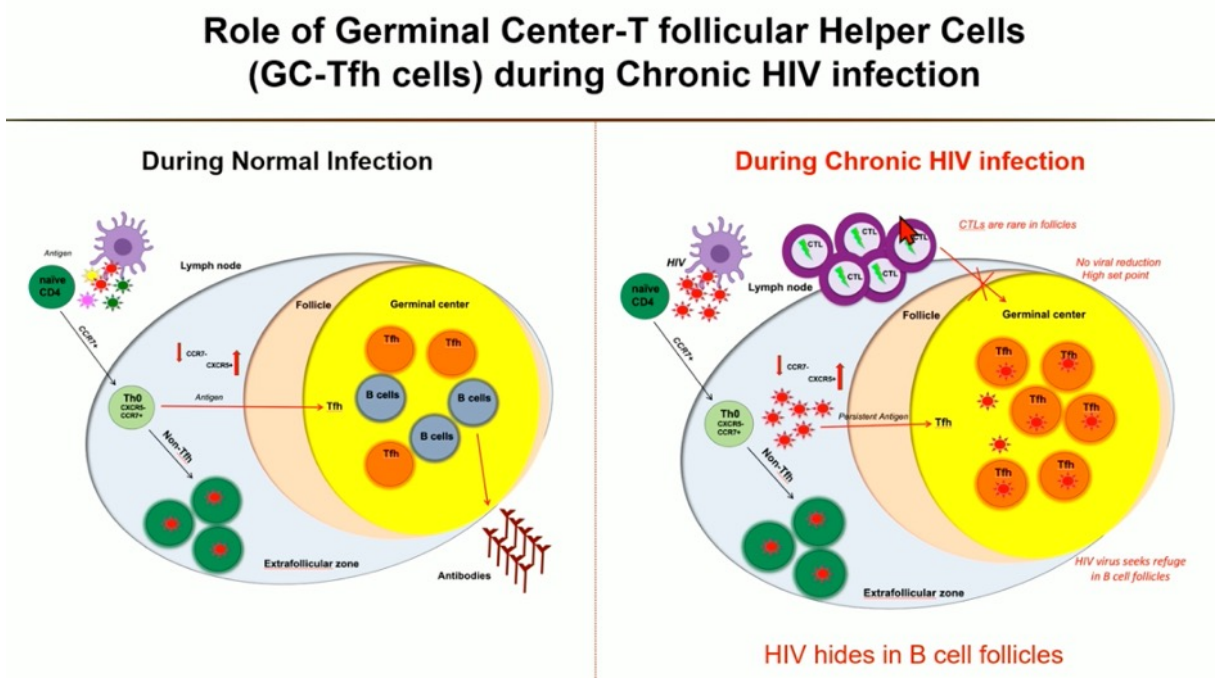
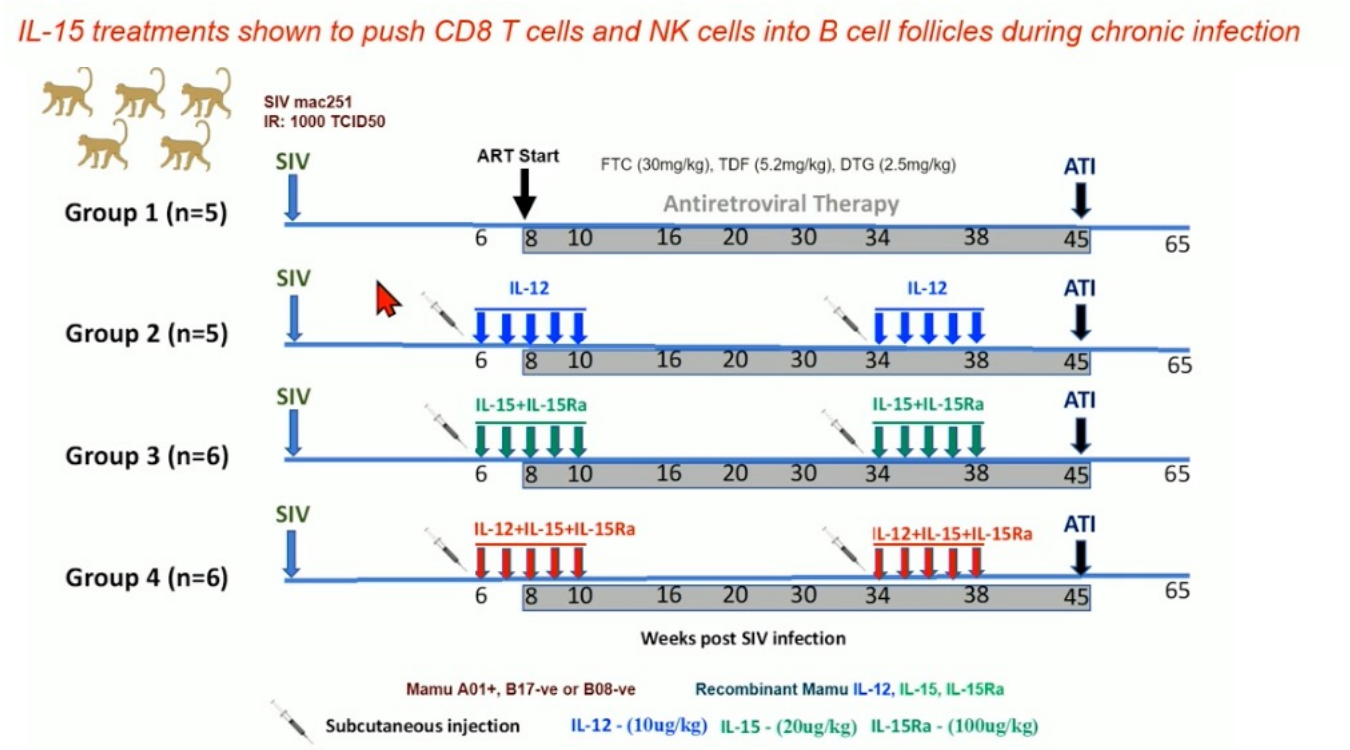
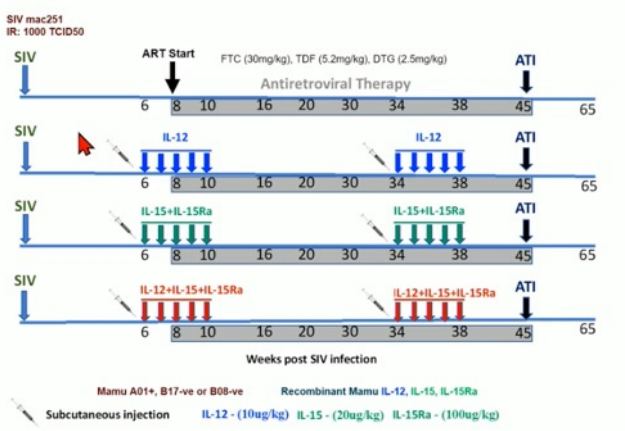
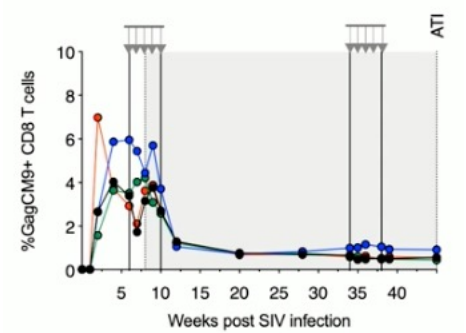
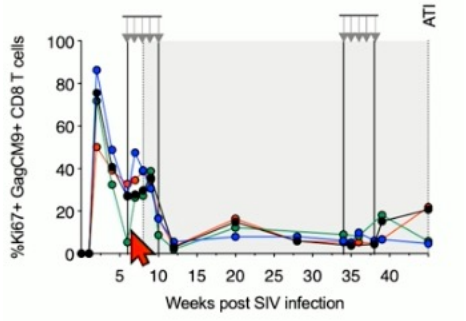






Expansion of Gag-specific CD8 T cells, Higher proliferative capacity





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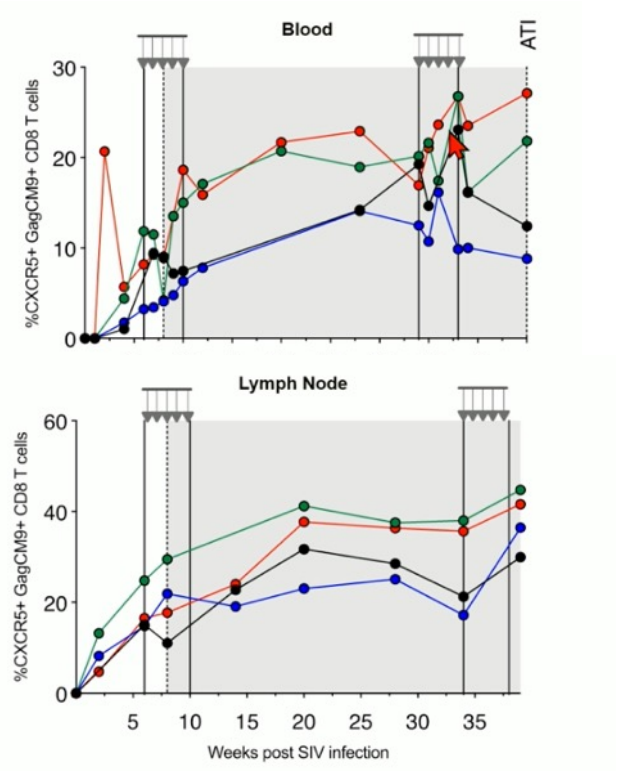
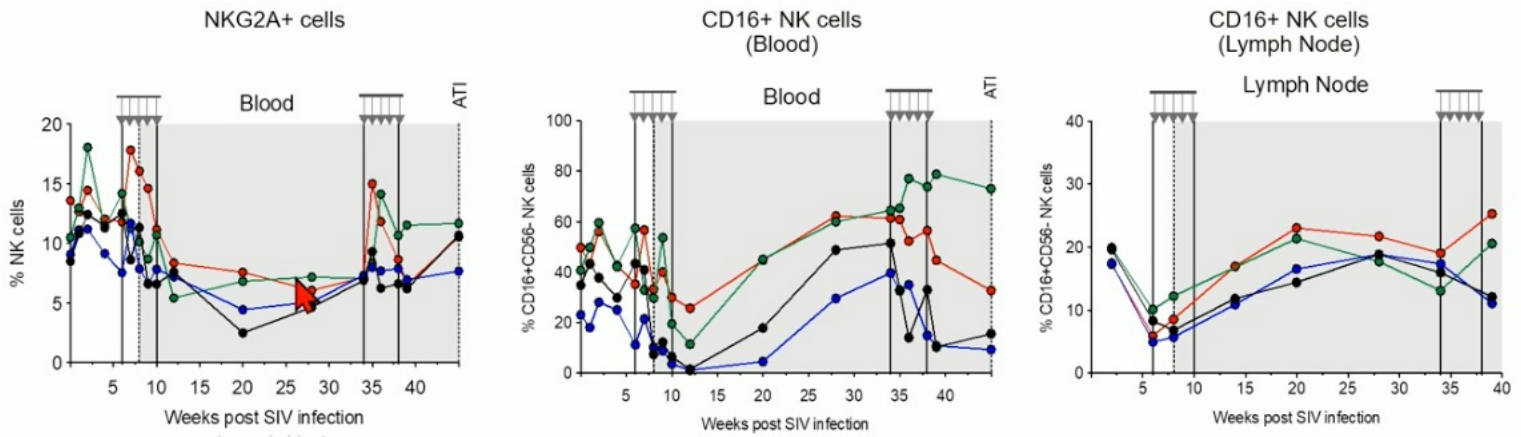
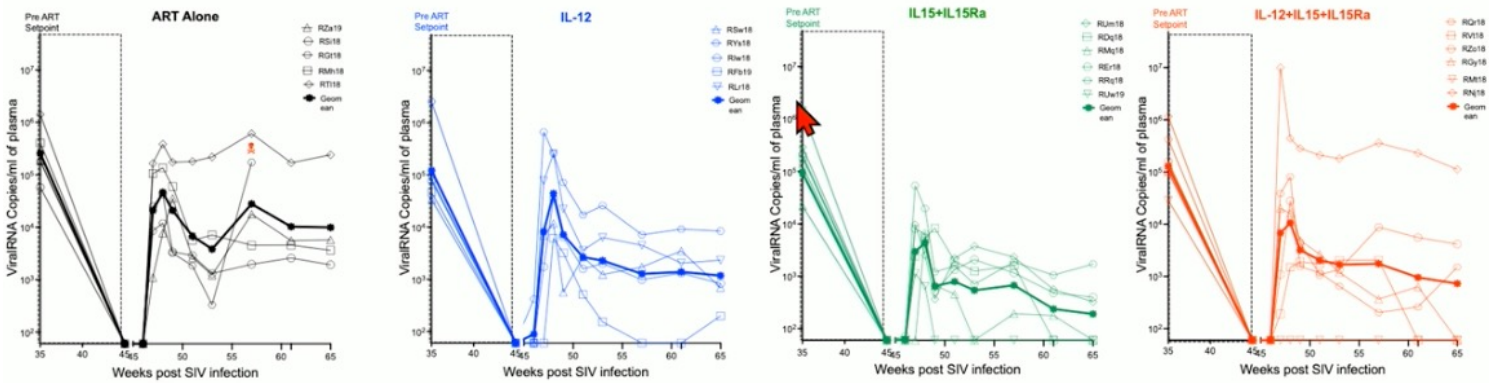


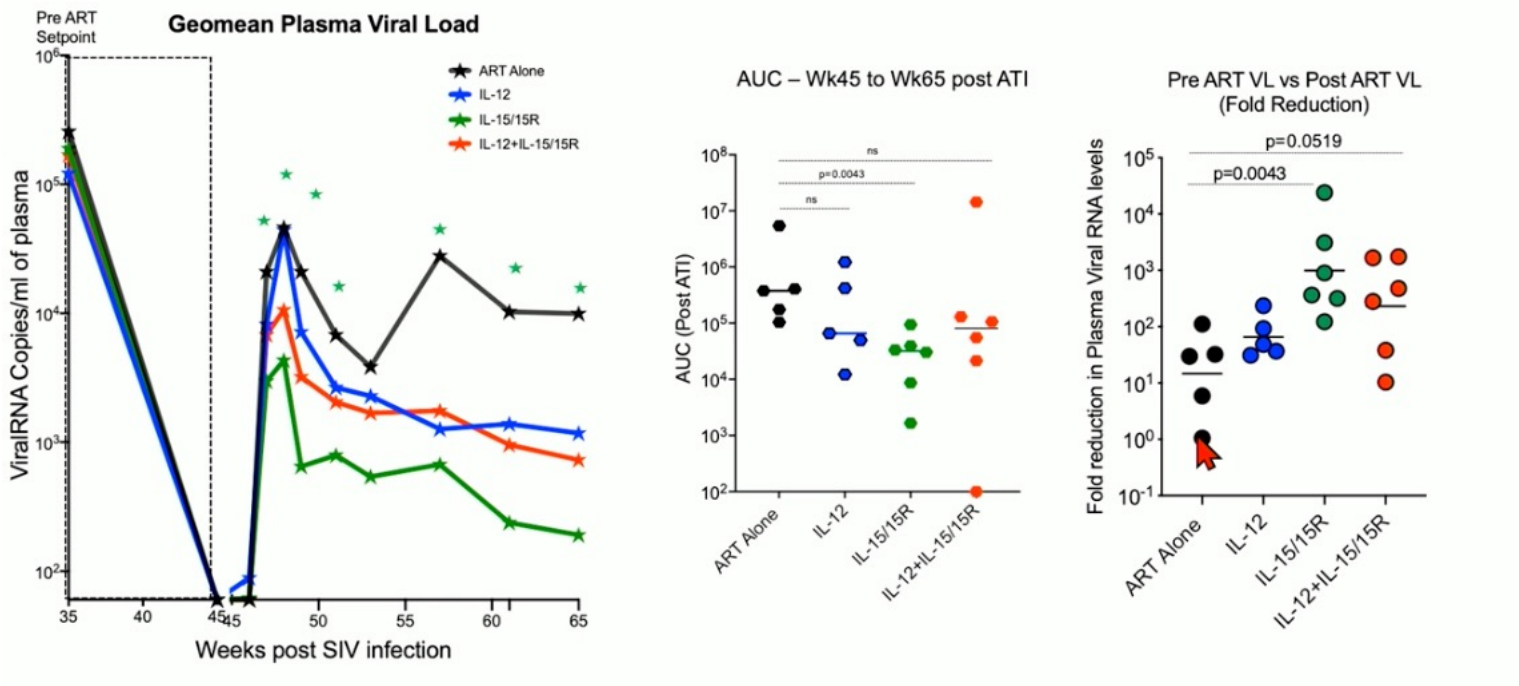
Expansion of total NK



Effect on viral rebound : no delayed rebound, but blunted viremia andlower setpoint levels



Blunt in remerging peak viremia was observed in IL-15/IL-15Ra treated group compared to other groups



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STI

Orals

Tuesday 5th
OA - STI

Final Results of ANRS 174 DOXYVAC: A Randomized Trial to Prevent STI in MSM on PrEP
Jean-Michel G. Molina

Tuesday 5th
Symposium New Frontiers in Hepatitis B

Advances in HBV Immunotherapy: The Beginning of the End?
Adam Gehring

Wed 6th
Special session O-LB

HepB-CpG Vaccine Is Superior to HepB-alum in People With HIV and Prior Vaccine Nonresponse: A5379
Kristen Marks

Posters

379 - Sex-Based Differences in Antibody Responses Induced by a Native-Like HIV-1 Envelope Trimer Vaccine

383 - Mucosal HIV Vaccine Targeting Host Epithelial Stem Cells for Long-Term Immunity

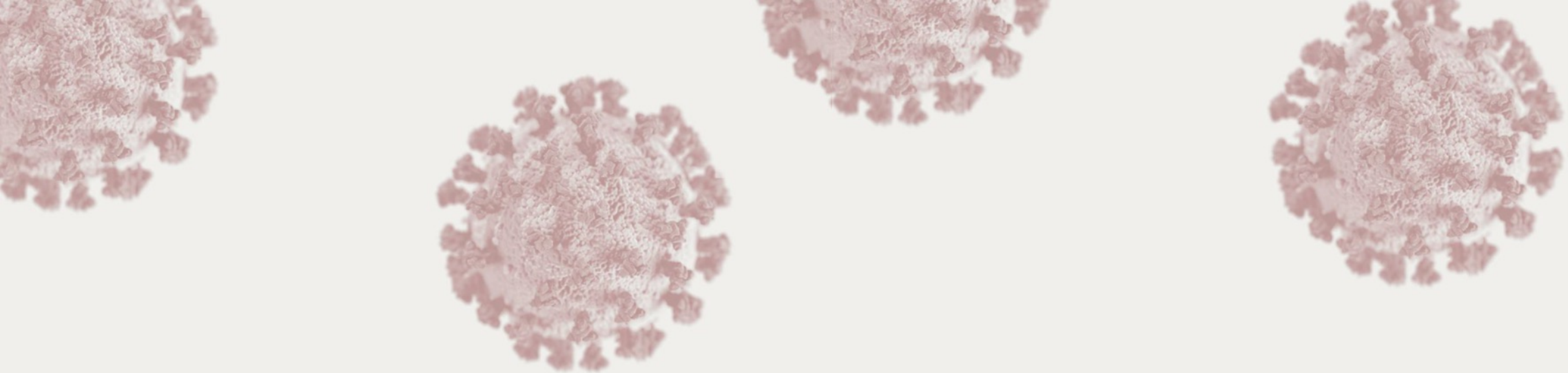
414 -Targeting HIV-Infected Cells for Immunotherapy Through HLA-E

529 - Vaccination Combined With PD-1 Blockade Provides Sustained SIV Suppression in Mamu-A01(+) Macaques

506 - Immune Profile During ATI in AELIX-002 HTI Vaccine Trial and Its Role in Post-Intervention Control

446 - Post-Intervention HIV Control Linked to Early In Vivo CD8+ T-Cell Proliferative Response to Rebound

407 - Characterizing New and Boosted HIV-Specific T-Cell Responses Elicited by an HIV Therapeutic Vaccine (PENNVAX)



¡MUCHAS GRACIAS!

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