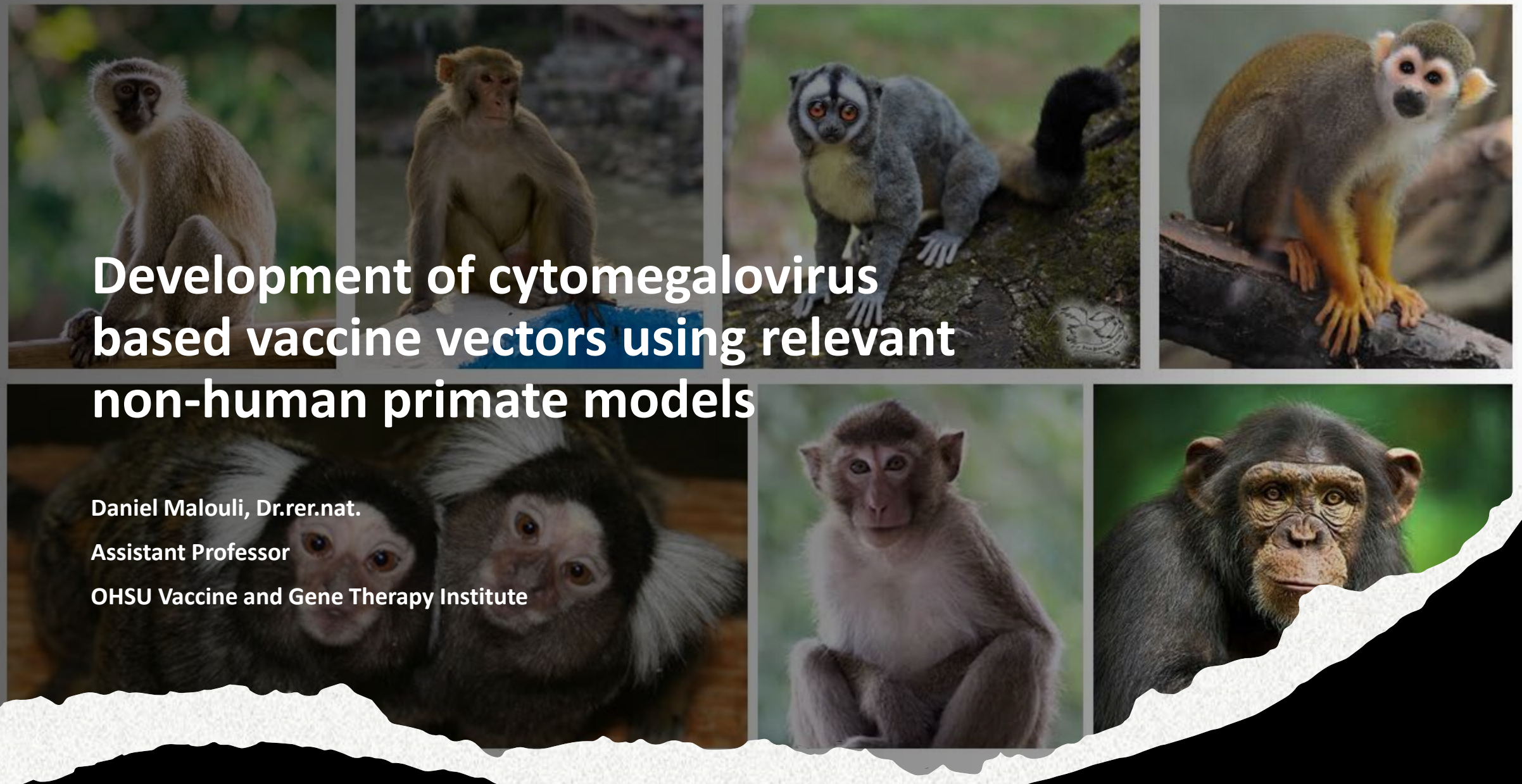

Development of cytomegalovirus based vaccine vectors using relevant non-human primate models

Daniel Malouli, Dr.rer.nat.

Assistant Professor

OHSU Vaccine and Gene Therapy Institute


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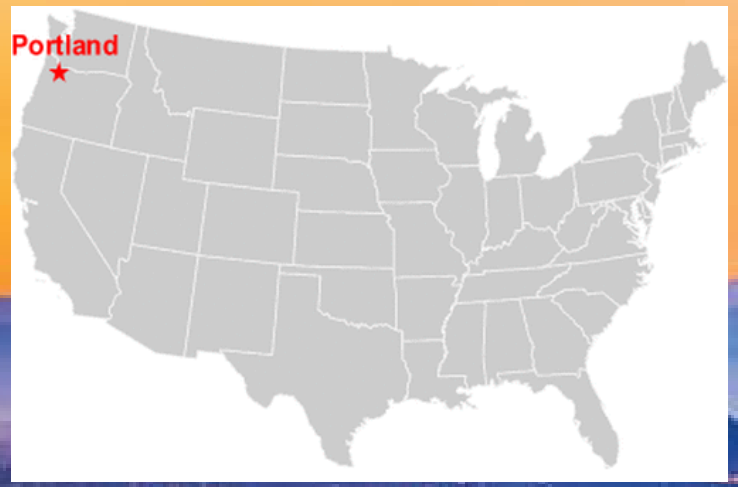
Oregon
OLD TOWN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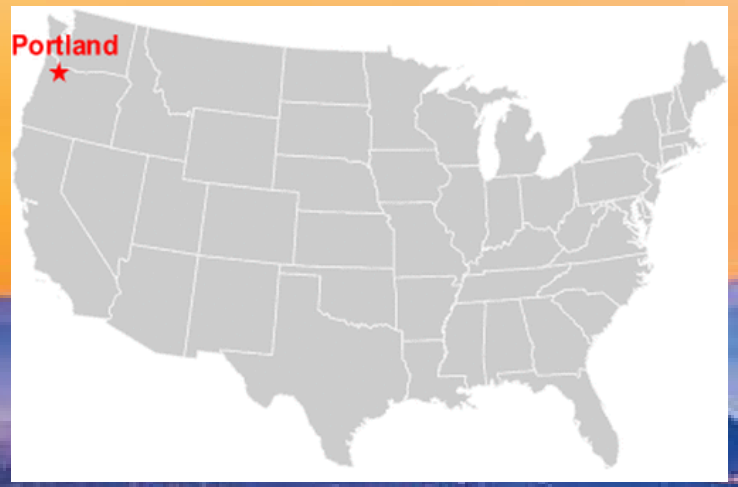
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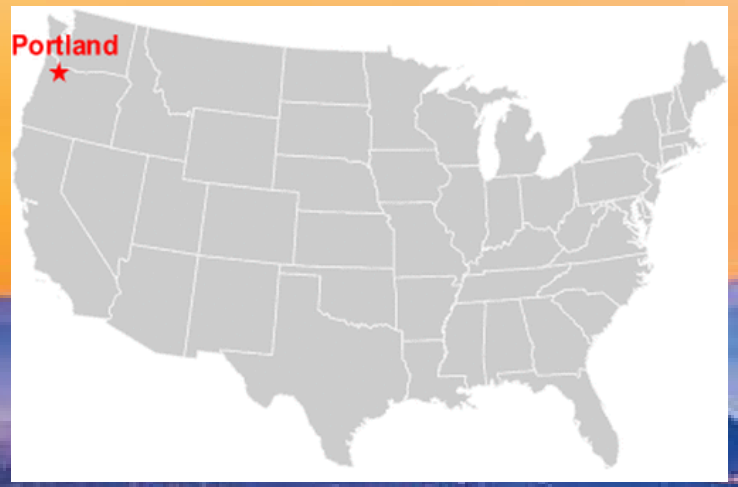
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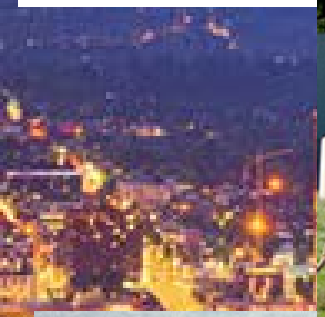

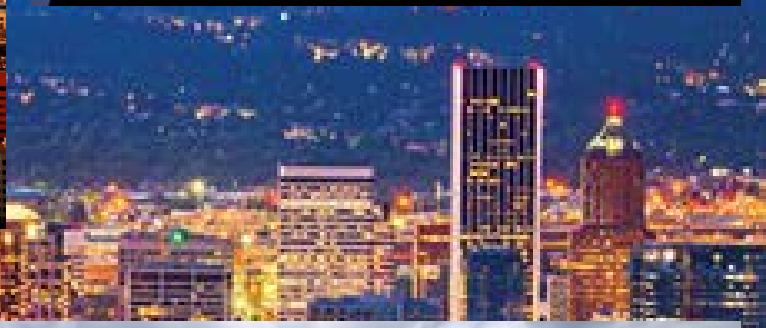

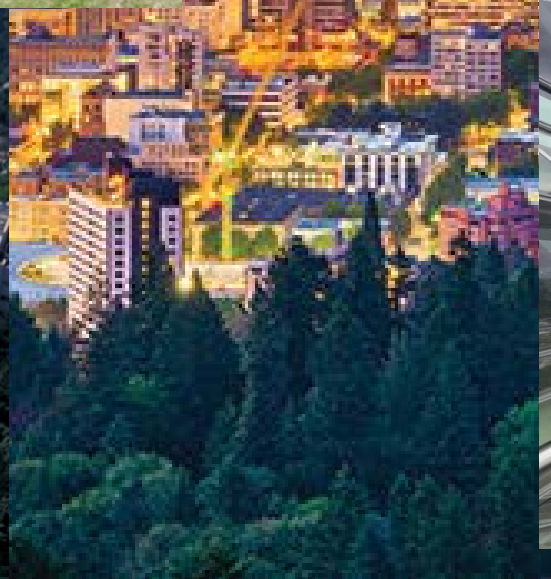


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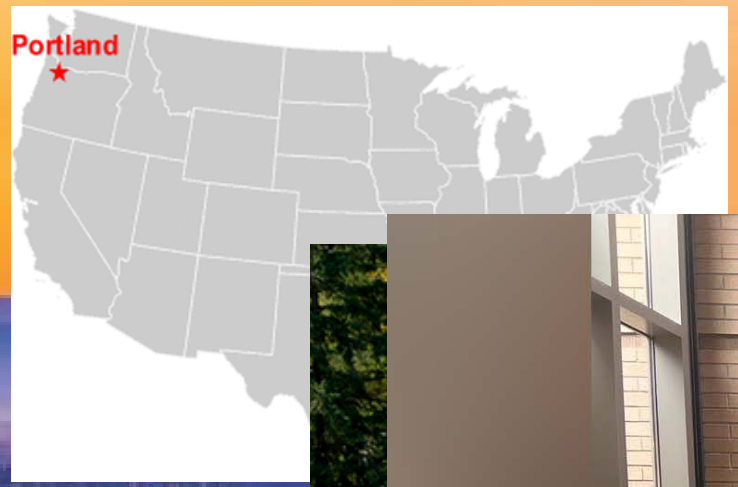
OHSU OREGON HEALTH SCIENCES UNIVERSITY
OREGON NATIONAL
PRIMATE RESEARCH CENTER
VACCINE & GENE THERAPY INSTITUTE
VISITOR REGISTRATION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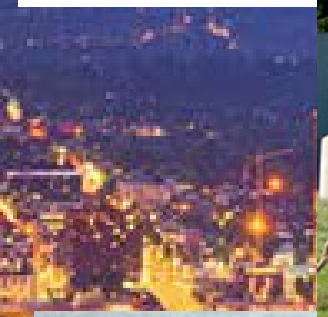
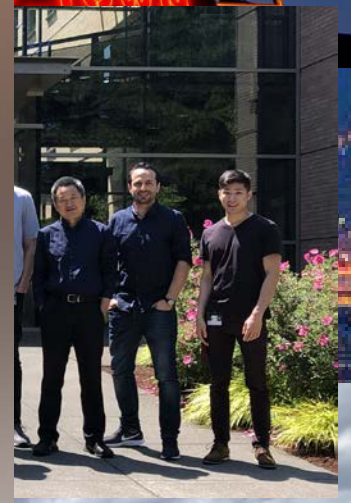
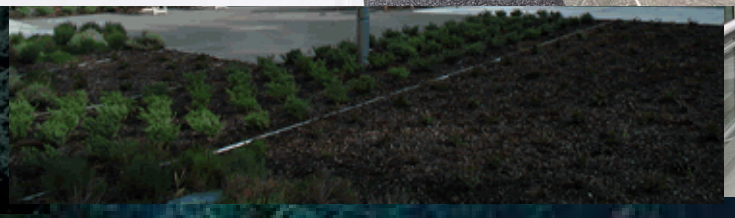
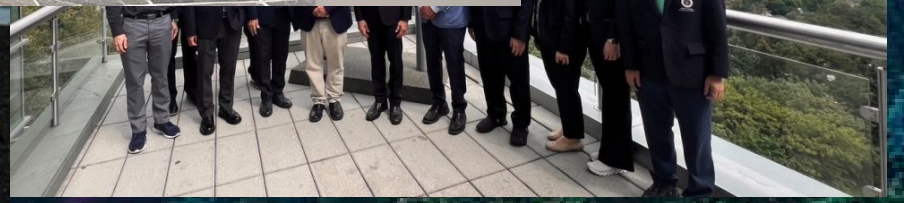
Vaccine and Gene Therapy Institute
VACCINE & GENE THERAPY INSTITUTE
Seminar Series
Engineering human host defense proteins to
nature medicine









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Oregon National Primate Research Center

OREGON HEALTH & SCIENCE UNIVERSITY

UNIVERSITY of WASHINGTON

Fred Hutch Cancer Center

NCIatFrederick

leidos

Scientific Leadership Team:

Development of CMV-based HIV vaccine in the NHP model: Understanding Virologic and Immunologic Mechanisms underlying "Replication Arrest" Efficacy

(and how to replicate these mechanisms in humans!)

November 4, 2024

Investigators:


Louis Picker


Klaus Früh


Jay Nelson

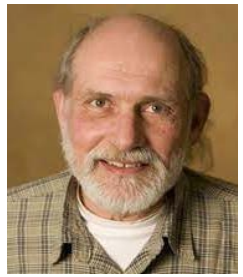

Jake Estes


Michael Gale


Scott Hansen


Ben Bimber


Daniel Malouli


Mike Axthelm

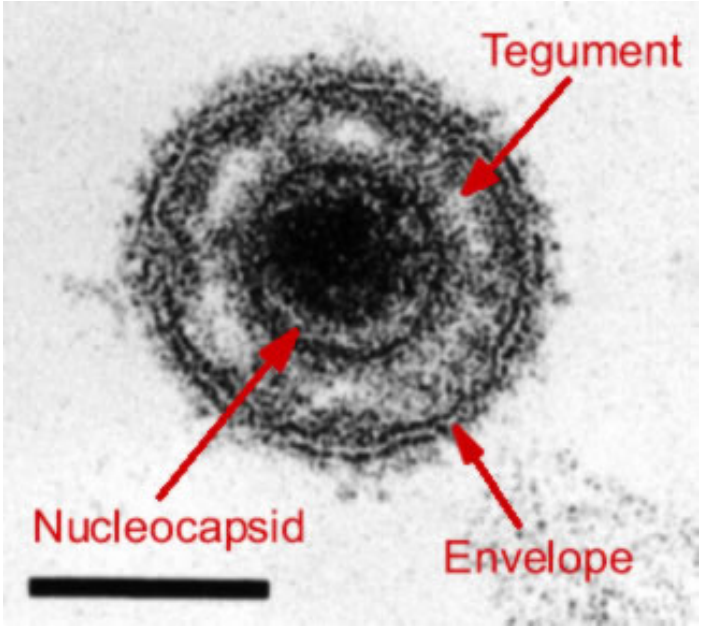

Jeffrey Lifson


Paul Edlefsen


Jonah Sacha


Meaghan Hancock

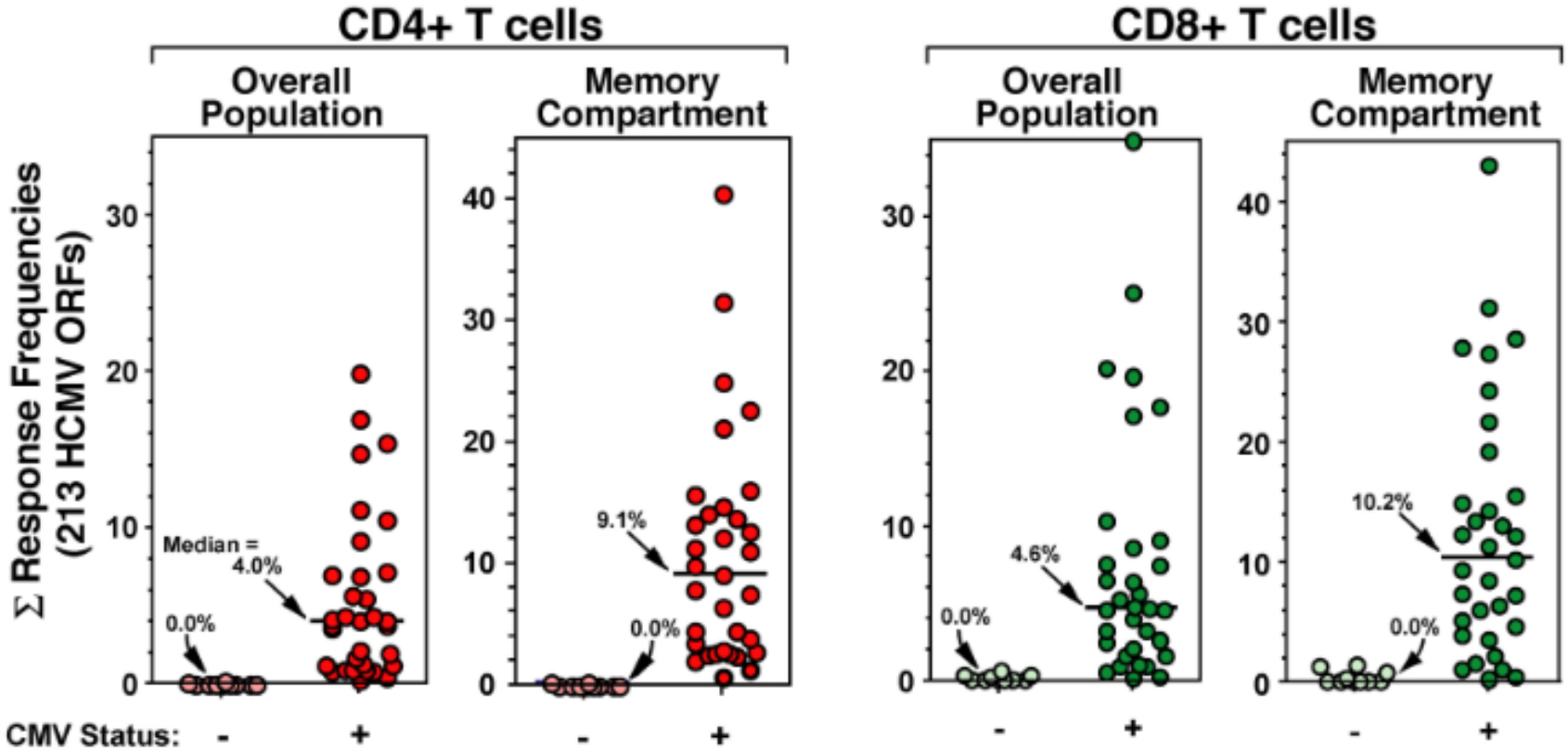
Cytomegalovirus (CMV)



- One of nine human herpesviruses
  - α-herpesvirinae: HSV1, HSV2, VZV
  - β-herpesvirinae: **CMV**, HHV6A, HHV6B, HHV7
  - λ-herpesvirinae: EBV, KSHV
- Large genome of 235 kb with170+ ORFs
  - Only 48 OFRs are essential for growth *in vitro*
- Ubiquitous around the world
  - Developed world ≈50%, Developing World close to 100%
- Highly species specific
- life-long persistent/latent infection
  - Reactivation upon immunosuppression
- Infection of immunocompetent host is generally asymptomatic
  - Exception: congenital infection (cCMV), transplant patients

The virus is highly immunogenic!

CMV-specific T cell responses in peripheral blood in seropositive subjects.



Sylwester et al., J Exp Med., 2005

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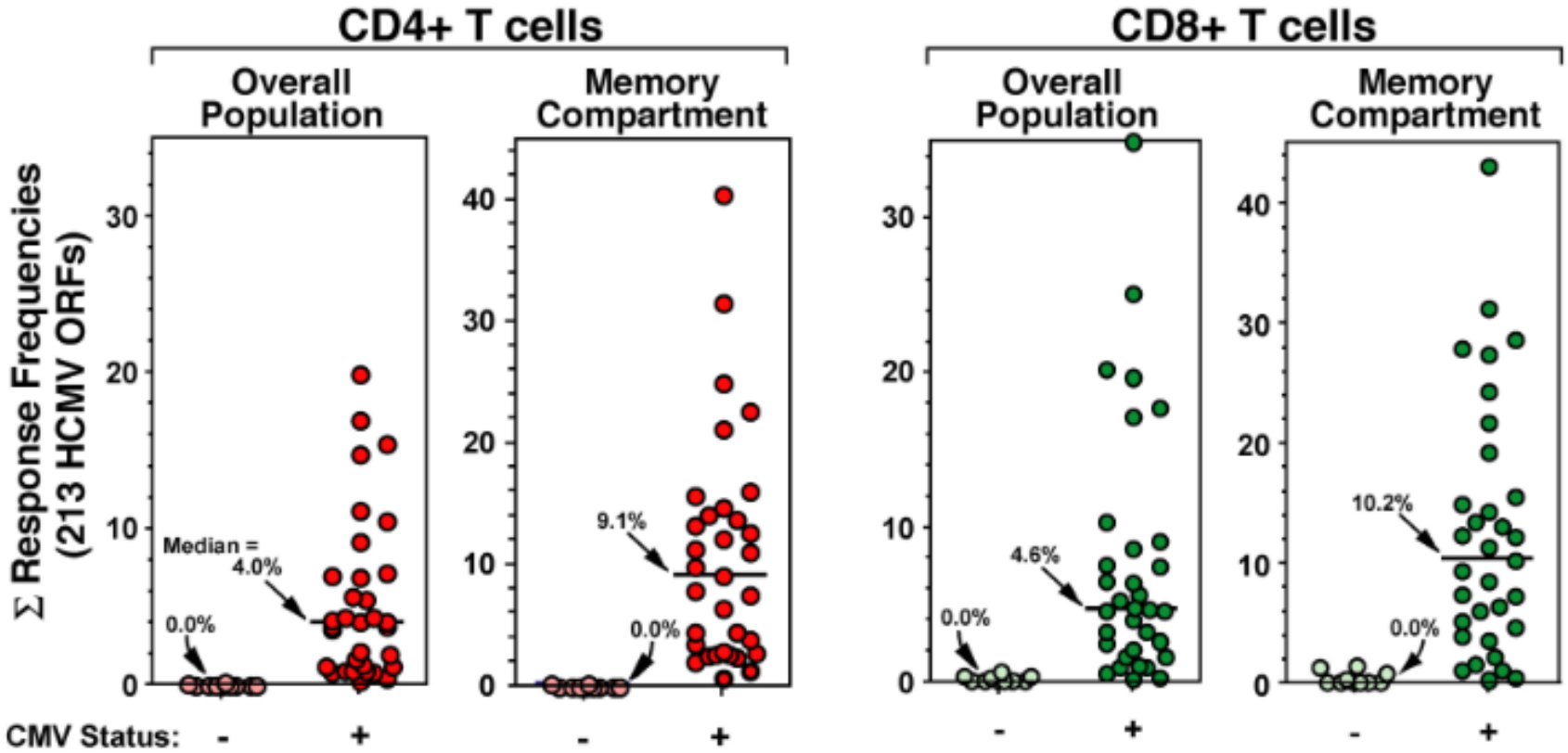
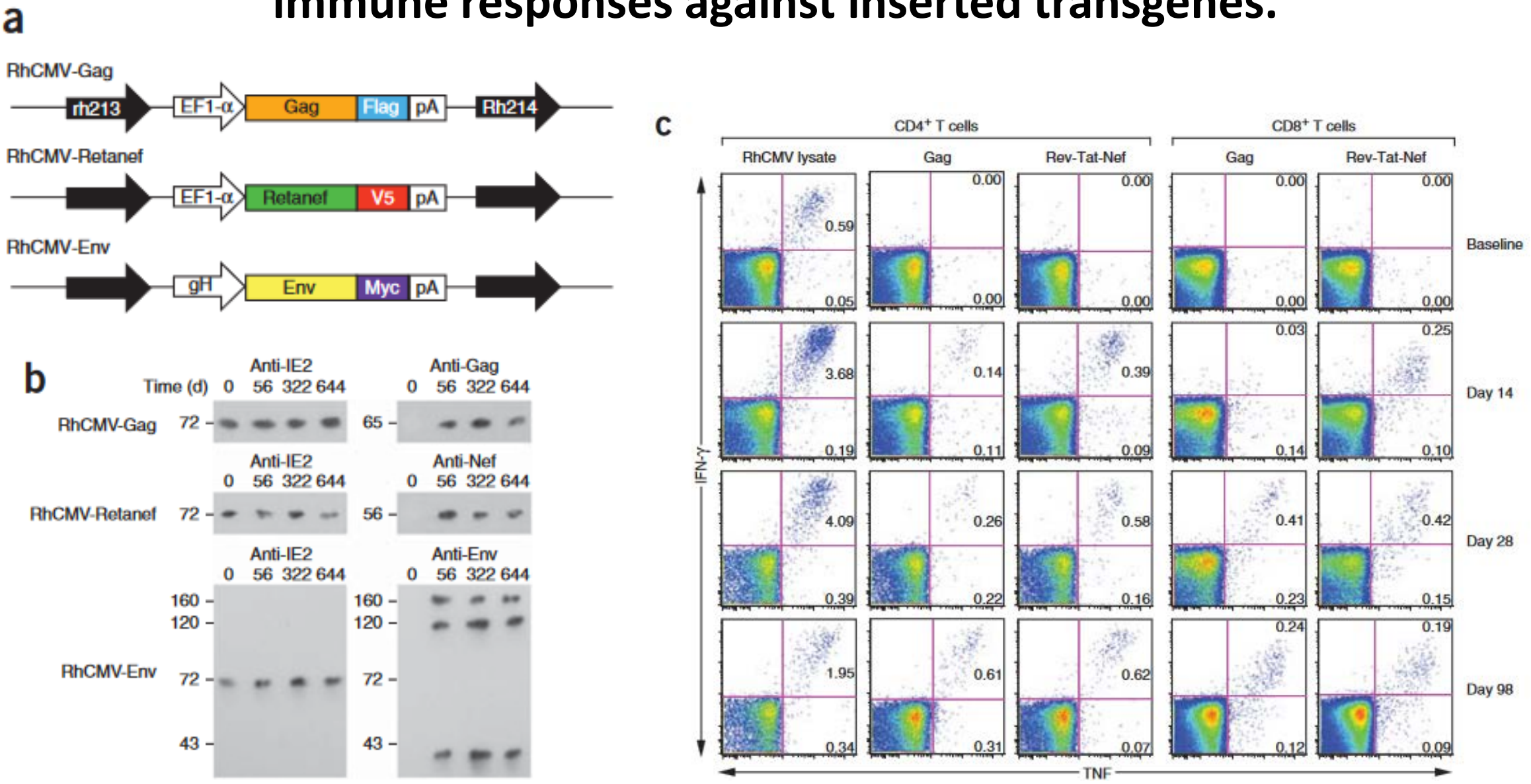


Can we design an effective T-cell vaccine against HIV?

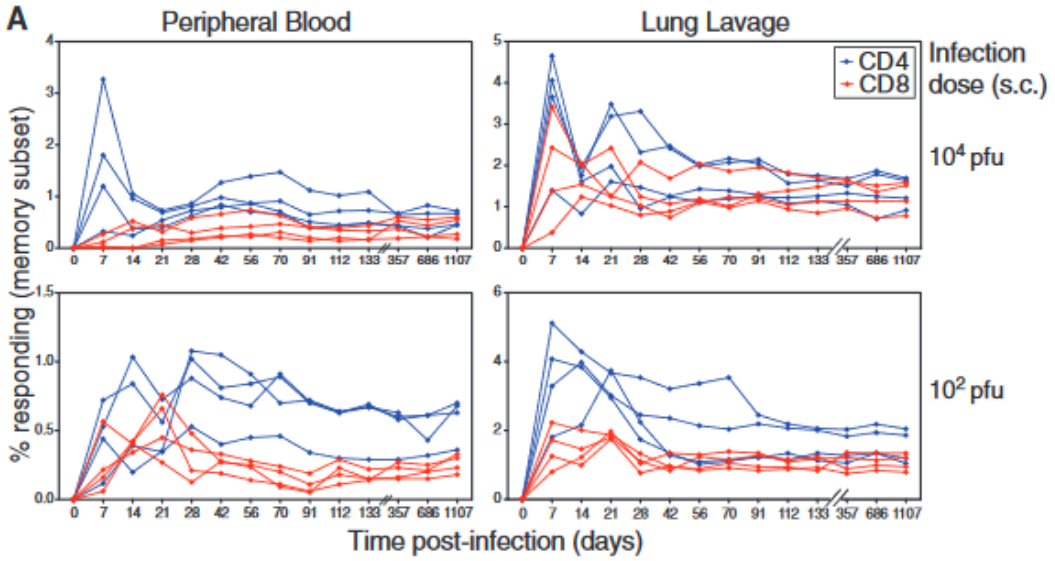
Sylwester et al., J Exp Med., 2005

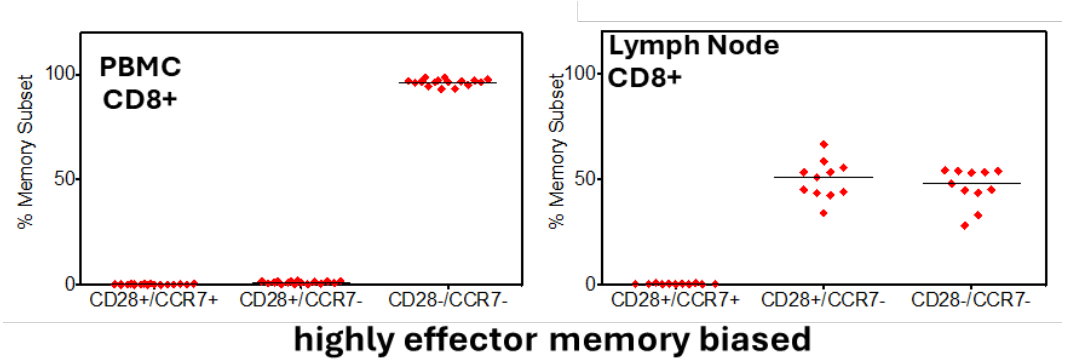
RhCMV strain 68-1 based vaccine vectors can induce strong cellular immune responses against inserted transgenes.



Hansen et al., (Nat Med., 2009)

RhCMV strain 68-1 based vaccine vectors induce TEM responses in vaccinated rhesus macaques.





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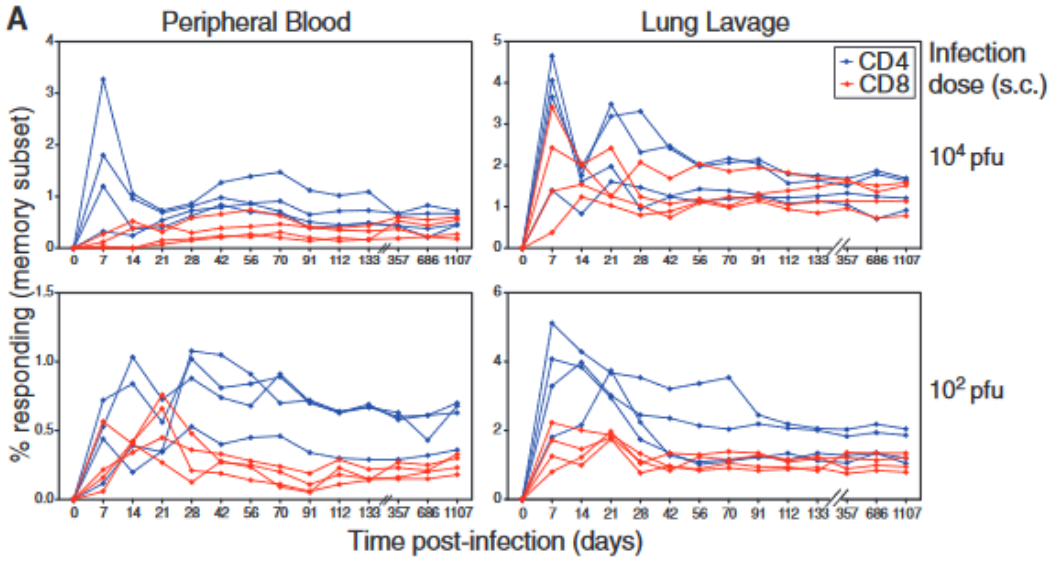
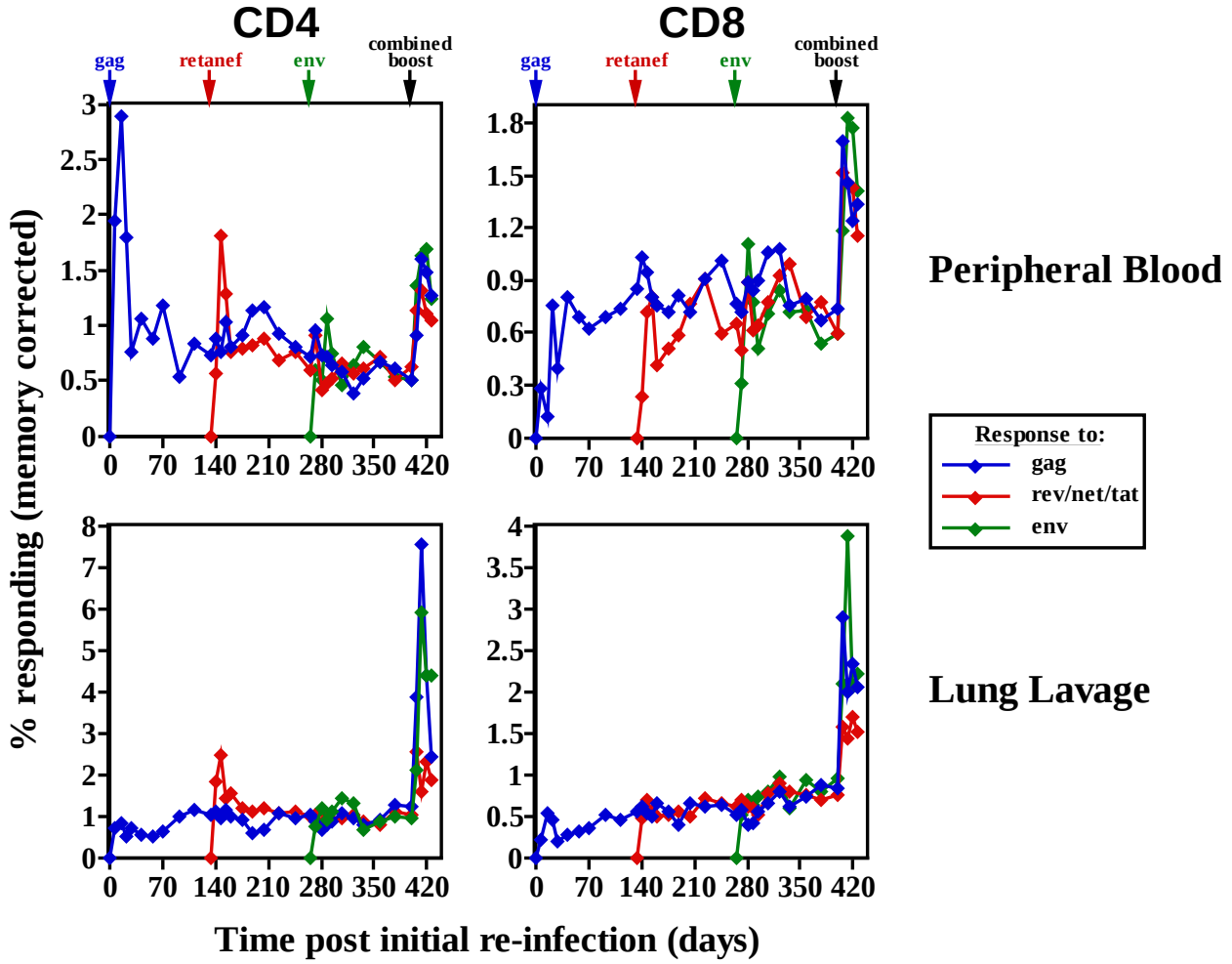
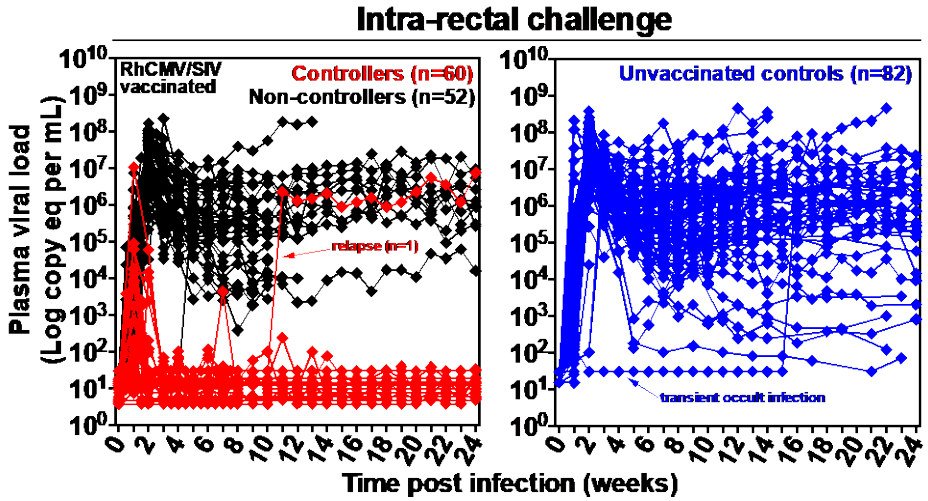
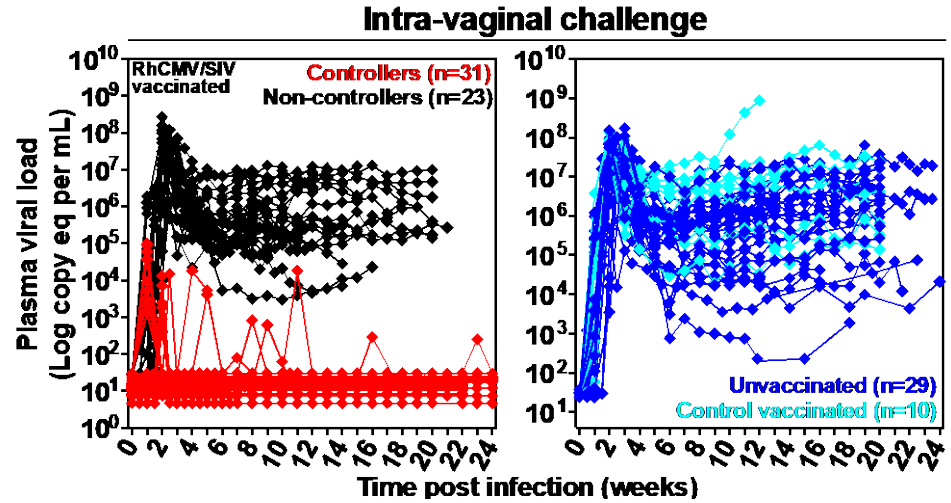




Hansen et al., (Nat Med., 2009)

We observe unprecedented protection of vaccinated rhesus macaques from repeated low dose challenge with SIVmac239.





Intra-Rectal Challenge*
54% initial
53% over 6 months

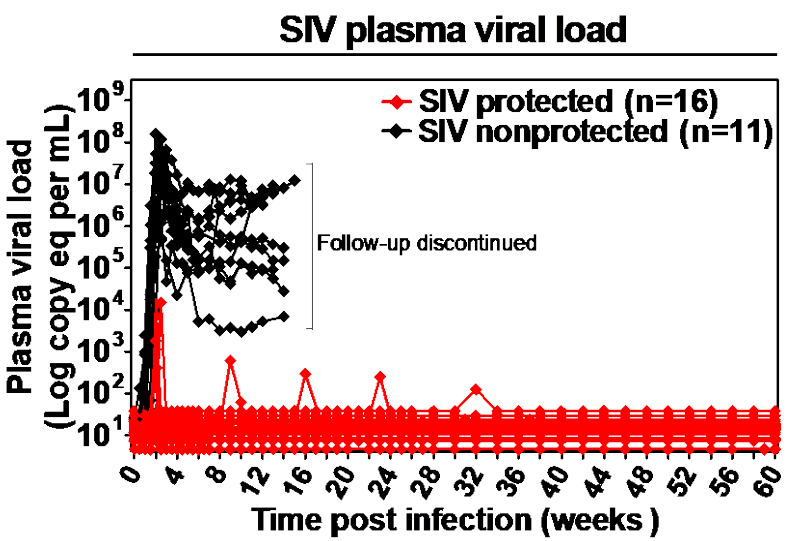
[inserts: Gag, Pol, Rev/Nef/Tat, ± Env]

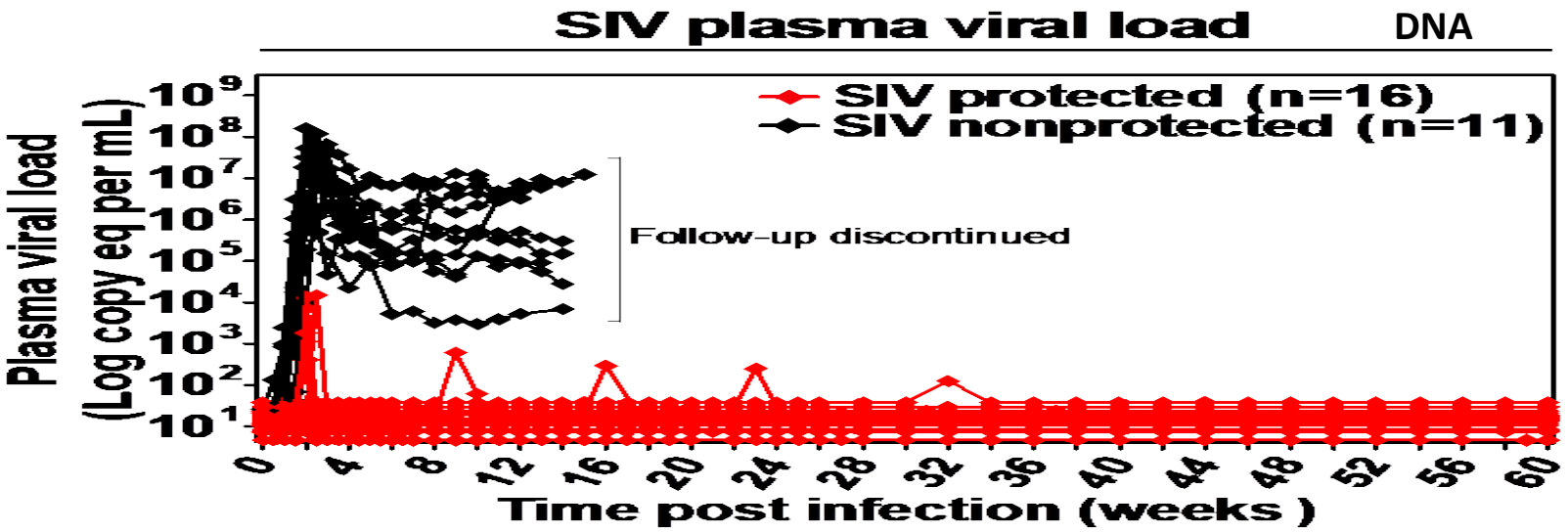
Intra-Vaginal Challenge*
57% initial
57% over 6 months

*Repeat limiting dose challenge to infection

Overall efficacy = 55% (91/166 vaccinees)

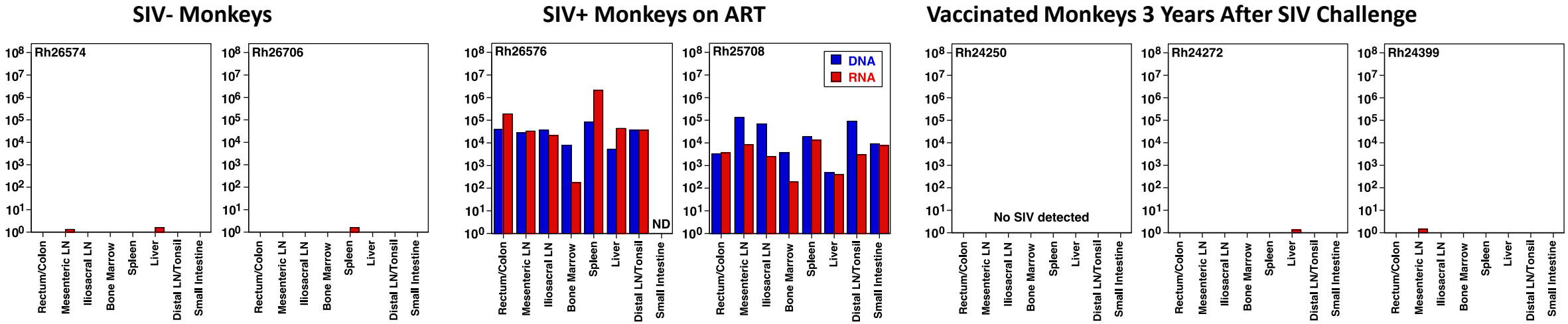
Protected animals are initially SIV positive.

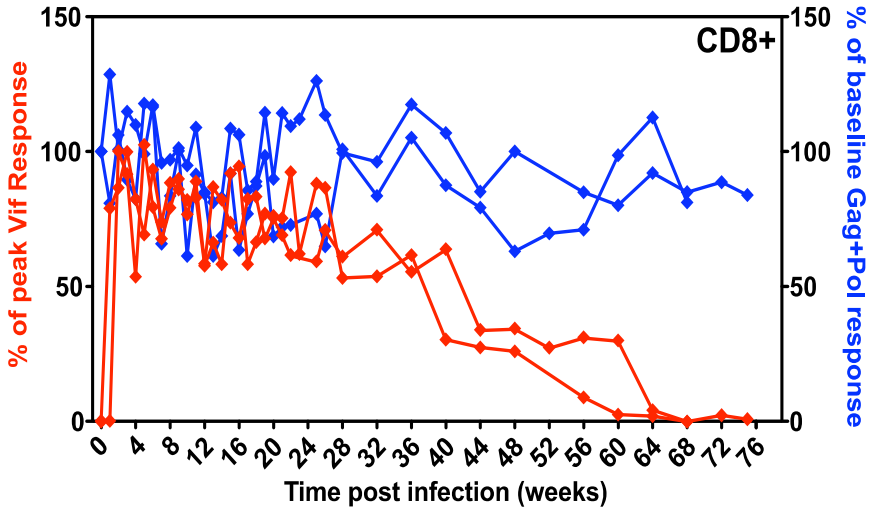


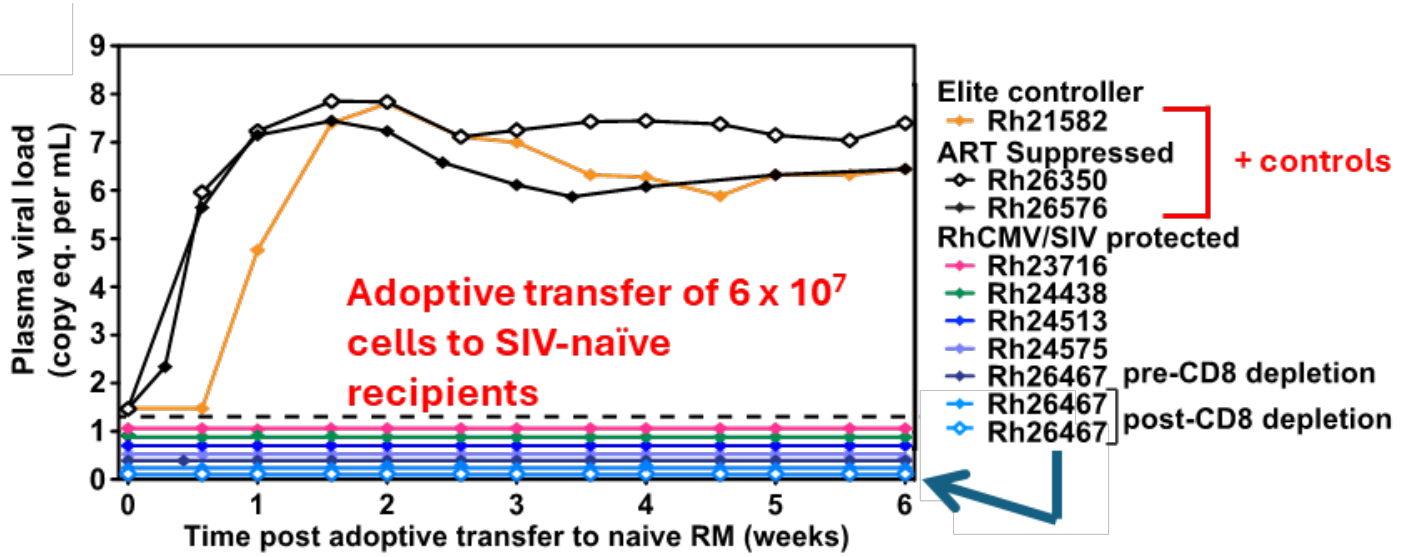


Hansen et al., (Nature., 2013)

But they can control and clear the infection.

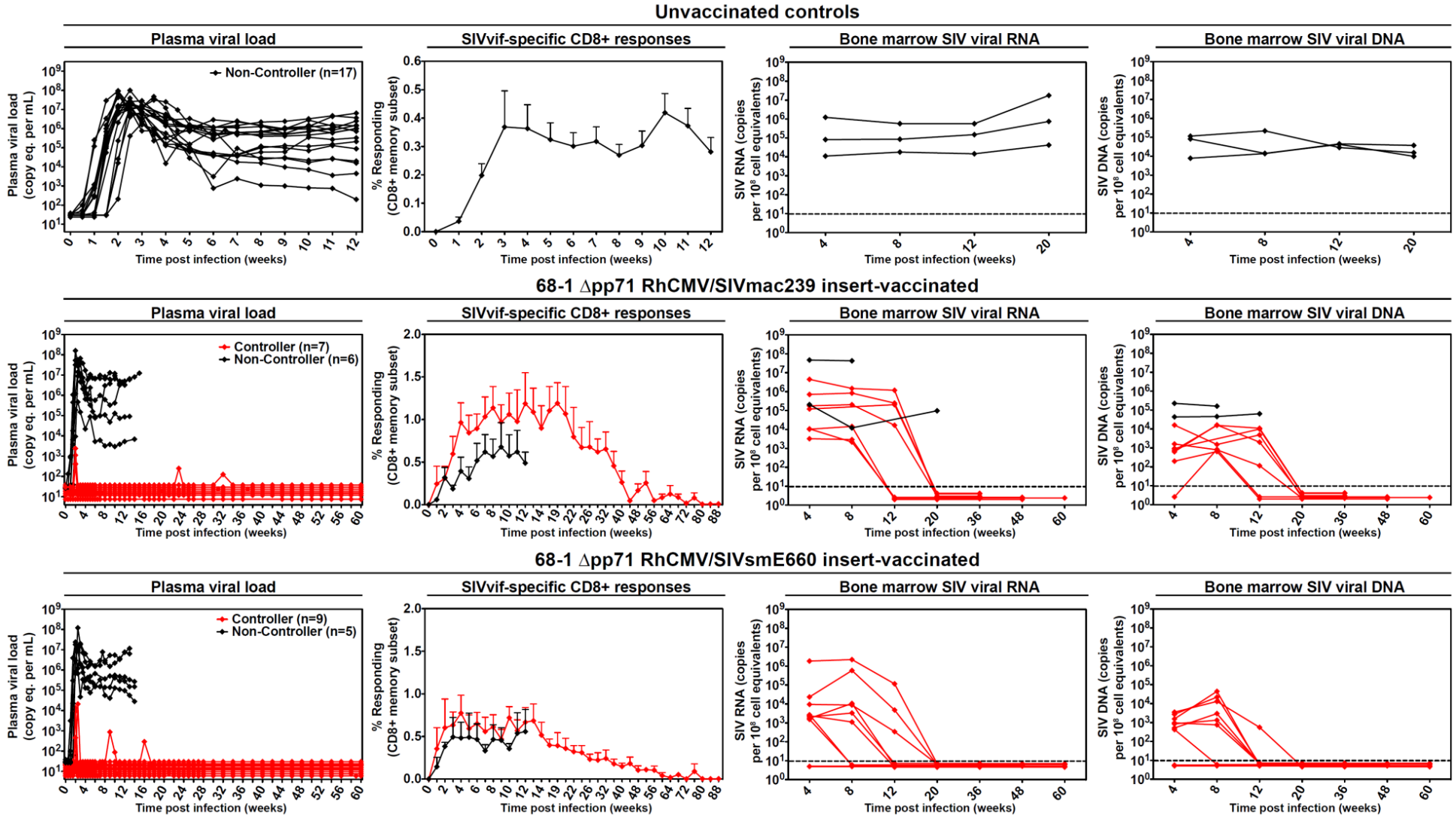






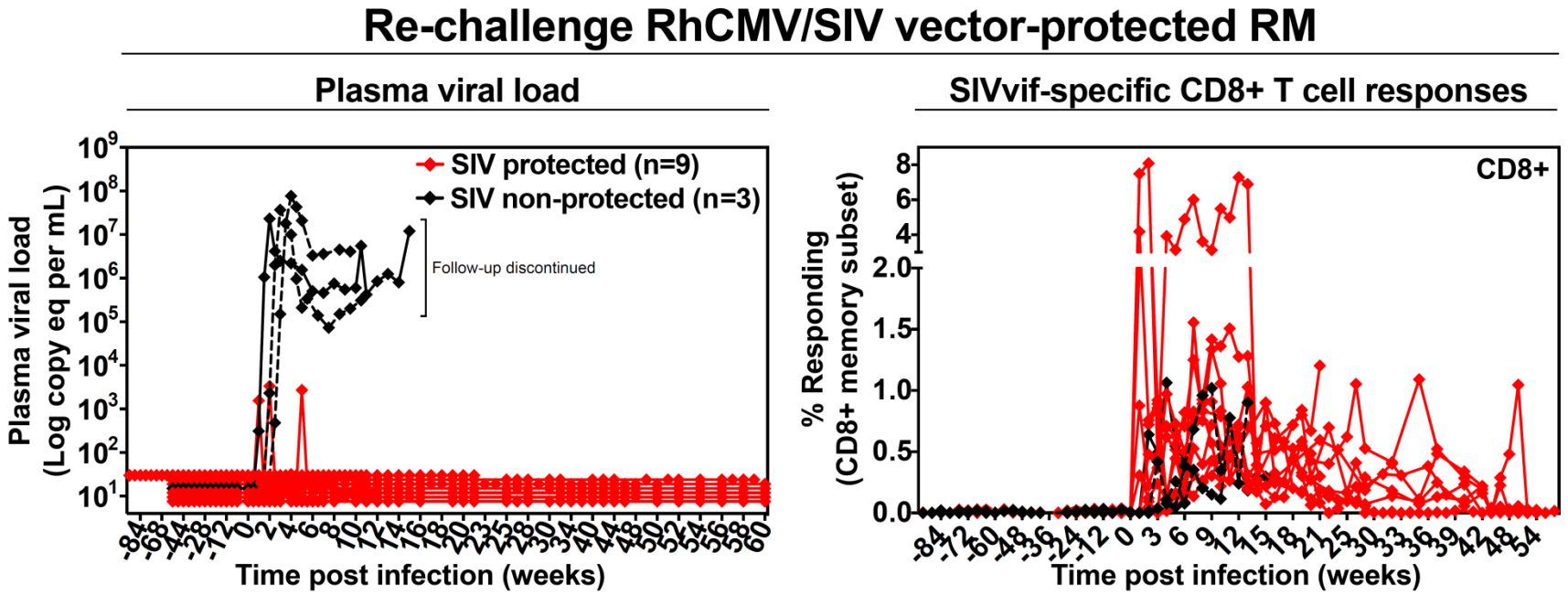
Hansen et al., (Nature., 2013)

Attenuated vaccine vectors show the same level of protection.

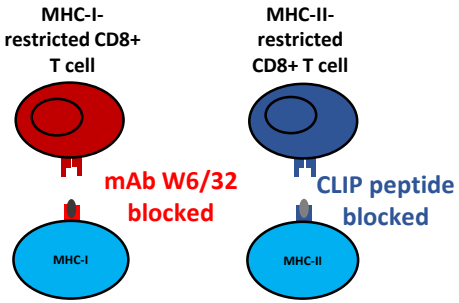


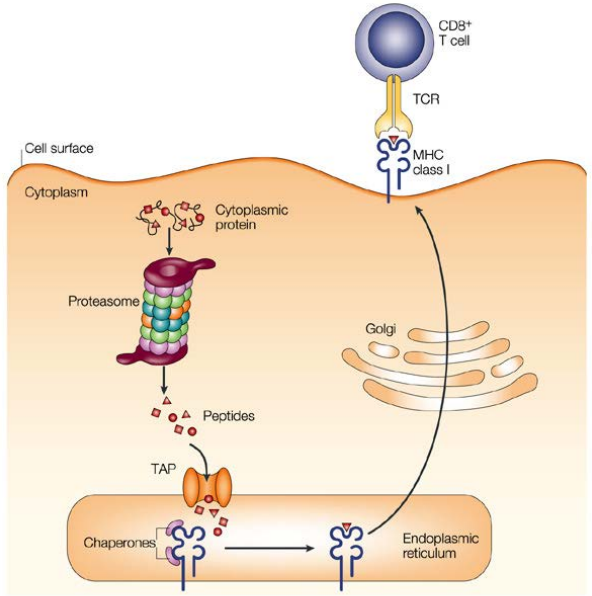
Hansen et al., (Sci Transl Med., 2019)

Controllers re-challenged year after controlling the initial SIV-infection are not necessarily protected.

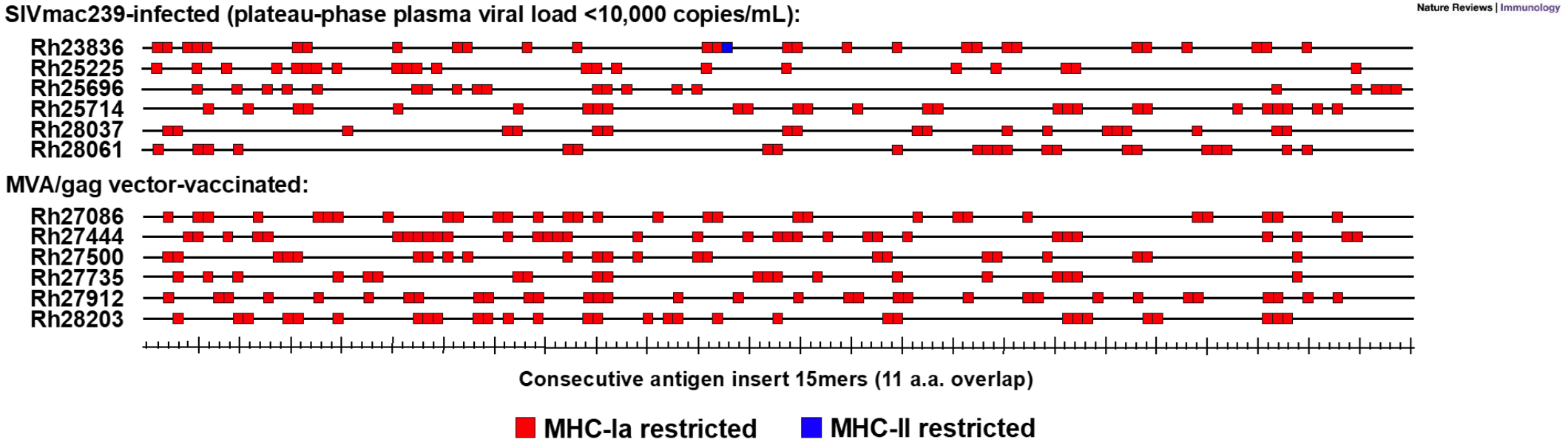


Viral infections and conventional vaccine vectors elicit CD8+ T cells that recognize peptides presented by polymorphic MHC-Ia molecules



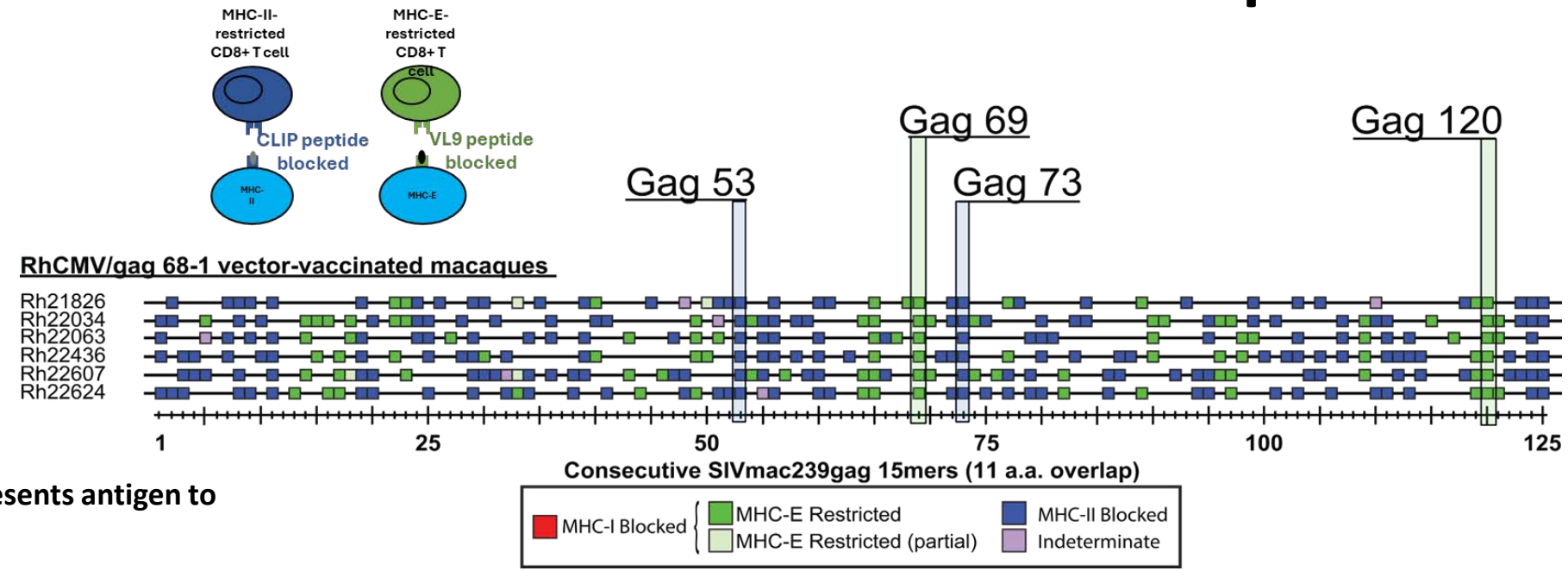


Nature Reviews | Immunology



- Each square represents the location of a given SIVgag peptide recognized by CD8+ T cells of RhCMVgag-immunized animals as measured in PBMC by intracellular cytokine staining
- The color represents the restriction element as determined by blocking antibodies or peptides

RhCMV 68-1 vector vaccination elicits only unconventional MHC-II and MHC-E restricted CD8^{+} T-cell responses.



- **MHC-II also presents antigen to CD4+ T cells**
- **The main function of MHC-E is to present the MHC-Ia leader peptide VMAPRTLLL (VL9) to NK cells**

Hansen et al., (Science., 2013)

Hansen et al., (Science., 2016)

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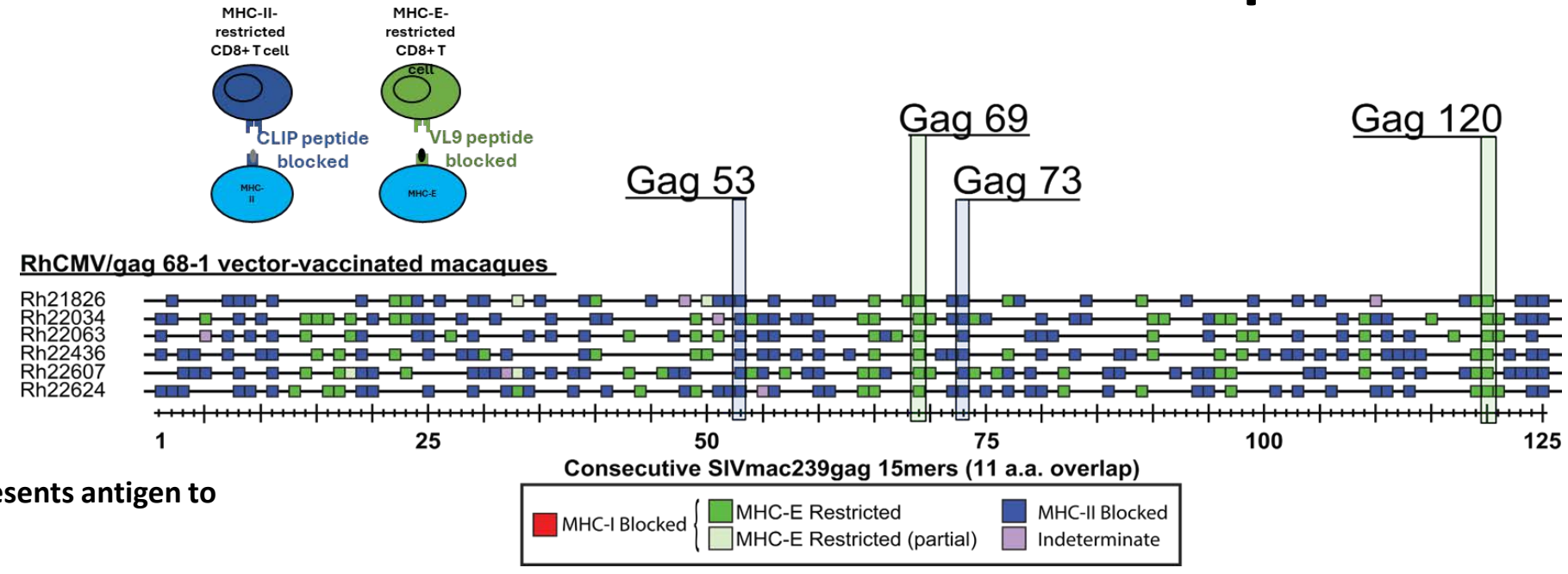

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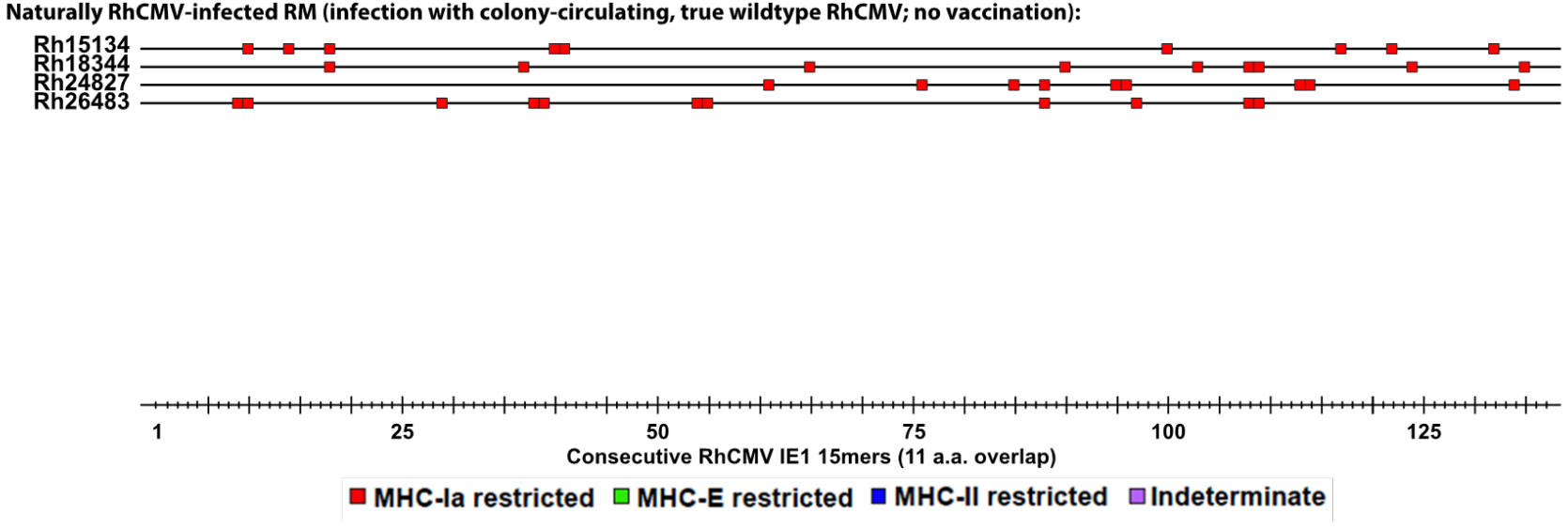

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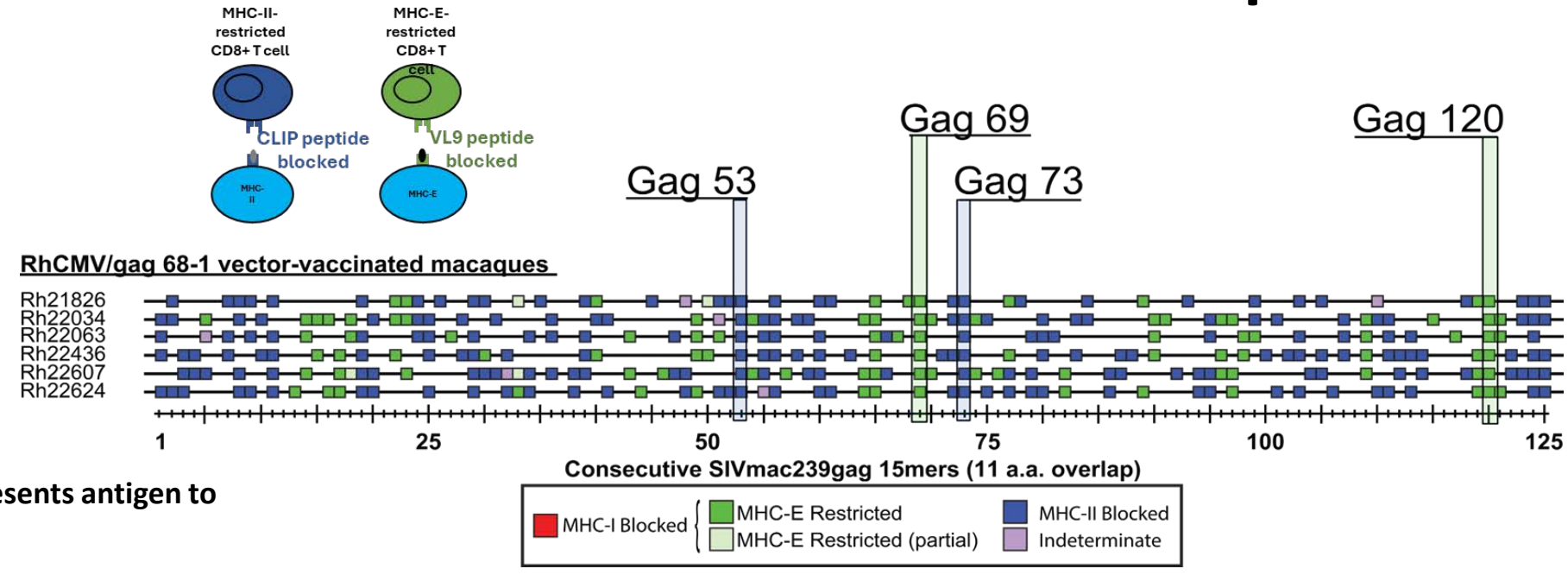

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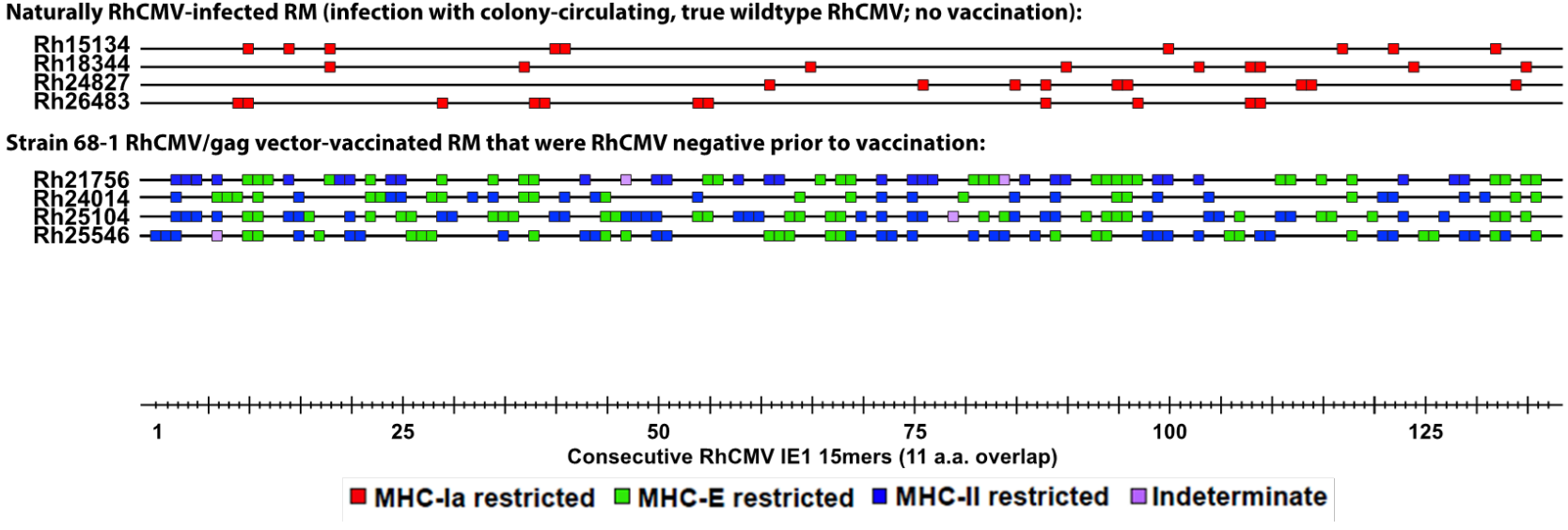

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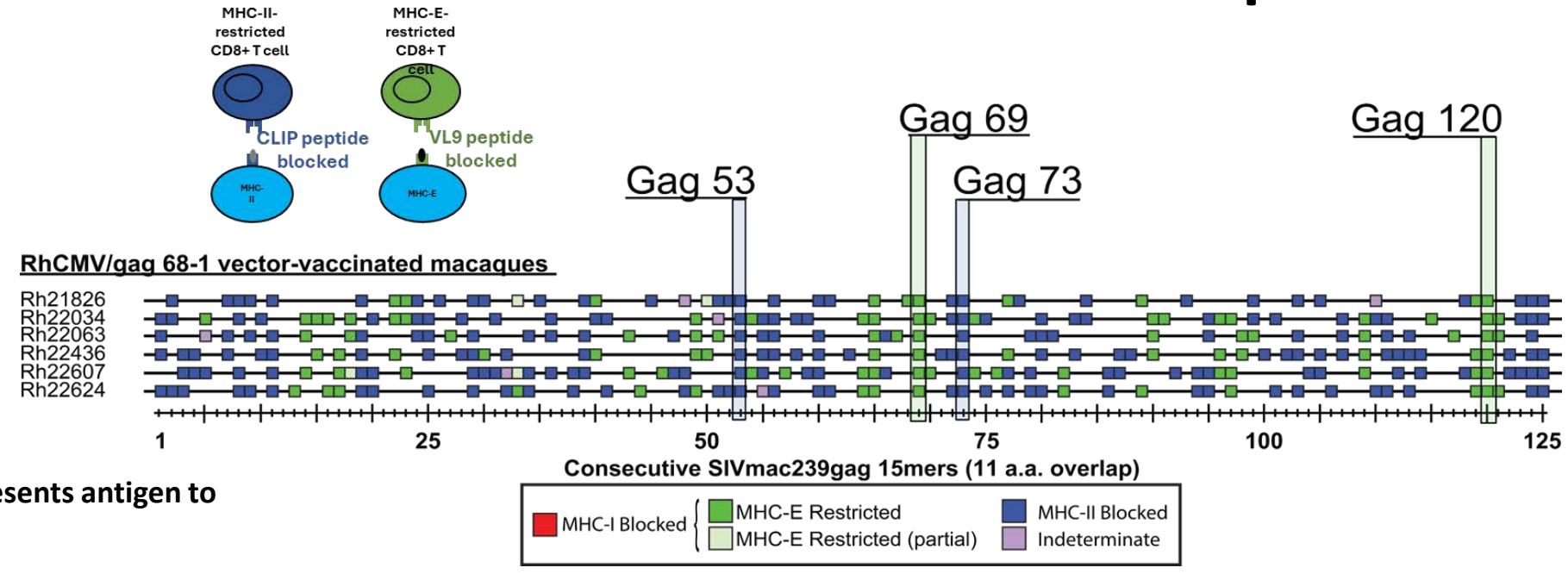
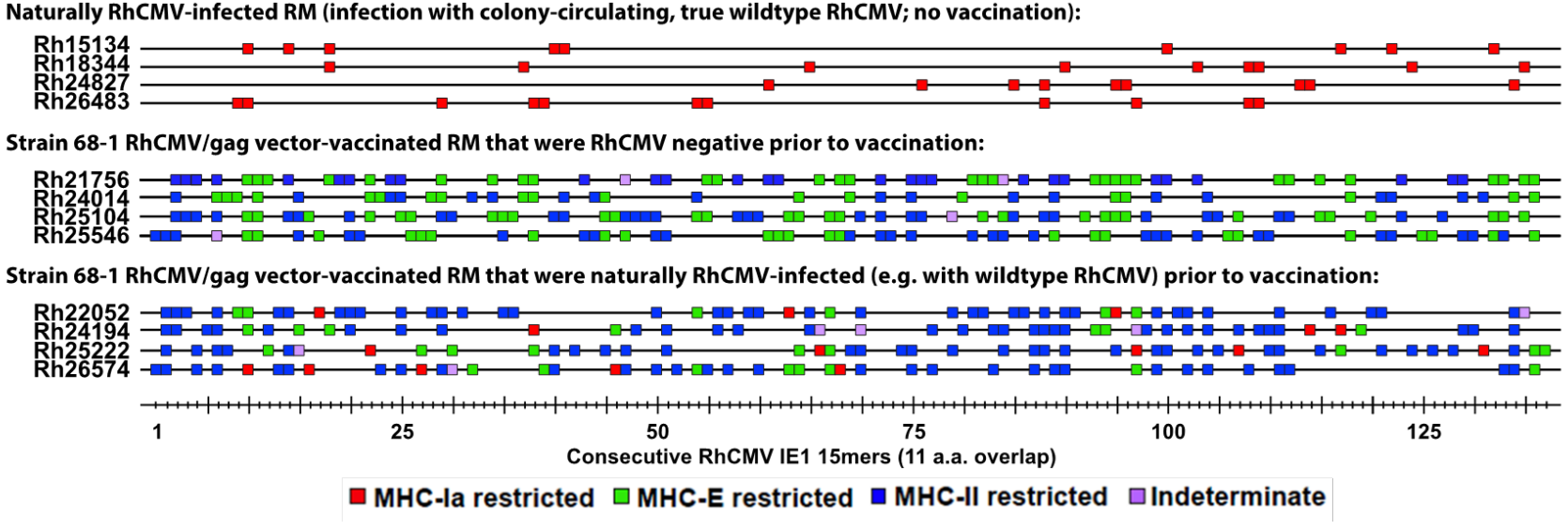


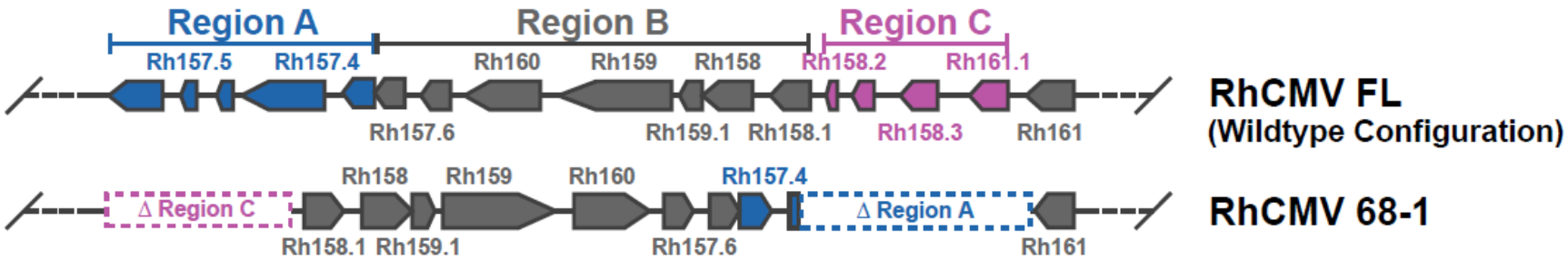
- MHC-II also presents antigen to CD4+ T cells
- The main function of MHC-E is to present the MHC-Ia leader peptide VMAPRTLLL (VL9) to NK cells



Hansen et al., (Science., 2013)

Hansen et al., (Science., 2016)

RhCMV 68-1 is a fibroblast-adapted strain with gene deletions in two genomic regions.



MHC-Ia restricted MHC-E restricted MHC-II restricted Indeterminate

Malouli et al., (Sci Immunol. 2021)

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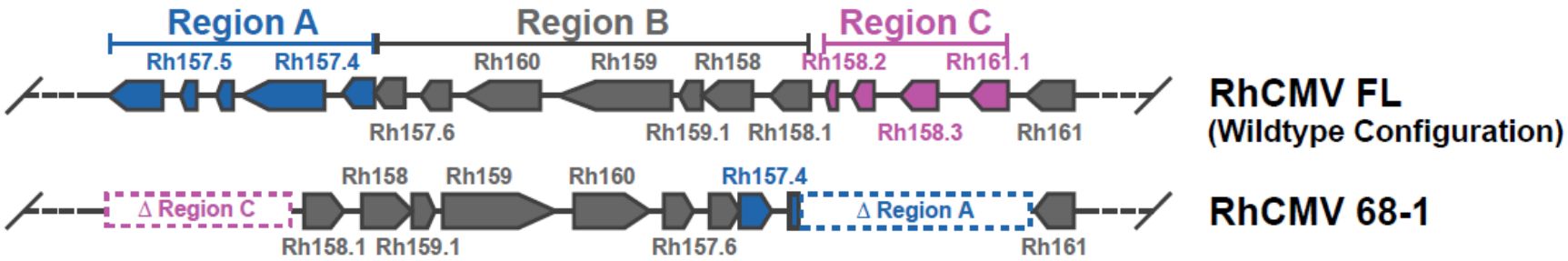

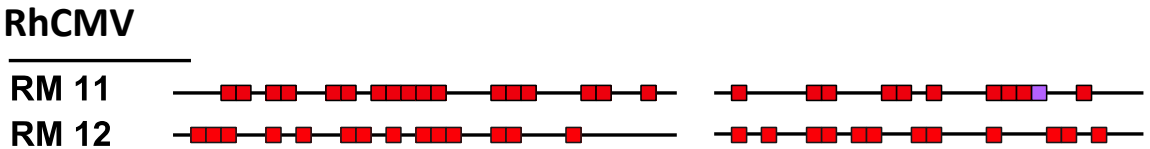

- **Repair of deletions results in vectors that elicit conventional MHC-Ia-restricted CD8+ T cells.**

MHC-Ia restricted **MHC-E restricted** **MHC-II restricted** **Indeterminate**

Malouli et al., (Sci Immunol. 2021)

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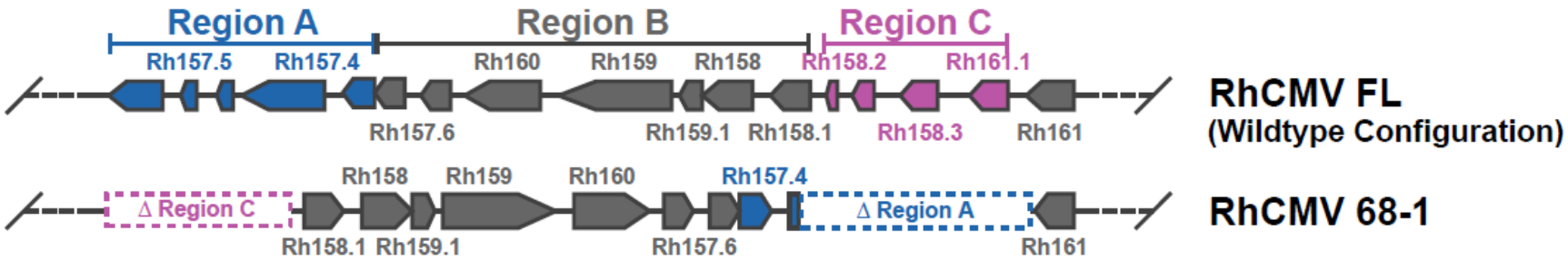

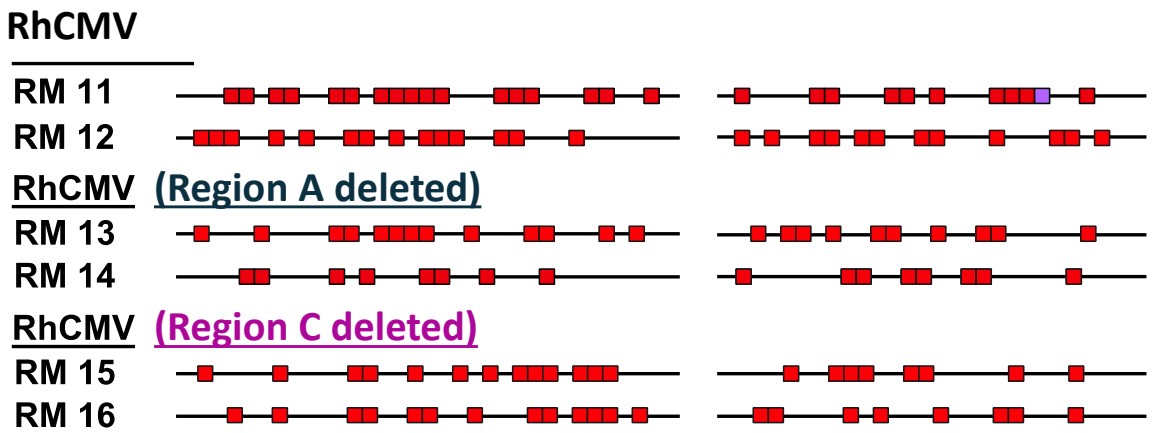

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■ MHC-Ia restricted ■ MHC-E restricted ■ MHC-II restricted ■ Indeterminate

Malouli et al., (Sci Immunol. 2021)

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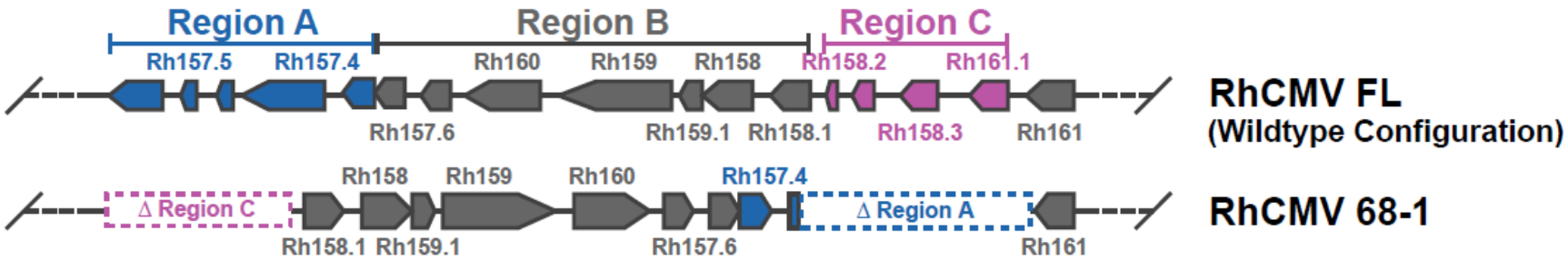
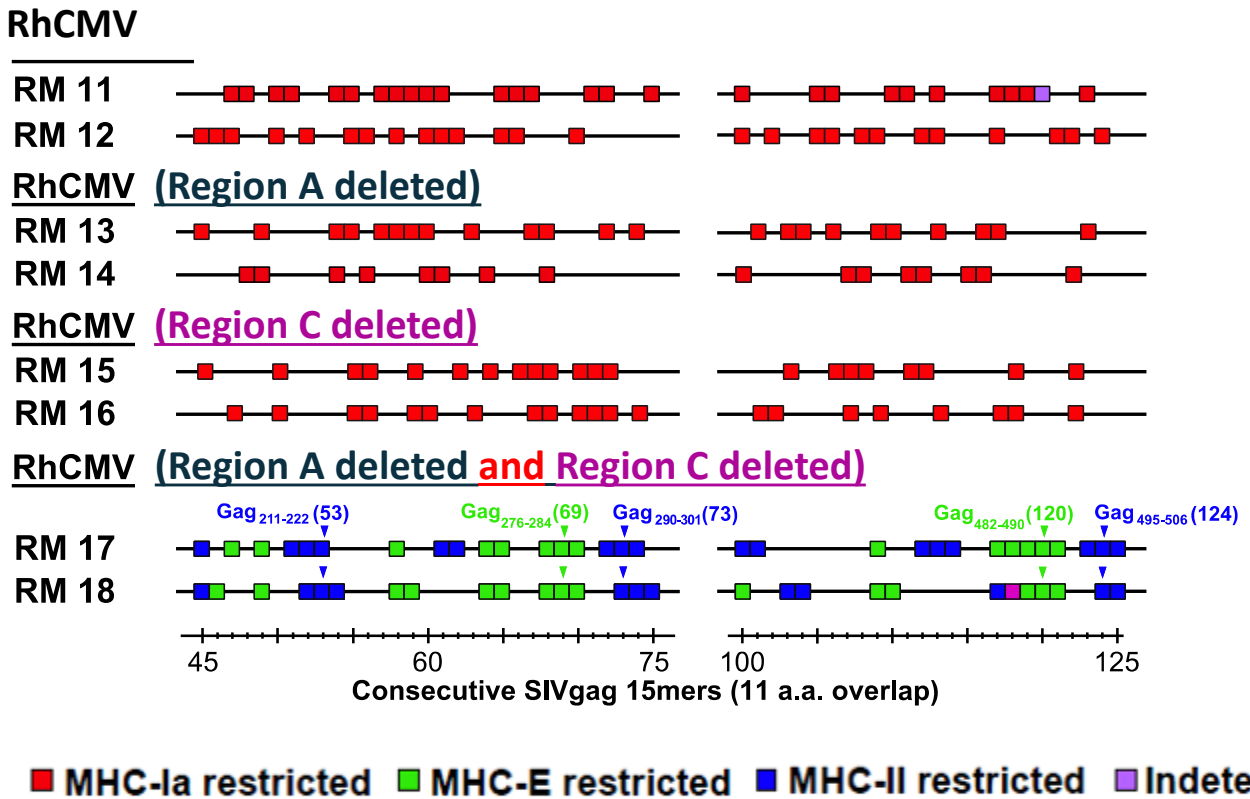
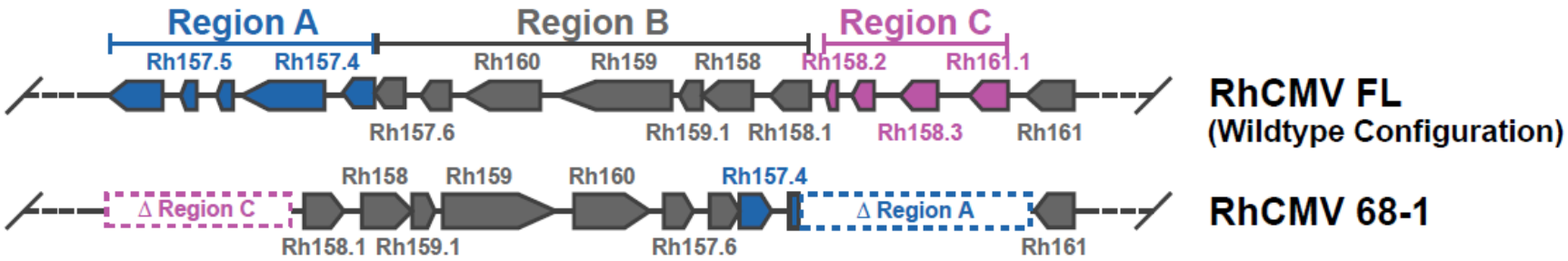


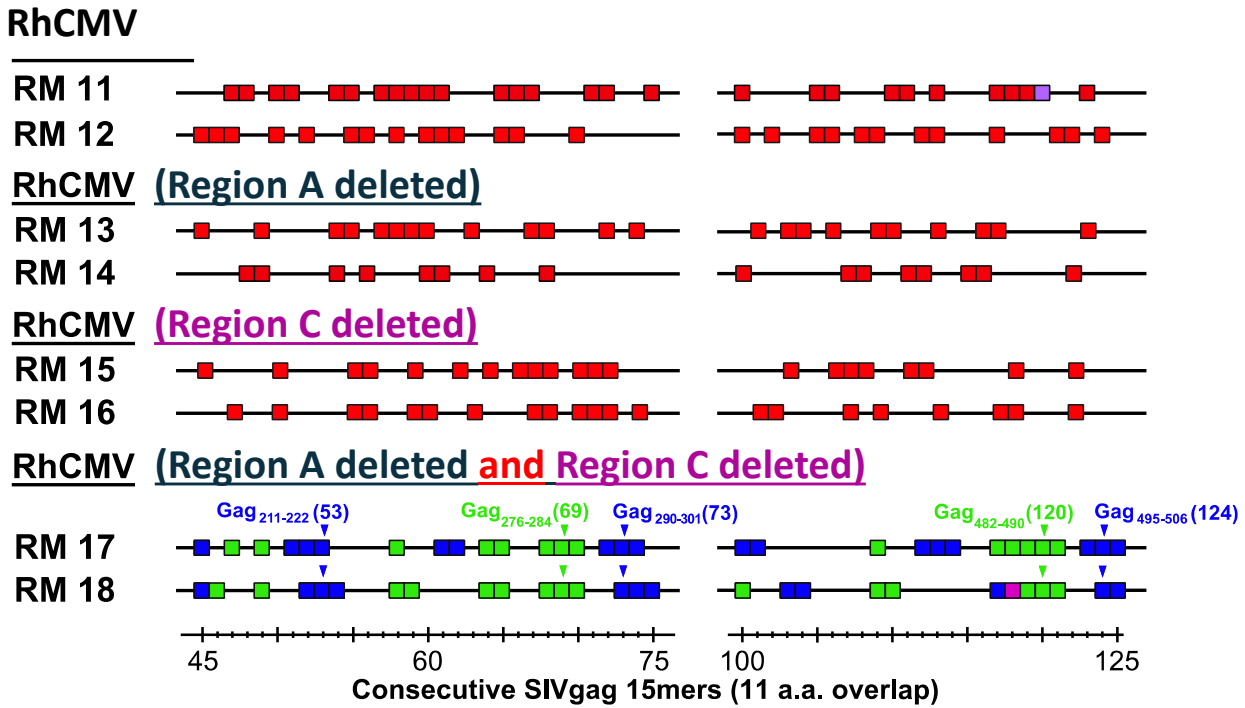


- Repair of deletions results in vectors that elicit conventional MHC-Ia-restricted CD8+ T cells.
- Both regions need to be deleted to elicit MHC-II and MHC-E-restricted CD8+ T cells

Malouli et al., (Sci Immunol. 2021)

RhCMV 68-1 is a fibroblast-adapted strain with gene deletions in two genomic regions.





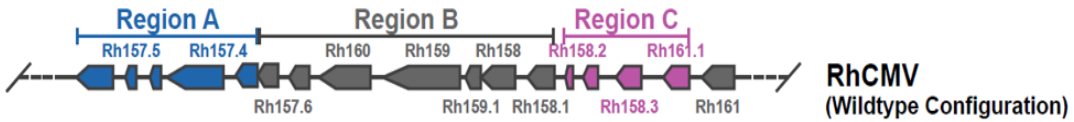
- Repair of deletions results in vectors that elicit conventional MHC-Ia-restricted CD8+ T cells.
- Both regions need to be deleted to elicit MHC-II and MHC-E-restricted CD8+ T cells

What is the role of conventional versus unconventional CD8+ T cells for vaccine efficacy of CMV-based vectors?

MHC-Ia restricted MHC-E restricted MHC-II restricted Indeterminate

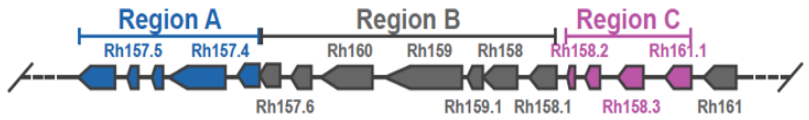
Malouli et al., (Sci Immunol. 2021)

MHC-E restricted, SIV-specific CD8+ T cell are needed for protection against SIV



(1) Malouli et al., (Sci Immunol. 2021); (2) Verweij et al., (Science., 2021); (3) Hansen et al., (Sci Immunol. 2022)

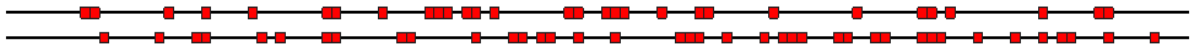
MHC-E restricted, SIV-specific CD8+ T cell are needed for protection against SIV



RhCMV
(Wildtype Configuration)

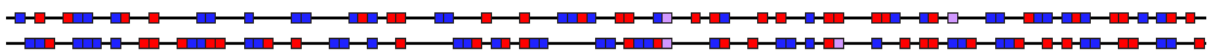
CD8+ T-cell restriction

FL RhCMV/SIV vectors (wildtype)



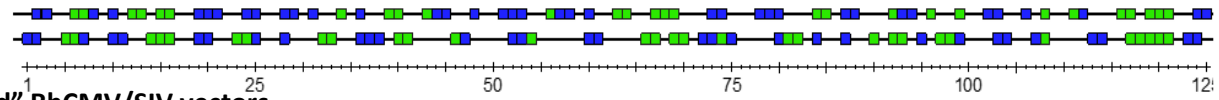
MHC-Ia

FL RhCMV/SIV vectors (c Region A partially deleted and Region C deleted



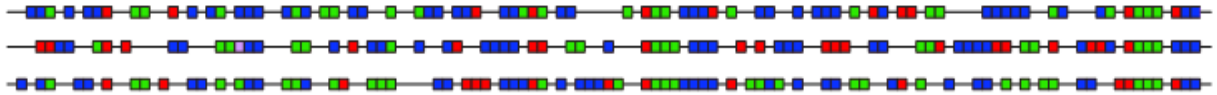
MHC-Ia + MHC-II

FL RhCMV/SIV vectors (c Region A deleted and Region C deleted



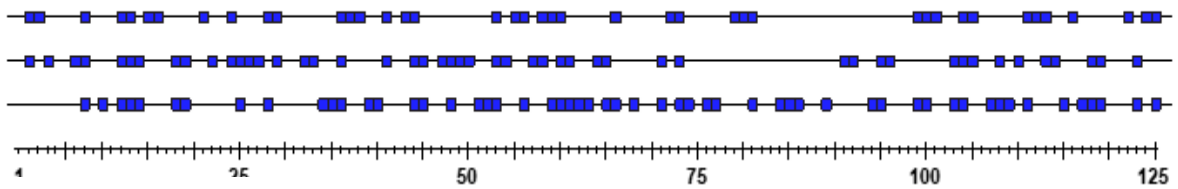
MHC-II + MHC-E

"intact" + "deleted" RhCMV/SIV vectors



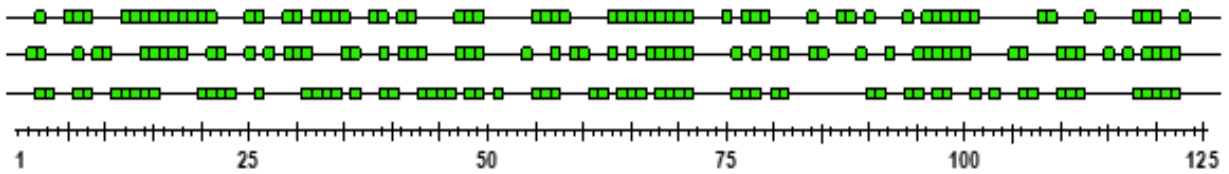
MHC-Ia + MHC-E + MHC-II

68-1 RhCMV/SIV vectors lacking viral VL9



MHC-II

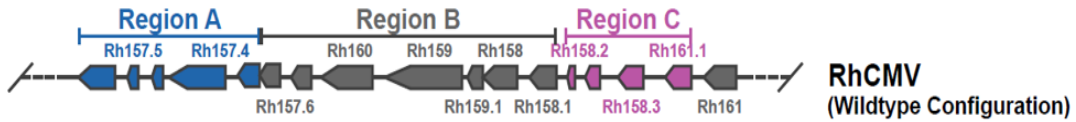
miR126-targeted 68.1 RhCMV/SIV vectors



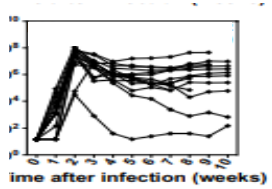
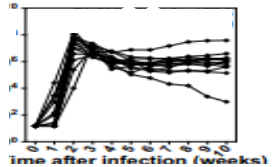
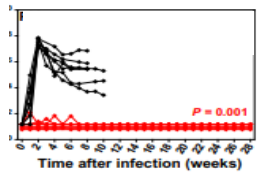
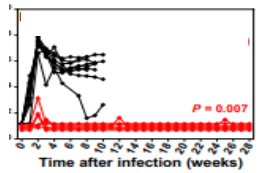
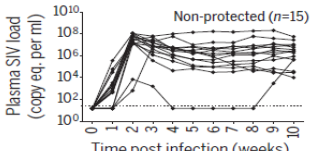
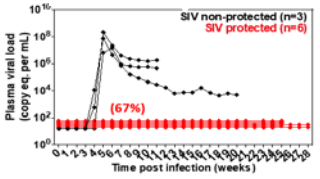
MHC-E

(1) Malouli et al., (Sci Immunol. 2021); (2) Verweij et al., (Science., 2021); (3) Hansen et al., (Sci Immunol. 2022)

MHC-E restricted, SIV-specific CD8+ T cell are needed for protection against SIV



RhCMV
(Wildtype Configuration)

	CD8+ T-cell restriction	Protection against SIV	
FL RhCMV/SIV vectors (wildtype)	MHC-Ia	No (1)	
FL RhCMV/SIV vectors (Region A partially deleted and Region C deleted	MHC-Ia + MHC-II	No (1)	
FL RhCMV/SIV vectors (Region A deleted and Region C deleted	MHC-II + MHC-E	Yes (1)	
"intact" + "deleted" RhCMV/SIV vectors	MHC-Ia + MHC-E + MHC-II	Yes (1)	
68-1 RhCMV/SIV vectors lacking viral VL9	MHC-II	No (2)	
miR126-targeted 68.1 RhCMV/SIV vectors	MHC-E	Yes (3)	

(1) Malouli et al., (Sci Immunol. 2021); (2) Verweij et al., (Science., 2021); (3) Hansen et al., (Sci Immunol. 2022)

Clinical Translation:

- Due to species-specificity we need to use human CMV for vaccine development in the human population
- HCMV homologs of RhCMV genes involved in immune programming are functionally conserved
  - UL40 (Rh67): Viral decoy required for MHC-E responses
  - US28 (Rh214, Rh220): required for MHC-E responses
  - UL128, UL130 (Rh157.5, Rh157.4): pentamer subunits and inhibitors of MHC-E responses
  - UL146, UL147: chemokine homologs and inhibitors of MHC-II and MHC-E-restricted CD8+ T cell responses

VIR

BILL & MELINDA GATES *foundation*

VIR-1111 is an HIV vaccine candidate that is being tested in a randomized, placebo-controlled clinical trial:

•**Trial name**: NCT04725877
•**Purpose**: Evaluate the safety and immunogenicity of VIR-1111 in healthy adults who are at low risk of HIV infection
•**Participants**: Healthy adults aged 18–50 who are seropositive for cytomegalovirus (CMV)
•**Treatment**: Two doses of VIR-1111 or placebo given by subcutaneous injection
•**Assessments**: Safety, reactogenicity, tolerability, and immunogenicity
•**Follow-up**: An optional long-term follow-up study for up to three years after the first dose

- Safety and immunology data from the initial two cohorts of the proof-of-concept Phase 1 trial of VIR-1111, an investigational HIV T cell vaccine based on human cytomegalovirus (HCMV), show no safety signals and no vector shedding or viremia reported to date. No sustained HIV insert-specific T cell responses have been observed in the lower dose cohorts 1 and 2. Safety and immunology data from the highest dose cohort 3 are expected in the first half of 2023. This trial is being funded in part by the Bill and Melinda Gates Foundation.
- Learnings from VIR-1111 have informed the design of VIR-1388, a next generation candidate, for which the Company expects to initiate a Phase 1 trial in the second half of 2023. This trial is being funded in part by the Bill and Melinda Gates Foundation and the National Institutes of Health's Division of AIDS, through the HIV Vaccine Trials Network.

Vir Biotechnology press release 11/03/2022

What could have been the problem?

- Does HCMV encode inhibitors of unconventional CD8+ T cell responses not found in RhCMV
  - ~40 genes in the HCMV genome do not have a direct homologue in RCMV
  - Would any of these genes prevent T cell stimulation if incorporated into 68-1 RhCMV?

Screen of HCMV ORFs not conserved inRhCMV

68-1 RhCMV vector	HCMV ORF inserted into Rh13.1	Transgene replacing Rh107
1	RL6	SIV(pol-5')
2	RL8A	SIV(pol-5')
3	RL9A	SIV(pol-5')
4	RL10	SIV(pol-5')
5	RL12	SIV(pol-5')
6	UL1	SIV(pol-5')
7	UL2	SIV(pol-5')
8	UL4	SIV(pol-5')
9	UL6	SIV(rtn)
10	UL7	SIV(rtn)
11	UL9	SIV(rtn)
12	UL10	SIV(rtn)
13	UL11	SIV(rtn)
14	UL15A	SIV(rtn)
15	UL18	SIV(rtn)
16	UL74A	SIV(rtn)
17	UL142	SIV(rtn)
18	UL140	SIV(gag)
19	UL139	SIV(gag)
20	UL138	SIV(gag)
21	UL136	SIV(gag)
22	UL135	SIV(gag)
23	UL133	SIV(gag)
24	UL148A	SIV(gag)
25	UL148B	SIV(gag)
26	UL148C	SIV(gag)
27	UL148D	SIV(gag)
28	UL150	Mtb(ESAT6-Ag85A)
29	UL150A	Mtb(ESAT6-Ag85A)
30	US7	Mtb(ESAT6-Ag85A)
31	US9	Mtb(ESAT6-Ag85A)
32	US15	Mtb(ESAT6-Ag85A)
33	US16	Mtb(ESAT6-Ag85A)
34	US33A	Mtb(ESAT6-Ag85A)
35	US34	Mtb(ESAT6-Ag85A)
36	US34A	Mtb(ESAT6-Ag85A)

- Each HCMV gene was inserted into the defective ORF Rh13.1 (RL13 homologue)
- In addition, each vector contained an immunological marker. Different markers permit testing several vectors in the same animal
- Each Marker contained previously defined MHC-II and MHC-E supertopes. This allows for the rapid screening for the presence of MHC-II and MHC-E restricted CD8+ T cells

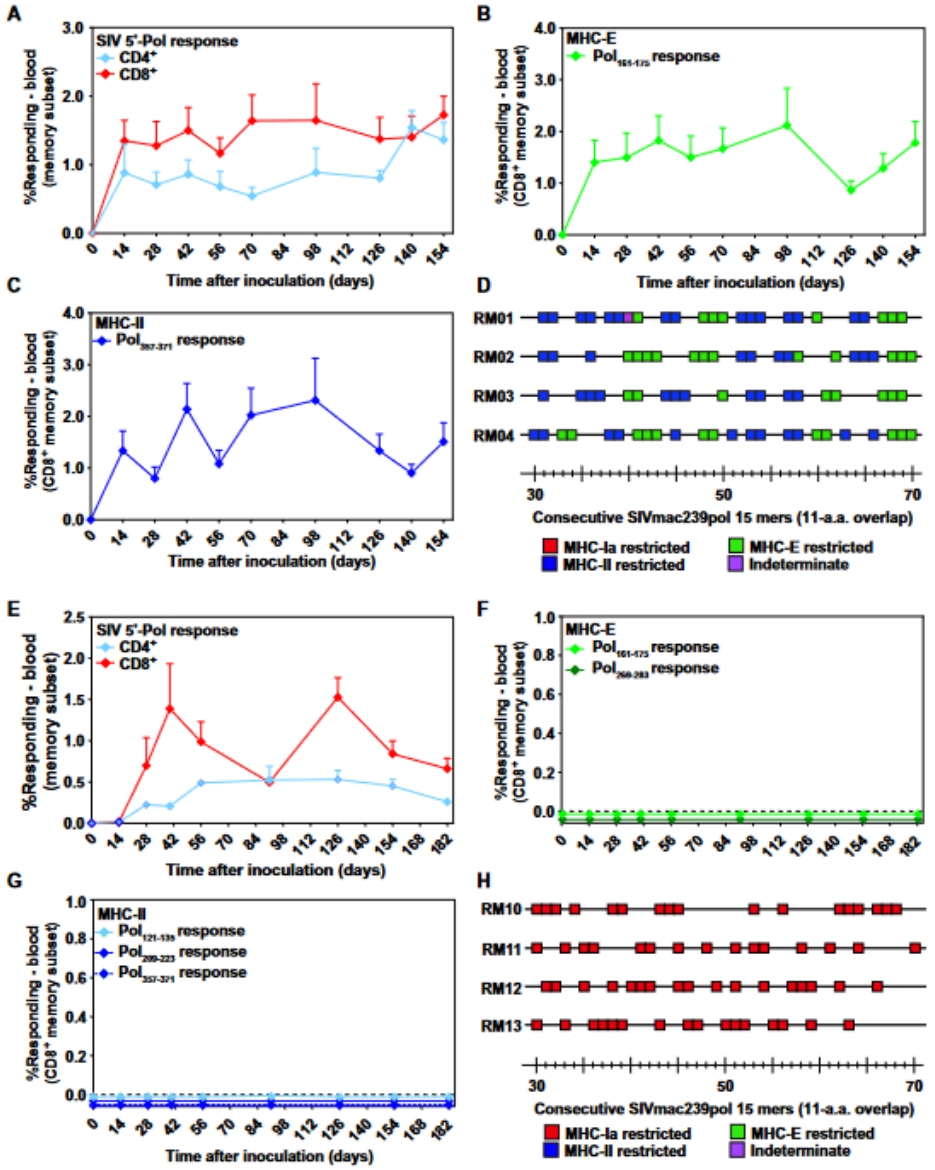
Malouli et al., (Sci Immunol. 2024)

RhCMV 68-1 expressing UL18 fails to elicit CD8+ T cells to MHC-II and MHC-E-supertopes

68-1 RhCMV vector	HCMV ORF inserted into Rh13.1	Transgene replacing Rh107	Pooled transgene specific Immune responses	transgene specific MHC-E supertope responses	transgene specific MHC-II supertope responses
1	RL6	SIV(pol-5')	√	√	√
2	RL8A	SIV(pol-5')	√	√	√
3	RL9A	SIV(pol-5')	√	√	√
4	RL10	SIV(pol-5')	√	√	√
5	RL12	SIV(pol-5')	√	√	√
6	UL1	SIV(pol-5')	√	√	√
7	UL2	SIV(pol-5')	√	√	√
8	UL4	SIV(pol-5')	√	√	√
9	UL6	SIV(rtn)	√	√	√
10	UL7	SIV(rtn)	√	√	√
11	UL9	SIV(rtn)	√	√	√
12	UL10	SIV(rtn)	√	√	√
13	UL11	SIV(rtn)	√	√	√
14	UL15A	SIV(rtn)	√	√	√
15	**UL18**	**SIV(rtn)**	√	x	x
16	UL74A	SIV(rtn)	√	√	√
17	UL142	SIV(rtn)	√	√	√
18	UL140	SIV(gag)	√	√	√
19	UL139	SIV(gag)	√	√	√
20	UL138	SIV(gag)	√	√	√
21	UL136	SIV(gag)	√	√	√
22	UL135	SIV(gag)	√	√	√
23	UL133	SIV(gag)	√	√	√
24	UL148A	SIV(gag)	√	√	√
25	UL148B	SIV(gag)	√	√	√
26	UL148C	SIV(gag)	√	√	√
27	UL148D	SIV(gag)	√	√	√
28	UL150	Mtb(ESAT6-Ag85A)	√	√	√
29	UL150A	Mtb(ESAT6-Ag85A)	√	√	√
30	US7	Mtb(ESAT6-Ag85A)	√	√	√
31	US9	Mtb(ESAT6-Ag85A)	√	√	√
32	US15	Mtb(ESAT6-Ag85A)	√	√	√
33	US16	Mtb(ESAT6-Ag85A)	√	√	√
34	US33A	Mtb(ESAT6-Ag85A)	√	√	√
35	US34	Mtb(ESAT6-Ag85A)	√	√	√
36	US34A	Mtb(ESAT6-Ag85A)	√	√	√

Malouli et al., (Sci Immunol. 2024)

HCMV UL18 inhibits the generation of unconventionally restricted CD8+ T-cell responses



SIV-specific CD8+ T cell responses elicited by 68-1 RhCMV recognize peptides presented by MHC-II and MHC-E

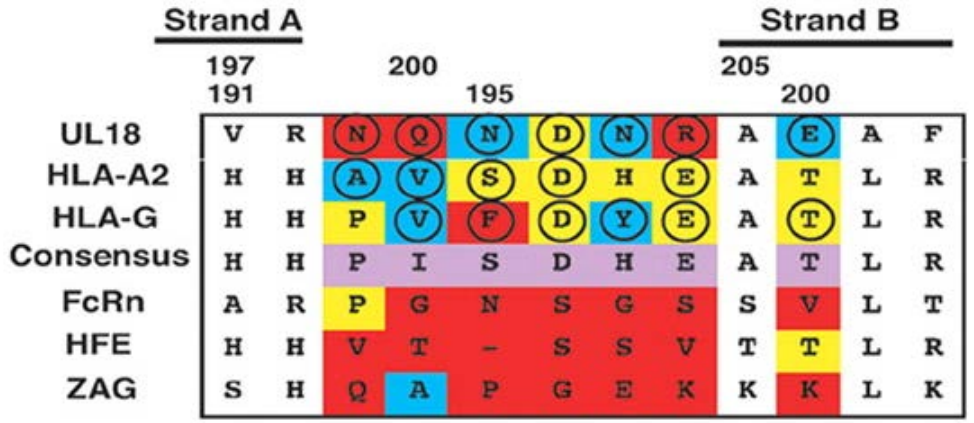
- MHC-I-restricted responses are the default pathway when MHC-II and MHC-E restricted responses are inhibited.
- UL18 = inhibitor of unconventionally restricted CD8+ T cell responses

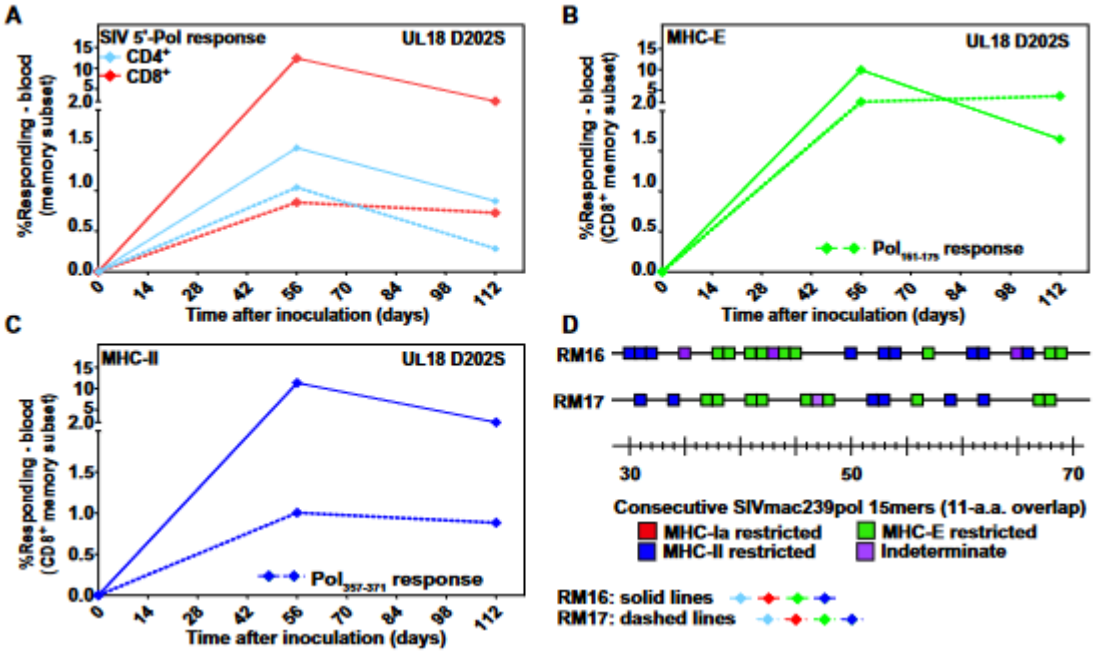
SIV-specific CD8+ T cell responses elicited by UL18- expressing 68-1 RhCMV recognize peptides presented by MHC-I

Malouli et al., (Sci Immunol. 2024)

UL18 mutants in LIR-1 interaction domain

- Viral homologue of MHC-I heavy chain
  - Forms trimeric complex with host beta2 microglobulin and peptide
  - Also binds to VL9 of UL40
- Structurally very similar to MHC-I, but highly glycosylated
  - Glycans prevent TCR interaction
- Ligand for leukocyte immunoglobulin-like receptor 1 (LIR1)
  - A.k.a. CD85j, LILRB1, ILT2, MIR7
  - Much higher affinity than natural HLA-I ligands
  - LIR1 is highly expressed in HCMV-specific T cells





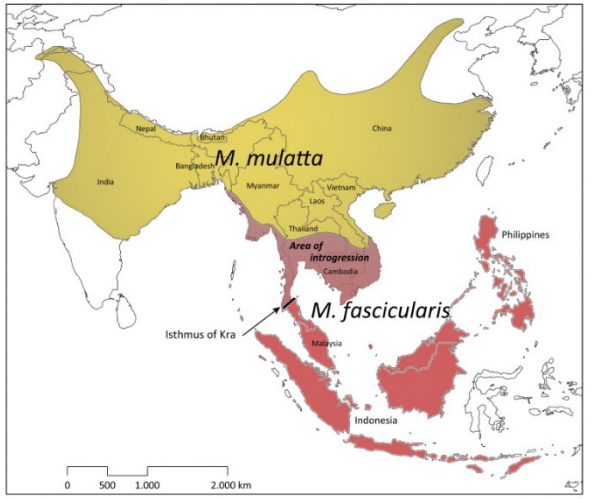
Malouli et al., (Sci Immunol. 2024)

Can we elicit MHC-E restricted CD8+ T-cell responses in another primate species?

Mauritian cynomolgus macaques (MCM)

- Probably of Indonesian origin **(Tosi & Coke, *Mol Phylogenet Evol,* 2007).**
- Likely introduced by Dutch or Portuguese sailors in the early 17th century **(Sussman & Tattersall, *Folia Primatologica,* 1986).**
- Founder population of ≈ 5 animals (4 male, 1 female)

  (Lawler et al., *Am J Phys Anthropol*, 1995).
- There are now over 75,000 cynomolgus macaques living on the island.



Haus et. al., Trends Genet. 2014 Nov;30(11):482-7.

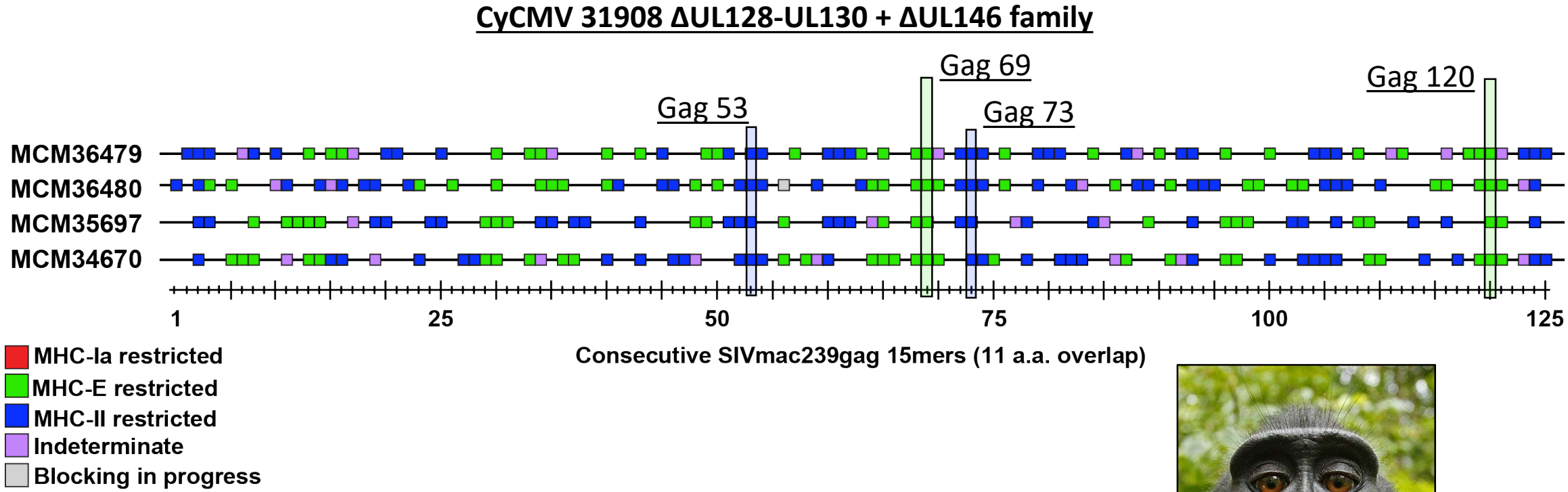
	# alleles identified (population)	Sequence identify (α1-α2)	# of alleles per individual
Human	2	99%	1-2
Rhesus macaque	33	88%	1-4
Mauritian cynomolgus macaque (M1-M3)	2	99%	1-2

The Journal of Immunology

The Role of MHC-E in T Cell Immunity Is Conserved among Humans, Rhesus Macaques, and Cynomolgus Macaques

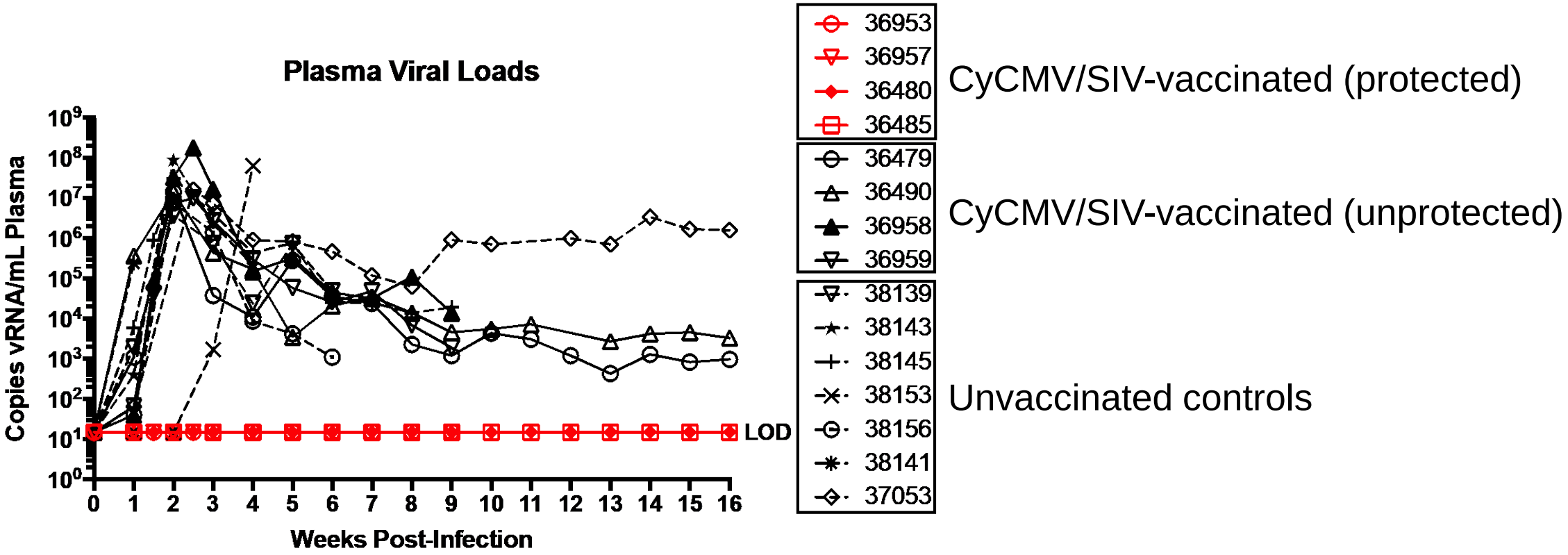
Helen L. Wu, Roger W. Wiseman, Colette M. Hughes, Gabriela M. Webb, Shaheed A. Abdulhaqq, Benjamin N. Bimber, Katherine B. Hammond, Jason S. Reed, Lina Gao, Benjamin J. Burwitz, Justin M. Greene, Fidel Ferrer, Alfred W. Legasse, Michael K. Axthelm, Byung S. Park, Simon Brackenridge, Nicholas J. Maness, Andrew J. McMichael, Louis J. Picker, David H. O'Connor, Scott G. Hansen and Jonah B. Sacha

Deletion of UL128, UL130 and all six UL146 family members enables CyCMV to elicit MHC-E restricted CD8+ T cells.



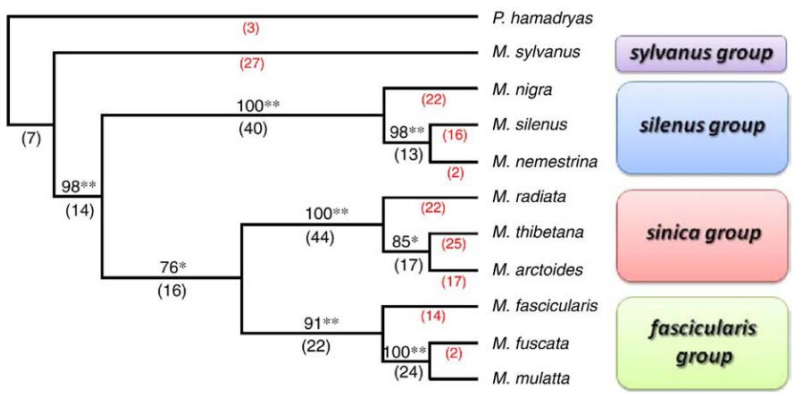
Malouli et al., (Cell Host Microbe. 2022)

CyCMV vectors capable of inducing MHC-E restricted immune responses protect 50% of MCM from repeated low dose SIV challenge.



CMV vectors can induce MHC-E restricted CD8+ T-cell responses in species-matched vaccination, but not in cross-species vaccination.

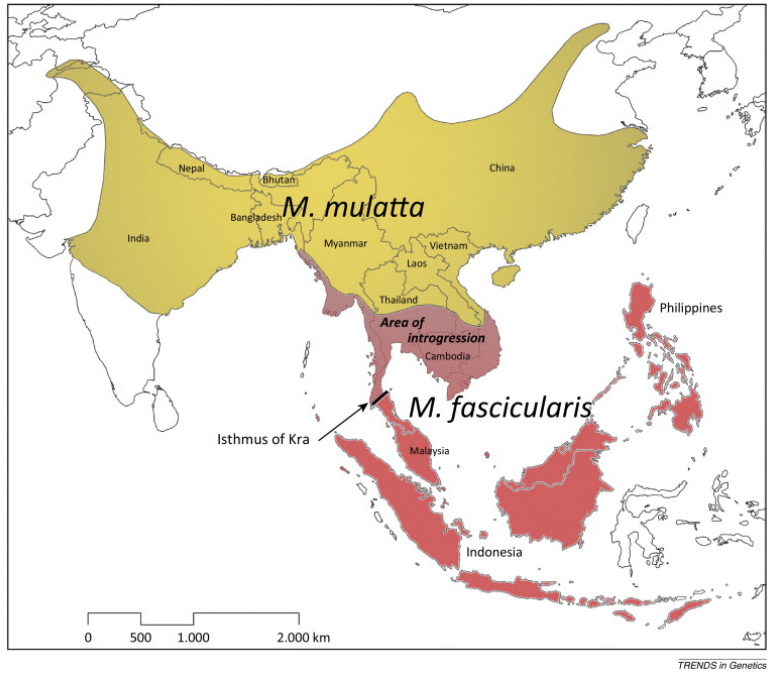
Li et al., Gene. 2009 Dec 15;448(2):242-9.



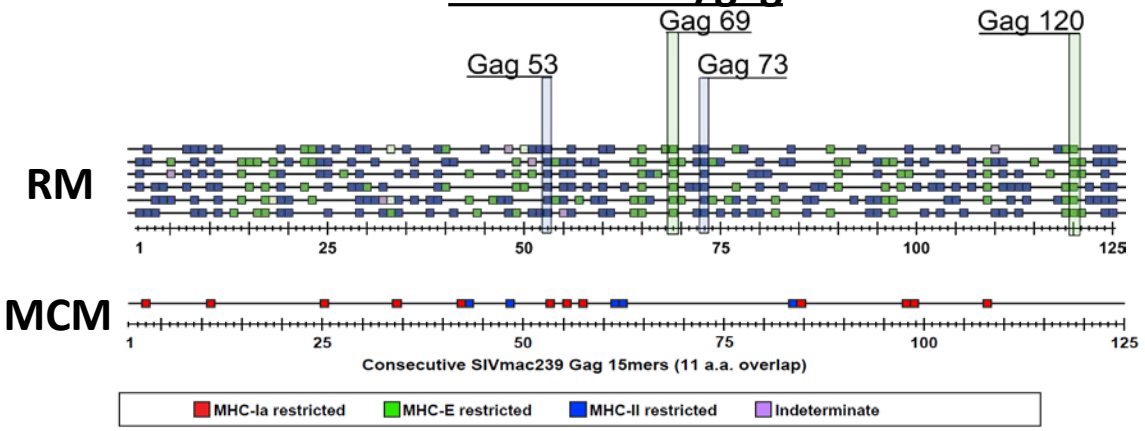
rhesus macaque

cynomolgus macaque

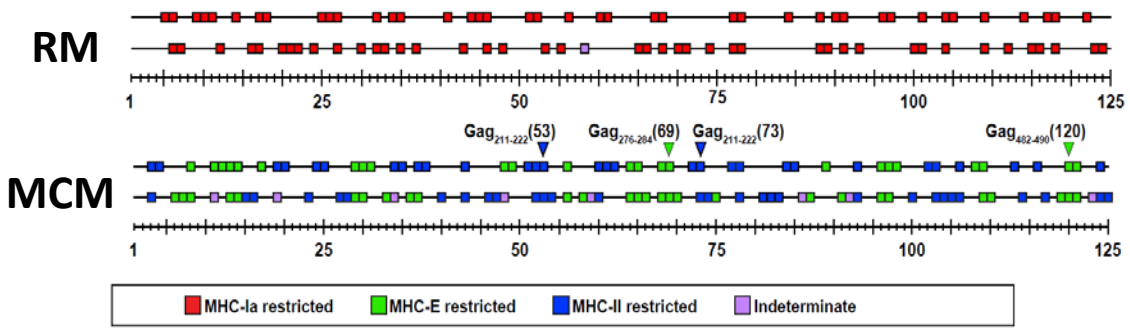
Haus et. al., Trends Genet. 2014 Nov;30(11):482-7.



RhCMV 68-1/gag

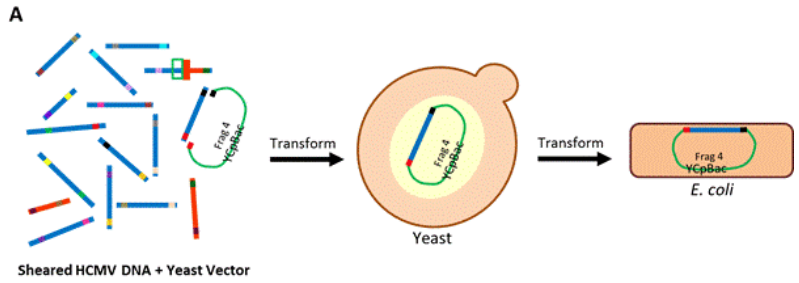


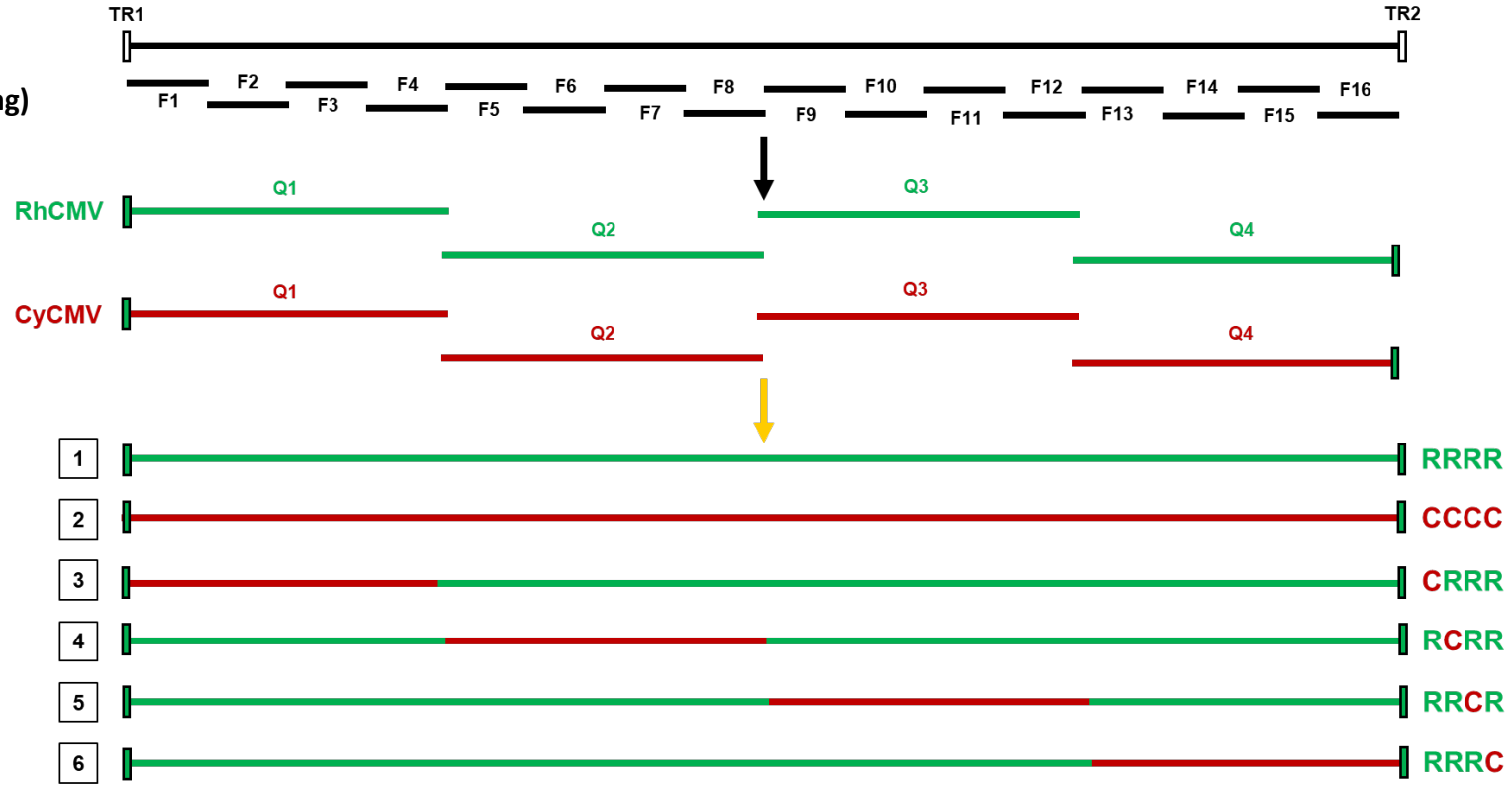
CyCMV "68-1"/gag



Cloning strategy to identify the species-specific factor required for the generation of MHC-E restricted T-cells.

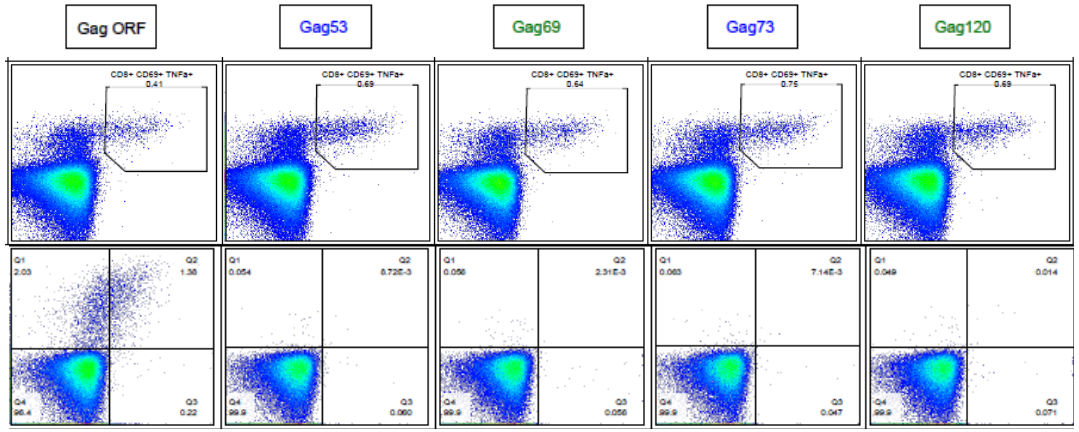
Yeast-Based Transformation-Associated Recombination (TAR cloning)





- These are the first CMV chimeras containing large genome segments from different species.
- All constructed chimeras reconstituted and replicated in primary rhesus fibroblasts.
- Infection of RhCMV+ rhesus macaques induced transgene specific T-cell responses.

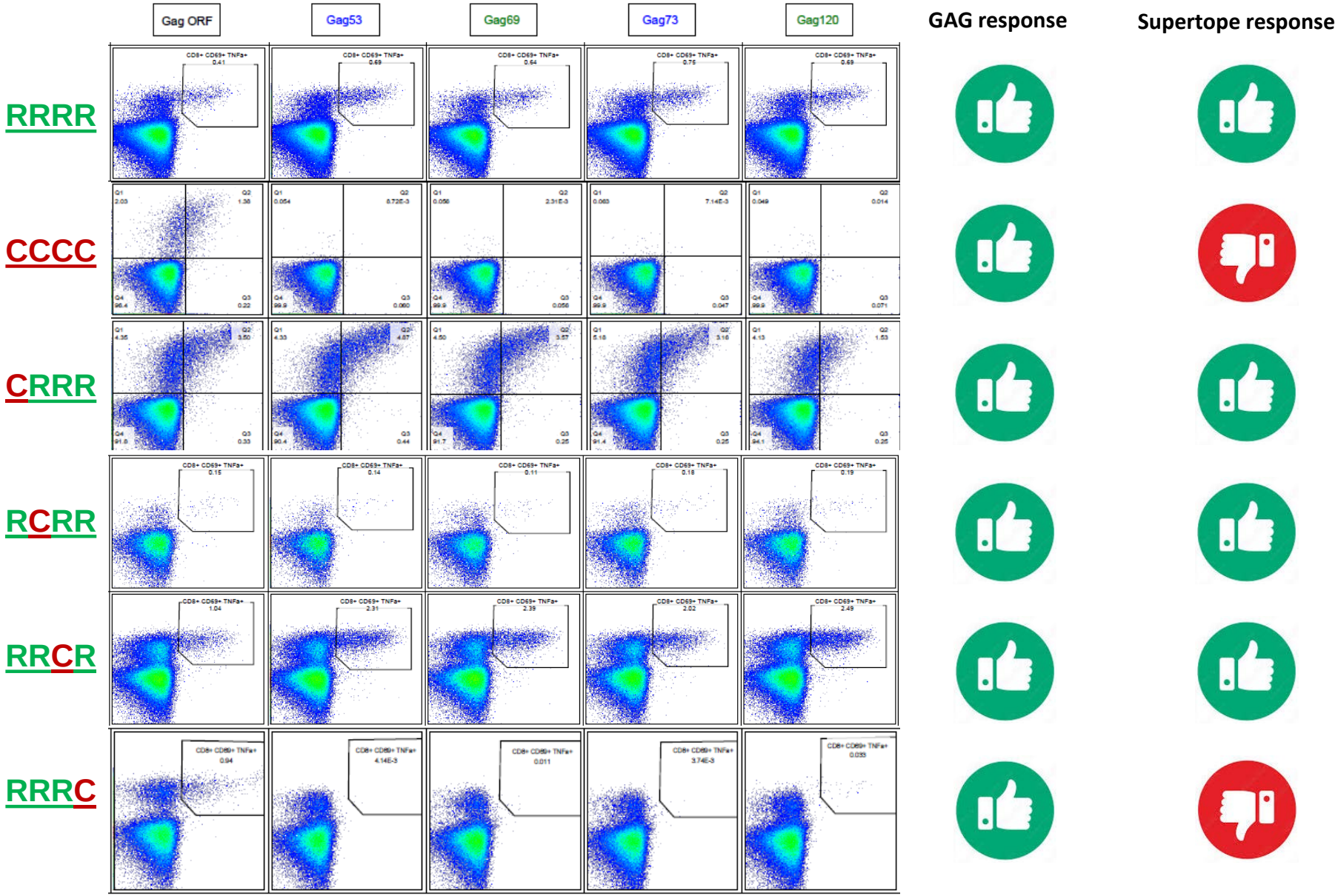
Infection of rhesus macaques with a RhCMV/CyCMV chimera containing a CyCMV 3’terminus does not induce MHC-E restricted CD8+ T-cell responses.



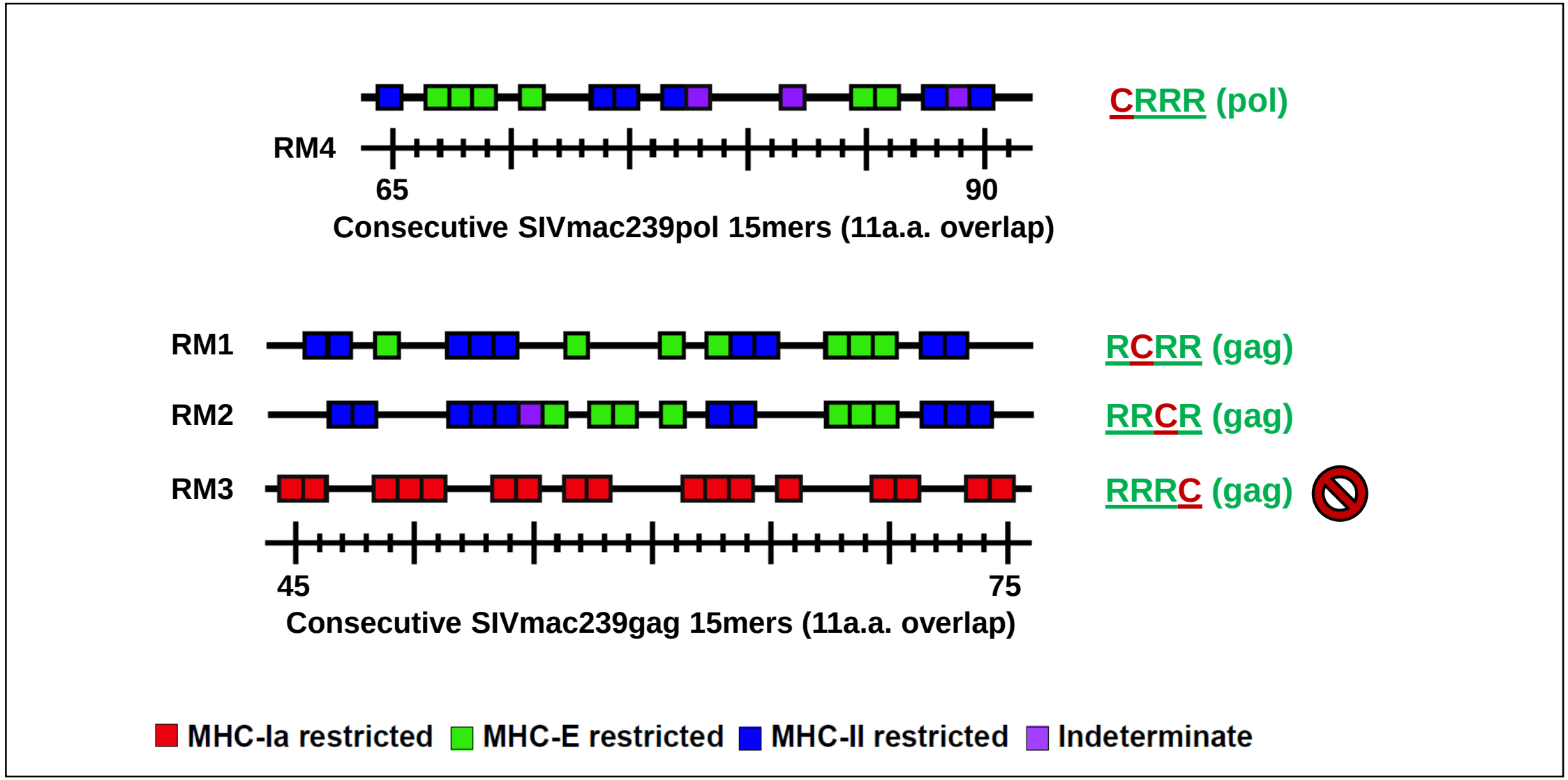
GAG response

Supertope response

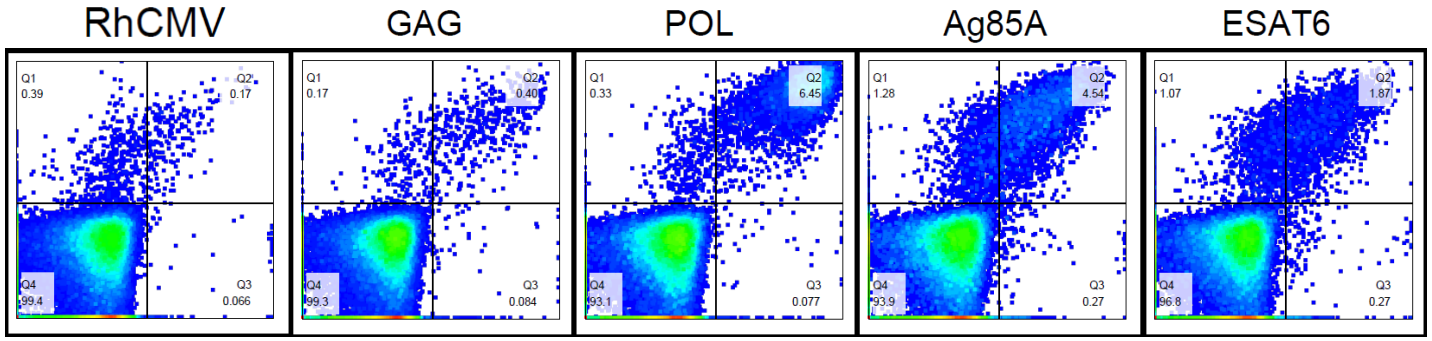
Infection of rhesus macaques with a RhCMV/CyCMV chimera containing a CyCMV 3’terminus does not induce MHC-E restricted CD8+ T-cell responses.



Deconvolution of the transgene-specific CD8+ T-cell responses.



But, the RhCMV/CyCMV chimera RRRC can induce MHC-E restricted CD8+ T-cells in cynomolgus macaques.

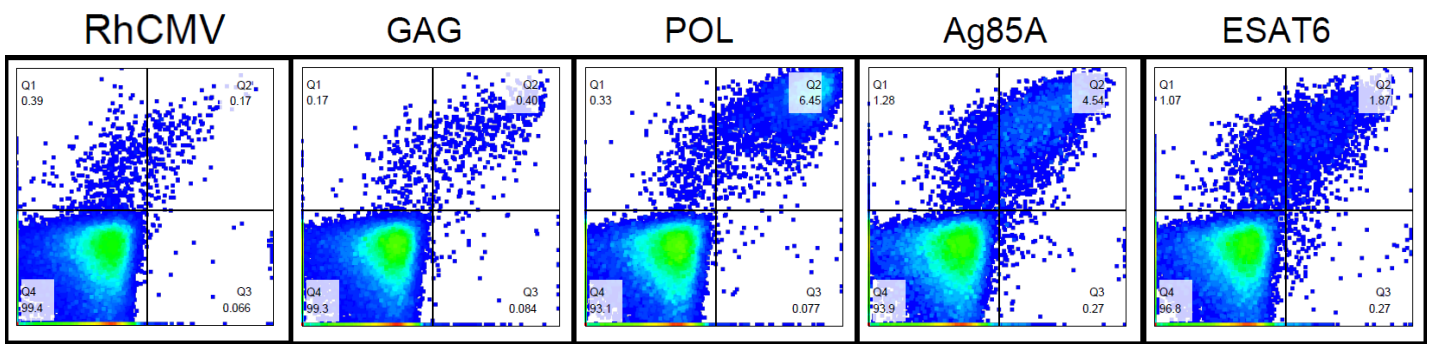


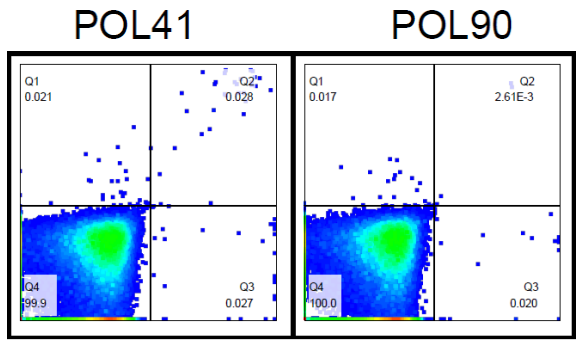
CRRR
(pol)

RCRR
(Ag85A/Esat-6)

RRRC
(gag)

But, the RhCMV/CyCMV chimera RRRC can induce MHC-E restricted CD8+ T-cells in cynomolgus macaques.





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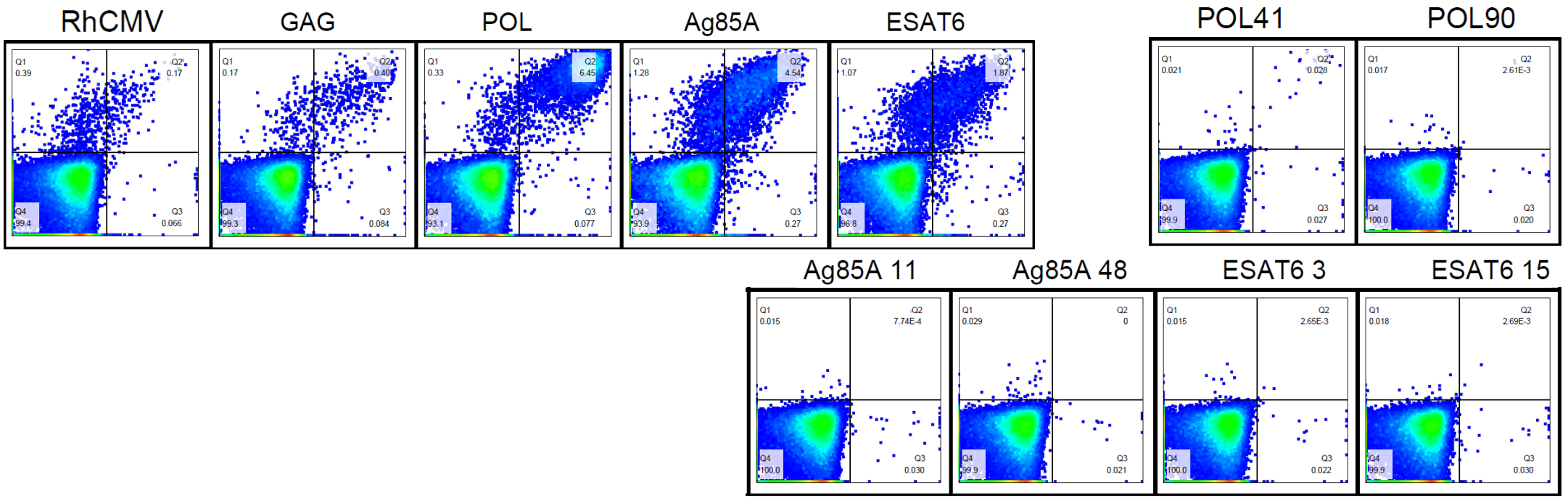

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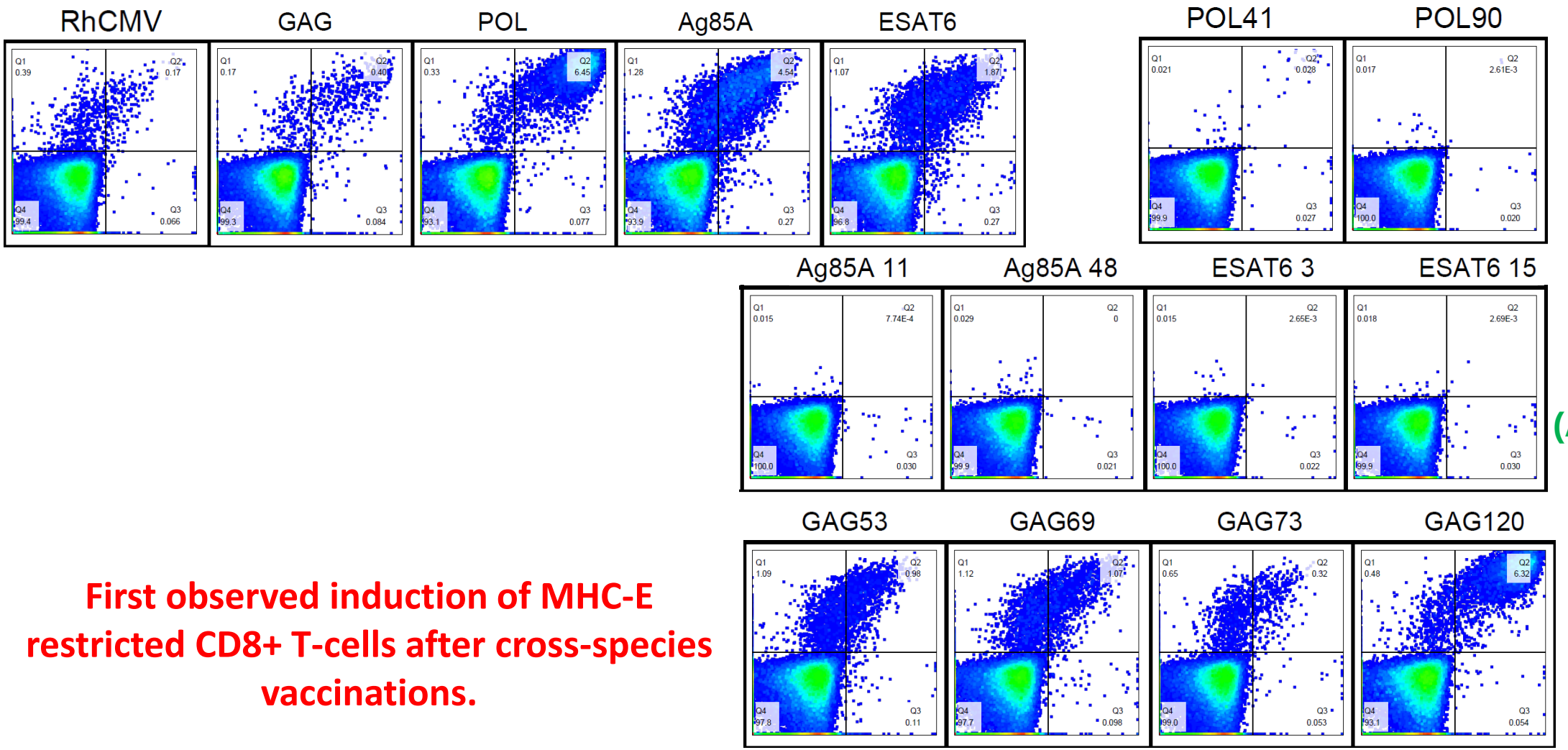


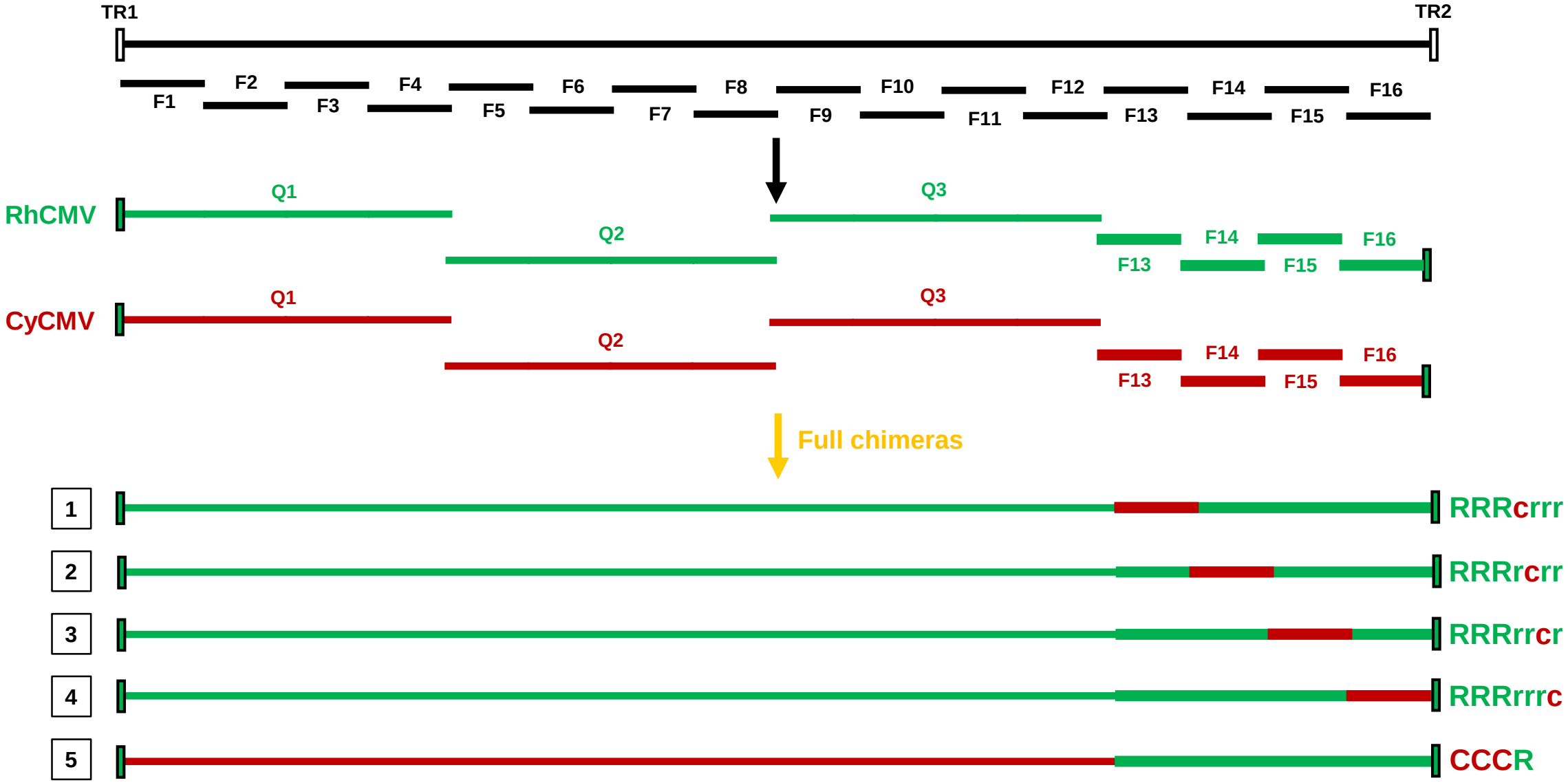
CRRR
(pol)

RCRR
(Ag85A/Esat-6)

RRRC
(gag)

First observed induction of MHC-E restricted CD8+ T-cells after cross-species vaccinations.

Cloning strategy to construct further RhCMV/CyCMV chimeras to map the species-specific factor needed to induce MHC-E restricted CD8+ T-cells.



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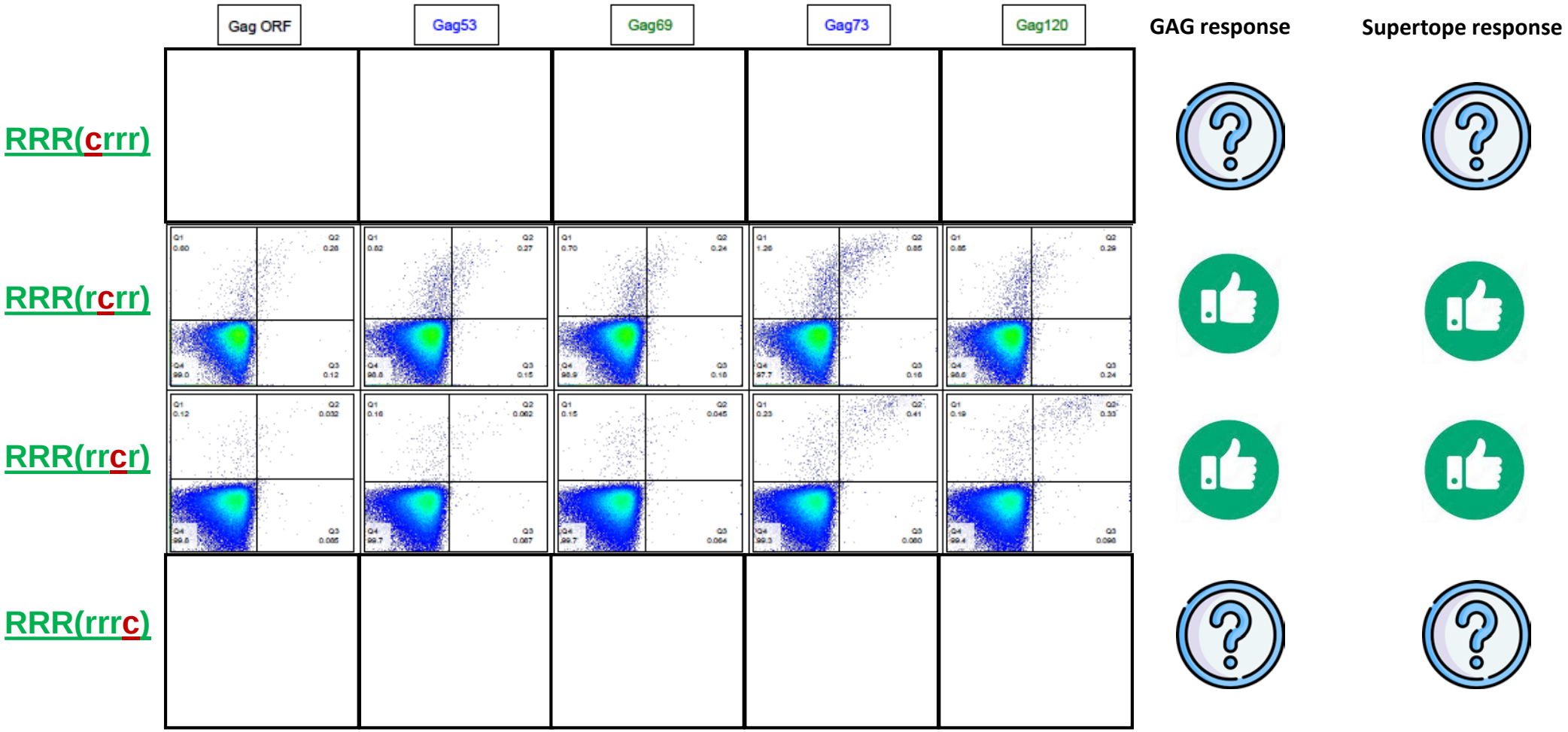
The chimeras tested so far still induced MHC-E restricted CD8+ T-cell responses in rhesus macaques.



Conclusions

- We have established CMVs as a novel vaccine vector platform.
  - **Protection from SIV challenge in 55% of the animals.** (Hansen at al., Nature. 2013)
  - **Reduced the overall *Mtb* disease by 68% with 41% of all animals showing no clinical signs of disease.** (Hansen at al., Nat Med . 2018)
  - **Protection from heterologous Influenza H5N1 challenge in more than half the animals.** Malouli et al., (Nat Commun. 2024)
  - **Delayed the appearance of *Plasmodium knowlesi* blood stage parasites.** (Hansen et al., PLoS One. 2019)
  - **Can elicit T cell responses to self-antigens in cancer models.** (Iyer et al., Sci Adv . 2024)

- In our SIV challenge model, the observed protection provided by our RhCMV vectors is dependent on the induction of HLA-E restricted CD8+ T-cell responses.

- Induction of these responses requires appropriate vector design, as RhCMV encodes for proteins needed for their generation as well as various inhibitors.
  - These genes are conserved in HCMV and can function in rhesus macaques when inserted into RhCMV.

- Yet, so far, we have not observed HLA-restricted responses using an HCMV vectors (VIR-1111) in humans.
  - VIR-1388 is currently being evaluated in a Phase I human clinical trial.

- But, we have demonstrated that CyCMV can induce HLA-E responses in cynomolgus macaques, indicating a conserved ability across primate CMVs.

- And we have identified a mechanism that could allows us to determined whether HCMV can induce these responses in rhesus macaques.
  - Alternatively, it might allow us to use RhCMV in humans.

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- Christine Meyer
- Nessy John
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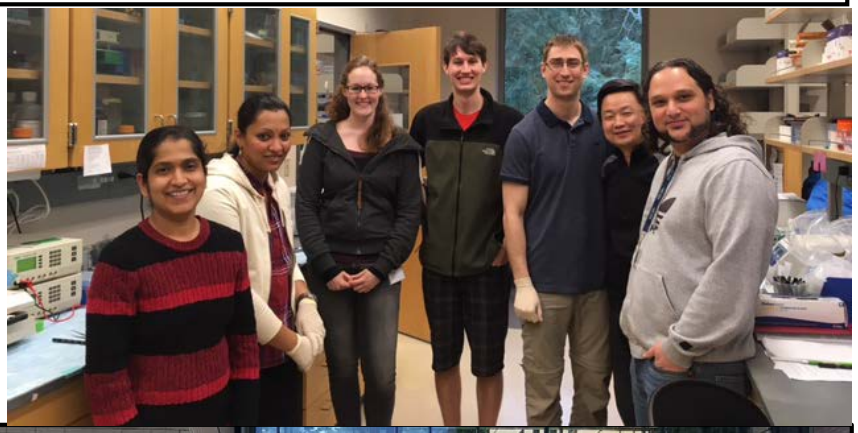
- Linh Khan Nguyen



OHSU has licensed CMV technology, of which Dr. Malouli is an inventor, to VIR Biotechnology, a company in which both OHSU and Dr. Malouli have significant financial interest. Potential individual and institutional conflicts of interest have been reviewed and are actively managed by OSHU.