New Science Enabled by New Partnering Mechanisms or…. Monkey Business at Frederick National Lab

Jeffrey D. Lifson, MD
AIDS and Cancer Virus Program
SAIC Frederick, Inc.
Frederick National Laboratory

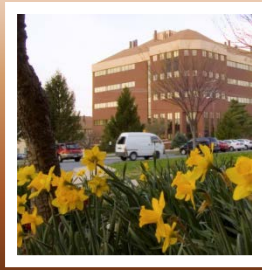
Presentation for the NCI-Frederick Advisory Committee

24 September 2013

Frederick National Laboratory

SAIC Frederick

AIDS and Cancer Virus Program



AIDS and Cancer Virus Program

Expanding ACVP Core Support of the Extramural Community

- Contractor M-CRADA mechanism to allow cost recovery should allow expansion of support to extramural community
- Will require new administrative procedures

FROM PRESENTATION TO NFAC, 25 JANUARY 2012

CRADAs: They're Not Just for NCI Anymore

Advancing scientific discovery is increasingly dependent on diverse and innovative partnerships, and the Cooperative Research and Development Agreement (CRADA) is an essential tool for establishing partnerships. CRADAs allow a federal laboratory to enter into collaborative research and development (R&D) projects with outside parties (commercial or nonprofit).

CRADAs have been successfully used at NCI for more than two decades, and they have led to several effective products, including Avastin (for certain types of colorectal, lung, and renal cancer, as well as glioblastoma) and Velcade (for multiple myeloma).

As the contractor operating a government-owned, contractoroperated facility like the Frederick National Laboratory for Cancer Research (FNLCR), SAIC-Frederick also has the legal authority to engage in CRADAs, but to date has not had an official program for CRADAs.

New c-CRADA Allows Contractor to Partner Independently

Recently, administrative staff from both SAIC-Frederick and NCI received approval for the contractual and policy modifications necessary to launch a contractor CRADA (c-CRADA) program at FNLCR.

Under the c-CRADA, SAIC-Frederick initiates and manages CRADA projects that do not involve direct participation from NCI staff in the research. Procedures have been established to effectively identify potential c-CRADA partners, develop the prospective c-CRADA project with the partner, review and approve the c-CRADA, and monitor the progress of the R&D project. Under these agreements, NIH CRADA subcommittee approval is not required; instead, c-CRADAs are approved locally by the NCI contracting officer, with input from the NCI technology transfer and program staff.

The new c-CRADA program was established to enhance partnering opportunities highlighting the contractor's unique capabilities at FNLCR. These unique capabilities and the construction of the Advanced Technology Research Facility (ATRF), whose primary function is to foster partnerships, are the driving forces behind the c-CRADA program.

New FNL Partnering Mechanisms

Technical Services Agreement (TSA)

Streamlined agreements executed under CRADA statute allow FNL labs to provide well-defined, established but unique research services to the scientific community. Pre-approved services are authorized by Contracting Office.

Contractor Cooperative R & D Agreement (cCRADA)

Individual agreements involve research collaborations with intellectual and material contributions by FNL scientists and external partner(s), with no participation in the joint work scope by government personnel. Useful for projects of significant scope and duration, especially translational research and technology development, with defined resource commitments and future intellectual property considerations.

Contractor Cooperative Research and Development Agreements (cCRADAs) at FNL

- **Processes established for proposal generation, review and approval**

- **Three cCRADAs executed:**

  “Evaluation of Adjunctive Antifibrotic Therapy in SIV Infected Rhesus Macaques”
  Dr. T. Schacker, U. Minn -- Dr. J. Lifson, ACVP/FNL

  “Overcoming host restriction factors to develop better animal models for HIV/AIDS”
  Dr. T. Hatziioannou, ADARC -- Dr. J. Lifson, ACVP/FNL

  “Screening and Pilot Production of Recombinant Proteins for Early Discovery”
  Dr. T Harris, Biogen Idec MA, Inc. -- Dr. D. Esposito, PEL/FNL

- **Additional agreements in process**

Technical Service Agreements (TSAs) at FNL

- **Processes developed for proposal, review, approval of new TSAs**

- **23 different TSA services on approved list; additional ones pending**

- **“Blanket TSA” mechanism allows ongoing users to efficiently utilize available services according to need, with minimal “administrative viscosity”**

- **59 different TSAs executed to date; more pending**

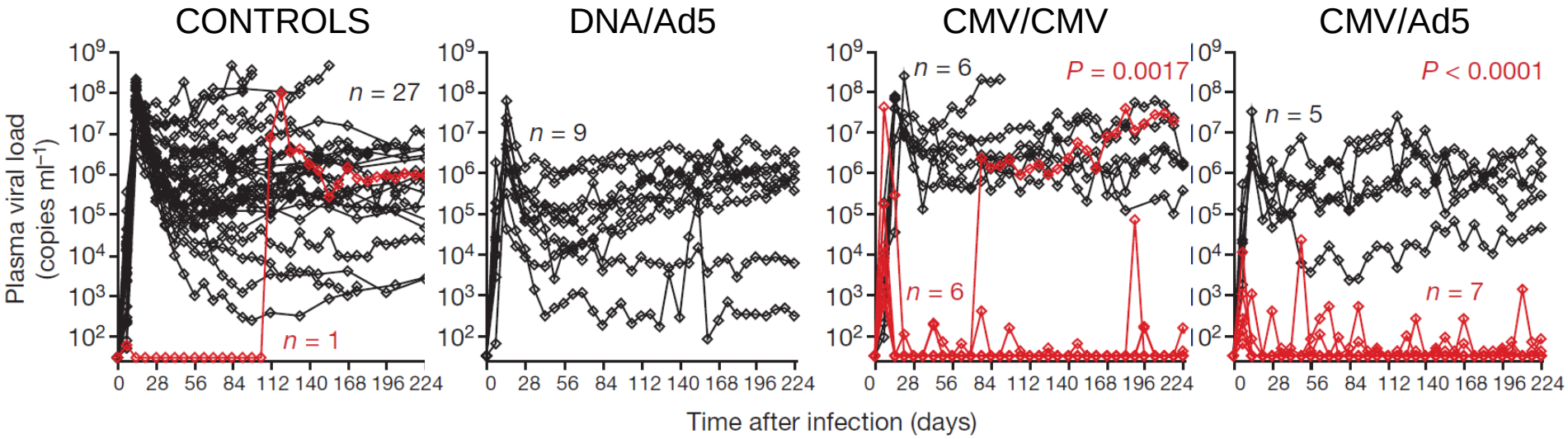
Rh-CMV/SIV Vaccine Generates Distinctive Immune Responses and Mediates Unusual, Profound Control of Pathogenic SIV Infection

nature

26 MAY 2011 | VOL 473 | NATURE | 523

Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine

Scott G. Hansen[1], Julia C. Ford[1], Matthew S. Lewis[1], Abigail B. Ventura[1], Colette M. Hughes[1], Lia Coyne-Johnson[1], Nathan Whizin[1], Kelli Oswald[2], Rebecca Shoemaker[2], Tonya Swanson[1], Alfred W. Legasse[1], Maria J. Chiuchiolo[3], Christopher L. Parks[3], Michael K. Axthelm[1], Jay A. Nelson[1], Michael A. Jarvis[1], Michael Piatak Jr[2], Jeffrey D. Lifson[2] & Louis J. Picker[1]



Rh-CMV/SIV Vaccines: What We Knew Then

- **Negligible Ab responses but extremely broad T_{EM} biased virus specific responses by $CD4^+$ and $CD8^+$ T cells, missing canonical MHC-I restricted immunodominant responses**

- **Responses broadly tissue distributed and indefinitely persistent; protection at portal of entry?**

- **Durable stringent control of highly pathogenic SIVmac239 infection in ~50% of animals after i.r. challenge, with initial infection confirmed virologically and immunologically**

Rh-CMV/SIV Vaccines: What We Have Learned Since Then

- Immune responses
- Vaccine protection
- Implications and applications

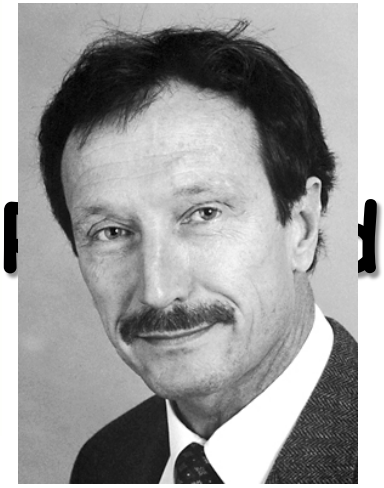
Science

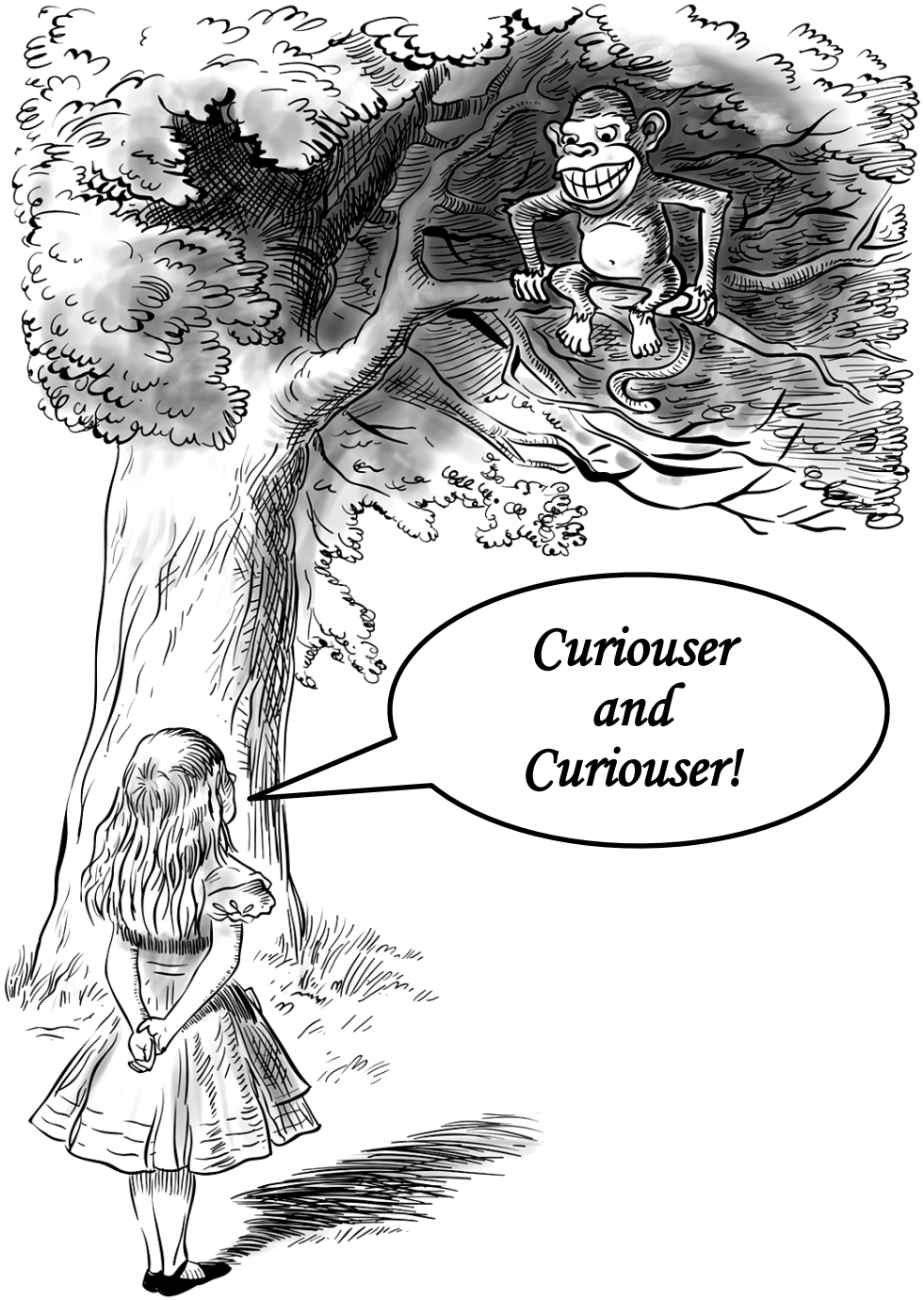
RESEARCH ARTICLE

VOL 340 24 MAY 2013

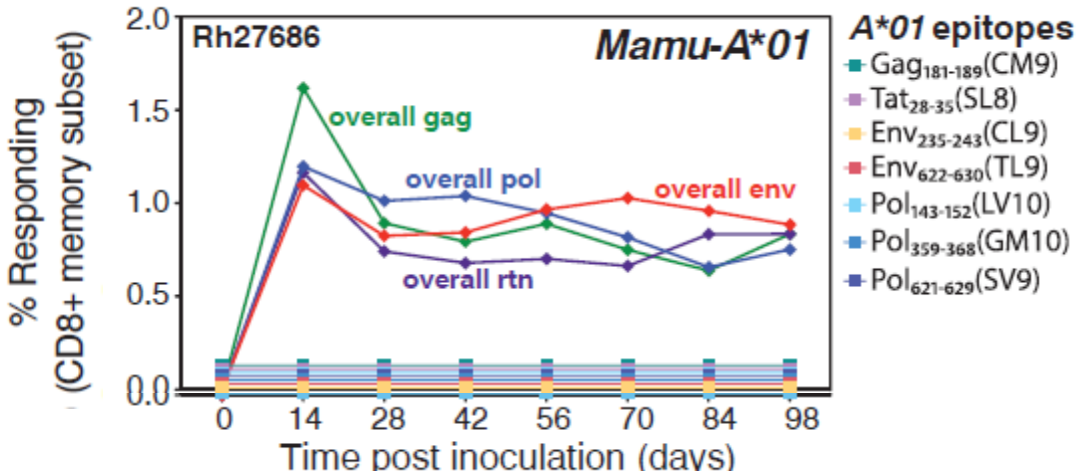
Cytomegalovirus Vectors Violate CD8+ T Cell Epitope Recognition Paradigms

Scott G. Hansen,[1] Jonah B. Sacha,[1] Colette M. Hughes,[1] Julia C. Ford,[1] Benjamin J. Burwitz,[1] Isabel Scholz,[1] Roxanne M. Gilbride,[1] Matthew S. Lewis,[1] Awbrey N. Gilliam,[1] Abigail B. Ventura,[1] Daniel Malouli,[1] Guangwu Xu,[1] Rebecca Richards,[1] Nathan Whizin,[1] Jason S. Reed,[1] Katherine B. Hammond,[1] Miranda Fischer,[1] John M. Turner,[1] Alfred W. Legasse,[1] Michael K. Axthelm,[1] Paul T. Edlefsen,[2] Jay A. Nelson,[1] Jeffrey D. Lifson,[3] Klaus Früh,[1] Louis J. Picker[1]*

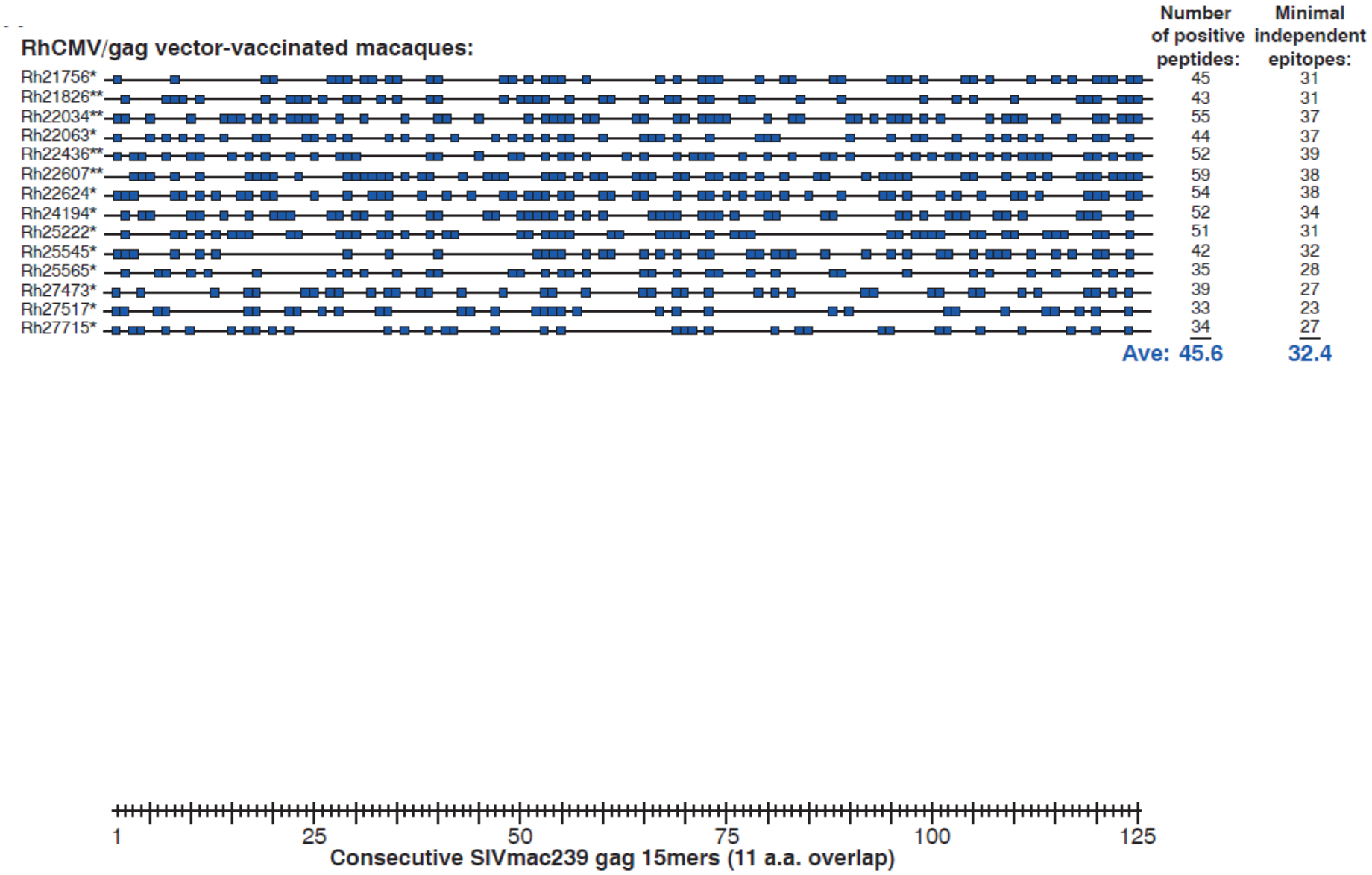



Curiouser
and
Curiouser!

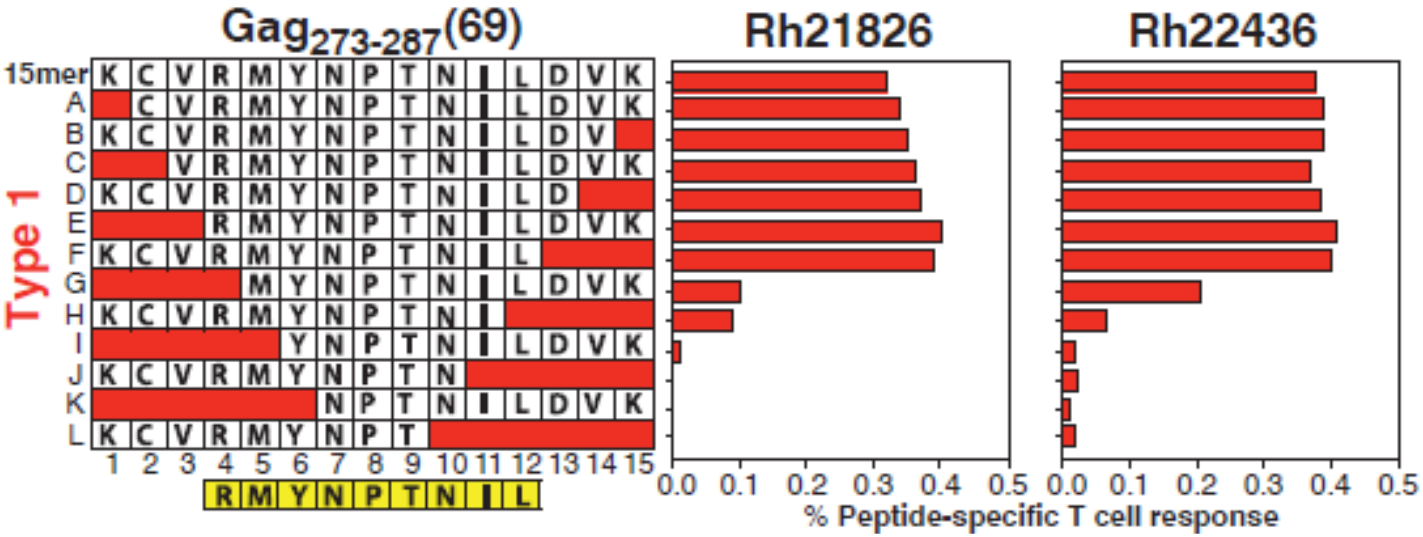
Rh-CMV/SIV Induced CD8+T Cell Responses Do Not Overlap with Conventional Anti-SIV CD8 Responses



Extraordinary Epitope Breadth of Rh-CMV/SIV Induced CD8+T Cell Responses

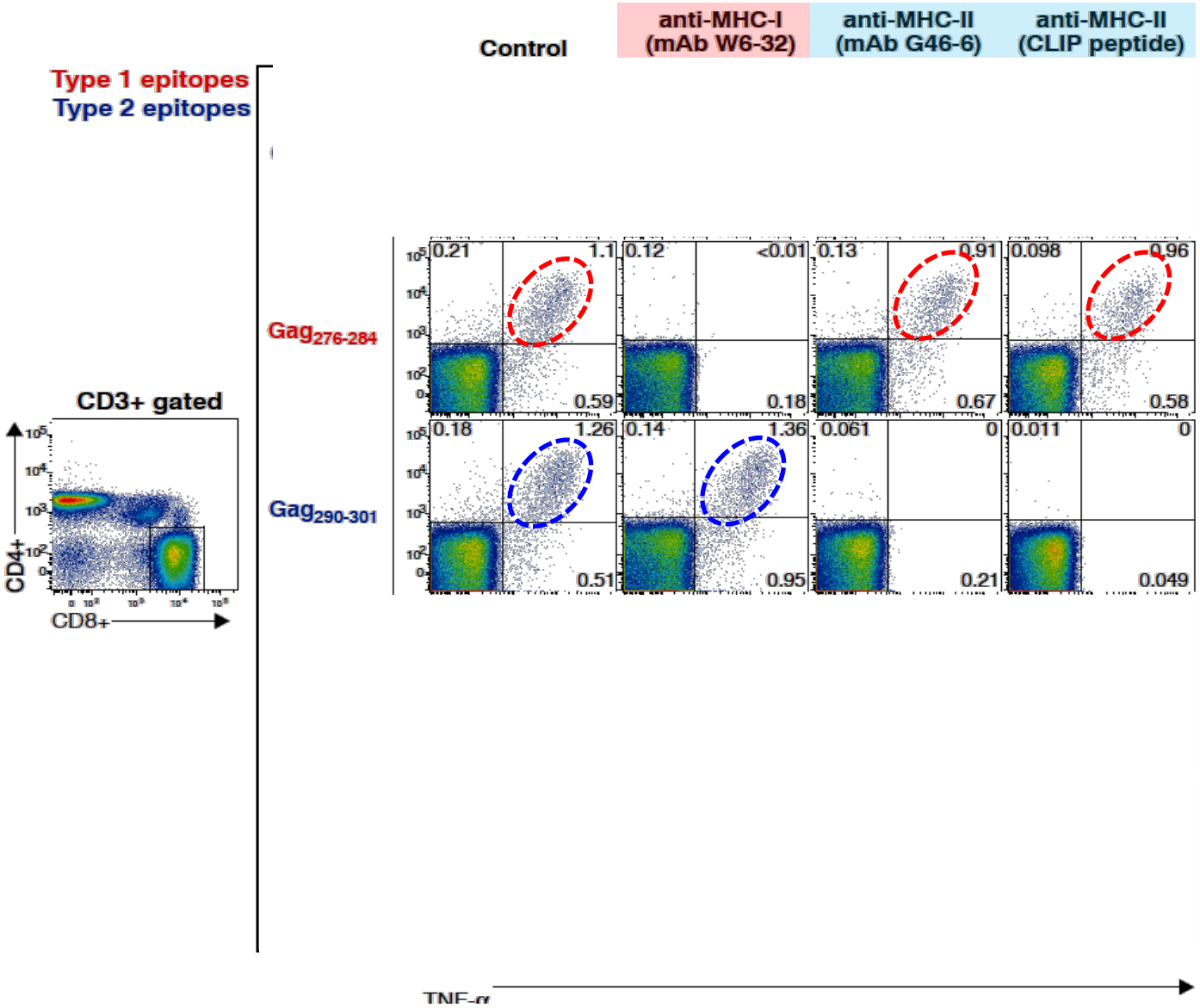


Rh-CMV/SIV Induced CD8+T Cell Responses Show Unusual Optimal Epitope Peptide Length



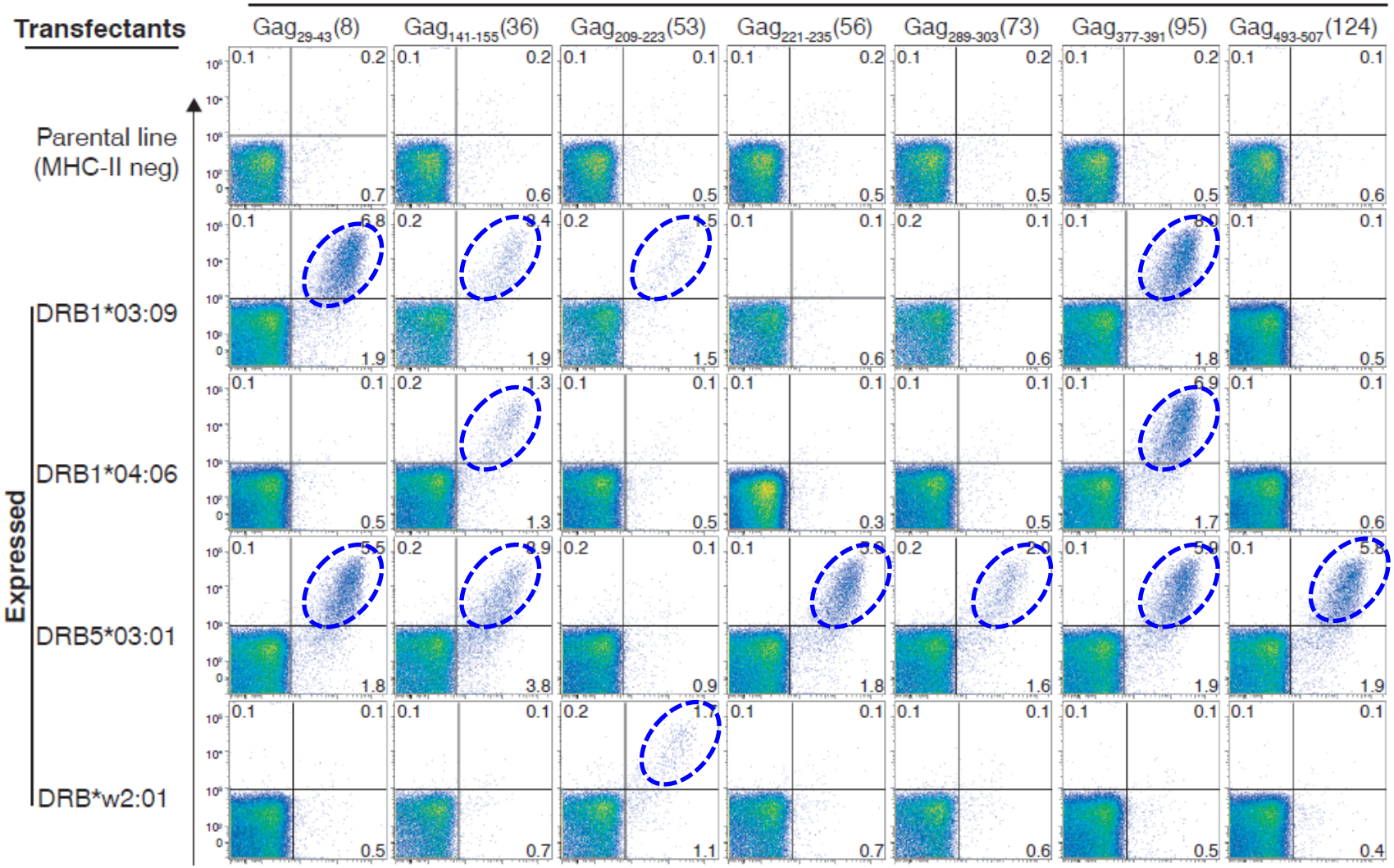
~ 1/3

Unusual MHC Restriction of Most Rh-CMV/SIV Induced CD8+T Cell Responses



Supertopes and Promiscuity:

Multiple MHC II Allomorphs Can Present the Same Optimal Type II Epitope Peptide, and the Same MHC II Allomorph Can Present Different Type II Epitope Peptides for Rh-CMV/SIV Induced CD8+T Cell Responses



Unusual Properties of CD8+ T Cell Responses to Rh-CMV/SIV Vaccines Are Likely Related to Vector Dependent Variant Pattern of Ag Presentation

- **Rh-CMV strain used for vaccine (68.1) is "wild type", not wild type (fibroblast passage)**

- **Rh189 *(US11) when present*, prevents recognition of canonical MHC-I restricted immunodominant epitopes, not solely through MHC-I downregulation**

- **Rh157.5, Rh157.4, and Rh157.6 *(UL128, UL130, and UL131) when absent*, allow responses to highly promiscuous unconventional epitopes (MHC II restricted), likely due to alteration of host cell tropism and resulting antigen presentation**

- **Engineering vectors based on these properties may allow tailoring of desired vaccine induced responses**

LETTER

nature

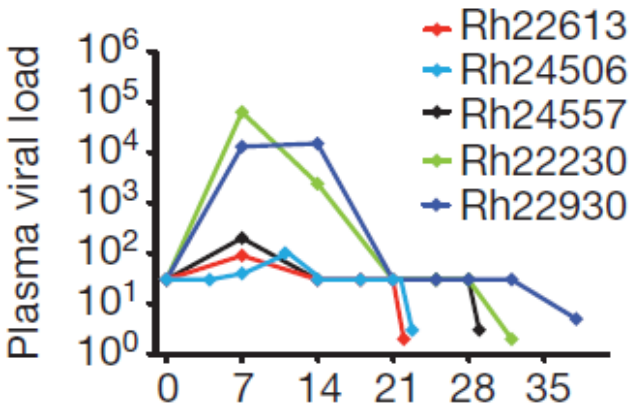
doi:10.1038/nature12519

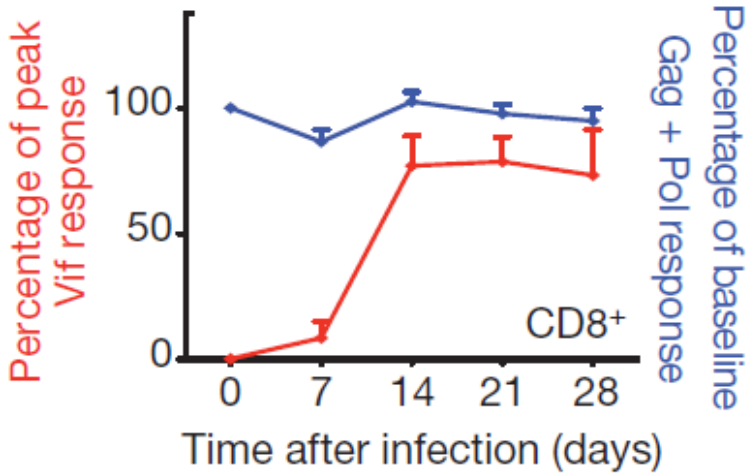
Immune clearance of highly pathogenic SIV infection

Scott G. Hansen[1]*, Michael Piatak Jr[2]*, Abigail B. Ventura[1], Colette M. Hughes[1], Roxanne M. Gilbride[1], Julia C. Ford[1], Kelli Oswald[2], Rebecca Shoemaker[2], Yuan Li[2], Matthew S. Lewis[1], Awbrey N. Gilliam[1], Guangwu Xu[1], Nathan Whizin[1], Benjamin J. Burwitz[1], Shannon L. Planer[1], John M. Turner[1], Alfred W. Legasse[1], Michael K. Axthelm[1], Jay A. Nelson[1], Klaus Früh[1], Jonah B. Sacha[1], Jacob D. Estes[2], Brandon F. Keele[2], Paul T. Edlefsen[3], Jeffrey D. Lifson[2] & Louis J. Picker[1]

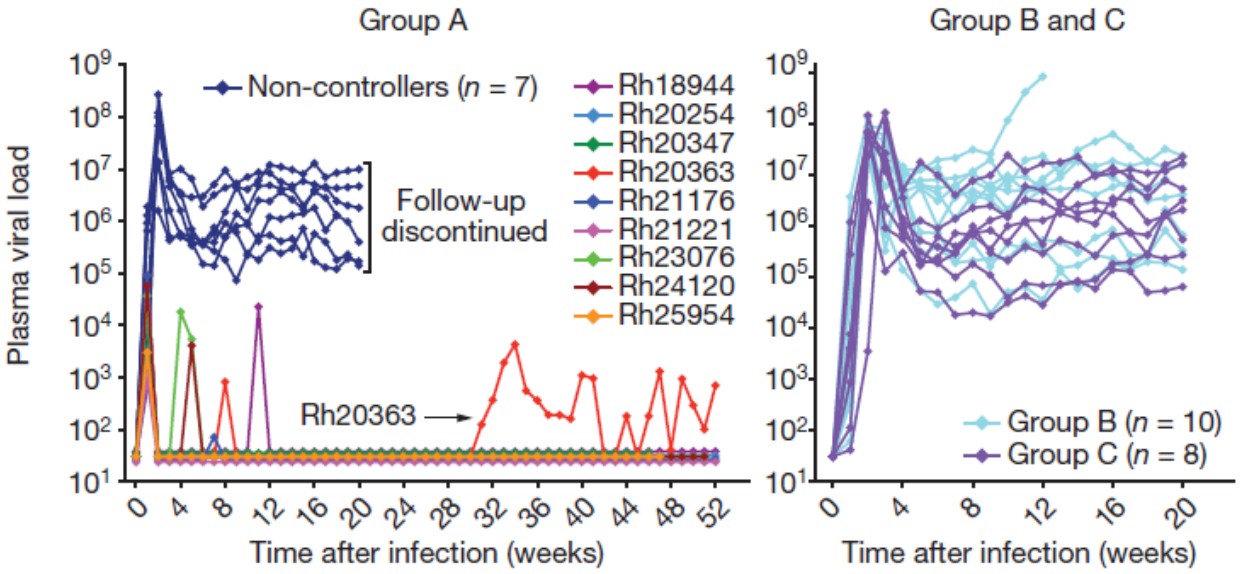
- **Viral control after i.r, i.vag., and i.v. challenge**
- **Control established over disseminated infection, not just at portal of entry**
- **Progressive clearance of virus over time, including from tissue sites**
- **“Functional cure” and apparent eradication in protected animals**

Rh-CMV/SIV Protected Animals Show Virologic and Immunologic Evidence of Infection in Blood and Tissues



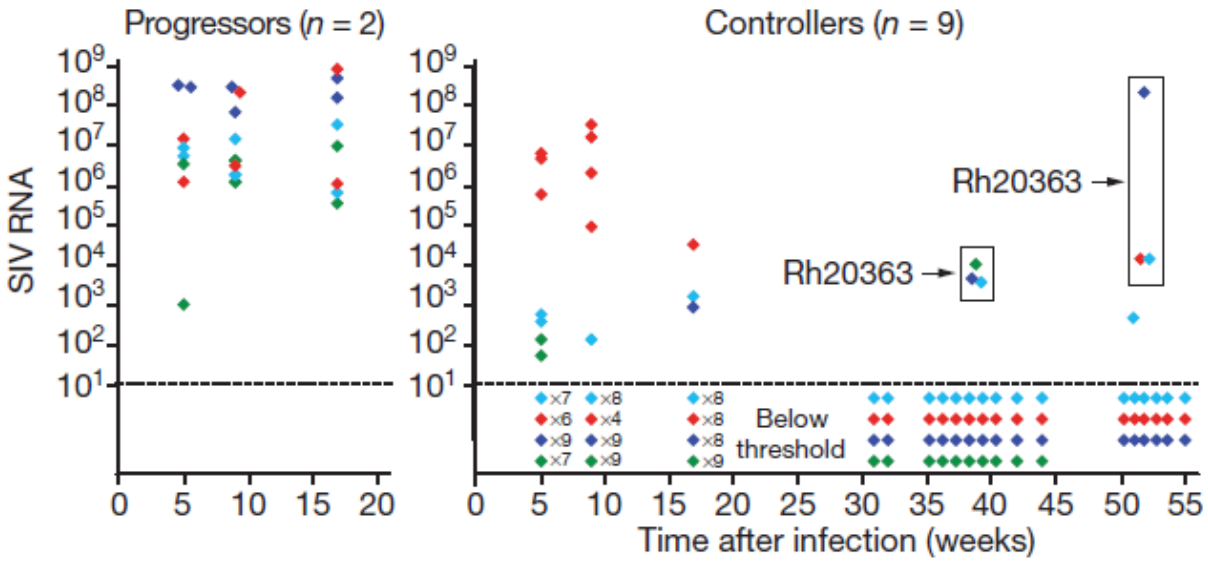


Longitudinal Analysis of Rh-CMV/SIV Mediated Protection After Intravaginal Infection



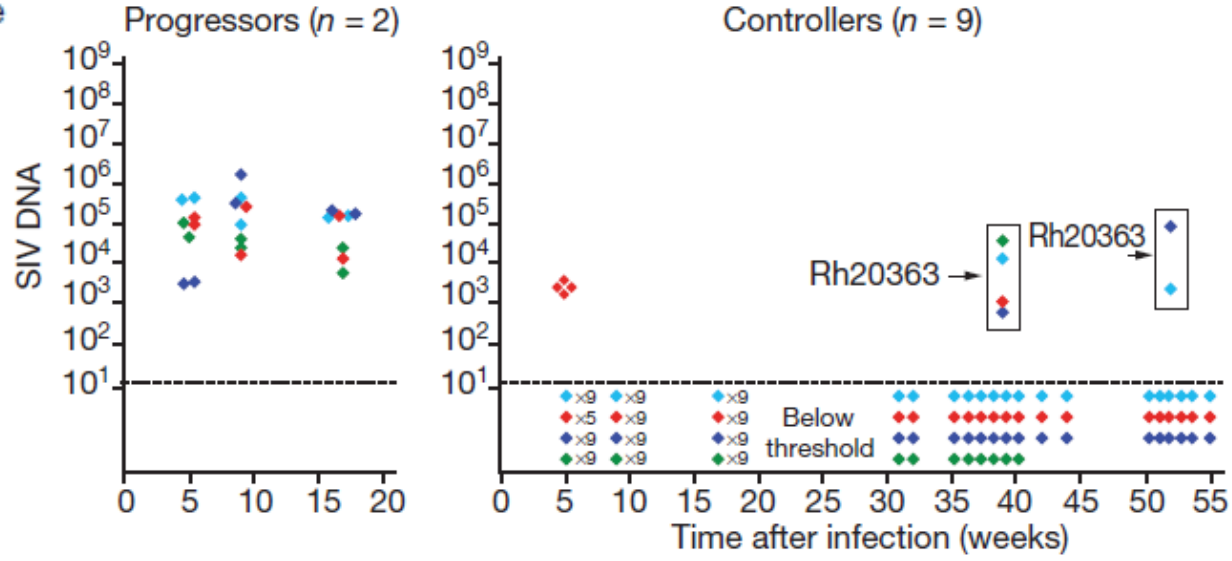
Longitudinal Analysis of Rh-CMV/SIV Mediated Protection After Intravaginal Infection: Tissue Viral Load

SIV RNA

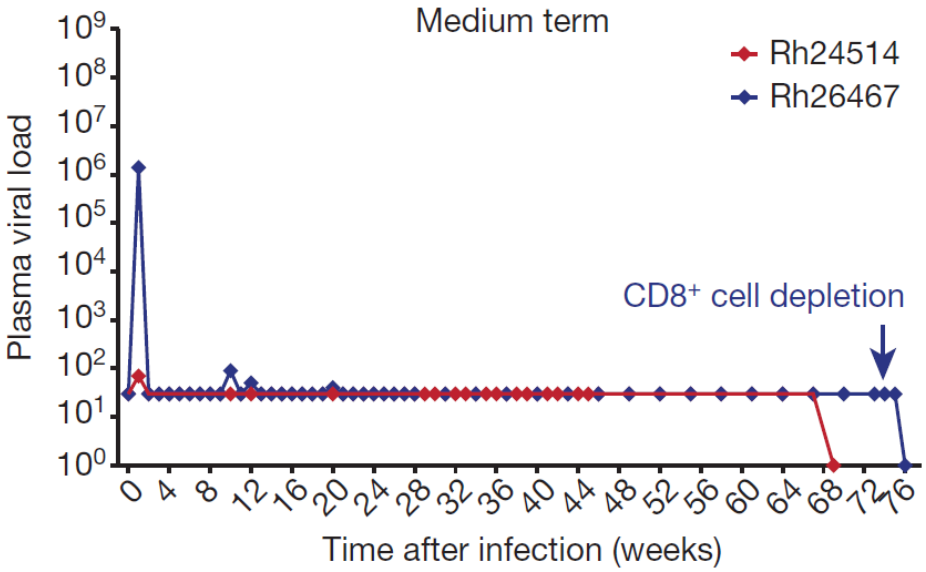


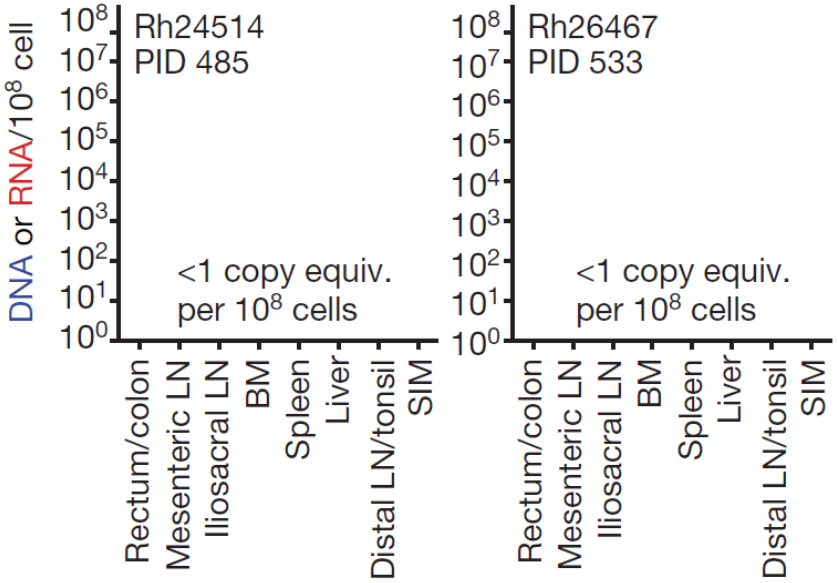
- PBMC
- Bone marrow
- Lymph node
- Small intestine mucosa

SIV DNA

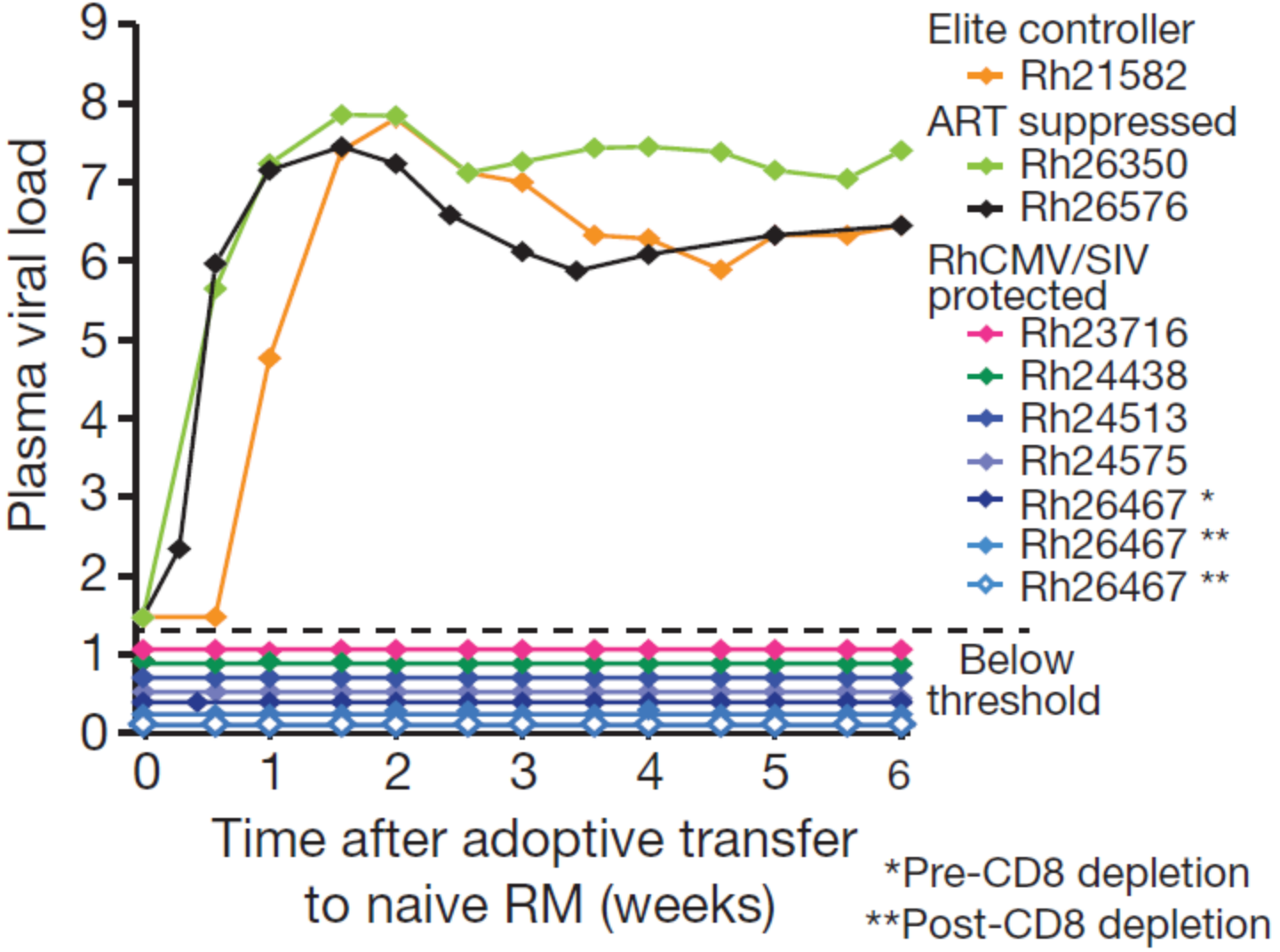


Analysis of Medium Term Rh-CMV/SIV Mediated Protection





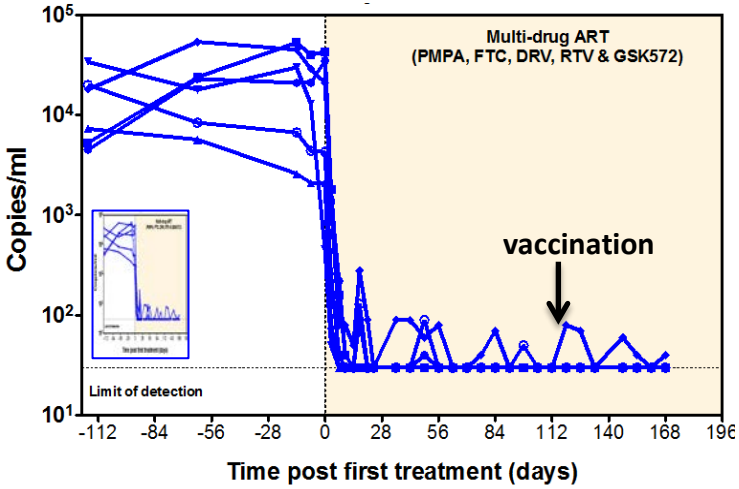
Adoptive Transfer to Naïve Hosts: No Evidence of Residual Infectious Virus



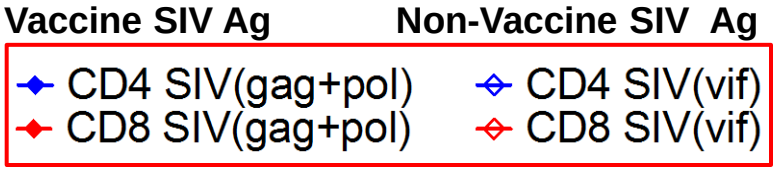
Rh-CMV/SIV Vaccines: Summary/Future

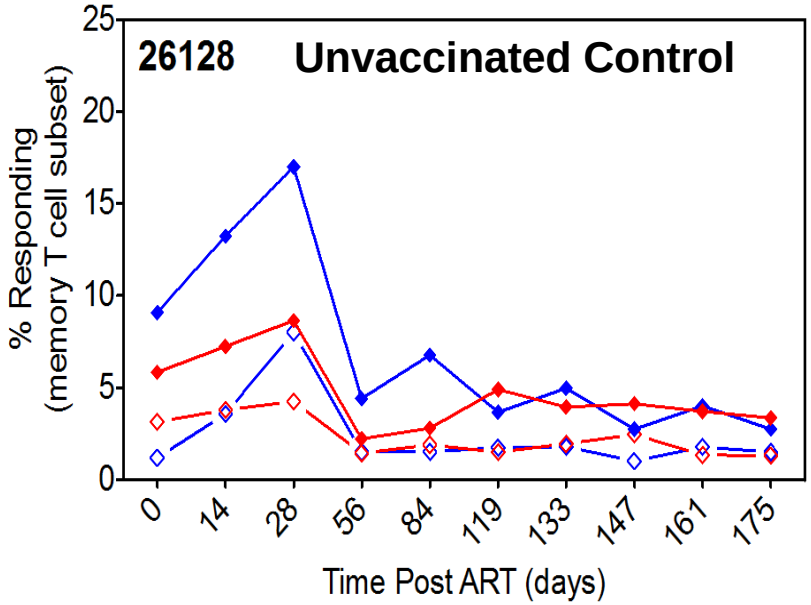
- Unusual immunology
- Control after infection via i.r., i.vag, and i.v. routes
- Control of infection disseminated to tissues, not just portal of entry
- Indefinitely persistent immune surveillance associated with progressive viral clearance to functional cure, apparent eradication
- Extremely broad epitope coverage, targeting epitopes not recognized in natural infection, including promiscuous supertopes, provides advantages for both prophylactic and therapeutic vaccination
- Future plans

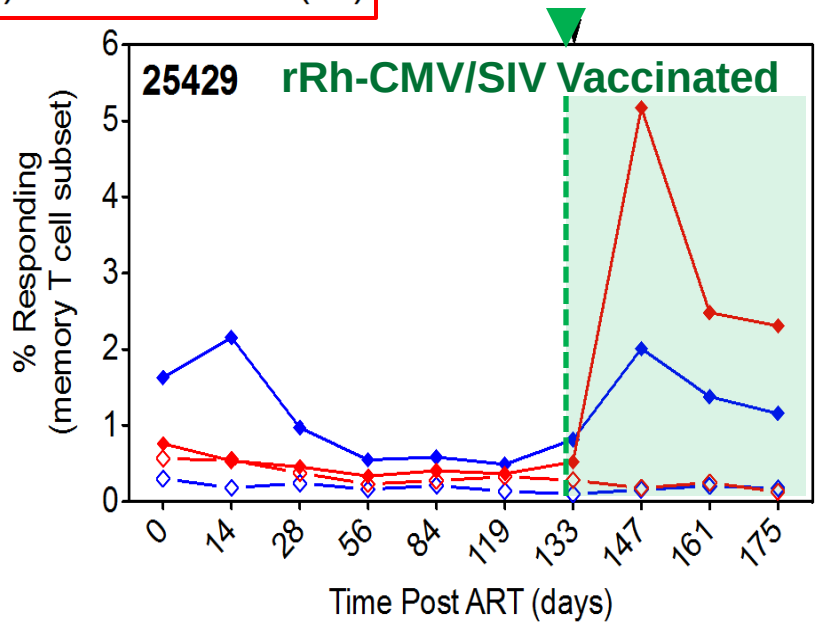
rRhCMV/SIV Vaccines are Immunogenic in SIV-infected Macaques on Suppressive Antiretroviral Drug Treatment



- Effective ART Suppression
- Decline of antiviral responses on ART
- Strong CD4 and CD8 T cell responses to vaccine SIV antigens (but not non-vaccine SIV antigens) with vaccination







Recap

- cCRADA and TSA collaboration mechanisms:
  - Procedures established and operating
  - Initial agreements executed and implemented
- Rh-CMV/SIV vaccines:
  - Unique immunology
  - Unique, promising antiviral effects
  - Evaluation in therapeutic vaccination proof of concept study next
  - Human CMV vector development in progress