Investigator Initiated and Collaborative Research in the AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research

Presentation for the Frederick National Laboratory Advisory Committee

Jeffrey D. Lifson, MD
Director, AIDS and Cancer Virus Program

24 October 2019

AIDS, Cancer and NCI: Clinical Manifestations

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

THE LANCET, SEPTEMBER 19, 1981

KAPOSI'S SARCOMA IN HOMOSEXUAL MEN—A REPORT OF EIGHT CASES

KENNETH B. HYMES
JEFFREY B. GREENE
AARON MARCUS
DANIEL C. WILLIAM
TONY CHEUNG
NEIL S. PROSE
HAROLD BALLARD
LINDA J. LAUBENSTEIN

Department of Medicine, Divisions of Hematology, Oncology, and Infectious Diseases, New York University Medical Center; Department of Dermatology, Downstate Medical Center, Brooklyn; and Department of Hematology, New York Veterans Administration Medical Center, New York City, New York

THE LANCET, SEPTEMBER 18, 1982

OUTBREAK OF BURKITT'S-LIKE LYMPHOMA IN HOMOSEXUAL MEN

JOHN L. ZIEGLER
RICHARD C. MINER
ERNEST ROSENBAUM
EVELYNE T. LENNETTE
EDWARD SHILLITOE
CONRAD CASAVANT
W. LAWRENCE DREW
LAWRENCE MINTZ
JAY GERSHOW
JOHN GREENSPAN
JAY BECKSTEAD
KENNETH YAMAMOTO

Veterans Administration Medical Center, San Francisco, California, U.S.A.; Mount Zion Hospital and Medical Center, San Francisco; Virolab, Inc., Emeryville, California; University of California San Francisco Schools of Medicine and Dentistry; and St Mary's Hospital, San Francisco

AIDS, HIV and NCI: Virus Discovery

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

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Proc. Natl. Acad. Sci. USA
Vol. 77, No. 12 pp. 7415–7419, December 1980
Medical Sciences

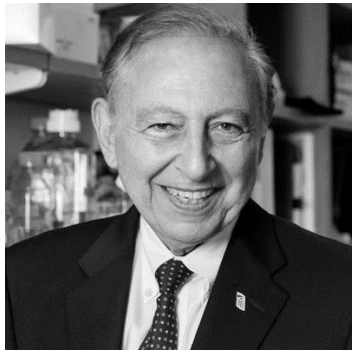
Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma

(mycosis fungoides/T-cell growth factor/RNA tumor virus/reverse transcriptase)

BERNARD J. POIESZ*, FRANCIS W. RUSCETTI*, ADI F. GAZDAR†, PAUL A. BUNN†, JOHN D. MINNA†, AND ROBERT C. GALLO*‡

*Laboratory of Tumor Cell Biology, Building 37, National Cancer Institute and †National Cancer Institute–Veterans Administration Oncology Branch, National Institutes of Health, Bethesda, Maryland 20205

Communicated by Henry S. Kaplan, August 4, 1980



SCIENCE, VOL. 218, 5 NOVEMBER 1982

A New Subtype of Human T-Cell Leukemia Virus (HTLV-II) Associated with a T-Cell Variant of Hairy Cell Leukemia

Abstract. *Human T-cell leukemia virus (HTLV) is a human type-C RNA tumor virus (retrovirus) previously identified in and isolated from several patients with T-cell leukemias or lymphomas. The known virus isolates from the United States and Japan are closely related and are found in adults with an acute malignancy of mature T cells. A related retrovirus has been found in a patient (Mo) with a somewhat different disease (a T-cell variant of relatively benign hairy cell leukemia). Serum from Mo contains antibodies to the major internal core protein (p24) of HTLV. A T-cell line established from the spleen of Mo expresses HTLV antigens. However, HTLV from Mo is significantly different from all previous HTLV isolates in immunological cross-reactivity tests of p24. The usual prototype HTLV isolate is represented as HTLV-I, and the HTLV from Mo is represented as HTLV-II. Individual members of each subgroup may then be identified by subscript initials of the patient [for example, HTLV-$I_{(CR)}$, HTLV-$I_{(MB)}$, and HTLV-$II_{(Mo)}$].*

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AIDS, HIV and NCI: Virus Discovery

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

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Detection, Isolation, and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS

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ELIZABETH READ
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Serological Analysis of a Subgroup of Human T-Lymphotropic Retroviruses (HTLV-III) Associated with AIDS

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MATTHEW A. GONDA
Program Resources, Inc. NCI–Frederick Cancer Research Facility, Frederick, Maryland 21701
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ROBERT C. GALLO
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Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS

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JAMES OLESKE
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BIJAN SAFAI
Dermatology Service, Memorial Sloan Kettering Cancer Center, New York 10021
GILBERT WHITE
PAUL FOSTER
Department of Medicine, University of North Carolina, Chapel Hill 27514
PHILLIP D. MARKHAM
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Science
May 1984

Antibodies Reactive with Human T-Lymphotropic Retroviruses (HTLV-III) in the Serum of Patients with AIDS

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AIDS, HIV and NCI: Early Therapies



Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 7096–7100, October 1985
Medical Sciences

3′-Azido-3′-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*

Proc. Natl. Acad. Sci. USA
Vol. 83, pp. 1911–1915, March 1986
Medical Sciences

Inhibition of the *in vitro* infectivity and cytopathic effect of human T-lymphotrophic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2′,3′-dideoxynucleosides

(acquired immunodeficiency syndrome)

Science 28 Jul 1989:
Vol. 245, Issue 4916, pp. 412-415

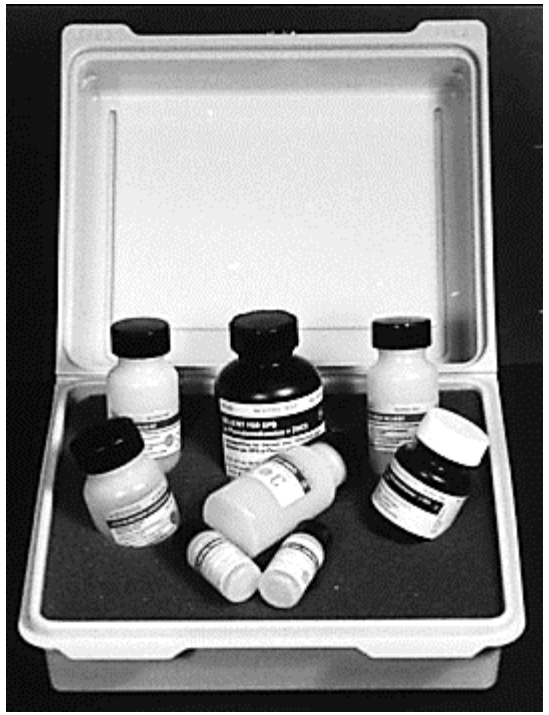
In Vivo Activity Against HIV and Favorable Toxicity Profile of 2′,3′-Dideoxyinosine

Robert Yarchoan, Hiroaki Mitsuya, Rose V. Thomas, James M. Pluda, Neil R. Hartman, Carlo-Federico Perno, Kathy S. Marczyk, Jean-Pierre Allain, David G. Johns, Samuel Broder

AIDS, HIV and NCI: Basic and Applied Studies

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research
sponsored by the National Cancer Institute



THE LANCET, MARCH 22, 1986

HTLV-III ANTIBODY IN A BREEDING CHIMPANZEE NOT EXPERIMENTALLY EXPOSED TO THE VIRUS

Program Resources, Inc,
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Frederick, Maryland 21701, USA

RAYMOND V. GILDEN
LARRY O. ARTHUR

NCI-Frederick Cancer Research Facility

W. GERARD ROBEY

Primate Research Institute,
New Mexico State University,
Holloman Airforce Base, New Mexico

JOHN C. KELLIHER
CHARLES E. GRAHAM

National Cancer Institute,
Bethesda, Maryland

PETER J. FISCHINGER

Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*

NATURE | VOL 397 | 4 FEBRUARY 1999 |

Feng Gao*, Elizabeth Bailes†, David L. Robertson‡, Yalu Chen*, Cynthia M. Rodenburg*, Scott F. Michael*§, Larry B. Cummins‖, Larry O. Arthur¶, Martine Peeters#, George M. Shaw*☆, Paul M. Sharp† & Beatrice H. Hahn*

* *Departments of Medicine and Microbiology, University of Alabama at Birmingham, 701 S. 19th Street, LHRB 613, Birmingham, Alabama 35294, USA*
† *Institute of Genetics, University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH, UK*
‡ *Laboratory of Structural and Genetic Information, CNRS, Marseilles 13402, France*
‖ *Southwest Foundation for Biomedical Research, San Antonio, Texas 78245, USA*
¶ *AIDS Vaccine Program, National Cancer Institute-Frederick Cancer Research and Development Center, SAIC Frederick, Frederick, Maryland 21702, USA*
# *Laboratoire Retrovirus, ORSTOM, BP 5045, Montpellier 34032, France*
☆ *Howard Hughes Medical Institute, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA*

AIDS and Cancer Virus Program: Presentation Overview

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

- Introduction to the ACVP
- Overview of Selected Investigator Initiated Research Projects
- Overview of Selected Collaborations with non-ACVP NIH Investigators
- Overview of Selected Collaborations with Extramural Investigators

AIDS and Cancer Virus Program: Introduction

Frederick National Laboratory
for Cancer Research
sponsored by the National Cancer Institute

MISSION

Conduct investigator initiated basic and applied research to improve the diagnosis, treatment and prevention of HIV/AIDS and infections with cancer associated viruses, *developing novel research methods, analytical techniques and reagents, proactively making these available to the broader research community*

AIDS and Cancer Virus Program: Origins/History

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

APPLIED MICROBIOLOGY, Dec. 1974, p. 1040–1046

Vol. 28, No. 6
Printed in U.S.A.

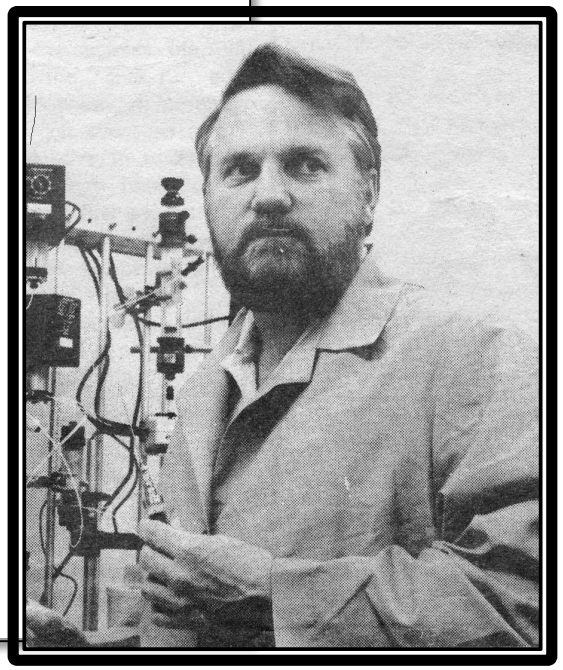
In Vitro System for Production of Mouse Mammary Tumor Virus

D. L. FINE, L. O. ARTHUR, J. K. PLOWMAN, E. A. HILLMAN, AND F. KLEIN

Frederick Cancer Research Center, Frederick, Maryland 21701

Received for publication 17 September 1974

An in vitro system for production, purification, and concentration of mouse mammary tumor virus is described. Monolayer cultures of C_3H mouse mammary tumor cells propagated at 34 C in roller bottles in the presence of dexamethasone, a glucocorticoid hormone, release B-type particles which possess ribonucleic acid and a ribonucleic acid-dependent deoxyribonucleic acid polymerase. One thousandfold concentration by ultracentrifugation with subsequent gradient fractionation yielded $> 7 \times 10^{10}$ particles per ml in the 1.16- to 1.18-g/ml region. Mouse mammary tumor virus produced in this system was free of detectable C-type virus.



AIDS and Cancer Virus Program: Distinctive Features

Frederick National Laboratory
for Cancer Research
sponsored by the National Cancer Institute

- FNLCR, FFRDC, GOCO, LBRI, ACVP
- Not a typical contractor support group for gov't investigators; 100% contractor staffed
- PIs/Investigator Initiated Research
- Technology/Reagent/Assay development with proactive sharing with broader research community
- Structured mechanisms for extramural collaborative support; TSA, cCRADA

AIDS and Cancer Virus Program: Distinguishing Features

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

- **Small PI headed research sections, organized by interest/expertise**
- **Highly interactive, collaborative, within, outside**
- **Research Support Cores: arise from need; capabilities established as Cores based on demonstrated ongoing demand (including outside ACVP)**
- **Extensive interactions with/support of investigators outside of ACVP (intra- and extramural) by PIs and Cores**
- ***FNL and ACVP as a national resource***

AIDS and Cancer Virus Program: Organization Structure / Approach

Frederick National Laboratory
for Cancer Research
sponsored by the National Cancer Institute

- **Integrated, multidisciplinary, interactive research in basic and applied virology and immunology of retroviruses and cancer associated viruses relevant to HIV/AIDS**
- **Five PI headed Research Sections and eight Research Support Cores**
- **Investigator initiated research**
- **Special/Unique capabilities** ***(NHP model development, NHP studies, viral quantitation, sequencing, tissue analysis, scaled virus production/purification, KSHV studies)***
- **Collaborative support of other NCI, NIH and extramural research**
- **BSC/Site Visit reviews q 4 yrs, courtesy of CCR**

AIDS and Cancer Virus Program: Collaborative Facilitation of Research

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

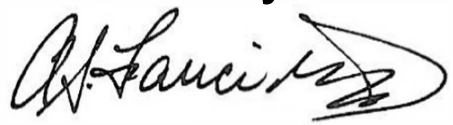
sponsored by the National Cancer Institute

"…great strength of your program is its ability to provide a wide array of research support services to the independent investigators of the NIH intramural research community as well as to the extramural community…

…***The quality of the work from your laboratory is universally recognized as the gold standard for work in non-human primate models of HIV infection.***

…This expertise and input not only go into the measurements that are made and reagents that are provided but also into the development of the animal protocols, the interpretation of data and the preparation of manuscripts. ***It is a unique collaborative relationship that exemplifies in my mind the best of a federally funded research and development campus established to support the mission of the NCI and by extension the rest of the NIH.***"

Sincerely



Anthony S. Fauci, MD
Director, NIAID

AIDS and Cancer Virus Program: Presentation Overview

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

- "But don't we have drugs for that now?"
- Some key frontier areas in HIV/AIDS research, 2019
  - Prevention (pathogenesis of transmission, vaccines, passive immunoprophylaxis, LA-PrEP)
  - U = U, but Treated ≠ Uninfected (non-AIDS morbidity)
  - Residual virus during ART ("viral reservoir")

NHP Models in AIDS Research: A Personal History

AIDS and Cancer Virus Program
Frederick National Laboratory for Cancer Research
sponsored by the National Cancer Institute

THE LANCET, MARCH 31, 1984

HUMAN RECOMBINANT INTERLEUKIN-2 PARTLY RECONSTITUTES DEFICIENT IN-VITRO IMMUNE RESPONSES OF LYMPHOCYTES FROM PATIENTS WITH AIDS

JEFFREY D. LIFSON, CLAUDIA J. BENIKE, DAVID F. MARK, KIRSTON KOTHS, EDGAR G. ENGLEMAN

Department of Pathology, Stanford University School of Medicine, Stanford, California; and Cetus Corporation, Emeryville, California, USA

Summary The lymphokine interleukin-2 is required for the development of various cell-mediated immune functions that are known to be deficient in patients with acquired immunodeficiency syndrome (AIDS). The effects of pure human recombinant interleukin-2 (rIL-2), produced by *Escherichia coli* containing the cloned human gene, on in-vitro immune responses were studied in 16 patients with AIDS and 10 age-matched healthy heterosexual men. Exposure of lymphocytes from most AIDS patients to 1–100 U/ml rIL-2, increased mitogen and alloantigen induced proliferation and augmented natural killer (NK) cell function in a dose-dependent manner. NK activity was the function most consistently improved, with deficient patient responses uniformly restored to normal after incubation of effector cells with rIL-2. Patient responsiveness to rIL-2 did not appear to depend upon the primary manifestation of disease (opportunistic infection, Kaposi's sarcoma, or both) or other clinical variables. rIL-2 also augmented the responses of lymphocytes from healthy subjects, but to a lesser degree. Pure rIL-2 seems capable of at least partly reconstituting some in-vitro immunological defects characteristic of AIDS. The availability of highly purified rIL-2 makes in-vivo testing feasible.

SCIENCE • VOL. 259 • 19 MARCH 1993

High Levels of HIV-1 in Plasma During All Stages of Infection Determined by Competitive PCR

M. Piatak, Jr., M. S. Saag, L. C. Yang, S. J. Clark, J. C. Kappes, K.-C. Luk, B. H. Hahn, G. M. Shaw, J. D. Lifson*

JOURNAL OF VIROLOGY, June 1996, p. 3741–3752 Vol. 70, No. 6
0022-538X/96/$04.00+0

Patterns of Viral Replication Correlate with Outcome in Simian Immunodeficiency Virus (SIV)-Infected Macaques: Effect of Prior Immunization with a Trivalent SIV Vaccine in Modified Vaccinia Virus Ankara

VANESSA M. HIRSCH,[1]* THOMAS R. FUERST,[2] GERD SUTTER,[3] MILES W. CARROLL,[3] LIMEI C. YANG,[4] SIMOY GOLDSTEIN,[1] MICHAEL PIATAK, JR.,[4] WILLIAM R. ELKINS,[1] W. GREGORY ALVORD,[5] DAVID C. MONTEFIORI,[6] BERNARD MOSS,[3] AND JEFFREY D. LIFSON[7]

Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, Rockville, Maryland 20852[1]; 1511 Blackbird Lane, San Antonio, Texas 78248[2]; Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20892[3]; Becton Dickinson Diagnostic Instrument Services, Sparks, Maryland[4]; Data Management Services[5] and Laboratory of Retroviral Pathogenesis, SAIC Frederick,[7] National Cancer Institute-Frederick Cancer Research Center, Frederick, Maryland 21702; and Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710[6]

AIDS and Cancer Virus Program: Investigator Initiated Research

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

Nonhuman Primate Model Development and Application:

- NHP models provide powerful systems to experimentally address key questions in research on HIV/AIDS including control of:
  - Virus identity (incl. “designer viruses”), route, dose, timing
  - Longitudinal sampling of blood, other fluids, tissues
  - Interventional latitude; safety, POC, treatment flexibility
- ACVP partnership with Laboratory Animal Sciences Program
- Innovative viruses, NHP models

AIDS and Cancer Virus Program: Presentation Overview

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

- Introduction to the ACVP
- Overview of Selected Investigator Initiated Research Projects
- Overview of Selected Collaborations with non-ACVP NIH Investigators
- Overview of Selected Collaborations with Extramural Investigators

Understanding SIV Transmission with Sequence Tagged Synthetic Swarms *(B. Keele)*

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

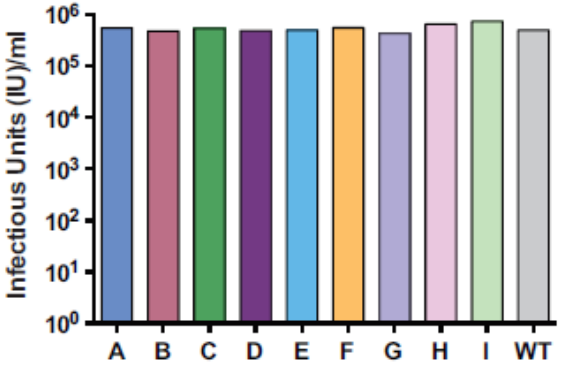
sponsored by the National Cancer Institute

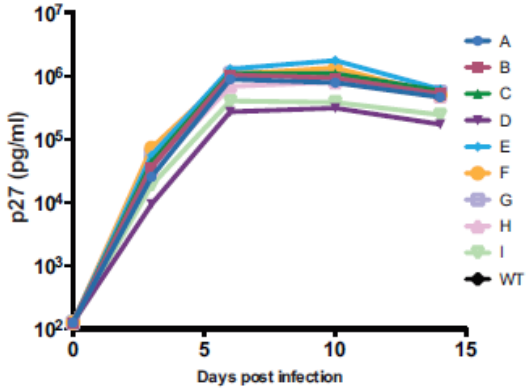
JVI Journals.ASM.org

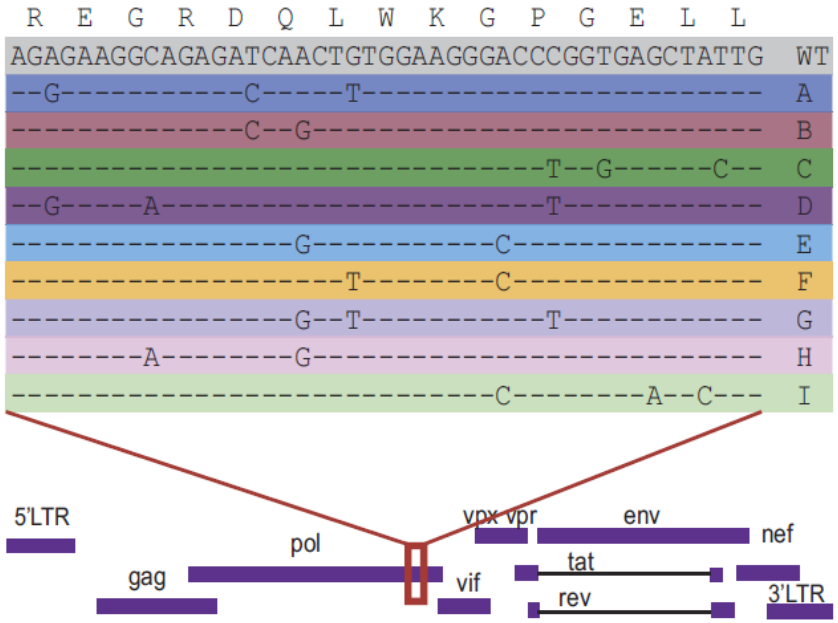
Molecularly Tagged Simian Immunodeficiency Virus SIVmac239 Synthetic Swarm for Tracking Independent Infection Events

Gregory Q. Del Prete,[a] Haesun Park,[b,c] Christine M. Fennessey,[a] Carolyn Reid,[a] Leslie Lipkey,[a] Laura Newman,[a] Kelli Oswald,[a] Christoph Kahl,[c] Michael Piatak, Jr.,[a] Octavio A. Quiñones,[d] W. Gregory Alvord,[d] Jeremy Smedley,[e] Jacob D. Estes,[a] Jeffrey D. Lifson,[a] Louis J. Picker,[b,c] Brandon F. Keele[a]

AIDS and Cancer Virus Program,[a] Statistical Consulting, Data Management Services[d], and Laboratory Animal Sciences Program,[e] Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, Maryland, USA; Vaccine and Gene Therapy Institute[b] and Oregon National Primate Research Center,[c] Oregon Health and Science University, Beaverton, Oregon, USA







SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

Defining early SIV replication and dissemination dynamics following vaginal transmission

Claire Deleage[1], Taina T. Immonen[1], Christine M. Fennessey[1], Arnold Reynaldi[2], Carolyn Reid[1], Laura Newman[1], Leslie Lipkey[1], Timothy E. Schlub[3], Celine Camus[1], Sean O'Brien[1], Jeremy Smedley[4]*, Jessica M. Conway[5], Gregory Q. Del Prete[1], Miles P. Davenport[2], Jeffrey D. Lifson[1], Jacob D. Estes[1†‡], Brandon F. Keele[1†]

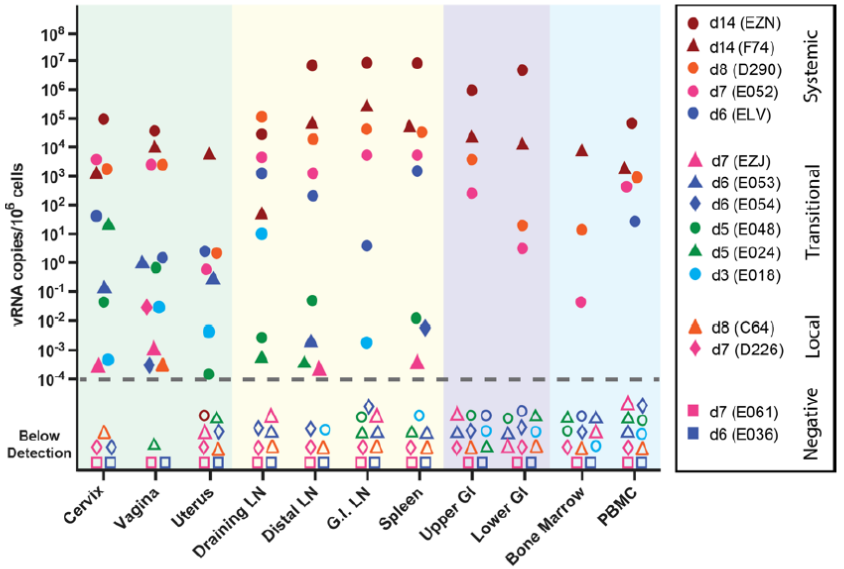
Understanding SIV Transmission with Sequence Tagged Synthetic Swarms *(B. Keele)*

AIDS and Cancer Virus Program

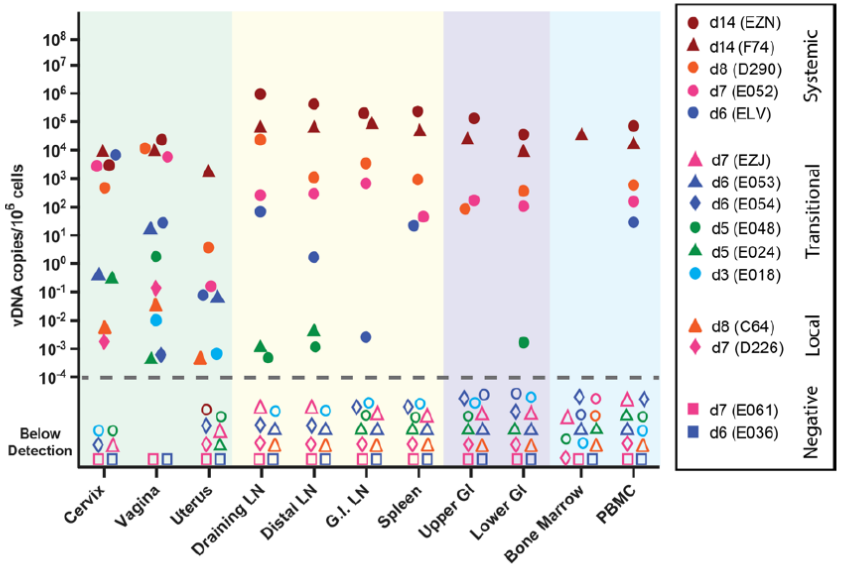
Frederick National Laboratory for Cancer Research

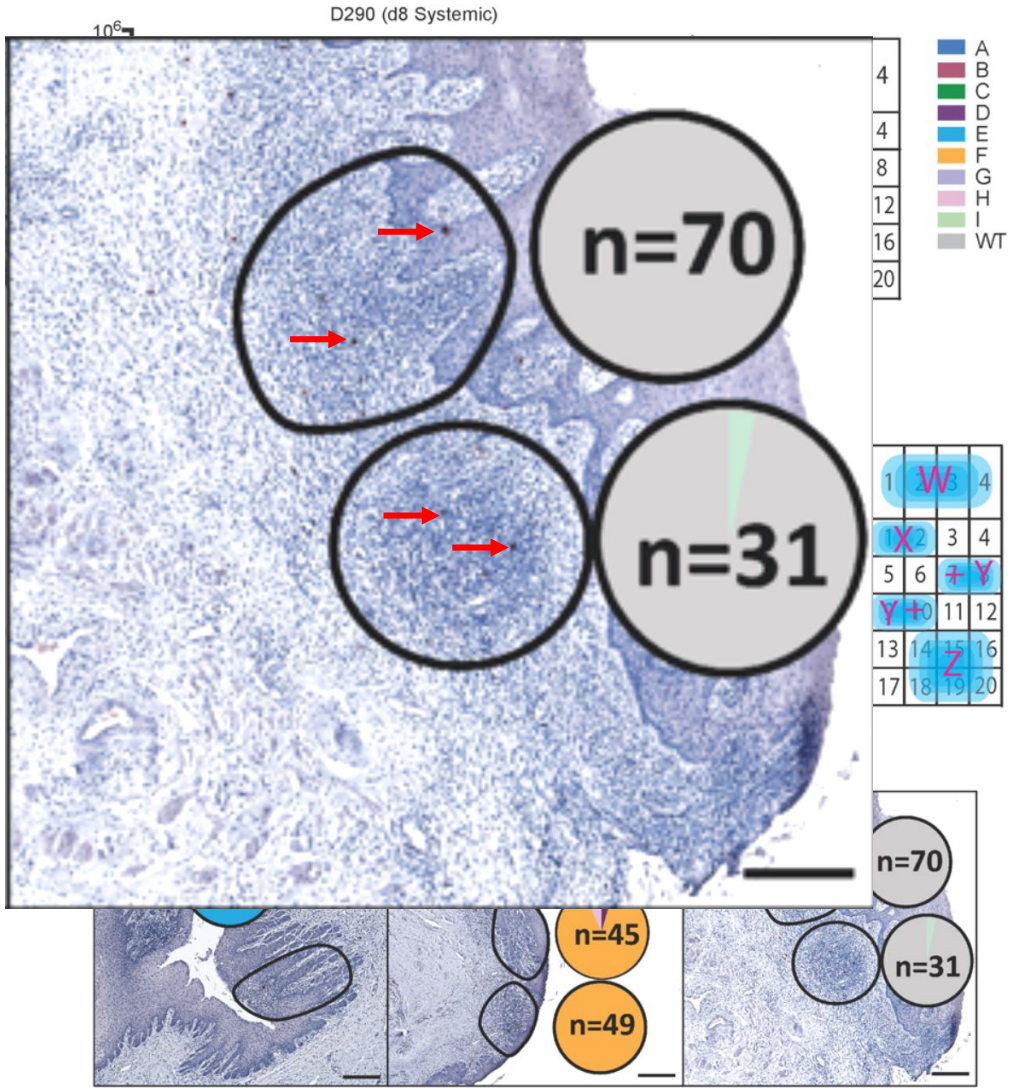
sponsored by the National Cancer Institute

vRNA



vDNA





Understanding Viral Reservoirs and Recrudescence with Sequence Tagged Synthetic Swarms *(B. Keele)*

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

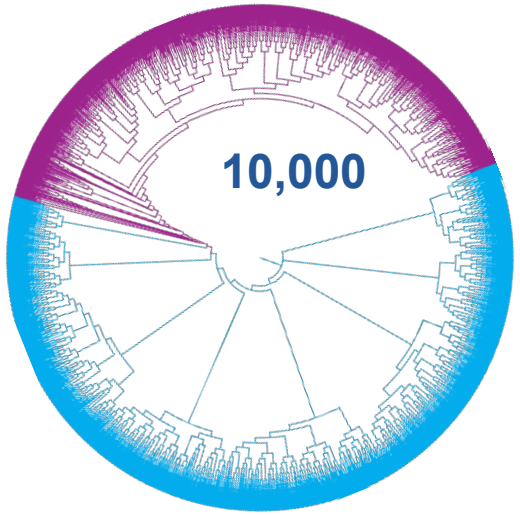
PLOS | PATHOGENS

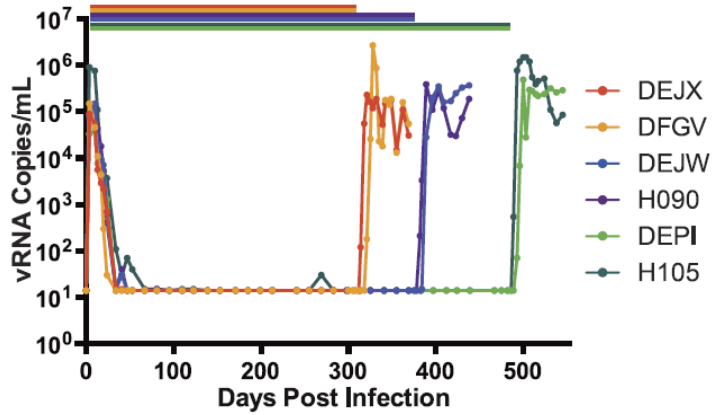
RESEARCH ARTICLE

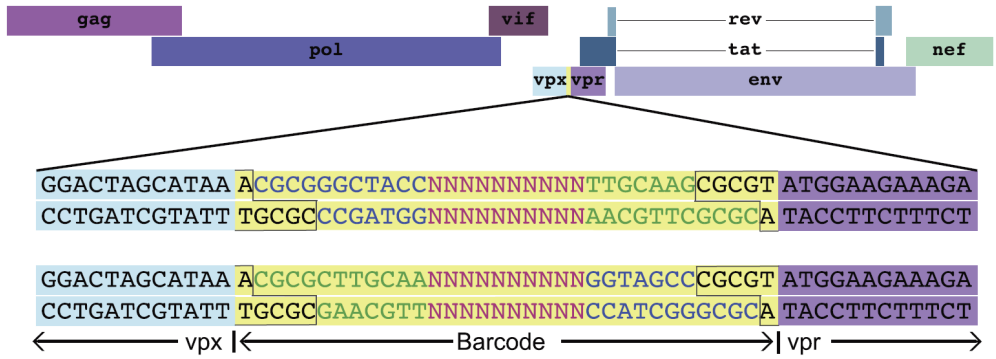
Genetically-barcoded SIV facilitates enumeration of rebound variants and estimation of reactivation rates in nonhuman primates following interruption of suppressive antiretroviral therapy

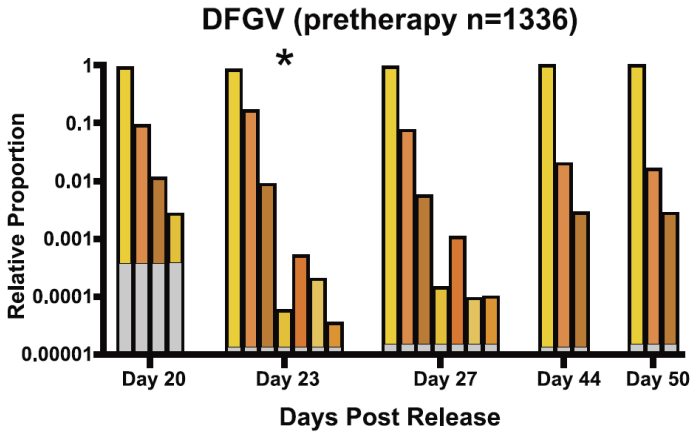
Christine M. Fennessey[1], Mykola Pinkevych[2], Taina T. Immonen[1], Arnold Reynaldi[2], Vanessa Venturi[2], Priyanka Nadella[1], Carolyn Reid[1], Laura Newman[1], Leslie Lipkey[1], Kelli Oswald[1], William J. Bosche[1], Matthew T. Trivett[1], Claes Ohlen[1†], David E. Ott[1], Jacob D. Estes[1], Gregory Q. Del Prete[1], Jeffrey D. Lifson[1], Miles P. Davenport[2]*, Brandon F. Keele[1]*

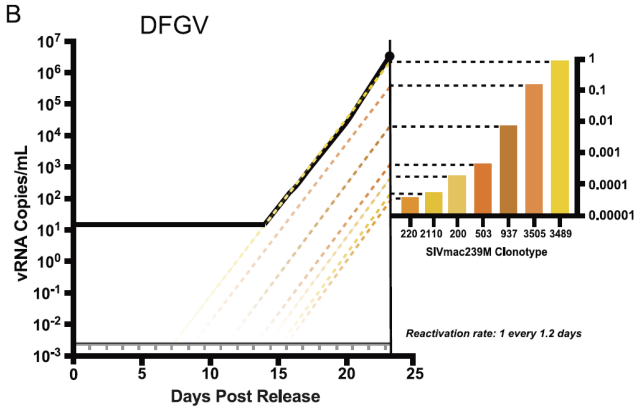
1 AIDS and Cancer Virus Program, Leidos Biomedical Research Inc., Frederick National Laboratory for Cancer Research, Frederick, Maryland, United States of America, **2** Infection Analytics Program, Kirby Institute for Infection and Immunity, UNSW Australia, Sydney, NSW, Australia











Targeting Residual Virus in Immune Privileged Sanctuary Sites *(J. Lifson)*

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

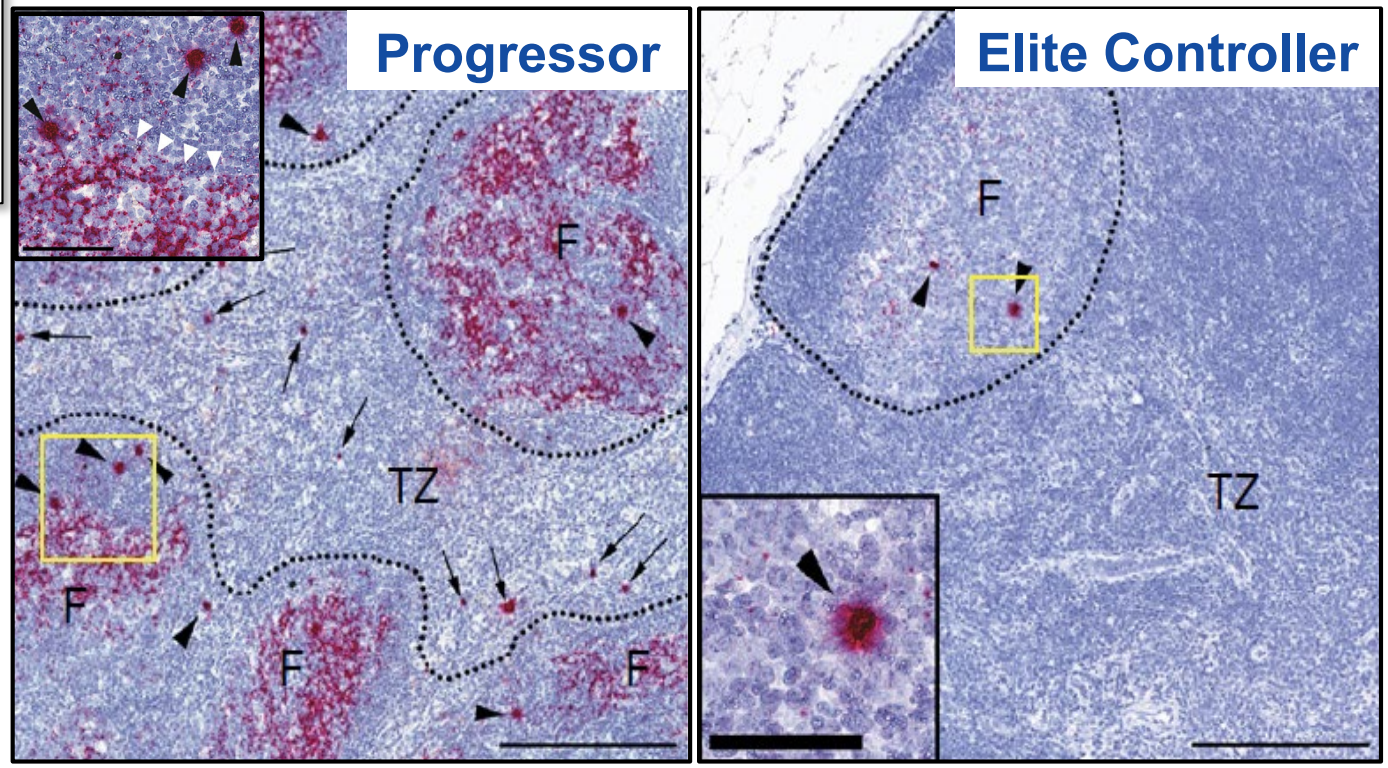
ARTICLES

nature medicine

B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers

Yoshinori Fukazawa[1,2], Richard Lum[1,2], Afam A Okoye[1,2], Haesun Park[1,2], Kenta Matsuda[3], Jin Young Bae[1,2], Shoko I Hagen[1,2], Rebecca Shoemaker[4], Claire Deleage[4], Carissa Lucero[4], David Morcock[4], Tonya Swanson[1,2], Alfred W Legasse[1,2], Michael K Axthelm[1,2], Joseph Hesselgesser[5], Romas Geleziunas[5], Vanessa M Hirsch[3], Paul T Edlefsen[6], Michael Piatak, Jr[4], Jacob D Estes[4], Jeffrey D Lifson[4] & Louis J Picker[1,2]

- **In Mamu B*08+ rhesus macaques (similar to HLA-B*57+ human "elite controllers"), and macaques on ART, residual virus in lymphoid tissues is largely restricted to CD4+ TFH in B cell follicles**



- **CD8+ (CXCR5-) T cells able to clear virus from other tissue sites do not readily access B cell follicles**

Targeting Residual Virus in Immune Privileged Sanctuary Sites *(J. Lifson)*

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research
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CXCR5-Directed Localization of Infused, Engineered CD8+ T Cells to B Cell Follicles, In Vivo

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology®

June 2017 Volume 91 Issue 11 e02507-16

PATHOGENESIS AND IMMUNITY

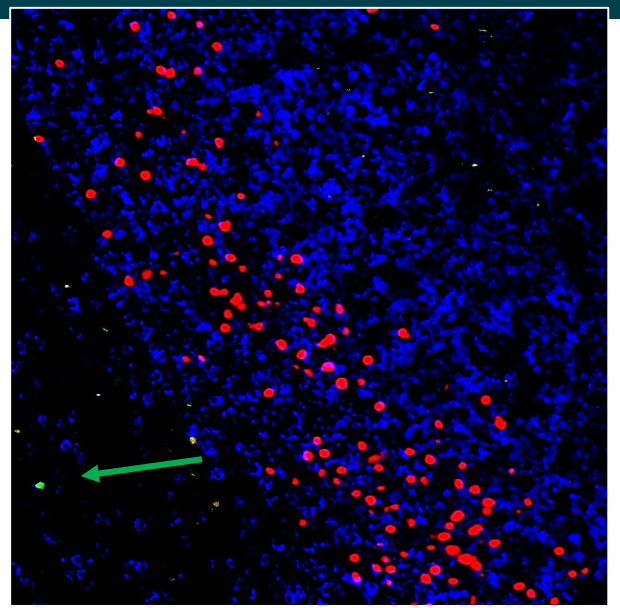
Check for updates

CXCR5-Dependent Entry of CD8 T Cells into Rhesus Macaque B-Cell Follicles Achieved through T-Cell Engineering

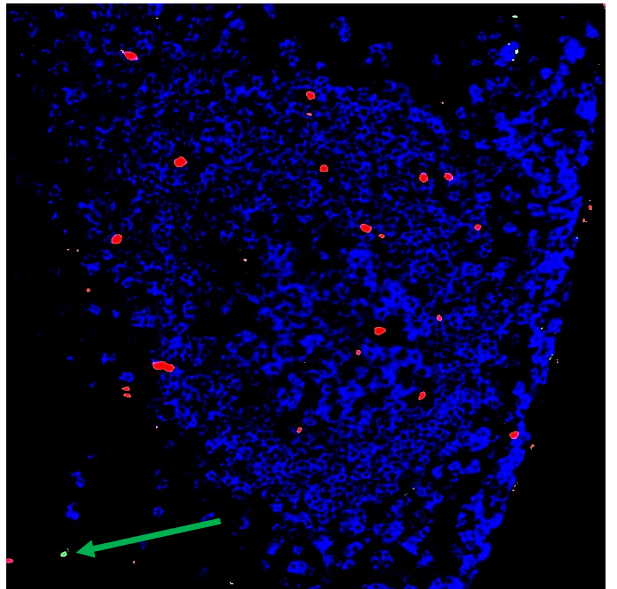
Victor I. Ayala,[a*] Claire Deleage,[a] Matthew T. Trivett,[a] Sumiti Jain,[a*]
Lori V. Coren,[a] Matthew W. Breed,[b] Joshua A. Kramer,[b] James A. Thomas,[a]
Jacob D. Estes,[a] Jeffrey D. Lifson,[a] David E. Ott[a]

AIDS and Cancer Virus Program,[a] and Laboratory Animal Science Program,[b] Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, Maryland, USA

CD20⁺ B Cells
CXCR5 Transduced Infused Cells
Untransduced Infused Cells



Lymph Node



Spleen

Enhanced Activity of Engineered T Cell Immunotherapy + rRhHetIL-15

- Localization of bulk CD8+ T cells to B cell follicles by CXCR5 transduction
  - SIV-specific TCR + CXCR5 co-expression→ localization + antiviral function?

- rRhHet-IL-15 (rhesus IL-15/IL-15Ra)
  - Ongoing collaboration with G. Pavlakis (CCR/NCI); purification, characterization
  - Circulating form of IL-15; desirable pharmacologic properties
  - Activation, proliferation, enhanced cytotoxic potential (Granzyme B) for CD8+ T cells, NK cells; follicular localization

- Enhanced activity of engineered T cell immunotherapy + rRhHet IL-15?

SIV Specific TCR + CXCR5 Engineered CD8+ T Cell Adoptive Immunotherapy Targets Virus in Follicular Sanctuary Sites

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Mamu B*08 Restricted
TCR + CXCR5 Engineered Cells

"Immune Privileged Sanctuary"

"Follicle Targeted Immune Clearance"?

SIVmac239

Tenofovir

rRhHet IL-15

Mamu B*08+ RM

- Bleeds/LN/GI Bxs
- Persistence, trafficking, in vivo proliferation
- RNAScope/DNAScope
- Plasma viral dynamics

Infused TCR + CXCR5 Engineered Cells Persist, Proliferate, and Localize to LN In Vivo

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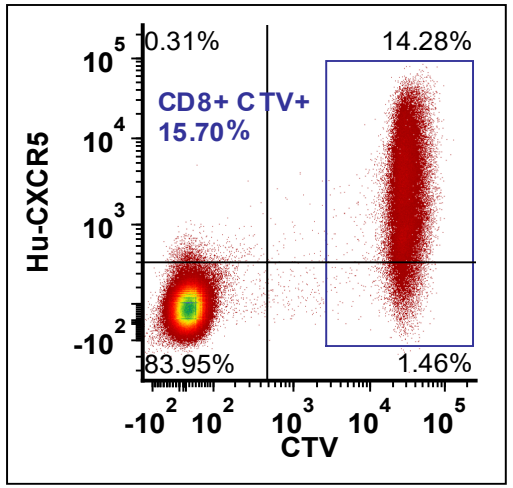
PBMC CD8+ d 0



Decreased Cell Trace Violet signal = Cellular Proliferation

Infused TCR + CXCR5 Engineered CD8+ T Cells Localize to LN Follicles, with Reduction in SIV RNAscope Signal

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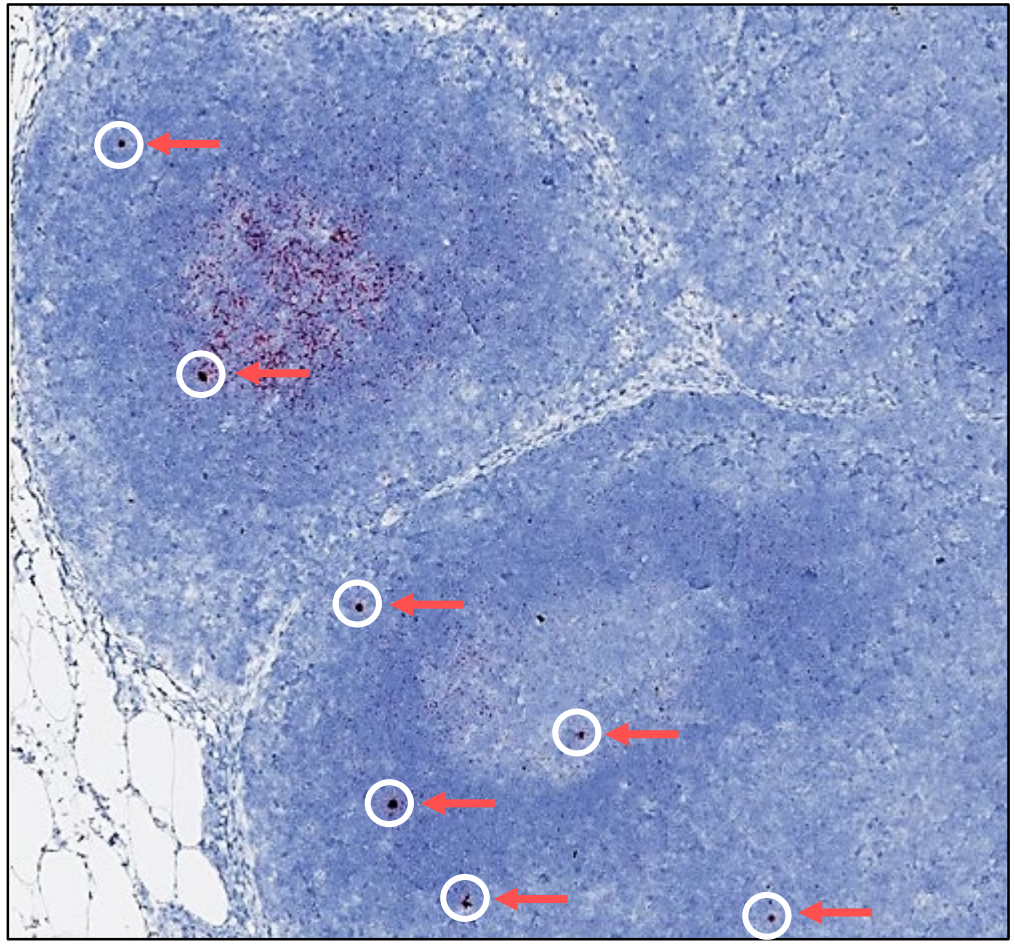
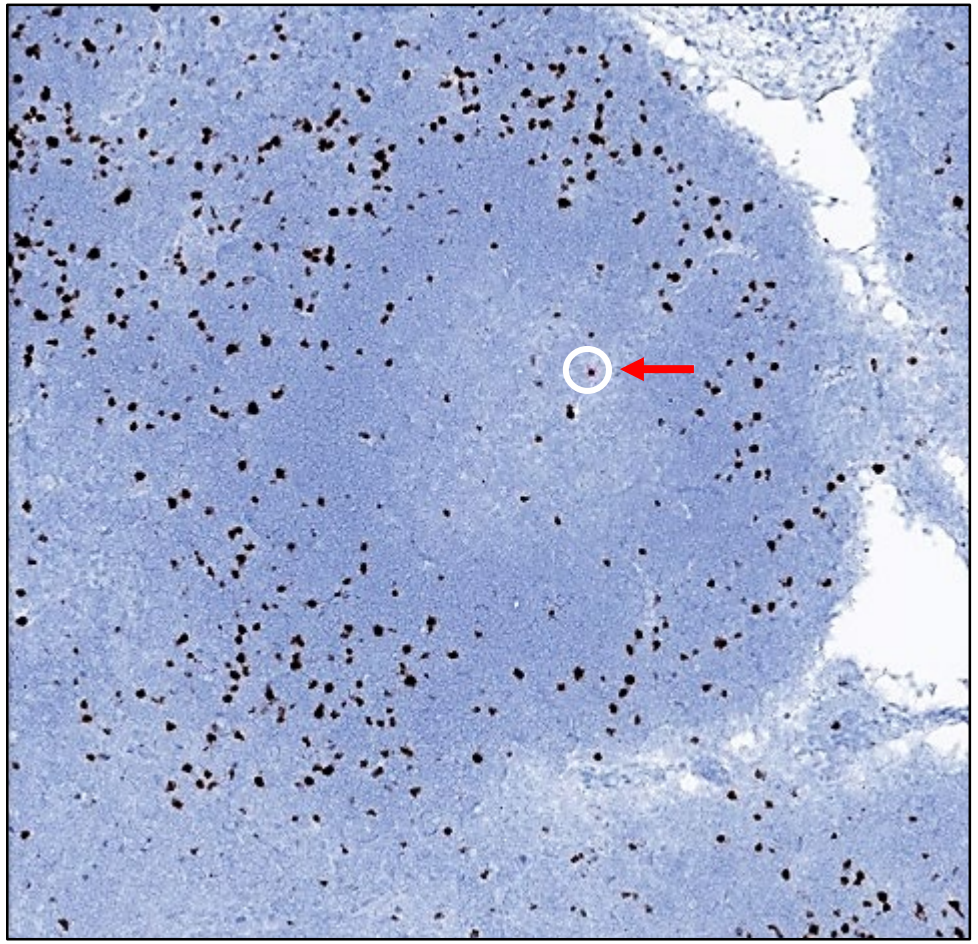
Preinfusion



4 Days Post-infusion



SIV RNA

Infused Cells

Infusion of TCR + CXCR5 Engineered CD8+ T Cells + rRhHet-IL-15 →Reduced Plasma Viremia

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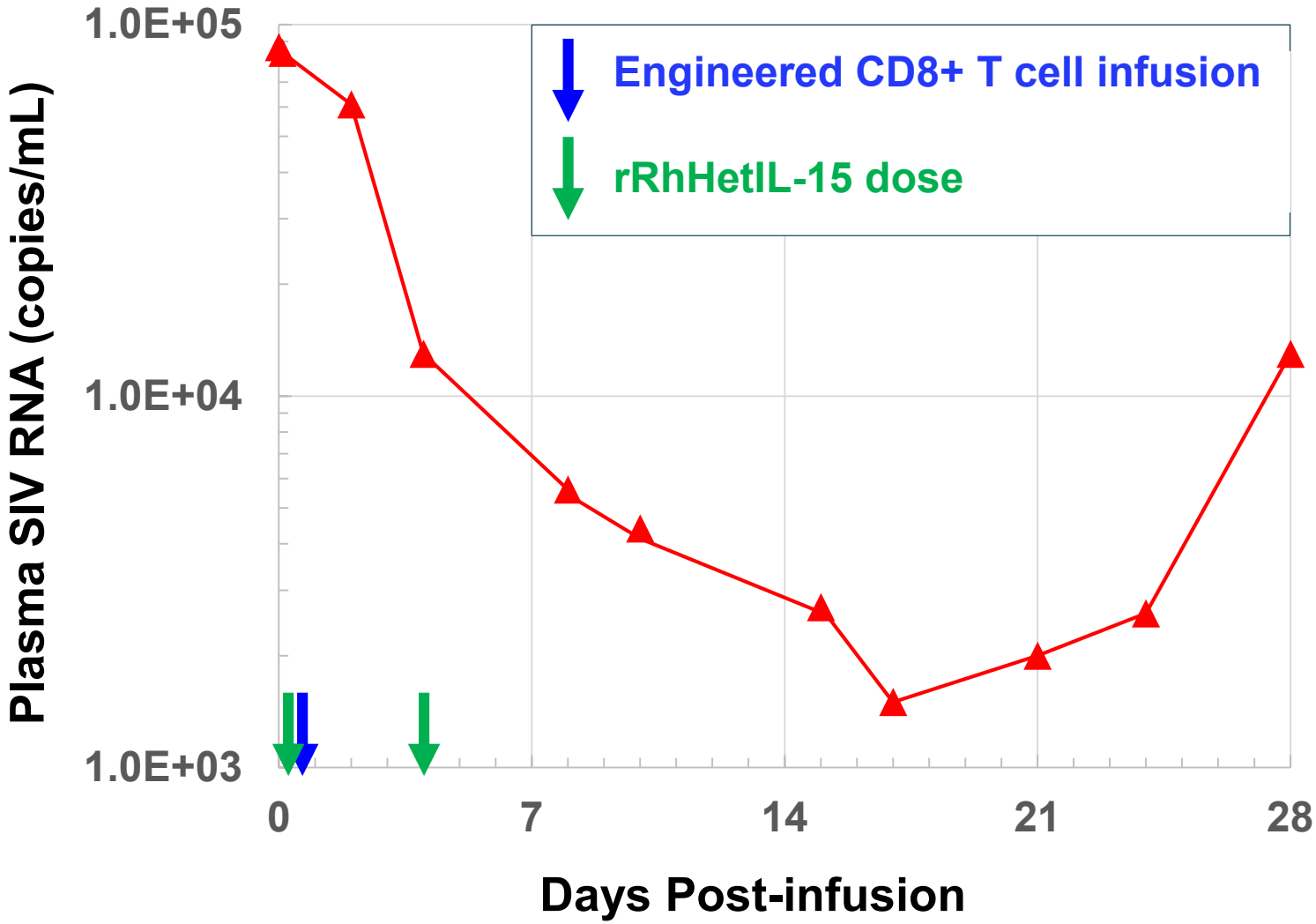

AIDS and Cancer Virus Program: Presentation Overview

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

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- Introduction to the ACVP
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AIDS and Cancer Virus Program: Collaborative Research with NCI Investigators

(S. Hughes/HIV-DRP/CCR and J. Lifson)

AIDS and Cancer Virus Program

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RESEARCH ARTICLE

HIV LATENCY

Specific HIV integration sites are linked to clonal expansion and persistence of infected cells

F. Maldarelli,[1*] X. Wu,[2*] L. Su,[2] F. R. Simonetti,[1,3] W. Shao,[2] S. Hill,[1] J. Spindler,[1] A. L. Ferris,[1] J. W. Mellors,[4] M. F. Kearney,[1] J. M. Coffin,[5] S. H. Hughes[1†]

HIV LATENCY

Proliferation of cells with HIV integrated into cancer genes contributes to persistent infection

Thor A. Wagner,[1,2*] Sherry McLaughlin,[1,2*] Kavita Garg,[3] Charles Y. K. Cheung,[3] Brendan B. Larsen,[2] Sheila Styrchak,[1] Hannah C. Huang,[1] Paul T. Edlefsen,[2,3] James I. Mullins,[2*] Lisa M. Frenkel[1,2*†]

PLOS | PATHOGENS

RESEARCH ARTICLE

Proviruses with identical sequences comprise a large fraction of the replication-competent HIV reservoir

John K. Bui[1,2], Michele D. Sobolewski[1], Brandon F. Keele[3], Jonathan Spindler[4], Andrew Musick[4], Ann Wiegand[4], Brian T. Luke[5], Wei Shao[5], Stephen H. Hughes[4], John M. Coffin[6], Mary F. Kearney[4], John W. Mellors[1]*

1 Division of Infectious Diseases, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America, 2 Howard Hughes Medical Research Fellows Program, Howard Hughes Medical Institute, Bethesda, Maryland, United States of America, 3 AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research operated by Leidos Biomedical Research, Inc., Frederick, Maryland, United States of America, 4 HIV Dynamics and Replication Program, National Cancer Institute, Frederick, Maryland, United States of America, 5 Advanced Biomedical Computing Center, Frederick National Laboratory for Cancer Research operated by Leidos Biomedical Research, Inc., Frederick, Maryland, United States of America, 6 Department of Molecular Biology and Microbiology, Tufts University, Boston, Massachusetts, United States of America

Check for updates

JEM Article

Proliferation of latently infected CD4$^+$ T cells carrying replication-competent HIV-1: Potential role in latent reservoir dynamics

Nina N. Hosmane,[1] Kyungyoon J. Kwon,[1] Katherine M. Bruner,[1] Adam A. Capoferri,[1] Subul Beg,[1] Daniel I.S. Rosenbloom,[2] Brandon F. Keele,[3] Ya-Chi Ho,[1] Janet D. Siliciano,[1] and Robert F. Siliciano[1,4]

[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205
[2]Department of Biomedical Informatics, Columbia University Medical Center, New York, NY 10032
[3]AIDS and Cancer Virus Program, Leidos Biomedical Research Inc., Frederick National Laboratory for Cancer Research, Frederick, MD 21702
[4]Howard Hughes Medical Institute, Baltimore, MD 21205

AIDS and Cancer Virus Program: Collaborative Research with NCI Investigators

(S. Hughes/HIV-DRP/CCR and J. Lifson)

AIDS and Cancer Virus Program

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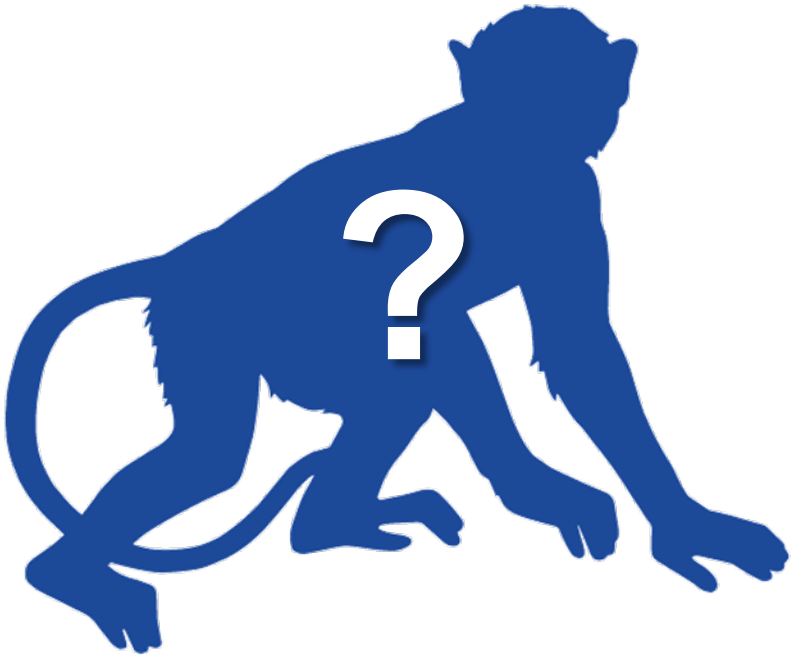
Can SIV-Infected Rhesus Macaques on Suppressive ART Provide a Useful Model for the Study of the Role of Expanded Clones of CD4+ T Cells in Rebound Competent Viral Reservoir Establishment, Persistence, and Recrudescence?



In vitro infection integration site analysis

- HIV → Human cells
- SIV → Human cells *(virus)*
- SIV → Rhesus cells *(host cell)*

In vivo integration site analysis

- SIV infected rhesus macaques
  - Pre-ART
  - On extended ART

Strong Overlap in Global and Local Characteristics of *In Vitro* and *In Vivo* Integration Sites of HIV/SIV in Human and Rhesus CD4 Cells

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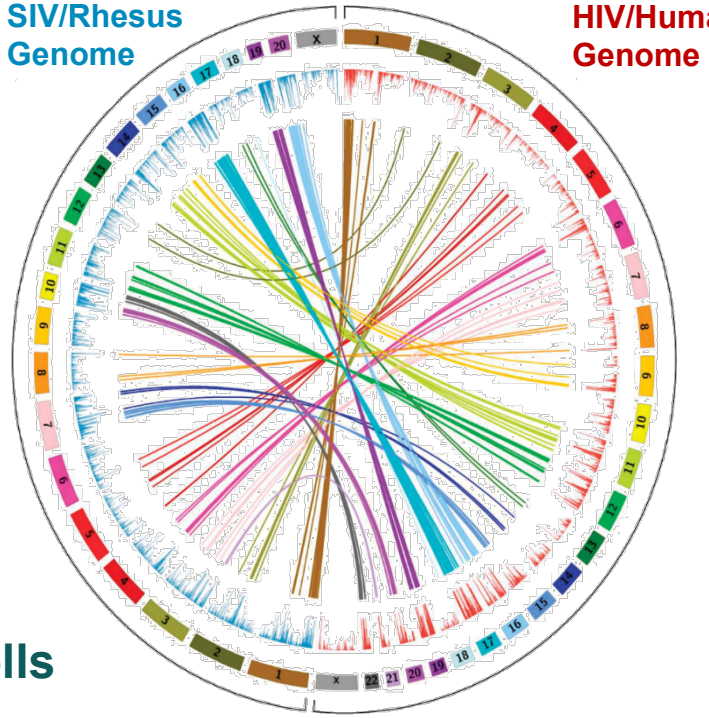
PLOS | PATHOGENS

RESEARCH ARTICLE

Clonal expansion of SIV-infected cells in macaques on antiretroviral therapy is similar to that of HIV-infected cells in humans

Andrea L. Ferris[1], David W. Wells[2], Shuang Guo[2], Gregory Q. Del Prete[3], Adrienne E. Swanstrom[3], John M. Coffin[4], Xiaolin Wu[2], Jeffrey D. Lifson[3], Stephen H. Hughes[1]*

1 HIV Dynamics and Replication Program, National Cancer Institute Frederick, National Institutes of Health, Frederick, MD, United States of America, **2** Cancer Research Technology Program, Leidos Biomedical Research Inc., Frederick National Laboratory for Cancer Research, Frederick MD, United States of America, **3** AIDS and Cancer Virus Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD, United States of America, **4** Department of Molecular Biology and Microbiology, Tufts University, Boston MA, United States of America



Correlative RNASeq and IS Analysis of in vitro infected primary CD4 cells

- HIV and SIV integrate preferentially into highly expressed gene loci, in both human and rhesus macaque primary CD4+ T cells
- Extensive, statistically significant overlap in global characteristics and specific mapped integration sites between HIV/human cells, SIV/human cells, SIV/rhesus cells
- Expanded clones of infected CD4+ T cells seen in vivo in infected macaques; properties similar to HIV in humans

Collaborative Research: Expanded Clones- HIV/SIV Integration Sites in Humans and Macaques, and Mechanism Studies

AIDS and Cancer Virus Program

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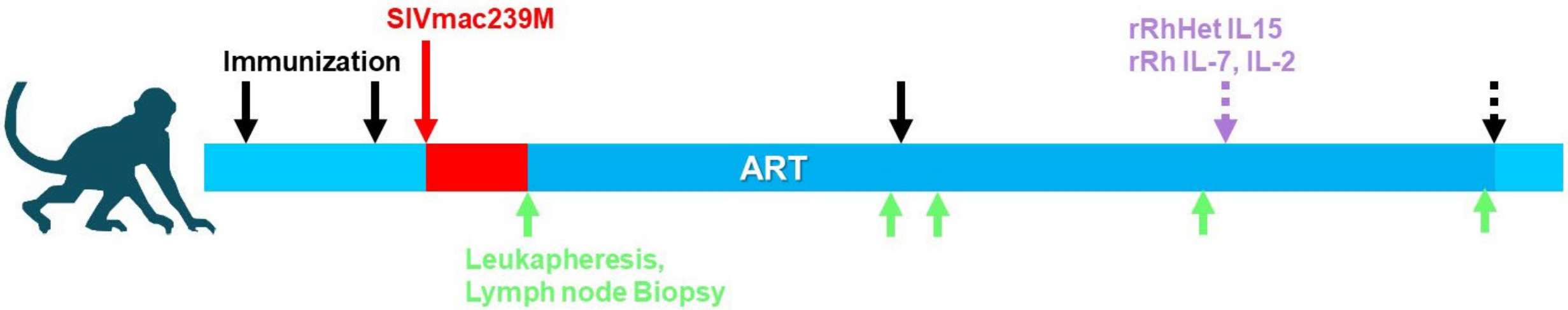

Antigen Driven Proliferation vs. Homeostatic (cytokine) Driven Proliferation?

Neutral Honest Broker In Evaluation of Controversial Results

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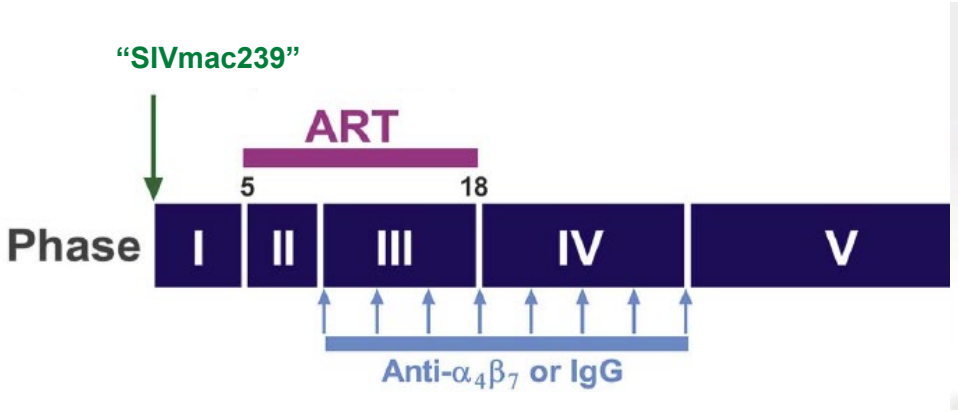
RESEARCH ARTICLE

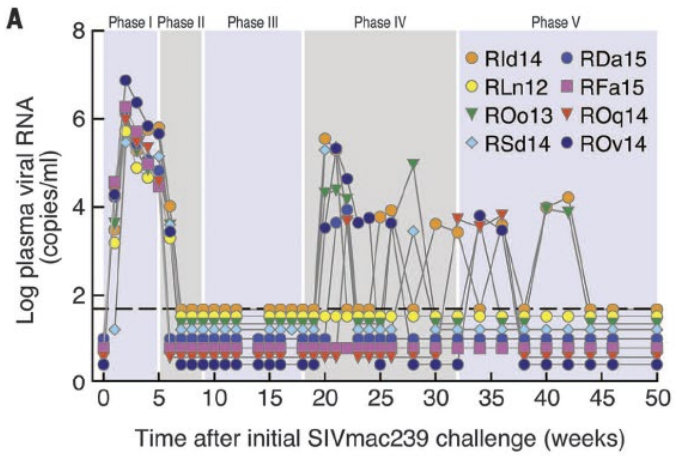
HIV-1 THERAPY

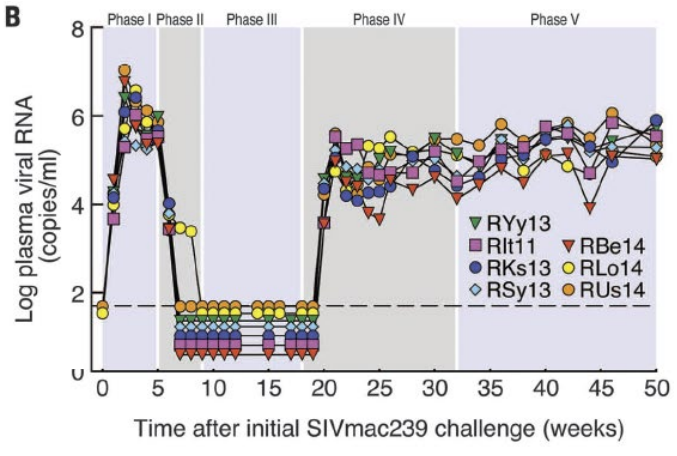
Sustained virologic control in SIV$^+$ macaques after antiretroviral and $\alpha_4\beta_7$ antibody therapy

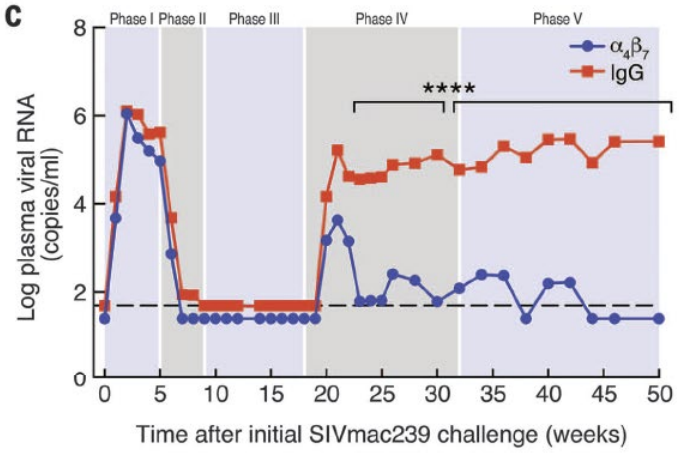
Siddappa N. Byrareddy,[1*†] James Arthos,[2*] Claudia Cicala,[2*] Francois Villinger,[1,3‡] Kristina T. Ortiz,[1] Dawn Little,[1] Neil Sidell,[4] Maureen A. Kane,[5] Jianshi Yu,[5] Jace W. Jones,[5] Philip J. Santangelo,[6] Chiara Zurla,[6] Lyle R. McKinnon,[7§] Kelly B. Arnold,[8] Caroline E. Woody,[8] Lutz Walter,[9] Christian Roos,[9] Angela Noll,[9] Donald Van Ryk,[2] Katija Jelicic,[2] Raffaello Cimbro,[10] Sanjeev Gumber,[3] Michelle D. Reid,[1] Volkan Adsay,[1] Praveen K. Amancha,[3] Ann E. Mayne,[1] Tristram G. Parslow,[1] Anthony S. Fauci,[2] Aftab A. Ansari[1||]

"STUDY DESIGN
…the animals were each infected intravenously with 1 ml of PBS containing 200 $TCID_{50}$ of a stock of SIVmac239."









Neutral Honest Broker In Evaluation of Controversial Results

AIDS and Cancer Virus Program

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REPORT

HIV TREATMENT

Evaluation of an antibody to $\alpha_4\beta_7$ in the control of SIVmac239-*nef-stop* infection

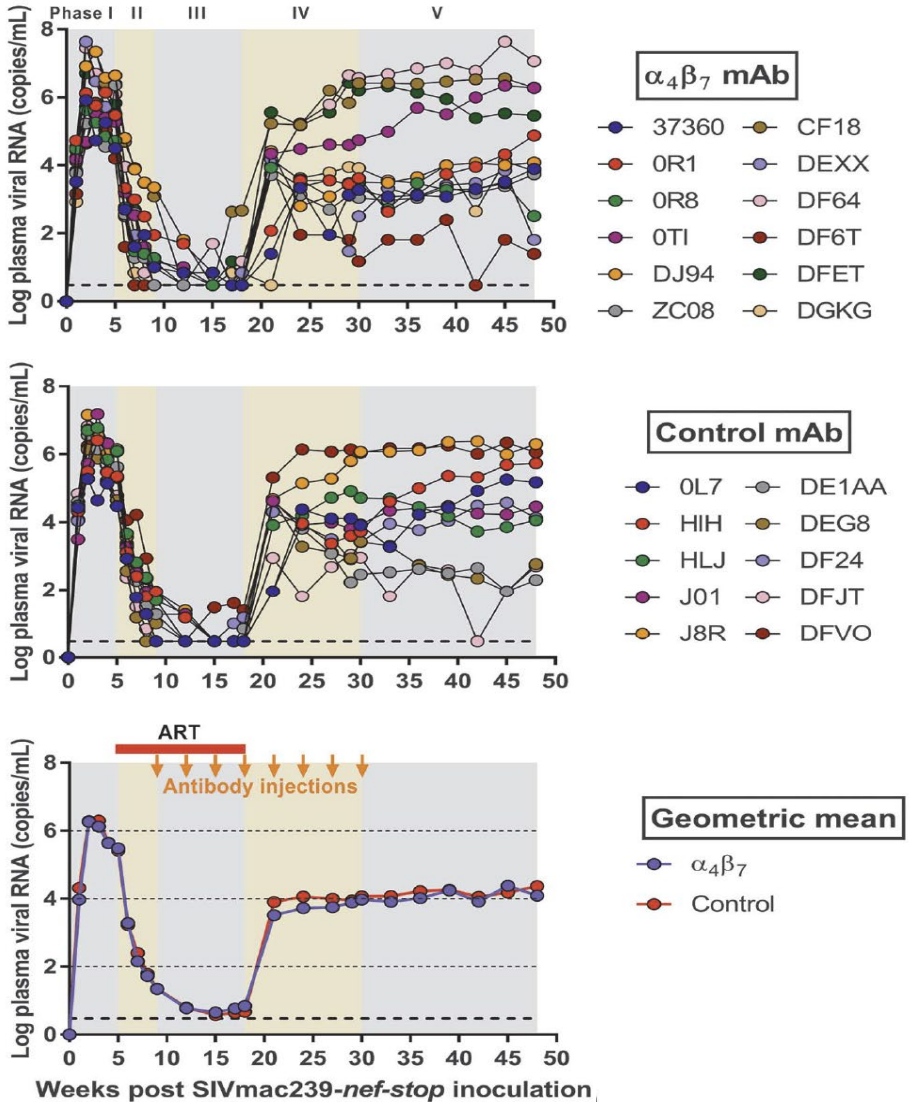
M. Di Mascio[1*], J. D. Lifson[2], S. Srinivasula[3], I. Kim[4], P. DeGrange[5], B. F. Keele[2], A. J. Belli[6], K. A. Reimann[6], Y. Wang[8], M. Proschan[7], H. C. Lane[8], A. S. Fauci[8]

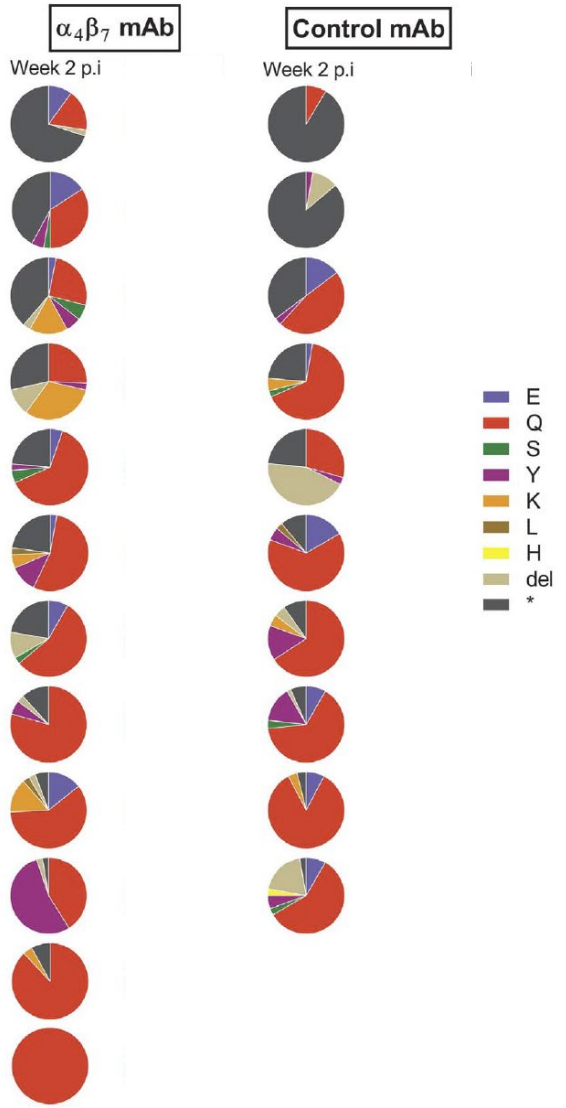
HIV TREATMENT

Blocking $\alpha_4\beta_7$ integrin binding to SIV does not improve virologic control

Nami Iwamoto[1], Rosemarie D. Mason[1], Kaimei Song[1], Jason Gorman[1], Hugh C. Welles[1], James Arthos[2], Claudia Cicala[2], Susie Min[2], Hannah A. D. King[1], Aaron J. Belli[4], Keith A. Reimann[4], Kathryn E. Foulds[1], Peter D. Kwong[1], Jeffrey D. Lifson[3], Brandon F. Keele[3], Mario Roederer[1*]

A study in nonhuman primates reported that infusions of an antibody against $\alpha_4\beta_7$ integrin, in combination with antiretroviral therapy, showed consistent, durable control of simian immunodeficiency virus (SIV) in rhesus macaques. The antibody used has pleiotropic effects, so we set out to gain insight into the underlying mechanism by comparing this treatment to treatment with non-neutralizing monoclonal antibodies against the SIV envelope glycoprotein that only block $\alpha_4\beta_7$ binding to SIV Env but have no other host-directed effects. Similar to the initial study, we used an attenuated strain of SIV containing a stop codon in *nef*. The study used 30 macaques that all began antiretroviral therapy and then were divided into five groups to receive different antibody treatments. Unlike the published report, we found no sustained virologic control by these treatments in vivo.





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Extramural Collaboration: Louis Picker, OHSU
RhCMV-vectored SIV Vaccines

AIDS and Cancer Virus Program

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LETTERS

nature medicine

Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge

Scott G Hansen[1], Cassandra Vieville[1], Nathan Whizin[1], Lia Coyne-Johnson[1], Don C Siess[1], Derek D Drummond[1], Alfred W Legasse[1], Michael K Axthelm[1], Kelli Oswald[2], Charles M Trubey[2], Michael Piatak Jr[2], Jeffrey D Lifson[2], Jay A Nelson[1], Michael A Jarvis[1] & Louis J Picker[1]

LETTER

doi:10.1038/nature10003

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]

LETTER

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]

RhCMV 68.1 Vectored Vaccine

- T cell responses to SIV inserts mimic CMV responses:
  - Good take/immunogenicity in seropositives
  - Effector memory differentiation biased
  - Broadly tissue distributed
  - Indefinitely persistent
- Extreme epitope breadth
- T cell vaccine; negligible antibody responses
- Unusual restriction of T cell responses
- Does not prevent infection; in ~ 55% of vaccines, initial infection is stringently controlled, and eventually ***cleared***
- 55-65%"Protection" vs. i.r., i.vag, and i.v. challenge

Extramural Collaboration: Louis Picker, OHSU
RhCMV-vectored SIV Vaccines

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research
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Science RESEARCH ARTICLE

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]*

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

A live-attenuated RhCMV/SIV vaccine shows long-term efficacy against heterologous SIV challenge

Scott G. Hansen[1], Emily E. Marshall[1]*, Daniel Malouli[1], Abigail B. Ventura[1], Colette M. Hughes[1], Emily Ainslie[1], Julia C. Ford[1], David Morrow[1], Roxanne M. Gilbride[1], Jin Y. Bae[1], Alfred W. Legasse[1], Kelli Oswald[2], Rebecca Shoemaker[2], Brian Berkemeier[2], William J. Bosche[2], Michael Hull[2], Jennie Womack[1], Jason Shao[3], Paul T. Edlefsen[3], Jason S. Reed[1], Ben J. Burwitz[1], Jonah B. Sacha[1], Michael K. Axthelm[1], Klaus Früh[1], Jeffrey D. Lifson[2], Louis J. Picker[1†]

Role of:

- Unconventionally restricted CD8 T cell responses in protection (MHC-II, MHC-E)
- IL-15 signaling pathways
- Immunogenicity and protective efficacy demonstrated for safety attenuated variants

NIH and Extramural Collaborations: Enabling Analytical Capabilites Quantitative Molecular Diagnostics Core

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research

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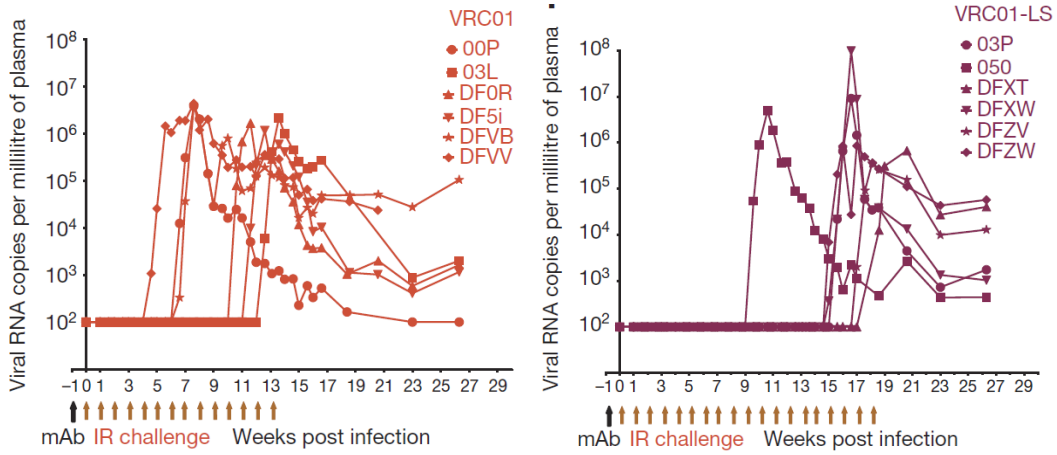
LETTER

doi:10.1038/nature17677

A single injection of anti-HIV-1 antibodies protects against repeated SHIV challenges

Rajeev Gautam[1]*, Yoshiaki Nishimura[1]*, Amarendra Pegu[2], Martha C. Nason[3], Florian Klein[4,5,6], Anna Gazumyan[4], Jovana Golijanin[4], Alicia Buckler-White[1], Reza Sadjadpour[1], Keyun Wang[2], Zachary Mankoff[2], Stephen D. Schmidt[2], Jeffrey D. Lifson[7], John R. Mascola[2], Michel C. Nussenzweig[4,8] & Malcolm A. Martin[1]

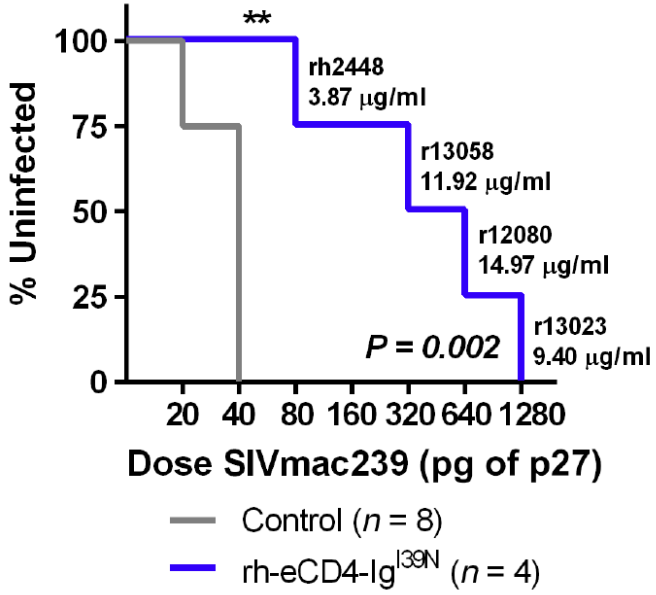


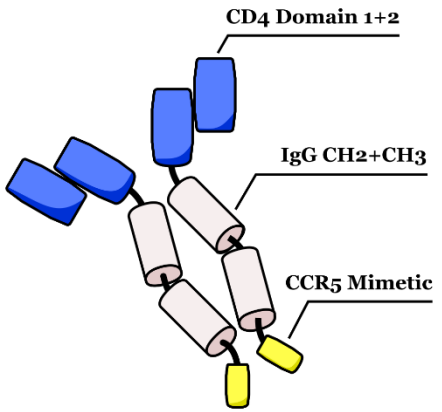
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

AAV-delivered eCD4-Ig protects rhesus macaques from high-dose SIVmac239 challenges

Matthew R. Gardner[1]*†, Christoph H. Fellinger[1]*, Lisa M. Kattenhorn[2‡], Meredith E. Davis-Gardner[1], Jesse A. Weber[1], Barnett Alfant[1], Amber S. Zhou[1], Neha R. Prasad[1], Hema R. Kondur[1], Wendy A. Newton[3], Kimberly L. Weisgrau[3], Eva G. Rakasz[3], Jeffrey D. Lifson[4], Guangping Gao[5,6], Nancy Schultz-Darken[3], Michael Farzan[1]





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Immunity
Report

CellPress

Adeno-Associated Virus Delivery of Anti-HIV Monoclonal Antibodies Can Drive Long-Term Virologic Suppression

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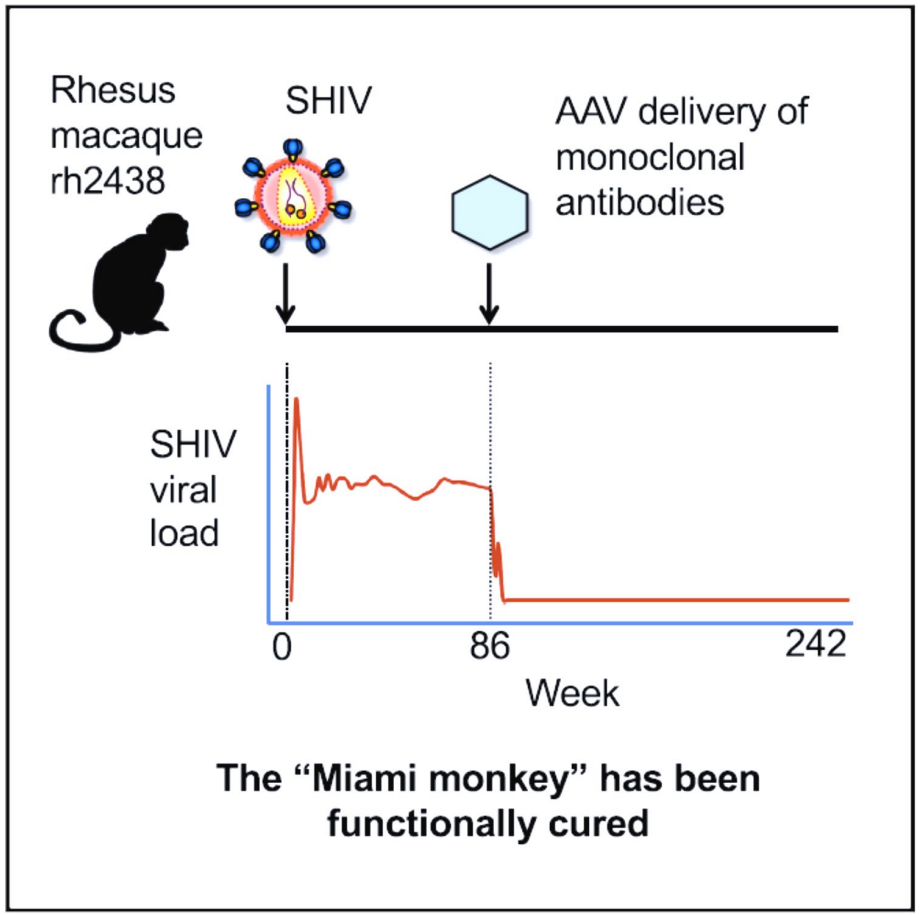

The "Miami monkey" has been functionally cured

AIDS and Cancer Virus Program: Enabling Capabilites
Dr. Rob Gorelick, HIV Molecular Monitoring Core

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research
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Safety and efficacy of VRC01 broadly neutralising antibodies in adults with acutely treated HIV (RV397): a phase 2, randomised, double-blind, placebo-controlled trial

*Trevor A Crowell, Donn J Colby, Suteeraporn Pinyakorn, Carlo Sacdalan, Amélie Pagliuzza, Jintana Intasan, Khunthalee Benjapornpong, Kamonkan Tangnaree, Nitiya Chomchey, Eugène Kroon, Mark S de Souza, Sodsai Tovanabutra, Morgane Rolland, Michael A Ell Dominic Paquin-Proulx, Diane L Bolton, Andrey Tokarev, Rasmi Thomas, Hiroshi Takata, Lydie Trautmann, Shelly J Krebs, Kayv Adrian B McDermott, Robert T Bailer, Nicole Doria-Rose, Bijal Patel, Robert J Gorelick, Brandie A Fullmer, Alexandra Schuetz, Po Robert J O'Connell, Julie E Ledgerwood, Barney S Graham, Randall Tressler, John R Mascola, Nicolas Chomont, Nelson L Michael Nittaya Phanuphak, Jintanat Ananworanich, for the RV397 Study Group**

nature medicine

BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-018-0026-6

Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig I acute HIV infection

Donn J. Colby[1], Lydie Trautmann[2,3], Suteeraporn Pinyakorn[2,3], Louise Leyre[4], Amélie Pagliuzza[4], Eugène Kroon[1], Morgane Rolland[2,3], Hiroshi Takata[2,3], Supranee Buranapraditkun[2,3,5,6], Jintana Intasan[1], Nitiya Chomchey[1], Roshell Muir[7], Elias K. Haddad[7], Sodsai Tovanabutra[2,3], Sasiwimol Ubolyam[8], Diane L. Bolton[2,3], Brandie A. Fullmer[9], Robert J. Gorelick[9], Lawrence Fox[10], Trevor A. Crowell[2,3], Rapee Trichavaroj[11], Robert O'Connell[11], Nicolas Chomont[4], Jerome H. Kim[2,13], Nelson L. Michael[2], Merlin L. Robb[2,3], Nittaya Phanuphak[1], Jintanat Ananworanich[1,2,3,12]*
and The RV411 study group

AIDS and Cancer Virus Program: Enabling Capabilites
Dr. Claire Deleage, Tissue Analysis Core

AIDS and Cancer Virus Program

Frederick National Laboratory for Cancer Research
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JCI insight

RESEARCH ARTICLE

Combination anti–PD-1 and antiretroviral therapy provides therapeutic benefit against SIV

Geetha H. Mylvaganam,[1,2] Lynette S. Chea,[1,2] Gregory K. Tharp,[2] Sakeenah Hicks,[1,2] Vijayakumar Velu,[1,2] Smita S. Iyer,[1,2] Claire Deleage,[3] Jacob D. Estes,[3] Steven E. Bosinger,[2] Gordon J. Freeman,[4] Rafi Ahmed,[1,2] and Rama R. Amara[1,2]

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AIDS and Cancer Virus Program: Enabling Capabilites, Dr. Elena Chertova, Mr. Julian Bess, Jr.

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Cell Reports

Report

Site-Specific Glycosylation of Virion-Derived HIV-1 Env Is Mimicked by a Soluble Trimeric Immunogen

Weston B. Struwe,[1,2,8] Elena Chertova,[5,8] Joel D. Allen,[3,8] Gemma E. Seabright,[1,3] Yasunori Watanabe,[1,3] David J. Harvey,[3,7] Max Medina-Ramirez,[6] James D. Roser,[5] Rodman Smith,[5] David Westcott,[5] Brandon F. Keele,[5] Julian W. Bess, Jr.,[5] Rogier W. Sanders,[4,6] Jeffrey D. Lifson,[5] John P. Moore,[4,*] and Max Crispin[1,3,9,*]

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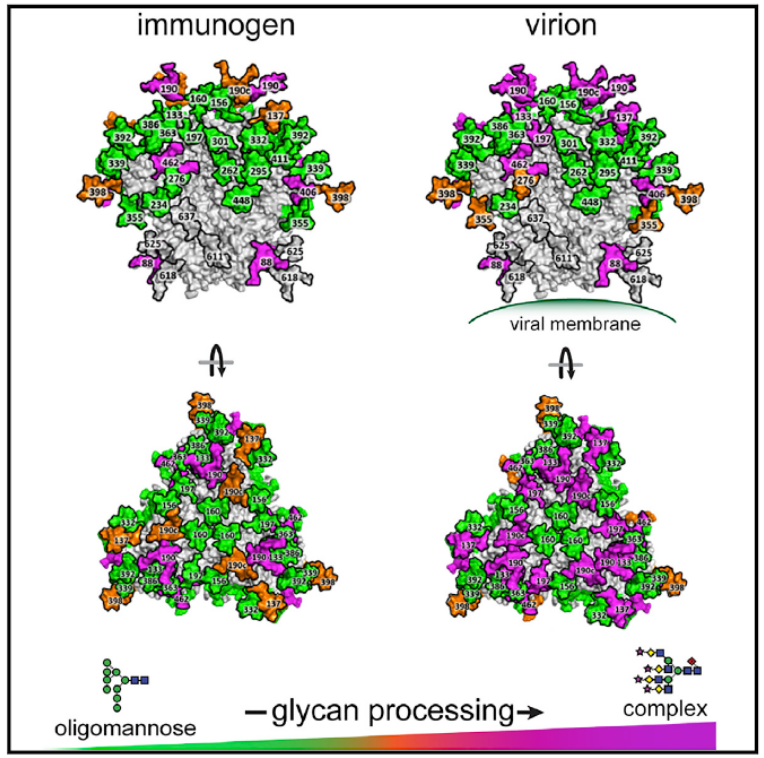

Highlights

- HIV envelope glycans are central features of broadly neutralizing antibody epitopes
- Recombinant mimetics of the HIV virus trimer are vaccine candidates
- Glycosylation of a leading trimer immunogen is similar to that of infectious virus

AIDS and *Cancer Virus* Program
Dr. Denise Whitby, Viral Oncology Section

AIDS and Cancer Virus Program

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Clin Cancer Res; 25(14) July 15, 2019

Clinical Trials: Targeted Therapy

Clinical Cancer Research

A Pilot Study of Liposomal Doxorubicin Combined with Bevacizumab followed by Bevacizumab Monotherapy in Patients with Advanced Kaposi Sarcoma

Ramya Ramaswami[1], Thomas S. Uldrick[1], Mark N. Polizzotto[1], Kathleen M. Wyvill[1], Priscila Goncalves[1], Anaida Widell[1], Kathryn Lurain[1], Seth M. Steinberg[2], William Douglas Figg[3], Giovanna Tosato[4], Denise Whitby[5], and Robert Yarchoan[1]

Risk factors for Kaposi's sarcoma associated herpesvirus (KSHV) DNA in blood and in saliva in rural Uganda

Angela Nalwoga[1,2], Marjorie Nakibuule [1], Vickie Marshall[3], Wendell Miley[3], Nazzarena Labo[3], Stephen Cose[1,2], Denise Whitby[3*], Robert Newton[1,4*]

Clin Infect Dis. 2019 Sep 26. pii: ciz916. doi: 10.1093/cid/ciz916. [Epub ahead of print]

PLOS PATHOGENS

RESEARCH ARTICLE

Gammaherpesvirus infection and malignant disease in rhesus macaques experimentally infected with SIV or SHIV

Vickie A. Marshall[1], Nazzarena Labo[1], Xing-Pei Hao[1,2], Benjamin Holdridge[1], Marshall Thompson[1], Wendell Miley[1], Catherine Brands[1], Vicky Coalter[1], Rebecca Kiser[1], Miriam Anver[2], Yelena Golubeva[2], Andrew Warner[2], Elaine S. Jaffe[3], Michael Piatak, Jr.[1†], Scott W. Wong[4], Claes Ohlen[1†], Rhonda MacAllister[5], Jeremy Smedley[5], Claire Deleage[1], Gregory Q. Del Prete[1], Jeffrey D. Lifson[1], Jacob D. Estes[1], Denise Whitby[1]*

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AIDS and Cancer Virus Program

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A unique program, with unique capabilities, conducting world class investigator initiated research, and providing extensive collaborative support to non-ACVP investigators at NIH and in the extramural community, seeking to advance the overall AIDS research enterprise, consistent with the mission of the NCI and the Frederick National Laboratory

Thank you!

Questions?