Nonhuman primate studies for the prevention of HIV infection

Studies of mucosal pathogenesis, transmission, and prevention in the macaque model of HIV

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Clinic, Lab, Office and Administratio

Breeding colony

Room for expansion

HIV-1 in humans	SIV in macaques
Lentivirus	Lentivirus
Gag, Pol, Env, Rev, Tat, Vpr, *Vpu*	Gag, Pol, Env, Rev, Tat, Vpr, *Vpx*
CD4/CK Rc tropism	CD4/CK Rc tropism
CCR5 tropic (most)	CCR5 tropic (most)
Asymptomatic stage (~10 yrs)	Asymptomatic stage (~1-3 yrs)
CD4+ T cell decline	CD4+ T cell decline
Initial viral peak followed by low levels	Initial viral peak followed by low levels
Persistent infection	Persistent infection
Wasting disease, diarrhea	Wasting disease, diarrhea
Lymphadenopathy	Lymphadenopathy
Massive intestinal CD4 depletion in acute infection	Massive intestinal CD4 depletion in acute infection
“Neoplasia”	“Neoplasia”
Lymphoma	Lymphoma
Kaposi’s sarcoma (HHV-8)	RRV infection (HHV-8 like)
AIDS (opportunistic infections)	AIDS (opportunistic infections)
M. Avium	M. Avium
Candida	Candida
E. Bienusii (Microsporidia)	E. Bienusii (Microsporidia)
Cryptosporidia	Cryptosporidia
CMV	CMV
Pneumocystis	Pneumocystis
Toxoplasmosis	Toxoplasmosis
EBV ~ lymphomas	EBV - like lymphocryptovirus
PML - JC virus (polyomavirus)	PML - SV40 virus (polyomavirus)

Macaque models for transmission, pathogenesis, and prevention studies

Asian macaque (*Macaca mulatta*)

a.k.a; rhesus macaque

Indian or Chinese origin - similar transmissibility
Seasonal breeders
Advantage; availability, established protocols and reagents

Pigtailed macaque (*Macaca nemestrina*)

Reportedly more susceptible to disease progression
Year-round cycling
Disadvantage; limited availability

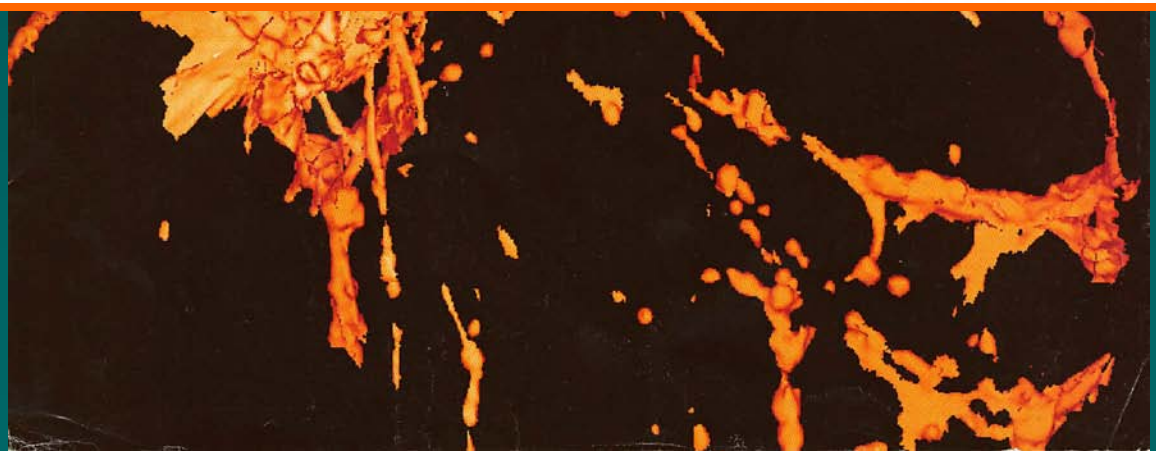
Cynomolgus macaque (Macaca fasicularis)

a.k.a. crab eating macaque, long tailed macaque
Reportedly less susceptible to disease progression
Advantage; available; smaller (less expensive)
Disadvantage; microbicide applications not well established, small vaginal lumen volume - endoscopy limited

Veazey et al, Animal Models for Microbicides; *Current HIV Research*, 2012

Gastrointestinal Tract as a Major Site of CD4$^+$ T Cell Depletion and Viral Replication in SIV Infection

Ronald S. Veazey, MaryAnn DeMaria, Laura V. Chalifoux, Daniel E. Shvetz, Douglas R. Pauley, Heather L. Knight, Michael Rosenzweig, R. Paul Johnson, Ronald C. Desrosiers, Andrew A. Lackner*

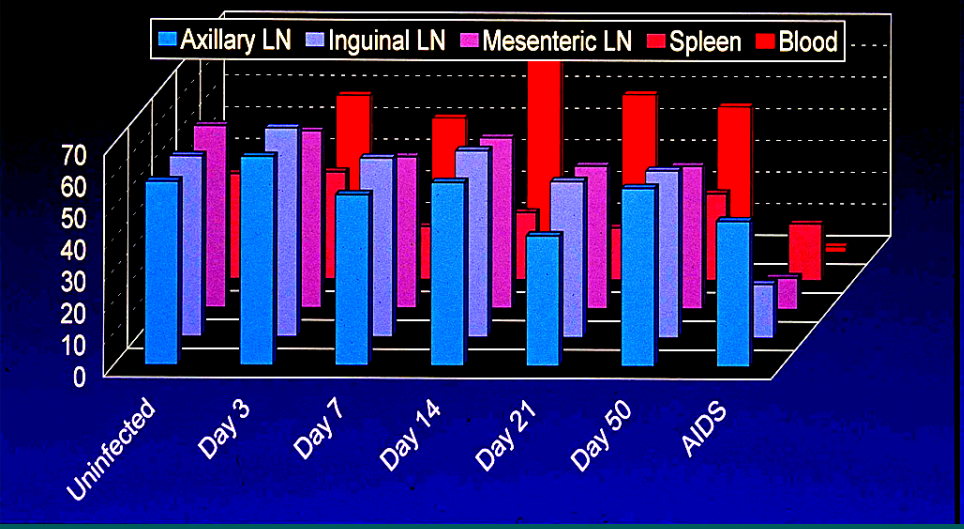


HIV Pathogenesis

HIV and SIV infection results in rapid and massive loss of intestinal CD4+ T cells

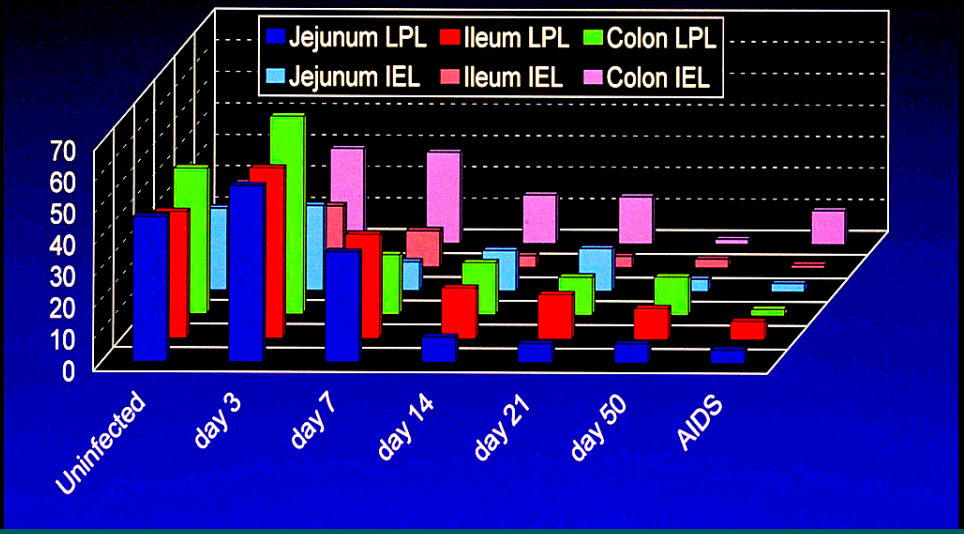
CD4+ cells remain stable in peripheral tissues in early infection

(%CD4+ gated on CD3+ lymphocytes)



CD4+ cell depletion occurs rapidly in the intestine

(%CD4+ gated on CD3+ lymphocytes)

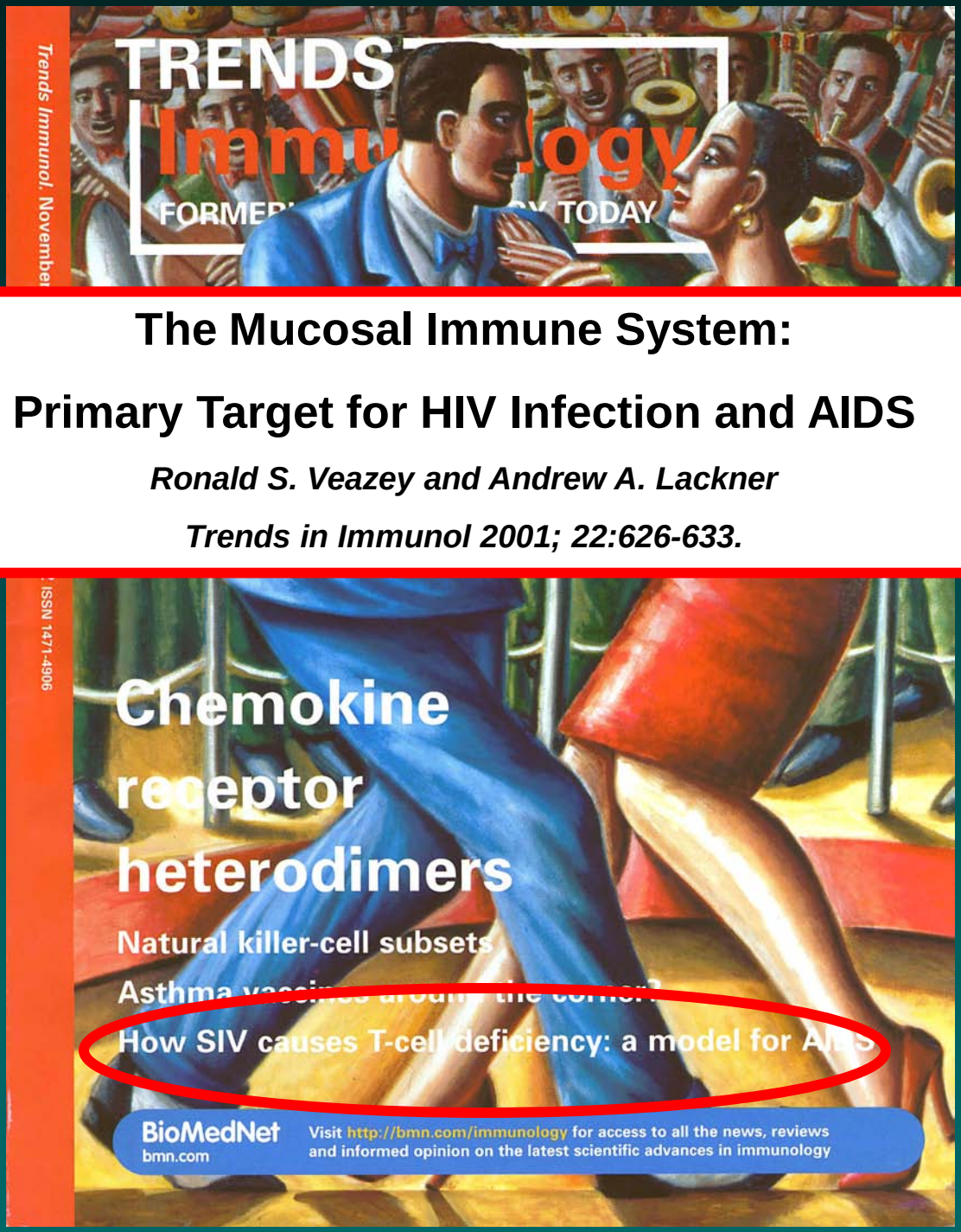


- Veazey, Lackner et al, Intestinal tract as a major site of CD4+ T cell depletion in early SIN infection; Science 1998.

CONFIRMED IN HUMANS 7 YEARS LATER:

- Brenchley, Douek, et al; CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J. Exp. Med., 2004.

- Mehandru, Markowitz, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. J. Exp. Med., 2004.



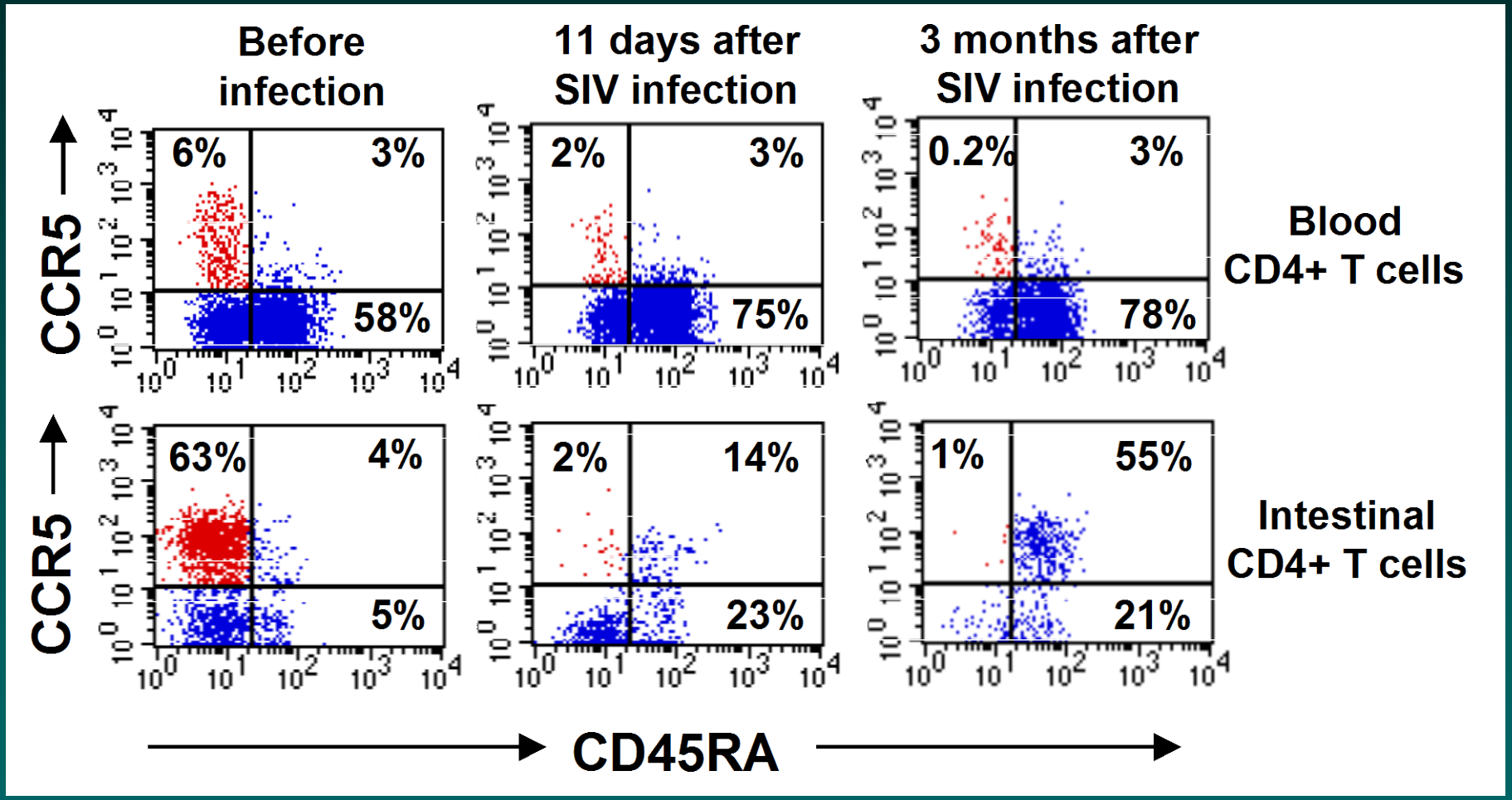
The Mucosal Immune System:

Primary Target for HIV Infection and AIDS

Ronald S. Veazey and Andrew A. Lackner

Trends in Immunol 2001; 22:626-633.

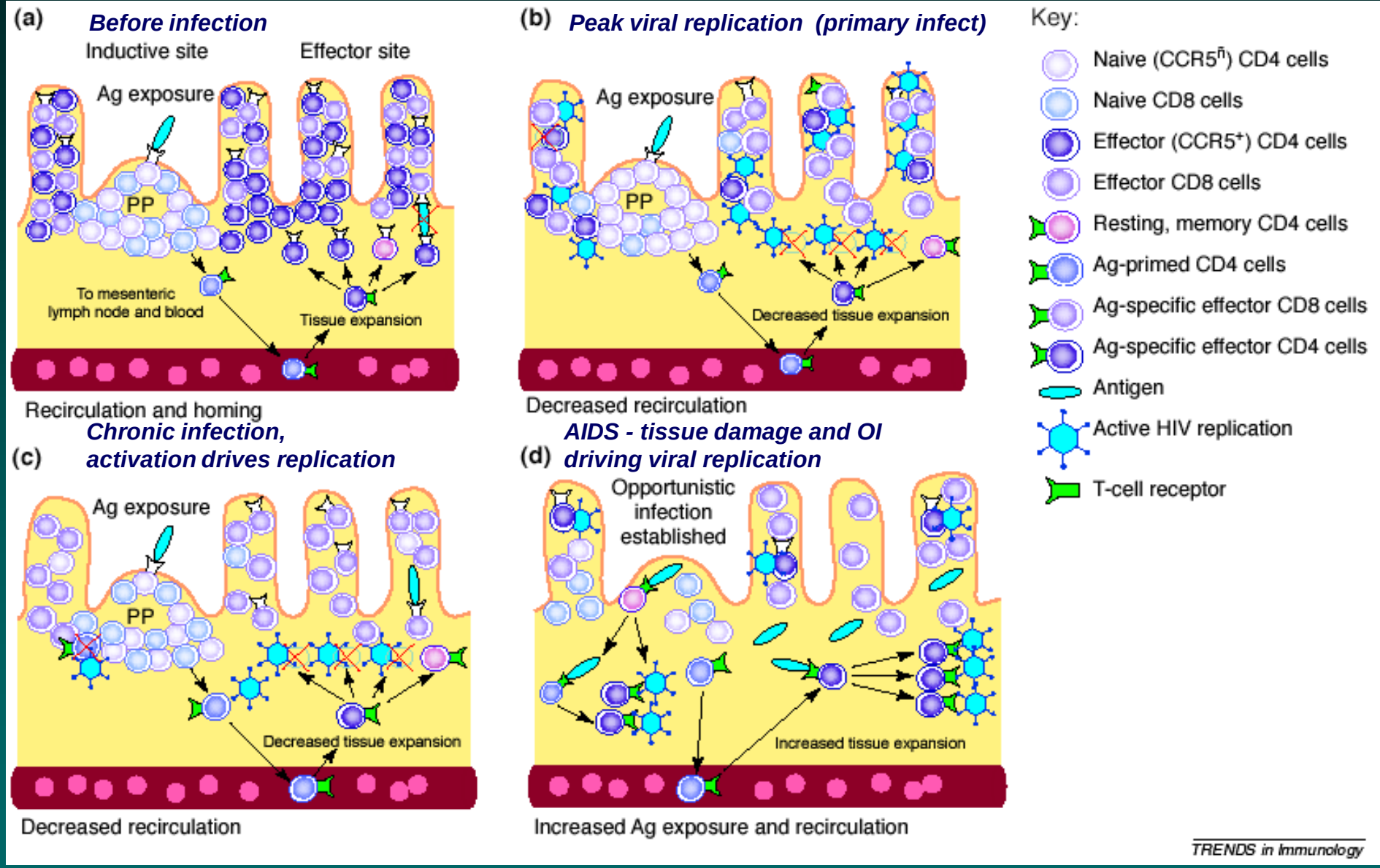
Memory CCR5+ CD4+ T cells are selectively lost in all tissues in early infection

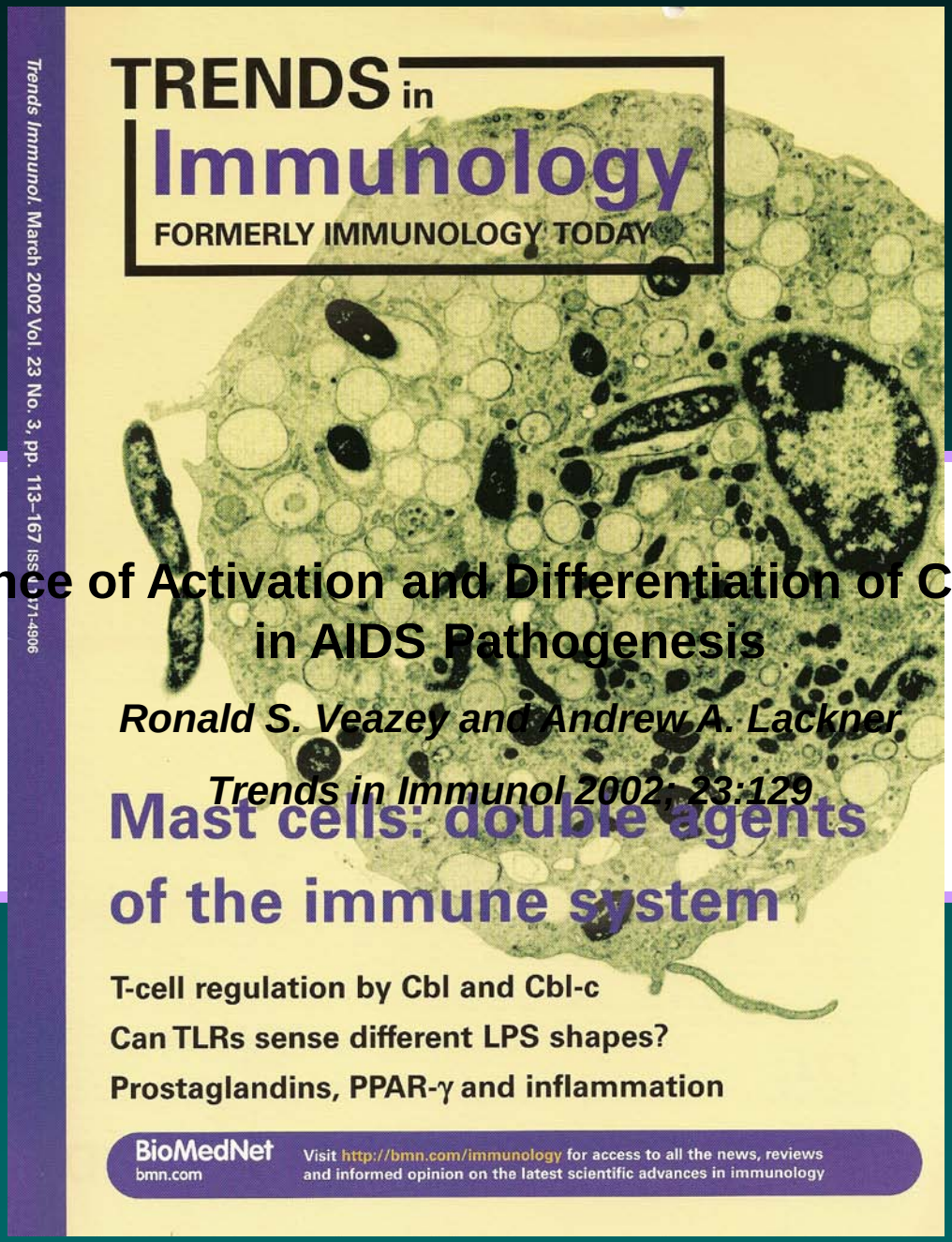


Veazey et al., J Virol 2000, Trends in Immunology, 2001

Activation of CD4+ T cells drives viral replication

(Veazey et al, Trends in Immunol, 2001)





Importance of Activation and Differentiation of CD4+ T cells in AIDS Pathogenesis

Ronald S. Veazey and Andrew A. Lackner

Trends in Immunol 2002; 23:129

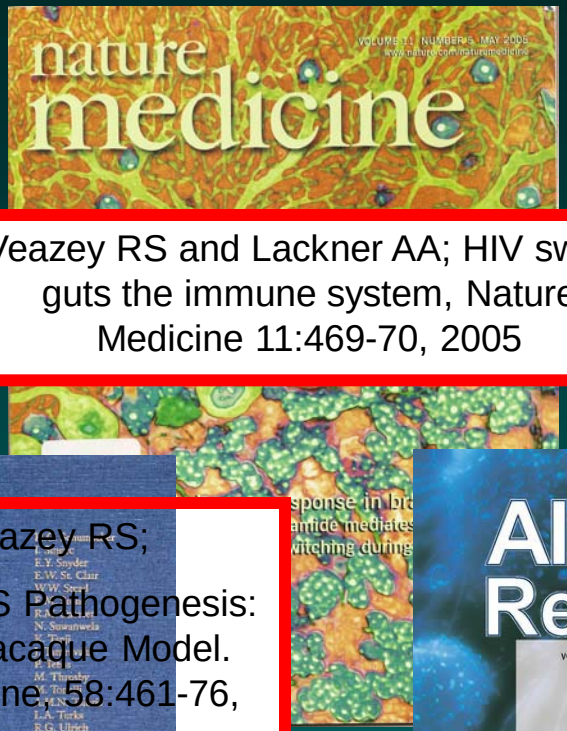
CONFIRMED IN HUMANS 5 YEARS LATER: Brenchley, Douk et al.; Nat Med 2006: Microbial translocation is a cause of systemic immune activation in chronic HIV infection

THEORETICAL DYNAMICS OF CD4+ T CELL ACTIVATION AND DESTRUCTION IN HIV

(Veazey RS, Future HIV Therapy, Vol 1, 2007)

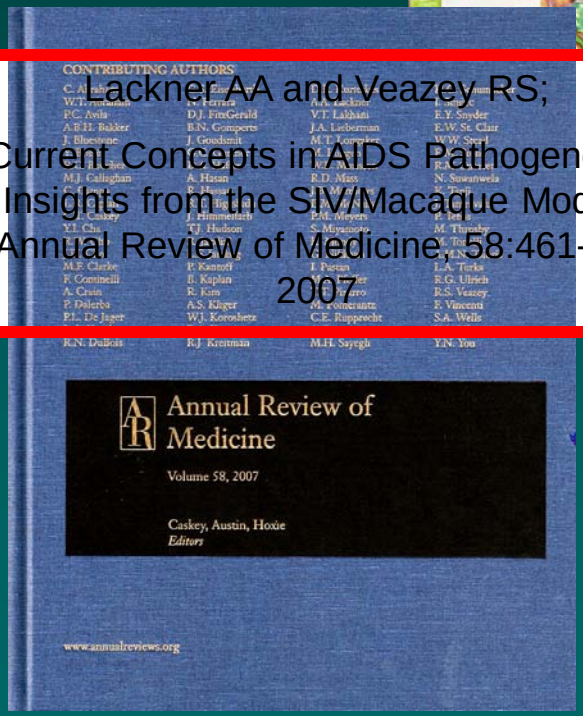
Wang, Veazey et al., Simian immunodeficiency virus selectively infects proliferating CD4+ T cells in neonatal rhesus macaques, *Blood* 2010

Selected invited reviews and papers

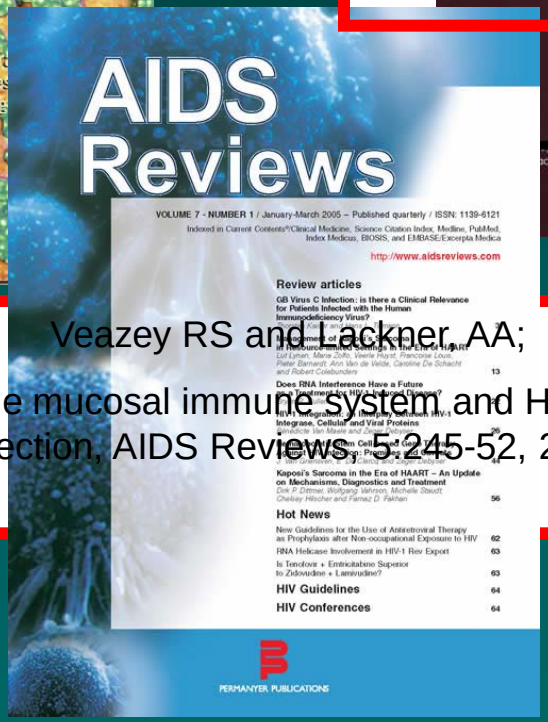


Veazey RS and Lackner AA; HIV swiftly guts the immune system, Nature Medicine 11:469-70, 2005

Veazey RS; Mucosal immunopathogenesis of HIV infection: implications for vaccine development, Future HIV Therapy 1: 103-112, 2007



ackner AA and Veazey RS; Current Concepts in AIDS Pathogenesis: Insights from the SIV/Macaque Model. Annual Review of Medicine, 58:461-76, 2007



Veazey RS and Lackner AA; The mucosal immune system and HIV-1 infection, AIDS Reviews, 5:245-52, 2003

1 March 2003
Volume 187
Number 5

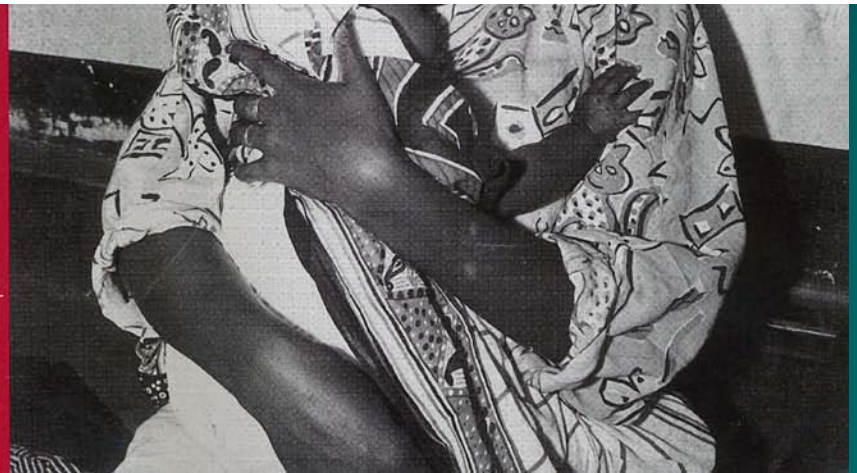
The Journal of Infectious Diseases

Vaginal CD4$^+$ T Cells Express High Levels of CCR5 and Are Rapidly Depleted in Simian Immunodeficiency Virus Infection

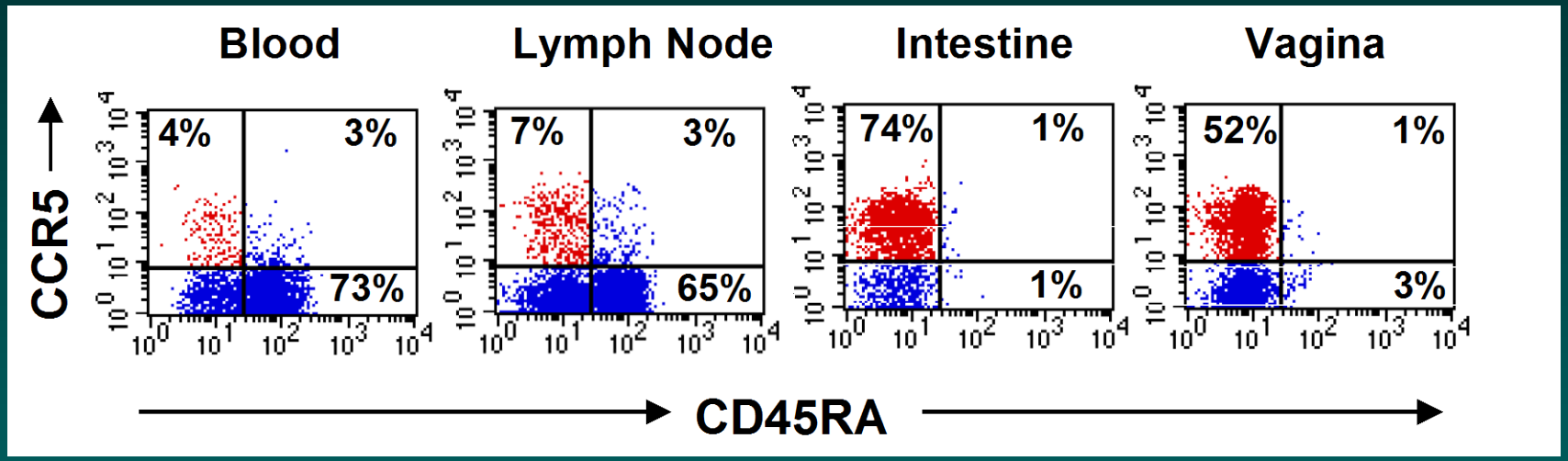
Ronald S. Veazey, Preston A. Marx, and Andrew A. Lackner

Tulane National Primate Research Center, Tulane University Health Sciences Center, Covington, Louisiana

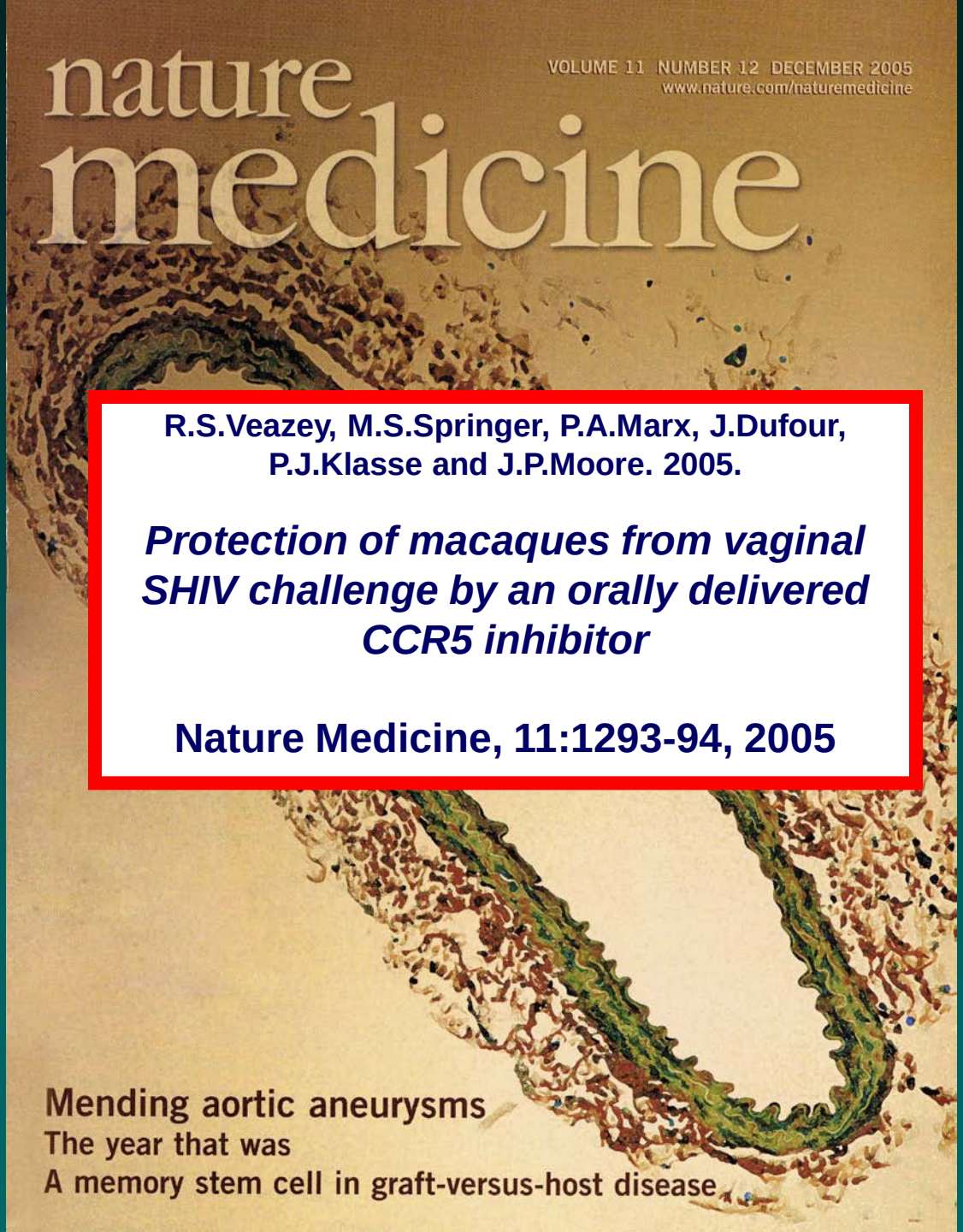
IDSA
An Official Publication of the Infectious Diseases Society of America



Target cell (CD4+CCR5+ memory T cells) distribution in different tissue compartments (Gated through CD4+ Lymphocytes)



Optimal viral target cells reside in mucosal tissues (Veazey, Trends in Immunology, 2001)



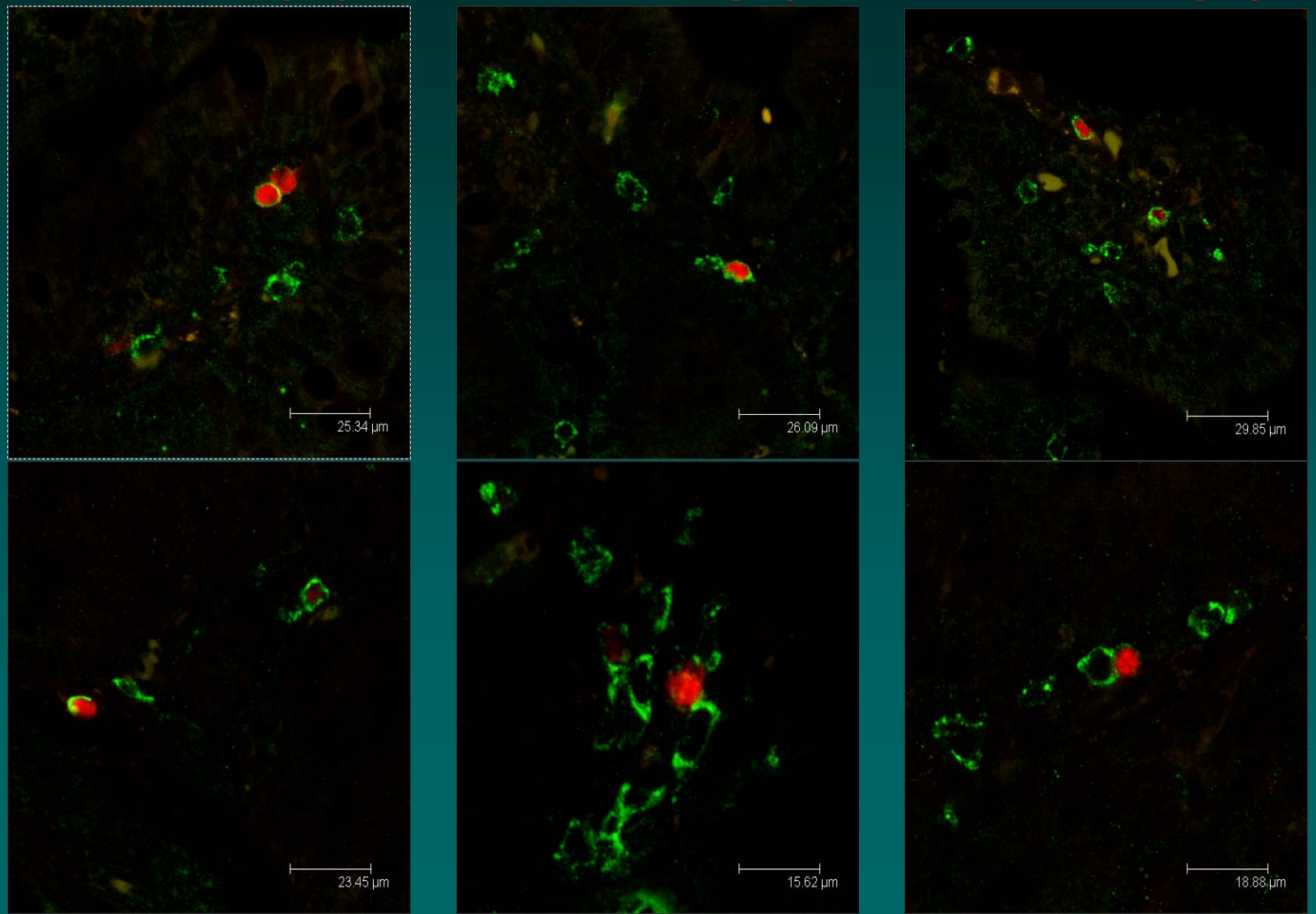
R.S.Veazey, M.S.Springer, P.A.Marx, J.Dufour, P.J.Klasse and J.P.Moore. 2005.

Protection of macaques from vaginal SHIV challenge by an orally delivered CCR5 inhibitor

Nature Medicine, 11:1293-94, 2005

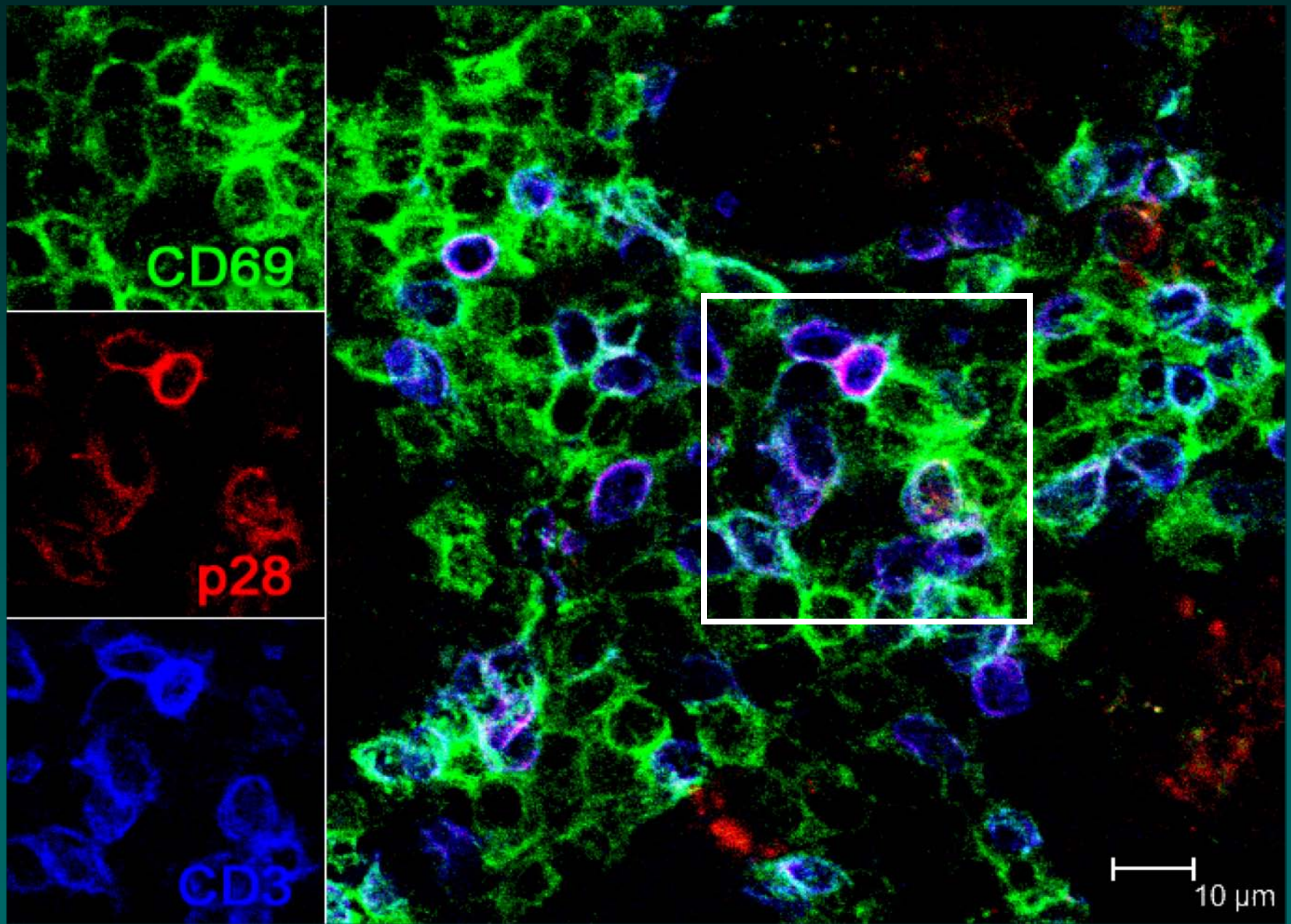
Phenotyping SIV infected cells in macaque intestines - Most infected cells in acute infection are CD4+CD45RO+ memory T cells

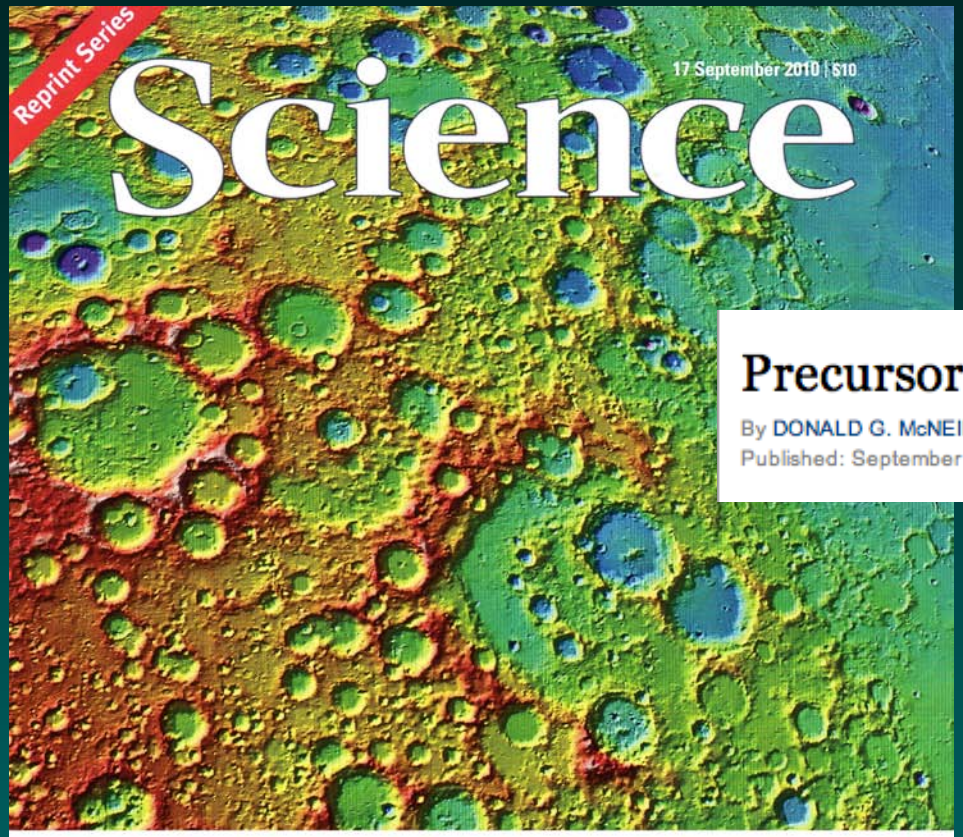
Wang,et al; Blood, 2007



Phenotype of productively infected T cells in intestine

CD69 + SIV (P28) + CD3



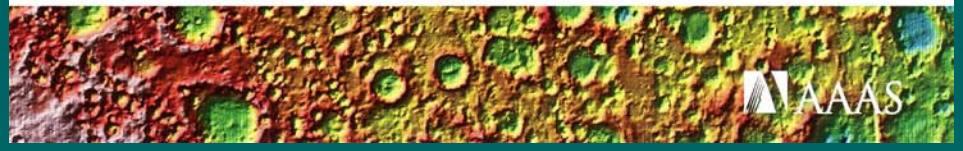


Precursor

By DONALD G. McNEIL
Published: September 1

Island Biogeography Reveals the Deep History of SIV

Michael Worobey,[1] Paul Telfer,[2,3] Sandrine Souquière,[3] Meredith Hunter,[2] Clint A. Coleman,[2] Michael J. Metzger,[2] Patricia Reed,[2,3] Maria Makuwa,[3] Gail Hearn,[4] Shaya Honarvar,[4] Pierre Roques,[3] Cristian Apetrei,[2] Mirdad Kazanji,[3] Preston A. Marx[2]*

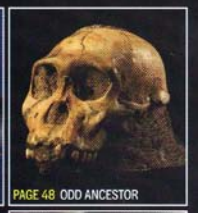


THE YEAR IN SCIENCE

DISCOVER

Science, Technology, and The Future

100 TOP STORIES OF 2010



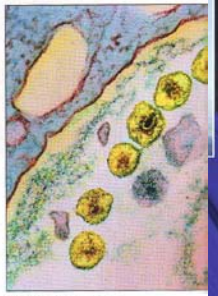
MEDICINE

20 AIDS Virus Has an Ancient History

HIV IS A NEWCOMER AMONG HUMAN pathogens, having caused the first known cases of AIDS within the past few decades. So scientists suspected that SIV, the primate virus that spawned HIV, was just a few hundred years older. Tulane University virologist Preston Marx published research in September that suggests otherwise: SIV seems to be at least 32,000 years old, meaning it coexisted with people nearly all that time before HIV emerged.

Marx's team did SIV tests on monkeys from Bioko Island, which was cut off from the African continent 10,000 years ago. The Bioko SIV strains all shared ancestry with strains from the African mainland, indicating the virus is at least that old and probably much older. "Events in the 20th century launched the virus from a benign monkey virus into a human epidemic," Marx says. The growing use of blood transfusions and the rise of crowded cities may have helped pass SIV around and let it evolve into HIV.

If we do not figure out what triggered the HIV epidemic, it will be hard to prepare for what might come next. "We could be making new strains without knowing how to stop or control them," Marx says. MONICA HEGER

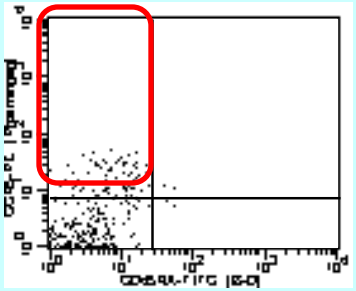


SIV, the yellow circles seen in this bone marrow culture, is the precursor to HIV.

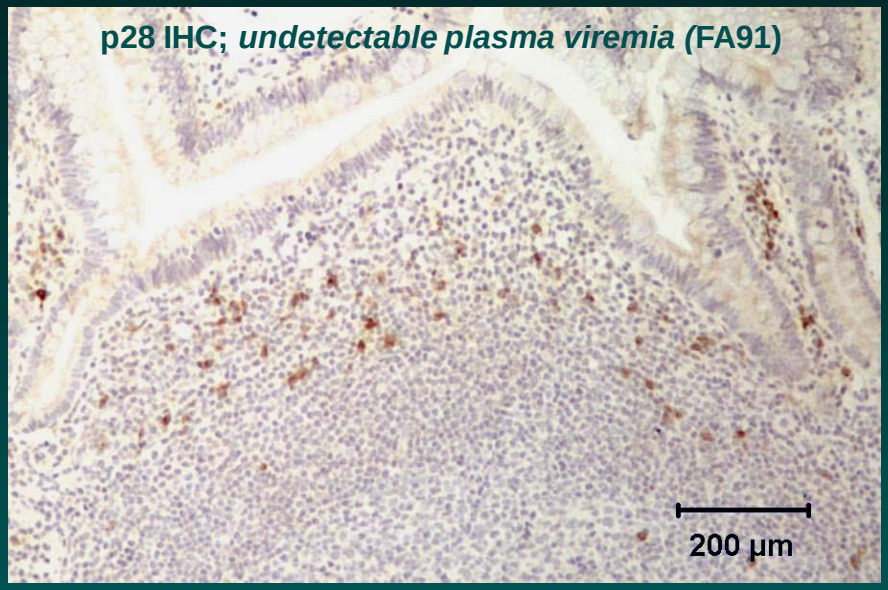
Non-progressing or “natural” primate hosts (African green monkeys and Sooty mangabeys) are naturally “missing” viral target cells in the intestine (Pandrea Veazey et al, Blood 2007)

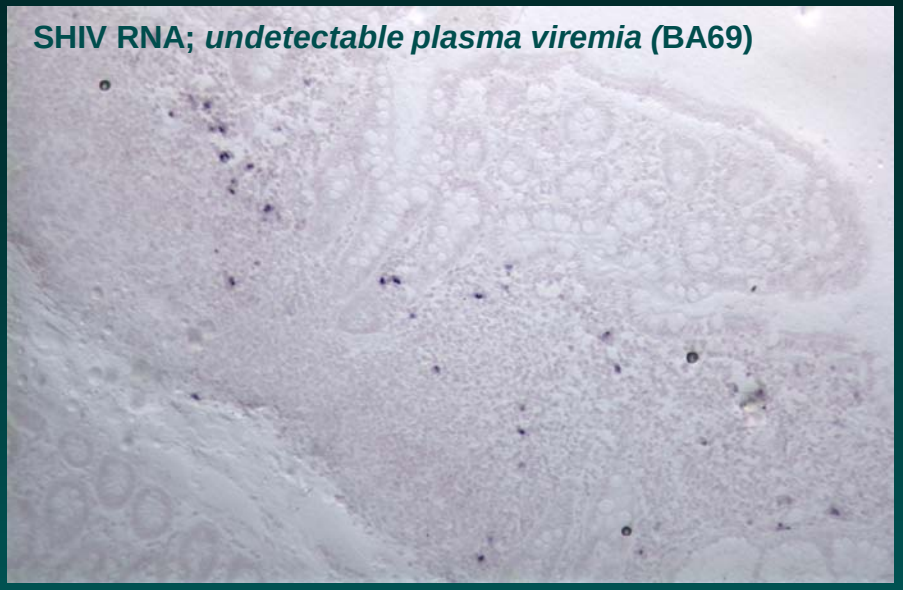
5%	37%
30%	29%

19%



Viral replication persists in *intestinal inductive sites* in SIV and SHIV Infected *macaques controlling viremia* (<125 RNA copies/ml plasma)





Viral replication persists in GALT in HIV infected patients on ART
Anton et al, AIDS 2003; Mehandru, Markowitz, et al, PLoS Med 2006

Intestinal CD4+ T cells are not fully restored in HIV patients on ART
Guadalupe et al, J Virol 2006; Mehandru, Markowitz, et al, PLoS Med 2006

Viral replication and continuing CD4+ T cell loss occurs in the gut, despite "HAART" or apparent "control" of plasma viremia

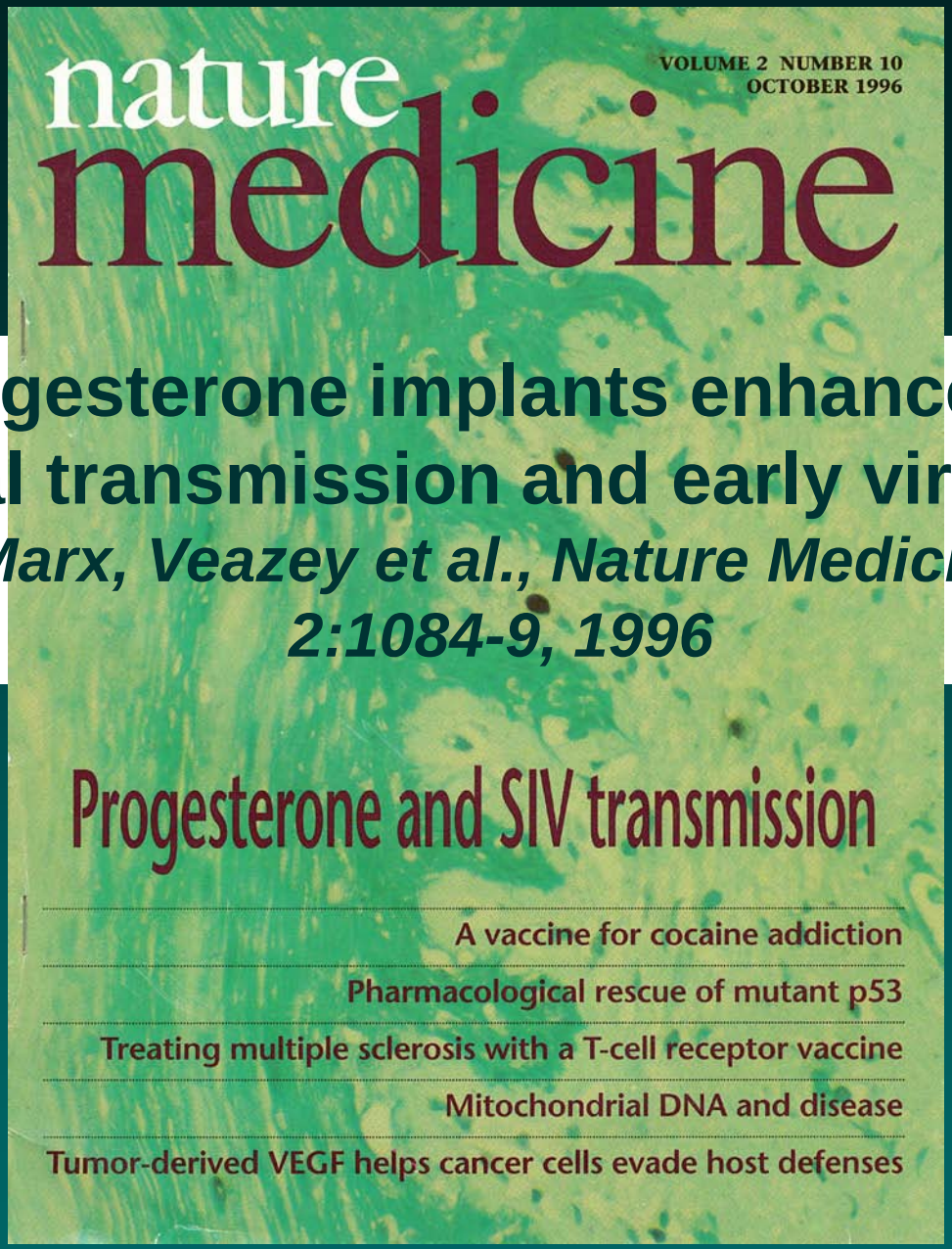
Activated, memory CD4+CCR5+ T cells in mucosal tissues (intestines) are major targets for *early* SIV/HIV infection and amplification

Activated (functional) CD4+CCR5+ memory cells predominantly reside in mucosal tissues

Natural hosts have *evolved?* to become less reliant on (reduce or eliminate) CCR5+CD4+ T cells in tissues

Mucosal cells play a major role in early HIV pathogenesis

Do CD4+ T cells play a role in transmission?

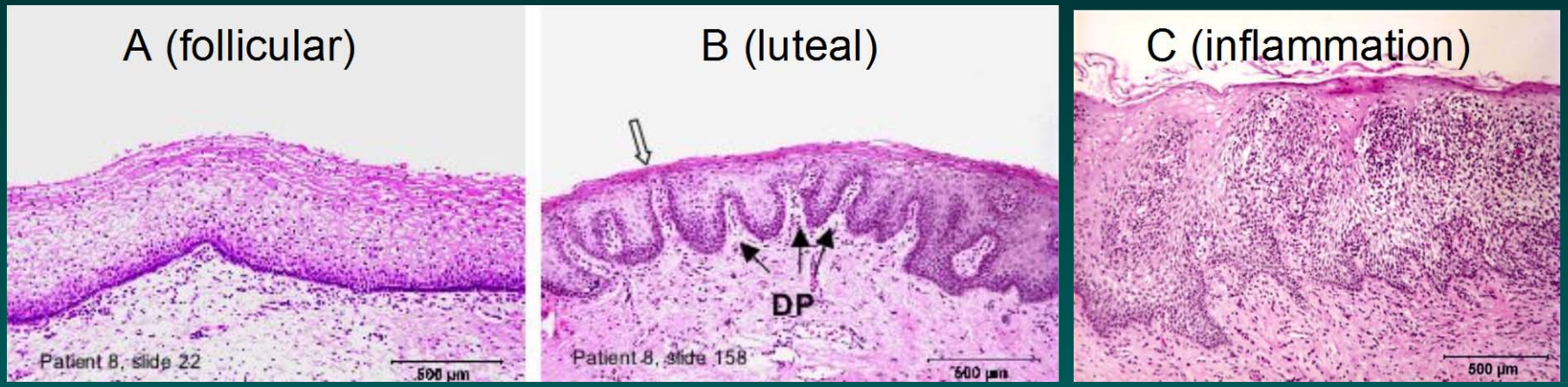


Progesterone implants enhance SIV vaginal transmission and early virus load.

Marx, Veazey et al., Nature Medicine 2:1084-9, 1996

CONFIRMED IN HUMANS 15 YEARS LATER: Heffron, R., Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study, Lancet Infect. Dis. 2011.

Mechanisms of vaginal HIV-1 transmission? Thinning or inflammation of the vaginal epithelium?

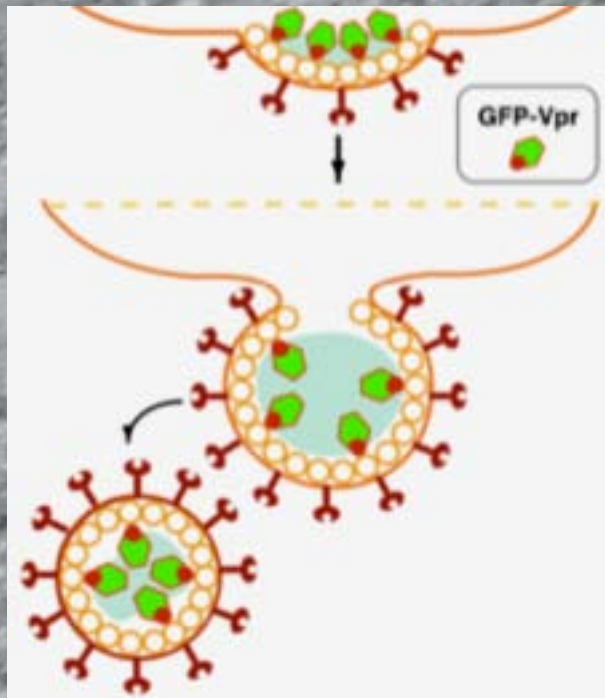


Vaginal biopsies from the same normal woman at peak follicular (A) and luteal (B) stage of menses. Note that the luteal phase has marked areas of thinning (open arrow) associated with dermal papillae (DP; arrows).

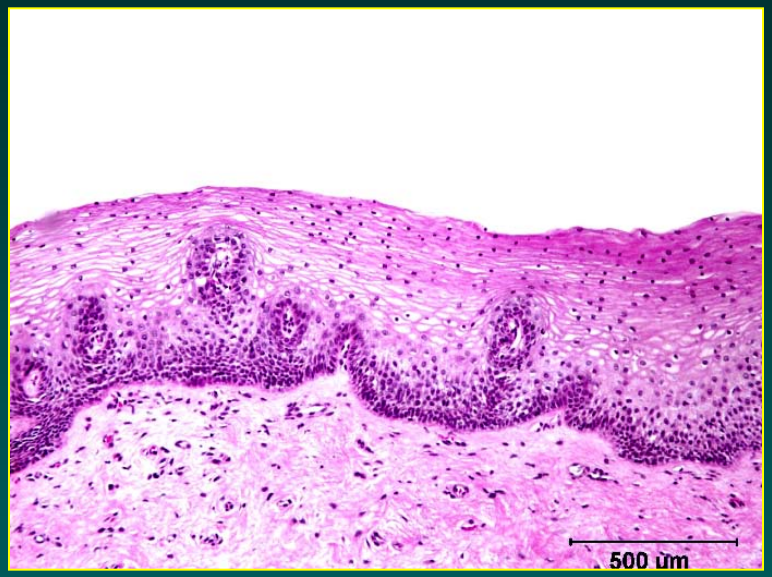
C shows marked inflammation and lymphocytic inflammation in the vaginal mucosa of a clinically "normal" woman.

ATTACHMENT OR FUSION INHIBITORS –

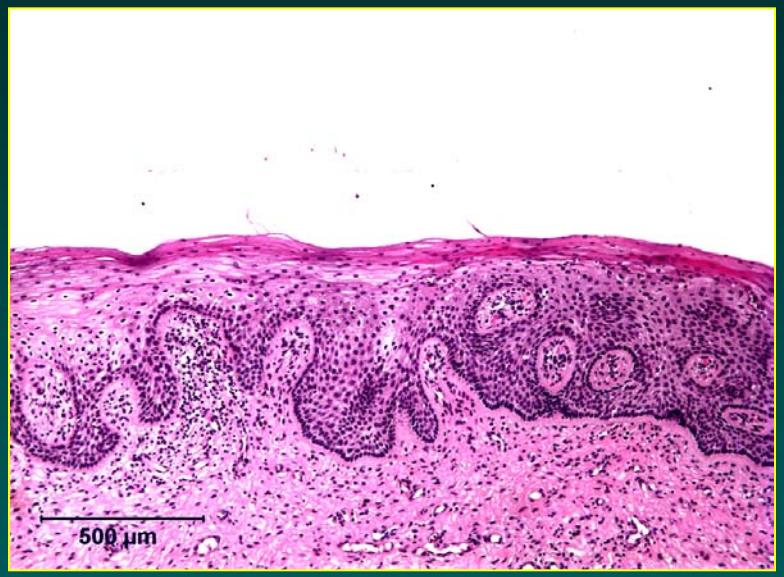
A SAFER APPROACH FOR MICROBICIDES?



Comparative histology of the vagina

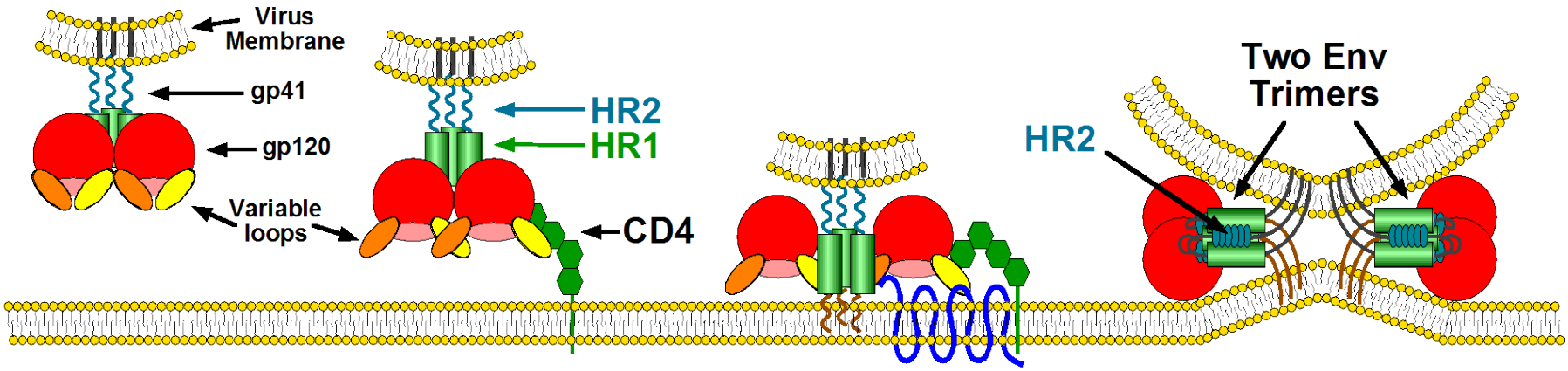


Human vagina
(luteal phase)



Macaque vagina
(luteal phase)

Fusion inhibitors in clinical development; Mechanisms of action



Native Trimer → **CD4 Binding** (T20 binding site exposure) → **CoR Binding** (Fusion peptide insertion?) → **6-Helix Bundle Formation** (Membrane fusion)

CD4 Binding	CoR Binding	6-Helix Bundle Formation
PRO 542 BMS-806 TNX-355	SCH-C, SCH-D AMD3100, AMD070 PRO-140, UK-427,857	T-20 (Enfuvirtide) T-1249

Moore JP, Doms RW. 2003. Proc Natl Acad Sci 100, 10598-10562.

nature medicine

VOLUME 9 NUMBER 3
MARCH 2003

www.nature.com/naturemedicine

Prevention of virus transmission to macaque monkeys by a vaginally applied monoclonal antibody to HIV-1 gp120

RONALD S. VEAZEY[1], ROBIN J. SHATTOCK[2], MELISSA POPE[3], J. CHRISTIAN KIRIJAN[1], JENNIFER JONES[3], QINXUE HU[2], TOM KETAS[4], PRESTON A. MARX[1], PER JOHAN KLASSE[5], DENNIS R. BURTON[6] & JOHN P. MOORE[4]

[1]*Tulane National Primate Research Center, Tulane University Health Sciences Center, Covington, Louisiana, USA*
[2]*Department of Infectious Diseases, St. George's Hospital Medical School, London, UK*
[3]*Center for Biomedical Research, The Population Council, New York, New York, USA*
[4]*Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, New York, USA*
[5]*Jefferiss Research Trust Laboratories, Wright-Fleming Institute, Imperial College, London, UK*
[6]*Departments of Immunology and Molecular Biology, The Scripps Research Institute, La Jolla, California, USA*
Correspondence should be addressed to J.P.M.; e-mail: jpm2003@med.cornell.edu

Immunotherapy

A microbicide for HIV?

Targeting T cells to tumors

Kaposi sarcoma and β-catenin

Blocking hyperglycemic damage

Alternative role for clotting factors in pregnancy

Science
15 October 2004
Vol. 306 No. 5695
Pages 357–556 $10

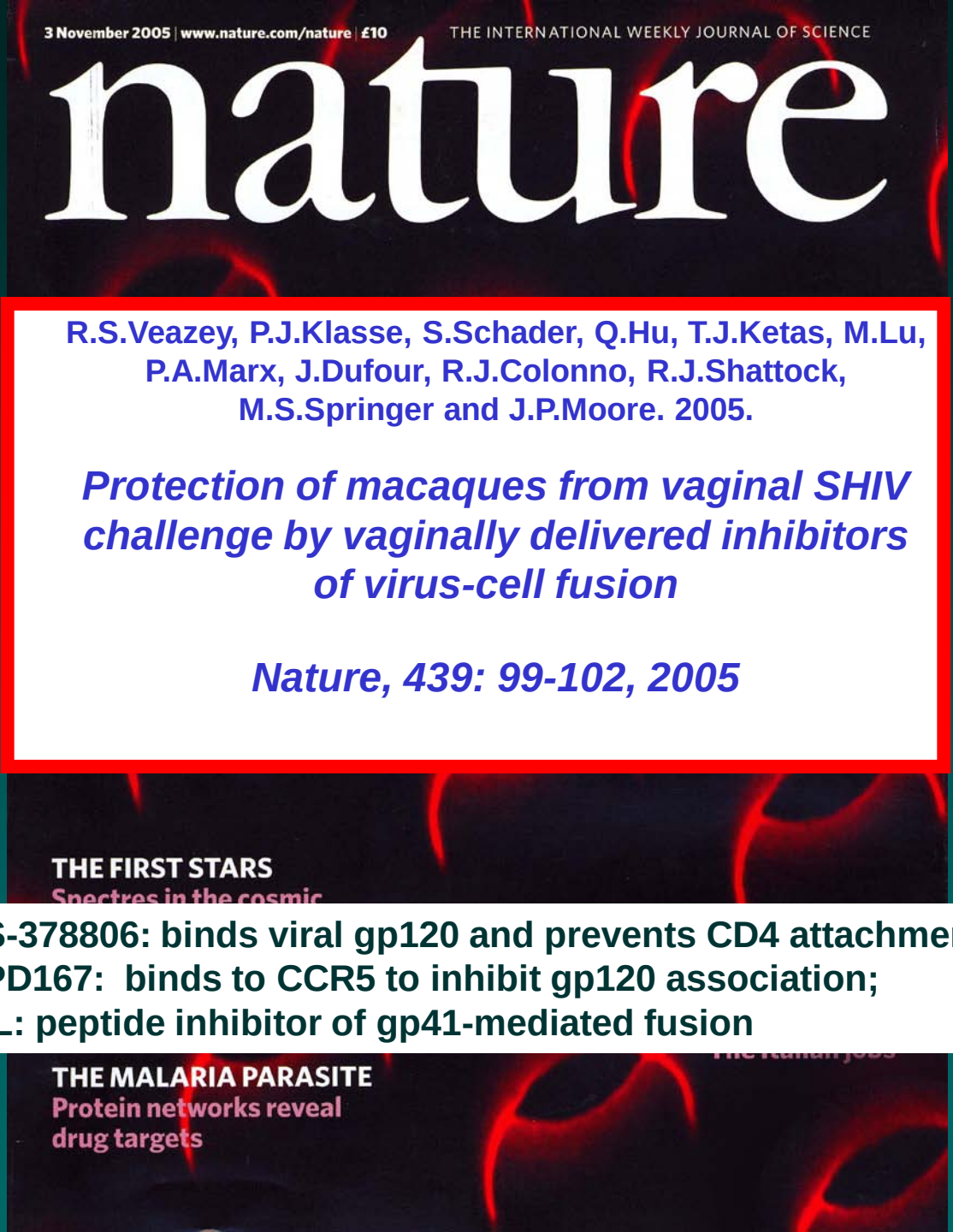
Prevention of Vaginal SHIV Transmission in Rhesus Macaques Through Inhibition of CCR5

Michael M. Lederman,[1*†] Ronald S. Veazey,[2*] Robin Offord,[3*] Donald E. Mosier,[4] Jason Dufour,[2] Megan Mefford,[2] Michael Piatak Jr.,[5] Jeffrey D. Lifson,[5] Janelle R. Salkowitz,[1] Benigno Rodriguez,[1] Andrew Blauvelt,[6‡] Oliver Hartley[3]

Topical agents, such as microbicides, that can protect against human immunodeficiency virus (HIV) transmission are urgently needed. Using a chimeric simian/human immunodeficiency virus (SHIV SF162), which is tropic for the chemokine receptor CCR5, we report that topical application of high doses of PSC-RANTES, an amino terminus–modified analog of the chemokine RANTES, provided potent protection against vaginal challenge in rhesus macaques. These experimental findings have potentially important implications for understanding vaginal transmission of HIV and the design of strategies for its prevention.

High dose of topical microbicides (mg/ml or mM) are required to prevent vaginal HIV-1 transmission

PSC-RANTES dose titration results (Lederman, et al., Science 2004)



R.S.Veazey, P.J.Klasse, S.Schader, Q.Hu, T.J.Ketas, M.Lu, P.A.Marx, J.Dufour, R.J.Colonno, R.J.Shattock, M.S.Springer and J.P.Moore. 2005.

Protection of macaques from vaginal SHIV challenge by vaginally delivered inhibitors of virus-cell fusion

Nature, 439: 99-102, 2005

BMS-378806: binds viral gp120 and prevents CD4 attachment:;
CMPD167: binds to CCR5 to inhibit gp120 association;
C52L: peptide inhibitor of gp41-mediated fusion

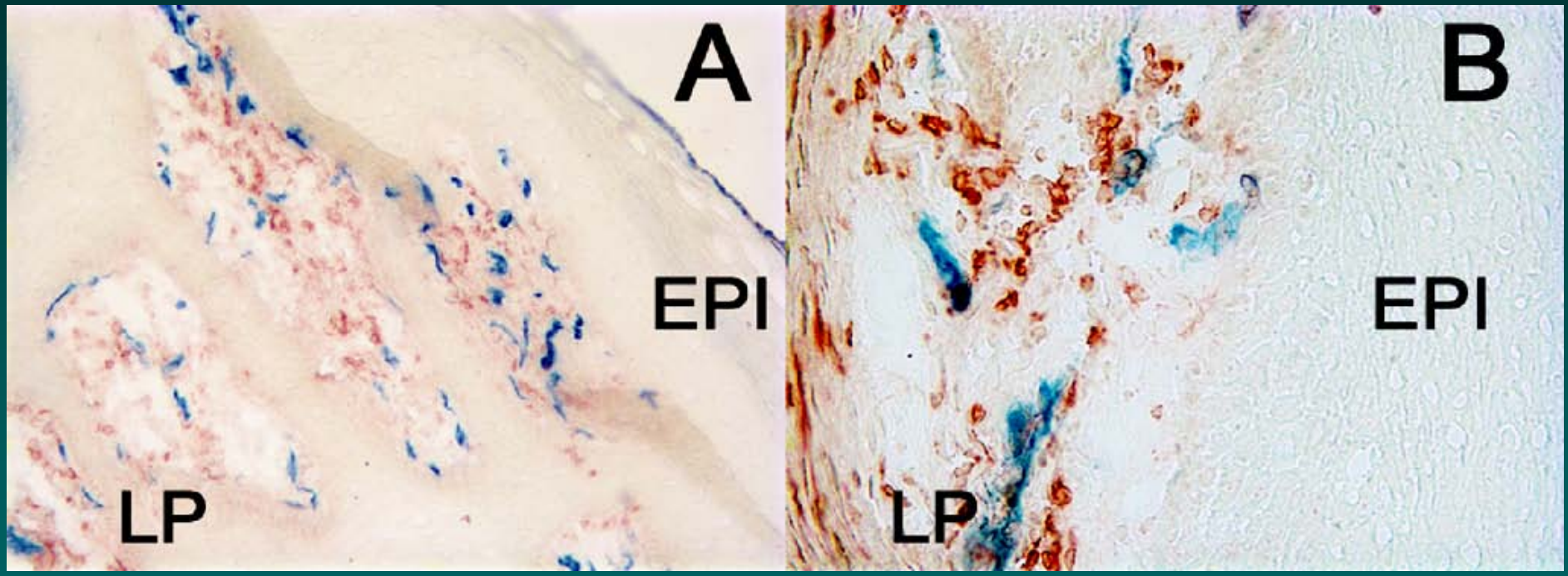
Blocking either CD4 or CCR5 receptors can completely prevent vaginal HIV transmission

Implications for transmission, vaccine development?

CD4+CCR5+ cells are the first cells infected, and critically involved in establishment of HIV infection

Blocking CD4 or CCR5 binding alone can completely prevent vaginal transmission

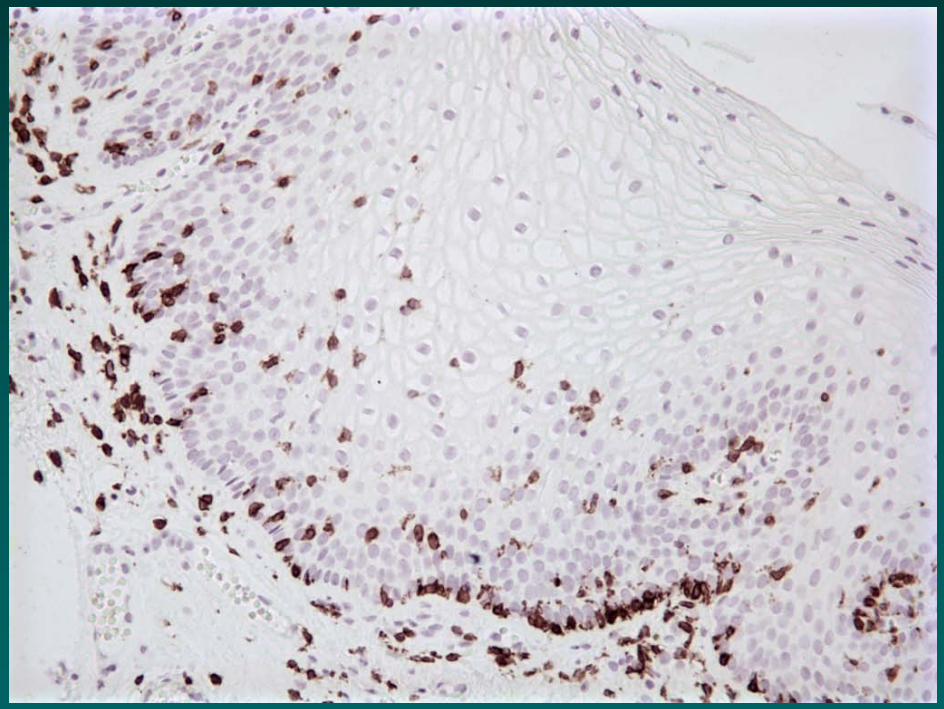
Target cells for HIV transmission in the vagina, Poonia et al, 06



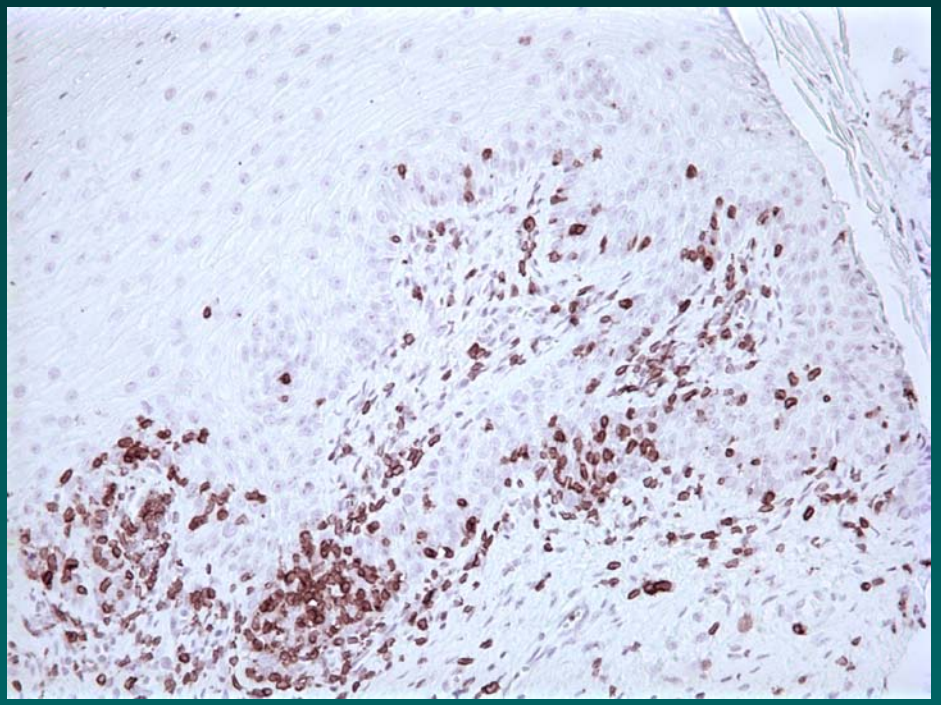
Dual-label immunohistochemistry for CD4 (red) and CCR5 (blue) in the vagina of normal (non-progestin treated) rhesus macaques. EPI=epithelium, LP=lamina propria

T cells in rhesus and human vagina

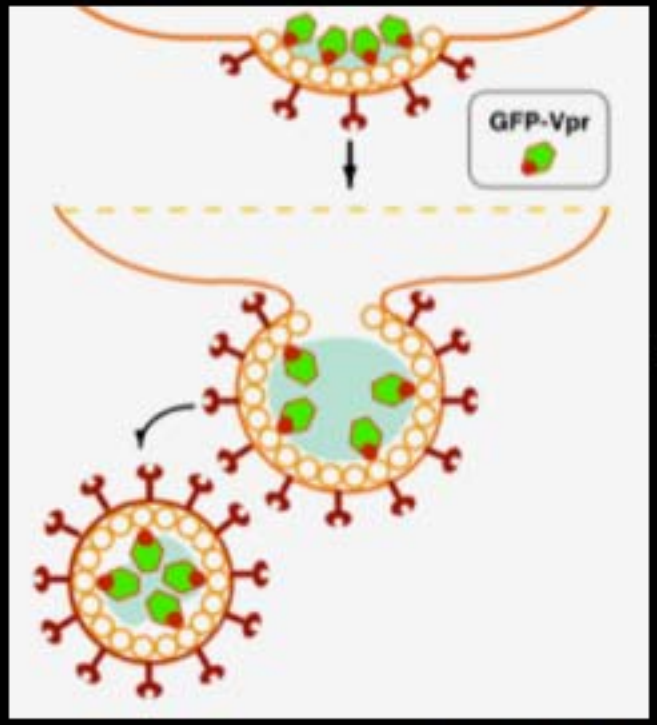
CD3 human vagina



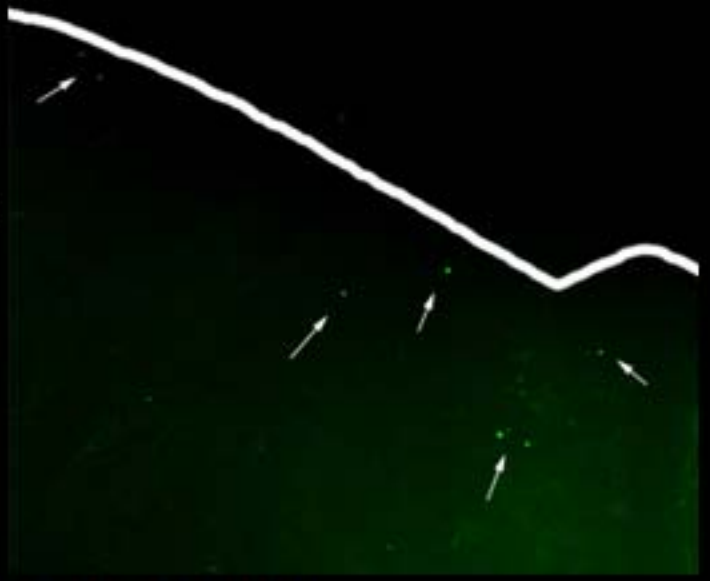
CD3 rhesus vagina



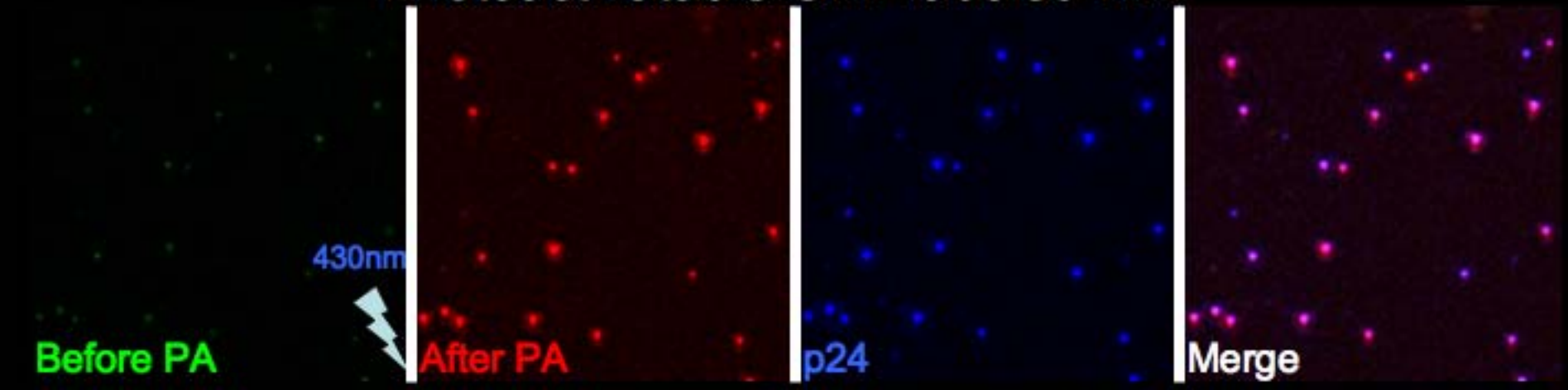
Visualizing HIV in Tissue



HIV in explants



Photoactivatable GFP labeled HIV



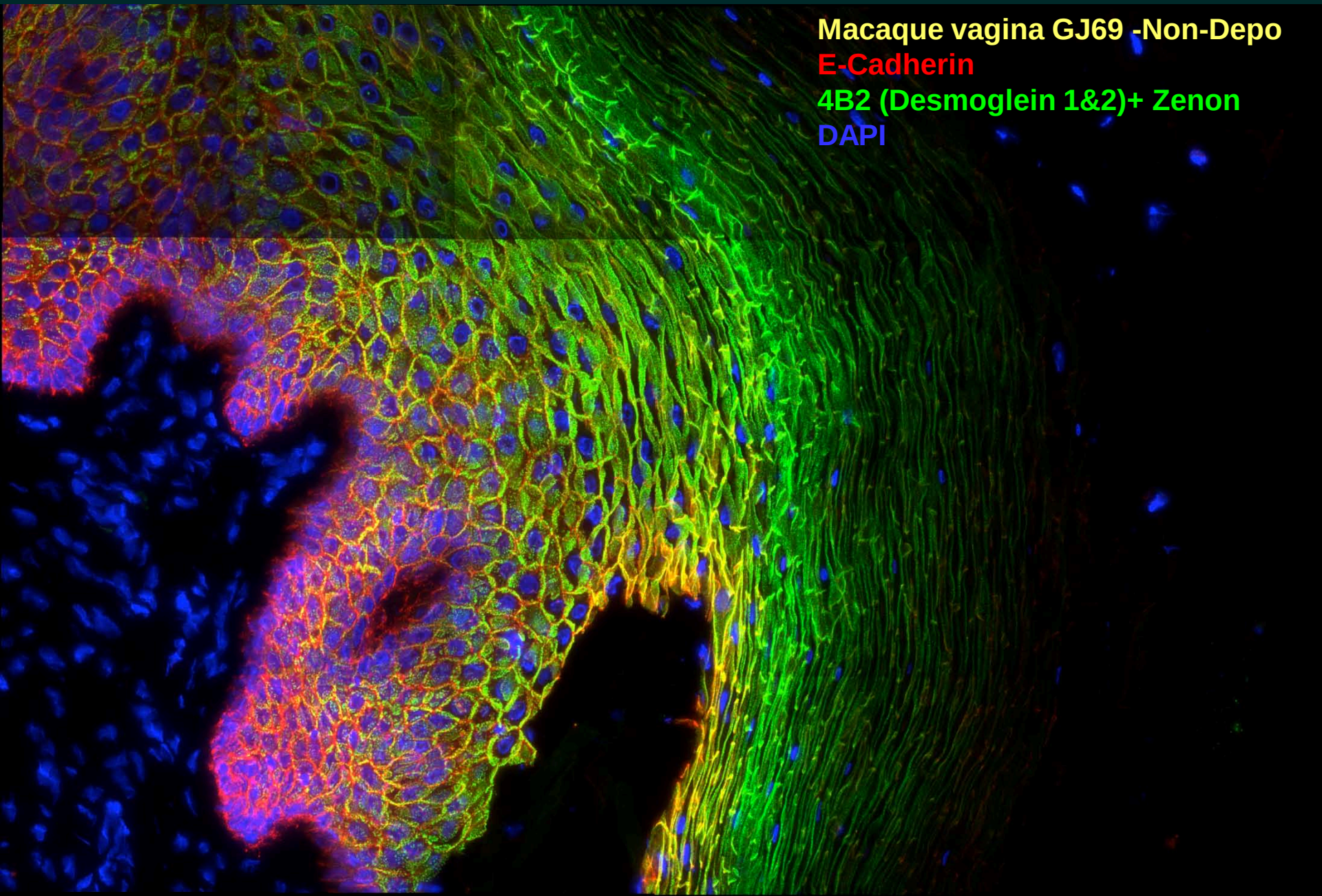
Virus Entry in Macaque Vagina

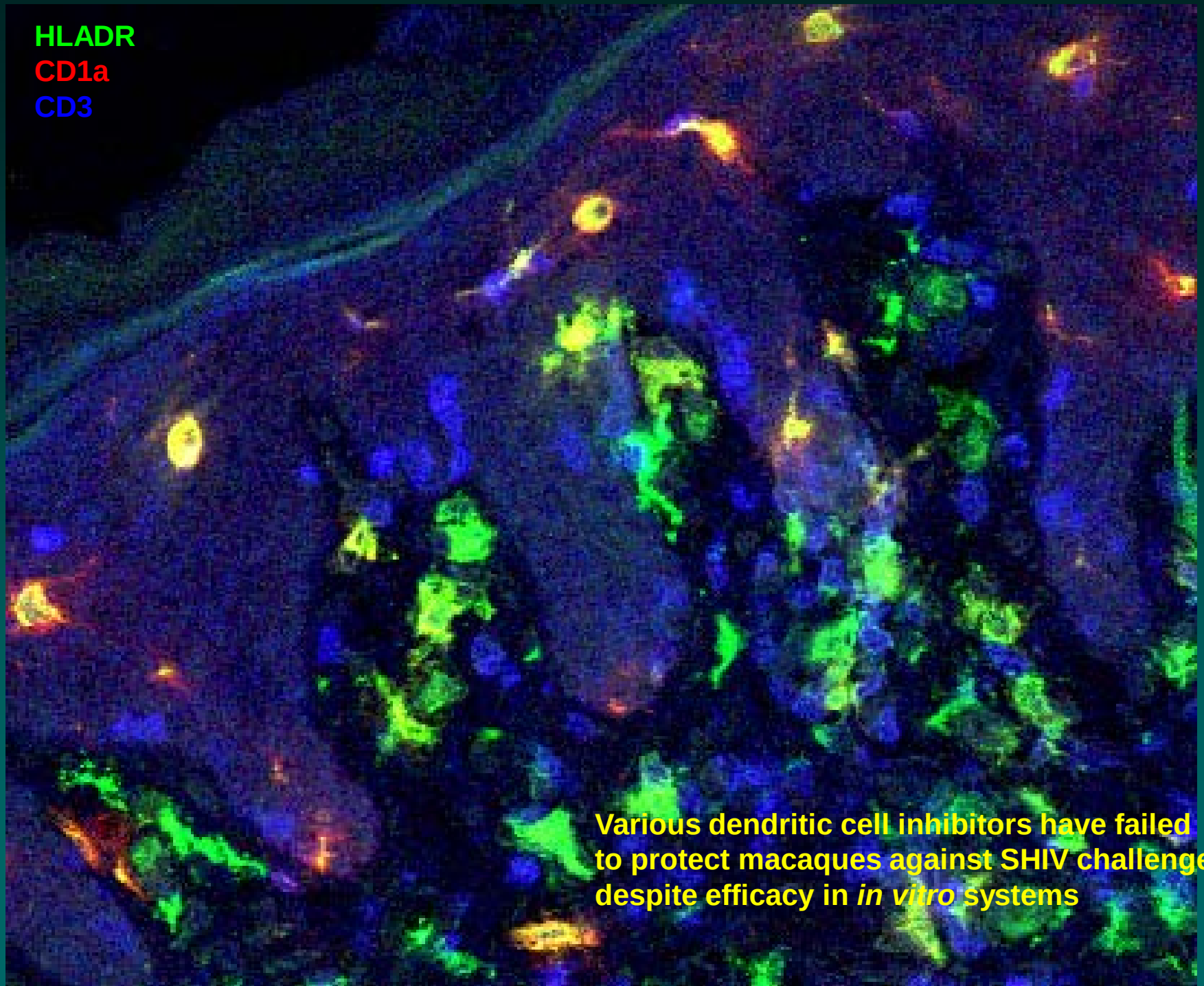
Ectocervix and vagina contain many virions

Virions enter interstitially

Virion penetration mimics human explant system

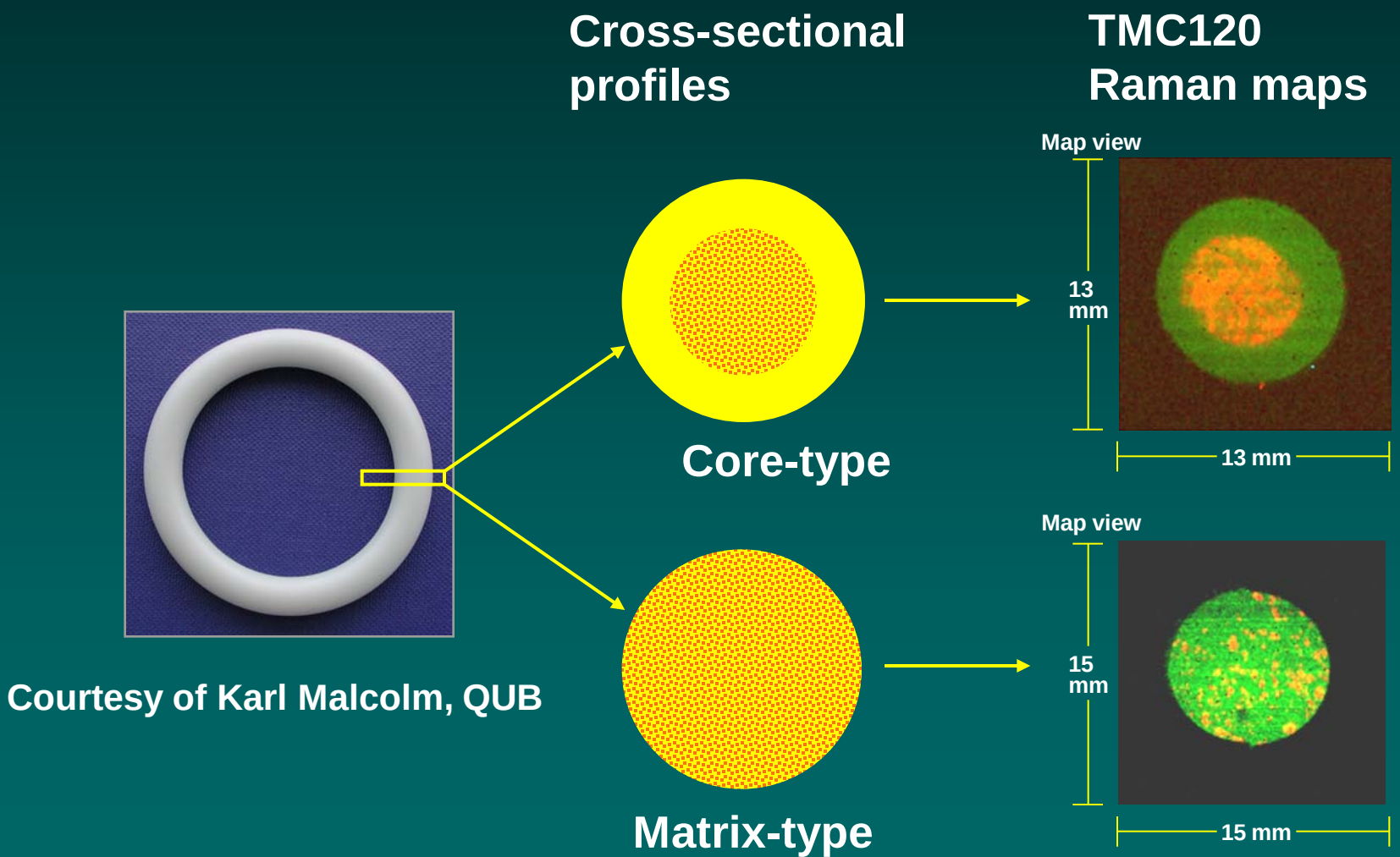
Studies of tight junctions and viral entry (Courtesy Tom Hope)



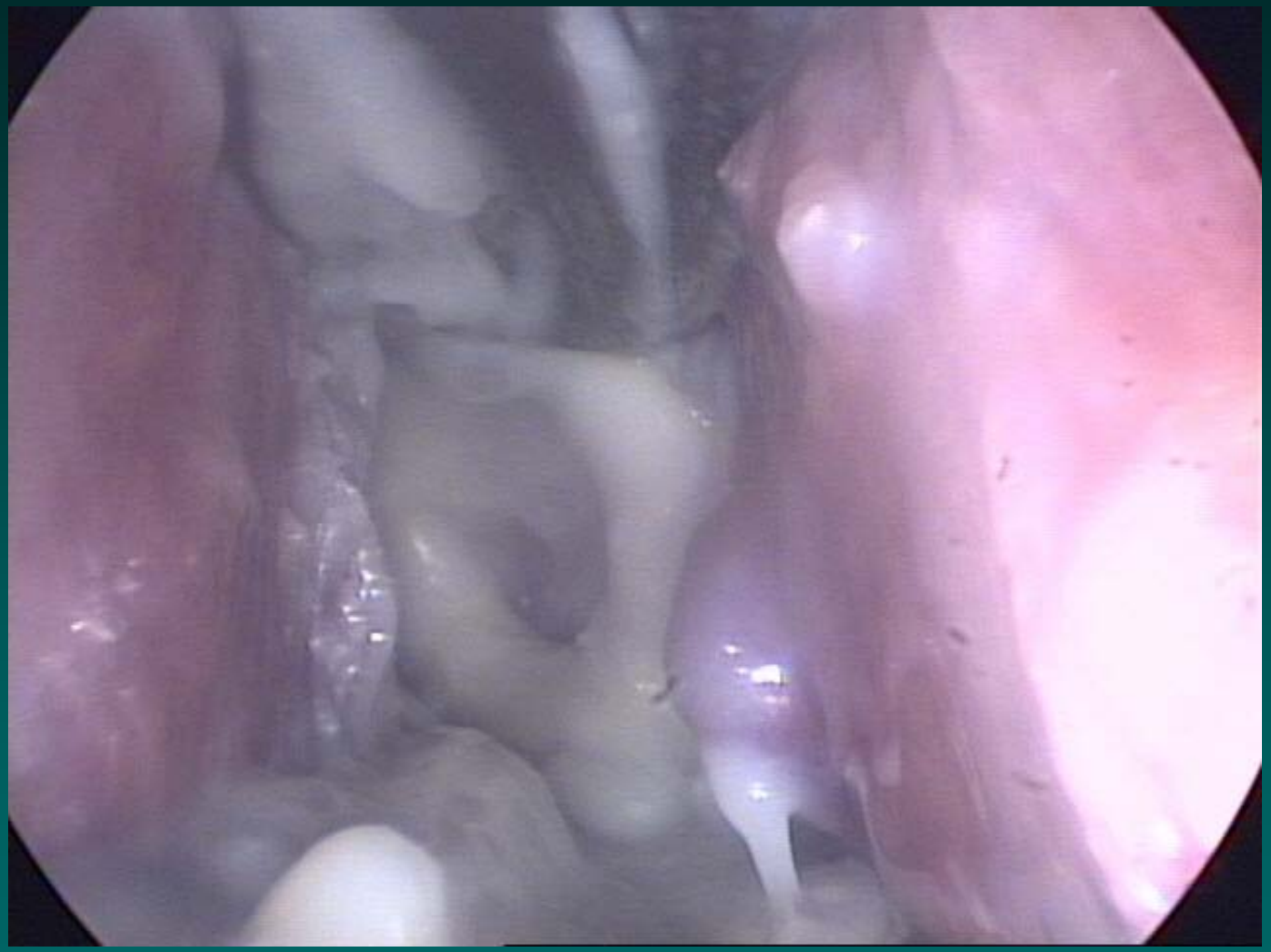


Various dendritic cell inhibitors have failed to protect macaques against SHIV challenge despite efficacy in *in vitro* systems

Reservoir vs. Matrix Type Vaginal Rings



Vaginal rings containing microbicides designed for macaques ongoing PK / PD studies of vaginal efficacy and safety



Malcolm, Veazey, Moore et al., Sustained release of the CCR5 inhibitors CMPD167 and maraviroc from vaginal rings in rhesus macaques, Antimicrobial Agents and Chemotherapy, 2012

Advances made through nonhuman primate research

The intestinal tract is the major site for initial HIV amplification and ongoing viral replication, even in "controllers" (discovered in macaques, confirmed in humans)

HIV-1 is a "machine" that requires "keys and fuel"; i.e., it infects and replicates in cells with appropriate receptors (keys), and that have a certain level of "activation" sufficient to promote mRNA translation; these *viral "fuel" cells are "activated" CD4+CCR5+ memory cells mucosal tissues*

Intestinal damage and systemic activation drive persistent HIV replication (discovered in macaques, confirmed in humans)

Non-progressing hosts have evolved to avoid AIDS by decreases dependence in CD4+CCR5+ cells for immunity; Nature could not cure this infection, so it changed the immune system of the host

Preservation (or restoration) of intestinal memory CD4+ T cells is the only correlate of protective immunity we have found to date

CD4+CCR5+ T cells in the vagina are the major source of vaginal transmission And infection can be completely prevented by blocking either receptor

- ***Nonhuman primate studies are essential and continue to guide all aspects of HIV research***

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