Preventing HIV-induced Cardiac Dysfunction
Novel Insights from the SIV/Macaque Model

JL Mankowski, DVM, PhD, DACVP

Department of Molecular and Comparative Pathobiology

Department of Neurology

Department of Pathology

Johns Hopkins University

Leading research in human and animal disease

Disclosures

Pfizer provided Maraviroc for these studies

Patent pending: Compositions and Methods for Treating or Preventing Cardiac and Neurological Disorders Using Chemokine Receptor Antagonists. JL Mankowski, First Inventor. Patent will be held by Johns Hopkins University

AN INVESTIGATION

INTO THE

PARASITES

IN THE

PORK SUPPLY OF MONTREAL.

BY

WILLIAM OSLER, M D., M.R.C.P., LOND.,

Professor of the Institutes of Medicine, McGill University; Lecturer on Helminthology, Montreal Veterinary College.

AND

A. W. CLEMENT (LAWRENCE, MASS.),

Student Montreal Veterinary College.

MONTREAL:

PRINTED BY THE GAZETTE PRINTING COMPANY.

1883.

glands. No hair follicles are seen. For the most part the cyst is surrounded by a narrow band of connective tissue or ovarian stroma, but at some points the epithelial cells have penetrated to the surface and cell-masses are found in the mesosalpinx and even between the layers of muscle-bundles in the tube-wall. The broad ligament also contains metastases, cell-nests being found in the lymph-spaces, and, in one place, in a large vein. The tubal mucosa is normal and no tumor elements are found on the upper surface of the tube-wall.

Left side.—The tumor is similar to that on the opposite side. The corpus luteum observed macroscopically presents the usual features and shows commencing organization.

DIAGNOSIS.—Carcinoma ovarii duplex associated with a small dermoid cyst in the right ovary. Corpus luteum in the left ovary. Practically normal uterine mucosa. Perisalpingitis. Subperitoneal cysts.

REFERENCES.

1. Hildebrandt: Ziegler's Beitr. z. path. Anat., 1890, Bd. VII, S. 169.
2. Bierman: Prager med. Wochenschr., 1885, No. 21, S. 201.
3. Heschl: Prager Vierteljahrsschr., 1860, Bd. LXVIII, S. 57.
4. von Wahl: St. Petersb. med. Wochenschr., 1883, S. 70.
5. Cohn: Zeitschr. für Geburtsh. und Gynäkol., 1886, Bd. XII, S. 36.
6. Veit: Zeitschr. für Geburtsh. und Gynäkol., 1890, Bd. XIX, S. 329.
7. Pomorski: Centralblatt für Gynäkol., 1889.
8. Babinski: Progrès Méd., Paris, 1884, XII, p. 29.
9. Himmelfarb: Centralblatt für Gynäkol., 1886, S. 569.
10. Krukenberg: Archiv für Gynäkol., 1887, S. 241.
11. Tauffer: Virchow's Archiv, 1895, Bd. CXLII, S. 389.
12. Thumin: Archiv für Gynäkol., 1897, S. 547.
13. Yamagiwa: Virchow's Archiv, 1897, Bd. CXLVII, S. 99.
14. Clark: Amer. Jour. of Obstet., 1898, Vol. XXXVIII, No. 3.
15. Lockhart and Anderson: Montreal Med. Jour., 1899 Vol. XXVIII, p. 116.
16. Cone: Johns Hopkins Hos. Bull., 1897, Vol. VIII, p. 208.
17. Friedländer: Virchow's Archiv, Bd. 56, S. 365.
18. Bierman: Prager med. Wochenschr., 1885, No. 21.
19. Faquet: Archiv. de Toc. et Gynécol., 1895, Vol. XXII, p. 629.

PULMONARY TUBERCULOSIS, WITH DIFFUSE PNEUMONIC CONSOLIDATION, IN A LION.

BY W. G. MACCALLUM, M. D., AND A. W. CLEMENT, V. S., *Baltimore, Md.*

While in Birmingham, Ala., in November, 1899, one of the lions belonging to the Hagenbeck menagerie, a large adult-male of the black-maned sort, which had been captured in South Africa and had been in captivity ten years, fell ill. The keeper noticed that the lion was not well and frequently refused food. On the removal of the menagerie to Baltimore it grew worse, developed a slight grunting cough, became very much thinner than normal, and, after an illness of about four weeks altogether, died.

The *autopsy* was performed the next day. The body was that of an adult male lion, said by the keeper to be about fourteen years old. The subcutaneous and omental fat were very

intervening lung-substance was gray or grayish-yellow, and somewhat gelatinous and translucent. The lower lobes were more firmly and uniformly consolidated, the firmness being due to a diffuse consolidation rather than to the translucent nodules which were more sparsely scattered throughout these lobes. The cut surface was, as in the upper lobe, grayish-yellow and somewhat translucent. In the posterior portion of the lobe, there were two well-defined cavities communicating with one another by a narrow channel, and marked off from the surrounding lung by the fibrous thickening of their walls. These cavities communicated with the bronchi; their walls were fairly smooth and covered with a purulent material.

Science. Vol. 183, No. 4130 (Mar. 22, 1974), pp. 1202-1203

Visna Virus Infection of American Lambs

Abstract. *Random-bred fetal and 4-week-old American lambs, inoculated intracerebrally with visna virus, developed a persistent infection in the brain and sometimes in the lung. The pathologic changes present in these lambs were similar to the early lesions of visna in Icelandic sheep, thus providing a possible model for the study of virus-induced demyelinating disease.*

OPENDRA NARAYAN
Departments of Animal Medicine and *Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205*
ARTHUR M. SILVERSTEIN
Department of Ophthalmology, Johns Hopkins University School of Medicine
DONALD PRICE
Departments of Pathology and *Neurology, Johns Hopkins University School of Medicine*
RICHARD T. JOHNSON
Departments of Neurology and *Microbiology, Johns Hopkins University School of Medicine*

Science, Vol. 227, No. 4683 (Jan. 11, 1985), pp. 173-177

Sequence Homology and Morphologic Similarity of HTLV-III and Visna Virus, a Pathogenic Lentivirus

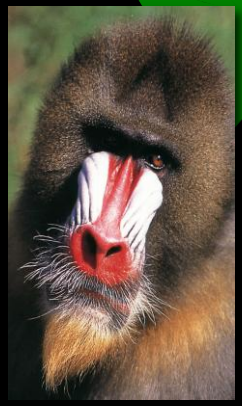
Abstract. *A study was conducted of the genetic relation between human T-cell lymphotropic retroviruses and visna virus. The human T-cell lymphotropic viruses include those associated with T-cell malignancies (HTLV-I and HTLV-II) as well as the etiologic agent of the acquired immune deficiency syndrome (HTLV-III). Visna virus, a slowly replicating and pathogenic but nononcogenic retrovirus of sheep, is a member of the subfamily Lentivirinae. Results obtained by molecular hybridization and heteroduplex analysis indicated that a greater extent of nucleotide sequence homology exists between HTLV-III and visna virus than between HTLV-III and any of the other viruses. The homology observed under conditions of low stringency spanned the entire genome, but was strongest in the* gag/pol *region. The morphogenesis and fine structure of HTLV-III and visna virus also demonstrated striking similarities. The data provide strong evidence for a close taxonomic and thus evolutionary relation between HTLV-III and the Lentivirinae subfamily.*

MATTHEW A. GONDA*
Laboratory of Cell and Molecular Structure, Program Resources, Inc., NCI–Frederick Cancer Research Facility, Frederick, Maryland 21701
FLOSSIE WONG-STAAL
ROBERT C. GALLO
Laboratory of Tumor Cell Biology, National Cancer Institute, Bethesda, Maryland 20205
JANICE E. CLEMENTS
OPENDRA NARAYAN
Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205 and *National Cancer Institute*
RAYMOND V. GILDEN
Program Resources, Inc., NCI–Frederick Cancer Research Facility


PREVENT HIV WITH ABC
Abstain from sex, or...
Be faithful to one partner, or...
Correctly use condoms every time.
Message brought to you by: San Pedro AIDS Commission and U.S. Embassy
For Information on HIV/AIDS, Please Call- 206-2085

Natural Hosts of SIV
African Primates

HIV

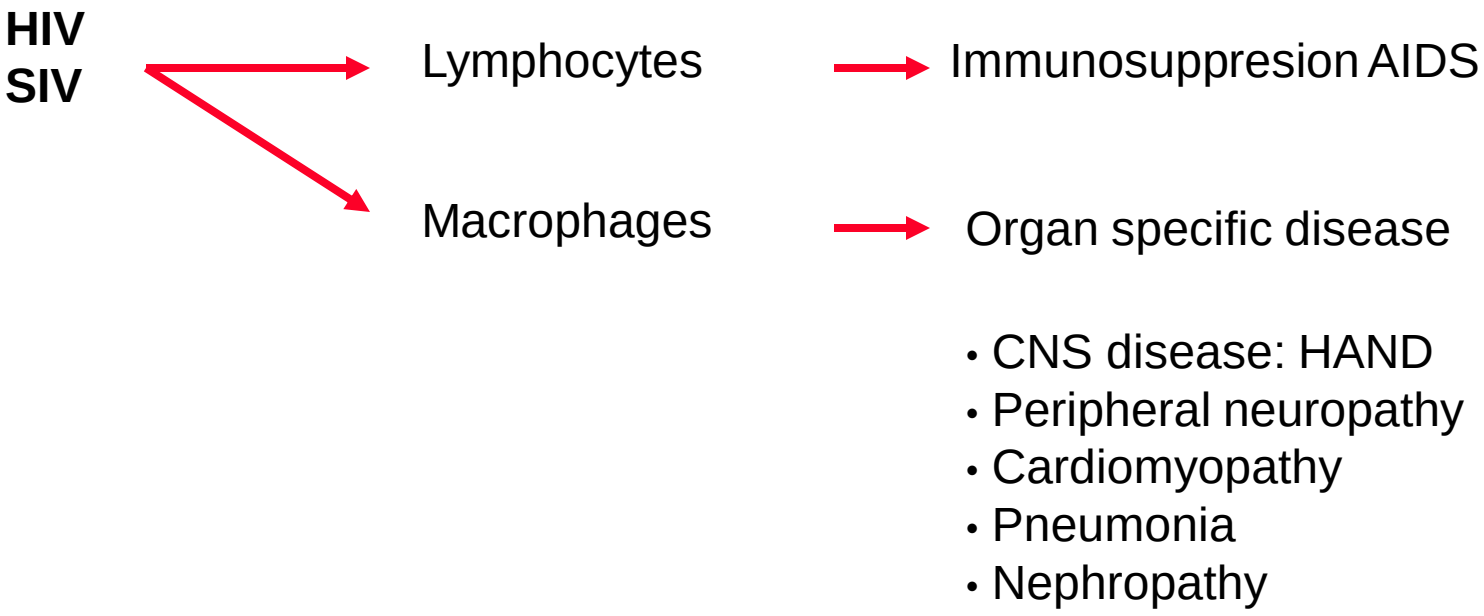


Moderate viral loads
No clinical disease

Abnormal Hosts
Asian Macaques

High viral loads
Clinical disease

HIV organ specific disease



HIV-associated cardiac dysfunction

- Overt clinical cardiac manifestations: ~20%
- Association of myocarditis with function decline undefined
- LV diastolic dysfunction
  - 60% of asymptomatic HIV+
  - HAART

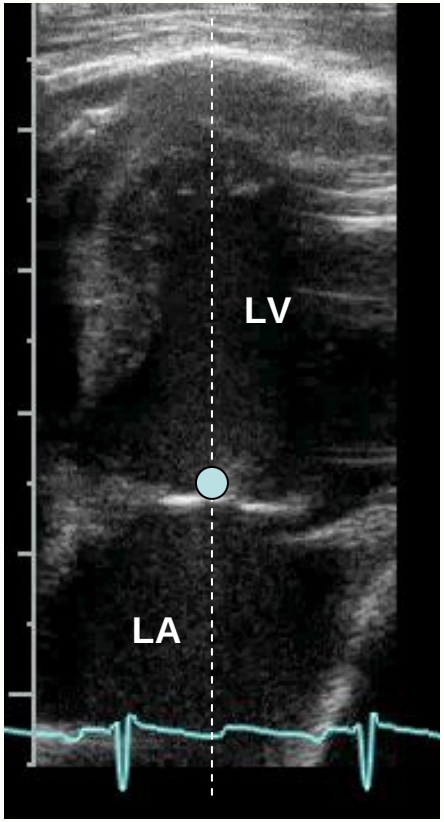
Diastolic dysfunction

- Functional abnormalities that exist during left ventricular relaxation and filling

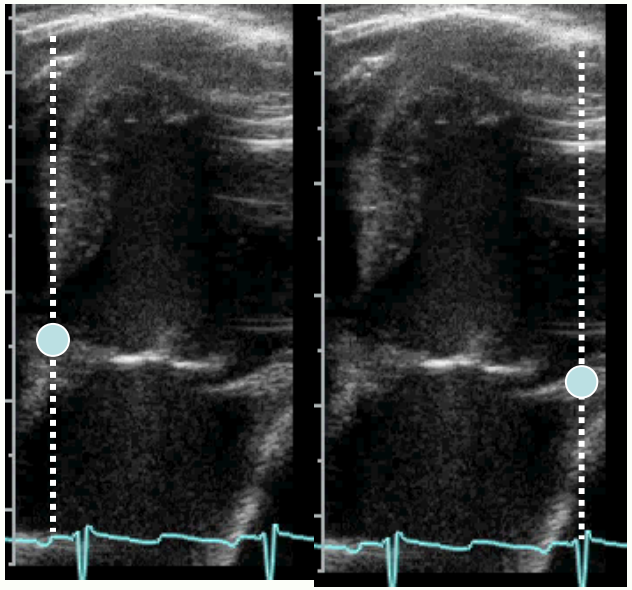
- At risk for development of heart failure and reduced survival

Assessing Cardiac Phenotype in SIV

Mitral Inflow Doppler Imaging

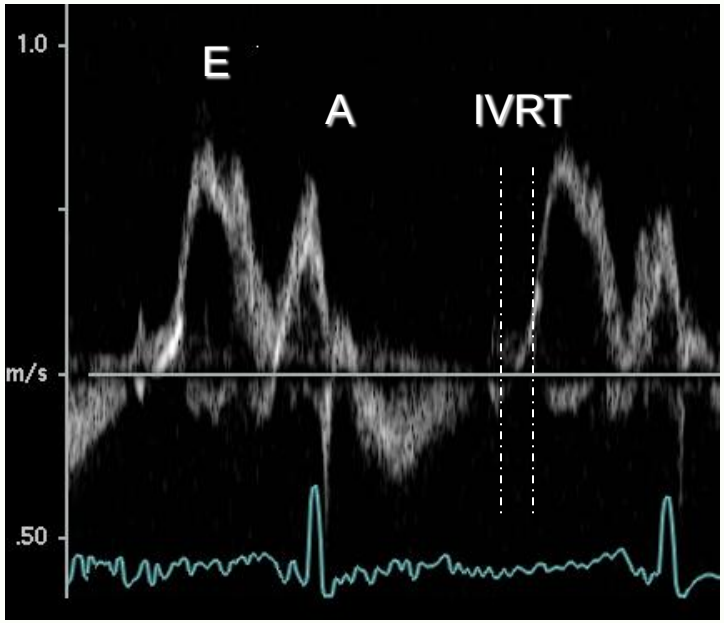


Tissue Doppler Imaging

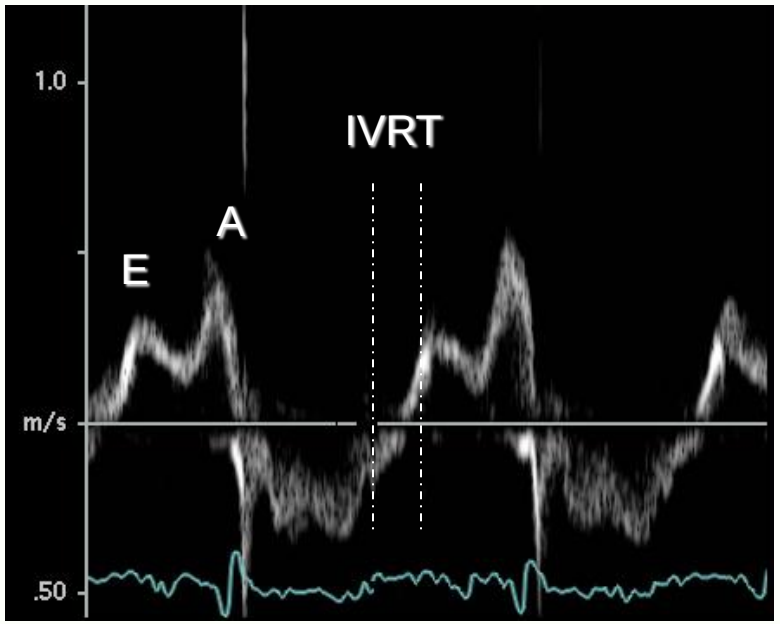


Assessing Cardiac Phenotype in SIV

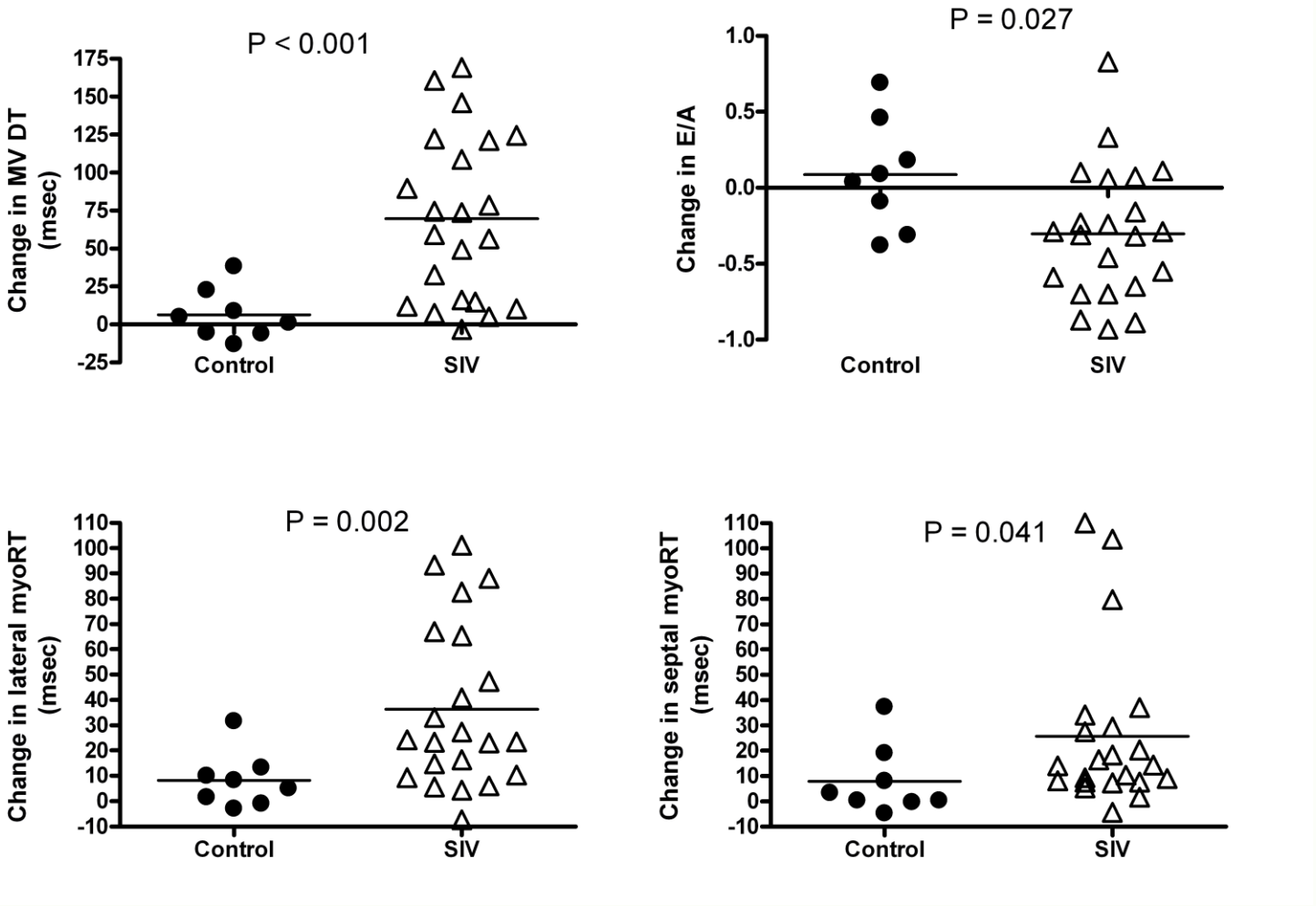
Control



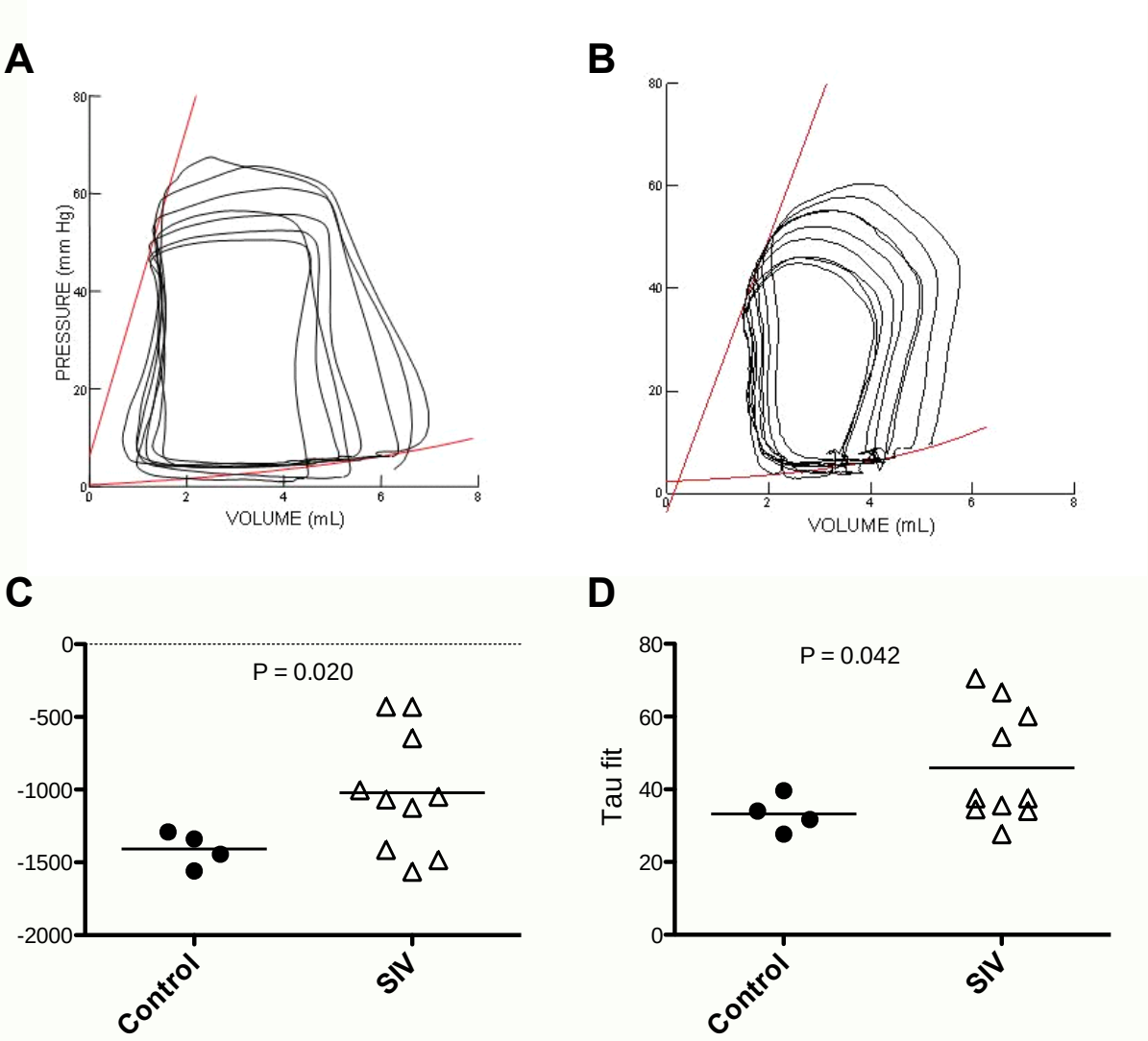
SIV



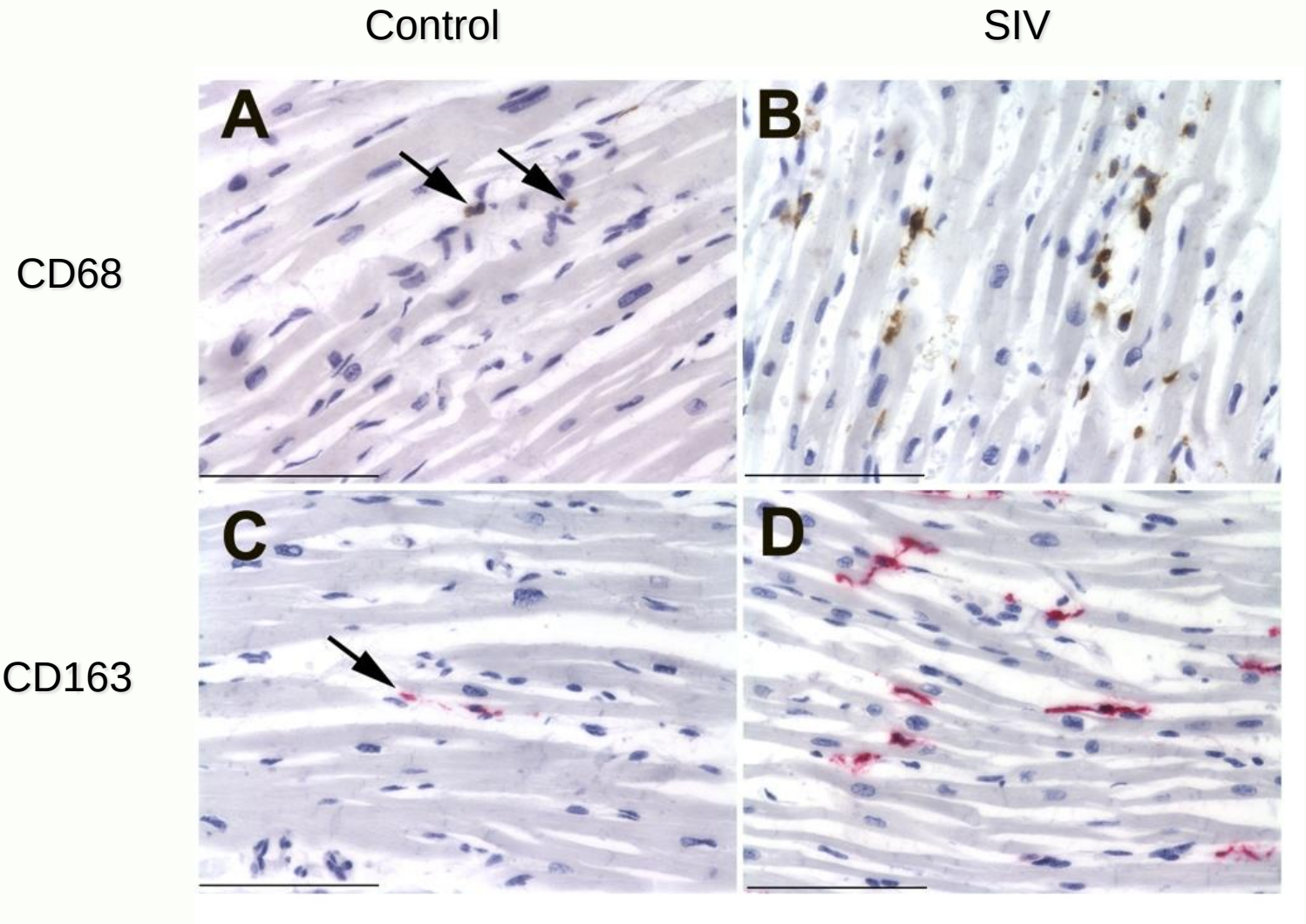
SIV-associated Diastolic Dysfunction



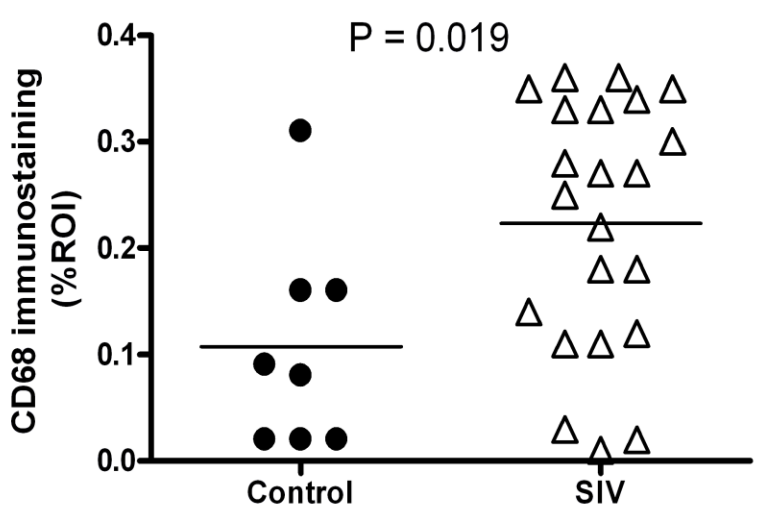
SIV-associated Diastolic Dysfunction

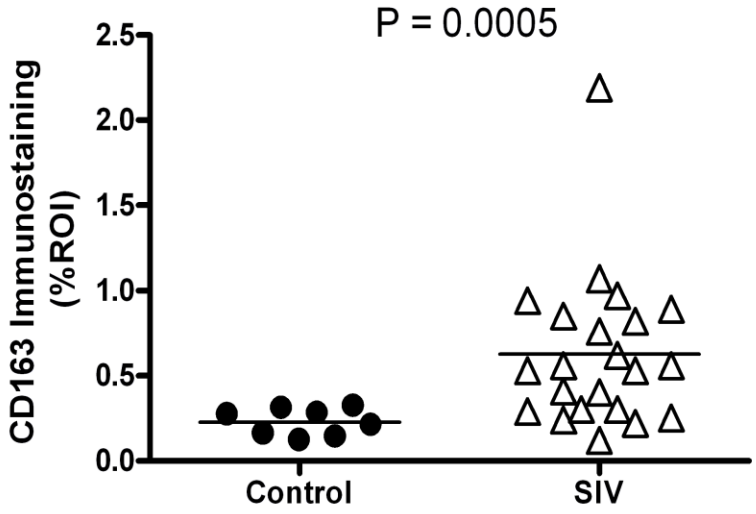


Macrophage Immune Activation in Myocardium

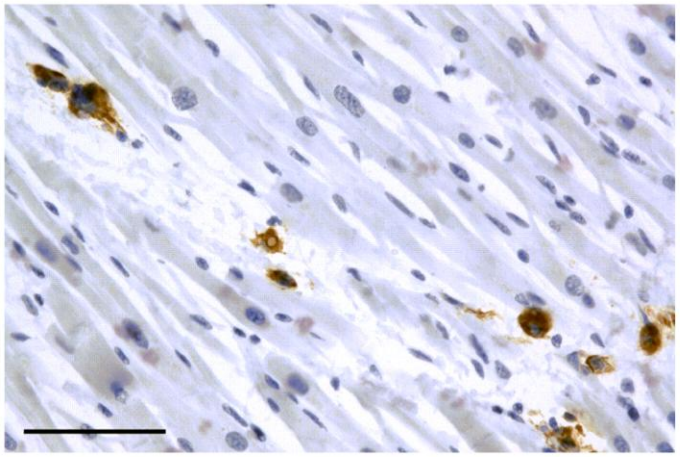


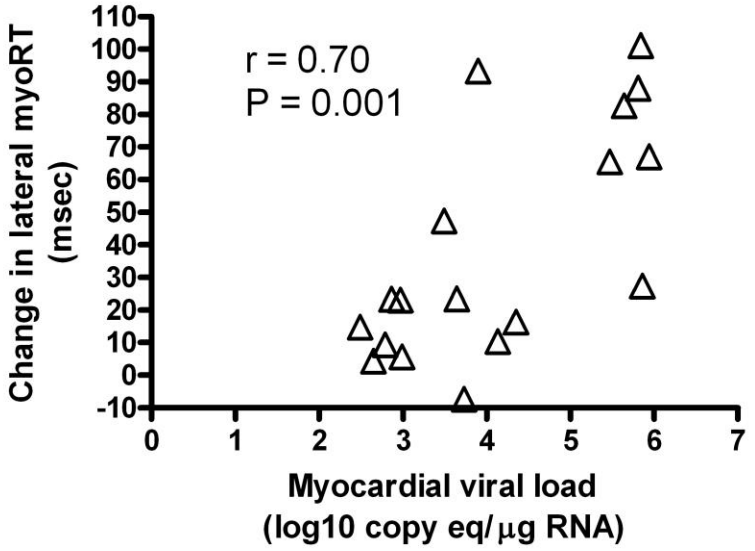
Macrophage Immune Activation in the Myocardium





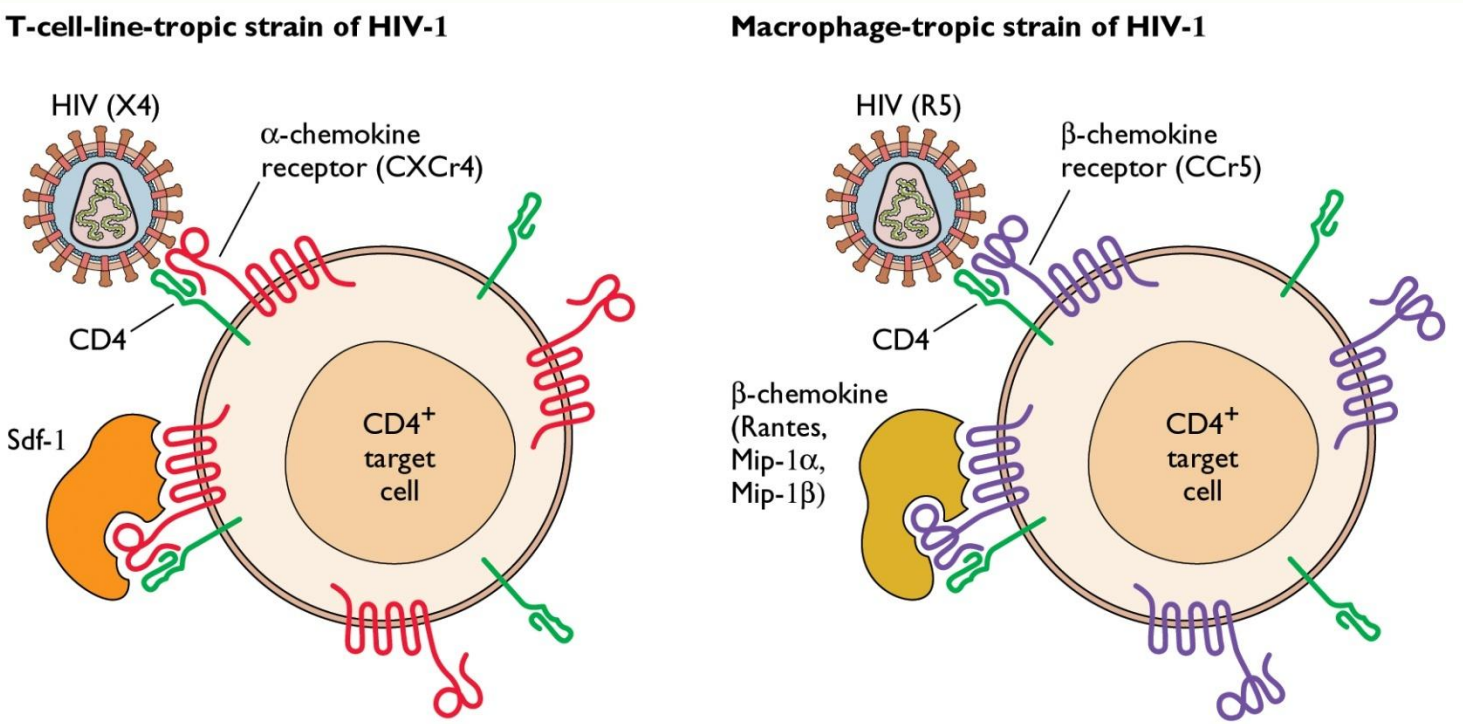
Myocardial SIV RNA and Diastolic Dysfunction



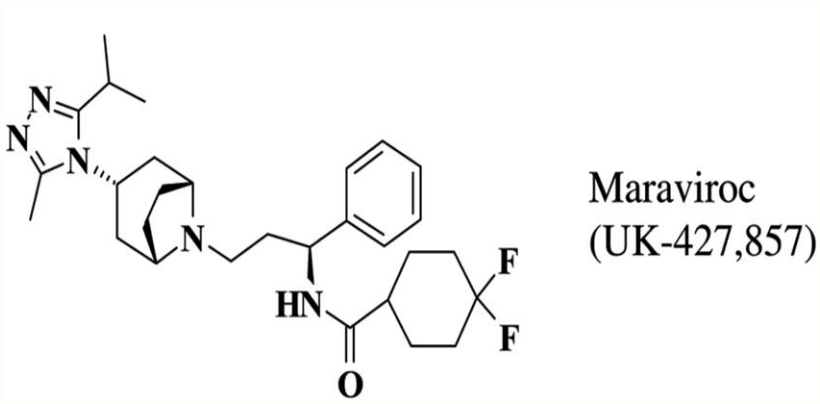


SIV/Macaque Model: Clinical Conclusions

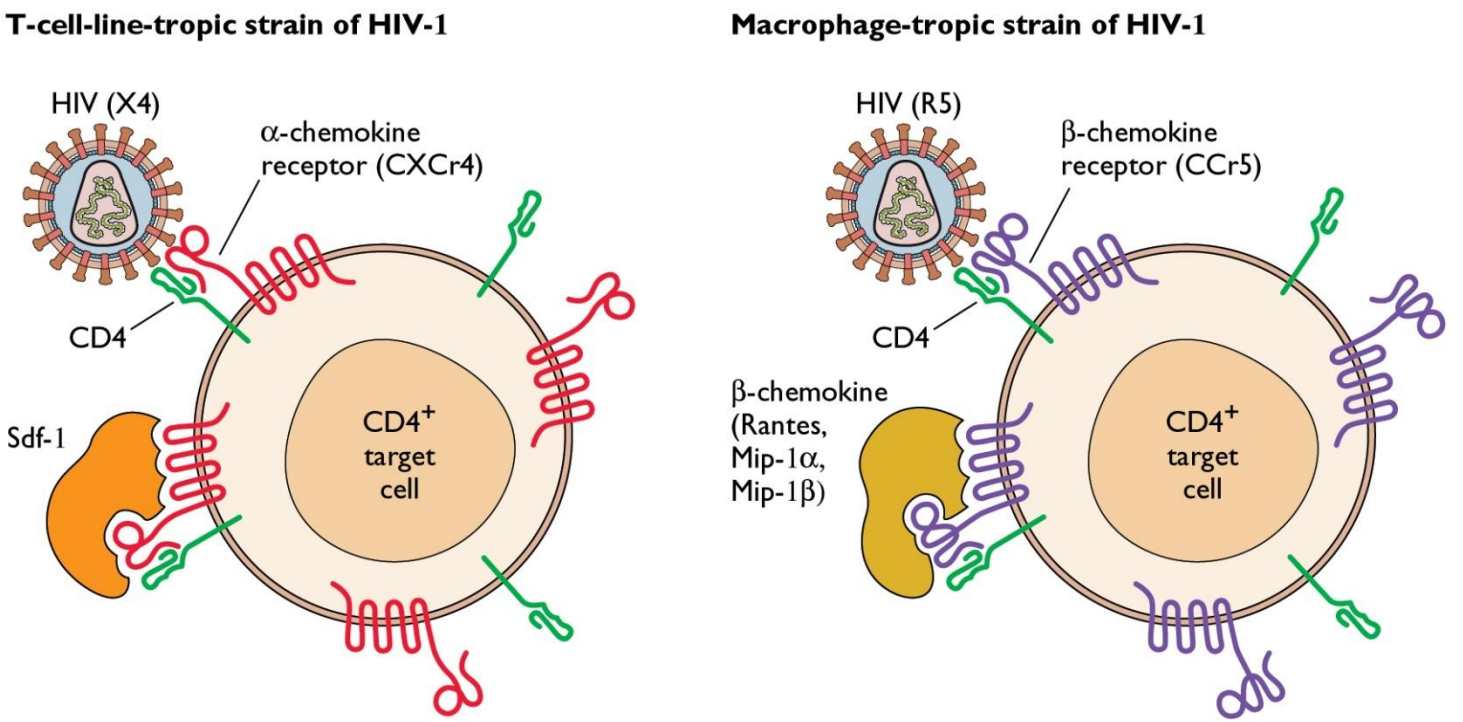
- **Diastolic dysfunction develops in SIV-infected macaques**
- **Diastolic dysfunction not correlated with macrophage activation**
- **SIV RNA in heart strongly correlated with cardiac dysfunction**



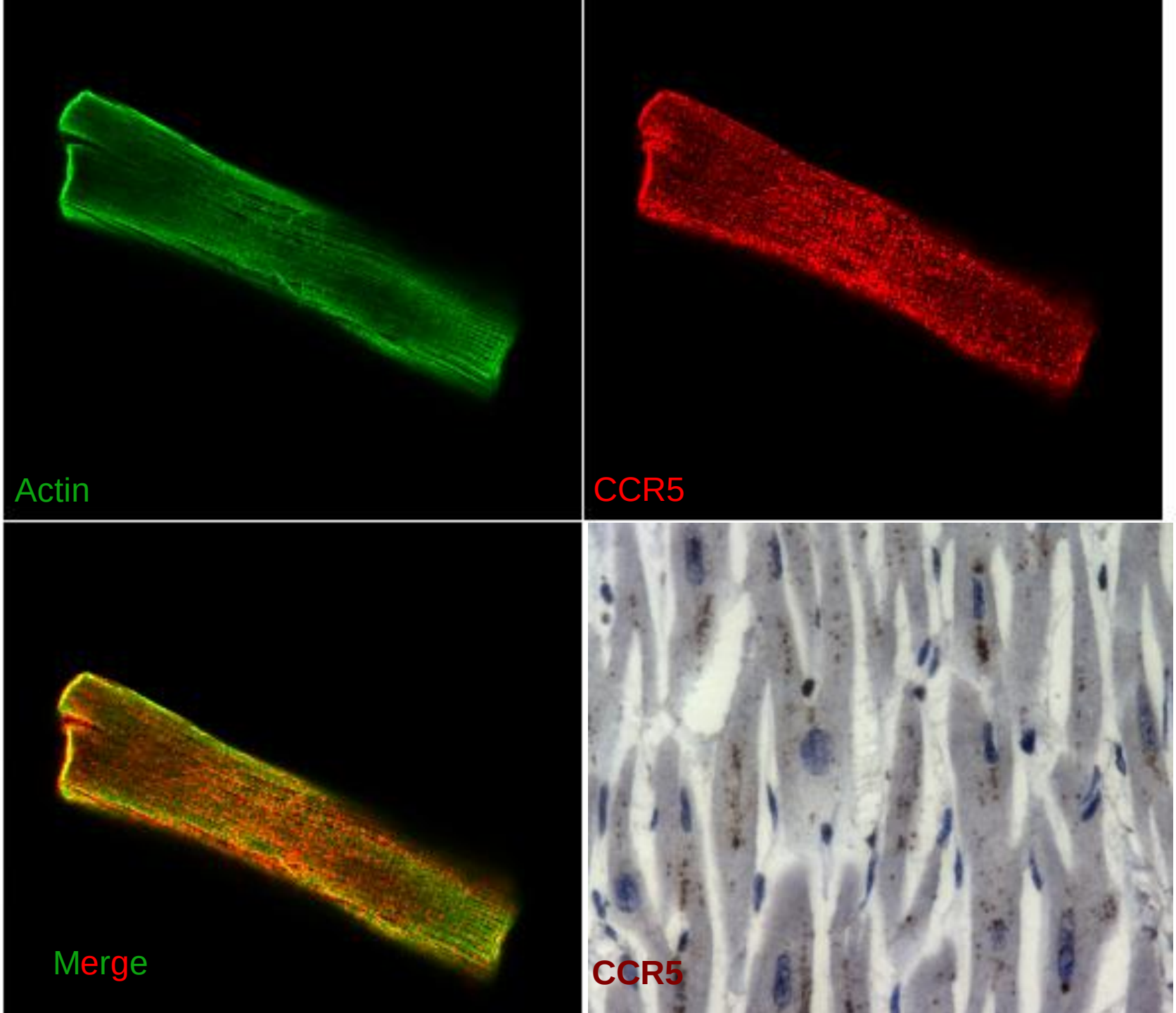
Adapted from Fig. 3 of A. S. Fauci, *Nature* **384:**529–533, 1996, with permission.



Maraviroc
(UK-427,857)

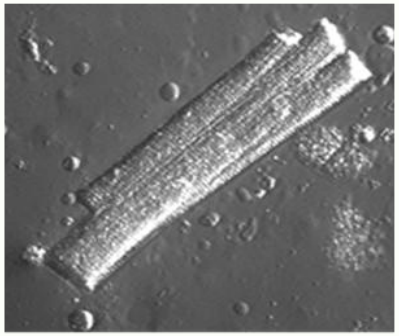


Adapted from Fig. 3 of A. S. Fauci, *Nature* **384:**529–533, 1996, with permission.


Actin
CCR5
Merge
CCR5

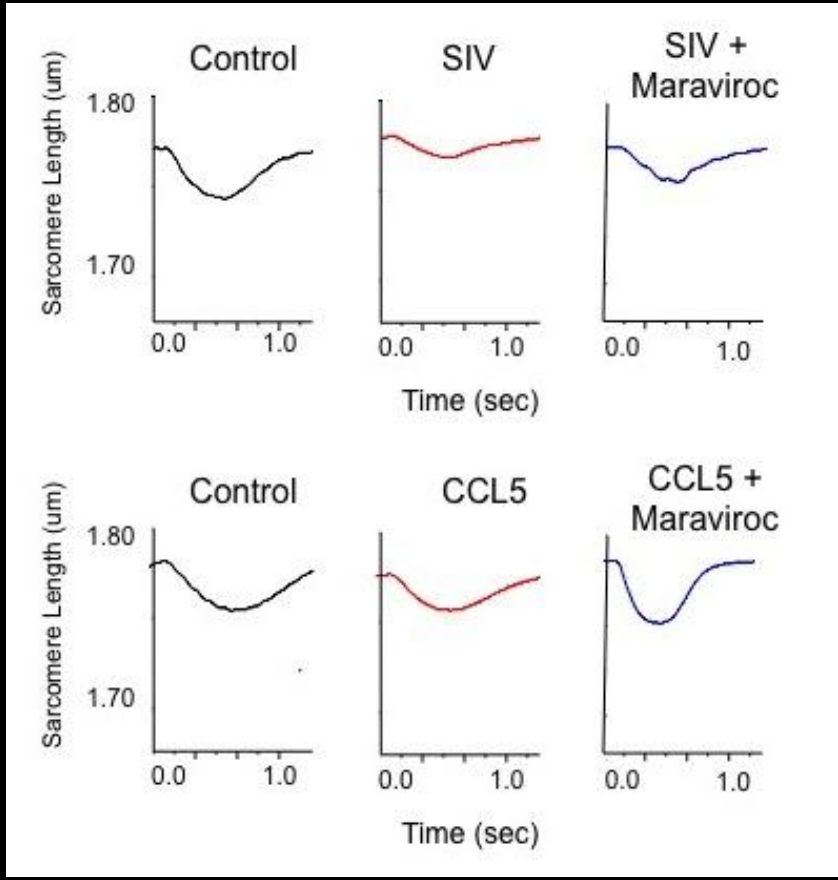
In vitro assessment of functional CCR5 expression on cardiomyocytes

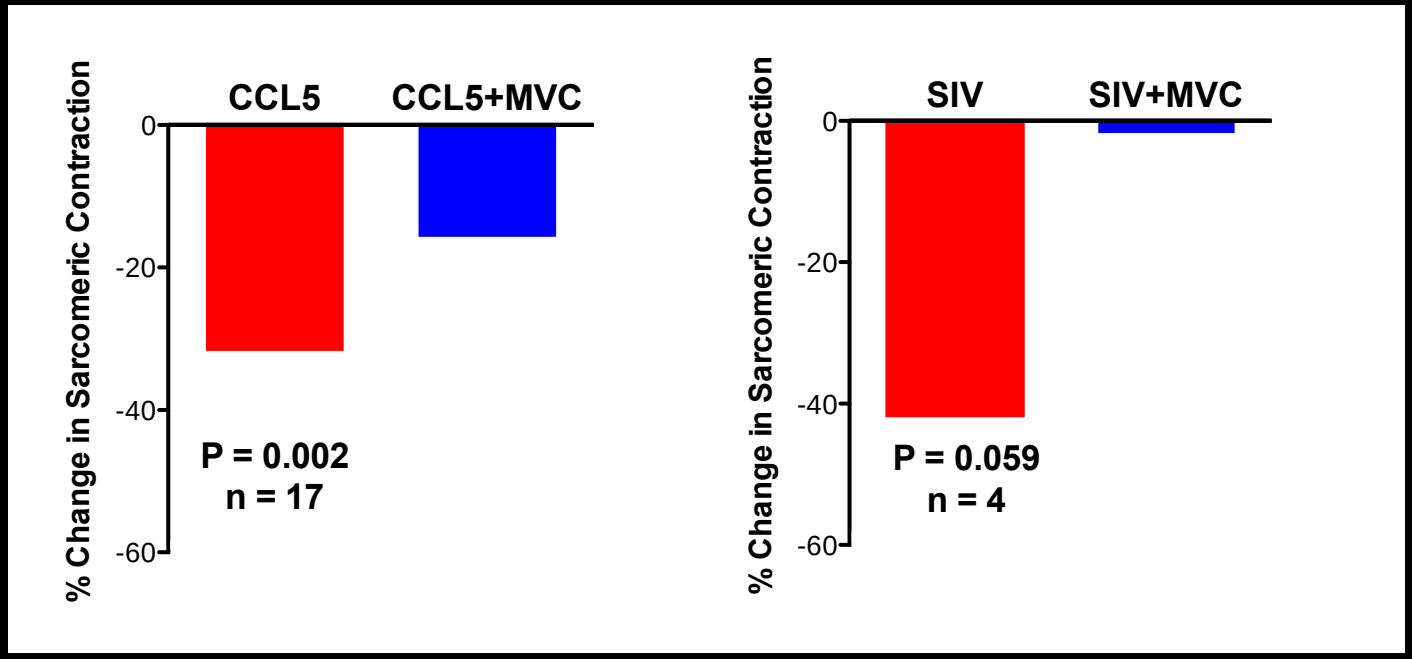
Isolation of rhesus ventricular cardiomyocytes



Single cell recordings of sarcomeric contraction and calcium transients measured over time in cells exposed to CCL5

Cells subsequently exposed to Maraviroc, sarcomeric contraction and calcium transients measured over time


Control
SIV
SIV +
Maraviroc
Sarcomere Length (um)
1.80
1.70
0.0
1.0
Time (sec)
Control
CCL5
CCL5 +
Maraviroc
Sarcomere Length (um)
1.80
1.70
0.0
1.0
Time (sec)

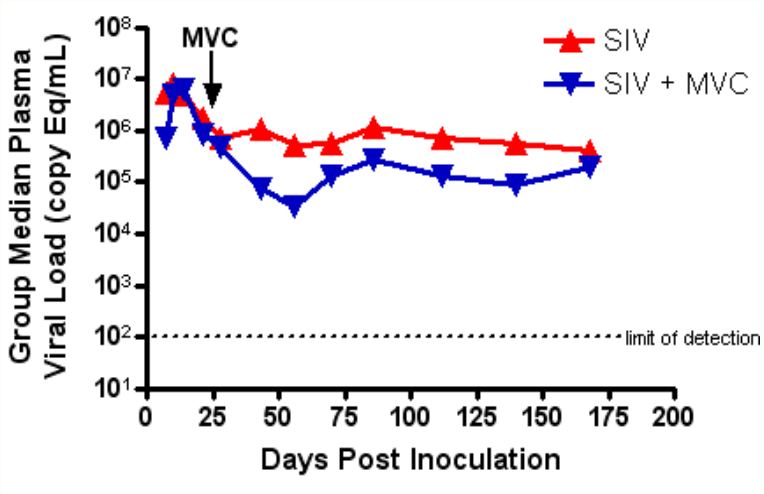

% Change in Sarcomeric Contraction
CCL5
CCL5+MVC
0
-20
-40
-60
P = 0.002
n = 17
% Change in Sarcomeric Contraction
SIV
SIV+MVC
0
-20
-40
-60
P = 0.059
n = 4

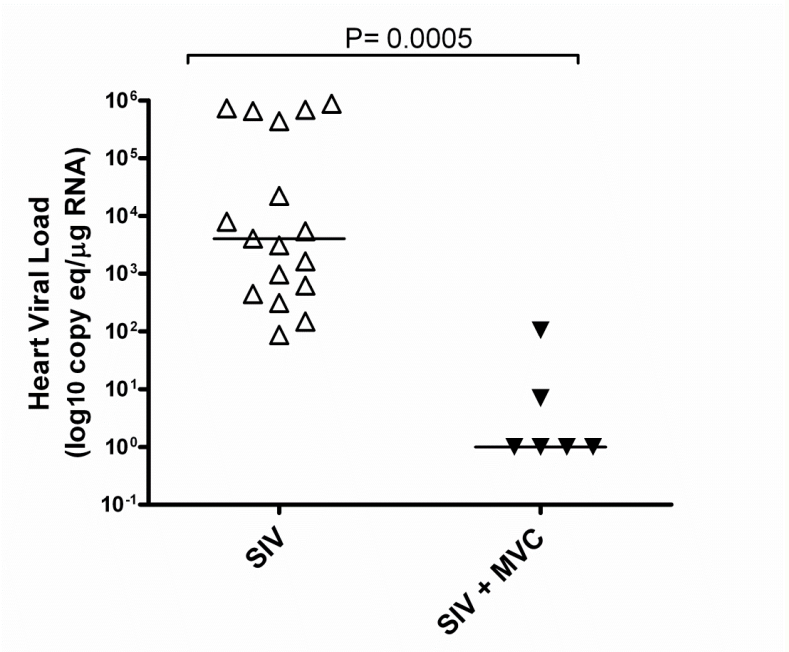
Maraviroc Study Design

Group	Number of animals	Days post-inoculation
SIV + Maraviroc	6	180
SIV	22	180
Uninfected	8	-

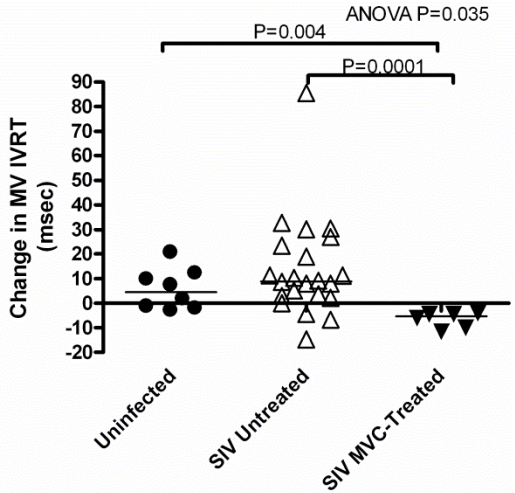
Maraviroc dose = 200 mg PO BID, started day 24 p.i.

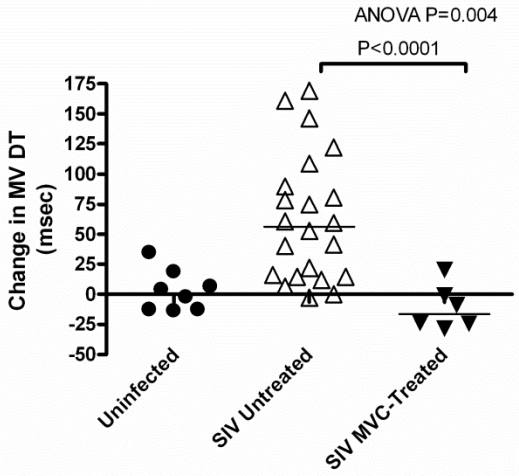
CCR5 Inhibition Modulates Viral Load

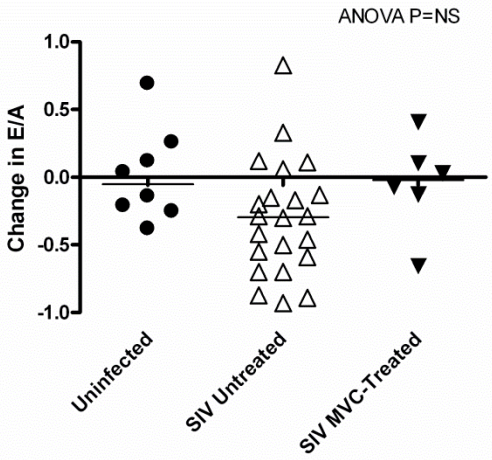


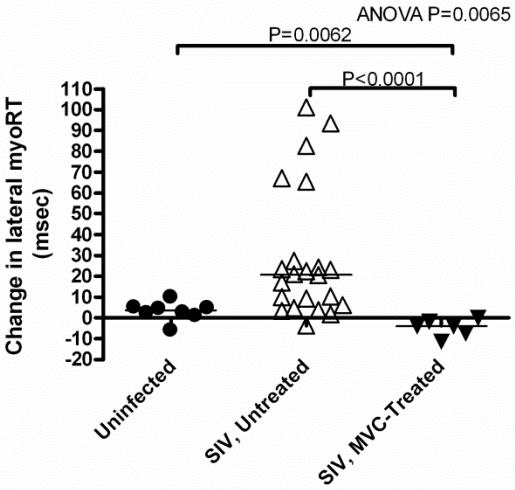


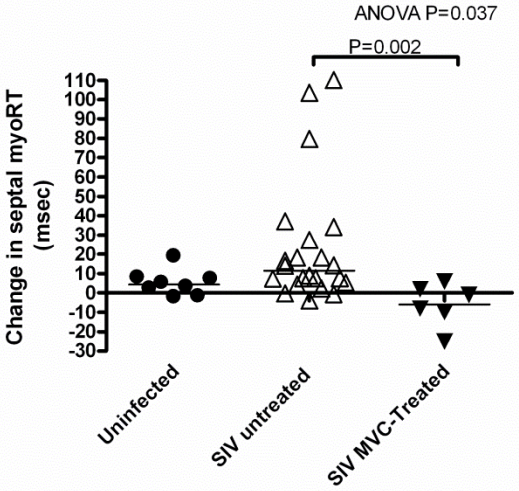
CCR5 Inhibition Preserves Diastolic Function









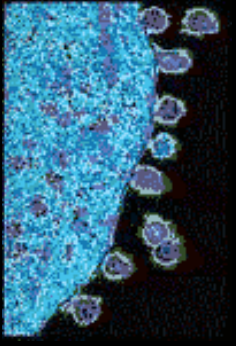


Conclusions

- SIV/macaque model established for HIV-associated cardiac disease
- Addition of CCL5 or SIV to isolated cardiomyocytes decreased contractility which was reversed by maraviroc
- Maraviroc monotherapy is cardioprotective in the SIV macaque model

Animal Models of Disease

- Model development- basis for translational research
- Foundation for pathogenesis studies – when and where
- Molecular mechanism discovery
- Improving diagnosis
- Platform for novel therapeutic and preventive approaches
- Cornerstone for team science – fostering interdisciplinary research emphasizing an integrative comparative approach



Johns Hopkins University School of Medicine

- Katie Kelly
- Sarah Beck
- Kelly Pate
- Lisa Mangus
- Suzanne Queen
- Jami Karper
- Jamie Dorsey
- Djahida Bedja

- Walter Hubbard
- Lindsay Avery

- Dave Kass
- Nazareno Paolocci
- Carlo Tocchetti
- Bob Adams
- Alexey Lysashkov

- David Graham
- Chris Zink
- Janice Clements
- Lucio Gama
- Ken Witwer

Paul Foster School of Medicine, El Paso

- Patrick Tarwater

NIH HL078479, T32-OD011089, P40-OD0013117, ACVP/STP Coalition