

Vaccination for HIV: preventing massive destruction of the immune system during acute infection



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HIV Vaccines

Over 15,000 people are infected with HIV every day. Vaccination is the only practical way to control this epidemic.

Vaccination against HIV is a serious challenge:

- Huge variability among strains around the world
- Significant mutation rate (new strains)
- Neutralizing antibodies are incredibly rare
- Sterilizing vaccination may be impossible

An effective cellular (T cell) response may contain pathogenesis in the absence of a sterilizing humoral (B cell) response

HIV Vaccines: Development

Our primary goal for immunogenicity measurements is to identify “correlates of efficacy”: what measurements will inform us whether a vaccination is likely to protect.

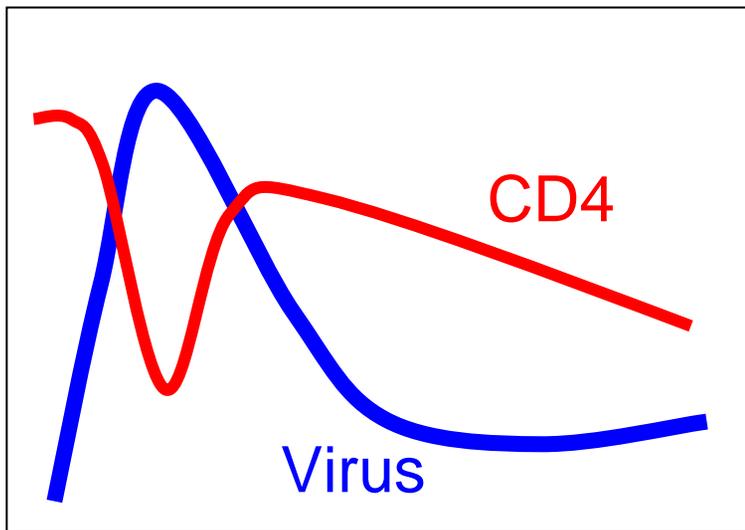
This requires a phase III (“efficacy”) trial.

It also requires that we make the right measurement!

But we don’t know what the right measurement is. We must make as many measurements as possible... for now, we base our hypotheses based on the study of HIV pathogenesis and on nonhuman primate models.

Acute Infection: SIV Model

Similar to HIV, current correlates of SIV pathogenesis are the loss of total CD4 T cells, and the peak and set-point viral loads.



But: CD4 cells are composed of a heterogeneous mixture of functionally distinct subsets with differential susceptibility to virus infection... and this composition varies by tissue.

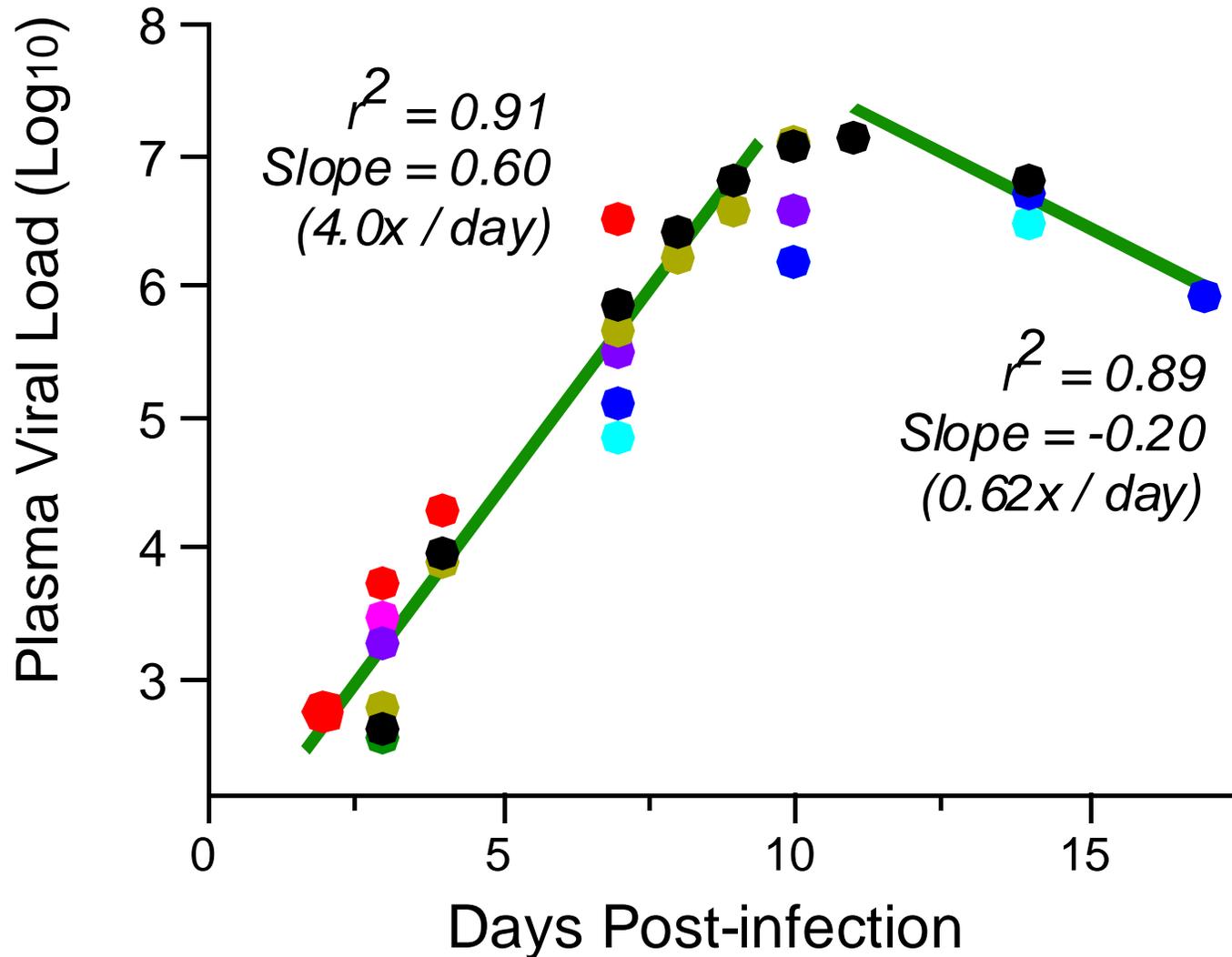
Acute Infection: SIV Model

CD4 & viral dynamics in multiple tissues

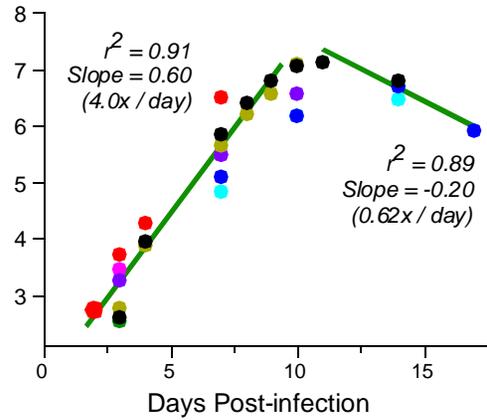
What causes the loss of blood CD4 T cells during acute infection?

- Redistribution?
 - Measure multiple tissues
- Direct viral infection (viral lysis / CTL)?
 - Measure SIV-specific T cell responses
 - Measure CD4-associated viral load
- or... Bystander killing?

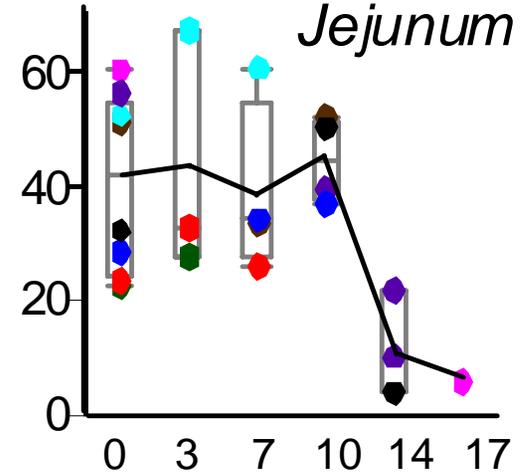
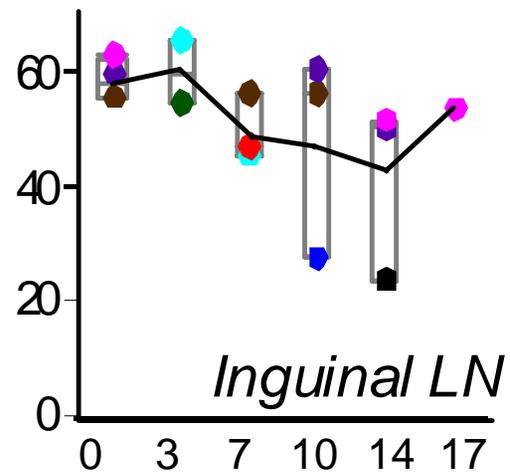
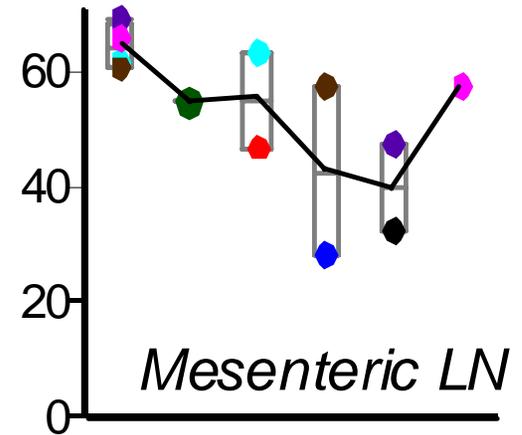
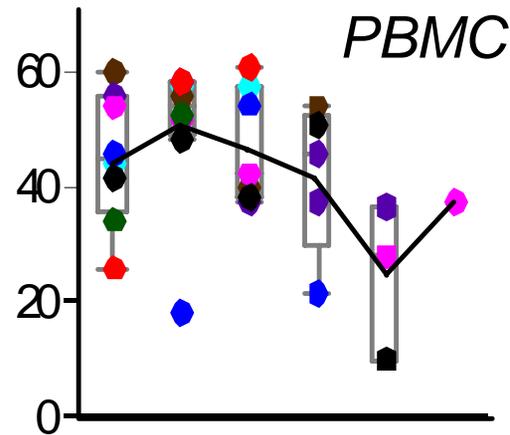
Acute Infection: Plasma Viral Loads



Dramatic CD4 Loss Only in Mucosal Tissue



CD4 T Cells, % of CD3+



Days Post-infection

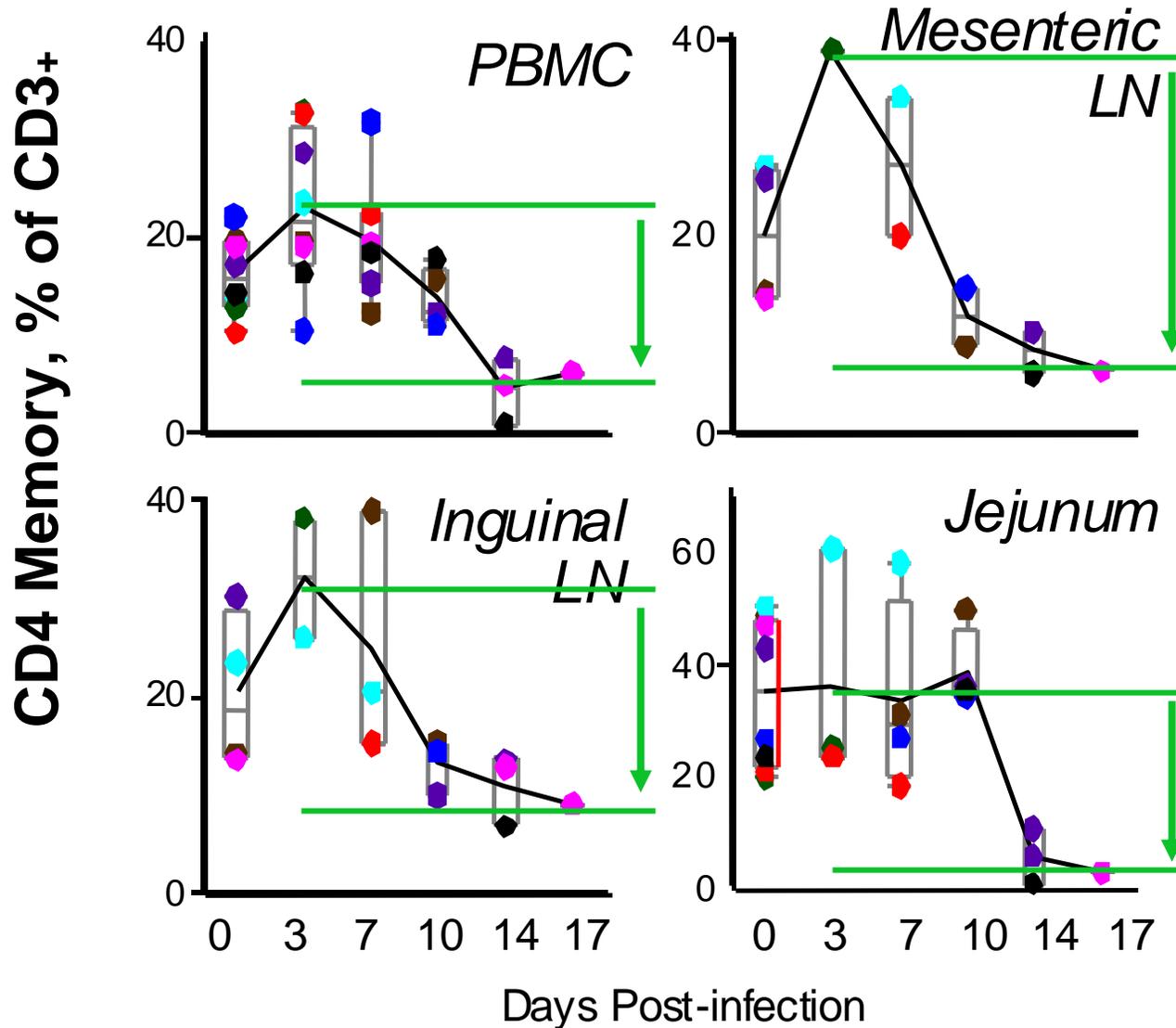
But... CD4 T Cells Are Heterogeneous

SIV and nearly all transmitted HIV infect *only memory CD4 T cells* (CCR5).

Therefore, we should ignore naïve CD4 T cells, *which are uninvolved* in the early infection—just like we ignore CD8 T cells

The representation of naïve CD4 T cells varies dramatically from subject to subject, as well as by tissue.

CD4 Memory T Cell Dynamics

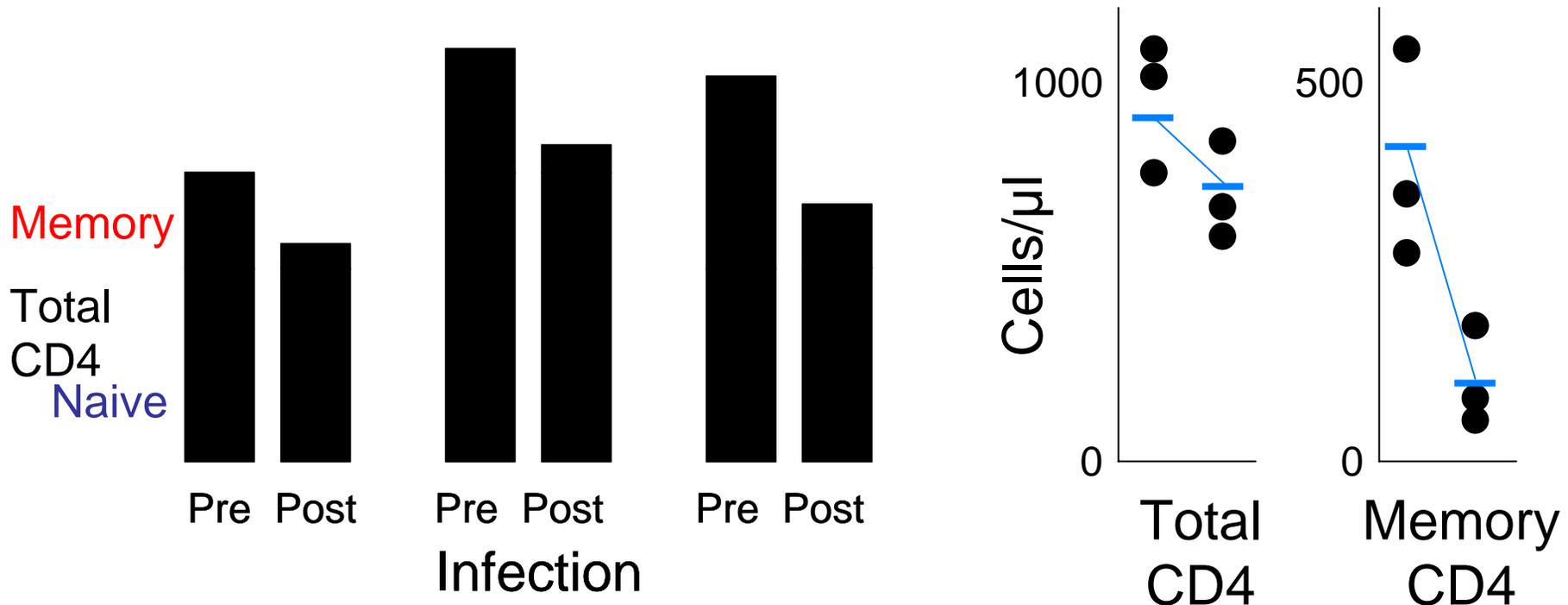


Loss of
~80% of
cells by
d. 17

CD4 Memory T Cell Dynamics

Memory CD4 T cells are dramatically and consistently affected in all tissues.

Measurement of total CD4 underestimates pathogenesis because of the high and variable contribution of naïve T cells.



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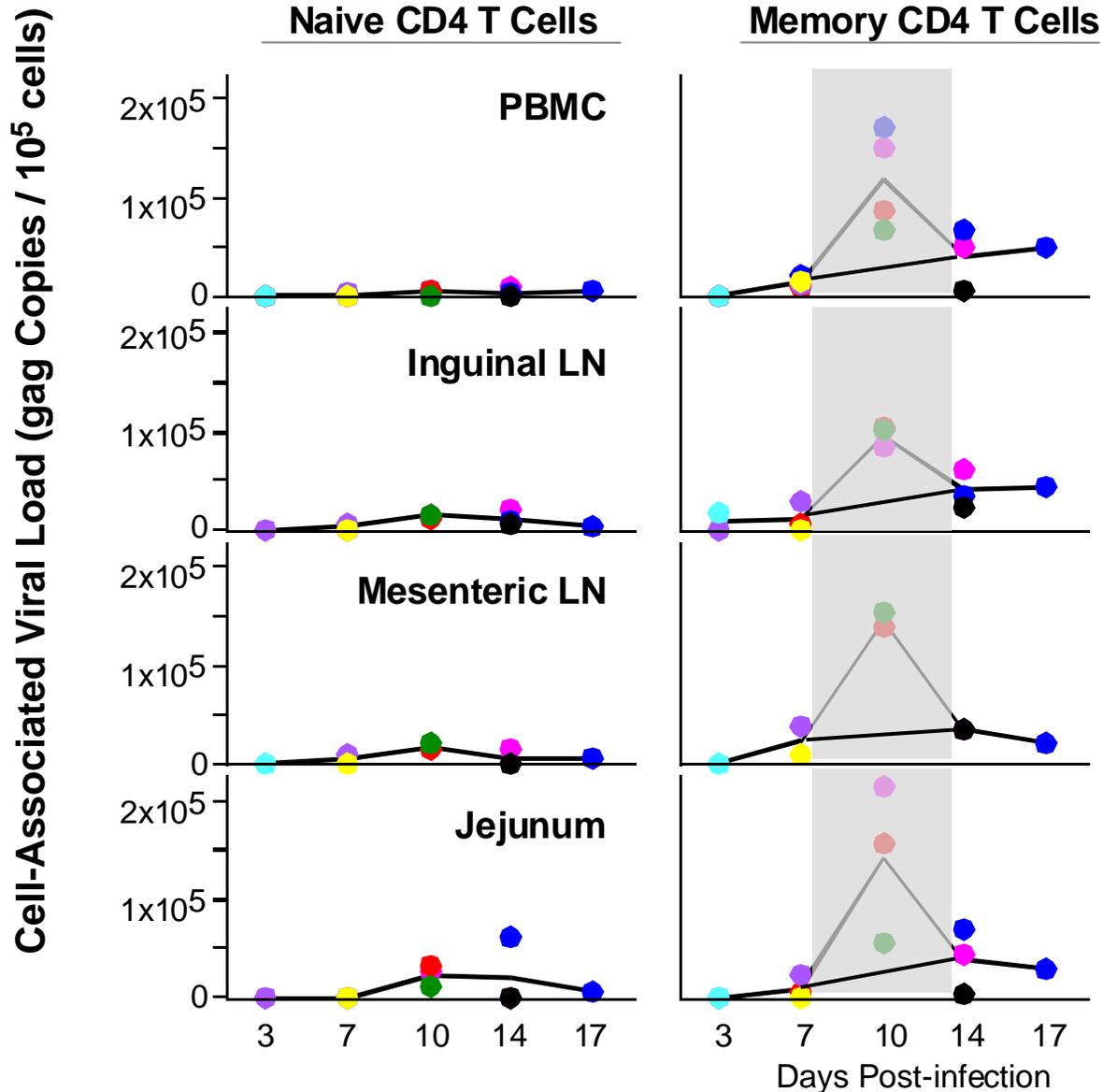
Measurement of total CD4 underestimates pathogenesis because of the high and variable contribution of naïve T cells.

This is not due to redistribution.

Is the loss a consequence of SIV infection?

We performed quantitative PCR to determine the number of SIV copies per cell.

Cell-Associated Viral Loads



Quantification of Cell-Associated Virus: Single Cell qPCR

At d. 10 post-infection, we found 10^5 copies of gag DNA per 10^5 memory CD4 T cells.

This could reflect 1 copy per cell (100% infection), or multiple copies per cell...

Even 10 copies per cell indicates a 10% infection rate!

Wain-Hobson found ~2 copies of gag/infected CD4 T cell in human lymph nodes.

We quantified by doing *quantitative* PCR on single (or low-number) cell sorts.

Quantification of Cell-Associated Virus: Single Cell qPCR

By depositing 1 cell per well by FACS, we quantified the number of copies per infected cell.

We calibrated the system using an SIV-infected cell line that has a single copy of integrated gag DNA.

Tissue	Gag Copies/Cell
PBMC	1.45
Mesn LN	1.51
Ing LN	1.45
Jejunum	1.61

Conclusions (Acute Infection)

- By d. 14, 80% of infected cells disappear: this represents a loss of ~50% of all CD4 memory cells in just 4 days... with more being lost later.
- The loss of memory CD4 T cells *can* be solely ascribed to the consequences of SIV infection.
- This is an enormous insult to the CD4 memory T cell compartment. ***The extent of this destruction during the acute phase may predict long-term outcome.***

Implications for HIV Pathogenesis

Mattapallil et al., Nature 434 (2005)

- HIV disease is *not* a slow disease (“**lenti**virus”). It is fast and furious.
- The damage done during the first weeks is devastating and likely permanent.
- The adaptive immune response does not control primary infection: the infection is self-limiting.
- Intervention is necessary *prior to symptoms...* i.e., vaccination or prophylactic drug therapy.

Questions remain...

Why are so many resting memory T cells infected and killed during acute infection? (SHIV: Naïve T cells)

Why are so few memory T cells infected during chronic infection?

Are remaining memory cells intrinsically resistant to productive infection? How else are they different than destroyed memory T cells?

Will the presence of an effective T cell response during acute infection change the dynamics?

Does Vaccination Alter Acute Dynamics?

We hypothesized that an effective antiviral response could temper the destruction of the CD4 compartment and thereby preserve preexisting memory T cell responses.

Vaccination:

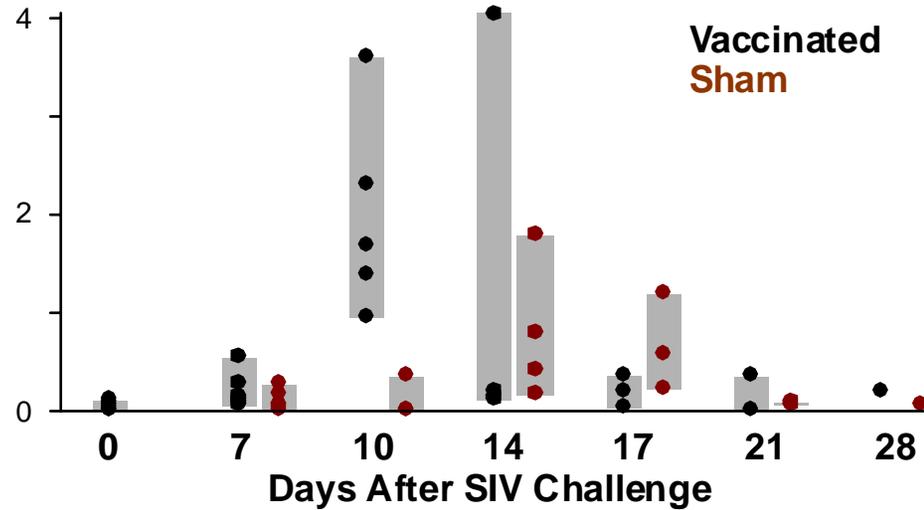
Prime: 3 shots of DNA (4.5 mg env, gag-pol); 0, 1, 2 mo

Boost: 1 shot of rAd (10^{11} particles env, gag-pol); 6 mo

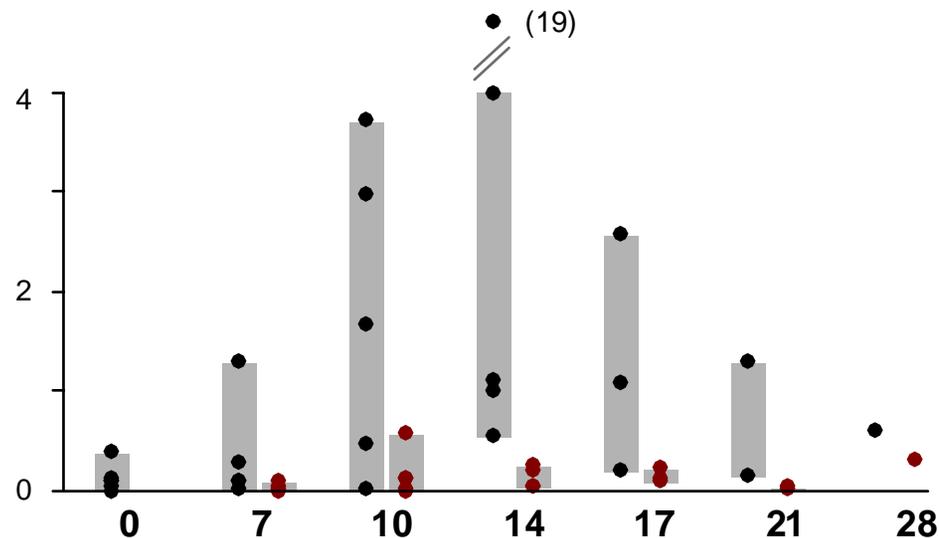
The same regimen is in phase II trials in humans

Kinetics of Cellular Response

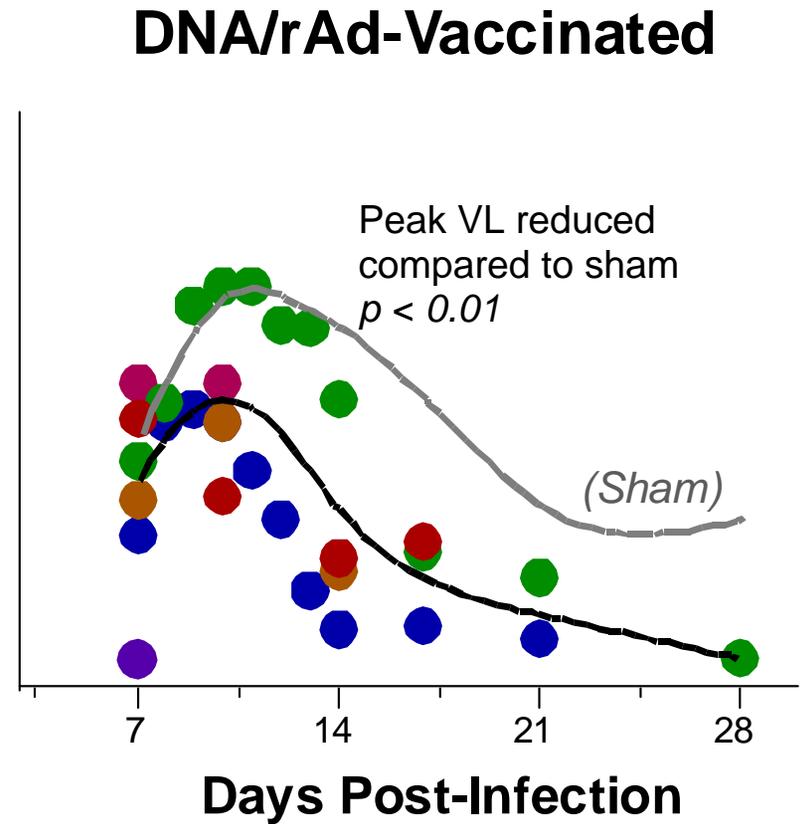
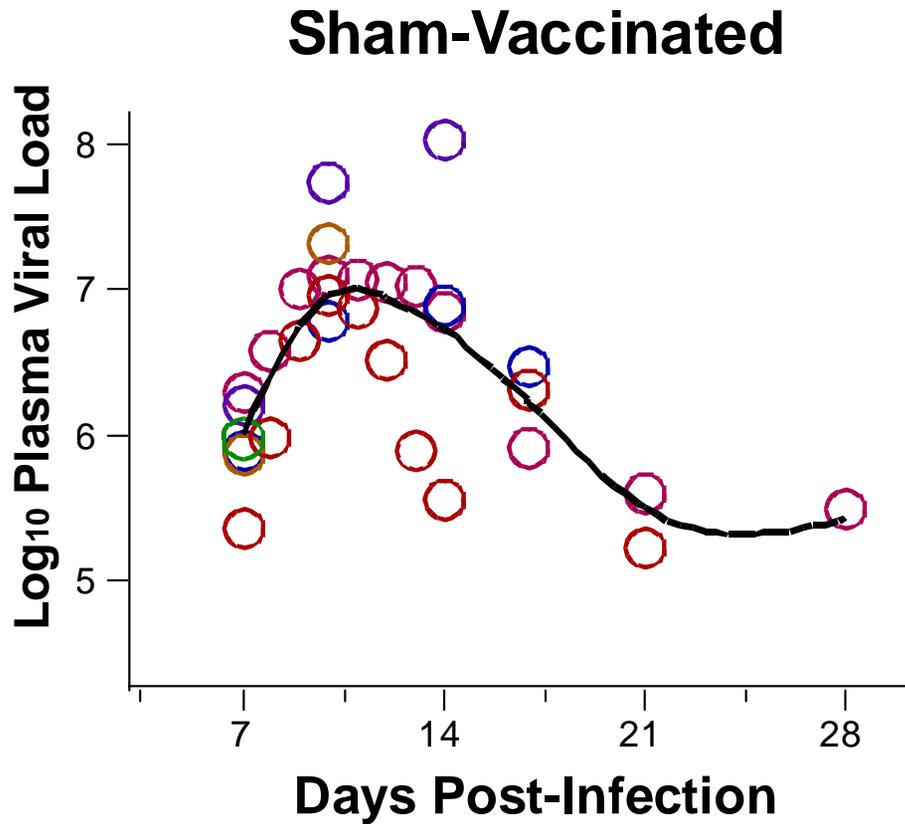
SIV-Specific
CD4 T Cells



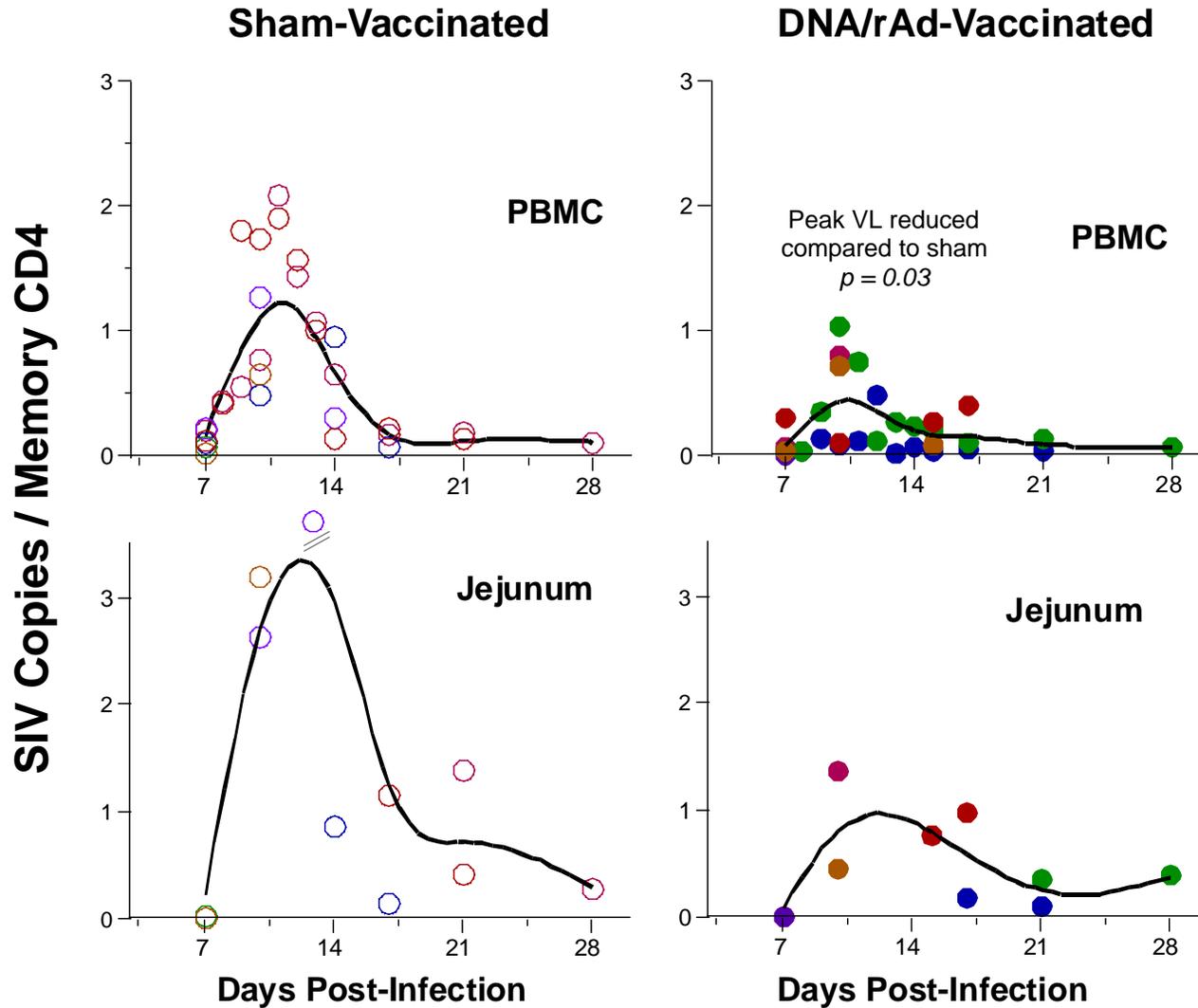
SIV-Specific
CD8 T Cells



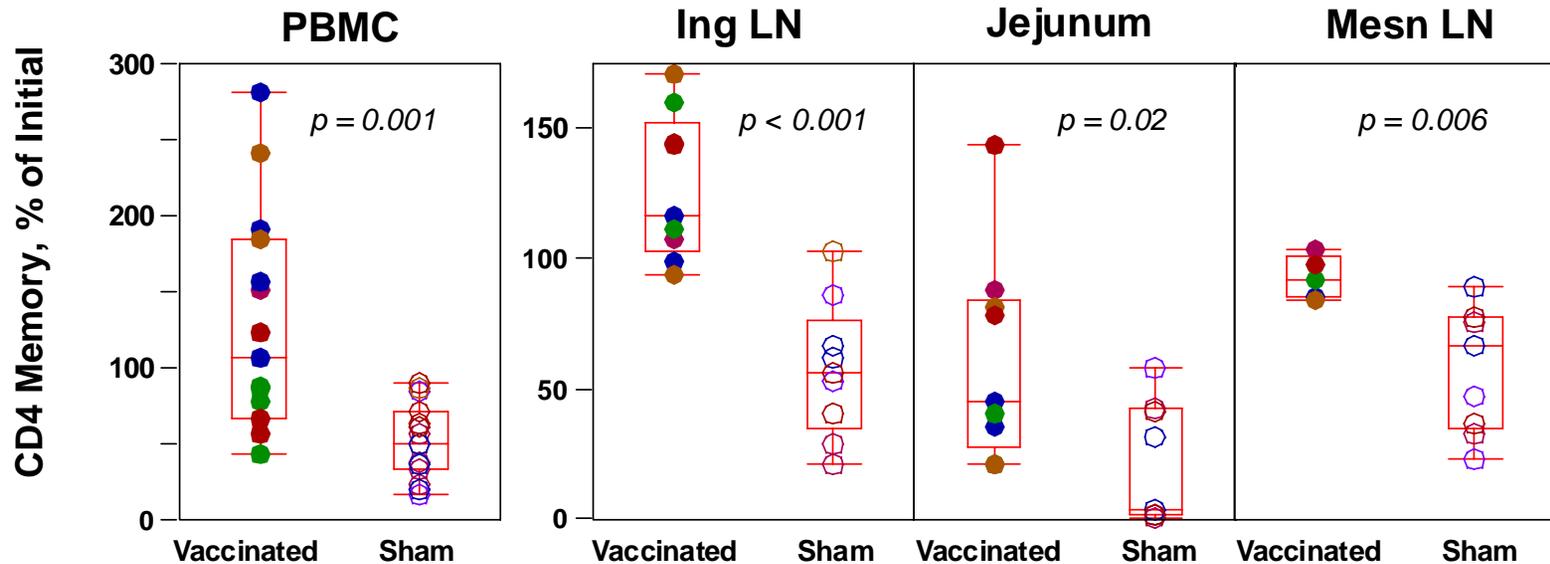
Prior Vaccination Reduces Peak Viremia



Vaccination Reduced Cell-Associated VL



Vaccination Protects CD4 Memory T Cells

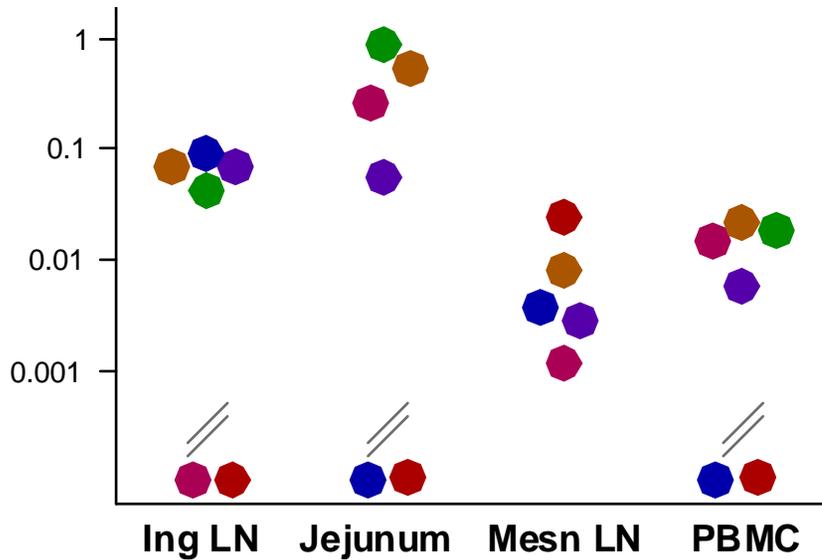


Protection observed in all tissues

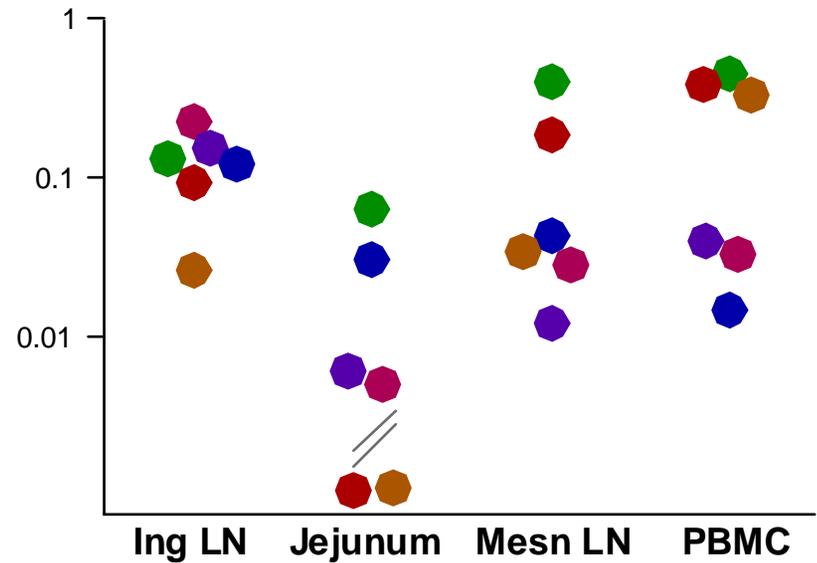
Somewhat less protection in mucosa

CD8 T Cell Responses

SIV-Specific CD4 T Cells

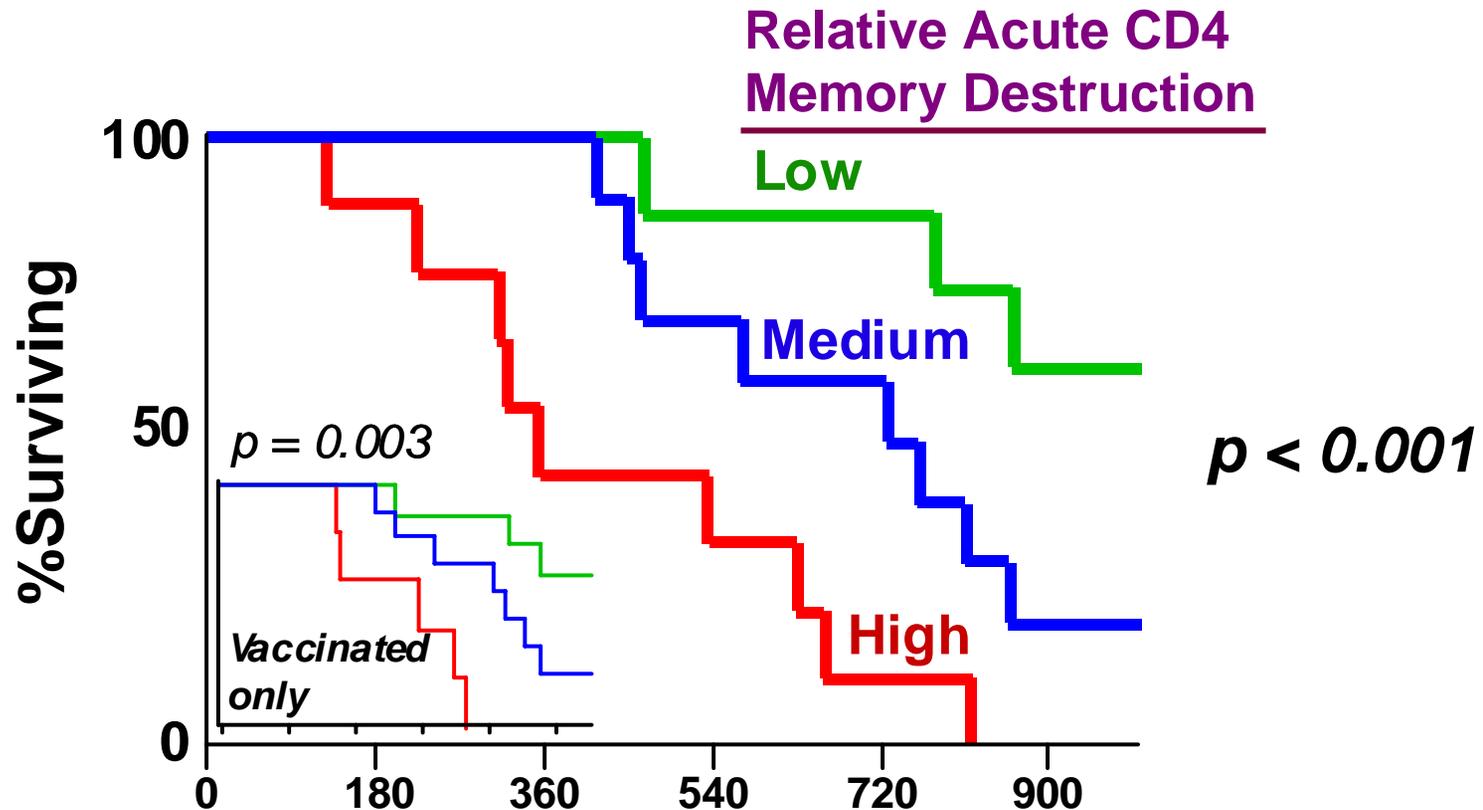


SIV-Specific CD8 T Cells



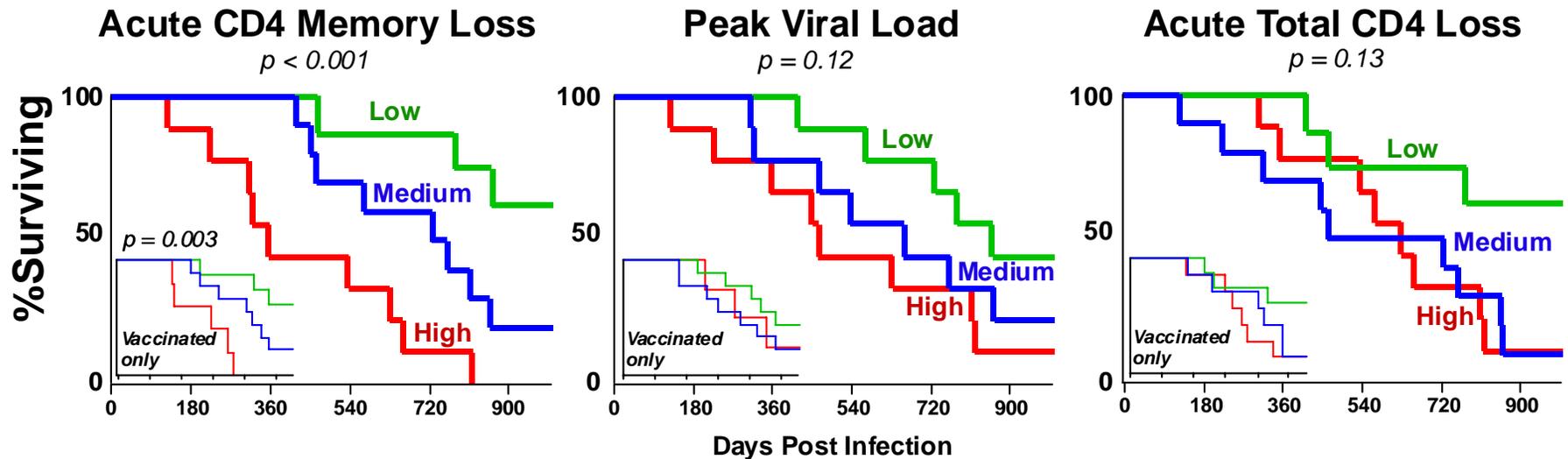
Better preservation of CD4 T cells may require enhanced mucosal CD8 T cell activity

Memory CD4 Destruction Predicts Survival



Animals divided in terciles based on the loss of absolute CD4 memory T cells between challenge and 28 days post-challenge.
 $n = 22$ vaccinated + 5 sham control animals.

During the Acute Phase, Only Memory CD4 Destruction Predicts Survival



For each analysis, animals were divided into tertiles based on that measurement. $n = 22$ vaccinated, 5 sham animals

Vaccination for SIV and HIV

Mattapallil et al., J. Exp Med (2006)

- Vaccination can protect against the destruction of the immune system during acute phase
- Systemic vaccination can protect at mucosal sites
- Protection strongly correlates with subsequent survival

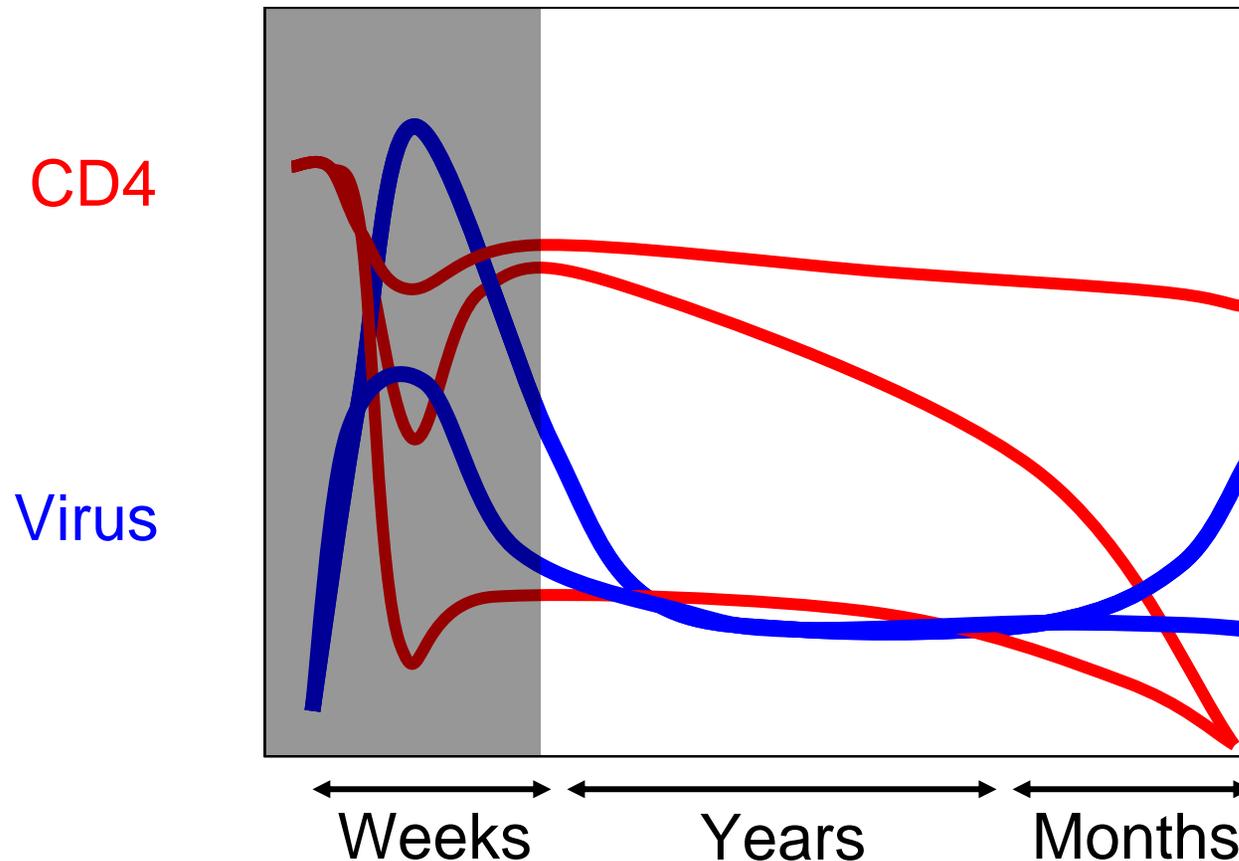
Vaccination, Disease Pathogenesis

Events during the first weeks define progression

Acute

Chronic

AIDS



On the Path to an HIV Vaccine

- **Vaccination *can protect* against the massive immunological damage occurring during acute infection**
 - Lower viral loads (lower transmission)
 - Decreased mortality (and morbidity?)
- **We have made substantial progress in developing the tools to identify immunological correlates and mechanisms of protection**
 - Rapid future vaccine development
- **The VRC will soon initiate a *Proof of Concept Efficacy Trial*, encompassing ~10,000 subjects worldwide**

Collaborators

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Turning fog into rainbows