
PATHOGENESIS OF HIV INFECTION

The CD4 Pool and Immune Activation

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Pathogenesis of HIV Infection

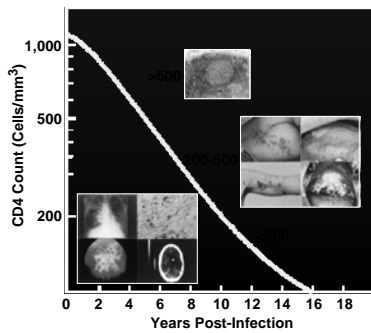
- Depletion of the CD4+ T Cell Pool leading to immunodeficiency.
- Activation of multiple elements of the immune system leading to a functional immunosuppression and state of inflammation/coagulation.
- Inadequate immune response to HIV infection allowing ongoing viral replication.

Pathogenesis of HIV Infection

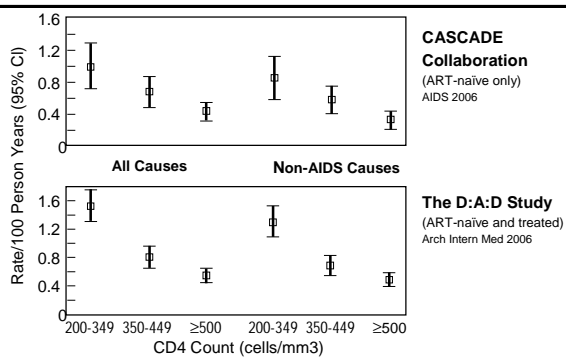
- Relationship between the peripheral blood CD4+ T cell count and the total CD4+ T cell pool.
- Dissection of immune activation and the role of inflammation in the expanded spectrum of HIV disease.
- Identification of a potential correlate of protective immunity to HIV.

RELATIONSHIP BETWEEN THE PERIPHERAL BLOOD CD4+ T CELL COUNT AND THE TOTAL CD4+ T CELL POOL

Correlation Between CD4 Count and Clinical Manifestations of HIV-1 Infection



Lower CD4 Counts are Associated with Higher Rates of Death from Non-AIDS Causes



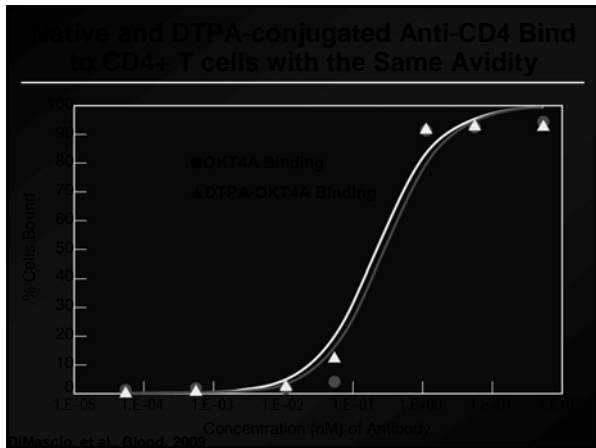
The Peripheral Blood CD4+ T cell Count is an Imperfect Marker of Disease Progression

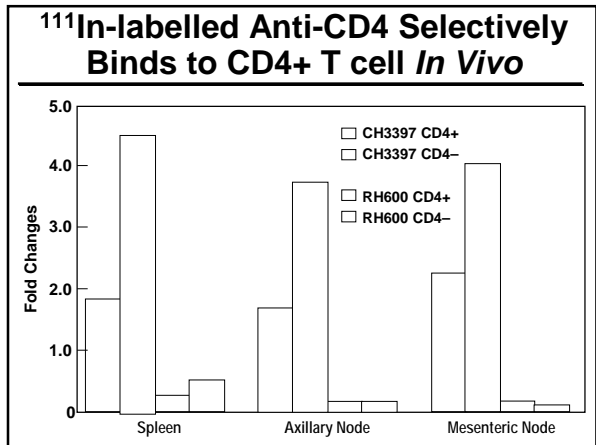
- Baseline CD4+ T cell counts explain only up to 30% of the variability in time to AIDS or death (Mellors, JAMA, 2007).
- In patients who have undergone splenectomy or who are receiving interferon-alpha therapy the CD4% is a better marker of immune competence than the CD4+ T cell count.
- Given that only a small (estimated at 2%) percentage of CD4+T cells are present in the blood even a slight change in the distribution of CD4+ T cells between lymphoid tissues and blood could lead to a large change in the peripheral blood CD4+ T cell count.

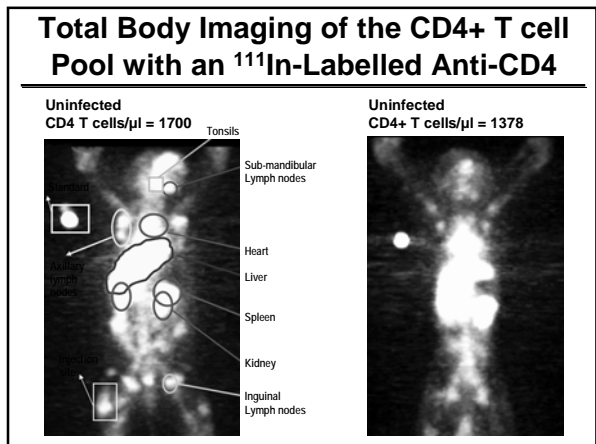
***In Vivo* Imaging of the CD4+ T Cell Pool**

Imaging the CD4 Pool with an Anti-CD4 Monoclonal Antibody

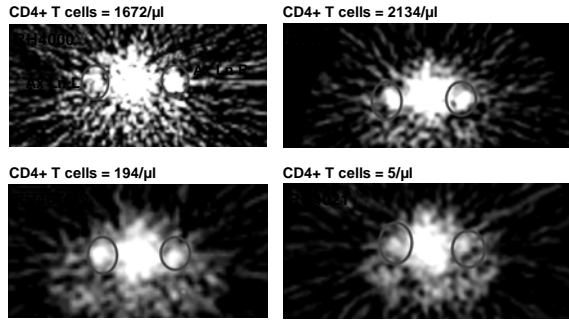
- In 1996 Rubin and colleagues described the use of an ¹¹¹Indium-labelled anti-mouse CD4 monoclonal antibody for studying CD4+ T cell distribution in mice (PNAS 93:7460, 1996).
- In order to apply this approach to non-human primates, and potentially to humans in the future, we have conjugated a non-depleting humanized monoclonal antibody that binds to CD4 molecules from humans and rhesus macaques (CDR-OKT4A/hlgG4) to ¹¹¹Indium.
- Semi-quantitative *in vivo* images were obtained using a SPECT camera and normalizing against liver uptake.
- Quantitative analysis of tissue binding of the antibody was determined by *ex vivo* analysis of tissue in a gamma counter and normalizing against activity in the liver.



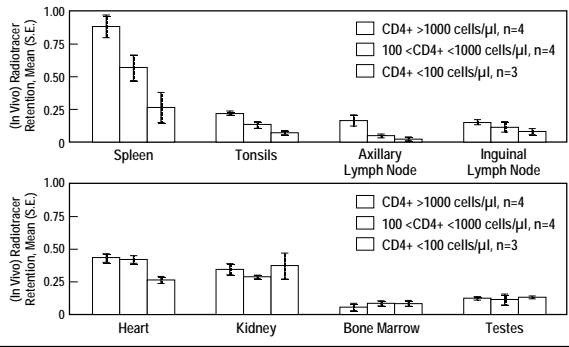




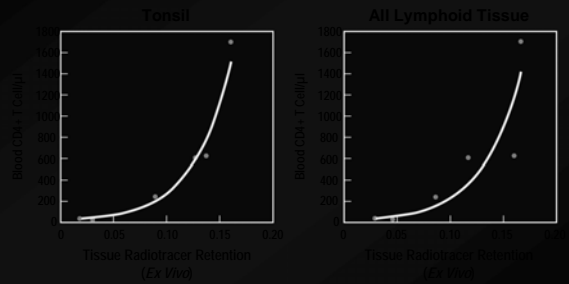
The Intensity of Anti-CD4 Staining of Axillary Lymph Nodes In Vivo is Proportional to the Peripheral Blood CD4+ T Cell Count



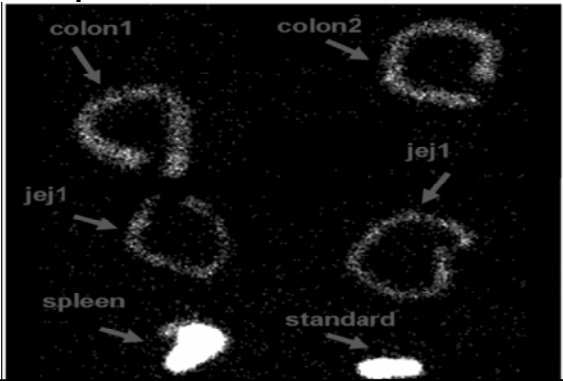
The *In Vivo* Intensity of Anti-CD4 Staining of Lymphoid Tissues is Proportional to the Peripheral Blood CD4+ T Cell Count



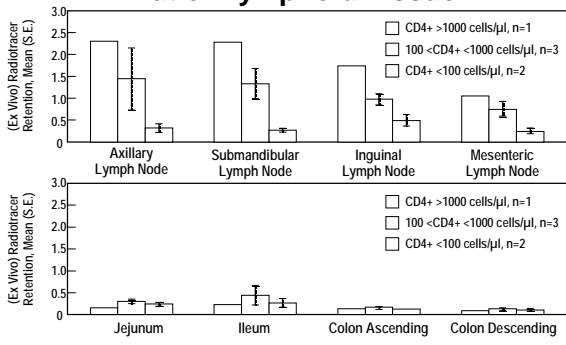
The Relationship Between *Ex Vivo* Radiotracer Retention and Peripheral Blood CD4+ T Cell Count is Exponential



SPECT Images of Colon, Jejunum and Spleen from an SIV-infected NHP



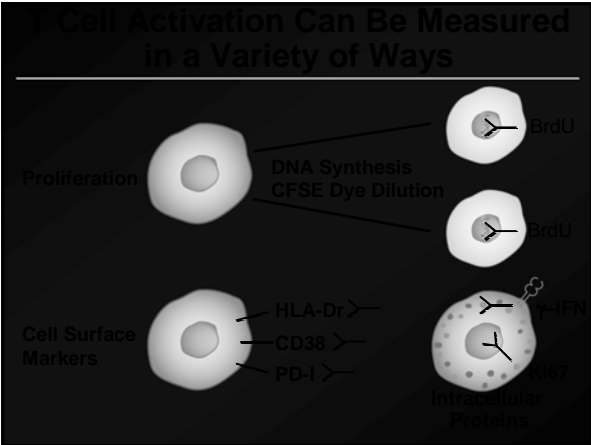
The Tissue Density of CD4+ T Cells in Intestinal Tissue is 10% or Less than That of Lymphoid Tissue

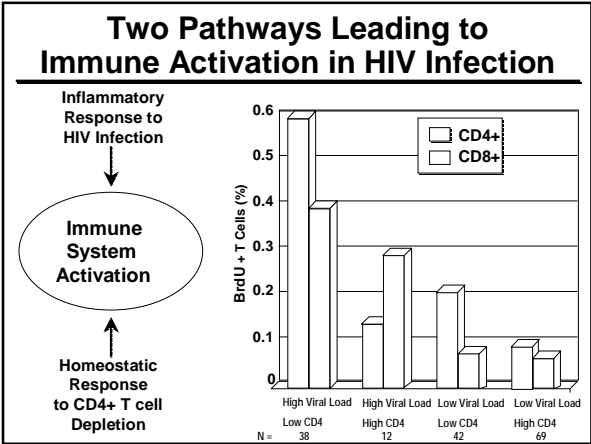


Preliminary Observations from *In Vivo* Imaging of the CD4+ T Cell Pool

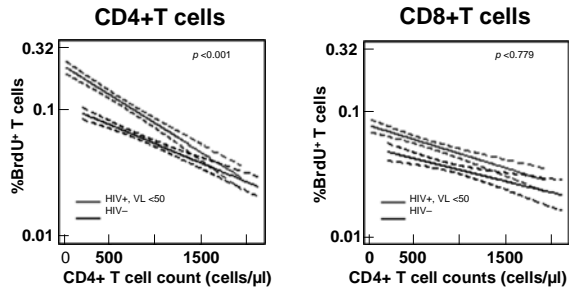
- A ¹¹¹In-labelled antibody can be used to visualize the CD4+ T cell pool in non-human primates.
- The relationship between the number of CD4+ T cells in tissue and the number of cells in blood is exponential.
- Additional observations:
 - The spleen constitutes approximately 15% of the total CD4+ T cell pool.
 - The GI tract contributes no more to the total pool than the spleen.

IMMUNE ACTIVATION IN THE PATHOGENESIS OF HIV INFECTION





CD4+, But Not CD8+, T cell Proliferation Normalizes at Higher CD4 Counts



Catalfamo, et al., PNAS, 2008

Inflammation as a Component of HIV Immune Activation

SMART STUDY: Non-AIDS Complications

Endpoints	No. of Patients with Events	Events per 100 Person-years		Hazard Ratio (DC/VS) (95% CI)
		DC	VS	
Major CVD, renal and hepatic complications	65	1.8	1.1	1.7

CVD (fatal or non-fatal)	48	1.3	0.8	1.6
Renal (fatal or non-fatal)	9	0.2	0.1	4.5 ▶
Hepatic (fatal or non-fatal)	10	0.3	0.2	1.5

Serious non-AIDS	186	3.2	2.0	1.7

◀ Favors DC Favors VS ▶

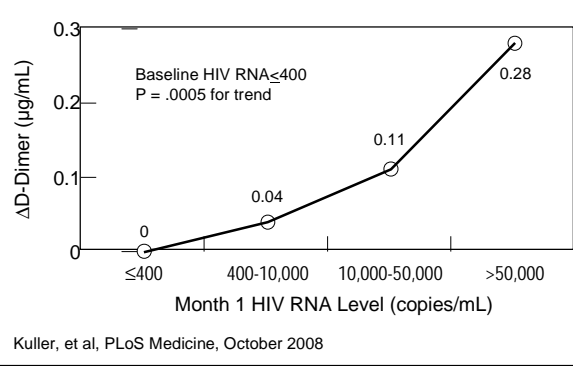
INSIGHT Network

Baseline Biomarkers and All Cause Mortality

Marker	Un-adjusted		Adjusted	
	OR (4 th /1 st)	P-value	OR (4 th /1 st)	P-value
Hs-CRP	2.0	0.05	2.8	0.03
Amyloid A	2.2	0.07	2.6	0.09
Amyloid P	0.7	0.39	1.1	0.84
IL-6	8.3	<0.0001	11.8	<0.0001
D-dimer	12.4	<0.0001	26.5	<0.0001
F1.2	1.0	0.92	1.2	0.66

Kuller, et. Al, PLoS Medicine 2008

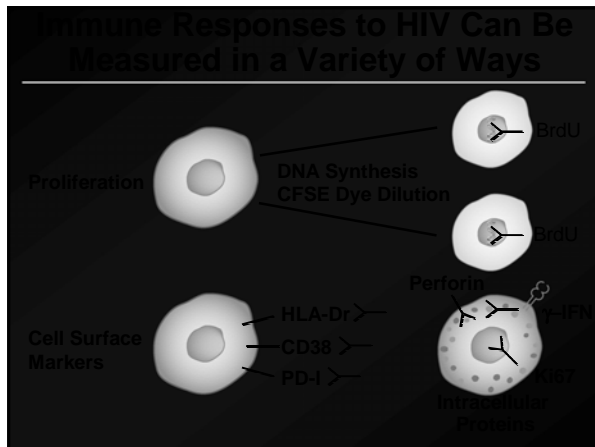
Change in D-Dimer (µg/mL) from Baseline to 1 Month after Stopping HAART



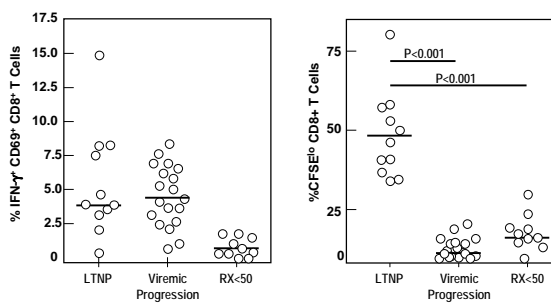
HOST CONTROL OF HIV INFECTION

Immunologic Control of HIV

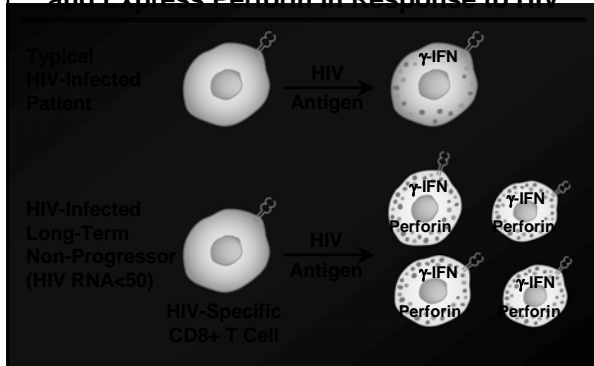
- Most individuals fail to restrict HIV replication despite a high frequency (10-40%) very broad (15-20 epitopes) CD8+ T cell response to autologous virus.
- The exceptions are a group of patients who maintain HIV RNA levels <50 copies/ml and normal CD4 counts in the absence of therapy.
- This phenotype is highly associated with certain HLA genotypes, particularly HLA-B*5701.
- Achieving an understanding of the precise immunologic mechanisms leading to this control is of great importance in the development of vaccines and immune based therapies.



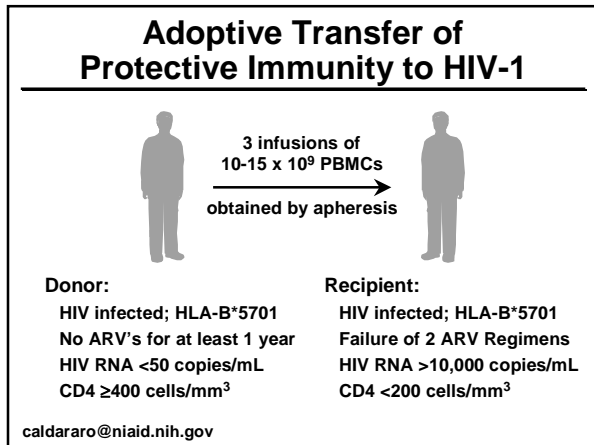
The Immune Responses of Long-Term Non-Progressors to HIV are Characterized by CD8+ T Cell Proliferation



CD8+ T Cells from Long-Term Non-Progressors Undergo Clonal Expansions and Express Perforin in Response to HIV



Adoptive Transfer of Protective Immunity to HIV-1



Summary

- HIV infection leads to a depletion of the CD4+ T cell pool that may be better quantitated by in vivo imaging than peripheral blood CD4+ T cell counts.
- The immune activation of HIV infection is driven by both viral load and homeostatic forces and creates a state of chronic inflammation that may lead to significant end organ damage outside the immune system.

Summary

- A small subset of patients with HIV infection are able to control viral replication in the absence of treatment. This control appears to be mediated via a unique CD8+ T cell response that identifies an important target for HIV vaccine development and HIV-specific immune based therapies.

Acknowledgements

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 - Stephen Migueles
 - Joe Kovacs
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