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Nationales  
d'Infectiologie

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Cité des Congrès de Nantes



**Nantes**  
et la région Pays de la Loire



# Immunosénescence et VIH

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Fight Aging and STress department (FAST)  
**SORBONNE Université**, Paris, France



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**Kumamoto University**, Kumamoto, Japan









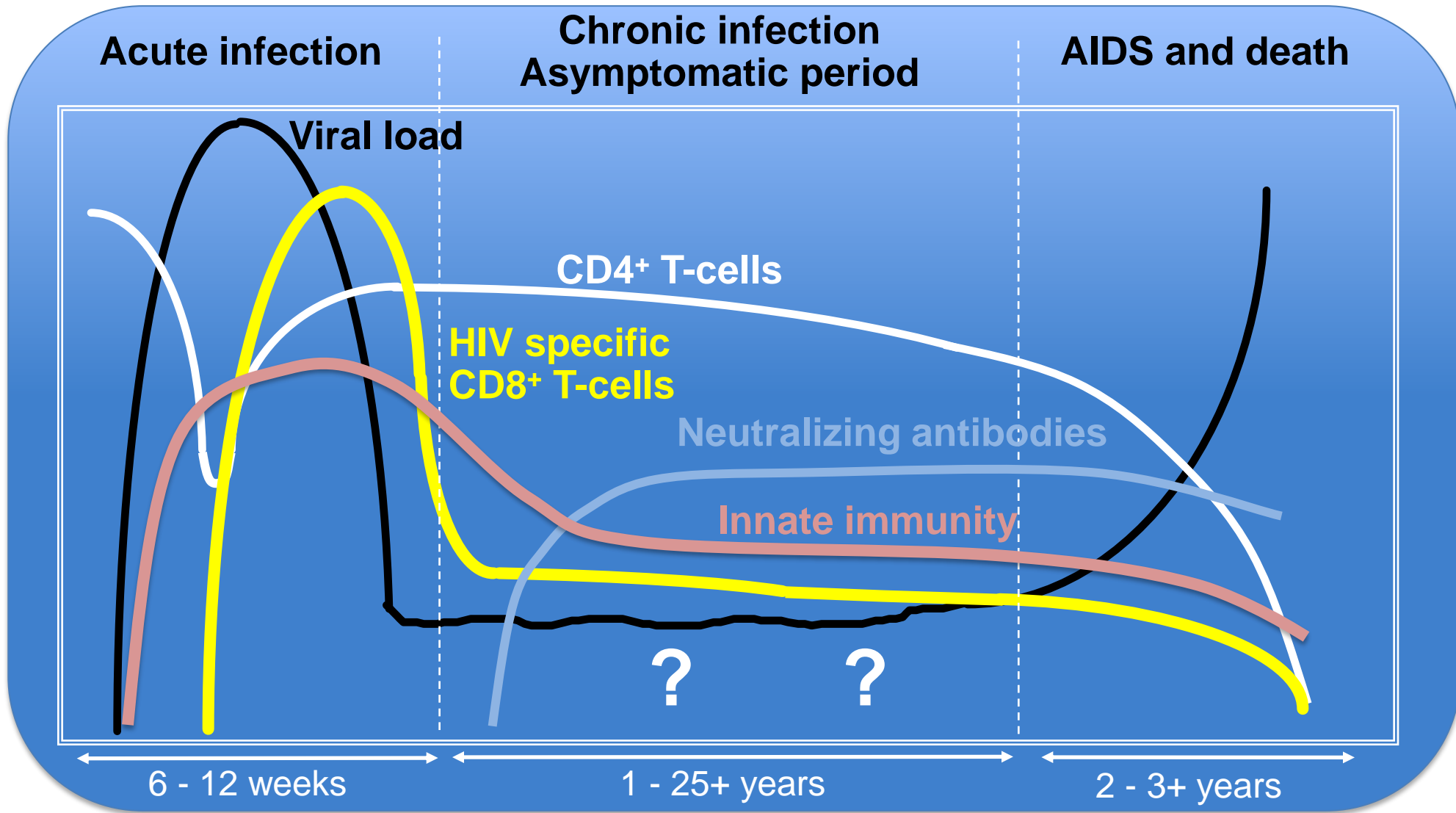
**Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :**

**Intervenant :** Victor Appay

**Titre :** Immunosenescence et VIH

-  Consultant ou membre d'un conseil scientifique  OUI  NON
-  Conférencier ou auteur/rédacteur rémunéré d'articles ou documents  OUI  NON
-  Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations  OUI  NON
-  Investigateur principal d'une recherche ou d'une étude clinique  OUI  NON

# Course of HIV infection



**=> better understand disease progression...**

# Immune activation and progression towards AIDS

## HIV infection and replication

Main target: activated CCR5+ CD4+ T lymphocytes



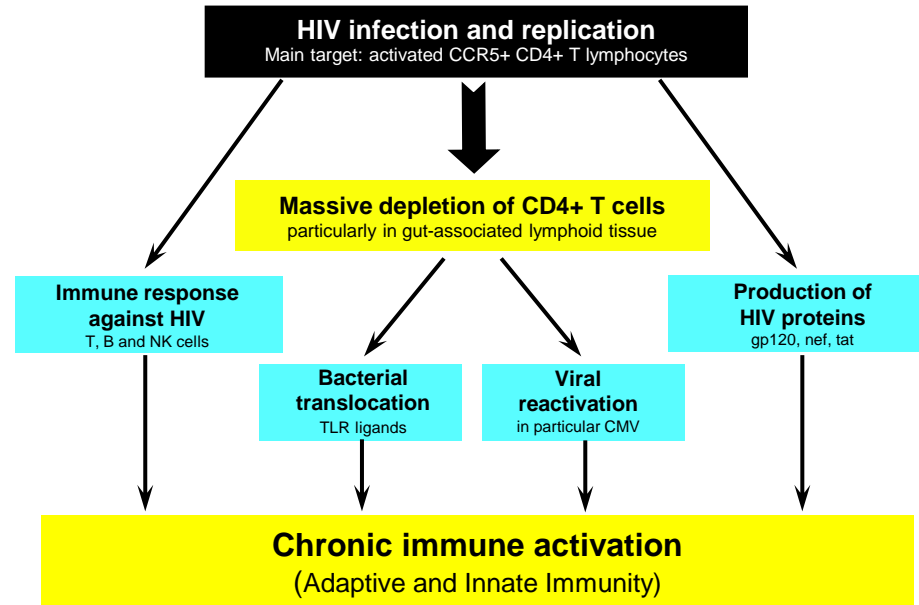
**Chronic immune activation**  
(Adaptive and Innate Immunity)



**Collapse of the immune system / AIDS**

# Immune activation and progression towards AIDS

## Causes



## Consequences

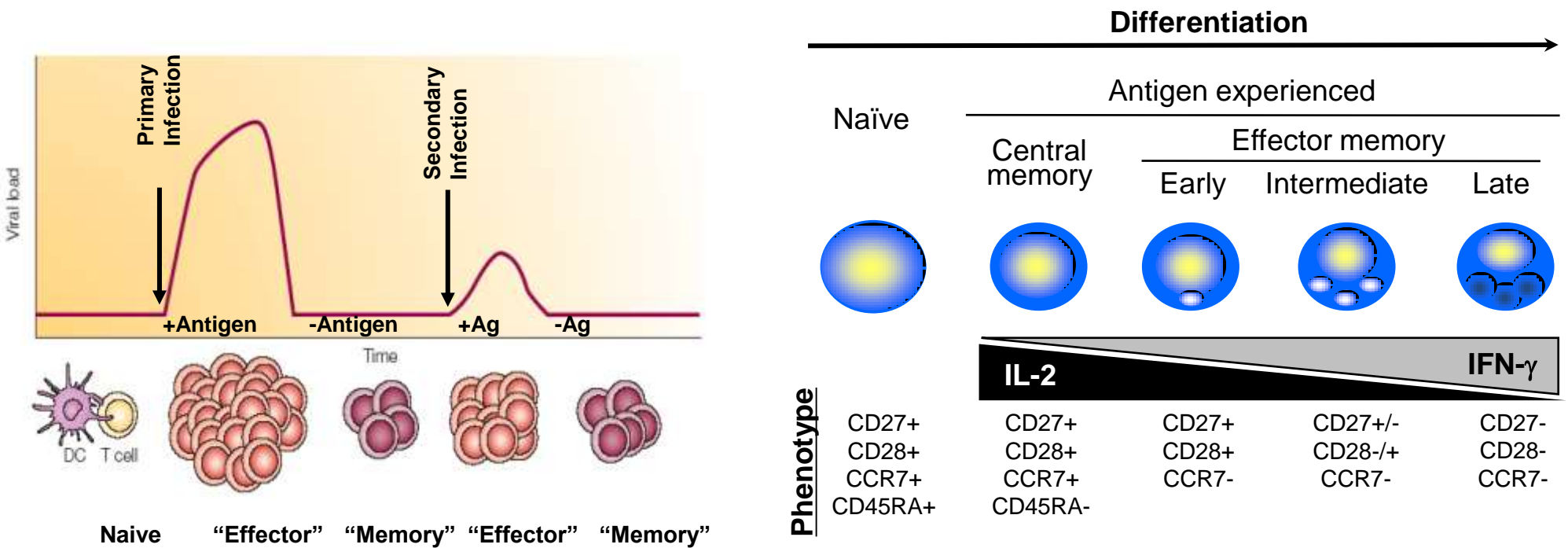
??

**Immune exhaustion /  
Immunosenescence?**

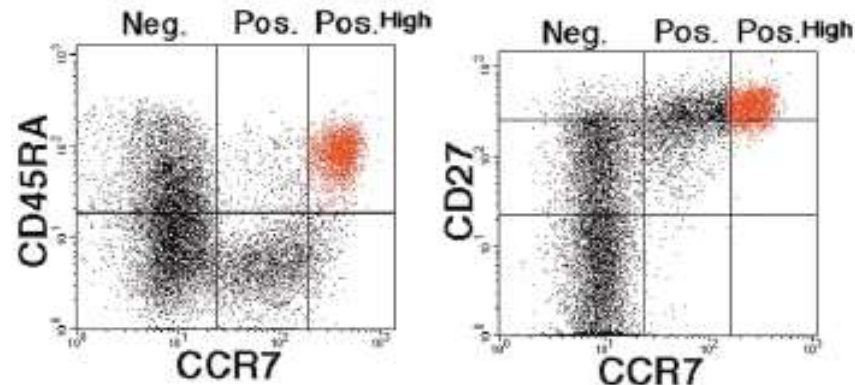


**Collapse of the immune system / AIDS**

# Subpopulations of T lymphocytes (CD4 & CD8)

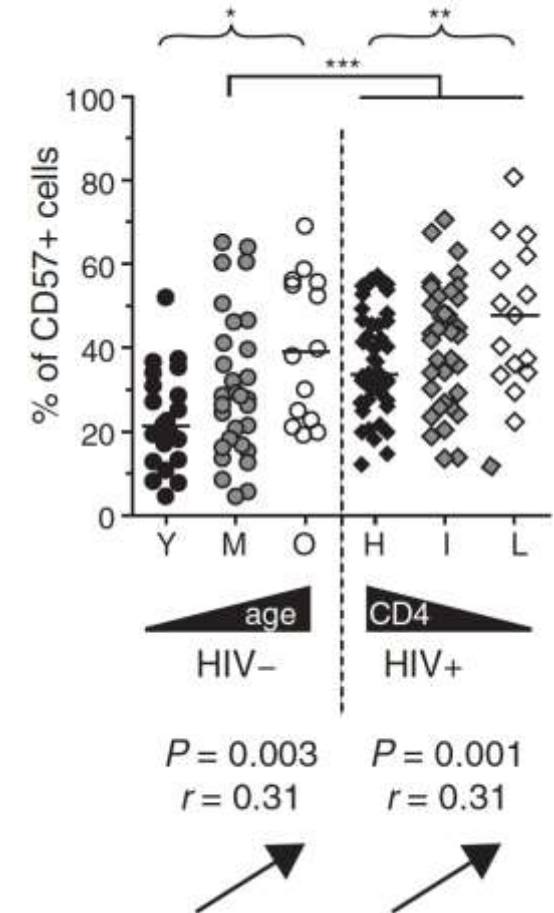
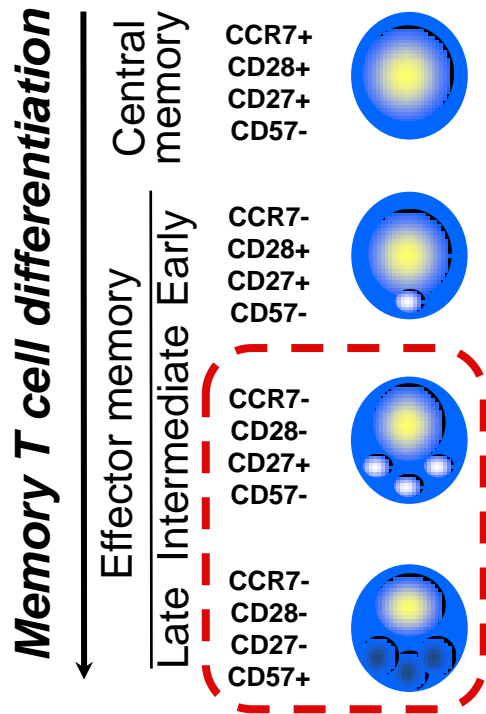


Identification  
by flow cytometry



# 1. Initial evidence of immune aging in HIV infected patients: High frequency of highly differentiated / old memory T cells

## Memory T cell subsets & Aging features



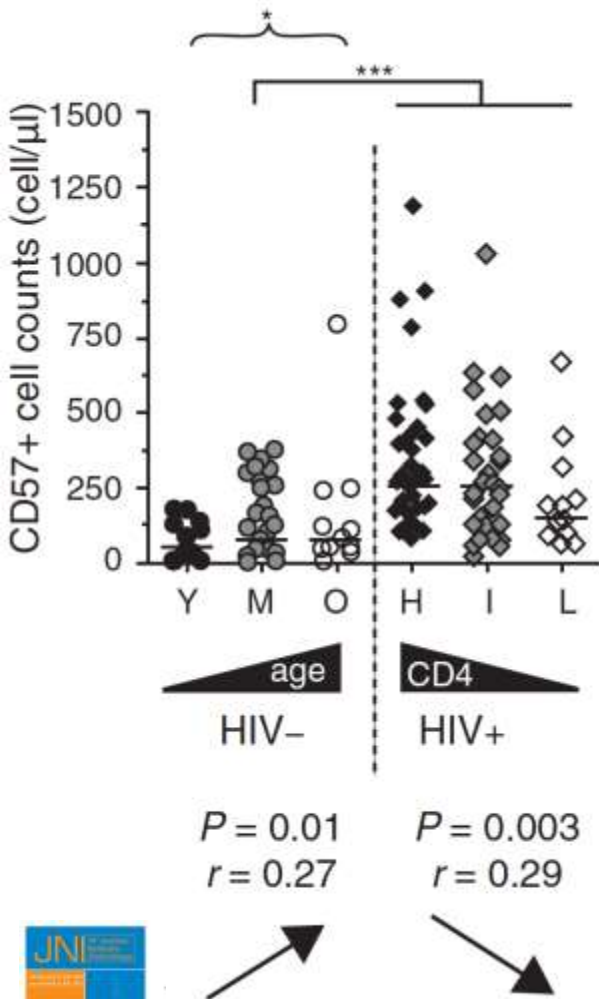
**↗↗ with age and HIV-1 infection**

**=> CD28- CD57+ T cells => "marker of immunosenescence"**

*Effros RB et al, AIDS, 1996*  
*Brenchley et al, Blood, 2003*  
*Papagno et al, Plos Biol, 2004*

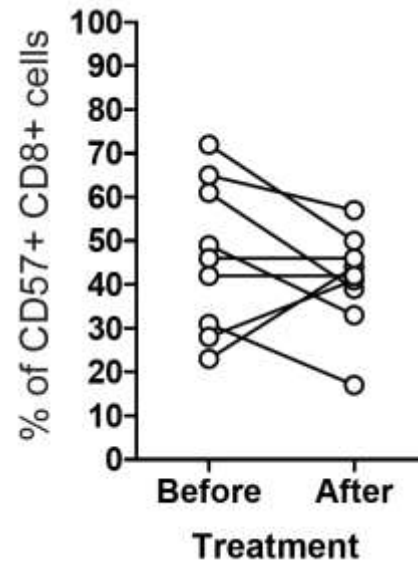
# Is increased frequency of CD28-/CD57+ T cells such a relevant marker of immune aging and HIV disease progression?

## Absolute numbers

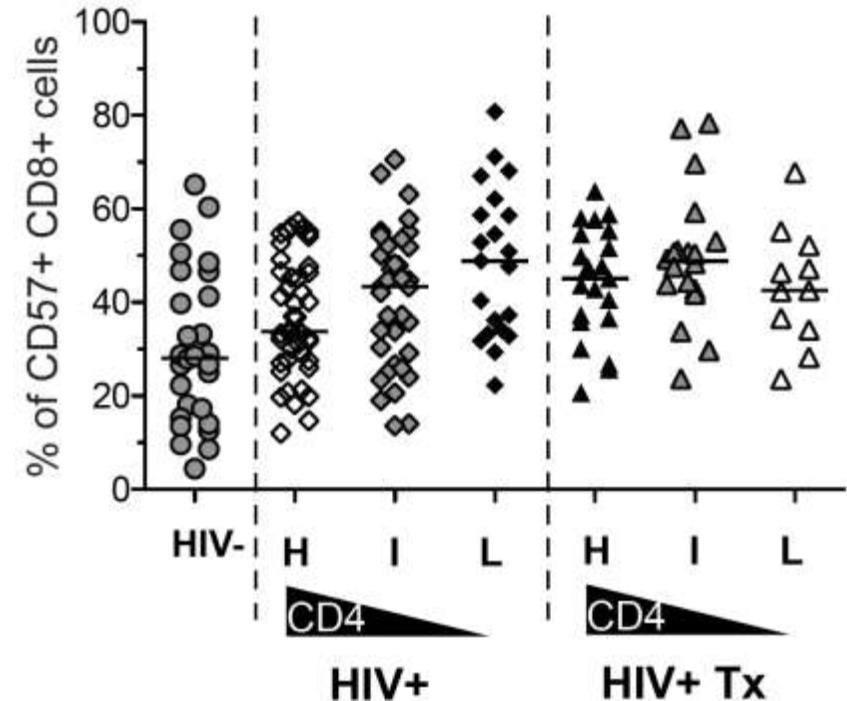


## Evolution with ART

### Longitudinal



### Transversal



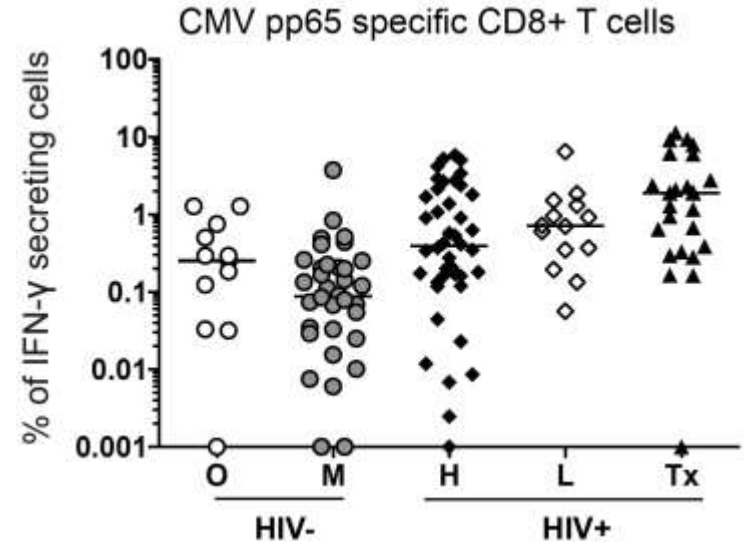
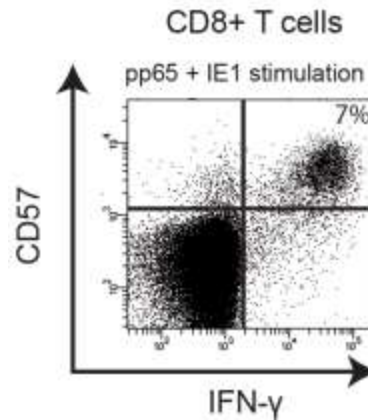
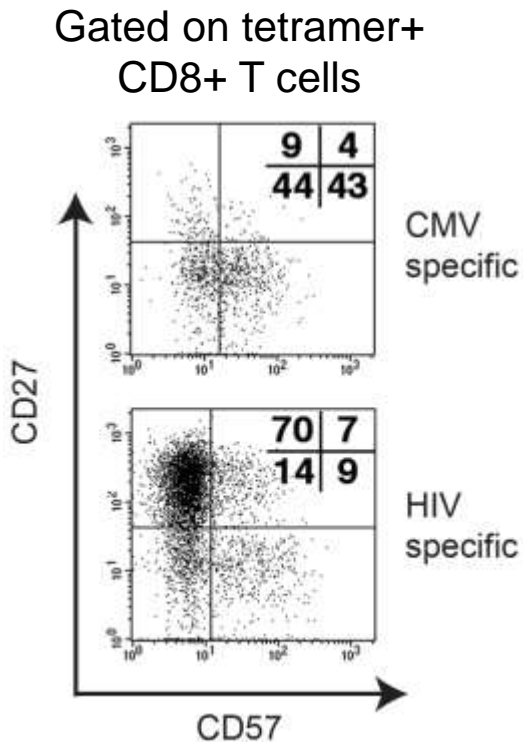
=> No clear association with disease progression



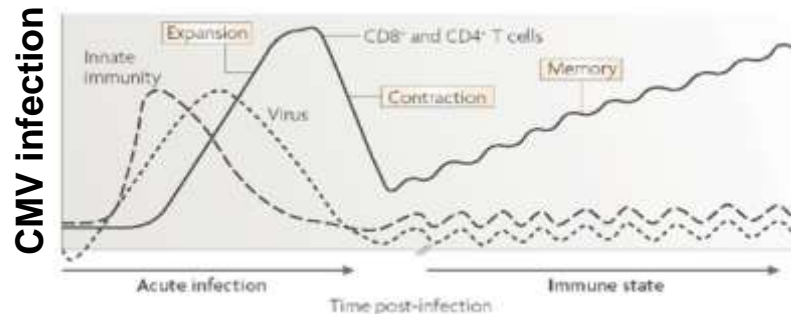
# What drives the accumulation of CD57+ memory T-cells?

=> **CMV specific CD8+ T cells** are highly differentiated

=> In **HIV+ patients (specially ART+)**: strong CMV specific responses



=> **Memory inflation**



**CMV => Confounding factor of the immune parallel between Aging and HIV disease progression**

# CMV co-infection in HIV infected patients

## -Impact on immune profile in HIV infected patients

=> Main driver of accumulation of CD28-/CD57+ T cells

## - Impact on chronic immune activation and inflammation

(increased CD38+ T cells, IL-1b, IL-6, IP-10 levels) (*Hunt, JID 2011, Freeman, CID 2016*)

=> Influence of immune reconstitution capacity (*Appay, AIDS 2011*)

=> Co-infections e.g. HCV (*Kuniholm, Plos One 2013*)

=> Comorbidities: cardiovascular and neurocognitive disorders

Carotid artery intima-media thickness & CMV IgG or T cells

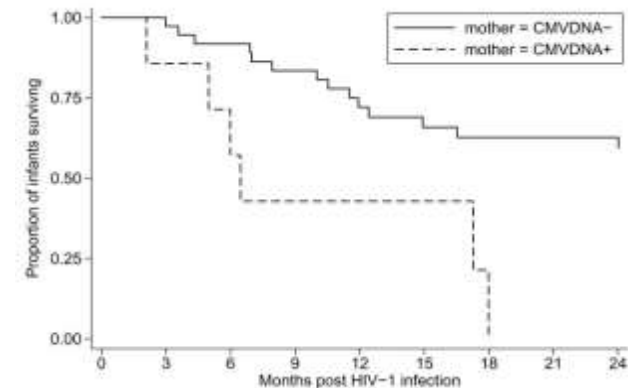
(*Hsue, AIDS 2006; Parrinello, JID 2012*)

## - Impact on mortality (non AIDS events)

=> Infants born from CMV/HIV coinfecting women

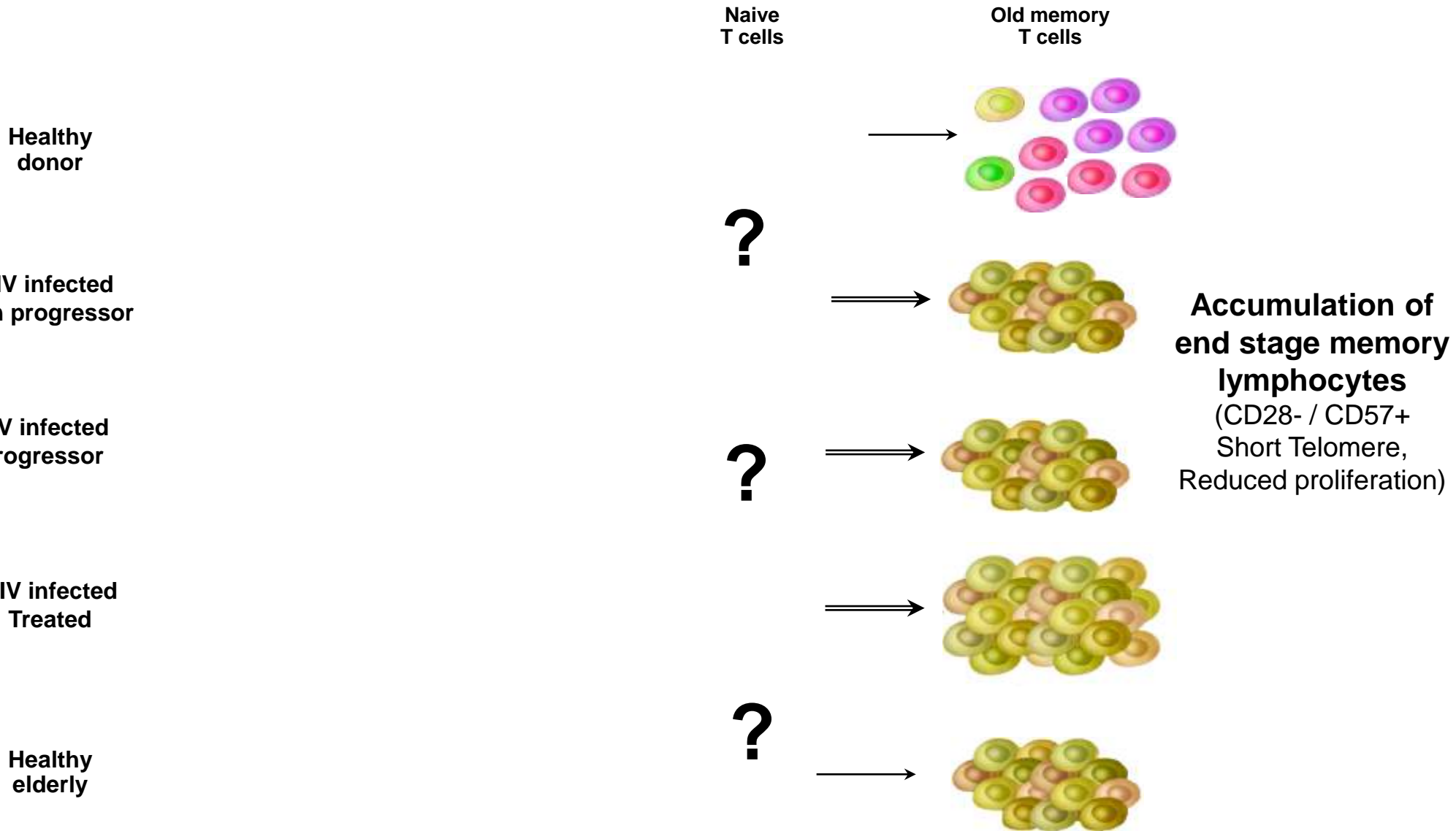
=> CMV/HIV coinfecting adult patients

(*Slyker, AIDS 2009; Lichtner, JID 2015*)



**CMV => Risk co-factor of multiple comorbidities in HIV infected patients**

# Premature immune aging in HIV infection



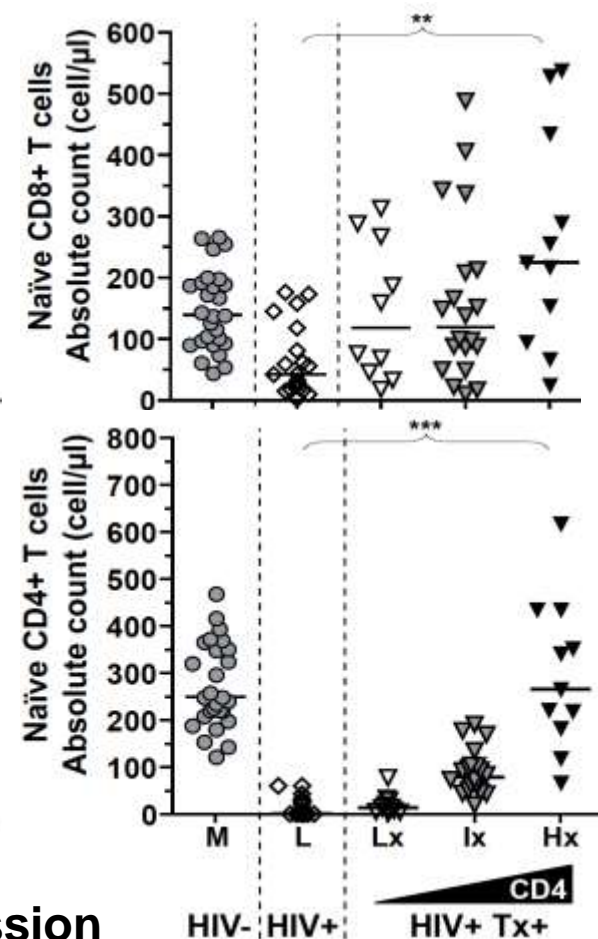
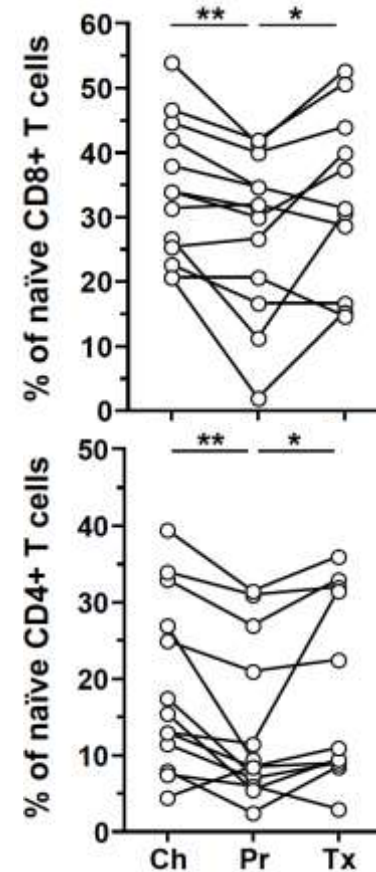
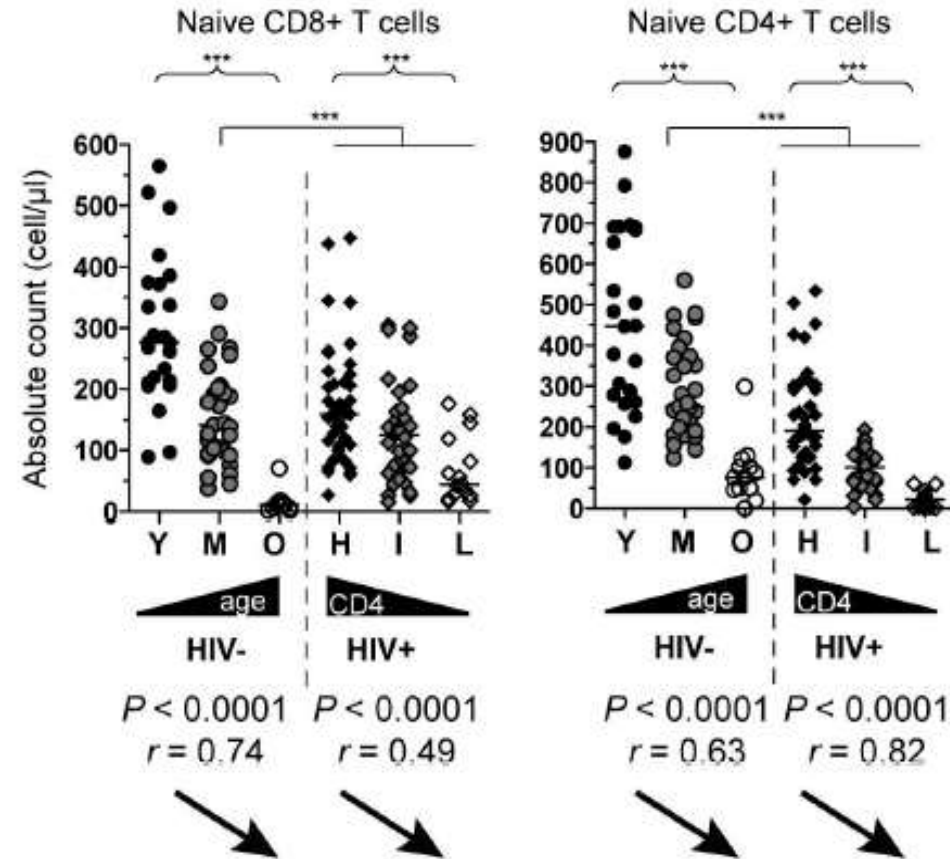
## 2. Collapse of naive T cell frequencies with HIV disease progression and aging

### Absolute numbers

### Evolution with ART

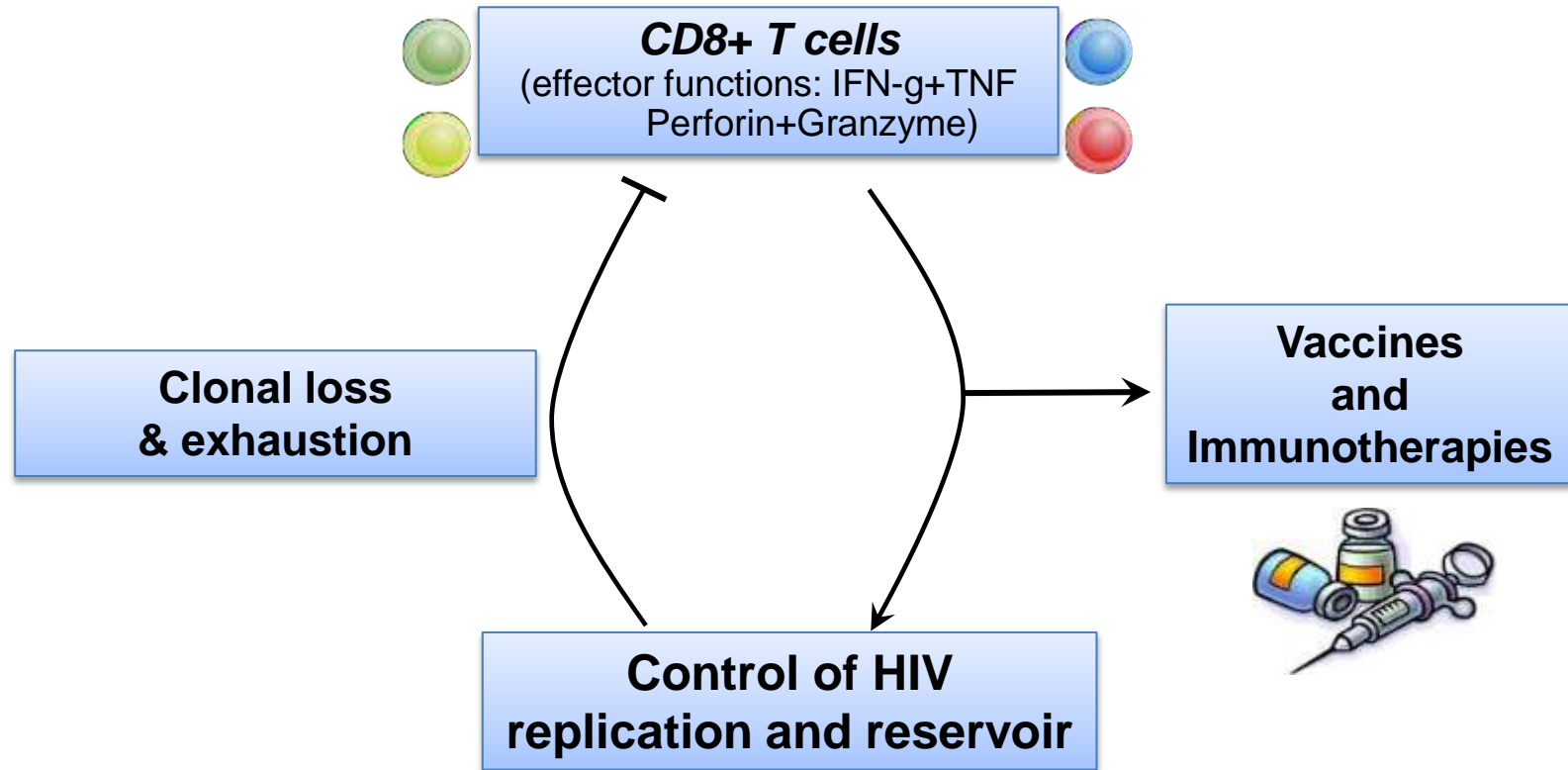
#### Longitudinal

#### Transversal



**=> Strong association with HIV disease progression and immune aging**

# CD8+ T-cell priming efficacy and HIV infection?



**Genomic instability of HIV:** ⇒ Creation of neoantigens  
⇒ Escape of immune recognition

⇒ Key role of **CD8+ T cell naïve pool and priming capacity** to fight HIV

**Impact of immunosenescence on capacity to mount new CD8+ T cell responses in HIV infected patients?**

# Measure the efficacy to induce a *de novo* CD8+ T cell response => use of a simple *in vitro* model of naïve CD8+ T cell priming

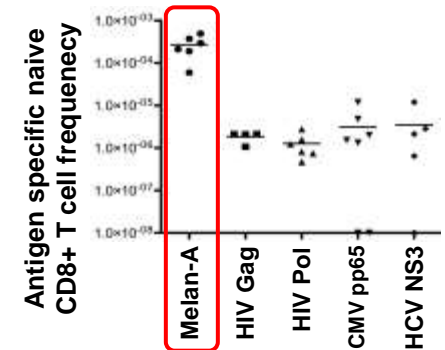
## I. Founding element



Healthy HLA-A2 blood donor

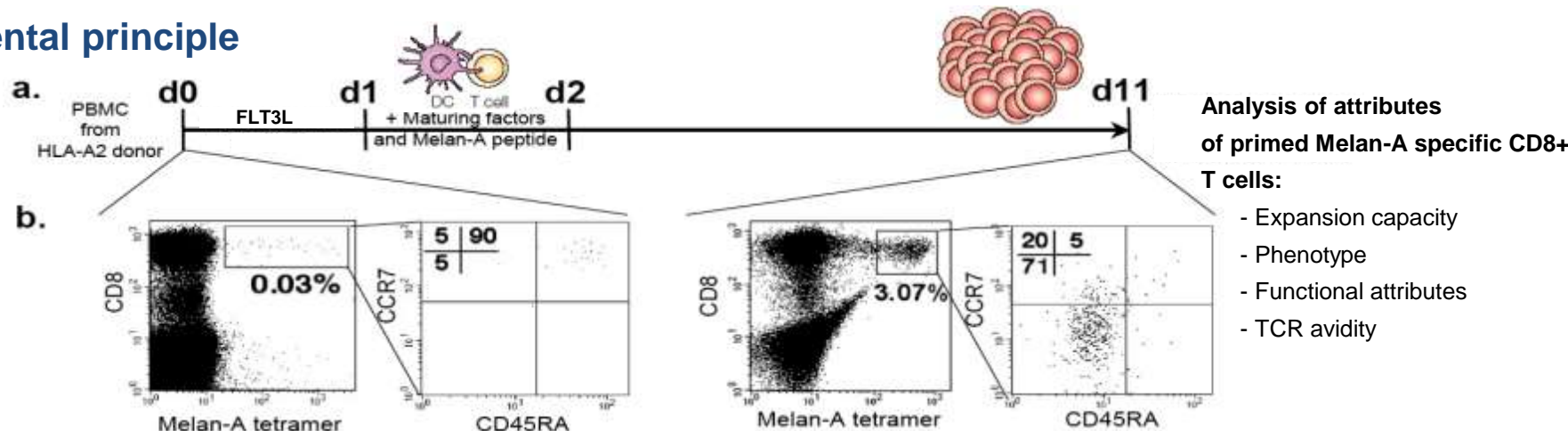
### High frequency of Melan-A specific naïve CD8+ T cells

- $\sim 2 \cdot 10^{-4}$  circulating Melan-A specific CD8+ T cells
- CCR7<sup>+</sup> CD45RA<sup>high</sup> CD45RO<sup>-</sup> CD28<sup>+</sup> CD27<sup>+</sup>
- High levels of TRECS
- Long telomeres
- Polyclonal



**Melan-A / ELA = antigen model**

## II. Experimental principle



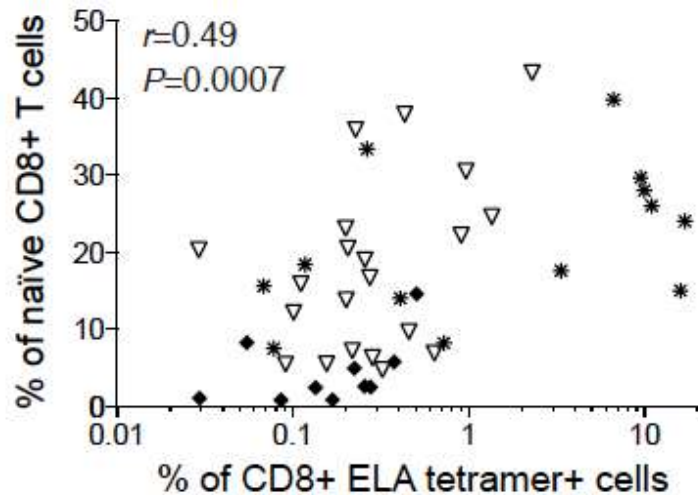
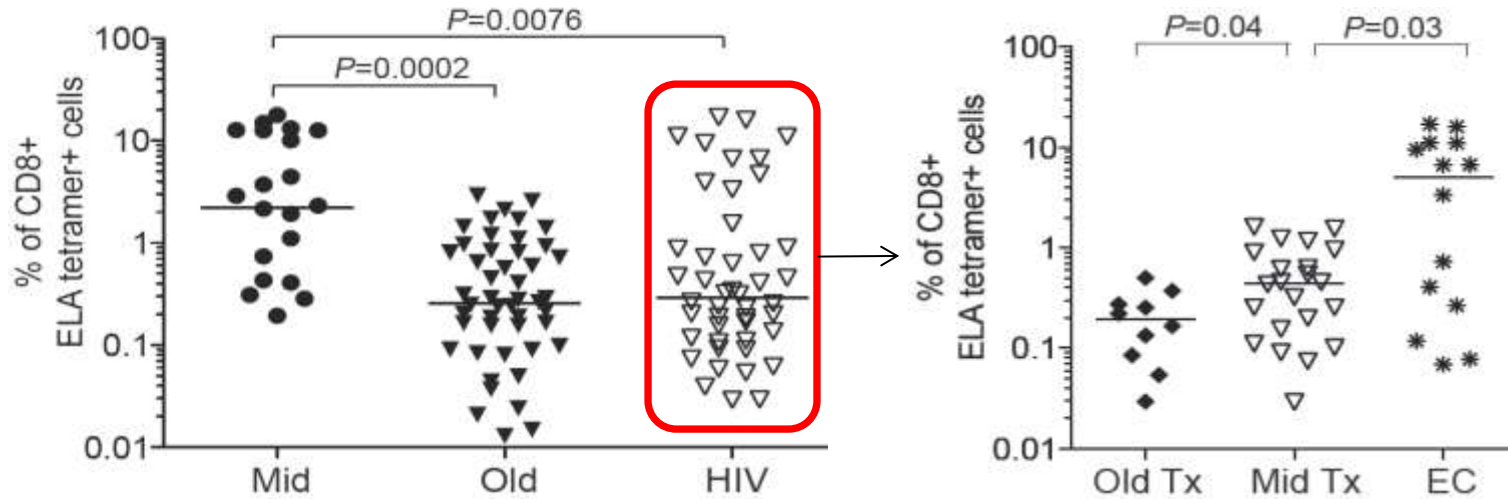
## III. Advantages

- Simple human setting
- Using little biological materials
- Large panel of donors (HLA-A2)

=> Large comparative studies of human samples

# Assessment of *in vitro* CD8+ T cell priming efficacy in HIV-1-infected donors (with low viral replication)

Frequency of *in vitro* expanded tetramer+ cells => Priming efficacy



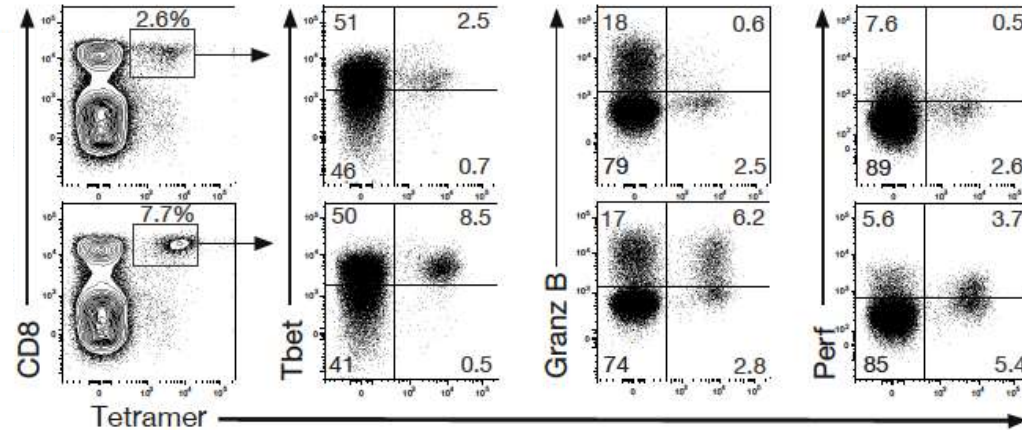
**=> Quantitative reduction of CD8+ T cell priming in HIV infected patients**

# Qualitative analysis of primed CD8<sup>+</sup> T cells

Priming conditions:

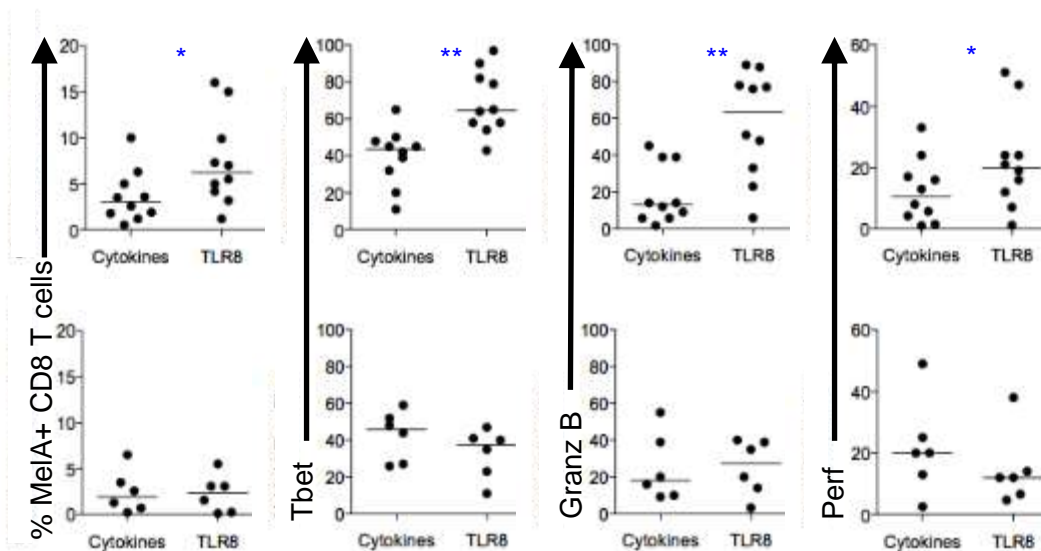
FLT3L  
+ Cytokines

FLT3L  
+ HIV ssRNA40  
(= TLR8L)



HIV-  
PBMC

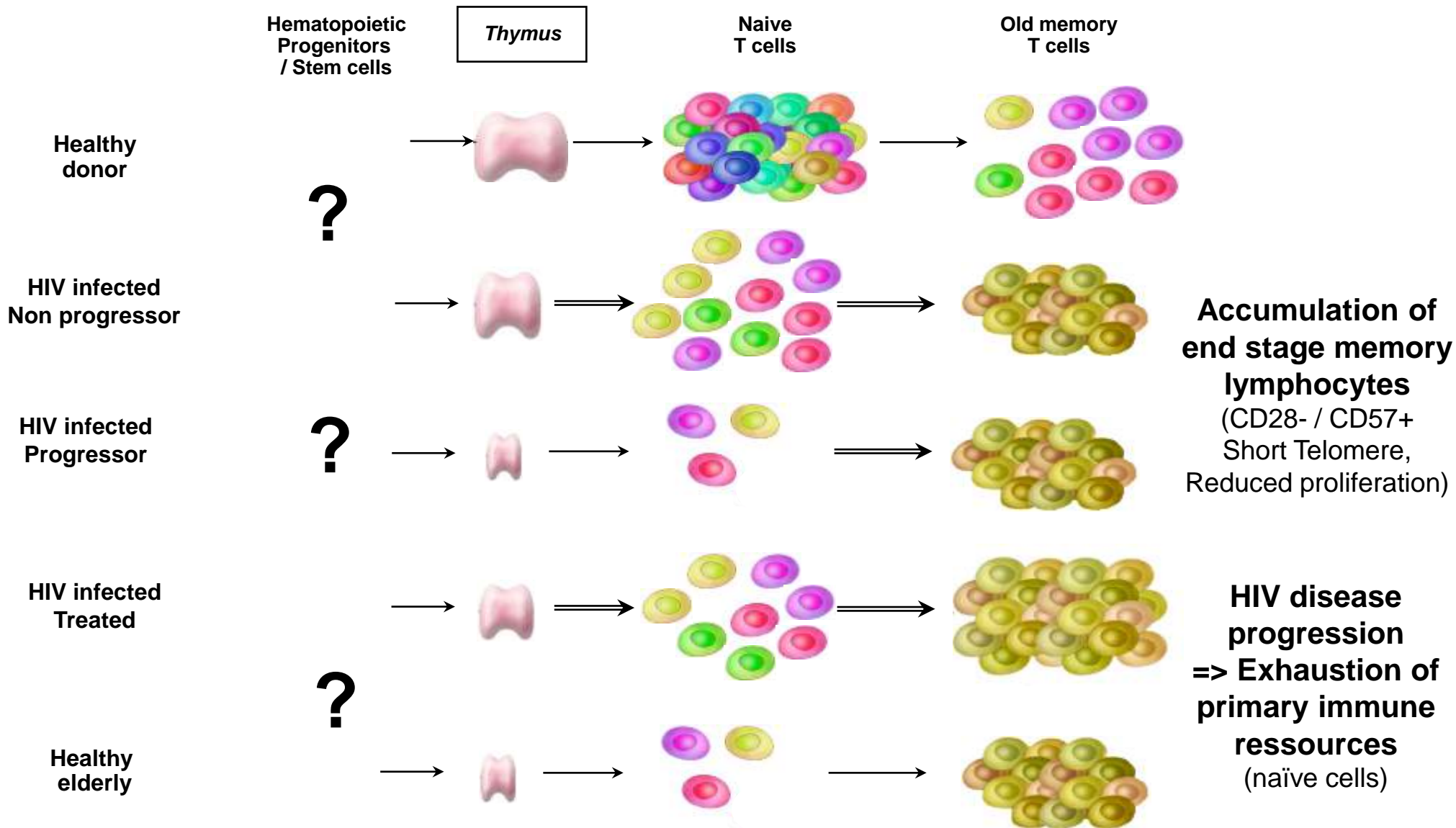
HIV+ prog  
PBMC



⇒ Qualitative reduction of T cell priming efficacy  
(similar to T cell priming with old donor PBMC)



# Premature immune aging in HIV infection

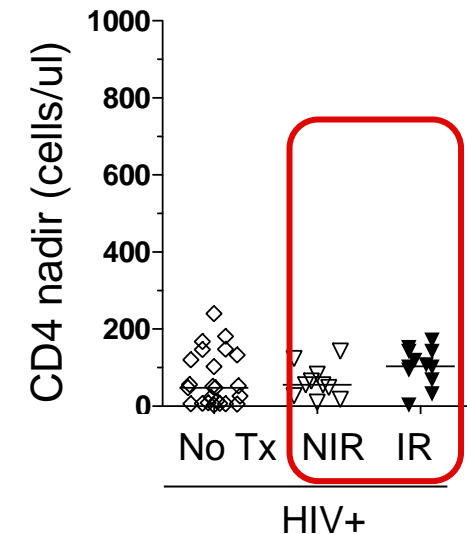
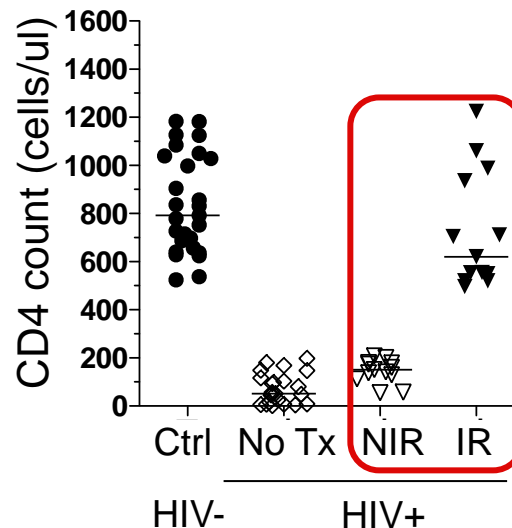
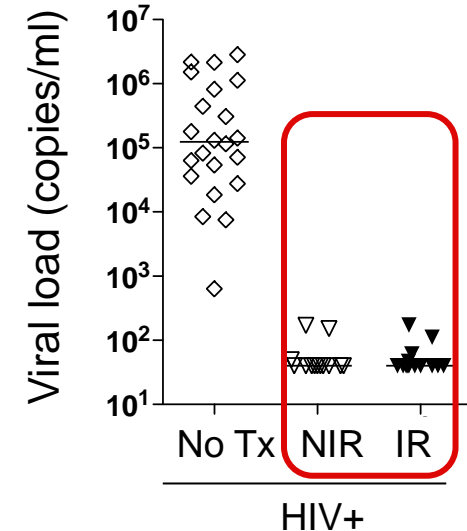
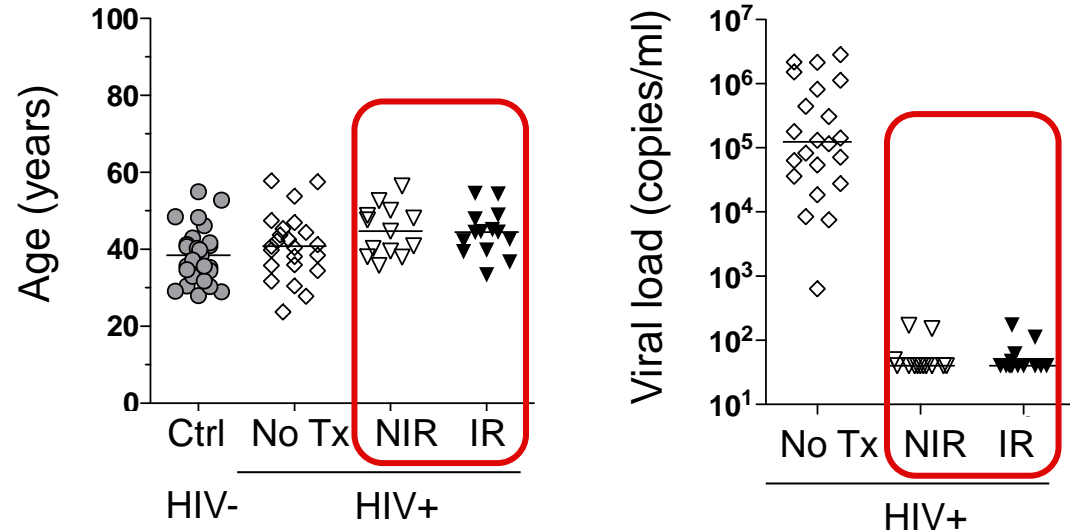


# Immunological failure with ART

**Aim => Characterize the circulating HPC compartment in HIV-1 infected patients with good or poor immune reconstitution under ART**

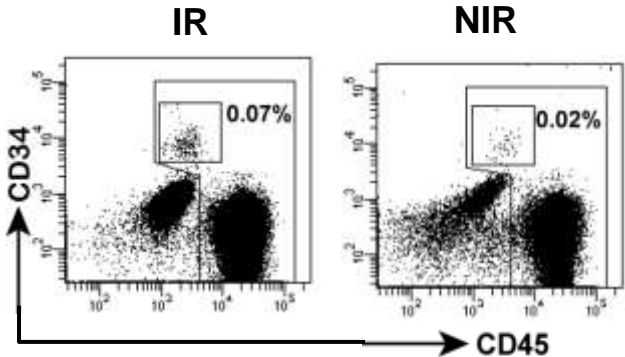
**IR: Immune Responder**  
(good immune reconstitution under ART)

**NIR: Non Immune Responder**  
(poor immune reconstitution under ART)

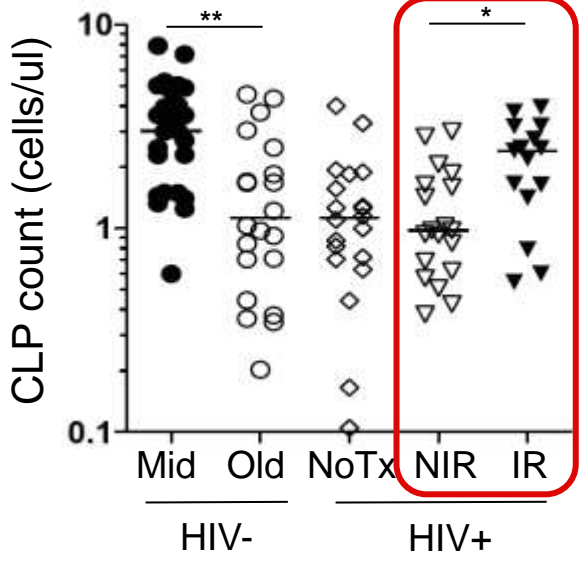
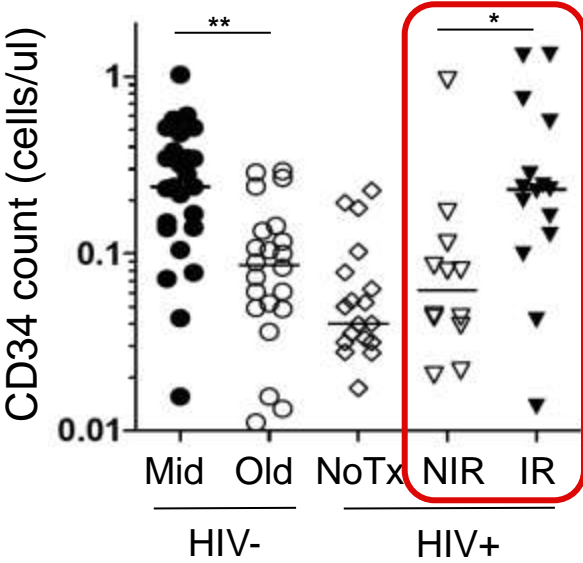
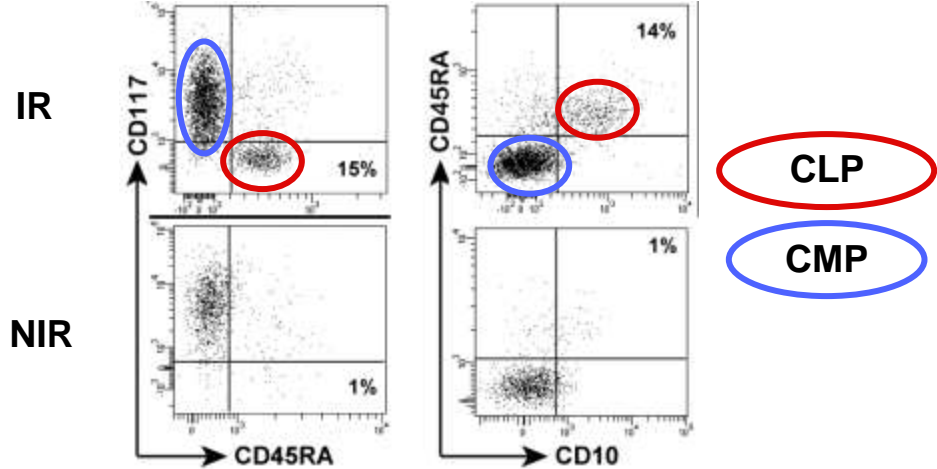


# Disruption of the hematopoietic compartment in treated HIV-1 infected patients

## CD34+ cell counts



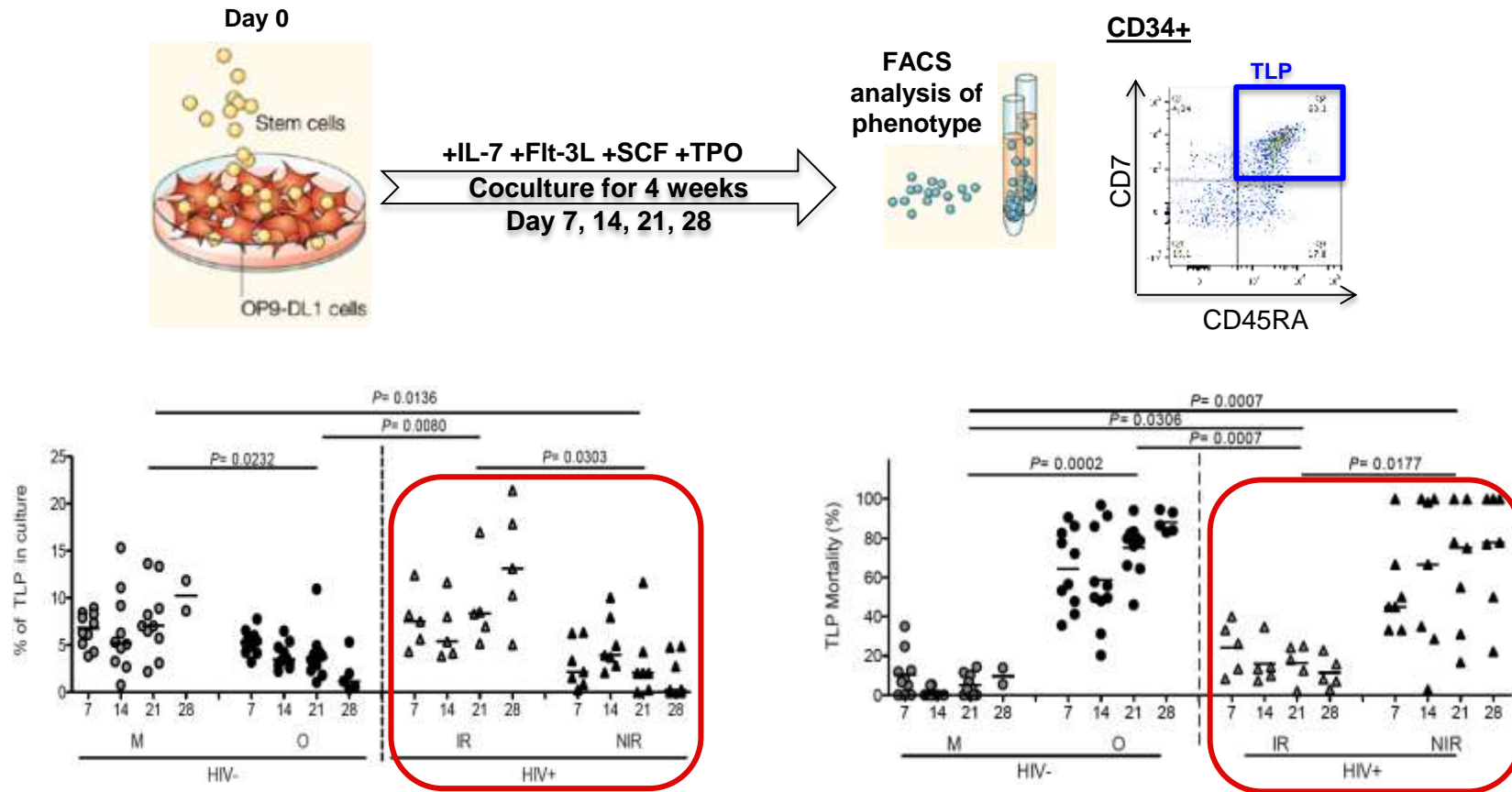
## Phenotype (lymphoid vs myeloid)



⇒ NIR = low CD34 cell frequency, in particular CLP (lymphopoiesis)

# Impaired lymphopoietic capacity of CD34+ cells from treated HIV-1 infected patients

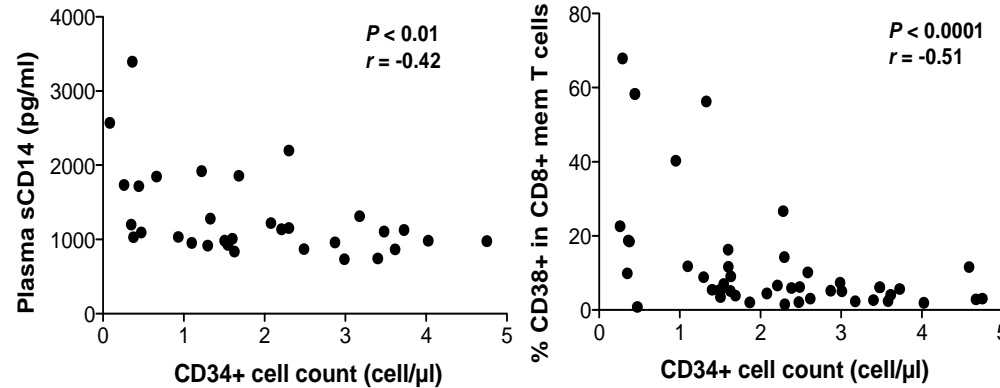
Clonogenic potential of CD34+ hematopoietic progenitors  
 => Lymphopoietic and reconstitution capacity of donors



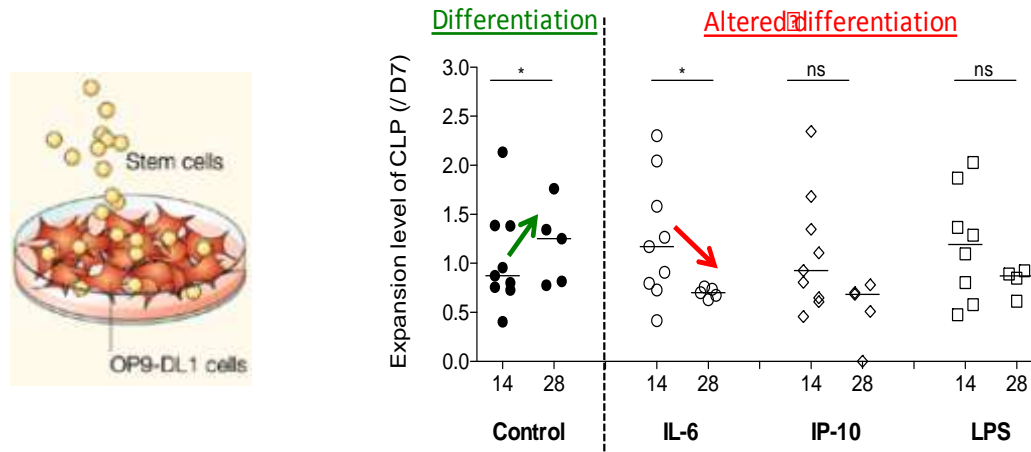
**=> Reduced and skewed lymphopoietic capacity and increased mortality (pyroptosis) of hematopoietic progenitors from NIR**

# Altered hematopoiesis and inflammation

*Ex vivo* association between CD34+ cell numbers and inflammation markers

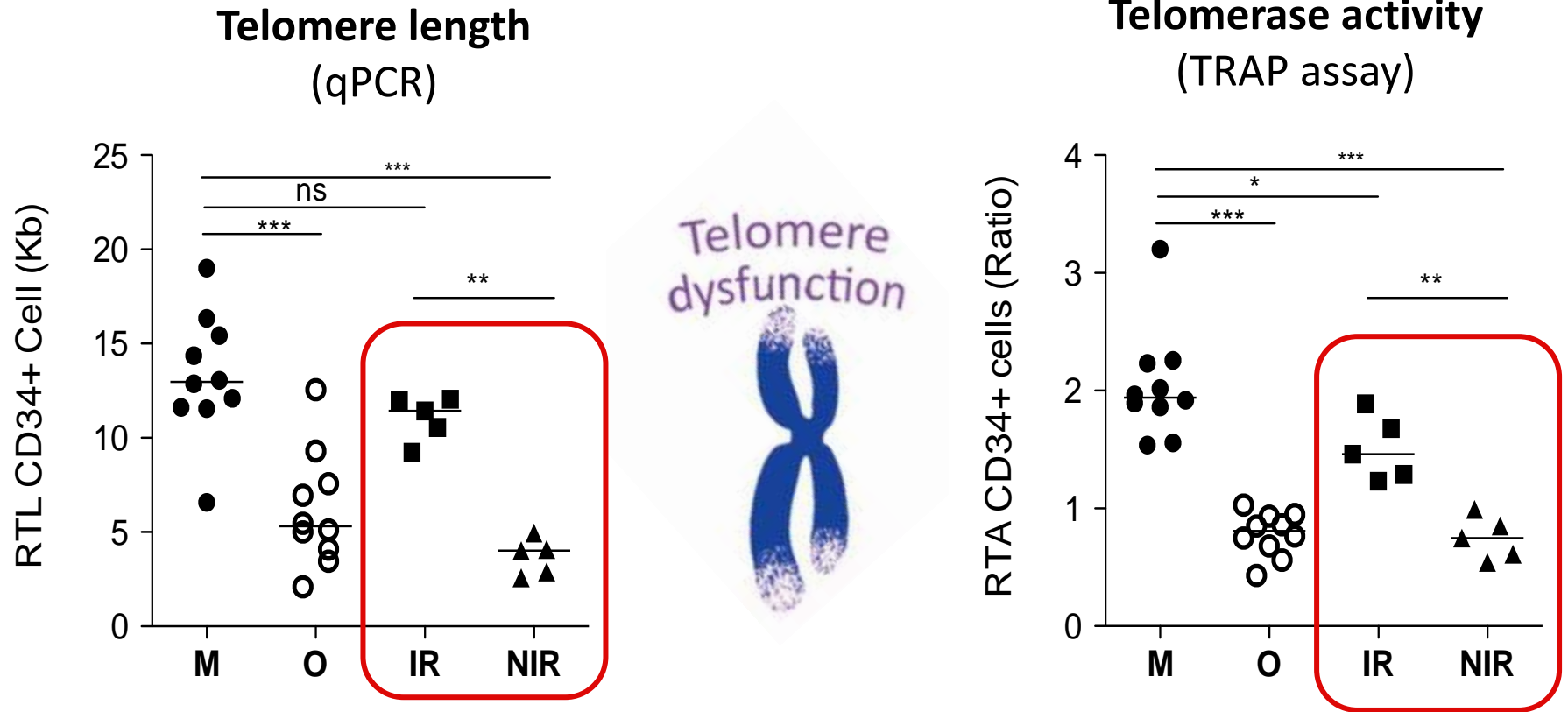


Reduced *in vitro* TLP induction in the presence of inflammatory molecules



**Inflammation => impaired lymphopoiesis  
= EXTRINSIC FACTOR**

# Evidence of senescence in hematopoietic progenitors from HIV infected patients



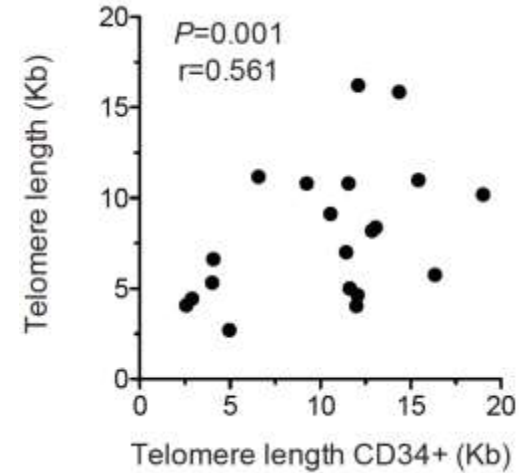
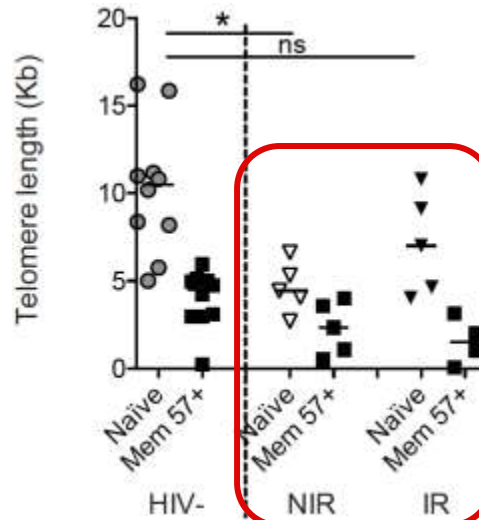
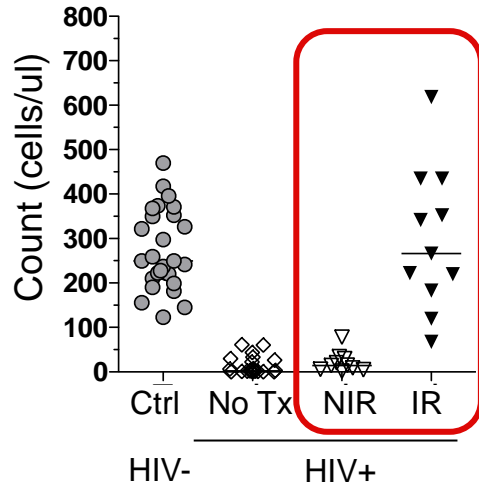
**Hematopoietic progenitors in NIR => approach senescence  
= INTRINSIC FACTOR**

# Impact on naïve T cell compartement in HIV infected patients

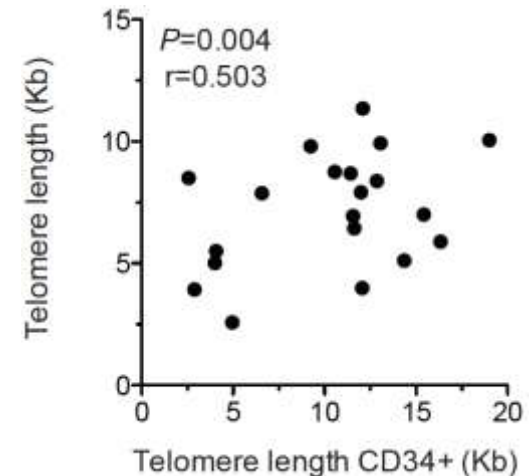
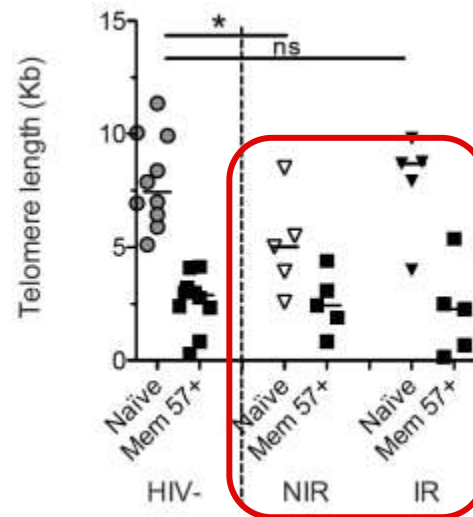
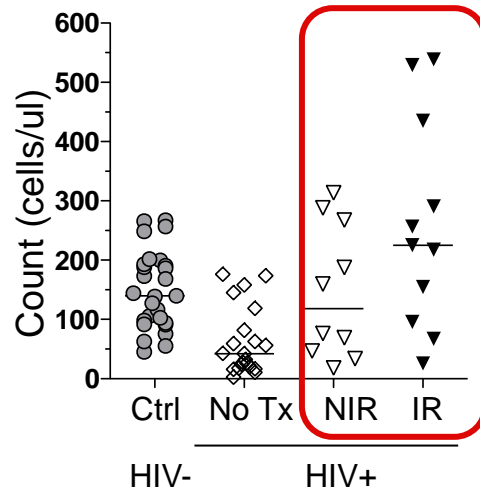
Absolute counts

Telomere length

Naïve CD4+ T cells

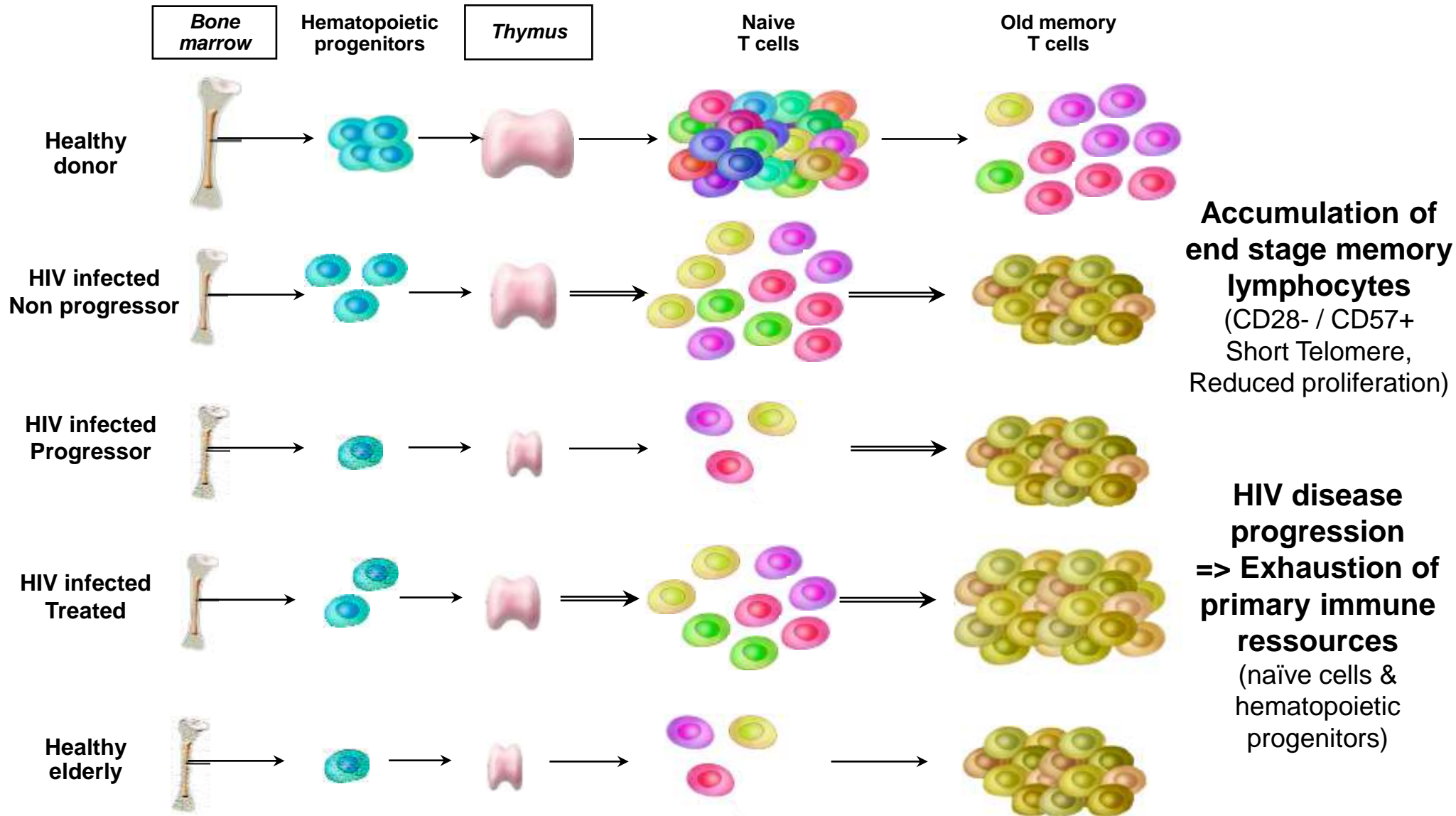


Naïve CD8+ T cells



=> Legacy from HPC to naïve T cell compartement in NIR

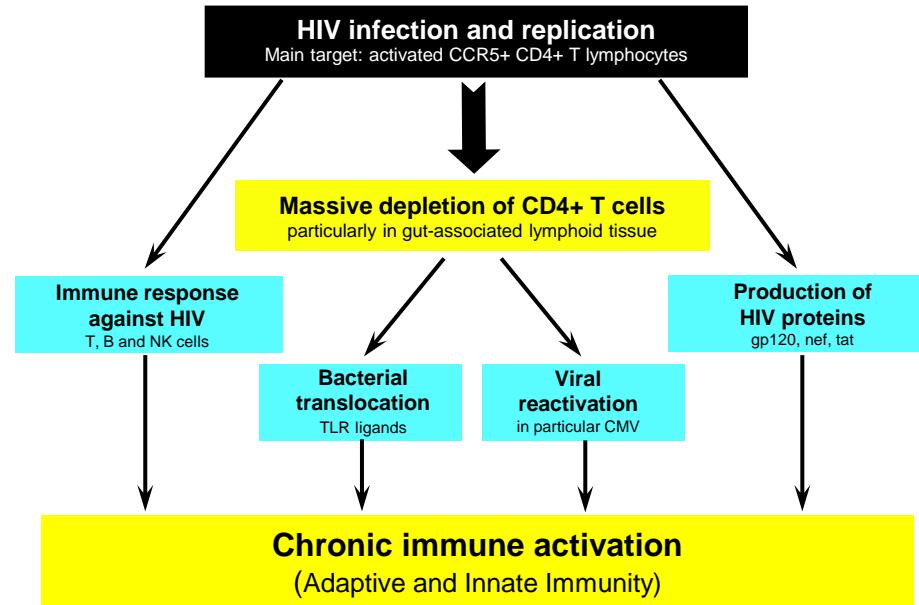
# Premature immune aging in HIV infection





# Immune activation and progression towards AIDS

## Causes



## Consequences

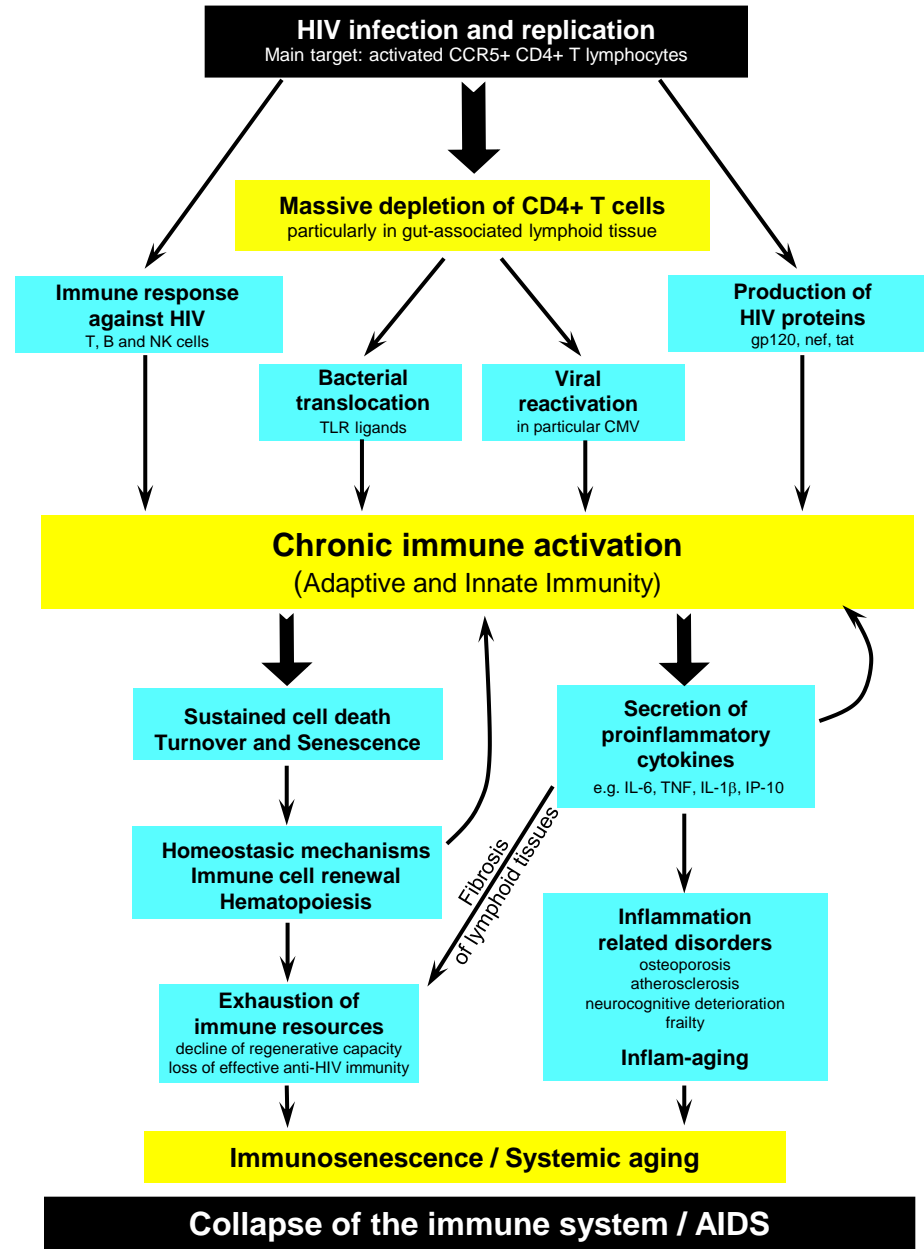


**Collapse of the immune system / AIDS**

# Immune activation and progression towards AIDS

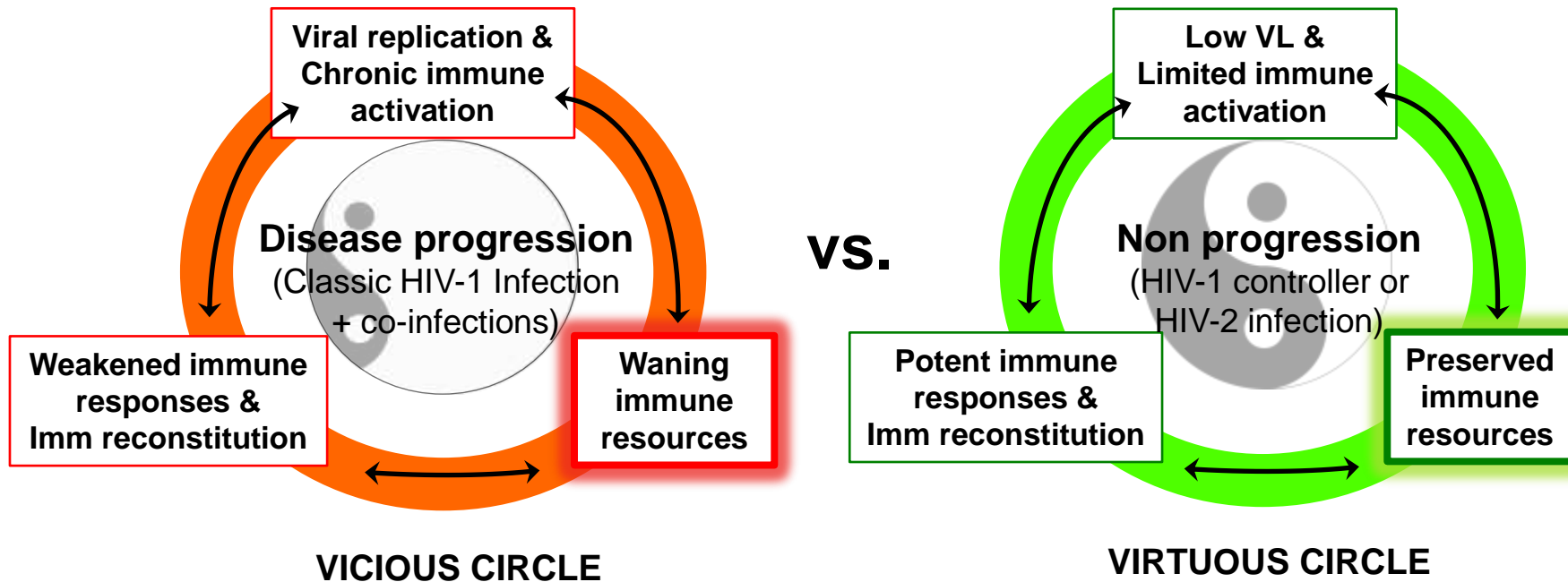
## Causes

## Consequences



Appay and Sauce, *J Pathol*, 2008

# Implications: “Unhealthy vs. healthy” HIV infection



=> Promote preservation of primary immune resources  
in HIV-1 infected patients:

- Early immune control (vaccine)
- Early ART initiation
- Restore hematopoietic resources (pharma, reprogramming)

# Acknowledgements

## VA team INSERM Paris

- ✓ Delphine Sauce
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- ✓ Helene Vallet
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- ✓ Charles Bayard
- ✓ Tinhinane Fali
- ✓ Anna Lissina
- ✓ Olivia Briceno
- ✓ Francesco Nicoli



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- ✓ Judith Cohen Bittan

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- ✓ Roland Tubiana
- ✓ Olivier Lambotte
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- ✓ Sophie Matheron
- ✓ Yasmine Dudoit
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Patients and  
volunteers



INSERM Cochin, Paris

- ✓ Roberto Mallone
- ✓ Georgia Afonso

Institut Pasteur, Paris

- ✓ Asier Saez Cirion
- ✓ Mathieu Angin

Kumamoto University, Japan

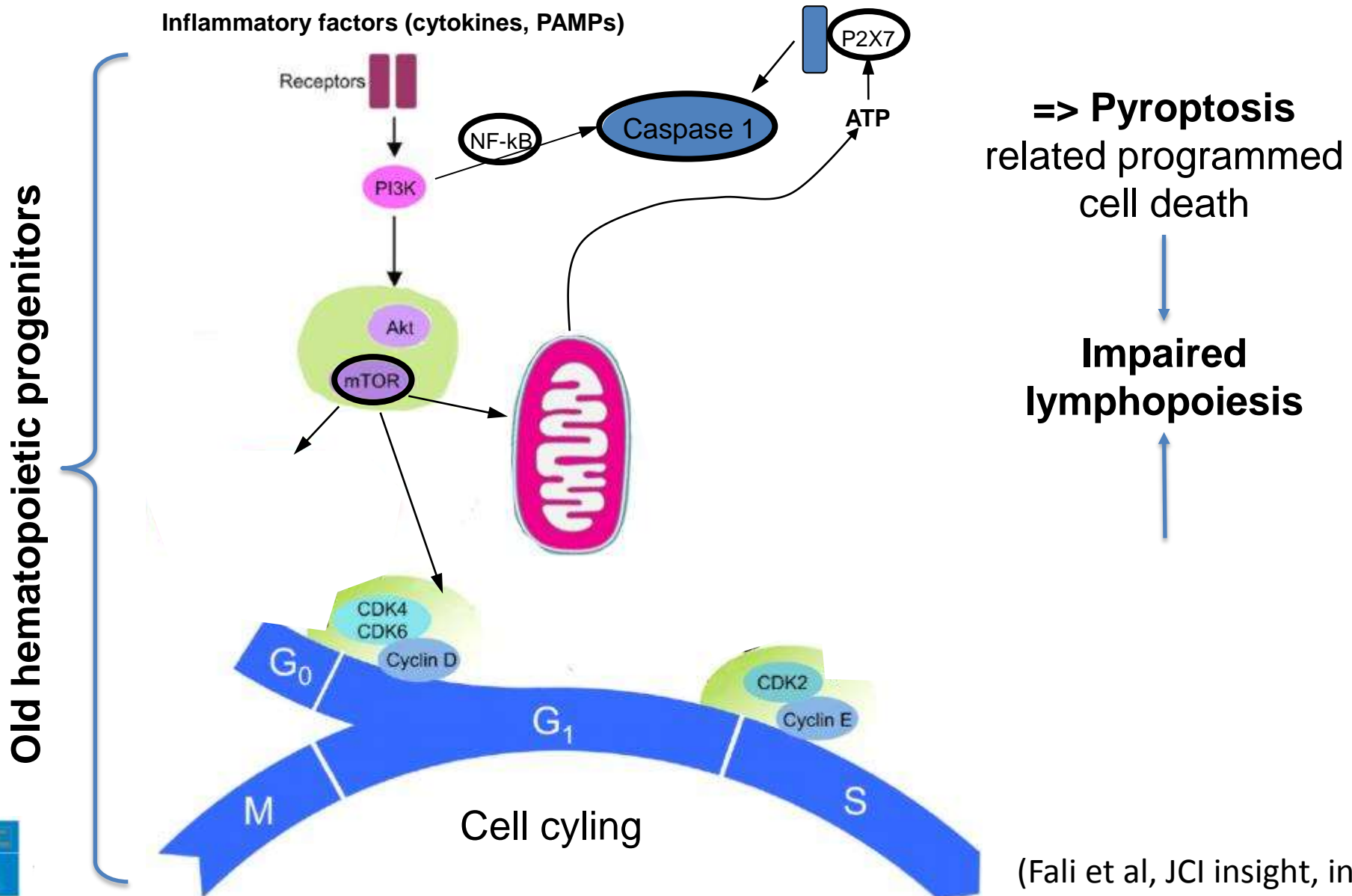
- ✓ Masafumi Takiguchi
- ✓ Nozomi Kuze

Institute of Infection & Immunity, UK

- ✓ David Price
- ✓ Emma Grant



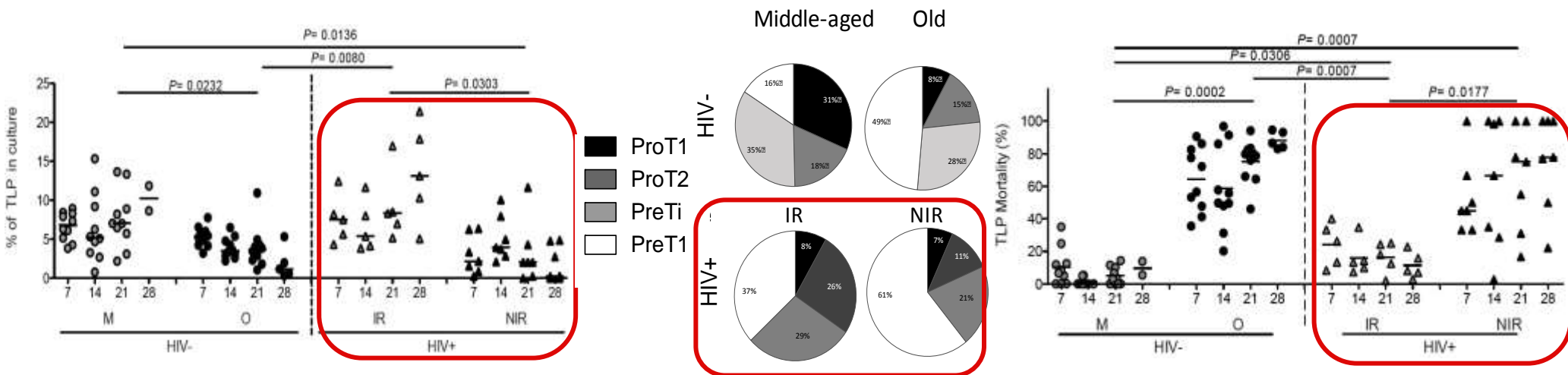
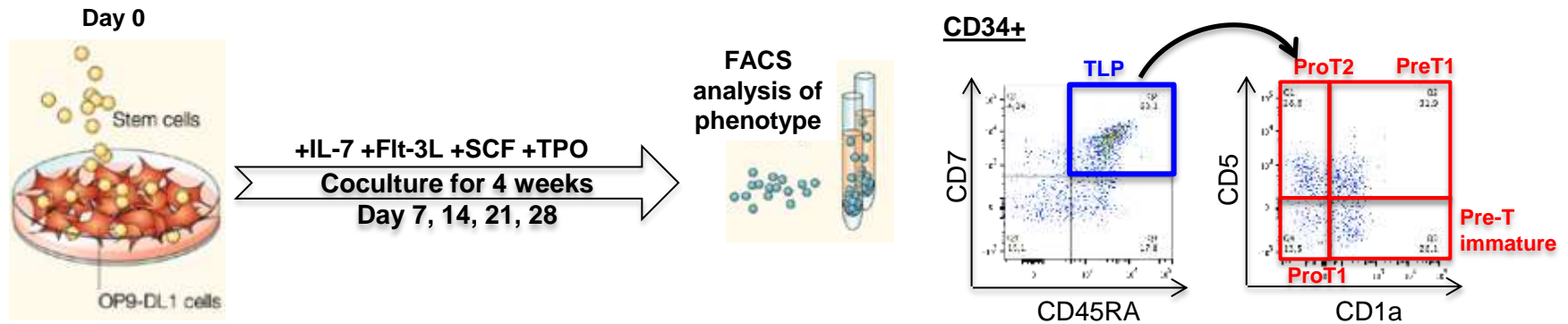
# Colliding cell cycle/mTOR, cell death, and senescence pathways in hematopoietic progenitors from the elderly (HIV-)



(Fali et al, JCI insight, in press)

# Impaired lymphopoietic capacity of CD34+ cells from treated HIV-1 infected patients

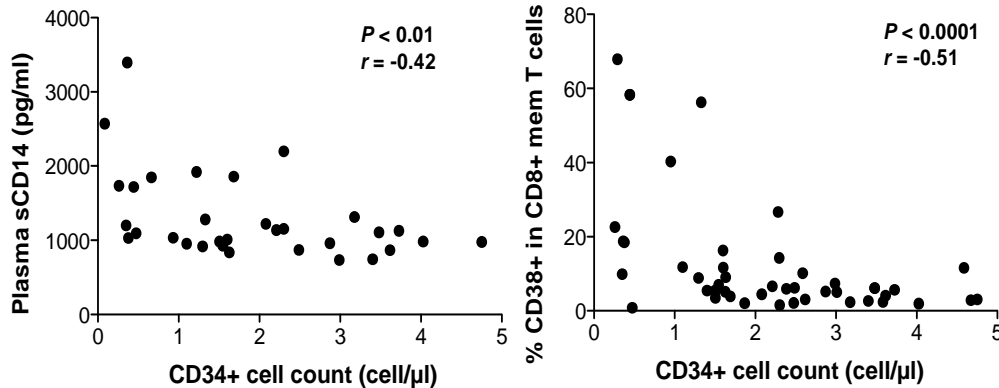
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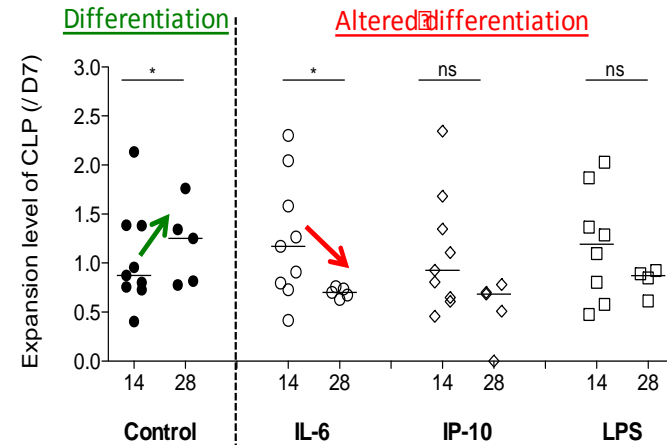
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# Altered hematopoiesis and inflammation

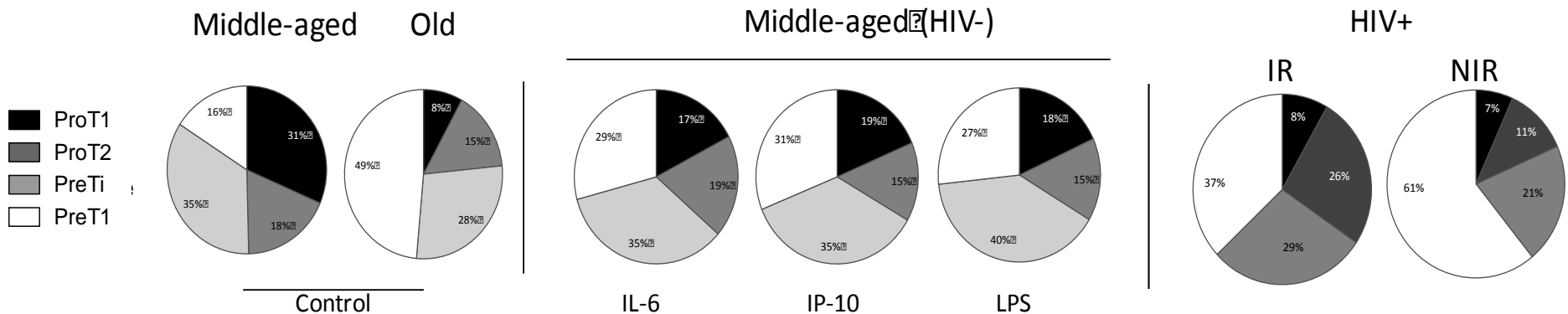
**Ex vivo association between CD34+ cell numbers and inflammation markers**



**Reduced *in vitro* TLP induction in the presence of inflammatory molecules**



***In vitro* TLP distribution in the presence of inflammatory cytokines**



**Inflammation => impaired lymphopoiesis  
= EXTRINSIC FACTOR**