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HIV infection of Human Treg cells downregulates
Foxp3 expression and produces a loss of the
suppressive capacity of these cells

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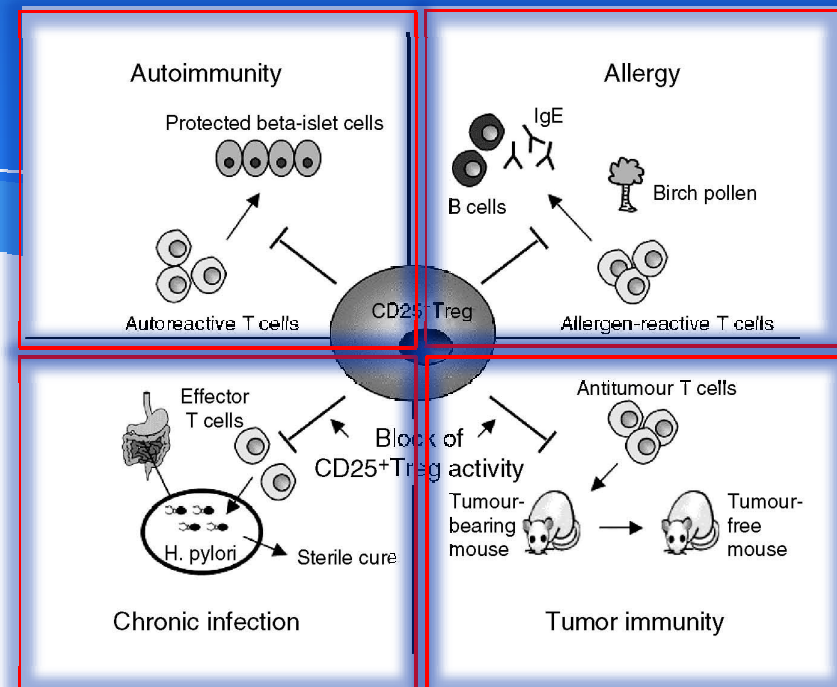
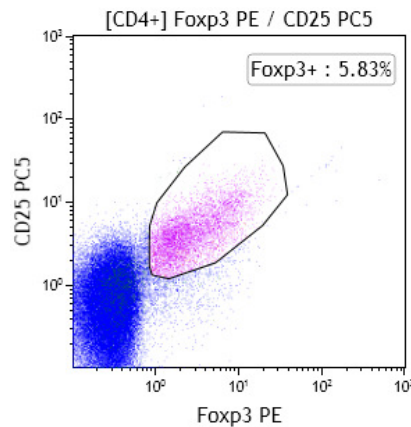
Laboratory of Immune-regulation

Institute of Health Research "Gregorio Marañón" (IISGM). Madrid (Spain)

Regulatory T cells (Treg) → Subpopulation of CD4+ T cells with a suppressive activity

- Treg are identified as CD4+CD25+Foxp3+ cells
- Treg are considered a crucial component of immune system for preserving peripheral tolerance and the correct immune homeostasis

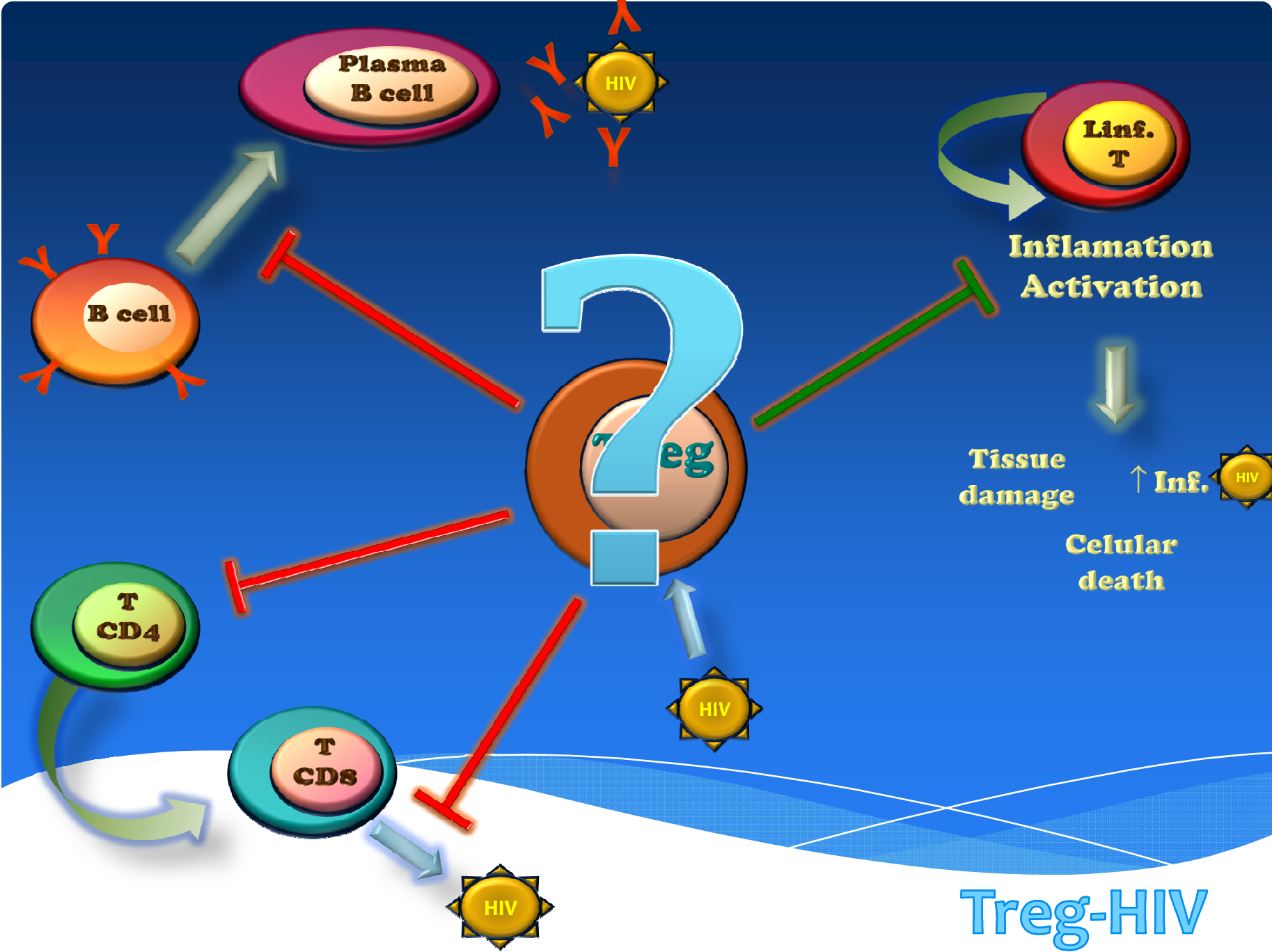
Treg cells



- The potent suppressor function of Tregs might present a serious obstacle to establishing robust protective immunity toward pathogens.
- Tregs play an essential role in controlling immune response-mediated inflammation.
- Studies suggest that by limiting late immune responses to an infectious agent, Tregs minimize associated tissue damage but also diminishing pathogen clearance.

Treg cells in infections

Thus, with several scenarios proposed, the role for Tregs during HIV infection remains unclear.



Treg-HIV

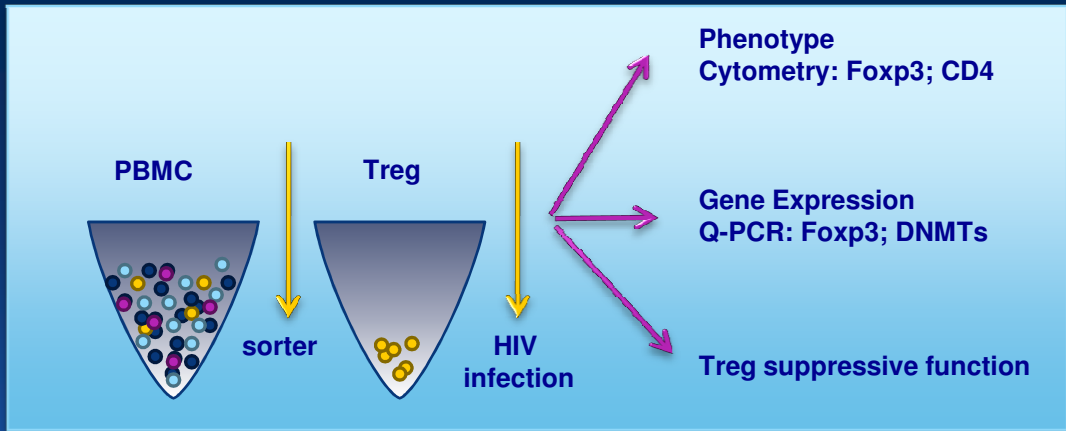
Precedents

- Treg are recruited and expanded in infections to control the immune hyperactivation. Does not work in HIV-infected patients
- Treg cells express CD4, CCR5 and CXCR4 (viral entry) and could be susceptible of being infected by HIV
- The effect of HIV infection in the phenotype and function of Treg was unknown.

Objectives

- To investigate whether Treg cells from healthy donor are infected *in vitro* by HIV.
- In that case, to study the effects of HIV infection on the phenotype and function of Treg
- To investigate the role of Treg cells in HIV-infected patients

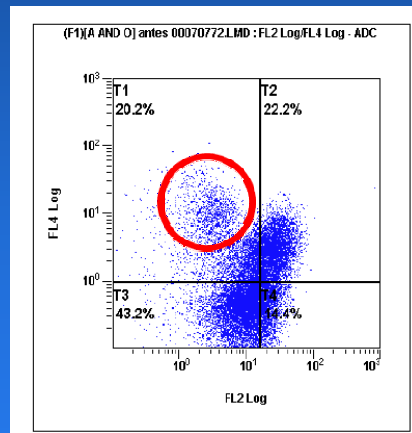
Treg-HIV



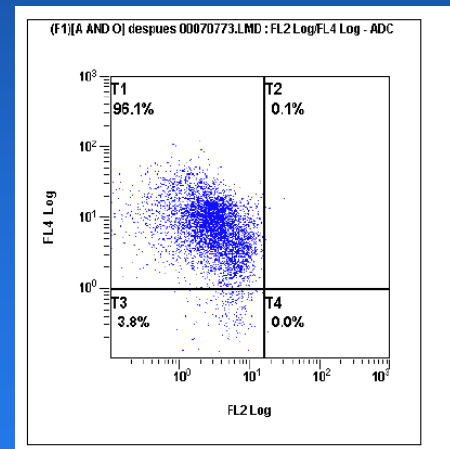
Blood from 15 healthy volunteers

Age: 25-40 years

Purity of isolated Treg > 95 %

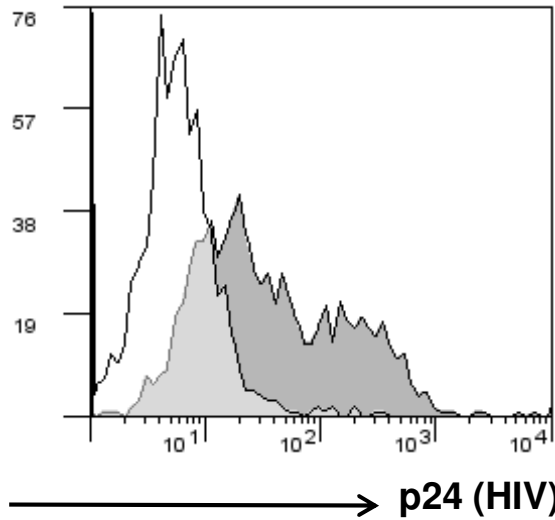


Sorter



Methods

HIV infection of Treg



HIV infection
2 hours

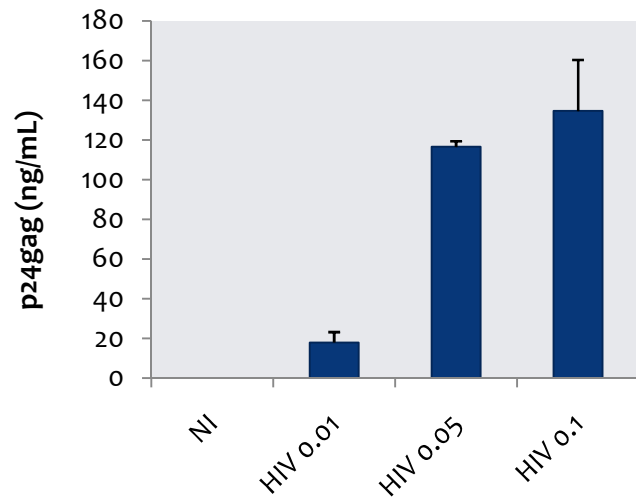
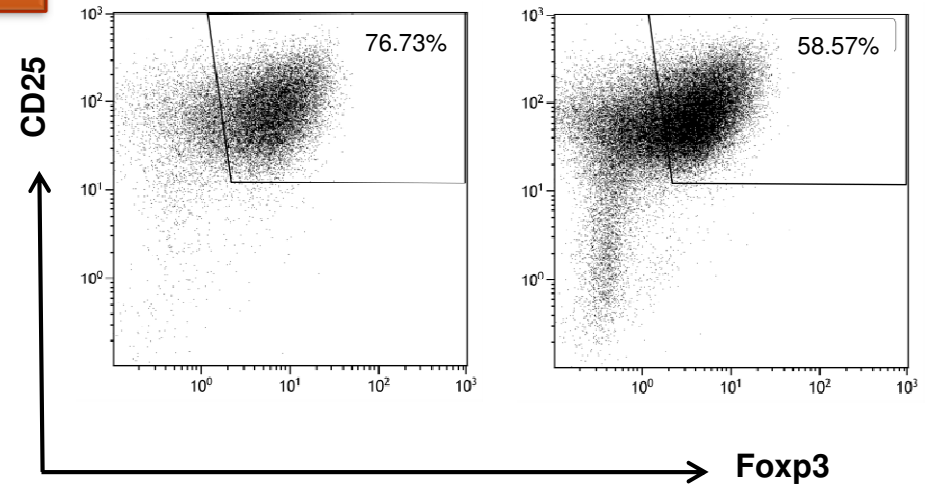
Wash virus

Treg culture
3 → 7 days

Day 3

Non-Infected

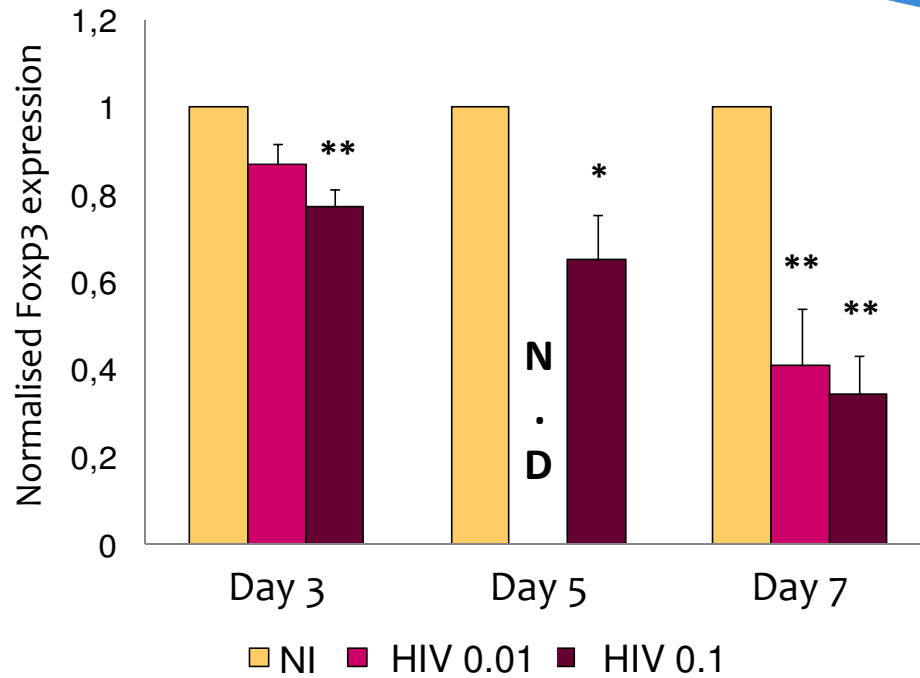
HIV 0.1



HIV infects and replicate in Treg cells

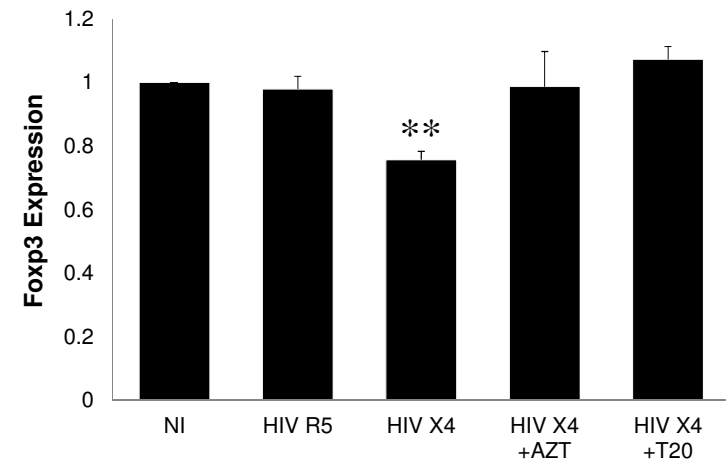
HIV-infection decrease Foxp3 expression

HIV infection of Treg



HIV effect on Foxp3 expression is dose-dependent

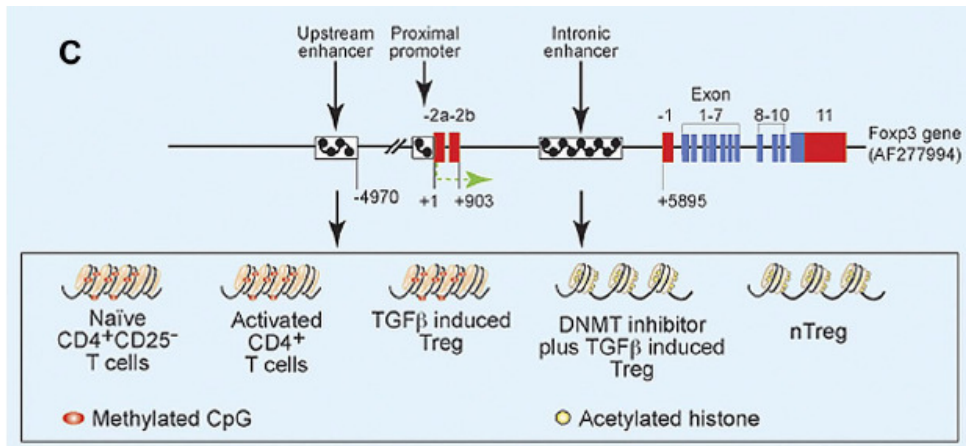
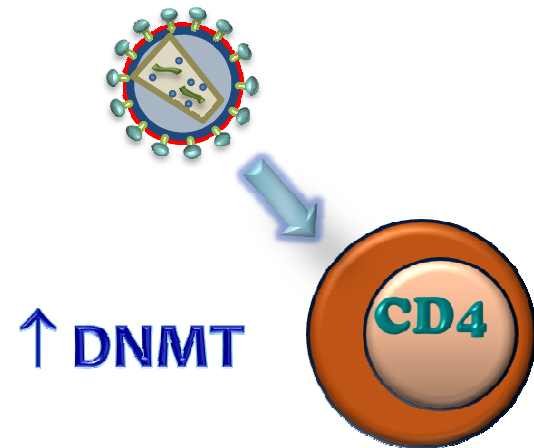
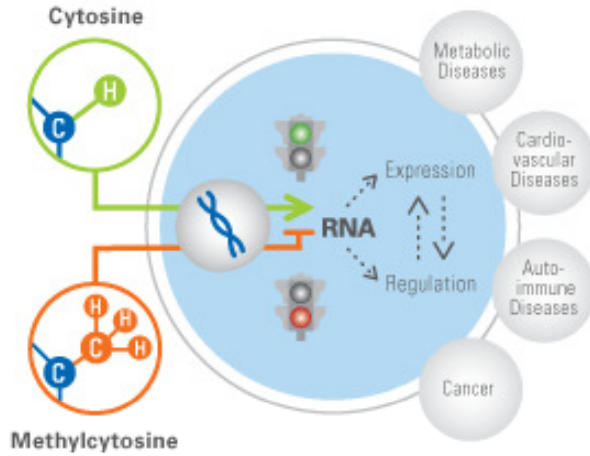
but is not observed with R5-tropic viruses



Foxp3 expression

Epigenetic Control

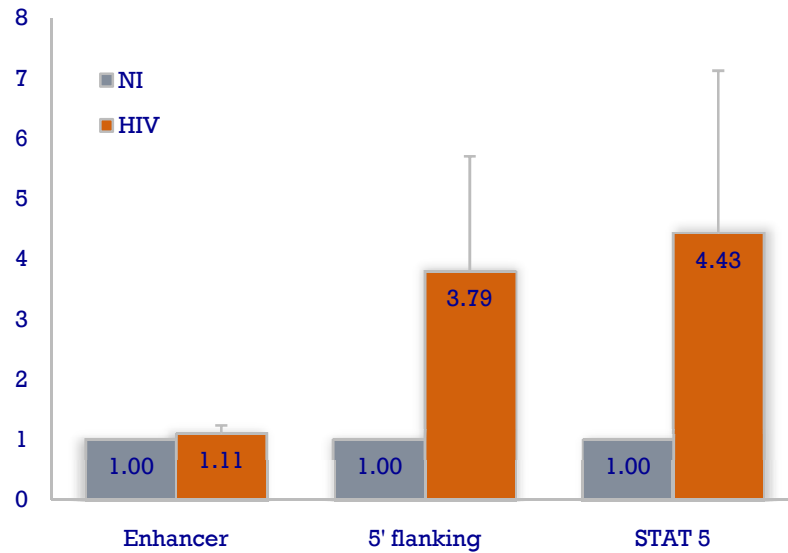
METHYLATION



HIV infection of Treg cells modifies the methylation pattern of Foxp3 gene ?

Mechanism ↓ Foxp3

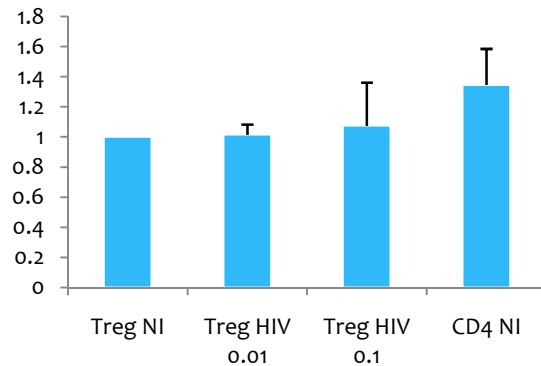
Methylation increase



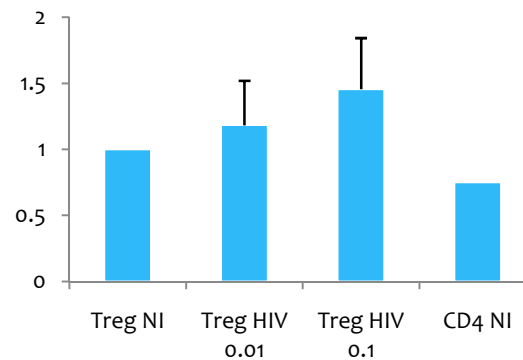
Increased DNMT3b expression and subsequent methylation would be responsible of HIV-mediated decrease in Foxp3

- “de novo” methylation
- binding site in Foxp3 gene

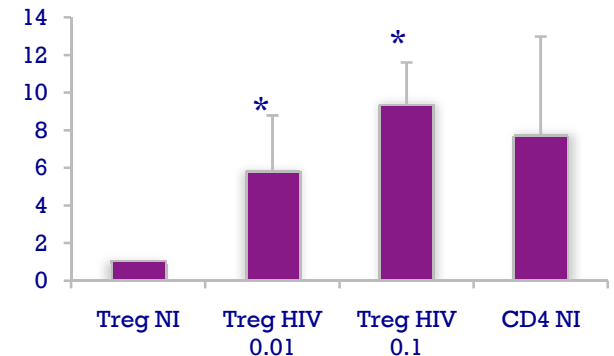
Dnmt1



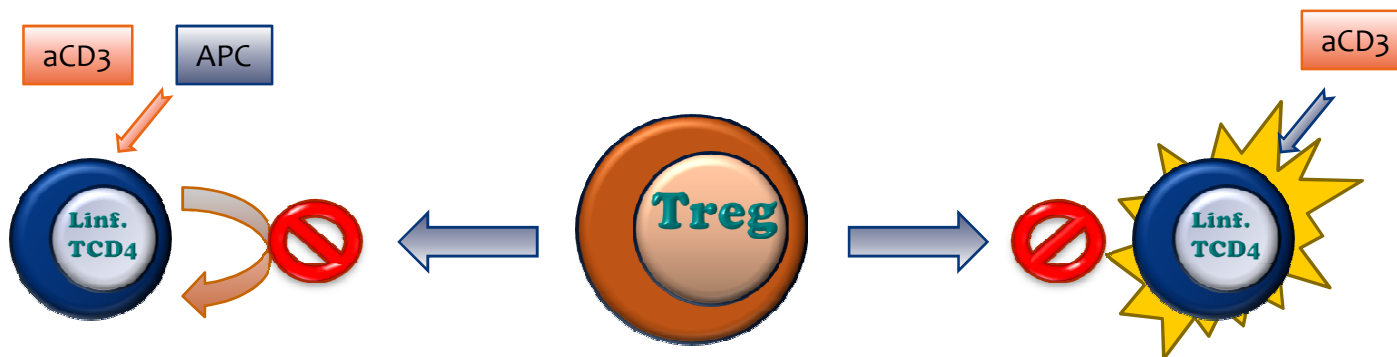
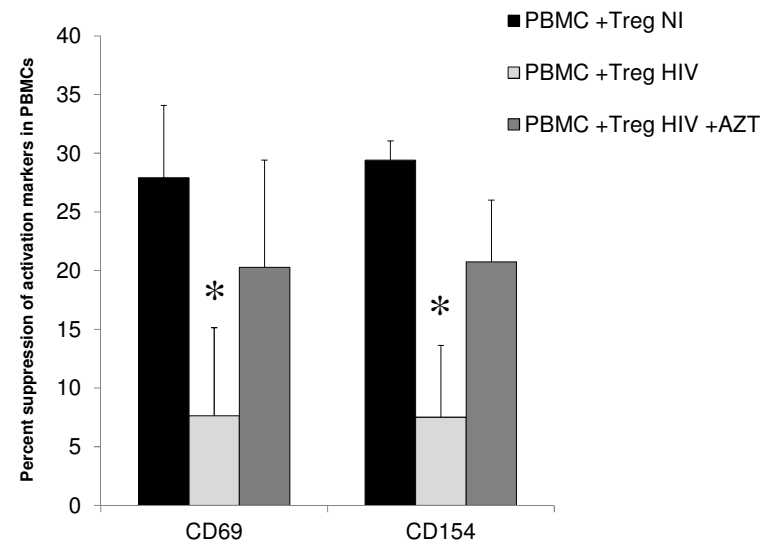
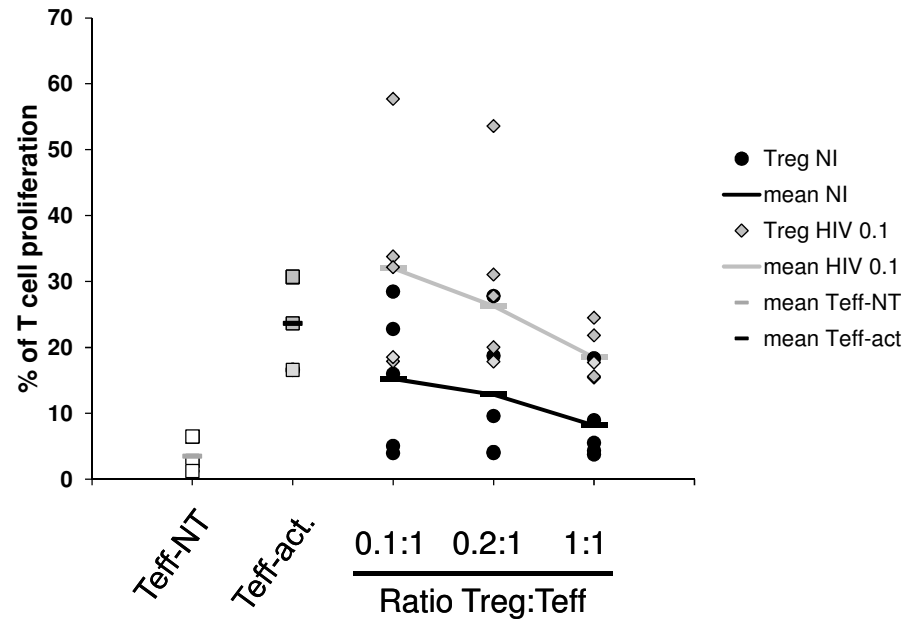
Dnmt3a

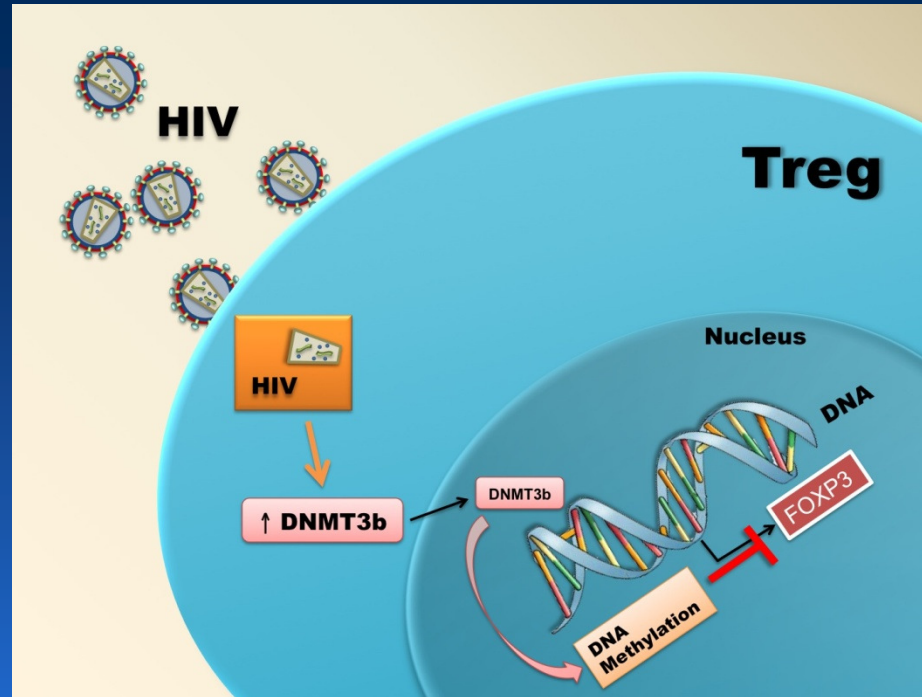


Dnmt3b



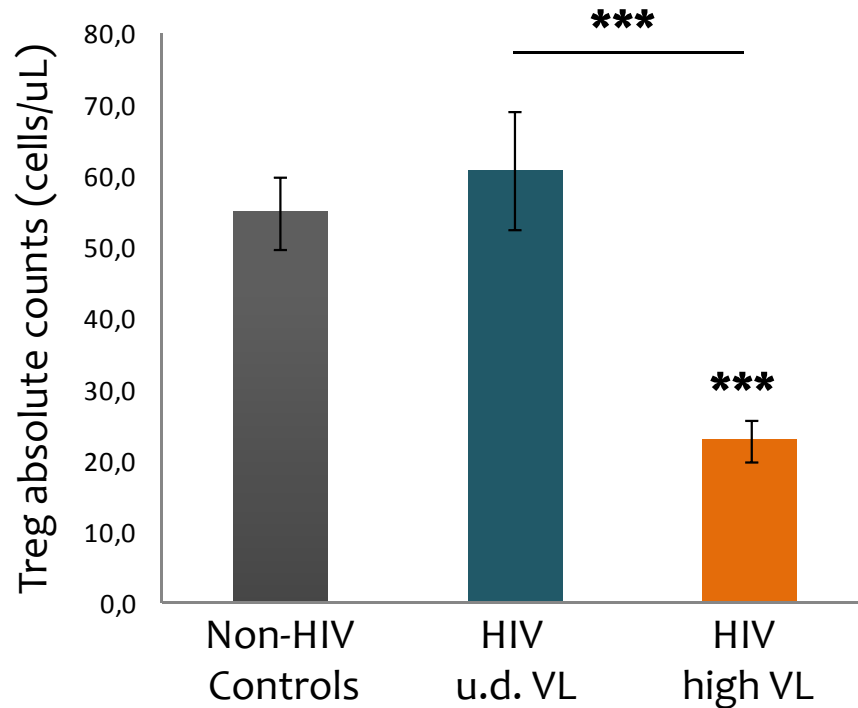
Treg suppressive function





- HIV-infected Treg loss the Foxp3 expression and decrease its suppressive capacity
- The impairment in Treg population and the loss of its suppressive function could be related with the presence of the immune hyperactivation in HIV-infected patients, which has been correlated with the progression of the disease

HIV-infected patients

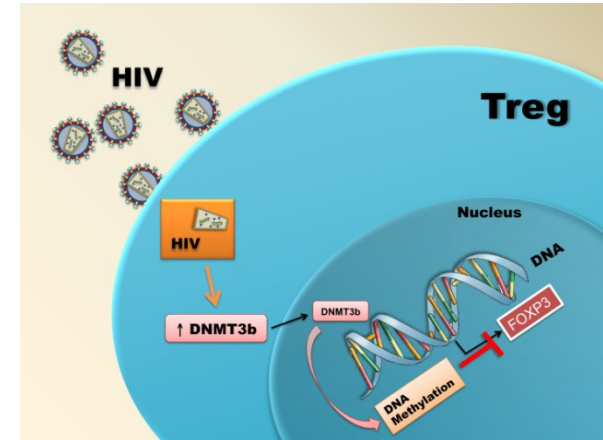
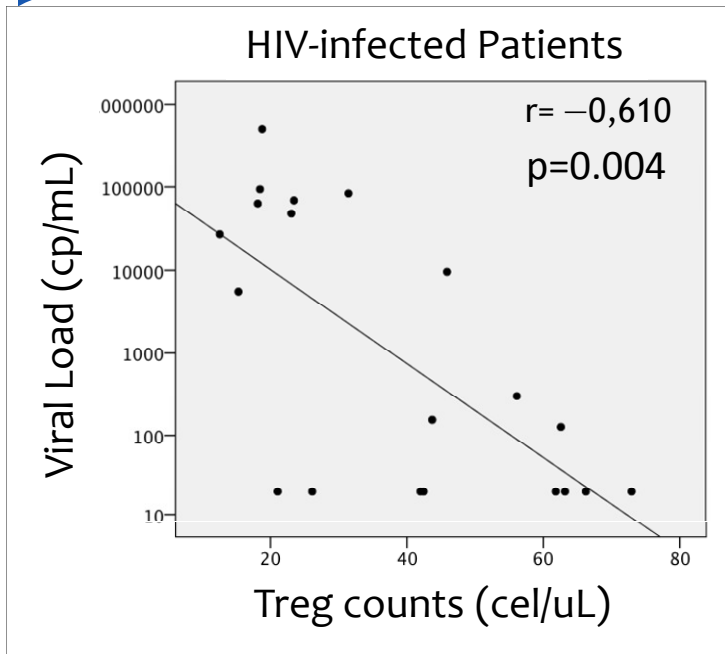


- ❖ 14 non-infected Controls
- ❖ 20 HIV-infected patients with undetectable VL
- ❖ 15 HIV-infected patients with VL >5,000 copies

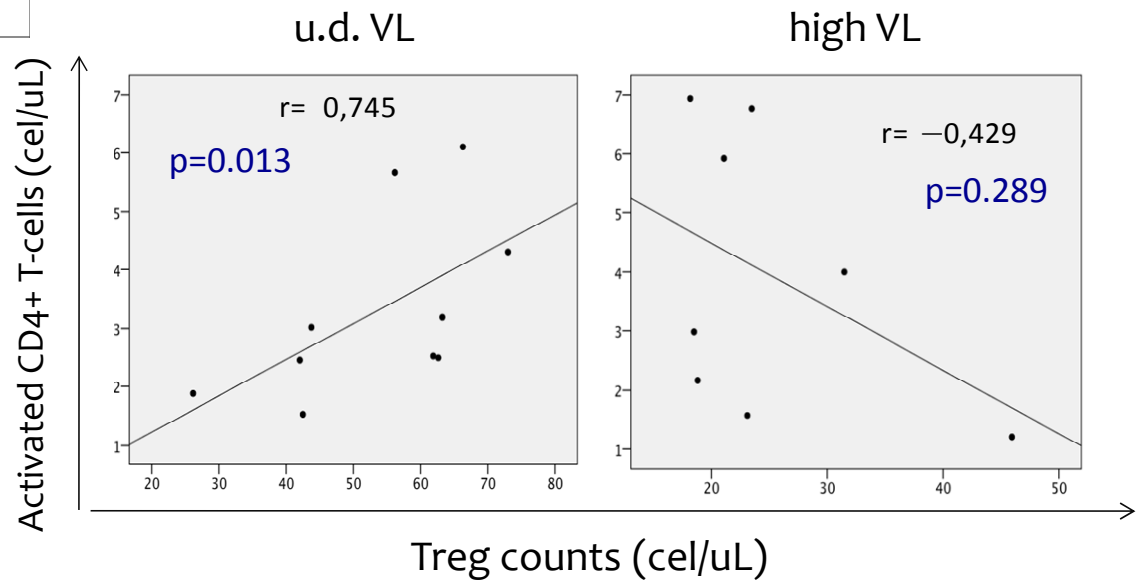
- HIV-infected patients has decreased number of Treg cells
- Which is the effect of VL in Treg counts ?
- Treg decrease is related with immune hyperactivation ?

(Data not published)

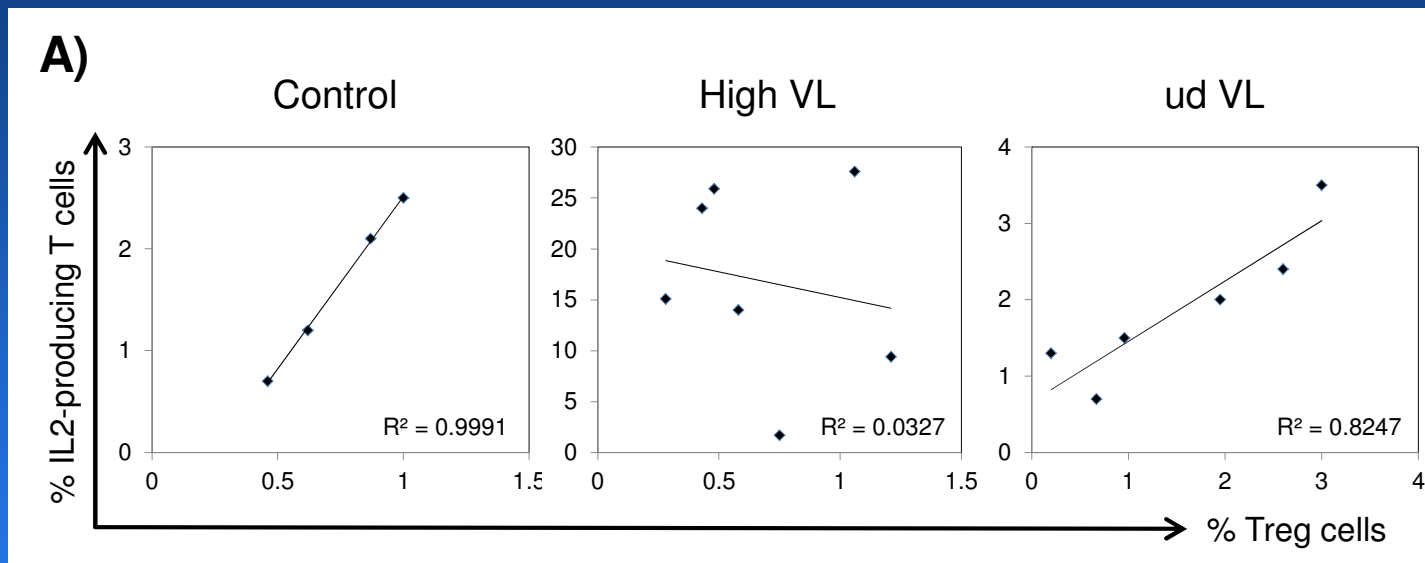
HIV-infected patients



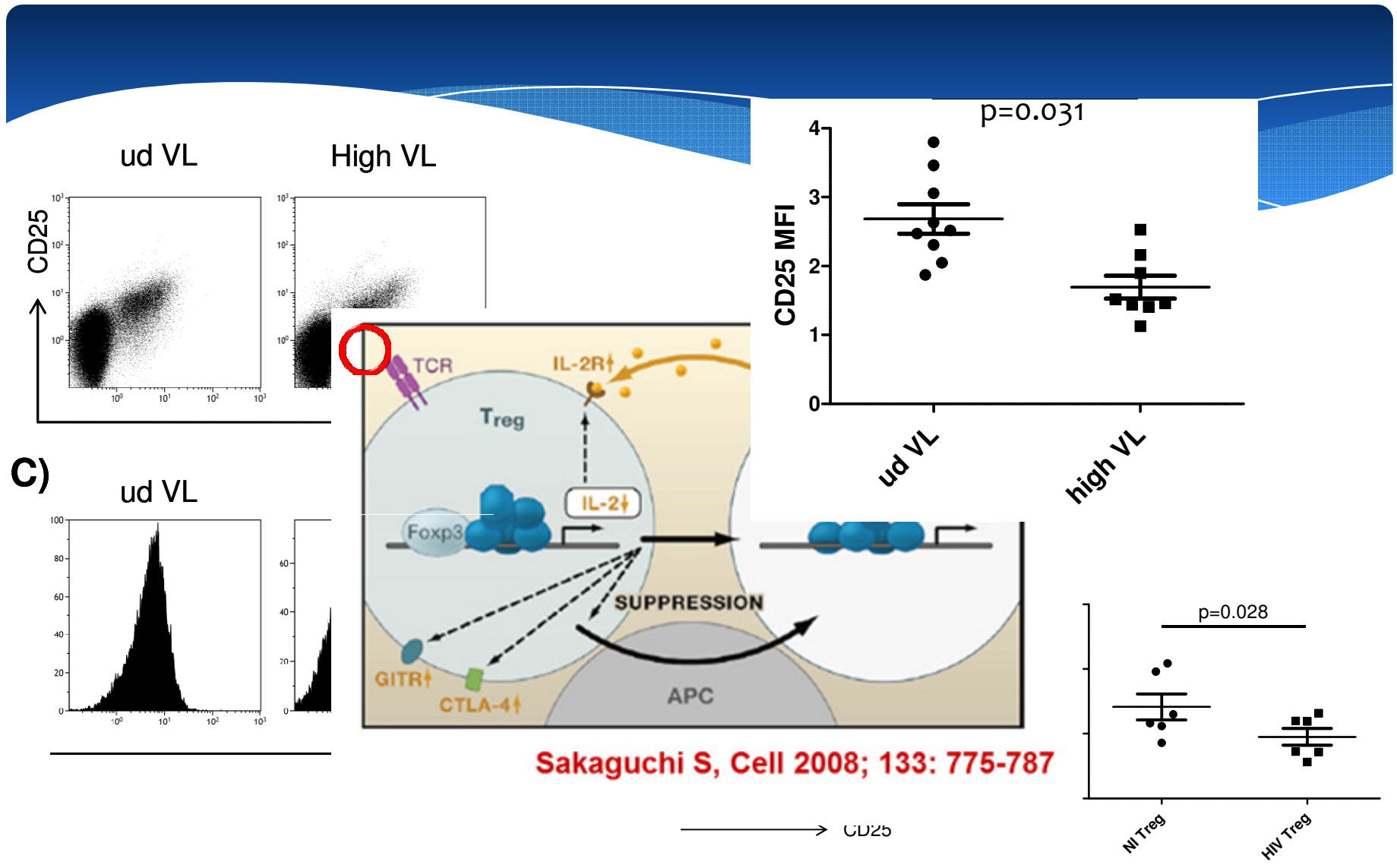
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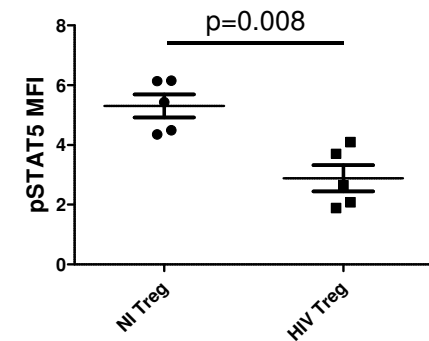
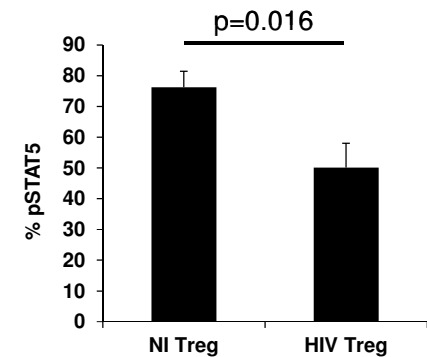
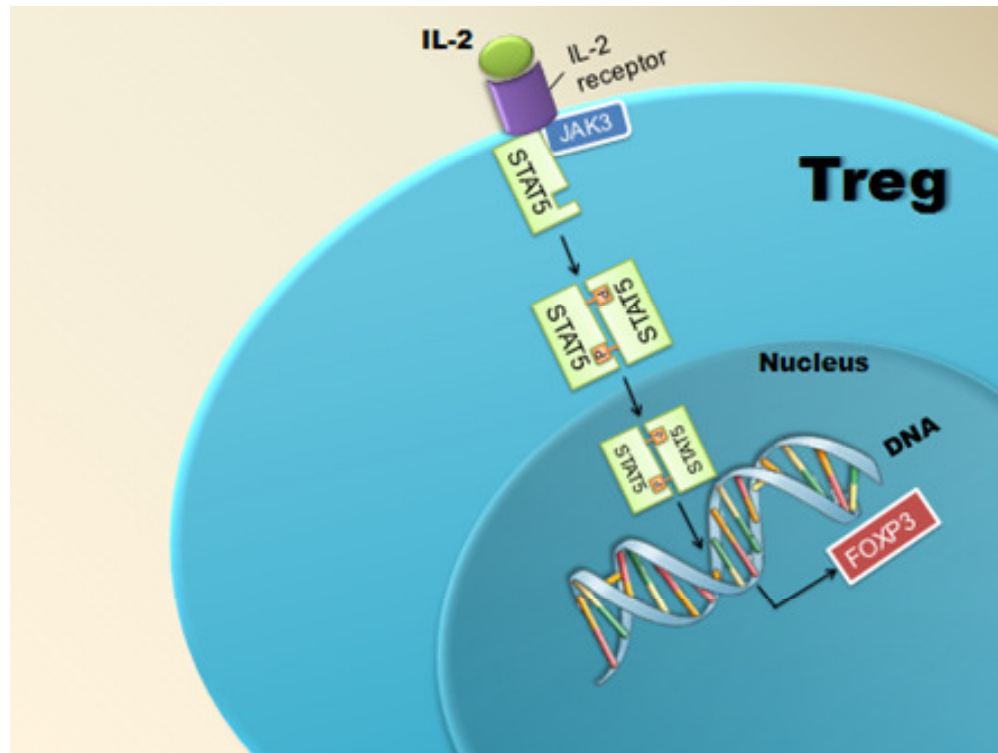
Mechanism of Treg/ T-effector imbalance in HIV-infected patients



The balance between Treg and effector T-cells is broken in HIV-infected patients

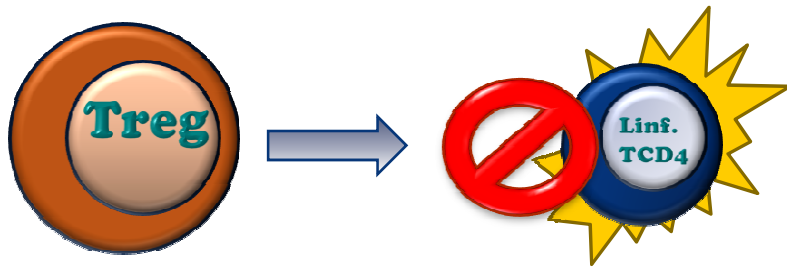


- Treg from HIV-infected patients show a deficient expression of IL2-Rc (CD25)
- *In vitro* experiments confirms that CD25 downregulation is due to the direct HIV infection

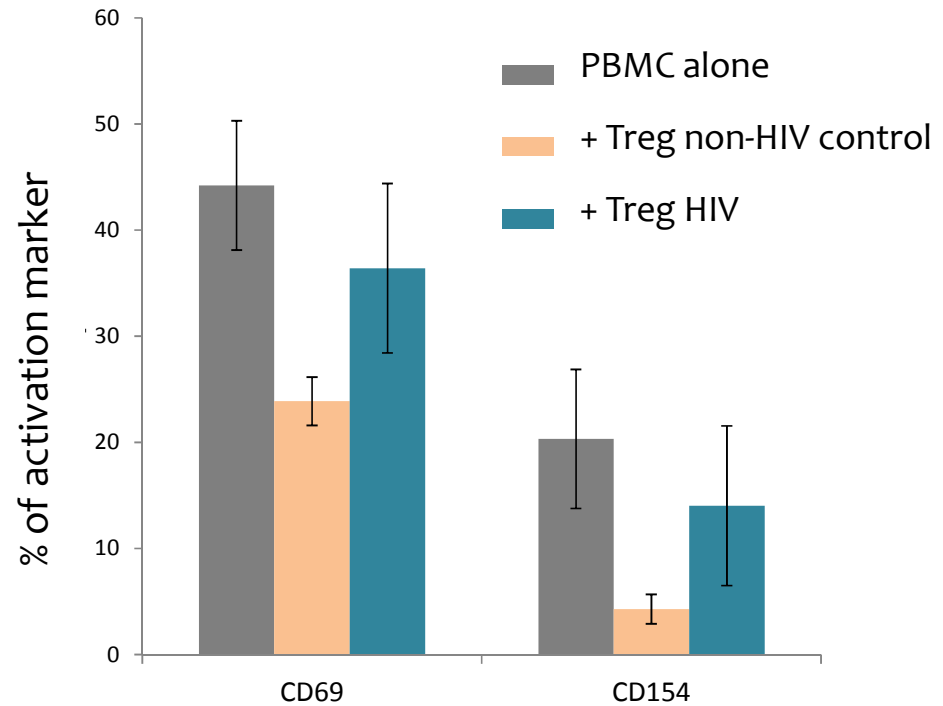


HIV infection decreases IL2-Rc expression in Treg, diminishing the IL-2 signal that maintain the balance between effector and Treg cells

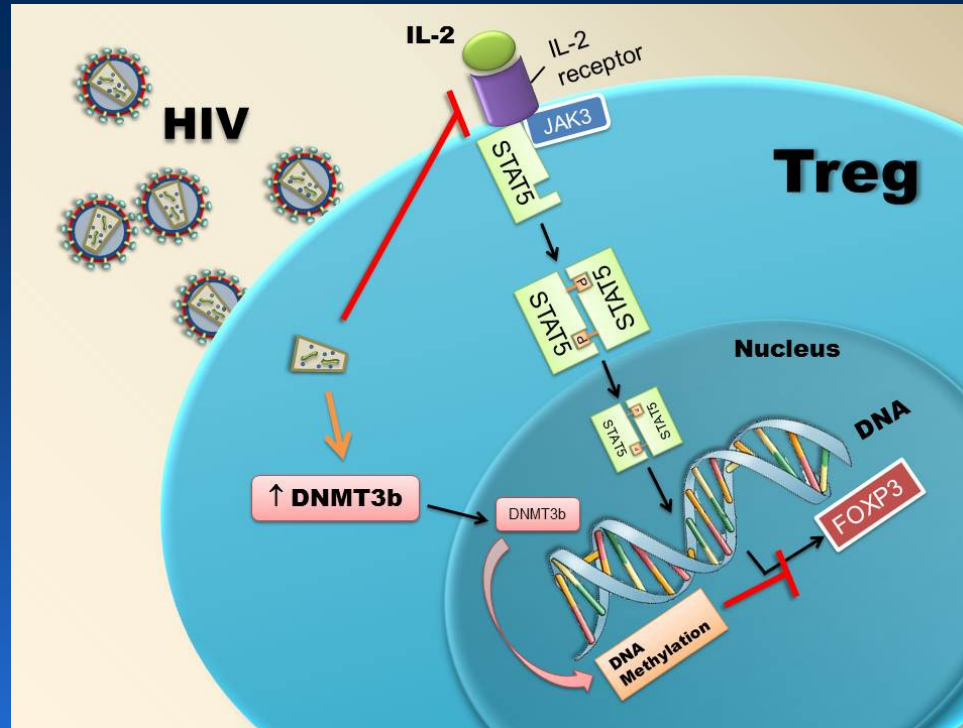
HIV-infected patients



The suppressive capacity of Treg cells is impaired in HIV-infected patients



(Data not published)



- The impairment of Treg suppressive function could be responsible of immune hyperactivation in HIV-infected patients, which is related with the progression of the disease.
- Preserving or boosting Treg population could avoid the deterioration of immune system and to improve the immune homeostasis in these patients.

Treg-HIV

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