

# Recombinant Interleukin-7 (CYT107) Expands CD4 T Cells in Peripheral Blood and Gut Mucosa of Chronically HIV-Infected Immunological Non-Responder Patients.

10 Center Drive,  
Bldg 10/11B07A  
Bethesda, MD 20892  
isereti@niaid.nih.gov  
P: 301-496-5533



Irina Sereti<sup>1</sup>, Jean-Pierre Routy<sup>2</sup>, Margaret Fischl<sup>3</sup>, Thérèse Croughs<sup>4</sup>, Stéphanie Beq<sup>4</sup>, Michel Morre<sup>4</sup>, Mohamed R Boulassel<sup>2</sup>, Michael Yao<sup>1</sup>, William Thompson<sup>1</sup>, Michael M Lederman<sup>5</sup>.

1. NIAID NIH, Bethesda, MD USA; 2. McGill University, Montreal, QC, Canada; 3. University of Miami, Miami, FL USA; 4. Cytheris, Paris, France; 5. Case Western Reserve University, Cleveland, OH, USA

## Background and Rationale

- IL-7 is an essential cytokine for thymopoiesis, homeostasis and maturation of peripheral T-cells
- CD4 T-cell depletion in gut mucosa is an early and key pathogenic event in HIV infection that is associated with T cell activation.
- Despite successful anti-retroviral therapy (ART), significant morbidity and mortality persists in HIV infection, particularly in patients who fail to restore normal CD4 T cell counts.
- Immune-based therapies, such as IL-7, which target expansion of the T cell pool in both peripheral blood and mucosal sites, may improve immune restoration in chronic HIV infection.

## Study Design and Methods

- INSPIRE 2 is an open-label, multicenter study of CYT107 (IL-7) in chronically HIV-infected persons with CD4 T cell counts between 101-400 cells/mm<sup>3</sup> and plasma HIV RNA < 50 copies/mL. 12 patients were enrolled and received 20 mcg/kg/week of CYT107 for 3 weeks.
- Twelve (12) patients underwent immunophenotypic analyses of cryopreserved PBMC by flow cytometry and a subset of 4 patients underwent rectosigmoid biopsies at baseline and between weeks 10-24.
- Median values and non-parametric testing were used for statistical analyses.

## Baseline Characteristics

Median (range)	N=12
Age (yr)	48 (29-55)
Time since HIV* (years)	5 (4-24)
Time since ARV (years)	3 (1-5)
CD4 count (cells/mm <sup>3</sup> ) <sup>a</sup>	272 (155-387)
CD8 count (cells/mm <sup>3</sup> ) <sup>a</sup>	554 (285-915)
Nadir CD4 count (cells/mm <sup>3</sup> )	36 (4-240)
Ratio CD4/CD8	0.54 (0.28-0.97)
HIV RNA (<50 cp/ml)	12

<sup>a</sup> - Baseline (BL) CD4 count = mean of 2 results in the last 6 months, 1 at screening, 1 at screening and 1 at D0

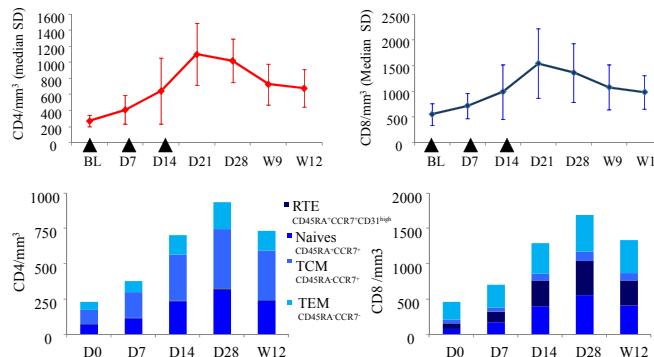
## Follow-up and Clinical Safety

All participants completed the study period (W12) and received all three doses of study drug

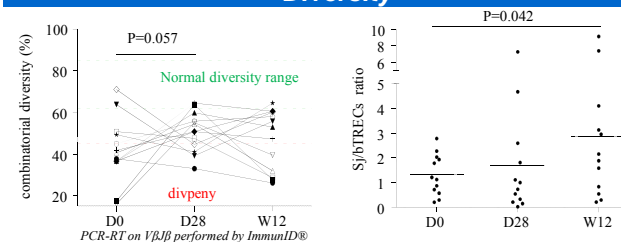
### Clinical and biological safety

- No serious adverse or other clinical events related to study drug were reported during the study period (baseline to W12)
- Grade 1 or 2 local injection sites reactions were commonly observed (10/12 pts, 80%)
- Systemic reactions: flu-like syndrome or fever, fatigue (16%)
- No neutralizing anti-IL-7 antibodies developed
- Transient HIV RNA "blips" (<500 copies/mL) were reported during IL-7 treatment or soon after in 7/12 pts (58%), in 1/12 pt (8%) at Week 12. All participants had HIV-RNA < 50 copies/mL at subsequent testing.

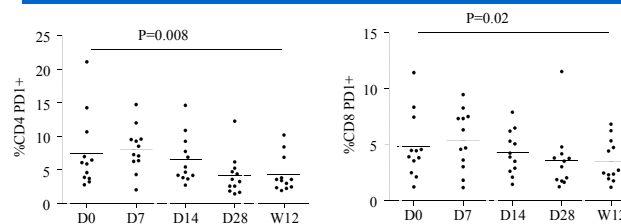
## 3 weeks IL-7 Treatment Increases all T cell Subsets



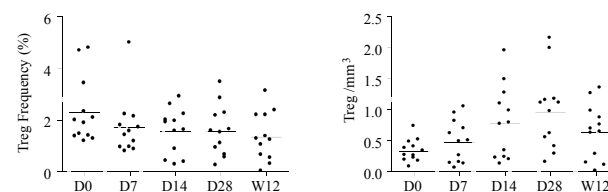
## IL-7 Increases Thymopoiesis and TCR Repertoire Diversity



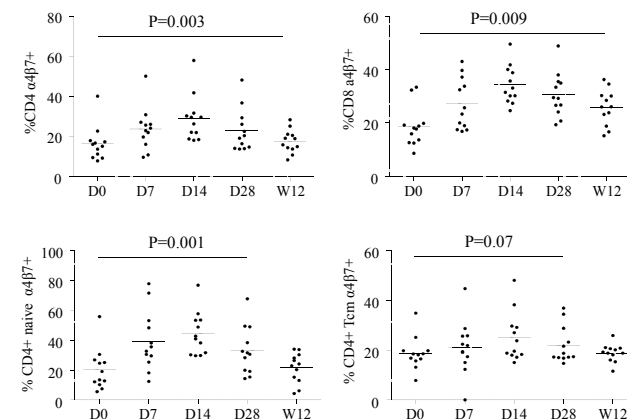
## IL-7 Treatment Decreases T cell Exhaustion



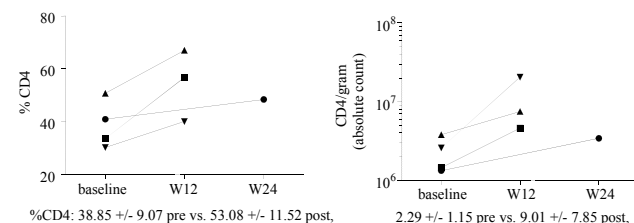
## Treg Proportion and Number are not Significantly Affected by IL-7



## IL-7 Increases expression of T cell Gut Homing Markers



## IL-7 and Gut CD4 Restoration



## Summary and Conclusions

- Administration of IL-7 in HIV+ patients with immune failure leads to substantial expansion of both CD4 and CD8 T cells, including naive and central memory subsets, without increases of Treg cells
- IL-7 increases the expression of gut homing molecules and decreases markers of activation (PD-1) in T cells
- These data suggest that administration of IL-7 to patients with immune failure may result in the restoration of the depleted CD4 population of the gut mucosa.
- Altogether these results encourage further trials evaluating IL7 as an immune-based therapy to reverse lymphopenia and immune dysfunction

## References

- Fry et al., JI 2001
- Meier et al., Immunity 2007
- Levy et al. JCI 2009
- Beq et al. Blood 2009