



## **Cytheris Announces Publication of IL-7 HIV Data in *The Journal of Clinical Investigation***

**Results of a phase I/IIa trial in lymphopenic HIV-infected patients further demonstrate the potential of Interleukin-7 to induce a dramatic and prolonged CD4 and CD8 T cell expansion, which is sustained for 48 weeks**

**Outcome suggests that this cytokine may offer the possibility of a convenient and intermittent adjunct therapy in combination with HAART**

*Paris (France) – March 17, 2009* – Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, today announced the publication of data from a multi-center Phase I/IIa study designed to investigate the safety of Interleukin-7 (IL-7) therapy in chronically HIV-1 infected patients whose CD4 T cell counts remained low despite treatment with anti-retroviral-therapies (HAART). After 48 weeks, patients treated at the higher dose level showed a median increase in CD4 and CD8 T cell counts (cells/microliters) of 75% and 58%, respectively, from baseline levels.

“Though viral load control in HIV-infected patients is an attainable goal with the current potent HAART regimen, the magnitude of CD4 restoration among patients remains variable and the length of time patients spend with low CD4 T cell counts is clearly associated with a higher morbidity,” said Yves Lévy MD, PhD, Scientific Director of the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) Vaccine Program, Service d’Immunologie Clinique, Hôpital Henri Mondor, Créteil, France and Inserm, Principle Investigator and lead author of the publication. “This study suggests that a new frontier in HIV therapy can be defined by the recovery and maintenance of a high level of CD4 T cells and that IL-7, with its potential ability to significantly impact naive and memory T cell subpopulations, may be a key to restoring the homeostatic equilibrium which is not achieved by the control of viral load alone under HAART. ANRS has a longstanding involvement with Cytheris in the clinical development of IL-7 and plans to maintain this relationship as together we continue to explore the clinical applications of IL-7 in unmet medical needs.”

"More and more data are accumulating to demonstrate that patients under HAART should maintain their CD4 counts above 500 cells/mm<sup>3</sup> and there is a developing consensus within the medical community towards initiating rather than deferring HAART in patients whose CD4 count is between 350-500 cells/mm<sup>3</sup>," said Thérèse Croughs, MD, Chief Medical Officer of Cytheris. "The results of this study as well as those in other ongoing investigations support the potential of IL-7 as an agent enabling patients with low CD4 counts to increase and maintain their CD4 count at >500 cells/mm<sup>3</sup> with just a short cycle of treatment, decreasing the risk of potentially fatal opportunistic infections and other HIV-related morbidity and mortality conditions."

The paper entitled "Enhanced T cell recovery in HIV-1-infected adults through IL-7 treatment" is published online in *The Journal of Clinical Investigation* (Lévy, Y et al, 2009, Vol. 119, No. 4). The full article can be found on the JCI website at <http://www.jci.org/articles/view/38052>. Interim results of this study were previously presented by Dr. Levy at CROI 2007 and 2008.

### **About the Study**

The hallmark of HIV infection is a defect in the function and homeostasis of CD4 T lymphocytes leading to the development of opportunistic infections and malignancies. Highly Active Anti Retroviral Therapies (HAART), usually combining a protease inhibitor or a non nucleoside reverse transcriptase inhibitor with 2 nucleoside analogs, has markedly improved the prognosis of HIV infected patients.

HAART has been observed to both control HIV replication and to maintain or restore a CD4 T cell count above 200 cells/mm<sup>3</sup>. A few months after this restoration, prophylaxis of opportunistic infections can be stopped, a protective immune response against the pathogens being usually reconstituted.

However, several major issues are not solved by these treatments:

- approximately 5 to 15% of the treated population are immunological non-responders i.e., their CD4 T cell count remains <200 cells/mm<sup>3</sup>, despite having controlled HIV replication, several months after the initiation of HAART;
- approximately 5 to 10% of the treated population fails to respond to HAART, both virologically and immunologically, i.e., their viral load in circulation remains high and thus the CD4 T cell pool continues to decline;
- chronic co-infection by other viruses e.g., Hepatitis C (HCV) is a source of additional complication;
- the vast majority of the HAART treated patients never develop effective HIV specific CD4 and CD8 T cell responses, despite an optimal control of HIV replication and the recovery of a nearly normal CD4 T cell count.

With the aim of addressing these unresolved HIV treatment issues, the Phase I/IIa trial was designed to investigate the safety and biological activity of IL-7 therapy in chronically HIV-1 infected patients with low CD4 counts (100-400 CD4/microliter) and plasma HIV RNA <50 cp/ml for at least 6 months while on HAART. Six and 8 patients were included in the first (3 microgram/kg) and second (10 microgram/kg) dose level, respectively. Patients received 8 subcutaneous injections (3 times/week; days 1-16) of r-hIL-7. Clinical, biological and virological safety parameters were monitored until week 48. HIV Gag-specific T cell responses were assessed by intra-cellular cytokine staining in the 10 microgram/kg group.

The long-term results for this group of patients, defined as "immune non-responders", indicate that the IL-7 induced rapid expansion of CD4 and CD8 T cell counts was sustained for up to 48 weeks from study entry. Importantly, 48 weeks after initiation of this IL-7 short course of therapy, patients treated at the 10 microgram/kg dose level showed a median percent increase in CD4 and CD8 T-cell counts (cells/microliters) of 75% and 58%, respectively, from baseline levels.

General study conclusions include the following:

- IL-7 administered as 3 microgram/kg (Cohort 1) and 10 microgram/kg (Cohort 2) subcutaneous injections over a period of 16 days, was clinically and biologically well tolerated.
- There were no signs that suggested activation of the immune system. No major safety concerns regarding vital signs or laboratory parameters were identified.
- IL-7 did not directly impact the cellular HIV DNA content (reservoir) although a possible transient effect on HIV replication was detected in some patients treated with the higher dose.
- Both doses investigated were biologically active, leading to an increase in CD4 cell count of at least 50% between baseline and the value reached on Day 28. The median percent increase was 68% in Cohort 1 and 212% in Cohort 2.
- IL-7 was consistently active, increasing both the CD4 and CD8 T cells from Day 7 onwards. In addition to a rapid onset of effect, T cell expansion was sustained with IL-7, all patients having an improvement from baseline in their CD4 and CD8 cell counts at Week 48. The benefit of treatment was apparent at both levels studied, although the effect was strongly dose dependent.
- IL-7 increased preferentially naïve and central memory CD4 and CD8 T cell populations
- At the higher dose, IL-7 induced, in some patients, a significant increase in the median frequency of CD4 T cells producing Interferon-gamma and IL-1-2, showing that the functional capacity of T cells can be preserved or increased.

The study results support additional investigation into the role of IL-7 as a physiological immuno enhancer, which fosters restoration of T cells in lymphopenic patients, and improves T cell responses against chronically expressed antigens.

### **About Interleukin-7**

IL-7 plays multiple roles in the differentiation and the expansion of T cells from lymphoid progenitors, and in the survival of T cells. Studies in animal experimental models have shown that IL-7 can enhance the proliferation and expansion of T lymphocytes. By its action, IL-7 may provide a novel approach for the restoration and/or improvement of the CD4 T cell pool and immune functions in patients infected with HIV.

Recombinant human Interleukin-7 is a critical growth factor for immune T cell recovery and enhancement. As a growth factor and cytokine physiologically produced by marrow or thymic stromal cells and other epithelia, IL-7 has an important and, at some steps, a non-redundant stimulating effect on T lymphocyte development, notably on thymopoiesis and, down-stream from the thymus, on homeostatic expansion of peripheral T cells.

The first-generation form of rhIL-7 (CYT 99 007) used in this HIV study has also been shown in pre-clinical and Phase I studies in oncology to be well tolerated in repeated dose trials, with long-lasting increases in both CD4 and CD8 T cells. A second-generation, fully glycosylated rhIL-7 product (CYT107) is made by Cytheris via a recombinant mammalian cell culture system and is being used in all ongoing clinical trials.

### **About Cytheris' Interleukin-7 Clinical Development**

Ongoing clinical development includes six interpatient dose escalation studies, with starting doses varying from 3 microgram/kg/week to 60 microgram/kg/week, to evaluate the safety and biological activity of CYT107 in various indications. These studies include:

- **CLI-107-04:** a monocentric Phase I interpatient dose escalation non-controlled study in oncology (metastatic melanoma or renal cell carcinoma), conducted at the US National Cancer Institute, Bethesda, Maryland.
- **CLI-107-06 (the INSPIRE study):** a Phase I/IIa interpatient dose escalation randomized placebo controlled single-blind multi-center study in chronically HIV infected patients conducted in the United States, Canada, Italy and France.
- **CLI-107-05 (ECLIPSE-1):** a Phase I interpatient dose escalation non-controlled multi-center study in treatment naive, non-responder (no EVR at week 12) HCV infected patients conducted in France, Italy and Switzerland assessing CYT107 in combination with a peg-IFN and RBV bi-therapy.
- **CLI-107-07 (ECLIPSE-2):** a Phase I/IIa dose escalation non-controlled study in HCV infected patients conducted in France and Italy evaluating CYT107 in combination with peg-IFN and RBV bi-therapy in patients with genotype 1 and 4 previously non-responsive to standard treatment.

- **CLI-107-09 (ECLIPSE-3):** a Phase I/IIa dose escalation non-controlled study in chronically infected HCV patients conducted at multiple sites in Taiwan evaluating CYT107 in combination with peg-IFN and RBV bi-therapy in patients with genotype 1 previously non-responsive to standard treatment.
- **CLI-107-08:** a monocentric Phase I interpatient dose escalation non-controlled study in recipients of HLA matched ex-vivo T-cell depleted bone marrow or peripheral blood stem cell transplant to restore CD4+ and CD8+ counts following T-cell depletion, conducted at the Memorial Sloan-Kettering Cancer Center in New York City.

**About Cytheris – [www.cytheris.com](http://www.cytheris.com)**

Cytheris SA is a privately held clinical-stage biopharmaceutical company focused on research and development of new therapies for immune modulation. These drugs aim at reconstituting and enhancing the immune system of patients suffering from cancer, chronic viral or bacterial infections such as HCV, HBV and HIV, or lympho-depleting treatments such as chemotherapy, radiotherapy, bone marrow transplantation (BMT) and hematopoietic cell transplantation (HCT). The company operates from its headquarters and laboratories in Issy-les-Moulineaux, a suburb of Paris, and its U.S. subsidiary in Rockville, Maryland.

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