



Cytheris Announces Publication of Preclinical Study in *Nature Medicine* Showing Combination of Interleukin-7 with Viral Vaccine Boosts Immunity to Tumors

The ability of adjuvant IL-7 to antagonize inhibitory networks at the cellular and molecular level has major implications for immunotherapy in the treatment of tumors

Paris (France) – May 26, 2009 – Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, today announced publication of data showing that following a vaccine-induced immune response, adjuvant interleukin-7 (IL-7) improves anti-tumor responses and survival in an animal model. The study was conducted by an international team of researchers at the Campbell Family Institute for Breast Cancer Research, University Health Network, Toronto, Canada.

The paper entitled “Adjuvant IL-7 antagonizes multiple cellular and molecular inhibitory networks to enhance immunotherapies” is published in *Nature Medicine*, (Marc Pellegrini, Thomas Calzascia, Alisha R. Elford, Arda Shahinian, Amy E. Lin, Dilan Dissanayake, Salim Dhanji, Linh T. Nguyen, Matthew A. Gronski, Michel Morre, Brigitte Assouline, Katharina Lahl, Tim Sparwasser, Pamela S. Ohashi and Tak W. Mak, [2009 May; 15\(5\) 528-36. Epub 2009 April 26](#)).

“Studies such as the one described in this paper provide tantalizing evidence for the potential of immunotherapies to marshal the body’s own defenses in treating cancer,” said Michel Morre, DVM, President and CEO of Cytheris. “By augmenting and sustaining the vaccine-induced anti-tumor response described in this paper, IL-7 enhances tumor-specific immunity and harnesses the response to directly target spontaneously arising tumors. Most importantly, the resulting immune-mediated anti-tumor effect profoundly improves survival.”

About the Study

Considerable effort has been expended in the scientific community to induce anti-tumor immunity with various vaccine strategies. Despite much enthusiasm and optimism, numerous trials have shown minimal efficacy. This highlights the need for new approaches to augment anti-tumor immunity *in vivo*.

To investigate the effectiveness of exogenous recombinant human IL-7 in sustaining a primary *in vivo* response, the investigators treated lymphocytic choriomeningitis virus (LCMV)-vaccinated tumor-bearing RIP (GP x TAG2) mice with IL-7 or with a buffer for 14 days. Treatment was initiated 8 days after LCMV infection, coinciding with the peak of the cytotoxic T lymphocyte (CTL) response, viral elimination and the onset of the contraction phase. Mice receiving IL-7 tended to have a faster onset and more pronounced level of euglycemia or mild hyperglycemia than the buffer-treated control mice; this was most obvious at late time points, suggesting an enhanced anti-tumor response.

Survival of IL-7-treated mice was prolonged by over 100 days compared to control mice. This profound increase in survival was dependent on efficient vaccination and the expression of glycoprotein (GP) on the tumor. Histology revealed that tumors from IL-7-treated mice were heavily infiltrated with both CD4+ and CD8+ T cells compared to buffer-treated mice, who consistently had larger tumors. The enhanced tumor immune response directly correlated with a significant accumulation and persistence of GP-specific T cells at the tumor site.

The study also explored whether the effects of IL-7 in the LCMV vaccination model are applicable to other vaccines and clinically relevant approaches. The investigators found that adjuvant IL-7 potently enhanced anti-tumor immune responses initiated by dendritic cell (DC) vaccination or vaccinia virus immunization in mice with spontaneous pancreatic tumors. In vitro-differentiated and matured DCs pulsed with GP33, GP276 and GP61 were transferred into RIP(GP x TAG2) tumor-bearing mice. IL-7 was administered at the time of transfer and continued daily for 2 weeks, at which time mice were analyzed for anti-tumor immune responses.

Mice receiving DC vaccination together with IL-7 showed an enhanced anti-tumor response. Similarly, RIP(GP x TAG2) tumor-bearing mice immunized with recombinant vaccinia virus expressing LCMV GP and treated concurrently with IL-7 for 2 weeks had a pronounced anti-tumor response compared to buffer-treated mice. These data underscore the potential clinical relevance and impact of IL-7 therapy in promoting efficacy using various protocols.

To rationally use IL-7 as a therapeutic tool and maximize its efficacy, a thorough understanding of the cellular and molecular networks affected by this cytokine in the relevant pathological settings is essential. This study shows that IL-7 combined with vaccination has functions beyond its simple survival- and proliferation-promoting roles. Effector cells isolated from IL-7-treated mice showed enhanced functional activity at the single-cell level. Importantly, following IL-7 treatment CTLs acquire a more pathogenic phenotype with higher expression of granzyme B, faster and amplified degranulation kinetics, and more effective cytolytic activity.

IL-7 also affected CD4+ T cells in the spontaneous tumor model, causing an 18-fold increase in the number of IL-17-secreting CD4+ effector cells, indicating a strong skewing toward TH17 differentiation.

Furthermore, in comparison with heterologous models based on grafted tumors, the experimental model using transgenic animals described in this paper is especially compelling because it is based on the cure of spontaneously produced tumors expressing self antigens for the mice and thus closely mimics the human disease condition.

Finally, the investigators found that the effect of IL-7 on anti-tumor immune responses was dependent on efficient vaccination, a major issue that stresses the need for optimal vaccination strategies to translate IL-7-based therapy to human cancers and chronic infections.

About Interleukin-7

Investigational recombinant human Interleukin-7 (r-hIL-7) is a critical growth factor for immune T-cell recovery and enhancement. Cytokines that signal via the common gamma chain (γ_c) represent promising therapeutics based upon their potential to augment T cell expansion and increase the effectiveness of immune based therapies. Within this family, IL-7 is a prototypic homeostatic cytokine, produced constitutively by non-lymphoid cells. Its receptor (IL-7Ra) is expressed on resting T cells, then rapidly down-regulated following T cell activation or IL-7 signaling.

IL-7 is essential for T cell development in mice and humans and for T cell homeostasis since it is required to maintain naïve CD4+ and CD8+ T cells *in vivo*. IL-7 levels rise in serum and tissues following T cell depletion and fall upon recovery.

In preclinical studies, IL-7 therapy exerts marked effects on T cell immune reconstitution in mice and primates. IL-7 augments effector and memory responses to vaccination in mice with preferential enhancement of responses to weak subdominant antigens. In preclinical models, IL-7 therapy augments anti-tumor responses leading to improved survival when combined with anti-tumor vaccines.

Clinical trials conducted on more than 110 patients in Europe, North America and Taiwan suggest the potential of IL-7 in expanding and protecting CD4+ and CD8+ T-cells. Cytheris is currently conducting multiple clinical studies of IL-7 in HIV, HCV and cancer.

About Cytheris – 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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