Cytheris Announces Publication of Preclinical Study in *Cell* Showing That Interleukin-7 Engages Multiple Mechanisms To Overcome Chronic Viral Infection and Limit Organ Pathology

Study provides insights into the inhibitory pathways that function to impede immune responses in chronic viral infections while elucidating the attributes of IL-7, which have profound implications for its use as a therapeutic in the treatment of viral diseases such as HIV and hepatitis

Paris (France) – February 22, 2011– 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 IL-7 is able to overcome many of the factors that thwart an effective immune response during chronic overwhelming viremia in diseases such as HIV infection and viral hepatitis. The results of this study also suggest how in the context of the reduced viral load established by current treatments for chronic viral diseases, IL-7 therapy could be used to produce and expand specific T cells and promote a broad and durable immune mediated antiviral response.

The paper, entitled "IL-7 Engages Multiple Mechanisms to Overcome Chronic Viral Infection and Limit Organ Pathology" by Marc Pellegrini, Thomas Calzascia, Jesse G. Toe, Simon P. Preston, Amy E. Lin, Alisha R. Elford, Arda Shahinian, Philipp A. Lang, Karl S. Lang, Michel Morre, Brigitte Assouline, Katharina Lahl, Tim Sparwasser, Thomas F. Tedder, Ji-hye Paik, Ronald A. DePinho, Sameh Basta, Pamela S. Ohashi, and Tak W. Mak, is published in the current issue of *Cell*, Vol. 144, No. 4:601-613.

"The data generated in this study provide insights into the inhibitory pathways that function to impede immune responses in chronic infections such as HIV, HCV and HBV," said Marc Pellegrini, PhD, Laboratory Head, Division of Infection and Immunity, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, and lead author on the study. "The elucidation of the molecular mechanism whereby IL-7 is able to overcome the immune inhibitory effects of massive viral load and promote extensive expansion of naive and effector T cells has major implications for our understanding of chronic viremia and the potential therapeutic use of IL-7."

The study utilized the murine model of lymphocytic choriomeningitis virus (LCMV) infection, a well-defined in vivo system for studying protective cytotoxic T lymphocyte (CTL) responses involving the variant clone-13. Importantly, the model is characterized by a chronic infection having a high viral turnover in mice, thereby mimicking the massive viral antigen levels associated with the three most common human viral disease infections, HIV, HCV and HBV. Clone-13 infection has served as a powerful tool in characterizing the dysfunctional immune response associated with chronic viremia, and numerous parallels with these three most common infections have been described in the literature. In this context, the study elucidates various molecular mechanisms whereby IL-7 is able to overcome the immune inhibitory effects of massive viral load.

In their accompanying editorial note, entitled "IL-7 Knocks the Socs Off Chronic Viral Infection" (Cell, Vol. 144, No. 4: 467-468), Ian A. Parish and Susan M. Kaech of the Howard Hughes Medical Institute and Yale University School of Medicine underscore how IL-7 treatment downregulates levels of a critical repressor of cytokine signaling in immune cells, Socs3, thus allowing for the extensive expansion of naive and effector T cells. In addition, IL-7 also enhanced thymic output to expand the naive T cell pool, including T cells that were not LCMV specific.

Though in this study, IL-7 alone was used to reduce viral load, the data suggest that IL-7 therapy may become a useful adjuvant to antiviral treatments in chronic HIV, HCV and HBV infection. Antiretroviral therapy is successful in reducing viral load to an undetectable level in HIV infection and the same is true for the new antivirals in late stage development for HCV and those already on the market for treatment of HBV infection. In this setting of a significantly reduced viral load, T cells become more responsive to IL-7 through restoration of the IL-7 receptor (IL-7R), which then enables their rescue. Following this reduction in viral load, IL-7 therapy can be used to produce and expand specific T cells and promote a broad and durable immune mediated antiviral response. In addition, the study suggests that the secondary cytoprotective effects of IL-7, mediated by IL-22, have therapeutic implications for the management of hepatitis C virus infections as well.

"Preclinical studies like the one reported here, that combine a well defined animal model with definitive clinical end points together with a precise elucidation of the immune mechanisms supporting the therapeutic effect, have great prospective value," said Michel Morre, DVM, President and CEO of Cytheris. "By choosing the clone-13 chronic LCMV model, reaching viral clearance and detailing the antiviral mechanisms triggered by IL-7, this preclinical study sheds new light on the ways IL-7 activity participates in the effective treatment of chronic viral diseases. In the clinic, we are progressively identifying the full set of these same immune effects supporting IL-7 antiviral activity and are in the process of accumulating definitive clinical proof of this activity against CMV, EBV, the JC virus and, now, against HCV in patients previously resistant to standard of care (PEG-Interferon + Ribavirin)."

About the Study

Much attention has focused on modulating immune responses in an attempt to promote clearance of chronic viral infections. This is particularly relevant to chronic HCV and HBV hepatitis infections in which the immune system fails to clear the virus and eventually succumbs to uncontrolled viral turnover. Understanding the mechanisms that circumvent immune responses in cases of overwhelming viral replication and massive antigen expression underlies any rational attempt to augment immunity. However, in the specific case of HIV, it is important to emphasize here that simply enhancing the immune specific response against infected cells, although it might improve viral control, is unlikely to be sufficient to clear the viral reservoir -- a critical element in any attempt to achieve a cure for this complex virus.

Elucidating the factors that impede immune responses to persistent viruses is essential to designing therapies for chronic viral infections. Mice infected with LCMV clone-13 have persistent high-level viremia, which is correlated with a dysfunctional immune response. Interleukin-7, which is critical for immune development and homeostasis, was used in this study to promote immunity toward clone-13, thus enabling a better understanding of the inhibitory pathways underlying impaired antiviral immune response.

Mechanistically, IL-7 downregulated a critical repressor of cytokine signaling, Socs3, resulting in amplified cytokine production, increased T cell effector function and numbers, and viral clearance. IL-7 enhanced thymic output to expand the naive T cell pool, including T cells that were not LCMV specific. Additionally, IL-7 promoted production of cytoprotective IL-22 that abrogated liver pathology. The IL-7-mediated effects were dependent on endogenous IL-6. These attributes of IL-7 have profound implications for its use as a therapeutic in the treatment of chronic viral diseases and suggest that a more favorable outcome may be achieved if IL-7 therapy is applied after first reducing massive viral load by application of specific antiviral treatments.

About the Study Team
The study was conducted by Marc Pellegrini and Thomas Calzascia and an international team led by Tak W. Mak and Pamela S. Ohashi, both of the Campbell Family Cancer Research Institute, Ontario Cancer Institute, Toronto, Canada, and included researchers from multiple institutions, including: The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; Laboratory of Immunology and Vascular Biology, Department of Pathology, Stanford University School of Medicine, Stanford, CA USA; Institute for Infection Immunology, TWINCORE, Centre for Experimental and Clinical Infection Research, Hanover, Germany; Department of Immunology, Duke University Medical Center, Durham, NC USA; Belfer Institute for Applied Cancer Science, Department of Medical Oncology, Department of Medicine and Department of Genetics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA USA; and, the Department of Microbiology and Immunology, Queen's University, Kingston, ON, Canada.

About Recombinant Human Interleukin-7 (CYT107)
Recombinant human interleukin-7 (CYT107) is a critical immune-modulator 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 a critical and, at some steps, a non-redundant stimulating effect on T lymphocyte development, notably on thymopoiesis and, downstream from the thymus, on homeostatic expansion of peripheral T-cells.

Clinical trials conducted on more than 160 patients in Europe, North America, South Africa and Taiwan have demonstrated the potential of IL-7 to expand and protect CD4 and CD8 T-cells. Currently, Cytheris is conducting multiple international investigations of IL-7 in HIV, HCV, HBV, post-BMT and cancer. Additional studies include a NIAID/NIH-sponsored trial (ICICLE) in idiopathic CD4 lymphocytopenia (ICL); a cancer vaccine study in children with Ewing's sarcoma family of tumors or similar genetic tumors sponsored by US National Cancer Institute; and, a multi-company/institutional study (EraMune 01) sponsored by ORVACS (the international HIV organization funded by the French Bettencourt Schueller Foundation) aimed at attacking the HIV viral reservoir.

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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