



Press Release

**STUDY SHEDS LIGHT ON THE MECHANISMS OF INCREASED RISK OF
HIV INFECTION IN THE STEP HIV VACCINE TRIAL**

- NEW AVENUES FOR VACCINE RESEARCH -

Lausanne, Switzerland and Montpellier, France, November 3, 2008 -- A study published today online in *The Journal of Experimental Medicine* sheds light on the potential mechanisms responsible for the increased incidence of HIV infection that was observed in the failed STEP HIV vaccine trial in 2007. Through the development of an experimental in vitro model, the study shows that the immune complexes formed by antibodies and the adenovirus vector (the Trojan horse for the delivery of the vaccine) induce a strong activation signal of key cells, i.e. dendritic cells, responsible for the activation of the cellular arm of the immune response including CD4 T-cells, the primary target for HIV. The ultimate result of the activation mediated by antibodies and adenovirus vector complexes is the induction of vigorous replication of HIV in this experimental model.

The study is the result of the collaboration between scientists at the Institut de Génétique Moléculaire de Montpellier, Université Montpellier I & II, Montpellier, France, the Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Lausanne and at the Swiss Vaccine Research Institute, Lausanne, Switzerland.

The STEP HIV vaccine trial, which evaluated an adenovirus vector-based vaccine and enrolled 3,000 high-risk HIV seronegative subjects, was prematurely terminated last year. The primary objectives of the study were to determine the effects of the vaccine on i) the reduction of the acquisition of HIV infection, and ii) the reduction of



the HIV viremia. STEP was stopped due to a lack of efficacy and a 2-fold increase in the incidence of HIV acquisition among vaccinated recipients previously exposed to the wild type adenovirus and therefore with high levels in the serum of antibodies against the vector.

Several hypotheses have been proposed to explain the increased acquisition of HIV infection and a number of strategies have been developed to tackle this issue. Most of the investigations have been focused on mechanisms of activation of CD4 T-lymphocytes, the primary target for HIV. These investigations have failed to generate a clear model to explain the increased incidence of HIV infection among vaccine recipients with high levels of adenovirus antibodies in the serum.

“The STEP vaccine trial has clearly shown a strong correlation between the serum levels of adenovirus antibodies and increased susceptibility to HIV infection. We therefore favored the hypothesis that anti-vector antibodies were directly involved in mechanisms of increased acquisition of HIV infection,” says Matthieu Perreau, the talented scientist who developed the experimental model. The key issue was to understand how the anti-adenovirus antibody response was linked to increased susceptibility to HIV infection.

“We reasoned that because pre-existing adenovirus antibodies will rapidly bind the vaccine following the administration, it was possible that, as shown in other pathological conditions, immune complexes were inducing a powerful activation signal”, says Dr. Eric Kremer, one of the two scientists leading the study. “It is likely that the critical events associated with enhanced infection occur at the mucosal levels (the port of entry of adenovirus during natural infection). Therefore, the microenvironment of the mucosa may be optimal for creating the chronic permissive infection for HIV”, says Dr. Giuseppe Pantaleo, the other scientist leading the study.

These observations provide the basis for developing novel monitoring strategies to assess the impact of pre-existing immunity in the case of vaccine platforms which make use of virus vectors.

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Notes to editors:

A vaccine is a preparation made of micro-organisms, which once introduced into our bodies, triggers our immune system and teaches the body to defend itself. A likely vaccine against HIV should at the same time stimulate neutralizing antibodies to block penetration of HIV (humoral response) and stimulate a cellular immune response. Some experimental HIV vaccines in development use attenuated adenoviruses, or other viruses, as “Trojan horses” for the delivery of the vaccine to induce an immune response. In the case of adenovirus- based vaccine, people that have previously naturally been exposed to adenoviral infection have already developed antibodies against the adenovirus and this may result in unexpected immune activation.

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