Scientists gain insight into HIV vaccine failure

July 20 2009

A team of researchers from The Wistar Institute and the University of Pennsylvania reports new evidence refuting a popular hypothesis about the highly publicized failure in 2007 of the Merck STEP HIV vaccine study that cast doubt on the feasibility of HIV-1 vaccines. The findings were published on-line July 20 in *Nature Medicine*.

The phase II STEP vaccine trial was stopped after an interim analysis showed no efficacy in preventing HIV infection in at-risk individuals. It was noted that a subset of participants who had previous immunity in the form of neutralizing antibodies to the adenovirus 5 (Ad5) vector used to deliver the vaccine actually showed a trend toward an increased rate of HIV infection. Finding an explanation for this increased susceptibility to infection remains a major focus for HIV vaccine researchers.

These individuals were found to have high blood Ad5 neutralizing antibody (nAb) titers, the main immune gatekeeper in most vaccine strategies. Antibodies produced in response to previous infection neutralize viruses by binding to them and preventing their entry into host cells. They work in concert with other immune cells, including CD4 T-cells, which build a memory bank against future infection. In HIV infection, the virus attaches specifically to CD4 receptors on activated CD4 T-cells, establishing a stronghold and replicating.

Of the STEP findings, many researchers hypothesize that the T-cells of individuals in this high-Ad5-antibody group were activated by the Ad5-vaccine vector, creating more activated CD4 T-cells which then

served as targets for the HIV virus to establish an infection.

"Our findings disprove the favored hypothesis," says co-lead author Hildegund C.J. Ertl, M.D., director of The Wistar Institute Vaccine Center. "There was nothing to indicate that pre-existing neutralizing antibodies correlated with numbers of activated CD4 T-cells to Ad5, which could have provided additional targets for HIV infection following subsequent exposure."

Seeking to understand the relationship between previous neutralizing antibodies to Ad5 and Ad5-specific T-cell responses, the team, headed by Michael R. Betts, Ph.D., of the University of Pennsylvania School of Medicine Department of Microbiology, Center for AIDS Research, and Wistar Institute Vaccine Center, analyzed blood samples from 40 healthy participants in the phase I safety trial of the STEP HIV vaccine for immune response to Ad5 particles. The blood samples, which came from individuals with both high and low nAb titers and thus varying degrees of pre-existing neutralizing antibodies to Ad5, had been taken from participants at baseline, before administration of the Ad5 vector vaccine under study. From their current Ad5 assay, the team found no correlation between nAb titers at baseline and CD4 T-cell frequency.

"Ad-specific CD4 T-cells are exceptionally common in humans, regardless of the level of neutralizing antibodies to Ad5," says Betts. "This is probably the major factor that disproves the main hypothesis proposed to explain the STEP trial results."

The team next questioned whether the Ad5-specific CD4 T-cells functioned any differently before or after administering the Ad5 vector. They found no significant difference in activation or expansion of CD4 T-cells in either the high- or the low-Ad5 antibody groups.

"It doesn't appear that vaccination increases the pool of potentially

infectable CD4 T-cells in people with pre-existing immunity to Ad5," Ertl says. "When you look at the data together, they suggest we must look elsewhere to explain the link between previous Ad5 immunity and increased acquisition of HIV infection."

Source: The Wistar Institute