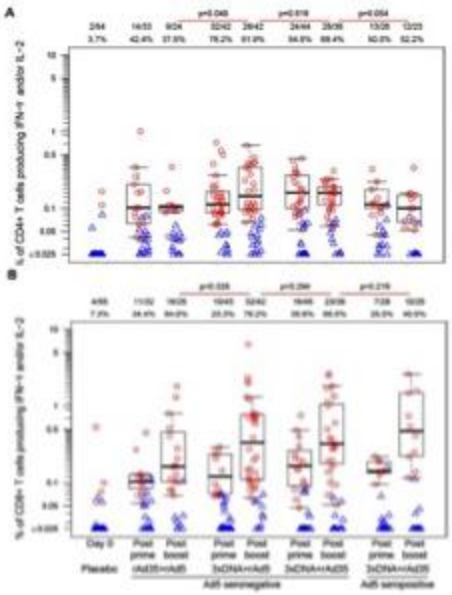
Ad5 vs Ad35: the match of the year

January 17, 2016

L Pattacini



HIV-specific CD4+ (A) and CD8+ (B) responses following the different vaccination schedules.

Figure adapted from the publication.

Adenoviruses (Ad) represent an attractive platform for vaccines, as they can induce innate and adaptive immune responses. They have been proposed as vectors for different vaccines, such as for HIV. The Step study was a trial designed to test the efficacy of a recombinant Ad5-vectored construct encoding for HIV clade B Gag, Pol and Nef. The study had to be stopped after ad interim efficacy analyses showed futility of the vaccine in preventing HIV, and surprisingly, a higher rate of HIV infections in a subset of vaccine recipients with pre-existing high Ad5 antibody titers. It has been hypothesized that vaccine administration increased the number of CD4+ T cells, target cells for HIV infection, in the periphery by triggering pre-existing Ad5 immunity. Ad5 is a very common serotype, especially in developing countries where the HIV vaccine would be needed the most; therefore, it is an unlikely candidate for future trials. An alternative is urgently needed and the use of less common serotype vectors might represent the solution to the problem.

Recently, the HIV Vaccine Trial Network conducted a phase IB trial to evaluate safety and immunogenicity of an Ad35-vectored HIV vaccine. The trial was designed to compare three different prime-boost regimens: Ad35 prime followed by Ad5 boost, versus DNA prime Ad5 boost, versus DNA prime Ad35 boost. The design was meant to clarify the immunogenicity of Ad35 as a prime compared to DNA, and as a boost compared to Ad5. The results of the study, presented in the

Journal of AIDS Clinical Research, are the product of a collaboration between scientists at Fred Hutch and several other institutions in the US.

A total of 192 volunteers were recruited and 90% completed the four vaccination- regime. Vaccine components were overall well tolerated and proved to be safe. For immunogenicity, both antibodies and T-cell responses were measured for a more comprehensive evaluation of the adaptive immune responses. All vaccines tested induced high frequency and magnitude antibody responses. Importantly, vaccine-induced antibodies were able to recognize cross-clade Env proteins, which makes this strategy usable in different geographic areas. V1/V2 Env loop specific-IgG were also tested as they were found to correlate with protection from HIV infection in the RV144 (Thai) trial, and in the same way, they were induced by the different vaccines tested.

A high rate of subjects also developed T cell responses, measured as IFN-γ and IL-2 producing T cell. DNA prime followed by Ad35 boost in Ad5 seronegative individuals induced the highest response of CD4+ T cell responses, whereas Ad5 boost induced a higher rate of CD8+ T cell responses. Noticeably, pre-existing Ad5 immunity did not significantly modified T-cell responses. DNA prime followed by either Ad boost induced more polyfunctional responses, as measured by their capacity to produce the cytolytic molecule granzyme B as well as the cytokine TNF-α.

This critical work demonstrated that Ad35 is comparable to Ad5 in its safety profile as well as its immunogenicity, but presents the advantage of being a much less frequent serotype, lowering the risk of re-activating a pre-existing response that would have constituted a problem for Ad5 applications. Will one Adenovirus family member prove safe and effective as an HIV vaccine? We surely hope so!

The study was supported by National Institutes of Health.

Fuchs JD, Bart P-A, Frahm N, Morgan C, Gilbert PB, Kochar N, DeRosa SC, Tomaras GD, Wagner TM, Baden LR, Koblin BA, Rouphael NG, Kalams SA, Keefer MC, Goepfert PA, Sobieszczyk ME, Mayer KH, Swann E, Liao H-X, Haynes BF, Graham BS, McElrath MJ, Network NHVT. 2015. Safety and Immunogenicity of a Recombinant Adenovirus Serotype 35-Vectored HIV-1 Vaccine in Adenovirus Serotype 5 Seronegative and Seropositive Individuals. *J AIDS Clin Res*. 6(5):461.