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Therapeutic conserved elements (CE) DNA vaccine increases T-cell responses against highly conserved viral sequences in the setting of pre-existing immunodominant responses induced by chronic viral infection

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Background: We have previously shown that in SIV-infected rhesus macaques undergoing antiretroviral therapy (ART), therapeutic DNA immunization protected ~50% of animals from viral rebound after discontinuing ART. To improve this approach, we are investigating a novel conserved elements (CE) therapeutic DNA vaccine which consists exclusively of CE sequences. We hypothesize that a CE DNA vaccine will achieve a more profound functional cure by forcing immune escape mutations in regions of the virus that would have the greatest impact on viral fitness. A question that must first be addressed is whether immunization with a vaccine expressing conserved, but generally subdominant epitopes, can induce responses against CE in the setting of an immunodominant response induced by infection. To investigate this question, we compared immunogenicity of a CE DNA vaccine to a DNA vaccine expressing whole SIV Gag in rhesus macaques chronically infected with SHIV, as well as the role of CE specific responses in long term viral control.

Methods: Two groups of rhesus macaques chronically infected with SHIV89.6P were immunized with either a traditional DNA vaccine expressing whole SIV Gag or an SIV CE DNA vaccine. An IFN-γ ELISpot assay was employed to map T cell responses induced in the blood and gut against the full SHIV proteome and the CE sequences. Intracellular cytokine staining was also used to assess functional quality of T cell responses directed against CE.

Results: Prior to immunization, both groups had similar responses to variable and immunodominant regions of Gag with little to no detectable responses to CE. Animals immunized with whole Gag exhibited no significant increase in responses against CE. In contrast, CE vaccinated animals developed a nearly ten-fold increase in IFNg and cytolytic T cell responses against CE.

Conclusions: These results illustrate that a CE DNA vaccine was able to overcome immunodominant responses associated with a viral infection and re-direct the cellular response toward increased targeting of the subdominant conserved viral sequences when compared to a traditional full length Gag DNA vaccine. These results support the feasibility of developing a therapeutic CE DNA vaccine to induce a functional cure against AIDS.

Under embargo until 14.30 on 22 July 2015