Background: HIV sequence diversity and potential "decoy" epitopes are hurdles in the development of an effective AIDS vaccine. We tested the hypothesis that a vaccine candidate composed of highly Conserved Elements (CE) of the HIV proteome excluding the variable regions would help overcome these problems. CE were selected based on both stringent conservation and association of specific elements with immune control. A prototype HIV DNA vaccine, expressing 7 CE identified in p24gag as a single protein, was able to induce robust cross-clade specific immune responses in mice.

Methodology: Macaques were immunized by IM injection followed by electroporation with two DNA plasmids providing potential epitopes found in >99% of all HIV-1 M group sequences. Cellular immune responses were compared to those obtained upon vaccination with gag DNA only. As a second test of this concept, we also developed SIVp27gag CE vaccine and tested immunogenicity in DNA vaccinated macaques.

Results: HIV CEgag DNA vaccination induced robust immunity in all 10 vaccinated macaques, whereas full-length gag DNA vaccination elicited CE responses in only 5 of 11 animals targeting fewer CE per animal. CE DNA vaccination elicited highly cytotoxic T cells against CE, capable of Granzyme B production and degranulation, desired features for an effective vaccine. Importantly, boosting CE-primed macaques with DNA expressing full-length p55gag increased both magnitude of CE responses and breadth of Gag immunity, demonstrating altered immunodominance hierarchy in the presence of pre-existing CE-specific responses. Similarly, we found the vaccination with SIV p27gag CE induced antigen-specific responses. In contrast, vaccination with SIV p57gag induced poor CE-specific responses found only in 50% of the vaccinees. As for HIV CE, the SIV CE-specific responses were boosted by vaccination with DNA expressing complete Gag.

Conclusions: Combination of conserved elements and full-length immunogen provides a novel strategy to increase the magnitude and breadth of immune responses to Gag, and allows for the development and expansion of subdominant responses. This vaccine allows the immune system to target the 'Achilles heel' of the virus, for which few escape pathways exist. Inclusion of a conserved element immunogen provides an effective strategy to broaden responses against any highly diverse pathogen by avoiding decoy epitopes, while focusing responses to critical and invariable viral elements.