Novel Conserved Element HIV/SIV DNA Vaccines Maximize Breadth and Magnitude of Immune Response

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Background
HIV-1 sequence diversity and potential "decoy" epitopes are hurdles in the development of an effective AIDS vaccine. To target immune responses towards inevitable viral regions, we engineered DNA-based immunogens encoding conserved elements (CE) of HIV-1 selected on the basis of stringent conservation, functional importance, broad HLA-coverage, and association with viral control.

Methods
DNA vectors were generated expressing 7 co-linearly arranged CE from p24gag to cover >98% of group M sequences. By analogy, a similar vaccine was developed against SIV Gag. Heterologous DNA regimens of CE prime were followed by a boost with DNA expressing either full-length Gag or a combination of CE-full-length Gag. Immune responses were evaluated in macaques vaccinated by IM/intrapertion

Results
All HIV and SIV CE DNA-vaccinated macaques developed robust CE-specific memory responses with a significant fraction of cytotoxic T cells. In contrast, vaccination with HIV or SIV full-length gag DNA was very inefficient in inducing CE responses (50% responders, fewer CE recognized). Subsequent gag DNA vaccination significantly boosted the existing CE responses. Interestingly, vaccination with a combination of CE-gag DNA efficiently increased the breadth of pre-existing CE responses, indicating a significant change in epitope hierarchy both for the HIV and SIV vaccine regimens. The induced T cell responses rapidly disseminated into secondary lymphoid organs and effector mucosal sites. CE responses were maintained for ~2 years. A single booster vaccination with CE DNA resulted in rapid increase of pre-existing responses reaching up to ~7% of total T cells.

Conclusion
Priming with CE DNA is critical to induce broad responses to vulnerable sites of the virus while avoiding variable or decoy targets that may divert effective T cell responses towards less protective viral determinants. Combination of CE and full-length immunogens provides a novel strategy to increase the breadth and magnitude of cellular and humoral immunity. This strategy allows for the development of robust T cell responses targeting a broad number of epitopes, including subdominant conserved viral epitopes. The expanded breadth of the responses could provide an advantage in restricting viral propagation. This vaccine regimen is currently under development for testing in an HIV clinical trial.

Development of Unique Conserved Element (CE) Immunogens Targeting the Achilles’ Heel of HIV

Problem:
HIV sequence diversity and potential “decoy” epitopes are hurdles in the development of an effective AIDS vaccine

Solution:
Focus on conserved immunogenic core sequences to avoid non-escaped epitopes
- Focus on the immune response to Gag. Role of Gag responses in virus control in HIV infected humans and macaques

Identification of 7 Highly Conserved Elements

All 7 CE Are Immunogenic in Rhesus Macaques Inducing Cellular and/or Humoral Responses

Efficient Boosting of CE-specific Cellular Responses by Full-length p55

Optimized Conserved Element pDNA Vaccine Regimen (CE prime-ce-gag Boost) Maximizes Breadth and Magnitude of Cellular Immune Responses

CE DNA Vaccine Regimen Induces Long-Lasting Memory T-cell Responses that Are Rapidly Boosted upon a Single CE DNA Vaccination after ~2 Years of Rest

SIV CE Prime/Co-Delivery of SIV CE-gag pDNA Booster Vaccination Regimen Maximizes Breadth and Magnitude of Responses

Conclusions
- Conserved element CE pDNA vaccination targets the ‘Achilles heel’ of the virus, i.e., the highly conserved regions
- CE pDNA prime shifts the immunodominance hierarchy and induces immune responses to subdominant epitopes
  - Similar data were obtained for CE pDNA vaccines focusing on highly conserved regions in SIV Gag and in HIV Env
  - Combination of CE and full-length immunogens provides a novel strategy to increase the breadth and magnitude of cellular and humoral immunity
  - Development of robust T cell responses targeting a broad number of epitopes, including subdominant conserved viral epitopes
- CE pDNA vaccine regimen induces robust T cell responses in naive and SIV-infected animals
  - Application as preventive and therapeutic vaccine platforms

Summary

CE prime 100% response rate inducing T cell responses to highly conserved subdominant Gag epitopes

Induction of highly cytotoxic T cells

CE prime – gag pDNA boost Maximizes magnitude of CE response

CE prime – ce-gag pDNA boost Maximizes magnitude and breadth of CE response

CE pDNA prime/co-delivery of CE-gag pDNA booster vaccination regimen induces broadest responses

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