Novel Dendritic Cell Receptor-Targeted Multi-Antigen HIV Vaccine Induces Antigen-Specific Cellular and Humoral Immune Responses

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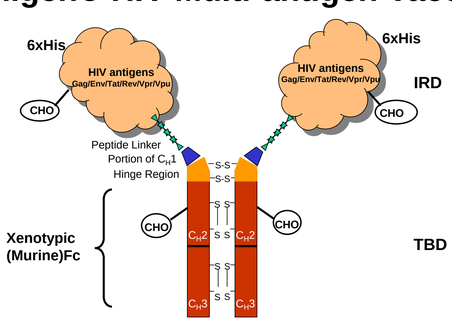
INTRODUCTION

Chimigen® Vaccines are chimeric recombinant fusion proteins of selected antigen(s) and specific xenotypic antibody fragments including the Fc region. These chimeric molecules bind to specific receptors on dendritic cells (DCs) and other antigen presenting cells (APCs) for antigen uptake. They are processed through both proteasomal and endosomal pathways and presented through MHC class I and class II molecules to T cells or B cells, generating cellular and humoral immune responses against the chosen antigens in the absence of any added adjuvant.

According to UNAIDS, an estimated 35 million people worldwide were living with HIV in 2012, and approximately 2 million people became newly infected. The current treatment for HIV infection, combination antiretroviral therapy (ART), can slow the progression of the disease; however, viral reservoirs persist in the body even with treatment. In addition, millions of infected individuals globally do not have access to ART. At present, there is no prophylactic or therapeutic vaccine available for HIV. Therefore, development of an effective and highly protective vaccine for HIV is a major global health priority.

Chimigen® Platform Technology has been used to design a novel DC receptor-targeted HIV vaccine that incorporates multiple HIV-1 antigens: Gag, Env, Tat, Rev, Vpr and Vpu. This vaccine is capable of inducing antigen-specific cellular and humoral immune responses and has prophylactic and early intervention therapeutic applications. In this study, we have evaluated the ability of the vaccine to elicit HIV antigen-specific T cell and B cell responses in PBMCs derived from uninfected healthy donors and in a rat animal model.

Chimigen® HIV Multi-antigen Vaccine



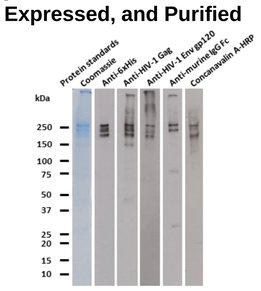
Unique Characteristics of a Chimigen® Vaccine

- Fusion protein comprised of antigen(s) (Immune Response Domain - IRD) and the Fc portion of a xenotypic monoclonal antibody (Target Binding Domain - TBD)
- Adaptable platform; can incorporate any relevant antigen into IRD
- Targets receptors on APCs, especially DCs
  - The TBD facilitates binding to Fcγ receptors
  - Glycosylation facilitates binding to C-type lectin receptors
- Increased immunogenicity due to the xenotypic nature of the TBD and expression in insect cells, which imparts non-mammalian glycosylation
- Antigen presentation *via* MHC class I and class II pathways
- Generates cellular and humoral immune responses; defined by IRD
- No added adjuvant
  - Eliminates many adverse events
  - Eliminates T cell sequestration, dysfunction & deletion
- Effective at low doses (µg)

RESULTS

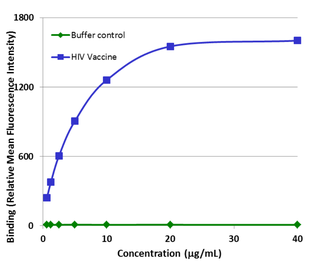
Characterization of the Chimigen® HIV Vaccine

Chimigen® HIV Vaccine was Cloned, Expressed, and Purified



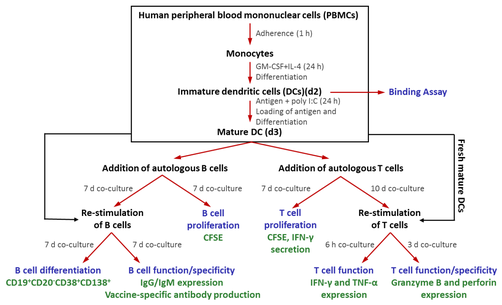
The N- and C-termini & HIV antigens are intact, and the vaccine is glycosylated

Binding of the Chimigen® HIV Vaccine to 48 h Cultured Immature DCs



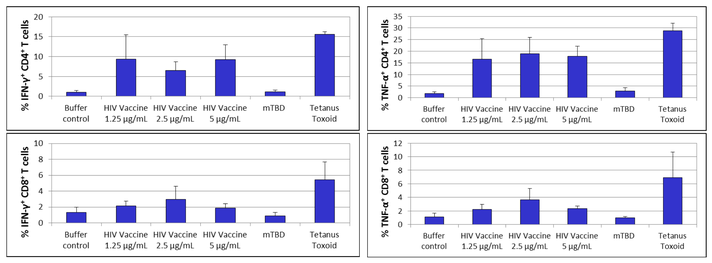
Binding of the vaccine to immature DCs is dose-dependent and saturable

Immune Responses, *ex vivo*: Antigen Presentation Assay (APA)



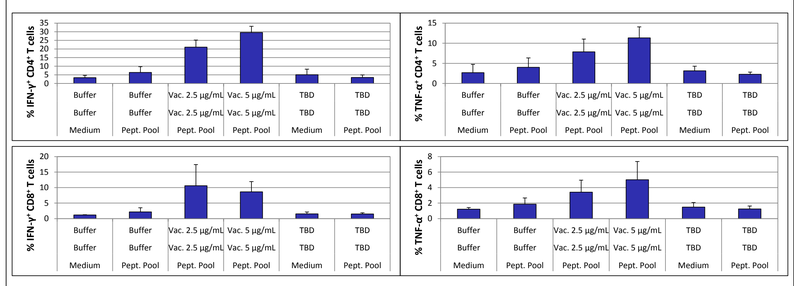
Chimigen® HIV Vaccine Induces IFN-γ and TNF-α Production in CD4+ and CD8+ T Cells

Induction of Th1 Cytokine Expression by the Chimigen® HIV Vaccine in T Cells Following Re-stimulation with Vaccine-loaded Mature DCs (Two Rounds of Antigen Presentation)



A second exposure of T cells to vaccine-pulsed mature DCs resulted in the enhanced expression of IFN-γ and TNF-α in both CD4+ and CD8+ T cells

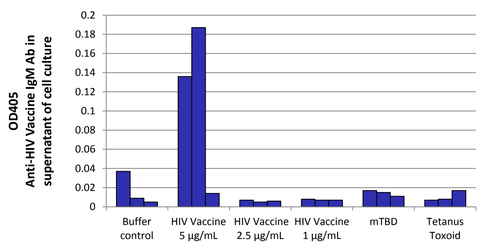
Induction of Th1 Cytokine Expression by Chimigen® HIV Vaccine in T Cells Following Stimulation with ProMix™ HIV Peptide Pool (Three Rounds of Antigen Presentation)



Vaccine-primed T cells re-stimulated with an HIV peptide pool showed an increase in CD4+ and CD8+ T cell IFN-γ and TNF-α production
Chimigen® HIV Vaccine induces an antigen-specific T cell recall response

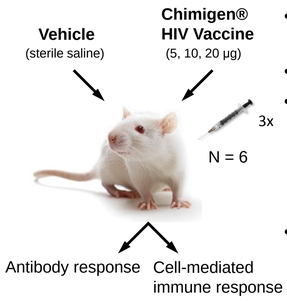
Chimigen® HIV Vaccine Induces Production of Antigen-specific IgM in B cells

Antigen-specific IgM Expression in PBMC-derived B Cells Following a Second Stimulation with the Chimigen® HIV Vaccine



Chimigen® HIV Vaccine stimulates the differentiation of B cells into plasma cells, which produce vaccine-specific IgM antibodies

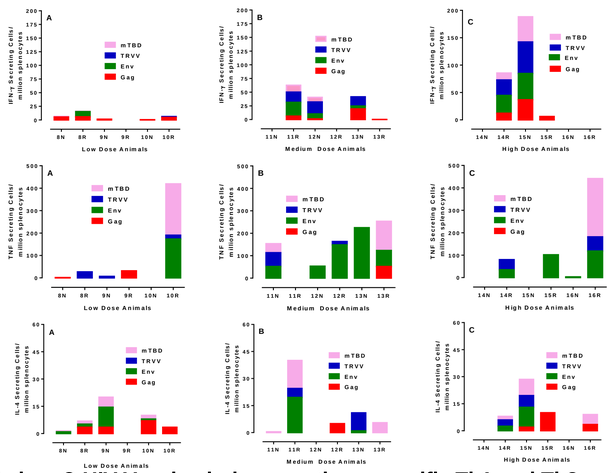
Immune Responses, *in vivo*: Sprague Dawley Rats



- Animals vaccinated subcutaneously three times (days 0, 28, and 56)
- Chimigen® HIV Vaccine dose: 5, 10, or 20 µg
- Splenocytes were isolated two weeks after the third immunization (day 70) to assay for specific T cell responses to the HIV antigens Gag, Env, and Tat-Rev-Vpr-Vpu (TRVV) and murine IgG1 Fc (mTBD) by ELISPOT
- Serum was sampled every week for ELISAs to measure antigen-specific antibody responses

Chimigen® HIV Vaccine Induces IFN-γ, TNF-α and IL-4 Secretion by Rat Splenocytes

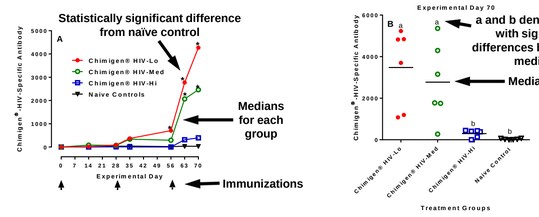
Summation of IFN-γ, TNF-α and IL-4 Secretion After the Third Immunization: Splenocytes Re-stimulated with Individual HIV Antigens (Recall Response)



Chimigen® HIV Vaccine induces antigen-specific Th1 and Th2 cytokine production in rat splenocytes

Chimigen® HIV Vaccine Induces Production of Vaccine-specific IgG

Vaccine-specific IgG Detected in Rat Serum Samples



The low and medium doses of Chimigen® HIV Vaccine induced significant vaccine-specific IgG antibody responses after the third immunization

CONCLUSIONS

- Chimigen® HIV Vaccine is immunogenic; induces antigen-specific T and B cell responses *ex vivo* (human PBMCs) and *in vivo* (rats)
- The vaccine binds to human PBMC-derived immature dendritic cells
- T cell response
  - Induction of Th1 and Th2 cytokine production (IFN-γ, TNF-α and IL-4)
  - Vaccine induces a T cell response in all rats except one
- Antibody response (IgM, IgG)
  - Response is dependent on dose
  - Significant response following the third immunization in rats
- No added adjuvant; effective at low doses
- Chimigen® HIV Vaccine is very effective at inducing systemic cellular and humoral immune responses, and therefore, shows potential for development as a prophylactic/early intervention therapeutic HIV vaccine

Acknowledgements

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