Chimigen® HIV: A Novel Dendritic Cell Receptor-Targeted Multi-Antigen HIV Vaccine

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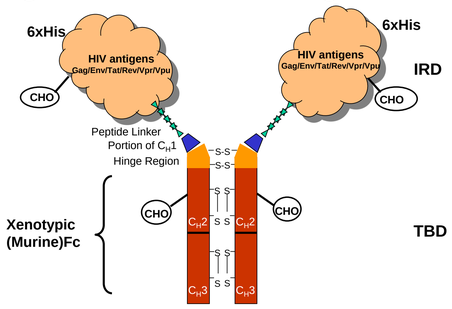
INTRODUCTION

Chimigen® Platform Technology has been used to design a novel dendritic cell (DC) receptor-targeted HIV vaccine that incorporates multiple HIV-1 antigens and is capable of inducing antigen-specific cellular and humoral immune responses for prophylactic and early intervention therapeutic applications.

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 DCs and other antigen presenting cells for antigen uptake. They are processed through both proteasomal and endosomal pathways and presented to T cells through MHC class I and class II molecules, stimulating cellular and humoral immune responses against the chosen antigens.

The Chimigen® HIV Vaccine, containing the HIV-1 Gag, Env, Tat, Rev, Vpr and Vpu antigens, was expressed in Sf9 insect cells and purified. DC-binding experiments and antigen presentation assays using human peripheral blood mononuclear cell-derived DCs, T cells and B cells *ex vivo* demonstrated that the Chimigen® HIV Vaccine binds to immature DCs in a dose-dependent manner, induces $CD4^+$ and $CD8^+$ T cell activation and proliferation, and promotes increased production of IFN-γ and TNF-α from both $CD4^+$ and $CD8^+$ T cells. Furthermore, B cells stimulated with vaccine-loaded DCs produced antigen-specific IgM antibodies. Evaluation of immune responses to the vaccine *in vivo*, in Sprague Dawley rats, confirmed that all antigenic components of the HIV vaccine are immunogenic and that the vaccine induces both HIV-specific cell-mediated and humoral immune responses. This study established safety and "proof of concept" and therefore shows potential for development of the Chimigen® HIV Vaccine as a prophylactic/early intervention therapeutic vaccine against HIV infections.

Chimigen® HIV Multi-antigen Vaccine



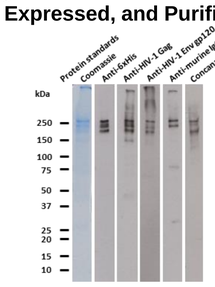
Unique Characteristics of a Chimigen® Vaccine

- 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
- A COVID-19 Multi-antigen Vaccine is currently in development
- 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

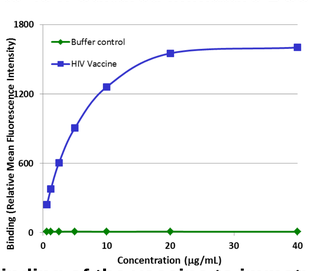
Characterization of the Chimigen® HIV Vaccine

Chimigen® HIV Vaccine was Cloned, Expressed, and Purified



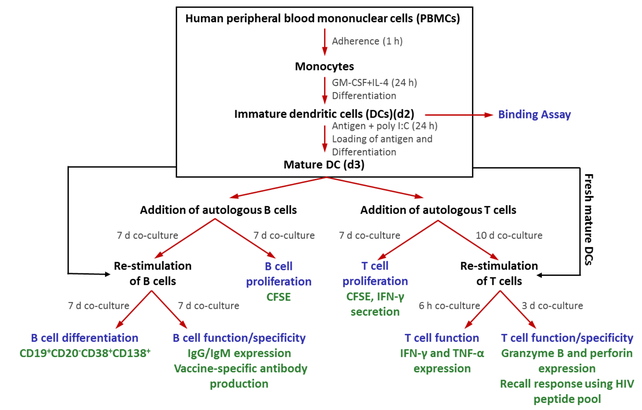
The N- and C-termini & HIV antigens are intact, and the vaccine is glycosylated

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



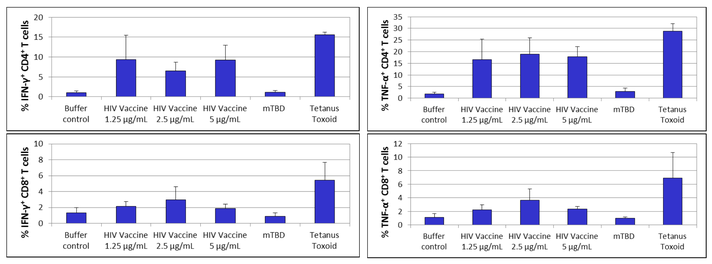
Binding of the vaccine to immature DCs is dose-dependent and saturable

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



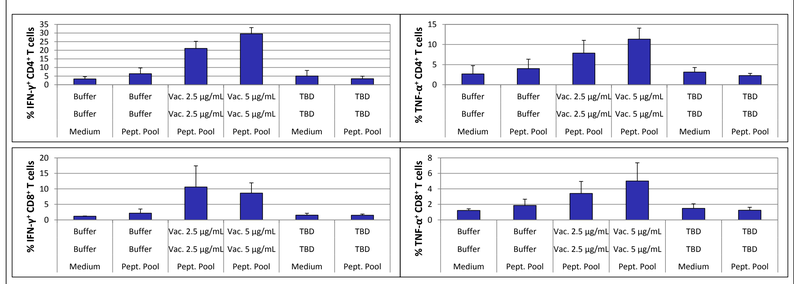
Chimigen® HIV Vaccine Induces IFN-γ and TNF-α Production in $CD4^+$ and $CD8^+$ T Cells

Induction of Th1 Cytokine Expression by Chimigen® HIV Vaccine in T Cells Following Re-stimulation with Vaccine-loaded Mature DCs



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

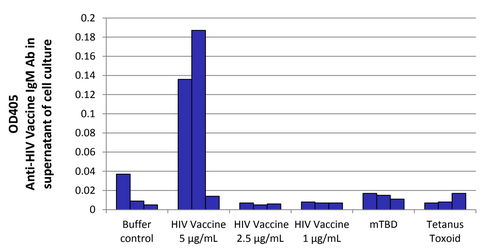
Induction of Th1 Cytokine Expression by Chimigen® HIV Vaccine in T Cells Following Re-stimulation with an HIV Peptide Pool (Recall Response)



Chimigen® HIV Vaccine induces antigen-specific IFN-γ and TNF-α production in vaccine-primed T cells re-stimulated with the ProMix™ HIV peptide pool

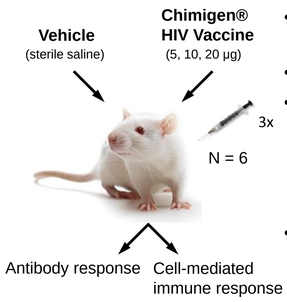
Chimigen® HIV Vaccine Induces Production of Antigen-specific IgM in B cells

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

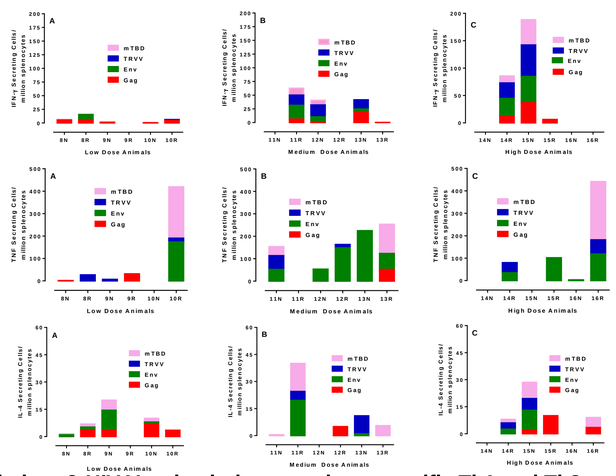
Immune Responses, *in vivo*: Sprague Dawley Rats



- 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

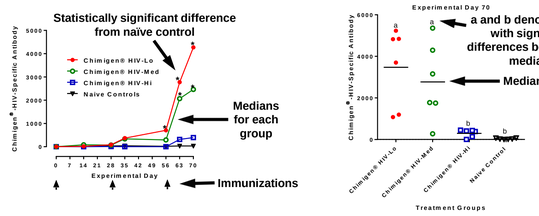
Summation of IFN-γ, TNF-α and IL-4 Secretion After the Third Immunization: Splenocytes Re-stimulated with Individual HIV Antigens (Recall Response)



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
  - Production of IgM (measured *ex vivo*), and IgG (*in vivo*)
  - 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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