We hypothesize that 3S, a highly conserved motif of HIV-1 gp41, is a key target for an immunotherapeutic and immunoprotective vaccine (1-4). This peptide binds to gp41, leading to expression of CD4+ MHC-I on CD8+ T cells (CD4). This interaction induces a molecular pathway that leads to expression of CD95 on the surface of CD8+ T cells (M44). M44 is the natural ligand of Fas (CD95), which expresses as an activated natural killer (NK) cells. M44/M44 interaction provokes NK-mediated cytotoxicity via apoptosis of CD8+ T cells. The apoptosis of CD8+ T cells may indirectly induce inflammation and chronic immune activation (3-5).

Proof-of-concept in a non-human primate model for AIDS was carried out with nine cynomolgus macaques that were chronically infected with the SFOE virus. Four immunized with the S30 peptide containing vaccine and control with the virus control. CD8+ T cells, salivary, porcine, cell activation and apoptosis were analyzed in the peripheral blood, the lymph nodes, spleen and rectum by flow cytometry. Anti-3S antibodies were shown to prevent M44 expression on CD8+ T cells or visa versa preventing the peripheral blood CD8+ T cells in S30-vaccinated animals. Anti-3S antibodies also limited the NK cytotoxic activity against autologous CD4+ T cells. CD4 activation, proliferation and apoptosis in secondary lymphoid tissue (SL). VAC-3S-dose ranging, GTP toxicity and local tolerability assessments were performed in rhesus (5).

We have thus developed a novel immunotherapeutic vaccine (VAC-3S), comprised of 3S and commercially used carrier protein and adjuvant (7,10). Secondary endpoints include NKp44L expression, lymphocyte activation/differentiation. We hypothesize VAC-3S therapeutic effect would encompass the following clinical applications & benefits: VAC-3S vaccine has shown safety, evidence of immunogenicity at 10 µg dose (6). The gp41 3S motif of HIV-1 binds to its specific receptor (gC1qR) on CD4+ T cells (6).

In 3S-immunized depleted and activated of CD8+ T cells, Example by (C) higher absolute central memory CD8+ T cell counts from peripheral blood of 3S-vaccinated macaques (solid lines or closed bars) compared with controls (dotted lines or open bars).

Clinical observation: anti-3S antibodies in 5 cohort studies (Total N=923 patients) correlated with a lack of CD4 decrease and/or HIV disease progression (4,5 and InnaVirVax / in vivo data on file). We have thus developed a novel immunotherapeutic vaccine (VAC-3S), comprising of 3S and commercially used carrier protein and adjuvant (7,10).

Methods

The first-time-in-human clinical trial is a phase I dose-ranging / safety study in 12 healthy volunteers (6). The four doses were 100, 1000, 10,000, and 100,000 µg of VAC-3S (6). The primary safety endpoints were side effects, laboratory toxicities, and local reactions (6).

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