Background: Failure to induce broadly neutralizing antibodies to the CD4 binding site (CD4bs) is commonly associated with incomplete and variable induction of antibodies to CD4bs-dependent and CD4bs-independent mutations of antibody germline genes. Our approach to HIV vaccination derives from the observation that antibodies recognize epitopes of both the CD4bs and the primary interaction site (PIS) of the virion envelope glycoprotein gp120. A coreceptor-dependent vaccine approach thereby involves eliciting antibodies to the CD4bs and PIS-CD4bs epitopes. This Vaccine design enables CD4bs recognition by a small antibody subset produced constitutively by non- infected human B cells. CD4-specific antibodies induced in this way amplify the responses to an electrophilic gp120 gp120 vaccine that binds and stimulates B cell co-stimulators.

Methods: Antibodies were isolated and induced using electrophilic phosphate-containing glycoprotein (E-gp120) and a peptide spanning the CD4bs (P49HD-6S-416-433). Neutralization of autologous HIV isolates was tested by measuring inhibition of peripheral blood mononuclear cells (PBMCs). Antibody titers were compared to those elicited by LDAg. Antibodies were isolated from sera of vaccinated monkeys by affinity chromatography.

Results: About 0.05% of serum antibodies and recombinant antibody fragments specific for the CD4bs isolated were polyclonal from non-immunized humans neutralized diverse HIV strains, including 35 of 39 HIV-1 clinical isolates. CD4bs antibodies isolated from rhesus monkeys with 10 μg of E-gp120 induced a mixture of neutralizing and non-neutralizing antibodies that neutralized subtypes A, B, C and D of HIV. The CD4bs-specific antibodies neutralized more than 100 covalent immunizations but neutralized the contemporary inactivated HIV isolate, suggesting the absence of an escape mutant.

Conclusions: Amplification of the subset of constitutive antibodies specific for the CD4bs is a viable route to HIV vaccination. Electrophilic gp120 is suitable for further development as a candidate HIV vaccine capable of inducing broadly neutralizing antibodies.

INTRODUCTION

No effective HIV vaccine is available. Numerous polyclonal immunogens are highly mutable, and cannot elicit epitopes of sufficient affinity to induce broadly neutralizing antibodies, and (3) The number of naive CD4+ T cell receptors capable of producing CD4-specific antibodies is so large that vaccination is unlikely to induce antibodies that neutralize the contemporary inactivated HIV isolate, suggesting the absence of an escape mutant.

The CD4bs is a potential vaccine target. Unlike other vaccine targets, the CD4bs is a superantigen epitope. While superantigens are buried by germline antibodies, they are accessible to CD4bs antibodies. They can induce the selection of B cells capable of responding to this epitope. In humans, CD4bs antibodies can be induced by vaccination with electrophilic gp120.

METHODS

Electrophilic and isoelectronic gp120 (CD4bs)-glyco and gp120-416-433 contain the conserved subunit gp120 416-433 and the chemically electrophilic or neutral gp120 conjugates (E-gp120 and E-gp120-416-433). The gp120 and gp120-416-433 preparations were as in [5]. Preparation of gp120, the electrophilic conjugates of length gp120, and neutral conjugates of gp120-416-433 were compared to those of a competitive pressure of antibodies to the CD4bs.