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Letter

HIV-1 candidate vaccines can induce antibodies which share specificity with human monoclonal antibodies capable of neutralizing primary isolates

Sera from individuals involved in trials of candidate human immunodeficiency virus type 1 vaccines fail to neutralize primary strains of the virus[1,2]. Although these sera neutralize cell-line adapted strains, primary strains are more likely to reflect the properties of virus involved in natural challenge. Their failure therefore represents a potential constraint on the progress towards the adoption of these vaccines for phase III trials. However, primary strains are not inherently resistant and can be neutralized by sera from seropositive patients and by monoclonal antibodies[3]. While human, neutralizing monoclonal antibodies bind preferentially to multimeric glycoproteins[4], some also bind to monomeric, recombinant HIV-1 envelope glycoproteins similar to those used in human vaccine trials[5,67]. Their epitopes are therefore exposed and available to induce antibodies when such recombinant glycoproteins are used as vaccines. This work was undertaken to determine whether these epitopes are immunogenic.

Three human monoclonal antibodies, IgG1 b12 to the CD4-binding site[5], supplied by Dr Dennis Burton (Scripps Research Institute), 447-52D to the V3 region[6] and 697-D to the V2 region[7] (Cellular Products, Buffalo) were radiolabelled[8] and separately mixed with a dilution series of sera from sheep injected with recombinant envelope glycoproteins of HIV-1. The mixtures were allowed to bind to solid-phase glycoproteins, prepared as previously described[8], and the antibody which bound in the presence of competing antibodies was expressed as a percentage of that bound in their absence. Sera from non-injected sheep were included as control. Sera and recombinant products were supplied through the MRC AIDS directed programme reagent project. The sera were raised by Dr Mark Page of the National Institute for Biological Standards and Control, Potters Bar to CHO-derived HIV-1 SF2 (Chiron) or BH10 (Celltech) gp120, or baculovirus-derived HIV-1 IIIB gp120 (American Biotechnologies Inc.) or gp160 (MicroGeneSys) or vaccinia-derived HIV-1 IIIB gp160 (Immuno). Sheep were primed with 100–250 mg in Freund's Complete

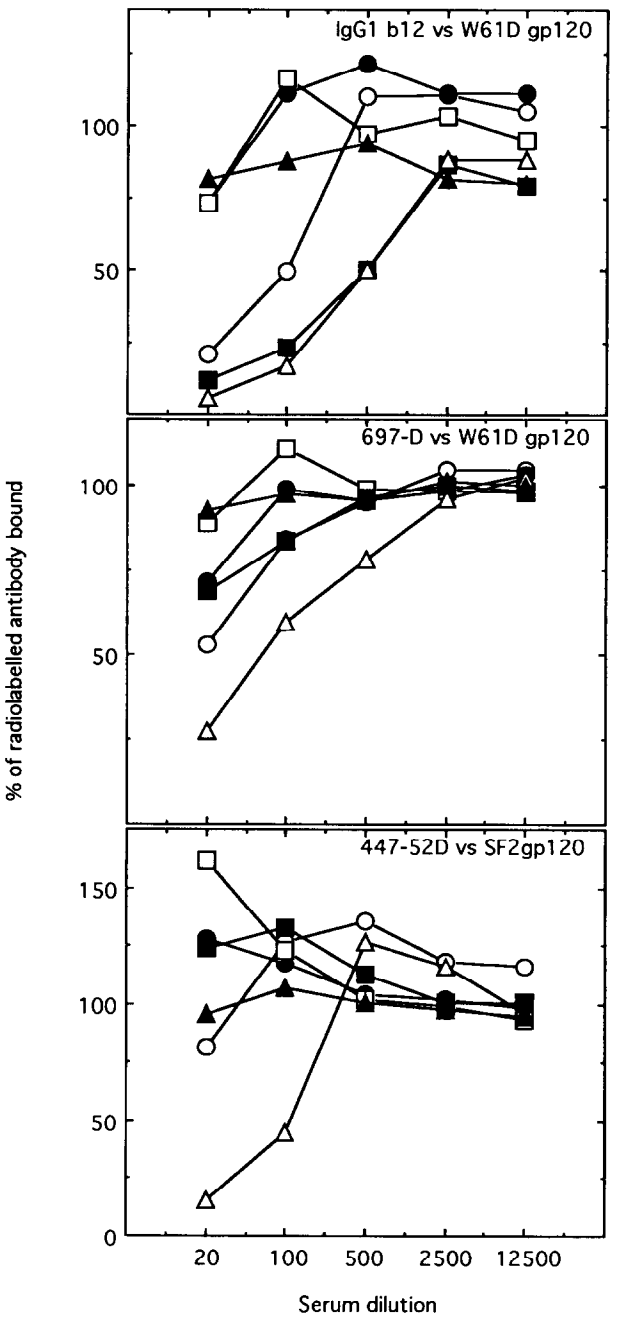

Figure 1 Inhibition of binding of radiolabelled human monoclonal antibodies, IgG1 b12 to the CD4-binding site, 447-52D (V3) or 697-D (V2), to solid-phase HIV-1 W61D gp120 or HIV-1 SF2 gp120 by dilutions of sera from sheep injected with recombinant envelope glycoproteins: CHO-derived HIV-1 SF2 (Chiron △) or BH10 (Celltech ○) gp120, or baculovirus-derived HIV-1 IIIB gp120 (American Biotechnologies Inc. ■) or gp160 (MicroGeneSys ●) or vaccinia-derived HIV-1 IIIB gp160 (Immuno □). Sera from non-injected sheep were included as control (▲)

Adjuvant and boosted at monthly intervals with immunogen in Freund's Incomplete Adjuvant. Solid phases were prepared from HIV-1 SF2 gp120, supplied by Dr Nancy Haigwood (Chiron) or HIV-1 W61D gp120 supplied by Dr Claudine Bruck (SmithKline Beecham).

Antibodies to the external envelope glycoprotein (gp120) but not its precursor (gp160) competed at all three epitopes (*Figure 1*). Some specificity of binding between the polyvalent antisera and the solid-phase antigen may be required for competition to occur within the V3 region since antibodies to HIV-1 IIIB but not HIV-1 SF2 gp120 competed with 447-52D when HIV-1 IIIB gp120 was used as solid phase (data not shown).

Currently available candidate vaccines therefore have the potential to produce antibodies capable of neutralizing primary strains. Several factors may contribute to the failure to detect these antibodies. Firstly, powerful adjuvants may be required to produce them with an adequate titre. Freund's adjuvants were used to raise antisera in the sheep but these are not available for human use. Alternatively, antibodies may not share the precise specificity as the neutralizing monoclonal. High titres of antibodies can be detected to solid-phase peptides representing the homologous V3 region in the sheep serum to HIV-1 SF2 gp120 (data not shown), but these fail to compete when heterologous gp120 is used as solid phase. A third option is that antibodies are produced but their effect is balanced by the presence of enhancing antibodies. Point mutations can render cloned, primary isolates either resistant to neutralization or susceptible to enhancement to the same monoclonal antibody[9]. Most primary isolates are heterogeneous so that antibodies may neutralize one genotype while enhancing the infectivity of another within the same mixture of polymorphic variants.

It is possible that a new generation of oligomeric, recombinant products will need to be developed to produce an effective vaccine. However, a strategy involving priming of the immune response with recombinant glycoproteins and boosting selected epitopes with peptides would have the advantage of utilizing the known safety of the currently available monomeric candidates. Peptides which bind to human neutralizing monoclonal antibodies could be constructed with mimotope technology[10].

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