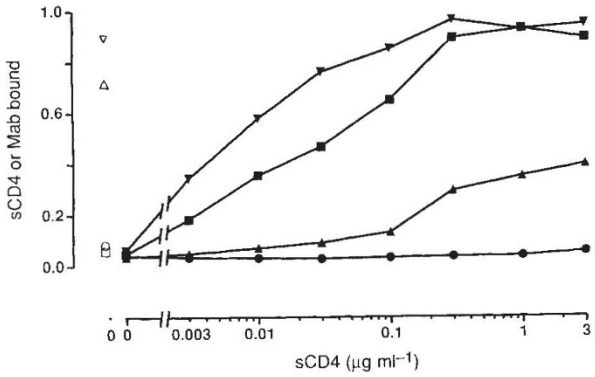
Which gp160 vaccine?

SIR — The lobbying efforts by MicroGeneSys Inc. (MGS) to win 'pork-barrel' funding from the US Congress for its HIV-1 gp160 vaccine candidate have attracted much criticism[1,2]. Little attention has, however, been paid to the actual product, which is a baculovirus-expressed, recombinant version of the outer envelope glycoprotein precursor gp160 from the HIV-1 LAI isolate.

Many companies and research laboratories have produced gp160 or its derivative gp120 for research or clinical purposes, including American BioTechnologies Inc., Celltech Ltd, Chiron Inc., Genentech Inc., Immuno AG, Repligen Inc., Smith–Kline Beecham Biologicals SA and Transgène SA. Without exception, their products are predominantly native glycoproteins which bind CD4 with high affinity. Uniquely, MGS has made a gp160 molecule which is misfolded and substantially denatured and which binds CD4 very poorly compared with others (see figure). The residual CD4 binding to MGS gp160 probably reflects the presence of a small percentage of native molecules in the product, rather than a homogeneous product of low affinity for CD4, although we cannot be certain of this. If so, we estimate that the active fraction is considerably less than 1% of the total. Similarly, the gp120 sold by MGS binds CD4 extremely poorly[3].



Binding of sCD4 to different recombinant gp120/gp160 preparations. gp120 (0.1 μg ml^{-1}) or gp160 (0.5 μg ml^{-1}) in TBS containing 10% FCS and 1% NP-40 nonionic detergent was captured onto a solid phase via sheep antibodies to the last 15 amino acids of gp120 (ref. 3). sCD4 was titrated against each gp120 and bound sCD4 (closed symbols) was detected with anti-CD4 antibodies[3]. The presence of gp160 on the solid phase was confirmed using human monoclonal antibody 50-69 to the immunodominant region of gp41 (open symbols), a gift from S. Zolla-Pazner. No gp120/gp160 (○, ●); Celltech CHO-expressed LAI gp120 (□, ■); MGS baculovirus-expressed LAI gp160 (△, ▲). Smith–Kline Beecham Biologicals vaccinia-expressed LAI gp160 (▽, ▼). The last two proteins were obtained from the UK MRC AIDS-Directed Programme. We tested two batches of MGS gp160; data from that giving the stronger sCD4 binding are shown.

Because of the predominantly denatured state of MGS gp160, it does not detectably bind neutralizing, human monoclonal antibodies to discontinuous or conformationally sensitive gp120 epitopes (G. K. L. *et al.*, manuscript in preparation). Neither have we been able to isolate murine hybridomas specific for such epitopes after immunization with MGS gp160; all the antibodies recognize linear epitopes and most bind poorly, if at all, to native, recombinant gp120. Antibodies against conformational or discontinuous epitopes of gp120 are far more prevalent than those to linear epitopes in HIV-1-infected people and are responsible for much of the neutralizing activity in serum[4–6]. Thus MGS gp160 is unable to mimic the native glycoproteins normally seen by the human immune system. Furthermore, because the MGS protein is derived from the LAI sequence, its principal neutralizing V3 domain is not representative of the types of virus circulating in the population[7]. Consequently, MGS gp160 induces V3 loop antibodies capable of cross-reactivity with more representative V3 loops only very inefficiently[8]. Moreover, inbred strains of mice immunized up to six times with MGS gp160 lacked any serum-neutralizing antibodies, in marked contrast to their responses to native gp120s from other manufacturers[8]. Other studies with denatured envelope glycoproteins have confirmed their inferior immunogenicity compared with native forms[9,10].

It is by no means certain that immunotherapy with envelope glycoproteins will be beneficial to its recipients; available results from pilot studies with MGS gp160 appear to be disappointing[11,12]. But if social and political pressures force the undertaking of large-scale clinical trials, it is crucial that they do not focus only on a single product. Better quality native gp120 or gp160 proteins are available from several other sources, in some cases with a V3 loop sequence more relevant than that of HIV-1 LAI (refs 10,13).

We do not know what form of envelope glycoprotein is best for use *in vivo*. The optimal properties of a recall antigen or an inducer of cellular immunity may differ from those of a stimulator of a *de novo* antibody response. However, uptake of gp120 into monocytes for processing and antigen presentation can be a CD4-dependent process[14] which presumably is most efficient with a native form of gp120. To determine these factors, different immunogens would need to be evaluated in small-scale comparative studies. However, *in vitro* analyses and immunogenicity studies in small animals do have a bearing on the ability of MGS gp160 to stimulate humoral immunity. The information described here strongly suggests that the ability of MGS gp160 to induce the production of relevant antibodies is severely limited by its properties. Its failure to act as an efficient inducer of neutralizing antibodies in mice bodes ill for its likely activity in humans.

Although broadening the immune response to HIV proteins may be useful[15], it is not clear to us what is the importance for humoral immunity of antibodies raised to a denatured protein that are unable to recognize native viral glycoproteins. In short, based on existing *in vitro* data, our opinion is that there could not be a worse choice from the current envelope glycoprotein vaccine candidates than MGS gp160 to stimulate at least one important arm of the human immune system, the production *de novo* of cross-neutralizing antibodies to the V3 loop and discontinuous epitopes around the CD4-binding site.

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