

Abstract

Research towards an effective HIV-1 vaccine has been ongoing for almost four decades with no vaccine candidate showing a clear ability to induce a protective immune response. The main challenge has been the inability of currently tested immunogens to elicit potent, broadly neutralizing antibodies (bNAbs). Conventional immunogen approaches are based on HIV-1 envelope glycoproteins (Env) that are structurally stable and as close to the native HIV-1 trimer conformation as possible, for example SOSIP trimers. In addition, such immunogens should have antigenic capabilities of displaying the correct neutralizing antibody (nAb)-inducing epitopes common among the extremely high genetically diverse HIV-1 isolates, while at the same time, masking immunodominant but irrelevant sites. As such, novel insights into HIV-1 immunogen designs, in particular the differential display of conserved epitopes and the resulting effect on the immune system is beneficial to vaccine development.

Work done previously has shown that covalently complexing various HIV-1 Env to two-domain CD4^{S60C} (2dCD4^{S60C}) has resulted in immunogens capable of eliciting a consistent antibody-mediated immune response in small animals, that is broad and potent. The aim of this work was to develop a next generation immunogen composed of a SOSIP trimer covalently complexed to 2dCD4^{S60C}. An HIV-1 founder virus consensus C Env (FVC_{ENV}) which epitomizes all the collective properties of subtype C transmitted/founder (T/F) viruses) and the well characterized subtype A BG505 Env (control) were used in this study and each were covalently coupled to a 2dCD4 protein to form Env:2dCD4 complexes. The structural and conformational stability of the complexes were tested by evaluating the ability of broadly neutralizing antibodies to effectively recognize the immunogens in ELISA. Conformational dynamics studies - used to probe some of the attributes of the covalently complexed immunogen – were done on the FVC_{ENV} covalent immunogen complex (FVC_{ENV}:2dCD4^{S60C})

in comparison to its non-covalently bound equivalent complex ($\text{FVC}_{\text{Env}}:2\text{dCD4}^{\text{WT}}$). Lastly, the immunogenicity of the covalent complexes ($\text{FVC}_{\text{Env}}:2\text{dCD4}^{\text{S60C}}$ and $\text{BG505}_{\text{Env}}:2\text{dCD4}^{\text{S60C}}$) was established in rabbits by testing the presence and scope of antigen recognizing antibodies in the rabbit sera following immunization and using the Env-pseudotyped neutralization assay against a panel of heterologous Tier 2 viruses.

The newly created covalent bond effectively locks the $\text{FVC}_{\text{Env}}:2\text{dCD4}^{\text{S60C}}$ immunogen in the open, CD4-bound conformation thereby exposing the highly conserved CD4 induced epitopes. Hydrogen-deuterium exchange experiments revealed that covalent linkage between Env and 2dCD4 result in a drastic change in the dynamics and solvent exposure of domain 2 of CD4, which advances our knowledge of the improved immunogenicity of the complex. The founder virus consensus C envelope (FVC_{Env}) trimer covalently complexed to 2dCD4 remarkably displayed optimal immunogenicity, with all the rabbits who received the complex showing the ability to elicit antibodies with up to 76,5% breadth (13 out of 17 heterologous viruses neutralized). Such consistently elicited immune responses from a singular adjuvanted recombinant protein immunogen administered in a simple regimen are encouraging and underscore the potential of this SOSIP immunogen as a prime candidate for further developments of vaccine regimens.

The findings highlighted in this study provide evidence that an efficient bNAb response can be successfully elicited in a pre-clinical setting using SOSIP.664 Env-based immunogens designed to expose conserved epitopes. The high success rate (5/5 animals) in inducing a strong immune response and the magnitude of the response (high titers) against some of the viral isolates show the potential sustainability of the antibody response and the feasibility that small improvements to the immunogen complex and/or the immunization strategy could yield a ‘panacea’ immunogen.