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# The HIV-1 Glycan Shield: Strategically Placed Kinks in the Armor Improve Antigen Design

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**Dense glycosylation on the HIV-1 envelope glycoprotein hampers the induction of broadly neutralizing antibodies against HIV-1. Zhou et al. remove key glycans to unmask sites of vulnerability and enable the induction of neutralizing antibodies.**

The HIV-1 envelope glycoprotein is decorated with a dense array of glycans that masks nearly the entire surface of the infectious envelope, posing a significant barrier to antibodies that aim to target sites of neutralization vulnerability. Thus, the HIV-1 envelope glycan shield has been regarded as a significant impediment to the induction of protective antibody responses (Wei et al., 2003). However, emerging antibody isolation technologies linked to sophisticated structural analyses have shown that viral glycans are tolerated near broadly neutralizing antibody epitopes and commonly form part of the epitopes themselves (McCoy and Burton, 2017), arguing that antibodies are able to work around the glycan shield to access the viral protein surface. Moreover, while broadly neutralizing antibodies recognizing glycans alone are rare, glycan-dependent HIV-1 neutralizing antibodies that target a combination of glycans and the underlying protein (glycopeptide) are not uncommon. In fact, these glycopeptide-targeting antibodies are frequently generated during natural infection (Cohen et al., 2015), suggesting that an HIV-1 vaccine able to drive humoral immunity that may overcome or tolerate the glycan shield may successfully induce broadly neutralizing antibodies. However, the development of broadly neutralizing antibodies during infection takes years, often requiring extensive affinity maturation and unusual antibody modifications to reach the HIV-1 envelope between glycans. Thus, approaches are urgently needed to accelerate this process.

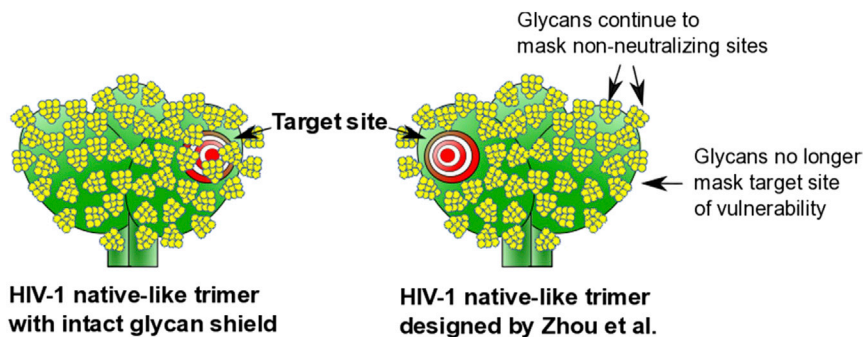
In this issue of *Cell Reports*, Zhou et al. (2017) explore a new immunization strategy aimed at initiating the evolution of broadly neutralizing antibodies to protein epitopes within key sites of viral vulnerability that may then evolve with later boosts to tolerate glycans. Specifically, they attempt to facilitate the induction of humoral immunity to the CD4 receptor binding site by using native-like soluble envelope protein immunogens with deletions of key blocking glycans surrounding the CD4 binding site, enabling easier access for B cell receptors to the underlying protein epitope (Figure 1). This strategy builds on the observation that glycan “holes” in the HIV-1 envelope trimer protein allow antibodies to evolve to exposed protein surfaces, providing a means to focus the immune response upon vaccination (McCoy et al., 2016). Along the same lines, removal of a single glycan proximal to the CD4 binding site enabled the binding and activation of CD4 binding site-specific antibody B cell receptor precursors that were otherwise blocked by the glycan (McGuire et al., 2013).

To rationally design an optimal CD4 binding site glycan “hole,” Zhou et al. (2017) model the dynamics of the HIV-1 glycan shield on the crystal structure of native-like soluble envelopes. They then generate immunogens of HIV-1 clade A, B, and C with three to four glycan deletions based on those most likely to interfere with access of the CD4 binding site-specific broadly neutralizing antibody, VRC01. The optimized immunogens maintain a desired prefusion-closed state, as demonstrated by negative stain EM. They also exhibit enhanced binding

to CD4 binding site-specific broadly neutralizing antibodies, highlighting the impact of glycan removal on improved CD4 epitope antigenicity. Guinea pigs and rhesus macaques vaccinated with the glycan-optimized mutants generate neutralizing responses against the CD4 binding site of autologous glycan-optimized mutants, but these responses are unable to neutralize wild-type glycosylated viral variants. However, the HIV-1 clade C CH505 glycan-optimized variant can induce a CD4 binding site-specific serum response with substantial neutralization breadth against glycan-deleted envelope proteins in guinea pigs and rhesus macaques. The neutralizing breadth induced by this immunogen can be further increased following vaccination with a mix of glycan-deleted immunogens from different viral clades. Finally, to determine if the size of the access surface area around a vulnerable site plays an essential role in immune focusing, they immunize with glycan-depleted immunogens where only single deleted glycans were reintroduced. The efficiency of vaccine-induced serum neutralization is directly and proportionally linked with surface area accessibility, highlighting the critical need to design holes in a rational and strategic manner.

Unlike previous studies, Zhou et al. (2017) integrate molecular dynamics modeling to design optimal glycan “holes” within the HIV-1 glycan shield to generate their glycan-optimized candidate immunogens. Thus, the authors are able to both exploit the blocking effects of the glycan shield to prevent the induction of non-neutralizing antibody





**Figure 1. The HIV-1 Envelope Is Covered by a Dense Array of Glycans—Termed the Glycan “Shield”—which Block Antibody Access to Sites of Vulnerability, Preventing the Induction of Broadly Neutralizing Antibodies**

Zhou et al. (2017) used molecular dynamics modeling to identify a specific set of glycans that, once removed, created a glycan “hole” that improved immunogen antigenicity and resulted in the induction of neutralizing antibody responses.

responses and exploit glycans to focus the immune response to a key site of vulnerability. This strategy enables modeling of the consequences of glycan deletions on both neighboring and distant glycan mobility and interactions that can both directly or indirectly impact antibody access and antigenicity (Behrens et al., 2016), providing critical insights into the link between surface area accessibility and neutralization. While others have aimed to develop minimal scaffolded antigens that mimic the CD4 binding site (Briney et al., 2016), Zhou et al. (2017) offer a simple solution to focus the initial humoral immune response to sites of neutralizing vulnerability via the simple exploitation of the glycan shield. The data suggest that the glycan-deleted immunogens may be

suitable as the first antigen in a sequential HIV-1 vaccine strategy, aimed at kick starting the humoral immune response, which may be followed by fully glycosylated, otherwise-engineered immunogens or even combinations of immunogens aimed at broadening the response. However, the authors leave room for speculation related to the utility of this methodological approach to focus the immune response to other sites on the viral envelope, as well as related to the overall comparability of this approach to the minimal antigen-design strategies.

In summary, Zhou et al. (2017) demonstrate that a targeted CD4 binding site-specific neutralizing antibody response can be induced via the design of immunogens that permit unhindered access to the

targeted epitope. Thus, Zhou et al. (2017) describe a novel class of immunogens that provide an exciting straight-forward solution to focus the immune response to key sites of viral vulnerability.

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