



When On-Target Misses the Mark: Lessons from HIV Immunogens

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Despite 40 years of intense research, the [urgently-needed](#) vaccine for HIV still eludes us.

The target of the HIV vaccine is the surface glycoprotein *Env*, which initiates viral entry into host cells and is blocked by neutralizing antibodies. Due to immense immune pressure and the high error rate of HIV's reverse transcriptase, *Env* has exceedingly high levels of sequence diversity. It is estimated that *Env* can vary by 30%-35% between HIV lineages.

Therefore, it's crucial that an Env-targeting HIV vaccine induces broadly neutralizing antibodies (bnAbs) that bind conserved epitopes and neutralize infection by many strains. This is quite challenging: even during natural infection, many people never develop bnAbs. Those that do often acquire them after prolonged immunogenic stimulation from months or years of high viral load.

It's been especially difficult to make HIV neutralizing antibodies via vaccination. In fact, Fred Hutch researchers were the [first to report](#) induction of HIV neutralizing antibodies from a subset of vaccinated volunteers—and that was only last year! (Other Fred Hutch researchers are taking a different approach by engineering B cells to produce bNabs directly: check out this month's feature on the one such study from the Kiem Lab [here](#).)

One particularly potent group of HIV bnAbs that vaccine researchers focus on is called VRC01-class antibodies. When made in a lab and passively infused into animals or vulnerable people, VRC01-type antibodies can block infection by many HIV subtypes.

However, VRC01-class antibodies are difficult to generate. This is for a few reasons: 1) their specific heavy and light chain composition are rare—only about 1 in 300,000 B cells have this pairing—and 2) they are heavily mutated away from the germline sequences of the naïve precursor B cells.

Another challenge is that unmutated VRC01 precursor B cells don't bind recombinant *Env* and cannot neutralize HIV. Instead, the response to *Env* is typically off-target—meaning that the majority of antibodies produced are non-VRC01 and react with non-conserved epitopes.

So, how do we guide the development of VRC01-type antibodies through HIV vaccination?

This question motivates the [McGuire](#) and [Stamatatos](#) Labs in the Vaccine and Infectious Disease Division. They have a long-standing collaboration on HIV vaccine design using bespoke immunogens.

“It’s widely expected that eliciting broadly neutralizing antibodies against HIV-1 will require specifically designed or selected immunogens to prime precursor B cells followed by sequential immunizations to drive somatic mutation,” says Dr. McGuire. He is corresponding author on a recent publication in [NPJ Vaccines](#) that compares two of types of immunogens in a prime then boost strategy.

The idea is: priming with germline-targeting immunogen activates the VRC01 precursor through binding its B cell receptor (BCR, which is essentially an antibody embedded in the B cell membrane). This recruits the B cell to germinal centers, where it expands and begins somatic hypermutation to refine its BCR affinity to the antigen. A boost with a second antigen more like *Env* then encourages the progeny of this germline-VRC01 to refine their BCR affinity to native *Env*.

In other words, the first vaccine nudges the immune system in the right direction with an engineered protein, then the second shot a few weeks later uses an immunogen closer to the virus to guide the immune response towards producing antibodies capable of neutralizing HIV.

The McGuire and Stamatatos groups have constructed different immunogens that can potentially target germline VRC01 B cells. One, called 426.Core, is derived directly from *Env*. (You can read about their development of 426.Core [here](#) and [here](#).) Although being specifically designed to engage VRC01 precursors, virus-derived antigens such as 426.Core have extraneous epitopes that can cause off target B cell responses.

A different strategy uses anti-idiotypic antibodies (ai-mAbs)-which are antibodies raised against other antibodies-to specifically stimulate VRC01 BCRs and reduce engagement of irrelevant B cells. (Read more about their previous work on HIV-related ai-mAbs [here](#).)

Recently, these groups [developed a fusion](#) of two ai-mAbs that target the rare heavy and light chains of VRC01. This bispecific antibody interacts with naïve germline-VRC01 B cells in cell culture and promotes their expansion in mouse models.

So, how does this bispecific ai-mAb perform as a priming agent compared to a germline-targeting immunogen derived directly from *Env*? Does the high specificity of the bispecific ai-mAb ensure that more VRC01 B cells expand upon priming, setting the stage for refinement upon boosting? Or, is the competition presented by off-target B cells important to enhance VRC01-specific B cell responses?

Image generated by Hannah Lewis

Naïve VRC01-precursor B cells (light green) are primed and boosted with different immunogens. Strategy 1: Priming with the ai-mAb (antibody with green tips) does not induce off-target antibodies, ultimately resulting in less efficient VRC01-class B cell expansion upon boost with either ai-mAb or 426.core. Moreover, boosting with ai-mAb reduces affinity for the VRC01 neutralizing epitope (light green). Strategy 2: Priming with virus-derived immunogen 426.Core induces off-target antibodies (yellow, orange, and purple), which promote expansion of VRC01-class B cells upon a boost with 426.Core. Image generated by H. Lewis

To answer these questions, the authors primed and boosted a mouse model with various immunogens, then measured on-target versus off-target B cell responses. To find the ideal prime/boost strategy, the team tested several combinations: prime and boost with bispecific ai-mAb only, prime and boost with 426.Core only, or prime with bispecific and boost with 426.Core.

The authors hypothesized that priming with the bispecific ai-mAb would “selectively expand VRC01 class B cells and enable a more efficient boost with 426c by ameliorating anamnestic off-target, non-VRC01 class B cell responses during boost immunizations.” However, this is not what they found.

Priming with the bispecific antibody and boosting with 426.Core was ultimately the *least* effective at promoting expansion and germinal center residence of inferred germline-VRC01 B cells. Priming and boosting with the bispecific was slightly more efficacious, but by far the best condition was priming and boosting with 426.Core.

To understand why, the team isolated the B cells after bispecific prime/boost and expressed their encoded antibodies. They found that priming with the bispecific ai-mAb induced mutations in these antibodies that decreased their affinity towards 426.Core even *lower than the original precursors*.

“We found the ai-mAb could activate the target cells *in vivo*,” explains Dr. McGuire, “but because the immunogen was not at all native like, it drove off-track mutations such that the B cells could not respond to a second immunization with a different Env immunogen.”

They were also curious why priming and boosting with 426.Core drove the best B cell responses. The engagement and expansion of off-target B cells—again, B cells that cannot produce VRC01-class antibodies—was higher in these animals. This led to the production of many off-target antibodies in the mouse serum.

The authors hypothesized that the off-target serum antibodies might somehow promote on-target B cell responses. To test this, they transfused serum antibodies from 426.Core-immunized animals to bispecific-primed animals at the same time as the boost. This experiment enhanced on-target B cell responses in bispecific-primed mice to the same level as 426.Core primed/boosted animals.

“Circulating antibodies elicited by a prime with an Env immunogen provided a positive feedback loop enhancing responses to the boost,” explains Dr. McGuire.

“Overall these highlight that more native like immunogens (derived from Env) as opposed to non-Env germline targeting immunogens might perform better at driving broadly neutralizing responses,” he concludes.

This study has important ramifications for HIV vaccine development but also impacts how we should think about vaccination against other challenging pathogens. Although the highly specific ai-mAb was not the ideal immunogen for this strategy, other ai-mAbs have shown promise for pathogens like [RSV](#), which can be neutralized by germline B cells. The maturity of the B cell response, immunogen design, and how to prime and boost will likely be different for different viruses; however, the more we test, the closer we get.

Fred Hutch/University of Washington/Seattle Children’s Cancer Consortium Member Dr. Andrew McGuire contributed to this research.

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