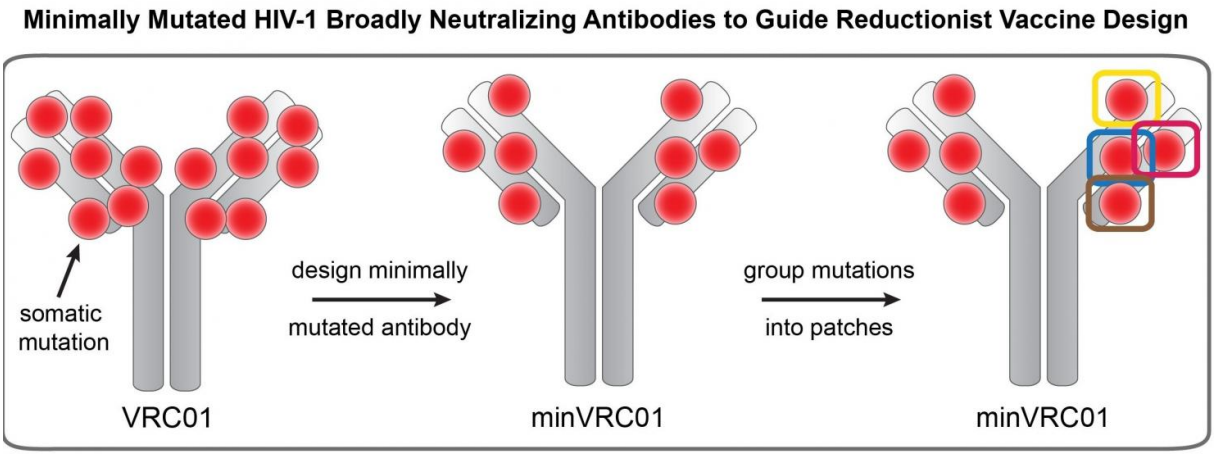
Broadly neutralizing HIV antibodies engineered to be better vaccine leads

August 25 2016



Patch	Region that requires affinity maturation	Immunogen to elicit mutations	Functional read-out
	antibody feature 1	immunogen 1	no neutralization
	antibody feature 2	immunogen 2	neutralization of virus missing key glycan
	antibody feature 3	immunogen 3	neutralization of virus with modified glycoforms
	antibody feature 4	immunogen 4	neutralization of virus with native glycans

Minimal mutation of HIV-1 broadly neutralizing antibodies to guide reductionist vaccine design. Credit: William Schief

One approach to HIV vaccine development relies on broadly neutralizing antibodies (bnAbs) that protect against different circulating HIV strains. bnAbs have been isolated from HIV-infected individuals, but they are highly evolved and unusual antibodies. A study published on August 25th in *PLOS Pathogens* reports on a rational approach to identify the essential features of bnAbs, come up with simplified versions that might be more suitable leads for HIV vaccine design, and then use analysis of the simplified bnAbs to guide design of vaccine proteins to elicit similar antibodies.

Broadly neutralizing antibodies, although arising in some HIV-infected individuals, have never been induced by vaccination. This might be because bnAbs are rare, unusual antibodies that result from continuous mutational adaptation driven by the evolution of HIV in the body over time.

Assuming that not all of the characteristics of bnAbs are essential for their desirable functions, Ian Wilson, Dennis Burton, William Schief and colleagues from The Scripps Research Institute and the IAVI Neutralizing Antibody Center in La Jolla, USA, set out to engineer HIV bnAbs with minimized rare features. To quantify the unusual features of the bnAbs, the researchers developed a computational method, which they called the Antibody Features Frequency (AFF) method. It compares the features in the DNA sequence encoding a bnAb with those in a large panel of reference sequences from human memory B cells (the cells that produce antibodies) from multiple healthy donors that had never been infected with HIV.

Applying the AFF to a panel of bnAbs, the researchers found a large (several orders of magnitude) difference in features frequencies between HIV bnAbs and "normal" human memory antibodies. This indicates, they say, "that the known potent HIV bnAbs generally provide poor direct leads to guide HIV vaccine development, because antibodies with

similar features are unlikely to be elicitable in a consistent manner". They also conclude "that engineering or discovery of potent HIV bnAbs with higher features frequencies [i.e., fewer rare features] will be needed to focus vaccine efforts toward epitopes targeted by more plausibly inducible potent bnAbs".

The AFF had shown that VRC01, a potent bnAb, was among the most unusual bnAbs, i.e, it shared very few features with normal human antibodies. On the other hand, structural analysis of VRC01 suggested that many of the unusual features might not be necessary for its ability to bind and neutralize HIV. The researchers therefore generated simplified derivatives of VRC01. They tested many candidates for their ability to bind multiple HIV strains, and ended up with two minimally mutated VRC01-class bnAbs with excellent neutralization breadth and whose potency was only slightly or moderately diminished compared to the parental bnAbs.

One of the two engineered antibodies, called Min12A21, has the highest features frequency (i.e., shares more features in common with normal memory antibodies) of all HIV bnAbs examined in this study, while retaining its specificity for HIV (one concern when altering antibodies is always that they might react also against antigens of the human host).

The researchers then divided the minimal mutations into spatial clusters at the interface between the antibody and its viral target protein. Using mutational and structural analyses together with neutralization assays, they determined the mutational steps required to go from antibodies elicited by initial contact with a vaccine to mature antibodies with bnAb activity. They also predicted the variations in the vaccine antigens at each step that might promote such mutations. Putting all of the data together, they proposed a sequential boosting strategy following the initial vaccination to select the mutation clusters in a logical order.

"We have", the researchers summarize, "developed potent HIV bnAbs that may be more tractable vaccine goals compared to existing bnAbs, and we have proposed a strategy to elicit them". Acknowledging that the strategy remains to be tested, they nonetheless suggest that "this reductionist approach to vaccine design, guided by antibody and antigen structure, could be applied to design candidate vaccines for other HIV bnAbs or protective Abs against other pathogens".

More information: Jardine JG, Sok D, Julien J-P, Briney B, Sarkar A, Liang C-H, et al. (2016) Minimally Mutated HIV-1 Broadly Neutralizing Antibodies to Guide Reductionist Vaccine Design. *PLoS Pathog* 12(8): e1005815. DOI: 10.1371/journal.ppat.1005815

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