Will mosaic vaccine immunogens expand immune response breadth to rival HIV-1 strain diversity?

Tracey A Day, Cecilia A Morgan & James G Kublin*

HIV-1 displays the most genetic diversity of any virus studied to date [1]. Within an infected individual, the virus constantly mutates, outpacing host immune responses and increasing the number of distinct isolates that may be transmitted. Contending with such extreme diversity poses an unprecedented challenge for HIV-1 vaccine development. Although few HIV-1 preventive vaccine efficacy trials have been conducted to date, thus far only partial efficacy in reducing infection risk has been observed in one study in a low-risk setting (RV144; vaccine efficacy = 30%) [2]. Serum binding antibodies specific for HIV-1 Env were shown to correlate with reduced infection risk in this study [3]. To date, no HIV-1 vaccine has definitively reduced viral load after infection or slowed disease progression. Expanding cellular and antibody immune response breadth will likely be necessary for achieving high levels of vaccine efficacy in the face of HIV-1’s extraordinary genetic diversity.

The first HIV vaccines containing mosaic antigen inserts will enter human testing later this year. This approach represents one of several in silico-based strategies to increase the cross reactivity of vaccine responses for diverse HIV-1 isolates. The original aim of mosaic antigens was to expand vaccine cellular response breadth (number of responses to distinct T-cell epitopes) and depth (number of responses to a given T-cell epitope). In nonhuman primate studies, vaccine-induced T-cell responses have been correlated with reduced viral loads [4–7]. In humans, a recombinant adenovirus serotype 5 vector (Ad5) vaccine inducing significant cellular responses was shown to exert immune pressure on HIV-1 divergence in infected individuals [8,9]. Vaccine-induced cellular responses were of limited breadth and depth and this may explain why the vaccine was not effective in reducing viral loads for infected vaccine recipients [10]. Increased breadth and depth for T-cell responses may help prevent infection or may block escape pathways and lead to earlier control of viral replication or slower disease progression for vaccinated individuals who become infected.

Mosaic antigen sequences encode composite full-length HIV-1 proteins that optimize coverage of potential T-cell epitopes [11]. Mosaic protein sequences are generated from a genetic algorithm in which natural sequences are repeatedly recombined in silico with the goal of computationally ‘evolving’ a protein sequence made up of the peptides most frequently represented in the database. Mosaic antigens may be generated based on a set of sequences from a single clade or from the entire M group sequence collection. The inclusion of multiple mosaic antigens into a polyvalent cocktail enables even greater coverage of T-cell epitopes and may potentially block viral escape pathways [12].

Consensus sequences are another strategy to improve T-cell response breadth. In this strategy, computational methods are used to generate a sequence representing

Keywords: HIV-1 • HIV Vaccine Trials Network • HVTN • immune response breadth • in silico immunogen design • mosaic antigen • preventive • T-cell response • vaccine
the most common amino acid residues at each position from a set of aligned sequences [13]. Like mosaic antigens, the sequence set may contain natural sequences from a single clade set or entire M group and results in a full length gene sequence.

“If the in silico designed antigens now entering human testing prove to broaden vaccine responses, further development of these approaches may overcome the limitations of clade-specific vaccine responses and provide an accelerated path to globally effective vaccines.”

Preclinical studies with mosaic and consensus antigens have elicited significant increases in T-cell response breadth and magnitude [12,14–16]. Both these concepts will enter Phase I evaluation by the HIV Vaccine Trials Network (HVTN) later this year. The trial, HVTN 099, is being collaboratively developed by the HVTN, the Division of Acquired Immunodeficiency Syndrome (National Institute of Allergy and Infectious Diseases [NIAID], National Institutes of Health), the Center for HIV/AIDS Vaccine Immunology, Los Alamos National Laboratory, the IPPOX Foundation in Switzerland, and the Bill and Melinda Gates Foundation. HVTN 099 will evaluate the safety and immunogenicity of a DNA prime/NYVAC boost vaccine regimen containing either a trivalent mosaic, group M consenus, or naturally transmitted/founder env insert sequence. The DNA/NYVAC platform is well characterized, thus allowing the focus to be on the comparative immunogenicity of the different env inserts. In addition, the use of similar vaccination schedules and standardized assays will allow comparison with results from other regimens. The key scientific question this trial seeks to address is whether a consensus or mosaic env insert is superior to a single natural env insert for eliciting the broadest immune response.

Other mosaic vaccine products being developed for clinical testing include recombinant adenovirus serotype 26 (Ad26) and modified vaccinia Ankara (MVA) vectors, both with mosaic gag-pol and env inserts (US Military HIV Research Program, Crucell, Beth Israel Deaconess Medical Center, and Integrated Preclinical/ Clinical AIDS Vaccine Development Program of NIAID). PaxVax, Inc. and NIAID are also developing a replicating adenovirus serotype 4 (Ad4) platform that includes a mosaic gag insert.

Aside from mosaic and consensus strategies, several other in silico antigen design approaches for eliciting more cross-reactive immune responses are being pursued. These include a prototype vaccine containing exclusively conserved viral sequences. The rationale behind this so-called conserved elements approach, is to focus vaccine responses to theoretically immutable portions of the viral proteome and simultaneously avoid generating potential ‘decoy’ responses to variable regions [17]. The HIVconsv immunogen represents another strategy to focus vaccine responses to conserved viral sequences. HIVconsv contains the 14 least variable segments of the HIV-1 proteome assembled into a single chimeric protein. This immunogen has been evaluated in a variety of vector modalities in macaques and shown to elicit broader responses than single-gene vaccines [18].

Collectively, clinical studies evaluating these various approaches have the potential to validate the use of in silico antigen design strategies as a means to increase cellular immune response breadth in humans. These immunogens may also be capable of inducing broader antibody responses. To further enhance antibody responses, the use of a DNA or viral vector prime with an in silico designed insert followed by a protein boost is also under consideration.

Expanding cellular and antibody immune response breadth will likely be necessary for improving upon the results of previous HIV-1 vaccine efficacy trials [2,19,20]. This may especially be the case for high-risk populations, and for geographical regions with high HIV-1 incidence where people may be repeatedly exposed to different HIV-1 isolates.

Development of multiclade HIV-1 vaccines that are more global than clade-specific is desirable for many reasons. The availability of multiclade HIV-1 vaccines would reduce the number of large-scale efficacy trials needed, thereby reducing the time and expense required for vaccine licensure, as well as reduce manufacturing- and deployment-associated costs. In addition, vaccines based on clade-specific inserts may prove less effective for regions where multiple clades or recombinant forms are in circulation. Increasing international travel may further limit the efficacy of clade-specific vaccines. If the in silico designed antigens now entering human testing prove to broaden vaccine responses, further development of these approaches may overcome the limitations of clade-specific vaccine responses and provide an accelerated path to globally effective vaccines.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
Will mosaic vaccine immunogens expand immune response breadth to rival HIV-1 strain diversity?

References