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HIV-1 vaccine design: Harnessing diverse lymphocytes to conquer a diverse pathogen

Sherri L. Surman¹, Robert Sealy¹, Bart G. Jones¹, and Julia L. Hurwitz^{1,2}

¹Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee 38105

²Department of Pathology, University of Tennessee, Memphis, Tennessee 38163

Abstract

In the Fall of 2007, the HIV-1 research field received news that their front-runner vaccine was not protective. In response to this disappointment, scientists are now reviewing the intricacies of the immune response toward HIV-1 to develop new and better strategies for vaccine development. Decades ago, researchers recognized the impressive amino acid and carbohydrate diversity of HIV-1, and the associated obstacles to vaccine development. At first glance, the diversity and other unique features of HIV-1 may seem insurmountable, but attention to vaccine successes in other fields serves to renew optimism. The newly-licensed rotavirus and papillomavirus cocktail vaccines remind scientists that diverse pathogens can be conquered and that the chronic nature of a virus infection need not thwart successful vaccine design. Here we describe current efforts to gain insights from other vaccine fields and to adopt a cocktail vaccine approach for the prevention of HIV-1 infections in humans.

Keywords

Multi-envelope; diversity; HIV-1 vaccine; B-lymphocytes; T-lymphocytes; cocktail; prevention

Introduction

HIV-1 vaccine development has met with much disappointment¹⁻³, as the virus presents more than one obstacle to the research scientist. First, the virus is highly diverse. Second, the virus establishes a chronic infection when an exposure occurs in the context of an unprimed immune system. Each of these features must be acknowledged by vaccine developers, but need not thwart vaccine success. Here, we will describe a multi-envelope vaccine strategy designed to tackle a diverse pathogen with diverse lymphocytes and to prevent HIV-1 infections in humans.

HIV-1 diversity

HIV-1 is characterized by highly diverse proteins, both external and internal, due to the function of an error-prone reverse transcriptase and a lack of polymerase-related proofreading function⁴. The envelope protein, which contains five regions of hyper-variability, differs not only in terms of amino acid sequences, but also in terms of length and sites of glycosylation⁵ (glycosylation accounts for more than half of the molecular weight of the HIV-1 envelope protein). Variable regions are frequent targets of immune activity^{6;7} while conserved regions

To whom correspondence should be sent: Julia L. Hurwitz, Department of Infectious Diseases, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, Phone: 901-595-2464; Fax: 901-595-3099, e-mail: julia.hurwitz@stjude.org.

are often masked; some conserved regions are hidden within the three dimensional structure of HIV-1 while others mimic ‘self’ antigens, against which humans are tolerant⁸. While vaccine developers often strive to elicit immune responses toward the conserved regions of HIV-1, this strategy has yielded disappointing results thus far in clinical trials¹.

One might be inclined to describe the diversity of HIV-1 proteins as limitless, but certain constraints are dictated by function. For example, the envelope protein must bind the highly conserved human CD4 molecule. Envelope must also bind co-receptors (e.g. CCR5)⁹ and must mediate the fusion of virus and host cell membranes. Thus, while protein diversity at the amino acid level may appear enormous, the number of mutually exclusive, functional three-dimensional structures need not be vast.

A diverse immune response can counter pathogen diversity

The human immune system consists of billions of lymphocytes, subdivided into B- and T-cell populations. As lymphocytes develop, each undergoes a sophisticated process of recombination/splicing at the nucleic acid level that leads to expression of a unique cell surface receptor (B-cells express antibodies while T-cells express T-cell receptors (TCR))¹⁰. Antibodies can bind pathogens directly while T-cell receptors bind antigenic peptides in association with major histocompatibility proteins. In each case, a structural lock-and-key type interaction is necessary for the lymphocyte receptor to engage its target. Because of the impressive diversity of receptors in the human immune system, virtually every pathogen can be countered by a ‘specific’ set of B-cell and T-cell populations.

Successful vaccines against diverse pathogens have been produced in other fields by grouping pathogens based on antigenic structure. Cocktails are formulated to encompass a representative antigen or antigenic complex from each group and to activate respective B-cell and T-cell populations. In this context, the antigens might be termed ‘immunotypes’ in that they activate different lymphocyte subsets. Lymphocytes responsive to each vaccine component then function in unison to conquer the breadth of diverse pathogens in nature.

As an example, developers of the influenza virus vaccine have recognized that the hemagglutinin molecules on virus surfaces can have variable structures (e.g. hemagglutinin H1 and hemagglutinin H3 antigens are structurally distinct and mark different groups of influenza viruses). Scientists therefore include representatives of the different hemagglutinin antigens in current vaccine cocktails; each immunogen elicits a different population of B-cells and respective antibodies. The ‘immunotype-specific’ antibodies (ISabs) need not be ‘broadly-neutralizing’ (i.e. H1-specific antibodies need not recognize H3 and vice versa) provided that the antibodies function together to target diverse hemagglutinin molecules.

Similar approaches have been used to formulate the pentavalent rotavirus vaccine¹¹, the quadrivalent papillomavirus vaccine¹² and the 23-component pneumococcus vaccine¹³. To date, the strategy has not been fully tested in the HIV-1 field. Although HIV-1 vaccines sometimes encompass more than one envelope, components have often been selected based on sequence (clade or subtype) rather than structure^{14;15} and clinical efficacy trials have been limited. Possibly, the application of this proven approach to HIV-1 vaccine development may be required for production of a successful product.

Will the chronic nature of HIV-1 infection hamper vaccine development?

The development of vaccines against papillomavirus and Varicella zoster virus (VZV) shows that the chronic nature of a virus infection need not hamper vaccine success. Accomplishments in other vaccine fields also illustrate the importance of establishing a robust immune response before (not after) a virus infection has been established. When the virus is encountered before

the immune system is primed, it may sequester in privileged sites and remain hidden from B-cell and T-cell surveillance. Then, when immune cells are finally activated by virus in the periphery, they cannot reach the sequestered target. Often the viruses that are associated with chronic infection co-exist with the host's immune response for years without incident. If, however, the immune system is compromised (as may be mediated by an unrelated insult), virus re-activation can overwhelm the host (e.g. shingles can result when VZV reactivates in an immunodeficient individual). The best way to avoid late-stage disease is to induce immune responses prior to virus exposure, and thus block virus at its site of entry ¹⁶.

Has an immune response toward an immunodeficiency virus ever been protective?

The ability of activated immune cells to prevent immunodeficiency virus infection was demonstrated approximately two decades ago^{17;18}. As one example, Hu et. al. prepared a vaccine comprising envelope glycoprotein (the outer coat protein) of simian immunodeficiency virus (SIV). One group of macaques was vaccinated with the envelope-based vaccine while another group of macaques served as controls. When later challenged with an infectious clone of SIV that expressed an envelope protein identical to that in the vaccine, all vaccinated animals were protected from infection ¹⁸. This result showed that the primate immune system is fully capable of preventing infection with an immunodeficiency virus provided that the vaccine and virus are antigenically matched.

Protection from superinfection has also been demonstrated in HIV/SIV systems in non-human primates. In other words, an animal is often infected when exposed to HIV or SIV for the first time, but resistant to infection when exposed to a second virus at a later date ¹⁹⁻²⁴. Why is this so? The protection is likely because virus is sequestered in privileged sites (similar to the situation for VZV and papillomavirus) and over the course of months, mutates extensively to naturally prime the immune system against a cocktail of antigens²⁵. Even though the second virus challenge may present new viral sequences, the antigens are similar to those seen following the first infection. Virus is therefore conquered by the previously-primed immune system.

In studies of HIV-1 infected humans, superinfection is also 'rare' in that it is difficult to document (although this is a topic of considerable controversy ²⁶⁻²⁸). For example, a recent survey of HIV-1-infected individuals within stable sero-concordant relationships revealed no transmission events²⁷. Possibly, HIV-1 superinfections occur most frequently in humans during early and late stages of infection, either when the immune system is relatively naïve to HIV²⁹, or when activated HIV-1-specific lymphocytes are destroyed by disease. Otherwise, similar to the case in macaques, it appears that the priming of immune cells with one virus (and its associated escape mutants) may be sufficient to confer protection against a second virus challenge.

Advancing a cocktail approach for vaccine development

A number of independent research groups have thus far studied vaccine cocktails with an intent to capture the diversity of HIV-1 in one vaccine^{7;15;30-33}. The creation of antigenic cocktails has generally been centered around HIV-1 envelope proteins or fragments, as envelope elicits both neutralizing antibodies and T-cell function (although diversity should also be considered when vaccines target internal HIV-1 proteins). Cocktails of envelopes have ranged in component size from 3 to >50 ^{15;30-33}. The number of components must be large enough to represent the diversity of functional HIV-1 structures (perhaps greater than 3), but small enough to facilitate the manufacture of vaccines for world-wide distribution. The qualitative improvement in immune responses toward cocktail versus single-component vaccines has been

repeatedly demonstrated^{31;34-36}. Even when an envelope contributes to only 1% of a mixed vaccine, it is capable of eliciting a unique population of responding cells³⁷.

At a time when research funds are shifting toward HIV vaccine discovery^{38;39}, there may be a renewed opportunity to conduct a more comprehensive study of envelope immunotypes and their respective ISabs. Systematic side-by-side comparisons of single-envelope and mixed-envelope vaccines in research animals could advance the current understanding of HIV-1 immunogens, and improve the design of second-generation cocktail vaccines. A variety of assays (both B-cell and T-cell)⁴⁰⁻⁴⁵ might be employed to define immunogen-specific activities, as there is currently no assay for which a clear correlate of protection against HIV-1 can be demonstrated. Results of systematic studies in research animals might then promote the testing of cocktails in advanced clinical trials and the ultimate prevention of HIV-1 infections in humans.

Conclusion

The recent front-runner vaccine in the HIV-1 field was specifically designed to elicit T-cell responses toward the internal proteins gag, pol and nef, each from a different clade B-isolate of HIV-1⁴⁶. The failure of this and other T-cell focused strategies^{1;3} encourages researchers to expand the capacities of future vaccines. To date, most successful vaccines have partnered B-cell and T-cell activities and many have activated a breadth of immune specificities and functions^{11-13;47;48}. Vaccine successes have demonstrated that a manageable cocktail of antigens can protect against infection and disease by diverse pathogens; cocktails are generally created by grouping pathogens by structure and representing each group by a different component in the vaccine cocktail. With views of harnessing the full capacity of a highly sophisticated immune system, researchers may gain optimism that similar efforts could yield a successful vaccine for human protection against HIV-1.

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