Current Topics in HIV-1 Vaccination Research

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Introduction

Human Immunodeficiency Virus (HIV) infections have been a global health concern since the first known cases in the early 1980s. Over the past quarter century, HIV has spread to all corners of the globe, resulting in one of the deadliest pandemics of modern times. With over 33 million individuals currently infected and 2.5 million new infections each year worldwide, the death rate for HIV-1 victims is not expected to decrease in the foreseeable future (Bongaarts et al., 2008). Although treatments are available to extend the lifespan of individuals infected with HIV-1, finding a vaccine to prevent initial infection is of paramount importance.

In 1984 the U.S. Secretary of Health and Human Services declared that a vaccine would be available within two years, but the medical community was unprepared for the difficulties it would encounter in this pursuit. Traditional methods of vaccination, such as introducing weakened or disabled viral agents in order to trigger an immune response, have proven ineffective in preventing HIV-1 infection. Vaccines based on live, weakened HIV-1 can mutate and regain their pathogenicity after introduction to the human bloodstream (Letvin, 2006). New and innovative approaches are necessary to address the spread of this virus.

There are two primary branches of research into an HIV-1 vaccine: Neutralization of the virus through the use of artificial antibodies and blocking the pathways the virus uses to enter host cells (Montefiori et al., 2007, Hütter et al., 2009). Both methods share the goal of preventing the virus from replicating, but attempt different methods to achieve this goal. The first, using HIV-1 specific antibodies to bind to important sites on the virus, neutralizes vital phases in the replication process, while the second method, removing proteins necessary for the invasion of host cells, would essentially isolate the virus and prevent opportunities to reproduce.

The major advantage of preventing the virus from replicating is the decreased chance of generating viral escape mutants (Anderson et al., 2007). An escape mutant is a version of the original virus that is not affected by the current treatment method. Mutant strains occur due to replication errors and occasionally result in modified forms of the virus that cannot be recognized by the immune system. Therefore, the immune system has no defense against the virus.

Thesis

As the global HIV-1 pandemic continues to spread at a rate of 2.5 million new infections per year (Bongaart et al., 2008), the need for an effective vaccine against the virus escalates. Three major obstacles must be addressed in the creation of an effective HIV-1 vaccine: latent infection, viral diversity, and the lack of an effective immune response (Johnson and Fauci, 2007). Failure to address any one of these obstacles will result in an ineffective long-term solution.

Latency and Diversity as Obstacles in HIV-1 Vaccination

One of the major complications in the development of an HIV-1 vaccine is the issue of viral latency. Viruses reproduce by injecting their RNA into replicating host cells, forcing the infected cells to produce copies of the virus using their own reproduction mechanisms. However, HIV-1 is a lentivirus, a virus capable of infecting non-replicating cells. If a non-replicating cell becomes infected, it can harbor the viral RNA until it either dies or begins to replicate. Since the infected cell remains externally identical to non-host cells, latent viral infections cannot be detected neither by the body’s immune system nor current screening methods (Jeeninga et al., 2008). Fortunately, non-replicating cells are rarely stable for more than a few days, and are not important for long-term latency (Jeeninga et al., 2008).

After developing an immune response to a pathogen, CD4 T-cells that recognize the pathogen enter a dormant state in order to be available to attack future infections (Jeeninga et al., 2008). T-cells, which have been infected with HIV-1 sometimes enter this dormant state, and will not replicate until the T-cells begin to replicate. These resting T-cells persist with an average half-life of 44 months and it can be estimated that it will take more than 60 years to eradicate this reservoir (Jeeninga et al., 2008). Attempts to activate these latent cells and expose the viral reservoirs have had limited success (Jeeninga et al., 2008).

Under ideal conditions, modern antiretroviral therapy is capable of reducing the HIV-1 viral load to undetectable levels, but patients tend to relapse immediately on discontinuation of highly active antiretroviral therapy (HAART) (Jeeninga et al., 2008). Once a relapse occurs, future treatment may become more difficult, as cells harboring latent HIV-1 have been linked to increased mutation rates (Marcello, 2006). As it replicates, the virus develops greater diversity within the infected individual, often developing resistance to antiretroviral therapy.

All reproduction methods can result in errors, called mutations, and viruses such as HIV-1 are no exception. The mutation rate in viruses is significantly higher than most other forms of life, as viruses lack a method of correcting replication errors. The result is a huge amount of variability within viral populations, including variants referred to as escape mutants (Poignard et al., 1999).

Escape mutants are versions of a parent virus with replication errors that make them different enough from the original virus that the host’s immune system is not able to recognize or target them (Anderson et al.,
be engineered and introduced into the host organism (Léourneau et al., 2007). These antibodies are capable of protecting CD4 T-cells against HIV-1 infection under controlled conditions, but face the enormous roadblock of enormous HIV-1 diversity (Poignard et al., 1999).

Antibodies neutralize the virus by binding to the surface gp120 and trans-membrane gp41 envelope glycoproteins, blocking HIV-1 entry into susceptible cells. However, the virus exploits several mechanisms to shield itself against antibody recognition, including a dense outer coating of sugar molecules and extreme variation of the aforementioned surface proteins (Montefiori et al., 2007). The outer coating protects the viral RNA from direct attacks, making indirect methods such as neutralizing the protein binding sites, a more feasible option of prevention.

There are four major approaches for dealing with HIV-1 diversity. The first is the development of an antibody based on a single clade, or variant, of the virus similar enough to all other clades to produce a cross-reactive immune response (Léourneau et al., 2007). This method is plausible due to the fact that all variants of a virus derive from a common ancestor and therefore, share a similar structure. By selecting the clade with the closest sequence to all others, an immune response could be generated capable of offering protection against all similar clades. This approach has been proven effective in test models, but only after antibody concentrations have been raised to high enough levels to make practical application impossible (Léourneau et al., 2007). This approach addresses HIV-1 variability within a limited scope, but does not effectively address the further diversification of the virus over time.

The second approach is to derive vaccine immunogens from centralized sequences of viral RNA. Despite the variability of HIV-1, all clades are similar enough that a common ancestral sequence could be extrapolated from currently circulating viruses (Léourneau et al., 2007). As with the first technique, these common sequences might also be able to target all circulating viruses. These centralized sequences are designed to minimize the difference between a vaccine immunogen and circulating viruses, but may not be able to offer optimal protection from all variants.

The third approach is to deliver a vaccine consisting of a cocktail of immunogens derived from different clades (Catanzaro et al., 2006). This "shotgun approach" is likely the simplest, as it uses multiple immunogens to target a variety of specific clades, rather than a single wide-spectrum immunogen targeting the same number of variants. Initial results with this technique have been encouraging, but doubts remain due to the possibility of interference between closely related peptide sequences in the vaccine, which may limit responses to some antigens (Léourneau et al., 2007).

The final major approach is the use of "mosaic" immunogens designed to optimize coverage of CD4
T-cell epitopes (Fischer et al., 2007). This technique involves assembling a polyvalent vaccine candidate capable of targeting multiple variants of HIV-1. Potential problems with this technique are similar to those of other cocktail techniques, such as immune interference (Léourneau et al., 2007). Another potential problem is the inclusion of both variable and conserved regions. Viral responses to variable regions of the immunogen may draw attention away from more useful conserved regions.

**HIV-1 Resistance and CCR5-Δ32**

In the mid 1990s, rare individuals were discovered who were resistant to HIV-1 even to the point of effective immunity (Liu et al., 1996). These individuals were found to have a homozygous defect in the Chemokine Receptor-Five (CCR5) allele resulting in a truncated protein incapable of serving as a receptor for HIV-1. The defective allele, called Delta-32 (Δ32) appears to have no significant negative effect on cellular function. Other chemokine receptors, such as CCR1, compensate for the deletion of CCR5, but do not act as receptors for HIV-1 (Liu et al., 1996, Galvani et al., 2003).

The theory surrounding the development of a CCR5-based vaccine is relatively simple: since HIV-1 enters the host cells by binding to a CD4 receptor and then interacting with a chemokine receptor, primarily CCR5 (Anderson et al., 2007, Hütter et al., 2009), disabling or sufficiently downregulating the protein could significantly hamper or even prevent viral replication (Liu et al., 1996, Hütter et al., 2009). Unable to replicate, the virus would present no threat to the infected individual and would eventually be forced out of the body.

The preventative potential of CCR5-Δ32 was demonstrated practically by Hütter et al. in 2007, when a patient suffering from both HIV-1 infection and acute myeloid leukemia received an allogeneic stem-cell transplantation with stem cells from an unrelated donor who had been screened for homozygocity for the CCR5-Δ32 allele (Allers et al., 2011). The patient, who had been diagnosed with HIV-1 ten years prior, discontinued HAART after the transplant. In this patient, no active replicating HIV could be detected 20 months after HAART had been discontinued (Hütter et al., 2009, Allers et al., 2011). The patient achieved complete chimerism, and his blood monocytes displayed a homozygous CCR5-Δ32 genotype (Hütter et al., 2009).

While this case clearly emphasizes the importance of CCR5-targeted treatment strategies, uncertainty remains over whether a cure for HIV-1 infection has been achieved in this patient (Allers et al., 2011). Despite HIV-1 levels dropping below measurable quantities, the virus may still be present in latent reservoirs. Mutation into a strain capable of entering host CD4 cells through other chemokine receptors, such as CXCR4, could result in a relapse.

Despite the proven effectiveness of allogeneic stem-cell transplants, the rarity of the CCR5-Δ32 homozygous genotype is extremely rare, occurring almost exclusively in populations of western European heritage, and only in 1% of those populations (Liu et al., 1996). The rarity of this genotype, combined with the expense of stem-cell transplants would make this therapy prohibitively expensive for general use. A plausible alternative is the use of gene therapy to disable the production of the CCR5 protein (Anderson & Akkina, 2007).

The expression of the CCR5 gene can be disabled by introducing small interfering RNA (siRNA) to interfere with the production of the associated protein (Anderson & Akkina, 2007). Several highly potent siRNAs have already been derived and have proven capable of almost completely disabling CCR5 expression. If these siRNAs can be mass-produced, they may represent a realistic vaccine against HIV-1.

**Conclusion**

The major advantage of preventing the virus from replicating is the decreased chance of generating viral escape mutants capable of avoiding the treatment (Anderson & Akkina, 2007). Since each replication cycle increases the chance both of generating an escape mutant and of developing latent reservoirs, viral replication must be prevented long enough for the host's body to purge the infection.

Downregulating the CCR5 gene could result in inactive CCR5 proteins, preventing HIV-1 from infecting host cells and reproducing. While this would prevent symptoms of infection from occurring, it may still be possible to spread the virus to unprotected individuals. Additionally, the only successful complete downregulation of CCR5 was the result of an allogeneic stem-cell transplant (Anderson & Akkina, 2007, Hütter et al., 2009, Allers et al., 2011), a procedure which would prove prohibitively expensive for mass vaccination even before screening for CCR5-Δ32 homozygocity (NBMT Link, 2010). Finally, CCR5 downregulation does not address the HIV-1 variants, which utilize other chemokine receptors. If only CCR5-specific HIV-1 strains are protected against, CXCR4-tropic strains may rapidly emerge (Anderson & Akkina, 2007).

Despite these concerns, downregulating the CCR5 gene remains the most plausible solution to the issue of HIV-1 vaccination. However, this therapy must be combined with additional measures in order to prevent intense selection of CXCR4-tropic strains; the emergence of which would negate the effectiveness of the treatment (Anderson & Akkina, 2007).
Works Cited


