HIV Vaccines and Your Immune System

The goal of HIV vaccines is to teach the immune system new and hopefully better ways to win the battle against the virus. There are different types of immune responses, those we were born with (*innate* immunity) and those we learn (*acquired* immunity). HIV vaccines exploit the side of the immune system that is learned (acquired) by providing information to cells in new ways in hopes of enhancing their learning and making them more effective fighters.

A little background

Typically the first line of defense against nearly every new infection or disease is our *innate* immune responses. It includes cells called dendritic cells (DCs) and natural killer cells (NK cells). These types of cells are out surveying the body looking for things that don't belong and trying to get rid of them. While extremely important in the big picture of keeping us healthy, they are not specifically targeted to any particular disease of infection. They're a bit like general surveillance or a neighborhood watch, looking for suspicious activity but not a specific perpetrator.

Our learned or *acquired* immune system is slower to respond at first, but it is highly specific in its activity and can respond fiercely and briskly once it has learned a task It includes specialized CD4+ T cells, CD8+ T cells (also called *antigen-specific* CD8+ cells) and B cells. Unlike the innate immune response, these specialized cells will walk right past a group of neighborhood thugs (e.g. the flu virus, the fungal infection, etc.) to find a specific wrong-doer (e.g. HIV). If they're HIV-specific cells, they will seek out and destroy HIV infected cells or if they are HIV-specific antibodies, they will seek out HIV floating in the blood.

HIV-specific cells learn by seeing. Other immune cells show CD4+ cells bits and particles of HIV that they have found while surveying the immune system for trouble. Once these other cells find a CD4+ cell that can learn about HIV (a *naïve* cell), the CD4+ cell communicates with other cells and provides instructions on how to respond. Depending on how HIV is shown or presented to the CD4+ cell, the cell will send out different chemical messages to activate a response. One type of response is antibody (also called *humoral*) responses, which are generated by B cells. Generally these battle virus that is free floating in the blood (outside of cells). Another type of response is cellular responses, which are largely carried out by CD8+ cells. These destroy HIV infected cells (eliminates virus that is inside of cells). HIV is clearly both inside of cells as well as in the blood, floating between cells en route to infecting other cells. Both *humoral* and *cellular* responses are believed to be important in controlling HIV replication, though some scientific debate remains about which, if any, is *more* important.

Vaccines and how they work

The process of recognizing a new critter (i.e. an *antigen*, e.g. HIV) and responding takes awhile. Also, if the way the particle of HIV was presented to the CD4+ cell wasn't done right, the entire process of *antigen* presentation, recognition and response could be crippled or ineffectual. Once a robust and effective response has been learned, however, the immune system marshals full force against the critter to specifically contain and hopefully control or eliminate it entirely (if possible).

In general, once a specific (HIV or other) immune response has been mounted, that response becomes part of our immunologic memory. If our body confronts that specific critter again the learned (*memory*) responses swiftly kick into high gear and theoretically contain it before it causes a problem. This immunologic memory is stored in what are called memory T-cells.

To illustrate, consider the flu vaccine. Before flu season comes around many people get a flu shot (vaccine). This usually is a severely weakened form of the flu virus, or a man-made flu virus particle that cannot cause disease. The weakened or man-made particle is mixed in with something that helps to stimulate our cells to respond. Sometimes this response causes a mild fever, swollen joints or stiffness, which are common signs that the immune system is doing some-

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thing. What's happening here is that the immune system is being taught how to recognize and respond to the flu virus. *Naive* cells are developing an immunologic *memory* for something they haven't seen before. When flu season comes around having been vaccinated doesn't prevent you from becoming infected with the flu virus. Rather, it arms your immune system to respond specifically and swiftly such that the virus is controlled thus avoiding symptoms of disease (the flu). Once an immune response has been learned, it can be a swift and potent first line of defense against disease.

What is a preventive vaccine?

The goal of HIV *preventive* vaccines is to give people who are *not* infected with HIV some form of HIV-specific memory responses that can act swiftly and effectively in controlling HIV if and when a person encounters the virus. Ideally, a preventive vaccine might prevent the establishment of HIV infection altogether, although vaccines seldom achieve this goal. Instead, they prime the immune system to act quickly enough to prevent the infection from becoming serious or dangerous. Whether an effective HIV preventive vaccine will be able to block the establishment of HIV infection altogether or merely alter the course of HIV disease in those who become infected is unknown. The flu vaccine does not block infection with the flu virus, per se, but it does stop the development of the disease. It is possible that the best we can hope for in an HIV *preventive* vaccine would be something that prevented or seriously slowed HIV disease progression in people who do become exposed and infected with HIV. To be completely effective in blocking infection, an HIV vaccine would have to make a very broad range of antibodies against HIV to block free floating virus from infecting cells and would create a strong cellular immune response against the virus in case any cells became infected. Currently there are no proven effective HIV preventive vaccines. If or when a vaccine is one day proven to have some benefit, it's highly likely that it will work best if combined with other proven HIV prevention efforts (e.g. safer sex practices, safe needle using practices, etc.)

What is a therapeutic vaccine?

The goal of HIV *therapeutic* vaccines is to offer continuing education to the immune system in hopes of shoring up a more potent and effective response against the virus. Whether or not it is possible to teach the immune system to better fight HIV remains to be seen. Some scientists believe that if continued production of HIV itself in the body does not provoke an immune response sufficient to control the infection, no therapeutic vaccine is likely to do so either. Still, researchers are exploring various strategies to improve HIV presentation and immune recognition and responses. Therapeutic vaccination is only one area of research aimed at trying to do this. Other experimental strategies include gene therapy, cell therapy, structured treatment interruption approaches (also called *autoimmunization*), passive immune therapy and cytokine therapy. Currently there are no proven effective HIV therapeutic vaccines. Many HIV *preventive* vaccine approaches are also being (and have been) tested to see if they have benefits in people living with HIV.

Therapeutic HIV vaccines: things to consider

Many HIV vaccines have already been tested in people living with HIV infection without achieving any compelling results. Studies conducted by the AIDS Clinical Trials Group, a federally sponsored network for conducting studies of experimental therapies for HIV, compared several HIV therapeutic vaccines candidates, including products developed by Genentech, Chiron Corporation, MicroGenSys and others. These studies showed that some products were more effective than others in inducing immune responses but it was wholly unclear if the responses had any impact in controlling HIV replication.

In the early 1990s, Genentech moved forward with a large study of its therapeutic vaccine candidate, rgp160. Results from this study suggested that the vaccine made no impact on HIV disease progression and there was some indication that people who received the vaccine did slightly worse than those who received the placebo. Genentech stopped the study and abandoned efforts in this arena. (Note: The Genentech vaccine was later sold to VaxGen, who modified it and is researching it as a preventive vaccine called AIDSVax).

Results of a large study of Immune Response Corp.'s (IRC) vaccine, the HIV-1 Immunogen (also known as Remune or the Salk HIV Vaccine) suggested that the product had little to no impact on CD4+ cell counts or viral load. Unfortunately the study was not large enough to detect differences in the rate of HIV disease progression among those receiving the vaccine compared to the placebo, but laboratory results on validated markers of HIV disease progression (e.g. viral load and CD4+ cell count) were not compelling. Pfizer Corporation, which was the principal investor in IRC, has also abandoned further development efforts of this product.

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Many therapeutic HIV vaccine products have been shown to elicit HIV antibody responses and some have been shown to induce HIV-specific cellular responses in animal, test tube and human studies. Studies currently enrolling and reports from complete and ongoing research will often highlight results from previous studies highlighting the products *immunogenicity*. Immunogenicity is the degree to which the vaccine induces immune responses. Whether or not these responses will have any impact on HIV disease is unknown. The reason for believing that they might is that human long-term non-progressors generally have very high levels of these responses. Long-term non-progressors are people who remain healthy for a long period without treatment despite HIV infection. Both the Genentech and the IRC vaccines were shown to induce at least transient and modest levels of HIV-specific immune responses but neither of these products demonstrated measurable benefits in people living with HIV. Whether larger and more lasting responses will make a difference remains to be seen. Ongoing studies should soon begin to provide answers to this question as some new vaccines, such as that from Merck, produce dramatically higher and longer lasting levels of these responses than any previous vaccine. If vaccines like this fail to produce meaningful results, it may suggest that this is dead end in research.

Some HIV vaccines have been shown to prevent HIV infection in animal studies, including the Genentech vaccine referred to above. The new DNA vaccine being developed by Merck did not prevent HIV infection, but it did appear to alter the course of the disease in animals that were subsequently infected with an aggressive animal virus similar to HIV. Prior vaccination did not wholly prevent the animals from developing disease, but it appeared to significantly slow disease progression. A few other vaccine products have shown similar results in animal studies. Humans do not react the same way to vaccines as animals. While results from animal studies may provide encouragement to vaccine developers to move forward into human studies, they may tell us very little about how the product will (or won't) work in humans. Also, not all animal models are the same – the types of animals used in a study are presumed to give better or worse information about what the human experience might be like. The kind of virus used to infect the animals in the studies might also make a difference in terms of the applicability of the information to the human setting.

One aspect of the excitement over animal study results of the Merck DNA vaccine may have to do with the kind of animal used in the studies. The animals used are known to develop a very aggressive form of AIDS following infection. That the product slowed disease in the animals was encouraging. Animals used in other studies do not develop disease following infection with HIV, so some researchers have been less enthused about results of studies where infection was blocked in those models. Of greater interest in the Merck studies is a compilation of new data showing that when the vaccine is used with the right adjuvant (a booster), it produces the strongest cellular immune responses yet seen. Still, researchers are not willing to predict whether it will work well enough to prevent infection altogether.

The way companies and researchers report therapeutic vaccine study results can be a little misleading and generally this is not intentional or deliberate. The only way, truly, to report on initial findings or small studies of candidate vaccines is to discuss the *immunogenicity* of the product and any safety concerns. Immunogenecity refers to the vaccines ability to elicit an immune response. Generally speaking, when you hear or read that a vaccine product or a treatment strategy enhances HIV-specific immunity (either cellular or antibody) it's wise to remember that at the current time we've no idea if that is *functional* immunity or what level of this type of immunity is needed to make a clinical difference. In other words, whether the way the vaccine impacts these specific responses will result in any improved control of HIV infection/disease. If the way that a particular approach or strategy increases HIV-specific immunity in humans correlates with containment of HIV replication, improvement in symptoms or decreased risk of disease progression, that would be meaningful and encouraging.

When considering therapeutic HIV vaccine human study results, look for the following:

Was the study *controlled* (did some people receive vaccine and others receive placebo)? This will help you to sort out if any observed increases in CD4+ cell count or decreases in HIV levels were associated with the vaccine or merely the use of anti-HIV therapy. If the study was not controlled it may not be possible to sort out other factors that might be influencing the outcome.

Did the report include information on *both* HIV-specific immune responses as well as viral load? Again, if the study was not *controlled* it is not really possible to say decreases in viral load were due to the vaccine product being researched. It's possible for the vaccine to be immunogenic (e.g. inducing HIV-specific immune responses) while anti-HIV therapy could be the factor controlling HIV replication.

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Discussion

Both preventive and therapeutic HIV vaccines are experimental. None have proven to be effective in preventing HIV infection or disease progression in humans. Several candidate vaccines are garnering interest from researchers and activists alike, including the Merck DNA vaccine and the Glaxo SmithKline HIV vaccine. Excitement for these particular products are due to the fact that they are moving forward into human studies and preliminary research suggests that they do something slightly different or novel compared to previous approaches that have been tested. Whether or not these products will prove useful in either the preventive or therapeutic arena remains to be seen and is wholly unknown.

Generally speaking, therapeutic vaccines are believed to be relatively safe. A likely scenario is that the vaccines will be given periodically, likely monthly, and side effects might predictably primarily be pain, redness and/or swelling at the site of injection and perhaps fever, fatigue and/or joint pain and stiffness – as one might expect with any vaccine. In some HIV vaccine studies, more serious injection site reactions have been observed (in a few rare cases of serious reactions there have been ulcerations at the injection site). It's quite likely/possible that people with some autoimmune diseases (e.g. lupus, arthritis, etc.) will be excluded from initial studies – as stimulating the immune system with vaccination has shown to worsen some of these conditions. It's even possible that stimulating the immune system with an HIV vaccine could worsen HIV disease progression. Results of previous studies of therapeutic vaccines don't suggest this is a major serious concern, but it is possible.

Undoubtedly, especially initially, new therapeutic HIV vaccines will be researched in conjunction with anti-HIV therapy. Some proposed study designs includes the use of therapeutic vaccine or placebo in a structured anti-HIV therapy interruption model. The hope is that the HIV-specific immune responses induced by the vaccine will suppress HIV rebound following therapy discontinuation longer than what might be observed among people not receiving the vaccine. If you're considering participating in such a study it's important to understand the potential risks of structured treatment interruption.

When HIV mutates and becomes resistant to the effects of ***drugs***, this is called *HIV drug resistance*. When HIV mutates and becomes resistant to the effects of the ***immune system*** this is called *immune* or *viral escape*. At least one previous study suggests that the virus can mutate around the immune response. Theoretically, it's possible that HIV can become resistant to new, functional and potent HIV-specific immune responses. How much this will present a problem for therapeutic or preventative vaccines remains to be seen.

Finally, the potential of HIV preventive and therapeutic vaccines are great. Despite years of research, however, this remains a field of study in its infancy. Many small studies have built the foundation for recent advances and researchers, activists and people living with HIV alike await the results of small studies of new vaccine approaches, such as the Merck DNA vaccine, to see where the next steps in this important area might lead.

The Bottom Line

- There are currently no proven effective therapeutic or preventive HIV vaccines
- Therapeutic HIV Vaccine Research is still in its infancy
- Many studies have reported information that is not encouraging
- We don't yet know if the ability of a vaccine to induce HIV-specific immune responses tells us, in and of itself, if the vaccine (or the immune responses) is useful in treating HIV
- New vaccines, including the Merck DNA Vaccine, have garnered much interest among activists, researchers and people living with HIV. Only results of human study will tell us if this enthusiasm is warranted. Initial studies are underway at several sites
- Therapeutic (and preventive) HIV vaccines researched to date have had minimal side effects, primarily pain, redness and swelling at the injection site and sometimes transient fever, fatigue and joint stiffness.
- In previous studies therapeutic vaccines were delivered monthly, by injection
- In the short-term, it's likely anti-HIV therapy will be required in experimental vaccine studies

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