Antibody Durability in HIV Vaccine Development

Website summary
Robert Seder of the Vaccine Research Center (VRC) at the US National Institute of Allergy and Infectious Diseases (NIAID) suggested that proof of principle that broadly neutralizing antibodies can protect in humans could come soon from passive administration studies the VRC and others are conducting with some of the recently isolated broadly neutralizing antibodies. Seder said durable memory was critical, but first you need proof of principle. Furthermore, once the principle of virus neutralization as the mechanism of action for protective antibodies is established in humans, we still need to identify immunogens that can induce these antibodies through vaccination. Nathanason said any study of durability has to be built around research that provides at least some idea of how to induce broadly neutralizing antibodies, what he called the giant elephant in the room. But when is the right time to be concerned with improving the durability of antibody responses to HIV, an issue that will continue to be important for the protective efficacy of any vaccine used on a broad scale?

Dennis Burton of the Scripps Research Institute and Gunilla Karlsson Hedes tam of the Karolinska Institutet argued that the issue of durability is interconnected with work to develop antigens, delivery vehicles, adjuvants and formulations to elicit broadly neutralizing antibodies and should therefore happen in parallel. Others, including veteran vaccinologist Stanley Plotkin of the University of Pennsylvania, asserted that valuable information about the factors that lead to durable immune responses can be gleaned from studies of existing vaccines and the incorporated into HIV vaccine research, as well as vaccineline development more broadly. Plotkin was also one of a few researchers who asserted that there is already cause to focus on improving durability of antibody responses: the fleeting protection observed in the RV144 trial. Efficacy of this viral vector/HIV protein prime-boost regimen was nearly 61% one year after initial vaccination but then declined to around 30% after three years, a problem that appears to be linked to waning antibody responses. The first thing to show is that we have a protective vaccine building on the RV144 vaccine, Plotkin said, adding that while antibody dependent cellular cytotoxicity (one mechanism through which the non-neutralizing antibodies induced by the vaccine regimen are thought to have afforded protection) is not the only response a vaccine should induce, the field should focus on how to extend these types of responses. Plans of future pox-protein trials are attempting to extend protection with adjuvants and an extra boost. While there was plenty of disagreement throughout the day’s discussions, nearly everyone agreed that a feasible HIV vaccine needs to elicit a durable antibody response and not require repeat immunizations to have the broadest public health impact, and therefore considered the issue of long-lived immune responses to HIV an important one. And in the end, the group coalesced on one concrete recommendation for the field. The participants agreed that the field should conduct studies in non-human primates comparing HIV Env to other viral glycoproteins to collect valuable information about the types and duration of antibody responses induced by HIV and whether they are inherently different from those induced by other viral proteins. Lessons from licensed vaccines

Lessons from licensed vaccines
of antigen is required day’s discussions. The quickly, Slifka said. Attenuated in humans persistence of immunity is often produce lower immunity than the magnitude and duration of the adaptive immune response to Vaccinia virus classic standard in terms of inducing durable immunological analyses of licensed vaccines that aren’t well understood. For example, the mumps vaccine has a problem with the decay in determining the durability of protection. Despite these similarities existing examples, and showed the relationships between peak initial titer, titer after boosting and rates of decay. Ballou’s presentation showed the context for comparing HIV vaccine durability to the rubella vaccine does not, which suggests the durability of immune responses isn’t entirely clear. Unfortunately, as Ballou, it doesn’t necessarily matter how high the antibody titer is based on a literature review of production thresholds required for protection. His threshold is rarely defined until you have a successful vaccine. Rolf Zinkernagel of the University Hospital Zurich argued repeatedly that the persistence of antigen and its role in antigen persistence is as compared to the viruses themselves. The decay rates were similar despite major differences in vaccine class. The decay curves were biphasic with antibodies reaching a peak soon after vaccination and then declining much more slowly. Antibody responses peak and the peak antibody titers achieved by the vaccines. In general, antibody responses peak and the peak antibody titers achieved by the vaccines. In general, antibody responses peak and the peak antibody titers achieved by the vaccines. In general, antibody responses peak and the peak antibody titers achieved by the vaccines.
Antigen and adjuvant selection and vaccination schedule
than 20 times the levels of antibodies directed to the V1 and V2 loops at peak than peak responses for vaccinated individuals in RV144. New adjuvants that can elicit high titer and durable antibody responses in non-human primates are also in development, according to Barnett, who is evaluating the longevity of antibody and T-cell responses induced by a novel self-amplifying messenger (SAM)-based adjuvant for HIV in macaques.

Reed discussed studies of new adjuvants for HIV that his group is developing and testing in early stage clinical trials in collaboration with Barton Haynes at the Duke Human Vaccine Institute and with Robin Shattock at Imperial College London. He argued that focusing on adjuvant formulation was a better avenue to improving durability than studying existing vaccines. Altering the vaccination schedule may be yet another way to improve the durability of immune responses. Barnett said they've seen better results when the prime and boost are co-administered, a strategy that is also being studied in one of the RV144 follow-up studies.

The topic of optimal vaccination schedules prompted some discussion. Participants debated whether giving the prime in one arm and boost in the other arm or spacing the subsequent booster immunizations out over a longer period of time might help improve durability of immune responses. In the wrap up discussion at the end of the day, it was suggested that HIV vaccine researchers should further investigate vaccination intervals because this was something that could be done rather simply and provide information on whether it extends the durability of immune responses.

There was also discussion about whether an adjuvant could be used to mimic viral persistence by creating a longer-term depot for the HIV antigen that would therefore stimulate the immune response over a longer period of time. This approach would be similar to using a live viral vector, something that is currently being explored by AIDS vaccine researchers but as of yet has not induced a robust antibody response. Both Seder and Nathanson argued that this would be an attractive feature for an adjuvant.

In addition to developing new adjuvants, researchers including Seder asked that pharmaceutical companies like GlaxoSmithKline share their existing adjuvants, such as AS01, with researchers so that they could do head-to-head studies to benchmark how different HIV antigens perform with the same adjuvant.

Harnessing systems biology

Part of the day's discussion was also centered on the utility of systems biology in elucidating factors that influence durability of vaccine-induced immune responses. This discussion followed presentations by Damien Chaussabel of the Benaroya Research Institute and Germain. Both argued the value of measuring multiple parameters and generating as much data as possible. But some attendees were skeptical of precisely what the systems biology approach could contribute, suggesting more data does not correlate with more knowledge.

Chaussabel said one example of how systems biology could be employed in HIV vaccine development is to compare data from trials using different adjuvants to see what similarities there are in the immune response profiles. He argued for researchers to share as much of their data as possible and input into an analysis tool like the one developed at the Benaroya Institute so that such comparisons could be made.

Germain also defended using a more holistic approach to understanding durability of vaccine-induced immune responses and said that systems biology allows researchers to pay attention to the connectivity of...
Antigen trafficking

Future studies
immune responses to vaccination, including the quantity of the initial immune response (the higher the peak antibody titer, the higher the persistent titer), the structure of the antigen, the selection of adjuvant, the persistence of antigen and where that occurs, the sub class of antibodies that are induced, and the role of T cells and Tfh cells in particular.

Plotkin implored researchers to collect more data from human clinical trials and from non-human primates when human studies aren't possible. He also argued for conducting studies of existing vaccines that generate both long- and short-lived responses in an attempt to elucidate how their immune response profiles differ, but it was unclear how many other participants shared this viewpoint.

Several other suggestions were also made. There was discussion about the need to standardize what antibody responses to HIV Env are measured (binding, neutralizing, ADCC, isotypes, etc.), in order to compare study outcomes, and to form a central group to promote standardization of monkey studies.

Hedestam suggested future studies be conducted to define the difference in immune responses induced by soluble versus particulate antigen and to look at how replicating versus non-replicating vectors affect durability of antibody responses but these suggestions always run into the obstacle of: should we learn more now or wait for the “best” immunogen that is “just around the corner.”

There was also a debate about whether long-lived plasma cells are the best biomarker for antibody responses. Germain noted that in addition to generating long-lived plasma cells, you also need to have a niche where they can live. In the end, there was no consensus on whether persisting antigen driving the continual generation of new plasmablasts or long-lived plasma cells have a greater impact on antibody durability.

Toward the end of our wrap-up discussion, Wilson asked if the attendees thought HIV Env induces inherently less durable immune responses than other glycoproteins and whether this was something the field should explore.

Plotkin’s opinion was that gp120 is less immunogenic than other viral proteins. Germain said the heavy glycosylation alters how HIV Env is processed. Dennis Burton of the Scripps Research Institute said while it isn’t known for certain if HIV gp120 is different from other viral antigens, evidence suggests it might be.

The attendees coalesced around the idea of conducting a head-to-head study in non-human primates comparing multiple trimeric HIV Env antigens, along with adjuvants, to other viral glycoproteins (possibly Influenza HA and another glycoprotein with exceptional durability such as Rabies) to see what can be learned about durability and whether HIV Env induces inherently less durable immune responses than other less heavily glycosylated viral glycoproteins.

It is undoubtable that durability of protective immunity is a critical barrier to successful vaccination against HIV; our panel was united in this view. However, unity around that theme belied clear differences between a camp expecting vaccine durability to improve during the normal course of product development and a camp believing that durability is a discreet aspect of vaccine science and should be approached as an unique research target that would enrich the success of many vaccines. By highlighting the differences in opinions of research leaders and showing the problems with simply defining vaccine durability or collecting relevant data, we emphasize the important of vaccine durability for the success of a future preventive vaccine against HIV.