Meeting Report -- AIDS Vaccine Research Subcommittee

The NIH held its regular AIDS Vaccine Research Subcommittee (AVRS) meeting on May 15-16, 2012. The meeting focused on the latest progress and challenges in NHP research and followed up on a similar AVRS meeting held in May of 2010.

Dr. Alan Schultz went over the history of vaccine research in NHPs and identified two recent game-changers: the development of the “low-dose” or titrated mucosal challenge as a more accurate model of HIV transmission in humans, and the results of the RV144 efficacy trial and correlates of risk analysis. One of the major current questions that was addressed at the meeting is the nature of the challenge virus in NHP experiments – which SIV to use, how to improve SHIV models, the choice between a clone virus and a swarm.

The last question was addressed by Dr. Brandon Keele, who described multiple applications of next-generation sequencing and new phylogenetic tools in NHP research.

- Founder-virus analysis allows one to measure vaccine efficacy not just in terms of absolute protection from infection, but also in terms of vaccine-mediated reduction in the number of transmitted variants if the challenge dose is high and results in 6-8 transmitted variants in the placebo group.
- Genetic analyses of challenge viruses currently used in the field show that genetically diverse populations of the (supposedly) identical challenge viruses are being used in different labs. This diversity likely affects the results of pathogenesis and vaccine trials.
- Using swarms for challenge allows one to figure out the number of transmitted variants (not possible with a clone) and, thus, better titer the challenge stock to better model the fact that in sexual transmissions of HIV the number of founder viruses is usually 1-3.
- The divergence between envelopes of mac251 and E660 viruses is approximately 20%, which makes them good models for heterologous challenge.
- Viruses are known to adapt to particular genetic backgrounds of hosts in different geographical regions. This phenomenon currently is not being reflected or modeled in NHP studies.
- The next goal is rational creation of single viruses and viral mixtures with properties necessary to answer specific questions. For example, viruses produced in two different cell lines can be mixed to assess the role of envelope glycosilation patterns in virus transmission. Several transmitter/founder viruses are being constructed right now.

The AVRS meeting in 2010 focused on the E660 virus and there were two updates at this meeting:

- Dr. Alan Schultz said that the virus is a primary swarm isolate with pathogenic properties in macaques. Its neutralization properties are peculiar in that it seems to be dominated by neutralization sensitive variants and a small number of variants that are very hard to neutralize. However, recent neutralization analyses of clones isolated from the E660 swarm at the Montefiori lab produced very confusing results: large differences in neutralization were
observed for the same clones depending on where they were produced (PBMC vs 293 cells) and where they were tested (PBMC, T2M-bl, M7-Luc).

- Dr. Vanessa Hirsch reported on significant progress in understanding TRIM5alpha restriction in macaques. The gene is very polymorphic (6-12 alleles), and has three main functional alleles: ddQ is permissive, while TFP and CypA are restrictive. Virus loads in animals with permissive alleles are ~100-fold higher than in animals with restrictive alleles. Several escape mutations in the capsid have been observed in viruses passed in restrictive animals (P127S and R233S are appearing multiple times). E660 clones that carry these mutations and are neutralization resistant have been created and will be analyzed for in vivo replication.

Dr. Jeff Lifson gave an overview of the history of SHIVs. Early SHIVs were non-pathogenic. Breakthrough came with passaging 89.6 SHIV in macaques, which became very pathogenic (89.6P). Later, research showed that its pathogenesis is very different from that of HIV – it primarily destroys naïve T cells, not memory T cells. Still, the approach for developing SHIVs is correct – passage the virus until the needed properties appear, then clone and sequence. What is needed now are SHIVs that can be mucosally transmitted, are based on founder viruses, result in sustained viral load and cause correct pathogenesis, and are based on clades C, A/E and B.

Dr. Normal Letvin described generation of four new SHIV constructs that look very promising in macaques, showing persistent viremia for 100-250 days post-infection. The constructs are based on HIV clade B isolate from Thailand, as well as on clade C virus and on CRF01_AE recombinant.

NIAID recently funded two large consortia to study HIV vaccine in NHPs:

- Dr. Dan Barouch and Dr. Paul Johnson said that their consortium will undertake a careful comparison of immune responses and early infection events for four types of vaccines: adenovirus and poxvirus vaccines, CMV vector vaccine, live-attenuated vaccine (LAV), passive antibody infusion, and antibody gene delivered by AAV vectors. Some of the latest findings include:
  - Repeat of Dr. Louis Picker’s CMV vaccine experiments using vaginal challenge (previous work was done via rectal challenge) shows very similar results (dichotomy between complete control and lack thereof). Virus DNA (not RNA) can be detected in colon, spleen and liver, indicating systemic control of the virus. Virus can be cultured from biopsies.
  - LAV-mediated protection matures over time (no protection on week 5, protection on week 20), allowing search for correlates. Both humoral and cellular correlates were identified, as well as some transcriptomic signatures.

- Dr. Eric Hunter and Dr. Rama Amara’s consortium will focus on the role of GM-CSF as an adjuvant in vaccines, looking at how it modulates DNA-MVA vaccine. Specifically, they will look at innate control of immunity, role of follicular T helper cells, effect on antibody class-switching and maturation, and interaction with neutrophils.
One interesting project is the development of Ab-like molecules in lampreys. These fish don’t have regular Ab, instead they employ a similar system that is based on pentameric variable leucine-rich molecules. These molecules are very stable, easy to design and produce, and can be raised against proteins that are highly conserved in vertebrates.

Jon Warren described NIAID’s support of transcriptomics approaches to the search for protection mechanisms and showed some recent data from a Barouch/Aderem/Zack collaboration, which found distinctive signatures for innate inflammatory genes in four different vectored vaccines. The strength of the signal was Ad5 < Ad26 < Ad35 < NYVAC.

Dr. Alan Schultz provided a summary of a recently organized workshop on vaginal challenges in NHPs. Multiple issues make this challenge model more complicated than rectal challenge:

- Rhesus vagina is physiologically quite different (thicker) than human, becomes thin only during the luteal phase of the menstrual cycle
- Use of Depo-Povera thins the epithelium, but it’s not clear whether this thinning is physiologically-similar to natural thinning, and whether it does not have any additional effects that might influence vaccine efficacy. Also the dosing may be too high to be physiological.
- Unlike some other monkeys, Rhesus females kept together do not synchronize their cycles
- In mice, the vagina dramatically changes after the first pregnancy. It should be investigated whether this happens in rhesus too.
- Bacterial vaginosis is very frequent in macaques. Some groups address this factor by doing routine antibiotic treatment before challenges.

Two groups are modeling the RV144 vaccine trial in NHPs:

- Dr. Nancy Miller is using an SIV challenge model, which makes it necessary to re-create the vaccine with SIV antigens (they used transmitter/founder variant). Also, since alum does not work well in macaques, an additional arm of the study will adjuvinate the protein with MF59. Immunizations begun in January and challenges (with mac251) will start in July 2012. The study will undertake extensive immunological analyses to search for correlates of protection:
  - Ab in serum and in mucosal washes, neutralization, ADCC, binding, ICS, lymph node biopsies (ICS, NK, B, TF-H), rectal biopsies (ICS, NK), bone marrow (B cells, ICS). Samples will also be stored for microarray analysis.
- COL. Nelson Michael is using a SHIV challenge model, which allows them to use the exact same vaccine that was used in RV144. Vaccinations will start in July. SHIV162P3 will be used as the challenge virus.

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