



New Primate Models: Will They Help HIV Vaccine Development?

Roundtable session 2

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Moderator: Nancy Haigwood

Rationale for search for predictive model



- Save time, money
- Perform challenge studies
- Test many approaches in parallel
- Discriminate between multiple, similar products for most efficacious
- Test risky approaches such as live attenuated, or vaccination of newborns



Summary of models

- Natural hosts--no disease
 - Sooty mangabeys--SIVsm
 - African green monkeys--SIVagm
 - Chimpanzees--SIVcpz
- Experimental hosts--variable time to disease
 - Chimpanzees--HIV-1
 - Baboons--HIV-2
 - Asian macaques (*M. mulatta*, *M. fascicularis*, *M. nemestrina*)--SIVmac, SIVmne, SIVsm, SHIVX4, SHIVR5

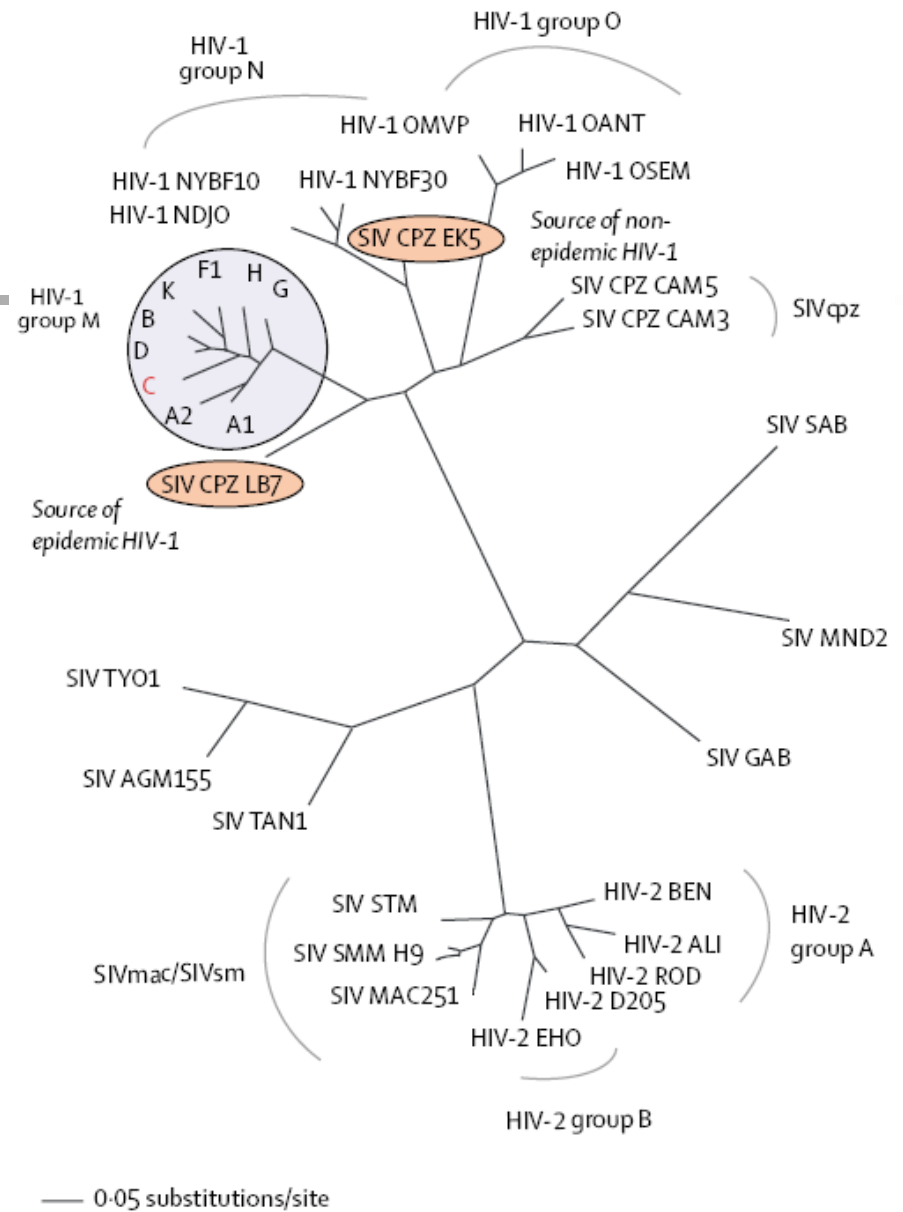


Limitations of experimental NHP challenge models

- Nonhuman and human primate biology are not identical
- Viral Envelopes differ (HIV-1 vs. HIV-2/SIV)
- Challenge routes (mucosal vs parenteral)
- Challenge regimens (dose, number of exposures)
- SIV isolates, virulence, titer
- SHIV adaptation by passage required
- Phylogenetic variants of SIV are limited in number compared with group M of HIV-1



Phylogeny



Uses of NHP models to inform prophylactic vaccines



- Loss of T cells in GALT, periphery
- Routes of infection and superinfection
- Passive transfer of IgG, serum, adoptive transfer of T cells show role for immunity
- Transient cell depletion (CD8, CD20) indicate roles for both T cells and antibodies
- Contribution of MHC alleles to better outcomes
- “Transient” infection can progress to disease

Uses of NHP models to inform prophylactic vaccine design



- Envelope subunits
- Prime boost modality
- Multiple antigens
- DNA vaccines, with cytokines
- Live attenuated vaccines depend on replication, differentially pathogenic
- Parenteral administration and mucosal challenge
- Mucosal challenge requires high single dose



Major issues causing us to rethink conclusions from NHP

- Many (most) of the earlier studies were performed with very small group sizes and “sterilizing” immunity as an outcome in the pre-PCR era
- Vaccines that “succeeded” against moderately replicating viruses failed to protect against high virulence challenge
- Challenges were all high dose, regardless of route--is this relevant to heterosexual exposure?
- Challenges were typically closely homologous with vaccine immunogens and may not predict “real world”

Ranking vaccines by virus load reduction using SIV/NHP



Requires parallel construction of SIV vaccines

- No assumptions re: immune correlates
- Factors in innate and adaptive responses
- Efficacy can be measured with VL assays that are sensitive and comparable
- Most stringent criterion, as most vaccines fail in stringent challenge model
- Most similar to clinical endpoints in human trials

Ranking vaccines by immune responses in SIV/NHP



Requires parallel construction of SIV vaccines

- Immunogenicity in blood samples from humans and NHP can be directly compared
- Same standardized methods for both types of samples, with some specialized reagents
- Level of “protective” immunity not known
- Many assumptions inherent in this approach
 - Immunogenicity predicts efficacy
 - NHP immunity predicts human immunity with accuracy
 - NHP immunity is a reliable surrogate for efficacy (protection)
 - NHP immunity elicited by similar vaccines can be reliably ranked



Key questions

- What is the current most preferred standardized SIV and NHP combination?
- What kinds of challenge regimens will be most informative for human mucosal acquisition/exposure?
- How do we best model genetic heterogeneity in the SIV model--role for SHIV?
- What progress is there in identifying optimal assays, correlates, or new models?



Round Table participants

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