Challenge Challenges: Considerations in the use of non-human primate models for studies of AIDS virus transmission and vaccine evaluation

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Overview

- NHP challenge models
- Recent developments in mucosal challenge models
- Impact of host factors
  - Protective MHC alleles
  - TRIM5α polymorphisms
- Current status and future developments
Why Non-human Primate Models for AIDS Vaccine Studies?

- Immunize and *challenge*!

- Experimentally defined infection parameters:
  - Infect with known virus with defined properties
  - Control timing, inoculum size, route

- Sample blood, tissues, at defined times relative to infection

- Interventions

- Proof of concept for novel vaccine approaches, comparative immunogenicity, basic questions relevant to vaccine development
Elements of a NHP Transmission/Vaccine Model

- Macaque species
- Challenge virus
- Challenge mode
  - Route
  - Dose
  - Single or repeat challenge(s)
Different Models

- Same Virus, Different Monkeys
- Different Virus, Same Monkeys
- Different Virus, Different Monkeys
- Same Virus, Same Monkeys, Different Challenge Route/Mode
- Same Name, Different Virus
Non-human Primate Models for AIDS Vaccine Studies

Monkeys

- Experimental ("non-natural") hosts
  - M. mulatta (*Rhesus*)
    - Indian, Chinese, Other
  - M. nemestrina (*Pigtail*)
  - M. fascicularis (*Cynomolgus, long tailed, crab eating*)
    - Mauritian cynos
Challenge Viruses for NHP Studies

Considerations:
- **Swarms vs. Clones**
- Production (transfection, infection, host cells)
- Homologous, heterologous

Viruses:
- **SIVs**: SIVmac 251, SIVmac239, SIVsmE660, SIVsmE543-3
- **Others**
- **SHIVs**: X4- SHIV89.6P (caveats), R5- SHIV 162P3/P4, SHIV AD8, SHIV1157 (Clade C “early”)
- **MANY OTHERS!**

Need for additional viruses...
Challenge Modes

Routes \textit{(cell free virus)}:

- Intravenous, intrarectal, intravaginal, penile, oropharyngeal/tonsillar

Dose:

- In vitro or in vivo titered, RNA, CA

Challenge number:

- Single, double, repeat
- Repeat titered mucosal challenges
THE ONE BEST SUITED TO ANSWER THE EXPERIMENTAL QUESTION OF INTEREST
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Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection

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The precise identification of the HIV-1 envelope glycoprotein (Env) responsible for productive clinical infection could be instrumental in elucidating the molecular basis of HIV-1 transmission and in designing effective vaccines. Here, we developed a mathematical model of random viral evolution and, together with phylogenetic tree construction, used it to analyze 3,449 complete env sequences by single genome amplification from 102 subjects with early infection. Viral env genes evolving from founder viruses generally exhibited a star-like topology, whereas those which by bulk or near-limiting dilution PCR amplification of viral nucleic acid [provisional DNA or viral (v)RNA], followed by cloning, sequencing, and phylogenetic analysis (2–12). Alternatively, bulk amplification of viral nucleic acids were analyzed by heteroduplex tracking analysis (HTA) where only a small fraction of the gene of interest was interrogated by selective annealing of a short oligonucleotide to followed by differential migration of the heteroduplex (3–5). Although these approaches provide an approximation of the diversity of virus populations in acute and early infection, they have significant limitations. HTA, for example, does not pro...
HIV-1: Single virus infection with low diversity
HIV-1 subtype B / intrapatient diversity

Max. Diversity 15% Chronic Subtype B

Max. Diversity 1.6%
2 yrs infected

Max. Diversity 1.9%
4 yrs infected

Max. Diversity 3.2%
4 yrs infected

Max. Diversity 3.2%
6 yrs infected
Characterization of Challenge SIV Stocks

- Diversity between vaccine and challenge stocks: Representative of real world heterologous challenge, within/between clades?

- Diversity within stocks: Representative of within transmitter variation?
“Heterologous” challenge (251 vs. E660) is a good approximation of intrasubtype variation
Inoculum Diversity

“SIVmac251”

Max. Diversity 2.7%

“SIVsmE660”

Max. Diversity 1.8%
SIVmac251 diversity

- Tulane
  Max. Diversity 1.4%

- Ron Desrosiers
  Max. Diversity 2.3%
  SIVmac251-2000
  SIVmac251-2006

- Letvin/Barouch
  Max. Diversity 0.8%

- Chris Miller
  Max. Diversity 1.1%
Low-dose rectal inoculation of rhesus macaques by SIVsmE660 or SIVmac251 recapitulates human mucosal infection by HIV-1

Brandon F. Keele,1 Hui Li,1 Gerald H. Learn,1 Peter Hraber,2 Elena E. Giorgi,2,3 Truman Grayson,1 Chuanxi Sun,1 Yalu Chen,1 Wendy W. Yeh,4 Norman L. Letvin,4,5 John R. Mascola,5 Gary J. Nabel,5 Barton F. Haynes,6 Tanmoy Bhattacharya,2,7 Alan S. Perelson,2 Bette T. Korber,2,7 Beatrice H. Hahn,1 and George M. Shaw1

Low-Dose Mucosal Simian Immunodeficiency Virus Infection Restricts Early Replication Kinetics and Transmitted Virus Variants in Rhesus Monkeys†

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Intrarectal Titration with SIVmac251

1:100 dilution ir challenge

1:1000 dilution ir challenge

Liu et al. JVI Oct 2010
A Limited Number of Simian Immunodeficiency Virus (SIV) env Variants Are Transmitted to Rhesus Macaques Vaginally Inoculated with SIVmac251

Mars Stone, \textsuperscript{1,2,3,\dag} Brandon F. Keele, \textsuperscript{3,\dag} Zhong-Min Ma, \textsuperscript{1,2} Elizabeth Bailes, \textsuperscript{5} Joseph Dutra, \textsuperscript{2} Beatrice H. Hahn, \textsuperscript{3,4} George M. Shaw, \textsuperscript{3,4} and Christopher J. Miller, \textsuperscript{1,2,5}

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IVAG Infection with Single Variant \( (10^3 \text{ TCID}_5) \)
IVAG Infection with Multiple Variants (\(10^5\) TCID\(_{50}\))
Min. number of unique transmitted lineages

- **Vaccinees median 1.5**
- **Control median 8**

- Tissue
- Plasma

Franchini, et al
LCM SGA Sequencing of Cervical SIV+ Foci

Section 1
Penile Infection with Single SIVmac251 Variant ($10^5$ TCID$_{50}$)

Miller, Keele, Lifson, et al
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**NOTES**

The High-Frequency Major Histocompatibility Complex Class I Allele 
*Mamu-B*^17^ Is Associated with Control of Simian Immunodeficiency 
Virus SIVmac239 Replication

Levi J. Yant,\(^1,2\) Thomas C. Friedlich,\(^1\) Randall C. Johnson,\(^3\) Gemma E. May,\(^1\) Nicholas J. Maness,\(^1,2\) Alissa M. Enz,\(^1\) Jeffrey D. Lifson,\(^4\) David H. O'Connor,\(^1,2\) Mary Carrington,\(^3\) and David I. Watkins\(^1,2\)\(^*\)

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Control of Chronic Phase SIVmac239 Viremia in Mamu B*08+ Rhesus Macaques

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Intrinsic Susceptibility of Rhesus Macaque Peripheral CD4⁺ T Cells to Simian Immunodeficiency Virus In Vitro Is Predictive of In Vivo Viral Replication

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The cytoplasmic body component 
TRIM5α restricts HIV-1 infection 
in Old World monkeys

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Specific recognition and accelerated uncoating of 
retroviral capsids by the TRIM5α restriction factor

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TRIM5α Modulates Immunodeficiency Virus Control in Rhesus Monkeys

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TRIM5 Suppresses Cross-Species Transmission of a Primate Immunodeficiency Virus and Selects for Emergence of Resistant Variants in the New Species

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Polymorphisms in Rhesus Macaque TRIM Coding Sequence

Impact of TRIM Polymorphisms on SIVsmE543-3 Infection

Differential Viral Restriction by Rhesus TRIM Alleles

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NHP Challenge Models: Summary

- NHP models an invaluable component of basic and applied AIDS research
- Multiple NHP models available; understand options and pick model best matched to experimental question of interest
- Much progress, more authentic mucosal challenges possible with characterized challenge stocks; repeat titered mucosal challenge emerging as a standard; demanding
- Impact of host factors; identified and not yet identified
- Additional models needed and under development:
  - SIVs, R5 SHIVs, stHIVs
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