



Transcriptional profiling of the host response to SIV infection in Rhesus Macaques and Sooty Mangabeys

Steven Bosinger, PhD

University of Pennsylvania

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“For this field to make progress, we need to become evolutionist and learn more about natural SIV hosts. We need to think about ways to harness the human immune system to adapt to the virus in the same way.”

Dr. Warner Greene, Chair - Final Remarks of the NIAID Summit on AIDS Vaccines, Bethesda, March 25th 2008.

Sooty Mangabeys are a natural host of SIV infection



Cercocebus atys

- West African monkeys, natural reservoir of SIVsmm
- SIVsmm is the origin of HIV-2 and SIVmac viruses
- Infection common in the wild and in captivity

SIVsmm infection

- Absence of disease
- Chronic high viral load (10^4 - 10^6 copies/ml)
- Preservation of blood CD4+ cell in >90% of animals
- Low levels of T cell activation, proliferation and apoptosis

Disease resistance is not due to:

- ✗ Reduced virus cytopathicity
- ✗ Restricted virus tropism
- ✗ Better adaptive antiviral immune responses

Comparative studies of natural vs non-natural host SIV infection

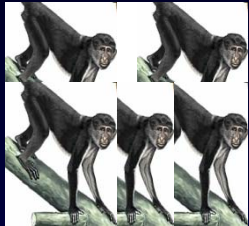
	Non-Natural	Natural
Species	Rhesus Macaque	Sooty Mangabey
Disease	Yes	No
Viremia	High	High
CD4 depletion blood	Yes	Rare
CD4+ depletion gut	Yes	Yes
Acute Immune Activation	Yes	Yes
Chronic Immune Activation	Yes	No

Objectives

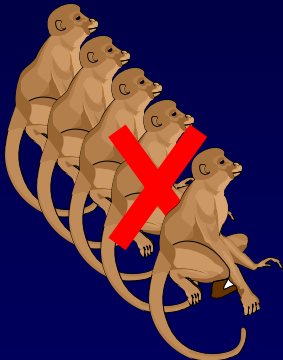
- 1. Compare the profile of gene expression during acute and chronic SIV infection of sooty mangabeys and rhesus macaques.**
- 2. Identify molecular pathways involved in the differential regulation of the host immune responses in the two species.**

Experimental Design

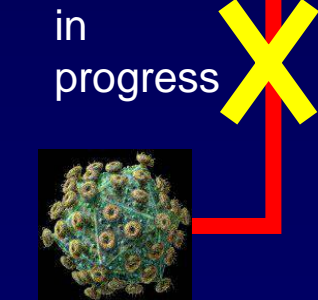
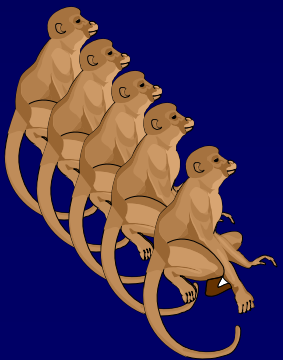
5 SMs



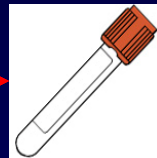
5 RMs



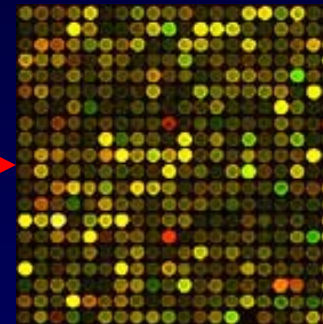
8 RMs



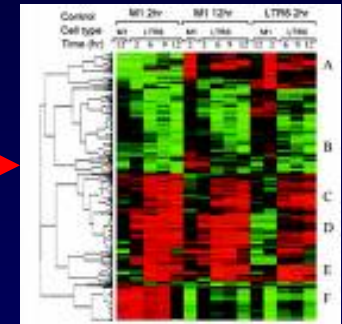
Whole
blood RNA
collection



Affymetrix
Rhesus
arrays:



Data
analysis

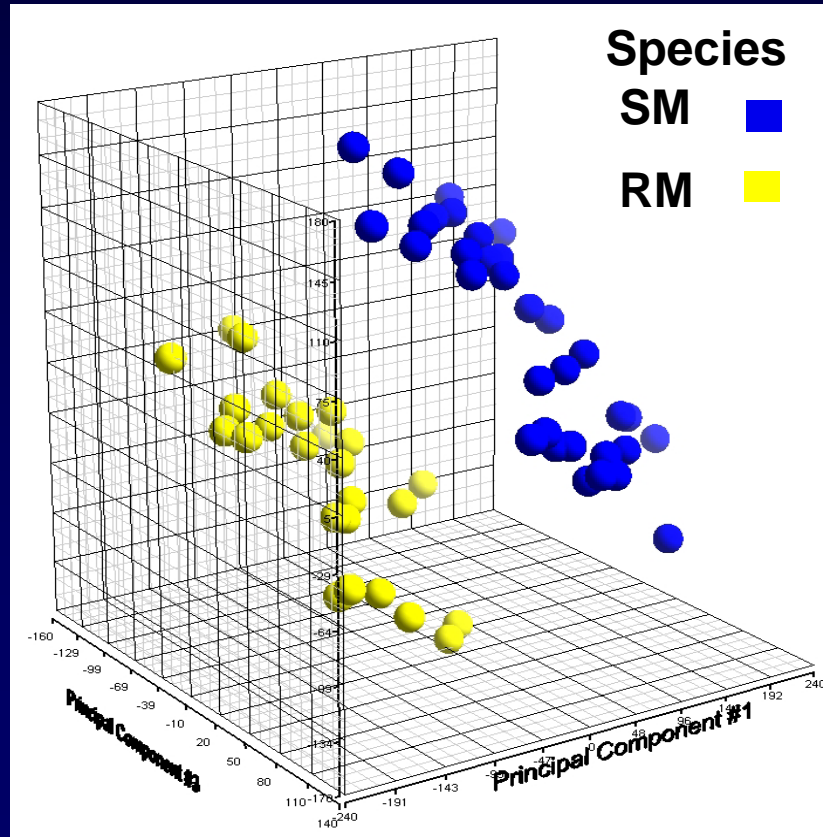


Acute (d)	-5, 3, 7, 10, 14, 30
Chronic (d)	180

Gene expression is fundamentally different between host species

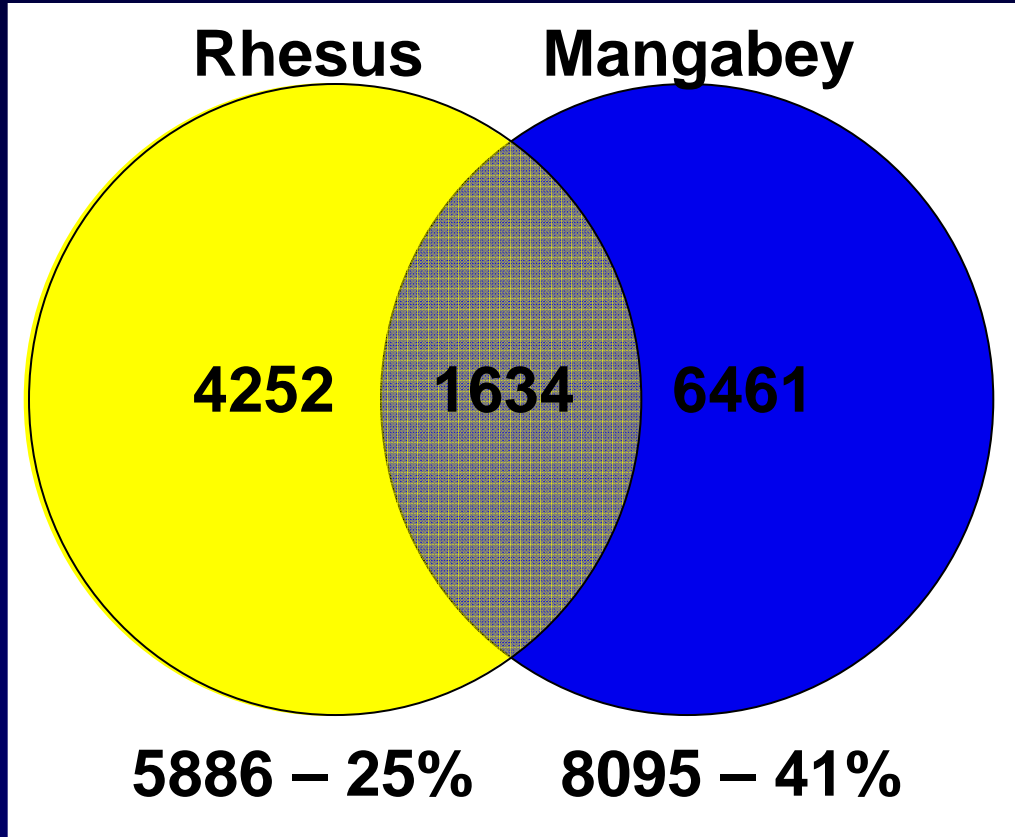
Principal Component Analysis

All present genes



ANOVA

Genes regulated by SIVsmm infection



SIV induced genes clustered by expression pattern

Species

■ SM

■ RM

Infection

■ Uninfected

■ Acute – 3-30 d

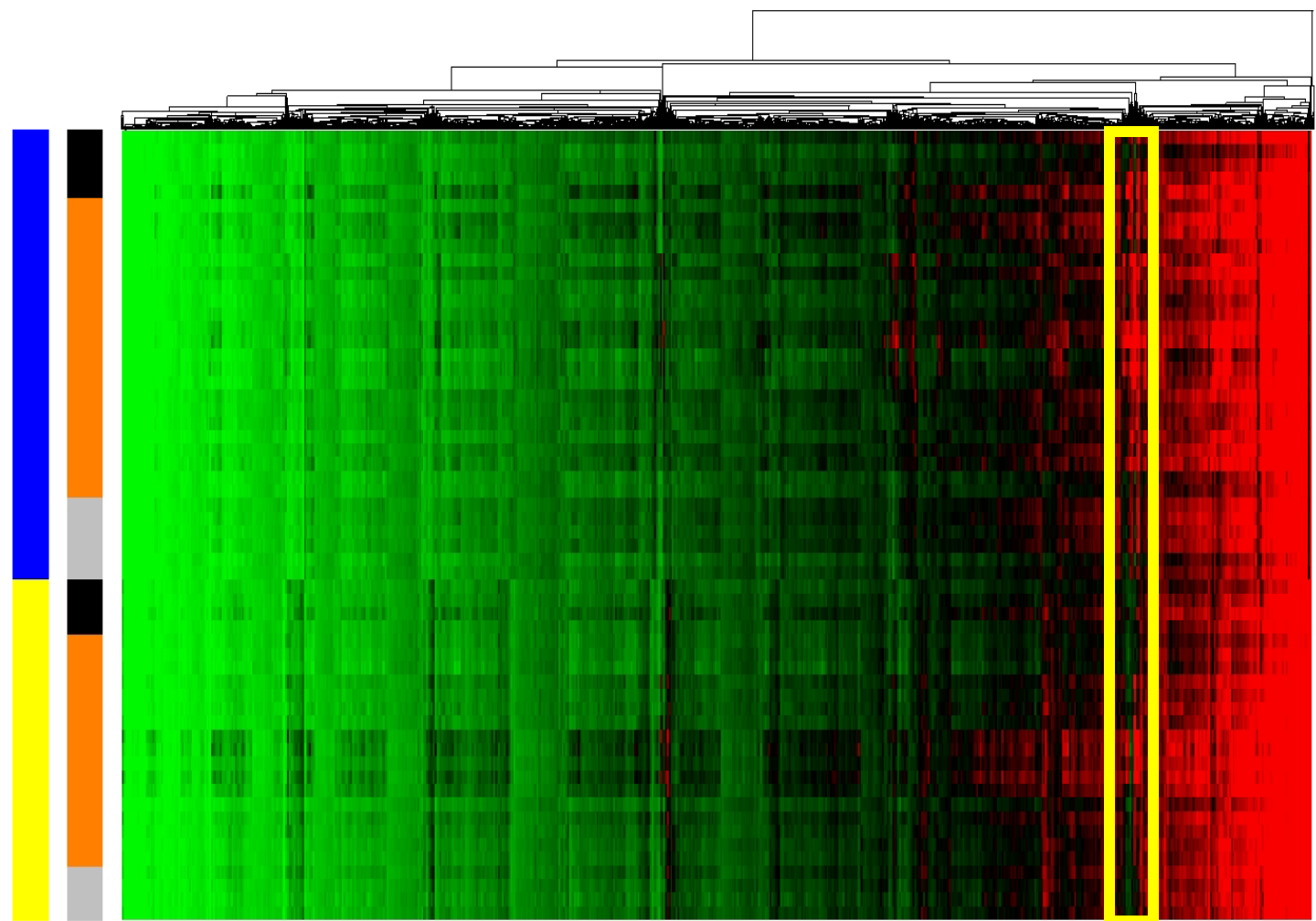
■ Chronic – 180 d

Log Intensity

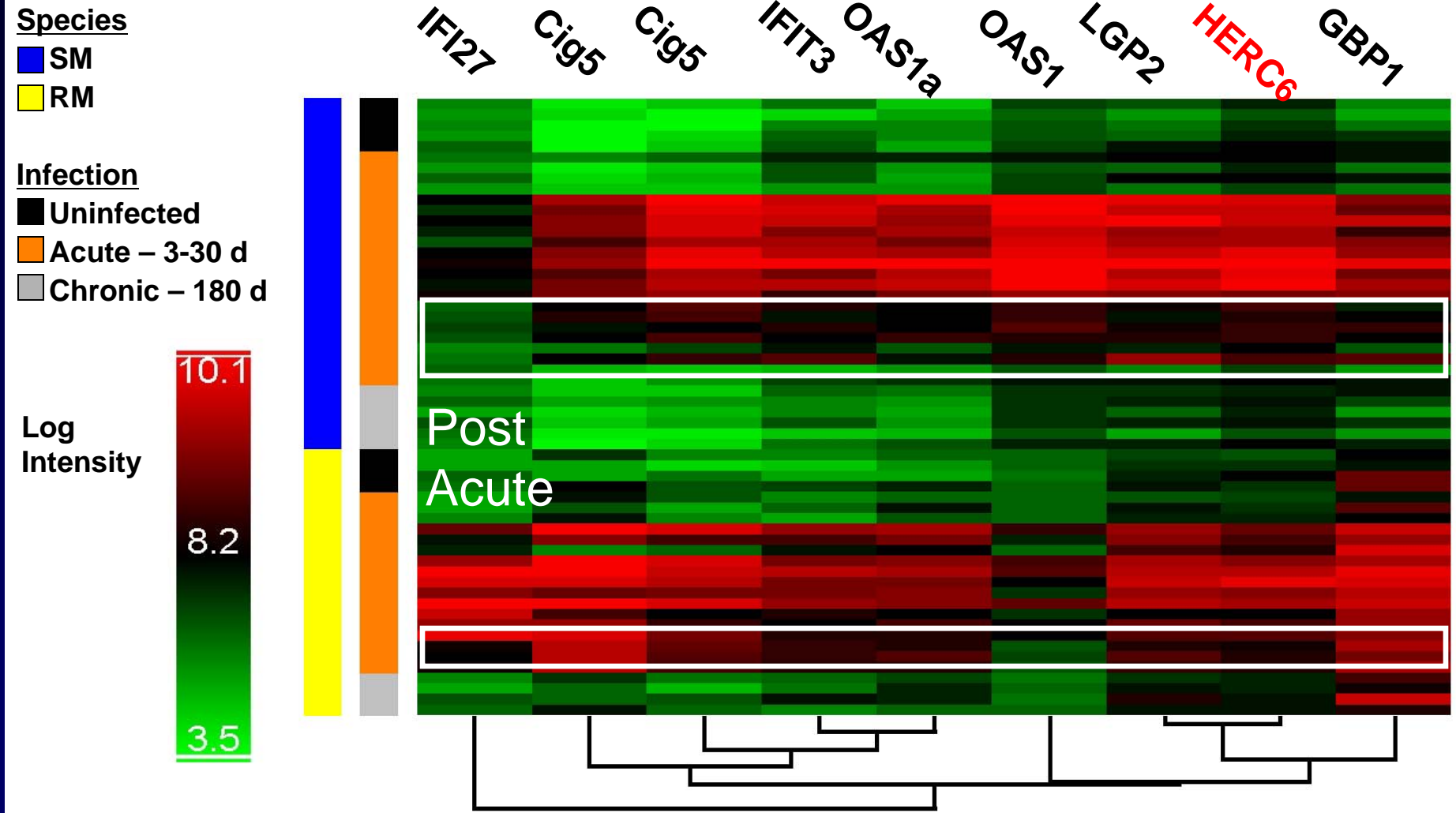
10.1

8.2

3.5



Type I Interferon Stimulated Genes (ISGs) induced during SIV infection



ISG expression in SMs during SIVsmm infection

- 1. We observed a strong (~4-5 log), but transient induction in Type I interferon stimulated genes (ISGs) in SMs during acute SIVsmm infection**
- 2. SM pDCs produce lower amounts of IFN α in response to TLR7/9 ligands than RM (Mandl et al., 2008)**
- 3. The clear upregulation of ISG expression in SMs observed in the current study may be related to:**
 - IFN α production by other cell types and/or in response to other stimuli**
 - Threshold of TLR7/9 activation may be lower during acute SIV infection**
- 4. Low IFN α production by pDCs and down-regulation of ISGs may prevent systemic immune activation during chronic SIV infection of SMs**

Preliminary Conclusions:

- **SIV induced gene expression is fundamentally different between SM and RM.**
- **SMs exhibit a robust but transient up-regulation of ISG mRNA during acute infection.**
- **Previously unrecognized genes involved in the host response to SIV in SMs are currently being identified.**

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