Investigating Viral Dynamics

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INTRODUCTION

► Simian immunodeficiency virus (SIV) infection of non-human primates reproduces key elements of HIV

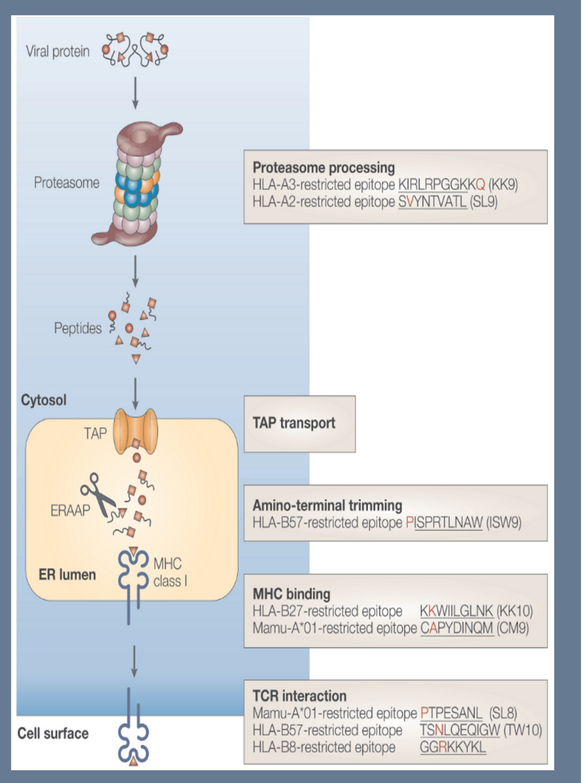
► Virus infects CD4+ cells

► CD8+ T cells recognize short viral peptides presented by MHC and kill infected cells

► Viral peptide has mutations which may prevent MHC binding and CD8+ T cell killing

► Mutations bear fitness cost

► CD8+ T cells exert selection pressure resulting in outgrowth of certain mutations



Mechanisms of mutational escape in HIV and SIV
Goulder PJ, Watkins DI. *HIV AND SIV CTL ESCAPE: IMPLICATIONS FOR VACCINE DESIGN,* Nature Immunology (2004)

THE EXPERIMENT AND OBJECTIVES

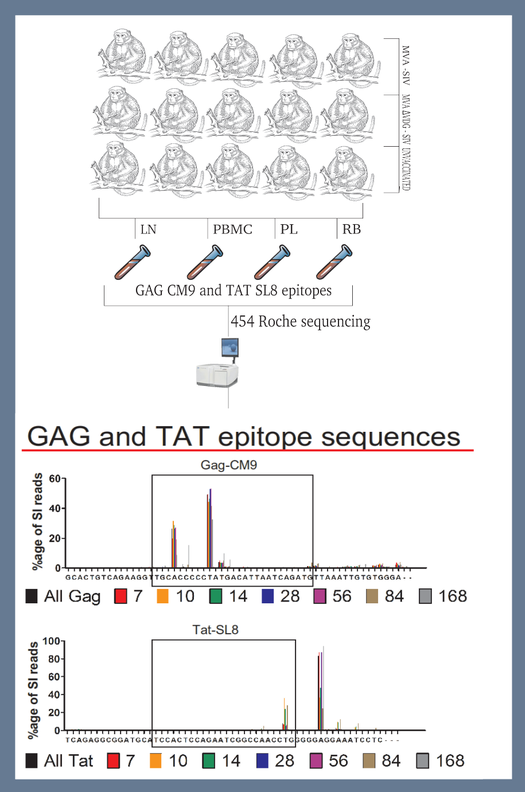
To understand and investigate, after infection of macaques by SIV, the :

► viral escape rates estimates in different tissue compartments for Gag and Tat proteins.

► comparison of escape rates between vaccinated and non-vaccinated animals.

► comparisons of escape rates between different tissue compartments.

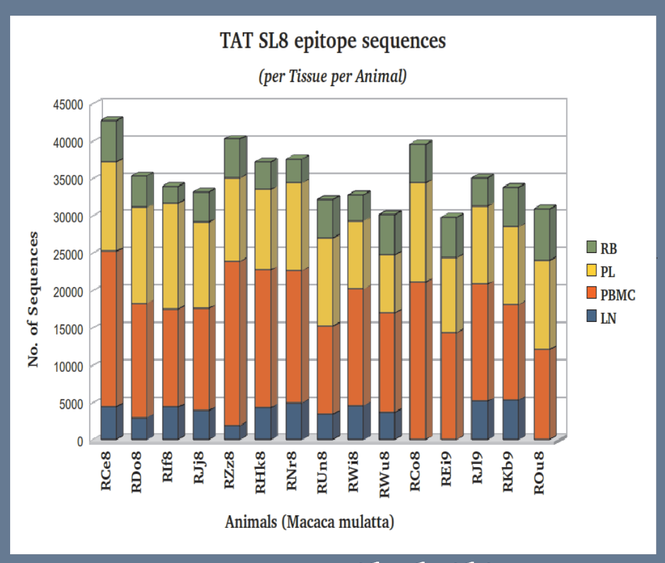
► to develop a software for the detailed investigation of viral mutational kinetics.



SIV Viral experiment flowchart
Four tissue samples from 15 animals were ultra deep sequenced for Gag CM9 and Tat SL8 epitopes

RESULTS

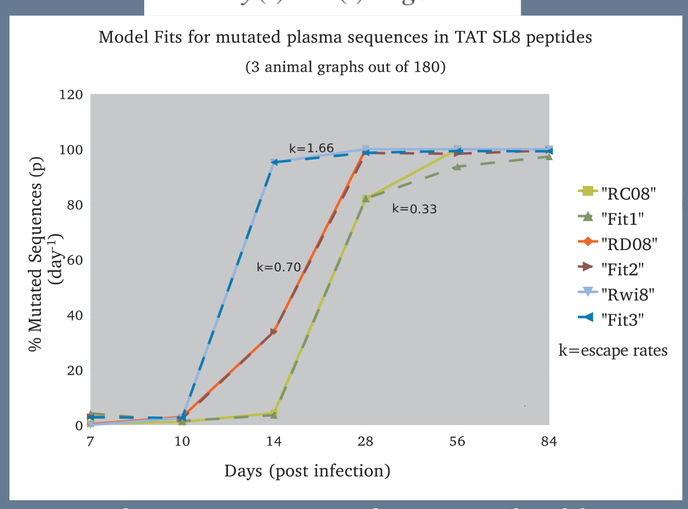
Viral Next Generation Sequencing Data Analysis Pipeline



Data Availability

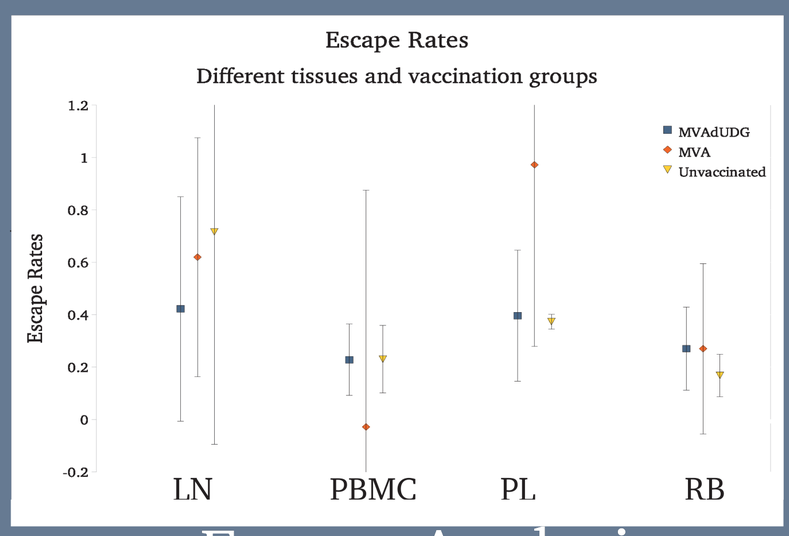
Raw Data Availability for Tat Protein
Ultra deep sequencing data was analysed for estimating viral sequence mutation values for both Gag and Tat proteins (~ 1 million seq)

$$p(t) = \frac{x(t)}{y(t) + x(t)} = \frac{1}{ge^{-kt} + 1} \quad (1)$$



Mathematical Modelling

Estimating Escape Rates using Mathematical Modelling
Three out of 360 graphs are displayed which show the fits of the mathematical model of Tat sequence data from plasma



Escape Analysis

Viral Mutational Kinetics among animal groups and tissues
Averaged animal group escape rates shows the variance of mutational kinetics (mutation and reversion) in differnt animal tissues.

CONCLUSIONS

► Tat contains more mutations (60%) than Gag epitope sequences (7%).

► Lymph Node sequences from Tat have high variation in escape rates from unvaccinated animals as compared to other tissue compartments.

► All sequences contain mutations as Day 28 in Tat SL8 epitope except Rectal Biopsy.

► Epitope predictions determine that 80% of mutated Tat peptide sequences will bind to MHC for a threshold of 500nm.

► Animal RDo8 vaccinated with MVA ΔUDG shows rapid reversion in LN and rapid escape in other tissues.

► Vaccination had little effect on the viral escape kinetics.

Future Work

►Comparison of viral lytic and non lytic model.

►Analysing more days and tissues for detail investigation.

►Conversion of data analysis pipelines to an R package.

References

►Asquith, B., and A. R. McLean. 2007. Invivo CD8+ T-cell control of immunodeficiency virus infection in humans and macaques. Proc. Natl. Acad. Sci. USA 104:6365-6370

We thanks our collaborators for sharing the viral sequence data