Convergence of the NF-κB Pathways Increase HIV-1C Transcriptional Fitness

Hrimkar Bhargav Buch[1], Aboli Srikant Varunjikar[1], Manisenthil Shanmugam[2] Udaykumar Ranga[1] for the Research Group HIV-AIDS Laboratory
[1] Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru, Karnataka, India
[2]Y.R. Gaitonde Centre for AIDS Research and Education, Chennai, Tamil Nadu, India

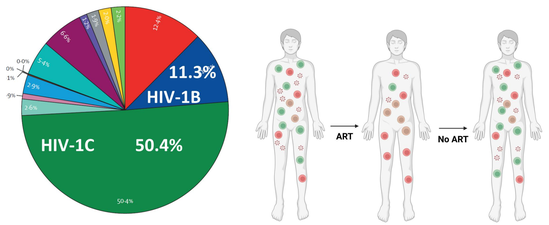
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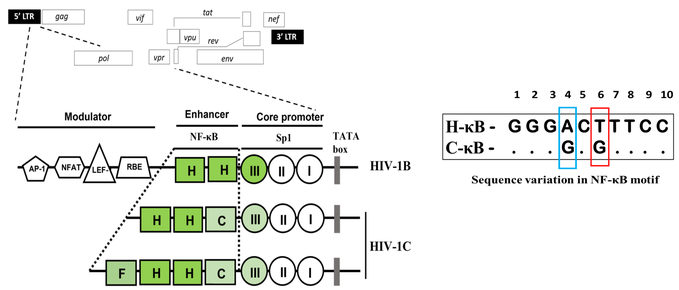
Introduction

HIV-1C Global Dominance

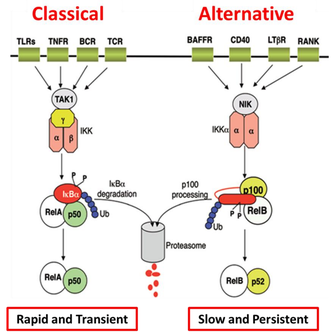


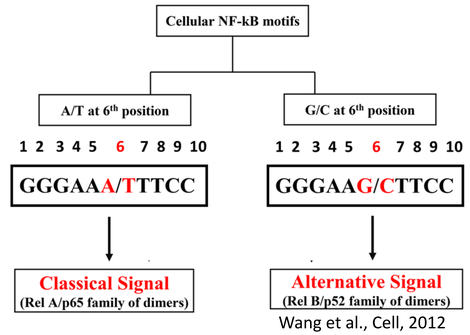
J Hamelaar et al., Lancet Microbe, 2024

HIV-1 promoter architecture and NF-κB motif sequence variations



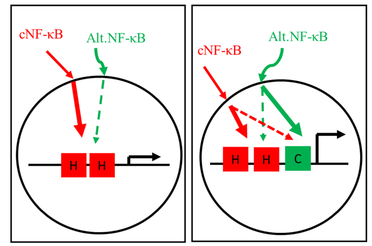
NF-κB signaling pathways and motif specificity





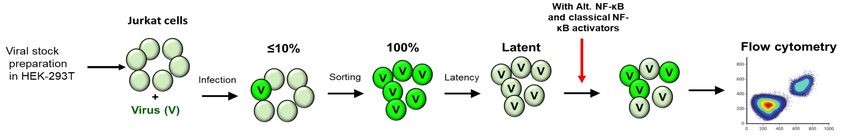
Wang et al., Cell, 2012

Working Hypothesis

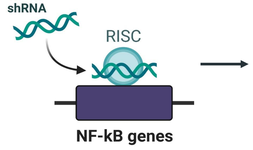


Methodology and Experimental Design

Jurkat Latency Reversal Model

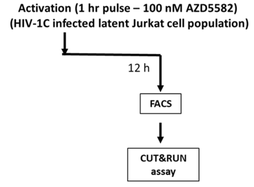


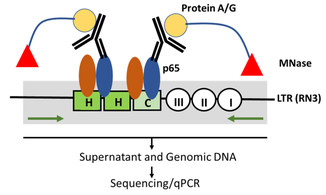
shRNA Knockdown stable cell lines



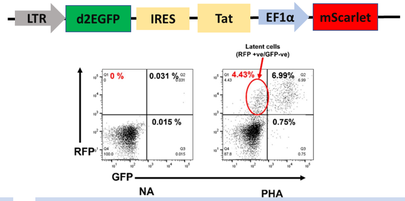
Signalling pathway analyses

CUT&RUN assay to characterize TF recruitment



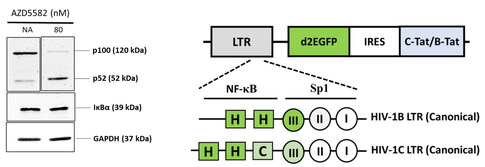


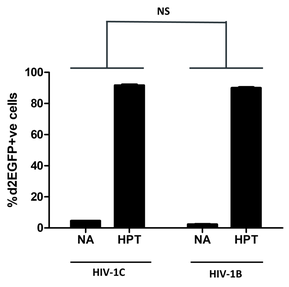
Primary CD4 T-Cell Model for Latency reversal



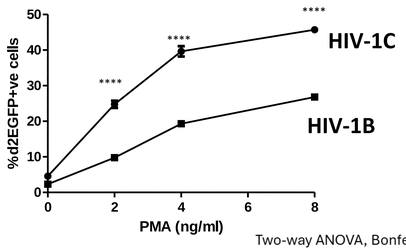
Results

HIV-1C LTR is more receptive to both classical and alternative NF-κB signalling

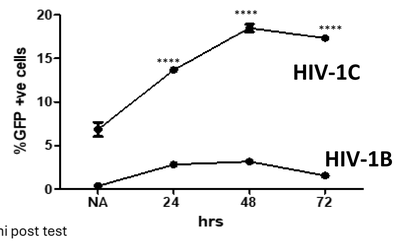




Classical Pathway (PMA)

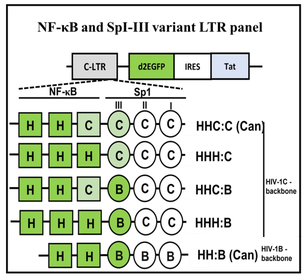


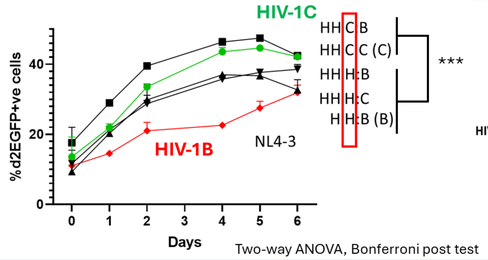
Alternative Pathway (AZD5582[1])



Two-way ANOVA, Bonferroni post test

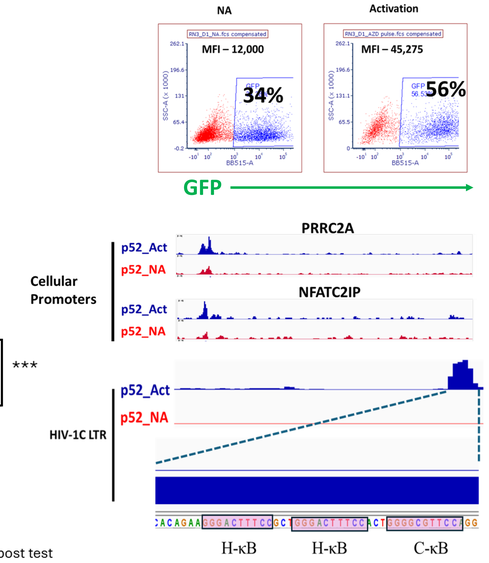
The C-κB motif of the HIV-1C confers superior receptivity to the Alternative NF-κB pathway





Two-way ANOVA, Bonferroni post test

Alternative NF-κB member p52 activates HIV-1C LTR- CUT&RUN seq



Summary and Future Work

- The unique C-kB motif in the HIV-1C LTR enhances responsiveness to both classical and alternative NF-kB pathways.
- The Alternative NF-kB factor p52 binds to the HIV-1C LTR, promoting viral transcription.
- Alternative NF-kB pathway activators will be tested for inducibility of latent reservoirs from clinical samples and primary cell models.

[1]L Pache et al., Cell Rep Med, 2020

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Contact Information

- Email - hrimkarbuch@jncasr.ac.in
- Linkedin – Hrimkar Buch