CALIFORNIA HIV/AIDS RESEARCH PROGRAM

HIV-1 Cotranscriptional Splicing: Roles for Tat and NELF

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This proposal is based on preliminary indications from our research that HIV-1 Tat expression in T cells may depend on the efficiency of Tat mRNA splicing, and that this may be different in TCR and TNF signaling cells. This idea is novel and supported by the observation that host cell TNF response genes are regulated in this manner, but as yet we lack preliminary data to support the hypothesis. The question is exceptionally well-suited to genome-wide ChIP-seq and GRO-seq analysis, which will allow much more quantitative comparison and assessment of the mechanism of HIV-1 nascent mRNA accumulation and how it compares with that of host cell TNF early- and late-response promoters. Bioinformatics could further extrapolate much information about how the sequence of HIV-1 core promoter compares to that of these host cell genes, and would further reveal whether NELF-regulated pausing is a gene-specific property that could be coupled with the need for slow elongation, to enhance incorporation of weak exons that might otherwise get skipped in the TNF signaling environment. However, at present we have no funding that would cover any ChIP-seq or GRO-seq analysis for HIV-1, nor have we previously had a reason to carry out such a study. Moreover, a full extrapolation of all of this data would extend well beyond the scope of this proposal. Nevertheless, carrying out the studies described in Aim 1, and in particular obtaining the ChIP-seq and GRO-seq data and finishing the initial assessment of whether splicing of Tat mRNAs are delayed in TNF compared to TCR-treated T cells would provide the most important information that would be needed to support a new RO-1 application to investigate this question.

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