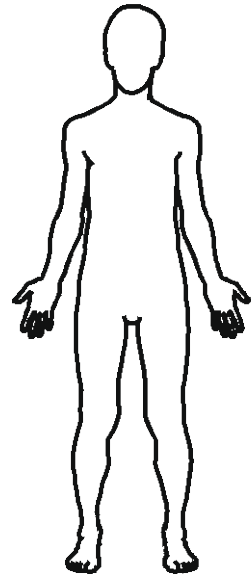




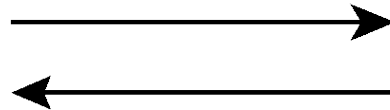
# My lab is interested in understanding how genetic variation at host-pathogen interfaces drives differences in disease severity and clinical outcome

- Functional genomics
- Transcriptomics
- Proteomics
- Molecular virology

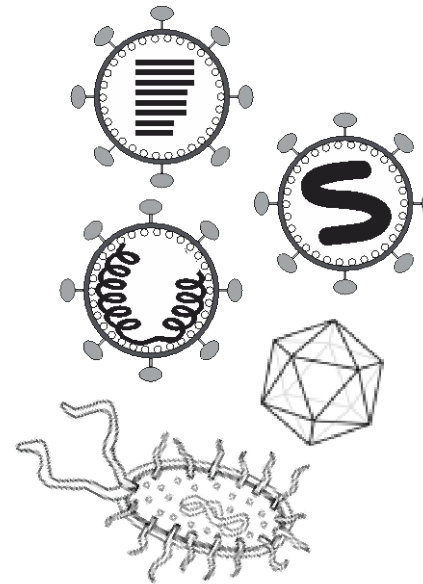


Host

Host  
response

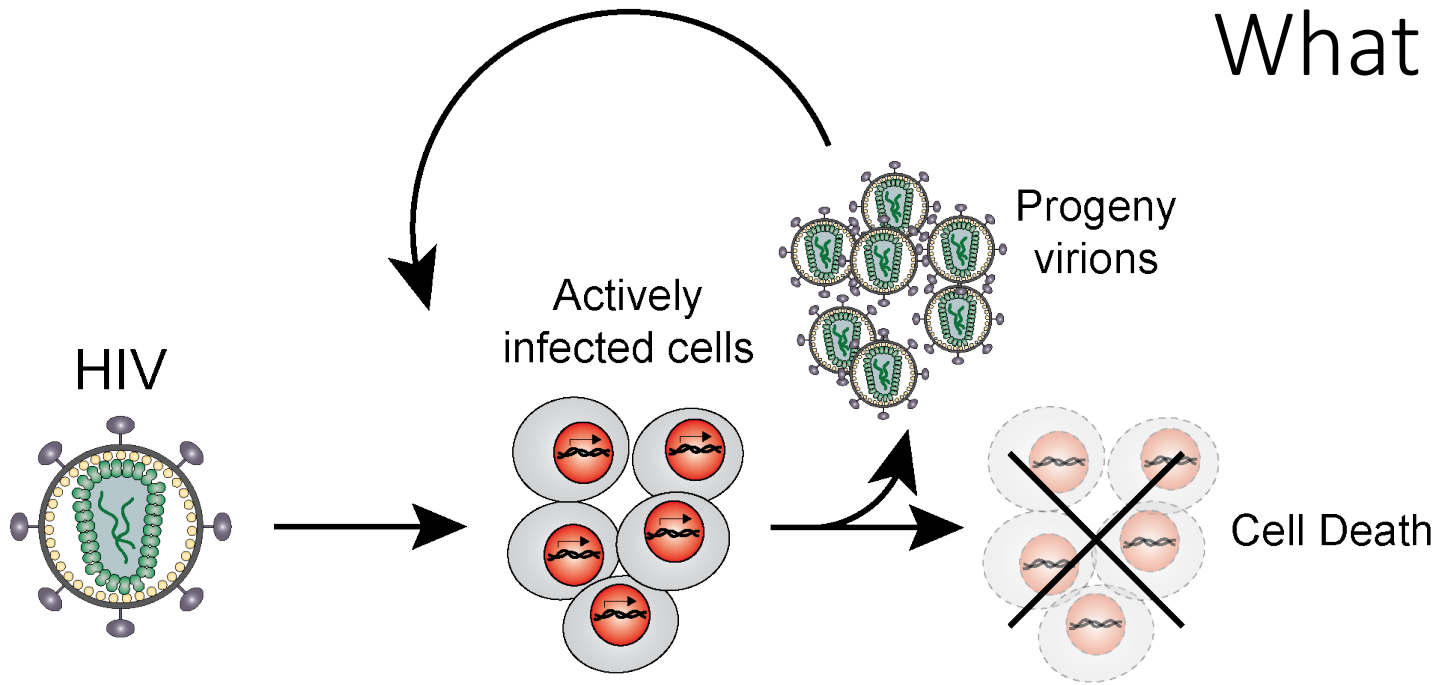


Replication  
and Rewiring



Pathogen

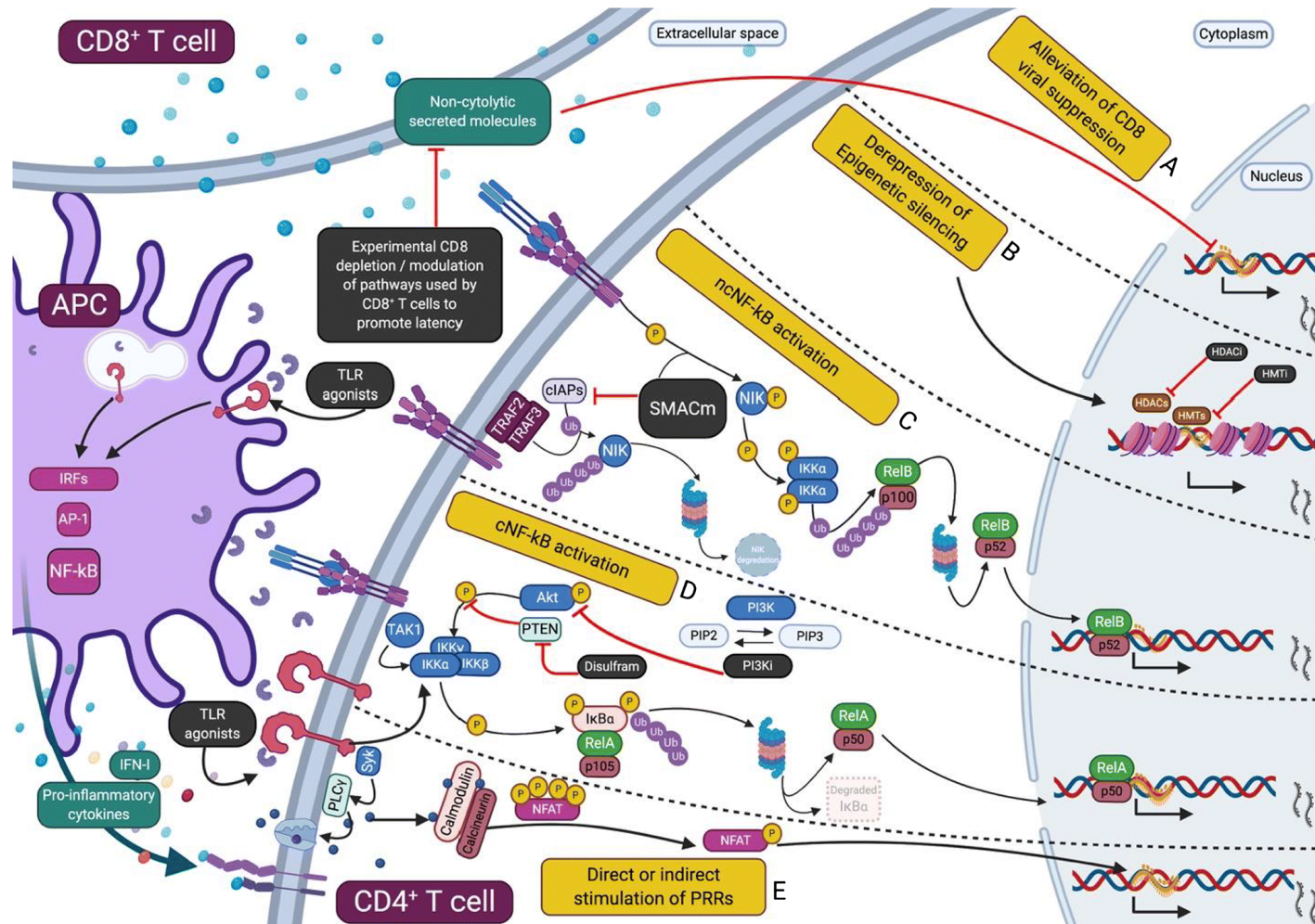
- Deep sequencing
- Pathogen genomics
- Translational methods
- Modeling



What are the host factors that regulate HIV latency?

*Can we eliminate the latent reservoir using small molecules that activate viral transcription?*

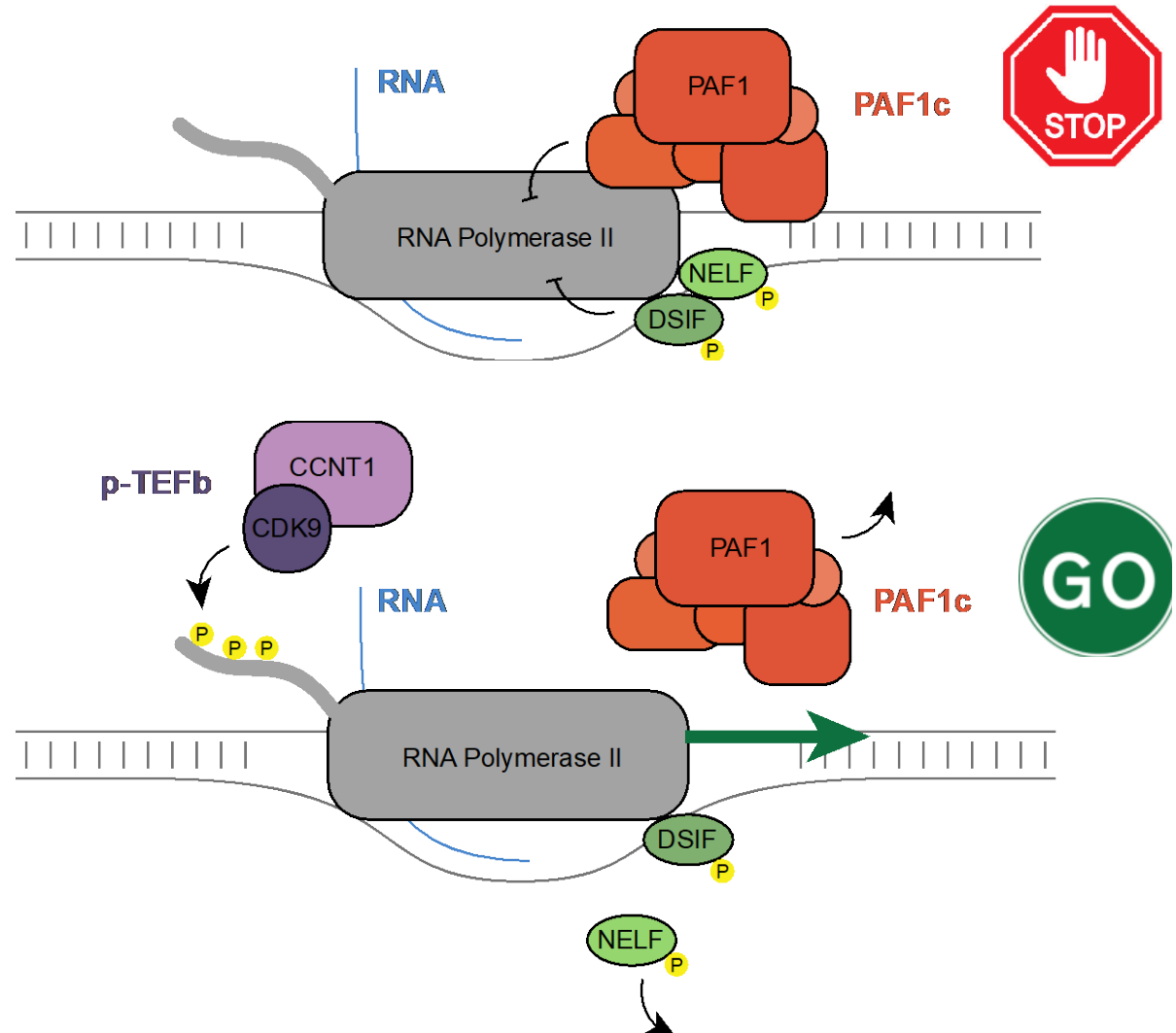
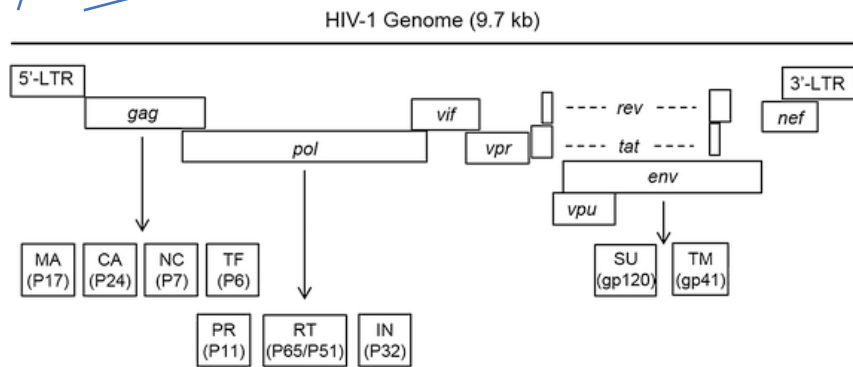
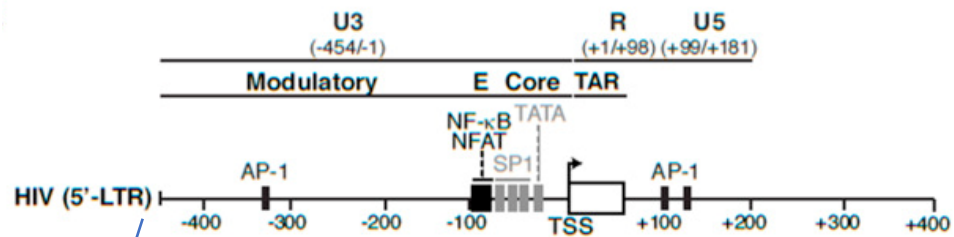
# Multiple latency reversing agents have been developed, but none have been successful in the clinic



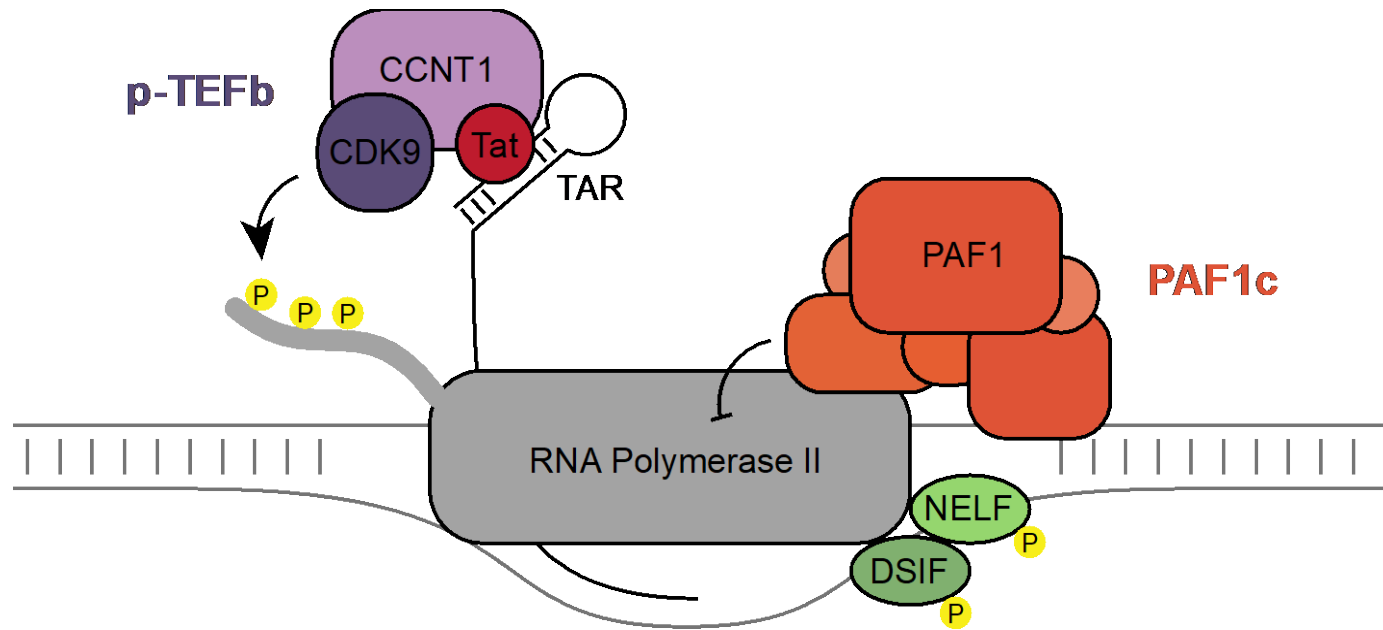
- Over 15 clinical trials have tried using LRAs to disrupt viral latency.
- Most have had some success in inducing viral transcription.
- None have meaningfully impacted the size of the viral reservoir.
- *Current research is looking at new drug targets and synergistic combinations*



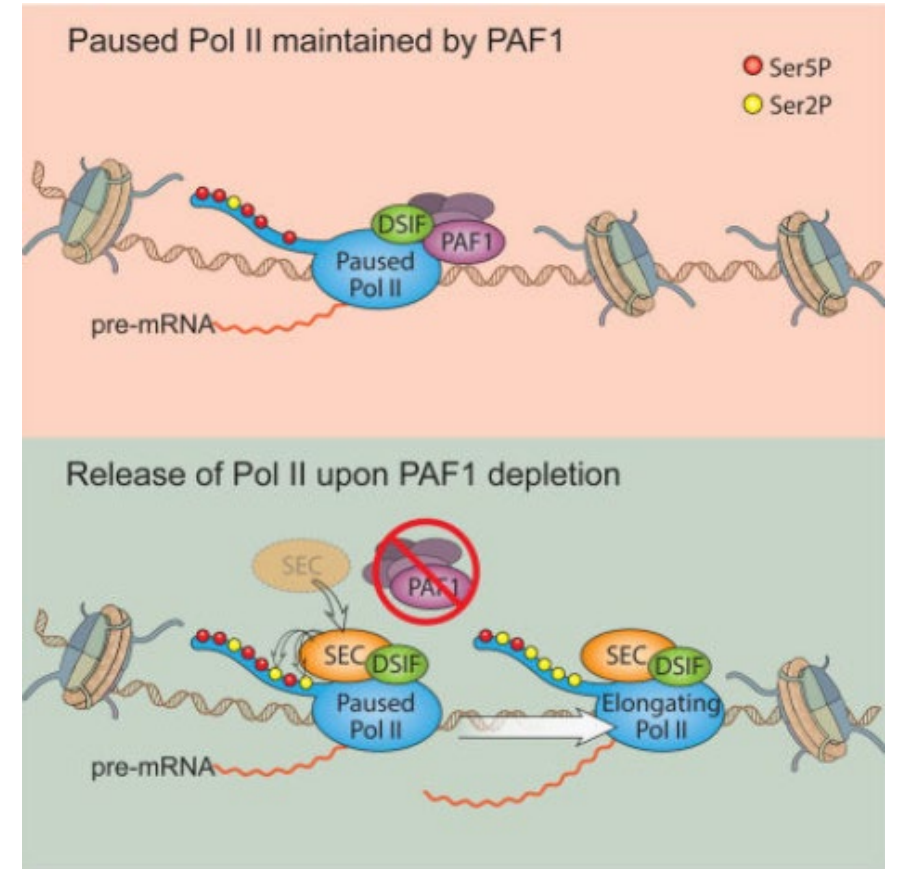
# Integrated HIV proviruses are transcribed by RNA Pol II and are subject to proximal promoter pausing



HIV overcomes this block by directly recruiting p-TEFb to sites of nascent transcription via the viral Tat protein



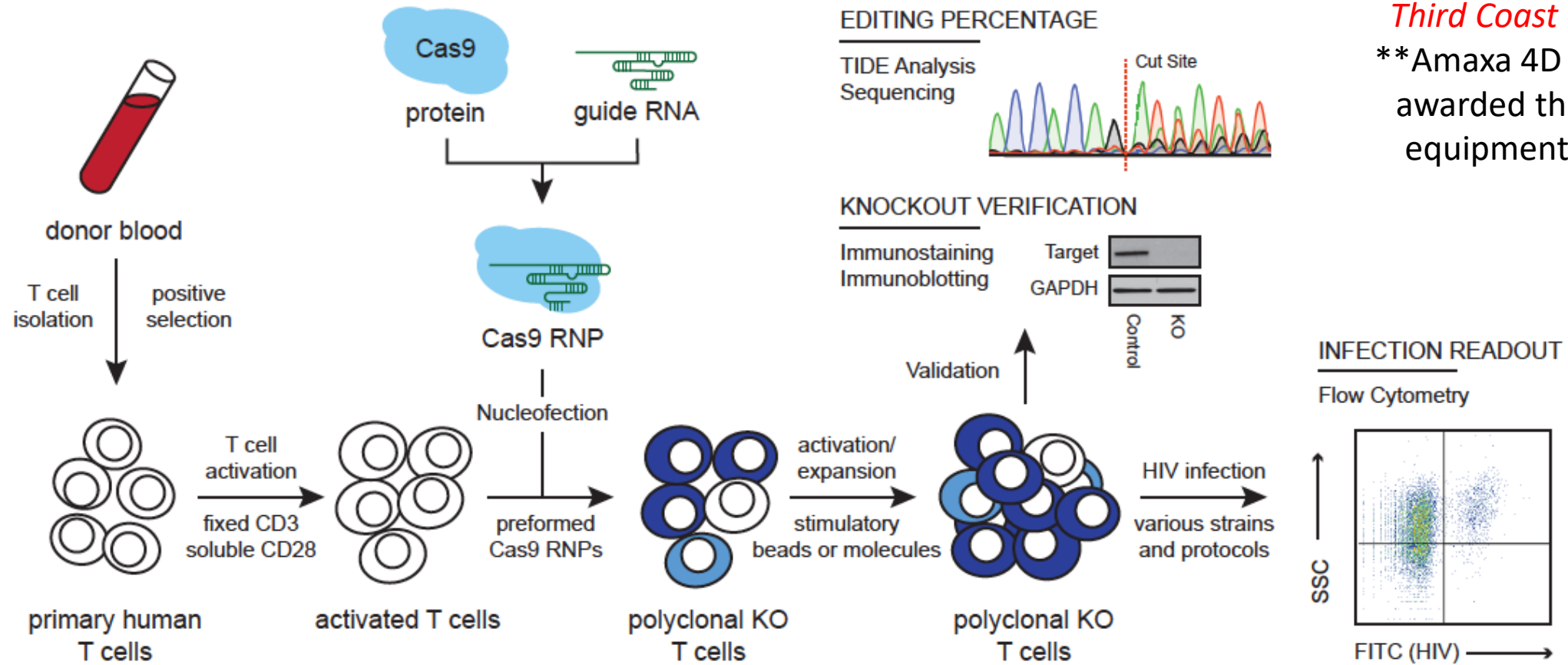
*Can we activate viral transcription by inhibiting the PAF1 complex?*



# Primary Cell CRISPR-Cas9 Gene Editing



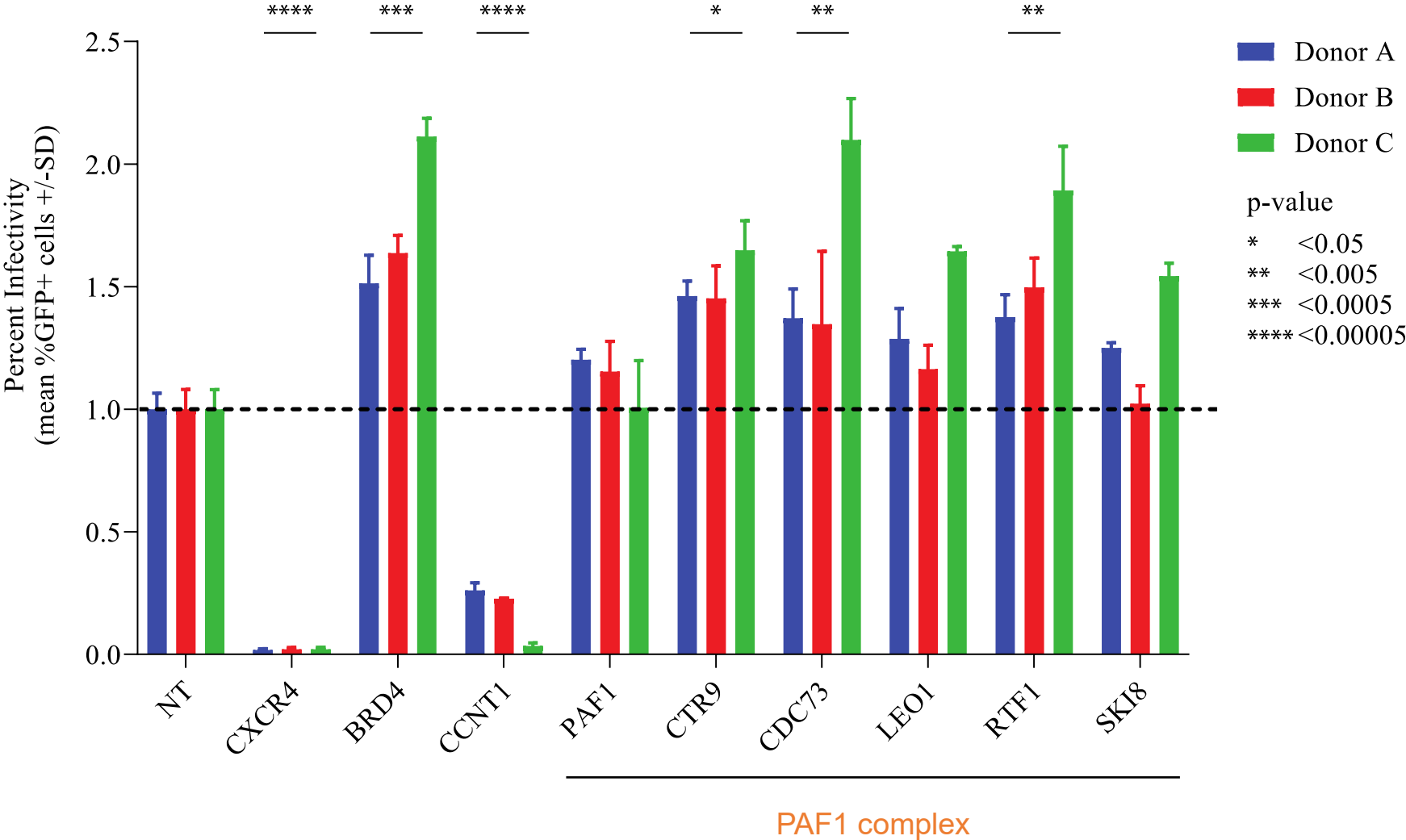
**Third Coast CFAR SERVICE**  
\*\*Amaxa 4D Electroporator  
awarded through a CFAR  
equipment supplement



# Knock-out of the PAF1 complex increases HIV-1 replication in primary CD4+ T cells



Will Cisneros

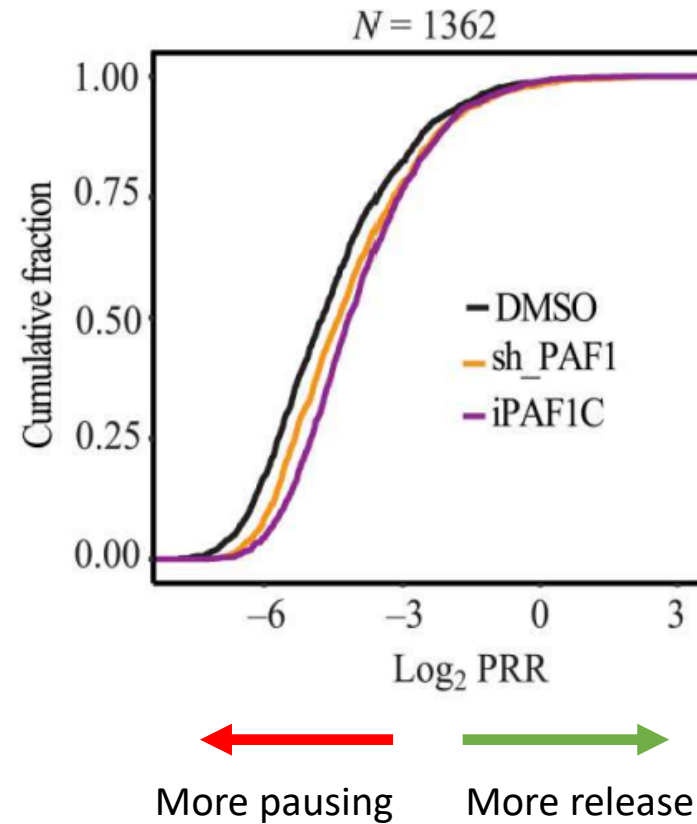
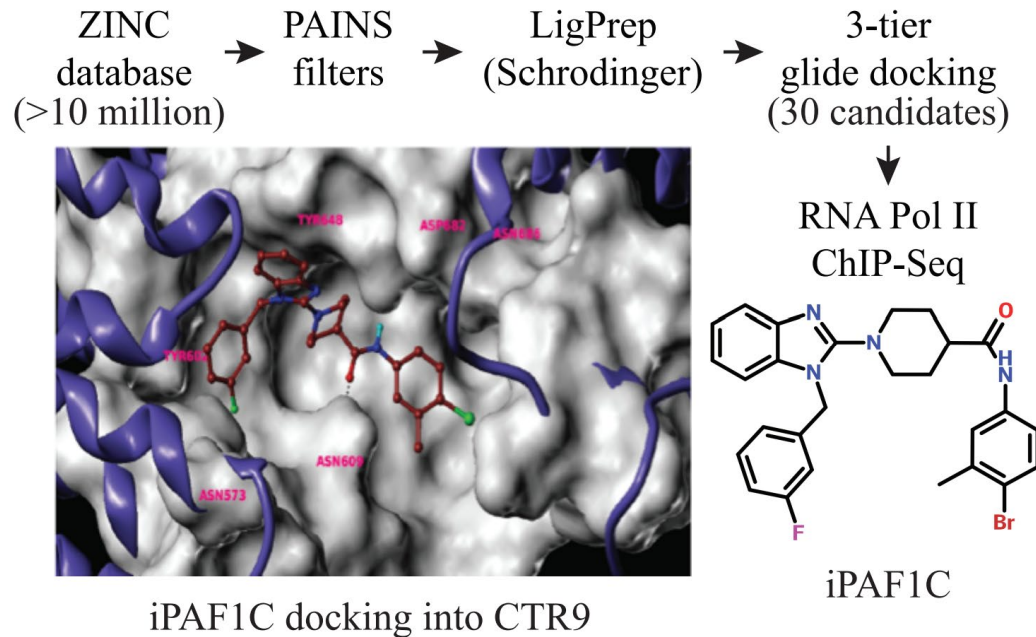




# Development of a first-in-class small molecule inhibitor of the PAF1 complex, iPAF1C



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\*\*Supported by a CFAR supplement award

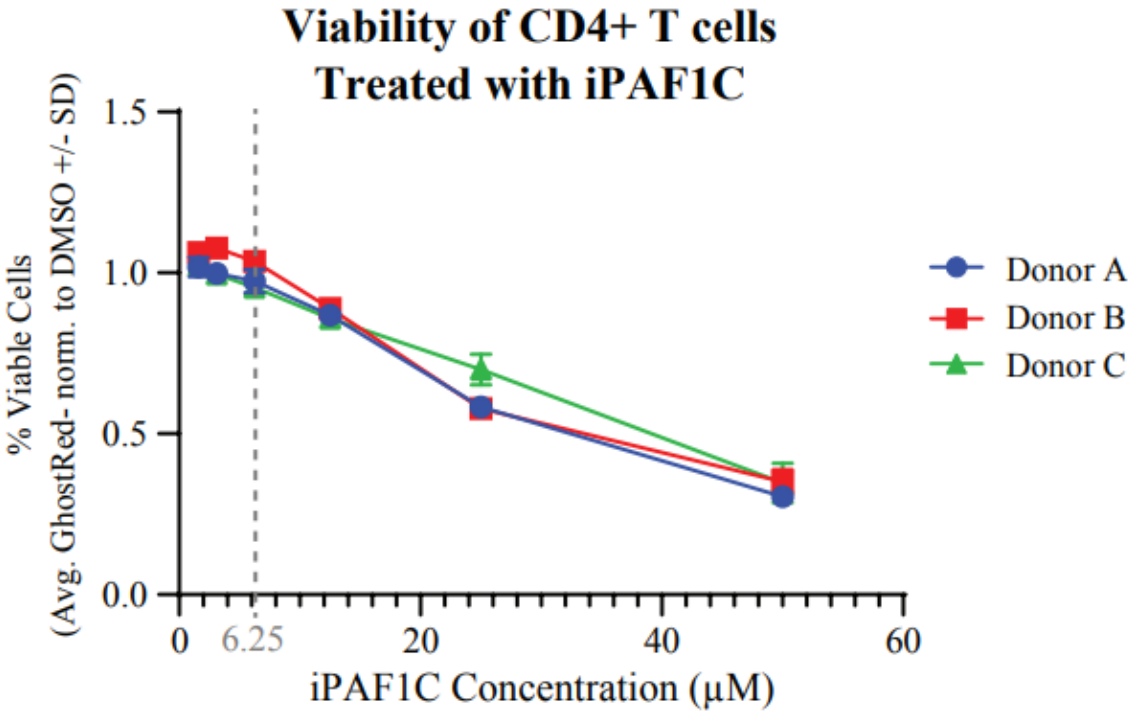
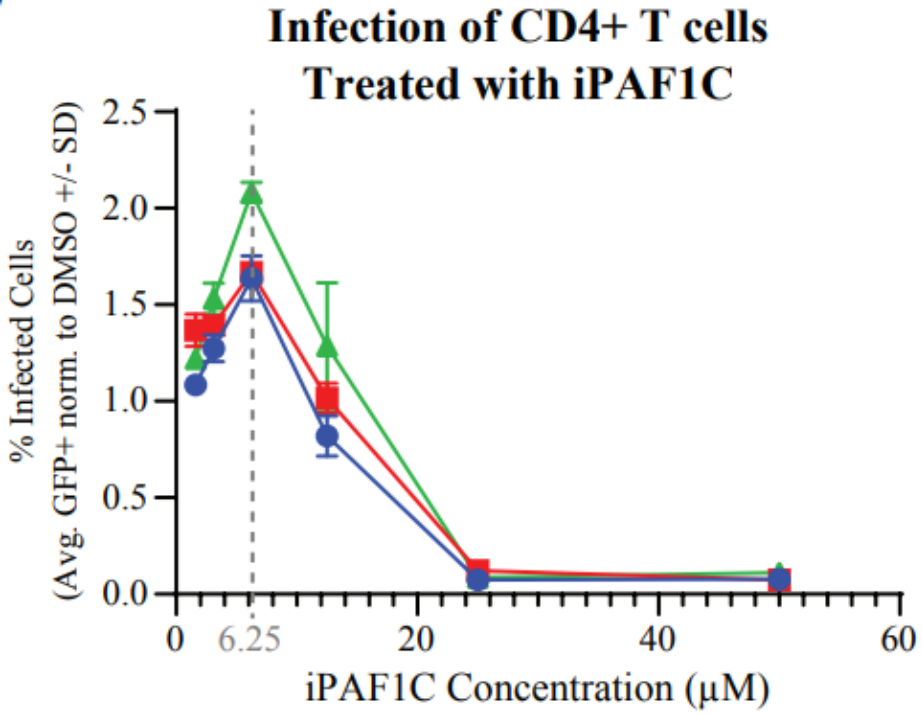


Ali Shilatifard

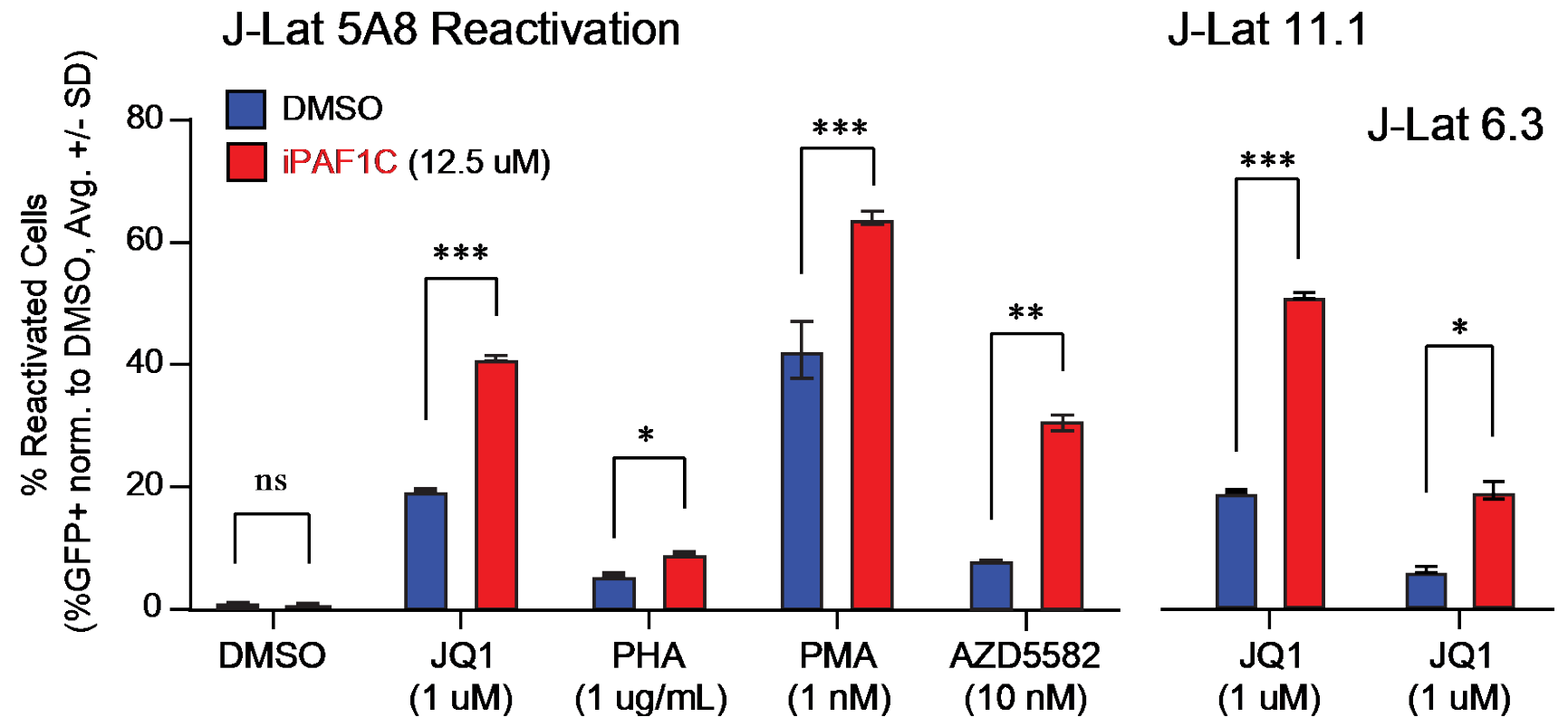
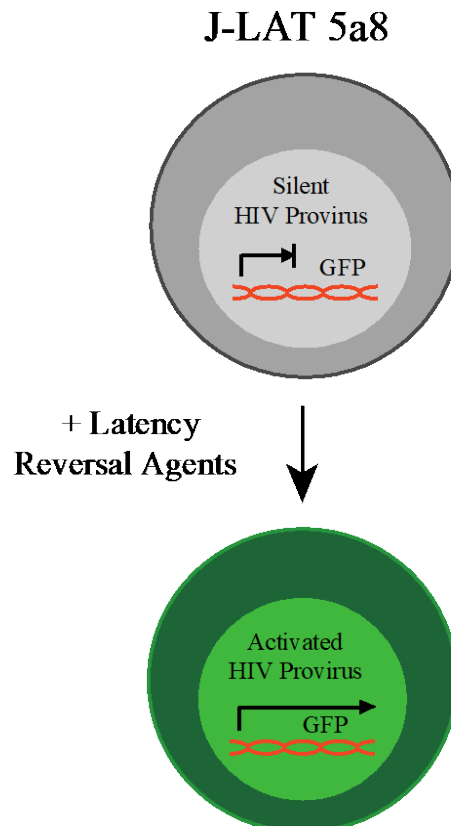


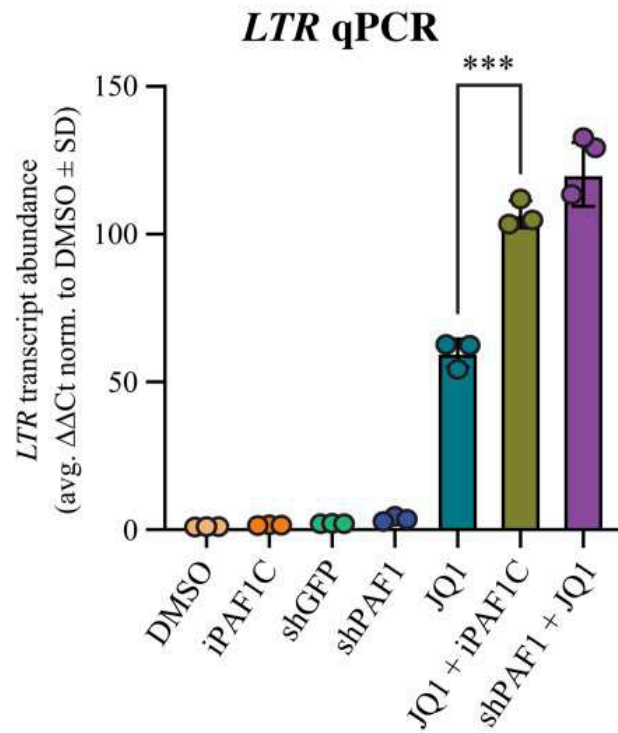
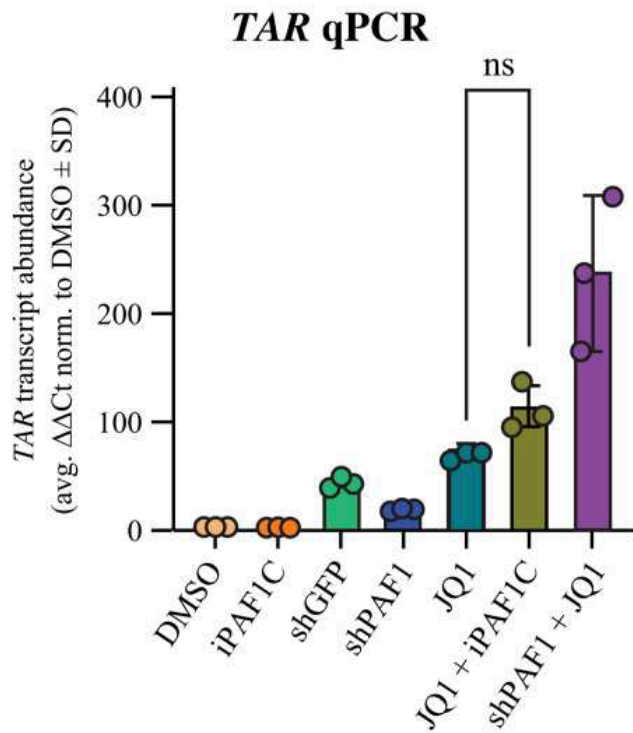
Shima Soliman

# iPAF1C increases HIV infection in primary CD4+ T cells, consistent with the knockout data



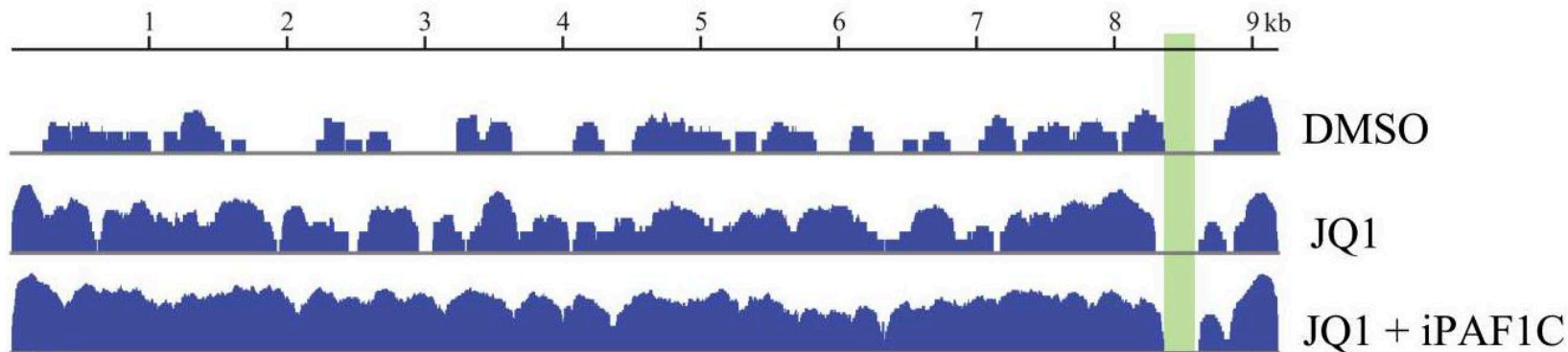
# PAF1c inhibitors synergize with latency reversing agents to increase latency reactivation in J-Lat cells





PAF1c inhibitors enhance transcriptional elongation and RNA Pol II release into the HIV proviral gene body

### RNA Pol II ChIP-seq

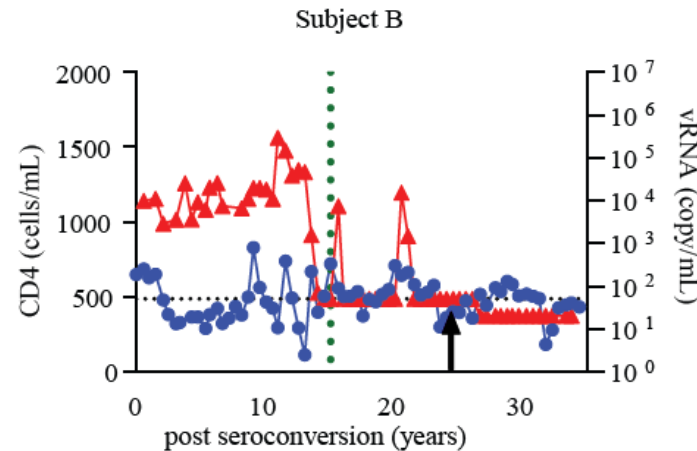
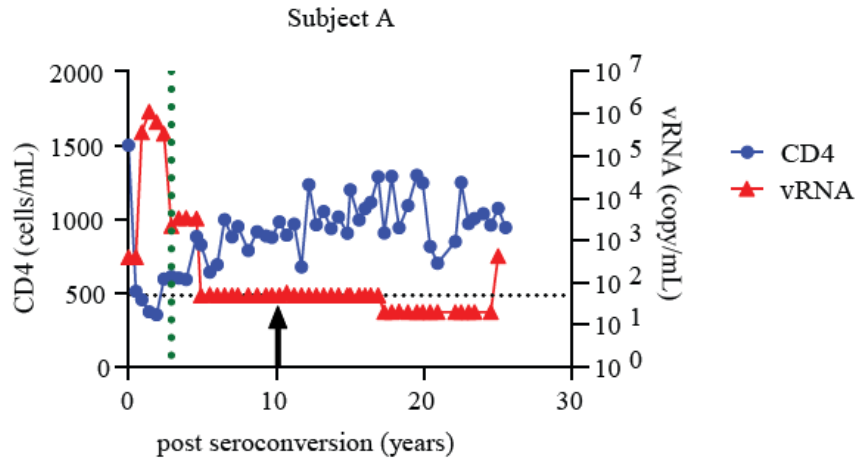


**Third Coast CFAR**  
 \*\*Supports assays for viral lifecycle staging

# What effect does iPAF1C have in cells from PLWH?



*Third Coast CFAR*  
\*\*Linkage to clinical  
specimens

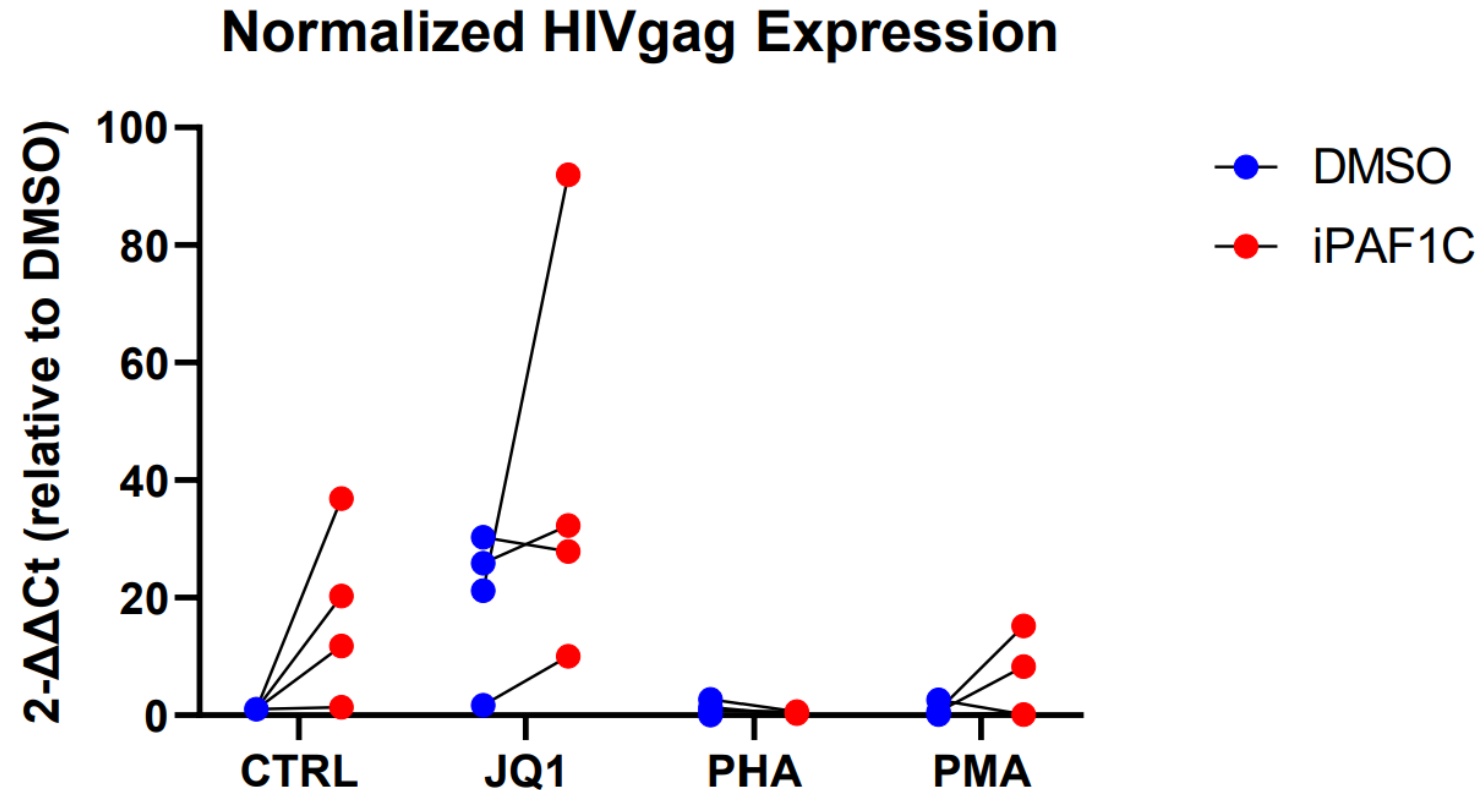


## Experimental Background

- 4 HIV+ patients in MACS cohort
- 5+ cumulative years of ART
- At time of blood draw, had undetectable viral RNA levels



# PAF1c inhibitors increase expression of cell-associated HIV RNA in cells from PLWH



# Inhibitors of transcriptional elongation represent novel tools to target the latent reservoir

SCIENCE ADVANCES | RESEARCH ARTICLE

## BIOCHEMISTRY

### Enhancing HIV-1 latency reversal through regulating the elongating RNA Pol II pause-release by a small-molecule disruptor of PAF1C

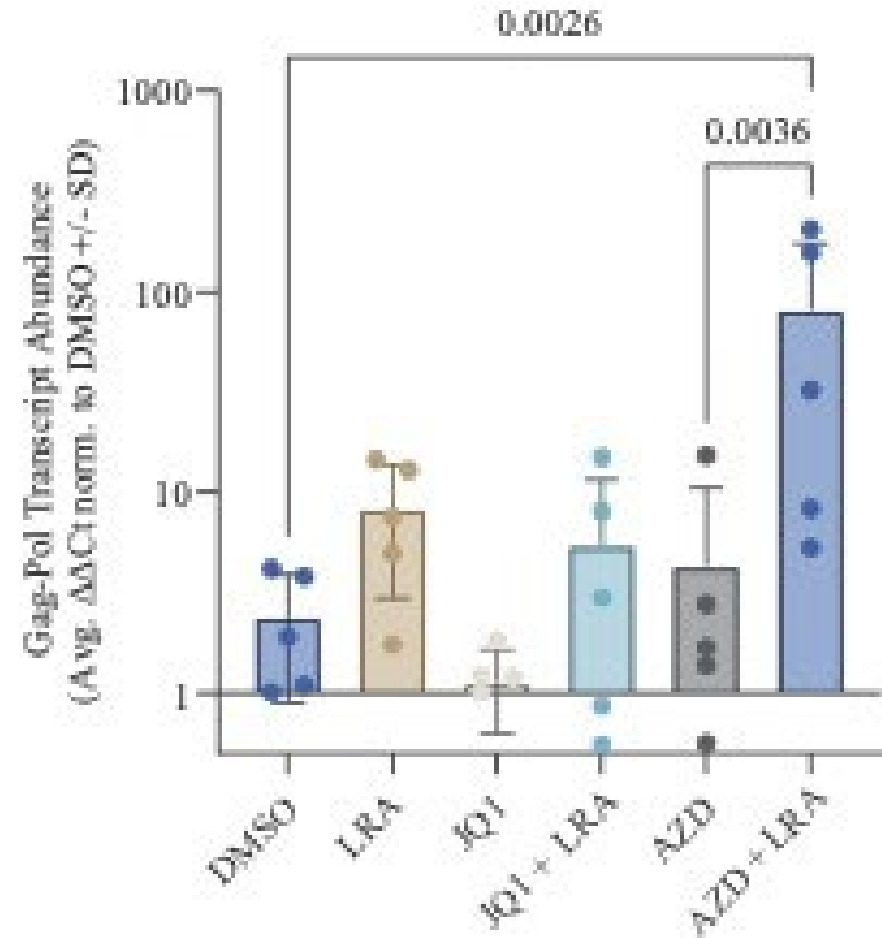
Shimaa H. A. Soliman<sup>1</sup>, William J. Cisneros<sup>2,3</sup>, Marta Iwanaszko<sup>1</sup>, Yuki Aoi<sup>1</sup>, Sheetal Ganesan<sup>1</sup>, Miriam Walter<sup>2</sup>, Jacob M. Zeidner<sup>1</sup>, Rama K. Mishra<sup>1</sup>, Eun-Young Kim<sup>2</sup>, Steven M. Wolinsky<sup>2</sup>, Judd F. Hultquist<sup>2,3</sup>, Ali Shilatifard<sup>1\*</sup>



*Third Coast CFAR*

\*\*Supported R21 application to NIAID

R21 AI174864





# Acknowledgements



Ali Shilatifard



Steve Wolinsky



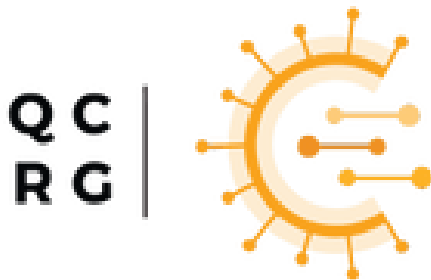
Shimaa Soliman



Will Cisneros



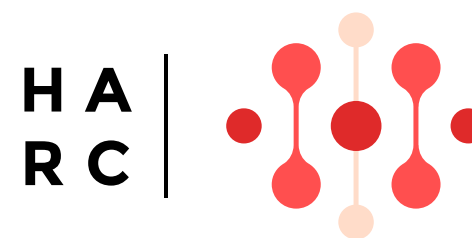
U19 AI135964



U19 AI171110



P30 AI117943



U54 AI170792

R01 AI176599 (Martinelli)  
R01 AI167778 (Fujinaga)  
R01 AI165236 (Hultquist)  
R01 AI150455 (Diaz-Griffero)  
R01 AI150998 (Hope/Bieniasz)  
R21 AI174864 (Hultquist)  
R56 AI174877 (Ebrahimi)