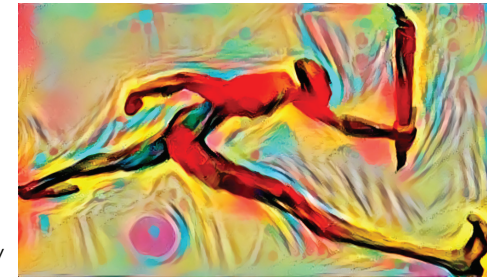




**Weill Cornell  
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Research Enterprise to Advance a Cure for HIV



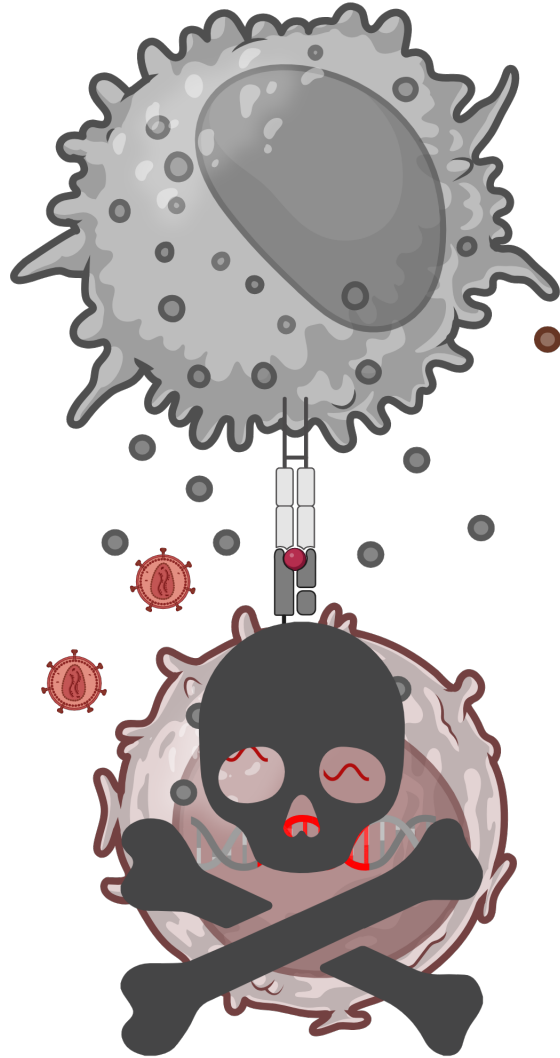
# **A Novel HIV-1 Immune Evasion Strategy: How Softer HIV-1 Infected cells Preferentially Resist Cytotoxic T Lymphocytes (CTLs)**

Louise Leyre, Lab of Dr. Brad Jones, New York

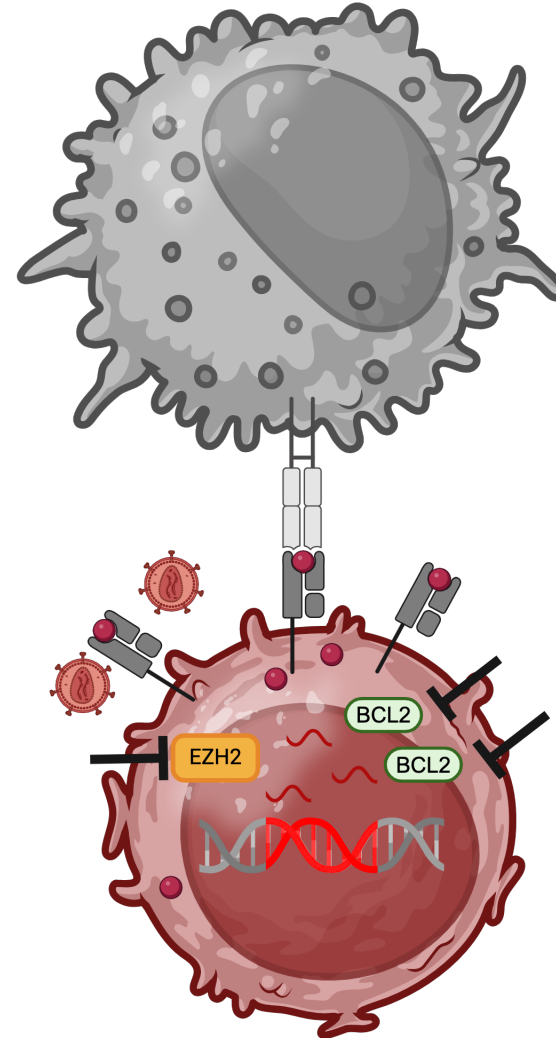
Highlighted Short talks interest II - 12/12/2024

# A subset of HIV-infected CD4<sup>+</sup> T cells resist CTL attack under ART

HIV-specific  
cytotoxic T  
lymphocyte  
(CD8<sup>+</sup> T cells)



HIV-expressing  
CD4<sup>+</sup> T cells  
**Eliminated**



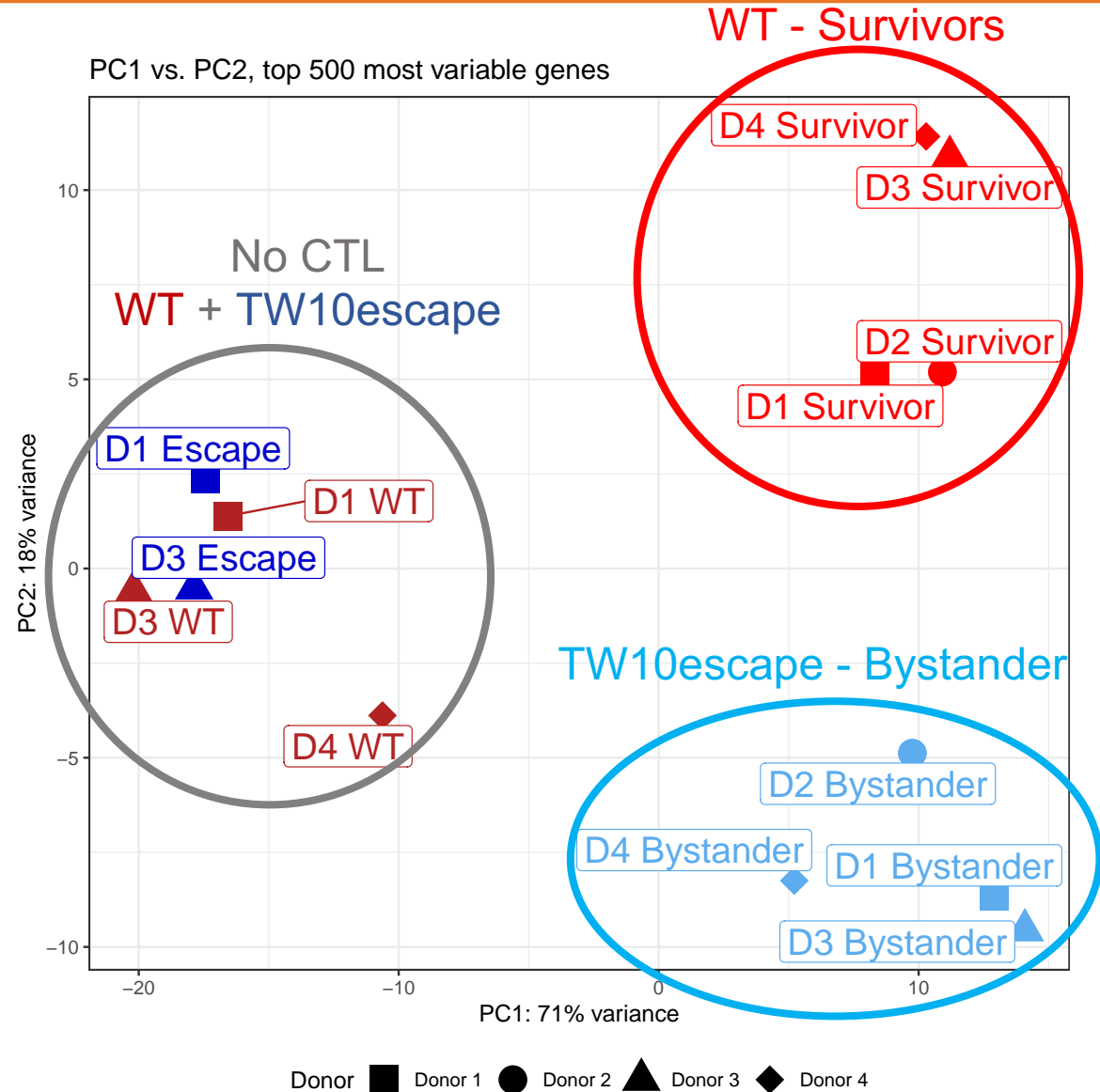
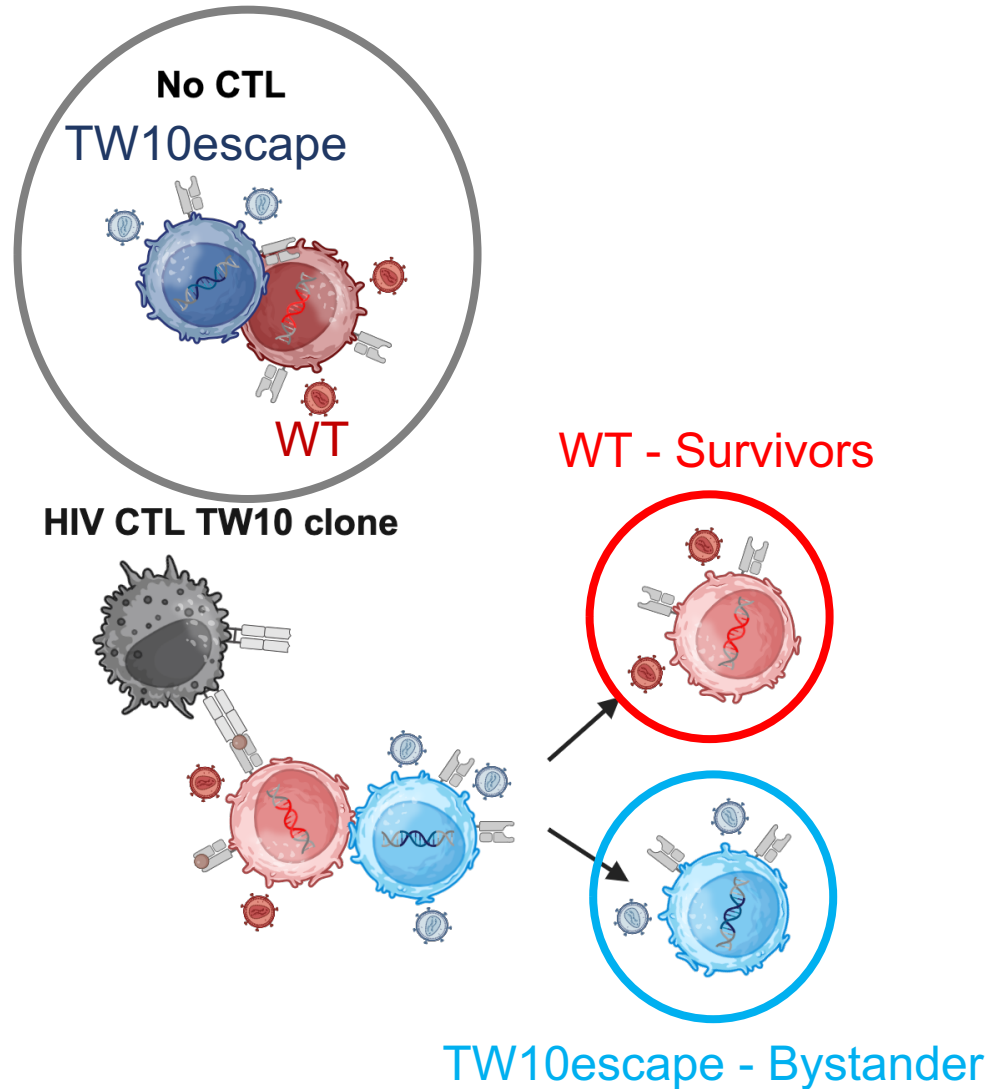
JCI 2020  
Y. Ren, R. B. Jones  
et al.  
**BCL2 inhibitor  
Venetoclax  
Clinical trial  
NCT05668026**

In review, Immunology  
A. Gramatica, I. Miller, R.  
B. Jones et al.

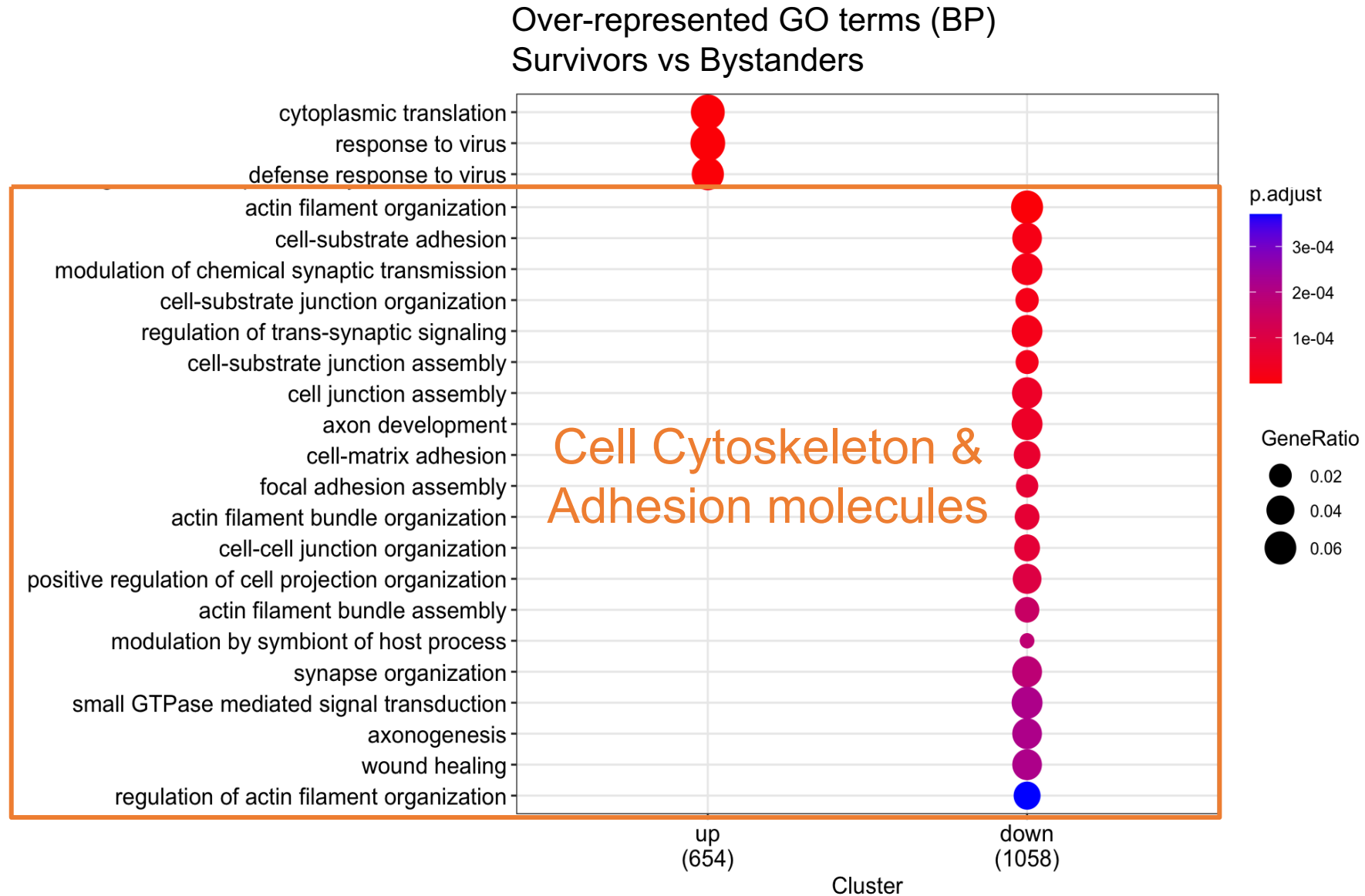
**EZH2 inhibitor  
Tazemetostat  
to begin in clinical  
trial soon**

HIV-expressing  
CD4<sup>+</sup> T cells  
**Resist**

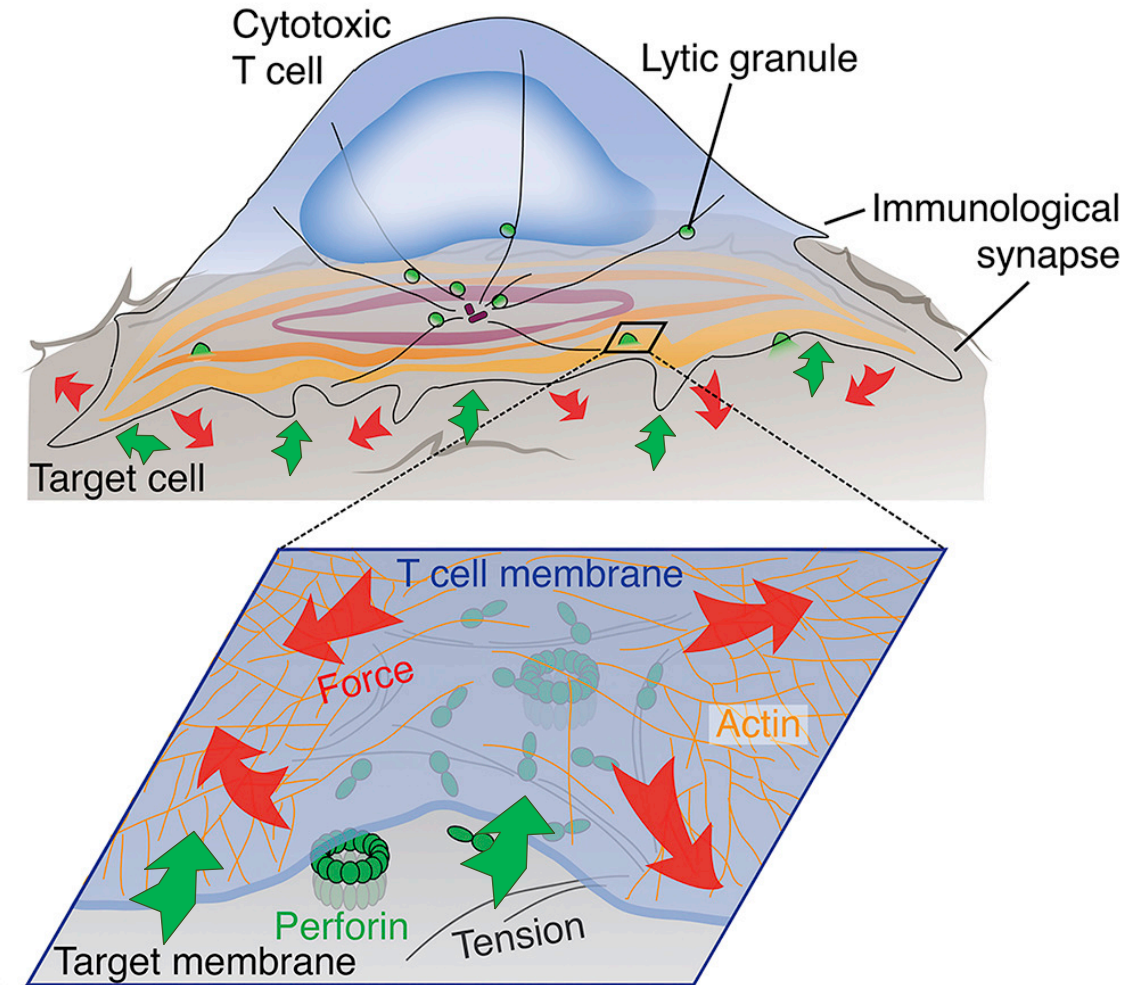
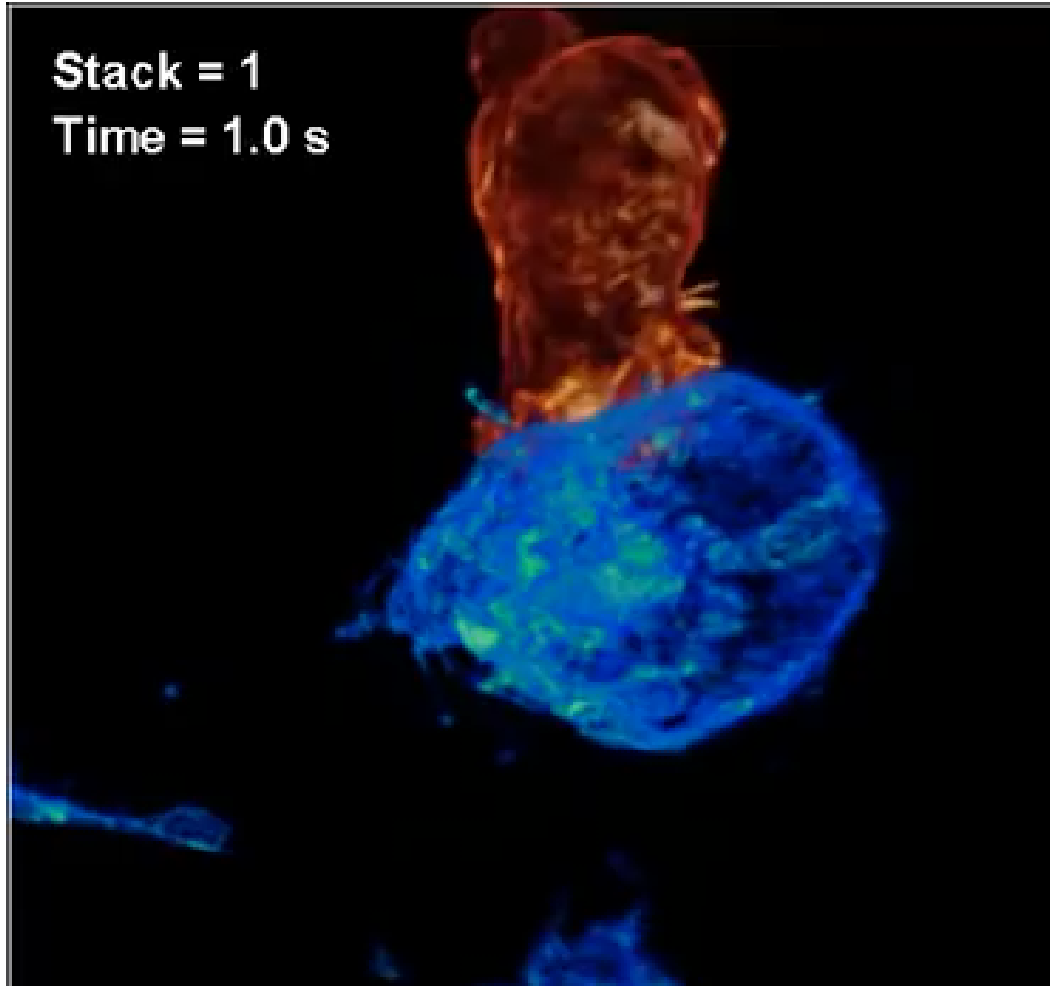
# HIV-infected CD4<sup>+</sup> T cells surviving CTL attack have a unique transcriptional profile



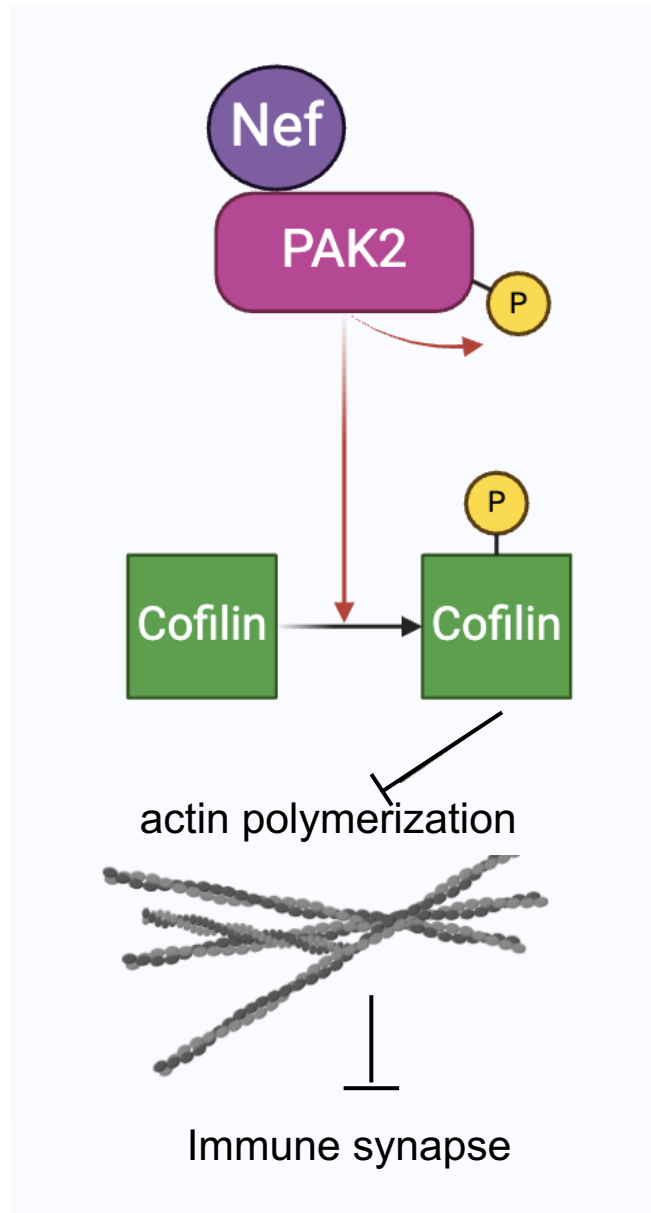
# HIV-infected CD4<sup>+</sup> T cells surviving CTL attack have a unique transcriptional profile



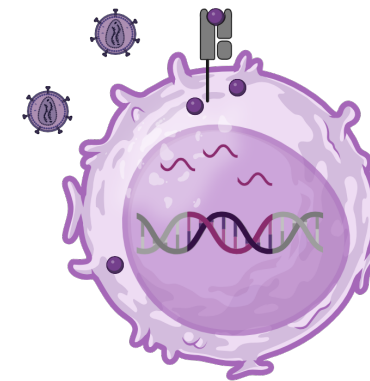
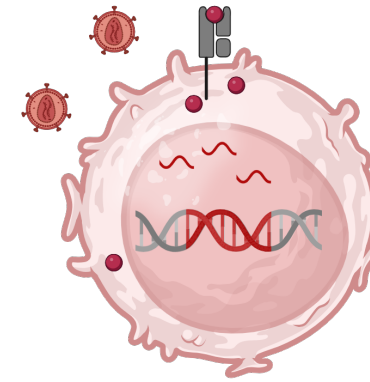
# Cytoskeleton drives Cytotoxic T Lymphocyte (CTL) attack processes



# HIV Nef disrupts T cell actin dynamics via PAK2-mediated cofilin phosphorylation

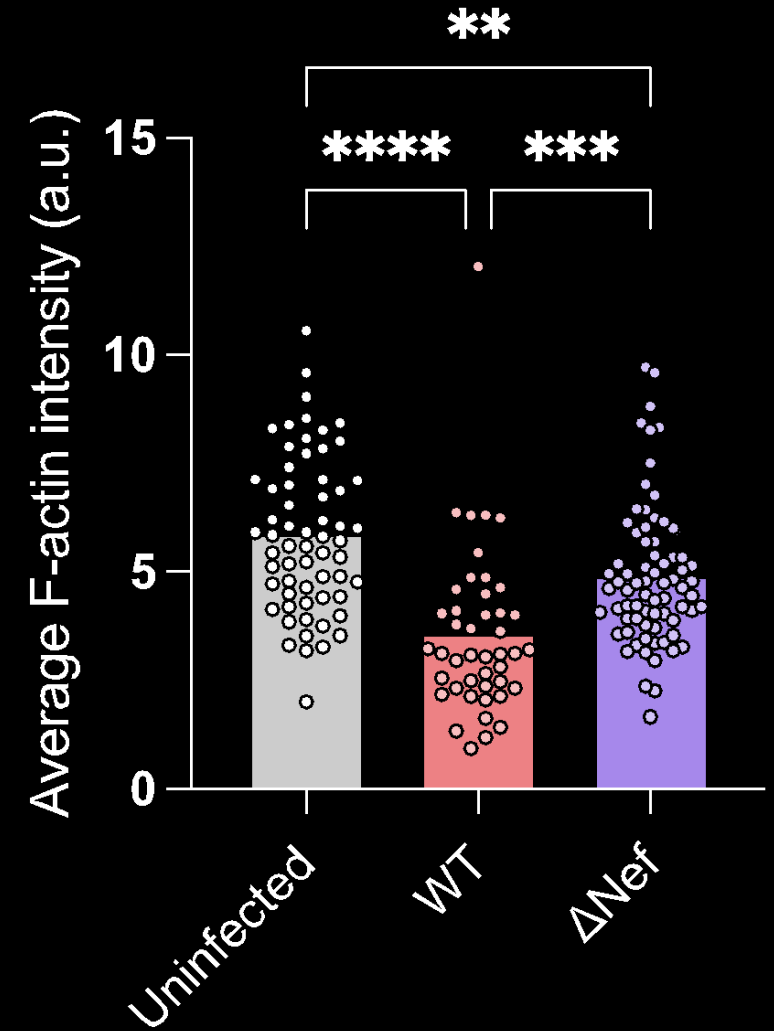
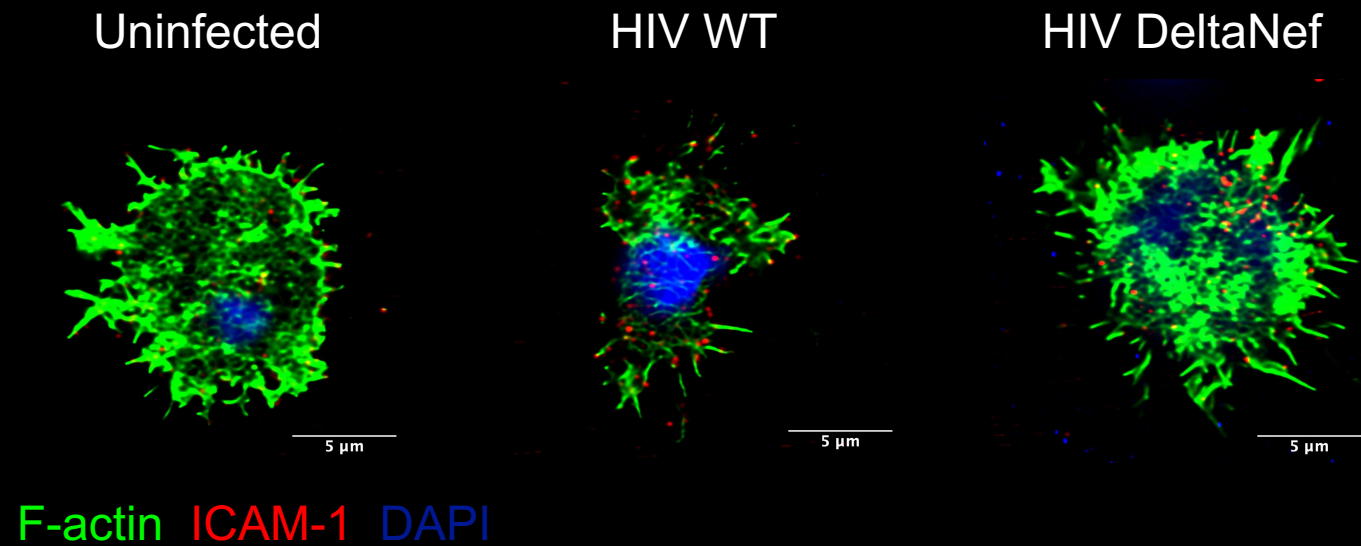


WT JRCSF



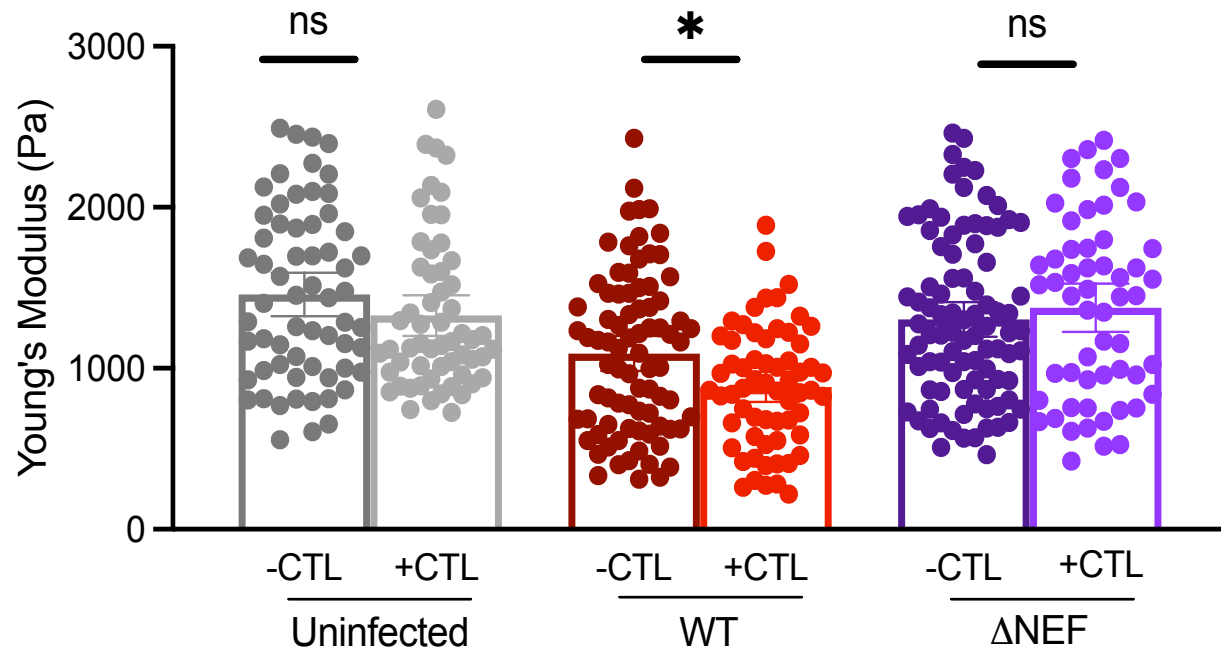
ΔNEF JRCSF

# Actin remodeling is dysregulated upon HIV infection

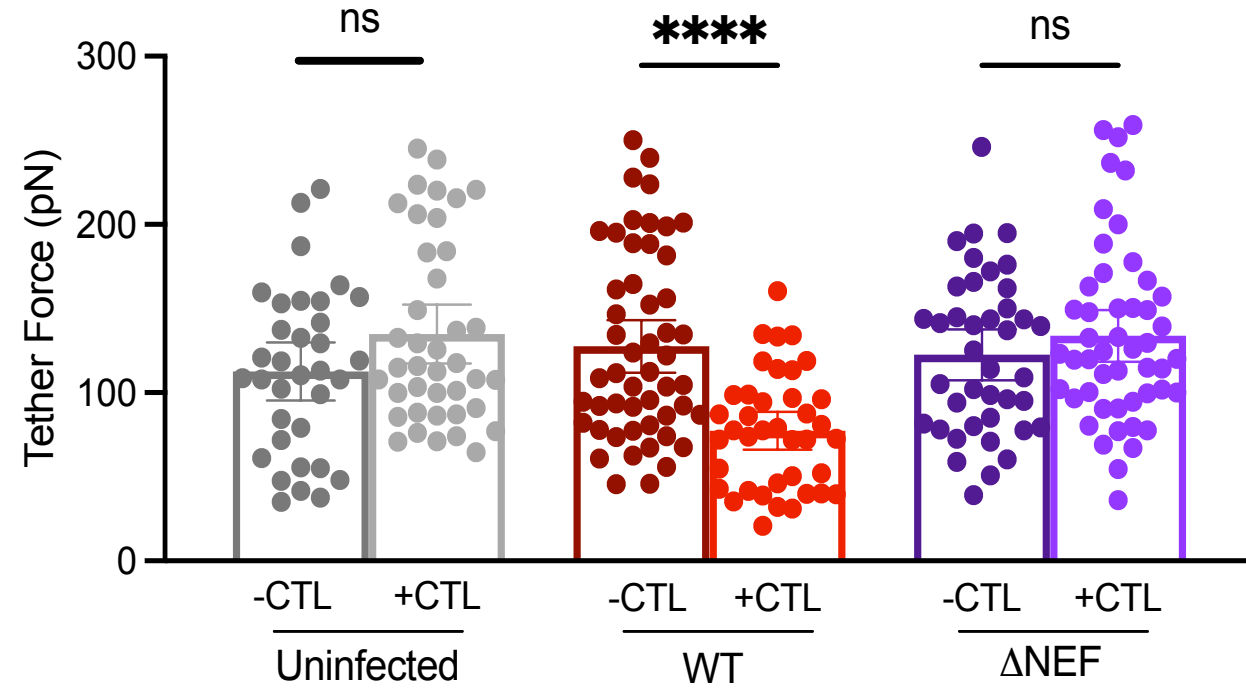


# Nef-deficient survivors are stiff with a high membrane tension in comparison to WT survivors

## Stiffness [Atomic force microscopy]



## Membrane tension [Optical Tweezer]





# Nef has multiple interactions with host-proteins to prevent CTL attack

HIV-NEF $\Delta$ MHCI

N-terminal alpha-helix domain

V

V<sup>16</sup>REIRARR<sup>22</sup>

Akari et al., Journal of Virology, 2000

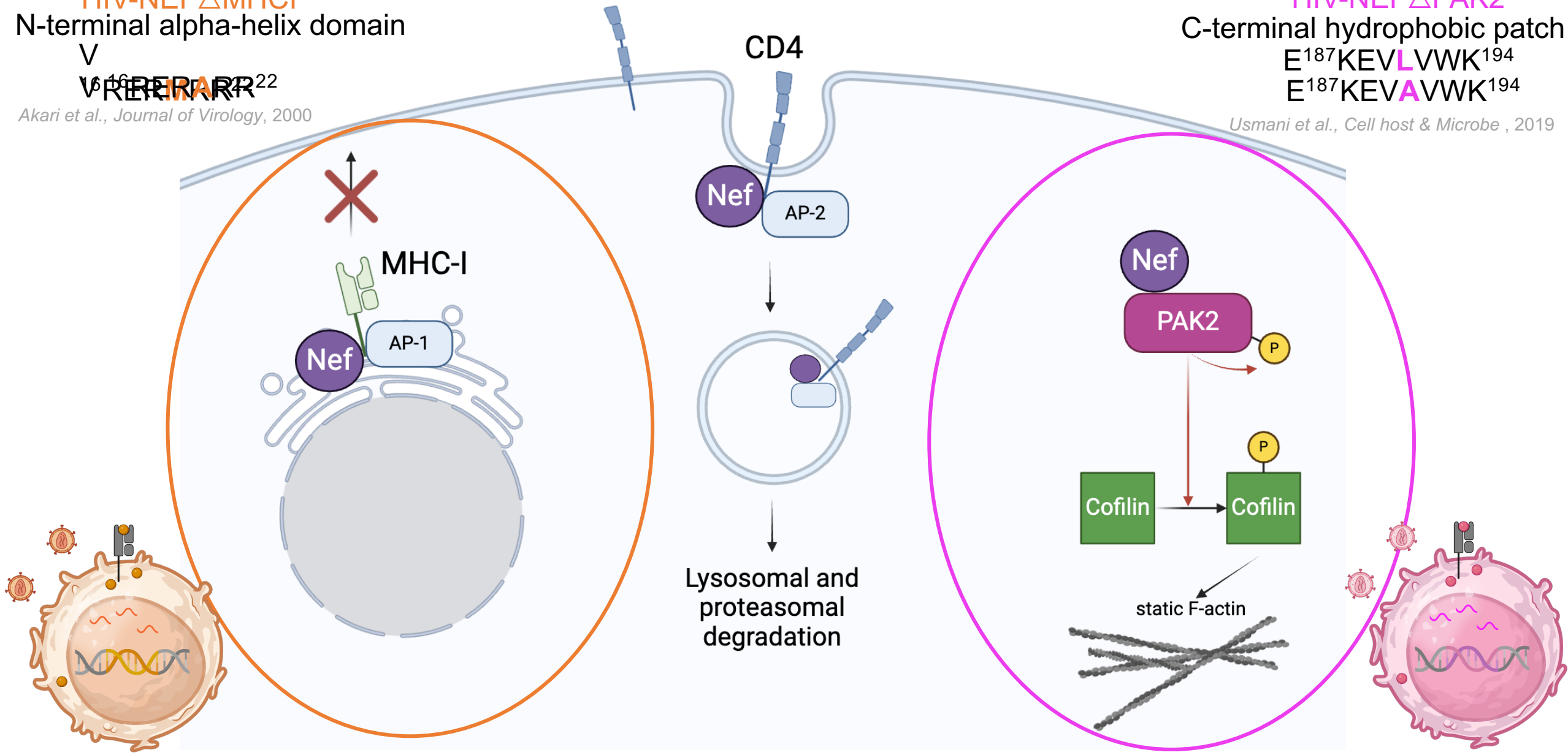
HIV-NEF $\Delta$ PAK2

C-terminal hydrophobic patch

E<sup>187</sup>KEV<sup>L</sup>VWK<sup>194</sup>

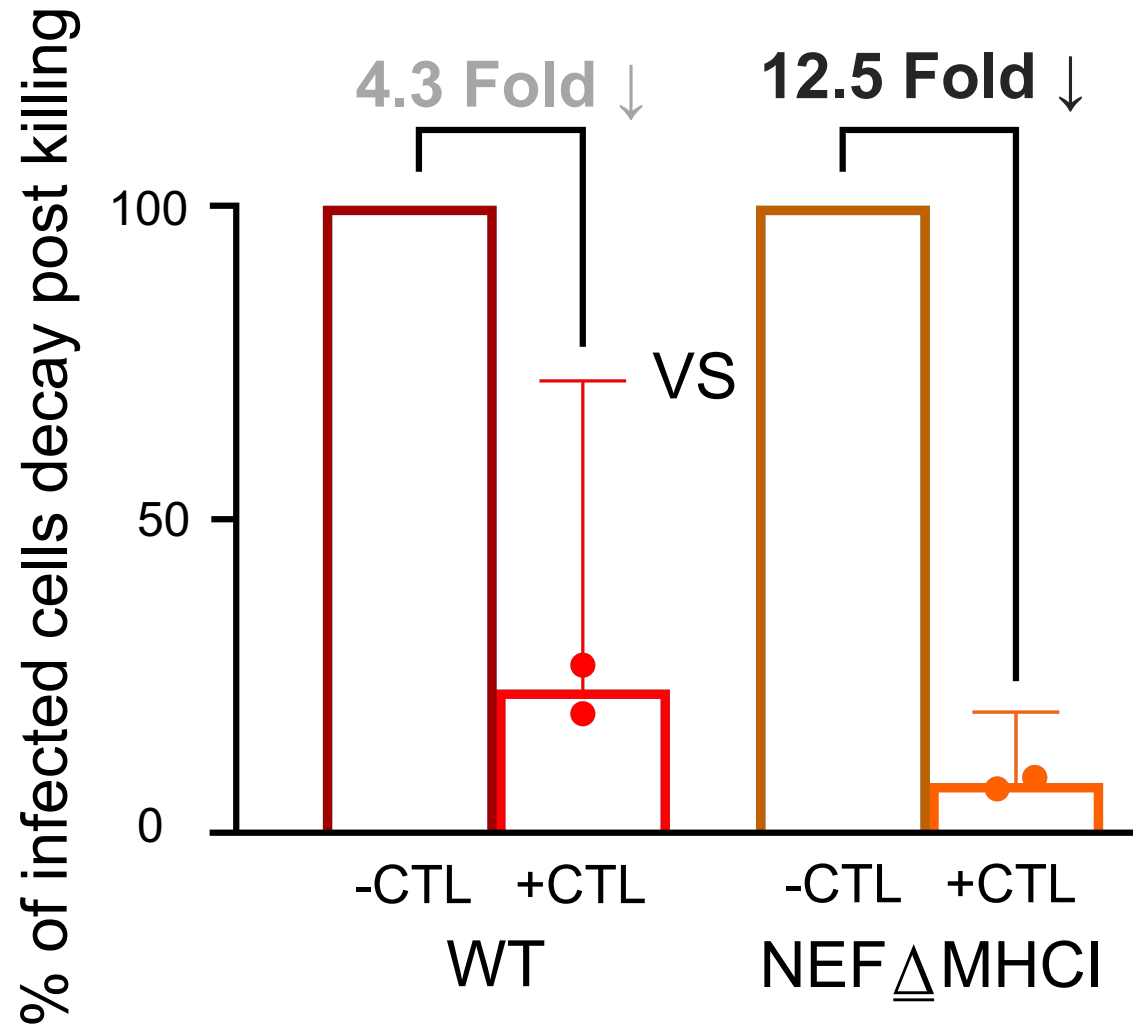
E<sup>187</sup>KEV<sup>A</sup>VWK<sup>194</sup>

Usmani et al., Cell host & Microbe, 2019



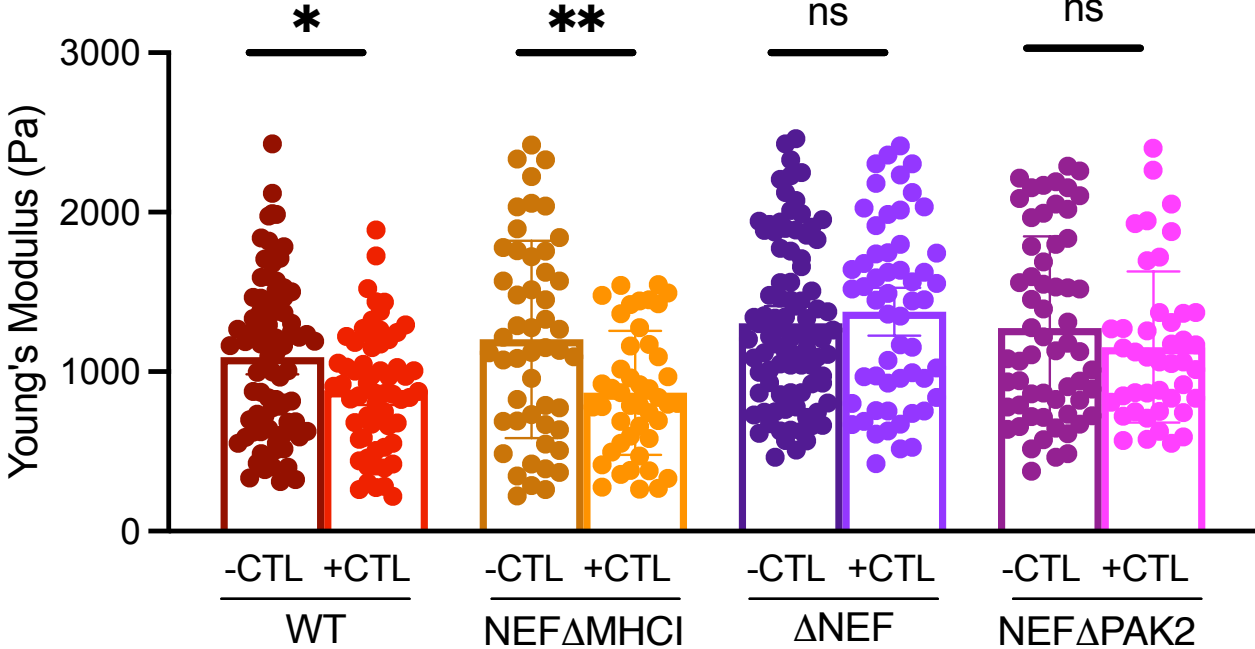
# Disrupting Nef-PAK2 interaction enhances CTL-killing of HIV-infected cells

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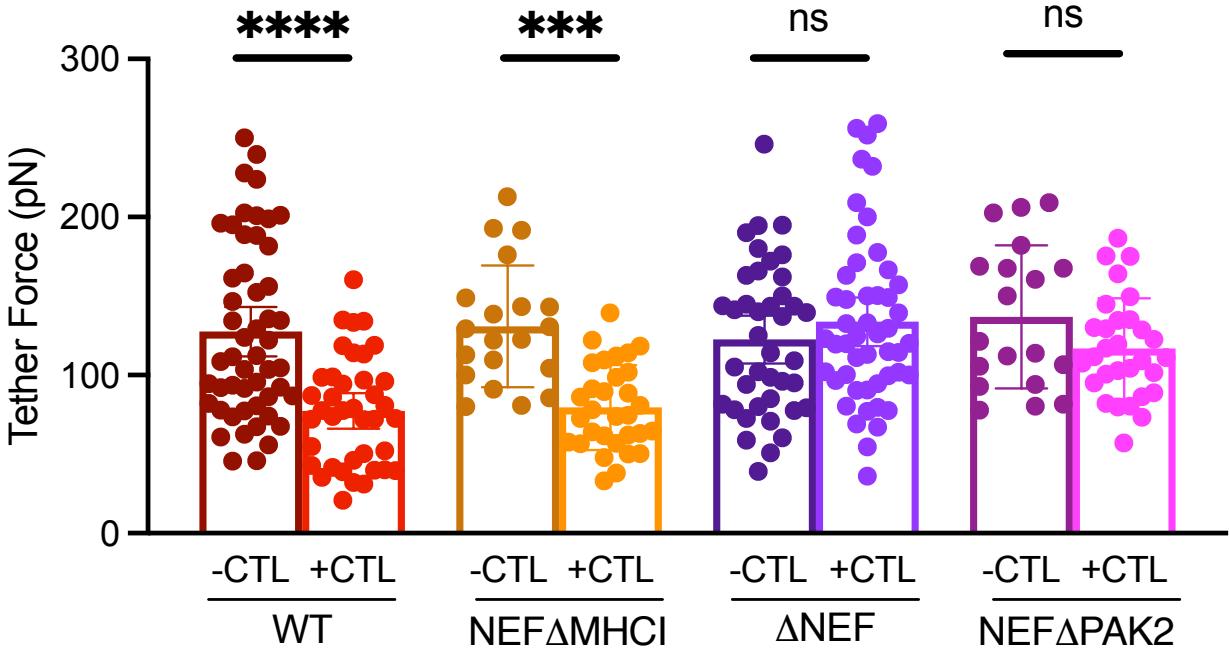


# Nef, through activating PAK2, lowers both membrane tension and stiffness

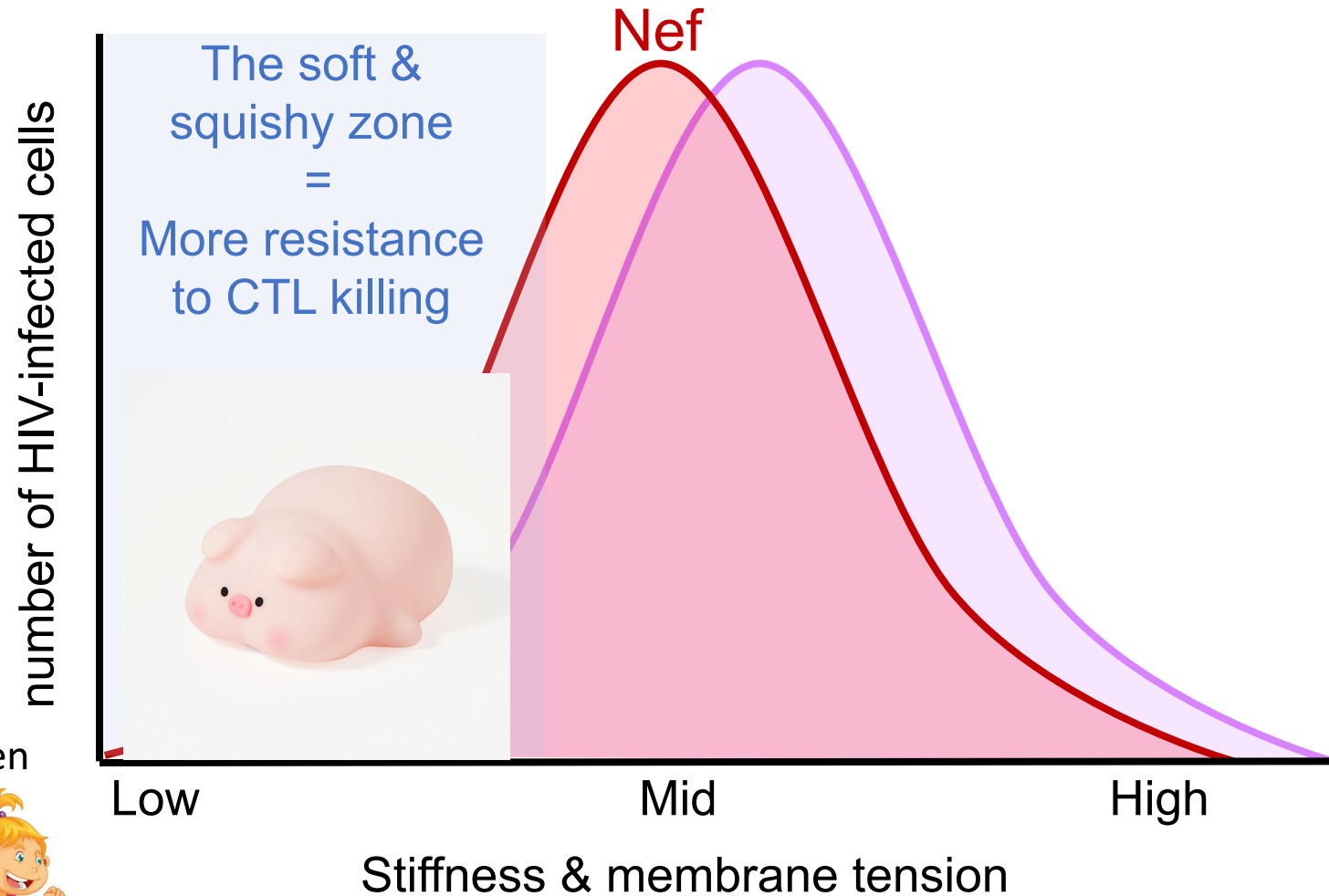
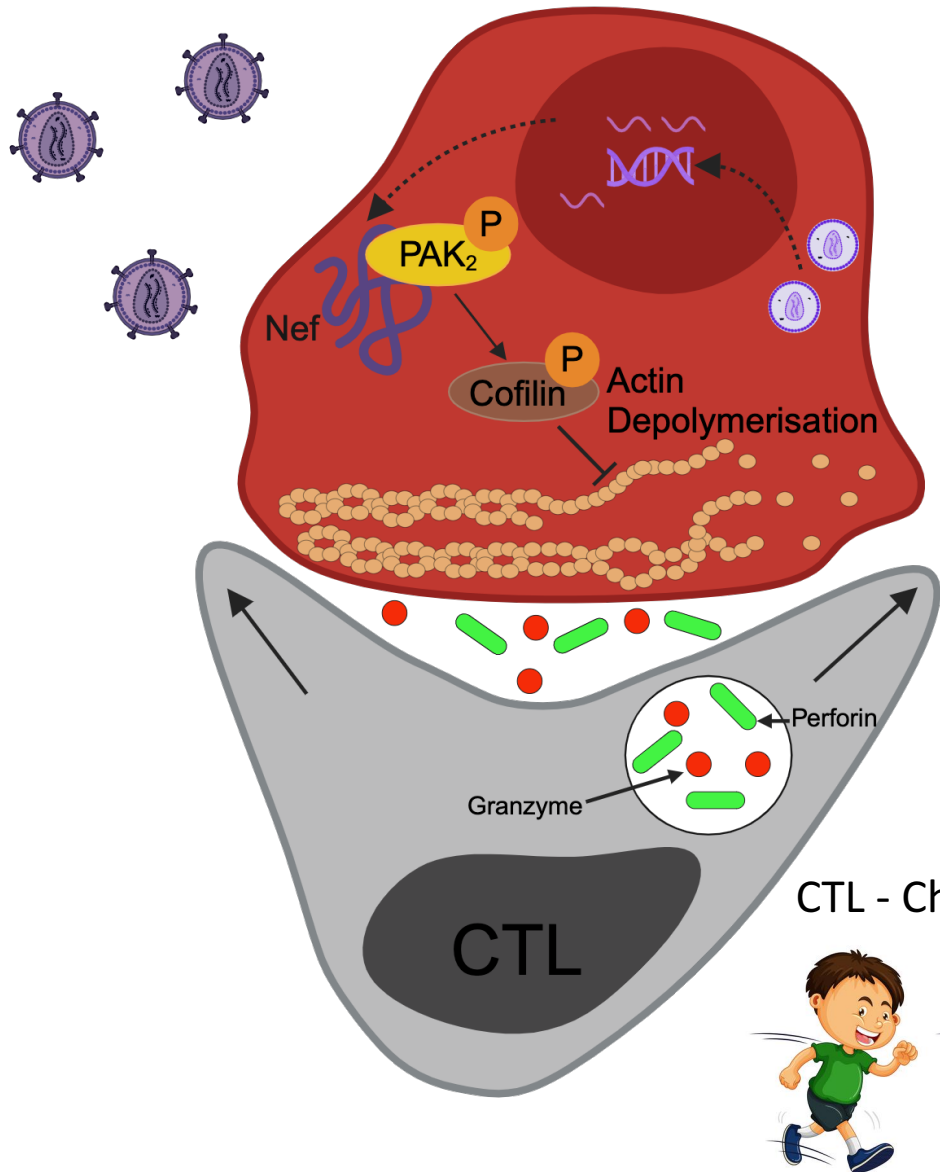
### Stiffness [Atomic force microscopy]



### Membrane tension [Optical Tweezer]



# Soft and Squishy on the outside, yet resilient to CTL attack



# Thank You



**Farah Mustapha**



**Morgan Huse**



**Paul Zumbo**



**Esther Lee**



**Kiera Clayton**



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Research Enterprise to Advance a Cure for HIV

