Cigarette Smoking disproportionately impairs nitric oxide signaling in pulmonary endothelial cells in HIV: Role of viral and host factors

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Disclosure

I have nothing to disclose

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Lung Diseases in PLWH

Pre ART Era

- Opportunistic lung infections

Post ART Era

- Inflammatory lung co-morbidities:

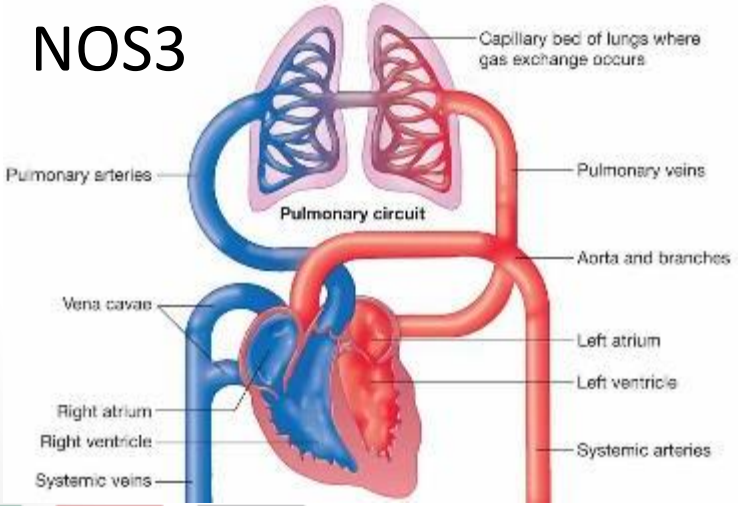
1. COPD
2. PAH
3. Increased mortality from ALI/ARDS

Endothelial Dysfunction in Lung Diseases

PAH

- Pulmonary Artery Endothelial Cells

1. Decreased Nitric Oxide Production from NOS3



ALI & ARDS

- Lung Microvascular Endothelial Cells

1. Increased reactive species and cytotoxicity
2. Impaired endothelial barrier

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How is HIV associated with Endothelial Dysfunction in Lung Diseases ?

Viral Factor

- Viral Protein: Nef

Released from HIV infected cells as a cargo protein in extracellular vesicles

Host Factor

- Chemokine receptor: CXCR4

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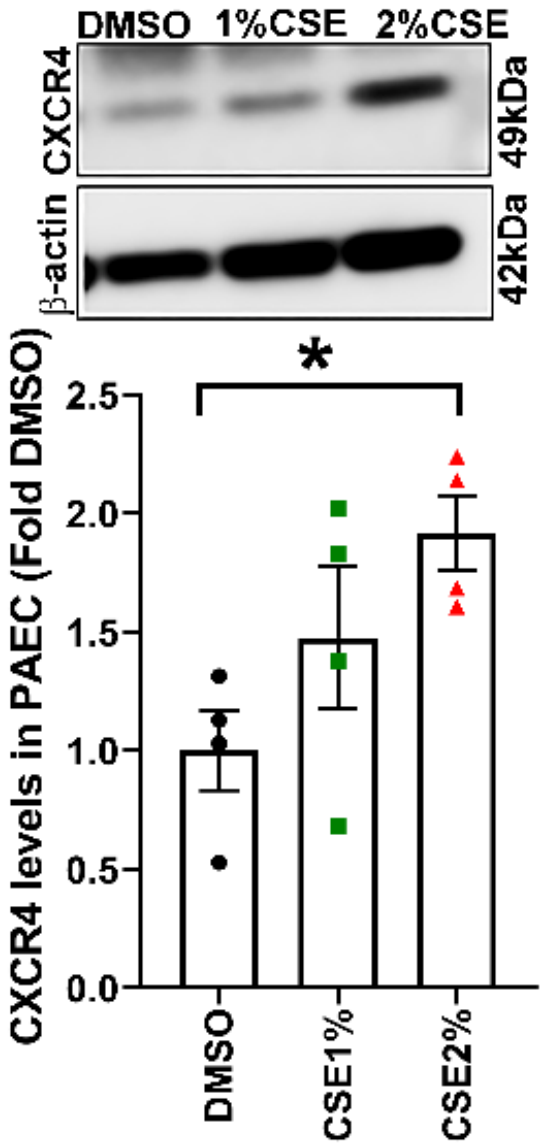
Exposure to CSE Increases CXCR4 Levels in HPAECs



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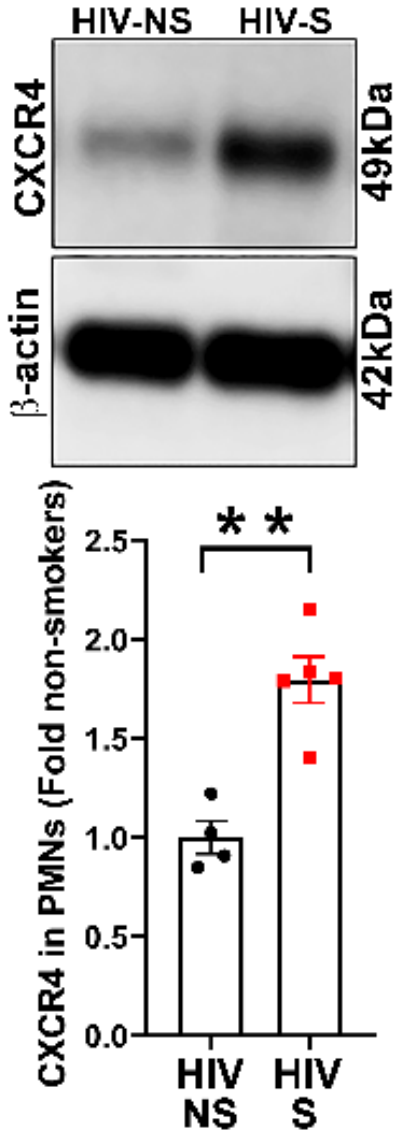
Smoking Increases CXCR4 Levels in PLWH



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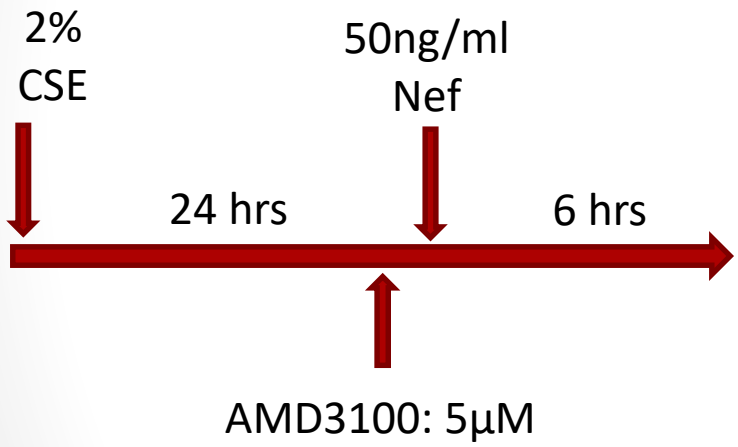
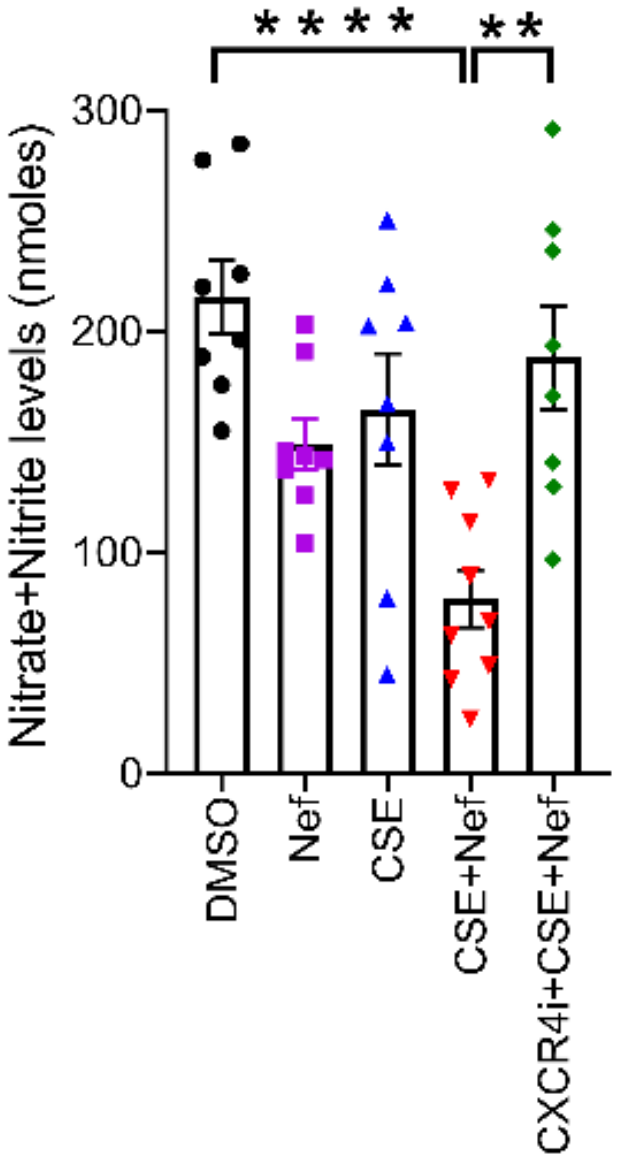
CS Facilitates Nef-CXCR4 Mediated Reduction of NO Levels in HPAECs





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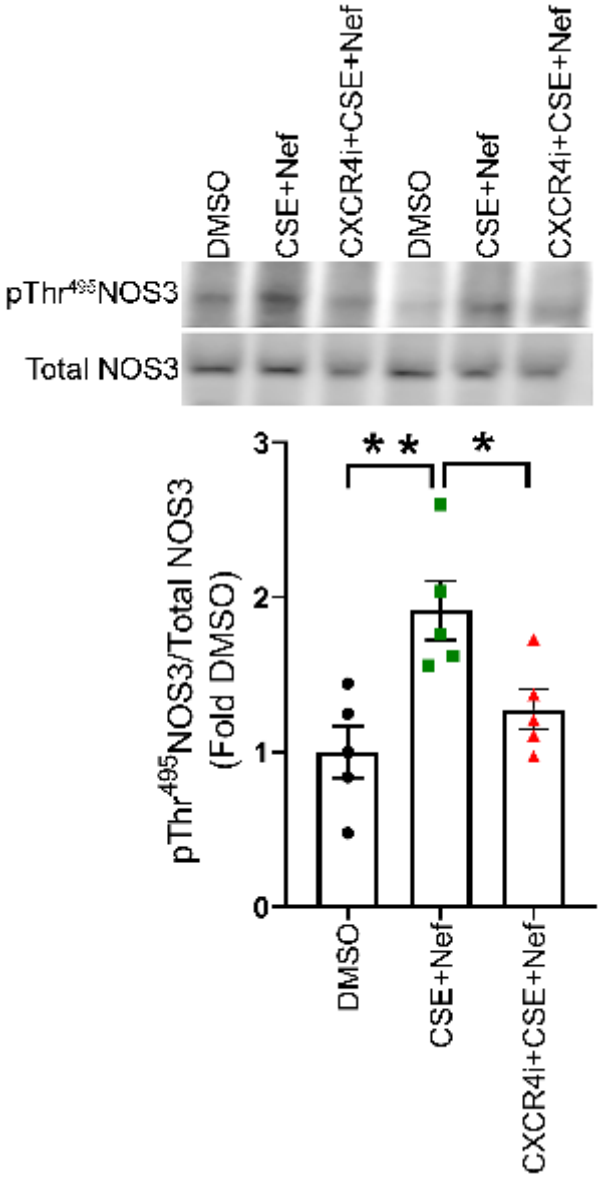
CSE Facilitates Nef-CXCR4 Mediated Phosphorylation of NOS3 at Thr 495



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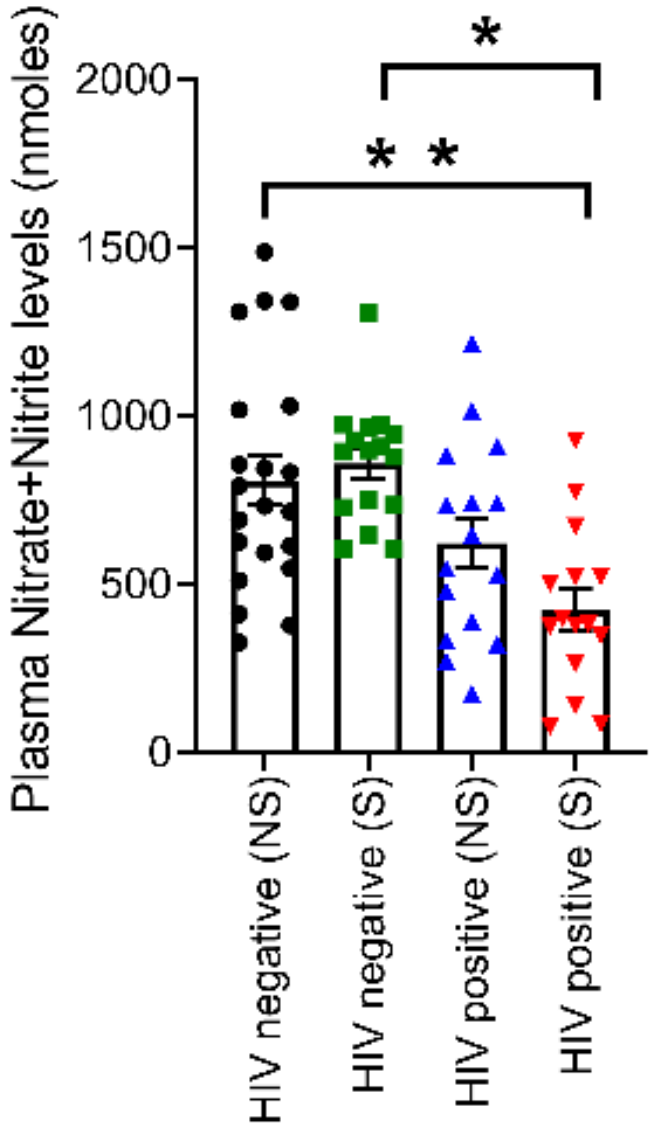
Smoking Disproportionately Attenuates Plasma Nitric Oxide Levels in PLWH



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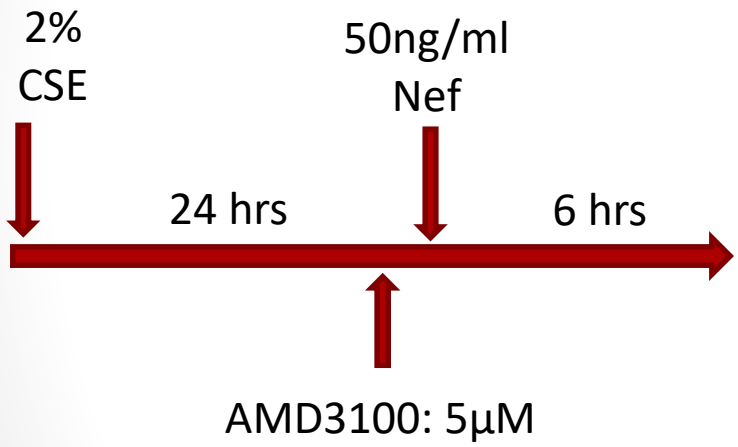
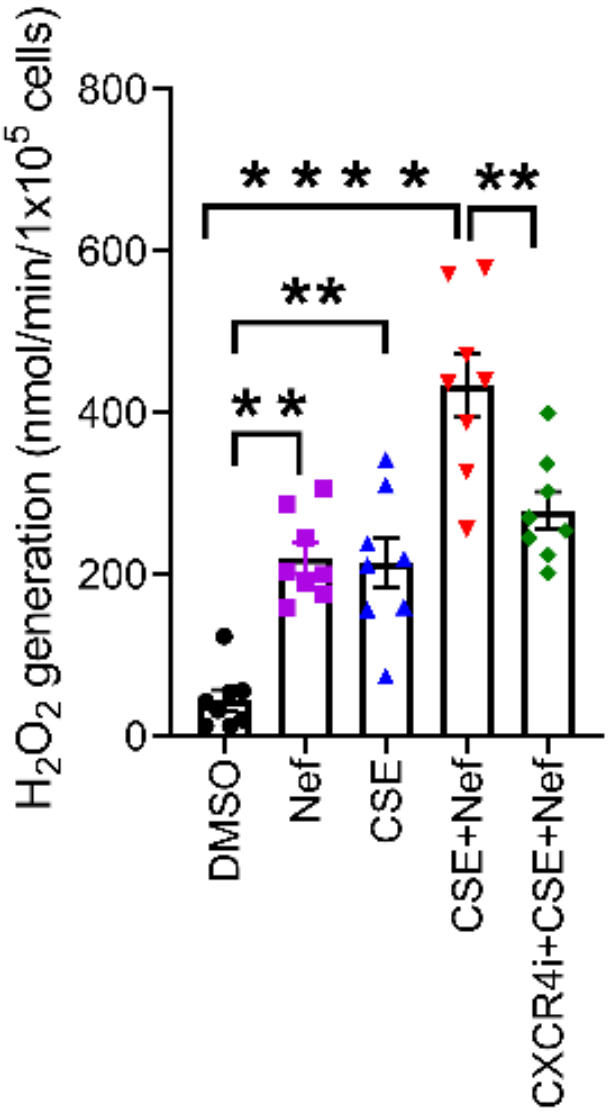
CSE enhances Nef-CXCR4 Mediated Increase in Reactive Species in HLMVECs





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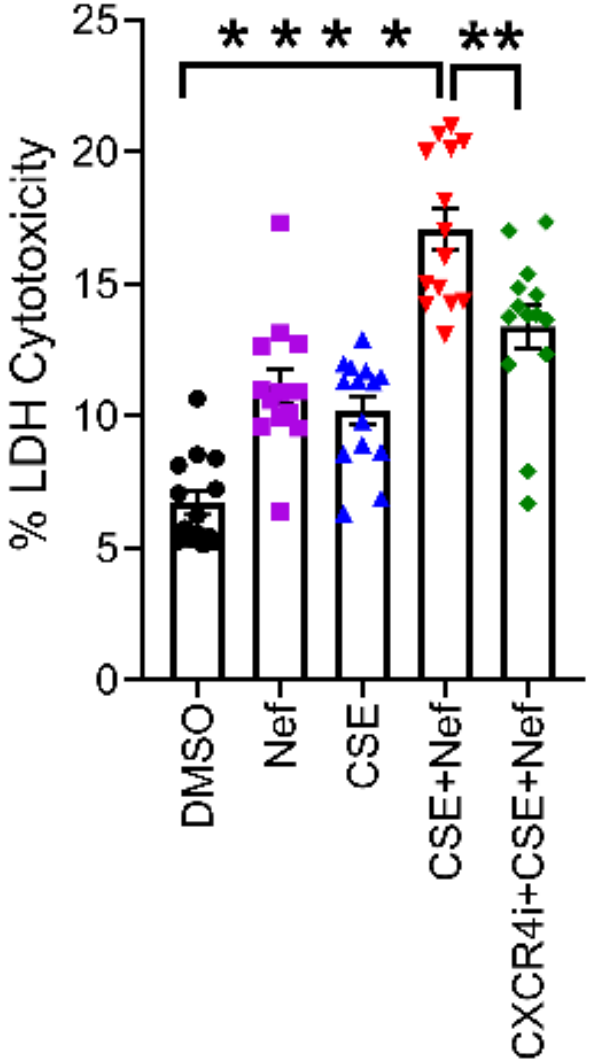
CSE Increases Nef-CXCR4 Mediated Cytotoxicity in HLMVECs



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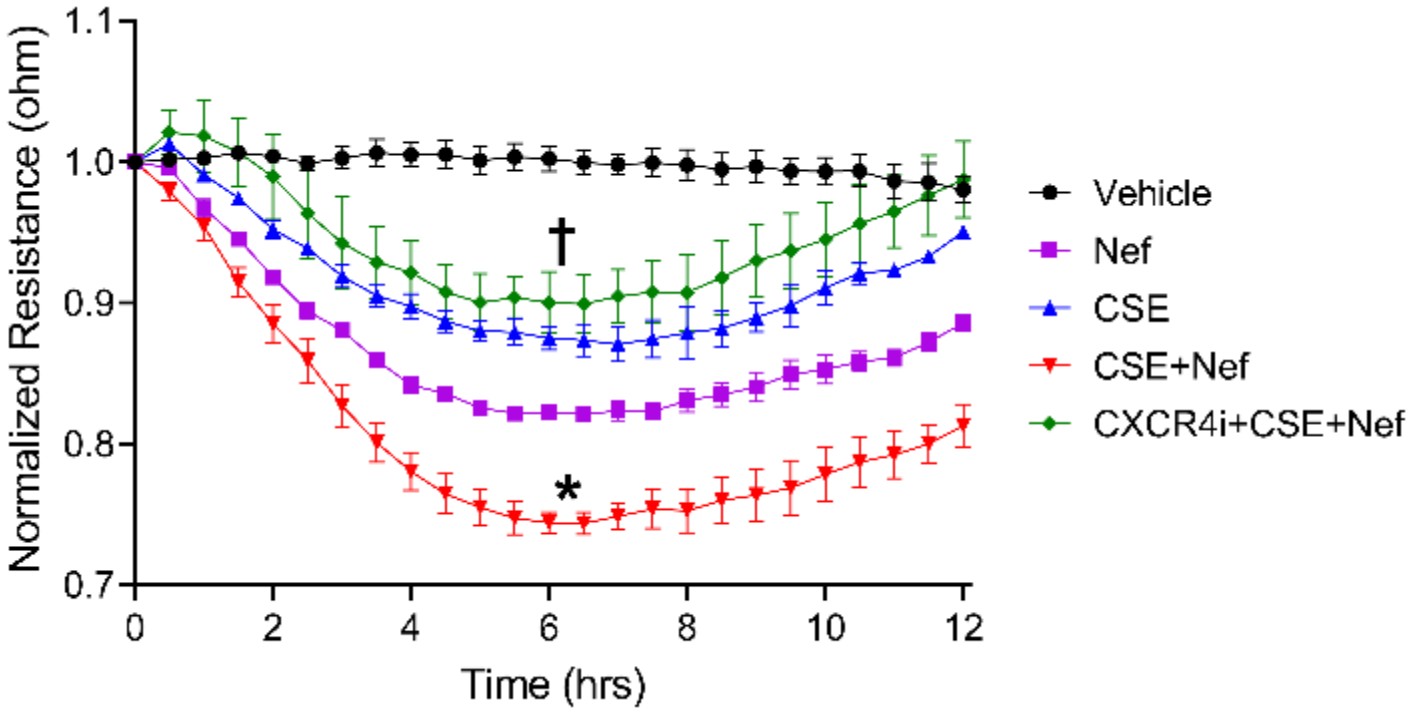
CSE Promotes Nef-CXCR4 Mediated Endothelial Barrier Dysfunction



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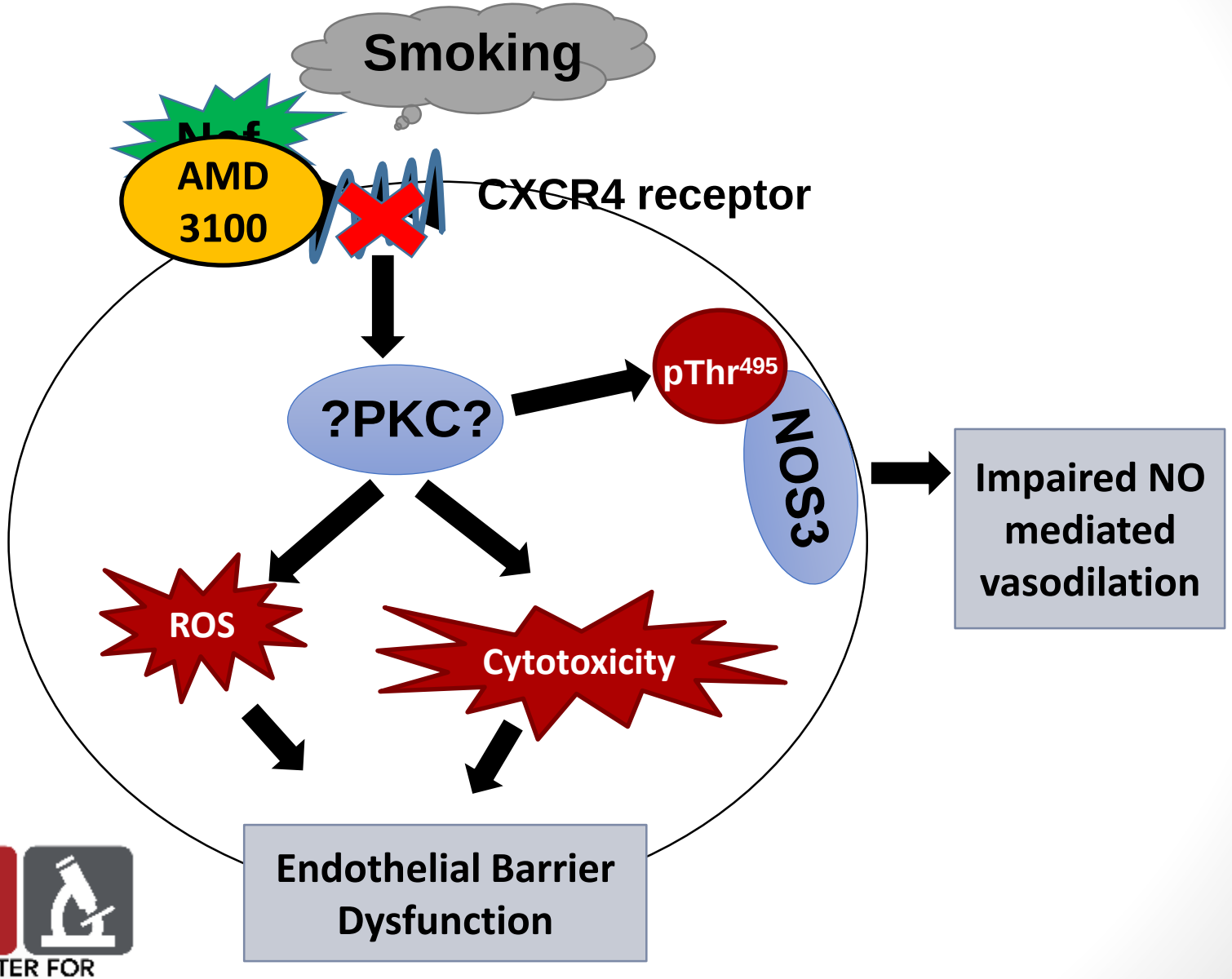
Conclusion



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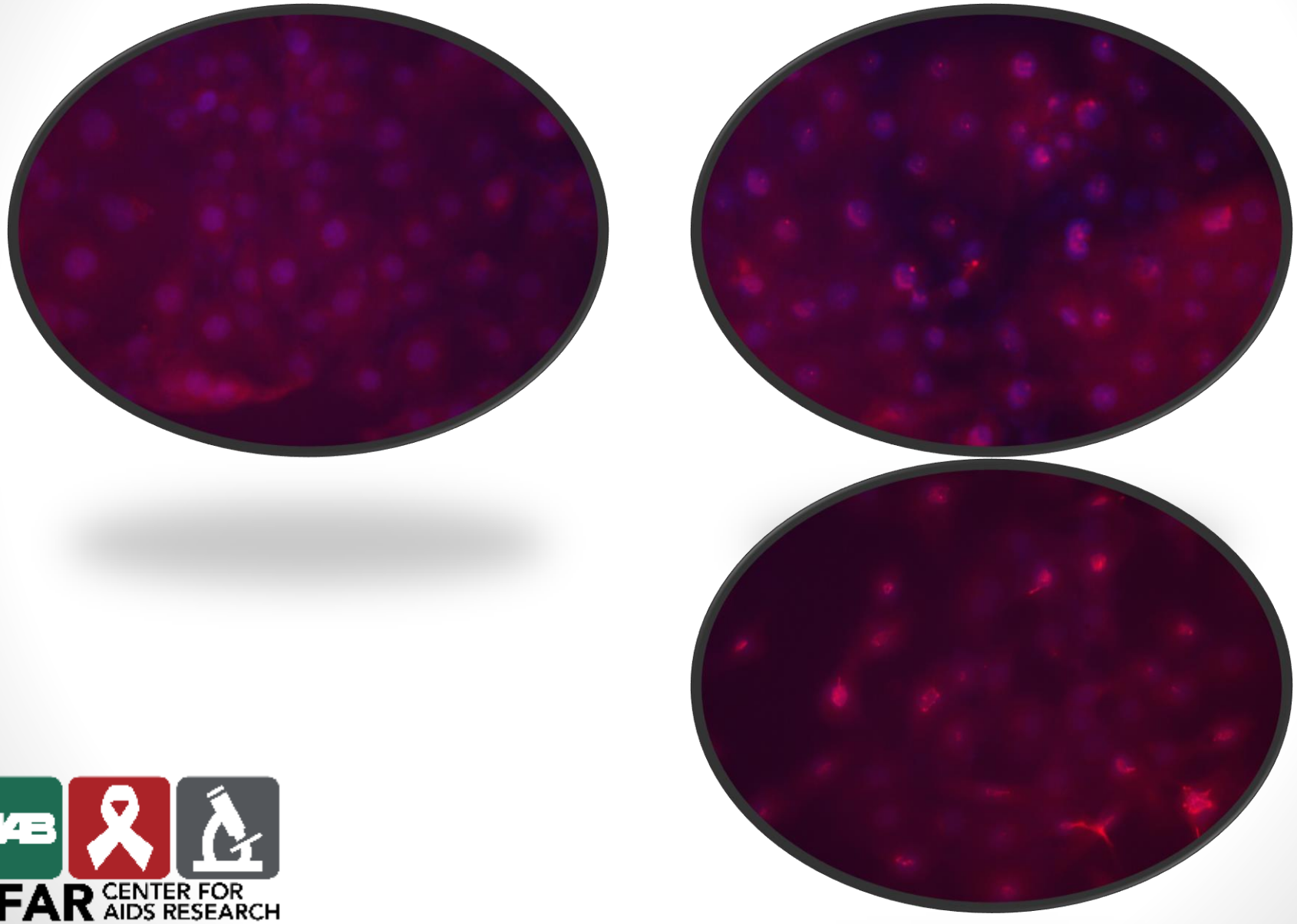
CS Attenuates Plasma NO Levels in PLWH



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Questions to be addressed

- Does CS disproportionately increases the risk of endothelial dysfunction in HIV?
- What is the mechanism of endothelial in HIV smokers?
- What are potential therapeutic targets to mitigate endothelial dysfunction?

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Specific Aim 2

Determine the mechanism through which the Nef-CXCR4 axis impairs PAEC function

- Investigate whether CSE increases CXCR4 expression and intracellular Nef translocation in human PAEC
- Investigate whether inhibition of CXCR4 prevents CSE-induced translocation of Nef into PAECs
- Investigate whether Nef impairs the post-translational modification of NOS3, the migration of NOS3 from the Golgi to plasma membrane, and NOS3 activity in PAECs

Specific Aim 3

Determine if inhibiting CXCR4 prevents the development of PAH in HIV-1 transgenic (HIV-1Tg) rats exposed to CS

- Investigate if these rats are disproportionately more susceptible than WT rats to CS-induced pulmonary vascular remodeling and PAH
- Investigate the effect of CS on CXCR4/Nef expression, NOS3 levels/function, and other parameters of endothelial function in HIV-1Tg rats
- Investigate whether AMD3100 (plerixafor), a CXCR4 antagonist, ameliorates PA remodeling and PAH in HIV-1Tg rats exposed to CS

Table 1.	HIV-1 transgenic (Tg) rat	HIV+ clinical population
Gene expression		
env	√	√
*gag**		√
*pol**		√
tat	√	√
rev	√	√
vif	√	√
vpr	√	√
vpu	√	√
nef	√	√
Viral proteins		
gp160 ↓	√	√
gp120	√	√
gp41	√	√
Reduction in CD4+ cells	√	√
Elevated cytokines		
IL-1b	√	√
TNFa	√	√
IFNg	√	√
Neurocognitive deficits	√	√

Expresses a non-replicative provirus that encodes for one of three genes needed to produce viral particles, plus regulatory and supplementary genes. Viral proteins are continually expressed throughout the animal's life, similar to HIV-infected individuals on ART with substantially suppressed viral replication.

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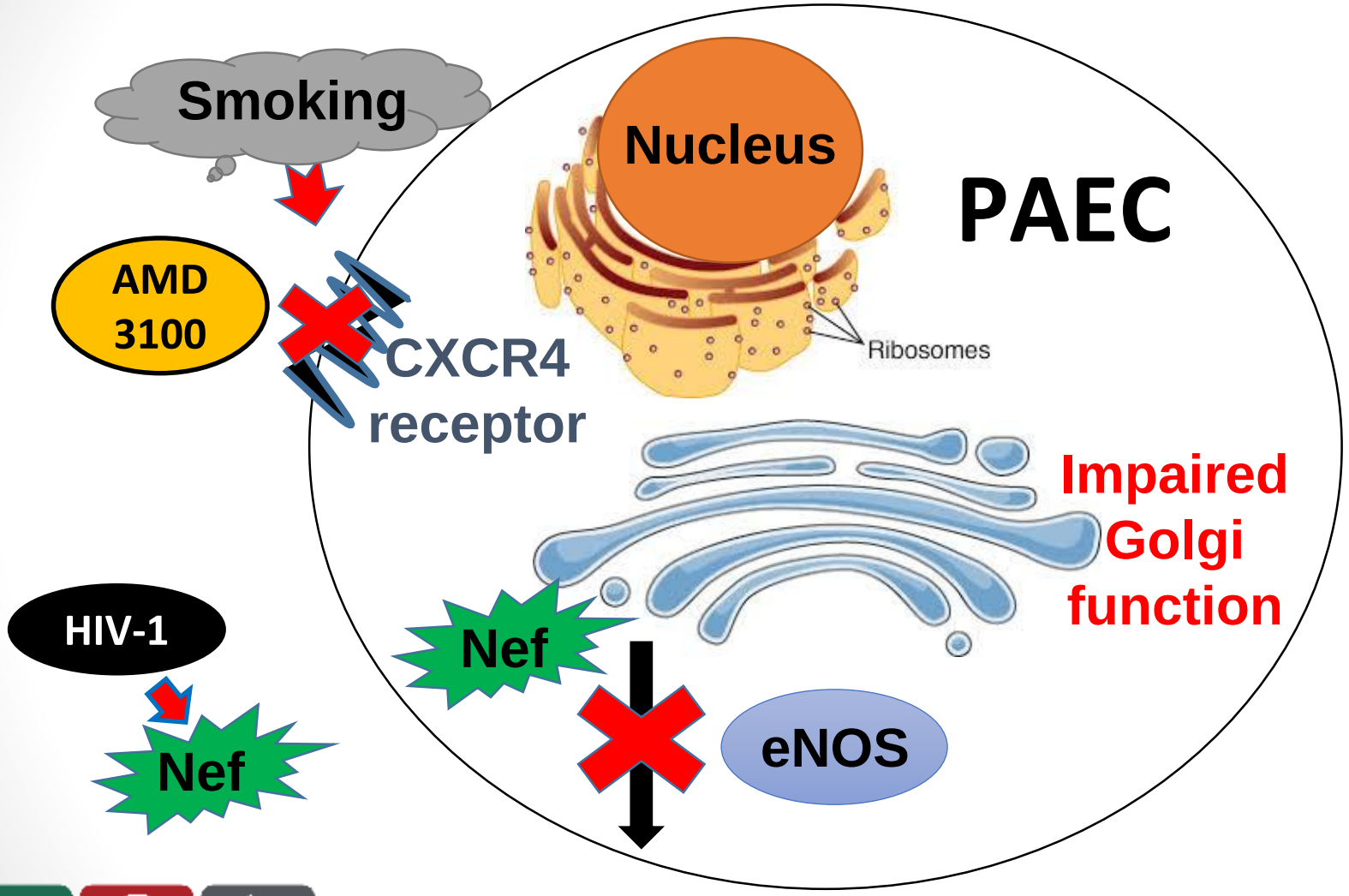
Expected outcome of the study



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Specific Aims