

11TH EDITION

DECEMBER 10-13, 2024

HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop



Modulation of HIV Reservoir Dynamics in Brain Pericytes

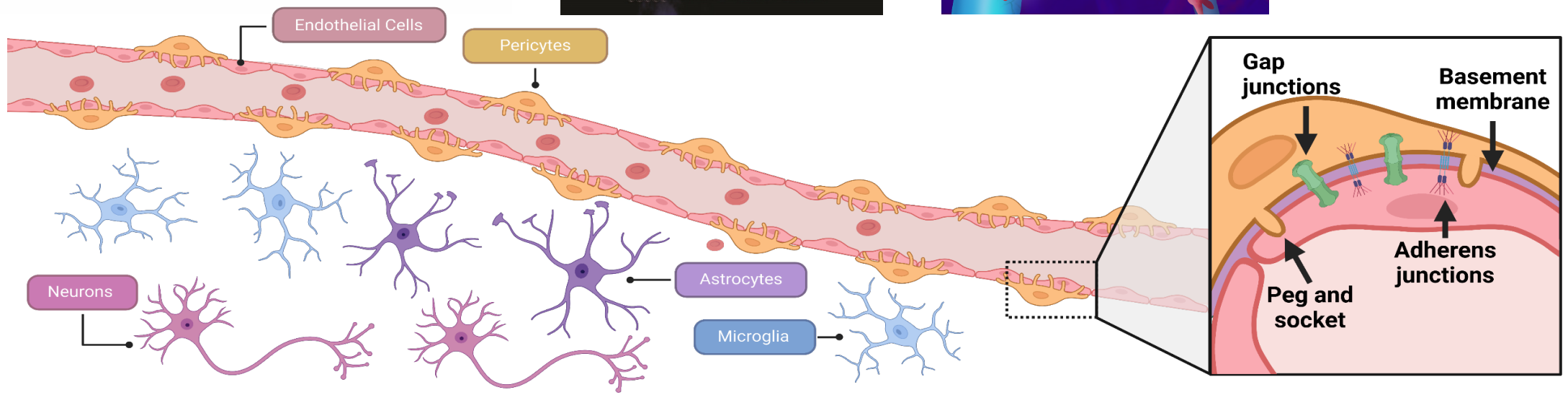
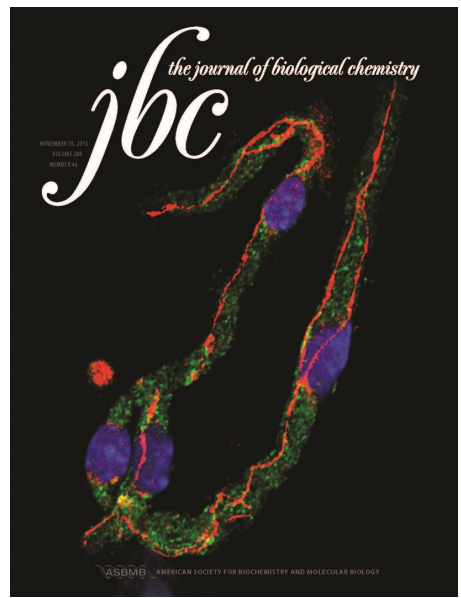
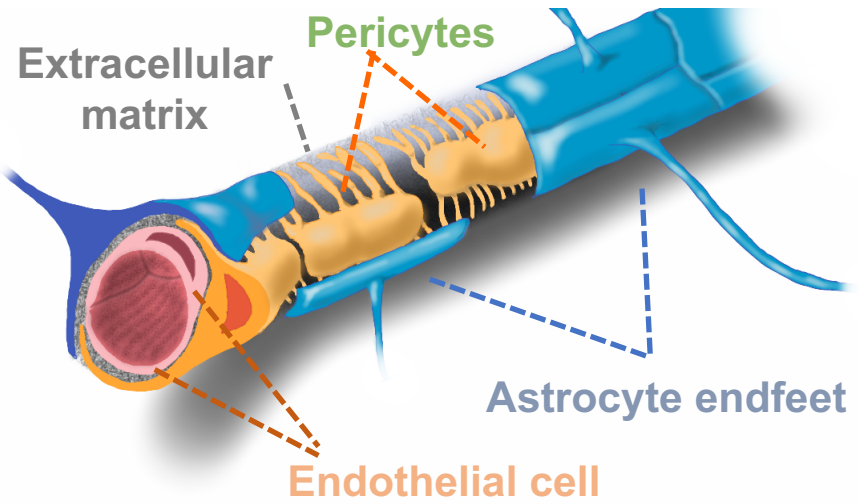
Oandy Naranjo, Sarah Schmidlin, Mario Stevenson, Michal Toborek

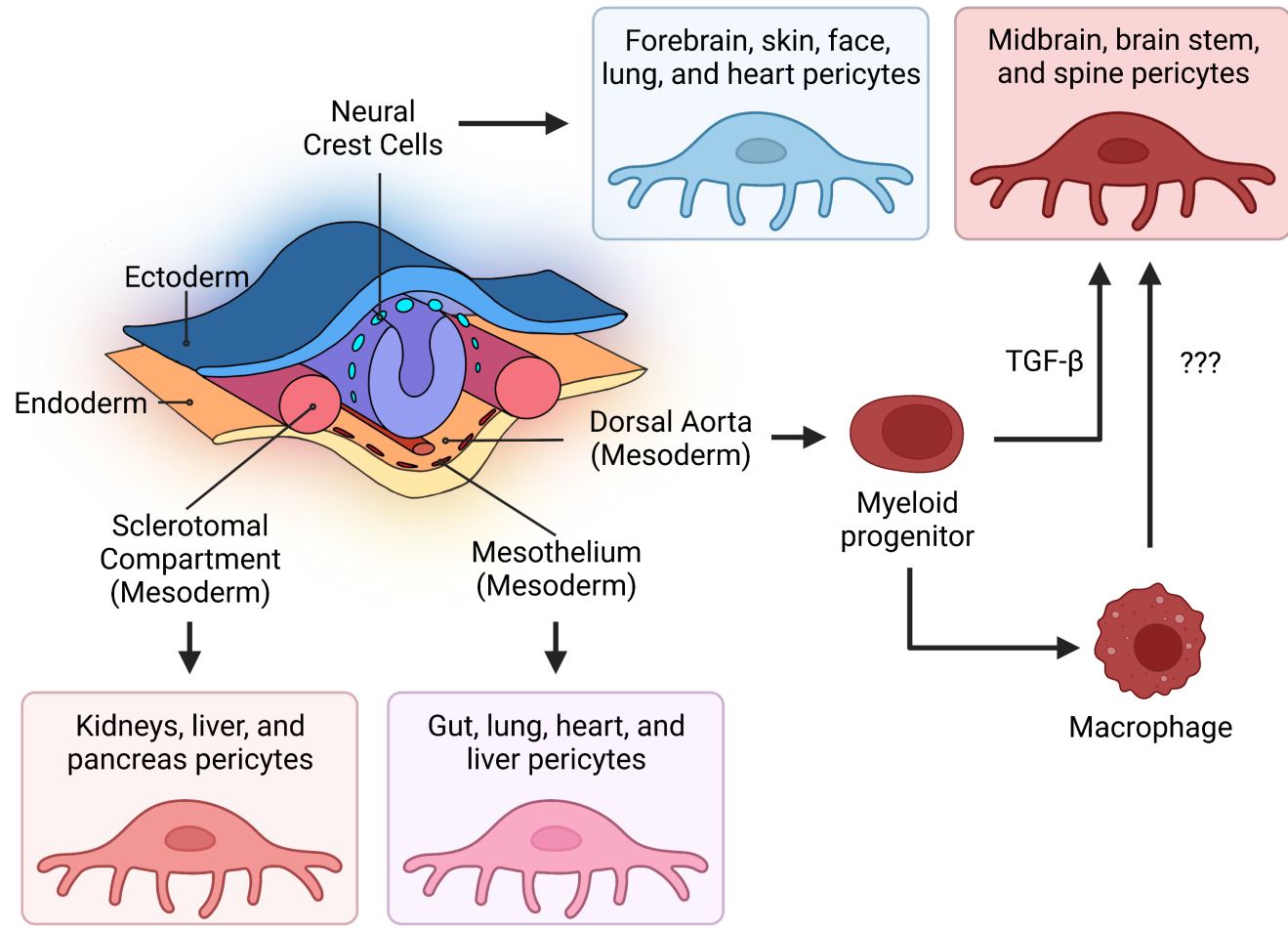
Department of Biochemistry and Molecular Biology, University of Miami School of Medicine,
Miami, FL

www.hiv-persistence.com

CONFLICTS OF INTEREST

Nothing to disclose

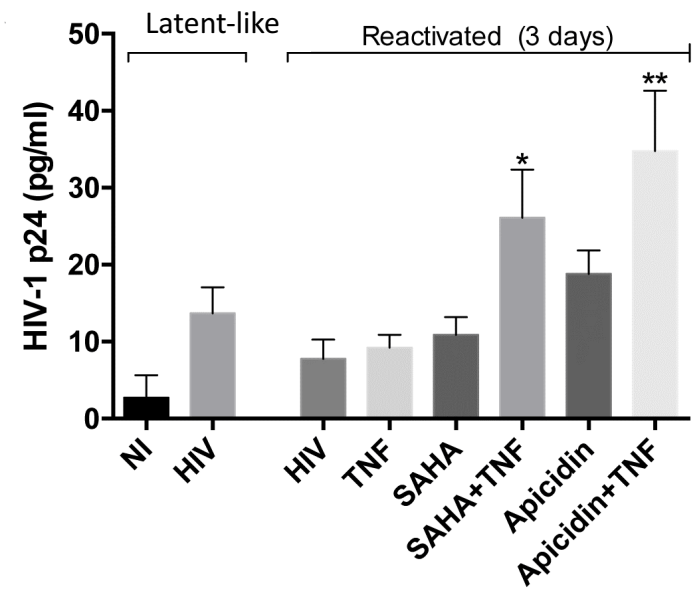
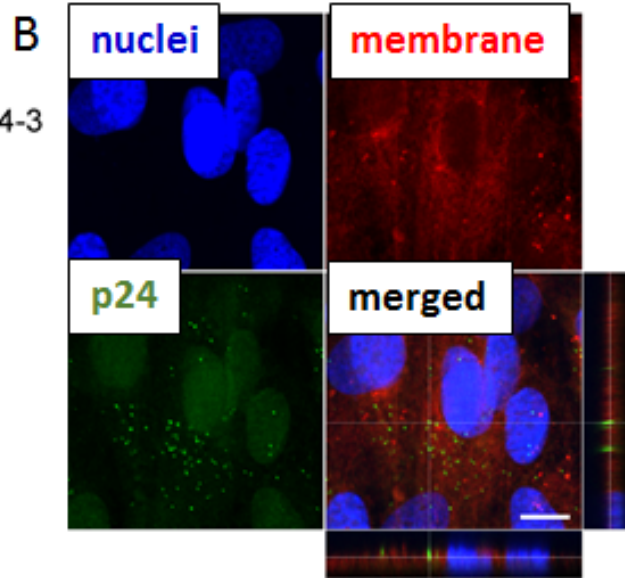
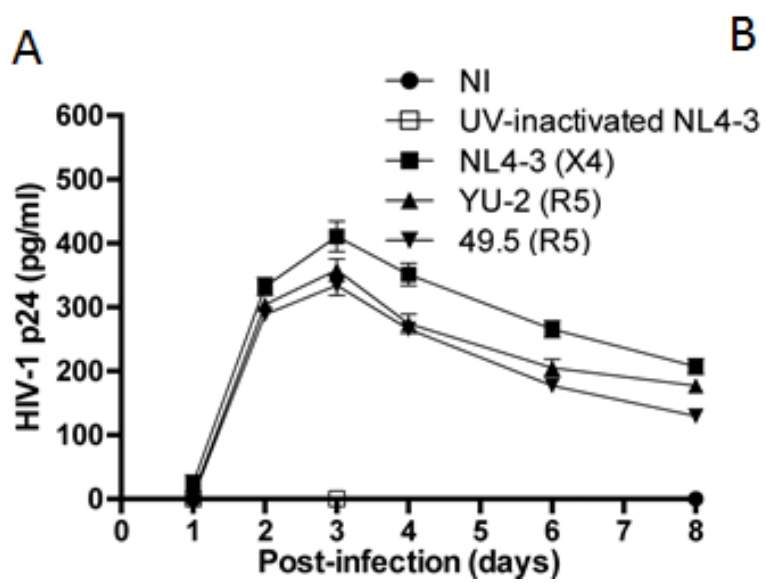
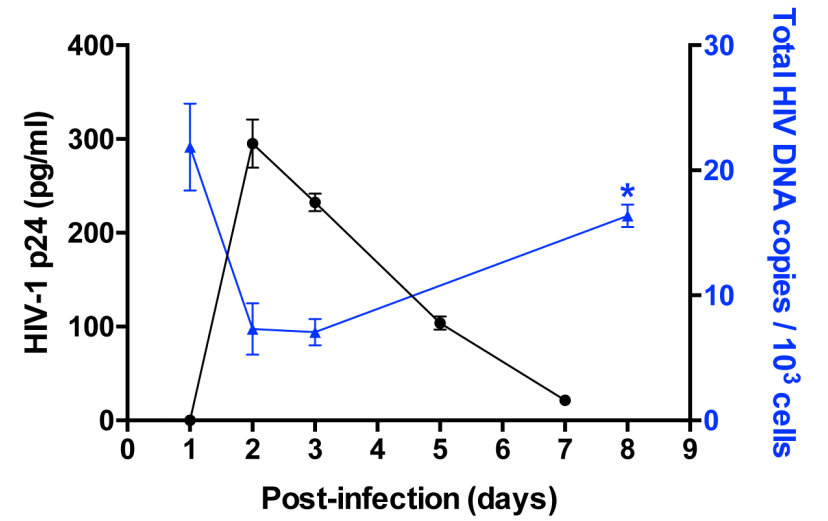
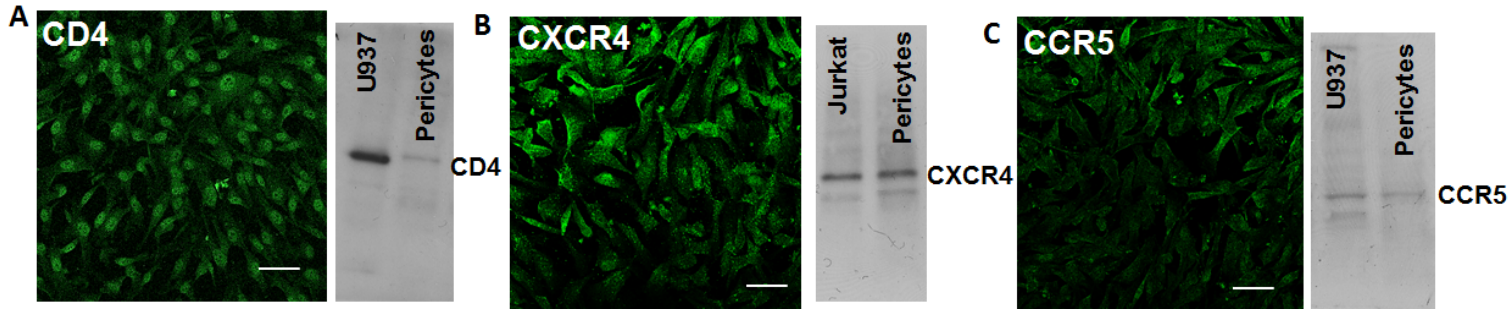




Pericyte ontogeny

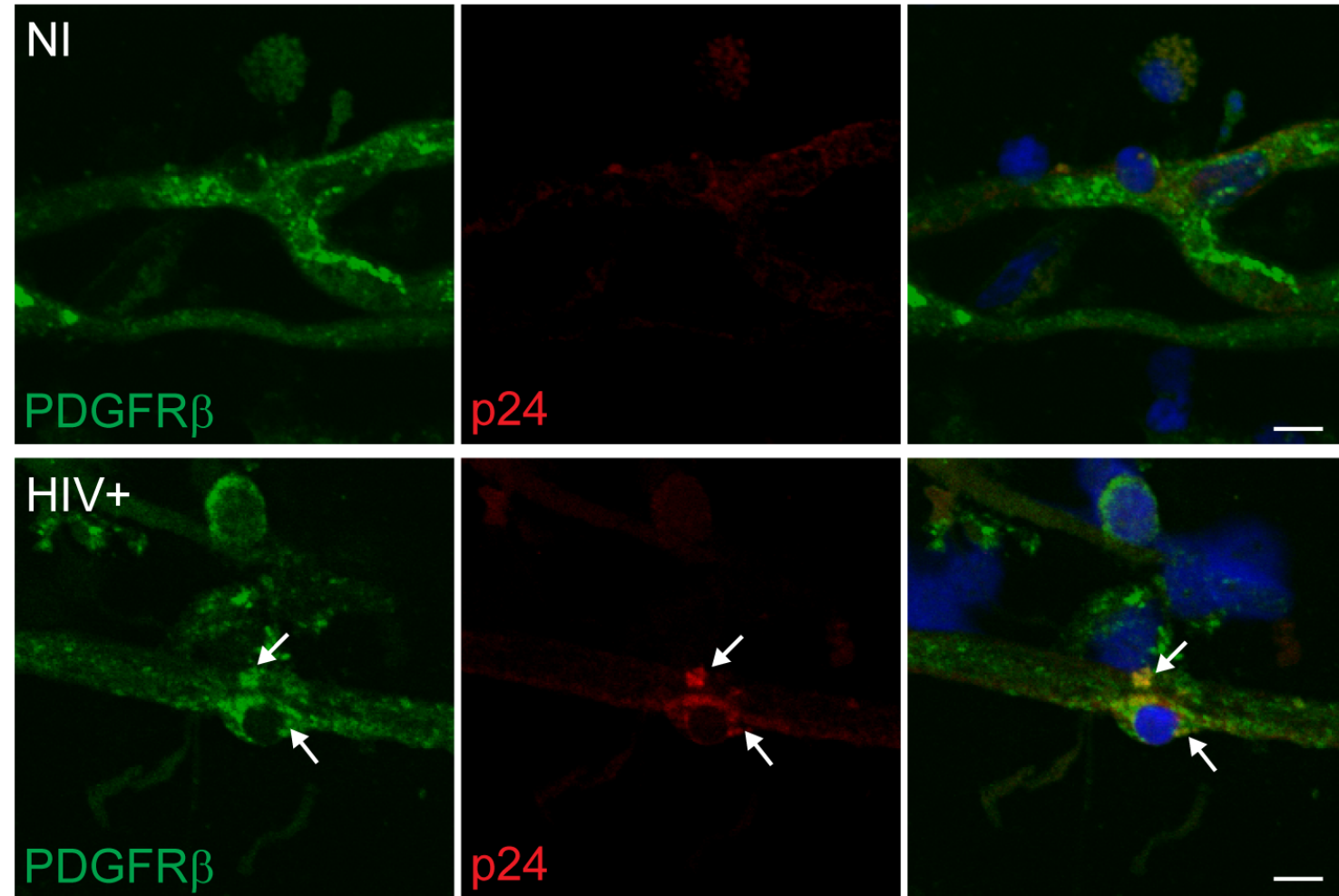
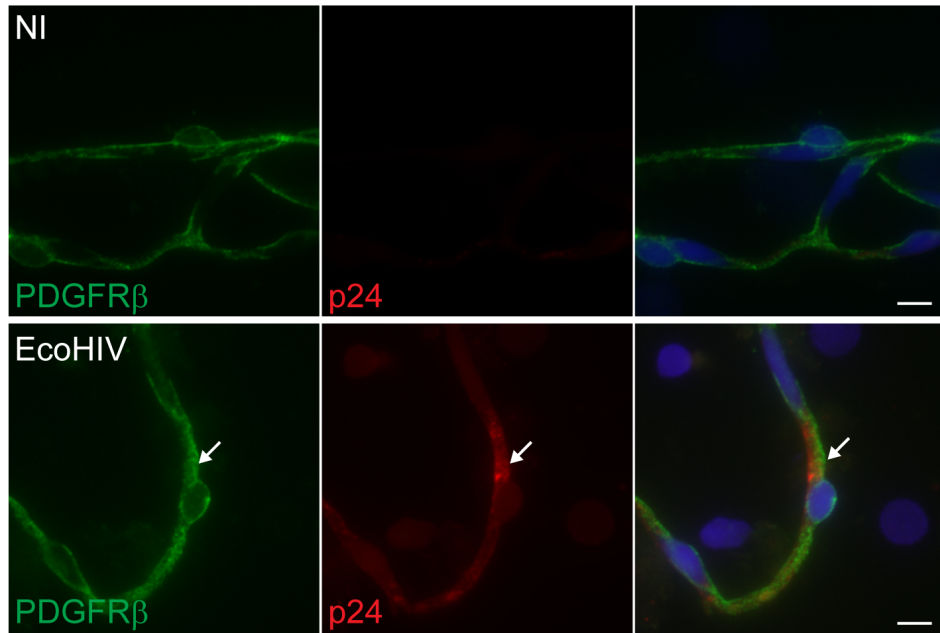
- Pericyte origins are varied depending on the target organ
- Several tissues have pericytes of different origins
- **A substantial subpopulation of brain pericytes originates from myeloid progenitors from dorsal aorta mesoderm and yolk-sac-derived macrophage progenitors**

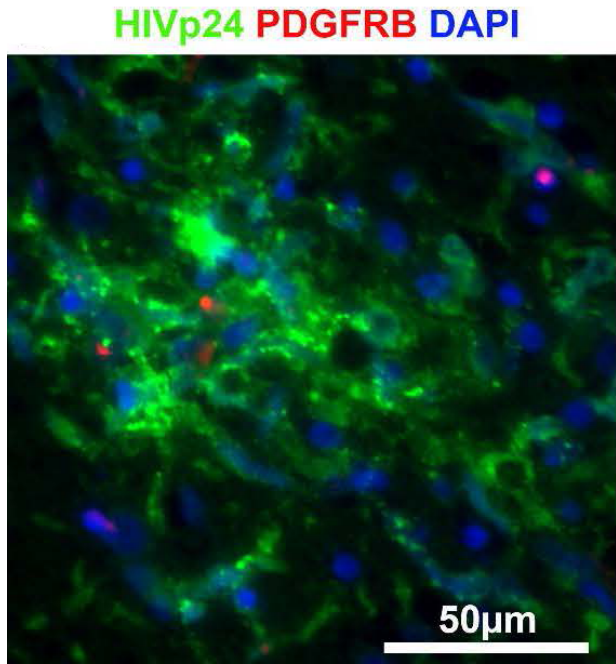
Naranjo et al., *Pericyte infection by HIV-1: a fatal attraction*. *Retrovirology*. 2022 Dec 7;19(1):27.



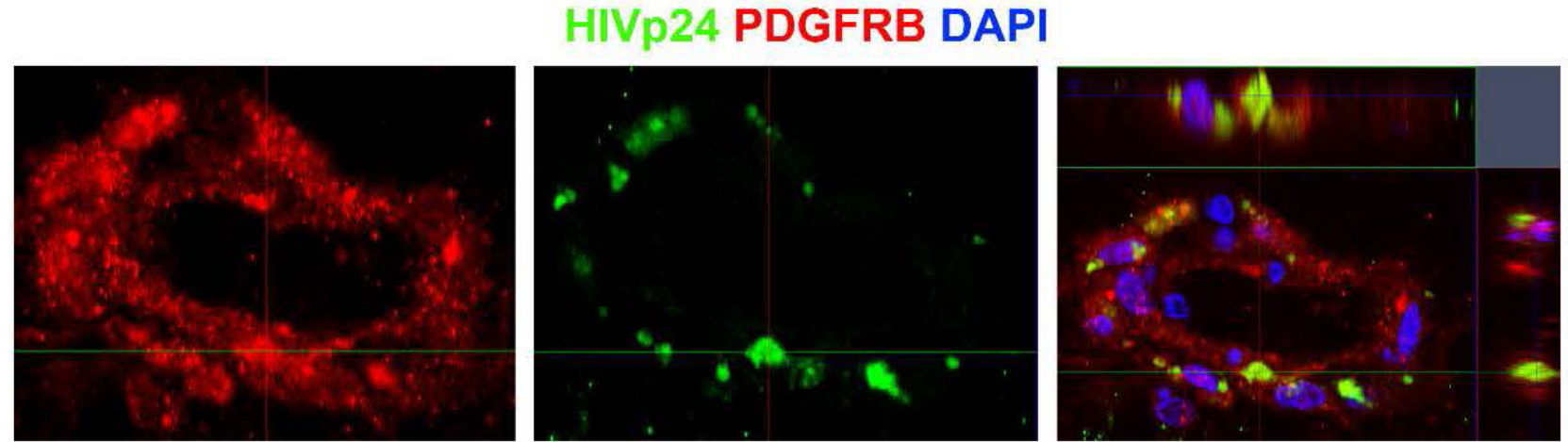
Human brain microvessels

Mouse brain microvessels





Adult male rhesus macaques (*Macaca mulatta*; Tulane National Primate Research Center) intravenously infected with SIVmac251 or SIV0302-2.



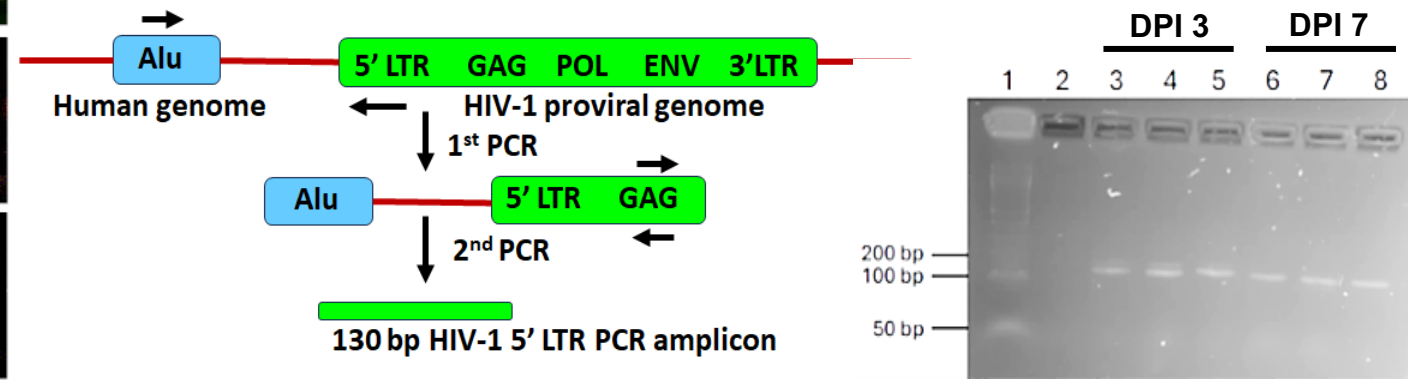
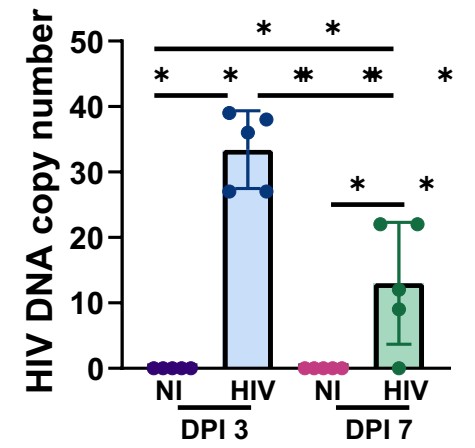
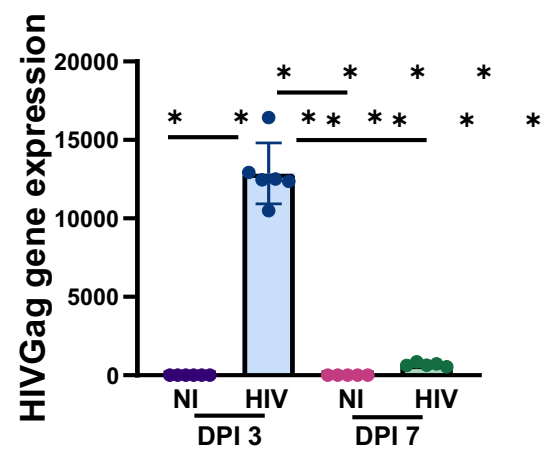
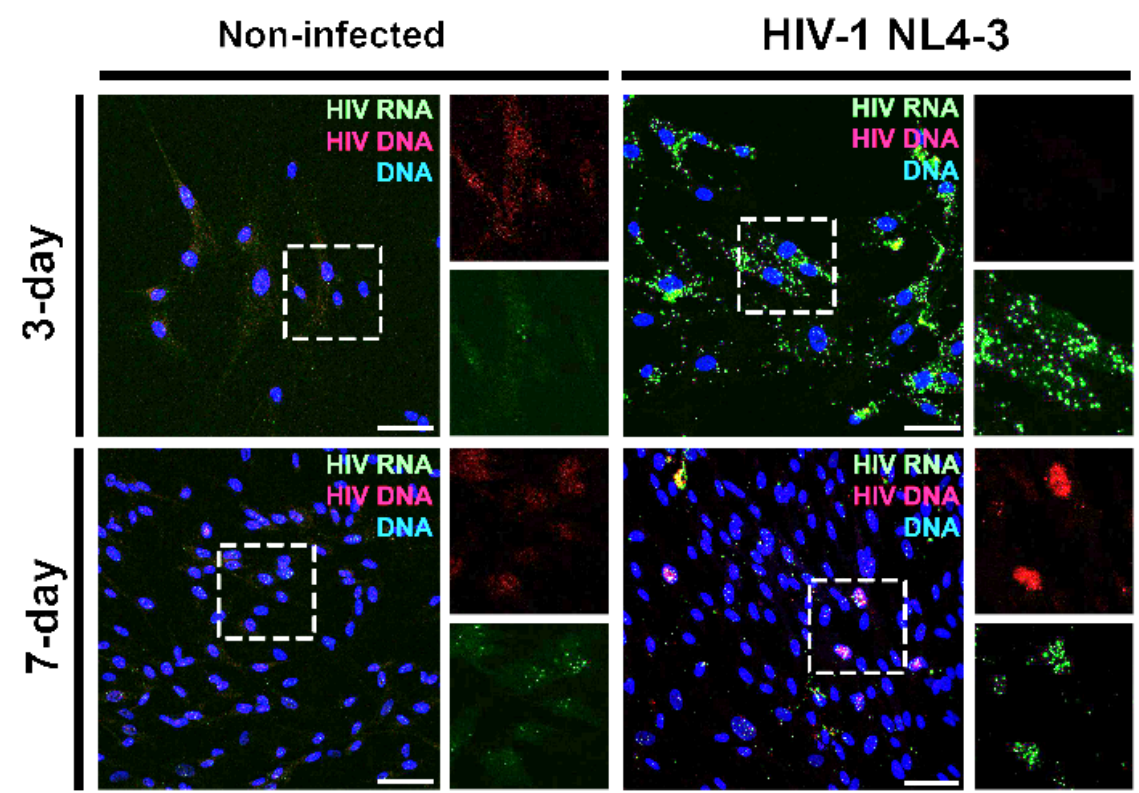
HIVE patients

Dysregulation of Sonic Hedgehog Pathway and Pericytes in the Brain after Lentiviral Infection

Diana G. Bohannon¹, Allen Ko¹, Adam R. Filipowicz¹, Marcelo J. Kuroda², Woong-Ki Kim^{1*}

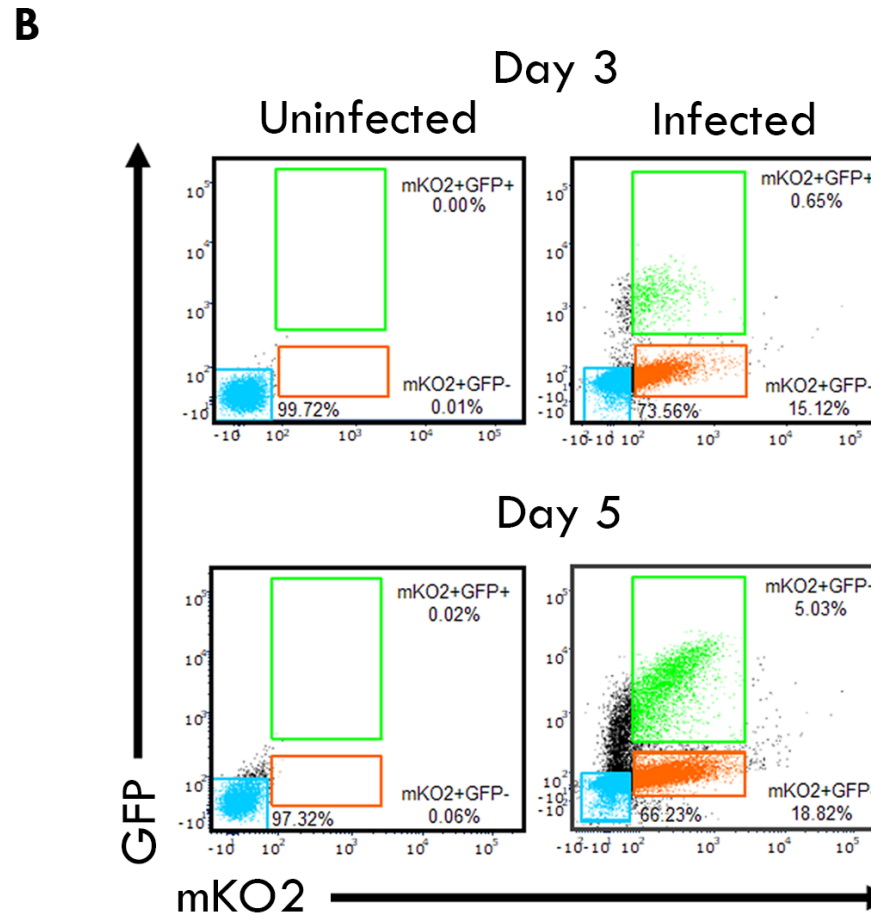
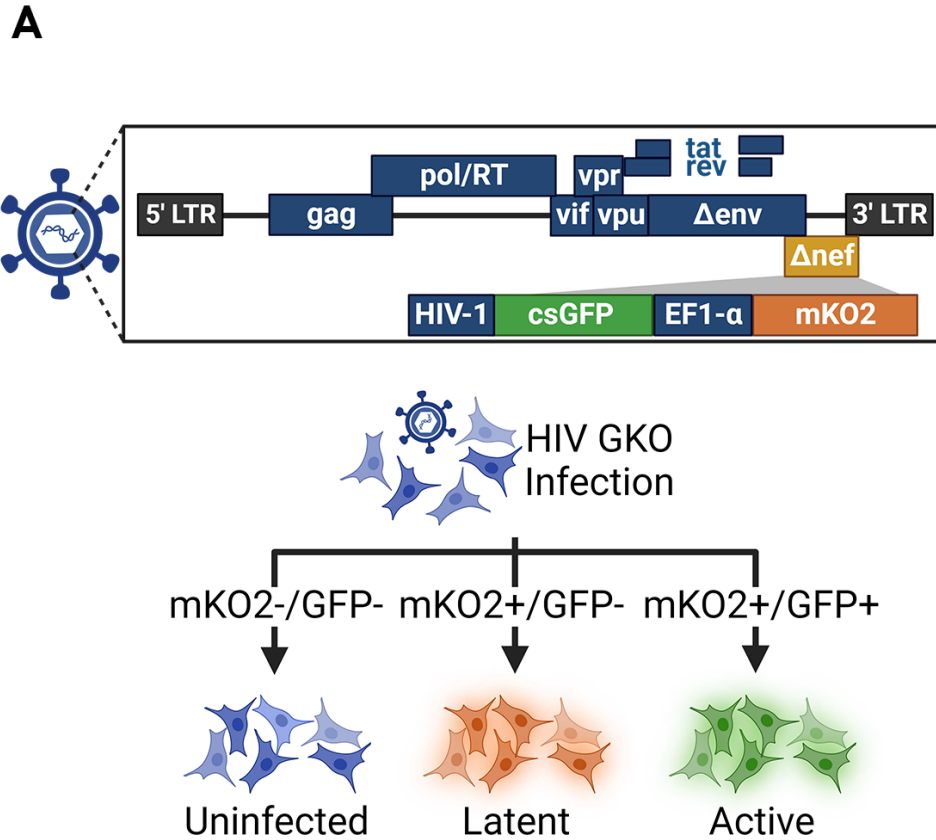
¹Department of Microbiology and Molecular Cell Biology, Eastern Virginia Medical School, Norfolk, Virginia

²Division of Immunology, Tulane National Primate Research Center, Covington, Louisiana



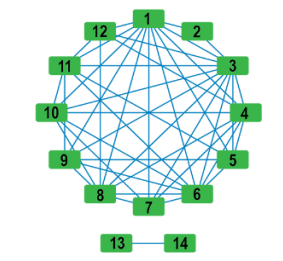
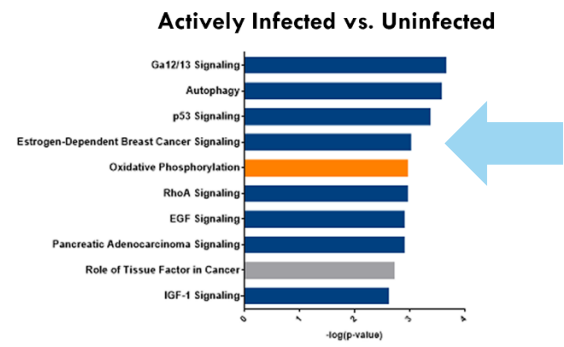
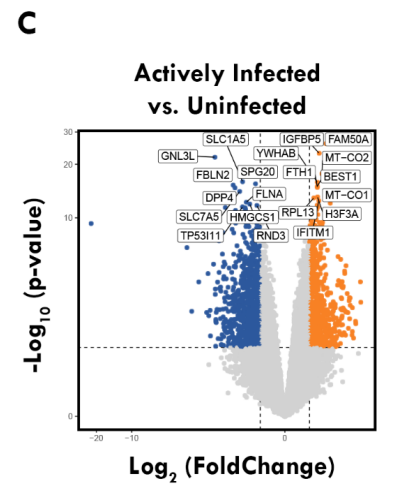
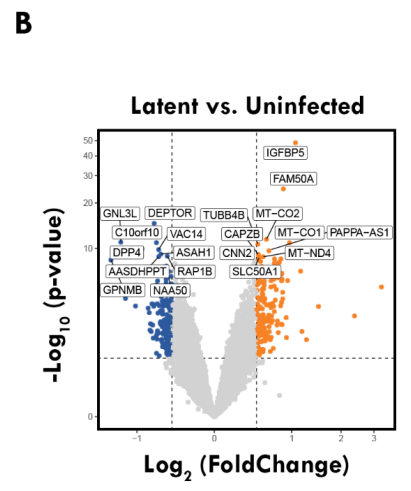
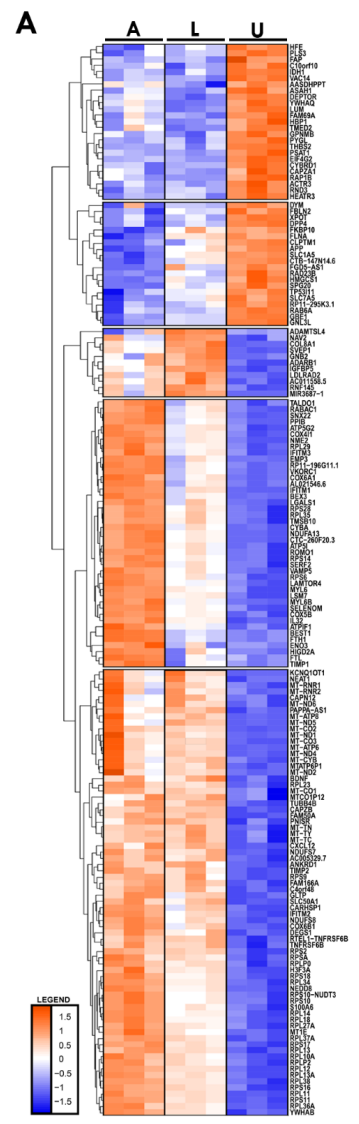
Collaboration with Siddappa Byrareddy, University of Nebraska

HIV GKO

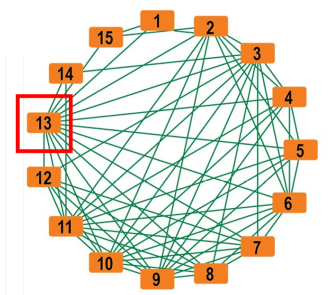
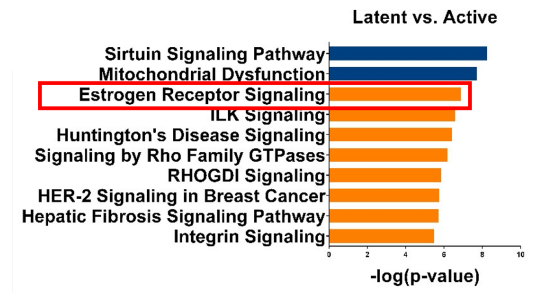
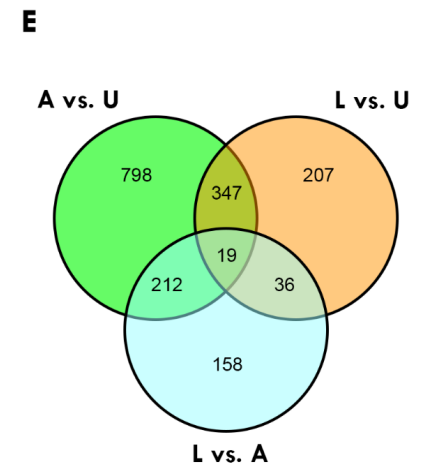
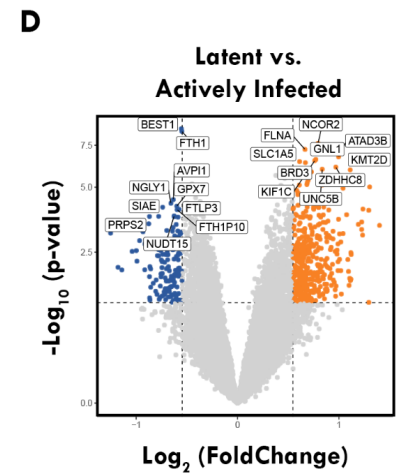


HIV GKO was a gift from Eric Verdin (Addgene plasmid # 112234 ; <http://n2t.net/addgene:112234> ; RRID:Addgene_112234)

Naranjo et al., J Biol Chem



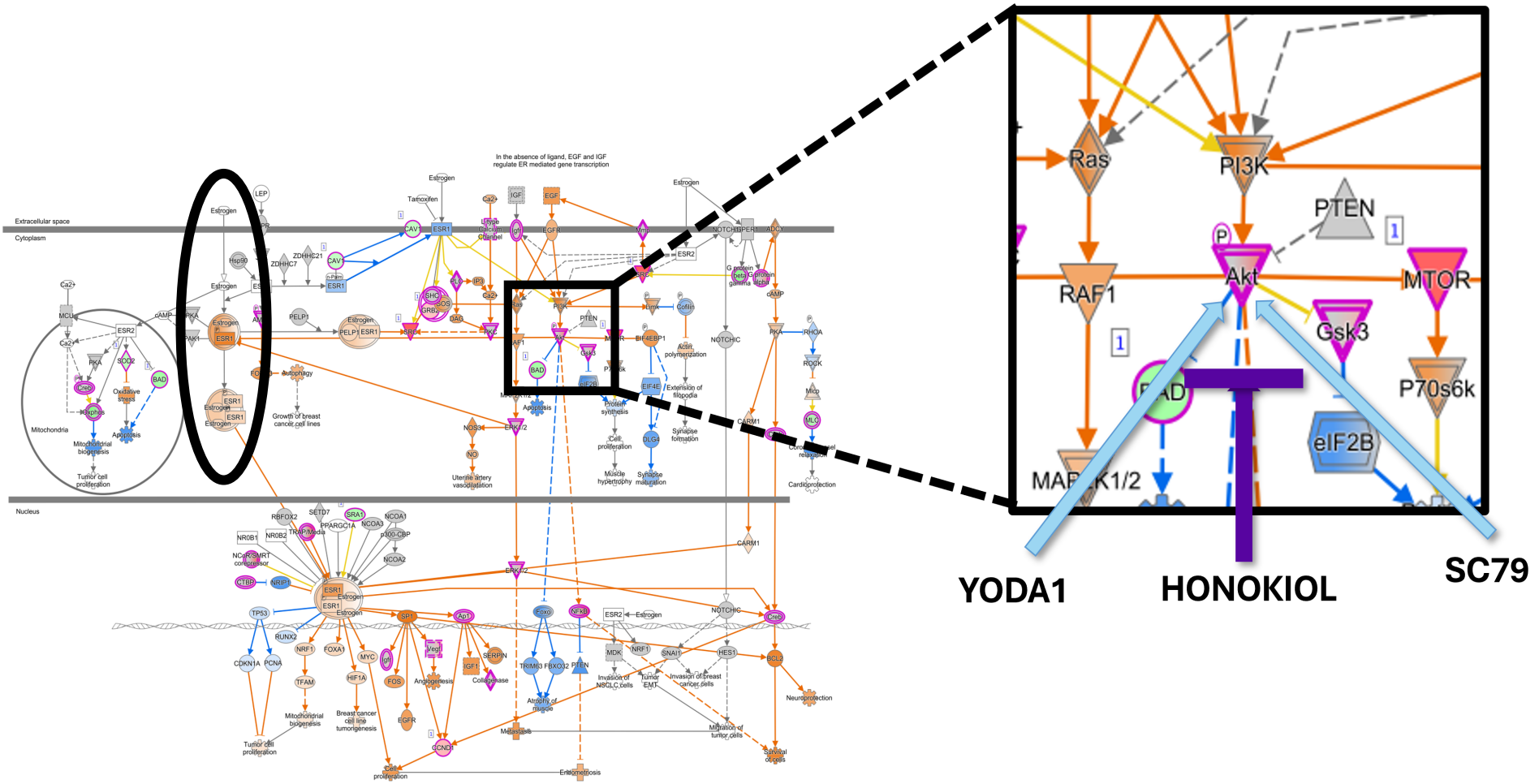
- 1 Molecular Mechanisms of Cancer
- 2 p53 Signaling
- 3 Ga12/13 Signaling
- 4 Estrogen-Dependent Breast Cancer Signaling
- 5 Role of Tissue Factor in Cancer
- 6 EGF Signaling
- 7 IGF-1 Signaling
- 8 RANK Signaling in Osteoclasts
- 9 Reelin Signaling in Neurons
- 10 Autophagy
- 11 Ovarian Cancer Signaling
- 12 Pancreatic Adenocarcinoma Signaling
- 13 Oxidative Phosphorylation
- 14 Mitochondrial Dysfunction



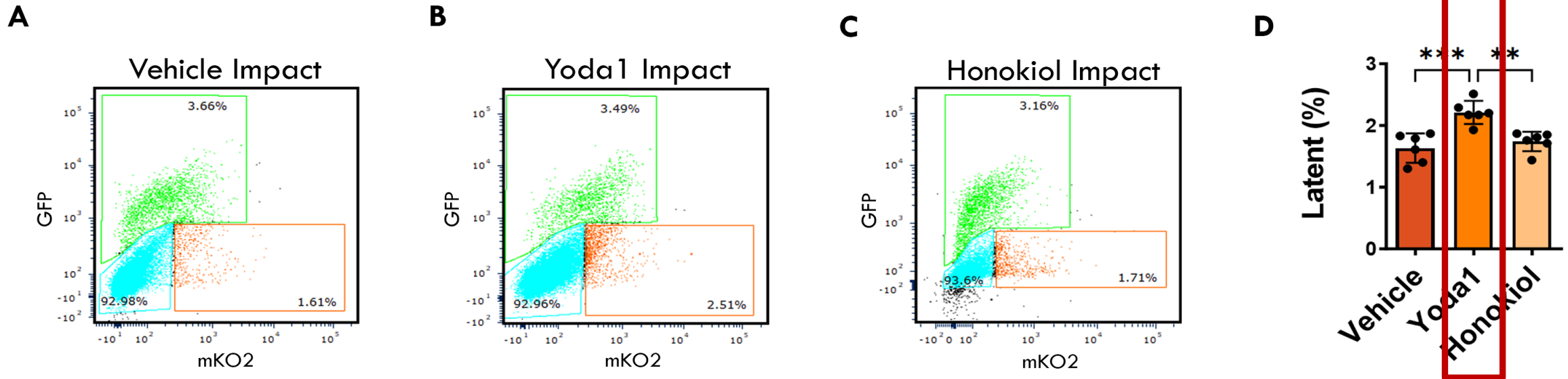
- 1 Sirtuin Signaling Pathway
- 2 Mitochondrial Dysfunction
- 3 ILK Signaling
- 4 CLEAR Signaling Pathway
- 5 NRF2-mediated Oxidative Stress Response
- 6 HER-2 Signaling in Breast Cancer
- 7 Signaling by Rho Family GTPases
- 8 Integrin Signaling
- 9 Huntington's Disease Signaling
- 10 Molecular Mechanisms of Cancer
- 11 Hepatic Fibrosis Signaling Pathway
- 12 RHO GDI Signaling
- 13 Estrogen Receptor Signaling
- 14 Hepatic Fibrosis / Hepatic Stellate Cell Activation
- 15 Oxidative Phosphorylation

Directionality
 Downregulated
 Upregulated

Data set now publicly available on the Neuroscience Multi-omic Data Archive (NeMO)



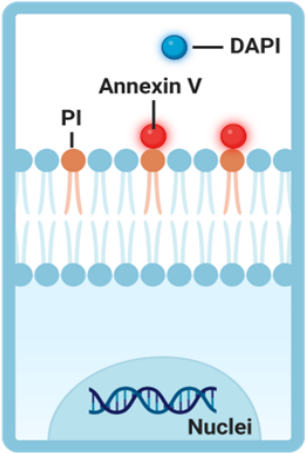
Modulating Reservoirs



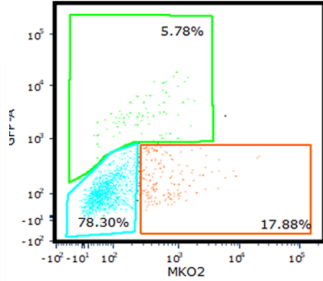
Yoda 1: activator of Akt
Honokiol: inhibitor of Akt

Early Apoptotic Cells

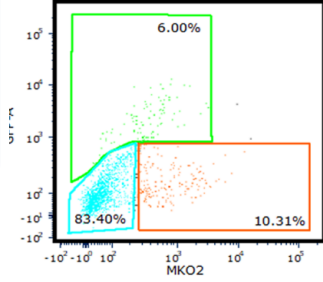
Early-Stage Apoptosis



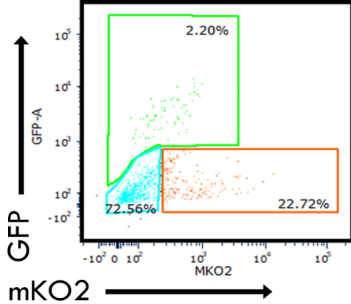
Vehicle Impact



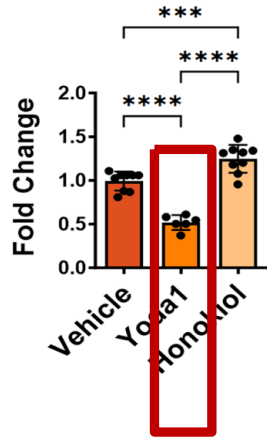
Yoda1 Impact



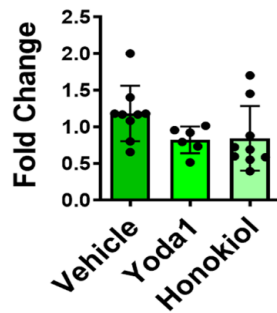
Honokiol Impact



**Early Apoptosis
(Latently Infected)**

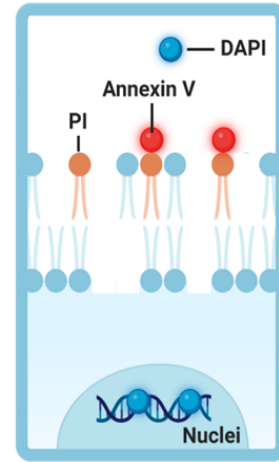


**Early Apoptosis
(Actively Infected)**

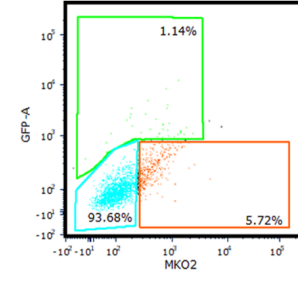


Late Apoptotic Cells

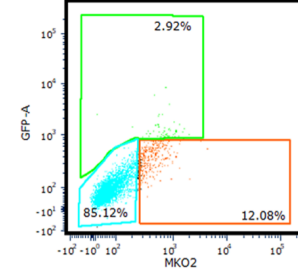
Late-Stage Apoptosis



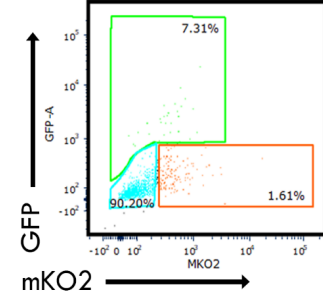
Vehicle Impact



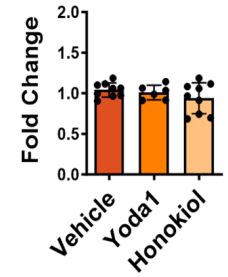
Yoda1 Impact



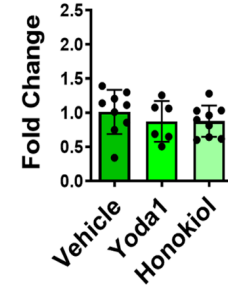
Honokiol Impact



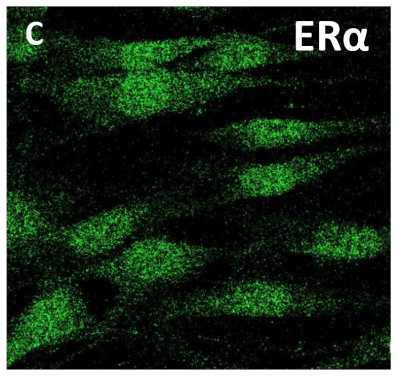
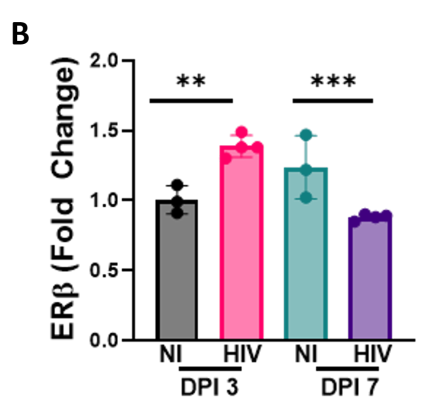
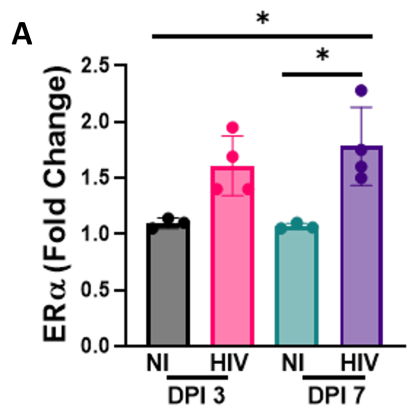
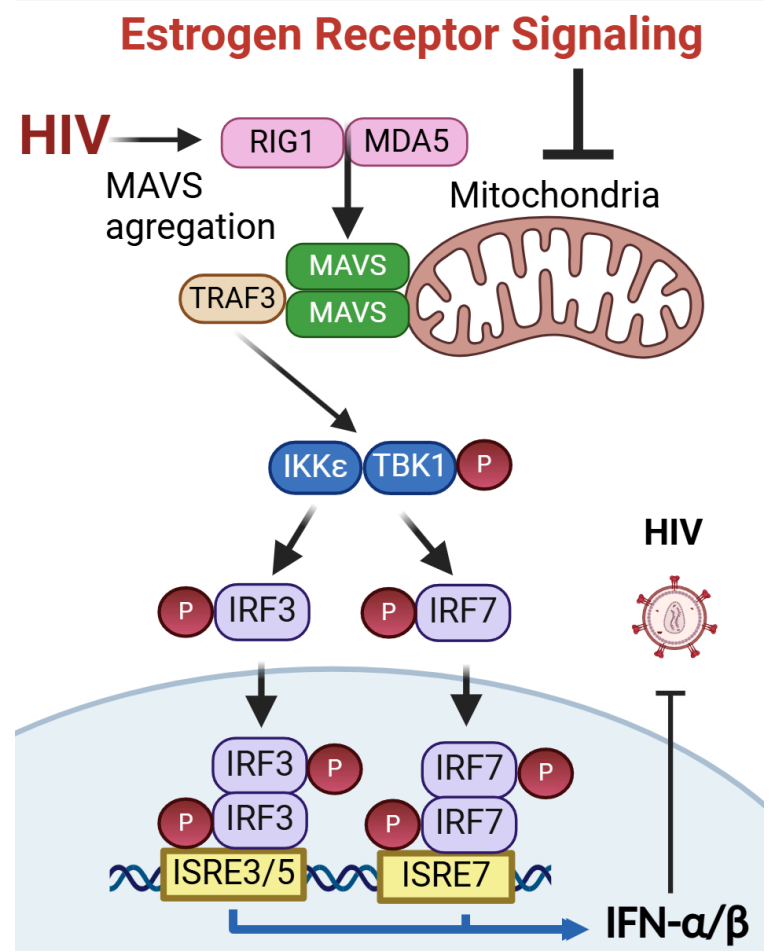
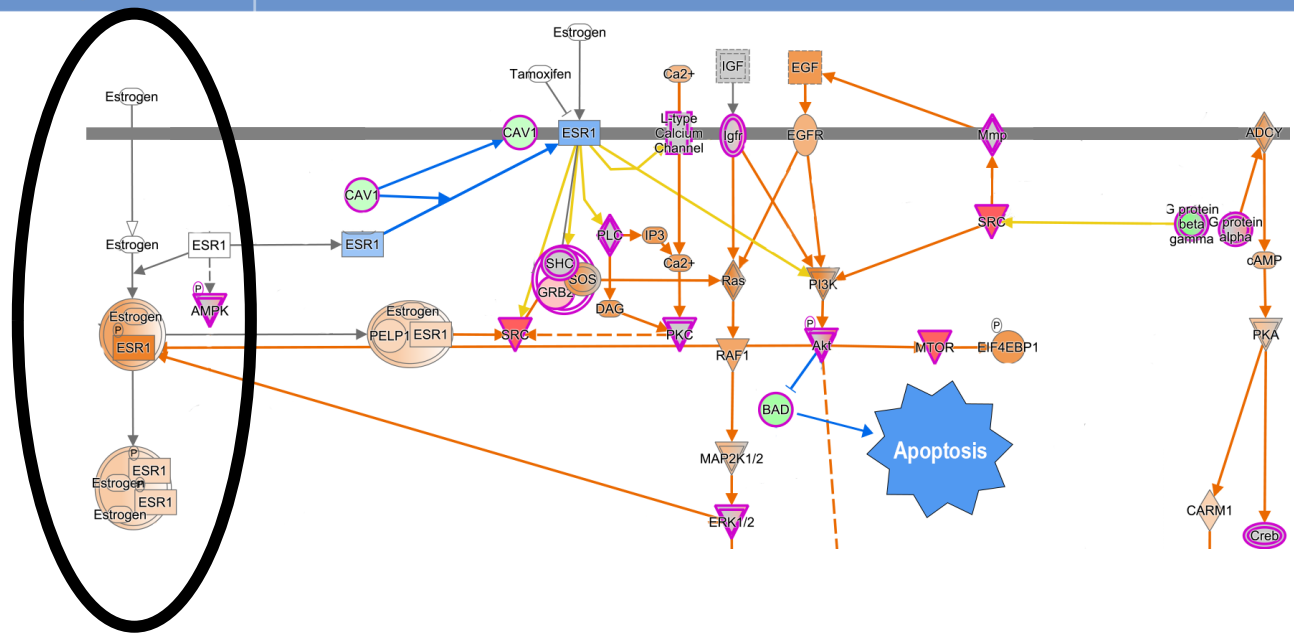
**Late Apoptosis
(Latently Infected)**



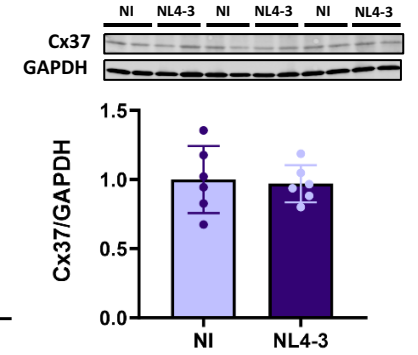
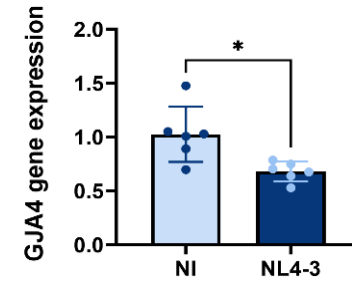
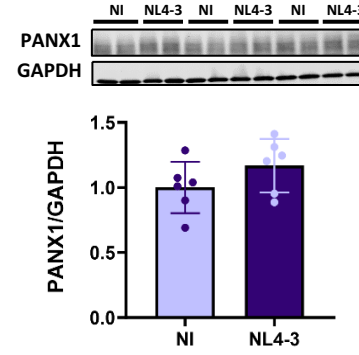
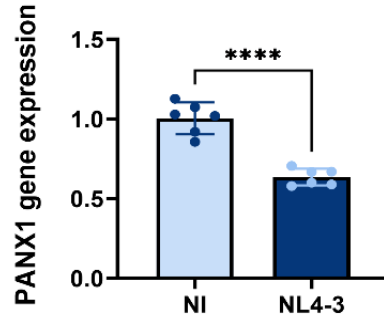
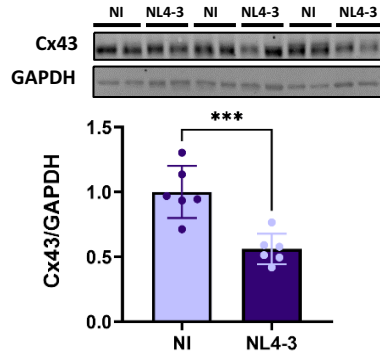
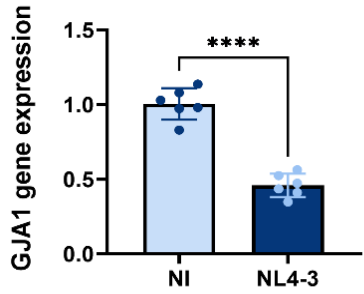
**Late Apoptosis
(Actively Infected)**



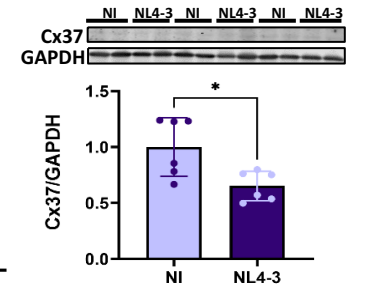
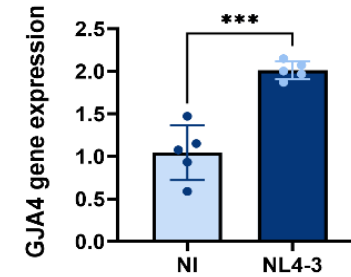
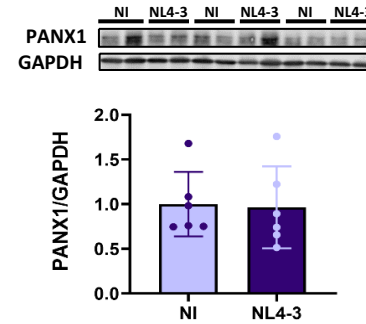
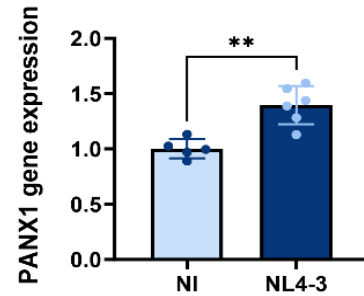
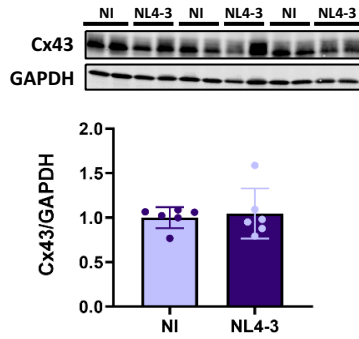
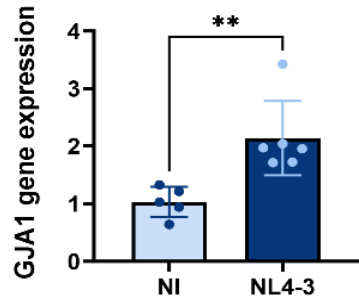
Yoda 1: activator of Akt
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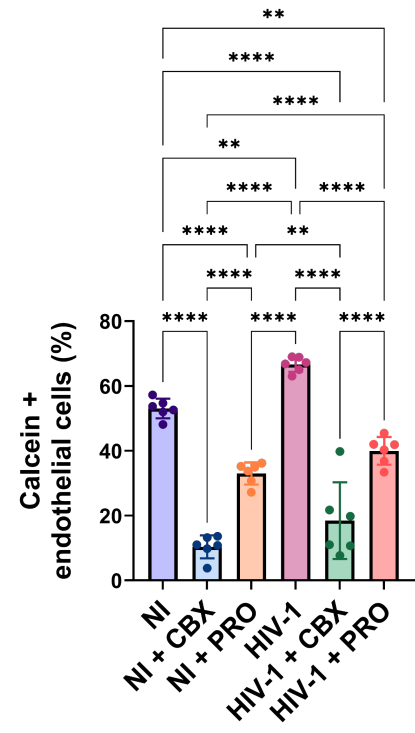
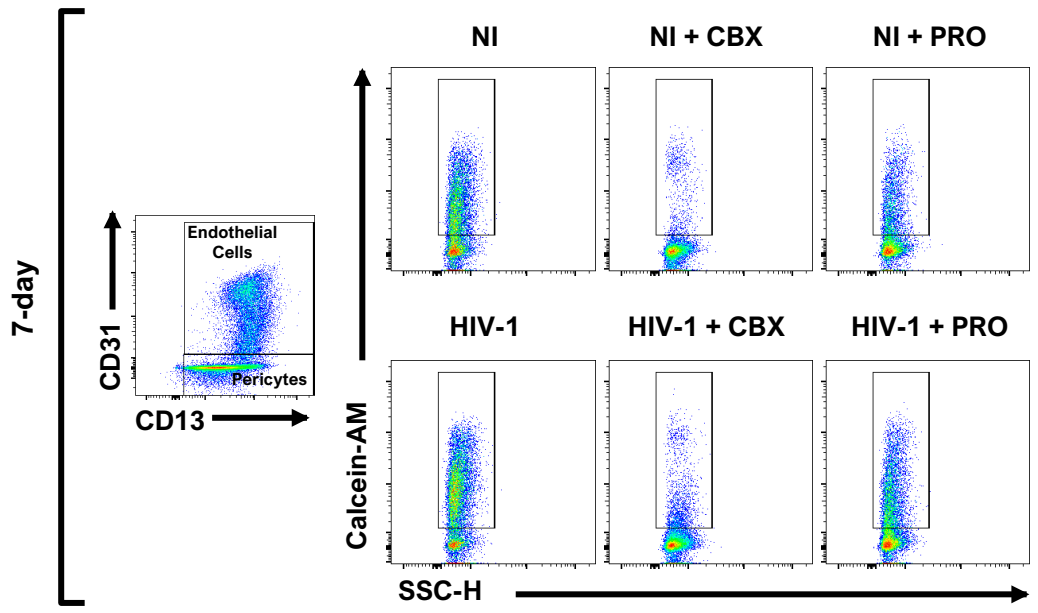
3-day



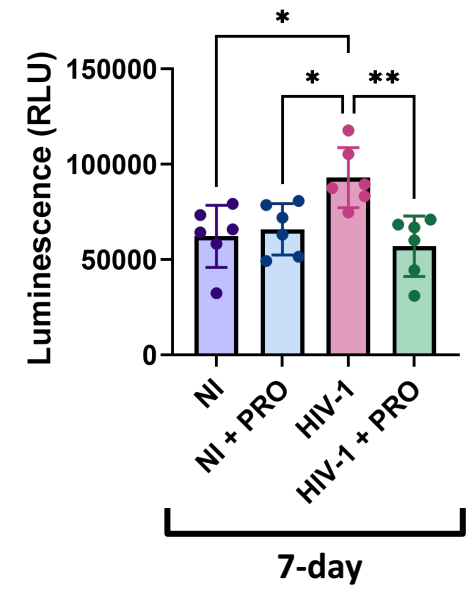
7-day



GJ Functional Assay

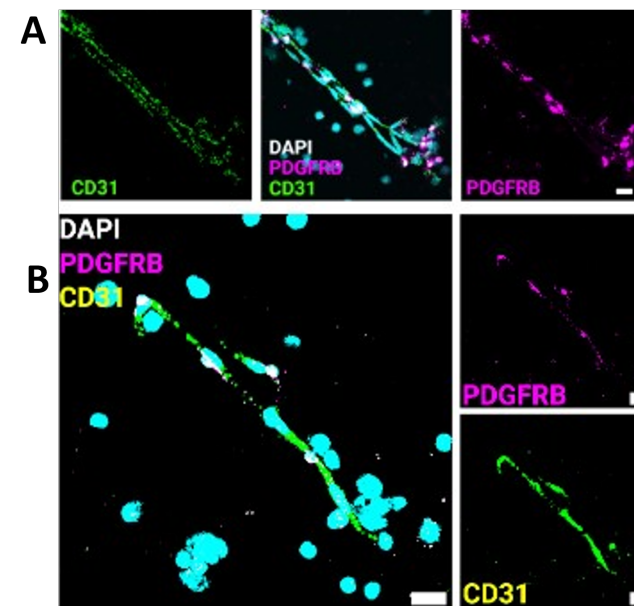
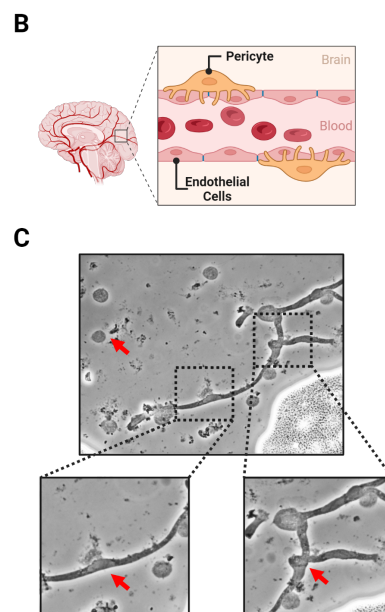
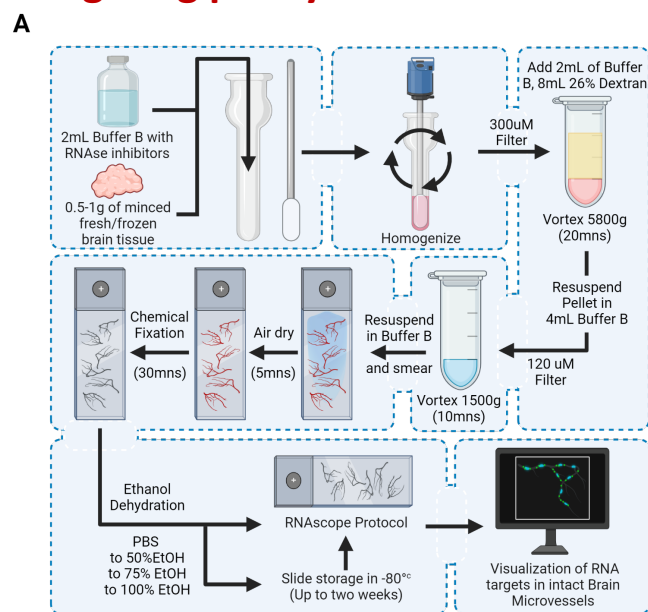


Hemichannel Functional Assay



Research priorities and gap areas:

1. Demonstrate latent pericyte infection in human brains.
2. Mechanisms of latent infection of human brain pericytes.
3. Contribution of pericyte HIV reservoir to the overall CNS reservoirs. Reactivation of pericyte reservoir in response to CNS and/BBB injury. Spreading HIV infection to other CNS cells and periphery.
4. Biological significance of pericyte HIV reservoir: impact on neuroinflammation, aging, ischemic stroke, and other cerebrovascular comorbidities.
5. Targeting pericyte reservoirs via the blood-brain barrier for HIV cure.



Naranjo et al., Microvessel isolation protocol for RNA visualization and profiling. *Sci Rep* 14, 25558, 2024

Osborne et al., Protocol for the isolation of brain microvessels and visualization of RNA fluorescence in mice and humans. *STAR Protoc*, 2024

- Pericytes are prone to HIV infection and may be involved in the generation of HIV reservoirs in the CNS.
- BBB pericytes express distinct molecular signatures during latent and actively infected stages of the HIV-1 life cycle.
- Estrogen receptor related network proteins appear altered between latent and actively infected cells.



**This work was supported by the National Institutes of Health
MH128022 and MH072567-15**

MIAMI HEAT DANCERS

