

10th
EDITION

HIV PERSISTENCE DURING THERAPY™

Reservoirs & Eradication
Strategies Workshop



DECEMBER 13-16, 2022
www.hiv-persistence.com

FLORIDA
MIAMI USA

Histone deacetylation regulates HIV-1 transcription and can be modulated to control HIV-1 latency

Theresa Simermeyer, PhD

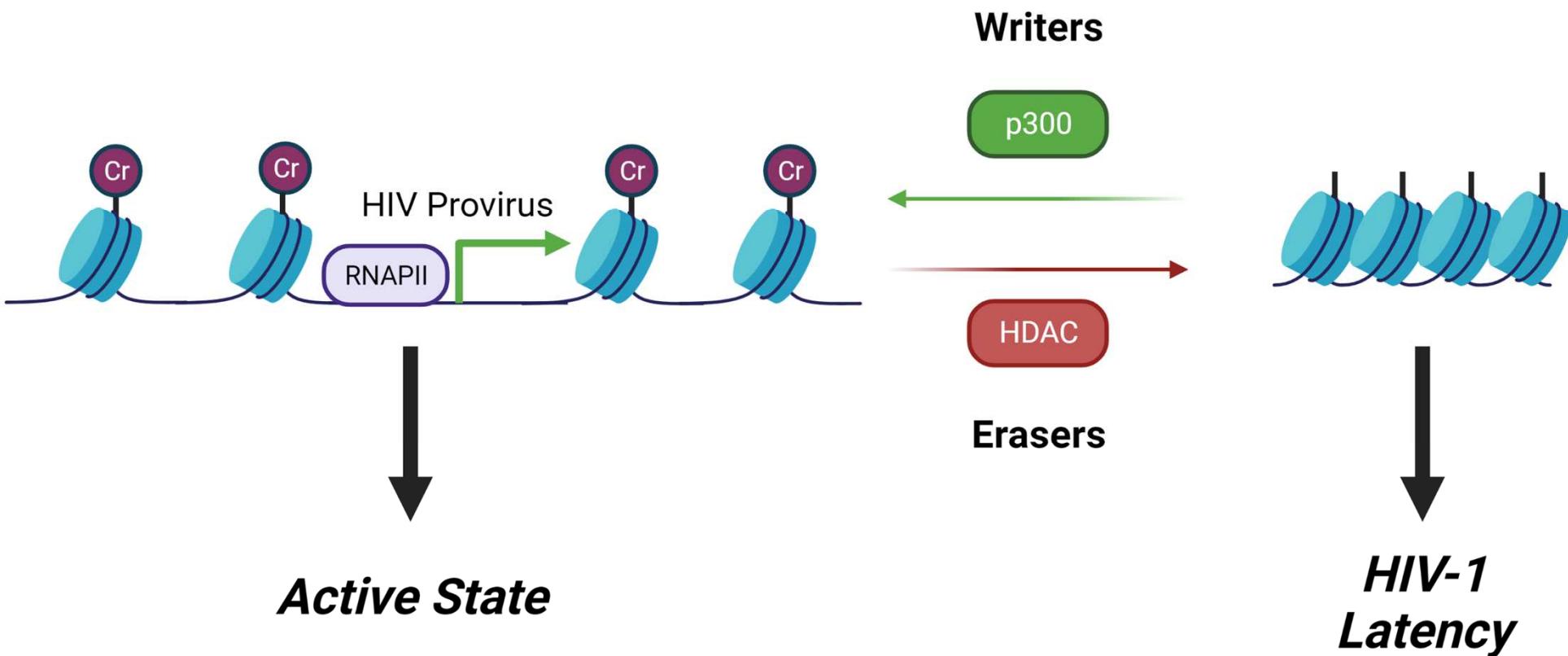
Jiang Lab

UNC HIV Cure Center

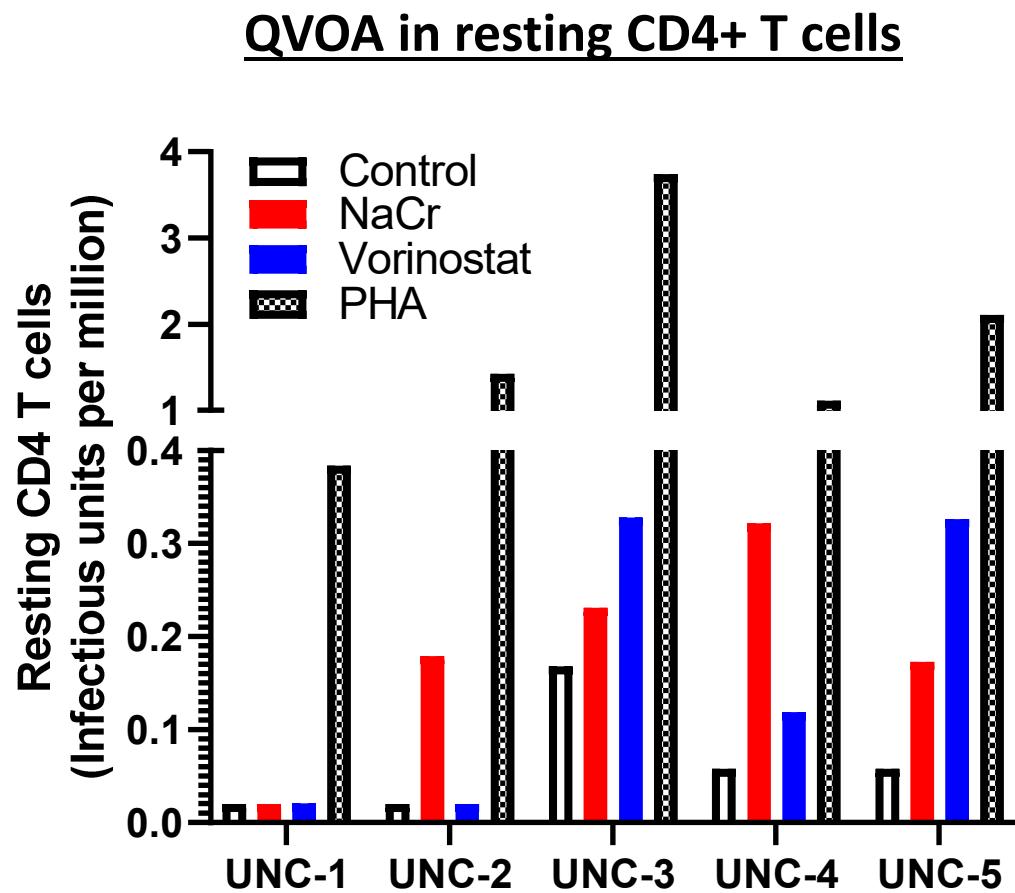


www.hiv-persistence.com

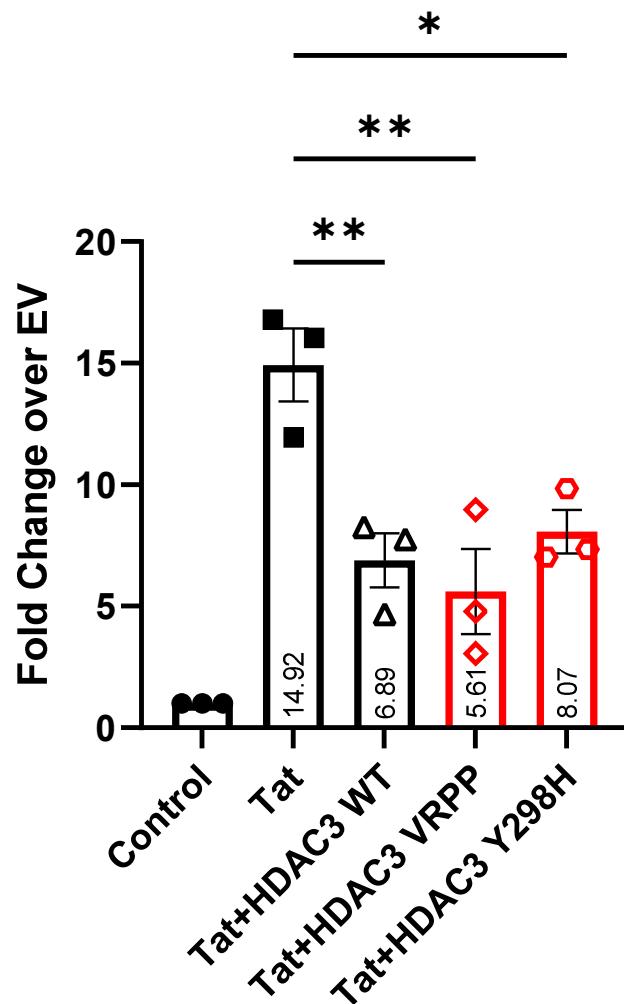
Epigenetic regulation of HIV transcription and latency



Induction of histone crotonylation increases HIV expression from latent infection in CD4+ T cells isolated from PWL on ART



Decrotonylation also regulates Tat transactivation



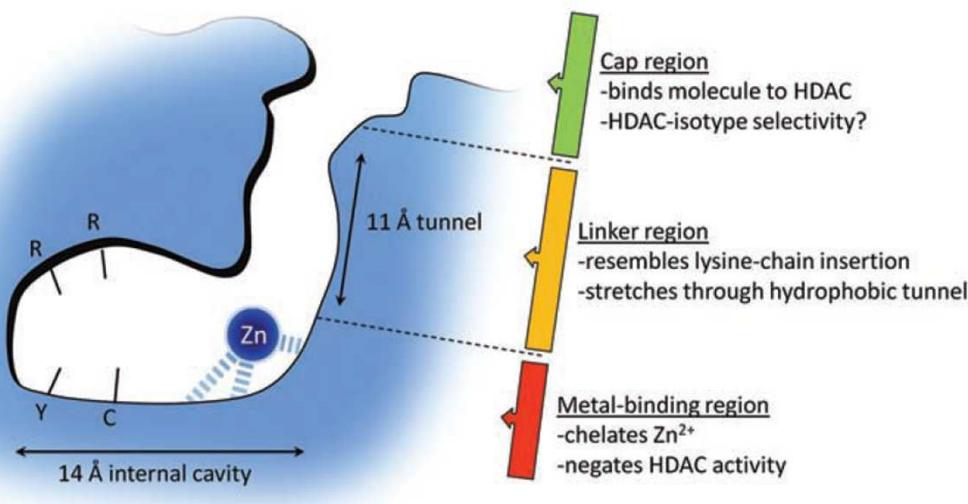
HDAC3 VRPP and HDAC3 Y298H
are decrotonylase only variants

Wei W et al., 2017

Song et al., 2021

Liu X et al., Cell Discovery 2017

Exploring decrotonylase inhibition by HDAC inhibitors

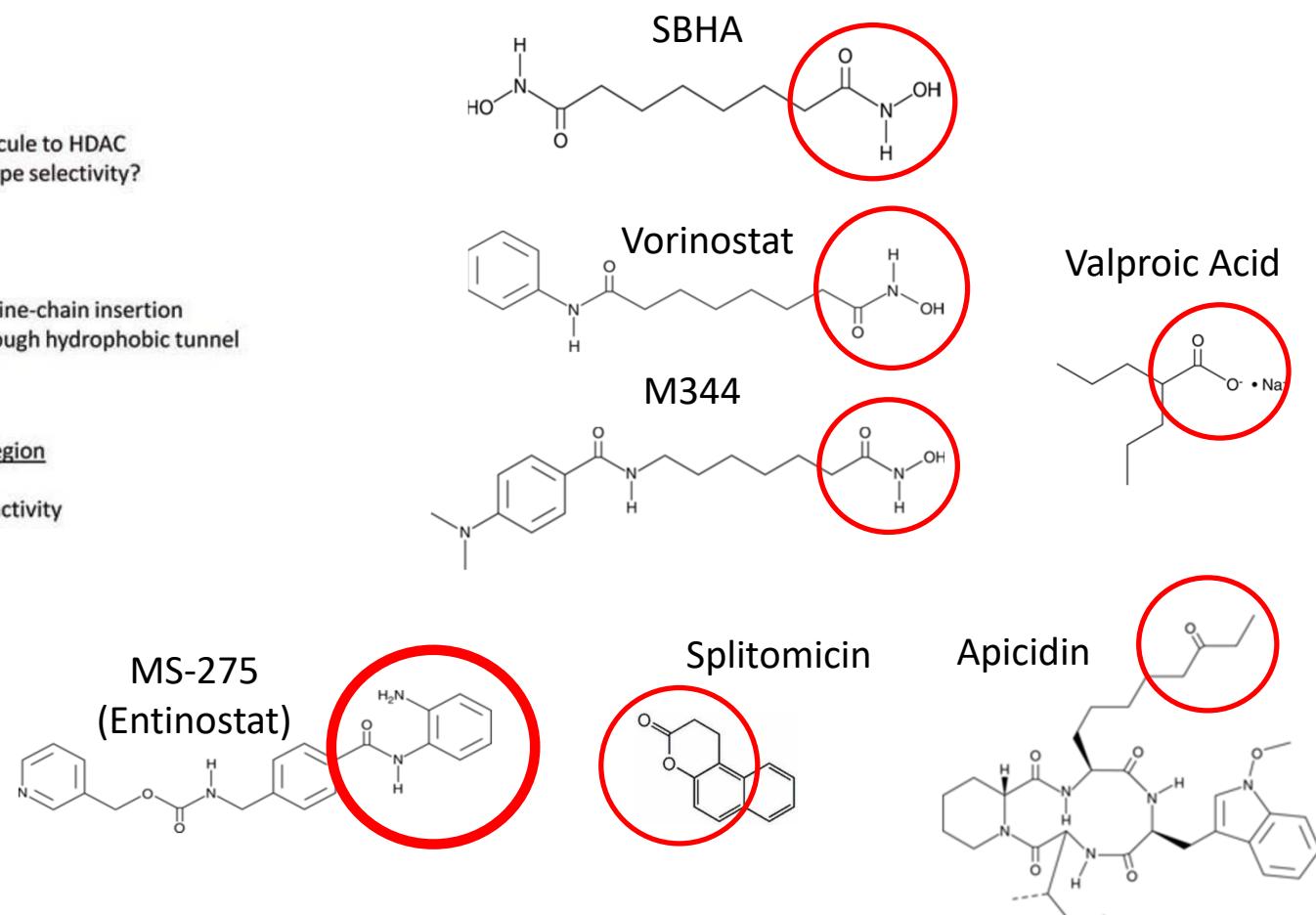


HDAC inhibitor therapy in autoimmunity and transplantation

Wayne W Hancock,¹ Tatiana Akimova,¹ Ulf H Beier,² Yujie Liu,¹ Liging Wang¹

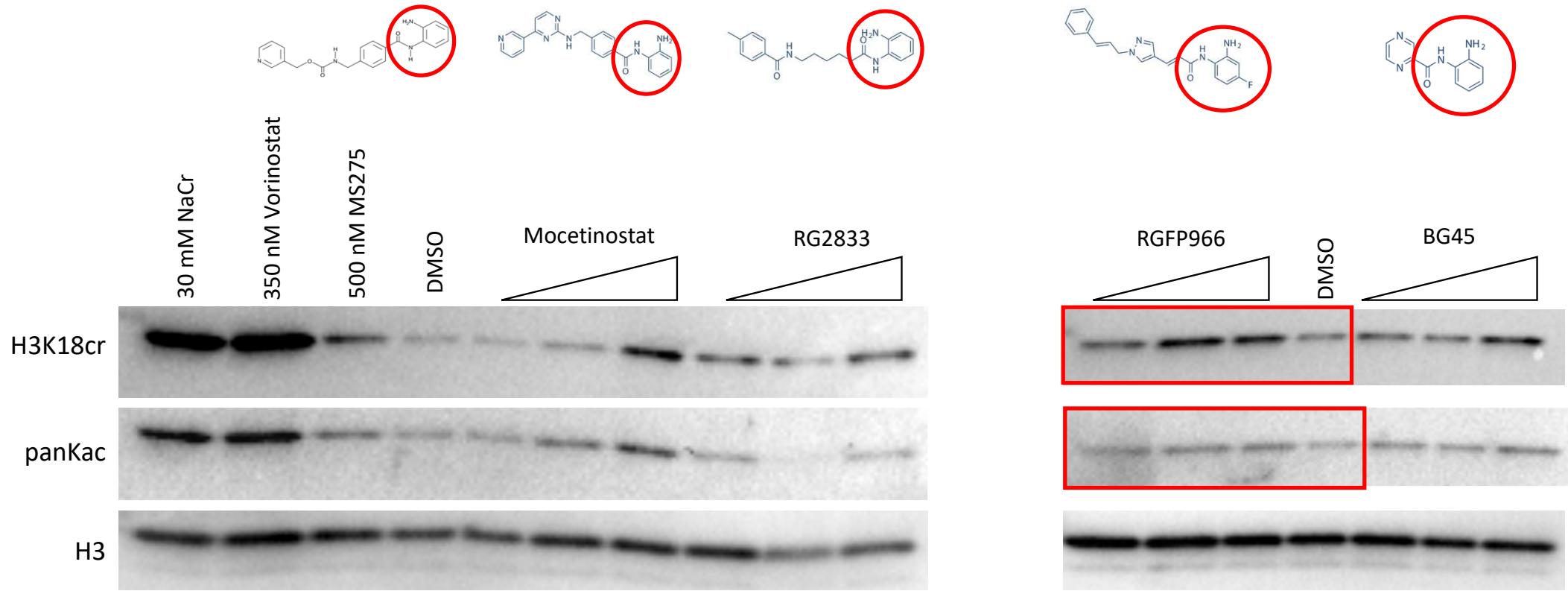
Strategies To Design Selective Histone Deacetylase Inhibitors

Jelena Melesina,^[4] Conrad V. Simonen,^[5] Lucas Praetorius,^[6] Emre F. Bülbül,^[7] Dina Robaa,^[8] and Wolfgang Sippel^[8]



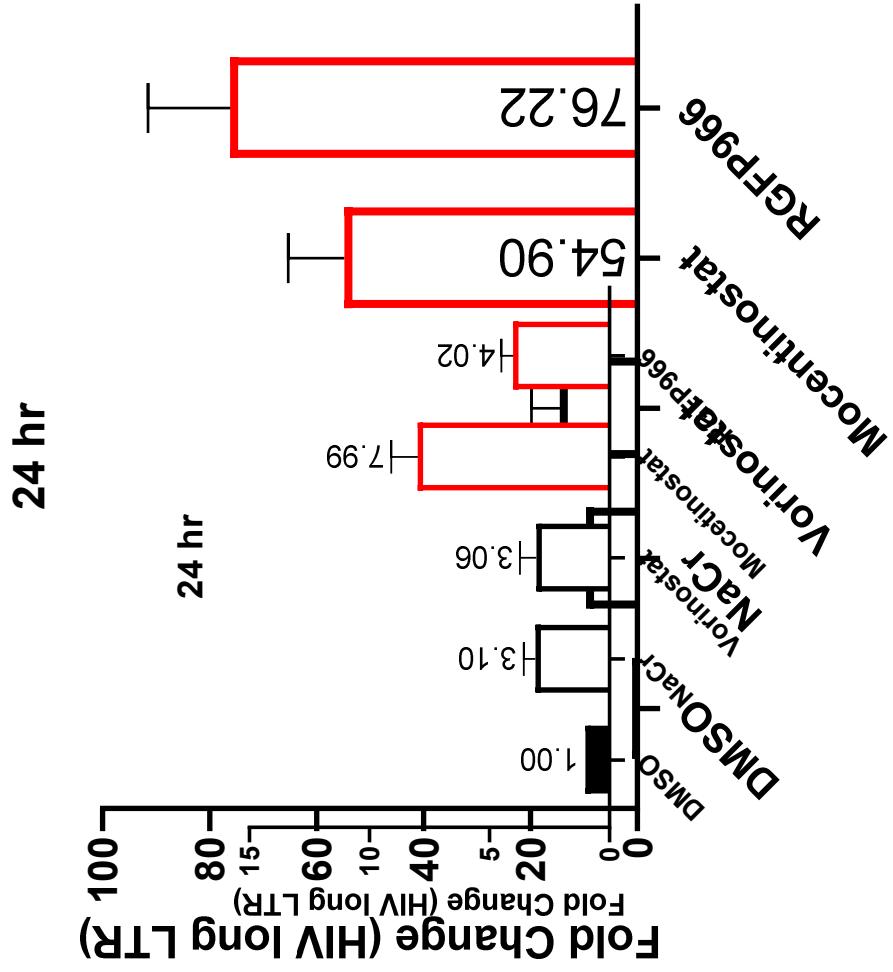
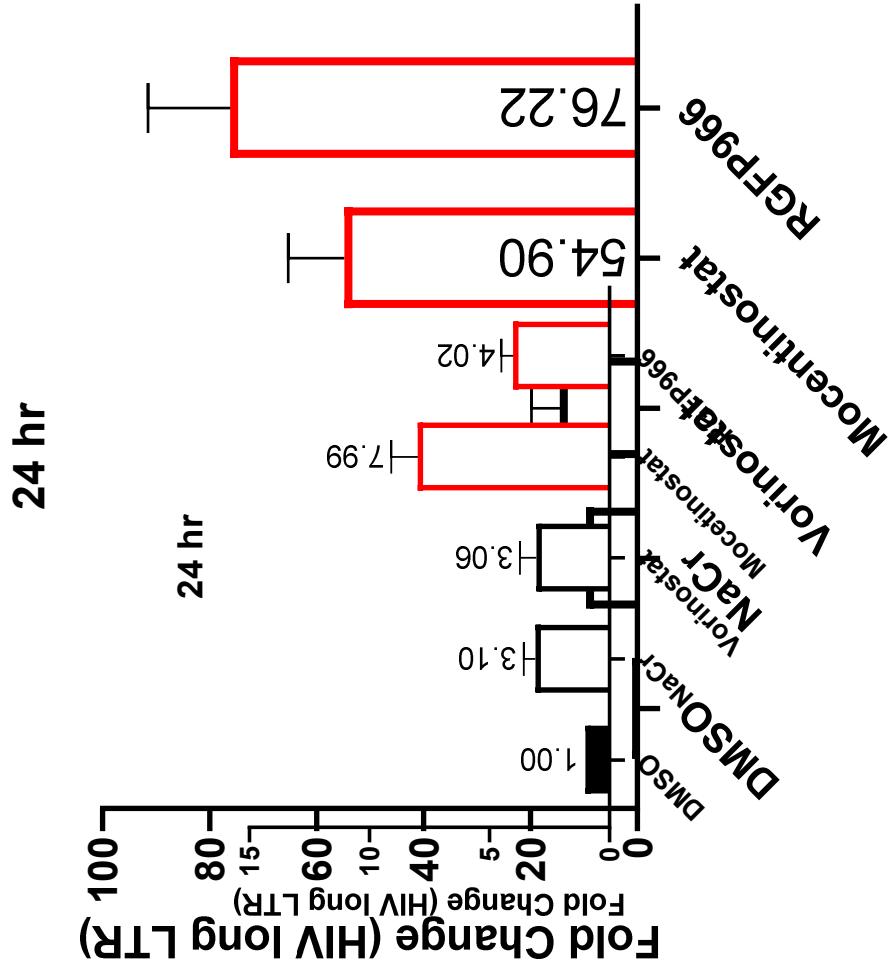
HDACi with Benzamide Zn²⁺ binding group are more selective and potent HDACi

Primary T cell Model of Latency

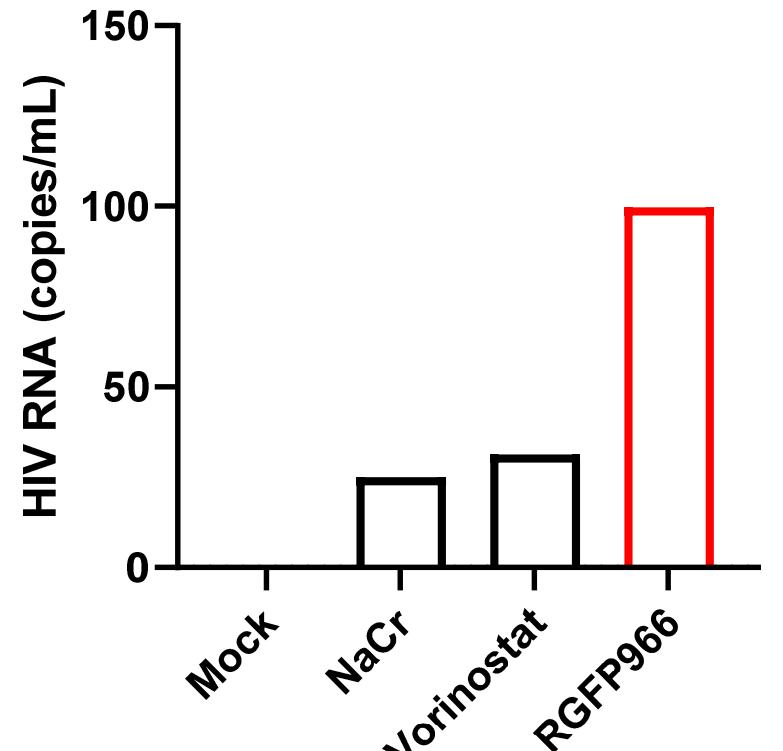
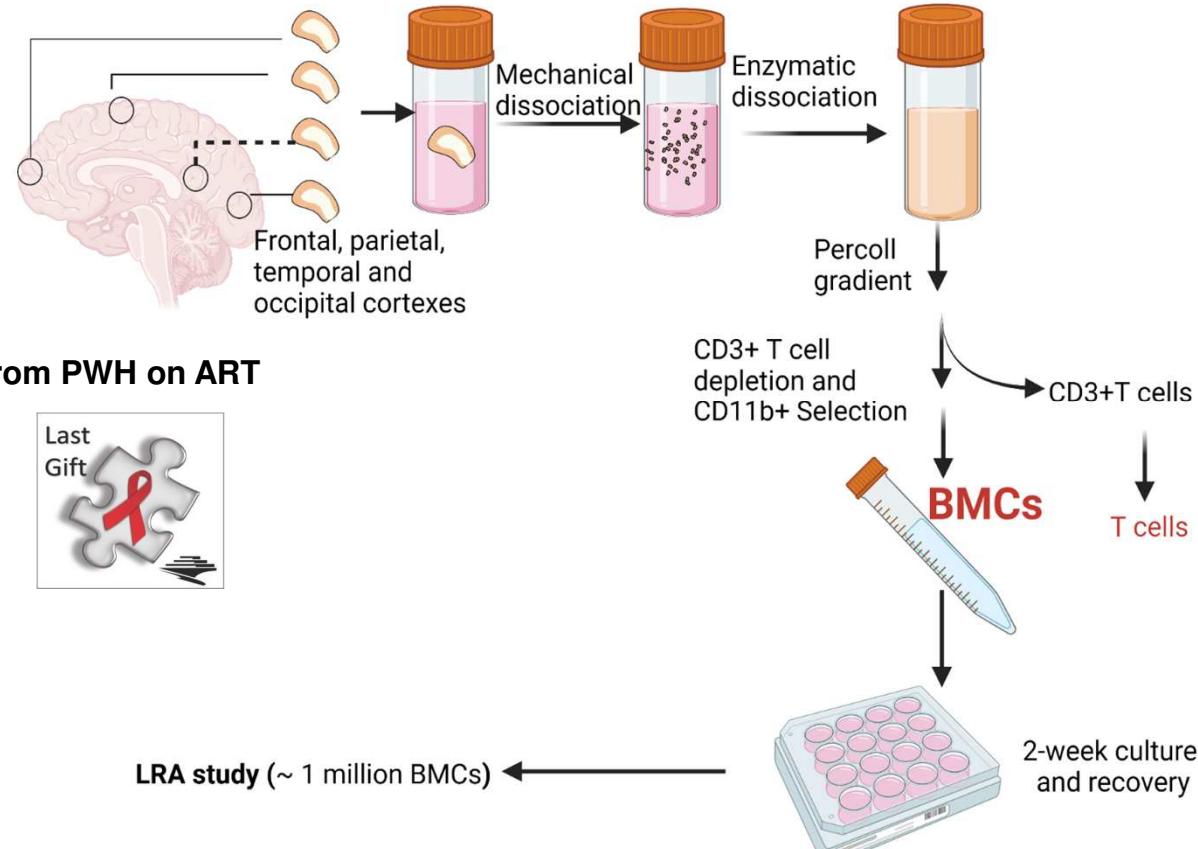


HDACi act as LRAs in both 2D10 cells and the primary T cell model of latency

2D10:
Primary T cells:



Benzamide HDCRi RGFP966 is potent to disrupt latent HIV in non-T cells



BMCs from cortex in donor LG34



COMMUNITY SUMMARY

- Key question

- Histone crotonylation is a new regulator of HIV latency. Can decrotonylation inhibitors play a special role as Latency Reversal Agents?

- Key findings

- Crotonylation has a role distinct from acetylation in regulating HIV transcription.
 - Specific Decrotonylase inhibitors may offer advantages as Latency Reversal Agents

- What are the next steps?

- Validate the latency reversal activity of histone decrotonylase inhibitors in CD4 + T cells isolated from people with HIV (PWH)
 - If validated, develop better and more selective Decrotonylation inhibitors and explore activity in CD4+ T cells and Microglia

Acknowledgements

Jiang Lab

Theresa L. Simermeyer

Lilly Wong
Daijiang Li
Yuyang Tang

Eduarda Blaschke
Ed de la Perra Polina
Daniel Zhong
Jiayi Du
Smaran Sivashankar

HIV Cure Center

David Margolis Lab
Ed Browne Lab

Christopher Aquino
Katherine Sholtis James

David (Beau) Miller-Martini



Poster Presentation 1.4