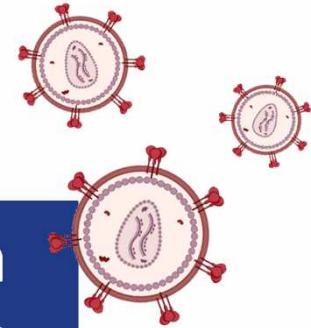




Potent latency reversal enables in-depth
transcriptomic analyses of the translation-
competent HIV-1 reservoir



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CONFLICTS OF INTEREST

This work was done in collaboration with Janssen

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Studies assessing the transcriptome of the inducible HIV-1 reservoir

[Nat Med](#). Author manuscript; available in PMC 2018 Oct 23.

PMCID: PMC5972543

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NIHMSID: NIHMS951436

[Nat Med](#). 2018 May; 24(5): 604–609.

PMID: 29686423

Published online 2018 Apr 23. doi: [10.1038/s41591-018-0017-7](#)

Clonal CD4+ T cells in the HIV-1 latent reservoir display a distinct gene profile upon reactivation

Lillian B. Cohn,¹ Israel T. da Silva,² Renan Valieris,² Amy S. Huang,¹ Julio C. C. Lorenzi,¹ Yehuda Z. Cohen,¹

Joy A. Pai,¹ Allison L. Butler,¹ Marina Caskey,¹ Mila Jankovic,^{1,†} and Michel C. Nussenzweig^{1,3,†*}

[Sci Transl Med](#). Author manuscript; available in PMC 2020 Nov 13.

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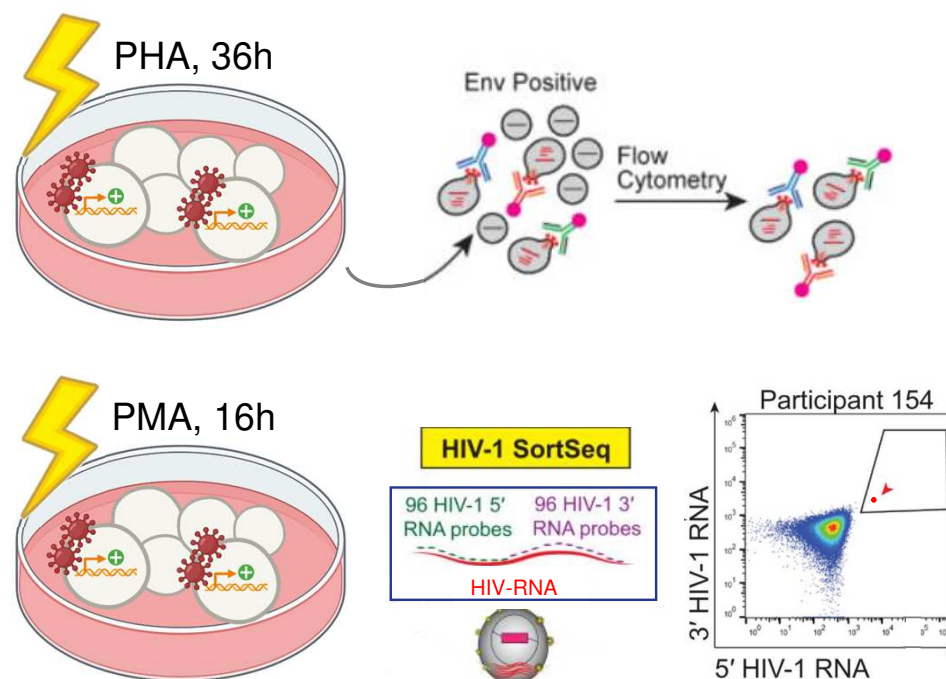
[Sci Transl Med](#). 2020 May 13; 12(543): eaaz0802.

PMID: 32404504

doi: [10.1126/scitranslmed.aaz0802](#)

Single-cell transcriptional landscapes reveal HIV-1–driven aberrant host gene transcription as a potential therapeutic target

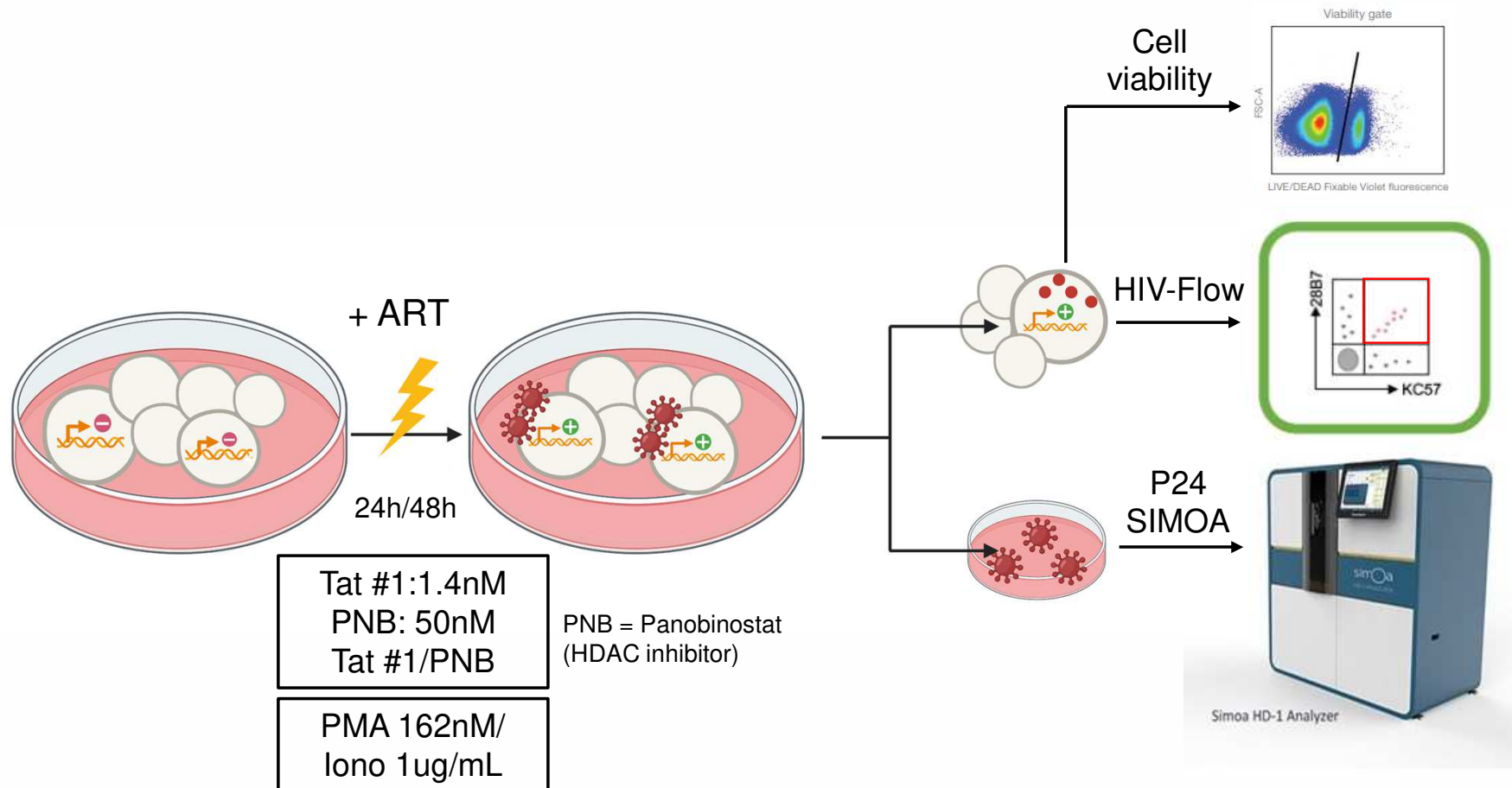
Runxia Liu,^{1,*} Yang-Hui Jimmy Yeh,^{1,*} Ales Varabyou,^{2,*} Jack A. Collora,¹ Scott Sherrill-Mix,³ C. Conover Talbot, Jr.,⁴ Sameet Mehta,⁵ Kristen Albrecht,¹ Haiping Hao,⁴ Hao Zhang,⁶ Ross A. Pollack,⁷ Subul A. Beg,⁷ Rachela M. Calvi,⁸ Jianfei Hu,⁹ Christine M. Durand,⁷ Richard F. Ambinder,⁷ Rebecca Hoh,¹⁰ Steven G. Deeks,¹⁰ Jennifer Chiarella,⁸ Serena Spudich,⁸ Daniel C. Douek,⁹ Frederic D. Bushman,³ Mihaela Pertea,^{2,11} and Ya-Chi Ho^{1,†}



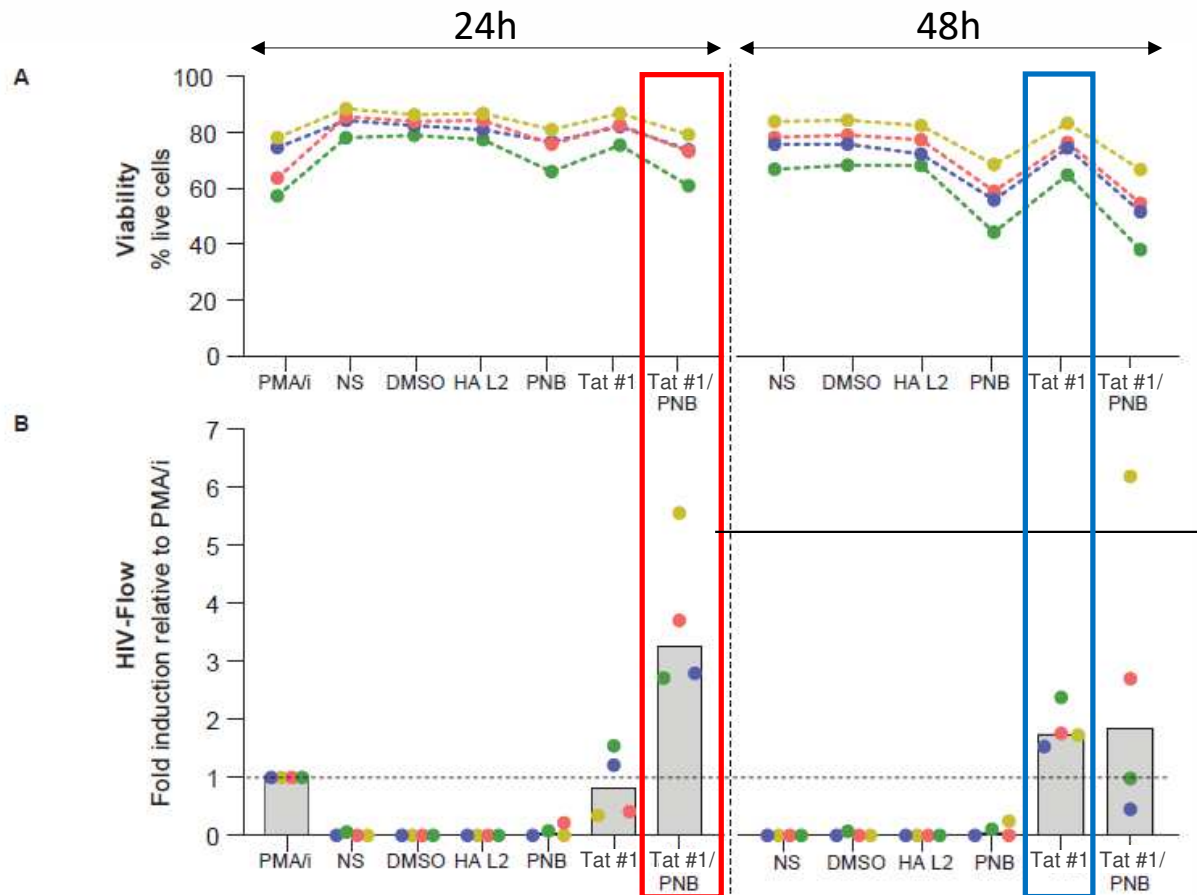
Mitogens induce global T cell activation → modifications in the transcriptome

Identifying compounds that reactivate HIV efficiently **without modifying the transcriptome/phenotype of the cells** is of interest to study the profile of the inducible HIV-1 reservoir in its near-native state

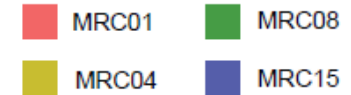
Assessing the reactivation capacity of Tat #1



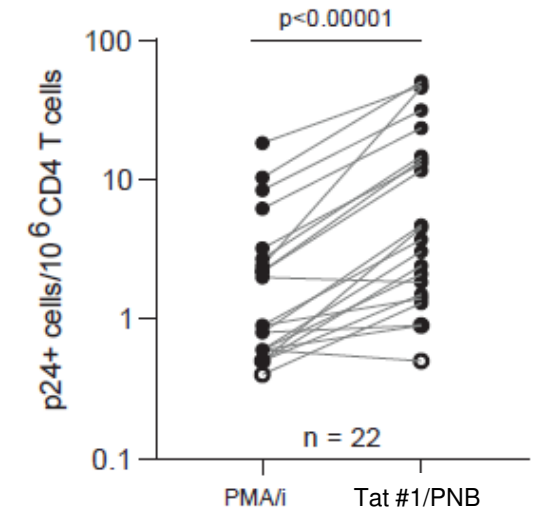
HIV-Flow: Frequency of p24+ cells following latency reversal



Participants:

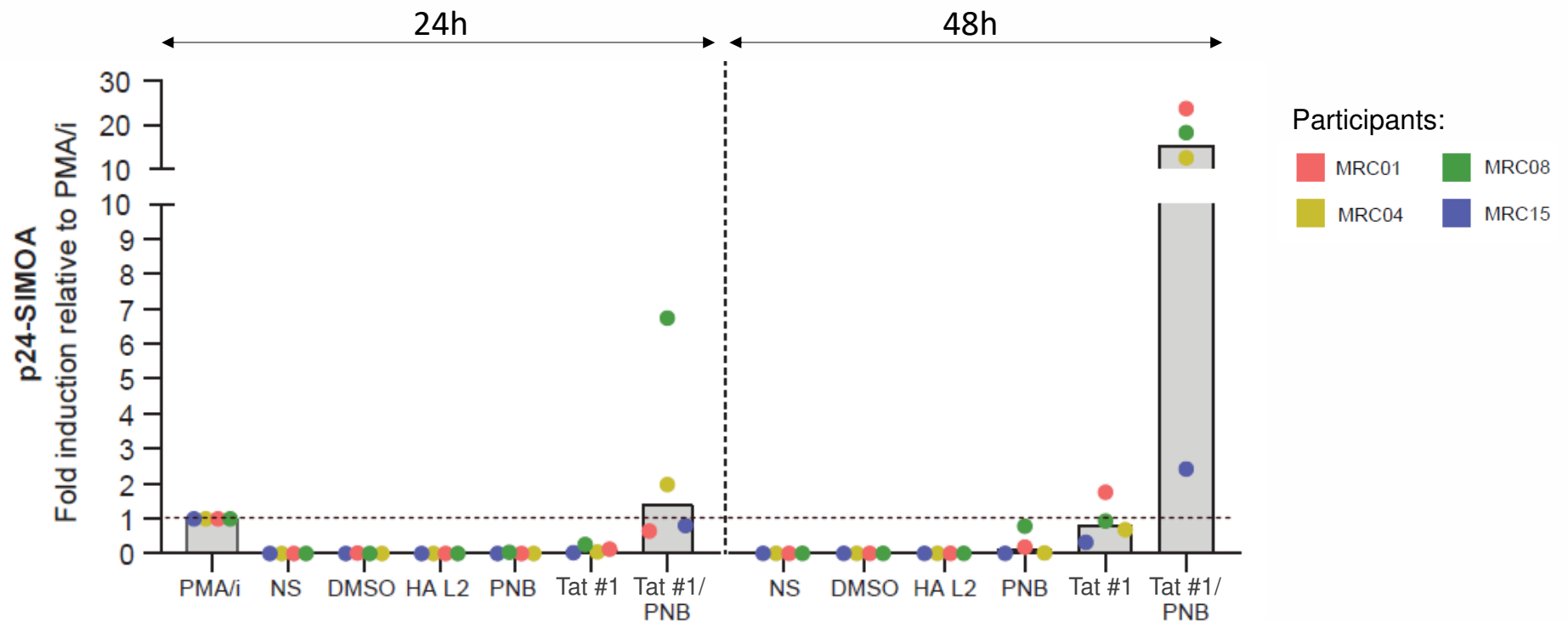


PNB = Panobinostat



➤ The highest fold induction relative to PMA/i is observed at 24H post-stim with the combination Tat #1/PNB

SIMOA: p24 release in the supernatant following latency reversal

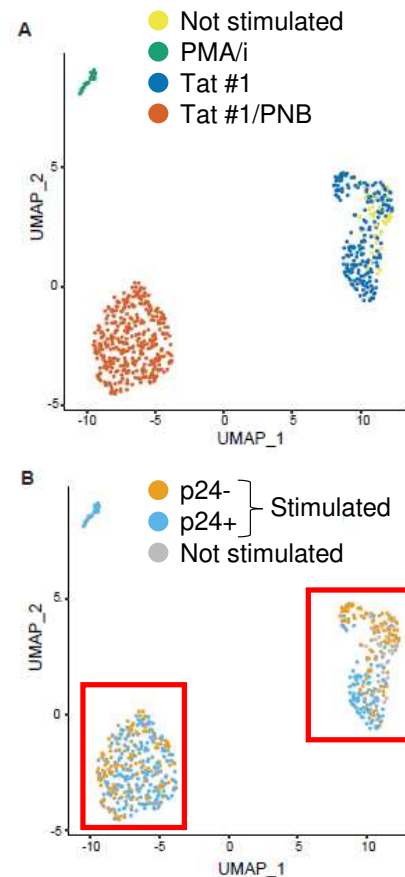


- Stimulation with Tat #1 alone or in combination with panobinostat leads to viral particles release in the culture supernatant

Smart-seq2: Transcriptomic analyses of p24+ cells following latency reversal

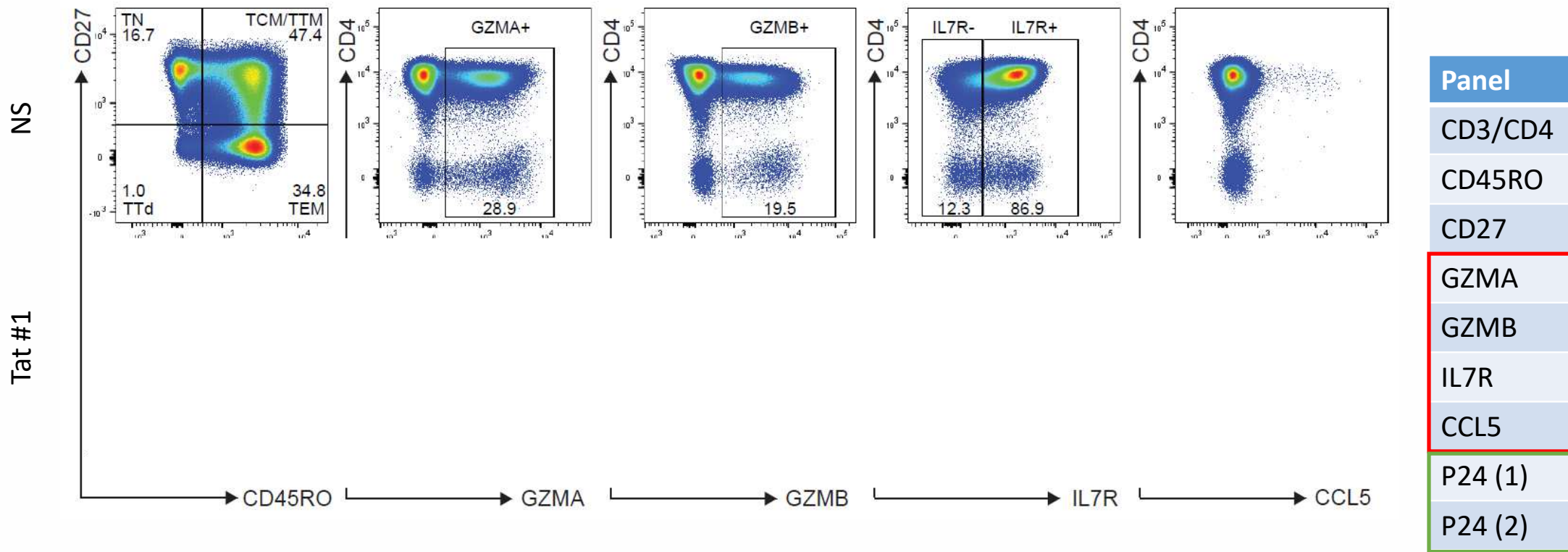
- **Tat #1**: 108 p24+ cells
- **Tat #1/PNB**: 212 p24+ cells
- **PMA/i**: 28 p24+ cells
- **+ 309 p24- cells (CD45RO+)**

N = 7 ART-treated individuals



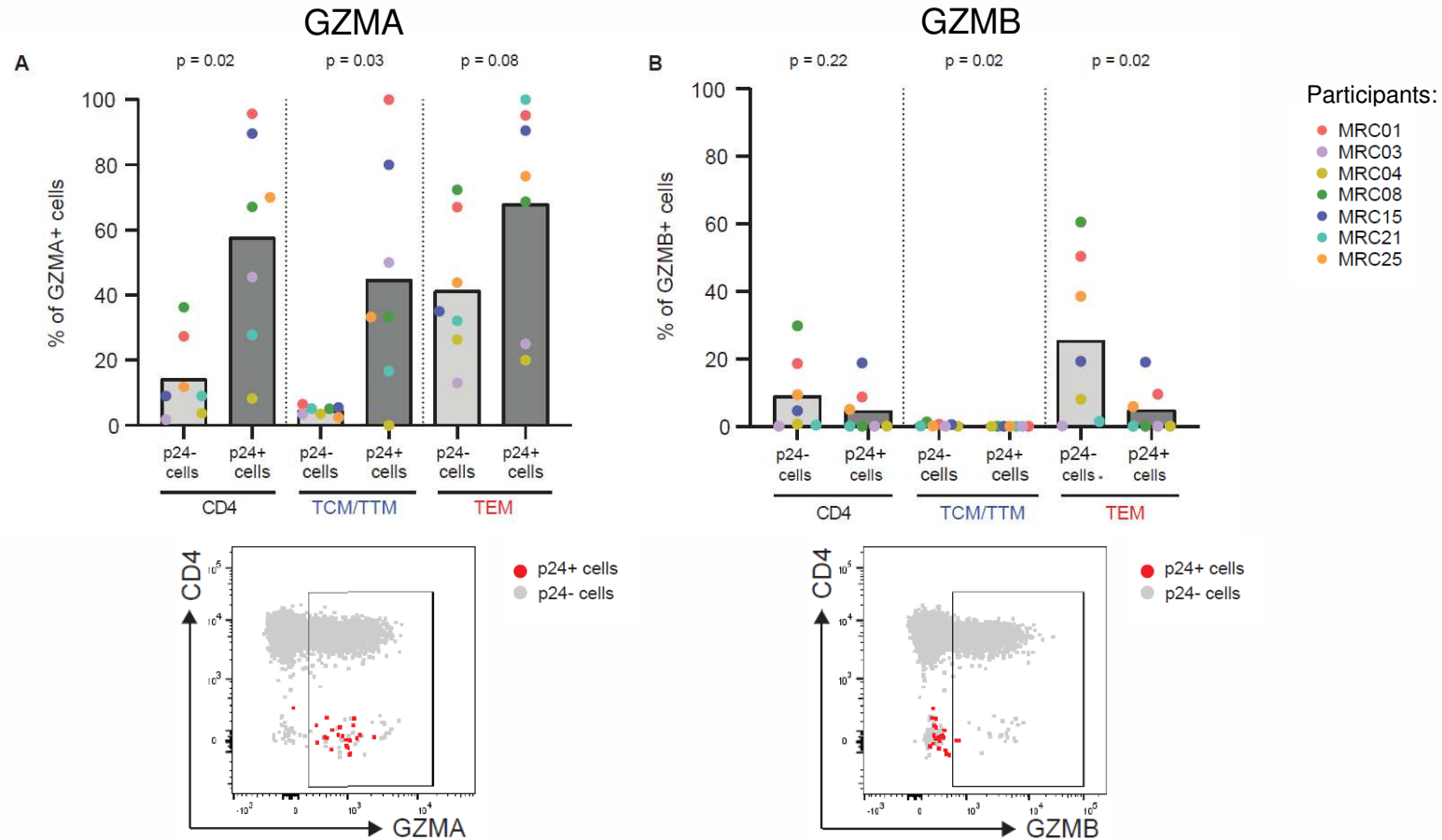
- P24+ cells display a distinct transcriptional landscape compared to p24- cells
- 6 DEG between p24+ and p24- cells: 4 upregulated, 2 downregulated in p24+ vs p24-

Confirmation of the transcriptomic hits at the protein level



➤ Stimulation with Tat #1 alone does not modify the expression of the markers of interest

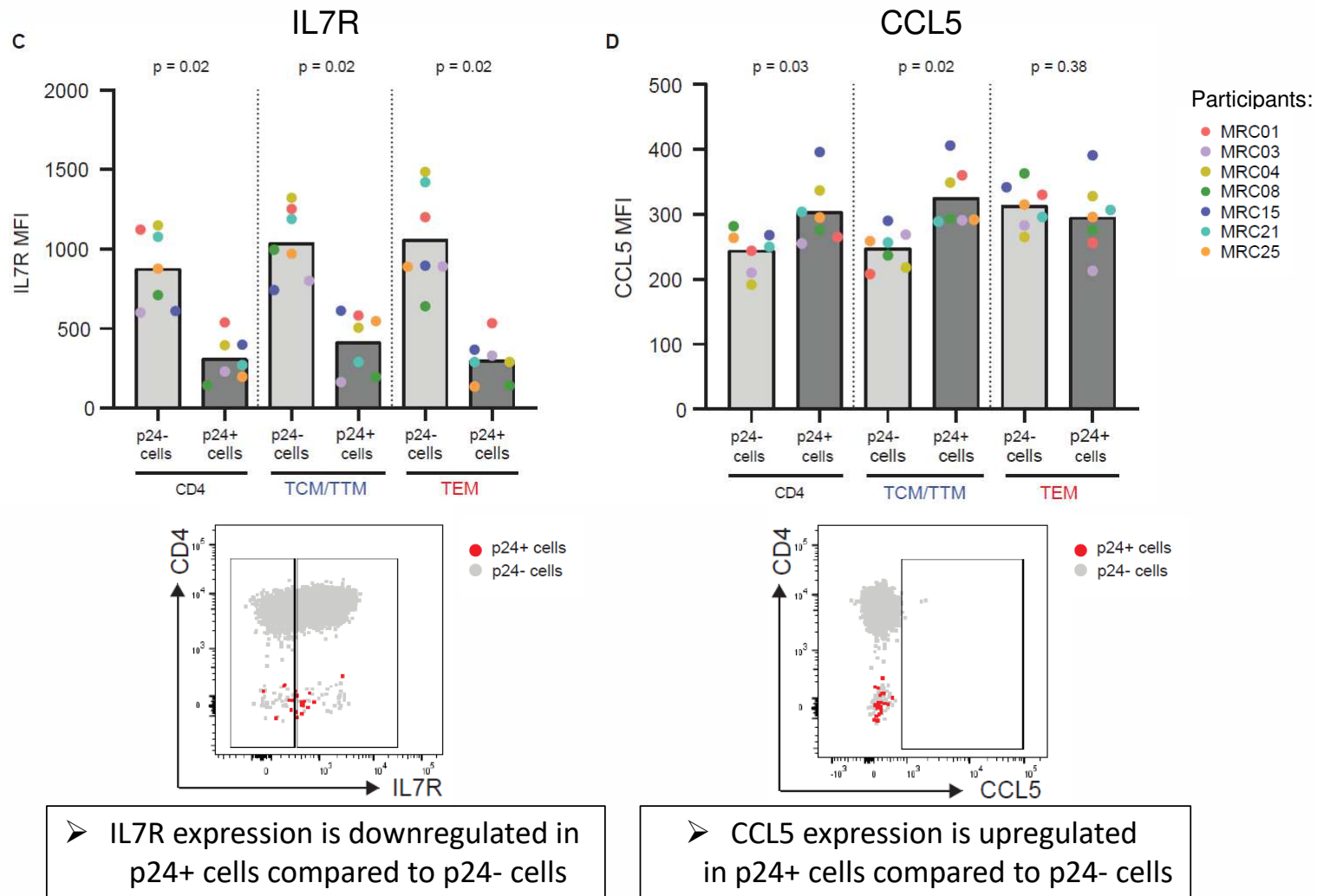
Confirmation of the transcriptomic hits at the protein level



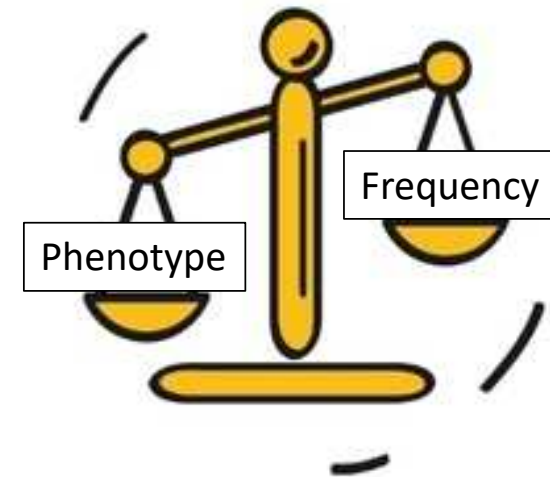
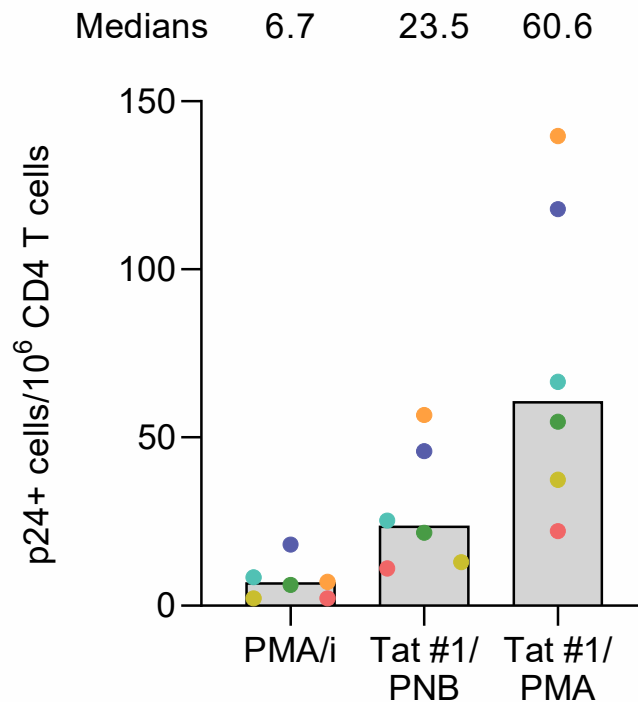
➤ The percentage of GZMA+ cells is higher in p24+ cells compared to p24- cells

➤ The percentage of GZMB+ cells is lower in p24+ cells compared to p24- cells

Confirmation of the transcriptomic hits at the protein level



Can we still increase the frequency of p24+ cells following latency reversal?



- Higher frequencies of p24+ cells are observed following Tat #1/PMA stimulation compared to PMA/i (median fold increase: 9.5) and Tat #1/PNB (median fold increase: 2.5)



COMMUNITY SUMMARY

- Tat #1 (*in vitro*):
 - Reactivates HIV from latency in primary CD4 T cells from ART-treated individuals
 - Does not impact cell viability of CD4 T cells
 - Does not modify the transcriptome of CD4 T cells
- Tat #1 in combination with other LRAs induces latency reversal in a higher proportion of latently infected cells than PMA/i
- Tat #1 can be used as a tool to study the transcriptional landscape of the translation-competent HIV reservoir
 - p24+ cells have a distinct transcriptional landscape compared to p24- cells
- Tat #1 will be used to study the inducible HIV-1 reservoir in lymphoid tissues from ART-treated individuals

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