In-depth single-cell analysis of translation-competent HIV-1 reservoirs identifies cellular sources of plasma viremia

Basiel Cole

GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

HIV Cure Research Center

fwo

9th BREACH symposium
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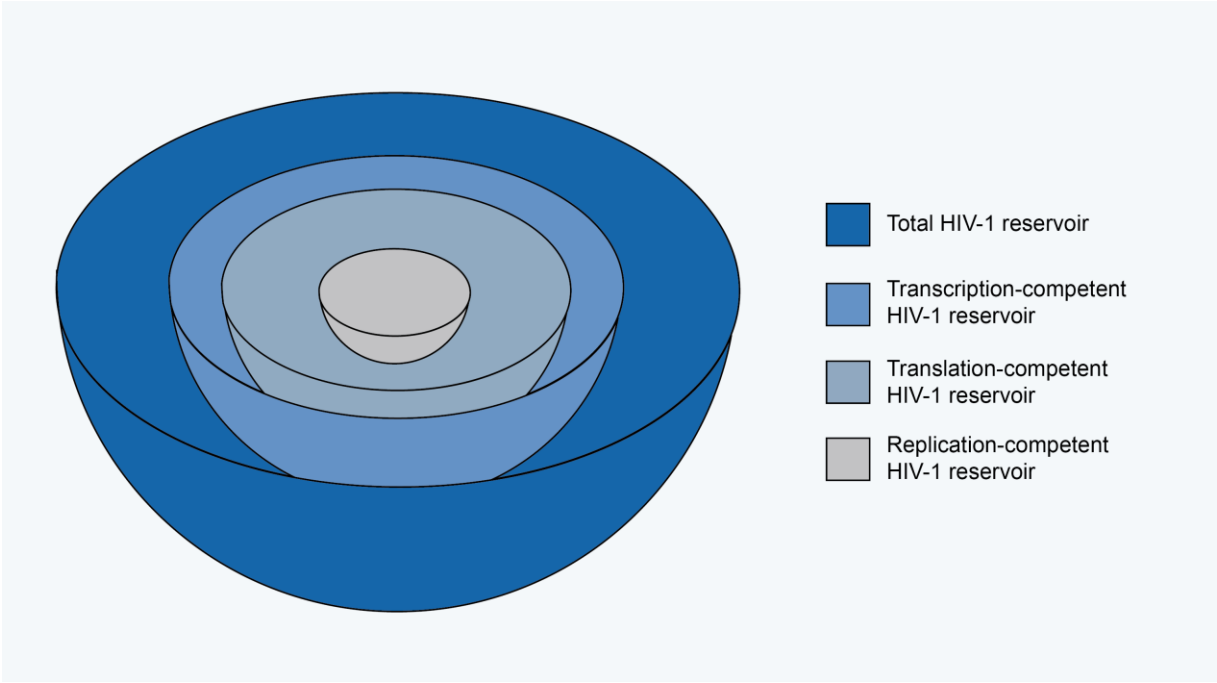
Introduction

- HIV-1 infection remains incurable
  - Persistent viral reservoir
- **Translation-competent reservoir**
  - Infected cells that harbor a provirus that is capable of producing viral proteins
- Clinically relevant component of the reservoir



How can we study this reservoir?

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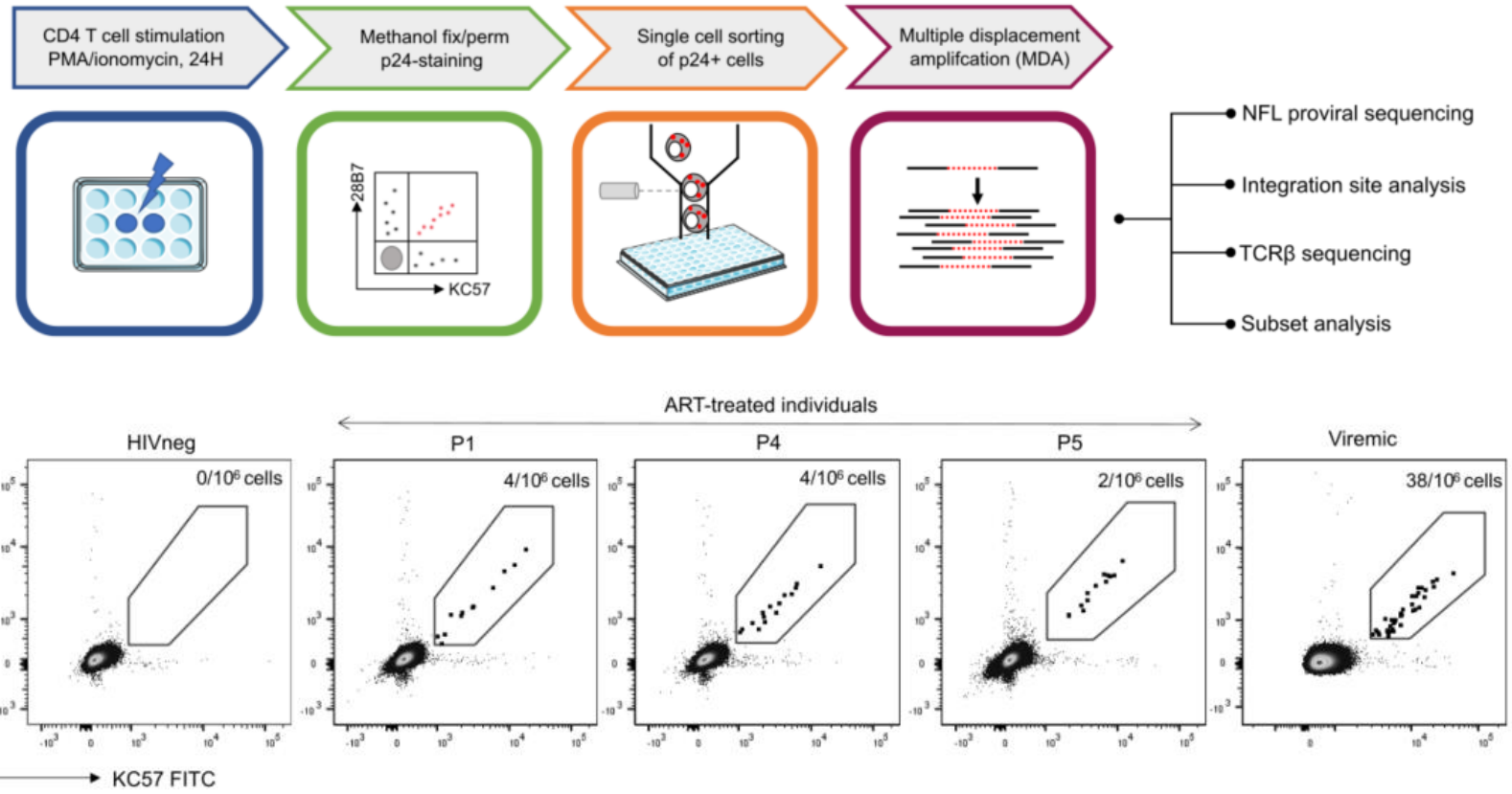
STIP-Seq assay

Simultaneous **T**CR, **I**ntegration site and **P**rovirus sequencing



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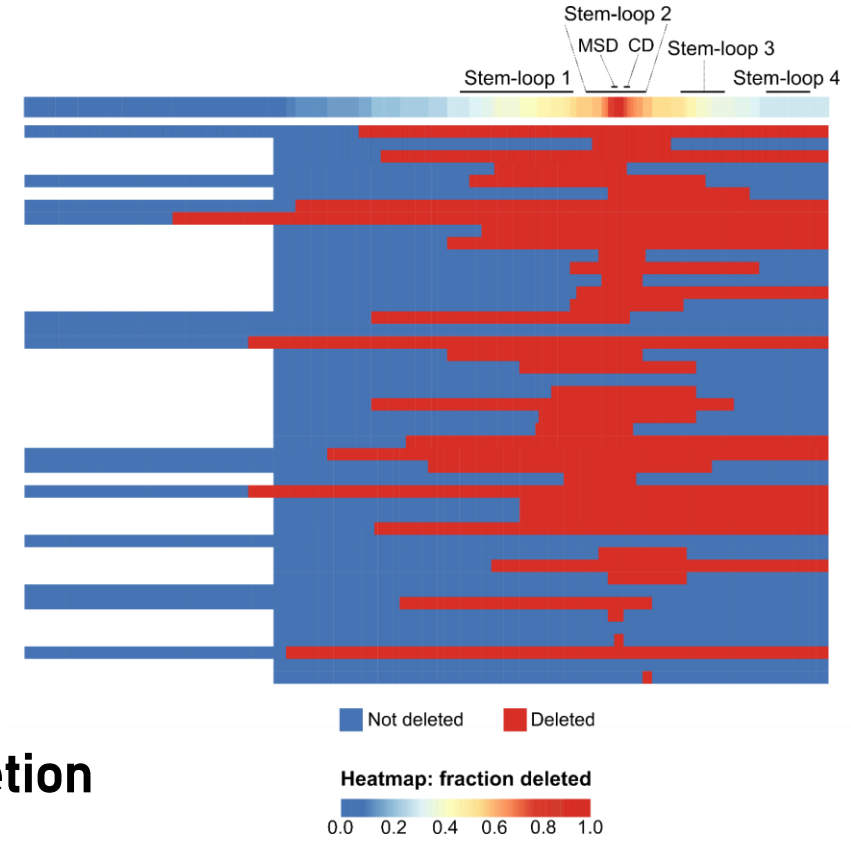
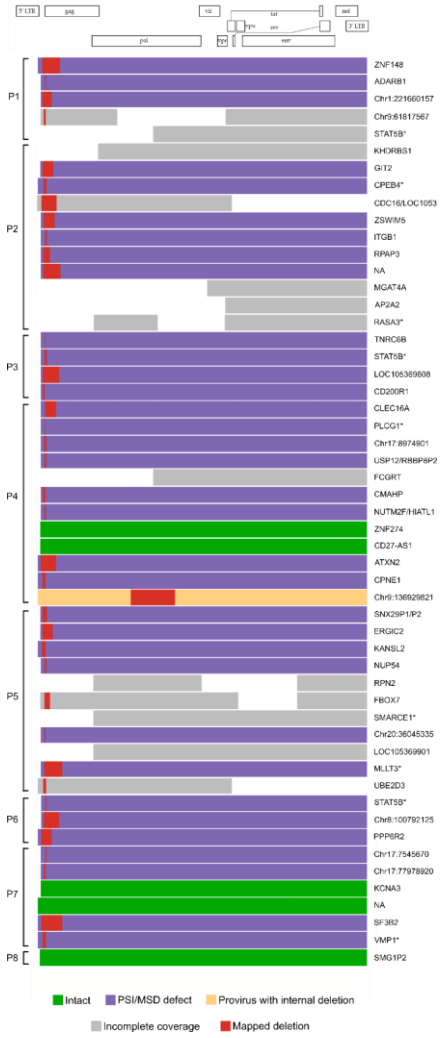
STIP-Seq on 8 cART-suppressed individuals

- 40 distinct proviral genomes
- 9 integrated in cancer-related gene
- Genome intact: 5/40 (12.5%)
- Large internal deletion: 1/40 (2.5%)
- Packaging signal (PSI) and/or major splice donor (MSD) defect: 34/40 (85%)





MSD in stem-loop 2 hotspot for deletion

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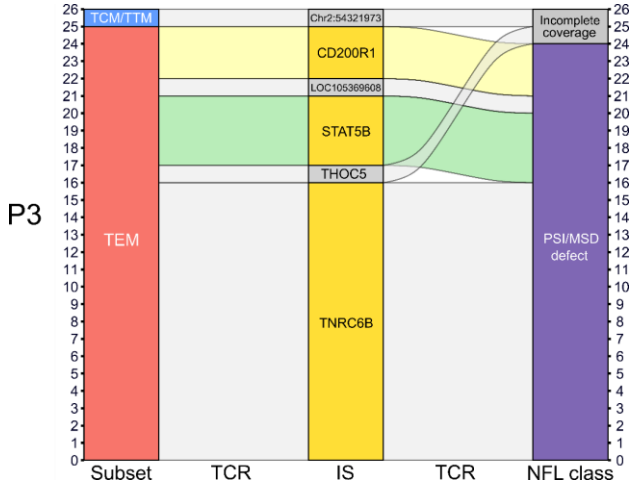
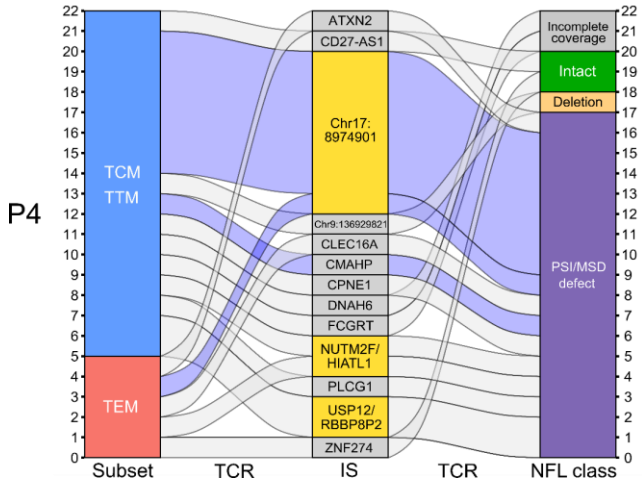
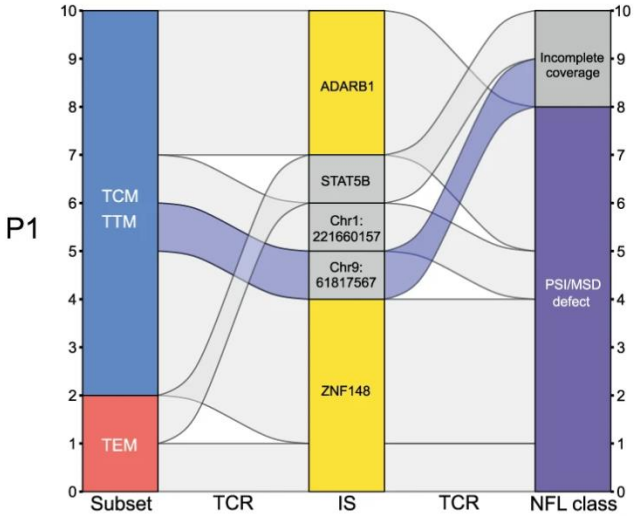
STIP-Seq on 8 cART-suppressed individuals

- TCRβ sequencing revealed infected clones with predicted pathogen-specificity (CMV, *M. tuberculosis*, Influenza)
- Integration site in gene involved in proliferation (e.g. *STAT5B*)

Potential synergy between antigen- and integration site-driven mechanisms







Predicted TCR specificity

- *M. tuberculosis*
- Influenza
- Multiple (*M. tuberculosis*, Influenza, CMV)
- Unknown

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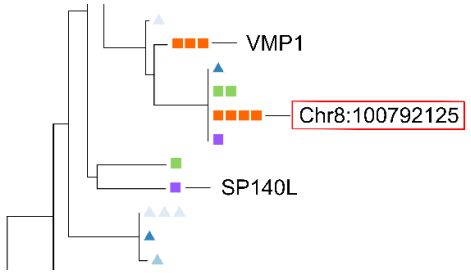
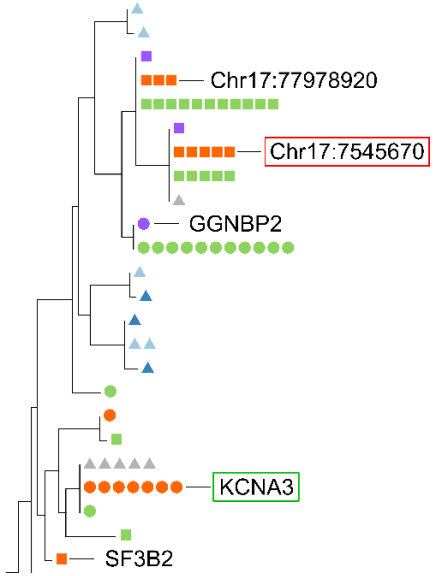
STIP-Seq in the context of an analytical treatment interruption (ATI)

P6



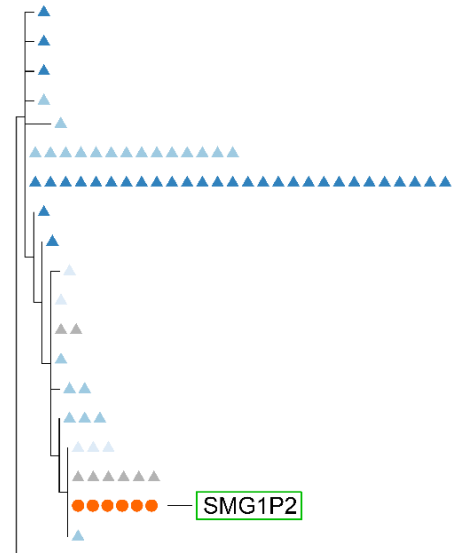
- Match between defective provirus and T4 rebound virus
- Part of p17 deleted

P7

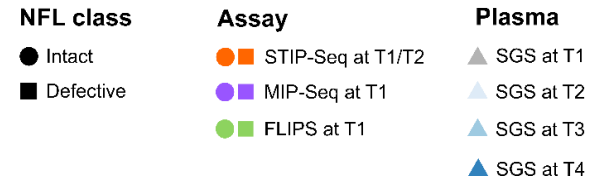


- Match between defective provirus and T1 virus: 5bp deletion in MSD.
- Match between intact provirus and T1 virus

P8



- Match between intact provirus and T1-T2-T3 virus



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Conclusions

- STIP-Seq captures 4 layers of information of translation-competent proviruses
- Translation-competent proviruses are not as intact as we thought: PSI defects
- STIP-Seq seems to enrich for clinically relevant proviruses

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