18ª edición

POSTCROI 2021

Una actualización de la 28ª Conference on Retroviruses and Opportunistic Infections

Investigación básica:

Curación del VIH y anticuerpos neutralizantes

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FUNDACIÓN LUCHA CONTRA EL SIDA Y LAS ENFERMEDADES INFECCIOSAS

FLS SCIENCE

PROGRAM COMMITTEE WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES

ADVANCES IN MOLECULAR VIROLOGY OF HIV AND SARS-CoV-2

Frank Kirchhoff, *Ulm University Medical Center, Ulm, Germany*

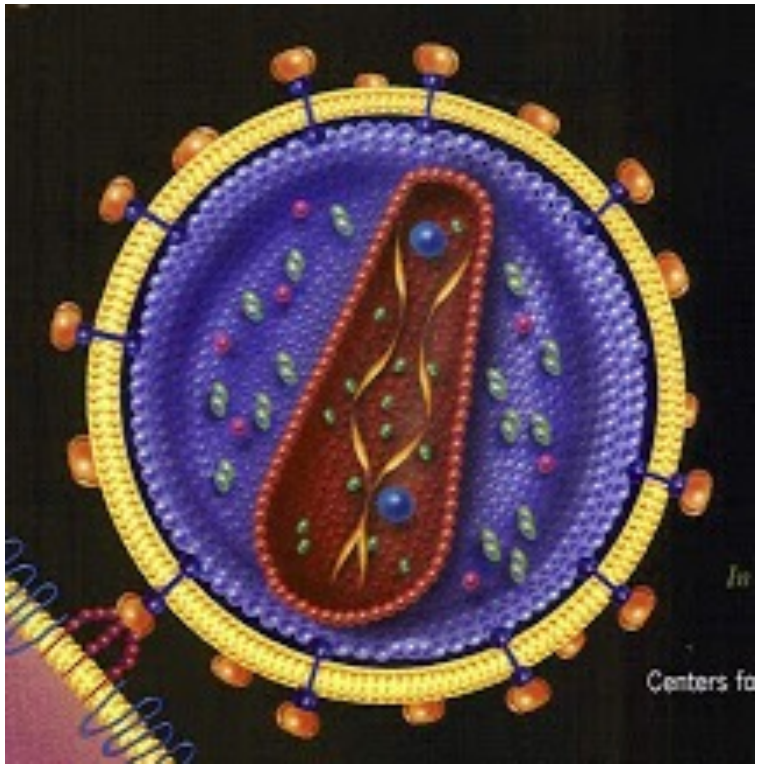
ADVANCES IN HIV AND SARS-CoV-2 IMMUNOLOGY

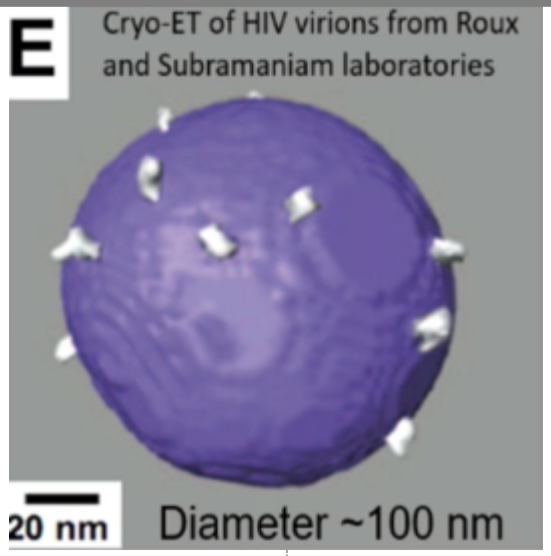
Galit Alter, *Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA*

ADVANCES IN HIV CURE

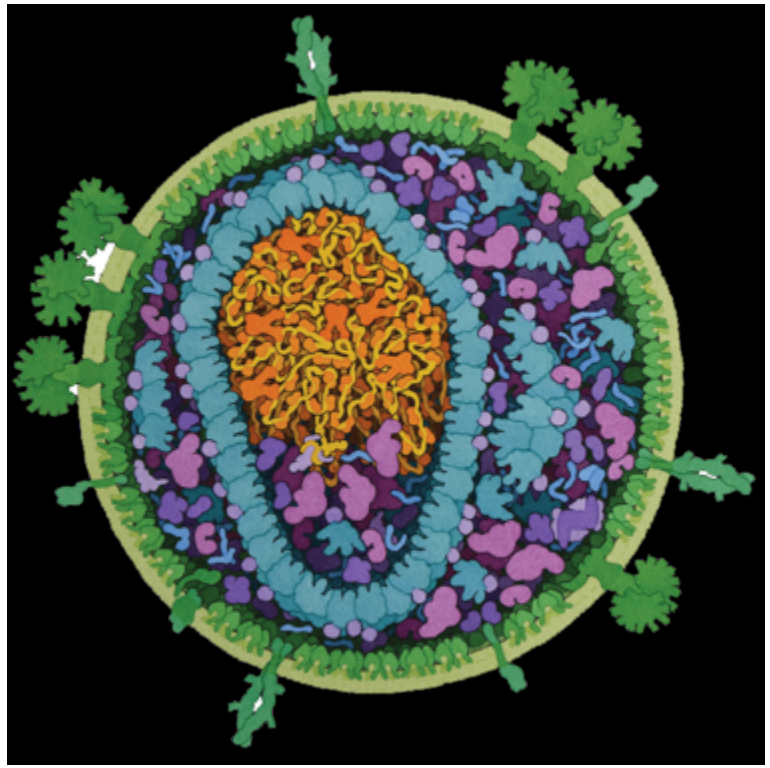
Katherine J. Bar, *University of Pennsylvania, Philadelphia, PA, USA*

Changes in the CROI logo over the years

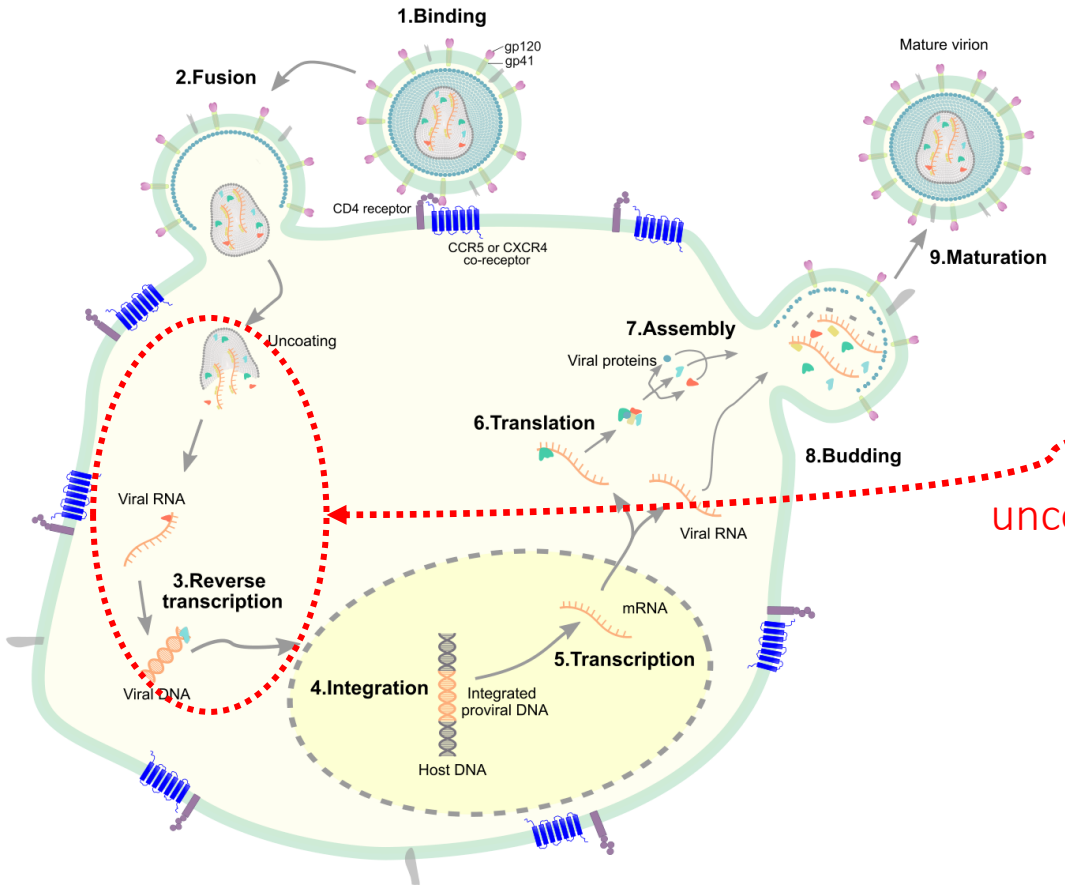




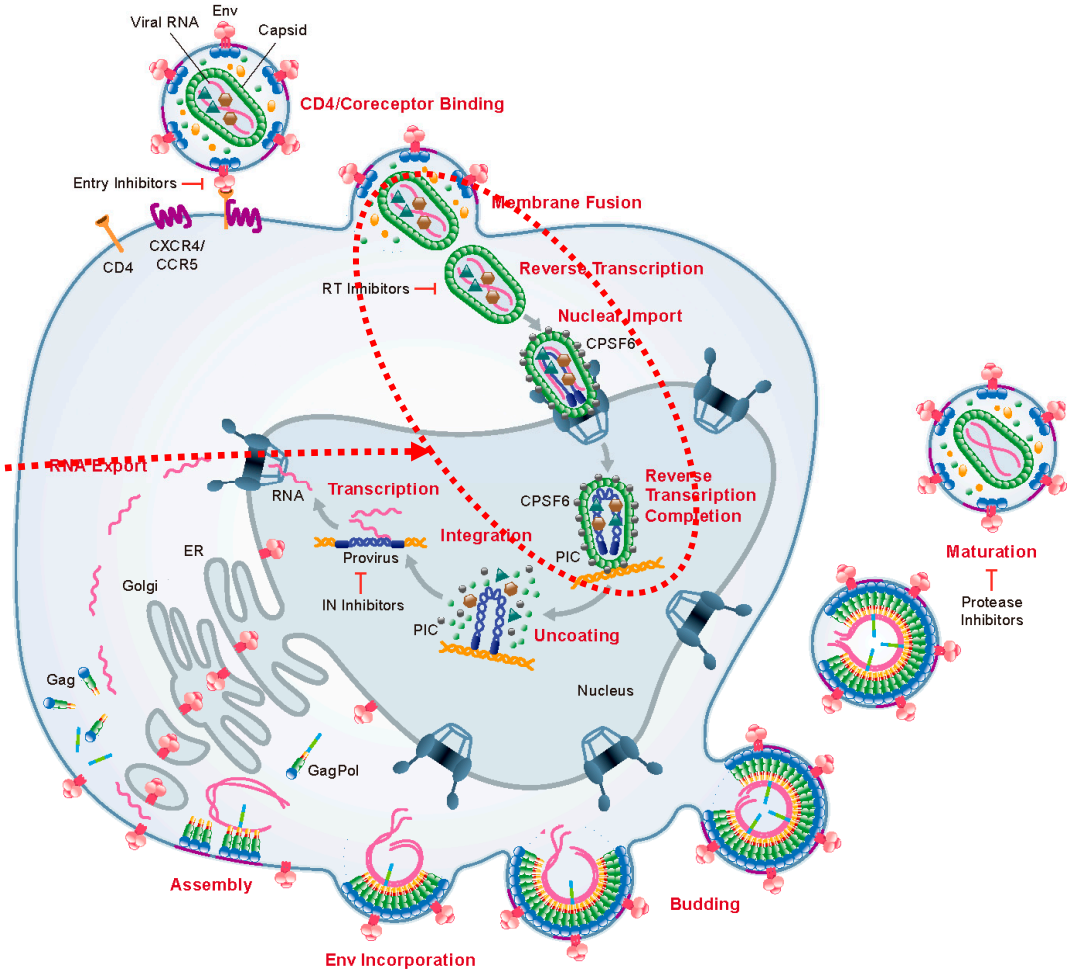
Zhu et al. 2006 Nature



HIV Replication Cycle



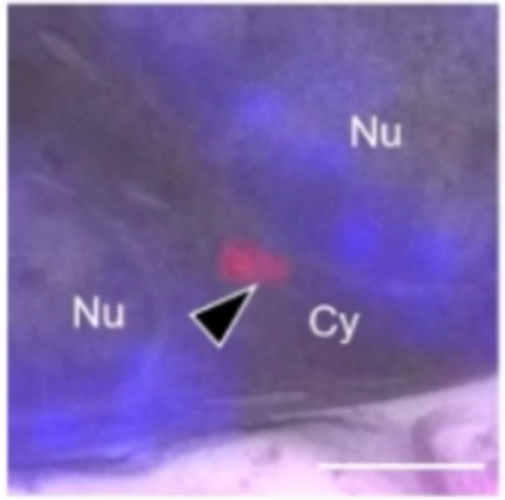
uncoating

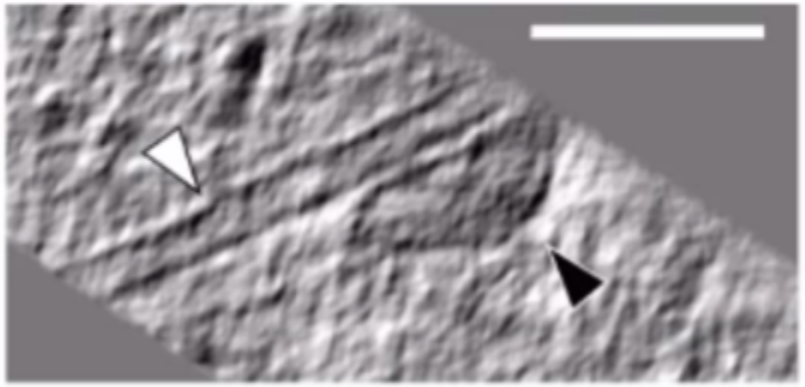


Kleinpeter & Freed. 2020. Viruses

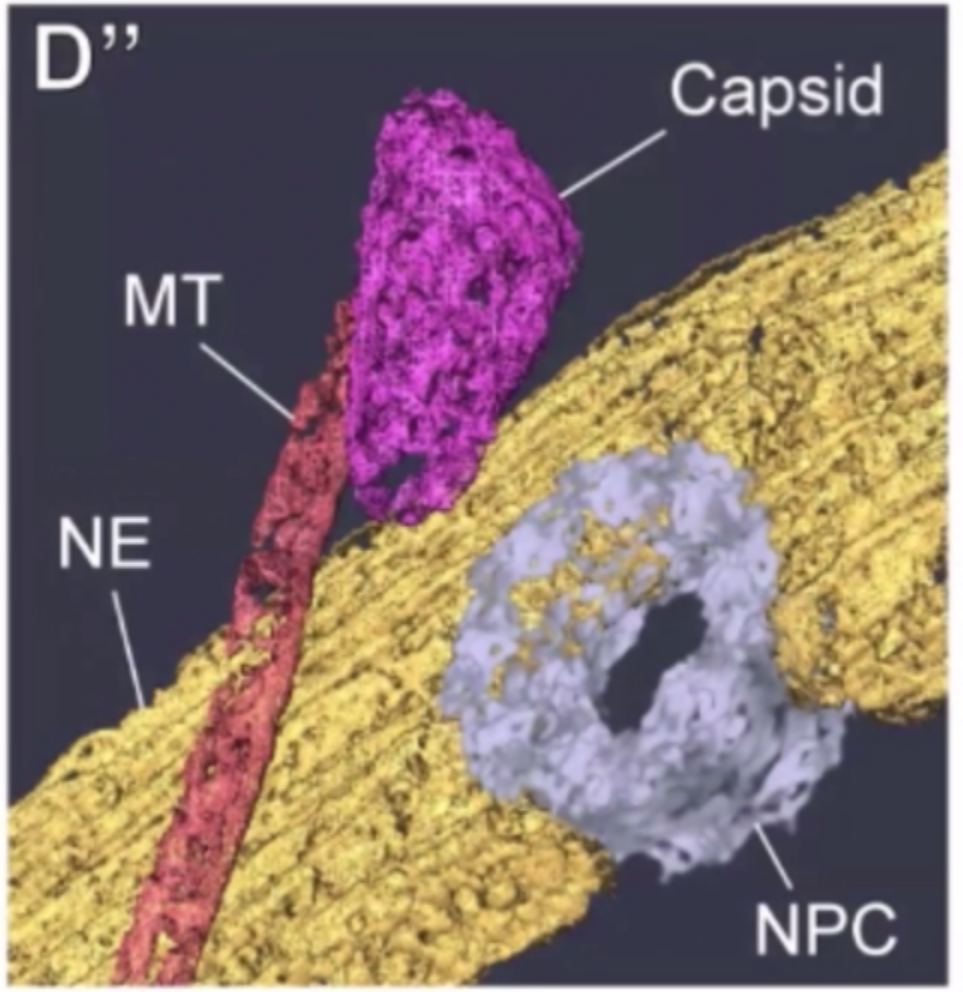
Post-fusion HIV capsids traffick on microtubules to the nuclear pore

Correlative Electron Tomography of cytoplasmic HIV complexes





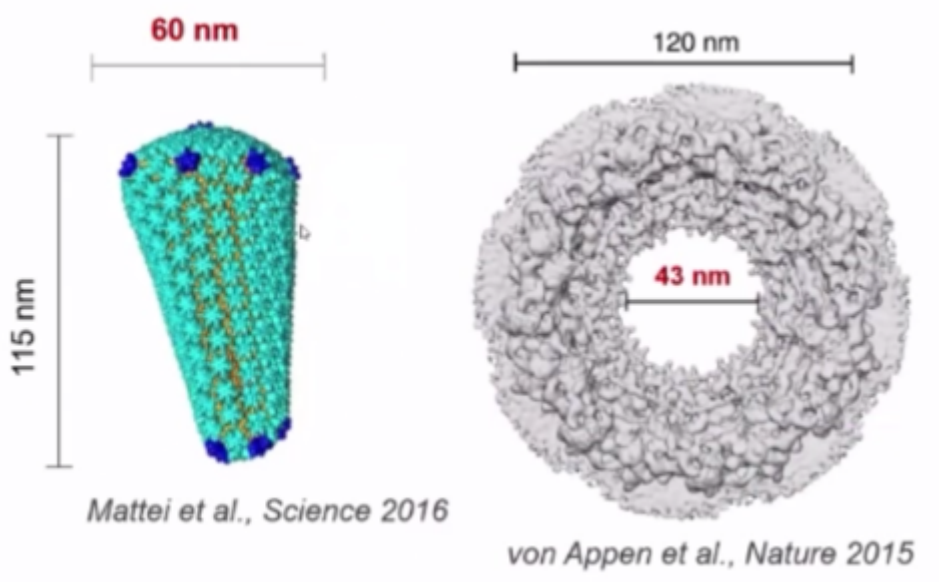
80% of complexes at the NPC associated with microtubules



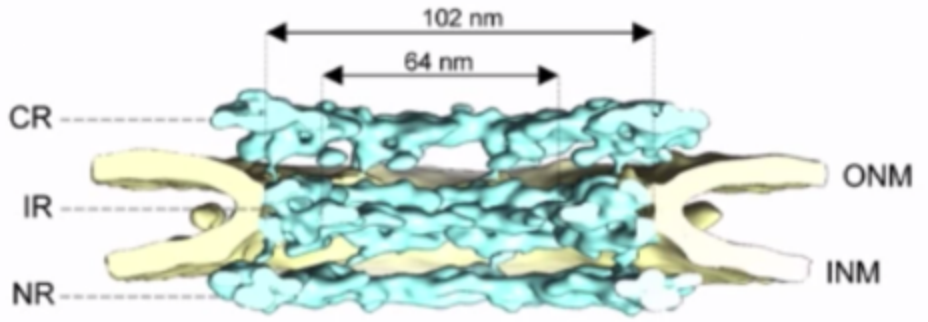
Krausslich #14; Zila *et al* 2021. Cell

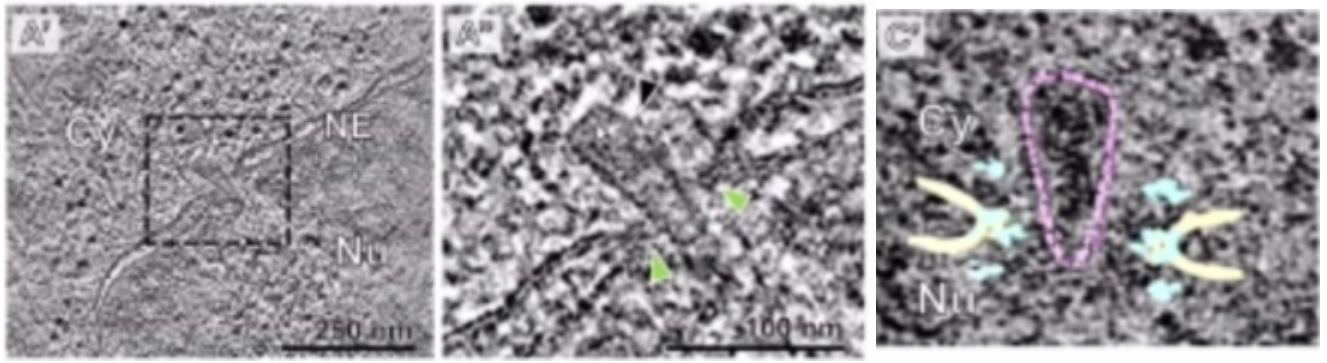
Cone-shaped HIV-1 capsids are transported through intact nuclear pores

- How does the capsid get through the nuclear pore?



- Ø of the nuclear pore is larger than previously determined
- The intact capsid can pass through the nuclear pore

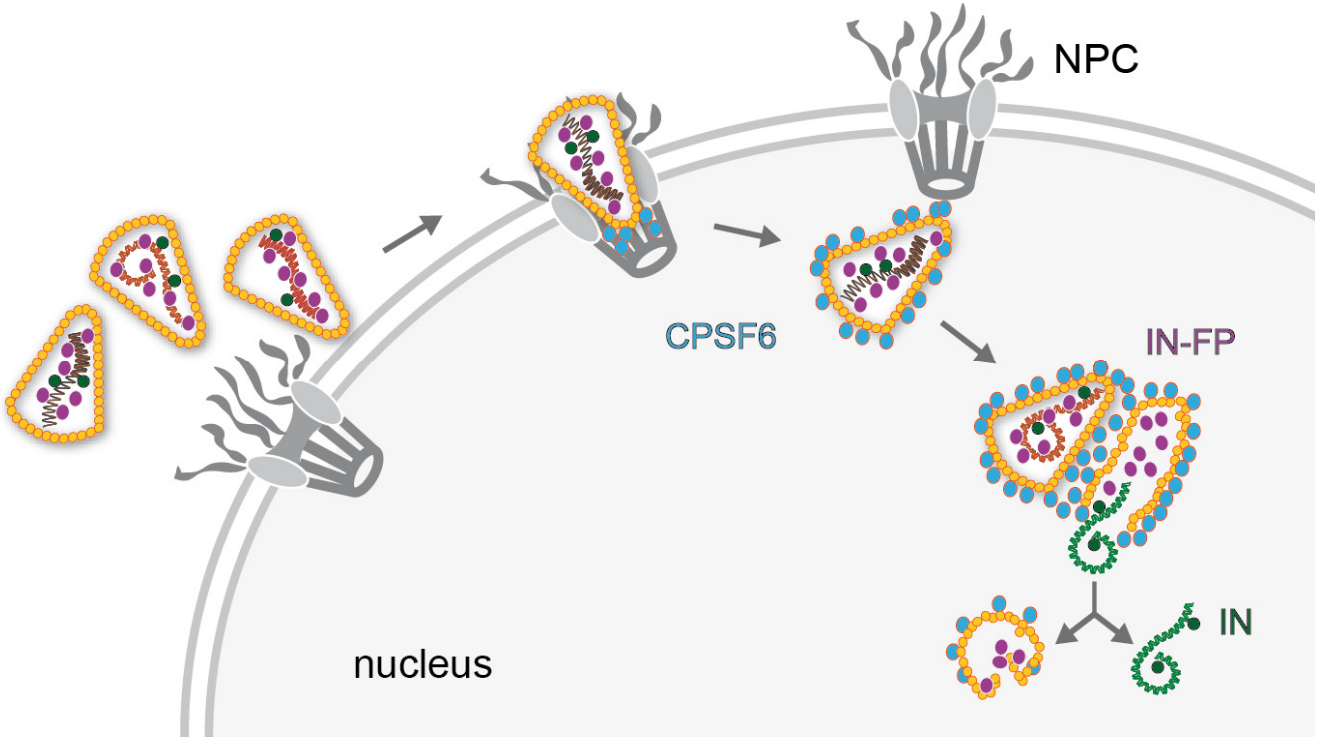


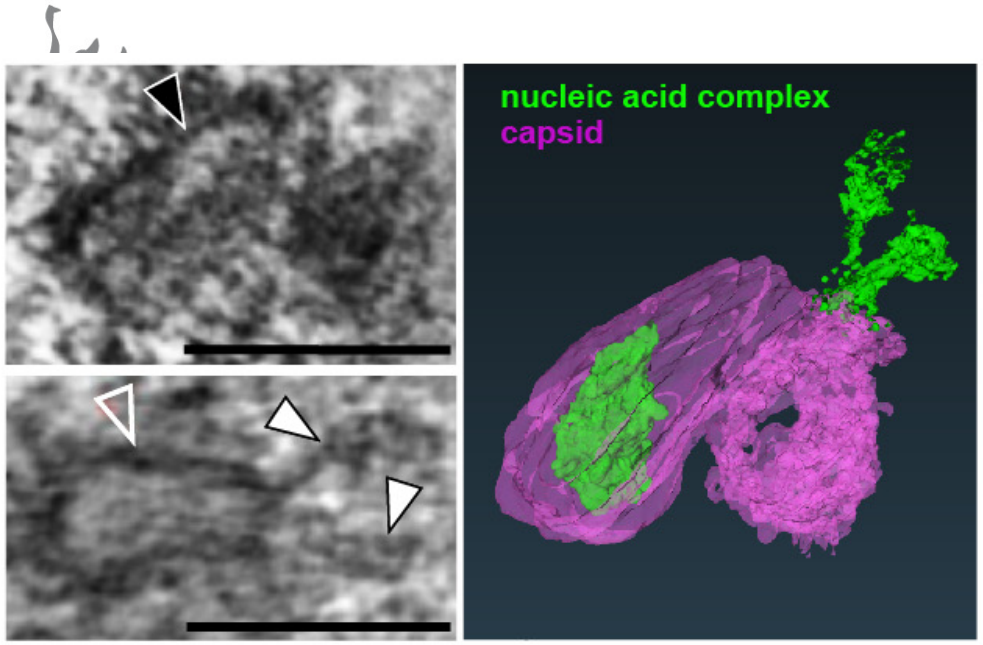


Krausslich #14; Zila *et al* 2021. Cell

Uncoating occurs by breakage of the capsid lattice in the nucleus

- CPSF6 releases the cores from the nuclear pore and cluster on nuclear capsids.
- +sDNA synthesis of the viral cDNA is completed
- Physical disruption of the capsid releases the completed cDNA into the nucleoplasm
- It becomes integrated into the host cell genome in the vicinity of the uncoating site

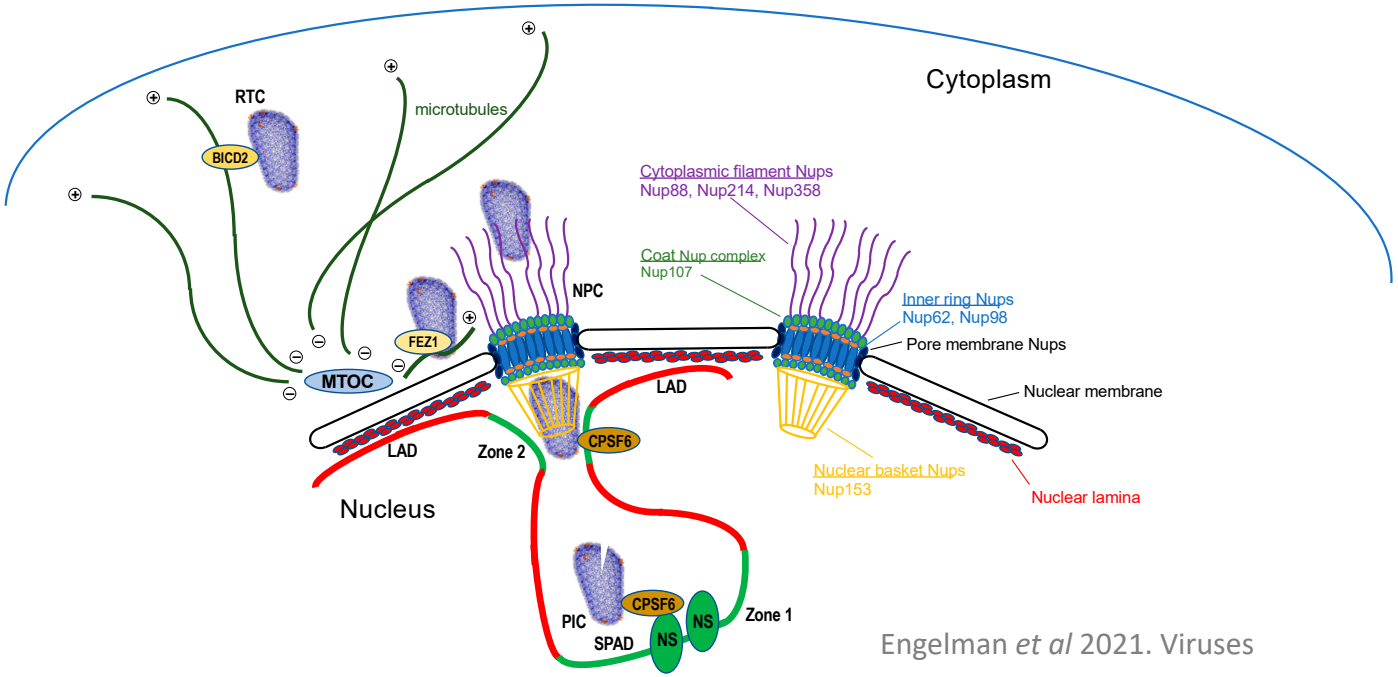




Krausslich #14; Müller *et al* 2020. BioRvix

Why HIV uses intact capsids to traffic to the nucleus ?

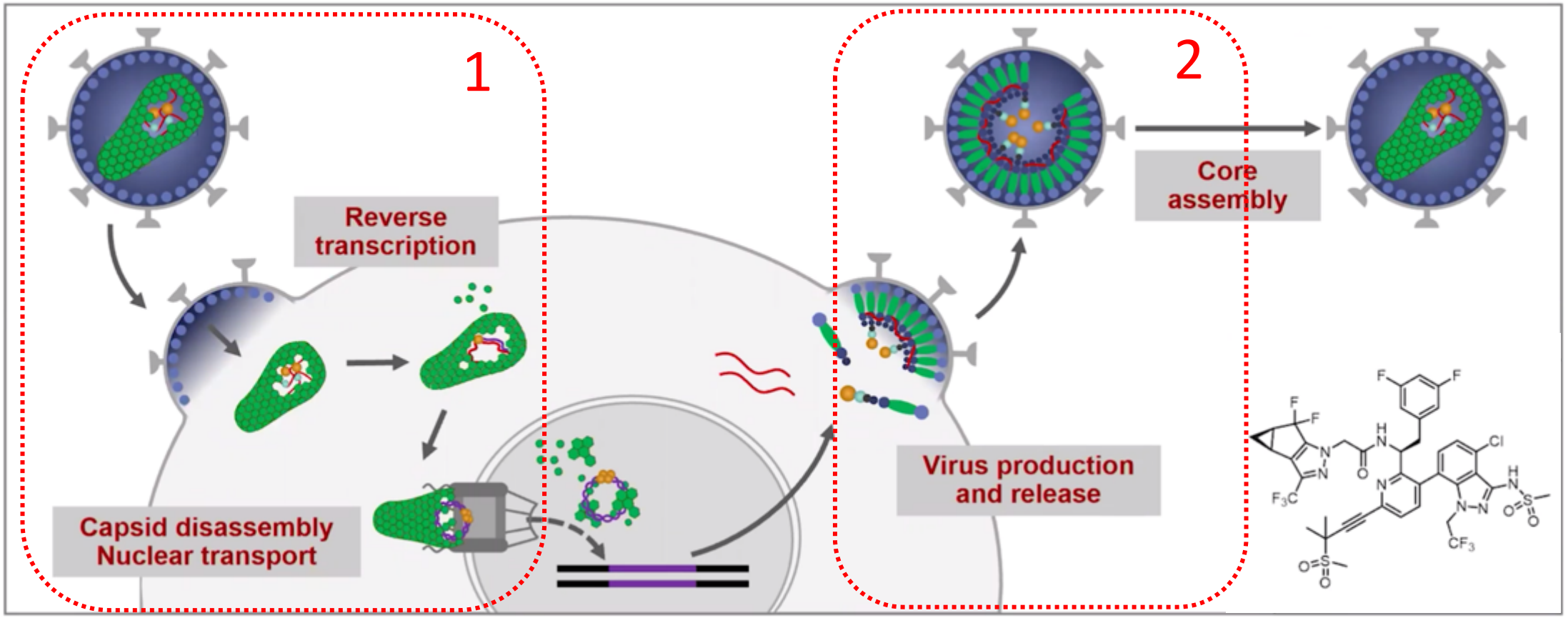
- Reaction container for reverse transcription: *initiated in the cytosol*
- Trafficking module in the cytosol: *along the cytoskeleton of the cell*
- Shield from cytolytic DNA sensors: *restriction factors!*
- Nuclear import vehicle: *shape matters …*
- Nuclear breakage of the capsid releases the genome complex for integration



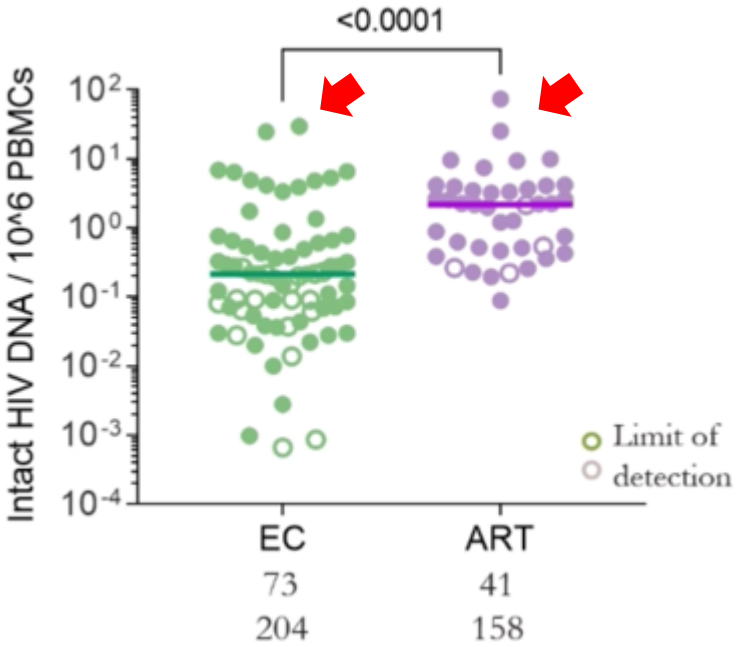
Engelman *et al* 2021. Viruses

Lenacapavir (GS-6207): First-in-class Inhibitor of the HIV Capsid

- pM, Long-active, Long-acting, All HIV subtypes, No Cross Resistance
- Interferes with the assembly, disassembly and traffic of capsid core
- Binds at a conserved interface between capsid monomers stabilizing the core



The thousand faces of the Elite Controller



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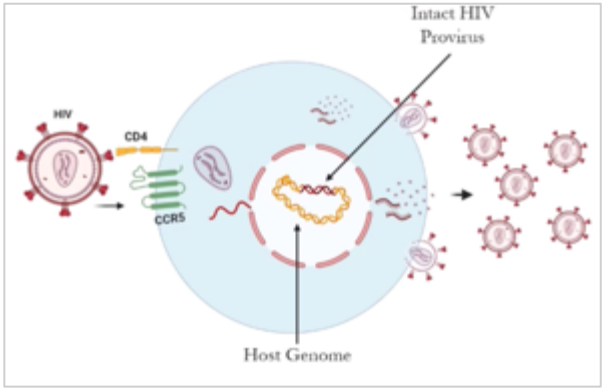
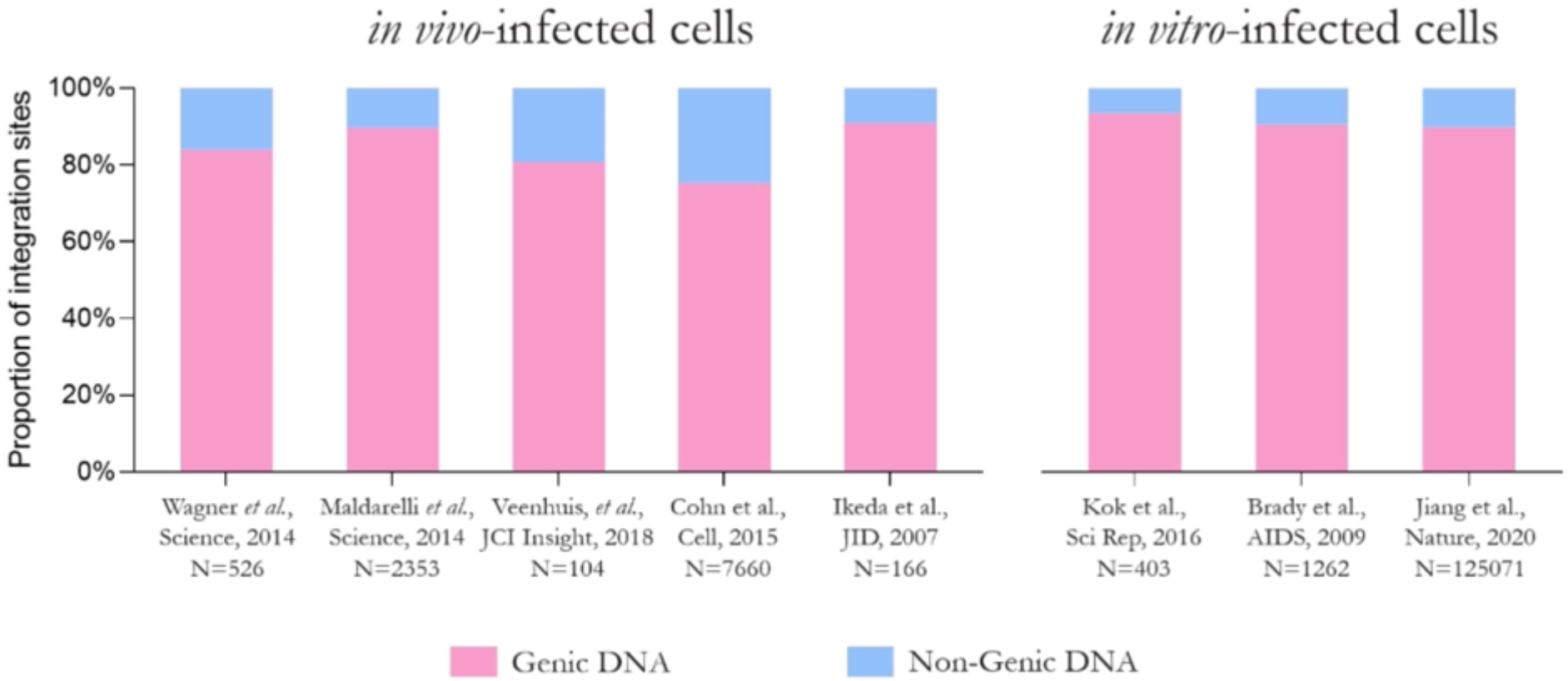


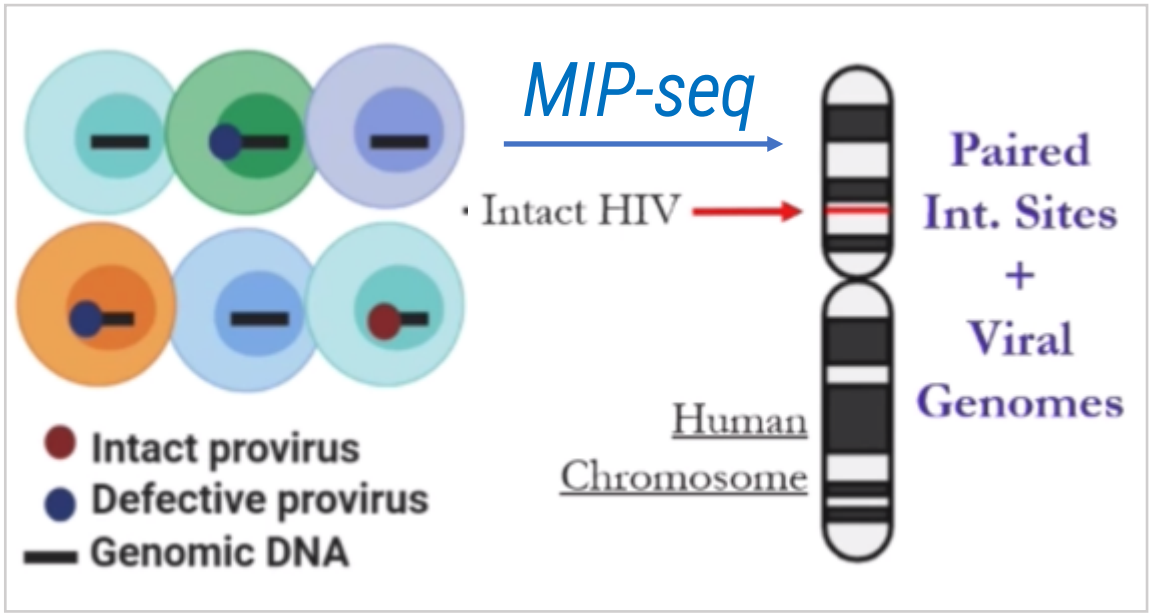
Yu #57; Jiang. 2020. Nature

Integration Site Analysis in the Host Chromosome

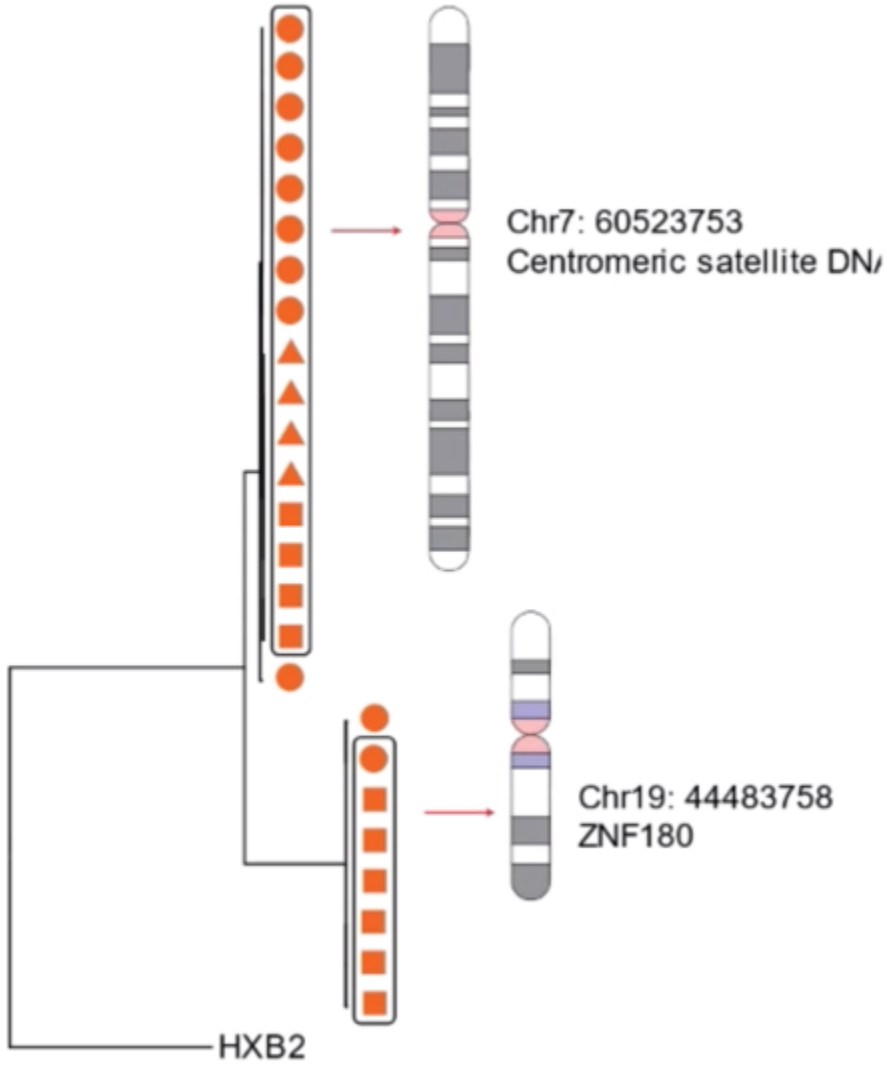


Yu #57; Jiang. 2020. Nature

Matched Integration Site and Proviral Sequencing Assay

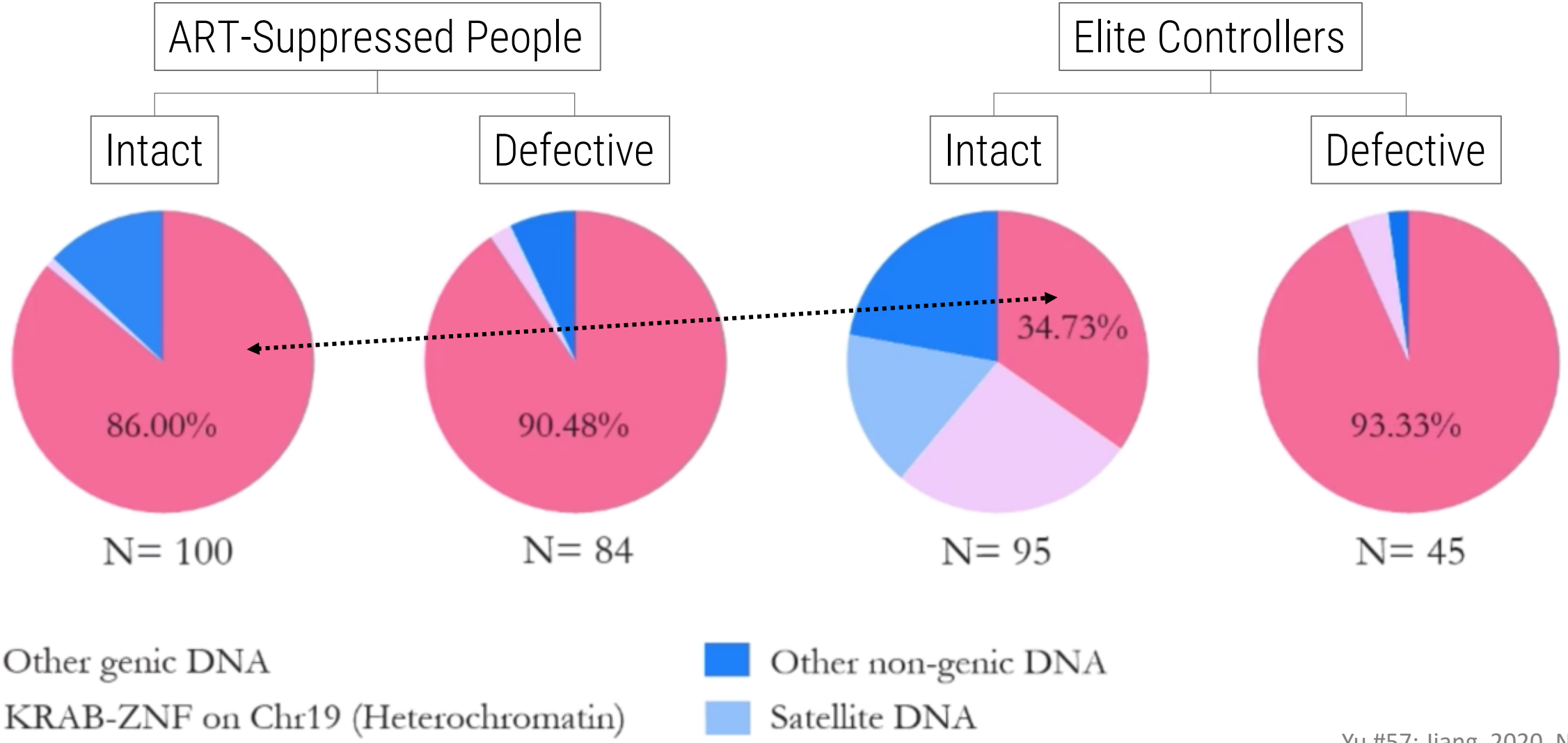


Clonally-expanded intact proviral genomes in Elite Controllers accumualte in Centromeric regions and KRAB-ZNF genes



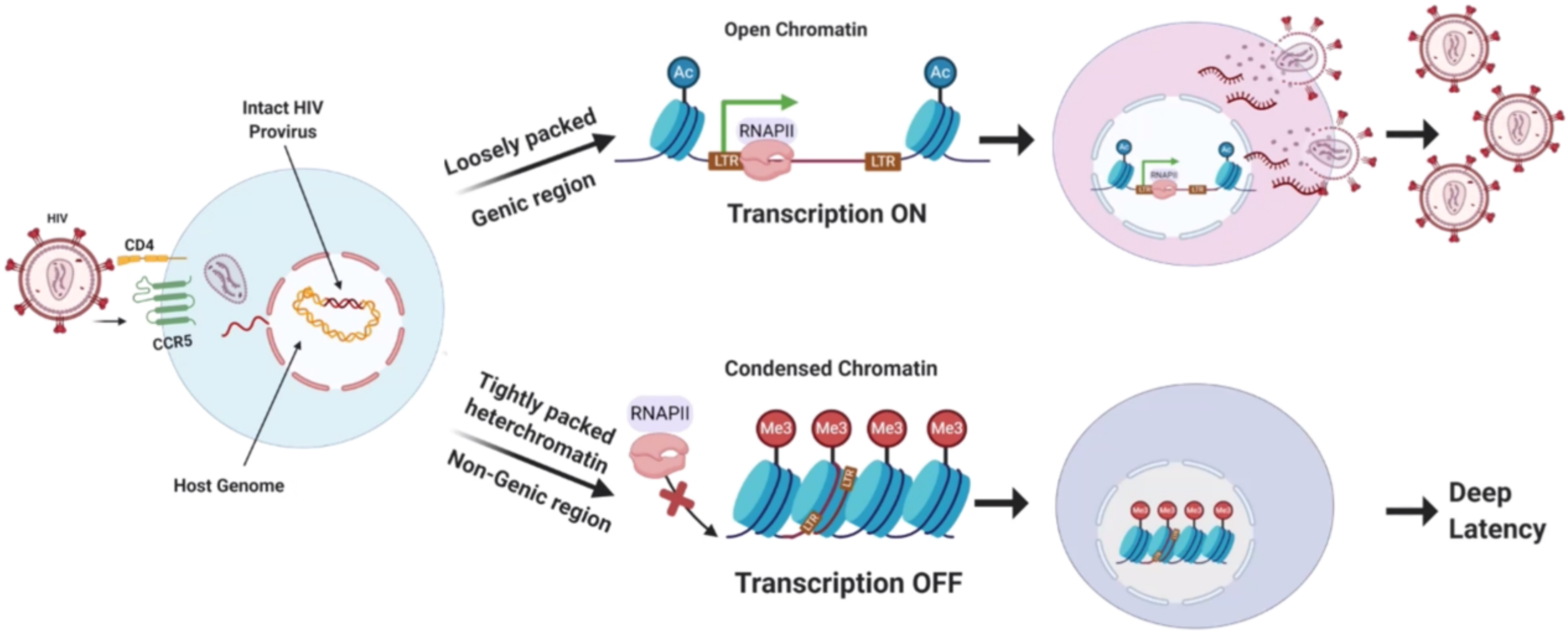
Yu #57; Jiang. 2020. Nature

Intact proviral genomes in EC in: non-genic, satellite or heterochromatin regions

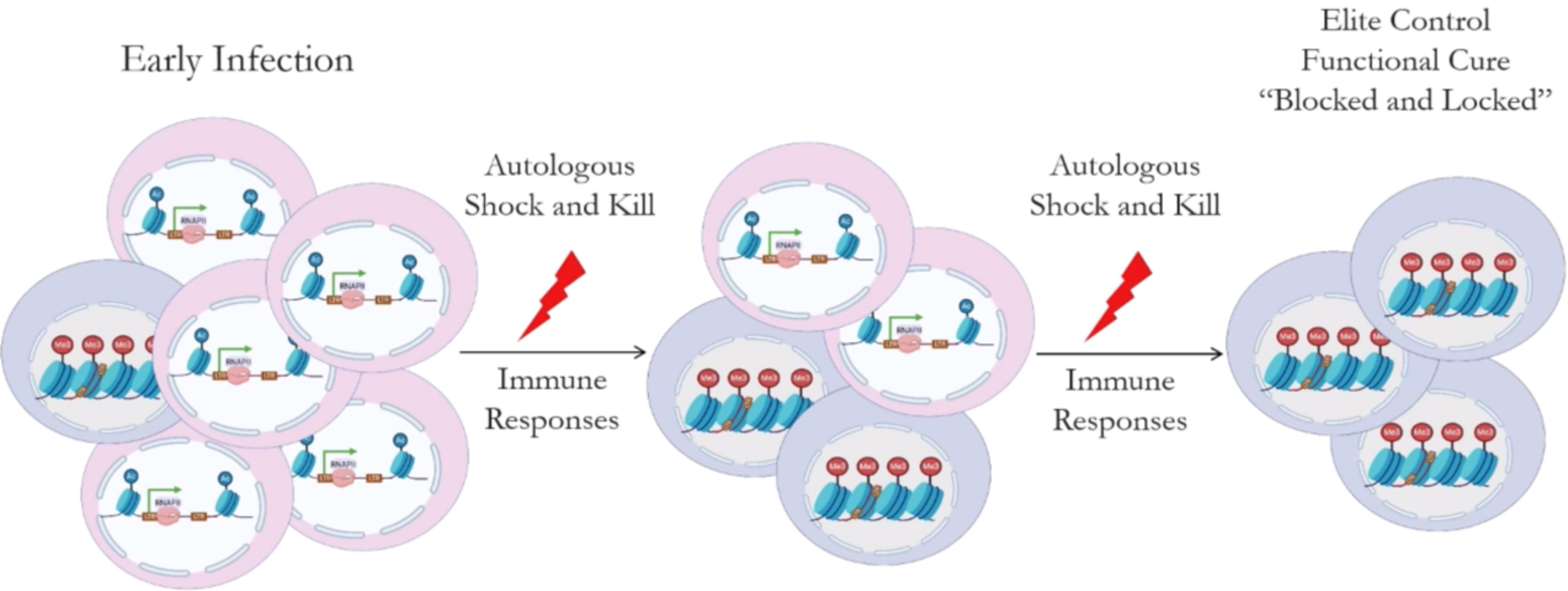


Yu #57; Jiang. 2020. Nature

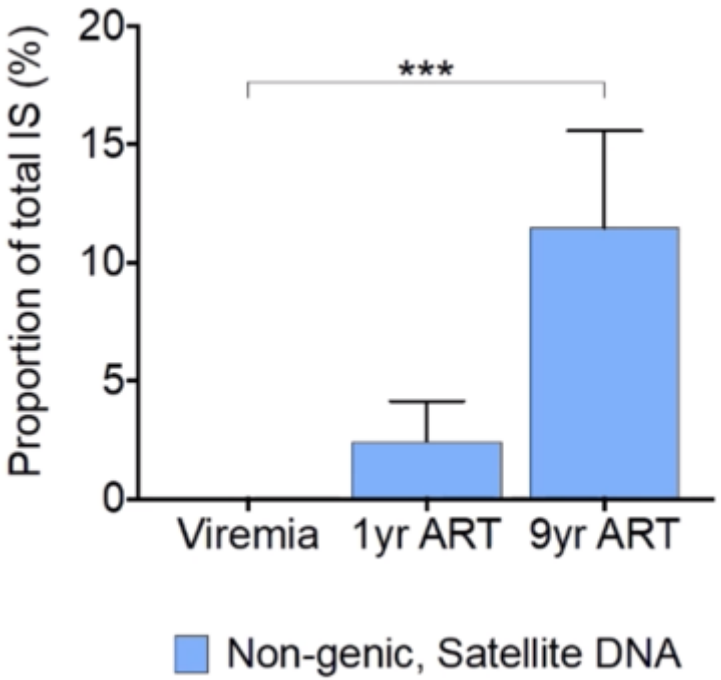
Chromosomal Location Matters

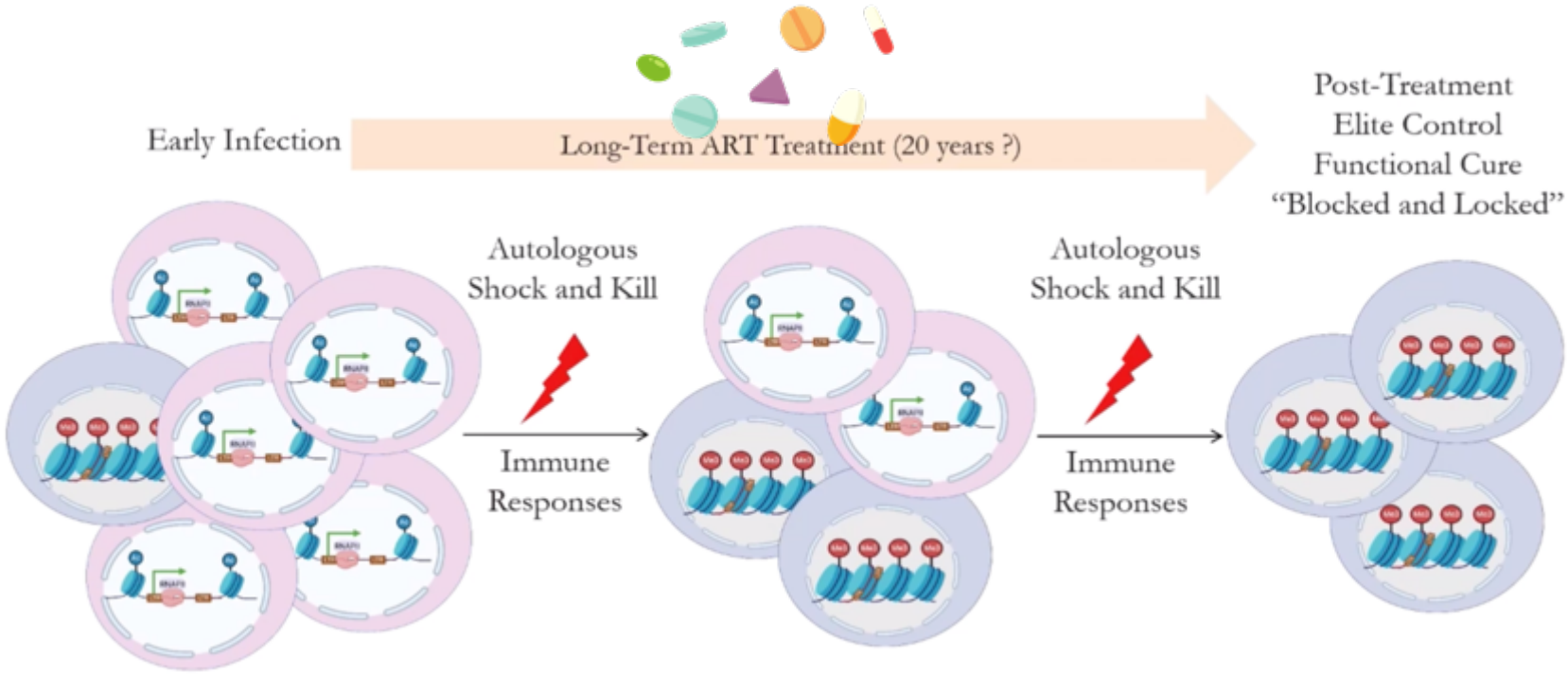


"Autologous Shock and Kill" Immune Selection



Do intact viruses in ”deep latency” undergo immune selection during ART ?

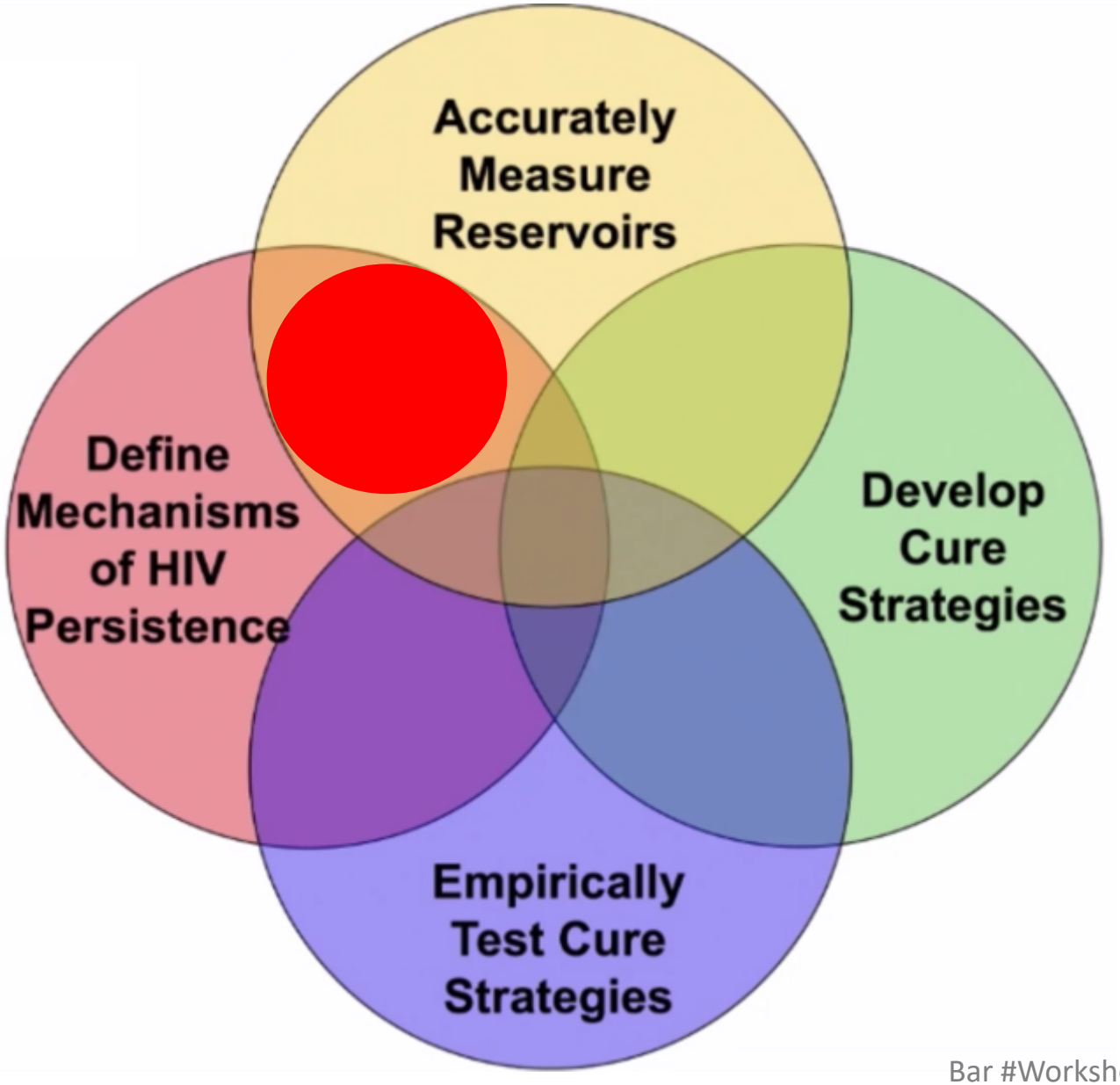




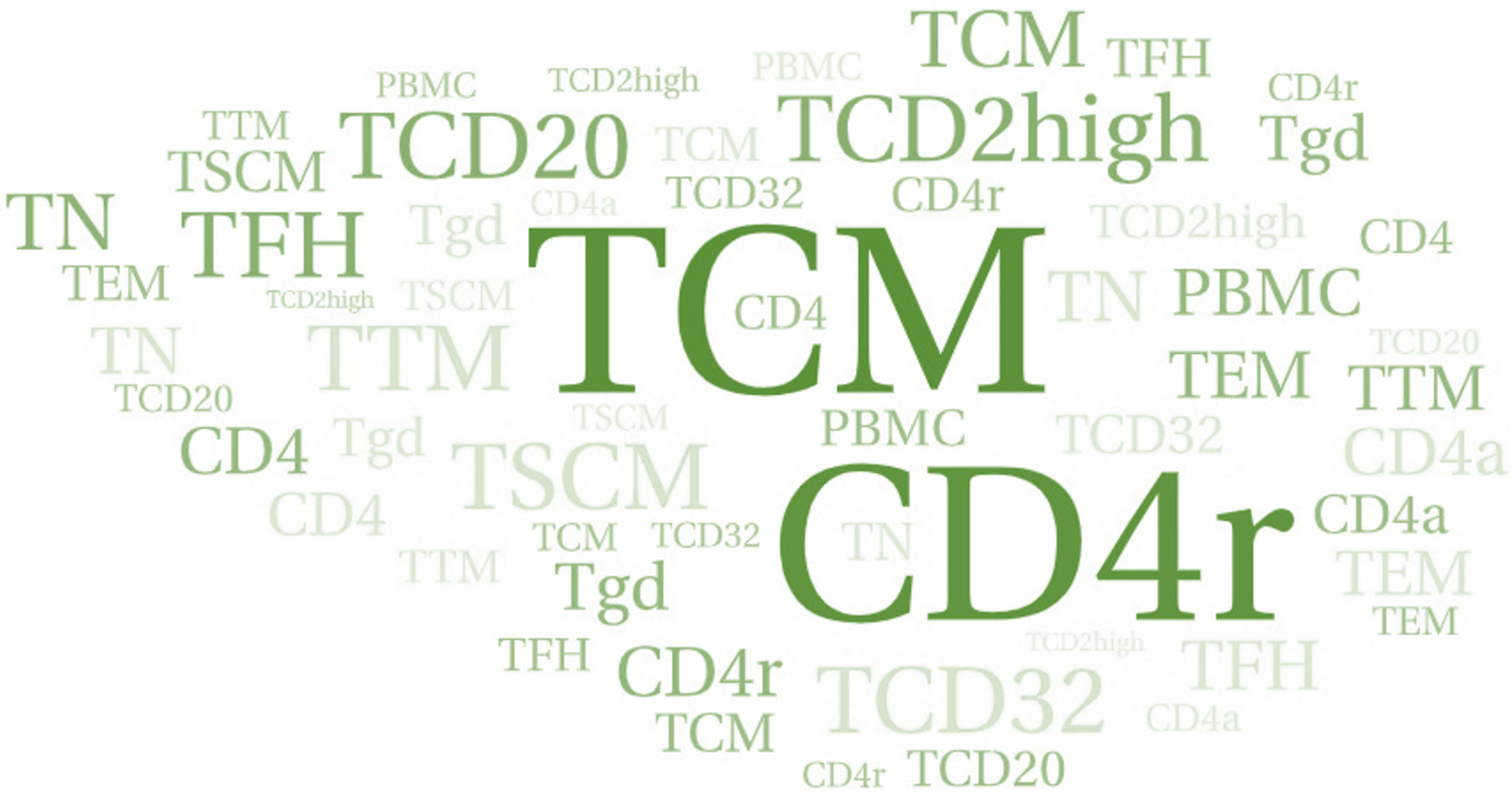
Einkauf #155; Liang #309

HIV Cure Research Priorities

Overlapping, mutually dependent priorities to elucidate and overcome barriers to HIV cure

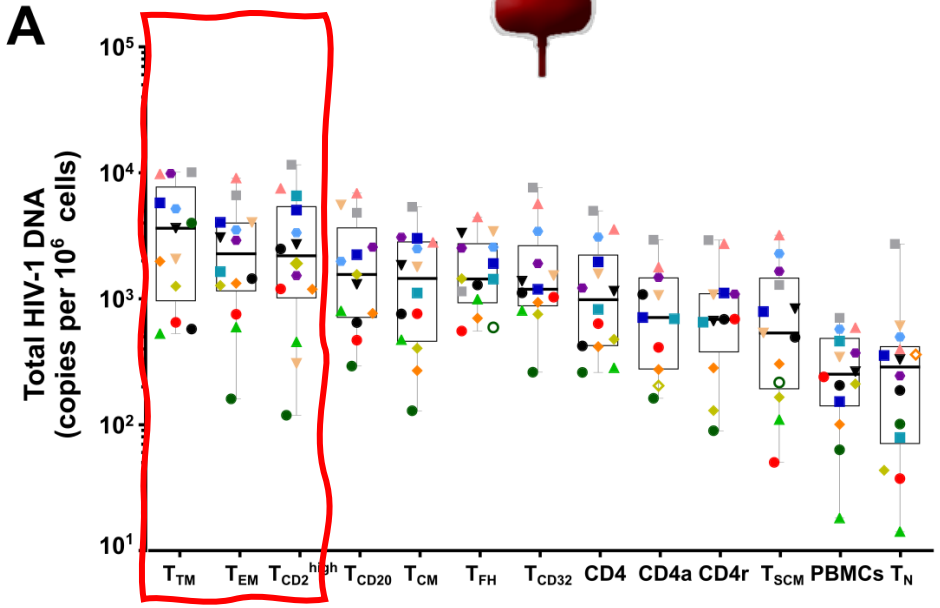


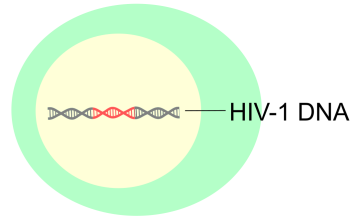
HIV Reservoir Atlas in Peripheral Blood



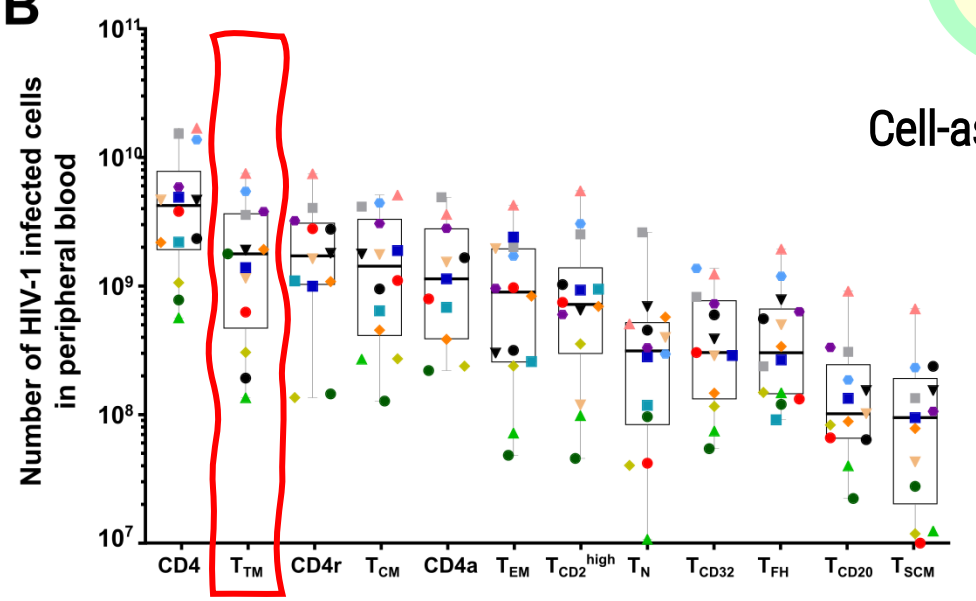
The most infected subpopulations had a memory phenotype

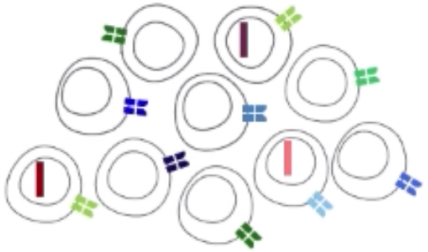
500ml blood drawn

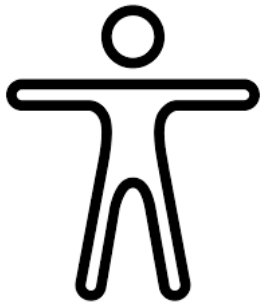




Cell-associated HIV-DNA

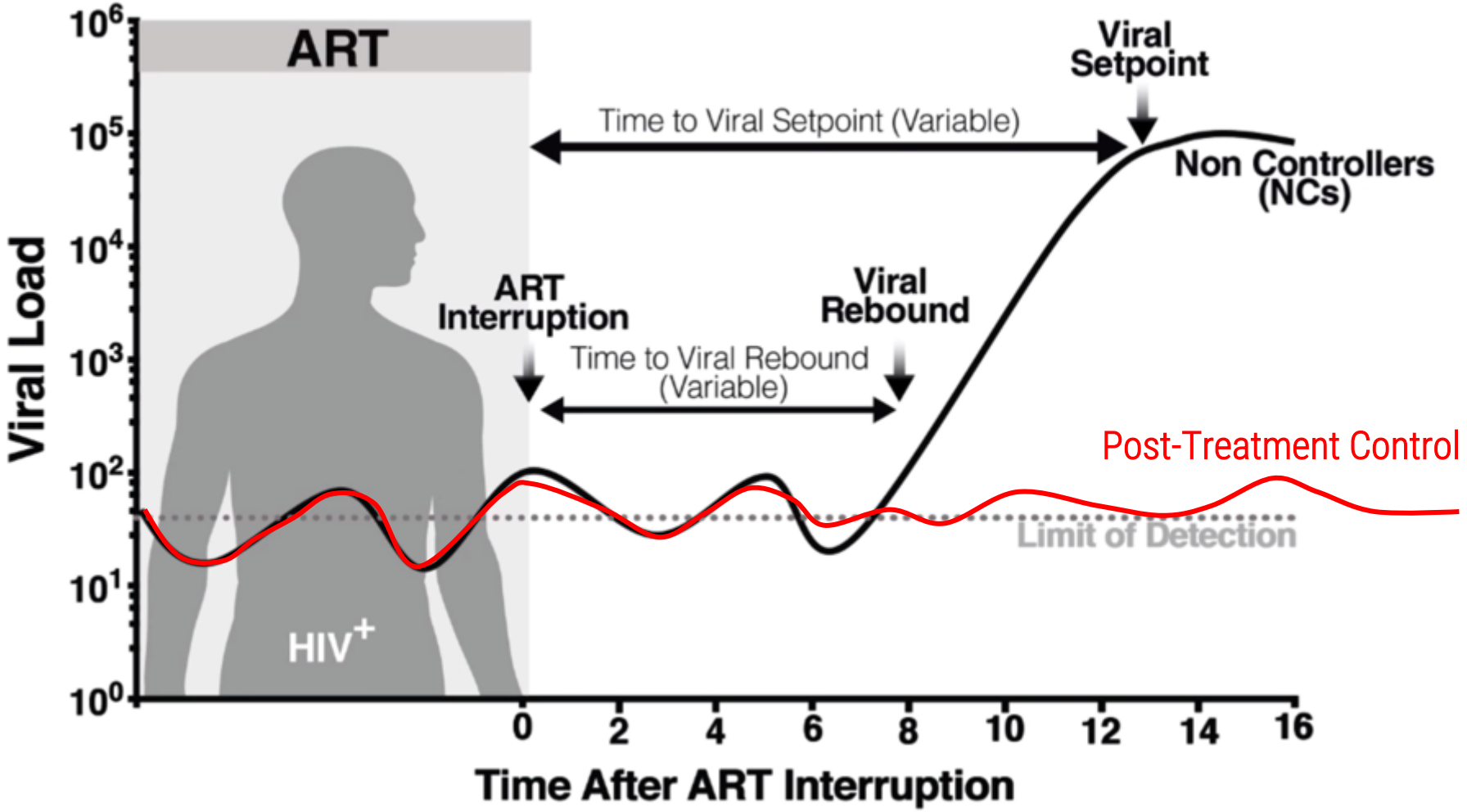






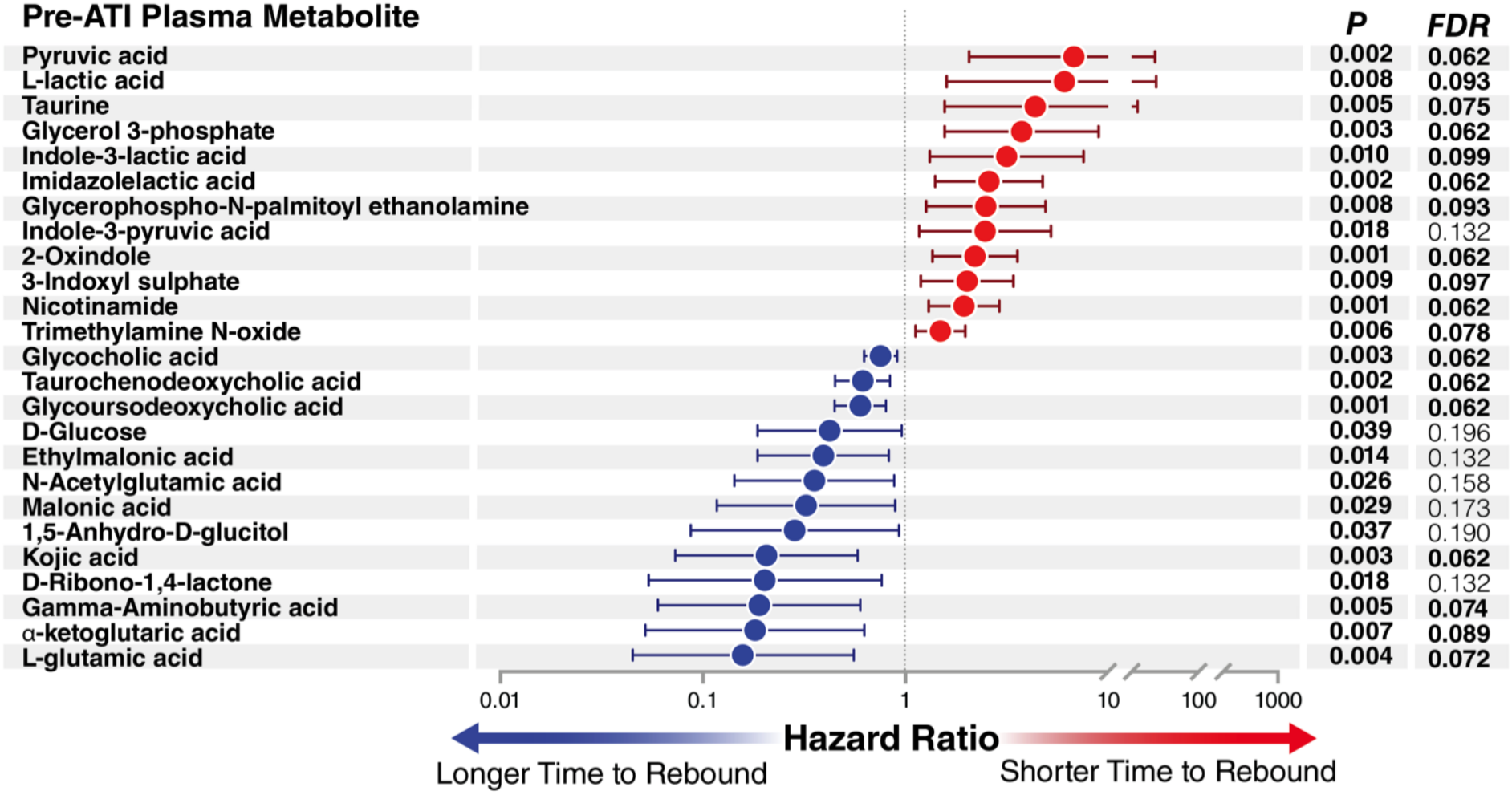
Predictors of Viral Rebound

Non-invasive plasma glycomic and metabolomic biomarkers of post-treatment HIV control
Improve the safety of analytic treatment interruption



Predictors of Viral Rebound

Plasma metabolites associate with time-to-viral-rebound in the Philadelphia Cohort



Predictors of Viral Rebound

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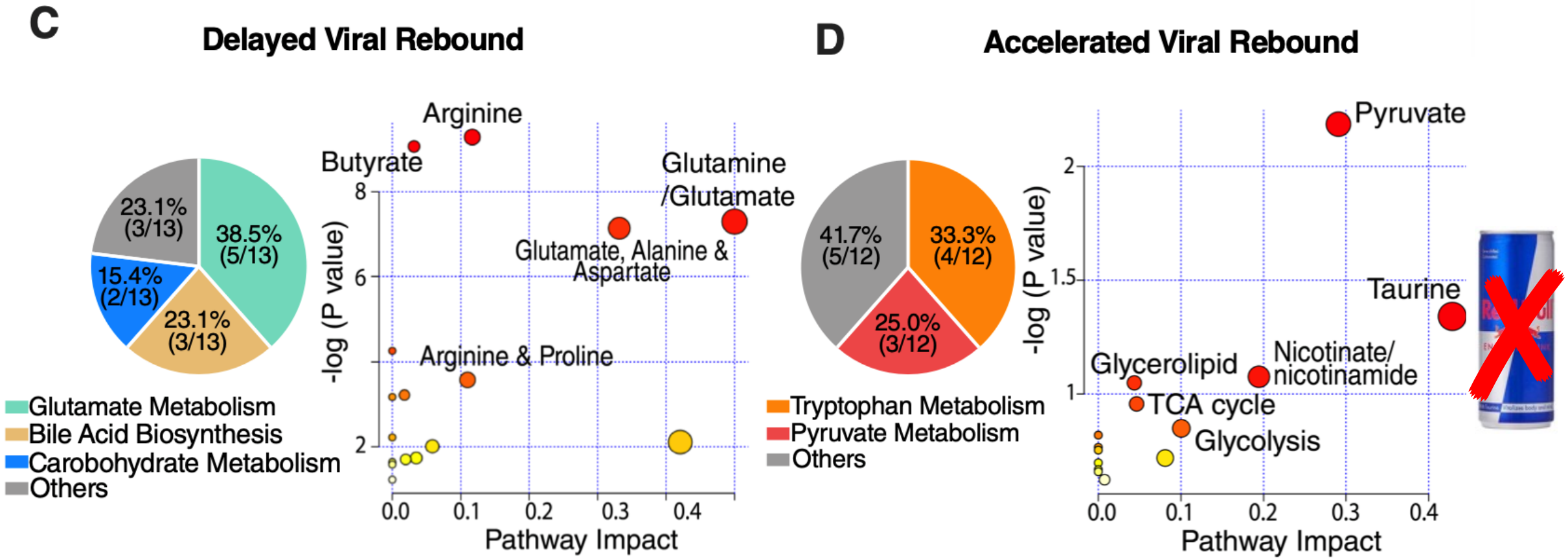
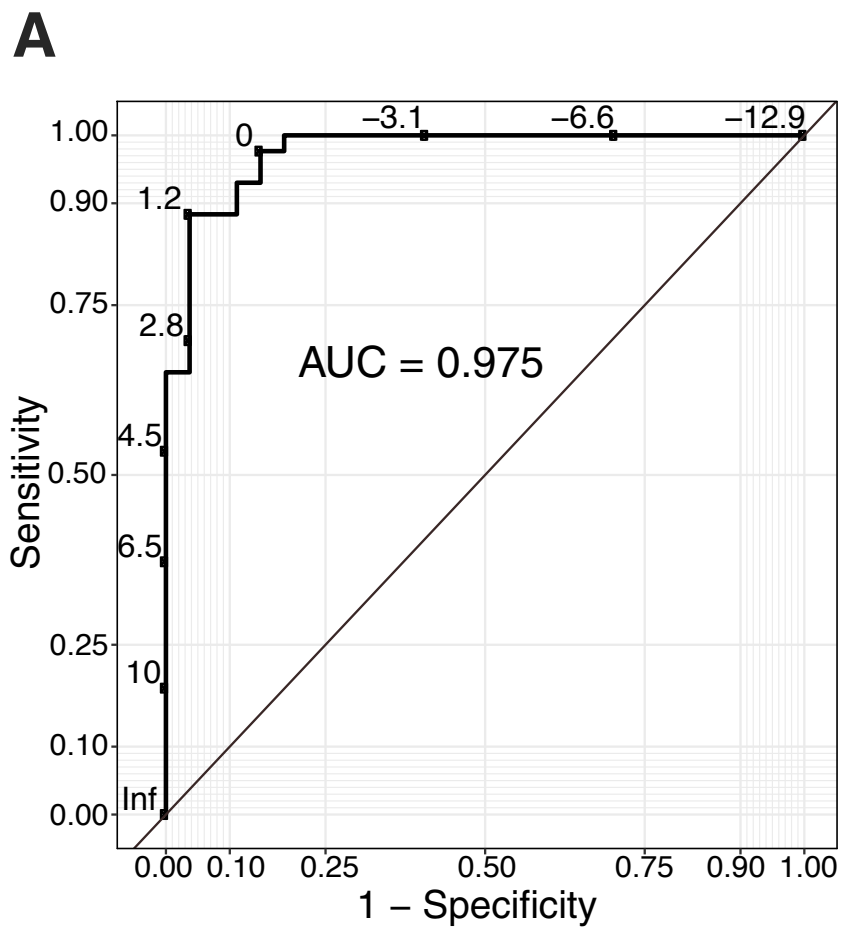
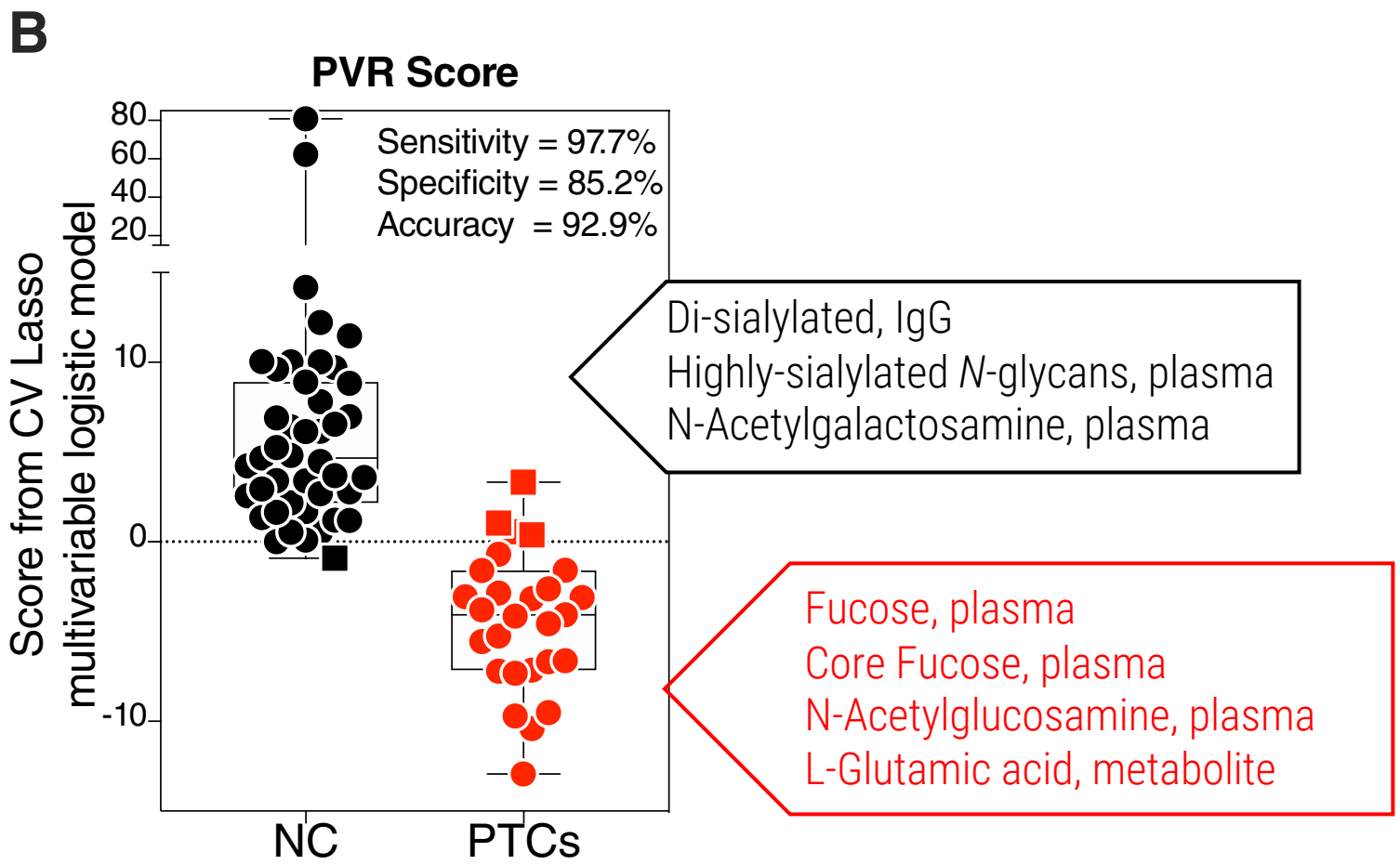


Predictors of Viral Rebound

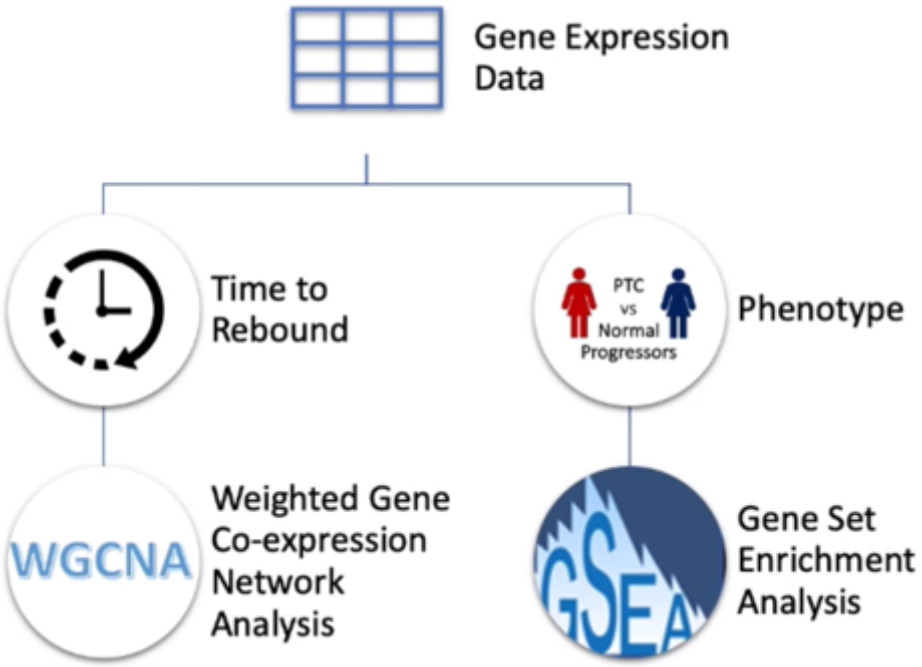
A multivariable logistic model selected variables predicts probability of viral remission post ATI

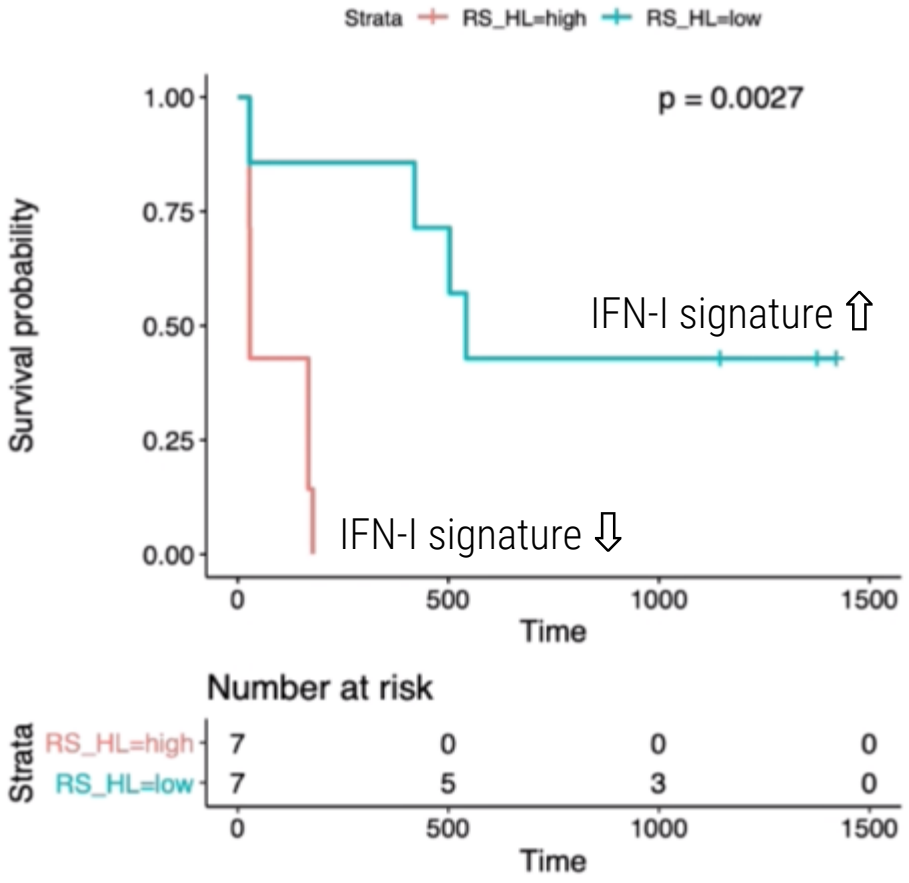




Predictors of Viral Rebound

IFN-I-associated gene expression predicts time to viral rebound after ART interruption



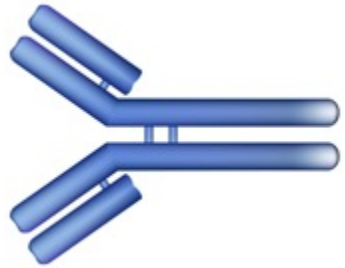


Risk Score

ISG15
TRIM25
XAF1
USP18

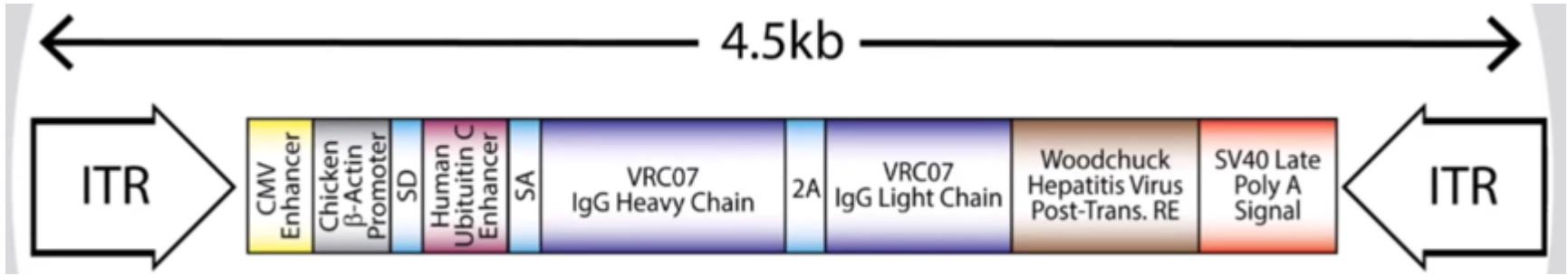
All with negative coefficient

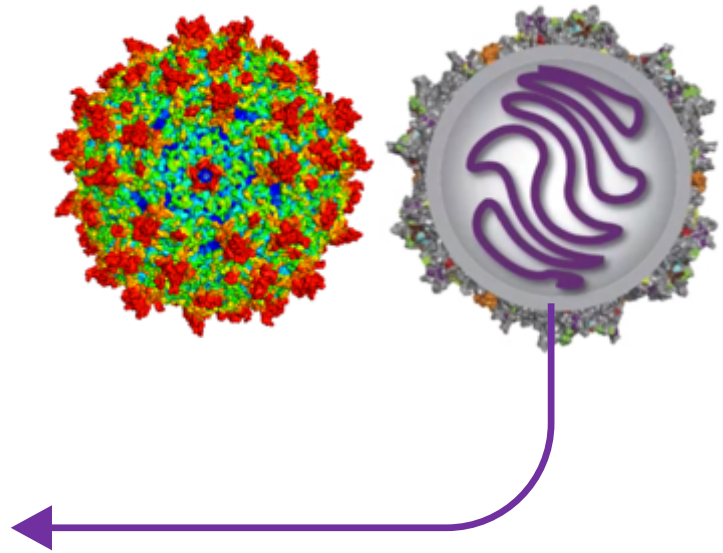
HIV-1 bNAbs: Looking ahead



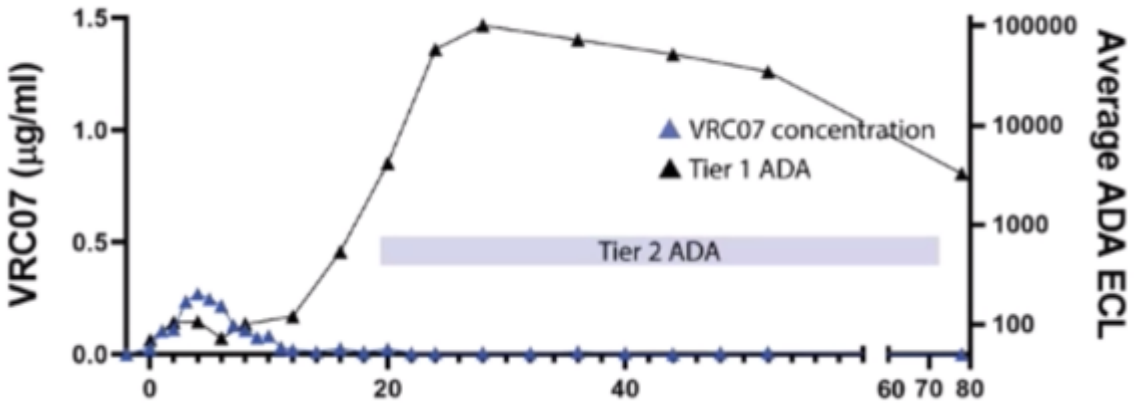
- Proof-of-concept for Ab-mediated PREVENTION
- Emergence evidence that bNAbs can maintain viral suppression as THERAPY
- Early promising data with LONG-TERM CONTROL, through delivery systems
- Safety in humans
- Promising results in NHP
- Challenges:
  - *pre-existing resistance*
  - *emergence of anti-drug Abs*
  - *cost*
- Future:
  - *new molecules*
  - *combinations*
  - *multiple studies for the next 2 yrs*

Durable HIV-1 Ab production in humans after AAV8-mediated gene transfer





- First-in-human RCT with bNAbs for HIV-1 (n=8, 3 IM doses, 2-3 yrs follow-up)
- No reactogenic production of difficult to induce functional neutralizing Abs
- Induction of anti-drug Abs



- How HIV-1 capsid navigates to the cell nucleus
  - *A new way to understand the HIV replication cycle?*
- Chromosomal location of HIV-1 matters …
  - *In elite controllers and some people in long-term ART*
- Simultaneous comparison of CD4 T cell in peripheral blood
  - *Memory CD4 T cells form the most abundant reservoir*
- Predicting viral rebound through
  - *Plasma metabolites*
  - *IFN-I-signatures*
- bNAb: their role in treatment, prevention and cure strategies
  - *Durable HIV Ab production in humans after AAV8-mediated gene transfer*
  - *SARS-CoV-2: a win-win situation in bNAb development*

¡MUCHAS GRACIAS!

Javier Martinez-Picado

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