Diverse paths to broadly neutralizing antibody escape among HIV-1 strains

576

Alex C. Stabell[1,2], Songhee Lee[2], Debby J. Park[2], Christy L. Lavine[3], Sebastian Mejia Espinosa[3], Viren A. Baharani[2,4], Michel C. Nussenzweig[4,5], Marina Caskey[4], Michael S. Seaman[3], Paul D. Bieniasz[2,5], **Theodora Hatziioannou**[2].

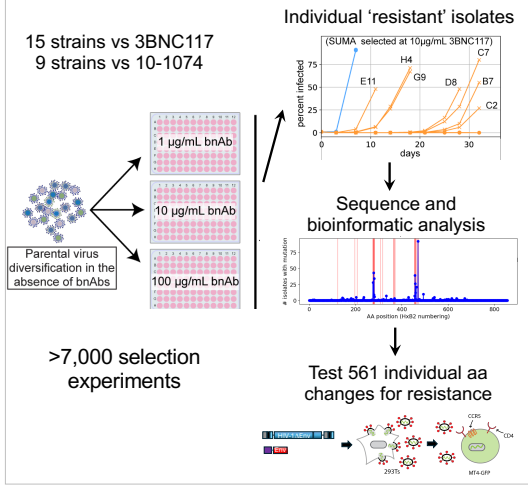
[1] Weill Cornell, Department of Infectious Diseases, New York, NY, 10065, USA; [2] Laboratory of Retrovirology, The Rockefeller University, New York, NY, 10065, USA; [3] Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.; [4] Laboratory of Molecular Immunology, The Rockefeller University, New York, NY, 10065, USA.; [5] Howard Hughes Medical Institute, The Rockefeller University, New York, NY, 10065, USA

BACKGROUND

Broadly neutralizing antibodies (bnAbs) are among the most promising agents in HIV-1 treatment and prophylaxis. With numerous clinical trials across the world seeking to evaluate application of potent bnAbs, the issue of viral escape and resistance is pressing and important. However, thus far, our understanding of bnAb resistance pathways among diverse HIV-1 clades remains limited. Our study addresses these limitations with the development of medium-high throughput assays that allow the simultaneous analysis of multiple HIV-1 strains for their ability to escape bnAb neutralization.

METHODS

- Diversified viral stocks of were used to infect indicator T-cells (MT4-R5-LTR-GFP) and plated in 96-wells with varying concentrations of a bnAb.
- Virus isolates from individual GFP positive wells were expanded, resistance confirmed and analyzed by sequencing.
- Putative resistance mutations were identified using a bioinformatic pipeline that prioritized mutations rare prior to selection but frequent in independent resistant viruses.
- Individual amino acid changes were tested for resistance in pseudotyped assays.

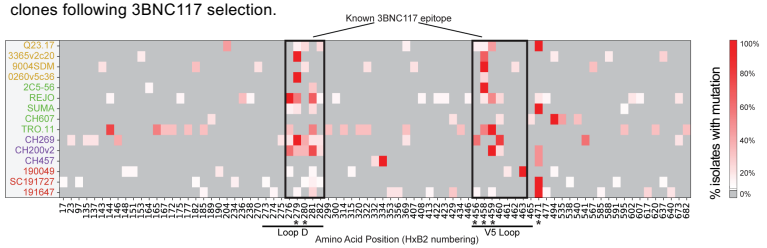


Low genetic barrier to bnAb escape

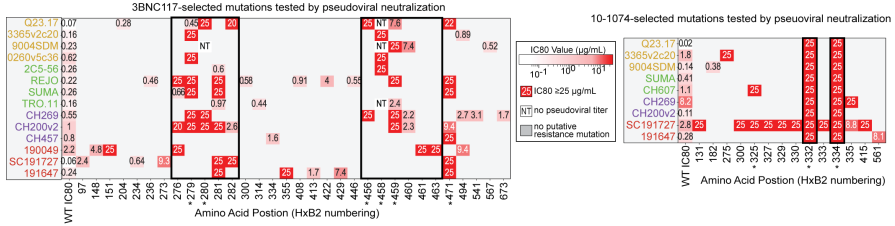
RESULTS

- The majority of HIV-1 strains can escape bnAbs with single amino acid substitutions.
- The identity of mutations that confer bnAb resistance is highly variable among HIV-1 strains and context dependent.
- Unconventional mechanisms of escape from CD4-binding site targeting bnAbs were uncovered for a small number of strains.
- Resistance mutations were either highly specific for the selecting bnAb or conferred resistance to other bnAbs targeting overlapping epitopes.

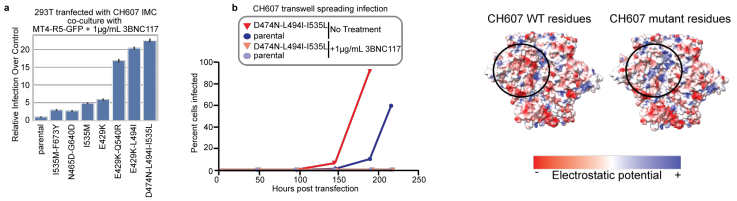
- Putative escape amino acid substitutions identified following sequencing and bioinformatic analysis of individual clones following 3BNC117 selection.



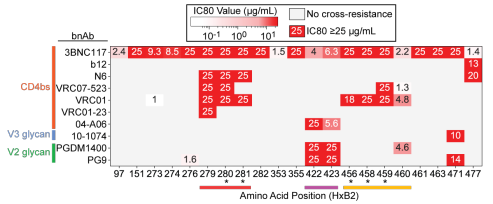
- Single amino acid substitutions confer bnAb resistance

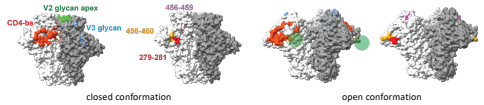


- Alternative escape pathways.



- Selection for 3BNC117 resistance can cause resistance to additional bnAbs





CONCLUSIONS

- This study identifies previously unappreciated pathways of bnAb escape
- The genetic barrier to bnAb resistance is generally low
- bnAb breadth is likely due to their rarity rather than an intrinsically high barrier to resistance
- Our approach can identify combinations of bnAbs with a higher barrier to escape that could guide strategies to minimize the development of resistance.

Acknowledgements

This study was supported by the National Institutes of Health (NIH) grant U01 AI169385 to MN, MCN, TH, PDB and MSS. ACS was supported by NIH grants T32 AI007613 to Cornell Medical School and 5KL2TR001865 to Rockefeller University. MCN and PDB are Howard Hughes Medical Institute (HHMI) investigators.

PLAIN LANGUAGE SUMMARY

This study shows that HIV-1 resistance to broadly neutralizing antibodies (bnAb) in clinical development can develop easily and would compromise their use. Nevertheless, it also identifies bnAb combinations that would minimize development of resistance.