Enhanced clearance of HIV-1–infected cells by broadly neutralizing antibodies against HIV-1 in vivo

Ching-Lan Lu,[1,2] Dariusz K. Murakowski,[3] Stylianos Bournazos,[4] Till Schoofs,[1] Debolina Sarkar,[3] Ariel Halper-Stromberg,[1] Joshua A. Horwitz,[1] Lilian Nogueira,[1] Jovana Golijanin,[1] Anna Gazumyan,[1] Jeffrey V. Ravetch,[4] Marina Caskey,[1] Arup K. Chakraborty,[3,5,6,7,8†] Michel C. Nussenzweig[1,9†]

[1] Laboratory of Molecular Immunology, The Rockefeller University
[2] Weill Cornell Medical College
[3] Department of Chemical Engineering, Massachusetts Institute of Technology
[4] Laboratory of Molecular Genetics and Immunology, The Rockefeller University
[5] Ragon Institute of MGH, MIT, and Harvard
[6] Department of Physics, Massachusetts Institute of Technology
[7] Department of Biological Engineering, Massachusetts Institute of Technology
[8] Institute for Medical Engineering and Science, Massachusetts Institute of Technology
[9] Howard Hughes Medical Institute.
†Corresponding author

Category: Infectious diseases, Immunology

Although combination antiretroviral therapy (cART) suppresses HIV-1 viremia to undetectable levels in a majority of infected patients, viral rebound occurs 2~3 weeks following cART interruption. Recent studies show that broadly neutralizing antibodies **(**bNAbs) are not only effective as an immunoprophylaxis for HIV-1 acquisition, but can also suppress viral loads to undetectable levels in chronically infected humanized mice and macaques. Unlike ART, which prevents new infections by interfering with various elements required for HIV-1 replication, antibodies block infection, and accelerate the clearance of free virions from the blood of macaques. Antibodies also have the potential to kill infected cells *in vivo* and have been shown to do so *in vitro* by FcγR-mediated mechanisms. However, the majority of infected cells die rapidly by apoptosis or pyroptosis and whether bNAbs can accelerate their clearance *in vivo* has not been tested directly.

To determine whether bNAbs can utilize these cellular effector functions to mediate killing of infected cells *in vivo*, we used mathematical modeling to examine the kinetics of HIV-1 suppression in infected individuals who were enrolled in bNAb 3BNC117 phase I clinical trail. The analysis showed that neutralization of the virus alone doesn't explain the steep drop in the virus levels observed in patients, suggested that the effects of the antibody are not limited to free viral clearance and blocking new infection but also include acceleration of infected cell clearance. Consistent with these observations, we find that broadly neutralizing antibodies can target CD4+ T cells infected with patient viruses and can decrease their in vivo half-lives by a mechanism that requires Fcγ receptor engagement in a humanized mouse model. The results indicate that passive immunotherapy can accelerate elimination of HIV-1–infected cells.