OA2-6 LB
CD4 mimetics sensitize HIV-1-infected cells to ADCC

J. Richard1,2, M. Veillette1,2, N. Brassard1, S.S. Iye1, M. Roger1,2, L. Martin1, M. Pazgier5, A. Schön6, E. Freire6, J.-P. Routy7, A.B. Smith rd3, J. Park3, D.M. Jones3, J.R. Courter3, B.N. Melillo3, D.E. Kaufmann1,2,8, B.H. Hahn3, S. Permarl9, B.F. Haynes9, N. Madani10,11, J. Sodroski10,11, A. Finzi1,2

1The CHUM Research Center, Montreal, Canada, 2University of Montreal, Montreal, Canada, 3University of Pennsylvania, Philadelphia, United States, 4dCEA, iBiTecS, Service d’Ingénierie Moléculaire des Protéines, Gif sur Yvette, France, 5University of Maryland School of Medicine, Baltimore, United States, 6The Johns Hopkins University, Baltimore, United States, 7McGill University, Montreal, Canada, 8Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard, Cambridge, United States, 9Duke Human Vaccine Institute, Duke University Medical Center, Duke, United States, 10Dana-Farber Cancer Institute, Boston, United States, 11Harvard School of Public Health, Boston, United States

Background: Prevention of HIV-1 transmission and progression likely requires approaches that can specifically eliminate HIV-1-infected cells. There is increasing evidence supporting a role of Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) in controlling HIV-1 transmission and disease progression. Importantly, the interaction of HIV-1 envelope (Env) glycoproteins with the CD4 receptor was recently reported to be required for efficient exposure of ADCC-mediating Env epitopes. In that context, HIV-1-infected cells presenting HIV-1 Env in the CD4-bound conformation on their surface were found to be preferentially targeted by ADCC-mediating antibodies present in sera of HIV-1-infected individuals. However, HIV-1 has evolved a sophisticated mechanism to avoid exposure of ADCC-mediating Env epitopes by downregulating CD4 and by limiting the overall amount of Env at the cell surface.

Methods: Rationally-designed CD4-mimetic compounds (CD4mc) have been shown to induce thermodynamic changes in HIV-1 Env similar to those induced by CD4 and sensitize HIV-1 particles to neutralization by otherwise non-neutralizing CD4-induced antibodies. In this study, we explored the capacity of such compounds to promote the CD4-bound conformation of Env and thereby sensitize HIV-1-infected cells to ADCC mediated by sera, cervico-vaginal lavages and breast milk from HIV-1-infected individuals. However, HIV-1 has evolved a sophisticated mechanism to avoid exposure of ADCC-mediating Env epitopes by downregulating CD4 and by limiting the overall amount of Env at the cell surface.

Results: We observed that certain CD4mc induce the CD4-bound conformation of Env and thereby sensitize cells infected with primary HIV-1 isolates to ADCC mediated by prevalent and easy-to-elicit antibodies present in sera from early converters and chronically-infected individuals. Importantly, CD4mc also enhanced recognition and ADCC-mediated elimination of HIV-1-infected cells by antibodies present in breast milk and cervico-vaginal lavages of HIV-1-infected women. Finally, we identified one CD4mc with the capacity to sensitize endogenously-infected ex-vivo-amplified primary CD4 T cells to ADCC killing mediated by autologous sera and effector cells.

Conclusions: By pushing Env into the CD4-bound conformation, CD4mc might represent an alternative and/or complementary approach to currently-available drugs for preventing viral transmission and might represent a new strategy aimed at eradicating the viral reservoir.