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Session: **BS3**: Saturday May 2 – 15:00:17:00 – Cure, Vaccines and immunology

Track:	Basic Sciences
Subject:	Eradication Strategies Towards an HIV Cure
Presentation Type:	Oral
Title of Abstract:	**Productively-infected CD4 T cells are resistant to non-neutralizing antibodies**
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Abstract

The conformation of the HIV-1 envelope glycoprotein (Env) substantially impacts antibody recognition and ADCC responses. In its unliganded form, the Env samples a closed conformation that is preferentially recognized by broadly-neutralizing antibodies (bNAbs). CD4 engagement drives Env into the “open” CD4-bound conformation, preferentially targeted by non-neutralizing Abs (nnAbs). The virus prevents exposure of CD4-induced epitopes by downregulating CD4 via Nef and Vpu. Despite significant advances on the understanding of HIV resistance to ADCC, the capacity of nnAbs to mediate ADCC against productively-infected cells remain controversial. Here, we used multiparametric flow cytometry and RNA-flow fluorescent in situ hybridization (FISH) techniques to characterize cell populations targeted by bNAbs and/or nnAbs in the context of HIV-1-infected primary CD4+ T cells. Productively-infected cells are recognized by bNAbs, efficiently downregulate CD4, express high levels of Nef and p24 proteins and are enriched in HIV-1 mRNA ($CD4^{-}p24^{+}Nef^{+}$HIV $mRNA^{+}$). In contrast, cells targeted by nnAbs are CD4-positive, express little or no p24 and are negative for Nef expression and HIV-1 mRNA ($CD4^{+}p24^{-}/p24^{LOW}$Nef-HIV $mRNA^{-}$). Moreover, cells recognized by nnAbs are Env mRNA negative, suggesting that they represent cells coated with either shed Env and/or non-infectious viral particles. As expected, we observed that CD4 downregulation precedes the expression of HIV-1 late transcripts. Thus, confirming that the $CD4^{+}p24^{LOW}Nef^{-}$HIV $mRNA^{-}$ cells targeted by nnAbs are not part of the viral replication cycle. Finally, we found that *ex vivo* expanded CD4+ T cells isolated from HIV-1-infected individuals are sensitive to ADCC mediated by bNAbs but resistant to those mediated by nnAbs. This information is important for the development of immunotherapy-based strategies aimed at targeting and eliminating productively-infected cells.