OA1-5 LB

Teaching new dogs new tricks: An *in vitro* model of autologous HIV-1 immunotherapy induces CTL from naïve precursors in subjects on ART

K. Smith[1], R. Mailliard[2], W. Jiang[2], J. Mullins[3], C. Rinaldo[2]
[1]*University of Pittsburgh School of Medicine, Microbiology and Molecular Genetics, Pittsburgh, United States,* [2]*University of Pittsburgh Graduate School of Public Health, Infectious Diseases and Microbiology, Pittsburgh, United States,* [3]*University of Washington School of Medicine, Microbiology, Seattle, United States*

Background: A recent surge in HIV-1 research has focused on developing immunotherapies to eradicate the autologous viral reservoir via cytotoxic T lymphocyte (CTL)-mediated immune responses. To clear infection, new CTL must be primed from naïve precursors, as pre-existing effector memory T cells fail to control viral replication during ART interruption. We have therefore established an *in vitro* model of dendritic cell (DC) immunotherapy for defining efficient priming of naïve $CD8^+$ T cells during ART with engineered DC expressing antigens specific for the autologous HIV-1 reservoir.

Methods: We isolated highly pure populations of naïve and memory $CD4^+$ and $CD8^+$ T cells from HIV-1 infected subjects on ART or from these same subjects prior to HIV-1 seroconversion in the Multicenter AIDS Cohort Study. T cells were stimulated with autologous DC loaded with inactivated HIV-1 derived from the autologous ART reservoir to induce primary $CD8^+$ T cell responses from naïve precursors, or to "re-condition" memory populations. IFN-gamma ELISpot and viral suppression assays were used to evaluate primary CTL effector function against autologous viral antigen.

Results: Mature, type I polarizing DC derived from HIV-1 infected subjects on ART induced primary CTL that suppressed viral replication and survival of autologous virus-infected $CD4^+$ T cells. These primary CTL were specific for the autologous Gag proteome and specifically enhanced the breadth of responses to p17 compared to those found in memory populations. Primary responses during ART did not differ from those induced pre-seroconversion.

Conclusion: We show for the first time that naïve T cells from HIV-1 infected subjects on ART can respond to primary *in vitro* DC vaccination against the autologous virus reservoir and are capable of suppressing viral replication. Thus, chronic, untreated HIV-1 infection did not irreparably impair priming of CTL to autologous virus. These data support the use of DC immunotherapies targeting the autologous reservoir in HIV-1 infected subjects on ART.