[1]Emory University, Yerkes National Primate Research Center, Atlanta, GA, United States, [2]Emory University, Department of Pathology, Atlanta, GA, United States

Background: The germinal center (GC) resident T follicular helper cells (Tfh) represent a significant fraction of total pool of HIV/SIV infected cells during chronic infection and HAART. The GC are generally thought to exclude CD8 T cells and anti-viral CD8 T cells with potential to migrate to GC (follicular CD8) may enhance HIV/SIV control and reduce viral reservoirs. Here we studied the follicular CD8 in a cohort of DNA/MVA vaccinated rhesus macaques (RM) that controlled or did not control a pathogenic SIV infection.
Methods: RM were vaccinated with a DNA/MVA SIV vaccine and challenged intrarectally with SIVmac251. Animals with viral load below 1,000 copies at set point were defined as controllers. All controller RM (n = 19) were vaccinated and non-controller RM (n = 18) consisted of both vaccinated and unvaccinated.
Results: Post challenge, we observed an aberrant enrichment of SIV+ PD-1^{hi} CD4 T cells in the LN and rectum of non-controllers but not controllers. The enhanced viral control was associated with higher frequency of Gag CM9 Tet+ CD8 T cells in the LN of controller RM compared to non-controller RM. This was not evident in blood. Interestingly, a significant fraction of anti-viral CD8 T cells in the controller RM co-expressed CXCR5 (required for homing to B cell follicles/GC). The frequency of Tet+ CXCR5+ granzyme B+ cells was also higher in the LN of controller RM and higher frequencies correlated with lower Tfh and enhanced viral control. Immunofluorescence staining revealed co-localization of CD8 T cells with PD-1^{bright} cells in IgD- GC, a phenomena not observed in the non-controller RM. Impressively, the CXCR5+ CD8 T cells from the controller RM restricted the anti-CD3 driven expansion of CM9 peptide pulsed Tfh cells in vitro suggesting their killing potential.
Conclusions: Our results reveal a novel subset of anti-viral CD8 T cells that may contribute to enhanced control of pathogenic SIV infection by infiltrating to GC of lymphoid sites and limiting SIV replication in Tfh in a vaccine setting.

OA29.06
A Novel T-cell Vaccine Eliciting T-cell Specificities Associated with Control of HIV-1 In Humans Is Highly Immunogenic in Mice and Macaques

Beatriz Mothe[1,2], Xintao Hu[3], Anuska Llano[1], Margherita Rosati[3], Alex Olvera[1], Viraj Kulkarni[3], Antonio Valentin[3], Candido Alicea[3], Niranjan J. Sardesai[4], Muntsa Rocafort[1], Manel Crespo[5], Jorge Carrillo[1], Andrés Marco[6], James I. Mullins[7], Lucy Dorrell[8], Tomáš Hanke[9], Bonaventura Clotet[1,2,10], George N. Pavlakis[3], Barbara K. Felber[3], Christian Brander[1,2,11]

[1]IrsiCaixa AIDS Research Institute-HIVACAT, Hospital Germans Trias i Pujol, Badalona, Spain, [2]Universitat de Vic – Universitat Central de Catalunya, Vic, Spain, [3]Human Retrovirus Section-National Cancer Institute, Frederick, MD, United States, [4]Inovio Pharmaceuticals, Inc., Blue Bell, PA, United States, [5]HIV Unit, Hospital de la Vall d'Hebrón, Barcelona, Spain, [6]Centres Penitenciaris BCN, Barcelona, Spain, [7]University of Washington, Seattle, WA, United States, [8]MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, University of Oxford, The John Radcliffe, Oxford, United Kingdom, [9]Jenner Institute, University of Oxford, Oxford, United Kingdom, [10]Universitat Autònoma de Barcelona, Barcelona, Spain, [11]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Background: A top-down strategy was used to search for beneficial viral targets in large human immunogenicity data and to identify potential decoy targets that should be avoided in future vaccine designs.
Methods: Through the identification of beneficial T cell responses in more than 1000 individuals, the HIVACAT T-cell immunogen (HTI) was designed to contain 16 HIV-1 protein segments of 10-70 amino acids in length, covering > 50 optimal defined CD4$^+$ and CD8$^+$ T-cell epitopes with > 40 different HLA restrictions, without overrepresentation of B27/B57/B58 restricted epitopes. Heterologous prime-boost regimens combining DNA (D) and MVA (M) expressing HTI were assessed in C57BL/6 mice and four Indian rhesus macaques. Cellular responses were characterized using IFN-γ ELISPOT and intracellular cytokine assays.
Results: In C57BL/6 mice, DNA.HTI induced broad CD4$^+$ and CD8$^+$ T-cell responses to all segments within Gag, Pol, Vif and Nef. These responses were strongly increased by using heterologous regimens consisting of 3x DNA.HTI prime followed by MVA.HTI boost compared to 3 or 4x DNA.HTI only (median magnitude DDDM of 3,051 vs 1,401 and 1,353 SFC/10^6 splenocytes in DDD and DDDD groups respectively, p = 0.0087). In rhesus macaques, DDD (administered IM in combination with macaque IL-12 DNA as molecular adjuvant using *in vivo* electroporation) induced 0.4-1.5 % of specific T cells that persisted over a period of 4.5 months. MVA.HTI boosted the responses by 3- to 20-fold, reaching 0.4-3.2 % IFN-γ T-cells. DDDM induced central and effector memory responses with a significant fraction of the vaccine induced IFN-γ^+CD8$^+$ T cell being either CD107a$^+$ or GzmB$^+$.
Conclusions: HTI delivered in a DDDM regimen was highly immunogenic in mice and macaques. The responses were CD8$^+$ and CD4$^+$ effector T cells with cytotoxic potential as well as CD4$^+$ central memory T cells indicating long-term immunological persistence. These data justify further testing of the HTI approach in human clinical trials.

Antibody Functions and Protection

OA30.01
Synthetic Nucleic Acid Antibody Prophylaxis with Electroporation Drives Biologically Relevant Anti-HIV-1 Envelope Responses *In Vivo*

Kar Muthumani[1], Seleeke Flingai[1], Megan Wise[1], Colleen Tingey[1], Kenneth E. Ugen[2], Niranjan Y. Sardesai[3], Joseph J. Kim[3], David B. Weiner[1]

[1]University of Pennsylvania School of Medicine, Pathology and Lab. Medicine, Philadelphia, PA, United States, [2]University of South Florida Morsani College of Medicine, Department of Molecular Medicine, Tampa, FL, United States, [3]Inovio Pharmaceuticals, Inc., Blue Bell, PA, United States

Background: Monoclonal Ab's have demonstrated therapeutic utility against several malignancies and infectious diseases. A drawback of this strategy is the time-consuming and expensive process requiring purification and scale up production of the Ab's for clinical use. A method to produce antibodies *in vivo* would be significant improvement for this platform. It would be