ImmunoTools *special* Award 2014

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Specificity, functionality and phenotype of the HIV-specific T-cell response during acute/early infection and its association with disease progression.

Human Immunodeficiency Virus (HIV) still represents a major public health concern. Although the instauration of Highly Active Antiretroviral Treatment (HAART) had a tremendous impact on the epidemic dynamics, the development of an effective prophylactic vaccine is still a main objective in the HIV-related research field. As HIV is highly diverse among different isolates, it evolves continuously under selective pressure, infects immune cells, and encodes proteins with the capacity to modulate immune cell functions, it imposes definite challenges that should be overcome in the race of getting a successful vaccine. However, the description of i) infected subjects able to control HIV replication over long periods of time to very low levels without therapy (known as Long Term Non Progressors -LTNP- and Elite Controllers -EC-), ii) uninfected subjects who, despite being highly exposed to the virus, remain seronegative (exposed seronegatives, ESN), and iii) the results from the Thai vaccine trial RV-144, which showed 30% efficacy, suggests that the objective is reachable. In this line, much of the research work conducted over the past few years was aimed to define the immune correlates of protection, i.e. desirable characteristics that the vaccine-elicited immune response should have in order to contain viral challenge. Special emphasis has been focused on the HIV-specific $CD8^+$ cytotoxic T lymphocytes (CTLs) which are thought to play a key role in reducing viral replication. Within this field, the identification of phenotypic and functional properties of the $CD8^+$ T-cell subsets associated with viral control is urgently needed to aid in the design and performance evaluation of an effective HIV vaccine.

In this project, we seek to analyze multiple aspects of the HIV-specific $CD8^+$ T-cell compartment (specificity, ex vivo viral inhibitory capacity, polyfunctionality and phenotype) arising early after infection in a cohort of acute/early HIV-infected subjects, in comparison with the response found in viremic chronics and elite controllers, with the aim to delineate

$CD8^+$ T-cell features that best associate with disease control and that would contribute to rational vaccine design. To accomplish with this aim, we will obtain blood samples from: 20 healthy HIV-seronegative donors (HD) and 80 HIV infected patients of whom: 50 will be enrolled during acute/early primary HIV infection (PHI), 15 will be chronically infected patients (Chronics) and 15 were Elite Controllers (EC). Plasma viral load and $CD4^+$ T-cell count will be determined. Specificity will be determined by IFN-γ enzyme-linked immunospot (ELISPOT) assays. Production of cytokines and degranulation of HIV-specific cells will be measured upon stimulation with specific peptides and subsequent intracellular and surface staining followed by flow cytometry analysis. Additionally, ex vivo $CD8^+$ T-cell capacity to inhibit viral replication in primary autologous $CD4^+$ T-cells will be determined. Finally, T-cell phenotypic (CCR7, CD45RO, CD38, HLA-DR) and functional (PD-1) markers will be measured to characterize total and HIV-specific $CD8^+$ T-cell memory populations by flow cytometry.