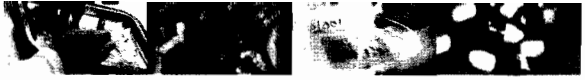

Keynote Lecture X

HIV, Dendritic Cells and Lymphocytes: Attack and Counterattack

Olivier Schwartz
Institut Pasteur, Paris, France

After graduating in Pharmacy and in Biological Sciences at Paris University, Olivier Schwartz obtained a PhD in 1993 at the Institut Pasteur. He then obtained a staff scientist permanent position at the same Institut in 1995. He has been director of the "Virus and Immunity Group" at the Institut Pasteur since 2002.

His main research contributions have been in the understanding of the virological and immunological interactions between HIV and its target cells. His group was the first to show that HIV is equipped with a protein, called Nef, whose task is to down-regulate surface expression of MHC-I molecules in infected cells, thus protecting infected cells against rapid recognition and killing by cytotoxic T lymphocytes (CTLs). He has also been studying other activities of Nef, and different aspects of the cellular and molecular mechanisms which regulate the infectivity of various viruses. More recently, his group described how the movement of endogenous retroviruses within the mammalian genome is controlled by important cellular proteins.

Dendritic cells (DCs) are key antigen-presenting cells for the induction of a specific immunity against pathogens such as HIV-1. DCs are also subverted by HIV-1, being infected by the virus at low levels and promoting viral spread to permissive lymphocytes. It is thus of interest to precisely understand the pathways of HIV capture, degradation, antigen processing and MHC presentation by DCs. A state-of-the-art of the literature will be presented, as well as some original results obtained in our laboratory. We have deciphered the cellular and molecular mechanisms involved in MHC-I antigen presentation by DCs, leading to CD8+ T cell activation. More recently, we have investigated how HIV antigens are presented by MHC-II molecules. To this end, we have generated several HIV-specific CD4+ T cell clones, by in-vitro priming of naive T cells. Upon contact with autologous monocyte-derived DCs, pulsed with HIV Gag peptides or exposed to HIV virions, these T cell clones are activated, produce cytokines and proliferate. With this relevant model, we show that in DCs, various entry pathways, including a DC-SIGN-mediated pathway of viral capture, lead to MHC-II antigen presentation. Viral antigens are processed in a lysosomal compartment, independently of viral and cellular membrane fusion. The differences between MHC-I and MHC-II processing pathways in DCs will be highlighted, illustrating the multiple destinies of incoming virions in DCs. Furthermore, these CD4 T cell clones provide a useful tool to study the links between HIV antigen presentation and preferential viral transfer to HIV-specific CD4+ T cells.