HAART
HIV correlated pathologies and other infections

Giuseppe Pantaleo - MD
Director of the Swiss Vaccine Research Institute – Lausanne
Chief of the Laboratory of AIDS Immunopathogenesis at the Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne

Giuseppe Pantaleo, M.D., Professor of medicine, is Chief of the Division of Immunology and Allergy. He is also Chief of the Laboratory of AIDS Immunopathogenesis at the Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Switzerland. During the past fifteen years, Professor Pantaleo's research has been focused on the delineation of the immunopathogenesis of HIV infection and of other viral infections such as cytomegalovirus and hepatitis C virus. His research activities have been focused on human T cell cloning, human T cell phenotypic and functional analysis, T cell activation, differentiation and memory, immunopathogenesis of HIV infection, HIV distribution in different anatomic compartments, antiretroviral therapy, immune reconstitution after antiretroviral therapy, immune-based therapeutic strategies and vaccines. Since 2007, Professor Pantaleo is the Director of the Swiss Vaccine Research Institute located in Lausanne.

Interview by
Stefano Rusconi
Ospedale Luigi Sacco– Milano

Prof. Giuseppe Pantaleo
ICAR: Italian Conference on Aids and Retrovirus- TORINO
May 12-14, 2013

Stefano Rusconi:
Is immunological control of HIV infection possible?

Prof. Pantaleo:
A small percentage (<1%) of chronically HIV infected individuals are able to control spontaneously virus replication for an undetermined period of time. Genetic factors such as certain HLA class I type B (HLA-B57 and HLA-B 27) and the polymorphism of the CCR5 HIV co-receptor are mostly associated with virus control. However, recent data also suggest that early initiation of treatment during primary HIV infection may be also associated with effective control of virus replication in a minor (<5) percentage of individuals despite the lack of association with any of the previously described genetic factors. These observations support the possibility that the host immune system can efficiently control the infection under certain conditions. It is highly likely that these conditions are associated with effective containment of the total virus load at the time of the establishment of HIV infection thus providing the possibility to the host immune response to limit virus replication and prevent the different mechanisms that HIV develops to escape from the immune response. The immune mechanisms of virus control are based on the development of cellular immunity, i.e. T-cell responses, while there is no evidence that antibodies play any role in the control of established chronic infection. In conclusion, immunological control of HIV infection is possible although to achieve immune control the balance between the virus and the immune system must tilt in favor of the immune system. This can be potentially achieved developing therapeutic strategies that substantially lower the residual virus reservoir, which does not seem to be affected by prolonged conventional antiretroviral therapy, and boost host HIV-specific T-cell immunity.

Stefano Rusconi:
AntiHIV vaccines: is this work in progress or a dead-end?

Prof. Pantaleo:
As the 30th anniversary of the discovery of HIV has come and gone, HIV remains a catastrophic public health concern with an estimated global prevalence of 34 million HIV-infected persons. Despite the remarkable advances in the development of several biomedical interventions for the prevention of HIV, the importance of developing an effective HIV vaccine has been recognized by a wide spectrum of the scientific community and civil society. Important milestones for the HIV vaccine field were the demonstration that a vaccine regimen could reduce HIV acquisition, and the identification of binding IgG envelope (env) antibodies as potential correlates of protection from HIV acquisition. However, broad neutralizing antibodies (bNAbs) are thought to be the main mechanism of protection of the currently available effective vaccines against a variety of pathogens. There are still major scientific gaps in understanding the generation of env bNAbs. Unfortunately, HIV vaccine candidates inducing potent T-cell responses have failed to show any protection of preventing acquisition from HIV infection and controlling HIV load in vaccinated volunteers who became infected with HIV. The primary goals are to improve the current vaccine regimens in the hope of improving efficacy from 30% with the vaccine combination, which has shown modest efficacy, to at least 50-60%. Although this level of efficacy may not be ideal for the developed world, it would substantially curtail the epidemic in the developing world. Major advances have been achieved in identifying vulnerable targets in the HIV env for bNAbs. However, it is still unclear how to stimulate the generation of bNAbs from the host immune system. In conclusion, although there is a certain degree of optimism regarding the possibility of improving the efficacy of the current vaccine regimens, whether it will be possible to induce the generation of bNAbs with a vaccine remains unclear.

Stefano Rusconi:
Are there new immunological targets for antiHIV therapy?

Prof. Pantaleo:
Therapeutic approaches have concentrated on targeting the HIV latent cell reservoir, i.e. a population of central memory CD4 T-cells. The overall challenges of this approach include: a) more than 80% of latently infected blood memory CD4 T-cells contain replication defective HIV, b) extremely low frequency of blood memory CD4 T-cells containing replication competent virus after prolonged antiretroviral therapy, c) methods to quantify the HIV latent reservoir (isolation of replication competent virus) require large numbers of purified memory CD4 T-cells (several hundred million cells), a long-time (2-3 weeks) and large resources. These methods are not feasible for clinical development programs. Their sensitivity is questionable and probably not able to measure moderate quantitative changes in the latent reservoir. We have identified two populations of memory CD4 T-cells residing almost exclusively in lymphoid tissues, which are the major reservoir for HIV infection, replication and production. These memory CD4 T-cell populations are defined by a unique surface phenotype:

a) CD4+PD-1+CXCR5+ (T follicular helper cells)

b) CD4+PD-1+CXCR5-

These cell populations are also enriched in HIV-specific CD4 T-cells.
Two therapeutic approaches were tested in the past and are currently being developed: a) therapeutic vaccination and b) reactivation of the latent reservoir. Therapeutic vaccines have shown limited/no efficacy. Possible explanations for the lack of efficacy include: a) limited immunogenicity in potentiat-

ing CD8 T-cell responses, b) single administration of the vaccine candidates or homologous prime/boost regimens, and c) poor study design with inadequate statistical power.

The second approach to purge the reservoir currently being tested involves the reactivation of the HIV latent reservoir. Reactivation of the latent reservoir through HDAC inhibitors may lead to: a) killing infected CD4 T-cells after virus reactivation by HIV-specific CD8 T-cells and b) killing infected CD4 T-cells as a result of direct virus cytopathicity. In light of the recent identification of the cell populations residing exclusively in the lymphoid tissues mostly responsible for HIV replication and production, it will be important to develop strategies targeting these cell populations directly. This can be achieved with the use of antibodies whose effector activity targets surface markers expressed at the cell surface.