

**AIDS 2002
BARCELONA
XIV International AIDS conference**

**Highlights
By Kendall A. Smith**

**Sunday, July 7th-
Satellite Symposium:
Therapeutic Vaccination for
HIV Infection**

Dr. Brigitte Autran, Hopital Pitie Salpetriere, presented data from a phase I non-randomized therapeutic vaccine trial where 50 subjects received 4 intramuscular doses of ALVAC canarypox vCP1433 HIV vaccine, which contains the HIV genes from *gag* & *env*, as well as selected sequences of *nef* & *pol*. After 12 weeks of vaccination, antiviral agents were discontinued at week 16, and 4 weeks later, antivirals were re-started if the plasma HIV concentration exceeded 50,000 mol/mL in the 1st 8 weeks, or if it exceeded 10,000 mol/mL after the 1st 8 weeks. **Results:** All subjects had a relapse of viremia after the discontinuation of their antiviral therapy, with a peak plasma HIV concentration of 120,000 mol/mL. 38/48 (79%) subjects had to restart antivirals, while 10 subjects remain off of antivirals with plasma HIV concentrations < 10,000 mol/mL, and 4 of these 10 subjects have HIV concentrations < 5,000 mol/mL. These results are similar to the data reported by the Swiss/Spanish group, which discontinued therapy in more than 100 subjects after a year of antivirals and intermittent 2-week therapy interruptions. Dr. Autran concluded that there are various issues regarding therapeutic immunization such as type of

vaccine, dose, route and frequency of administration that must be worked out with immunologic endpoints before larger scale trials are undertaken.

**Wednesday, July 10, 2002-
Symposium: Immune Response
to HIV**

Bruce Walker- “Harnessing the immune system to fight HIV infection” Dr. Walker, Massachusetts General Hospital, related data from one subject who was followed closely after early diagnosis and antiviral treatment, who underwent a treatment interruption. Initially, the individual maintained good control over viral replication, sustaining low plasma HIV concentrations over several months without antiviral therapy. A detailed analysis of CD8+ T cell responsiveness to HIV peptides, assayed by interferon- γ (IFN- γ) ELISPOT in response to HIV peptide matrices revealed strong and broad immune reactivity. While off antiviral therapy the individual practiced unsafe sex. Subsequently, the plasma HIV concentration increased dramatically, such that the previous good control over HIV replication appeared to have been lost. Analysis of the viral genome sequences of viruses isolated from the individual before and after the rise in viremia revealed that there was a substantial difference in genomic sequences, and furthermore that there was only ~ 50% of the breadth and depth

of immune recognition of the new virus, compared with the original viral isolates. Walker hesitated to conclude too much from this case, in that the observations were derived from only one individual. However, the implications are obvious: if there is not substantial cross reactivity between individual viral isolates, it may be difficult to develop a vaccine protective of all HIV clades & strains.

In light of this information, it is important to note what the data are actually telling us. They support the notion we already have had, i.e. that the quantity and quality of the immune response are both important for the efficacy of the immune system in combating a viral infection. Thus, the immune recognition of the original virus infection was found to be broad and the immune response could be detected to be functional, at least in terms of the capacity to produce IFN- α . However, the amount of cross reactivity between the first and second virus infection was not great enough to prevent infection by the second virus. In considering ways to counteract this relative deficiency, it will be important to augment both the quantity and quality of immune recognition and responsiveness, both in the therapeutic as well as the prophylactic setting.

Richard Koup-“HIV infection of naï ve vs. memory CD4+ T cells” To account for the apparent lack of proliferative responses of CD4+ T cells from subjects infected chronically with HIV, it has been proposed by Walker and Erickson that HIV-specific T cells have been preferentially infected and deleted compared with T cells that have not been recently activated by their specific antigen. Moreover, it has been proposed

that memory T cells are more susceptible to HIV infection than naï ve T cells, and there have been several reports supporting this hypothesis. Koup’s group at the Vaccine Research Center at the NIH examined this notion using flow cytometry to identify and analyze naï ve and memory T cells when exposed to HIV. They found, paradoxically, that naï ve CD4+ T cells were more susceptible to infection than memory T cells. By using new fluorescent molecules to monitor cell division, and monoclonal antibodies reactive with IFN- α , they found that memory T cells produced detectable IFN- α rapidly after activation by HIV antigens, while naï ve T cells did not. Instead, naï ve CD4+ T cells underwent several cellular divisions before IFN- α production was detectable. Since IFN- α is one of the major anti-viral cytokines responsible for inhibiting HIV infection, Koup and his co-workers suggest that memory CD4+ T cells are protected from infection by their differentiated state.

These considerations do not take into account the fact that during an infection that memory T cells should be able to produce enough IFN- α to protect themselves as well as neighboring naï ve cells. Moreover they do not take into consideration other cytokines and chemokines that may play a role in susceptibility vs. resistance to HIV infection. However, they do support the overall notion that cytokines such as IFN- α are important in determining the outcome of HIV infection, as has been shown in most other viral infections.

**Wednesday, July 10th-
Symposium: New Hope for an
AIDS Vaccine**

Emilio Emini-An HIV-1 vaccine using a replication-defective adenoviral vector

Emini, from the Merck Corporation related the work in progress at their company to develop prophylactic and therapeutic vaccines. Most of the data discussed were already presented at the 9th Conference on Retroviruses and Opportunistic Infections in February. Also, most of the data presented were from studies of SHIV in monkeys (Rhesus macaques). Merck has developed two vectors to immunize with gene products from HIV-1, a “naked DNA” vector and an attenuated (i.e. crippled) adenovirus vector. In both instances, they have inserted only the genes that encode the structural proteins of the virus, termed *gag*. They have found that when given alone, both vaccines are relatively poorly immunogenic, when tested by their capacity to elicit blood lymphocytes to secrete interferon-gamma (IFN- γ) after a short-term activation. The frequency of HIV-specific lymphocytes is < 1 cell/ μ L of blood. However, if the DNA vaccine is given 1st, followed by a “boost” with the adenovirus vaccine, there is a synergistic augmentation of the number of lymphocytes capable of responding to *gag* peptides by secreting IFN- γ . In this regard, it is important to emphasize that all of the vaccines now being tested, including the canarypox ALVAC vaccine that we are testing, have been rendered safe to inject in HIV+ individuals by attenuating their capacity to undergo replication (duplication). This is important so that the vaccine virus does not itself cause disease. However, all of the effective childhood vaccines for viruses such as poliovirus, measles virus, mumps virus etc. are capable of replicating and thereby they stimulate a strong immune response.

Merck is testing these vaccines in phase I toxicity trials now in both HIV-negative and positive volunteers. Their plans are to introduce additional HIV genes into these vectors, and to compare their efficacy with the *gag* vaccines that they now have.