Conference report: "30 years of HIV science. Imagine the future"

REPORT

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ABSTRACT

This report present major topics and debates of the symposium "30 years of HIV science. Imagine the future". It was organized by the Pasteur Institute, the U.S. National Institutes of Health, Agence Nationale de Recherche sur le Sida (ANRS) and SIDACTION in celebration of the 30th years since the identification of the human immunodeficiency virus (HIV) as causative agent of the acquired immunodeficiency syndrome (AIDS). Held in Paris, France, it was sponsored by the Pasteur Institute in Paris on May 21-23, 2013. The novel results presented and fruitful discussions at the meeting provided a glance on the goals for HIV research in the near future.

Keywords: human immunodeficiency virus, antiretroviral therapy, vaccine candidate, viral reservoir, cellular immunity, humoral immunity

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RESUMEN

Reporte de congreso: "30 años de ciencia sobre el VIH. Imaginando el futuro". Se describen los temas y debates fundamentales del simposio "30 años de ciencia sobre el VIH. Imaginando el futuro", organizado por el Instituto Pasteur, los institutos nacionales de salud de los Estados Unidos de América, la Agencia Nacional para la Investigación sobre el Sida (ANRS) y SIDACTION, en celebración del tiempo en que se identificó el virus de inmunodeficiencia humana (VIH) como agente causal del síndrome de inmunodeficiencia adquirida. Se celebró en París, del 21 al 23 de mayo de 2013, con el auspicio del propio Instituto Pasteur. Los novedosos resultados presentados y las provechosas discusiones proporcionaron una panorámica que favorecerá los objetivos de las investigaciones en un futuro cercano.

Palabras clave: virus de la inmunodeficiencia humana, terapia antirretroviral, candidato vacunal, reservorio viral, inmunidad celular, inmunidad humoral

*I*ntroduction

The symposium "30 years of HIV science. Imagine the future" was organized by the Pasteur Institute, the U.S. National Institutes of Health, ANRS and SIDACTION in celebration of the 30th years since the identification of the human immunodeficiency virus (HIV) as causative agent of the acquired immunodeficiency syndrome (AIDS). It was hosted by the Pasteur Institute in Paris, France and took place on May 21-23, 2013 [1]. This conference became an environment for the exchange of ideas where the current progress in the field was reviewed focusing on critical challenges and research priorities to achieve the control or even the cure of HIV infection in the future. In this paper the most interesting presentations are compiled (at the discretion of the author).

*T*he key lecture

The key lecture "The science of HIV/AIDS: much accomplished, much to do" was delivered by Dr. Anthony Fauci (NIAID/NIH, Bethesda, USA). He stated his belief that today we had the right to think in the eradication of the HIV pandemic, and that a few years ago he could not dare to make such an assertion. He recalled that the FDA has approved more than 30 antiretroviral drugs that have changed the lives of many people. However, only 46 % of HIV+ adults and 72 % children have access to antiretroviral therapy (ART). He stated that if all people living with HIV/AIDS are treated, the possibility to pass on the infection decreases greatly, considering that about half of the infections are caused by seropositive persons who did not take antiretroviral therapy. Therefore, he recommended that all HIV+ people were under treatment as soon as possible, i.e., immediately after diagnosed. He also believes in the importance of the pre-exposure prophylaxis (PrEP). He showed results from clinical trials in South Africa and Gambia, where there are high incidence of HIV infection and the use of PrEP, though with different degrees of coverage. There is still a significant decrease in the diagnosis of new seropositive persons which would indicate (in his view) that a significant number of people were protected from infection. Then, Dr. Fauci was a little further talking about the cure of HIV infection. In this regard, he considered three scenarios: 1) the eradication of the virus; 2) functional cure; and 3) the elite controllers. On eradication, he said that only an autopsy would provide a confirmation because in a living patient there would be always some tissues to test for HIV infection and doubts still remain. In his opinion, we have to be very careful when speaking of the viral reservoirs because it is a topic that is not yet well defined and there are some gaps on their location. On the functional cure, he spoke about the result obtained in France with the Visconti cohort, where a small number of HIV+ patients was treated reaching a functional cure. They would be classified as post-treatment virological controllers. He also talk about the case of the Mississippi patient and said that, as she was treated 30 h after birth, it might be considered a case of PrEP

1. 30 years of HIV science. Imagine the future. Paris: Institut Pasteur Events department. c2013 [cited 2013 Nov 30]. Available from: http://www.30yearshiv.org/

rather than a cure with virus removal. He concluded by saying that the eradication of HIV is possible. To achieve this goal, antiretroviral treatment should be provided to all HIV+ persons as soon as possible, and more powerful antiretroviral regimens and different ways to activate latent cells have to be developed in order to eliminate the viral reservoirs.

Conference sessions

Session 1. Interactions at molecular levels: Viral strategies of replication and host restriction mechanisms

Because many interesting works were presented, two sessions for presentations were arranged. In the plenary session 1A, Dr. Michael Malim (Dept. of Infectious Disease, King's College London, London, United Kingdom) talked about "Innate mechanisms of HIV-1 restriction and their viral countermeasures". He did an account of all innate mechanisms that reduce viral replication of HIV-1 within the cell. He referred in particular to a greater extension to TRIM5α that senses the formation of the viral capsid by inducing the cascade of type I interferons (IFNs). He explained that the IFN-α promotes an antiviral effect that reduces the viral load (VL) and inhibits infection of macrophages and CD4+ T-lymphocytes. Using genomics, they studied the cascade of IFN-α identifying a group of genes that may have antiviral effect, the MX2 gene for example is one which expression inhibits HIV-1 infection. The inhibitory effect of IFN-α is no longer observed when the expression of this gene is silenced. The MX2 gene is present in the human and mice genomes and belongs to the GTPase family of proteins that are induced by IFN-α. This gene has a 63 % homology with the MX1 gene and they dimers that interfere with viral replication, as well as inhibits the entry and integration of the viral cDNA. MX2 also inhibits other primate lentiviruses. At the end, some participants asked him some questions and one of them referred to the possible function of the gene MX2. Dr. Malim replied that the function of this gene is not well known. But, the important thing was that if you inhibit the cascade of IFN-α in the simian immunodeficiency virus (SIV) model, there is an increase in the VL. He also answered to another question that the MX2 gene is only expressed at high levels in the presence of IFN-α.

The session also included the lecture "From HIV inhibition to HIV escape: CCR5 conformations are differentially exploited by chemokines and R5 HIV-1" by Dr. Bernard Lagane (Institut Pasteur, Paris). He began exposing the paradoxical observation of low inhibition of viral infectivity in the presence of chemokines with high affinity for the CCR5 receptor. Then, he hypothesized that CCR5 has different conformations to which the chemokines and the virus bind differentially. He explained that CCR5 has different conformations that interact differently with a number of chemokines. On the basis of his results, there are conformations of CCR5 that show more affinity for gp120 than to chemokines. This might explain the limited inhibitory capacity of the chemokines. Chemokines that recognize a given conformation with the higher affinity will show a greater inhibitory effect. In his model, CCR5 only has two conformations: one when it is coupled to an intracellular G-protein and another when it is free. At the end of the conference someone asked him whether he think that the two conformations of CCR5 must be in dynamic equilibrium or not. He agreed and speculated that such equilibrium might depend on the activation state of the cell and there must be usually a higher percent of free CCR5 and that conformation enables the viral entry.

In the session 1B, Dr. Carine Van Lint (Université Libre de Bruxelles, Brussels, Belgium) delivered a talk on "Molecular mechanisms of HIV-1 post-integration latency". She showed some results identifying a group of human proteins forming a complex that interacts with the chromatin and promotes viral latency. In this regard, she proposed to develop therapeutic inhibitors targeting these proteins to stimulate the viral replication in reservoirs. In another presentation, Dr. Nevan J. Krogan (University of California, San Francisco, United States) in his lecture "Using systems approaches to study HIV biology" explained that they are carrying out experiments in Jurkat cells transformed to express some HIV-1 proteins. Then, the interactions of these viral proteins with the human proteins are studied. Later, they plan to purify up to hundreds of human proteins to identify and study in detail such interactions. As an example, he showed the case of Tat protein. Tat interacts with two of those isolated human proteins and he proposed to seek drugs to inhibit that interactions. Also, he explained that Vif interacts with three proteins in a complex that will be crystallized soon, to determine its structure, and they hope to develop inhibitors to this complex. In general, he said there are 415 human genes that are under the influence of HIV-1 proteins. They have sequenced such genes in a number of people living with HIV/AIDS and in people who show true viral control, trying to find any genomic imprint that would show some correlation with greater susceptibility or resistance to the virus. They are also studying the disturbances in cellular mechanisms of post-transcriptional modifications caused by HIV-1 infection. There are evidences that accessory proteins of the virus affect the function of the proteasome. For example, they are studying the hiper-ubiquitination of human proteins caused by Vif.

Session 2. Interactions at tissue & systemic levels: Viral strategies of infection and host responses

This session was also split due to the high number of presentations. In the session 2A, Dr. Persephone Borrow (Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom) in her lecture "Innate immune responses in acute HIV-1 infection: protective or pathogenic?" explained that natural killer (NK) cells are very important to control viral replication early after infection. Because the innate response is efficient on controlling viral replication, escape mutants resistant to type I IFNs (IFN-α) are selected and she showed viral sequences from different patients. She was asked whether the IFN-β is also important or not. She said that it is also important.

Later on, Dr. Eric Hunter (Emory Vaccine Center, Atlanta, USA) delivered his lecture "The replicative

capacity of transmitted HIV-1 contributes significantly to CD4 decline independent of VL and host contributions". He showed results obtained in discordant couples, where the viruses with low replicative capacity that maintain a viral load less than 1000 copies of viral RNA never cause a drop in CD4+ T-cells counts below 350 cells/microliter. He speculated that this might be generalized to any viral isolate independently of the subtype. He also explained that if there is viral transmission in a couple that shares its HLA haplotype, then the virus will show greater adaptability and the progression to AIDS would occur sooner. Additionally, they found significant correlations between the viral replicative capacity and the sequences of the *gag* gene in the viral isolates. A viral isolate with a high replicative capacity would promote greater inflammation, depletion of CD4+ T cells and greater microbial translocation from the gastrointestinal system to the systemic compartment. Because of that, he thinks that a vaccine that promotes a cellular immune response against isolates of high replicative capacity might be effective to prevent the progression to AIDS. Someone in the public asked him on which virus subtypes were investigated, and he answered that only subtype C isolates, because the study was done in Gambia. This observation emphasizes the importance of conducting similar studies in cohorts of patients infected with non-C subtypes of HIV-1, prior to generalizations. Dr. Leonid Margolis (NIH, Bethesda, United States) in his lecture "HIV exploits seminal cytokine network to promote its transmission to cervico-vaginal tissue. *Ex vivo* study" explained that the presence of IL-7 in the seminal fluid promotes greater efficiency of viral transmission in sexual relationships by inducing the activation of T lymphocytes. Although the results were obtained in *ex vivo* experiments he hypothesized that the presence of low levels of IL-7 in seminal fluid could explain the low transmission level in some couples. Someone in the public asked Dr. Margolis whether he had knocked-out the IL-7 gene expression to observe the consequences and he said that it would be done in the future.

In the session 2B, Dr. Victor Appay (Hôpital Pitié-Salpétrière, Paris, France) talked about "Deconvoluting the molecular arm race between HIV and the CD8+ T-cell response: Lessons from studying the HLA-B27 Gag specific response". He showed how the immune response by cytotoxic T lymphocytes (CTLs) controls the viral load when new viral variants are selected. These viral isolates known as *mutant escapes* have mutations that generate epitopes with lower avidity to the T cell receptor (TCR). This fact is explained because T cell clones with high avidity TCRs tend to be polyfunctional and allow a better viral control. Finally, in this competition the virus wins because the capacity of the immune system to generate compensatory mutations to generate an optimal TCR is limited. Therefore, an optimal CD8+ T lymphocytes response would be the one recognizing important determinants of the virus with high sensitivity (avidity) and, in turn, showing some crossreactivity versus different epitope variants. He concluded that, for vaccination purposes, immunogens that induce high crossreactivity for several viral proteins formulated with adjuvants that promote T cell clones with high avidity TCR sequences (with the lowest barrier of activation) should be preferred.

Session 3. Inflammation, immune activation & pathogenesis

The session began with the lecture of Dr. Daniel Douek (Vaccine Research Center, NIH/NIAID, Bethesda, United States) entitled "The good, the bad and the ugly of immune activation". He versed on the hypothesis that blocking the function of type I IFNs would result in an improvement of the chronic infection with SIV because this lowers the immune activation. To prove it, he obtained an anti-human-IFN-α antagonist that he tested in *Cynomolgus monkeys*. He observed that in acute phase, the viral load and inflammation increased similar to the placebo group. However, in chronic phase, the viral load fell with the inmunoactivation. In terms of survival to the viral challenge, it was noted that monkeys treated in the acute phase died a year after because they progressed to AIDS quickly. Then, the hypothesis was re-written as IFN-α promotes a better response early in the infection and a bad response in the chronic phase. They assessed the hypothesis for the acute phase using an *in vivo* model of a high dose intrarectal challenge. They observed that monkeys injected with IFN-α were more difficult to infect and when they did, the viral isolates showed less variability. The protection was associated with the presence of NK CD56+ cells and a lower CD4+/CD8+ T cell ratio due to an increase in the effector memory CD8+ T population with a decrease in the amount of central memory CD4+ T cells. He also replied that they did not know on the possibility that some IFN-γ secreted during the acute phase of infection would be influencing the results, when questioned.

Session 4. Clinical & translational research

It was started by Dr. Marina Cavazzana-Calvo (Université Paris Descartes, Paris, France) talked about "Gene Therapy approach for HIV-1 infection". She discussed on the case of the Berlin patient and how his group think to carry out a similar approach in other patients. The patient's stem cells would be obtained and transduced *in vitro* with viral vectors and then reinfused again to the same irradiated patients. She showed some results in a SCID mouse model where an 85 % survival rate of the infused cells was achieved. However, she also discussed some limitations of the strategy. In the first place, she said that when onco- and retroviruses are used, there is always a minimal risk (but real) to generate a tumor. In addition, he said that the infectivity of the vectors is low, in the range of 0.001-0.38 %, taking into account all the research done in the USA. To the question, would the human gene therapy be limiting to implement? She replied that the main problem would be ethical. You must obliterate the whole immune system of the patient prior to restocking with the transfected cells. This implies that you must be sure enough that the procedure is going to work and it would bring something positive to the patient. Otherwise, there is a huge risk for the patient's life. Next, Dr. Dan Barouch (Beth Israel Deaconess Medical Center, Boston, United States)

presented results on the use of Adenovirus (Ad) as vaccine vectors. He explained that the Phase IIb study HVTN 505 which consisted of stimulation with naked DNA and re-stimulation with Ad gave a result similar to that of the STEP trial, being a failure. Thinking in future studies, he showed a comparison among Ad serotypes 5, 26, 35 and 48. He showed that they have different tropisms, different cellular receptors, differential gene expression, etc. For instance, Ad5 causes an increased inflammatory response than the Ad26 promoting greater expression of PD-1 in memory T cells which suggests a lower functionality. It might explain the lower responses of Ad5 in comparison to Ad26 after boosting immunizations, although the primary response is higher. One of the most interesting conferences for their practical implications was delivered by Dr. Jacques Leibowitch (Infectious Disease Department, Raymond Poincaré Hospital, France) entitled "Four days a week and less on proper antiviral combinations provided long-term maintenance on 84 Patients' HIV / The ICCARRE PROJECT". He showed results in 84 patients who underwent a period of 3 years under antiretroviral treatment, with a regime of four generic drugs that combined a non-nucleoside reverse-transcriptase inhibitor (NNRTI) with three nucleoside reverse transcriptase inhibitors (NRTIs) during four and just one day a week. It seems that in these conditions the viral load remained undetectable and the CD4+ T cell counts remained unaffected.

Session 5. Strategies for HIV control & cure

Dr. Steve Deeks (UCSF, San Francisco, United States) explained "Why curing HIV might be easier than assumed". He observed, in relation to the cure of the Mississippi patient, that it suggests that patients receiving antiretroviral therapy within the first two weeks of infection would avoid the formation of viral reservoirs (primarily in central memory T cells). He also said that there is a patient of Dr. Fauci who eradicated the virus after 12 years under suppressive therapy. Although it does not seem to be something common, perhaps among patients who have been in therapy for a long period of time there might be some of them who have eliminated the virus. On the outcome of the French cohort Visconti, his opinion was that it cannot be generalized. Then he spoke about the drug Vorinostat that activates viral reservoirs and the antibiotic rapamycin that also decreased the reservoirs in some HIV+ patients who received kidney transplants. The latter antibiotic generally decreases the inflammation, as well as the activation status and proliferation of T-cells. He thinks that the reduction of inflammation could in turn reduce the viral reservoir. He said that they are ready to publish results in patients under antiretroviral therapy that were reinfused with allogeneic stem cells and were apparently cured from the infection. Dr. Asier Saez-Cirion (Unité des Régulations des Infections Rétrovirales, Institut Pasteur, Paris, France) in his talk "Natural and treatment induced control of HIV/SIV infections" evidenced that some elite controllers will need antiretroviral treatment in the future, given the increases in viral replication observed. He also commented on the case of a monkey infected with SIV which was depleted of CD8+ T cells and the VL remained undetectable. It shows that some mechanisms independently of CD8+ T cells may also control the viral replication efficiently. Perhaps, something similar happened with the virological post-ART controllers of the Visconti cohort, because they did not have protector HLA alleles. Someone in the audience asked Dr. Saez-Cirion about the replicative capacity of the isolates of the virological post-ART controllers taking into account the sequence of the *gag* gene, and he said that the study was in progress, but they cultured the virus and high viral titers were observed. Then, they concluded that these viral isolates have good replicative capacity.

Session 6. Future vaccine strategies

This was the last session of the meeting. Dr. Punnee Pitisuttithum (Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand) started it commenting on the results obtained in phase III RV 144 clinical trial. He explained that the greatest correlate of protection found was the antibody-dependent cell cytotoxicity (ADCC) in the sera. It also correlated with high titers of IgG and low titers of monomeric IgA. In other words, they found statistically higher IgA/IgG ratios in volunteers who became infected in comparison to the non-infected match pairs.

Debate sessions

Which strategy to achieve a cure for HIV-1 infection?

In this debate, Dr. Judith Currier (University of California at Los Angeles, USA) and Dr. Brigitte Autran (Hôpital Pitié-Salpétrière, Paris, France) presented their views and analysis. The first presentation was "Advances in Antiretroviral Therapy: A Critical Component of Cure Strategies" and emphasized that, beyond the capacity of the antiretroviral therapy to reduce the viral load to undetectable levels, very little is known about the drug combinations that do not cause immune-activation and their biodistribution into tissues of the central nervous system (CNS) and the gut. Dr. Currier showed tables indicating the differences among several drugs in terms of its ability to penetrate different tissues of the body. She also discussed a figure where the number of copies of viral RNA in serum and in the central nervous system (CNS) was plotted as a function of the time of infection. It was evident that early ART does not prevent the infection of the CNS. Then she showed four new drugs in clinical trials that show a low toxicity profile with good biodistribution in the gastrointestinal system and CNS. She concluded by saying that still some research need to be done on the best combinations of drugs to achieve low toxicity and high penetrability in the tissues where the viral reservoirs are located. It would allow ART for a long period of time increasing the possibility to cure the infection.

On the other lecture "Change of paradigms in Therapeutic immunization against HIV", Dr. Autran explained the new paradigm for therapeutic vaccination. Until the decade of the 2000's, the goal of therapeutic vaccination was to stimulate an anti-HIV immune response during ART that would promote the

viral control for some time off-therapy, which would result in a "rest" of the therapy and its associated toxicities. Since 2012, the new paradigm emerged as to immunize for stimulating an anti-HIV response, but in the presence of some agent stimulating viral replication in the reservoirs to promote its destruction by the immune system, and to ultimately achieve a functional cure. It is a strategy that looks for synergy. Then, based on the evidence found in elite controllers, she inferred what kind of immune response should generate a therapeutic vaccine to effectively control the virus. She concluded that it might be a response of CD8+ T cells that protect essentially the central memory CD4+ T cells. In the case of antibodies, anti-gp41 IgG2 might be useful although she doesn't have too much confidence about that.

Which are the most promising approaches to develop a vaccine against HIV-1?

This debate recruited several experts working in different approaches to develop vaccine candidates like naked DNA, live viral vectors, etc. All agreed on the importance of promoting a cellular response, but they did not agree on which immunogen would be the most appropriate.

Poster sessions

As for the oral presentations, the poster sessions were distributed in two consecutive days. Some of them are reviewed in the following paragraphs.

The poster "Characterization of a novel antiviral effect of the Interferon Induced transmembrane proteins against HIV-1" presented by Dr. Kévin Tartour *et al*. showed the first experimental evidence of decline in the infectivity of HIV-1 virions because of the effect produced by three transmembrane proteins induced by IFN. This effect is manifested at two levels: the target cell and the virion particles. It seems that such proteins can be inserted in the membrane of the virions which makes them infectiousless. The authors posed three potential causes that are not mutually exclusive: 1) the proteins induced by IFN affect the incorporation of the gp120 to the virion; 2) they might affect the step of membrane fusion; 3) they interfere with the recognition of the viral receptor. The future work was planned to elucidate at molecular level which of the previous hypotheses actually work.

One of the most interesting posters was presented by Dr. Mélanie Bouvin *et al*., "Evidence for a continuous drift of the HIV-1 species toward higher resistance to neutralizing antibodies over the course of the epidemic". They studied 40 male patients who have sex with other men and who were infected with subtype B isolates during three periods of time: 1986-1991, 11 patients; 1995-2000, 15; and 2005-2010, 14. These patients were enrolled in the study with less than three months of infection and belong to the French cohorts PRIMO and SEROCO. They found that there was a progressive increase of the resistance to the neutralization by polyclonal sera and monoclonal antibodies as a function of time, suggesting an adaptation of the field isolates to the neutralizing human response in the course of the epidemic. This study draws attention to the need for monitoring virus isolate genotypes and their resistances to therapies, which would influence the rational design and selection of suitable immunoprophylactic strategies based on neutralizing antibodies.

Dr. Héloïse Quillay *et al*. presented the poster "Human NK cells control HIV-1 infection at mucosal level". They aimed to explain why the vertical transmission of HIV-1 is so unlikely to occur in the first trimester of pregnancy. The authors studied decidual tissue finding that NK cells in this tissue had an important antiviral effect through soluble mediators, as well as through contacts with antigen presenting cells that would be targeted to infection. There were no molecular evidences on the possible soluble mediators or the cellular contacts that might be behind the antiviral effect found.

Two particular posters focused on the deleterious effects of Nef protein. Dr. Bettina Stolp *et al*. presented the work entitled "HIV-1 Nef interferes with T lymphocyte circulation through confined environments *in vivo*". They showed evidences, using a 3D collagen matrix, pointing to a new deleterious mechanism induced by the viral protein Nef that affects the location of the lymphocytes in secondary lymphoid organs. This effect would be the consequence of disturbances on cell polarity, as well as a decrease in motility in dense tissues and transendothelial migration. In the second poster, Dr. Christel Verollet *et al*. versed on "HIV-1 Nef alters podosomes and promotes the mesenchymal migration in human transduction mechanisms in macrophages". Using dense matrix (Matrigel®) the authors evidenced that infection of macrophages enhanced its migration into mesenchymal tissues and inhibited their amoeboid movement, being an effect mediated by the viral protein Nef. This is due to the fact that Nef promotes the formation of podosomes where high levels of F-actin accumulate, but the dynamics of this human protein decreases. The authors believe that this mechanism would explain the migration of macrophages to the CNS, and possibly the role of its accumulation in that tissue for the appearance of neurological disorders.

In another work entitled "Genetic & phenotypic characteristics of subtype C full length genome HIV-1 from linked heterosexual transmission pairs", Dr. Martin Deymier *et al*. showed the results in five discordant couples of Zambia which infections occurred by heterosexual contact with subtype C isolates of HIV-1. When studying the genomic sequences of the isolates in both sexual partners, it was found that only minor viral variants were transmitted within the context of a very large diversity of isolates due to the chronic infection. The transmitted isolates did not display higher replicative capacity compared to the other viral sequences found. This suggests that the transmission capacity does not depend on the replicative capacity of the viral isolates.

In the poster "HIV-1 Elite Controllers to display low surface CCR5 expression on CD4 T-cells ", Dr. Lea Brandt *et al*. showed that one of the possible explanations for the very low or undetectable VL found in elite controllers would be the significant decrease of CCR5 molecules on the surface of the central memory and effector memory CD4+ T cells, compared to normal progressors (50 patients included). However, no differences were found within the compartment of

naïve cells. It is a logical situation because these cells are not easily infected by HIV-1.

Seeking for a possible explanation for the fact that circumcised men still have a 40 % risk of becoming infected with HIV-1 through unprotected sexual relationships, Dr. Yonatan Ganor *et al*. presented the work "Urethral macrophages are key players in HIV-1 infection in the human male genital tract". As it is known, the HIV-1 can infect the tissue of the penis through the foreskin that is why the practice of circumcision ranges up to 60 % effectiveness in preventing the risk of infection. In this study, the authors used tissues donated by seronegative patients undergoing elective sex reassignment and samples of seropositive patients. It was shown (using *in situ* hybridization techniques) that the urethral tissue can be infected by HIV and that macrophages are the primary target. The infection of the urethra and the establishment there of a small viral reservoir might explain the partial protection achieved with the circumcision.

The work entitled "HBV resistance pattern and liver fibrosis in patients coinfected with HIV and HBV. Case series" by Dr. Oana Streinu-Cercelm *et al*., described a study of the serological status of 95 HIV+ approximately 21-year-old Romanian women. The results revealed that around 60 % of these women were or are infected with the hepatitis B virus (HBV).

And the poster entitled "Early initiation of combined antiretroviral therapy (c-ART) protects HIV-1 infected individuals from the alteration of the Treg/Th17 profile in the gut", by Dr. Ayrin Harunova-kök *et al*., was a comparative study between seronegative persons and HIV-infected patients treated with ART in the acute phase, and some other patients treated in the chronic phase. It demonstrated that the sooner ART is prescribed, a better protection is provided to the gastrointestinal mucosa from infection. In this sense, the early initiation of ART protects Th22, Th17 and Treg cell populations. Therefore, the study suggested that ART during the primary infection may prevent damage of the mucosal epithelium that eventually causes the translocation of microbes to blood and a state of permanent immune-activation that promotes and/or speeds up the progression to AIDS.

Our work at The Center for Genetic Engineering and Biotechnology was shown in the poster, entitled "Th2-Th1 shift with the multiantigenic formulation TERAVAC-HIV-1 in Balb/c mice". It referred specifically to the capacity of the vaccine candidate TERAVAC-HIV-1 to promote a Th1 type response in mice bearing a preexisting HIV-1-specific Th2 type response. This scenario simulated the possible immune response of seropositive patients to vaccination. Taking into account that a Th1 type cellular response is considered to be "protective", our results support the therapeutic use of this vaccine candidate.

Conclusions

In this meeting, a whole account of failures and successes in HIV investigation during the last 30 years was achieved. There were plenty of novel results and fruitful discussions. It helped to targeted new goals for the near future.

In general, the actual situation gives us cause for optimism. After successful therapeutic interventions in some patients it seems that the time to dream in of HIV eradication has come.

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