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Conference report

Report of the Cent Gardes HIV Vaccines Conference, Part 2: The cellular immune response. Fondation Mérieux Conference Center, Veyrier-du-Lac, France, 25–27 October 2015 ☆

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1. Introduction

The 2015 Cent Gardes HIV Vaccine meeting took place on October 25–27, 2015, at the Merieux Foundation Conference Center in Veyrier du Lac, near Annecy, France, with the goal to review progress in the field of HIV vaccines development and assess the hopes for an effective vaccine. New findings in the field of antibodies, especially broadly neutralizing antibodies, were reviewed in the preceding article [13]. Here we will concentrate on the cellular and mucosal immune responses to HIV infection, on how to elicit and master them through vaccination in order to possibly prevent HIV infection. We will also review the still dim chances for a cure of the infection and emphasize the new hope of achieving a functional cure.

2. Early events at time of HIV infection

As reviewed by Pr Eric Hunter (Emory University Vaccine Center and Yerkes National Primate Research center, Atlanta, GA), HIV-1 heterosexual transmission involves a severe genetic bottleneck, with up to 90% of transmission events being initiated by a single virus variant, the transmitted founder (TF) virus clone. TF virus clones replicate twice better than infectious molecular clones from chronically infected individuals, and they are more resistant to type 1 interferon (IFN), at least for those that belong to clade B HIV-1 strains. The Gag gene seems to play a major role in defining the replicative capacity of the TF clone, which is a major determinant of the peak and the set point of the viral load during the course of the subsequent infection. The viral load in turn controls the loss of $CD4^+$ T cells, which characterizes HIV infection and paves the way to AIDS. Thus, individuals with a set point viral load of $>10^5$ virus particles/mL will experience a rapid $CD4^+$ T cell loss and a rapid disease progression, whereas those with a set point viral load of $<10^3$ viral particles/mL can maintain a normal level of $CD4^+$ T cells for a long time. TF variants with high replicative capacity induce a very early inflammatory state, a high proliferation rate and marked dysfunction of both $CD4^+$ and $CD8^+$ T cells and a high viral burden in both central memory and naïve $CD4^+$ T cells [9].

The role played by type 1 IFNs in the early steps of HIV-1 infection was reviewed by Netanya Sandler-Utay (University of Texas at Galveston, TX), who showed in the SIV-rhesus macaque model that blocking IFN signaling resulted in decreased and delayed expression levels of virus restriction factors such as cGAS, MX2, APOBEC3G and tetherin, and resulted in the establishment of a larger SIV reservoir and a more rapid progression to AIDS after intra-rectal challenge. In contrast, IFN-treated monkeys needed 4–5 intrarectal challenges to become infected as compared to 1 only for untreated macaques. Ultimately, in fact, the IFN-stimulated gene regulator FOXO3a was induced, expression of virus restriction factors decreased, and the IFN-treated animals became readily infectable. Protection against systemic infection was therefore observed only as long as IFN-stimulated genes were expressed, but subsequent IFN tolerance actually lead to increased susceptibility and accelerated disease progression.

☆ Webcasts and slides from several of the presentations at the meeting can be viewed on the Fondation Mérieux website: <http://www.globe-network.org/en/cent-gardes-conference-hiv-vaccines-2015/background>.

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Another factor which plays an important role in the establishment of mucosal infection is the prevalence of activated $CD4^+$ T cells in the mucosa, as documented by Jay Berzofsky (Center for Cancer Research, NIH, Bethesda, MD), who showed that the prevalence of pre-challenge activated rectal $CD4^+$ T cells in naïve macaques correlated inversely with the number of rectal virus challenges required to infect the animals. The frequency of activated $CD4^+$ T cells in the rectal mucosa most likely depends on the composition of the gut microbiome, which therefore may play a key role in the susceptibility of the animals to infection and the subsequent level of acute virus load. The gastrointestinal tract is a major site of entry and persistence of HIV-1. Gabriella Scarlatti (San Raffaele Scientific Institute, Milano, Italy) was able to show that $CD11c^+$ dendritic cells in the lamina propria are actively recruited to sample virions in the gut and transfer infection to $CD4^+$ T cells across the intestinal mucosa [8].

In addition, and not surprisingly, mucosal inflammation plays a major role in the risk of infection, as was illustrated by Jo Ann Passmore (University of Cape Town, South-Africa) who showed that women in South Africa, especially young women, have a high rate of HIV acquisition, which appears to be strongly linked to elevated genital concentrations of inflammatory cytokines such as IL-1α, IL-1β, IL-6, TNF-α, IL-7, IL-8, GMCSF, and IL-10 and chemokines MIP-1α, MIP-1β and IP-10 [12]. Causes of inflammation were most often of bacterial origin, such as *Trichomonas vaginalis* or *Chlamydia trachomatis* infections, or, less frequently, *Neisseria gonorrheae* or HSV-2 infections [17].

3. The cellular immune response

The cellular immune response to infection is characterized by HIV-specific $CD8^+$ cytotoxic T cells (CTL), which are able to kill HIV-infected target cells. They have been identified as early as 1987. Although most anti-HIV-1 CTLs specifically target Gag epitopes, Pr Bruce Walker (Rangon Institute, Boston, MA) reported in his keynote lecture that upon infection, the initial $CD8^+$ T cell response is surprisingly not targeted to Gag. It can actually take as many as 28 weeks to see the appearance of the Gag-targeted $CD8^+$ T cell response. The follow-up of a cohort of 18–23 year-old females at high risk of infection in Kwazulu-Natal, where up to 45% of females are infected by the age of 24, allowed him to find out that, very early after infection, there is a massive expansion of the $CD8^+$ $CD38^+$ HLA DR^+ T cell population. However, these cells do not produce much IFN-¥, nor do they express the CD127 marker which is associated with durable memory responses. Instead, they rapidly express the Ki67 marker and become apoptotic. The $Ki67^{hi}$ $BCL2^{low}$ phenotype is also observed on $CD4^+$ T cells. Remarkably, starting anti-retroviral (ARV) therapy within a week after infection in these young females led to a total blunt of the viral load peak and allowed the treated individuals to stably remain seronegative over time.

The generation of Ab-secreting plasma cells depends critically on $CD4^+$ T follicular helper (Tfh) cells in the germinal center. As discussed by Hendrick Streeck (HIV Research Institute, University Duisburg-Essen, Germany), Tfh cells can also be found in the plasma where they can be identified as IL-21^+ $CXCR5^+$ $BCL6^+$ circulating $CD4^+$ T cells. The comparison of plasmas from volunteers from several HIV vaccine trials, including DNA-Ad5 and DNA-MVA vaccine trials, showed that only the ALVAC/AIDSVAX (RV144) regimen had elicited this particular subset of HIV-specific $CD4^+$ Tfh cells [22]. According to Persephone Borrow (University of Oxford, UK) there is a strong correlation between the proportion of circulating PD-1^+ $CXCR5^+$ Tfh cells and serum NAb breadth. In addition, circulating Tfreg:Tfh ratios were more reduced in subjects with high nAb breadth. This raises the possibility that vaccines that elicit strong Tfh responses and at the same time transiently impair Tfreg activity may be needed to elicit bNAb responses to HIV-1.

An effective T cell-based HIV vaccine should not however elicit an increase in activated target $CD4^+$ T cells. Guido Silvestri (Emory University, Atlanta, GE) compared different SIV vaccine regimens in rhesus macaques, including DNA given by electroporation, chimp Ad6 or Ad7, human Ad5, and vaccinia virus, all expressing SIV Gag/Tat. The monkeys were challenged repeatedly with low dose SIVmac239 by the rectal route. None of the tested vaccine regimens was protective, but monkeys with the highest percentage of activated $CCR5^+$ HLA-DR^+ Ki-67^+ $CD4^+$ T cells in the rectal mucosa were the most rapidly infected and showed the highest peaks of early viremia, suggesting that the levels of activated target T cells in the rectal mucosa were predictive of the risk of SIV acquisition [7]. This is very reminiscent of what may have happened in the STEP trial, which had to be stopped because of the higher number of HIV infections in the cohort of Ad5 vaccinees than in the placebo cohort: it is quite likely that the Ad5 vaccine reactivated memory Ad5-specific $CD4^+$ T cells that had been elicited following an earlier adenovirus infection.

Guido Silvestri also tested the hypothesis set forward in 2014 by Jean-Marie Andrieu who reported that immune tolerance elicited by intra-gastric immunization of Chinese rhesus macaques with AT-2 inactivated SIVmac239 mixed with *Lactobacillus plantarum* completely protected 23 of 24 animals challenged with a high dose of SIVmac239 by the rectal route for up to 48 months. Protection was linked to the induction of a new class of $CD8^+$ T regulatory cells that suppressed the activation of SIV-infected $CD4^+$ T cells [2]. The experiment was repeated by Guido Silvestri on 54 Indian Rhesus macaques, 17 of which were immunized intra-gastrically with inactivated SIV added with *Lactobacillus* as described by Jean-Marie Andrieu, and 26 of which received inactivated SIV alone, or *Lactobacillus* alone or a placebo. No protection could be observed upon intra-rectal challenge with SIVmac in any of the different groups, as 16 of the 17 immunized macaques and 25 of the 26 control animals became infected upon challenge. No difference in viral loads could be evidenced between the different groups.

Protective cellular immune responses against viral infection are primarily the responsibility of cytotoxic $CD8^+$ T cells that recognize viral peptide epitopes presented by major histocompatibility complex class Ia (MHC-Ia) molecules on the surface of infected cells [18]. Pr Louis Picker (Vaccine and Gene Therapy Institute, Oregon Health and Science University, Beaverton, OR) and his group have developed a recombinant SIV vaccine based on the use of rhesus macaque cytomegalovirus (RhCMV) strain 68.1 as a vector. This vaccine was found to elicit and maintain very high frequency, long-lived SIV-specific T effector memory (Tem) cells that were able to control and eventually clear SIV infection in 54% (64 out of 119) of vaccinated monkeys [14,15]. Monkeys which had thus cleared their infection remained seronegative and virus negative, and were protected for life against further challenge. The first surprising finding was that these monkeys developed SIV-specific $CD8^+$ T cell responses that were entirely non-overlapping with conventional MHC-Ia-restricted $CD8^+$ T cells and manifested three times the breadth of $CD8^+$ T cells elicited by conventional vaccines such as a recombinant MVA-SIV vaccine.

As reported by Pr Louis Picker at the meeting, the second surprise came from the finding that the cytotoxic $CD8^+$ T cells elicited by the recombinant 68.1 RhCMV/SIV vaccine were reactive to epitopes presented by nonclassical major histocompatibility complex E (MHC-E) molecules. Thus, among 42 rhesus macaques vaccinated with the 68.1 RhCMV/SIVgag vector, one could identify a median of 20 distinct $CD8^+$ T cell-recognized MHC-E-restricted SIV gag 15-mer epitopes per monkey. This is to be compared with the median 11 distinct MHC-Ia-restricted SIVgag-specific $CD8^+$ T cell responses that are elicited by more conventional SIV vaccines.

The induction of MHC-E restricted SIVgag specific $CD8^+$ T cell responses by the 68.1 RhCMV/SIVgag vector was therefore quite remarkable. Even more striking, perhaps, Louis Picker reported that these observations held only if the vector used was the 68.1 RhCMV strain in which genes Rh157.5 and Rh157.4 have been deleted, but they did not hold with natural CMV strains [16].

Because of the limited MHC-E polymorphism, a vaccine that would elicit MHC-E-restricted $CD8^+$ T cell responses would elicit largely similar responses in all or most vaccinees, regardless of their MHC-I genotype. The search for HuCMV Deltapp71 vectors able to elicit a MHC-E restricted cellular immune response is therefore most important. These vectors could actually be most useful not only for the construction of HIV-1 vaccines but also of vaccines against tuberculosis or malaria and, perhaps even, therapeutic vaccines against the same pathogens.

Finally, Olivier Schwartz (Institute Pasteur, Paris, France) reviewed the role of dendritic cells in HIV-1 infection and their activation by cGAMP (cyclic GMP-AMP synthase), which induces an antiviral state through activation of IFN genes. Amazingly, CGAMP can be efficiently transmitted within virus particles, including MVA [5]. Several groups at the Vaccine Research Institute (VRI) in Creteil, France, are working on DC targeting vaccines such as the antiCD40.HIV5pep vaccine successfully tested as a booster of HIV-specific T cells in MVA-primed animals. Clinical trials will tell whether it could also be a candidate therapeutic HIV-1 vaccine.

4. Update on clinical trials

Glenda Gray (South Africa Medical Research Council), reminded the audience that to date, only four HIV vaccine concepts have been evaluated in 5 HIV vaccine efficacy trials, of which only one, the RV144/Thai trial, has demonstrated a modest 31% efficacy with limited durability. This trial, which involved priming with a recombinant canarypox vector (ALVAC) and boosting with gp120/Alum, showed that binding IgG antibodies to the Env V1V2 region and antibody functions like ADCC, ADCP and virion capture were associated with protection from HIV. Strategies built on these concepts have led to the design and testing of an ALVAC/gp120 prime-boost regimen for the clade C epidemic of southern Africa, using MF59 as an adjuvant and adding one extra booster immunization at 12 month. The hope is that one will be able to reach a 50% protection level after 2 years. A phase I trial (HVTN097) has already been performed, a phase IIa trial is just finishing and a Phase IIb trial is planned to start in 2017 with results expected in 2020. The MF59 adjuvant performed well so far, in spite of a report that it was less effective than alum in a repeat of the ALVAC/gp120 trial in macaques. As noted by Georgia Tomaras (Human Vaccine Institute, Duke University Medical Center, NC), the HVTN097 trial clearly shows that, if it looks relatively easy to elicit protective IgG responses, it is however very difficult to get IgA responses at mucosal sites. Antiviral functions of these IgGs involve both recognition of HIV-1 virions or infected cells and FcR engagement of effector cells. In other words, HIV control seems to be mostly associated with polyfunctional HIV-specific antibody responses [1].

However, as pointed out by Pr Giuseppe Pantaleo (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), it may be that priming with the NYVAC vector expressing HIV-1 antigens rather than with ALVAC would elicit more potent HIV-1-specific $CD4^+$ T cell responses and higher magnitude HIV-1-specific $CD8^+$ T cell responses, as was observed in rhesus macaques [11]. Thus NYVAC might represent a favorable alternative candidate to ALVAC in the development of a future HIV-1 vaccine.

Jerome Kim (International Vaccine Institute, South Korea) reported that some of the RV144 study participants were enrolled in a further study, RV305, where they received an additional, late booster immunization. This elicited a ten-fold increase in their anti-HIV-1 IgG titers that was unfortunately very brief as titers were down about 20-fold 6 months later. Several volunteers in this late boosting study unexpectedly developed Abs with long HCDR3 regions and tyrosine accumulation, as observed in bNAbs, but these were unfortunately not broadly neutralizing. Some volunteers are planned to enter a new study, RV305A, where they will receive additional booster immunizations to see if the pattern continues.

Another novel approach advancing into efficacy trials include a multi-clade prime-boost vaccination using adenovirus serotype 26 for priming and either MVA or Ad26 and trimeric Env protein for boosting. This approach was developed by Pr Dan Barouch (Beth Israel and Harvard Medical School, Boston, MA) who tested the protective efficacy of Ad26/MVA and Ad26/Env vaccines against SIVmac251 and SHIV-SF162P3 challenges in rhesus monkeys [4]. Full protection was obtained in 50–66% of the vaccinated monkeys. Ad26 recombinants have already been tested for safety and immunogenicity in human volunteers [3].

5. The HIV reservoir

Daniel Douek (The Vaccine Research Center, NIH, Bethesda, MD) attempted to define the anatomical and cellular characteristics of the latent reservoir of HIV-1 in 40 HIV controllers with viral loads <1000 particles/mL. More than 95% of the viral genomes were found in $CD4^+$ Tem and Ttm cells but these were highly repeated sequences, corresponding to the long-term maintenance of an old virus strain, and showed little replication. In the lymph nodes of the same individuals, however, HIV-1-containing T cells showed a Tfh phenotype and were the site of active, low-rate HIV replication. In spite of their low virus load, HIV controllers therefore show continuous replication of the virus in their lymph nodes.

There have been numerous but so far unsuccessful attempts at purging the HIV reservoirs in HIV-infected persons under ART, as reviewed independently by Steven Deeks (University of California San Francisco, CA), and Monsef Benkirane (CNRS, Montpellier, France). Steven Deeks underlined how much cancer and HIV persistence share a number of similarities. The local environment in both instances is reshaped to prevent immune mechanisms from clearing the diseased cells, essentially through the development of a chronic inflammatory environment which stimulates immunosuppressive responses. Indeed, T cell activation, together with collagen deposition and lymphoid fibrosis, continue in HIV positive patients under ART as well as in elite controllers [21]. This has led to use drugs such as rapamycin to reduce T cell activation and proliferation, or Ipilimumab, to target cytotoxic T lymphocyte antigen 4 (CTLA-4) [23]. Combined anti-programmed death-1 (PD1) and anti CTLA-4 treatments are now been tested, in the hope that the recent advances in cancer therapy through blockade of immune checkpoint markers will eventually be translated into the HIV arena.

Other, considerable efforts have been directed to try to reactivate latent HIV-1 in ART-suppressed patients. James Whitney (Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, MA) showed for instance how the multiple administration of a TLR7 agonist to SIV-infected monkeys under ART suppression first induced transient plasma viremia, before eventually leading to reduced viral DNA content in PBMCs, colon and lymphoid tissues and finally to lower plasma virus set points after ART discontinuation. Still, however, the complete eradication of HIV-1 or SIV infection remains for the moment a very distant goal.

6. Concluding remarks

The conclusion to the meeting was drawn independently by Asier Saez-Cirion and by Françoise Barré-Sinoussi (both from the Pasteur Institute, Paris, France). There is yet no new vaccine available at this time and we clearly need data from new clinical trials to progress. Hopefully, the clinical study of the improved clade C-version of the RV144 trial (ALVAC/gp120 prime-boost regimen), which was moderately successful in Thailand in 2009, will presently progress to Phase IIb in South Africa. Moreover, clinical trials of Ad26/MVA prime-boost vaccine regimens are expected to be launched soon. Also, a very new approach is been developed based on the use of the 3S motif in gp41 [19]. Still, the greatest achievement in the field would be the development of a vaccine able to elicit bNAbs. In spite of a great many efforts and numerous attempts, this goal still remains out of reach at this time: the use of bNAbs is limited to passive immunization, or to vector immunoprophylaxis, which might offer an interesting alternative to vaccination. Both approaches are currently being tested in clinical trials.

Another current challenge is that although ART can effectively reduce the HIV viral load to undetectable levels, it does not eliminate the virus, which persists in latent reservoirs and actually continues to replicate slowly. This compells infected individuals to maintain ART for life, a difficult and costly endeavor which is not exempt of side effects. At this time, complete eradication of the virus still remains unachievable. Remission of HIV infection does however exist, as found in HIV controllers, who are able to naturally maintain a very low viral load without ever receiving any ART. In the same token, it was recently observed that the very early initiation of ART during acute infection can lead to complete virus remission upon later arrest of ART [6,10]. Several post-treatment controllers have thus been identified in the recent Visconti study [20], who showed various effective immune responses associated with control of infection, such as NK cell activation or IFN-Y production, but only poor $CD8^+$ T cell responses.

Given the impossibility to eradicate HIV-1, such a 'functional cure' appears to be the most reasonable goal to aim for at the present time.

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