Toward an HIV Cure Symposium 2012

Meeting Report

towards an HIV cure
people focused science driven

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25 YEARS OF COMMITMENT

On July 20 & 21, 2012, preceding the 19th International AIDS Conference (AIDS 2012) in Washington DC, USA, the International AIDS Society held a symposium focused on the research effort to cure HIV infection. The event built on momentum generated by the first IAS "Towards an HIV Cure" symposium held in Vienna in 2010[1], and was accompanied by the launch of an IAS Global Scientific Strategy laying out the key challenges that need to be addressed in order to achieve the long-sought goal of a cure for HIV[2]. The recommendations of the Global Scientific Strategy provided the framework for the agenda for the meeting, which was divided into seven topic areas in addition to the opening and closing sessions. Co-chairs were IAS President-elect Françoise Barré-Sinoussi from the Institut Pasteur and Steven Deeks from the University of California, San Francisco, who also co-led the international working group responsible for developing the scientific strategy documents.

Opening Session

Anthony Fauci, Director of the National Institutes of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health, Bethesda, USA, delivered opening remarks. Fauci cautioned against overselling the possible imminence of a cure for HIV, and highlighted the parallels between the current research field and nascent attempts to develop HIV therapeutics in the 1980s: the challenges lie in the realm of basic discovery, and it is uncertain if they can be overcome. But, Fauci noted, the eventual development of effective antiretroviral therapy (ART)—in the face of considerable skepticism as to whether a retroviral infection could ever be treated—offers an encouraging precedent. As a way to emphasize the continuing need for fundamental research, Fauci cited the studies conducted in the late 1990s that demonstrated ART alone was insufficient to eradicate HIV due to the existence of a latent viral reservoir in memory CD4 T cells[3,4,5]; this reservoir still remains the key obstacle to a cure today. Furthermore, Fauci reminded the audience that an early attempt at reservoir depletion using adjunctive IL-2 therapy appeared to have been effective based on assays demonstrating a lack of detectable replication-competent HIV in both lymph tissues and blood, but was unsuccessful in preventing viral load rebound upon ART interruption[6]. A sobering and perhaps underappreciated implication of this finding, Fauci argued, is that in the absence of any enhancement, HIV-specific immune responses are typically unable to contain even a small residual pool of viruses. Fauci went on to delineate the two major approaches to an HIV cure now being pursued by the field: complete viral eradication or a "functional cure," in which the virus is contained either by the host immune response or gene therapies that render target cells resistant to infection. Despite the challenges, Fauci stressed NIAID's commitment to cure research, citing the recent funding of three large consortia named the Martin Delaney Collaboratorys (after the respected community advocate and founder of Project Inform) and also a new letter of agreement between NIAID and the

French Agence Nationale de Recherche sur le Sida et les hépatites virales (ANRS) codifying their intent to work collaboratively.

Robert Siliciano, Professor of Medicine at the Johns Hopkins University School of Medicine, Baltimore, USA gave the keynote address entitled “HIV Eradication: understanding the magnitude of the problem.” Siliciano primarily focused on two important issues facing the field: the fate of infected resting CD4 T cells after reversal of HIV latency and the comparability of available assays that might be used to measure viral persistence. A variety of compounds have been shown to reverse HIV latency without inducing T cell activation, including histone deacetylase (HDAC) inhibitors such as SAHA (trade name Vorinostat) and perhaps also the anti-alcoholism drug disulfiram (identified by Siliciano’s laboratory in a screening effort funded by amfAR[7]). However, whether induction of latent HIV is sufficient to cause the death of infected cells has been unclear. Siliciano discussed recent work from his laboratory demonstrating that, in vitro, infected CD4 T cells do not die after reversal of viral latency by SAHA treatment. In order to achieve the elimination of the infected cells, the addition of functional CD8 cytotoxic T-lymphocytes (CTL) was required; CTLs sampled from elite controllers performed this task efficiently whereas, in all but one case, CTLs from chronically infected individuals on ART did not. Encouragingly, *in vitro* stimulation of CTL from the individuals with chronic infection, using HIV peptides, served to restore their killing capacity. These results imply that boosting HIV-specific CTL responses prior to reactivating latent HIV may be essential for successful eradication efforts[8].

Siliciano next described a collaborative study of assays for measuring HIV persistence, in cohorts of individuals who had started ART in either acute or chronic infection. The virus culture assay, which measures infectious units per-million cells (IUPM), readily detected replication-competent viruses in all samples, with no significant differences based on the timing of ART initiation. The major limitation of this test, Siliciano pointed out, is that it is cumbersome and expensive to perform. Another simpler approach is the measurement of proviral DNA using digital droplet PCR; this assay divides samples into several thousand microwells and performs PCR on the contents of each. Results for the microwells are binary: 0 for absence of a detectable signal and 1 if the target DNA sequence is present (hence the digital designation). A quantitative measure is then obtained by calculating a Poisson distribution for the results across all the microwells. Siliciano showed that there was no correlation between HIV DNA levels measured using this technique and the virus culture assay, and there was not a significant difference in HIV DNA levels between the acute and chronic infection cohorts. The last test to be assessed was the single copy assay (SCA) for HIV RNA; Siliciano noted that many individuals did not have detectable levels and that the dynamic range of SCA appeared very limited. He also highlighted that all of the assays showed substantial person-to-person variation over a 2-log range.

To further probe the large disconnect between the results of the virus culture and digital PCR assays, Siliciano's laboratory conducted an analysis of 179 proviral DNA sequences from infected resting CD4 T cells that did produce replicating virus after PHA stimulation. The majority of these "non-induced" proviral clones showed evidence of mutations rendering them non-functional: 53.6% had internal deletions, 26.3% were hypermutated, 1.75% displayed nonsense or frameshift mutations and 1.7% possessed a truncated packaging signal. But, surprisingly, 16.8% (range 6-36%) of the non-induced proviruses had intact open reading frames and, when cloned, were found to be replication-competent. These data suggest that the number of clinically relevant latently infected cells may be 50-fold greater than previous estimates based on virus culture assays.

Session 1: Determine cellular and viral mechanisms that maintain HIV persistence

Each symposium session began with an overview speaker, and the task first fell to Warner Greene, Director of the Gladstone Institute of Virology and Immunology, the Nick and Sue Hellman Distinguished Professor of Translational Medicine and Professor of Medicine, Microbiology and Immunology at the University of California, San Francisco, USA. Greene gave a guided tour of the molecular mechanisms that have been shown to promote HIV latency, highlighting that multiple factors are in play. Key among them is the repression of the transcription process that converts HIV genes into viral proteins; this can occur because the virus preferentially integrates into active cellular genes, and as the host cell goes about its normal business of transcribing these genes into proteins, HIV's transcriptional efforts are essentially trampled upon and prevented from proceeding. In scientific terms, this phenomenon is described as transcriptional interference. Processes involved in regulating expression of cellular genes are also involved, notably the shutting down of genes by histone proteins which can tightly wrap DNA and render it inaccessible to transcription factors. Greene pointed out that the long terminal repeat (LTR) of HIV is an "absolute magnet" for histone deacetylase (HDAC) enzymes, which function to modify histone proteins in a way that enhances their ability to lock down gene expression. For this reason, compounds that inhibit HDACs have emerged as lead candidates for reversing HIV latency.

Greene explained that while models of latency using cell lines have elucidated important transcriptional control mechanisms, they might differ in important ways from the in vivo situation. A number of research groups are attempting to address this shortcoming with primary cell models, including Greene's laboratory. He emphasized that these newer models are showing that the molecular modifications that are critical to modulating HIV expression are not restricted to changes in chromatin structure and histones, but also host and viral derived transcription factors, such as NF-kB and Tat. Greene concluded by noting that the kinetics and magnitude of reactivation of latent HIV after exposure to

potential anti-latency compounds will need to be carefully evaluated in an optimal primary cell model in order to guide clinical development.

Greene's talk was followed by several abstract presentations relevant to the topic area of the session, selected from submissions to the AIDS 2012 conference (as was the case for all the abstracts presented during the symposium). Lachlan Gray from the Burnet Institute and Monash University in Melbourne, Australia reported on factors associated with repression of HIV expression in astrocytes in the central nervous system (CNS). Using viruses isolated from autopsy issue, Gray found that the LTRs displayed reduced transcriptional activity that correlated with the presence of mutations that appeared to have been selected for by the astrocyte cellular environment (specifically, the presence of high levels of the transcription factor Sp3). The findings suggest that unique transcriptional mechanisms contribute to viral persistence and latency in the CNS[9].

Two presentations discussed the involvement of gene-regulating molecular complexes in mediating HIV latency. Virginie Gautier from University College Dublin, Ireland, showed that the SIN3/HDAC complex is involved in repressing HIV transcription and that knockdown of SIN3a expression in latently infected cells lines induced partial reactivation of HIV from latency and potentiated the effects of treatments such as the HDAC inhibitor SAHA[10]. Mudit Tyagi from George Mason University, Manassas, United States highlighted a related repressive epigenetic complex, CBF-1 (Latency-C-promoter binding factor 1), that induces both establishment and maintenance of HIV latency by recruiting the Polycomb Group (PcG) co-repressor complex to the LTR. Tyagi demonstrated that the knockdown of CBF-1 results in the reactivation of latent proviruses whereas, conversely, overexpression of CBF-1 facilitates latency. These results, Tyagi concluded, may support targeting CBF-1 as an anti-latency strategy in individuals with HIV infection. However, there are no compound leads so far and the toxicity profile has yet to be determined (and may be comparable to HDAC inhibitors)[11].

Session 2: Determine the tissue and cellular sources of persistent HIV in long-term ART-treated individuals

Janice Clements from Johns Hopkins University School of Medicine, Baltimore, USA opened this session with a presentation focusing on macrophages as a reservoir of SIV infection in a macaque model of suppressive ART. The model involves infection of animals with two different SIV isolates: the neurovirulent clone SIV/17E-Fr[12] and SIV/Delta B670, which consists of a swarm of at least 21 different genotypes (including neurovirulent genotypes)[13]. This combination of viruses produces high viral loads and the development of simian AIDS and CNS disease within three months, but viremia can be effectively suppressed with a combination of tenofovir, two protease inhibitors and an integrase inhibitor[14]. Clements showed that prior to treatment initiation perivascular macrophages and

microglial cells of the CNS harbor between 10^7 and 10^8 SIV copies per µg of RNA. High concentrations of SIV-infected macrophages are also detectable in the spleen. After ART contains viral replication, latent SIV can be detected in resting CD4 T cells and SIV DNA persists in the CNS. Ex vivo culture of microglial cells from animals on ART demonstrated outgrowth of replication-competent HIV, and the frequency of infected cells correlated with the severity of CNS disease observed prior to treatment.

One of the difficulties in developing macaque models for cure research is that not all antiretrovirals are active against SIV. In the first abstract presentation of the session, Zandrea Ambrose from the University of Pittsburgh School of Medicine, Pittsburgh, USA described the use of an RT-SHIV to circumvent this problem; the virus is a hybrid comprising the backbone of SIV with HIV's reverse transcriptase gene inserted, allowing the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in combination ART regimens. Ambrose employed this model to measure virus levels in multiple tissues of both ART-treated and untreated macaques. Lymph nodes and gut demonstrated the highest levels of viral DNA in both groups. Among virally suppressed macaques, quantities of viral DNA in lymph nodes were proportional to the level of pre-treatment viral load, but viral RNA was infrequently recovered from the tissues of these animals. Levels of viral DNA in circulating PBMCs did not decay with therapy[15].

Nitasha Kumar from the Burnet Institute and Monash University in Melbourne, Australia presented an in vitro model of HIV latency developed in the laboratory of Sharon Lewin. The novel aspect of this system is that it achieves substantial direct infection and latency in resting CD4 T cells by co-culture with syngeneic myeloid dendritic cells (MDCs). While it has been thought that HIV latency predominantly occurs as a result of infected activated CD4 T cells returning to a resting state, Kumar's data suggests this may not be the whole story. Kumar showed that cell-to-cell contact plays an important role by performing the co-culture with dendritic cells suspended in trans-wells, which significantly decreased latent infection in the resting CD4 T cells[16]. At the end of the symposium, Kumar received an IAS/ANRS Young Investigator Award in the Special HIV Cure category for this work.

One of the more controversial questions in HIV cure research is the extent to which ongoing low-level viral replication occurs in individuals on ART with undetectable viral loads in peripheral blood. Lina Josefsson from the Karolinska Institute in Solna, Sweden offered data addressing the issue from two small groups of individuals on long-term ART (five treated within six months of acute infection and three during chronic infection). Multiple phylogenetic analyses were performed using HIV sequences sampled from blood, gut and lymph nodes before ART initiation and after 4-12 years of viral load suppression, but no clear evidence of viral evolution was uncovered, indicating that ongoing replication was not contributing to persistence in these individuals (at least in the locations sampled). Josefsson also showed that proviral DNA reservoirs were significantly

smaller in the acute-treated group, and that hematopoietic progenitor cells from the bone marrow did not contribute to the HIV reservoir in these individuals[17] (echoing recently published data from the Siliciano laboratory[18]).

In 2011, a new subset of memory T cells with stem-cell like properties were identified[19]. Named the T stem cell memory subset (T_{SCM}), these cells represent the least differentiated form of memory T cells. In the final presentation of this session, Maria Buzon from the Ragon Institute at the Massachusetts General Hospital in Boston, USA, debuted results of the first analysis of the contribution of T_{SCM} to the HIV reservoir in individuals on ART. Buzon showed that latent HIV infection could be detected in these cells, and while they represented a small population overall (around 100 million PBMC had to be sorted to obtain 5,000 T_{SCM}), they contributed over 10% of the detectable latent HIV reservoir.

Session 3: Determine the origins of immune activation and inflammation in the presence of ART and their consequences for HIV persistence

Daniel Douek from the Vaccine Research Center at the National Institutes of Health, Bethesda, USA, provided the overview of the role of immune activation in HIV infection. He explained that the normal time-limited innate immune response during acute viral infection is typically beneficial, but in HIV infection activation of both innate and adaptive immunity persists into the chronic phase and becomes detrimental to the host. This has been demonstrated by a large number of studies showing that measures of T cell activation and inflammatory biomarkers correlate with disease progression and predict mortality. The evidence indicates that HIV, other chronic infections such as CMV and microbial translocation—the leakage of normally friendly bacteria across the gut lumen—all contribute to this phenomenon. This inflammatory environment also contributes to HIV persistence, with CD4 and CD8 T cell activation in the gut directly correlating with the size of the viral reservoir at that site.

Clovis Palmer from the Burnet Institute and Monash University, Melbourne, Australia, presented novel findings regarding Glut1, the main glucose transporter on T cells. Glut1 expression is up regulated after T cell activation and Palmer's studies found that levels of Glut1-expressing CD4 T cells were highest in untreated HIV infection, and although levels were lower in individuals on suppressive ART they remained elevated compared to HIV-negative controls. Furthermore, expression of the activation markers CD38 and HLA-DR was significantly higher in this CD4 T cell population. Of potential importance, the frequency of Glut1-expressing CD4 T cells correlated inversely with circulating CD4 T cell counts in both treated and untreated individuals. Palmer concluded that increased glucose metabolic activity in CD4 T cells might be playing an underappreciated role in HIV pathogenesis[20].

Martin Markowitz from the Aaron Diamond AIDS Research Center, New York, USA, offered evidence that initiation of ART during acute or early HIV-1 infection can prevent sustained systemic immune activation. The data derived from a randomized trial comparing treatment with combinations of 3 vs. 5 antiretroviral drugs. During acute infection, study participants displayed a significantly increased frequency of activated CD8 T cells, but by weeks 48 and 96, levels became comparable to HIV-negative individuals. There were also no significant elevations of the inflammatory biomarker sCD14 at baseline, or weeks 48 or 96[21].

Session 4: Determine host and immune mechanisms that control infection but allow viral persistence

Asier Saéz-Cirión from the Institut Pasteur in Paris, France delivered the opening talk for this session, focusing on examples of control of HIV replication in the absence of ART. Saéz-Cirión noted that the proportion of HIV-positive individuals that restrict viral replication to undetectable levels without treatment—a group referred to as elite controllers—is very small, citing an analysis carried out in France that identified 81 out of a cohort of 34,317 (a frequency of 0.24%). Factors that have been associated with elite control include efficient HIV-specific CD4 and CD8 T cell responses, low viral DNA levels and reduced susceptibility of CD4 T cells and macrophages to HIV infection. Saéz-Cirión highlighted a key question facing the cure research field: can therapeutic strategies induce an elite controller phenotype in HIV-positive people who do not control viral replication? Hints that this might be possible have emerged from an unusual group of individuals being studied by Saéz-Cirión and colleagues in France, named the Visconti cohort[22,23]. Participants initiated ART within ten weeks of infection, and a subset of 14 have now been identified who subsequently interrupted treatment (after an average duration of three years) and have since displayed sustained control of viral load to undetectable levels; average follow up without ART is around 6.5 years (range: 4-9.5). Dubbed post-treatment controllers (PTC), this group is not enriched for the favorable HLA alleles that are associated with elite control; in fact a large proportion possess the HLA B*35 allele that is associated with rapid disease progression in untreated HIV infection. All but one experienced symptomatic acute infection, which is also typically predictive of a poor prognosis. Analyses conducted to date have found lower levels of CD8 T cell activation compared to both elite controllers and individuals on ART. Saéz-Cirión characterized HIV-specific CD8 T cell responses in the PTC as weak and, in some instances, undetectable. Levels of HIV DNA are low, and in four intriguing cases these levels appear to be declining over time. Peripheral CD4 T cell counts—which can decline even in some elite controllers—have remained stable in the majority of the 14 PTC. Further studies are needed to better elucidate the mechanisms responsible for the virological control observed in these Visconti cohort members, but Saéz-Cirión suggested that limited viral reservoirs and reduced immune activation may be critical.

Abstract presentations addressed a number of potential contributors to host control of HIV replication. Lisa Chakrabarti, also from the Institut Pasteur, showed that controllers have higher levels of Th1-phenotype Gag-specific CD4 T cells that exhibit both cytotoxic potential and superior TCR avidity (conferring the ability to respond to low levels of antigen) compared to non-controllers[24,25]. Although the preponderance of evidence indicates neutralizing antibodies rarely contribute to elite control, Martyn French from the University of Western Australia School of Pathology and Laboratory Medicine, Perth, Australia, reported that several other types of antibody response may associate with the phenomenon, including Gag-specific IgG2 and antibody-dependent cellular cytotoxic responses targeting the Env gp140 protein. French also found that p24-specific IgG2 responses were more common in controllers lacking the class I HLA alleles associated with elite control[26].

The last two presentations shifted away from adaptive immunity and looked at the interaction between APOBEC3G (A3G), a member of a retrovirus restriction factor family that inhibits infection by HIV, and HIV Vif, an accessory protein that counteracts the activity of A3G. Tadashi Kikuchi from The Institute of Medical Science, University of Tokyo, Japan, showed that Vif isolated from circulating virions in controllers is less effective in counteracting A3G activity than Vif isolated from non-controllers[27]. Maria-Pia De Pasquale from Vanderbilt University School of Medicine, Nashville, USA, demonstrated that the levels of A3G in central memory (TCM) and effector memory (TEM) CD4 T cells were significantly higher in long-term non-progressors (LTNP) compared to individuals on suppressive ART. Both CD4 T cell types also contained less proviral DNA in LTNP, suggesting a restricting effect on the HIV reservoir[28].

Session 5: Study, compare and validate assays to measure persistent infection

Sarah Palmer from the Karolinska Institutet, Solna, Sweden, began this session with a discussion of the methods available to measure persistent infection. As an example of assays in action, Palmer reviewed recent controversial data derived from multiple analyses of blood and tissues that were altruistically donated by the lone individual considered cured of HIV infection, Timothy Brown. Eight different laboratories were involved in these studies, employing an array of different techniques to search for traces of HIV. Two out of four labs that looked for RNA in plasma detected extremely low numbers of copies in some, but not all, samples. No RNA was detected in gut, but some rectal samples scored positive for HIV DNA by PCR. Two independent labs employed virus culture assays to test PBMC, but neither could detect replication-competent HIV. Results from detuned antibody assays suggested a decline in HIV-specific antibodies over time. Palmer noted that the data exemplify the difficulties in formally proving HIV eradication given that the assays are operating at the edge of sensitivity under

these circumstances, and raised the question of whether a total absence of viral RNA and DNA is necessary to define a cure. Additional experiments, including the sequencing of detected RNA, are now being performed in hopes of shedding further light on the results.

Remi Fromentin from the Vaccine and Gene Therapy Institute (VGTI), Florida, USA, spoke about the development of a novel "HIV Persistence Detection Assay" (HPDA) that involves isolating CD4 T cells from virally suppressed patients and culturing them in the presence of AZT, raltegravir and efavirenz for nine days. RT-qPCR for HIV RNA is then performed on ultra-centrifuged supernatant from the culture. Fromentin stated that the assay is sensitive, has a wide dynamic range, and appears useful both for measuring the reservoir size and evaluating the effects of potential anti-latency compounds[29].

Gregory Del Prete from the AIDS and Cancer Virus Program, SAIC-Frederick, Inc., Maryland, USA, described the use of an ART regimen consisting of tenofovir, FTC, dolutegravir, and ritonavir-boosted darunavir to suppress SIVmac239 replication in macaques. The combination was effective in mimicking the degree of viral control seen with ART in HIV-positive individuals. Del Prete also discussed an assay his laboratory has developed to study anti-latency drugs in this model, which measures the frequency of CD4 T cells containing inducible SIV RNA by plating the cells in multiple replicate wells and calculating the percentage of RNA-positive cells after exposure to the compound of interest.

Session 6: Develop and test therapeutic agents or immunological strategies to safely eliminate latent infection in individuals on ART

David Margolis from the University of North Carolina at Chapel Hill, USA, presented the encouraging data from his first-in-man phase I trial of the HDAC inhibitor SAHA in HIV-positive individuals on suppressive ART. Resting memory CD4 T cells from all participants studied to date have displayed a significant increase in HIV RNA expression after a single dose of the drug; the average increase was 5.2-fold. No significant side effects were documented. The preliminary results of the trial were published in *Nature* a few days after the symposium[30].

Timothy Henrich from Brigham and Women's Hospital, Boston, Massachusetts, USA, described a small study that drew considerable publicity at the subsequent AIDS 2012 conference. The research pertained to two HIV-positive individuals who received reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of relapsed Hodgkin's lymphoma. Both were on suppressive ART at the time of their transplants and remained on therapy throughout. The treatment histories were complex; each had received chemotherapy and a prior autologous HSCT before relapsing. Furthermore, after

the allogeneic HSCT (which took place in 2008 and 2010, respectively) both developed graft-versus host disease necessitating immunosuppressive treatment of varying durations involving methotrexate, prednisone, tacrolimus and sirolimus. Henrich noted that both individuals were heterozygous for the CCR5Δ32 mutation before the allogeneic HSCT but became homozygous wild-type CCR5 after the new donor cells engrafted. The results that provoked interest derived from analyses of HIV reservoirs: there was a decrease in total proviral DNA post-HSCT (coinciding with donor engraftment), and no HIV DNA was detected after 8-17 months of additional follow-up. Ultrasensitive RNA assays with a lower limit of detection of <3 copies/mL were negative at all time points, as were tests for 2-LTR circles. Viral outgrowth assays were negative in both individuals, at day 652 and day 1,266 post-HSCT, respectively. HIV-specific antibody titers and avidity also declined over time. While the data raise the provocative possibility that the individuals may have been cured, Henrich stressed that both remain on ART and discussions regarding analytical treatment interruptions (to assess whether HIV replication rebounds) are now taking place[31].

Results from the first study of the anti-latency effects of SAHA in the SIV/macaque were debuted by Jeff Lifson from the AIDS and Cancer Virus Program, SAIC Frederick, Inc., Maryland, USA. Six rhesus macaques were treated with a six-drug ART regimen beginning four weeks after infection with SIVmac239. Four cycles of SAHA administration were initiated 22 weeks later, each lasting 21 days followed by a three-week rest period. No serious adverse events occurred and SAHA induced significant changes in histone acetylation in CD4 T cells. However, SAHA treatment did not alter plasma viral load and no consistent perturbations of cell-associated DNA or RNA could be documented[32]. Additional analyses are being conducted to try and better understand these outcomes.

Fabio Romerio from the Institute of Human Virology, Baltimore, Maryland, USA, outlined an in vitro primary CD4 T cell model of latency developed in his laboratory[33]. The model is now being used to search for identifying features of latently infected cells, in hopes of aiding efforts to specifically target this critical obstacle to curing HIV. Comparing infected and uninfected cells with microarray analyses, expression of the cell surface marker CD2 has emerged as a promising candidate. Romerio offered a glimpse at preliminary work conducted in collaboration with Nicolas Chomont from the VGTI, which so far appears to confirm that CD2 is preferentially expressed on latently infected cells sampled from individuals on ART[34].

Session 7: Develop and test strategies to enhance the capacity of the host response to control active viral replication

Guiseppe Pantaleo from the University Of Lausanne, Switzerland, reviewed the reasons why immune-based therapies (IBTs) might make an important contribution to achieving a functional cure. He cited a variety of factors relating to HIV-specific T cells that have been associated with host control of viral replication, including proliferative capacity, polyfunctionality, cytotoxic activity, TCR avidity, specific clonotypes, the absence of T cell exhaustion markers and targeting of Gag epitopes. The key genetic correlates are specific class I HLA alleles such as HLA B57, B27 and B5801. Pantaleo suggested that this background should inform the design of IBTs, noting that in addition to attempting to recapitulate parameters associated with virological control, an ideal intervention should also limit immune activation. Looking back at trials conducted to date, Pantaleo found that 13 out of a total 29 involving therapeutic vaccines reported very modest hints of efficacy. Out of four trials of cytokine therapies, only one suggested a limited beneficial effect. In order to improve upon these results, Pantaleo recommended that IBT research shift toward the study of combination approaches. In hopes of advancing the field, Pantaleo is joining with colleagues to launch a multi-stakeholder collaboration named the Collaboration for HIV/AIDS Immunological Therapy (CHAIT). Partners include the Swiss Vaccine Research Institute/Lausanne University Hospital, the Vaccine Research Institute in France, Boheringer Ingelheim, FIT Biotech, GSK Biologicals, Sanofi Pasteur and ViiV Healthcare.

In the abstract presentations, Yusuke Takahara from the National Institute of Infectious Diseases, AIDS Research Center, Tokyo, Japan, discussed results of a therapeutic vaccine study in the SIV/macaque model. ART-treated animals received two immunizations with a Sendai virus vector encoding SIV Gag and Vif proteins, followed by a treatment interruption. Vaccination induced both Gag- and Vif-specific CD8 T cell responses, and a significant difference between pre-ART and post-ART viral loads was documented among vaccines compared to controls. Takahara concluded that the results support the possibility of vaccine-induced CD8 T cell responses contributing to viral containment[35].

Closing Session

The last session of the symposium switched from biological to social science, featuring an enlightening presentation by Fred Verdult from Volle Maan, Amsterdam, the Netherlands, addressing the attitudes of HIV-positive individuals toward cure research. Verdult conducted an online survey seeking information on two overarching questions: why is a cure important? And which type of cure is preferred? Responses were received from 458 people; demographically fairly representative of the HIV-positive population in the Netherlands (79% acquired infection via homosexual contact and 10% heterosexual contact; however no respondents cited acquisition through injection drug use). The majority rated their current health as reasonable to very good. 94% cited being cured as very or somewhat important. To approach the question of why a cure is important,

respondents were asked about the most significant disadvantages of being HIV-positive. Although scientists often cite shortened life expectancy due to HIV infection as a key motivator for pursuing a cure, this did not emerge as the primary concern. Rather, uncertainty about the potential for future health problems, overall negative impact on health, concern about infecting others and stigma were the top issues cited.

In choosing the most preferable cure scenarios, all respondents favored a hypothetical complete cure that would eliminate any future risk of reinfection. Around two-thirds also responded that a complete cure that did not preclude the possibility of reinfection would be somewhat or very desirable. A functional cure that did not eliminate risk of transmitting HIV to others was less acceptable, with 56% respondents supporting the desirability of the scenario. Similarly, an uncertain cure requiring six-monthly monitoring found less favor (51%). In sum, Verdult found that discomfort with uncertainty about the future was a major factor driving responses to both the overarching questions, which is a concern given the inherent uncertainty associated with early cure research studies (the current lack of clarity as to whether all HIV has been eliminated from Timothy Brown is a notable example). The IAS is now collaborating with an array of stakeholders to foster additional research into the perspectives of people with HIV toward the cure field.

The symposium closed with comments from Françoise Barré-Sinoussi emphasizing the importance of building on the collaborative spirit displayed by the diverse array of attendees. The next “Towards an HIV Cure” symposium will be held in Kuala Lumpur, Malaysia, June 29-30, 2013, immediately ahead of the 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention.

Videos, presentations and complete rapporteur summaries are available online at: http://www.iasociety.org/Default.aspx?pageId=678

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