Converging roads: the latest science from the 2017 IAS HIV Cure and Cancer Forum

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Introduction

The 2017 IAS HIV Cure and Cancer Forum took place in Paris on 22–23 July. This year, the annual HIV cure meeting organised by the IAS had a change in format, with the forum specifically showcasing the interface between HIV cure or remission and cancer research. Symbolically, the meeting was held at the Institut Curie, an internationally renowned cancer research institute. The audience, limited to 200 to foster active interaction among the participants, included several oncologists and cancer researchers, in addition to members the HIV cure community.

The forum aimed to highlight the benefits of interdisciplinary research in the hope that this may lead to progress towards the goal of HIV remission. In part, this dialogue is of interest because people with HIV are living longer and as a consequence may go on to develop cancer. At this point the treatment options will have to take into account the presence of both diseases. A second point, which may prove to have even more pertinence, is that research into both HIV cure and cancer share many similarities, spanning basic science, diagnostics and innovative therapeutic approaches (Figure 1). The notion of identifying and quantifying the burden of disease is crucial in both areas, on the one side identifying HIV latently infected cells, and on the other, detecting cancerous cells. Equally relevant to the two areas is the understanding of the mechanisms responsible for re-shaping and affecting the immune response to prevent clearance of the diseased cells. Finally, many of the therapeutic strategies currently being investigated in the context of HIV cure and remission studies have also been used in cancer research, such as immune checkpoint blockers, cytokine therapy, modified T cell approaches and gene therapy.

Monsef Benkirane (CNRS, Montpellier, France), who delivered the keynote address, highlighted that the notions of persistence and resistance represent the barriers to cure in both HIV and several cancers. Both conditions can be regarded as residual diseases. Cancer stem cells retain similar characteristics to latently infected HIV cells and even though their molecular bases are very different, similar types of cure strategies are being developed. He then presented recently published work from his group that identified CD32a, a low-affinity IgG receptor, as a marker of a significantly enriched CD4 T cell reservoir [1]. This marker was identified using an *in vitro* model that uses SIV-derived *vpx* to overcome SAMHD1 restriction, thereby allowing infection of resting cells. To identify candidate genes that are differentially expressed between latently infected and uninfected cells, they compared the transcriptomic profiles of these two cell populations. CD32a expression on latently infected cells was confirmed in their model by flow cytometry. Cell sorting of patient samples demonstrated that CD32a is a marker of an enriched *in vivo* reservoir. CD4 T cells are not usually considered to express CD32a, making this finding unexpected. Finally, Benkirane spoke about how the chromatin spatial organisation can impact on HIV integration site selection. Recent advances have improved our ability to map interactions between genes and regulatory elements at distant DNA sites [2]. Using data obtained from previous studies mapping HIV integration sites [3,4], he showed that integration sites are enriched in the enhancer regions of specific clusters of genes that interact with one another (termed 3D clusters).

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Characterising the reservoir

For both HIV and cancer, a major barrier to finding a cure is the persistence of a rare population of cells capable of giving rise to relapse (for malignancies) or viral rebound (in the case of HIV) during treatment (Figure 2). Identifying, quantifying and characterising these cells are critical issues for designing therapies in both cases. Work presented at this forum demonstrated a number of innovative approaches to improve the understanding of these two analogous and rare cell populations.

Looking to define the exact anatomical location of functional viral reservoirs, Francois Villinger (University of Louisiana at Lafayette, USA) talked about the use of immuno-PET with CT scan as a tool for *in vivo* imaging of viral replication [5]. Using ^{64}Cu-labelled antibodies targeted against HIV *env* (as well as a number of non-HIV targets including CD4, CD8 and $\alpha4\beta7$), he was able to non-invasively measure the anatomical distribution of cells of interest in SIV-infected macaques. This technique is a promising tool for studying viral rebound dynamics following treatment interruption and the impact of therapies. Villinger also presented preliminary results from SIV-infected macaques treated with anti-$\alpha4\beta7$ (a promising therapy that has been shown to induce sustained virological remission in macaques) [6], showing that the monoclonal antibody aided CD4 restoration in gut, spleen and lymph nodes.

Measuring the HIV reservoir, which is largely present in lymphoid tissue, requires direct sampling of latently infected cells. The ability to accurately quantify reservoir size in tissues, without invasive biopsies, would be a significant step towards HIV cure. Sarah-Jane Dawson (Peter MacCallum Cancer Centre, Australia) presented her work using cell-free circulating tumour DNA (ctDNA) in plasma to monitor tumour progression in tissues. The ctDNA is identified as coming from a tumour source on the basis of specific genomic changes; its presence and levels can be used to monitor how treatment is progressing as well as detecting minimal residual disease post therapy [7,8]. This elegant solution highlights the analogous challenges in assessing remission in HIV and cancer – two conditions in which tissue represents a site of residual disease.

Our ability to study and target HIV reservoirs has been limited by the rarity of latently infected cells in patients on ART and the absence of specific biomarkers. Following on from the recent work identifying CD32a as a marker of an enriched CD4+ reservoir [1], Genevieve Martin (University of Oxford) presented a characterisation of CD32-expressing CD4 T cells in a cohort of individuals treated during primary HIV infection. These results confirmed enrichment of HIV DNA in CD32+ CD4 T cells, which

Box 1. HIV and cancer research: the community perspective

As new advances in innovative therapeutic strategies for HIV cure and remission move closer to the clinic, community engagement and participation of people living with HIV is crucial. A round-table discussion on the design of, and participation in, clinical trials provided the community perspective; this was voiced by Michael Louella (defeatHIV Community Advisory Board) and Gilliosa Spurrier (Melanoma France). Current inclusion criteria in many clinical trials are quite stringent, excluding large numbers of potential participants. For HIV remission studies, the majority of ongoing trials include participants who control the virus with antiretrovirals and are doing well overall. However, those who may have the most to gain from a potential remission do not necessarily meet these inclusion criteria. When trying to understand the motivation behind clinical trial participation, it should be considered that current participants are often motivated by altruism and a desire to help move research forwards, even with the understanding that this research will not necessarily benefit them directly. Among the reasons limiting the involvement of people living with HIV in clinical research, the panel cited inadequate engagement and education. Misleading media reports, sometimes promoting false hope and unrealistic timelines for HIV cure, are also clouding the issue, making it harder to get potential participants involved. In the interface between HIV and cancer, people living with HIV are often excluded from cancer trials and *vice versa*. Louella concluded with a *vade mecum* for improving community involvement in research:

- Increased funding for community engagement
- Planning for early involvement and future access
- Supporting effective community response
- Redress the balance of power between researchers and participants

Finally, the panel stressed the importance of expanding the selection of population groups to include more female participants, children and adolescents, and importantly, to ensure that participants from resource-limited settings are included, even if access issues remain present.

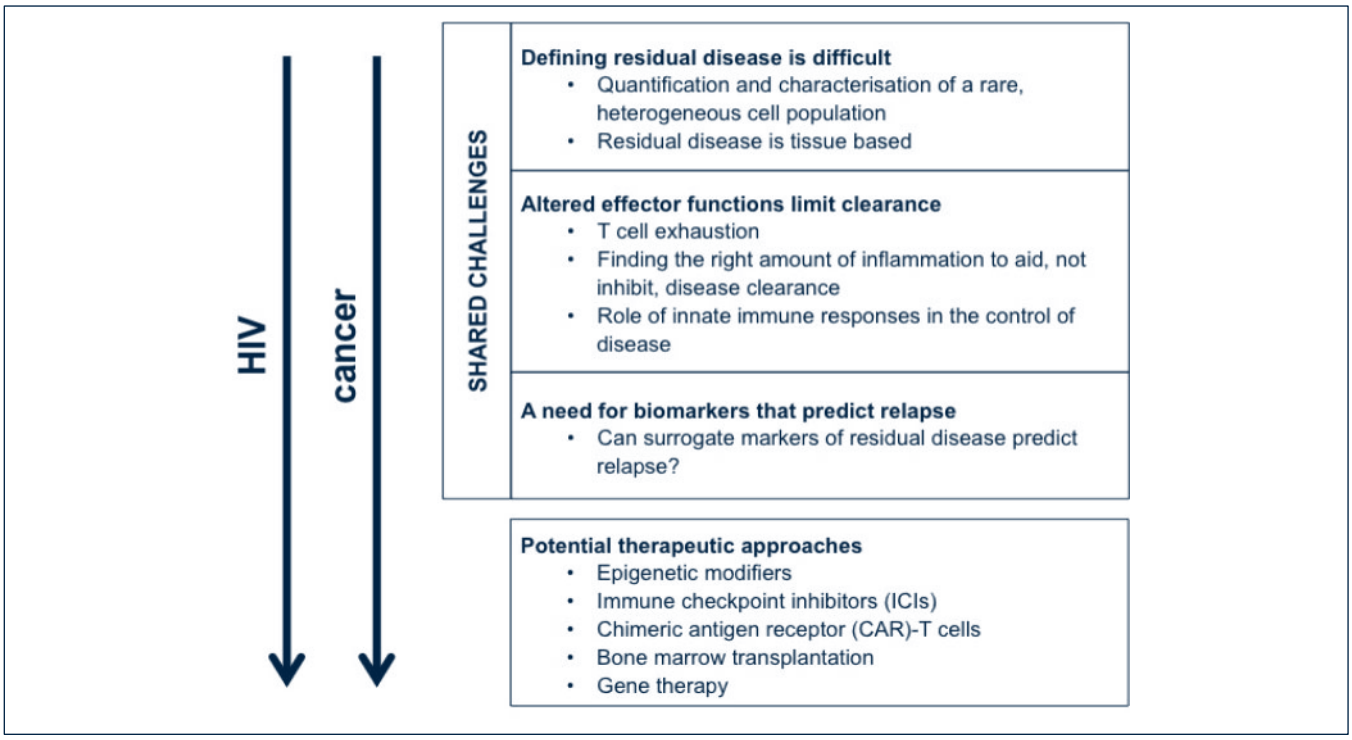

Figure 1. Parallels between HIV and cancer highlighted during the 2017 IAS Cure and Cancer Forum

also expressed high levels of immune checkpoint receptors PD-1, Tim-3 and TIGIT [9].

Epigenetic control

The broadening of our understanding of epigenetic control mechanisms was a key theme throughout the meeting. Jonathan Karn (Case Western Reserve University, Cleveland, USA) highlighted that epigenetic silencing is progressive and hierarchical – with histone deacetylation, as well as histone and DNA methylation all occurring to drive proviruses towards more permanent states of silencing. Histone deacetylase inhibitors (HDACis) have been investigated as latency-reversing agents (LRAs) in clinical trials [10-14]. Karn presented findings that showed several inhibitors of the histone methyltransferases EZH2 and EHMT2 were able to reverse latency *in vitro*, acting synergistically with vorinostat or IL-15 [15]. Looking then to DNA methylation around the provirus, Carine van Lint (Université Libre de Bruxelles, Belgium) presented work identifying UHRF1 as a factor which is recruited to the 5′ LTR and plays a role in DNA methylation-mediated silencing of viral expression. This molecule has not previously been linked to HIV latency, but as a potential therapeutic target for several malignancies, therefore inhibitors of UHRF1 could also play a role as LRAs [16].

The epigenetic work presented at the meeting not only focused around the regulation of proviral expression but also extended to include the epigenetics of effector cell fate. An initial example of this was described by Geneviève Almounzi (Institut Curie, France) who spoke about how the SUV39H1–H3K9me3–HP1α pathway, which is able to promote silencing of Th1 genes, ensures the stability of the Th2 lineage [17]. Using a *Listeria* infection model, Sebastian Amigorena (Institut Curie, France) also described a role for SUV39H1 in the silencing of genes that are involved in CD8 T cell memory differentiation. This work raises interesting possibilities about targeting the epigenome to augment anti-HIV or anti-tumour responses. Demonstrating that HIV infection itself can also induce epigenetic changes that impact on immunity, Stephanie Shiau (Columbia University, USA) presented a poster showing that early-treated HIV-infected children have DNA methylation dysregulation at a number of loci, including NLRC5, which regulates MHC class I expression [18].

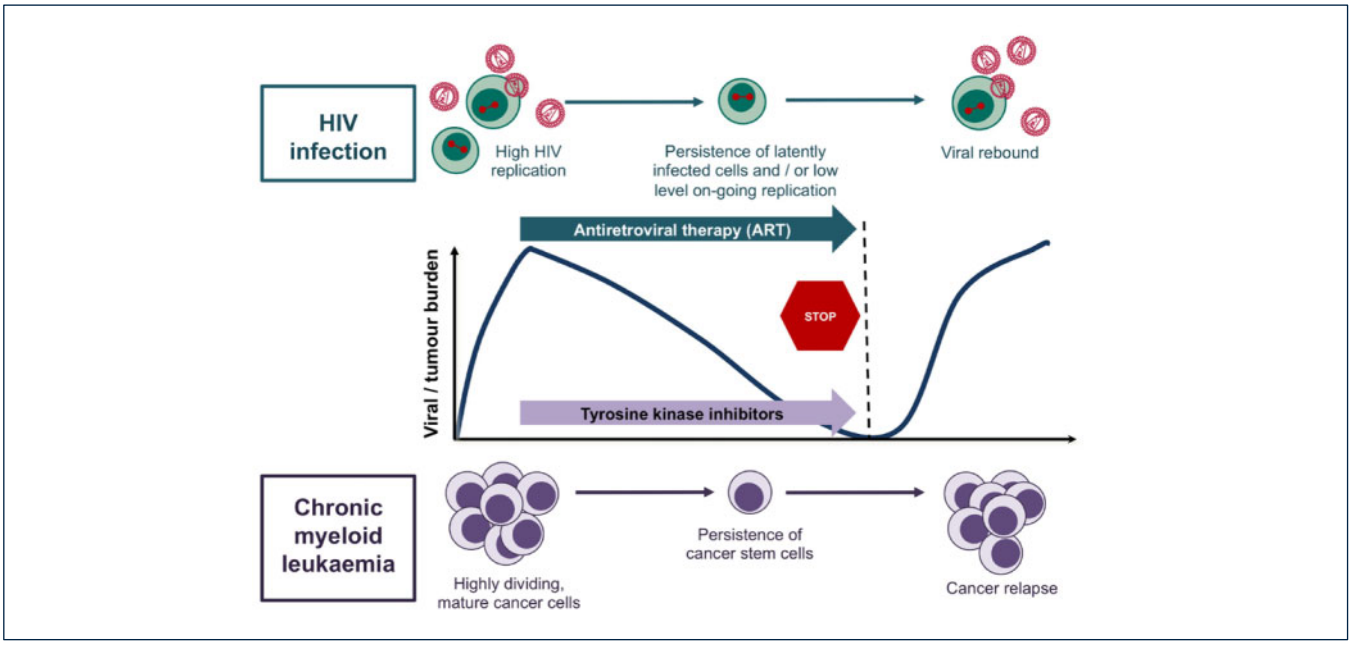

Figure 2. Residual disease in cancer and HIV infection is a common barrier to achieving cure. In HIV infection, antiretroviral therapy (ART) rapidly controls high viral replication in activated CD4 lymphocytes. However, latently infected lymphocytes are not targeted by ART and their persistence produces viral rebound upon treatment interruption. In chronic myeloid leukaemia, highly dividing mature cells are kept under control by tyrosine kinase inhibitors. Among the tumour population some cells are more resistant to treatment, but full remission can be achieved in the majority of patients. The persistence of cancer stem cells that are not eliminated with tyrosine kinase inhibitor treatment may give rise to relapse

Numerous therapeutic approaches to blocking or reactivating HIV were presented, targeting both the virus itself, as well as epigenetic pathways regulating its expression. Adam Capoferri (Johns Hopkins University School of Medicine, USA) presented data from AMC075, a Phase II study of conventional chemotherapy with or without vorinostat for individuals undergoing treatment for HIV-associated lymphoma. Consistent with another recent study using vorinostat [14], they did not observe any changes in HIV reservoir size (measured by quantitative viral outgrowth assay) with this therapy [19].

Several classes of licensed small-molecule drugs were described as either novel LRAs, or as possessing antiviral activity. Isa Muñoz-Arias (University of California San Francisco, USA) presented data showing that three small-molecule drugs used in cancer therapeutics (sunitinib, sorafenib and bortezomib) are able to reactivate latent virus from latently infected cell lines, as well as *ex vivo* from primary CD4 T cells. In patient samples, sunitinib was able to induce more cell-associated HIV RNA than either romidepsin or bryostatin [20]. A Jak inhibitor, baricitinib, was the focus of the work presented by Christina Gavegnano (Emory University, USA); this drug was shown to have antiviral activity and to prevent HIV reactivation in both lymphoid and myeloid cells [21]. Mayte Coiras (Instituto Carlos III, Spain) presented a poster demonstrating the antiviral and anti-proliferative activity of the tyrosine kinase inhibitors dasatinib and ponatinib, both of which are currently used in the treatment of chronic myeloid leukaemia (CML) [22]. The antiviral activity of these molecules was mediated through the inhibition of SAMHD1 phosphorylation and lymphocyte proliferation blocking [23].

Immunology and inflammation

Innate immunity revisited

The parallel evolution of innate and adaptive immune systems has allowed for both rapid responses to 'non-self', as well as targeted responses and the development of immunological memory. While the role of the adaptive immune system in targeting HIV has been extensively studied, recent work has underlined a major role of the innate immunity in the control of HIV infection and, particularly, with regard to the establishment of viral reservoirs. As with adaptive immune responses, there are parallels in the way innate immunity responds to infectious diseases and cancers. In particular, innate immune mechanisms, including interferon induction and natural-killer (NK) cell activity, are able to tackle both cancers and virally infected cells.

Michaela Müller-Trutwin (Institut Pasteur, France) compared the immune response in acute SIV infection between two non-human primate models, the African green monkeys (AGM) in which the infection is not pathogenic and the Asian macaques (AM), which develop AIDS. In both models there is high plasma viral load but new data presented at the meeting showed a decrease in SIV-RNA levels in lymph nodes in AGM but not in AM, particularly in B cell follicles. The control of viral load in lymph nodes was associated with the recruitment of a specific population of CXCR5+ NK cells to the follicles in AGM that was absent in AM. Redistribution of NK cells to the follicles was associated with high levels of membrane-bound IL-15 in follicular dendritic cells. Overall these findings unveil a new NK function in controlling viral replication specifically in lymph nodes, but not in other organs such as the gut-associated lymphoid tissue (GALT).

Mirko Paiardini (Emory University, USA) compared two groups of SIV-infected macaques treated with ART alone or in combination with IL-21 and IFNα. IL-21 was added with the aim of preserving Th17 cell activity and decreasing microbial translocation and inflammation. IFNα was introduced to improve natural immune responses and induce interferon stimulated genes (ISGs). Macaques treated with ART plus IL-21 and IFNα maintained lower levels of activation and had a reduced viral reservoir. In this group, viral rebound after treatment interruption was modestly delayed and reduced, probably in association with decreased activation and preservation of Th17 responses [24].

Further highlighting the role of interferons in HIV control, Paul Hertzog (Hudson Institute, Australia) gave an overview on the type I interferon (IFN) system. He presented original data on IFNε, which is expressed in the female genital tract and regulated by oestrogens

[25]. IFNε displays lower affinity for IFN receptors and lower specific activity than other members of type I IFNs, and is a good example of the functional diversity of type I IFNs. It displays antiviral activity, protecting from HSV-2 and chlamydia infections in murine models, as well as showing antiviral activity against HIV-1 *in vitro* [25,26]. Linking control mechanisms of viral infections and cancers, Hertzog presented data showing that IFNε also displays anti-tumoral activity, both through the regulation of anti-tumour immune cells and direct suppression of ovarian cancer development and dissemination. Linking type I interferons to the control and establishment of HIV reservoirs, Paul Cameron (Doherty Institute, University of Melbourne, Australia) presented a poster that extended previous observations [27] showing that treatment with IFNα and IFNβ prior to infection reduces the number of latently infected cells. However, once latency is established IFNα increases viral reactivation [28].

Overall, these studies suggest that innate immune mechanisms can play a major role not only in the establishment of the reservoirs in early infection, but also in their control during the chronic stage of infection.

Adaptive memory responses and the control of HIV reservoirs

Several presentations addressed the potential role of adaptive cellular responses in the control of HIV reservoirs. Ranjit Sivanandham (University of Pittsburg, USA) suggested a depletion of T regulatory cells (Tregs) as a means to decrease the size of the reservoir and enhance cytotoxic T lymphocyte (CTL) responses against HIV. This hypothesis is based on previous results showing that Tregs represent an important reservoir in SIV/HIV infections and contribute to the impairment of CTL responses [29]. Active depletion of Tregs using diphtheria immunotoxin coupled to CCR4 and IL-2 or low doses of cyclophosphamide (Cy) were assayed in SIV-infected macaques. Both immunotoxins were shown to be effective in depleting Tregs and inducing CTL responses, thus aiding in the control of viral replication [30].

Further investigations as to how we can augment the 'kill' needed to eradicate HIV were presented in the poster sessions. Victor Appay (Centre d'Immunologie et des Maladies Infectieuses, France) showed in a poster that it is possible to prime CD8 T cell responses against tumour antigens or HIV using stimulator of interferon gene (STING) ligands. In particular, cGAMP was extremely potent in inducing effector functions, including cytotoxic potential [31]. In a model of resting lymphocytes, Alba Ruiz (IrsiCaixa, Spain) measured HIV reactivation and cytotoxic T lymphocyte (CTL) killing driven by different combinations of LRAs. Cellular killing was directly related to both LRA potency but also the CTL activation state. Interestingly, besides its role as an LRA, bryostatin increased the activation status of CTLs, leading to enhanced cell killing [32].

Clinical approaches

A major focus of the forum was the recent developments in immunotherapy in the field of oncology, and the potential for this type of therapy to be applied to HIV. Aurélien Marabelle (Gustave Roussy Hospital, France) discussed the recent paradigm shift in cancer therapy, with therapies now targeting immune cells rather than the malignancy itself. This has been accomplished by using monoclonal antibodies against immune checkpoint molecules on T lymphocytes. Blockade of these pathways, which have been linked to T cell exhaustion, can restore effector function and generate a strong anti-tumour response. Immune checkpoint inhibitors (ICIs) targeting several molecules have been approved for clinical use; these include the anti-cytotoxic T lymphocyte antigen (CTLA-4) antibodies ipilimumab and tremelimumab, and the anti-programmed death-1 (PD-1) receptor antibodies nivolumab and pembrolizumab. Compared with conventional chemotherapy and radiation therapy, these drugs have dramatically improved the outcome of certain malignancies. They are remarkable in terms of the magnitude of clinical benefit seen, the broad range of cancers for which they have efficacy and a relatively durable response. These developments are heralding a new standard of care in the field of oncology.

Not all cancer patients, however, benefit clinically from immune checkpoint blockade and the identification of factors that can predict clinical response is needed. Moreover, there is significant associated toxicity – and caution needs to be exercised due to the predominantly autoimmune nature of this toxicity, which differs from conventional therapy. Pre-clinical work has already shown that combinations of ICIs might have increased efficacy, but combining these drugs is also likely to result in a worse safety profile. These drugs are expensive and the field needs to develop new clinical research methodology in order to identify the patients who will benefit most from them, and to refine their schedule and route of administration [33].

ICIs could potentially be used to augment anti-HIV immunity or act as LRAs, and this was a major theme of the work presented at the forum. The PD-1/PDL-1 axis has been shown to be a critical player in T cell exhaustion, a state of immune dysfunction encountered in cases of chronic infections and cancers [34]. Bulk CD4 and CD8 activated T cells also express high PD-1 levels during HIV infection [35] and PD-1 expression on HIV specific T cells is associated with T cell exhaustion and disease progression. PD-1 is significantly up-regulated on HIV-1 specific CD8 T cells, and some studies have already shown that blockade of the PD-1/PDL-1 pathway would increase HIV-specific CD4 and CD8 T cell function [36,37].

Sharon Lewin (Doherty Institute, University of Melbourne, Australia) presented work on the ability of ICIs to disrupt latency *in vitro*. In HIV-infected individuals on ART, the HIV reservoir is enriched in PD-1^{hi} cells and cells that express multiple immune checkpoint markers [38,39]. The work from her group aimed to address whether combinations of ICIs (including anti-PD-1) could be used to reverse latency, with the potential to be used as part of a strategy for cure. Lewin reported that when using an *in vitro* model, anti-PD-1 antibodies disrupt HIV latency in non-proliferating but not in proliferating T cells. In the non-proliferating cells latency reversal was possible only with the presence of T cell activation (with staphylococcal enterotoxin B, SEB) or with multiple ICIs. In proliferating cells latency reversal was only possible with multiple ICIs [40]. These findings suggest that co-expression of IC markers, especially of proliferating latently infected cells, may limit the potency of anti-PD-1 alone for latency reversal.

Thus far, ICI use in HIV-infected individuals has been limited, and initial studies have focused on HIV-infected individuals receiving immunotherapy for cancer [41,42]. Timothy Henrich (University of California San Francisco, USA) reported on three cART-suppressed individuals receiving multiple doses of anti-PD-1 therapy (nivolumab) for malignancies (head and neck, and cutaneous squamous cancer). Their results showed that anti-PD-1 treatment did not lead to sustained or consistent decreases in CD4 HIV-1 DNA or cell-associated RNA but was associated with a transient increase in CD8 T cell responses to HIV-1 [43]. Presenting further data on PD-1 blockade in HIV-infected individuals, Brigitte Autran (Hôpital Pitié-Salpêtrière, France) described a case series of 12 HIV-infected patients treated with nivolumab for non-small cell lung cancer (NSCLC) or melanoma [44]. Six of the 12 individuals had a partial tumour response or stable disease with nivolumab therapy, with the remainder having progressive disease.

Overall, therapy was well tolerated and all individuals had stable CD4 cell counts, and remained virologically suppressed, throughout nivolumab treatment. Two of these individuals were presented in more detail. In one, a transient increase in HIV DNA levels was observed, alongside an increase in HIV-specific CD8 T cells [41]. In the other, a three-fold decrease in HIV-DNA levels was observed and this coincided with a dramatic increase in HIV-specific T cells. In both individuals, a decreased expression of immune checkpoint receptors was also observed with nivolumab therapy. Taken together, these two studies suggest a potential effect of PD-1 blockade on anti-HIV CD8 responses. Changes in the HIV reservoir were observed in some, but not all, individual studies and further work is needed to establish whether PD-1 blockade has a consistent effect on HIV reservoir size.

The winner of the IAS-ANRS Dominique Dormont Prize, Maria Salgado (IrsiCaixa, Spain), presented her work in the IciStem consortium. She aimed to identify factors that relate to the reduction in the HIV reservoir size in HIV-infected individuals undergoing allogeneic stem cell transplant for malignancy. Five out of the six patients followed had undetectable HIV reservoirs following allogeneic transplant, and time to full donor chimerism and alloreactivity (graft-versus-host disease) were identified as factors that are potentially important for achieving this outcome [45].

Another novel strategy that is promising in targeting cancers, and potentially HIV, is the use of CAR-T cells (chimeric antigen receptor T cells). Some clinical data were presented by Lawrence Corey (Fred Hutchinson Cancer Research Center, USA) on the use of CD19-targeting CAR-T cells in haematological malignancy, with high response rates in refractory acute lymphoblastic leukaemia and non-Hodgkin's lymphoma. He highlighted that significant toxicities have been observed with CAR-T cells, in particular neurological side effects and cytokine release syndrome (CRS). Anti-HIV-1 CAR-T cells may have the potential to kill HIV-1-infected cells that have escaped endogenous immune responses. These cells have been shown to kill autologous virally infected cells *in vitro*. Corey suggested that CAR-T cells designed to target HIV will need to possess several characteristics in order to succeed *in vivo*. These include modifications to protect CAR-T cells from HIV-1 infection, access to immunological sanctuary sites (including germinal centres of B cell follicles) and long-term persistence.

Scientists working in HIV and cancer research share many challenges in the development of targeted and effective therapies for eradication. These parallel challenges mean that several therapeutic approaches developed in the cancer field are being investigated for HIV cure. The efficacy and safety of long-term ART means that there is, however, a significant difference in the acceptable level of toxicity between therapies for HIV cure and malignancies. Further work is needed to determine whether ICIs and CAR-T cell-based therapies are safe in the clinic before their use in attempting to cure HIV.

Conclusion

Specialists in the research fields of HIV and oncology came together in this one-and-a-half-day meeting in order to foster an exchange of ideas. The various sessions highlighted some of the similarities between the two areas (summarised in Figure 1). One area of particular interest was diagnostics, as it will be essential to characterise and quantify the rare cell population that is responsible for residual disease in both cancer and HIV. Ongoing collaboration between researchers in HIV and cancer will be important in the use of immunotherapy to manipulate the immune system to elicit adequate responses. While the scientific community remains cautious, conscious that effective therapies for cancer may not give the desired results for HIV cure or remission, data presented at the forum highlighted the fact that a synergistic approach will prove to be beneficial to both disciplines.

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