HIV infection: what should be considered in approaches for a cure?

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At a satellite meeting prior to the International AIDS Conference in Washington DC in July, a great deal of discussion was focused on finding a 'cure' for HIV infection [1]. Although this objective has been discussed at various times over the past decade, the real incentive for this goal comes from the encouraging findings with Timothy Brown, also known as the 'Berlin patient.' This HIV-infected man received hematopoietic stem cells for his leukemia from an human leukocyte antigen-matched donor whose genome naturally lacked CCR5, the major receptor for HIV. In over 5 years, after two transplants, Mr. Brown appears to be cured of HIV as well as leukemia [2]. Although potentially infected with both a virus that requires CCR5 for entry and a small population of viruses that can infect cells by another receptor, no infectious virus can be recovered from his blood and other tissues. This finding includes biopsies from the brain, bowel, and lymph nodes. Certainly his 'cure' encourages approaches that could mimic this achievement in all HIV-infected individuals.

One direction that might accomplish this goal involves genetic engineering in which the hematopoietic stem cell of an infected individual is manipulated genetically to lack CCR5 expression [3]. Then the genetically modified cells are administered back to the HIV-infected individual. These cells will repopulate the immune system and provide a defense against HIV that cannot be compromised by an HIV infection. This objective, however, has several hurdles including the replicative capacity of the altered stem cells, their differentiation potential and their extent of engraftment. Notably, moreover, although encouraged by some funding groups, the approach has been criticized because some believe it will be too difficult to apply to HIV-infected individuals worldwide. The answer to that critique is that history has shown that once a goal has been reached, it can be improved and applied to larger groups. Take for examples, the conquest of Mt. Everest, the landing on the moon, and the advances in computers from the time they occupied a full city block. Importantly, the creativity of scientists through innovation can provide new achievements universally by overcoming the global challenges.

The other approach toward a 'cure' that has gained enthusiastic support and could be undertaken relatively easily worldwide is to eliminate reservoirs of HIV in the immune system [4]. This objective is addressed through activation of cells that carry latent virus, particularly in the major target cell of HIV, the $CD4^+$ lymphocyte [5–7]. By this technique, certain compounds would be used to activate the virus from its silent state and have it replicate in the cells that are infected. The advocates for this approach believe that the replicating virus will kill the infected cell via cytolytic mechanisms, or the host immune system will now recognize the infected cell and eliminate it by killing.

This second direction toward a 'cure,' however, also has some problems and major misconceptions that need to be appreciated. First, it assumes that once HIV begins to replicate, it will kill the infected cell. Past research has indicated that HIV can replicate to varying degrees in $CD4^+$ cells and often does not kill these cells [8–10]. The extent of cytopathology depends on the amount of viral envelope glycoprotein produced by the cell [10]. Virulence is defined by the kinetics of virus replication

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in the cell, the extent of progeny production, and the cytopathic nature of the viral envelope protein [11]. Second, the compounds now being evaluated can be toxic and may not be very effective [12,13]. A better understanding of viral latency and approaches to achieve this objective of virus activation and infected cell killing are needed.

Third, a requirement that must be appreciated with the 'flushing out' technique is that the patients are on antiretroviral treatment (ART). A large number of studies have shown that such antiviral therapy reduces the antiviral responses. Anti-HIV antibodies may become virtually undetectable [14] and the cellular anti-HIV immune response is placed in a quiescent state [15–17]. These findings explain why after 10 or more years of successful antiviral therapy with plasma virus down to undetectable levels, HIV rebounds when ART is stopped [18,19]. The immune antiviral response essentially is driven by the presence of HIV antigens and once the virus is successfully suppressed, the immune system no longer is activated against it.

Another important fact that must be appreciated in achieving a 'cure' is the wide variety of reservoirs of HIV in the body. Whereas many consider the $CD4^+$ cell as the major target, and perhaps the only one that contains an important reservoir, several studies over the years have shown the presence of HIV in long-lived monocytes/macrophages [20], follicular dendritic cells [21] and cells in several tissues such as the brain, bowel, kidney, testes, heart, and liver [11,22]. These cells can replicate the virus at a low level and not undergo any cell death. How can one advance toward a 'cure' if such viral reservoirs still remain?

Regarding two approaches described above (i.e: 'flushing out' and targeting the HIV reservoir), a major direction to a 'cure' could be found in HIV-infected individuals considered long-term survivors, or elite controllers [23,24]. They have an active antiviral immune system, which can achieve undetectable viral levels in the blood and similar low levels of virus in tissues in the absence of therapy. In these people, the immune system continues to control the virus most likely by cellular immune mechanisms, as antibody levels in these individuals are often low. Retaining their protective response against HIV can be approached through immunization with viral antigens that can induce both innate and adaptive immune responses [25].

Several studies have shown that certain immunization procedures given to individuals receiving ART can maintain their anti-HIV immune responses [26–28]. Until now, these studies were aimed generally at demonstrating the value of therapeutic immunization in a structured treatment interruption approach to assess the impact of HIV replication on re-activating the immune system. The inability of this strategy to control virus rebound following ART cessation brought pessimism in the field.

Importantly, these previous studies evaluated therapeutic immunization using only one agent administered as a single round for a short period. The expected effect was measured only after a brief period of follow-up. However, other study designs with a longer follow-up period would be better suited to demonstrate an effect of therapeutic immunization on reducing the population of long-lived latently infected $CD4^+$ T cells (estimated at 10^5–10^7 cells) [29]. This residual pool of latently infected cells can be compared with the remaining malignant cells that can persist for a long time following chemotherapy in cancer patients. Complete HIV eradication can require multiple and iterative therapeutic immune interventions over an extended period as is needed to eliminate all cancer cells.

Toward this immunologic reconstitution, several vaccine candidates have been developed including viral vectors (e.g. pox virus) and dendritic cell-based vaccines that are much more immunogenic than previous designs [27]. Recent experimental studies have also shown that immunomodulators may synergistically enhance functional $CD8^+$ T-cell responses improving control of virus replication [30]. Notably, a combination approach utilizing several different immunologic strategies seem necessary to bring about virus eradication or a 'functional cure' [31].

Postinfection immunization therapy would be used in HIV-infected individuals receiving stem-cell therapy to help in the initial control of HIV and in those patients administered compounds, which activate HIV from latent reservoirs. Moreover, because death to cells, such as astrocytes in the brain or cells in the kidney and other tissues could be harmful, it would appear that encouraging immune responses that suppress HIV replication without killing the cell would be the ideal antiviral response [32].

These scientific challenges to the research community looking for a cure of HIV infection need to be appreciated, but not detract from an ultimate objective which we feel can be achieved: the ability of the immune system to control the virus in all HIV-infected individuals and effect a 'functional cure' in which eventually antiretroviral drugs are no longer needed. The latter objective may require booster immunizations in case there is residual virus that might reappear when the immune system recognizing HIV is not active.

An immune system mirroring what is seen in elite controllers could keep in check any viruses that remain in tissues for which activation cannot reveal their presence. Importantly, the induced anti-HIV immune responses can arrest the spread of the virus to other cells in the host and retain very low levels of virus expression, potentially

for a lifetime. The end result will be an achievement mirroring or approaching an HIV 'cure.'

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Conflicts of interest

There are no conflicts of interest.

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