



## Commentary

## DC-based immunotherapy as strategy to purge the HIV reservoir?

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Dendritic cells (DCs) are a specialized family of professional antigen presenting cells. After Ralph Steinman and Zanvil Cohn first isolated DCs from mouse spleens in the early 1970s [1], DCs have been found to be critical for inducing adaptive cellular and humoral immunity. DCs can also activate natural killer cells and exert antibody-dependent effector functions. In short, DCs function as crucial bridges between the innate and adaptive arms of the immune system. Therefore, engaging DCs plays a central role in many current HIV curative strategies, either through direct *in vivo* stimulation (e.g. using TLR7 or TLR9 agonists) or by *ex vivo* expansion, stimulation and reinfusion as a dendritic cell immunization. In the present issue of *EBioMedicine*, Kristoff and colleagues [2] report findings from an innovative study on the potential role of a subtype of DCs, antigen-presenting pro-inflammatory type 1-polarized monocyte-derived dendritic cells (MDC1), in the treatment of chronic HIV infection. Using *ex vivo* experiments, the authors found that cytomegalovirus- and HIV-antigen stimulated MDC1 can reverse HIV-1 latency in infected autologous CD4 T cells from HIV infected individuals on combination antiretroviral therapy (cART). In addition, the authors also report that HIV-antigen pulsed MDC1 can activate cytotoxic T cell lymphocytes (CTLs) which are capable of killing HIV-infected cells.

The work of Kristoff and colleagues is important because latently infected memory CD4+ T cells are believed to be the main barrier against a cure for HIV. While cART effectively prevents viral replication by blocking HIV's transcription, the treatment has no impact on transcriptionally silent, latent proviruses and does not promote HIV-specific immunity [3]. Consequently, uncontrolled viral replication resumes within weeks in the vast majority of individuals who stop cART. Thus, the dual effect of antigen-exposed MDC1s reported by Kristoff et al. has the potential to both demask the HIV reservoir through activation of viral transcription as well as to contribute to viral reservoir elimination by activating HIV-specific CTLs [2]. This two-step tactic is often referred to as the “kick and kill” approach to cure HIV infection. The central hypothesis of this approach is that a combined reduction in the size of the reservoir and potent HIV-specific immune response will induce a state of durable disease remission in the absence of cART [3].

Efforts towards developing a “kick and kill” HIV cure strategy have identified small-molecule drugs that can reverse HIV-1 latency *in vivo* [4]. However, despite the induction of viral transcription by these agents, latency reversal alone has not significantly delayed viral rebound after interrupting cART [4]. Nor has latency reversal led to a reduction in the replication competent proviral reservoir. These outcomes are likely due to limited potency of the latency reversing agents as well as inefficient immune mediated clearance of HIV-1 expressing cells [5]. The present study by Kristoff et al. proposes an alternative approach to tackle HIV latency using MDC1. Their approach is unique in that the investigators used primary cells from individuals on cART to create an autologous mature DC subtype which the authors demonstrated could both mediate latency reversal in freshly isolated CD4+ T cells and induce effector cells capable eliminating infected cells *ex vivo*. This report follows a recent study published in the same journal in which the combination of DCs and T cell receptor stimulation was shown to act synergistically in reversing HIV latency in primary cells [6]. The next major challenge is to determine if these promising *ex vivo* observations can be translated into effective clinical strategies.

To date, more than a dozen clinical trials have tested DC-based HIV immunotherapy as a strategy to induce virological control in the absence of cART among both treated and untreated HIV infected individuals and in so doing have pioneered clinical approaches that overcome major challenges to DC-based immunotherapies [7]. To achieve sufficient cell numbers for preparing autologous DC products, trial participants are usually subjected to leukapheresis – a method by which large numbers of peripheral blood mononuclear cells (PBMCs) can be harvested from the blood whilst preserving erythrocytes in the individual. Isolated monocytes are then exposed *ex vivo* to a cytokine cocktail to differentiate them into MDC which are subsequently stimulated with another combination of cytokines to induce maturation/activation. The procedure for this differentiation/maturation process varies from one study to another, as does selection of HIV antigens, how HIV antigens are loaded onto DCs, and the selected vaccine administration approach [7]. Overall, the results from the trials in HIV infected individuals have been disappointing. About half of these trials reported moderate decreases in plasma HIV RNA set-point (less than  $<1 \log_{10}$ ) and some trials also found transient increases in HIV-specific CTL responses but without any evidence of virological control in the absence of cART [7]. A gold standard in HIV or in cancer research for generating and delivering DC-based immunotherapy has not yet been established. However, one potential explanation for the lack of success could be sub-optimal DC function, evidenced by low IL-12 production, which has been attributed to a poor outcome [8]. MDC1 may overcome these

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limitations as they are deliberately programmed to subsequently release high amounts of the CTL-inducing cytokine IL-12p70 upon interaction with CD40L. Whether this *ex vivo* priming approach is sufficient to overcome the formidable challenge of inducing HIV remission in humans remains to be determined but new clinical trials testing MDC1 as immunotherapy in HIV infection are now underway that will help answer this question. In addition, the role of *in vivo* DC priming is also currently being explored in trials combining TLR7/9 agonists [9,10] with broadly neutralizing monoclonal antibodies against HIV envelope as well as with HIV immunization. Results from these upcoming trials will be extremely informative for the design and development of future DC-based immunotherapy approaches.

### Conflicts of interest

The author declare no conflicts of interest.

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