**Cancer immunotherapies: the holy grail for the HIV-1 cure?**

**Inmunoterapias del cáncer: ¿el Santo Grial para la curación del VIH-1?**

**Abstract**

The development of immunotherapies to boost the immune system are essential to advance towards the cure of people living with HIV-1. This article put into perspective the opportunities that current cancer immunotherapies can bring and the challenges to face in search of the holy grail for the HIV-1 Cure.

**Keywords:** HIV-1, cure, immunotherapies, cancer, immune checkpoint receptors.

The tremendous success of combined active antiretroviral therapy (cART) in the control of the HIV-1 pandemic has challenged scientists to advance the search for a cure. The curative strategies will need to face two crucial aspects of virus biology: 1. The maintenance of the HIV-1 reservoir distributed across tissue sanctuaries (Chun et al., Nat Med 1995); and 2. The immune dysfunction driven by persistent antigen activation despite fully suppressive cART (Wherry et al., Nat Immunol 2011). Therefore, immunotherapies aiming to boost the immune system are essential to advance towards the cure of people living with HIV-1.

In recent years, we have witnessed an unprecedented clinical revolution in the cancer field by the use of immunotherapies targeting immune regulatory pathways leading to durable tumour remission. These clinical studies have allowed the approval of immune checkpoint inhibitors (ICI) in various types of cancer (Ribas et al., Science 2018). In this context, it is possible to draw parallelisms between cancer and HIV-1. Both diseases lead to cellular persistence in specific locations or tissue sanctuaries, and the potential for disease recurrence is present at any time after stopping treatment. Encourage by these similarities cancer immunotherapies are a new therapeutic avenue for HIV-1 cure. The rationale behind is the potential activity to reactivate the HIV-1 reservoir while boosting antiviral immunity. Several clinical trials have demonstrated the safety of the use of ICI in HIV-1 individuals with solid tumours (Uldrich et al., Ann Oncol 2019; Cao et al., Ann Oncol 2020). Only one case report showed a sustained reduction of the viral reservoir after anti-PD-1 treatment (Ghiot et al., Ann Oncol 2018).

Meanwhile, additional clinical and case studies demonstrated the limited impact of ICI in the reduction of the reservoir despite increases in HIV-1 specific cellular immune responses (Blanch-Lombarte et al., J Clin Microbiol 2019, Garsia et al., AIDS 2015, Gay et al., J Infect Dis 2017). Therefore, further studies are needed to understand the potential of ICI for the cure. In this way, the challenge for current ICI is to balance immune activation while preserving tissues from off-target damage.

The complexity laying behind the immune regulatory pathways is enormous, and the diversity of immune checkpoint receptors (IC) very broad (Rumpret et al., Nat Rew Immunol 2020). Thus, the combinatorial expression of IC associated with immune exhaustion of HIV-1 specific CD8+ T-cells limiting their effectiveness to clear the reservoir (Ruiz et al., Front Immunol 2019). Besides, HIV-1 infection may alter the local tissue microenvironments and immune effector functions by the regulation of IC expression. Although multiple lines of evidence support the use of ICI targeting PD-1, PDL-1, TIGIT or TIM-3 among others IC for the recovery anti-HIV-1 immune functions (Day et al., Nature 2006; Chew et al., PloS Path 2016; Jones et al., J Exp Med 2008), the degree of functional reinvigoration and the impact in the reduction of the reservoir size is still unclear. Besides to ICI, the use of advance immunotherapies in T cell engineering such as CAR T cells, DARTs or BiTEs are showing promising results in cancer and should be further valuable approaches for the HIV-1 cure (Prado et al., Front Immunol 2020).

In summary, the present and the future for immunotherapies for HIV-1 will parallel efforts with the cancer field bringing challenges but also opportunities in search of the holy grail for an HIV-1 Cure.

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