

Depleting the latent HIV-1 cell population using ²²⁵Ac-labeled anti-CD4+ targeted radioimmunoconjugates

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Overview: A cure for HIV-1 has been elusive. Antiretroviral therapies eliminate the circulating viral load, but upon cessation of treatment the viral load rebounds from latent reservoirs. The Berlin patient is the only known patient cured of HIV-1 and underwent an aggressive ablation/transplant strategy where all T-cells were purged and replaced with T-cells resistant to infection. We present a targeted ablation strategy using a radioimmunotherapy (RIT). Anti-CD4 antibodies ibalizumab, recently FDA approved, and zanolimumab with a significant clinical track record are conjugated to an eight-membered macrocyclic chelator SCN-macropa, and then complexed with Actinium-225 to obtain ²²⁵Ac-ibalizumab or ²²⁵Ac-zanolimumab that specifically targets CD4+ T-cells. This RIT will be used to treat patient blood ex vivo. The amount of latent HIV in treated versus non-treated samples is compared. The objective of this research is to eliminate the latently infected HIV population.

Research methodology & results: SCN-macropa has been synthesized. Anti-CD4 antibodies zanolimumab and ibalizumab were obtained from a commercial source and found to be 93% and 74% pure respectively. Flow cytometry was used to determine their affinity for CD4+ cells isolated from PBMCs as 420 ± 60 pM and 520 ± 20 pM respectively. Conjugation with SCN-macropa resulted in constructs with purities of 83% and 95% and similar binding constants of 400 pM and 200 pM to CD4+ cells isolated from PBMCs. In vitro experiments will be performed using live-cell imaging to determine specific cell killing of CD4+ versus CD4- cells. Depletion on CD4+ cells in PBMCs will be measured using flow cytometry and the amount of HIV DNA in patient blood samples before and after treatment will be quantified by specifically amplifying and quantifying the amount of proviral HIV DNA using real-time PCR.

Significance: HIV-1 hides from treatment in resting immune cells, which means treatment must continue indefinitely. This preliminary study will allow us to determine if we can reduce or eliminate cells harboring latent HIV from patients' blood sample using ²²⁵Ac-ibalizumab or ²²⁵Ac-zanolimumab. Combined with other therapies this strategy could result in a cure for HIV-1.

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