Sialidase Conjugation Enhances the Anti-HIV Activity of the 10-1074 Antibody in Humanized Mice

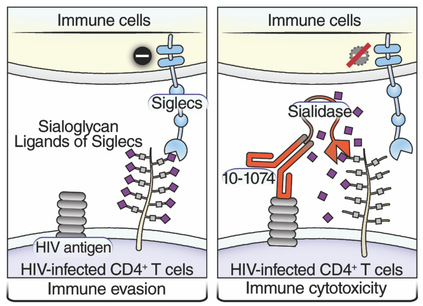
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Background

- HIV infection causes overexpression of sialic acid on the surface of infected cells, which binds to Siglecs, immune inhibitory receptors on innate immune cells such as monocytes and natural killer (NK) cells.
- This interaction triggers inhibitory signals in these immune cells that contribute to the ability of HIV-infected cells to evade immune surveillance.
- To counter this, we developed a targeted immunotherapy by conjugating sialidase, an enzyme that removes sialic acid, to the HIV antibody 10-1074 (referred to as 10-1074-Sia).
- This approach directs sialidase to HIV+ cells expressing Env antigen, stripping sialic acid from the infected cell surface and enhancing their immune elimination. We tested this strategy in vivo using a humanized mouse model of HIV infection.



Methods

- Five weeks old immunodeficient NSG mice (n=15) were humanized by engrafting memory CD4+ T cells from healthy donors.
- Mice were infected with HIV-1_{SUMA}, and a week later, were treated weekly for 5 weeks with either: 1) PBS (control), 2) 10-1074 combined with autologous NK cells and monocytes, or 3) 10-1074-Sia combined with autologous NK cells and monocytes.
- Plasma viral load and CD4+ T cell counts were monitored longitudinally by qPCR and flow cytometry, respectively. Human cytokine levels (e.g., TNFα, IFNγ, IP10) were measured longitudinally using multiplex arrays.

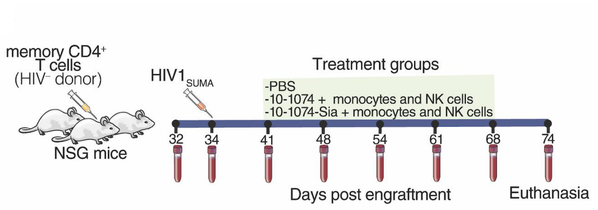


Figure 1: Study design

Results

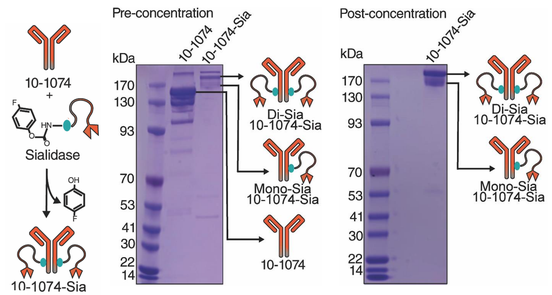


Figure 2: Schematic of sialidase (Sia) conjugation to HIV bNAb 10-1074, with SDS-PAGE gels confirming construction (left) and purity (right).

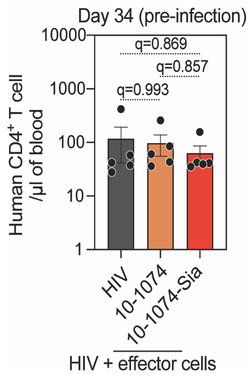


Figure 3: Peripheral blood human CD4⁺ T cell counts before HIV_{SUMA} infection, measured by flow cytometry.

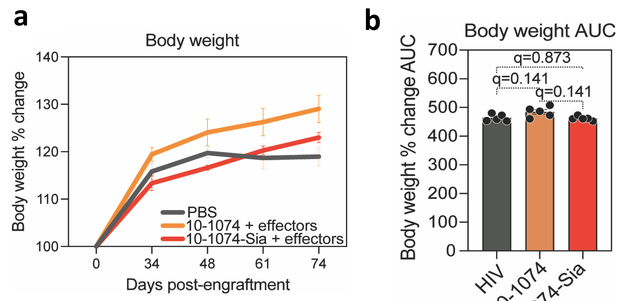


Figure 4: Treatment with 1010-74-SI is well tolerable *in vivo*. Mice treated with 10-1074-Sia did not experience significant weight loss compared to PBS-treated mice. NSG mice were weighed weekly **(a)**, starting before engraftment until the end of the study. The area under the curve **(b)** of body weight shows no difference over time. Data are presented as percentage changes from the initial weight.

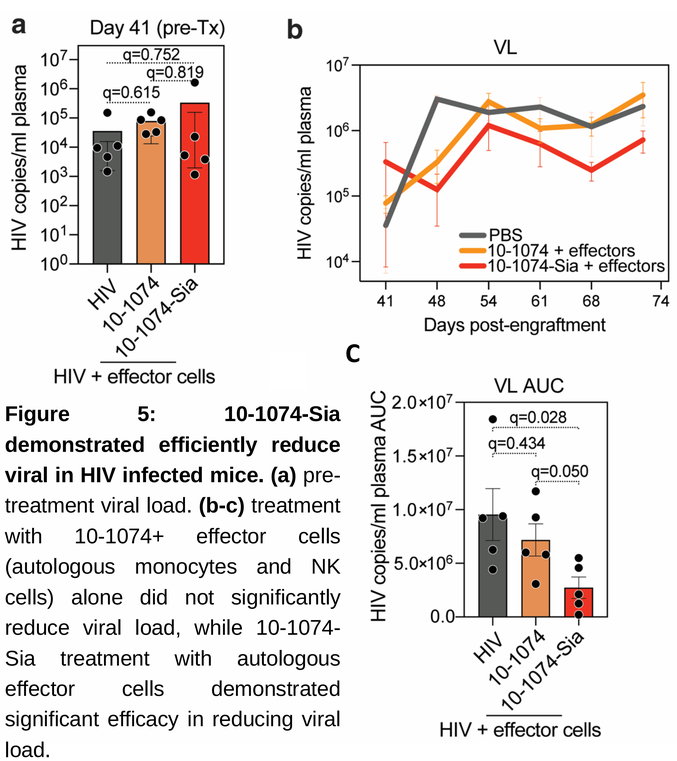


Figure 5: 10-1074-Sia demonstrated efficiently reduce viral in HIV infected mice. (a) pre-treatment viral load. **(b-c)** treatment with 10-1074+ effector cells (autologous monocytes and NK cells) alone did not significantly reduce viral load, while 10-1074-Sia treatment with autologous effector cells demonstrated significant efficacy in reducing viral load.

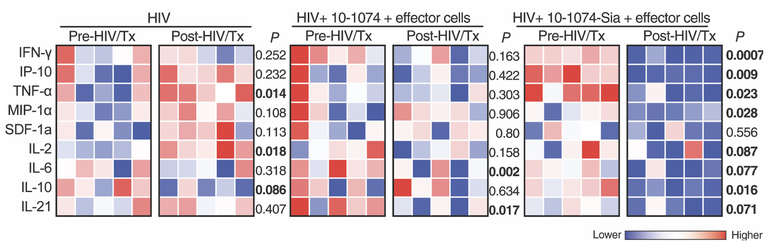


Figure 6: 10-1074-Sia reduce HIV associated inflammation. 10-1074 with effector cells were unable to reduce HIV-associated inflammation, while 10-1074-Sia with effector cells significantly reduced HIV-induced inflammatory markers such as TNFα (p=0.02), IFNγ (p=0.001), IP10 (p=0.01), and MIP1α (p=0.03). Heatmap showing plasma pro-inflammatory marker levels before and after HIV infection and treatment across groups.

Conclusions

- Conjugating sialidase to 10-1074 significantly enhanced the antibody's immune-potentiating effects, resulting in superior viral load control and improved inflammatory responses.
- These findings highlight 10-1074-Sia as a promising anti-HIV immunotherapeutic strategy. Further investigation into combining this approach with strategies such as shock-and-kill is warranted to explore its potential for eliminating infected cells during antiretroviral therapy.

Acknowledgment