VACCINE & IMMUNOTHERAPY CENTER (VIC)
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Targeting Siglec immune checkpoints potentiate NK clearance of HIV-infected cells

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BACKGROUND

- The functions of NK cells can be influenced by the cell-surface glycosylation of their target cells.
- NK cells express glycan-binding proteins, including Siglec-9.
- Siglec-9 is an MHC-independent inhibitory receptor expressed on a subset of the cytolytic CD56^{dim} natural killer (NK) cells.
- The Siglec-9 molecule, expressed on NK cells, binds to Sialic acid, expressed on target cells, and this binding induces an inhibitory signal to NK cells. As such, Siglec-9 functions as a “glyco-immune negative checkpoint”.
- Siglec-9 restrains NK cytotoxicity by binding to sialic acid on the surface of target cells
- Despite the importance of Siglec-9 interactions in tumor immune evasion, their role during HIV infection has not been investigated.

METHODS

- We characterized Siglec-9^{+} CD56^{dim} NK cells from 43 donors: 10 HIV^{-} controls; 11 HIV+ viremic; and 22 HIV+ on suppressive antiretroviral therapy (ART) by flow cytometry. We also measured HIV DNA in CD4+ T cells from HIV+ ART+ individuals by qPCR.
- We examined the functional ability of Siglec-9^{+} and Siglec-9^{-} NK cells to kill HIV+ cells in the presence or absence of Siglec-9 blocking antibody.
- Finally, we developed a proof-of-concept approach to selectively disrupt Siglec/sialoglycan interactions between NK and HIV+ cells by conjugating Sialidase (an enzyme that removes sialic acid) to several HIV broadly neutralizing antibodies (bNAbs).

Fig. 1. Siglec-9 defines an activated NK sub-population during HIV infection

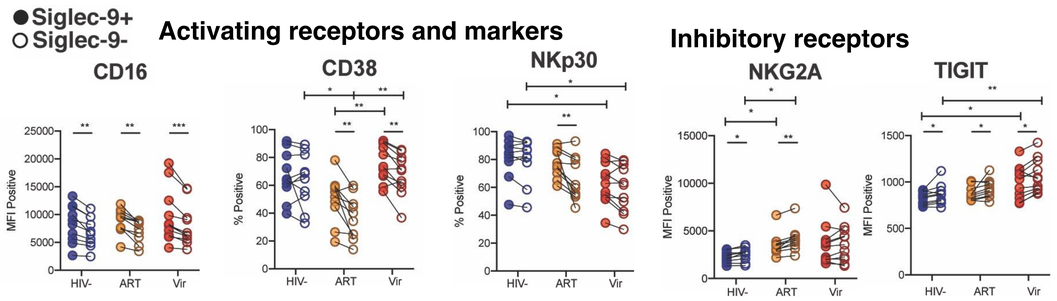


Fig. 2. Siglec-9+ NK cells exhibited higher cytotoxicity towards HIV+ cells compared to Siglec-9- NK cells

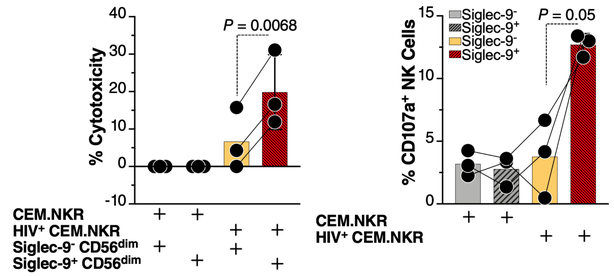


Fig. 3. Siglec-9+ NK cells correlate with lower HIV DNA

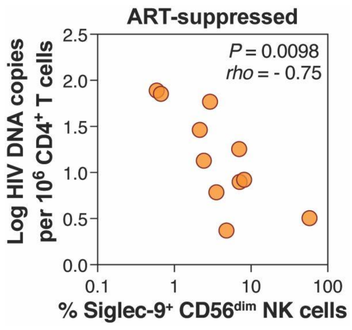


Fig. 4. Blocking Siglec-9 enhances NK cells’ ability to kill HIV+ cells in vitro and in autologous assays

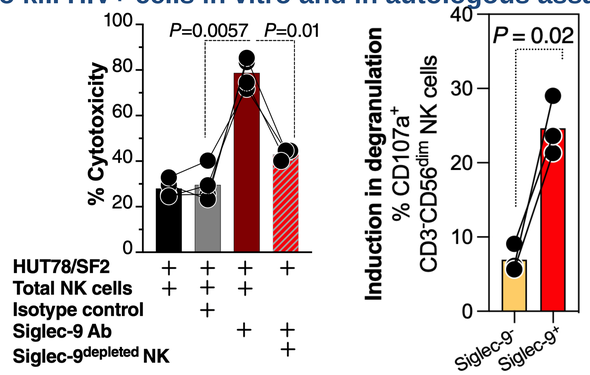
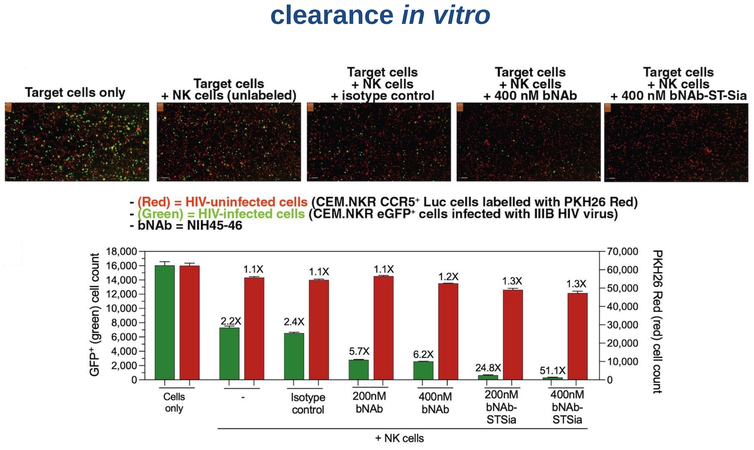
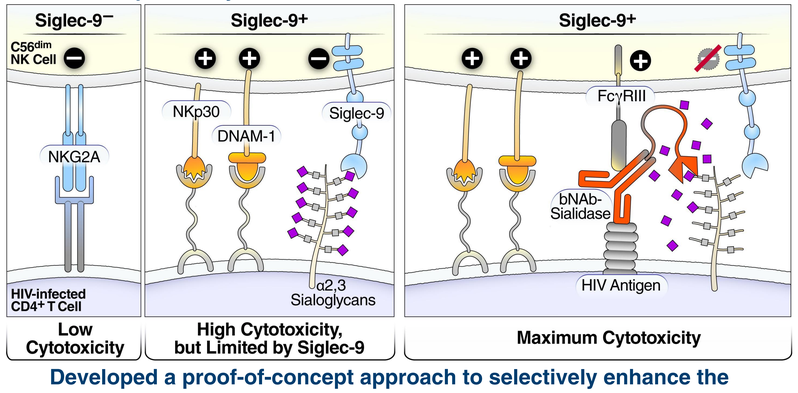


Fig. 5. bNAb-sialidase conjugate enhances the susceptibility of HIV-infected cells to NK-mediated clearance *in vitro*

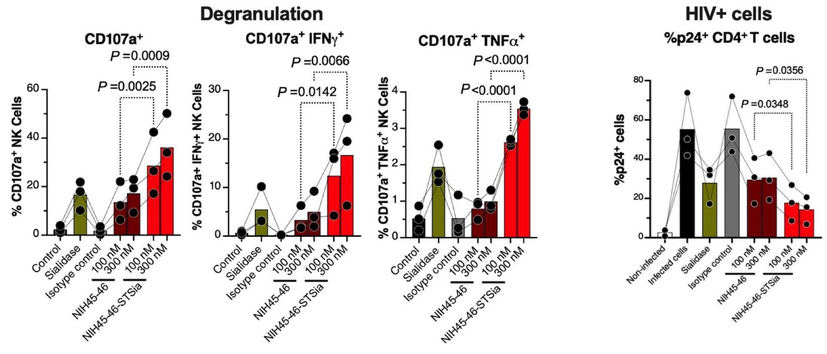


Siglec-9/Sialic acid axis is a novel glyco-immune checkpoint mechanism that may be exploited by HIV-infected cells to evade immune surveillance



Developed a proof-of-concept approach to selectively enhance the susceptibility of HIV-infected cells to immune-mediated clearance

… and in autologous primary cell-based assays



CONCLUSION

We identified a novel glyco-immune checkpoint mechanism that may contribute to the ability of HIV+ cells to evade NK immunosurveillance and developed an approach to break this interaction and enhance the susceptibility of HIV+ cells to NK-mediated clearance.

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