Generating glycoengineered broadly-neutralising antibodies to enhance NK cell-mediated elimination of the HIV reservoir

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Background:
HIV cure requires the reactivation and elimination of latent reservoirs which persist in T cells and macrophages despite antiretroviral therapy (ART). However, cure trials to date have been hampered by an inability of the endogenous immune system to eliminate reactivated HIV+ cells. Immunotherapy strategies to enhance endogenous NK cell-mediated elimination of HIV+ cells via antibody dependent cellular cytotoxicity (ADCC) may be useful to enhance HIV elimination *in vivo*.
Methods:
A panel of eight glycoengineered broadly neutralising anti-HIV antibodies (bNAbs) were generated with Fc modifications to reduce core fucose (afucosylation) and modify neonatal Fc receptor (FcRn) binding to enhance bNAb half-life in circulation (-LS mutation). The panel included the bNAbs 10-1074, 35O22, 3BNC117, CH103, EPTC112, N6 and VRC07-523. Chronically HIV-infected T cells (8E5 cells) were opsonised with afucosylated bNAbs (5 µg/mL) and ADCC response of NK cells was assessed by CD107a degranulation and loss of CD16.
Results:
The -LS mutation was successfully integrated without affecting Fc-CD16 binding or virus neutralisation. Maximal enhancement of Fc binding was achieved using a FUT8 knock-out cell line, decreasing fucosylation ≥65%. Afucosylation of bNAbs enhanced CD16 binding by 4- to 7-fold ($p<0.01$). Afucosylated bNAbs, such as NIH45-46, enhanced ADCC responses of NK cells against opsonised HIV+ T cell targets, significantly increasing degranulation (CD107a+, $p<0.01$, $n=4$), and loss of CD16 ($p< 0.01$). This translated to a 2- to 3-fold increase in NK cell ADCC responses, with the most potent responses elicited by afucosylated 10-1074, N6, NIH45-46 and VRC07-523.
Conclusion:
Novel bNAbs containing a unique combination of Fc modifications exhibit enhanced ADCC responses from NK cells against HIV+ targets. As many of these bNAbs are currently being assessed in clinical trials, these data suggest their efficacy for HIV cure may be further enhanced through glycoengineering approaches to increase ADCC-mediated elimination of reactivated HIV+ cells.
Disclosure of Interest Statement:
N/A.