Bispecific Antibodies Promote NK Cell-mediated Elimination of the HIV Reservoir

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Background

• The persistence of long-lived HIV-infected cells comprising the latent reservoir is the main barrier to a cure. "Shock and kill," a strategy for clearing the latent reservoir, involves selective reactivation of HIV gene expression through treatment with a latency reversing agent (LRA) followed by immune-mediated elimination of HIV-infected cells.

• To date, LRA-based clinical interventions in PLWH have failed to achieve a significant reduction in the latent reservoir despite observed transient increases in plasma and cell-associated viral RNA(1). A potential explanation for this discrepancy may be that the cytotoxic immune effector cells of PLWH exhibit compromised responses and are unable to efficiently recognize and eliminate cells expressing viral gene products(2-4). To ensure effective elimination of HIV-infected cells in the context of "shock and kill," novel immunotherapeutics must be developed to enhance HIV-specific cell-mediated cytolytic activity.

• Here, we evaluated novel bispecific antibodies and evaluated their ability to promote NK cell-mediated elimination of the infected cells comprising the HIV reservoir.

Generation of NK cell-engaging HIV-1-specific scDb

- scDb promotes NK cell-mediated elimination of HIV-infected cells

- scDb inoculate induce functional HIV-specific NK cell responses

- scDb eliminate cells harboring intact and inducible proviruses ex vivo

Conclusions

• Bispecific antibodies promote potent activation of NK cells and elimination of HIV-infected cells.

• Bispecific antibodies reduce the frequency of CD4+ T cells harboring intact, replication-competent proviruses ex vivo.

• Bispecific antibody-induced ex vivo elimination of intact provirus harboring cells is highly dependent on efficient latency reversal and single LRA treatments fail to induce sufficient latency reversal for targeting.

• Bispecific antibodies do not eliminate CD4+ T cells harboring defective proviruses with large deletions or extensive hypermutation, likely as a result of impaired Env expression.

• In combination with effective LRAs, the HIV-1-specific scDb described merit further preclinical evaluation as potential therapeutics for clearance of HIV-1 reservoir cells.

References & Acknowledgements

1. Arvin AM. Nature 2012
2. Shuker NM. Nature 2012
3. Reauprasert T, Lanket MF, Yu 2014
5. Lancot D, Nature 2013
7. Ruan Y, J Clin Invest 2020
8. DARE, HIV, and DARE NH Martin Delaney Collaboratives, by the Johns Hopkins Center for AIDS Research, by the Bill and Melinda Gates Foundation, and by the Howard Hughes Medical Institute