422 HIJACKING UPREGULATED E-SELECTIN WHILE BOOSTING SDF-1α SENSING REWIRES INFUSED NK CELLS TO THE AML-PERTURBED BONE MARROW

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Background Infusion of natural killer (NK) cells can induce anti-tumor responses in patients. Currently, most efforts to further improve the efficacy focuses on augmenting the NK cell cytotoxicity and persistence, while few addresses their tumor homing capacity, which is critical for proper tumor targeting *in vivo*. Indeed, increased bone marrow (BM) homing after adoptive NK cell immunotherapy has been associated with positive clinical outcome of myeloid leukemia.[1] As studies have shown that tumor development in the BM can impair the homing of cytotoxic lymphocytes[2,3] and that this has not yet been addressed in acute myeloid leukemia (AML), we here decipher how AML development alters the BM niche to impair NK cell infiltration and how insights can be utilized to solve this issue.

Methods Using NSG-SGM3 mice inoculated with AML cells, we assessed the microenvironmental changes in the BM during AML development using flow cytometry, immunohistochemistry, and ELISA. We genetically engineered NK cells using a clinically compliant method to equip them with selected homing molecules. Finally, we evaluated NK cell function *in vitro* and assessed their ability to home *in vivo* to different tissues in AML-bearing mice.

Results We demonstrate that NK cell BM infiltration is impaired in AML-bearing mice, closely linked to decreased levels of the CXCR4 ligand SDF-1α. Additionally, E-selectin^{+} endothelial cells were found increased within the BM during AML progression. Given the poor E-selectin-binding capacity of NK cells at steady-state, introduction of fucosyltransferase-7 (FUT7) to the NK cells per mRNA transfection resulted in potent E-selectin binding and stronger adhesion to E-selectin^{+} endothelial cells. Co-introduction of FUT7 and gain-of-function CXCR4 (CXCR4^{R334X}) rewired NK cell BM homing in AML-bearing mice nearly to the level observed in AML-free mice (figure 1).

Conclusions This work shows how impaired NK cell homing caused by AML-induced microenvironmental changes can be overcome by genetic engineering of the effector cells. We speculate that these insights can help advance future NK cell immunotherapy efforts against AML.

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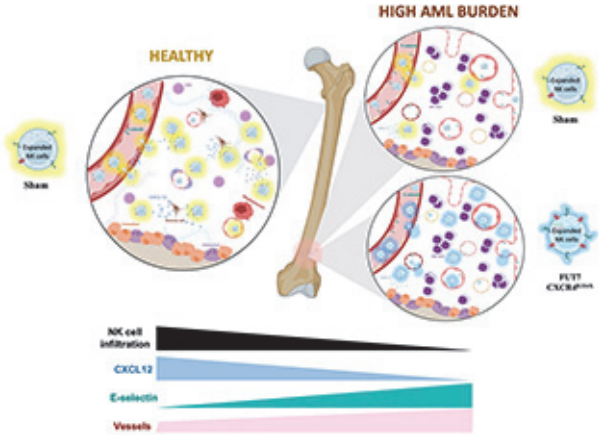
Ethics Approval Peripheral blood cells were collected from healthy blood donor buffy coats (Ethical approval Dnr 2006/229–31/3). Animal experiments were performed under ethical approval (ID1533 and 02250–2022) by Jordbruksverket, Sweden.



Abstract 422 Figure 1

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