CD16-IL15-CLEC12A Trispecific Killer Engager (TriKE) Drives NK Cell Expansion, Activation, and Antigen Specific Killing of Cancer Stem Cells in Acute Myeloid Leukemia

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BACKGROUND

• A majority of all deaths from hematopoietic malignancies are caused by acute myeloid leukemia (AML), which has had a poor five-year survival rate of 26%, highlighting the need for new therapies.
• The most common antigen used to target AML cells is CD33 however there are many limitations of developing therapies against CD33. 1. Not all cancer cells express CD33. This is especially significant in patients with refractory AML.

METHODS

2. All cells of the myeloid lineage and some cells of the lymphoid lineage like activated NK cells and T cells express CD33 leading to off-target toxicity.
3. Cancer stem cells, which are thought to facilitate relapse do not express CD33.

RESULTS

3. To address these limitations, we aim to target a novel antigen called C-Type Lectin-like molecule 1 (C-LL1) or CLEC12A.
1. CLEC12A is highly expressed on AML cells. About 70% of CD33 negative cells express CLEC12A.
2. The expression of CLEC12A is restricted to a subset of myeloid cells limiting off-target toxicity.

3. CLEC12A is present on leukemic stem cells but not hematopoietic stem cells.

4. To target cancer cells using Natural Killer (NK) cells, we developed a tri-specific killer engager (TriKE) molecule containing an anti-CD16 heavy chain antibody that activates NK cells, an IL-15 molecule that drives NK cell priming, expansion and survival, and an anti-CLEC12A single chain variable fragment (scFv) that engages cancer targets.

CONCLUSIONS AND FUTURE DIRECTIONS

The CD16-IL-15-CLEC12A TriKE:
1. Binds specifically to target cells expressing CLEC12A
2. Promotes proliferation of NK cells
3. Enhances function of NK cells
4. Promotes killing of AML cell lines in Incucyte zoom assays
5. Induces killing of primary AML Blasts

Future Experiments
• Assesses in vivo functionality using a patient derived xenograft mouse model developed by our collaborator Dr. Craig Eckfeldt
• Assesses in vivo functionality in a xenograft mouse model using HL-60 cells
• Test efficacy of dual targeting of CLEC12A and CD33