Effect of Anti-ADAM17 Monoclonal Antibody MEDI3622 on Proliferation of Natural Killer Cells in Multiple Myeloma Patients

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Introduction

- Natural Killer (NK) cells kill multiple myeloma cells through antibody-dependent cellular cytotoxicity (ADCC).
- CD16 transmembrane receptor allows NK cells to recognize antibody-coated tumor cells.
- Tri-specific killer engager (TriKE) was synthesized to contain an anti-CD16 domain, the NK stimulatory domain IL-15, and a domain specific to the tumor marker B7-H3.

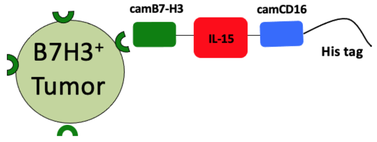


Figure 1. TriKE construct.

- It was proven that TriKE enhances ADCC of NK cells against high B7H3-expressing myeloma cell lines (MM1S, U266, and RPMI-8226), and lower b7H3-expressing H929 cells.

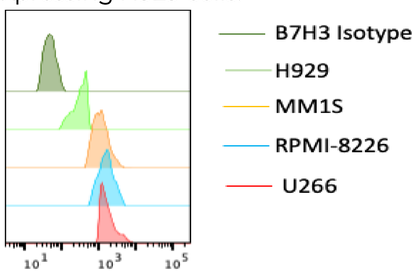


Figure 2.B7-H3 expression on four multiple myeloma cell lines using flow cytometry

- Some patient-derived NK cells do not efficiently kill MM and do not respond to TriKE.

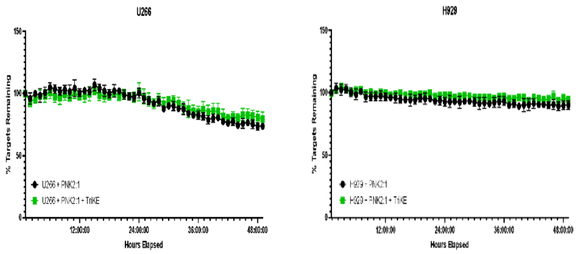


Figure 2. Live-cell imaging of TriKE cytotoxicity with patient-derived NK cells over 48 hours using U266 and H929 myeloma cell lines.

- Enhancing NK cell proliferation might restore TriKE function in patient samples that were unresponsive to TriKE.

- A disintegrin and metalloproteinase-17 (ADAM17) expressed by NK cells sheds regulatory receptors (i.e. CD16) extracellularly, potentially hindering NK cell proliferation.

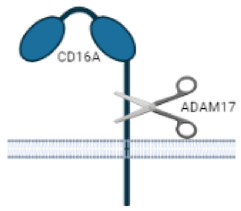


Figure 3. Model of ADAM17 function.

- Anti-ADAM17 monoclonal antibody MEDI3622 inhibits the function of ADAM17 and proved to enhance NK cell proliferation in healthy donors.

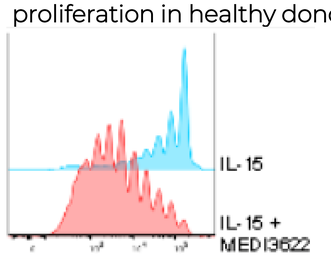


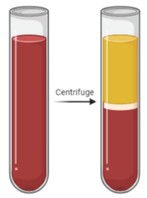
Figure 4. Flow cytometry histogram of cell trace violet dilution over time of CD56+ NK cells.
By our collaborators Anders Matson and Dr. Bruce Walcheck

Objective

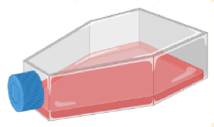
- Assess the effect of blocking ADAM17 function on NK cell proliferation and TriKE cytotoxicity in cancer patients.

Methods

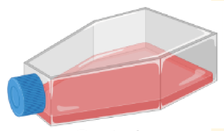
- Peripheral blood mononuclear cells (PBMCs) were labeled with Cell Trace Violet (CTV) and cultured for 7 days with IL-15 (10 ng/mL) +/- MEDI3622 (5ug/ml). After 7 days, CD56+ NK cells were analyzed for CTV dilution using flow cytometry.
- MM1S and U266 cytotoxicity 48-hour live-imaging incucytes were performed with the following conditions: NK cells enriched from control /experimental conditions +/- 3 ng/ml TriKE.



PBMCs extraction
(white layer)

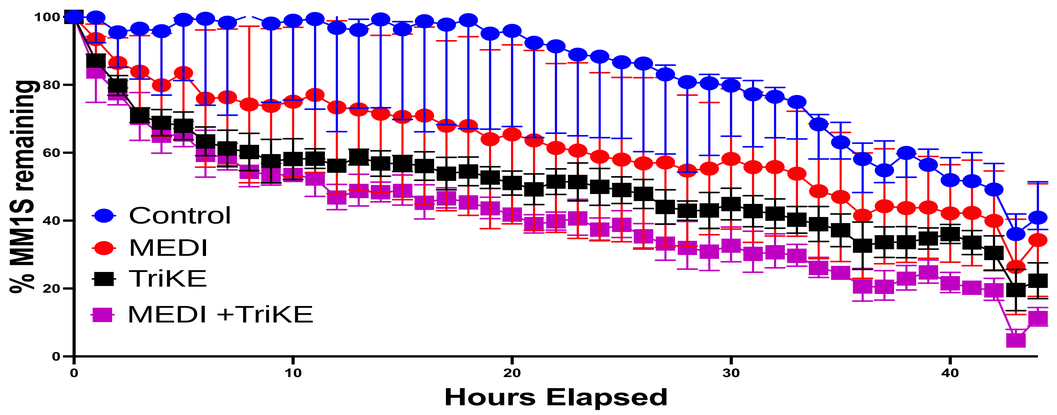


Experimental
(PBMCs+IL15+MEDI3622)



Control
(PBMCs+IL15)

Results



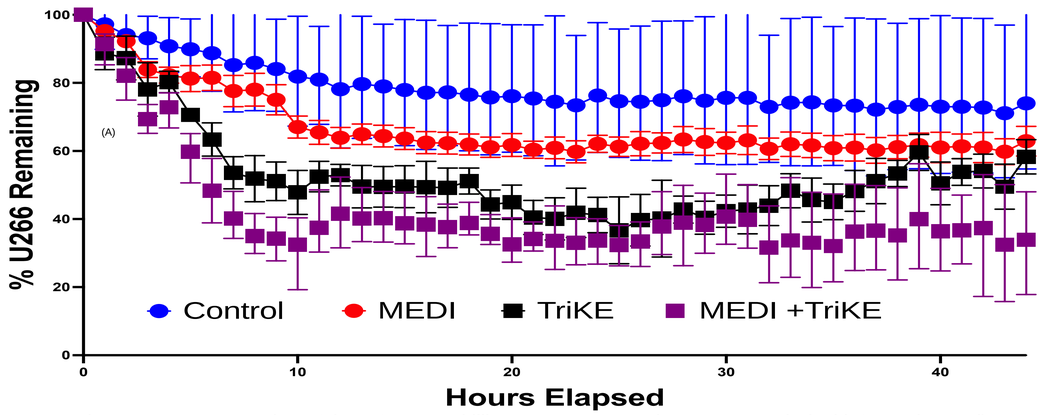


Figure 4. Representative 48 hour Incucyte killing assays comparing NK expanded with IL-15 (control) or MEDI with or without B7-H3 TriKE at Effector:Target ratios of 2:1 against MM1S (top) or U266 (bottom).

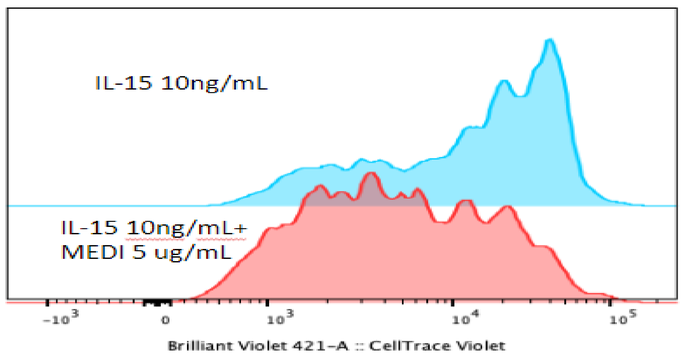


Figure 6. Representative bivariate plots of CD56+ NK cells demonstrating CTV dilution for Patients 1 and 2. Readout represents cellular proliferation.

Conclusion

- MEDI3622 enhanced NK cell proliferation.
- MEDI3622 enhanced TriKE cytotoxicity in both the B7-H3 expressing MM1S and U266 in vitro

References

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