Natural Killer cell Engagers activate innate and adaptive immunity and show synergy with proinflammatory cytokines

Katarina Bykova, Matthew S. Faber, Ke Liu, Noor Siddiqi, Matthew J. Bemett, Christine Bonzon, Juan E. Diaz, Dong Hyun Nam, Kendra N. Avery, Jing Qi, Rumana Rashid, Rena Bahjat, and John R. Desjarlais

Introduction
- Natural Killer cell Engagers (NKEs) are multifunctional molecules that target activating or inhibitory receptors on the surface of NK cells, bind to tumor associated antigens and engage Fc gamma receptors expressed on effector cells of the immune system.
- NKEs promote tumor cell lysis by redirecting NK cells to their targets, and drive activation and proliferation of NK cells.
- Developed NKE molecules showed enhanced NK mediated cytotoxicity and provided co-stimulatory signal to T cells. Combination of NKEs with proinflammatory cytokines resulted in increased cytotoxicity against tumor cells.

1. NKEs are designed to engage tumor antigen, NKG2D and FcγR

2. NKG2D engagement enhances FcγR mediated cytolysis

3. NKEs augment activation of NK cells

4. Loss of MHC I increases target cell sensitivity to NKEs

5. NKEs provide co-stimulation to T cells

6. IL15 and IL12 cytokines enhance NKE activity

Summary
- XmAb® bispecific NKE molecules B7H3 x NKG2D activate NK cells.
- Enhance NK cell mediated lysis of tumor cells and provide co-stimulation to T cells.
- B7H3 x NKG2D NKEs show synergistic cytotoxicity in combination with IL15-Fc XmAb306 analog and IL12-Fc XmAb662. This observation opens an opportunity for NK Engagers to be combined with cytokine therapies.