A novel class of NK cell engagers overcomes CD16A deficiency

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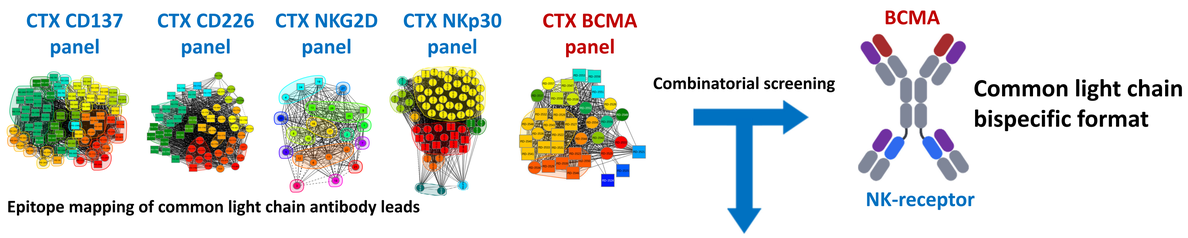
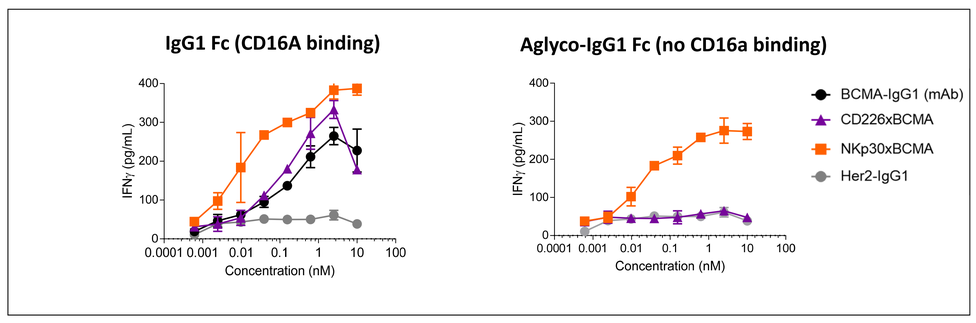
Background

Multiple myeloma (MM) is a malignant hematological disease characterized by a dysregulated growth of plasma cells. Different therapeutic options are available for MM patients; however, the disease remains mostly incurable. B-cell maturation antigen (BCMA) is a promising target in MM because of its restricted expression in normal and malignant plasma cells. NK cells have been implicated in the clinical efficacy of several therapies against MM and may contribute to the success of stem cell transplantation (SCT) by clearing residual cancer cells. In patients with advanced MM, NK cell function is affected by downregulation of CD16A (FcγRIIIA) that significantly impairs the efficacy of conventional mAbs currently undergoing clinical testing. In contrast, expression of NKp30 remains stable, providing a compelling rationale for the design of BCMA-targeted multispecific molecules that redirect NK cell killing by engaging NKp30 to overcome deficiencies in other activating NK receptors.

Results

Compass bispecific antibody discovery platform

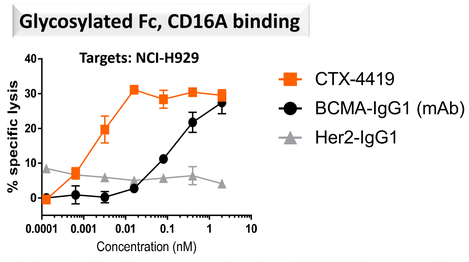


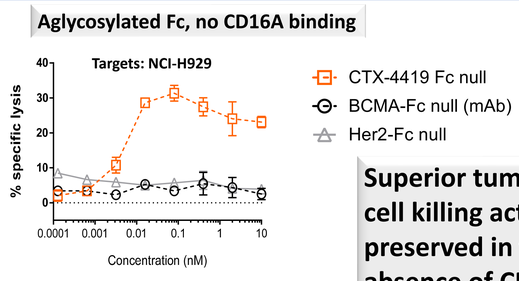


NKp30xBCMA BiAb Lead

CTX-4419

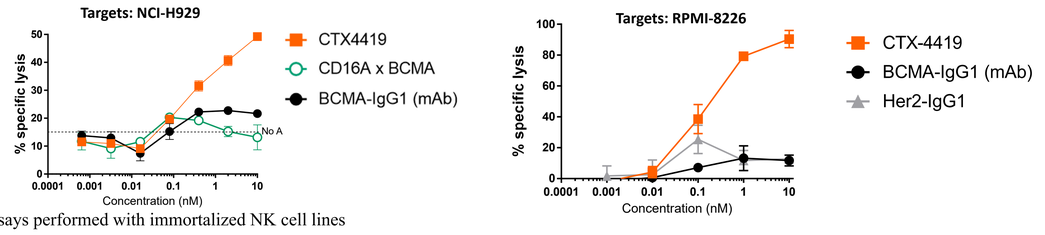
CTX-4419 potently induces tumor cell killing and IFN-γ production by NK cells in CD16A-independent manner





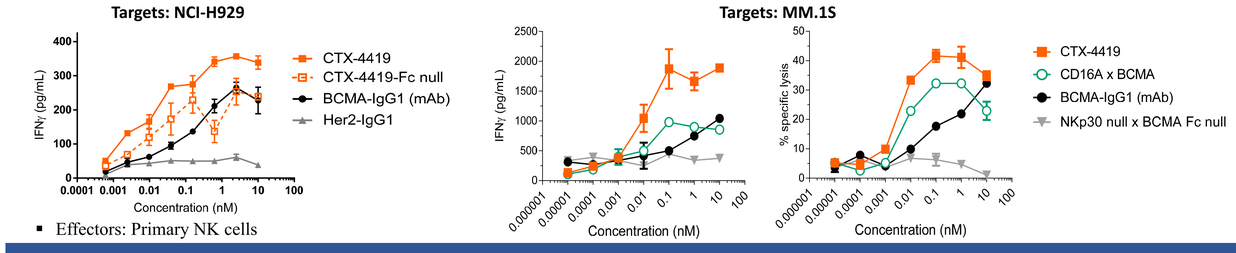
- Primary NK cells were tested against NCI-H929 tumor cells

Superior tumor cell killing activity preserved in the absence of CD16A engagement



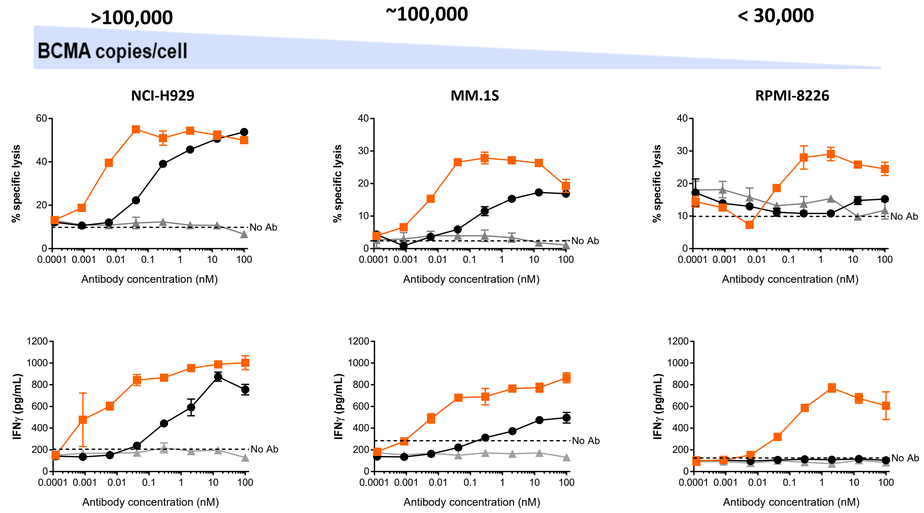
- Assays performed with immortalized NK cell lines

Superior activity by dual targeting of NKp30 and CD16A



- Effectors: Primary NK cells

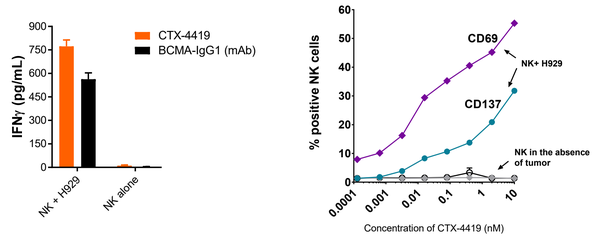
CTX-4419 induced NK cells cytotoxicity against tumor cells expressing low levels of antigen



Opportunity for rescuing patients with tumor target downregulation

- Primary NK cells (NKp30pos,CD16A pos) were tested against high, intermediate and low BCMA-expressing tumor cells

CTX-4419 activates NK cells only in the presence of tumor cells

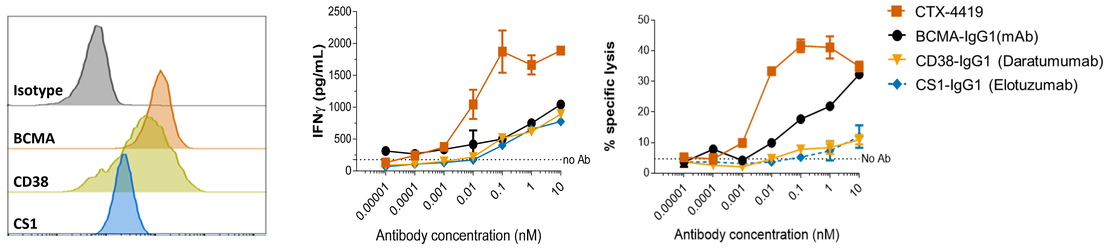


Better safety profile than T-cell based therapies

- Primary NK cells were tested against NCI-H929 tumor cells

More potent induction of target cell lysis than elotuzumab and daratumumab

Better efficacy than conventional antibodies currently undergoing clinical testing



- Primary NK cells were tested against MM.1S

Conclusions

- Compass NK cell engagers lower the threshold for NK cell activation and potently redirect NK cell killing of tumor cells expressing high, medium and low levels of antigen
- In contrast to other NK targeting antibodies, CTX-4419, a first-in-class NKp30xBCMA bispecific antibody, overcomes CD16A deficiency
- Compass highly modular bispecific platform can identify best combinations of TAAs and NK cells receptors tailored to target multiple indications
- Several other TAA combinations are currently under investigation