Novel Class of NK Engagers Targeting NKp30 Selected from Unbiased Screen of Common Light Chain Based Bispecific Antibodies

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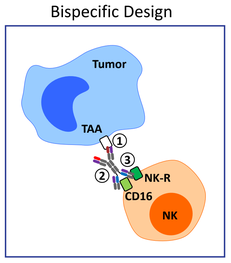
Background

Natural Killer (NK) cells have significant potential as effector cells for immuno-oncology due to their ability to mediate ADCC & cytokine production with reduced toxicity risk compared to T-cell therapies. Attempts to increase ADCC potency through Fc engineering have shown clinical promise but remain dependent on CD16a expression which can be lost due to downregulation, shedding, or FcγR competition. Leveraging Compass's proprietary common-light chain discovery and bispecific screening platforms, we generated panels of tumor targeting bispecifics capable of engaging both CD16a through the Fc domain and a second activating receptor on NK-cells through c-terminally fused antibody Fab fragments. From comparisons of bispecifics targeting 8 different NK receptors, we identified NKp30 as an optimal combination partner for its ability to significantly potentiate ADCC, NK-cell proliferation, and cytokine production both with and without CD16a engagement. NKp30 bispecifics are active against target cells expressing high, medium, and low levels of antigen, but have no activity in the absence of target, supporting a wide therapeutic window. Our lead NKp30 bispecific targeting BCMA activates and expands NK cells in the bone marrow of cynomolgus monkeys leading to potent depletion of bone marrow plasma cells. NKp30 bispecifics are highly manufacturable with comparable expression, stability, and aggregation propensity to monoclonal antibodies. Together, we believe that common-light chain NKp30 bispecifics represent a novel & differentiated platform for effector cell engagement and are developing bispecifics targeting multiple antigens in both hematological and solid tumor indications.

Results

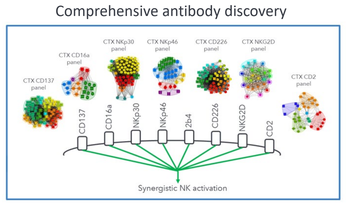
Empirical Selection of Bispecific NK Engagers

Bispecific Design



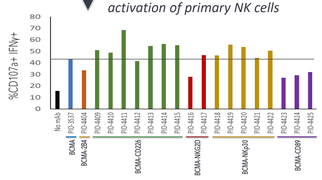
1. Target 1 or more tumor antigens (TAA's)
2. Engage CD16a through Fc
3. Engage additional activating receptors on NK & other effector cells

Comprehensive antibody discovery

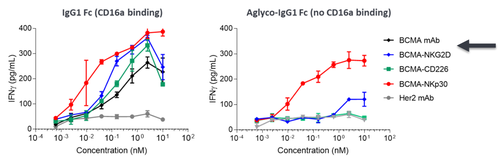


Panels of BCMA-NKR Common-LC bispecifics produced at 24 well scale

Primary Screen
Enhancement of IgG1 Fc induced activation of primary NK cells

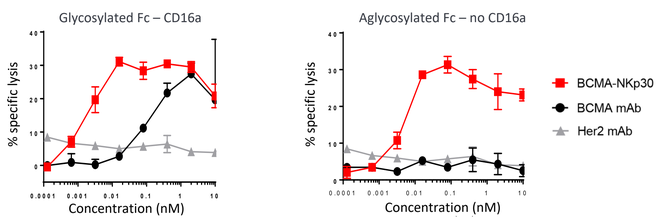


Secondary screen – *Effect of CD16a engagement*

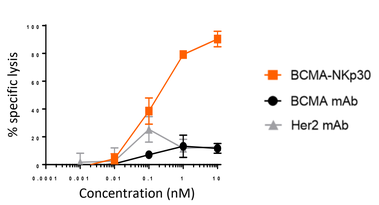


NKp30 Bispecifics Enhance ADCC Potency Independent of CD16a

Target cell killing by primary NK cells



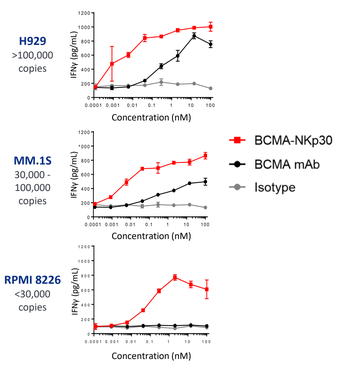
Target cell killing by CD16⁻ KHYG-1 cell line



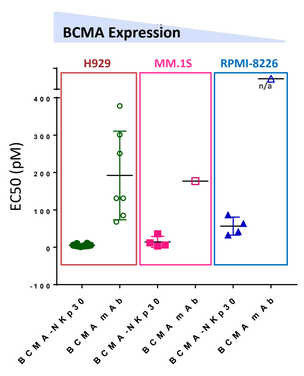
NCI-H929 target cells, 5:1 ET ratio, 4 hour incubation

NKp30 Bispecifics Are Active Against Targets With Low Antigen

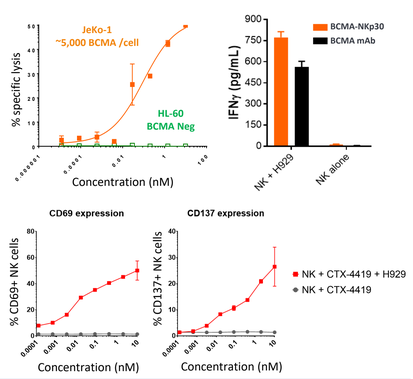
BCMA-NKp30 bispecifics activate NK cells in presence of target cells with high, medium, and low antigen



BCMA-NKp30 bispecific promotes pM potency target cell killing across range of BCMA expression

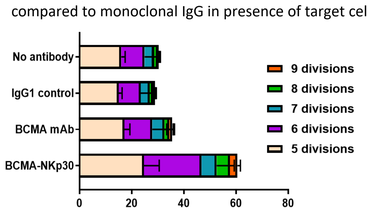


No activity in absence of BCMA expressing target cells



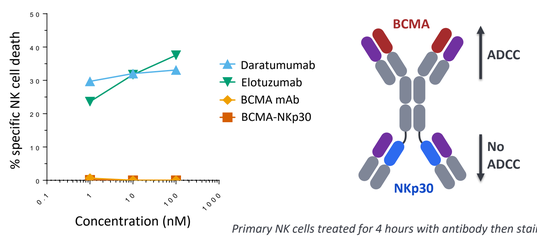
NKp30 Bispecifics Promote NK-cell Proliferation & Avoid NK Depletion

BCMA-NKp30 bispecifics increase NK-cell proliferation compared to monoclonal IgG in presence of target cells



CTV dilution in primary NK cells over 5 days in presence of NCI-H929 tumor cells and 10 nM antibody

BCMA-NKp30 bispecifics do not induce NK-cell depletion due to unidirectional ADCC

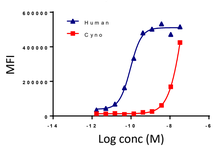


Primary NK cells treated for 4 hours with antibody then stained for viability

Single Dose of First Gen BCMA-NKp30 Potently Depletes BM Plasma Cells in Cyno

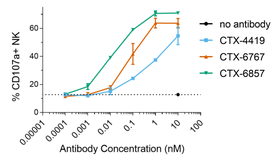
Single, 30 mg/kg dose of first generation BCMA-NKp30 bispecific CTX-4419 administered to cynomolgus monkeys to assess plasma cell depletion in the bone marrow, reductions in plasma Ig, activation and expansion of NK-cells in periphery & bone marrow, and bispecific PK

First Gen BCMA-NKp30 used in study, CTX-4419, has low binding affinity to cyno BCMA



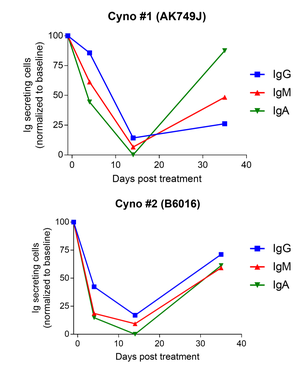
Binding to CHO-BCMA cell lines

Additional studies starting now with development lead CTX-6767 or cyno surrogate CTX-6857 with increased potency against cyno BCMA

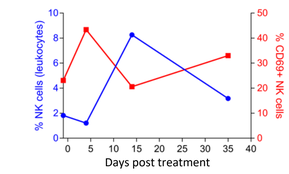


Activation of primary cyno NK-cells in presence of cyno-BCMA-CHO cells

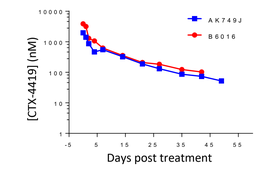
Bone marrow plasma cell depletion (ELISpot)



Activation & expansion of bone marrow NK-cells

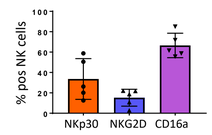


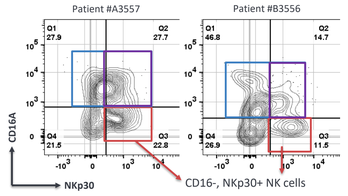
IgG-like PK with 16 day β-phase half-life



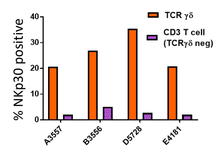
NKp30 is Expressed on NK & γδ T-cells in Bone Marrow of MM Patients

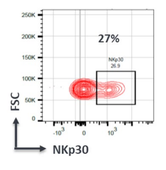
NKp30 is expressed on multiple myeloma patient BM NK cells, including 10-25% NKp30⁺CD16⁻



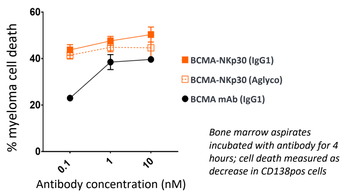


Bone marrow γδ T-cells express NKp30

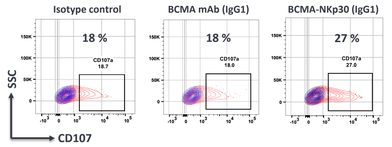




BCMA-NKp30 bispecific induces increased autologous MM cell killing & increased NK cell degranulation compared to monoclonal anti-BCMA

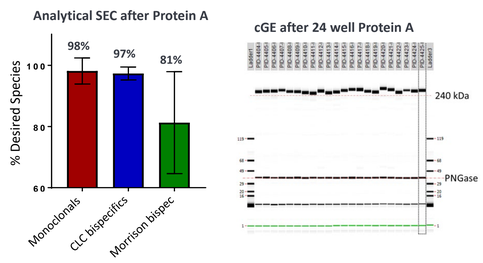


Bone marrow aspirates incubated with antibody for 4 hours; cell death measured as decrease in CD138pos cells

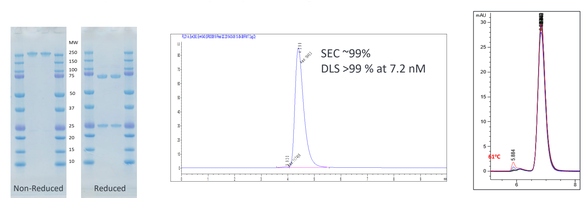


NKp30 Bispecifics Have Monoclonal-Like Drug Like Properties

Common LC platform generates highly expressed and stable bispecifics with minimal aggregation



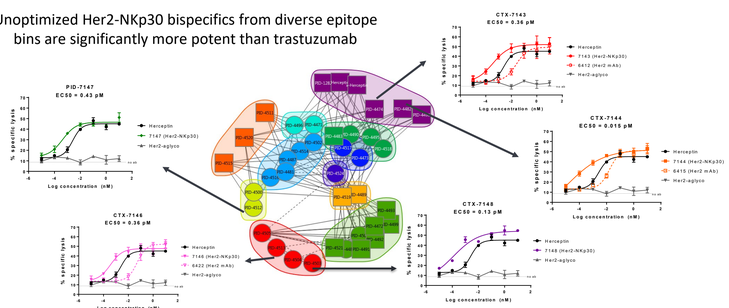
BCMA-NKp30 lead CTX-6767 is expressed at >1.5 g/L in unoptimized CHO pools with 99% purity after single round of Protein A



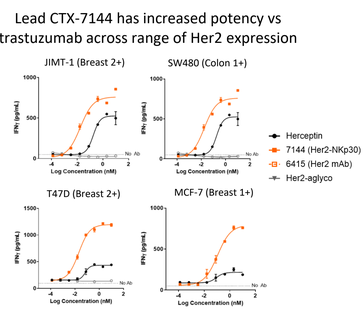
Accelerated stability - Minimal aggregation after 20 hours at 61°C

NKp30 Platform is Generalizable to Other TAA's – Her2-NKp30

Unoptimized Her2-NKp30 bispecifics from diverse epitope bins are significantly more potent than trastuzumab



Lead CTX-7144 has increased potency vs trastuzumab across range of Her2 expression



Conclusions

- **Novel class of NKp30 engaging bispecifics identified from unbiased screen leveraging Compass common-LC discovery platform**
- **Differentiated properties of NKp30 bispecifics**
  - **Significantly enhance ADCC, cytokine production, and NK-cell proliferation compared to monoclonal antibodies**
  - **Active against target cells with wide range of antigen expression, but no activity in absence of target**
  - **Resistant to CD16a downregulation**
  - **Potential to activate multiple effector cell-types including γδ T-cells**
  - **Highly manufacturable with monoclonal-like DLP's due to common-LC format**
  - **Potential to expand platform in future to tri- and tetra-specific molecules targeting more than 1 TAA or NK-R**
- **IND for lead program BCMA-NKp30 planned for 1H2020, with 8 additional programs in progress spanning hematological and solid tumor indications**