



# Disclosures

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Innate-Pharma, co-founder + CSO



Paris Saclay Cancer Cluster Association, President

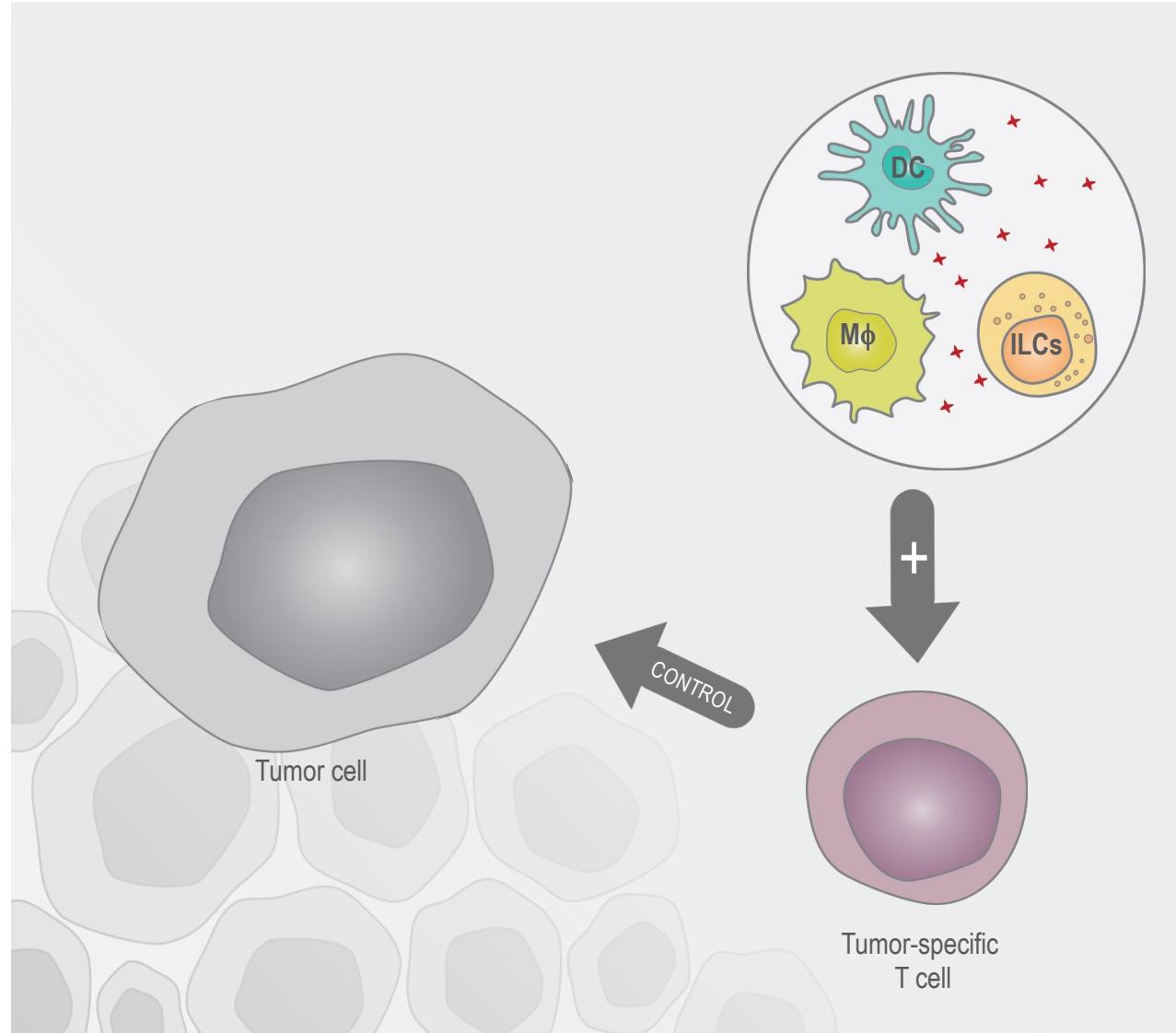


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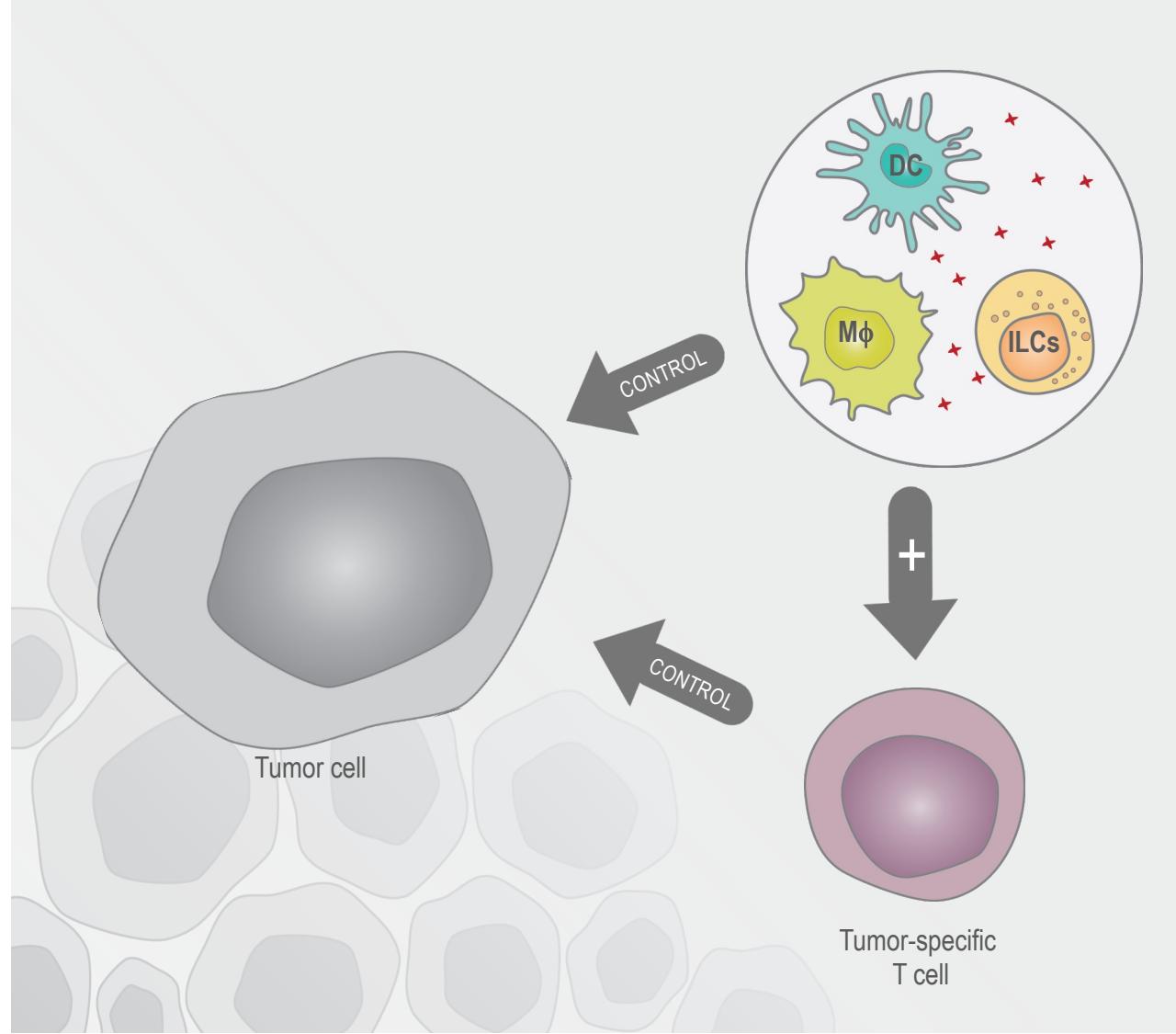
Academic partnership



# T cells are not autonomous in their anti-tumor functions



# Harnessing Innate Immunity in cancer therapies



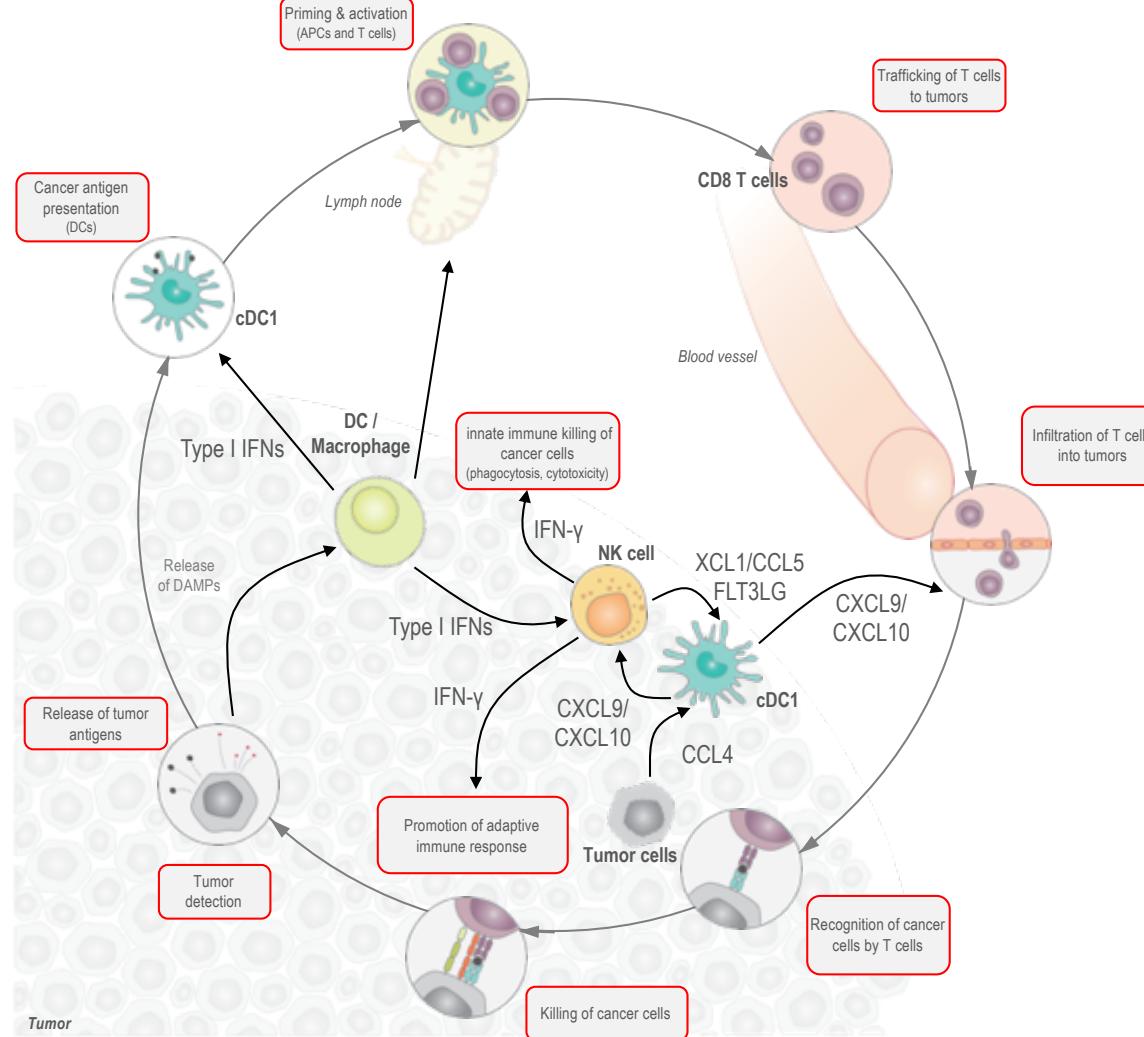
# Innate Lymphoid Cells (ILCs)

Stimuli	Mediators	Immune function
Tumors, intracellular microbes (Virus, bacteria, parasites)	NK ILC1 IFN- $\gamma$ Granzymes Perforin	Type 1 immunity (Macrophage activation, cytotoxicity)
Large extracellular parasites and allergens	ILC2 IL-4 IL-5 IL-13 IL-9 AREG	Type 2 immunity (Alternative macrophage activation)
Mesenchymal organizer cells (Retinoic acid, CXCL13, RANK-L)	LTi RANK Lymphotoxin TNF IL-17 IL-22	Formation of secondary lymphoid structures
Extracellular microbes (Bacteria, fungi)	ILC3 IL-22 IL-17 GM-CSF Lymphotoxin	Type 3 immunity (Phagocytosis, antimicrobial peptides)

# Innate Lymphoid Cells (ILCs)

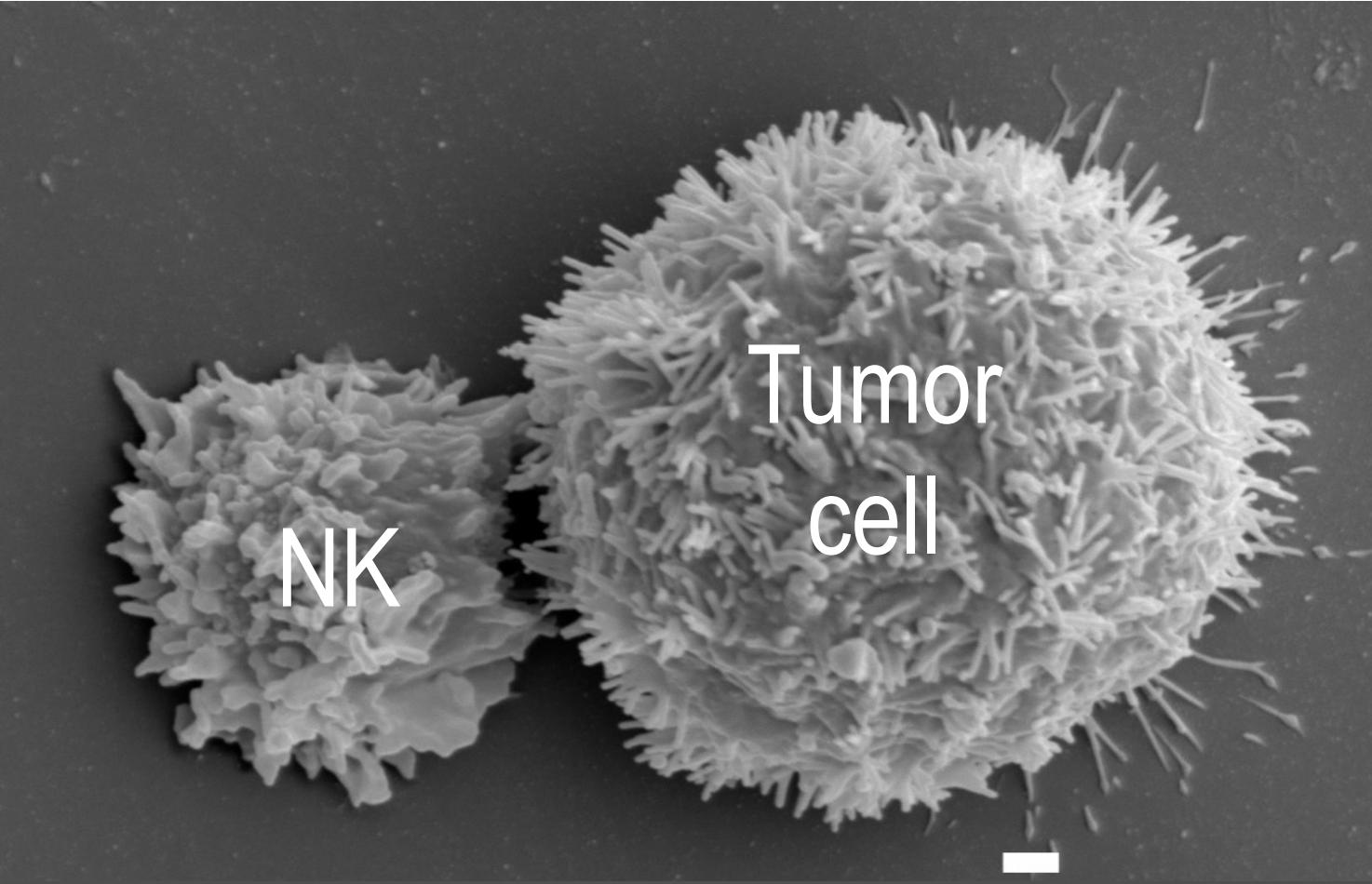
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# The cancer innate immunity cycle



# Bringing Natural Killer cells to the clinic

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Courtesy of Christina Trambas, Cancer Council of Tasmania

# Why NK cells?

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## NK Cells

- No antigen-specific priming required
- Kill a vast array of tumor cells
- Secrete cytokines and chemokines that initiate and shape T cell responses
- Anti-metastatic activity
- NK cell infusions:
  - Excellent safety profile
  - Clinical efficacy demonstrated in hematological malignancies

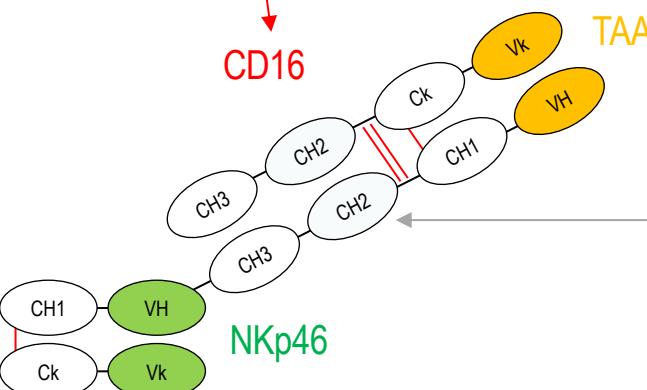
## T Cells

- Antigen priming required
- Antigen-specific
- Allogeneic T cells induce GVHD

# Antibody-based NK cell engager therapeutics (ANKET): a fit-for-all platform

CD16 binding options:

- Fc-wt (0.5-2  $\mu$ M)
- Fc-enh (~ 30-60 nM)
- Fc-null (No binding to Fc $\gamma$ Rs)



NKp46 binder options:

- Fab
- Cross-mAb-like Fab
- scFV

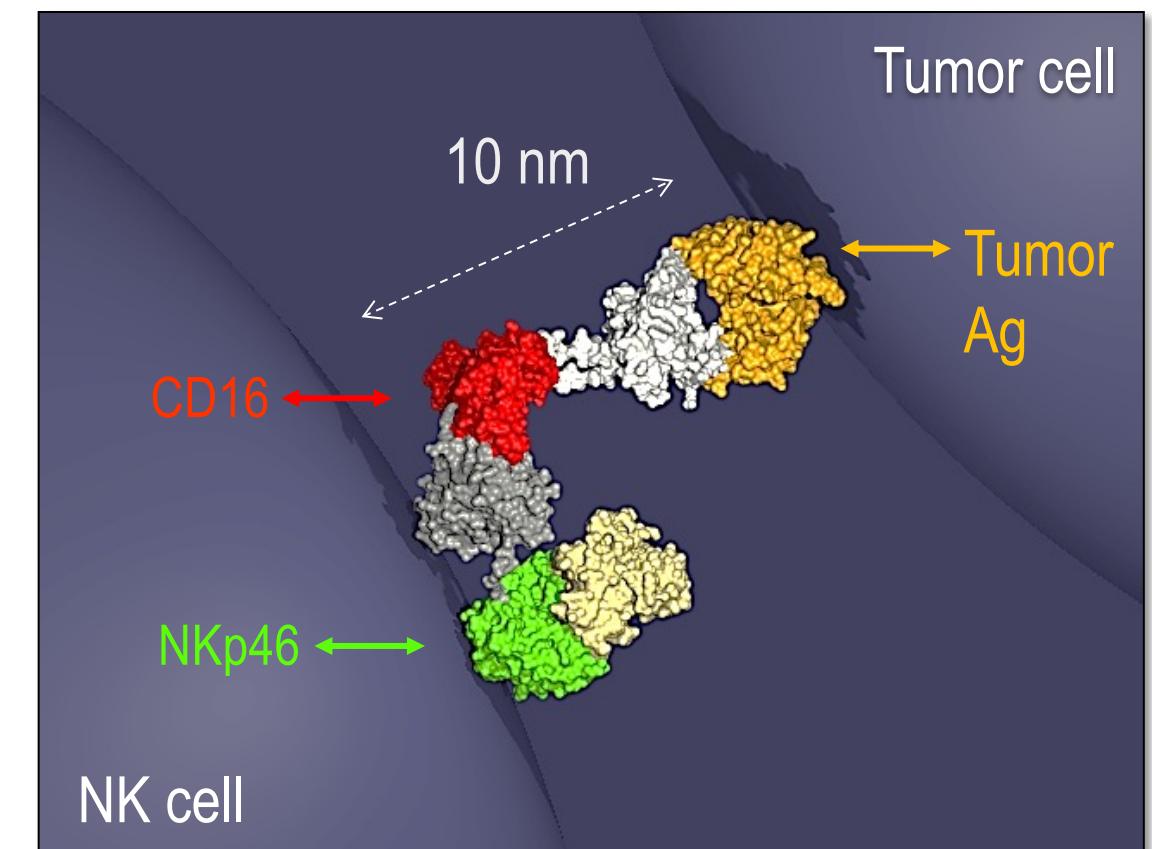
TAA binder options:

- Fab
- One scFV
- Two scFVs ( bivalent binder)
- Two scFVs (dual binder)

Additional Fc-engineering options to improve developability:  
(e.g. Knob & Hole,...)

ANKET3 regular trifunctional format

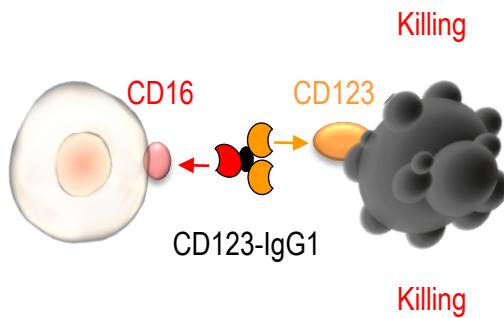
- Monovalent binding to NKp46
- Monovalent binding to TAA
- Co-engaging CD16



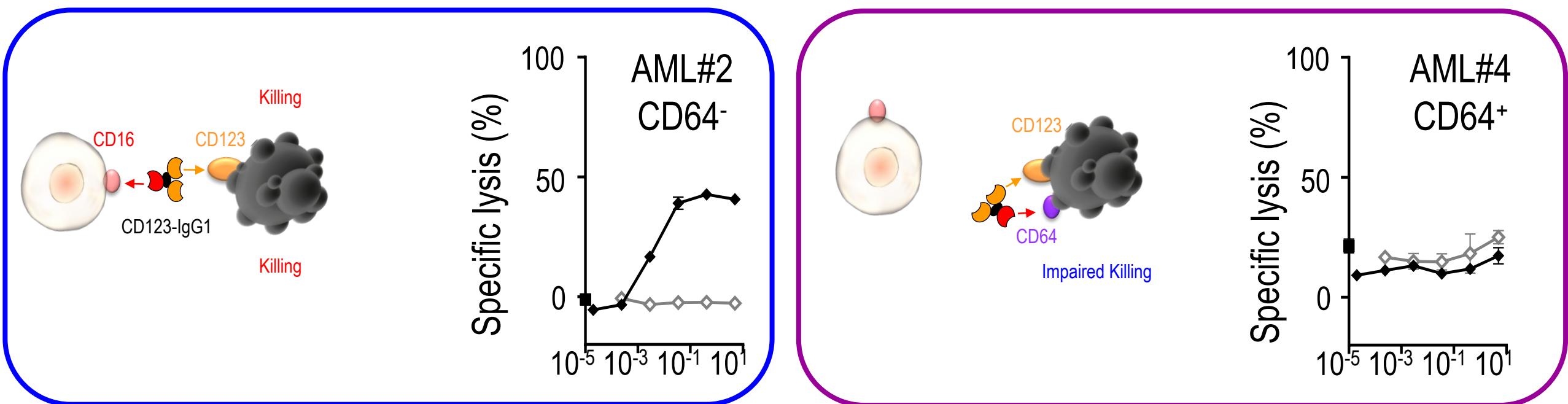
# Targeting CD123 in AML

Acute Myeloid Leukemia (AML): the most common acute leukemia in adults

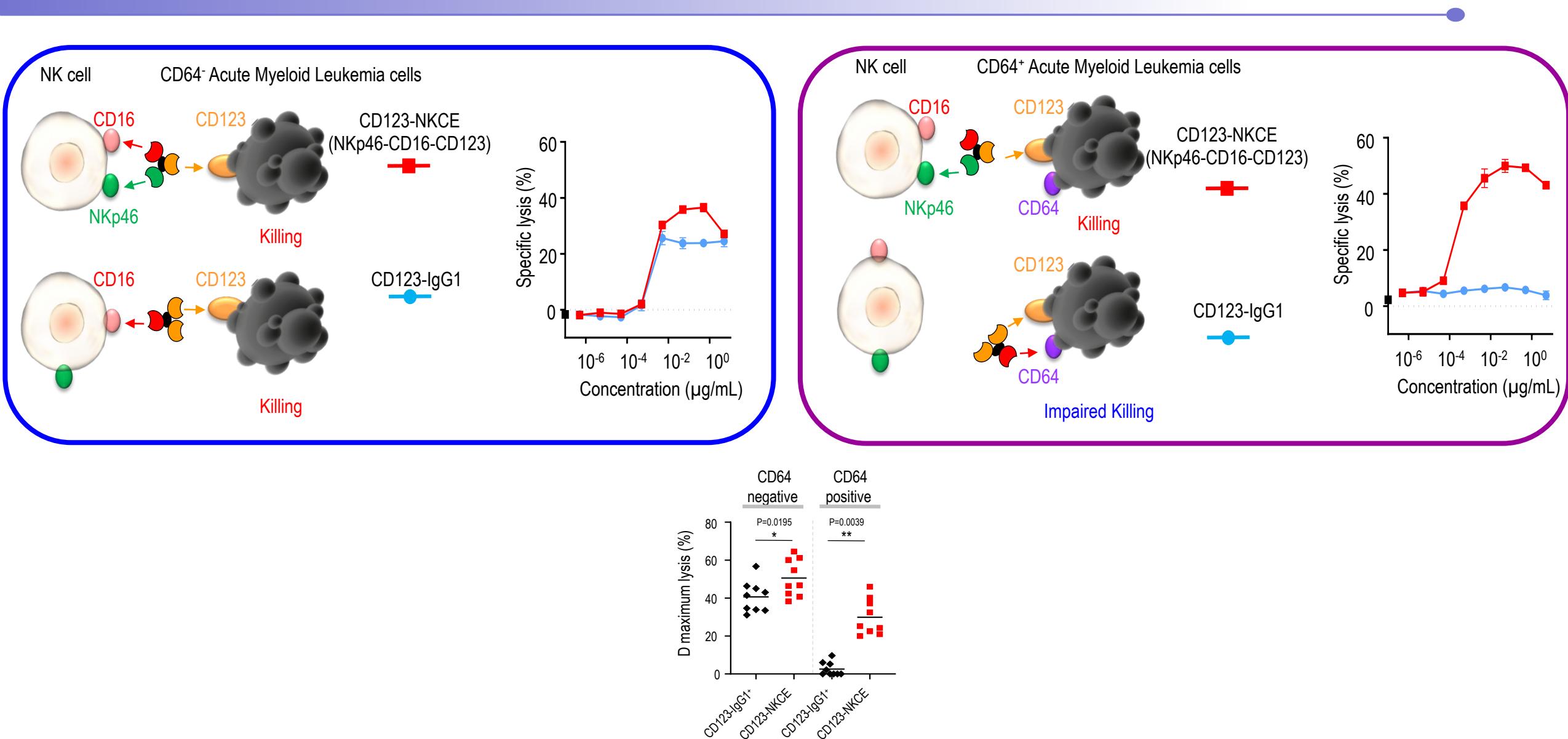
Cytotoxic antibodies targeting CD123 displayed limited antileukemic activity in clinical trials (Montesinos, P., et al. Leukemia, 2021)



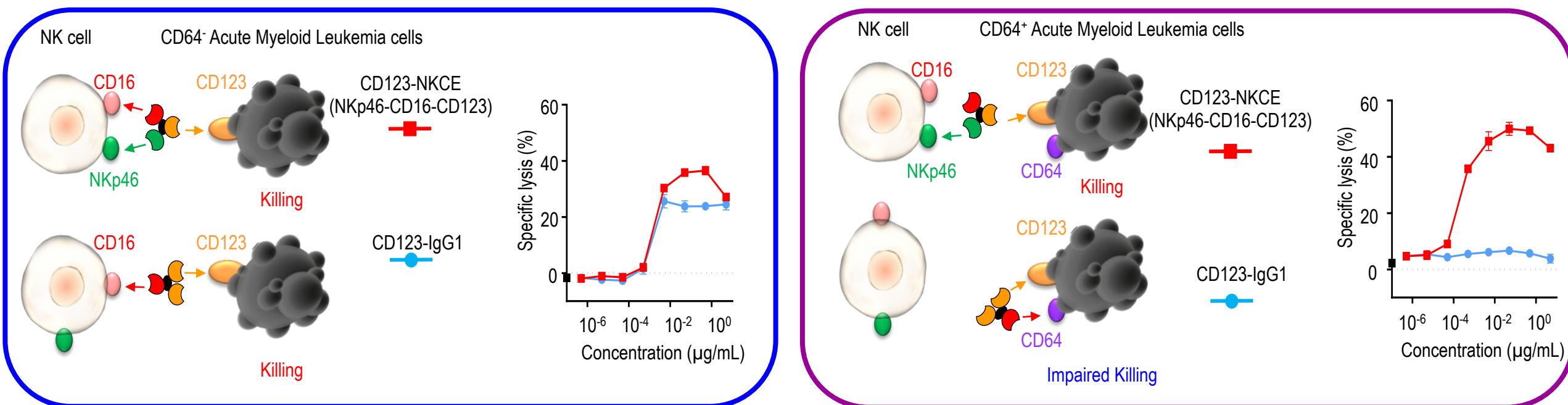
# Targeting CD123 in AML



# Control of AML by a trifunctional ANKET targeting CD123



# Control of AML by a trifunctional ANKET targeting CD123



First-in-human Study of SAR443579 Infusion in Male and Female Participants of at Least 12 Years of Age With Relapsed or Refractory Acute Myeloid Leukemia (R/R AML), B-cell Acute Lymphoblastic Leukemia (B-ALL) or High Risk-myelodysplasia (HR-MDS)

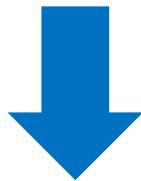
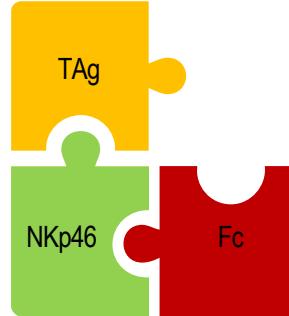
ClinicalTrials.gov Identifier: NCT05086315



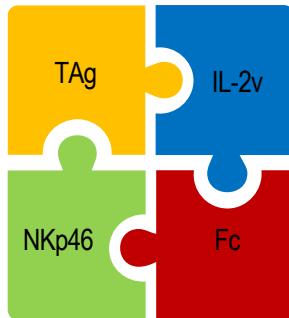
# From trispecific to tetraspecific ANKET



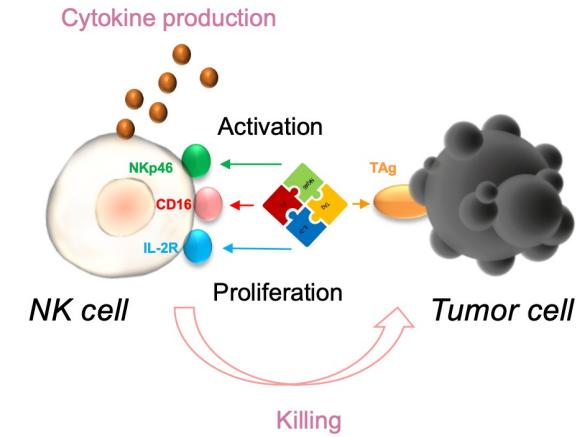
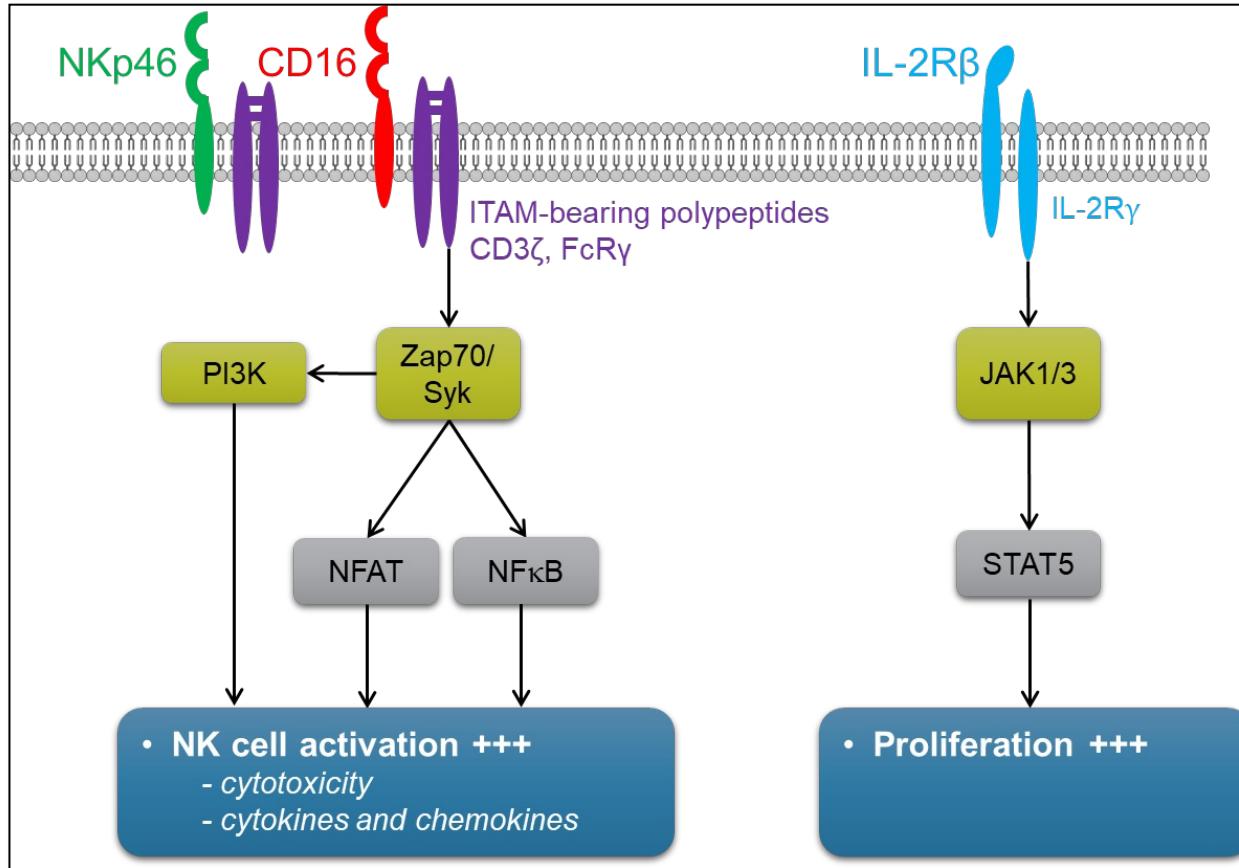
Trispecific



Tetraspecific



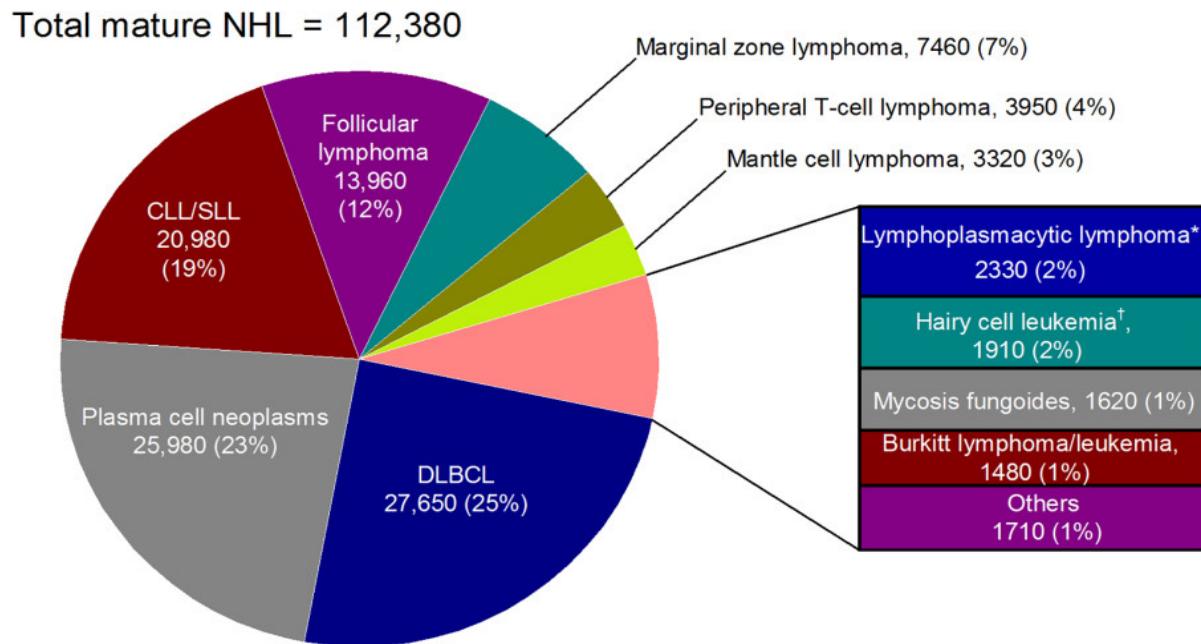
# Rationale for including IL-2v in tetraspecific ANKET



Complementarity between ITAM and IL-2R signaling pathways

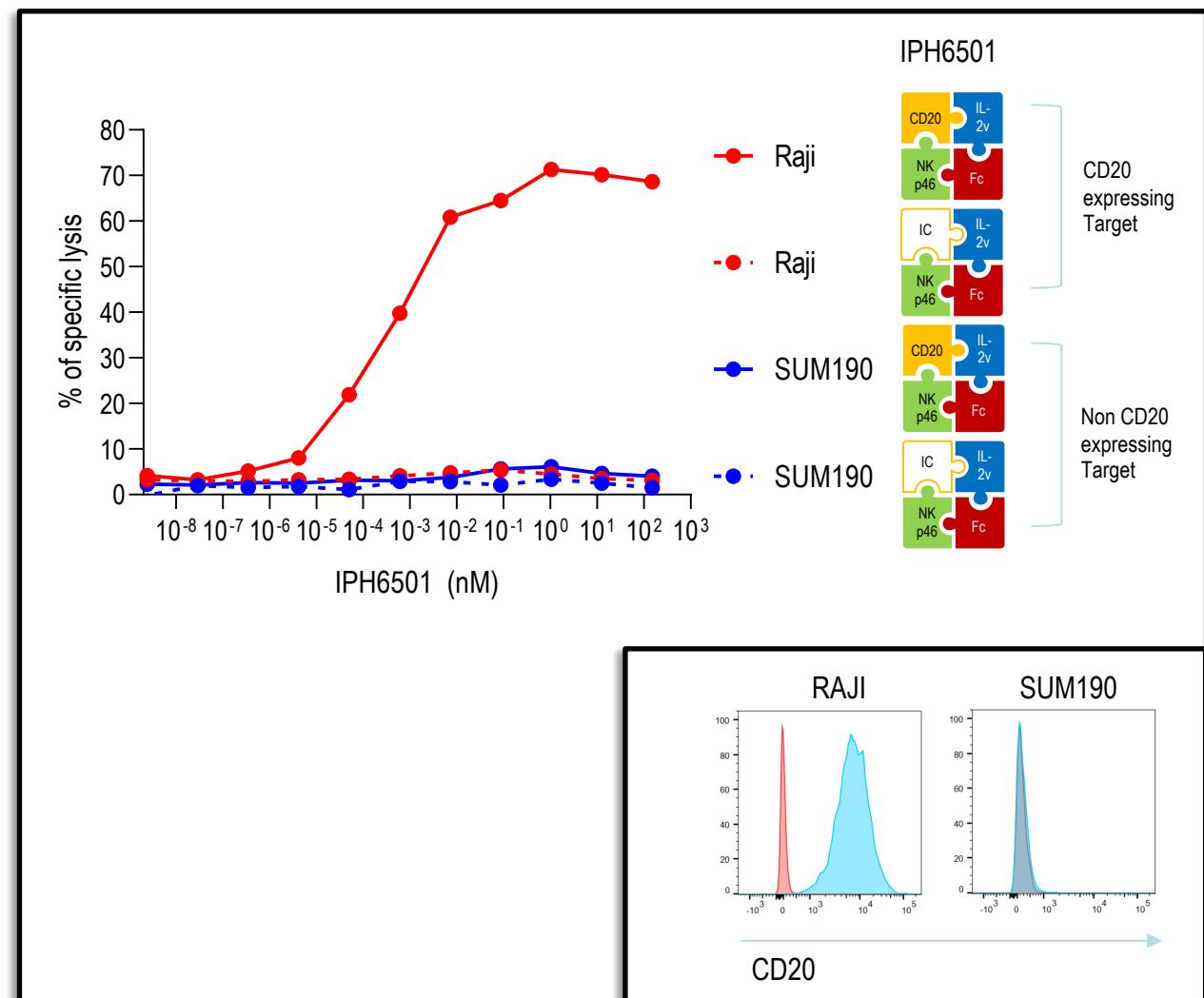
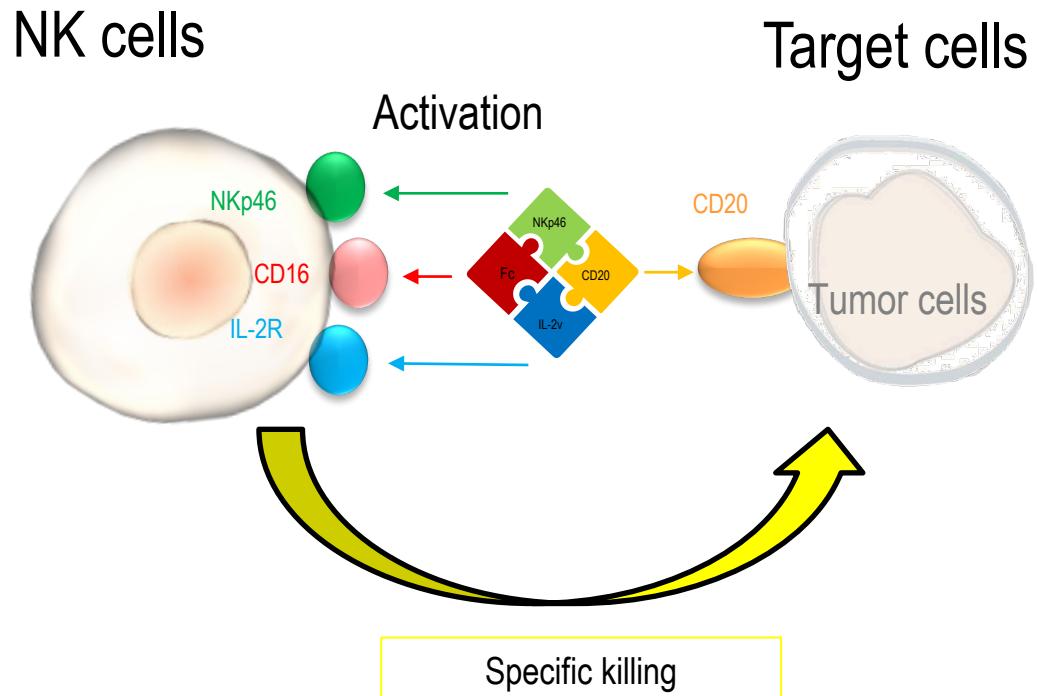
# Targeting CD20<sup>+</sup> B-NHL with tetraspecific ANKET

Estimated Cases and Distribution of Mature Non-Hodgkin Lymphoid Neoplasm Subtypes: United States, 2016

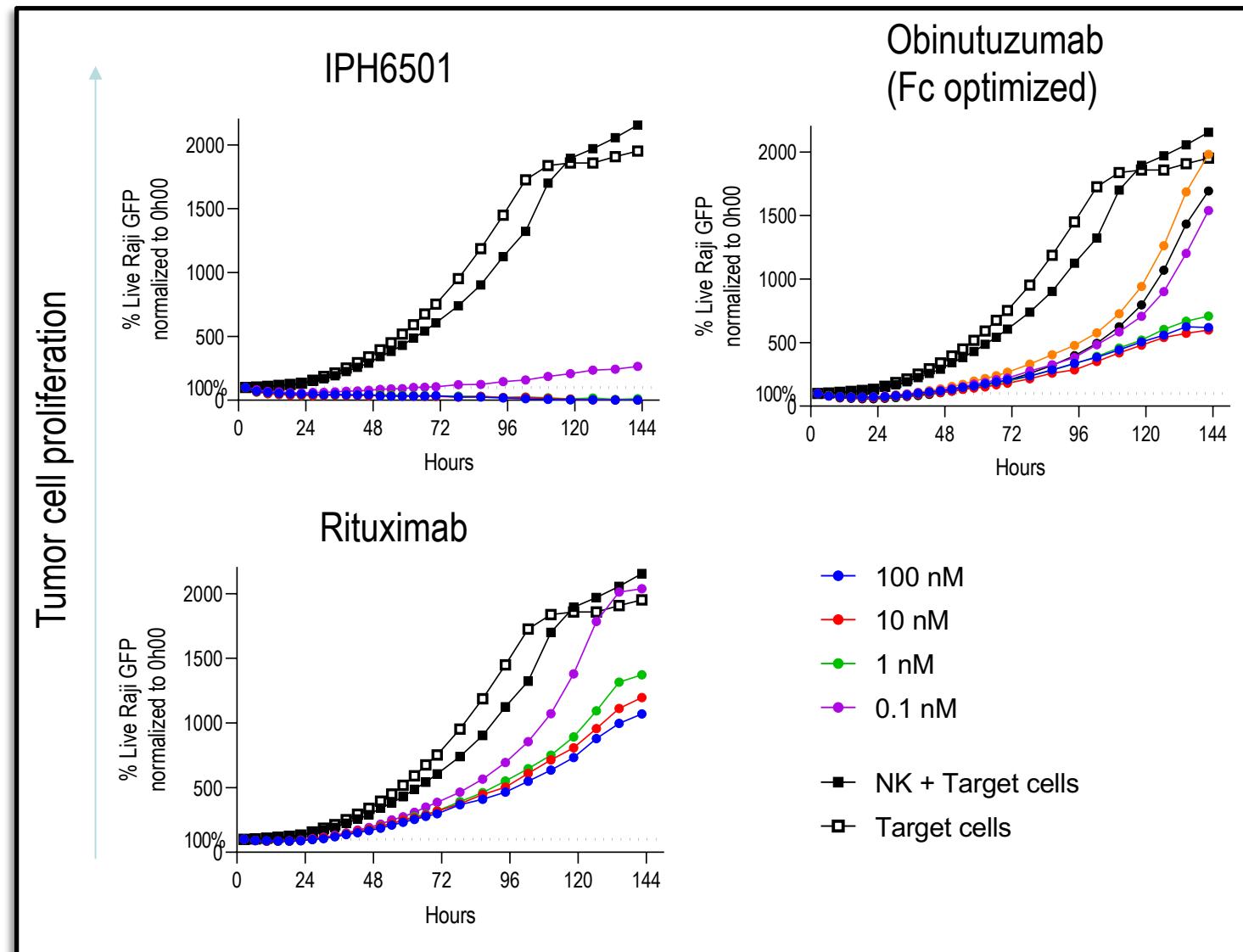
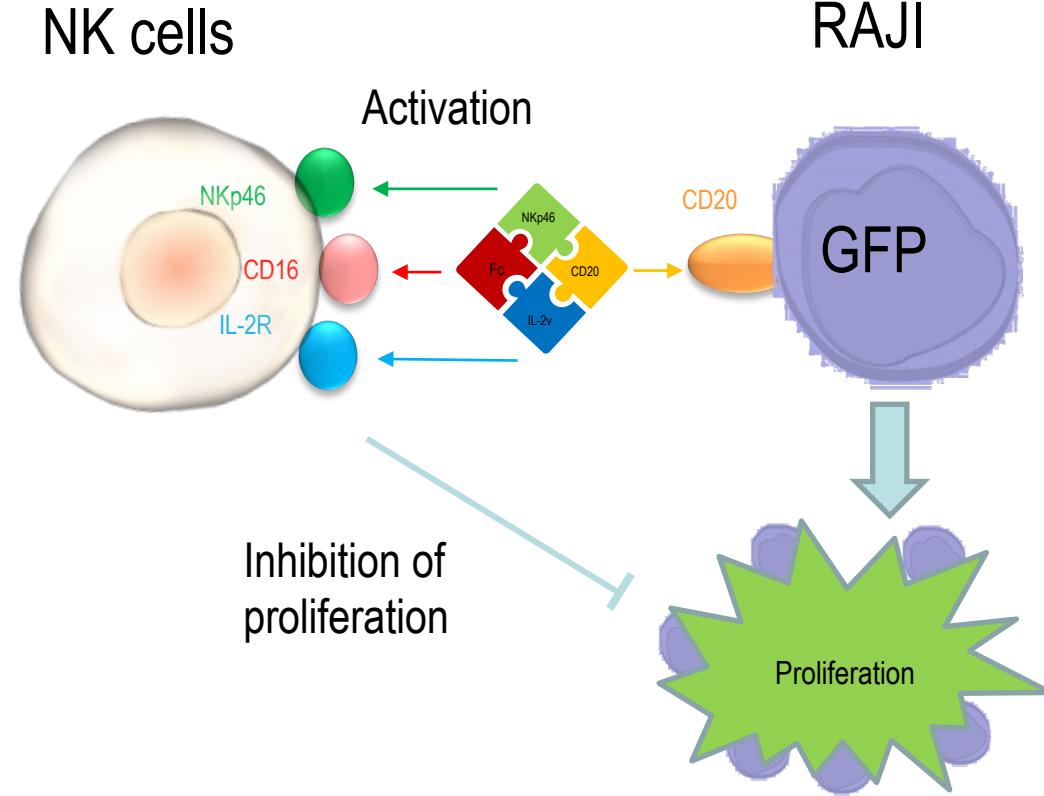


- NHL represent about 80% of all lymphomas (and HL the remaining 20%)
- Within NHL, 85% are B-cell and 15% T-cell
- CD20 is expressed on >90% of B-cell NHL

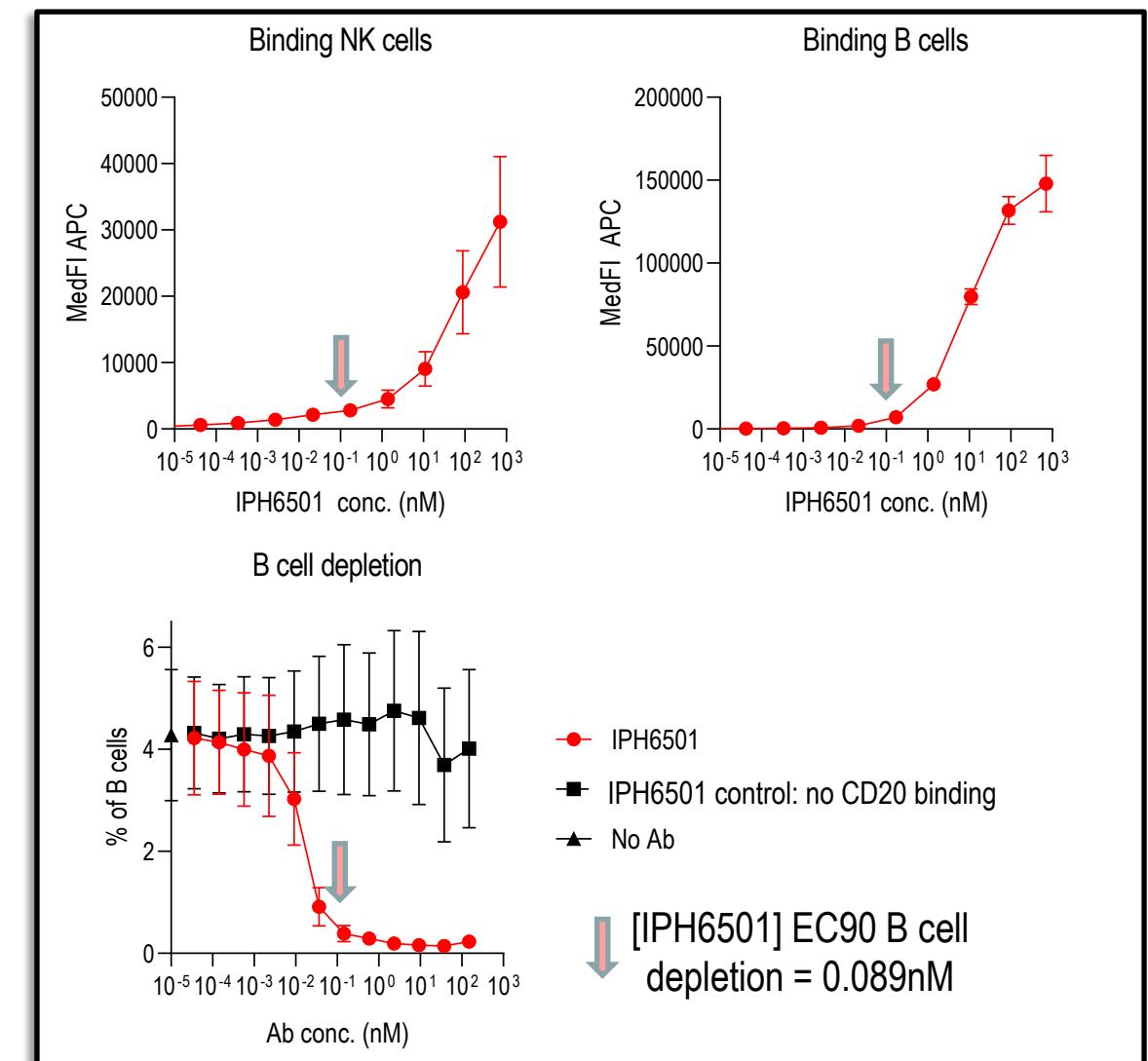
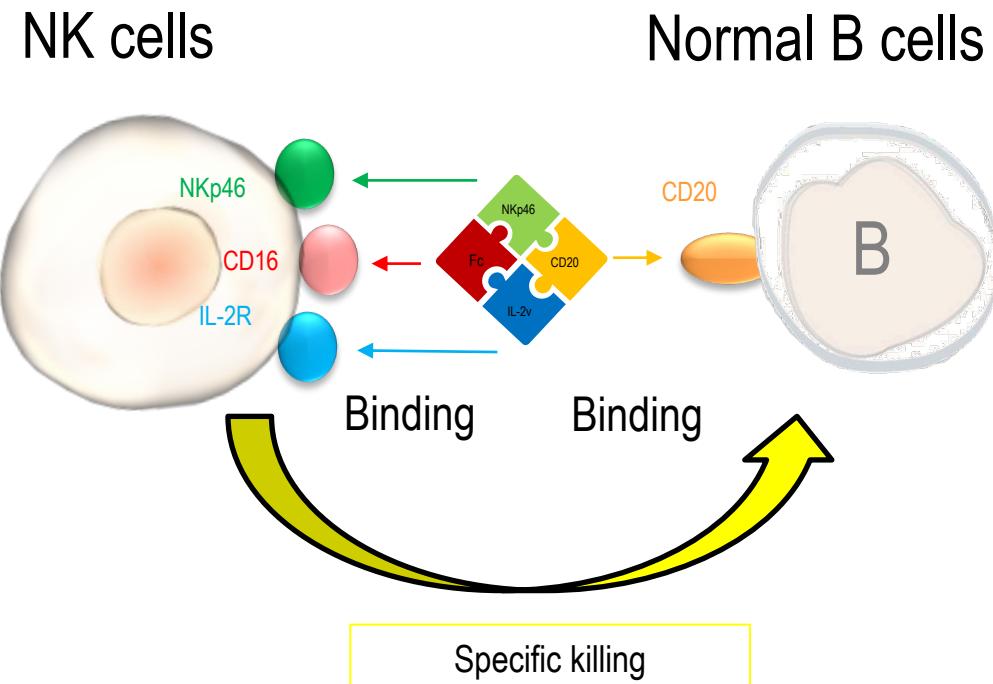
# IPH6501: first-in-class tetraspecific ANKET designed to target specifically CD20<sup>+</sup> cells



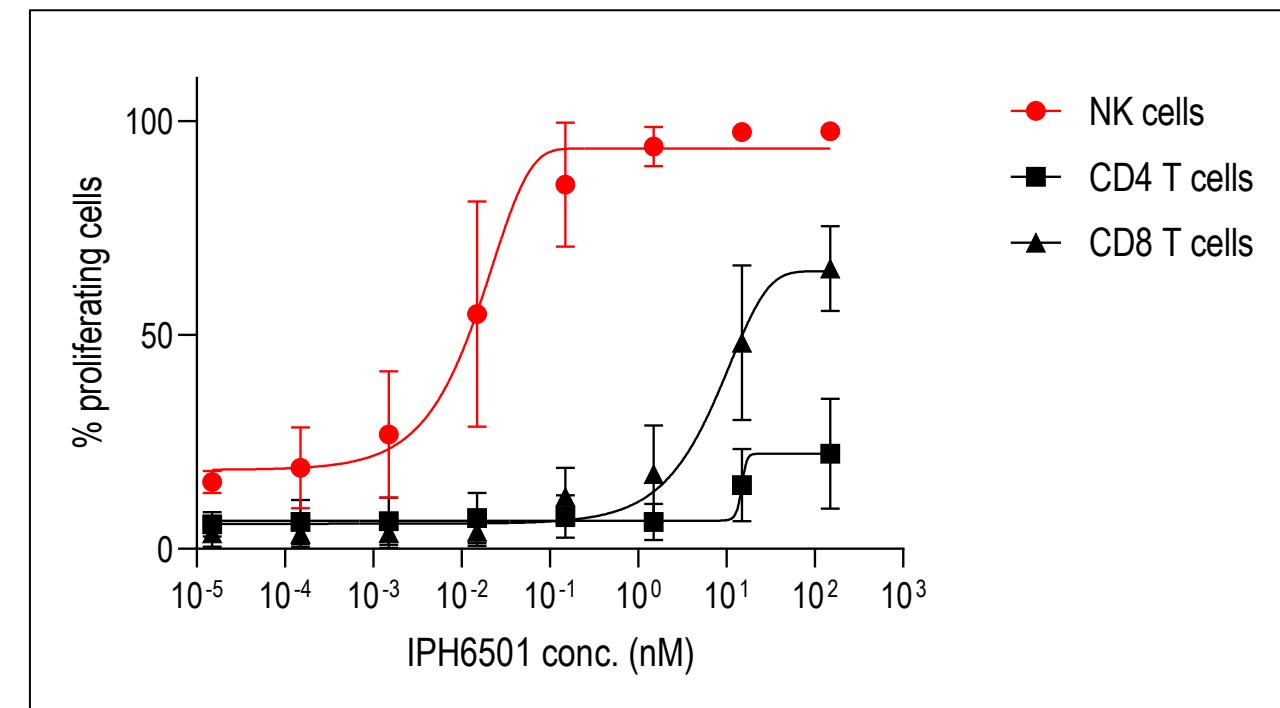
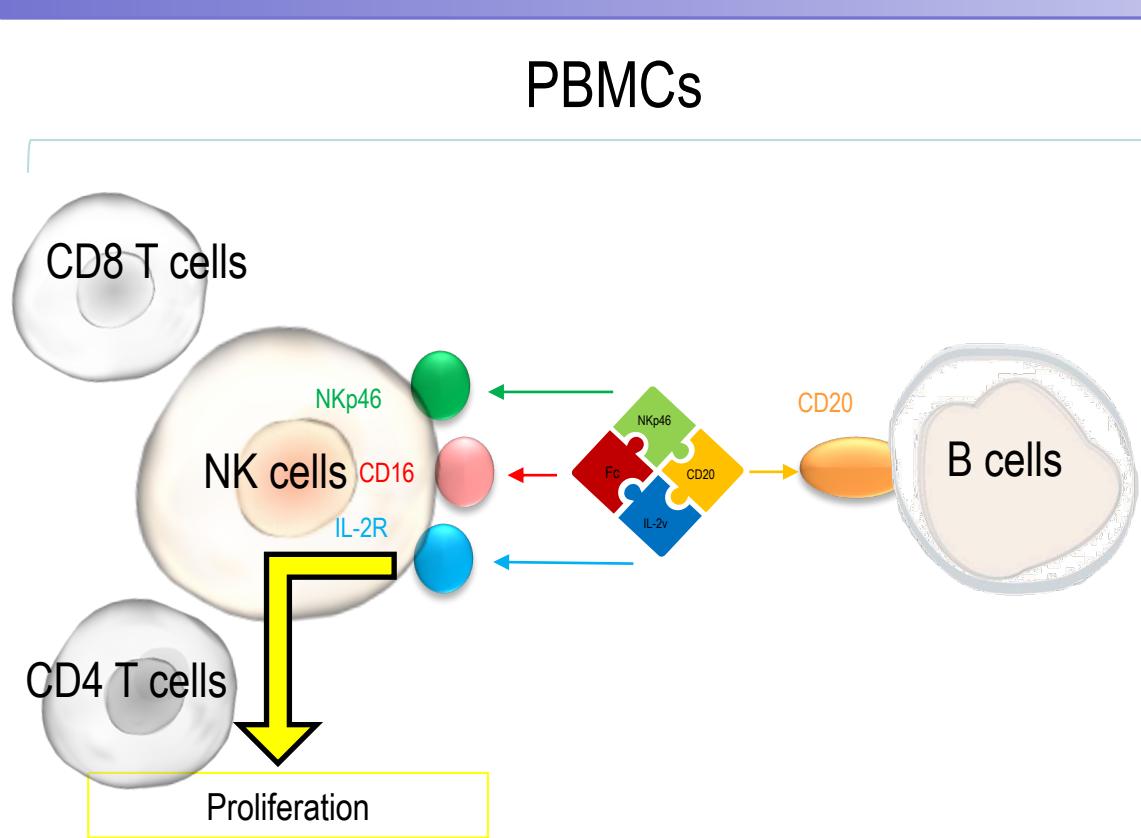
# IPH6501: first-in-class tetraspecific ANKET designed for improved activity as compare to IgG1 clinical antibodies



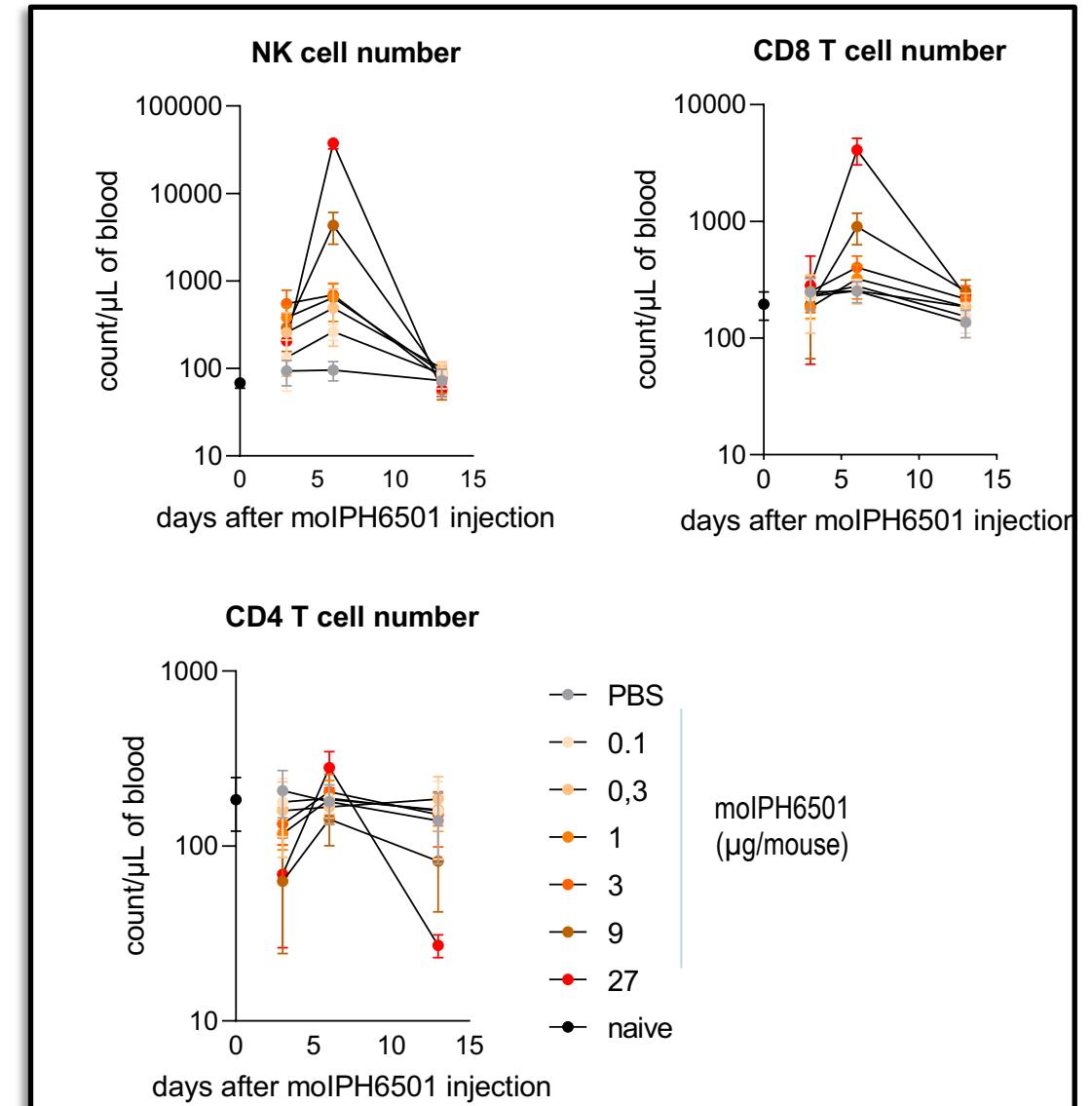
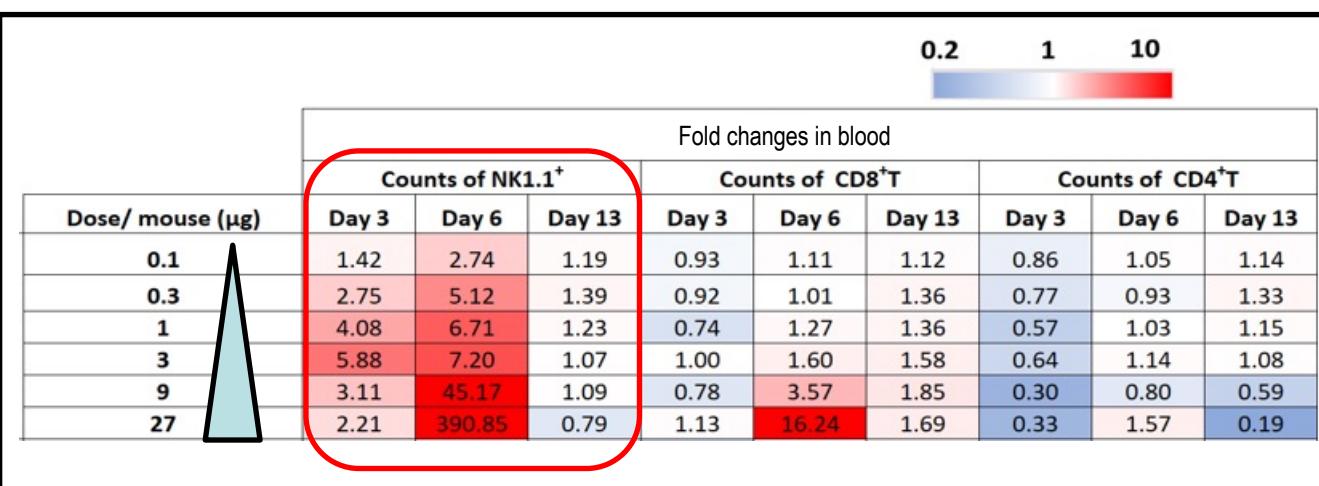
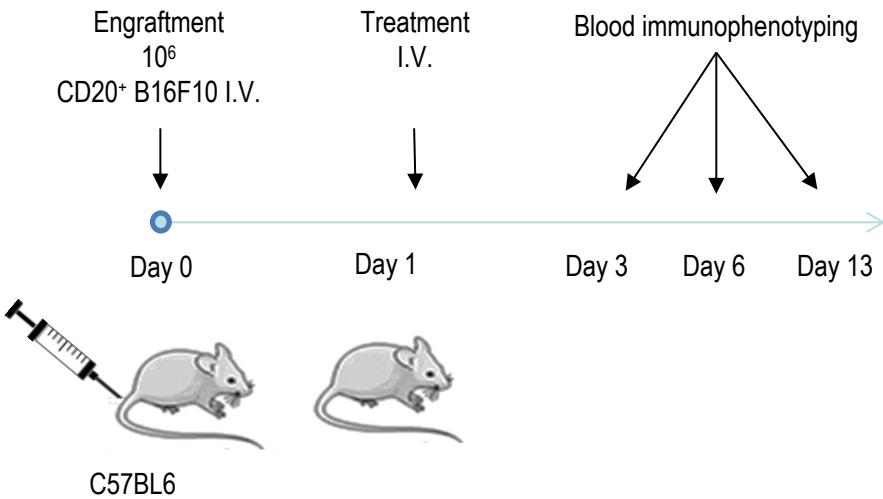
# IPH6501 induces killing activity at low receptor occupancy



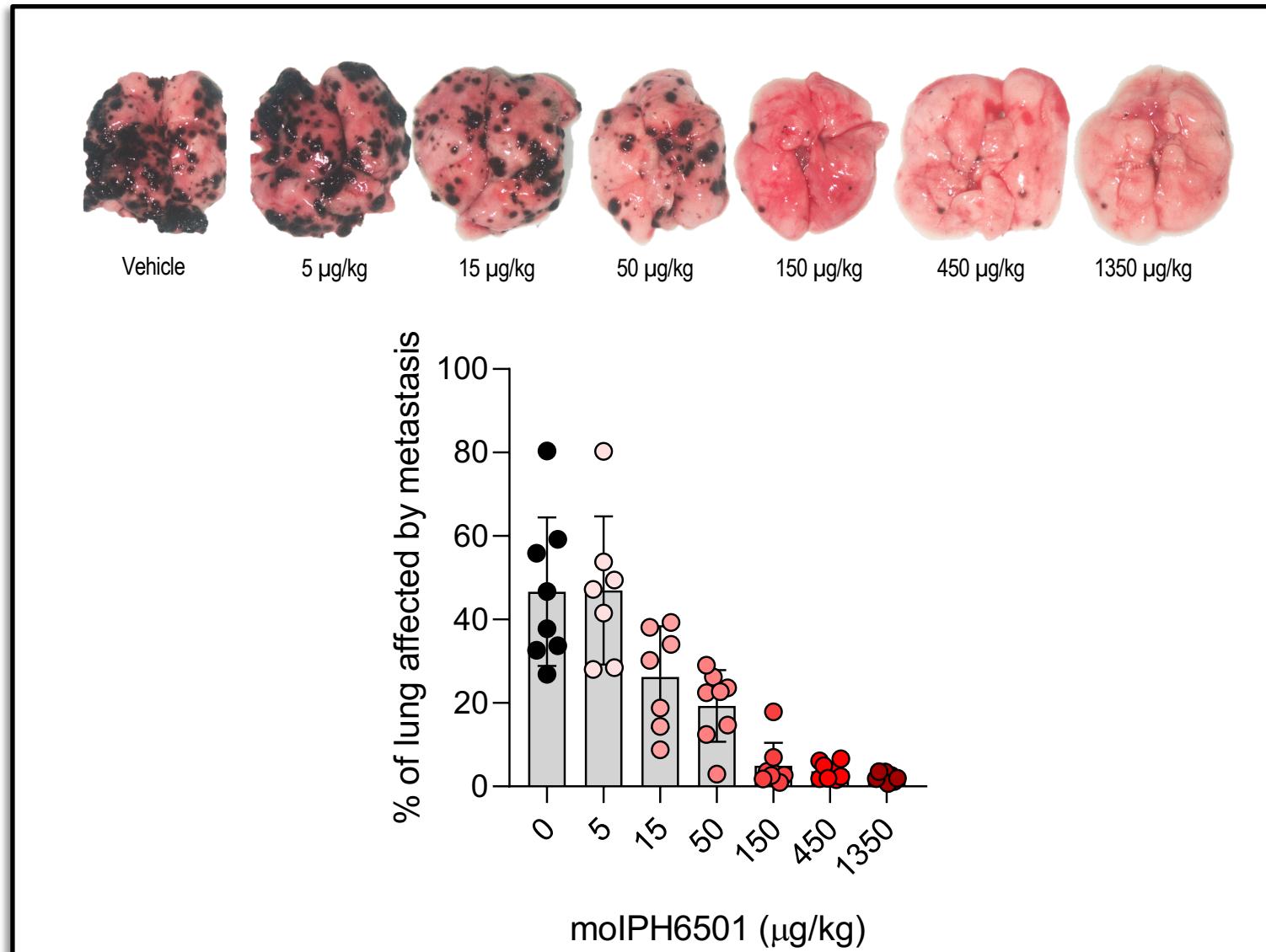
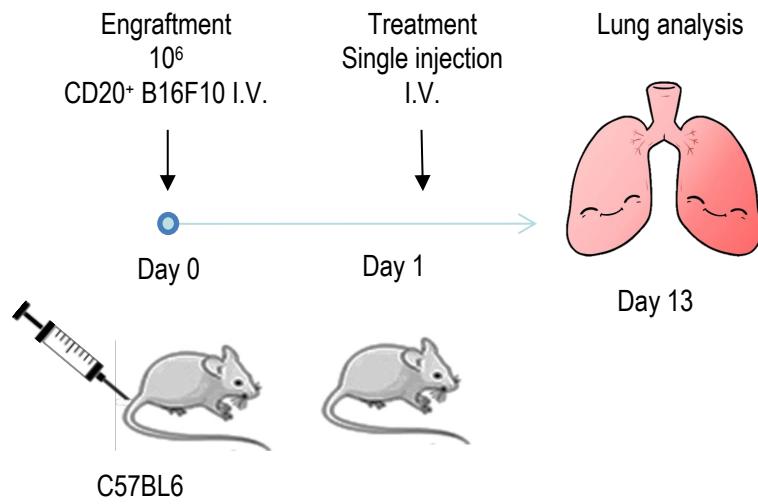
# IPH6501 induces preferential NK cell proliferation



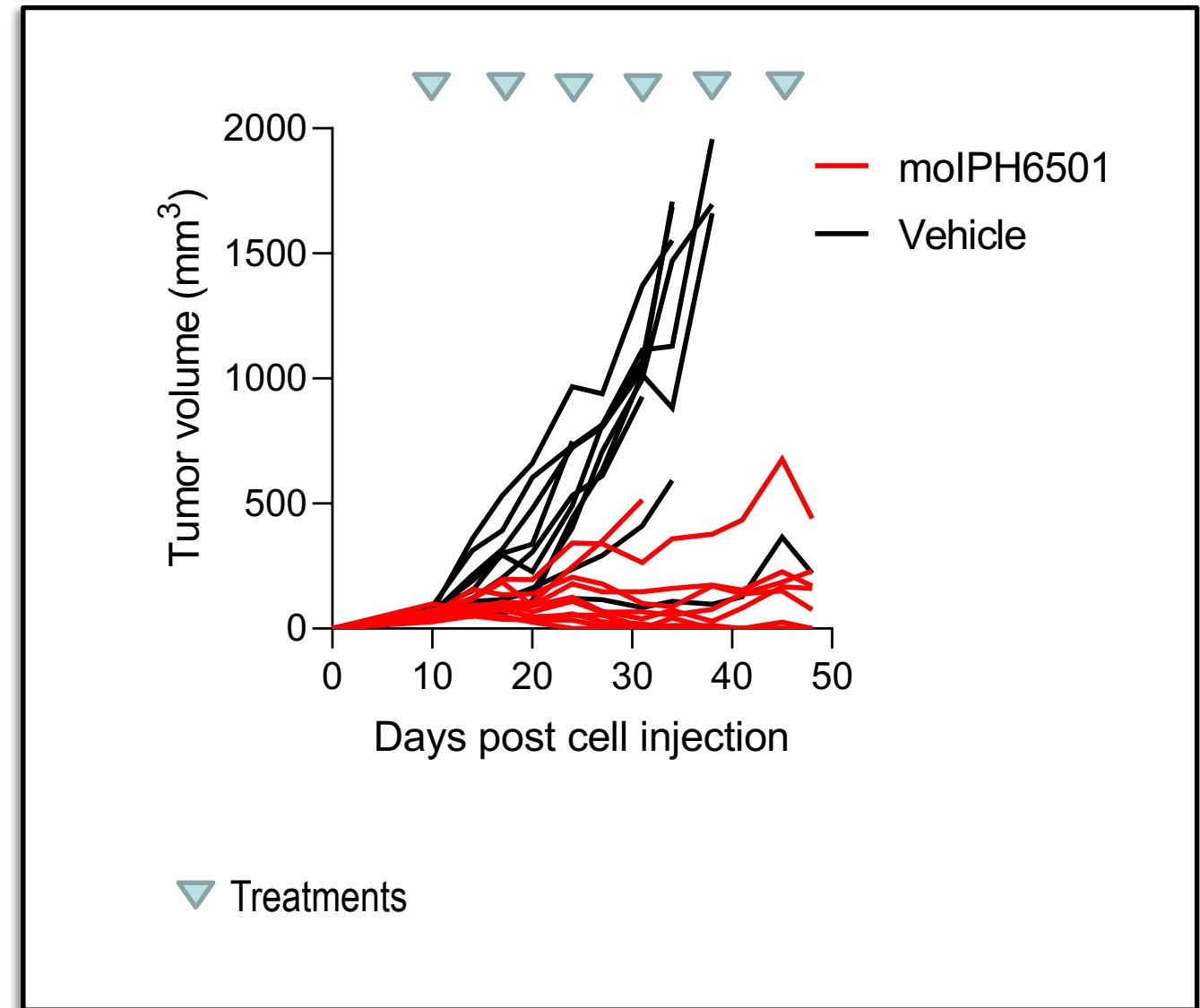
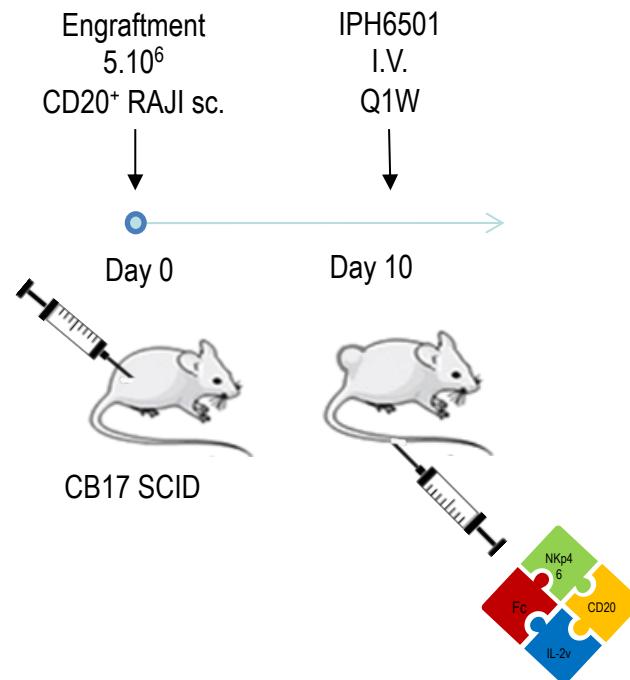
# Mouse IPH6501 surrogate induces preferential NK cell expansion *in vivo*



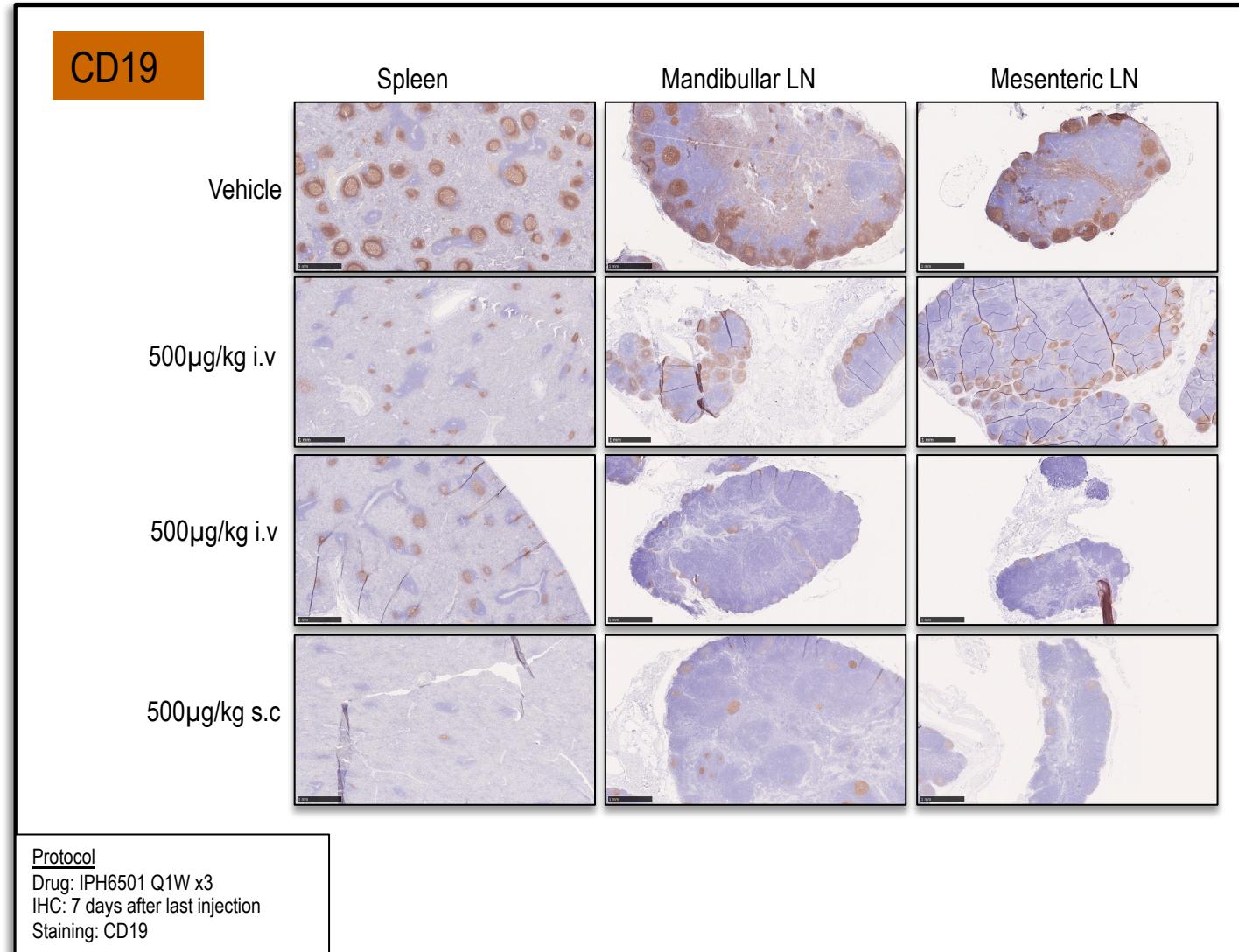
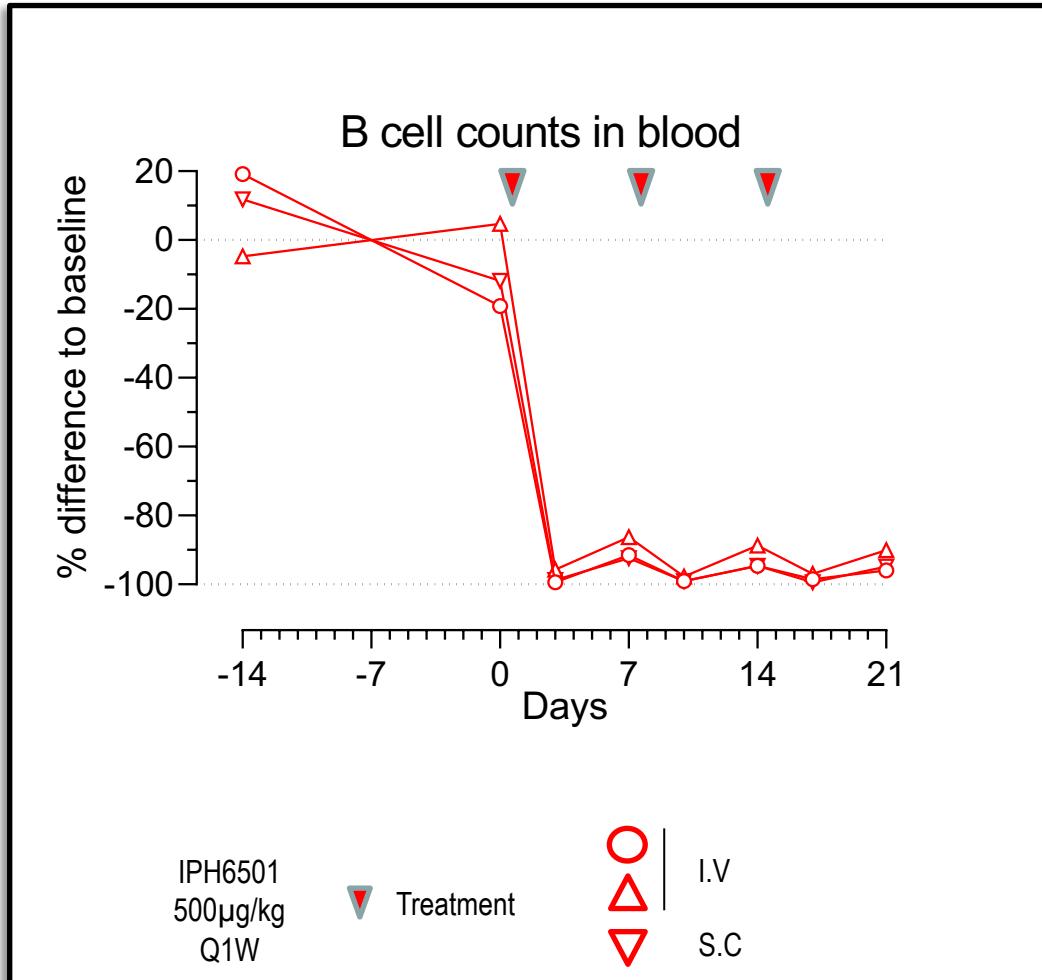
# Mouse IPH6501 surrogate induces potent *in vivo* efficacy in immunocompetent mice



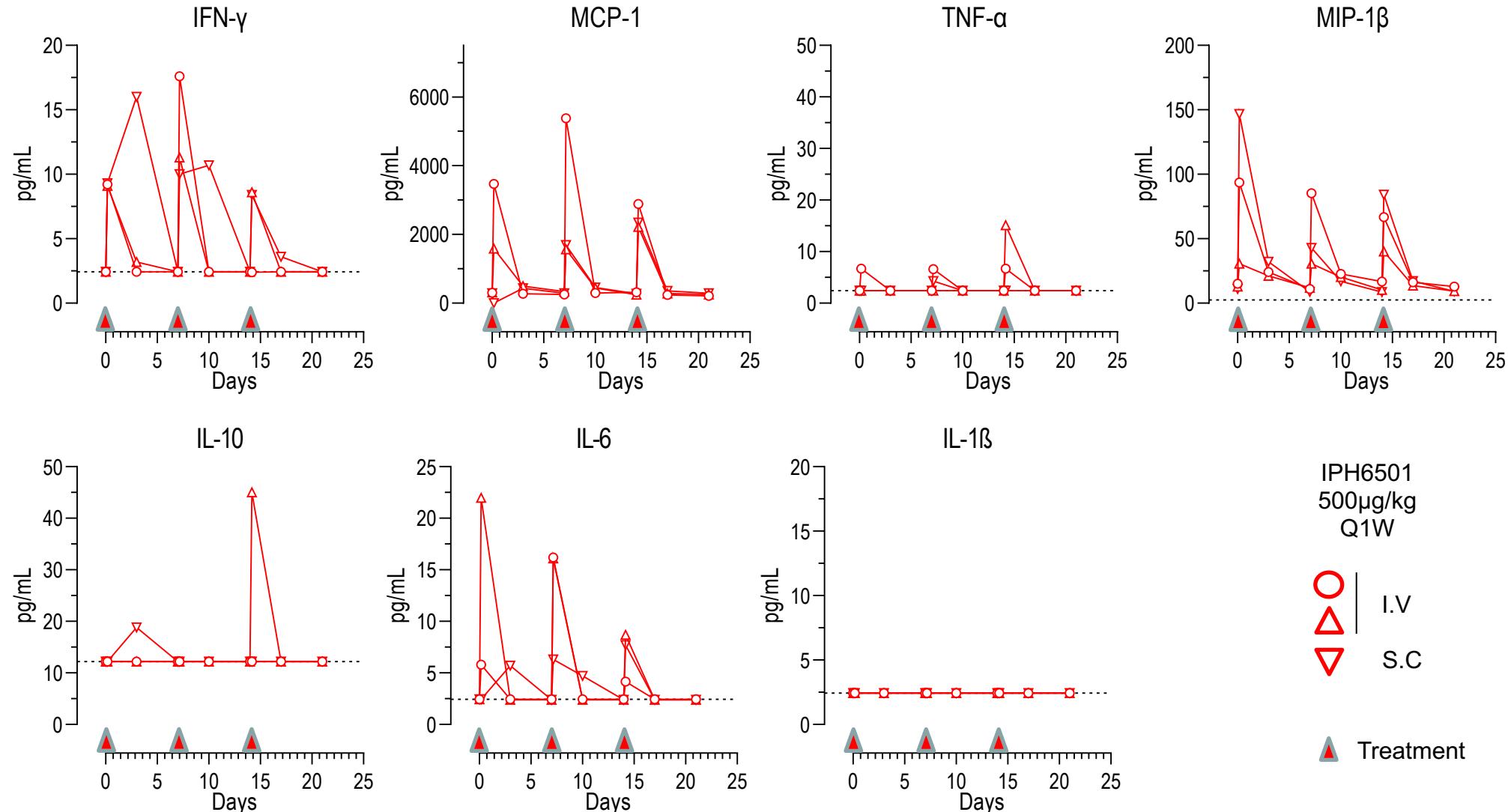
# Mouse IPH6501 surrogate induces B-NHL tumor control in a xenograft mouse model



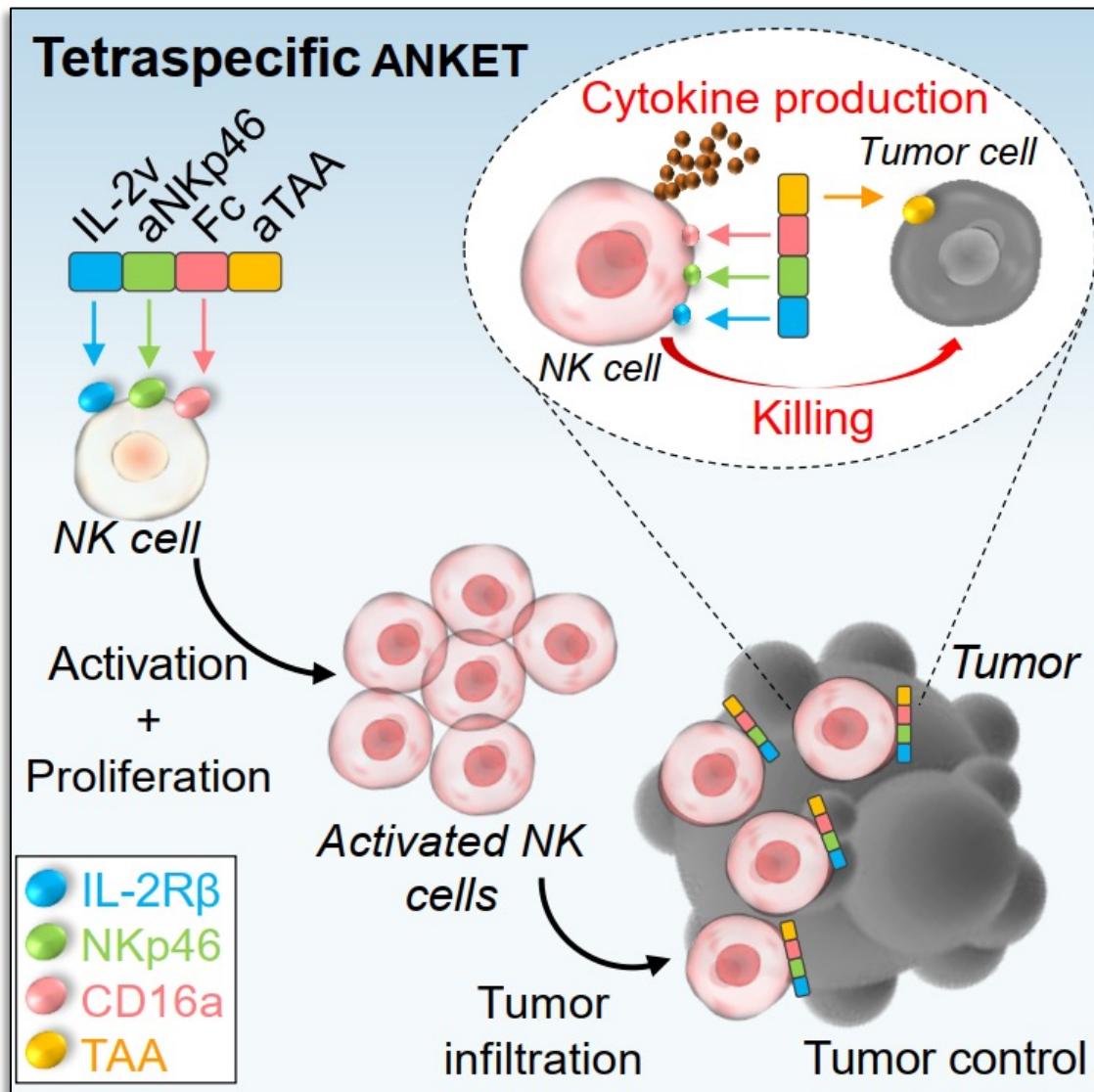
# IPH6501 efficacy in Non Human Primates (Cynomolgus)



# IPH6501 induces minimal cytokine release at effective dose in Non Human Primates (Cynomolgus)



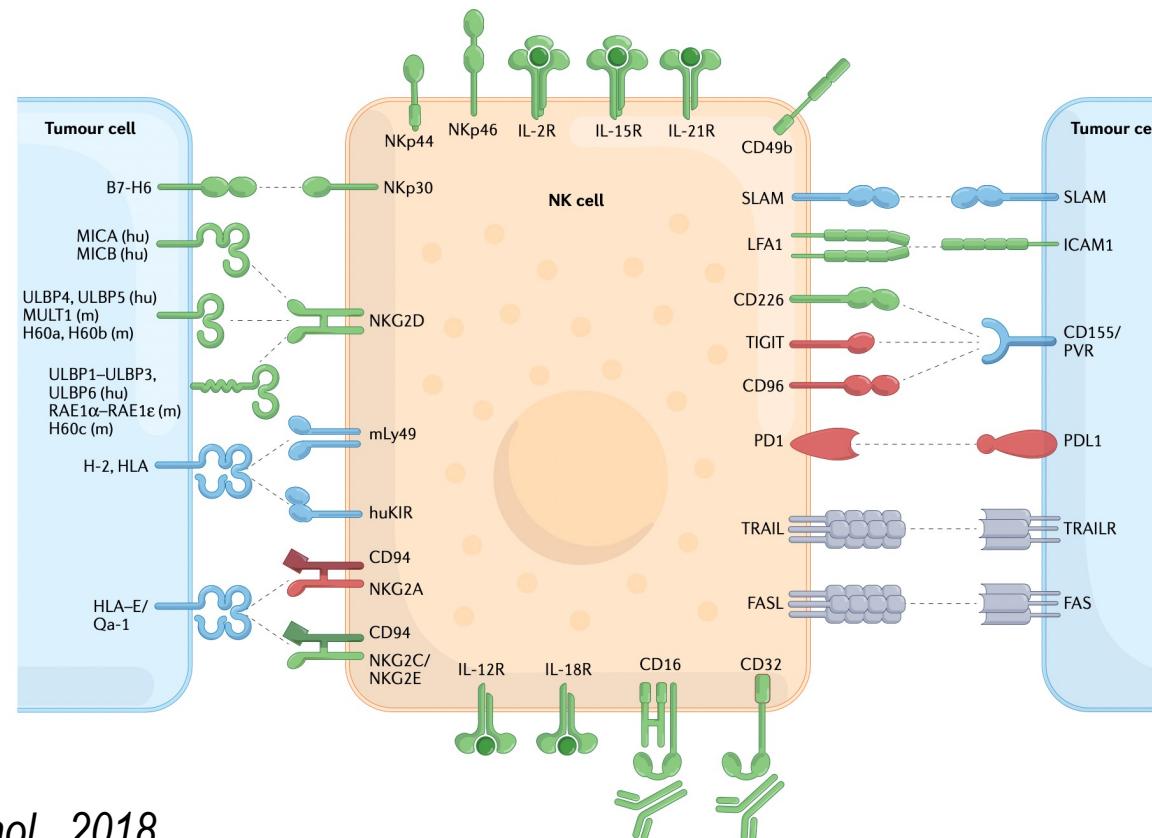
# NK cell harnessing with tetraspecific ANKET



- Tetraspecific ANKET constitute a versatile platform to harness NK cells in cancer
- Tetraspecific ANKET target NKp46, CD16a, IL-2R $\beta$  and a tumor antigen
- Tetraspecific ANKET stimulate NK cell proliferation, activation and antitumor functions
- In vivo, tetraspecific ANKET promote NK cell tumor accumulation and antitumor activity

# NK cell tumor immunity is controlled by several cell surface receptors

NK cells recognize a wide array of tumor cells across histotypes  
(hematological malignancies and solid tumors)



Vivier et al., *Nature Immunology* 2008

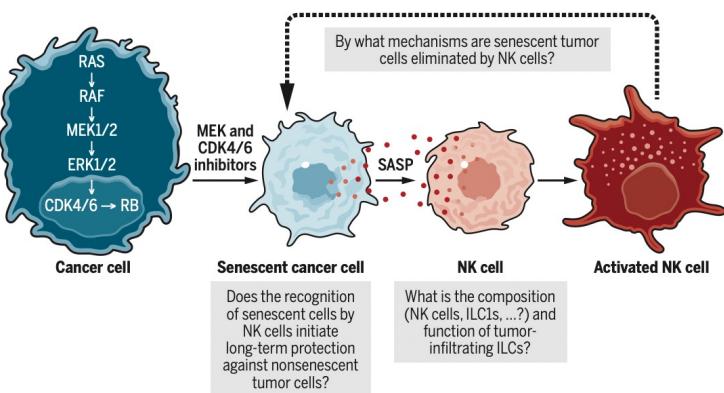
Vivier et al., *Science* 2011

Chiossone et al., *Nature Reviews Immunol.*, 2018

Wolf et al., *Nature Reviews Immunol.*, 2022

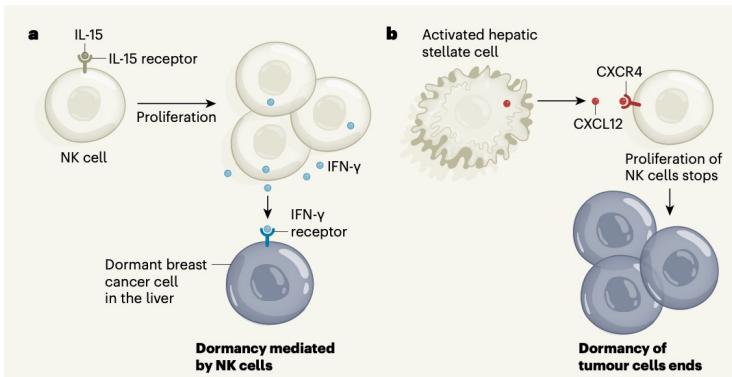
# NK cell recognition of tumor cells

## NK cells detect and eliminate senescent tumor cells



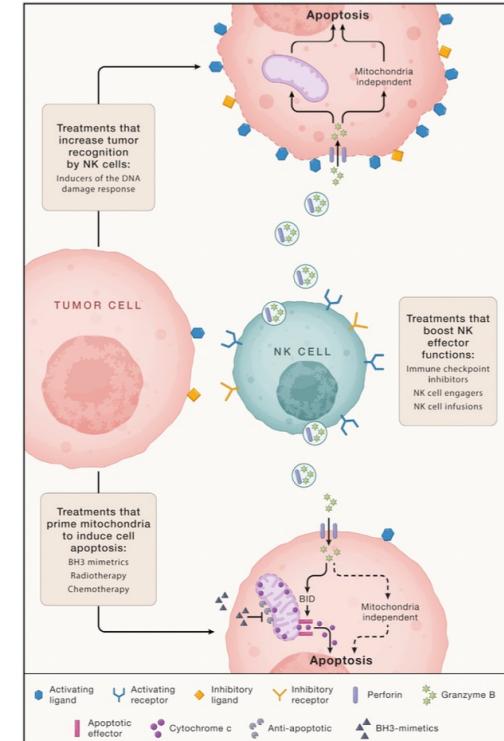
Ruscetti et al., *Science* 2018  
Cornen & Vivier, *Science* 2018

## Natural killer cells lull tumours into dormancy



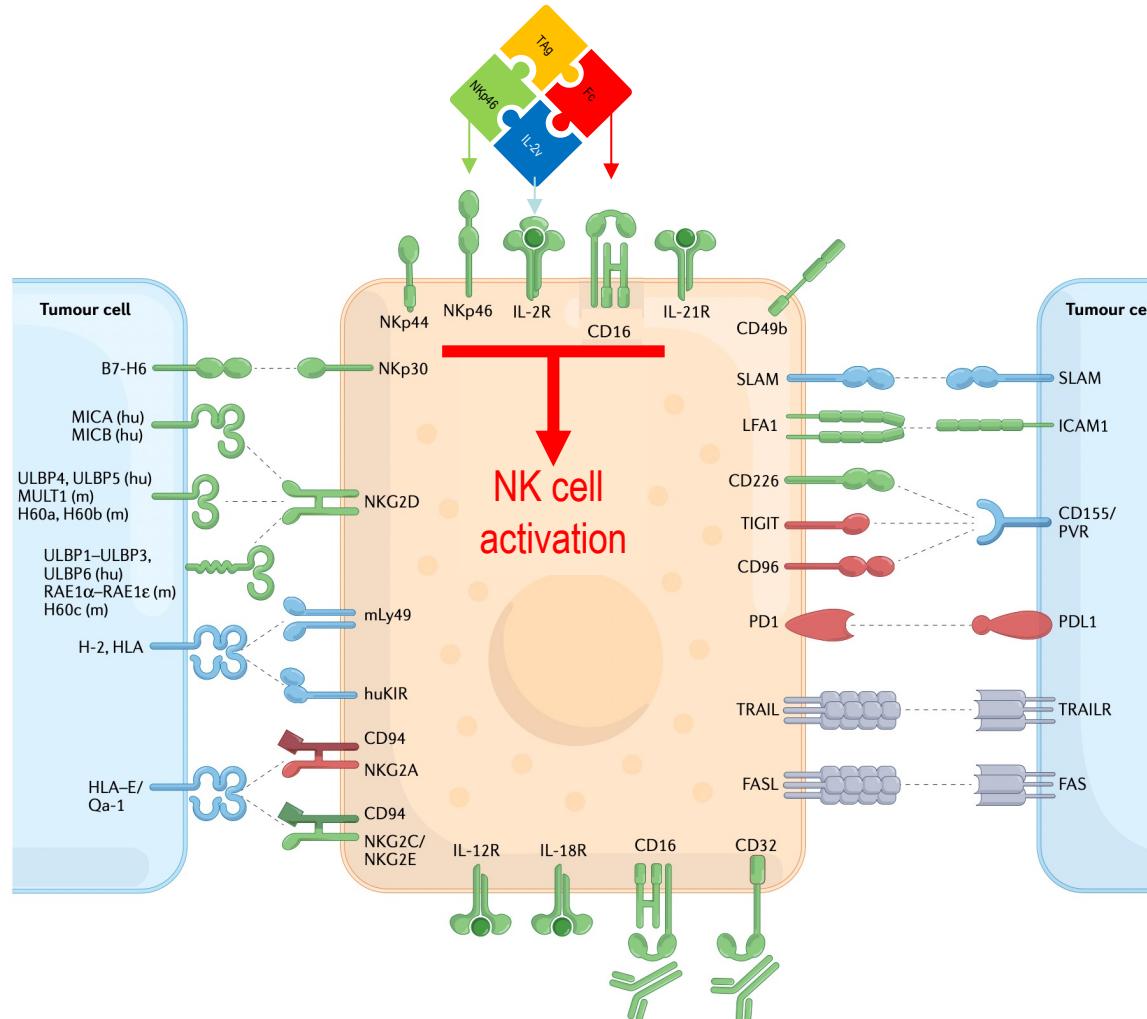
Correia et al., *Nature* 2021  
Lopes & Vivier, *Nature* 2021

## Sensitizing tumor cells to NK cell-mediated killing

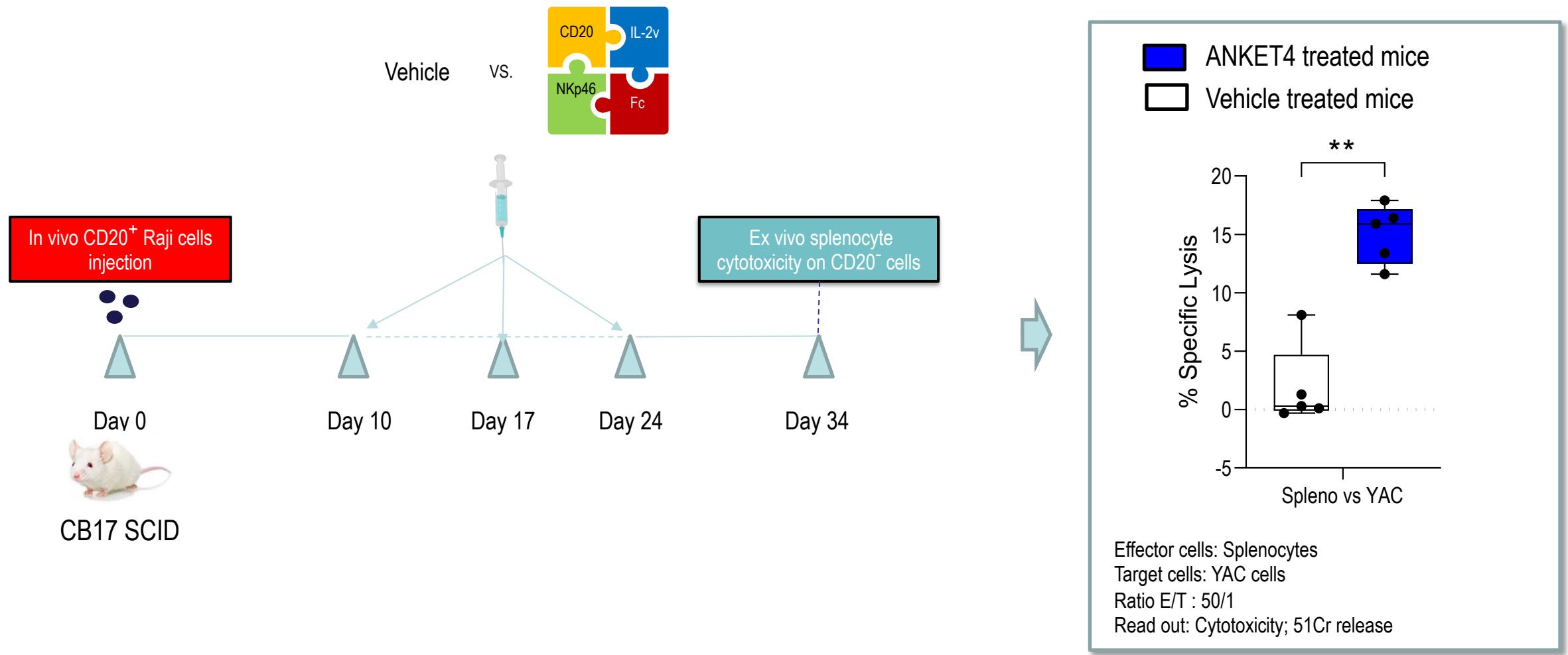


Pan et al., *Cell* 2022  
Narni-Mancinelli & Vivier, *Cell* 2022

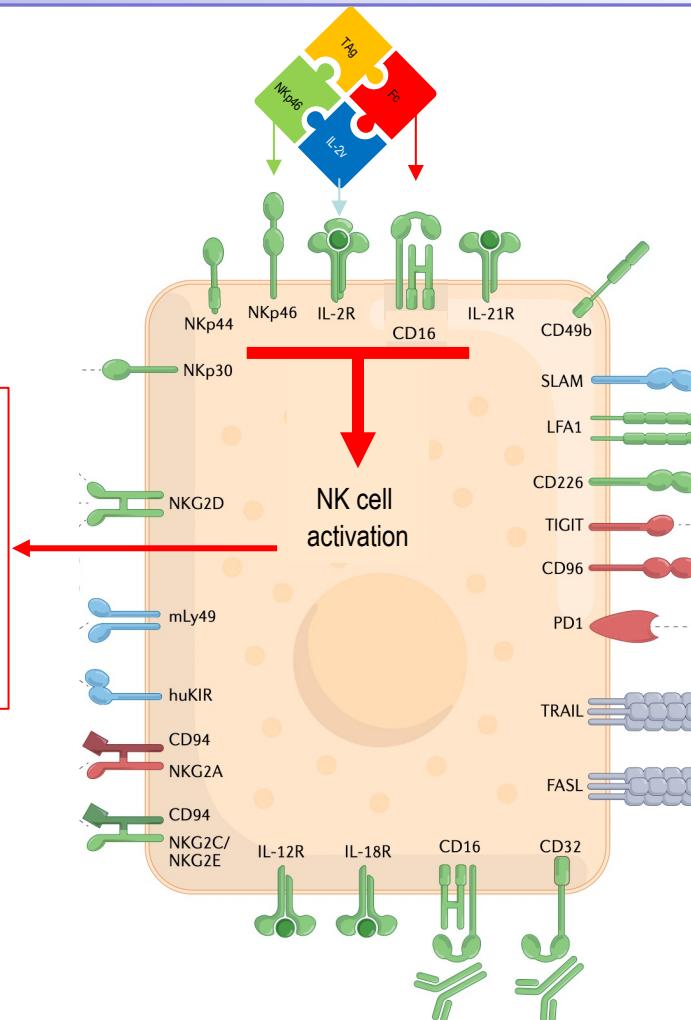
# ANKET boost NK cell immunity



# Tumor-agnostic NK cell immunity induced by tetraspecific ANKET



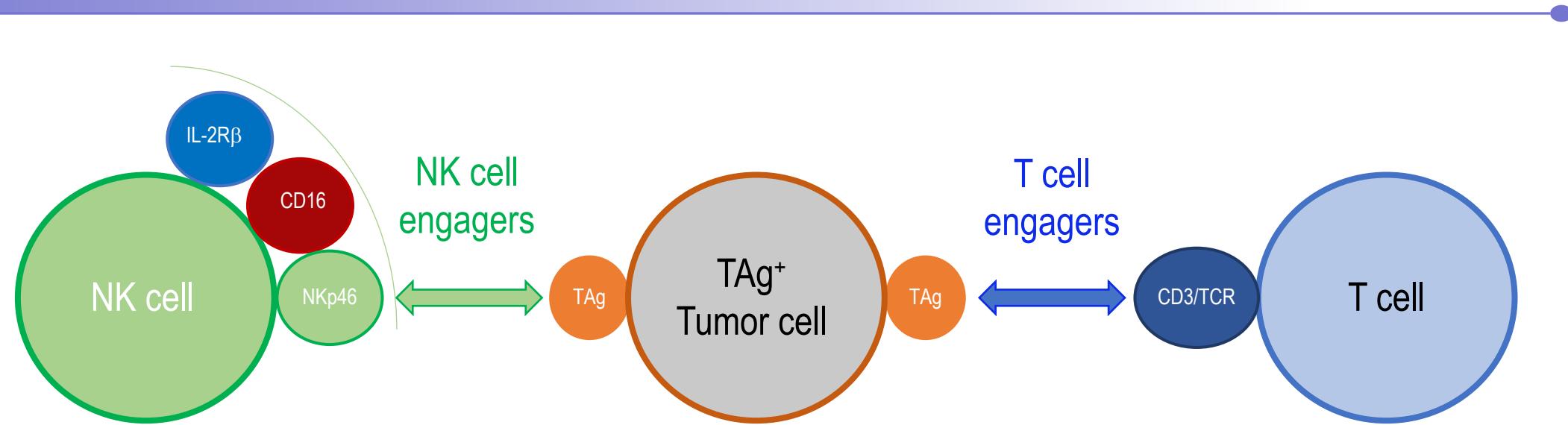
# ANKET: a strong add-on of NK cell anti-tumor immunity



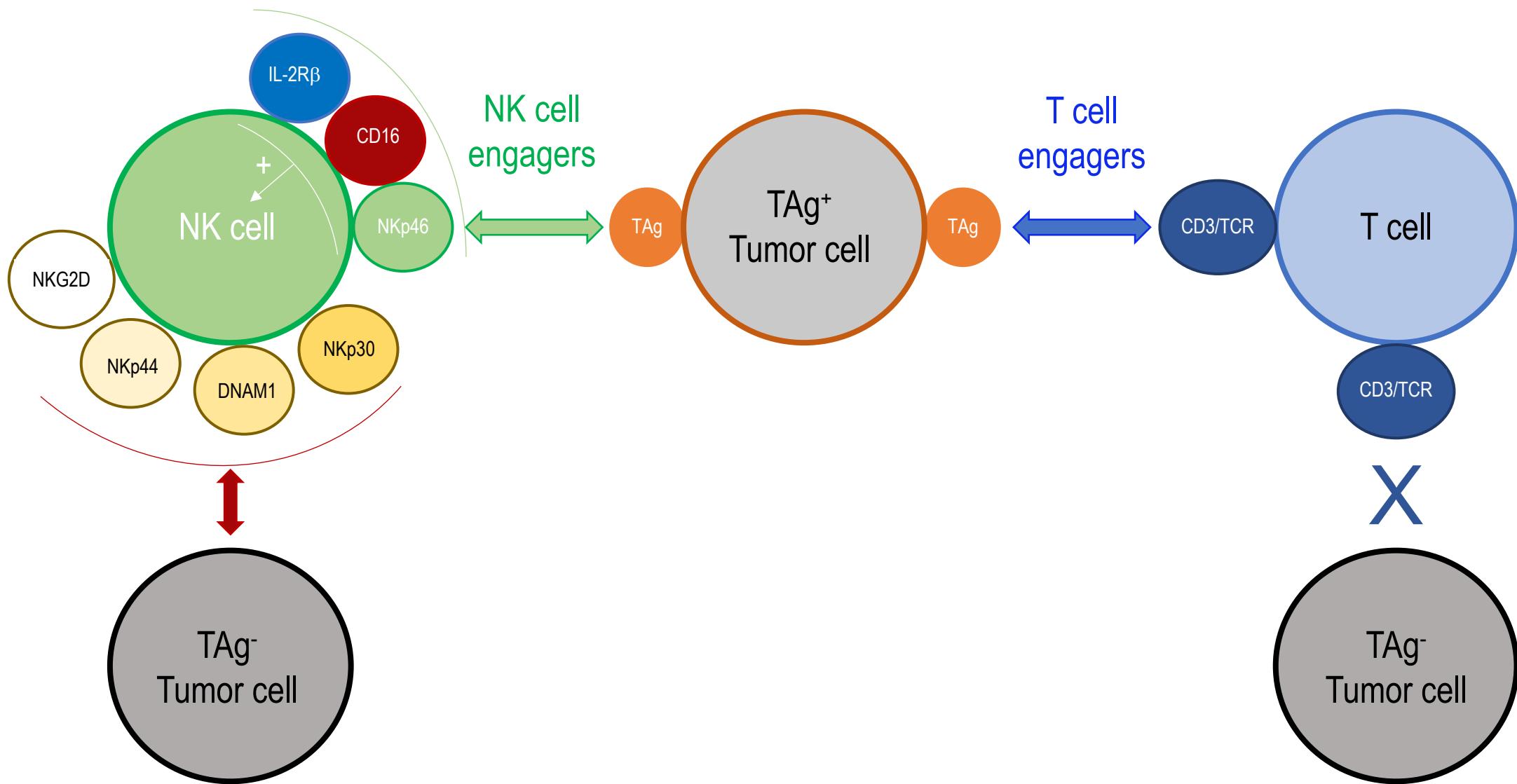
## Tetraspecific IL-2v ANKET boost:

- NK cell immunity against tumor Ag<sup>+</sup> cells
- NK cell immunity against tumor Ag<sup>-</sup> cells
- NK cell systemic proliferation

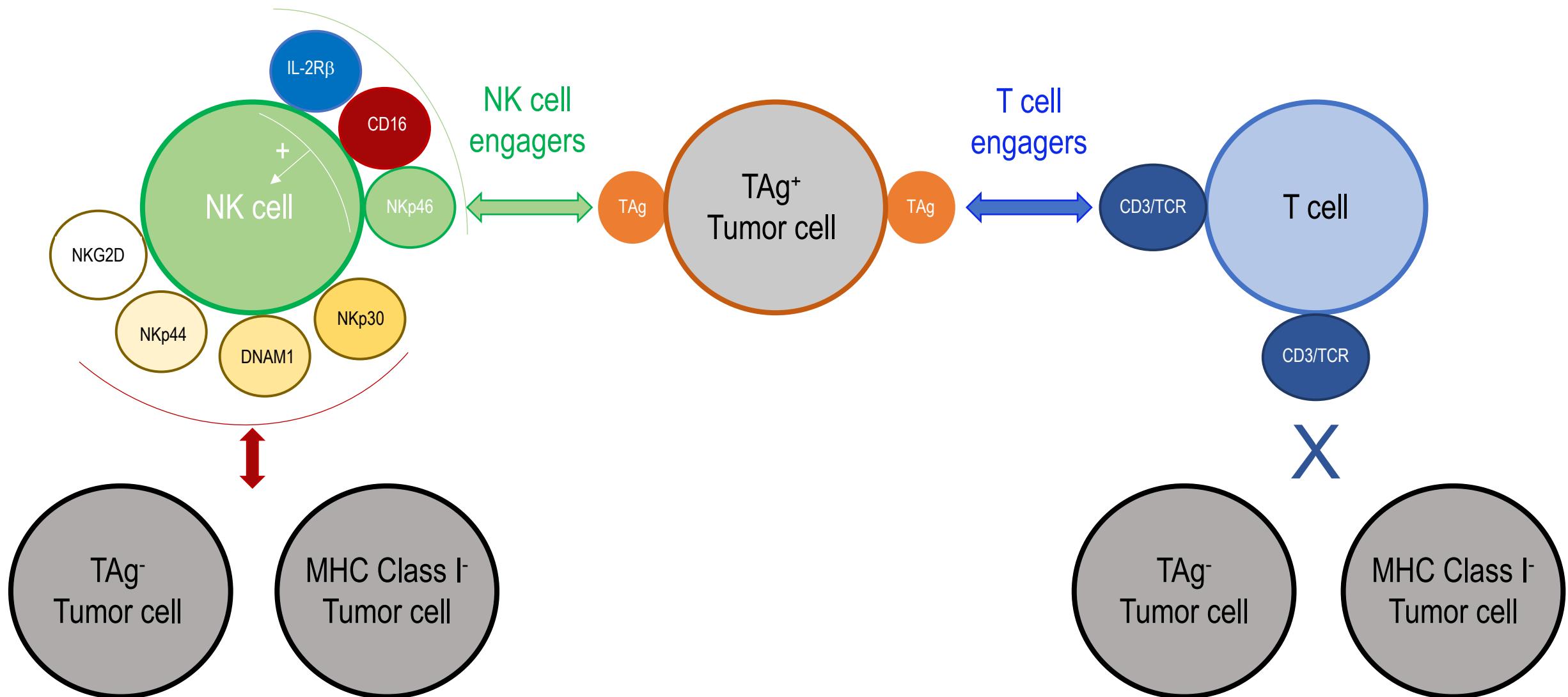
# NK vs. T cell engagers



# NK vs. T cell engagers



# NK vs. T cell engagers



## Anti-tumor immunity induced by tetrafunctional Natural Killer cell engagers armed with not-alpha IL-2 variant

Olivier Demaria\*, Laurent Gauthier\*, Marie Vétizou\*, Audrey Blanchard Alvarez, Guillaume Habif, Luciana Batista, Constance Vagne, Stéphanie Cornen, William Baron, Nourhène Belaïd, Mathilde Girard-Madoux, Cedric Cesari, Melody Caratini, Frédéric Bosco, Olivier Benac, Julie Lopez, Aurore Fénis, Barbara Carrette, Florent Carrette, Aurélie Maguer, Solène Jaubert, Audrey Sansaloni, Robin Letay-Drouet, Camille Kosthowa, Naouel Lovera, Arnaud Dujardin, Sivan Bokobza, Cécile Bonnafous, Sabrina Carpentier, Agnès Represa, Benjamin Rossi, Ariane Morel, Ivan Perrot, Yannis Morel



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