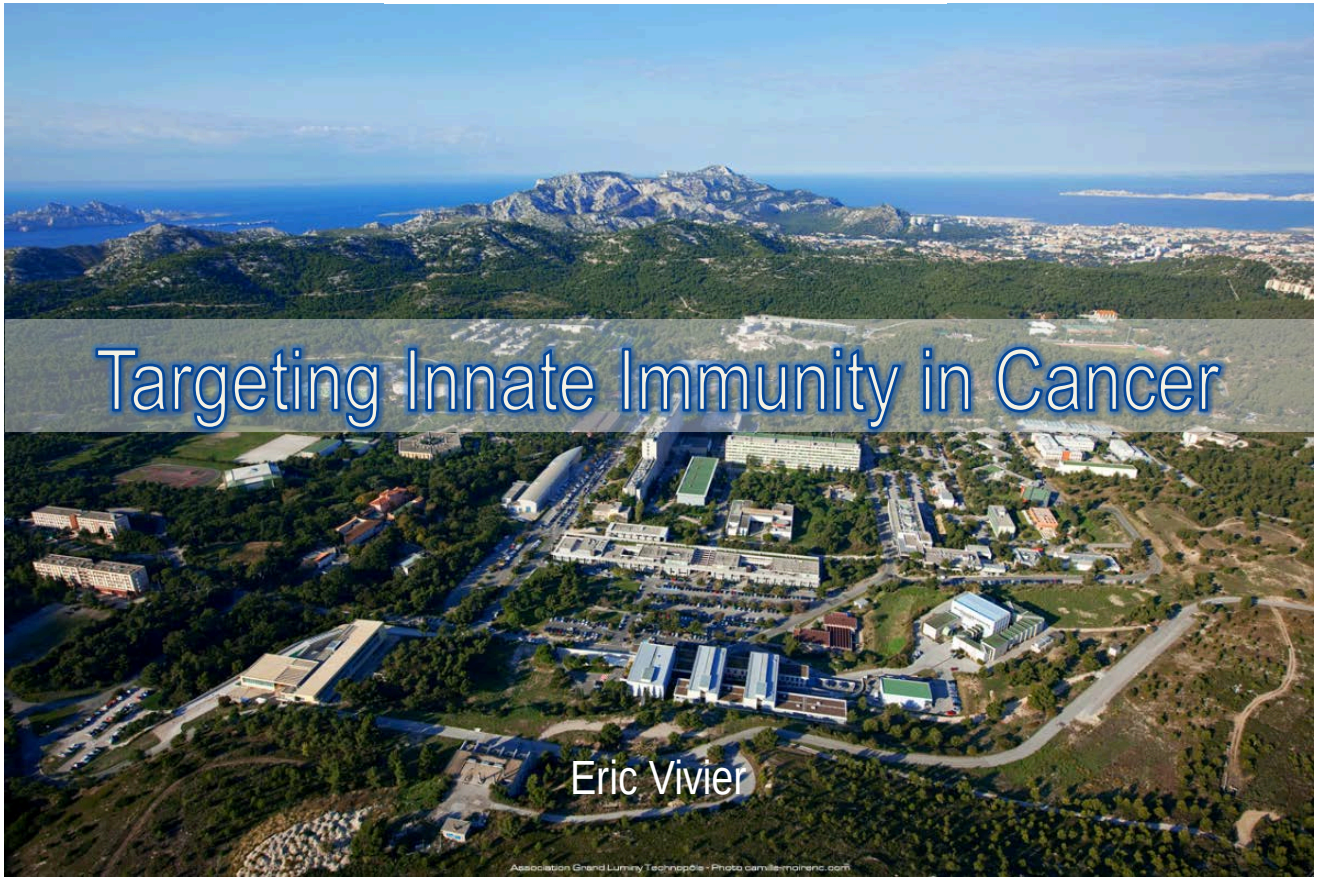
innate pharma



Aix*Marseille université

Inserm

cnrs

AP HM
Assistance Publique Hôpitaux de Marseille

Ciml IMMUNOLOGY

European Research Council erc

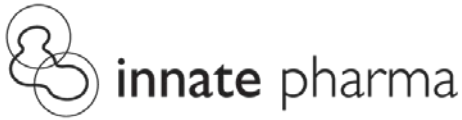
ANR

MSD AVENIR

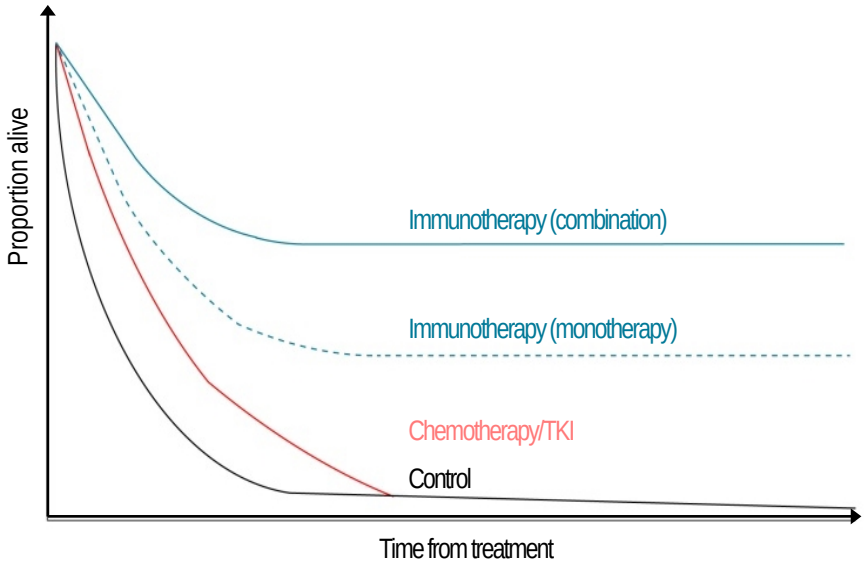
MARSEILLE IMMUNOPÔLE

Disclosures

- Innate-Pharma, co-founder + CSO



The Immuno-Oncology Revolution



Immune Checkpoints Inhibitors

Anti-CTLA4

- Ipilimumab (IgG1, YERVOY, BMS)
- Tremelimumab (IgG2, ASTRAZENECA)

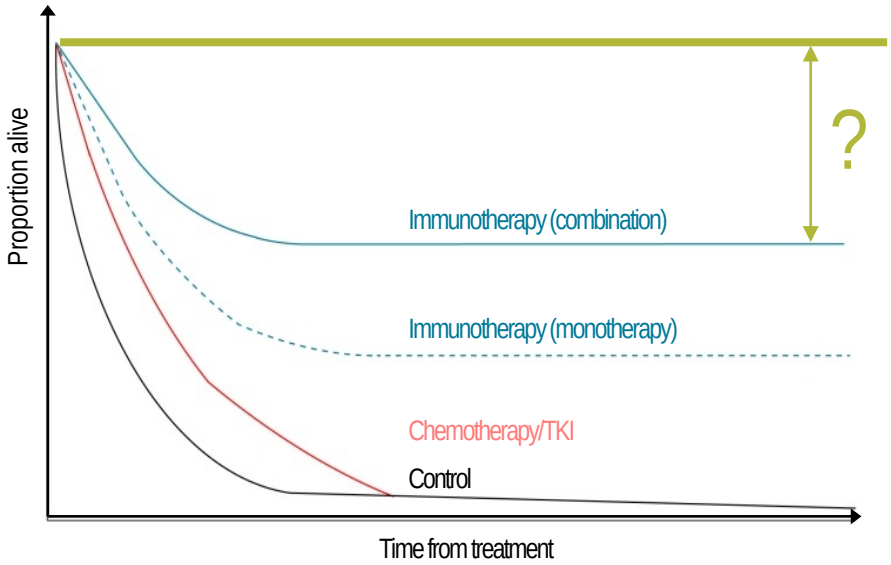
Anti-PD-1

- Nivolumab (IgG4, OPDIVO, BMS)
- Pembrolizumab (IgG4, KEYTRUDA, MERCK)
- Cemiplimab (IgG4, LIBTAYO, SANOFI/REGENERON)

Anti-PD-L1

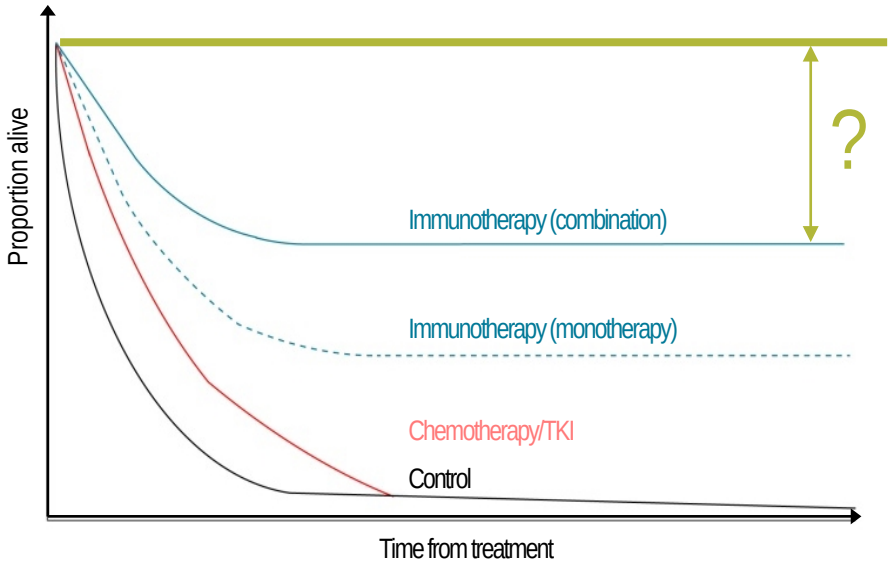
- Avelumab (IgG1, BAVENCIO, MERCK KGaA/PFIZER)
- Durvalumab (IgG1, IMFINZI, ASTRAZENECA)
- Atezolumab (IgG1, TECENTRIQ, GENENTECH/ROCHE)

The Immuno-Oncology Revolution



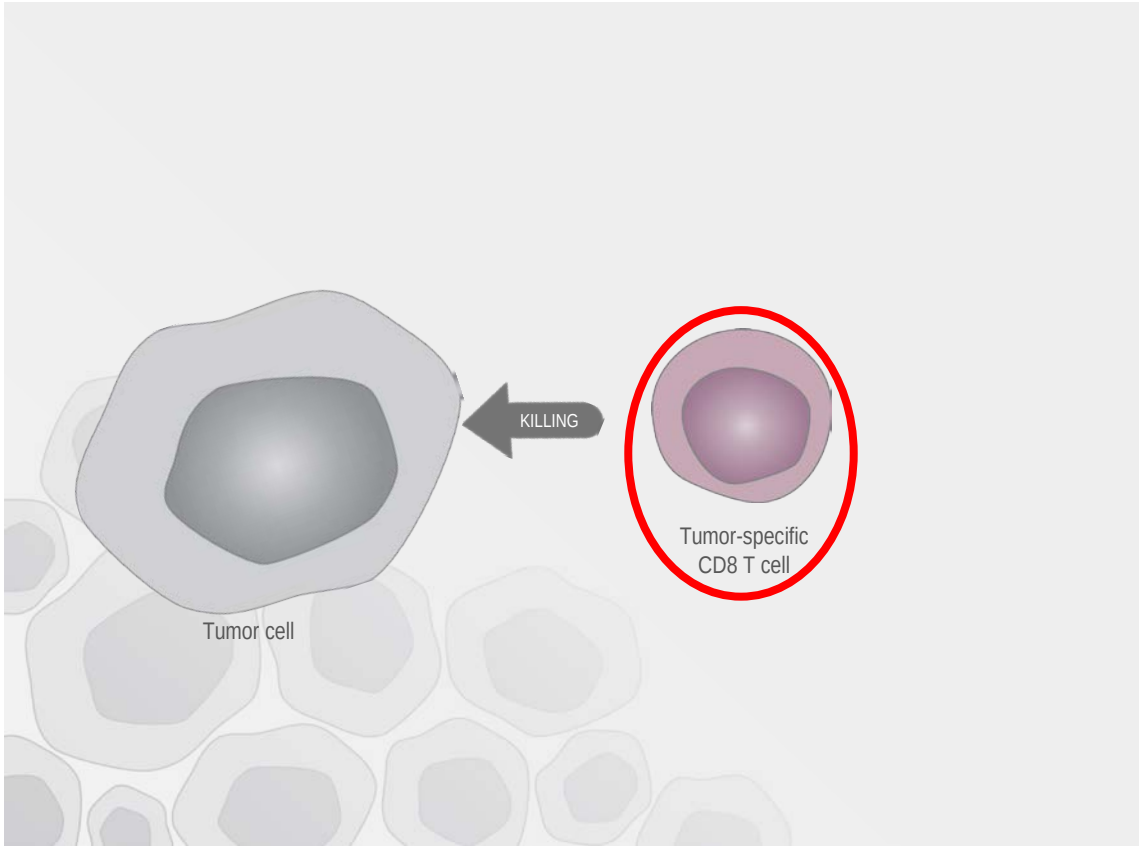
- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity

The Immuno-Oncology Revolution

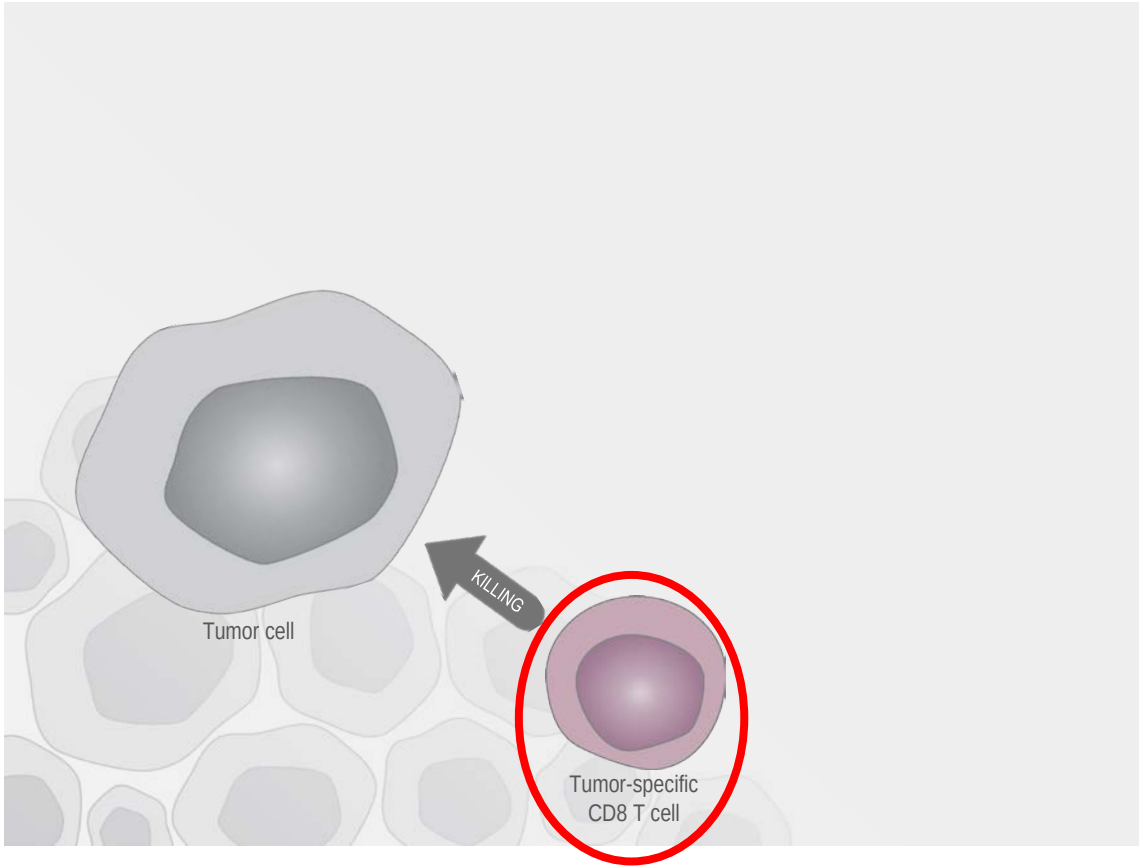


- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity
- Identify new targets (cells and molecules)
- Identify biomarkers

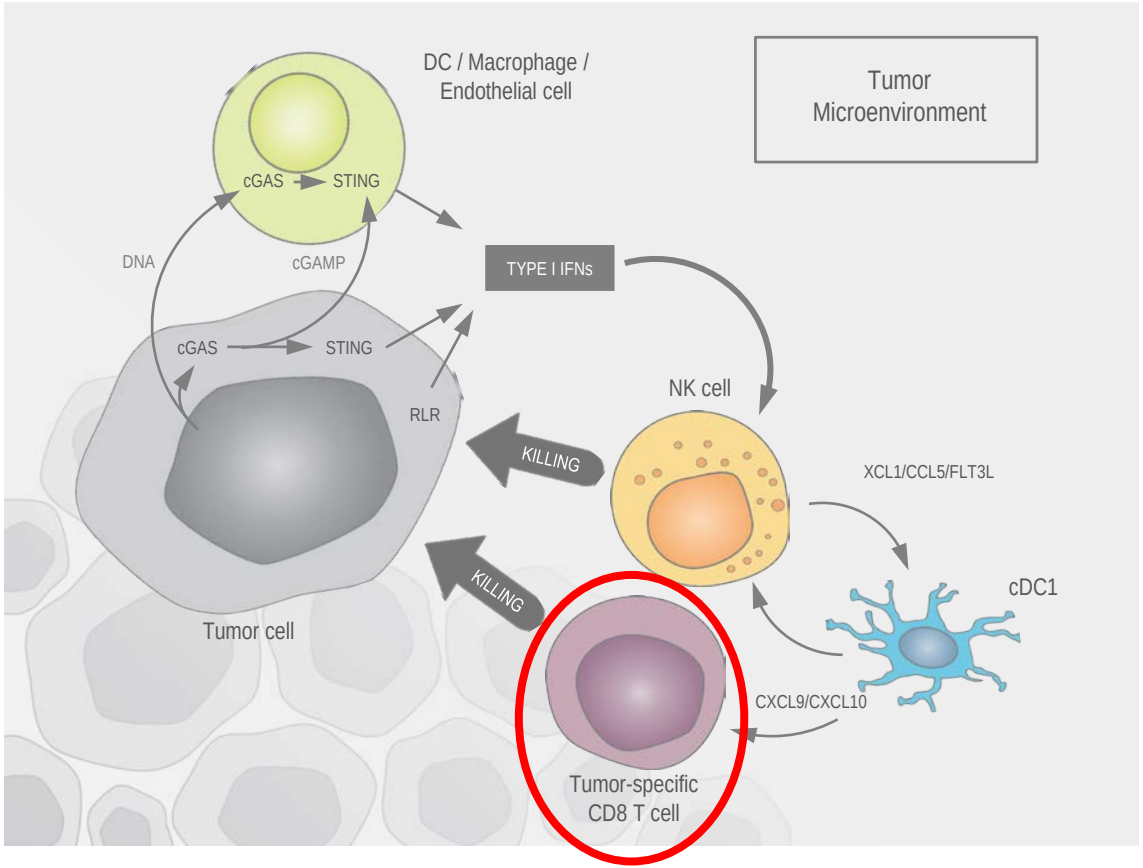
A pivotal role of T cells in tumor immunity



T cells are not autonomous in their anti-tumor functions

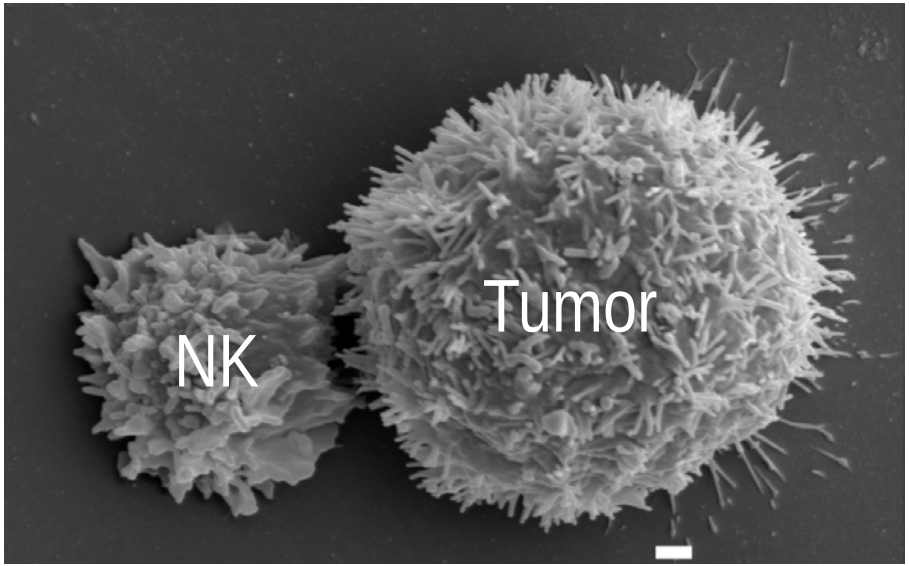


A pivotal role of innate immunity to mount anti-tumor T cell responses



Innate Lymphoid cells

Stimuli		Mediators	Immune function
Tumors, intracellular microbes (Virus, bacteria, parasites) →	NK, ILC1	IFN-γ 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)



Vivier et al., Nature Immunol. 2008
Vivier et al., Science 2011
Vivier et al., Cell 2018

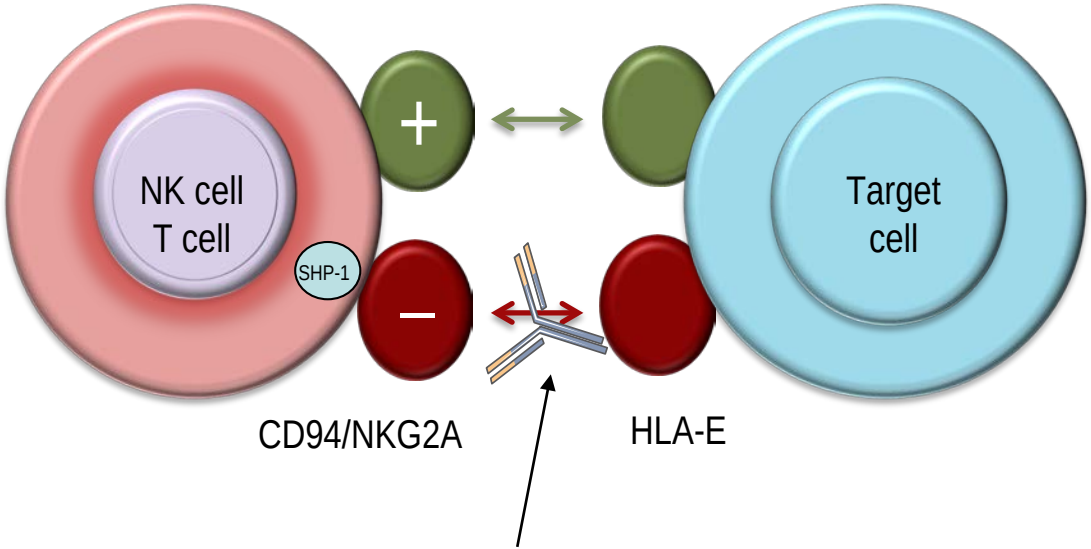
Targeting Innate Immunity in Cancer

- Targeting NK cells
  - Targeting inhibitory NK cell surface receptors
  - Targeting activating NK cell surface receptors

Targeting Innate Immunity in Cancer

- Targeting NK cells
  - Targeting inhibitory NK cell surface receptors: NKG2A
  - Targeting activating NK cell surface receptors

Blocking anti-NKG2A mAb: a novel immune checkpoint inhibitor in cancer immunotherapy



MONALIZUMAB (IPH2201) IS A FIRST-IN-CLASS ANTI-NKG2A HUMANIZED IGG4 BLOCKING MAB

innate pharma

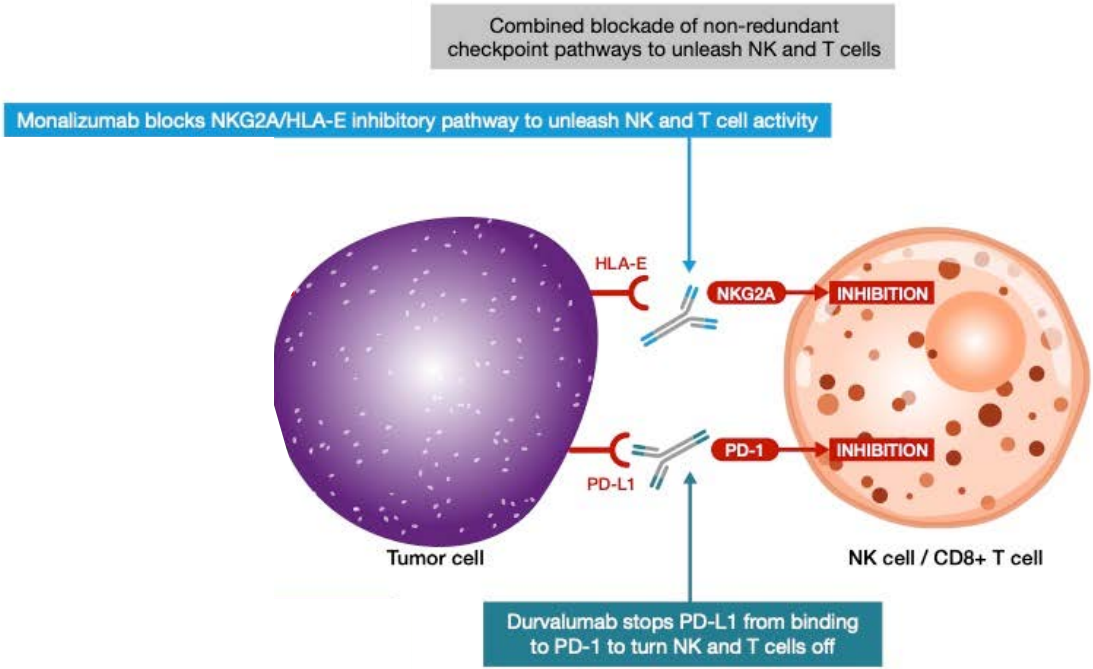
NKG2A targeting with monalizumab

Monalizumab is a novel checkpoint inhibitor promoting anti-tumor immunity by enhancing the activity of both T and NK cells, which may complement the activity of the first generation of active immunotherapies against cancer

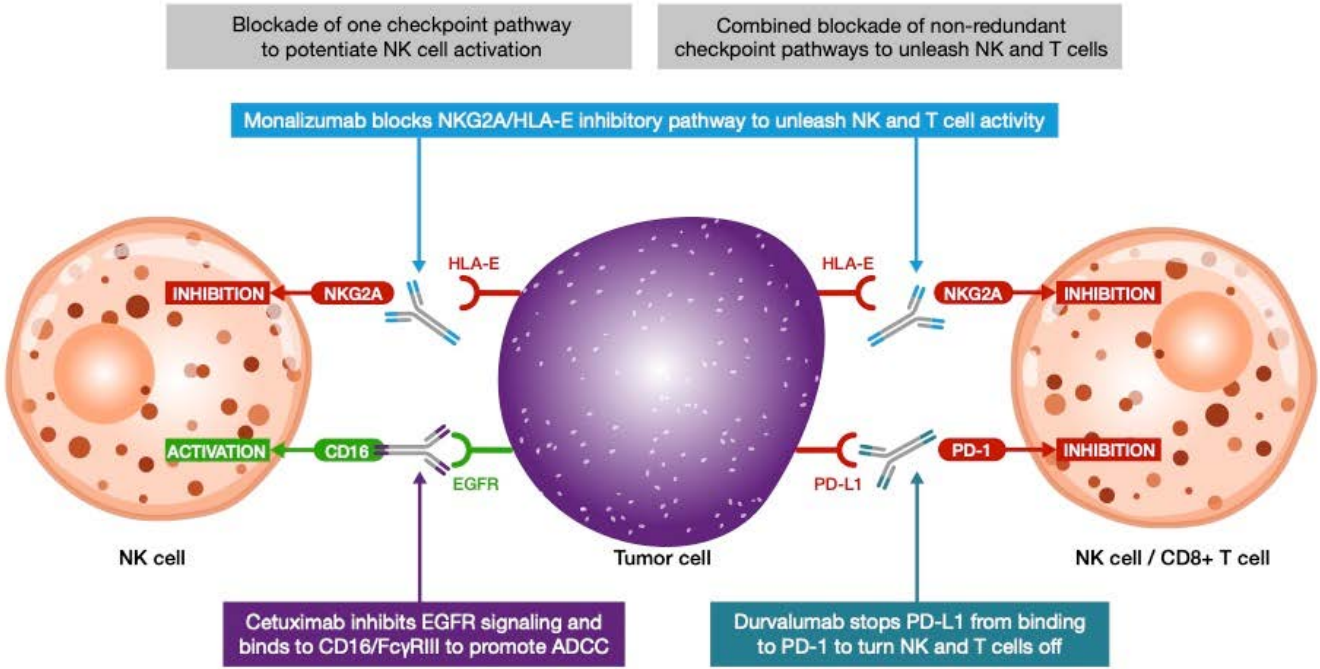


André et al., Cell 2018

Monalizumab: a large spectrum immune checkpoint inhibitor



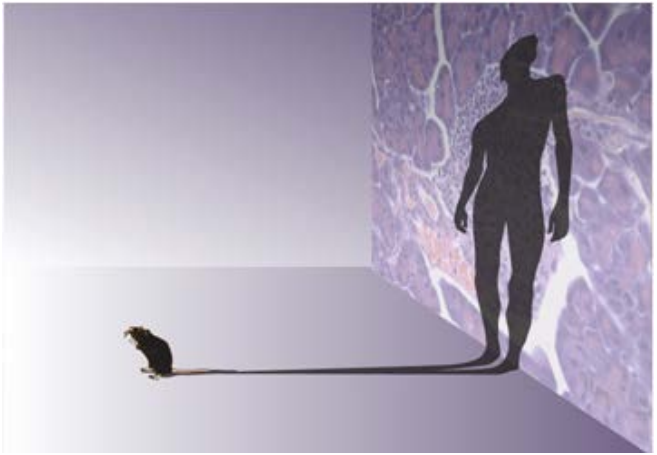
Monalizumab: a large spectrum immune checkpoint inhibitor



Targeting Innate Immunity in Cancer

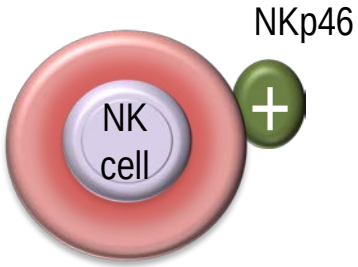
- Targeting NK cells
  - *Targeting inhibitory NK cell surface receptors: NKG2A*
  - Targeting activating NK cell surface receptors

NKp46 is a conserved activating cell surface receptor



Comparing mouse and human data

(65-75 Mya differences between mice and humans)





Alessandro Moretta

Multifunctional antibody technology engaging NK cells in oncology

Innovative multifunctional antibody technology for engaging NK cells to kill tumor cells through activating receptors expressed on NK cells

- Co-engaging CD16 and NKp46 on NK cells
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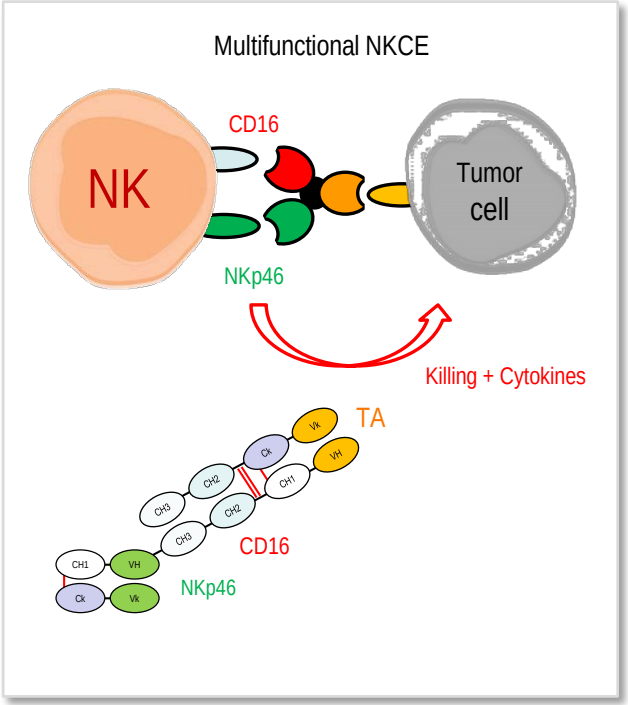
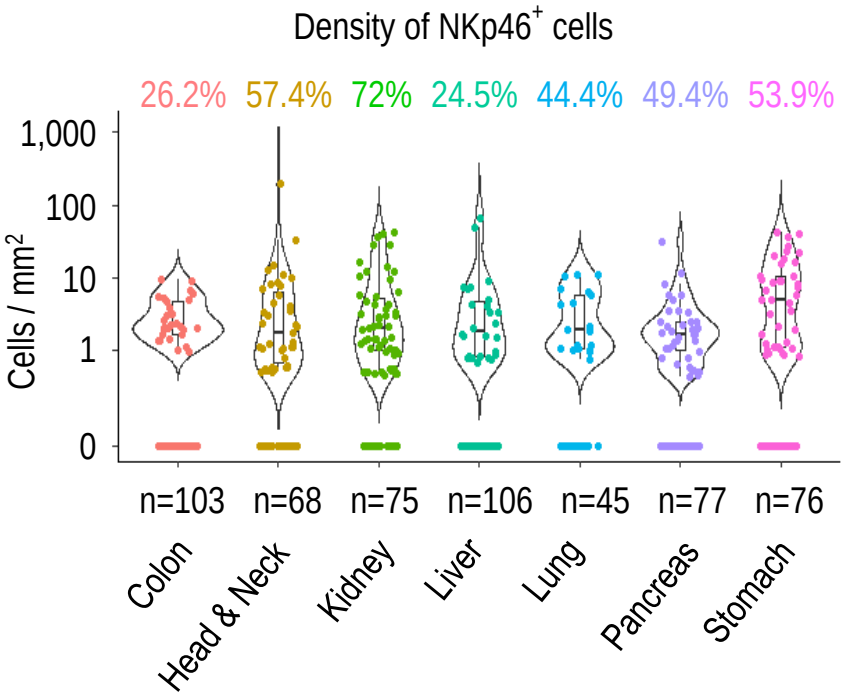
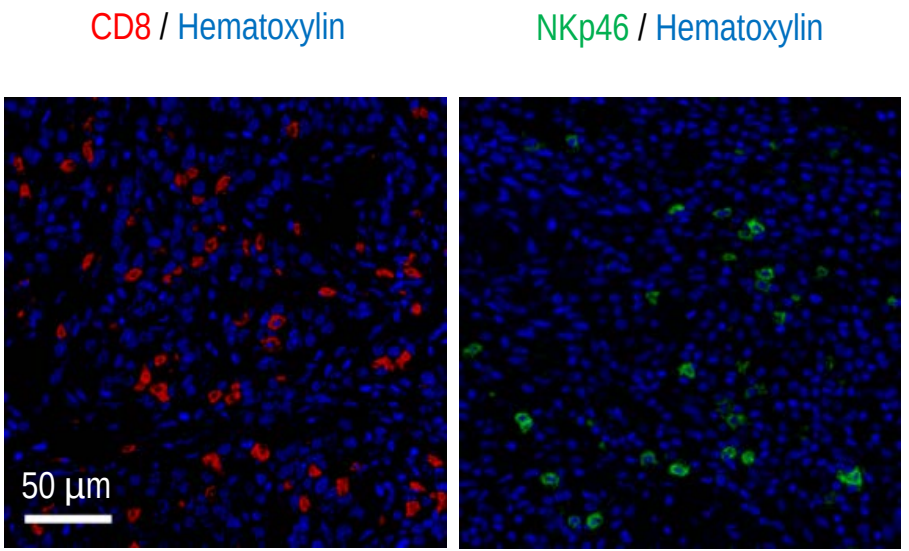


NKp46 is expressed at the tumor bed

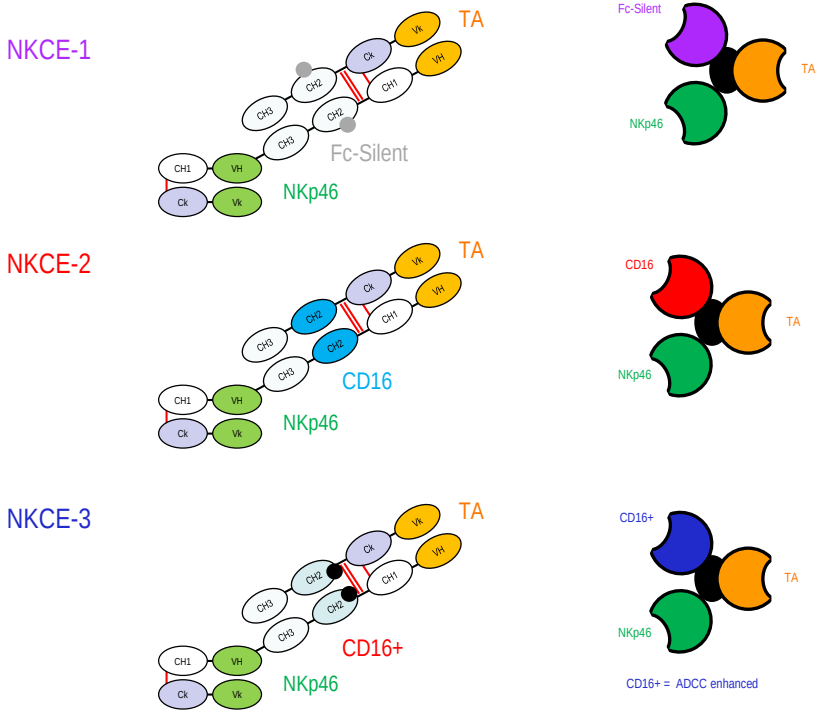




NKp46 NK cell engagers in oncology

- Correct chain pairing driven by affinity
- 100% antibody sequences
- Binding to Protein-A and FcRn
- Monovalent binding to NKp46

- FcγR binding options
  - ➢ NKp46 only : NKCE-1
  - ➢ NKp46 + CD16 : NKCE-2
  - ➢ NKp46 + ADCC enh. : NKCE-3



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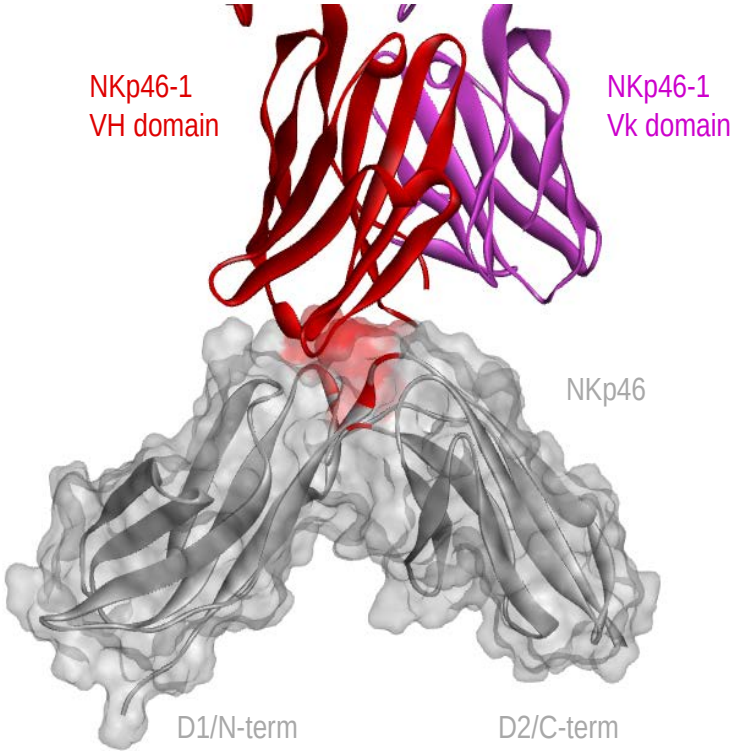
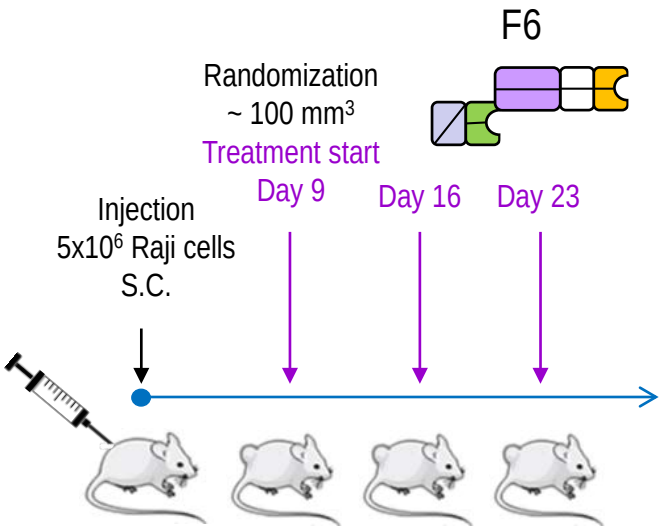
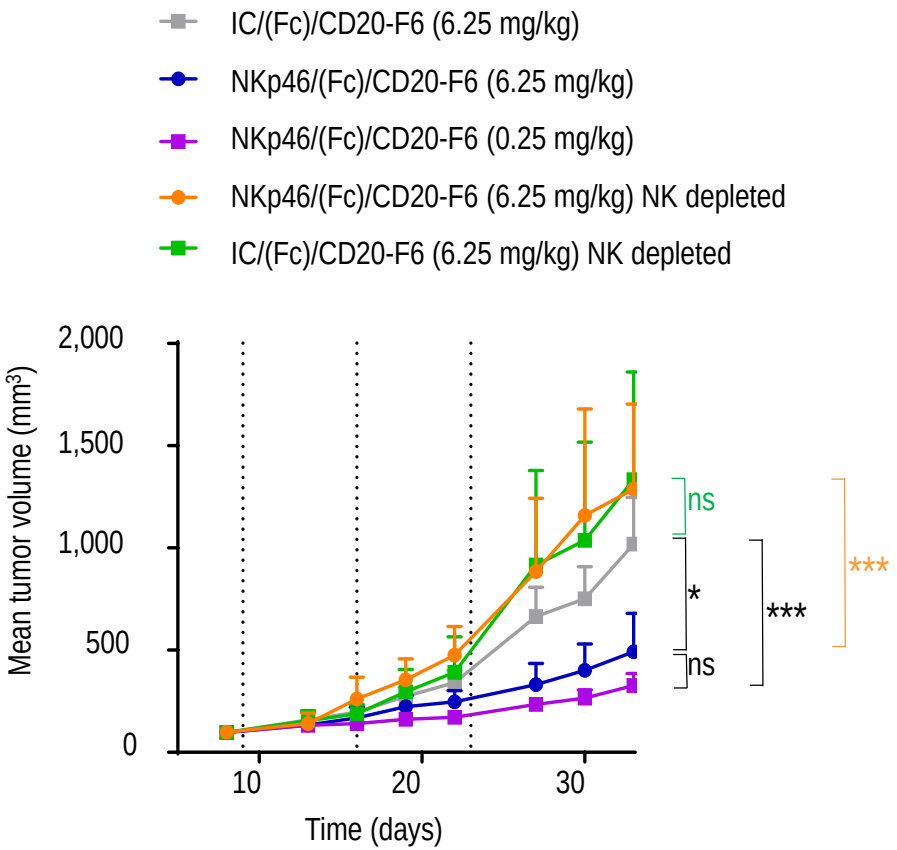


Bispecific NKCEs promote tumor control *in vivo*





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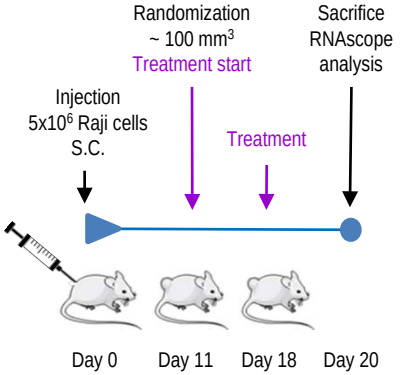
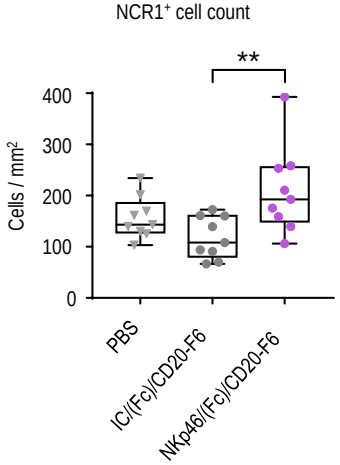
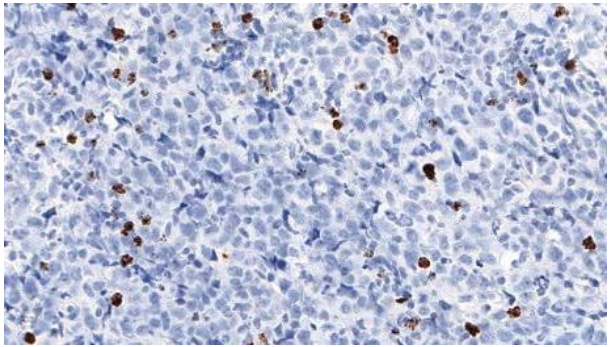
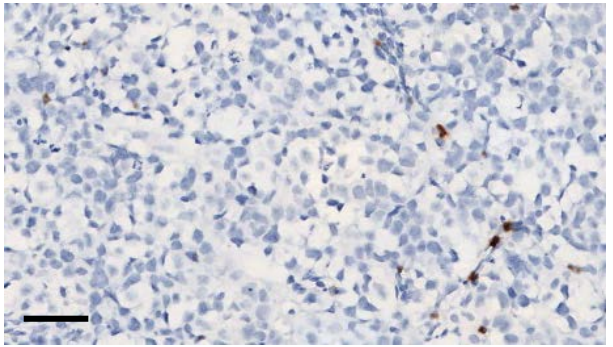




NKp46/(Fc)/CD20-F6

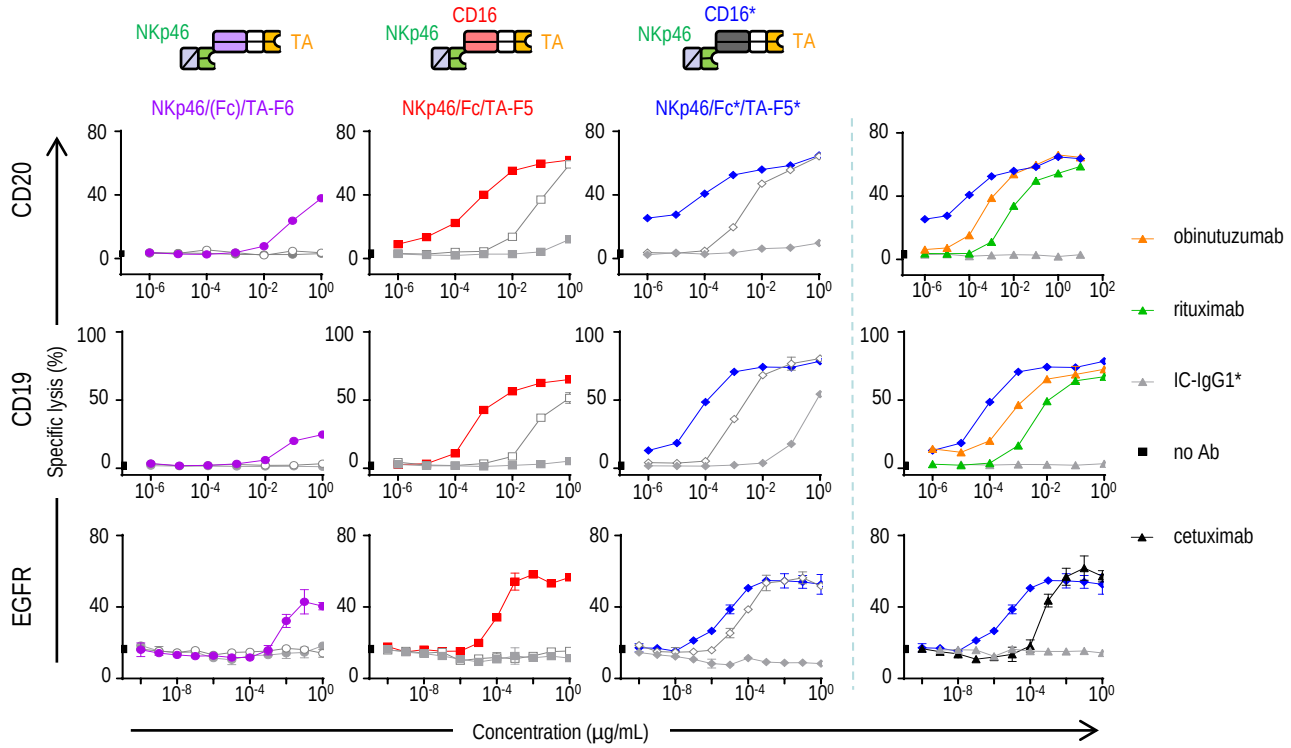


IC/(Fc)/CD20-F6

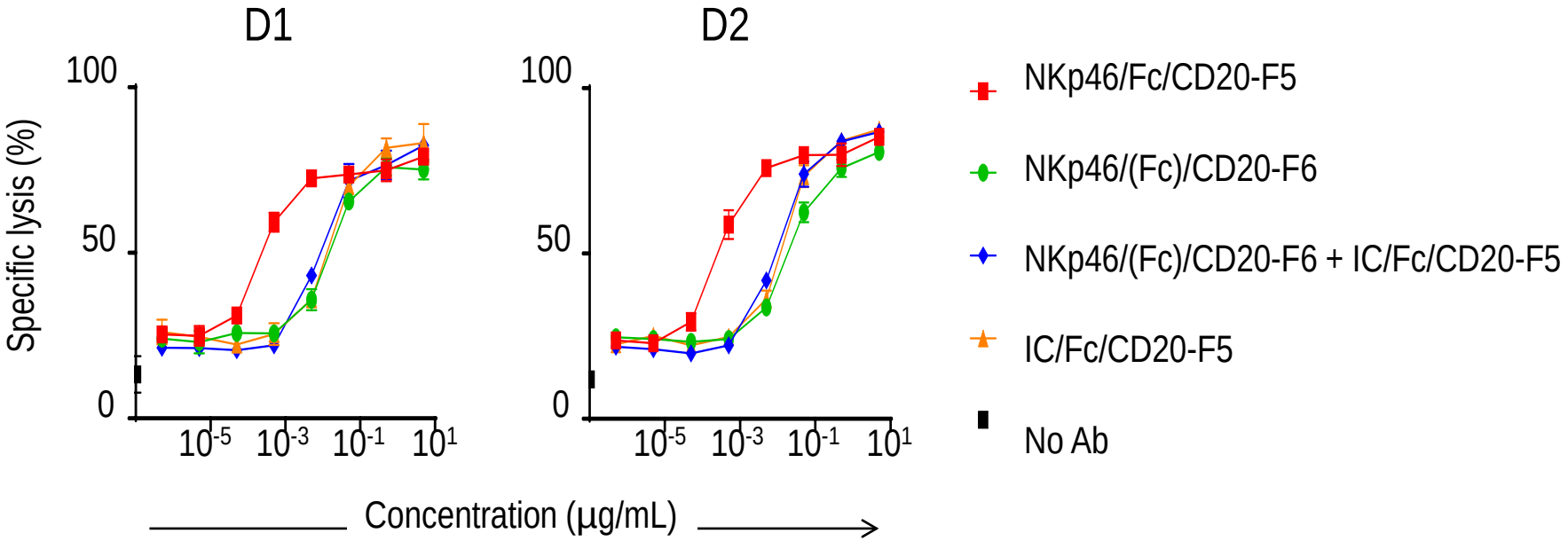


Bispecific NKCE treatment promotes the NK cell infiltration and/or proliferation within tumors

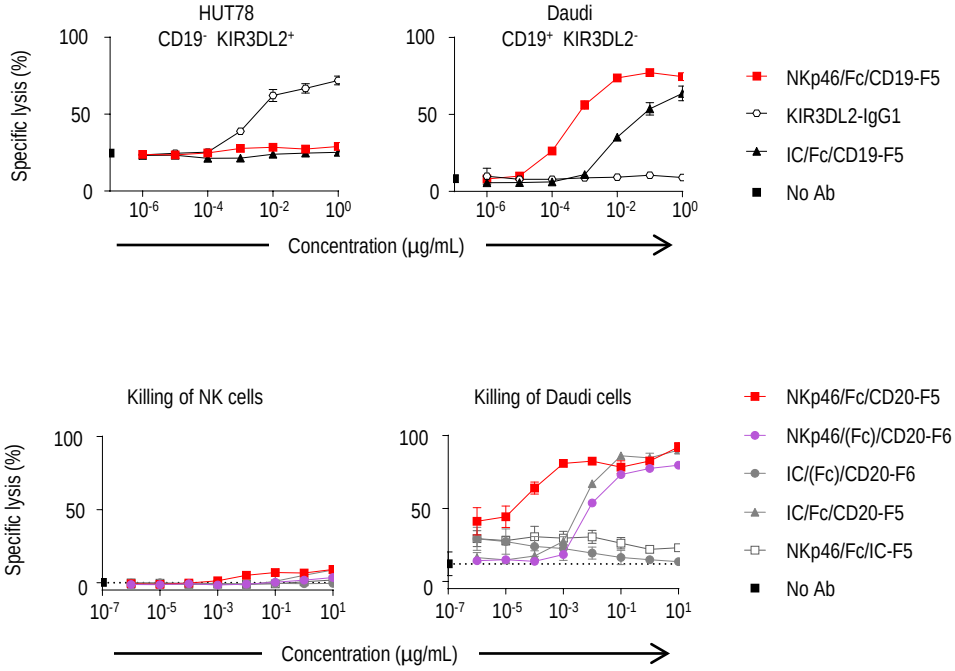
Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs



Trifunctional NKCEs are more potent than the combination of molecules activating NKp46 and CD16 separately



Trifunctional NKCEs do not mediate off-target killing nor NK-vs-NK toxicity



NKp46 NK cell engagers

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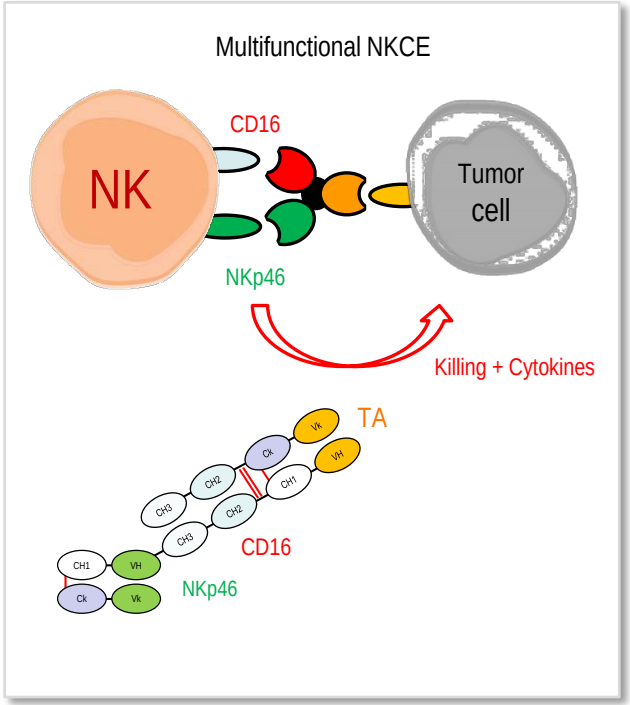




Gauthier et al., in press

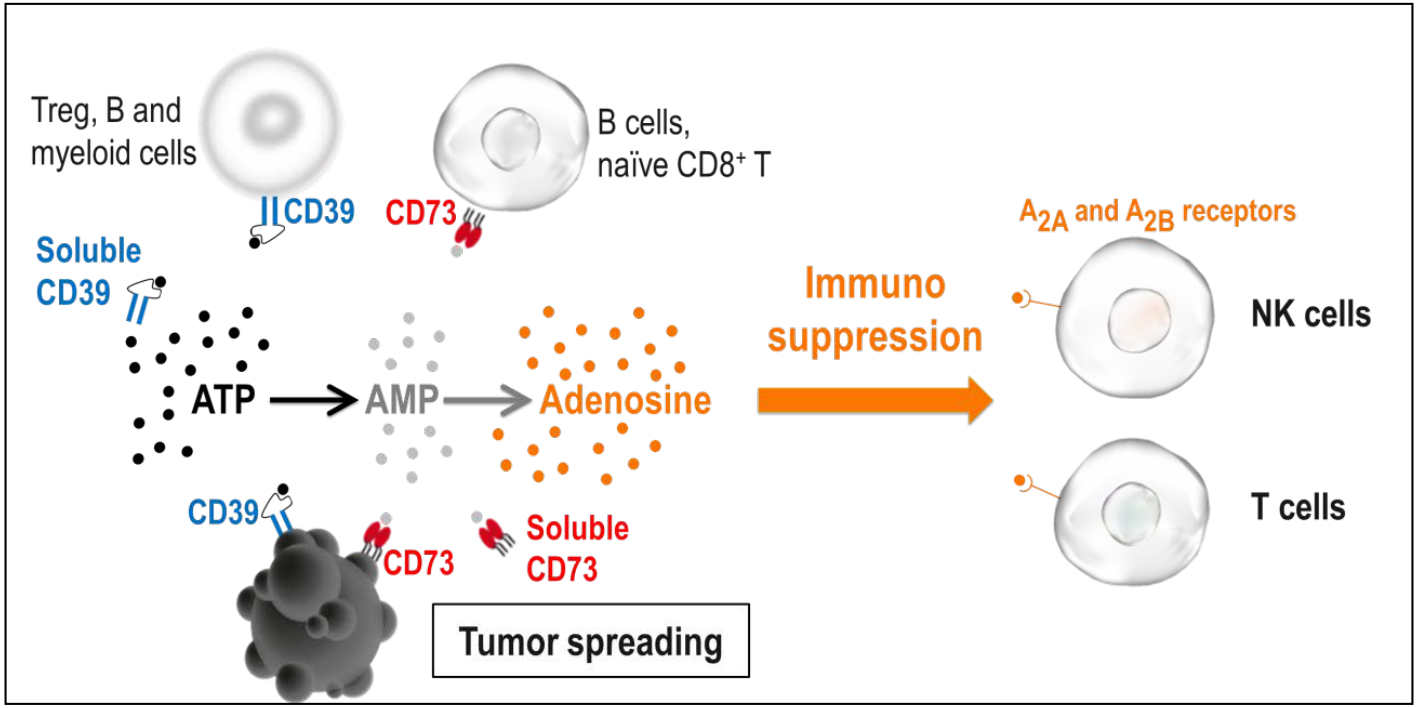
Next generation IO: 3 strategic key pillars to harness the potential of immunity

1	2
Immune Checkpoints MONALIZUMAB	Tumor Targeting NK CELL ENGAGERS

Next generation IO: 3 strategic key pillars to harness the potential of immunity

1	2	3
Immune Checkpoints MONALIZUMAB	Tumor Targeting NK CELL ENGAGERS	Tumor microenvironment ADENOSINE

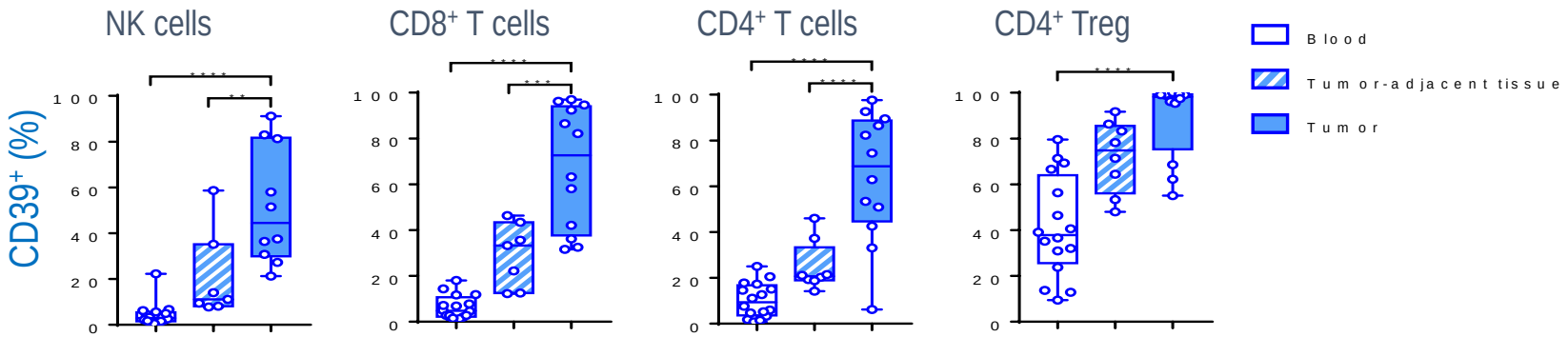
The adenosine pathway is immunosuppressive



ATP: Adenosine Triphosphate
AMP: Adenosine Monophosphate

CD39 is upregulated on TILs

A



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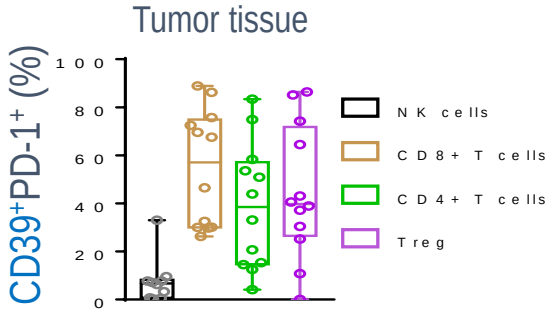
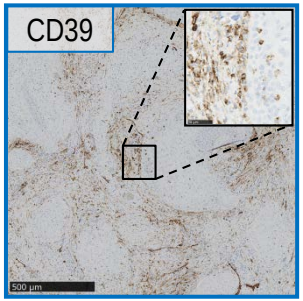
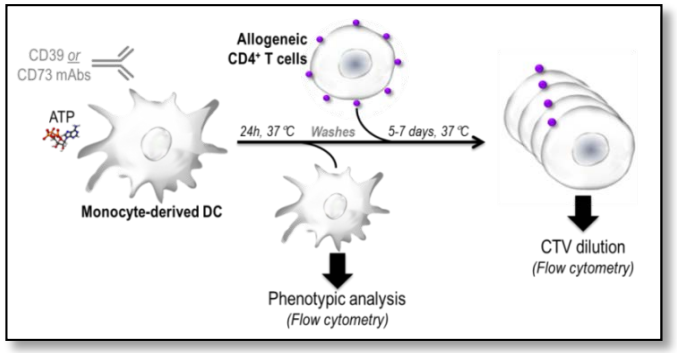


C



Expression on vascular endothelial cells and immune cells

IPH52 (anti-CD39) enhances ATP-mediated DC activation



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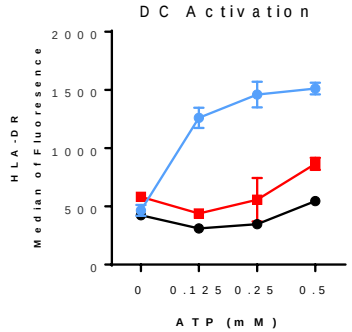

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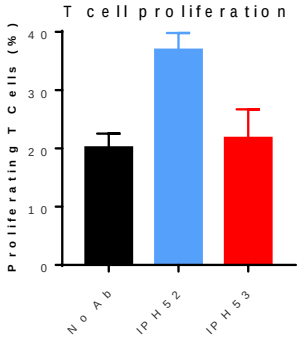
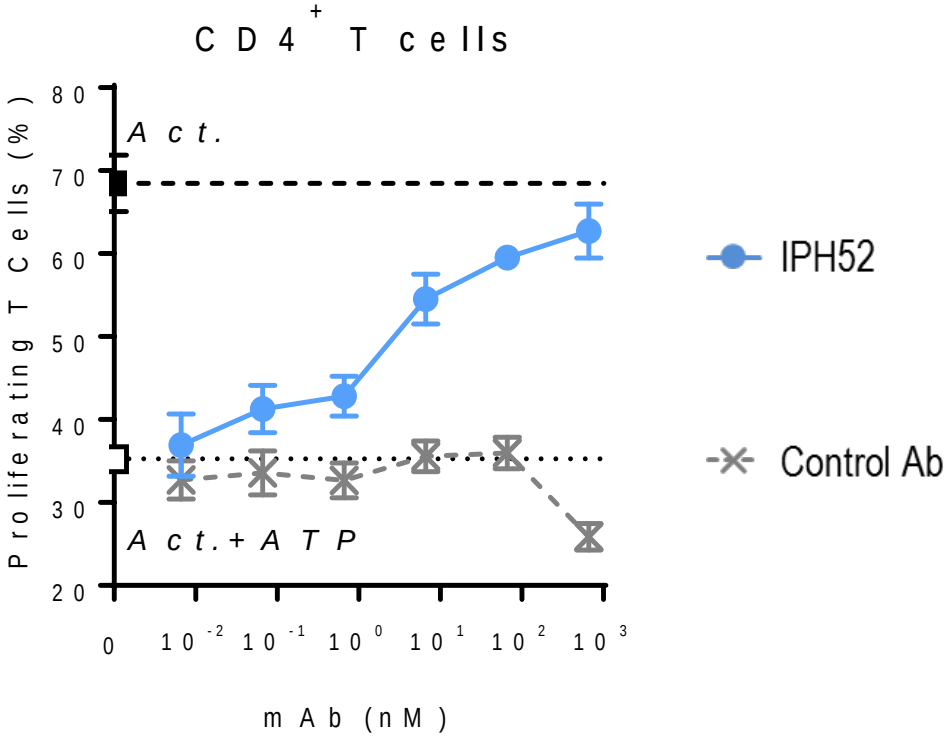
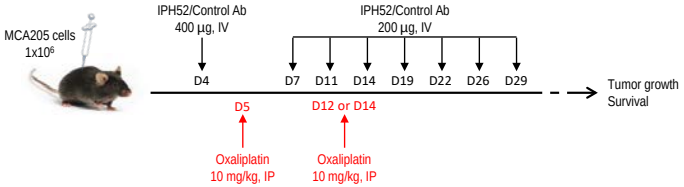


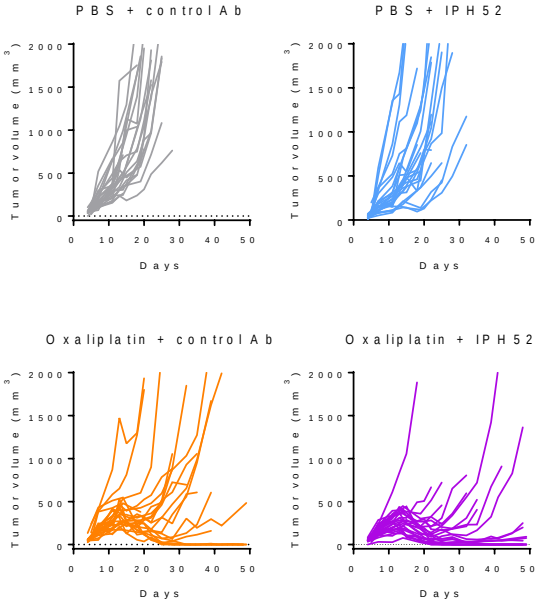


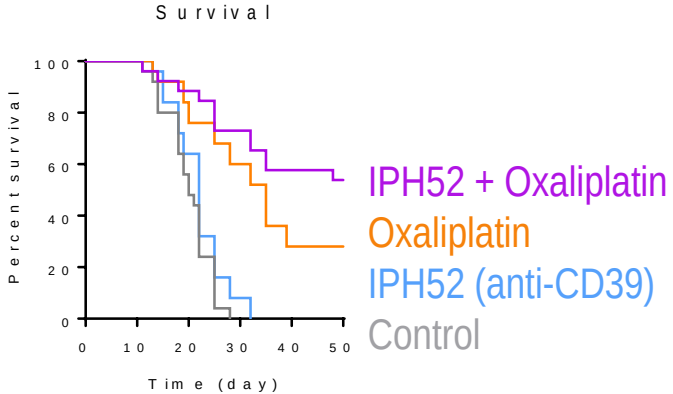
IPH5201 (anti-CD39) restores T cell proliferation



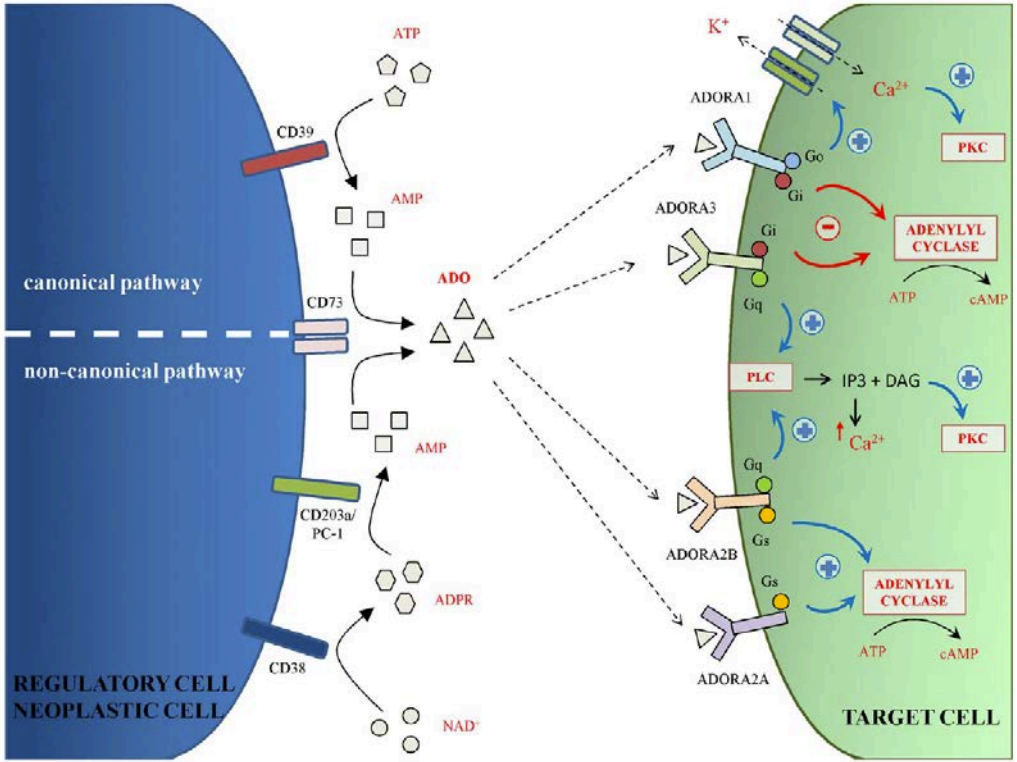
IPH52 (CD39) enhances tumor control in human CD39 KI mice







The adenosine pathway



Ferretti et al., Immunol. Letters 2019

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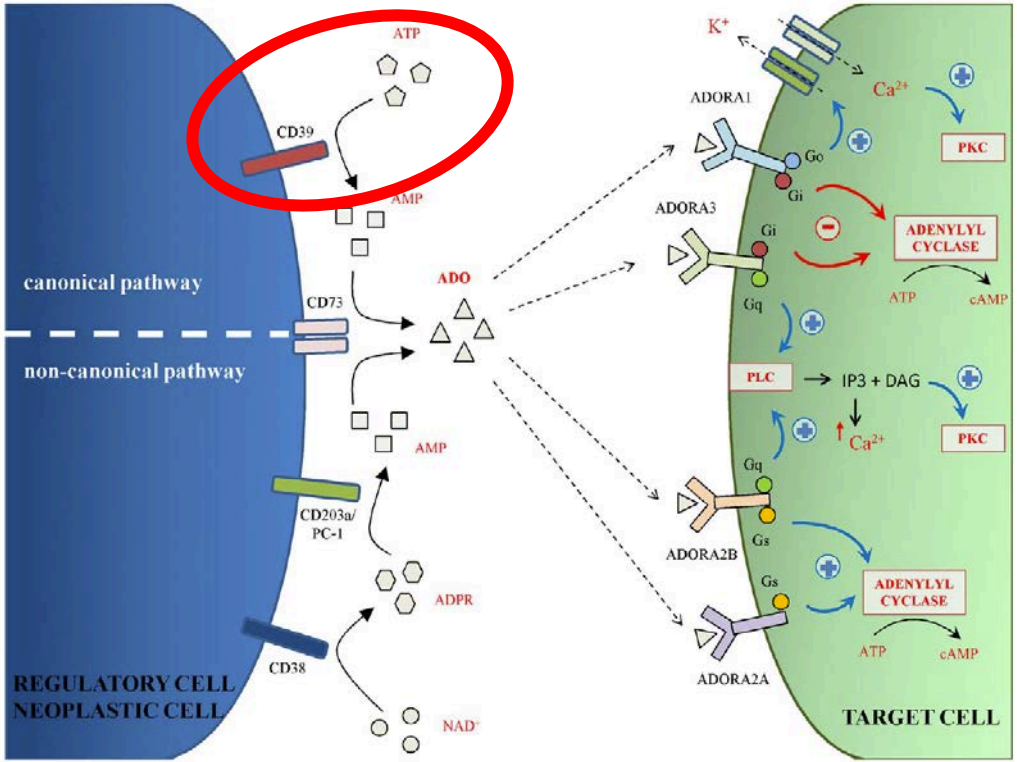

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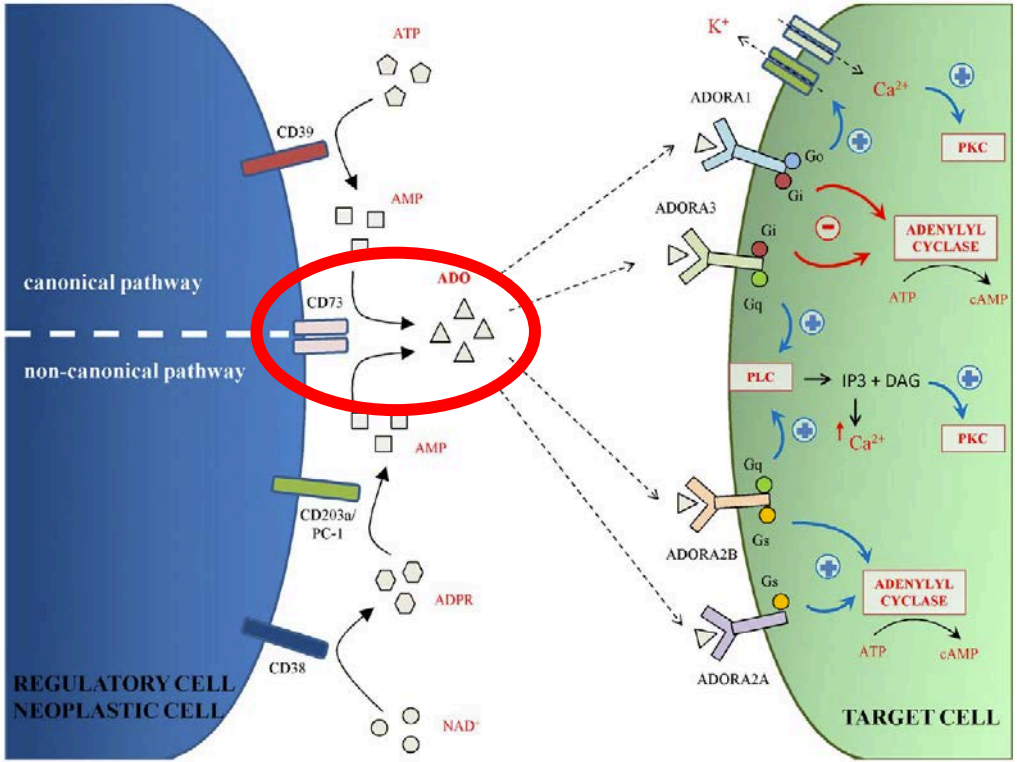
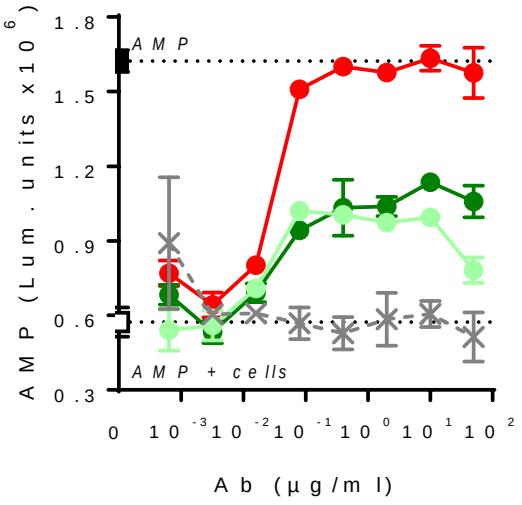
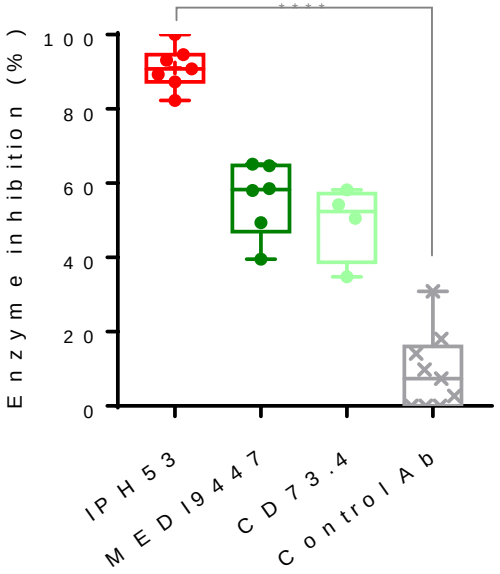


Ferretti et al., Immunol. Letters 2019

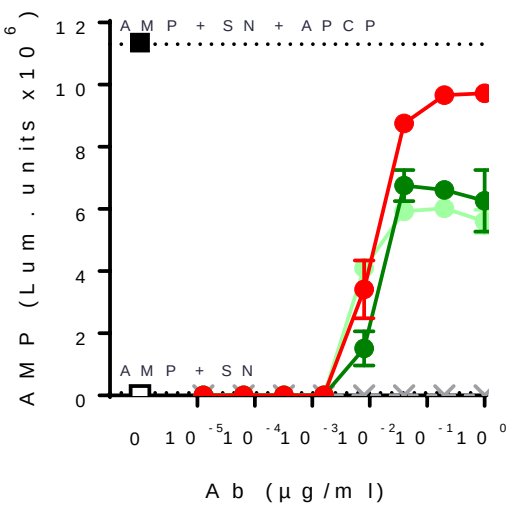
High efficacy of IPH53, a blocking anti-CD73 mAb

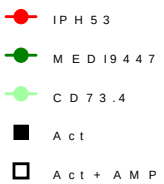
Cell-associated CD73





Soluble CD73





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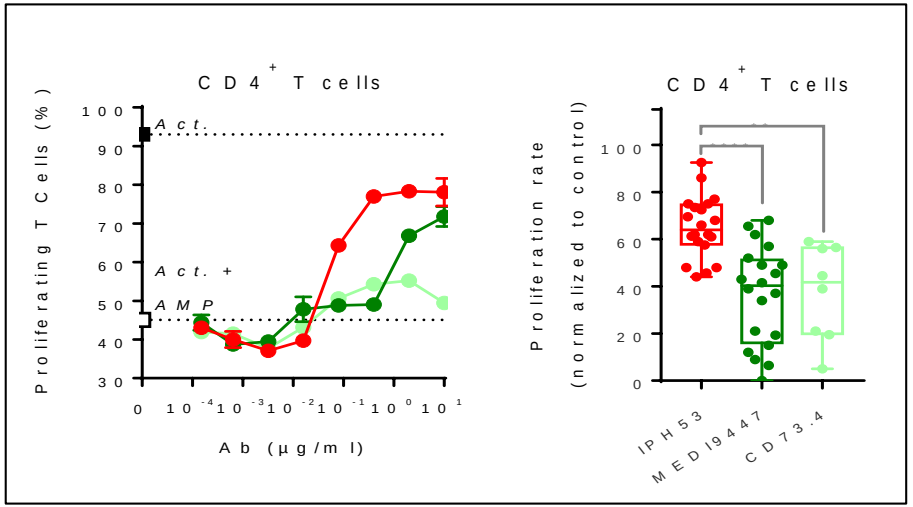
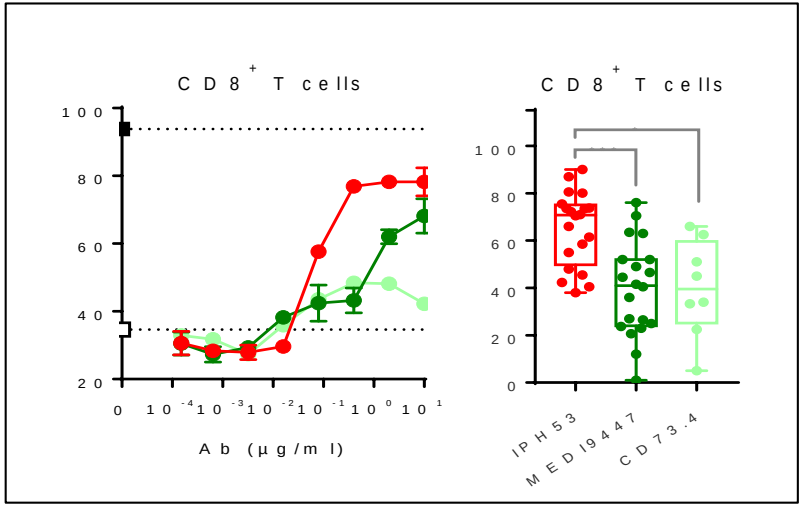
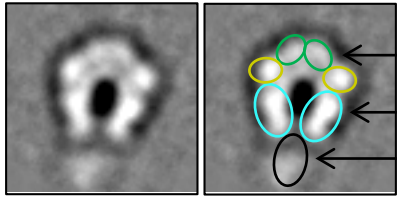




IPH53
MEDI9447
CD73.4
Act
Act + AMP

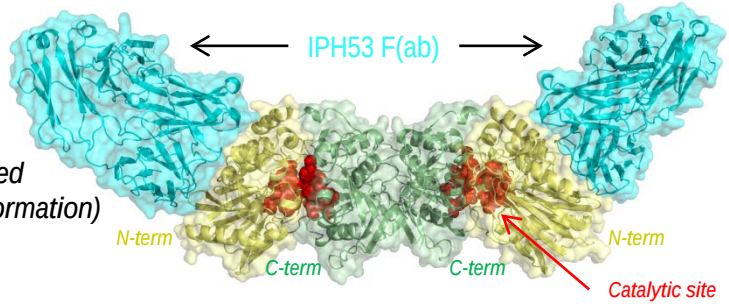
IPH53 blocks enzyme activity by constraining CD73 in an intermediate conformation



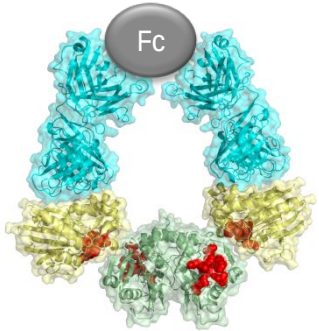
CD73 dimer

IPH53 F(ab)

IPH53 Fc



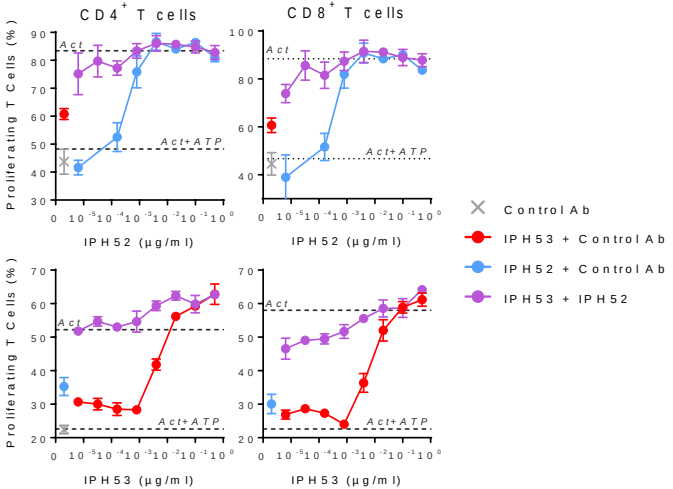
Preferred model

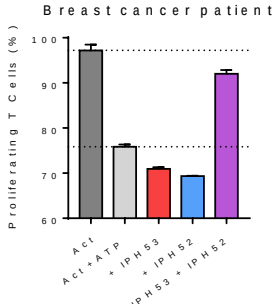


CD73
(intermediate conformation)

- The negative staining of the CD73-IPH53 complex analyzed by electron microscopy revealed that IPH53 mAb interacts with CD73 mainly in a 1:1 stoichiometry *(upper panel)*
- As shown on the CD73/IPH53 crystal *(middle panel)*, IPH53 F(ab) orientation on the N-terminal domain of CD73 is compatible with an intra-dimer binding mode as it is located right on the apex of the molecule, in contrast to Medi9447 and BMS mAbs whose epitopes are eccentric and that are described to interact with CD73 in an inter-dimer mode
- Our data support a model for the mode of action of IPH53, as which the intact mAb constraints CD73 in an intermediate state in which AMP could not be hydrolyzed *(lower panel)*

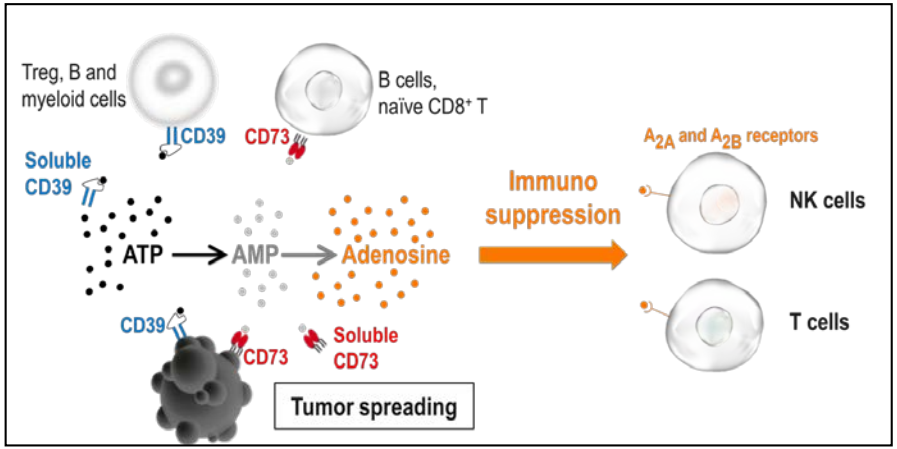
The combination of IPH52 and IPH53 releases ATP-mediated suppression of T cells from healthy donors and cancer patients





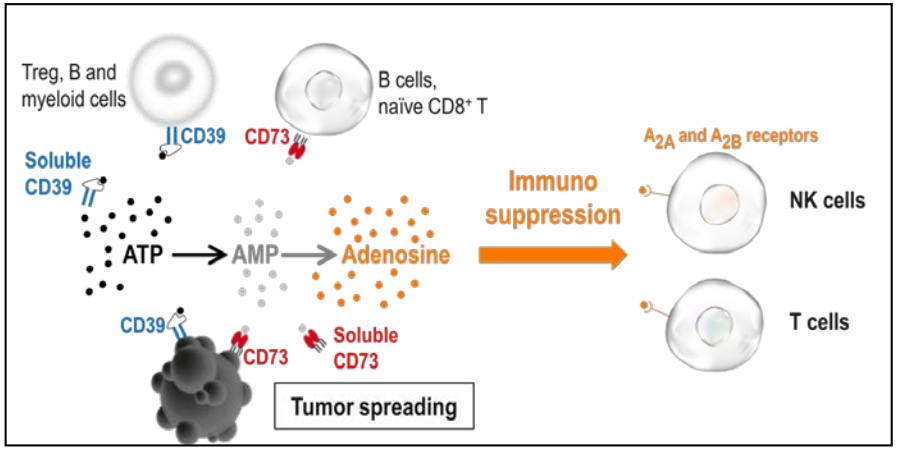
- When used in combination at inefficient suboptimal doses, the anti-CD39/CD73 mAbs acted in synergy to abrogate the suppressive effect of ATP and to promote the proliferation of T cells from healthy donors (purple lines to be compared to blue and red lines and dots) *(upper panel)*
- Similar results were obtained for T cells from breast cancer patient PBMC *(lower panel)*
- These data show that the concomitant blockade of CD39 and CD73 enzyme abolishes Ado-mediated T-cell inhibition

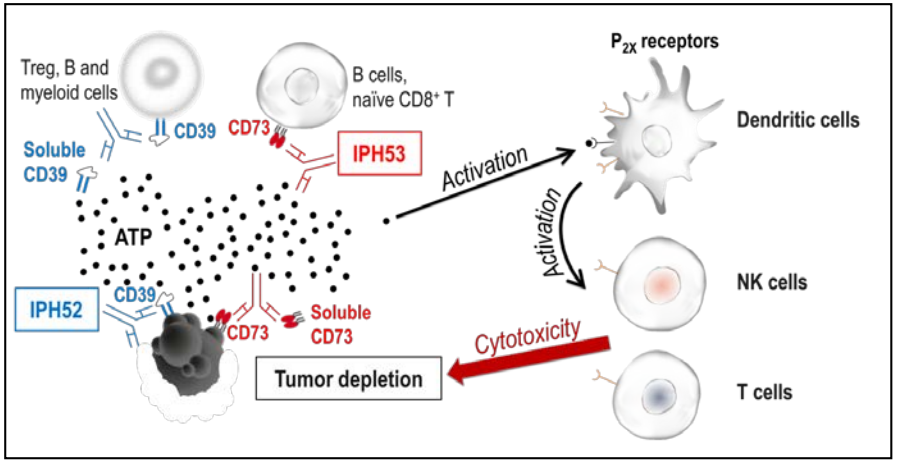
The adenosine pathway is immunosuppressive



ATP: Adenosine Triphosphate
AMP: Adenosine Monophosphate

The adenosine pathway can be controlled





ATP: Adenosine Triphosphate
AMP: Adenosine Monophosphate



Perrot et al., in press

Next generation IO: 3 strategic key pillars to harness the potential of immunity

1	2	3
Immune Checkpoints MONALIZUMAB	Tumor Targeting NK CELL ENGAGERS	Tumor microenvironment ADENOSINE

innate pharma

Anaïs BALSAMO
Carole BERRUYER
Adeline CRINIER
Bertrand ESCALIERE
Marion ETIENNOT
Marion FABRE
Justine GALLUSO
Sophie GUIA
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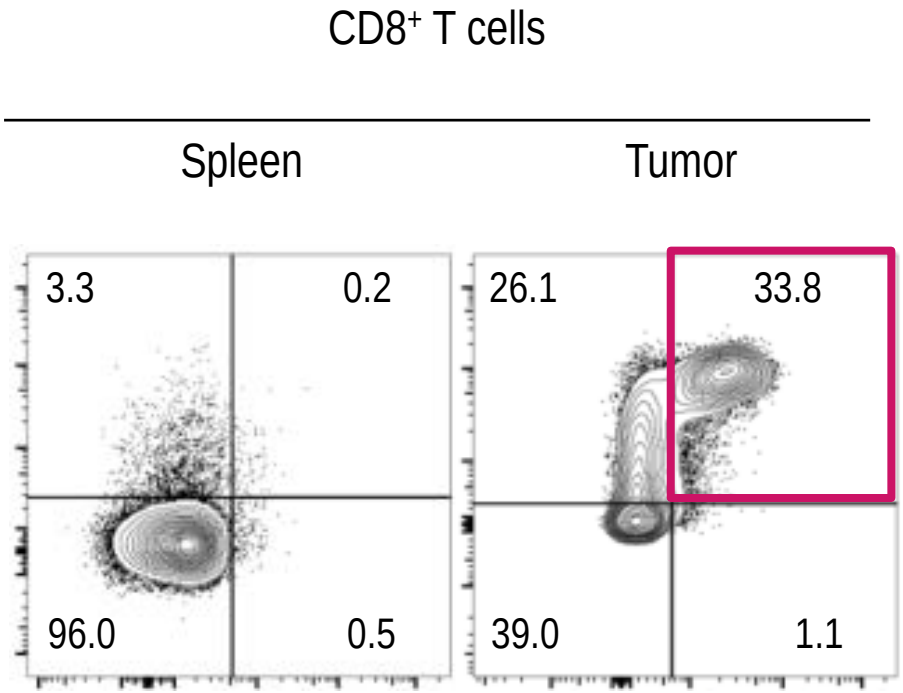
François ROMAGNE et al., MI-mAbs, Marseille
Roger B. COHEN, Abramson Cancer Center, Philadelphia
Jérôme FAYETTE, Centre Léon Bérard, Lyon
Olivier LANTZ , Institut Curie, Paris
Nathalie BONNEFOY, IRCM, Montpellier

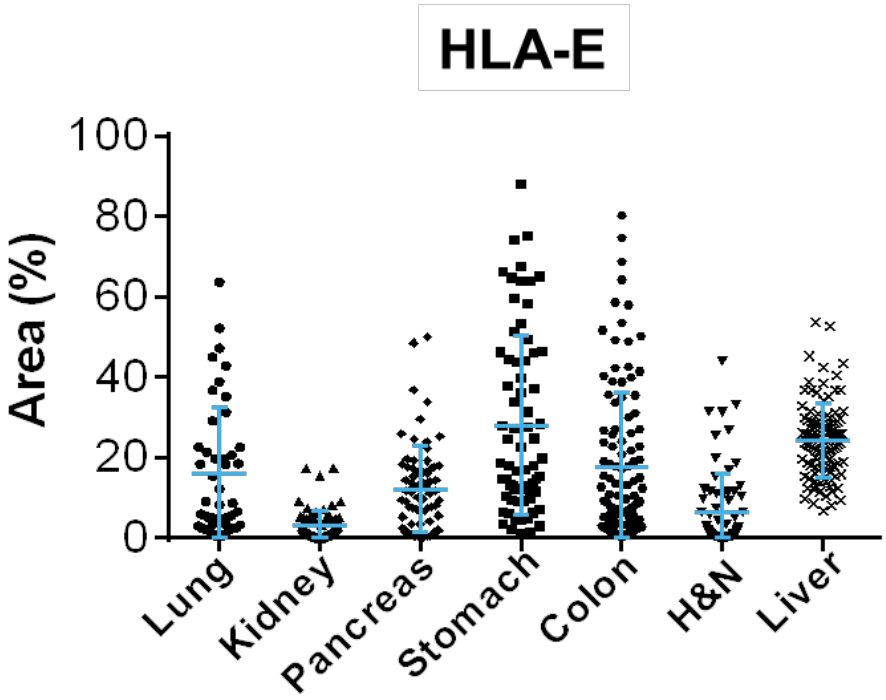
THANKS to PATIENTS
and their FAMILIES

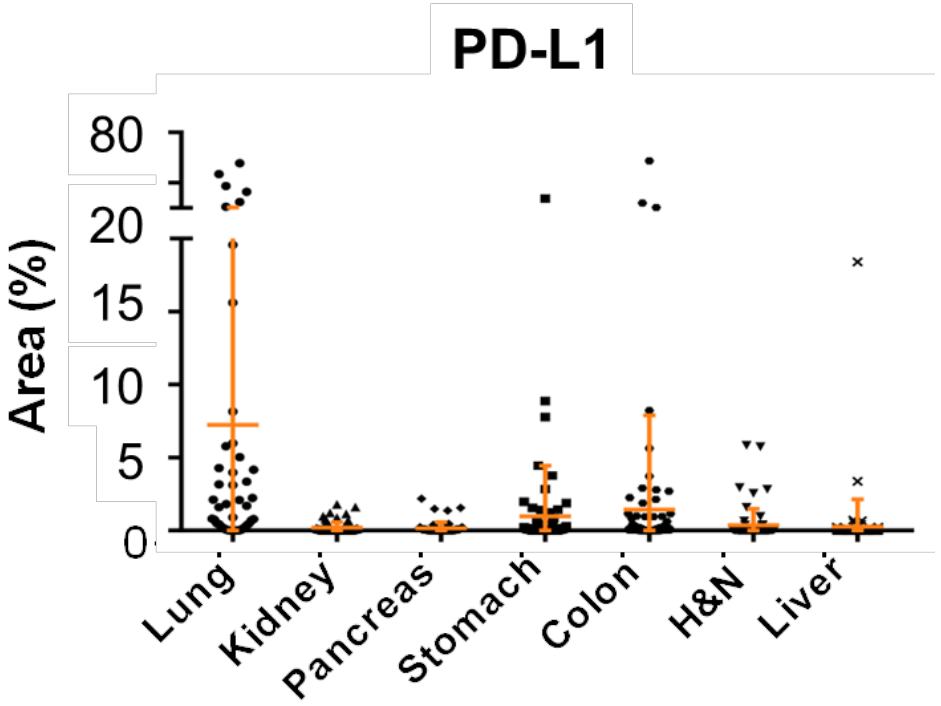
Co-expression of NKG2A and PD-1 in TILs



André et al., Cell 2018

HLA-E expression in human solid tumors





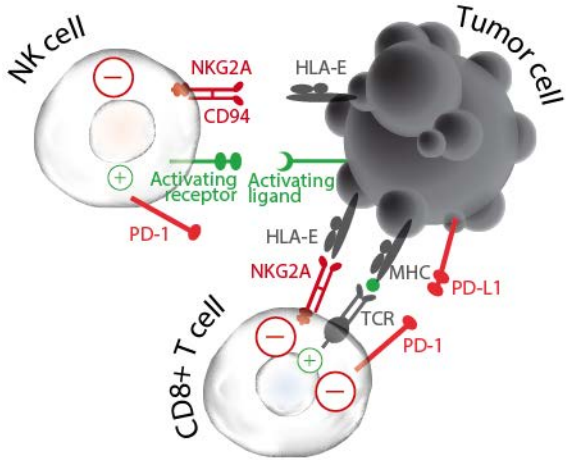
André et al., Cell 2018

Combination of monalizumab and durvalumab

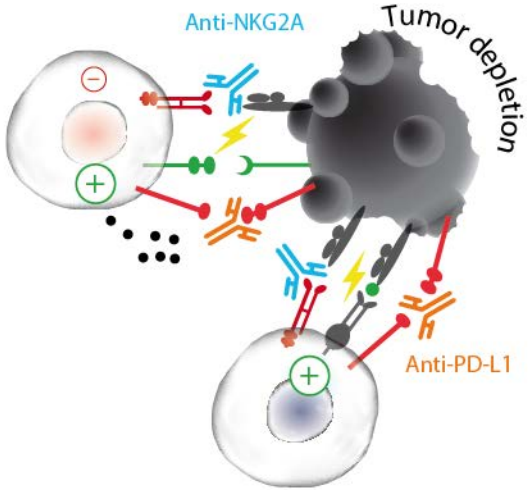
- Tumor infiltrating NK and $CD8^+$ T cells expressing NKG2A and/or PD-1 are present in several cancer types
- HLA-E is expressed by tumor cells in the large majority of solid tumors
- Blocking both NKG2A/HLA-E and PD-1/PD-L1 pathways can enhance responses of NK and $CD8^+$ T cells

André et al., Cell 2018

Anti-NKG2A as a novel immune checkpoint inhibitor in cancer



NK cell and T cell inhibition by NKG2A & PD-1

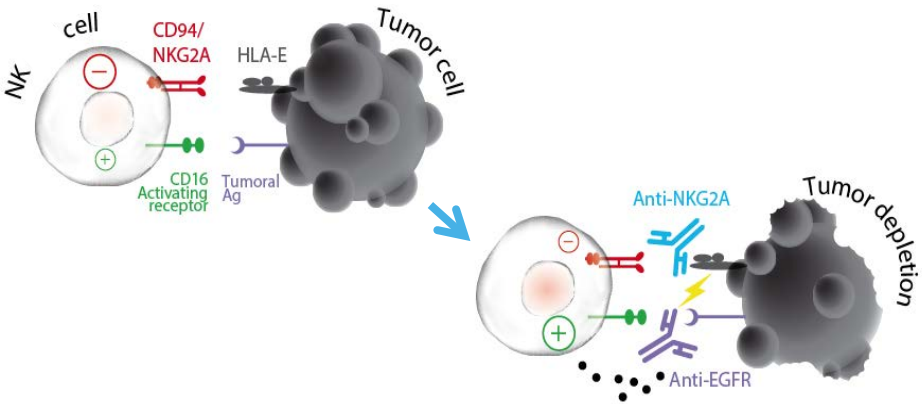




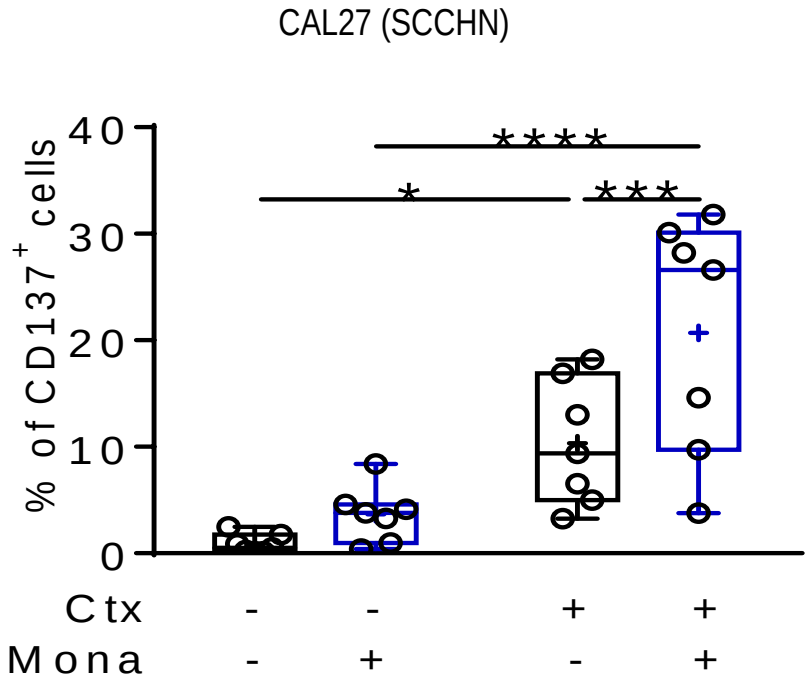
Activation by NKG2A & PD-L1 blockade

In vitro data support the rationale for ongoing clinical trial investigating the combination monalizumab/durvalumab

Monalizumab potentiates cetuximab-induced ADCC



ADCC enhancement by
NKG2A blockade



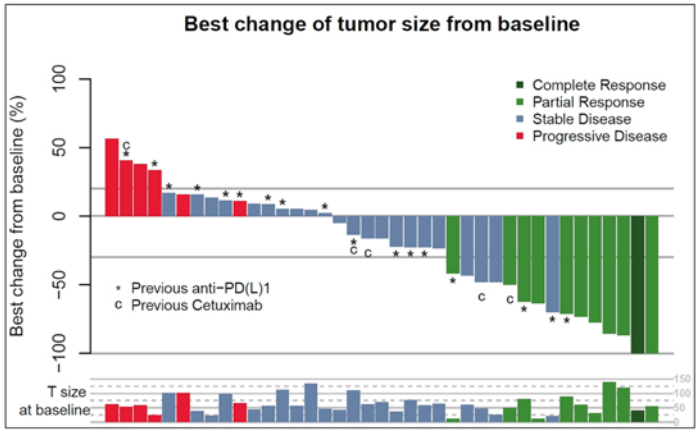
Cetuximab (Ctx): anti-EGFR
Monalizumab (Mona): anti-NKG2A

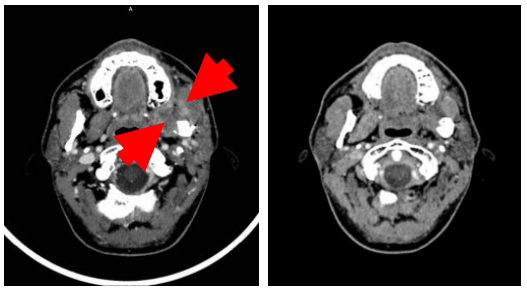
Phase II clinical trial in recurrent or metastatic SCCHN

KEY RESULTS	n (%) CI
Complete Response (CR)	1 (2.5%)
Partial response (PR)*	10 (25%)
Stable disease	22 (55%)
Overall Response Rate (ORR)	27.5% [16.1-42.8]
Median PFS	5.0 months [3.7-6.9]
Median OS	10.3 months [7.3.-NR]

Safety data:

- Good safety profile of the combination
- No potentiation of the cetuximab related AEs by monalizumab





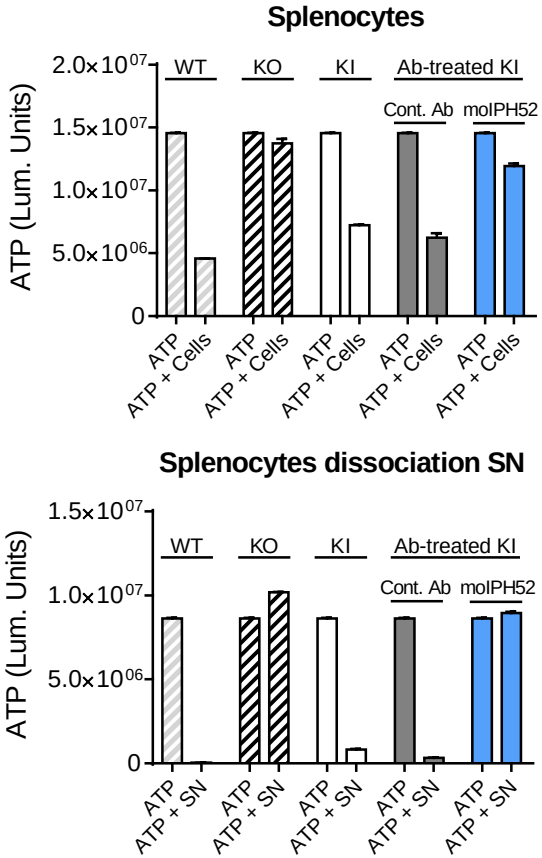
Baseline (July 2017)
Target lesion = 41mm

Under treatment (February 2018)
Target lesion = 0 mm

100% reduction in target lesion, no non-target lesions, no new lesions.

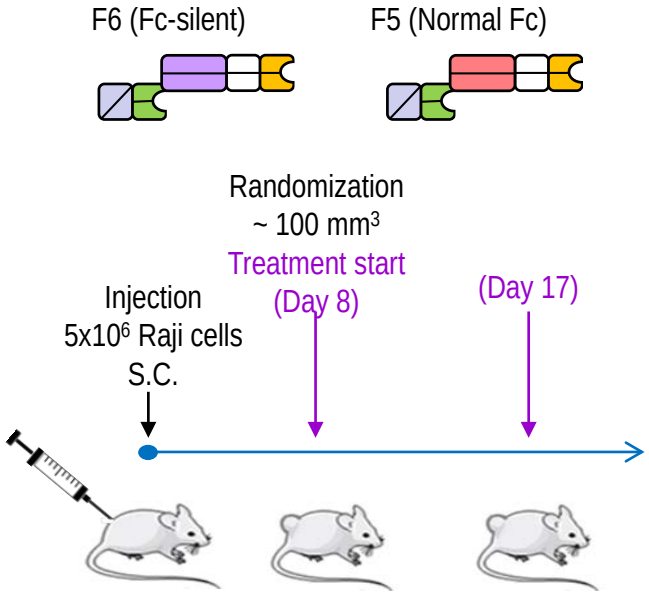
Cutoff data: Aug 31, 2018

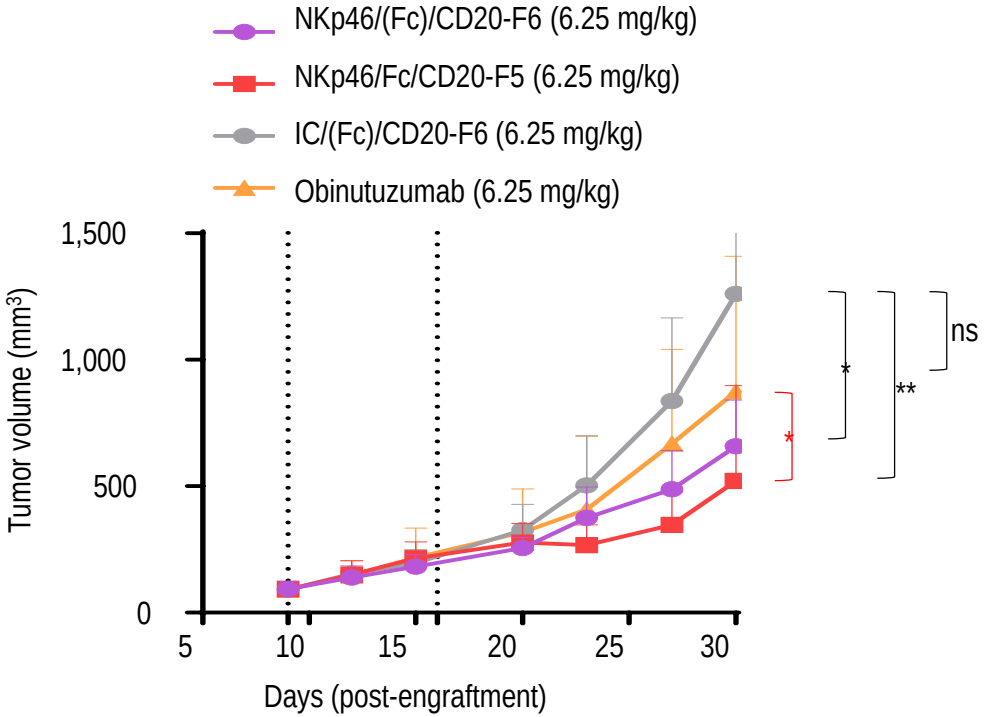
IPH52 blocks CD39 in human CD39 preclinical mouse model



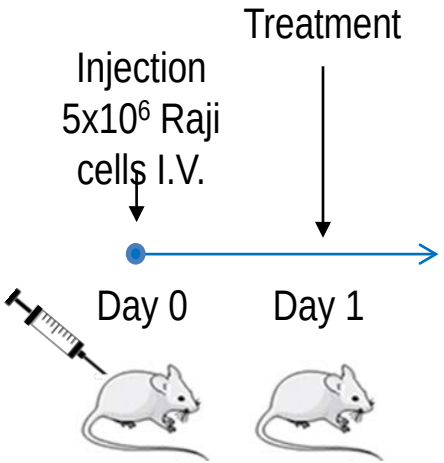
- We generated a human CD39 knock-in mice by replacing the mouse CD39 by human CD39 protein using a knock-out/knock-in (KI) molecular biology strategy
- In contrast to splenocytes from mouse CD39 KO mice, splenocytes from human CD39 KI mice are as efficient as WT mice to hydrolyze exogeneous ATP
- Murinized IPH52 (IPH52 with a mouse Fc silent IgG1 isotype) mouse treatment prevented ex vivo ATP hydrolysis by human CD39 KI cells (blue histograms)
- Similar results were obtained with spleen dissociation supernatants suggesting that moIPH52 was able to block both membrane associated and soluble CD39 enzyme activity

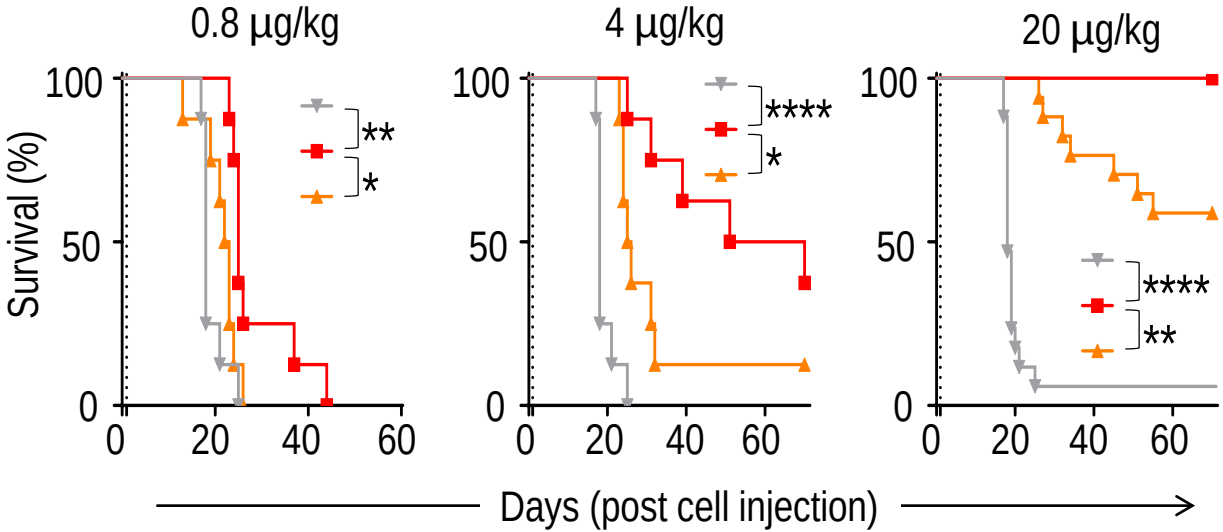
Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs *in vivo*





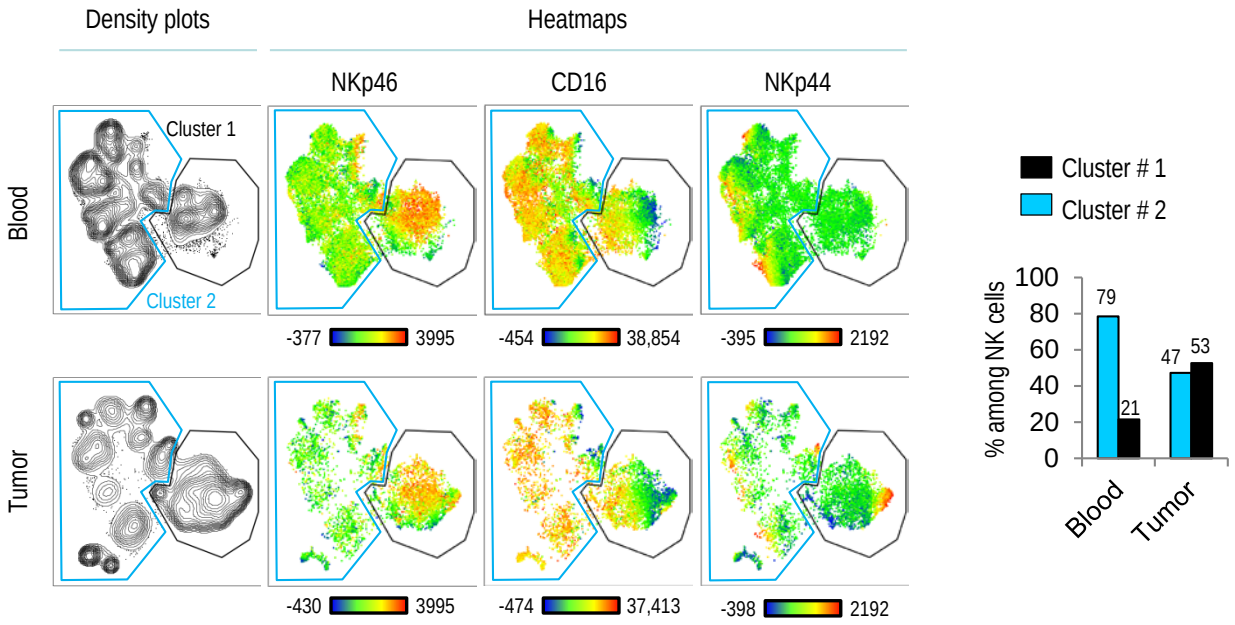
Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs *in vivo*





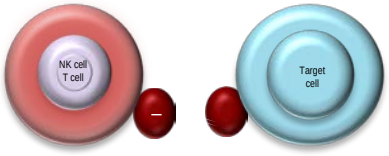
NKp46 expression is not downregulated in cancer

A

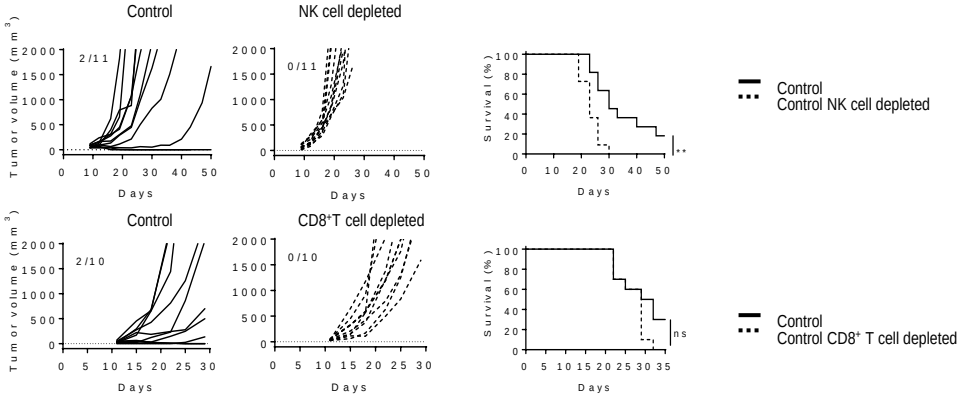


Qa-1^b expression blocks the anti-tumor efficacy of NK and CD8$^+$ T cells

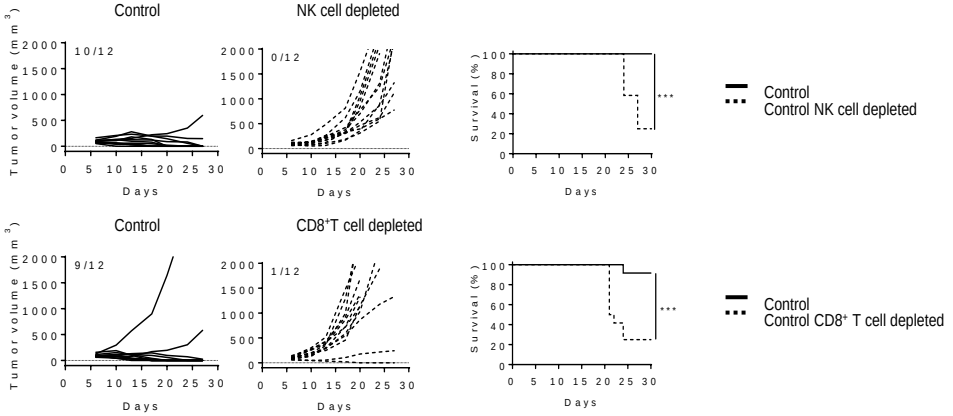
A20



CD94/NKG2A Qa-1^b

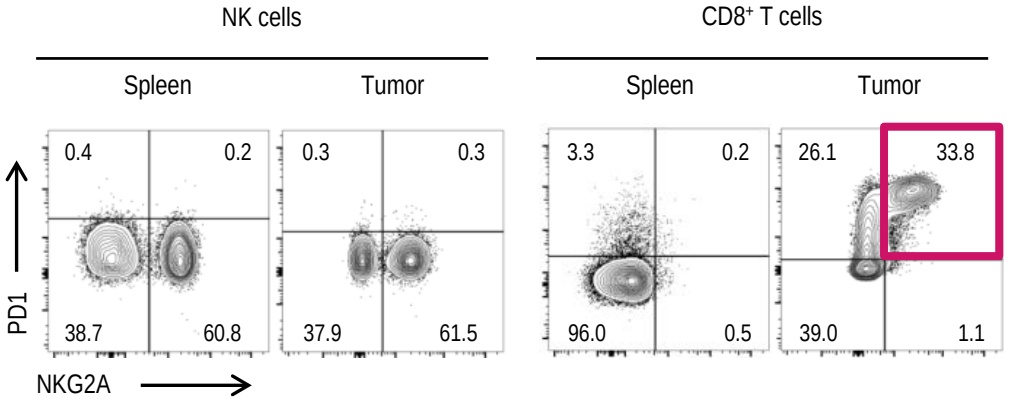


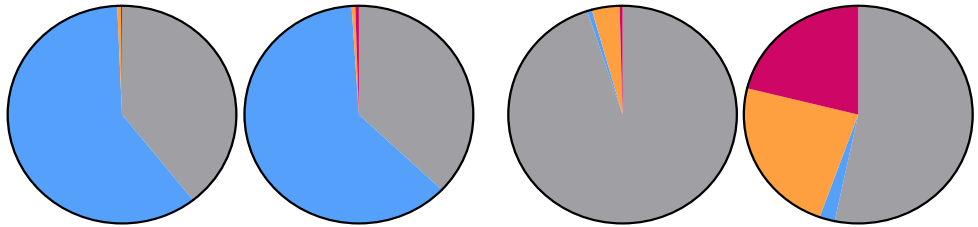
A20 Qa-1^b KO



Co-expression of NKG2A and PD-1

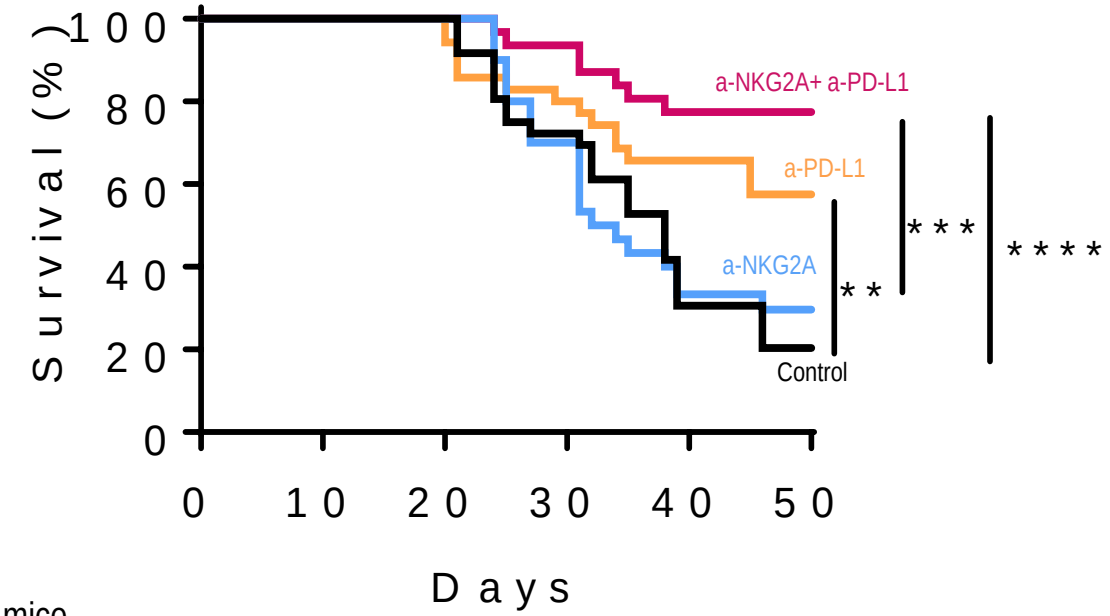
A20 tumor-bearing BALB/c mice





NKG2A+PD1-	60 ± 0.4	61.9 ± 2.9	0.7 ± 0.5	2.2 ± 0.9
NKG2A-PD1+	0.5 ± 0.3	0.5 ± 0.7	3.9 ± 2.1	23.4 ± 12.1
NKG2A+PD1+	0.1 ± 0.1	0.5 ± 0.6	0.4 ± 0.4	21.1 ± 10
NKG2A-PD1-	39.4 ± 1.3	37.1 ± 3.4	95.0 ± 0.8	53.3 ± 20.9

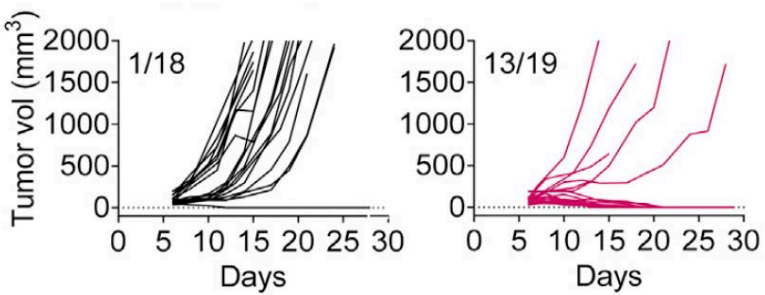
The combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity



A20 tumor-bearing BALB/c mice

Combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity in RMA Rae-1β tumor-bearing mice

RMA Rae-1β tumor-bearing C57BL/6 mice treated with anti-PD-L1 and anti-NKG2A mAbs



Combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity in RMA Rae-1β tumor-bearing mice

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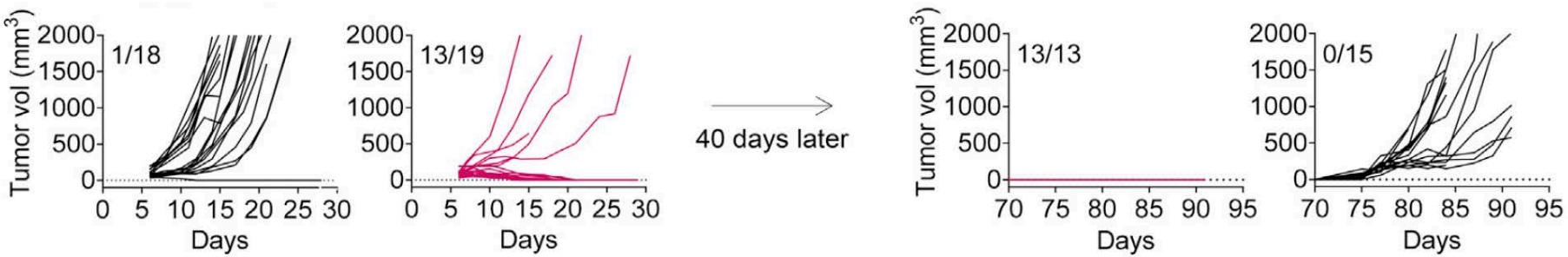
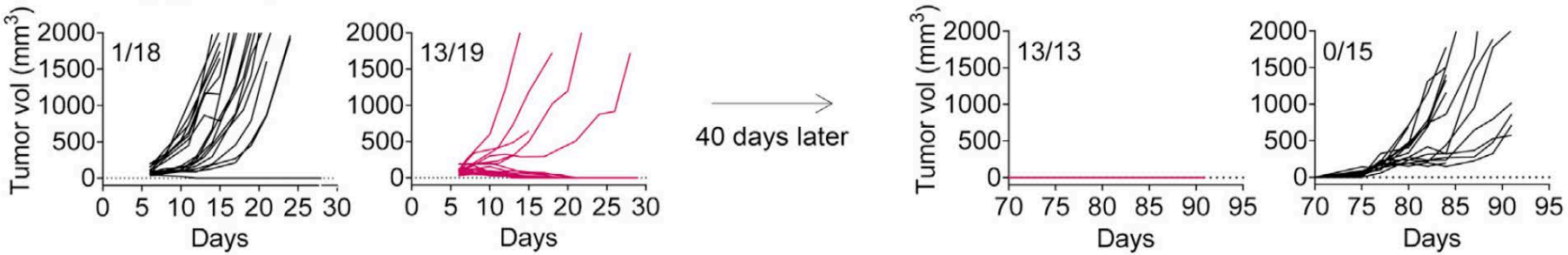
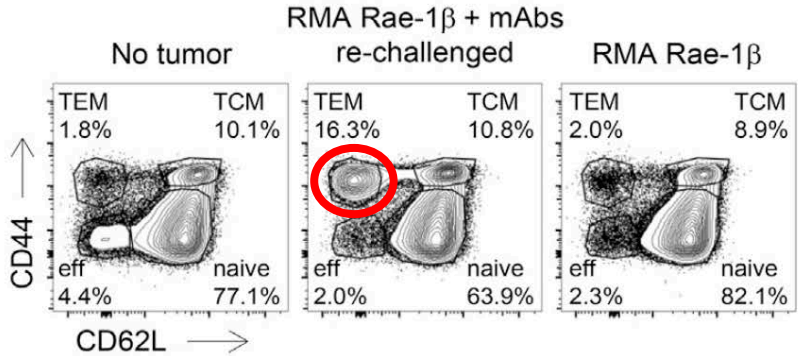
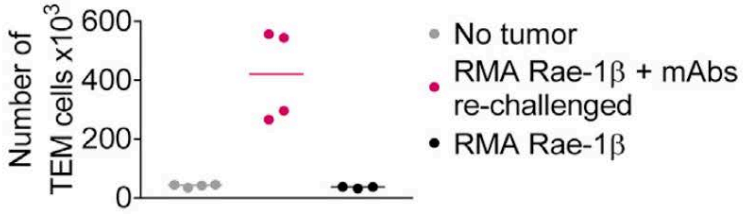


Combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity in RMA Rae-1β tumor-bearing mice

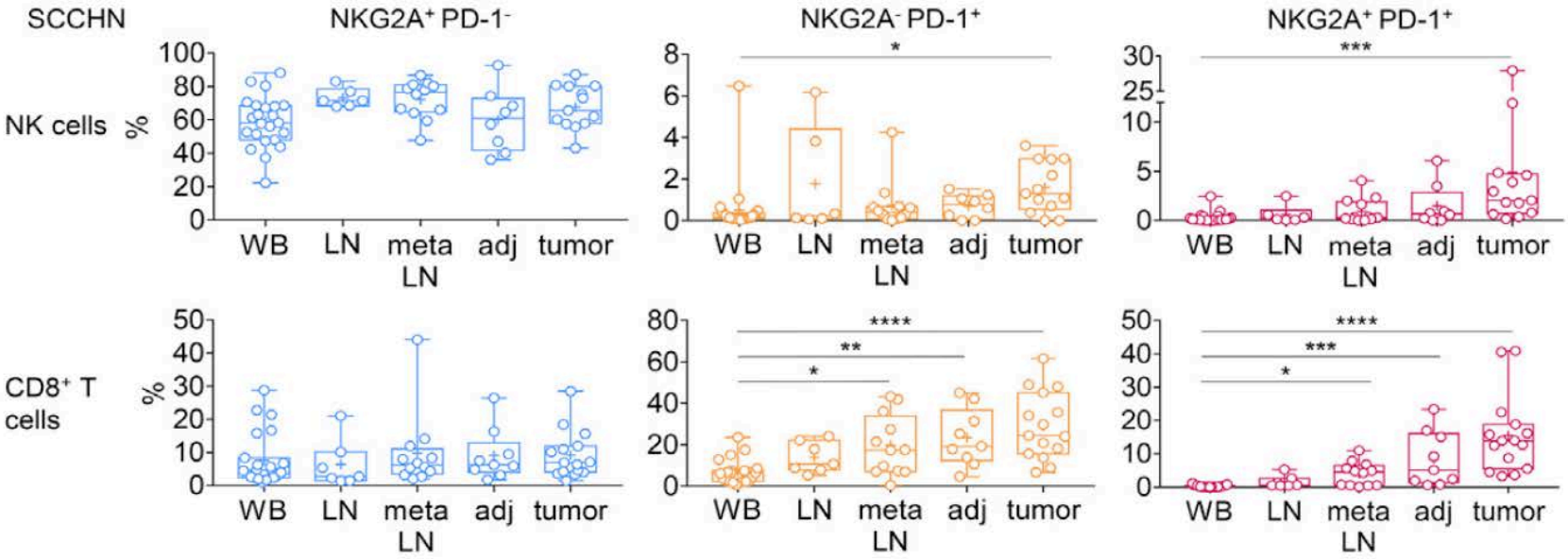
RMA Rae-1β tumor-bearing C57BL/6 mice treated with anti-PD-L1 and anti-NKG2A mAbs



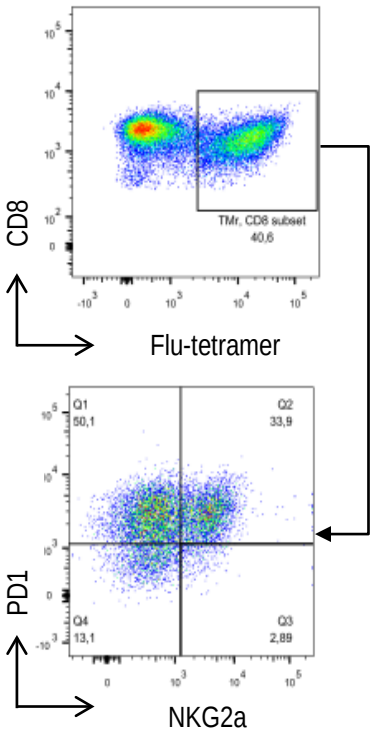




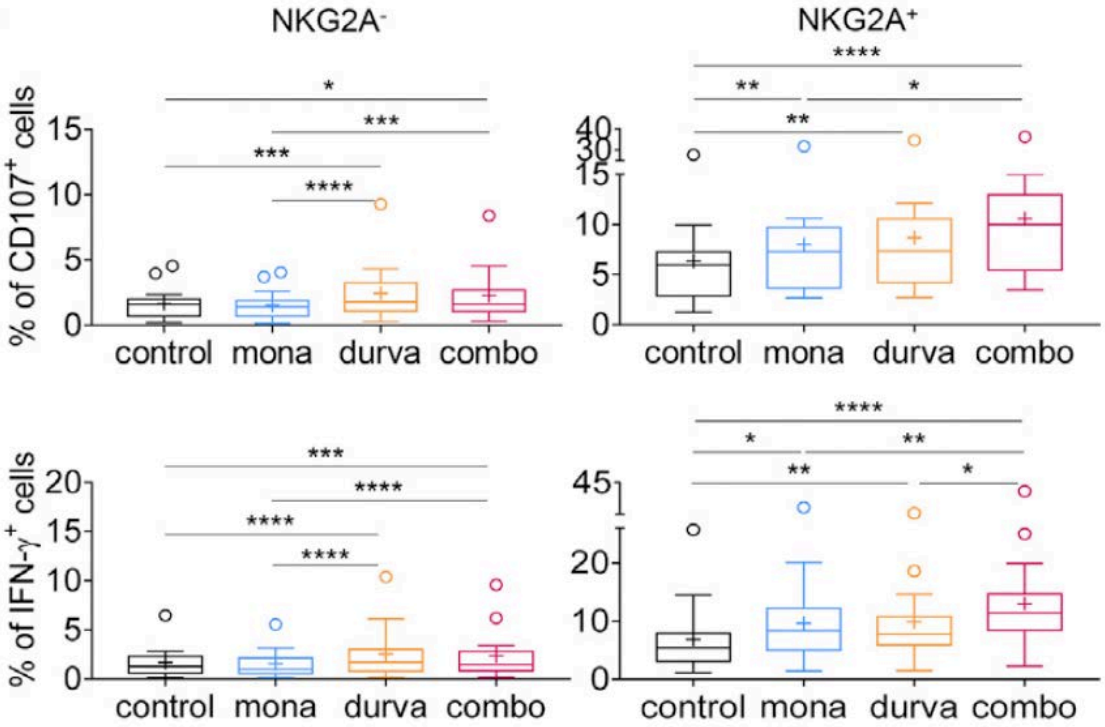
NKG2A expression by TILs in humans



Monalizumab unleashes human CD8$^+$ T cell function *in vitro* alone and with durvalumab

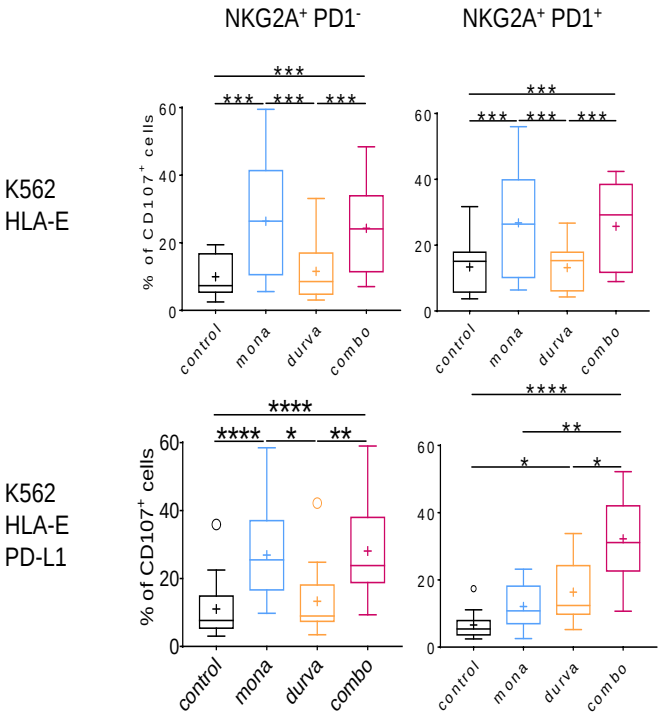


CD8$^+$ T cells cultured in vitro with monocytes, flu peptide and IL-15 (day 10)



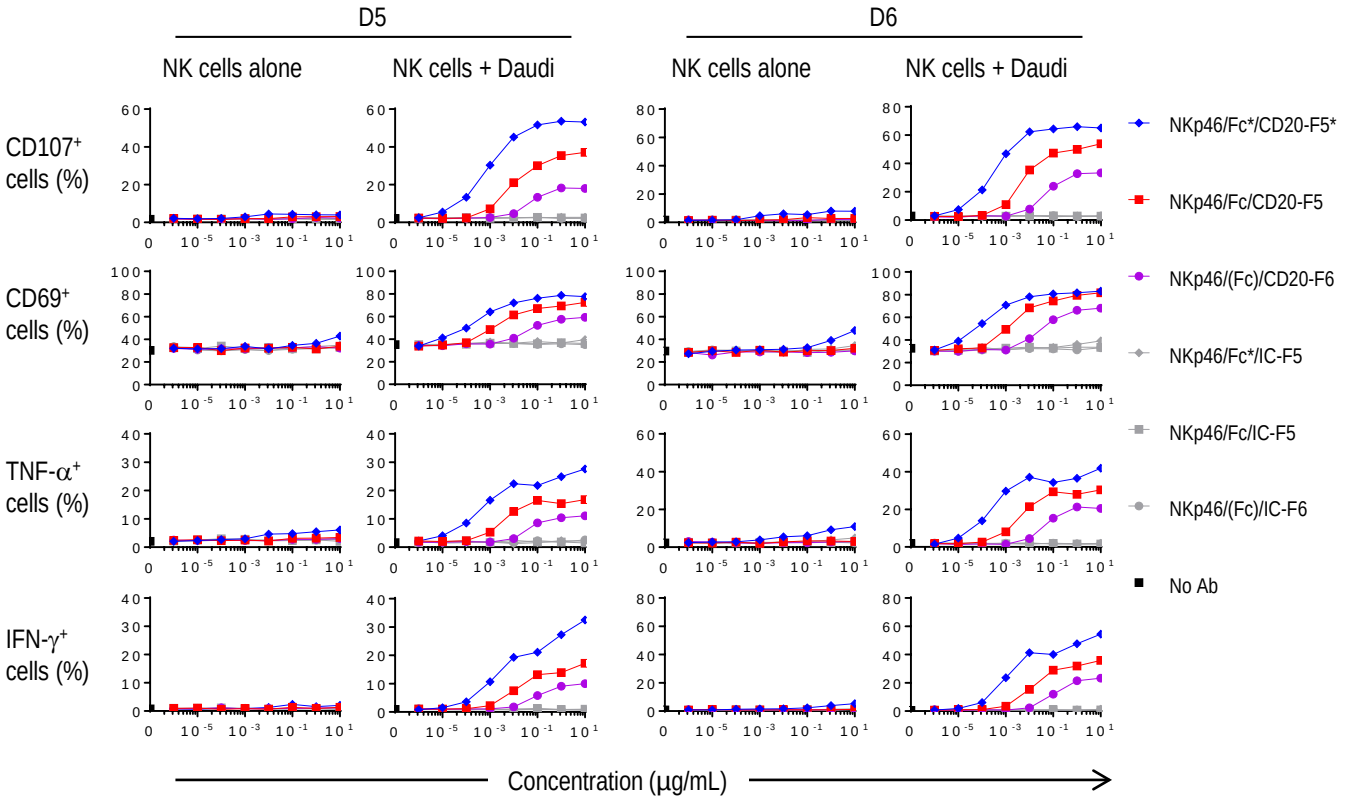
Flu-specific CD8$^+$ T cells challenged with flu peptide-pulsed K562 cells expressing PD-L1, HLA-E and HLA-A2

Monalizumab unleashes human NK cell function *in vitro* alone and with durvalumab



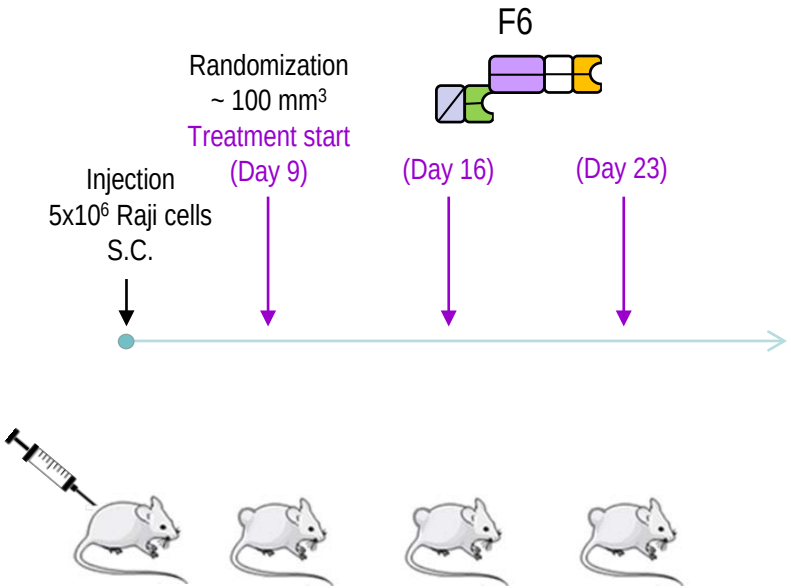
NK cells stimulated in vitro with IL-15 for 9 days

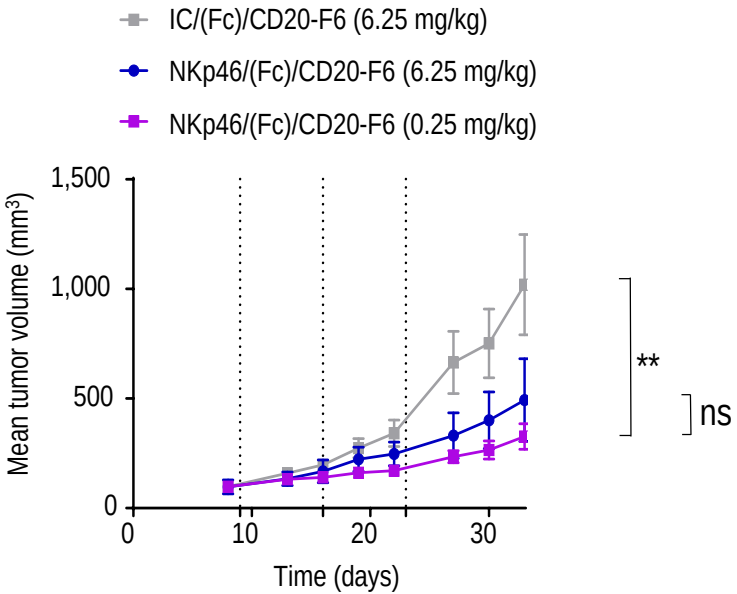
Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs



NKp46 NK cell engagers in oncology

Solid tumor model





NKp46 NK cell engagers in oncology

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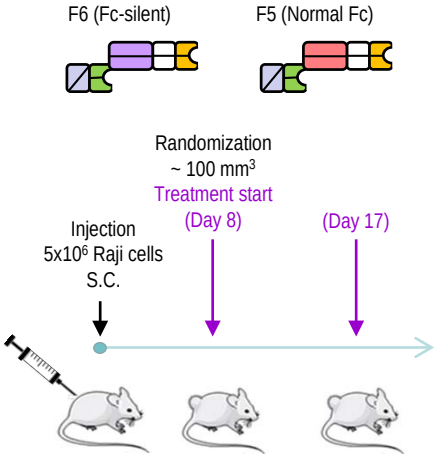
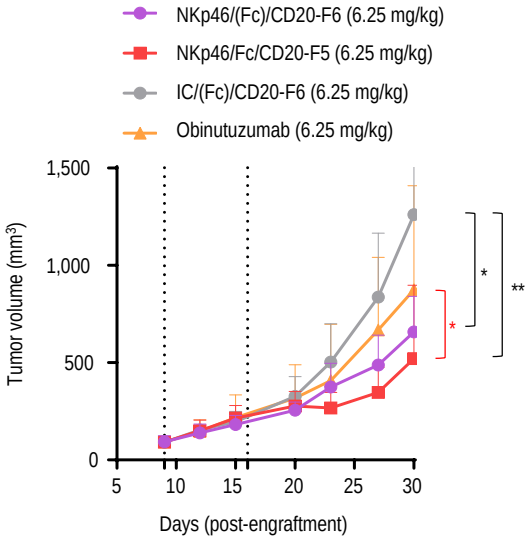
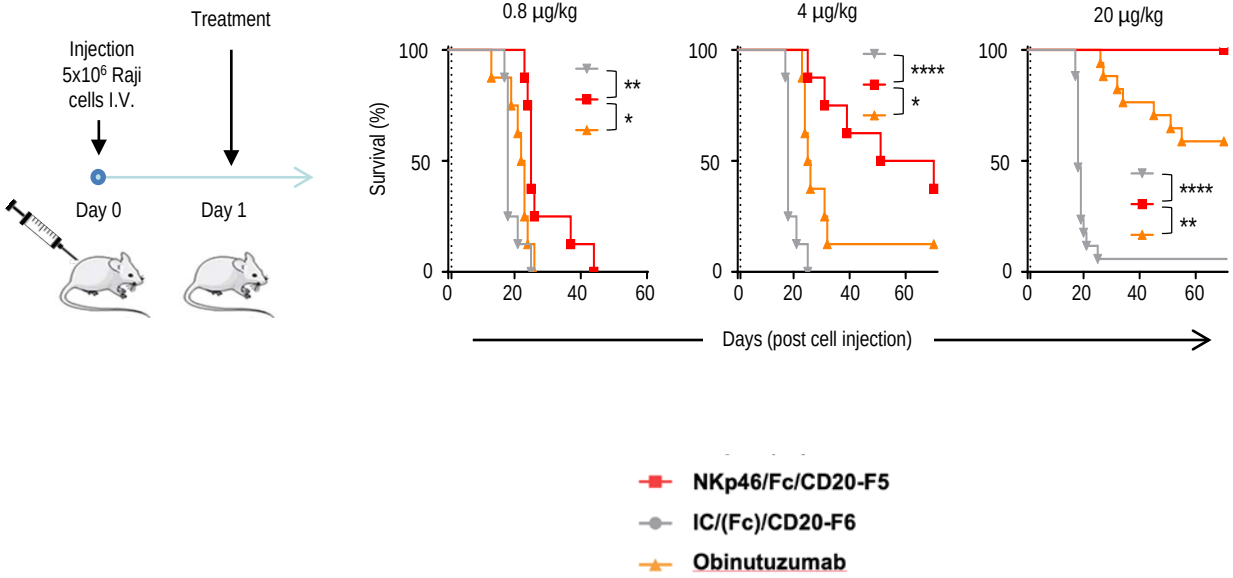




NKp46 NK cell engagers in oncology

Invasive tumor model



Gauthier et al.