SITC 2019

Gaylord National Hotel
& Convention Center

Nov. 6-10

NATIONAL HARBOR, MARYLAND

sitc Society for Immunotherapy of Cancer innate pharma

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Ciml
IMMUNOLOGY

Harnessing Innate Immunity in Cancer Therapy

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Inserm

cnrs

AP HM
Assistance Publique Hôpitaux de Marseille

European Research Council
erc

ANR
AGENCE NATIONALE DE LA RECHERCHE

ÉQUIPE LABELLISÉE PAR LA LIGUE CONTRE LE CANCER

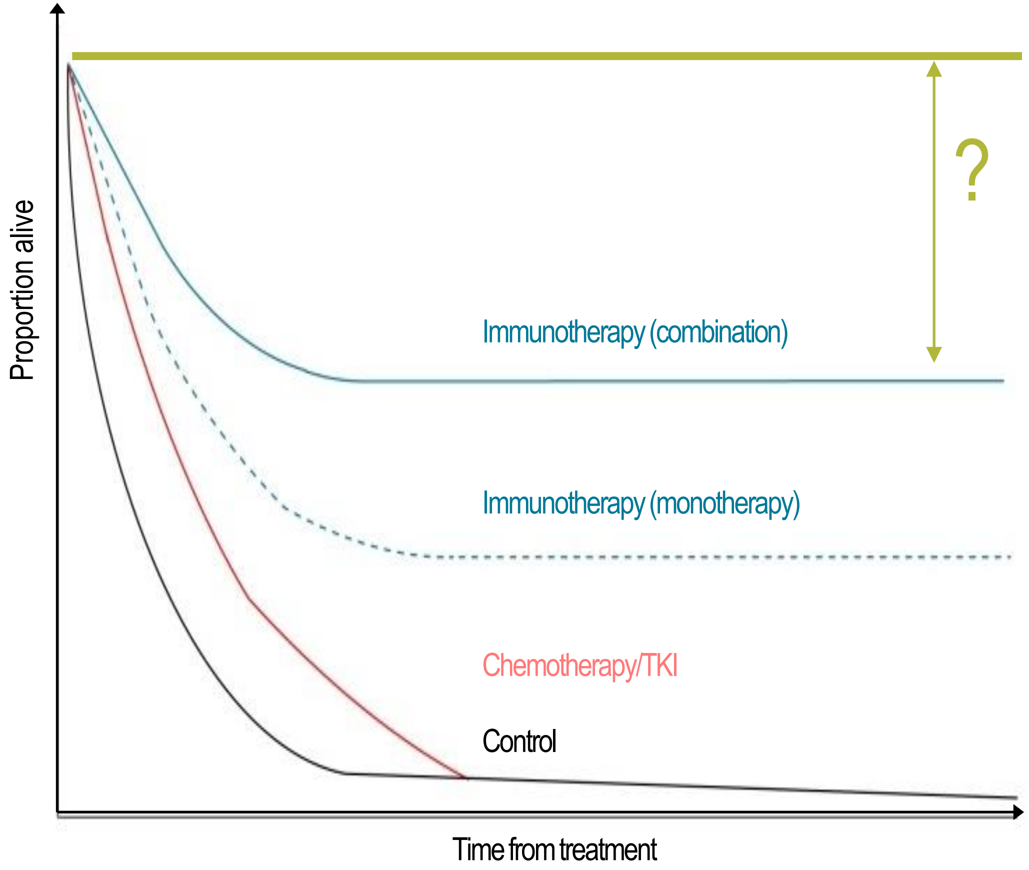
MSD AVENIR

MI
MARSEILLE IMMUNOPÔLE

Disclosures

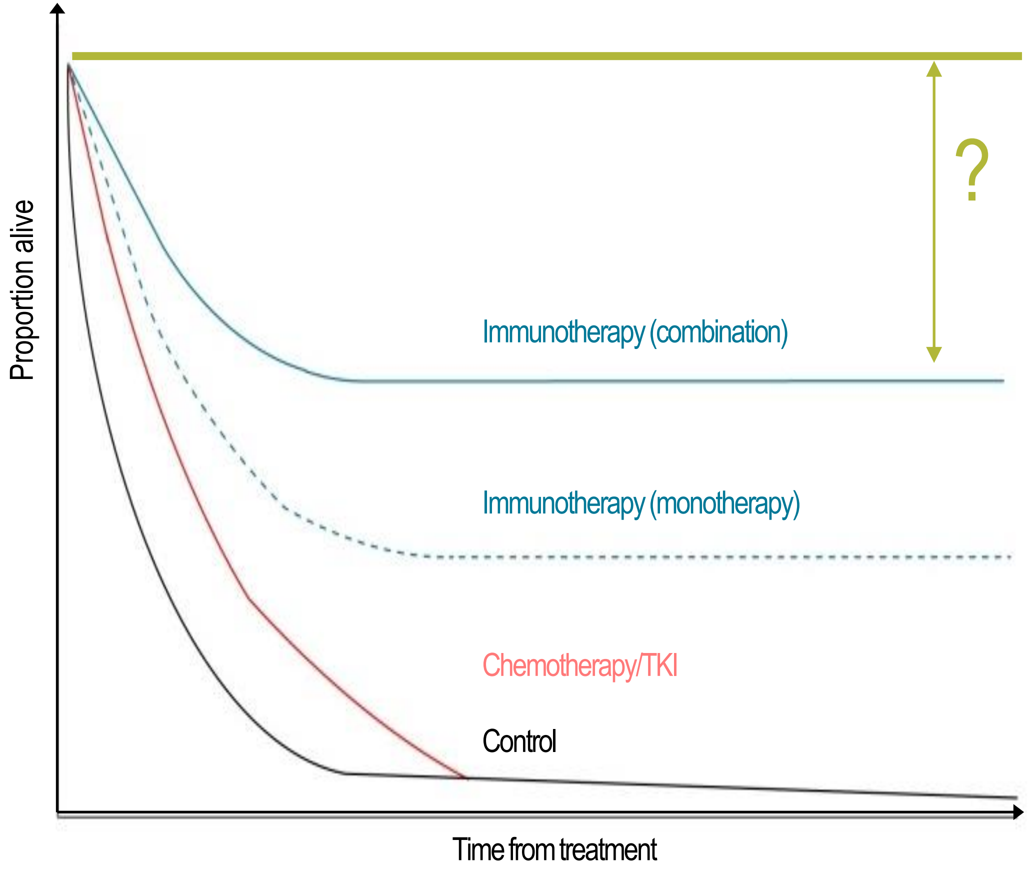
- Innate-Pharma, co-founder + CSO

The Immuno-Oncology Revolution



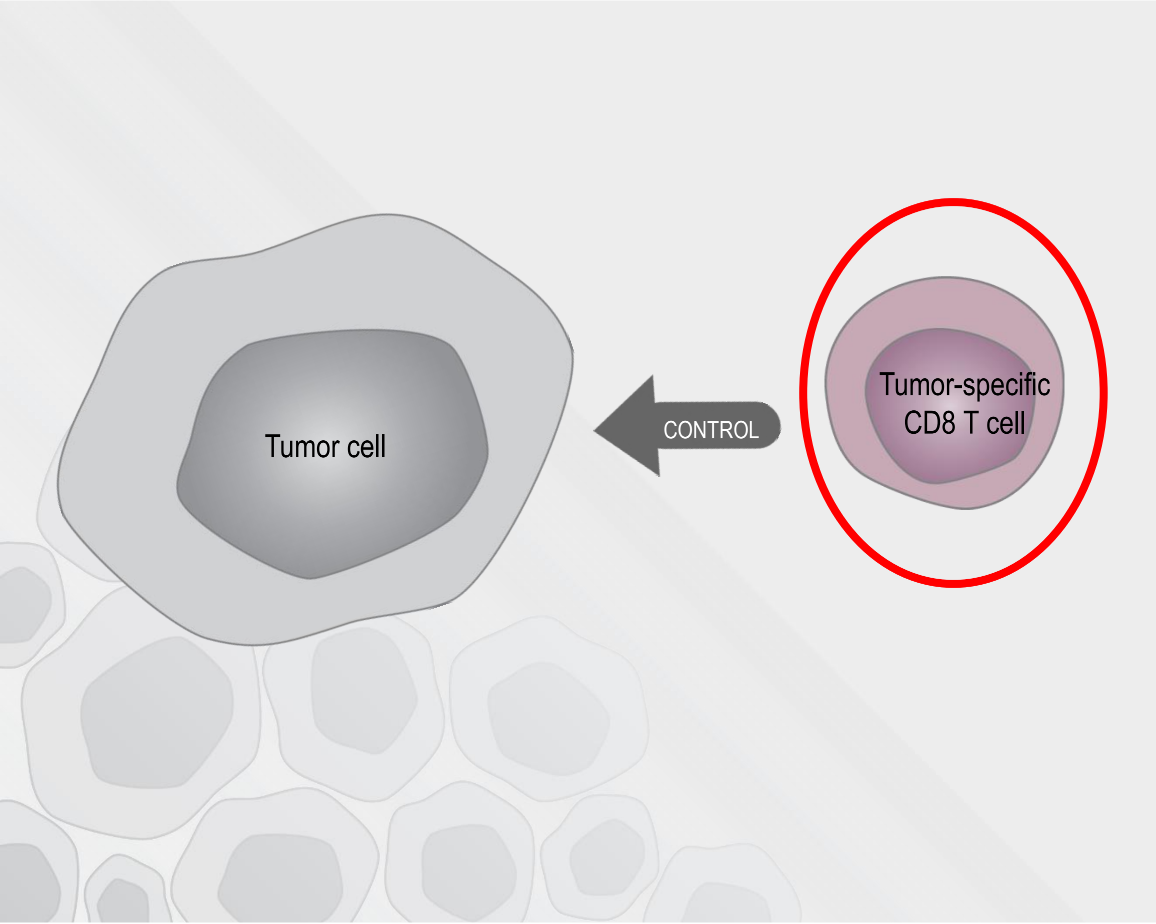
- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity

The Immuno-Oncology Revolution



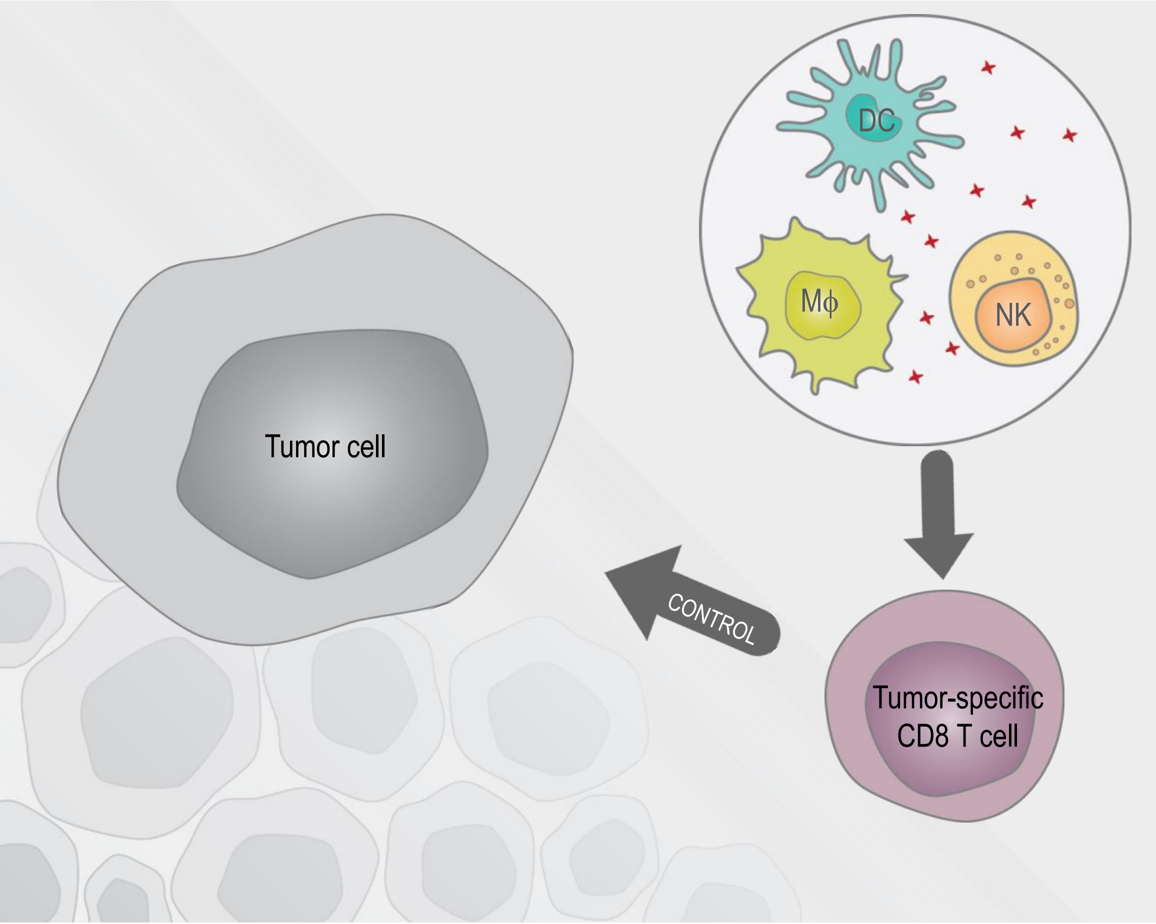
- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity
- Identify new targets (cells and molecules)
- Identify biomarkers

A pivotal role of T cells in tumor immunity



Pages, …, Galon, NEJM, 2005
Okazaki & Honjo, Int. Immunol. 2007
Chen & Mellman, Immunity 2013
Schumacher & Schreiber, Science 2015
Sharma & Allison, Science 2015
Chen & Mellman, Nature 2017

T cells are NOT autonomous



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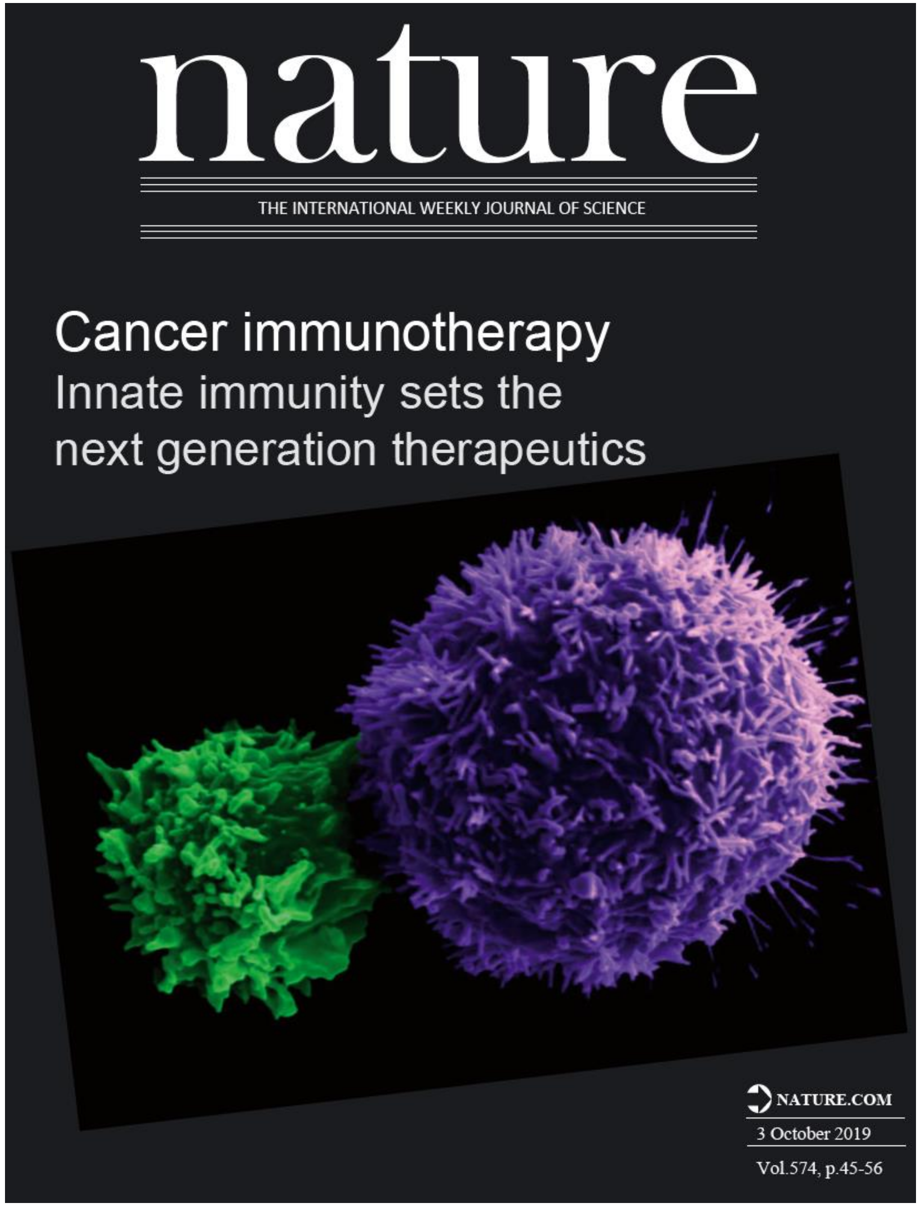
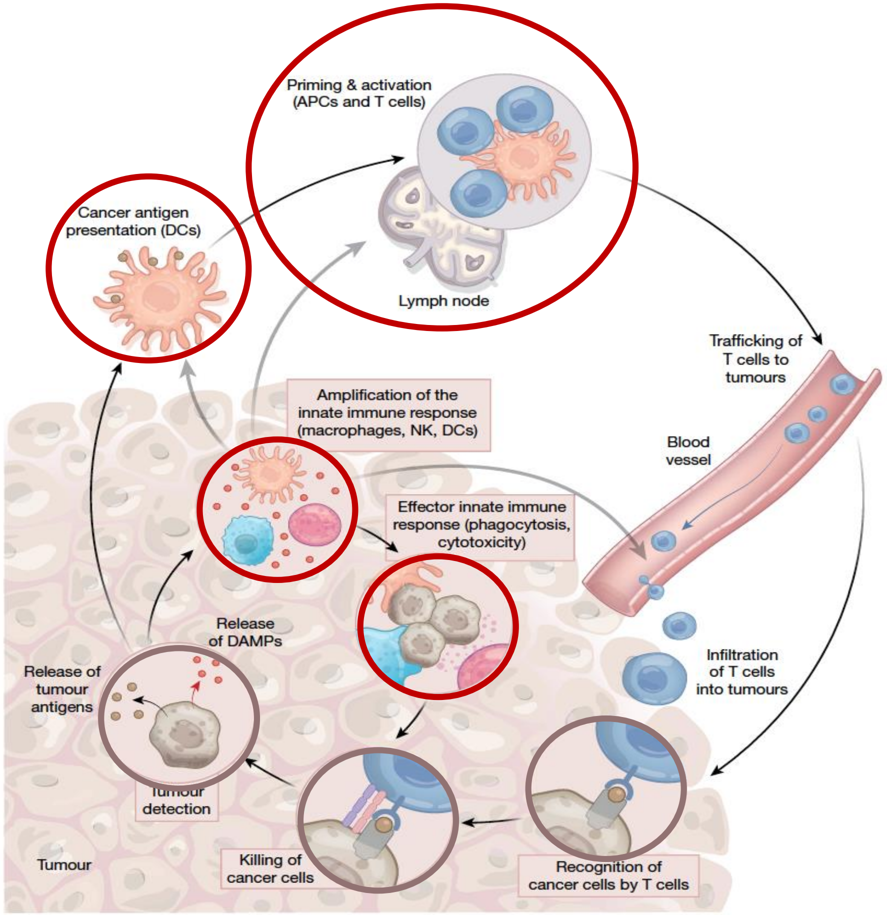


Demaria et al., Nature 2019

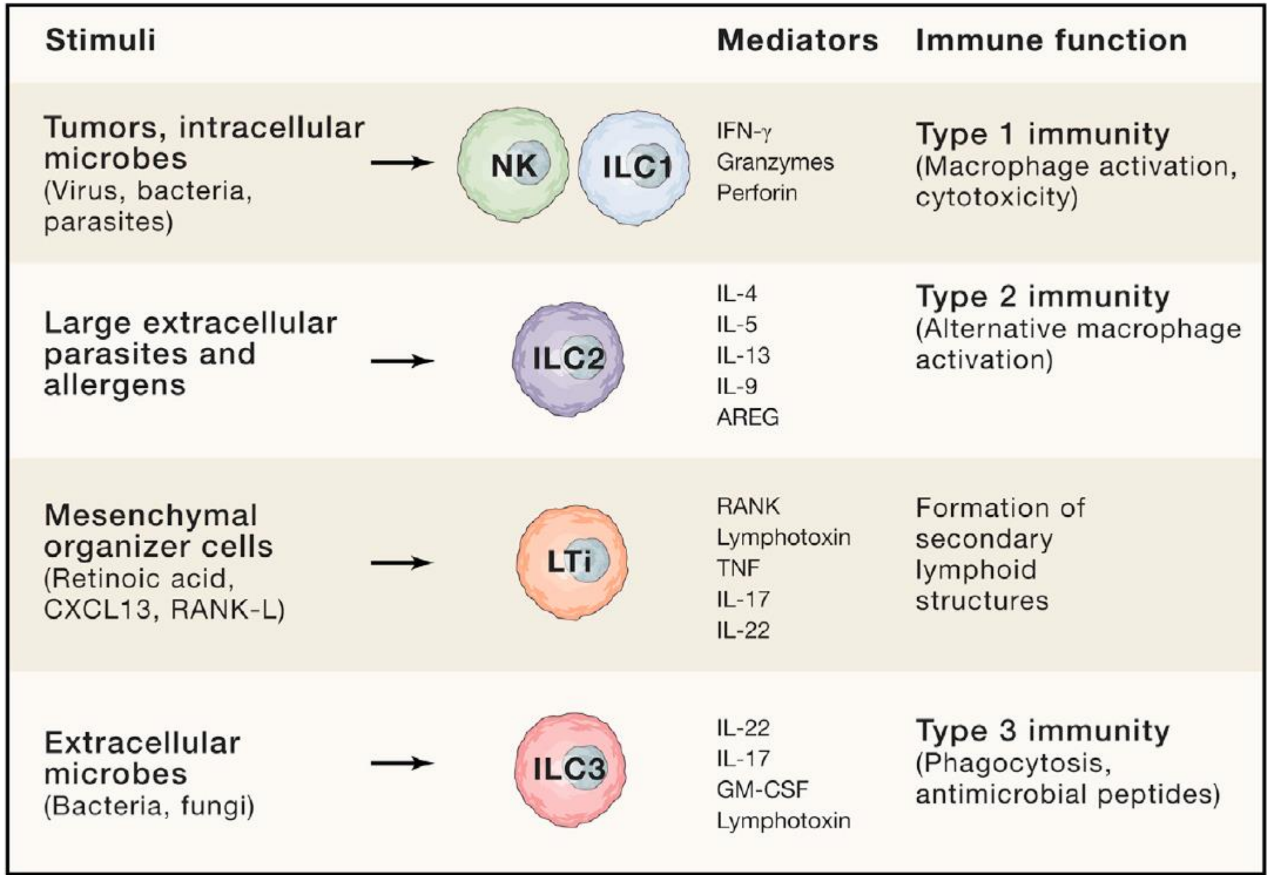
Innate immunity in the cancer immunity cycle



Demaria et al., Nature 2019

Targeting Innate Immunity in Cancer

Innate Lymphoid cells



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

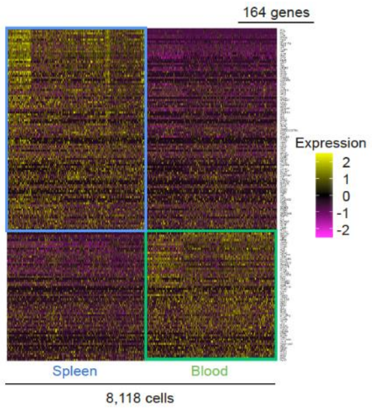
Targeting Innate Immunity in Cancer

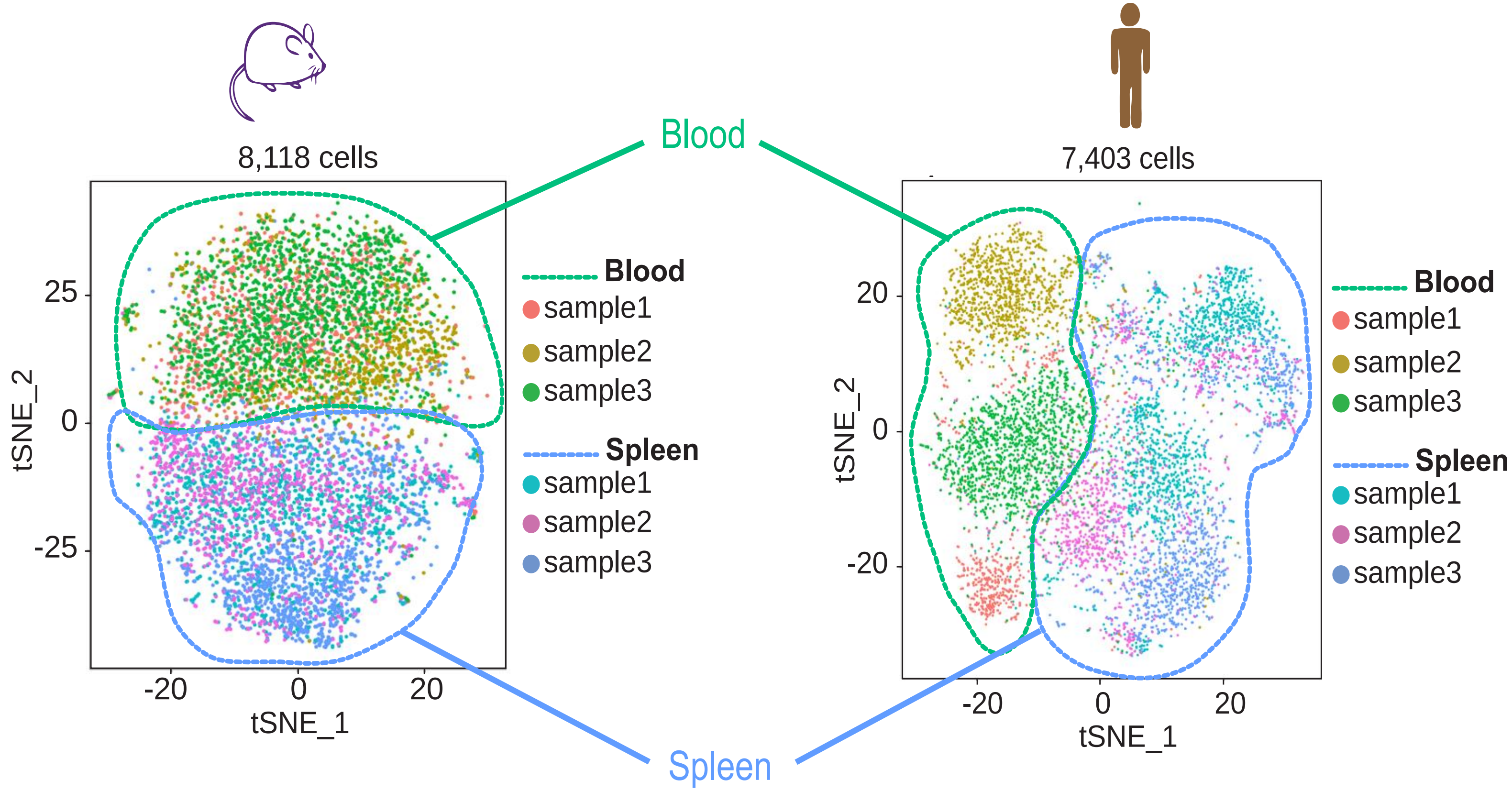
Innate Lymphoid cells

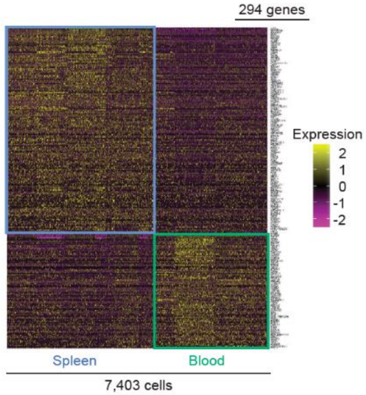
Stimuli		Mediators	Immune function
Tumors, intracellular microbes (Virus, bacteria, parasites) →	NK, ILC1	IFN-γ Granzymes Perforin	**Type 1 immunity** (Macrophage activation, cytotoxicity)
Large extracellular parasites and allergens →	ILC2	IL-4 IL-5 IL-13 IL-9 AREG	**Type 2 immunity** (Alternative macrophage 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

Profiling NK cells across organs and species



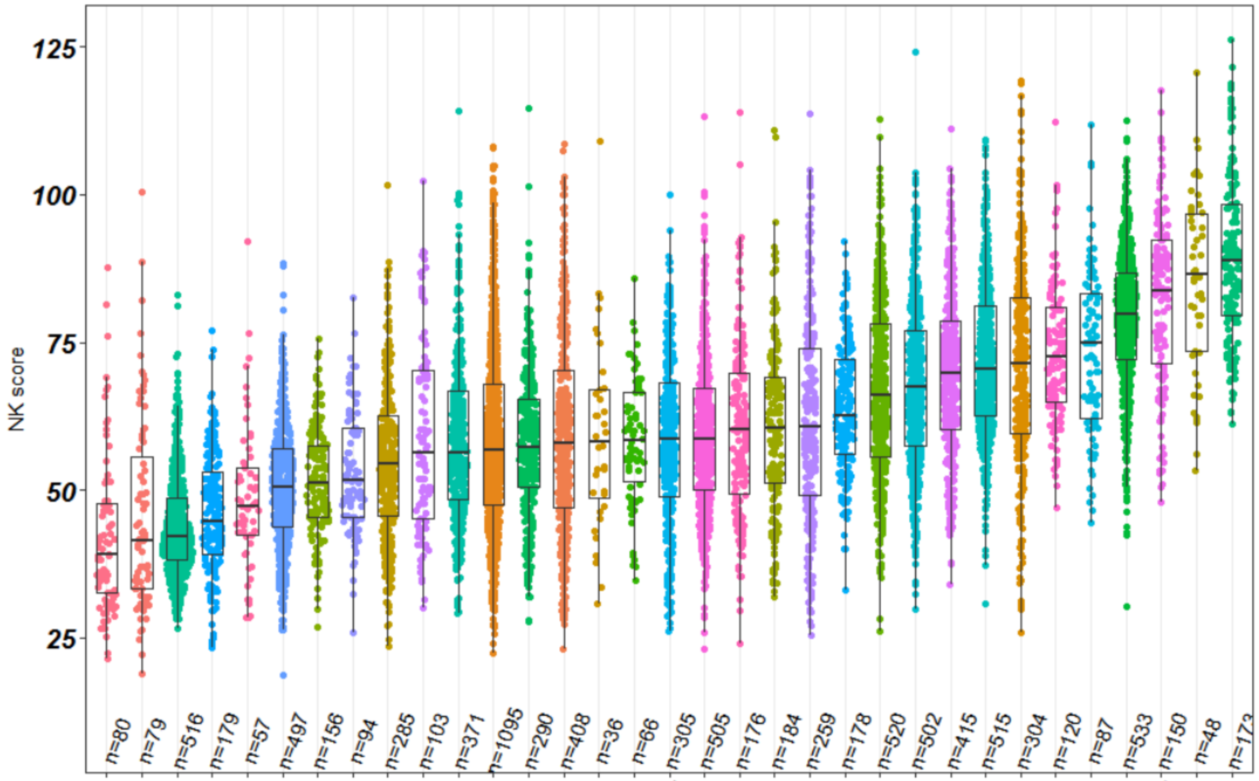




Crinier et al., Immunity 2018

NK cell infiltration at the tumor bed

Using NK cell transcriptomic signature

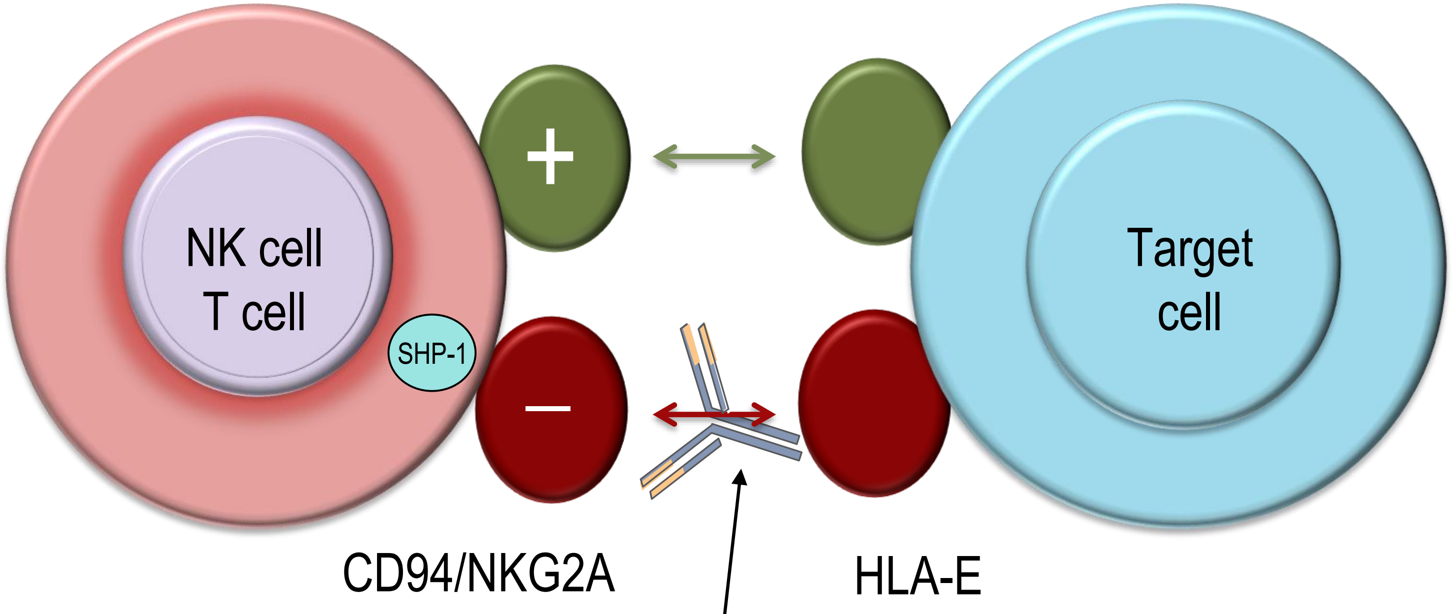


Carpentier et al., unpublished

Targeting Innate Immunity in Cancer

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

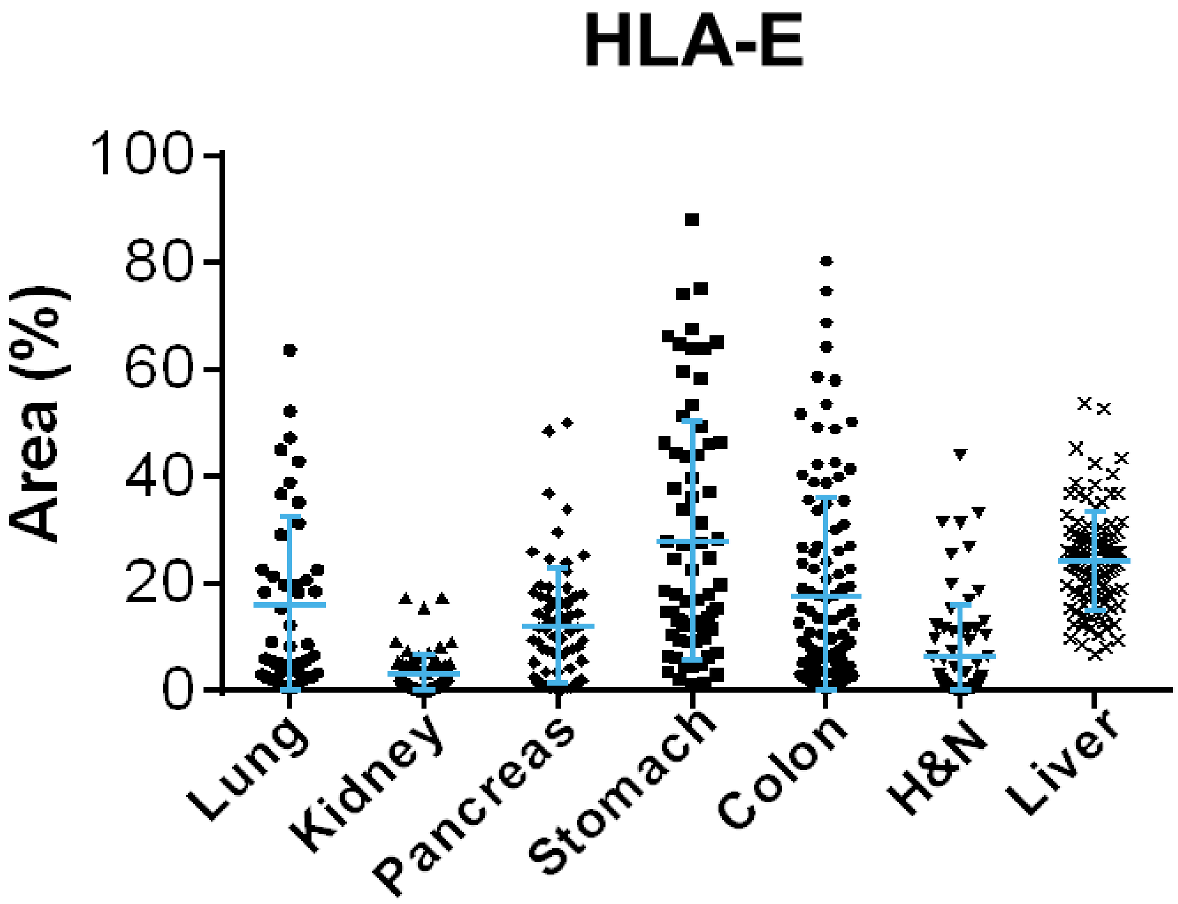
Blocking anti-NKG2A mAb: a novel immune checkpoint inhibitor in cancer immunotherapy

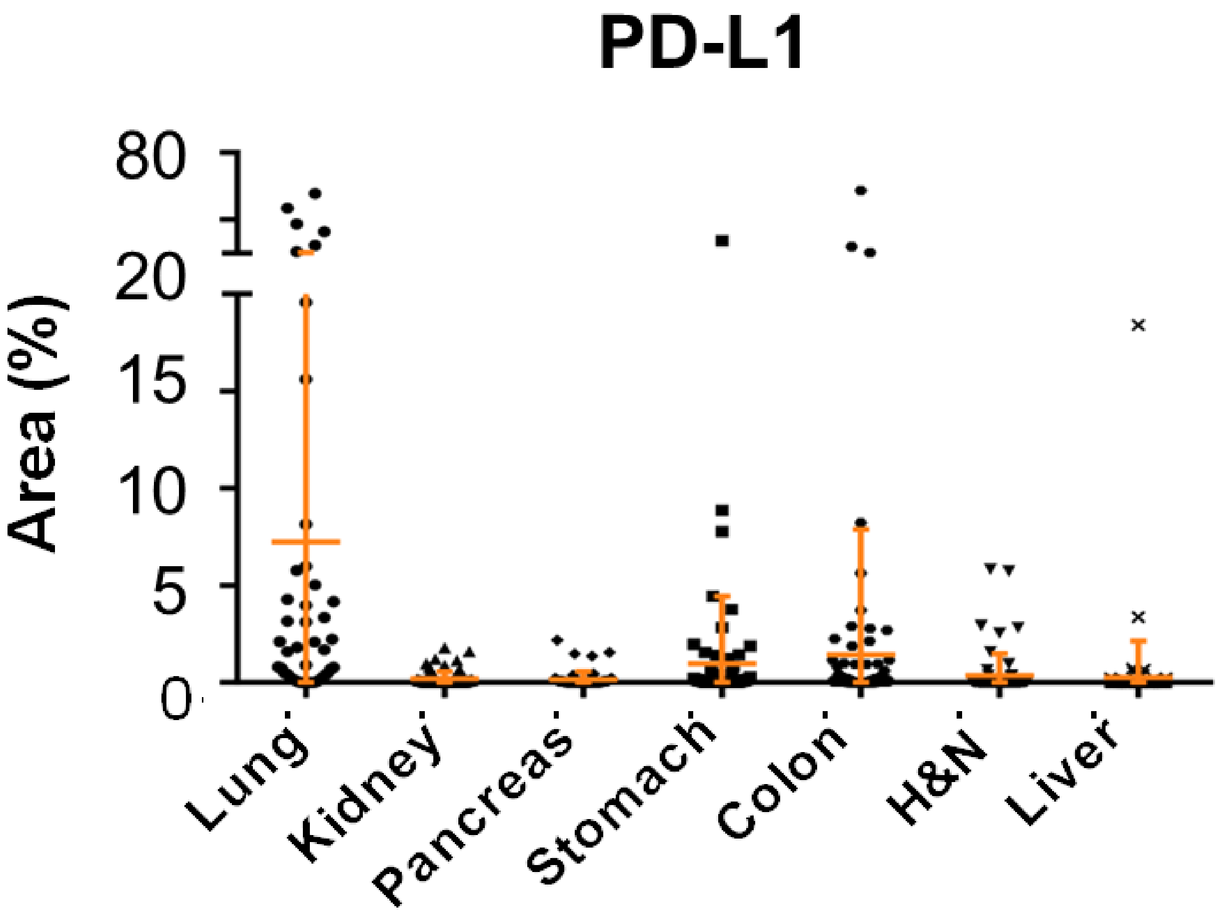


MONALIZUMAB (IPH2201) IS A FIRST-IN-CLASS ANTI-NKG2A HUMANIZED IGG4 BLOCKING MAB

innate pharma

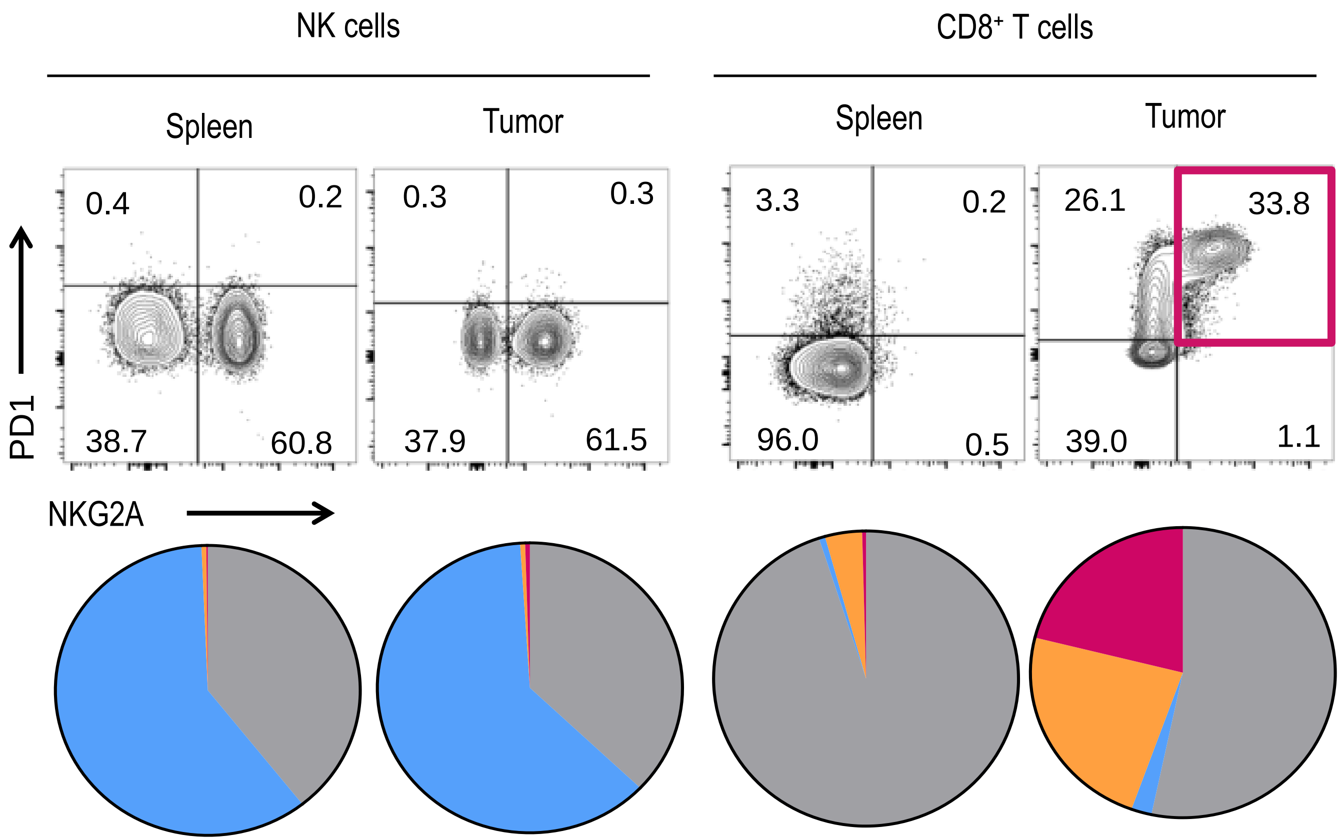
HLA-E expression in human solid tumors





Co-expression of NKG2A and PD-1

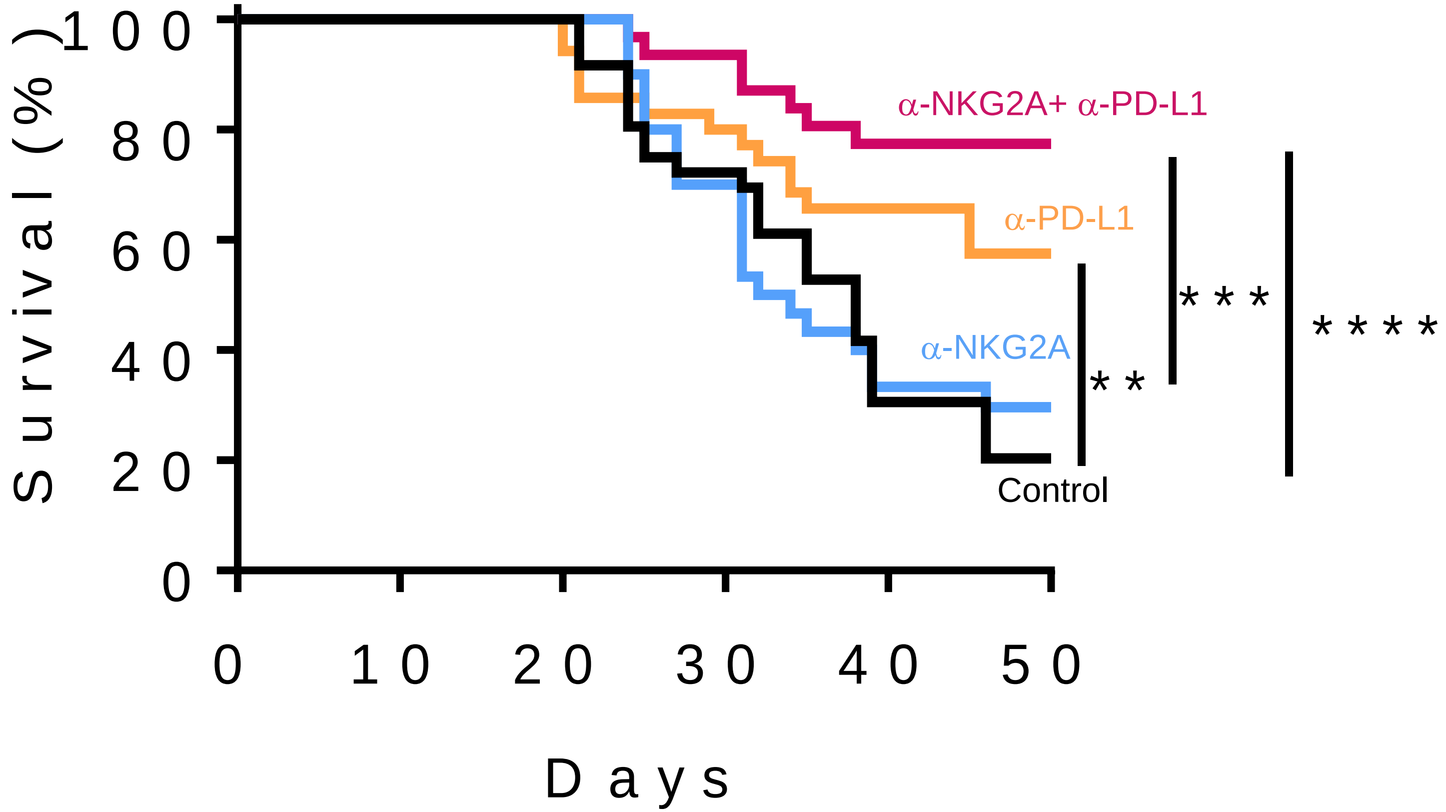
A20 tumor-bearing BALB/c mice



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

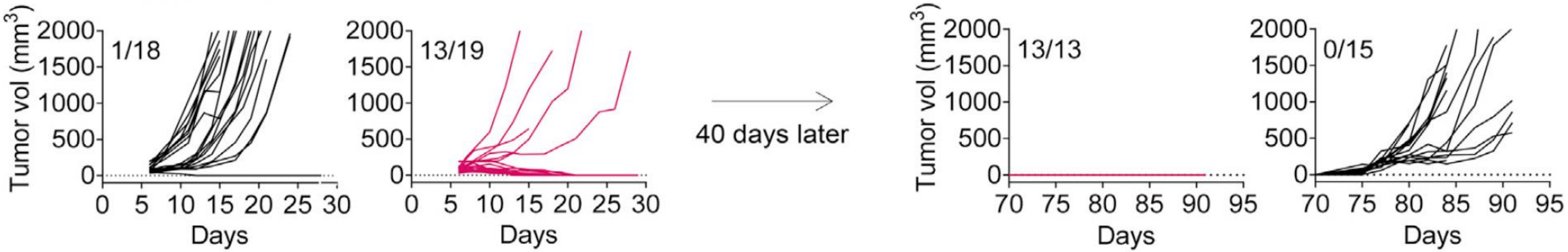
The combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity

A20 tumor-bearing BALB/c mice



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

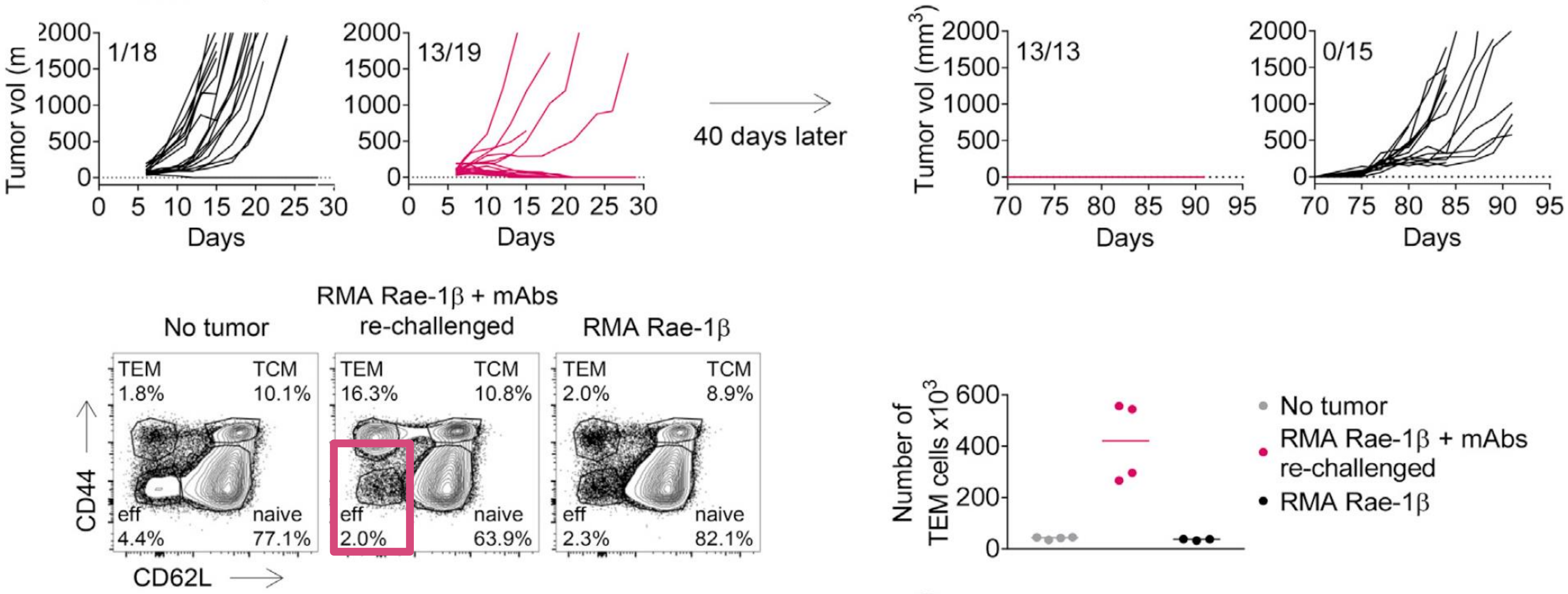
Control / anti-NKG2A + anti-PD-L1



RMA Rae-1β tumor-bearing C57/BL6 mice

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

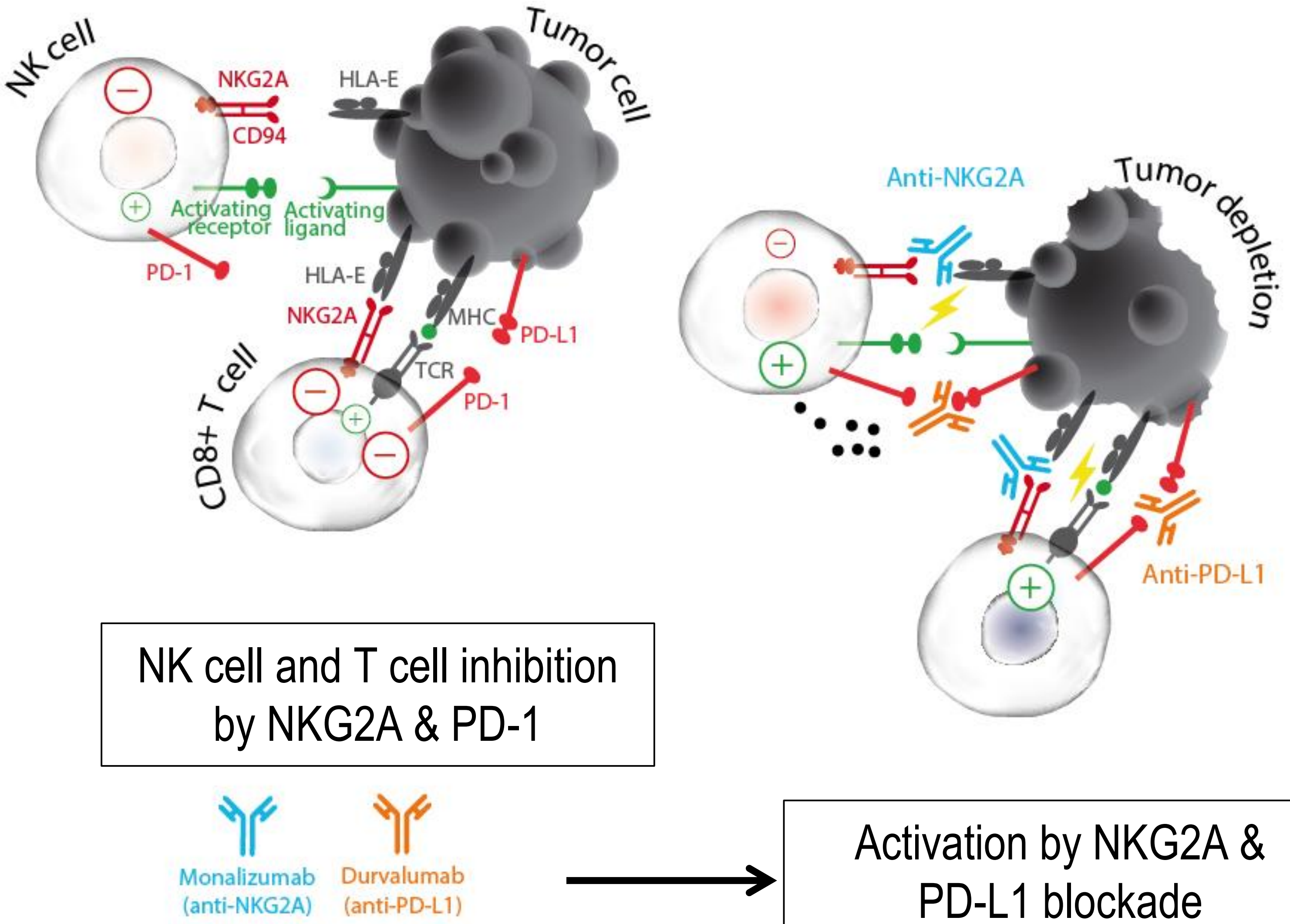
Control / anti-NKG2A + anti-PD-L1



Anti-NKG2A as a novel immune checkpoint inhibitor in cancer

- 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

Combination of monalizumab and durvalumab in cancer immunotherapy

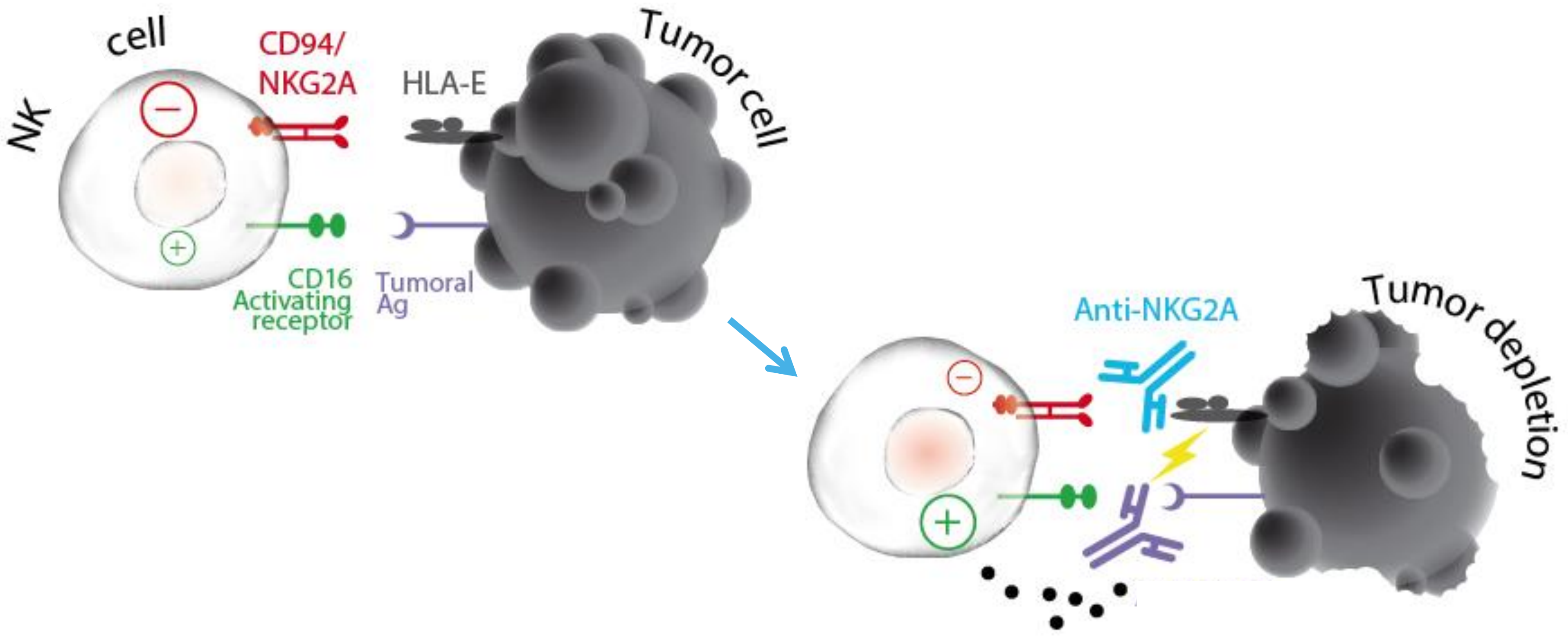


NK cell and T cell inhibition by NKG2A & PD-1

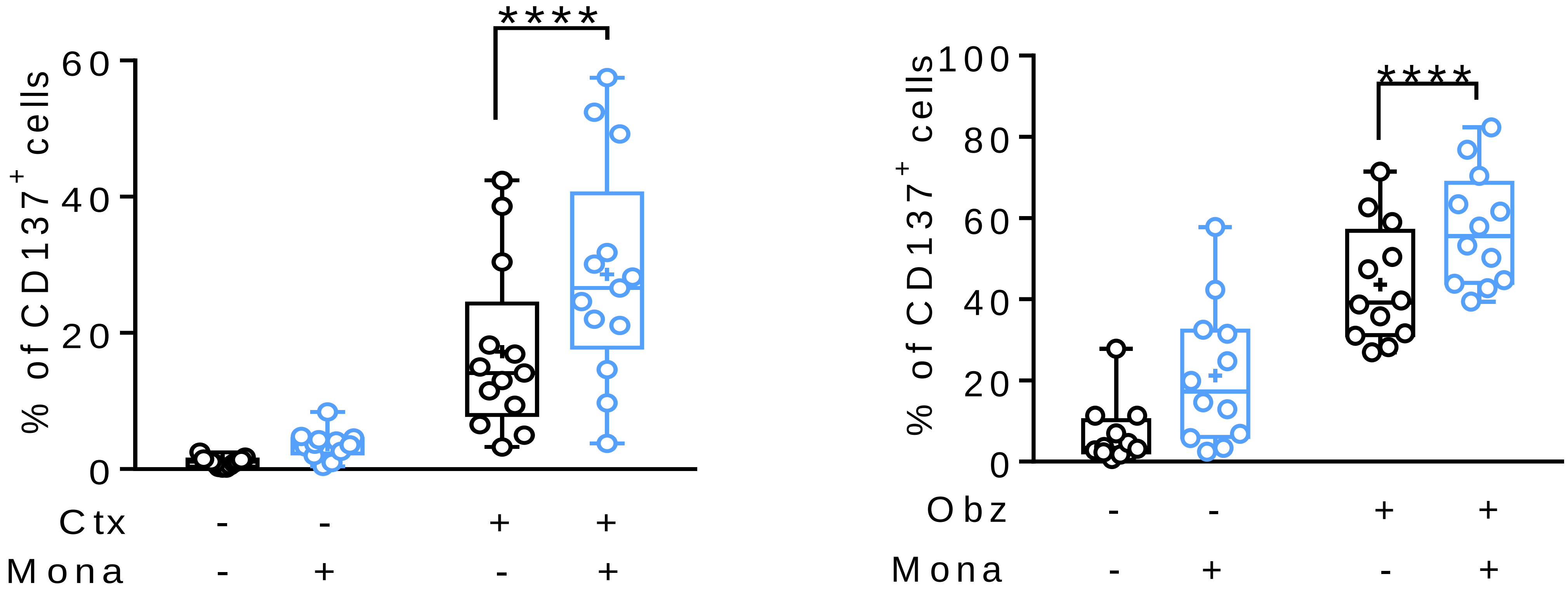
Activation by NKG2A & PD-L1 blockade

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

Can the NKG2A immune checkpoint blockade potentiate ADCC?



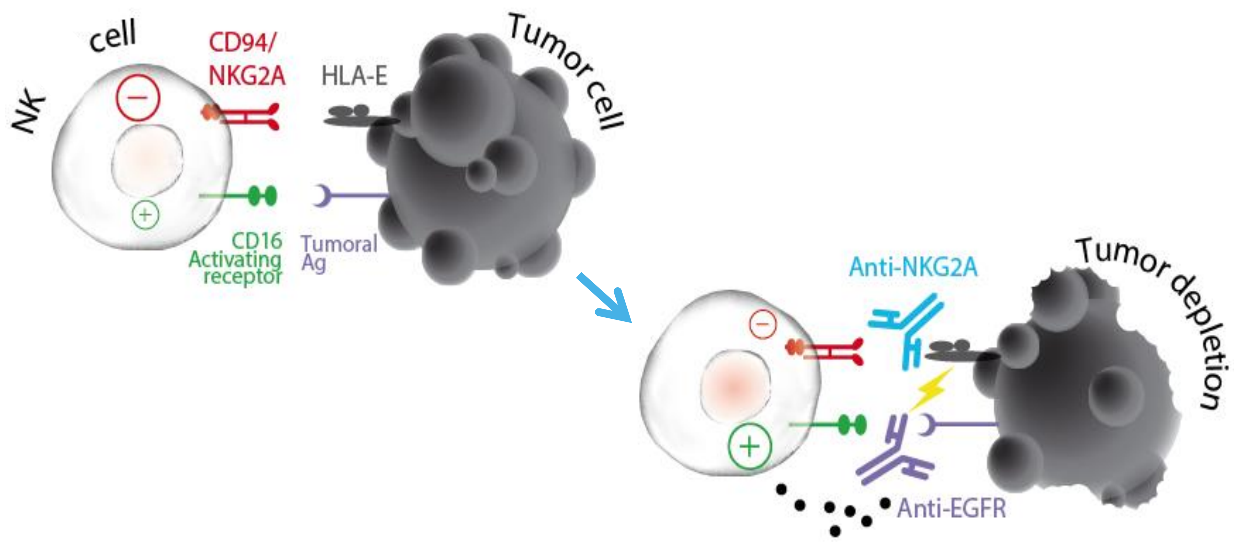
Monalizumab enhances human NK cell-mediated ADCC



Ctx: cetuximab (anti-EGFR)

Obz: obinutuzumab (anti-CD20)

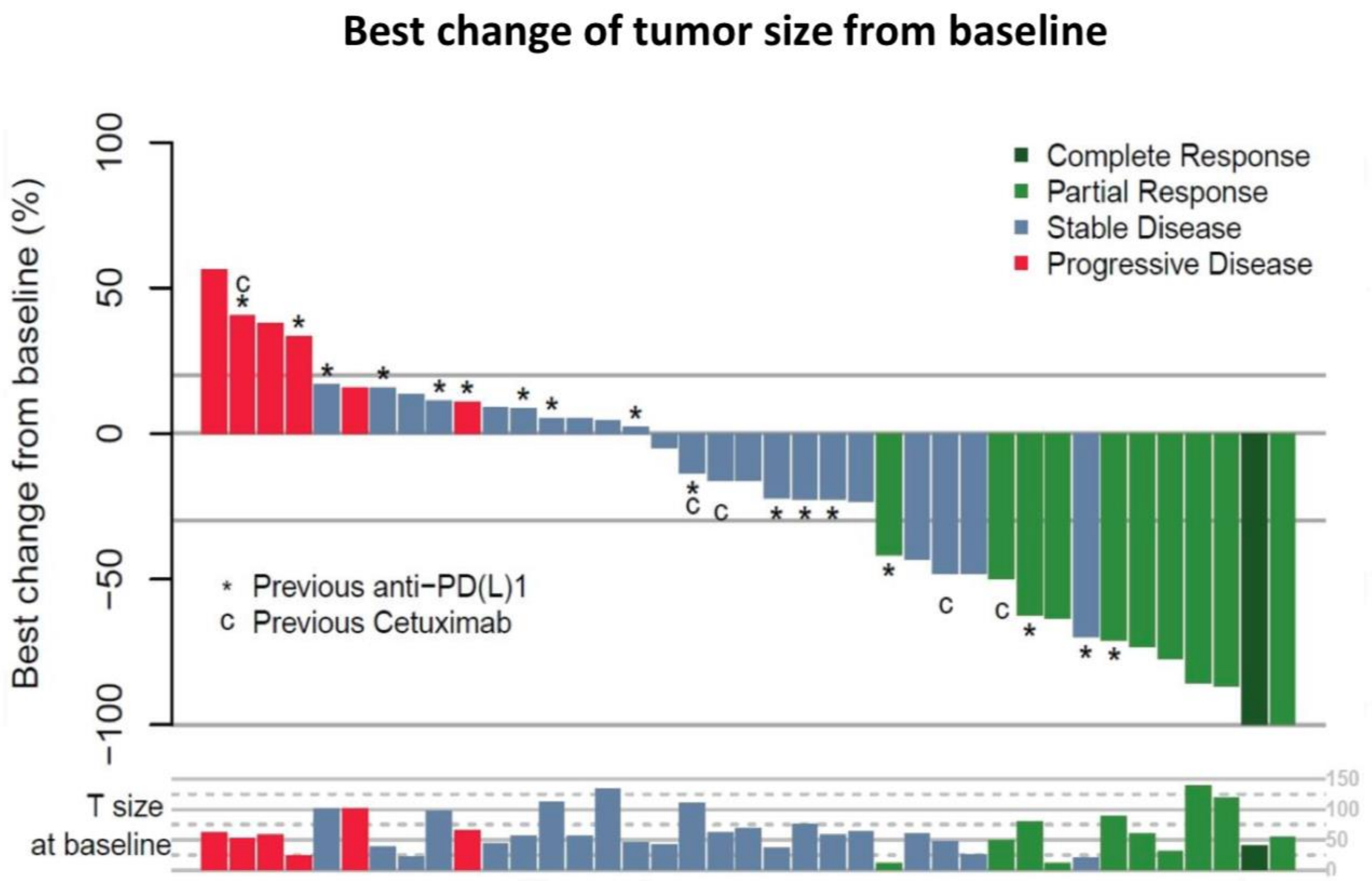
NKG2A immune checkpoint blockade potentiates cetuximab-induced ADCC in head and neck cancer



ADCC enhancement by NKG2A blockade

- SCCHN are infiltrated by NK and CD8$^+$ T cells expressing CD94/NKG2A
- HN tumor cells express HLA-E
- NKG2A blockade enhances cetuximab-mediated ADCC towards HN tumor cell lines
- These data support the rationale for investigating monalizumab in SCCHN patients and in combination with cetuximab in clinical trials (NCT02643550)

Monalizumab + Cetuximab combo in Head & Neck cancer

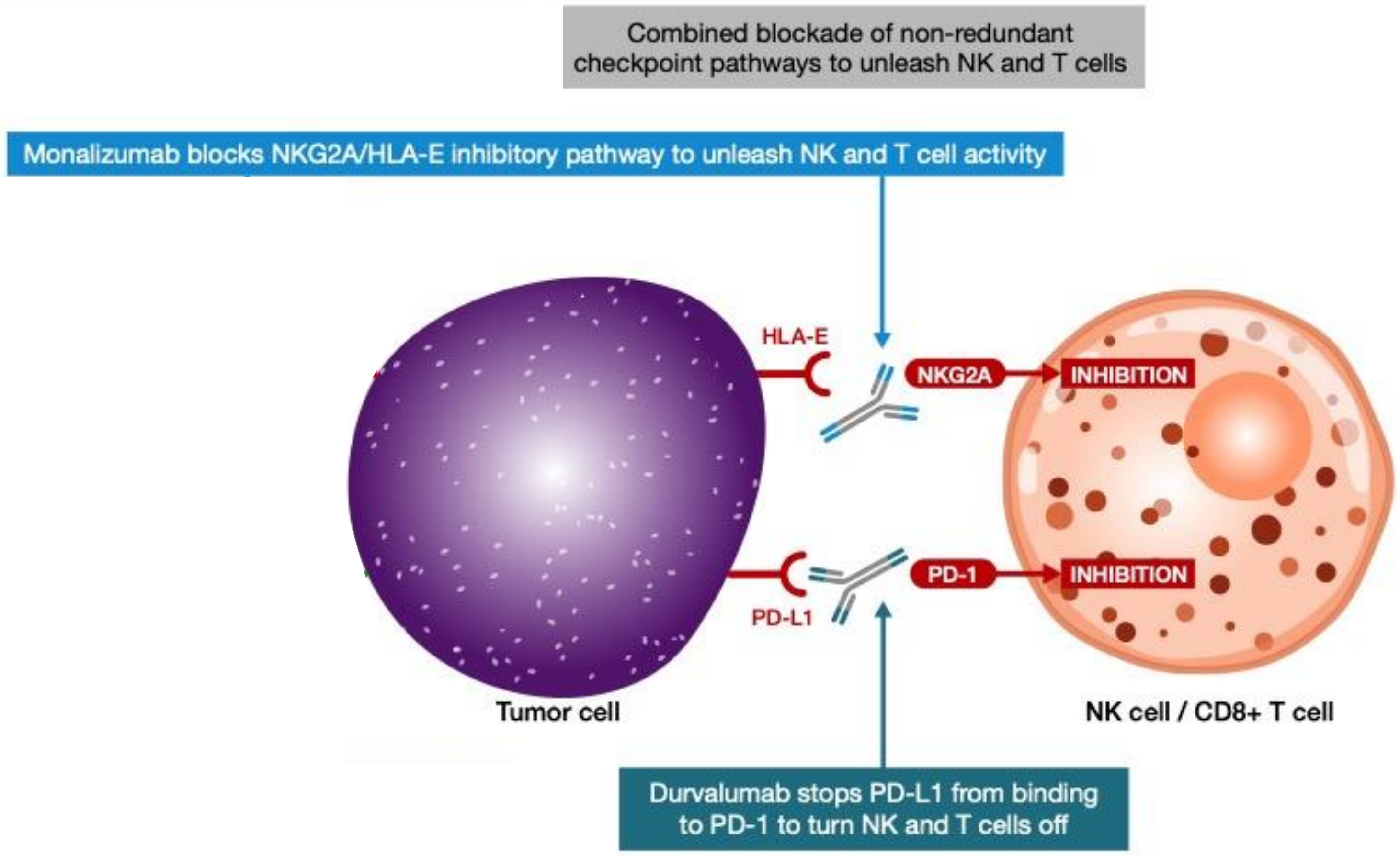


Key highlights from the Phase II of monalizumab in combination with cetuximab in patients with R/M SCHHN

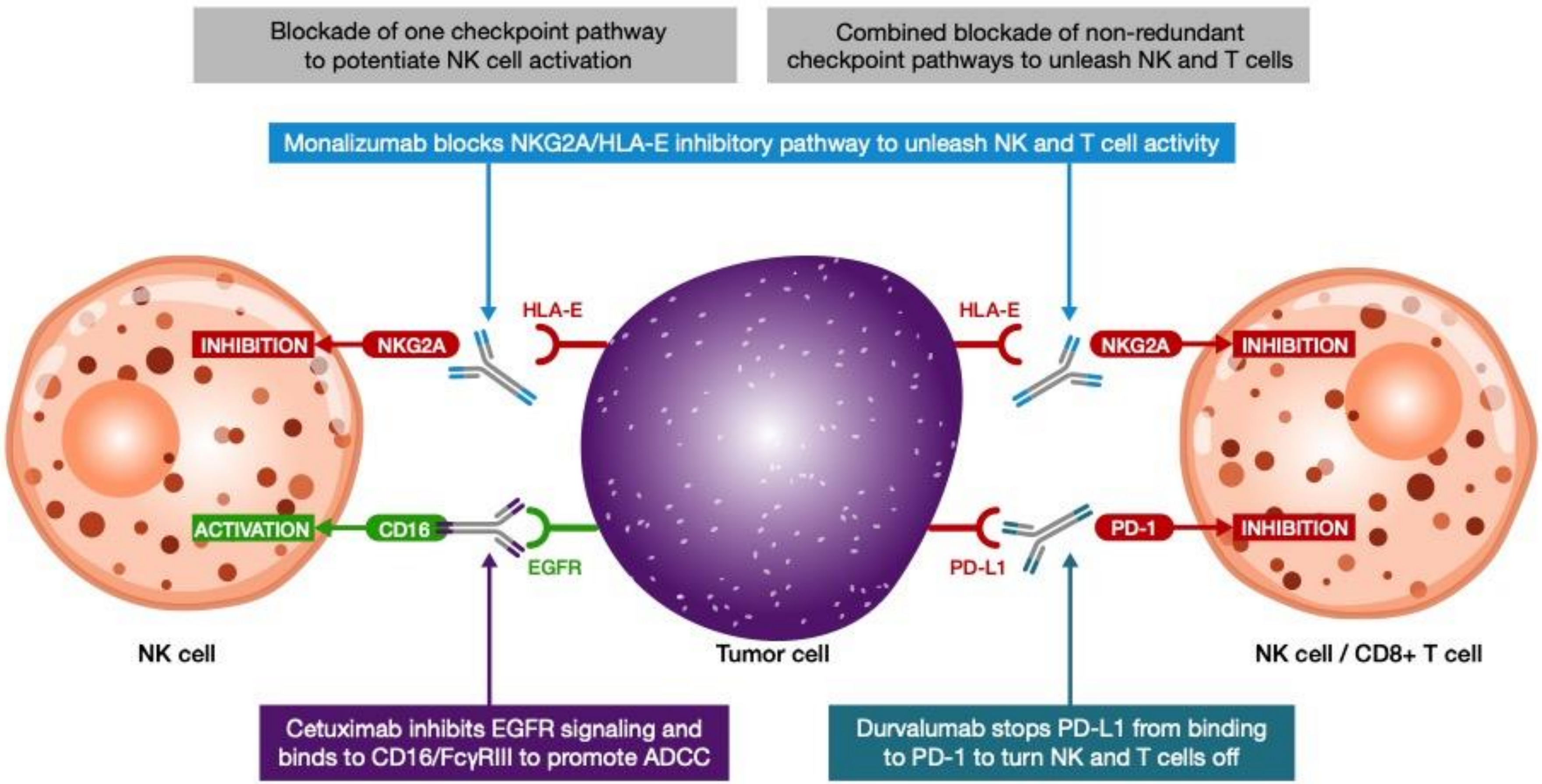
- Cohort of 40 patients of heavily pretreated SCCHN patients
- Acceptable safety profile: no potentiation of cetuximab side effects
- A high response rate of 27.5%
- Promising overall survival: with a median follow-up of 17 months, median OS is 8.5 months (14.1 months in IO-pretreated patients and 7.8 in IO-naïve patients, respectively), and a 12-month OS of 44% (60% in IO-pretreated and 32% in IO-naïve patients, respectively)
- Responses were observed in platinum-resistant patients, HPV positive and negative patients, and IO-naïve and IO-pretreated patients

	All n=40	IO Naïve n=22	IO Pretreated n=18
Best overall response			
Complete Response n (%)	1 (2.5%)	1 (4.5%)	0 (0%)
Partial response n (%)	10 (25%)	7 (32%)	3 (17%)
Stable disease n (%)	22 (55%)	10 (45.5%)	12 (66%)
Progressive disease n (%)	7 (17.5%)	4 (18%)	3 (17%)
Overall Response Rate % [95%CI]	**27.5% [16-43]**	**36% [20-57]**	**17% [6-39]**
Disease Control Rate at 24 weeks [95%CI]	37.5% [24-53]	36% [20-57]	39% [20-61]
Median Time to Response [95%CI]	1.6 months [1.5- 3.9]	1.7 months [1.5- 3.9]	1.6 months [1.6- 3.1]
Median Duration of Response [95%CI]	5.6 months [4.2-NR]	5.3 months [4.2-NR]	5.6 months [3.7-NR]
Median progression free survival [95%CI]	4.5 months [3.5-5.8]	3.9 months [3.5-6.9]	5.1 months [3.5-8.8]
Median overall survival (OS) [95%CI]	**8.5 months [7.5.-16.4]**	**7.8 months [6.9-15.8]**	**14.1 months [8.0.-NR]**
12 months OS [95%CI]	44% [31-63]	32% [17-59]	60% [41-88]

Monalizumab: a large spectrum immune checkpoint inhibitor



Monalizumab: a large spectrum immune checkpoint inhibitor

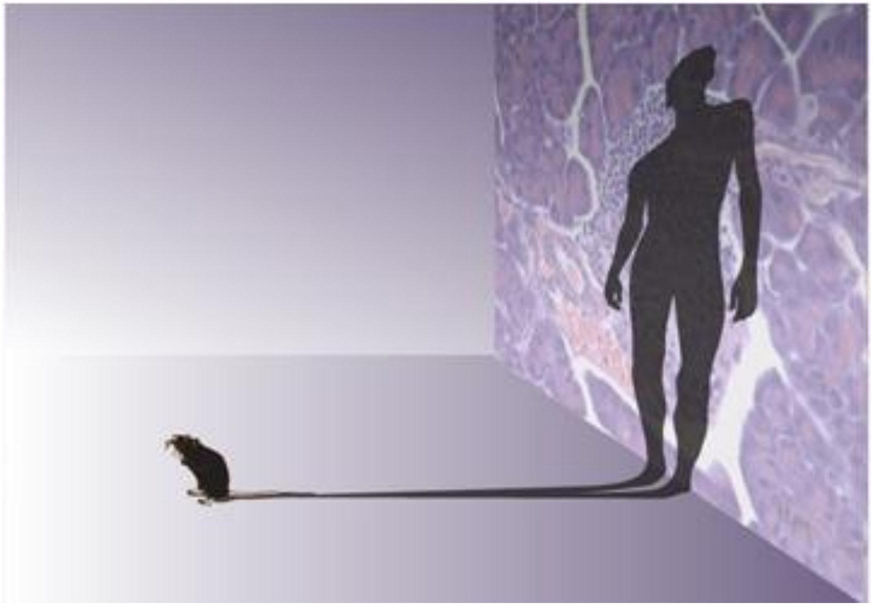


André et al., Cell 2018

Targeting Innate Immunity in Cancer

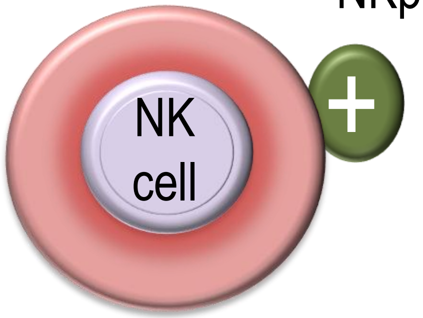
- Targeting NK cells
  - *- Targeting inhibitory NK cell surface receptors: NKG2A*
  - - Targeting activating NK cell surface receptors

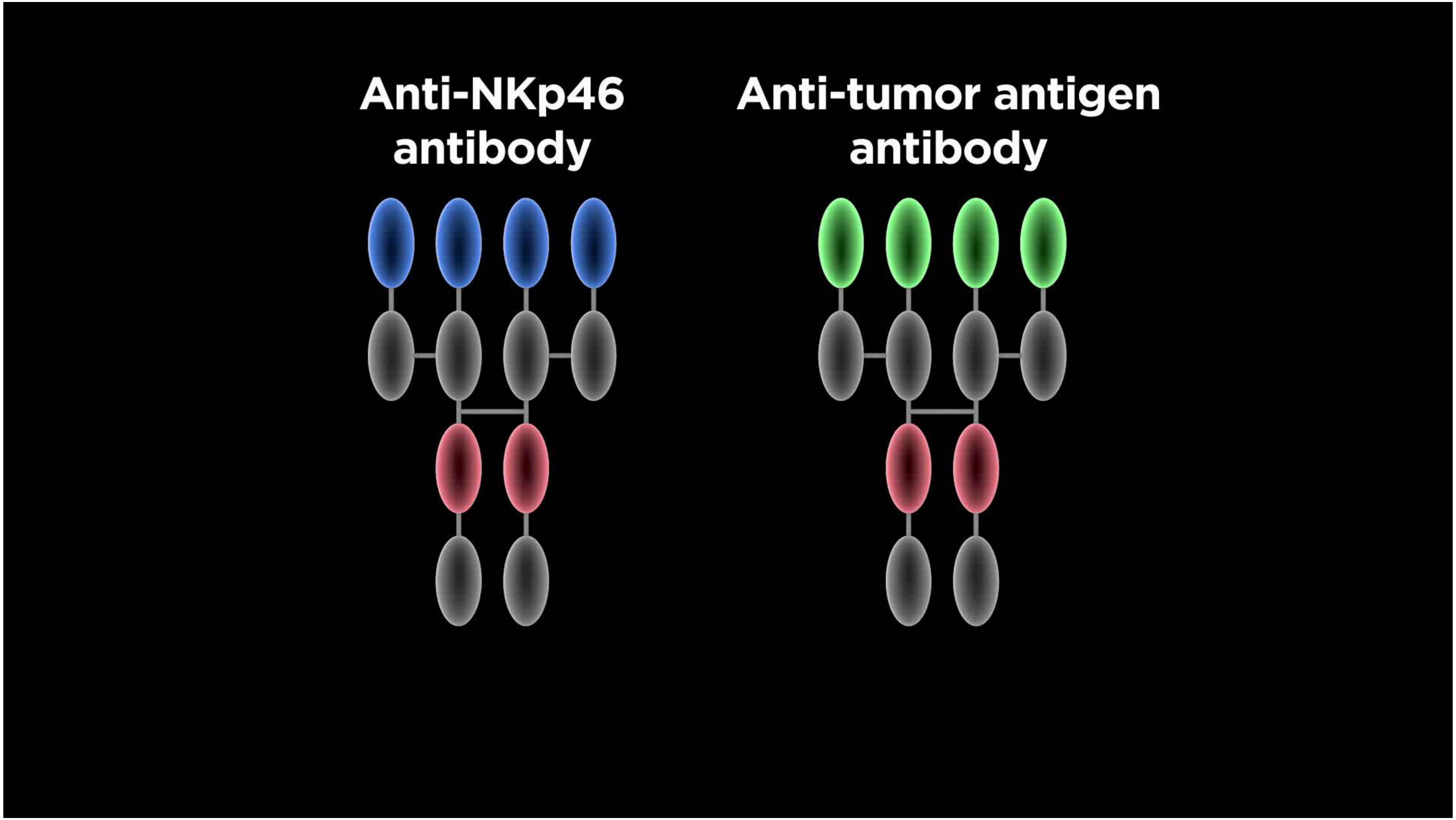
NKp46 is a conserved activating cell surface receptor



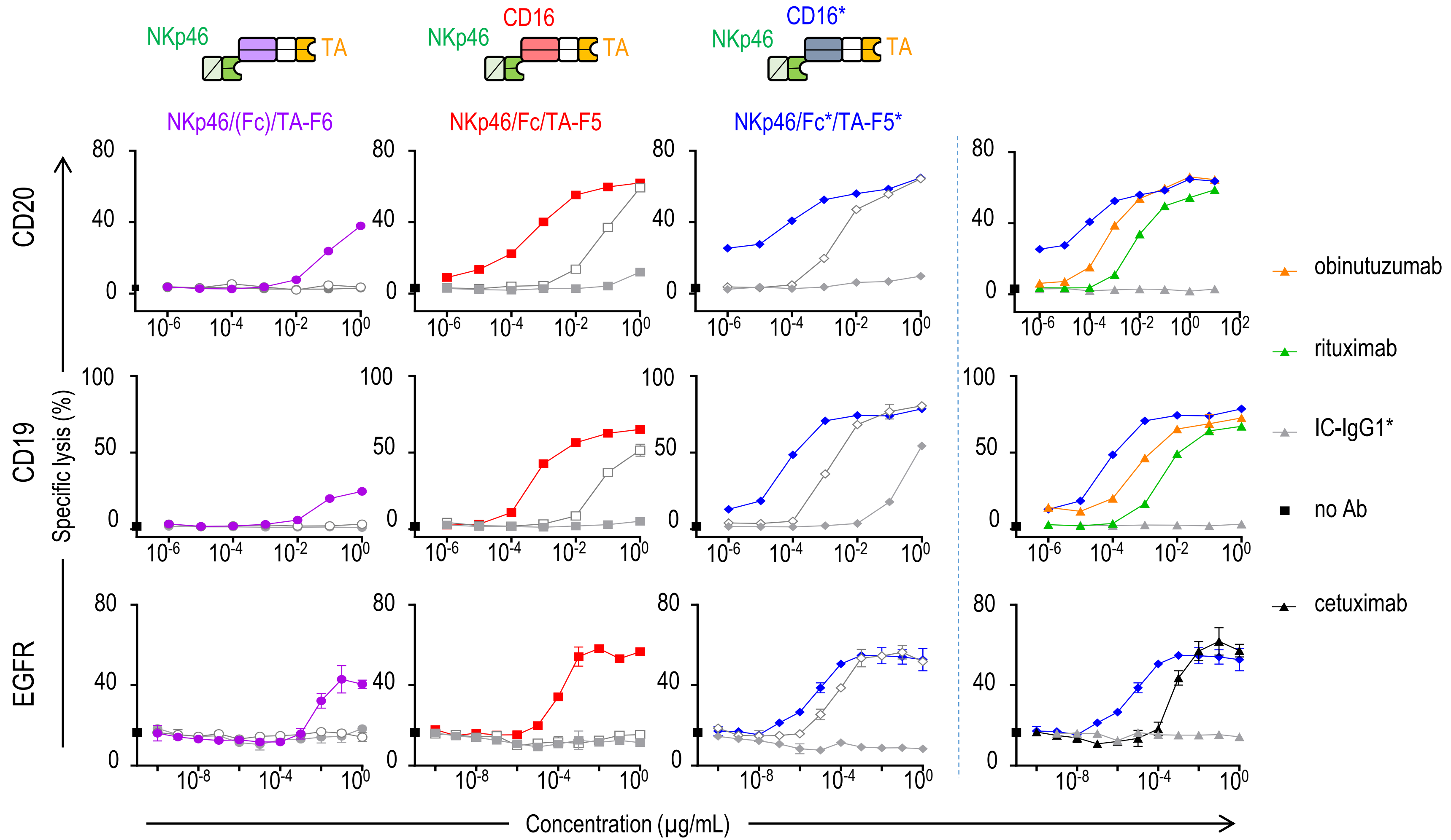
Comparing mouse and human data

(65-75 Mya differences between mice and humans)

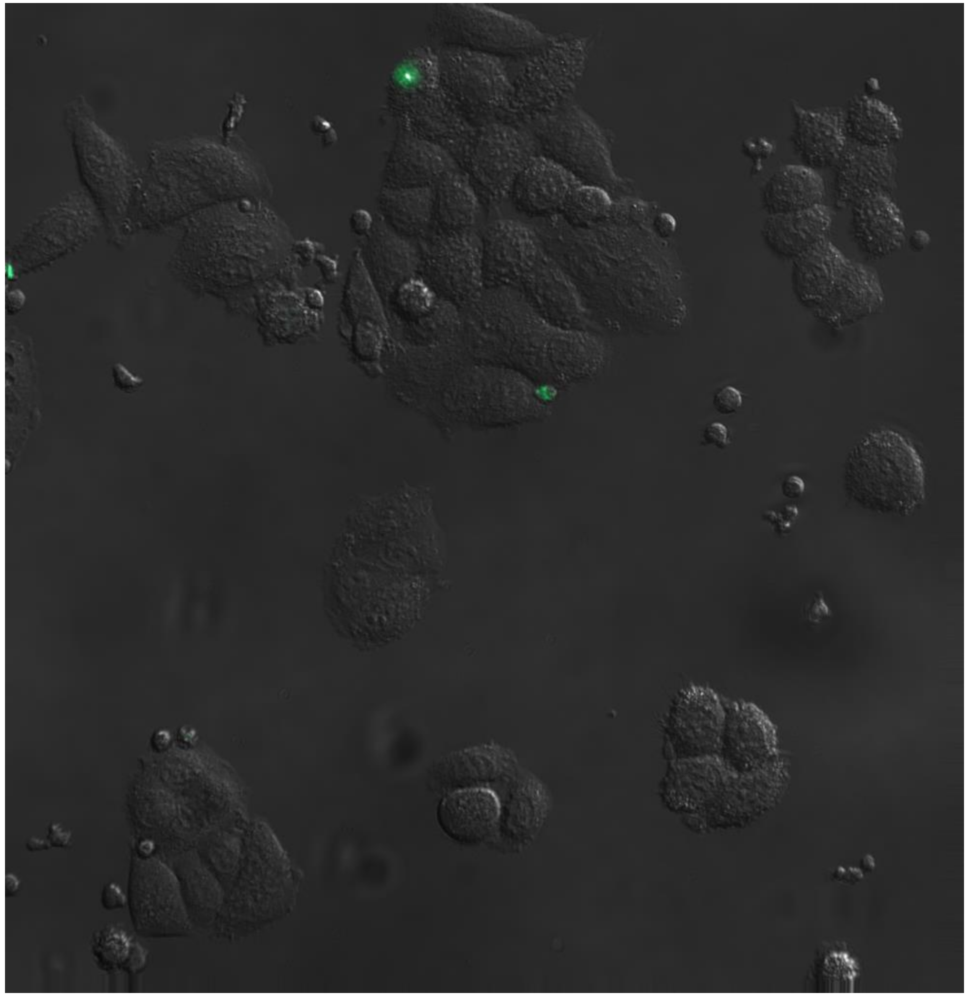


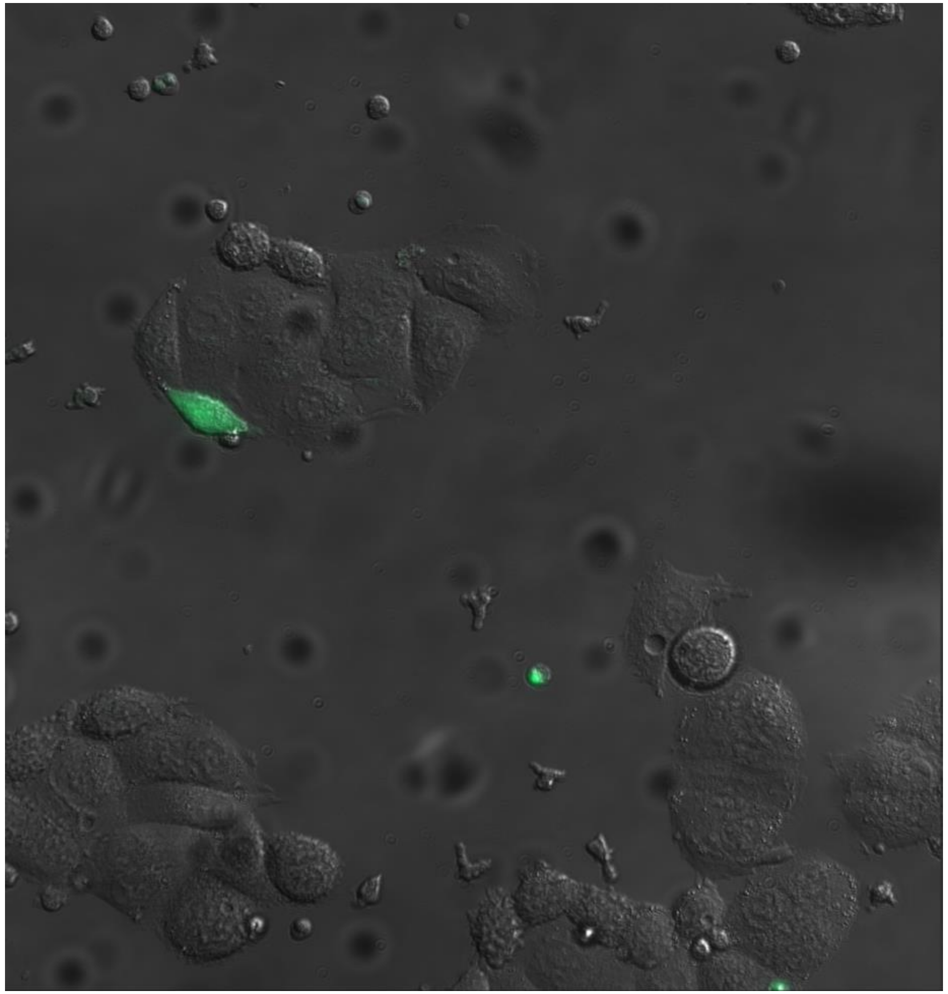

Anti-NKp46
antibody
Anti-tumor antigen
antibody

Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs



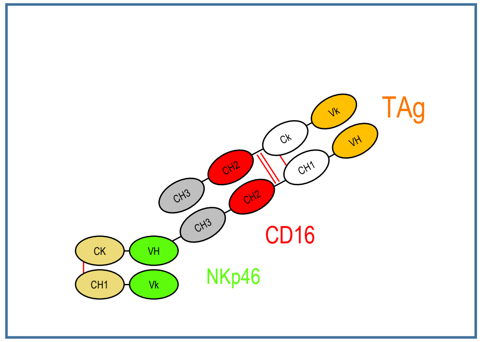
NKp46 NK cell engagers

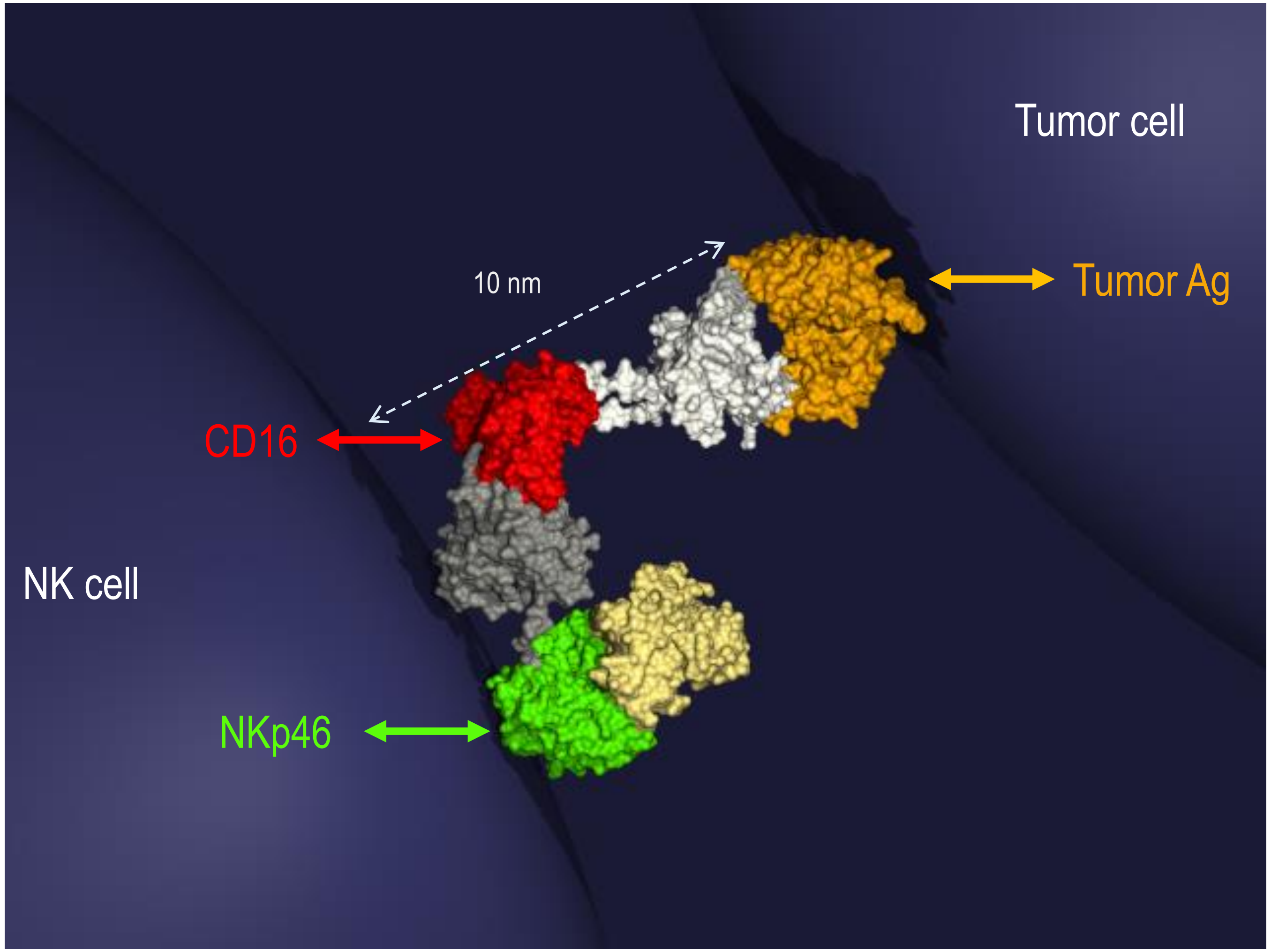


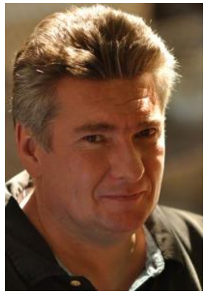


Video-microscopy: Mathieu Fallet / Sébastien Mailfert / CIML / CNRS / France Bio-Imaging

NKp46 NK cell engagers







Gauthier et al., Cell 2019

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

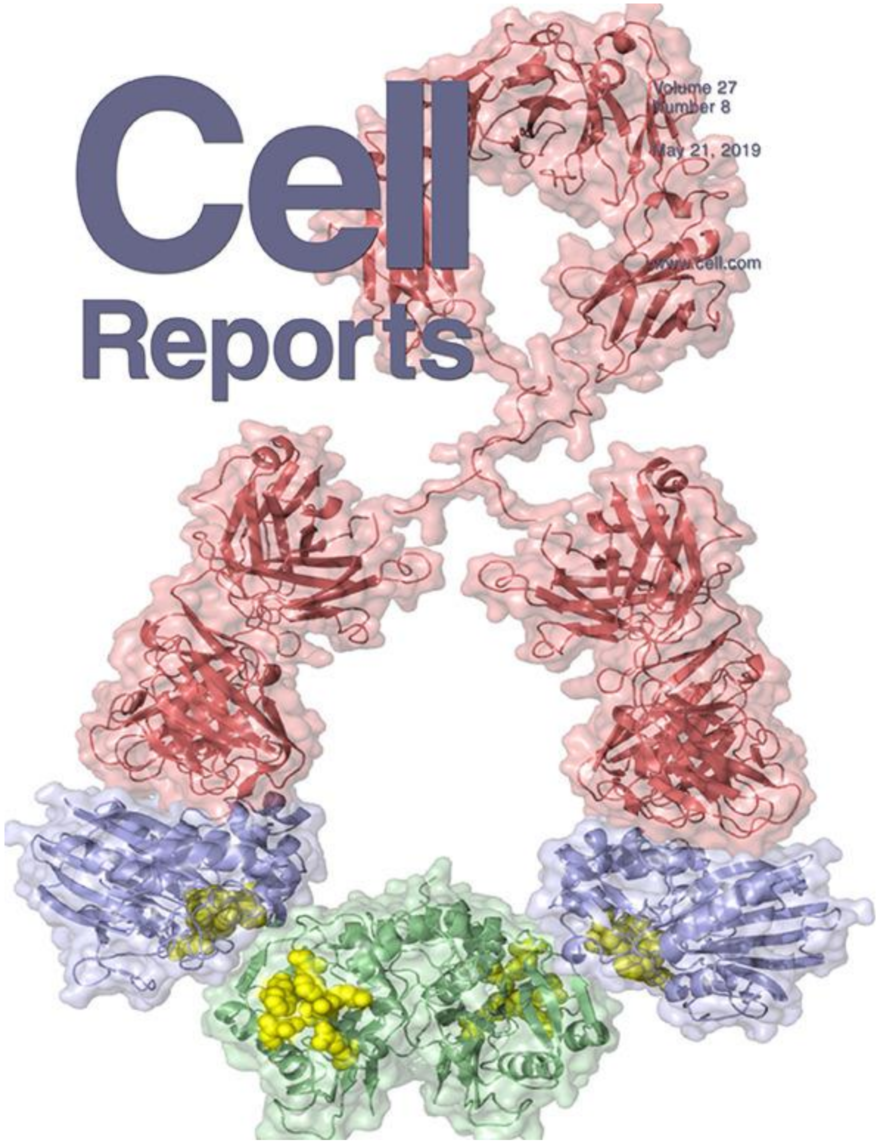
1	2	3
Immune Checkpoints **MONALIZUMAB**	Tumor Targeting **NK CELL ENGAGERS**	Tumor microenvironment **ADENOSINE**
André et al., Cell 2018	*Gauthier et al., Cell 2019*	*Perrot, Paturel et al., Cell Reports 2019*

Cell Reports

Article

Blocking Antibodies Targeting the CD39/CD73 Immunosuppressive Pathway Unleash Immune Responses in Combination Cancer Therapies

Perrot, Paturel et al., 2019



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

- IPH5301, a CD73 blocking antibody targeting the adenosine immunosuppressive pathway for cancer immunotherapy, Poster P323
  Friday November 8 | 12:30 - 2 pm & 6:30 – 8 pm

- IPH5201, a blocking antibody targeting the CD39 immunosuppressive pathway, unleashes immune responses in combination with cancer therapies, Poster P488
  Saturday November 9 | 12:35 - 2:05 pm & 7 - 8:30 pm

- IPH5401 anti-human C5aR antibody targets suppressive myeloid cells in the TME, Poster P268
  Saturday November 9 | 12:35 - 2:05 pm & 7 - 8:30 pm

- Multifunctional natural killer cell engagers targeting NKp46 trigger protective tumor immunity, Poster P776
  Saturday November 9 | 12:35 - 2:05 pm & 7 - 8:30 pm

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Marion FABRE
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