THE INNATE IMMUNITY COMPANY

innate pharma

# NEXT GENERATION IMMUNOTHERAPIES: NK CELLS AND OTHER TARGETS

**STEPHANIE CORNEN**

5TH IMMUNOTHERAPY OF CANCER CONFERENCE (*ITOC5*) MARCH 2018

IPH LISTED EURONEXT

afaq ISO 9001 Qualité AFNOR CERTIFICATION

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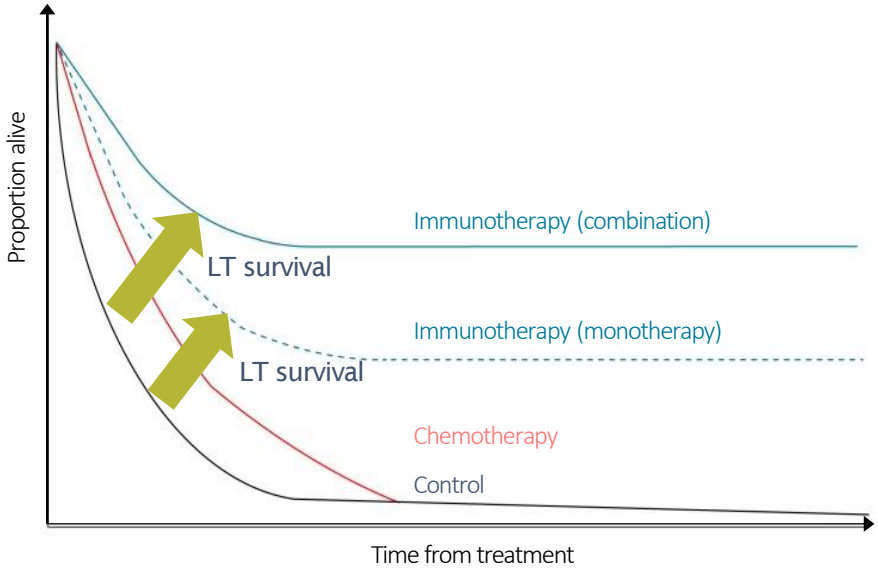
# THE IMMUNO-ONCOLOGY (IO) REVOLUTION



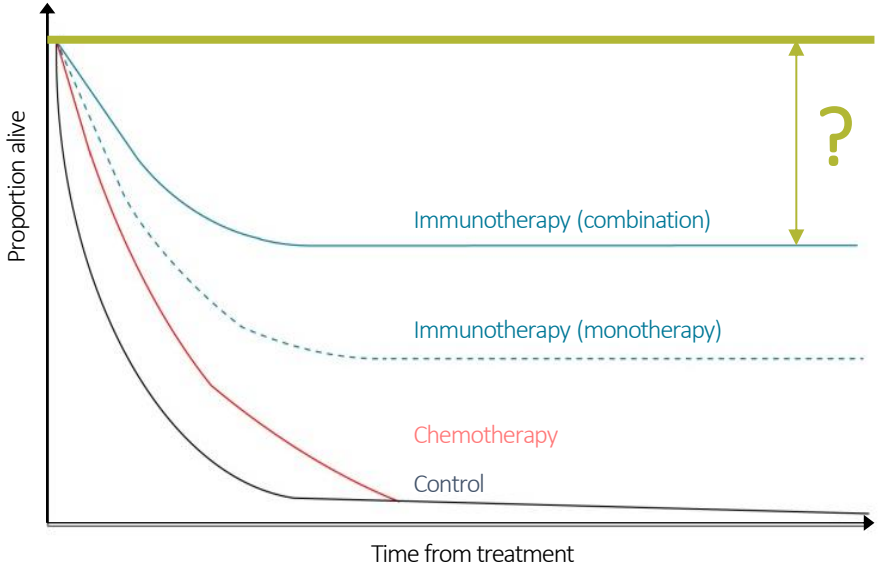

**Immune Checkpoint Inhibitors**

anti-CTLA4

anti-PD1

anti-PD-L1

# WHAT'S NEXT IN IO?

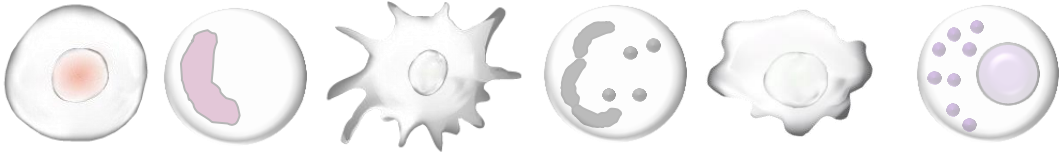



- Increase the fraction of patients sensitive to IO treatments
- Understand the acquired resistance to Immune Checkpoint Inhibitors
- Decrease toxicity

**Identify new targets (<u>cells</u> and <u>molecules</u>)**
**Identify biomarkers**

# THE IMMUNE SYSTEM

**CHALLENGES**
- **Microbial infections**
- **Tumors**



NK | Innate lymphoid cells Groups 1, 2, 3 | Dendritic cells | Neutrophils Eosinophils Basophils | Monocytes Macrophages | Mastocytes

**INNATE IMMUNITY**

- **Hours**
- **Whole body**

**EFFECTOR RESPONSE**

Naïve B&T cells

- **Days**
- **From lymphoid organs**

**ADAPTATIVE IMMUNITY**

# NEXT GENERATION IO

## 3 STRATEGIC KEY PILLARS TO HARNESS THE POTENTIAL OF IMMUNITY

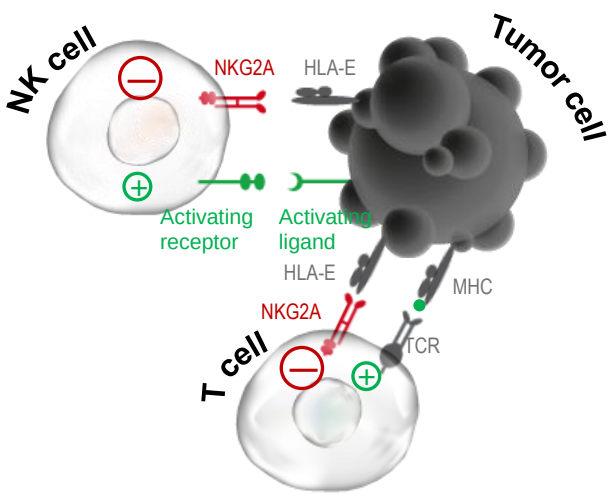
| 1 | 2 | 3 |
|---|---|---|
| NK cells checkpoints (NKCP) | Tumor targeting (TAg) | Tumor Microenvironment (TME) |

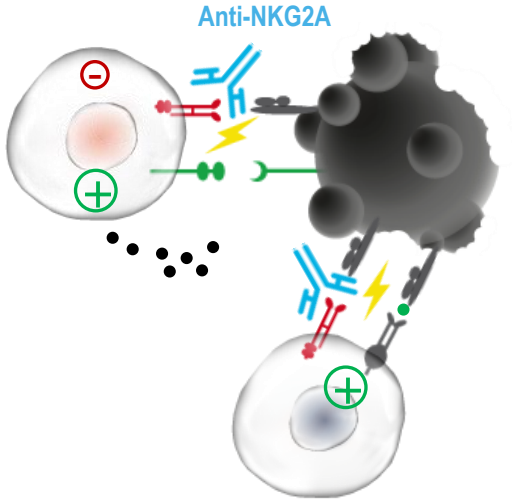
# INNATE PHARMA – PIPELINE
## FIRST-IN-CLASS IO ASSETS

| Target Discovery | Drug Discovery | Preclinical | Dose finding | Signal detection | Pivotal |
|---|---|---|---|---|---|
| ~20 targets or concepts under exploration | Anti-Siglec-9 | **IPH52** Anti-CD39 | **IPH5401** Anti-C5aR | **Monalizumab** Anti-NKG2A | |
| | SAN-NKCE-2 | **IPH53** Anti-CD73 | | **Lirilumab** Anti-KIR2DL1,2,3 | |
| | Other undisclosed targets | **IPH4301** Anti-MICA/B | | **IPH4102** Anti-KIR3DL2 | |
| | | **IPH61** SAN-NKCE-1 | | | |

# ANTI-NKG2A IS A NOVEL IMMUNE CHECKPOINT INHIBITOR IN CANCER

- Monalizumab (IPH2201) is a first-in-class anti-NKG2A humanized blocking antibody

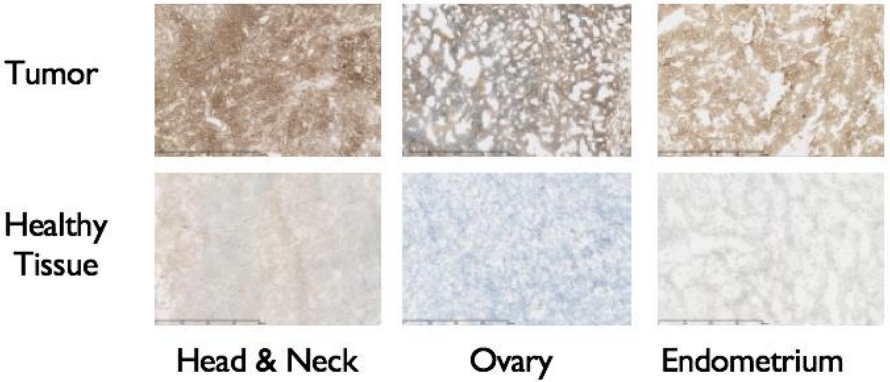


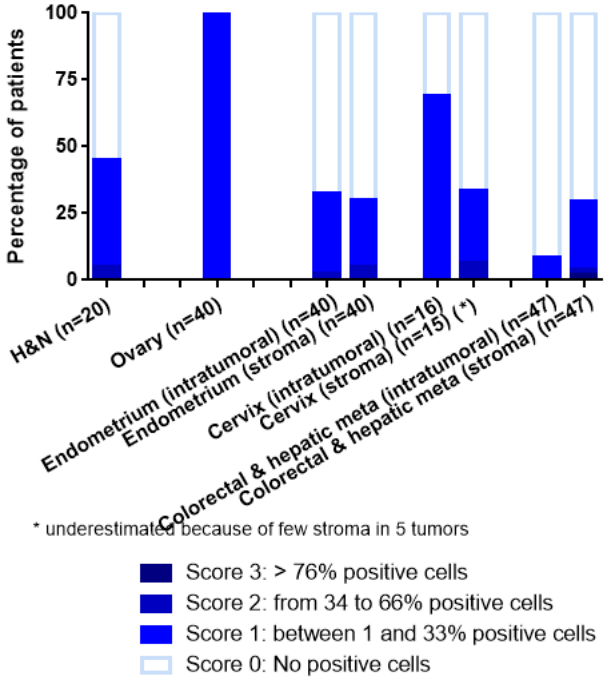

**NK cell and T cell inhibition by NKG2A** + **Activation by NKG2A blockade**

# NKG2A / HLA-E PATHWAY IS UPREGULATED IN TUMORS

## HLA-E on tumor cells

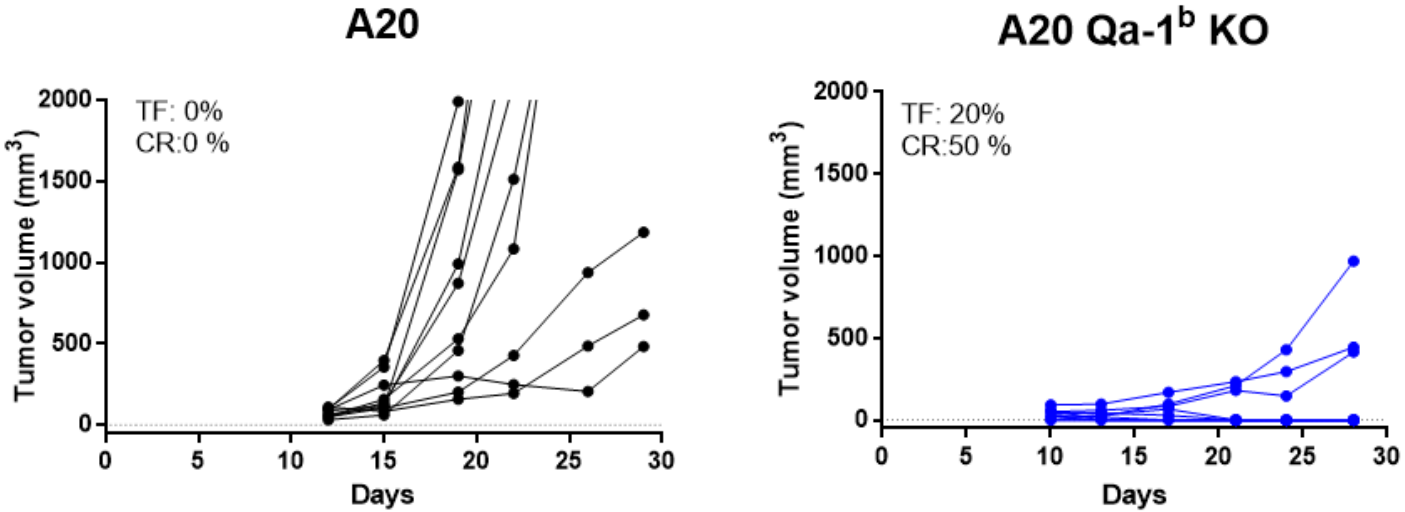



## NKG2A on TILs




***André et al. unpublished***

# NKG2A/$Q_A$-1$^b$ CONTROL TUMOR GROWTH

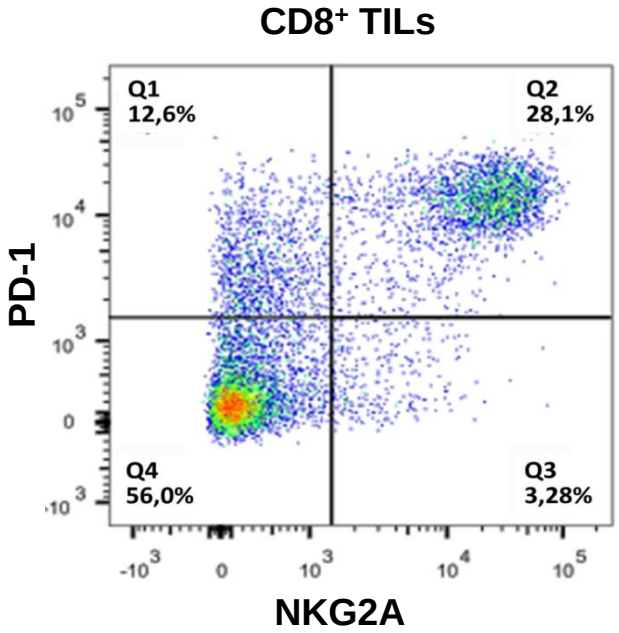



**Individual A20 and A20 Qa-1$^b$ KO tumor growth after sub-cutaneous engraftment of 5x10$^6$ A20 tumor cells (n=10) in BALB/C mice.**

TF: Tumor Free, CR: Complete Regression

***André et al. unpublished***

# PD-1$^{HIGH}$ CD8$^{+}$ TILS CO-EXPRESS NKG2A

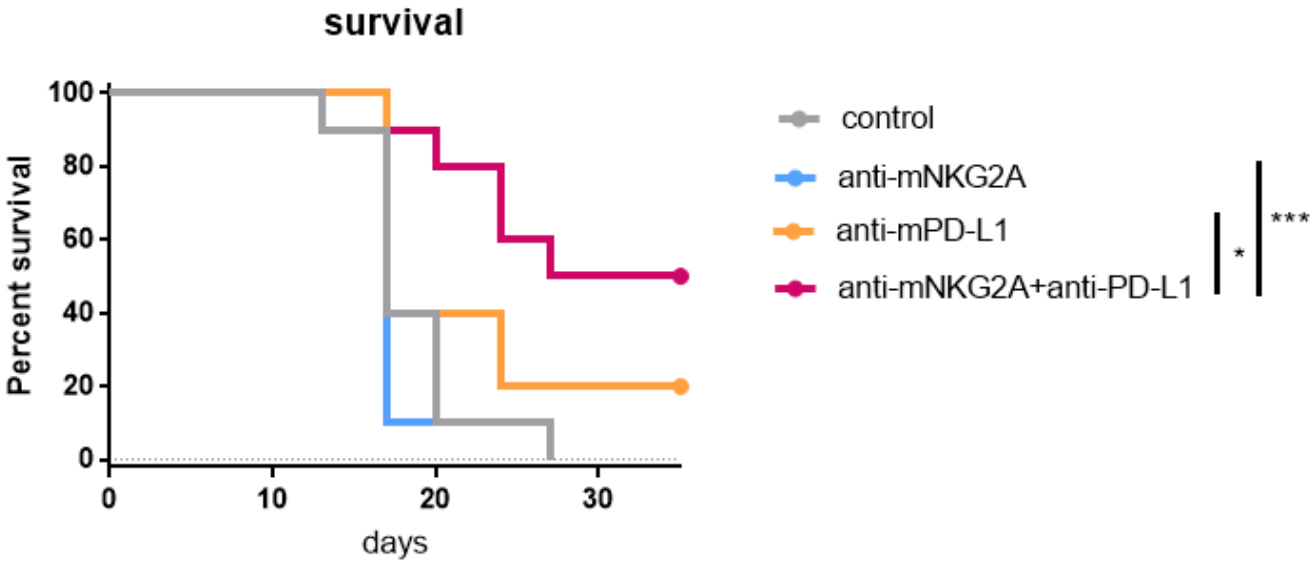



**Expression of NKG2A and PD-1 on isolated CD8$^{+}$ TILs (day 20)**

**A20 B cell lymphoma into BALB/C mice**

***André et al. unpublished***

# NKG2A BLOCKADE INCREASES PD-L1 ANTI-TUMORAL EFFICACY



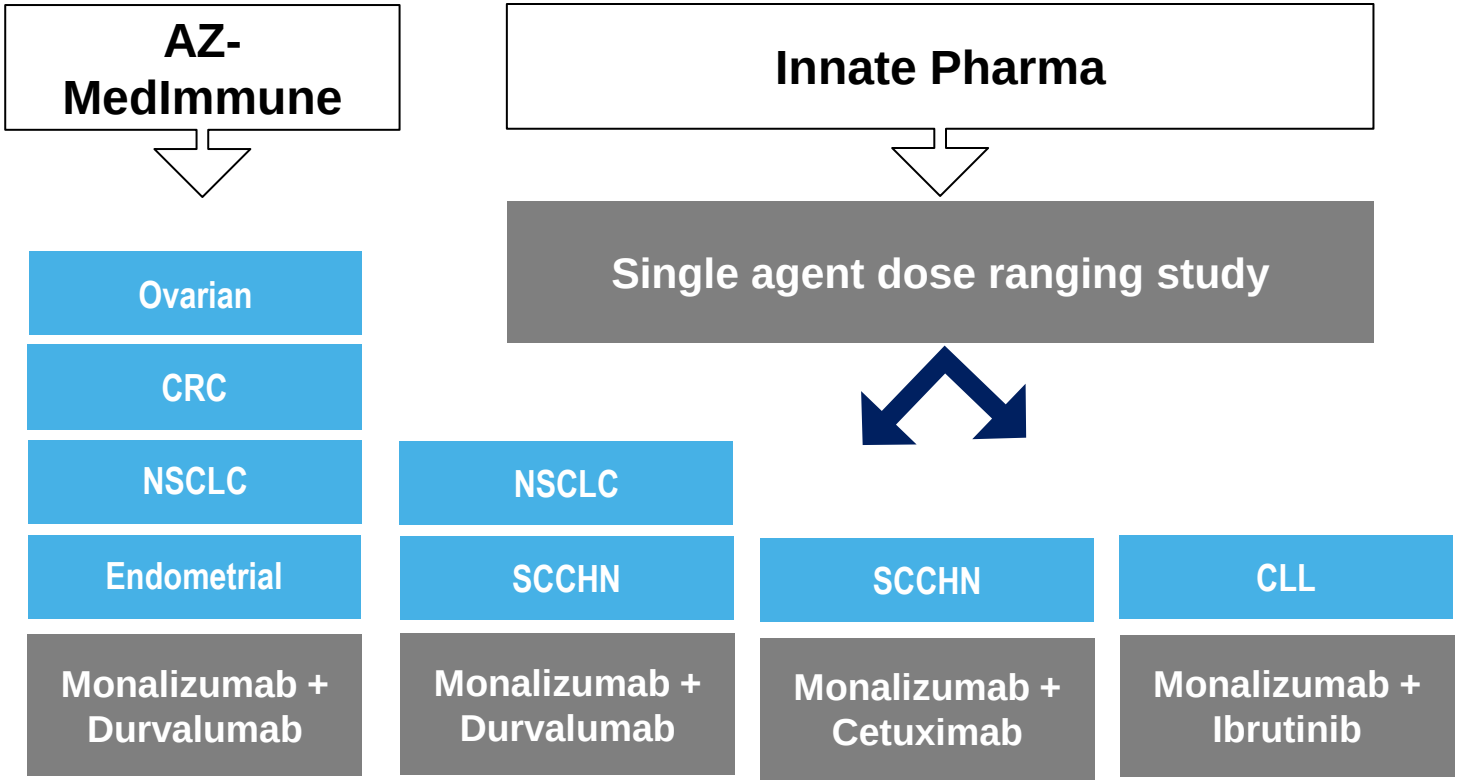

**RMA-Rae1 into B6 mice**

**P=0.03 (*), P=0.0006 (***), Grehan-Breslow-Wilcoxon test**

***André et al. unpublished***

# MONALIZUMAB – JOINT CLINICAL DEVELOPMENT PLAN

## FOCUS ON COMBINATIONS



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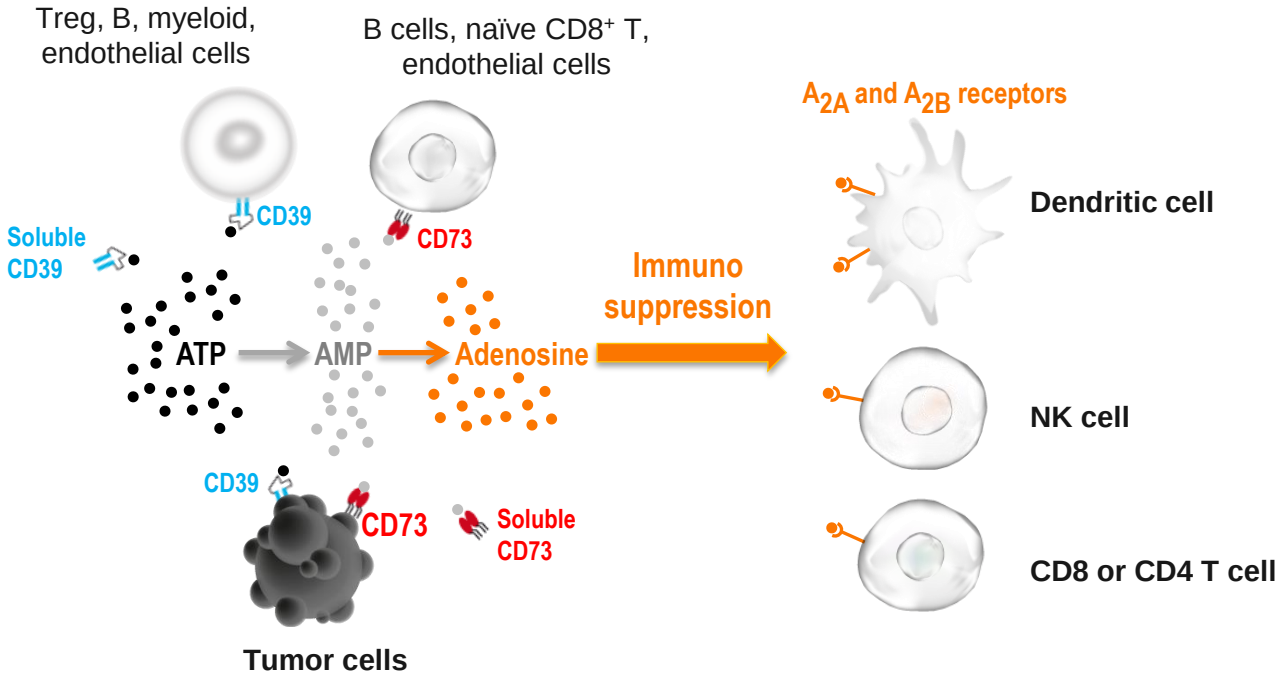
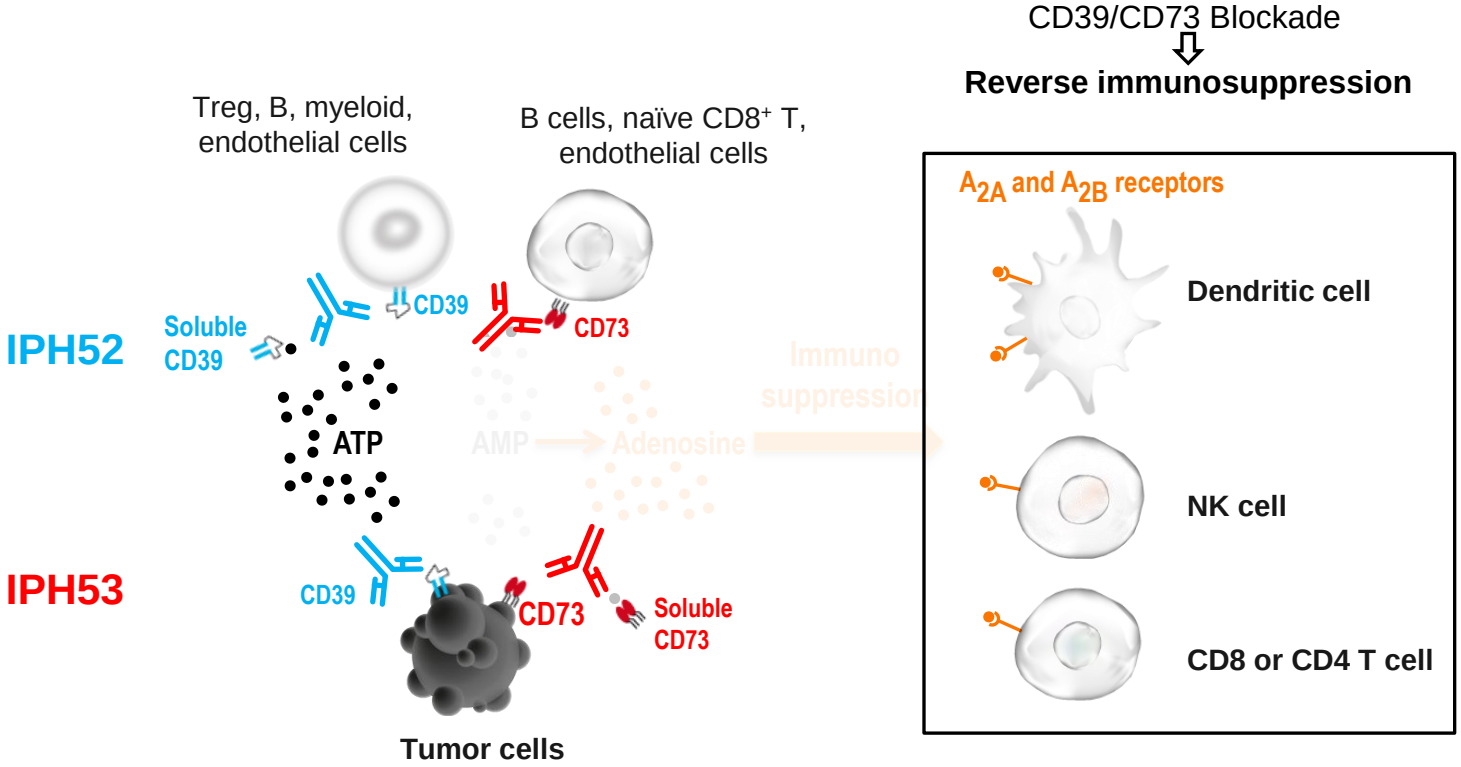
| | | **IPH61** SAN-NKCE-1 | | | |

# ATP/ADENOSINE PATHWAY



# BLOCKING ANTI-CD39 (IPH52) AND ANTI-CD73 (IPH53) ABS TO RESTORE ANTI-TUMOR IMMUNITY



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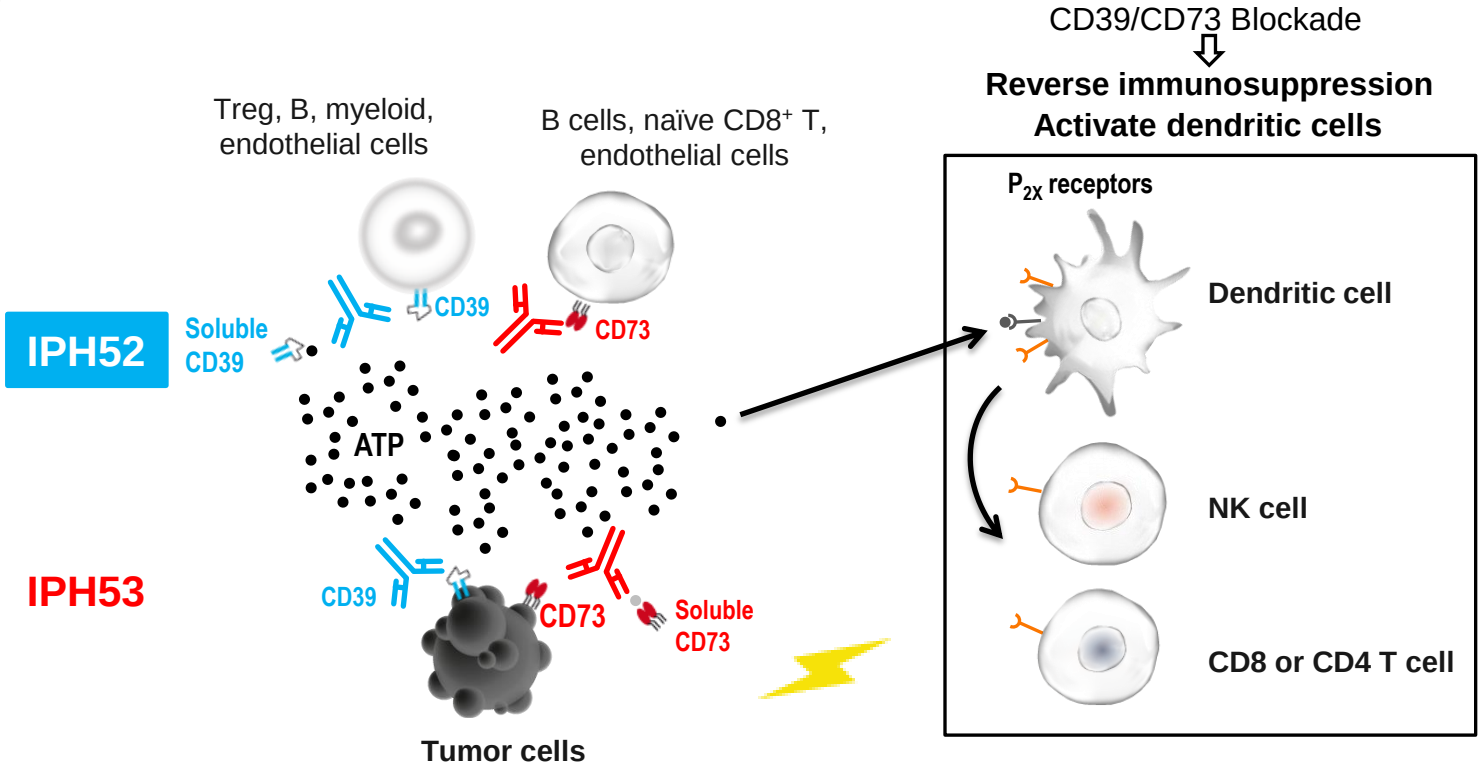
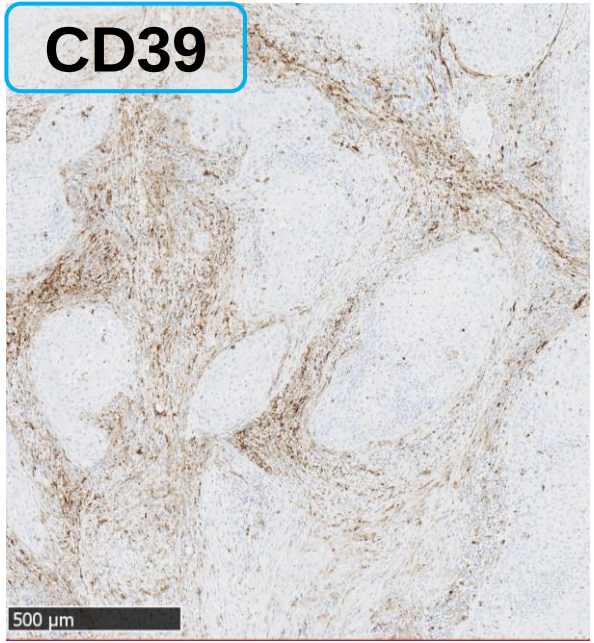
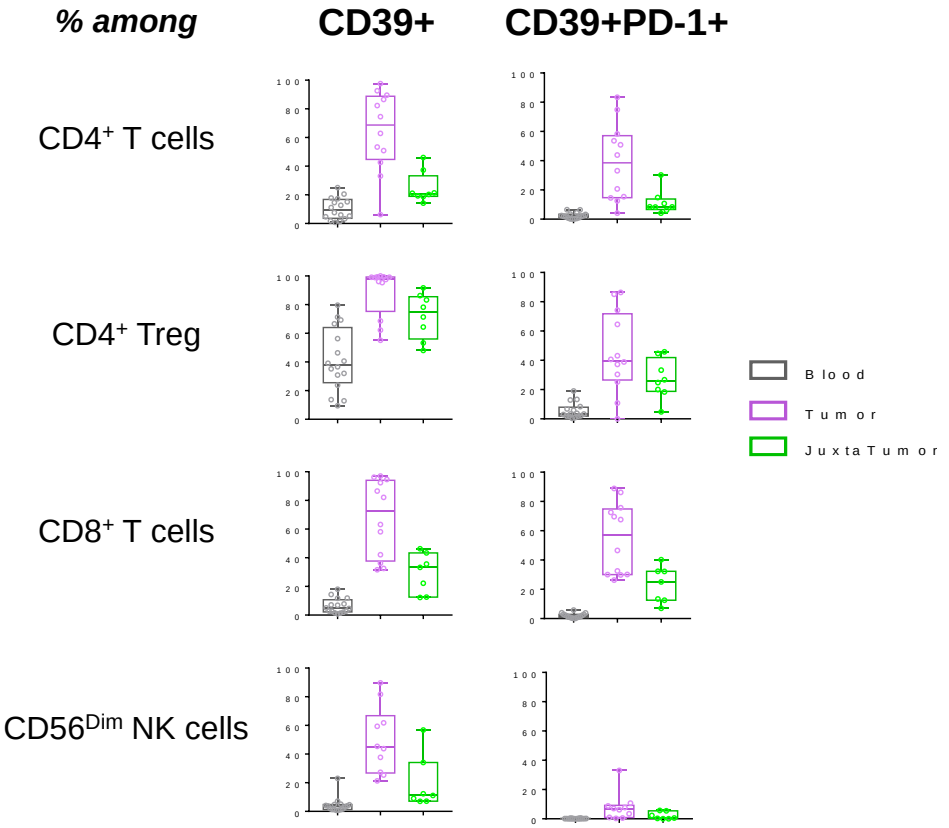


# CD39 EXPRESSION IN HEAD AND NECK TUMORS



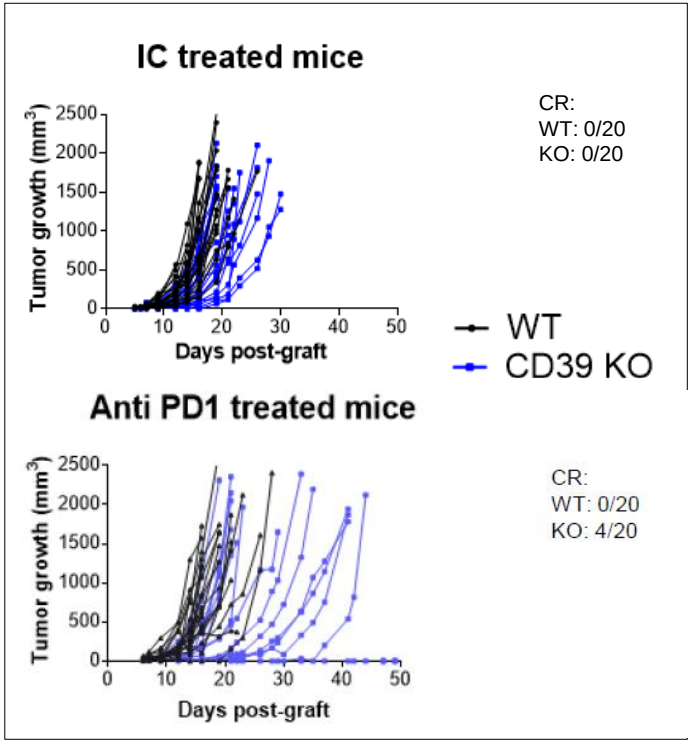

CD39 expression on endothelial cells and immune cells



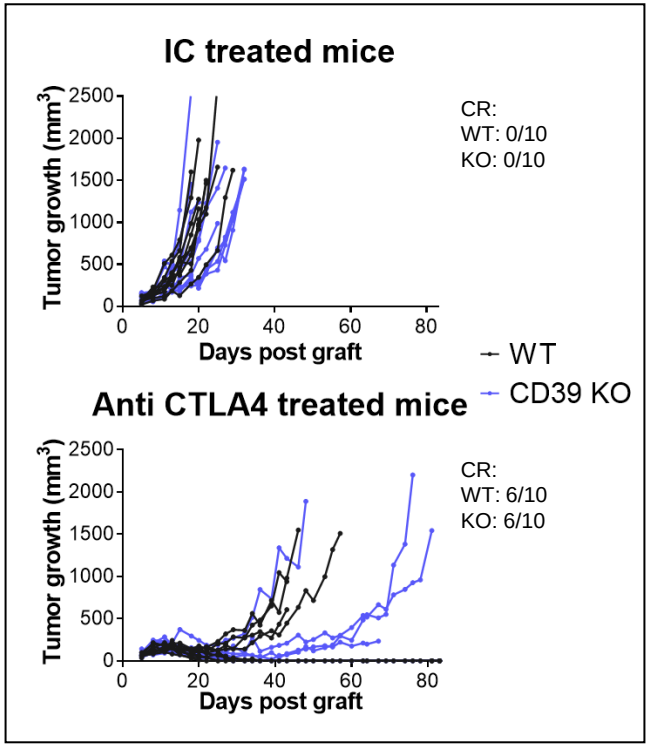

*Perrot, Paturel, Bonnefoy et al. unpublished*

# CD39 DELETION IMPROVES ICI ANTI-TUMOR EFFICACY

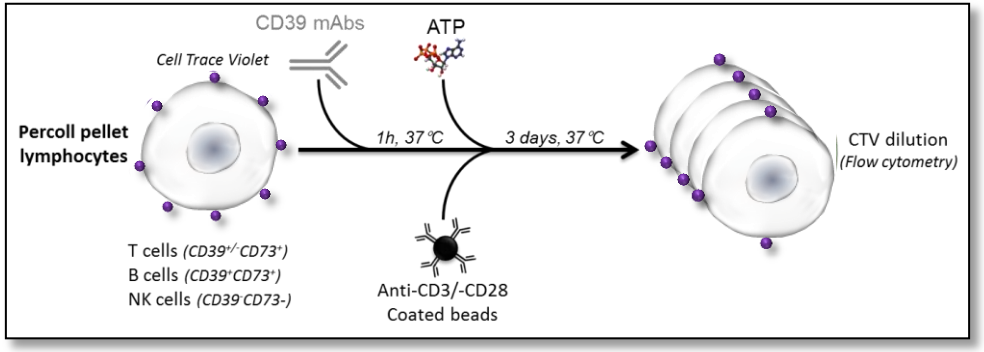
## B16 model

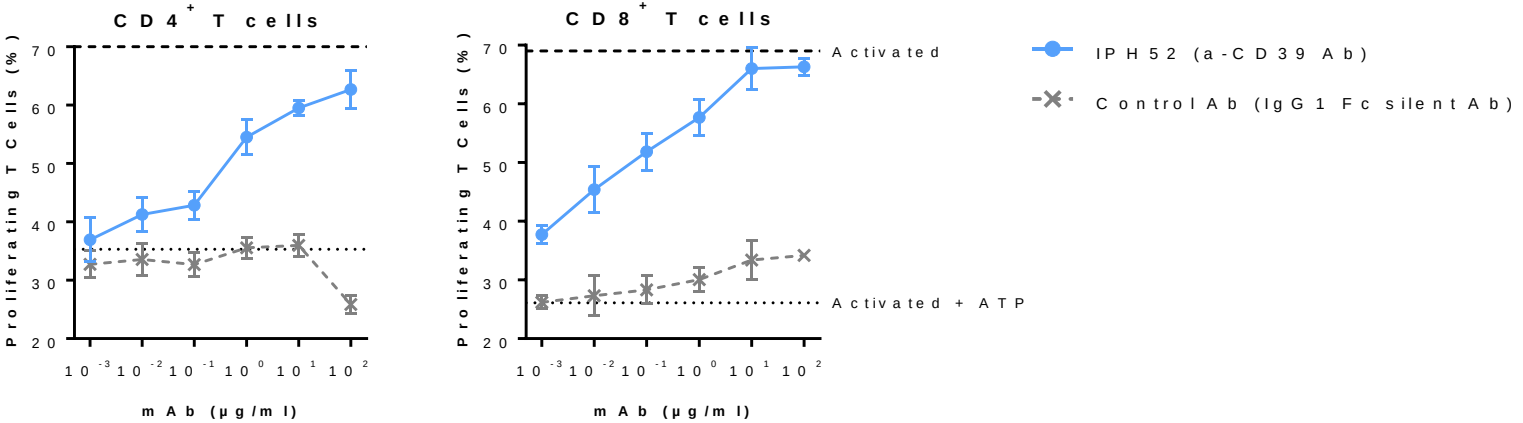



## MCA205 model



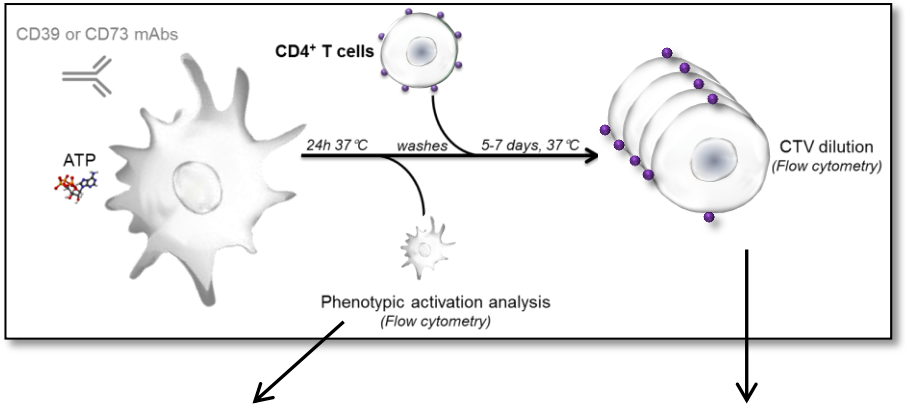
# IPH52 (a-CD39) REVERSES ATP-MEDIATED T CELL SUPPRESSION IN VITRO

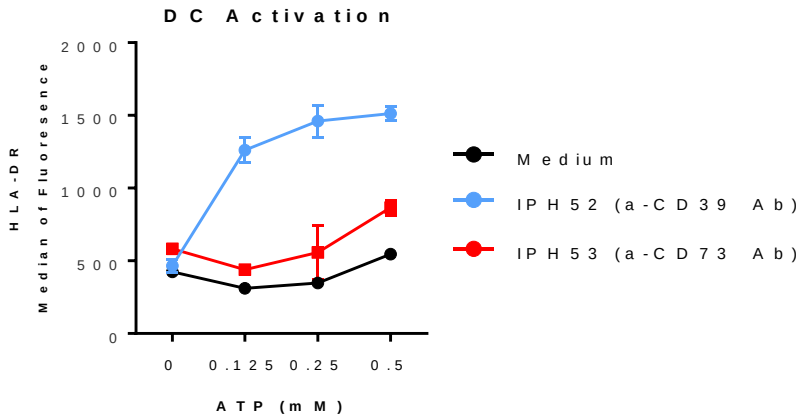


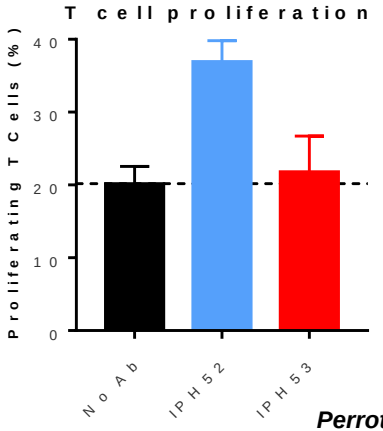




*Perrot, Paturel, Bonnefoy et al. unpublished*

# IPH52 (a-CD39) ENHANCES ATP-DEPENDENT DC ACTIVATION

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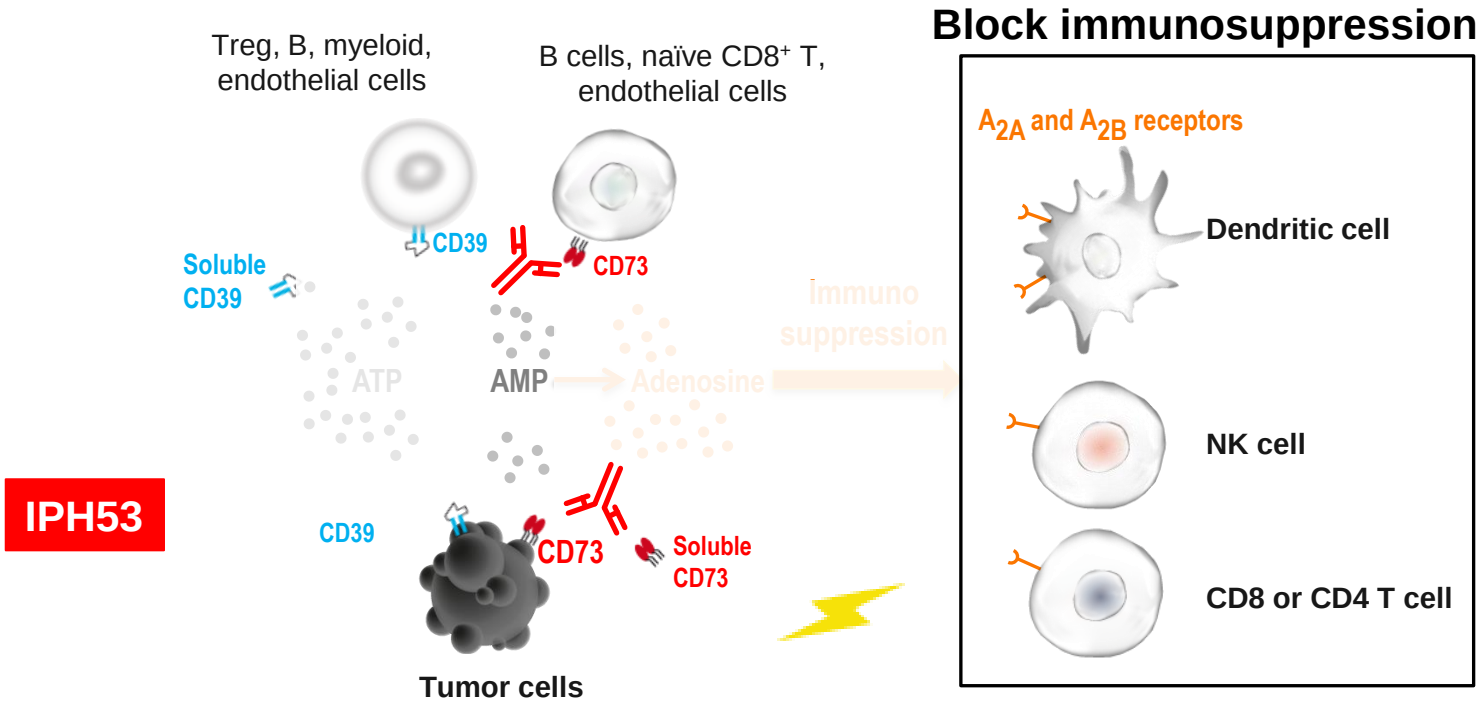
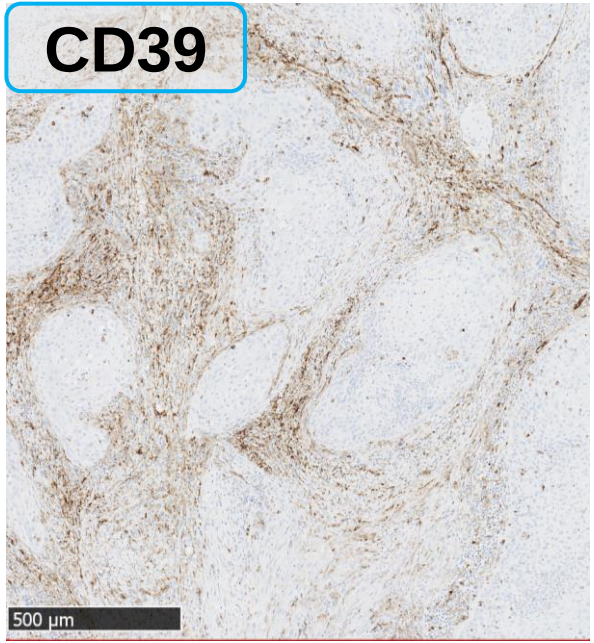
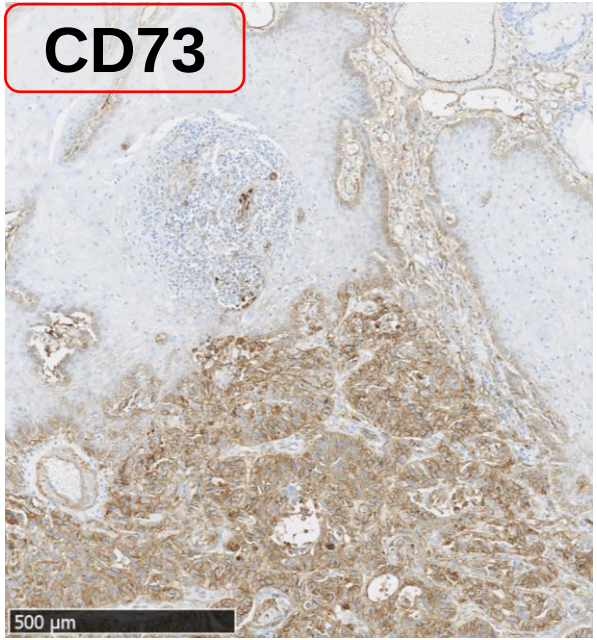
# BLOCKING ANTI-CD73 (IPH53) ABS TO RESTORE ANTI-TUMOR IMMUNITY



# CD39 AND CD73 EXPRESSION IN HEAD AND NECK TUMORS



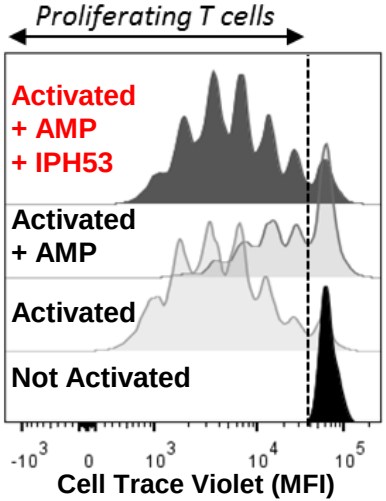

CD39 expression on vascular endothelial cells and immune cells

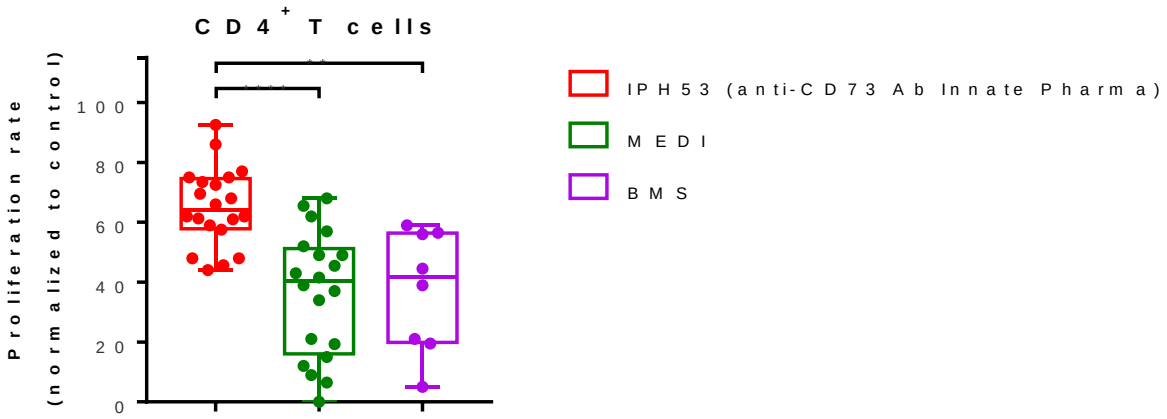



CD73 expression on vascular endothelial cells, immune and tumor cells

***Perrot, Paturel, Bonnefoy et al. unpublished***

# IPH53 (a-CD73) IS MORE POTENT THAN COMPETITION ABS TO REVERSE AMP-MEDIATED T CELL SUPPRESSION




*This program is developed within the TumAdoR project (www.tumador.eu), coordinated by Dr C. Caux (Centre Léon Bérard and Centre de Recherche en Cancérologie, Lyon, France), and funded under the European Community's seventh framework Program (European Community's Seventh Framework Program (FP7/2007-2013) under grant agreement n °602200).*

***Perrot, Paturel, Bonnefoy et al. unpublished***

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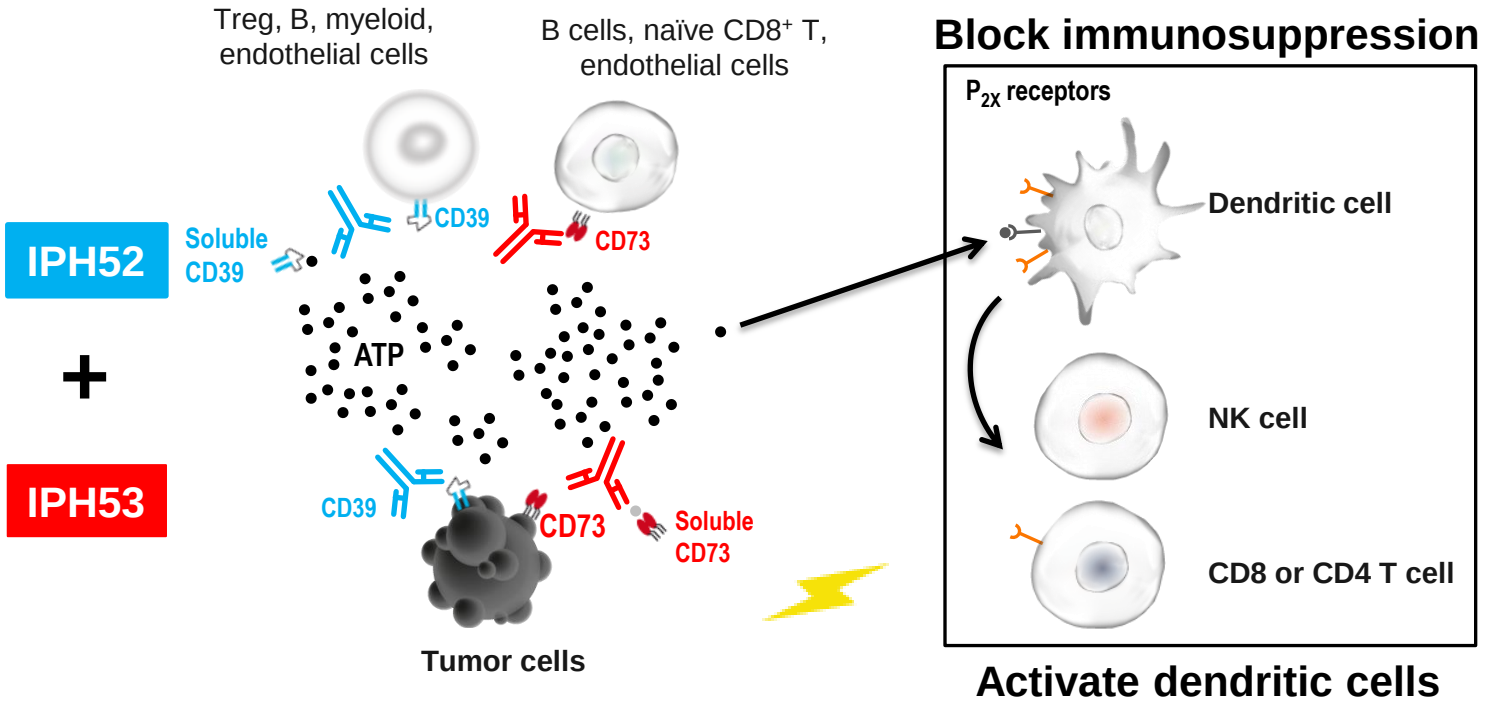
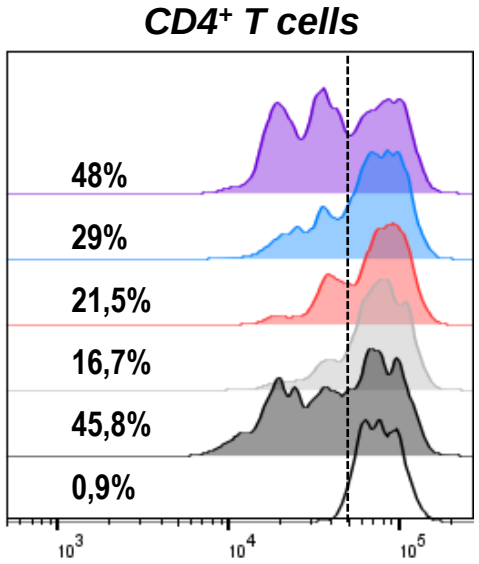
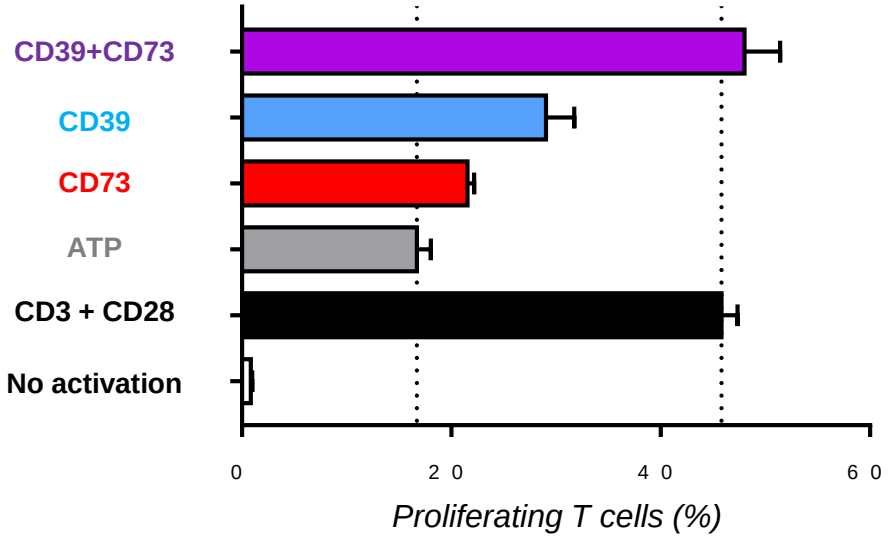


# CD39/CD73 BLOCKADE SYNERGIZE TO REVERSE ATP-MEDIATED T CELL SUPPRESSION



# CONCLUSION ON ANTI-CD39 AND ANTI-CD73 AB IPH PROGRAMS

## **IPH52** (Anti-CD39)

- Humanized Fc-silent IgG1 antibody
- Unique Ab blocking membrane and soluble CD39
- *In vitro* evidence of blockade of Adenosine suppression and increase of ATP stimulation
- *In vivo* POC in KO mice with PD-1, CTLA-4 and chemotherapy
- Evidence of CD39 up-regulation on TILs in patients

## **IPH53** (Anti-CD73)

- Humanized Fc-silent IgG1 antibody
- Blocking membrane and soluble CD73, no receptor down modulation
- Differentiated and superior *in vitro* to MEDI and BMS Phase I Abs
- Target validated in preclinical models
- CD73 expression on tumor cells is of bad prognosis

In conclusion, our results warrant the development of both therapeutic blocking anti-CD39 and anti-CD73 mAb targeting the tumor microenvironment.

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