MUNICH 2018 ESMO congress

CHANGES IN THE INNATE IMMUNE SYSTEM AS EARLY EVENTS IN CANCER

Lymphoid cells, Myeloid cells, Tumor microenvironment

Eric Vivier

Innate – Pharma

Aix Marseille Université – Assistance Publique Hôpitaux de Marseille

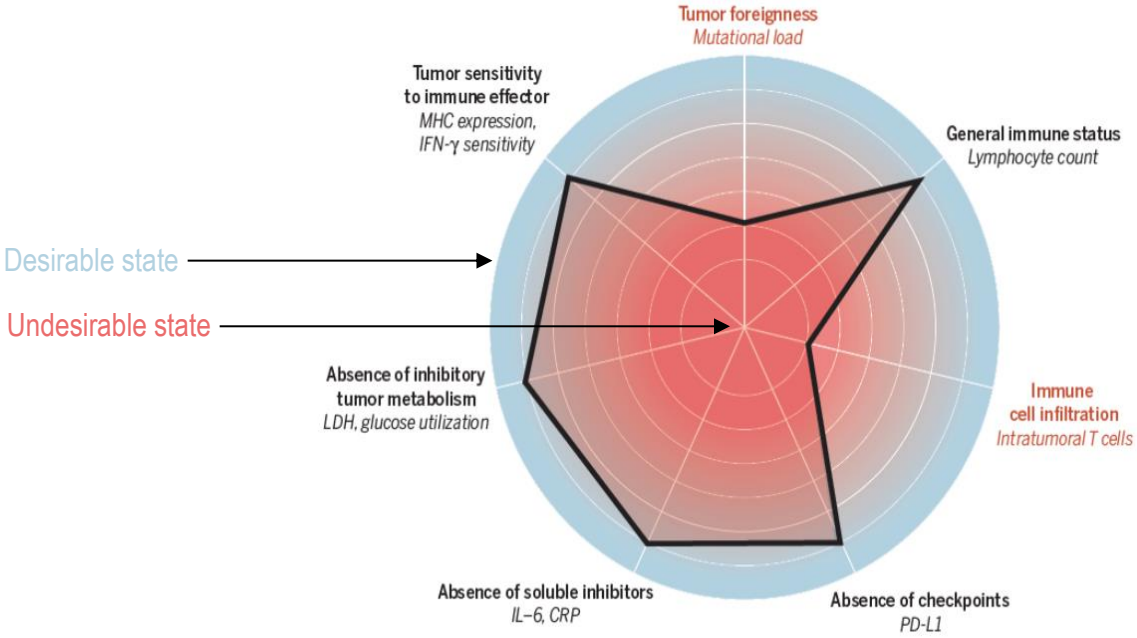
Special Symposium: Early detection of cancer using minimally invasive biomarkers

DISCLOSURE SLIDE

CSO Innate-Pharma

Changes in the immune system are key in cancer

The Immunogram concept



Blank et al., Science 2016

Changes in the immune system in cancer ?

Why is it important?

- Patient stratification
- Pronostic value
- Identification of therapeutic targets

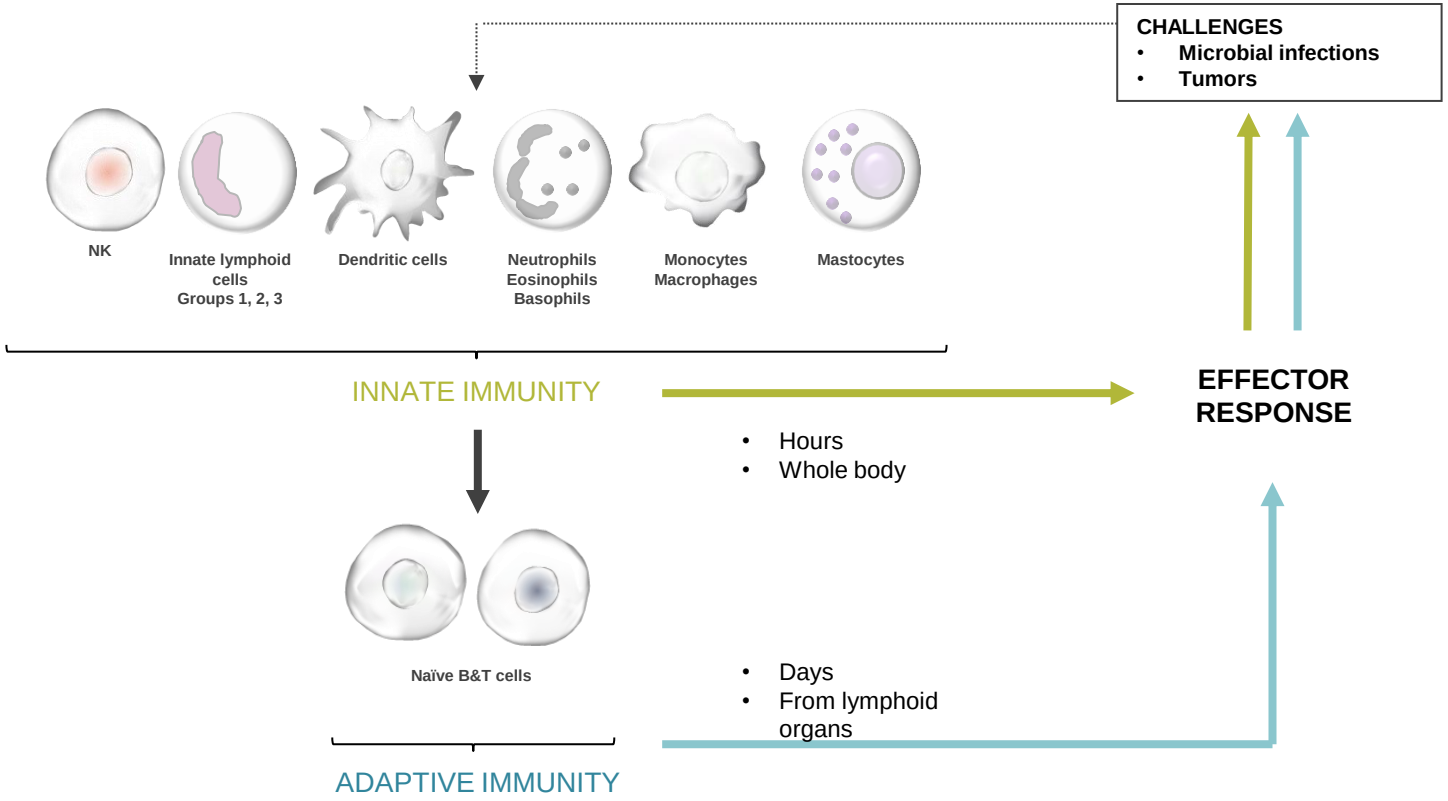
What kind of samples?

- At the tumor bed (solid tumors), and in blood

What kind of technology?

- Genome-wide approaches
- Gene candidate approaches

Changes in the innate immune system in cancer ?



Changes in the innate immune system in cancer ?

Why is it important?

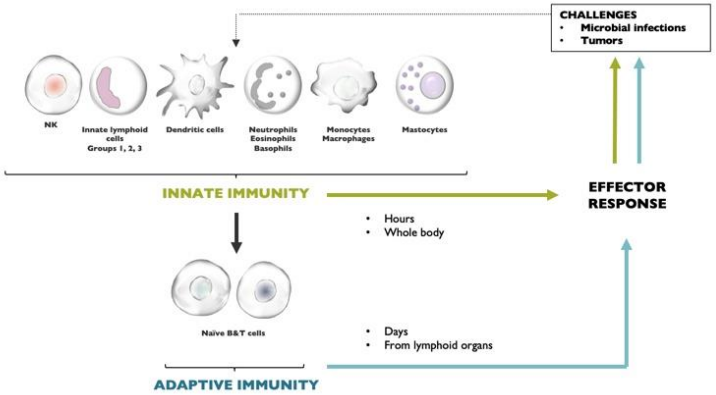
- Identification of therapeutic targets

What kind of samples?

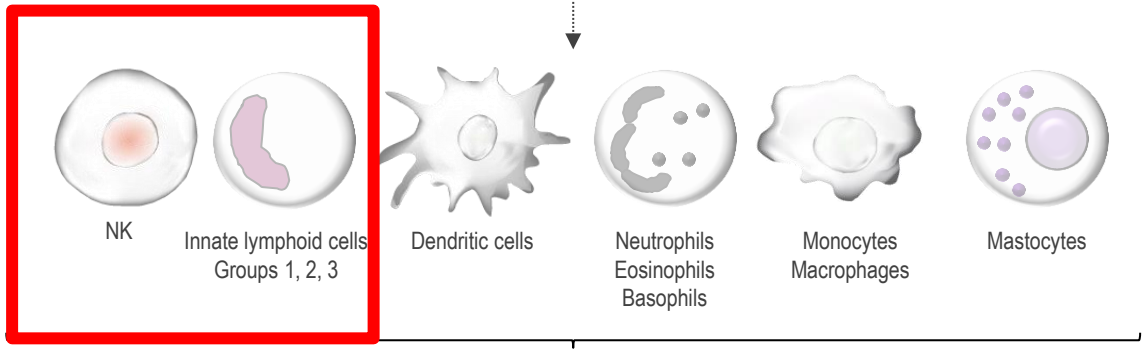
- At the tumor bed and in blood
- In both myeloid cells and lymphoid cells

What kind of technology?

- Genome-wide approaches
- Gene candidate approaches



The immune system



CHALLENGES
- Microbial infections
- Tumors

INNATE IMMUNITY

- Hours
- Whole body

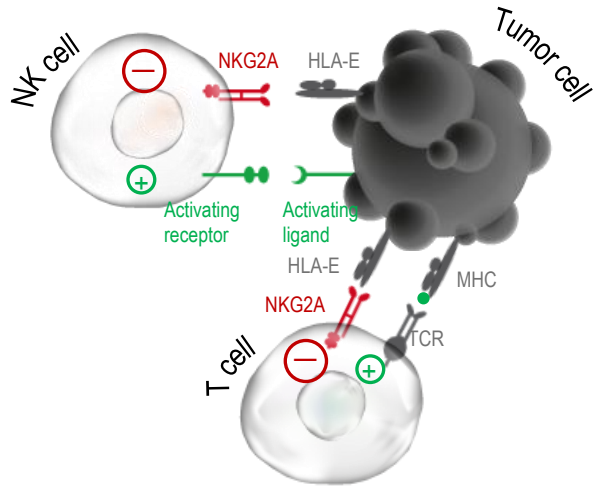
EFFECTOR RESPONSE

Naïve B&T cells

- Days
- From lymphoid organs

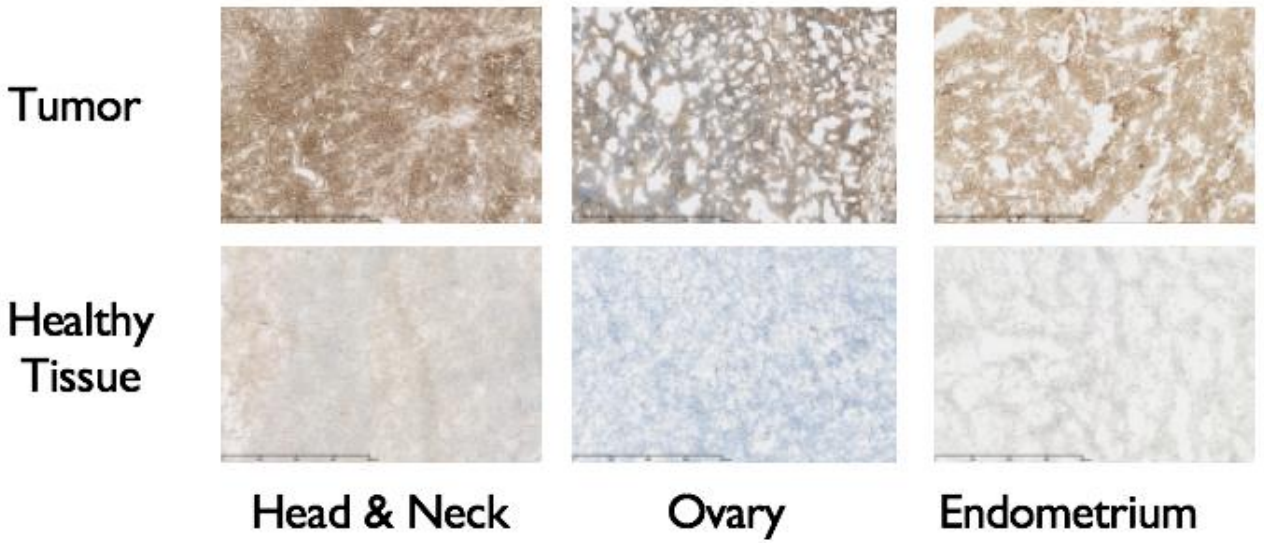
ADAPTIVE IMMUNITY

NKG2A – HLA-E: another inhibitory pathway in cancer

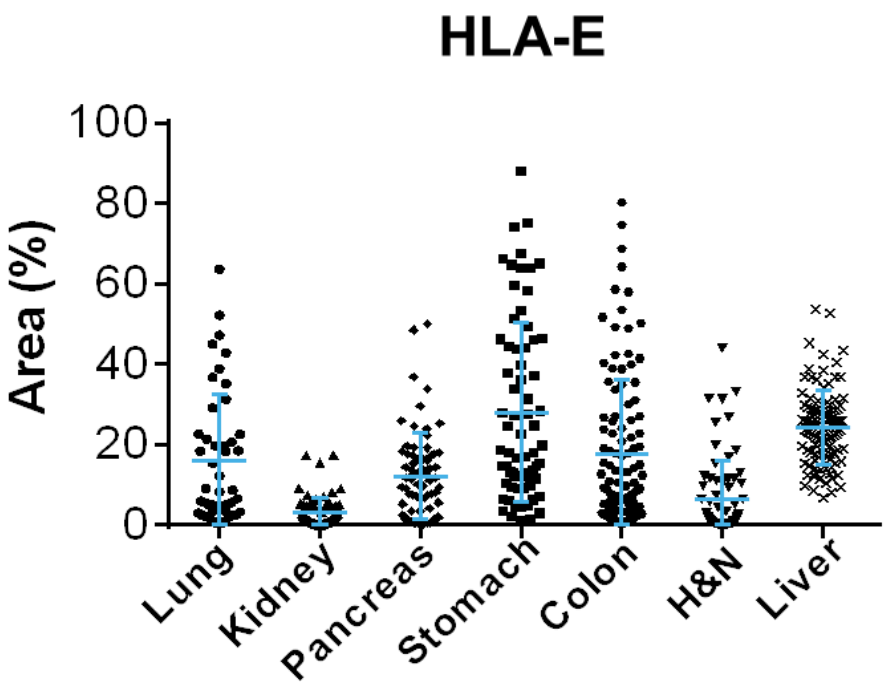


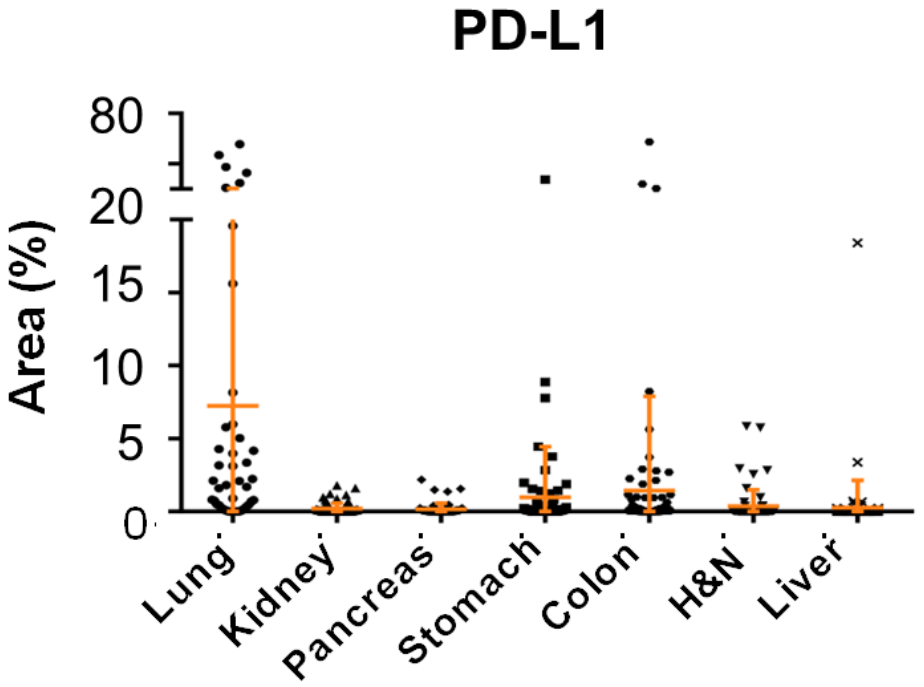
NK cell and T cell inhibition by NKG2A

HLA-E pathway is upregulated in tumors

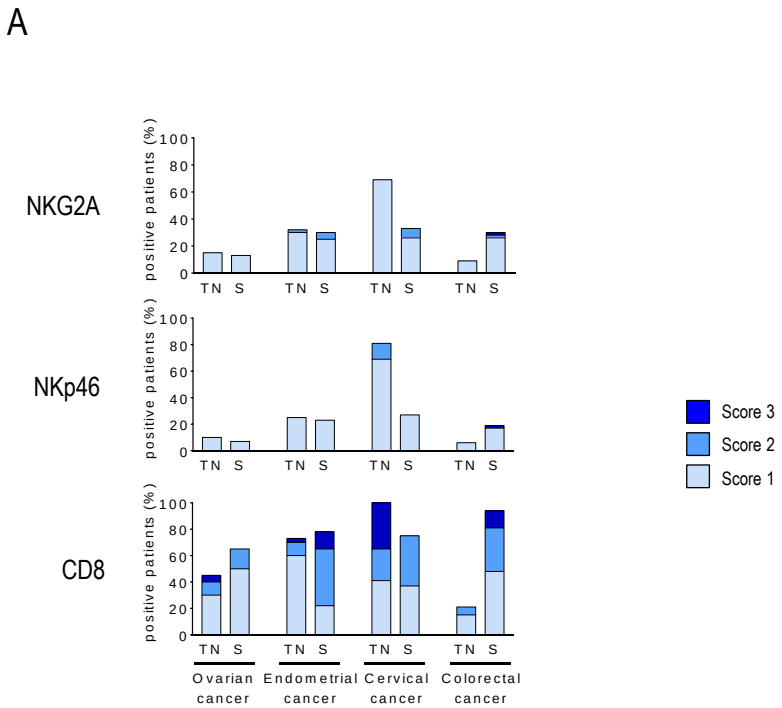


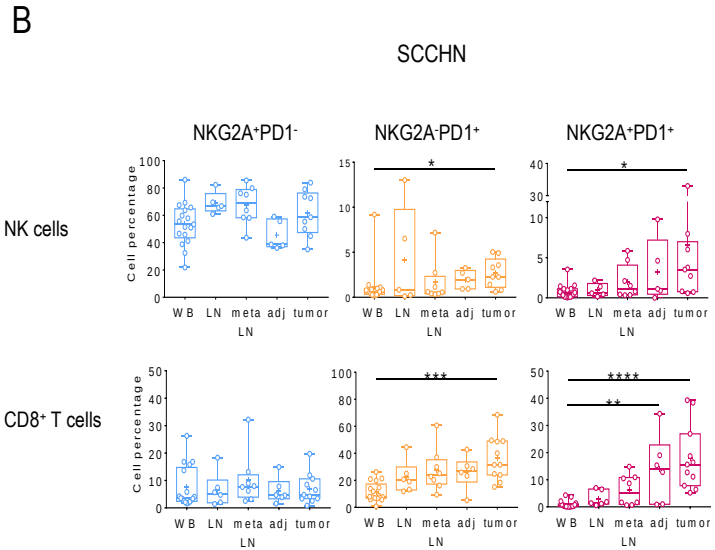
HLA-E pathway is upregulated in tumors



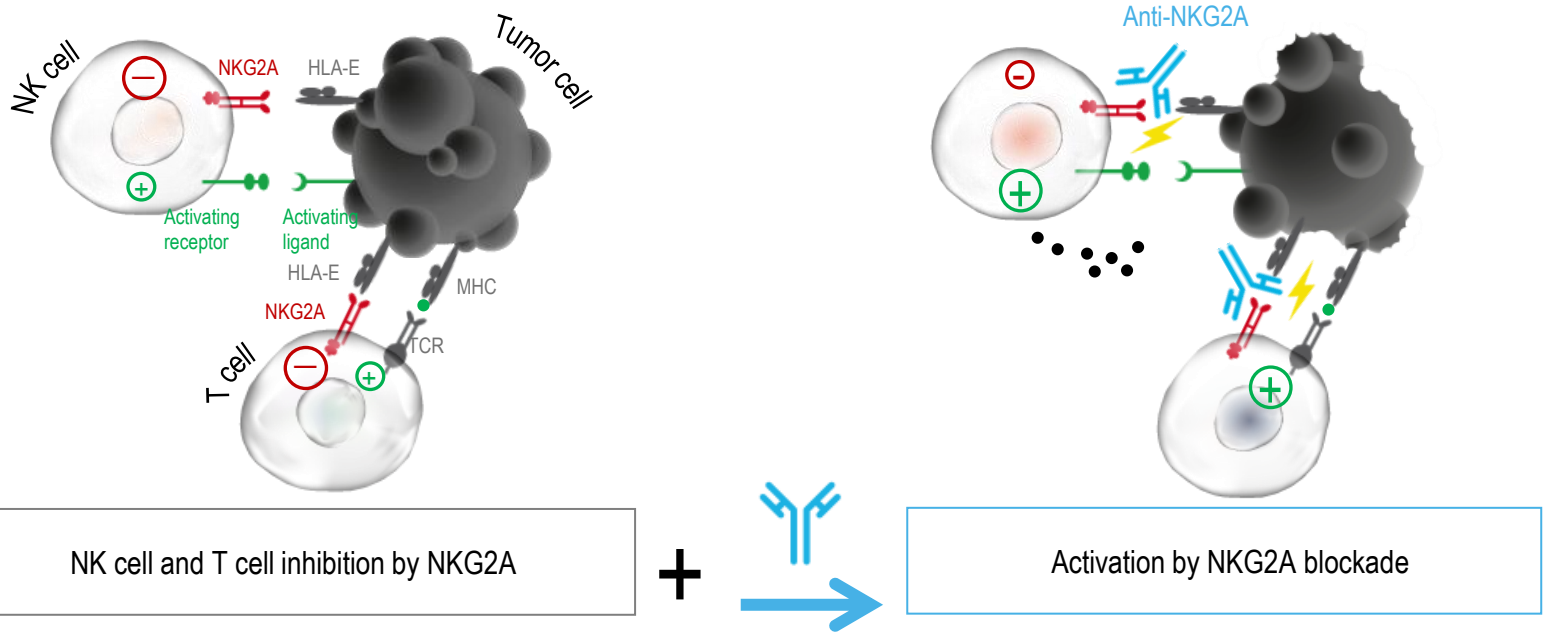


CD8+, NKp46+ or NKG2A+ immune cells are present in multiple types of HLA-E-expressing solid cancers





Anti-NKG2A is a novel immune checkpoint inhibitor in cancer

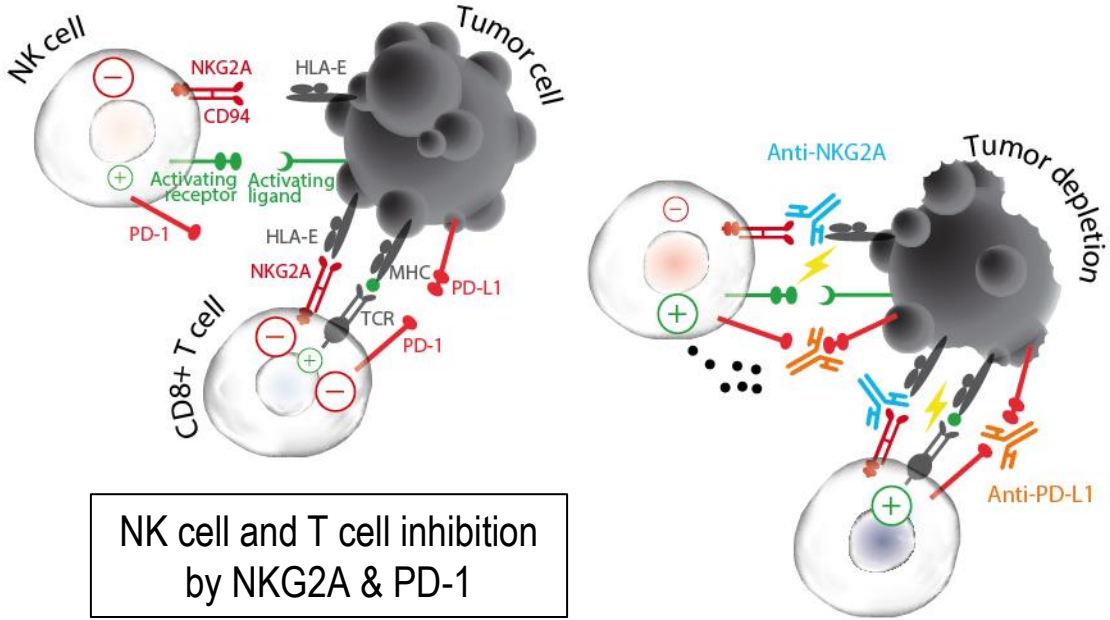


- Monalizumab:
  - first-in-class humanized IgG_4 targeting NKG2A on NK and tumor infiltrating $CD8^+$ T cells.
  - blocks binding of CD94/NKG2A to HLA-E reducing inhibitory signaling and thereby unleashing NK and T cell responses.

Rationale for combination therapy 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

Anti-NKG2A as a novel immune checkpoint inhibitor in cancer



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

Monalizumab (anti-NKG2A)

Durvalumab (anti-PD-L1)

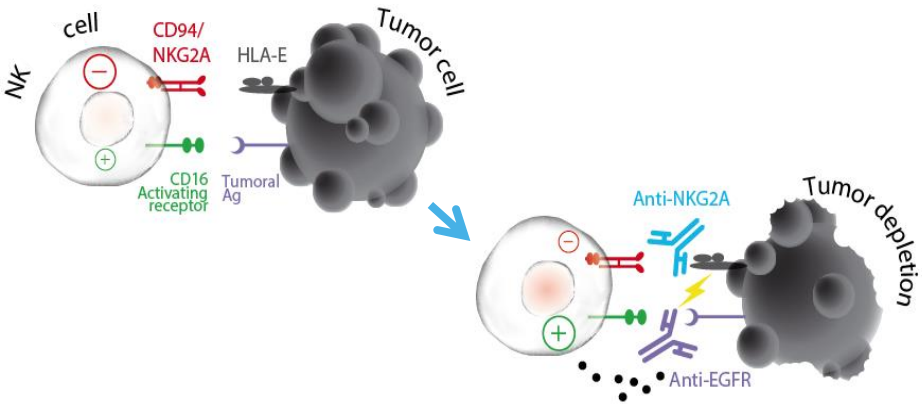
→

Activation by NKG2A & PD-L1 blockade

In vitro data support the rationale for ongoing clinical trial investigating the combination monalizumab/durvalumab: in metastatic Microsatellite-Stable Colorectal Cancer (MSS-CRC (*J. Diamond, 1194-P*)

MedImmune

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



ADCC enhancement by NKG2A blockade

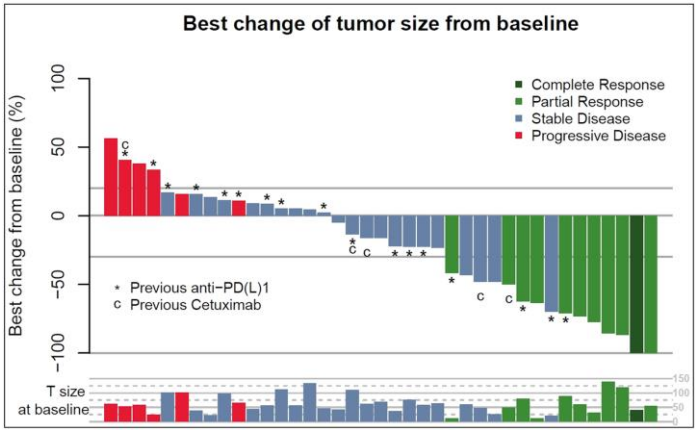
- SCCHN are infiltrated by NK and CD8^{+} T cells expressing CD94/NKG2A
- HN tumor cells express HLA-E
- NKG2A blockade enhances cetuximab-mediated ADCC towards HN tumor cell lines
- These data support the rationale for investigating monalizumab in SCCHN patients and in combination with cetuximab in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

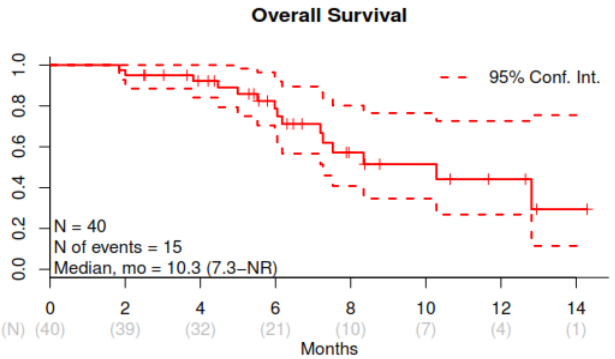
KEY RESULTS of MONALIZUMAB + CETUXIMAB

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





Cutoff data: Aug 31, 2018

J. Fayette et al., 1049 PD

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. 2018 Cell in press

Changes in the innate immune system in cancer ?

Why is it important?

- Identification of therapeutic targets

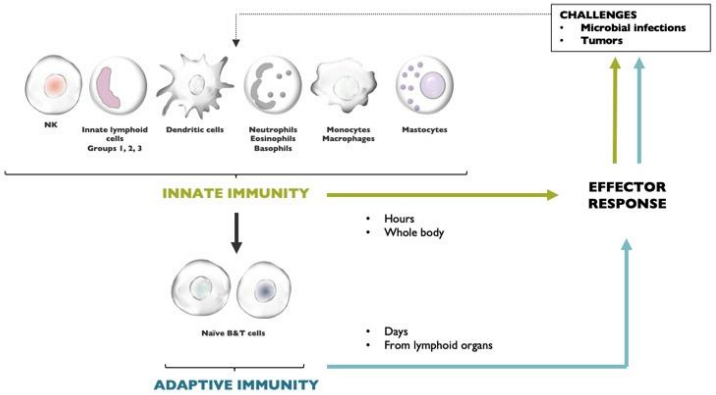
NKG2A – HLA-E

What kind of samples?

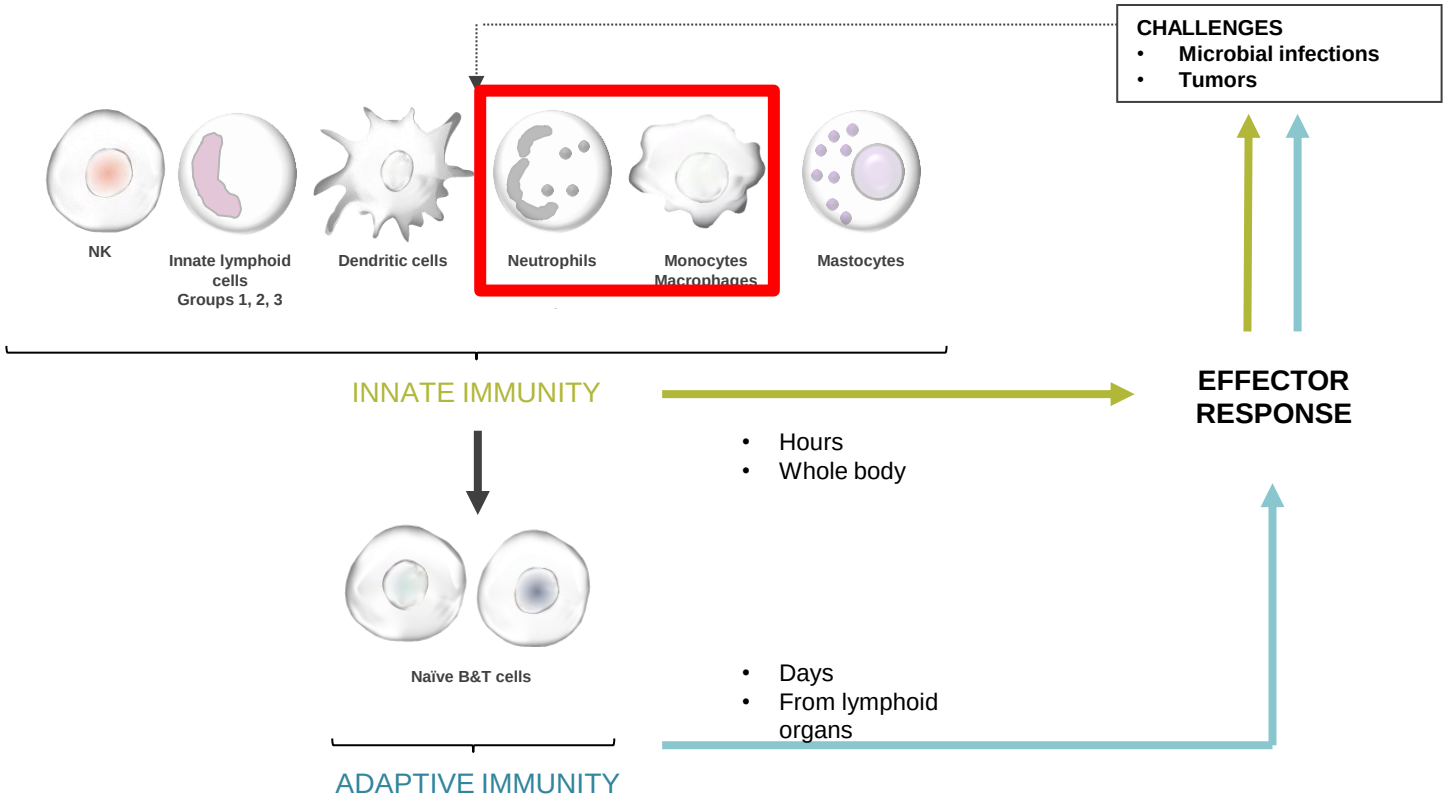
- At the tumor bed and in blood
- In both myeloid cells and lymphoid cells

What kind of technology?

- Genome-wide approaches
- Gene candidate approaches



The immune system

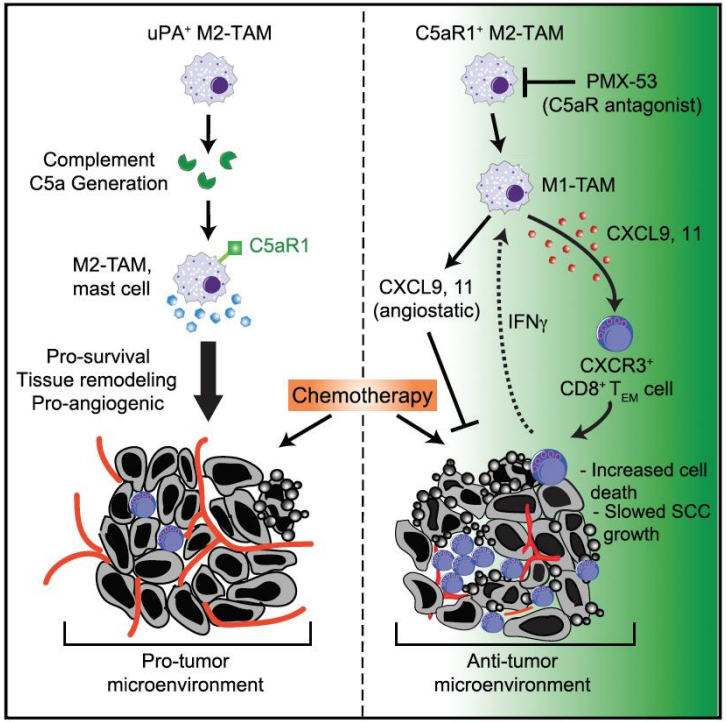


The C5a – C5aR pathway participate to the immunosuppressive tumor microenvironment

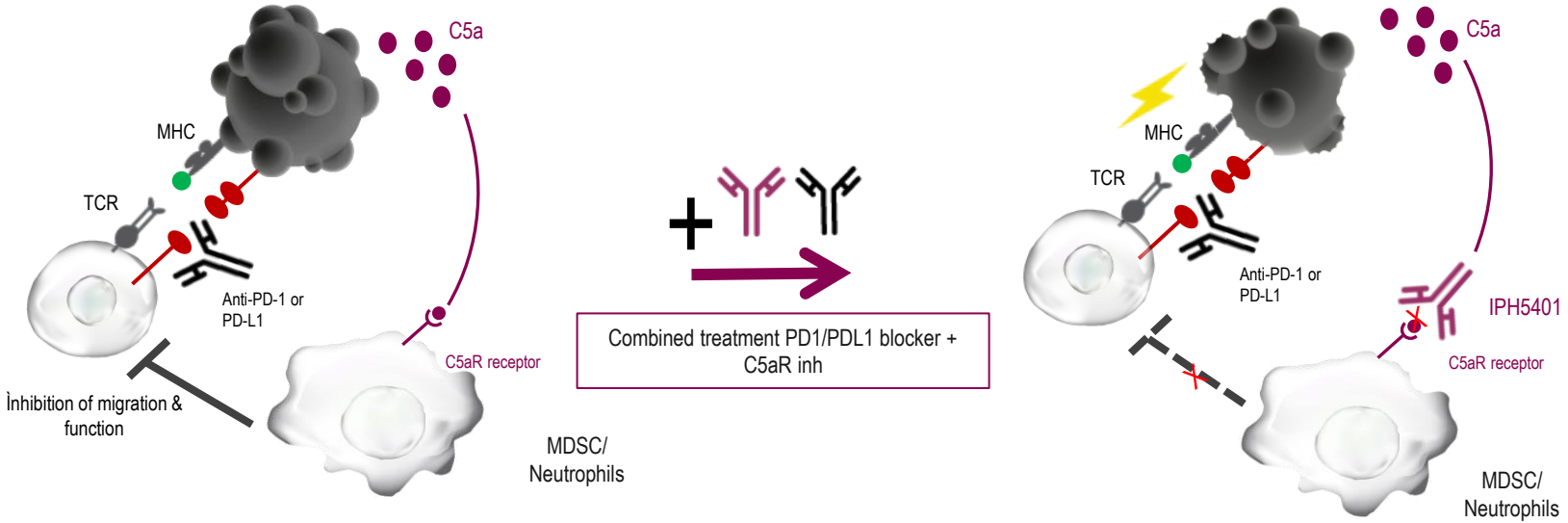
Cancer Cell
Article

Complement C5a Fosters Squamous Carcinogenesis and Limits T Cell Response to Chemotherapy

Terry R. Medler,[1] Dhaarini Murugan,[1] Wesley Horton,[2] Sushil Kumar,[1] Tiziana Cotechini,[1] Alexandra M. Forsyth,[1] Patrick Leyshock,[2] Justin J. Leitenberger,[3] Molly Kulesz-Martin,[1,3,4] Adam A. Margolin,[2,4] Zena Werb,[5] and Lisa M. Coussens[1,4,6,*]



IPH5401 - mode of action
Inhibition of C5aR restores the efficacy of PD-1/PD-L1 blockers



- IPH5401: monoclonal antibody targeting the C5a receptor (C5aR)
- C5a stimulates the recruitment and activation of suppressor cells and leads to the inhibition of immune effector cells
- Inhibition of C5aR signaling was shown to increase CD8 T cell infiltration and function
- C5a/C5aR blockade works in synergy with anti-PD-1/PD-L1 antibodies in a poorly infiltrated tumor model in vivo

Changes in the innate immune system in cancer ?

Why is it important?

- Identification of therapeutic targets

NKG2A – HLA-E

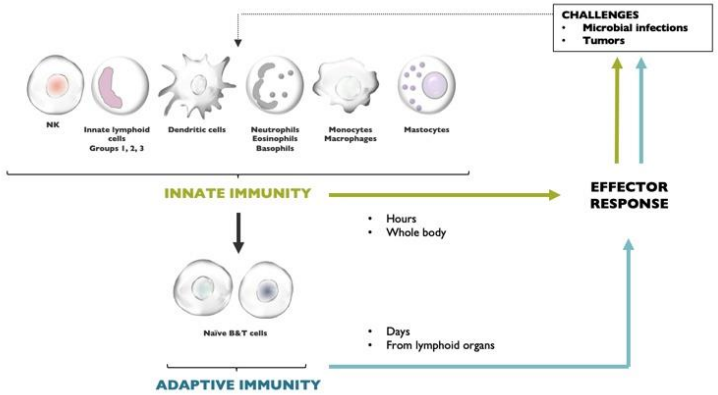
C5aR – C5a

What kind of samples?

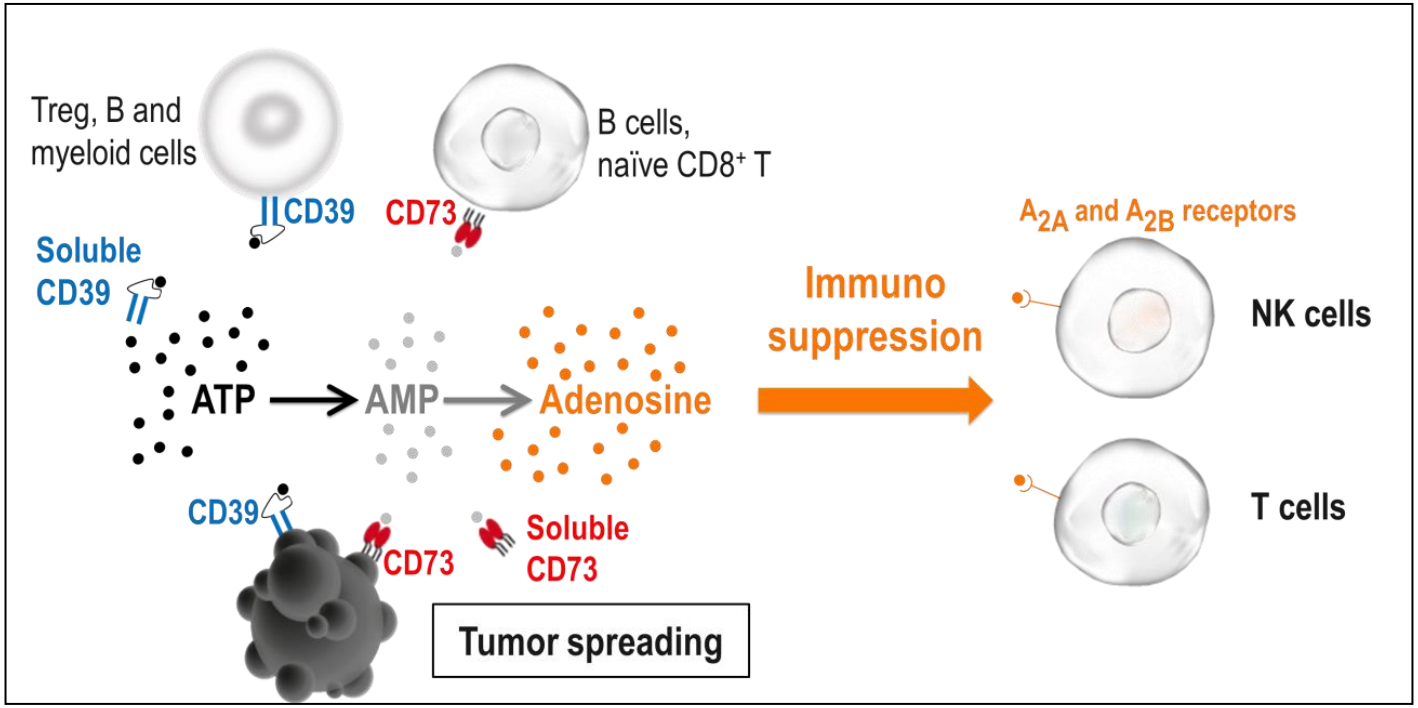
- At the tumor bed and in blood
- In both myeloid cells and lymphoid cells

What kind of technology?

- Genome-wide approaches
- Gene candidate approaches

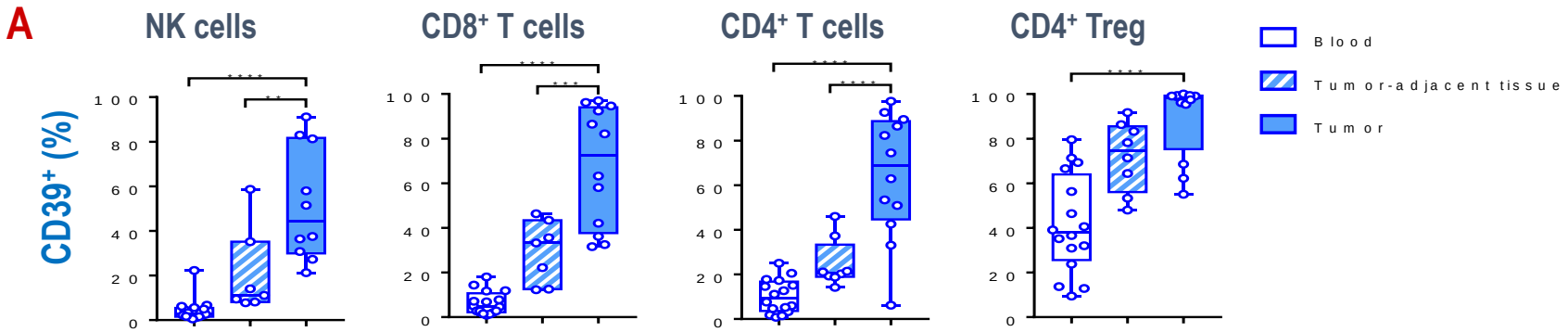


The adenosine pathway is immunosuppressive



ATP: Adenosine Triphosphate
AMP: Adenosine Monophosphate

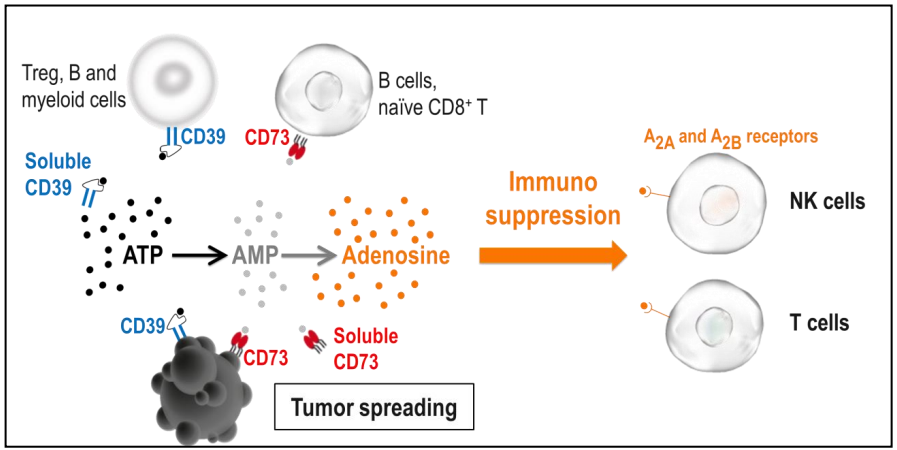
In human cancers, CD39 is upregulated on tumor infiltrated lymphocytes

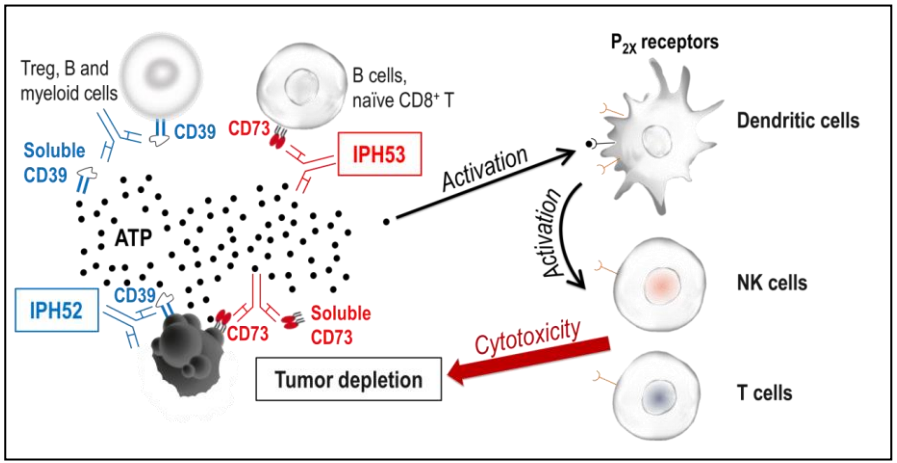


Expression on vascular endothelial cells and immune cells

Ivan Perrot, Carine Paturel et al.

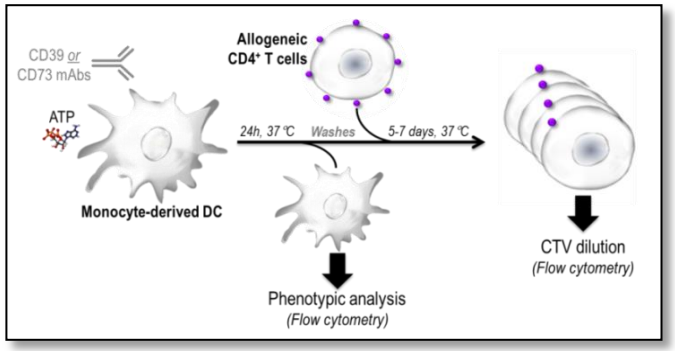
Counteracting the immunosuppressive adenosine pathway

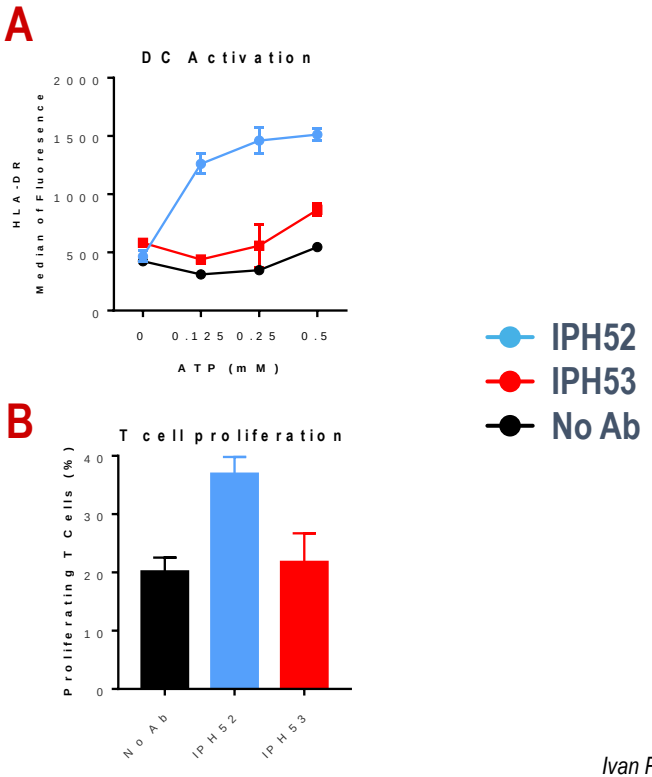




ATP: Adenosine Triphosphate
AMP: Adenosine Monophosphate

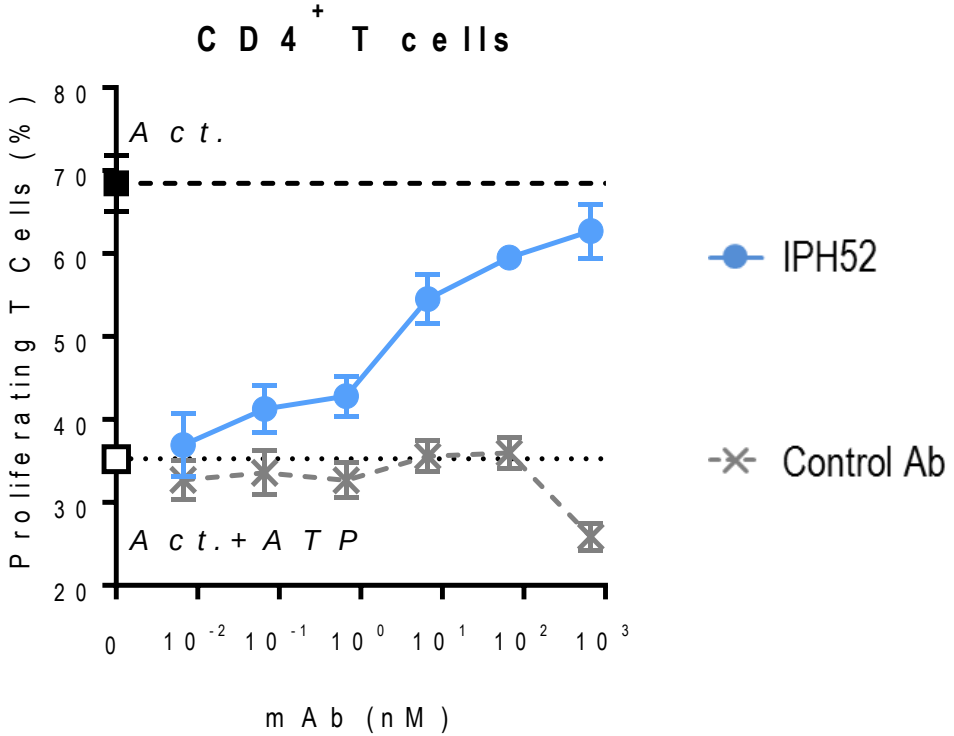
IPH52 (CD39) enhances ATP-mediated DC activation and T cell proliferation





Ivan Perrot, Carine Paturel et al.

IPH5201 (anti-CD39) restores T cell proliferation



Ivan Perrot, Carine Paturel et al.

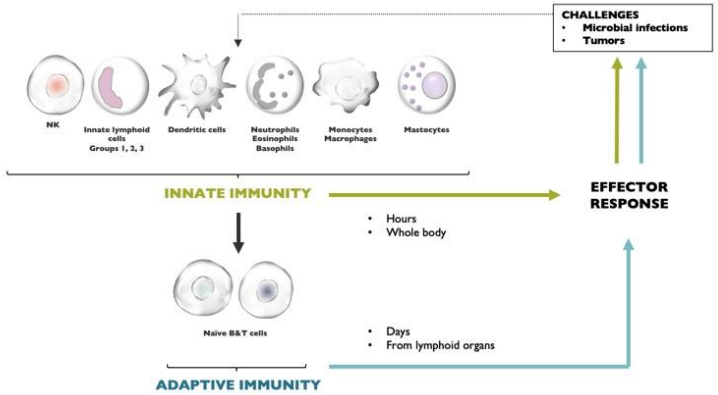
Changes in the innate immune system are key in cancer

It is important for
- Identification of therapeutic targets

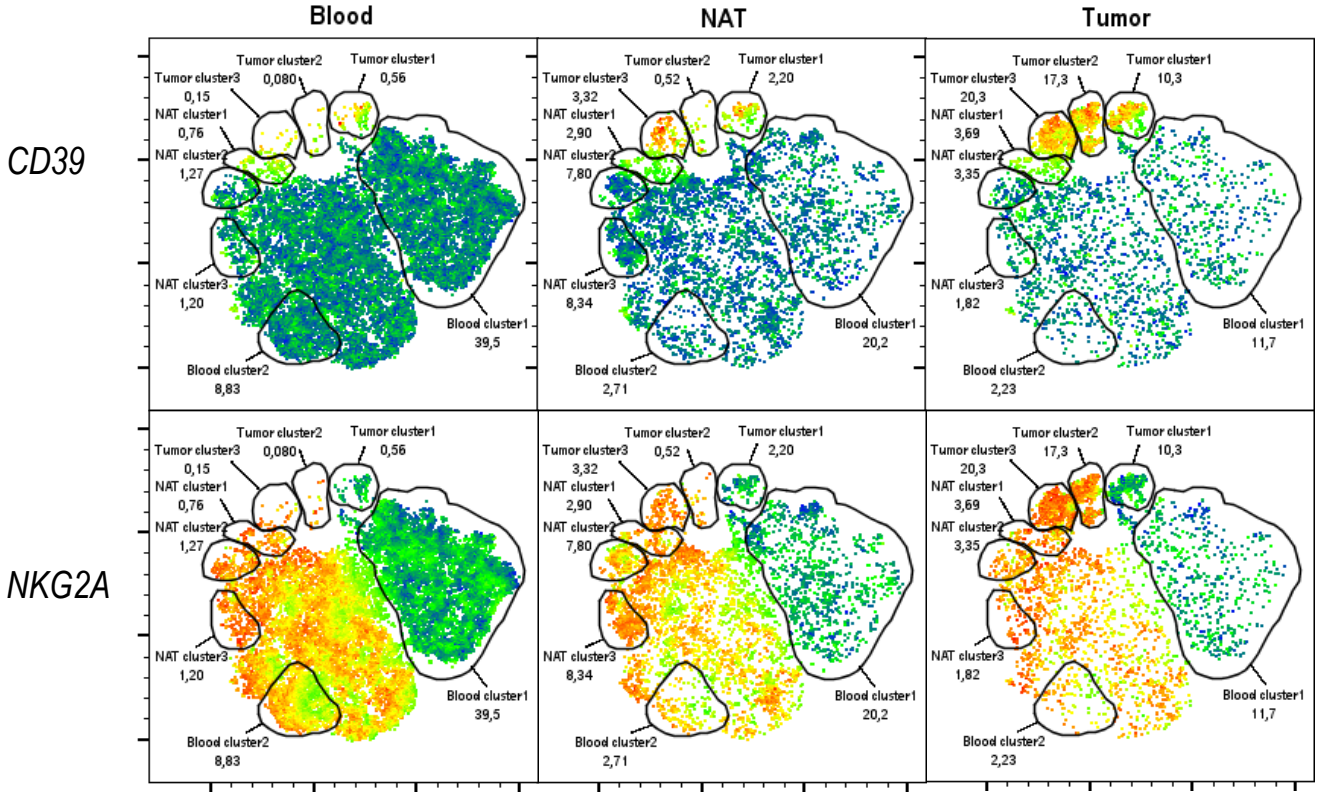
NKG2A – HLA-E
C5aR – C5a
CD39

What kind of samples?
- At the tumor bed and in blood
- In myeloid cells and in lymphoid cells

What kind of technology?
- Genome-wide approaches - scRNAseq
- Gene candidate approaches

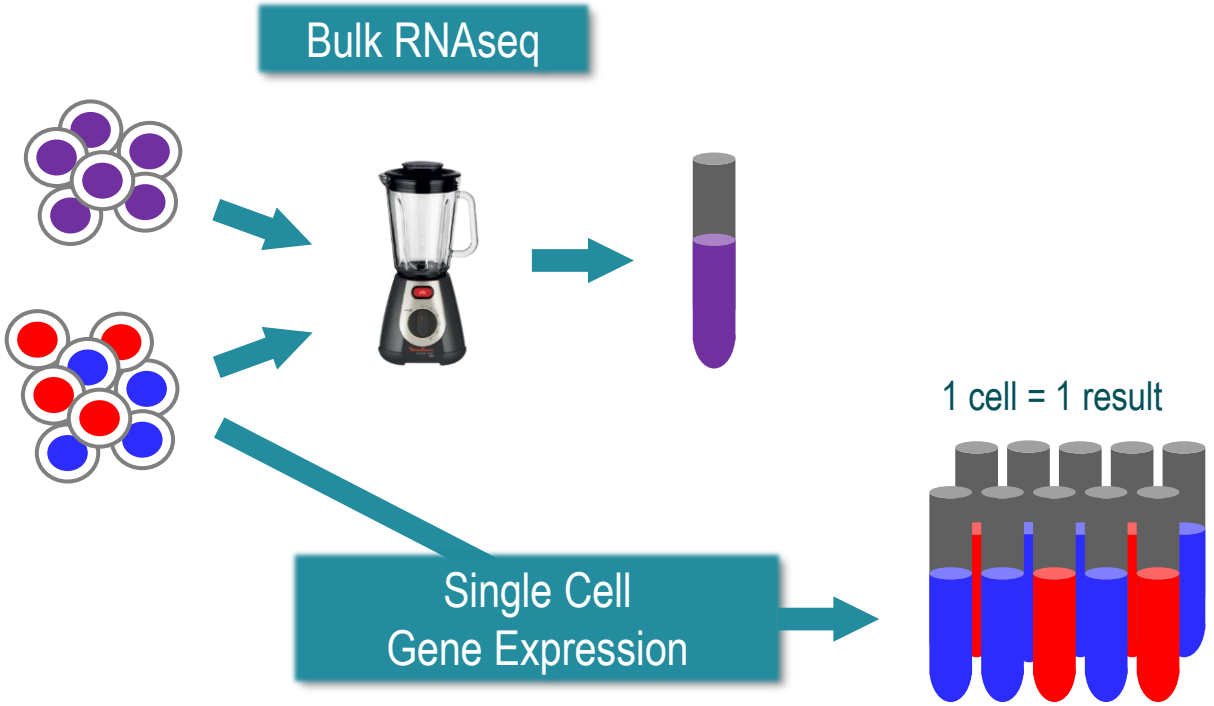


Using high-dimensional multi-parametric analysis



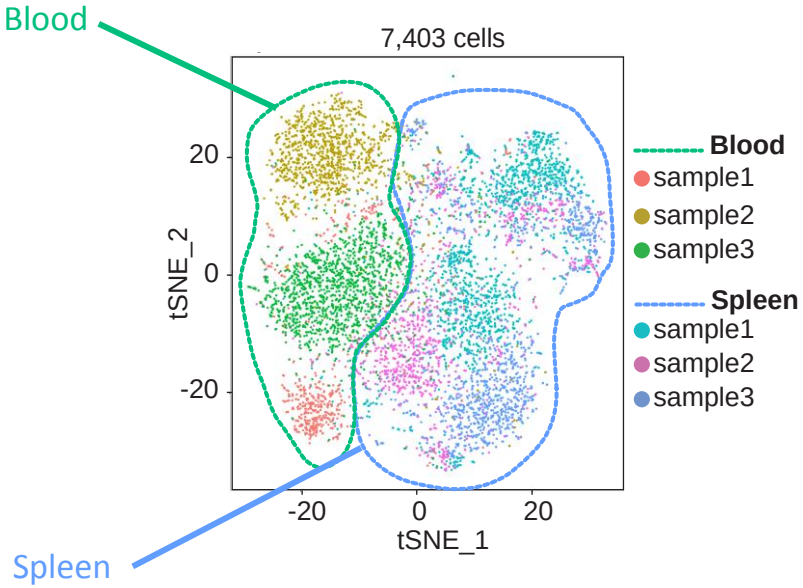
Guillaume Habif et al.

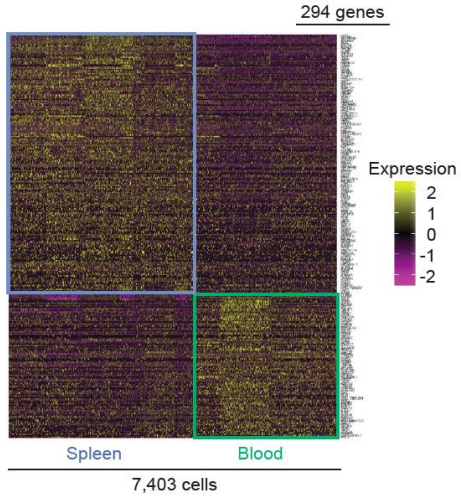
Using single-cell RNAseq



P. Milpied, Ciml

NK cells exhibit an tissue-specific transcriptomic profile





Crinier et al, Immunity in press

Pascale ANDRE
Agnès BOYER-CHAMMARD
Mathieu BLERY et al.
Cécile BONNAFOUS et al.
Caroline DENIS et al.
Pierre DODION
Laurent GAUTHIER et al.
Ariane MOREL et al.
Yannis MOREL
Romain REMARK et al.
Caroline SOULAS et al.
Robert ZERBIB

innate pharma

Maria L. ASCIERTO
Hormas GHADIALLY
Ronald HERBST
Robert W. WILKINSON

MedImmune

Roger B. COHEN, Abramson Cancer Center, Philadelphia
Jérôme FAYETTE, Centre Léon Bérard, Lyon
Olivier LANTZ et al., Institut Curie, Paris
François ROMAGNE et al., MI-mAbs, Marseille
Bernard MALISSEN et al., CIPHE, Marseille
Pierre MILPIED, CIML
Nathalie BONNEFOY, Montpellier

Ciml IMMUNOLOGY

Aix*Marseille université Initiative d'excellence

European Research Council erc

Anais BALSAMO
Adeline CRINIER
Bertrand ESCALIERE
Justine GALLUSO
Sophie GUIA
Yann KERDILES
Manon PETIT
Emilie NARNI-MANCINELLI
Margaux VIENNE
Christelle PIPEROGLOU
Frédéric VELY

Inserm

Equipe labellisée par la Ligue contre le cancer

cnrs

ANR Agence Nationale de la Recherche

AP-HM Assistance Publique Hôpitaux de Marseille

MSD AVENIR Améliorer la Vie Ensemble par l'Innovation et la Recherche

Sophie UGOLINI

THANKS to PATIENTS
and their FAMILIES

MARSEILLE IMMUNOPÔLE