CHANGES IN THE INNATE IMMUNE SYSTEM AS EARLY EVENTS IN CANCER

Lymphoid cells, Myeloid cells, Tumor microenvironment

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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

Desirable state

Undesirable state

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?

**Innate Immunity**
- NK cells
- Innate lymphoid cells (Groups 1, 2, 3)
- Dendritic cells
- Neutrophils
- Eosinophils
- Basophils
- Mastocytes

**Adaptive Immunity**
- Naïve B&T cells

**Effector Response**
- Hours
- Whole body
- Days
- From lymphoid organs

**Challenges**
- Microbial infections
- Tumors
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

INNATE IMMUNITY

- Hours
- Whole body

Effector response

ADAPTIVE IMMUNITY

- Days
- From lymphoid organs

Challenges
- Microbial infections
- Tumors

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

Naïve B&T cells
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

- NK cell and T cell inhibition by NKG2A
- Activation by NKG2A blockade

Monalizumab:
- first-in-class humanized IgG₄ 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

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)

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

Activation by NKG2A & PD-L1 blockade
NKG2A immune checkpoint blockade potentiates cetuximab-induced ADCC in head and neck cancer

- 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

#### Safety data:
- Good safety profile of the combination
- No potentiation of the cetuximab related AEs by monalizumab

<table>
<thead>
<tr>
<th>KEY RESULTS</th>
<th>n (%) CI</th>
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<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>1 (2.5%)</td>
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<tr>
<td>Partial response (PR)*</td>
<td>10 (25%)</td>
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<tr>
<td>Stable disease</td>
<td>22 (55%)</td>
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<tr>
<td><strong>Overall Response Rate (ORR)</strong></td>
<td>27.5% [16.1-42.8]</td>
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<tr>
<td>Median PFS</td>
<td>5.0 months [3.7-6.9]</td>
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<tr>
<td>Median OS</td>
<td>10.3 months [7.3-NR]</td>
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</tbody>
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Cutoff data: Aug 31, 2018

J. Fayette et al., 1049 PD
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
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What kind of technology?
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The immune system

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CHALLENGES
- Microbial infections
- Tumors

THE IMMUNE SYSTEM

NK
Innate lymphoid cells
Groups 1, 2, 3
Dendritic cells
Neutrophils
Monocytes
Mastocytes

EFFECTOR RESPONSE

Naïve B&T cells
The C5a – C5aR pathway participate to the immunosuppressive tumor microenvironment.
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

**Inhibition of C5aR restores the efficacy of PD-1/PD-L1 blockers**

Combined treatment PD1/PDL1 blocker + C5aR inh
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  NKG2A – HLA-E
  C5aR – C5a

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The adenosine pathway is immunosuppressive

ATP: Adenosine Triphosphate
AMP: Adenosine Monophosphate
In human cancers, CD39 is upregulated on tumor infiltrated lymphocytes

**A**

NK cells  
CD8+ T cells  
CD4+ T cells  
CD4+ Treg

**B**

Tumor tissue

**C**

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
IPH5201 (anti-CD39) restores T cell proliferation

**Graph:**
- **X-axis:** mAb (nM)
- **Y-axis:** Proliferating T Cells (%)
- **Data Points:**
  - **Act. + ATP**
  - **IPH52**
  - **Control Ab**

**Legend:**
- **Act.**
- **Act. + ATP**
- **Control Ab**

**Title:**
IPH5201 (anti-CD39) restores T cell proliferation

**Authors:**
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

Bulk RNAseq

Single Cell Gene Expression

1 cell = 1 result

P. Milpied, Citl
NK cells exhibit an tissue-specific transcriptomic profile

Crinier et al, Immunity in press