THE INNATE IMMUNITY COMPANY

NEXT GENERATION IMMUNOTHERAPIES: NK CELLS AND OTHER TARGETS

STEPHANIE CORNEN
5TH IMMUNOTHERAPY OF CANCER CONFERENCE (ITOC5) MARCH 2018
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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 (cells and molecules)
Identify biomarkers
THE IMMUNE SYSTEM

INNATE IMMUNITY

- Neutrophils
- Eosinophils
- Basophils
- Mastocytes
- Innate lymphoid cells Groups 1, 2, 3
- Dendritic cells
- Monocytes
- Macrophages
- NK cells
- Naïve B&T cells

ADAPTATIVE IMMUNITY

- Effecter response
  - Hours
  - Whole body
- Innate immunity
  - Days
  - From lymphoid organs

CHALLENGES
- Microbial infections
- Tumors
NEXT GENERATION IO

3 STRATEGIC KEY PILLARS TO HARNESS THE POTENTIAL OF IMMUNITY

1. NK cells checkpoints (NKCP)
2. Tumor targeting (TAg)
3. Tumor Microenvironment (TME)
### INNATE PHARMA – PIPELINE
**FIRST-IN-CLASS IO ASSETS**

<table>
<thead>
<tr>
<th>Target Discovery</th>
<th>Drug Discovery</th>
<th>Preclinical</th>
<th>Dose finding</th>
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~20 targets or concepts under exploration
ANTI-NKG2A IS A NOVEL IMMUNE CHECKPOINT INHIBITOR IN CANCER

- Monalizumab (IPH2201) is a first-in-class anti-NKG2A humanized blocking antibody.
NKG2A / HLA-E PATHWAY IS UPREGULATED IN TUMORS

HLA-E on tumor cells

Healthy Tissue

Tumor

Head & Neck  Ovary  Endometrium

NKG2A on TILs

Percentage of patients

- H&N (n=20)
- Ovary (n=40)
- Endometrium (intratumoral) (n=40)
- Endometrium (stroma) (n=40)
- Cervix (intratumoral) (n=16) (*)
- Cervix (stroma) (n=15) (*)
- Colorectal & hepatic meta (intratumoral) (n=47)
- Colorectal & hepatic meta (stroma) (n=47)

* underestimated because of few stroma in 5 tumors

- Score 3: > 76% positive cells
- Score 2: from 34 to 66% positive cells
- Score 1: between 1 and 33% positive cells
- Score 0: No positive cells

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 unpublished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 unpublished
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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**AZ-MedImmune**
- Ovarian
- CRC
- NSCLC
- Endometrial
- Monalizumab + Durvalumab

**Innate Pharma**
- Single agent dose ranging study
- SCCHN
- CLL
- Monalizumab + Cetuximab
- Monalizumab + Ibrutinib
## INNATE PHARMA – PIPELINE
### FIRST-IN-CLASS IMMUNO-ONCOLOGY (IO) ASSETS

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ATP/ADENOSINE PATHWAY

ATP → AMP → Adenosine

Tumor cells

B cells, naïve CD8+ T, endothelial cells

Treg, B, myeloid, endothelial cells

Soluble CD39

CD39

CD73

Dendritic cell

NK cell

CD8 or CD4 T cell

A2A and A2B receptors

Immuno suppression

B cells, naïve CD8+ T, endothelial cells

Tumor cells

Soluble CD39

CD39

CD73

A2A and A2B receptors

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

Tumor cells

B cells, naïve CD8+ T, endothelial cells

Breg, B, myeloid, endothelial cells

CD39/CD73 Blockade

Reverse immunosuppression

A2A and A2B receptors

Dendritic cell

NK cell

CD8 or CD4 T cell
BLOCKING ANTI-CD39 (IPH52) AND ANTI-CD73 (IPH53) ABS TO RESTORE ANTI-TUMOR IMMUNITY

Reverse immunosuppression
Activate dendritic cells

CD39/CD73 Blockade

B cells, naïve CD8+ T, endothelial cells

Treg, B, myeloid, endothelial cells

IPH52
Soluble CD39

CD39/CD73

IPH53
CD73

NK cell
CD8 or CD4 T cell

CD39/CD73

Dendritic cell

ATP

Tumor cells

P2X receptors
CD39 EXPRESSION IN HEAD AND NECK TUMORS

CD39 expression on endothelial cells and immune cells

<table>
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<th>% among</th>
<th>CD39+</th>
<th>CD39+PD-1+</th>
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<tr>
<td>CD4+ T cells</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
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<tr>
<td>CD4+ Treg</td>
<td><img src="image3" alt="Graph" /></td>
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<td>CD56^{dim} NK cells</td>
<td><img src="image7" alt="Graph" /></td>
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Perrot, Paturel, Bonnefoy et al. unpublished
CD39 DELETION IMPROVES ICI ANTI-TUMOR EFFICACY

B16 model

IC treated mice

WT: 6/10  
KO: 6/10

Anti PD1 treated mice

WT: 0/20  
KO: 0/20

MCA205 model

IC treated mice

WT: 0/10  
KO: 0/10

Anti CTLA4 treated mice

WT: 0/20  
KO: 4/20

WT: 6/10  
KO: 6/10
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

Perrot, Paturel, Bonnefoy et al. unpublished
BLOCKING ANTI-CD73 (IPH53) ABS TO RESTORE ANTI-TUMOR IMMUNITY

Tumor cells

CD39

Soluble CD39

ATP

AMP

Adenosine

B cells, naïve CD8⁺ T, endothelial cells

Treg, B, myeloid, endothelial cells

Block immunosuppression

A₂A and A₂B receptors

Dendritic cell

NK cell

CD8 or CD4 T cell

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

Block immunosuppression

Activate dendritic cells

Tumor cells

B cells, naïve CD8+ T, endothelial cells

Treg, B, myeloid, endothelial cells

Soluble CD39

CD39

CD73

Soluble CD73

IPH52

+ 

IPH53

NK cell

CD8 or CD4 T cell

Dendritic cell

P2X receptors
CD39/CD73 BLOCKADE SYNERGIZE TO REVERSE ATP-MEDIATED T CELL SUPPRESSION

**CD4+ T cells**

- CD39+CD73
- CD39
- CD73
- ATP
- CD3 + CD28
- No activation

**Proliferating T cells (%)**
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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