NOVEL CHECKPOINTS IN IMMUNO-ONCOLOGY

TARGETING CD39 AND CD73 TO IMPROVE ANTI-TUMOUR IMMUNE RESPONSES
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ATP/ADENOSINE PATHWAY
TARGETING IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT

ATP : adenosine triphosphate
AMP : adenosine monophosphate
CD39 AND CD73 EXPRESSION ON HEALTHY DONOR IMMUNE CELLS

**CD39+ proportion**

**CD73+ proportion**
CD39 EXPRESSION IN CANCER TISSUE

- CD39 can be expressed on tumor infiltrating cells, stromal cells or on tumor cells
CD39 IS OVER EXPRESSED ON TUMOR INFILTRATING CELLS

CRC Cancer
(Khaja 2017)

H&N Cancer
(Lechner 2017)

Breast and Ovarian Cancer
(Gourdin, in Revision)

Melanoma
(Bonnefoy)
CD73 EXPRESSION IN CANCER TISSUE

- CD73 is frequently expressed in Tumor tissues (for Review, see Wang 2017, Oncotarget; Antonioli 2016, Trends Cancer): on tumor cells, endothelial cells, as well as on lymphocytes (mostly B cells in TLS)
- CD73 expression is correlated with bad prognosis (Wang, 2017; Gao, 2014)
- CD73 is not upregulated on tumor immune infiltrating T cells

NSCLC (IPH)

CRC (IPH)

Breast and Ovarian Cancer
(Gourdin, in Revision)

Melanoma
(Bonnefoy)
ATP/ADENOSINE PATHWAY
TARGETING IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT

ATP: adenosine triphosphate
AMP: adenosine monophosphate

T reg, B Cell, Myeloid Cell

CD39

P2X receptor

Dendritic cell

B cell, CD4 T cell
Naïve CD8 T cell

NK cell

Tumor depletion

Activation

Immunosuppression

CD73

Anti-CD73

Anti-CD39

ATP

Adenosine

innate pharma
ANTI-CD73 AB IMPROVES ICI ANTI-TUMOR EFFICACY

Anti-moCD73 TY/23, in CD73+ MC38 models (Allard, 2013)
CD39 DELETION IMPROVES ICI ANTI-TUMOR EFFICACY

B16 model

MCA205 model

**IC treated mice**

- **B16 model**
  - WT: 6/10
  - KO: 6/10

- **MCA205 model**
  - WT: 0/10
  - KO: 0/10

**Anti PD1 treated mice**

- **B16 model**
  - WT: 0/20
  - KO: 0/20

- **MCA205 model**
  - WT: 0/20
  - KO: 4/20

**Anti CTLA4 treated mice**

- **B16 model**
  - WT: 0/20
  - KO: 0/20

- **MCA205 model**
  - WT: 6/10
  - KO: 6/10
CD39 DELETION IMPROVES CHEMOTHERAPY + ANTI-PD1 ANTI-TUMOR EFFICACY

MCA205 model

**IC treated mice**
- WT: 0/10
- KO: 0/10

**Oxa Treated mice**
- WT: 0/10
- KO: 0/10

**Anti PD1 treated mice**
- WT: 0/10
- KO: 0/10

**Oxa + Anti PD1 treated mice**
- WT: 6/10
- KO: 9/10

**CR**
- WT: 8/10
- KO: 10/10

Days post-graft

Tumor growth (mm²)

Graphs showing the tumor growth over days post-graft for different treatments and genotypes.
LEAD ANTI-CD73 AB INHIBITS SOLUBLE AND MEMBRANE CD73 ENZYME ACTIVITY, WITH NO CD73 DOWN MODULATION

Blocking of soluble rec CD73 activity

Down-modulation of membrane CD73

Blocking of cellular CD73 activity
LEAD ANTI-CD73 AB RESTORE IMMUNE RESPONSE IN THE PRESENCE OF AMP OR ATP

T cell proliferation assay

Allogeneic MLR
COMPARISON OF IPH ANTI-CD73 LEAD AB WITH MEDIMMUNE AND BMS ANTI-CD73 ABS

Blocking of soluble rec CD73 activity

Down-modulation of membrane CD73 activity

Blocking of cellular CD73 activity
LEAD ANTI-CD39 AB BINDS CD39 WITH HIGH AFFINITY AND SPECIFICITY

Binding to recombinant soluble CD39 and CD39-like proteins in ELISA

![Graphs showing binding of anti-CD39 to recombinant soluble CD39 and CD39-like proteins in ELISA.](image-url)
LEAD ANTI-CD39 AB INHIBITS SOLUBLE AND MEMBRANE CD39 ENZYME ACTIVITY

Blocking of soluble rec CD39 activity

Blocking of cellular CD39 activity

Binding to membrane CD39 in Flow Cytometry

Ramos (CD39+)

Ramos

\[ \text{Luminescence Units} \]

\[ \text{Ab (µg/ml)} \]

\[ \text{ATP} \]

\[ \text{Ramos (CD39+)} \]

\[ \text{Median of Flu} \]

\[ \text{Ab (µg/ml)} \]

\[ \text{Luminescence Units} \]

\[ \text{Ab or ARL (µM)} \]

\[ \text{Anti-CD39, IC, ARL} \]
LEAD ANTI-CD39 AB RESTORE IMMUNE RESPONSE IN THE PRESENCE OF ATP

T cell proliferation assay

DC activation

- CD4 T cells
- CD8 T cells

Ab (µg/ml)

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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