Immune Checkpoints

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Activation of T cells requires co-stimulation

1. TCR signal only
   - Antigen + MHC + TCR
   - No T cell proliferation

2. Positive costimulation
   - B7 + CD28
   - T cell proliferation
   - Cytokines

Tumor or epithelial cells
APC's (dendritic cells, macrophages)
CD28 induces direct effect on gene expression by regulation of transcription factors and increases mRNA stability.
T cells undergo three phases after antigen stimulation

Nature Reviews Immunology 12, 749-761 (November 2012)
Fine-tuning of the immune response
Fine-tuning of the immune response
immune checkpoints

S. Yao, Nature Reviews Drug Discovery 2013; 12, 130-146
Co-inhibition and co-stimulation determine the quality of the T cell response
Co-inhibition and co-stimulation determine the quality of the T cell response

Nature Reviews Drug Discovery 12, 130-146 (February 2013)
CD40/CD40L

Expression of CD40L
- T cells

Expression of CD40
- DC cells
- B cells
- Macrophages
- Tumor cells

FUNCTION
- Maturation of dendritic cells
- Activation/differentiation of T Cells
**FUNCTION on B cells**

- Activation
  - immunoglobulin switching
  - antibody secretion
- Rescue from apoptosis
- Development of germinal centres
- Survival of memory B cells
Treatments targeting CD40/CD40L

RO7009789
APX005M
OX40

- Following antigen stimulation on activated naïve CD4 and CD8 T cells

OX40L

- Following antigen stimulation on APCs \(\Rightarrow\) extent of T cell priming
- Following recognition of antigen on T cells \(\Rightarrow\) T cell-T cell interactions
OX40/OX40L determines the size of effector and memory T cell pools

Function
- Effector T cells \(\rightarrow\) clonal expansion
- Memory T cells \(\rightarrow\) generation and reactivation
OX40/OX40L

Function
- Regulatory T cells → inhibition by downregulation of CTLA4 and FoxP3
Rational for targeting OX40/OX40L
Targeting OX40/OX40L Ongoing

- In humans: Combination OX40L and 4-1BB (ESMO 2017)
- In mice: Concurrent PD-1 Blockade Negates the Effects of OX40 Agonist Antibody in Combination Immunotherapy through Inducing T-cell Apoptosis

On **T eff cells:**
Increases survival (protection from activation-induced cell death (AICD) and function
Boosts the effect of CD4 helpers

On **T regs:**
Diverts the cells to Th9 phenotype (chromatin remodelling)

On **NK cells:**
unclear role

*J Ex Med; 210(9), 1695–1710*
# Targeting GITR

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Target Tumor Types</th>
<th>Drugs</th>
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<tr>
<td><strong>Trial of TRX518 (Anti-GITR mAb) in Stage III or IV Malignant Melanoma or Other Solid Tumors</strong></td>
<td>- Unresectable Stage III or Stage IV Malignant Melanoma or Other Solid Tumor Malignancies</td>
<td>- Biological: TRX518</td>
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<tr>
<td><strong>Phase I/II Study of GWN323 Alone and in Combination With PDR001 in Patients With Advanced Malignancies and Lymphomas</strong></td>
<td>- Solid Tumors - Lymphomas</td>
<td>- Drug: GWN323 - Drug: PDR001</td>
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<td><strong>An Open-Label, Dose-Escalation, Safety Study of INCAGN01876 in Subjects With Advanced or Metastatic Solid Tumors</strong></td>
<td>- Advanced Cancer - Metastatic Cancer</td>
<td>- Drug: INCAGN01876</td>
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<td><strong>Phase 1/2 Study Exploring the Safety, Tolerability and Efficacy of INCAGN01876 Combined With Immune Therapies in Advanced or Metastatic Malignancies</strong></td>
<td>- Advanced Malignancies - Metastatic Malignancies</td>
<td>- Drug: INCAGN01876 - Drug: Nivolumab - Drug: Ipilimumab</td>
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Targeting GITR
at University Hospital Zurich

NCT02598960:
An Investigational Immuno-therapy Study of Experimental Medication BMS-986156, Given by Itself or in Combination With Nivolumab in Patients With Solid Cancers or Cancers That Have Spread

ASCO 2017, Abstr 104:
BMS-986156 ± nivolumab was well tolerated, with no DLTs and low immunogenicity. Antitumor activity was observed with BMS-986156 + nivolumab at doses predicted to be biologically active.
CD137 (4-1BB): CD137 (4-1BB)L

Expression of CD137:
• stimulated T cells
• T regs
• DCs
• NK cells

Function of CD137: CD137L

On T cells increasing:
- proliferation, resistance to apoptosis, IFNγ secretion
- increase in tumor-selective cytolytic T-cell activity

On T reg:
- Reduction of T reg infiltration

On DC
- Enhancing co-stimulation

On NK
- Enhanced ADCC (antibody-dependent cell-mediated cytotoxicity)
Clinical trials with Abs targeting CD137: the experience with Urelumab

Phase I, NCT00309023:
- low grade fatigue
- grade 2+ neutropenia, leukopenia, thrombocytopenia, increased in AST and ALT

Phase II NCT00612664:
- terminated due to high incidence of Grade IV, potentially fatal, hepatitis

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Co-inhibition and co-stimulation determine the quality of the T cell response

Nature Reviews Drug Discovery 12, 130-146 (February 2013)
Co-inhibition and co-stimulation determine the quality of the T cell response
Co-inhibitory molecules
Co-inhibitory molecules
Co-inhibitory molecules
CTLA4

• The immunoregulatory properties of CTLA-4

  – in CTLA-4 knockout mice → death of all animals by 3–4 weeks of age

  – Intrinsic control of tolerance: CTLA-4 expression of T effector cells shuts down immunity and can lead to tumor progression

  – Extrinsic control of tolerance: important role in the suppressive function of Tregs and affecting the function of DCs through CTLA-4-induced down modulation of B7 expression and production of the immunosuppressive enzyme IDO
CTLA-4 function on effector cells

Activation of T cells → proliferation and functional differentiation → inhibitory program → stop proliferation

CTLA-4 function on T regs

**On T regs:**
to aggregate around dendritic cells and inhibit their antigen-presenting activity

J Ex Med; 210(9), 1695–1710
Targeting CTLA-4

A Overall Survival

No. at Risk

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Hodi et al. NEJM 2010
Co-inhibitory molecules

PD-L1 is not stably expressed
The PD-L1 molecule

PD-L1 is expressed on:
Activated T cells, NK cells, macrophages, myeloid DCs, B cells, epithelial cells, vascular endothelial cells; tumor cells

Expression of PD-L1 is induced by:
Type 1 and Type 2 IFNs, TNFα, LPS, GM-CSF, VEGF, IL-10, IL4

Expression of PD-L1 can be downregulated by:
downregulation of PI3K; ALK/STAT3; NF-kB; miRNA513; wtPTEN

Adapted from J Exp Med 2014;211:781-790
PD-L1 is not stably expressed on tumor cells
The PD-L1/PD1 pathway leads to:

**Function**

- T cell death
- Down-regulation of activated T cells
- Reduction of T cells to kill tumor cells

Adapted from J. Immunology 2014, 193(8): 3835–3841
PD-L1 has also a direct tumor activity

PD-L1 enhances tumor cell glycolysis and thus depletes glucose from immune cells in the tumor microenvironment.

PD-L1 is important for Akt/mTOR signaling in tumors.
Targeting PD-1/PD-L1
NSCLC, 1st line

Population: > 50% PD-L1 positive

Co-inhibitory molecules

LAG3: binds to MHC II

Expression

- On exhausted T cells
- On TIL
- On T regs
- On NK

Adapted from Nature Reviews Immunology 15; 2015: 45-56
LAG3: binds to MHC II

Function

- Confers a Treg function on CD4 naïve T cells
- Negatively regulates
  - T-cell activation
  - Proliferation
  - Homeostatic expansion
Soluble LAG3 is an immunoadjuvant

Adapted from Nature Reviews Immunology 15; 2015: 45-56
Targeting LAG3

- Ascierto, ASCO 2017: Melanoma
- Ascierto, ESMO 2017: Melanoma
  - Responses are related to LAG3 expression
  - ? What about the soluble form?
- At the University Hospital Zurich
  - CA224-220: An Investigational Immuno-therapy Study to Assess the Safety, Tolerability and Effectiveness of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors
The aim
Thank you for your attention