Targeting the Immune System to treat cancer

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Immune Network and cancer

1) MHC molecules
2) Costimulation molecules
3) Inflammatory cytokines production

- TGF-β producing
- IDO producing
- VEGF...

Activation and expansion of effector cells

Inhibition of effector cells (anergy, apoptosis)

Tumor antigens

Expansion and/or induction

Soluble Factors
- IDO
- TGF-β
- IL-6
- IL-10
- COX2
- PGE2
- VEGF
- Ganglioside

Inhibition of effector cells

Expansion and/or induction

Inhibition of effector cells
How can we restore immunity in cancer patients

- Block tolerance **and** restore/induce immunity
- With what tools can we make it
  - Monoclonal antibodies targeting antigens but also targeting the IS itself
  - Conventional treatment (Chemotherapy/radiotherapy)
  - Targeted therapy
  - Vaccines
  - Cytokines
Are conventional treatments immunogenic?

Tolerogenic Cell Death

IL-10 TGFβ

Phagocytosis

IL-10 TGFβ

DC

Macrophage
Immunostimulatory effects of conventional anti-cancer therapies

- Lymphopenia and homeostatic T cells proliferation (Dummer W et al, JCI, 2002)
- Selective elimination of immunosuppressive populations: Treg, MDSC (Lutsiak, ME et al, Blood, 2005)
- ↑ recognition of tumor cells by immune effectors (Reits EA et al, JEM, 2006)
- ↑T cell infiltration in the tumor bed (Matsumura S, JI, 2008)
Endogenous danger signals that can lead to activation of innate immunity

Dying cell

Endogenous danger signals

Damage associated molecular pattern

HMGB1, HSP ↔ TLR-2, -4
DNA ↔ TLR-9
RNA ↔ TLR-3
ATP, uric acid ↔ NLRP3
SAP130 ↔ CLEC4A

Innate immunity

PRR

From Chen GY, Nat Rev Immunol, 2010
Can conventional anticancer treatments lead to immunogenic cell death?

Oxaliplatin, anthracyclins, Radiotherapy

Living tumor cell

IMMUNOGENIC SIGNALS?

IFNg

NK

LT CD8+

γδLT

cDC
Molecular events leading to immunogenic cell death

Oxaliplatin, anthracyclins, Radiotherapy
Calreticulin exposure dictates the immunogenicity of cancer cell death

Toll-like receptor 4–dependent contribution of the immune system to anticancer chemotherapy and radiotherapy

Activation of the NLRP3 inflammasome in dendritic cells induces IL-1β–dependent adaptive immunity against tumors

Apetoh, Nat Med 2007
Targeting Soluble Factors to diminish immunesupression

- Anti-VEGF ou VEGFR $\rightarrow$ Treg & MDSC; diminution of FAS-L
- Anti-TGFb/TGFbR
- Anti-IL10/IL-10R
- Anti-IL-6 ou IL-6R (Tocilizumab)
- IDO inhibitors
Targeting immune cells to induce and/or reinvigorate anti-tumor immunity

- Cytokines (non specific)
  - IL-2
  - IFNa
  - TNFα
  - Cytokines that are evaluated (Preclinical and phase I) l’IL-15; l’IL-7; la super-IL-2; la super-IL-15

- Therapeutic Vaccines (Specific)
  - BCG (ImmunostyTM) : Non invasive Bladder tumors
  - long peptides : HPV-16 onco-proteins E6 & E7 + incomplete Freund adjuvant (IFA).
  - Sipuleucel-T (CPA + PSA-GMCSF) HR metastatic prostate cancer
  - CIMAvax-EGF approved Cuba (CBNPC) ➔ leads to anti-EGF Abs

- Monoclonal antibodies: *immune check point blockade* (Blockers)
  - Anti-CTLA4 - Ipilimumab (approved Melanoma)
  - Anti-PD1; anti-PD-L1 (Melanoma; Lung; RCC)
  - Others ?…. Clinical studies are ongoing (anti-LAG; Tim-3; GITR; )

- Monoclonal antibodies (agonists; Clinical studies are ongoing)
  - Anti-OX40; anti-4.1BB; ICOS…

- Trivalent antibodies
  - Catumaxomab targets CD3/Epcam and FcR : Treatment of malignant ascites : EpCAM positive tumors
How to target T cells?
Anti-CTLA4 and anti-PD1: how it works?

- **CTLA4**
  - This system of peripheral tolerance intervenes at the time of the initiation of the immune response
  - Naïve or memory lymphocytes do not express CTLA4
  - The level of expression of CTLA4 is directly linked to the commitment of the TCR
  - Antigens of high affinity lead to a strong expression of CTLA4
  - Des antigènes de faible affinité induisent peu de CTLA4
  - It allows a sharp regulation of the amplitude of the immune response

- **PD1**
  - This system of peripheral tolerance intervenes on the site of the inflammatory reaction
  - Some inflammatory soluble factors allow the up-regulation of PD-L1:
    - Decrease the amplitude of T cell activation
    - Limit collateral damages
    - IFNγ induces PD-L1
  - An excessive expression of PD1 (PD1[^high]) is associated with T cell anergy. This excessive expression can be achieved during a chronic stimulation (ex: chronic infectious diseases (HIV; HCV); chronic inflammatory diseases as cancer.)
immune checkpoint blockade
immune check point blockade anti-CTLA4

- Response rate: 10-17%
- 20-40% of Immune Related Adverse Effects (irAE)
- % patient alive at 3 years: 20%
- Cost: 84,000 Euros/patients
- A real need to find predictive marker of efficacy
- Association with targeted treatment, with other immune check-point inhibitors?
- Association with local radiotherapy (MEL-IPI-RX trial)

Ca184-024 study
immune check point blockade anti-CTLA4: Immune Related Adverse Effects
immune check point blockade: anti-PD1  
(melanoma, NSCL, Prostatic, Renal-cell or colorectal cancer patients)

- Responses were observed in:
  - 18% of patients with NSCL,
  - 27% renal-cell
  - 28% melanoma
immune checkpoint blockade: anti-PDL1
(NSCL, melanoma, colorectal cancer, Renal-cell, ovarian cancer, pancreatic cancer, gastric or breast cancer patients)

The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthi, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.
### Combination anti-CTLA4 & Anti-PD1

<table>
<thead>
<tr>
<th>Mélanoine avancé Traitement</th>
<th>Réponses cliniques objectives</th>
<th>Diminution du cancer de plus de 80%</th>
<th>Survie à 2 ans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CTLA4 (1) n=502</td>
<td>11%</td>
<td>&lt;2%</td>
<td>28%</td>
</tr>
<tr>
<td>Anti-PD1 (2) n=135</td>
<td>38%</td>
<td>&lt;3%</td>
<td>43%</td>
</tr>
<tr>
<td>Anti-CTLA4 + Anti-PD1 (3) n=70</td>
<td>40%</td>
<td>31%</td>
<td>70%</td>
</tr>
</tbody>
</table>

(1) Robert et al. NEJM 2012  
(2) Hamid O et al. NEJM 2013  
(3) Volchok et al. ASCO 2013

However high rate of IRAE (>50% grade III/IV) ➔ A real need to find combo-therapy with a good tolerance profile
Immune checkpoint blockers: A revolution for cancer treatment?

- Immunotherapy is not any more a myth
- These therapeutic approaches are rapidly growing and show impressive clinical results
- L’anti-CTLA4 (ipilimumab) approved in France in 2013

However
- Better understand mechanisms of action
- Better understand the mechanisms that lead to IRAE (inflammatory diseases) to be able to anticipate and manage these IREA

Increase even more the survival of the patients
- Predictive biomarkers of Toxicity ➔ Better clinical management of IRAE
- Predictive biomarkers of response/resistance ➔ better selection
- Compensate for the patients with a failing immune system
- Find effective combo-therapy
  ➔ Increase number of patients being able to benefit from these treatments
What about Breast cancer and immunotherapy

**Innate Immunity**

- MDSC are increased in BC ➔ Could be targeted with IDO inhibitors (Yu JI 2014)
- Plasmocytoid dendritic cell (pDC) and BC (Sisirak IJC 2013; Faget CR 2012; Sisirak CR 2012; Treilleux Clinical CR 2004)
  - associated with amplification of Treg cells ➔ linked to poor prognosis (Role of ICOS/ICOSL axis and IL-10)
  - Restoration of IFNα secreted by pDC could restore an effective immunity (use TLR-7 agonist Resiquimode)
- NK cells might play a role in human breast cancer (Mamessier CR 2011; Mamessier JCI 2011)
  - BC seems to escape from NK cell immunity
What about Breast cancer and immunotherapy

Adaptive Immunity

- **Effector T cell infiltration and BC** (Loi, JCO 2013; Dieci, Annal Oncol 2014; Ladoire J. Pathol 2011)
  - Effector T cell infiltration is associated with good prognosis in human breast cancer
  - Effector/Treg ratio, after NACT, is associated with a better prognosis in human breast cancer
  - High T cell infiltration after NACT is associated with a better prognosis in triple negative BC
  - TIL increased after NACT in triple negative BC
  - Doxorubicin could enhance T cell infiltration and immunogenicity of tumor cells (Immunogenic cell death ➔
    Role of TLR4 in BC patients to be validated in prospective cohorts) (Apetoh, Nat Med 2009)

- **PD-1 /PD-L1 and BC**
  - PD-1-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer
    (Muenst; BCRT 2013)
  - PD-L1 expression is increased in tumors that have a higher proliferation index as measured by Ki-67. These
    observations suggest that the PD-L1/PD-1 pathway may be more important in certain breast cancer subtypes
    like **triple negative breast cancers** which have a higher proliferation rate, higher grade, and have a high
    lymphocytic response while in low grade tumors these molecules may play a role in the later stages contributing
    to their invasiveness (Ghebeh et al., 2007)
  - 20% triple negative breast cancers PD-L1+ (Mittendorf; CIR 2014)
  - Doxorubicin (but not docetaxel) could diminish surface expression of PD-L1 (Ghebeh ; 2010)…Implication
    for PD1/PD-L1 treatment?
There is a place for immunotherapy for the treatment of patients with BC

We must define which BC subtype
Triple negative BC should be a good target (highly infiltrated by T cells; express immune checkpoint ligands (PD-L1 and others as B7-H3)

Innate immunity as NK cells (good guys) or pDC/MDSC (bad Guys) could help for future immunomodulation approaches (RLI (super-IL-15) ; IDO inhibitors; TLR agonists...)

IMPAKT Breast Cancer Conference 2014
Thank you for your attention
Can the Immune System (IS) recognize the tumor?

**HUMAN**

Zhang L et al. The NEJM. 2003

Pagès et al, N EJM, 2005
### immune check point blockade

<table>
<thead>
<tr>
<th>Target</th>
<th>Biological function</th>
<th>Antibody or Ig fusion protein</th>
<th>State of clinical development*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA4</td>
<td>Inhibitory receptor</td>
<td>Ipilimumab</td>
<td>FDA approved for melanoma, Phase II and Phase III trials ongoing for multiple cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tremelimumab</td>
<td>Previously tested in a Phase III trial of patients with melanoma; not currently active</td>
</tr>
<tr>
<td>PD1</td>
<td>Inhibitory receptor</td>
<td>MDX-1106 (also known as BMS-936558)</td>
<td>Phase I/II trials in patients with melanoma and renal and lung cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MK3475</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT-011&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMP-224&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td>PDL1</td>
<td>Ligand for PD1</td>
<td>MDX-1105</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple mAbs</td>
<td>Phase I trials planned for 2012</td>
</tr>
<tr>
<td>LAG3</td>
<td>Inhibitory receptor</td>
<td>IMP321&lt;sup&gt;l&lt;/sup&gt;</td>
<td>Phase III trial in breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple mAbs</td>
<td>Preclinical development</td>
</tr>
<tr>
<td>B7-H3</td>
<td>Inhibitory ligand</td>
<td>MGA271</td>
<td>Phase I trial in multiple cancers</td>
</tr>
<tr>
<td>B7-H4</td>
<td>Inhibitory ligand</td>
<td></td>
<td>Preclinical development</td>
</tr>
<tr>
<td>TIM3</td>
<td>Inhibitory receptor</td>
<td></td>
<td>Preclinical development</td>
</tr>
</tbody>
</table>
The Tumor **IS NOT** ignored by the IS

- Targeting the IS
  - Which targets?
    - Tumor (Antigens; mutations...)
    - Soluble factors (VEGF; IL-10; TGFβ...)
    - Immune cells (T cells; NK cells; Myeloid cells...)