CANCER AND IMMUNITY REVISITED THROUGH COSIGNALS

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Canceropole Nord Ouest  18 Mai 2016
disclosures

- Founder and shareholder of Imcheck Therapeutics
- Research grants from GSK, Innate Pharma, Genentech, Servier
- Patents licensed to GSK and Janssen
1. Cancer: Transcriptome, IHC, Deep sequencing, RNA Seq
   - TAA and TSA typing
   - HLA typing
   - Preexisting immune response

2. Exogenous Immunisation
   - Peptides
   - Proteins
   - Viral vectors
   - DNA
   - anti CD mAb fused to TSA or TAA + adjuvant

3. Endogenous Immunisation
   - Chemo
   - Rx
   - Oncolytic viruses
   - Therapeutic Mabs
   - CARs, transfected TcR

4. Combo personalized medicine
   - 4.1 Immunosuppressive mechanisms
     - Cosignaling, galectins, enzymes IDO and others, Tregs, MDSC...
   - 4.2 Costimulation

5. Monitoring
   - PFS
   - Immune parameters
     - (FCM, transcriptome, RNAseq)
   - cytometry
   - transcriptome
   - ARNseq

Blaise, D. & Olive D., Cancer Vaccines, 2014
Objectives

• **Hallmarks of cancer revisited**
  • Scientific history
  • Immune system: T cells, Ab for beginners
  • Microenvironments and ways to modify them (Tom Gajewski)
  • The cancer immunity circle (Ira Mellmann)
  • Costimulation, cosignaling
  • Classical cosignalling 1 Anti-CTLA-4
  • Classical cosignalling 2 Anti-PD1 and anti-PDL1
  • Other cosignaling molecules involved in both adaptive and innate immunity (TIGIT, CD94, BTLA)
  • Additional classes 1 ICOS
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Introduction

“Though many lay unburied, birds and beasts would not touch them, or died after tasting them. The bodies of dying men lay one upon the other [But] those who had recovered from the disease had now no fear for themselves; for the same man was never attacked twice—never at least fatally.” Thucydides, History of the Peloponnesian War 431–428 B.C.

The concept of immunity (from the Latin immunitas for “freedom from service”) had been recognized by the great historian Thucydides almost 2500 years ago.
Cancer Immunosurveillance

- R. Virchow, leukocyte infiltration of tumors 1863
- P. Ehrlich, modifications of cells might make them recognized and eliminated by the immune system, 1909
- Definition of the cellular components necessary for allogenic tumor rejection Tumor Specific Antigens (Medawar 1950)
- Tumor Associated Antigens are involved in the tumor rejection (1957-59) Foley, Prehn & Main, Old, Klein
- Mac Farlane Burnet, Immunosurveillance, 1957
Cancer Immunosurveillance

- JF Miller, identification of the role of the thymus, 1961
- JF Miller then proposed existence of two major subsets of lymphocytes, 1967
- Denomination of B and T (Brook Lodge meeting 1968): first and last letters of bullshit
- B cell Hybridoma generation Cesar Milstein and Georges JF Kohler in 1975
- Development of the first anti-CD3 mAb OKT3 (Ortho Biotech) in 1979 by P. Kung and G. Goldstein
Cancer Immunosurveillance

- 1973 Stutman, no increased incidence of tumors in nude mice
- 1975 discovery of NK cells (R. Kiessling)
- 1998 increased incidence of spontaneous and induced tumors in mice deficient in IFNg response, RAG2−/−, IL-12 p40, TCR b et d, perforin, CD1d KO, NKG2D…(Schreiber et al., Smyth et al.)
Evidences of immune control and identification of immune targets in cancer patients

- **Molecular definition of Tumor associated antigens** P. van der Bruggen et al., Science. 1991
- **Clinical trials**: M. Marchand et al., Int J Cancer. 1995; Tumor regression responses in melanoma patients treated with a peptide encoded by gene MAGE-3.
- **Better prognosis of patients with epithelial ovarian cancer and intratumoral T cells,** (Zhang et al., NEJM, 2003, Georges Coukos). Extended to memory T cells in colon cancer (Pages et al., NEJM, 2005; Science 2006, Jérome Galon)
Evidences of immune control and identification of immune targets in cancer patients

- Immune signature associated to better prognosis with an extension to B cells and Tfh (Bindea et al., Immunity, 2013)
- Type I IFN is associated with a T cell infiltrate (Fuentes MB, J. Exp.Med., 2011)
- Role of suppressive mechanisms involving Treg, B, myeloid cells, cosignaling molecules (Dong et al., Nat. Med., 2002), IDO
Adaptive immunity

- T cells therapy induces cancer control after depletion of the immune cells (Dudley, Science, 2002)
- T cells engineered to express a TcR against TAA are able to persist and control cancer (Morgan et al., Science, 2006)
- T cells engineered to express a chimeric antigen receptor against CD19 are able to persist and control CLL (Porter et al., NEJM, 2011)
Innate immunity


- NKG2D receptors are expressed by tumor cells A. Diefenbach et al., Nature. 2001. Ligands of the NKG2D receptor stimulate tumour immunity. But NKG2D ligands are shed by the tumor and prevent NK and gdT cell function

- Similar evidences for macrophages, gdT cells, NKTs, mast cells, PMN...
Immunity = prime parameter:
→ to prevent tumoral clone emergence

Cytotoxic activity of lymphocytes:
Impact on incidence rates of cancer

→ for response to chemotherapy/radiotherapy

NKp30 isoforms expression profile:
Impact on the prognosis of GIST

→ for maintenance of a prolonged remission

NK cell function:
Predictors of breast cancer outcome
Innate immunity and or adaptive immunity?

Targeted therapies using mAbs

- 1997: anti-CD20 mAbs in NHL (Rituximab).
- 1998: anti-HER2/Neu mAb Herceptin (Trastuzumab) in breast cancer.
- 2002 CD16 gene polymorphism associated to CD20 mAb response. Extended to Herceptin.
- 2011 NK function independently of CD16 polymorphism is associated to Herceptin effects.
DEFINITIONS

• Most cancers in human are immunogenic (spontaneous responses)
• Do human tumors express immune targets and might be recognized by the immune system? Yes. Basis for vaccine trials and immunointervention
• There do exist tolerance and escape/resistance mechanisms to innate and/or adaptive Immunity
• Stimulate adaptive and innate immunity
• and both inhibit the inhibitors (anti-CTLA-4, anti-PD1) and costimulate (CD40, 4-1BB, ICOS)
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• Other cosignaling molecules involved in both adaptive and innate immunity (TIGIT, CD94, BTLA)
• Additional classes 1 ICOS
Phillip K. Darcy, Paul Neeson, Carmen SM Yong, Michael H. Kershaw

Manipulating immune cells for adoptive immunotherapy of cancer
Current Opinion in Immunology, Volume 27, 2014, 46 - 52
Figure 8-22 Immunobiology, 6/e. (© Garland Science 2005)
Engineering therapeutic monoclonal antibodies
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Cancer-immunity cycle.

A. Is the number of tumor-specific T cells adequate?
   - If NO:
     - Vaccines
     - Intratumoral modulation (TLRs, STING)
     - HD+IL2
     - IL7
     - IL15
     - Anti-CTLA-4
     - Anti-41BB
     - Anti-OX40
     - CAR T-cell therapy

B. Is trafficking and penetration of tumor by T cells sufficient?
   - If NO:
     - BRAF inhibitors
     - PI3K inhibitors
     - Anti-CTLA-4
     - Anti-PD-1/PD-L1
     - Activators of IFNγ
     - Anti-VEGF
     - Anti-CXCR4
     - Inhibitors to stroma components

C. Are activated anticancer T cells inhibited in the TME?
   - If YES:
     - Anti-PD-1/PD-L1
     - IDO inhibitor
     - Treg inhibitor
     - MDSC inhibitor

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Regulation of Adaptive Immunity by Costimulation and negative signaling

Signal 1

TCR

CMH

Signal 2

Cosignaling

Signal 3

IL-12

Activation

Inhibition

Deficiency (anergy, exhaustion, senescence)
+ chronic infection
+ Cancer

Deficiency
+ Inflammation
+ AID
+ Chronic infections
Schematic representation of the concept of immunostimulatory mAbs.

Press the gas pedal:
- Receptor agonists
  - CTLA-4
  - PD-1
  - B7-H1
  - BTLA
  - CD137
  - CD40
  - OX40
  - GITR
  - CD27

Release the brakes:
- Receptor antagonists
  - LAG-3
  - TGF-β
  - IL-10

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CCR Focus

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Tumor Expression</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDL2</td>
<td>Oesophageal, ovarian, pancreatic, hepatocellular, breast, Hodgkin, mediastinal large B-cell lymphoma, among others</td>
<td>233-238</td>
</tr>
<tr>
<td>B7-H3</td>
<td>Prostate, renal cell, non-small cell lung, pancreatic, gastric, ovarian, colorectal, urothelial cell, among others</td>
<td>239-246</td>
</tr>
<tr>
<td>B7-H4</td>
<td>Breast, renal cell, ovarian, oesophageal, gastric, pancreatic, melanoma, among others</td>
<td>247-257</td>
</tr>
<tr>
<td>HHLA2</td>
<td>Breast, lung, thyroid, melanoma, pancreas, ovary, liver, bladder, colon, prostate, kidney, oesophagus</td>
<td>129</td>
</tr>
<tr>
<td>Galectins</td>
<td>Non-small cell lung, colorectal, gastric, among others</td>
<td>258-261</td>
</tr>
<tr>
<td>CD30</td>
<td>Hodgkin lymphoma, embryonal, anaplastic, large cell lymphoma</td>
<td>262</td>
</tr>
<tr>
<td>CD70</td>
<td>Non-Hodgkin lymphoma, renal cell</td>
<td>263, 264</td>
</tr>
<tr>
<td>ICOSL</td>
<td>Glioblastoma, melanoma</td>
<td>265, 266</td>
</tr>
<tr>
<td>CD155</td>
<td>Kidney, prostate, pancreatic, glioblastoma</td>
<td>267</td>
</tr>
</tbody>
</table>

Nature Reviews | Drug Discovery
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CD28 and B7 family from costimulation to cosignaling

- Ledbetter JA et al. 1986 anti-CD3+tp44/CD28
- Bretscher P. 1992 The two-signal model of lymphocyte activation twenty-one years later
- Townsend SE, Allison JP Tumor rejection after direct costimulation of CD8+ T cells by B7-transfected melanoma cells. 1993.
Anti-CTLA-4

- Cloning as a novel IgSF member Brunet et al., 1987; Function and ligand (Linsley et al., 1991; Walunas et al., 1994); POC in animal models colonic cancer but not melanoma (Leach et al, 1996)
- Mechanism: Inhibition of negative signals and Treg depletion + others...
  - Tremelimumab (IgG2), Ipilimumab (IgG1)
- Clinical activity in unresectable stage III and IV melanoma patients (Hodi et al., NEJM, 2010) Issues with anti-CTLA therapy
  - Serious Adverse Events
    - Autoimmunity: immune related (58.2%) dermatologic, GI, endocrine
    - 10-15% grade 3 or 4; 2% deaths
- Activity in melanoma, prostate, rcc, bladder, ovarian and lung in subsets of patients
- Broaden the existing T cell repertoire (Robert et al., 2014)
- Induces tumor immune cell infiltration (Huang et al., 2011)
- Approved in metastatic melanomas refractory to treatment (2011/12/11) extended to non treated patients (2014)
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**PD-1 PDL-L1**

- Cloning Ishida et al., 1992; cosignaling molecule (Nishimura et al., 1998); POC in cancer (Dong et al., 2002)
- Two ligands PD-L1 and PD-L2
- Involved in tolerance (KO mice develop strain and organ dependent AID)
- Used in cancer treatment (inhibition of negative signals)
- Responses in large series of tumors except prostate and colon (except MSI)
- Does not expand clonal diversity
- Recurrences have been described
Inhibitory function of PD-1 and BTLA

TCR signals

Bcl-X
IL-2

ITIM (V/IxYxxL/V)
ITSM (TxEYxxV/I)
Innate (tumor cell intrinsic) resistance

Constitutive tumor signaling induces PD-L1 on tumor cells

Adaptive resistance

T cell induced PD-L1 up-regulation

Cross-presentation of tumor antigen?
PDL1, PDL2 gene amplification in HL and cancers

Ansell et al NEJM 2015
Overall Survival, Duration of Response, and Progression-free Survival in patients with NSCLC

Examples of adaptive immune resistance.

Antoni Ribas Cancer Discovery 2015;5:915-919
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Regulation of Adaptive Immunity by Costimulation and negative signaling

Signal 1: TCR

Signal 2: Co-stimulator, Co-inhibitor

Signal 3: IL-12

Activation: + chronic infection + Cancer

Inhibition: + Inflammation + AID + Chronic infections

Deficiency (anergy, exhaustion, senescence)

Antigen: APC

Cosignaling
HVEM LIGHT BTLA CD160 AXIS

TNF superfamily
- LT(3)
- LIGHT

Ig superfamily
- BTLA
- HSV1 gD
- CD160

LT(R) DcR3 HVEM MHC I

TNFR superfamily

+
BTLA-HVEM Serves as Negative Regulator of Immune Responses in Cancer

- Melanoma and leukemic specific T cell responses
  - BTLA highly expressed on melanoma antigen-specific effector CD8 T cells
  - BTLA activation suppresses cancer-specific CD8 T cells

- γδ T-mediated anti-lymphoma responses
  - BTLA strongly expressed on resting γδ T cells
  - BTLA-HVEM ligation suppresses γδ T responses
  - Lymphoma cells suppress γδ T cells proliferation via BTLA-HVEM ligation
  - Suppression blocked by BTLA-HVEM mAbs

- B cell responses
  - CpG upregulates BTLA in vitro & in vivo in melanoma
  - BTLA-HVEM ligation suppresses B cell responses
  - Suppression blocked by BTLA-HVEM mAbs
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Inducible T cells costimulator (ICOS)

ICOS-L downregulation

DC, B cells, Monocytes

Activated T cells, TFH, Tregs

Survival and proliferation

Th1
Th2
Th17
TFH

Differentiation

Cytokine production
IL-10, IL-4, IL-21, IFN-γ, TNF-α, ...

Cooperation (germinal center formation and antibody response)
Tregs: prognosis marker in tumor

- Adverse Prognosis marker on solid tumors (breast), positive prognosis marker (H&N, FL)

Mougiakakos et al, 2010
Yang et al, 2007, 2009
Martin-Orozco et al, 2010
Faget et al, 2012
Conrad et al, 2012
Tregs in B-cell lymphomas (FL)

1. Impact of ICOS/ICOSL pathways in mechanisms of Tregs generation?

2. Expression markers and function of Tregs in microenvironment of FL?

ICOS/ICOSL pathway: Tregs expansion in solid tumors

Ame-Thomas et al, 2012
Yang et al, 2007, 2009
Carreras et al, 2006
Tzankow et al, 2008

Martin-Orozco et al, 2010
Faget et al, 2012
Conrad et al, 2012
Accumulation of Tregs and ICOS$^+$ Tregs in FL
ICOS / ICOSL interaction

ICOSL is absent from B lymphoma cells, pDC, mDC from FL but present on DLBCL
ICOS / ICOSL interaction induces downregulation of ICOSL on follicular lymphoma B cells.
ICOS / ICOSL interaction induces enrichment of Treg in Follicular lymphoma
Role of Tregs in the development of FL B cells

Lymphoma infiltrating- Tregs suppress lymphoma B cells responses
Conclusions

Agonist anti-ICOS mAb would enhance Tregs proliferation and function.
Whereas antagonist anti-ICOS mAb would prevent Treg survival and function.
CD20, (CD33, CD25, CD44) ADC (CD30) PD1, CTLA-4

Bispecific CAR

Gleevec Dasatinib...

IMIDs, demethylating agents, TLR agonists, HDACi

1999- 2016

WT-1, PR1, MAGE-A3
Immunotherapy in leukemias and lymphomas using mAbs and derivatives

- Targeting the CD28/B7 family
  - CTLA-4: CTLA-4 polymorphism and relapse (Perez-Garcia, 2009); Ipilimumab (ongoing)
  - Nivolumab received US FDA breakthrough therapy designation for HL

- Targeting Tregs CD25 basiliximab, daclizumab, denileukin diftitox immunotoxin

- Targeting NK cells anti-KIR (Lirilumab, AML, Vey, 2012; myeloma, Benson, 2012); CD123/CD33/CD16 (Triplebody SPM2); CD16xCD33 Bispecific killer cell engager (BiKE)

- Naked mAbs
- ADC (brentuximab vedotin)
- Synthetic biology (CARs, TcR)
Drugs and vaccines regulating immune responses in cancer patients

- 1985 ex vivo expanded LAK and TILs for melanoma patients
- 1992 Interleukin 2 in metastatic renal cell cancer then for expansion of CD8 and NK cells. At a preclinical stage complex of IL2 and anti-IL2 (SAB6, MAB602)
- 1997 anti-CD20 (rituximab) for non hodgkin lymphoma then Herceptin and others
- Therapeutic vaccine trials by GSK ASCO 2006 increased survival in patients vaccinated with MAGE-A3 protein in NSCLCC. Phase III stopped due its negative results
- PROVENGE® (sipuleucel-T) (FDA Approved)
- mAbs against cosignaling molecules (2002 then 2010) anti-CTLA-4 FDA approved 2011, anti-PD1 FDA approved 2014 melanoma followed by NSCLCC, H&N, urothelial, HL...
- Bispecific mAbs (blinatumomab FDA approved 2014 Amgen)
- CARs (FDA approved 2014, Novartis, Juno Therapeutics, KITE)
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   TAA and TSA typing
   heterogeneity
   HLA typing
   Preexisting immune response

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   Peptides
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cytométrie
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Blaise, D. & Olive D., Cancer Vaccines, 2014
Gene therapies: synthetic biology
Annu. Rev. Med. 65:333–47
Gene-modification of peripheral blood lymphocytes.

Steven A. Rosenberg, and Nicholas P. Restifo Science
2015;348:62-68
Persistence of CTL019.

Truncated protein isoforms of CD19 provide proliferative advantage while evading CART-19.

Elena Sotillo et al. Cancer Discov 2015;5:1282-1295
Current CAR design allows for MHC-independent antigen recognition and incorporates costimulatory signal(s) endowing the transduced T cell with potent cytotoxic activity.
Figure 3 Chimeric antigen receptors

Mackall, C. L. et al. (2014) Immune-based therapies for childhood cancer
General schema for the preparation, transduction, and infusion of CAR-modified T cells.
Lymphodepleting preparatory regimens can enhance the efficacy of adoptive cell therapy.
IL-6 signaling and inhibition by tocilizumab.

Treatment algorithm for management of CRS based on the revised CRS grading system.

Gene therapies: synthetic biology
Gene-modification of peripheral blood lymphocytes.

Steven A. Rosenberg, and Nicholas P. Restifo Science 2015;348:62-68
Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.

MS Lawrence et al. Nature **000**, 1-5 (2013) doi:10.1038/nature12213
Radial spectrum plot of the 2,892 tumour samples with at least 10 coding mutations.

MS Lawrence et al. Nature **000**, 1-5 (2013) doi:10.1038/nature12213
Mutation rate varies widely across the genome and correlates with DNA replication time and expression level.

Figure 2 Tumour cell death induced by monoclonal antibody based therapeutics

Mackall, C. L. et al. (2014) Immune-based therapies for childhood cancer
Blocking antagonist, e.g. Fc-null IgG
Depleting antagonist; mouse IgG2a or human IgG1
FcyR-dependent agonist, mouse IgG1 being most potent
Human IgG2 FcyR-independent agonist
Activatory FcyR
Inhibitory FcyRIIB
Inhibitory ligand
Inhibitory receptor
Immunostimulatory receptor (mostly TNFR)
Target Antigen for cytotoxic Ab
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- Approved in metastatic melanomas refractory to treatment (2011/12/11) extended to non treated patients (2014)
Immunohistochemical analysis of CD8+ cell infiltration before and after tremelimumab in 4 representative patients.

Rong Rong Huang et al. Clin Cancer Res 2011;17:4101-4109
Somatic Neoepitopes of Melanomas and Benefit from CTLA-4 Blockade.

Daniel S. Chen, Ira Mellman

Oncology Meets Immunology: The Cancer-Immunity Cycle

Immunity Volume 39, Issue 1 2013 1 - 10
Figure 1 Selected cell surface molecules with important roles in immune-based therapies

Mackall, C. L. et al. (2014) Immune-based therapies for childhood cancer
Classes of cosignaling molecules

- Regulating costimulation
- Inhibiting inhibitory pathways
- Checkpoint blockade inhibitors and others
- Regulating different immune effector populations
- Innate effectors and B cells
Fig. 1 Nonsynonymous mutation burden associated with clinical benefit of anti–PD-1 therapy.

Naiyer A. Rizvi et al. Science 2015;348:124-128

Published by AAAS
Fig. 2 Molecular smoking signature is significantly associated with improved PFS in NSCLC patients treated with pembrolizumab. PFS in tumors characterized as TH by molecular smoking signature classifier (n = 16) compared to TL tumors (n = 18) (HR 0.15, 95% 0.06 to 0.39, log-rank P = 0.0001).

Naiyer A. Rizvi et al. Science 2015;348:124-128

Published by AAAS
Fig. 3 Mutation burden, clinical response, and factors contributing to mutation burden. Total exonic mutation burden for each sequenced tumor with nonsynonymous (dark shading), synonymous (medium shading), and indels/frameshift mutations (light shading) displayed in the histogram.

Naiyer A. Rizvi et al. Science 2015;348:124-128

Published by AAAS
Fig. 4 Candidate neoantigens, neoantigen-specific T cell response, and response to pembrolizumab.

Naiyer A. Rizvi et al. Science 2015;348:124-128

Published by AAAS
Escape mechanism involving BTLA and HVEM in NHL?
HVEM, BTLA and CD160 expression in NHL lymph nodes
BTLA blockade restores autologous gd T cell proliferation in coculture with Follicular Lymphoma
Treatment selection based on detecting adaptive immune resistance.

Block adaptive immune resistance

Bring T cells into tumors:
- + anti-CTLA-4
- + immune-activating antibodies or cytokines
- + TLR agonists or oncolytic viruses
- + macrophage inhibitors
- + targeted therapies

Generate T cells:
- Vaccines
- TCR-engineered ACT
- CAR-engineered ACT

Antoni Ribas Cancer Discovery 2015;5:915-919
T cell targets for immunoregulatory antibody therapy.

I Mellman et al. Nature 480, 480-489 (2011) doi:10.1038/nature10673
Types of tumor microenvironment to tailoring cancer immunotherapeutic modules.

Michele W.L. Teng et al. Cancer Res 2015;75:2139-2145