What is Cancer Immunotherapy?

• Treatment of cancer by immunologic approach…
Key Events in the History of Cancer Immunotherapy

**Enthusiasm Phase** 1978-1985
- 1953: Coley's work first published
- 1976: Immune component to spontaneous regressions in melanoma
- 1978: Tumor specific mAb

**Skepticism Phase** 1985-1997
- 1978: INF-α approved as HCL cancer immunotherapy
- 1985: Adoptive immunotherapy for patients with cancer & hybridoma methodology
- 1986: INF-α approved as adjuvant therapy
- 1991: First tumor-associated antigen cloned (MAGE-1)
- 1996: IL-2 approved for RCC & melanoma

**Renaissance Phase** 1997-
- 1998: IFN-α approved as adjuvant therapy
- 2004: Avastin & Cetuximab approved
- 2006: Panitumumab approved
- 2010: First cellular immunotherapy approved for prostate cancer (Provenge)
- 2011: - Peg IFN approved (adjuvant)
  - Ipilimumab/Anti-CTLA-4 Approved for advanced melanoma

Innate vs. Adaptive Immune Players

G. Dranoff Nature Reviews Cancer Jan 2004; Moran, A from SITC
Mechanisms of Immune Suppression

Tumor Microenvironment

Elimination

Escape

Monjazeb et al. frontiersin. Jul 2013
Activation of T cells requires two signals.

Sharma P, Alison JP. Science 2015;348:56
Direct Evidence that Immunity is Important in Cancer

- Immune deficient mice are more susceptible to spontaneous and carcinogen-induced tumor growth.
- Interleukin-2 has anti-tumor activity in murine and human tumors (Rosenberg, S et al. NEJM 1985).
- Checkpoint protein inhibition with anti-CTLA-4 antibody is active in melanoma (Hodi, S et al. NEJM 2010).
- Infusion of T cells (TIL) has anti-tumor efficacy in melanoma (Dudley, M et al. JCO 2013).
<table>
<thead>
<tr>
<th>Year</th>
<th>Citation Title</th>
<th>Journal</th>
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<tr>
<td>2012</td>
<td>Tumor immunotherapy-leukocytes take up the fight</td>
<td>Nat Rev Immunol</td>
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<td>Immunotherapy: Combinations that work</td>
<td>Nat Rev Cancer</td>
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<td>Immunotherapy: A killer combination</td>
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<td>The blockade of immune checkpoints in cancer immunotherapy</td>
<td>Nat Rev Cancer</td>
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<td>2013</td>
<td>Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy</td>
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<td>Cancer immunotherapy for the elderly</td>
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<td>Neuroblastoma: developmental biology, cancer genomics and immunotherapy</td>
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<td>Immunotherapy: Immunological bullets against Alzheimer’s disease</td>
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<td>Immunotherapy: Cancer mutation-specific immune responses</td>
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<td>Immunotherapy: Understanding side effects</td>
<td>Nat Rev Cancer</td>
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<td>2014</td>
<td>Thermal ablation of Tumors: biological mechanisms and advances in therapy</td>
<td>Nat Rev Cancer</td>
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<td>Tumor antigens recognized by T lymphocytes: at the core of cancer immunotherapy</td>
<td>Nat Rev Cancer</td>
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Px Immune system
Immunotherapy Strategies

- Antibodies
- Cancer Vaccines
- Modulators of Immune responses (MOIs) e.g. cytokines
- Adoptive T cell therapies
- Combination of the approaches
Antibody

Autologous tumor-associated antigens (TAAs) include New York-esophageal-1 (NY-ESO-1), p53, human epidermal growth factor receptor 2 (Her2)/neu, survivin, folate receptor-a, sperm surface protein Sp17, WT1, MUC1, melanoma associated antigen-3 (MAGE3) and human telomerase reverse transcriptase (hTERT).

Role of an Antigen-Presenting Cell

1. Phagocytosis of enemy cell (antigen)
2. Fusion of lysosome and phagosome
3. Enzymes start to degrade enemy cell
4. Enemy cell broken into small fragments
5. Fragments of antigen presented on APC surface
6. Leftover fragments released by exocytosis

Normal cell

Tumor-associated antigens

Normal cell-surface antigens
Monoclonal antibodies for cancer. ADEPT, antibody directed enzyme prodrug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity; MAb, monoclonal antibody; scFv, single-chain Fv fragment

Immune checkpoint therapy

Activating receptors:
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory receptors:
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Agonistic Abs

Blocking Abs

T cell stimulation
Cancer Vaccine

• Majority used for treatment not prevention
• May offer method that can enhance the immune response against cancer
• HPV vaccine: Immunity to the virus causing cervical Ca.
• Traditional prophylactic vaccines: provide immunity to a particular disease
• Cancer vaccines
  – Dendritic cell, Antigen, Anti-idiotype, DNA, Tumor cell
• **OncoVax**
  – Autologous vaccine for Stage II colon cancer
  – 254 patients received either OncoVAX or placebo
  – Improves 5-year survival and recurrence-free interval
  – 57.1% relative risk reduction

• **Sipuleucel-T (Provenge)**
  – Asymptomatic Androgen-Independent Prostate Cancer (AIPC).
  – Target-prostatic Acid Phosphatase (PAP)
  – 3.3 months or 21% improvement in MS
Modulators of Immune responses (MOIs)

Cytokines in cancer pathogenesis and cancer therapy, Nature Reviews Cancer 4, 11-22 (January 2004)
Tumor Immunity: Stimulation vs Inhibition

1. Release of cancer cell antigens
   - Immunogenic cell death
   - Tolerogenic cell death

2. Cancer antigen presentation
   - TNF-α
   - IL-1
   - IFN-α
   - CD40L/CD40
   - CDN
   - ATP
   - HMGB1
   - TLR
   - IL-10
   - IL-4
   - IL-13
   - Stimulatory factors
   - Inhibitors

3. Priming and activation
   - CD28/B7.1
   - CD137/CD137L
   - OX40/OX40L
   - CD27/CD70
   - HVEM
   - GITR
   - IL-2
   - IL-12
   - CTLA4/B7.1
   - PD-L1/PD-1
   - PD-L1/B7.1
   - Prostaglandins

4. Trafficking of T cells to tumors
   - CX3CL1
   - CXCL9
   - CXCL10
   - CCL5

5. Infiltration of T cells into tumors
   - LFA 1/ICAM1
   - Selectins
   - VEGF
   - Endothelin B receptor

6. Recognition of cancer cells by T cells
   - T cell receptor
   - Reduced pMHC on cancer cells

7. Killing of cancer cells
   - IFN-γ
   - T cell granule content
   - PD-L1/PD-1
   - LAG-3
   - Arginase
   - IDO
   - MICA/MICB
   - TGF-β
   - B7-H4
   - BTLA
   - TIM-3/phoephopholipids
   - VISTA

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<thead>
<tr>
<th>Cytokine</th>
<th>Therapeutic actions</th>
<th>Clinical administration</th>
<th>Phase of clinical trials</th>
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<tr>
<td>IL-2</td>
<td>Enhances NK cell and CD8+ T-cell function; increases vascular permeability</td>
<td>Systemic, local</td>
<td>III</td>
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<tr>
<td>IL-3</td>
<td>Enhances tumour antigen presentation</td>
<td>Systemic</td>
<td>II</td>
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<td>IL-4</td>
<td>Enhances eosinophil function and T-cell activation</td>
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<td>IL-6</td>
<td>Enhances T-cell and B-cell function; inhibition of IL-6 reduces lymphoproliferation</td>
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<td>IL-7</td>
<td>Enhances T-cell function</td>
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<td>IL-10</td>
<td>Inhibits tumour antigen presentation</td>
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<td>IL-12</td>
<td>Enhances T_H_1 immunity and cytotoxicity; inhibits angiogenesis</td>
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<td>IL-13</td>
<td>Inhibits cytotoxicity against viral neoplasms</td>
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<td>IL-15</td>
<td>Enhances cytotoxicity</td>
<td>Pending</td>
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<td>IL-18</td>
<td>Enhances T_H_1 immunity and cytotoxicity; inhibits angiogenesis</td>
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<td>M-CSF</td>
<td>Enhances macrophage function</td>
<td>Systemic</td>
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<td>GM-CSF</td>
<td>Enhances tumour antigen presentation</td>
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<td>IFN-α</td>
<td>Enhances tumour antigen presentation and cytotoxicity</td>
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<tr>
<td>IFN-γ</td>
<td>Enhances tumour antigen presentation and cytotoxicity</td>
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<td>III</td>
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<td>TNF-α</td>
<td>Induces tumour-cell apoptosis; activates endothelium and granulocytes</td>
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<tr>
<td>TRAIL</td>
<td>Induces tumour-cell apoptosis</td>
<td>Pending</td>
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<td>FLT3 ligand</td>
<td>Stimulates dendritic-cell and NK-cell function</td>
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<td>Lymphotactin</td>
<td>Enhances T-cell recruitment</td>
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<td>TGF-β</td>
<td>Inhibits T-cell effector function</td>
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</table>
Adoptive T cell therapies

- TIL (Tumor infiltrating lymphocyte)
- T cell clones
- Transduced TcR T cells
- Chimeric antigen receptor T cells (CAR)
- NK/NKT cells
Adoptive Cell Transfer (ACT) Therapies
Nicholas P. R et al, Nature Reviews, April 2012
Targeted therapy

a Pro-apoptotic signal

b Increased antigen presentation

c Decreased immunosuppression

Recruitment and activation of adoptively transferred T cells

Recruitment and activation of endogenous T cells

Treatment with cytokines, chemokines, anti-angiogenic factors

Dying tumour cells

Adoptive cell transfer

Tumour antigen

APC

Tumour-derived peptide

MHC class I

TCR

Killing

Proliferation

Tumour cells

T_{Reg} cell

MDSC

T cells
WHAT ARE THE IMPEDIMENTS TO SUCCESSFUL ANTI-TUMOR IMMUNITY?
What are the impediments to successful anti-tumor immunity?

• Most tumor antigens that could be recognized by T cells are self related, to which we are tolerant; high affinity anti-tumor T cells may be deleted in embryonic cells

• Chemotherapy-treated patients have weak immunity

• The tumor microenvironment has many suppressive influences
  – High levels of suppressive cytokines
  – T regulatory cells
  – Myeloid derived suppressor cells
  – Low expression of MHC molecules, antigens
  – High expression of PD-L1 by tumors
  – High levels of checkpoint proteins by T cells
Toxicity of ACT when targeting antigens shared by tumors and normal tissue

• Marked potency of T cells enables the recognition of minute levels of Ag expressed on normal cells
• Expressed on normal tissues but overexpressed on tumor → severe on-target, off-tumor toxicity
  – Skin, eyes and ears of PTs d/t expression of melanocytes in these organs
  – Renal ca: T cells encoding CAR (Carbonic anhydrase 9 target) → severe liver toxicity d/t expression of this Ag in biliary duct epithelium
  – Colorectal ca: high-affinity TCR against CEA → life-threatening colitis & colonic hemorrhage
• Unexpected toxicities
  – MAGE-A3 (Cancer testes Ag): severe damage to brain gray matter
  – CARs - toxicity against self-Ag, Acute pulmonary toxicity
  – Affinity-enhance TCRs by altering AA → fatal cardiogenic shock
• Cytokine storm featuring high levels of IL-6 complicate treatment
• CNS symptoms, high fevers and hypotension have been a problem
Conclusion

- Tumor immune surveillance is a real phenomenon
- Tumor immunity faces many hurdles due to the escape from elimination of many tumor antigens
- Mutated neoantigens and viral antigens may be the best antigens for generation of potent immunity
- Immune suppressive mechanisms that exist in cancer might be overcome as shown by the recent success of checkpoint protein inhibition
- Highly expensive cost is another barrier
- Promising prognostic or predictive marker is necessary
감사합니다