TUMOR IMMUNOLOGY & CANCER IMMUNOTHERAPY

new advancement in cancer treatment

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Overview

- Introduction
- Milestones in Immuno-Oncology
- Immunosurveillance of Cancer
- Immunotherapy
  - Antigen-specific Immunotherapy
    - Active Immunotherapy
    - Passive Immunotherapy
  - Immune Checkpoint Blockade
    - Blocking B7/CTLA-4 Interaction
    - Blocking PD1/PD-L1 Interaction
  - Beyond Immune Checkpoint Blockade
Introduction

Cancer is a major health problem worldwide and is one of the most important causes of morbidity and mortality in children and adults.

**Tumor immunology is the study of**

- antigenic properties of transformed cells
- host immune response to these tumor cells
- immunologic consequences to the host of the growth of malignant cells
- means by which the immune system can be modulated to recognize tumor cells and promote tumor eradication
Goal of cancer treatment

1. Cure
2. Prolong life
3. Improve quality of life
4. Target symptoms rather than disease

VA Study 75: Coumadin vs. Placebo with Chemo for Various Cancers

Zacharski, Cancer 1984
Advances can come in two flavors

• Improve the identification of patients likely to benefit from therapy. Response 100%.

• Improve response and survival for the whole group of patients.
Milestones of Immuno-Oncology

- **1860**: First Tumor-Immunotherapy using bacteria (Wilhelm Busch)
- **1890s**: Vaccination with bacteria extracts; William Coley (Coley-Toxin)
- **1900**: "Magic bullets" recognize tumor cells (Paul Ehrlich)
- **1957**: Tumor Immunosurveillance Hypothesis (F. Burnet Thomas)
- **1969**: First allogeneic stem cell transplantation in leukemia in Seattle (Edward D. Thomas)
Milestones of Immuno-Oncology

- **1970**: Immune system induces spontaneous regression of melanoma
- **1980**: Cloning of first Tumor-antigen (MAGE-1)
- **1990**: Approval of IL-2 therapy for metastatic RCC and melanoma (US)
- **2000**: Approval of Rituximab for the therapy of B-Zell-lymphoma
- **2011**: Approval of the first Checkpoint Inhibitory molecule Ipilimumab for the treatment of metastatic melanoma

**Key Events**
- **1970**: Discovery of Dendritic cells
- **1971**: Approval of BCG (Bacillus Calmette-Guérin) for bladder cancer
- **1980**: First tumor-specific monoclonal antibody
- **1990**: First adoptive T-cell Immunotherapy
- **1990**: Discovery of Checkpoint Inhibitory Molecules
- **1990**: Approval of IFN-α as adjuvant therapy of melanoma
- **2000**: Approval of Immunotherapy for prostate cancer (Sipuleucel-T)
CinicalTrial.gov: ~2000 immunotherapy trials
Immunosurveillance Hypothesis

- 1909 „... the immune system recognizes and eliminates developing tumors...“
  Paul Ehrlich

- 1957 „... the primary function of cellular immunity is in fact not to promote allograft rejection but rather to protect from neoplastic disease, thereby maintaining tissue homeostatis in complex multicellular organisms.“
  Lewis Thomas

„It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction with regression of the tumour and no clinical hint of its existence.“
  Sir Macfarlane Burnet

- 1964 „In large, long-lived animals, like most of the warm-blooded vertebrates, inheritable genetic changes must be common in somatic cells and a proportion of these changes will represent a step towards malignancy. It is an evolutionary necessity that there should be some mechanism for eliminating or inactivating such potentially dangerous mutant cells and it is postulated that this mechanism is of immunological character.“
  Sir Macfarlane Burnet
Evidence supporting the concept of immunosurveillance

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathologic and clinical observations: lymphocytic infiltrates around</td>
<td>Immune responses against tumor inhibit tumor growth</td>
</tr>
<tr>
<td>some tumors and enlargement of draining lymph nodes correlate with better</td>
<td></td>
</tr>
<tr>
<td>prognosis</td>
<td></td>
</tr>
<tr>
<td>Experimental: transplants of a tumor are rejected by animals previously</td>
<td>Tumor rejection shows features of adaptive immunity (specificity and memory) and is mediated by lymphocytes</td>
</tr>
<tr>
<td>exposed to that tumor; immunity to tumor transplants can be transferred</td>
<td></td>
</tr>
<tr>
<td>by lymphocytes from tumor-bearing animals</td>
<td></td>
</tr>
<tr>
<td>Clinical and experimental: immunodeficient individuals have an increased</td>
<td>The immune system protects against the growth of tumors (the concept of</td>
</tr>
<tr>
<td>incidence of some types of tumors</td>
<td>immune surveillance)</td>
</tr>
</tbody>
</table>
Spontaneous tumors in immunodeficient mice

RAG2-/-: no B and no T cells
STAT1-/-: defect in IFNγ signaling

Shankaran V, Nature 2001
Successful immunosurveillance in humans?

Ovarian cancer St. III, IV

Zhang et al. NEJM 2003

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Tumor antigens: Classification by specificity of the antigens

Tumor-specific antigen (TSA):
• Antigens found only in tumor cells.

Tumor-associated antigen (TAA):
• Antigens found not only in tumor cells, but also in some normal cells, but the quantity is significantly higher in tumors than that in normal tissues.
Tumor antigens: Classification by the origin and the nature of the antigens

- **Mutated self protein**: TSAs that are induced by carcinogens or radiation.

- **Product of oncogene or mutated tumor suppressor gene**: mutated Ras, Bcr/Abl fusion proteins; mutated p53 protein.

- **Overexpressed or aberrantly expressed self protein**: Tyrosinase, gp100, MAGE, MART proteins.

- **Oncogenic virus antigen**: human papillomavirus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV-induced lymphomas.
Immune responses against cancer

- **Innate immunity**
  - natural killer cells (NK-cells)
  - complement
  - macrophages

- **Acquired immunity**
  - antibodies
  - helper cells (CD4\(^+\) T-cells)
  - Cytotoxic T-cells (CD8\(^+\) T-cells)
T cells and immune responses against cancer

**CD8\(^+\) T cells: Cytotoxic T Lymphocytes (CTL)**

- CTLs are very effective in killing of tumor cells when the number of tumor cells is less, e.g. at the early stage or after surgical removal of the tumor.
- Kill tumor cells via perforins and apoptosis

**CD4\(^+\) T cells: Th cells**

- Th1 cells secrete cytokines such as IFN-\(\gamma\) and IL-2 that help activation of CD8\(^+\) CTLs or kill tumor cells.
- Th1 cells express FasL that induce apoptosis of tumor cells.
- Th2 cells help B cells to produce antibodies that may kill tumor cells.
B cells and immune responses against cancer

- Serve as APCs to present tumor antigens to T cells.
- Secrete tumor specific antibodies that may kill tumor cells by CDC and ADCC, which is effective mostly against non-solid tumors.
- Opsonization of tumor cells: opsonized tumor cells are killed more readily.
- Blockade of adhesive properties of tumor cells, hereby inhibiting outgrowth and metastasis of tumor.
NK cells and immune responses against cancer

- Involved in immune surveillance
- Non-specific, non-MHC restricted
- Kill by direct contact via perforins
- Kill by ADCC
- Important in early stage - before CTLs
Macrophages and immune responses against cancer

- Mφ are important in tumor immunity as APCs to stimulate the immune response and as potential effector cells to mediate tumor lysis.

- Activated Mφ may produce cytotoxic factors (such as reactive oxygen intermediates, TNF-α, etc.) that mediate killing of tumor cells.

- Studies in knockout mice have shown that the production of nitric oxide (NO), which is a mediator of tumor apoptosis, may be the most critical mechanism employed by Mφ.
Induction of T cell responses to tumors

Induction of a tumor-specific CTL response

**Signal 1 + Signal 2**

- ICAM-1
- LFA-1
- LFA-3
- CD40-CD40L
- CD27-CD70
- IL-2

**activation**

**Signal 1**

- T
- B7
- CD28

**anergy deletion**
Mechanisms by which tumors evade immune responses

- Lack of tumor antigens or low antigenicity
- Loss of MHC antigens, or non-classical MHC (MHC-I↓)
- Lack of Co-stimulatory molecules
  Tumor cells lack B7 and other adhesion molecules (LFA-1, LFA-3, ICAM-1); anergy
- Tumor cells express FasL or Bcl-2 induces apoptosis of T-cell
- Tumor cells can upregulate the expression immune check point inhibitors like PD-1 or PDL1 which can promote peripheral T cell exhaustion
- Poor function of antigen-presenting cells
- Immunosuppressive substances
  Tumor derived (TGF-β), IL-10, VEGF...
- Immunoselection
  Immune attack selects tumors cells of low (no) immunogenicity
- Host immunodeficiency (genes, infection, suppression/depression)
- Induction of suppressor cells
  Tumors activate suppressor cell activity (T, Mϕ, Myeloid-derived suppressor cells, toleragenic DC...)
Cancer Immunity cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Chen and Mellman, 2013
Immunosurveillance and Immunoediting

Transformed
- MICA/B1
- ULBP
- Tumor antigens
- Rae-1
- H60 (Mouse)

Danger: uric acid, ECM products
- e.g., ↓ p53
- ↓ Rb
- ↑ Ras

Carcinogens
- Radiation
- Chronic inflammation
- Inherited
- Viruses

Normal

Elimination (Cancer Immunosurveillance)
- Innate & Adaptive Immunity
- IFNγ
- Perforin
- TRAIL

Equilibrium
- Genetic instability/immune selection

Escape
- CD8+
- CD4+ Treg
- Galactin-1
- MHC-I

Protection
- NK
- CD8
- CD4

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Immune checkpoints: T cell exhaustion

- naive T-cell
- effector T-cell
- antigen
- antigen is eliminated
- antigen persists
- «exhausted» T-cell
- Memory T-cell
- Effector-function
- Apoptosis
- PD-1
- TIM-3
- LAG-3
- ....and many more
Exhaustion of cancer-specific T cells

Exhausted gene set enrichment in Melan-A-specific T cells from TILN

Baitsch L, J Clin Invest 2011
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Cancer immunotherapy

Active Immunization
- Inactivated tumor cells
- Tumor antigens, peptides
- Dendritic cells
- DNA vaccination
- Viral vectors

Passive Immunization
- Infusion of autologous T cells
- DLI of allogenic T cells after bone marrow transplantation
- Infusion of monoclonal antibodies

Immune Modulation
- Checkpoint Inhibitors
- IDO
- Depletion of Tregs, MDSCs
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Active immunotherapy for tumors

Vaccination of the patient or animal model with tumor vaccines to enhance the active anti-tumor immunity

**Types of tumor vaccines**

- Cell extracts and oncolysates
- Whole tumor cell vaccine
  - Wild-type tumor cells
  - Gene-modified tumor cells
- Tumor DNA vaccine
- Tumor peptide vaccine
- Viral vectors
- Dendritic cells
Autologous Cell Vaccines

(1) Harvest tumor cells

(2) Prepare vaccine

(3) Administer to same patient
Multivalent Cell Vaccines

Antigens are processed and pooled from several melanoma cell lines to make a multivalent vaccine
DNA Vaccines

1. Insert genes to be expressed (peptide antigen genes, GM-CSF gene, IL2 gene, etc.) into plasmid vector(s)

2. Prepare vaccine (usually an adjuvant of some type plus naked plasmid DNA)

3. Genes are expressed in skeletal muscle cells or adipocytes where they facilitate an immunologic response
Recombinant (DNA) Cell Vaccines

(1) Harvest tumor cells

(2) Genetic manipulation of cells

(3) Irradiate cells

(4) Prepare live cell vaccine

(5) Inject vaccine into same patient
Vaccination
Peptide-based Immunizations
Adjuvants!

The immunologists dirty little secret


- enhance immunogenicity
- depot effect

- Aluminium salts
- Tensoactive compouds (Saponin)
- Microorganism-derived adjuvants (LPS, CpG)
- Emulsions (Freund‘s, Montanide)
- Cytokines (GM-CSF)
Shrinkage of melanoma metastasis after peptide immunisation

4 cm mass prior to vaccination

70% regression 4 months post-vaccine
# Phase II/III studies with active vaccination (NSCLC)

<table>
<thead>
<tr>
<th>Investigational agent</th>
<th>Study</th>
<th>n</th>
<th>Patients</th>
<th>Primary endpoint</th>
<th>Treatment-group</th>
<th>Control</th>
<th>Significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tecemotide</strong></td>
<td>II</td>
<td>171</td>
<td>IIIB or IV, SD or OR after 1. L chemotherapy</td>
<td>OS</td>
<td>17.2 m</td>
<td>13 m</td>
<td>ns</td>
<td>Butts 2011</td>
</tr>
<tr>
<td>peptide vaccine, which targets the exposed core peptide of MUC-1</td>
<td>III</td>
<td>1513</td>
<td>IIIA, SD or OR after 1. L chemoradiotherapy</td>
<td>OS</td>
<td>25.6 m</td>
<td>22.3 m</td>
<td>ns</td>
<td>Butts 2014</td>
</tr>
<tr>
<td><strong>Blengpumatumucel-L</strong></td>
<td>II</td>
<td>75</td>
<td>II, IIIA, IIIB and IV; after chemotherapy</td>
<td>OS</td>
<td>Dose related improvement in OS</td>
<td>NA</td>
<td></td>
<td>Nemunaitis 2006</td>
</tr>
<tr>
<td>allogeneic tumor cell vaccine</td>
<td>III</td>
<td>532</td>
<td>IIIA, IIIB, and IV SD or OR after 1. L chemotherapy</td>
<td>OS</td>
<td>20.3</td>
<td>17.8</td>
<td>ns</td>
<td>Giaccone 2013</td>
</tr>
<tr>
<td><strong>MAGE A3 vaccine</strong></td>
<td>II</td>
<td>182</td>
<td>IB/II MAGE-A3 expressing tumors</td>
<td>DFI</td>
<td>HR 0.74</td>
<td></td>
<td>ns</td>
<td>Vansteenkiste 2007</td>
</tr>
<tr>
<td>protein-based vaccine</td>
<td>III</td>
<td>2312</td>
<td>IB/II and IIIA MAGE-A3 expressing tumors</td>
<td>DFI</td>
<td>60.9</td>
<td>57.9</td>
<td>ns</td>
<td>Vansteenkiste 2015</td>
</tr>
</tbody>
</table>
Dendritic cell immunization

- Professional antigen presenting cells
- Express co-stimulatory molecules that activate T cells

Tumor cell

- lysis
- Acid elution
- synthesis
- extraction

Cell lysate

Native peptide

Antigen peptide

mRNA

cDNA

Transfection

vector

TAA cDNA

Fusion

Antigen presentation to T cell
## Immunotherapy: Dendritic cell immunization

<table>
<thead>
<tr>
<th>Tumor (Stage IV)</th>
<th>antigen</th>
<th>DC</th>
<th>immune Response</th>
<th>clinical response CR+PR</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>melanoma</td>
<td>MAGE-3 peptide</td>
<td>Mo-DC</td>
<td>8/8</td>
<td>0/8</td>
<td>Schuler et al. J Immun 2000</td>
</tr>
<tr>
<td>melanoma</td>
<td>4 peptides</td>
<td>CD34 derived</td>
<td>16/18</td>
<td>7/17</td>
<td>Banchereau et al. Cancer Res. 2001</td>
</tr>
</tbody>
</table>
The Nobel Assembly decided to award the half of the 2011 Nobel Prize in Physiology or Medicine jointly to

**Ralph M. Steinman**

**Discovery of the dendritic cell and its role in adaptive immunity**
Negative Phase III trials (significantly negative!)

EORTC 18961 (Melanoma Stage II)
- Ganglioside / Carrier / Adjuvants

MMAIT-III (Melanoma Stage III)
- allogeneic irradiated melanoma cells

Eggermont AM, ASCO 2010

Morton DL, ASCO 2007
Sipuleucel-T immunization in prostate cancer

During manufacturing

1. Antigen (substance that stimulates the immune system)
2. APC (presenting cell) takes in the antigen and becomes activated.
3. APC processes the antigen.

In the patient

4. APC is fully activated.
5. APC seeks out and alerts T-cells.
6. T-cells attack prostate cancer cells.
7. T-cells

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Universitätsklinik für Medizinische Onkologie, Inselspital Bern
Sipuleucel-T immunization in prostate cancer

- Leukapheresis: APH collection at approved center
- Transport via courier to CPC for processing
- Further enrichment of mononuclear cells
- Day 0 Process
- PA2024 antigen added
- Culture step ~40 hrs
- APC activation/antigen processing
- Day 2 Process
- Final product released for transport
- Transport via courier to infusion center for delivery to patient
- 3-4 Days
Dendritic cell Immunization current phase III trails

- NCT00045968; Northwest Therapeutics: RCT to test DCVax®-L in patients with newly diagnosed Glioblastoma (GBM) in addition to standard radiochemotherapy

- NCT01582672; ADAPT trial, Argos Therapeutics: RCT to test autologous dendritic cell immunotherapy plus standard treatment (Sunitinib) in advanced renal cell carcinoma

1. vaccination of subjects with resected tumors and thus lower tumor burden
2. vaccination in combination with other therapy
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Adoptive cellular Therapy

- Adoptive cellular immunotherapy is the transfer of cultured immune cells that have anti-tumor activity into a tumor-bearing host.
  - Lymphokine-activated killer (LAK) cells.
  - Tumor-infiltrating lymphocytes (TILs) cella.
Adoptive T cell Therapy

1. Harvest PBMCs by apheresis
2. Excise tumor mass
3. T cell activation
4. Transduction
5. TIL cell isolation
6. TIL cell expansion
7. CART cells
8. TCR T cells
9. Infusion
10. Lymphodepleted cancer patient
11. Host condition chemotherapy
Adoptive T cell therapy: TIL

1. Isolation of TIL from different tumor sites
2. Cultivation in vitro for 24-56 days
3. Expansion of T cells 300-45x10^6 fold
4. Infusion of 3-75x 10^{10} cells

Ramesh SA et al. NEJM 1988
1. lymphodepletion: Fludarabin + Endoxan
2. adoptive transfer of lymphocytes
3. IL-2 i.v.

Dudley et al. Science 2002
Differentiation of T cells

**Therapeutic efficacy**
Self renewal  
Survival  
GVHD

**Senescence**
Differentiation  
Effector function

<table>
<thead>
<tr>
<th>Differentiation States</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN (Naive)</td>
<td>CD45RA+</td>
</tr>
<tr>
<td></td>
<td>CD62L+</td>
</tr>
<tr>
<td></td>
<td>CCR7+</td>
</tr>
<tr>
<td></td>
<td>CD95+</td>
</tr>
<tr>
<td>TSCM (Central Memory)</td>
<td>CD45RA-</td>
</tr>
<tr>
<td></td>
<td>CD62L-</td>
</tr>
<tr>
<td></td>
<td>CCR7+</td>
</tr>
<tr>
<td></td>
<td>CD95+</td>
</tr>
<tr>
<td>TCM (Effector Memory)</td>
<td>CD45RA-</td>
</tr>
<tr>
<td></td>
<td>CD62L-</td>
</tr>
<tr>
<td></td>
<td>CCR7+</td>
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<tr>
<td></td>
<td>CD95+</td>
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<tr>
<td>TEM (Effector)</td>
<td>CD45RA-</td>
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<tr>
<td></td>
<td>CD62L-</td>
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<tr>
<td></td>
<td>CCR7-</td>
</tr>
<tr>
<td></td>
<td>CD95+</td>
</tr>
</tbody>
</table>
In vitro stimulation of TILs

Stimulation with the *target antigen*

**T cell clones**
- Selection of one single CD8⁺ T cell
- Expansion to $10^{11}$

**T cell lines**
- Enrichment of a polyclonal antigen-specific T cell population
- Contains CD8⁺ and CD4⁺ T cells
## Classification of tumor antigens

<table>
<thead>
<tr>
<th>Tumor Antigens</th>
<th>Specificity</th>
<th>Tolerance</th>
<th>Avidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutational antigens</td>
<td>patient, tumor</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Viral antigens</td>
<td>tumor</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Cancer-testis antigens</td>
<td>various tumors</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Differentiation antigens</td>
<td>tissue of origin</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Overexpressed gene products (oncogens)</td>
<td>most tumors</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

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Selection of target antigens for ACT

Antigens expressed on cancers that are non-essential human tissues
CD19, CD20, CD22, CD23, CD30, CD133, ROR-1

Private tumor antigens
«neo-antigens»
Mutational rate of tumors

Alexandrov LB, Nature 2013
Generation of neo-epitope specific T cells

T-cell transfer therapy targeting mutant KRAS in cancer

Infusion of $1.48 \times 10^{11}$ tumor-infiltrating lymphocytes, which consisted of approximately 75% KRAS G12D-specific CD8+ T cells ($1.11 \times 10^{11}$ cells)

Tran E et al. NEJM 2016
## ACT trials using TCR T cells

<table>
<thead>
<tr>
<th>Cancer Histology</th>
<th>Target</th>
<th>Patients</th>
<th>CR + PR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>MART-1</td>
<td>15</td>
<td>13%</td>
<td>Morgan, 2006</td>
</tr>
<tr>
<td>Melanoma</td>
<td>MART-1 Gp100</td>
<td>20 16</td>
<td>30% 19%</td>
<td>Johnson, 2009</td>
</tr>
<tr>
<td>Colon</td>
<td>CEA</td>
<td>3</td>
<td>33%</td>
<td>Parkhurst, 2011</td>
</tr>
<tr>
<td>Different tumors</td>
<td>NY-ESO-1</td>
<td>17</td>
<td>53%</td>
<td>Robbins, 2011,</td>
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<tr>
<td>Melanoma</td>
<td>MAGE-A3</td>
<td>9</td>
<td>56%</td>
<td>Radvanyi, 2013</td>
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<tr>
<td>Melanoma Myeloma</td>
<td>MAGE-A3</td>
<td>2</td>
<td>0%</td>
<td>Linette, 2013</td>
</tr>
</tbody>
</table>
Chimeric Antigen Receptor (CAR) T cells

Remove blood from patient to get T cells

Make CAR T cells in the lab
Insert gene for CAR

CAR T cells bind to cancer cells and kill them

Cancer cell
Antigens
CAR T cell

Grow millions of CAR T cells

Infuse CAR T cells into patient

Cancer cell

Engineering patients’ own immune cells to recognize and attack the tumors
The first CAR T-cells were developed in the late 1980s.

Chimeric antigen receptors (CARs) are composed of three components:

1. **Extracellular antigen-binding domain** derived from a tumor-specific monoclonal antibody single chain variable fragment (scFv).
2. **Transmembrane domain** anchoring CAR to T cell-derived from CD3, CD4, CD8 or CD28.
3. **An intracellular T cell activation domain** of CD3ζ W/O costimulatory molecules.

**Evolution of CARs**

Chimeric Antigen Receptor (CAR) T cells

Sometimes cancer cells develop ways to fool the immune system,
CAR-T therapy side effects

- Cytokine storm
- Fever
- Nausea
- Skin reaction
- Hypotension
- Needs close monitoring and early recognition
Summary: adoptive T cell therapy

**Stimulation of TIL with antigen**
- + targeted to tumor antigen
- - massive expansion
- - low affinity TCR

**TIL**
- + polyspecific
- + antigen not characterized
- - massive expansion
- - low affinity TCR

**TCR T cells**
- + less expansion needed
- + surface and internal antigens
- + driver antigens?
- + high affinity TCR
- - off-tumor toxicity
- - dependent on MHC-I

**CAR T cells**
- + less expansion needed
- + not dependent on MHC-I
- - only surface antigens
- - selection of antigens (solid tumors)
Monoclonal antibodies

Immune effects

Lymphoma
Breast cancer
Colon cancer
Head/Neck cancer

Blocking pathways

Immune cell

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Novel antibody formats: bispecific antibodies

- Phase II trial in refractory B precursor ALL
- 189 patients
- 41% compete remissions
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    - Active Immunotherapy
    - Passive Immunotherapy
  - Immune Checkpoint Blockade
    - Blocking B7/CTLA-4 Interaction
    - Blocking PD1/PD-L1 Interaction
    - Other pathways
Immune checkpoints

- Activating Receptors: CD28, OX40, GITR, CD137
- Inhibitory Receptors: CTLA-4, OX40L, CD39, CD70, HVEM

T cell stimulation

- Agonist Abs: CD28, OX40, GITR, CD137
- Blocking Abs: CTLA-4, OX40L, CD39, CD70, HVEM
Immune Modulation

(Immune checkpoint inhibitors)

- Priming phase (lymph node)
- Effector phase (peripheral tissue)
Immunecheckpoint Modulation
CTLA-4 Blockade
Lungenmetastasen vor Therapie
(Dezember 2011)

Keine Lungenmetastasen nach Immuntherapie
(seit März 2012)
Anti-PD-1 and Anti-PD-L1 mAbs block distinct interactions

PD-1 Blockade
OF T CELL

Blocks PD-L1 and PD-L2 binding to PD-1

PD-L1 can still engage B7-1
Anti-PD-1 and Anti-PD-L1 mAbs block distinct interactions

PD-L1 Blockade
OF TUMOR CELL

Blocks PD-L1 binding to PD-1 and B7-1

PD-L2 can still engage PD-1
**PD-L1 expression**

PD-L1 is broadly expressed in different tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Estimated PD-L1 Prevalence (≈ %)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (SCC)</td>
<td>50%</td>
</tr>
<tr>
<td>NSCLC (adeno)</td>
<td>45%</td>
</tr>
<tr>
<td>Colon</td>
<td>45%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>40%</td>
</tr>
<tr>
<td>Renal</td>
<td>20%</td>
</tr>
</tbody>
</table>

Nearly all human tumors include a subset that expresses PD-L1

High sensitivity and specificity in FFPE samples
### PD-1 targeting antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Kd Binding Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Optivo)</td>
<td>Human IgG4</td>
<td>3 nM</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Humanized IgG4 kappa</td>
<td>28 pM</td>
</tr>
</tbody>
</table>

### PD-L1 targeting antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Kd Binding Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab, MPDL3280A</td>
<td>ADCC reduced, engineered IgG1</td>
<td>NA</td>
</tr>
<tr>
<td>Durvalumab, MEDI4736</td>
<td>ADCC reduced, engineered IgG1 kappa</td>
<td>NA</td>
</tr>
<tr>
<td>Avelumab, MSB0010718C</td>
<td>fully human IgG1</td>
<td>NA</td>
</tr>
</tbody>
</table>
Nivolumab (anti PD-1) first line in metastatic melanoma

Pembrolizumab versus Chemotherapy for PD-L1-positive Non-Small Cell Lung Cancer (Keynote 024)

NSCLC St IIIb, IV PD-L1 expression > 50% PS 0–1 (n=305)

1:1

Pembrolizumab 200mg q 3wk
Platinum-based standard

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.17–0.53) P=0.001

Hazard ratio for death, 0.60 (95% CI, 0.41–0.89) P=0.005

Reck M, NEJM 2016
PD1/ PD-L1 efficacious in all tumors?

- Very efficacious
  - Melanoma
  - Lung cancer
  - Hodgkin’s lymphoma
  - Renal cell carcinoma

- Very promising
  - Bladder cancer
  - HeadNeck Carcinoma

- Less promising (with the exception of subgroups)
  - Breast cancer
  - Colon cancer
  - Prostatic cancer

Efficacious not in all, but in many different tumors
Immune checkpoint blockade of PD-1/PD-L1 pathway

ORR: approximate objective response rate

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Mutational Rate and Clinical Response

Alexandrov LB, Nature 2013
High mutational burden predicts response to pembrolizumab in NSCLC

Predicted neo-epitopes: Mutant nanomers with $\leq 500nM$ binding affinity to HLA alleles

Rizvi NA, Science 2015

Cut off: 178 mutations
HR 0.19, $p=0.004$

$\text{High nonsynonymous burden}$
$\text{Low nonsynonymous burden}$

$n=17$

$\text{Percent progression-free}$

$n=17$

$\text{Percent progression-free}$

$p=0.002$

$\text{Months}$

$\text{Months}$
The Nobel Assembly decided to award the 2018 Nobel Prize in Physiology or Medicine jointly to

James P. Allison & Tasuku Honjo

Discovery of cancer therapy by inhibition of negative immune regulation
Side effects of Immune Checkpoint Modulation
Anti-CTLA-4 blockade adverse events

Gastrointestinal
Signs and symptoms such as:
- Diarrhoea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

Neurologic
Symptoms such as:
- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

Liver
Signs such as:
- Abnormal liver function tests (e.g. AST, ALT or total bilirubin)

Endocrine
Signs and symptoms such as:
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

Skin
Symptoms such as:
- Pruritus
- Rash

Other adverse reactions including ocular manifestations
Immune-checkpoint inhibition resistance

Anti-PD(L)1 resistance

Sharma P et al, 2017, Cell
Overcome immune-checkpoint inhibition resistance with chemotherapy
## Combination of immune-checkpoint inhibition

<table>
<thead>
<tr>
<th>1. Immune checkpoint inhibitor</th>
<th>2. Immune checkpoint inhibitor</th>
<th>phase</th>
<th>Tumor types</th>
<th>Trial Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-LAG-3</td>
<td>Anti-PD1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAG525</td>
<td>PDR001</td>
<td>1/2</td>
<td>Advanced cancer</td>
<td>NCT02460224</td>
</tr>
<tr>
<td>BMS-986016</td>
<td>Nivolumab</td>
<td>1</td>
<td>Advanced cancer</td>
<td>NCT01968109</td>
</tr>
<tr>
<td>Anti-TIM3</td>
<td>Anti-PD1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBG453</td>
<td>PDR001</td>
<td>1/2</td>
<td>Advanced cancer</td>
<td>NCT02608268</td>
</tr>
</tbody>
</table>

### Ipilimumab + nivolumab OS in Melanoma

![Survival curve for Ipilimumab + Nivolumab in Melanoma](image)

Hodi et al 2016, NEJM
Ongoing clinical combinations

Chemotherapy + anti-PD-1 1st L NSCLC

Adapted from A. Marabelle
Indoleamine 2,3 dioxygenase (IDO) inhibition

Abstract 3003: Perez et al. Epacadostat plus nivolumab in patients with advanced solid tumors: Preliminary phase I/II results of ECHO-204

<table>
<thead>
<tr>
<th>Disease</th>
<th>Overall Response Rate (CR/PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
</tr>
<tr>
<td>Treatment-naive Melanoma</td>
<td>62.5% (25/40)</td>
</tr>
<tr>
<td>SCCHN (&lt; 2 prior treatment)</td>
<td>25.8% (8/31)</td>
</tr>
<tr>
<td>Ovarian Ca (prev treated)</td>
<td>14% (4/29)</td>
</tr>
<tr>
<td>CRC (prev treated)*</td>
<td>3.8% (1/26)</td>
</tr>
</tbody>
</table>

- Response durability seen across tumor subtypes

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Adenosine receptor (A2A) inhibition

ATP → CPI-444 → Adenosine → CD8

Abstract 3004: Fong et al. Safety and clinical activity of adenosine A2a receptor (A2aR) antagonist, CPI-444, in anti-PD1/PDL1 treatment-refractory renal cell (RCC) and non-small cell lung cancer (NSCLC) patients
How to change a cold tumor in a hot tumor

Chen and Mellman, Nature, 2017
Zhou et al, 2016, Science Transl Med
Personalized immunotherapy

- Immune
- Elimination → Equilibrium → Escape

- Regulation
  - Checkpoint blockade
  - Regulatory cytokines
  - Tregs, MDSC

- Exclusion
  - Radiation
  - Oncolytic viruses
  - BiTe

- Ignorance

- Editing
  - Generate new effectors
    - ACT
    - Vaccination

Universitätsklinik für Medizinische Onkologie, Inselspital Bern

Ramin Radpour
Challenges on the way...!
Take Home Points...!

• Immunotherapy is the 4th pillar in treating cancer patients.
• More patients are going to be on immunotherapy in the future.
• Different cancers respond differently to immunotherapy.
• Melanoma have the best responses while others like prostate cancer have minimal responses.
• Side effects are unique and very different from traditional chemotherapy.
• Steroids help with side effects but should be used judiciously.
• Enrollment in clinical trials is very important
Cancer Immunotherapy

Surgical operation

Radiotherapy

Chemo- & Targeted Therapies

Immunotherapy

Any questions?

Ramin Radpour