Outline

**Introduction**
- What is immunotherapy?
- Targets
- Immune responses against cancer

**Cancer therapy**
- Vaccines
- Antibodies
- Adoptive Cell Therapy
- Combination therapies

**Summary**
Cancer therapy

• Drugs designed to interfere with specific molecules necessary for tumor growth and progression.

• Traditional chemotherapies usually kill rapidly dividing cells in the body by interfering with cell division.

• Aim: fight cancer cells with more precision and potentially fewer side effects

• Immunotherapy is excellent targeted therapy:
  - very specific
  - the immune system has memory

What is cancer?

• Cancer is uncontrolled growth of the cells in the human body

• Ability of cancer cells to migrate from the original site and spread to distant sites
**Immunotherapy**

*Therapeutic vaccines* designed to stimulate the patients’ T cells. Need time to work.

*Therapeutic monoclonal antibodies* target specific cell surface antigens, such as transmembrane receptors or extracellular growth factors (e.g. trastuzumab/Herceptin)

*Cellular therapy* redirecting patients’ T cells to target a particular type of cancer cell by introducing a specific receptor

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**Importance of T-Cell Infiltration for Survival**

![Graph showing disease-free survival vs time for different groups of CD4+ and CD8+ cells.](image)

- **CD4+ and CD8+ cells**
  - High-high expression, n=96
  - High-low/low-high expression, n=198
  - Low-low expression, n=75

*P* = 0.001

*Al-Shibli 2008, Clin Cancer Res*

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Tumour and Immune System Interaction: Immunoediting

(a) Elimination
(b) Equilibrium
(c) Escape

Immune system components and their interactions in the context of tumour and immune system interaction.

Different immunotherapies

Active immunotherapy
- Cancer vaccines
  - Peptide vaccines
  - Dendritic cell vaccines

Passive immunotherapy
- Antibodies
- Adoptive cell therapy
  - Tumour infiltrating lymphocyte therapy
  - Redirected T cells

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Active Immunotherapy: Cancer Vaccines

- ACT treatments increase T-cell activation, but can also induce severe toxicity
- Cancer vaccines can specifically activate T cells with less adverse events
- Can be used in an adjuvant setting (after surgery if relapse is expected)

Telomerase Peptide Vaccine in Stage IV Non-Small Cell Lung Cancer

- Phase I/II vaccination trial with long peptide from telomerase (hTERT, GV1001)
- Immune response correlated with significantly increased survival

Brunsvig, Kyte et al 2011 Clin Cancer Res
Dendritic cell vaccination

Nobel Prize in Physiology and Medicine 2011 to Ralph Steinman

O’Hagan and Valiante 2003, Nat Rev Drug Discov

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Phase I/II Study of DC Vaccine with Tumour Stem Cell mRNA in Glioblastoma Patients

Vik-Mo, Langmoen et al, 2013

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Cancer vaccines

Advantages

- Survival benefit compared to standard therapy
- Applicable in broad patient population (depending on target)

Challenges

- Loss of target antigen
- HLA downregulation (tumour escape)
- Normally do not cure patients with very advanced disease

Monoclonal antibodies

Table 1

<table>
<thead>
<tr>
<th>Generic name (trade name)</th>
<th>Genetic origin</th>
<th>Iso type (isotype)</th>
<th>Target</th>
<th>Approved indication(s)</th>
<th>Initial approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconjugated Mabs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herceptin (Trastuzumab)</td>
<td>Human</td>
<td>IgG1</td>
<td>HER2</td>
<td>Breast and gastroesophageal cancer, gastric cancer</td>
<td>1998</td>
</tr>
<tr>
<td>Keytruda (Pembrolizumab)</td>
<td>Human</td>
<td>IgG1</td>
<td>PD-1</td>
<td>Melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, Merkel cell carcinoma</td>
<td>2015</td>
</tr>
<tr>
<td>Dendron (Denisomab)</td>
<td>Human</td>
<td>IgG4</td>
<td>PD-1</td>
<td>Melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, Merkel cell carcinoma</td>
<td>2015</td>
</tr>
<tr>
<td>Yervoy (Ipilimumab)</td>
<td>Human</td>
<td>IgG1</td>
<td>CTLA-4</td>
<td>Melanoma</td>
<td>2011</td>
</tr>
<tr>
<td>Immunoconjugates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Innategen (Oncofill)</td>
<td>Human</td>
<td>IgG1</td>
<td></td>
<td>Melanoma</td>
<td>2010</td>
</tr>
<tr>
<td>Pymol (Pymol)</td>
<td>Human</td>
<td>IgG1</td>
<td></td>
<td>Melanoma</td>
<td>2010</td>
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<td>2010</td>
</tr>
</tbody>
</table>

Redman et al., Mol Immunol 2015

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Immunomodulating Antibodies: PD-1

Deactivated T cell

Activated T cell

M. Guha, The Pharmaceutical Journal Nov 2014

Antibodies

**Advantages**
- Effective in a patient subpopulation
- Feasible in large population

**Challenges**
- Severe adverse events (e.g. low blood counts, heart problems, hepatitis, bleeding)
- Obtaining clinical responses in large number of patients
- Loss of target antigen
Adoptive Cell Transfer (ACT)

• ACT uses T cell-based cytotoxic responses to attack cancer cells

• T cells with natural or genetically engineered reactivity to a patient's cancer are generated in vitro and given back to the patient

Humphries et al 2013
CAR targeting CD19 in chemotherapy resistant leukemia

Table 2. CD19 CAR therapy for ALL

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number/age of subjects</th>
<th>Complete remission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentjens, et al. (74)</td>
<td>5 adults</td>
<td>100%</td>
</tr>
<tr>
<td>Grupp, et al. (75)</td>
<td>2 children</td>
<td>100%</td>
</tr>
<tr>
<td>Davila, et al. (76)</td>
<td>16 adults</td>
<td>88%</td>
</tr>
<tr>
<td>Lee et al. (78)</td>
<td>20 children</td>
<td>70%</td>
</tr>
<tr>
<td>Maude, et al. (77)</td>
<td>25 children</td>
<td>90%</td>
</tr>
<tr>
<td>Frey, et al. (107)</td>
<td>12 adults</td>
<td>89%</td>
</tr>
<tr>
<td>Park, et al. (108)</td>
<td>27 adults</td>
<td>89%</td>
</tr>
</tbody>
</table>

Sadelain, JCI, 2015
Chimaeric Antigen Receptor (CAR) transfer

**Advantages**
- Clinical responses in patients failing all other therapy
- Not dependent on HLA expression

**Challenges**
- Limited target antigens
- On-target toxicity
- Tumour lysis syndrome

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TCR based therapy

- Isolation of endogenous peripheral T cells
- T cell receptor gene transfer
- Clonal expansion of genetically modified T cells
- Infusion of engineered T cells
- Tumour regression
- Lymphodepletion, Cytokine therapy, vaccination

Cancer patient

Offringa, Science 2006
TCR targeting mutated protein in colorectal cancer

- Goal to be in the clinic with TCR therapy within 2 years

- Patient group:
  Patients with recurrent TGFβRII\textsuperscript{mut} positive cancer and prophylactic use in patients with inherited risk of developing HNPCC

In vivo colorectal cancer model

[Graph and image description]

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### Side effects of targeted cellular therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Reason</th>
<th>Cancer type</th>
<th>Clinical problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-Target off-tumour</td>
<td>Target antigen expressed outside tumour</td>
<td>ALL/CLL/lymphoma</td>
<td>CD19 CAR: Lack of B cells</td>
</tr>
<tr>
<td>Off-target</td>
<td>Cross-reactivity: TCR reactive with another antigen</td>
<td>Melanoma, multiple myeloma</td>
<td>TCR against MAGE A3 reactive against titin in the heart; 2/2 patients died</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melanoma, sarcoma</td>
<td>TCR against MAGE A3 reactive against other MAGE in brain; 2/9 patients died</td>
</tr>
<tr>
<td>On target</td>
<td></td>
<td>ALL/CLL/lymphoma</td>
<td>CD19 CAR: Tumour lysis syndrome, CEA: colitis</td>
</tr>
<tr>
<td>Allergy</td>
<td>Foreign epitopes in CAR/TCR</td>
<td>Mesothelioma</td>
<td>Mesothelin CAR: Allergic shock after treatment break</td>
</tr>
<tr>
<td>T-cell activation</td>
<td>Too strong activation of many T cells</td>
<td>ALL/CLL/lymphoma</td>
<td>CD19 CAR: Cytokine storm</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Break on immune system released</td>
<td>Melanoma</td>
<td>Iplimumab: Colitis etc.</td>
</tr>
</tbody>
</table>

### T-cell Receptor (TCR) Transfer

**Advantages**
- Clinical responses in patients failing all other therapy
- Can target large variety of tumour antigens

**Challenges**
- Target antigen safety
- Off-target toxicity (cross-reactivity)
- HLA class I downregulation (tumour escape)
Summary

• Immunotherapy has had dramatic clinical benefit in patients with incurable disease

• Cancer vaccines can be effective, but in early stage cancer or after surgery

• Potent therapy can also give side-effects or unwanted effects and must be well tested

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