BASIC PRINCIPLES OF IMMUNOTHERAPY

Ivan Borrello, M.D.
Sidney Kimmel Cancer Center at Johns Hopkins
DISCLOSURES

• WindMIL Therapeutics - Receipt of Intellectual Property Rights/Patent Holder
• Bristol-Myers Squibb, Celgene Corporation - Contracted Research
• I will be discussing non-FDA approved treatments during my presentation.
Effect of Immune Infiltration on Overall Survival

Colon Cancer

![Graph showing disease-free survival for colon cancer with different immune infiltration levels.](image)

Ovarian Cancer

![Graph showing progression-free survival and overall survival for ovarian cancer with different immune infiltration levels.](image)

Galon Science 2006

Zhang et al NEJM 2003
The Immune Editing Hypothesis (3E’s)
Types of Anti-Tumor Immunotherapy

- **Cancer Vaccines** – educate T cells to better recognize and kill the pre-existing tumor
- **Adoptive Immunotherapy** – activate and increase T cell numbers to better kill tumor
- **Immunomodulation** – use drugs or antibodies to either:
  - increase immune stimulation
  - overcome immune inhibition
Mechanisms of Tumor-induced Immune Tolerance
CANCER VACCINES
Normal Host:

Vaccine → Expansion of vaccine primed T cells

Cancer Patient:

Vaccine → Inability to expand T cells with vaccination
Cancer Vaccine Design

Vaccine Requirements

• Contain a desired antigen(s)
• Possess an adjuvant capable of stimulating/generating an immune response
Vaccine Antigens

Single Antigen Approaches
• Nucleic Acids: RNA or DNA
  • generally targets a single antigen
• Peptides
• Proteins

Multiple Antigen Approaches
• Pulsed Dendritic Cells
• Tumor cell – Dendriitc Cell Fusions
• Whole cell vaccines
Cancer Vaccine Goal ....

Dendritic Cells Traffic and Present Antigen To Specific CD4 and CD8 T Cells in the Draining Lymph node through a process known as Cross Presentation.
Issues Around Tumor Vaccines

Benefits:
• Capable of generating a durable, long-lived response
• Delivered with minimal toxicity
• May be an “off-the-shelf” product
• Can be combined with additional immunotherapies to enhance overall efficacy.

Disadvantages:
• Can take several weeks to generate a meaningful systemic response
• Likely works best in a setting of minimal disease or a slow growing tumor
• Relapses of antigen-specific vaccines may be with the generation of antigen escape variants
T CELL THERAPIES
T Cell Therapy

- CARs – chimeric antigen receptors
- TCRs – T cell receptors
- TILs – Tumor infiltrating lymphocytes
- MILs – Marrow infiltrating lymphocytes
- Allogeneic BMT
Composition of a CAR

Annu. Rev. Med. 65:333–47
CAR’s

First
- scFv
- Hinge
- TM
- Signaling chain
- ITAM chain
- Cytotoxicity ↑
- Proliferation ↑
- Cytokine secretion ↑
- Resistance ↑
- In vivo persistence ↑

Second
- CM I: CD28/CD134
- CD137/ICOS
- Cytotoxicity ↑
- Proliferation ↑
- Cytokine secretion ↑
- Resistance ↑
- In vivo persistence ↑

Third
- CM I: CD28
- CM II: CD134/CD137
- Cytotoxicity ↑↑
- Proliferation ↑↑
- Cytokine secretion ↑↑
- Resistance ↑↑
- In vivo persistence ↑↑

TCR Engineered T cells

- TCR cloned for a specific CD8 restricted antigen-specific peptide
- T cells genetically engineered to express this TCR
- T cells are HLA-restricted for the specific peptide
Non-gene modified T cells

• TILs
  • obtained surgically from metastatic lesions
  • present in 40-60% of patients
  • able to be expanded in 50% of those patients
  • expansion takes 2-4 weeks
  • available as therapy to ~25% of patients
  • shown efficacy in metastatic melanoma
Non-gene modified T cells

- MILs
  - found in 100% of the bone marrow of patients
  - expanded in virtually all patients
  - expansion in 7-10 days
  - has broad antigenic specificity
  - potentially beneficial in solid tumors
Immune Checkpoint Modulators

CD28/CTLA-4 Ig family

<table>
<thead>
<tr>
<th>Target</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4</td>
<td>Approved</td>
</tr>
<tr>
<td>PD-1</td>
<td>Ph III accruing</td>
</tr>
<tr>
<td>BTLA</td>
<td>Preclinical</td>
</tr>
<tr>
<td>LAG3</td>
<td>Preclinical</td>
</tr>
<tr>
<td>ICOS</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

PD-L1 | Ph II accruing

KIR   | Ph II accruing

TNF superfamily

<table>
<thead>
<tr>
<th>Target</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD40</td>
<td>Ph I</td>
</tr>
<tr>
<td>OX40</td>
<td>Ph I accruing</td>
</tr>
<tr>
<td>CD137</td>
<td>Ph II</td>
</tr>
<tr>
<td>GITR</td>
<td>Ph I accruing</td>
</tr>
<tr>
<td>CD27</td>
<td>Ph I accruing</td>
</tr>
</tbody>
</table>

TIM-3 | Preclinical

Annu. Rev. Med. 65:185–202
Anti-CTLA-4

T cell

HLA

T Cell Receptor

Signal 1

B7.1/2

CD28

Signal 2

Antigen

Presenting Cell
CTLA-4Prevents Normal T Cell Activation

Signal 1

T Cell Receptor

HLA

B7.1/2

CTLA-4

Antigen Presenting Cell

Signal 2

T cell

CD28

Ag

Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, Restoring T Cell Activation
Role of Checkpoint Inhibitors

Annu. Rev. Med. 64:71–90
BiTE
Limitation of Current BiTEs

• Absence of an Fc responsible for short half-life
• Act through engagement of CD3+ cells
• Combines the benefit of antibody targeting with a T cell response
• Require a continuous infusion because of their short half-life
Rationale for Combination Chemo-Immunotherapy