Cancer Vaccine Immunotherapy

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New paradigm needed for cancer vaccines

The classic vaccine paradigm to prevent virus infection:
    Acute virus infection results in viral clearance and long-lasting protection.
    A vaccine just needs to mimic the natural infection.

The exception: Cancer and chronic viral infections:
    Inadequate immunity allows chronic infection or malignancy to persist.

In these cases, we must induce better immunity than induced by the cancer or
the natural infection.
Cancer vaccines are distinct from most other vaccines:

Vaccines harness the exquisite specificity of the immune system to selectively target cancer cells. To do so, we need to identify the molecules that are unique to, or highly overexpressed in, the cancer cells to target with vaccines, to distinguish them from normal cells.

Most vaccines are preventive vaccines. Cancer vaccines are primarily therapeutic, to treat existing cancers.

Longstanding cancers may have tolerized immune cells that could recognize them. We need to overcome this tolerance.

Cancers exploit immunosuppressive mechanisms to suppress the immune response against them. We need to overcome this suppression.
Cancer vaccines act fundamentally differently from all conventional forms of cancer therapy.

Thus, vaccines require an intact immune system.
Antibodies detect surface antigens. CD8⁺ Cytotoxic T cells can detect endogenous antigenic proteins even if not expressed intact on the cell surface.
Adenoviral vaccine vector expressing Her-2 causes regression of established breast cancers
(subcu TUBO tumor model)

• Independent of effector CD8+ or CD4+ T cells.
• Completely dependent on induction of antibodies to HER2.
• Mechanism different from that of trastuzumab.

We have an open phase I trial of an adeno-Human HER2 vaccine in patients with advanced metastatic HER2+ cancers who failed all prior therapy, showing promising early results (frequent objective responses or stable disease lasting ≥ 6 months).

Park et al., Cancer Research 2008
Adeno-Her-2 vaccine induces regression of established lung tumors after IV injection of breast cancer cells

Unvaccinated

Control, sacrificed day 15
Control, sacrificed 30

Vaccinated day 15

Ad-ECTM day 15, Sacr day 29
Ad-ECTM day 15, Sacr day 35
Ad-ECTM day 15, Sacr day 48

Note early progression for 3 weeks prior to complete response.

Park et al., Cancer Research 2008
New immune-related Response Criteria (irRC) instead of RECIST criteria for immunotherapy

**RECIST Response Criteria**

<table>
<thead>
<tr>
<th>Evaluation of Target Lesions</th>
<th>CR Complete Response</th>
<th>Disappearance of all <em>target</em> lesions.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR Partial Response</td>
<td>≥ 30% decrease in sum of the LD of target lesions, taking as reference the baseline sum LD.</td>
</tr>
<tr>
<td></td>
<td>PD Progressive Disease</td>
<td>≥ 20% increase in sum of LD target lesions, taking as reference the smallest sum LD recorded since treatment start or the appearance of one or more new lesions.</td>
</tr>
<tr>
<td></td>
<td>SD Stable Disease</td>
<td>Neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since treatment start.</td>
</tr>
</tbody>
</table>

**Immune-Related Response Criteria**

<table>
<thead>
<tr>
<th>Evaluation of Target Lesions</th>
<th>irCR Complete Response</th>
<th>Complete disappearance of <em>all lesions</em> (whether measurable or not, and no new lesions).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>irPR Partial Response</td>
<td>≥ 50% decrease in tumor burden relative to baseline.</td>
</tr>
<tr>
<td></td>
<td>irPD Progressive Disease</td>
<td>≥ 25% increase in tumor burden relative to nadir (minimum recorded tumor burden).</td>
</tr>
<tr>
<td></td>
<td>irSD Stable Disease</td>
<td>Not meeting criteria for irCR or irPR, in absence of irPD.</td>
</tr>
</tbody>
</table>

**New Measurable Lesions (≥ 5x5mm)**

- *Always* represent PD

**New Non-Measurable Lesions(< 5x5mm)**

- *Always* represent PD

**Non-Target Lesions**

- Contribute to defining BOR of CR, PR, SD, and PD.

**Incorporated into tumor burden**

**Do not define progression (but preclude irCR)**

**Contribute to defining irCR (complete disappearance required)**

Antibodies detect surface antigens. CD8+ Cytotoxic T cells can detect endogenous antigenic proteins even if not expressed intact on the cell surface.
Sipuleucel-T = autologous PBMC cultured with human PAP fused to GM-CSF

IMPACT Trial: Overall Survival Additional Analysis (349 events)

HR = 0.759 (95% CI: 0.606, 0.951)

$P = 0.017$ (Cox model)

Median Survival Benefit = 4.1 months

Control (n = 171)
Median Survival: 21.7 mo
36 mo. survival: 23.0%

Sipuleucel-T (n = 341)
Median Survival: 25.8 mo
36 mo. survival: 32.1%

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Sipuleucel-T</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>341</td>
<td>171</td>
</tr>
<tr>
<td>12 mo</td>
<td>274</td>
<td>133</td>
</tr>
<tr>
<td>24 mo</td>
<td>142</td>
<td>59</td>
</tr>
<tr>
<td>36 mo</td>
<td>56</td>
<td>22</td>
</tr>
<tr>
<td>48 mo</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>60 mo</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
CellDex Vaccine of EGFRvIII peptide-KLH conjugate vaccine + bevacizumab in glioblastoma

Overall Survival

<table>
<thead>
<tr>
<th>Median, months (95% CI)</th>
<th>OS 12</th>
<th>OS 18</th>
<th>OS 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rindopepimut + BV</td>
<td>11.3 (9.9, 16.2)</td>
<td>44%</td>
<td>32%</td>
</tr>
<tr>
<td>Control + BV</td>
<td>9.3 (7.1, 11.4)</td>
<td>32%</td>
<td>13%</td>
</tr>
</tbody>
</table>

HR = 0.53 (0.32, 0.88)
p = 0.0137*

Per-protocol population analyses:
HR = 0.53 (0.31, 0.90)
p = 0.0177*

Reardon et al, Soc NeuroOncology 2015
PUSH-PULL Approach to Optimizing Vaccine-induced T-cell Immunity

Improve: Quantity Quality (avidity, longevity, function)

Antigen

Optimize
(e.g. epitope enhancement)

Optimize

PUSH (& steer)
- Cytokines (e.g. IL-15, IL-12)
- Costimulatory molecules
- Toll-like receptor ligands (e.g. CpG, Poly I:C, MALP-2)
- NKT Cell Agonists

Optimized Immune Response

Block negative regulation (PULL)

Negative Regulators
(e.g. Treg, reg NKT, MDSC, M2 Macrophages, tBregs, Mast cells CTLA-4, PD-1, IL-13, TGF-β)
Epitope enhancement: modifying the peptide sequence to increase affinity for the HLA molecule

T cell receptor (TCR)

Epitope enhancement: modifying the peptide sequence to increase affinity for the HLA molecule

T cell receptor (TCR)

T cell contact residue of peptide

peptide

Anchor residues of peptide

class I HLA

Modified anchor residues of peptide

enhanced peptide

class I HLA
TARP Prostate Cancer Vaccine Epitope Enhancement

- **TARP**: a 58 amino acid protein expressed in ~90-95% of prostate cancer and ~50% of breast cancer (discovered by Ira Pastan’s lab).

- We mapped 2 HLA-A*0201 TARP epitopes: TARP27-35 and TARP29-37.

**Epitope enhancement**: TARP29-37 ----> TARP29-37-9V, → increased binding affinity & immunogenicity for TARP-specific T cells that kill human tumor cells expressing TARP.

Phase I trial in Stage D0 Prostate Cancer:
- Primary tumor removed
- Rising PSA indicating microscopic recurrence
Result: Almost ¾ showed decreased PSA slope at one year.

Oh et al, Cancer Research 2004
PUSH-PULL Approach to Optimizing Vaccine-induced T-cell Immunity

Improve: Quantity
Quality (avidity, longevity, function)

Antigen

Optimize
(e.g. epitope enhancement)

Optimize
(e.g. IL-15, IL-12)

Costimulatory molecules

Toll-like receptor ligands
(e.g. CpG, Poly I:C, MALP-2)

NKT cell agonists

Block negative regulation (PULL)

Negative Regulators
(e.g. Treg, reg NKT, MDSC, M2, CTLA-4, PD-1, IL-13, TGF-β)

PUSH (& steer)

Cytokines (e.g. IL-15, IL-12)

Costimulatory molecules

Toll-like receptor ligands
(e.g. CpG, Poly I:C, MALP-2)

NKT cell agonists
Three major categories of regulatory elements inhibiting CD8⁺ T cells

- Regulatory Cell
  - CD4⁺ T-regulatory cell
  - Regulatory NKT cell
  - Myeloid Derived Suppressor cell
  - M2 Macrophage
  - Regulatory Dendritic cell
  - Regulatory B cell

- Presenting Cell
  - CD8⁺ Cytolytic T Cell

- Regulatory Receptors
  - PD-1
  - CTLA-4

- Regulatory Cytokines
  - TGF-beta
  - IL-10
  - IL-13

Cancer Cell
Anti-TGF-β synergistically enhances efficacy of anti-tumor whole cell vaccine: a new checkpoint inhibitor

Takaku et al., Int J Cancer 2010
Identifying antigens unique to the tumor
Frequency of somatic mutations in different kinds of cancer

Some of these mutations are in sequences predicted to bind to a patient’s HLA molecules, constituting a “neoantigen.”

Neoantigen frequency predicts responsiveness of cancers to PD-1 blockade therapy

DCB = Durable Clinical Benefit
NDB = No durable benefit

From Rizvi et al., Science 348: 124, 2015
Ras Mutations as Tumor Neoantigens

- Mutant ras is a driver mutation.
- Without extensive tumor genome sequencing, we know that one commonly expressed neoantigen is mutant ras.
- The common ras codon 12 and 13 mutations fall in a sequence that can be presented by HLA-A*0201, the most common human class I HLA molecule.
Ras Codon 12 & 13 mutations occur in an HLA-A2 binding decapeptide

- Wild type Ras 5-14: K L V V V G A G G G V
- Ras 12 V (PR5V10): _ _ _ _ _ _ _ _ V _ _
- Ras 12 D (PR6V10): _ _ _ _ _ _ _ _ D _ _
- Ras 12 A (PR7V10): _ _ _ _ _ _ _ _ A _ _
- Ras 12 C (PR18V10): _ _ _ _ _ _ _ _ D _ _
- Ras 13 D (PR54V10): _ _ _ _ _ _ _ _ _ _ _ D _

Survival correlated with interferon-γ T cell response to mutant Ras or p53

\[ P = 0.017 \]


New rapid sequencing technology may allow revisiting this personalized vaccine therapy.
Immuno-pharmacodynamics is fundamentally different from classical pharmacodynamics (PD):

Classical PD: one target cell
- Chemo
- Radiation
- Surgery

Immuno- PD: two target cells
- Vaccine
- Immune Cell

Cancer Cell
Restrictions on vaccine animal models and testing

Vaccines require an intact immune system:
They cannot be tested in xenograft models in immunodeficient mice.
They can be affected by prior lympho-depleting Rx.
MHC restriction requires HLA matching between T-cell specificity and target tissue => syngeneic mouse models must be used.

Because cancer vaccines
1) Require an intact immune system
2) Don’t target cancer cells directly
3) Have a slower onset and require immune-related Response Criteria instead of RECIST criteria,
Cancer vaccines must be viewed as quite distinct from cancer therapies to which we are accustomed.
Cast (in order of appearance)

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