F141: Advanced Melanoma: Mechanisms of Immune Therapies beyond Checkpoint blockade

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The Immune System and Cancer

[Diagram showing normal cells transforming into transformed cells, with patrolling immune cells and attacking abnormal cells indicated.]

Fatal Melanoma Transferred in a Donated Kidney 16 years after Melanoma Surgery

» 1998: a woman died of a brain aneurysm, two kidneys were donated
» That female donor had a primary melanoma 16 years before sudden death (unrelated to melanoma diagnosis 16 years earlier)
» Melanoma was removed, with no residual tumor, followed in melanoma clinic for 15 years and was discharged, apparently tumor free, in 1997
Incidence of certain cancers is higher in immune-suppressed transplant recipients

<table>
<thead>
<tr>
<th>Site of Cancer</th>
<th>No. of Cases Observed</th>
<th>No. of Cases Expected</th>
<th>Ratio: Observed:Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmall-cell lung</td>
<td>17</td>
<td>6.1</td>
<td>2.8</td>
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<tr>
<td>Thyroid</td>
<td>30</td>
<td>5.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Adrenal, gonadal</td>
<td>22</td>
<td>1.9</td>
<td>16.0</td>
</tr>
<tr>
<td>Testis, male</td>
<td>29</td>
<td>0.8</td>
<td>34.8</td>
</tr>
<tr>
<td>Bone, Hodgkin lymphoma</td>
<td>36</td>
<td>5.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Brain</td>
<td>26</td>
<td>5.1</td>
<td>5.1</td>
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<tr>
<td>Bladder</td>
<td>26</td>
<td>4.7</td>
<td>5.5</td>
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<tr>
<td>Colon</td>
<td>36</td>
<td>10.3</td>
<td>3.6</td>
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<tr>
<td>Lung</td>
<td>20</td>
<td>12.3</td>
<td>1.6</td>
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<tr>
<td>Ovary</td>
<td>15</td>
<td>8.5</td>
<td>1.8</td>
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<tr>
<td>Prostate</td>
<td>11</td>
<td>6.2</td>
<td>1.8</td>
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<tr>
<td>Melanoma</td>
<td>7</td>
<td>6.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Breast</td>
<td>15</td>
<td>13.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>


Generating anti-cancer immunity is a multistep challenge

2013 Cancer Immunotherapy Breakthrough of the Year
Identify key immunologically relevant concepts in the treatment of cancer

» Cytokines
» Checkpoint blockade
» Cells
» Microbes
» Antigens

Rationale for type I Interferon

» Breast cancer, melanoma and GI cancer patients show reduced IFN-α signaling in T and B cells, and reduced IFN-γ signaling in B cells.
» Early and persistent defect, independent from stage and chemotherapy.

Impaired interferon signaling is a common immune defect in human cancer
IFN-alpha:

- Increases hematopoietic stem cell proliferation, increases pool of cells
- Increased migration of immune cells
- Increased cells in lymph nodes, activation of Dendritic cells to stimulate T cells
- Activated Dendritic cells take up tumor antigen to stimulate T cells, IFN-α also increases MHC on tumor cells

T-Cell Activation and Proliferation

- Cognate T-Cell Receptor and MHC presentation of peptide antigen
- Costimulatory signal
T-Cell Activation and Proliferation

IL-2 Cytokine
Growth Factor;
T cell expansion

Stimulate the immune system

Interleukin – 2

Response to Ipilimumab 10 mg/kg x 2 doses

No progression 5+ years
T cell Autoregulation blocked

T-cell activation

T-cell inhibition

T-cell remains active

Blocking CTLA-4 and PD-1

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab/pembrolizumab)

I am exhausted

Melanoma

Modified from Blood 2013 121:1485-1486
The intestinal microbiota influences the efficacy of PD-1 blockade

Fecal Microbiota Transplant

- Placement of fresh or frozen stool harvested from a healthy individual into the gastrointestinal tract of the recipient
- 4th century China, Ge Hong, a famous Chinese Doctor prescribed human fecal suspension by mouth for food poisoning or severe diarrhea
- 16th century China, Ming dynasty, Li ShiZhen described the use of fermented, fresh or dried feces (aka "yellow soup") to treat severe diarrhea, pain, fever, vomiting and constipation in the medical text 本草綱目 (Compendium of Medical Herbs)
Adoptive cell therapy with antigen-specific T cells

Makalowski and Abken. ACT of Melanoma, DOI: 10.5772/53619

Talimogene laherparepvec (T-VEC) - An HSV-1 Derived Oncolytic Immunotherapy

- Selective viral replication in tumor tissue
- Accumulation of the virions / lysis of cancer cell = oncolytic effect
- Systemic tumor-specific immune response
- Death of distant cancer cells
'Final common pathway' of human cancer immunotherapy: targeting random somatic mutations

Potential strategies for enhancing clinical responses to cancer neoantigens

- Use T cells recognizing neoepitopes for ACT
- Utilize TCRs recognizing neoepitopes in Tg TCR
- Combine above with other immune therapy
- Neoepitope/peptide therapeutic "vaccination"

Controlling the immune system is not as simple as driving a car