What is Immunotherapy & Its Mechanisms of Action

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Disclosure

James Gulley has no relevant disclosures
The Immune System

• Adaptive defense system
  – protects against invading microorganisms and cancer

• Consists of two activities
  – Recognition
  – Response
Hematopoetic cell lineage

Immune system

- It is made up of many cell types.
  - Trainers / Teachers
    - Antigen presenting cells (e.g., Dendritic Cells)
  - Soldiers
    - B-cells
    - T-cells
Immune system: selective targeting

B-cell

Can be trained to recognize proteins (targets) on cell surface

Make Antibodies (Cruise missiles)

T-cell

Can be trained to recognize any protein (target) made by cell

Direct contact (Hand-to-hand) through T-cell receptor
Anatomy of the Lymphoid system

- Lymphocytes and lymph return to blood via the thoracic duct
- Naive lymphocytes enter lymph nodes from blood
- Antigens from sites of infection reach lymph nodes via lymphatics
Immunotherapy: The Perfect Anti-cancer Therapy

- Ideal therapeutic should effect only on damaged / diseased cells with no impact on normal cells.

- Recognition
  - T-cells $10^{18}$ unique targets
  - B-cells $10^{22}$ unique targets

- Multiple weapons systems
  NO, $H_2O_2$, Superoxides, FasL Trail, Perforin, Granzyme, Phagocytosis, Compliment

- Mutations only add targets

- Memory response
1. Antigen presenting cells in skin-Antigen uptake
1. Antigen presenting cells in skin - Antigen uptake

2. Antigen presentation in lymph nodes
How vaccines activate TAA specific T-cells

Tarassoff, …Gulley *The Oncologist*, 2006
1. Antigen presenting cells in skin - Antigen uptake

2. Antigen presentation in lymph nodes

3. Tumor attack
T-cell mediated killing of Tumor cells

- Cell death via caspase cascade
- Tumor cells
- T-cell
- FAS
- MHC
- TCR
- ICAM
- LFA-1
- FAS-L
- Granzymes
1. Antigen presenting cells in skin-Antigen uptake

2. Antigen presentation in lymph nodes

3. Tumor attack

4. Cross-presentation of multiple tumor antigens in draining lymph nodes
A. Degenerating tumor expresses different immunogenic targets

- Spontaneous immune response
- Induced immune response (vaccine, adoptive therapy)
A. Degenerating tumor expresses different immunogenic targets

B. Immature dendritic cell phagocytoses dying tumor cell along with a transfer of tumor-specific antigens
A. Degenerating tumor expresses different immunogenic targets

B. Immature dendritic cell phagocytoses dying tumor cell along with a transfer of tumor-specific antigens

C. Mature dendritic cells present tumor-specific antigens to T-cells
A. Degenerating tumor expresses different immunogenic targets

B. Immature dendritic cell phagocytoses dying tumor cell along with a transfer of tumor-specific antigens

C. Mature dendritic cells present tumor-specific antigens to T-cells

D. Newly activated tumor-specific T-cells form in greater concentration and variation

- Dying tumor cells
  - PAP
  - PSCA
  - Neo-Ag
  - PSA

- Newly activated tumor-specific T-cells
A. Degenerating tumor expresses different immunogenic targets

B. Immature dendritic cell phagocytoses dying tumor cell along with a transfer of tumor-specific antigens

C. Mature dendritic cells present tumor-specific antigens to T-cells

D. Newly activated tumor-specific T-cells form in greater concentration and variation

E. Fully activated T-cell destroys tumor cells

Dying tumor cells

PAP

PSCA

Neo-Ag

PSA
1. Antigen presenting cells in skin - Antigen uptake
2. Antigen presentation in lymph nodes
3. Tumor attack
4. Cross-presentation of multiple tumor antigens in draining lymph nodes
5. Broadened immune response/attack at secondary tumor site
Antigen Cascade

Improved clinical outcomes associated with antigen cascade (aka antigen spreading)


- Hardwick N, et al. Epitope spreading contributes to effective immunotherapy in metastatic melanoma patients. *Immunotherapy* 2011


Gulley JL. Therapeutic vaccines: The ultimate personalized therapy? *Hum Vaccin Immunother*, 2012
## Immunotherapy vs. Conventional Therapy

<table>
<thead>
<tr>
<th></th>
<th>Conventional Therapy</th>
<th>Immunotherapy</th>
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</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Tumor or its microenvironment</td>
<td>Immune system</td>
</tr>
<tr>
<td><strong>Pharmacodynamics</strong></td>
<td>Often immediate action</td>
<td>Delayed (adaptable, may get better over time)</td>
</tr>
<tr>
<td><strong>Memory Response</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Tumor Evolution / new mutations</strong></td>
<td>Resistance to therapy</td>
<td>New immunogenic targets</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Toxicity</td>
<td>Requires adequate immune system function (both systemically and at tumor site)</td>
</tr>
</tbody>
</table>

Gulley et al., ASCO Education Book, 2013
Tumor Growth Rate

Madan RA, *Oncologist*, 2011
T cell recognition of tumor cell
T cell function at tumor cell: to kill
T cell function at tumor cell: or not to kill
Balance in Immune System Activation

- Too little: cancer
- Too much: autoimmunity
3 E’s

(a) Elimination

(b) Equilibrium

(c) Escape

Genetic instability/tumor heterogeneity

Immune selection
Therapies

• Steering
  – Therapeutic Vaccines (Sipuleucel-T TVEC)
  – Adoptive Cellular Therapy (CAR-T)
• Brakes / Gas
  – Cytokines (IL-2, GM-CSF, IFN)
  – Immune Checkpoint Modulators (Ipilimumab, nivolumab, pebrolizumab)

FDA approval
Ipilimumab in Advanced Melanoma: Overall Survival

Pooled OS Data from PhII + PhIII Trials of Anti-CTLA4 in Metastatic Melanoma: 1861 Patients

Median OS, months (95% CI): 11.4 (10.7–12.1)

3-year OS rate (95% CI): 22% (20–24)

Schadendorf et al., ESMO 2013
Immune response capable of being:

- Rapid
- Durable
- Self propagating
- Adaptable
anti-PD1 or anti-PD-L1

Lung Cancer

Bladder Cancer

Pancreas Cancer

Ovarian Cancer

Gastric Cancer

Gastroesophageal Cancer

Modified from a Slide Courtesy of “Mac” Cheever
Avelumab, an anti-PDL1 antibody (EMD Serono / Pfizer)

PR in metastatic clear cell

- 65 years old; 6 prior lines for metastatic disease
- 4th assessment cycle, still on treatment
- Safety: well tolerated (grade 1-2 rigors; grade 1 flu-like symptoms and fatigue)
- PR by RECIST ongoing at time of analysis

Baseline: 69 mm RLL lesion

Week 25: 41 mm (-40.6%)

Presented By Mary Disis at 2015 ASCO Annual Meeting

Courtesy of Dr. S. Ejadi, Scottsdale, AZ
Summary: Pipeline radar chart

Solid Tumors
- MS0010718C
- Pembrolizumab (NSCLC)
- MED14736
- Pembrolizumab + cabemertinib
- Magp3470A + bevacizumab
- Anti-LAG3 (BMS-986016) + nivolumab
- Pancreatic
- Nivolumab + ipilimumab
- Melanoma, NSCLC
- Pembrolizumab
- Nivolumab
- Malignant Gliomas
- Pembrolizumab
- Nivolumab
- Hodgkin Lymphoma, Myeloma, MDS, NHL
- Pembrolizumab
- Nivolumab
- Hepatocellular
- Pembrolizumab
- Nivolumab
- Glioblastoma
- Pembrolizumab
- Nivolumab
- Gastric, SCLC, TNBC, HNC, Urothelial
- Pembrolizumab
- MPDL3280A
- Colon Cancer
- Pembrolizumab
- MPDL3280A
- RCC

Source: @PDRennart, pic.twitter.com/pg9UtTNfHX June 2015
Hodge et al., OncoImmunology, 2013
Growth Rates with Combination Therapy

- Vaccine
- Cytotoxic Therapy
- Combination
Potential Multiple Effects of Local Irradiation of Tumors

May facilitate broader immune response - antigen spreading

Hodge …Gulley et al., Oncology 22:1064-70.
Treatment of LnCaP prostate cancer cells with palliative doses of $^{153}\text{Sm}$ results in the upregulation of TAAs:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PS A</th>
<th>PSM A</th>
<th>PAP</th>
<th>PSA</th>
<th>CE A</th>
<th>MUC -1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Gy</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>25 Gy</td>
<td>2.79</td>
<td>4.14</td>
<td>29</td>
<td>9</td>
<td>10.3</td>
<td>3.67</td>
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</table>

Treatment of LnCaP prostate cancer cells with palliative doses of $^{153}\text{Sm}$ results in increased sensitivity to multiple CTLs:

![Graph showing % Lysis vs. Day 4 Sm-153 delivered Dose (Gy)]

Chakraborty, Wansley…Schlom, Hodge, NCI. Clin Cancer Res. 2008

Collaboration with Nuclear Medicine Branch
Patient Population: CRPC Metastatic to bone

Arm A: PSA-TRICOM + $^{153}$Sm (n=34)

Arm B: $^{153}$Sm (n=34)

Vaccine: rV-PSA/TRICOM s.c. d 1
rF-PSA/TRICOM s.c. d 15, 29, q 4 wks

$^{153}$Sm: 1 mCi/kg d 8, may be repeated q 12 wks upon hematologic recovery.

NCT00450619; PI Gulley
CINJ (DiPaola) and UC (Stadler)
\[^{153}\text{Sm} +/- \text{PSA-TRICOM}: \text{Prolonged PFS and Favorable PSA Response Profile}\]

- Final data of \(n = 44\) patients with mCRPC
- 1º endpoint: PFS
- Progression defined by utilizing PCWG, but not PSA criteria

\[
\text{Percent without Progression} \\
\begin{array}{cccc}
0.00 & 0.25 & 0.50 & 0.75 & 1.00 \\
\end{array}
\]

\[
\begin{array}{c}
\text{Days from On-Study Date} \\
0 & 100 & 200 & 300 \\
\end{array}
\]

\[
\text{\[^{153}\text{Sm Alone}\] TTP = 1.7 months} \\
\text{\[^{153}\text{Sm+PSA-TRICOM}\] TTP = 3.7 months} \\
\text{\(P_{2}=0.03\)}
\]

PCWG = Prostate Cancer Working Group response criteria

Heery...Gulley ASCO GU 2013
Immunogenic Intensification

Schadendorf et al., ESMO 2013
Effect of Vaccination on Tumor PD-L1 Expression

No anti-tumor immune response for ICM to unleash

ICM can unlock / unleash ineffective underlying immune response

Gajewski T et al. Current Opinion in Immunology, 25, 1-9 2013
Effect of Vaccination on Tumor PD-L1 Expression

CEA-Tg mice
MC38 (CEA) cells s.c.

rMVA-CEA-mTRICOM
8

rF-CEA-mTRICOM
15

22

Harvest tumors for IHC

Similar results with LLC lung carcinoma cells
Conclusions

Key Points

• Immunotherapy is powerful and can lead to **durable, adaptable responses**.
• Therapeutic Vaccines and Immune Checkpoint Modulators have been FDA approved for indications such as Prostate Cancer, Melanoma and Lung Cancer with multiple other indications under late stage investigation
• Immunotherapy can be combined with other therapies (vaccines with immune checkpoint inhibitors)

Lessons Learned

• Immunotherapy may take time to generate clinically meaningful responses
• Patients with an underlying immune response may benefit best from immune checkpoint modulators

Potential Impact on the Field

• Could be that in 10 years most cancers will be treated with immunotherapy
Examples of Therapeutic Vaccines*

- APC based vaccine (Sipuleucel-T, Dendreon; NW Biotherapeutics)
- Antigen Based Vaccine
  - Protein (HER2 Peoples)
  - Peptide (long vs. short)
  - DNA / RNA (VBIR Pfizer, RNAActive CureVac)
  - Vector
    - Bacteria (Listeria [CRS-207] Aduro)
    - Yeast (GI-6301, Globelimmune / Celgene)
- Whole Tumor Cell Vaccine (GVAX, Aduro)
- Oncolytic Vaccine (T-Vec, Amgen)

*Selected partial list for brevity, 2 agents FDA approved to date