Immunotherapy in Ovarian Cancer

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Roswell Park Cancer Institute
Buffalo, NY
I have no financial relationships to disclose.
Objectives

• How immunotherapy approaches may expand shared tumor antigen specific T cells.

• Highlight the role of vaccines, PD-1/PD-L1 and other immune checkpoints in ovarian cancer.

• **Beyond PD-1/PD-L1**: highlight how amino acid metabolism (tryptophan) represents a potent mechanism of immune escape in ovarian cancer.

• Adoptive T cell immunotherapy
Discriminating “self” from “non-self”: a fundamental feature of the immune system

1. Confront the external threat of infectious pathogens
   - Create a diverse repertoire of TCRs (via V(D)J recombination):
     - foreign pathogens/epitopes
     - endogenously expressed self epitopes (shared tumor antigens).

2. Avoid immunological self destruction (*horror autotoxicus*)
   - Clonal deletion of αβ T cells specific for self (Burnet, 1959).
     - Implication:
       
       T cells recognizing self antigens should be deleted in the thymus, which conceptually should render shared antigen-based approaches ineffective.
Prevailing dogma: central tolerance is a barrier for “self antigens” in immunotherapy

Adapted from Hacohen et al Cancer Immunol Res 2013
Evidence for inefficient deletion of “self” reactive CD8⁺ T cells

Clonal Deletion Prunes but Does Not Eliminate Self-Specific αβ CD8⁺ T Lymphocytes

Wong Yu,¹,² Ning Jiang,³,⁸ Peter J.R. Ebert,¹ Brian A. Kidd,¹,⁹ Sabina Müller,⁴ Peder J. Lund,¹ Jeremy Juang,¹ Keishi Adachi,¹,¹⁰ Tiffany Tse,¹ Michael E. Birnbaum,¹ Evan W. Newell,¹,¹¹ Darrell M. Wilson,⁵ Gijsbert M. Grotenbreg,⁶,¹² Salvatore Valitutti,⁴ Stephen R. Quake,³,⁷ and Mark M. Davis¹,⁷,*
Clonal deletion prunes T cell repertoire without eliminating self-reactive T cells

Expand and/or rescue function via:
- vaccination
- checkpoint blockade
- immunomodulation
- adoptive cell therapy
- oncolytic virotherapy

to self tumor antigens…

Kitz et al. Immunity 2015
Improved outcome in ovarian cancer patients with elevated CD8+ TIL levels: Evidence of Immune Recognition

Zhang et al. NEJM 2003;348:203
(Coukos)

Sato et al. PNAS 2005;102:18538
(Odunsi)
Can immune responses be generated against shared “self” antigens vs mutational antigens?

**Shared self antigen**
- Differentiation antigens: tyrosinase, MART-1, NY-BR
- Cancer Germline (CG or CT) antigens: MAGE family, NY-ESO-1
- Over-amplified antigens: HER2/neu, WT1, CD20
- Stemness antigens: SOX2, OCT4

**Neoantigen**
- Mutational antigens: B-raf, p53

**Foreign antigen**
- Viral antigens: HPV-derived E6 and E7
Potential contribution of NY-ESO-1 specific CD8\(^{+}\) T cells

Expression limited to germ cells and cancer cells; immunogenic tumor antigen

- Focal, 1+ to 4+
- Humoral response: 30%

Odunsi et al Cancer Res 2003
Can immune responses be generated against shared “self” antigens? NY-ESO-1 vaccine trials at RPCI

<table>
<thead>
<tr>
<th>Protocol</th>
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<th>NY-ESO-1 targeted intervention</th>
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<td>RP 02-28</td>
<td>N/A (LUD02-011)</td>
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<td>ovarian (n=50)</td>
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<td>I 277115</td>
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<td>recombinant protein + MIS416 adjuvant + rapamycin</td>
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<tr>
<td>I 288216</td>
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<td>DEC205-NY-ESO-1 + guadecitabine + atezolizumab</td>
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## NY-ESO-1 vaccine trials at RPCI

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NY-ESO-1 canary pox vaccine schedule

- **rCNP vector for delivery of NY-ESO-1**
- **TRICOM** T cell co-stimulatory molecules (LFA-3/ICAM-1/B7.1)
- **GM-CSF** enhances efficacy of APCs

≥ 5x10⁶ CCID₅₀ rCNP/TRICOM
(s.c. 1x/mo)

100 μg GM-CSF
(s.c. day 1-4)
NY-ESO-1-specific humoral response to rCanary pox/TRICOM vaccination (n=12)
Targeting NY-ESO-1 for immune responses improves clinical outcomes in NY-ESO-1\(^+\) patients

NY-ESO-1\(^-\) patients

NY-ESO-1\(^+\) patients – no trial:
- n=340
- OS=38 mo

NY-ESO-1\(^+\) patients – NY-ESO-1 trial:
- n=68
- OS=75 mo

Szender et al in revision
Distinct roles of CTLA-4 and PD-1 in the regulation of antitumor T-cell responses

Brahmer JR, Pardoll DM. Cancer Immunol Res. 2013
MDX-1105 (anti-PD-L1) in ovarian cancer patients

1/17  (6%) had partial response
3/17  (18%) had stable disease lasting ≥24 weeks (10 mg dose)

rate of PFS at 24 weeks:
22% (2-43)

Brahmer et al, NEJM 2012
Safety and Antitumor Activity of Anti–PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer: I

2 cases with a Complete response

<table>
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<tr>
<th>Nivolumab dose</th>
<th>Number of OC patients</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mg/kg</td>
<td>10</td>
<td>1 PR (10%)</td>
</tr>
<tr>
<td>3mg/kg</td>
<td>10</td>
<td>2 CR (20%)</td>
</tr>
</tbody>
</table>

- Best overall response was 15%
- DCR: 45%
- PFS: 3.5 months (95% CI, 1.7 to 3.9 months)
- OS: 20.0 months

Hamanashi J. J Clin Oncol 2015 Dec 1;33(34):
Avelumab (anti-PD-L1) in patients with previously treated, recurrent or refractory ovarian cancer

refractory or recurrent ovarian cancer (no PD-L1 preselection) → avelumab 10 mg/kg IV Q2W → safety tolerability PFS, OS

- Tumor size decrease ≥30% observed in 12/124 patients (9.7%)
- SD: 44.0% additional patients
- DCR: 54.7%

Disis et al, ASCO Abstract 2015
Pembrolizumab (anti-PD-1) in patients with PD-L1 positive advanced ovarian cancer

<table>
<thead>
<tr>
<th>Patients (n = 26)</th>
<th>n</th>
<th>%</th>
<th>CI&lt;sub&gt;95&lt;/sub&gt;</th>
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<tr>
<td><strong>Best response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate</td>
<td>3</td>
<td>11.5</td>
<td>2.4 – 30.2</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>3.8</td>
<td>0.1 – 19.6</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>7.7</td>
<td>0.9 – 25.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6</td>
<td>23.1</td>
<td>9.0 – 43.6</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>17</td>
<td>65.4</td>
<td>44.3 – 82.8</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>9</td>
<td>34.6</td>
<td>17.2 – 55.7</td>
</tr>
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</table>

Varga et al, ASCO Abstract 2015
What are the mechanisms of resistance and limited efficacy of vaccines and checkpoint inhibitors in ovarian cancer?
Why are vaccines and PD-1 pathway blockade only of modest benefit in ovarian cancer?

Activating receptors

- CD28
- OX40
- GITR
- CD137
- CD27
- 4-1BB

Inhibitory receptors

- CTLA-4
- PD-1
- TIM3
- BTLA
- VISTA
- LAG3

agonist antibodies

antagonist antibodies
Expression of PD-1, LAG-3 and CTLA-4 on NY-ESO-1 specific CD8+ cells at the tumor site

The capacity for IFN-γ production is diminished in LAG-3+ and PD1+ subsets of tumor-antigen-specific T cells.
Dual LAG-3 and PD-1 pathway blockade during priming efficiently restores frequency and effector function of NY-ESO-1–specific CD8+ T cells.

<table>
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<tr>
<th>APC derived from</th>
<th>CD8− PBL</th>
<th>CD8− TIL</th>
</tr>
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<tbody>
<tr>
<td>LAG-3 blockade</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PD-1 blockade</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

![Image showing flow cytometry results](image.png)
Lack of improved survival in ovarian tumor challenged $\text{Lag3}^{-/-}$ or $\text{Pdcd-1}^{-/-}$ mice

Huang, R et al., Oncotarget, 2015
Question #2: Do immune checkpoints collaborate?

**CD8⁺ T cells from Lag3⁻/⁻Pdcd1⁻/⁻ mice exhibit enhanced effector phenotype**

CD8⁺ T cells isolated from WT Lag3⁻/⁻ Pdcd1⁻/⁻ Lag3⁻/⁻Pdcd1⁻/⁻ DBKO

- anti-CD3/anti-B7-1 activation
- 6 h (IL2, TNFα, IFNγ)
- 24 h (Granzyme B)

Huang, R et al., Oncotarget, 2015
Enhanced anti-tumor immunity in Lag3−/−Pdcd1−/− mice

IE9mp1(OVA) ovarian tumor cells IP

Enhanced survival

Increased CD8+ T cell infiltration

Enhanced T cell function

Huang, R et al., Oncotarget, 2015
Dual LAG3 and PD1 blockade synergistically enhances anti-tumor immunity

Increased CD8+ T cell infiltration

Enhanced survival

Increased proliferation

Enhanced function

Huang, R et al., Oncotarget, 2015
Compensatory upregulation of immune checkpoints in murine OVC after blockade of single checkpoint pathway

Huang, R et al., Oncoimmunology, 2016
Multiple co-inhibitory molecules are expressed by exhausted T cells.

LAG-3+PD-1+ T cell subset preferentially accumulates at the ovarian tumor site.

Dual blockade of PD-1 and LAG-3 restores effector function of antigen specific CD8+ T cells.

Compensatory upregulation of immune checkpoints on TILs in ovca after blockade of a single checkpoint pathway

Improved outcomes in ovarian tumor bearing hosts, but not cure.

Metabolic regulation of T cell function: energy, amino acids (tryptophan, arginine).

Role of indole-amine 2,3 dioxygenase
Tryptophan catabolism: a pivotal regulator of innate and adaptive immunity - IDO1, IDO2, TDO

- T cells sense ↓TRP levels via high levels of uncharged tRNA. 
- Activation of GCN2 kinase. 
- Triggers a stress-response program. 
- Results in cell cycle arrest, differentiation.

**Diagram:**
- T cells sense ↓TRP levels via high levels of uncharged tRNA.
- Activation of GCN2 kinase.
- Triggers a stress-response program.
- Results in cell cycle arrest, differentiation.

**Figure:**
- T cell cycle arrest
- Treg generation
- Treg activation

• ↓Tryptophan catabolism, accompanied by low TILs (IDO\textsuperscript{loTIL\textsuperscript{hi}}) associated with the most favorable outcome in ovarian cancer patients.

• Pharmacological inhibition as a strategy for overcoming IDO1 mediated immune suppression – converting tumors to IDO\textsuperscript{loTIL\textsuperscript{hi}}?
Clinical Trial Hypotheses: IDO1 inhibition will (i) decrease immune suppression and increase immune response within tumor (ii) enhance efficacy of vaccination targeting NY-ESO-1 in ovarian cancer patients.

INCB024360
parallel clinical trials

- Newly diagnosed patients
- No NY-ESO-1 requirement
- Phase 0
- Neo-adjuvant efficacy

SPORE
- Patients in remission
- NY-ESO-1 positive tumors
- Phase I/II
- Combined with NY-ESO-1 vaccine
Hypothesis: IDO1 inhibition will decrease immune suppression and increase immune response within tumor (n=12)

n=12 patients with evaluable pre-op tissue

n=9 adequate biopsy
n=4 inadequate biopsy
n=2 pending
Neoadjuvant INCB024360 is well-tolerated

Reduction in Kyn:Trp ratio – hitting the target in the TME

Elevated ratio of CD8+ TIL infiltration

IFN signature change in tumor after treatment.

Allows for rational design of combination regimens.

**Future:** Studies underway to evaluate response to tumor antigens and nature of clonal response.
Classification of tumor microenvironments based on TIL and PD-L1 Expression

Adaptive immune resistance

TIL+ PD-L1+ IDO+

Immunological Ignorance

TIL- PD-L1- IDO-

Tolerance (other suppressors)

TIL+ PD-L1- IDO-

Intrinsic Induction

TIL- PD-L1+ IDO+
Q: Can immunotherapy be selected based on the immune landscape?

- PDL1\textsuperscript{hi}
- IDO\textsuperscript{hi}
- Neoag\textsuperscript{hi}
- TIL\textsuperscript{+}
- IDO/PDL1\textsuperscript{hi or lo}
- TIL\textsuperscript{−}

+ checkpoint blockade
+ IDO inhibitor
+ vaccines
+ TCR/CAR-engineered ACT
+ oncolytic viruses

What do you do for a non-inflamed tumor?

adapted from Ribas et al. Cancer Discov 2015
Advantages of adoptive T cell therapy

dramatic regressions
melanoma, synovial sarcoma
up to $10^{11}$ anti-tumor T cells grown *in vitro*
favorable *in vitro* activation
absence of inhibitory factors
manipulation of the TME before cell transfer
Adoptive T cell therapy (ACT) targeting a shared tumor antigen (NY-ESO-1-TCR) results in regression of large bulky tumors.

perihepatic chest wall lesion in Pt #16

multiple lung metastases in Pt #13

Robbins et al JCO 2011
Generating T cells for adoptive transfer

**TIL**
Tumor-infiltrating lymphocytes

**TCR/CAR**
Engineered T cells

**ETC**
Endogenous T cells

**Receptor Transfer**

**Generating T cells for adoptive transfer**

1. **TIL**
   - Tumor-infiltrating lymphocytes
   - IL-2 enrichment
   - TIL enrichment

2. **TCR/CAR**
   - Engineered T cells
   - TCR
   - CAR

3. **ETC**
   - Endogenous T cells
   - Antigen-specific T cell enrichment
   - Cloning
   - Cell sorting
Phase I trial evaluating safety and efficacy of autologous T cells expressing NY-ESO-1 TCR in patients with recurrent or treatment refractory ovarian cancer

eligibility criteria: NY-ESO-1+ & HLA-A0201+

NY-ESO-1^{c259} (1x10^9 – 40x10^9 max)

Response assessments

Day

-5 -4 0 1 7 30 60 90

CTX

additional sites
CoH, MD
Anderson, Stanford, Miami

NCT01567891
AdaptImmune
Phase I/II ACT trial examining safety and efficacy of TGFβ signaling blockade

Activation March 2017
Conclusions and Future of Immunotherapy for Ovarian Cancer

• Effectiveness of vaccines and current immune checkpoint therapies in ovarian cancer may be limited by the multiple immune suppressive networks in the TME.

• Reprogram the TME from tolerogenic to immunogenic via combination strategies (e.g. targeting metabolic dysfunction by IDO, PDL-1, LAG3, TIM3).

• CD8 TCR cell therapy in ovarian cancer may be limited by poor persistence.

• Abrogation of TGF-β signaling in T cells enhances persistence.

• Combination strategies, minimizing toxicities.
Which patients are most likely to respond?
Biomarkers of responsiveness?
   PD-L1 / IDO expression (other ligands)
   Mutational load
   Degree of T cell infiltration
Mechanisms of resistance to checkpoint blockade?
Beyond PD-1/PD-L1 and CTLA4: Advancing combinations rapidly and balancing toxicity?
Incorporation of Adoptive T cell therapy (cost, logistics, toxicity)
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