Immune Checkpoint Blockade in Cancer Therapy

Jim Allison

Nobel Prize in Physiology or Medicine Lecture 2018
Dynamic Integration of TCR and Costimulatory Signals

circa 1996

No Proliferation
Anergy?

Activation, Initiation

Inhibition

Restricted
Proliferation

IL-2

p27\textsuperscript{kip}

p\text{Rb}

Cdk6

Cdk4

Cyclin D1

Cyclin D2

Bcl\text{-}xL,\gamma

Antigen Presenting Cell

TCR  CD28  CTLA-4

Peptide/MHC  B7-1,2

Gross, Harding, Krummel, Chambers, Brunner, Egen, Kuhns
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Proliferation

Tumor

APC

Necrotic Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
“Targeted” Therapies

TCR
CD28
Peptide/MHC
B7-1,2

CTLA-4
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation

Necrotic Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
“Targeted” Therapies
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation

Unrestrained Proliferation

Tumor

Necrotic Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
“Targeted” Therapies

APC

CTLA-4

CD28

B7-1,2

TCR

Peptide/MHC

IL-2

Unrestrained Proliferation
The longest survivor on ipilimumab

May 2001, after progression on IL-2

Baseline and post-MDX-010 treatment CT scans of patient with metastatic melanoma (status post dendritic cell vaccine) who experienced regression of all known sites of disease. The patient continues without relapse at last reported follow-up visit.

10 years later

Lung Mass

Pleural Effusion

Pre-treatment

Post-treatment
Ipilimumab in Metastatic Melanoma
(pooled data from 4846 patients)

3-year OS Rate (95% CI): 21% (20–22%)
Programmed Death 1 (PD-1)
Anti-PD-1 Phase I
(Nivolumab, BMS)

296 Patients with Metastatic Cancer
1, 3, 10 mg/kg, MTD not reached

Safety: Adverse events similar to Ipilimumab, but 4% pneumonitis

Clinical Activity:
Melamona (n=94): 28% CR/PR, 6% SD
NSCLC (n=76): 18% CR/PR, 7% SD
RCC (n=33): 27% CR/PR, 27% SD
CRC (n=19), CRPC (n=13): No responses

Topalian ASCO, NEJM 2012
Where do we go from here?

Combinations
Ipi/Nivo vs. Ipi in Metastatic Melanoma

Hodi NEJM 2015
Immune checkpoint blockade FDA approvals

**Melanoma** – *Ipilimumab, Pembrolizumab, Nivolumab, Ipilimumab + Nivolumab*

**Melanoma (adjuvant)** – *Ipilimumab, Nivolumab*

**Pediatric melanoma** – *Ipilimumab*

**Non-small cell lung cancer** - *Nivolumab, Pembrolizumab, Atezolizumab*

**Renal cell carcinoma** – *Nivolumab*

**Hodgkin’s lymphoma** – *Nivolumab, Pembrolizumab*

**Bladder cancer** – *Atezolizumab, Nivolumab, Durvalumab, Avelumab, Pembrolizumab*

**Head and neck cancer** – *Nivolumab, Pembrolizumab*

**Merkel cell carcinoma** – *Avelumab*

**MSI-H, dMMR** – *Pembrolizumab (any histology), Nivolumab (colorectal)*

**Gastric/gastroesophageal cancer** – *Pembrolizumab*

**Hepatocellular carcinoma** - *Nivolumab*
Critical issues for further clinical development of immune checkpoint targeting

• Determination of the cellular and molecular mechanisms involved in the anti-tumor effect

• Determination of the impact of other therapeutic agents on the immune system

• Combining the best standard-of-care therapies with immune checkpoint agents

• Targeting new molecules to improve efficacy

• Identification of predictive, prognostic or pharmacodynamic biomarkers
<table>
<thead>
<tr>
<th><strong>Anti-CTLA-4</strong></th>
<th><strong>Anti-PD-1</strong></th>
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<tbody>
<tr>
<td>• Hard wired</td>
<td>• Induced resistance</td>
</tr>
<tr>
<td>• Targets CD28 pathway</td>
<td>• Targets TCR pathway</td>
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<tr>
<td>• Works mainly during priming</td>
<td>• Works mainly on exhausted T cells</td>
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<tr>
<td>• Expands clonal diversity</td>
<td>• Does not expand clonal diversity</td>
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<tr>
<td>• Primarily effects CD4 T cells</td>
<td>• Primarily effects CD8 T cells</td>
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<tr>
<td>• Can move T cells into “cold” tumors</td>
<td>• Does not move T cells into tumors</td>
</tr>
<tr>
<td>• Responses often slow</td>
<td>• Responses usually rapid</td>
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<tr>
<td>• Adverse events relatively frequent</td>
<td>• Adverse events less frequent</td>
</tr>
<tr>
<td>• Disease recurrence after response rare</td>
<td>• Disease recurrence after response significant</td>
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</table>
Can we identify checkpoint blockade responsive T cell populations?

CyTOF analysis of murine TILs (43 Parameters) +/− checkpoint blockade

Unsupervised population identification

Identify associations with treatment and outcome

Spencer Wei
Mass cytometry analysis of MC38 TILs

8-week old C57BL/6

Inoculate MC38 s.c.

Antibody

Antibody

Antibody

Harvest TILs Day 13

CyTOF analysis (43 Parameters)

Wei et al Cell 2017
MC38 infiltrating T cell populations

Gated for CD45+, CD3ε+

Control
αCTLA-4
αPD-1

Wei et al Cell 2017
MC38 TIL

Wei et al Cell 2017
Checkpoint blockade modulates MC38 infiltrating T cell population frequencies

Wei et al. Cell 2017
Summary

• The therapeutic mechanisms of αCTLA-4 and αPD-1 are distinct

• These mechanisms are the same in a highly immunogenic and a poorly immunogenic tumor

• These distinct mechanisms may explain why the combination is so effective

• Specific CD4 and CD8 T cell subtypes contribute to the therapeutic effects in both therapies

• Monitoring these subtypes rather than total CD4 or CD8 cells correlates better with outcome and may be much predictive of outcome
Are similar mechanisms involved in patients?

TILS from treated melanoma patients

Normal PBMC       Ipilimumab (αCTLA-4)
Nivolumab (αPD-1)  Ipi + Nivo

Total CD45+ cells

Wei et al Cell 2017
Checkpoint blockade modulates the frequency of specific TIL populations in melanoma patients

Exh CD8
CD45RO+
CD69+
PD-1+
Lag3+
Th1-like
ICOS+ CD4
CD45RO+
ICOS+
PD-1low
CD69+

% of CD45

Normal donor PBMC
Ipi
PD-1
Ipi + Nivo

T cells
CD8
CD4
Other

Clusters
B cells
Myeloid and DC
Other

Th1-like
ICOS+ CD4
CD45RO+
ICOS+
PD-1low
CD69+

Treg
How do these cellular mechanisms interact?
Mass cytometry analysis of MC38 TILs

C57BL/6 mice

Inoculate MC38 s.c.

Day 0  Day 5  Day 8  Day 11

Antibody  Antibody  Antibody

Harvest TILs Day 13

CyTOF analysis
(43 Parameters)

Wei et al unpublished
Expansion of phenotypically exhausted CD8 T cells

Wei et al unpublished
Combination therapy differentially affects CD8 subsets

Wei et al. *unpublished*
Combination therapy differentially affects CD8 subsets

Wei et al unpublished
Do phenotypically exhausted CD8 T cells have the same function in the context of combination therapy?

Wei et al. *unpublished*
Do phenotypically exhausted CD8 T cells have the same function in the context of combination therapy?

Wei et al *unpublished*
Effects on the CD4 effector compartment?
Expansion of Th1-like CD4 T cells following combination therapy

PD-1+ ICOS^{int} TBET^{+}  
Th1-like CD4 effector

Wei et al *unpublished*
What is the role of costimulation in the regulation of T cell differentiation?
T cell differentiation is complex
How are phenotypes, lineages, and boundaries defined?

Does negative costimulation regulate T cell differentiation?

- Maximum signal under normal conditions
- Attenuated signal due to CTLA-4 regulation
- Maximum in the absence of CTLA-4?

Effect on differentiation?
*Ctla-4* T cells display distinct phenotypes

Wei et al *unpublished*
New T cells phenotypes arise in the absence of CTLA-4
Specific expansion of CD4 T cell subsets

Wei et al. unpublished
What underlies the generation of these subsets?

- Not due to differences in T cell proliferation
- Not due to differences in T cell activation
- Not due to defects in thymic development

Do these populations represent new types of T cells?

Wei et al *unpublished*
Comprehensive profiling of peripheral T cells in the absence of CTLA-4

Mass cytometry analysis of Ctl-4−/− and littermate controls

39 Parameter T cell panel
Activation, surface, lineage markers
Lineage transcription factors

Wei et al. unpublished
CD4 archetypes reside in \textit{Ctla-4}\textsuperscript{-/-} specific regions

Wei et al \textit{unpublished}
Reconstruction of CD4 T cell differentiation paths

Graph structure of data

Randomly select $m$ out of $k$ nearest neighbor

Compute shortest path between two archetypes

Protein expression along differentiation pseudo-time
Transcription factor ratios identify lineage commitment events

Psuedotime
(along T cell differentiation paths)

Wei et al unpublished
Potential implications

Evidence for a ‘nuanced model’ of T cell differentiation

Role of T cell differentiation in mechanisms of immunotherapies


Inducible Costimulator (ICOS)

- Member of CD28/CTLA-4 superfamily
- Usually associated with Tfh or Treg
- Role in cancer (Sharma 2008)
Identification of unusual ICOS+ Th1-like CD4 cells that arise after CTLA-4 Blockade

Clinical Studies

• 2-10 fold increase in tumor and blood after Ipi
• Contains tumor specific IFNγ– & TNFα–producing CD4 cells
• Increase associated with longer survival
• Pharmacodynamic marker of Ipi activity

Mouse Studies

• Essential for optimal efficacy of CTLA-4 blockade
• Signaling via PI3K binding motif enhances Tbet expression
• Can be targeted to enhance efficacy of CTLA-4 blockade
Engaging the ICOS pathway with agonist vaccine increases efficacy of anti-CTLA-4

Combinations to enhance immune checkpoint targeting resulting in \textit{CURES}

- Blocking multiple checkpoints (negative and positive)
- Enhancing innate immunity
  - Oncolytic viruses
  - Local ablation
- Blocking other immunosuppressive factors
  - Conventional therapies
    - Radiation
  - Vaccines, shared and individual
    - Genomically targeted therapies
Improving Survival with Combination Therapy

% Survival

Time

Control
Standard or Other Therapy
Improving Survival with Combination Therapy

- Control
- Standard or Other Therapy
- Immunotherapy (anti-CTLA4)
Improving Survival with Combination Therapy

% Survival

Time

Control
Standard or Other Therapy
Immunotherapy (anti-CTLA4)
Combination
**Allison Lab & Alumni**

Jane Gross  
Fiona Harding  
Max Krummel  
Dana Leach  
Cynthia Chambers  
Andrea Van Elsas  
Sergio Quezada  

Karl Peggs  
Tyler Simpson  
Michael Curran  
Dmitryi Zamarin  
Sumit Subhudi  
Xiaozho Fan  
Spencer Wei  

Naveen Sharma  
Colm Duffy  
Stephen Mok  
Nana-Ama Anang  
Cecele Denman  
Alexandria Cogdill  

**Collaborators**

Dana Pe'er (MSKCC)  
Jacob Levine  

Jen Wargo  
Alexandre Rueben  
Christine Spencer  

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