Harnessing the Immune System to Fight Cancer

May 21st 2021, 18th Focus on Melanoma Conference
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Cancer Immunotherapy: Science Breakthrough
Cancer Immunotherapy: Science Breakthrough
Immunotherapy: “Amphibious assault on cancer”

Source: U.S. Department of Defense photo via Wikimedia Commons
CD8 T cells: Foot soldiers of the immune army
CD8 T cell exhaustion

Effective Immune Response

Ineffective Immune Response
CD8 T cell exhaustion

No Exhaustion  Partial Exhaustion  Mild Exhaustion  Moderate Exhaustion  Extreme Exhaustion

T cell

Tumor

Slide courtesy of John Wherry
CD8 T cell exhaustion
CD8 T cell reinvigoration

Does blocking PD-1 reactivate exhausted T cells?

Image credit: Parker Institute and https://pennaelectric.com/electrician-blog
When does the immune response happen after blocking PD-1

Clinical Response

Clinical Progression

Key Questions

- What happens after PD-1 is blocked
- What factors decide clinical response?
Measuring the immune response to blocking PD-1

Week: 0 3 6 9

Ki67

CD8 T cells

3.5% 6.7% 2.4% 2.4%
Laboratory science informing clinical trial design

**Clinical Trial of Blocking PD-1 Before Surgery**

- Stage III
- Biopsy
  - PD-1 Ab
  - 3 weeks
- Resection
  - PD-1 Ab

T. Mitchell  G. Karakousis  G. Xu  M. Farwell
Tissue Processing Pipeline

Biopsy

Resection

Paraffin

Frozen

Single Cells

G. Karakousis

G. Xu
PD-1 antibody reaches the tumor

<table>
<thead>
<tr>
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<th>Pre (Biopsy)</th>
<th>Post (Resection)</th>
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<tbody>
<tr>
<td>pembro</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>PD-1</td>
<td>14.8</td>
<td>25.7</td>
</tr>
<tr>
<td>% pembro bound</td>
<td>0.0</td>
<td>50.4</td>
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</table>

Tumor: % pembro bound
Blocking PD-1 results in increased CD8 T cells in the tumor
Intratumoral response after a single dose of PD-1 treatment predicts clinical benefit

- Intratumoral Response
  - Complete: 5/27 (30%)
  - Major (>90%): 3/27
Intratumoral response after a single dose of PD-1 antibody predicts clinical benefit

Can we improve outcomes for patients with less than 90% tumor destruction
Question 1: When is the immune response to blocking PD-1
   ➢ Immune response occurs after the first dose, within 3 weeks

Question 2: What happens after PD-1 is blocked?
2. What happens after PD-1 is blocked?

**Deep Immune Profiling**
- High dimensional cytometry
- TCR and RNA sequencing
- Tumor Whole Exome Sequencing
- Microscopy

**Computational Analysis**
PD-1 treatment is reinvigorating exhausted CD8 T cells

- Multiple inhibitory receptors
- RNA signature of exhausted T cells
- Same T cell clones found in tumor
Dimensional reduction technique reveal additional therapeutic targets

Week 3 Tumor

- Ki67
- PD-1
- Tim-3
- CTLA-4

Expression
- High
- Low
Dimensional reduction technique reveal additional therapeutic targets

Can we use drugs to block new targets on exhausted CD8 T cells?
Question 1: When is the immune response to blocking PD-1

- Immune response to occurs after the first dose, within 3 weeks

Question 2: What happens after PD-1 is blocked?

- PD-1 blockade is reinvigorating exhausted CD8 T cells

Question 3: What factors decide clinical response?
Machine learning approach reveals that regulatory T cells limit clinical response to PD-1 treatment
Machine learning approach reveals that regulatory T cells limit clinical response to PD-1 treatment

Can we personalize treatment (precision immuno-oncology)

Can we therapeutically remove regulatory T cells for certain patients?
T-cell invigoration to tumour burden ratio associated with anti-PD-1 responses

A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma

Huang, Amaravadi, Xu, Schuchter, Karakousis, Mitchell, Wherry et al, Nature 2017
Huang, Orlowski, Amaravadi, Schuchter, Xu, Farwell, Karakousis, Wherry, Mitchell, Nature 2019
Immune fingerprint in peripheral blood

- Severe COVID-19
- Recovered COVID-19
- Not infected

Can we be more precise in measuring the immune response to checkpoint blockade?
Tumor-Specific T cells

- BB515
- BV785
- BV650
- BV605

PE

TAG

0.4%

BB515

0.01%

EBV EVNA

gp100_ALN

0.05%

Tumor-Specific T cells

- Tyrosinase
- MageA1_EAD
- MageA3
- Aim2
- N-Ras (Q61R)
- Mart-1
- gp100_IMD
- gp100_YLE
- gp100_KTW
- LAGE-1
- SSX-2
- NY-ESO-1
- GnTV
- PRDX5
- gp100_ALL
- gp100_LIY
- gp100_ALN
- TAG
- MageA1_SLF

Response

Responder
Non-responder

Log10 %freq

0
-1
-2
-3
-4
-5
Immune Health Report

Adapted from John Wherry
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