Principles of Cancer Immunotherapy

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Disclosure of Conflict of Interest

Consultant for:

PACT Pharma, Inc.
Neon Therapeutics
Achilles Therapeutics
Key traits that make immunotherapy an attractive alternative for cancer treatment

Specificity

Cytotoxicity

Long term memory responses

Immunesurveillance
Key traits that make immunotherapy an attractive alternative for cancer treatment

- Specificity
- Cytotoxicity
- Long term memory responses
- Immunesurveillance

Possibility of inducing durable tumor regression
Tumor categories based on the existence of an inflammatory response

Inflamed

Pre-existing Immunity

Excluded Infiltrate

Non-inflamed

Immune Desert

“Hot” tumors

“Cold” tumors
Immunotherapeutic strategies differ according to the existence of an inflammatory response

1) Modulate the naturally occurring immune response
   For “HOT” tumors that elicit an immune response: melanoma, kidney cancer, lung cancer, bladder cancer, tumors with microsatellite instability
   **Immune checkpoint inhibitors, cytokines**

2) Induce an immune response against cancer
   For “COLD” tumors which are not naturally infiltrated
   **Vaccines, adoptive cell transfer, bi-specific antibodies**

3) Combination of both, and combination with other cancer therapies
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Modulating a pre-existing immune response

Releasing the brakes of the immune response against cancer: Immune Checkpoint Inhibitors (ICI)

**CTLA-4**
limits the priming of T cells in LNs

**PD-1**
Limits the effector function of T cells

A.K. Abbas et al. Cellular and Molecular Immunology, 2017
Releasing the brakes of the immune response against cancer: Immune Checkpoint Inhibitors (ICI)

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Approved indications for anti-PD-1/PD-L1 therapies

- **Squamous Cell Head & Neck Cancer**
  - 1L/2L nivolumab after platinum chemotherapy
  - 1L/2L pembrolizumab after platinum chemotherapy

- **Malignant Melanoma**
  - Adjuvant/1L ipilimumab
  - 1L nivolumab ± ipilimumab
  - Adjuvant nivolumab
  - 1L pembrolizumab

- **Merkel Cell Carcinoma**
  - 2L avelumab

- **Cutaneous Squamous Cell Carcinoma**
  - 1L cemiplimab

- **Hepatocellular Carcinoma**
  - 2L nivolumab after sorafenib
  - 2L pembrolizumab after sorafenib

- **Adv. Renal Cell Carcinoma**
  - 1L nivolumab plus ipilimumab
  - 2L nivolumab after anti-angiogenic therapy

- **MSI-H or dMMR Cancers**
  - 2L nivolumab in CRC
  - 2L nivolumab plus ipilimumab in CRC
  - 2L pembrolizumab in any MSI-H/dMMR cancer

- **Cervical Cancer**
  - 2L pembrolizumab CPS≥1

- **Small Cell Lung Cancer**
  - 3L nivolumab

- **Non-Small Cell Lung Cancer**
  - 1L pembrolizumab TPS≥50%
  - 1L pembrolizumab + pemetrexed & platinum-salt in non-squamous NSCLC
  - 1L pembrolizumab + carboplatin & (nab-)paclitaxel in squamous NSCLC
  - 1L atezolizumab + bevacizumab, paclitaxel & carboplatin in non-squamous NSCLC
  - 2L pembrolizumab TPS≥1%
  - 2L nivolumab
  - 2L atezolizumab
  - Maintenance durvalumab after chemoradiation

- **Gastric & GEJ Carcinoma**
  - 3L pembrolizumab after fluoropyrimidine- and platinum-chemotherapy +/- HER2 therapy & CPS≥1

- **Classical Hodkin Lymphoma**
  - 4L pembrolizumab
  - 3L nivolumab after auto-HSCT and BV
  - 4L nivolumab and after auto-HSCT

- **PMBCL**
  - 3L pembrolizumab

- **Locally Adv. or Met. Urothelial Cancer**
  - 1L/2L nivolumab after platinum chemotherapy
  - 1L/2L pembrolizumab
  - 1L/2L atezolizumab after platinum chemotherapy
  - 1L/2L avelumab after platinum chemotherapy
  - 1L/2L durvalumab after platinum chemotherapy

Updated on 11-Dec-2018 - citations on last page - medi-paper.com
2018 Nobel Prize in Physiology or Medicine for the discovery of CTLA-4 and PD-1 immune checkpoints

James P. Allison
Tasuku Honjo
Is there a predictive biomarker of response?
Immune infiltrate and expression of pro-inflammatory markers in “HOT” tumors

Tumors with higher CD8+ infiltrate and expression of PD-1 and PD-L1 respond better to anti-PD-1
Expression of PD-L1 is induced through CTL mediated pro-inflammatory cytokine secretion as a way for the tumor to adapt to the presence of the antitumor immune response.
Mutations influence the immunogenicity of cancer cells by generating **neoantigens:**

peptides derived mutated gene products that bind to HLA and elicit T-cell responses
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Mutations influence the immunogenicity of cancer cells by generating **neoantigens**: peptides derived mutated gene products that bind to HLA and elicit T-cell responses.
Few biomarkers are being used to select patients for treatment with anti-PD-1/PD-L1 therapies

Inflamed

Pre-existing Immunity

- CD8 T infiltrate
- IFNg signature
- TILs
- PD-L1
- Specific Microbiome
- PD-1
- TCRB frequency/diversity
- Mutational load
- HLA diversity

Can respond to immune checkpoint inhibitors

Excluded Infiltrate

Non-inflamed

Immune Desert

Need to be converted to an inflamed state prior to treating with ICB

Pembrolizumab in 1st and 2nd line NSCLC with PD-L1 staining

Anti-PD-1/PD-L1 for metastatic, refractory, MSI-H or dMMR solid tumors or CCR detected by IHC or PCR test

Immunotherapeutic strategies differ according to the existence of an inflammatory response

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3) Combination of both, and combination with other cancer therapies
Inducing an immune response against cancer

J. Weiden et al. Nature Reviews Immunology, 2017
Active immunization with vaccines

Preventive vaccines
Vaccines to Human Papilloma Virus and to Hepatitis B virus have reduced very significantly the incidence of Cervical Carcinoma and of Hepatocarcinoma

Therapeutic vaccines
Intensive investigation of vaccines targeting neoantigens
Will likely need combination with immune checkpoint inhibitors

http://2018.igem.org/Team:Tongji_China/Neoantigen
Adoptive transfer of T cells targeting cancer neoantigens
August 2017: US FDA Approves anti-CD19 CAR T cells for pediatric ALL
Specific considerations for immunotherapy
Pseudoprogression can be oversved occasionally as a result of an acute inflammatory antitumor response. Increase in tumor size—pseudoprogression—is observed before antitumor regression is apparent.
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Treatment with immunotherapy can induce autoimmune toxicities
Take-home message
Summary

1) Tumors can be categorized into inflamed and non-inflamed

2) Immune checkpoint inhibitors can reinvigorate a pre-existing immune response against cancer and have been approved in growing number of indications

3) The identification of biomarkers is complicated by the complexity of the immune response

4) Vaccines and adoptive cell transfer can be used to induce an immune response in tumors that are “COLD” or refractory to immune checkpoint inhibitors

5) Rational combination of immune checkpoint with other therapies will contribute to unleash the full potential of immunotherapy
Recognition of tumor cells by T cells is determined by the interaction between TCR-pMHC
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pMHC complex:
HLA alpha heavy chain, B2 microglobulin, peptide

Highly polymorphic in the peptide binding sites

Each HLA allele binds to specific peptides based on its affinity for specific residues (anchor peptides)

Each patient encodes for 3-6 different HLA-I alleles

HLA-I alleles together with specific tumor transcriptome determines the personalized immunopeptidome presented to CD8+ T cells
The majority of peptides presented on HLA-I derive from intracellular proteins
Types of tumor-rejection antigens

P. G. Coulie et al, Nat Rev in Cancer 2014
Tumors accumulate genetic alterations and some will give rise to non-self peptides that can be presented by HLA and be recognized as foreign antigens.

T cell responses targeting neoantigens are not subject to central tolerance and should be safe.

Neoantigen-specific lymphocytes can be detected in 82% of cancer patients screened, regardless of their histology or mutation burden (Parkhurst M, et al. Cancer Discovery 2019)

-Gastrointestinal Cancer (Tran E, et al. 2015)
-Ovarian Cancer (Deniger DC, et al. 2018)
-Cervical Cancer (Stevanović S, et al. 2017)

Correlative data suggest neoantigen-specific lymphocytes play an important role in the effectiveness of cancer immunotherapies.

**Why are neoantigens derived from tumor-specific somatic mutations optimal targets for cancer immunotherapy?**
Targeting of neoantigens using personalized T-cell therapies may extend the antitumor efficacy of TILs to other tumors

Adoptive transfer of a population of mutation-specific CD4+ T cells in a patient with cholangiocarcinoma induced tumor regression

E. Tran et al, Science 2014
Adoptive transfer of a population of mutation-specific CD4+ T cells in a patient with cholangiocarcinoma induced tumor regression.

Targeting of neoantigens using personalized T-cell therapies may extend the antitumor efficacy of TILs to other tumors.

E. Tran et al, Science 2014
The specificity of TILs expanded from independent tumor fragments is heterogeneous and after all the screenings vs. neoantigens, the specificity of many TILs is still unknown.

Efforts to interrogate the immunogenicity of cryptic antigens are ongoing.

Improved identification of personalized antigens targeted by TILs will be critical for the development of more efficacious vaccines and T-cell therapies.
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### Table 1. Anti-PD-1/PD-L1 Immunotherapies, Indications and diagnostic assay requirement

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Drug(s)</th>
<th>Drug target(s)</th>
<th>Indications in EU</th>
<th>Indications in EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Unresectable or metastatic</td>
<td>Unresectable or metastatic or low tumour PD-1 expression</td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Unresectable or metastatic</td>
<td>Unresectable or metastatic or low tumour PD-1 expression</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab + ipilimumab</td>
<td>PD-1, PD-L1</td>
<td>Unresectable or metastatic</td>
<td>Unresectable or metastatic or low tumour PD-1 expression</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Metastatic disease with progression or after platinum-based chemotherapy or after FDA-approved treatment if EGFR+ or ALK+</td>
<td>Locally advanced or metastatic disease after prior chemotherapy in adults</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>1st line monotherapy if EGFR+/ALK+</td>
<td>If progression after chemotherapy or after targeted treatment if EGFR+ or ALK+</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>2nd line monotherapy if progression and after platinum-based chemotherapy or after FDA-approved treatment if EGFR+ or ALK+</td>
<td>If progression or after platinum-based chemotherapy or after targeted treatment if EGFR+ or ALK+</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Advanced disease after prior anti-angiogenic therapy</td>
<td>Advanced disease after prior therapy</td>
</tr>
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<td>Classical Hodgkin lymphoma</td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Relapsed or progressed disease after auto-HCT and BV, or 3 or more lines of therapy including auto-HCT</td>
<td>Relapsed or refractory disease after auto-HCT and treatment with BV</td>
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<td>Bladder cancer</td>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Locally advanced or metastatic urothelial carcinoma who have disease progression or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjacent treatment with platinum-containing chemotherapy</td>
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<td>Gastrointestinal cancer</td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Recurrent locally advanced or metastatic gastrointestinal or gastrointestinal stromal tumours with disease progression or after two or more prior lines of therapy including fluoropyrimidines and platinum-containing chemotherapy and, if appropriate, HER2/neu targeted therapy</td>
<td>No</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Hepatocellular carcinoma previously treated with sorafenib</td>
<td>N/A</td>
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<td>NSCLC or dMMR- deficient solid tumours</td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Unresectable or metastatic solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with fluoropyrimidines, oxaliplatin, and irinotecan</td>
<td>No</td>
</tr>
<tr>
<td>NSCLC or dMMR- deficient colorectal cancers</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan</td>
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*CD8 T IFNγ signature TILs PD-L1 Specific Microbiome PD-1 TCRβ frequency Mutational load*