Basic Principles of Tumor Immunotherapy

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Disclosures

Research grants:

- Bristol-Myers-Squibb; Merck; Celldex Therapeutics; ArmoBiosciences; Aztra-Zeneca/MedImmune

Consultant/advisor:

- Bristol-Myers-Squibb; Amgen; Alexion; Genentech, Celldex

I will not be discussing non-FDA approved uses of drugs
Cancer Immunotherapy: Timeline

1890s
1st cancer immunotherapy (Coley)

1976
1st Study of BCG in bladder cancer

1985
1st study of adoptive T-cell transfer in cancer

1990
CTLA-4 discovered (Allison)

1998
IL-2 approved for melanoma

2011
1st Checkpoint inhibitor approved (ipilimumab for melanoma)

1973
Dendritic cell discovered (Steinman)

1978
Tumor specific mAbs discovered

1996
1st cytokine approved (IFN-alpha for hairy cell leukemia)

2010
1st vaccine approved (sipuleucel-T for prostate Ca)
Timeline of Cancer Immunotherapy

- 2014: Pembrolizumab and nivolumab (anti-PD-1 antibody) FDA approved for advanced melanoma
- 2014: “Breakthrough” designation to GVAX (GM-CSF based vaccine) for patients with metastatic pancreatic cancer
- 2014: “Breakthrough” designation to Nivolumab (anti-PD-1 antibody) for Hodgkin’s Lymphoma
- 2014: “Breakthrough” designation to MPDL-3280A (anti-PD-L1 antibody) for bladder cancer
- 2015 Nivolumab approved in renal cell cancer
- 2015 Nivolumab and Pembrolizumab approved in NSCLC
- 2016: Ipilimumab plus Nivolumab approved in Melanoma
Cancer Immunotherapy

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark.

History’s path is uncharted when it’s not yet past but present, when we are still standing in the middle of it. That’s what made Science’s selection of this year’s Breakthrough of the Year such a topic of internal debate, even anxiety. In celebrating cancer immunotherapy—harnessing the immune system to battle tumors—did we risk hyping an approach whose ultimate impact remains unknown? Were we irresponsible to label as a breakthrough a strategy that has touched a tiny fraction of cancer patients and helped only some of them? What do we mean when we call something a breakthrough, anyway?

Ultimately, we concluded, cancer immunotherapy passes the test. It does so because this year, clinical trials have cemented its potential in patients and swayed even the skeptics. The field hums with stories of lives extended: the woman with a grapefruit-size tumor in her lung from melanoma, alive and healthy 13 years later; the 6-year-old near death from leukemia, now in third grade and in remission; the man with metastatic kidney cancer whose disease continued fading away even after treatment stopped a grounded-in-reality bunch, say a corner has been turned and we won’t be going back.

With much pressure these days to transform biological insights into lifesaving drugs, there’s a lesson to be learned from immunotherapy’s successes: They emerged from a careful decoding of basic biology that spanned many years. The early steps were taken by cancer immunologist James Allison, now at the University of Texas MD Anderson Cancer Center in Houston. In the late 1980s, French researchers who weren’t thinking about cancer at all identified a new protein receptor on the surface of T cells, called cytotoxic T-lymphocyte antigen 4, or CTLA-4. Allison found that CTLA-4 puts the brakes on T cells, preventing them from launching full-out immune attacks. He wondered whether blocking the blocker—the CTLA-4 molecule—would set the immune system free to destroy cancer.

Allison’s rationale was untested.

Science’s Breakthrough of the Year
Features of Cancer Immunotherapy

- **Adaptable**: Ability to adapt the response beyond the initially targeted antigen.
- **Specific**: Ability to recognize and target only tumor cells.
- **Long Lasting**: Capacity for memory can result in durability of tumor responses.
- **Universal**: Potentially applicable to all cancers.
## Cancer Immunotherapies: Different Approaches

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Not all antibodies are immunotherapy

Monoclonal antibodies for cancer. ADEPT, antibody directed enzyme prodrug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity; MAb, monoclonal antibody; scFv, single-chain Fv fragment

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What is a cancer vaccine?

“A preparation of a tumor antigen that upon administration stimulates antibody production or anti-tumor cellular immunity”
Routes of vaccine administration and migration of immune cells

- Vaccine
  - DNA
  - RNA
  - SLP
  - Recombinant virus

- Intradermal
- Subcutaneous
- Intramuscular

- Lymph node
  - Afferent lymph
  - Efferent lymph
  - Via thoracic duct
  - Bloodstream

- T cell activation

- Antigen-loaded APC

- Tumor microenvironment
  - IDO
  - MDSC
  - Treg
  - Cytokines and chemokines

Melief, JCI, 2015
1. ANTIGEN

2. ADJUVANT

3. DELIVERY

4. BLOCK SUPPRESSION

VACCINATION SITE

TUMOR SITE

TUMOR

CTL

CTL

CTL

CTL

vaccine
Choice of Immunogen

• Choice of Antigen
  – Differentiation antigen (MART-1, gp100)
  – Cancer testis antigen (NY-ESO-1, MAGE)
  – Overexpressed in tumors (KIT, HER2)
  – Mutated antigen (Neoantigen)

• Choice of Format:
  – Protein (broader antigenic selection)
  – Peptide (more stable in vivo, lower cost, HLA restriction).
    Long versus short
  – Viral vector
  – DNA, RNA
  – Whole tumor cells
  – Dendritic cells pulsed with protein or peptide
Toll Like Receptor Agonists

Danger is represented by:
- Bacteria
- Virus
- Cell death

Fungi

These have molecular features that distinguish them from our own cells:
- Endotoxin
- DS RNA
- Lipopeptides
- CpG DNA
- SS RNA
- Flagellin

Our immune systems have evolved to recognize them:
- TLR4
- TLR3
- TLR7/8
- TLR5
- TLR9
- TLR1,2,6

Sipuleucel-T: Vaccination With Fresh (Functional) APCs: Generate ex vivo and Reinfuse

Phase III Trial of Sipuleucel-T Immunotherapy in mCRPC (IMPACT): OS

Median OS benefit: 4.1 months
HR : 0.78 (95% CI: 0.61-0.98; P = .03)

## Cancer Vaccines in Late Stage Development / approved

<table>
<thead>
<tr>
<th>Name</th>
<th>Tumor</th>
<th>Antigen</th>
<th>Antigen Delivery</th>
<th>Immune Response</th>
<th>Clinical Activity</th>
</tr>
</thead>
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<tr>
<td>Siplileucel-T</td>
<td>Prostate Ca</td>
<td>PSA</td>
<td>Cell based - Monocytes</td>
<td>Yes</td>
<td>Yes – FDA approved</td>
</tr>
<tr>
<td>GVAX + CRS-207</td>
<td>Pancreatic Cancer</td>
<td>Mesothelin</td>
<td>Live attenuated listeria, prime - boost</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>IMA 901</td>
<td>Renal Cell Carcinoma</td>
<td>Tumor associated peptides (TUMAP)</td>
<td>Peptides with GM-CSF</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Synthetic Long E6/7 Peptide vaccine HPV-01</td>
<td>HPV-induced malignancies (e.g vulvar neoplasia)</td>
<td>HPV E6 and E7</td>
<td>Mixture of 13 long peptides (25-35 AA)</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Talimogene Laherparepvec (TVEC)</td>
<td>Melanoma</td>
<td>“Whole tumor” (in situ vaccination with oncolytic virus)</td>
<td>Oncolytic virus (modified herpes virus encoding GM-CSF)</td>
<td>Yes</td>
<td>Yes - FDA approved</td>
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<td>Rindopepimut</td>
<td>Glioblastoma</td>
<td>Mutated EGFRvIII</td>
<td>14-mer peptide, KLH</td>
<td>Yes</td>
<td>Yes</td>
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<td>Fowlpox-PSA-TRICOM</td>
<td>Prostate Ca</td>
<td>PSA</td>
<td>Fowlpox expressing antigen + TRICOM (B7.1, ICAM-1, LFA-3)</td>
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Immune Modulatory Receptors

Activating
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Activating antibodies

T-cell stimulation

Blocking antibodies

Immune-checkpoint inhibition

Anti-PD1

Anti-CTLA-4

Tumour cell

Dendritic cell

T-cell receptor

MHC

PD-L1

PD1

PD-L2

CD28

B7

CTLA-4

Adapted from Sznol M, et al. Presented at ASCO 2013: oral presentation CRA9006
A. Lympathic tissue

IL-2/IFN-γ/CTL function ↑

B. Peripheral Tissue/Tumor

IL-2/IFN-γ/CTL function ↑

© 2013 American Association for Cancer Research

CCR Focus

Ott, Hodi, Robert Clin Cancer Res; 19(19) October 1, 2013
Pooled Overall Survival Analysis of 4846 Melanoma Patients Treated with Ipilimumab

Median OS (95% CI): 9.5 (9.0–10.0)

3-year OS Rate (95% CI): 21% (20–22%)
PD-1/PD-L1 Pathway: Biology

Antigen Presenting Cell

PD-L1
B7-1
MHC 1
PD-L2
PD-L1

B7-1
CD28
TCR
PD-1

T cell

Activation
PD-1/PD-L1 Pathway: Biology

Antigen Presenting Cell

PD-L1, B7-1, MHC 1

T cell

B7-1, CD28, TCR, PD-1

Activation
PD-1/PD-L1 Pathway: Biology

Antigen Presenting Cell

PD-L1
B7-1
MHC 1
PD-L2

T cell

Activation

PD-1
CD28
TCR
B7-1
PD-L1 plays an important role in dampening the anti-tumor immune response

PD-L1 expression in the tumor microenvironment can inhibit anti-tumor T cell activity:

1. PD-L1 expression by tumor infiltrating **immune cells**
2. PD-L1 expression by **cancer cells**
Anti-Tumor Activity of Anti-PD1 antibodies

- Nivolumab
- Pembrolizumab

Hamid et al, NEJM 2013
Topalian et al, NEJM 2012
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Adoptive Cell Therapy (ACT) with Antigen Specific T-cells

- Single Cell Suspension Incubated with IL-2
- T Cells Proliferate
- Cancer Cells Die

Courtesy of Patrick Hwu MD, PhD – MD Anderson Cancer Center
Derivation of TCRs and CARs for the genetic modification of T cells

Kershaw NATURE REVIEWS | CANCER 2013
Chimeric Antigen Receptor (CAR) T cells
Targeting CD19 in B Cell Cancers

Successive Generations of CARs

First generation
- CD8
- CD3ζ

Second generation
- CD28
- TRAF1
- ZAP70
- ASK1
- MKK
- MAPK
- RAS
- CAN
- PKCα
- NFAT
- ATF2

Third generation
- Extracellular antibody domain
- PI3
- K Parallel B2
- CD137

Signal intermediates
- VAV
- LAT
- SLP76
- PLCγ
- IκB
- mTOR
- DAG

Transcription factors
- ATF2
- NFAT
- NF-κB

Proliferation, survival and cytokine production
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Ipilimumab + sargramostim in Advanced Melanoma

Hodi, JAMA, 2014
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T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

Local Effect:
Virally-Induced Tumor Cell Lysis

Systemic Effect:
Tumor-Specific Immune Response

Kaufman et al. ASCO 2014
T-VEC Responses in Injected And Uninjected Lesions

Cycle 1

Cycle 13

Kaufman et al. ASCO 2014, J Clin Oncol 31, 2013 (suppl; abstr LBA9008)
**T-Vec + Ipi in Unresected Stage IIIB-IV Melanoma: Max Change in Tumor Burden**

**Investigator-Assessed Responses, n (%)**

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<th>Response</th>
<th>n (%)</th>
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<tr>
<td>Overall response</td>
<td>10 (56)</td>
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<tr>
<td>(95% CI: 31-79)</td>
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<tr>
<td>Complete response</td>
<td>6 (33)</td>
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<tr>
<td>Partial response</td>
<td>4 (22)</td>
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<tr>
<td>Stable disease</td>
<td>3 (17)</td>
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<td>Progressive disease</td>
<td>5 (28)</td>
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*Only patients who received both T-Vec and ipilimumab. CR, CRu, and PD included.
† One patient with PD not shown in the plot because tumor burden could not be accurately calculated (missing post-baseline data)
‡ Percentage change from baseline: 538
§ Percentage change from baseline: 265

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Puzanov I, et al. ASCO 2014
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Reversal of Immunosuppression

Sheridan Nature Biotechnol. 2015
Potential immunotherapy combinations

- Future is likely in combination
  - Multiple checkpoints
    - (PD-1 + CTLA-4, LAG3 etc.)
  - Small Molecules Inhibitors
    - (VEGFi or iNOS modulation + PD-L1)
  - Radiation
  - Chemotherapy
    - (Cyclophosphamide to deplete T_{reg} prior to checkpoint blockade)
  - Costimulatory receptors (OX40, CD137, GITR, CD40)
  - Novel Vaccines
  - Adoptive Cell Therapy
Questions?