Overview of Immune Therapeutic Strategies

Marcus Butler, MD
Personalized Cancer Medicine
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Disclosures

Advisory boards for

Bristol-Myers Squibb

Merck & Co.

Novartis Pharmaceuticals

Patent (co-inventor)

artificial antigen presenting cell
Immune Therapy Principles

- Tumors evolve in the context of the immune system
- Specificity
- Aims to manipulate non-malignant processes
- Responses may be delayed
- Holds the promise of long-term benefit and immunologic memory
Pathways of Tumor Immunity

Mellman, Coukos, Dranoff. Nature 2011;480:480-489
Lymphocytic Inflammation in Tumors

Medullary breast carcinoma

Malignant melanoma of the skin

Tumor cells

Lymphocytes
Ovarian Cancer TIL


186 patients
TIL and Ovarian Cancer


Immunotherapy Balance

• Tumor Promoting
  – Suppressive macrophage
  – Lymphocytes (T reg)
  – Cytokines (TGF-beta, IL-10, IDO)

• Anti-Cancer
  – Dendritic cells
  – Lymphocytes (CD8 T cells)
  – Cytokines (IL2, IFN-\(\gamma\))
Specificity
Tumor Associated Antigens

Tissue associated
• MART1, gp100, PSA, CEA, Mesothelin, CA125, folate receptor-α, HER2/neu

Abnormally expressed
• p53, MUC1

Paraneoplastic
• cerebellar degeneration-related protein cdr2

Cancer-testis
• NY-ESO-1, MAGE family members

Universal
• Survivin, hTERT
Tumor Derived Neoantigens

Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs.

MS Lawrence et al. *Nature** 000, 1-5 (2013) doi:10.1038/nature12213
Pathways of Antigen Processing

Antigen uptake -> Antigen processing -> MHC biosynthesis -> Peptide-MHC association

Class I MHC pathway:
- Cytosolic protein
- Proteasome
- Peptides in cytosol
- TAP
- MHC
- CD8+ T cell

Class II MHC pathway:
- Endocytosis of extracellular protein
- Invariant chain (Ii)
- Class II MHC
- CD4+ T cell
T cell Recognition of Peptide-MHC

- T cell contact residue of peptide
- Polymorphic residue of MHC
- Anchor residue of peptide
- "Pocket" of MHC
- Peptide
- MHC
- T cell receptor
Goal of Immune Therapy: Manipulation of Host Response
Therapeutic Strategies

• Induction of new responses
  • Vaccination
  • Oncolytic virus/epitope spreading
  • Adoptive therapy
• Augmentation of pre-existing responses
  • Checkpoint blockade
  • TIL therapy
  • Immune modulation, cytokines
Vaccination

Whole tumor cell vaccines
Peptide vaccines
Dendritic cell vaccines
Targeting with oncolytic virus

Mellman, Coukos, Dranoff. Nature 2011;480:480-489
Clinical Breakthroughs: Immune Checkpoints, CTLA-4 & PD1/PDL1

Ipilimumab (Anti-CTLA-4)

Stage IV or Unresectable Stage III Melanoma
Pathways of Tumor Immunity

Mellman, Coukos, Dranoff. Nature 2011;480:480-489
Adoptive Cell Therapy

Mellman, Coukos, Dranoff. Nature 2011;480:480-489
Adoptive Cell Therapy (ACT) with TIL

NCI Experience

• Highly selected TIL
• Rapid expansion protocol

• Lymphodepletion
  - Increase IL2, IL7, IL15
  - Reduce regulatory T cells

• High dose IL-2

Adoptive Immunotherapy with TIL
## 20+ Years of ACT at the NIH
(All receive High Dose IL-2)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cells</th>
<th>Response Rate</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lymphodepletion (1980’s)</td>
<td>LAK</td>
<td>Melanoma: 22% (6/27)</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All enrolled: 28% (24/85)</td>
<td></td>
</tr>
<tr>
<td>No lymphodepletion (1988-1992)</td>
<td>TIL</td>
<td>34% (29/86)</td>
<td>++</td>
</tr>
<tr>
<td>• Cytoxan: 60 mg/kg/d x 2</td>
<td></td>
<td>49% (21/43)</td>
<td>++</td>
</tr>
<tr>
<td>• Fludarabine: 25 mg/m²/d x 5</td>
<td></td>
<td>2 Gy: 52% (13/25)</td>
<td>++</td>
</tr>
<tr>
<td>• Fludarabine: 25 mg/m²/d x 5</td>
<td></td>
<td>12 Gy: 72% (18/25)</td>
<td>++</td>
</tr>
<tr>
<td>• TBI: 2-12 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Expansion and Characterization of Human Melanoma Tumor-Infiltrating Lymphocytes (TILs)

Linh T. Nguyen¹, Pei Hua Yen¹, Jessica Nie¹, Nicole Liadis¹, Danny Ghazarian², Ayman Al-Habeeb², Alexandra Easson³, Wey Leong³, Joan Lipa⁴, David McCready³, Michael Reedijk³, David Hogg⁴, Anthony M. Joshua⁴, Ian Quirt⁴, Hans Messner⁴, Patricia Shaw², Michael Crump⁴, Eran Sharon³,⁴, Pamela S. Ohashi¹,⁵

Adapted from Restifo, Dudley and Rosenberg, Nature Reviews Immunology 2012

1) Tumor sample

2) Initial expansion of TILs (+ interleukin-2)

3) Rapid expansion of TILs (OKT3, feeder cells, IL-2 (LOWER DOSE))

4) Cyclophosphamide, fludarabine -> TILs -> LOWER DOSE IL-2 therapy
Pretreatment

PR (78% decrease in hilar nodule @ 2 months)

Non-measurable non-index lesions @ 2 months:
- Pulmonary nodules - stable
- Right hilar nodes – absent
- Subcutaneous lesion - absent

Pretreatment

2 Months
Immune Therapy: Delayed and Repeated Responses
Delayed responses to ipilimumab; paradoxical interim increases

Harmankaya K, et al: Presented at EADO 7th World Congress of Melanoma 2009, Vienna, Austria
Metastatic cancer lesions are made up mainly of cancer cells and stromal cells, with a very limited immune and inflammatory infiltrate by lymphocytes and macrophages.
Ovarian Cancer Response Associated with Anti-NY-ESO-1 Immunity

OV65 (82 yo): Autologous Ovarian GVAX Followed by Ipilimumab

Maintenance on ipilimumab: 8 years
Long-term Disease Control and Memory
Ipilimumab Can Produce Durable Benefit

Stage IV or Unresectable Stage III Melanoma
Pooled OS Analysis Including EAP Data: 4846 Patients

Median OS, months (95% CI): 9.5 (9.0–10.0)

3-year OS rate, % (95% CI): 21 (20–22)

Schadendorf, Hodi FS, Robert et al. ESMO 2013
Adoptive Transfer of T Cells

Kandalaft L E et al. JCO 2011;29:925-933

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Artificial APC for the Generation of CTL for Adoptive Immunotherapy

- K562 erythroleukemia cell line
  - Engineered to express CD80, CD83, HLA-A2
  - Able to present peptide
- CTL generated from purified CD8
  - Low dose IL-2 and IL-15
  - No feeder cells
A Pilot Study of the Adoptive Transfer of MART1/Melan-A CTL for Metastatic Melanoma

- Target: MART1/Melan-A, a melanoma-associated antigen
- No lymphodepletion, IL-2, anti-CTLA-4, or vaccine
- 35 day cycles with 2 CTL infusions
Anti-Tumor Activity of Infused MART1 CTL

Patient 3: mixed response

Patient 5: complete response 54+ months
CTL Induce Anti-tumor Immune Response (Patient 5 Tumor Biopsy)
Long-term Persistence of Infused MART1 T Cells

MART1 pentamer+ T cells (% CD8)

Pre-infusion  Day 14  Day 49

Patient 7

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/sex</th>
<th>Stage</th>
<th>Notable Comorbid Conditions</th>
<th>Best Response Overall</th>
<th>Time to next therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74M</td>
<td>M1c:</td>
<td>liver, adrenal, spleen, lung, skin</td>
<td>Died on day 51</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>high blood pressure, history of bowel obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>69M</td>
<td>M1b:</td>
<td>lung, skin</td>
<td>Progressive disease</td>
<td>Day 103</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>deep vein thrombosis, on warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>49F</td>
<td>M1c:</td>
<td>lung, adrenal</td>
<td>Mixed response</td>
<td>Day 146</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>68M</td>
<td>M1c:</td>
<td>muscle, lung, mediastinum, cardiac</td>
<td>Stable</td>
<td>Day 140</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>asbestosis, cardiac metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>66M</td>
<td>M1a:</td>
<td>multiple lymph nodes</td>
<td>Complete Response</td>
<td>54+ months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>diabetes, high blood pressure, coronary artery disease (MI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>55M</td>
<td>M1b:</td>
<td>lung</td>
<td>Stable</td>
<td>Day 287</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>high blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>70F</td>
<td>M1b:</td>
<td>lung, skin</td>
<td>Progressive disease</td>
<td>Day 335</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>diabetes, coronary artery disease (MI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>80M</td>
<td>M1b:</td>
<td>lung, mediastinal nodes</td>
<td>Stable</td>
<td>Day 372</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>coronary artery disease (MI), s/p CABG, pacemaker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>64M</td>
<td>M1b:</td>
<td>lung, mediastinal nodes</td>
<td>Progressive disease</td>
<td>Day 146</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High blood pressure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CTLA-4 Blockade: MART1 T Cells with Memory Phenotype Expand (Patient 2)

<table>
<thead>
<tr>
<th>Pre-Infusion</th>
<th>Post-Infusion</th>
<th>Anti-CTLA-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>day 74</td>
<td>day 167</td>
</tr>
<tr>
<td>CD8 (10^0 to 10^3)</td>
<td>0.04%</td>
<td>0.09%</td>
</tr>
<tr>
<td>CD45RA (10^0 to 10^3)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>CD62L (10^0 to 10^3)</td>
<td>84</td>
<td>38</td>
</tr>
</tbody>
</table>

α-CTLA-4

Images showing cell counts and phenotypes before and after infusion with anti-CTLA-4.
## Patient Response to Subsequent Ipilimumab

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/sex</th>
<th>Time to further therapy</th>
<th>CTLA-4 Blockade</th>
<th>Outcome</th>
<th>Duration of response (months)</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>69M</td>
<td>Day 103</td>
<td>Ipilimumab (10 mg/kg)</td>
<td>Partial response</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>49F</td>
<td>Day 146</td>
<td>Ipilimumab (10 mg/kg)</td>
<td>Partial response</td>
<td>60+</td>
<td>60+</td>
</tr>
<tr>
<td>7</td>
<td>70F</td>
<td>Day 335</td>
<td>Ipilimumab (3 mg/kg)</td>
<td>Stable</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>80M</td>
<td>Day 372</td>
<td>Ipilimumab (3 mg/kg)</td>
<td>Stable</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>64M</td>
<td>Day 146</td>
<td>Ipilimumab (10 mg/kg) + bevacizumab</td>
<td>Partial response</td>
<td>42+</td>
<td>42+</td>
</tr>
</tbody>
</table>
Conclusion

• Tumors develop in immune context
• Goal of immunotherapy
  • Modulate individual immune reactivity
  • Induction of tumor-specific response
    • Vaccination (direct or indirect)
    • Adoptive transfer
• Induce long-term responses, immunologic memory, and cures
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