Tumor Immunotherapy

Sarah Adams, MD
August 4, 2014
Objectives

- Development of immune therapy for cancer
- T cell therapies
- Dendritic cell therapies
- Checkpoint blockade
- Immunomodulation by chemotherapeutics
- Future directions
William B. Coley, 1891
Coley’s vaccine
Coley’s vaccine

1999 study comparing historic cases treated with Coley’s fluid with modern SEER data
Immune regulation of cancer
Fig. 1 A general classification of tumor immunotherapy approaches. Various tumor immunotherapy strategies can be grouped into tumor antigen-specific and non-specific. Specific immunotherapy (SIT) targets one or several particular tumor-associated antigens ...

Marius M. Strioga, Adas Darinskas, Vita Pasukoniene, Agata Mlynska, Valerijus Ostapenko, Virgil Schijns

Xenogeneic therapeutic cancer vaccines as breakers of immune tolerance for clinical application: To use or not to use? Vaccine, Volume 32, Issue 32, 2014, 4015 - 4024
A model for the induction of a cytotoxic T cell response

APC: Antigen-presenting cell
TLR: Toll-like receptor
A model for the induction of a cytotoxic T cell response
A model for the induction of a cytotoxic T cell response
T CELL THERAPY
Tumor-infiltrating T cells are associated with improved survival

Survival of patients with ovarian cancer: Tumor Infiltrating Lymphocytes (TIL)

TIL represent a robust prognostic biomarker

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio, Random, 95% CI</th>
<th>Hazard Ratio, Random, 95% CI</th>
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<tbody>
<tr>
<td>Zhang(2003)</td>
<td>0.61</td>
<td>0.18</td>
<td>12.5%</td>
<td>1.84 [1.29, 2.62]</td>
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<tr>
<td>Sato(2005)</td>
<td>1.11</td>
<td>0.307</td>
<td>8.8%</td>
<td>3.03 [1.66, 5.54]</td>
<td></td>
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<td>Hamanishi(2007)</td>
<td>2.031</td>
<td>0.518</td>
<td>4.8%</td>
<td>7.62 [2.76, 21.04]</td>
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<tr>
<td>Callahan(2008)</td>
<td>0.548</td>
<td>0.222</td>
<td>11.2%</td>
<td>1.73 [1.12, 2.67]</td>
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<tr>
<td>Han(2008)</td>
<td>0.563</td>
<td>0.258</td>
<td>10.1%</td>
<td>1.76 [1.06, 2.91]</td>
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<td>Tomsova(2008)</td>
<td>1.308</td>
<td>0.296</td>
<td>9.1%</td>
<td>3.70 [2.07, 6.61]</td>
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<tr>
<td>Adams(2009)</td>
<td>0.694</td>
<td>0.315</td>
<td>8.6%</td>
<td>2.00 [1.08, 3.71]</td>
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<tr>
<td>Clarke(2009)</td>
<td>0.282</td>
<td>0.106</td>
<td>14.5%</td>
<td>1.33 [1.08, 1.63]</td>
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<tr>
<td>Leffers(2009)</td>
<td>1.02</td>
<td>0.251</td>
<td>10.3%</td>
<td>2.77 [1.70, 4.54]</td>
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<tr>
<td>Stumpf(2009)</td>
<td>0.895</td>
<td>0.258</td>
<td>10.1%</td>
<td>2.45 [1.48, 4.06]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 2.24 [1.71, 2.92]

Heterogeneity: Tau² = 0.12; Chi² = 29.38, df = 9 (P = 0.0006); I² = 69%
Test for overall effect: Z = 5.92 (P < 0.00001)

The goal of immune therapy is to amplify a cytotoxic T cell response against tumor antigens.
The diagram illustrates the process of immune cell therapy in the context of cancer treatment. Here is a description of the steps depicted:

1. **Fragmentation of Tumour Mass**: The tumour mass is fragmented, allowing for the exposure of new antigens that the immune system can recognize.

2. **Activation and Selection of T Cells**: T cells are activated and selected for their ability to recognize and respond to these new antigens.

3. **Expansion of Tumour-Specific T Cell Populations**: The selected T cells are then expanded in culture to generate a sufficient number of cells.

4. **Infusion of Tumour-Specific T Cells into Patient**: The expanded T cells are infused into the patient, where they can recognize and attack the tumour cells.

5. **Chemotherapy and Irradiation**: These treatments are applied to reduce the size of the tumour and enhance the effectiveness of the immune response.

This process aims to harness the patient's immune system to combat cancer, using various therapeutic strategies to enhance the immune response and target the tumour cells.
Trial 3
Extract and Expand TILs

Debulking surgery performed

Tumor infiltrating lymphocytes administered into the patient

Lymphocytes isolated

Lymphocytes expanded
T cell recognition of tumors improves survival

Cancers can escape immune surveillance

- Secretion of suppressive cytokines
- Induction of suppressive T cells
- Promotion of immunologic tolerance
- Down-regulation of antigenic epitopes, MHC molecules

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Tumors promote the development of suppressive regulatory T cells
Therapeutic strategies to reduce regulatory T cells in the tumor environment
Restriction of suppressive signaling is expected to promote tumor clearance by effector T cells.
Genetically altered T cell receptors
Chimeric antigen receptor (CAR) T cells
CELLULAR ATTACK

Adoptive cell transfer (ACT) attacks cancer using either tumour-infiltrating lymphocytes (TILs) or genetically engineered T cells. Engineered cells are given either a new T-cell receptor (TCR) or an antibody-like molecule called a chimaeric antigen receptor (CAR); both activate the T cell when they encounter a particular cancer antigen.

1. **Harvest T cells from biopsy or blood.**
   - **TIL** or **TCR** or **CAR**
2. **Genetically engineer cells.**
3. **Isolate and expand tumour-infiltrating lymphocytes (TILs).**
4. **Immune depletion with chemotherapy or radiation allows introduced T cells to take hold and multiply.**
5. **Add T cell receptor (TCR) for a cancer antigen.**
6. **Add a chimaeric antigen receptor (CAR), which recognizes a specific cancer antigen.**
7. **T-cell activation**
8. **Infuse cells back into patient, where they attack the tumour.**
Strategies for generating genetically engineered T cells
Considerations in T cell therapy development

![Diagram of T cell development stages.

- **Naive CD8+ T cell**: CD45RA+ CD95- IL-2Rβ- CCR7+ CD62L+.
- **‘Stem cell memory’ T cell**: CD45RA+ CD95+ IL-2Rβ+ CCR7+ CD62L-.
- **Central memory T cell**: CD45RO+ CD95+ IL-2Rβ+ CCR7+ CD62L+.
- **Effector memory T cell**: CD45RO+ CD95+ IL-2Rβ+ CCR7- CD62L-.

**Graph showing the relationship between APC signal strength and T cell function:**

- **Strength of APC signal**:
  - High signal leads to strong proliferation and effector function.

- **Proliferative capacity**:
  - Increases with stronger APC signal.

- **Functional differentiation**:
  - Increases with stronger APC signal.

- **Antitumour efficacy**:
  - Low signal leads to low efficacy.

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Nature Reviews | Immunology
F5 study outline.

Postinfusion peripheral blood levels of MART-1 TCR transgenic cells at various time points in patients receiving cryopreserved transgenic cells.

Pre- and posttreatment day 30 PET scans indicating initial antitumor activity.

Pre- and posttreatment day 35 PET/CT (F5-10) and CT (F5-13) showing evidence of initial antitumor activity.

Postinfusion peripheral blood levels of MART-1 TCR transgenic cells at various time points in patients receiving freshly harvested transgenic cells.


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And yet, the process of choosing an antigen present only in the tumor, and not elsewhere in the body, remains by no means straightforward—a fact borne out by several devastating and at times lethal toxicities seen in recent ACT trials.

In one case, T cells engineered to express a TCR recognizing a peptide from the tumor antigen MAGE-A3 presented by HLA-A*0201 were injected into nine patients bearing a variety of metastatic MAGE-A3+ tumors (J. Immunother. 36, 133–151, 2013). Within only a few days, three patients suffered neurological toxicities and two died; T cells were detected in their brains. In another case (Mol. Ther. 18, 843–851, 2010), after being injected with autologous T cells engineered to express an ERBB2-specific CAR, a patient with metastatic colon cancer suffered respiratory distress within just 15 minutes and died 5 days later; T cells were detected in her lungs.

Thanks to extensive follow-up work by the researchers involved, it is now clear investigators must carefully weigh in every trial whether sufficient information is known about patterns of expression of the intended target antigen, and its homologs, on healthy tissue. For example, MAGE-A3 was an appealing target in part because it is classified as a cancer-testes antigen, widely assumed to be absent from normal healthy adult tissues. However, follow-up work using quantitative PCR, NanoString and deep sequencing analysis revealed that a related cancer testes antigen MAGE-A12 was expressed in normal human brain tissue, potentially leading to the neurological toxicity observed.

In other cases, the issue may not be cross-reactivity with normal tissue antigens, but patient-to-patient variability. In some patients the presence of a low amount of target antigen in healthy tissues is not deleterious so long as a much higher amount of target antigen is expressed on the tumor. For other patients, it is deleterious. As yet, the quantitative limits of this 'window' of T-cell tolerance remain unknown.

Which raises the question: what practical steps can be taken to ameliorate these problems in future trials?
Fig. 2 Types of tumor-associated antigens (TAAs). Classification of protein TAAs, based on their tissue/viral origin and mutational status. Non-protein TAAs, including carbohydrates and (glyco)lipids, which constitute of distinct category of TAAs, are not ...
Clinical considerations

Safety
- Thymidine kinase^{164}
- Inducible caspase 9 (REF. 165)
- CD20 (REF. 167)
- EGFR^{168}

Specificity
- TCR^{141}
- CAR^{140}

Enhance activity
- Increase TCR and CAR affinity^{30,51}
- More signalling domains^{45}
- Alternative hinge regions^{53}
- Decrease TCR mispairing^{32,36,39}
- Ubiquitin-resistant LAT^{50}

Microenvironment
- Upregulate AKT^{91}
- DN-TGFB receptor^{92}
- PD1–CD28 chimaera^{96}
- IL-12 (REF. 98)

T cell survival
- Downregulate FAS and BID^{66,67}
- Upregulate BCL-X\textsubscript{L} and BCL-2 (REFS 68,69)
- Chimeric CTLA4–CD28 (REF. 70)
- Stem cells^{75}

Trafficking
- CXCR2 (REF. 56)
- CCR4 (REF. 57)
- CCR2B^{58}
- VEGFR2 CAR^{59}

Proliferation
- CD137 and CD134 CARs^{76,77}
- Cytokines or their receptors^{78}
- Drug resistance^{79}
- Downregulate CBII and SHP1 (REFS 80,81)
- Dual-specific T cells^{81}
DENDRITIC CELL VACCINES
The goal of immune therapy is to amplify a cytotoxic T cell response against tumor antigens.
A schematic representation of the process of using an irradiated, cytokine-secreting tumour cell vaccine to activate dendritic cells (DCs) with tumour antigens. The activated DCs are then infused into the patient where they present the tumour antigens to CD4+ and CD8+ T cells. This process leads to the phagocytosis of tumour cells by DCs, resulting in their killing in situ.

Key steps:
1. Irradiated, cytokine-secreting tumour cell vaccine
2. Activated DCs with tumour antigens
3. Infuse into patient
4. Tumour-specific CD4+ and CD8+ T cells
5. Tumour cells killed in situ by drug therapy are phagocytosed by DCs
HOW THE CANCER VACCINES WORK

In the immune system, dendritic cells can be used to trigger a response against cancer cells in various ways. In these two examples, antigens are introduced directly into the dendritic cells or generated in situ using tumour RNA. The cells then produce tumour antigens and direct T cells to seek out and destroy the cancer cells.

Tumour RNA is inserted into a dendritic cell

or

Tumour antigen is inserted into a dendritic cell

The dendritic cell matures, produces tumour antigens, and is injected back into patient

The dendritic cell displays tumour antigen and activates T cells

Activated T cells attack the cancer cell
Sipuleucel-T dendritic cell vaccine for the treatment of prostate cancer
Survival outcomes for Sipuleucel-T

A Primary Efficacy

No. at Risk

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<tr>
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<th>Sipuleucel-T</th>
<th>Placebo</th>
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<tr>
<td>Months since Randomization</td>
<td>341  274  129  49  14  1</td>
<td>171  123  55  19  4  1</td>
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Trial 1
Dendritic Cell Vaccine
**A** Increase in immune effector response
- Adoptive T-cell therapy
- Increase of lymphopenia-associated cytokines

**B** Reversal of immunosuppression
- Decrease of Tregs, MDSCs
- Decrease of tumour mass; immunogenic cell death

**C** Decrease in tumour burden
- Increase in tumour immunogenicity

- Chemotherapy
- Radiation therapy
- Hormone therapy

**Patient selection**
- MRD or low tumour burden (increase in likelihood of developing immunity)
- Early disease stage (increase in time for immunity to develop)
CHECKPOINT BLOCKADE
Costimulatory and coinhibitory ligand–receptor interactions between a T cell and a dendritic cell, a tumor cell, and a macrophage, respectively, in the tumor microenvironment.
CTLA-4 and PD-1 modulate different aspects of the T-cell response: A, CTLA-4 is upregulated after antigen-specific activation of a naïve or memory T cell in lymphatic tissue, leading to decreased effector function (early activation phase).

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<th>Lymphatic tissue</th>
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<tr>
<td>IL-2/IFN-γ/CTL function ↑</td>
<td></td>
</tr>
<tr>
<td>CTLA-4</td>
<td></td>
</tr>
<tr>
<td>CD28</td>
<td></td>
</tr>
<tr>
<td>B7.1/2</td>
<td></td>
</tr>
<tr>
<td>TCR</td>
<td></td>
</tr>
<tr>
<td>HLA</td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
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<tr>
<td>APC</td>
<td></td>
</tr>
<tr>
<td>T cell</td>
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</table>

| IL-2/IFN-γ/CTL function ↓ |
| CTLA-4 |
| B7.1/2 |

| IL-2/IFN-γ/CTL function ↑ |
| CTLA-4 |
| CD28 |
| B7.1/2 |

<table>
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<th>B</th>
<th>Peripheral tissue/tumor</th>
</tr>
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<tbody>
<tr>
<td>IL-2/IFN-γ/CTL function ↑</td>
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<tr>
<td>T cell (resting)</td>
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<tr>
<td>CD28</td>
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</tr>
<tr>
<td>B7.1/2</td>
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</tr>
<tr>
<td>TCR</td>
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<tr>
<td>HLA</td>
<td></td>
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<td>Peptide</td>
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<tr>
<td>T cell</td>
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| IL-2/IFN-γ/CTL function ↓ |
| PD-1 |
| B7-H1 |

| IL-2/IFN-γ/CTL function ↑ |
| PD-1 |
| B7-H1 |

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CCR Focus

Phase 3 study of anti-CTLA4 antibody for the treatment of metastatic melanoma
Ipilimumab induces durable objective responses in a relatively small proportion of patients, leading to a plateau towards the end, but no shift of the early portion of the survival curve.

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CCR Focus

CHEMOTHERAPY
Chemotherapeutics can alter tumor immunogenicity and anti-tumor immune responses.
Anti-CTLA4 synergizes with PARP-inhibition to reduce IP tumor burden and improve survival in a murine ovarian cancer model.
Future directions: combination therapy
Advantages

- Demonstrated safety
- Minimal toxicity
- Induction of immunologic memory
- Evidence of clinical benefit
- Personalized approach to cancer therapy

Limitations

- Potential for autoimmune toxicity
- Cost
- Technical requirements for production
- Requirement for second surgery or banked tumor
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Tomoe Higuchi, MD, PhD

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The Ovarian Cancer Research Fund Liz Tilberis Award

Thank you – any questions?