Adoptive Cellular Therapy
SITC Primer
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Gangnam Style
T-cell therapy at the threshold

Carl June, Steven A Rosenberg, Michel Sadelain & Jeffrey S Weber

Despite impressive clinical activity in B-cell lymphoma and melanoma, questions remain about the immunobiology of adoptive T-cell therapies.

Adoptive T-cell therapy in advanced metastatic melanoma or B-cell leukemias is garnering increasingly encouraging clinical data. Nature Biotechnology approached several experts in the field to seek their insights into some of the challenges of optimizing and commercializing these experimental treatments.

What factors in the host and tumor microenvironment might compromise T-cell therapy?

Michel Sadelain: The tumor microenvironment is the battlefield where immune effectors either eradicate a tumor or fail, succumbing to various inhibitory mechanisms promoted by the tumor. The sources of such inhibition are multiple, including regulatory T cells, type 2 macrophages, myeloid suppressor cells and the tumor cells themselves. The players are multiple and differ between tumor types and individuals. Although it is not a black box anymore, a lot remains to be learned. Extratumoral factors affect adoptive T-cell therapy in many ways. Examples include medi-ullary or splenic reservoirs of myeloid suppressor cells; dysfunctional dendritic cells in lymph nodes; and extratumoral expression of antigen or cross-reactive peptides, which are the cause of ‘on-target, off-tumor’ side effects.

Steven A. Rosenberg: There clearly are aspects of the immune system that can regulate if not suppress immune reactions, and dealing with them is important for immunotherapy. In fact, with adoptive T-cell transfer therapy, the critical aspect of getting it to work is first lymphodepleting the patient before we return to the patient either natural antitumor cells or gene-modified antitumor cells. This prior lymphodepletion, using chemotherapy and sometimes with whole body irradiation, eliminates T-regulatory cells, myeloid-derived suppressor cells and other suppressive influences, and that’s what can lead to complete durable regression in patients with melanoma who receive cell transfers. So dealing with the tumor microenvironment is critical.

Carl June: Our data show that replicative capacity of the transferred T cells may be a key factor that is required for efficacy of the procedure.

In previous studies with Nan-ping Weng and Richard Nodes [at the US National Institutes of Health], we found that the replicative capacity of memory and naive T cells decreases with age. Thus, it is possible that T cells from aged patients may be less potent than those from younger patients.

Beyond lymphomas and melanomas, are there certain cancers that would be particularly challenging targets for T-cell therapy?

SAR: This whole area of genetically engineering of lymphocytes to express either conventional or T-cell receptors or CARs [chimeric antigen receptors] is a way to expand the range of immunotherapy to other cancer types. That was first shown in our papers in Blood [116: 4099–4102, 2010] and the Journal of Clinical Oncology paper [29: 917–924, 2011]. You can transduce chimeric receptors encoding CD19 and successfully treat patients with B-cell lymphomas or traditional α-β T-cell receptors and treat patients with synovial cell sarcomas.

MS: There are still very few known common, tumor-specific antigens. The cancer/testes antigens are attractive, but they are inconsistently expressed in all cases of the tumor types where they tend to appear or in all cells of positive tumors. CD19 is a great target for CAR therapy, but few other cell-surface molecules possess such a favorable profile—high expression on most tumor cells and expression in normal cells restricted to a dispensable cell type. Target identification remains a major research goal.
Vaccine Therapy  Adoptive Therapy
Adoptive T Cell Therapy
## Choice of Effectors

<table>
<thead>
<tr>
<th>TIL</th>
<th>Transferred Receptors CAR/TCR</th>
<th>Endogenous Receptor</th>
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</table>

- **TIL**
  - Requires tumor HD IL-2 dependence
  - Transduction efficiency
  - Regulatory approval

- **Transferred Receptors CAR/TCR**
  - Least labor intensive
  - Uniform specificity
  - Most efficient
  - Most physiologic
# Choice of Effectors

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<td></td>
</tr>
</tbody>
</table>
Tumor Infiltrating Lymphocytes (TILs)

Melanoma
RCC
Ovarian
Breast
Colorectal
# Tumor Infiltrating Lymphocyte

<table>
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<th>TIL</th>
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<td>Most physiologic</td>
</tr>
<tr>
<td>Least labor intensive</td>
<td></td>
<td>Most efficient</td>
</tr>
</tbody>
</table>

Labor-intensive
Tumor Infiltrating Lymphocyte

Adoptive Therapy following
Non-myeloablative Lymphodepletion

Study Design

- Patients with metastatic melanoma
- Treated at time of progression, refractory disease
- TIL expanded in vitro to > $10^{10}$ cells

\[ \begin{align*}
\text{CY} & \quad 60 \text{ mg/kg x 2} \\
\text{FLU} & \quad 25 \text{ mg/m}^2 \times 5 \\
\text{HD IL-2} & \quad 720\text{K u/kg TID}
\end{align*} \]

Dudley et al, Science 2002
Tumor Infiltrating Lymphocyte
Tumor Infiltrating Lymphocyte

- 18 / 35 responders (3 CR, 15 PR)

- Serious adverse events (≥Grade 4)
  - Uveitis
  - PCP
  - EBV-LPD
  - Intubation

- Clonal response at tumor site
Tumor Infiltrating Lymphocyte

TIL INFUSION

↑↑
CY
60 mg/kg x 2

↑↑↑↑
FLU
25 mg/m² x 5

↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑
TBI

↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑
High-Dose IL-2 (600,000 u./kg q8)
# Tumor Infiltrating Lymphocyte

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>PR</th>
<th>CR</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%) of patients (duration in mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No TBI</td>
<td>43</td>
<td>16 (37)</td>
<td>5 (12)</td>
<td>21 (49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 7, 4, 4, 2, 2, 2</td>
<td>82+, 81+, 79+, 78+, 64+</td>
<td></td>
</tr>
<tr>
<td>200 TBI</td>
<td>25</td>
<td>8 (32)</td>
<td>5 (20)</td>
<td>13 (52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14, 9, 6, 6, 5, 4, 3, 3</td>
<td>68+, 64+, 60+, 57+, 54+</td>
<td></td>
</tr>
<tr>
<td>1,200 TBI</td>
<td>25</td>
<td>8 (32)</td>
<td>10 (40)</td>
<td>18 (72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21, 13, 7, 6, 6, 5, 3, 2</td>
<td>48+, 45+, 44+, 44+, 39+, 38+, 38+, 38+, 37+, 19</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>32 (34)</td>
<td>20 (22)</td>
<td>52 (56)</td>
</tr>
</tbody>
</table>
Tumor Infiltrating Lymphocyte

Overall survival of patients receiving TILs with the chemotherapy preparative regimen alone (no TBI) or plus 2 or 12 Gy TBI.

Tumor Infiltrating Lymphocyte

- Significant responses
- Durability?
- Patient eligibility
- Facilities available
- 2\textsuperscript{nd} and 3\textsuperscript{rd} generation TIL
  - Gene-modification
  - Selection
## Choice of Effectors

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<td>Requires tumor</td>
<td>Transduction efficiency</td>
<td>Requires tumor</td>
</tr>
<tr>
<td>HD IL-2 dependence</td>
<td>Regulatory approval</td>
<td>HD IL-2 dependence</td>
</tr>
<tr>
<td>Least labor intensive</td>
<td>Uniform specificity</td>
<td>Least labor intensive</td>
</tr>
<tr>
<td></td>
<td>Most efficient</td>
<td></td>
</tr>
</tbody>
</table>
Transferred Receptor: TCR / CAR

Tumor Cell

TCR

CAR

Receptor Transfer

Chimeric TCR + zeta

Chimeric Ig +

T Cell Expansion & Infusion

19
Transferred Receptor: TCR / CAR

Requirement for a costimulatory signal
**Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia**
David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

**T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia**
Michael Kalos, Bruce Levine, David Porter, Sharyn Katz, Stephan Grupp, Adam Bagg, Carl H. June
*Sci Transl Med* 10 August 2011: Vol. 3, Issue 95, p. 95ra73

3 Patients with advanced CLL. Lymphodepletion but no IL-2 post-infusion
CAR: anti-CD19 + CD137/CD3-zeta

<table>
<thead>
<tr>
<th>BM 70% CLL</th>
<th>Bendamustine</th>
<th>1.6 x 10^7</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM 95% CLL</td>
<td>Bendamustine/Rituximab</td>
<td>1.0 x 10^6</td>
<td>PR</td>
</tr>
<tr>
<td>BM 40% CLL</td>
<td>Pentostatin/CTX</td>
<td>1.5 x 10^5</td>
<td>CR (Tumor lysis)</td>
</tr>
</tbody>
</table>

Persist > 6 months, > 1000-fold expansion, >1000:1 killing, > 1 kg tumor
No immunogenicity to vector
Transferred Receptor: TCR / CAR
Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias.


Anti-CD19-CD28/zeta

10 patients

Up to 3 x 10^7/kg +/- cyclophosphamide conditioning
no post-infusion IL-2

8/9 well tolerated
3 of 3 with bulky CLL + CY conditioning -> (1 PR, 2 SD)
Persistence 4-6 weeks in 2/7 by BM
Persistence copy number .01 – 1.0/ 100 cells 30 days+
Transferred Receptor: TCR / CAR

Tumor Cell

TCR

CAR

Receptor Transfer

T Cell Expansion & Infusion
<table>
<thead>
<tr>
<th>Antigen</th>
<th>CAR or TCR</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>MART-1, gp100</td>
<td>TCR</td>
<td>Melanoma</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>TCR</td>
<td>Sarcoma, Myeloma, (Breast, Lung)</td>
</tr>
<tr>
<td>MAGE-A3</td>
<td>TCR</td>
<td>Any cancer MAGE-A3+</td>
</tr>
<tr>
<td>P53</td>
<td>TCR</td>
<td>Any cancer overexpress p53</td>
</tr>
<tr>
<td>CD19</td>
<td>CAR</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>EGFRvIII</td>
<td>CAR</td>
<td>Glioblastoma, Breast, Lung</td>
</tr>
<tr>
<td>Kappa Light Chain</td>
<td>CAR</td>
<td>CLL, B cell NHL</td>
</tr>
<tr>
<td>Her2Neu</td>
<td>CAR</td>
<td>Osteosarcoma, Breast</td>
</tr>
<tr>
<td>CD30</td>
<td>CAR</td>
<td>Lymphoma (NHL and HD)</td>
</tr>
<tr>
<td>GD2</td>
<td>CAR</td>
<td>EBV-specific CTL targeting GBM</td>
</tr>
</tbody>
</table>
**Transferred Receptor: TCR / CAR**

**Completed Clinical Studies**

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**Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes**
Richard A. Morgan et al.
*Science* 314, 126 (2006); DOI: 10.1126/science.1129003

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**Table 1. Recent Clinical Success using Gene Modified T Cells**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Target Antigen</th>
<th>Gene-Vector</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>GD2</td>
<td>CAR-RTV</td>
<td>Cell persistence better in viral-specific CTL</td>
<td>Pule et al., 2008</td>
</tr>
<tr>
<td>Indolent B-NHL and mantle cell lymphoma</td>
<td>CD20</td>
<td>CAR-EP</td>
<td>Successful demonstration of non-viral gene transfer</td>
<td>Till et al., 2008</td>
</tr>
<tr>
<td>Melanoma</td>
<td>MART-1</td>
<td>TCR-RTV</td>
<td>30% response rate with on-target/off-tumor toxicity</td>
<td>Johnson et al., 2009</td>
</tr>
<tr>
<td>Melanoma</td>
<td>gp100</td>
<td>TCR-RTV</td>
<td>19% response rate with on-target/off-tumor toxicity</td>
<td>Johnson et al., 2009</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>CD19</td>
<td>CAR-RTV</td>
<td>Near complete response with concomitant elimination of B cells.</td>
<td>Kochenderfer et al., 2010</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>CEA</td>
<td>TCR-RTV</td>
<td>Responses associated with on-target/off-tumor toxicity</td>
<td>Parkhurst et al., 2010</td>
</tr>
<tr>
<td>Synovial sarcoma and melanoma</td>
<td>NY-ESO-1</td>
<td>TCR-RTV</td>
<td>50% response rate with no toxicity.</td>
<td>Robbins et al., 2011</td>
</tr>
</tbody>
</table>

Abbreviations: CAR, Chimeric Antigen Receptor; TCR, T Cell Receptor; RTV, gamma-retroviral vector; EP, electroporation.
Transferred Receptor: TCR / CAR

Molecular Construct Issues

• CAR/TCR: affinity
  • Phage display, mutations
  • HSC, iPS + Notch ligand
• TCR: pairing
  • Disulfide, murine, zipper
• Transfection efficiency
  • Lentiviral, SB transposon
• Cell type
  • ?
• Immunogenicity
Transferred Receptor: TCR / CAR

Clinical Issues

• Cytokine release syndrome toxicity
• On-target Toxicities

• Minimize/escalate conditioning
• Dose escalation
• Split infusion dosage
# Choice of Effectors

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Endogenous Receptor

T Cell

Stimulator Cell

pMHC

Target Antigen

Dendritic Cells

Antigen-specific T Cell Enrichment

T Cell Expansion & Infusion
Endogenous Receptor

Artificial Antigen Presenting Cells

- HLA molecule
- CD28
- MHC-dimer (MHC-Ig)

T cells

Insect cells

- 4-1BBL(CD137L)
- ICAM-1(CD54)
- B7.1(CD80)
- HLA molecule
- Anti-CD3 Ab
- Fc receptor (CD32, CD64)
- TCR

Magnetic bead

aAPC

K562

HLA molecule was transfected
Endogenous Receptor

Adoptive T Cell Therapy: Basic Protocol

Isolate/Enrich  Clone/Select  (Genetically Modify)
Lymphoid Homeostasis

other growth signals
other cytokines
IL-15
IL-7
Lymphodepletion
building a better environment

Increase 'space' for transferred T cells
Eliminate 'suppressor cells'
Supply Growth Factors
Increase 'space' for transferred T cells
Eliminate 'suppressor cells'
Supply Growth Factors
Endogenous Receptor

- CY 60 mg/kg x 2
- FLU 25 mg/m² x 5
- TBI
- High-Dose IL-2 (600,000 u./kg q8)
Endogenous Receptor

- CY: 60 mg/kg x 2
- FLU: 25 mg/m² x 5
- TBI
- Low-Dose IL-2 (250,000 U s.c q12 h)
Endogenous Receptor

Objectives:
- Evaluate Safety
- Evaluate T Cell Persistence
- Evaluate anti-tumor efficacy

Eligibility Criteria:
- Stage IV (Metastatic)
- HLA-A2

T Cell Infusion:
- Antigen-specific CD8+ T cell clones
- Targeting MART-1, gp100
- Dose: $10^{10}$ cells / m$^2$

Low-Dose IL-2 (250,000 U s.c q12 h)

Chapuis A. et al, PNAS. March 2012
Endogenous Receptor
On-target toxicity
Endogenous Receptor

T cell persistence in vivo

CD45 RO+
CD28-
CD127-lo

CD45 RO+
CD28++
CD127-hi
### Endogenous Receptor

## Clinical Response

<table>
<thead>
<tr>
<th>Patient</th>
<th>Target</th>
<th>Toxicity</th>
<th>Persistence</th>
<th>Disease Sites</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2140-1</td>
<td>Tyrosinase</td>
<td>F,N,R</td>
<td>&gt;290 days</td>
<td>Cervical, supraclavicular LN, Chest Wall, Breast Pulmonary nodules</td>
<td>MR</td>
</tr>
<tr>
<td>2140-2</td>
<td>Tyrosinase</td>
<td>F</td>
<td>16 days</td>
<td>Mediastinal, Pulmonary nodules</td>
<td>PD</td>
</tr>
<tr>
<td>2140-3</td>
<td>gp100</td>
<td>F,N,R</td>
<td>&gt;85 days</td>
<td>Mesenteric LN, scapular subcutaneous dz</td>
<td>CR (&gt;12 mths)</td>
</tr>
<tr>
<td>2140-4</td>
<td>MART-1</td>
<td>F, N, R</td>
<td>&gt;30 days</td>
<td>Pulmonary, inguinal, subcutaneous</td>
<td>SD</td>
</tr>
<tr>
<td>2140-5</td>
<td>MART-1</td>
<td>F, N, R</td>
<td>&gt;30 days</td>
<td>Right and left kidneys, adrenal, liver</td>
<td>PR</td>
</tr>
<tr>
<td>2140-6</td>
<td>MART-1</td>
<td>F, N, R</td>
<td>&gt;30 days</td>
<td>Mediastinal, supra clavicular, mammary chain, periportal, portacaval nodes.</td>
<td>PR</td>
</tr>
</tbody>
</table>
Endogenous Receptor

• aAPCs (K562, CD80, CD83, HLA-A2)
• MART-1 specific CTL + IL-2/ IL-15
• Treatment plan:
  – CTL alone (no conditioning or IL-2)
## Endogenous Receptor

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/sex</th>
<th>Metastatic disease at study entry</th>
<th>Previous therapy</th>
<th>Total cells infused</th>
<th>Status on day 70</th>
<th>Time to next therapy</th>
<th>Outcome after CTL or next therapy</th>
<th>Duration of response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74/M</td>
<td>Liver, adrenal, spleen, lung, skin</td>
<td>LND; carboptin, paclitaxel, sorafenib; gp100 vaccine</td>
<td>$4.0 \times 10^8$</td>
<td>None</td>
<td>Death on day 51</td>
<td>Died without therapy</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>69/M</td>
<td>Lung, skin</td>
<td>WLE; LND; temozolomide; melphalan limb perfusion</td>
<td>$4.0 \times 10^8$ $4.0 \times 10^8$</td>
<td>PD</td>
<td>Day 103 ipilimumab (10 mg/kg)</td>
<td>PR</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>49/F</td>
<td>Lung, adrenal</td>
<td>WLE; LND; RT; HD IL-2</td>
<td>$4.3 \times 10^8$ $4.3 \times 10^8$</td>
<td>MR</td>
<td>Day 146 ipilimumab (10 mg/kg)</td>
<td>PR</td>
<td>31+</td>
</tr>
<tr>
<td>4</td>
<td>68/M</td>
<td>Skeletal muscle, lung, mediastinum, cardiac</td>
<td>Small-bowel resection; HD IL-2; ipilimumab versus gp100 versus both</td>
<td>$3.8 \times 10^8$ $3.8 \times 10^8$</td>
<td>SD</td>
<td>Day 140 RAF265</td>
<td>SD</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>66/M</td>
<td>Lymph nodes</td>
<td>WLE; LND</td>
<td>$4.4 \times 10^9$ $2.5 \times 10^9$</td>
<td>PR</td>
<td>No other therapy</td>
<td>CR to CTL day 140</td>
<td>25+</td>
</tr>
<tr>
<td>6</td>
<td>55/M</td>
<td>Lung</td>
<td>WLE; LND; pulmonary nodule resection</td>
<td>$1.8 \times 10^9$ $3.4 \times 10^9$</td>
<td>SD</td>
<td>Day 287 HD IL-2</td>
<td>Death due to line sepsis</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>70/F</td>
<td>Lung, skin</td>
<td>WLE; LND; adjuvant IFN</td>
<td>$4.0 \times 10^9$ $4.0 \times 10^9$</td>
<td>PD</td>
<td>Day 335 ipilimumab (3 mg/kg)</td>
<td>SD</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>80/M</td>
<td>Lung, mediastinum</td>
<td>LND; RT; temozolomide</td>
<td>$3.6 \times 10^9$ $3.6 \times 10^9$</td>
<td>SD</td>
<td>Day 372 ipilimumab (3 mg/kg)</td>
<td>SD</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>64/M</td>
<td>Lung, skin</td>
<td>WLE; LND; adjuvant IFN</td>
<td>$4.4 \times 10^9$ $4.4 \times 10^9$</td>
<td>PD</td>
<td>Day 146 ipilimumab (10 mg/kg)</td>
<td>PR</td>
<td>13+</td>
</tr>
</tbody>
</table>
Endogenous Receptor

- Effective, Relatively low toxicity
- Clinical Responses (RECIST)
- Longterm persistence
- Reversion to Memory (?)
- Effector Cell type?
- Time to generation of Effector Cells
The bigger picture...
Adoptive T Cell Therapy: Basic Protocol

**Isolate/Enrich**

**Clone/Select**

**Logically (Genetically Modify)**

PNAS Yee et al. 2002
Adoptive T Cell Therapy: Extended Protocol

**Intrinsic**
- **Isolate/Enrich**
  - Cytokine modulation
- **Clone/Select**
  - Phenotype
    - CD8/CD4
    - Memory phenotype
- **Genetically Modify**
  - TCR
  - Chimeric receptor
  - Costimulatory/Inhibitory modification
  - Suicide gene

**Extrinsic**
- **Pre-infusion Immunomodulation**
  - Lymphodepletion
    - Chemotherapy/TBI
- **Post-infusion Immunomodulation**
  - Cytokine help
    - Low-dose IL-2
    - High-dose IL-2
    - Other γ-chain receptor cytokines
  - Anti-CTLA4, Anti PD-1
  - Vaccine + adoptive therapy

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Metastatic breast cancer, NY-ESO-1+, T-cells targeting HLA A*2402/NY-ESO-1

Ribas A, Glaspy J, Chapuis A, Yee C
Adoptive T Cell Therapy: Extended Protocol

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LEUKAPHERESIS

24 days

DC

T Cell

14 days

+ 14 days

14 days

+ 14 days

DC+ peptide

STIM 1

+IL-2

+IL-7

STIM 2

+IL-2

+IL-7

STIM 3

+IL-2

+IL-7

Expansion

80 days
LEUKAPHeresis

10 days

3 hours

14 days

APC

PBMC

CD25 depletion

APC + superagonist APL

+ IL-21

24 days

+ IL-21
+ CD 25 depl
+ sorter*
+ APL

Expansion

Cell sort

Tetramer+
Immunologic monitoring

• Cellular level:
  – Epimax
  – SCBC
  – Tetramer multiplex slides
  – TCR sequencing

• Host level
  – Biopsy
  – Noninvasive imaging
Prospects for Adoptive Cellular Therapy

• Clinical indications
• Clinical setting
• Combination Therapy
• Advances in technology
  – In vitro generation of effectors
  – Combinational reagents
  – Immunologic monitoring
• Immunologic monitoring
Antigen Receptor

Which of the following is *not* true:

a. The TCR recognizes fragments of whole proteins (peptides) presented on the surface of cells by MHC molecules

b. T cells can target peptides derived from both surface and intracellular proteins

c. Chimeric antigen receptors (CARs) are fusion products of TCR alpha and beta region and cytoplasmic signaling domains

d. T cells engineered to express CARs can recognize tumor cells expressing a target surface or intracellular protein
Antigen Receptor
Which of the following is *not* true:

c. Chimeric antigen receptors (CARs) are fusion products of TCR alpha and beta region and cytoplasmic signaling domains
TIL

- Tumor infiltrating lymphocytes
  a. Are comprised almost exclusively of CD8 T cells (CTL)
  b. Are found only in melanoma tumor samples
  c. Can only be expanded in vitro using high-dose IL-2
  d. Are a source of antigen-specific T cell
TIL

- Tumor infiltrating lymphocytes

d. Are a source of antigen-specific T cell
CD4 T cells

• The following statement regarding CD4 T cells is not true:
  a. Recognize peptide presented by Class I MHC
  b. Can kill tumor cells directly
  c. Can recruit other nonspecific effector cells to the tumor site
  d. Can be regulatory / suppressor T cells
CD4 T cells

• The following statement regarding CD4 T cells is not true:
  a. Recognize peptide presented by Class I MHC
Peptide-MHC multimers

• Which are the following statements is not true:

• Peptide-MHC multimers
  a. Can be used to identify antigen-specific CD8 T cells
  b. Can be used to sort and isolate rare antigen-specific T cells
  c. Can be used for immunohistochemistry staining
  d. Cannot be used to identify antigen-specific CD4 T cells
Peptide-MHC multimers

• Which are the following statements is not true:
• Peptide-MHC multimers

  d. Cannot be used to identify antigen-specific CD4 T cells
Current Events

• The artist known as ________ is famous for popularizing the ‘Gangnam-style’ of dancing:

a. Jerry Garcia  
b. ___  
c. ICE-T  
d. PSY
Current Events

• The artist known as ________ is famous for popularizing the ‘Gangnam-style’ of dancing:

  d. PSY