Micro 204
Tumor Immunology

Lewis.Lanier@ucsf.edu
Part 1  Immunosurveillance & “Immunoediting”

Tumor Antigens - definition & discovery

Part 2  Cancer Immunotherapy
Immunological Surveillance
Ehrlich, Burnet & Thomas

Paul Ehrlich (1909) Concept of cancer immunosurveillance. Predicted that cancer would occur at “incredible frequency” if host defenses did not prevent the outgrowth of continuously arising cancer cells

Lewis Thomas (1957) “primary function of cellular immunity….is to protect from neoplastic disease”

Macfarland Burnet (1957) “It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provide an effective immunological reaction with regression of this tumor and no clinical hint of its existence”
Evidence for immune surveillance in humans

Increased incidence of EBV+ B cell lymphomas in transplant patients treated with immunosuppressive drugs

Increased incidence of Kaposi’s sarcoma & EBV+ B cell lymphomas in AIDS patients

Gastric cancer associated with *H. pylori* infection

Cervical cancer caused by human papillomavirus

Liver cancer caused by hepatitis B & C
Anti-Tumor Effector Mechanisms

CD4^+ T cells, CD8^+ CTL, and NK cells

- direct cytotoxicity or ADCC (NK cells) via perforin & granzymes and/or TNF family members
- cytokine release (e.g., TNF, IFNγ, GM-CSF) leading to:
  a) lysis of tumor cells
  b) disruption of angiogenesis
  c) recruitment and activation of DC, macrophages, & granulocytes

B cells

- production of tumor-specific antibodies leading to:
  a) complement-mediated killing
  b) ADCC
  c) antibody-mediated apoptosis by disrupting oncogenic signals

Macrophages

- killing via ADDC
- killing via production of cytokines such as TNF
- killing via production of toxic oxygen or nitrogen intermediates
Immunotherapy Strategies

Cytokine infusions (e.g. IFNa, IL-2)

Induction of inflammation (e.g. CpG)

Tumor-targeted antibodies (e.g., Herceptin)

Adoptive transfer of tumor-specific T cells

Donor lymphocyte infusions after BMT/HSCT (allogeneic bone marrow or hematopoietic stem cell transplant)

Vaccination
Immune Surveillance - Revival

IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity


Nature 410:1107, 2001
Increased Incidence of MCA-Induced Tumors Detected in Mice With Well-Defined Genetic Immunodeficiencies


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- **SubQ MCA Injection**: 80–160 days

- **Lack T and B cells**: RAG2−/−

- **Lack IFNγR or signaling capacity**: WT

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<table>
<thead>
<tr>
<th>Host genotype</th>
<th>WT</th>
<th>RAG2−/−</th>
<th>IFNGR1−/−</th>
<th>STAT1−/−</th>
<th>RkSk</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>57</td>
<td>52</td>
<td>20</td>
<td>30</td>
<td>18</td>
</tr>
</tbody>
</table>

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**Wild Type (normal mice)**
Spontaneous tumors in wild-type and immunodeficient mice
T cells control latent tumors

Tumors arising in immunodeficient mice are more immunogeneic than tumors arising in wild-type mice

Assayed by transplanting tumors into wild-type or immunodeficient mice
Tumor Elimination - Equilibrium - Escape

Schreiber et al. Immunity 2004
Tumor-infiltrating lymphocytes correlation with survival in ovarian cancer patients

Zhang et al. NEJM 348:203, 2003
Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon, Anne Costes, Fatima Sanchez-Cabo, Amos Kirilovsky, Bernhard Mlecnik, Christine Lagorce-Pagès, Marie Tosolini, Matthieu Camus, Anne Berger, Philippe Wind, Franck Zinzindohoué, Patrick Bruneval, Paul-Henri Cugnenc, Zlatko Trajanoski, Wolf-Herman Fridman, Franck Pagès

D

Center of the Tumor (CT)

Invasive Margin (IM)

Combined regions analysis

Disease-Free Survival

Survival (months)

**
Melan-A/MART-1-specific
CD8\(^+\) T cells in lymph nodes of melanoma patients

Romero et al. *J. Exp. Med.*, Volume 188(9), 1998 1641-1650
Tumor Antigens

Tumor-specific antigens
  – Expressed by tumors ONLY

Tumor-associated antigens
  – Preferentially expressed by tumors

Oncofetal antigen
  – Expressed by tumors in adult, but also expressed by fetal (not adult) tissues
### Types of Tumor Antigens Recognized by T cells

<table>
<thead>
<tr>
<th>Normal host cell displaying multiple MHC-associated self antigens</th>
<th>Not recognized by T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor cells</strong></td>
<td></td>
</tr>
<tr>
<td>Mutated self protein</td>
<td>CD8+ CTL</td>
</tr>
<tr>
<td>Over-expressed or aberrantly expressed self protein</td>
<td>CD8+ CTL</td>
</tr>
<tr>
<td>Oncogenic virus</td>
<td>Virus antigen-specific CD8+ CTL</td>
</tr>
</tbody>
</table>

The diagram illustrates the types of tumor antigens recognized by T cells. The normal host cell displays multiple MHC-associated self antigens, which are not recognized by T cells. In contrast, tumor cells exhibit various antigenic profiles, including mutated self proteins, over-expressed or aberrantly expressed self proteins, and oncogenic viruses, which can be recognized by CD8+ cytotoxic T lymphocytes (CTLs).
Neo-epitopes

Normal cell presents self peptides bound to MHC molecules

A point mutation in a self protein allows binding of a new peptide to MHC molecules

A point mutation in a self peptide creates a new epitope for recognition by T cells
## Potential tumor rejection antigens have a variety of origins

<table>
<thead>
<tr>
<th>Class of antigen</th>
<th>Antigen</th>
<th>Nature of antigen</th>
<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor-specific mutated oncogene or tumor-suppressor</td>
<td>Cyclin-dependent kinase 4</td>
<td>Cell-cycle regulator</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>β-Catenin</td>
<td>Relay in signal transduction pathway</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>Caspase-8</td>
<td>Regulator of apoptosis</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Germ cell</td>
<td>MAGE-1, MAGE-3</td>
<td>Normal testicular proteins</td>
<td>Melanoma, Breast, Glioma</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Tyrosinase</td>
<td>Enzyme in pathway of melanin synthesis</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>Surface Ig</td>
<td>Specific antibody after gene rearrangements in B-cell clone</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Abnormal gene expression</td>
<td>HER-2/neu</td>
<td>Receptor tyrosine kinase</td>
<td>Breast, Ovary</td>
</tr>
<tr>
<td>Abnormal post-translational modification</td>
<td>MUC-1</td>
<td>Underglycosylated mucin</td>
<td>Breast, Pancreas</td>
</tr>
<tr>
<td>Oncoviral protein</td>
<td>HPV type 16, E6 and E7 proteins</td>
<td>Viral transforming gene products</td>
<td>Cervical carcinoma</td>
</tr>
</tbody>
</table>

Fig 14.11 © 2001 Garland Science
Epitope Landscape in Breast and Colorectal Cancer

Neil H. Segal,¹² D. Williams Parsons,⁴ Karl S. Peggs,²³ Victor Velculescu,⁴ Ken W. Kinzler,⁴ Bert Vogelstein,⁴ and James P. Allison²³

to identify candidate tumor antigens. Analysis of 1,152 peptides containing missense mutations previously identified in breast and colorectal cancer revealed that individual cancers accumulate on average ~10 and ~7 novel and unique HLA-A*0201 epitopes, respectively, including genes implicated in the neoplastic process. These data suggest
Use of Human Tumor Ag-Specific Cloned CTL for Identification of Tumor Antigens

Generation of tumor-specific CTL clones

- Surgically resect tumor
  - Tumor cells
  - Melanoma cell line
- Purify mononuclear cells from tumor site
  - Tumor cells
  - Patient's mononuclear cells
- Coculture mononuclear cells and melanoma cells
- Isolate and clone activated CD8+ CTLs
Identification of tumor antigens recognized by tumor-specific CTLs

1. Tumor cDNA library
2. Coculture with CTL clone
3. Melanoma cell line
4. Transfect into class I MHC+ target cell line
5. Isolate transfected DNA and sequence
6. Gene encoding tumor antigen recognized by melanoma-specific CTL

TNFα Production:
- -
- -
+ -
Serological identification of tumor antigens - Serex

Some cancer patients have antibodies reactive with their own tumor

Use patients’ sera to expression clone the tumor antigens

Surprisingly, many of the antisera recognized the same tumor-associated antigens that detected by CTL
Passive Immunotherapy

Anti-tumor monoclonal antibodies

(a billion dollar business)
Antibody-dependent cellular cytotoxicity
**Rituxan Pivotal Trial: Treatment of Patients With Relapsed B Lymphoma**

**Rituxan® 375 mg/m² (IV)**

- Monitoring every 3 months x2 years

<table>
<thead>
<tr>
<th>Weeks</th>
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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<table>
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<tr>
<th>Evaluative Patients</th>
<th>166</th>
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<tbody>
<tr>
<td>Overall Response</td>
<td>80 (48%)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>10 (6%)</td>
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<tr>
<td>Partial Response</td>
<td>70 (42%)</td>
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</table>

CD16 (FcγRIII) mediates Herceptin and Rituxan mediate human tumor elimination in nude mice

*Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets*

Raphael A. Clynes¹, Terri L. Towers¹, Leonard G. Presta² & Jeffrey V. Ravetch¹

doi: 10.1038/74704
Tumor-specific antibody

Antibodies bind to the tumor cell

NK cells with Fc receptors (CD16) are activated to kill the tumor cells

Tumor-specific antibody conjugated to toxin

Antibody-toxin conjugates bind to the tumor cell

Conjugates are internalized, killing the cell

Tumor-specific antibody conjugated to radionuclide

Radioactive antibody binds to the tumor cell

Radiation kills the tumor cell and neighboring tumor cells
Active Immunotherapy

Vaccination
First vaccine to prevent human cancer!

vaccine for papilloma virus for cervical cancer!

San Francisco Chronicle

Cervical cancer vaccine due soon
Federal panel urges it go to all girls, 11-12, not a must for school

Erin Allday, Chronicle Staff Writer
Friday, June 30, 2006

Panel's suggestions

The federal Advisory Committee on Immunization Practices recommended:

-- That the cervical cancer vaccine routinely be given to all 11- and 12-year-old girls.

-- That girls and women ages 13 to 26 receive the vaccine, regardless of whether they are sexually active.

-- That physicians have the option of giving the vaccine to girls as young as 9.
Successful Active Vaccination against Virus-induced Cancers

Vaccine to feline leukemia virus for cats

Vaccine to herpes virus (Marek’s virus) in chickens

Vaccine to hepatitis B in humans to prevent liver carcinoma

Vaccination to HPV prevents cervical cancer
Active Immunization - Tumor cells or antigens

- Tumor cells or extracts (Melacin)
- Tumor peptide + adjuvant vaccine
- Tumor peptide loaded on dendritic cell
- Tumor antigen cDNA vaccination
- Tumor antigen in recombinant virus
- Feeding dendritic cells dead tumors
- Feeding dendritic cells tumor RNA
FDA NEWS RELEASE
For Immediate Release: April 29, 2010
Media Inquires: Shelly Burgess, 301-796-4651, shelly.burgess@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA, OCOD@fda.hhs.gov

FDA Approves a Cellular Immunotherapy for Men with Advanced Prostate Cancer

Provenge
load autologous DC with prostatic acid phosphatase
inject into prostate cancer patient

<table>
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<th>Summary of Overall Survival Analysis Results</th>
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<table>
<thead>
<tr>
<th></th>
<th>Sipuleucel-T</th>
<th>Placebo</th>
<th>Sipuleucel-T vs. placebo</th>
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<tbody>
<tr>
<td></td>
<td>Median N</td>
<td>Median N</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>D9902B (N=512)</td>
<td>341</td>
<td>171</td>
<td>0.775 (0.614, 0.979)</td>
</tr>
<tr>
<td>D9501 (N=127)</td>
<td>82</td>
<td>45</td>
<td>0.586 (0.388, 0.884)</td>
</tr>
<tr>
<td>D9502A (N= 98)</td>
<td>65</td>
<td>33</td>
<td>0.786 (0.484, 1.278)</td>
</tr>
<tr>
<td>Integrated Studies (N=737)</td>
<td>488</td>
<td>249</td>
<td>0.734 (0.612, 0.881)</td>
</tr>
</tbody>
</table>

1. Hazard Ratio (HR), confidence interval (CI), and p-value estimated according to the primary analysis method.
2. HR, CI, and p-value estimated based on unadjusted Cox model and log rank test as presented in the individual clinical trial report. The analysis methods for overall survival were not pre-specified.
3. HR, CI, and p-value estimated based on Cox model with treatment as independent variable, stratified by study.
4. Based on a Kaplan-Meier estimate (in months).

No difference between the two study arms in time to objective disease progression, progression free survival, time to clinical progression, or time to prostate-specific antigen (PSA) doubling time was observed in any of the Phase 3 studies. The reason for the dissociation between overall survival and these other outcome measures is unclear. However, overall survival is the most reliably measured and clinically meaningful of these endpoints.
Mechanisms of Tumor Escape from Immune Responses

• Loss of MHC or TAP
• Loss of co-stimulatory molecules
• Antigenic variation
• Secretion of immunosuppressive factors
  – E.g. TGF-β, IL-10
• T cells don’t penetrate solid tumors
• Exhaustion of T cells
• T regulatory cells suppress anti-tumor responses
Cancer immunotherapy in the clinic

Lawrence Fong
Professor of Medicine

University of California San Francisco
Immune recognition of cancer

The Cancer-Immunity Cycle is a cyclic process that can be self-propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit the immunity. This cycle can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the killing of cancer cells. Each step is described above, with the primary cell types involved and the anatomic location of the activity listed. Abbreviations are as follows: APCs, antigen presenting cells; CTLs, cytotoxic T lymphocytes.

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

(Chen and Mellman, Immunity 2013)
Candidate targets for immunotherapy

(Chen and Mellman, Immunity 2013)
Co-stimulation and co-inhibition

(Pardoll. NRC 2012)
Anti-CTLA-4 in metastatic melanoma

- Patients with metastatic melanoma
- Ipilimumab vs. vaccine/ipilimumab vs. vaccine
- OS: 10 vs. 10.1 vs. 6.4 months
- FDA approved 3/2011

(Hodi et al, NEJM 2010)
Anti-PD-1 in metastatic melanoma

(Robert et al. NEJM 2015)
Combining anti-CTLA-4 and anti-PD-1

Table 2. Response to Treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with BRAF Wild-Type Tumors</th>
<th>Patients with BRAF V600 Mutation–Positive Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab plus Ipilimumab (N=72)</td>
<td>Ipilimumab (N=37)</td>
</tr>
<tr>
<td></td>
<td>Nivolumab plus Ipilimumab (N=23)</td>
<td>Ipilimumab (N=10)</td>
</tr>
<tr>
<td>Best overall response — no. (%)*</td>
<td>Complete response 16 (22)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Partial response 28 (39)</td>
<td>4 (11)</td>
</tr>
<tr>
<td></td>
<td>Stable disease 9 (12)</td>
<td>13 (35)</td>
</tr>
<tr>
<td></td>
<td>Progressive disease 10 (14)</td>
<td>15 (41)</td>
</tr>
<tr>
<td></td>
<td>Could not be determined 9 (12)</td>
<td>5 (14)</td>
</tr>
<tr>
<td></td>
<td>Patients with objective response — no. (% [95% CI])‡</td>
<td>44 (61 [49–72])</td>
</tr>
</tbody>
</table>

*Relative to baseline; **Relative to ipilimumab monotherapy group; ‡95% confidence intervals; CI, confidence interval; NR, not reported; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease; DCR, durable complete response; DOR, durable overall response.
Combining anti-CTLA-4 and anti-PD-1

B

\[ \begin{array}{c}
\text{During treatment} \\
\text{After treatment} \\
\text{discontinuation} \\
\text{First response} \\
\text{Ongoing response}
\end{array} \]

C

Death or Disease Progression
\[ \text{no. of patients/total no.} \]

Median Progression-free Survival
\[ \text{mo (95% CI)} \]

Nivolumab plus Ipilimumab

Ipilimumab

\[ \begin{array}{c}
30/72 \\
25/37
\end{array} \]

4.4 (2.8–5.7)

Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001

No. of patients/total no.

Progression-free Survival
\[ \text{(% of patients)} \]

Months

Nivolumab plus ipilimumab (N=72)

Ipilimumab (N=37)

No. at Risk

\[ \begin{array}{cccccccc}
\text{Nivolumab plus ipilimumab} & 72 & 54 & 45 & 38 & 20 & 1 & 0 \\
\text{Ipilimumab} & 37 & 20 & 9 & 6 & 2 & 0 & 0
\end{array} \]

(Postow et al. NEJM 2015)
Adoptive CELL THERAPY (ACT)

- Tumor is resected and cut into small fragments
- Tumor fragments are grown in multiple cultures containing high-dose IL-2
- Tumor infiltrating lymphocytes (TILs) are expanded for ~3 weeks
- Expanded TILs are assayed and pooled for reinfusion after conditioning lymphodepleting chemotherapy

Chimeric antigen receptor (CAR) T cells

- Specificity of a monoclonal antibody
- Not dependent on MHC
- Activates T cells with Signals 1 & 2
Making Better Chimeric Antigen Receptors

We attempted to address this question, which is of major importance. The position of the epitope and its distance to the cell surface are expected to affect the binding. From human libraries or invariant human ligands, they may prove to be more immunogenic than Fabs derived from well-characterized monoclonal antibodies. However, immunoglobulins are commonly used, as they are easily derived from libraries; or (iii) nature ligands that engage their cognate receptors (see Fig. 1, first-generation CARs). Successful CARs therefore recognize antigen on any HLA background, in contrast to TCRs, which need to be matched to the haplotype of the patient. Furthermore, CARs can target tumor cells that have downregulated HLA expression or possess both activating and costimulatory properties, possessing both activating and costimulatory components incorporated into the cytoplasmic domain of CAR.

Binding moiety of the CAR is not only a targeting device but also is integral to CAR function, which is not solely defined by the signaling components incorporated into the cytoplasmic domain of CAR. The rules for selecting optimal epitopes for CAR targetting are rapidly evolving and show great promise for their success. CARs are being rapidly evolved and show great promise for their success.

The moieties used to bind to antigen fall in three general categories: (i) single-chain variable fragment (scFv) derived from antibodies; (ii) Fab fragment antigen-binding (Fab) selected from libraries; or (iii) nature ligands that engage their cognate receptors. CAR TARGETING

The first-generation CAR has activation only. mAb scFv, monoclonal antibody.

The second-generation CAR has dual signaling. mAb scFv, monoclonal antibody.

The third-generation CAR has multiple (≥3) signaling. mAb scFv, monoclonal antibody.

CAR SIGNALING

First-generation CAR activation only
Second-generation CAR dual signaling
Third-generation CAR multiple (≥3) signaling

(Sadelain et al. Can Disc 2013)
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

- 0.76 \times 10^6\text{ to } 20.6 \times 10^6\text{ CTL019 cells/kg IV}
- 27/30 (90\%) children and adults with relapsed ALL achieved complete remission.
- All patients developed a cytokine release syndrome.
- 73\% with relapse-free B cell aplasia.

(Maude, NEJM 10/2014)
B-cell ALL.

The proliferation of CTL019 cells was measured by a quantitative polymerase-chain-reaction (PCR) assay in intervals. The assay showed very high levels of proliferation of CTL019 cells; (Fig. 1C).

There was no discernible effect of the density of CD19 antigen or cell dose on either efficacy of donor lymphocytes, and the disease remained in remission, and the disease remained in remission without minimal residual disease at the time of transplantation, short persistence of chimeric antigen receptor T cells is unlikely to produce long-term engraftment.

The patients were treated for relapse of T-cell ALL that aberrantly expressed CD19, was refractory to two intensive reinduction regimens, and entered a morphologic remission 7 to 12 months after the infusion of CTL019. Patients who were ineligible for stem-cell transplantation, had a post-transplantation leukapheresis was 100% (range, 68 to 100). No patient with the longest remission (2 years), B-cell aplasia (absence of CD19-positive cells) (Fig. 2C) and data not shown). This assay showed functional persistence of CTL019 cells below the limits of detection by flow cytometry, where subsequently had persistence of CTL019. In the patient with the longest remission 2 years in this cohort and for more than 3 years since the administration of CTL019 to receive other therapy.

The myelodysplastic syndrome developed and led to overt acute myeloid leukemia after the infusion of CTL019, but the patient subsequently had persistence of CTL019. In the 18 patients who were treated for relapse after administration of CTL019, nine had minimal residual disease (0.09%). She subsequently received bortezomib and an infusion of CTL019 for Relapse after Allogeneic Stem-Cell Transplantation, short persistence of chimeric antigen receptor T cells is unlikely to produce long-term engraftment as CTL019 remained detectable by means of the limits of detection by flow cytometry, where continued for a year after the loss of CTL019.

C levels of CTL019 DNA in peripheral blood

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(Maude, NEJM 10/2014)
Cytokine Release Syndrome

- Fever
- Hypotension requiring vasopressors
- Hypoxemia requiring mechanical ventilation

![Graphs showing levels of Interleukin-6 and Baseline Disease Burden in patients with and without Cytokine Release Syndrome](Maude, NEJM 10/2014)
Discussion Groups

1. What is the best cell or cells for CAR therapy? CD8$^+$ T cells, CD4$^+$ T cells, $\gamma\delta$ T cells, NK cells? Macrophages?

2. How would you make an “off-the-shelf” CAR T cell population that could be introduced into allogeneic recipients?

3. In addition to introducing a CAR into T cells, how else might you genetically modify the recipient cells to make them more effective or more safe?