CELLULAR THERAPIES
REVOLUTIONIZING CANCER THERAPY

Carl June
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UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

Penn Medicine
Center for Cellular Immunotherapies
Disclosure Information

*Carl June*

I have the following financial relationships to disclose:
- Consultant for: Celldex, Globeimmune, Immune Design
- Speaker’s Bureau for:
- Grant/Research support and royalties from: Novartis
- Scientific Founder: Tmunity
- Stockholder in: Tmunity
- Honoraria from:
- Employee of:

- and -

I will discuss investigational use in my presentation:
  CTL019
Updated history of immunotherapy: December 2013

2013 Breakthrough
- Cancer Immunotherapy

The Runners-Up
- CRISPR
- CLARITY
- Human Stem Cells from Cloning
- Mini-Organs
- Cosmic Particle Accelerators Identified
- Perovskite Solar Cells
- Why We Sleep
- Our Microbes, Our Health
- In Vaccine Design, Looks Do Matter
Approaches to Overcome Self Tolerance
ACT and Checkpoint Therapies

Adoptive Cell Therapy: 3 Approaches in Advanced Development

Science Trans Med, 2015
Questions facing the CAR field

- Is long term persistence of CAR cells desired?
- Which approaches give durable persistence of CARTs?
- What is the best vector to introduce the CAR: retroviral vector or lentiviral vector?
- What is the optimal T cell type and composition of the infused product?
- How can checkpoint therapy and CAR T therapy be combined?

CAR T Cells: they are bionic!

- CAR scFv or TCR can reprogram specificity of T cells for tumor target. Specificity is important to avoid toxicity.

- CAR signaling domains can reprogram T cell metabolism. This can enhance survival in tumor microenvironment and effector function:
  - CD28 domains: enhance glycolysis via “Warburg” effect. This leads to enhanced effector function and decreased persistence.
  - 4-1BB domains: enhance mitochondrial biogenesis, and are associated with enhanced persistence.

Omkar Kawalekar
Immunity, in press
Adult Chronic Leukemia Study Overview*

1. Leukapheresis
2. T-cell activation/transduction
3. Modified T-cell expansion
4. Chemotherapy
5. Modified T-cell infusion

* ClinicalTrials.gov #NCT01029366
## CTL019 Phase I Trial for r/r CLL: 5 yr follow up

### Summary of patient baseline characteristics

*N= 14 patients, protocol 04409 (NCT01029366)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statistics, N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>14</td>
</tr>
<tr>
<td><strong>Age at infusion in years</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>66.9 (8.1)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>66 (51-78)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (85%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (14%)</td>
</tr>
<tr>
<td><strong>Number of prior therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.3 (2.8)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>5 (1-11)</td>
</tr>
<tr>
<td><strong>P53 or 17p deletion</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (43%)</td>
</tr>
<tr>
<td><strong>IGHV mutation</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>

- Overall response rate: 57%
- CR 4/14 (28%)
- PR 4/14 (28%)
- NR 6/14 (43%)

Long term persistence and expression of CTL019 in CLL patients with durable remission

Persistence for first year after infusion

IGH deep sequencing analysis: eradication of malignant CLL clone

Durable anti-tumor activity

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Source</th>
<th>Timepoint</th>
<th>Total reads of IgH</th>
<th>Total unique IgH reads</th>
<th>Tumor clone reads</th>
<th>CLL clone % of total</th>
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</thead>
<tbody>
<tr>
<td>01 PB</td>
<td>baseline</td>
<td>408,579</td>
<td>48</td>
<td>407,592</td>
<td>99.76%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo 6</td>
<td>285,305</td>
<td>7362</td>
<td>0</td>
<td>0.00%</td>
<td></td>
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<tr>
<td></td>
<td>yr 1</td>
<td>41</td>
<td>12</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yr 3</td>
<td>174</td>
<td>6</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yr 3.5</td>
<td>123</td>
<td>8</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo 1</td>
<td>179</td>
<td>3</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>01 BM</td>
<td>mo 6</td>
<td>202,535</td>
<td>4451</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo 12</td>
<td>18,506</td>
<td>231</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo 24</td>
<td>88</td>
<td>2</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>02 PB</td>
<td>baseline</td>
<td>1,385,340</td>
<td>4544</td>
<td>1,285,862</td>
<td>92.82%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo 6</td>
<td>25,041</td>
<td>38</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mo 32</td>
<td>88</td>
<td>8</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yr 3</td>
<td>160</td>
<td>8</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yr 4</td>
<td>212</td>
<td>10</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>02 BM</td>
<td>yr 1</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>yr 2</td>
<td>601</td>
<td>25</td>
<td>0</td>
<td>0.00%</td>
<td></td>
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</table>
Persisting CTL019 cells remain polyfunctional > 2 years after infusion: a living drug!

- 1.5% CAR cells
- Mostly CD8+

**CTL019 function 1039 days after infusion:**

- PBMC reisolated from subject 02. Cells expressing CAR identified with anti-idiotype
- Stimulated for 6 hours with CD19+ or control tumor.cells. Cytokine induction and degranulation

Jos Melenhorst
Simon Lacey
What about CART19 in r/r ALL?

>200 patients with CLL, ALL, NHL, MM have gotten CTL019

- For ALL, 59 r/r pediatric and young adult ALL pts: 55 of 59 in CR at 1 mo (93%)
- 6 went to subsequent transplant
- 6-month RFS: 76%
- No relapses past 1 year

updated at ASH 2015
Please excuse Emily from school - she was with me!

THE PRESIDENT
State of the Union: Obama Announces Cancer 'Moon Shot'

1/12/2016 10:15PM

President Obama announced a new national effort to cure cancer in his final State of the Union address, to be headed by Vice President Joe Biden, who lost his son to cancer in 2015. Photo: Getty
R/R ALL Pt #1: Deep Molecular Remission After CTL019

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Timepoint (day)</th>
<th>Number of input genomes (cell equivalents)</th>
<th>Total TCRb reads</th>
<th>Total IGH reads</th>
<th>Dominant clone reads</th>
<th>Tumor clone frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>-1</td>
<td>111,340</td>
<td>525,717</td>
<td>189</td>
<td>185</td>
<td>97.88</td>
</tr>
<tr>
<td>Marrow</td>
<td>-1</td>
<td>317,460</td>
<td>348,687</td>
<td>59,791</td>
<td>59,774</td>
<td>99.97</td>
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<tr>
<td></td>
<td>23</td>
<td>362,819</td>
<td>1,712,507</td>
<td>37</td>
<td>33</td>
<td>89.19</td>
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<tr>
<td></td>
<td>87</td>
<td>645,333</td>
<td>425,128</td>
<td>10</td>
<td>10</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>952,381</td>
<td>800,670</td>
<td>45</td>
<td>0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

- No chemotherapy was given
  → ~ 5-log tumor reduction following CTL019
- 6 months for all tumor to become unmeasurable using sensitive assays.
  Other patients: rapid tumor clearance
- Points to advantage of long lasting CAR T cells

Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell ALL (ELIANA)

Stephan Grupp, Children’s Hospital of Philadelphia
Stella Davies, Cincinnati Children’s Hospital
Christian Capitini, University of Wisconsin
Ted Laetsch, Children’s Medical Center of Dallas
Doug Myers, Children’s Mercy Kansas University
Enelda Nemecek, Oregon Heath & Science University
Krysta Schlis, Stanford University
Michael Verneris, University of Minnesota
Alan Wayne, Children’s Hospital Los Angeles
Gary Yanik, University of Michigan
Paul Martin, Duke University
Francoise Mechinaud, Royal Children’s Hospital (Australia)
Henrique Bettencourt, Hospital St. Justine (Canada)

Clinicaltrials.gov NCT02435849
In pediatric and adult ALL, there is a >90% CR at 1 month.

To date, there have been 15 relapses in the first 50 patients given CART19:
- No patient has relapsed beyond year
- 15 patients have relapsed
- Early relapses associated with loss of B cell aplasia (n=5)
- Late relapses are associated with target loss (CD19 negative leukemia, n=10)

CART19 Toxicities

- **B cell aplasia**
  - observed in all responding patients to date
  - managed with replacement therapy

- **Tumor lysis syndrome (TLS)**
  - may be delayed for 20 to 50 days post infusion

- **Cytokine release syndrome (CRS)**
  - reversible, on-target toxicity
  - Severity related to tumor burden: Treat MRD as outpatient?

- **Macrophage activation syndrome (HLH / MAS)**
  - elevated serum ferritin (>500,000 ng/ml), CRP, D-dimer
  - elevated cytokines: IL-6, IFN-gamma
  - Reversed with tocilizumab
Tocilizumab Anti-Cytokine Therapy for Cytokine Release Syndrome

Temp (deg F)

7. 7, 7, 7, 8, 8, 9, 9, 9, 10, 10, 10, 10, 10, 11, 11, 11, 11, 12, 12, 12, 12, 12, 13, 13, 13, 14, 14, 14, 14, 12a, 6a, 12p, 6p, 12a, 6a, 12p, 6p, 12a, 6a, 12p, 6p, 12a, 6a, 12p, 6p, 12a, 6a, 12p, 6p

Tocilizumab, d10

CLL Pt 04409-09

David Porter, MD
Persistence for first year after infusion

01-CR 02-CR 09-CR 10-CR
03-PR 05-PR 12-PR 22-PR
06-NR 07-NR 14-NR 17-NR
18-NR 25-NR

Lessons Learned from Patient #10

- Progeny derived from a single CTL019 TCRVβ5.1+ CD8+ T cell were responsible for the eradication of massive tumor burden in patient #10.

- *Still to be learned:* The effects of *Tet2* disruption on normal CD8+ T cell function are largely unknown. *Tet2* is driver in CD4+ angioimmunoblastic lymphoma and Tfh cells.

- Since *Tet2* can increase HSC stem cell renewal, would inhibition or intentional disruption of *Tet2* increase CAR T cell proliferation and/or function?
CD19: An Ideal Tumor Target in B-Cell Malignancies

• CD19 expression is generally restricted to B cells and B cell precursors\(^1\)
  – CD19 is not expressed on hematopoietic stem cells\(^1\)

• CD19 is expressed by most B-cell malignancies\(^1\)
  – CLL, B-ALL, DLBCL, FL, MCL\(^1\)

• Antibodies against CD19 inhibit tumor cell growth

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CAR T Therapy for Multiple Myeloma

- What about CD19 as a target?
  - CD19 is expressed on normal bone marrow plasma cells.
  - Multiple myeloma is classified as “CD19 negative”

- BCMA (B-cell maturation antigen): trial open and accruing

Garfall et al, NEMJ 2015
Multiple factors impact safety and efficacy of CAR T cells:
Summary: CAR T Cells

- Durable remissions >5 years in CLL after CTL019 infusion
- Fate mapping indicates that a single CTL019 cell is sufficient to eradicate large tumor burden in CLL
- Durable remissions in ALL >3 years after CTL019 infusion
- Promising responses in myeloma after CTL019 infusions
- CAR T plus checkpoint blockade…
Health Care Challenges

Issues
- Patient specific “n of 1”
- Blood bank model?
- Central manufacturing?

Chris Mason et al, Regen Med. 2011
Levine and June, Nature. 2013
Colleagues and Collaborators: Thank you!

ACC Translational Research
Anne Chew
Regina Young
Dana Hammill
Katie Marcucci
Joseph Fraietta
Omkar Kawalekar
Avery Posey
John Scholler
Shannon McGettigan
Biliang Hu
Anthony Lin
Mauro Castellarin
Gabriela Plesa

T Cell Engineering
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Jiangtao Ren
Chongyun Fang
Xiaojun Liu
Shuguang Jiang

CVPF
Bruce Levine
Don Siegel
Zoe Zheng
Suzette Arostegui
Theresa Colligon
Clare Taylor
Anne Lamontagne
Alex Malykhin
Neel Manvar
Matt O’Rourke

PDCS
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Jos Melenhorst
Simon Lacey
Felipe Bedoya

Johnson Lab
Laura Johnson
Alex Cogdill
Alina Boesteanu

PENN Medicine
David Porter
Noelle Frey
Stephen Schuster
Edward Stadtmauer
Al Garfall
Marcela Maus
Lynn Schuchter

Gill Lab
Saar Gill
Saad Kenderian
Marco Ruella
Olga Shestova

Powell Lab
Daniel Powell

Albelda Lab
Edmund Moon

Milone Lab
Michael Milone
Roddy O’Connor
Saba Ghassemi
Enxiu Wang

Stephan Grupp
David Barrett
Shannon Maude
David Teachey

Novartis
Usman Azam
Hans Bitter
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Glenn Dranoff
Phil Gotwals
Bill Sellers