Status and Update of HIV Gene Therapy Clinical Trials

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University of Pennsylvania
## Disclosures

<table>
<thead>
<tr>
<th>Relations that could be relevant for the meeting</th>
<th>Company names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsorship or refund funds (to Upenn)</td>
<td>• Merck, Viiv, Gilead, Inovio, Genone, Sangamo</td>
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<tr>
<td>Payment or other financial remuneration</td>
<td>• Merck, Viiv, Gilead</td>
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<tr>
<td>Shareholder rights</td>
<td></td>
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<tr>
<td>Other relations</td>
<td></td>
</tr>
</tbody>
</table>
Gene therapy for HIV and cancer. Two fields complementing each other

Historical overview of HSC gene therapy

Cynthia E. Dunbar et al. Science 2018;359:eaan4672
Lentiviral vectors led the way to CAR-T cell therapy

A Phase II Randomized Study of HIV-Specific T-Cell Gene Therapy in Subjects with Undetectable Plasma Viremia on Combination Antiretroviral Therapy


Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia


Clinical studies

Discovery of T Cells
Discovery of NK Cells
Retroviral Vectors
Primary T Cell Engineering
CD28/CD3ζ CAR
CD19 as CAR Target
T-body (CD3ζ CAR)
4-1BB/CD3ζ CAR

Scientific advances

Cynthia E. Dunbar et al. Science 2018;359:eaan4672
The 2 HIV cures have been “gene therapy”

<table>
<thead>
<tr>
<th>Berlin Patient</th>
<th>London Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Malignancy</strong></td>
<td>Acute Myeloid Leukemia, diagnosed June 2006</td>
</tr>
<tr>
<td><strong>Therapies Prior to CCR5Δ32</strong></td>
<td>Induction (2X), and consolidation (1X) chemotherapy</td>
</tr>
<tr>
<td><strong>Stem Cell Donor</strong></td>
<td>10/10 HLA match + CCR5Δ32</td>
</tr>
<tr>
<td><strong>Transplant #1</strong></td>
<td>February 2007. Conditioning included fludarabine, cytarabine, amsacrine (FLAMSA), cyclophosphamide, rabbit antithymocyte globulin (ATG), 400-cGy TBI</td>
</tr>
<tr>
<td><strong>ART Discontinued</strong></td>
<td>Day of transplantation</td>
</tr>
<tr>
<td><strong>ART-Free HIV-1 Remission</strong></td>
<td>Over 12 years</td>
</tr>
<tr>
<td><strong>GVHD</strong></td>
<td>Grade I following first transplant</td>
</tr>
</tbody>
</table>

Although they may be “a cure” it is not “the cure”

### Outcomes of BMT with delta 32 donors

<table>
<thead>
<tr>
<th>Location of Transplantation</th>
<th>Age of Patient yr</th>
<th>Type of Cancer</th>
<th>Type of Graft</th>
<th>Outcome after Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin†</td>
<td>40</td>
<td>Acute myeloid leukemia</td>
<td>HLA-matched unrelated</td>
<td>Alive after 7 yr, no viral rebound, no ART</td>
</tr>
<tr>
<td>Utrecht, the Netherlands‡</td>
<td>53</td>
<td>Myelodysplastic syndrome</td>
<td>Combined haploidentical bridge with umbilical-cord blood</td>
<td>Died from relapse of the myelodysplastic syndrome and pneumonia after 2 mo</td>
</tr>
<tr>
<td>Münster, Germany§</td>
<td>51</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-mismatched unrelated</td>
<td>Died from infection after 4 mo</td>
</tr>
<tr>
<td>Essen, Germany¶</td>
<td>30</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-matched unrelated</td>
<td>CXXR4-tropic HIV-1 rebound, died from relapse of non-Hodgkin’s lymphoma after 12 mo</td>
</tr>
<tr>
<td>Minneapolis§</td>
<td>12</td>
<td>Acute lymphoblastic leukemia</td>
<td>Umbilical-cord blood</td>
<td>Died from GVHD after 3 mo</td>
</tr>
<tr>
<td>Santiago, Chile§</td>
<td>46</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-matched related</td>
<td>Died from pneumonia shortly afterward</td>
</tr>
<tr>
<td>Barcelona§</td>
<td>37</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Combined haploidentical bridge with umbilical-cord blood</td>
<td>Died from relapse of non-Hodgkin’s lymphoma after 3 mo</td>
</tr>
</tbody>
</table>

* ART denotes antiretroviral therapy, and GVHD graft-versus-host disease.
† Data are from Hütter et al.¹
‡ Data are from Kwon et al.³
§ Data are from a personal communication with the transplantation center.
¶ Data are from Kordelas et al.²

1. Traditional gene therapy approaches

Engineering cells resistant to HIV

**STEPS**

1. Isolate your cell of interest (CD4 or CD34)
2. Ex vivo modification/s to render them resistant to HIV
3. Reinfuse
4. In vivo positive selection during ATI

Modification to make it simpler: in vivo modification using vectors with the same resistance to HIV features

Gene therapy trials with Stem cell transplantation for lymphomas

- Autologous CD4+ T lymphocytes and CD34+
- Cal-1 lentiviral vector
- shRNA against CCR5 and C46

**Academy to Military Medical Sciences, China**

CRISPR CCR5 modified CD34+ cells

**AMC**

Stem cells gene-modified with CCR5 shRNA/TRIM5alpha/TAR decoy

**City of Hope**

Stem cells gene-modified to encode multiple anti-HIV RNAs (rHIV7-shI-TAR-CCR5RZ)

Mol Ther Methods Clin Dev. 2019 Feb 26;13:303-309
Gene therapy trials with Stem cell transplantation and T cells for people without medical need

<table>
<thead>
<tr>
<th>Gene Therapy</th>
<th>Target</th>
<th>Cell</th>
<th>Conditioning</th>
<th>Company (Univ)</th>
<th>Clin.gov</th>
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<tbody>
<tr>
<td>Cal-1</td>
<td>CCR5</td>
<td>CD34</td>
<td>Busulfan</td>
<td>Calimmune (City of Hope)</td>
<td>NCT01734850</td>
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<tr>
<td></td>
<td>C46</td>
<td></td>
<td></td>
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<tr>
<td>SB-728-T</td>
<td>CCR5</td>
<td>CD4/8</td>
<td>CTX</td>
<td>Sangamo (Case)</td>
<td>NCT03666871</td>
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<tr>
<td>C34-CXCR4</td>
<td>CXCR4</td>
<td>CD4/8</td>
<td>NA</td>
<td>Sangamo (Penn)</td>
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<tr>
<td>SB-728mR-HSPC</td>
<td>CCR5</td>
<td>CD34</td>
<td>Busulfan</td>
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<tr>
<td>shRNA</td>
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<td>CD34</td>
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<td>Kanglin Biotech (Shanghai PH)</td>
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A Phase I Study of Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases SB-728 in HIV-Infected Patients

10B CCR5 ZFN treated CD4 T cells Are expanded Of which only 5-10% CCR5 defective Infused in a human that has between 300B and 600B CD4 T cells
• CCR5 ZFN frequency correlated with time to rebound and viral set point
• Survival advantage of the genetically modified cells in the presence of HIV

Sangamo reported other Δ32 CCR5 heterozygotes (2) treated with CCR5 ZFNs demonstrated sustained control of HIV-1 in the absence of HAART. Control is some individuals was observed for more than 300 days
Can we do better, increase the engraftment of genetically modified cells?

Cohort 1
- ZFN no CTX
- N=3

If no DLT, if DLT dose will be maintained

Cohort 2
- WT CCR5
- Open simultaneously

Cohort 3
- Δ32 heterozygous

ZFN + CTX
- 1g/m²
- N=3
- 1.5g/m²
- N=3

ZFN + CTX
- 1g/m²
- N=3
- 1.5g/m²
- N=3
Schedule of Events

**STEP 1**
Baseline evaluation manufacturing

**STEP 2**
ZFM CD4 alone
ZFN CD4 + 1 g/m² CPM
ZFN CD4 + 3 g/m² CPM

**STEP 3**
Analytical Treatment Interruption

**STEP 4**
ART Monthly visits until HIV BLQ

Leukapheresis
Rectal biopsy
Safety labs
HIV RNA

Cell infusion (d 0)
Cyclophosphamide (d-2)

16 week analytical treatment interruption

Successful ART

End of study
Apheresis- 6 Months after ART control

www.iasociety.org
Infusion of CCR5 ZFN Treated Cells Results in a Delay of Viral Rebound

Time to Virologic Rebound (VL > 200 copies/ml)

- ACTG (N=93)
- Cohort 1 (N=3)
- Cohort 2 (N=6)
- Cohort 3 (N=4*)
*Excludes Pt 305

Time since ATI (weeks)

Proportion Suppressed

p = 0.03

Tebas et al. CROI 2019
CD4 T cells with CCR5 ZFN disrupted alleles durably persist
Why only a small fraction of modified cells should have an effect?

Improved HIV-specific immune after infusion of CCR5 ZFN treated CD4 T cells

CD4 reconstitution and reduction of reservoir in HIV-positive patients following a single infusion of CCR5 modified autologous CD4 T cells (SB-728-T)


However, no effect on the replication competent reservoir

Conclusions:

1. Manufacturing T cells with ZFN disrupted alleles is feasible and can be safely infused into HIV infected individuals.

2. Infusion of CCR5 ZFN T cells can delay viral rebound.

3. These cells stably engraft. Some individuals from our initial trial still maintain >1% of T cells with CCR5 ZFN disrupted alleles. CTX helped engraftment but the effect was modest.

4. We observed improved CD8 but not CD4 T cell responses after CD4 T cell infusions.

5. The HIV reservoir was unaffected by these cell infusions but
2. New gene therapy approaches
Engineering cells that produce antiviral proteins


3. New gene therapy approaches. CAR T Engineering the “kill” (and protecting the cells at the same time)

R.S. Leibman, J.L. Mol. Ther., 23 (2015), pp. 1149-1159
BEAT HIV CAR T trial

CD4 CAR+ CCR5 ZFN- modified T cell

Weeks: -15 0 (d1) 4 8 12 16 20 24 28 32 36 M3 M6 M9

Restarting rule (HIV c/ml):
- > 200
- >1,000 for 6 weeks
- > 200

N=6
- HIV+ Treated for at least 1 year
- VL<50 c/mL for at least 6 months
- CD4 > 450 cells/μL

N=6
- Cell Manufacturing
- ART+ CAR/ZFN
- ATI +CAR/ZFN
- ART
- ART

Cell infusion:
- Screening/entry
- Safety labs/CD4
- VL
- Leucopheresis/rectal biopsy

Optional continued ATI (CD4/VL every 2 weeks)

STEP Weeks: -15 0/0 4 8/0 4 8 12 16/0 4 8 12 M3 M6 M9
Study objectives

• Primary
  – Safety and tolerability

• Secondary objectives
  – Effects on HIV reservoir
  – Effects on CD4 T cell count
  – Antiviral effects
  – Evaluate persistence, frequency, and tracking
  – Evaluate emergence of viral resistance
  – Effects on immune function
  – Examine transcriptional profile
The risks of CAR T cell therapy

Neurotoxicity
- Delirium
- Aphasia
- Seizures
- Cerebral edema
- Intracranial hemorrhage

Hemodynamic instability
- Tachycardia
- Hypotension
- Capillary leak syndrome

Organ dysfunction
- AST and ALT elevation
- Hyperbilirubinemia
- Respiratory failure

Carl H. June et al. Science 2018;359:1361-1365
Long term safety of this particular CAR T

RESEARCH ARTICLE

ADOPTIVE T CELL TRANSFER

Decade-Long Safety and Function of Retroviral-Modified Chimeric Antigen Receptor T Cells

John Scholler,¹* Troy L. Brady,²* Gwendolyn Binder-Scholl,¹ Wei-Ting Hwang,³ Gabriela Plesa,¹ Kristen M. Hege,⁴ Ashley N. Vogel,¹ Michael Kalos,¹ James L. Riley,² Steven G. Deeks,⁵ Ronald T. Mitsuyasu,⁶ Wendy B. Bernstein,⁷ Naomi E. Aronson,⁷⁺ Bruce L. Levine,¹ Frederic D. Bushman,²⁺ Carl H. June¹⁺

<table>
<thead>
<tr>
<th>Annual</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>Total</th>
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<td>20</td>
<td>25</td>
<td>33</td>
<td>31</td>
<td>28</td>
<td>25</td>
<td>24</td>
<td>13</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>212</td>
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<td>Tested</td>
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<td>15</td>
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<td>4</td>
<td>1</td>
<td>221</td>
</tr>
</tbody>
</table>

Science translational medicine. 2012 May 2;4(132):132ra53-. 
4. New gene therapy approaches
Editing out HIV from the reservoir (in vivo).
Using CRISPR and LASER ART

Gene therapy and HIV cure

- The N=2 cases of remission/functional cure support our efforts in finding a cure for HIV.
- Advances in immunotherapy, cell and gene engineering and delivery systems will make these approaches easier to implement in the future.
- Gene therapy may be a part of a combination approach to HIV cure.
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Carl June
Bruce Levine
Jim Riley
Richard Carroll
Julie
Liz Veloso

Wistar Institute
Luis Montaner

Penn CFAR
Clinical Core
Ian Frank

Immunology Core
John Wherry
Hong Kong
Kevin Gayout

Viral/Molecular core
Farida Shaheen
Katie Bar
Ron Collman
Rick Bushman
Jim Hoxie

ViRxsSys
Sangamo
Adaptaminue
Tmunity

Penn CTRC

NIH-NIAID