The Philadelphia patient*  

*I did not pick the title
The 4 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>Hodgkin’s Lymphoma, diagnosed December 2012</td>
</tr>
<tr>
<td><strong>Therapies Prior to CCR5Δ32</strong></td>
<td>First line and salvage chemotherapies including anti-CD30</td>
</tr>
<tr>
<td>Induction (2X), and consolidation (1X) chemotherapy</td>
<td></td>
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<tr>
<td><strong>Stem Cell Donor</strong></td>
<td>9/10 HLA match + CCR5Δ32</td>
</tr>
<tr>
<td>10/10 HLA match + CCR5Δ32</td>
<td></td>
</tr>
<tr>
<td><strong>Transplant #1</strong></td>
<td>May 2016. Conditioning included lomustine, ara-C, cyclophosphamide, etoposide (LACE), and anti-CD52</td>
</tr>
<tr>
<td>February 2007. Conditioning included fludarabine, cytarabine, ara-c, cyclophosphamide, rabbit antithymocyte globulin (ATG), 400-cGy TBI</td>
<td></td>
</tr>
<tr>
<td><strong>ART Discontinued</strong></td>
<td>16 months post-transplantation</td>
</tr>
<tr>
<td>Day of transplantation</td>
<td></td>
</tr>
<tr>
<td><strong>Transplant #2</strong></td>
<td>N/A</td>
</tr>
<tr>
<td>March 2008. Conditioning included cytarabine, gemtuzumab ozogamicin (anti-CD33), 200-cGy TBI</td>
<td></td>
</tr>
<tr>
<td><strong>Immunosuppression</strong></td>
<td>Cyclosporine A, short-course methotrexate. &lt;1 year treatment.</td>
</tr>
<tr>
<td>Cyclosporine A, methylprednisolone, mycophenolate mofetil, ended 38 months post-transplantation. &gt;3 years treatment.</td>
<td></td>
</tr>
<tr>
<td><strong>GVHD</strong></td>
<td>Grade I, 77 days post-transplant</td>
</tr>
<tr>
<td>Grade I following first transplant</td>
<td></td>
</tr>
<tr>
<td><strong>ART-Free HIV-1 Remission</strong></td>
<td>18 months</td>
</tr>
<tr>
<td>Over 12 years</td>
<td></td>
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</tbody>
</table>

They tend to be named after the city where the intervention was done

The Philadelphia patient is not a “cure”
CCR5 modification. Can we do better, increase the engraftment of genetically modified cells by conditioning with CTX? Can you avoid AD5 vectors?
Schedule of Events

- **Leukapheresis**
- **Rectal biopsy**
- **Safety labs**
- **HIV RNA**
- **Cell infusion (d 0)**
- **Cyclophosphamide (d -2)**

**STEP 1**
Baseline evaluation manufacturing

**STEP 2**
SB-728mR T ± CTX
- Alone
- CTX 1 g/m²
- CTX 1.5 g/m²

**STEP 3**
Analytical treatment interruption

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

Successful ART

16 week analytical treatment interruption

Successful ART

-10 weeks

0 1 2 3 4 6 8 9 10 12 14 16 20 24 >48 weeks

weeks

weeks

weeks
The frequency of modification is similar using mRNA
Is the delay related to effects on the reservoir?
Effects on the HIV reservoir (IPDA, Accelavir)

A

5' defective viruses per million CD4+ T cells

P = 0.63

B

3' defective viruses per million CD4+ T cells

P = 0.14

C

Intact viruses per million CD4+ T cells

P = 0.54

Before After

202

204

205

206

301

302

303

304

305
If there are no effects on the reservoir, why there is a delay in rebound?

We looked at the HIV-specific CD8+ T cell gag responses before and after against multiple peptide pools.
Lower viremia
Greater ATI duration
Are the modified CD8 putting pressure on the virus?
Engineering T cells to redirect specificity from peptide/MHC to HIVEnvelope

HIV-infected cell

HIV-specific CAR T cell

Chimeric Antigen Receptor

Mitigate the possibility of HIV escape
Avoid MHC downregulation

Costimulation (4-1BB, CD28)

TCR signaling component

HIV entry receptor
A Pilot Study of T Cells Genetically Modified by CCR5-specific ZFNs and CD4 Chimeric Antigen Receptor in HIV-infected Subjects (NCT03617198)

**Steps**

1. **Cell Manufacturing**
   - Duration: -15 weeks

2. **ART + CAR/ZFN**
   - Duration: 0 weeks
   - Cohort 1: 1 day
   - Cohort 2: 8 weeks

3. **Treatment Interruption + CAR/ZFN**
   - Duration: 3 weeks
   - Cohort 1: 16 weeks
   - Cohort 2: 24 weeks

4. **Treatment Interruption + CAR/ZFN**
   - Duration: 4 weeks
   - *Only if HIV VL remains ≤1000 copies/ml at end of Step 3

5. **ART**
   - Duration: 5 weeks
   - Monthly visits until HIV BLQ

**WEEKS**

- Cell infusion at Day 0
- Cohort 1- engraftment (step 2) of 1 day before ATI
- Cohort 2- engraftment (step 2) 8 weeks before ATI

1. To what extent does ongoing HIV replication contribute to the maintenance of the HIV reservoir?
2. Can engineered T cells restore functionality to endogenous HIV-specific T cell populations?
3. Can engineered T cells provide durable control of HIV replication?
4. When is the best time to do the ATI?
Results

In **blue** participants that started ATI 1 day after the infusion
In **red** participants that waited for 8 weeks
Results
Participant 205, 301 and 2-third time is a charm?

<table>
<thead>
<tr>
<th>Study ID#</th>
<th>Sex</th>
<th>Race</th>
<th>Age at Consent</th>
<th>Historic VL copies/mL</th>
<th>Historical VL Date</th>
<th>Years HIV infection</th>
<th>Screening CD4 abs (cells/μl)</th>
<th>Viral Load Set Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4CAR-ZFN-02</td>
<td>M</td>
<td>Caucasian</td>
<td>58</td>
<td>165,810</td>
<td>08/24/2009</td>
<td>10</td>
<td>1785</td>
<td>165,810</td>
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</table>

Viral Load: CD4ZFN-02

Viral Load SB728mR-301

The Journal of Clinical Investigation

CCR5-edited CD4+ T cells augment HIV-specific immunity to enable post-rebound control of HIV replication

Pablo Tebas, Julie K. Jadlowksy, Pamela A. Shav, Lifeng Tian, Erin Esparza, Andrea L. Brennan, Sung Yong Kim, Soo Yu Naing, Max W. Richardson, Ashley N. Vogel, Colby R. Maidim, Yong Hong, Xiaojun Liu, Simon F. Lacey, Anya M. Bauer, Felicity Mampoe, Lee R. Richman, Carl Lee, Dale Ando, Bruce L. Levine, David L. Portnoy, Yangbing Zhao, Don L. Siege, Katharine J. Bae, Carl H. June, and James L. Riley
Conclusions and questions

Safety: So far so good

Persistence: this is a big problem in the absence of antigen

How can we expand the CAR T cells?

Trafficking

Protection. A CD4 CAR makes the cell susceptible to HIV. Best strategy for protection

Best methods for genome editing

Best CAR signaling

Improving CAR persistence and effector function: Dual CARs
Future directions: ACTG proposal: Dual CAR plus vaccination
Acknowledgements

Penn ACTU
   Larisa/Amber/Jenna/Mark/Su Kim
   Joe Quinn/Eileen Donaghy/Jamie
   Rob Roy MacGregor

Jacoby Medical Center
   David Stein
   Angelo Seda

U. Penn Abramson Inst.
   Carl June
   Bruce Levine
   Jim Riley
   Richard Carroll
   Julie Jadlowsky
   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

ViRxSys
Sangamo
Adaptaminue
Tmunity
Penn CTRC
NIH-NIAID