Approaching a Cure for AIDS

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Defining an AIDS Cure

Definition: “Treat a disease such that the patient no longer needs to continue treatment, as opposed to suppression or management of the disease as is presently required in diabetes, rheumatoid arthritis, and HIV.” *

Specific: Functional vs. sterilizing cures

*Fauci A. XVIIth International AIDS Conference, Mexico City, Aug 3-8, 2008, Abst WES9101
We want to cure HIV.

“Viruses can’t be cured.”

“Viruses can’t be cured...so far”

AIDS Cure Research
For Everyone

• In 2009, NIAID spent $41 million on HIV cure research, 3% of budget
• (~$600 million spent on vaccine research)
• amfAR filling the gaping hole

A Cure for AIDS

• AS Fauci: “We need a cure for AIDS.”*
• ART is a life-long commitment
• Current ART, and likely every newly developed antiretroviral drug, will have long-term, potentially life-limiting, adverse effects
• 2.7 million people were newly HIV infected in 2007, with ART reaching only 30% of those who needed it
• It is unlikely that we can treat our way out of this pandemic: For every person started on ART, 2-3 are newly infected

*Fauci A. XVIIth International AIDS Conference, Mexico City, Aug 3-8, 2008, Abst WES9101
“The U.S. spends about $20 billion every year on AIDS (both for programs in the U.S. and globally). The money is keeping millions of people alive around the world and preventing millions of infections. But a cure is needed, and it is unacceptable that something less than 0.5% (less than about $100 million) of U.S. spending on AIDS is funding AIDS cure research.”

-The AIDS Policy Project, 2010
Low-level Persistent Viremia in Patients on Suppressive ART

![Graph showing plasma HIV-1 RNA levels over time.](chart.png)


FOUR APPROACHES TO A CURE FOR AIDS

1. **Change a person’s immune system**
   - Alter a person’s immune system so that cells normally vulnerable to HIV infection are rendered invulnerable. The major focus for such research is the HIV co-receptor CCR5, and there are two approaches: a stem cell transplant with a CCR5-/- donor (the “Berlin patient”), and gene therapy to render a person’s own stem cells CCR5-/-.

2. **Identify and activate HIV reservoirs**
   - Induce active HIV replication in long-lived, latently-infected HIV cells so that they can be detected and killed.

3. **Selectively kill latently-infected HIV reservoirs**

4. **Treatment intensification**
   - Some studies suggest that very low levels of HIV replication (<1 copy/ml plasma) persist despite HAART, in peripheral blood and/or tissue reservoirs (such as the gut and CNS). This may contribute to maintenance of a latent state of infection, and be amenable to addition of new anti-HIV drugs.
Chemokine Receptors and HIV-1 Cell Tropism

Homozygous Δ32 Deletion in 2nd extracellular loop of CCR5 in humans leads to HIV-1 resistance

“The case was presented to scientists earlier this year at the Conference on Retroviruses and Opportunistic Infections. In September, the nonprofit American Foundation for AIDS Research, amFAR, convened a small scientific meeting on the case. ... The scientists agreed that the patient is ‘functionally cured.’”

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**Case report: patient’s history**

40-year-old patient

- HIV infection since ’96
- HAART since 2002
- HIV-1 RNA < detection limit
- CD4+ T-cells 300–400 /μl
- No AIDS defining illnesses

Donor request: 232 HLA identical!

- AML
- FAB M4
- 46XY

Spring 2006 weakness

June ’06 anemia

July ’06 pancytopenia
• Chemotherapy:
  - fludarabine (30mg/m²)
  - araC (2g/m²)
  - amsacrine (topoisomerase II inhibitor, 100mg/m²)
  - cyclophosphamide (60mg/kg)
• Anti-thymocyte globulin (20mg/kg)
• Total Body Irradiation (2-4 Gy)
• GVHD prophylaxis: cyclosporine A, mycophenolate mofetil

HAART continued: efavirenz, FTC, tenofovir
Treatment of HIV-1 by allogeneic CCR5Δ32/Δ32 SCT

Figure 1
PCR genotyping patterns of different CCR5-alleles. The patient displayed a heterozygous genotype before transplantation (day −1) and changed to CCR5-Δ32/Δ32 ongoing engraftment after day +61.

Immunohistology of intestinal mucosa (day +159)

CCR5+
Treatment of HIV-1 by allogeneic CCR5Δ32/Δ32 SCT

<table>
<thead>
<tr>
<th>Day</th>
<th>Source</th>
<th>cDNA env</th>
<th>cDNA LTR</th>
<th>Plasma viral load</th>
<th>Anti HIV-1/2 antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>PB</td>
<td>&gt;15</td>
<td>&gt;15</td>
<td>&lt;15</td>
<td>+</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+20</td>
<td>PB</td>
<td>5-15</td>
<td>5-15</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>+61</td>
<td>PB</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;15</td>
<td></td>
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<td>&lt;5</td>
<td>&lt;15</td>
<td>+</td>
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<tr>
<td>+97</td>
<td>PB/BM</td>
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<td>&lt;5</td>
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<tr>
<td>+145</td>
<td>RecB</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;15</td>
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<tr>
<td>+187</td>
<td>PB</td>
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</tr>
<tr>
<td>+285</td>
<td>PB</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;15</td>
<td>+</td>
</tr>
</tbody>
</table>


Serodeconversion

HIV-2
### ELISPOTs for interferon-γ (per 100,000 PBMCs)

<table>
<thead>
<tr>
<th></th>
<th>day -20</th>
<th>day +152</th>
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<tbody>
<tr>
<td>HIV</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>CMV</td>
<td>100</td>
<td>100</td>
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</tbody>
</table>

### Determination of patient’s virus

- **97.1% R5**
- **2.9% X4 oder dual**

- env6537s and 7264aenv565s

![Virus Determination Diagram]
“AIDS Patient is Reported Cured in Berlin with a Rare Treatment”

“It’s very nice, and it’s not even surprising,’ said Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases. ‘But it’s just off the table of practicality.’ [Yet] Doctors say the case gives hope for therapies that artificially induce the Delta32 mutation.”

<table>
<thead>
<tr>
<th>ETHNIC GROUP</th>
<th>ALLELE FREQUENCY (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish</td>
<td>13.7</td>
</tr>
<tr>
<td>Russian</td>
<td>13.6</td>
</tr>
<tr>
<td>Australian</td>
<td>11.8</td>
</tr>
<tr>
<td>British</td>
<td>11.7</td>
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<tr>
<td>Spanish</td>
<td>9.8</td>
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<td>French</td>
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<td>Italian</td>
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<tr>
<td>Greek</td>
<td>4.4</td>
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<tr>
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<tr>
<td>Pueblo/Cheyenne Indian</td>
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</tr>
<tr>
<td>Korean/Chinese</td>
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</tr>
<tr>
<td>African/African-American</td>
<td>0.0</td>
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<tr>
<td>Oceanic</td>
<td>0.0</td>
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</table>

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Sponsors</th>
<th>Vector</th>
<th>Transduced Genes Encode</th>
<th>Protocol</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerome Zack and Ronald Mitsuyasu, UCLA</td>
<td>Johnson &amp; Johnson Research, Sydney, Australia, NIH</td>
<td>Moloney murine leukemia virus</td>
<td>Ribozyme that targets HIV tat</td>
<td>CD34+ cells, no conditioning</td>
<td>74 patients in non-randomized, controlled phase II trial, Results expected early 2008</td>
</tr>
<tr>
<td>Carl June, University of Pennsylvania</td>
<td>VIRxSYS, Gaithersburg, Maryland, NIH</td>
<td>Modified HIV</td>
<td>Antisense that targets HIV env</td>
<td>CD34+ cells, no conditioning</td>
<td>Two studies with 65 patients, First results expected in fall</td>
</tr>
<tr>
<td>Carl June</td>
<td>Sangamo BioSciences, Richmond, California, NIH</td>
<td>Adenovirus</td>
<td>Zinc finger nucleases that target CCR5</td>
<td>CD34+ cells, no conditioning</td>
<td>12 patients, expected to start later this year</td>
</tr>
<tr>
<td>Donald Kohn, Children’s Hospital Los Angeles</td>
<td>NIH</td>
<td>Modified HIV</td>
<td>RevM10 that overrides HIV rev</td>
<td>CD34+ cells, partial ablation with busulfan</td>
<td>12 patients failing therapy expected to start in early 2008</td>
</tr>
<tr>
<td>John Rossi and John Zule, City of Hope, Duarte, California</td>
<td>NIH</td>
<td>Modified HIV</td>
<td>Short RNA against HIV rev and tat, ribozyme against CCR5, and TAR decoy against HIV Tat</td>
<td>CD34+ cells, no conditioning</td>
<td>5 patients with AIDS lymphoma, enrolling</td>
</tr>
<tr>
<td>Dorothee von Laer, Georg-Speyer-Haus, Frankfurt, Germany</td>
<td>Fresenius Biotech, Vision7 GmbH, EU</td>
<td>Moloney murine leukemia virus</td>
<td>Peptide that disrupts HIV’s gp41</td>
<td>CD34+ cells, partial ablation with chemotherapy</td>
<td>5 patients with AIDS lymphoma, start later this year</td>
</tr>
<tr>
<td>David Baltimore and Pamela Björkman, Caltech, Pasadena</td>
<td>Bill and Melinda Gates Foundation</td>
<td>Modified HIV</td>
<td>Lentiviral anti-HIV antibody</td>
<td>CD34+ cells</td>
<td>Mouse studies</td>
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<tr>
<td>Irvin Chen, UCLA</td>
<td>NIH</td>
<td>Modified HIV</td>
<td>Short interfering RNA that targets CCR5</td>
<td>CD34+ cells</td>
<td>Monkey studies</td>
</tr>
</tbody>
</table>

Cohen J. Science 2007; 317:612-614
Zinc-finger Nuclease (ZFN)-mediated Disruption of CCR5 and Protection from HIV-1 Infection


Reduction in Viremia and Selection for CCR5 ZFN-modified CD4+ T-Cells in Mice

Stable reduction of CCR5 by RNAi, with decreased susceptibility to SIV, through hematopoietic STC in rhesus macaques

An DS, et al. Proc Natl Acad Sci USA 2007;104:13110-13115

IV treatment with siRNA/scFvCD7-9R complexes prevents CD4+ T-cell loss and HIV replication in mice reconstituted with HIV+ human PBMCs

UPCOMING amfAR GRANT OPPORTUNITIES

Cycle 49 Exploring the mechanisms for HIV persistence and the potential for HIV eradication (=cure)

Cycle 49 Mathilde Krim Fellows in Basic Biomedical Research

Cycle 50 ARCHE renewal/continuation

A consortium is more than the sum of its parts:
• Test an FDA-approved drug in a small clinical trial
• Investigate tissue samples stored for 10 years

In-person meeting of ARCHE scientists June 18, 2010