Update on HIV Gene Therapy Clinical Trials

Jim Riley

The University of Pennsylvania has determined that Dr. Riley has a FCOI as the data presented here has been licensed to a company (Tmunity) in which he has an equity interest. The University is actively managing this conflict.
Can HIV be Cured? At least 2-3 people says Yes!

Timothy Ray Brown, London patient and maybe Dusseldorf patient proves that HIV can be cured.

However

Challenging to repeat because every patient is different.

Several patients have been enrolled in similar protocols and cure rate is low

Very intensive and high risk protocol-hard to imagine how this could be employed on a wide

But....HIV can be cured!
What is Gene Therapy and why is it a promising approach for HIV Cure strategies?

• Through 40 years of HIV research, we have learned much about the virus.

• Through the study of HIV infected individuals, we have gained insight into why some individuals control HIV replication better than others.

• By directly altering a person’s genome, we can attempt to convert someone who does not naturally control HIV replication to someone who does.
Active HIV gene therapy clinical trials

• A Study Evaluating the Safety of Cal-1 (LVsh5/C46) Drug Product in HIV-1 Infected Patient With High Risk Lymphoma
• Gene Therapy in Treating Patients With Human Immunodeficiency Virus-Related Lymphoma Receiving Stem Cell Transplant
• An Efficacy and Safety Study of shRNA-modified CD34+ Cells in HIV-infected Patients.
• VRC 603: A Phase I Dose-Escalation Study of the Safety of AAV8-VRC07 (VRC-HIVAAV070-00-GT) Recombinant AAV Vector Expressing VRC07 HIV-1 Neutralizing Antibody in Antiretroviral-Treated, HIV-1 Infected Adults With Controlled Viremia.
• CD4 CAR+ ZFN-modified T Cells in HIV Therapy
• CCR5-modified CD4+ T Cells for HIV Infection
• Safety of Transplantation of CRISPR CCR5 Modified CD34+ Cells in HIV-infected Subjects With Hematological Malignancies

711 active cancer gene therapy clinical trials- NIH clinical trial.gov (https://clinicaltrials.gov/)
Rationale behind T cell based gene therapy

• T cells are a white blood cells whose job is to eliminate viruses and tumors.

• T cells are absolutely ingenious and are able to customize their activity based on the type of pathogen they are trying to eliminate.

• T cells are designed to be unique. The T cells you have to fight HIV are different from the ones that fight the flu (or coronavirus).

• HIV preferentially kills HIV-specific CD4 T cells. This causes a lot of problems
  • Poorly functioning HIV-specific CD8 T cells
  • CD4 T cells are really important to producing effective antibody responses
Rationale behind T cell based gene therapy (cont)

• Thus, the goal of T cell gene therapy approaches is two-fold
  • Can we protect T cells so that they resistant to HIV infection?
    • CCR5 targeting
    • Fusion inhibitors
  • Can we take T cells that were specific to something else and now make them specific for HIV?
    • Chimeric antigen receptors (CARs)
Manufacturing CAR T cells

1. Leukapheresis
2. Counterflow centrifugal elutriation
3. ZFN, CRISPR
4. Virus
5. T cell
6. Bioreactor
7. Quality control samples
8. Engineered T cell concentration and wash
9. Final engineered T cell product

Modified from Feswick, Levine and June
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
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.
IF DELAY IN VIRAL REBOUND CORRELATES WITH THE NUMBER OF CCR5 DISRUPTED ALLELES, THEN IF WE ENGRAFT MORE T CELLS, WILL WE SEE IMPROVED CONTROL OF VIRAL REBOUND?
Schedule of Events

**STEP 1**
- Baseline evaluation
- Manufacturing

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

**STEP 3**
- Analytical Treatment Interruption
- Monthly visits until HIV BLQ

**STEP 4**
- ART
- End of study
- #2
- Apheresis
  - 6 Months after ART control

- **Leukapheresis**
- **Rectal biopsy**
- **Safety labs**
- **HIV RNA**
- **Cell infusion** (d 0)
- **Cyclophosphamide** (d -2)
- **Successful ART**
Infusion of CCR5 ZFN Treated Cells Results in a Delay of Viral Rebound

Proportion suppressed

Time since ATI (weeks)

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

p = 0.03
Three Individuals had sustained ATI with interesting viral load peaks and valleys

Viral Loads – extended ATI

- SB-728mR 203
- SB-728mR 301
- SB-728mR 303

ART restarted

Viral Load (copies/ml)

Week of ATI

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52
Improved HIV-specific immune after infusion of CCR5 ZFN treated CD4 T cells

Pre-infusion

CD107+ 0.34

IFN+ 0.18

Post-infusion ~6 months after ART

CD107+ 1.79

IFN+ 1.44

Gag pool 21; #303
Three Individuals (203, 301, 303) had sustained improvement in CD8 HIV-specific immune response
Number of replication competent HIV is unchanged by infusion of CCR5 ZFN treated T cells

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 T cell responses after CD4 T cell infusions and this correlates with durable control of HIV replication during ATI

5. The HIV reservoir was unaffected by these cell infusions

IPDA assay run by Accelevir
CD4-based chimeric antigen receptor confers HIV Envelope specificity

- Avoid MHC restriction & downregulation
- Unlikely that HIV will adapt
- Safety profile
- Mediates HIV entry

Maldini et al 2018 NRI
4-1BB promotes CD4 CAR T cell to durably control HIV replication
A Pilot Study of T Cells Genetically Modified by Zinc Finger Nucleases SB-728mR, and CD4 Chimeric Antigen Receptor in HIV-infected Subjects (NCT03617198)

**Steps**

1. **Cell Manufacturing**
2. **ART + CAR/ZFN**
3. **Treatment Interruption + CAR/ZFN**
4. **Treatment Interruption + CAR/ZFN***
5. **ART**

**Weeks**

-15 0 15 0 15

- **Cell infusion at Day 0**

**Cohort Details**

- Cohort 1: 1 day
- Cohort 2: 8 weeks
- Cohort 1: 16 weeks
- Cohort 2: 24 weeks

*only if HIV VL remains ≤1000 copies/ml at end of Step 3

**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?
Challenges of CAR-T cell Therapy for HIV Infection

- Latent reservoir can remain latent for a long time. Can HIV-CARs persist long term in presence of minimal antigen?
- Can HIV CAR-T cells traffic to all places HIV is hiding?
- Can HIV-CAR T cells remain resistant to HIV infection?
- How long does someone need to have an undetectable viral load before they are pronounced cured?

HIV Cure, under any definition, is a high hurdle to jump
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