A Continuing Medical Education Activity

The 18th Conference on Retroviruses and Opportunistic Infections (CROI):

Online Expert Poster Review and Discussion

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A Novel Approach to HIV Therapy: Successful and Persistent Engraftment of ZFN-Modified CCR5-Disrupted Autologous CD4 T-cells (SB-728-T) in Aviremic HIV-infected Subjects on HAART

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Lalezari J, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 46.

Sangamo Phase I Study (SB-728-T): Background and Rationale

- CCR5 is the major co-receptor for HIV entry
- CCR5 delta-32 mutation produces a nonfunctional form of the protein
  - Homozygotes are resistant to HIV infection
  - Heterozygotes have slower disease progression
- The “Berlin Patient” is HIV-free w/o HAART for 3.5 years following hematopoietic stem cell transplant (HSC) from an allogeneic, HLA matched, CCR5 delta-32 donor
- Zinc Finger Nuclease (ZFN) technology enables precise genetic modification of CCR5 resulting in elimination of receptor expression
- The therapeutic potential of CCR5 modification as seen in the natural mutation can be extended with ZFN modification of autologous CD4+ T-cells in HIV subjects

Mechanism of ZFN-mediated Targeted CCR5 Gene Disruption

1. Endogenous CCR5 gene targeted for disruption

2. ZFNs dimerize and introduce a double stranded DNA break in the CCR5 gene

3. Break repaired by either homologous or non-homologous end-joining (NHEJ) – resulting in permanent CCR5 gene disruption

3. CCR5 gene disrupted

A 5-bp duplication (Pentamer) occurs in 25% of modified cells at target site allowing PCR quantification

Sangamo SB-728-0902 Phase 1 Study Design

- Open label, single-dose study
- Study population – HIV+ subjects on HAART
  - Aviremic
  - CD4 T-cells 200 – 500 cells/mm^3
- Single infusion of SB-728-T
  - Cohort 1 (N=3): 0.5 – 1.0 x 10^{10} cells
  - Cohort 2 (N=3): 2.0 x 10^{10} cells
  - Cohort 3 (N=3): 3.0 x 10^{10} cells

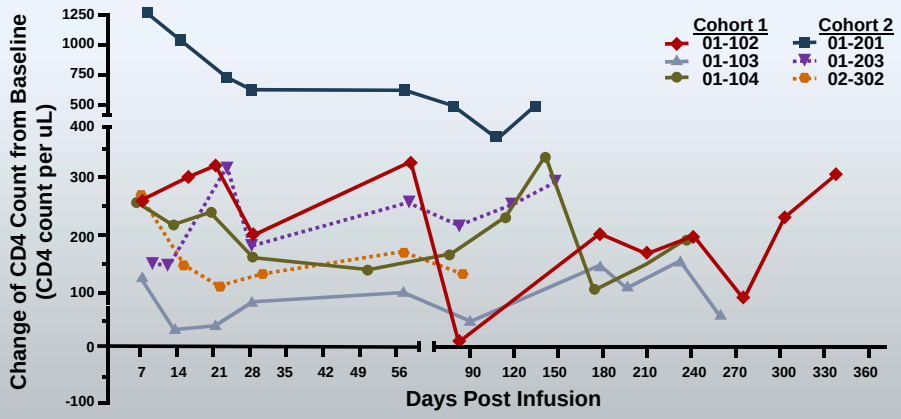
Clinical Outcomes

- Safety and tolerability
- Change in CD4 count, CD4:CD8 ration
- Engraftment and expansion, persistence and distribution of ZFN CCR5 disrupted T-cells

SB-728-T Infusion is Safe and Well Tolerated (Cohort 1 & 2)

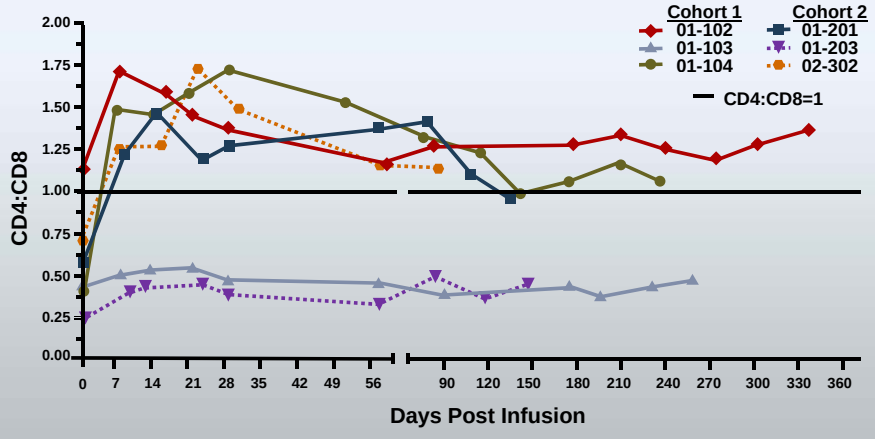
- **Serious Adverse Events**
  - None reported to date with a median follow up of 192 days (range: 85-366 days)
- **Adverse Events** – 32 AEs reported by 6 subjects
  - 30 of mild severity and 2 of moderate severity (flatulence, sweats)
  - 24 drug related occurring within 48 hours of infusion
    - Include: chills, fever, headache, sweats, dizziness, fatigue, and a garlic body odor
- **Immunogenicity**
  - Engraftment and expansion of CCR5 disrupted T-cells despite a transient increase in anti-adenoviral antibodies post-infusion
  - One subject with higher pre-infusion anti-adenoviral antibodies had lower level engraftment.

Increased CD4 T-cell Counts from Baseline After Single SB-728-T Infusion



Sustained increase from baseline observed in 5 of 6 subjects at most time points

Normalization of CD4:CD8 T-cell Ratio After Single SB-728-T Infusion



CD4:CD8 reversal (from <1 to >1) in 3 of 5 subjects

Samgamo SB-728-0902 Summary

- **SB-728-T can be manufactured at doses of 10-30 billion cells from a single apheresis with a CCR5 disruption frequency of ~25%**
- **SB-728-T treatment is well-tolerated**
  - Minor reversible infusion-related symptoms
- **Improved and sustained increase in total CD4+ T-cell counts seen in 5/6 subjects**
- **Normalization of CD4:CD8 ratios seen in 3/5 subjects**
- ZFN-modified T-cells engraft, expand, and persist in peripheral blood
  - ZFN-modified CD4+ T-cells detected at frequencies up to 7-fold higher (median 2.9) than predicted input on day 14
  - Expansion of ZFN-modified T-cells in PBMC may be due to cell proliferation and/or altered distribution
- **ZFN-modified T-cells engraft and persist in rectal mucosa**
  - Engraftment and persistence of ZFN-modified T-cells in rectal mucosa demonstrated normal homing to this important tissue