A Dose Escalation Study of Cyclophosphamide (CTX) to Enhance SB-728-T Engraftment

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SB-728-1101 Cytoxan Study Rationale

- **CCR5** is a major co-receptor for HIV entry
  - Mutation produces a non-functional protein
  - Homozygotes are resistant to HIV infection
  - Cytokines increase CCR5 expression
  - ZFP-FN (ZFP) reduces CCR5 gene expression in T-cells
  - Cyclophosphamide has been used successfully to enhance engraftment of T-cells in a SCID mouse model
  - CCR5 inhibitors are producing new drug therapies for HIV infection

Current study undertaken to increase SB-728-T engraftment

SB-728-1101 Cytoxan Study Design

- **Open-label, multicenter, cyclophosphamide dose escalation**
  - Single-institution study
  - 5 cohorts:
    - Cohort 1: 0 mg/m²
    - Cohort 2: 0.5 g/m²
    - Cohort 3: 1.0 g/m²
    - Cohort 4: 1.5 g/m²
    - Cohort 5: 2.0 g/m²

- **Visits**
  - BASELINE
  - CTX
  - 0 30 60 90 120 150 180 210 240
  - Pentamer
  - Absolute CD8 count
  - Viral Load
  - Days from baseline
  - Treatment interruption

- **Viral Load Drop from Peak After CD4 SB-728-T**
  - CTX at Doses up to 1 gm/m² Increases CD4 T-cell Engraftment
  - Rationale for Maintaining CD8 T-cells in SB-728-T
  - Treatment with SB-728-T Modified CD4 T-cells
  - Expansion of dendritic cells
  - Create space in the bone marrow
  - Current study undertaken to increase SB-728-T engraftment

- **Subject Demographics**
  - Cohort 1: 0 mg/m²
  - Cohort 2: 0.5 g/m²
  - Cohort 3: 1.0 g/m²
  - Cohort 4: 1.5 g/m²
  - Cohort 5: 2.0 g/m²

- **Summary and Conclusions**
  - CYTOXAN T-cells after Cytoxan Conditioning
    - Genetically modified to express ZFP
    - Pre-existing adoptive therapy can increase CD8 T-cells and CD4 modified T-cells with recent infection

- **SB-728 CD4/CD8 T-cells after Cytoxan Conditioning**
  - These subjects have been treated with a ZFPmodified CD4 cells and four remain on long-term treatment interruption (40-71 weeks after treatment interruption).

- **SB-728 CD4/CD8 T-cells after Cytoxan Conditioning**
  - Subject 03-011 received 1000 mg/m² CYTOXAN + CD8
  - Subject 04-046 received 1000 mg/m² CYTOXAN + CD8
  - Subject 01-070 (CTX 1000 mg/m² + CD8)
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  - Subject 01-070 (CTX 1000 mg/m² + CD8)

- **Subject 03-011 (CTX 1000 mg/m² + CD8)**
  - Subject received 17.6 x 10⁹ CD4 (50.2%) 8.83 x 10⁹
  - CD8 (38.0%) 6.69 x 10⁹
  - VL = 23,700

- **Subject 01-070 (CTX 1000 mg/m² + CD8)**
  - Subject received 5.58 x 10⁹ CD4 (27.6%) 5.58 x 10⁹
  - CD8 (43.5%) 3.52 x 10⁹
  - VL = Below LOQ

- **Viral Load Drop from Peak After CD4 SB-728-T**
  - Four Subjects Continue on Prolonged TI
  - CTX at Doses up to 1 gm/m² Increases CCR5 Modified Cell Engraftment
  - Activated CD8 and Low CCR5 are Associated with Elite Control in 92 Subjects
  - Pentamer Duplication / Virus
  - CTX day 27.2
  - Delayed onset of viremia

- **Pentamer**
  - CD4/8
  - CD4 T-cells >500 cells/µl
  - Aviremic
  - Mild infusion reactions
  - No evidence of hematuria or hemorrhagic cystitis
  - Nausea and vomiting increases with increasing CTX dose
  - Platelets >200,000/mm³
  - Neutrophil count >500 cells/mm³
  - R5 tropic virus

- **Summary and Conclusions**
  - CD4 (27.6%) : 5.58 x 10⁹
  - CD8 (43.5%) : 3.52 x 10⁹
  - Δ VL (copies/mL) 0.4
  - Control (F = 0.0000)
  - Important variables that predict “elite” control

- **Subject 04-046 (CTX 1000 mg/m² + CD8)**
  - Subject received 1000 mg/m² + CD8
  - CD4 (40.4%) : 3.27 x 10⁹
  - CD8 (43.5%) : 3.52 x 10⁹
  - VL = 18,200

- **Subject 01-070 (CTX 1000 mg/m² + CD8)**
  - Subject received 1000 mg/m² + CD8
  - CD4 (40.4%) : 3.27 x 10⁹
  - CD8 (43.5%) : 3.52 x 10⁹
  - VL = Below LOQ

- **Subject 03-011 (CTX 1000 mg/m² + CD8)**
  - Subject received 1000 mg/m² + CD8
  - CD4 (40.4%) : 3.27 x 10⁹
  - CD8 (43.5%) : 3.52 x 10⁹
  - VL = Below LOQ