

Mary Ellen Conley, M.D.

**Director, Program Genetic Immunodeficiency
Dept of Immunology
St. Jude Children's Research Hospital**

**Clinical Overview of SCID-X1 and Outline of
LVXSCID-ND**

SCID-X1 (*common γ chain defect*)

- Usually presents between 3-9 months of age
- Respiratory distress
- Chronic diarrhea
- Opportunistic infections
- Failure to thrive
- Transplant or gene transfer are the only treatment options

SCID Transplant

Variables chosen by physicians

Donor

matched sib

matched unrelated

cord blood

haploidentical (parental)

megadose CD34 stem cells

SCID Transplant

Variables chosen by physicians

Pre-treatment of patient

none

anti-lymphocyte antibodies

chemotherapy

variant chemotherapy

Preparation of stem cells

unmanipulated bone marrow

bone marrow vs. peripheral stem cells

T cell depleted

stem cell selected

SCID-X1 Transplant Outcomes

- Mortality - 25-40%
- Inadequate antibody production - 60-70%
- Abnormal NK cell number or function - 90%
- Autoimmunity or GVHD
- Endocrine problems?
- Cognitive problems?
- Decline in T cell function?

LVXSCID-ND Overview

Patients between 3 and 12 months of age will be enrolled. The mutation in the common γ chain will be documented. Baseline clinical and immunological studies will be done. HLA typing will be performed and a search for a MUD will be initiated. The patient's clinical status will be stabilized and the patient will be maintained in protective isolation.

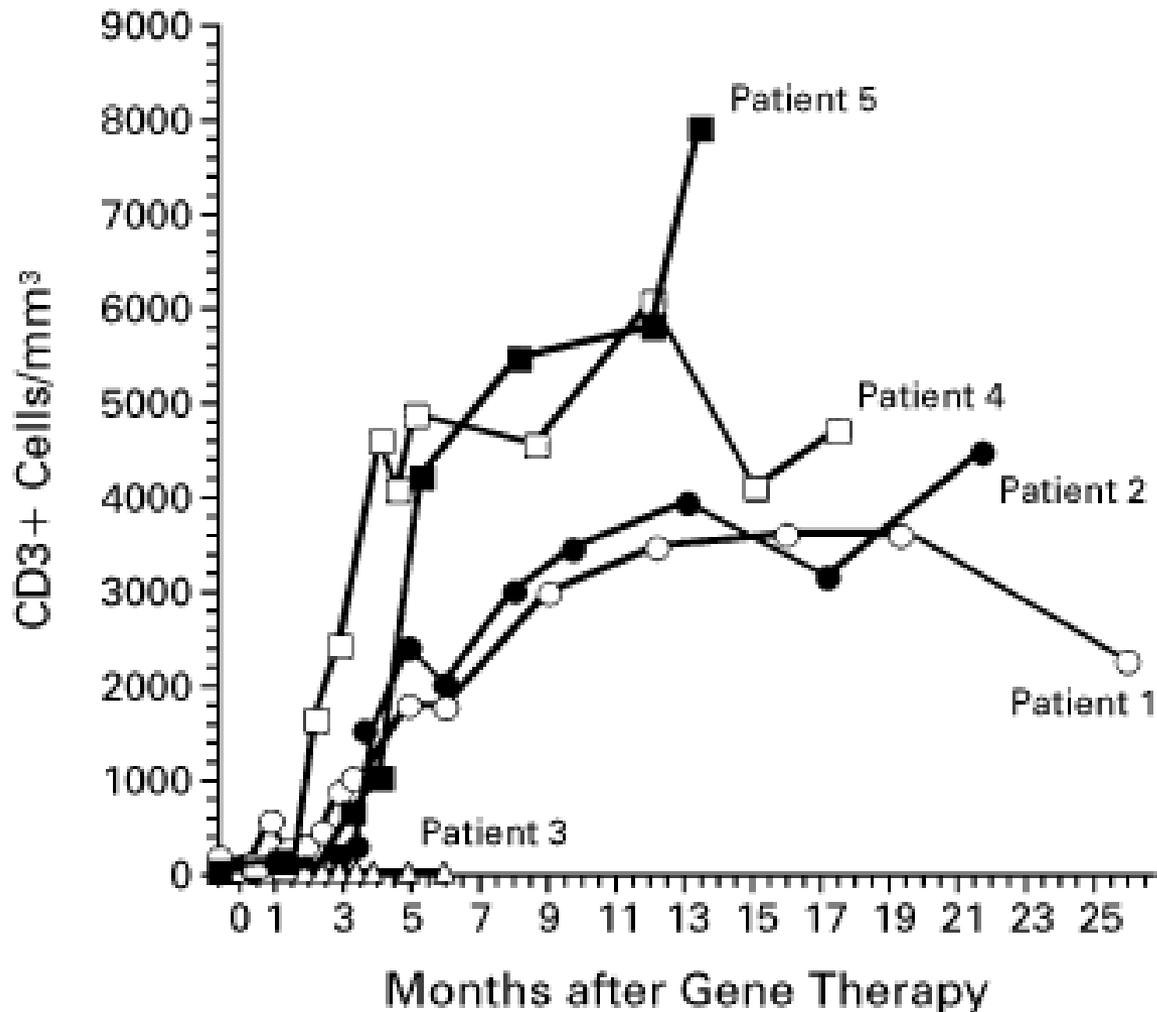
LVXSCID-ND Overview

Bone marrow will be harvested under general anesthesia and CD34+ cells will be purified by the CliniMax system. These cells will be cultured in serum free media and transduced with the CL20-4i-EF1 α -h γ_c OPT vector. At least 3×10^6 cells/kg of transduced cells must be available for infusion. Routine laboratory studies and immunologic findings will be followed.

LVXSCID-ND Overview

If the patient has no evidence of T cell development (TRECs <500 , CD3+ $<150/\text{mm}^3$ and proliferation in response to PHA $<25\%$ of control) at 16 weeks post infusion, the patient will be taken off study and offered an allogeneic transplant. Patients who remain on study will continue to be evaluated at frequent intervals.

T cell reconstitution kinetics in French trial NEJM, 2002, Cavazzano-Calvo et al



LVXSCID-ND Overview

At 52 weeks post infusion, the patient's immunologic status will be evaluated and compared to that seen in patients who have been treated in the gamma retroviral gene therapy studies or treated with a T cell depleted parental transplant. The patients will continue to be monitored at 6 month intervals.

Inclusion Criteria for LVXSCID-ND

- A clinical diagnosis of SCID-X1
- Documented mutation in the common γ chain
- Age > 3 months; < 12 months
- Less than 12% CD3 T cells in circulation
- Adequate social situation

Exclusion Criteria for LVXSCID-ND

- HLA matched sib donor available
- Prior allogeneic stem cell transplant
- Positive for HIV infection by PCR
- Expected survival less than 120 days
- A medical contraindication to anesthesia or bone marrow harvest

Stopping Rules

Two failures in the 1st 3 patients or

One failure in the 1st 3 patients and a second failure in the next 3 patients

Failure:

- 1) $<3 \times 10^6$ cells/kg for gene transfer
- 2) lack of T cells at 16 weeks (< 500 TREC, or PHA $> 25\%$ of control, or CD3 $>150/\text{mm}^3$ blood)
- 3) any grade 3 or 4 toxicity directly related to gene therapy

End Points

- At 52 weeks post gene transfer, T cell number and function will be determined and compared to earlier gene transfer trials
- B cell function will be determined by measuring serum immunoglobulins, antibody response to vaccination and the number of common γ chain corrected cells
- NK cell numbers and function will be evaluated

End Points

- Sorted T cells, B cells, NK cells, monocytes and granulocytes will be evaluated for vector copy number and the proportion of corrected cells
- Vector insertion sites in sorted cells will be determined by LAM-PCR and deep sequencing
- The clinical status of patients will be evaluated: growth and development, history of infections and attainment of childhood milestones

T cell reconstitution kinetics in UK trial

Lancet, 2004, Gaspar B et al

