

Lentiviral Gene Transfer for Treatment of Children Older Than One Year of Age with X-Linked Severe Combined Immunodeficiency

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Objectives:

- To assess the efficacy of treatment of older children with XSCID with *ex vivo* gene transfer using a lentivector.
- To determine the safety of gene transfer using a self-inactivating, insulated, lentivector

Research Subject Populations:

- Group A- Insufficient clinical benefit from previous haploidentical bone marrow transplants (BMT).
(Despite 1 or more BMTs, patients have persistent and clinically significant immune deficiency.)
- Group B-No previous BMT, likely represent atypical variant of XSCID with late presentation (>1 year), and less severe disease

Eligibility Criteria:

Up to 12 patients with significant immune impairment will be enrolled. The immune impairment will be based on both laboratory and clinical parameters:

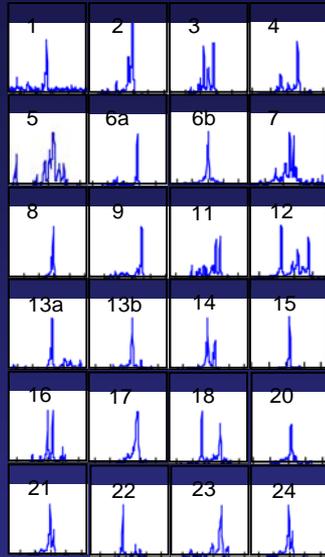
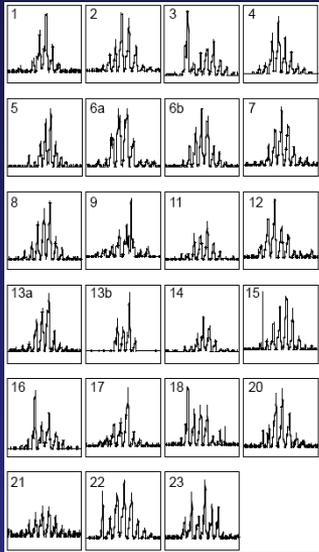
- **Laboratory (3 of 4):**
 - i. Lymphopenia
 - ii. Low TRECS
 - iii. Poor T cell function
 - iv. Abnormal TCR repertoire
- **Clinical (4 of 8):**
 - i. Infections
 - ii. Pulmonary dysfunction
 - iii. Gastrointestinal disease
 - iv. Growth impairment
 - v. Need for nutrition supplement.
 - vi. Immune dysregulation
 - vii. Skin-warts
 - viii. Mucocutaneous candidiasis

*Rationale for complicated criteria list-heterogenous group of patients.

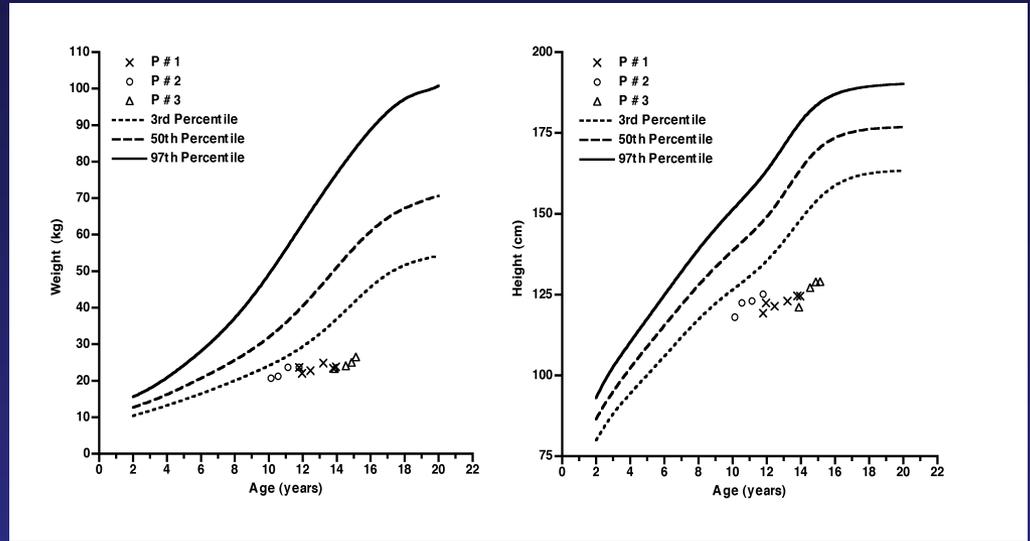
Spectratype

a. Normal

b. XSCID patient



Growth Charts



Autoimmune alopecia

Molluscum contagiosum

Clubbing, wart



Main Exclusion Criteria:

1. Available HLA-matched sibling donor
2. Any hematologic or childhood malignancies in the patient or first degree relatives, or known genotype that confers predisposition to cancers

Study Implementation:

- Screening phase
- Treatment Phase
 - Mucositis prophylaxis
 - Busulfan
 - Infusion of Transduced CD34+ cells
 - In-patient until $ANC > 500$ x3 days
- Follow up Phase-first 2 years to Primary Endpoint
- Safety Follow Up-5 years
- Long Term Follow Up-15 years

Patient Alternative Therapy Discussion Algorithm:

At enrollment, perform HLA search for potential donor.



No HLA matched unrelated donor



Gene Transfer

Matched unrelated donor available

- Discuss pros and cons of gene transfer and MUD transplant (exposure to subablative conditioning; GVHD)
- Family seek consultation from other Transplant and/or Immune Deficiency Centers
- Patient/family decide
- Offer MUD transplant at NIH or other center



Study Endpoints:

- Primary Endpoints:
 1. Efficacy of treatment formally evaluated at 2 years after treatment
 - A. Laboratory immunological parameters
 - T cell reconstitution-numbers of total and subsets of T cells, their function, repertoire and evidence of thymic output
 - B cell reconstitution- γ c expressing B cells, and trough serum IgG levels
 - NK cell numbers
 - B. Clinical parameters

Infections, pulmonary and gastrointestinal function, status of immune dysregulation, skin and mucocutaneous candidiasis
 2. Evaluation of serious adverse events related to the gene transfer
- Secondary Endpoints
 1. Molecular characterization of gene transfer
 2. Integration site distribution

Study Stopping Rules:

For lack of efficacy:

- Proviral sequences (by PCR) not detectable in any circulating blood cell lineages by 3 months post infusion in the first two patients

For toxicity:

- Any grade 3 or 4 toxicity NOT listed as expected AE
- Any positive RCL
- Loss of polyclonality due to outgrowth of a clonal cell population
- Any death or leukemia potentially related to gene transfer

Individual Patient Stopping Rules: (Offer Alternate Therapy)

1. Lack of significant proviral marking in any circulating blood cell lineages by 3 months post infusion
 2. At one year post infusion, failure to meet minimal laboratory criteria for partial success
- *rationale for evaluation at one year-unless a minimal level of gene marking is achieved, clinical benefits (expected to lag behind improvements in laboratory parameters) is unlikely.