

Protocol #0810-950

Gene transfer for SCID-X1 using a self-inactivating (SIN) gammaretroviral vector

Presentation to Recombinant DNA Advisory Committee

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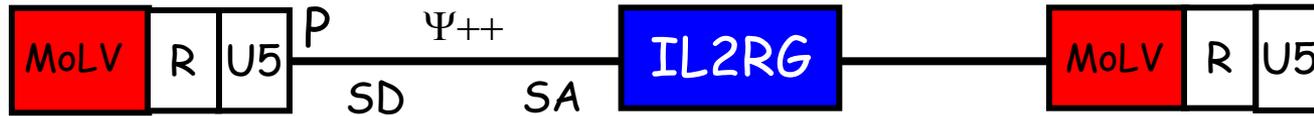
September 13, 2011

Outline of presentation

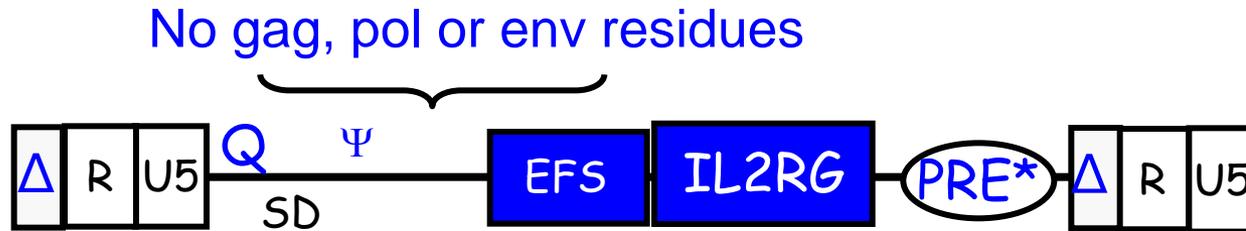
- Overview of gene transfer study for X-linked SCID
- Rationale for exclusion of patients <3.5 months
- New data to support offering enrollment to patients <3.5 months
- Proposed changes to protocol and informed consent

Safer vector designed to reduce insertional mutagenesis

LTR-driven gammaretroviral vector: **MFG** γ C



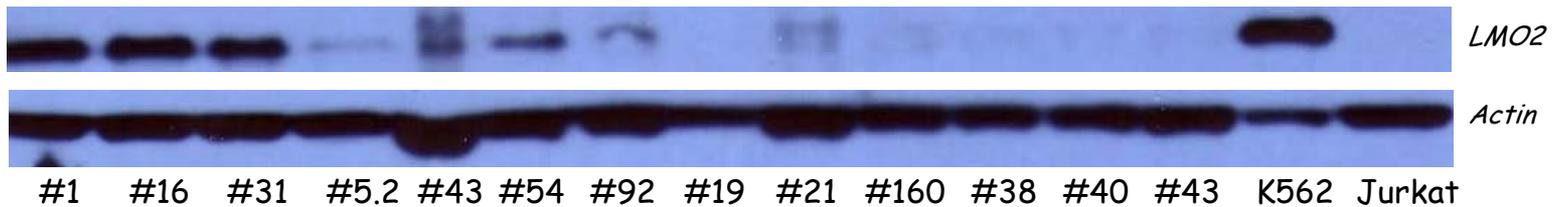
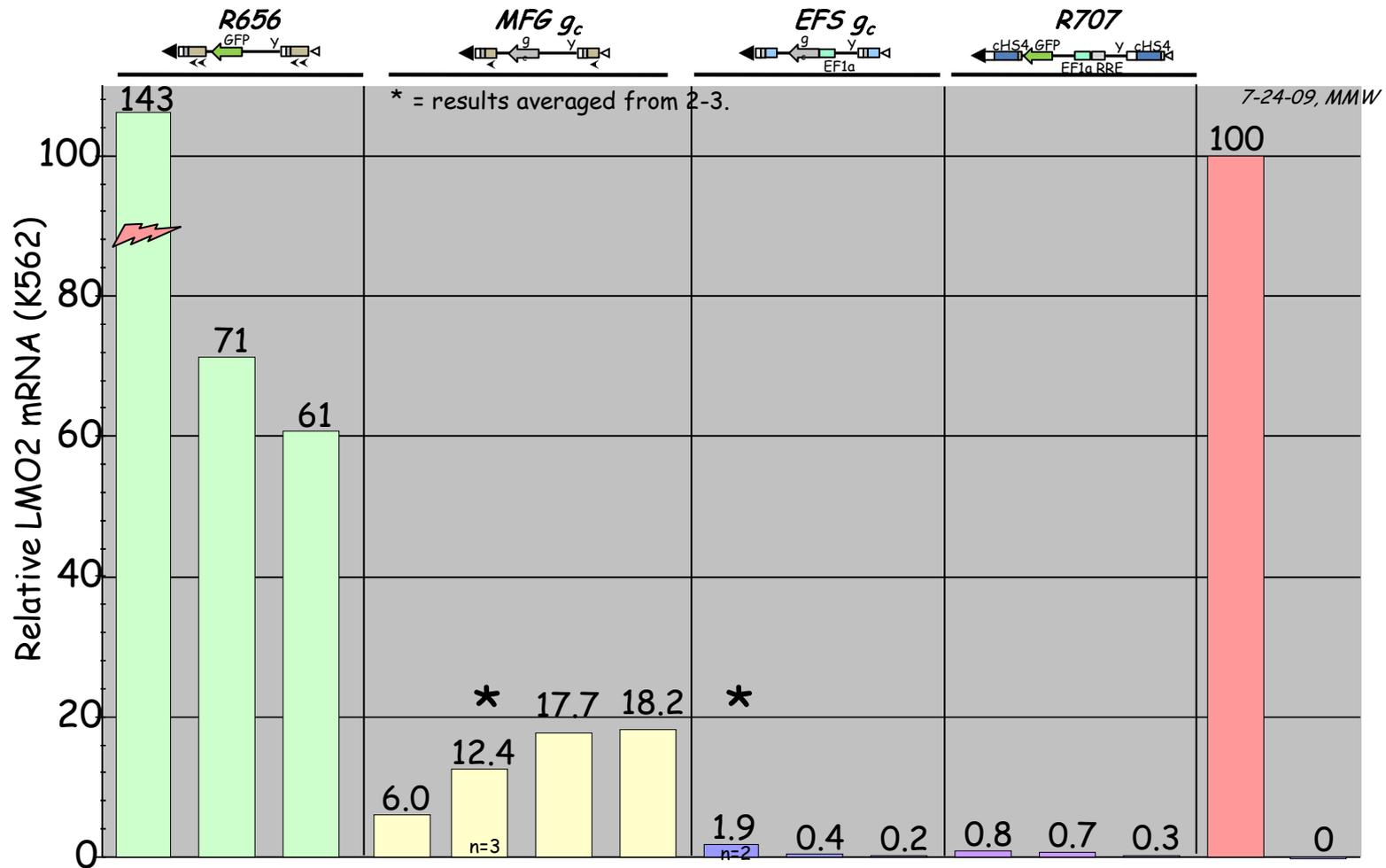
New gammaretroviral SIN vectors: **SRS11**



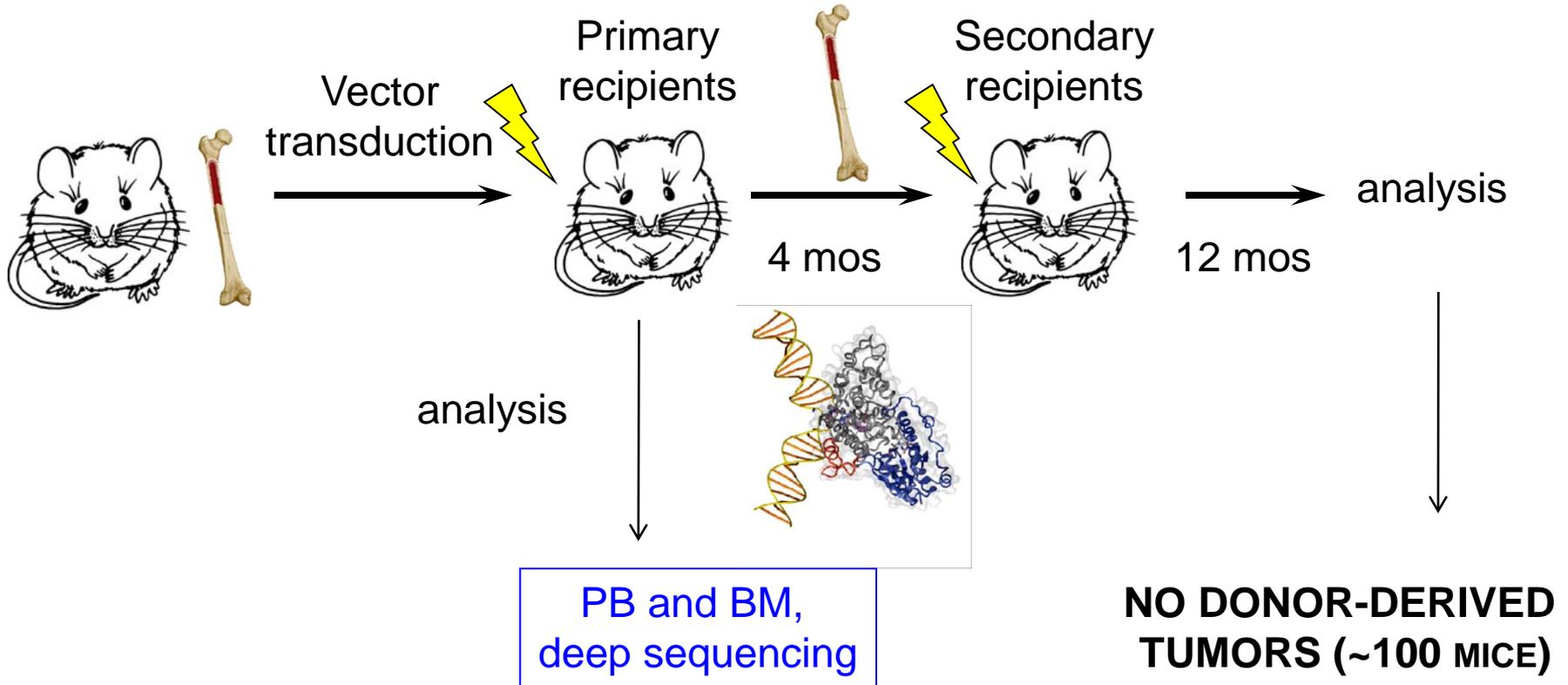
Key modifications compared to Paris/London MFG vector:

- removal of viral LTRs (MoLV U3 regions) to reduce transactivation of neighboring genes
- removal of all gammaretroviral coding regions
- cellular EFS (EF1 α) promoter to drive transgene expression in an internal position
- modification of PRE (posttranslational regulatory element) to enhance expression
- other modifications to improve titer

Relative LMO2 expression (Jurkat cell line)



Clonal dominance assay

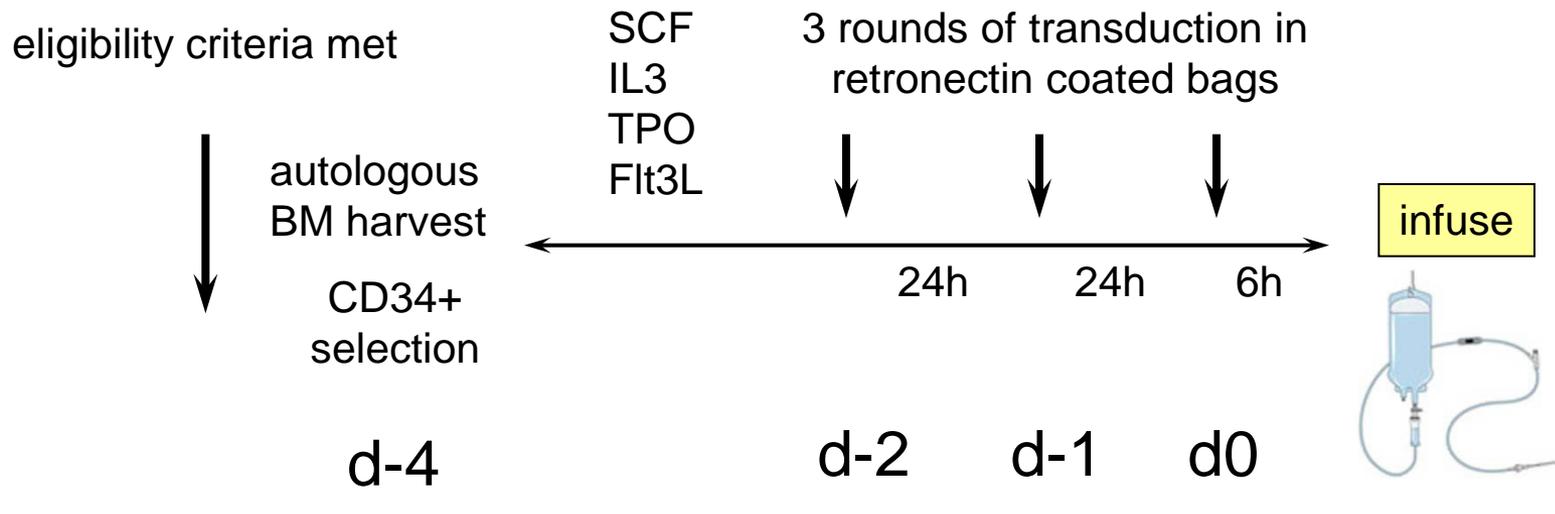
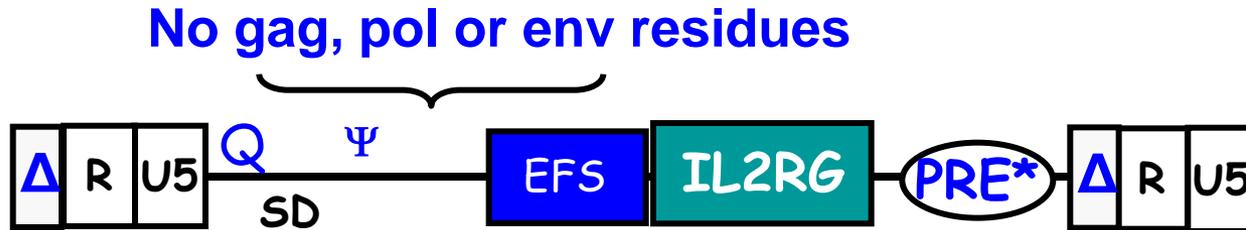


Insertion in Evi1
MFG: 8 out of 3621 insertions
SRS: 0 out of 2690 insertions

Chris Baum (Hannover)
Chad Harris (Boston)
Martijn Brugman (Hannover)

SCIDX1 gene transfer schema

Self-inactivating gammaretroviral vector



Original inclusion criteria

1. Diagnosis of SCID-X1 based on <200 CD3+ autologous T cells, and confirmed by DNA sequencing

AND at least one of the following:

- 2a. No readily available HLA identical (A, B, C, DR, DQ) related or unrelated donor (within 6 weeks of searching, available for transplant within 3 months of diagnosis)
- 2b. Patients with an active, therapy-resistant infection or other medical condition that significantly increase the risk of allogeneic transplant

Rationale for excluding patients <3.5 months

- new vector, efficacy uncertain
- single institution data for early HCT after SCID showing excellent survival

Rationale for excluding patients <3.5 months

Healthy infants with X-SCID who are less than 3.5 months old should be excluded because they should be treated with a haploidentical transplantation which offers proven efficacy at their age.

RAC 950 PI letter, 2008

Cohort	n	f/u	survival	survival
<3.5 months	48	9.2 y	45/48	94%
>3.5 months	113	8.5 y	81/113	69%

Current inclusion criteria

1. Diagnosis of SCID-X1 based on <200 CD3+ autologous T cells, and confirmed by DNA sequencing
2. Lack of an HLA identical (A, B, C, DR, DQ) related donor

AND either of the following:

- 3a. **Patients in good clinical condition, greater than age 3.5 months**, who do not have a readily available HLA identical (A, B, C, DR, DQ) unrelated donor (within 6 weeks of searching, available for transplant within 3 months of diagnosis)

OR

- 3b. Patients of any age with an active, therapy-resistant infection or other medical condition that significantly increase the risk of allogeneic transplant

Current exclusion criteria

1. No available molecular diagnosis confirming SCID-X1.
2. Patients who have an available HLA-identical related donor.
3. Diagnosis of active malignant disease other than EBV-associated lymphoproliferative disease.
4. Age under 3.5 months in good clinical condition for whom a haplo-identical related donor is available.
5. Patients with evidence of infection with HIV-1.
6. Previous gene transfer.
7. Major (life-threatening) congenital anomalies.
8. Other conditions which in the opinion of the P.I. or co-investigators, contraindicate collection and/or infusion of transduced cells or indicate patient's inability to follow the protocol.

Response to exclusion of patients <3.5 months

- new vector, efficacy uncertain

new efficacy data from current trial

- single institution data of outcome after early HCT for SCID showing excellent survival

survival update after GT including current trial
new multi-institutional survival data after HCT

- gene transfer would avoid GVHD entirely--what is the incidence of GVHD after early haploidentical HCT?

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GT 00001 (Children's Hospital Boston)

γ c expression at day +171 after GT

Boy from Argentina
Diagnosed at birth (+FH)
IL2RG: Y98C

Pre-GT

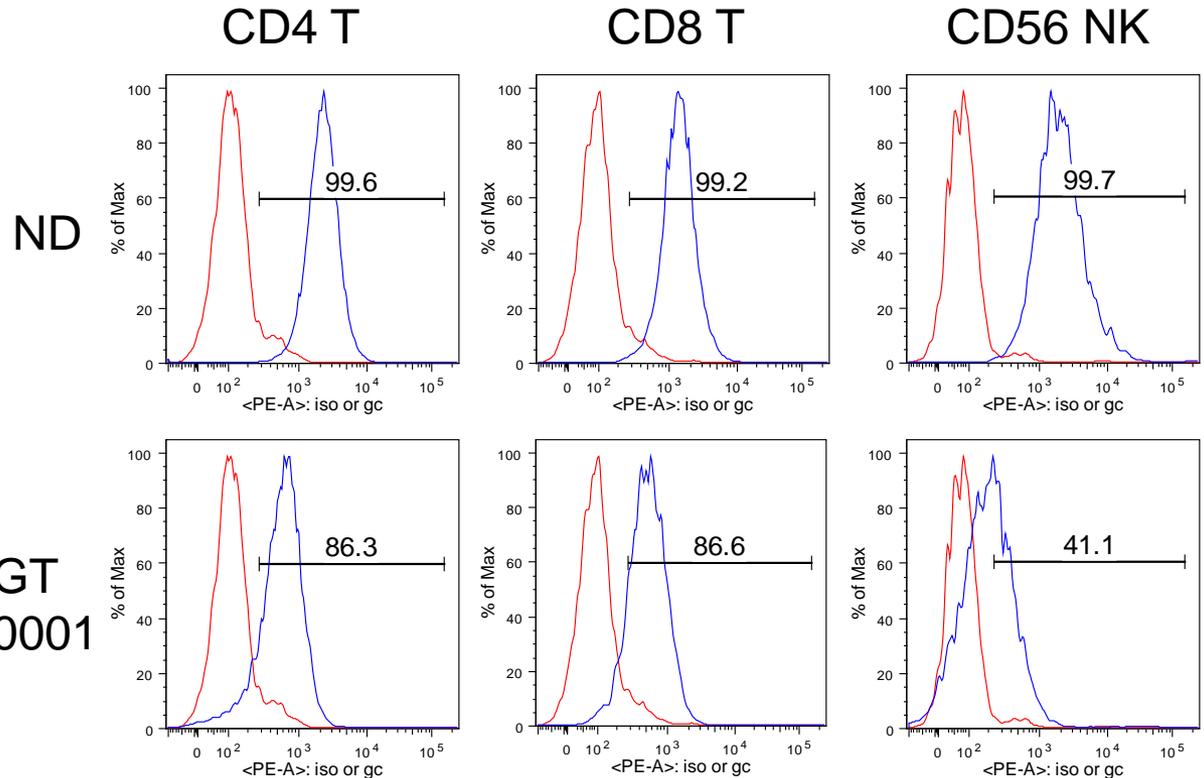
CD3: 5

CD19: 1866

CD16: 86

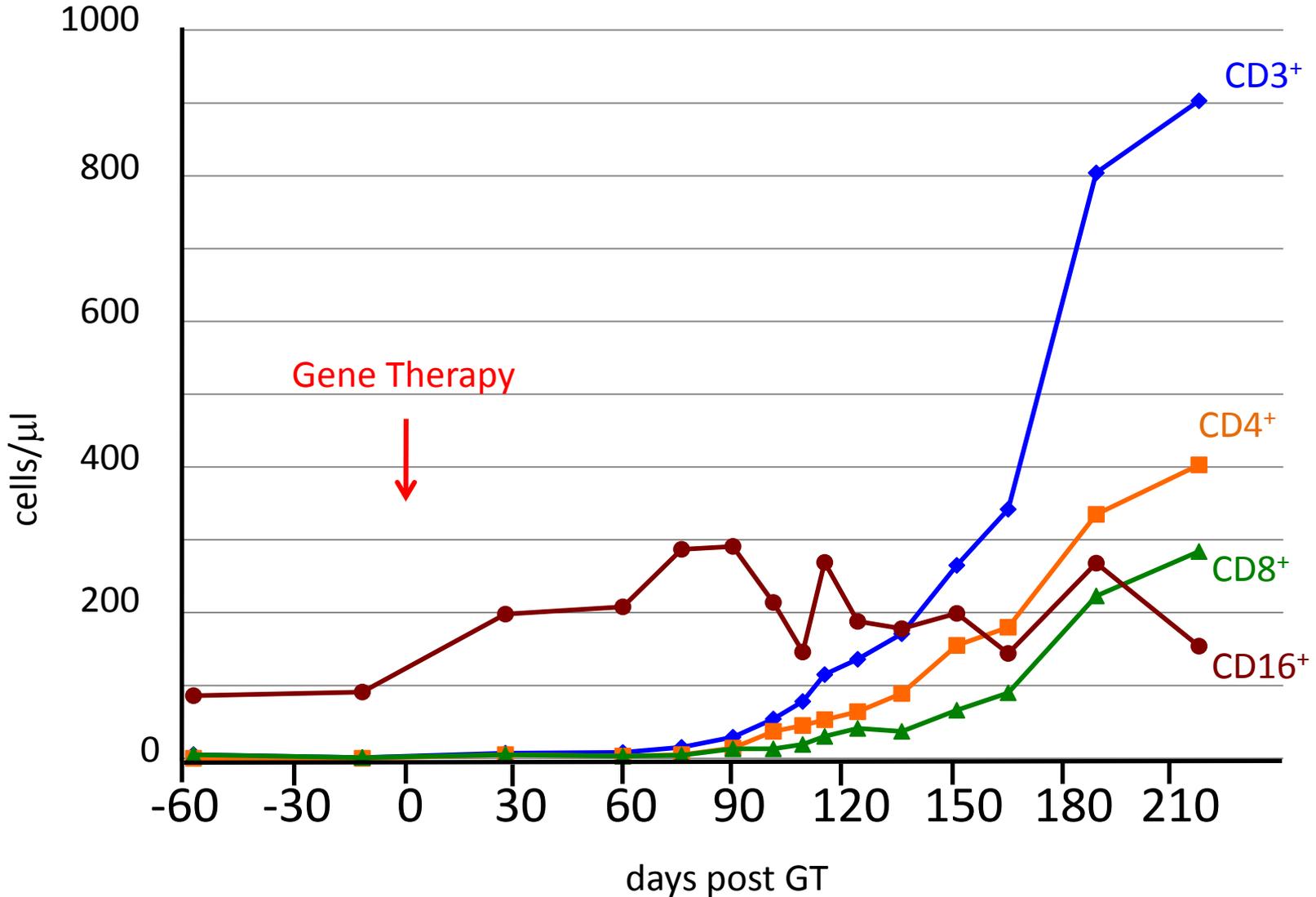
Therapy-resistant oral
ulcers

Underwent GT age 5.5
months

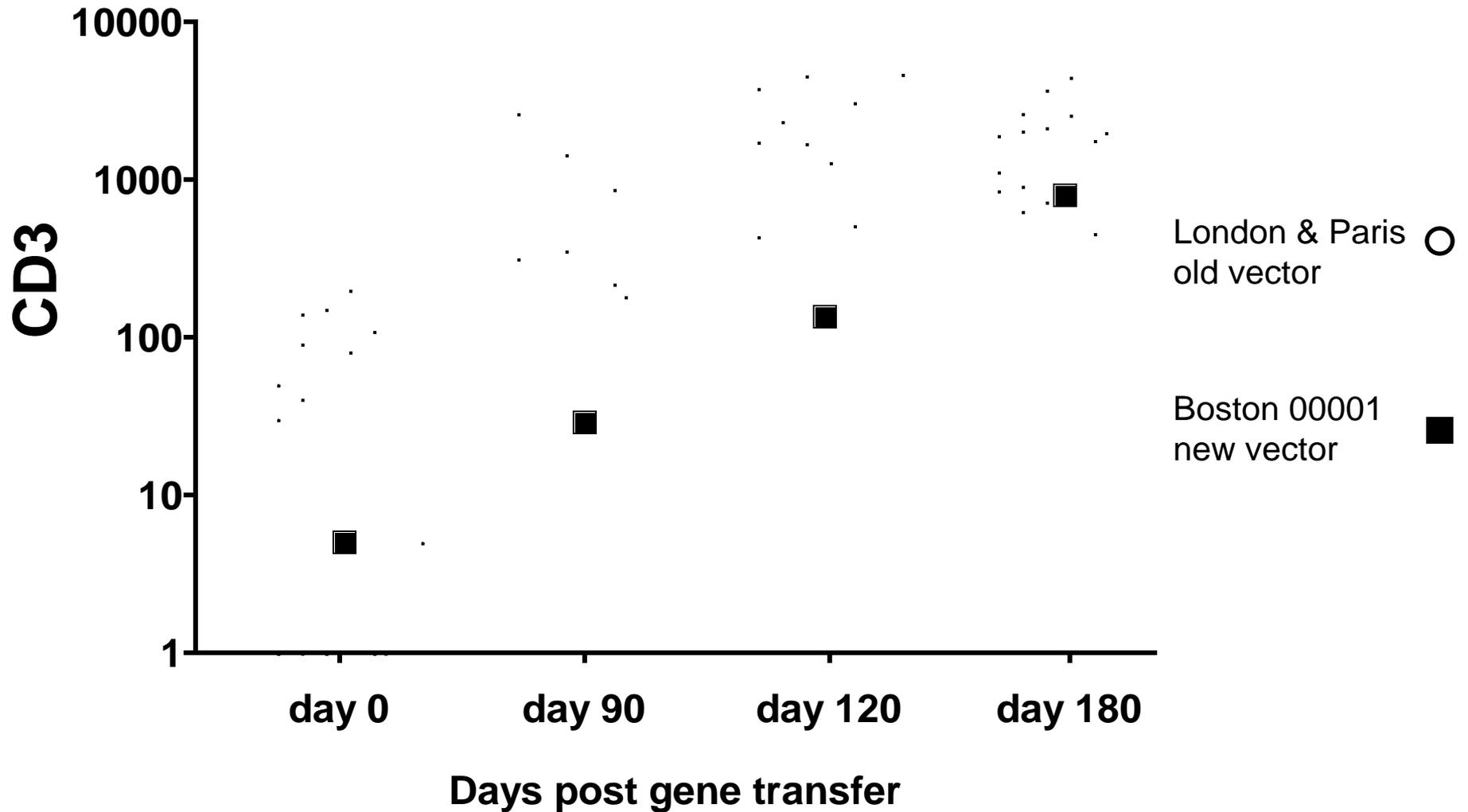


γ c

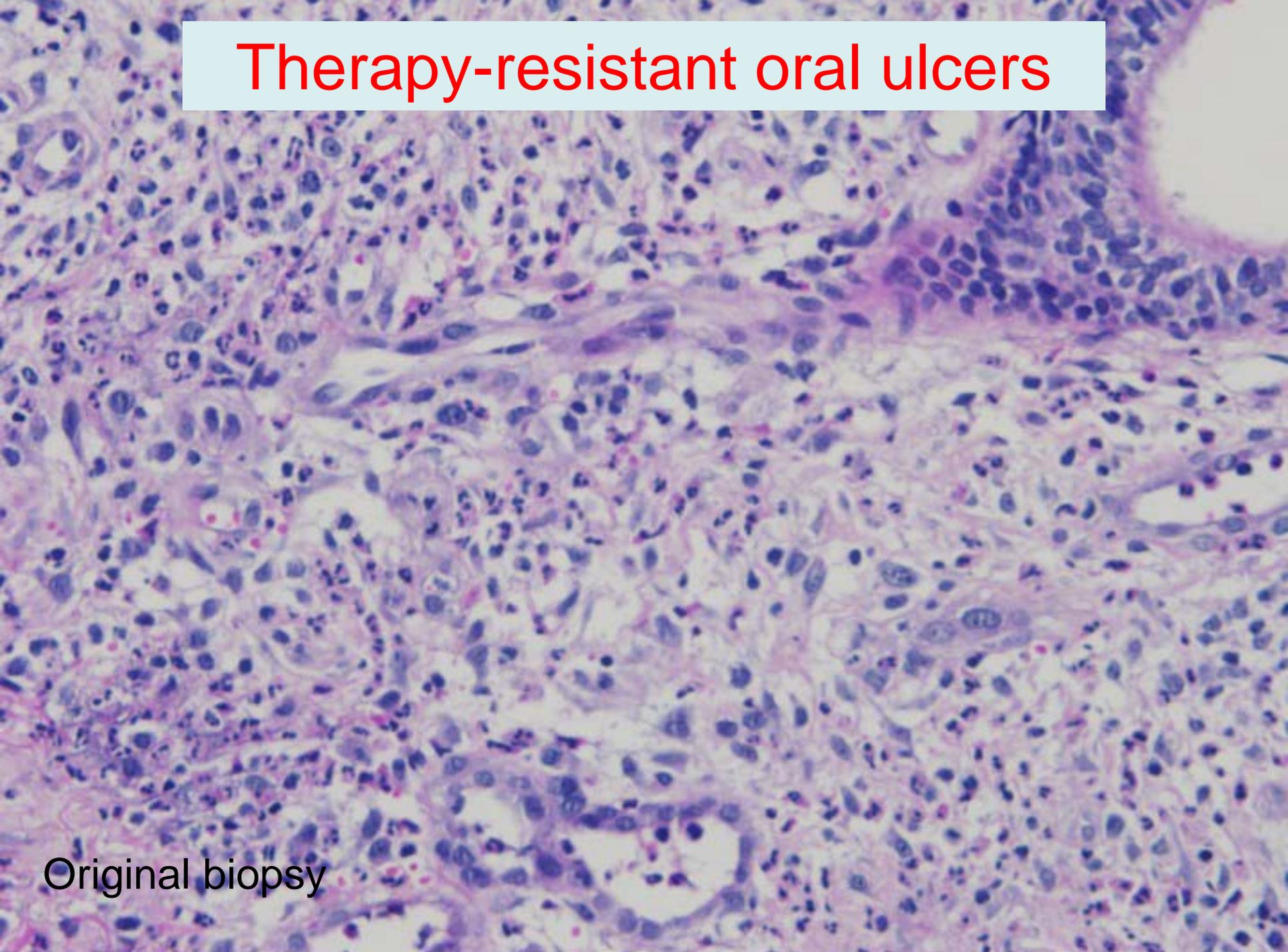
Immune reconstitution after gene therapy for X-SCID in GT 00001



Early reconstitution of GT 00001 is comparable to previous trial

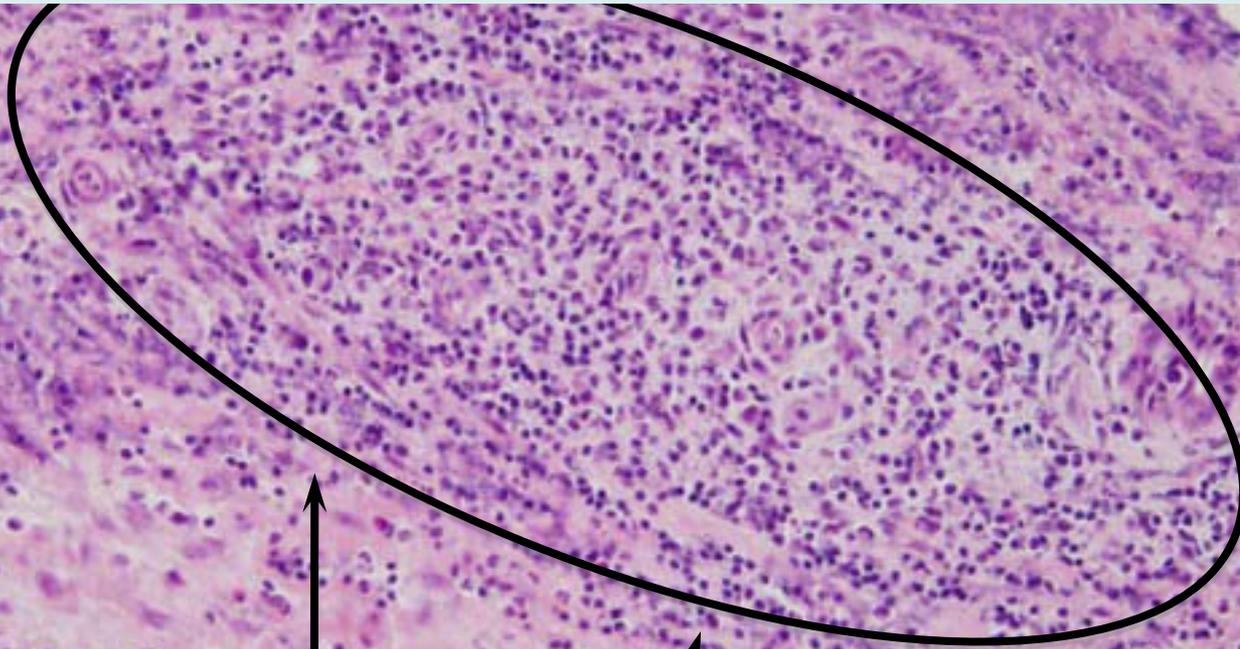


Therapy-resistant oral ulcers



Original biopsy

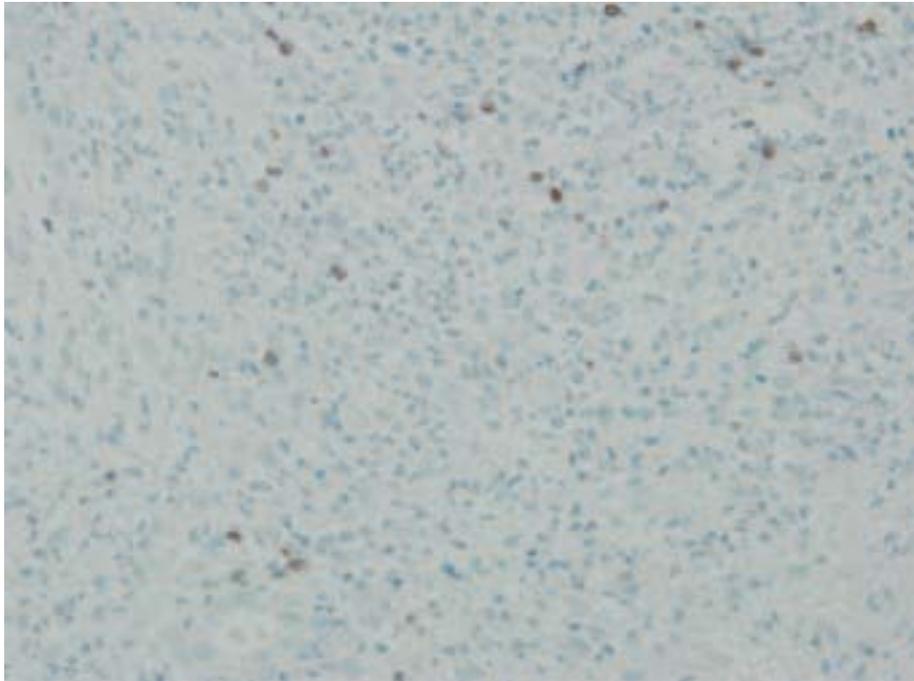
Therapy-resistant oral ulcers



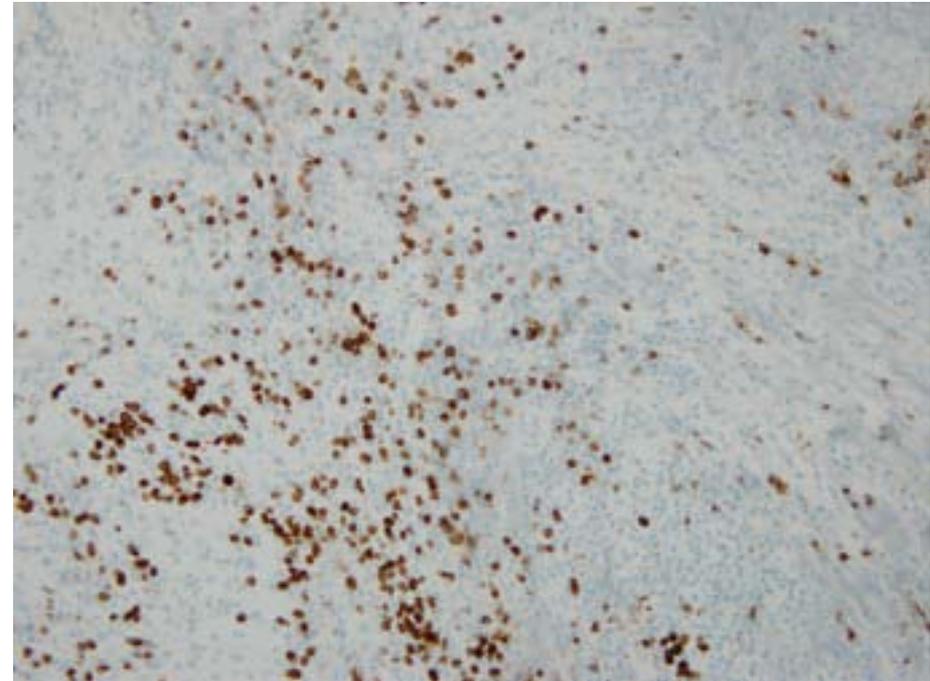
Infiltrating mononuclear cells

day +50 biopsy

Infiltration of oral mucosa of GT00001 with T cells as a result of GT



CD3, original biopsy



CD3, day +50 biopsy

gene marking confirmed in peripheral T cells
full clinical resolution by day +70 after GT

Follow-up of 3 patients treated to date

	Boston P1		Paris P1		Paris P2	
	Pre-GT	Last f/u	Pre-GT	Last f/u	Pre-GT	Last f/u
Age (months)	5.7	11.7	8	15	5.5	9.5
Infections	oral ulcers	Cleared oral ulcers & intercurrent rotavirus	dissem. BCG	dissem. BCG	dissem. BCG, RSV pneumonia, CMV+, EBV LPD	dissem BCG (improved)
Maternal engraftment?	ND	-			Yes, high	Yes, persisting
CD34 cells/kg	7.39 x 10e6		2.3 x 10e6 (gc+)		3.0 x 10e6 (gc+)	
CD3/ul	5	804	0	608	8,000	6,060
naïve (corrected) CD3/ul	-	445	-	303	-	493
CD16/56	91	268	0	128	0	73
PHA	206	95,901	ND	7,700	ND	NE

Data from Paris courtesy of A. Fischer, M. Cavazzana-Calvo, S. Hacein-Bey-Abina

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Response to exclusion of patients <3.5 months

- new vector, efficacy uncertain

early immune reconstitution in 3 subjects

- single institution data of outcome after early HCT for SCID showing excellent survival

survival update after GT including current trial
new multi-institutional survival data after HCT

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Current survival after GT for X-linked SCID compared to HCT at a young age

Study	Pts	Age	N	Survival (crude)	%	Institution/ Reference
HCT	all SCID, haplo & sib	<3.5m	48	45/48	94%	Railey et al 2009, Buckley et al 2011
HCT	all SCID, ID at birth	-	60	54/60	90%	Brown et al 2011
HCT	T-B+ SCID, haplo	<3.5m	46	40/46	87%	SCETIDE
Gene transfer	X-SCID	all	23	21/23	91%	Paris, London, Boston

Response to exclusion of patients <3.5 months

- new vector, efficacy uncertain
early immune reconstitution in 3 subjects
- single institution data of outcome after early HCT for SCID showing excellent survival
survival after GT 91% (21/23 alive)
comparable to single institution 94% (45/48)
and multi-institutional results 86.9% (40/46)
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Outcome of haploidentical HCT at age <3.5 months in 46 infants with T-B⁺ SCID

(SCETIDE Registry, August 2011, L. Brown & H.B. Gaspar)

Survival

Alive = 40/46 (86.9%)

Deceased = 5

Lost to F.U. = 1

Acute GvHD grade ≥ 2 = 10/46 (22%)

Chronic GvHD = 4/46 (9%)

Response to exclusion of patients <3.5 months

- new vector, efficacy uncertain
current trial shows early immune reconstitution in
3 subjects
- single institution data of outcome after early HCT for
SCID showing excellent survival
survival after GT 91% (21/23 alive)
comparable to single institution 94% (45/48)
and multi-institutional results 86.9% (40/46)
- what is the incidence of GVHD after early
haploidentical HCT?
Haploidentical HCT age <3.5 months results in
aGVHD 22%, cGVHD 9%
Gene transfer avoids GVHD entirely

Summary

- Based on extensive pre-clinical data, we expect the current vector to at least as safe as the previous vector.
- Survival data for the current and previous gene therapy trials in X-SCID compares favorably with survival data of allo-transplants in infants <3.5 months. There is no pre-autologous transplant chemotherapy utilized in this protocol.
- Preliminary data shows efficacy with the new vector in three patients with respect to engraftment and early reconstitution of lymphoid cells.
- There is no GVHD reported in any patient receiving autologous, gene-corrected cells. This compares favorably with the ~20% risk of acute GVHD and ~8% risk of chronic GVHD seen in haplo-transplants for infants <3.5 months treated for T- B+ SCID.

**We believe these data warrant offering this protocol
as an option with appropriate informed consent
for infants <3.5 months.**

Current inclusion criteria

1. Diagnosis of SCID-X1 based on <200 CD3+ autologous T cells, and confirmed by DNA sequencing
2. Lack of an HLA identical (A, B, C, DR, DQ) related donor

AND either of the following:

- 3a. **Patients in good clinical condition, ~~greater than age 3.5 months~~**, who do not have a readily available HLA identical (A, B, C, DR, DQ) unrelated donor (within 6 weeks of searching, available for transplant within 3 months of diagnosis)

OR

- 3b. Patients ~~of any age~~ with an active, therapy-resistant infection or other medical condition that significantly increase the risk of allogeneic transplant

Current exclusion criteria

1. No available molecular diagnosis confirming SCID-X1.
2. Patients who have an available HLA-identical related donor.
3. Diagnosis of active malignant disease other than EBV-associated lymphoproliferative disease.
4. ~~Age under 3.5 months in good clinical condition for whom a haplo-identical related donor is available.~~
5. Patients with evidence of infection with HIV-1.
6. Previous gene transfer.
7. Major (life-threatening) congenital anomalies.
8. Other conditions which in the opinion of the P.I. or co-investigators, contraindicate collection and/or infusion of transduced cells or indicate patient's inability to follow the protocol.

Proposed changes in Informed Consent

We are selecting people for this study that have SCID-X1 and have a higher chance of complications or problems after standard stem cell transplant. We offer the study if:

Your child has either of the following.

1. Your child ~~is over 3 ½ months of age and~~ does not have a closely matched unrelated donor after searching for 6 weeks.
2. Your child has an infection that is untreatable or uncontrolled infection despite the right antibiotics, or has a medical condition that makes stem cell transplant especially risky.

Proposed changes in Informed Consent (section on “How is SCID-X1 usually treated?”)

Donors may also be parents or closely matched people outside the family, but the results are not as good as with a fully matched brother or sister. Stem cell transplants using parents as donors can be done with or without chemotherapy (when parents are donors the transplant may have to be repeated). Sometimes the transplant does not fully fix the immune system and those patients need lifelong infusions of antibodies.

(continued next slide)

Proposed changes in Informed Consent (section on “How is SCID-X1 usually treated?”)

According to published and unpublished studies, survival after stem cell transplant from a parent is approximately 60-80% for children older than 3.5 months and 85-90% for children younger than 3.5 months at the time of transplant. (1-3) The proportion of these children who need lifelong antibody replacement varies depending on whether chemotherapy is given prior to stem cell transplant or not (approximately 30-40% for those who do and approximately 60% for those who do not). (1-6)

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Proposed changes in Informed Consent (section on “How is SCID-X1 usually treated?”)

Transplants from closely matched people outside the family usually do not have to be repeated and usually results in full replacement of the immune system but requires high doses of chemotherapy for the stem cell transplant to work, which has long-term side effects.

Stem cell transplant using parents or unrelated people can be complicated by graft versus host disease (GVHD), a disease where the new immune system attacks the patient's body. **Around 20% of children receiving these types of transplants may develop GVHD, that may require strong and prolonged immune suppression medicine to treat.**

Proposed changes in Informed Consent (from section “...what are the other choices?”)

If you do not wish for your child to participate in this study, your child can be treated with stem cell transplant, in other words bone marrow, blood, or cord blood transplantation. This is the standard therapy for curing SCID. Stem cell transplant from a parent without chemotherapy is an option that is standard in many institutions and is an important alternative for treatment that you should consider, **especially if your child is less than 3.5 months old**. Another option is stem cell transplant using stem cells from an unrelated person who is not fully matched, with chemotherapy.