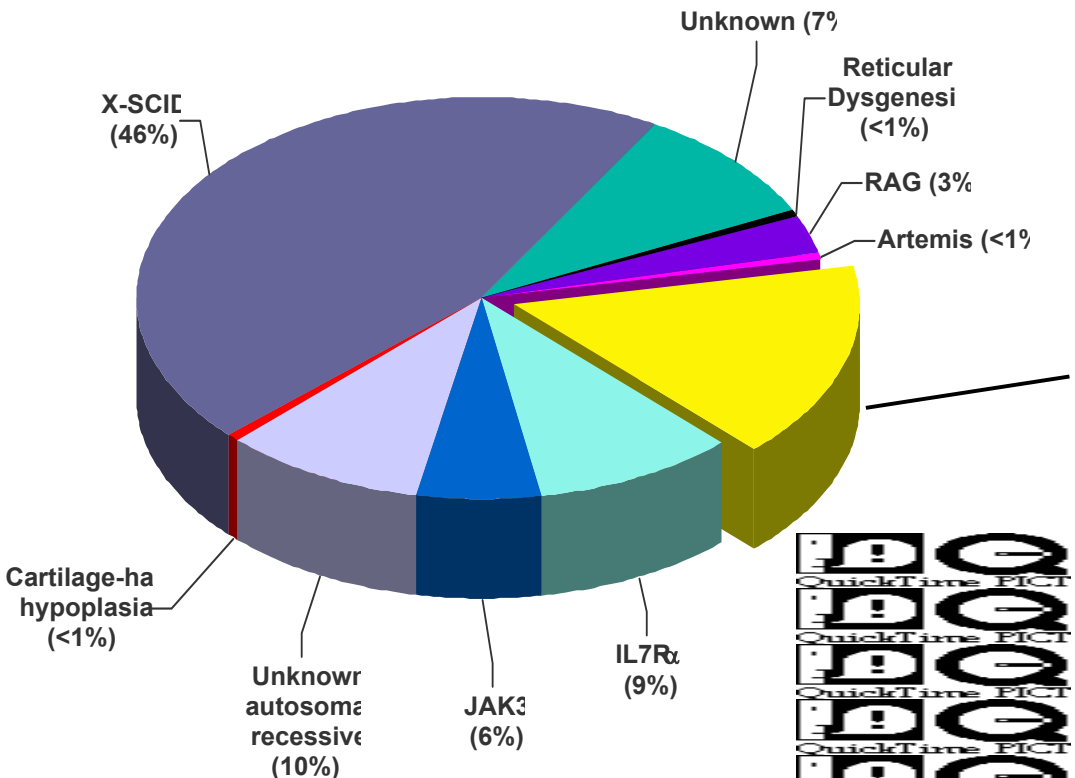
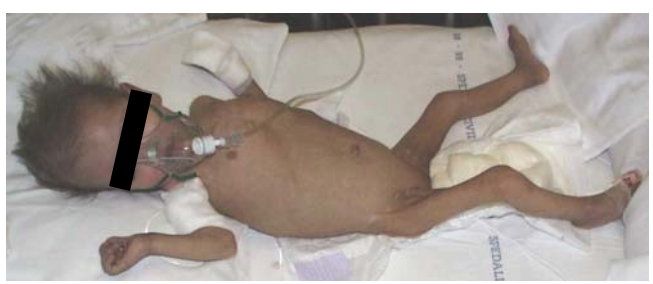
Severe Combined Immunodeficiencies



ADA Deficiency (16%)

- Autosomal Recessive



Buckley RH,
BRMAC FDA Washington DC
October 2002

ADA deficiency - Conventional Treatments

Allogeneic Bone Marrow Transplantation

Lancet 2003, 361:553

- HLA-identical: 73% survival (n=18)
- Haploidentical: 23.5% survival (n=25)

PEG-ADA

M.S. Hershfield, Duke University Medical Center, NC, USA

- 122 pts - 61 in the US
- 80% protective immunity; 20% minimal improvement
- >50% require IVIG
- 10% develop neutralizing antibodies
- 74% survival

ADA Gene Therapy Trials

Target cell	Country	Year	No. of patients
T lymphocytes	USA	1990	2
T lymph + BM-HSCs	Italy	1992	3
Cord blood HSCs	USA	1993	3
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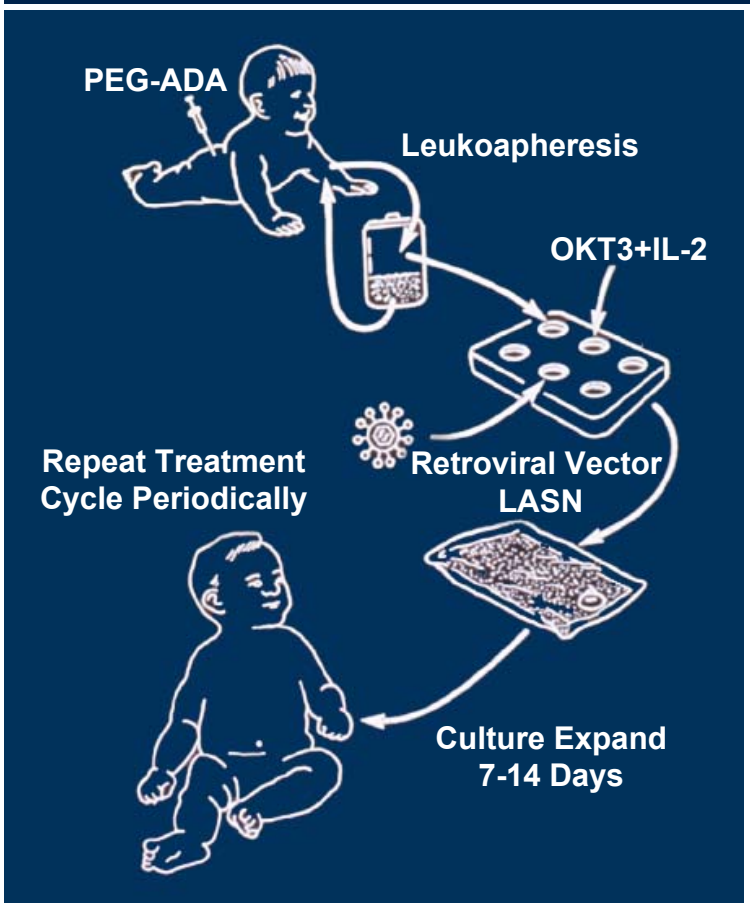
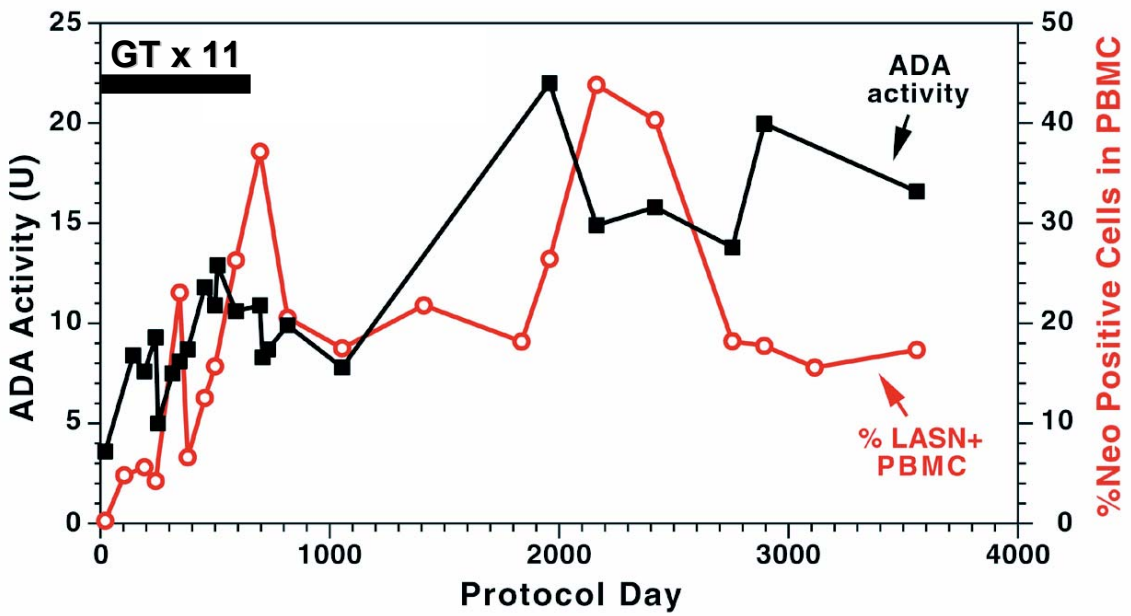
BM-HSCs	USA	2001	4
BM-HSCs	Japan	2003	2
BM-HSCs	UK	2003	1

Persistence and expression of the adenosine deaminase gene for 12 years and immune reaction to gene transfer components: long-term results of the first clinical gene therapy trial

Linda Mesler Muul, Laura M. Tuschong, Sherry Lau Soenen, G. Jayashree Jagadeesh, W. Jay Ramsey, Zhifeng Long, Charles S. Carter, Elizabeth K. Garabedian, Melinna Alleyne, Margaret Brown, Wendy Bernstein, Shepherd H. Schurman, Thomas A. Fleisher, Susan F. Leitman, Cynthia E. Dunbar, R. Michael Blaese, and Fabio Candotti

BLOOD, 1 APRIL 2003 • VOLUME 101, NUMBER 7





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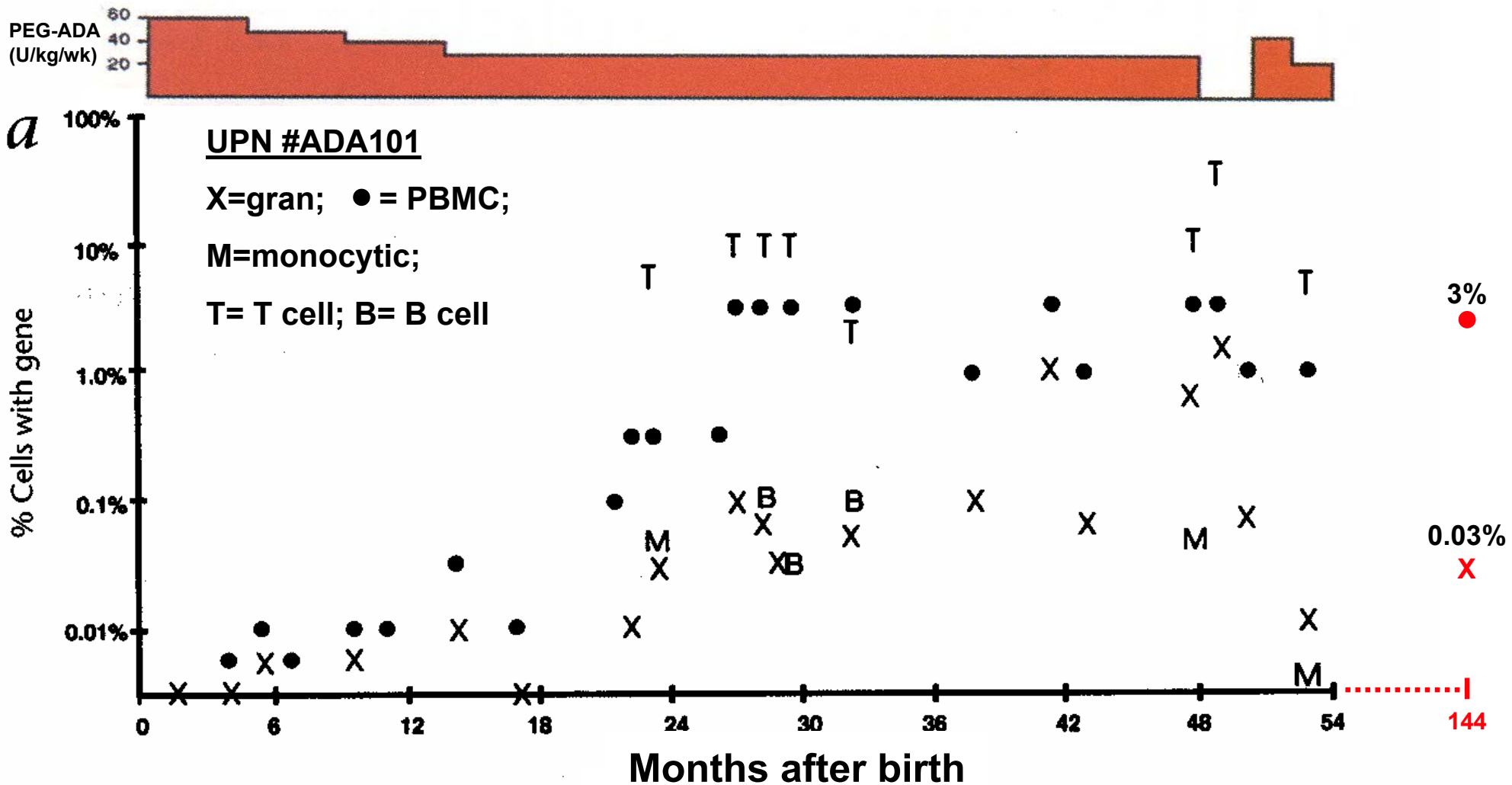
Frequency of Gene-Containing Leukocytes



Kohn et al, *Nat Med* 4:775-780, 1998 and D.B. Kohn personal communication, February 2005

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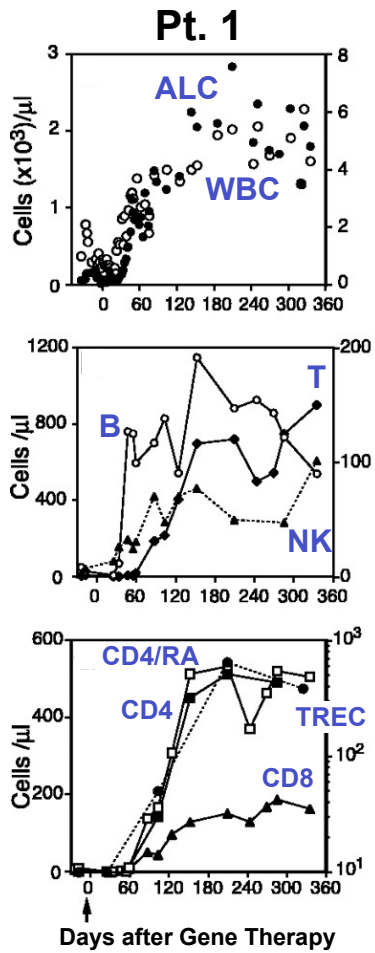
Gene Therapy for ADA deficiency: Role of Preparative Chemotherapy

Correction of ADA-SCID by Stem Cell Gene Therapy Combined with Nonmyeloablative Conditioning

Alessandro Aiuti,[1] Shimon Slavin,[2] Memet Aker,[2] Francesca Ficara,[1] Sara Deola,[1] Alessandra Mortellaro,[1] Shoshana Morecki,[2] Grazia Andolfi,[1] Antonella Tabucchi,[3] Filippo Carlucci,[3] Enrico Marinello,[3] Federica Cattaneo,[1] Sergio Vai,[1] Paolo Servida,[4] Roberto Miniero,[5] Maria Grazia Roncarolo,[1,6] * Claudio Bordignon[1,6]*†

28 JUNE 2002 VOL 296 SCIENCE



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BM-HSCs	USA	2001	4
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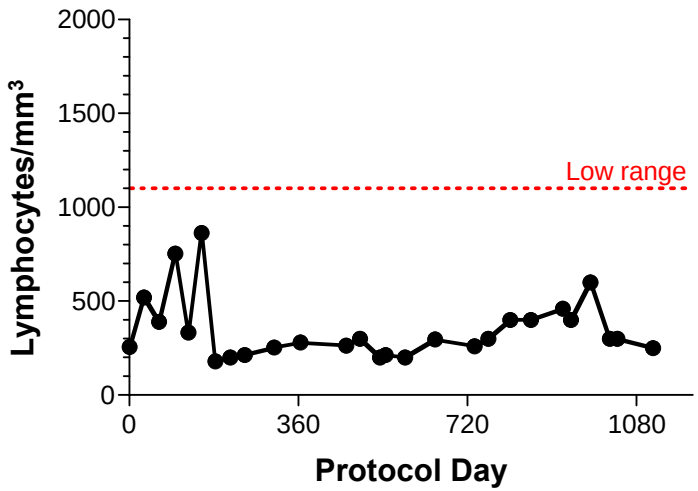
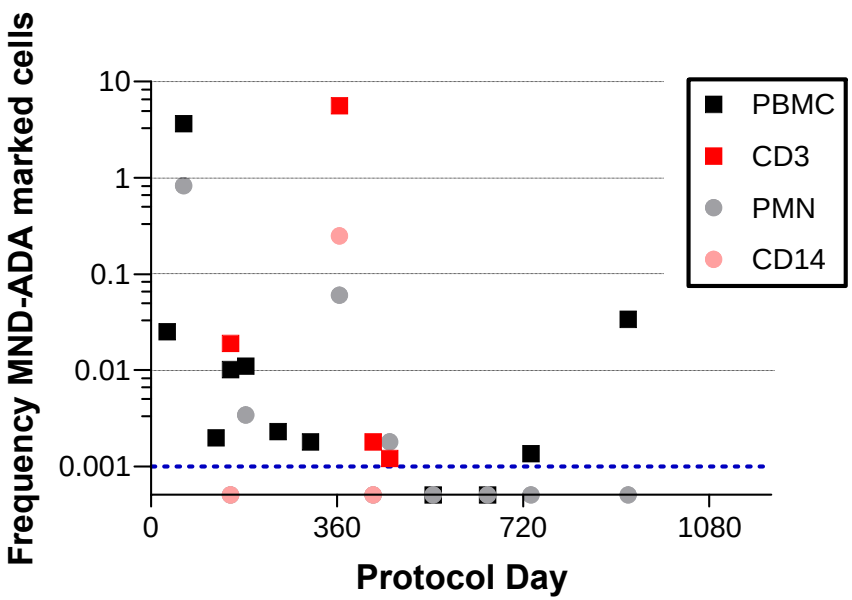
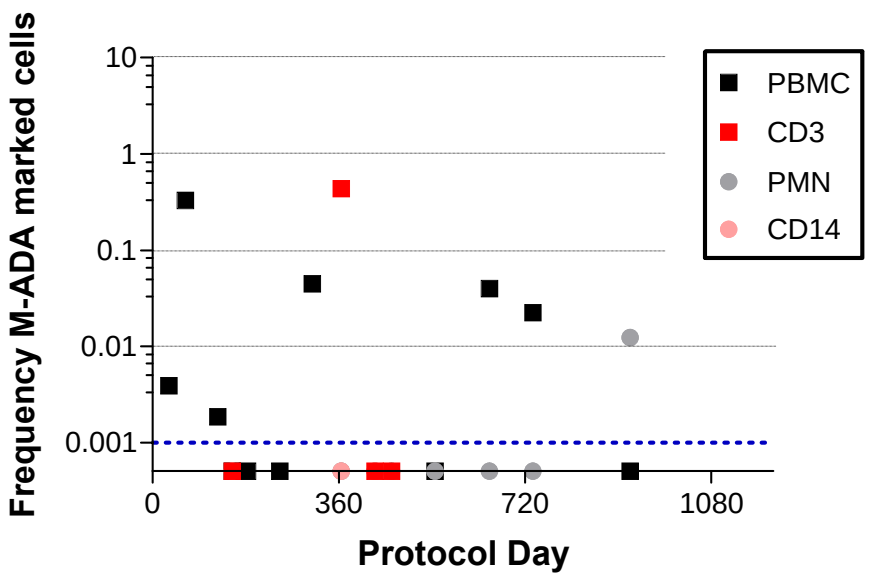
BM-HSCs	UK	2003	1

Patient ADA202N: Transduction and Marking Data

				CD34+ Transduction		Vector-positive CFUs		ADA activity	
PIN	Sex	Age (yrs)	Infused CD34^{+}/Kg	MND	M-ADA	MND	M-ADA	MND	M-ADA
202	F	5	12 x 10^{6}	40%	66%	35%	62%	76 U	235 U







Summary

- Low level of multi-lineage marking
  - ≥ 1 year in 2 patients
  - < 6 months in 2 patients
- Higher marking in younger patients
- Higher marking in lymphoid cells
- No adverse events, no clinical benefit

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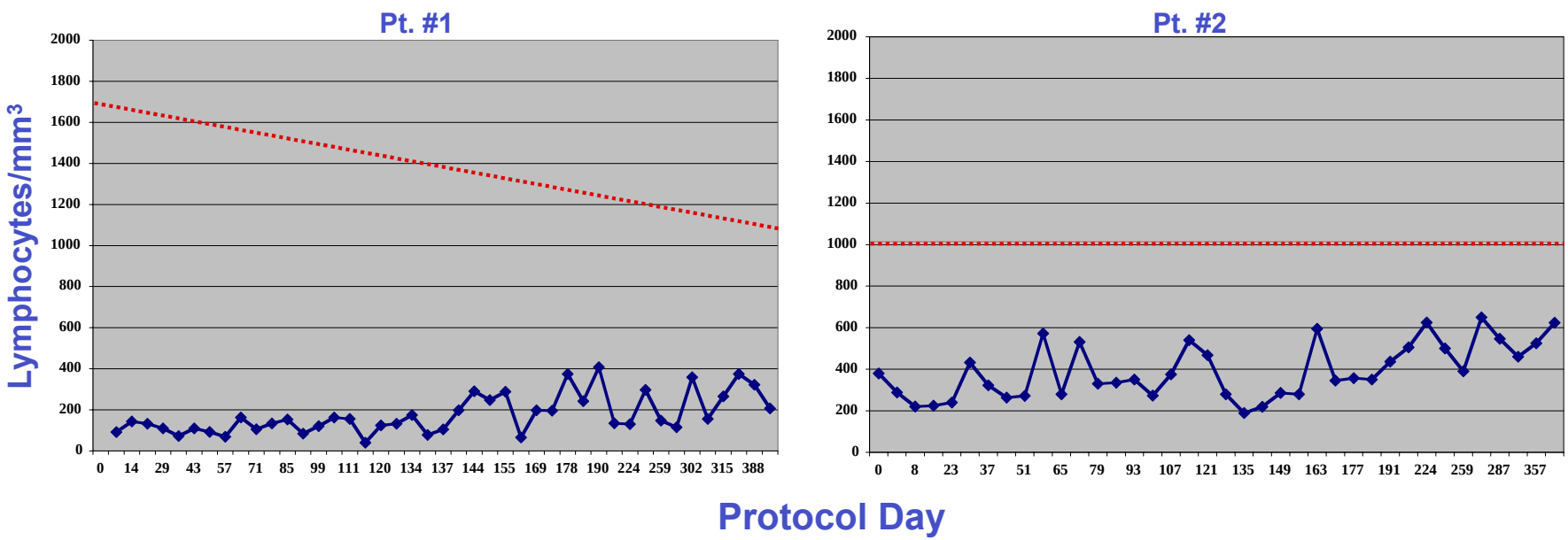
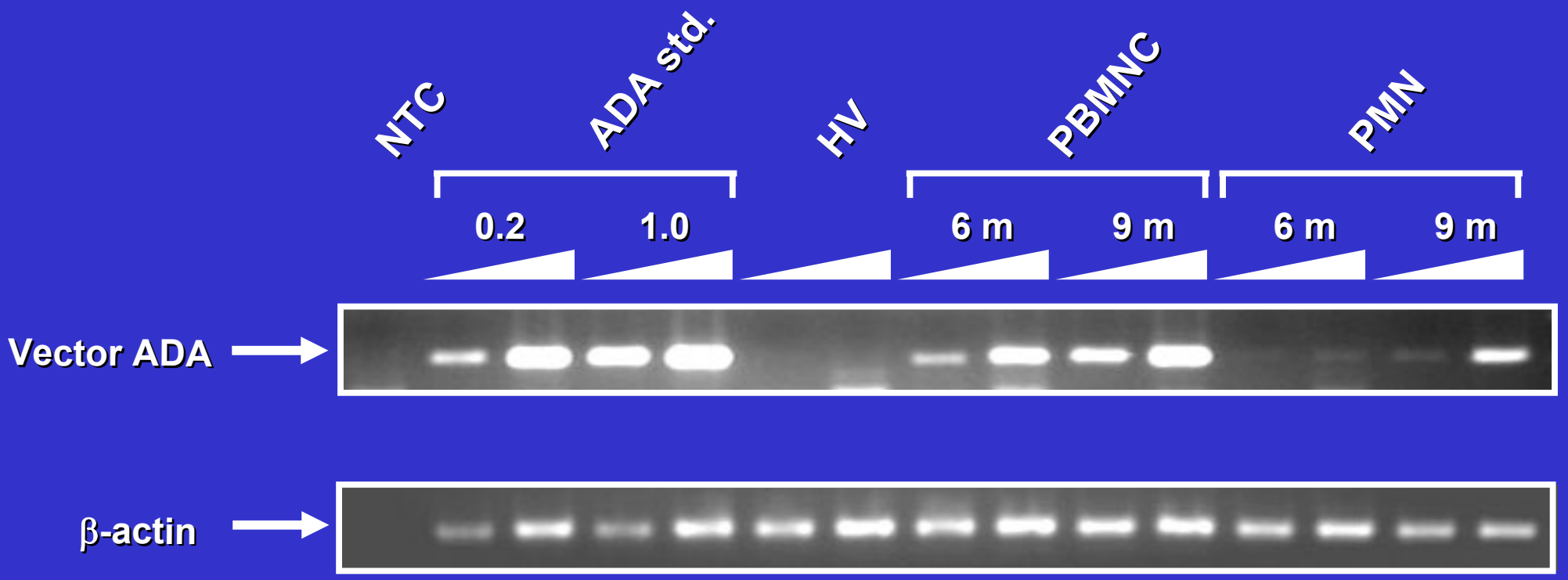
Japanese ADA Gene Therapy Trial

	Age	Infused CD34+ cells/kg	Vector-positive CFU (%)	ADA activity (U/min)
Pt. #1	4	1.38×10^6	40	318.2
Pt. #2	13	0.92×10^6	50	299.4

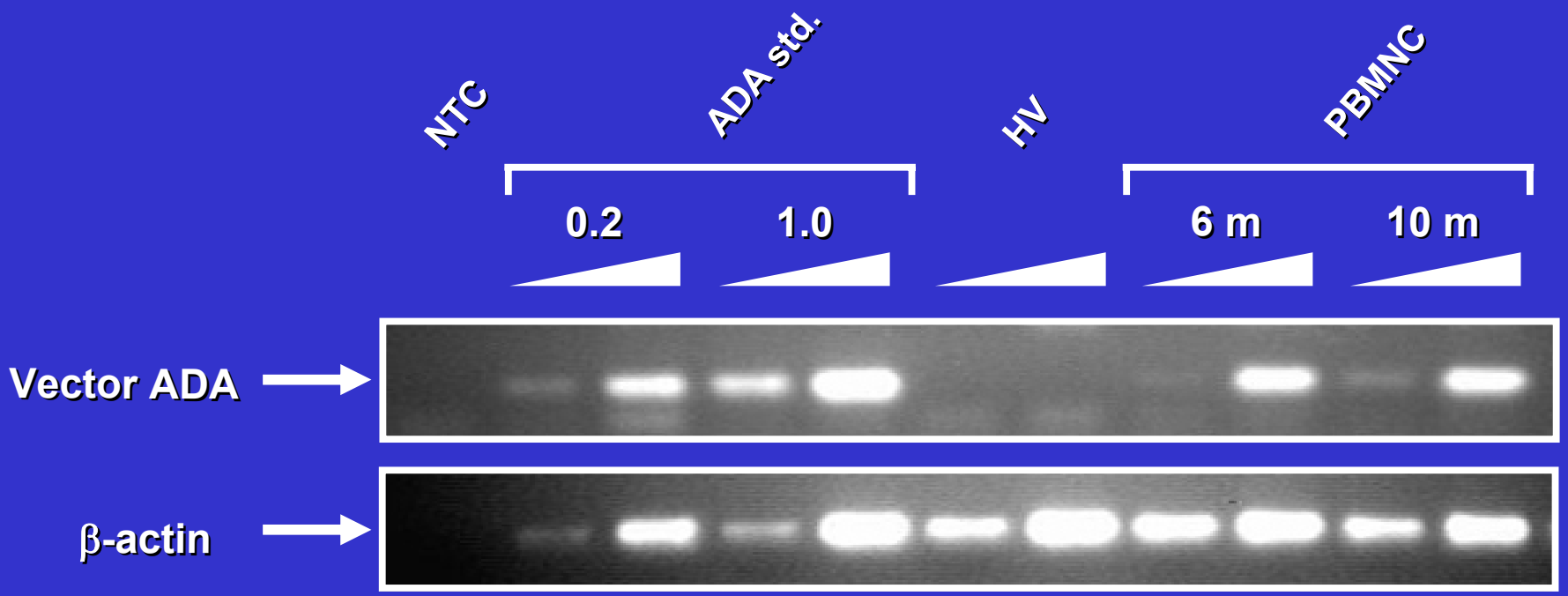


Detection of ADA transgene by PCR analysis (Pt. 1)



NTC: no template control
HV: healthy volunteer

Detection of ADA transgene by PCR analysis (Pt. 2)



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British success heralds gene therapy revolution

By Roger Highfield, Science Editor
(Filed: 11/03/2005)

A hereditary disease has been successfully treated by Britain's leading centre for gene transplants, showing that the revolutionary promise of gene therapy is at last being realised.

The advance marks a renewed attempt to treat ADA deficiency - called bubble baby syndrome because victims must be protected in a sterile environment - the subject of the world's first gene therapy trial.

Mustaf had ADA deficiency and was unable to fight infection

The pioneering trial, which began 15 years ago in America, produced results which were, at best, ambiguous. Now Britain joins Italy in managing the first clearly successful treatment of this potentially fatal genetic disorder by using a virus to transplant "healthy" genes into the body.

The team - Prof Adrian Thrasher and Dr Bobby Gaspar from Great Ormond Street Hospital in London - is one of only three to have reported success with gene therapy, among hundreds of failed attempts.

The team has already used gene therapy to treat another bubble baby disorder.

HSC Gene Therapy for ADA deficiency: Summary

- 22 patients treated
  - 19 infants/children
  - 2 adolescents
  - 1 adult
- 8 patients with gene marking for ≥30 months
- 7 patients showed clinical benefit
- No lymphoproliferative complications
- RVV integration pattern similar to X-SCID trials