Haematopoietic Stem Cell Gene Therapy
…. moving toward standard of care ?

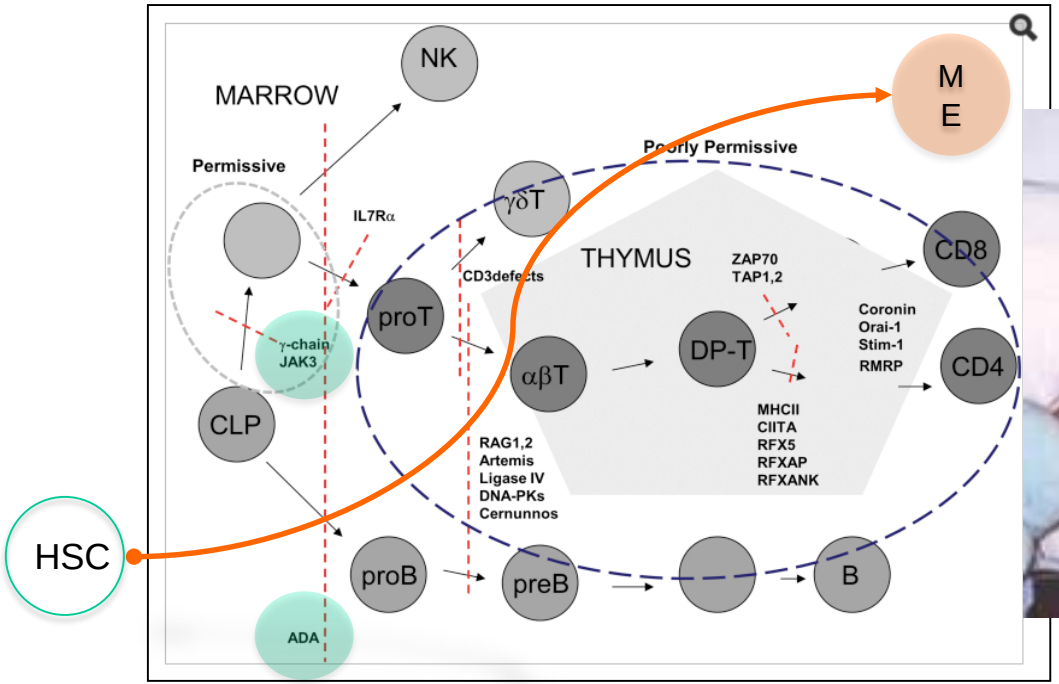
Hong Kong 2018
2nd International Summit on HUMAN GENOME EDITING

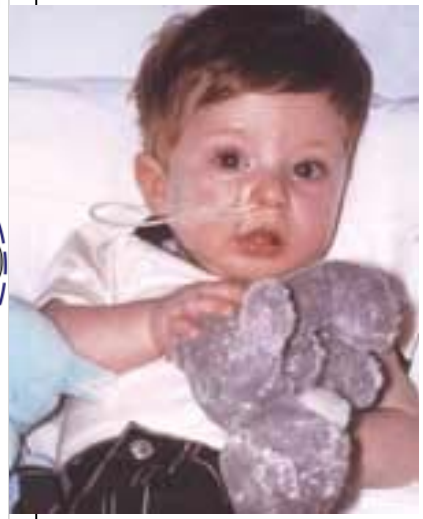
Adrian J Thrasher
UCL Great Ormond Street Institute of Child Health
London WC1N1EH

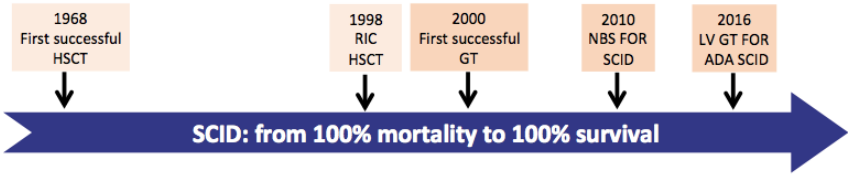
Disclosures….

Founder and consultant at Orchard Therapeutics.
Consultant for Rocket Pharmaceuticals, Generation bio, and 4Bio Capital Partners

Primary immunodeficiency: a rare disease paradigm....

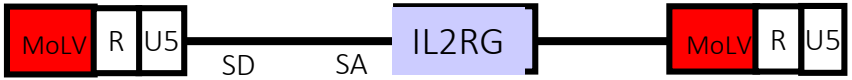


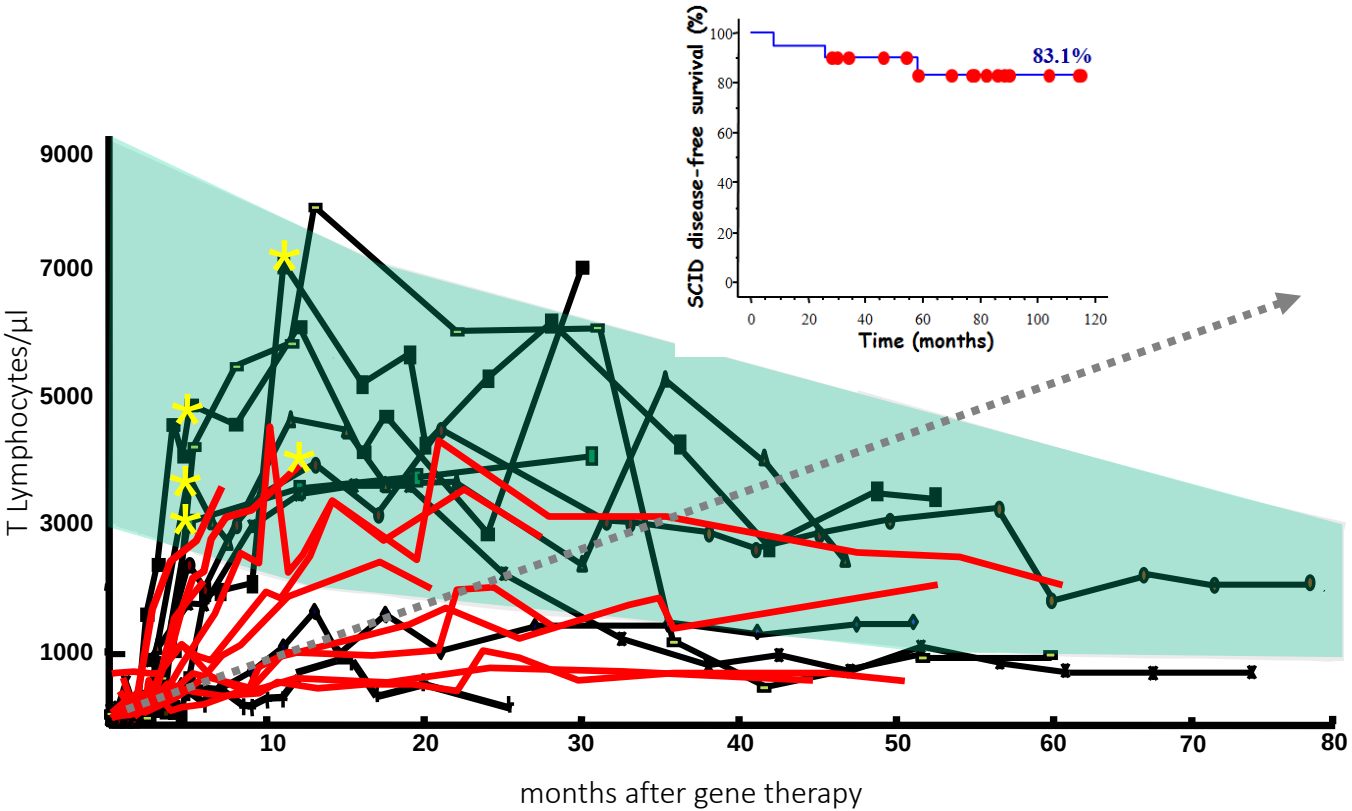




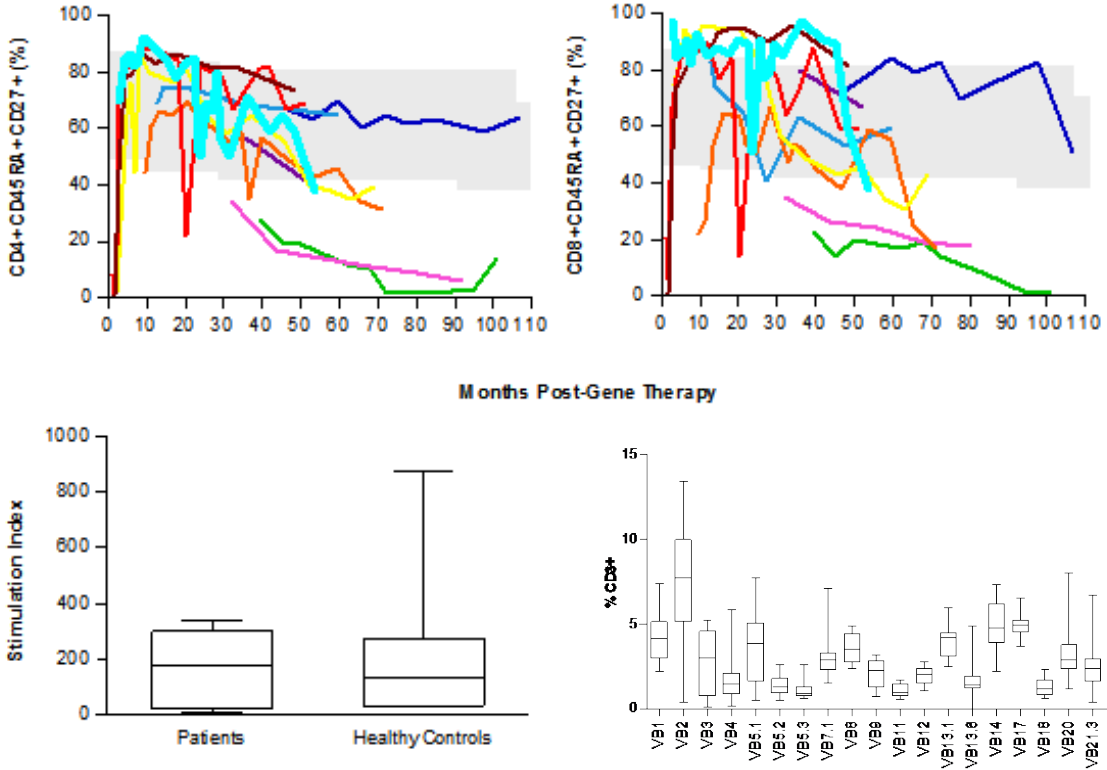
Newborn screening

SCID-X1 Gene Therapy (UK/France, 20 patients)

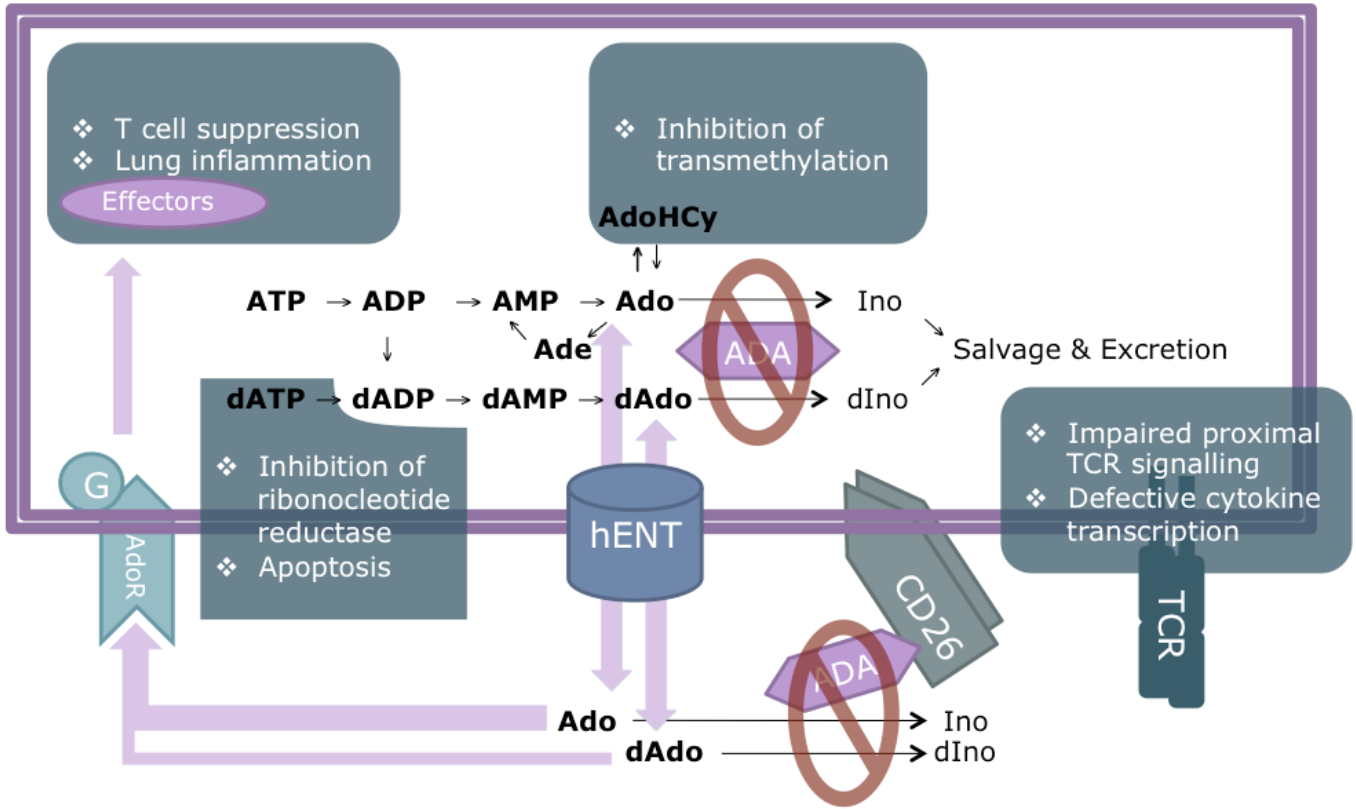




SCID-X1 gene therapy, (UK 10 patients, 10-17yr fu)…



ADA-SCID: disease pathophysiology…



Summary of ADA-Deficient SCID Patients Retroviral Vectors, Myelosupressive Conditioning

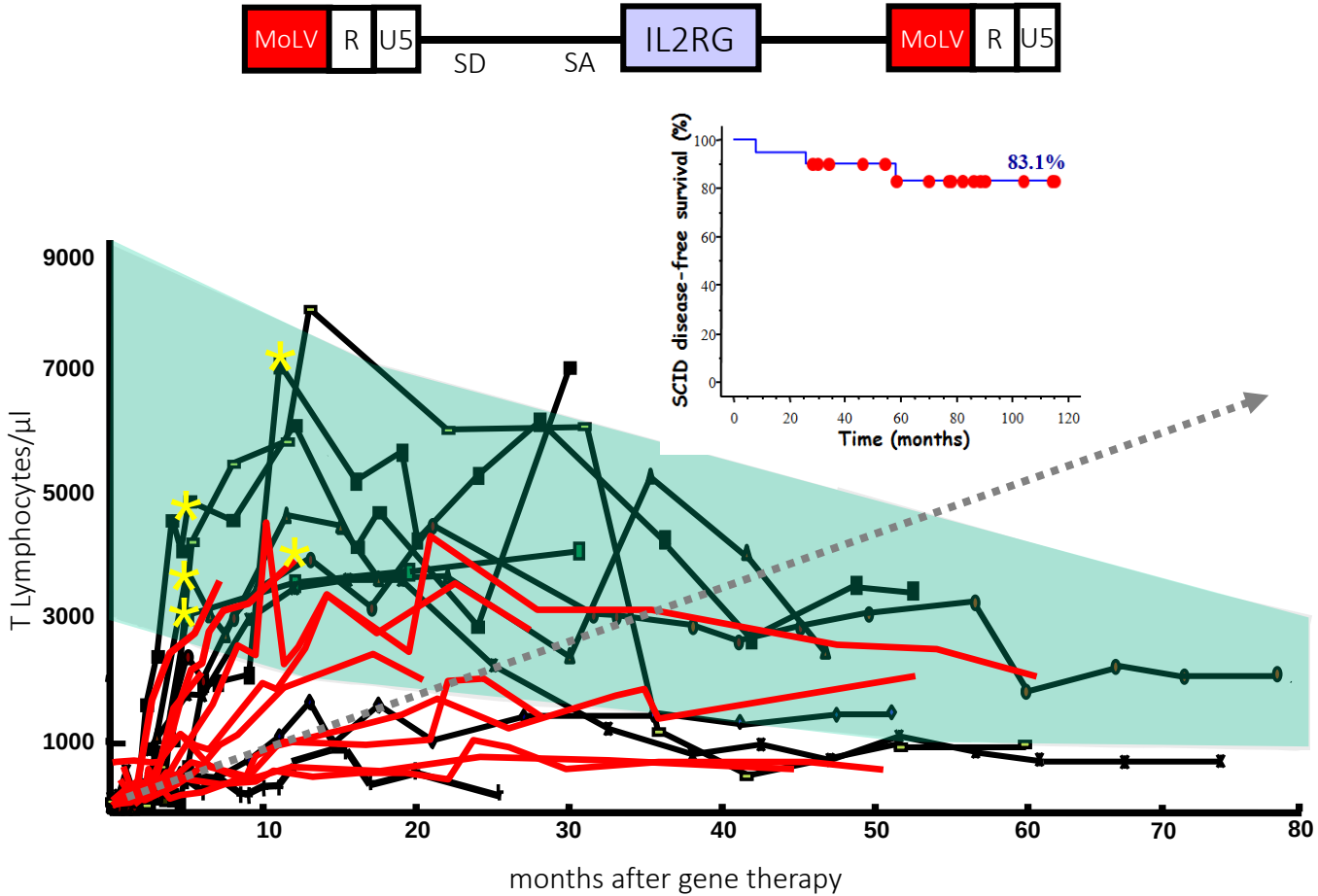
Center	# Pts	F/U (yrs)[1]	Off Enzyme	Survival	DFS[2]
Milan	18	0.8 – 11.5	15/18	100%	83.3%
London	8	0.5 – 7.5	4/8	100%	50%
CHLA-NHGRI	6	3–7	3/6	100%	50%
UCLA-NHGRI	10	0.2-4	9/10	100%	90%
TOTAL	42	0.2 – 11.5	31/42	100%	73.8%

[1] As of January 2013

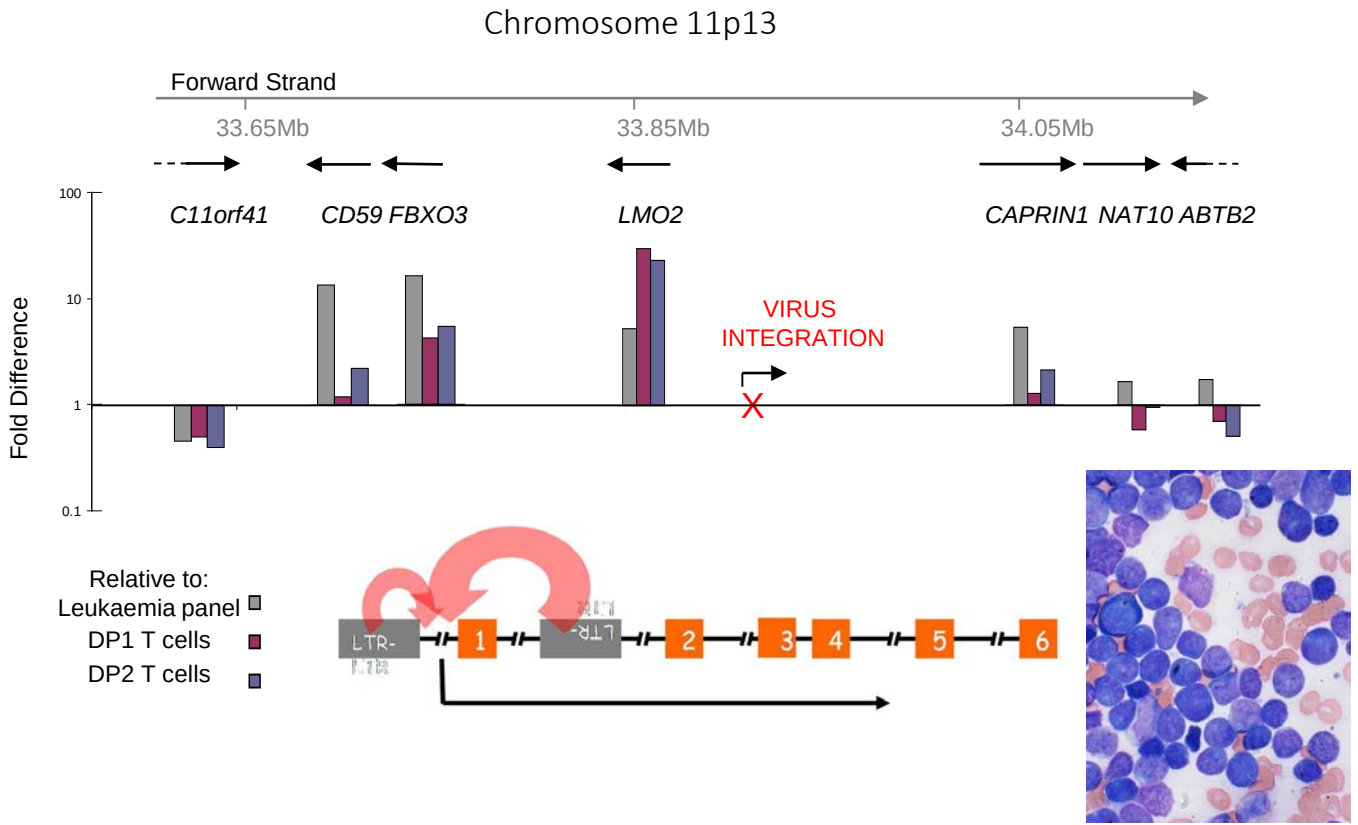
[2] DFS ≡ Alive without BMT or PEG-ADA re-start

Gaspar, Aiuti, Kohn, unpublished

SCID-X1 Gene Therapy (UK/France, 20 patients)



Enhancer-mediated insertional mutagenesis...



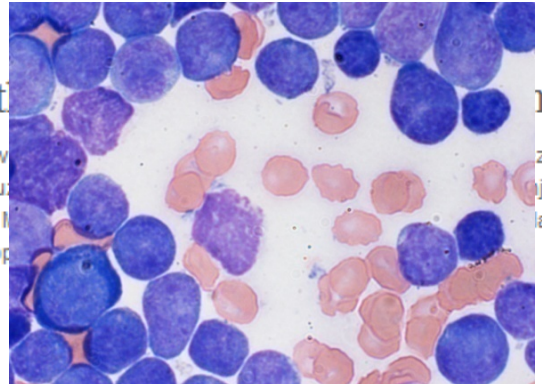
The NEW ENGLAND JOURNAL of MEDICINE

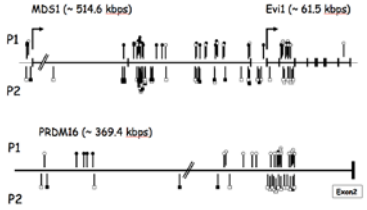
ORIGINAL ARTICLE

Stem-Cell Gene Therapy for t…me

Kaan Boztug, M.D., Manfred Schmidt, Ph.D., Adrian Schw…z, Ph.D., Ricardo A. Dewey, Ph.D., Marie Böhm, M.Sc., Ali Nowrou…ja Naundorf, M.Sc., Klaus Kühlcke, Ph.D., Rainer Blasczyk, M…lan S. Orange, M.D., Ph.D., Christof von Kalle, M.D., and Christop…

N Engl J Med 2010; 363:1918-1927 | November 11, 2010



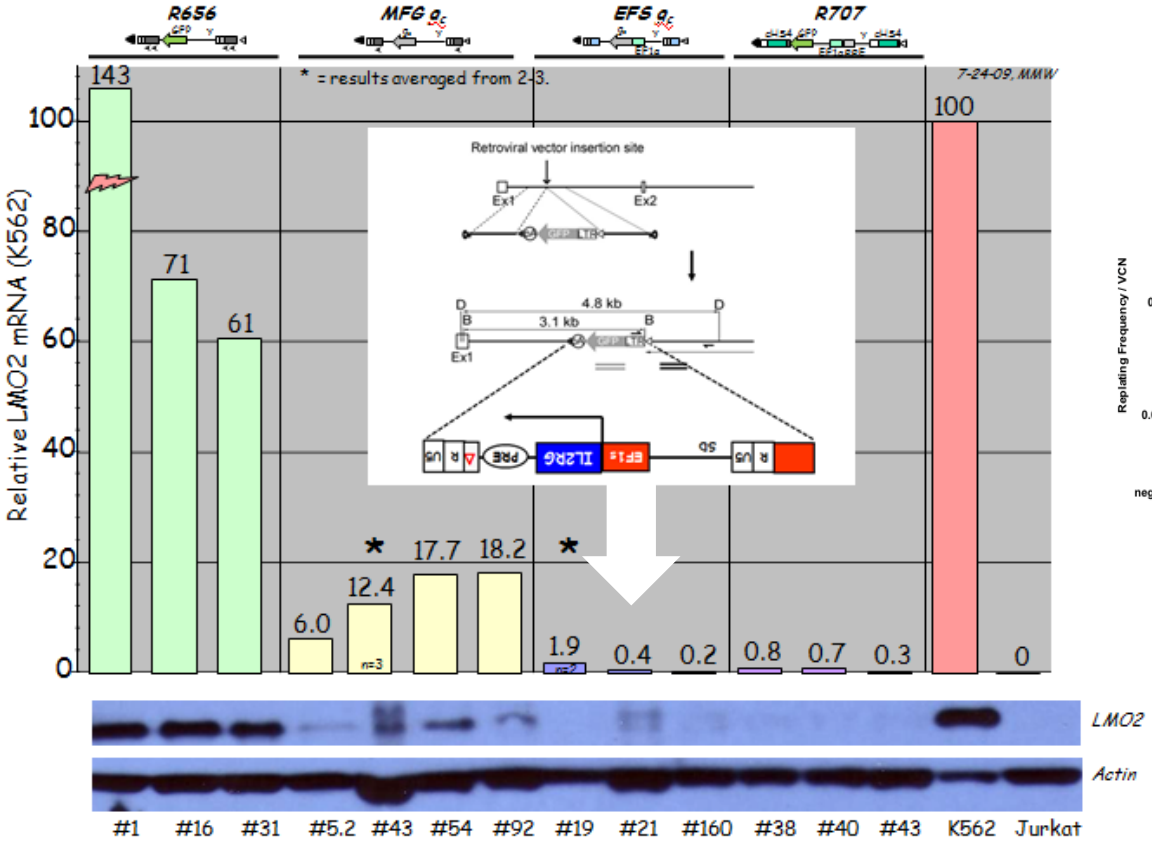


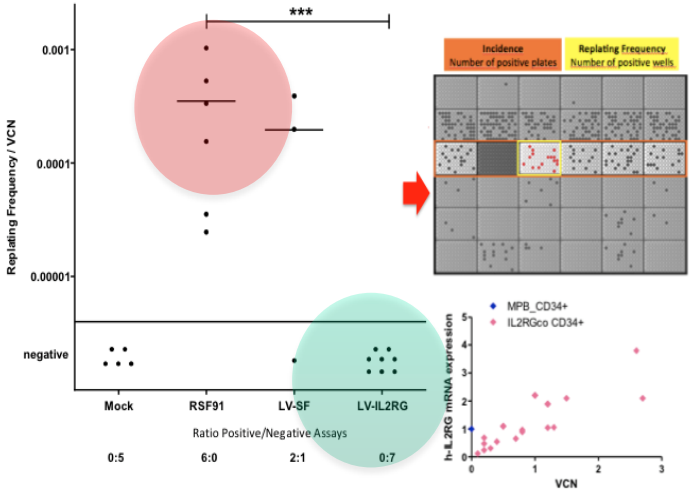
RESEARCH ARTICLE | GENE THERAPY

Gene Therapy for Wiskott-Aldrich Syndrome—Long-Term Efficacy and Genotoxicity

Christian Jörg Braun[1,*], Kaan Boztug[2,*,†], Anna Paruzynski[3,*], Maximilian Witzel[1,*], Adrian Schwarzer[2,4], Michael Rothe[4], Ute Modlich[4], Rita Beier[2], Gudrun Göhring[5], Doris Steinemann[5], Raffaele Fronza[3], Claudia Regina Ball[3,6], Reinhard Haemmerle[4], Sonja Naundorf[7], Klaus Kühlcke[7], Martina Rose[8], Chris Fraser[9], Liesl Mathias[10], Rudolf Ferrari[11], Miguel R. Abboud[12], Waleed Al-Herz[13], Irina Kondratenko[14], László Maródi[15], Hanno Glimm[3,6], Brigitte Schlegelberger[5], Axel Schambach[4], Michael Heinrich Albert[1], Manfred Schmidt[3,*], Christof von Kalle[3,6,*] and Christoph Klein[1,*,‡]

Measuring mutagenesis *in vitro*....



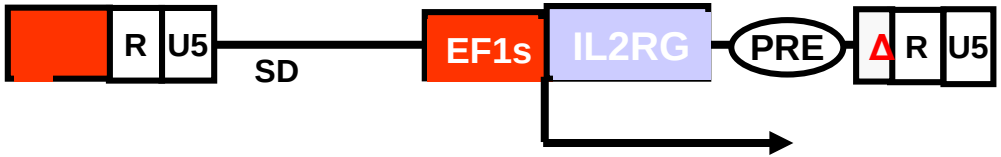


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Modified γ-Retrovirus Vector for X-Linked Severe Combined Immunodeficiency

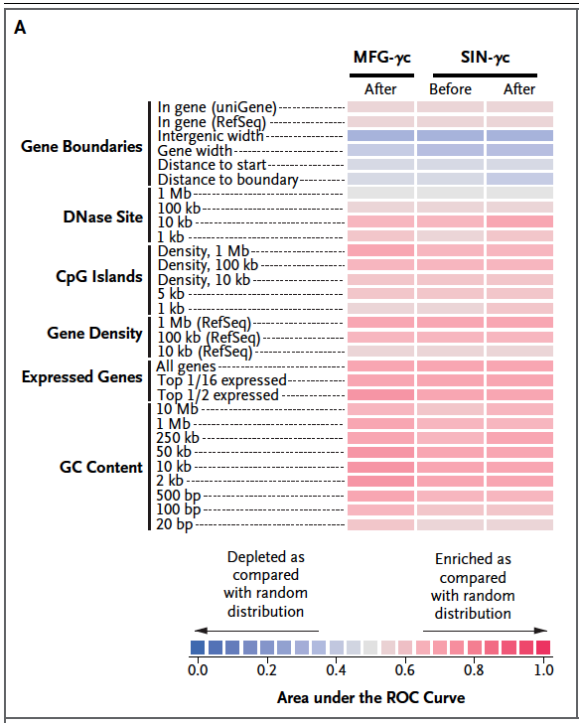
S. Hacein-Bey-Abina, S.-Y. Pai, H.B. Gaspar, M. Armant, C.C. Berry, S. Blanche, J. Bleesing, J. Blondeau, H. de Boer, K.F. Buckland, L. Caccavelli, G. Cros, S. De Oliveira, K.S. Fernández, D. Guo, C.E. Harris, G. Hopkins, L.E. Lehmann, A. Lim, W.B. London, J.C.M. van der Loo, N. Malani, F. Male, P. Malik, M.A. Marinovic, A.-M. McNicol, D. Moshous, B. Neven, M. Oleastro, C. Picard, J. Ritz, C. Rivat, A. Schambach, K.L. Shaw, E.A. Sherman, L.E. Silberstein, E. Six, F. Touzot, A. Tsytsykova, J. Xu-Bayford, C. Baum, F.D. Bushman, A. Fischer, D.B. Kohn, A.H. Filipovich, L.D. Notarangelo, M. Cavazzana, D.A. Williams, and A.J. Thrasher

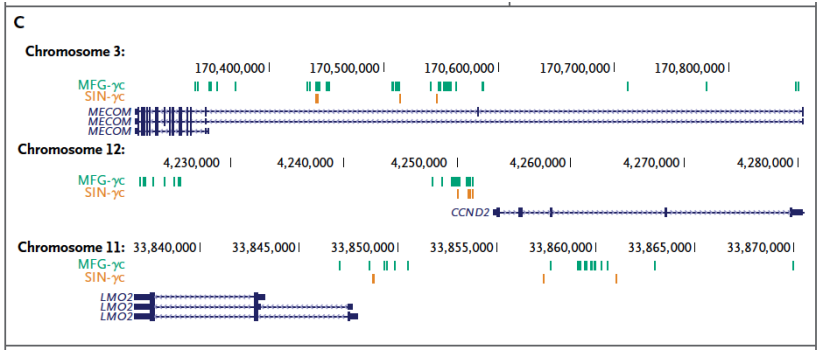


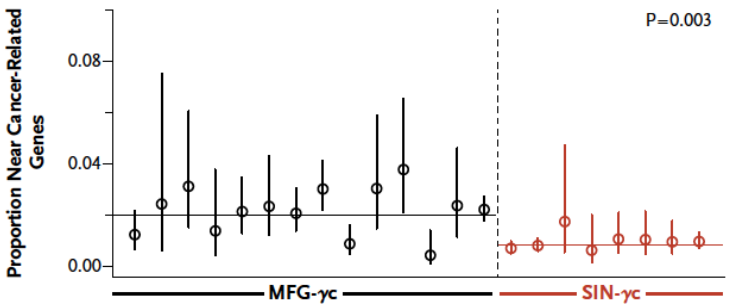
Parallel trials in US (Boston, Cincinnati, Los Angeles), Paris, London
Interim efficacy and safety analysis of the first 9 patients enrolled
Median follow-up 29.1 months (12.1-38.7)
No myelosuppressive conditioning

Insertion near lymphoid proto-oncogenes are far less frequent….

Frederic Bushman, University of Pennsylvania

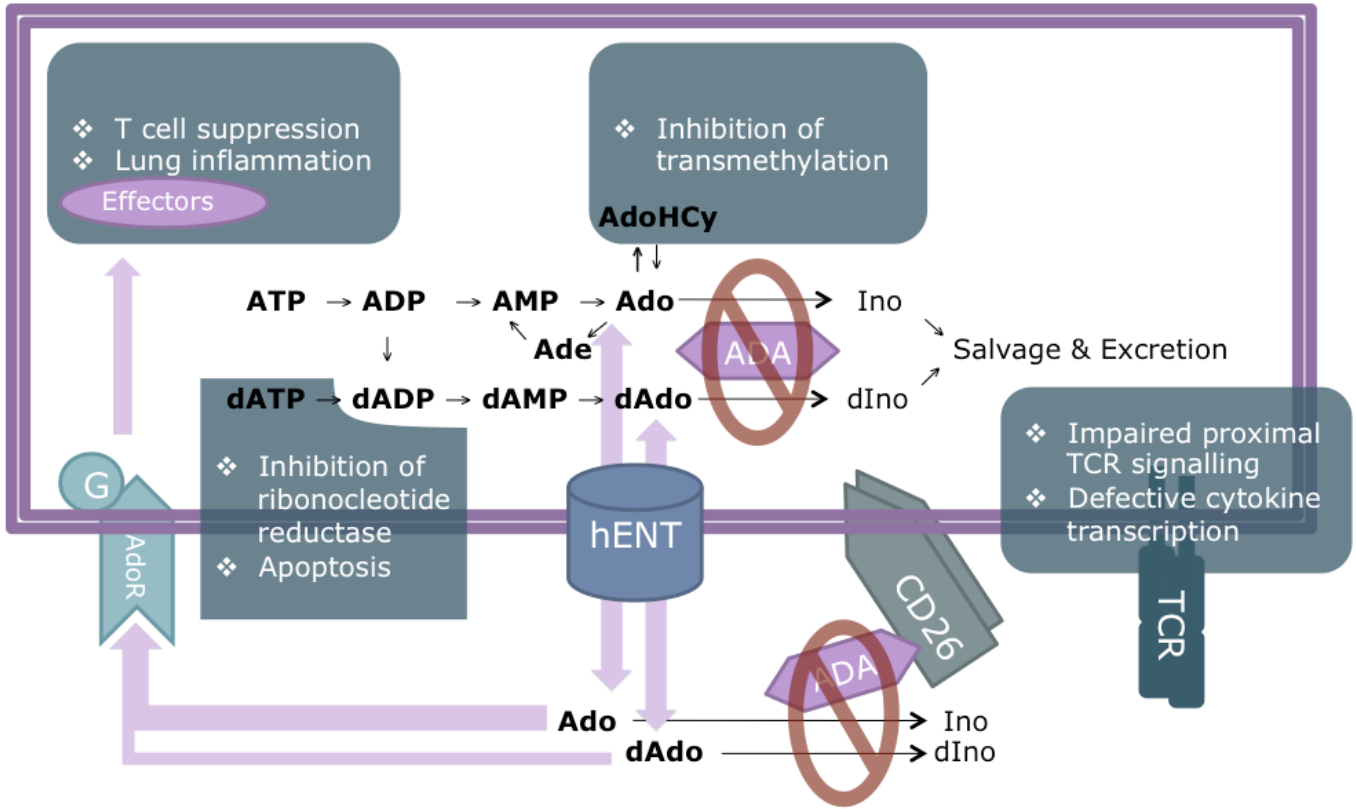




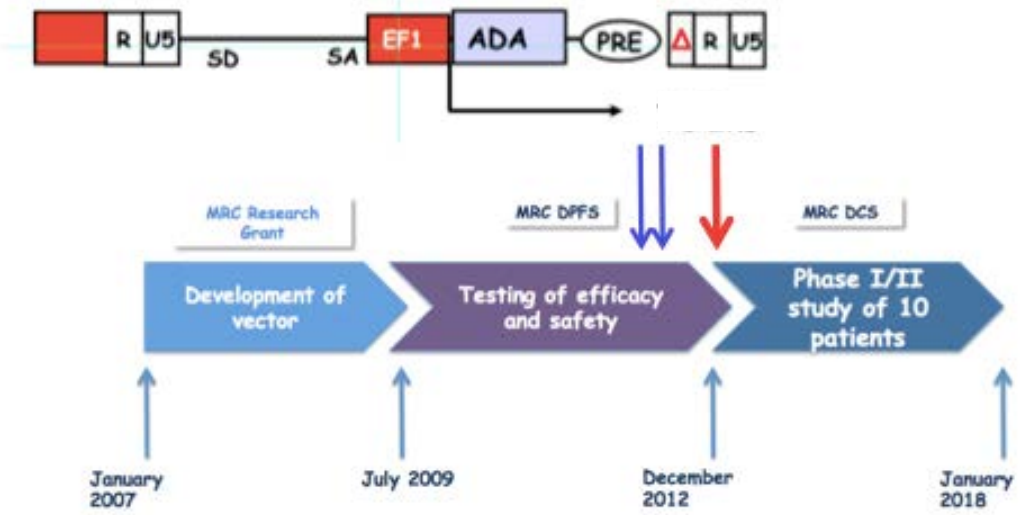


Hacein-Bey-Abina, Pai et al, NEJM 2014

ADA-SCID: disease pathophysiology…



Phase I/II, open-label, non-randomised, trial to assess the safety and efficacy of EF1αS-ADA lentiviral vector mediated gene modification of autologous CD34+ cells from ADA-deficient individuals



UCL-GOSH and UCLA: enrolled >50 patients August 2018

LV gene therapy for ADA SCID (OTL101) – cumulative data

Cohort size	48 patients treated (follow-up of 1-60 months) as of June 2017
Survival	100% survival
Immunological and metabolic recovery	• Immunological and metabolic recovery in 47/48 patients • 47/48 patients with > 6 months follow-up off ERT
Patients off immunoglobulin replacement therapy	majority with > 18 months follow-up off IgRT
Risk of leukaemia	No evidence of persistent clonal dominance

CD34+ cells transduced with lentiviral vector, fresh and cryopreserved formulations

Choice of therapies….

	Allogeneic HSCT (MUD / haploidentical)	Chronic ERT (Adagen®)	Ex-vivo autologous GT
Single intervention	✓	✗	✓
Survival	✗ • **67% (1-year) MUD** (#1) • **43% (1-year) haploidentical** (#1)	+/- short term ✗ long-term **78% survival at 20 years** (#1)	✓ **100% survival** (#3)
Long-term immune reconstitution	✓	+/- Declining immune function from 2 years post initiation or ERT	✓
Morbidity & Safety profile	✗ • Risk of acute and chronic graft-versus host disease • Risk of rejection • Conditioning-related infertility	✓ • No risk of GvHD / rejection • Overall favourable safety profile • Frequent monitoring required • Risk of immunogenicity	✓ • No risk of GvHD / rejection • Overall favourable safety profile

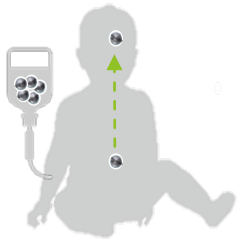
Broadening HSC gene therapy landscape……

Disease	Current phase
SCID conditions	
LV ADA SCID	Phase I/II - registration
LV SCID-X1	Phase I/II - registration
RAG 1	Phase I/II in preparation
RAG2	Proof of concept
Artemis	Phase I/II in preparation
Other immunodeficiencies	
Wiskott-Aldrich Syndrome	Phase I/II - registration
X-linked chronic granulomatous disease	Phase I/II
AR Chronic Granulomatous Disease	Proof-of-concept; Phase I/II in prep
Perforin deficiency	Proof-of-concept; Phase I/II in prep
Munc 13-4 deficiency	Proof-of-concept
X-linked lymphoproliferative disease	Proof-of-concept
Leukocyte Adhesion deficiency	Proof-of-concept; Phase I/II in prep
X-linked agammaglobulinaemia	Proof-of concept
Metabolic Diseases	
X-linked adrenoleukodystrophy	Phase I/II - registration
Metachromatic leukodystrophy	Phase I/II - registration
MPS-I – Hurler syndrome	Phase I/II
MPS-II – Hunter syndrome	Pre clinical development
MPS-IIIA – Sanfilippo A	Proof-of concept
MPS-IIIB – Sanfilippo B	Proof-of concept
GLD – Krabbe disease	Pre clinical development
INCL – Batten's disease	Pre clinical development
Gaucher disease	Proof-of-concept
Fabry's disease	Phase I/II
Pompe disease	Proof-of-concept
Haemoglobinopathies	
β-thalassaemia	Phase I/II - registration
Sickle Cell Disease	Phase I/II
Bone Marrow Failure Syndromes	
Fanconi Anaemia A	Phase I/II

Clinical phase

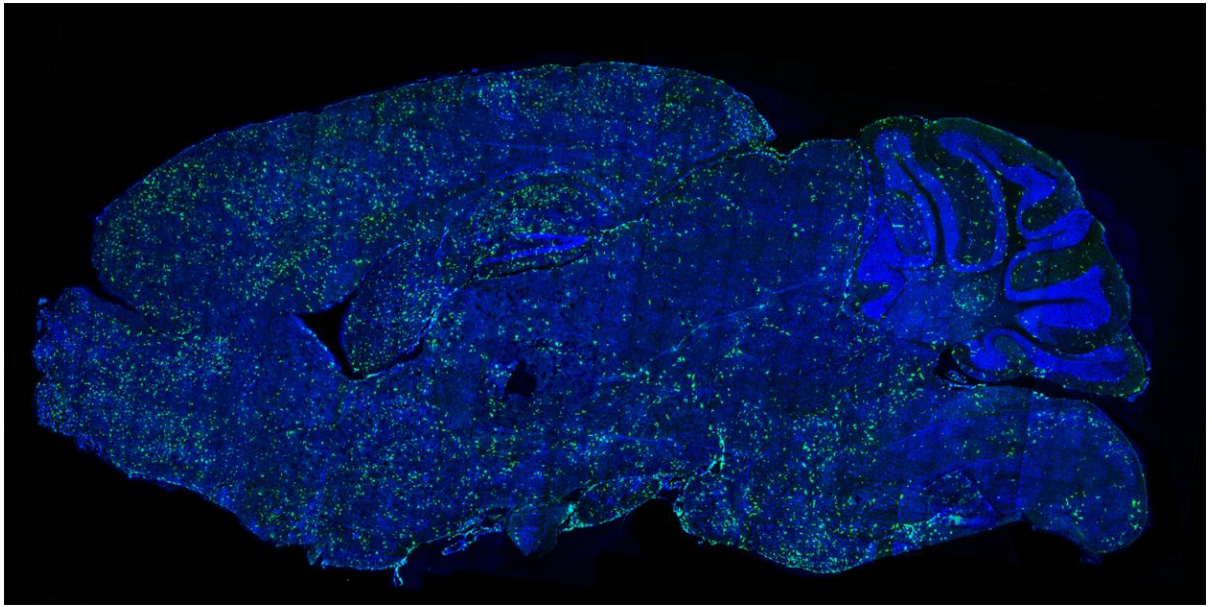
~200 patients and rising

HSC gene therapy: delivery of proteins to other tissues
Potential to treat diseases with CNS manifestations



HSC-derived myeloid cells migrate into brain across BBB

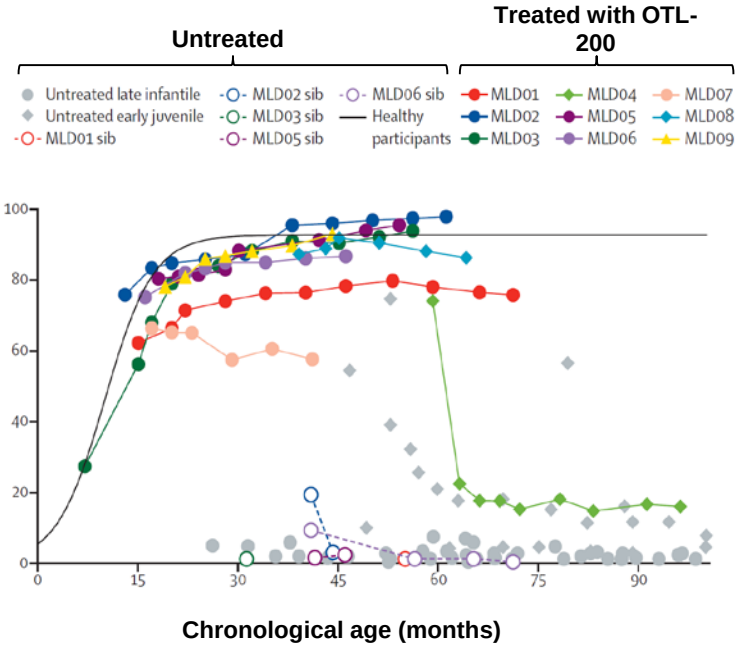
Distribution of genetically modified cells in mouse brain



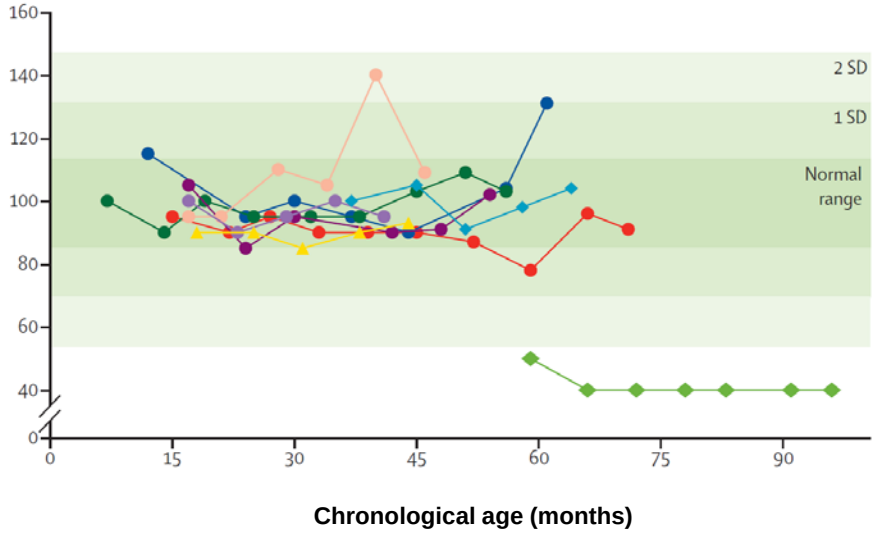
Source: Capotondo et al. PNAS 2012;109:15018-15023

Brain of a wildtype mouse transplanted with GFP-LV transduced HSPCs after Busulfan conditioning
Green = GFP (green fluorescent protein); **blue** = nuclei staining
Morphology of the ramified parenchymal cells resemble microglia at different stages of maturation (source: A. Biffi)

MLD: preservation of motor and cognitive function (Biffi et al.)



Motor function stable or comparable to healthy participants in 7/9 patients

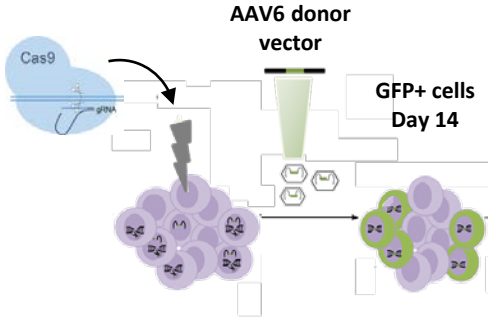


Cognitive function within normal range in 8/9 patients

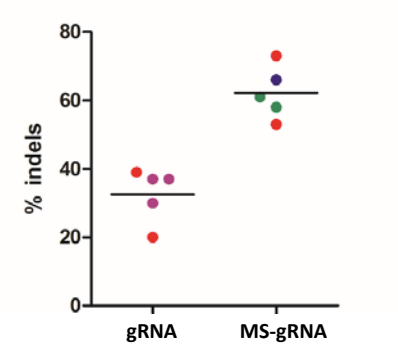
GMFM: gross motor function measure

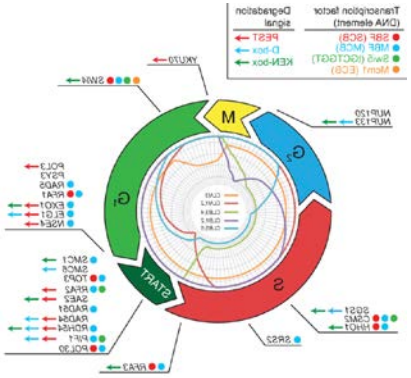
Data from Sessa (Lancet Neurology 2016) in 9 patients. Median follow-up: 36 months (18-54 months)

Gene editing: efficient targeting of HSPCs ?…

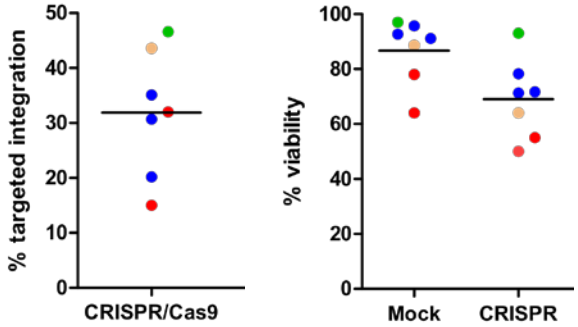


Genome editing in HSPCs

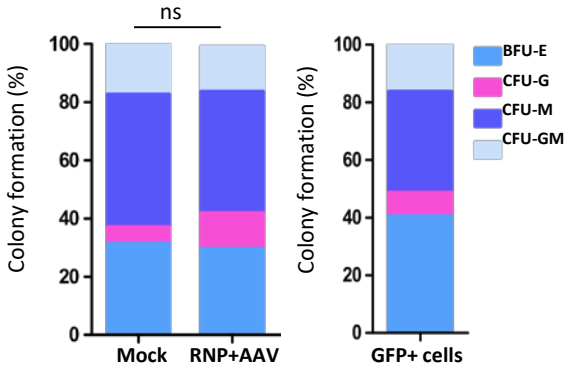




PGK-GFP knock-in in HSPCs

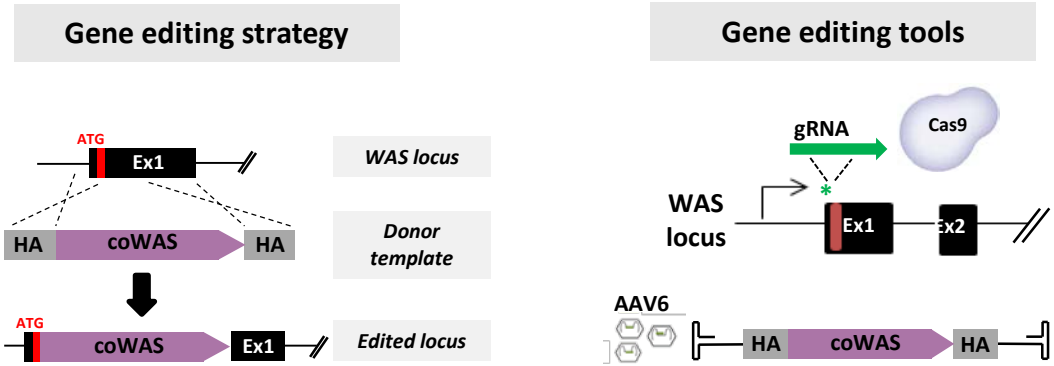


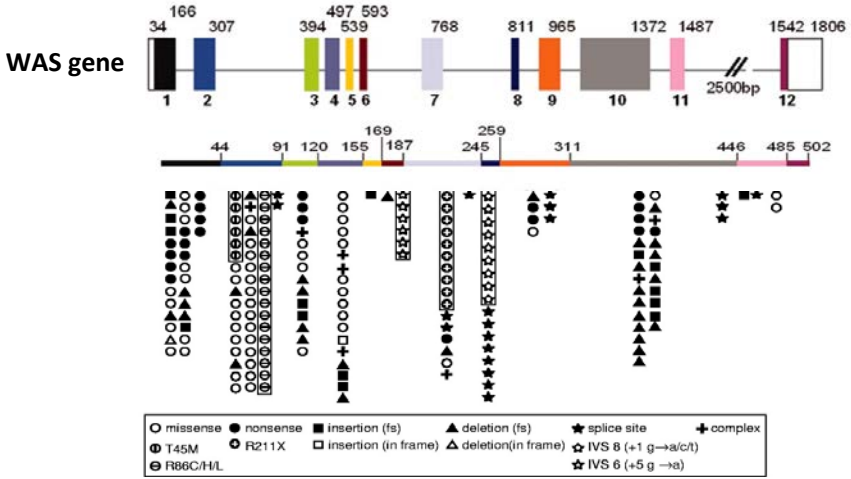
Colony forming efficiency in edited HSPCs



No lineage skewing observed *in vitro*

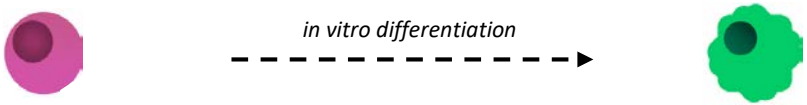
Gene editing approaches for WAS…





Alessia Cavazza

Successful editing of WAS HSPCs…



WASP$^{-/-}$ HSPCs

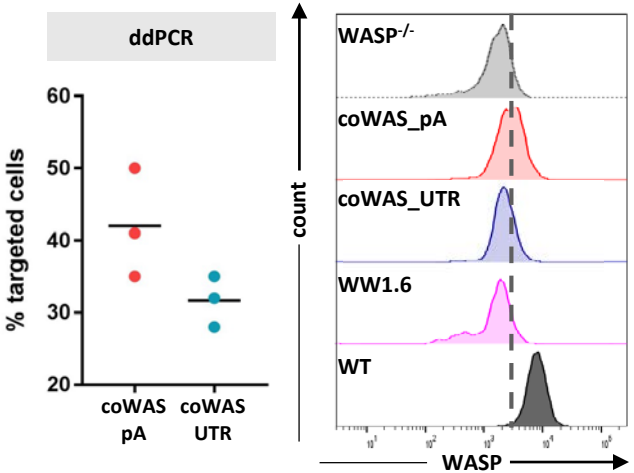
WASP expression (FACS)

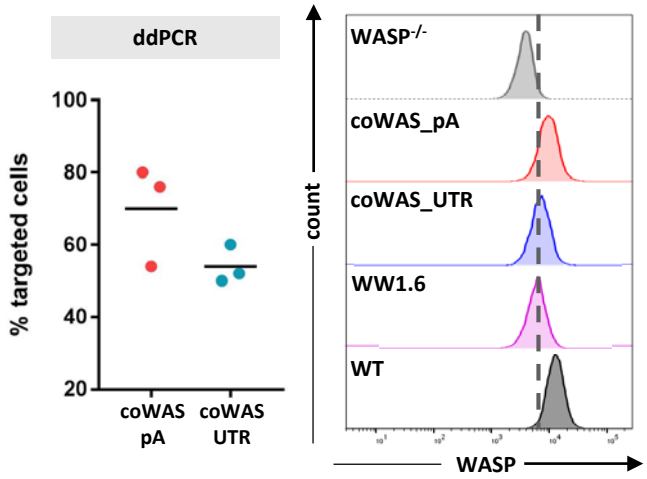
Gene Targeting (ddPCR)

Macrophages

WASP expression (FACS)

Gene Targeting (ddPCR)

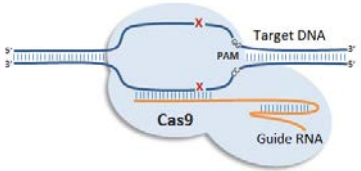


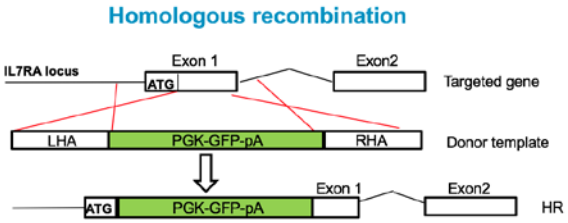


	coWAS_pA	coWAS_UTR	WW1.6
mean WASP %	40	25	5
Copy Number	1	1	1.2

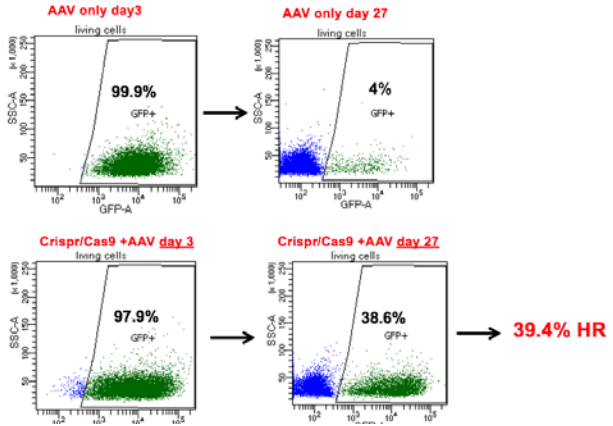
	coWAS_pA	coWAS_UTR	WW1.6
mean WASP %	75	45	20
Copy Number	1	1	3.5

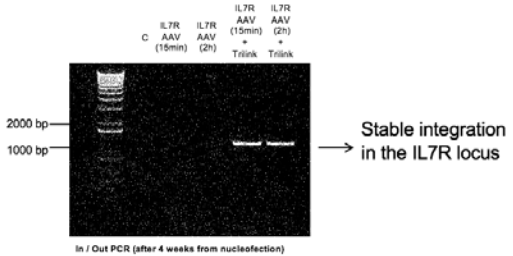
Gene editing and repair: CRISPR Cas9 IL7Ra SCID.....



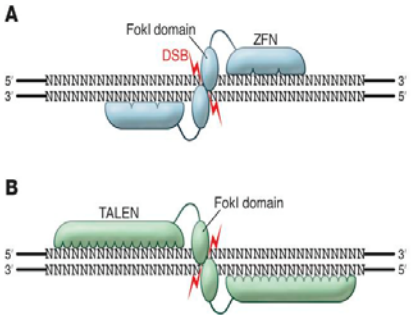


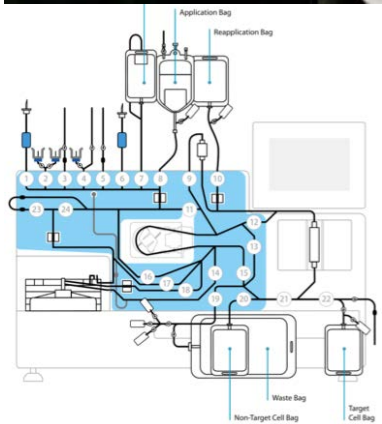
Adeno-associated virus (AAV6)

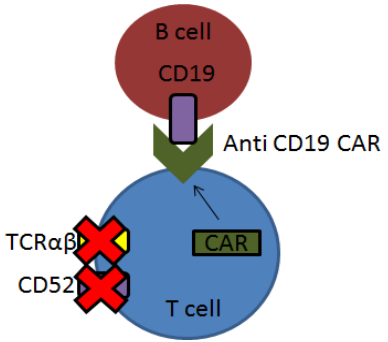




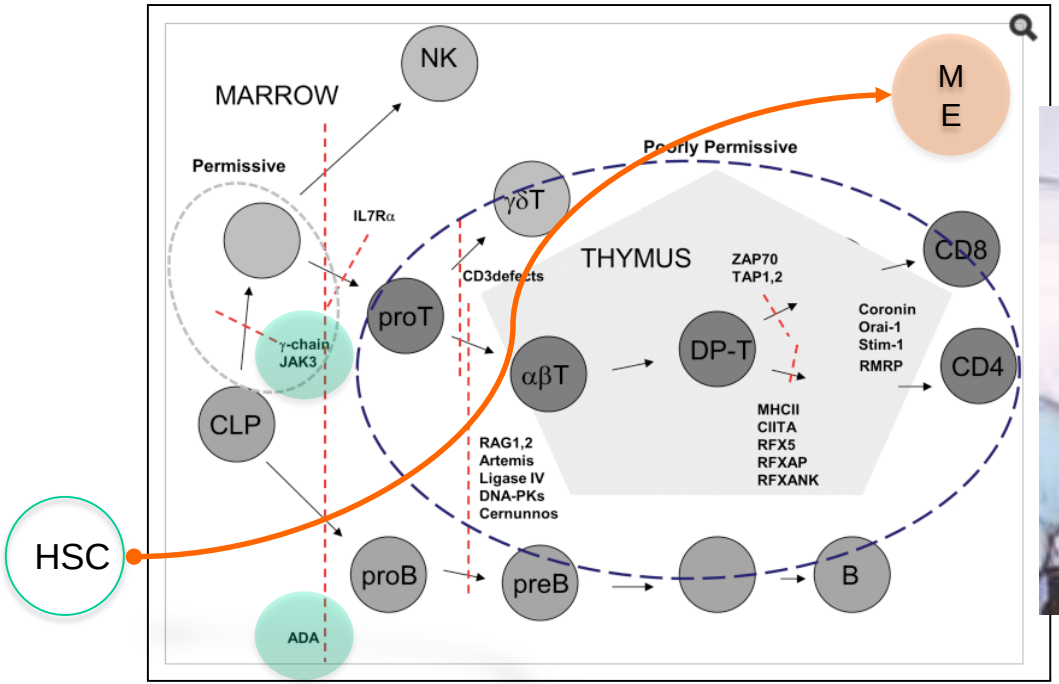
Efficient gene editing in allogeneic T cells (Qasim, Veys…)….

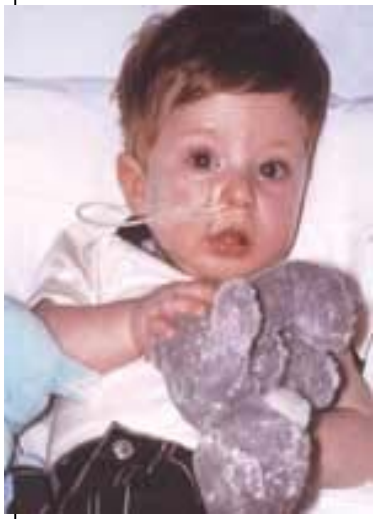


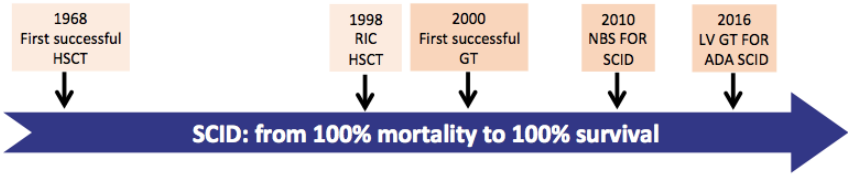




Primary immunodeficiency: a rare disease paradigm....







Newborn screening

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Collaborators

David Williams
Luigi Notarangelo
Sung-Yun Pai
Lisa Filipovich
Chris Baum
Axel Schambach
Christof von Kalle
Manfred Schmidt
Rick Bushman
Marina Cavazzana
Alain Fischer
Salima Hacein-Bey
Don Kohn
Denise Carbonaro Sarracino
Manuel Grez
Harry Malech
Anne Galy
Fulvio Mavilio
Sabine Charrier
Juan Bueren
Paula Rio
Elena Almarza

California Institute of Regenerative Medicine (CIRM)

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