AGGIORNAMENTO SULLA TERAPIA GENICA DELLE SINDROMI TALASSEMICHE

Santina Acuto

Ospedali Riuniti Villa Sofia-Cervello, Palermo-Italy

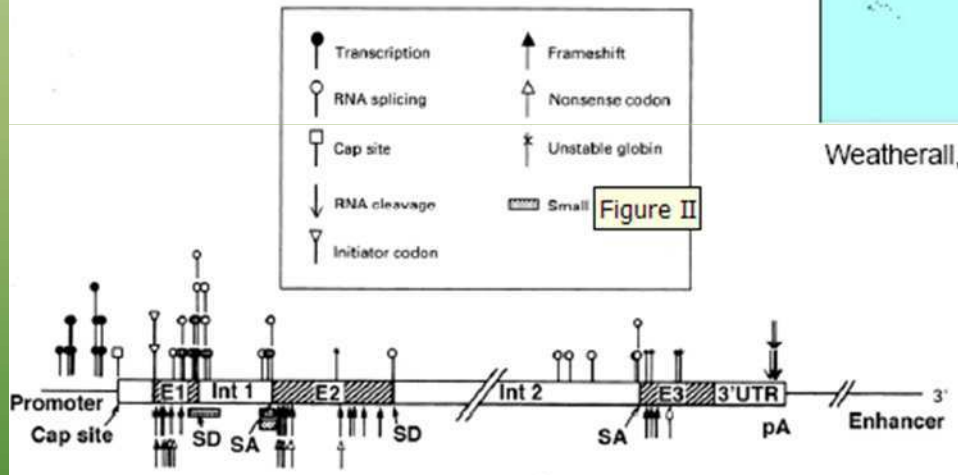
Palace Hotel Mondello, Palermo dal 18/10/2012 al 20/10/2012

β-THALASSEMIA AND β-GLOBIN GENE MUTATIONS

Geographical distribution of thalassemia syndromes

Weatherall, D.J., BMJ, 1997

Human β-globin and location of classes of point mutations causing β-thalassemia.



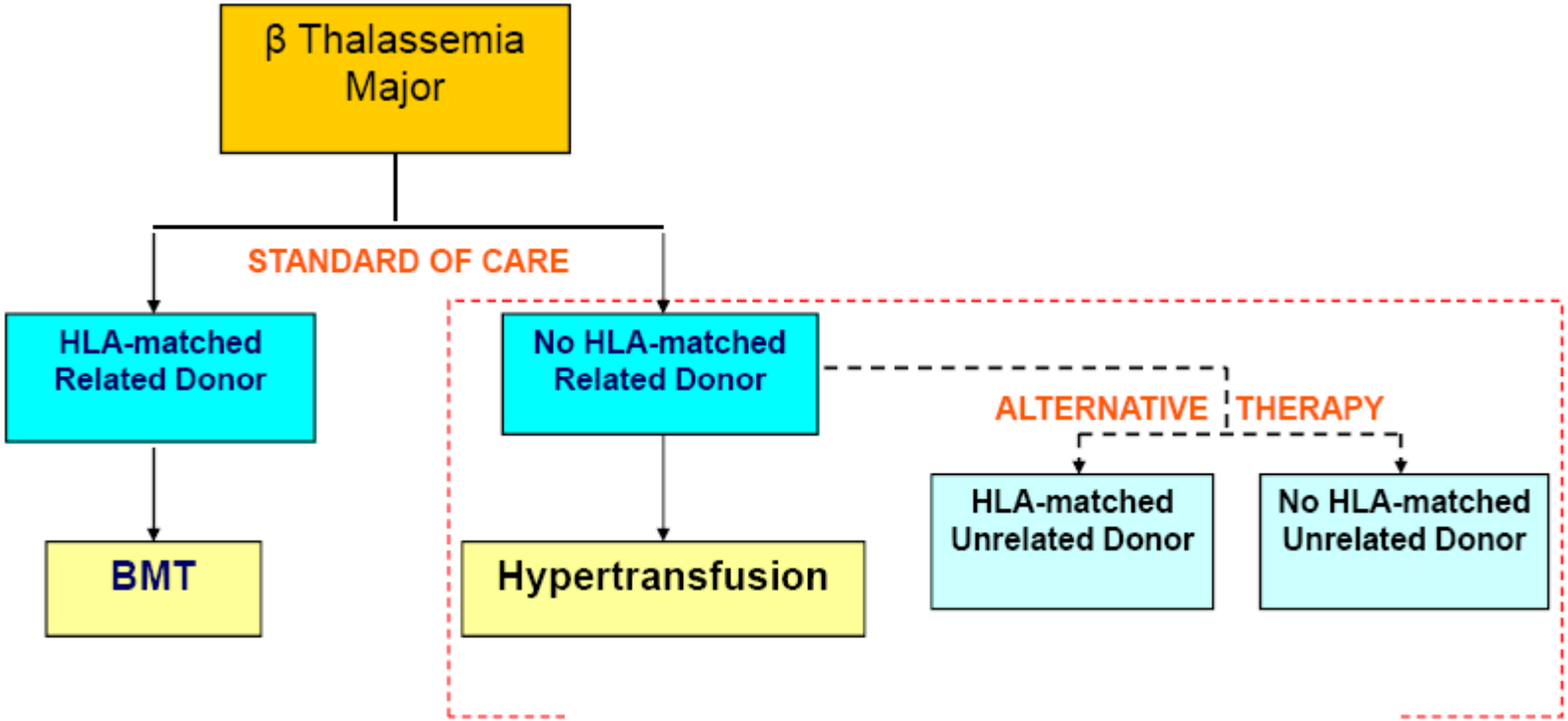
Adopted from Orkin S.H. and Nathan D.G. The Thalassemias, in: Hematology of Infancy and Childhood, 1998.

Possible treatments:

- **Red Blood Cell Transfusion**
- **Bone Marrow or Cord Blood Transplantation**
- **Engineered stem cells**

Si ringrazia per il sostegno alla Ricerca

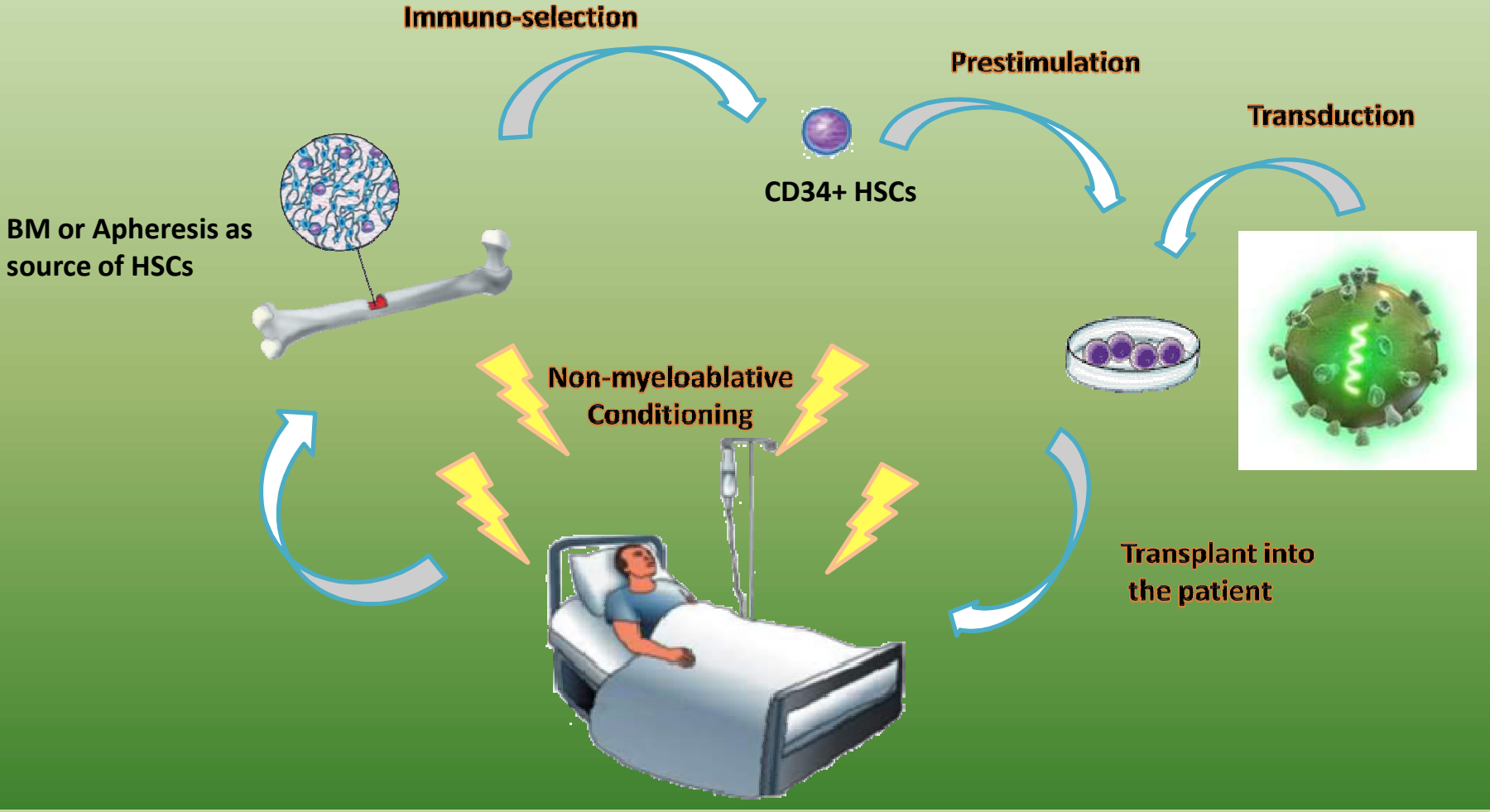
TREATMENT OPTIONS FOR THALASSEMIC SUBJECTS



Patient candidates for gene therapy

Si ringrazia per il sostegno alla Ricerca

GENE THERAPY FOR β-THALASSEMIA



Si ringrazia per il sostegno alla Ricerca

AZIENDA OSPEDALIERA OSPEDALI RIUNITI VILLA SOFIA - CERVELLO PALERMO

Dipartimento di Oncologia ed Ematologia

SANTINA ACUTO

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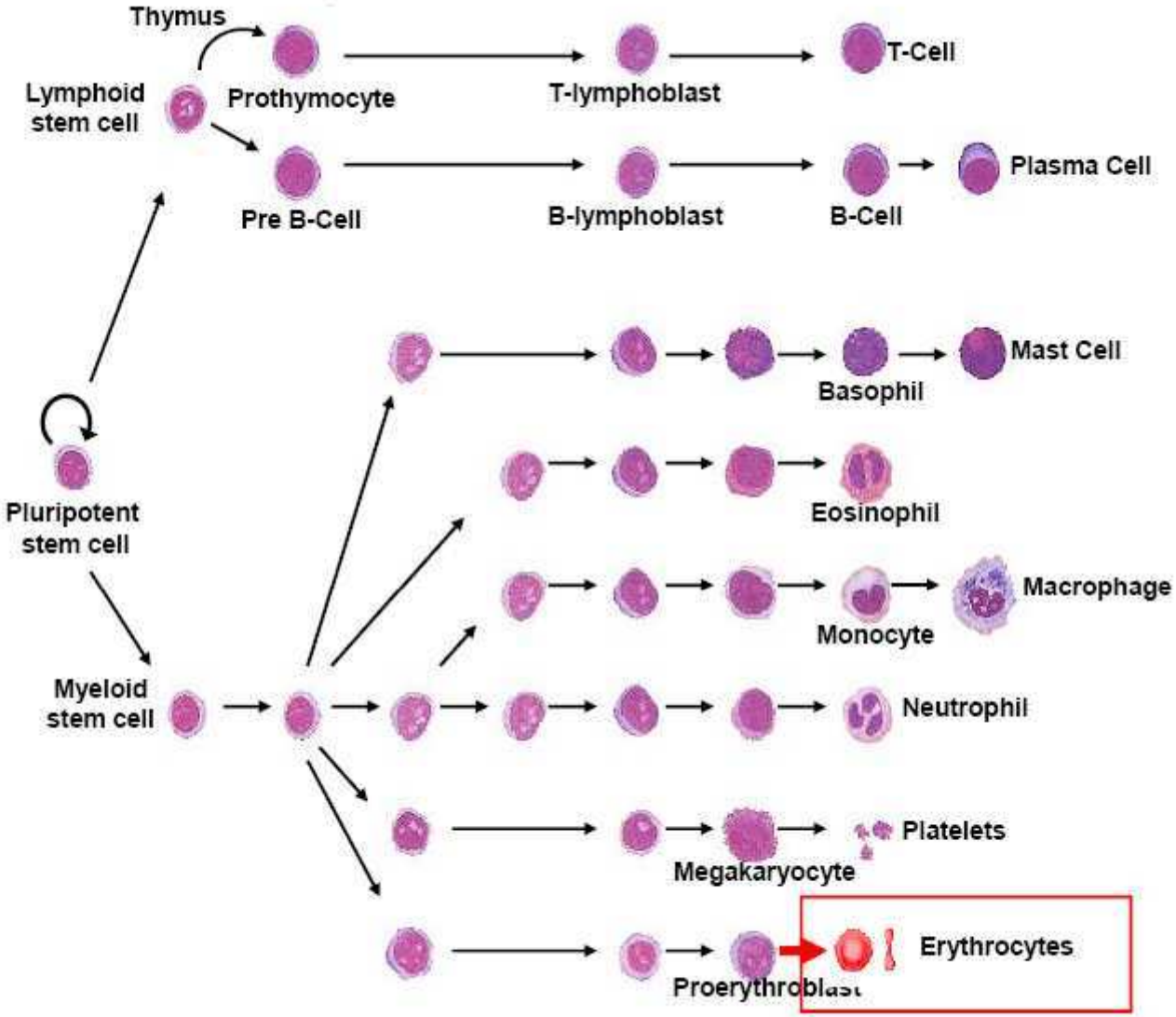
Fondazione Franco e Piera Cutino Guarire dalla TALASSEMIA

Requirements for globin vector expression

- Lineage-restricted, erythroid-specific
- Differentiation stage-specific
- Elevated
  - therapeutic (anemia)
  - safe (1-2 vector copies per cell)
- Position-independent (copy number-dependent)
- Sustained over time

Si ringrazia per il sostegno alla Ricerca



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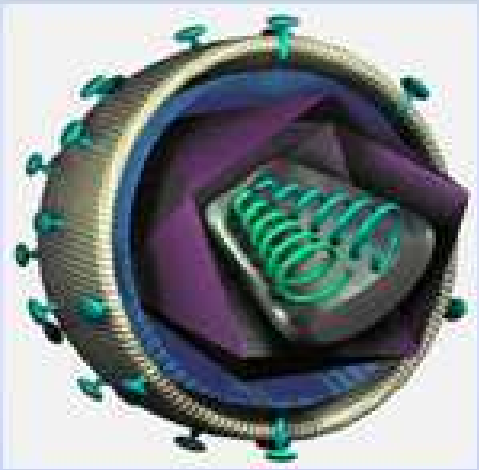
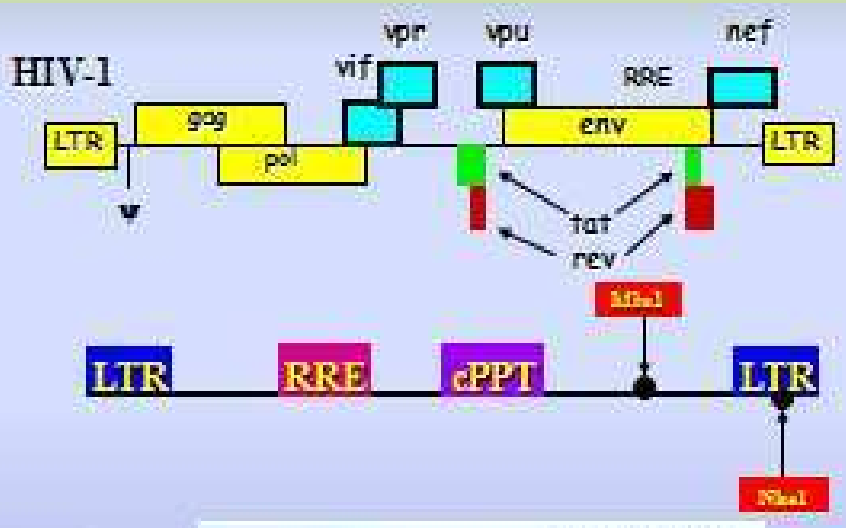
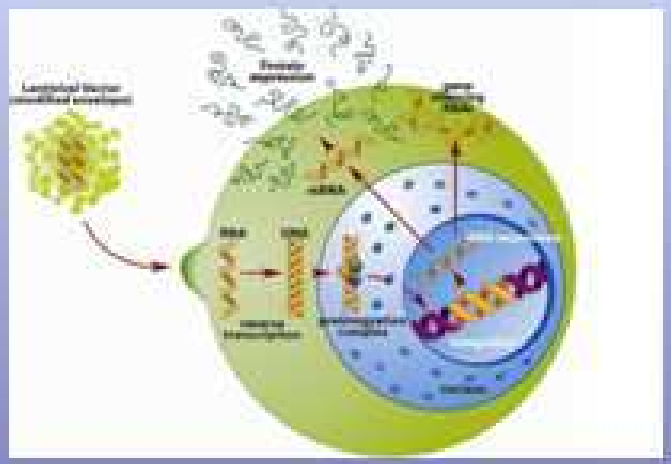
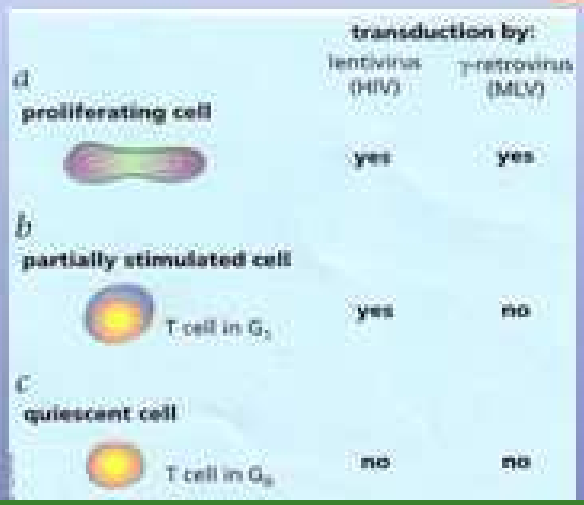
Lentiviruses and integration









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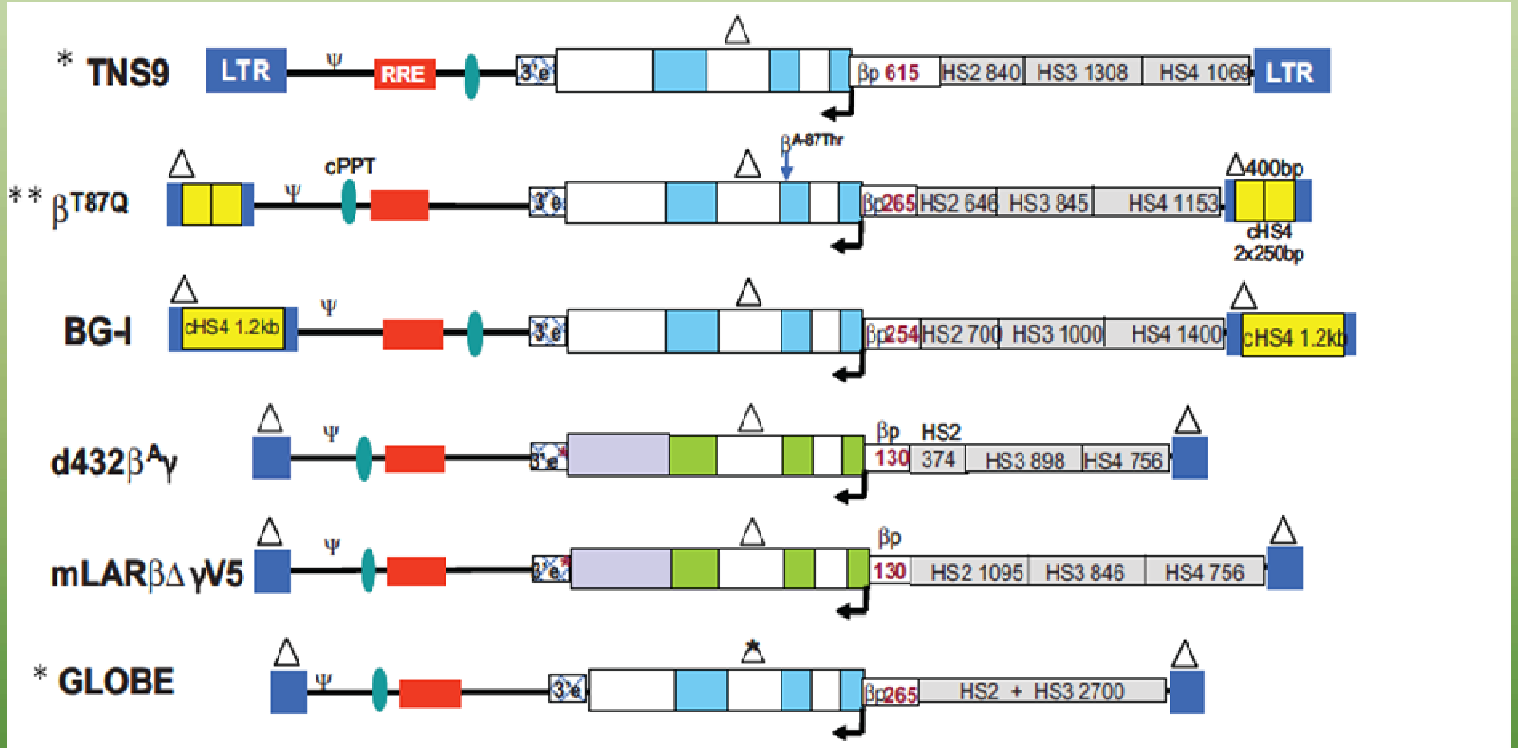
GLOBIN LENTIVIRAL VECTORS DEVELOPED FOR GENE THERAPY OF β-THALASSEMIA

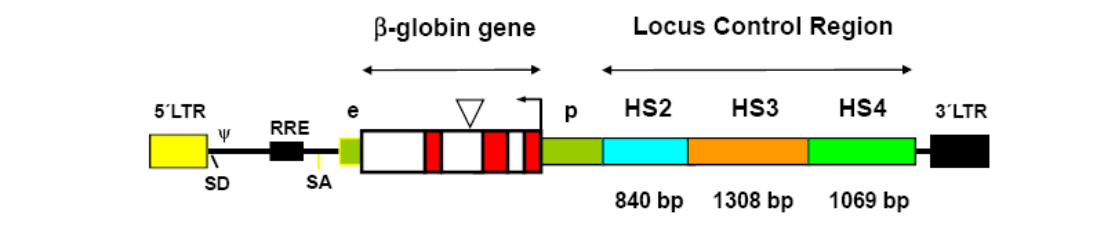


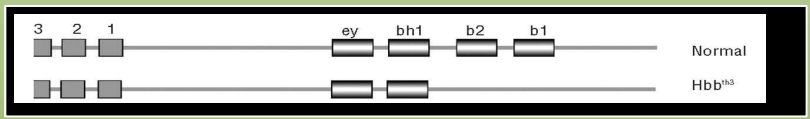
(**)-vector entered in the French clinical trial; (*)- vectors entering in upcoming clinical trials

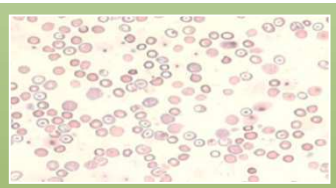
from: **Arumugam P, Malik P** (2010). Hematology

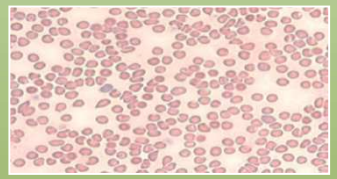
Si ringrazia per il sostegno alla Ricerca

Il vettore lentivirale TNS9ha curato l'anemia nel modello di topo talassemico









C57BL6Hbb$^{Th3+/-}$

C57BL6 w.t.

- correction of anemia
- prevention of secondary organ damage

- long-term expression
- peripheral selective advantage

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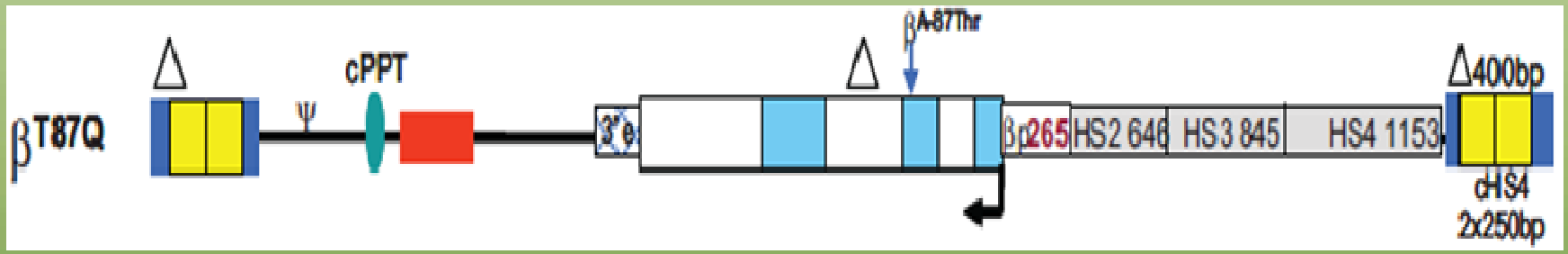
THE GLOBIN LENTIVIRAL VECTORS β^{T87Q} ENTERED IN THE FRENCH CLINICAL TRIAL



Si ringrazia per il sostegno alla Ricerca

nature Vol 467|16 September 2010|doi:10.1038/nature09328

LETTERS

Transfusion independence and *HMGA2* activation after gene therapy of human β-thalassaemia

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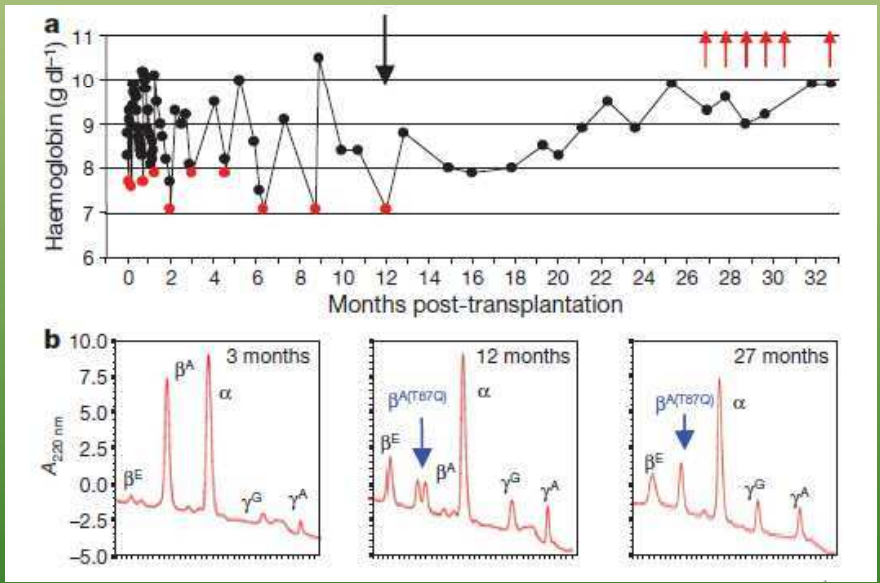
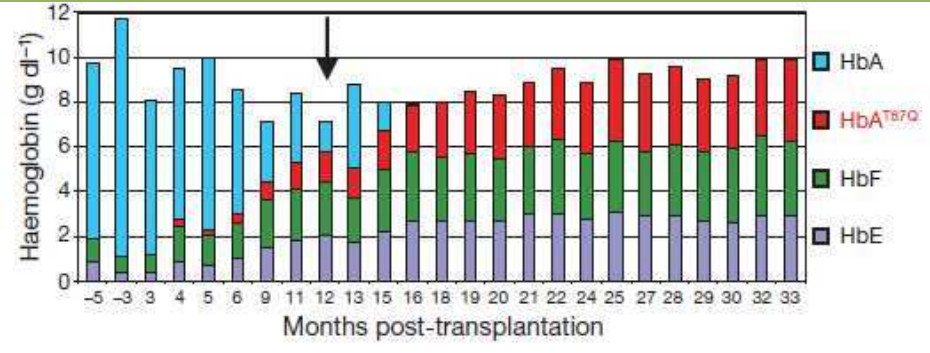


Conversion to transfusion independence



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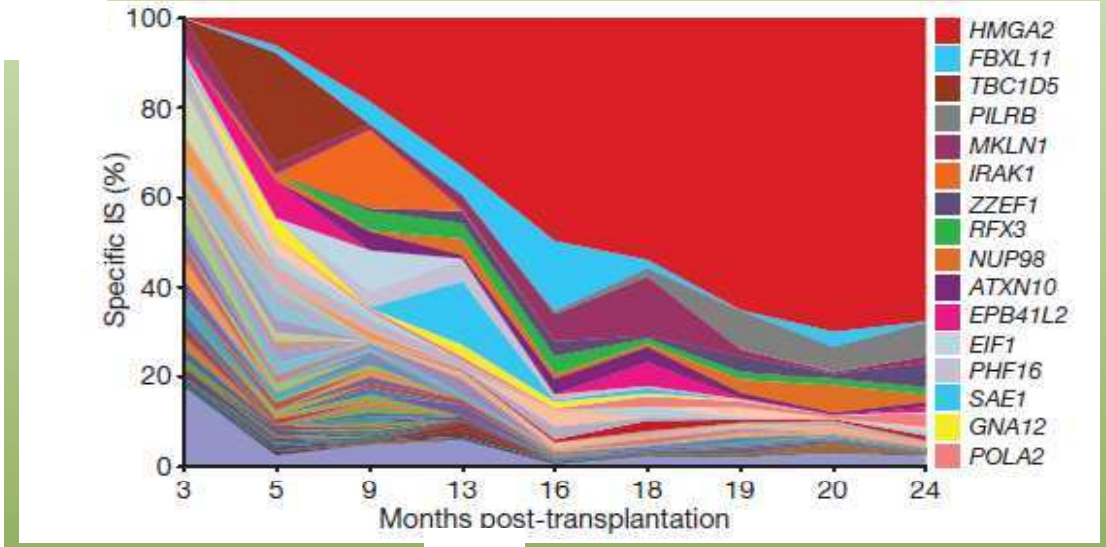
GENOME-WIDE INTEGRATION SITE (IS) DISTRIBUTION STUDIES: CLONAL DOMINANCE OF HMGA2*



Relative abundance of vector-bearing cell clones in (one colour per IS, with the predominant HMGA2 IS in red).

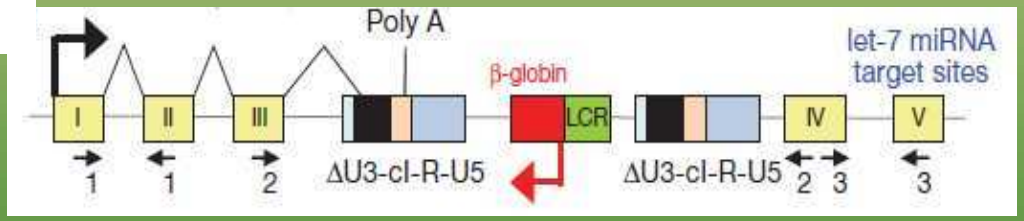


Diagram of the vector at the HMGA2 IS, showing abnormal splicing and polyadenylation/cleavage of the truncated transcript within the vector provirus

** HMGA2= HIGH-MOBILITY GROUP AT-HOOK 2*

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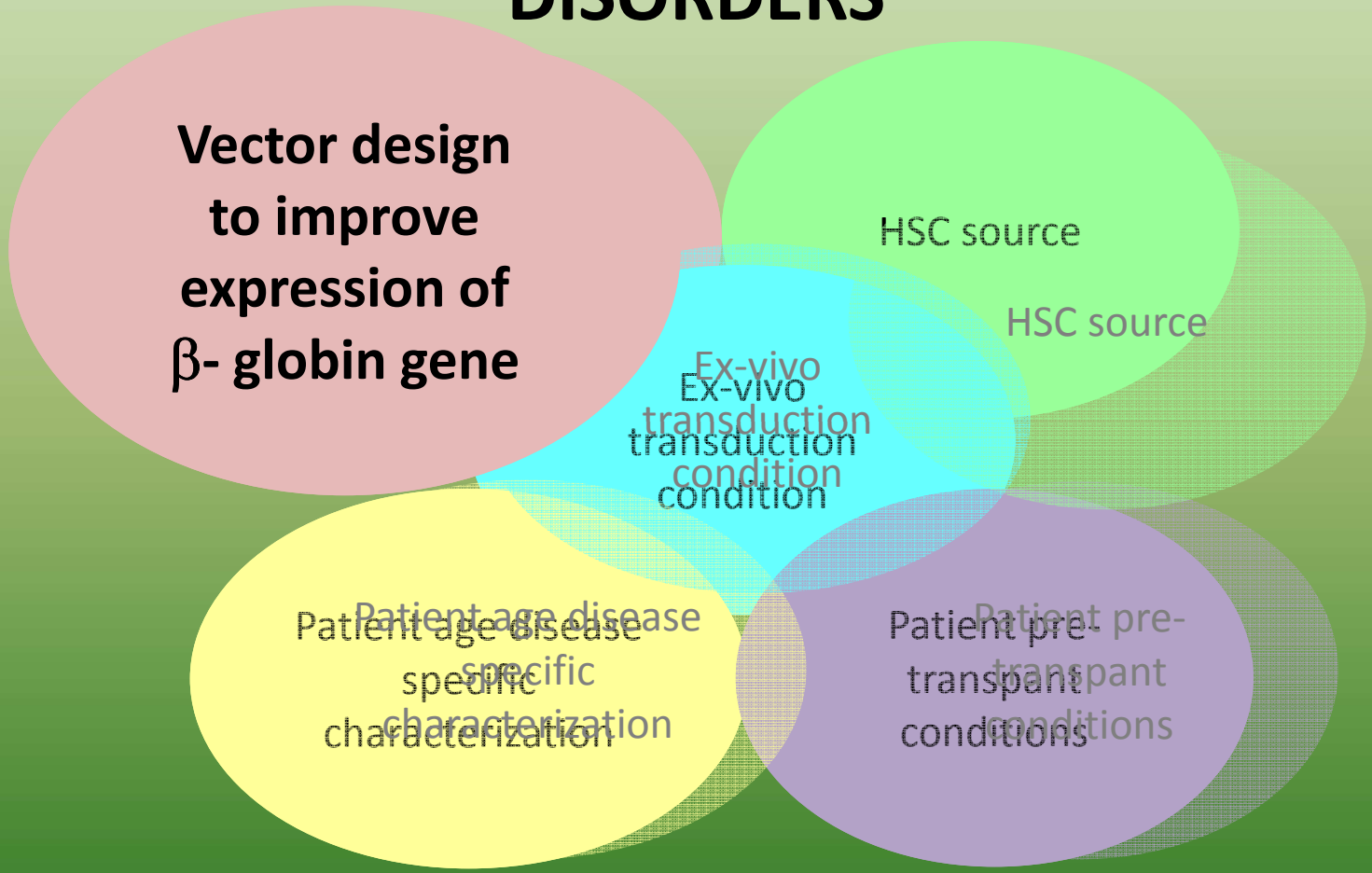
FACTORS INFLUENCING THE OUTCOME OF A GENE TRANSFER TRIAL FOR THE HEMOGLOBIN DISORDERS



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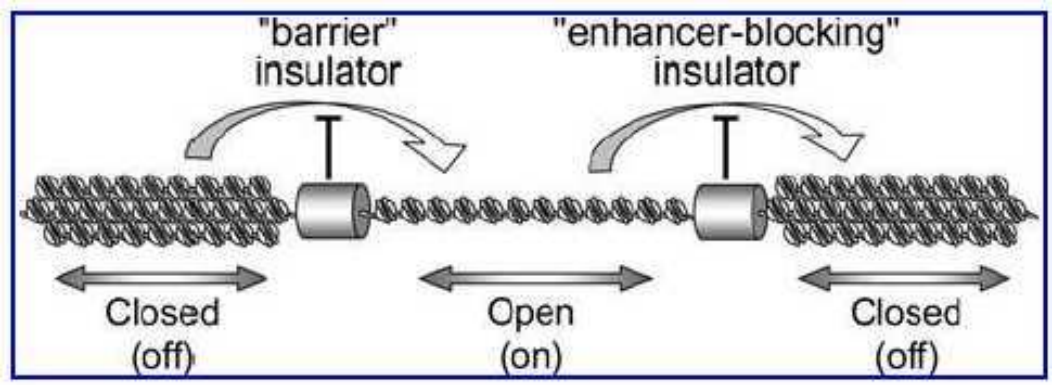
CHROMATIN INSULATORS AND HOW THEY FUNCTION IN EUKARYOTIC CELLS



By acting as **barriers**, insulators prevent the spread of condensed chromatin able to silence expression.

By acting as **enhancer-blockers, insulators** restrict the long-range activation of enhancers limiting their influence to to the target promoter.

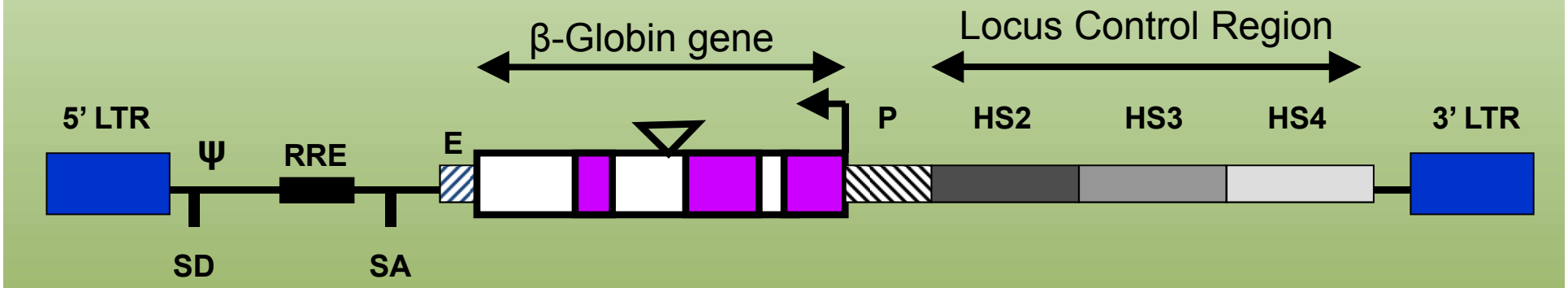
THE INCLUSION OF CHROMATIN INSULATORS IN RECOMBINANT VECTORS SHOULD IMPROVE BOTH EFFICACY AND SAFETY OF GENE THERAPY

-The blocking enhancer activity prevents the activation of neighboring cellular genes from enhancers present in the vector.

-The barrier activity limits the number of transgenes necessary for the therapeutic effect and, in so doing, reduces the mutagenesis risk.

Si ringrazia per il sostegno alla Ricerca

SNS-5 INSULATING TNS9.3 VECTOR



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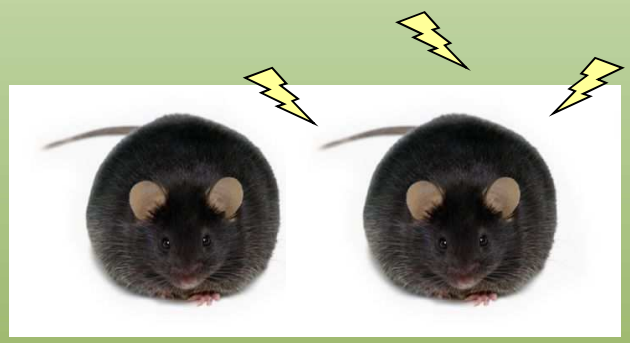
IN VIVO EXPERIMENTAL PLAN



Lin$^-$ cells activation (o.n.)

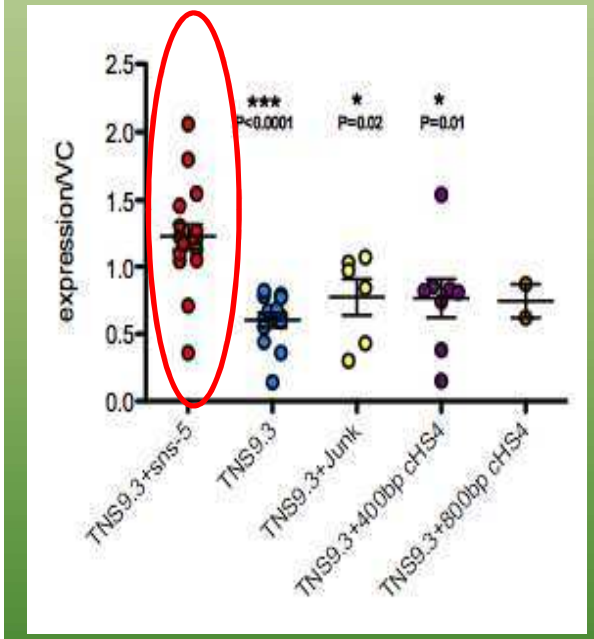
Lin$^-$ cells transduction (8hr) and BMT

VCN evaluation
β-globin mRNA levels
β-globin protein analysis

Si ringrazia per il sostegno alla Ricerca

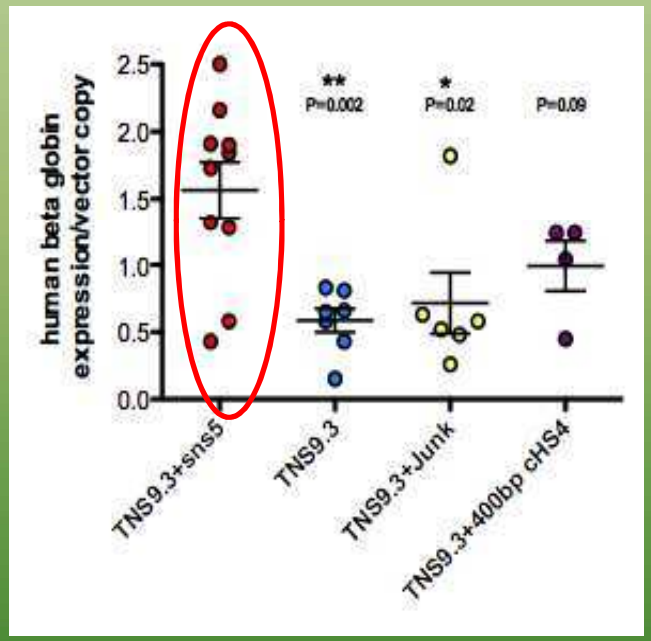
SNS5 INCREASES THE EXPRESSION OF THE TRANSGENE IN LONG TERM MOUSE CHIMERAS

6 weeks after BMT



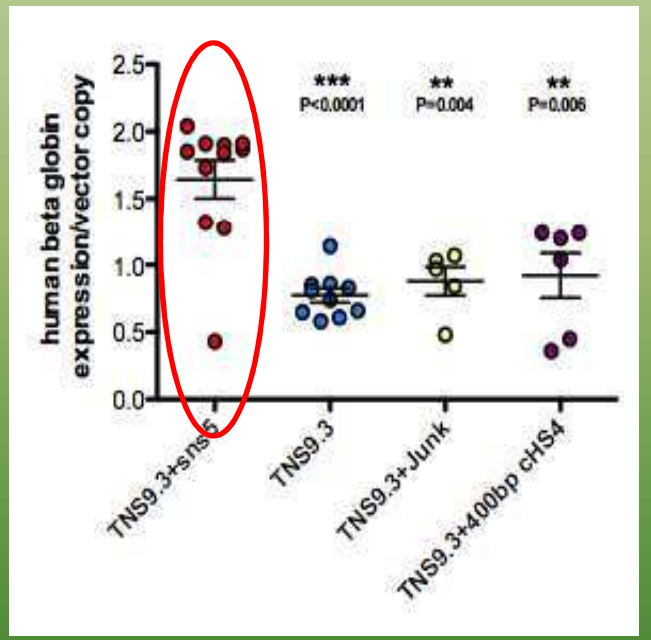
N=16 N=13 N=6 N=8 N=2

14 weeks after BMT



N=10 N=7 N=6 N=4

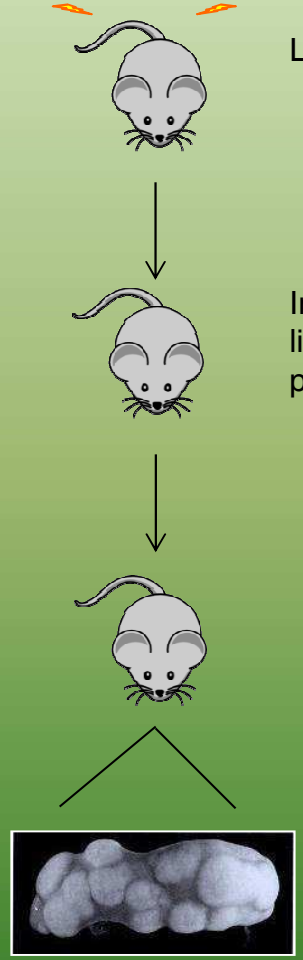
40 weeks after BMT



N=11 N=10 N=5 N=6

Si ringrazia per il sostegno alla Ricerca

SnS-5 reduces variability of β-globin gene expression in single copy vector spleen colonies

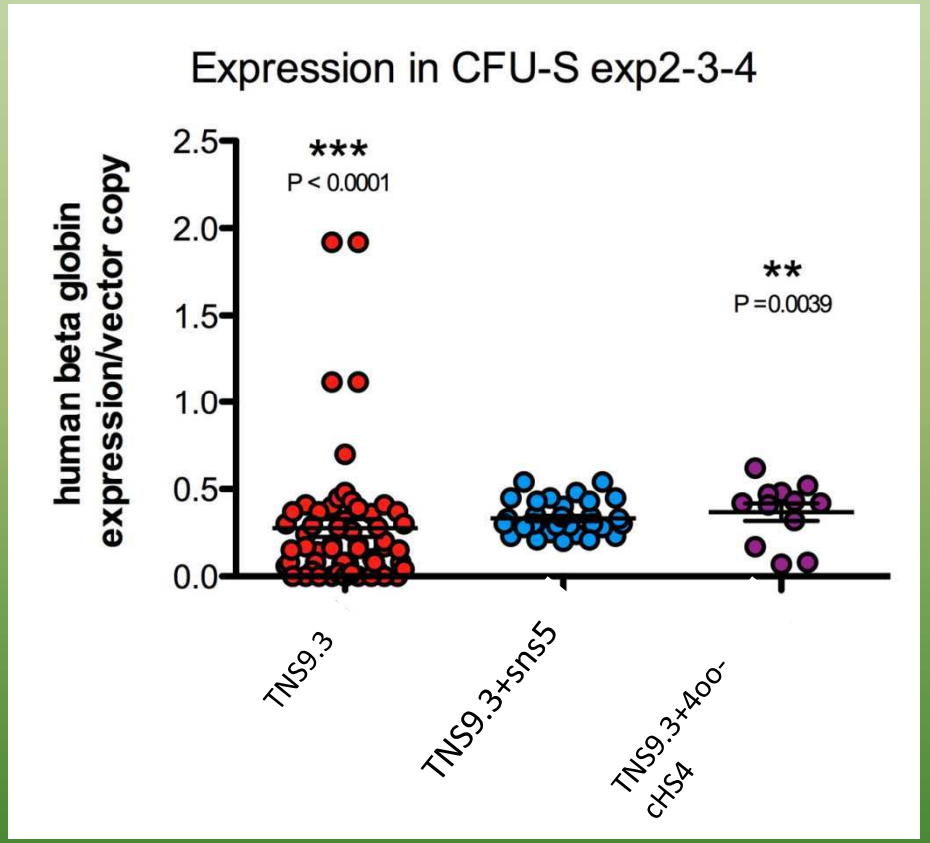


Lethal irradiation

Inject transduced lin$^-$ cells from primary mice

12 days

Each spleen nodule contains a clone of hematopoietic cells



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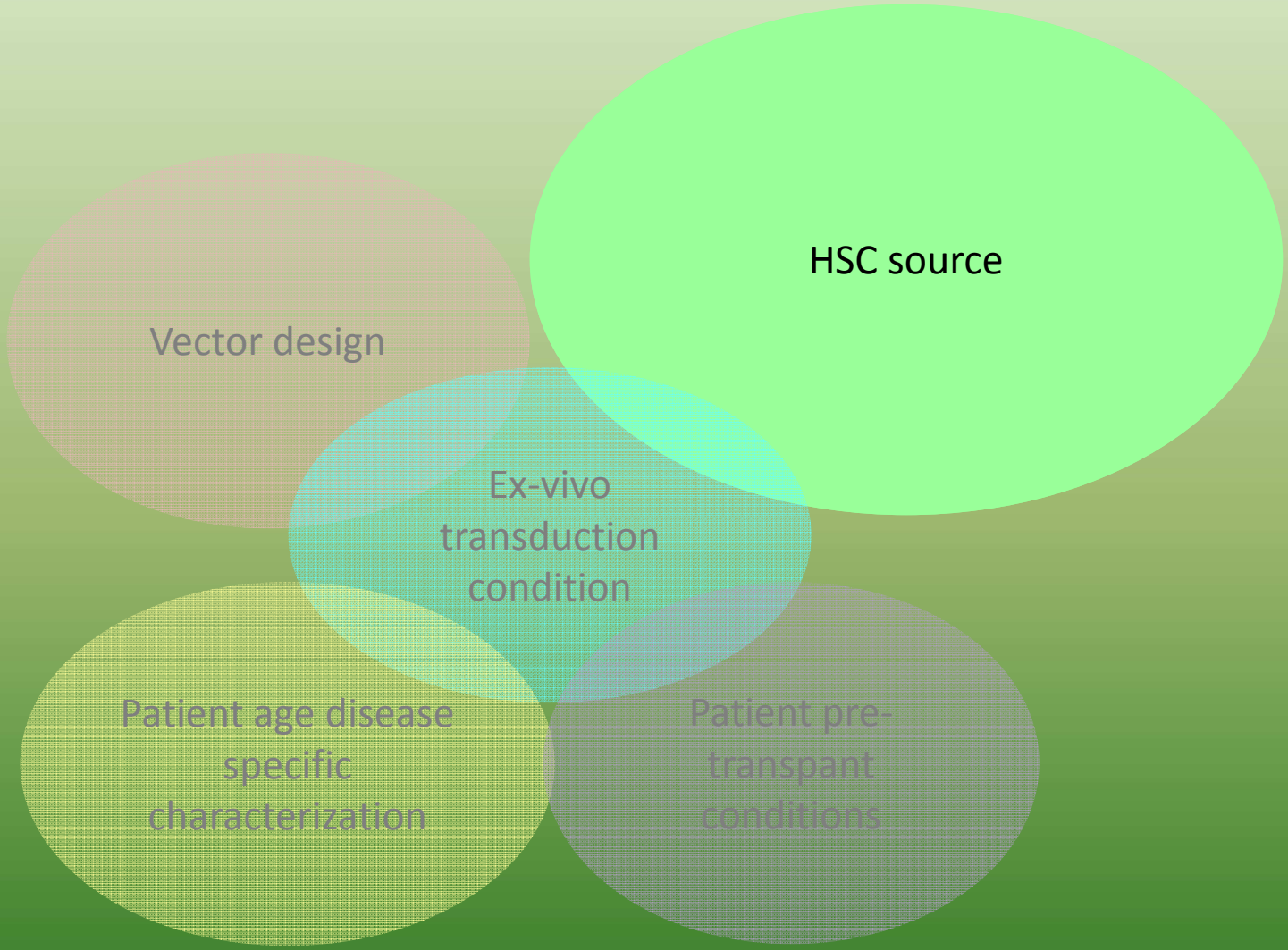

Si ringrazia per il sostegno alla Ricerca

A PILOT TRIAL TO ASSESS THE FEASIBILITY AND SAFETY OF G-CSF MOBILIZATION OF CD34+ HEMATOPOIETIC PROGENITOR CELLS IN PATIENTS WITH BETA-THALASSEMIA MAJOR

(NTC000658385 SU CLINICALTRIALS.GOV)

- Preliminary protocol involving **Mobilization of CD34+ hematopoietic progenitor cells** and ex-vivo processing with the TNS9.3 lentiviral vector *without* reinfusion of transduced cells.

- ***Objectives:***
  - To investigate the **feasibility** and **safety** of peripheral blood hematopoietic progenitor cell (HPC) mobilization with G-CSF in patients with β- thalassemia major
  - To determine the **yield** of CD34+ HPCs mobilized
  - To determine the ability of the collected HPCs to be **transduced** with a lentiviral vector encoding the normal ß-globin gene

- ***Subject Population:***

  - Male and female patient-subjects - age ≥18
  - diagnosed with ß-thalassemia major
  - maintained by hypertransfusion, ≥100 mL/kg/yr AND ≥8 transfusions/yr.
  - Patients splenectomized OR without palpable spleen at evaluation.
  - No prior history of thromboembolic disorders.

Si ringrazia per il sostegno alla Ricerca

SUCCESFUL G-CSF MOBILIZATION IN FIVE PATIENTS WITH THALASSEMIA MAJOR

		+1	+2	+3	+4	+5	+6
Pt #1	*%CD34+*					*0.2%*	*NA*
	Total CD34+					3.03×10^6	4.95×10^6
Pt #2		+1	+2	+3	+4	+5	+6
	%CD34+					*0.2%*	*0.1%*
	Total CD34+					6.4×10^6	5.6×10^6
Pt #3		+1	+2	+3	+4	+5	+6
splenectomized	*%CD34+*					*0.1%*	*0.1%*
	Total CD34+					4.0×10^6	4.5×10^6
Pt #4		+1	+2	+3	+4	+5	+6
splenectomized	*%CD34+*					*0.4%*	*0.3%*
	Total CD34+					6.2×10^6	2.7×10^6
Pt #5		+1	+2	+3	+4	+5	+6
splenectomized	*%CD34+*						-
	Total CD34+					2.98×10^6	-

PBSC collected: 8-12 x 10^6 CD34 cells/Kg

Post transduction – Vector copy: 0.8 -1.0 cell

Si ringrazia per il sostegno alla Ricerca

A PHASE IIB MULTICENTER RANDOMIZED CLINICAL TRIAL TO EVALUATE PERIPHERAL MOBILIZATION OF CD34+ HEMATOPOIETIC PROGENITOR CELLS IN PATIENTS WITH BETA-THALASSEMIA MAJOR

(Ospedali Riuniti Villa Sofia-Cervello)

OBJECTIVES:

- TO EVALUATE MOBILIZATION EFFICACY AND SAFETY COMPARING THREE DIFFERENT PROTOCOLS:
  - **G-CSF**
  - **Plerixafor**
  - **G-CSF+Plerixafor**
- TO DETERMINE STEMNESS AND ABILITY OF THE COLLECTED HPC TO BE TRANSDUCED WITH A LENTIVIRAL VECTOR ENCODING THE NORMAL ß-GLOBIN GENE

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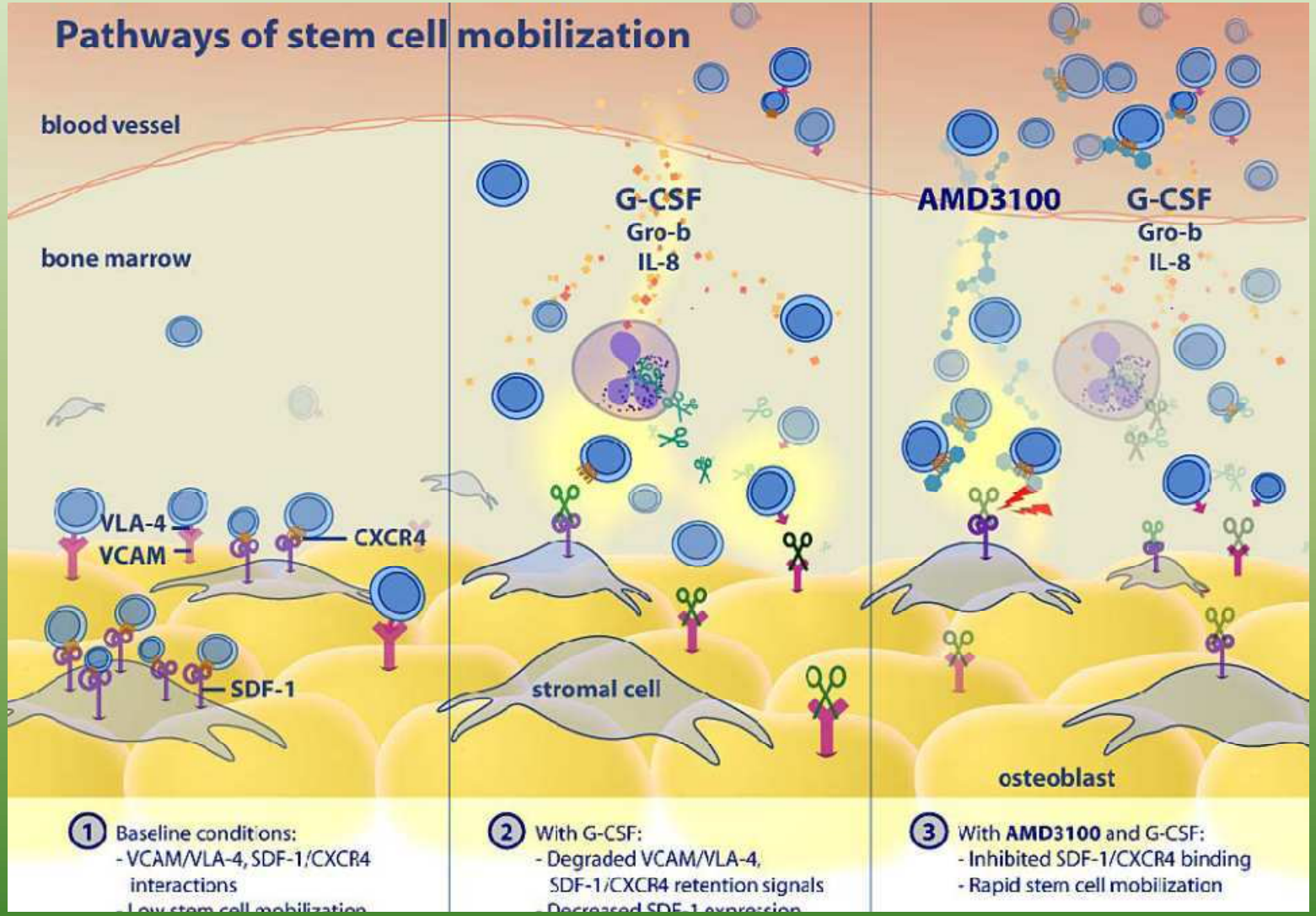

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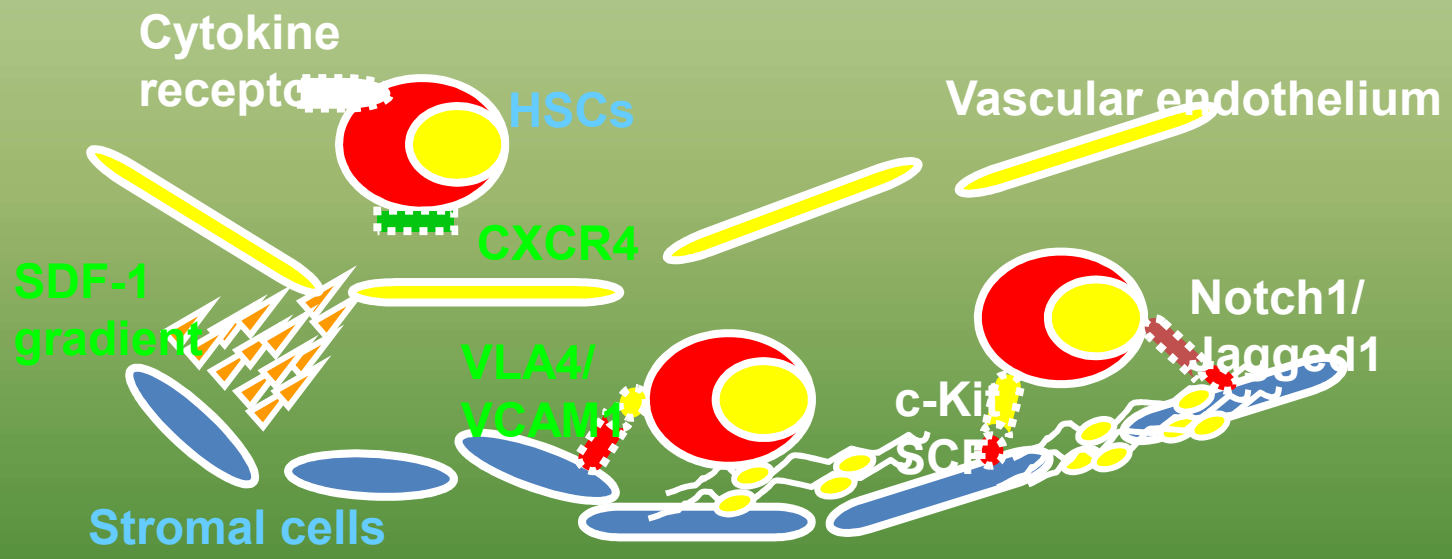
Mobilization of HSCs

Mechanisms

GCSF induces the breaking of the link between
CXCR4 of HSC and VLA4 ckit in the niche cells



Extracellular matrix proteins and soluble cytokines

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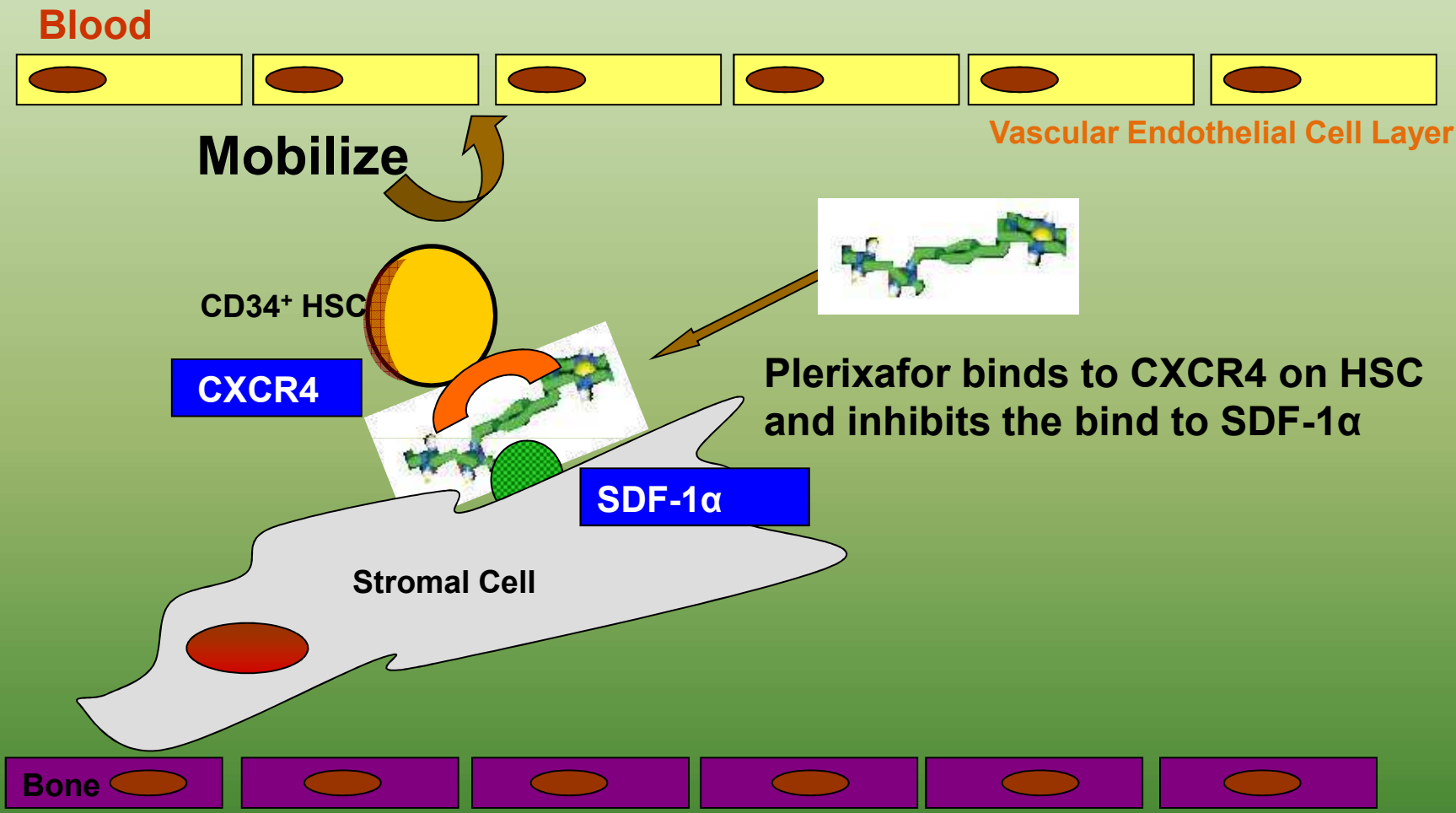
PLERIXAFOR Mobilization



Plerixafor binds to CXCR4 on HSC and inhibits the bind to SDF-1α

Si ringrazia per il sostegno alla Ricerca

Programma

- **G-CSF:** 1,6 ml s.c. dal giorno +1 al giorno +4

- PLERIXAFOR: 0,5 ml s.c. la sera del giorno +4 ed, eventualmente, la sera del giorno +5

Aferesi prevista per il 5° ed, eventualmente, per il 6° giorno.

Si ringrazia per il sostegno alla Ricerca
Fondazione Franco e Piera Cutino Guarire dalla TALASSEMIA

D.V.

Giorno +1 (17/09/11)

WBC	6.600/mmc	PLT	294.000/mmc
Hb	11.5 g/dL	CD34+	0.05% (4 x 10E6/L)

Giorno +2 (18/09/11)

WBC	25.000/mmc	PLT	260.000/mmc
Hb	10.9 g/dL	CD34+	0.03% (7.7 x 10E6/L)

Giorno +3 (19/09/11)

WBC	32.100/mmc	PLT	262.000/mmc
Hb	10.7 g/dL	CD34+	0.03% (10 x 10E6/L)

Giorno +4 (20/09/11)

WBC	30.000/mmc	PLT	279.000/mmc
Hb	10.6 g/dL	CD34+	0.16% (48 x 10E6/L)

Giorno +5 (21/9/11)

WBC	60.300/mmc	PLT	318.000/mmc
Hb	10.6 g/dL	CD34+	0.6% (361 x 10E6/L)
Conta cell. CD34+ collezionate	29 x 10° 6/Kg	Volume di sangue scambiato	8780 ml

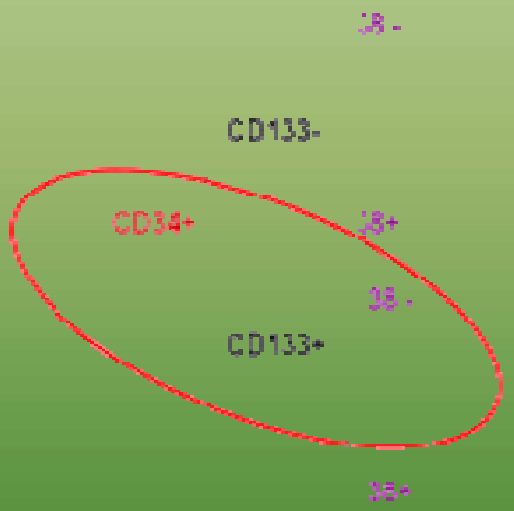
Giorno +6 (22/9/11)

WBC	19.400/mmc	PLT	211.000/mmc
Hb	10 g/dL	CD34+	
Conta cell. CD34+ collezionate	----	Volume di sangue scambiato	----

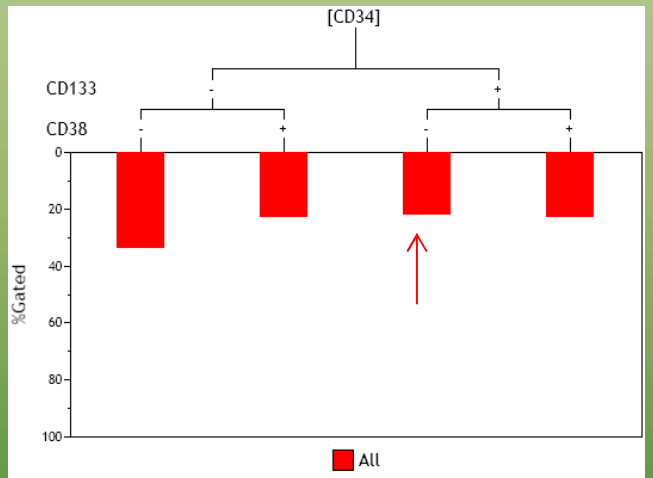
Si ringrazia per il sostegno alla Ricerca

D.V.

	+1	+2	+3	+4	+5	+6
CD34+/L	4 x 10^6	7.7 x 10^6	10 x 10^6	48 x 10^6	361 x 10^6	80 x 10^6
CD34%	0.05	0.03	0.03	0.16	0.6	0.5
WBC/mmc	6600	25000	32100	30000	60300	19000
GCSF/PLERIXAFOR	GCSF	GCSF	GCSF	GCSF	GCSF + PLERIXAFOR	

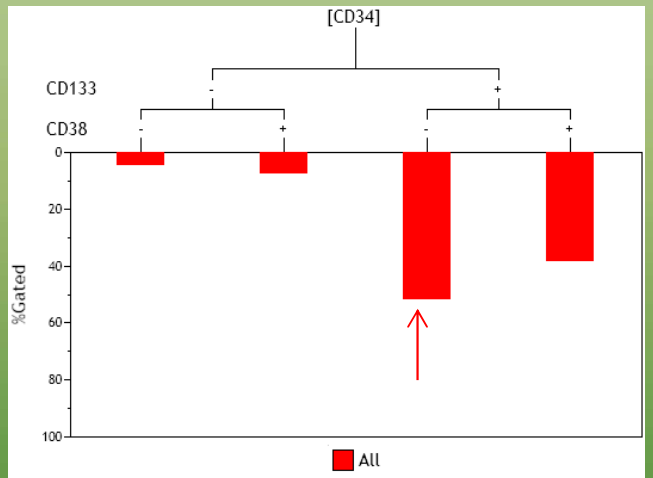


4° day



Gate	Number	%Total	%Gated
All	93	0,13	100,00
CD133-CD38-	31	0,04	33,33
CD133-CD38+	21	0,03	22,58
CD133+CD38-	20	0,03	21,51
CD133+CD38+	21	0,03	22,58

5° day

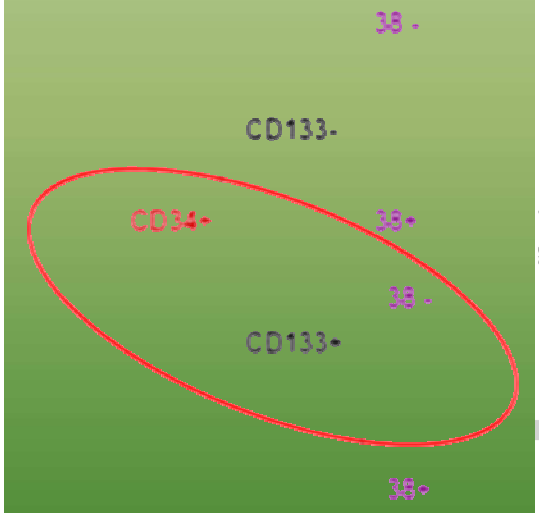


Gate	Number	%Total	%Gated
All	877	0,53	100,00
CD133-CD38-	35	0,02	3,99
CD133-CD38+	60	0,04	6,84
CD133+CD38-	449	0,27	51,20
CD133+CD38+	333	0,20	37,97

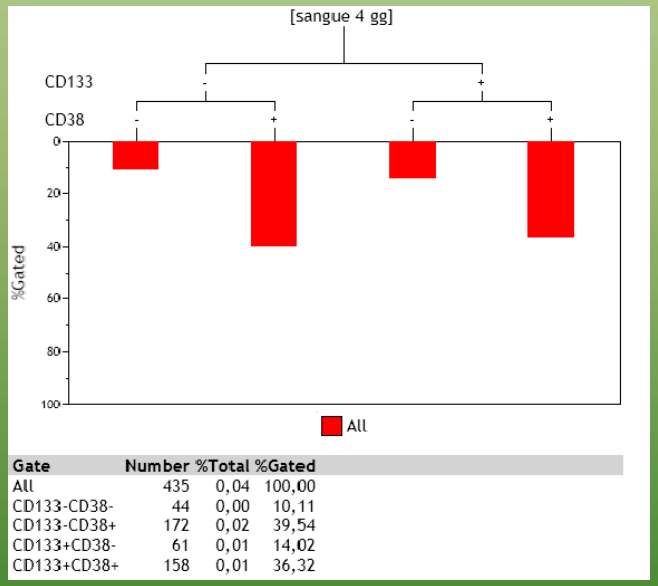
Si ringrazia per il sostegno alla Ricerca

F. S.

	+1	+2	+3	+4	+5	+6
CD34+/L	6 x 10^6	6 x 10^6	6 x 10^6	22x 10^6	92 x 10^6	-
CD34%	0.1	0.01	0.001	0.004	0.1	-
WBC/mmc	12800	60200	56000	55800	92200	-
GCSF/PLERIXAFOR	GCSF	½ GCSF	½ GCSF	½ GCSF	½ GCSF + PLERIXAFOR	

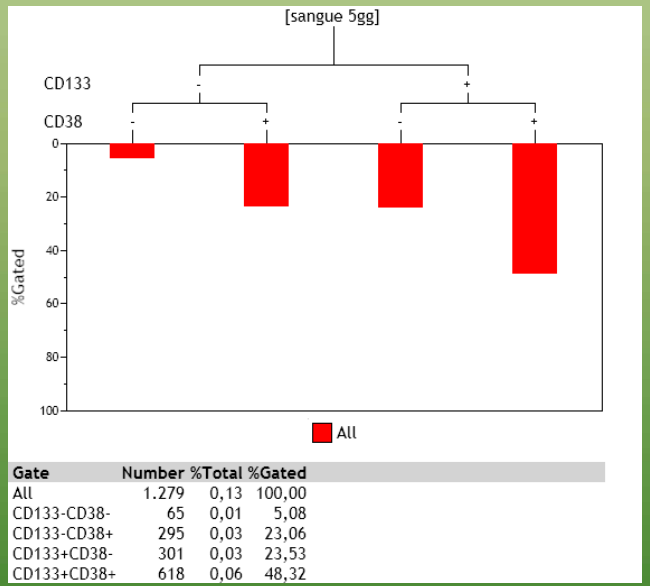


4° day



Gate	Number	%Total	%Gated
All	435	0,04	100,00
CD133-CD38-	44	0,00	10,11
CD133-CD38+	172	0,02	39,54
CD133+CD38-	61	0,01	14,02
CD133+CD38+	158	0,01	36,32

5° day



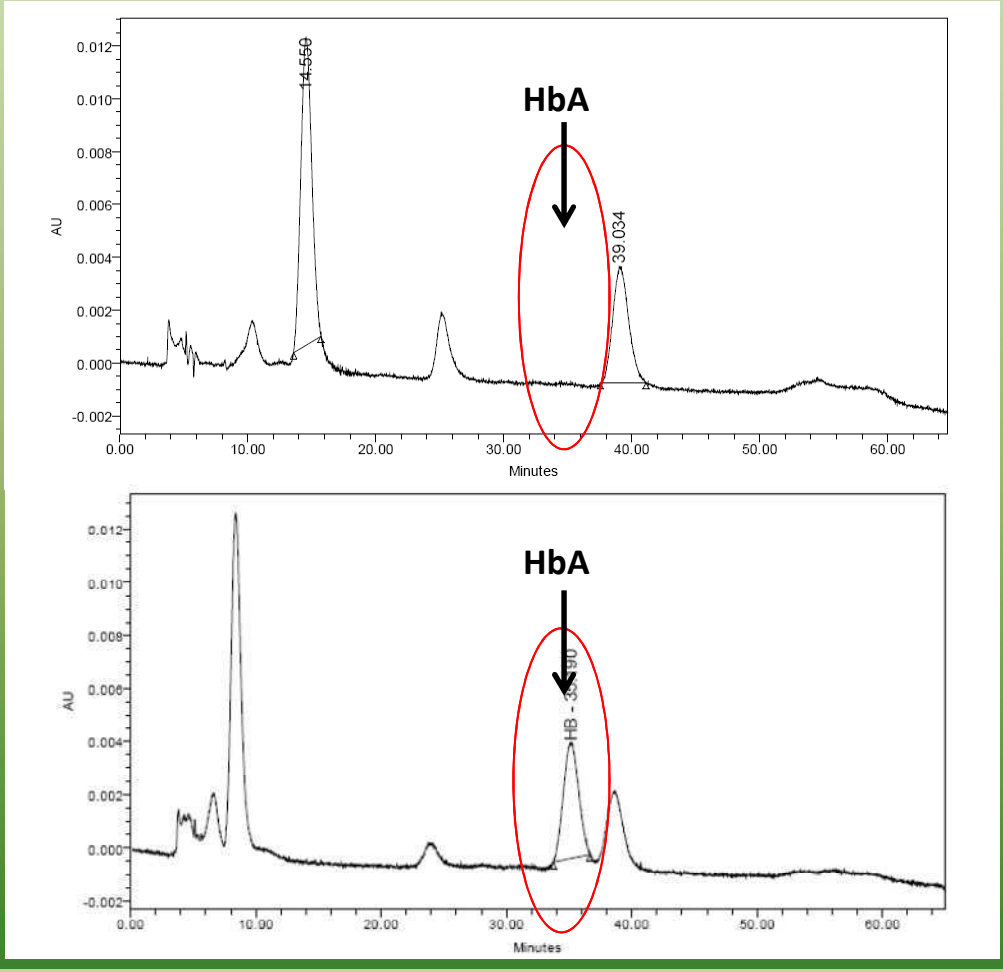
Gate	Number	%Total	%Gated
All	1.279	0,13	100,00
CD133-CD38-	65	0,01	5,08
CD133-CD38+	295	0,03	23,06
CD133+CD38-	301	0,03	23,53
CD133+CD38+	618	0,06	48,32

Si ringrazia per il sostegno alla Ricerca

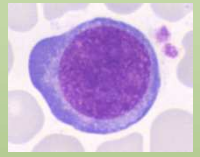
HPLC ANALYSIS: ADULT HEMOGLOBIN PRODUCTION IN TNS9.3 LV-VECTOR TRANSDUCED ERYTHROID CELLS FROM β°/β° THALASSEMIA PATIENT

Untrasduced cells

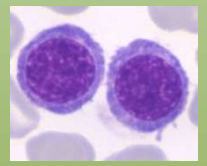
Cells transduced with TNS9.3 LV-vector



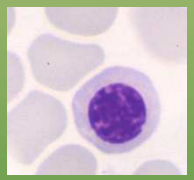
CORRECTION OF INEFFECTIVE ERYTHROPOIESIS



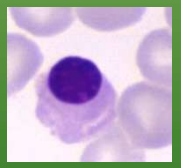
proeritroblasto



basofilo

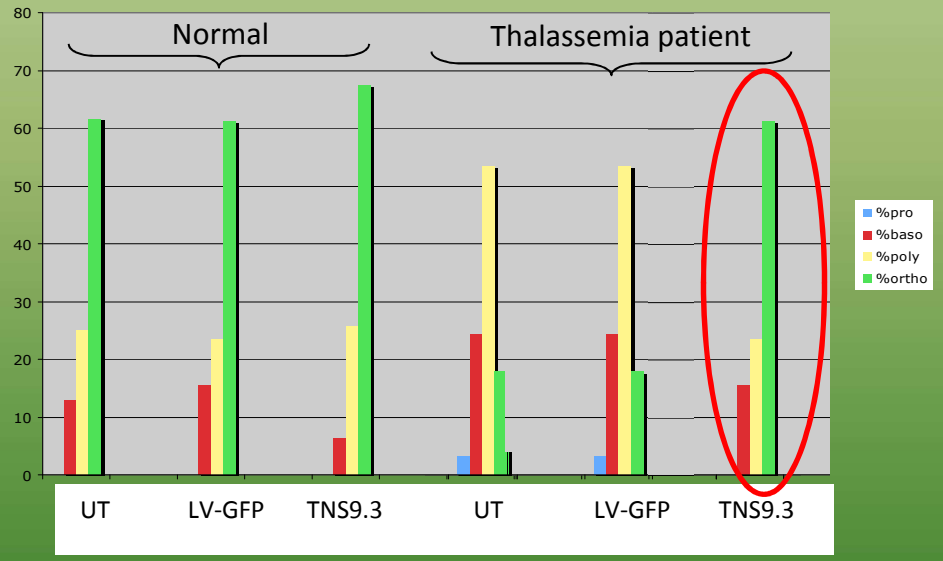


policormatofilo



ortocromatico

Cell population at day 15 of erythroid colture in transduced and non transduced cells from thalassemia patient and from normal control



Si ringrazia per il sostegno alla Ricerca

SANTINA ACUTO

"AGGIORNAMENTO SULLA TERAPIA GENICA DELLE SINDROMI TALASSEMICHE"

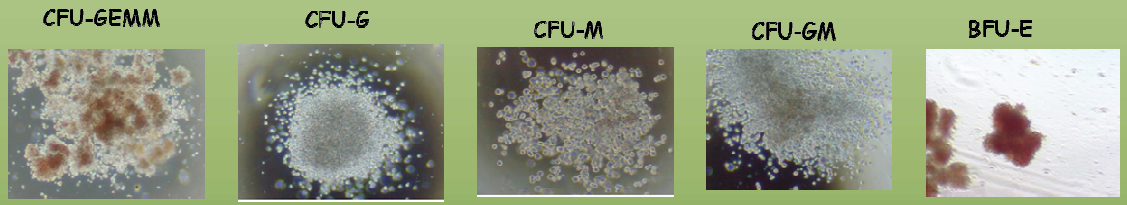
IN LABORATORIO

Le cellule raccolte saranno valutate per:

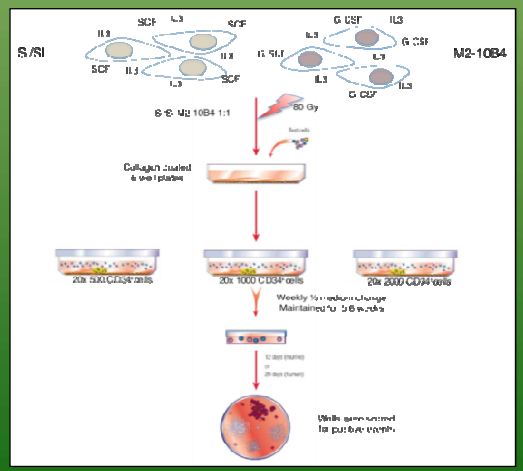
1) il numero assoluto e percentuale di cellule CD34+ e di linfociti T CD34+;

2) il grado di staminalità/differenziamento cellulare mediante pannelli di anticorpi monoclonali caratteristici di HSC o progenitori; (33 DR 45 34 38)

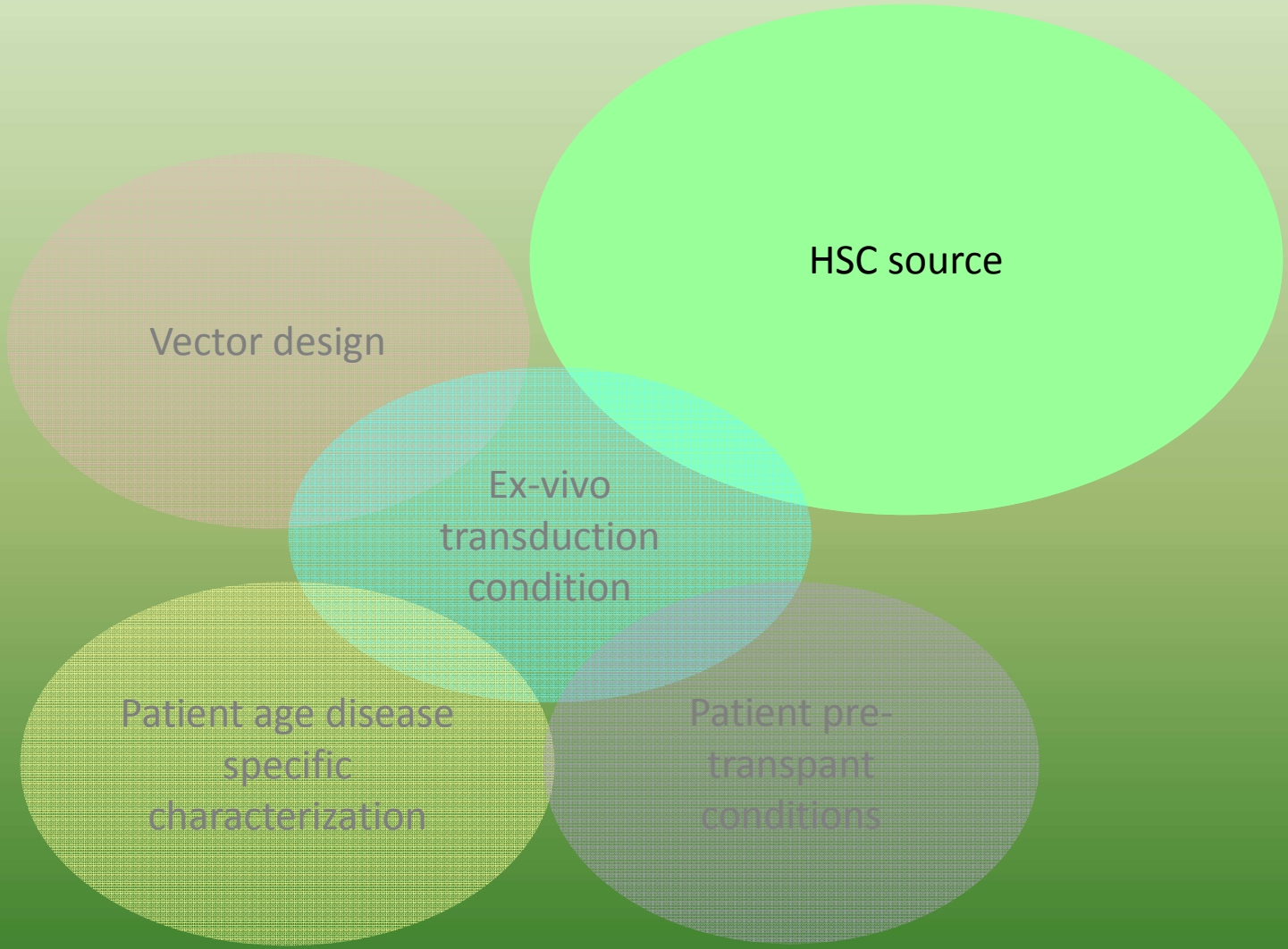
3) il grado di staminalità/differenziamento cellulare mediante saggi clonogenici in vitro a breve (colonie in methilcellulose)



4) e lungo termine (LTC-IC)



5) ed in vivo (ricostituzione sistema ematopoietico in zebrafish)

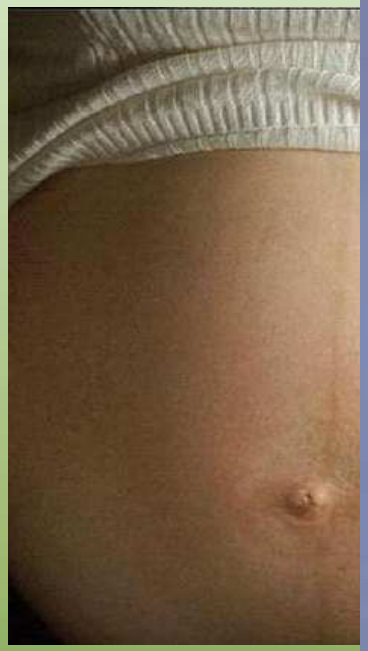


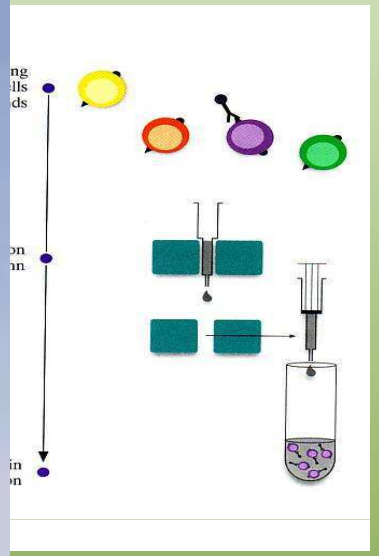
Si ringrazia per il sostegno alla Ricerca

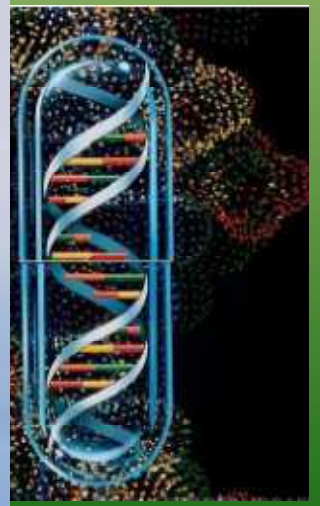
CELLULE STAMINALI EMATOPOIETICHE DA SANGUE DI CORDONE OMBELICALE

- ✓ perché facilmente reperibili
- ✓ perché hanno un più alto potenziale clonogenico
- ✓ perché più permissive alla trans-infezione con i vettori lentivirali
- ✓ ma…… una unità cordonale contiene un numero limitato di CSE

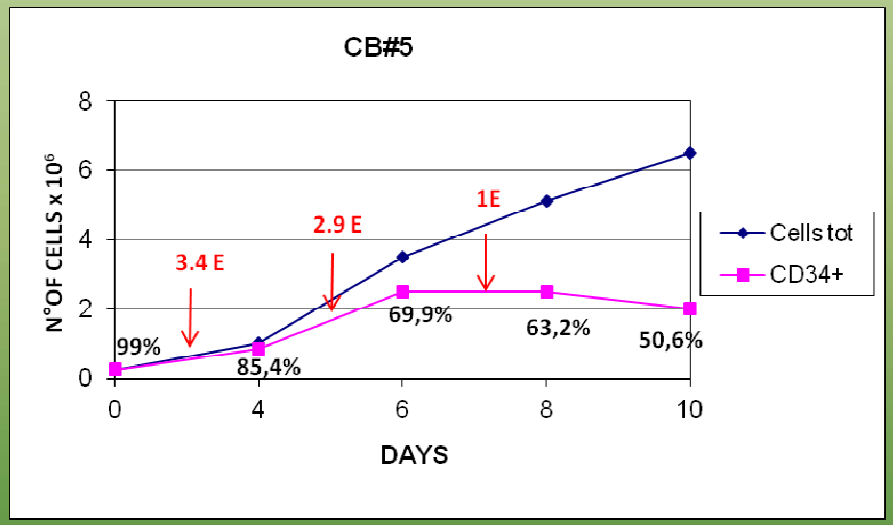
Si ringrazia per il sostegno alla Ricerca

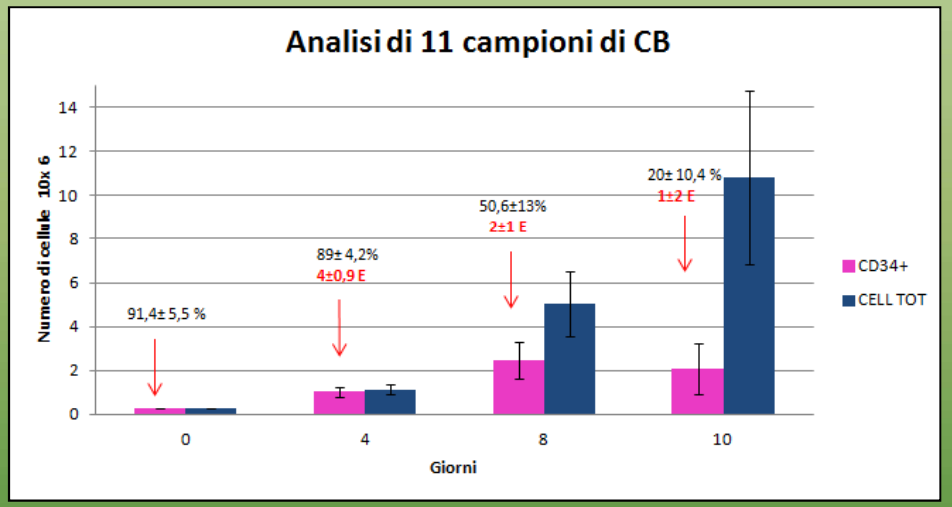






EXPANSION PROFILES OF HEMATOPOIETIC STEM CELLS FROM UMBILICAL CORD BLOOD

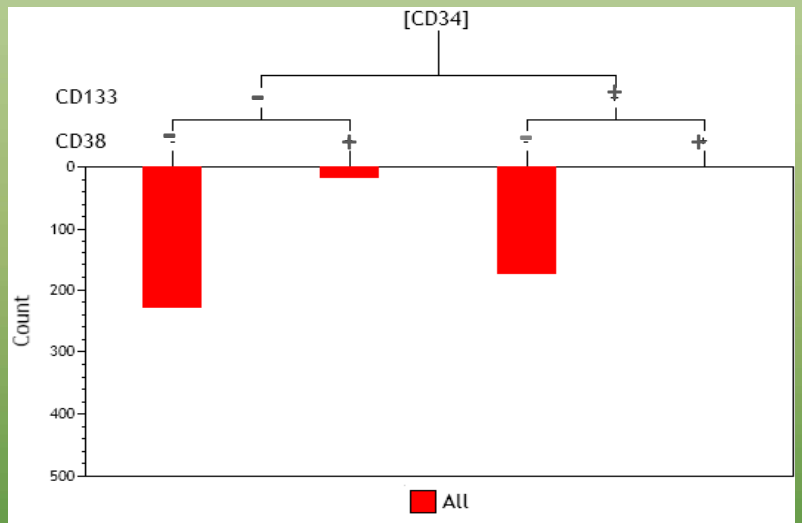




Si ringrazia per il sostegno alla Ricerca

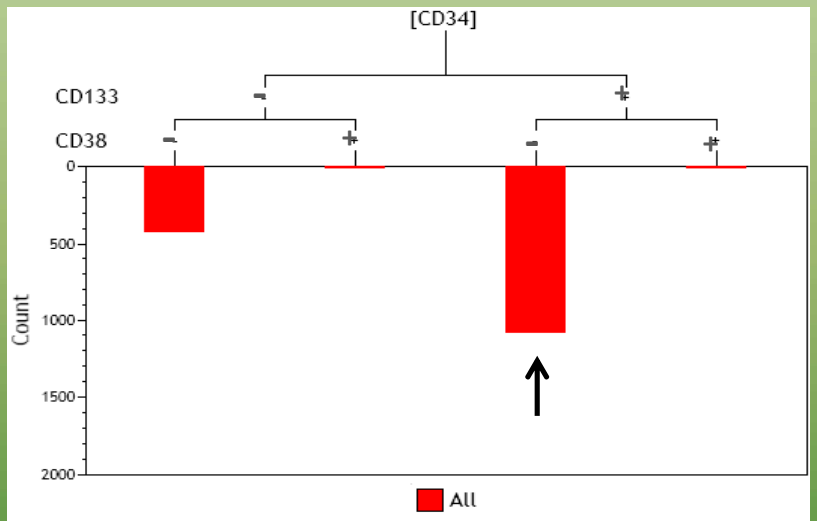
CORD BLOOD HSC EX VIVO EXPANTION SHOWS MAIN STAMINAL FINDINGS OF CD34+ CELLS

Cord Blood CD34+ sub-populations



Gate	Number	%Total	%Gated
All	414	0,63	100,00
CD133-CD38-	226	0,34	54,59
CD133-CD38+	16	0,02	3,86
CD133+CD38-	172	0,26	41,55
CD133+CD38+	0	0,00	0,00

CD34+ sub-populations after 4 days EX-vivo expansion



Gate	Number	%Total	%Gated
All	1.499	33,96	100,00
CD133-CD38-	416	9,42	27,75
CD133-CD38+	2	0,05	0,13
CD133+CD38-	1.078	24,42	71,91
CD133+CD38+	3	0,07	0,20

Si ringrazia per il sostegno alla Ricerca

AZIENDA OSPEDALIERA OSPEDALI RIUNITI VILLA SOFIA - CERVELLO PALERMO

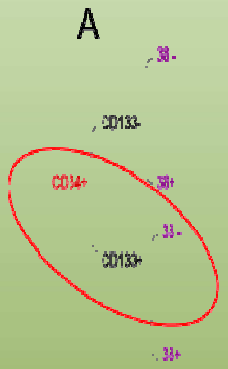
Dipartimento di Oncologia ed Ematologia

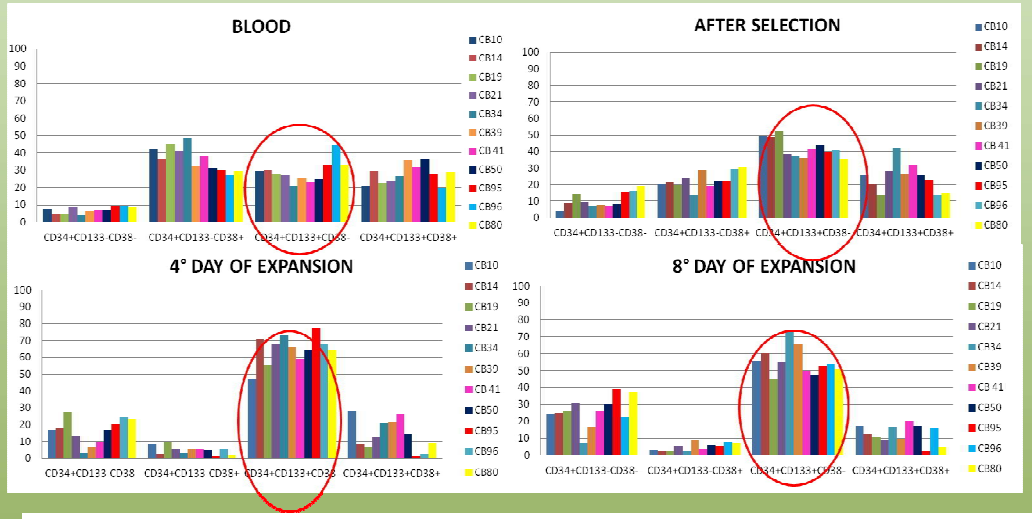
SANTINA ACUTO

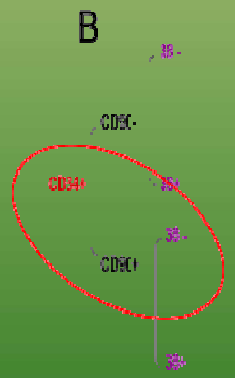
"AGGIORNAMENTO SULLA TERAPIA GENICA DELLE SINDROMI TALASSEMICHE"

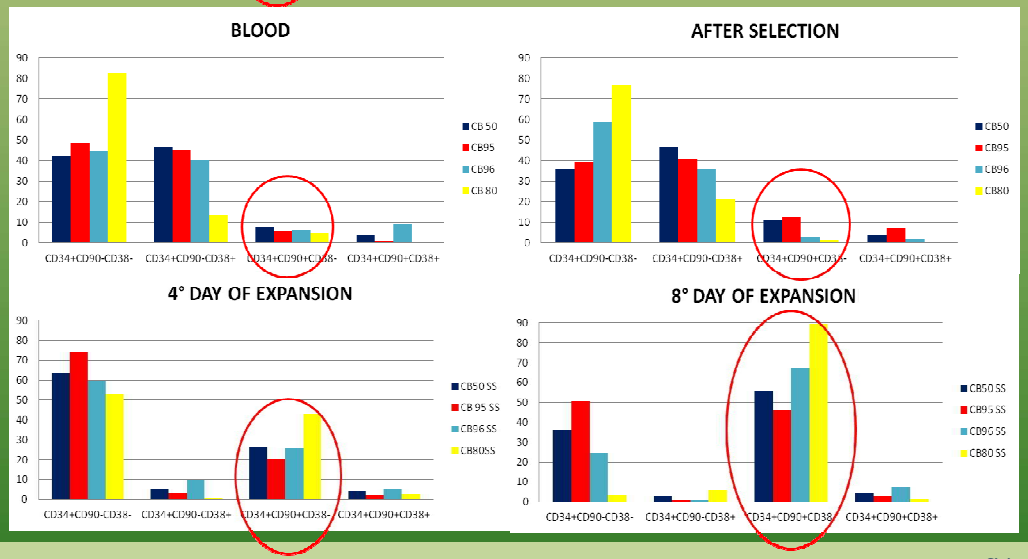
Fondazione Franco e Piera Cutino Guarire dalla TALASSEMIA

HSCS IN CULTURE SHOW A CELL SURFACE ANTIGEN EXPRESSION PATTERN CHARACTERISTIC OF PRIMITIVE HEMATOPOIETIC CELLS









Si ringrazia per il sostegno alla Ricerca

AZIENDA OSPEDALIERA
OSPEDALI RIUNITI VILLA SOFIA - CERVELLO
PALERMO

Dipartimento
di Oncologia ed Ematologia

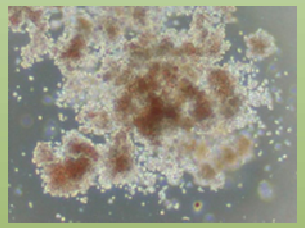
SANTINA ACUTO

"AGGIORNAMENTO SULLA TERAPIA GENICA DELLE SINDROMI TALASSEMICHE"

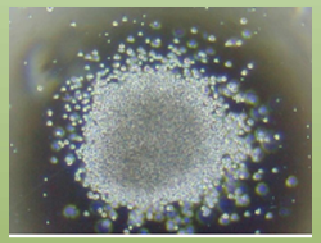
Fondazione
Franco e Piera Cutino
Guarire dalla TALASSEMIA

THE FREQUENCY OF DIFFERENT PROGENITOR CELLS WAS MAINTAINED DURING ONE WEEK OF CULTURE

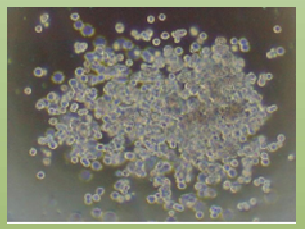
CFU-GEMM



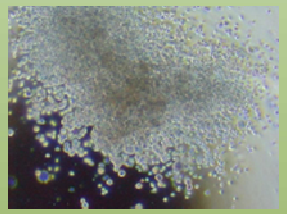
CFU-G



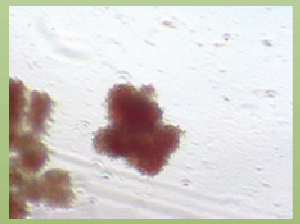
CFU-M



CFU-GM



BFU-E



Colonie	Giorno 0	Giorno 4	Giorno 8
BFU-E	24 ± 5,3%	26± 4,7%	24 ± 3,8%
CFU-GM	24 ±3,4%	19± 1,4%	20 ± 2,8%
CFU-GEMM	**4± 1,7%**	**3± 1,4%**	**3 ± 1,5%**
CFU-M	27 ± 6,3%	31± 5,2%	37 ± 3,5%
CFU-G	21± 5%	20±7%	17 ± 6,3%

Si ringrazia per il sostegno alla Ricerca

Vector design to improve efficacy and safety

***Ex-vivo* transduction conditions**

Influence the efficacy and safety of gene therapy

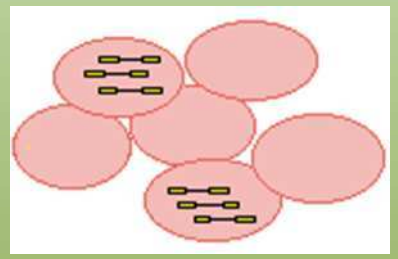
HSC source

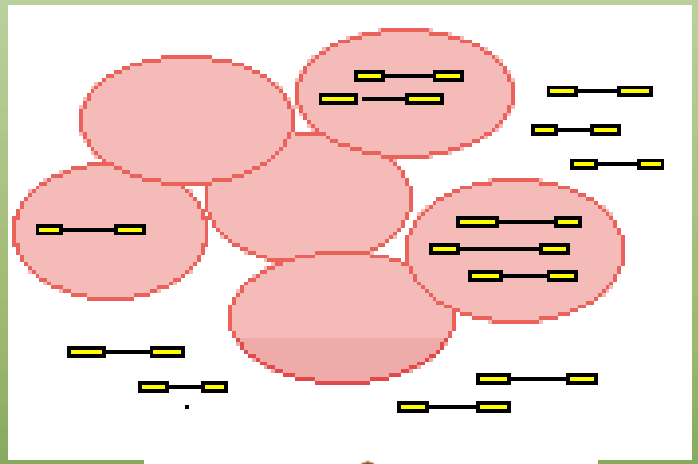
Patient age disease specific characterization

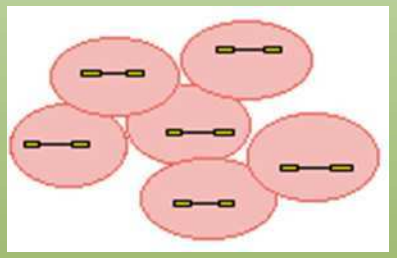
Patient pre-transpant conditions

Si ringrazia per il sostegno alla Ricerca

SUCCESSFUL GENE THERAPY REQUIRES EQUILIBRIUM BETWEEN NUMBER OF GENETICALLY CORRECTED CELLS AND NUMBER OF VECTORS PER CELL





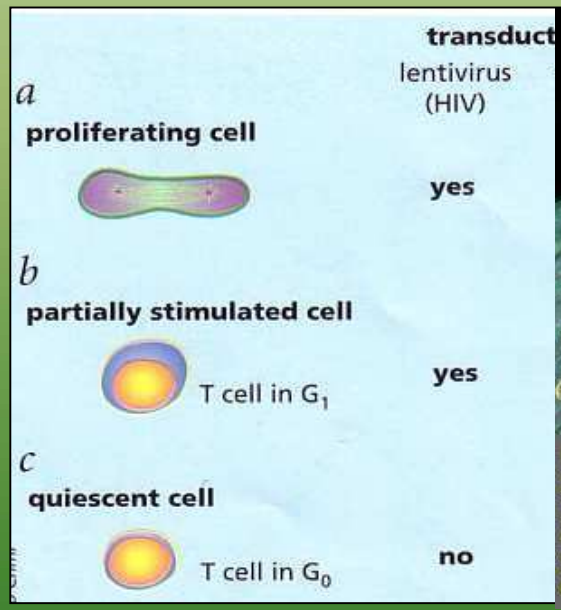


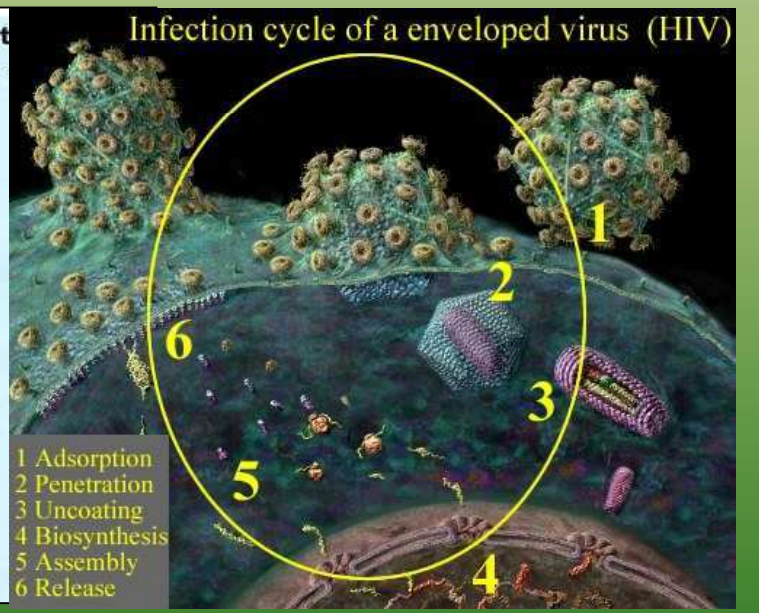
EFFICIENCY **GENOTOXICITY**

Si ringrazia per il sostegno alla Ricerca

FACTORS INFLUENCING THE TRANS-INFECTION EFFICIENCY

- Number of vector particles/cell (MOI, molteplicity of infection)
- Number of virus-specific receptors on cell membrane
- Cell cicle status

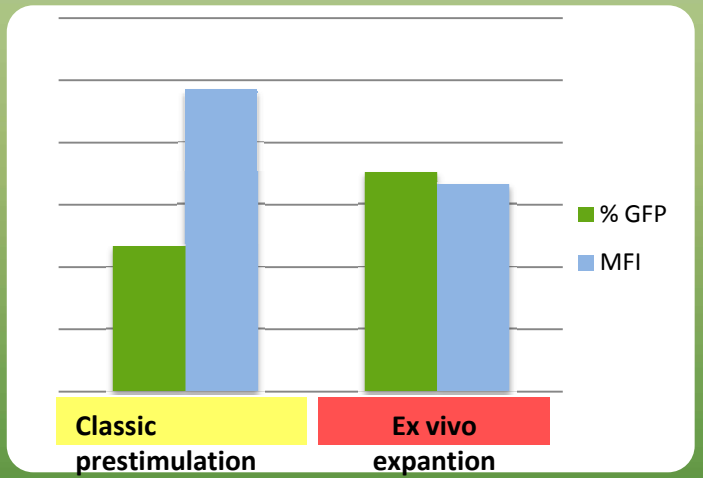




Si ringrazia per il sostegno alla Ricerca

EXPANDED HSCS ARE MORE LIKELY TO BE TRANSDUCED BY LV-VECTORS AND RESULTS IN A BETTER DISTRIBUTION OF VECTOR COPY NUMBER PER CELL

Stimulation conditions	MOI	9 days erythroid liquid culture % GFP	MFI	VCN/Cells	Frequency of VCN/cell in methylcellulose colonies
ex-vivo-15	6	22 %	46,8	0.67	3 to 7 VC/cell (65%) 2 VC/cell (20%) 1 VC/cell (15%)
ex-vivo-15	6	25 %	50,3	0.85	
expansion	6	32,7 %	34	1	
expansion	6	31,2 %	28,8	0.86	3 VC/cell (10%) 2 VC/cell (20%) 1 VC/cell (70%)
expansion	6	34,6 %	31	0.86	
expansion	6	42,8 %	39,8	1.3	



Si ringrazia per il sostegno alla Ricerca

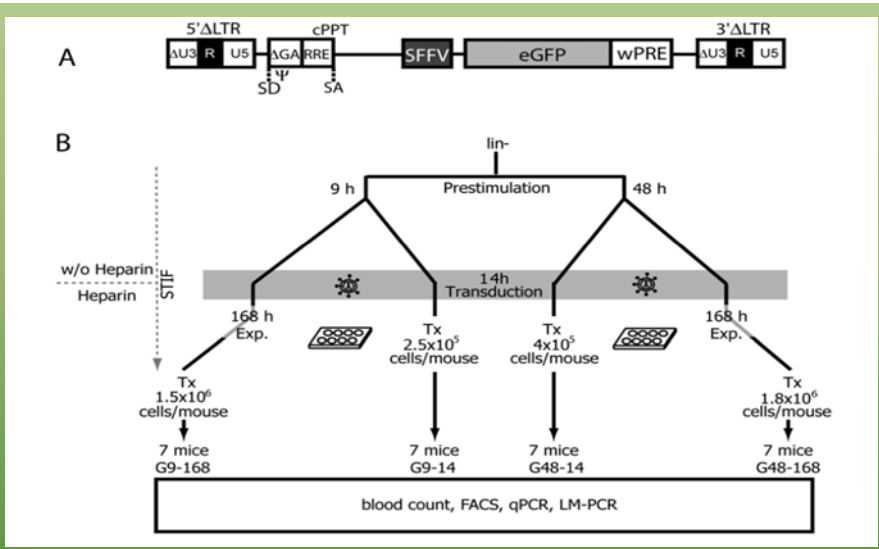
ADVANTAGES OF HEMATOPOIETIC STEM CELLS (HSC) *EX VIVO* EXPANSION AND TRANSDUCTION

blood

Prepublished online Jan 19, 2011;
doi:10.1182/blood-2010-08-303222

Polyclonal fluctuation of lentiviral vector-transduced and expanded murine hematopoietic stem cells

Tobias Maetzig, Martijn H Brugman, Stefan Bartels, Niels Heinz, Olga S Kustikova, Ute Modlich, Zhixiong Li, Melanie Galla, Bernhard Schiedlmeier, Axel Schambach and Christopher Baum

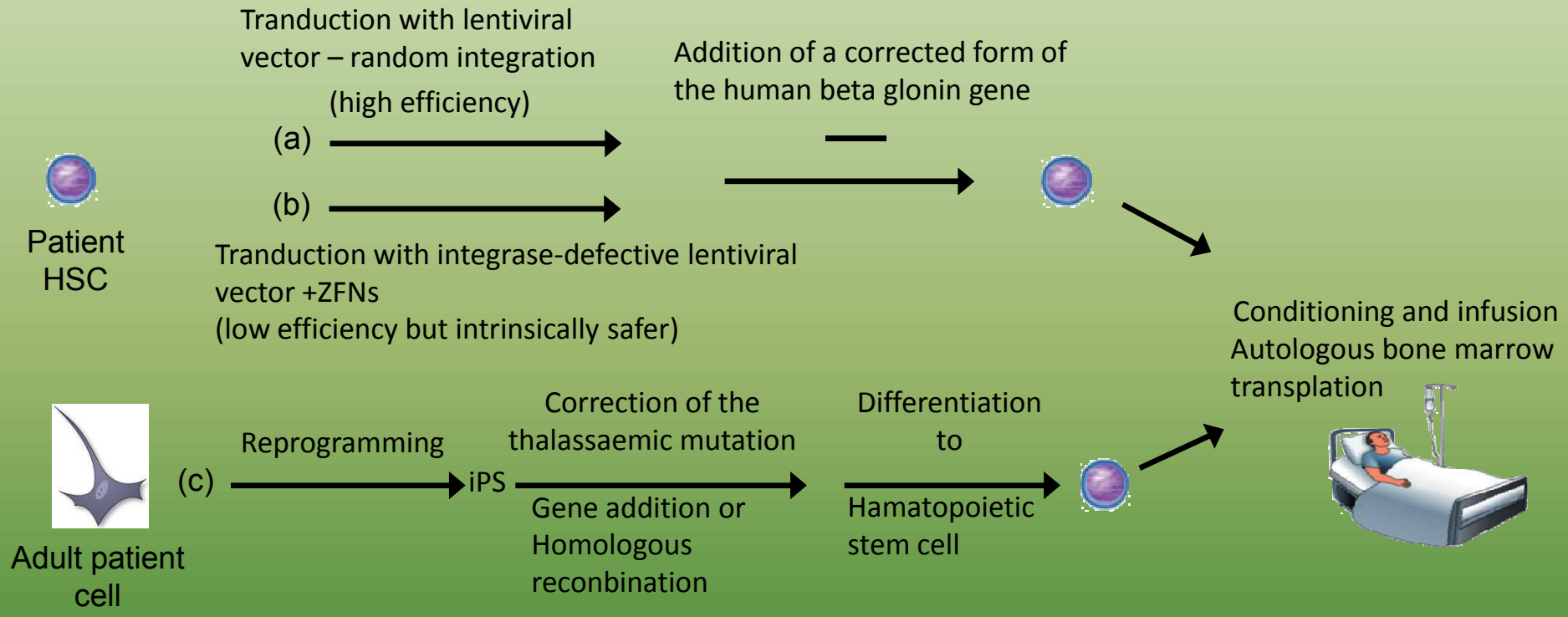


- **CONCLUSIONS : a brief period of prestimulation and a long period of *ex-vivo* expansion determine a more rapid, polyclonal and long term hematopoietic system reconstitution with a lesser degree of deregulation of genomic expression .**

Si ringrazia per il sostegno alla Ricerca

What is new on the gene therapy front

Si ringrazia per il sostegno alla Ricerca



Si ringrazia per il sostegno alla Ricerca

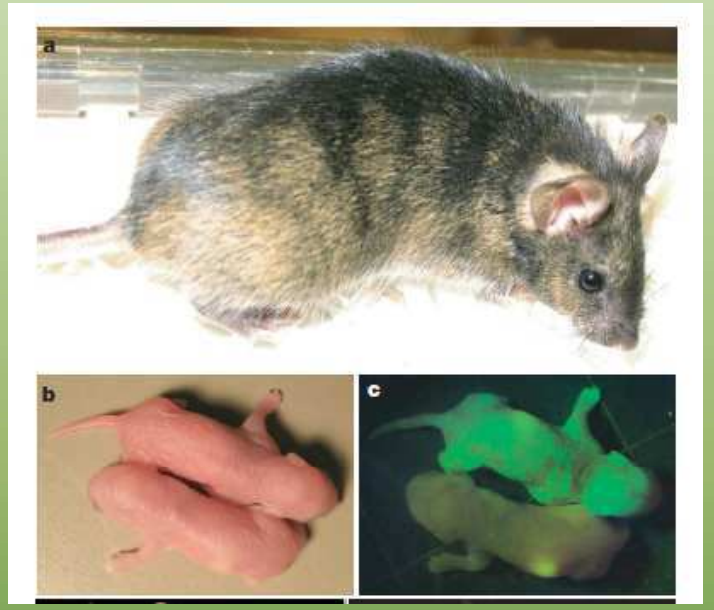
INDUCED PLURIPOTENT STEM CELLS (iPS)

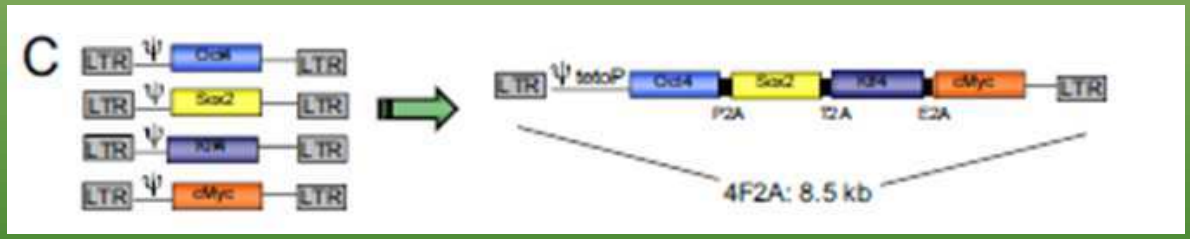
nature Vol 448 | 19 July 2007 | doi:10.1038/nature05944

ARTICLES

In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state

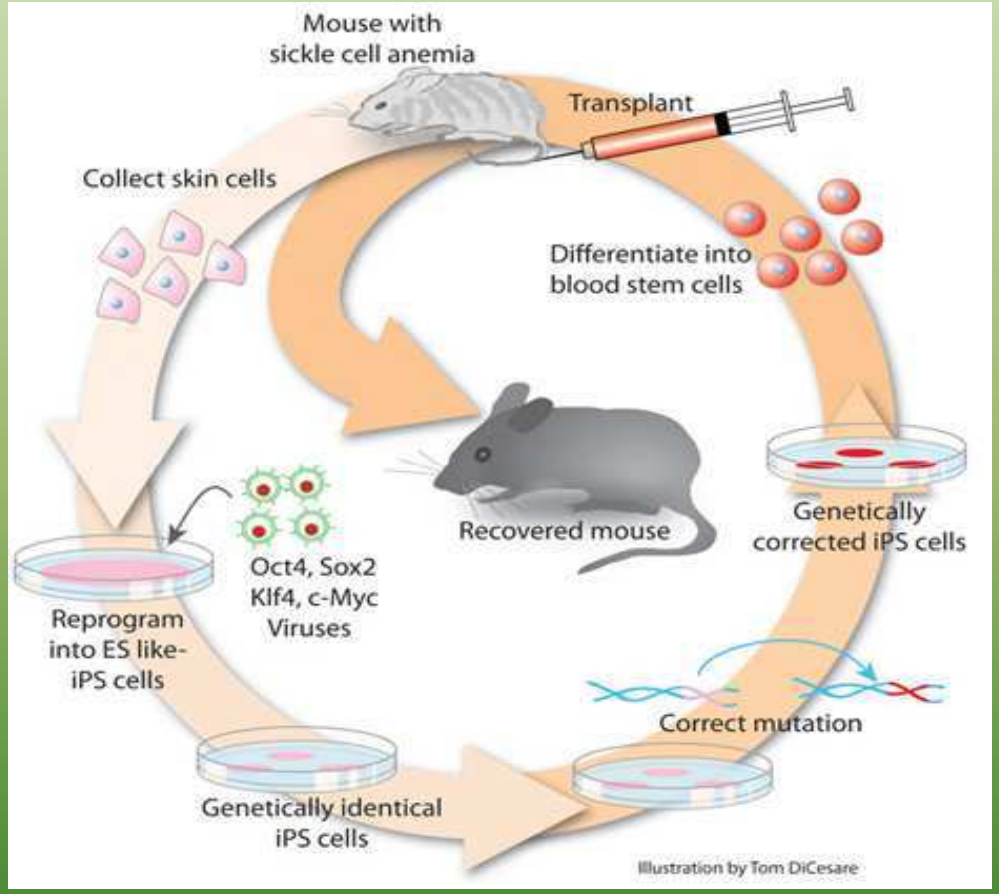
Marius Wernig[1]*, Alexander Meissner[1]*, Ruth Foreman[1,2]*, Tobias Brambrink[1]*, Manching Ku[3]*, Konrad Hochedlinger[1]†, Bradley E. Bernstein[3,4,5] & Rudolf Jaenisch[1,2]





Si ringrazia per il sostegno alla Ricerca

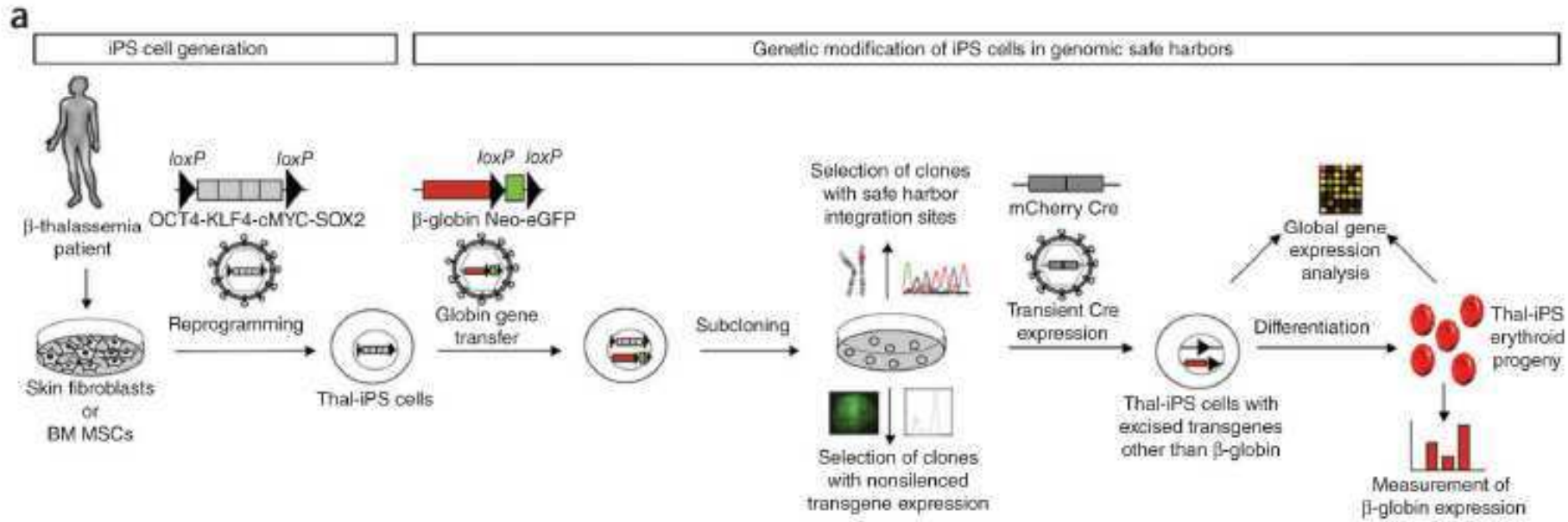
TREATMENT OF SICKLE CELL ANEMIA MOUSE MODEL WITH iPS CELLS GENERATED FROM AUTOLOGOUS SKIN



Hanna J et al. Science 2007

Si ringrazia per il sostegno alla Ricerca

GENOMIC SAFE HARBORS PERMIT HIGH B-GLOBIN TRANSGENE EXPRESSION IN THALASSEMIA INDUCED PLURIPOTENT STEM CELLS



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