Nuovi approcci di trapianto nel bambino con immunodeficienza primitiva

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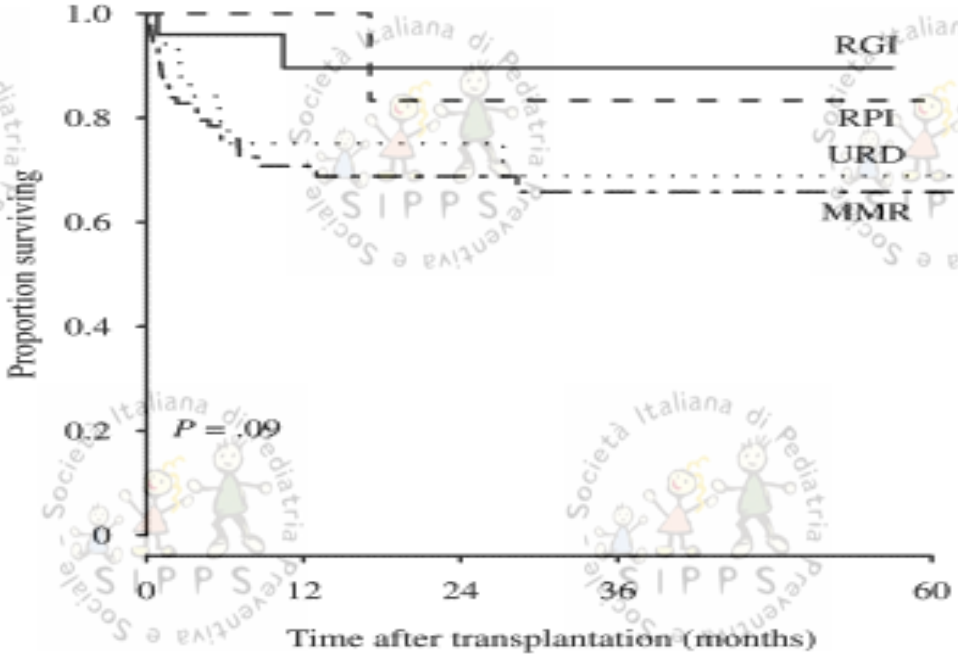
Diseases responsive to allogeneic HSCT

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Chronic myeloid leukemia
- Myelodysplastic syndromes
- Lymphomas/myeloma
- Congenital aplasia (Fanconi anemia, congenital dyskeratosis)
- Diamond-Blackfan anemia
- Severe aplastic anemia
- Chronic granulomatous disease
- Infantile malignant osteopetrosis
- Hemoglobinopathies
- Severe combined immune-deficiencies (SCID)
- Wiskott-Aldrich Syndrome
- Hemophagocytic lymphohistiocytosis
- Chédiak-Higashi Syndrome
- Immune-deficiency with hyper-IgM
- Congenital errors of metabolism (Hurler, Maroteaux-Lamy, adrenoleukodystrophy, metachromatic leukodystrophy)

Selected types of autoimmune diseases (?)

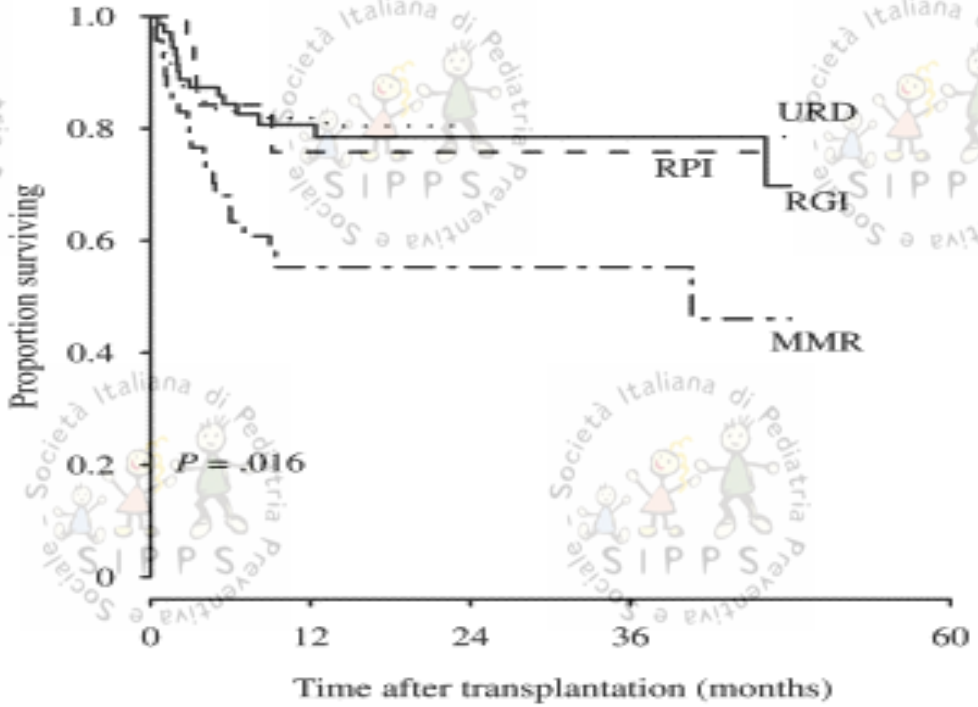


Months	0	6	12	24	36	60
Number at risk						
RGI	25	22	12	6	3	0
RPI	14	9	7	2	1	0
URD	46	30	18	16	7	2
MMR	96	50	37	25	15	2

Cumulative probability of survival in patients with SCID after HSCT according to donor source (related or URD) and HLA matching for the period 2000 to 2005. MMR, Mismatched related; RGI, related genoidentical; RPI, related phenoidentical.

Gennery AR, Slatter MA, Grandin L, et al. **Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: Entering a new century, do we do better?** Journal of Allergy and Clinical Immunology, Volume 126, Issue 3, 2010, 602–610.e11

http://dx.doi.org/10.1016/j.jaci.2010.06.015



Months	0	6	12	24	36	60
Number at risk						
RGI	73	55	37	20	13	0
RPI	23	14	8	5	2	0
URD	124	88	60	41	21	0
MMR	47	28	18	13	8	0

Cumulative probability of survival in patients with non-SCID PID after HSCT according to donor source (related or URD) and HLA matching for the period 2000 to 2005. MMR, Mismatched related; RGI, related genoidentical; RPI, related phenoidentical.

Gennery AR, Slatter MA, Grandin L, et al. **Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: Entering a new century, do we do better?** Journal of Allergy and Clinical Immunology, Volume 126, Issue 3, 2010, 602–610.e11

Looking for a donor…

Family donor

1%

1 HLA locus disparate

25%

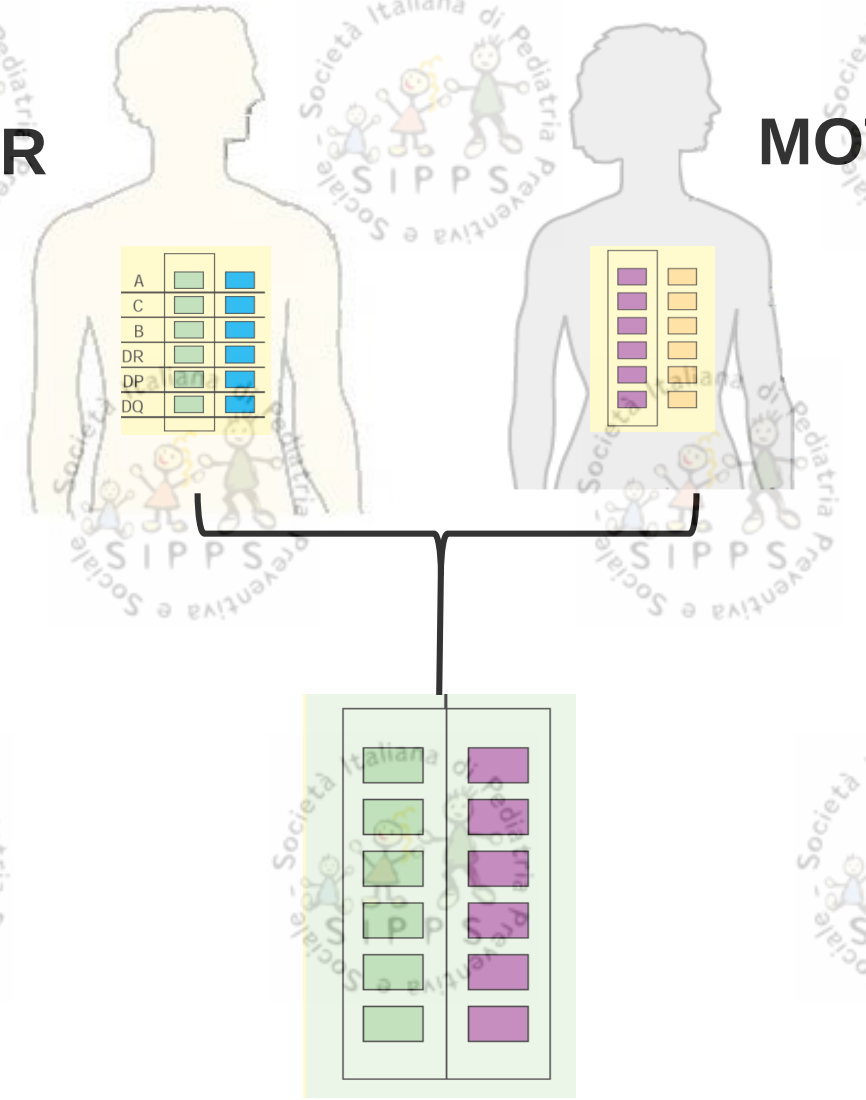
HLA-compatible

70-75%

Need alternative donors

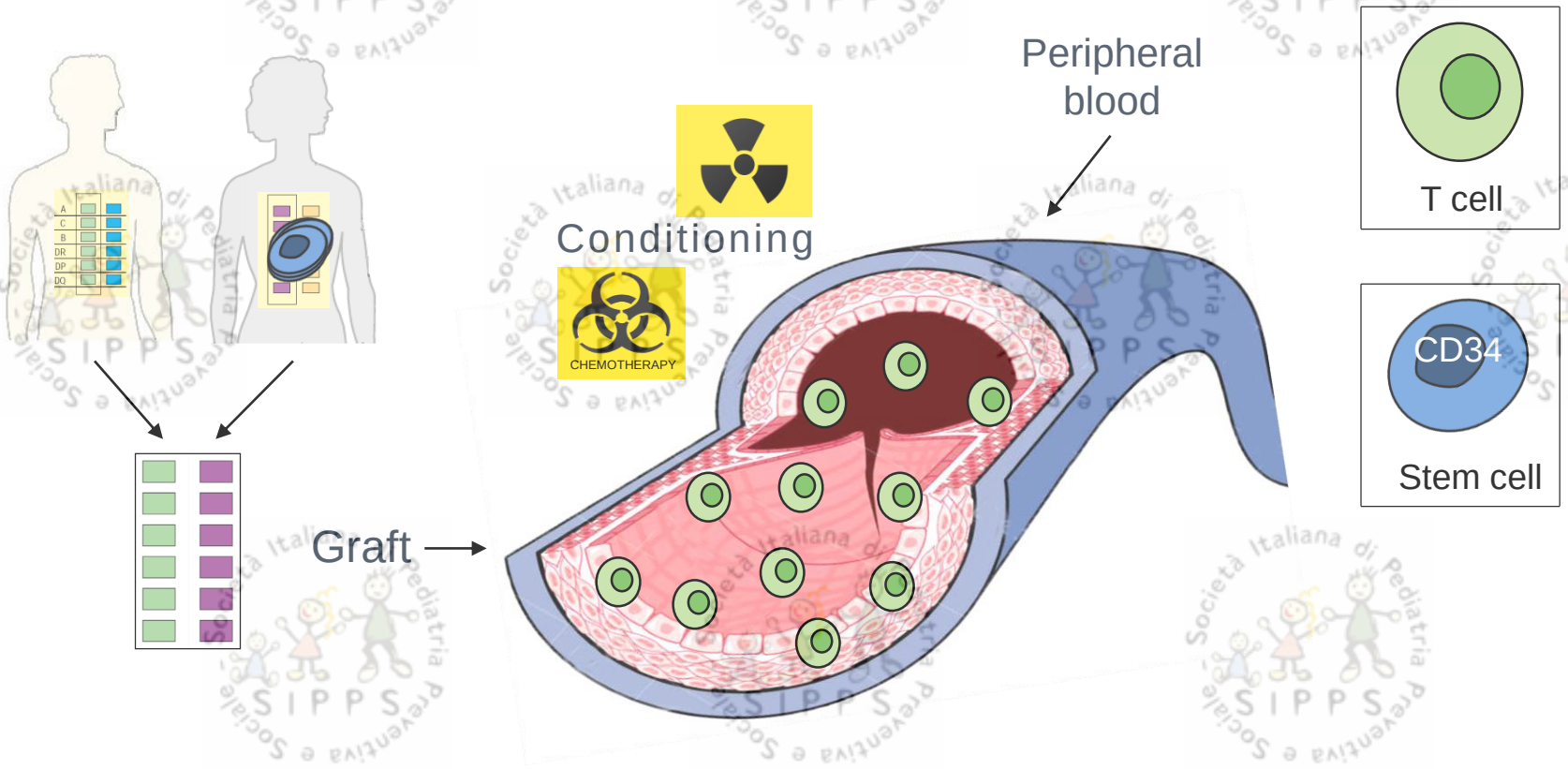
FATHER

MOTHER



RECIPIENT

High doses of T cell-depleted stem cells allow transplants across HLA barriers (>90% engraftment, <10% GvHD)



ADVANTAGES

It's applicable in all cases

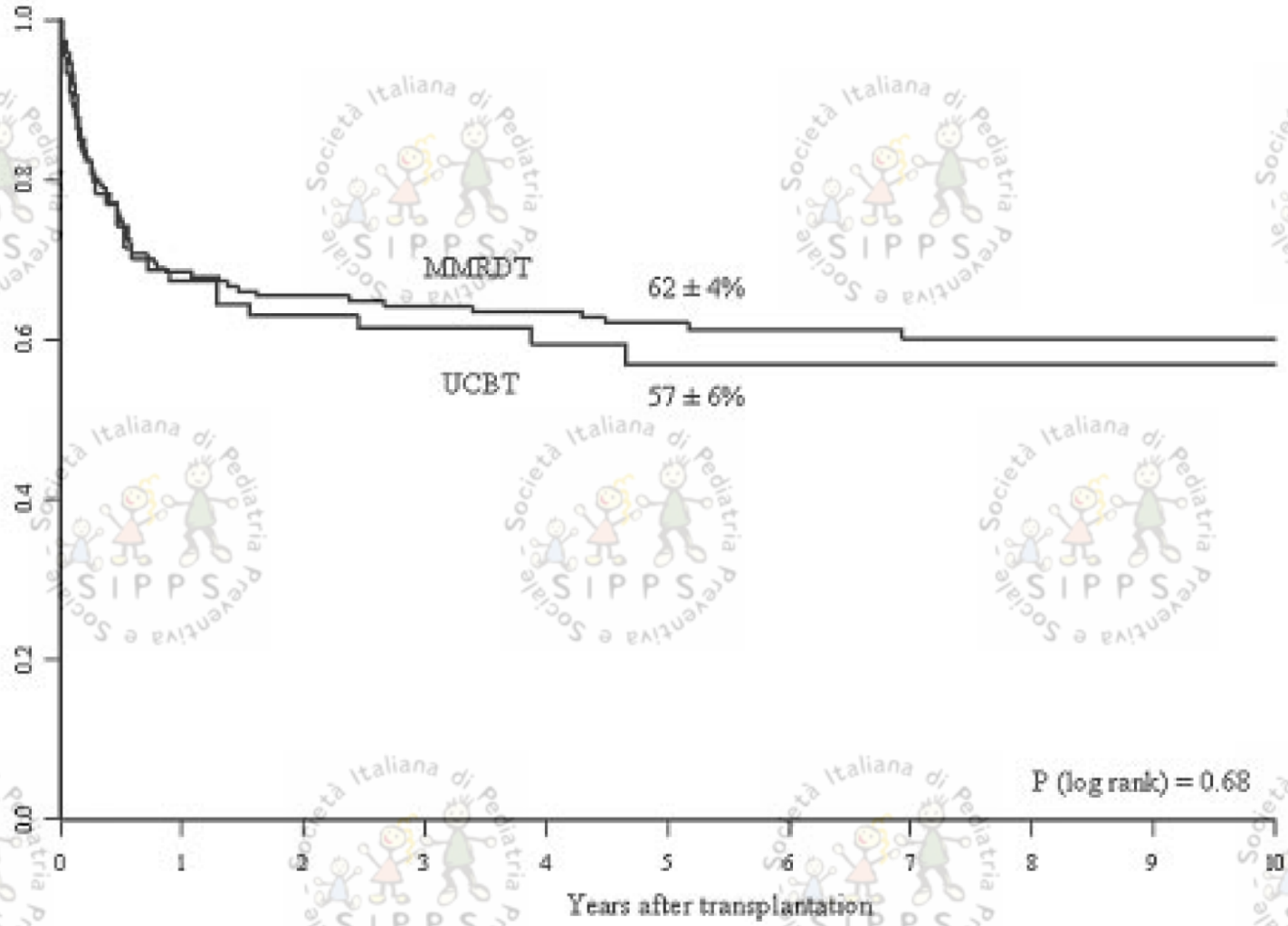
It responds to the need of an urgent transplant

POTENTIAL PROBLEM

Delayed immune recovery

Transplantation in patients with SCID: mismatched related stem cells or unrelated cord blood?

Juliana F. Fernandes,[1,2] Vanderson Rocha,[1,2] Myriam Labopin,[3] Benedicte Neven,[4] Despina Moshous,[4] Andrew R. Gennery,[5] Wilhelm Friedrich,[6] Fulvio Porta,[7] Cristina Diaz de Heredia,[8] Donna Wall,[9] Yves Bertrand,[10] Paul Veys,[11] Mary Slatter,[5] Ansgar Schulz,[6] Ka Wah Chan,[12] Michael Grimley,[12] Mouhab Ayas,[13] Tayfun Gungor,[14] Wolfram Ebell,[15] Carmem Bonfim,[16] Krzysztof Kalwak,[17] Pierre Taupin,[18,19] Stéphane Blanche,[4] H. Bobby Gaspar,[11] Paul Landais,[18,19] Alain Fischer,[4,19] Eliane Gluckman,[1] and Marina Cavazzana-Calvo,[19,20] on behalf of Eurocord and the Inborn Errors Working Party of the European Group for Blood and Marrow Transplantation

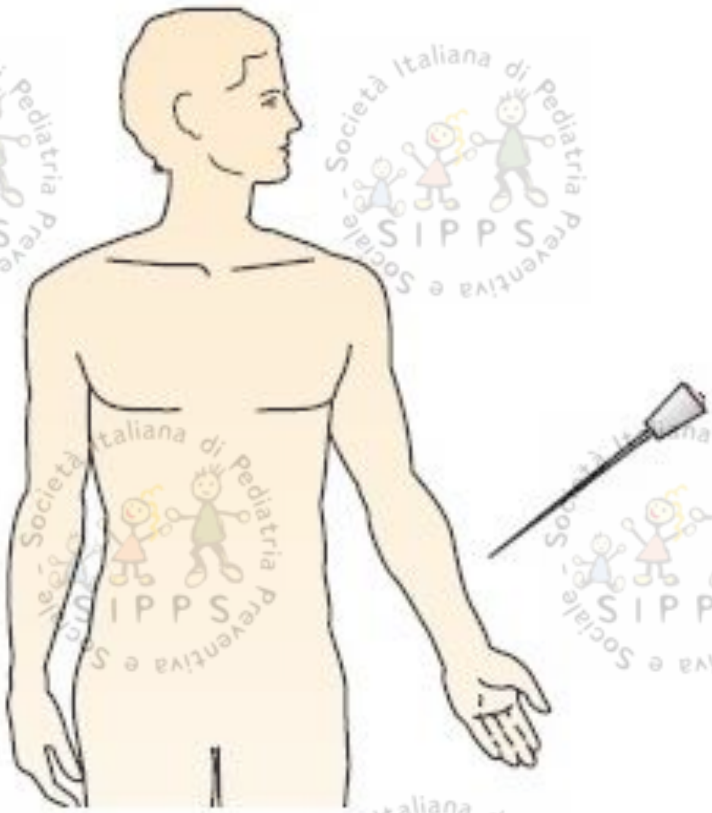


Haploidentical Donors: Evolution of T-cell Depletion Strategy

1995 — 1. CD34+ Selection “pure stem cells”

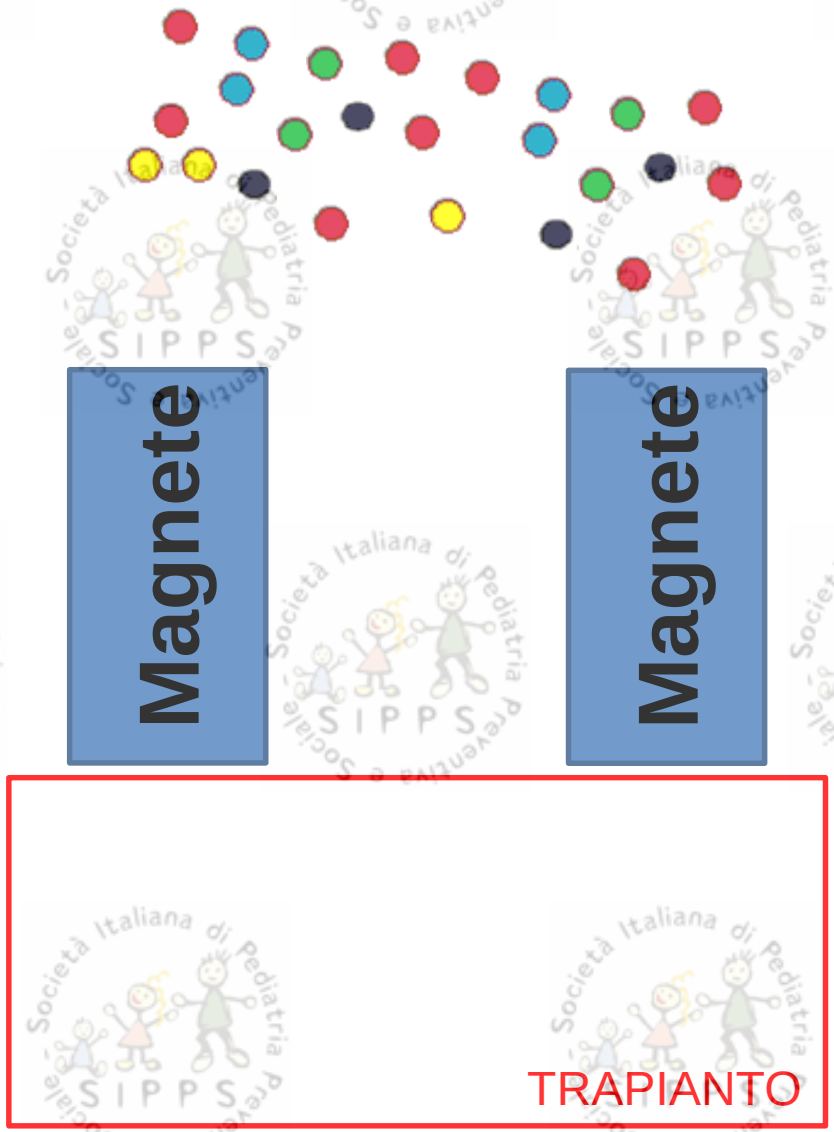
2010 — 2. TCRαβ/CD19 Depletion stem cells + effectors (NK cells + γδ T cells)

AFERESI (dopo stimolazione)

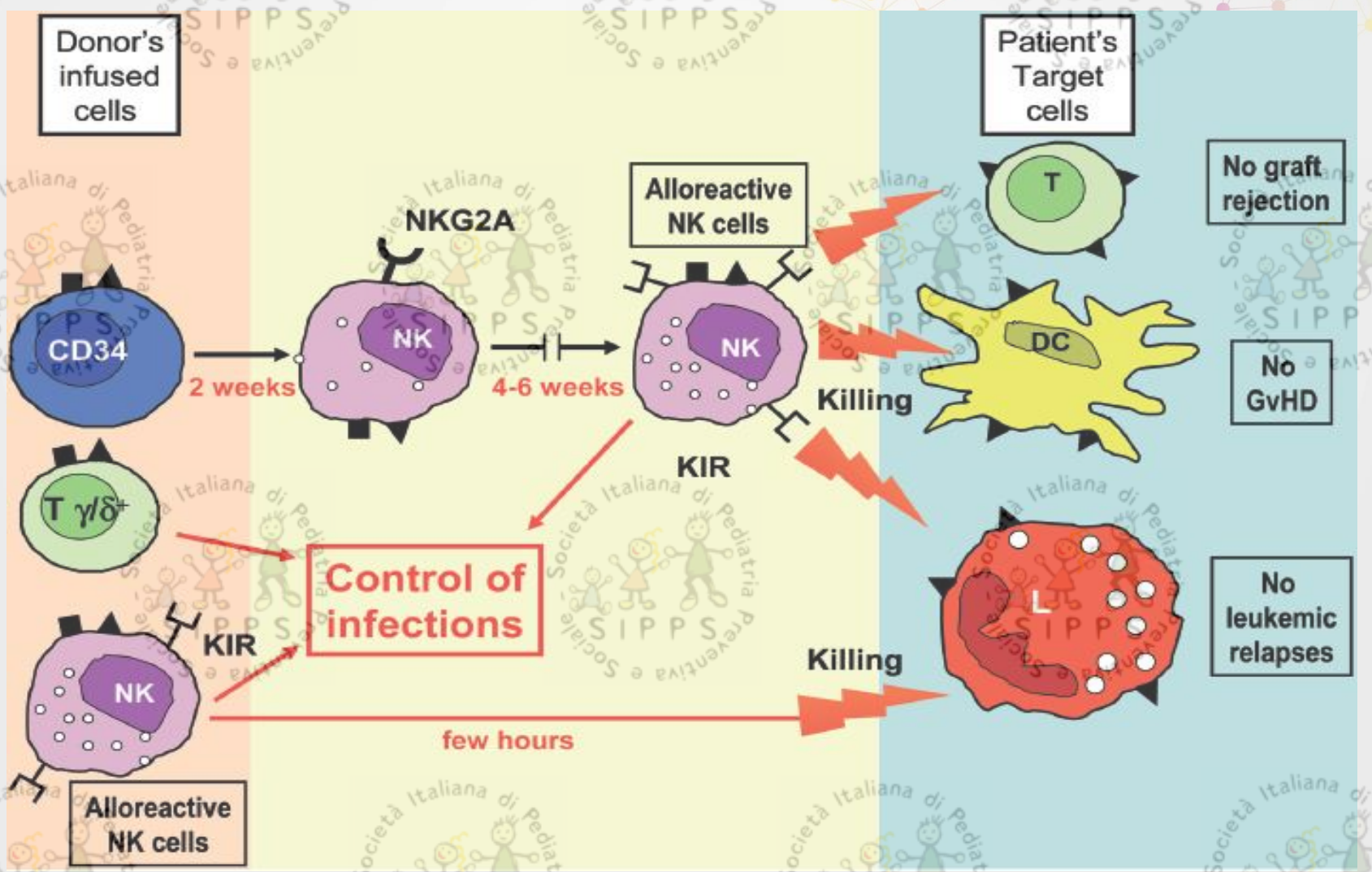


- Cellula staminale ematopoietica (CD34+)
- Linfocita T αβ
- Linfocita T γδ
- Natural Killer
- Linfocita B

Manipolazione



A Novel Strategy for HSCT from Haploidentical Donors: Depletion of α/β T Cells



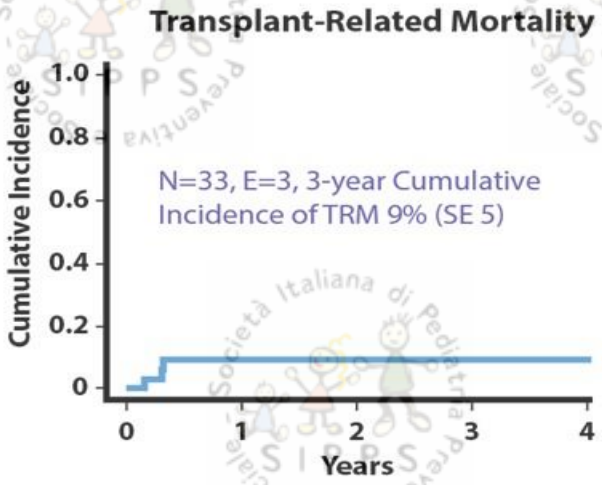
Locatelli F et al, Front Immunol 2013

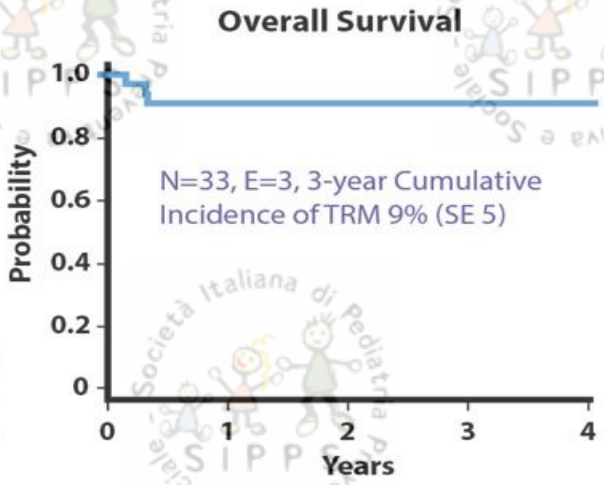
Brief Report

BLOOD, 31 JULY 2014 • VOLUME 124, NUMBER 5

HLA-haploidentical stem cell transplantation after removal of $\alpha\beta^+$ T and B cells in children with nonmalignant disorders

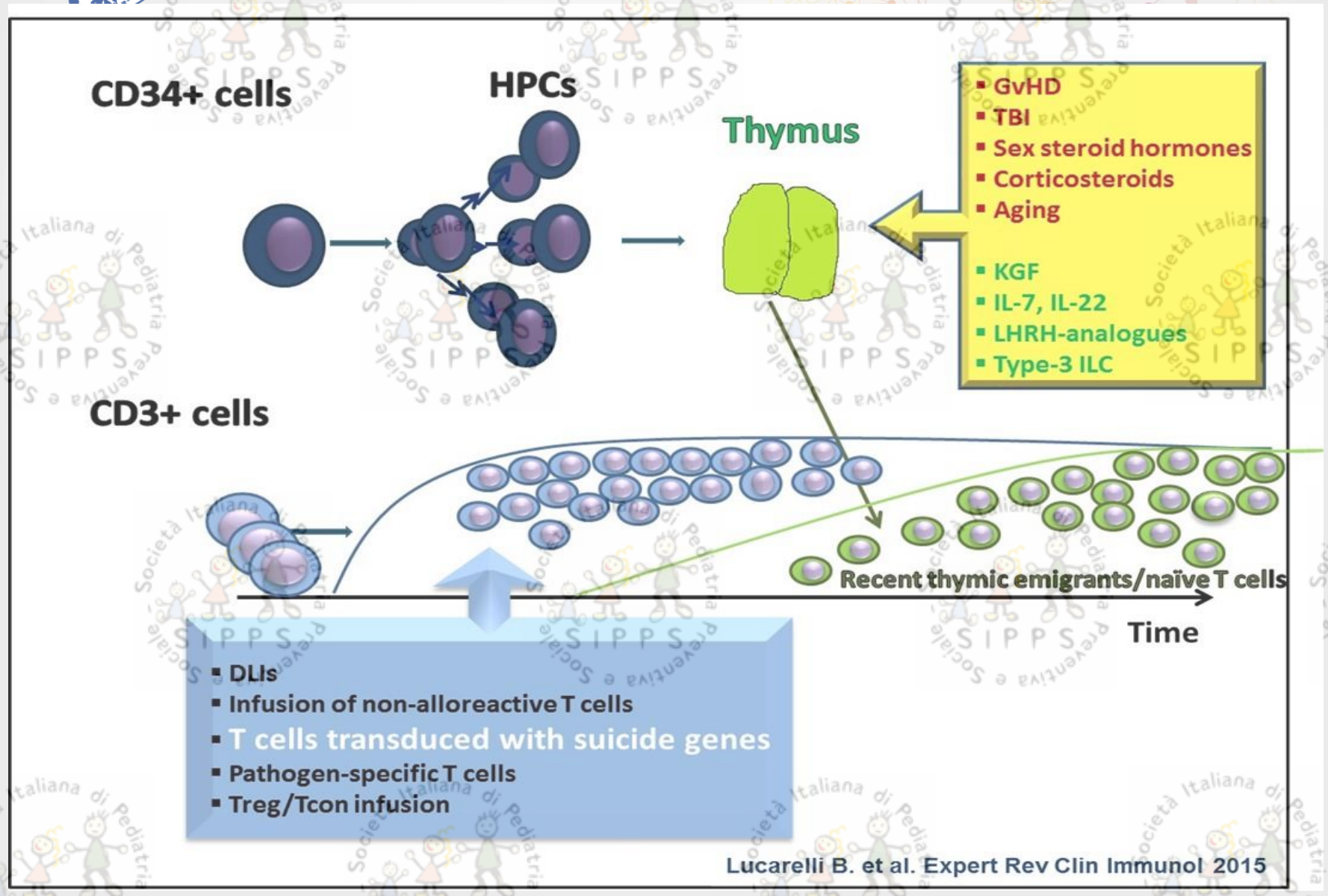
Alice Bertaina,[1] Pietro Merli,[1] Sergio Rutella,[1,2] Daria Pagliara,[1] Maria Ester Bernardo,[1] Riccardo Masetti,[3] Daniela Pende,[4] Michela Falco,[5] Rupert Handgretinger,[6] Francesca Moretta,[1] Barbarella Lucarelli,[1] Letizia P. Brescia,[1] Giuseppina Li Pira,[1] Manuela Testi,[7] Caterina Cancrini,[8] Nabil Kabbara,[9] Rita Carsetti,[1] Andrea Finocchi,[8] Alessandro Moretta,[10] Lorenzo Moretta,[5] and Franco Locatelli[1,11]





All lethal events were due to uncontrollable viral infections

- **Infusion of BPX-501 T cells to improve immune reconstitution**
- **BPX-501 T cells contain the iCasp9 suicide gene to provide safety**


CD34+ cells
HPCs
Thymus
GvHD
TBI
Sex steroid hormones
Corticosteroids
Aging
KGF
IL-7, IL-22
LHRH-analogues
Type-3 ILC
CD3+ cells
Recent thymic emigrants/naïve T cells
Time
DLIs
Infusion of non-alloreactive T cells
T cells transduced with suicide genes
Pathogen-specific T cells
Treg/Tcon infusion
Lucarelli B. et al. Expert Rev Clin Immunol 2015

Rimiducid (AP1903) Mechanism of Action

A.

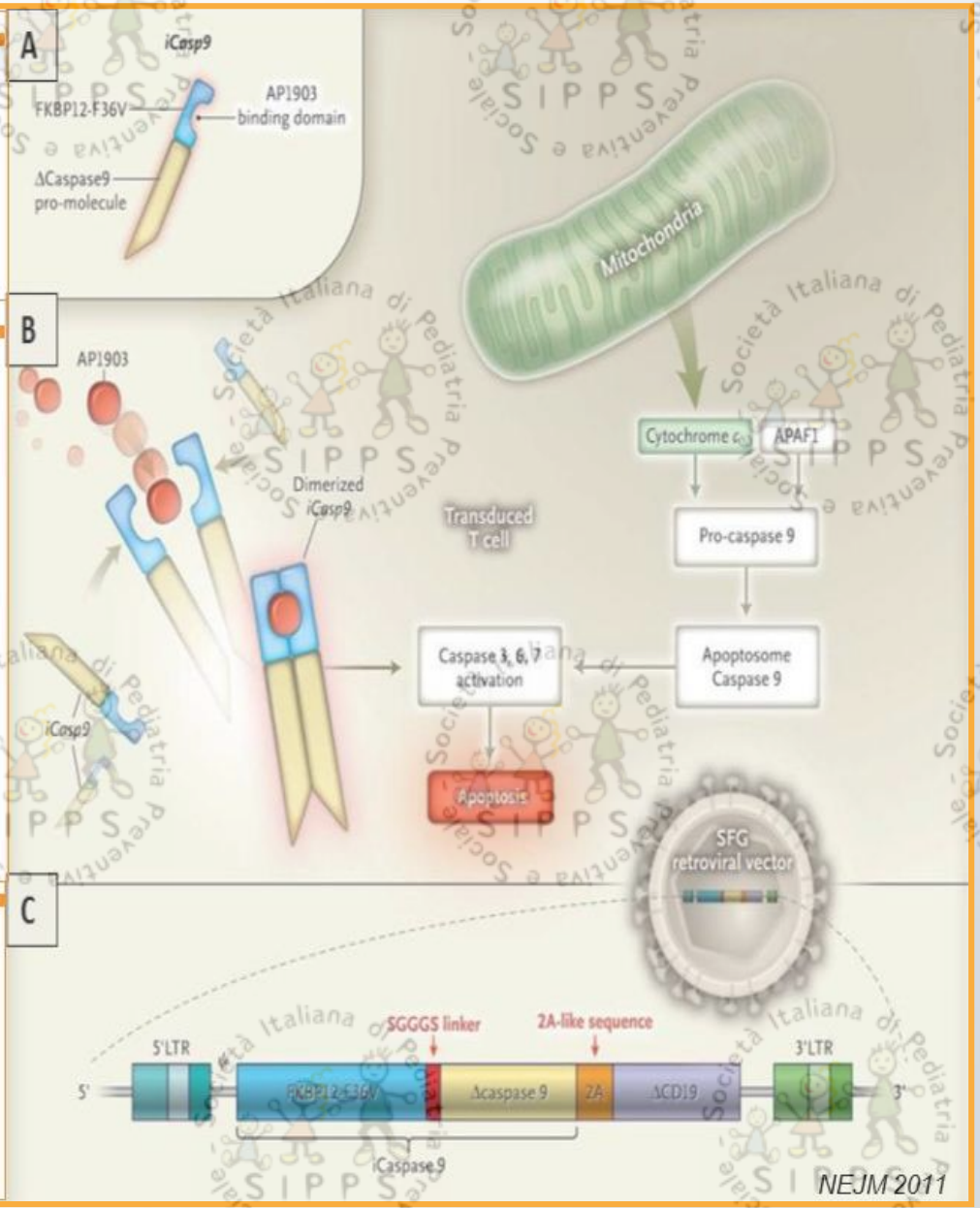
- Caspase 9 gene with FKBP mutant-with rimiducid binding domain (iCasp9)
- Rimiducid specifically designed to bind FKBP variant

B.

- Rimiducid induces dimerization of the FKBP-caspase 9
- Caspase cascade activated
- Resulting in rapid apoptosis and cell-death (clinical symptoms start to resolve in 1 hour, generally resolved in 24 hours)

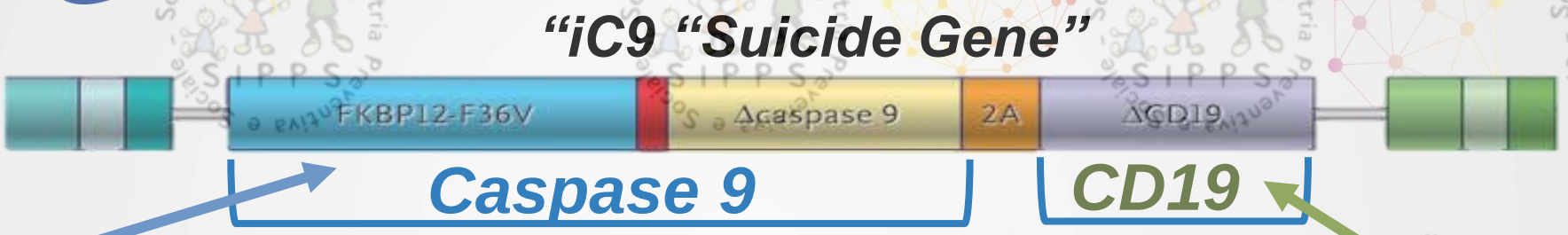
C.

- iCasp9 gene containing truncated CD19 marker, integrated into T cells through retroviral vector



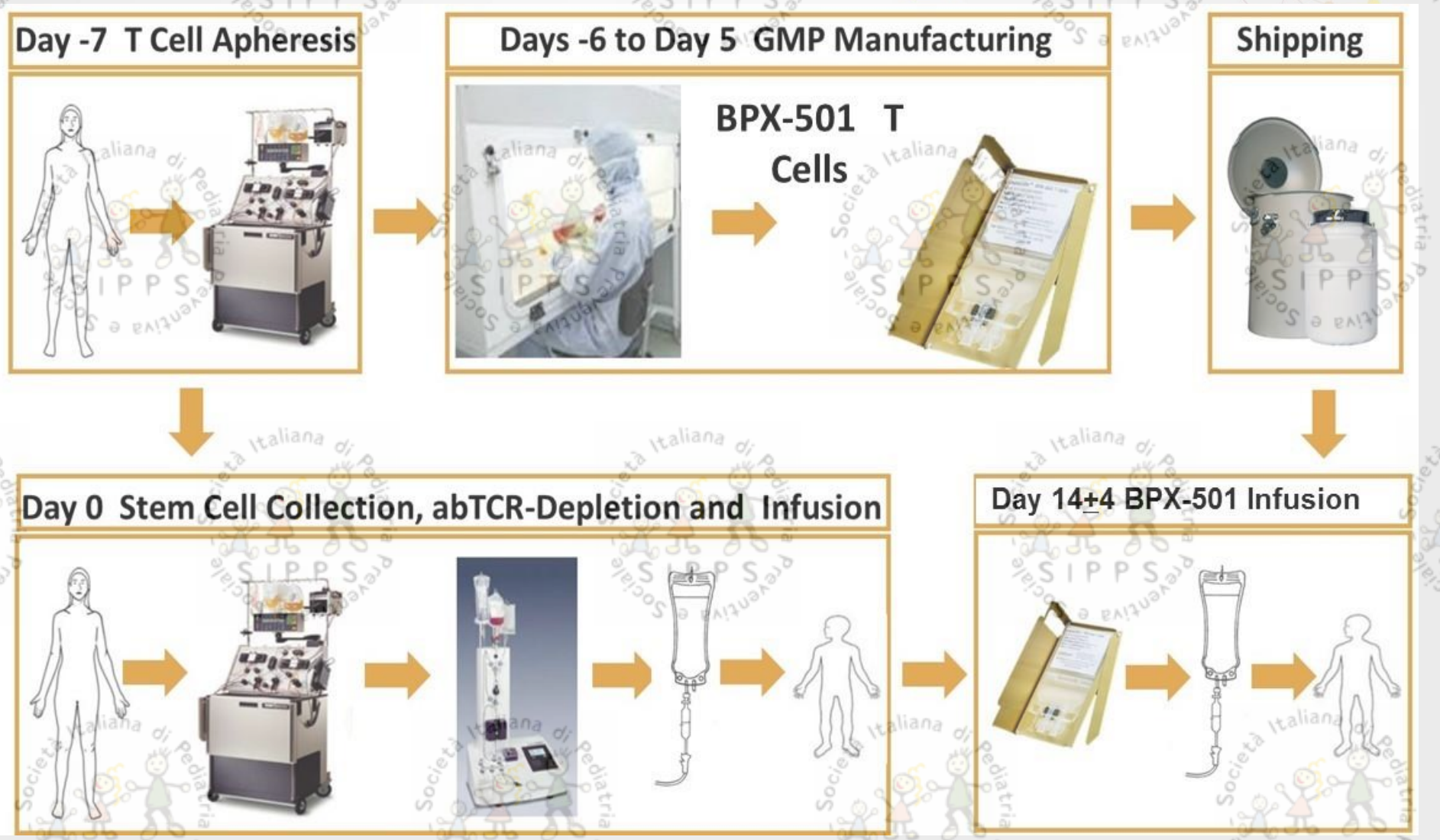
NEJM 2011

BPX–501: Inducible Caspase 9 T cells



- **From normal donor leukapheresis -- GMP facilities US / Europe**
- **Activated and expanded in culture, transduced with the iC9 suicide gene and selected for CD19+ cells**
- **Cryopreserved and stored in liquid nitrogen**
- **Maintain characteristics of normal T cells**
  - Broad T cell repertoire
  - Antiviral and antigen specific activity

BPX-501 after αβ+ T depleted Haplotransplant



BP-004 Study design

Phase I portion: **Classical 3+3 design**

2.5 X 10^5, 5 X 10^5 and 1 X 10^6 BPX-501 T Cells/kg

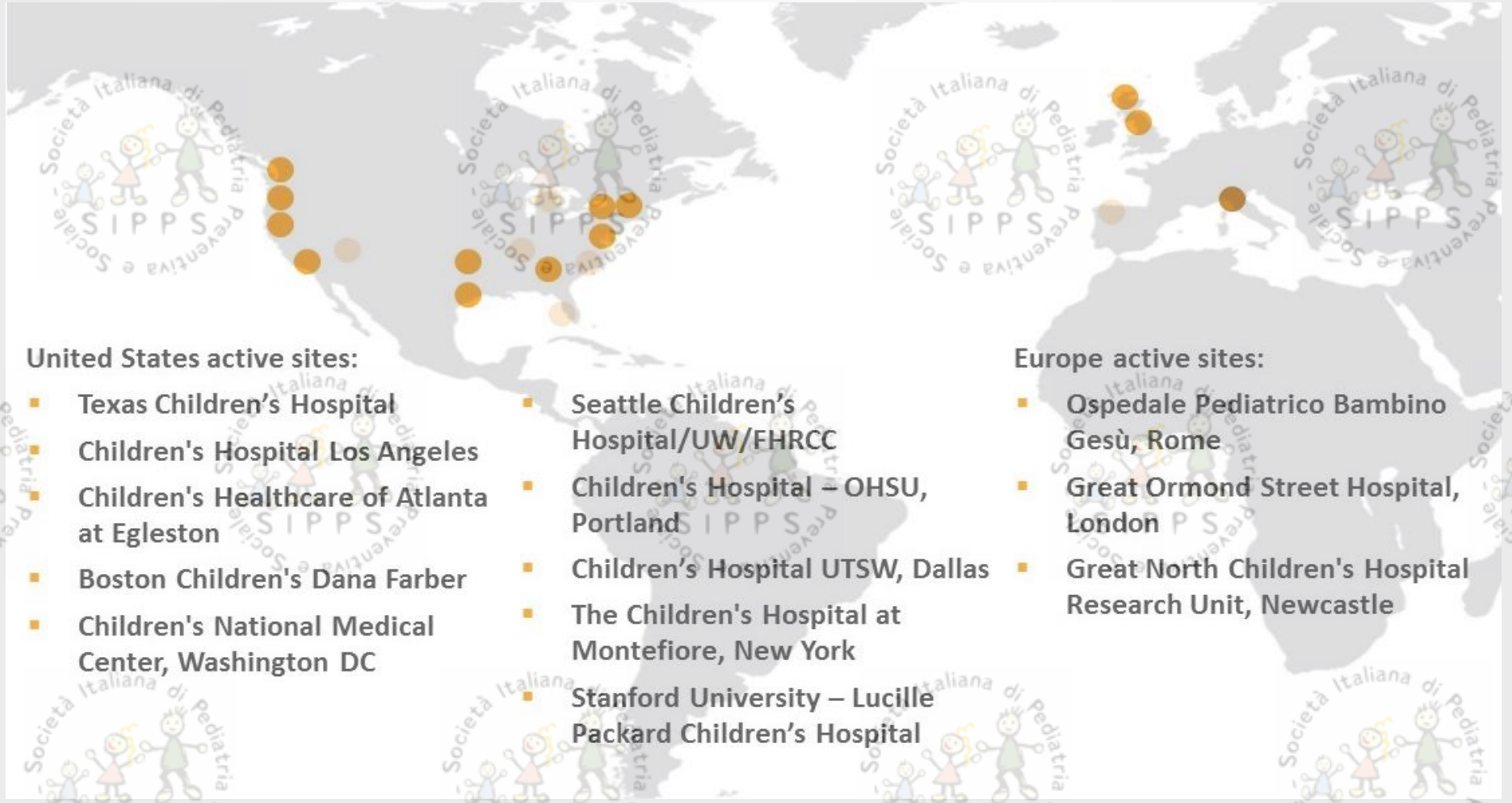
Phase II portion: **MTD/RD**

1 X 10^6 BPX-501 T Cells/kg

- Haploidentical donor (usually a parent)
- Non-mobilized apheresis for BPX-501 product
- TCRαβ/CD19-Depleted Allograft
- BPX-501 T cells Infused Day 14 ± 4 post Tx
- No Post-Transplant GVHD Prophylaxis
- Rimiducid (AP1903) Used for Uncontrollable GVHD

BP-004 Clinical Trial Sites

- OPBG Lead Clinical Site – 3 additional sites in EU
- Multiple sites in US



United States active sites:

- Texas Children's Hospital
- Children's Hospital Los Angeles
- Children's Healthcare of Atlanta at Egleston
- Boston Children's Dana Farber
- Children's National Medical Center, Washington DC
- Seattle Children's Hospital/UW/FHRCC
- Children's Hospital – OHSU, Portland
- Children's Hospital UTSW, Dallas
- The Children's Hospital at Montefiore, New York
- Stanford University – Lucille Packard Children's Hospital

Europe active sites:

- Ospedale Pediatrico Bambino Gesù, Rome
- Great Ormond Street Hospital, London
- Great North Children's Hospital Research Unit, Newcastle

BP-004 Outcomes

BP-004 Evaluation-Non-Malignant & Malignant (EU and US)

With ≥ 100 days F/U *(as of 1/20/17)* N=91

Selected Non-Malignant Subset evaluation (EU and US)

PID (≥ 100d F/U) *(as of 1/20/17)* N=25

Thalassemia $\beta_0\beta_0$ (≥ 100d F/U) *(as of 1/20/17)* N=9

Fanconi anemia (≥ 60d F/U) *(as of 3/20/17)* N=9

Selected Malignant Subset evaluation (EU-OPBG only)

Acute Leukemia (≥ 60d F/U) *(as of 3/20/17)* N=43

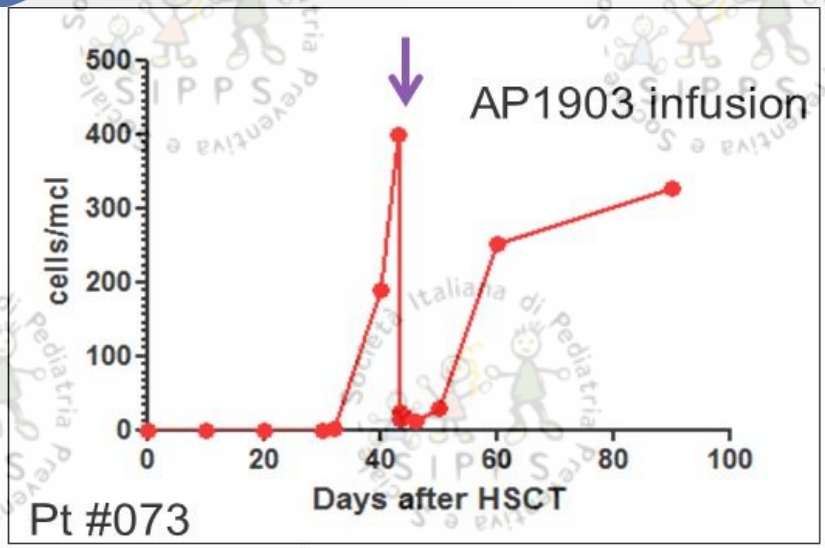
ALL & AML (CR1, CR2)

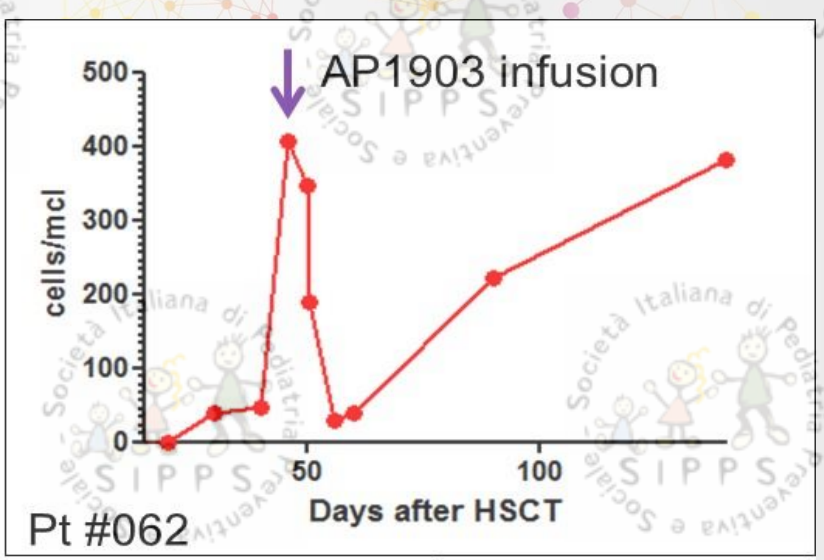
Uncontrolled aGvHD: Use of Rimiducid

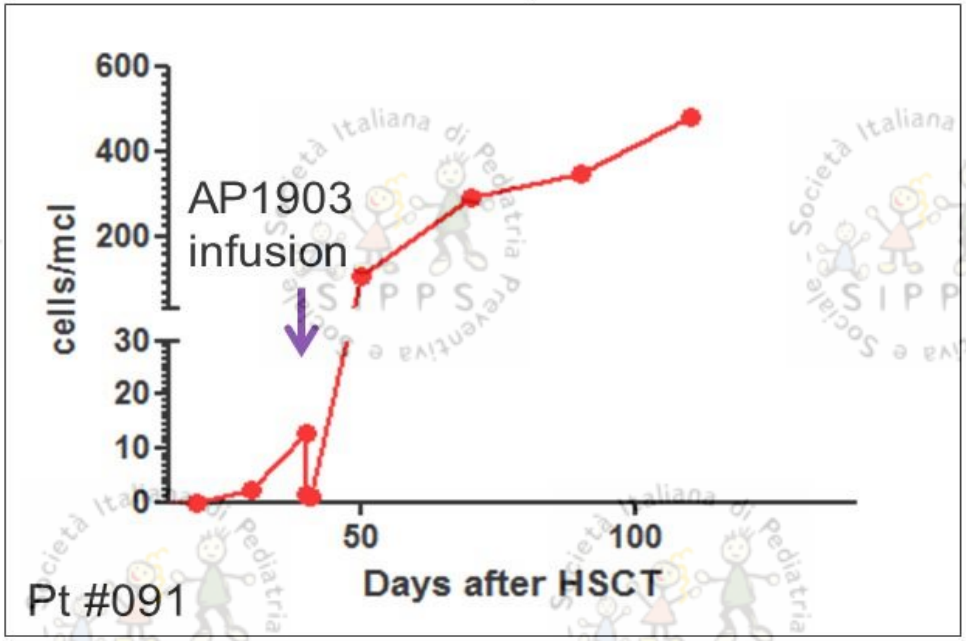
5 cases of uncontrolled Grade 1 or 2 aGvHD rapidly resolved with rimiducid

Underlying Disease	GvHD Diagnosis		Outcome	
IFN-γ deficiency	Skin Grade 1		Resolved	
HLH	Skin Grade 2		Resolved	
B-ALL	Skin Grade 2		Resolved	
HLH	Gut Grade 2		Resolved	
PID	Gut Grade 2		Resolved	

Recovery after rimiducid (AP1903) use



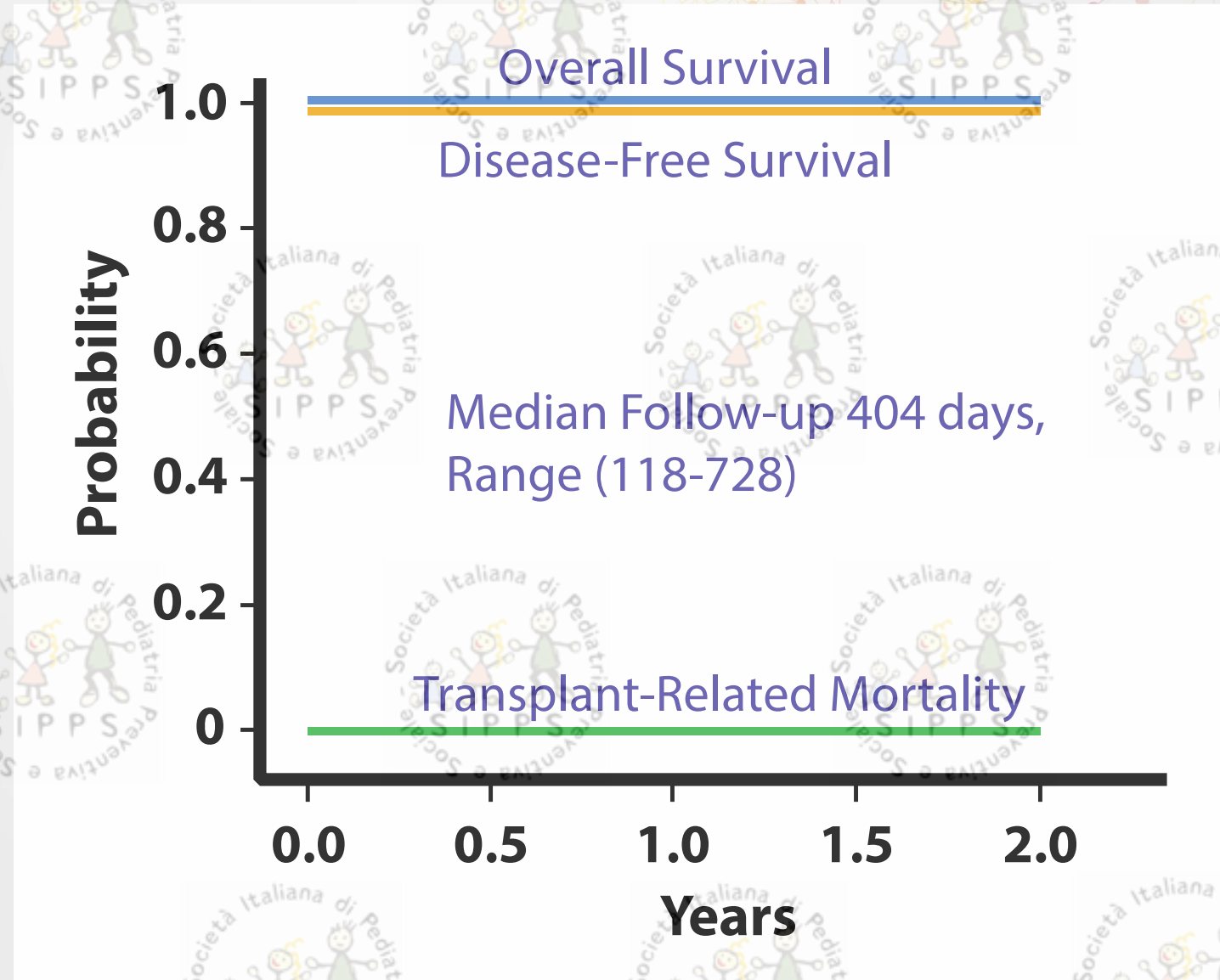




BP-004 PID Demographics: (N=25; ≥ 100d F/U; EU and US)

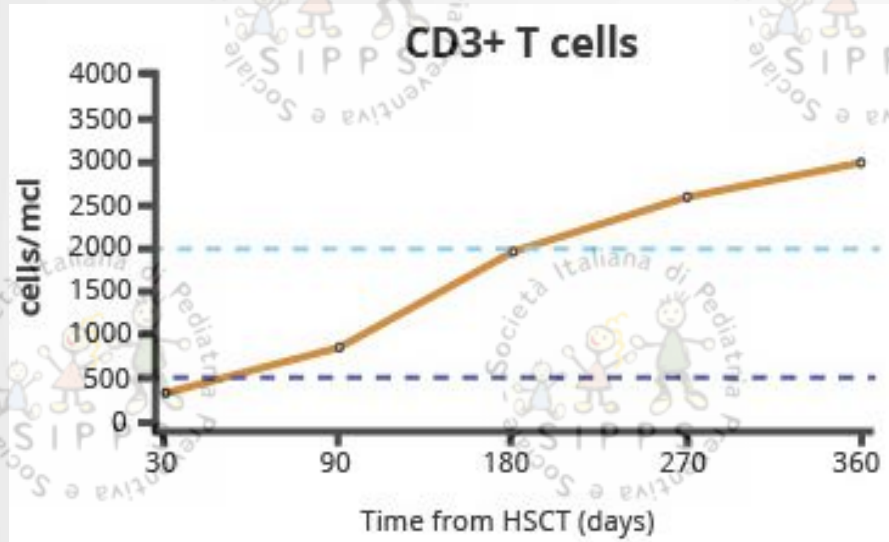
	TOTAL (N=25)
Gender	N
Male	17
Female	8
Median Age at HSCT (yrs)	1.09 (0.25 - 15.61)
Diagnosis	
SCID	11
RAG1	3
RAG2	1
JAK3	1
gamma-chain deficiency	2
ADA-deficiency	1
IL-2 receptor deficiency	1
unknown	2
WAS	6
Score 5	2/6
Score 4	2/6
Score 3	2/6
CGD	3
CID	1
XIAP-deficiency	1
IL-2 Receptor deficiency	1
IL-10 RB deficiency	1
IFN gamma-receptor 1 deficiency	1

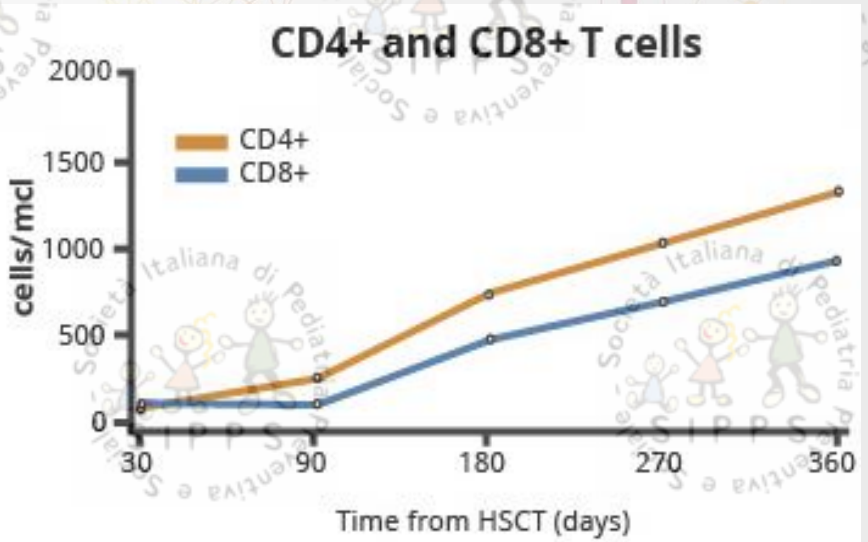
PID Outcomes: TRM (N=25: ≥ 100d; EU and US)

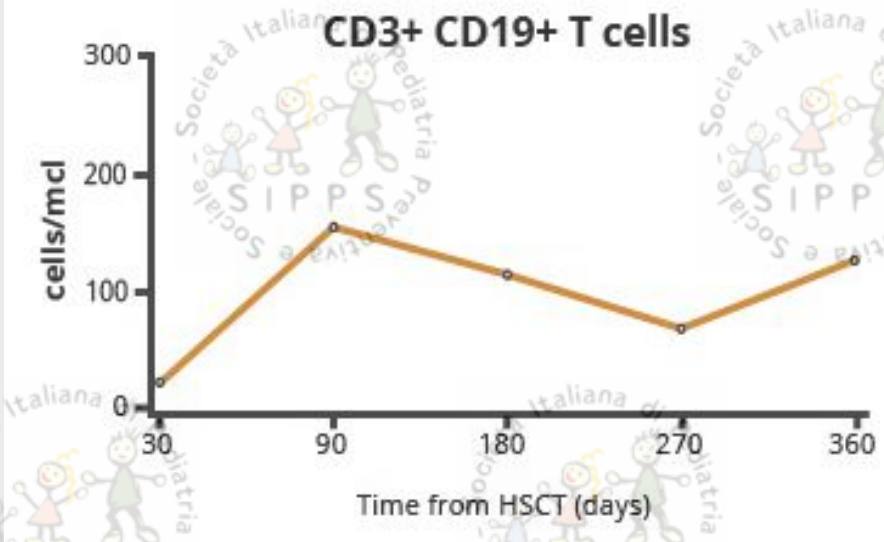


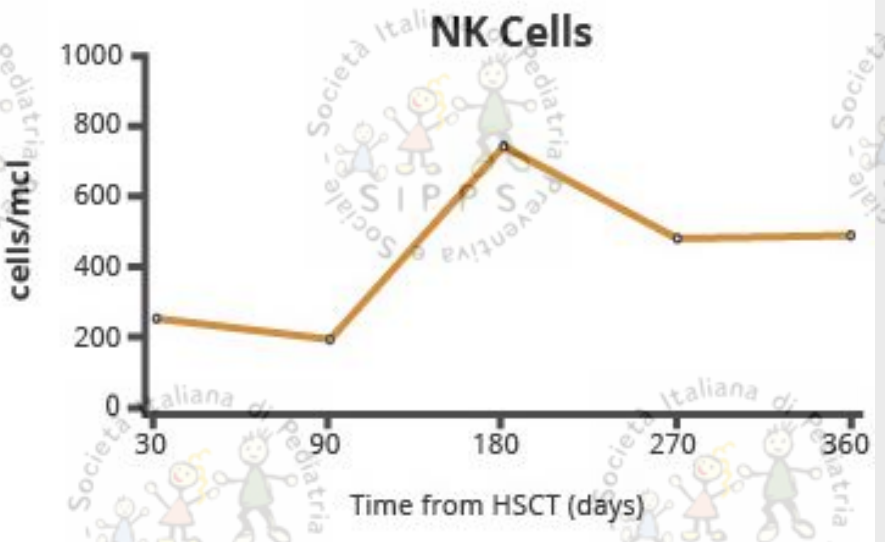
ASH, 2016

PID Outcomes: Cellular Immune Reconstitution (N=25; ≥ 100d F/U; EU and US)

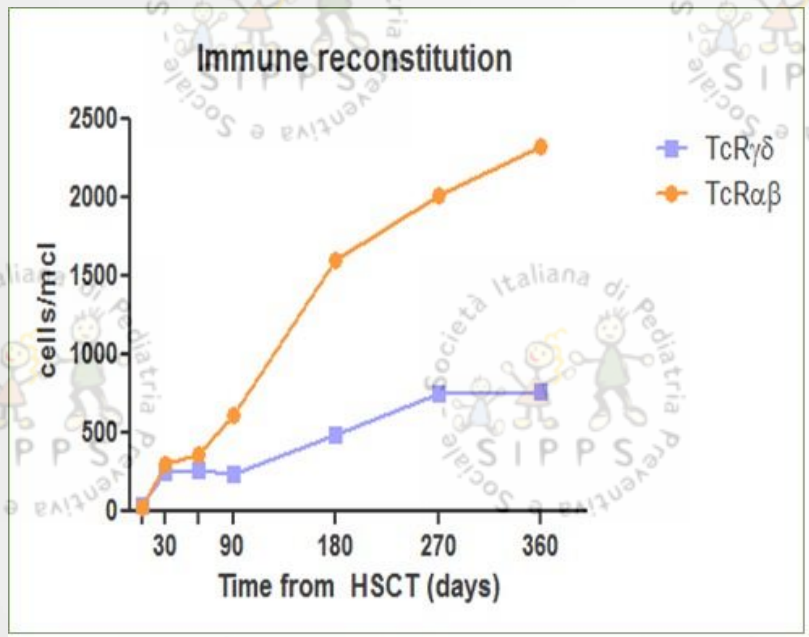


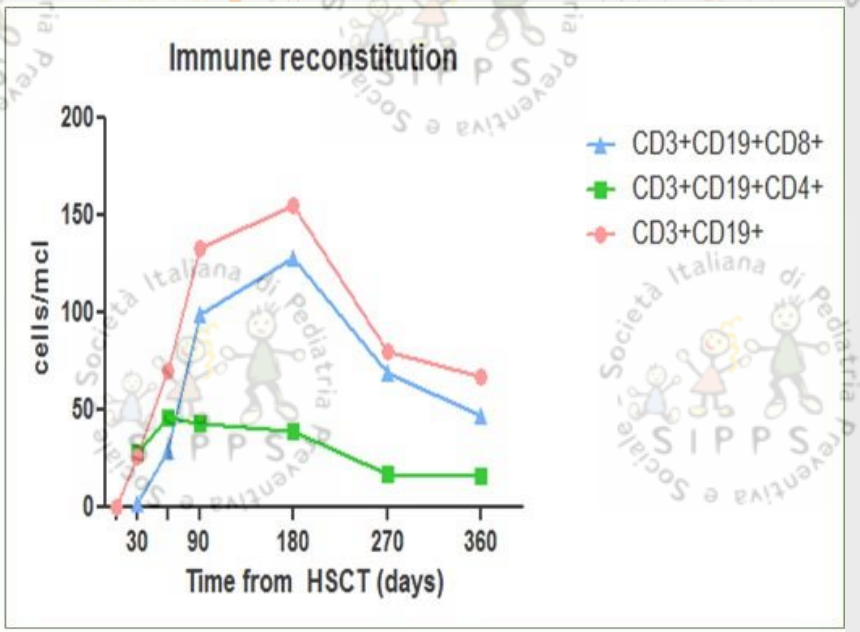


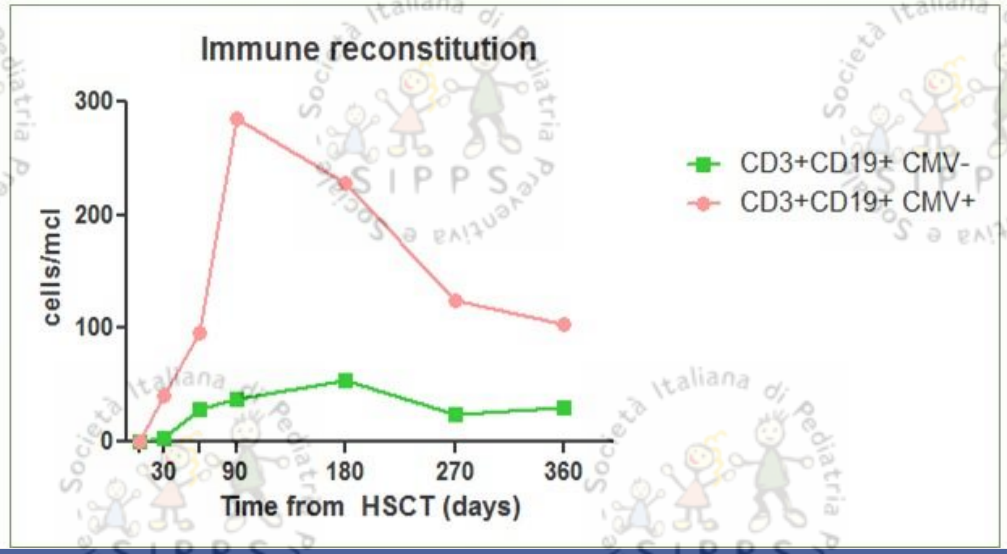




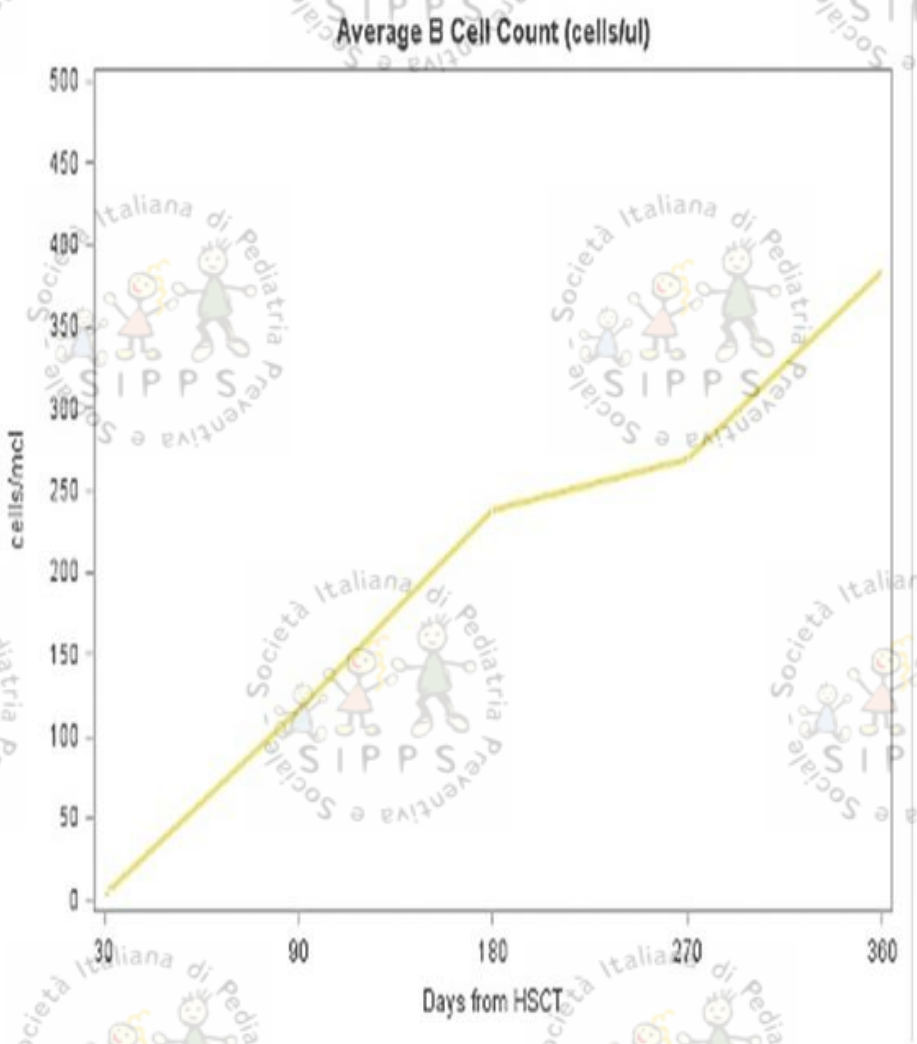
PID Outcomes: Viral-specific BPX-501 T cells

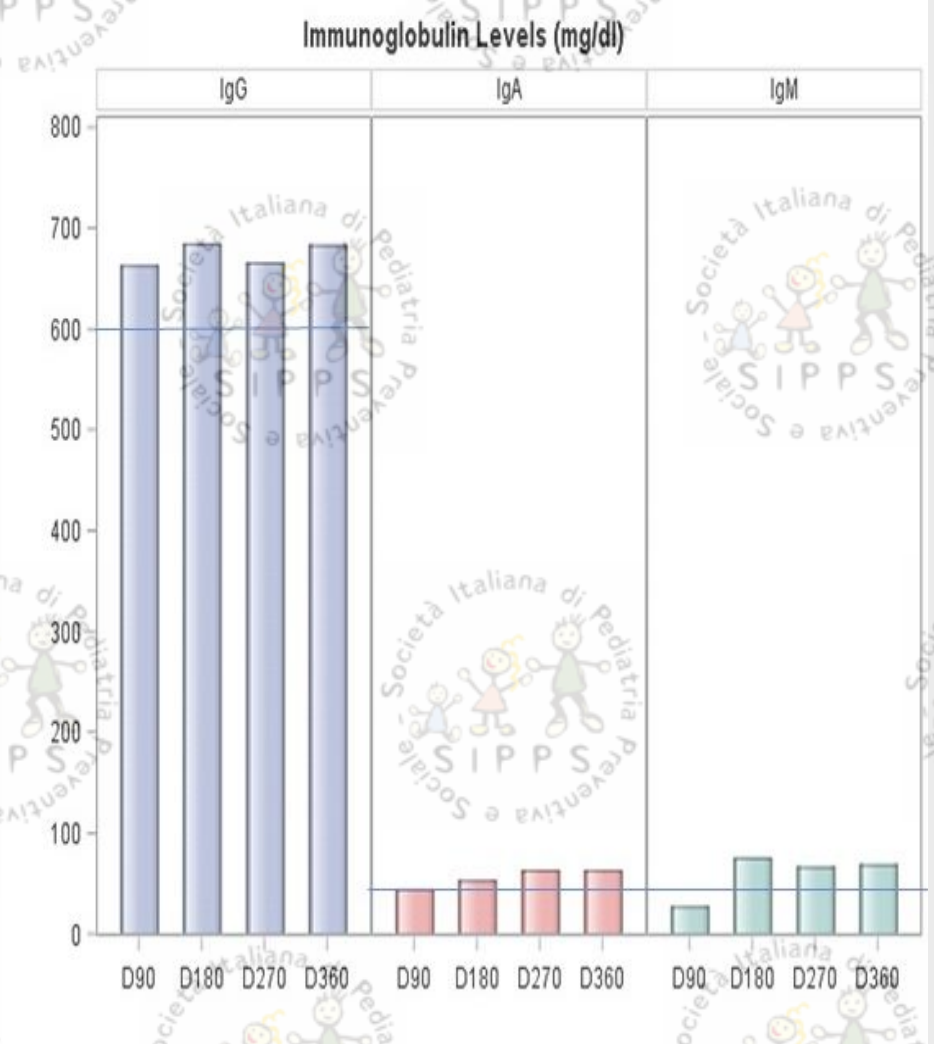






PID Outcomes: Humoral immunity (N=25; ≥ 100d F/U; EU and US)





Mean +/- SEM in children with WAS

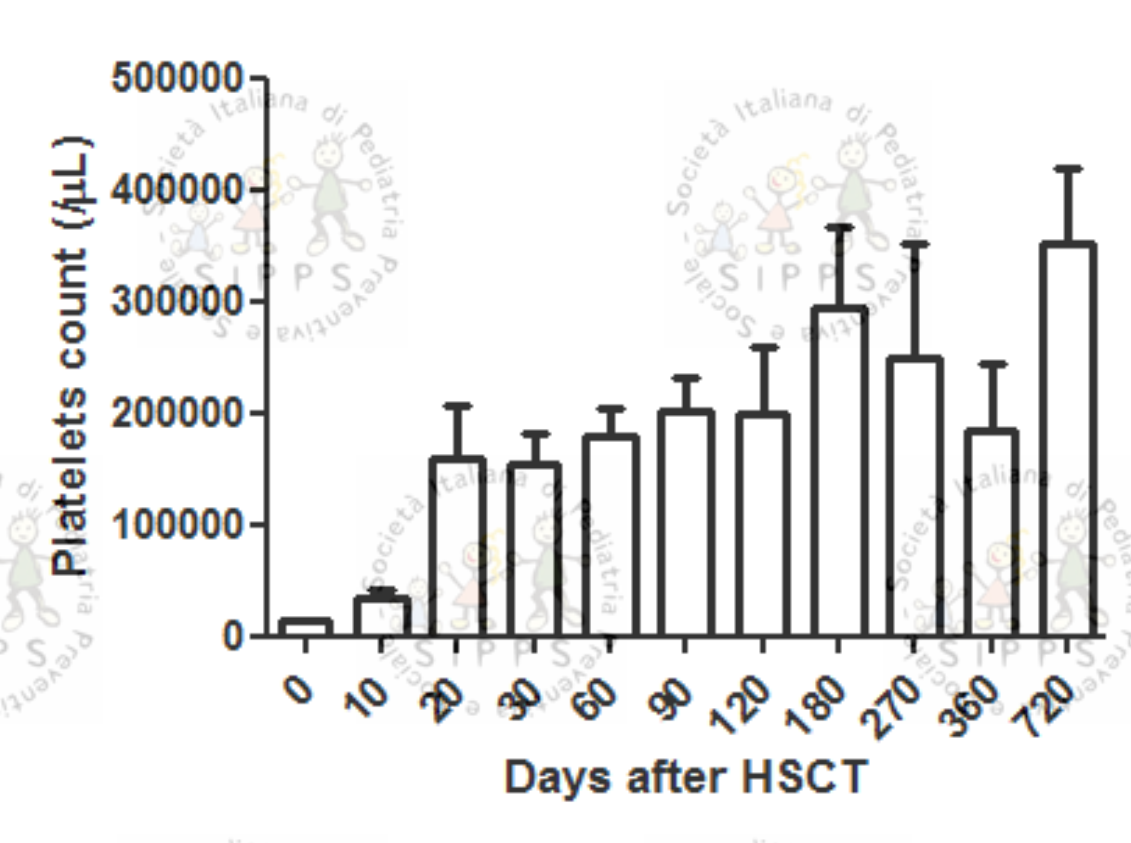
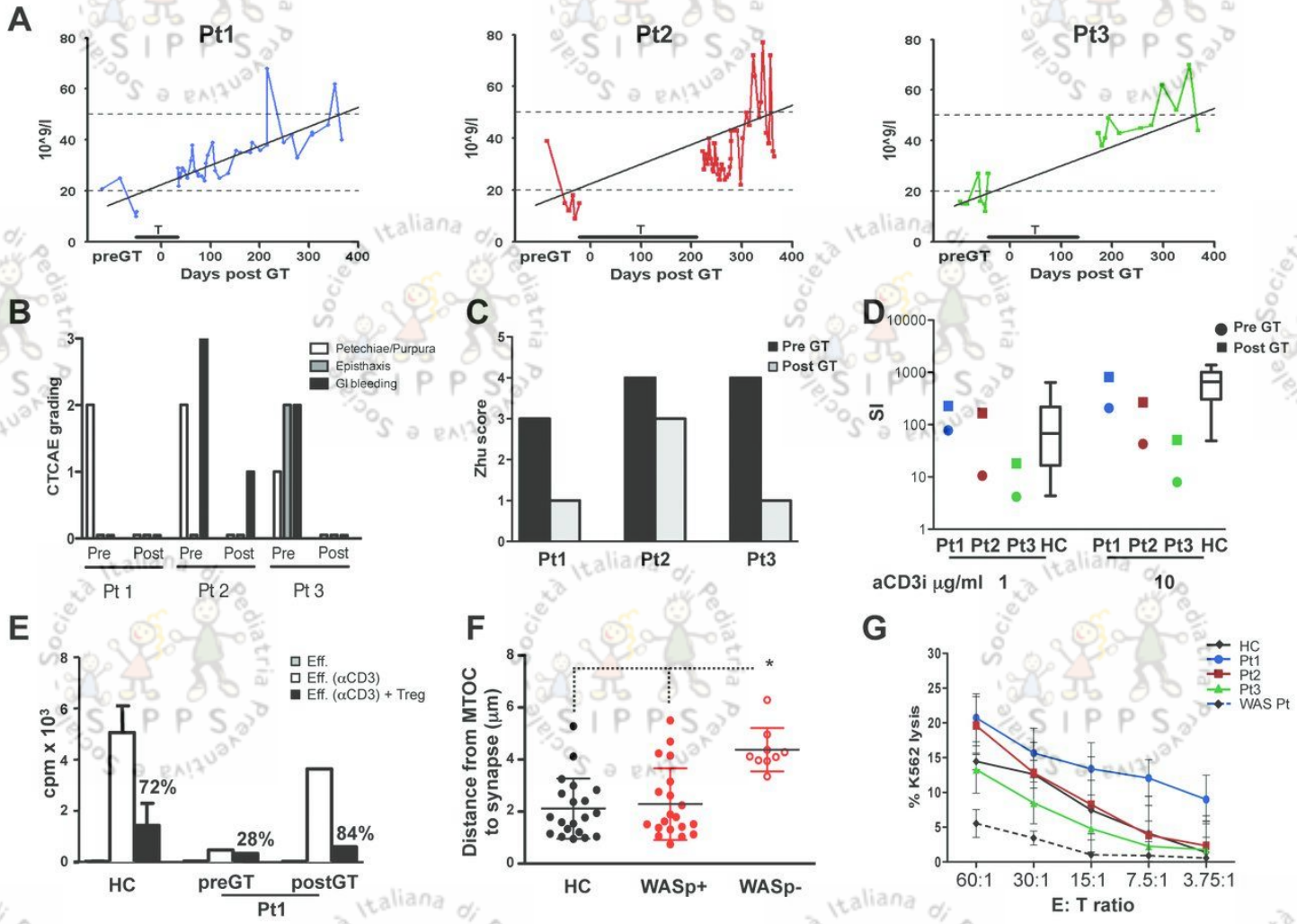
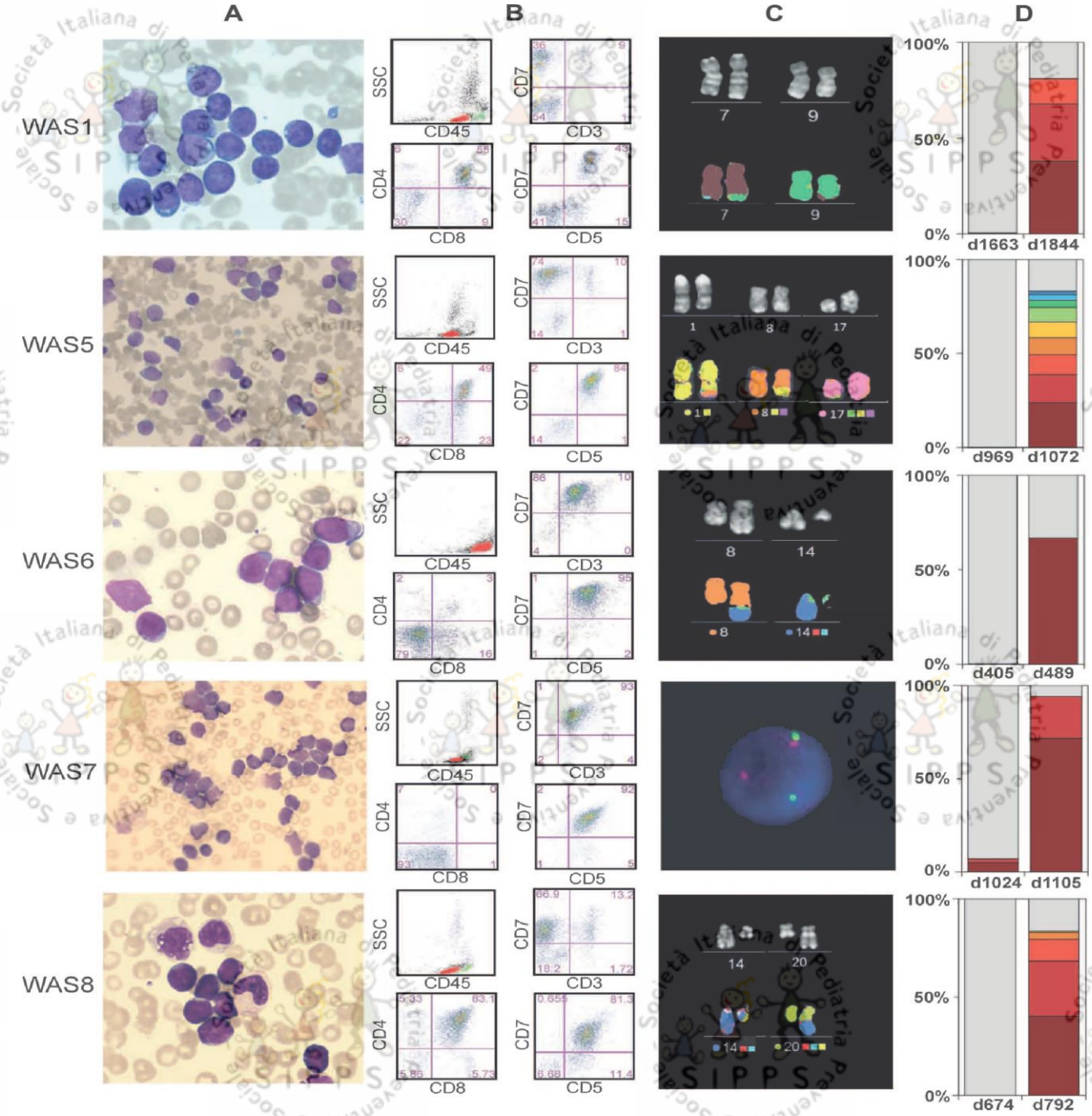


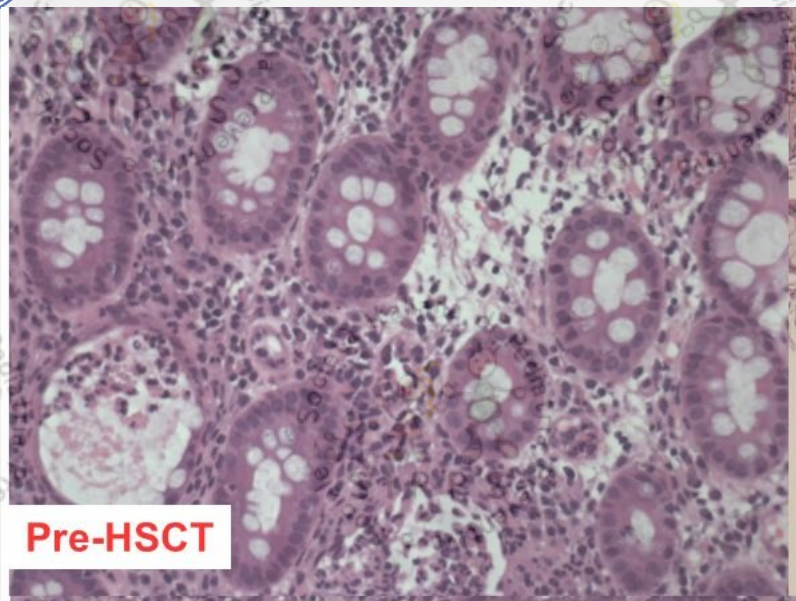
Fig. 2 Clinical features and immune function of WAS patients after gene therapy.(A) Platelet counts before and 1 year after gene therapy.

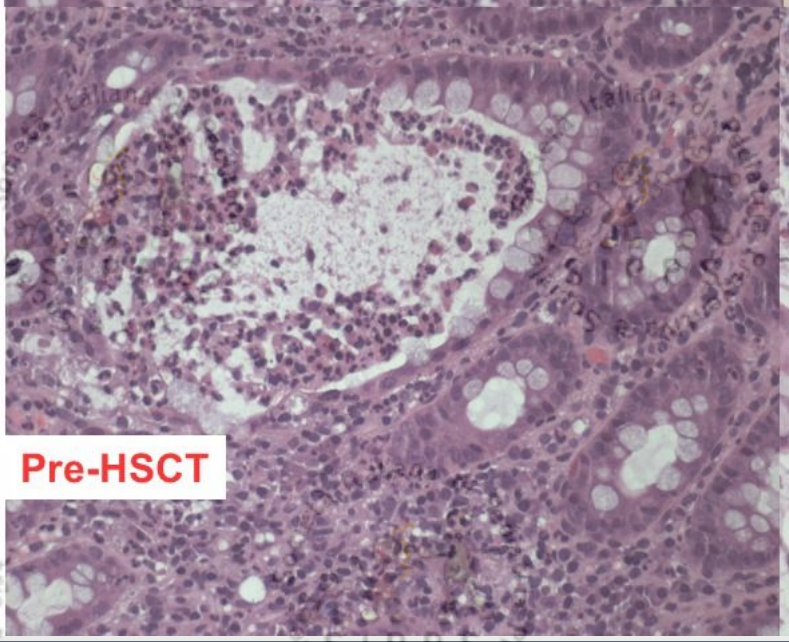


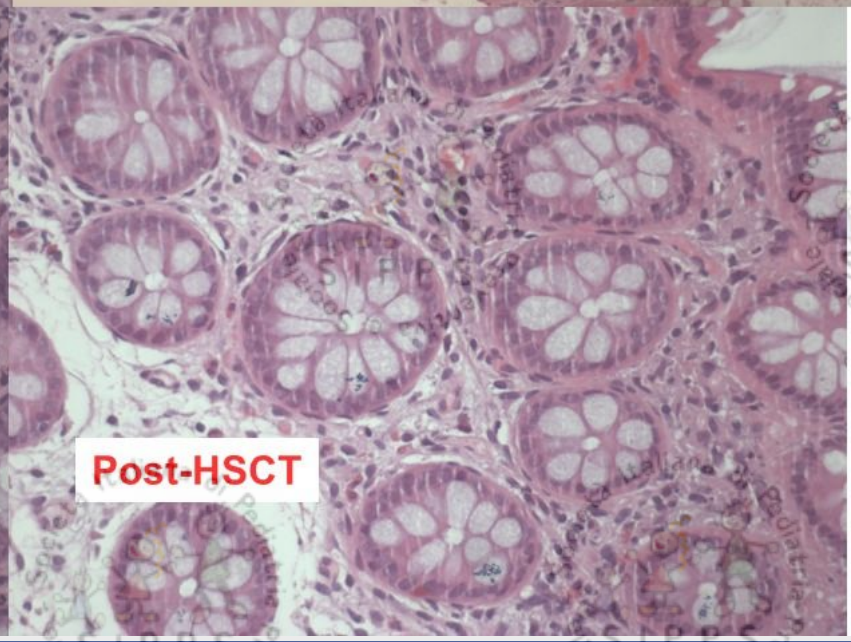
Aiuti A, et al. Science 2013;341:1233151


A
B
C
D
WAS1
WAS5
WAS6
WAS7
WAS8
SSC
CD45
CD4
CD8
CD7
CD3
CD5
100%
50%
0%
d1663
d1844
d969
d1072
d405
d489
d1024
d1105
d674
d792

PID Outcomes: Gut Histology XIAP-deficiency







Summary

Outcomes of patients who undergo haplo-transplantation with TCRαβ/CD19-depleted allograft followed by BPX-501 T cells (BP-004 trial) demonstrate:

- **High engraftment rate with fast ANC and PLT recovery**
- **Low GVHD incidence (primarily involving the skin)**
- **Enhanced cellular and humoral immunity with viral-specific activity**
- **Impressively high cure rate in many different PIDs**

Thus, haplo-transplantation with TCRαβ/CD19-depleted allograft followed by BPX-501 T cells is now a suitable option, for this rare and fragile patients

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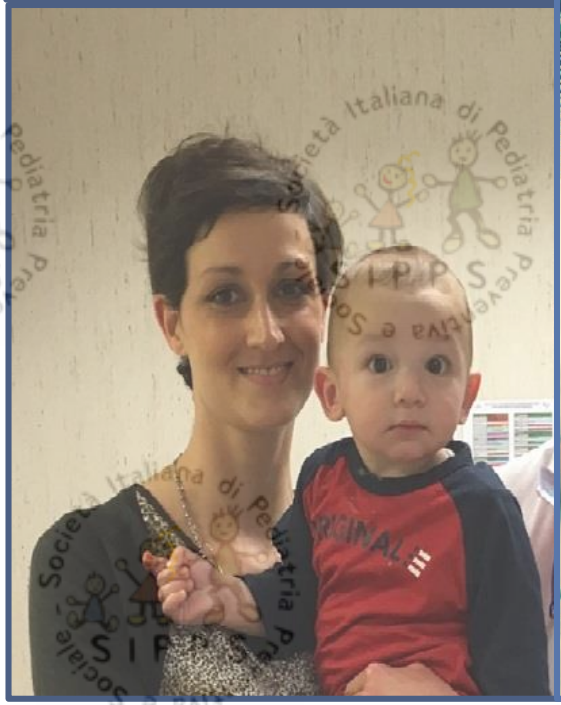
AIRC




Allianz
NOVEMBRE