Immune lessons from allo-HSCT:

MESENCHYMAL STROMAL CELLS

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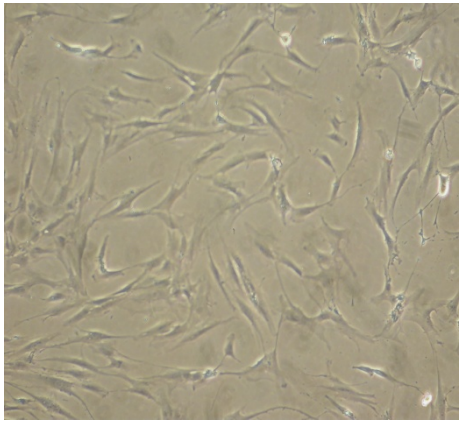
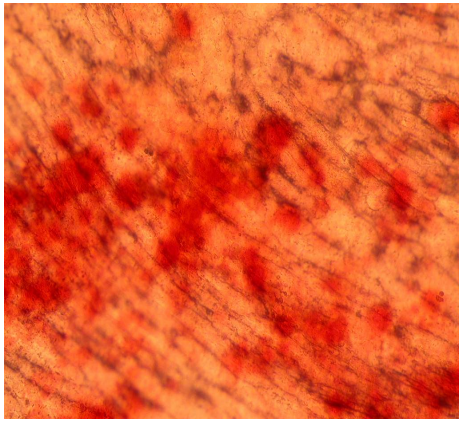
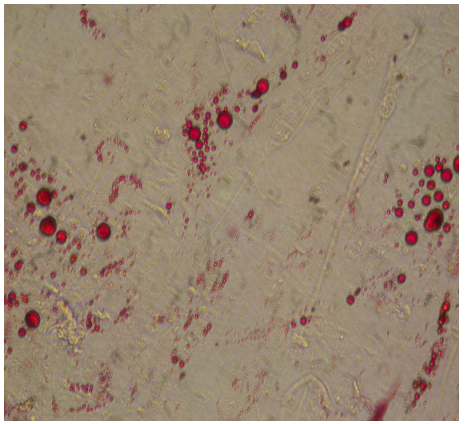
PROPERTIES of MESENCHYMAL STROMAL CELLS

- **Multipotent cells**
  capable of differentiation into several mesenchymal lineages
- **Remarkable expansion after *ex vivo* culture**
- **Enhancement of hematopoietic stem cell engraftment**
- **Immunosuppressive properties**
- **Tissue repair properties**

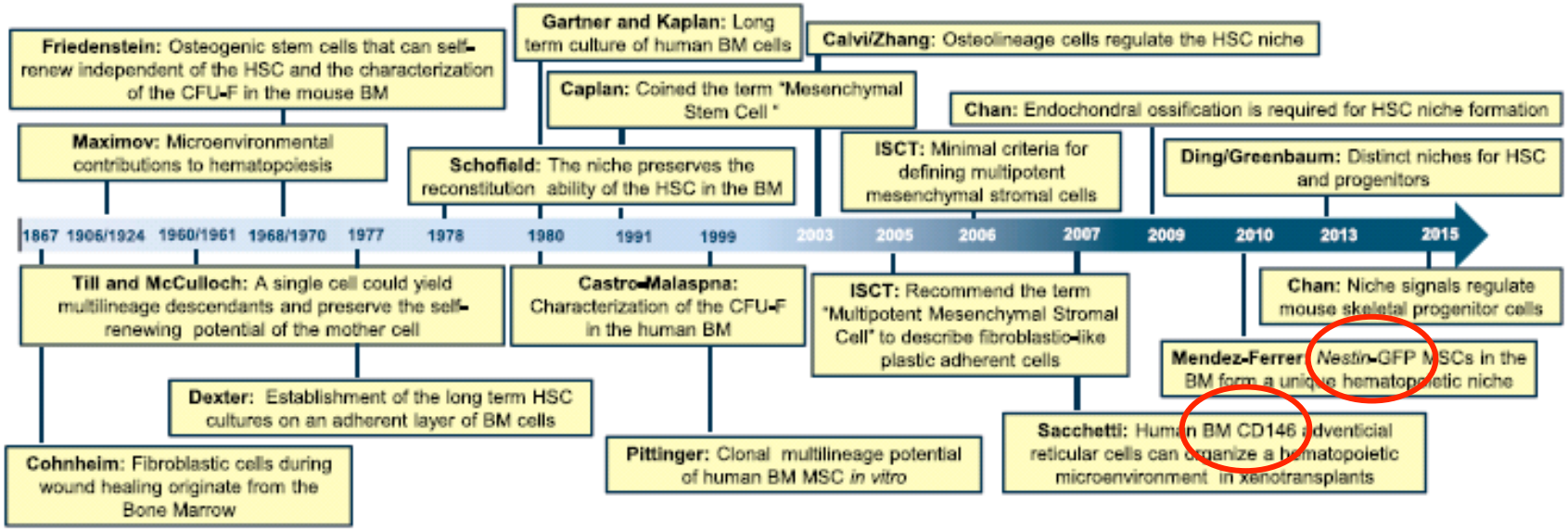






What happended since Friedenstein (1968)?

TIMELINE REPRESENTATION OF MAJOR DISCOVERIES THAT SHAPED THE UNDERSTANDING OF MSCs



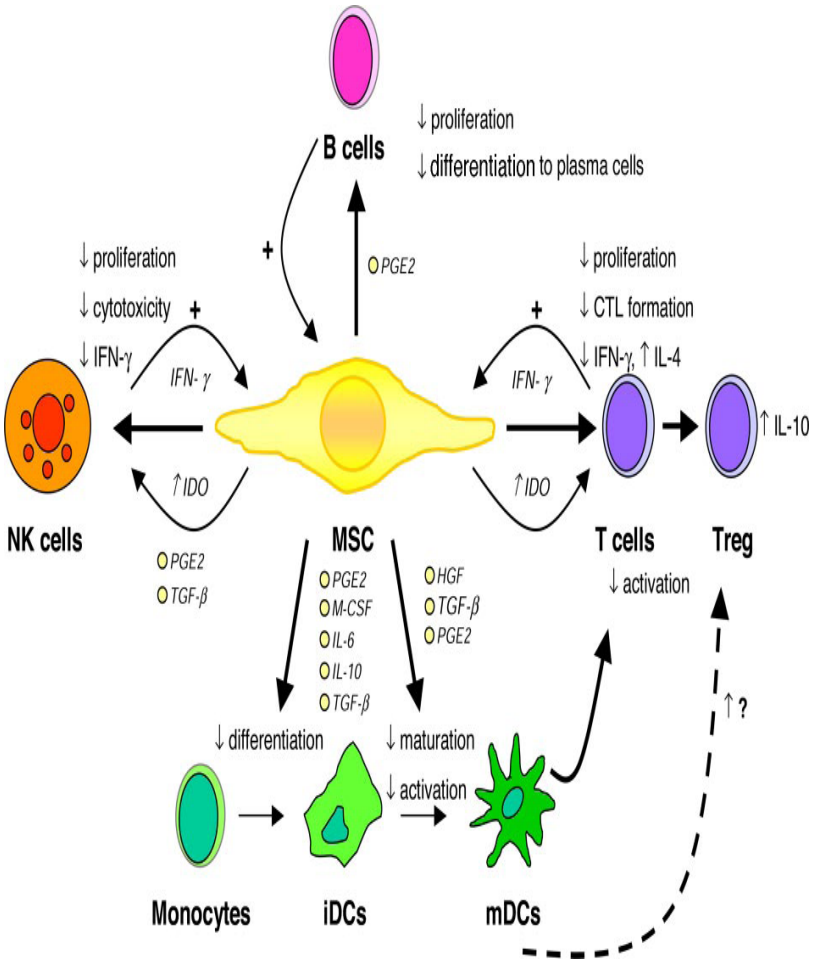
IDENTIFICATION OF MARKERS FOR THE PROSPECTIVE ISOLATION of MSCs from BM:

- **CD146, CD271: human *(Sacchetti et al.; Tormin et al.)***
- **Nestin: murine *(Mendez-Ferrer et al.)***

Kfoury Y and Scadden D. Cell Stem Cell 2015

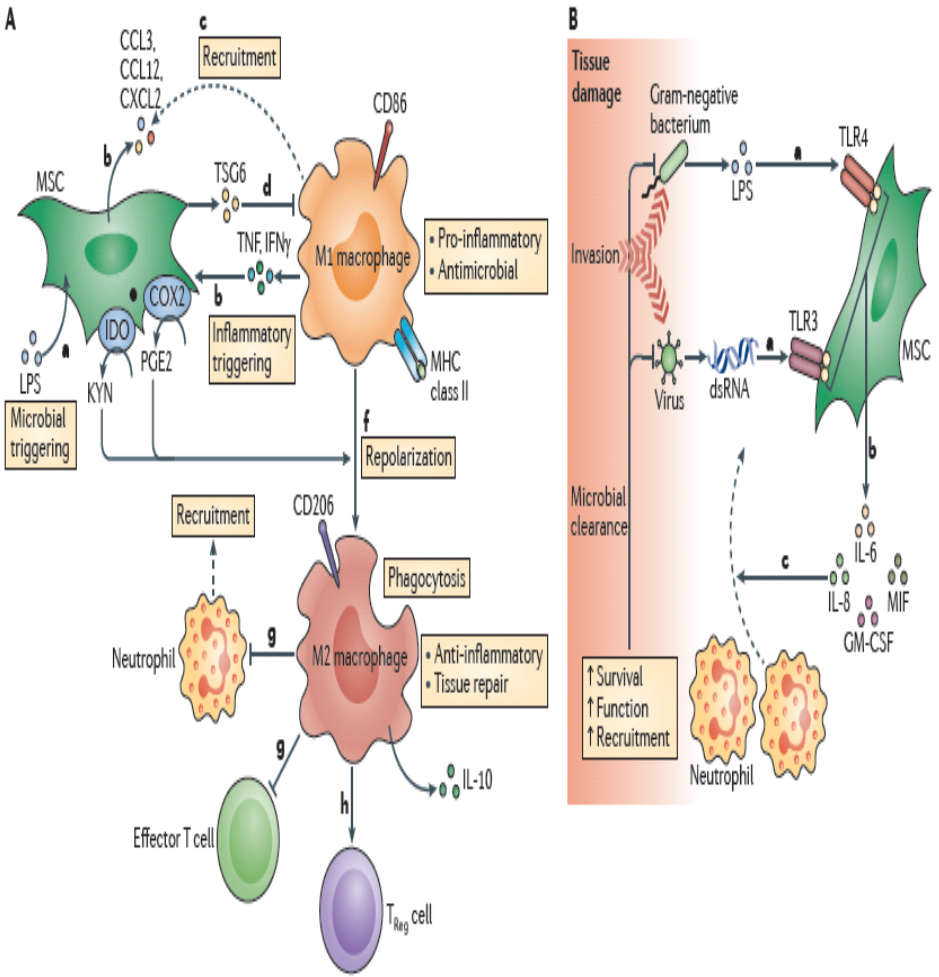
THE MSCs' PARADIGM SHIFT

THE OLD PARADIGM



Nauta & Fibbe. Blood 2008

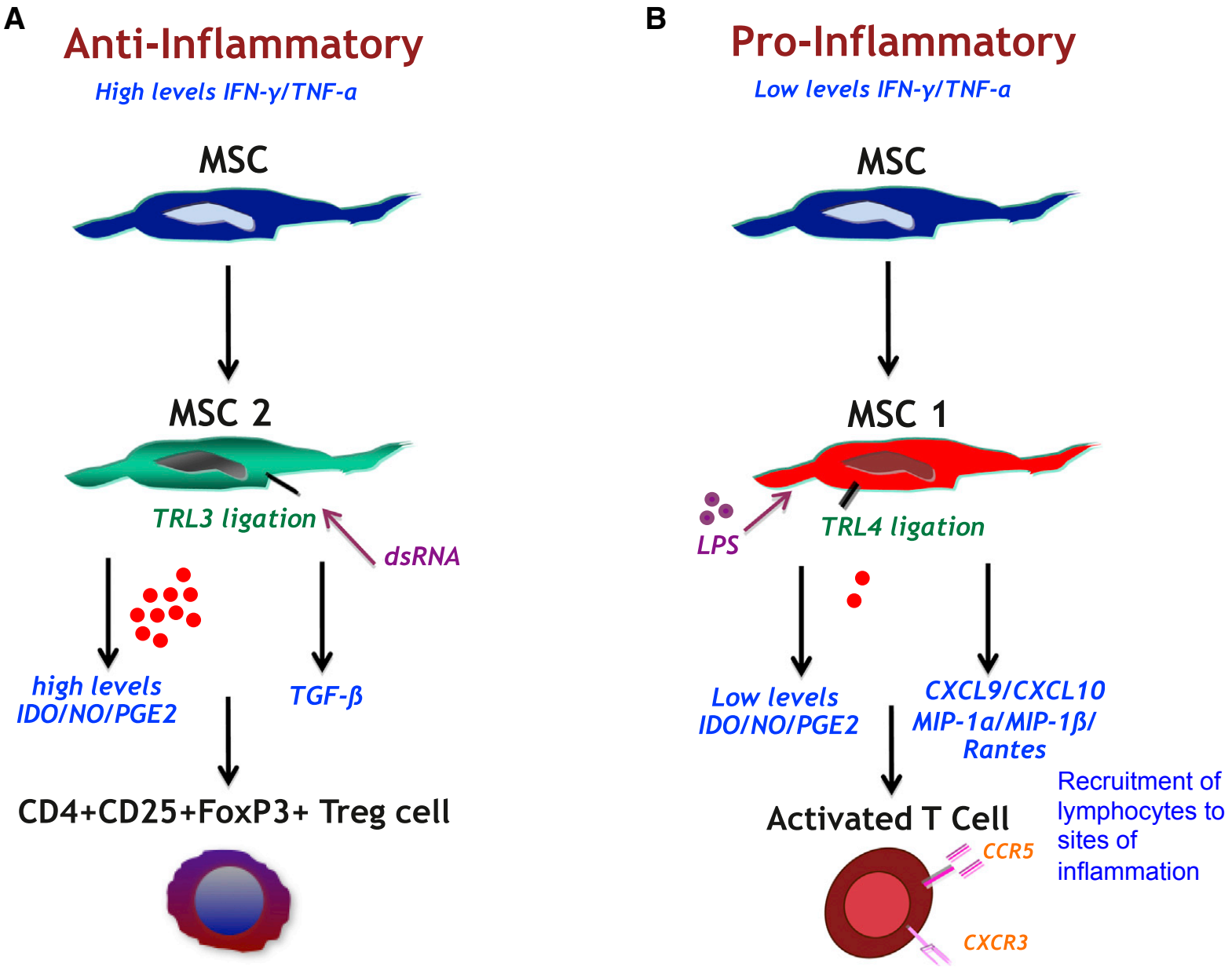
THE NEW PARADIGM



Mougiakakos and Le Blanc, Nat Rev Immunol 2012

MSCs from IMMUNOREGULATORY to ANTI-INFLAMMATORY CELLs

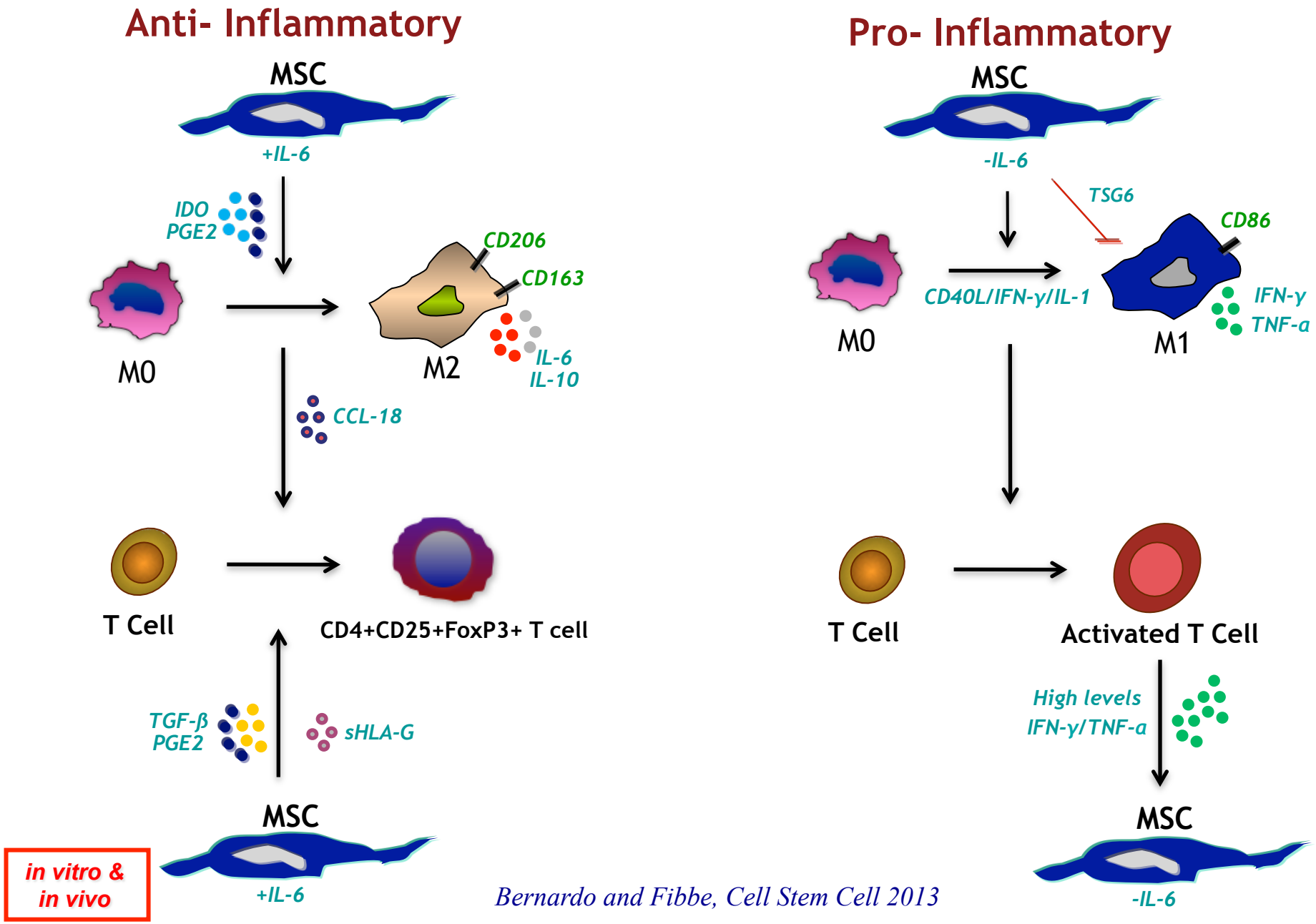
MSCs: SENSORS and SWITCHERS of INFLAMMATION



in vitro & in vivo

Bernardo and Fibbe, Cell Stem Cell 2013

MSCs POLARIZE MONOCYTES M0 INTO M1 & M2



Bernardo and Fibbe, Cell Stem Cell 2013

CLINICAL APPLICATIONS of MSCs IN HSCT (& BEYOND)

I. **Co-infusion of MSCs and HSCs to enhance hematopoietic engraftment** after allo-HSCT in HAPLO- and CB-HSCT

II. **Treatment of steroid-resistant acute GvHD**

III. **Ex-vivo expansion of CD34+ cells on MSCs for improved engraftment**

IV. **Treatment of acute tissue damage after allo-HSCT**

(case reports in hemorragic cystitis, pneumothorax and pneumomediastinum, peritonitis)

& BEYOND…**REGENERATIVE MEDICINE**

repair of bone and cartilage degenerative disorders, Crohn's disease, kidney and liver repair

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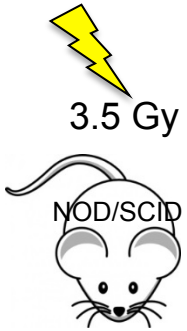
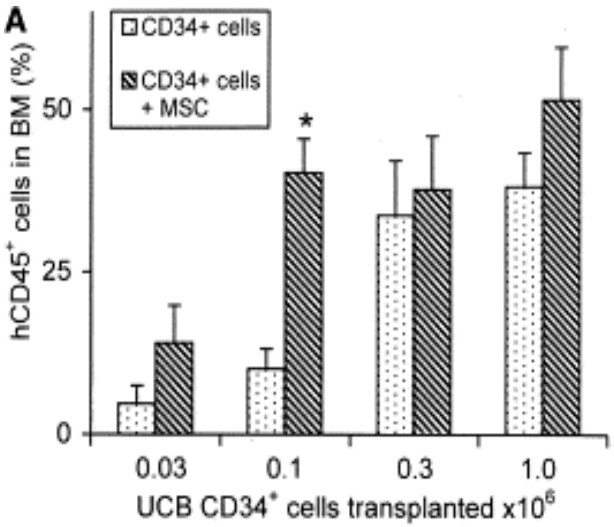
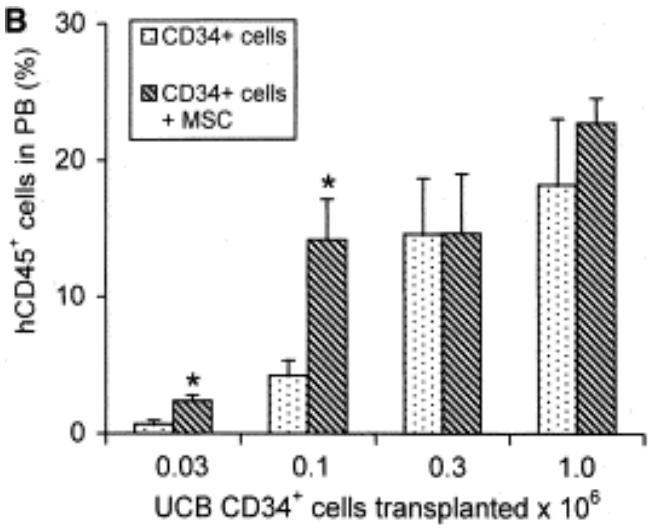
MSCs and ENGRAFTMENT in MICE

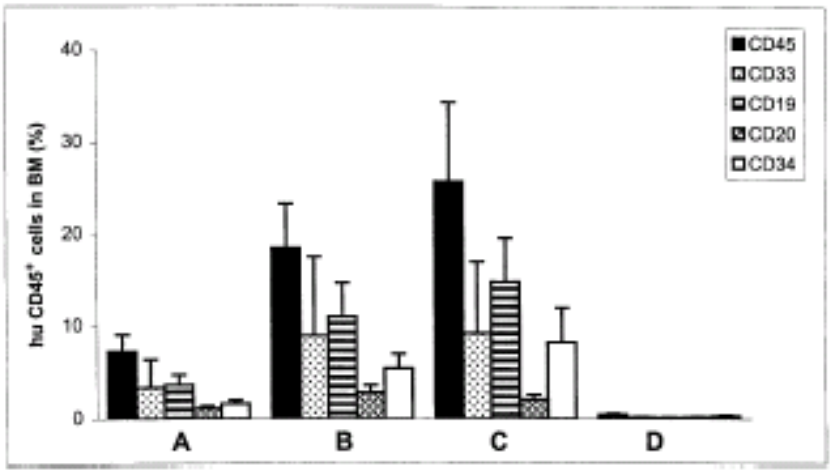
Co-Tx of human fetal lung- and BM-derived MSCs enhances engraftment of human UCB CD34+ cells in NOD/SCID mice







Co-Tx:
UCB CD34+ (0.1 x 10e6)
+
MSC (1 x 10e6)
non expanded or ex-vivo expanded



Noort W. ...and Fibbe W.E. Exp. Hematology 2002 and 2003

Phase I/II trial of Co-infusion of Haploidentical HSCs and MSCs in pediatric patients

	Patients (n = 20)	Controls (n = 52)
Transplant years (range)	Dec. 2004 – July 2007	March. 1998- Nov. 2004
Mean age (range) years	8 (1-16)	8 (1-17)
Patient gender		
Male	14 (70%)	31 (60%)
Female	6 (30%)	21 (40%)
Original diseases		
Haematological malignancies	16 (80%)	40 (77%)
AML	7 (35%)	12 (30%)
MDS	2 (10%)	5 (12.5%)
ALL	7 (35%)	23 (34.5%)
Immune deficiencies	2 (10%)	2 (4%)
Other non-malignant disorders	2 (10%)	10 (19%)
Conditioning regimen		
TBI-based vs. Chemotherapy-based	12:8 (60 vs. 40%)	30:22 (58 vs. 42%)
Donor gender		
Male : Female	10 : 10	29 ; 23

Ball L, Bernardo ME,...Locatelli, et al. Blood 2007

MSC Co-transplantation in Haploidentical SCT

	Patients (n = 20)		Controls (n = 52)
Transplant years (range)	Dec. 2004 – July 2007		March. 1998- Nov. 2004
Graft characteristics			
Number of CD34+ cells infused x 10^6/kg (median, range)	21.3 (11.2 – 38.6)		23.0 (12.1 – 47.5)
Number of CD3+ cells infused x 10^5/kg	0.3 (0.3)		0.5 (0.7)
Number of MSC x 10^6/kg (median, range)	1.6 (1-3.3)		0
Haematopoietic recovery			
Days to Leukocyte count> 1,000/mL	11.5 (9-16)	p=0.01	16.5 (14.1-17.9)
Days to PMN recovery	12 (10-17)		14 (9-28)
Days to PLT recovery	11 (9-24)		13 (9-100)
Days to reticulocyte recovery	12 (10-31)		23 (9-41)
Post-HSCT complications			
Graft failure	0 (0%)	p=0.03	11 (20%)
Primary			7
Secondary			4
Acute GvHD			
Grade I-II	2 (10%)		12 (23%)
Grade III-IV	0 (0%)		2 (3%)
Chronic GvHD	1 (5%)		6 (12%)

Ball L, Bernardo ME et al. Blood 2007

Phase I/II study of Co-Tx of UMBILICAL CORD BLOOD-derived HSCs and MSCs

Patient characteristics

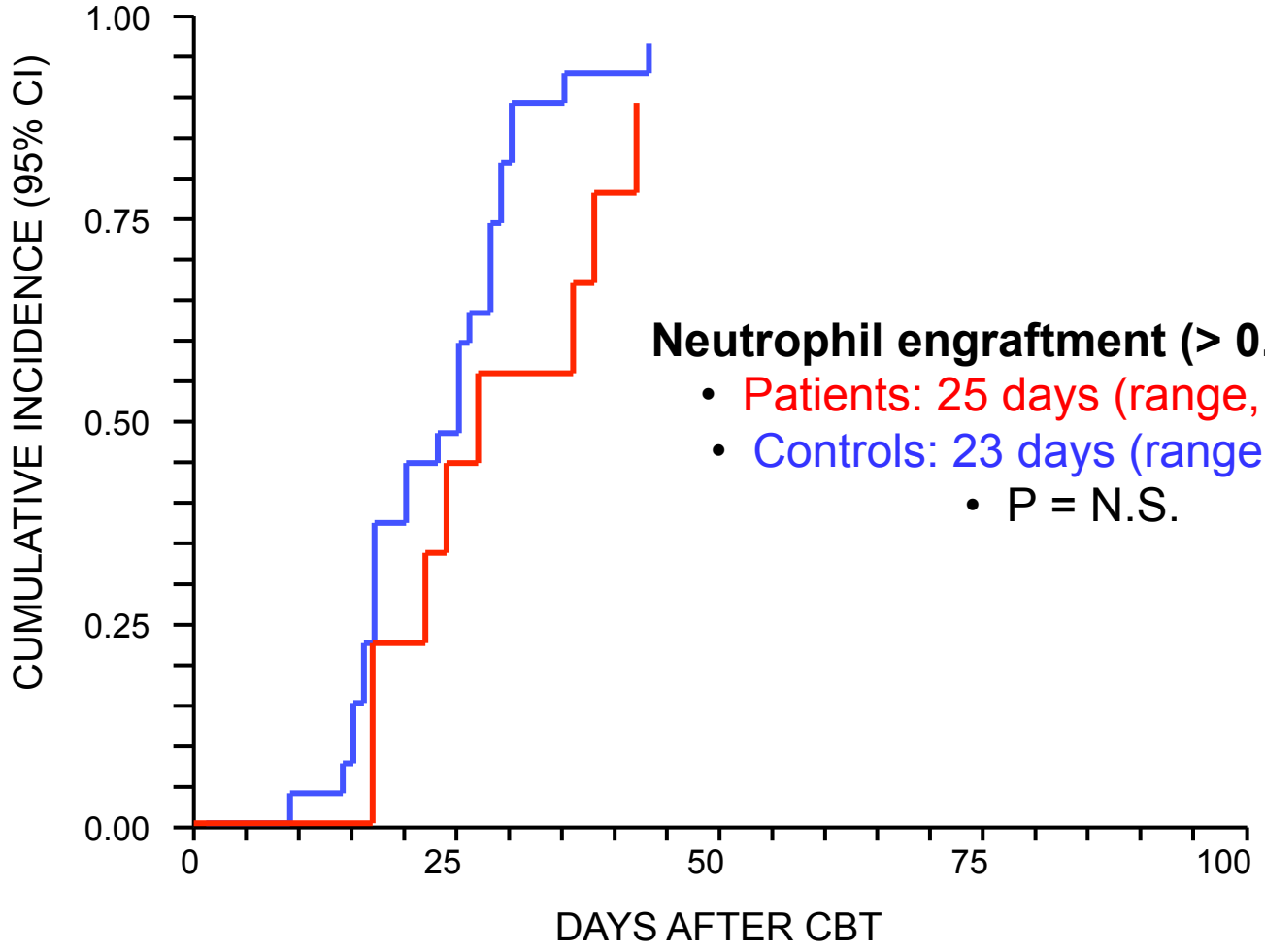
	Patients	Controls	Total
Number of patients	9	27	36
Gender: M / F	6 / 3	12 / 15	18 / 18*
Median age (years, and range)	4 (0.8 – 14)	4 (0.3 – 10)	4 (0.3 – 14)
Diagnosis:			
ALL	5 (56%)	15 (56%)	20 (56%)*
Hemoglobinopathies	2 (22%)	6 (22%)	8 (22%)
Other inborn errors	2 (22%)	6 (22%)	8 (22%)
Disease status at HSCT:			
1st CR	3 (33%)	3 (12%)	6 (17%)*
2nd or 3rd CR	2 (22%)	12 (44%)	14 (39%)
Disease present	4 (45%)	12 (44%)	16 (44%)
Nucleated cells (x 10^7/Kg):	4.4 (1.4 – 13)	3.9 (2 – 18)	4 (1.4 – 18)
CD34+ cell (x 10^5/Kg):	2.4 (0.6 - 6.6)	2 (0.6 – 6)	2.2 (0.6 –6.6)

MSC (x 10^6/Kg): 1.9 (1 – 3.3)

* Chi-square P = N.S.

Bernardo ME et al. Bone Marrow Transpl. 2010

Neutrophil engraftment (> 0.5 x 10^9/L)



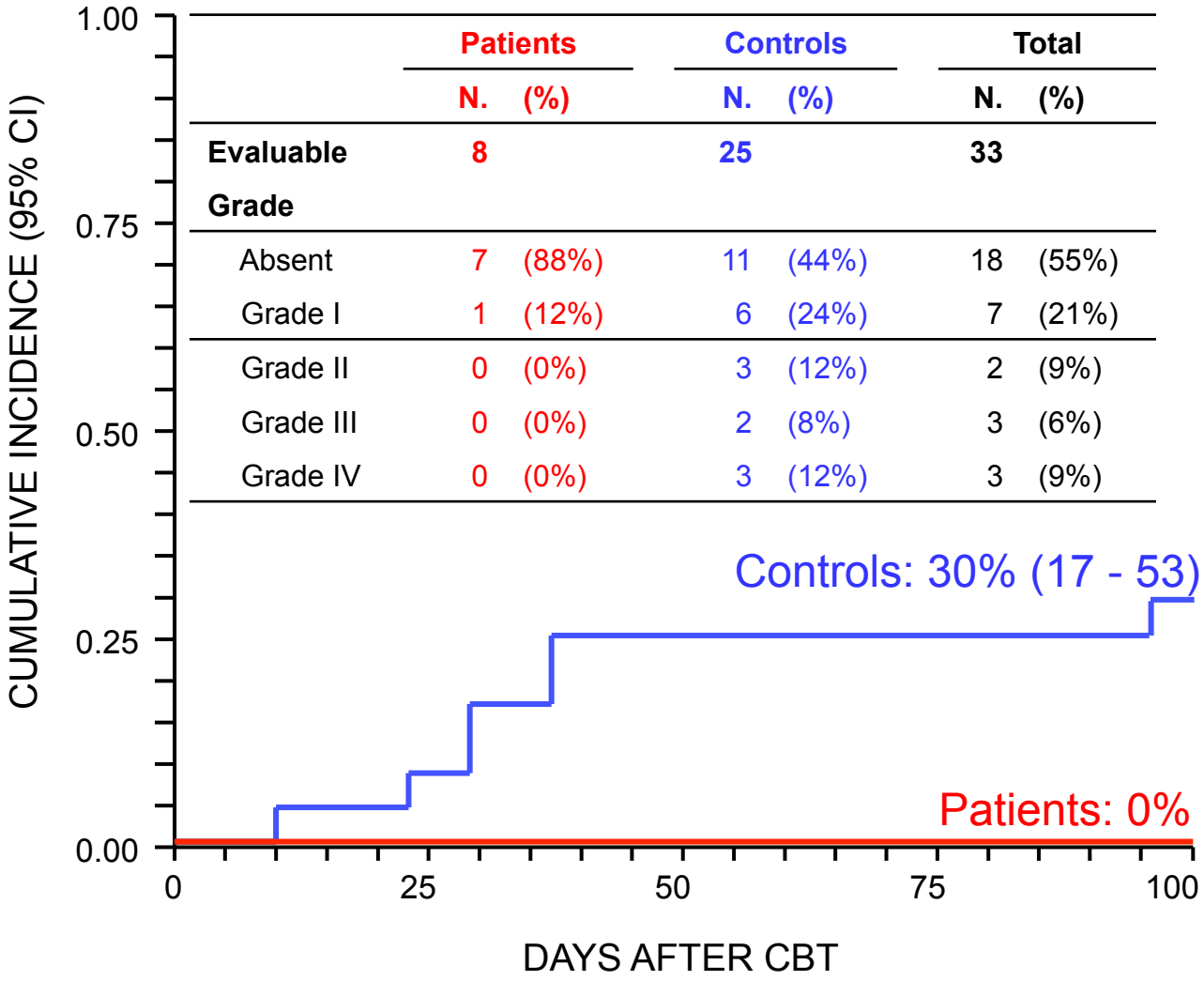
Neutrophil engraftment (> 0.5 x 10^9/L):

- Patients: 25 days (range, 17 – 42)
- Controls: 23 days (range, 8 – 42)
- P = N.S.

Bernardo ME et al. Bone Marrow Transpl. 2010

Grade II-IV acute graft-versus-host disease

	Patients		Controls		Total	
	N.	(%)	N.	(%)	N.	(%)
Evaluable	**8**		**25**		**33**	
Grade						
Absent	7	(88%)	11	(44%)	18	(55%)
Grade I	1	(12%)	6	(24%)	7	(21%)
Grade II	0	(0%)	3	(12%)	2	(9%)
Grade III	0	(0%)	2	(8%)	3	(6%)
Grade IV	0	(0%)	3	(12%)	3	(9%)



Bernardo ME et al. Bone Marrow Transpl. 2010

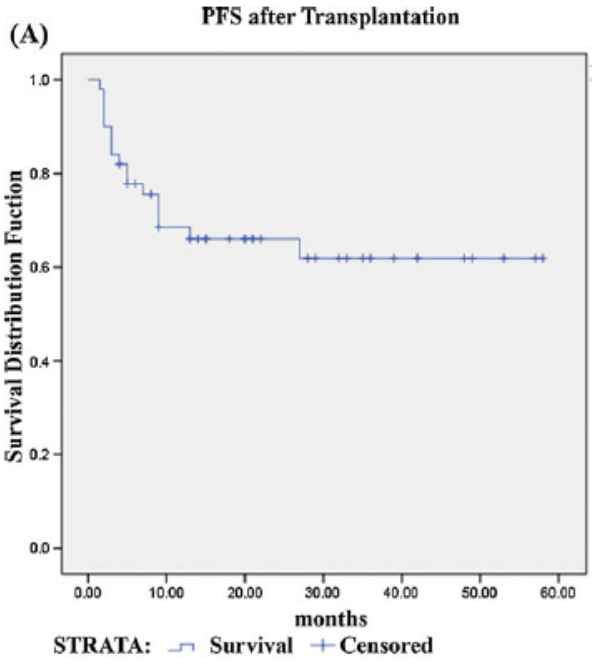
I. MSCs TO PROMOTE ENGRAFTMENT:
summary of PHASE I-II TRIALS

Table 1
Clinical applications of MSCs to facilitate HSC engraftment in phase I/II clinical trials.

Clinical context	MSC source		N of pts	Outcome	Refs.
Breast cancer; autologous HSCT	BM	Auto	28	No tox. Rapid haematopoietic recovery	[68]
Hematological malignancy; allogeneic HSCT	BM	Allo	46	No tox. Prompt haematopoietic recovery	[69]
Hematological disorders; haploT-cell depleted HSCT	BM	Haplo	14 c	No tox. Graft rejection prevention. Accelerated leukocyte recovery	[9]
Hematological disorders; UCBT	BM	Haplo	8 c	No tox. Prompt haematopoietic recovery	[70]
Hematological disorders; UCBT	BM	Haplo	13 c	No tox. No effect on engraftment and haematopoietic recovery. GvHD prevention	[10]
Hematological disorders; UCBT + 3rd-party HSCs	BM	Haplo	9	No tox. No effect on kinetics of engraftment and GvHD	[71]
SAA, haplo HSCT	UCB	3° party	21	No tox. Sustained donor engraftment	[72]
Hematological malignancy; haplo HSCT	UCB	3° party	50 also c	No tox. Sustained donor engraftment	[73]

N of pts: number of patients enrolled; c: children; HSCT: haematopoietic stem cell transplantation; BM: bone marrow; UCB: umbilical cord blood; tox.: toxicity; UCBT: umbilical cord blood transplantation; aGvHD: acute graft-versus-host disease; [illegible]: haematopoietic stem cell.

Bernardo and Fibbe, Immunol Lett.2015



Ph. I/II: HAPLO-Tx in 50 pts. with relapsed MALIGNANCIES

- PMN engraftment: d+12 (9-20)
- PLT engraftment: d+15 (10-28)

Grade II-IV aGvHD: 24%

PFS at 2 yrs: 66% (no increased risk of relapse)

Wu Y, et al. Ann Hematol 2013

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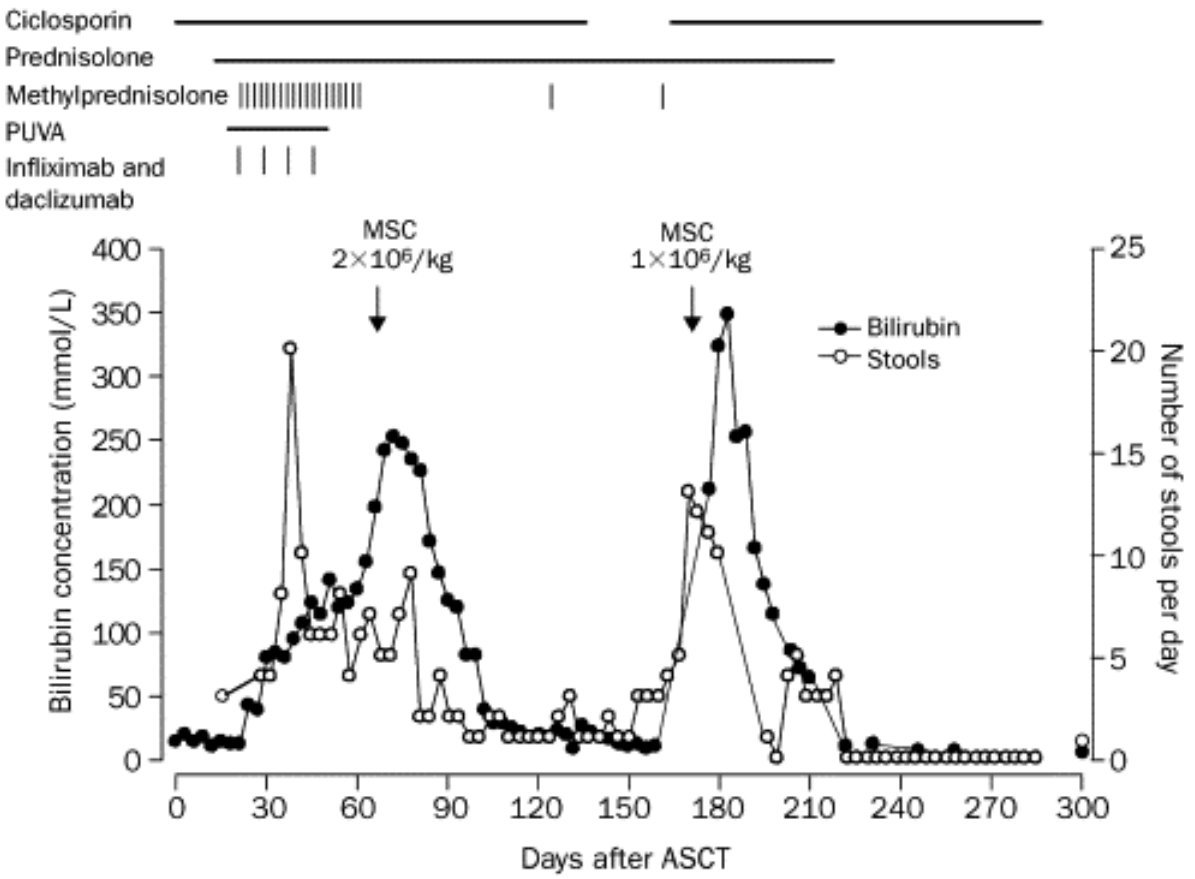
repair of bone and cartilage degenerative disorders, Crohn's disease (IBD), kidney and liver repair, ARDS

MSCs FOR THE TREATMENT OF STEROID-RESISTANT, SEVERE, GRADE II-IV ACUTE GVHD (1)

Seminal case: treatment of severe aGvHD
with third-party haploidentical MSCs



Le Blanc K, et al. The Lancet 2004

MSCs FOR STEROID-RESISTANT, SEVERE, GRADE II-IV ACUTE GVHD: *largest* PHASE II STUDY (2)

55 patients, adults+peds, gr. III/IV aGvHD

	Measure
Donors	
Number of donors	45
Donor sex (male/female)	25/20
Donor age	36 (1–67)
Number of infusions by donor type	
HLA-identical sibling	5
HLA-haploidentical donor	18
Unrelated HLA-mismatched donor	69
Volume of bone marrow harvested (mL)	60 (32–220)
Median MSC cell dose (×10⁶/kg, range)	1·4 (0·4–9)
Culture passage at MSC harvest	
Passage 1	14
Passage 2, 2+3	42, 7
Passage 3, 3+4	23, 2
Passage 4	4
Number of MSC infusions	
One	27
Two	22
Three	4
Four	1
Five	1

Data are number or median (min-max range). MSC=mesenchymal stem cell.

Table 3: **Mesenchymal-stem-cell donor and graft characteristics**

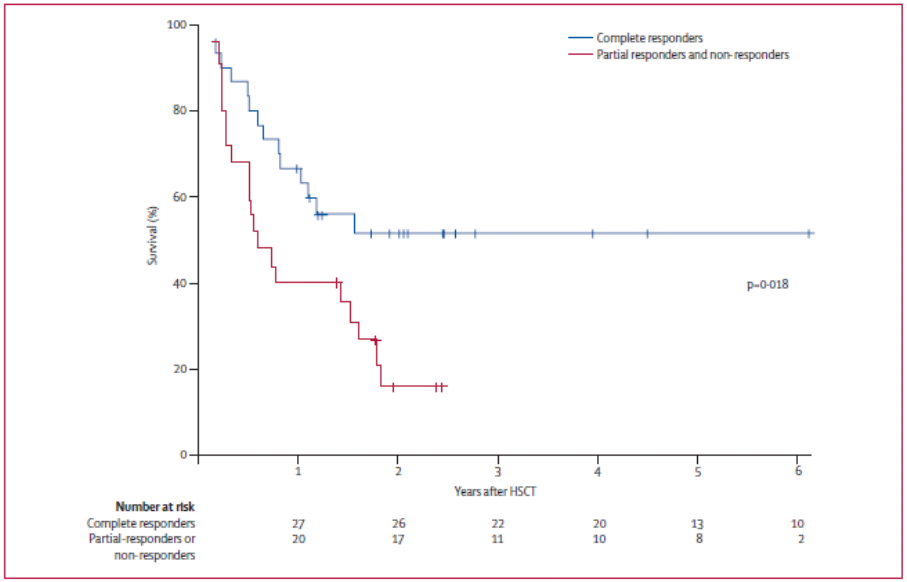
3°-party BM-MSCs

	Children (n=25)	Adults (n=30)	All patients (n=55)
Complete response	17	13	30
Partial response	4	5	9
Stable disease	2	1	3
Progressive disease	2	11	13
Overall response	21	18	39
Survival*	13	8	21
Limited chronic GVHD	2	0	2
Extensive chronic GVHD	4	2	6

*At last data collection, March, 2007.

Table 4: **GVHD response and outcome**

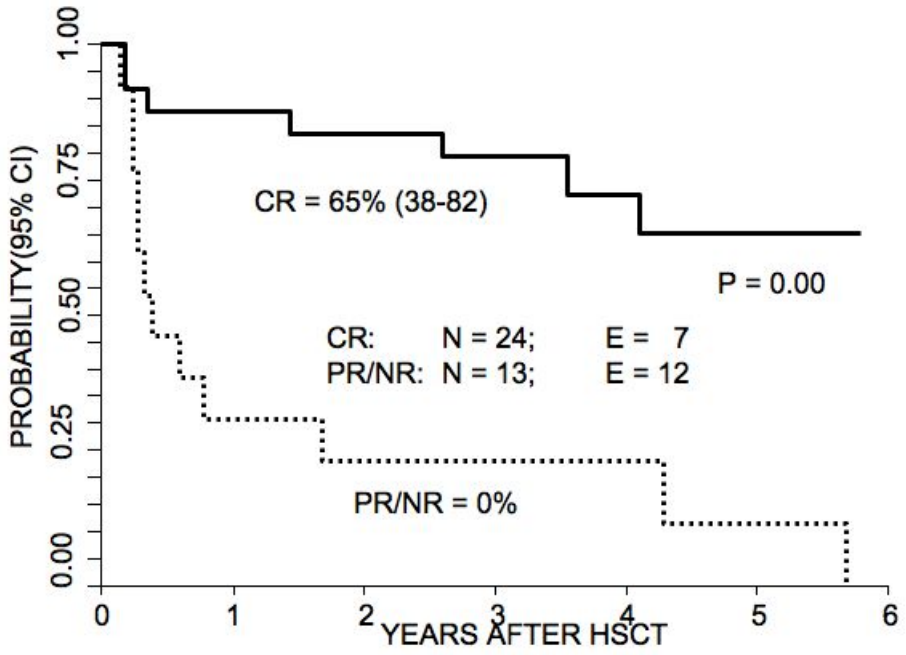
Overall response: 39/55 (71%)



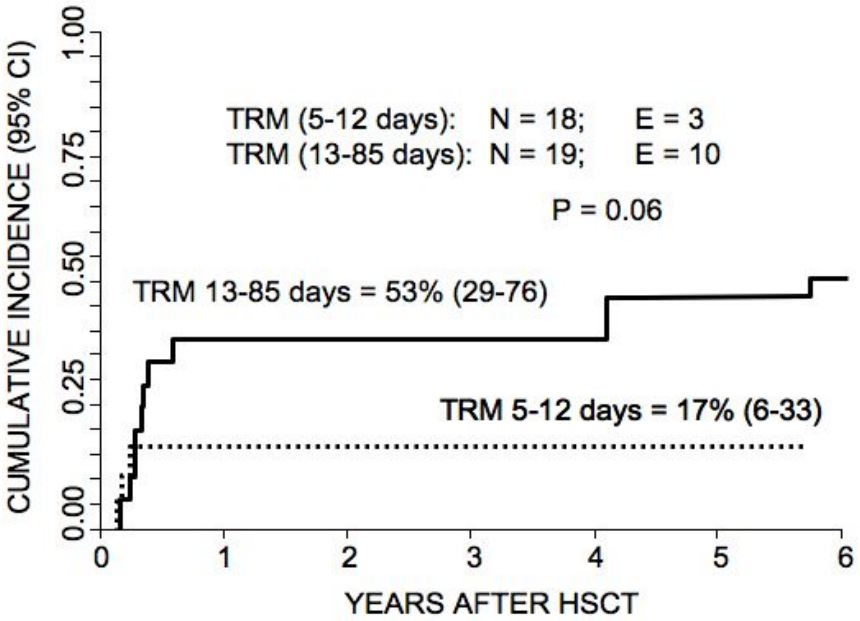
Le Blanc K, ...Bernardo ME, Locatelli F, et al. Lancet 2008

MSCs FOR THE TREATMENT OF STEROID-RESISTANT, aGVHD in PEDs (3): PHASE II STUDY

PROBABILITY of OS for CHILDREN with CR after MSC is SIGNIFICANTLY SUPERIOR to that of CHILDREN with PR/NR



TREND for a LOWER TRM in CHILDREN with EARLY MSC as compared with CHILDREN with LATE MSC

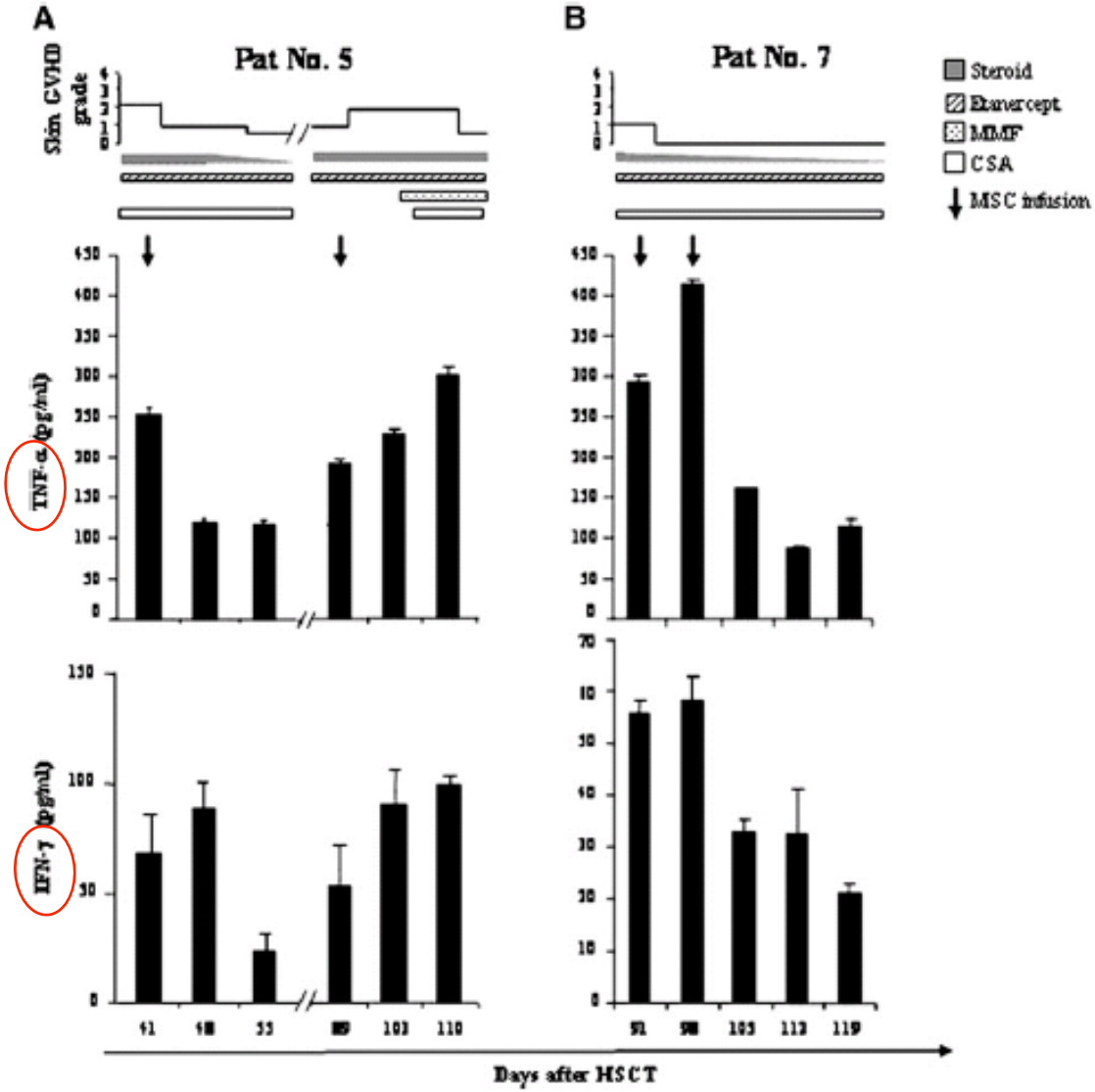


37 patients (all peds)

Ball LM, Bernardo ME, et al. Br J Haematol 2013

3rd-PARTY BM-MSCS EXPANDED IN PLATELET LYSATE FOR CHILDREN WITH STEROID-RESISTANT aGvHD (4)

- 11 PEDs (4-15 yrs.):
  - 8 aGvHD,
  - 3 cGvHD
- MSC dose: 1.2 x 10e6/Kg (0.7-3.7)
- **Overall Response 71% (CR 24%)**



Response correlates with levels of TNF-α and IFN-γ

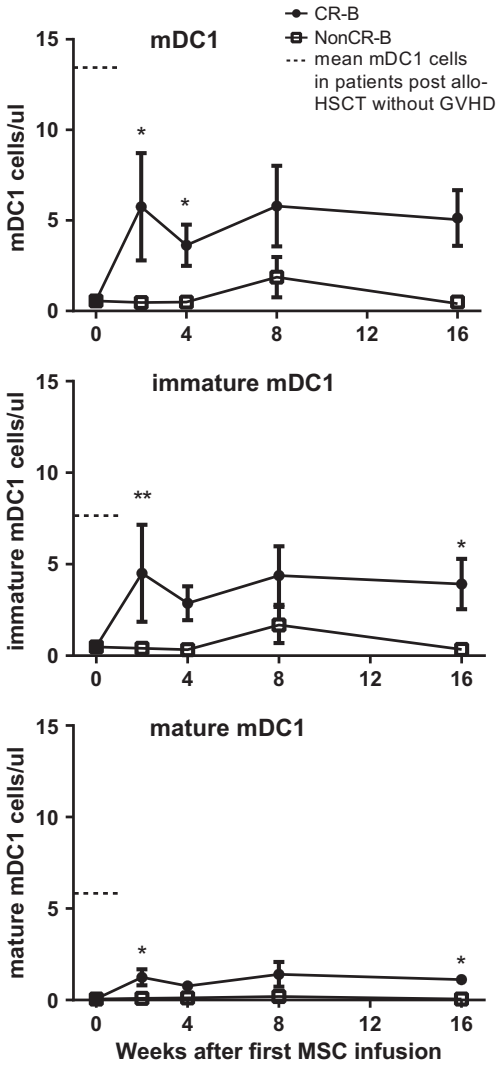
Lucchini G et al. BBMT 2010

PLASMA BIOMARKERS AND LEVELS OF iDC CORRELATE WITH MORTALITY AFTER MSC INFUSION

Ph. II study: 48 patients

Table 3. Biomarkers that associate with 1-year mortality

	Outcome 1-year mortality			
	Variable	*HR*	*CI*	P-*value*
Day 0	Age	1.032	1.005–1.059	0.02
	Levine biomarker formula	2.924	1.485–5.758	0.002
Day 14	Immature mDC1 at day 14	0.554	0.389–0.790	0.001
	ST2 at day 14	2.389	1.144–4.989	0.02



- Ferrara biomarker panel levels were predictive for mortality when measured before MSC treatment
- Increase in immature myeloid DC early after MSC treatment associated with decreased mortality

te Boome et al. Leukemia 2015

MSCs TO TREAT ACUTE GVHD: summary of CLINICALTRIALS

Table 2. Clinical applications of MSCs to treat GvHD

Clinical context	MSC source	N of pts	Outcome	Ref. n.
Grade IV aGvHD after allogeneic HSCT	BM haplo	1 c	Complete resolution of grade IV acute GVHD	75
Grade II-IV aGvHD after allogeneic HSCT/DLI	BM 3rd party	55 also c	OR: 69%; improved OS in responders	16
Grade II-IV aGvHD after allogeneic HSCT/DLI	BM 3rd party	37 c	CR 59%; improved OS, especially if early MSC treatment	76
Grade II-IV aGvHD after allogeneic HSCT/DLI	BM 3rd party (PL)	11 c	OR: 71%; CR: 24%	77
Grade II-IV aGvHD after allogeneic HSCT/DLI	BM 3rd party (PL)	40 also c	OR: 67.5%; CR: 27.5%. Better in children and grade II	78
Grade II-IV aGvHD after allogeneic HSCT/DLI (Phase III)	BM 3rd party	240also c	No significant increase of CRs as compared with placebo; better if gastrointestinal and liver GvHD	-
Ext. Sclerodermatous cGvHD after allogeneic HSCT	BM 3rd party	4	Improvements of the signs of cGvHD (intrabone	80
Refractor[illegible]GvHD after allogeneic HSCT	BM 3rd party	23	injection)	81
			OR: 20/23 treated pts. Increase in Bregs	

Phase II

N of pts: numbe[illegible]of patients enrolled; c: children; HSCT: haematopoietic stem cell transplantation; DLI, dono lymphocyte infusion; BM: bone marrow; aGvHD: acute graft-versus-host disea[illegible] cGvHD: chronic graft-versus-host disease; OR: overall response; OS, overall survival; CR, complete response; PL: platelet lysate expanded MSC; Ext: extensive.

Bernardo and Fibbe, Immunol Lett.2015

OSIRIS: company-driven RANDOMIZED trial of MSCs for steroid-resistant aGvHD

- 2:1 **randomization**, 163 patients received 8 infusions of 3rd-party BM-MSCs and 81 were given placebo.
- Infusional toxicity, infection rates, and incidence of recurrent malignancy were similar in the two arms.
- **No difference** was observed in achieving the primary end-point of a **durable complete response for 28 days** (35 vs. 30%), although there was a **trend** in favor of MSCs for patients with VISCERAL INVOLVEMENT.

Treatment of se **al stromal cells.**

A ph **study.**

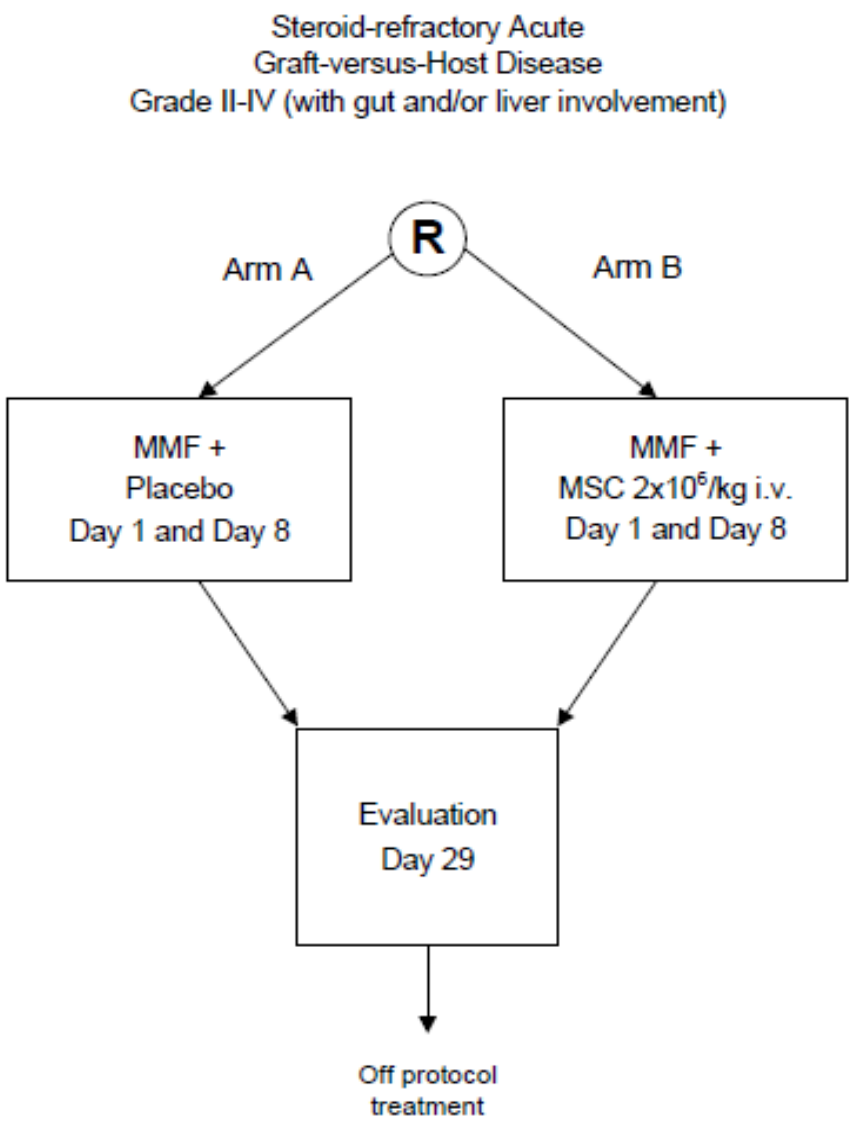
Principal Investiga

Sponsor

EudraCT number

HOVON

Scheme of study



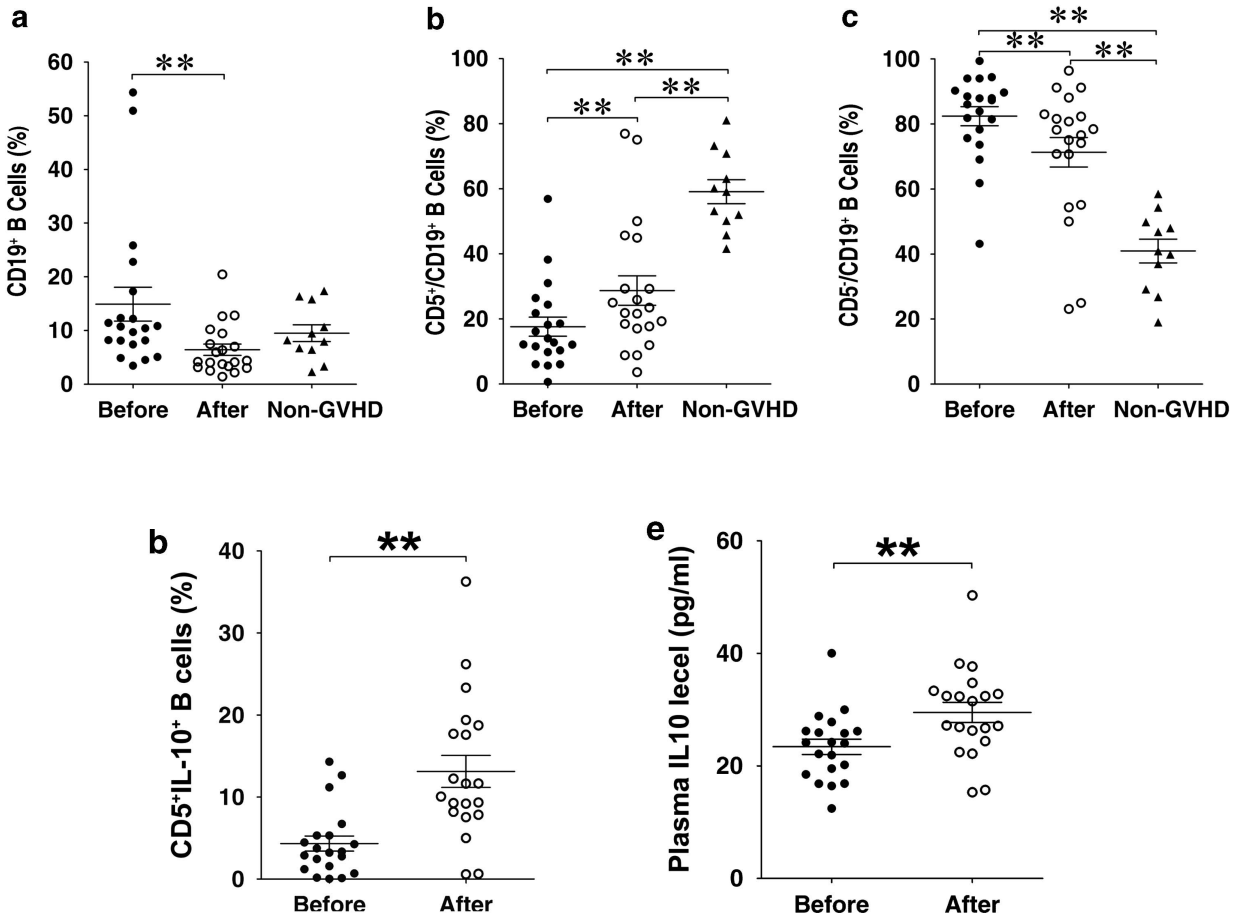
MSCs FOR THE TREATMENT OF CHRONIC GVHD

23 pts with mainly extensive cGvHD: 20/23 CR or PR
Response to MSC is associated with an increase in CD5+ regulatory B cells producing IL-10

Table 1. Clinical characteristics of cGVHD patients

	cGVHD (N = 23)	*Non-GVHD (N = 11)*	P-*value*
Median age, year (range)	31 (14–51)	34 (15–49)	0.83
Sex (%)			0.72
Females	5 (21.7)	3 (27.3)	
Male	18 (78.3)	8 (72.7)	
Median time post-HSCT, month (range)	12.5 (6–56)	11 (5.5–44)	0.54
Source of graft (%)			0.70
Peripheral blood	20 (87.0)	9 (81.8)	
Bone marrow	3 (13.0)	2 (18.2)	
Transplant type (%)			>0.99
Myeloablative	22 (95.7)	10 (90.9)	
Nonmyeloablative	1 (4.3)	1 (9.1)	
HLA matching (%)			>0.99
Matched, unrelated	2 (8.7)	1 (9.1)	
Matched, related	19 (82.6)	9 (81.8)	
Mismatched	2 (8.7)	1 (9.1)	
Prophylaxis (%)			—
CsA	3 (13.0)	—	
CsA+prednisolon	18 (78.3)	—	
CsA+prednisolon +MM	2 (8.7)	—	
Disease (%)			0.97
AML	8 (34.8)	6 (54.4)	
ALL	4 (17.4)	2 (18.2)	
CML	6 (26.1)	3 (27.3)	
NHL	1 (4.3)	0 (0)	
Other	4 (17.4)	1 (9.1)	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute monocytic leukemia; CML, chronic monocytic leukemia; CsA, cyclosporin A; cGVHD, chronic graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MM, mycophenolate mofetil; NHL, non-Hodgkin lymphoma.



Peng et al. Leukemia 2015

CLINICAL APPLICATIONS of MSCs IN HSCT (& BEYOND)

I. **Co-infusion of MSCs and HSCs to enhance hematopoietic engraftment** after allo-HSCT in HAPLO- and CB-HSCT

II. **Treatment of steroid-resistant acute GvHD**

III. **Ex-vivo expansion of CD34+ cells on MSCs for improved engraftment**

IV. **Treatment of acute tissue damage after allo-HSCT**

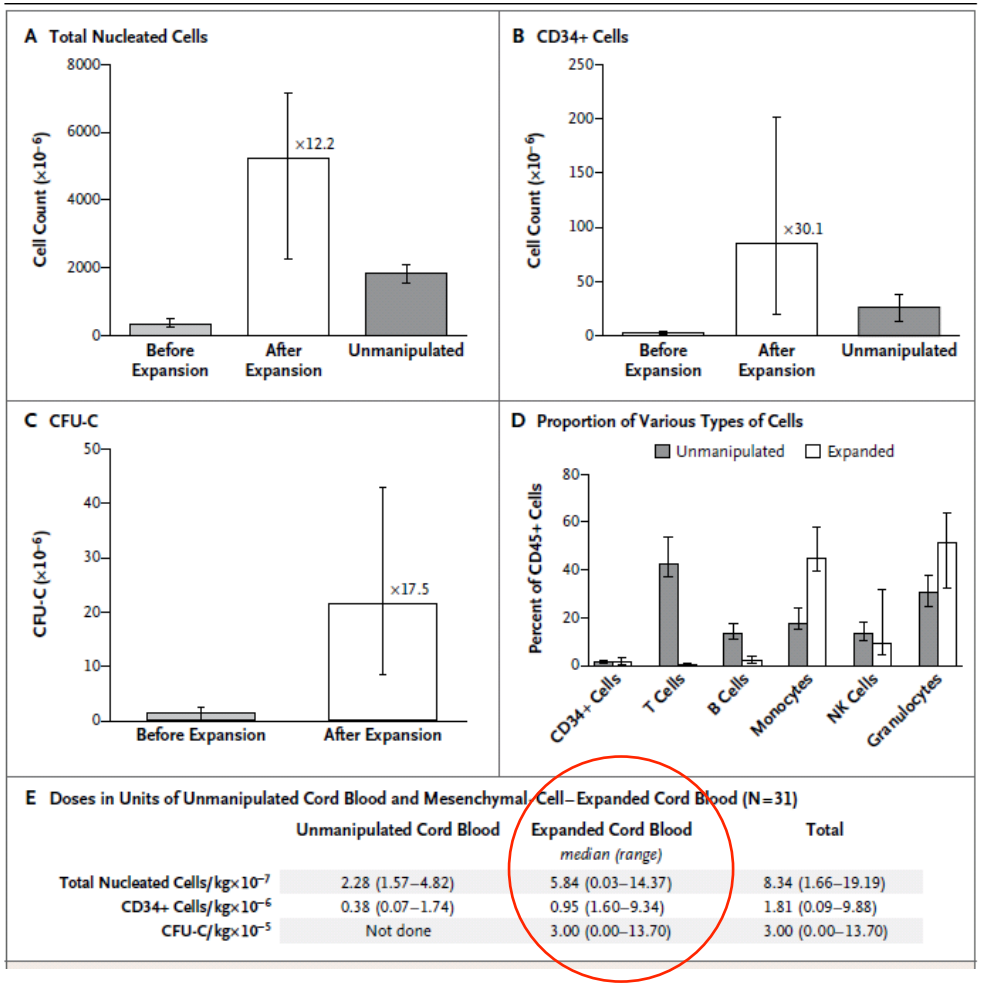
(case reports in hemorragic cystitis, pneumothorax and pneumomediastinum, peritonitis)

& BEYOND…**REGENERATIVE MEDICINE**

repair of bone and cartilage degenerative disorders, Crohn's disease, kidney and liver repair

III. EX-VIVO EXPANSION of CB-CD34+ CELLs and IMPROVED ENGRAFTMENT

3rd-party BM-MSCs

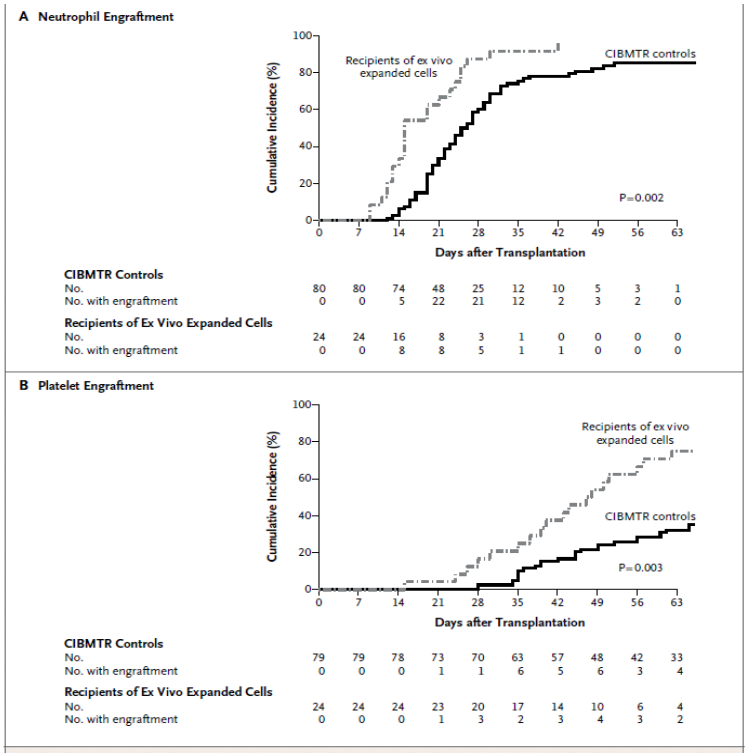


E Doses in Units of Unmanipulated Cord Blood and Mesenchymal Cell–Expanded Cord Blood (N=31)

	Unmanipulated Cord Blood	Expanded Cord Blood *median (range)*	Total
Total Nucleated Cells/kg×10^{-7}	2.28 (1.57–4.82)	5.84 (0.03–14.37)	8.34 (1.66–19.19)
CD34+ Cells/kg×10^{-6}	0.38 (0.07–1.74)	0.95 (1.60–9.34)	1.81 (0.09–9.88)
CFU-C/kg×10^{-5}	Not done	3.00 (0.00–13.70)	3.00 (0.00–13.70)

Table 2. Engraftment in Recipients of Ex Vivo Expanded Cells and MDACC and CIBMTR Controls.

Engraftment	Recipients of Ex Vivo Expanded Cells (N=24)	MDACC Controls (N=60)	P Value*	CIBMTR Controls (N=80)	P Value†
Neutrophil engraftment					
No. of patients	23	51		67	
Time to engraftment — days					
Median	15	21	0.08	24	<0.001
Range	9–42	6–45		12–52	
Cumulative incidence — % (95% CI)					
By 26 days	88 (66–96)	62 (48–73)	0.006	53 (41–63)	<0.001
By 42 days	96 (74–99)	83 (71–91)	0.05	78 (67–86)	0.005
Platelet engraftment					
No. of patients	18	38		37	
Time to engraftment — days					
Median	42	41	0.33	49	0.03
Range	15–62	26–126		18–264	
Cumulative incidence — % (95% CI)					
By 60 days	71 (48–85)	52 (38–63)	0.10	31 (21–41)	<0.001
By 180 days	75 (53–88)	63 (50–74)	0.28	46 (35–58)	0.01



DOUBLE CBT: 1 expanded, 1 unmanipulated

Median NC/Kg= 8.34 x 10^7

Median CD34+/Kg= 1.81 x 10^6

De Lima, et al. New England J Medicine 2012

CLINICAL APPLICATIONS of MSCs IN HSCT (& BEYOND)

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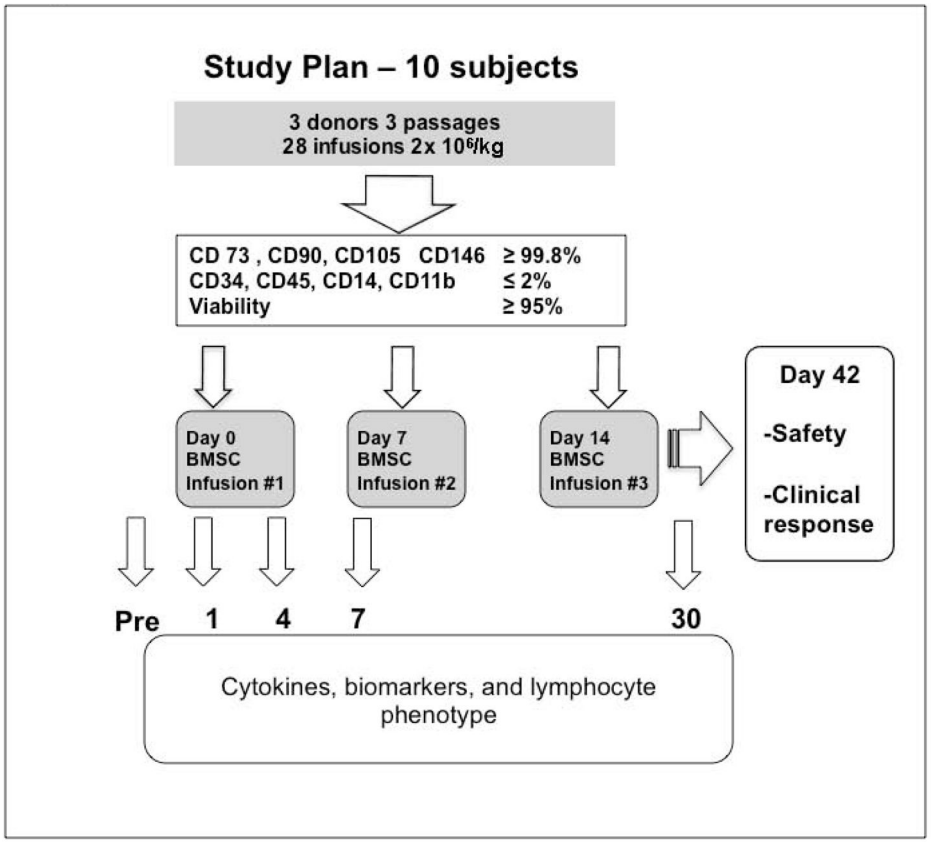
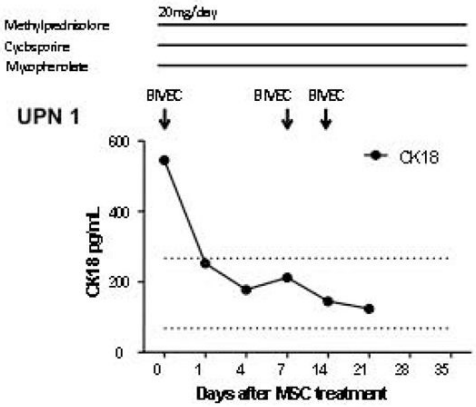
repair of bONE and CARTILAGE degenerative disorders, Crohn's disease (IBD), kidney and liver repair, ARDS

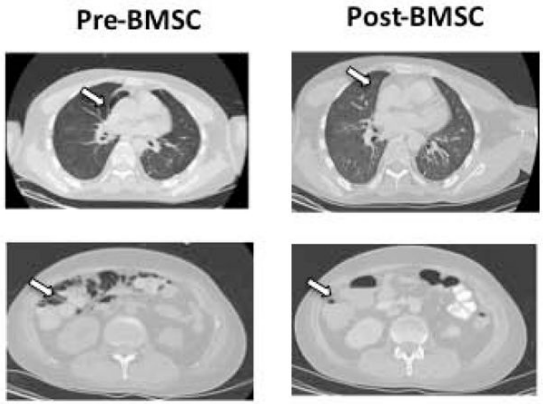
IV. MSC TO TREAT TISSUE DAMAGE IN ALLOGENEIC HSCT RECIPIENTS

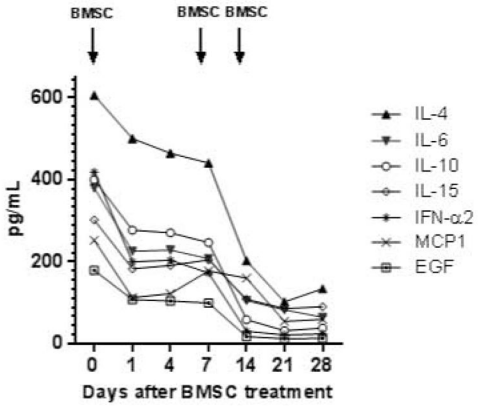


MSC possess anti-inflammatory properties which can be employed to heal therapy-induced tissue toxicity after allo-HSCT:

- **Hemorrhagic cystitis**
- **Pneumomediastinum**
- **Perforated colon with perotonitis**







Ringden et al. Leukemia 2007 *Yin et al. Stem Cells 2014*

CONCLUSIONS FROM MSC TRIALS TO IMPROVE OUTCOME IN ALLO-HSCT

- ✓ Infusion of MSCs appeared to be **safe** and no major toxicities were observed.
- ✓ **3rd-party BM-MSCs** may provide an **effective therapy for patients with severe aGvHD** who do not respond to treatment with corticosteroids (Phase III ongoing). *The earlier the better*
- ✓ **Randomized clinical trials** are needed to define the role of MSCs in steroid-resistant GvHD and to identify pts. that will benefit most from the treatment
- ✓ MSC may be employed to expand HSC and to repair tissue damage after allo-HSCT
- ✓ Current MSC *in vitro* assays are not predictive of the efficacy *in vivo*. Need for identification of **potency assays** *in vitro* able to predict outcome in patients
- ✓ Need for **harmonization** in MSC manifacturing across Europe:

EMBT survey on MSC manufacturing

Working towards harmonisation

On behalf of CTIWP

Trento C, Bernardo ME, Bonini C, Dazzi F

Participants to the survey: N. 17 EBMT centers

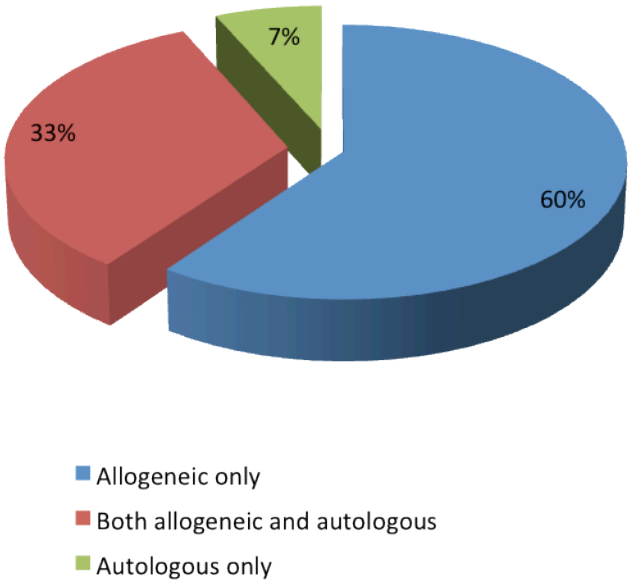
- Germany
- Israel
- Italy
- Netherlands
- Belgium
- Austria
- United Kingdom
- Lithuania
- Sweden

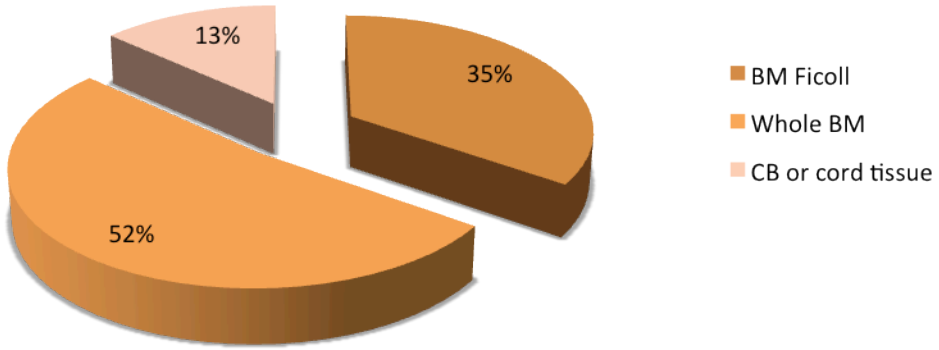
Considered variables:

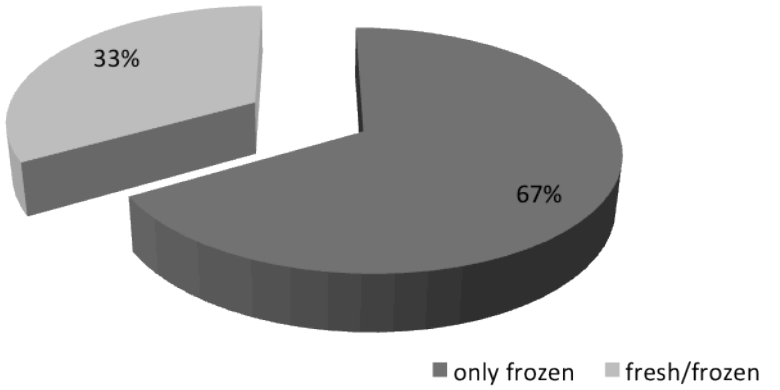
- MSC source,
- MSC donor matching,
- medium additives for ex-vivo expansion,
- data on MSC product specification for clinical release

Manufacture of MSCs

mainly BM, mainly ALLOGENEIC/THIRD PARTY, mailny FROZEN



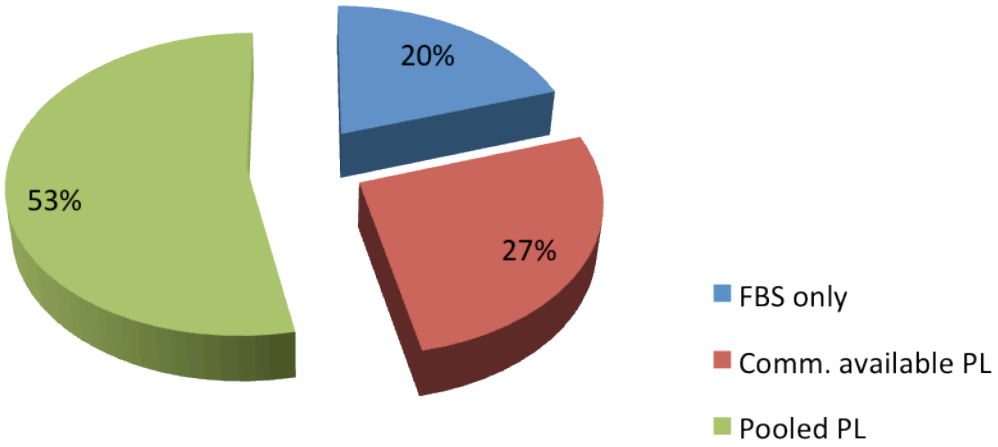




Trento C, Bernardo ME, et al. Submitted

Media used for manufacture

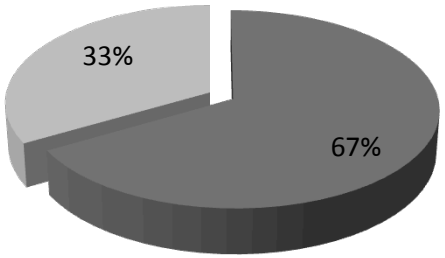
mainly PLATELET LYSATE

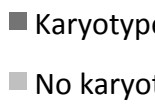


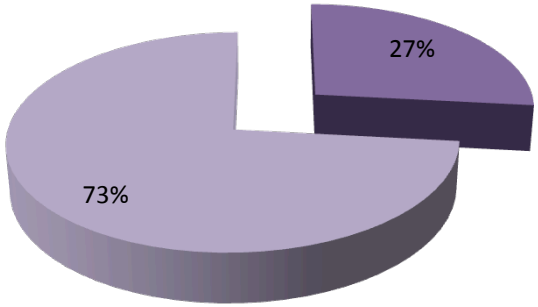
Trento C, Bernardo ME, et al. Submitted

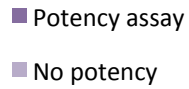
Product specification

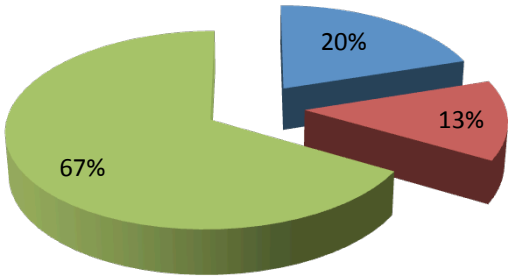
Variability in release criteria for clinical use
Only 27% performs POTENCY ASSAY

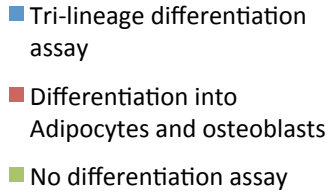


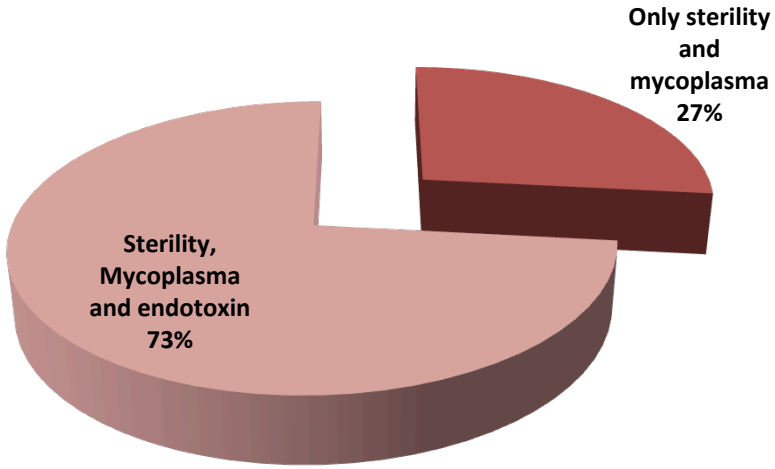












Trento C, Bernardo ME, et al. Submitted

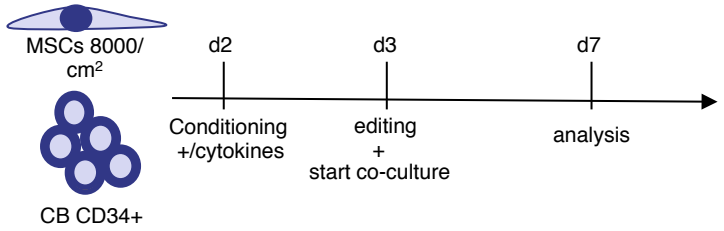
CONCLUSIONS FROM THE EBMT SURVEY ON MSC

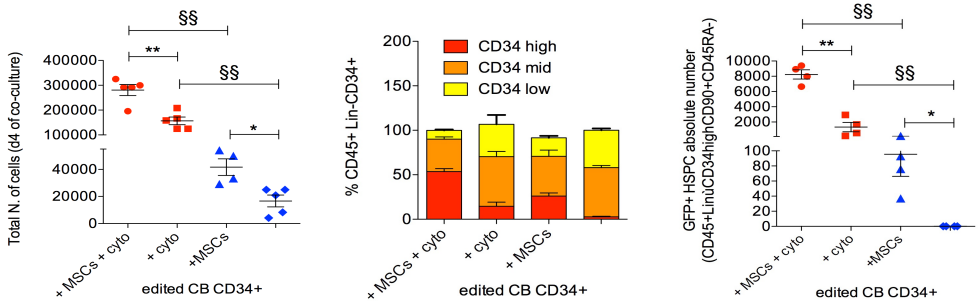
- ✓ Very few centers have developed a potency assay that could predict patient's outcome
- ✓ Data collected highlight the high variability in MSC manufacturing as clinical product and the need for harmonization.
- ✓ Until more meaningful potency assays become available, a more homogenous approach to cell production may at least reduce variability in clinical trials and improve interpretation of results.

FUTURE: MSC to optimize the outcome of HSC-GENE THERAPY

- ***MSC support of gene-edited (GE) HSPC in 2D co-culture***

MSC significantly increase the number of primitive GE-HSPC, identified as Lin- CD34high, CD90+ and CD45RA-

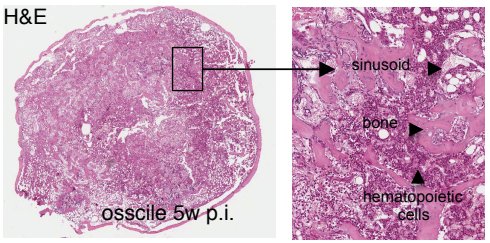


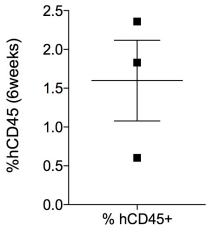


- ***In vivo ossicle 3D model with humanized niche to support engraftment of GE-HSPC***

- humanized BM niche present at 5 weeks after the implantation of scaffolds pre-seeded with huMSC and EC into non-irradiated NSG mice

- huCD45+ cells were detected in PB already at 6 weeks after HSCT





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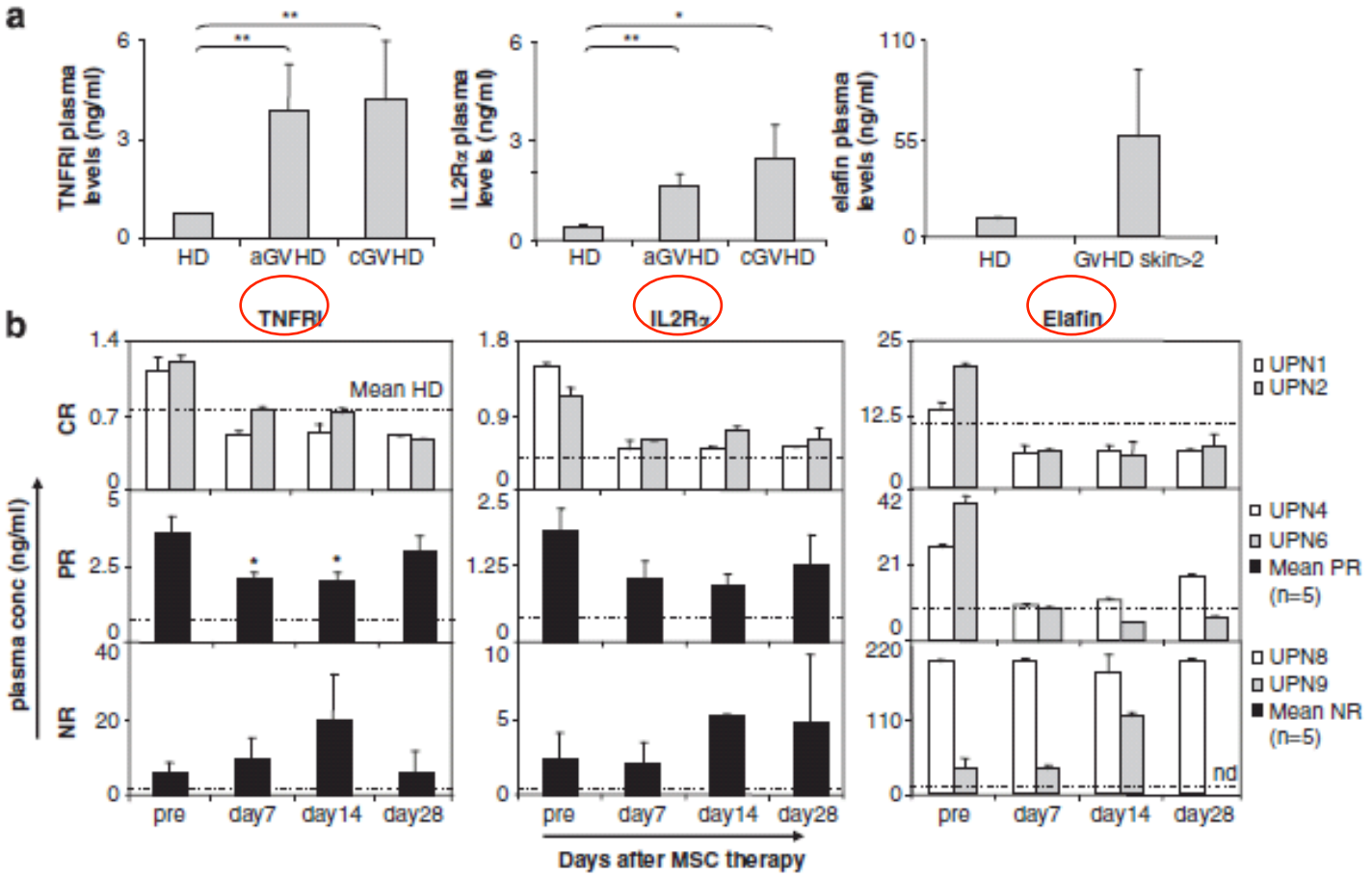
PLASMA BIOMARKERS FOR aGVHD RESPONSE AFTER MSC THERAPY



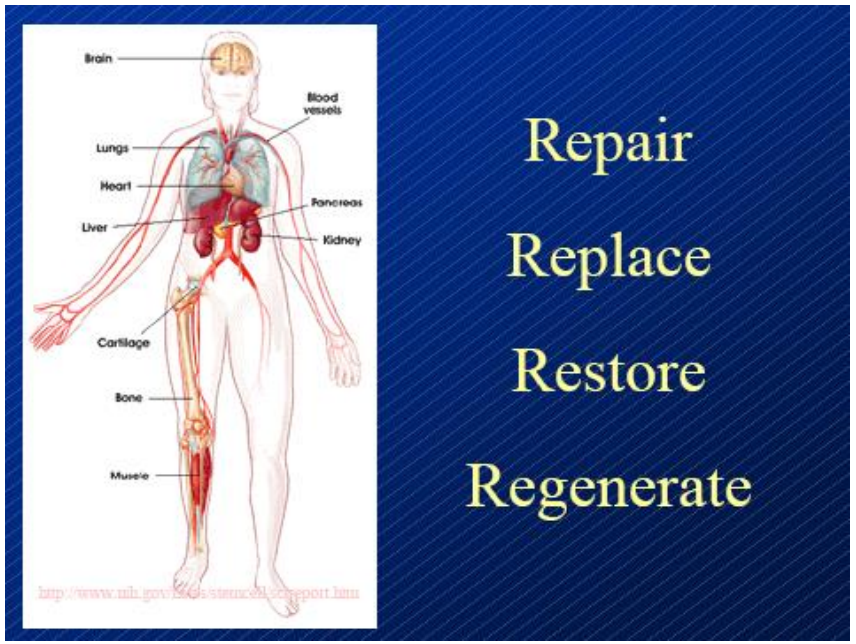
TNFRI, **IL2Ralpha** and **ELAFIN** can be employed as biomarkers for monitoring patients' response to MSC therapy

Dander E et al., Leukemia 2012

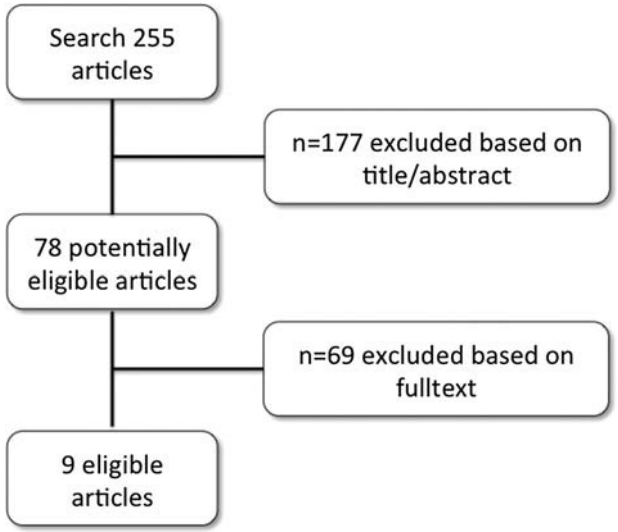
CLINICAL APPLICATIONS of MSCs as ANTI-INFLAMMATORY AGENTS in REGENERATIVE MEDICINE

In REGENERATIVE MEDICINE:

- repair of BONE and CARTILAGE degenerative disorders
- **IBD (Crohn's disease)**
- Kidney and liver repair
- Hemophagocytic Lymphohistiocytosis
- Acute Respiratory Distress



IN PHASE II STUDIES GvHD RESPONSE CORRELATES WITH OS



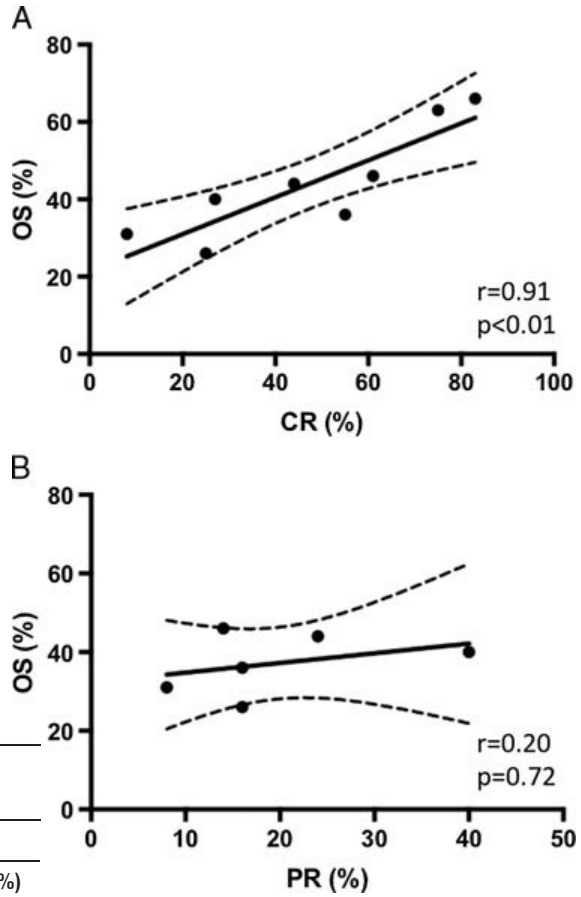


TABLE 2.

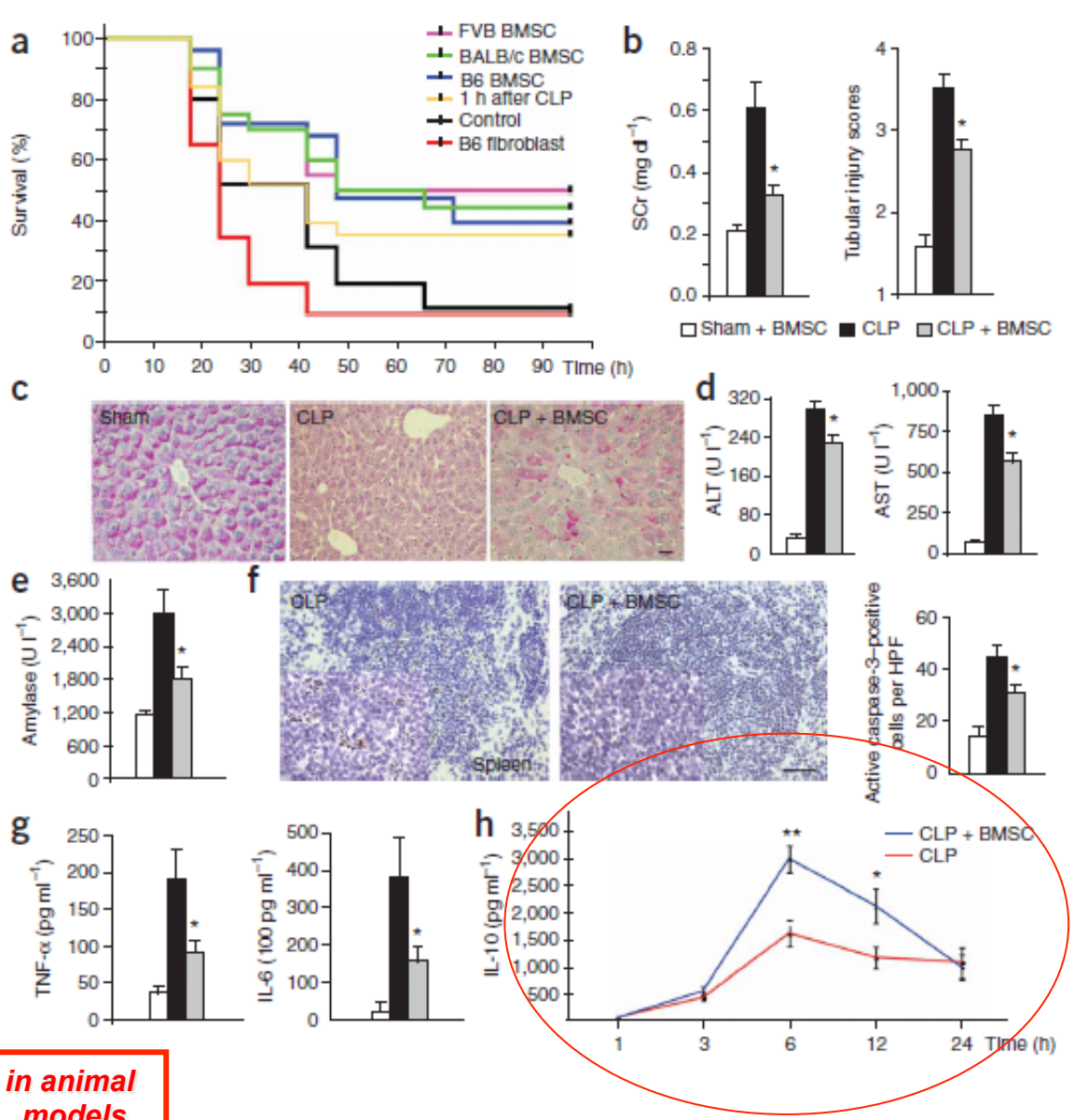
Response rates and survival

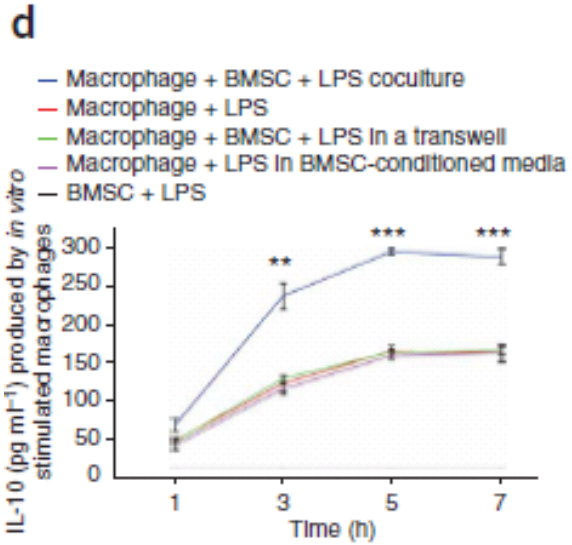
First Author		Outcome CR (%)	PR (%)	MR (%)	Survival Relapse (%)	TRM[a] (%)	OS (%)
Ringden (2006)	pts	6/8 (75)			0/8 (0)	3/8 (38)	5/8 (63)
	co	NM			NM	NM	0/16 (0)
Fang (2007)		5/6 (83)			1/6 (17)	1/6 (17)	4/6 (66)
Le Blanc (2008)		30/55 (55)	9/55 (16)		3/55 (5)	CR 11/30 (37)	16/30 (53)
						PR/NR 18/25 (72)[b]	4/25 (16)[b]
Von Bonin (2009)		1/13 (8)	1/13 (8)	5/13 (38)	0/13 (0)	9/13 (21)	4/13 (31)
Resnick (2013)		17/50 (34)	16/50 (32)		1/50 (2)	CR/PR 6/33 (18)	NM
Sanchez (2014)		11/25 (44)	6/25 (24)		2/25 (8)	CR/PR 7/17 (41)	8/11 (67)
						NR 5/8 (71)	3/14 (21)
Introna (2014)		11/40 (27)	16/40 (40)		6/40 (15)	18/40 (45)	16/40 (40)
Zhao (2015)	pts	17/28 (61)	4/28 (14)		2/28 (7)[c]	12/28 (43)	…/28 (46)[d]
	co	5/19 (26)	3/19 (16)		1/19 (3)[c]	13/19 (68)	…/19 (26)
Te Boome (2015)		12/48 (25)					…/48 (44)

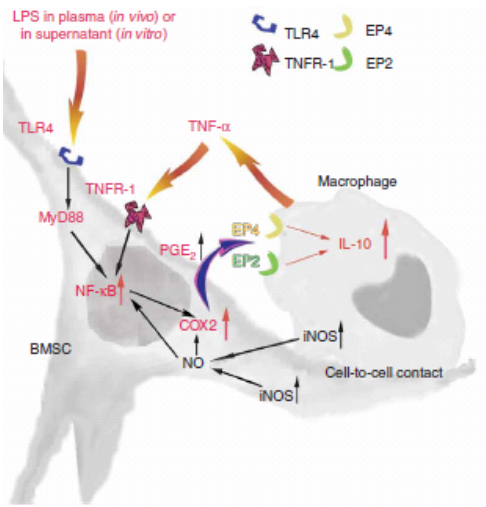
Munneke et al. Transplantation 2016

Hashmi et al. Lancet Hematol 2016

MSCs ATTENUATE SEPSIS VIA PGE2-DEPENDENT REPROGRAMMING OF HOST MACROPHAGES







in animal models

Nemeth et al, Nat Med 2009