THERAPIE CELLULAIRE
DANS LES MALADIES AUTOIMMUNES

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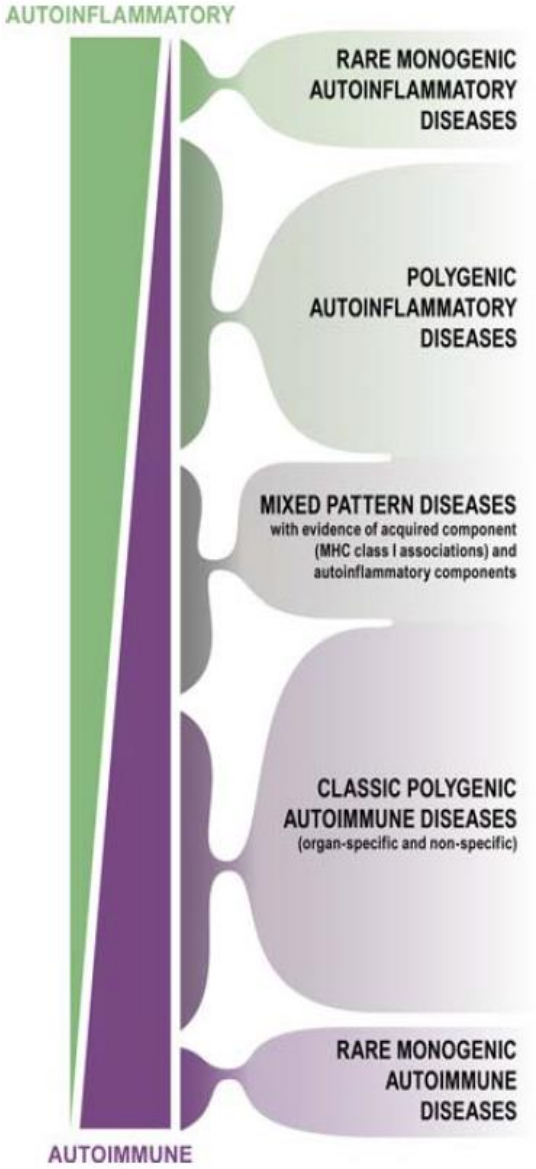
www.mathec.com

PLAN THERAPIE CELULAIRE DANS LES MALADIES AUTOIMMUNES

- Les Greffes de moelle dans les maladies autoimmunes
  - Rationnel expérimental
  - Consensus europeen
  - Examples
    - Sclérodermie Systémique
    - Sclérose en Plaque
    - Maladie de Crohn
- Utilisation des Cellules Souches Mésenchymateuses
  - Définition
  - Rationnel expérimental
  - Développement clinique

SYSTEMIC AUTOIMMUNE DISEASES: (AD):6-8 %

a single continum ≠ clinico-pathological classification



Type of Disease	Inflammatory Disorder Gene/Protein	Cellular Distribution/Function
FMF	*MEFV*/pyrin	Neutrophils, early monocyte lineage, stromal cells/regulation of inflammatory response
HIDS	*MVK*/mevalonate kinase	Widespread/cholesterol biosynthesis, prenylation
TRAPS	*TNFRSF1A*/ TNFR1	Widespread/TNF receptor
Crohn disease	*NOD2*/NOD2	Macrophages, Paneth cells/bacterial sensing
Ankylosing spondylitis Reactive arthritis Psoriasis/psoriatic arthritis Behcet Syndrome Uveitis (HLA-B27 associated)		
SLE, TID, AITD	*CTLA-4*/CTLA-4	Regulation of T lymphocytes activation
RA, SLE, T1D	*PTPN22*/PTPN22	Regulation of T lymphocytes activation
Many disorders	MHC associations	Multiple T cell functions, including B cell help
APS-1	*AIRE*/AIRE	Thymic epithelium/negative T cell selection
IPEX	*FOXP3*/FOXP3	Regulatory T cells/immunomodulation
ALPS	*FAS*/FAS	Widespread/key role in lymphocyte apoptosis

SSc : a GVHd like disease in the autologous setting!

Mc Gonagle Plus One 2006

Autoimmune + Autoinflammatory Diseases

Proposal for a Definition of Autoinflammation

Self-directed inflammation, whereby local factors at sites predisposed to disease lead to activation of innate immune cells, including macrophages and neutrophils, with resultant target tissue damage. For example, disturbed homeostasis of canonical cytokine cascades (as in the periodic fevers), aberrant bacterial sensing (as in Crohn disease), and tissue microdamage predispose one to site-specific inflammation that is independent of adaptive immune responses

Generic Definition of Autoimmunity

Self-directed inflammation, whereby aberrant dendritic cell, B and T cell, responses in primary and secondary lymphoid organs lead to breaking of tolerance, with development of immune reactivity towards native antigens. The adaptive immune response plays the predominant role in the eventual clinical expression of disease. Organ-specific autoantibodies may predate clinical disease expression by years and manifest before target organ damage is discernible.

Factors determining disease manifestations	Local tissue factors at disease-prone sites, including tissue trauma, necrosis, mechanical factors, and bacteria or their constituent molecules	Clinical disease expression determined by events taking place in primary and secondary lymphoid tissues, including bone marrow, thymus, lymph nodes, and spleen
	Innate immune activation	Adaptive immune activation
Immunological basis	Genetically related to perturbations of innate immune function, including pro-inflammatory cytokine signalling abnormalities/ bacterial sensing/local tissue abnormalities	Acquired immune perturbation key-to-disease expression

Cellules Souches Hématopoiétiques : Moelle Osseuse, Périphérie, Cordon

REINDUCTION de la TOLERANCE

Greffe Moelle ..... **CSM**

Cyclophosphamide *po*, iv
Biothérapies

CORTICOIDES

Serum Antilymphocytaire **CYCLOSPORINE A**

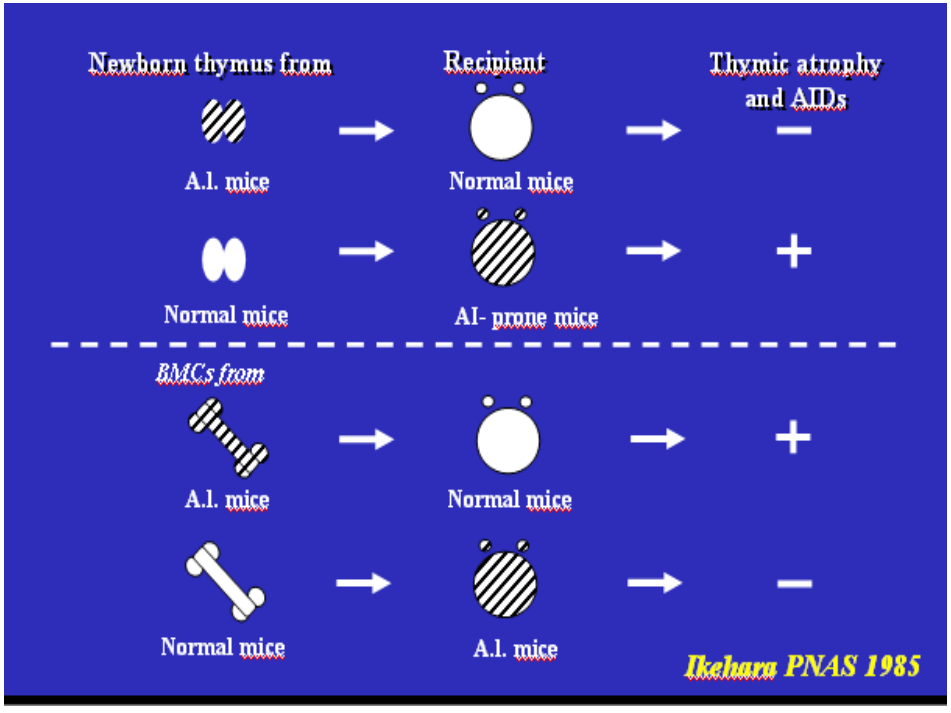
1960 **1970** **1980** **1990** **1995** **2000** 2005 **2010** **2020**

- Formes sévères or rapidement évolutives de MAI :
- Sclérodermie systémique[1]
  - Survie 5 ans 30 % 40 - 50%
- Lupus Systémique[2]
  - Survie 10 ans /IR 70/50 % 90/35 %
- Sclérose en plaques[3] : biothérapies
- Crohn's[4] : immunosuppresseurs, immunomodulations
- Diabète type I non acido-cétosique[5] : insuline à vie

1/ Farge D, et al. Bone Marrow Transplantation 2017;1-9. doi: 10.1038/bmt.2017.56. 2/ Illei GG, et al. Ann Rheum Dis 2011,70(12):2071-4. 3/ Muraro PA, et al. JAMA Neurol 2017;74(4):459-69. 4/ Lindsay JO, et al. Lancet Gastroenterol Hepatol 2017;2:399-406. 5/ Snowden J, et al. Bone Marrow Transplant 2012;47:770-90.

BM ? Treat AD in human *IKEHARA PNAS 1985*

T cell dysfonction <= thymic involution AD mice + aN HSC



1985: first succes allo BM in SLE mice
Imporved results with fetal BM: **stroma cells ? CSM** ?

Autoimmune strain	Disease	Effect
NOD	Diabetes	Resolution of insulinitis
B/W, BXSB	Glomerulonephritis	Regression of glomerular damage; reduction in circulating immune complexes or complete cure
MRL/lpr	Glomerulonephritis	Complete cure
MRL/lpr	Glomerulonephritis and arthritis	Complete resolution of glomerulonephritis arthritis and correction of immunological abnormalities
Old MRL/+	Pancreatitis and sialoadenitis	Cure of pancreatitis and sialoadenitis, normalization of T- and B-cell functions

V BEKKUM Best Pract Res 2004

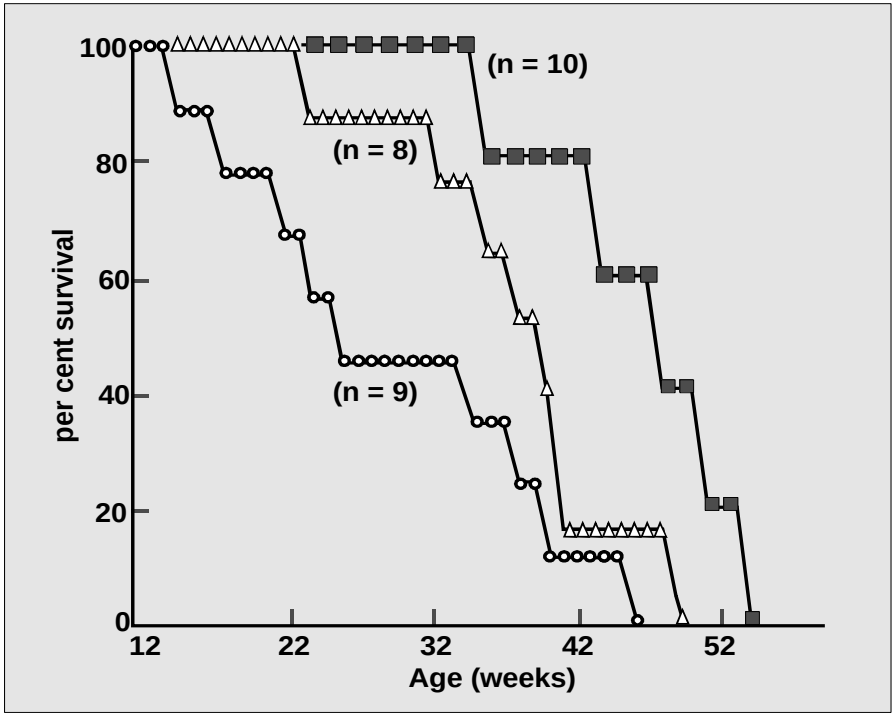
Disease	Effect
Adjuvant arthritis[a] (rats)	Complete remission
Collagen induced arthritis[a] (mice)	No remission, complete prevention of progression
Experimental allergic encephalomyelitis[b] (rats)	Complete remission, few relapses
Biozzi mice[a]	
Treated in acute phase:	Complete remission, few relapses
Treated in chronic phase:	No effect

Immunomodulation of AI in MRL/Lpr mice with syngeneic BMT

Karussis Clin Exp Immunol 1995; 100: 111

SLE associated mortality with:

- **Untreated mice**
- **TBI + syngenic BM (+ spleen cells)**
- **-CY + TBI + syngenic BM (+spleen cells)**



VAN BEKKUM :

. Inflammatory AD ◄ initiated + maintained by activated T cells ***! Eliminate***

. Cy alone < Cy + TBI

. Relapse ◄ memory T cells ***! Radiation > Cy***

. Search for specific lymphocytolytic agents: Fludarabine , ATG?

. Immune reconstitution (? stem cell): recapitulation of ontogenesis

Haematopoietic stem cell transplantation (HSCT) in severe auto-immune diseases: updated guidelines written on behalf of the EBMT ADWP and PDWP

J Snowden, R Saccardi, M Allez, S Ardizzone, R Arnold, R Cervera, C Denton, JM van Laar, M Labopin, G Mancardi, R Martin, JJ Moore, J Passweg, C Peters, M Rabusin, M Rovira, D Farge ***BMT 2011on line, C***

Per Ljungmann BMT 2009 Level II = **at least one well designed clinical trial without randomisation:** cohort or case controlled analytical studies (preferably > one centre), multiple time series studies

Disease	Sib donor	Well matched unrelated	Mismatched donor	Autologous
MS	D/III	GNR/III	GNR/III	Level I
SSc	D/III	GNR/III	GNR/III	Level I
SLE	D/III	GNR/III	GNR/III	CO / II
Crohn's	GNR/III	GNR/III	GNR/III	Level II
RA	GNR/III	GNR/III	GNR/III	CO/II
Vasculitis	GNR/III	GNR/III	GNR/III	CO/II
Polymyositis-Dermatomyositis	GNR/III	GNR/III	GNR/III	CO/II
CIPD	GNR/III	GNR/III	GNR/III	CO / II
Cytopenia	CO/II	D/III	GNR/III	CO / II
T1D	GNR/III	GNR/III	GNR/III	D / III

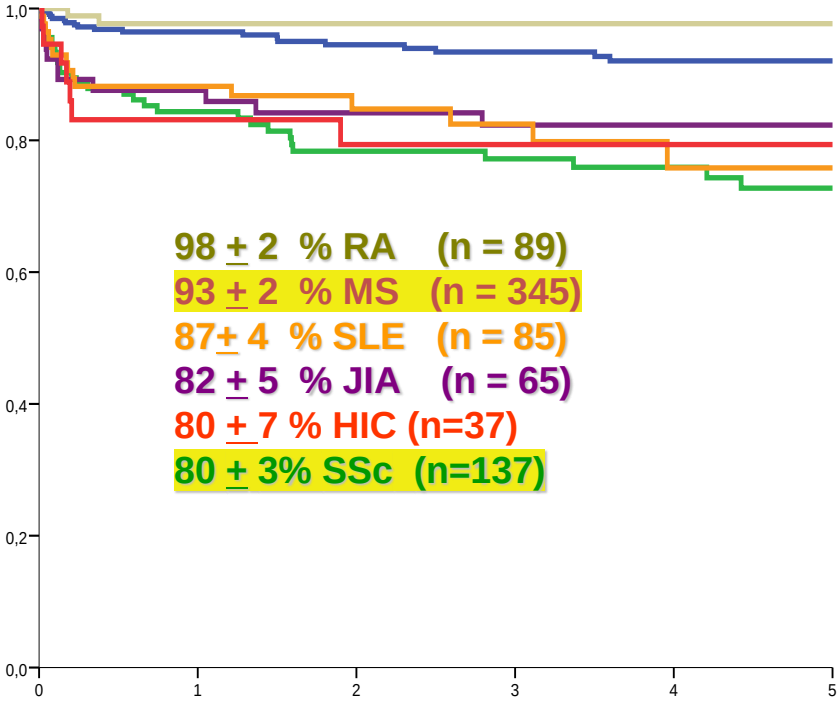
Special report Blood and marrow stem cell transplants in auto-immune disease: a consensus report written on behalf of the EULAR and the EBMT A Tyndall and A Gratwohl **BMT 1997**

Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases

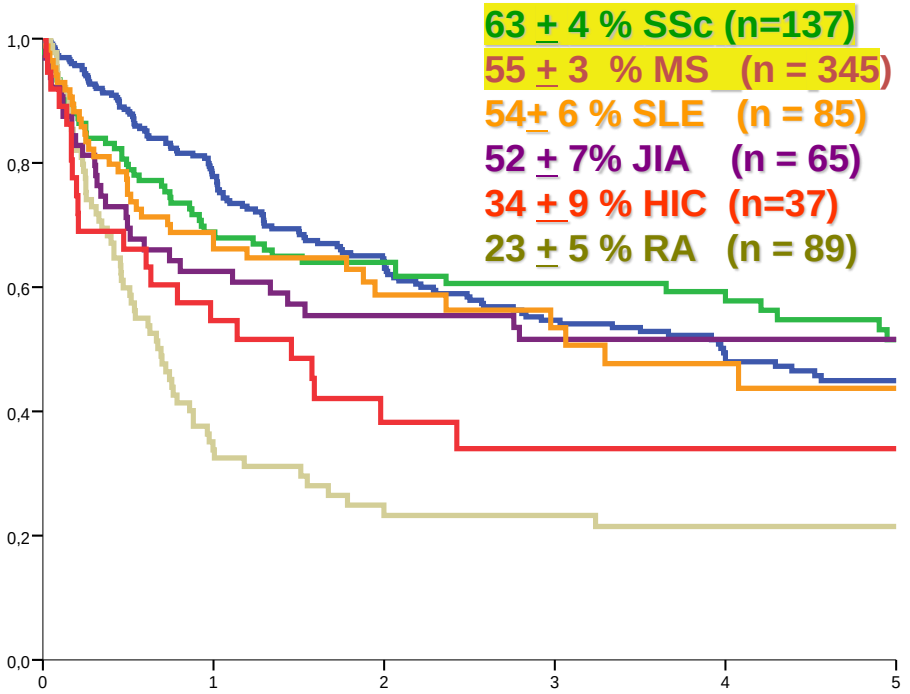
Dominique Farge,[1] Myriam Labopin,[2] Alan Tyndall,[3] Athanasios Fassas,[4] Gian Luigi Mancardi,[5] Jaap Van Laar,[6] Jian Ouyang,[7] Tomas Kozak,[8] John Moore,[9] Ina Kötter,[10] Virginie Chesnel,[11] Alberto Marmont,[12] Alois Gratwohl,[13] and Riccardo Saccardi[14]

haematologica | 2009; 95(2)

Overall Survival 3 yrs (n= 900)



PFS 3 yrs (n=900)

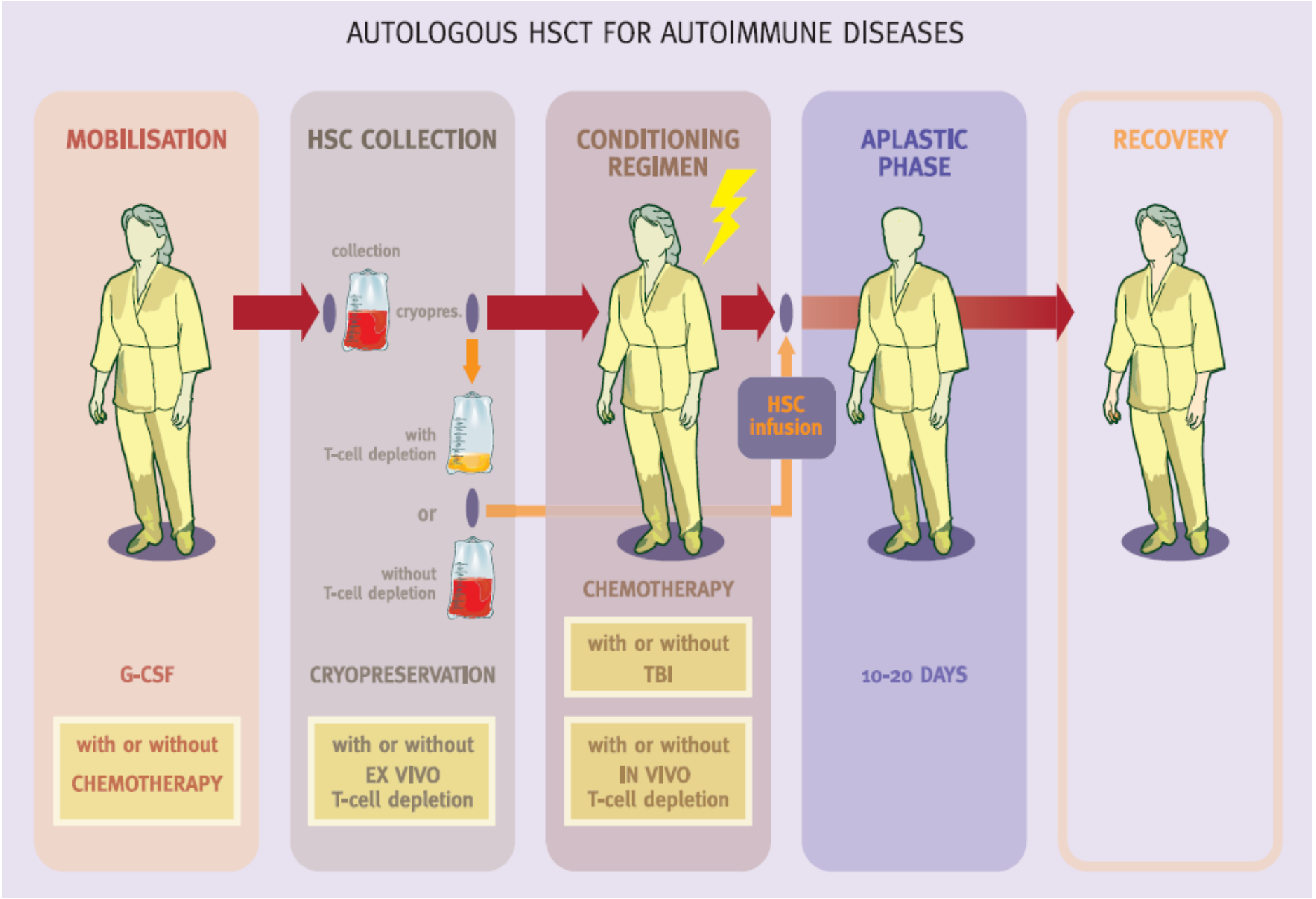


CENTRE EFFECT ON TRM, OS, PFS : According to activity center (n ≥ 13);

100 D TRM for SSC : 6 %

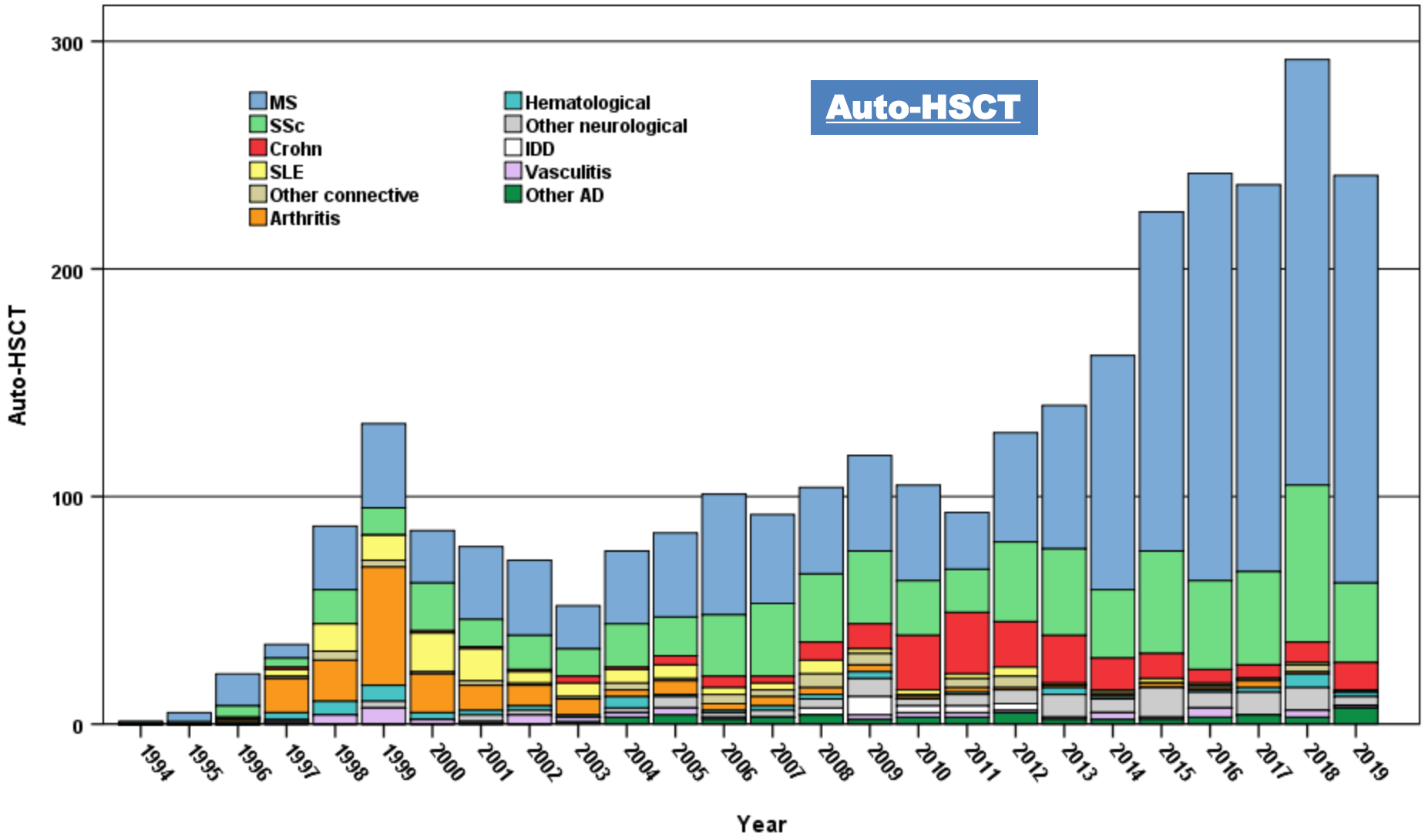
in 2019: 500 SSc in the EBMT registry

100-day transplant-related mortality*	P	HR	95.0% IC
Centers' experience	0.003	0.32	0.16-0.69
Diagnosis	0.03		
Multiple sclerosis		1.78	0.21-14.8
Systemic sclerosis		4.45	0.56-35.4



Saccardi R, Gualandi F, Autoimmunity, 2008

Auto-HSCT for AD: diagnosis per year
1994-2019 (n = 3018) – February 2020

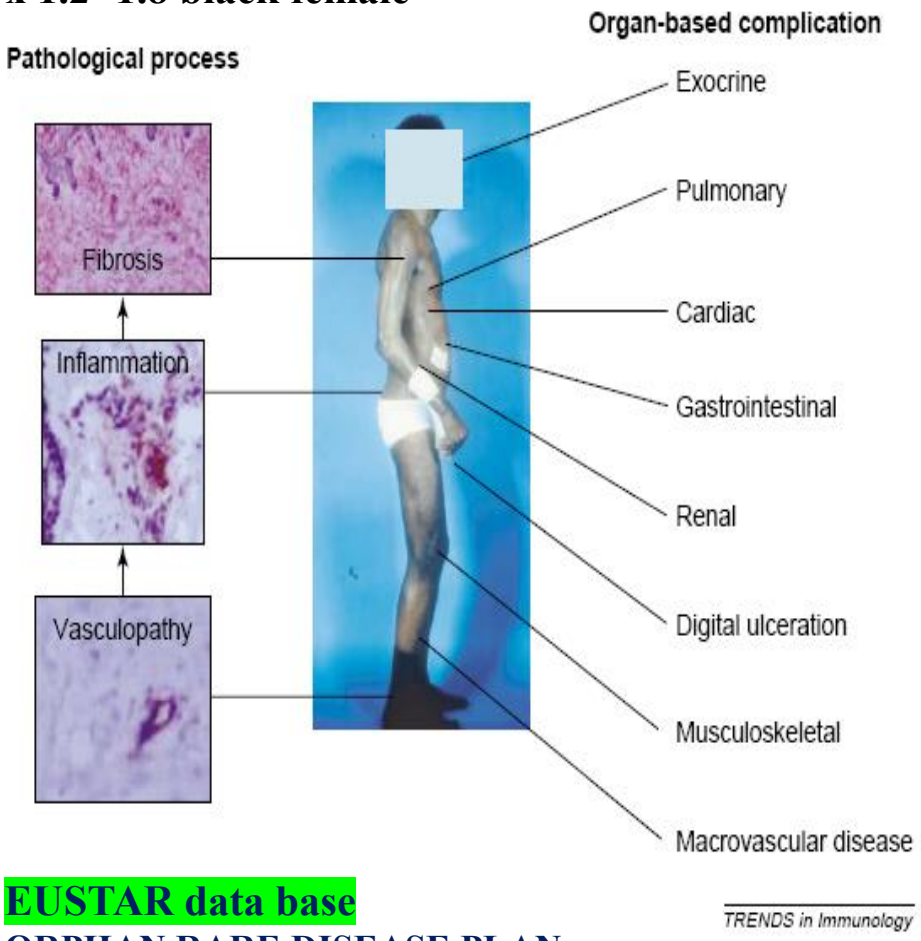


ADWP - Number of HSCT: 3260
EBMT Registry – February 2020

▶ **MULTIPLE SCLEROSIS**	**1603**
▶ **CONNECTIVE TISSUE**	**814**
SSc	638
SLE	118
PM-DM	18
Sjogren	4
Antiphosph. Syndrome	6
Other/Unknown	*30*
▶ **ARTHRITIS**	**191**
Rheumatoid arthritis	82
Juvenile chronic arthritis :	
**Systemic JIA*	63
**Other JIA*	18
**Polyarticular JIA*	17
Psoriatic arthritis	3
Other	*8*
▶ **INFLAMMATORY BOWEL**	**246**
Crohn's disease	200
Ulcerative colitis	4
Other	*42*
▶ **HAEMATOLOGICAL**	**128**
ITP	36
AIHA	29
Evans'	26
Other	37
▶ **VASCULITIS**	**62**
Wegener's	14
Behcet's	13
Takayasu	3
Polyarteritis	4
Churg-Strauss	2
Other/Unknown	26
▶ **OTHER NEUROLOGICAL**	**124**
NMO	26
CIDP	57
Myasthenia gravis	10
Other/Unknown	31
▶ **INSULIN DEPENDENT DIABETES**	**20**
▶ **OTHER**	**72**

Systemic Sclerosis: 1996 - 2020

Prevalence : **7 - 1580 / M** Incidence : **0.6 -19 / M**
x 1.2 -1.8 black female

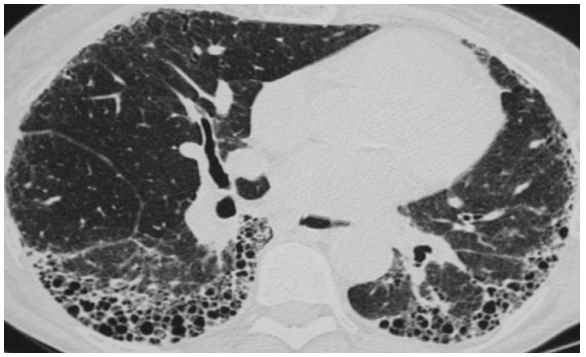


EUSTAR data base
ORPHAN RARE DISEASE PLAN
EURORDIS Patients association
ADWP EBMT registry

⇒ **Better awareness / pronostic factors : PHT**
⇒ **Earlier diagnosis EULAR 2013**
⇒ **Disease evaluation Activity criteria**

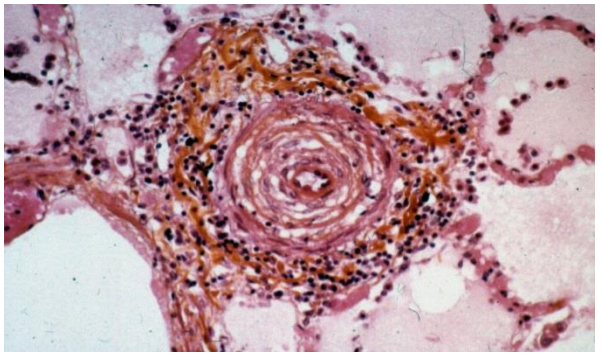
FIBROSIS

Skin, Lung digestive, heart



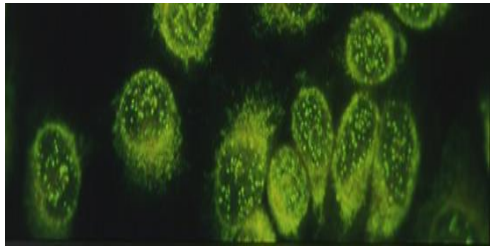
HYPERVASCULAR REACTIVITY

Raynaud, renal crisis, PHT



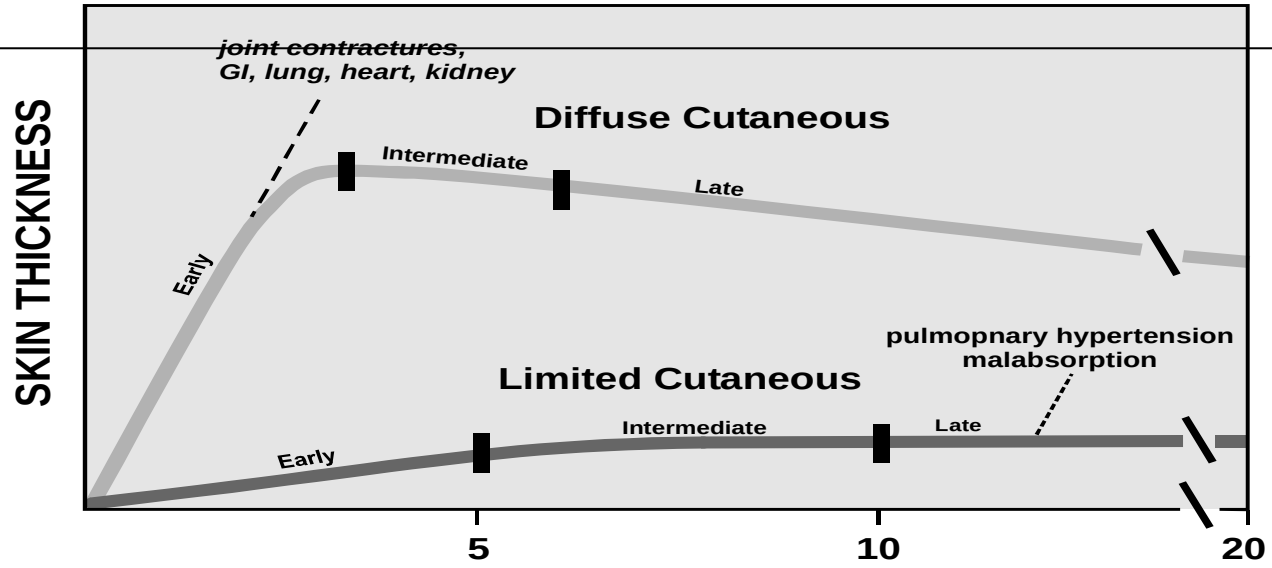
AUTOIMMUNITY

Anti Scl, Anti centromeres, Anti RNPo III



Systemic Sclerosis ? 1996-2019

Prevalence : **7 - 1580 / M** Incidence : **0.6 à 19 / million x 1.2 -1.8 black female**



Clinical prediction of 5yr survival in SSC *Fransen J et al Ann Rheum Dis 2012* *www.eustar.org*

	Univariate		Multivariate	
	OR	p Value	OR	p Value
Age	1.04	< 0.0001	1.03	0.002
Male gender	2.55	< 0.0001	1.93	0.061
Presence of urine protein	2.9	0.0009	2.29	0.063
ESR ≥25 mm/h	2.83	< 0.0001	1.89	0.038
DLCO <70%	3.11	< 0.0001	1.94	0.033

No of risk factors	Total no of patients	No of patients deceased	Mortality (%)	Mortality (%) Bryan *et al*[6]
0	509	12	2.2	7.1
1	349	45	12.9	22.8
2	168	55	32.7	54.8
3	23	7	30.4	100

The table presents the number of risk factors according to the prognostic model of 5-year survival for newly diagnosed systemic sclerosis.[6] The number of patients and mortality in the current study are compared with the mortality in the original study by Bryan *et al*.[6]

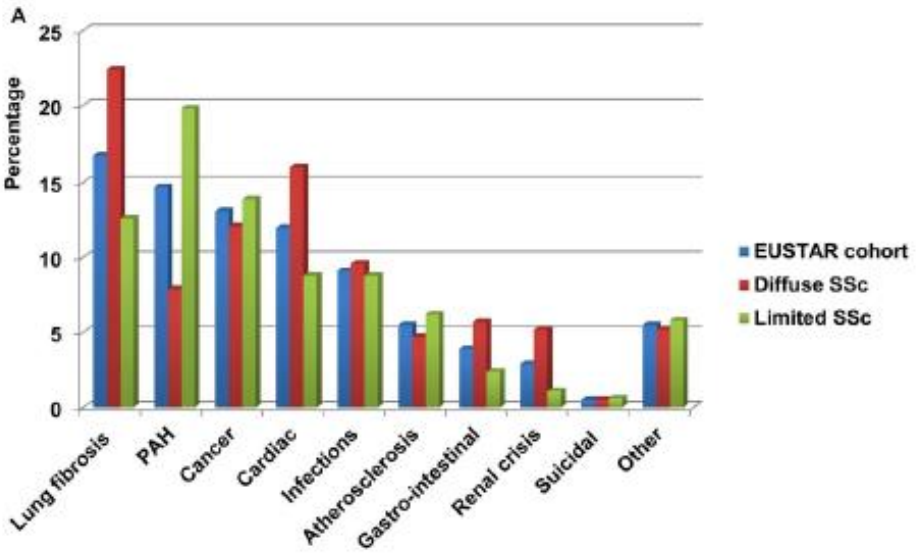
Mapping and predicting mortality from systemic sclerosis

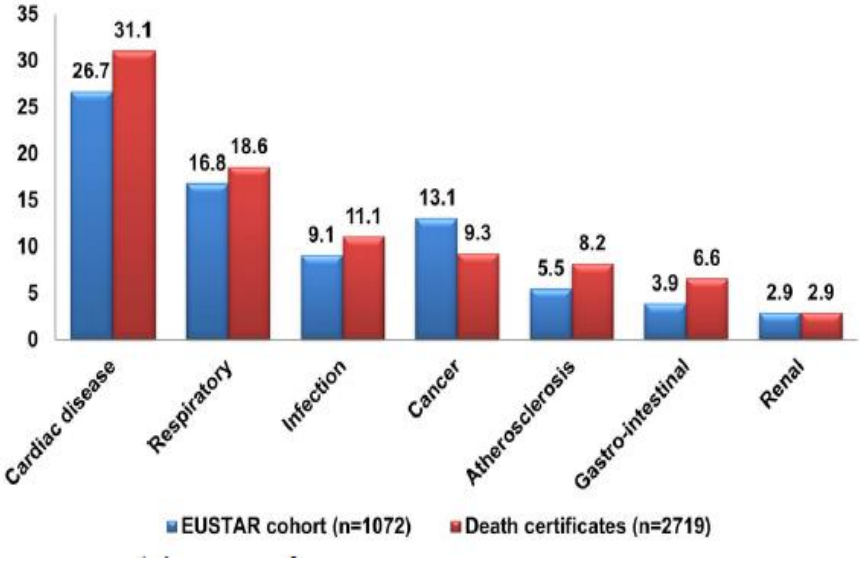
(http://dx.doi.org/10.1136/annrheumdis-2017-211448).

Muriel Elhai,[1] Christophe Meune,[2] Marouane Boubaya,[3] Jérôme Avouac,[1]

Primary heart disease: 30% of the deaths

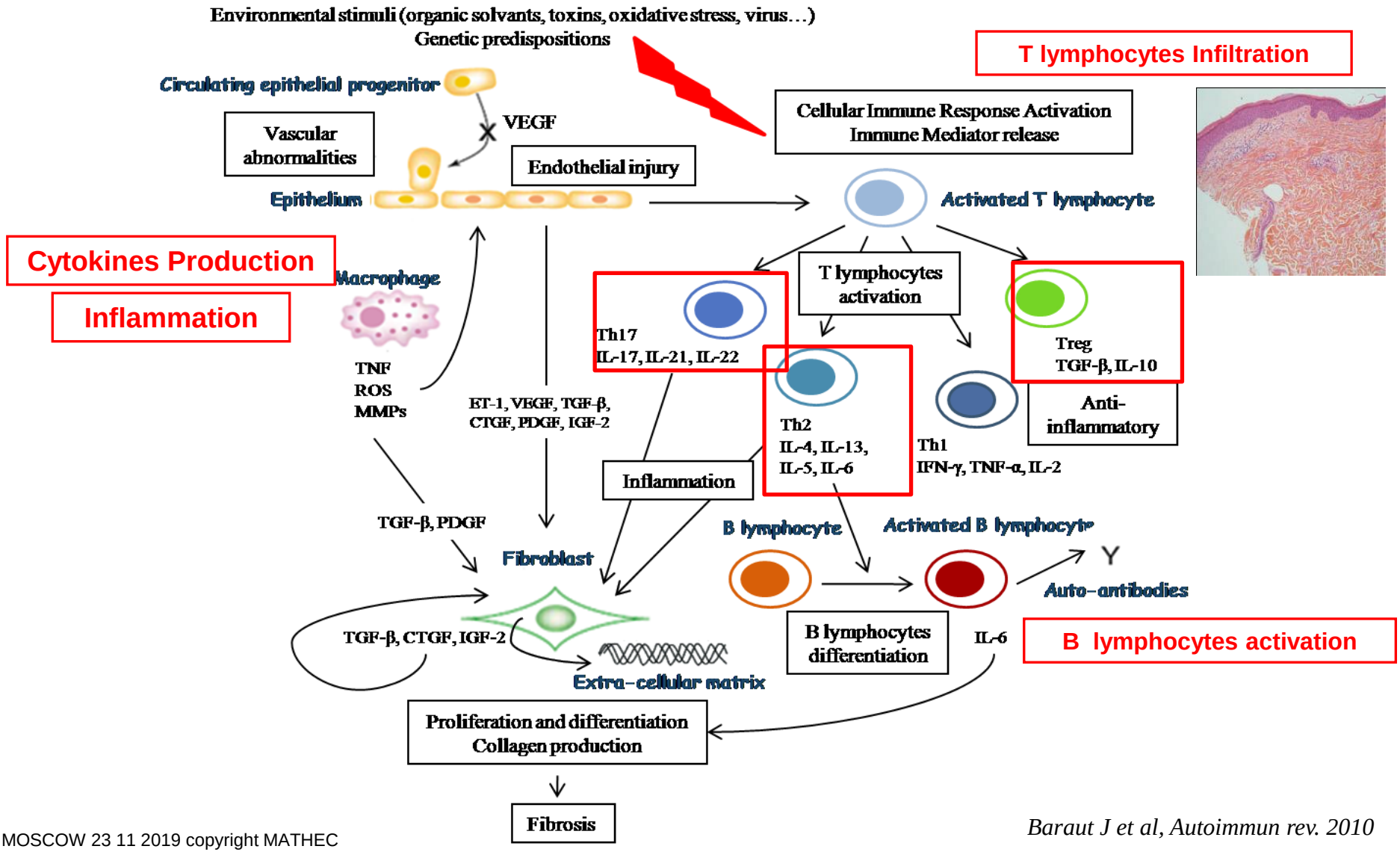
SMR : 1.03 (2000) to 0.6 (2011) per 10⁵ men and women





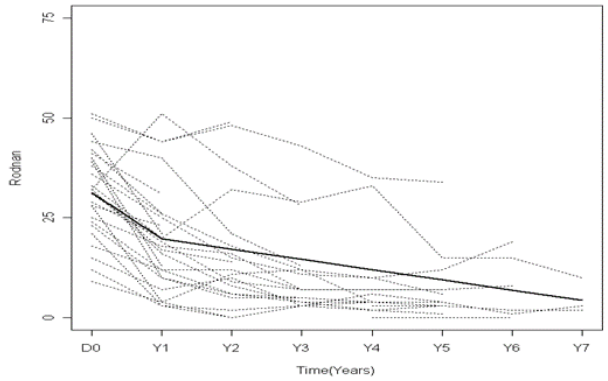
2011 : EUSTAR cohort deaths + French death certificates

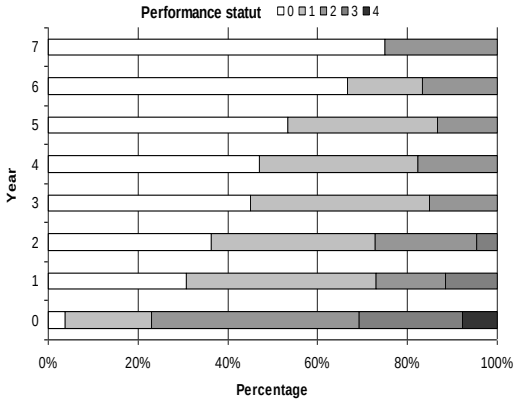
SSC PATHOLOGICAL PATHWAYS : VASCULAR DAMAGE + AUTOIMMUNITY + FIBROSIS



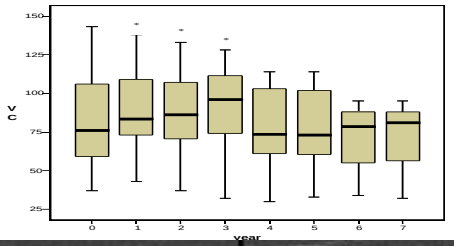
Baraut J et al, Autoimmun rev. 2010

CLINICO PATHOLOGICAL RESULTS from the phase I-II studies: Skin and lung fibrosis regression + Improved functionnal status

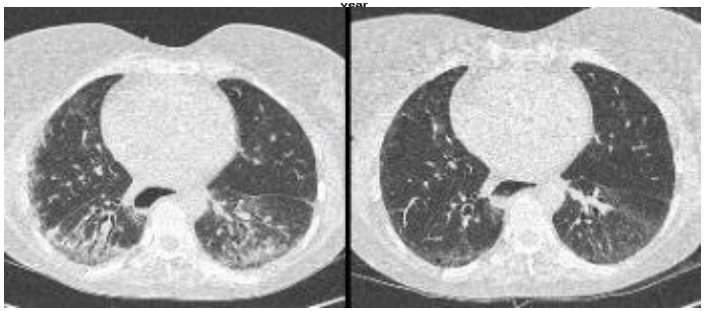




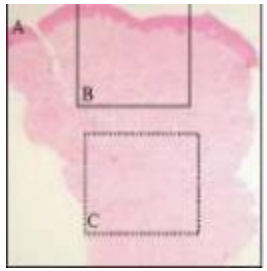
Farge et al BJH 002 , Ann Rheum 2004 , Vonk et al Ann Rheum 2008

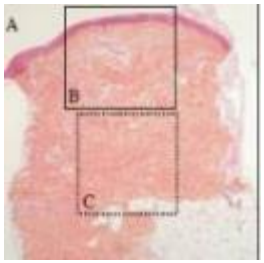


FVC

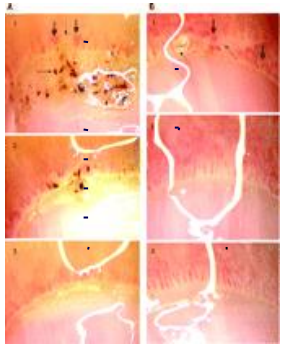


Launay D J Rheumatol 2009 VFC + DLCO + scanner

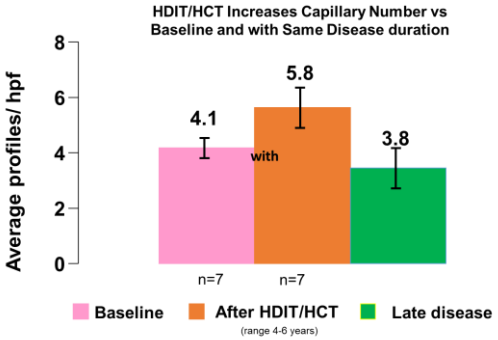




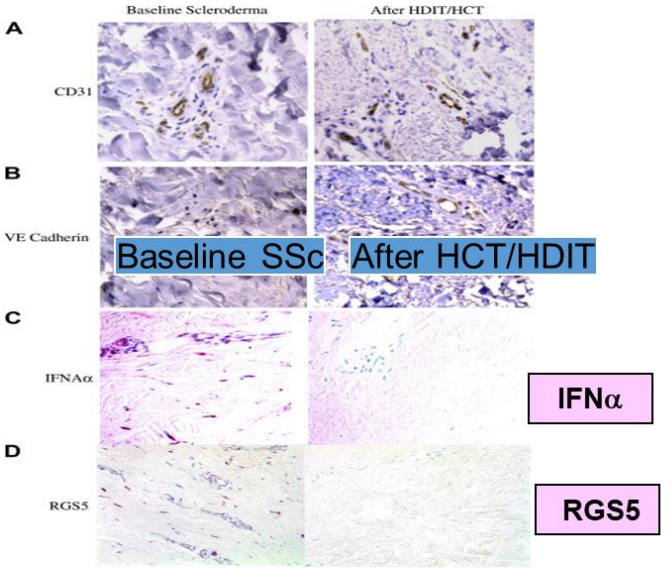
Verrecchia F, O Verola Rheumatology 2007



Aschwanden et al ARD 2008



Fleming JN et al 2008



Assassi et al 2010

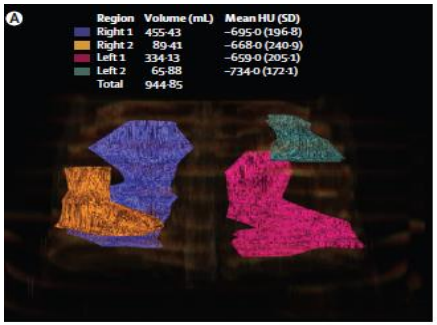
Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial

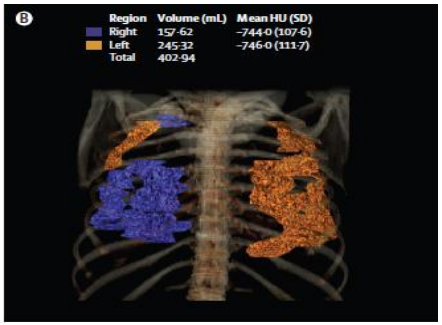
Lancet 2011; 378: 498–506

Richard K Burt, Sanjiv J Shah, Karin Dill, Thomas Grant, Mihai Gheorghiade, James Schroeder, Robert Craig, Ikuo Hirano, Karin Marshall, Eric Ruderman, Borko Jovanovic, Francesca Milanetti, Sandeep Jain, Kristin Boyce, Amy Morgan, James Carr, Walter Barr*

Age (years)	45 (32–58)	44 (26–54)
Sex (female)	9	8
Ethnicity		
White	7	8
Hispanic	1	0
Black	2	1
Disease duration from diagnosis (months)	13·6 (2–33)	18 (6–36)
History of Raynaud's	9	9
Modified Rodnan skin score	28 (6–48)	19 (4–45)
Systemic sclerosis		
Diffuse	8	7
Limited (with lung involvement)	2	2
Gastrointestinal		
Gastrointestinal reflux disease	10	9
Patulous (gaping) oesophagus	6	5
Small bowel involvement	1	0
Lung		
Forced vital capacity	62% (53–70)	67% (43–84)
Diffusing capacity of CO_2 corrected	58% (29–82)	75% (29–111)
Involvement on high-resolution chest tomography	7	8
Non-specific interstitial pneumonia	6	8
Usual interstitial pneumonia	1	0
Bronchiectasis	1	0
Honeycombing	1	0
Nodules or micronodules	0	3
Cardiac		
Abnormal electrocardiogram	8	2
Tricuspid annular plane systolic excursion (cm)	2·24 (NA)	2·42 (NA)
Cardiac catheterisation		
Pulmonary artery systolic pressure (mm Hg)	29 (4·5)	28 (6·9)
Mean pulmonary artery pressure (mm Hg)	20 (4·0)	19 (4·8)

	Before switch to transplantation				
	Cyclophosphamide group (n=9)		Transplant group (n=10)		p value
	Baseline	1 year	Baseline	1 year	
Predicted forced vital capacity (%)					
Mean (SD)	67% (17·0)	61% (19·8)	62% (15·0)	74% (15·7)	0·004
Median (range)	78% (43–84)	69% (35–83)	62% (36–85)	82% (52–96)	..
Rate of change (%)†	..	−9%	..	15%	0·006
Predicted total lung capacity (%)					
Mean (SD)	83% (14·8)	74% (18·7)	76% (14·6)	80% (17·9)	0·005
Median (range)	89% (59–99)	69% (45–95)	73% (57–102)	72% (62–104)	..
Predicted DLCO corrected for haemoglobin (%)					
Mean (SD)	75% (27·5)	74% (37·0)	58% (21·8)	69% (18·6)	0·36
Median (range)	80% (29–111)	73% (28–120)	58% (29–94)	67% (33–90)	..
Volume diseased lung (mL)‡					
Mean (SD)	877 (240·6)	985 (277·1)	823 (268·9)	551 (277·1)	0·001
Median (range)	961 (462–1195)	858 (808–1189)	850 (359–1095)	546 (240–1118)	..
Modified Rodnan skin score					
Mean (SD)	19 (13·7)	22 (14·2)	28 (13·6)	15 (7·9)	0·0004
Median (range)	16 (6–45)	22 (3–44)	30 (6–47)	16 (2–29)	..





Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis A Randomized Clinical Trial

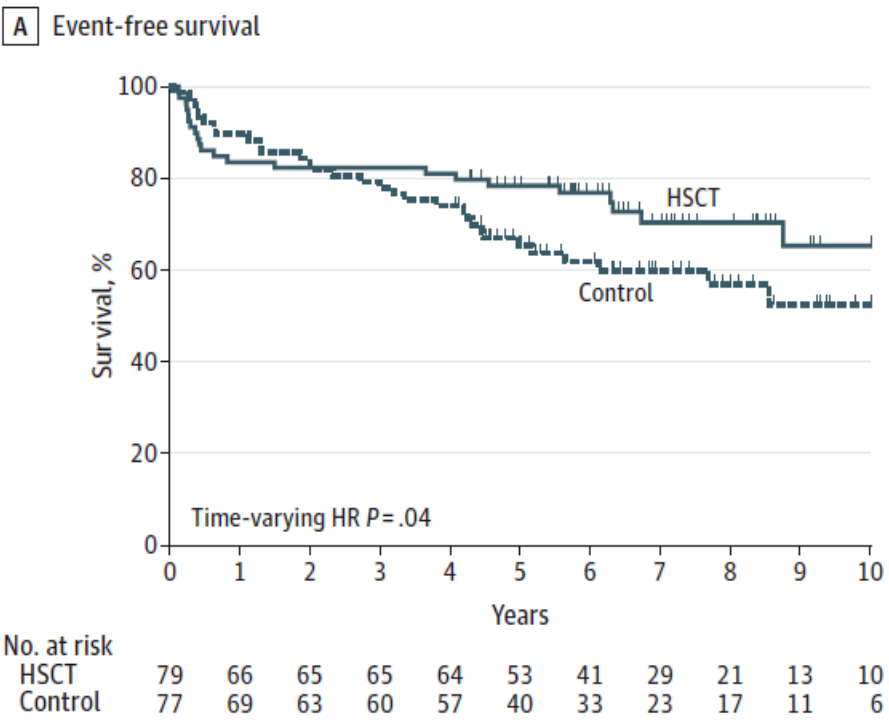
Original Investigation Research

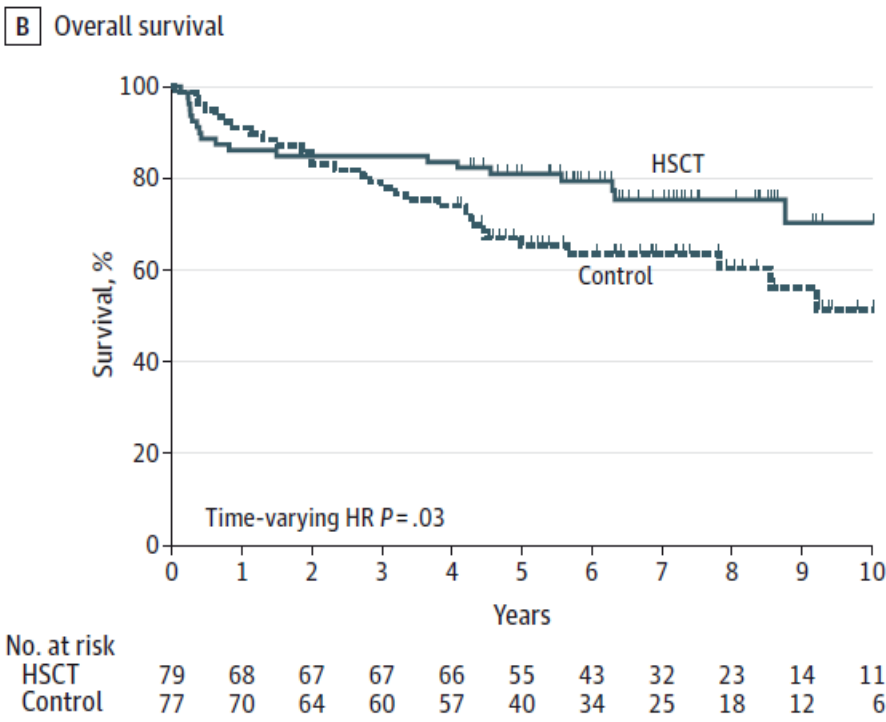
Van Laar JVL and Farge D et al

JAMA. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368

10% TRM in ASTIS: 15 yrs recruitement

Figure 2. Event-Free and Overall Survival During 10-Year Follow-up

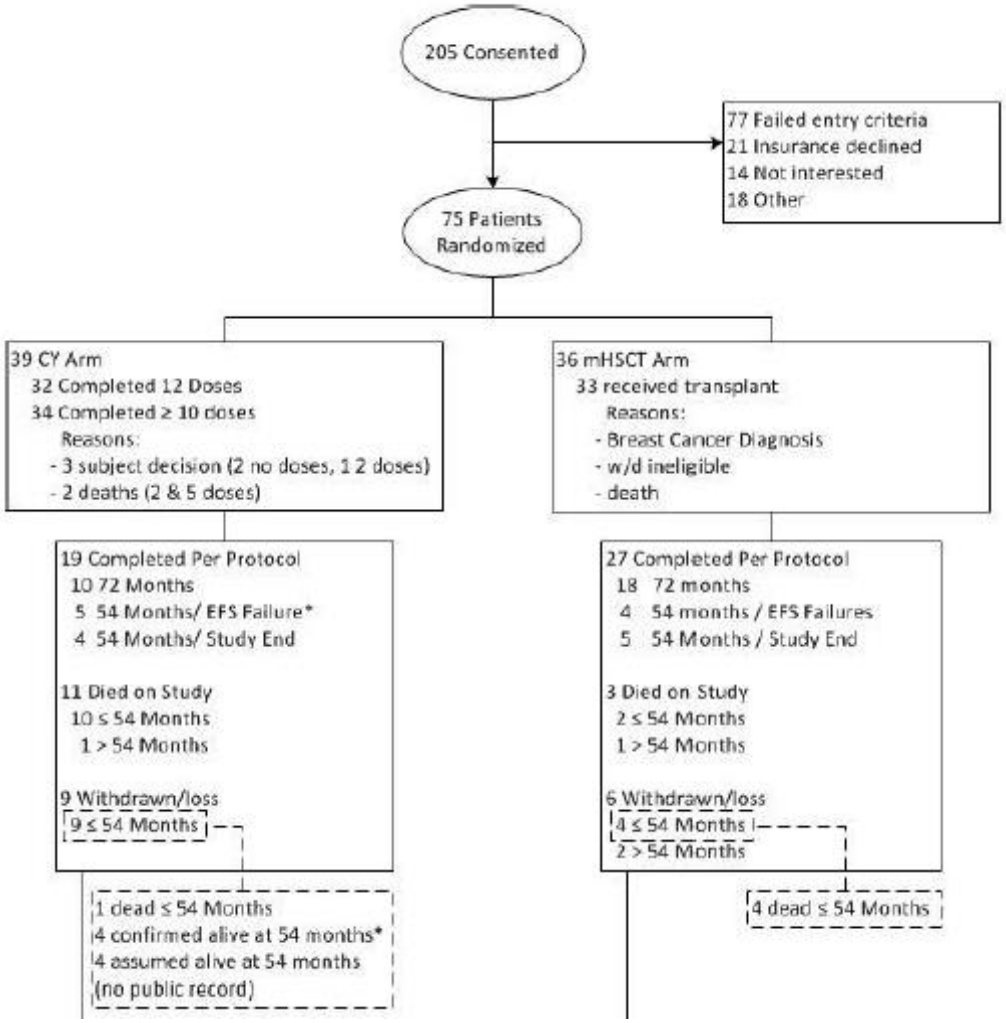




Hazard ratios (HRs) and 95% CIs were calculated by Cox regression. Hazard ratios were time-varying. The hazard (slope of the survival curve) in the hematopoietic stem cell transplantation (HSCT) group is initially high because of treatment-related mortality but gradually improves. At 1-year follow-up, the HR already favors the HSCT group, which leads to the crossing of the survival curves at 2 years' follow-up. A, Three-month follow-up: HR, 2.01 (95% CI, 0.74-5.49); *P* = .17; 6-month follow-up: HR, 1.35 (95% CI, 0.62-2.96); *P* = .45; 1-year follow-up: HR, 0.52 (95% CI, 0.28-0.96); *P* = .04; 2-year follow-up: HR, 0.35 (95% CI, 0.16-0.74); *P* = .006; 3- through 10-year follow-up: HR, 0.34 (95% CI, 0.16-0.74); *P* = .006. B, Three-month follow-up: HR, 2.40 (95% CI, 0.75-7.67); *P* = .14; 6-month follow-up: HR, 1.50 (95% CI, 0.61-3.68); *P* = .38; 1-year follow-up: HR, 0.48 (95% CI, 0.25-0.91; *P* = .02; 2-year follow-up: HR, 0.29 (95% CI, 0.13-0.65); *P* = .002; 3- through 10-year follow-up: HR, 0.29 (95% CI, 0.13-0.64); *P* = .002.

SCOT US trial Sullivan K. et al

N Engl J Med 2018;378:35-47.



STATISTICAL ANALYSIS

The trial was originally designed for 226 participants, with event-free survival as the primary end point. Low accrual prompted amendments, first to broaden entry criteria, then, ultimately, to reduce the sample size by changing the primary end point to the global rank composite score. Power for the new design with 114 participants.

board recommended stopping randomization at 75 participants.

2 types of analysis:

per protocol : only on data from pts who effectively underwent the all procedure

Intent to treat: real life analysis of data from all enrolled patients (**gold standard)**

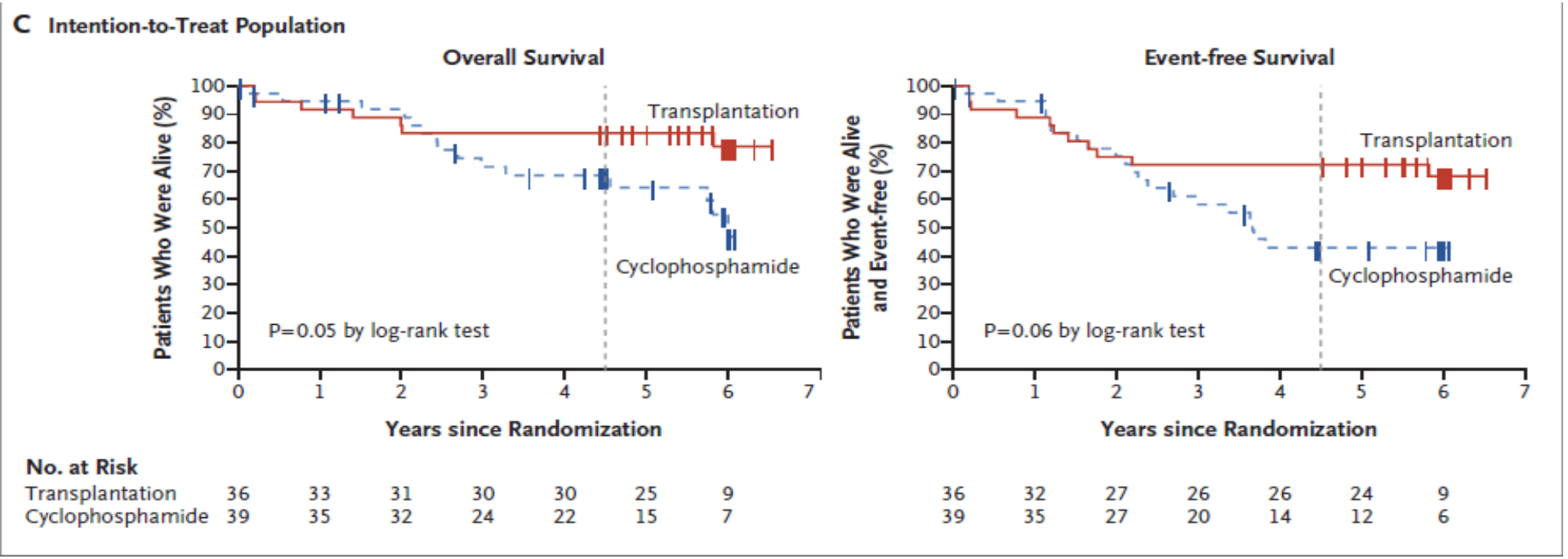
The intention-to-treat population was defined as all the participants who had undergone randomization. The per-protocol population was defined as participants who received a transplant or completed nine or more doses of cyclophosphamide. Because pulmonary and renal toxic effects are expected and reversible during the recovery period after autologous stem-cell transplantation, events of respiratory failure or renal failure were not evaluated in either treatment group until month 14 and month 8, respectively.

SCOT US trial Sullivan K. et al NEJM 2018

Death from any cause — no. (%)			
By 54 mo	6 (17)	11 (28)	0.28
By 48 mo	6 (17)	11 (28)	0.28
Treatment-related death — no. (%)§			
By 54 mo	1 (3)	0	0.48
By 48 mo	1 (3)	0	0.48

SCOT: per Protocol

A 72 mths : TRM : 6% ASCT vs 0% cyclo
Overall survival : 86% ASCT vs 51% cyclo



Health-related quality of life in systemic sclerosis before and after autologous haematopoietic stem cell transplant—a systematic review

Mathieu Puyade *et al.*

doi:10.1093/rheumatology/kez300

Study	No. of patients with data *vs* no. of patients in the study	Follow-up at time data collected, years	HAQ-DI					
			Baseline	After treatment				
				Absolute score Difference				
			Mean (s.d.)	Mean (range)	Mean (IC95)	% improved	*P*-value	Reported or calculated differences in scores
RCTs								
van Laar *et al.*, 2014 [20]	AHSCT (*n*=68/79)	2	1.3 (0.7)		−0.6 (1.1)[a]		0.02	−0.6
	CYC (*n*=73/77)		1.4 (0.8)		−0.2 (0.8)[a]			−0.2
Sullivan *et al.*, 2018 [21]	AHSCT (*n*=36/36)	4.8 (4.5–6.0)[b]	1.2 (0.6)			53%[c]	0.01	Unknown
	CYC (*n*=39/39)		1.4 (0.9)			16%[c]		
Non-randomized studies								
Farge *et al.*, 2002 [16]	AHSCT (*n*=9/11)	1 (*n*=7)	1.8 (0.0–0.8)[b]	0.4 (0.0, 1.6)				−1.4
McSweeney *et al.*, 2002 [15]	AHSCT (*n*=14/19)	1 (*n*=10)	2.1 (0.8–2.5)[d]		−1.7 (−2.3, 0.0)		0.002	−1.7
Nash *et al.*, 2007 [17]	AHSCT (*n*=26/34)	1.5 (*n*=23)	1.9 (0.3–2.9)[d]		−1.3 (−1.6, −0.9)		<0.001	−1.3
		4 (*n*=26)			−1.0 (−1.4, −0.7)		<0.001	−1.0
		7.5 (*n*=11)			−1.5 (−1.9, −1.1)		<0.001	−1.5
Moore *et al.*, 2012 [42]	AHSCT (*n*=10/10)	1 (*n*=8)	2.0 (1.8, 2.3)[b]	1.4 (1.1, 1.7)			<0.05	−0.6

SYSTEMIC SCLEROSIS

Autologous HSCT is efficacious, but can we make it safer?

Richard K. Burt and Dominique Farge

NATURE REVIEWS | RHEUMATOLOGY

doi:10.1038/nrrheum.2018.34
Published online DD Mon 2018

Trial	Patients treated with HSCT (*n*)	Regimen	End points	HSCT-related deaths	Incidence of cancer	Overall survival
ASSIST	10	Non-myeloablative • CYC 200 mg/kg • rATG 6.5 mg/kg	Clinical improvement (mRSS or FVC) ($P = 0.00001$)	0%	0% (0 of 10)	100% (2 years)
ASSIST regimen	89	Non-myeloablative • CYC 200 mg/kg • rATG either 6.5 mg/kg or 4.5 mg/kg	• OS = 78% • RFS = 70% • mRSS ($P = 0.0003$) • FVC ($P = 0.004$)	6%	0% (0 of 89)	78% (5 years)
ASTIS	75	Non-myeloablative • CYC 200 mg/kg • rATG 7.5 mg/kg	• EFS ($P = 0.006$) • mRSS ($P < 0.001$) • FVC ($P = 0.004$)	10%	1.3% (1 of 75)	• 82% (5 years) • OS ($P = 0.002$)
SCOT	33	Myeloabaltive • TBI 800 cGy • CYC 120 mg/kg • eATG 90 mg/kg	EFS (2005–2010) • ITT ($P = 0.06$) • PP ($P = 0.02$) GRCS (after 2010) • ITT ($P = 0.01$) • mRSS (ITT, $P = 0.05$; PP, $P = 0.01$) • FVC (ITT, $P = 0.3$; PP, $P = 0.5$)	6%	9% (3 of 33)	• 86% (54 months) • 54 months OS ($P = 0.28$) • 72 months OS ($P = 0.02$)

= > CONDITIONING LESS TOXIC:

CYCLO 60 mg/kg x 2 + Fludarabine 30mg/m2x3 or 60 mg/kg x 2 + Fludarabine 30mg/m2 x 3

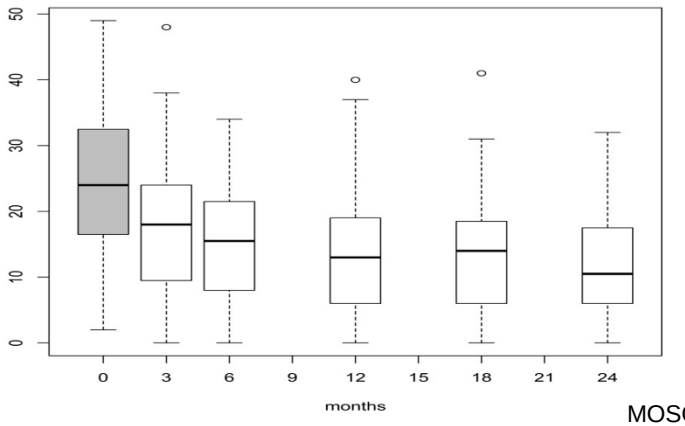
=> RATG 0.5 mg/Kg/D at D-5, 1.5 mg/Kg/D-4 to D-1for other days + steroids 1 mg/Kg/ D-5 to D-1

NISCC1 prospective non-interventional study from the ADWP EBMT

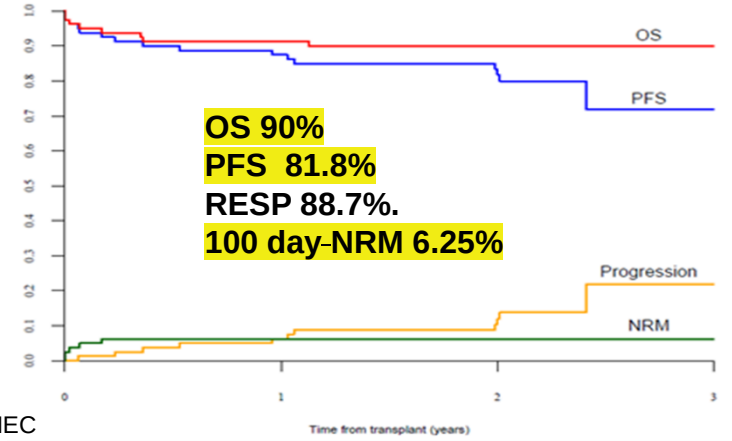
J Henes et al Hematology 2020

Baseline characteristics of study patients (n=80)	
Age (years), median (range)	43 (20 - 62)
Sex (Female), n (%)	56 (70%)
Disease duration from diagnosis (months), median (range)	23.8 (5.3 - 103.7)
Modified Rodnan Skin score (mRSS), median (range)	24 (2 - 49)
Abnormal thoracic computed tomography (HCTR) N/available (%)	66/77 (85.7%)
FVC, % of predicted value	72 (43 – 132)
DLCO, % of predicted value	59 (34.3 – 120)
Abnormal 24h Holter ECG; N/available (%)	12/60 (20%)
Pericardial effusion (echo); N/available (%)	5/79 (6.3)
LVEF by cardiac echo (%)	65 (47 - 84)
PASP by cardiac echo (mm Hg)	29 (8 - 59)
Anti-nuclear antibody positive	74 (92.7)
Anti-Topoisomerase I (Scl70) positive	57 (71.3)
Anti-centromere positive	3 (4.2)

Treatment		N (%)
Mobilization		
	CYC 2 g/m²	45 (57.7)
	CYC 4 g/m²	23 (29.5)
	Other dose	10 (12.8)
	G-CSF, yes	78 (97.5)
CD34-selection		
	Yes	35 (43.8)
	None	45 (56.3)
Conditioning regimen		
	CYC 200 mg/kg	72 (90.0)
	CYC other dose mg/kg	4 (5.0)
	CYC 100mg/kg + Thiotepa 10mg/kg	4 (5.0)
ATG	Yes	80 (100)
TBI	No	80 (100)
GCSF administration after conditioning		34 (43.0)



4 deaths
cardiac events



https://www.mathec.com/soignants/recommandations-de-bonnes-pratiques/

Phases I-II

Phases II-III

Recommandations

1997 Special Report : **Blood and marrow stem cell transplants in auto-immune disease: a consensus report written on behalf of the European League against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT)** **Tyndall** A, Gratwohl A.- BMT

2002 **Autologous bone marrow transplantation in the treatment of refractory systemic sclerosis: early results from a French multicentre phase I-II study.** Farge D et al., Br J Haematol.

2004 **Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry.** Farge D et al. Ann Rheum Dis.

2008 **Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis.** Vonk MC et al, Ann Rheum Dis.

2011 **Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial.** Burt RK et al, Lancet.

2014 **Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial.** van Laar JM and Farge D, et al JAMA.

2012 **Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation.** Snowden JA et al, BMT **GRADE 1 EVIDENCE**

2015 **SCT for severe autoimmune diseases: consensus guidelines of the European Society for Blood and Marrow Transplantation for immune monitoring and biobanking.** Alexander T, BMT

2017 **Cardiopulmonary assessment of patients with systemic sclerosis for hematopoietic stem cell transplantation: recommendations from the European Society for Blood and Marrow Transplantation Autoimmune Diseases Working Party and collaborating partners** Farge D, BMT

Indications et suivi des autogreffes de cellules souches hématopoïétiques dans les maladies auto-immunes et auto-inflammatoires : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire **(SFGM-TC)** Grégory Pugnet, Bull Cancer

Protocole National de Diagnostic et de Soins 2017 Sclérodermie Systémique

SCLEROSE EN PLAQUES

Prevalence /100 000 : 83 Europe, 117 France*

> 2 M au monde

SNC chez adulte jeune : 20-40 ans; 2F /1 H

1er handicap sévère non traumatique sujet jeune

Répercussion ++ au plan individuel et social

≈1 Milliard € (CNAMTS 2013)

Terrain génétique + FDR environnement,

Auto-inflammation + Auto-immunité (CD4+T)

Démyelinisation, lésion axonale, proliferation gliale

Manifestations cliniques variables

15% progressive d'emblée

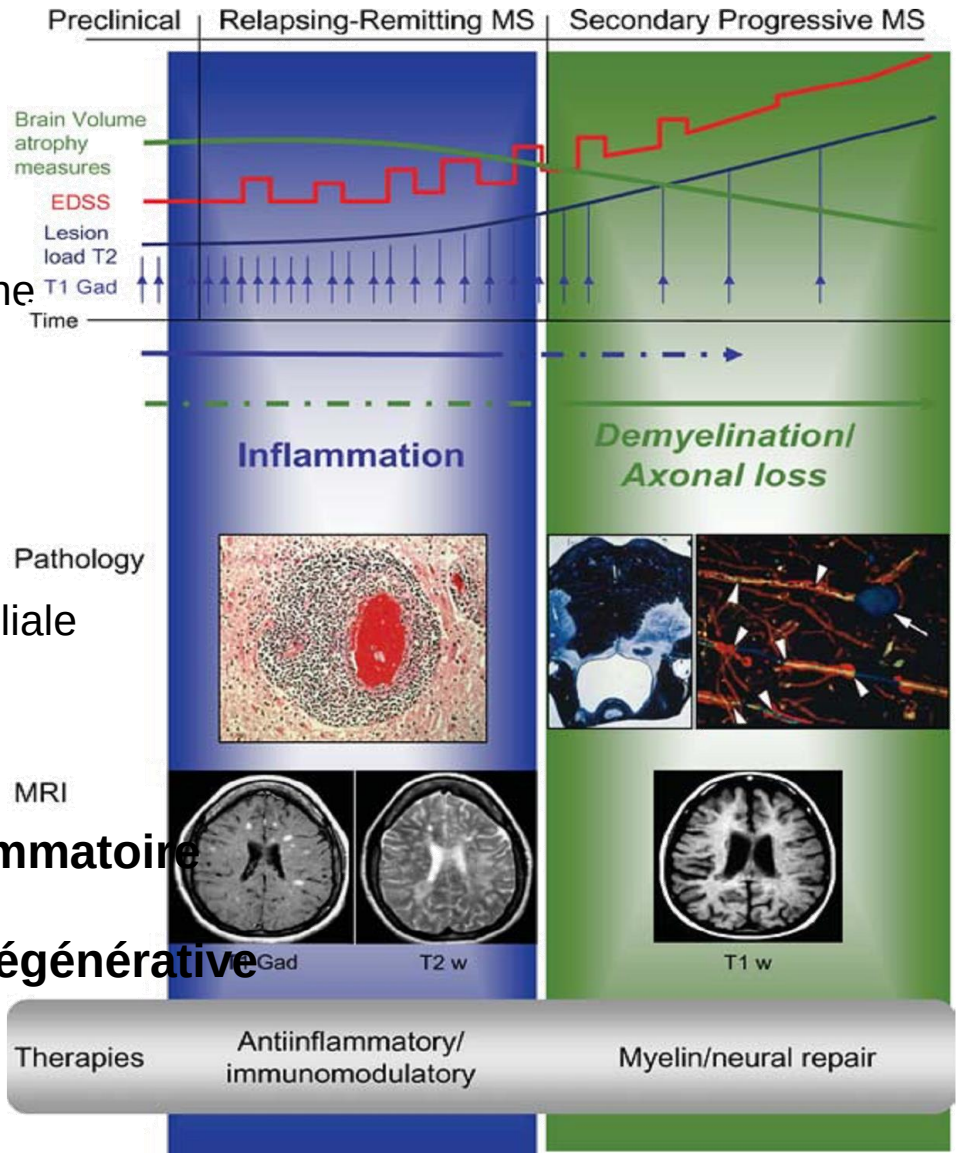
Phase initiale hétérogène: activité inflammatoire

formes agressives et autres bénignes

Phase progressive homogène: lésion dégénérative

quelle que soit l'agressivité initiale

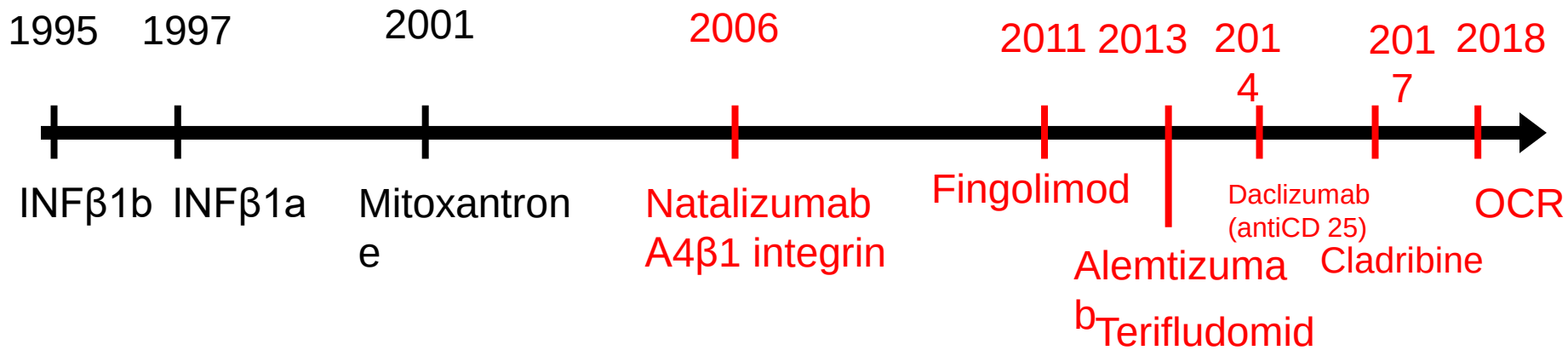
15% progressive d'emblée



Sospedra M . Annu Rev Immunol 2005 ; Reich DS NEJM 2018

Sniiram-PMSI . Revue d'Epidemiologie et de Santé Publique 2015

Traitements de fond et critères d'évaluation



- **Paramètres cliniques**

  Poussées : Taux annualisé de poussées, patients libres de poussée

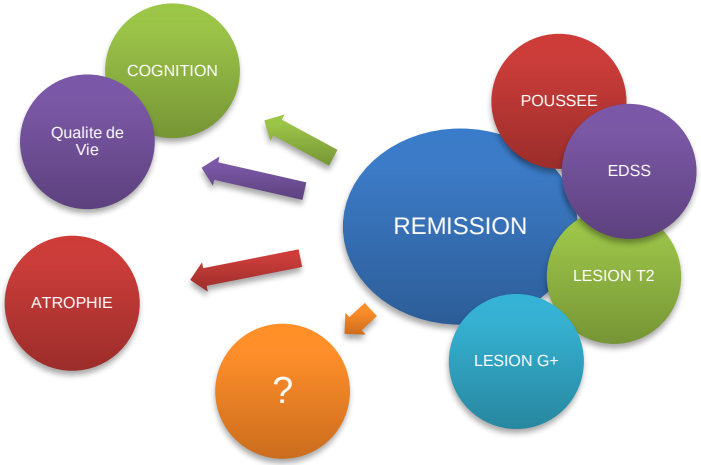
  Handicap: Aggravation / Amélioration de **EDSS** confirmée à 3 / 6 mois, AUC`

- **Paramètres IRM** : Ross L. PRENTICE Stat Med 1989;8:431-440

  Lésion T2: Volume lésionnel T2, Nouvelle lésion T2 ou augmentée de taille

  Atrophie cérébrale :

Modifications de la prise en charge de la SEP



Modification des objectifs thérapeutiques : Rémission

NEDA : Absence d'évidence d'activité de la maladie

Prise en compte des risques associés aux traitements

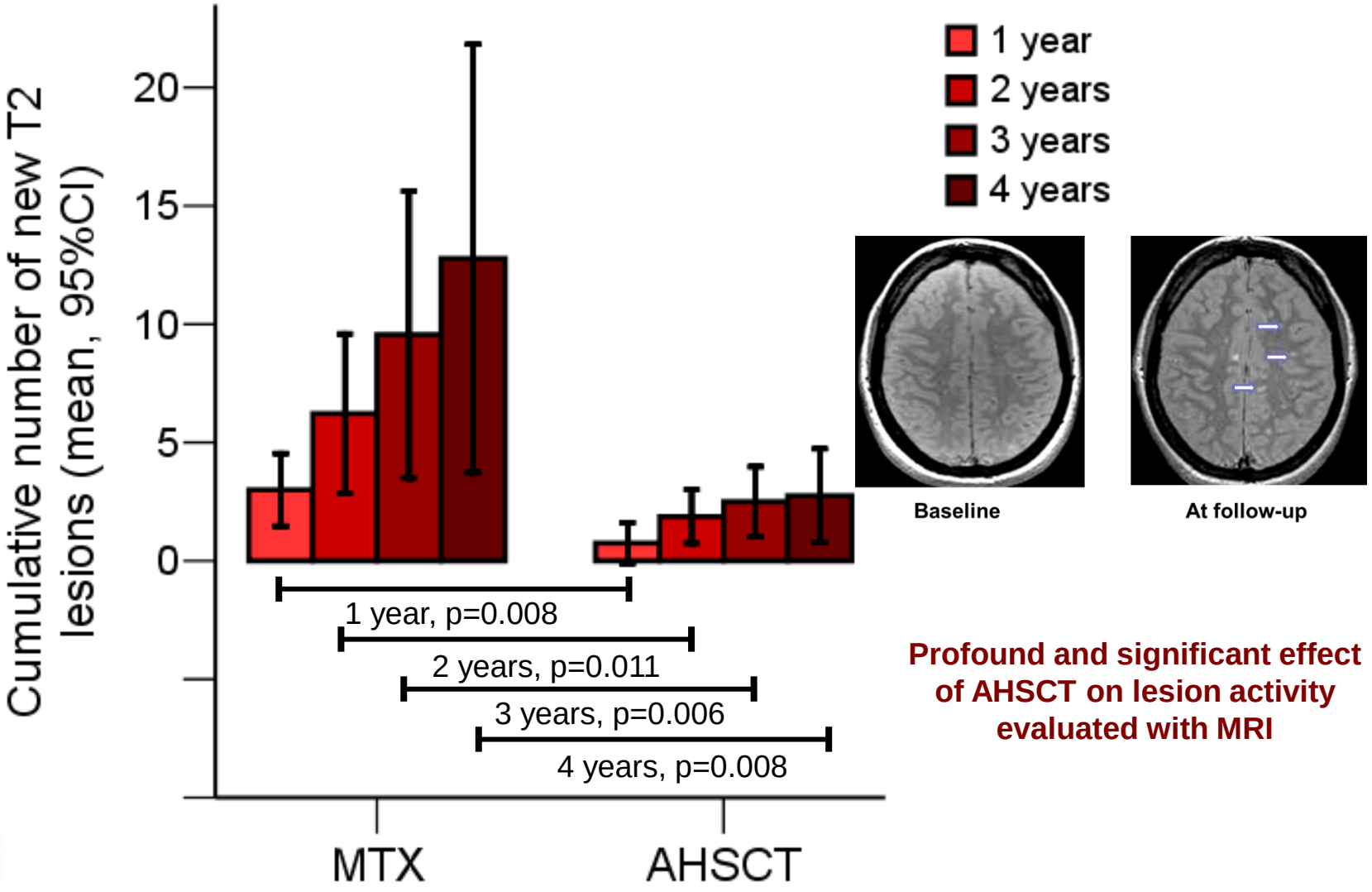
- Infectieux : LEMP, cryptocoque, BK, VZV, hépatite
- Néoplasie : Leucémie, mélanome
- MAI induites : thyroïdite, hépatite, PTI, glomérulopathie
- Rebond à l'arrêt des traitements suspensifs

=>plan gestion des risques et de stratification si possible

Cumulative nber of new T2 MRI lesions over 1,2,3 4 years

Mancardi et Al, Neurology 2015

Primary endpoint, ITT population



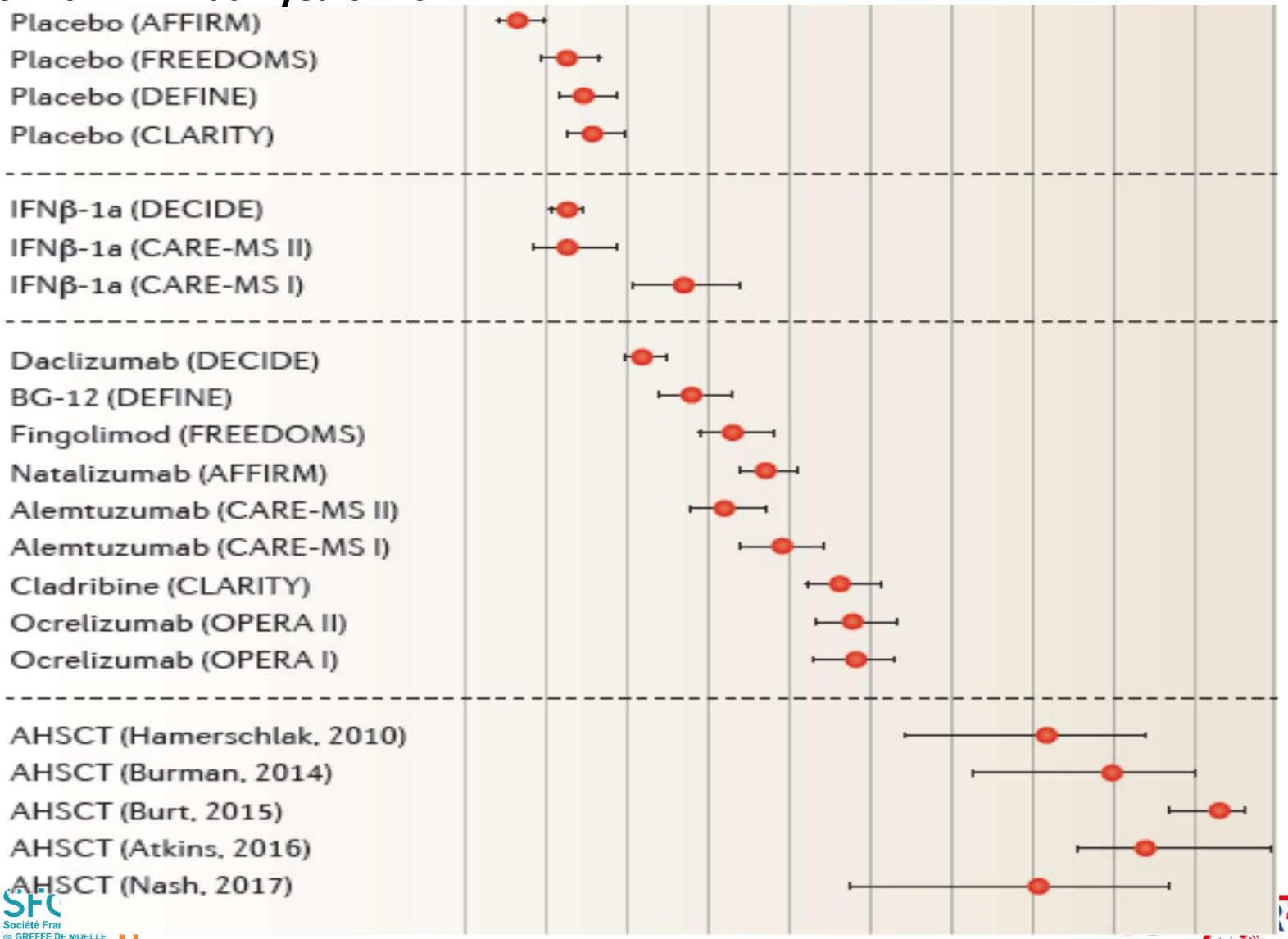
Profound and significant effect of AHSCT on lesion activity evaluated with MRI

No evidence of disease activity: new goals for RR-MS

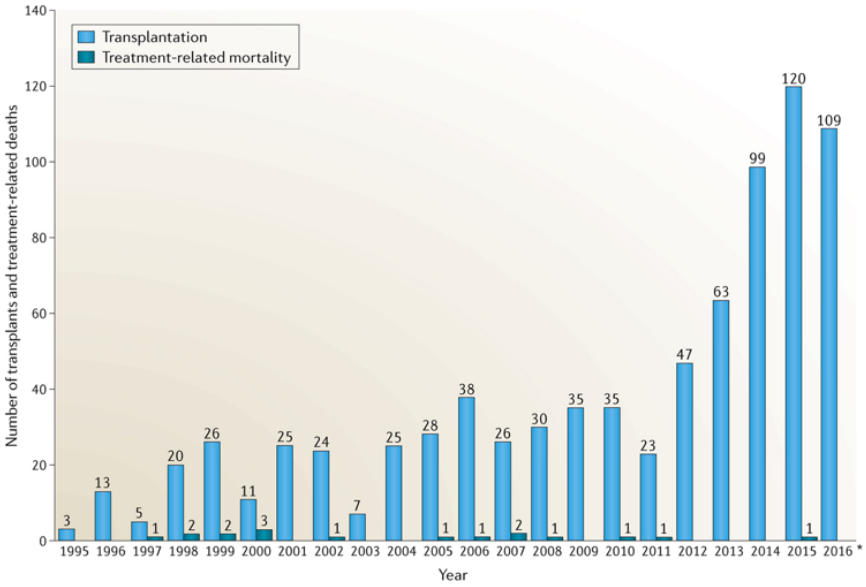
No relapse No ▲disability progression No new or active lesions on MRI

Sormani MP, et al. Mult Scler 2017

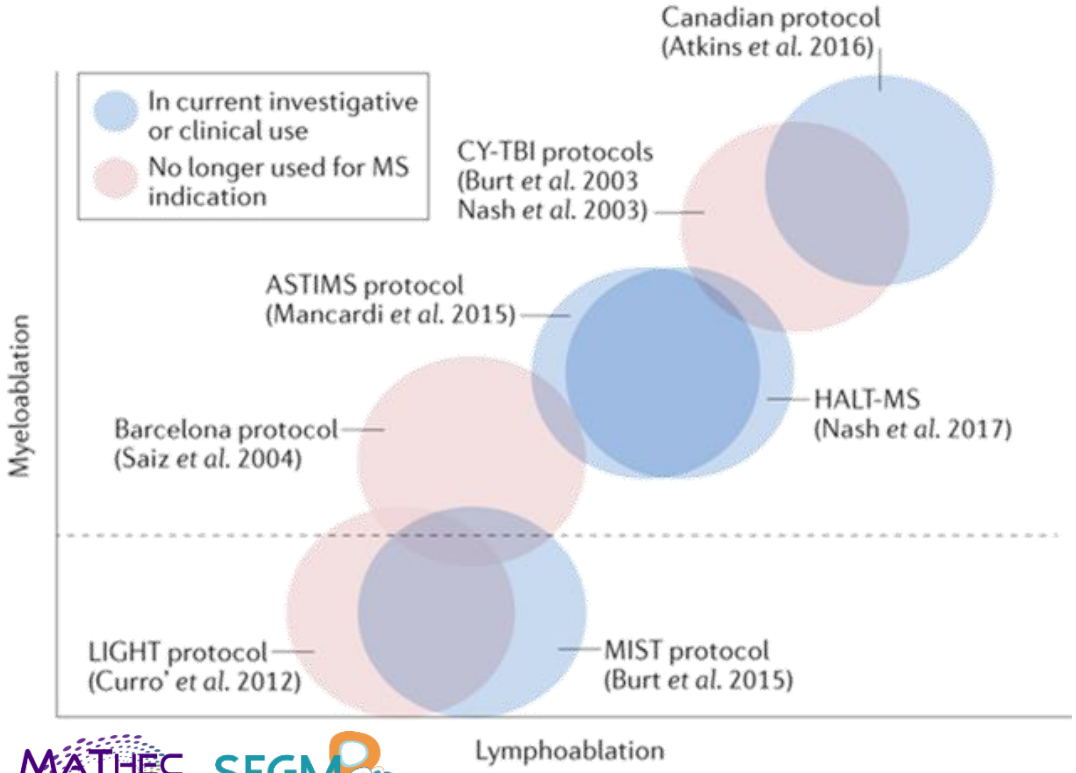
% of pts with NEDA at 2 years with



Nb of AHSCT procedures for MS and TRM



Estimated lymphoablative and myeloablative effects of AHSCT protocols for MS



Cyclophosphamide for mobilization

↓ incidence of Cytokine-related MS flare

↓ nber of Lymphocytes in the graft Disease-modifying effect

High intense regimen do not seem to provide benefits over intermediate/low

Irregular distribution of conditioning regimens and graft manipulation across the diagnosis

Is low intensity (Cyc/ATG) enough?

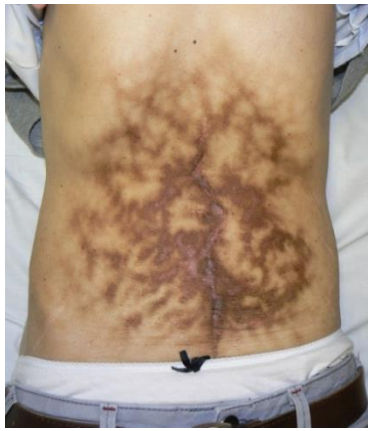
Recent data with intense regimens are missing

Muraro PA, et al. JAMA Neurol 2017;74(4):459-69.

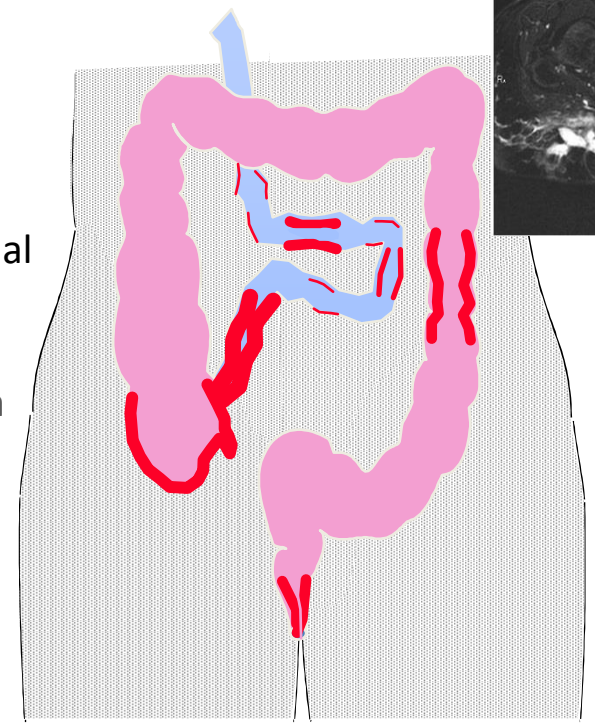
Crohn's Disease: 27-48 per 100 000

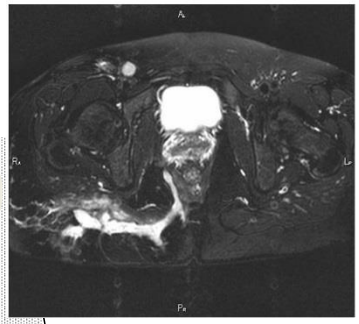
Smokers
Industrial countries
Family cases

Distribution
Ileal or ileo-caecal
Perianal
Colonic
Other: - Small bowel
- Gastroduodenal



Mechanisms
. Inflammation
. Obstruction





Symptoms
Pain
Diarrhoea
Discharge
Weight loss
Fistula
Fever

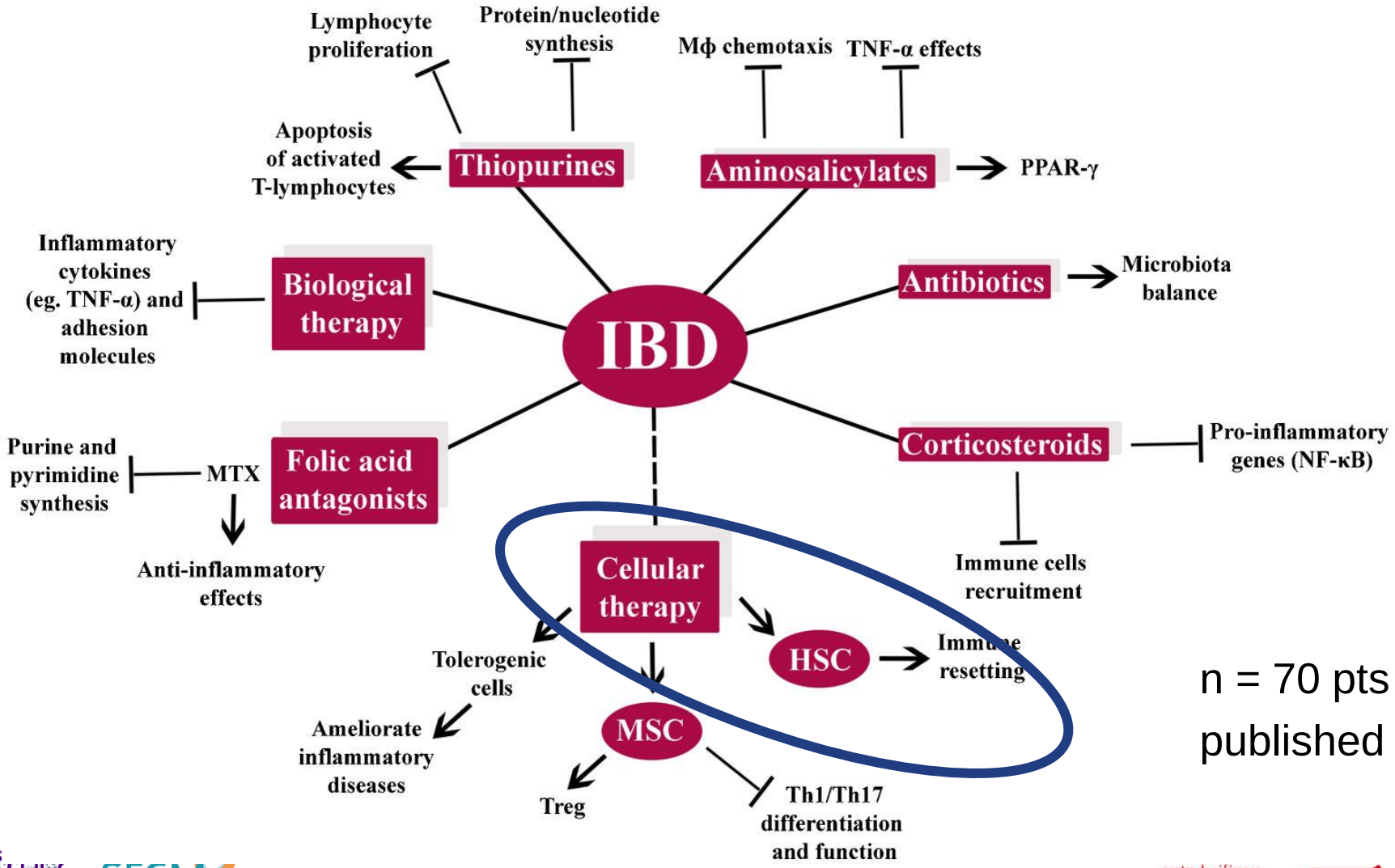
Malabsorption
Short bowel
BA malabsorption
No Ileocaecal valve
Colonic disease
Perianal fistulae
Other fistulae
Nutrition

- 30-50% pts require surgery
- % SMR: 1.19 (95% CI, 1.06-1.35) UC SMR: 1.38 (95% CI, 1.23-1.55) CD
- ↑┼ colorectal cancer, pulmonary disease, nonalcoholic liver disease

SMR: standardized mortality ratios. UC: ulcerative colitis. CD: Crohn's disease.

IBD : steroids, immunosuppressive and biologic control the symptoms only rather than cure the disease => surgery in the course.

1/3 pts fail antiTNF; 10% pts do not tolerate or primary non responders; 1/3 pts transient responders:



n = 70 pts published

IBD: inflammatory bowel disease.

Original Investigation

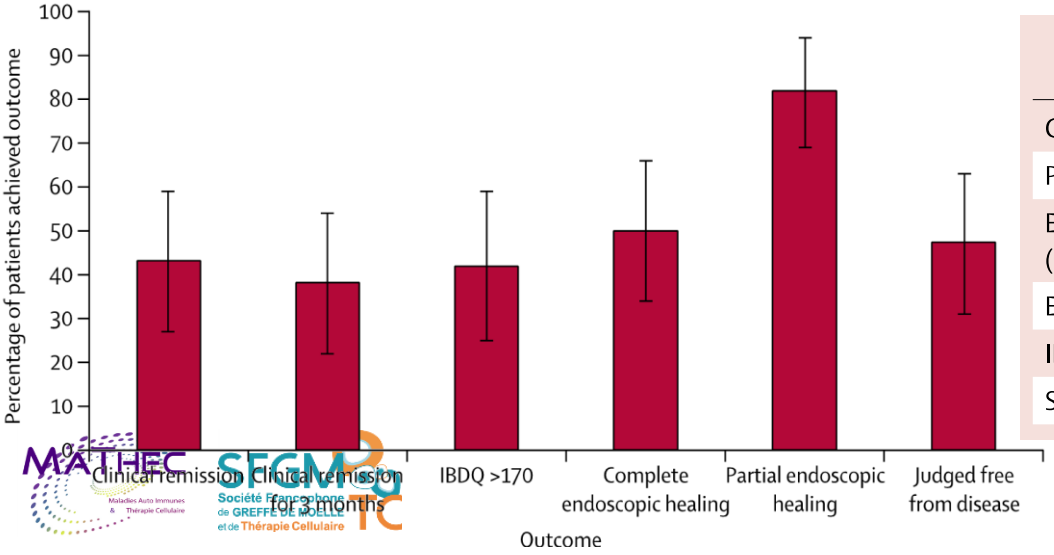
Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease

A Randomized Clinical Trial

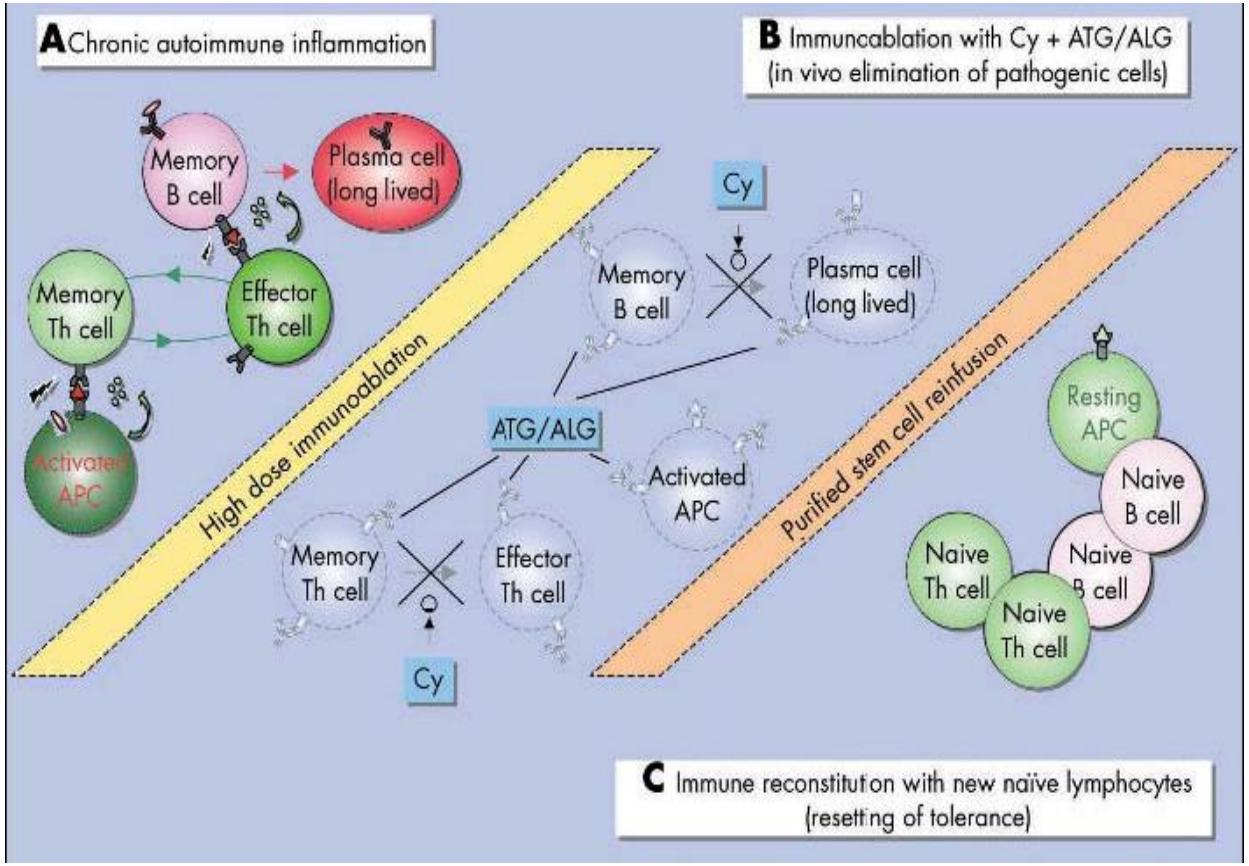
- **23 pts HSCT (** 76 SAE + 1 death) **22 standard treatment (controls)** 38 **SAE**

	No. (%)			
	HSCT	Control	Difference (95% CI), %	*P* Value
Sustained disease remission	2 (8.7)	1 (4.5)	4.2 (−14.2 to 22.6)	.60
Secondary outcomes				
No active treatment	14 (60.9)	5 (22.7)	38.1 (9.3 to 59.3)	.01
CDAI <150	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.052
Free of active disease	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.054

Combined HSCT pts at any time during the ASTIC program *Lindsay JO, et Lancet Gastroenterol 2017*



	Baseline	1 year	p value (paired)
CDAI (n=37)	336·73 (112·26)	195·95 (133·29)	<0·0001
PRO-2 (n=37)	24·03 (10·56)	12·45 (9·78)	<0·0001
EQ-5D index (n=27)	0·752 (0·104)	0·801 (0·164)	0·033
EQ-VAS (n=29)	53·55 (21·42)	72·72 (22·50)	0·00016
IBDQ (n=30)	119·57 (33·54)	152·23 (45·15)	<0·0001
SES-CD (n=36)	14·11 (9·03)	5·44 (6·57)	<0·0001



Radbruch A, et al.
Ann Rheum Dis 2004

Yes we can induce reset of tolerance!

Elimination of: −
- autoreactive T-effector cells
- long-living plasma cells
- antigen-presenting cells

\+
- Increased T-regulatory cells
- Restoration of thymic function
- Normalization of T-receptor repertoire
- Reduced auto-antibodies
- Long-lasting lymphopenia

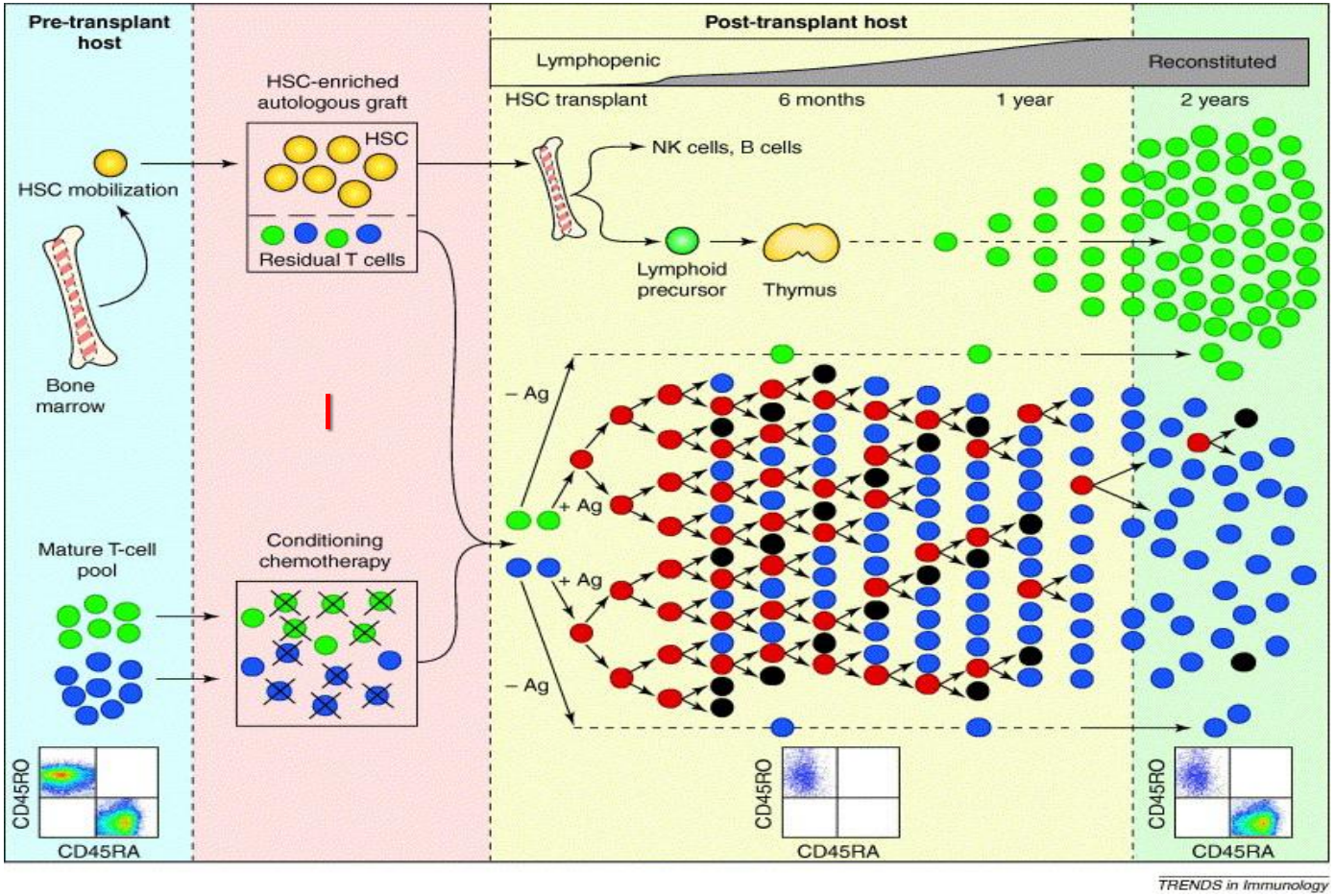
AUTOIMMUNITY — TOLERANCE

Immune reconstitution after AHSCT: renewal of the immune repertoire

Type I : replacement of mature T/B memory repertoire with naïve, non-pathogenic cells

Type II : reinstatement of Immune Regulation increased nb and/or function of regulatory cells

immunophenotyping, TREC (Thymic output), **CDR3 spectratyping / nucleotide sequencing**



Naïve

Memory

Senescent

Farge Arthritis Rhum 2008 (n = 7), Barault BMT2013 (n = 7), Michel BMT 2016 (n=7), Farge Hemato Oncol 2017 (n=12), Coelho Blood Advances 2018

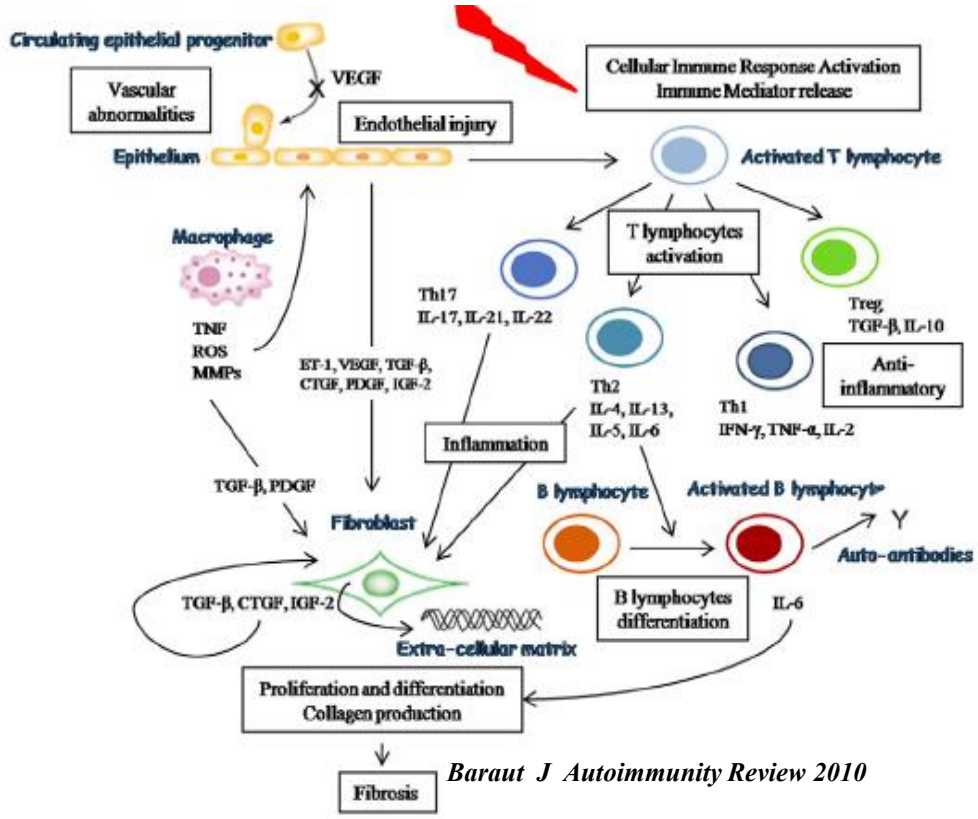
↑ **T regulatory cells Foxp3**

↑ **naive B cells after HSCT**

↑ **$CD4^+CD25^{high}FoxP3$** ↑**regulatory T cells**

↑ **$CD8^+FoxP3$** ↑ ↑ **suppressive function**

DETERMINANTS OF IMMUNE RESPONSE AFTER HSCT

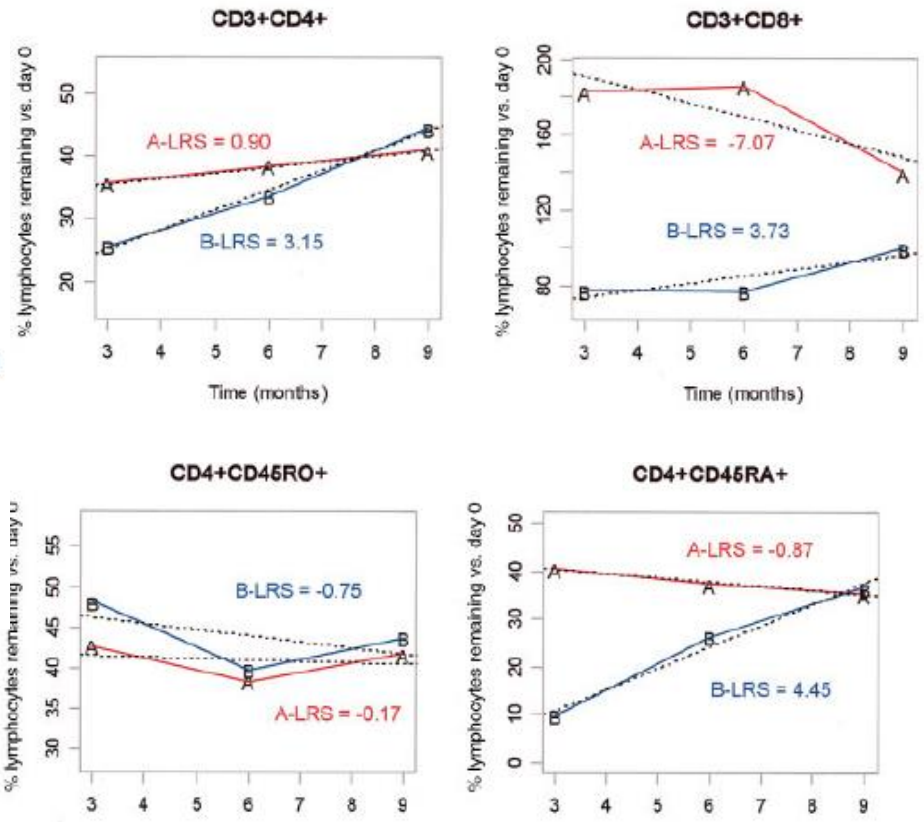


Baraut J Autoimmunity Review 2010

PATIENTS (n =14) : ns

Rodnan : 17 ± 10 vs 43 ± 7, p < 0.03

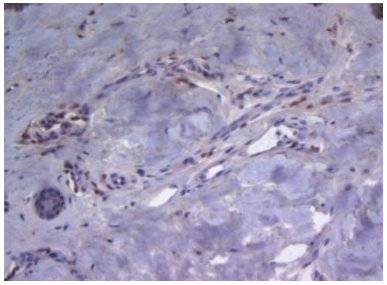
SHAQ : 0.8 ± 0.7 vs 2.3 ± 0.2, p < 0.05



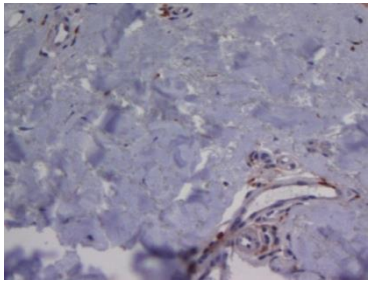
CD19+ et CD20+ et AC anti SCL70 (r = 0.27, p<0.05)

Lymphopenie T CD4+, CD4+CD45RA+: favorable SSc

TREC /CRP: rp< 0.001, TREC / CD19+: rp< O.OO1 (PR, SEP)



CD4 +



CD 25 +

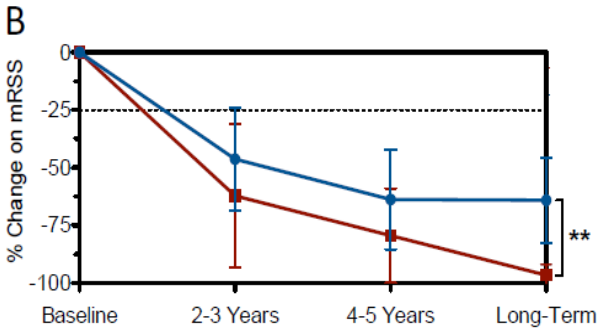
Barault 2013

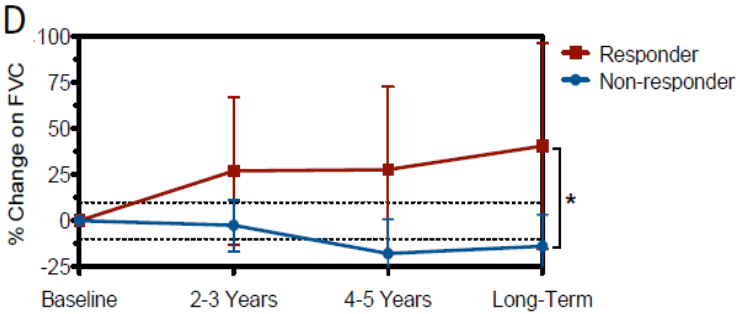
Farge Arthr Rheum 2005

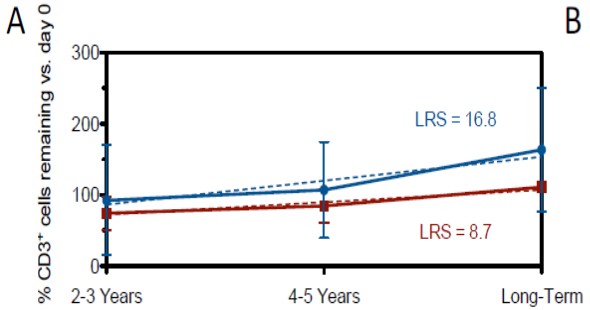
Long-term immune reconstitution and T-cell repertoire analysis after autologous HSCT in systemic sclerosis patients

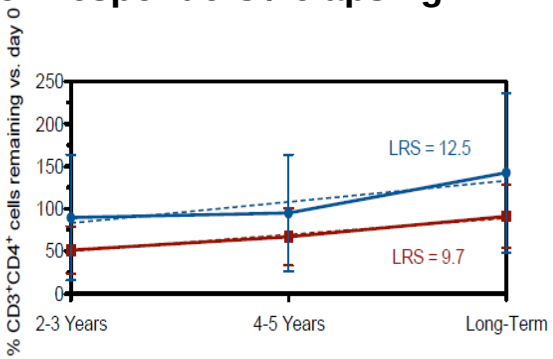
Farge et al. Journal of Hematology & Oncology (2017) 10:21

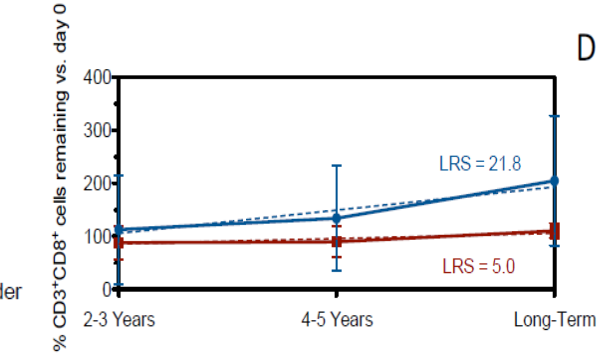
Long-term mRSS fall > 25% more pronounced in those improving FVC% > 10% (*P*=0.026
Pretransplant B cell clonal expansion + faster T-cells IR after aHSCT in non-responders /relapsing

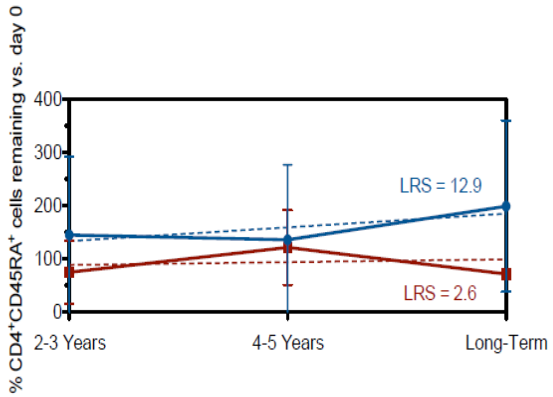


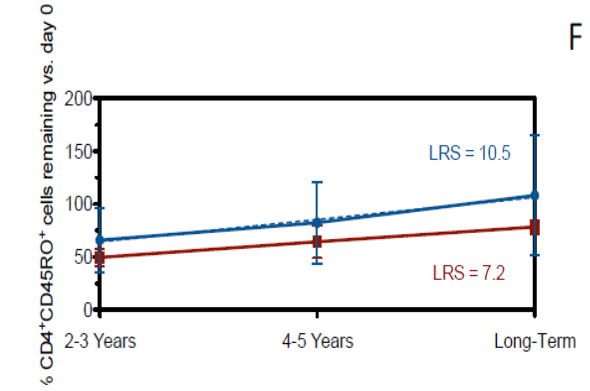












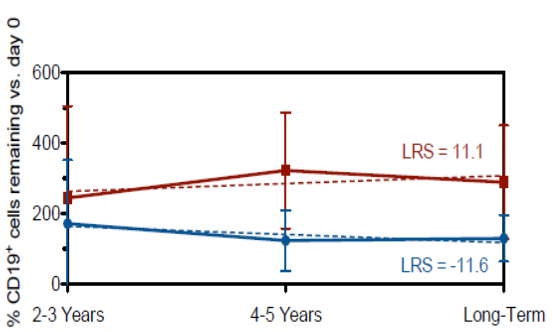


Table 3 Anti-scl-70 autoantibodies

	Group A patients					Group B patients				
	1	2	3	4	5	1	2	3	4	5
Anti-Scl-70 antibodies, U/ml										
Baseline	120	+[a]	0	102	+[a]	0	+[a]	39.1	130	21.3
2–3 years	32.9	0	0	0	390	0	240	31.1	106.5	0
4–5 years	11.6	0	0	0	257	0	352	15.9	+[a]	0
Long term	0	0[b]	0[b]	0	>8[b]	0	3.8[b]	>8[b]	250	0

Anti-Scl-70 antibodies were measured at pre-transplant period (baseline) and sequentially during follow-up by enzyme-linked immunosorbent assay as described in methods section. Quantified results are expressed in arbitrary units/ml as previously published ([8])
[a]Positive for Anti-Scl-70 antibodies
[b]Anti-Scl-70 antibodies levels measured by BioPlex ANA Screen

Farge *et al. Journal of Hematology & Oncology* (2017) 10:21
DOI 10.1186/s13045-016-0388-5

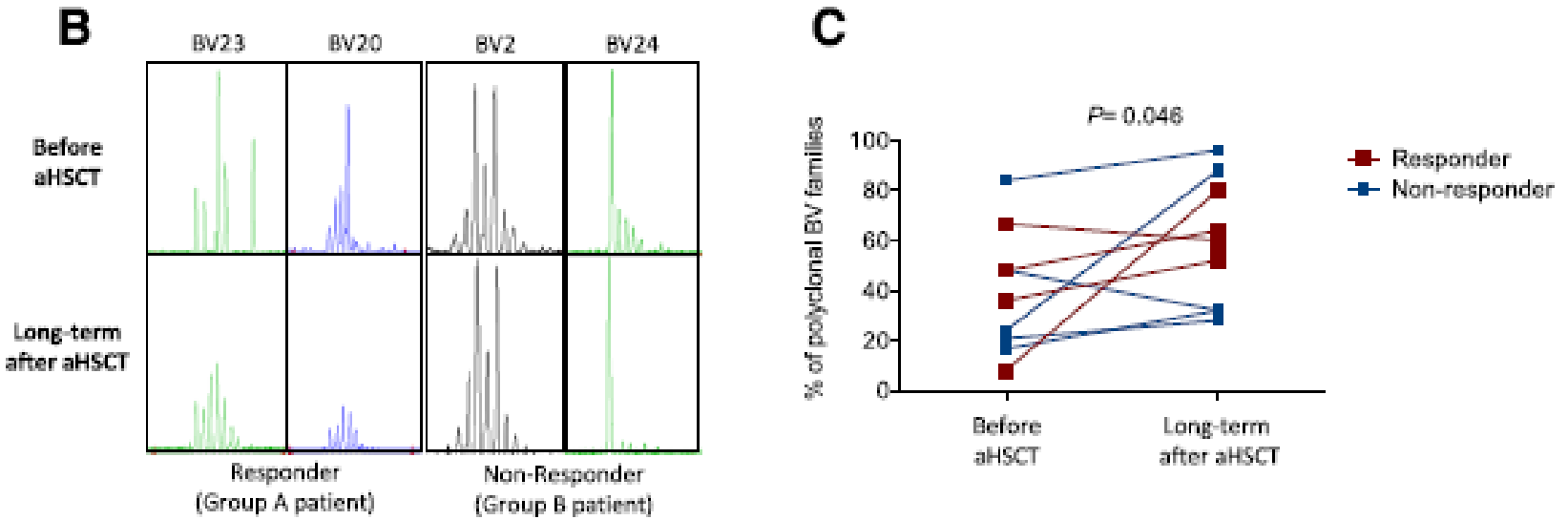


Fig. 3 TCR-Vβ family expression and T cell receptor β-chain spectratyping before and at long-term after aHSCT. **a** Quantification of each TCR-Vβ family at baseline (*white bars*) and at long-term (*dark bars*) after aHSCT in 10 dcSSc patients. Data are presented as mean ± SD. There are no differences between the clinical groups. **b** TCR-Vβ chain third complementarity-determining region size distribution profile of selected families at baseline (pre, *upper level*) and at long-term time point (*lower level*) for representative dcSSc patients who underwent autologous hematopoietic stem cell transplantation. *Left*: Polyclonal distribution achievement at long-term time point post-HSCT from a skewed and disturbed repertoire at baseline (patient 3, group A, responder). *Right*: Sustained disturbed distribution at long-term time point post-HSCT from a previously skewed profile at baseline (patient 1, group B, non-responders or relapse or necessitating immunosuppression). **c** T cell repertoire diversity as measured by the percentage of polyclonal TCR-Vβ families in all 10 dcSSc patients at baseline and at long-term follow-up (at least 6 years) after aHSCT

REGULAR ARTICLE

blood advances

Immune rebound associates with a favorable clinical response to autologous HSCT in systemic sclerosis patients

Lucas C. M. Arruda,[1,2] Kelen C. R. Malmegrim,[2,3] João R. Lima-Júnior,[2,4] Emmanuel Clave,[5,6] Juliana B. E. Dias,[7] Daniela A. Moraes,[7] Corinne Douay,[5] Isabelle Fournier,[5] Hélène Moins-Teisserenc,[5,6] Antônio José Alberdi,[6,8] Dimas T. Covas,[2,7] Belinda P. Simões,[2,7] Pauline Lansiaux,[9] Antoine Toubert,[5,6,*] and Maria Carolina Oliveira[1,2,7,*]

[1]Basic and Applied Immunology Program, Ribeirão Preto Medical School, [2]Center for Cell-based Therapy, Regional Hemotherapy Center of the Ribeirão Preto Medical School, [3]Department of Clinical, Toxicological and Bromatological Analysis, School of Pharmaceutical Sciences of Ribeirão Preto, and [4]Graduate Program on Bioscience Applied to Pharmacy, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; [5]INSERM Unité Mixte de Recherche 1160, Institut Universitaire d'Hématologie, Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris (AP-HP), Paris, France; [6]Institut Universitaire d'Hématologie, Université Paris Diderot, Sorbonne Paris Cité, Paris, France; [7]Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil; [8]Plateforme Technologique, Institut Universitaire d'Hématologie, Paris, France; and [9]Unité de Médecine Interne, Maladies Autoimmunes et Pathologie Vasculaire, UF 04, AP-HP, Centre de référence des maladies auto-immunes systèmiques rares d'Ile-de-France (site constitutif), FAI2R, Hôpital Saint-Louis, Paris, France

Submitted 27 July 2017; accepted 18 November 2017. DOI 10.1182/bloodadvances.2017011072.

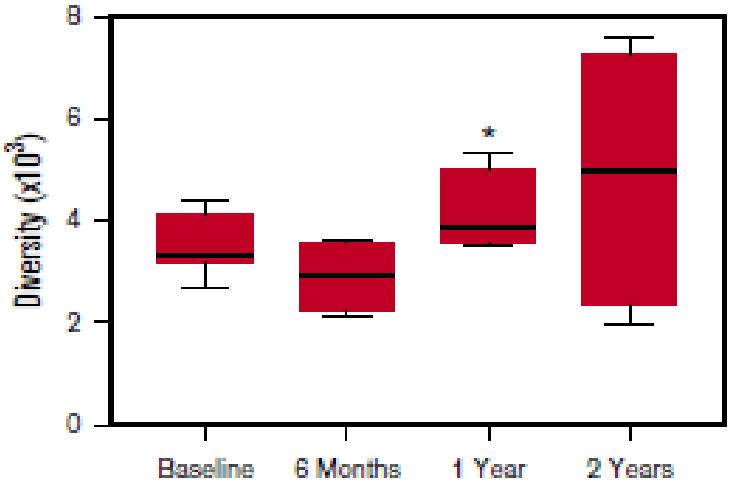
*A.T. and M.C.O. contributed equally to this study.

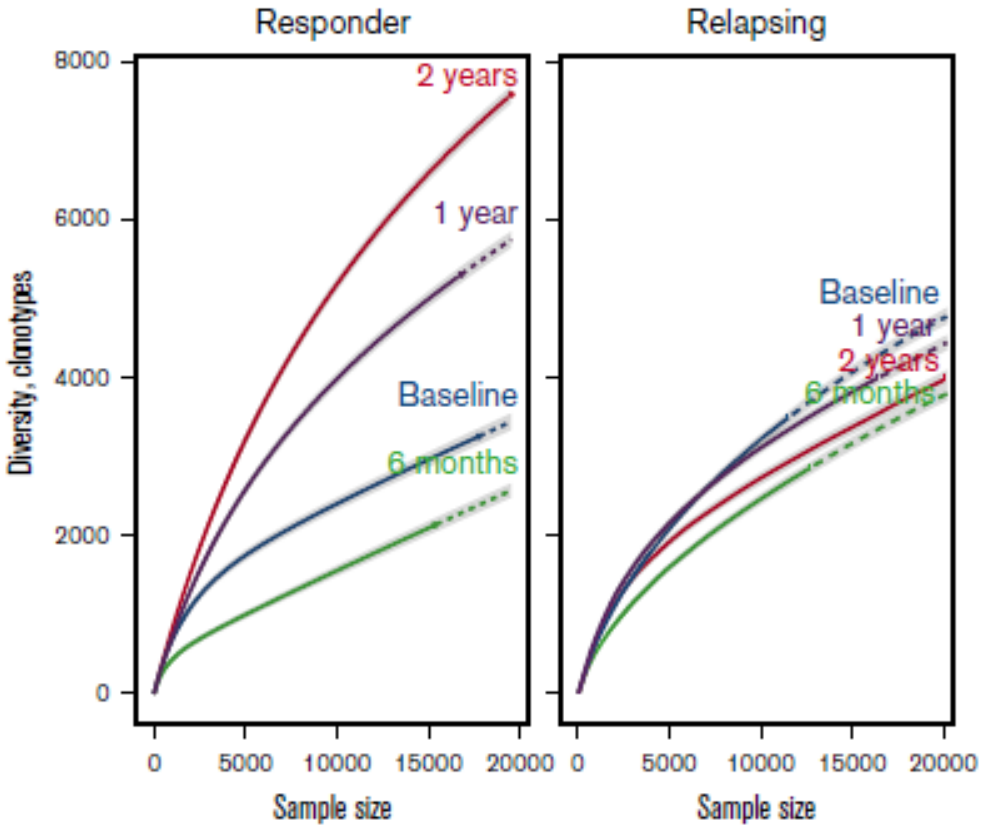
The data reported in this article have been deposited in the National Center for Biotechnology Information database (accession number SRP106516).

The full-text version of this article contains a data supplement.

Analysis of T-cell clonotypes using TCR sequencing

Superiority of TCR diversity after AHSCT
and low clonotype overlap
in responder group

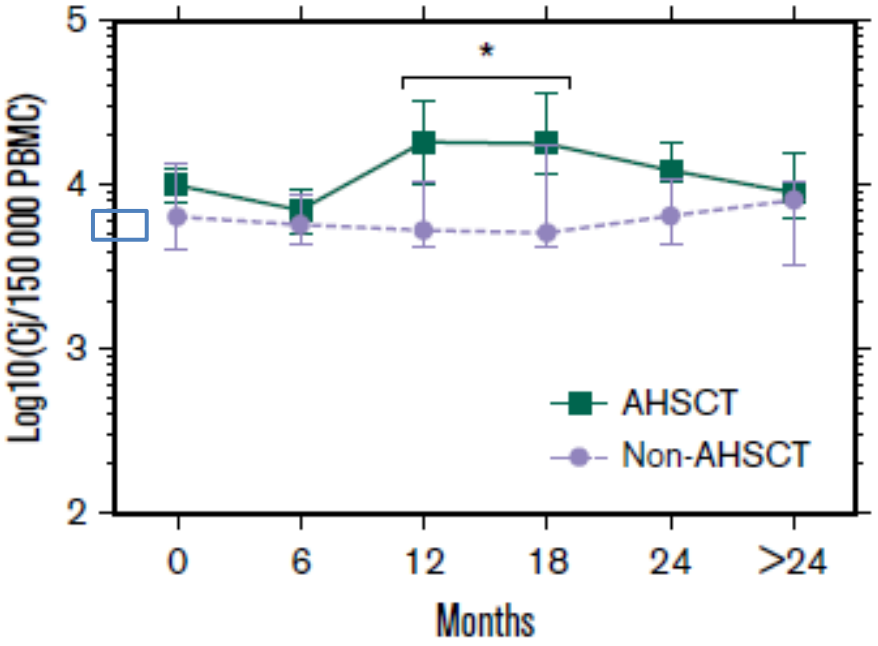


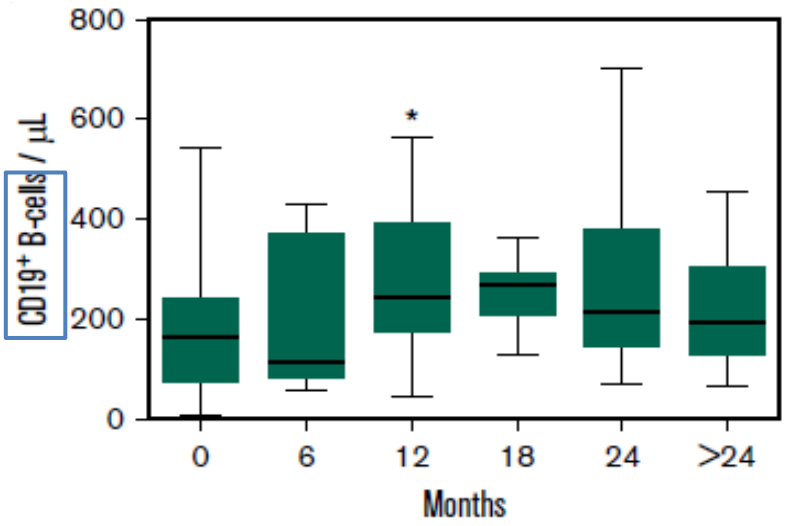


Arrruda Lc et al Blood Adv. 2018

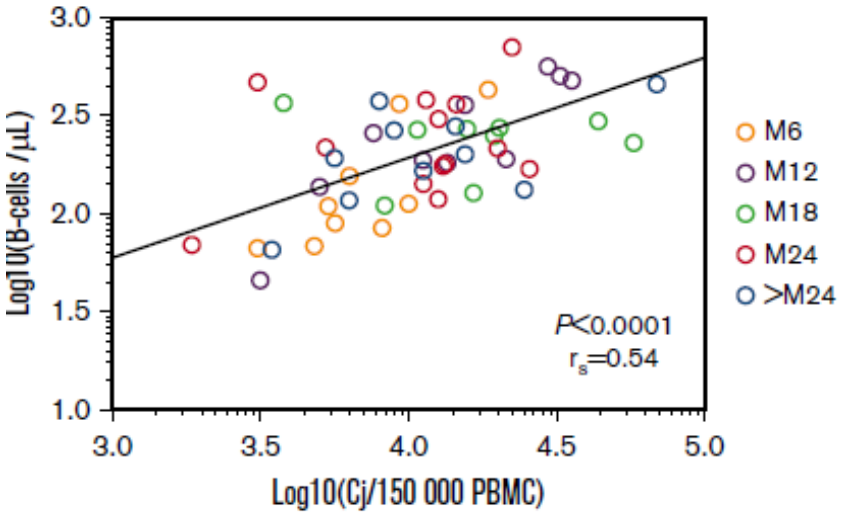
Analysis of newly-generated Naive B-cells

Increase of naive B-Cells and total B-Cells after AHSCT



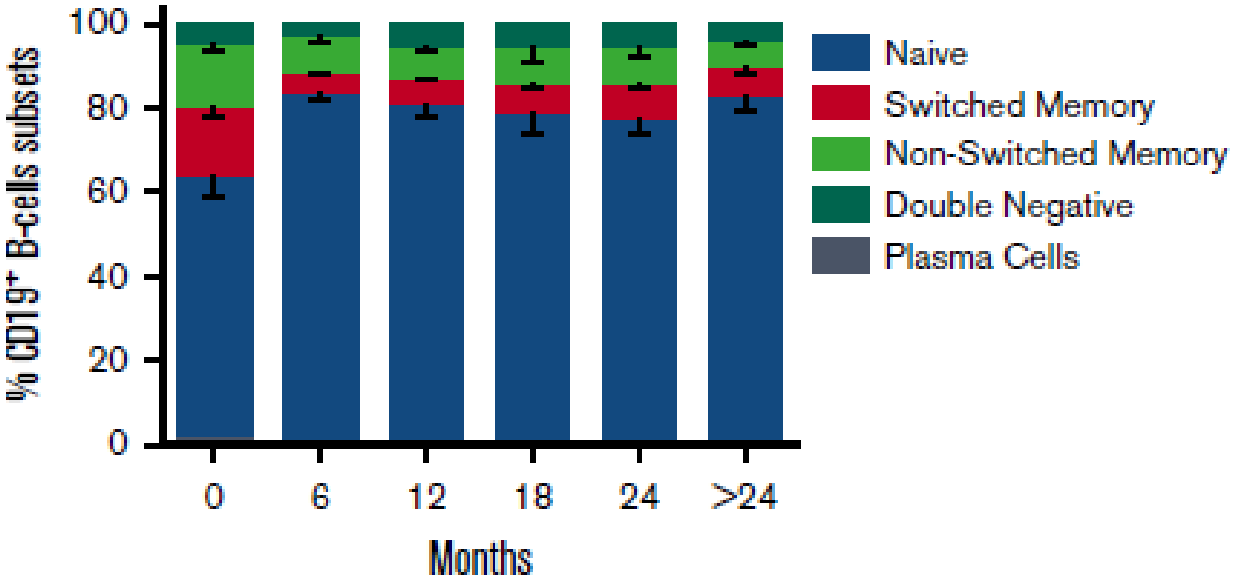


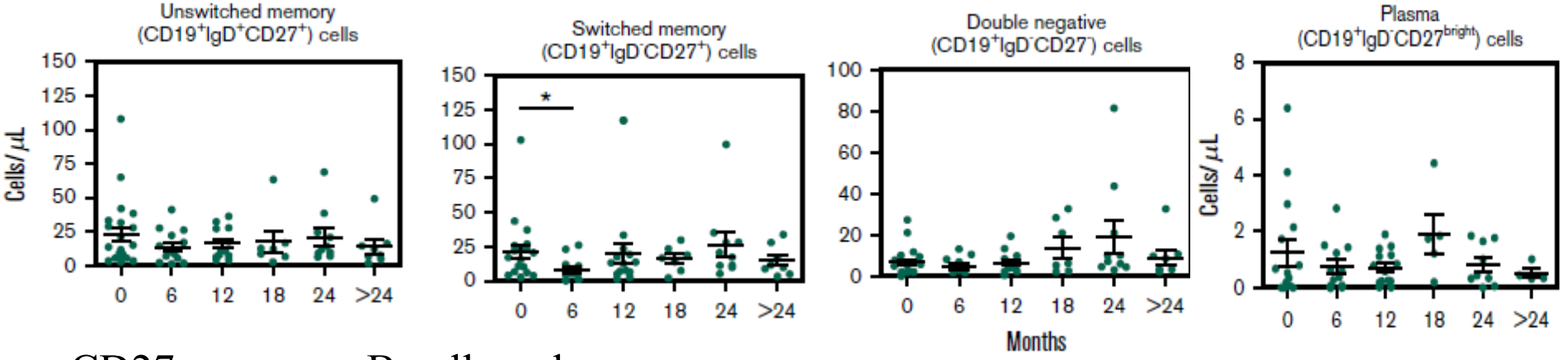
Increase of total B-cell (cjKREC)



Analysis of B-cells différenciation : from naive to memory B-cells

Number of memory B-cell (CD27+) and plasma cells are not modulated by AHSCT





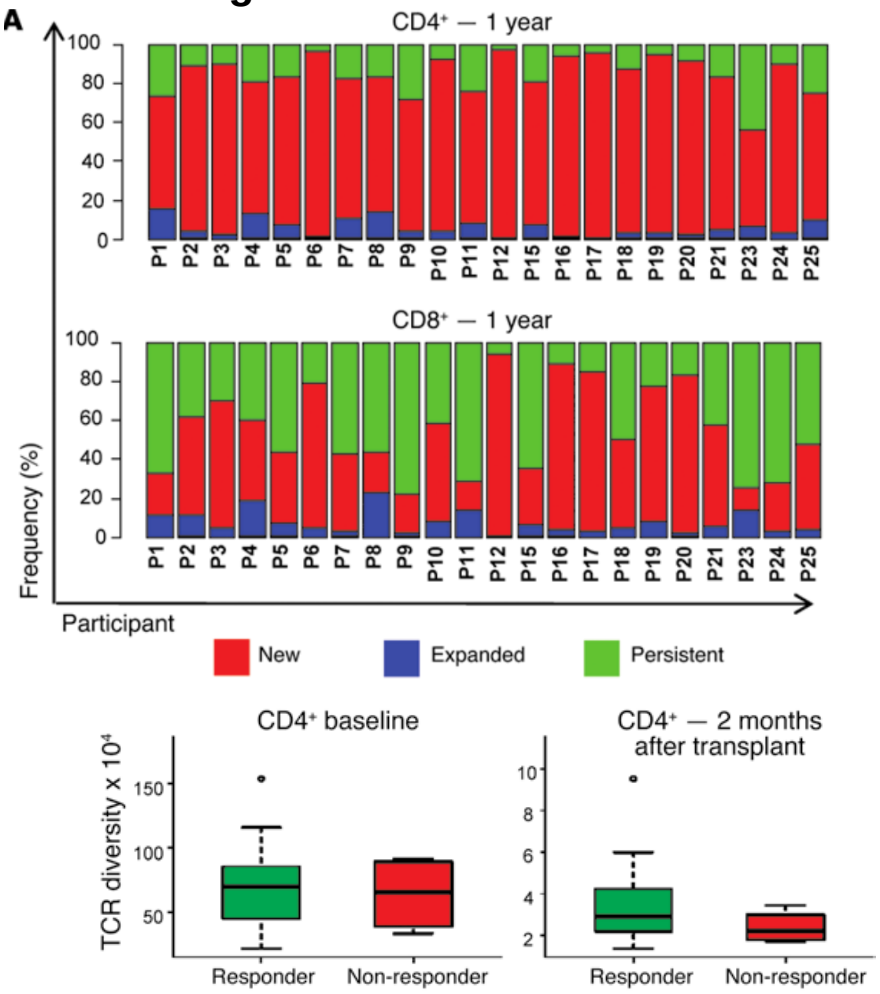
CD27 : memory B-cell marker

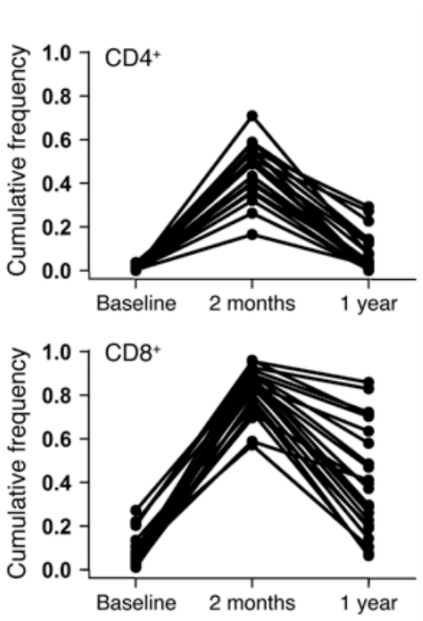
4
4

ANALYSE DU REPERTOIRE APRES AUTOGREFFE DE MOELLE DANS LA SEP

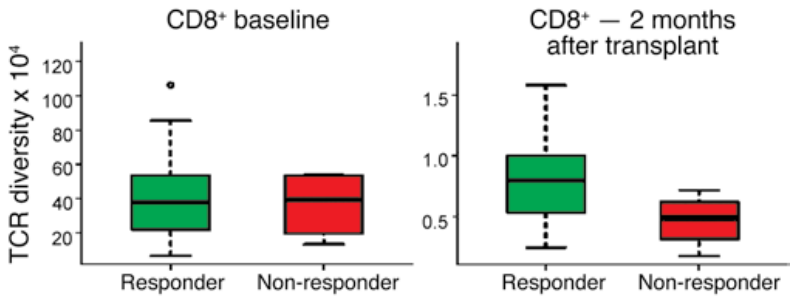
J Clin Invest 2014;124(3):1168-72.

Longitudinal evaluation of T cell clones after HSCT





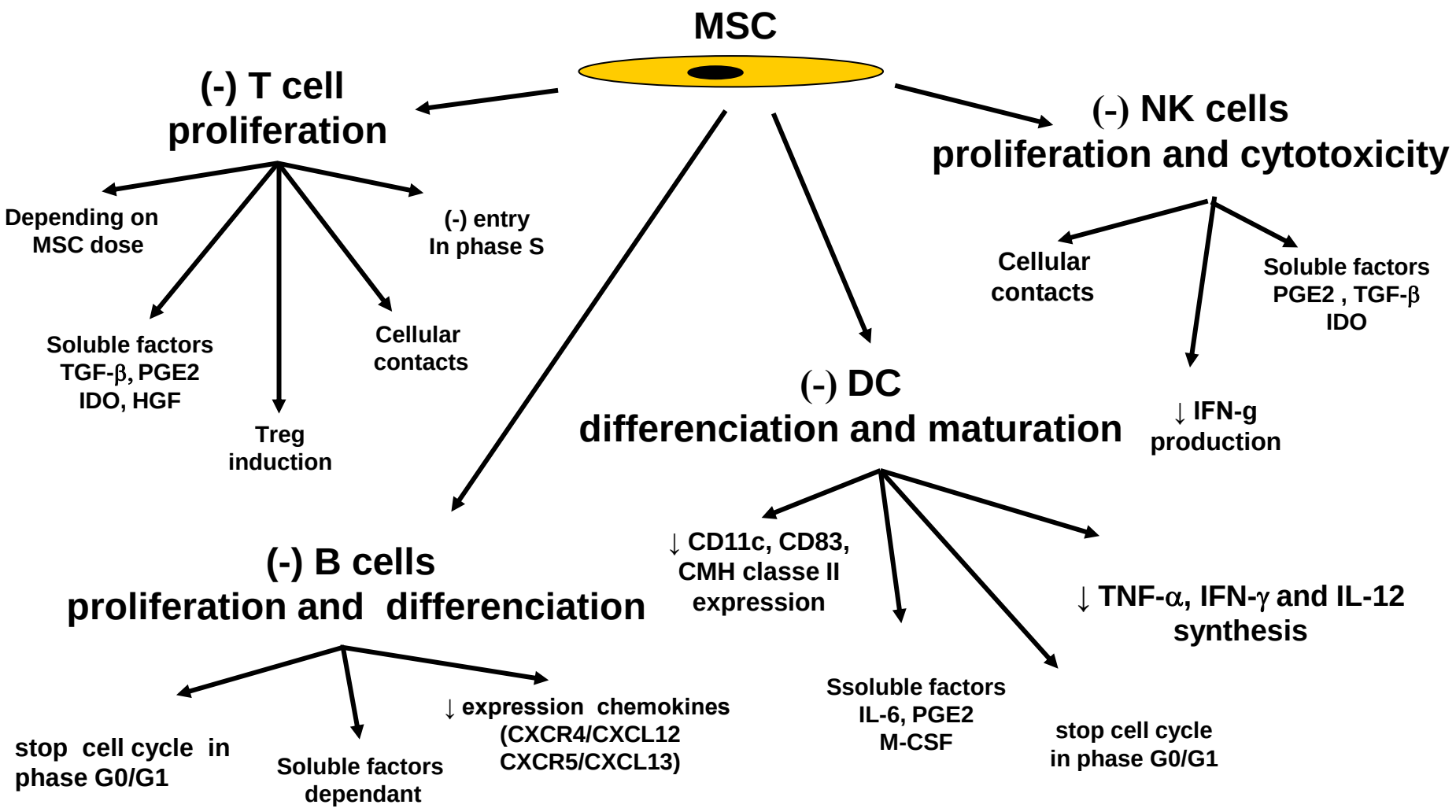
A Evolution of individual clonal frequencies. “New” refers to clones not present before treatment; “expanded” clones have increased from 1+ or 2+ before treatment to 3+ or 4+; and “persistent” clones have not changed their classification frequency.
B Proportional representation of the clones that were found to be the 100 most frequent at 2 months after transplant in CD4+ (top) and CD8+ (bottom) T cells.



Mesenchymal stem cells and immunomodulation: Toward new immunosuppressive strategies for the treatment of autoimmune diseases?

J. Larghero [a,b], L. Vija [c,d], S. Lecourt [a,b], L. Michel [c,d], F. Verrecchia [c,d], D. Farge [c,*,d]

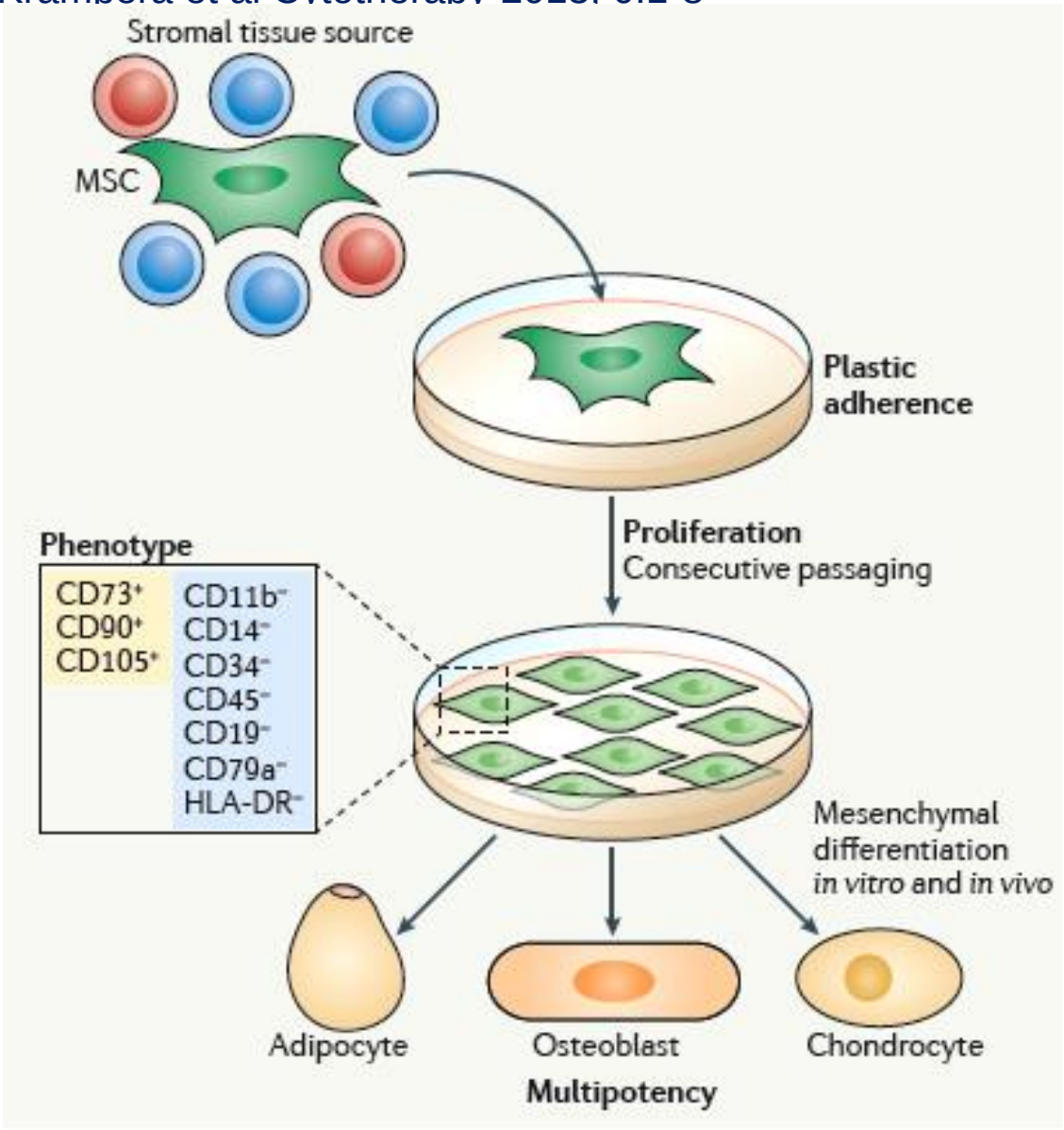
La Revue de médecine interne 30 (2009) 287–299



Multipotent MSC: Definition and characterization

International Society for Cellular Therapy ISCT®

Krampera et al Cytotherapy 2013; 0:1-8



✓ Plastic adherence in standard culture conditions

✓CFU-F

✓Phenotype + ≥ 95% / - ≤ 2%

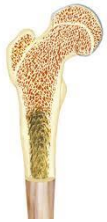
cells to exclude HSC contamination

✓ Differenciation in adipocyte,

ostéoblaste and chondrocyte

MSC sources :
BM, adipose tissue, dental tissue, umbilical cord ,

MSC : Isolation and expansion



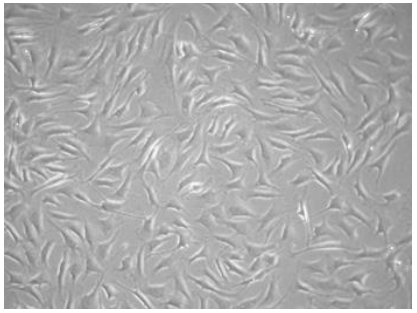
Ponction médullaire

Cellules médullaires totales

Milieu de culture
αMEM
10% SVF
FGF2

2 semaines de culture
Changement de milieu tous les 3 jours

Cellules adhérentes



Trypsinisation à confluence

Expansion

- MSC = 0.01- 0.001% Bonne Marrow mononuclear cells
- High expansion rate (25 mL BM = 2 to 5.10^8 MSC in 5 weeks)
- Limited long term proliferative potential (20-40 doubling population according age)
- Long term replication senescence

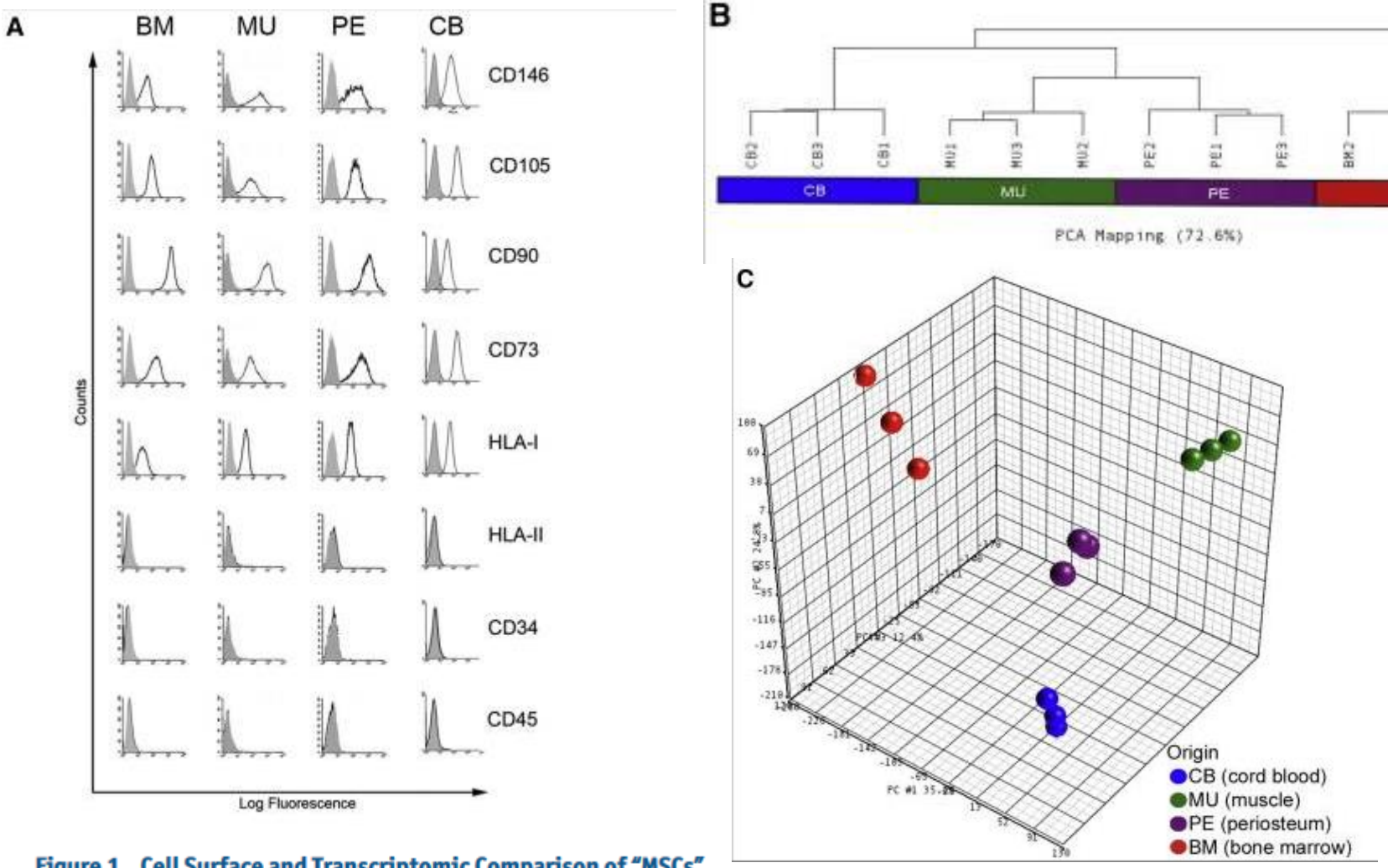


Figure 1. Cell Surface and Transcriptomic Comparison of "MSCs" from Different Tissues

(A) Fluorescence-activated cell sorting (FACS) analysis of multiclonal BM, MU (muscle), PE (periosteum) and CB cells strains express the canonical in vitro phenotype of "MSCs" and CD146 (isotype controls indicated in gray). Hierarchical clustering (B) and the principal component analysis (C) revealed that gene-expression profiles of CD146+ cells are clearly separated by the origin factor.

Sachetti, Stem cell reports, 2016

SHORT REPORT Open Access

Age, atherosclerosis and type 2 diabetes reduce human mesenchymal stromal cell-mediated T-cell suppression

Ozge Kizilay Mancini[1], Dominique Shum-Tim[2], Ursula Stochaj[3], José A. Correa[4] and Inés Colmegna[5,6*]

Kizilay Mancini et al. Stem Cell Research & Therapy (2015) 6:140
DOI 10.1186/s13287-015-0127-9

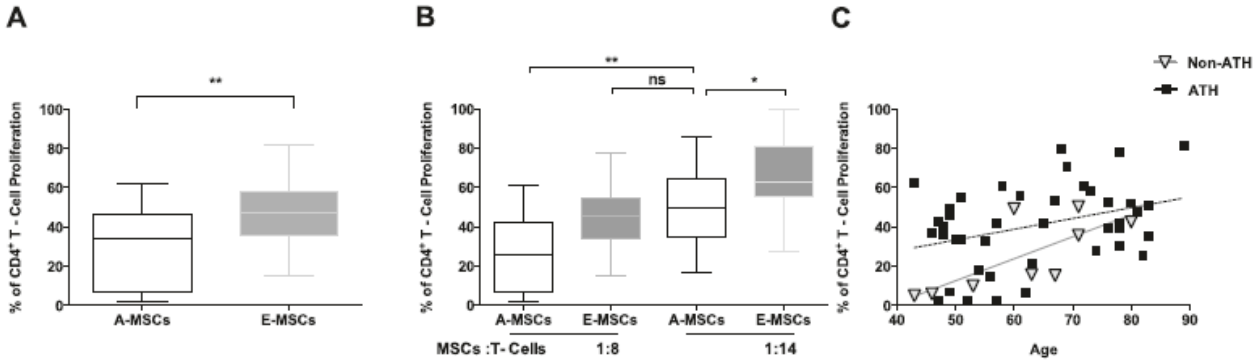


Fig. 1 Age-associated decline in mesenchymal stromal cell (MSC)-mediated $CD4^+$ T-cell suppression capacity. **a** MSCs from elderly donors (E-MSCs, ≥65 years, n = 23) are less efficient than those of non-elderly adults (A-MSCs, <65 years, n = 27) to suppress $CD4^+$ T-cell proliferation at 1:8 MSC:$CD4^+$ T cell ratio (**$p = 0.003$). **b** The suppressive effect of MSCs on $CD4^+$ T cells depends on the MSC:$CD4^+$ T-cell ratio (**$p = 0.004$). Twice the number of E-MSCs are required to affect $CD4^+$ T-cell suppression to the same extent as A-MSCs ($p > 0.9$). **c** The effect of MSC donor age on the decline of $CD4^+$ T-cell suppression is observed in patients with atherosclerosis (ATH; n = 18; $p = 0.02$, $r = 0.4$) and without ATH (non-ATH; n = 9; $p = 0.02$, $r = 0.7$)

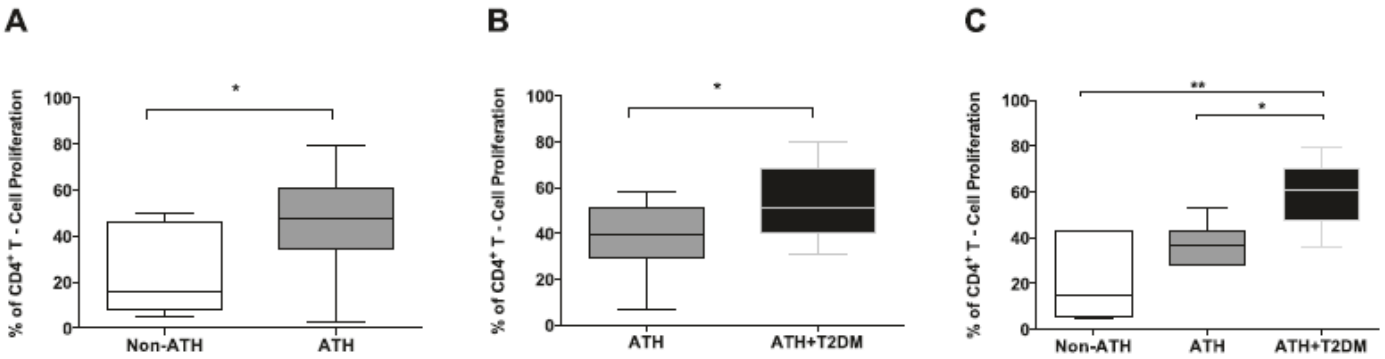
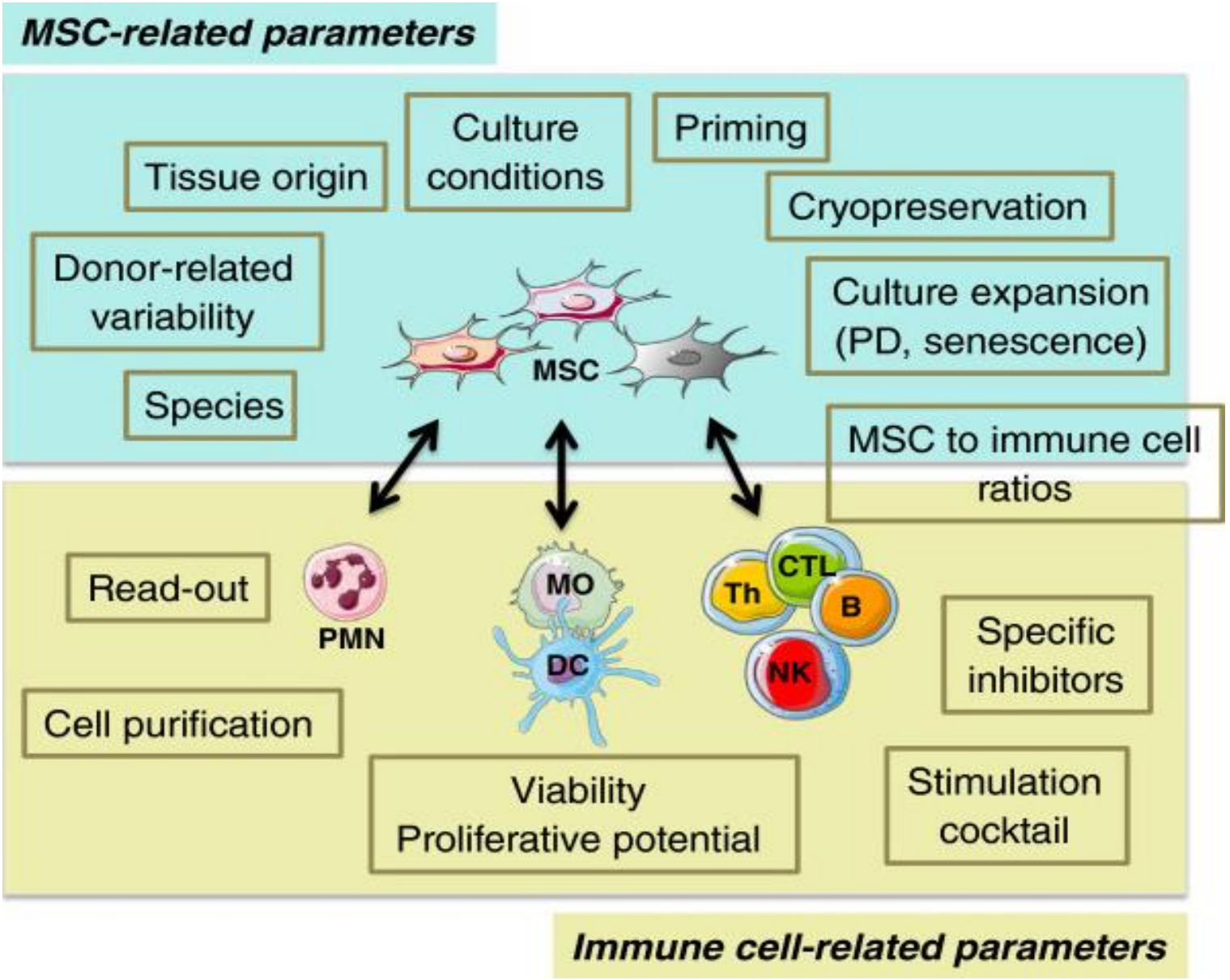


Fig. 2 Reduced MSC-mediated T-cell suppression capacity in patients with atherosclerosis and type 2 diabetes. **a** MSCs from patients with atherosclerosis (ATH; n = 18; *$p = 0.02$) have a decreased capacity to suppress $CD4^+$ T-cell proliferation at 1:8 MSC:$CD4^+$ T cell ratio compared to age-matched controls without atherosclerosis (non-ATH, n = 9). **b** MSCs from patients with ATH (n = 12) and type 2 diabetes mellitus (T2DM) (n = 12) have impaired suppressive capacity compared to age-matched ATH controls (*$p = 0.04$). **c** MSC function is compromised in age-matched patients with chronic inflammatory diseases (non-ATH < ATH < ATH+T2DM; n = 7 per group; *$p = 0.02$, **$p = 0.002$)

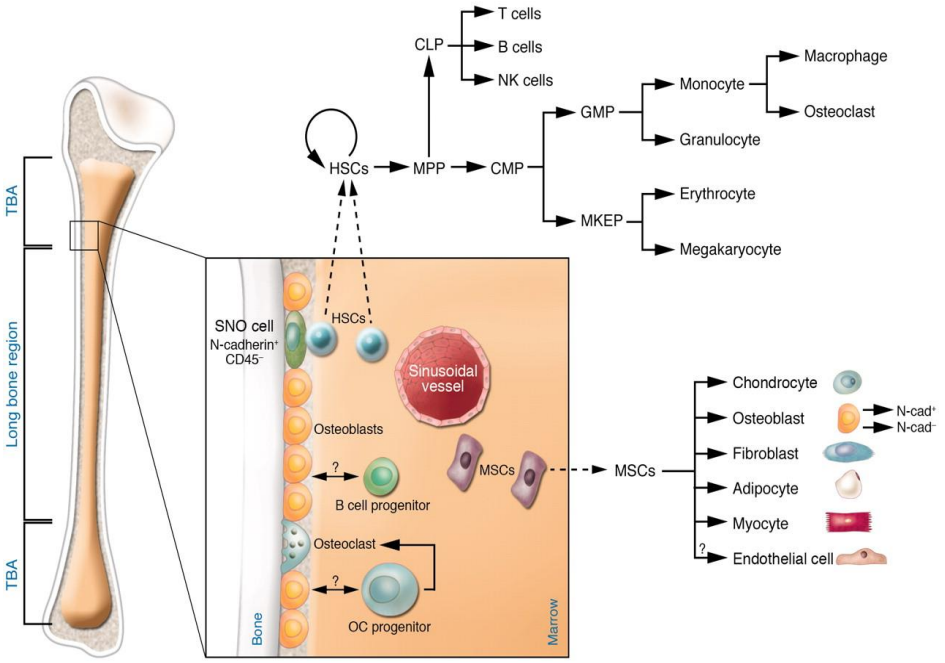
Critical parameters for assessment of MSC immunomodulatory potential. Standardization of these parameters is of utmost importance to ensure reproducibility of the experiments.



Ménard C and Tarte K, 2013 Stem Cell Research & Therapy

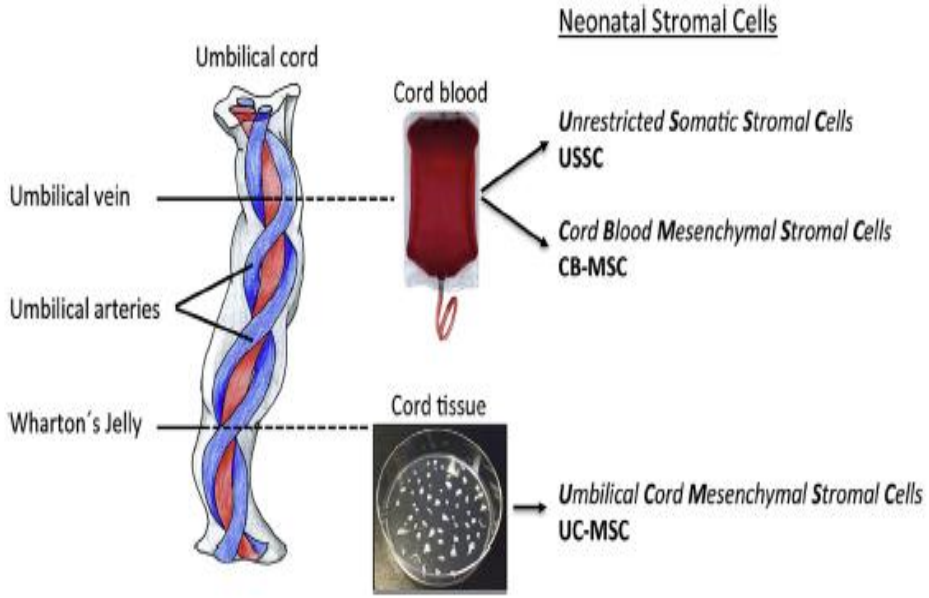
Should we use cord blood or bone marrow as a source of cells for treating AD : SC : Bone Marrow and Umbilical Cord blood human

Int J CLIN EXP Med 2010; 3: 248



MSCs = 0.001–0.01% total BM nucleated cells

- viral exposure
- proliferative/differentiation capacity with age



More primitive, less likely immunological

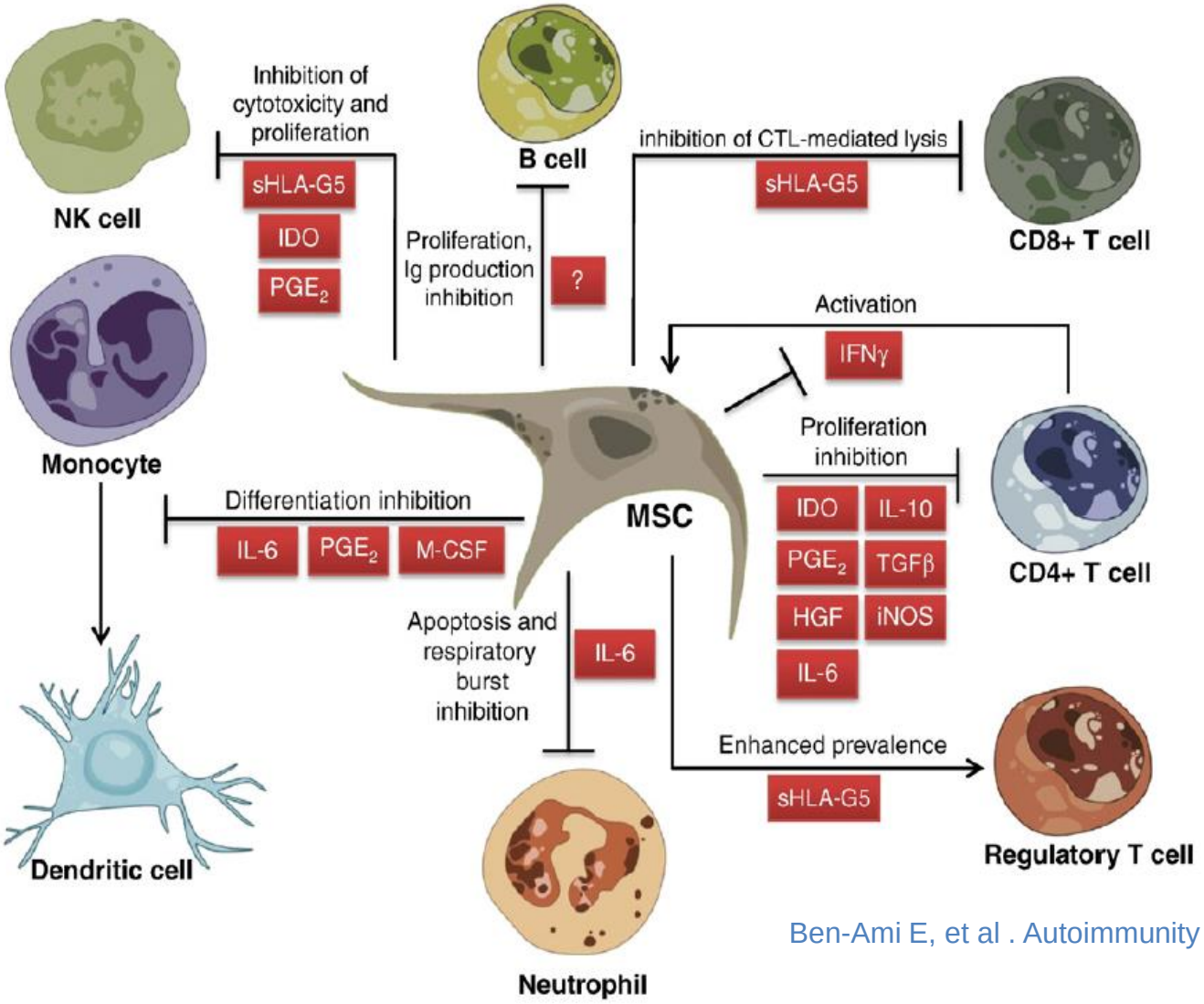
Allogenic use , collection easy, non invasive

no ethical / technical issues

Lower success for isolating 63% UCB vs 100% BM

Banking

1. CFUF frequency : UC > BM
2. Proliferation hUCMSC Faster (P30) > BM (P6)
3. Lower expression CD106 and HLADR UB > BM



Ben-Ami E, et al . Autoimmunity reviews 2011;

Fig. 1. Possible mechanisms by which MSCs influence innate and adaptive immunity. Abbreviations: IFN gamma (interferon γ), IDO (indoleamine 2,3-dioxygenase), IL-10 (interleukin 10), IL-6 (interleukin 6) prostaglandin E2 (PGE2), transforming growth factor beta (TGFβ), hepatocyte growth factor (HGF), induced nitric oxide synthases (iNOS), soluble human leukocyte antigen G5 (sHLA-G5), macrophage colony stimulating factor (M-CSF).

Main mechanism: paracrine soluble factors secretion (transwell) ; cell to cell contact amplifies process IDO = enzyme whose activation depletes environment in tryptophan; NO release = cytotoxic T and NK cells

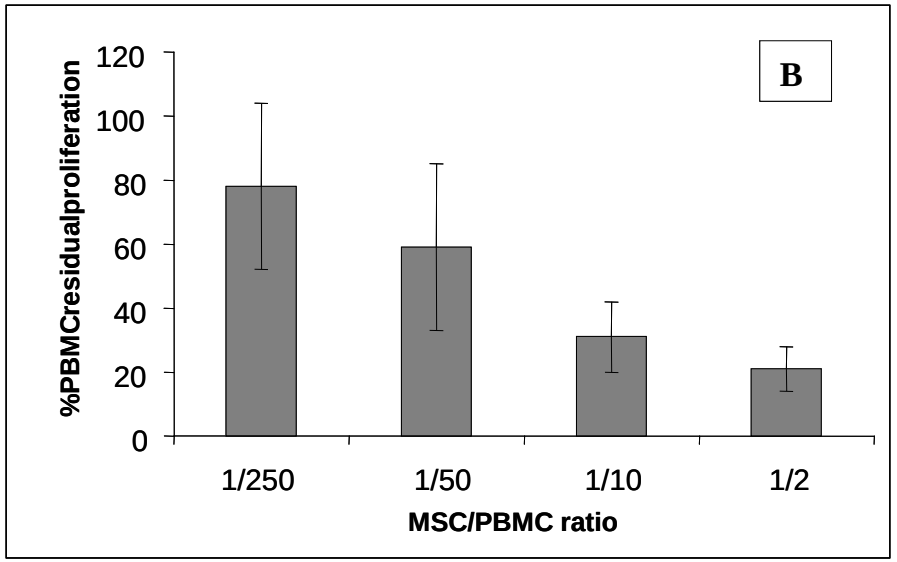
MSCs FUNCTIONS from SSc patients ? (n < 100)

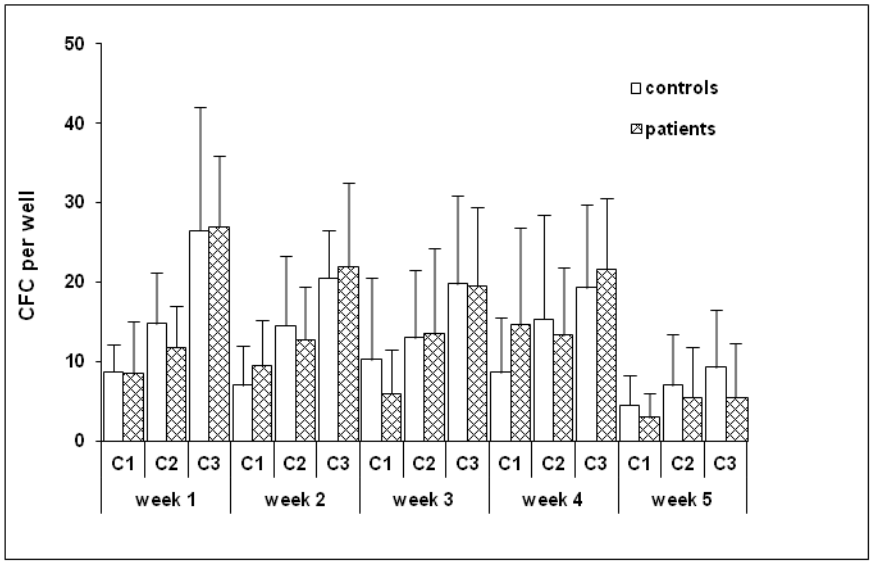
Del Papa N, Arthr Rheum 2006 (14 pts): no adipogenic /osteogenic differentiation potential, ↓ long term hematopoiesis support and early senescence.

Cipriani P Arthr Rheum 2007: ↓ in vitro endothelial differentiation but normal adipogenic/ osteogenic differentiation. Premature senescence ?

Larghero J Ann Rheum Dis 2007 Normal MSC in 12 pts + 9 C: phenotype, proliferation (CFU-F) + bFGF, differentiation, (-) CML, support hematopoiesis

Vanneaux et al *BMJ open 2012 :* ↑TGF-β RII signaling in SSc CSM



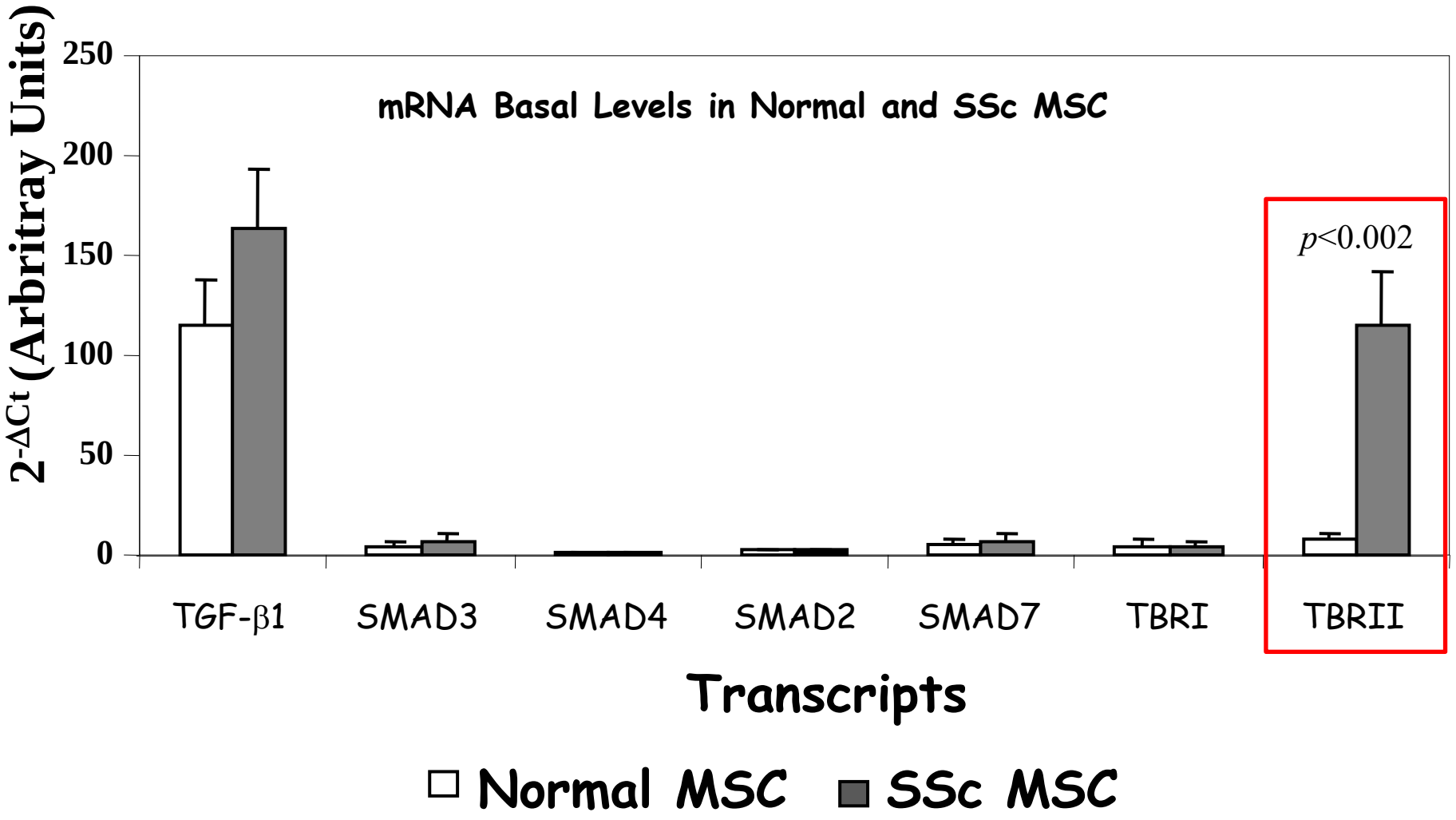


MSC IMMUNOMODULATION IN SSc PATIENTS:? since the standardisation of MSCs definition and expansion by the EBMT + International Society Cellular Therapies (ISCT)

n = 1 ***Christopeit M Leukemia 2007*** 41 yr female with advanced SSc. Allogeneic (father) BM MSC => marked improvement" 7 mth Follow Up

n= 1 Guiducci S et Al, Ann Intern Med, 2011 ♀ 24yrs, SSc with LAC+ vasculitis, resistant to Steroids, Azathioprine, Cyc, plasmaexchange. Autologous, expanded MSCs ($1x10^6$/Kg), infused at 0, +30 and + 60.

Enhanced expression mRNA levels of TGF-βRII in MSc from SSc patients

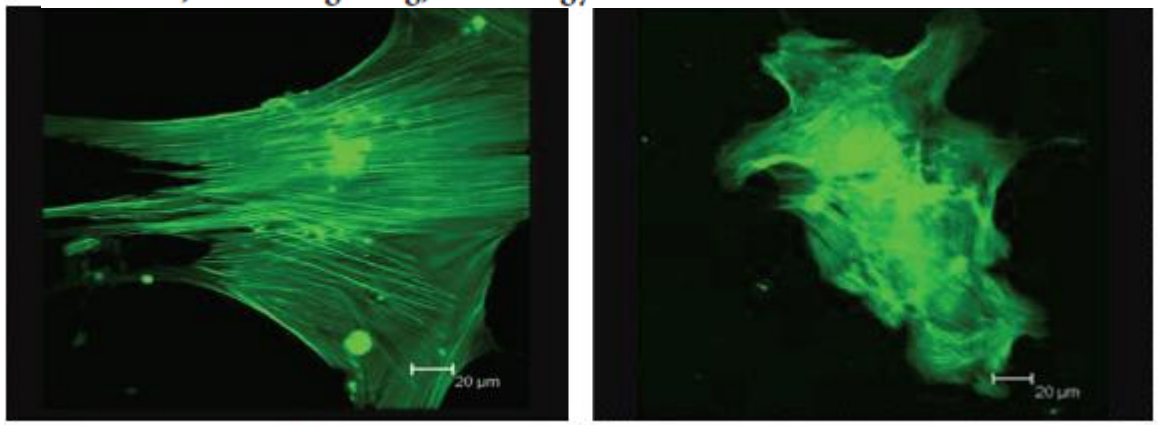


Vanneaux et al., BMJ Open 2012

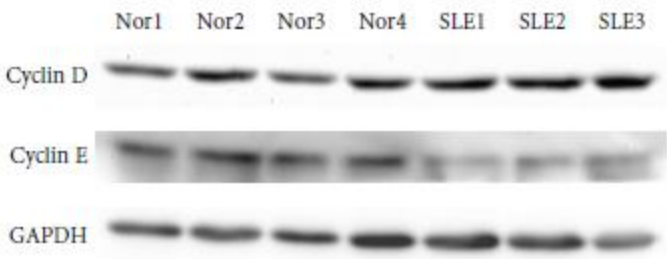
Gene Expression Profile Reveals Abnormalities of Multiple Signaling Pathways in Mesenchymal Stem Cell Derived from Patients with Systemic Lupus Erythematosus

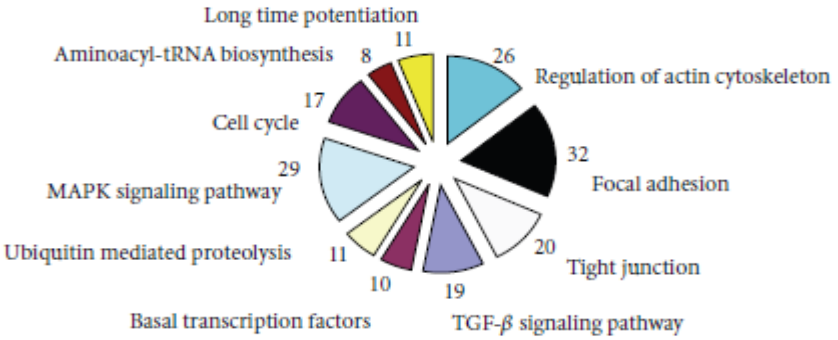
Yu Tang,[1] Xiaolei Ma,[1] Huayong Zhang,[1] Zhifeng Gu,[1] Yayi Hou,[2] Gary S. Gilkeson,[3] Liwei Lu,[4] Xiaofeng Zeng,[5] and Lingyun Sun[1]

Clinical and Developmental Immunology
Volume 2012, Article ID 826182, 12 pages



(c) (d)





Rux2, Msx2, and osterix [40]. According to the results of the microarray, most of genes in the BMP pathway were decreased including Smad-1, Smad-5, BMPR1A and the target gene Id-1. As the phosphorylation process controls the activity of Smad-1, Smad-5, and BMPR1A, we only confirmed the mRNA level of some of the target genes and the protein level of BMP-5.

patients. Furthermore, we found abnormalities in cell cycling regulation, BMP/TGF-β and MAPK pathways. Our findings suggest BMMSCs, as a component of bone marrow, may play an important role in the etiopathogenesis of SLE.

Therapeutic Effects of Umbilical Cord Blood-Derived Mesenchymal Stem Cell Transplantation in Experimental Lupus Nephritis

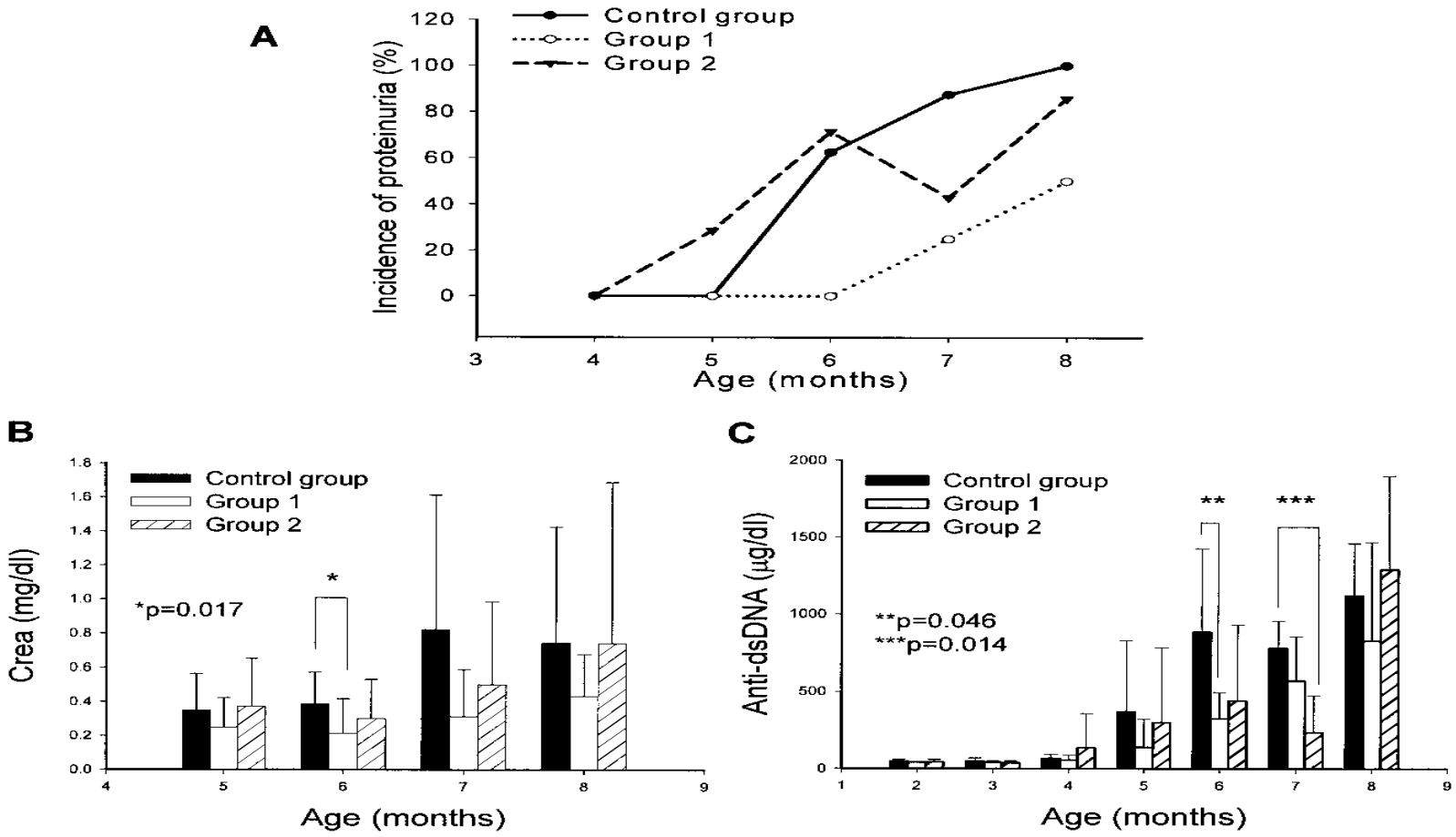


Figure 1. uMSCs improve proteinuria, serum creatinine levels, and decrease anti-dsDNA titer. (A) Incidence of proteinuria in NZB/W F1 mice. Mice treated with uMSCs transplantation showed lower incidence of proteinuria compared to the control group at 6 and 7 months of age ($p = 0.007$ and $p = 0.039$ by chi-square tests, respectively). (B) Serum creatinine levels of the experimental animals. A significant difference was found in creatinine between group 1 and the control group at 6 months of age ($*p = 0.017$). (C) Anti-dsDNA antibody titers. Group 1 showed lower levels with respect to the control group at 6 months of age ($**p = 0.046$). There was a significant difference among groups ($p = 0.019$) and group 2 showed lower levels with respect to the control group ($***p = 0.014$) at 7 months of age.

Safety and feasibility of umbilical cord mesenchymal stem cells in treatment-refractory systemic lupus erythematosus nephritis: time for a double-blind placebo-controlled trial to determine efficacy

Woodword and Furst arth Resear 2016

Table 1 Overview of open-label phase I/II studies to evaluate mesenchymal stem cells (1×10^6 per kg) in treatment-refractory systemic lupus erythematosus

Authors (date)	ClinicalTrials.gov protocol number	Study design/duration of follow-up	Number of patients	MSC type/regimen	Conditioning	Safety: deaths/serious infection	PD marker[a]	Efficacy
Sun *et al.* [2]	NR	Single-arm/median of 8.25 months (range of 3 to 28 months)	16 (15 SLEN)	UC, single infusion	CYC 0.8 to 1.8 mg/kg intravenously, 2 to 4 days	0/0	Percentage of Treg cells increased at 3 months ($P = 0.03$)	'Decreasing SLEDAI and proteinuria[b] in all patients'
Liang *et al.* [3]	NCT 00698191	Single-arm/17.2 ± 9.5 months	15 SLEN	BM, single infusion	Included in protocol, but NR	0/0	Percentage of Treg cells increased at 1 week and 3 and 6 months ($P < 0.05$)	'Decreasing SLEDAI and proteinuria[b] in all patients'
Wang *et al.* [4]	NCT 00698191	Unblinded-randomized, 2-arm/12 months	58 (~88% SLEN)	BM, UC, single versus 2× (7 days apart)	CYC 10 mg/kg per day, day 4, 3, and 2	1/NR	ND	CR single: 16/30 (53%); double: 8/27 (29%)
Wang *et al.* [5]	NR	Single-arm/mean of 27 months	87 (84% SLEN)	BM, UC, single infusion, 18 patients retreated at relapse	CYC 10 mg/kg/day, day 4, 3, and 2	5/NR	ND	CR in 23/83, relapse 10/83
Wang *et al.* [1]	[c]NCT 01741857	Single-arm	40 (38 SLEN)	UC, 2× infusion, 7 days apart)	No	3/4	ND	MCR 13/PCR 11, 7 relapse

SSc treatement by allogenic MSC n= 8 / 20

PHRC 2011 Multicenter phase I-II trial

D Farge, PHRC 2011 St Louis Hospital, Paris 7, France
AP-HP INSERM U 976, INSERM U 1160, MATHEC FAI2R

Primary objective: Feasibility and tolerance of allogeneic MSC treatement for severe SSC refractory to Cyclo iv or AHSC

Primary Outcome: Immediate tolerance % pts with at least one grade III or IV secondary effects according to CTCAE (Common Terminology Criteria for Adverse Events v3.0)

Secondary Outcome:

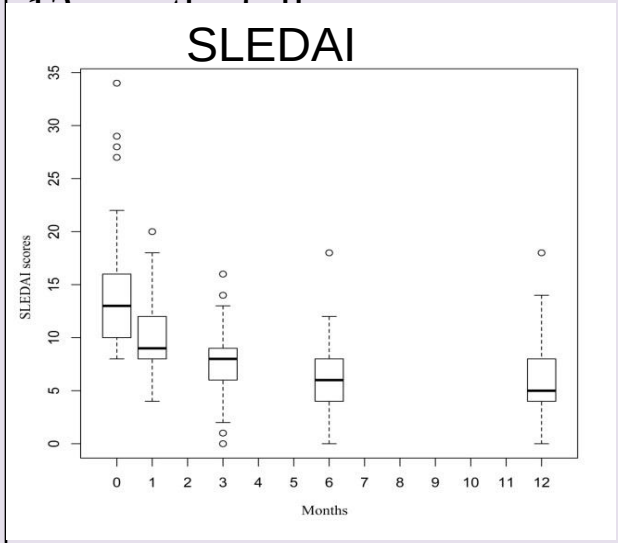
1) Tolerance: 3 mths after injection (no malignancy)
2) Clinical response SSc: evolution on a quaterly FU up to 2 yrs
3) Immune reconstitution and immunomodulation

Healthy allogeneic Bone marrow donor intrafamilial.
Dose of injected MSC:1 x 10_6 CSM /kg body wt of the recipient
Patient selection : severe progressive SSC resistant to CY or HSCT

Patient number : 20 patients total in 3 years

SLE treatment with UC-MSC

Littérature and MATHEC AP-HP collaboration with Nanjin

2010: Sun et al, Arthritis & Rheumatism **n=16**	Regression disease activity, serologica changes, and stabilization of proinflammatory cytokines
2016: Wang et al, *Clin Exp Med* **n=9**	Good long-term (6 years) safety profile
2018: Wang et al , Stem Cell Reports **n=81 (15 BM, 8 BM+UC, 58 UC)**	5 years follow-up: OS: 84%, CR 27%, PR 7%, relapse 24%
2019: Wen et al, Stem Cell in Press **N=69 (BM + UC) with SLEDAI score ≥ 8 at baseline** Prognostic factors for clinical response Low disease activity (LDA): SLEDAI ≤ 4 without major organ activity, and prednisone ≤ 145 7.5 mg/day, with or without maintenance CYC, MMF, LEF and, Clinical remission (CR): SLEDAI < 3 without major organ activity, and ≤ 5 mg/day prednisone with or without maintenance CYC, MMF, LEF.	 SLEDAI median (range) Baseline: 13 (8-34) 1 month: 9 (4-20) 3 months: 8 (0-16) 6 months: 6 (0-18) 12 months: 5 (0-18) **LDA : 58%** **CR : 23%**

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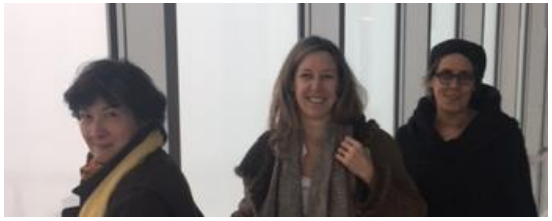

M Labopin; M Badoglio,
Pr E Gluckman
EBMT -ADWP members

EBMT
European Society for Blood and Marrow Transplantation