Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

Ospedale San Giuseppe
MultiMedica S.p.A.

PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

Le terapie cellulari nella Sclerosi Sistemica

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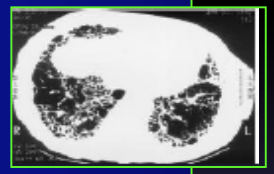
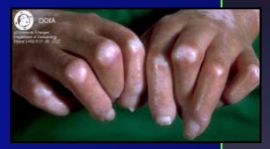
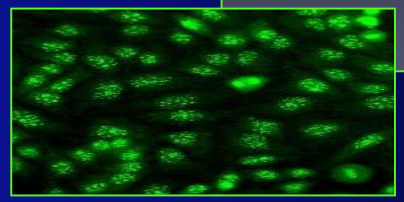
UOC Day Hospital di Reumatologia

Systemic Sclerosis

Heterogeneity and complexity







Gut
Heart

FIBROSIS

MICROANGIOPATHY

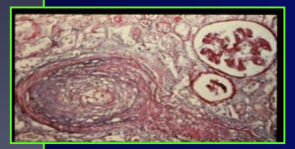
ROS

Skin sclerosis
Interstitial
Pneumonia

Anti-nuclear antibodies
anti- scl70
anti-centromere

IMMUNITY

Raynaud's
phenomenon
Digital ulcers
Telangiectasia
Pulmonary Arterial
Hypertension
Renal crisis



The clinical involvements and their impact are very heterogeneous

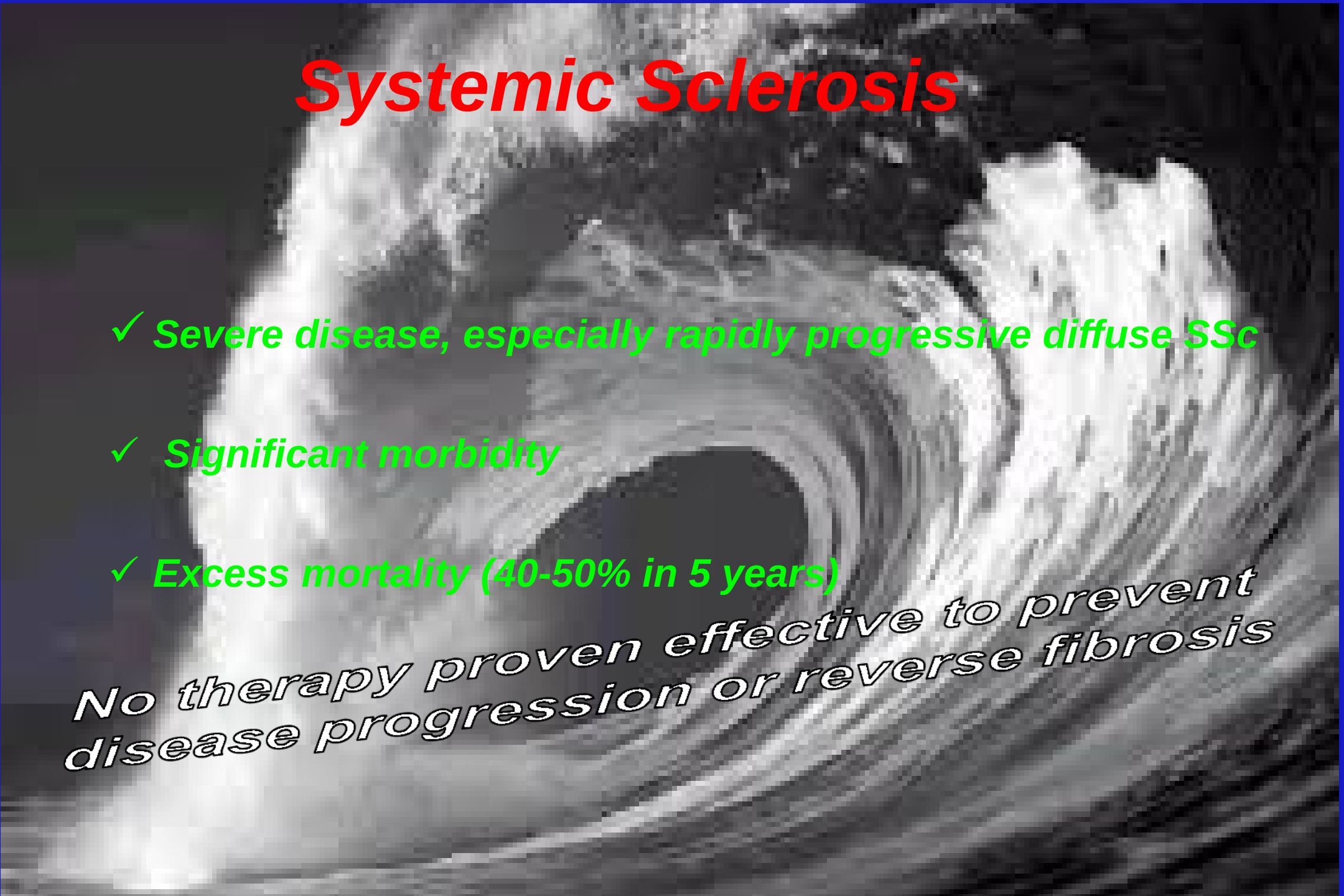
The spectrum of the disease is really wide

Organ functions

Survival

Quality of life

Systemic Sclerosis



- ✓ Severe disease, especially rapidly progressive diffuse SSc
- ✓ Significant morbidity
- ✓ Excess mortality (40-50% in 5 years)

No therapy proven effective to prevent disease progression or reverse fibrosis

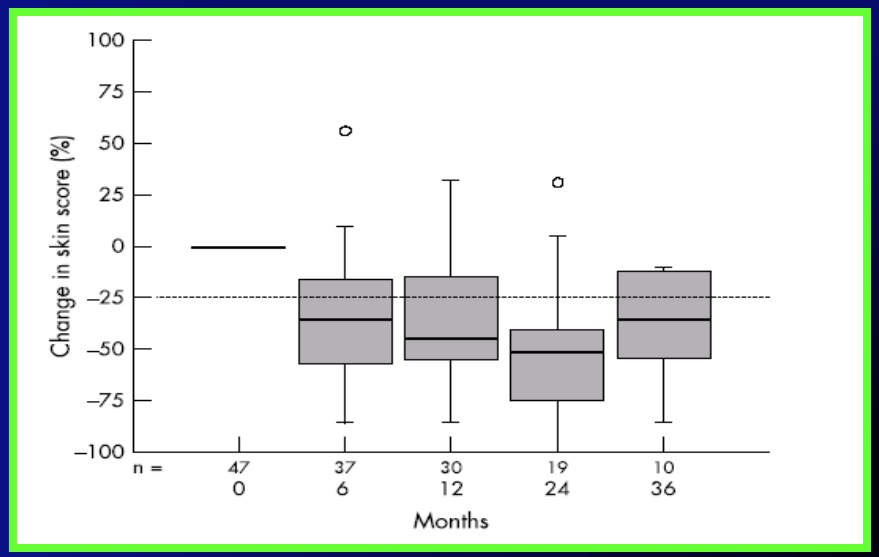
Cellular therapies in SSc

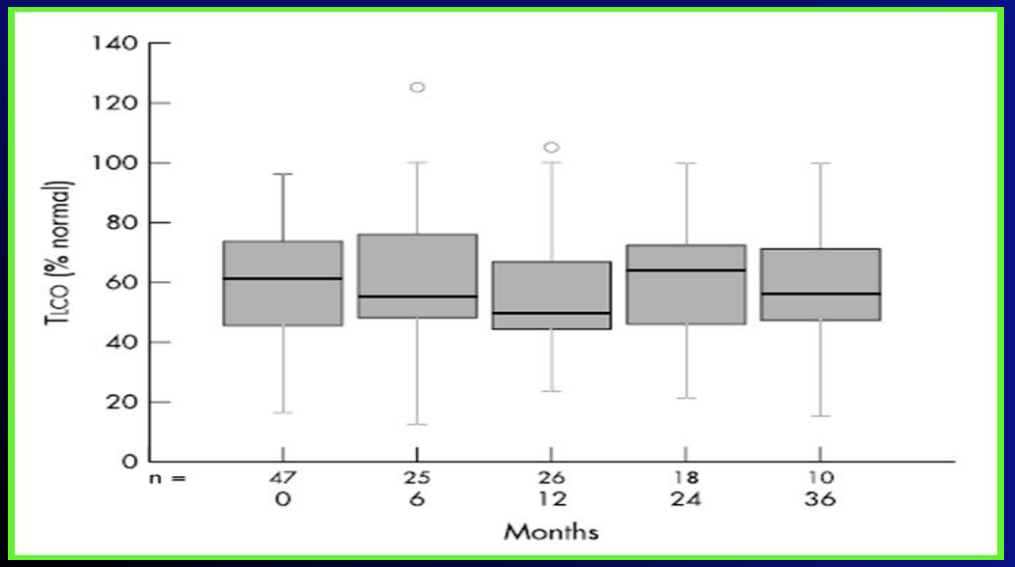
aHSCT → *may be actually effective in changing the natural history of the disease??*

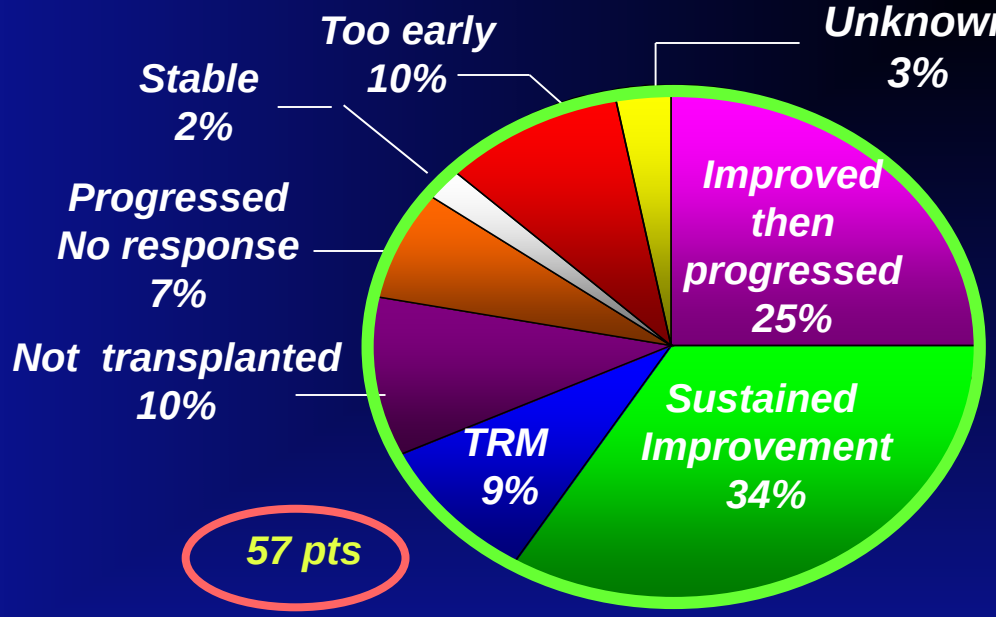
MSCs → *to be studied*

……a change in rheumatologists' mind is required

Clinical outcome in SSc after transplantation







Intensive immunosuppression may reverse skin thickening, stabilise lung involvement and improve the physical functions of patients

Farge D. Ann Rheum Dis 2004; 63:974–81

Stem cell therapy
ASTIS trial

Autologous Stem Cell Transplantation International Scleroderma trial

Patients with severe SSc

Immunoablation + SCT

1. ***Mobilisation (CYC 2x2 g/m², G-CSF 10 mg/kg)***
2. ***Leukapheresis/CD34 selection***
3. ***Conditioning (CYC 200 mg/kg, rabbit ATG 7.5 mg/kg)***
4. ***Reinfusion CD34+ cells***

61 pts

Control treatment

12x monthly
iv pulse CYC 750 mg/m²

54 pts

ASTIS trial

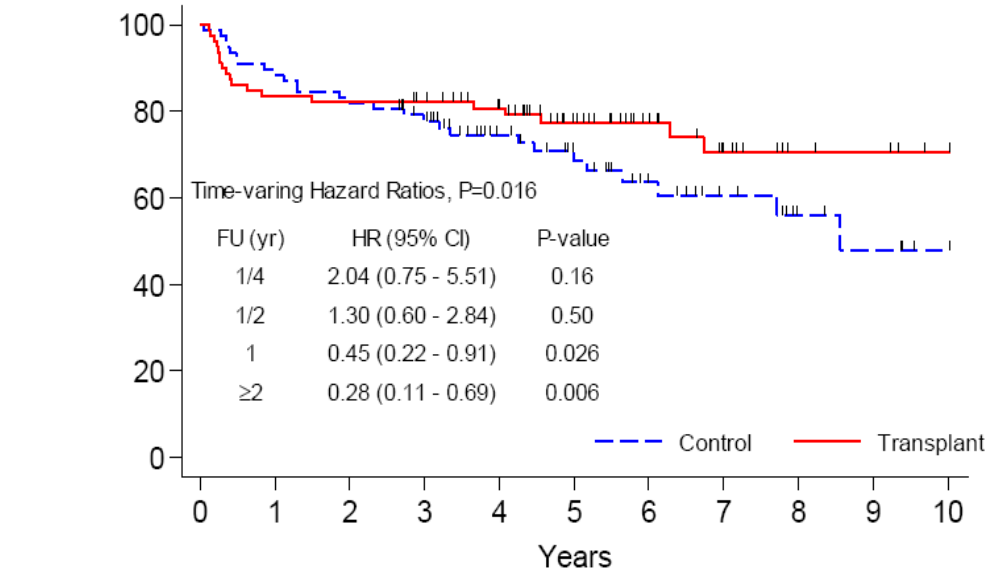
Table 2. Treatment Responses in Clinical Outcome Variables, Change in the Area under the Time Response Curve from Baseline until 2 Years Follow-up*

Clinical outcome variable	Treatment: Transplant (n=67)	Treatment: Control (n=64)	*P* value
Weight (kg)	-0.5 ± 9.1	-0.7 ± 9.1	0.87
Modified Rodnan skin score	-19.6 ± 10.2	-8.6 ± 12.1	<0.001
Creatinine clearance (ml/min)†	-11.9 ± 28.6	-0.95 ± 22.9	0.017
LVEF (%) by cardiac echo	-1.8 ± 14.7	-1.9 ± 13.7	0.96
VC (% predicted)	5.7 ± 18.1	-2.8 ± 17.2	0.006
DLCO (% predicted)	-4.7 ± 13.4	-4.1 ± 17.6	0.84
HAQ-DI score	-0.55 ± 1.14	-0.19 ± 0.77	0.040
SF-36 score			
Physical component	9.0 ± 15.3	3.7 ± 10.7	0.028
Mental component	1.3 ± 13.9	3.1 ± 16.6	0.50

Van Laar et al. , JAMA, 2014

ASTIS trial

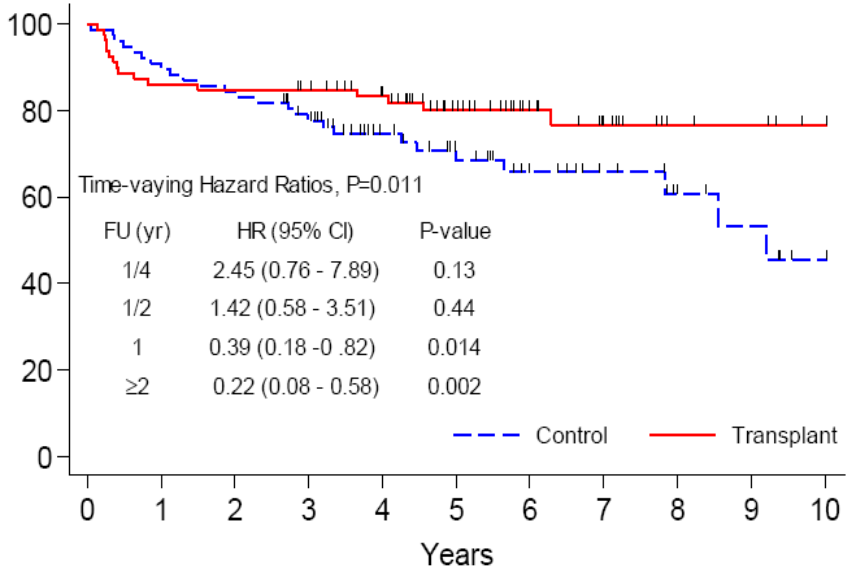
A Event-free Survival



Number at risk

Control	77	68	63	55	40	31	21	14	8	6	3
Transplant	79	66	65	62	53	37	25	17	11	10	6

B Overall Survival



Number at risk

Control	77	69	64	55	40	31	21	15	9	7	3
Transplant	79	68	67	64	55	39	26	19	12	11	7

J. Van Laar JAMA 2014

ASTIS trial

conclusions

In patients with early, severe diffuse cutaneous systemic sclerosis, HSCT was more effective than cyclophosphamide, but was associated with severe toxicities including treatment-related mortality of 10.1% and viral infections.

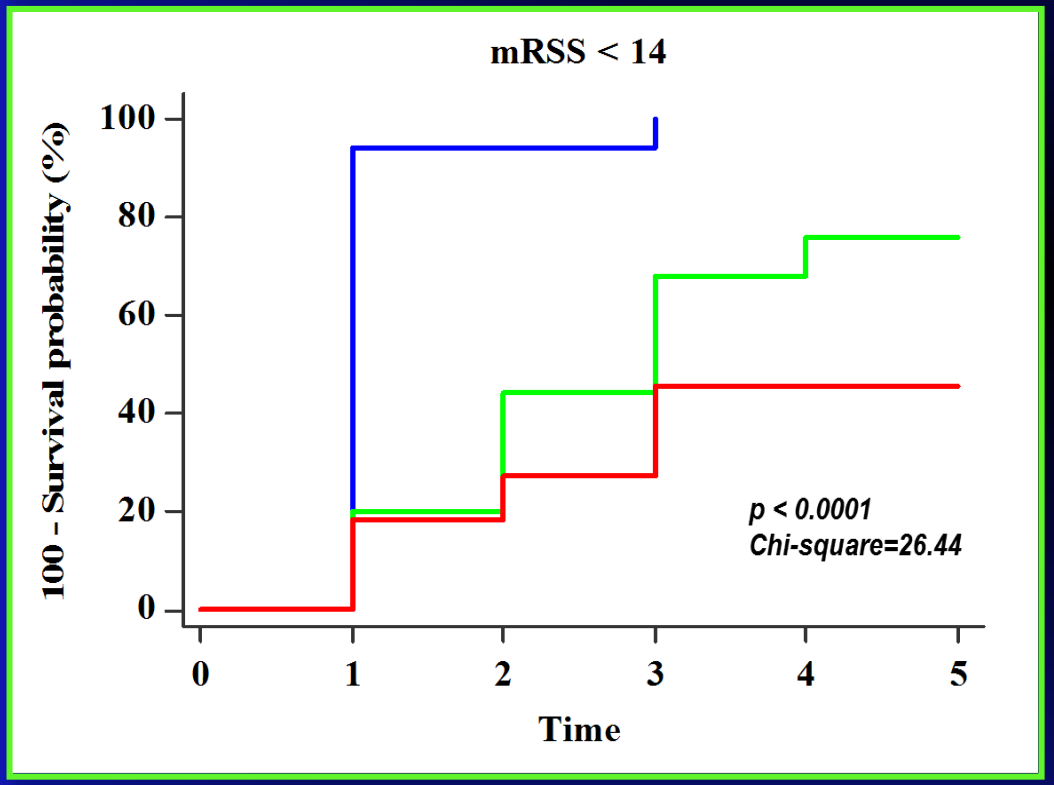
Number of patients and their epidemiological data

	N° pts	F/M	Enrolment period	Mean age at HSTC /disease worsening (years)	Disease duration (months)	mRSS	DLCO	ESSG
HSTC	**17**	**12/5**	**2003-2009**	**41** (20-64)	**24** (18-47)	**21.9** (19.6-24.2)	**68.9** (61-76.8)	**5.4** (4.9-5.8)
Case control	**36**	**26/10**	**1991-2010**	**44** (19-62)	**26.3** (21-31.6)	**20.4** (18.7 -22.1)	**67.7** (64.7-70.7)	**5.0** (5.1-5.7)

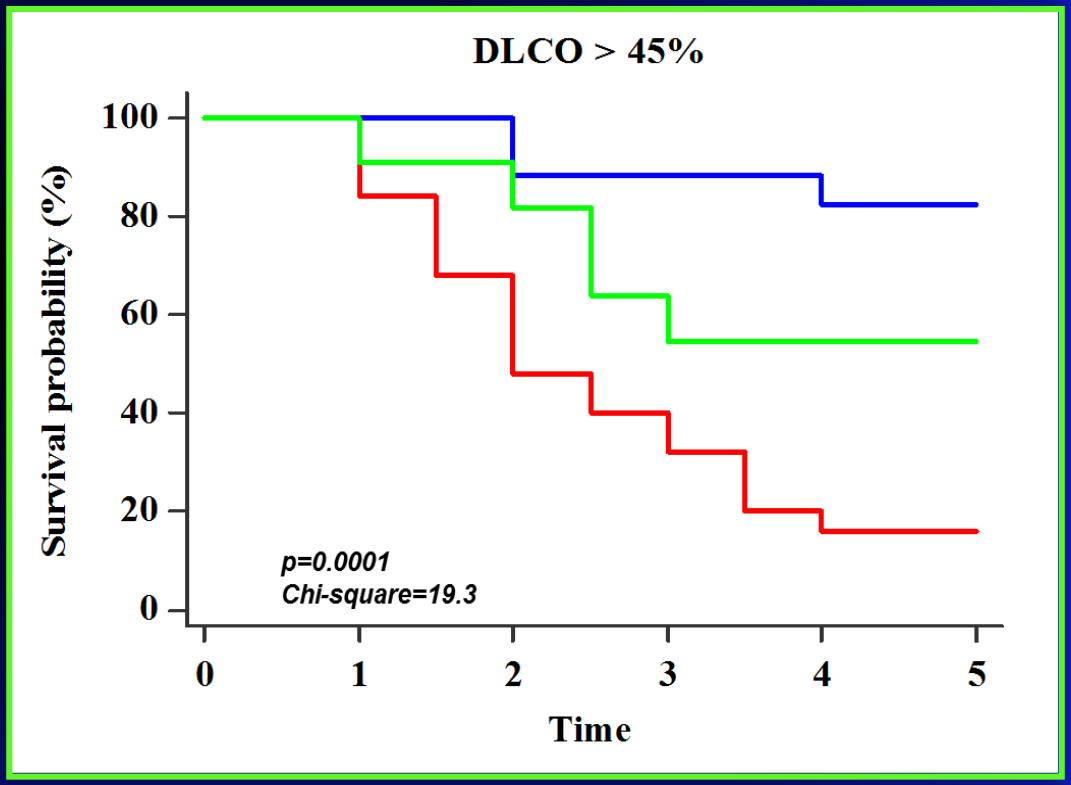
Del Papa et al. Bone Marrow Transplantation 2016

HSCT-treated patients with SSc show significant improvement of outcome parameters, with respect to matched not-trasplanted patients.

mRss Remission curve



DLCO Survival curve

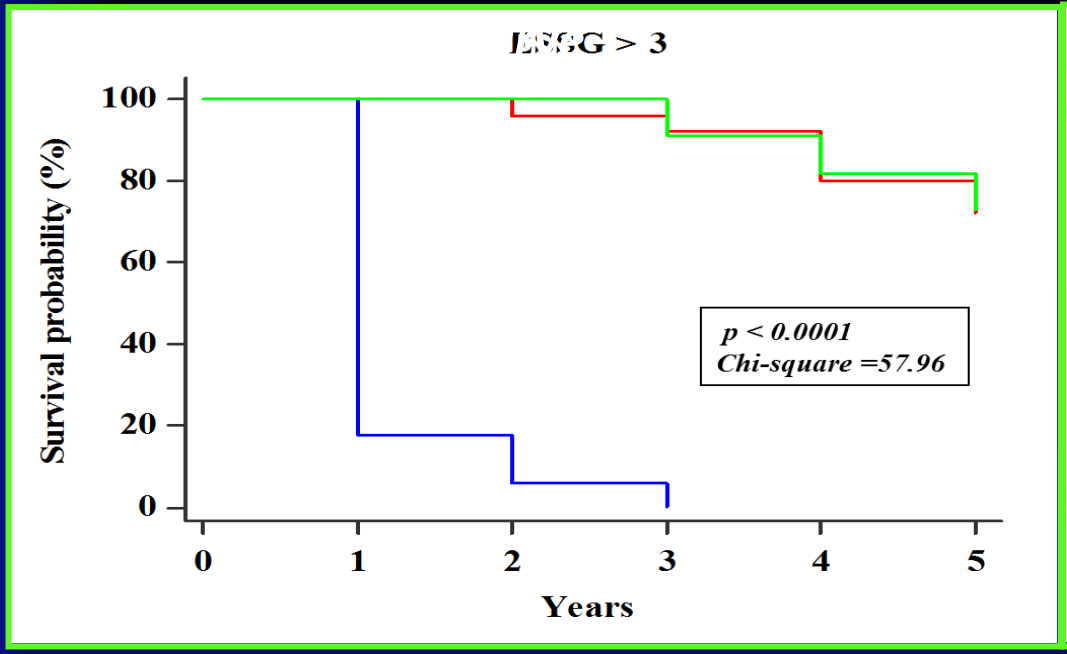


HSCT pts
CTX controls
noCTX controls

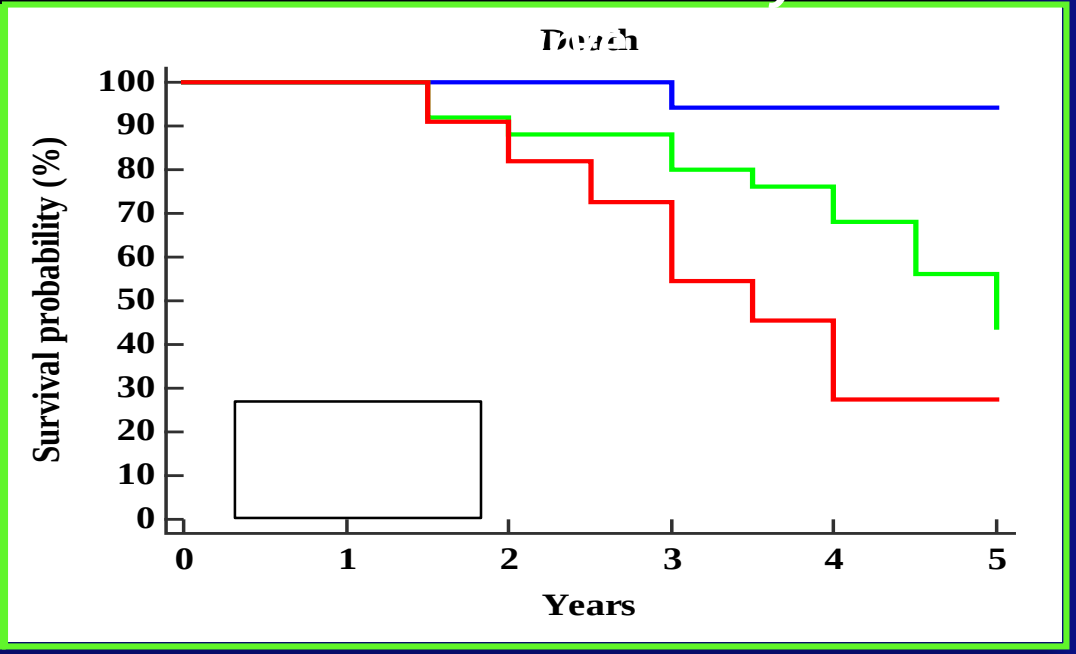
Del Papa et al. Bone Marrow Transplantation 2016

HSCT-treated patients with SSc show significant improvement of several outcome parameters, including disease activity and death, with respect to matched not- trasplanted patients

ESSG Survival

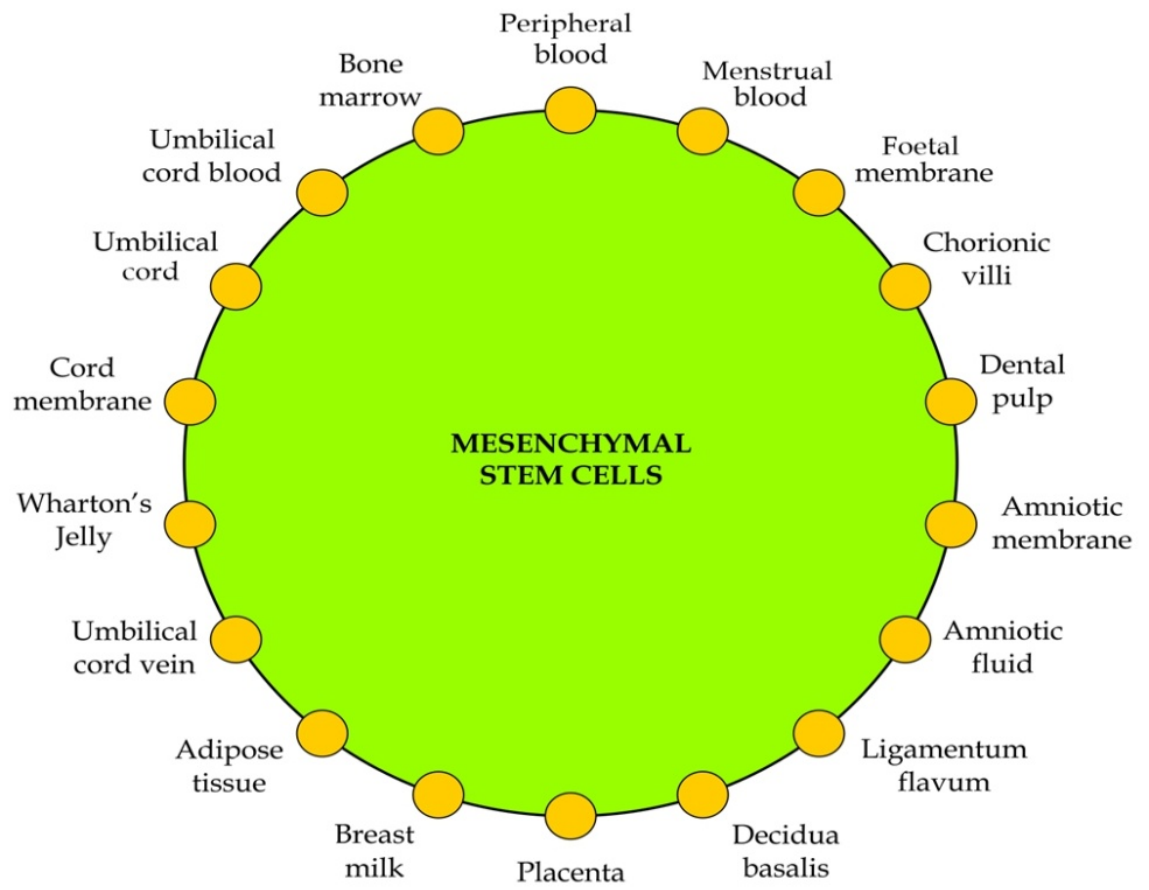


Survival Probability

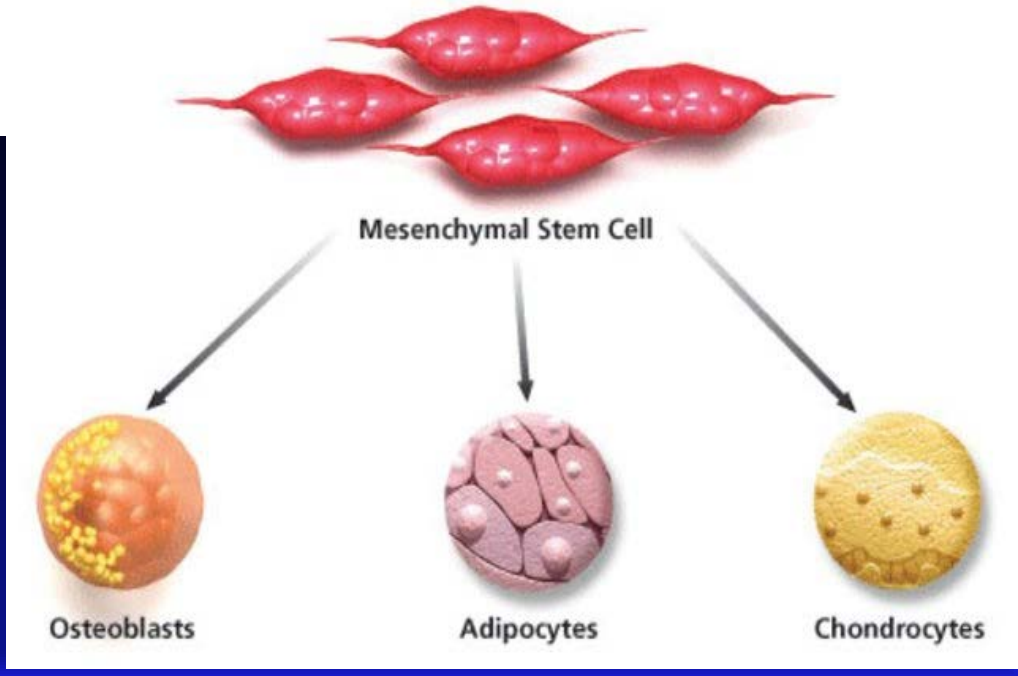


HSCT pts
CTX controls
noCTX controls

Del Papa et al. Bone Marrow Transplantation 2016

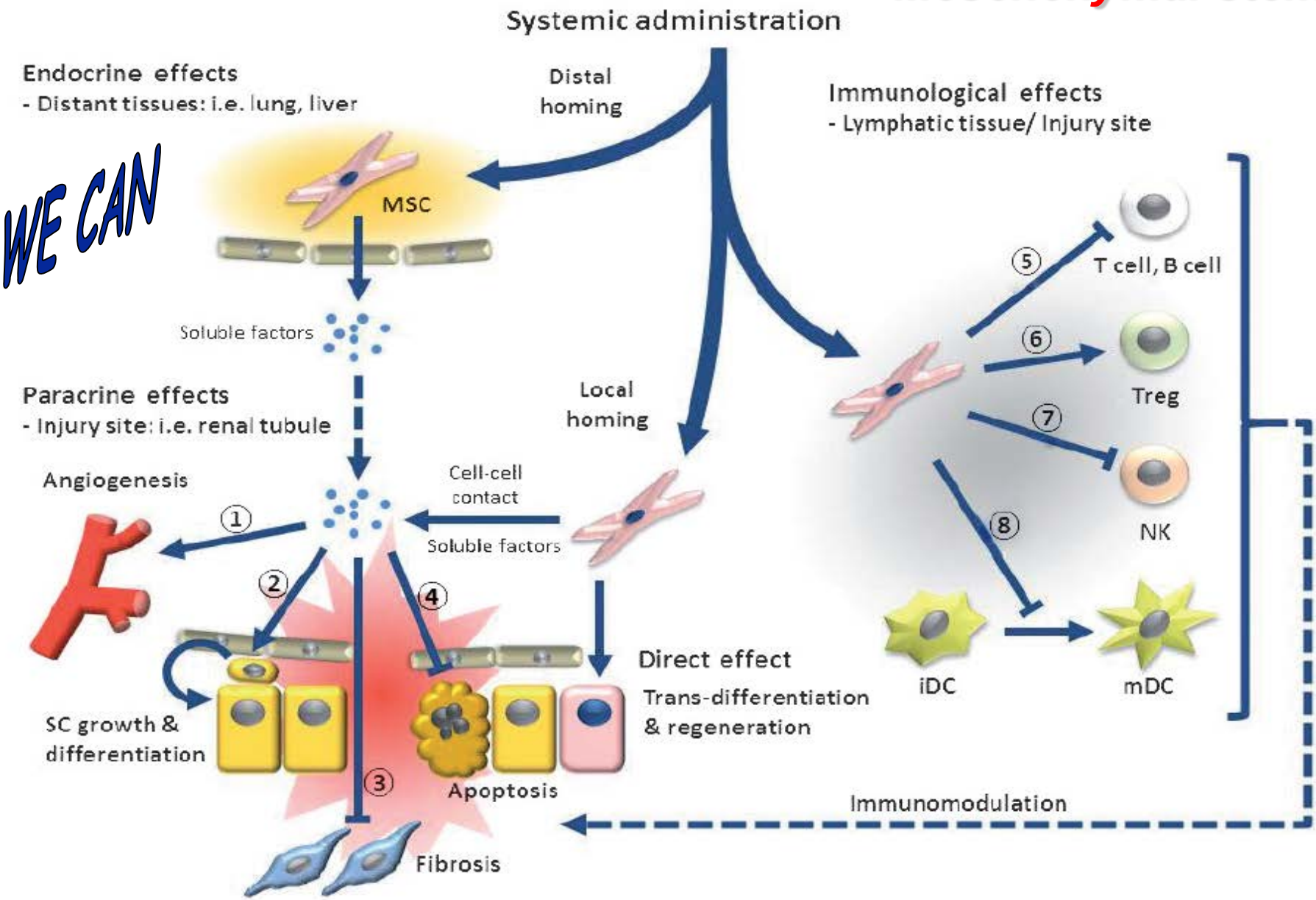


MSCs as multipotent cells



Mesenchymal stem cells

YES, WE CAN

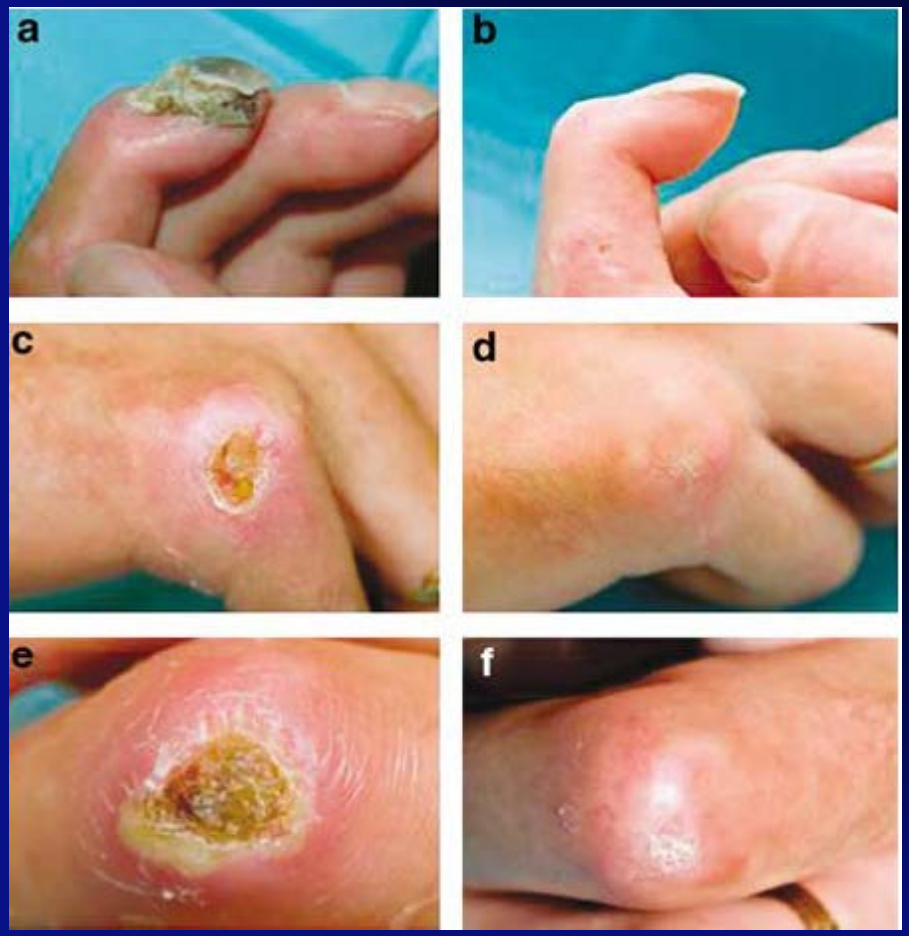


Systemic administration of mesenchymal stem cells can trigger distal (endocrine) or local (paracrine) effects that include cell mediated actions.

Marked improvement of severe progressive systemic sclerosis after transplantation of mesenchymal stem cells from an allogeneic haploidentical-related donor mediated by ligation of CD137L

M Christopeit[1,4], M Schendel[2,4], J Föll[3], LP Müller[1], G Keysser[2] and G Behre[1]

Leukemia (2008) **22,** 1062–1064; doi:10.1038/sj.leu.2404996; published online 1 November 2007



	right hand sept 12, 2006	left hand sept 12, 2006	right hand mar 19, 2007	right hand mar 19, 2007
$tcpO_2$ [mmHg]				
patient lying	30	23	**49.8**	**48.4**
hand below cardial niveau	32	30	**53.8**	**56.8**
Color-coded Duplex Ultrasound				
Arteria brachialis				
V_{max}/V_{min} [m/s]	1.02/0.13	0.84/0.06	0.83/0.13	0.74/0.09
RI	0.87	0.92	**0.84**	**0.88**
volumetric flow rate [ml/min] / diameter [mm]	91/3.2	48/3.2	59/2.7	48/2.7
Arteria radialis				
V_{max}/V_{min} [m/s]	0.59/0.1	0.48/0.07	0.67/0.17	0.72/0.17
RI	0.83	0.85	**0.74**	**0.77**
volumetric flow rate [ml/min] / diameter [mm]	10/1.4	--/1.5	17/1.7	15/1.5
Arteria ulnaris				
V_{max}/V_{min} [m/s]	0.61/0.13	0.4/0.04	0.48/0.1	0.45/0.08
RI	0.79	0.9	**0.79**	**0.82**
volumetric flow rate [ml/min] / diameter [mm]	7/1.2	--/0.9	2/0.7	--/--

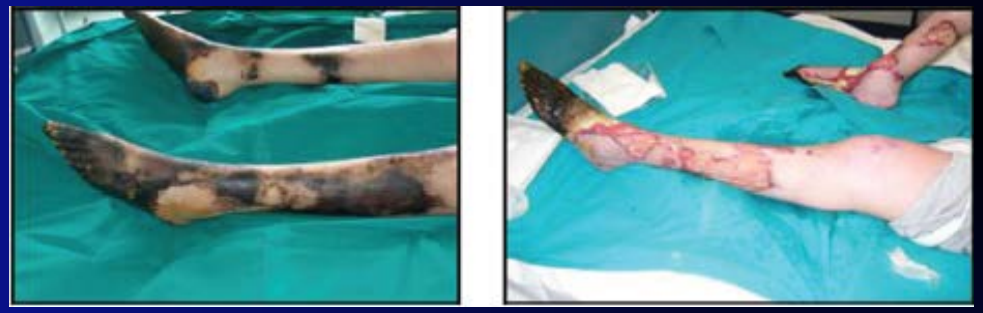
Representation of results of vascular ultrasound before and 6 months after transplantation.

ORIGINAL RESEARCH | Annals of Internal Medicine

Autologous Mesenchymal Stem Cells Foster Revascularization of Ischemic Limbs in Systemic Sclerosis

A Case Report

Serena Guiducci, MD; Francesco Porta, MD; Riccardo Saccardi, MD; Stefano Guidi, MD; Lidia Ibba-Manneschi, MD; Mirko Manetti, PhD; Benedetta Mazzanti, BSc; Simone Dal Pozzo, BSc; Anna Franca Milia, PhD; Silvia Bellando-Randone, MD; Irene Miniati, MD; Ginevra Fiori, MD; Rossana Fontana, MD; Laura Amanzi, HP; Francesca Braschi, HP; Alberto Bosi, MD; and Marco Matucci-Cerinic, MD, PhD



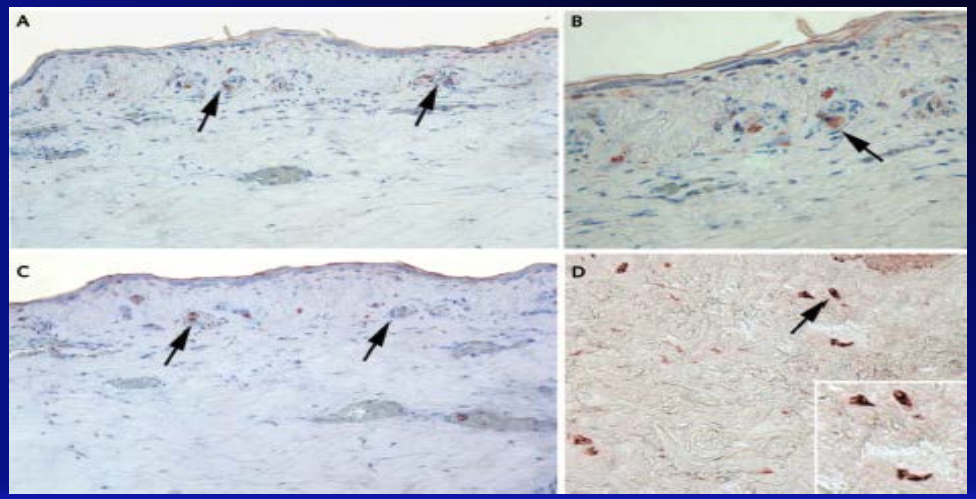
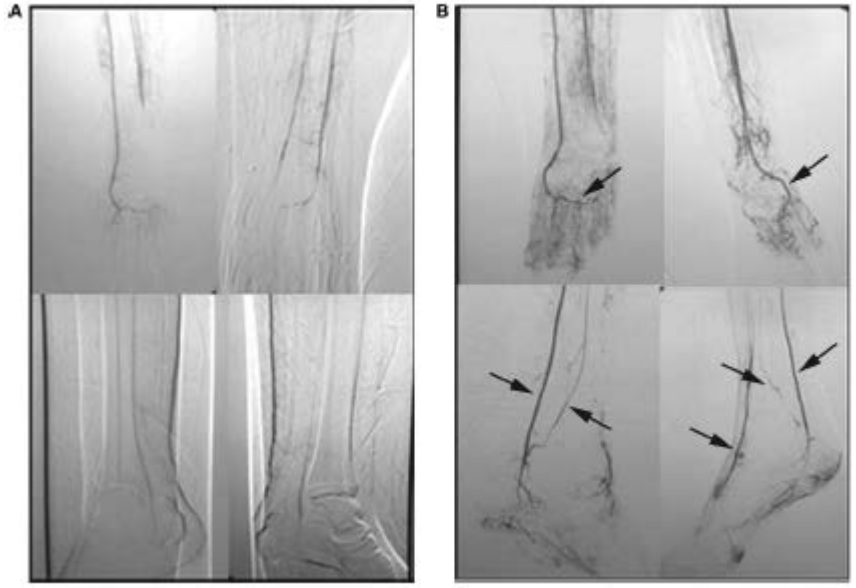


Figure 2. Angiography of patient at admission (*A*) and after receiving 3 cycles of expanded autologous bone marrow–derived mesenchymal stem cells by intravenous infusion (*B*).



Arrows highlight principal areas of change, with clear blood flow in the arteries of the upper and lower limbs.

MSCs and SSc

Preliminary results

- ***Improvement of dcSSc following allogenic MSCs***
  (Christopeit et al. Leukemia 2008)

- ***Revascularization of leg ischemia following autologous MSCs***
  (Guiducci et al. Ann Intern Med 2011)

- ***5 cases of scleroderma treated with MSCs***
  (Keyszer et al. Arthritis Rheum.2011)

- ***Skin & ASC***

Scuderi et al. Cell Transplant 2012
Bank et al. J Plast Reconstr Surg 2014
Del Papa et al. Cell Transplant 2014
Granel et al. Ann Rheum Dis 2014
Del Papa et al. Cell Transplant 2015

Autologous adipose tissue in Raynaud's phenomenon

13 refractory RP

(21 treated hands)

- 2 CTD; 9 SSc; 2 PRP

All received Botulinum toxin and 11 prior sympathectomy

18 months of follow-up

(57%

Bank et al. 2014

Autologous adipose tissue in Raynaud's phenomenon

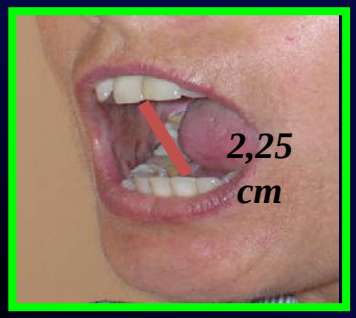
- Improvement in Pain ($p < 0.001$)
- Number, duration and severity of cold attacks ($p < 0.001$ for all)
- Reduction in number of ulcers ***(57% → 5%)*** ($p = 0.016$)

Bank et al. 2014

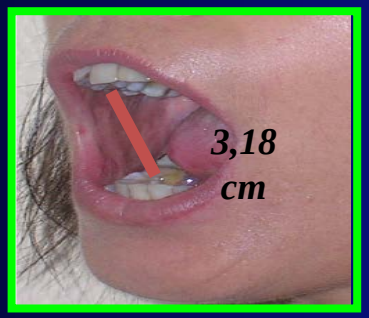
AUTOLOGOUS FAT GRAFTING IN THE TREATMENT OF FIBROTIC PERIORAL CHANGES IN PATIENTS WITH SYSTEMIC SCLEROSIS

Demonstration of functional effects on mouth opening and biological changes in local vascularization

Baseline 1 month 3 months

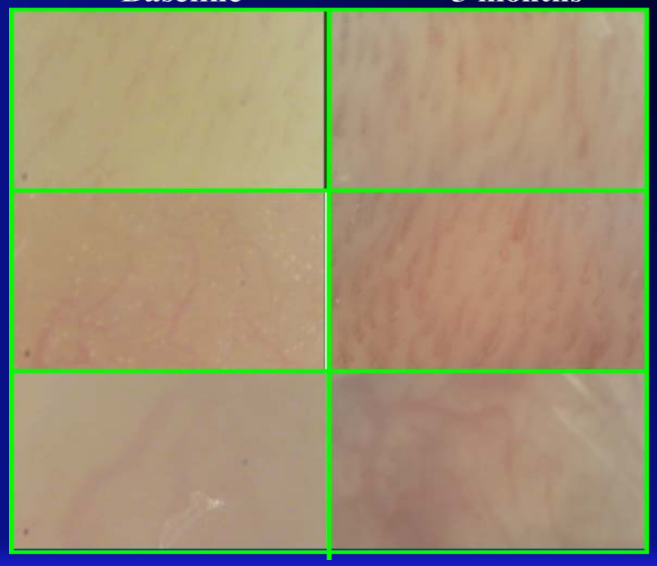


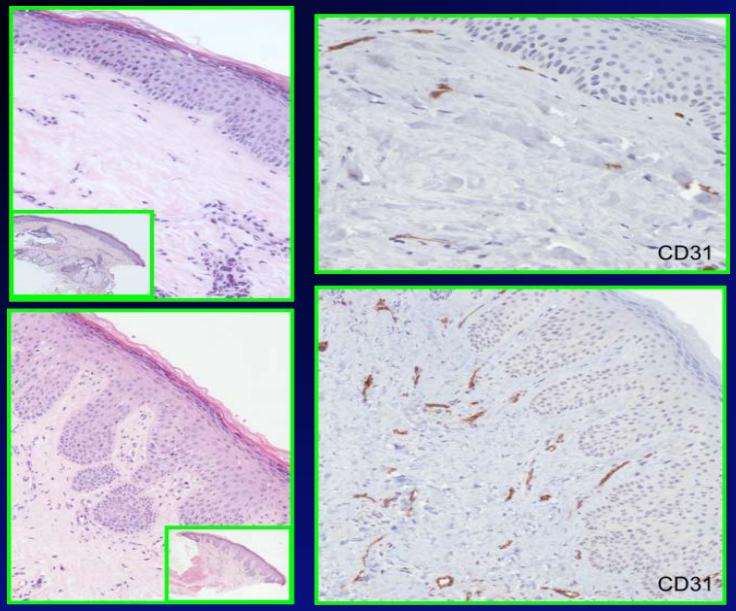
Baseline



3 months

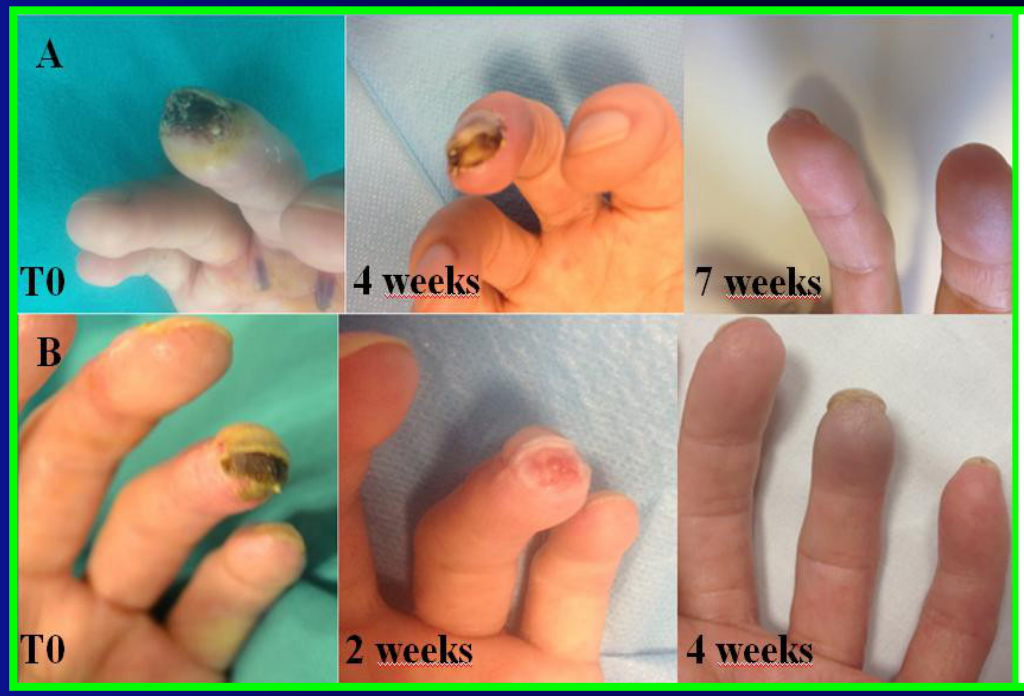
Baseline 3 months

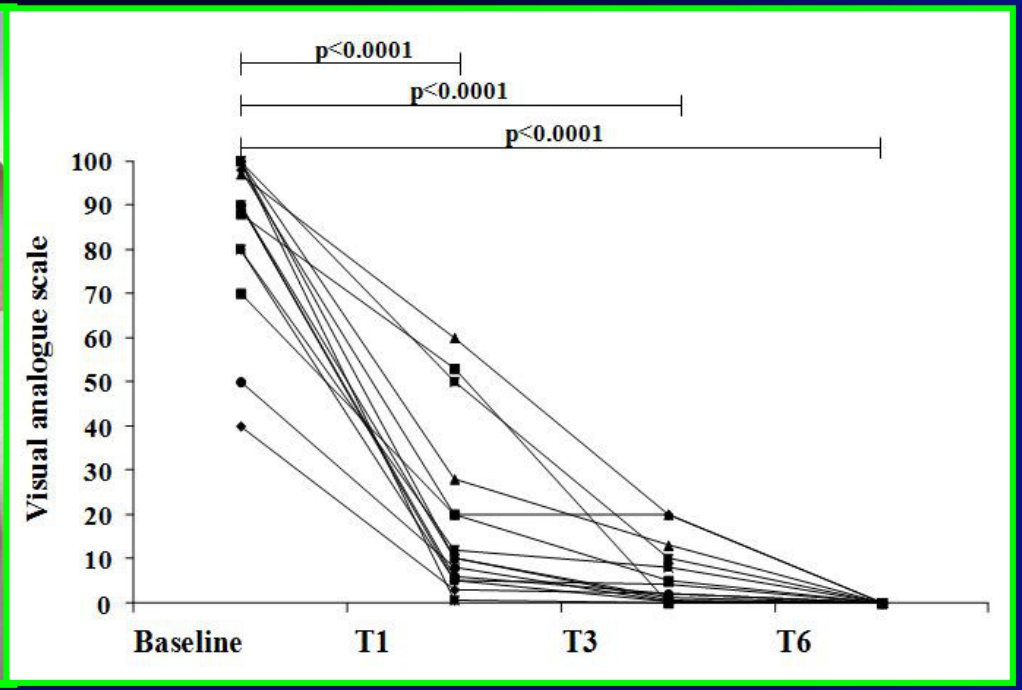




Del Papa et al. Cell Transplantation 2013

Implantation of autologous adipose tissue-derived cells induces a prompt healing of long-lasting digital ulcers in SSc, rapid resolution of DU-related pain and improvement in local vascular features





Del Papa et al. Cell Transplantation 2015

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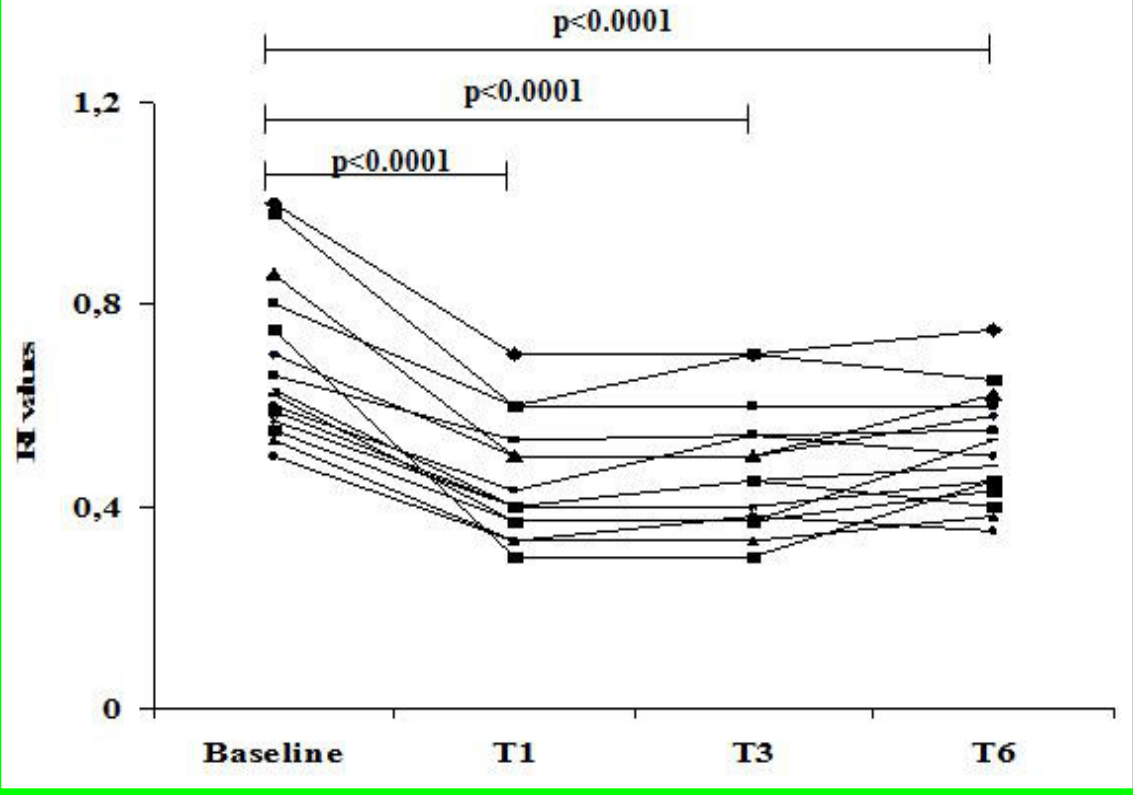
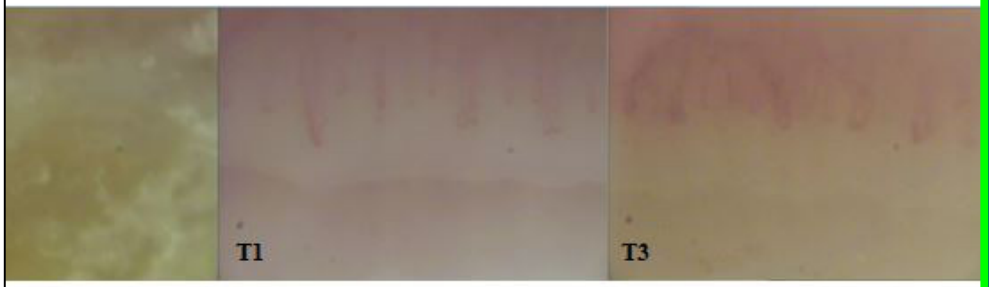
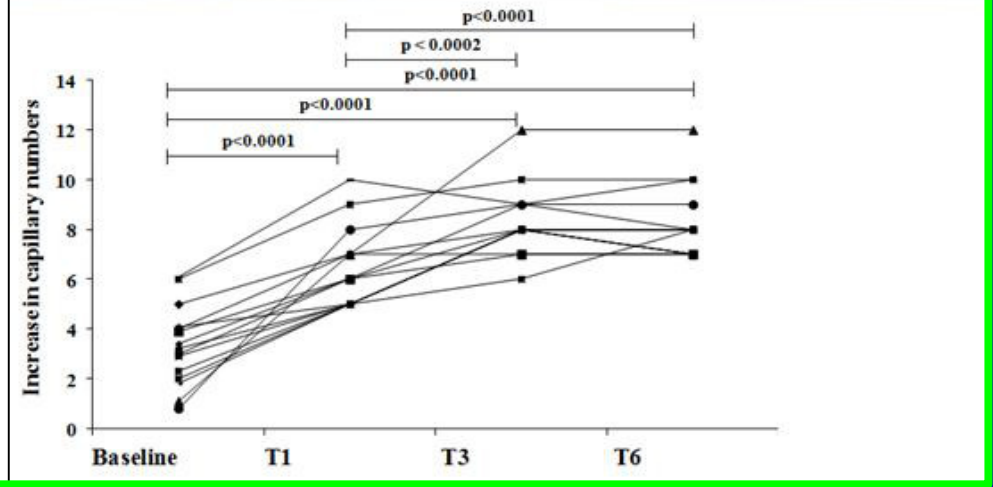






Del Papa et al. Cell Transplantation 2015

Effect of autologous adipose tissue injection on vascular manifestations

	Baseline	2 months	Change (2 months– baseline)	p Value*	6 months	Change (6 months– baseline)	p Value†
RCS/10							
Mean±SD	7.2±0.9	4.5±1.9	−2.7±2.2	**<0.001**	2.9±1.4	−4.3±2.1	**<0.001**
Median (range)	7.5 (6.5–8.0)	5.0 (4.0–5.5)	−2.0 (−6.5–−1.0)		3.0 (2.5–3.0)	−4.5 (−7.0–−1.5)	
Hand visual analogue scale/100							
Mean±SD	59.4±17.2	21.6±17.5	−37.8±28.6	**0.001**	17.8±15.3	−41.7±22.7	**<0.001**
Median (range)	58.5 (50.0–72.5)	19.0 (7.0–40.0)	−39.0 (−80.0–21.0)		13.6 (9.0–26.0)	−44.0 (−80.0–10.0)	
Capillaroscopy data							
Number of capillary loops							
Dominant hand							
Mean±SD	136.3±78.9	124.1±60.1	−12.2±40.9	**0.325**	138.5±60.8	2.3±47.9	**0.874**
Median (range)	124.0 (42–298)	118.0 (30–226)	−12.5 (−98–61)		132.5 (48–232)	8.0 (−97–92)	
Non-dominant hand							
Mean±SD	159.5±96.9	142.1±71.0	−23.5±54.1	**0.181**	152.3±75.2	−11.7±42.0	**0.377**
Median (range)	122.0 (45–298)	139.0 (42–277)	−13.0 (−137–33)		131.5 (70–308)	−10.0 (−103–34)	
Number of giant capillaries							
Dominant hand							
Mean±SD	20.3±20.3	17.8±18.0	−2.4±8.4	**0.341**	15.3±17.9	−4.9±7.8	**0.035**
Median (range)	12.0 (0–64)	13.0 (1–67)	1.0 (−22–7)		9.0 (0–63)	−1.0 (−17–6)	
Non-dominant hand							
Mean±SD	18.3±11.7	18.2±20.5	−5.5±7.9		18.1±18.6	−5.1±8.9	**0.074**
Median (range)	13.0 (0–39)	12.5 (0–77)	−3.0 (−20–3)	**0.046**	13.0 (0–72)	−3.0 (−23–4)	
Number of dystrophic capillaries							
Dominant hand							
Mean±SD	23.3±26.8	13.0±11.6	−10.3±17.9	**0.115**	11.0±10.3	−12.3±20.2	**0.047**
Median (range)	14.0 (0–79)	14.0 (0–30)	−2.0 (−53–6)		8.5 (0–29)	−1.0 (−57–5)	
Non-dominant hand							
Mean±SD	23.2±22.8	11.2±9.5	−11.4±14.9		9.7±6.7	−13.5±19.8	**0.047**
Median (range)	17.0 (0–58)	8.0 (0–29)	−4.0 (−37–6)	**0.030**	10.5 (0–22)	−6.0 (−45–15)	

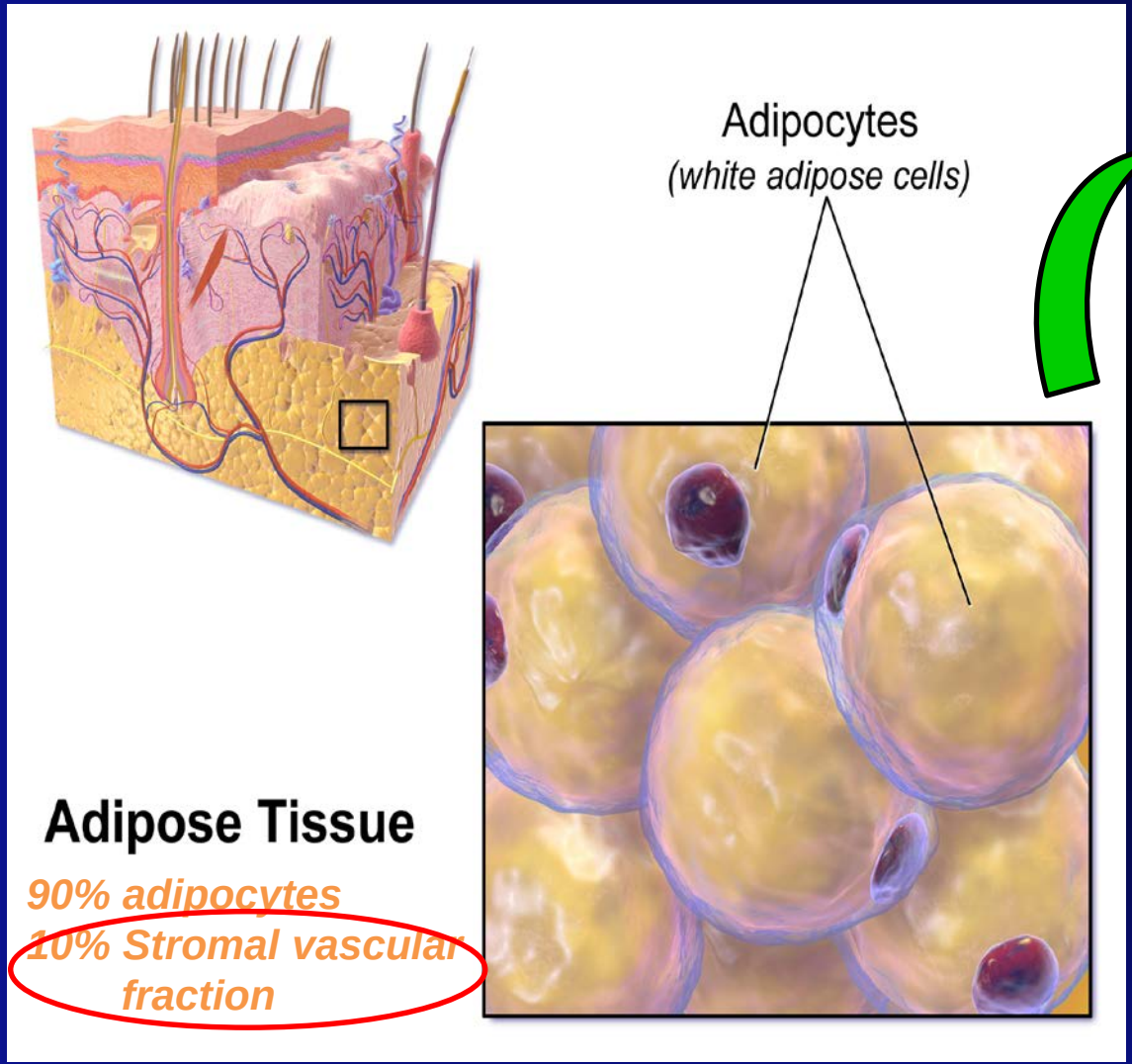
Granel B. et al . Ann Rheum Dis 2015

Effect of autologous adipose tissue injection on scleroderma and skin thickness

	Baseline	2 months	Change (2 months– baseline)	p Value*	6 months	Change (6 months-– baseline)	p Value†
Mean circumference of F1–F5 (ring size)							
Dominant hand							
Mean±SD	**61.9±2.2**	**60.7±2.3**	**−1.2±1.4**	**0.013**	**59.8±2.4**	**−2.1±1.1**	**<0.001**
Median (range)	**61.8 (58.8–66)**	**60.8 (57–65)**	**−0.9 (−4.6–0.6)**		**60 (56–64.4)**	**−2.3 (−4.6-–0.4)**	
Non-dominant hand							
Mean±SD	**60.7±2.3**	**59.3±1.7**	**−1.3±1.4**	**0.008**	**58.1±2.2**	**−2.5±1.5**	**<0.001**
Median (range)	**61 (57–64.2)**	**59 (56.8–63.4)**	**−1.2 (−3.4–0.8)**		**58 (54–62.8)**	**−2.5 (−4.8–0.4)**	
MRSS applied to hand/18							
Whole population							
Mean±SD	**10.9±4.9**	**10.0±5.3**	**−0.9±1.6**	**0.067**	**9.9±6.0**	**−1.0±2.8**	**0.246**
Median (range)	**11.5 (3–18)**	**10.5 (2–18)**	**−0.5 (−4–1)**		**12 (1–18)**	**−2 (−5–4)**	
Global MRSS/51							
Whole population							
Mean±SD	**13.9±9.8**	**11.7±9.8**	**−2.3±2.5**	**0.010**	**11.5±10.1**	**−2.4±2.8**	**0.013**
Median (range)	**12 (3–32)**	**9 (2–29)**	**−2 (−6–3)**		**8.5 (1–29)**	**−2 (−7–2)**	

Granel B. et al . Ann Rheum Dis 2015

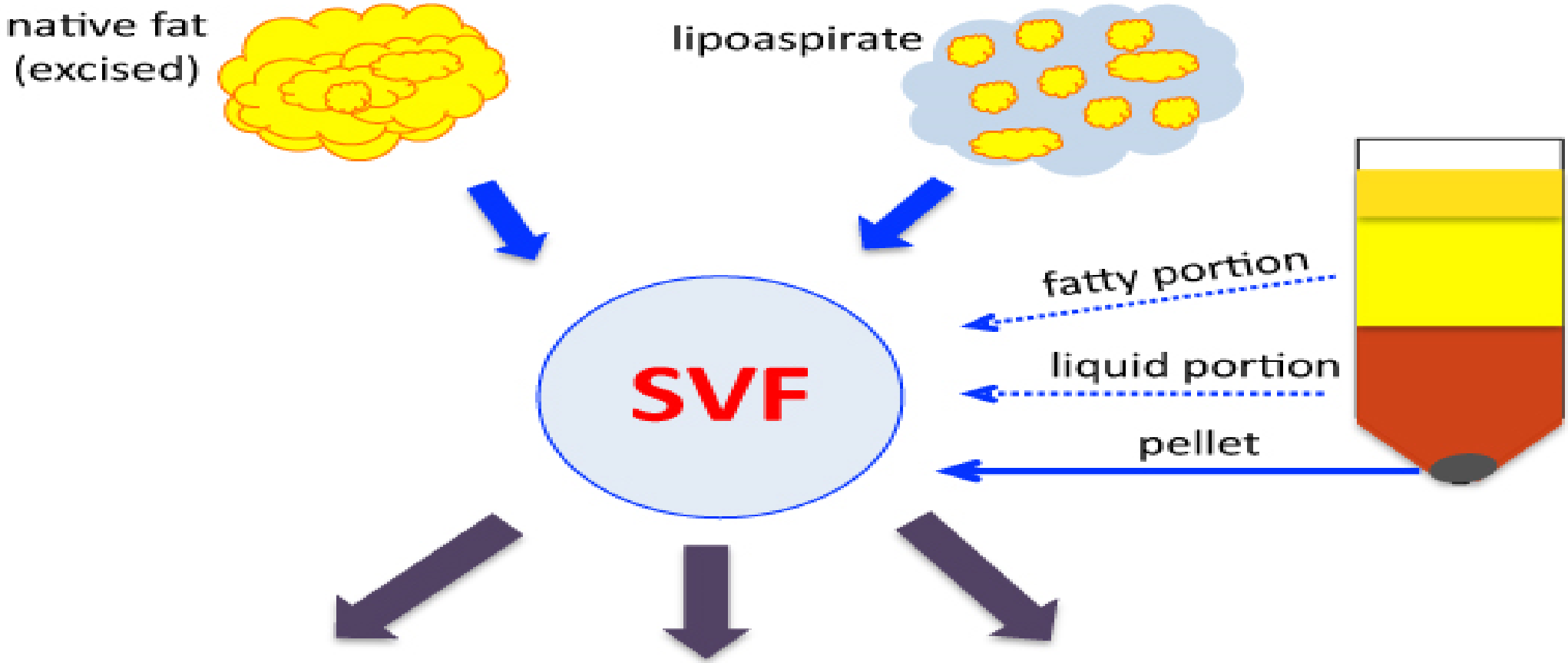
Adipose tissue as source of stem cells



Respond to insulin

Secrete adipokines (leptin and adiponectin)

Store triglycerides



mature

Adipocytes

Fibroblasts

Smooth muscle cells

Endothelial cells

Blood cells

progenitors

Endothelial Progenitor Cells (EPC)

Preadipocytes

Vascular progenitors

Hematopoietic progenitors

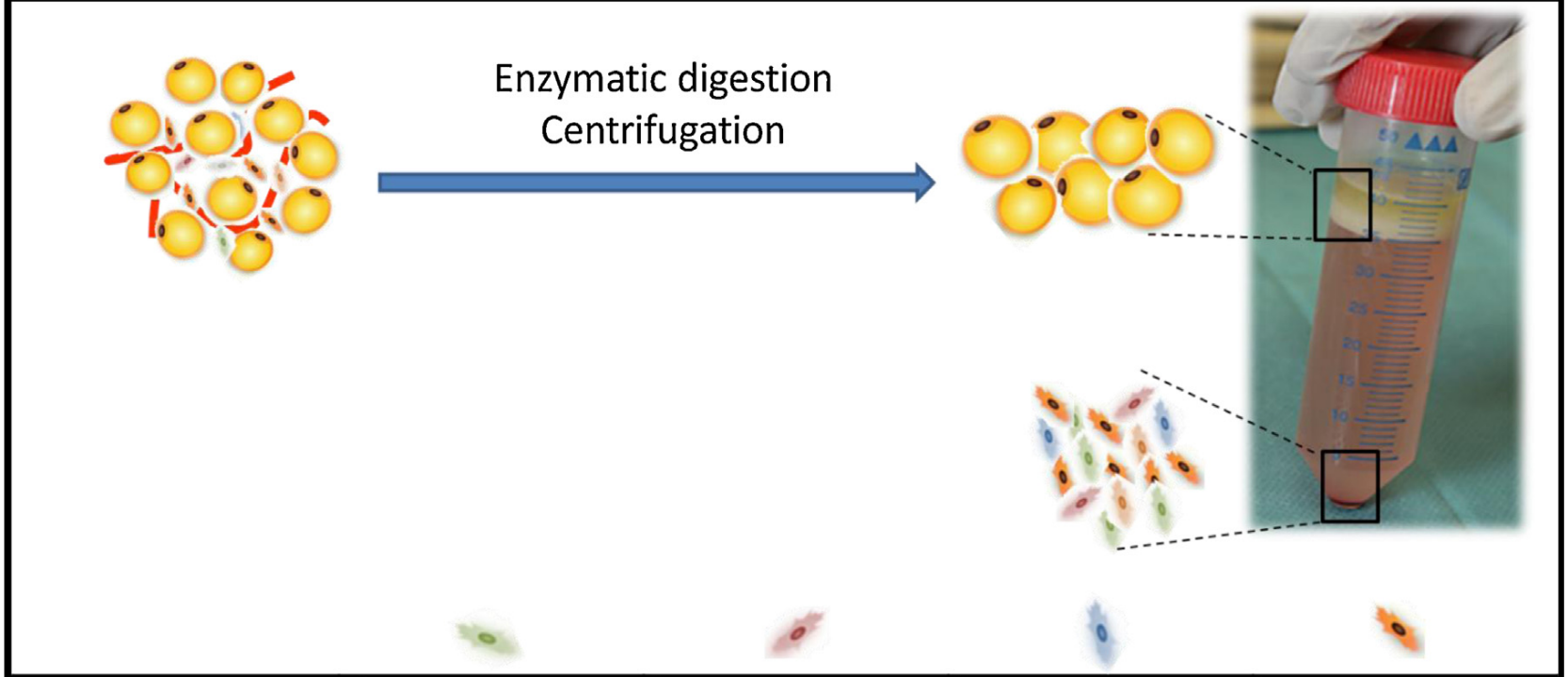
stem

Mesenchymal Stromal Cells (MSC)

Hematopoietic Stem Cells (HSC)

Pericytes

Supra-adventicial cells



Cells	Stromal (including ASC)	Pericytes	Endothelial (mature and progenitors)	Hematopoietic
% ADSVF	15-30	3-5	10-20	25-45
Immunomodulation	++			To be investigated
Angiogenesis	+	+	+++	
Tissue reparation	+++	To be investigated	+ (vessels)	
Secretome	+++			To be investigated

BM-MSC phenotypes and properties in SSc

- ***Impairment of Endothelial Cell Differentiation From Bone Marrow–Derived Mesenchymal Stem Cells***

  (Del Papa et al. Arthritis Rheum, 2006; Cipriani et al Arthritis 2007)

- ***Immulogical properties*** ***(Larghero et al. ARD 2008)***

- ***Altered phenotypes and hyperexpression of TGFbRII***

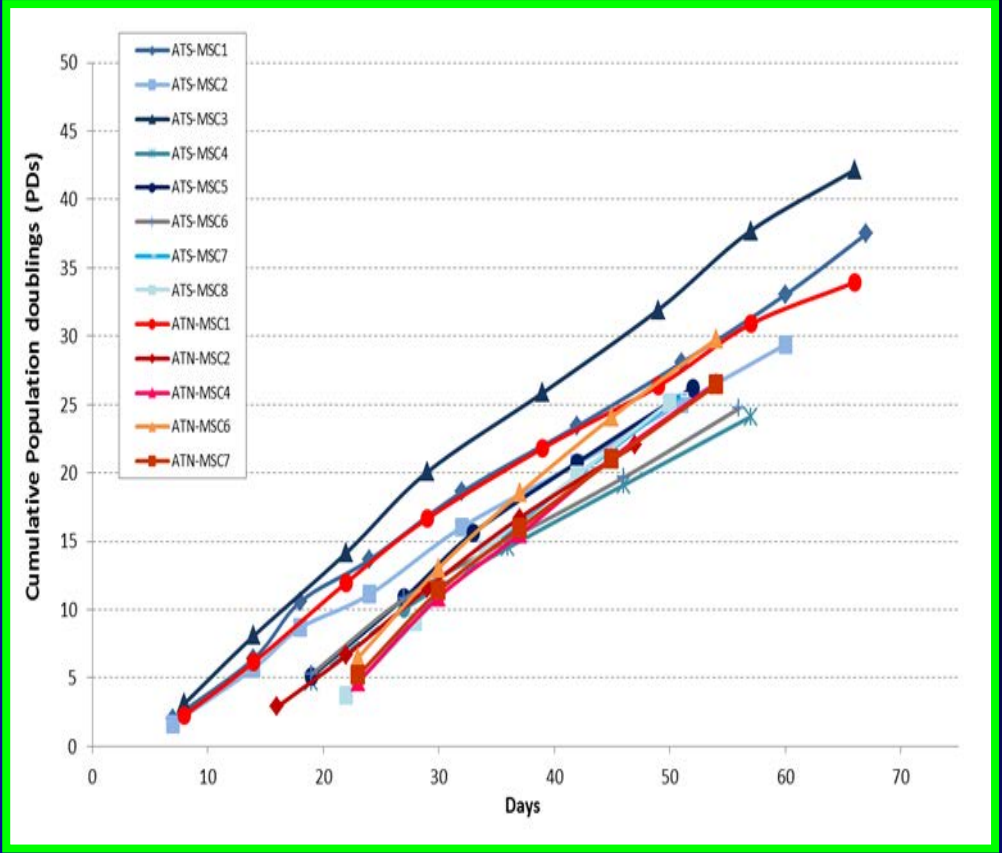
  (Vanneaux et al. BMJ 2013)

- ***Senescent phenotype but preserved immunomodulation properties***

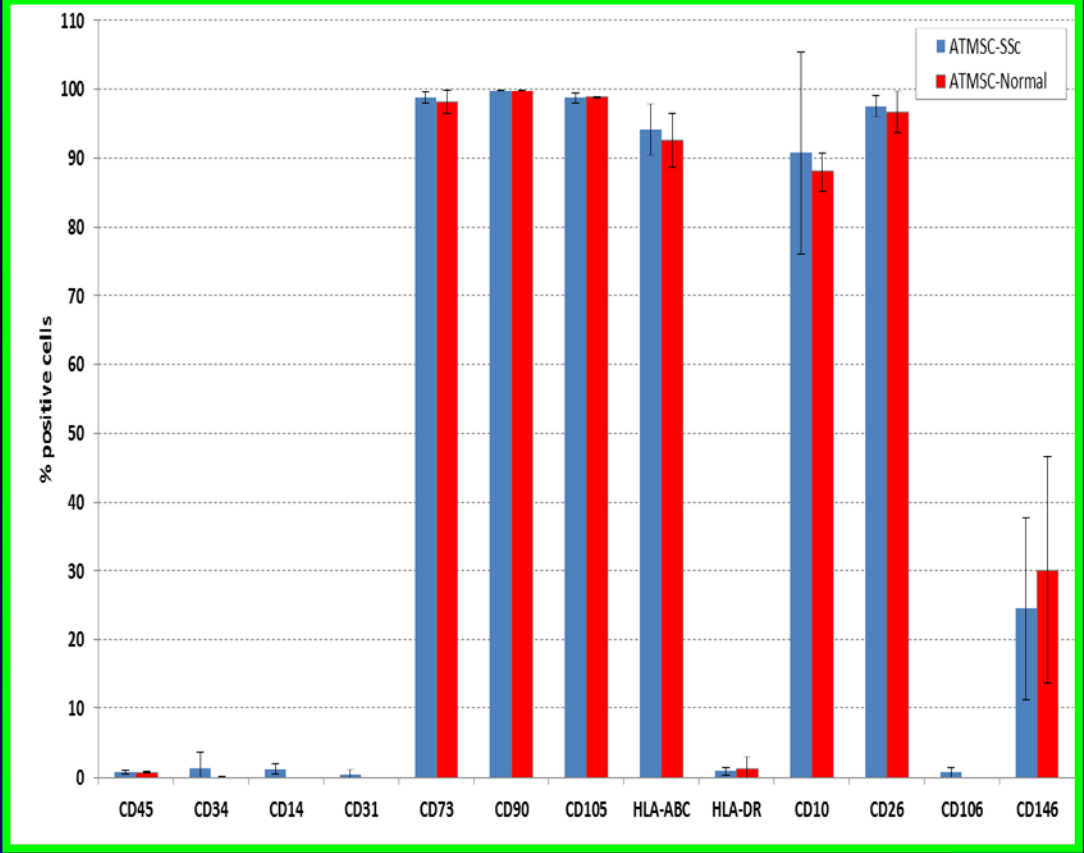
  (Cipriani et al. Clin Exp Immunol 2013)

Adipose-derived MSCs from SSc patients have phenotypical and functional properties similar to normal donors

Population Doublings



Immunophenotype



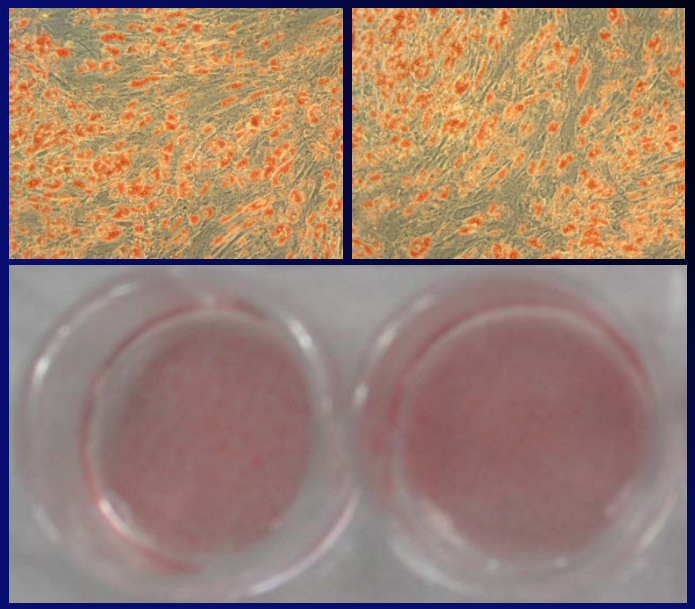
Del Papa et al. submitted

Adipose-derived MSCs from SSc patients have phenotypical and functional properties similar to normal donors

Differentiation

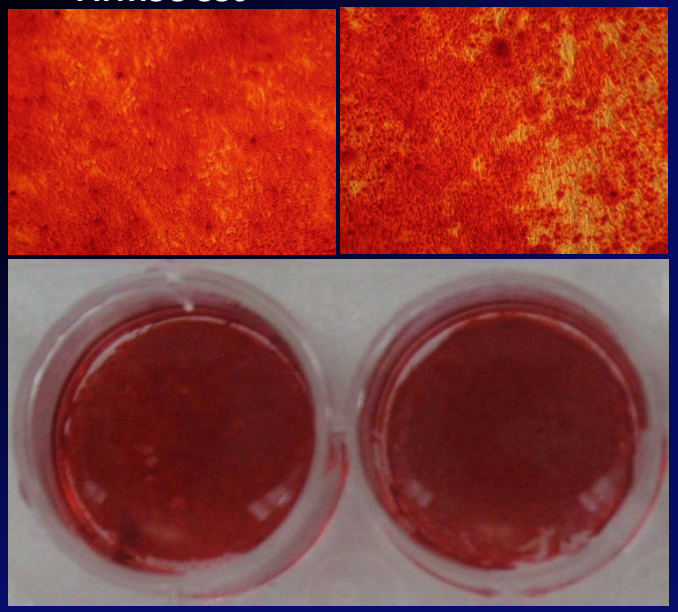
Adipogenic

ATMSC-SSc *ATMSC-Normal*



Osteogenic

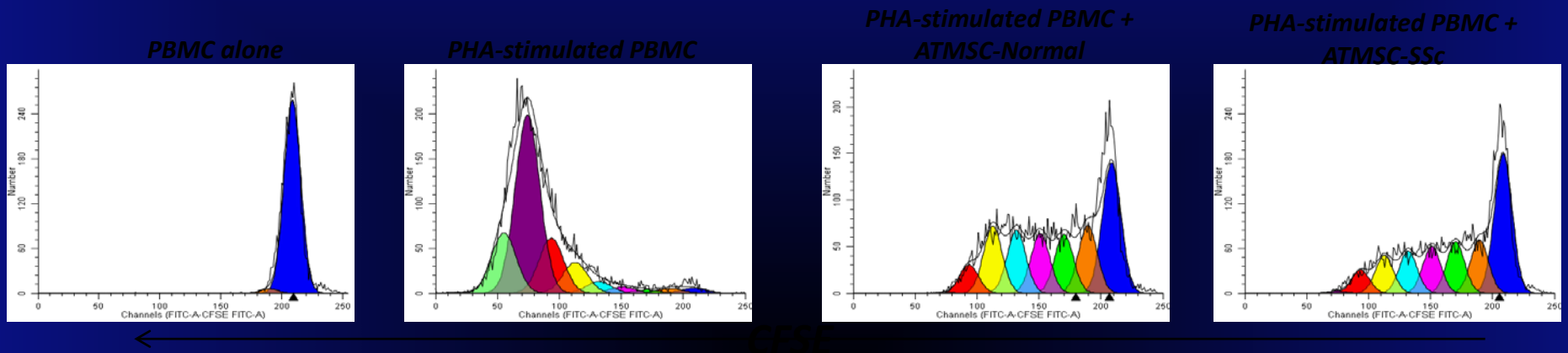
ATMSC-SSc *ATMSC-Normal*

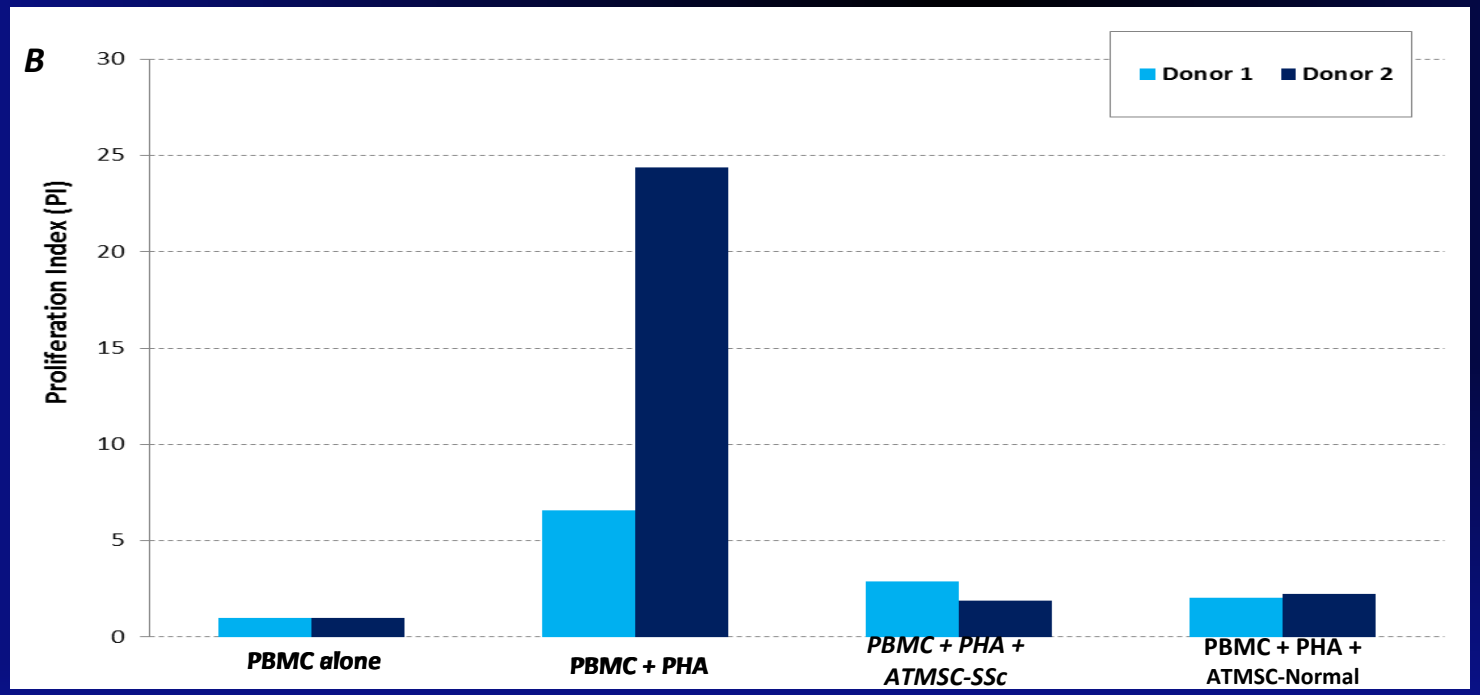


Del Papa et al. submitted

Adipose-derived MSCs from SSc patients have functional properties similar to normal donors

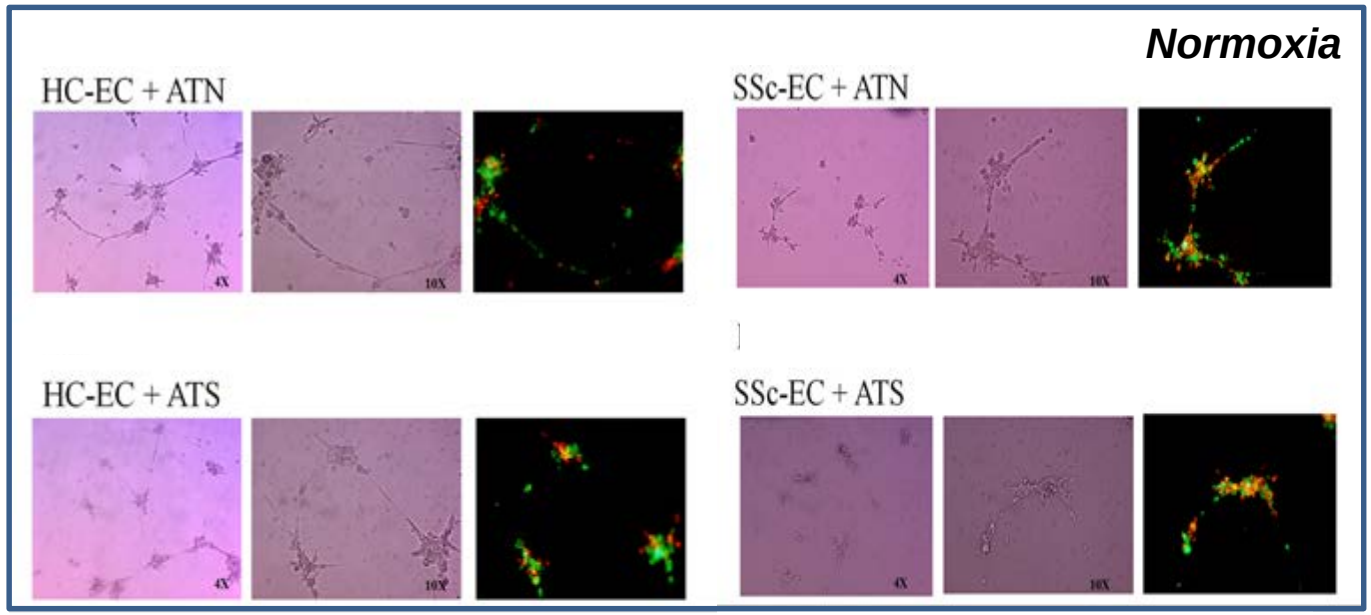
Immunosuppression

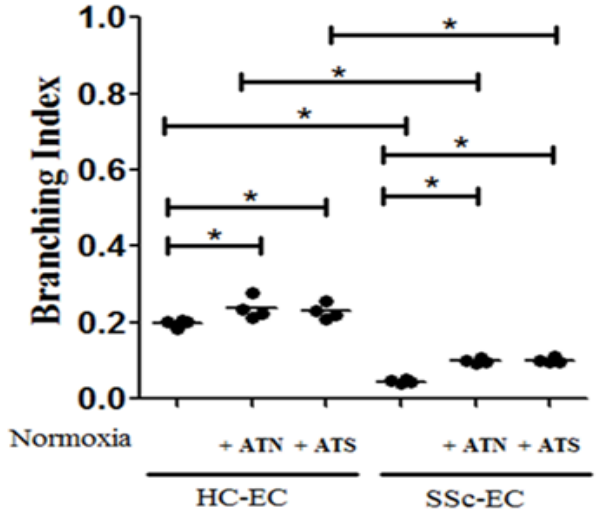


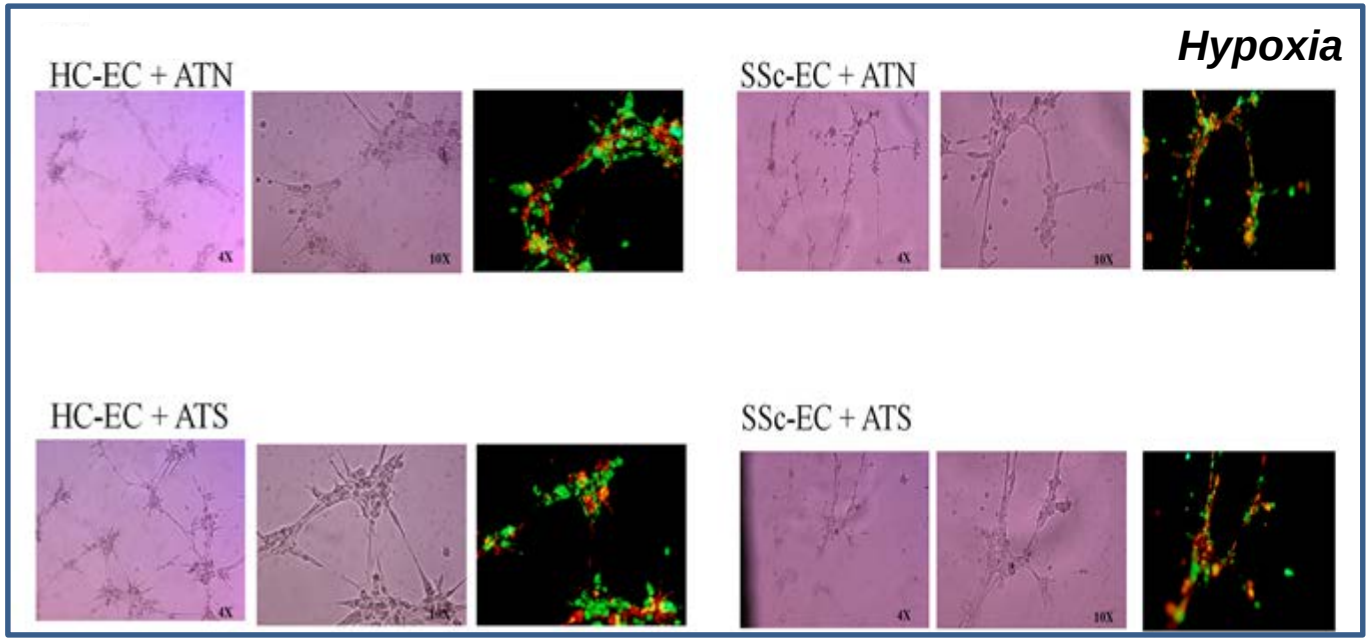


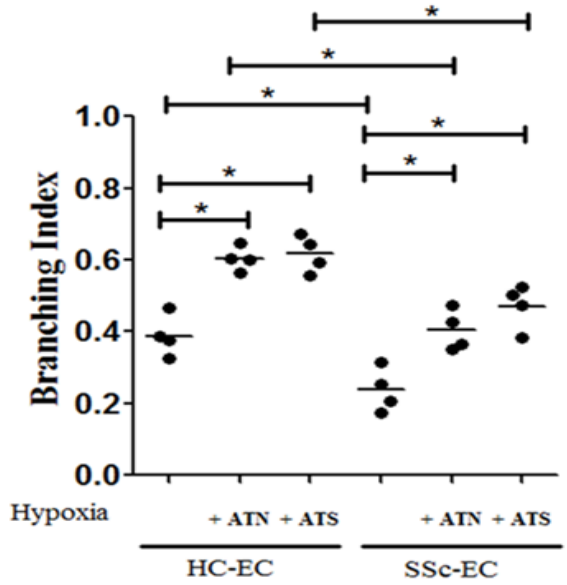
Del Papa et al. submitted

ATN and ATS-MSCs assist Normal-ECs and SSc-EC tube formation









Journal of Autoimmunity 70 (2016) 31–39

Contents lists available at ScienceDirect

Journal of Autoimmunity

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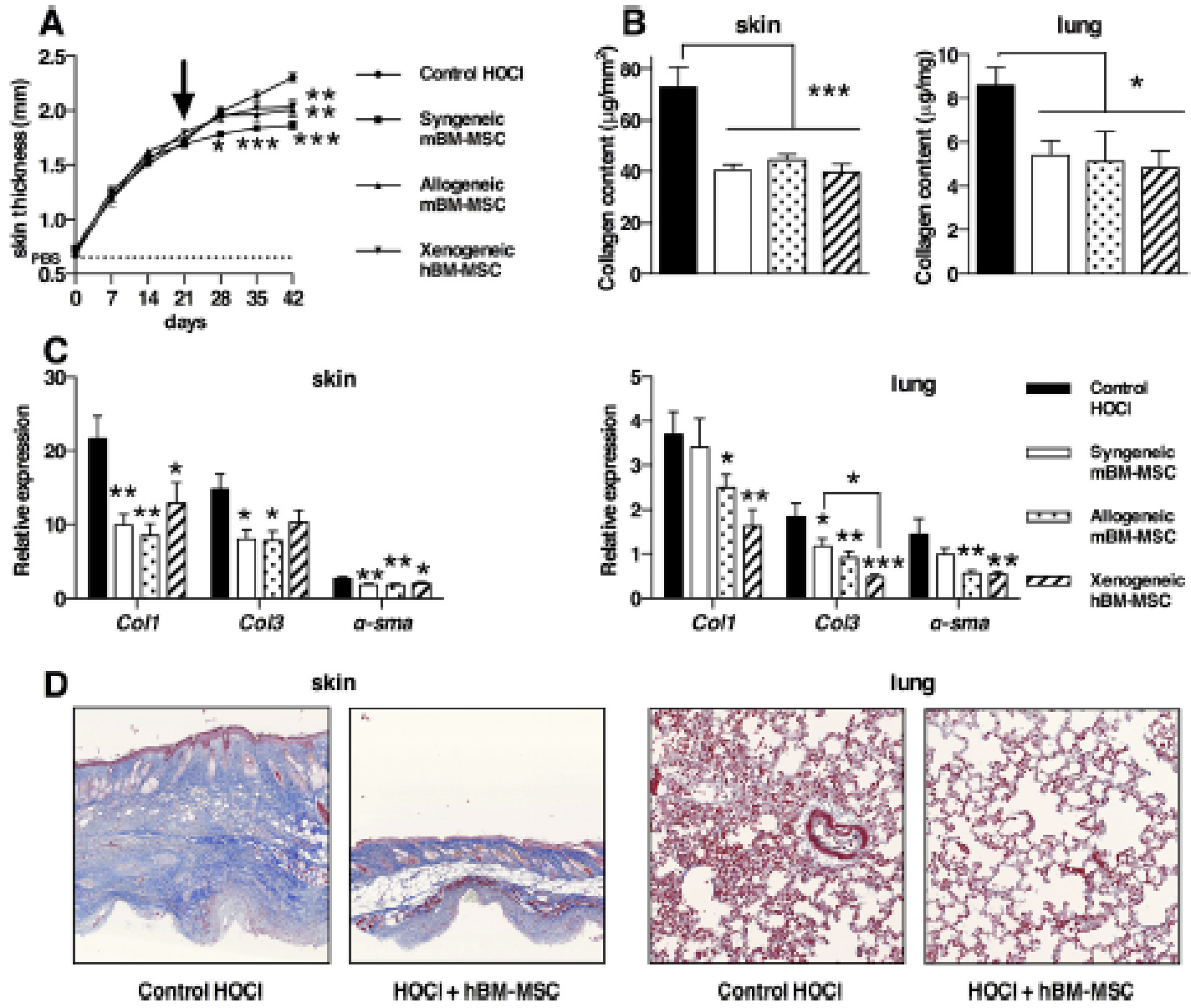
Human adipose mesenchymal stem cells as potent anti-fibrosis therapy for systemic sclerosis

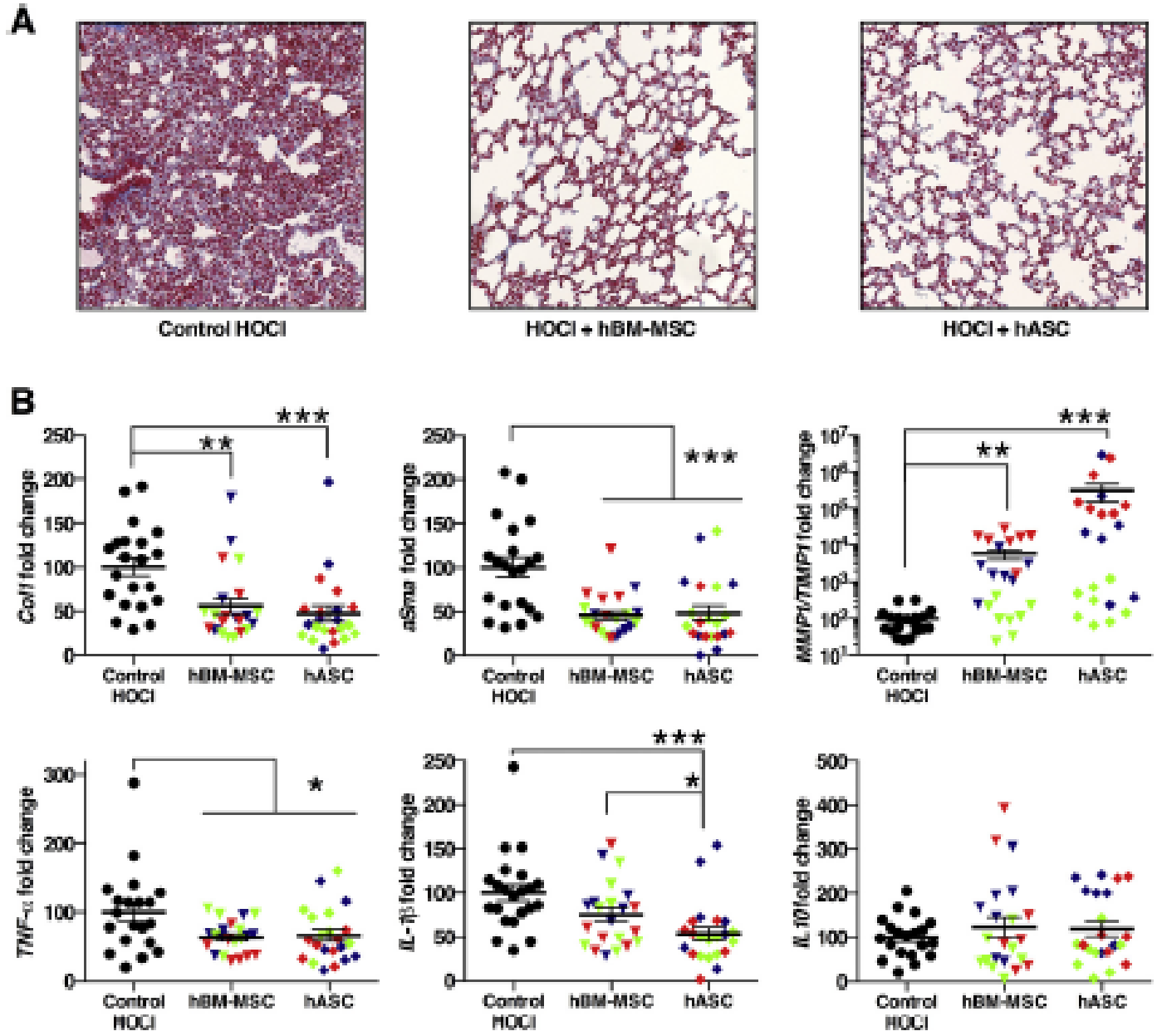
Alexandre T.J. Maria [a, b, c], Karine Toupet [a, b], Marie Maumus [a, b], Guillaume Fonteneau [a, b], Alain Le Quellec [b, c], Christian Jorgensen [a, b, d], Philippe Guilpain [a, b, c, 1], Danièle Noël [a, b, d, *, 1]

Effect of BM-MSCs in the HOCl-induced SSc murine model



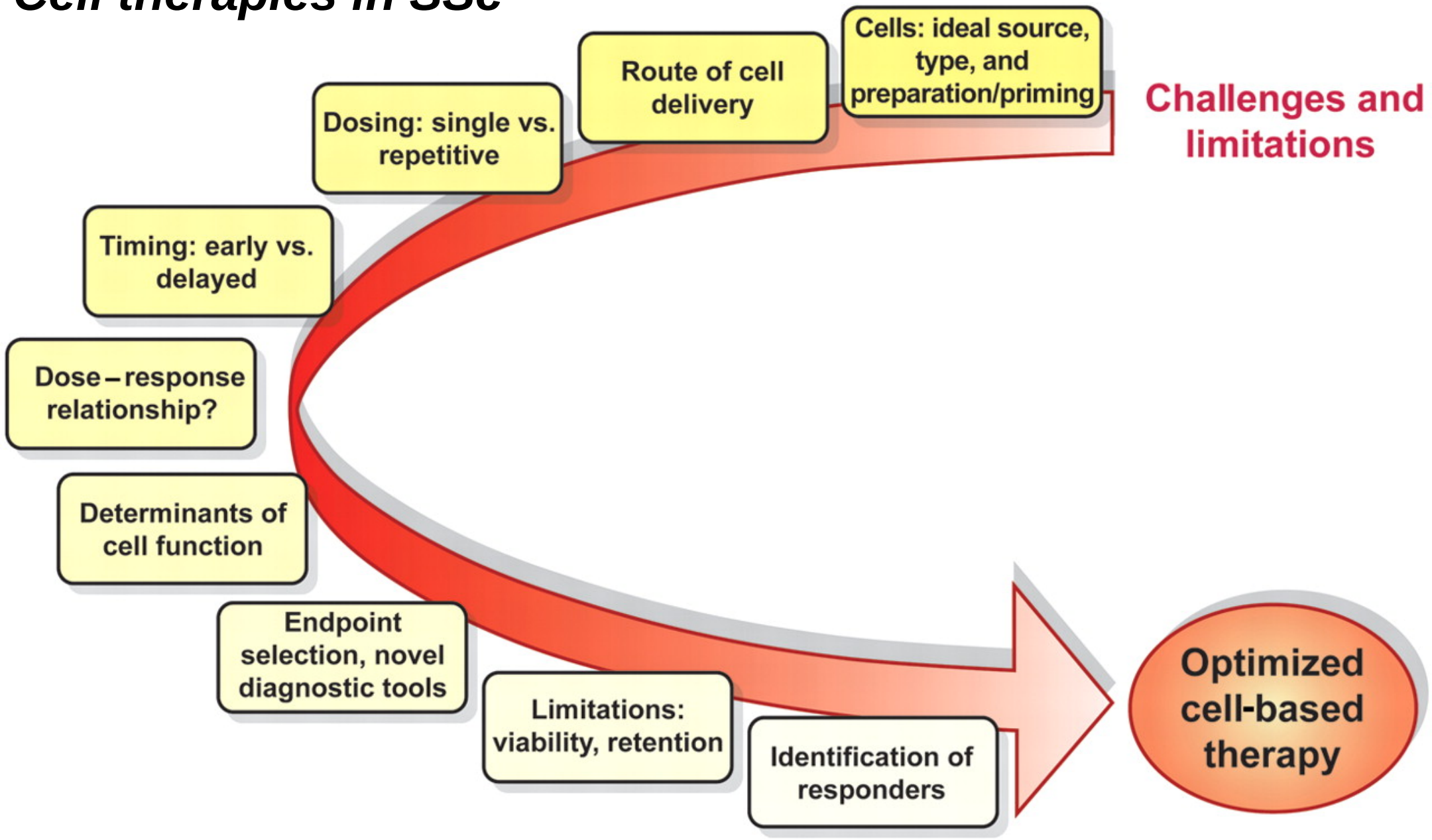
Maria ATJ et al. J Autoimmunity 2016

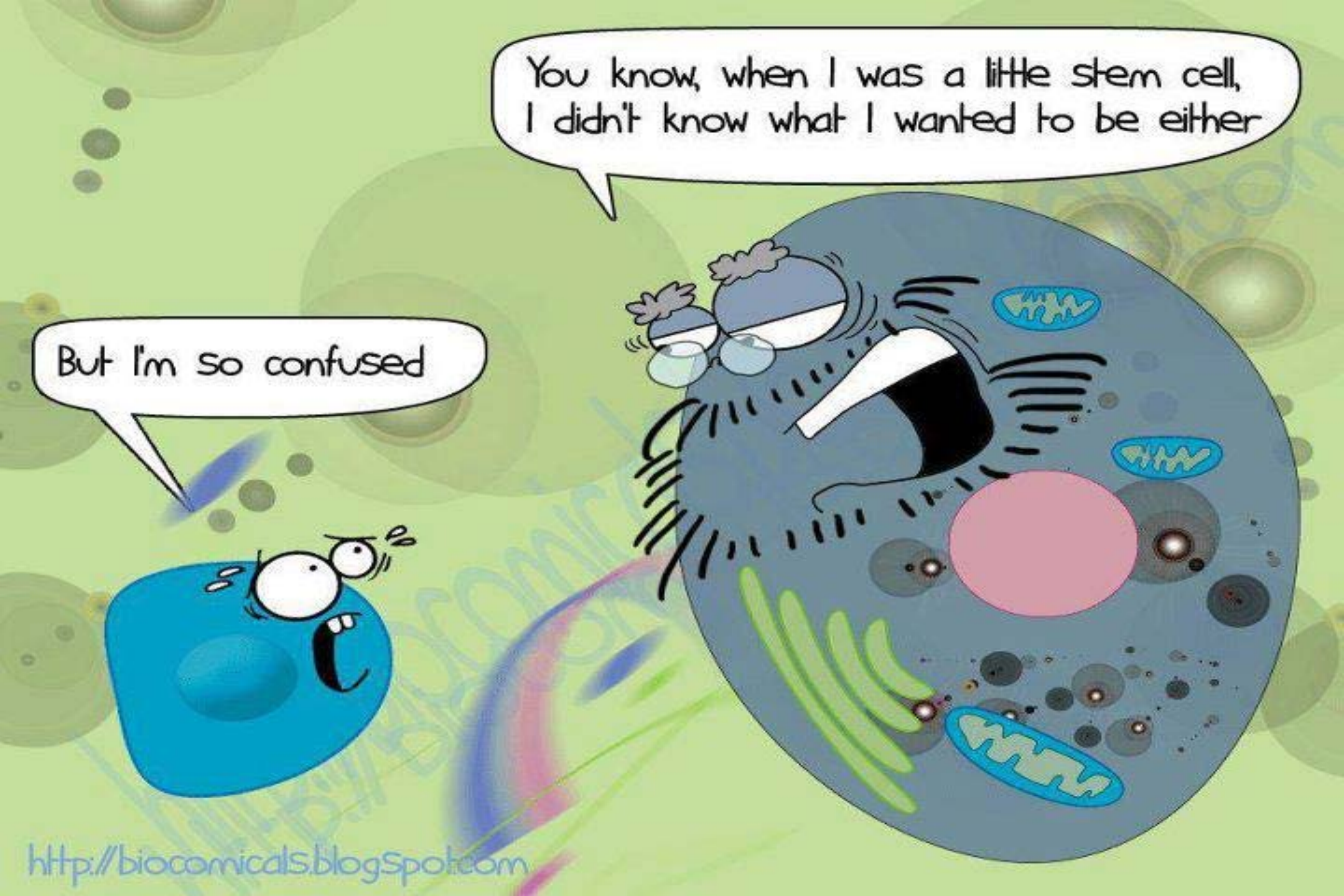
Effect of human BM-MSC and ASC in lungs in the HOCl-induced SSc model



Maria ATJ et al. J Autoimmunity 2016

Cell therapies in SSc




You know, when I was a little stem cell, I didn't know what I wanted to be either
But I'm so confused
http://biocomicals.blogspot.com