Mesenchymal Stem Cell Applications in the Clinics

" From Bench to Bedside" 13-17 May 2013 Kayseri

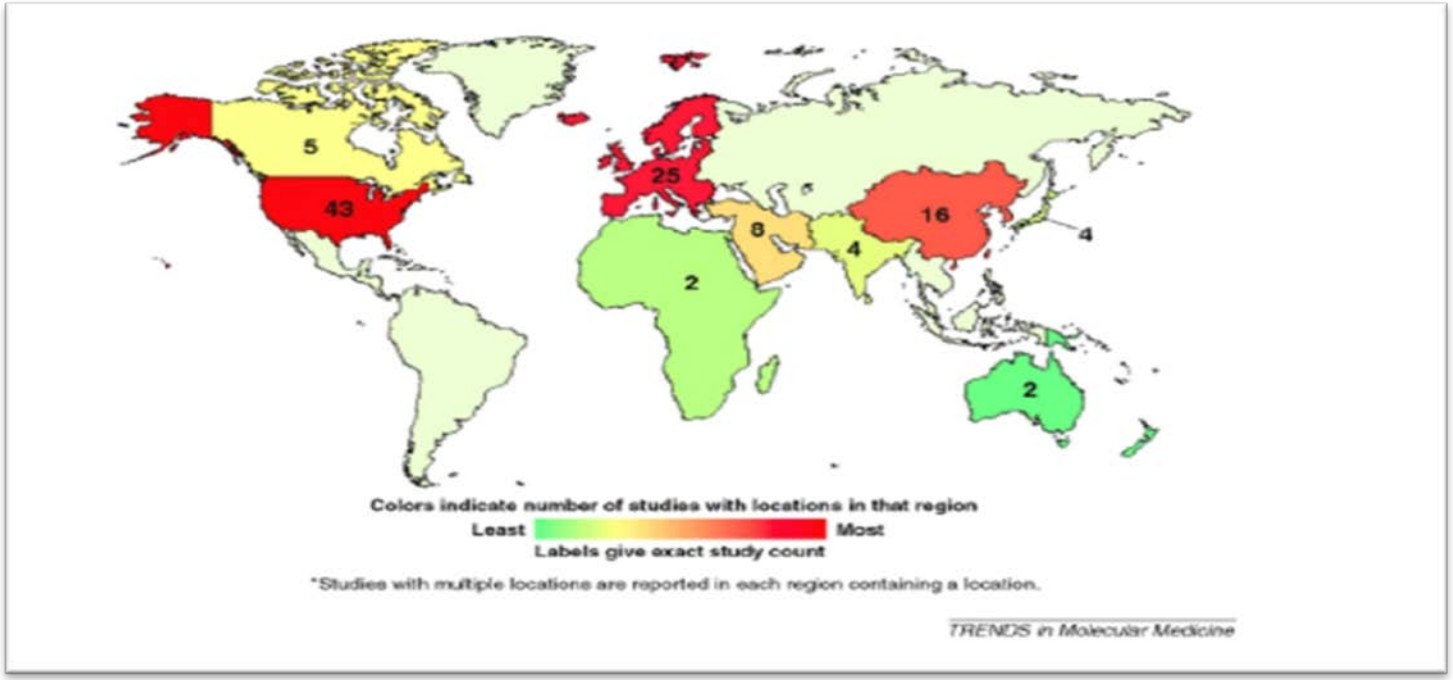
Dr. Mustafa ÇETİN

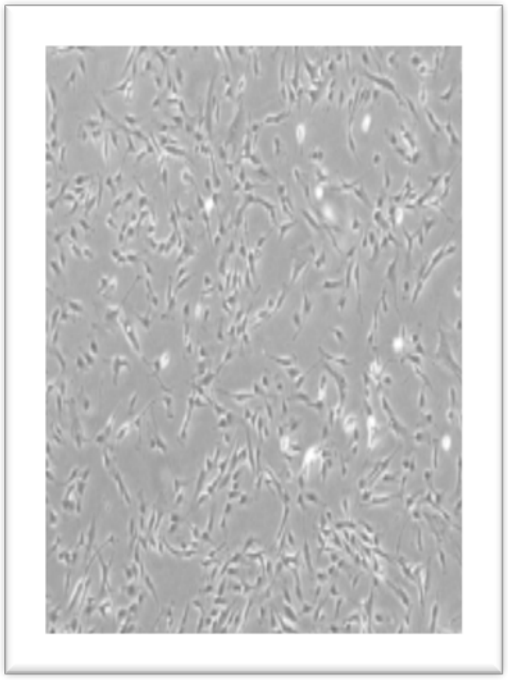
Erciyes University Faculty of Medicine
Department of Hematology
Erciyes (Cappadoccia) Transplantation Center

Translational Progress in the Adherent Stem Cell Space

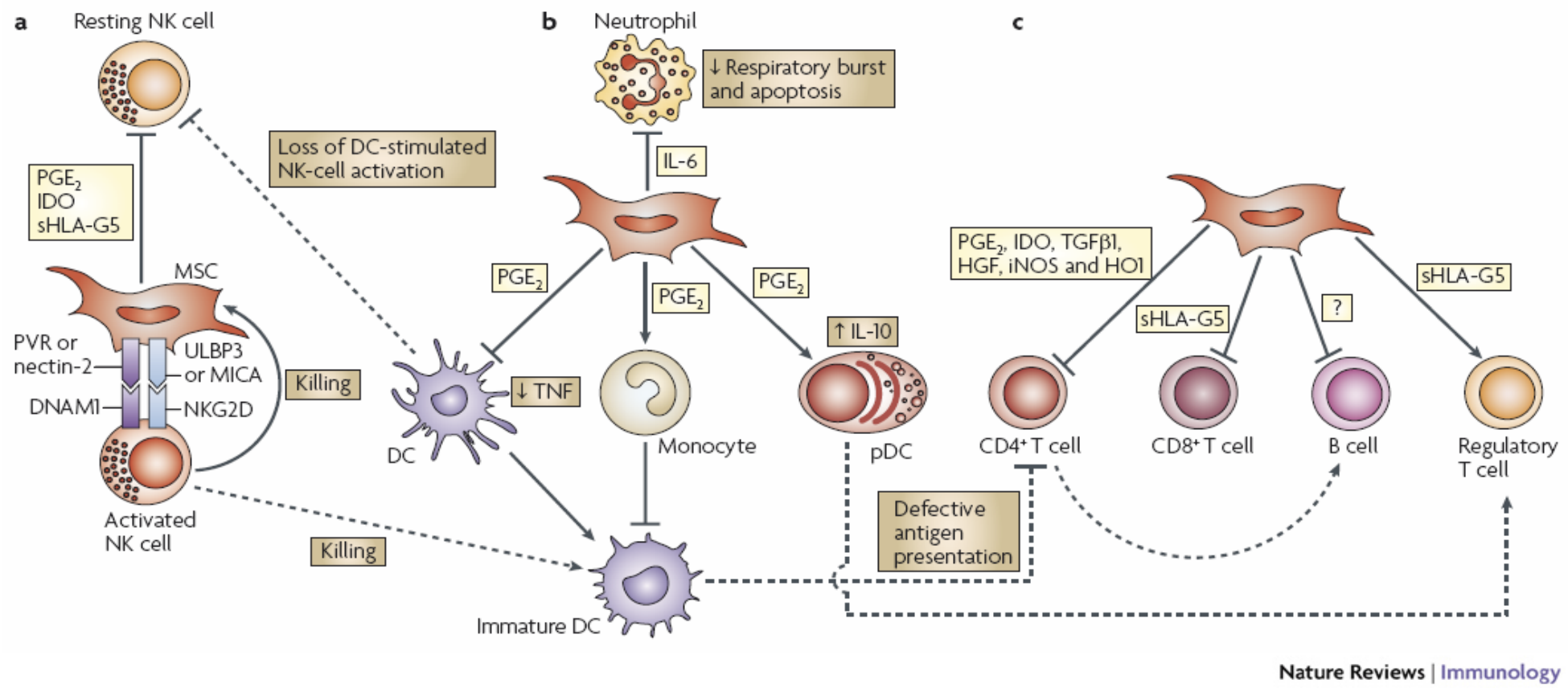
- Till 2010, Over 5400 patients have received adherent stem cell (MSC) treatment, in over 100 trials in over 14 indications

- Since 2011, more than 200 clinical trials have been conducted to test the feasibility and efficacy of MSCs therapy

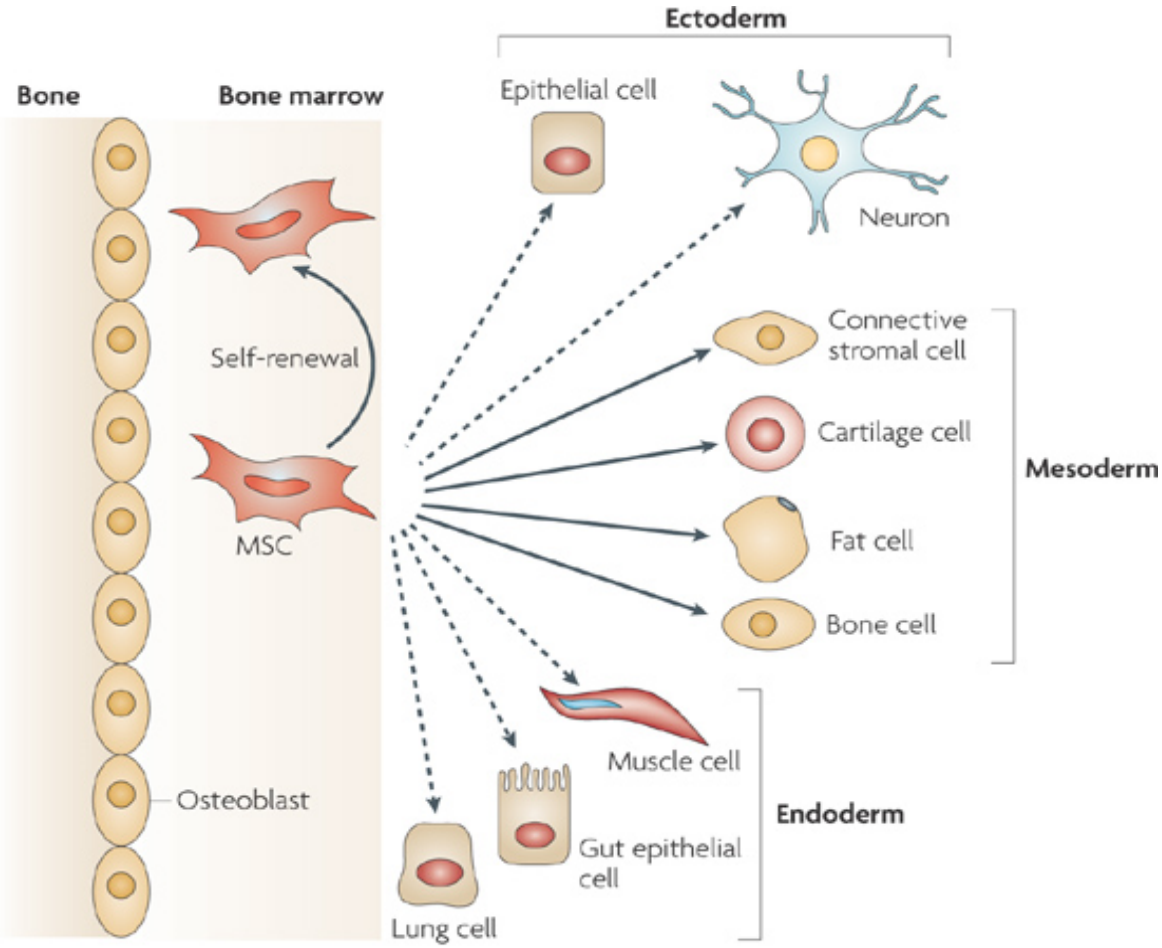




Ankrum, J 2010 Trends Mol Med



Nature Reviews | Immunology



Nature Reviews | Immunology

nature REVIEWS
MOLECULAR CELL BIOLOGY

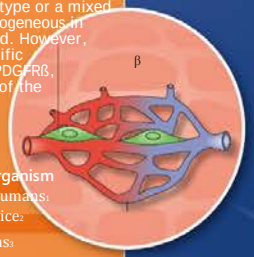
The identity and properties of mesenchymal stem cells

César Nombela-Arrieta and Leslie E. Silberstein

MSCs are self-renewing, multipotent precursors. They were originally found to reside in the stromal adherent fraction of the bone marrow, where they sustain the homeostatic turnover of non-haematopoietic stromal cells, regulate HSC maintenance and might contribute to vascular stability. The physiological roles of MSCs in anatomical locations other than the bone marrow remain largely undefined. MSCs can be expanded *in vitro* to generate mesenchymal stromal cell cultures, which, under appropriate conditions, can differentiate into adipocytes, chondrocytes and osteoblasts. In more recent studies multipotent mesenchymal stromal cell cultures have been derived from perivascular stem cells expressing pericyte markers in many postnatal tissues. The differentiation capabilities, extraordinary paracrine potential and ease of isolation of *in vitro*-expanded mesenchymal stromal cells have attracted great interest into, and efforts towards, the exploitation of MSCs and their expanded progeny as therapeutic agents for tissue regeneration and repair.

MSCs in postnatal tissues

MSCs were first identified in the adherent fraction of bone marrow stroma. They were termed CFU-Fs because of their ability to generate single cell-derived colonies, in analogy to their haematopoietic counterparts, CFU-Cs. CFU-Fs from almost all embryonic and postnatal tissues can be expanded *in vitro* to generate cell cultures that conserve trilineage potential. The role of MSCs in multiple anatomical locations, and whether they constitute a specific homogeneous cell type or a mixed population of tissue-specific cells heterogeneous in nature and origin, is not well understood. However, these progenitors express pericyte-specific cell-surface markers, such as NG2 and PDGFRß, and are located in perivascular regions of the different tissues in which they reside.

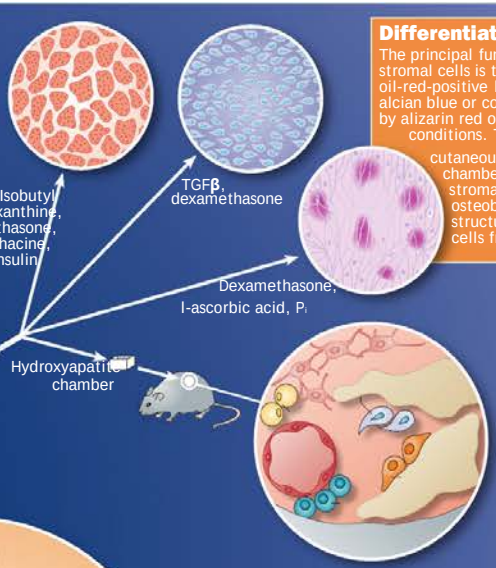


Markers defining cells enriched in MSC activity

Marker	Anatomical location	Organism
CD146	Bone marrow	Humans[1]
PDGFRα–SCA1	Bone marrow	Mice[2]
CD146–NG2–PDGFRβ	Postnatal and embryonic tissues	Humans[3]
Nestin–GFP	Bone marrow	Nestin–GFP transgenic mice[4]

Mesenchymal stromal cell expansion *in vitro*

MSCs can be expanded *in vitro* when cultured in two-dimensional monolayers of adherent cells in specialized medium. The expanded cells, sometimes termed multipotent mesenchymal stromal cells, are defined by the expression of CD73, CD90 and CD105 and the lack of CD11b, CD19, CD34, CD45 and HLADR. Here we use the term mesenchymal stromal cells to refer to these *in vitro*-expanded cells.

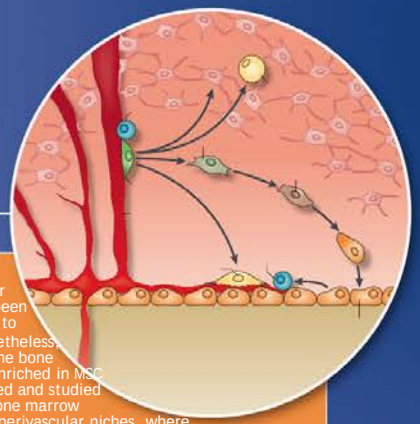


Differentiation potential

The principal functional criterion defining multipotent mesenchymal stromal cells is their ability to give rise to mature adipocytes (in vitro oil-red-positive lipid vesicles accumulate), chondrocytes (identified by alcian blue or collagen-specific staining) and osteoblasts (identified by alizarin red or von Kossa staining) when placed in specific culture conditions. This trilineage capability can be probed *in vivo* by subcutaneous implantation inside ceramic cubes (hydroxyapatite chambers) in mice. Within these implants, mesenchymal stromal cells differentiate into adipocytes, chondrocytes, osteoblasts and haemosupportive stroma, giving rise to bone structures termed ossicles, which recruit haematopoietic cells from the recipient mice to the implant.

MSC roles *in vivo*

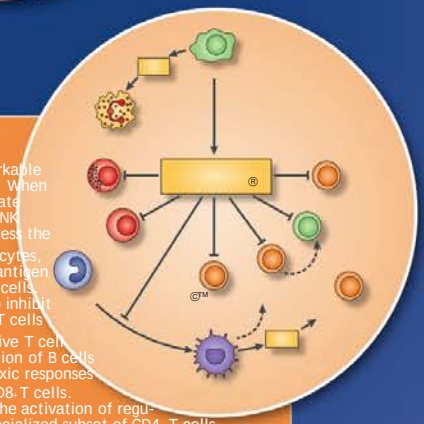
The study of MSCs in their native environment has been hindered by the inability to identify them *in situ*. Nonetheless, rare cell populations in the bone marrow that are highly enriched in MSC activity have been isolated and studied *in vitro* and *in vivo*. In the bone marrow parenchyma, MSCs lie in perivascular niches, where they associate with HSCs, exerting a key regulatory effect on early stages of haematopoiesis. MSCs enter differentiation pathways to replenish mature osteoblasts, adipocytes and haemosupportive stroma in the bone marrow. Recent studies have shown that bone marrow-residing nestin+ MSCs are innervated by sympathetic nervous system fibres and mediate neural control of haematopoiesis.



Immunoregulatory properties *in vitro*

MSCs are endowed with remarkable immunoregulatory properties. When co-cultured *in vitro* they modulate the responses of neutrophils, NK cells and NKT cells, and suppress the maturation of DCs from monocytes, which may lead to defective antigen presentation to CD4+ helper T cells. MSCs have also been shown to inhibit the activation of CD4+ helper T cells (potentially leading to defective T cell help to B cells), the proliferation of B cells and the activation and cytotoxic responses mediated by γδ T cells and CD8+ T cells. Furthermore, MSCs promote the activation of regulatory T cells, which are a specialized subset of CD4+ T cells that can suppress the responses of other T cells.

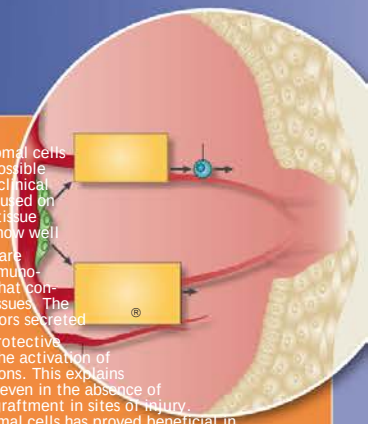
The immunosuppresive effects of mesenchymal stromal cells mainly rely on their ability to secrete various soluble factors, such as IDO, NO and PGE2. Whether tissue-resident MSCs play a physiological part in directly modulating immune responses *in vivo* is still unknown.



Therapeutic potential

Expanded multipotent mesenchymal stromal cells are being extensively studied for their possible therapeutic properties in numerous pre-clinical and clinical settings. Studies initially focused on using their stem cell-like properties for tissue regeneration and repair. However, it is now well established that their beneficial effects are mostly derived from the secretion of immunomodulatory and cytoprotective factors that contribute to the regeneration of injured tissues. The current hypothesis is that paracrine factors secreted by mesenchymal stromal cells provide protective microenvironmental cues and promote the activation of local tissue-resident progenitor populations. This explains why favourable effects can be observed even in the absence of prolonged mesenchymal stromal cell engraftment in sites of injury.

Systemic infusion of mesenchymal stromal cells has proved beneficial in different pre-clinical models of acute lung injury, myocardial infarction, diabetes as well as hepatic failure. Some of the human conditions for which the safety and efficacy of mesenchymal stromal cell-based therapies are being, or will soon be, studied in clinical trials include acute graft-versus-host disease, multiple sclerosis, osteogenesis imperfecta, stroke, spinal injury, lupus erythematosus and cardiovascular disease.



Abbreviations

CARC, CXCL12-abundant reticular cell; CFU-Cs, colony-forming unit-cells; CFU-Fs, colony-forming unit-fibroblasts; CXCL12, CXC-chemokine ligand 12; DC, dendritic cell; FGF, fibroblast growth factor; GFP, green fluorescent protein; GM-CSF, granulocyte macrophage colony-stimulating factor; HGF, hepatocyte growth factor; HLA, human leukocyte antigen; HSC, haematopoietic stem cell; IDO, indoleamine 2,3-dioxygenase; IGF1, insulin growth factor 1; IL, interleukin; LIF, leukaemia inhibitory factor; NG2, nerve/glial antigen 2; NK, natural killer; NKT, natural killer T; NO, nitric oxide; PGE2, prostaglandin E2; MSC, mesenchymal stem cell; PDGFR; platelet-derived growth factor receptor; Pi, inorganic phosphate; PlGF, placental insulin growth factor; SCA1, surface cell antigen 1; SCF, stem cell factor; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor.

References

1. Sacchetti, B. *et al. Cell* **131**, 324-336 (2007).
2. Morikawa, S. *et al. J. Exp. Med.* **206**, 2483-2496 (2009).
3. Crisan, M. *et al. Cell Stem Cell* **3**, 301-313 (2008).
4. Mendez-Ferrer, S. *et al. Nature* **466**, 829-834 (2010).

Further reading

Salem, H. K. & Thiemermann, C. *Stem Cells* **28**, 585-596 (2010). | Meirelles Lda, S. *et al. Cytokine Growth Factor Rev.* **20**, 419-427 (2009). | Nombela-Arrieta, C., Ritz, J. & Silberstein, L. E. *Nature Rev. Mol. Cell Biol.* **12**, 126-131 (2011). | Uccelli, A., Moretta, L. & Pistoia, V. *Nature Rev. Immunol.* **8**, 726-736 (2008).

Contact information

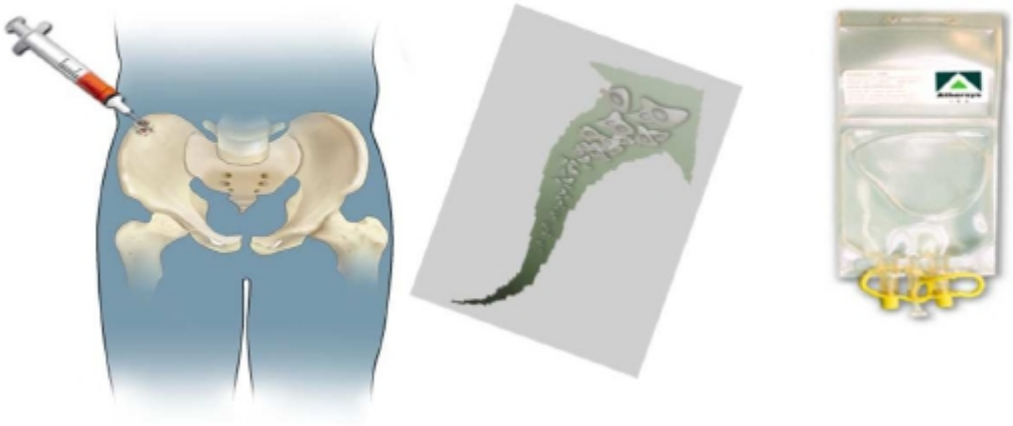
Cesar.NombelaArrieta@childrens.harvard.edu; Leslie.Silberstein@childrens.harvard.edu

The authors declare no competing financial interests.

Edited by Rachel David; copyedited by Antony Bickenson; designed by Vicky Summersby.

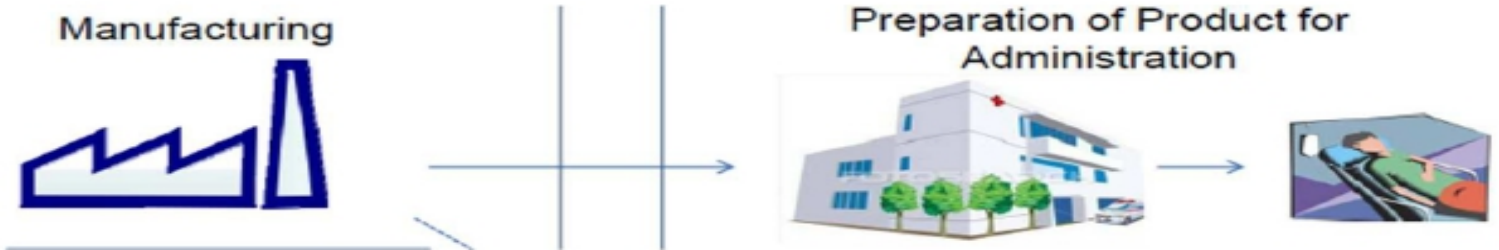
http://www.nature.com/nrm/posters/mscs

Clinical Development in MSC. Phase I, II, III

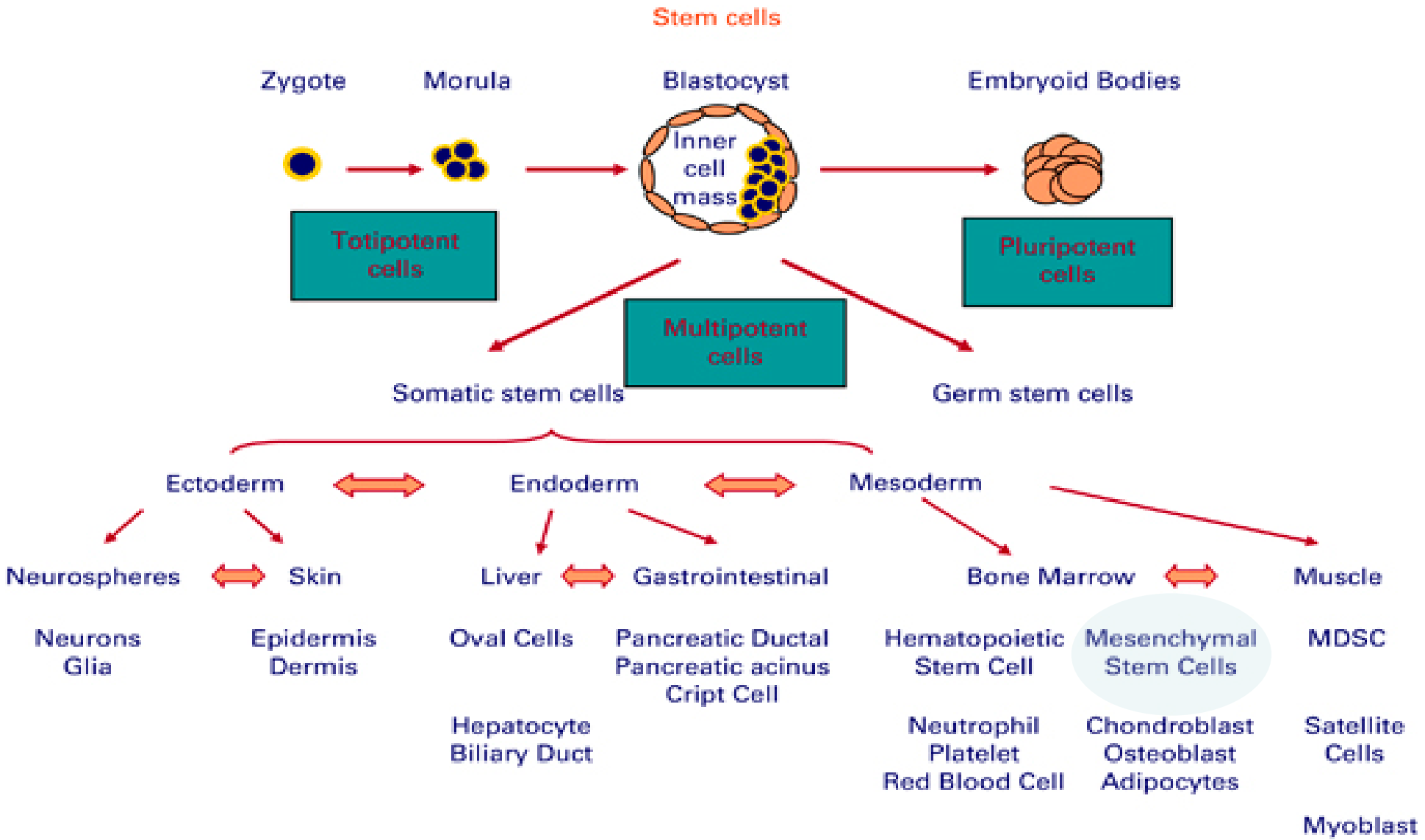


- **Global issues** towards adherent stem cell therapy
  (Commercialization moves to medical centers without enought experience)

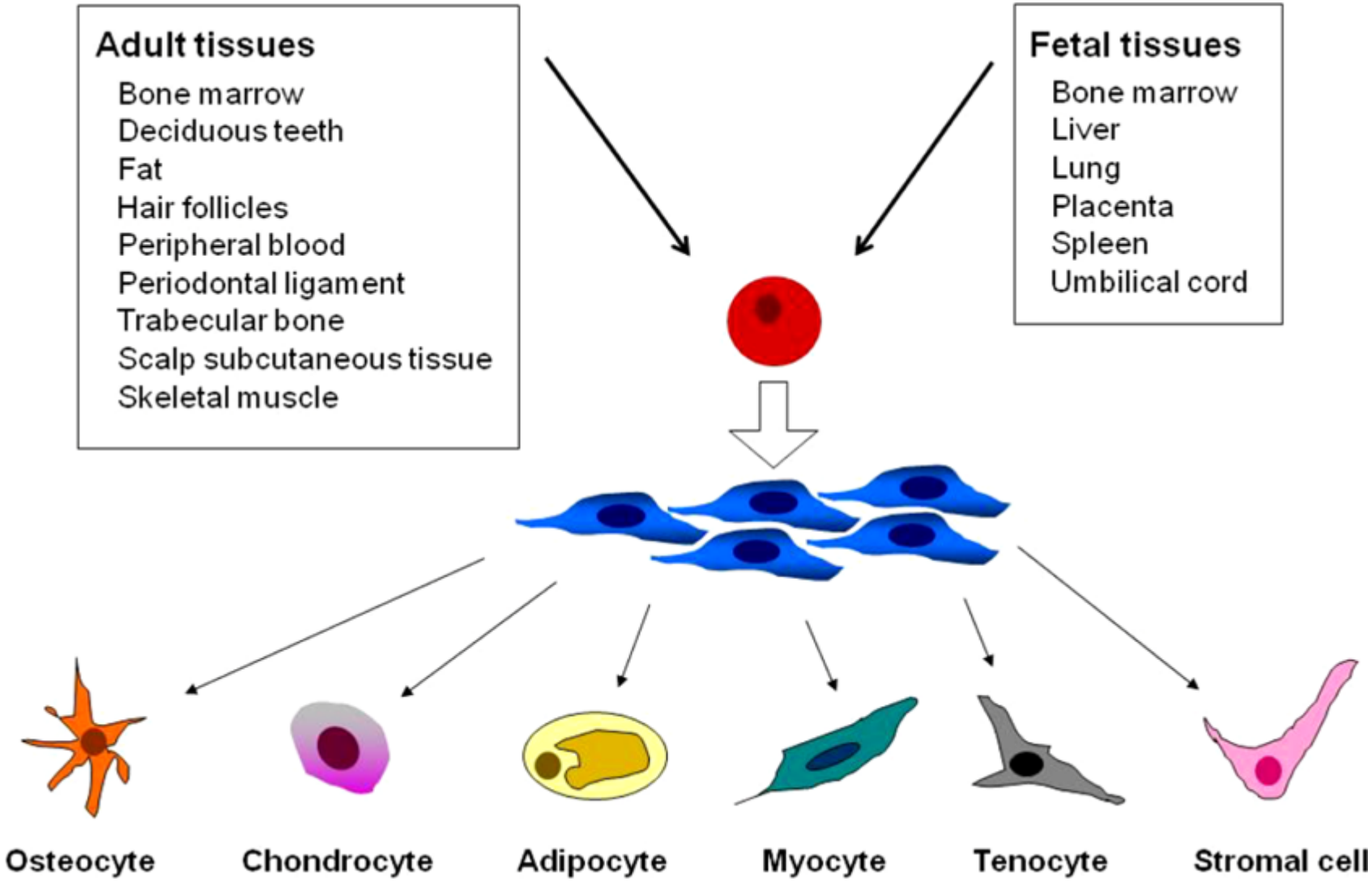
- Solution –
  Good manufacturing Product-quality-vitality-purity-marketing-labeling-delivery
  Good Clinical Practice –indications- capacity-(potency) - toxicity-and-survival
  Phase Studies: randomized controlled



Human Stem Cells

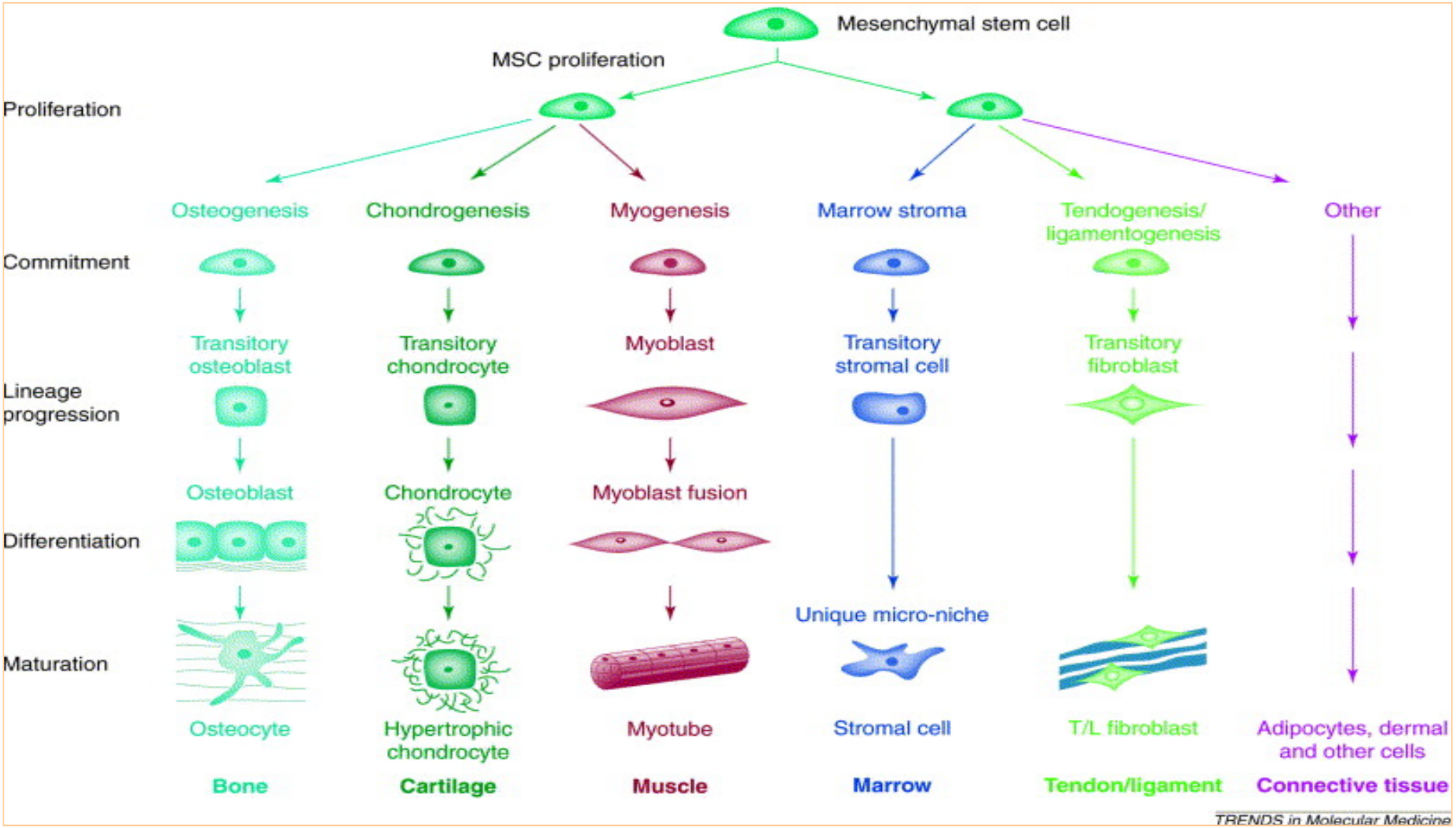


Mesenchymal Stem Cells



Baksh, Yao, & Tuan, 2007; Da Silva Meirelles, Chagastelles, & Nardi, 2006).

Mesenchymal Stem Cells



- Easy isolation, high expansion, reproducible

According to the International Society for Cellular Therapy, human MSCs under standard culture conditions must satisfy at least three criteria:

(1) They must be plastic-adherent;

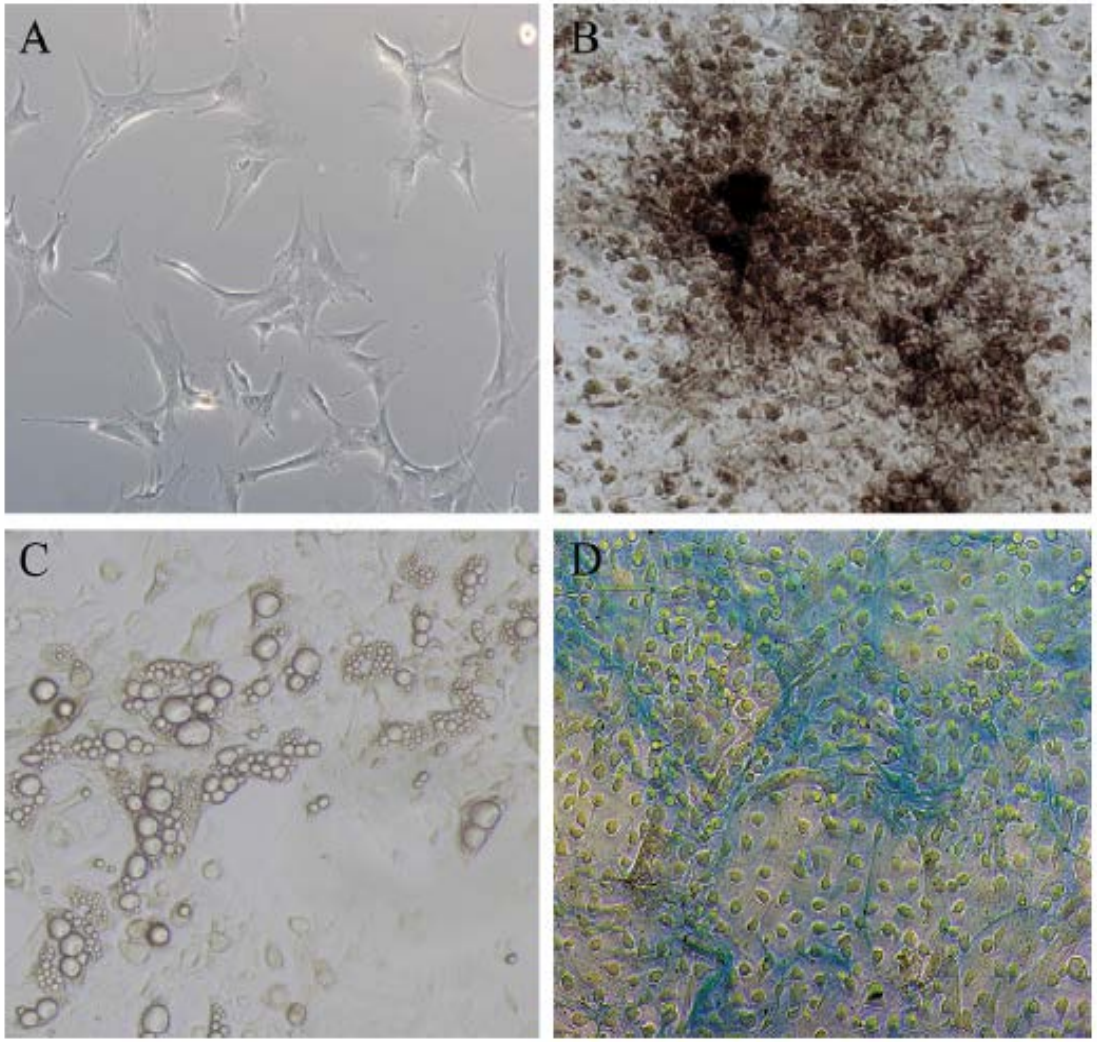
(2) They must express **C105, CD73** and **CD90** and not CD45, CD34, CD14, CD11b, CD79 or CD19 and HLA-DR surface molecules by flow cytometry;

(3) They must be capable of differentiating into osteoblasts, adipocytes and chondroblasts

- Other markers that are generally accepted include CD44, CD71, Stro-1, and adhesion molecules such as CD 106, CD166, and CD29

M. Dominici, K. Le Blanc, I. Mueller et al., "Minimal criteria for definingmultipotentmesenchymal stromal cells: the International Society for Cellular Therapy," *Cytotherapy*, vol. 8, no. 4, pp. 315–317, 2006.

Cultured Mesenchymal Stem Cells; could readily adhere to culture dishes, form fibroblast-like colonies, and are capable of differentiating into adipogenic, chondrogenic, and osteogenic lineages.



(A) Undifferentiated MSCs grown in monolayer culture

(B) Cells expressed **ALP** at the 21st day in osteogenic medium.

(C) **Lipid droplets** were detectable after 2 weeks' inducing.

(D) Chondrocytes that were detected by **alcian blue** staining, which stains matrix secreted by these cells.

Biological Characteristics of Mesenchymal Stem Cells

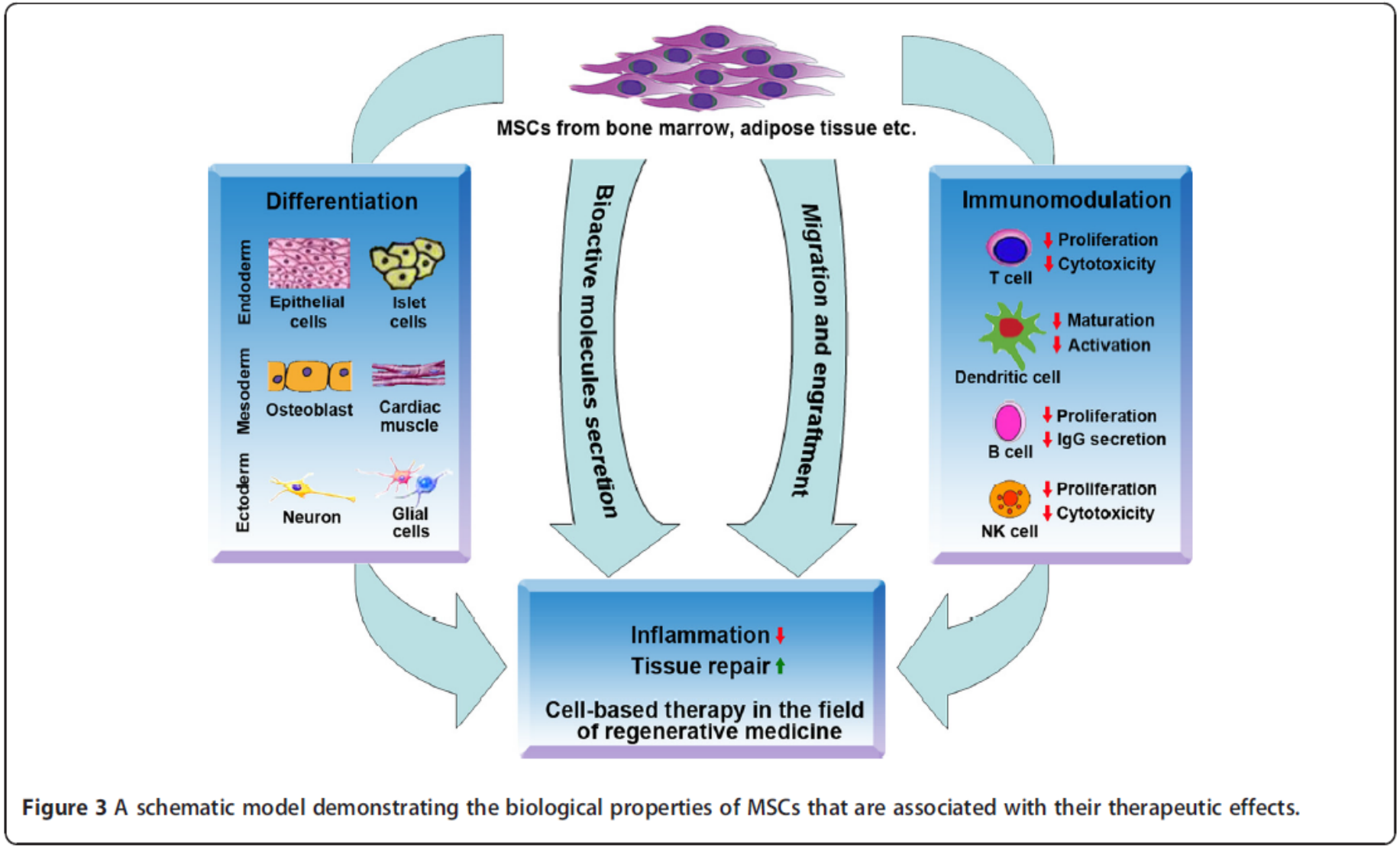


Figure 3 A schematic model demonstrating the biological properties of MSCs that are associated with their therapeutic effects.

Their biological characteristics that contribute to the therapeutic effects...

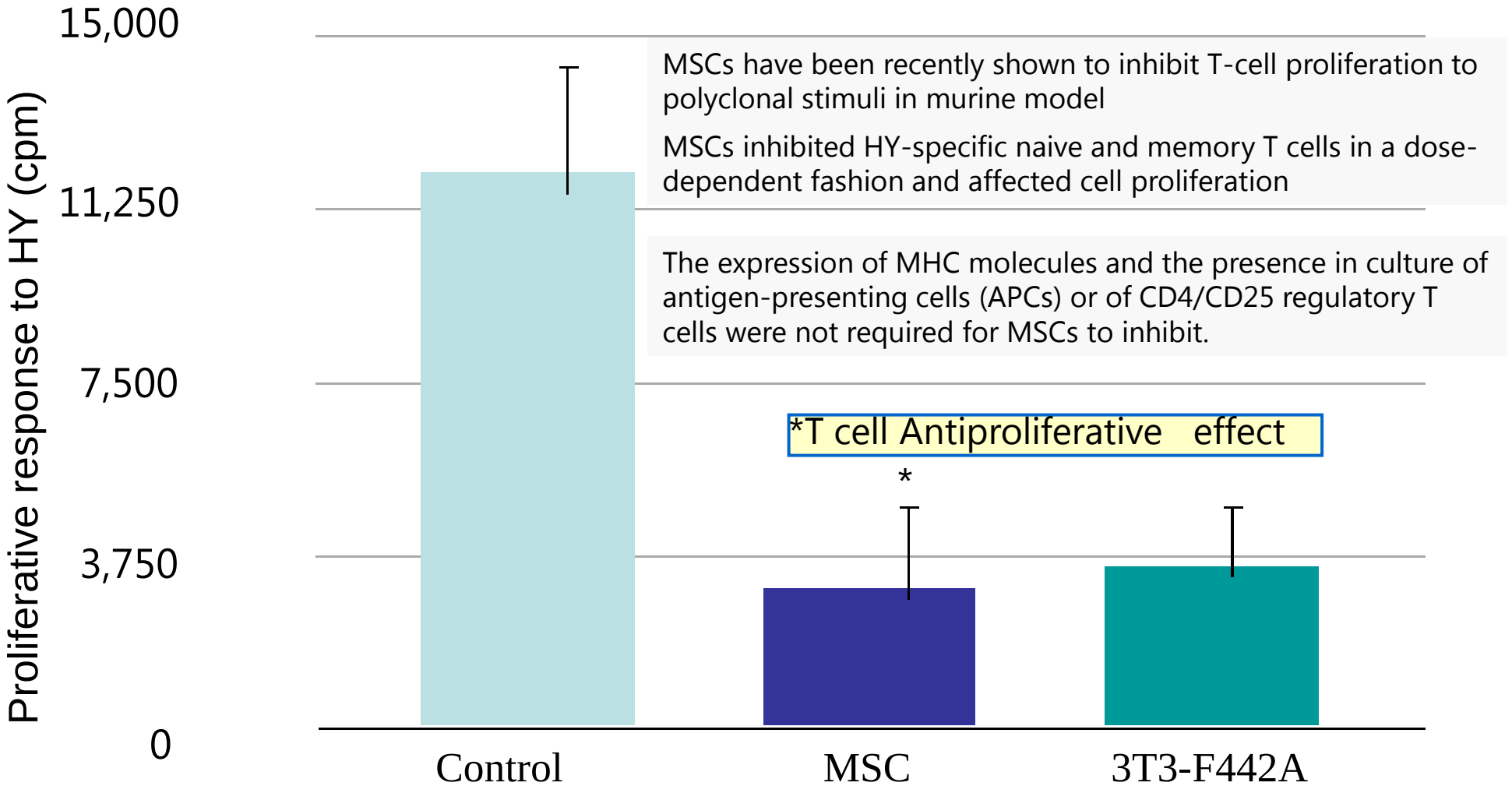
Outline

Mesenchymal Stem Cells

- What type and mechanisms of immunosuppression?
- Bioactive moleculs secreted by MSC'c
- Tissue repair and nisch activity,
- Differentaion of the MSC to other cells
- Conditions for therapeutic applications

CLINICAL APPLICATIONS: PRE-CLINICAL MODELS

T CELL inhibitory effect of MSC



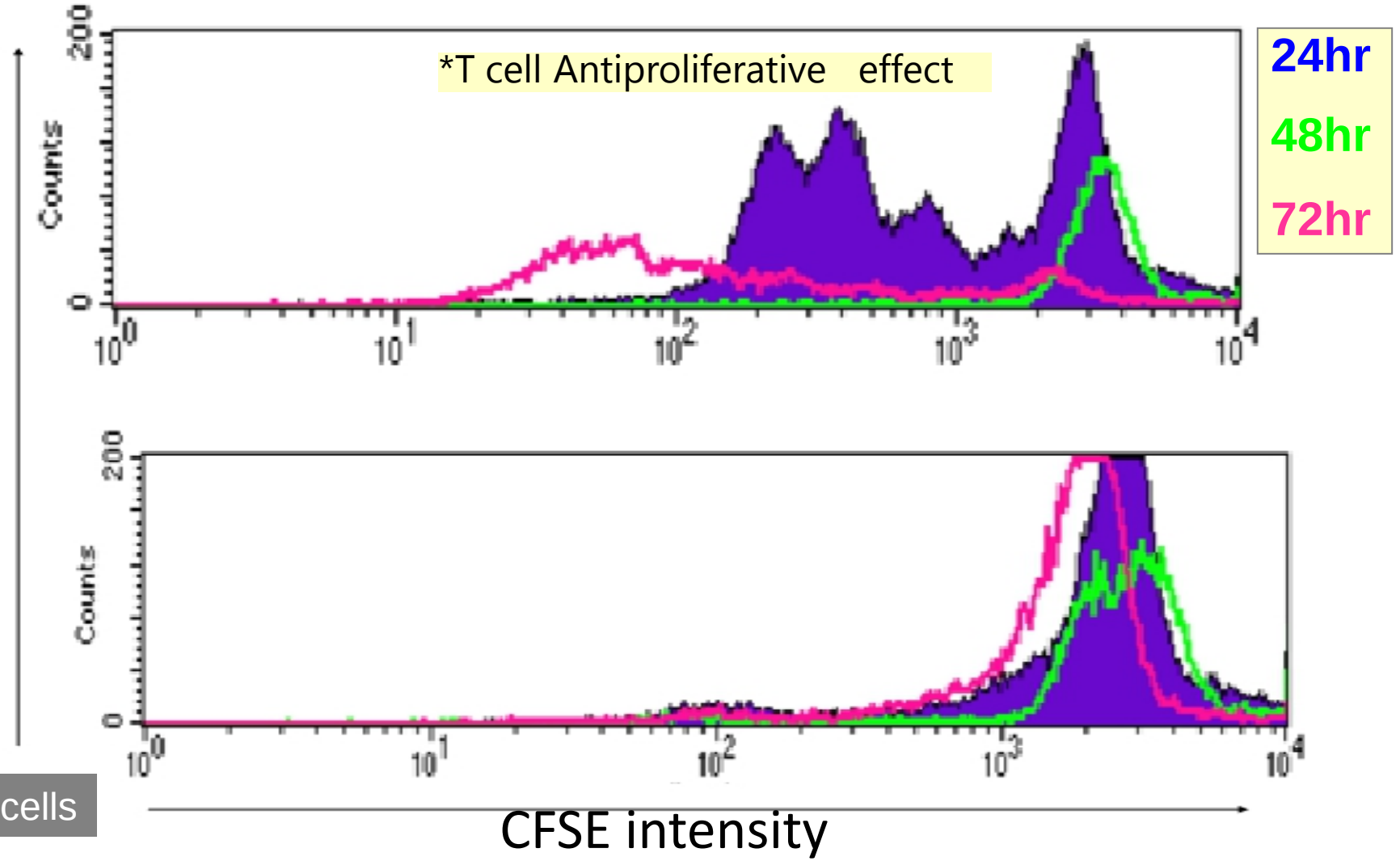
MSCs have been recently shown to inhibit T-cell proliferation to polyclonal stimuli in murine model

MSCs inhibited HY-specific naive and memory T cells in a dose-dependent fashion and affected cell proliferation

The expression of MHC molecules and the presence in culture of antigen-presenting cells (APCs) or of CD4/CD25 regulatory T cells were not required for MSCs to inhibit.

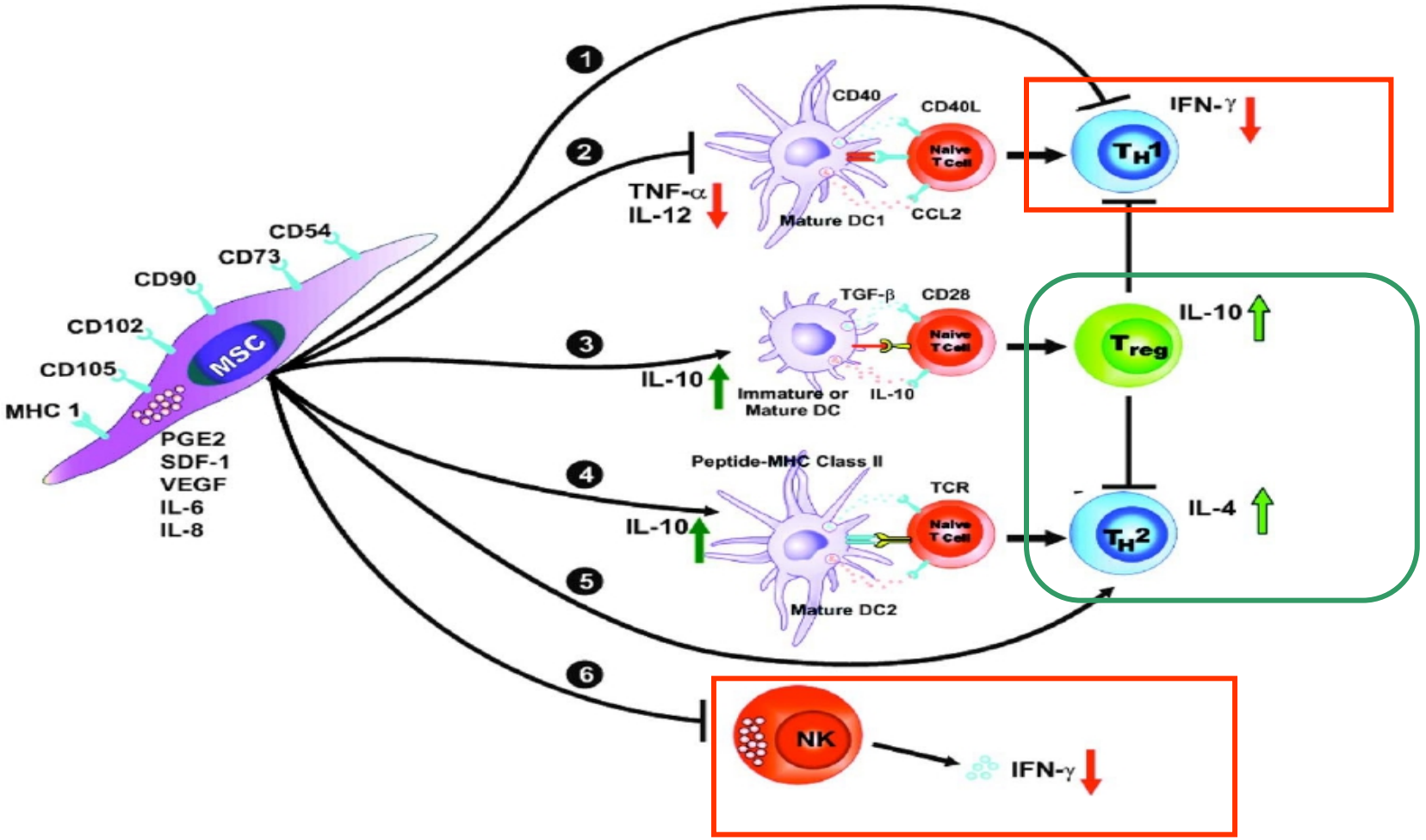
Krampera et al, Blood 2003

MSC completely inhibit T cell division



Krampera et al, Blood 2003

MSC’c and APC interactions

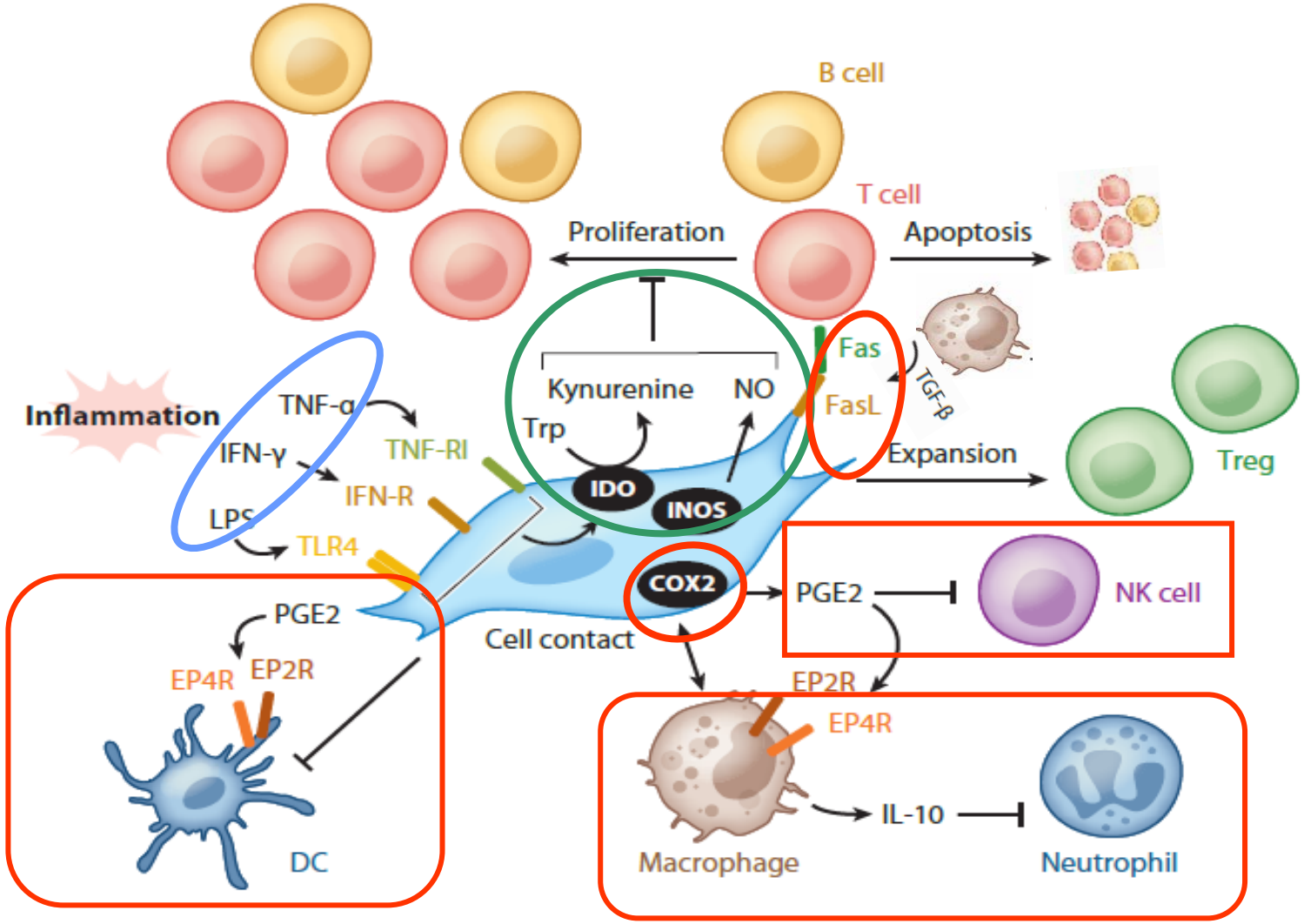


hMSCs promote Th2 responses by inhibiting IFN- γ and TNF- α and increasing IL-10.

Also hMSCs alter antigen-presenting cell maturation and induce T-cell unresponsiveness

Aggarwal & Pittenger Blood 2005;105:1815

Schematic illustration of the interactions between MSC's and cells of the immune system



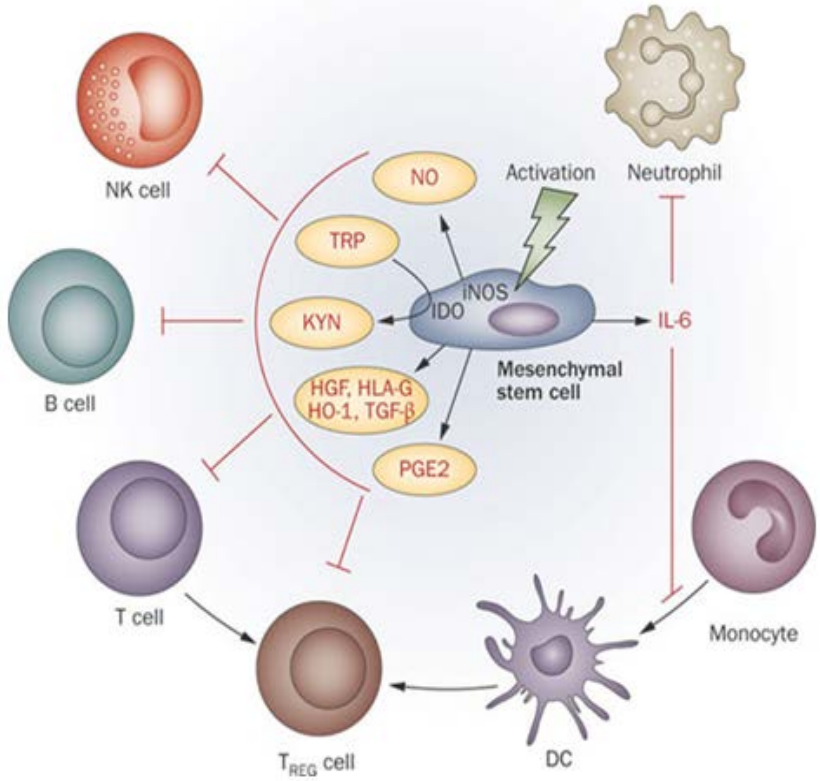
Immune modulation by MSCs.

Annu. Rev. Immunol. 2013. 31:285–316
The *Annual Review of Immunology* is online at immunol.annualreviews.org

Schematic illustration of the interactions between MSC's and cells of the immune system

Immunomodulatory effects of MSCs on immune cells

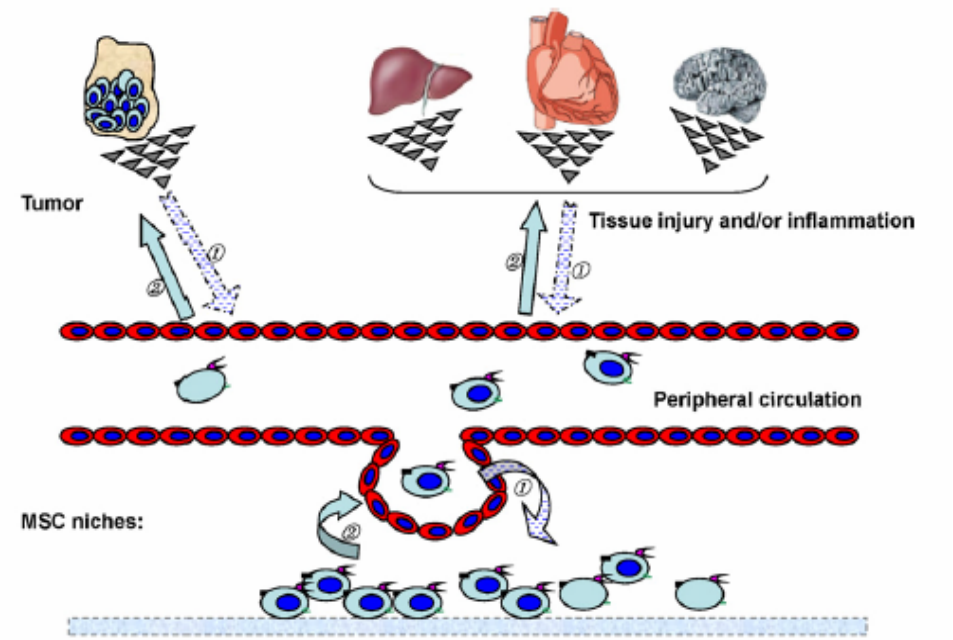
Immune cell type	MSCs' effects
T lymphocyte	Suppress T cell proliferation induced by cellular or nonspecific mitogenic stimuli [44]
	Alter the cytokine secretion profile of naive and effector T cells [56]
	Promote the expansion and function of Treg cells [57]
B lymphocyte	Inhibit proliferation of B lymphocyte [58]
	Affect the chemotactic properties of B cells [59]
	Suppress B-cell terminal differentiation [60]
NK cell	Alter the phenotype of NK cells and suppress proliferation, cytokine secretion, and cyto-toxicity against HLA-class I- expressing targets [61,62]
Dendritic cells (DCs)	Influence differentiation, maturation and function of monocyte-derived dendritic cells [63]
	Suppress dendritic cell migration, maturation and antigen presentation [64]
	Induce mature DCs into a novel Jagged-2-dependent regulatory DC population [65]



Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2009.104

MSCs show a strong propensity to ameliorate tissue damage in response to injury and disease.

MSCs to secrete soluble factors that alter the tissue microenviroment functionally outweighs their trans-differantation ability in affecting tissue repair.



- Hepatocyte growth factor,
- Transforming growth factor-1,
- IL-1, IL-3, IL-6, IL-7, IL-11,
- Stem cell factor,
- FMS like tyrosine kinase 3 ligand,

These factors may enhance regeneration ability of injured tissues, stimulate proliferation and differentiation of endogenous stem-like progenitors found in most tissues, decrease inflammatory and immune reactions (Baddoo et al., 2003).

Conclusions (I)

MSC's exhibit;

- Potent immunosuppressive properties
- Anti-proliferative effect
- Anti-inflamatory effect

Manage ''İmmunomodulatory effects'' and ''Stem cell niche activity – Regenerative Medicine'' and ''Cytoprotective & tissue repair activity''

CLINICAL APPLICATIONS: PRE-CLINICAL MODELS

"Immunomodulating activity"

"Tissue Protection"

''Regenerative Medicine

CLINICAL APPLICATIONS: PRE-CLINICAL MODELS

"Immunomodulating activity"

"Tissue Protection"

''Regenerative Medicine

GvHD

Graft rejection

Autoimmune diseases

Type 1 Diabetis

Crohn's DS. ,Colitis

CLINICAL APPLICATIONS: PRE-CLINICAL MODELS

"Immunomodulating activity"

GvHD

Graft rejection

Autoimmune diseases

Type 1 Diabetis

Crohn's DS. ,Colitis

"Tissue Protection"

Pulmonary fibrosis

Myocardial infarction

Renal ischaemia

Tissue repair

''Regenerative Medicine

CLINICAL APPLICATIONS: PRE-CLINICAL MODELS

"Immunomodulating activity"

GvHD

Graft rejection

Autoimmune diseases

Type 1 Diabetis

Colitis

"Tissue Protection"

Pulmonary fibrosis

Myocardial infarction

Renal ischaemia

Liver cirrhosis

''Regenerative Medicine

Bone & cartilage repair

Haemopoietic recovery

Type 2 Diabetis

Wang *et al. Journal of Hematology & Oncology* 2012, **5**:19
http://www.jhoonline.org/content/5/1/19

JOURNAL OF HEMATOLOGY & ONCOLOGY

Clinical applications of mesenchymal stem cells

Shihua Wang, Xuebin Qu and Robert Chunhua Zhao*

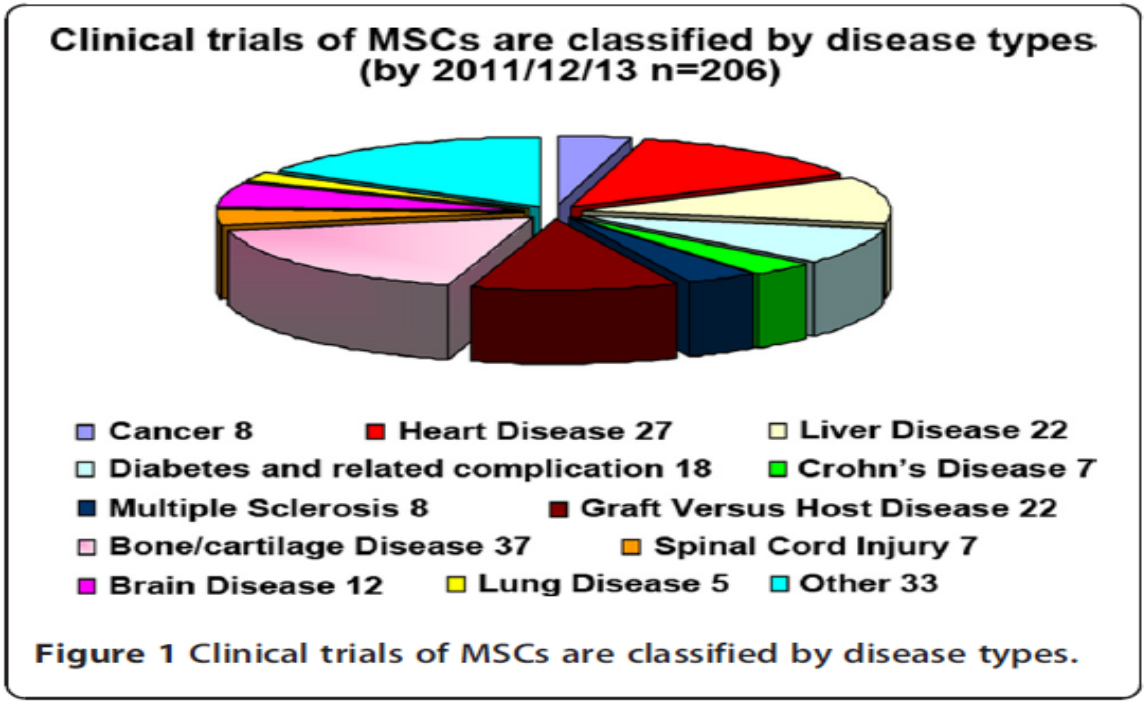


Figure 1 Clinical trials of MSCs are classified by disease types.

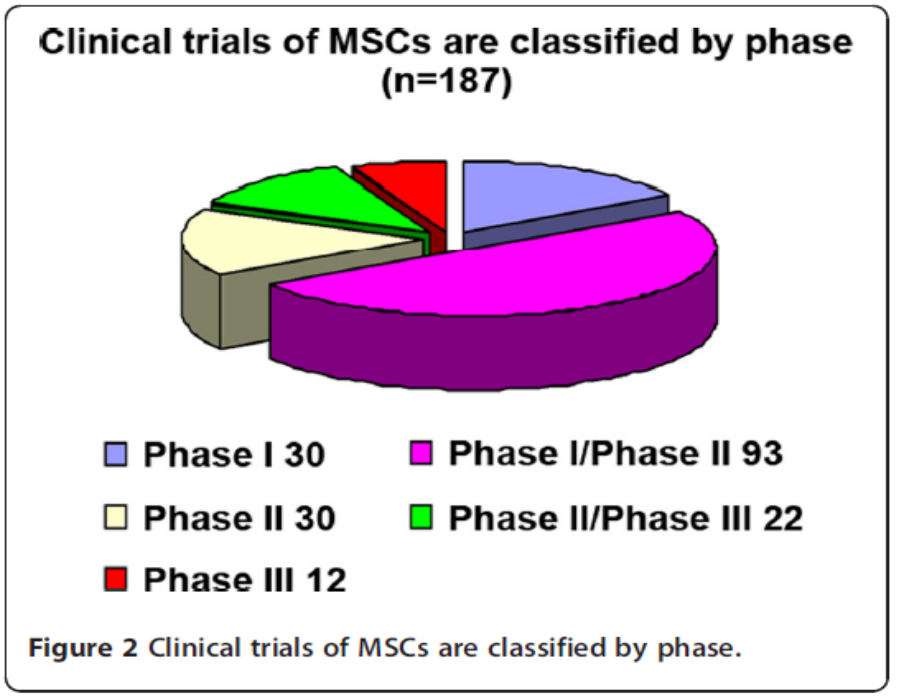


Figure 2 Clinical trials of MSCs are classified by phase.

Clinical applications of mesenchymal stem cells

Journal of Hematology & Oncology 2012, **5**:19

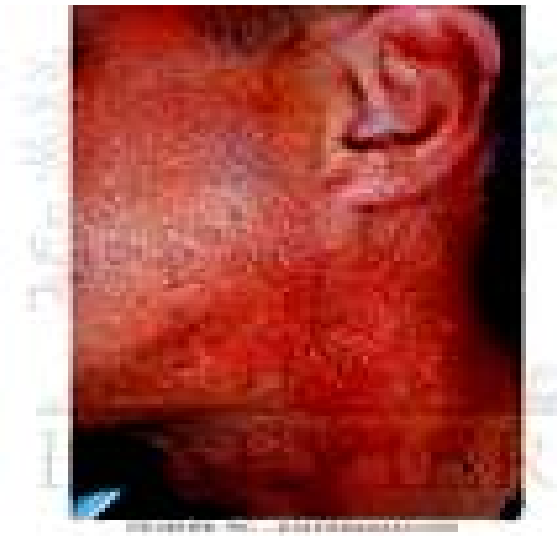
Indication	Number of studies
Immunomodulation	**48**
Multiple sclerosis/atherosclerosis	12
Type 1 diabetes	12
Crohn's disease	10
Systemic lupus erythematosus/colitis	4
Rheumatoid arthritis/Sjögren's syndrome	3
Buerger's disease/sickle cell disease	2
HIV	1
Limbus corneae insufficiency syndrome	1
Periodontitis	1
Progressive hemifacial atrophy	1
Retinitis pigmentosa	1
Tissue protection	**76**
Myocardial infarction/stroke/ischemia	34
Liver cirrhosis	20
Alzheimer's/Parkinson's disease	4
Amyotrophic lateral sclerosis	4
Fibrosis/emphysema	4
Necrosis	4
Acute kidney injury	2
Bronchopulmonary dysplasia	2
Multiple system atrophy/multiple trauma	2

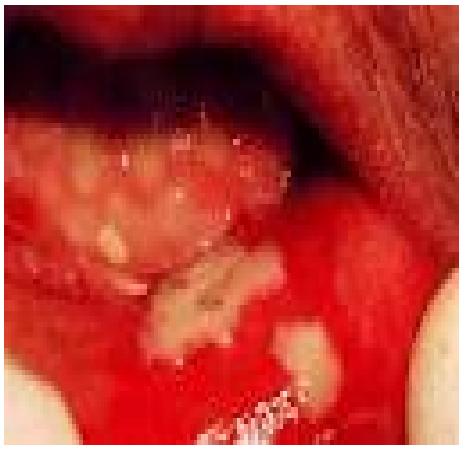
Indication	Number of studies
Regenerative medicine	**69**
Osteoarthritis/osteogenesis imperfecta	22
Bone/cartilage repair	18
Spinal cord injury/neuroblastoma	8
Anemia	4
Type 2 diabetes	4
Dilated cardiomyopathy	4
Wound healing/umbilical cord varices	3
Ataxia	2
Autism	1
Epidermolysis bullosa	1
Erectile dysfunction	1
Wilson's disease	1
Graft enhancement	**27**
GvHD	23
Hematopoietic malignancies	4

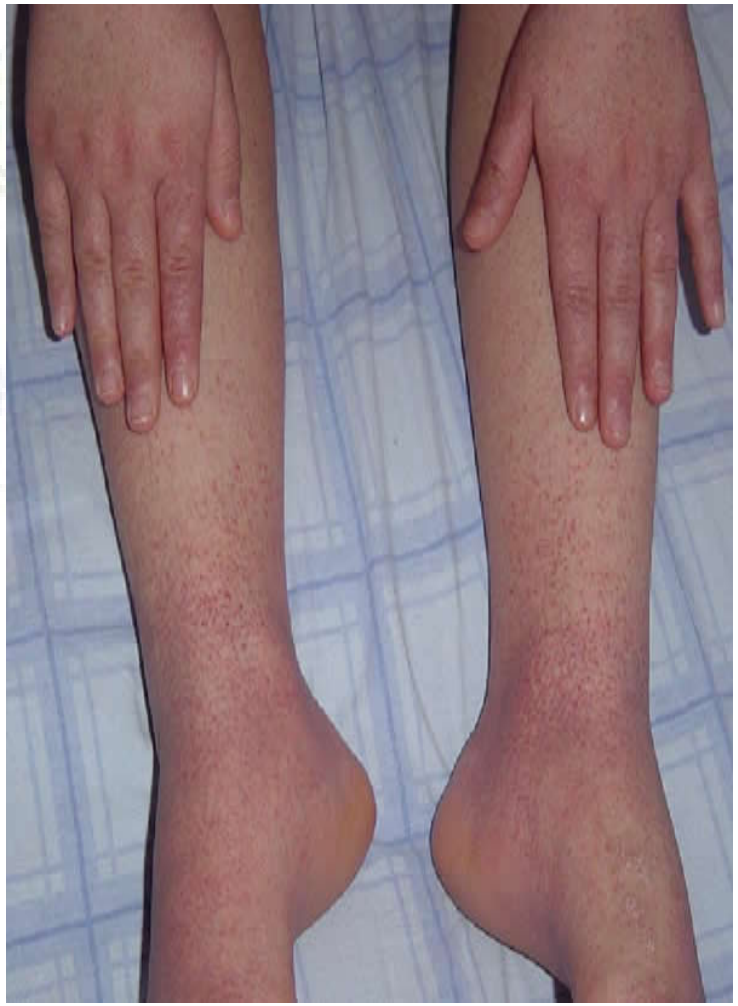
Table 1 Clinical trials (registered as of June 2, 2012) using mesenchymal stem cells

Graft-versus-host disease
GVHD

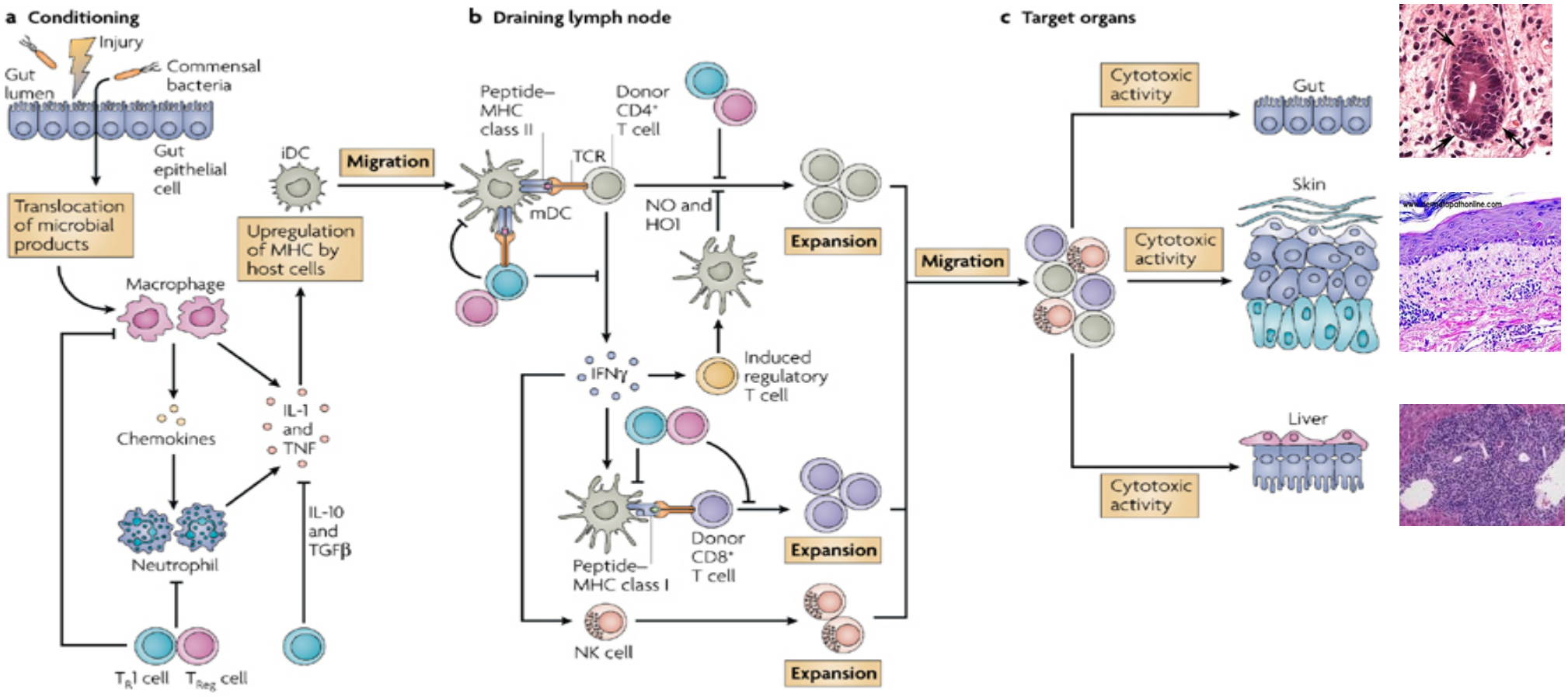
GVHD occurs after allogeneic hematopoietic stem cell transplant and is associated with high morbidity and mortality. Currently, corticosteroids are the gold standard for initial treatment of aGVHD. However, they are only effective for some patients





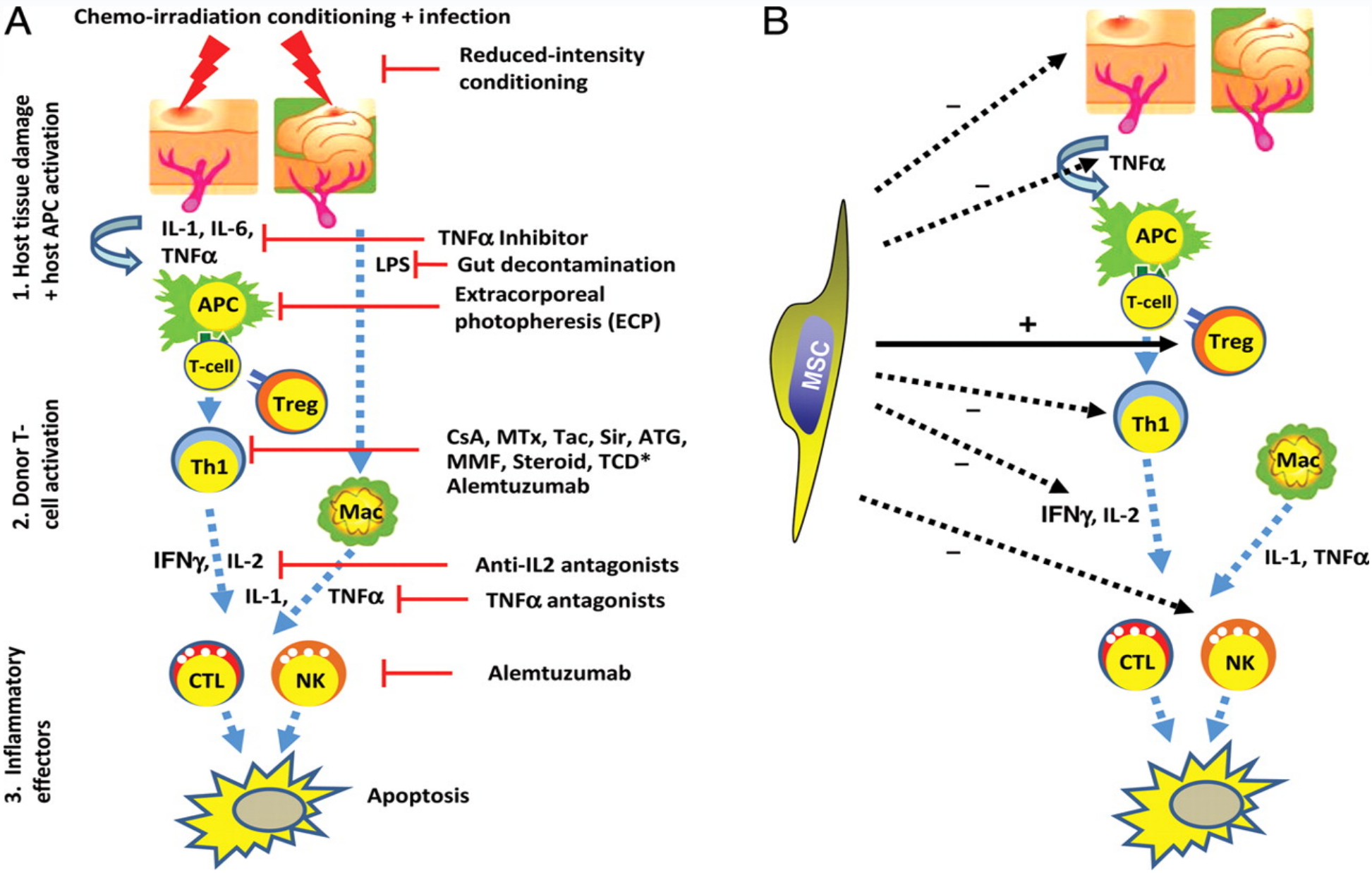


GVHD



Nature Reviews | Immunology

GVHD


A
Chemo-irradiation conditioning + infection
Reduced-intensity conditioning
1. Host tissue damage + host APC activation
IL-1, IL-6, TNFα
TNFα Inhibitor
LPS
Gut decontamination
APC
Extracorporeal photopheresis (ECP)
T-cell
Treg
2. Donor T-cell activation
Th1
CsA, MTx, Tac, Sir, ATG, MMF, Steroid, TCD*
Alemtuzumab
Mac
IFNγ, IL-2
Anti-IL2 antagonists
IL-1, TNFα
TNFα antagonists
3. Inflammatory effectors
CTL
NK
Alemtuzumab
Apoptosis
B
TNFα
APC
T-cell
Treg
MSC
Th1
Mac
IFNγ, IL-2
IL-1, TNFα
CTL
NK

MSC therapies have been most extensively studied in steroid-refractory GvHD

- The first case of successful treatment of severe refractory acute GvHD of the gut and liver in a pediatric patient using ex vivo expanded haplo-identical human MSC was reported by Le Blanc.
- While a prompt amelioration of GvHD was observed after the administration of MSC, symptoms recurred. However, these symptoms were responsive to a second administration of MSC

(Le Blanc et al., 2004)

GVHD

Compassionate use: Now(5/2006) APPROVED for PAYMENT & USE

- 12 pediatric patients [5months to 15 years of age]
- Suffering from treatment resistant GVHD
- Prochymal (MSC) infusions (3-21

  (12/12) showed a CLINICAL RESPONSE

  (7/12) , 58% achieving COMPLETE RESPONSE.
- No infusion toxicity or adverse events.

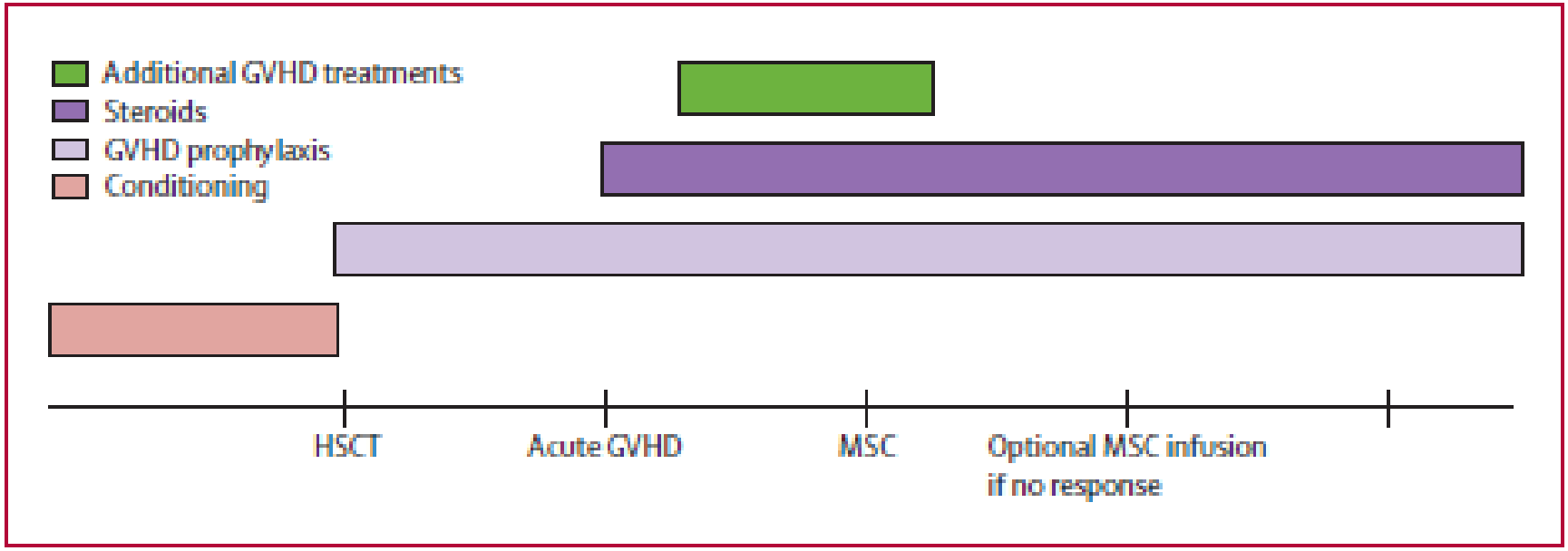
MSC increase survival of aGVHD patients

The clinical response was striking, with improvement of liver and intestinal function.

THE LANCET

Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study

Katarina Le Blanc, Francesco Frassoni, Lynne Ball*, Franco Locatelli, Helene Roelofs, Ian Lewis, Edoardo Lanino, Berit Sundberg,*



- A later phase II clinical study (25 children and 30 adults)
- 55 steroid-resistant patients with severe acute disease

Le Blanc et al, 2008

MSC increase survival of aGVHD patients

The clinical response was striking, with improvement of liver and intestinal function.

THE LANCET

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

*At last data collection, March, 2007.

Table 4: GVHD response and outcome

Mesenchymal Stem Cell Expansion EBMT Consortium,

- 55 patients with acute GVHD grade 2–4.
- Transfer of a median 1 4×10^6 cells/kg-bw

Complete responses in 55%

Partial or complete responses in 71%

Cells were expanded ex vivo and generated from either HLA-identical siblings, haploidentical donors, or third-party mismatched donors.

MSC increase survival of aGVHD patients

The clinical response was striking, with improvement of liver and intestinal function.

THE LANCET

	Measure
Donors	
Number of donors	45
Donor sex (male/female)	25/20
Donor age	36 (1–67)
Number of infusions by donor type	
HLA-identical sibling	5
HLA-haploidentical donor	18
Unrelated HLA-mismatched donor	69
Volume of bone marrow harvested (mL)	60 (32–220)
Median MSC cell dose (x10^6/kg, range)	1·4 (0·4–9)
Culture passage at MSC harvest	
Passage 1	14
Passage 2, 2+3	42, 7
Passage 3, 3+4	23, 2
Passage 4	4
Number of MSC infusions	
One	27
Two	22
Three	4
Four	1
Five	1

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

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

- Most interestingly, there was no difference in the response rates or side-effects between patients receiving mesenchymal stem cells from third-party mismatched donors compared with those in patients receiving cells from HLA-identical siblings or from haploidentical family members
- **MSCs induced a 70% initial response rate that was not related to HLA match**.
- None of the patients had side effects either during or immediately after the MSC infusion

Le Blanc et al, 2008

MSC increase survival of aGVHD patients

The clinical response was striking, with improvement of liver and intestinal function.

THE LANCET

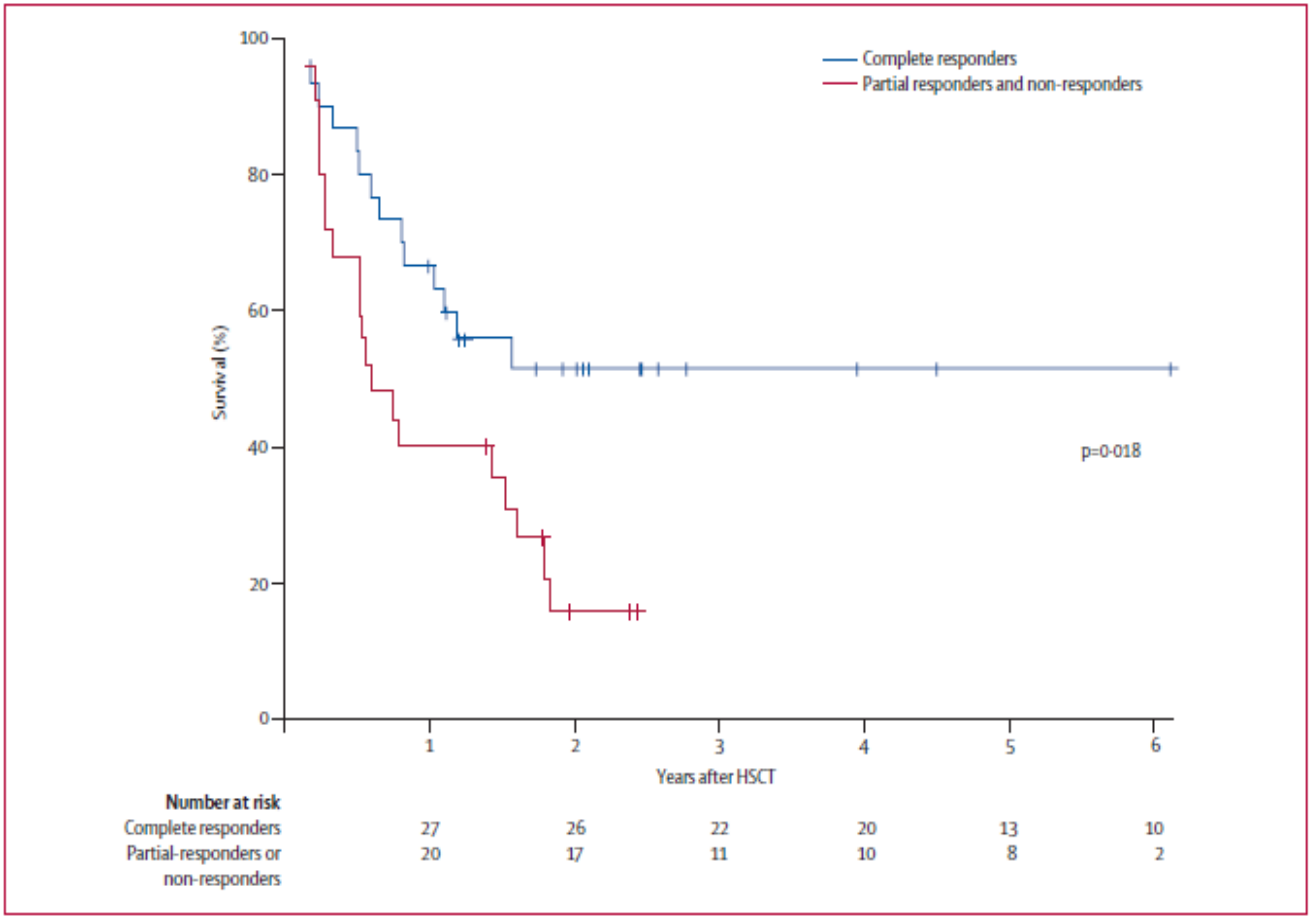


Figure 2: **Survival from time of haemopoietic-stem-cell transplantation in patients given mesenchymal stem cells**
Survival at the end of follow-up was 52% (95% CI 34–70%) for the 30 complete responders and 16% (0–32%) for the 25 partial responders or non-responders.

MSC's derived from bone marrow might be a safe and eff ective treatment for patients with severe, acute GVHD who do not respond to corticosteroids and other immunosuppressive therapies.

Just over half of patients with a complete response were alive at 2 years.

Le Blanc et al, 2008

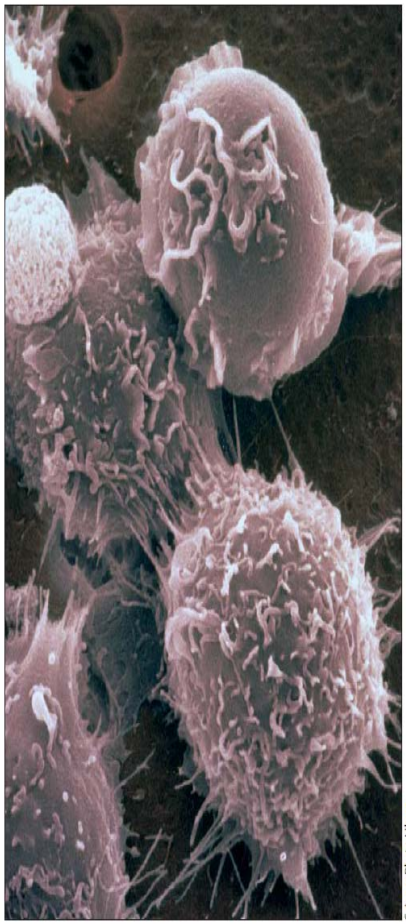
MSC increase survival of aGVHD patients

The clinical response was striking, with improvement of liver and intestinal function.

THE LANCET

Mesenchymal stem cells as cellular immunosuppressants

- Dendritic cells (DC) are potent APC for naïve T-cells, and are critical in donor T-cell activation during acute G*v*HD (Shlomchik, 2007).
- MSC inhibit differentiation of monocytes to DC, and furthermore, affect DC differentiation, activation, and function (Uccelli et al., 2008).
- MSC also inhibit natural killer (NK) cell proliferation and cytokine production, and could potentially modulate DC function through their effects on NK cells (Spaggiari et al., 2006).
- In the light of these effects, MSC might suppress allo-reactivation of donor T-cells against the host in the setting of G*v*HD



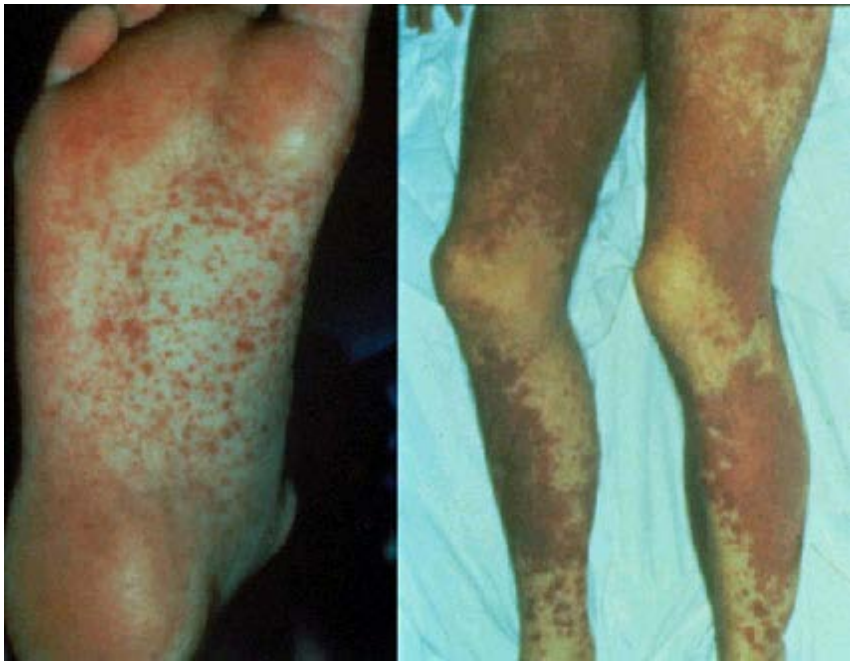
Within the context of innate immunity, MSC alter antigen-presenting cell (APC) development, maturation, and function

Editorial: Dominik Wolf, **Vol 371 May 10, 2008**

MSC as an adjunct to steroid therapy in the treatment of steroid responsive acute G*v*HD

A randomized, prospective, open label trial at 16 cancer centers in the USA with 32 patients with grades II-IV GVHD. *Now FDA OK PHASE III.*

- 77% complete remission in 28 days.
- 61% at 6 months had a durable response requiring
- No additional immunosuppressive therapy or clinical intervention
- 95% were alive at 6 months compared to patients receiving additional immunosuppression (25% survival).
- No adverse events



Study	*N*	Age (range)	G*v*HD organ/ grade	MSC source	Passage/ media	Dose (M, 10^6 MSC)/schedule	Results
Kebriaei et al. (2009)	32	52 (34–67)	Grade II: 21 Grade III: 8 Grade IV: 3	BM, third party (Prochymal)	5/FBS	2 or 8 M/kg at 1 and 3 days after G*v*HD + steroids	94% initial response (77% CR, 16% PR), 61% sustained CR; No difference between high/low MSC dose; No infusional toxicity; three disease relapse

Phase II clinical trials of third-party MSC to ameliorate steroid-refractory acute G*v*HD

(Further to the EBMT MSC trial, a pediatric phase II study of third-party, "off-the-shelf," mismatched MSC (Prochymal®, Osiris Therapeutics, Inc.) for steroid refractory acute G*v*HD has also been reported)

Study	*N*	Age (range)	G*v*HD organ/ grade	MSC source	Passage/ media	Dose (M, 10^6 MSC)/schedule	Results
Ringden et al. (2006)	8	56 (8–61)	All GI Grade III: 6 Grade IV: 2	BM, third party/slb/ haplo	1–4/FBS	1 M/kg (range 0.7–9); 1 dose, $n = 5$; 2 dose, $n = 3$	6/8 CR (1/2 kids); 5/8 OS; no infusional toxicity; one disease relapse
Fang et al. (2007)	6	39 (22–49)	S+L or GI Grade III: 2 Grade IV: 4	Adipose, third party/ haplo	5/FBS	1 M/kg MSC; 1 dose, $n = 5$; 2 dose, $n = 1$	5/6 CR, 4/6 OS at 40 months; no infusional toxicity; one disease relapse
Le Blanc et al. (2008)	55	22 (0.5–64)	S10, GI 31, L2 Grade II: 5 Grade III: 25 Grade IV: 25	BM, third party/slb/ haplo	2 (1–4)/FBS	1.4 M/kg (range 0.4–9); 1 dose (range 1–5)	CR: 68% kids, 43% adults; PR: 16% kids, 17% adults; 2-year OS: 53% for CR vs. 16% others; no infusional toxicity; 3 relapse
Von Bonin et al. (2009)	13	58 (21–69)	All S+L+GI Grade III: 2 Grade IV: 11	BM, third party	1–2/platelet lysate	0.9 M/kg (range 0.6–1.1); 2 doses (range 1–5);	2/13 CR, 5/13 mixed response; 4/13 OS at median 257 days; No infusional toxicity; no relapse
Muller et al. (2008)	2	4, 14	Grade II (S, GI) Grade III (S, L, GI)	BM, haplo/ third party	Max 6 weeks culture/FBS	0.4 M/kg, 3 M/kg 1 dose	1 CR, 1 NR with subsequent relapse; no infusional toxicity
Lucchini et al. (2010)	8	10 (4–14)	Grade I: 3, S Grade II: 1,S Grade III: 0 Grade IV: 4, GI	BM, third party	Platelet lysate	1.2 M/kg (range 0.7–2.8); 1 dose	3/8 CR, 2/8 PR, 3/8 NR 5/8 OS; no infusional toxicity; no relapse
Kurtzburg et al. (2009)	59	8	Grade II: 6 Grade III: 20 Grade IV: 33	BM, third party (Prochymal)	5/FBS	2 M/kg; 8 biweekly × 4 weeks, followed by 4 infusions weekly × 4 if PR	64% ORR at day 28; 76 vs. 9% survival at day 100; no infusional toxicity
Martin et al. (2010)	260	44 MSC; 40 control	MSC/ control B: 38 vs. 23 C: 88 vs. 50 D: 47 vs. 14	BM, third party (Prochymal)	5/FBS	2 M/kg; 8 biweekly × 4 weeks, followed by 4 infusions wkly × 4 if PR	No diff in durable CR between MSC and control; liver, GI G*v*HD significantly better response 81 vs. 68%, $p = 0.035$

MSC as a cellular therapy to ameliorate chronic G*v*HD

Significant improvements have been reported following MSC therapy in patients with sclerodermal-type chronic G*v*HD

- Patients with extensive skin changes and ulcers showed significant improvement when treated with four to eight intra-bone marrow injections of MSC at a dose of 1–2 × 10^7 MSC/kg.
- The administration of MSC and improvement in chronic G*v*HD was associated with an increase in the proportion of Th2 lymphocytes and a reduction in the proportion of Th1 lymphocytes.

One change noted following MSC administration and possibly associated with the improvement in the symptoms of chronic G*v*HD was a reversal in the Th1 to Th2 lymphocyte ratio. (Zhou et al., 2010).

Study	*N*	Age (range)	G*v*HD organ/ grade	MSC source	Passage/ media	Dose (M, 10^6 MSC)/schedule	Results
Zhou et al. (2010)	4	42 (38–43)	Extensive, sclerodermal features	BM, third party	3–6/FBS	1–2 × 10^7MSC/kg; 4–8 intra-BM injections per patient	4/4 significant improvement; no infusional toxicity

MSC; in the treatment of chronic-extensive GvHD

Table 3 | Results of clinical trails utilizing MSC for chronic GvHD.

Study	*N*	Age (range)	GvHD organ/ grade	MSC source	Passage/ media	Dose (M, 10^6 MSC)/schedule	Results
Muller et al. (2008)	3	15 (15–17)	Extensive chronic	BM, third party/sib/ haplo	Max 6 weeks culture/FBS	2.0 M/kg (range 1.4–3.0); 1 dose, $n = 1$; 2 dose, $n = 2$	1/3 improvement; no infusional toxicity; no relapse
Lucchini et al. (2010)	5	9 (5–15)	Chronic skin + mucosa, $n = 4$; chronic skin + liver, $n = 1$	BM, third party	expanded in platelet-lysate medium	1.1 M/kg (range 0.7–1.4); 1 dose, $n = 4$; 2 dose, $n = 1$	1/5 CR with reflare, 2/5 PR, 2/5 NR; no infusional toxicity; no relapse; *in vivo* immunomodulation noted in responsive group
Zhou et al. (2010)	4	42 (38–43)	Extensive, sclerodermal features	BM, third party	3–6/FBS	1–2 × 10^7MSC/kg; 4–8 intra-BM injections per patient	4/4 significant improvement; no infusional toxicity
Weng et al. (2010)	19	29 (18–39)	Extensive chronic	BM, third party	2–3/FBS	0.6 M/kg (range 0.2–1.4); 1–5 doses	74% ORR (4 CR, 10 PR), five patients able to stop immunosuppression, 2 year OS 78%; *in vivo* immunomodulation noted in responsive group

STEM CELLS®

Translational and Clinical Research

Fetal membrane cells for treatment of steroid-refractory acute graft-versus-host disease †

Olle Ringdén[1,‡,*], Tom Erkers[1], Silvia Nava Issue

The placenta protects the fetus from the mother's immune system. We have previously found that fetal membrane cells (FMCs) isolated from term placenta prevent alloreactivity in vitro. FMCs share many features with bone marrow-derived mesenchymal stromal cells (MSCs), which we previously introduced to treat severe acute graft-versus-host disease (GVHD). Here, we tested FMCs for treatment of steroid-refractory acute GVHD.

After two passages in culture, approximately 10^9 FMCs were obtained from one single placenta, although not all cells from passage 0 and passage 1 were used for expansion. The FMCs were positive for CD29, CD44, CD73, CD90, CD105, and CD49d but were negative for hematopoietic, endothelial, and epithelial markers. Microsatellite polymorphism analysis showed that FMCs were of maternal origin. All FMCs used showed normal karyotype.

Nine patients who had undergone hematopoietic stem cell transplantation and who had developed steroid-refractory grade III--IV acute GVHD were given 0.9--2.8 x 10^6 FMCs/kg at 15 infusions. Median age was 57 years. There was no toxicity from infusion of FMCs in eight patients. One patient had seizures after infusion. Two of eight evaluable patients had a complete response and four had a partial response, giving an overall response rate of 75%. Two patients showed no response at all. Three patients are alive from 6 to 21 months after HSCT. One patient is well and two have chronic GVHD.

Thus, FMCs may be successfully used for immune modulation and tissue repair.

2013 Jan. [Epub ahead of print]

Important questions; which might impact the clinical efficacy of MSC as a cellular therapy for G*v*HD

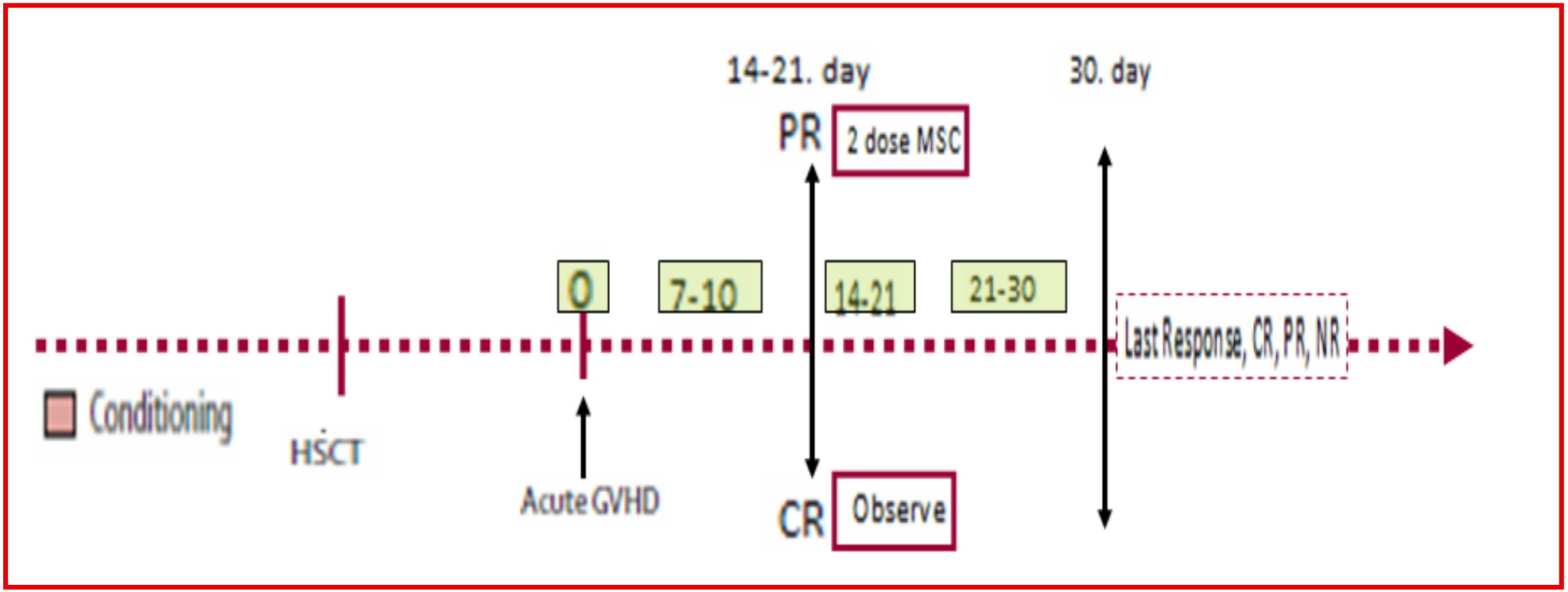
Such questions include:

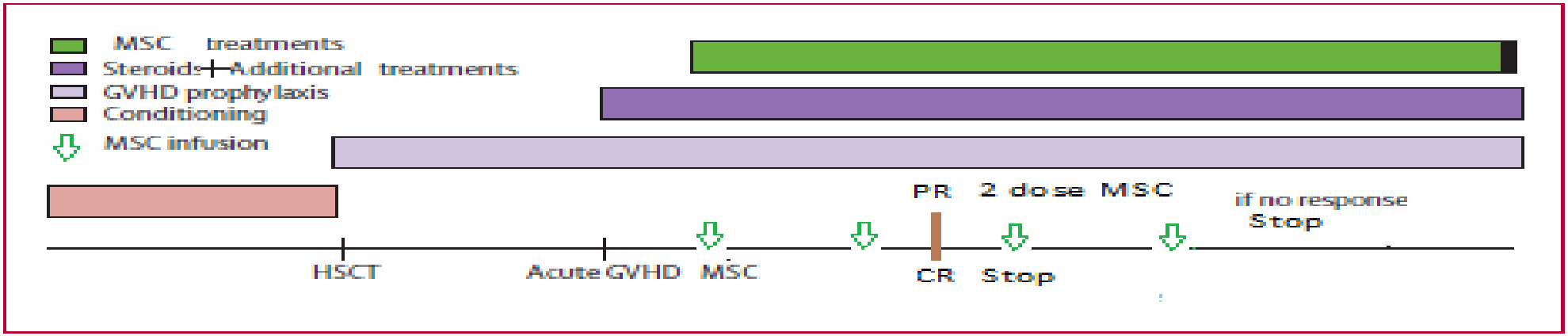
(a) Defining the optimal dose of MSC,

(b) Determining the correct time for administration of MSC, and

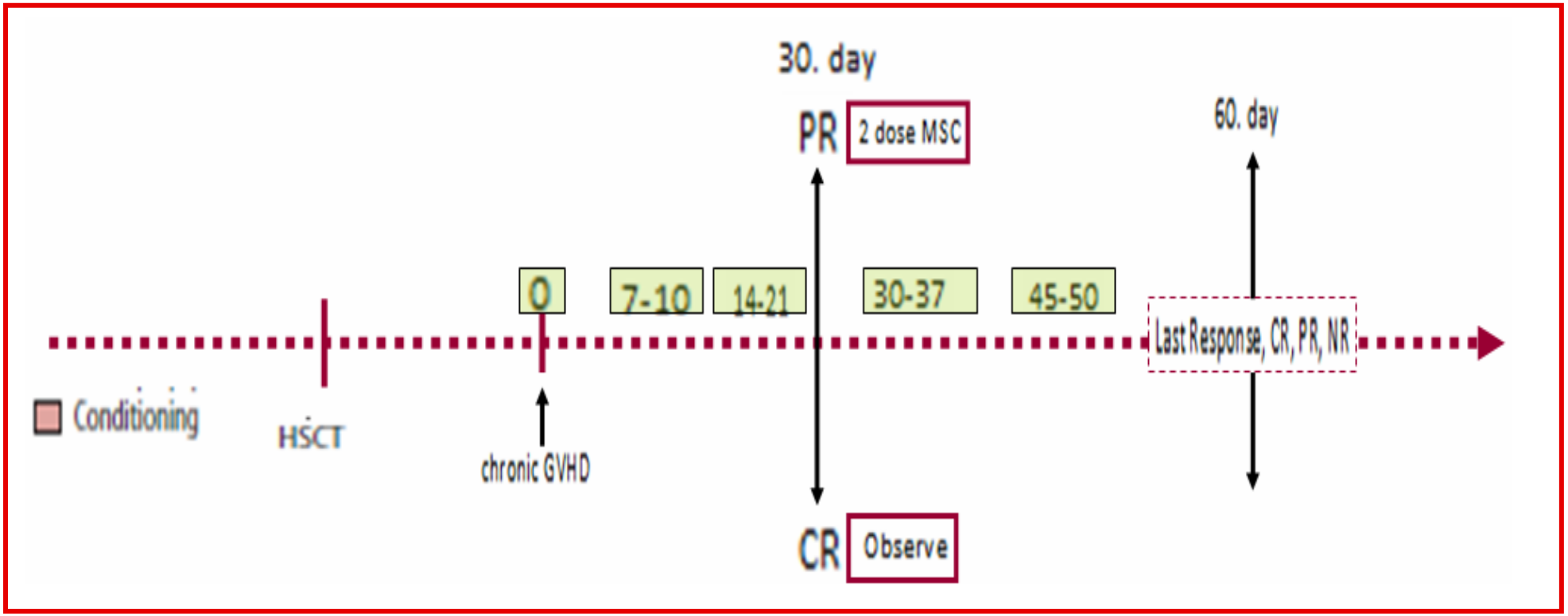
(c) Studying the biodistribution of MSC.

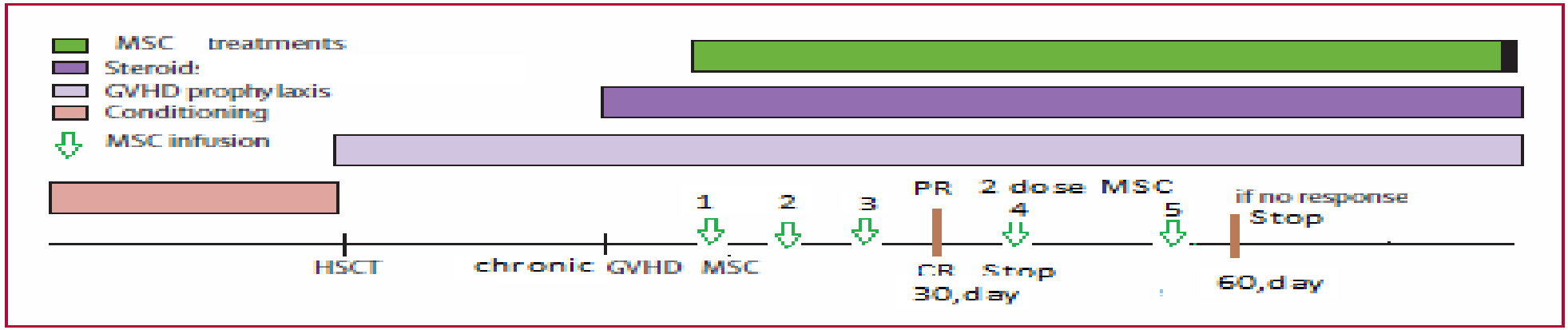
MSC: Phase III Study in acute GVHD [MSC &ATG]

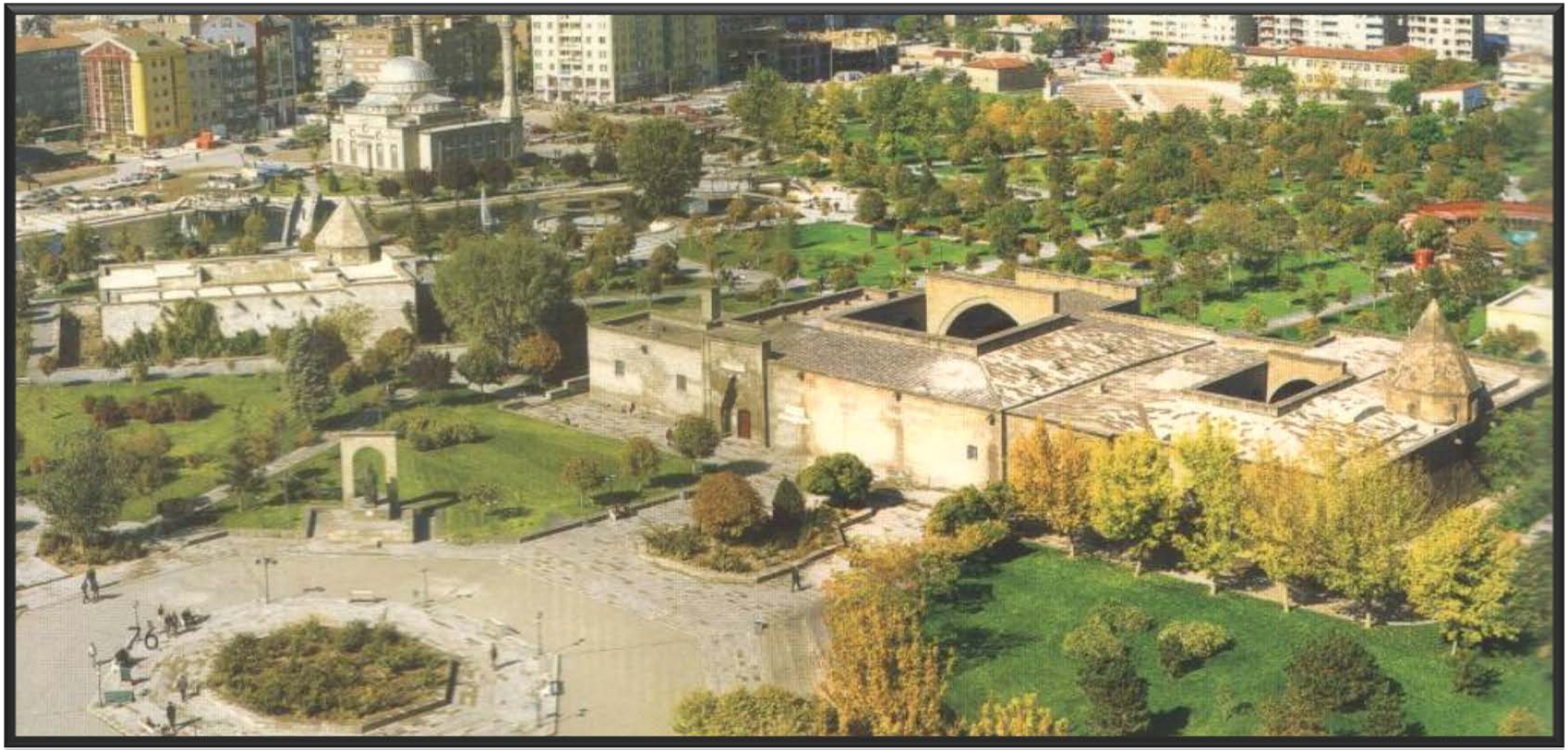




MSC: Phase III Study in chronic GVHD [MSC &ATG]







(Gevher Nesibe Madrasa: the first medical school)

In the Seljuks Periods: a large number of historical works of art such as mosques, madrasas

In That time ; thirty-two madrasas (universities) were maintained their education program

Kaniş-Karum (Kültepe) near the Kayseri: The center of Assyrian state

Kanish and Karum ruins, the first trade centers of the wold A lot of trade aggrement signed on stone tablets between Assyrian and Hittites & Egypt

Four thousand years before the first written trade agreement in Anatolia was made and written documents were found in the excavations of Kayseri Kültepe-Karum, 22 km to the east of KAYSERI.

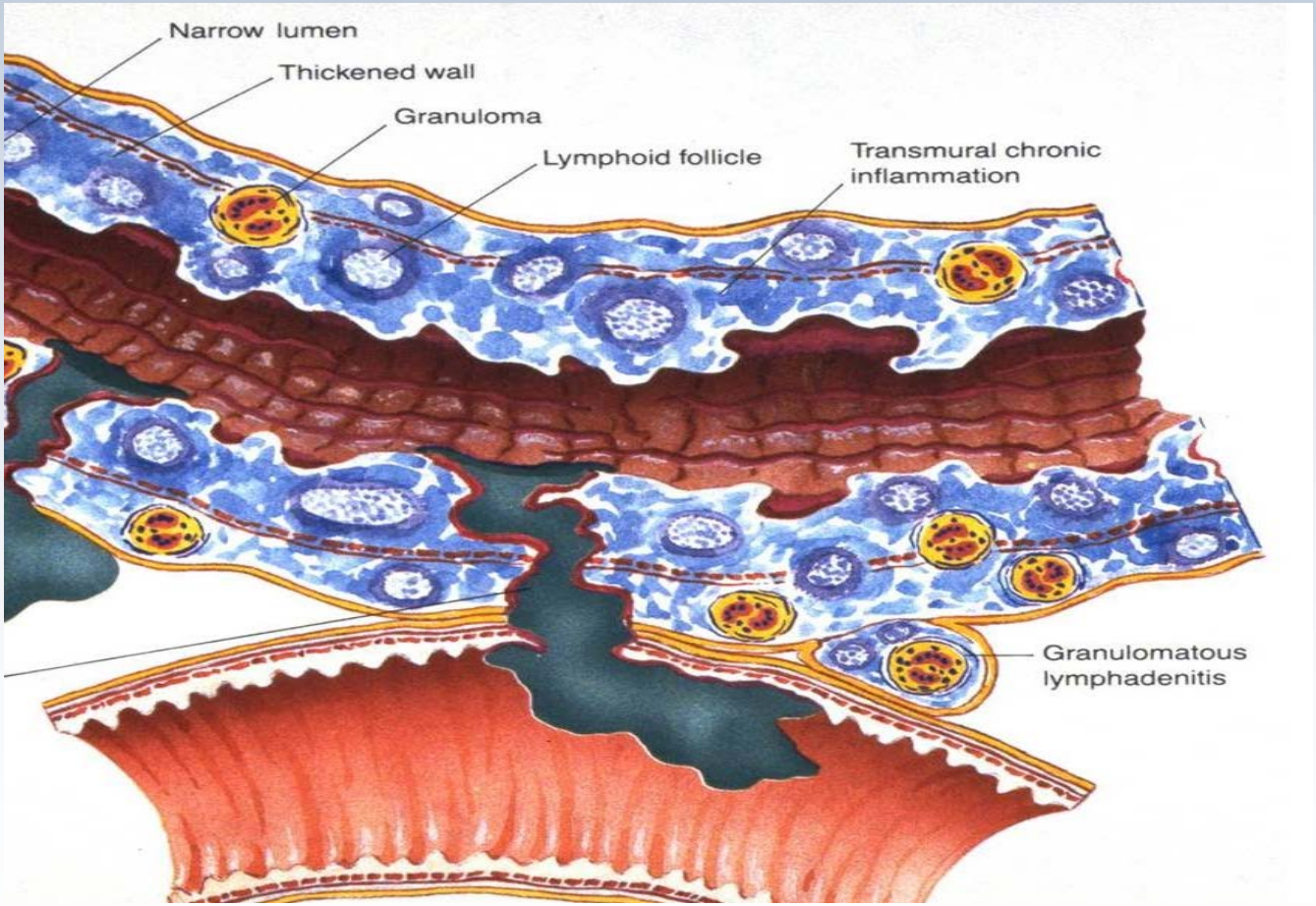
Fernando E. Figueroa

Biol Res 45: 269-277, 2012

Mesenchymal Stem Cell treatment for autoimmune diseases: a critical review

Mesenchymal stem cells (MSCs) are now known to display not only stem cell multipotency, but also robust antiinflammatory and regenerative properties. After widespread *in-vitro* and *in-vivo* preclinical testing, autologous and allogeneic MSCs have been applied in a range of immune mediated conditions, including graft versus host disease, Crohn´s disease, multiple sclerosis, refractory systemic lupus erythematosus and systemic sclerosis. Current data suggests that MSCs may not only replace diseased tissues, but also exert several trophic, regenerative and antiinflammatory effects. While the clinical outcome in case reports and phase I-II trials seems occasionally striking, these limited results point to the need to perform controlled multicenter trials. Future advances from stem cell science can be expected to pinpoint significant MSC subpopulations and/or stem cell markers for improved regenerative or immunoregulatory properties.

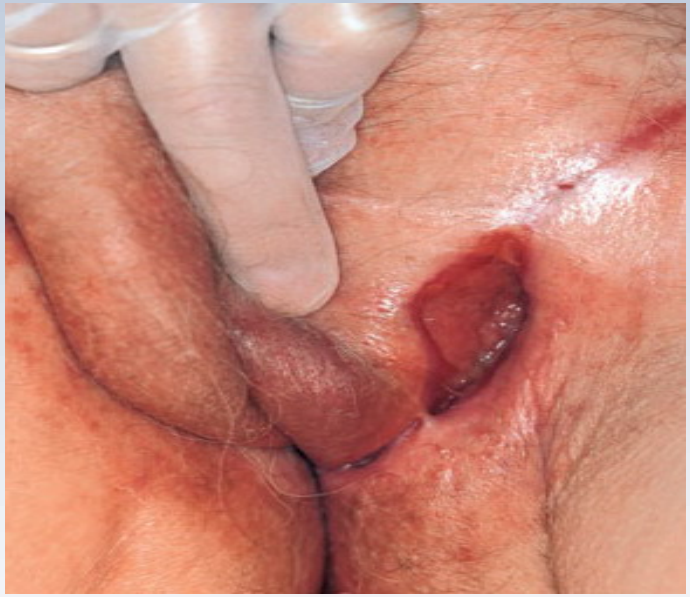
Crohn Disease; Crohn's disease is an inflammatory bowel disease

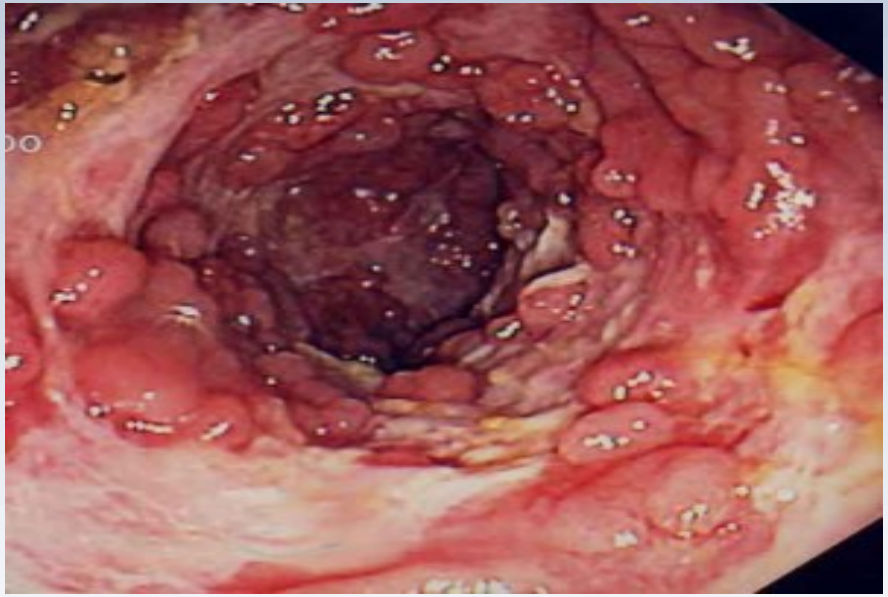


Crohn causes inflammation of the lining of your digestive tract, which can lead to abdominal pain, severe diarrhea and even malnutrition.

Crohn Disease;

involve the entire gastrointestinal tract with persistent transmural inflammation and fistulization.





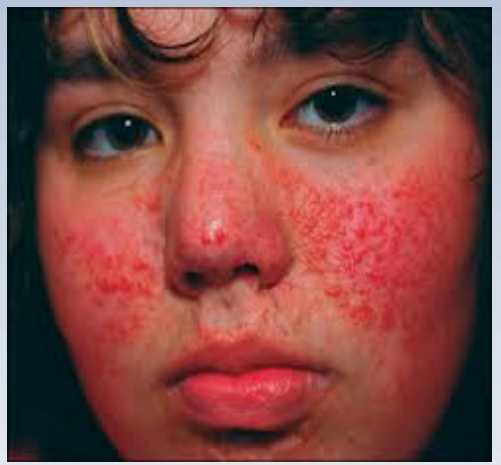
- The first report of a phase I clinical trial of cell therapy using autologous adipose-derived MSCs was published in 2005. **Local injection led to healing of fistulas (6/8) with no adverse effects** (Garcia-Olmo et al.)

- Onken et al. reported a clinical response (**≥100 point reduction in the Crohn Disease Activity Index) in 3/9 (33.3%)** patients, (2006)

Systemic Lupus Erythematosus (SLE)

SLE is a chronic autoimmune disease that can affect almost any organ system; thus, its presentation and course are highly variable, ranging from indolent to fulminant

Perhaps the most successful results of human MSC therapy emerge from clinical trials aimed at severe treatment refractory SLE (Liang et al., 2010).



Butterfly-shaped rash

- *Tögel et al. reported that remarkable improvement renal conditions and the other SLE symptoms of SLE (2009)*
- *A second trial from this group in China, (Sun et al., 2010), reporting the use of umbilical cord-derived MSCs in severe lupus patients (n=16). Follow-up was only 8.25 months, but significant improvement was verified for SLEDAI score, serum albumin, 24h urinary protein, serum creatinine, serum complement and anti-dsDNA antibodies.*

ORIGINAL ARTICLE

Mesenchymal SCT ameliorates refractory cytopenia in patients with systemic lupus erythematosus

X Li[1], D Wang[1], J Liang, *Bone Marrow Transplantation* advance online publication, 15 October 2012; doi:10.1038/bmt.2012.184

- 35 SLE patients with refractory cytopenia
- 20 patients had leukopenia, 24 with anemia or thrombocytopenia.
- The average follow-up period after MSCT was 21 months
- Significant improvements in blood cell count were found after MSCT
- Most patients, in parallel with the decline of disease activity.

ORIGINAL ARTICLE

Mesenchymal SCT ameliorates refractory cytopenia in patients with systemic lupus erythematosus

X Li[1], D Wang[1], J Liang, *Bone Marrow Transplantation* advance online publication, 15 October 2012; doi:10.1038/bmt.2012.184

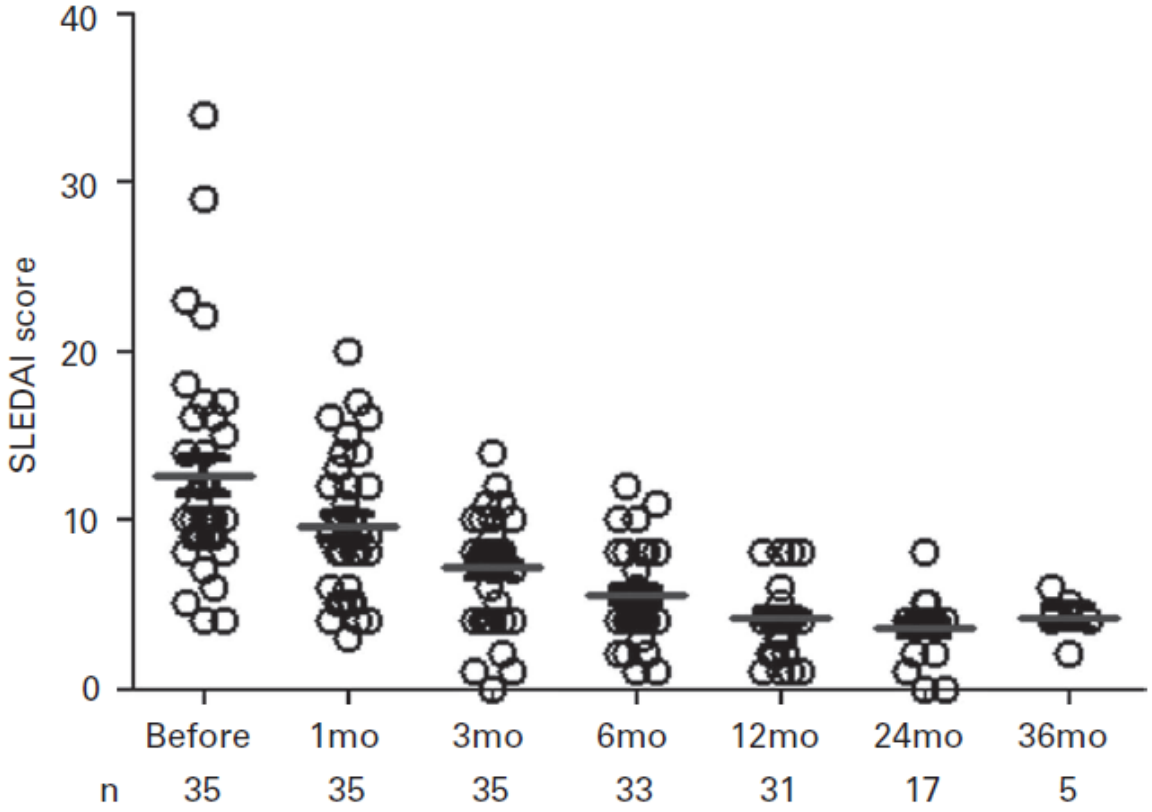
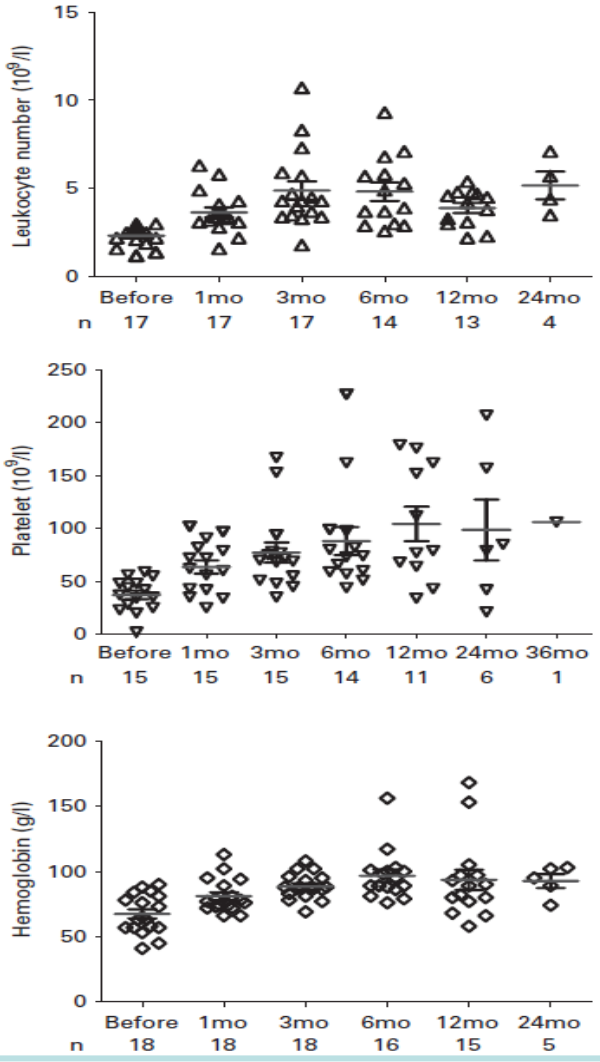
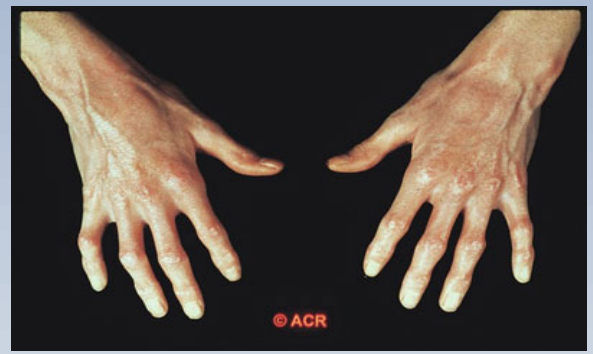


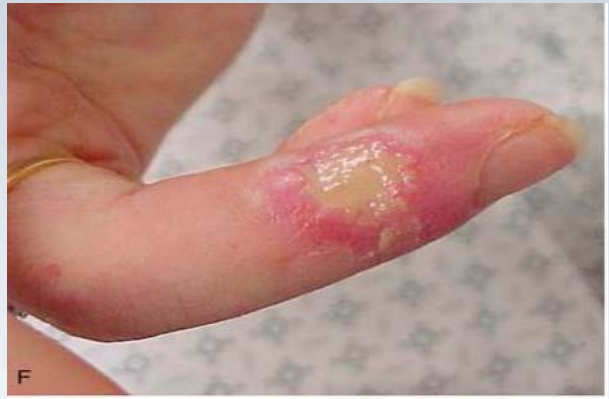
Figure 2. SLE Disease Activity Index (SLEDAI) score for each patient pre- and post- MSCT. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.



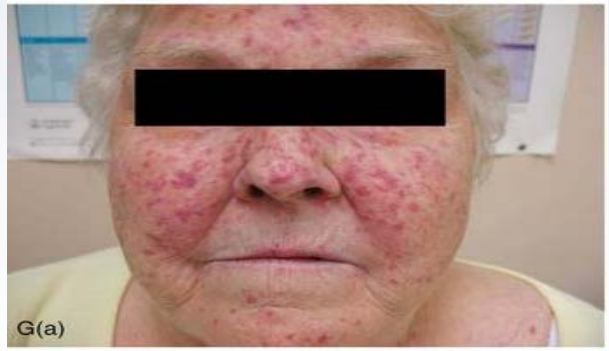
Systemic Sclerosis (SS)

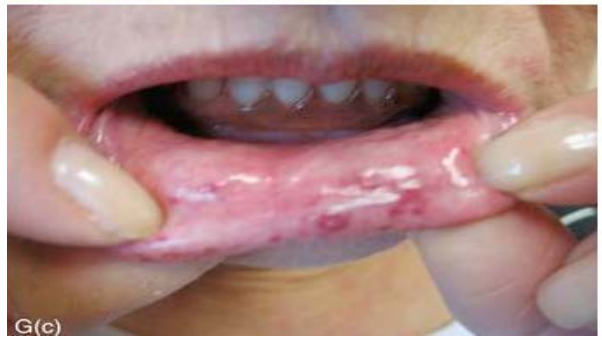


SSc is a systemic autoimmune connective tissue disease. Characteristics of disease include vasomotor disturbances; fibrosis; subsequent atrophy of the skin, subcutaneous tissue, muscles, and internal organs (eg, alimentary tract, lungs, heart, kidney, CNS);



- In a most interesting investigation by Akiyama
- Transplantation of allogeneic MSCs in 5 patients with SS
- Triggered the induction of T cell apoptosis,
- Triggered the lymphopenia and Treg induction
- Leading to skin ulcer healing in one case

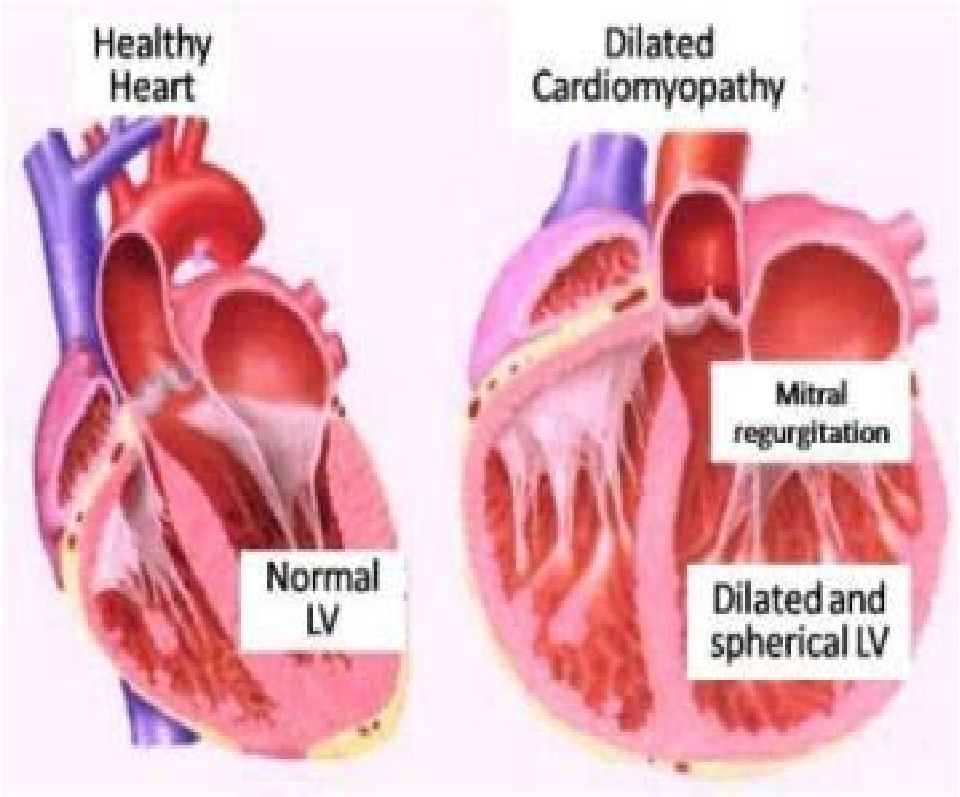




Significant improvement in the Skin Score, Health Assessment Questionnaire and autoantibody titer in the whole group. (Guiducci et al., 2007) (Akiyama et. al., 2012).

İSCHAEMİC CARDİOMYOPATHY

- MSCs have also been used in with promising results .
- However, the benefits of MSC treatment may be due to paracrine effects of MSCs instead of their capacity to differentiate into cardiomyocytes after injection.

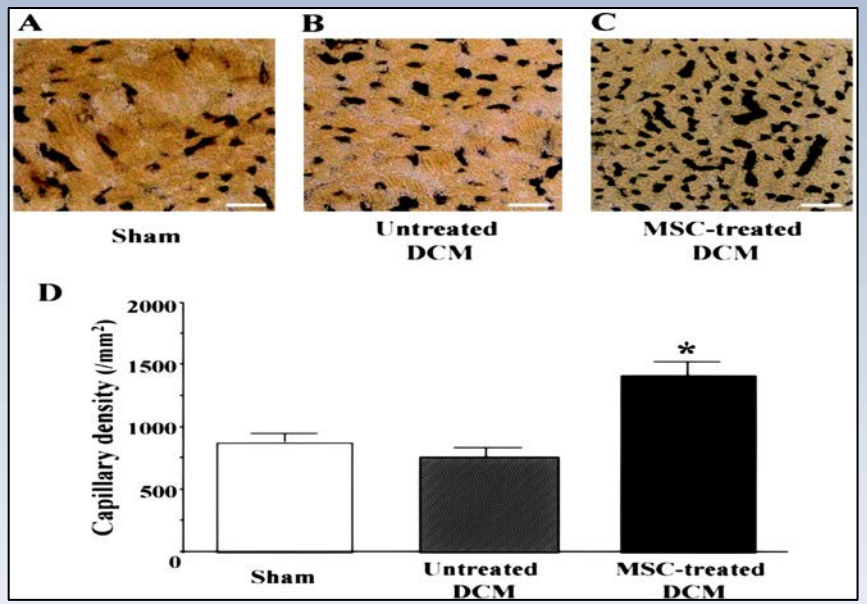


S. Chen, Z. Liu, N. Tian et al., “Intracoronary transplantation of autologous bone marrow mesenchymal stem cells for ischemic cardiomyopathy due to isolated chronic occluded left anterior descending artery,” *Journal of Invasive Cardiology*, vol. 18, no. 11, pp. 552–556, 2006.

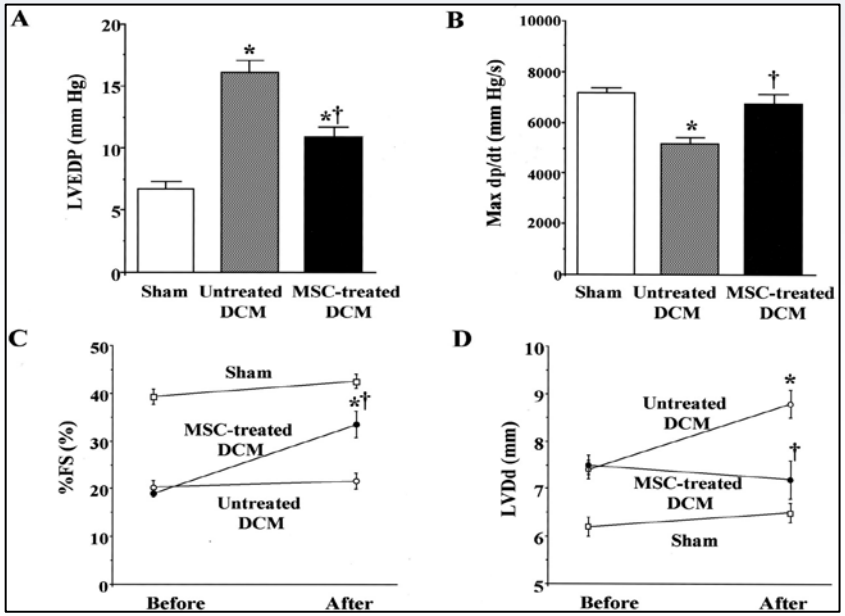
MSCs for cardiovascular repair

Nagaya N et al found that MSC transplantation

- In a rat model of dilated cardiomyopathy
- Significantly increased capillary density
- Decreased left ventricular end-diastolic pressure
- Increased left ventricular maximum



Representative samples of ALP staining of myocardium.



Effects of MSC transplantation on hemodynamic parameters.

Nagaya N, et al: Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. Circulation 2005, 112:1128–1135

Clinical trials using MSCs to improve cardiac function have also demonstrated encouraging results

- İn a pilot study, sixty-nine patients who underwent primary percutaneous coronary intervention within 12 hours after onset of acute myocardial infarction
- They were randomized to receive intracoronary injection of autologous bone marrow mesenchymal stem cell or standard saline.
- Several imagining techniques demonstrated that MSCs significantly improved left ventricular function [22].

Chen SL, et al: Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. Am J Cardiol 2004, 94:92–95.

TABLE 2 Comparison of Left Ventricular Hemodynamics in the Two Groups of Patients

Variables	BMSC Group	Control Group	p Value
Patients (n)	34	35	0.20
Functional defect (%)			
Just before BMSC implantation	32 ± 11	33 ± 10	0.20
At 3-mo follow-up	13 ± 5	28 ± 10	0.001
Infarcted area movement velocity (cm/s)			
Just before BMSC implantation	2.17 ± 1.3	2.19 ± 1.5	0.20
At 3-mo follow-up	4.2 ± 2.5	2.7 ± 1.7	0.01
Left ventricular ejection fraction (%)			
Just before BMSC implantation	49 ± 9	48 ± 10	0.20
At 3-mo follow-up	67 ± 11	53 ± 18	0.01
At 6-mo follow-up	67 ± 3	54 ± 5	0.01

TABLE 3 Cardiac Functional Indexes at Three-month Follow-up in the Two Groups of Patients

Variables	Control Group	BMSC Group	p Value
Patients (n)	35	34	0.20
LV ESV (ml)	162 ± 27	136 ± 31	0.001
LV ESV (ml)	88 ± 19	63 ± 20	0.01
Circumferential shorting (mm/s)	21.7 ± 5.9	24.8 ± 4.2	0.10
P_{syst}/ESV (mm Hg/ml)	2.84 ± 1.30	1.72 ± 1.23	0.01
Perfusion defect by PET (cm^2)	185 ± 87	134 ± 66	0.001

ESV = end-systolic volume; LV = left ventricular; PET = positron emission tomography; P_{syst} = left ventricular end-systolic pressue.

TABLE 4 Cardiac Functional Index by NOGA System in the BMSC Group

	Pretransplantation (n = 15)	At 3-mo Follow-up (n = 15)	p Value
			0.20
Line local shortening (%)	7.32 ± 1.86	11.29 ± 1.64	0.01
Unipolar voltage (mV)	7.61 ± 1.09	10.38 ± 1.12	0.01
Perfusion defect (%)	36 ± 6	20 ± 5	0.01
Stroke volume index (%)	40 ± 11	58 ± 10	0.01
LV end-diastolic volume (ml)	169 ± 21	131 ± 19	0.01
LV end-systolic volume (ml)	76 ± 18	58 ± 13	0.01

LV = left ventricular.

Phase 1 Trial of Autologous Bone Marrow Mesenchymal Stem Cell Transplantation in Patients with Decompensated Liver Cirrhosis

In a phase I trial, four patients with decompensated liver cirrhosis were included. They received autologous MSC infusion through a peripheral vein. There were no side-effects in the patients during followup. The quality of life of all four patients improved by the end of follow-up

Mohamadnejad M:. Arch Iran Med 2007, 10:459–466.

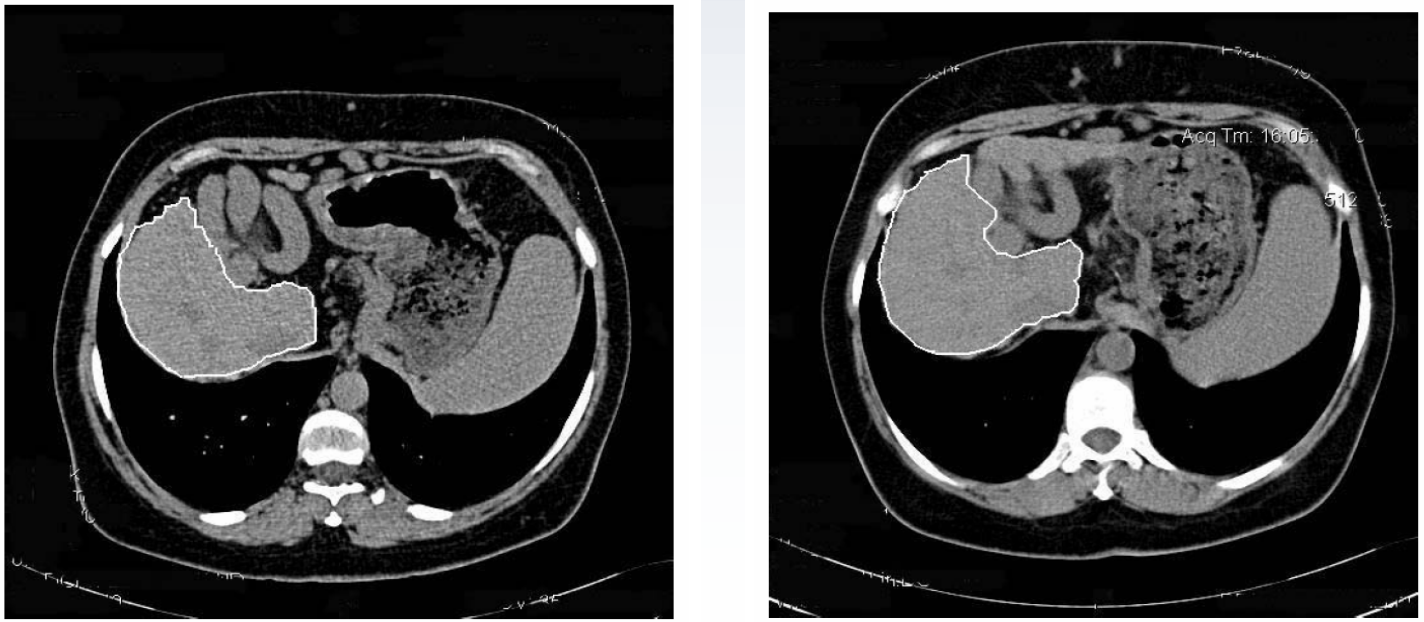


Figure 2. A) Transverse slices of CT scans obtained before, and B) Six months after MSCs infusion in patient I. White outline in CT scans indicates the right liver lobe.

Phase 1 Trial of Autologous Bone Marrow Mesenchymal Stem Cell Transplantation in Patients with Decompensated Liver Cirrhosis

Table 2. Clinical and laboratory parameters of the patients at baseline and at the end of follow-up.

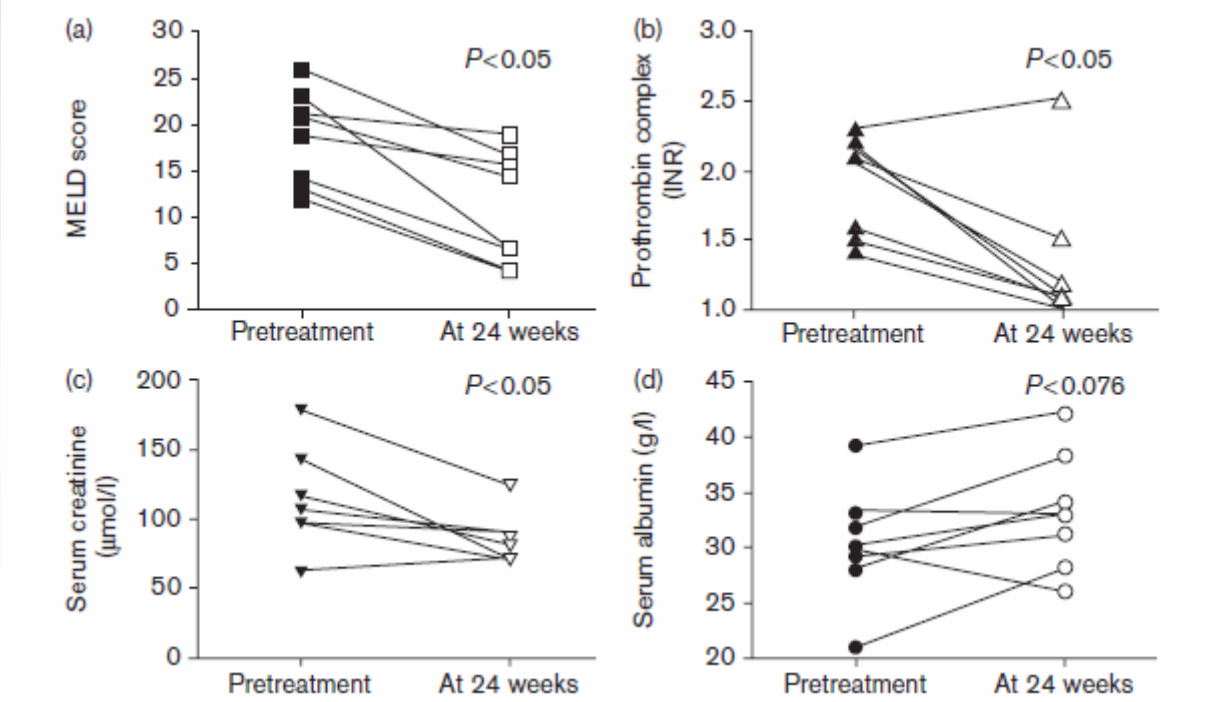
Parameter	Patient 1			Patient 2			Patient 3			Patient 4		
	B	M 6	M 12	B	M 6	M 12	B	M 6	M 12	B	M 6	M 12
Edema*	2+	0	0	2+	1+	1+	2+	0	1+	2+	0	0
Ascites	None	None	None	None		None	Mild	None	None	None	None	None
Serum albumin (g/dL)	2.9	3.8	3.5	2.8	2.9	3	4.1	4.3	3.9	3.4	3.2	3.2
PT (seconds)	18.5	13	15.2	20.1	18.8	18	15.7	15.1	15.5	19.1	13.8	15.5
INR	2.2	1.2	1.6	2.01	2	1.7	1.4	1.3	1.4	1.9	1.1	1.4
Cr (mg/dL)	0.7	0.88	0.80	1.1	0.74	1	0.55	0.85	0.66	0.73	0.92	0.70
Total bilirubin (mg/dL)	1.3	2	0.9	2.7	5.32	3.2	4.43	3.25	3.33	2.18	1.9	2.6
Direct bilirubin (mg/dL)	0.4	0.5	0.5	1	0.91	1.2	1.7	1.25	1.24	0.44	0.49	0.39
AST (IU/mL)	66	149	77	67	59	49	63	74	49	39	43	33
ALT (IU/mL)	53	127	52	24	34	23	81	71	57	25	30	17
AFP (µg/L)	2.6	2	5.5	4.1	2.5	5.5	2.5	2	2	1.5	2.3	0.66
MELD score	16	11	12	19	20	20	16	14	15	17	10	14
Liver volume (cm^3)	495	814		555	843		1115	872		795	940	—

PT=prothrombin time; INR=international normalized ratio; Cr=serum creatinine; AST=aspartate aminotransferase; ALT=alanine aminotransferase; AFP=alpha fetoprotein; MELD=model for end-stage liver disease, B=baseline; M=month.
*Peripheral edema was graded as follows: 0=no edema; trace=indention caused by pressure over the dorsum of the foot; 1+ =indention at shin; 2+ =indention at knee; 3+ =indention above knee; 4+ =generalized edema (indention over hip and low back).

Mohamadnejad M:. Arch Iran Med 2007, 10:459–466.

Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I–II clinical trial

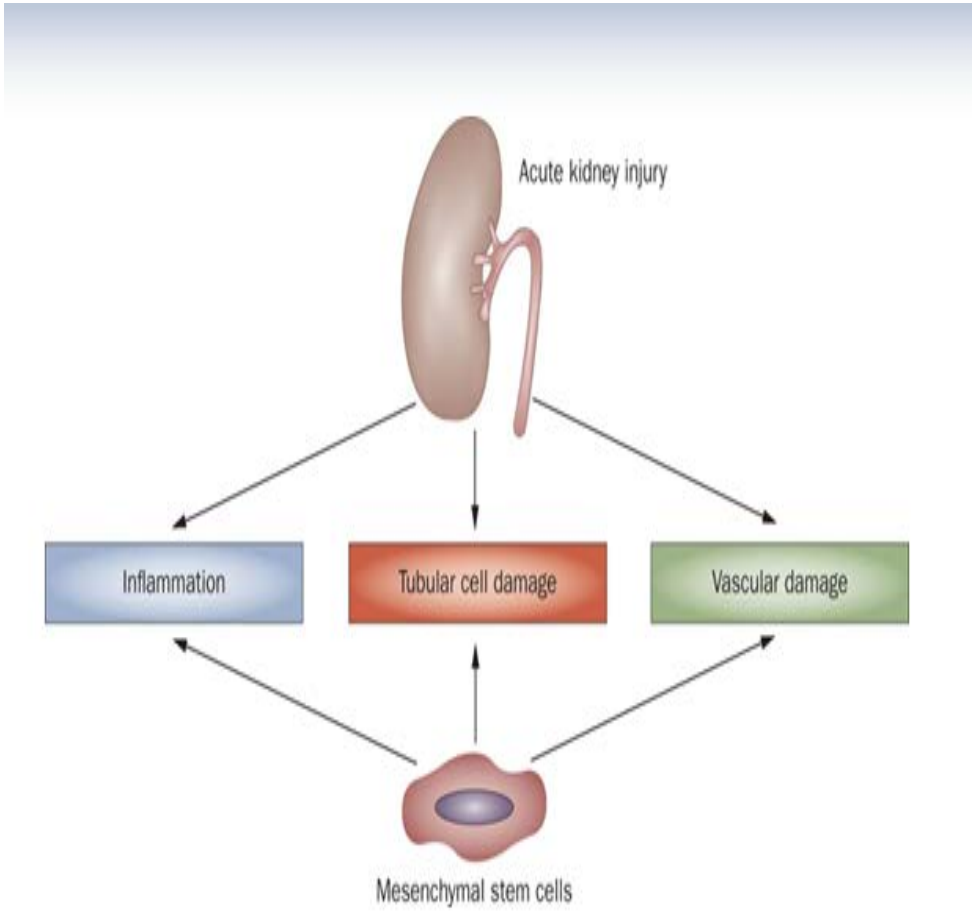
- In another phase I-II clinical trial, 8 patients (four hepatitis B, one hepatitis C, one alcoholic, and two cryptogenic) with end-stage liver disease were included.
- After autologous MSCs injection, all patients tolerated well and their liver function improved, suggesting the feasibility, safety, and efficacy of using MSCs as a treatment for end-stage liver disease



Diagrams of liver function indices before and after injection of mesenchymal stem cells. (a) Model for End-Stage Liver Disease (MELD) score. (b) prothrombin complex. (c) Serum creatinine. (d) Serum albumin. Filled symbols denote pretreatment values; open symbols denote values 24 weeks posttreatment. INR, international normalized ratio.

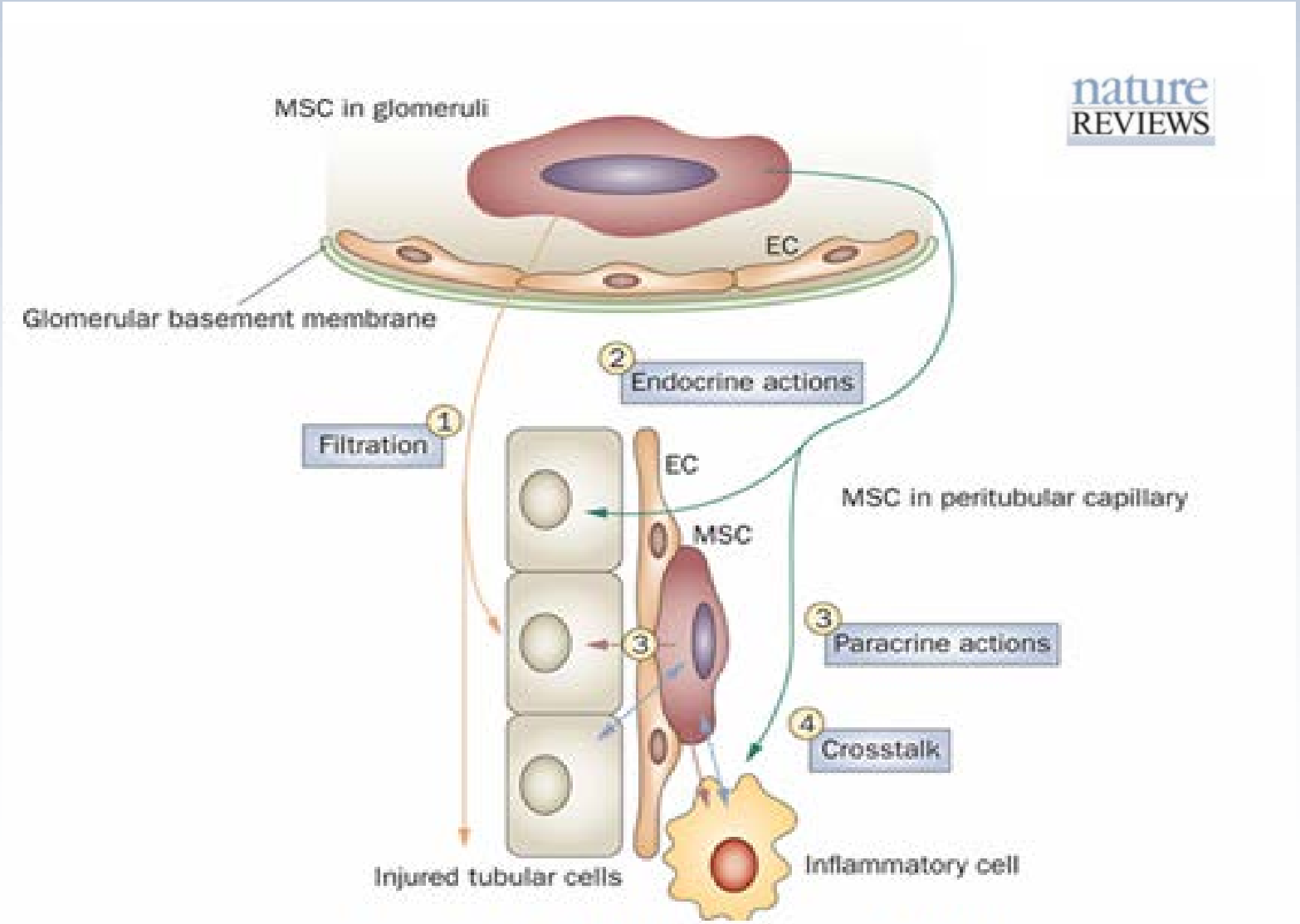
Mesenchymal stem cells target all pathophysiological components of acute kidney injury

- Major axes of the pathophysiology of AKI include inflammation, vascular and tubular damage. Inflammation is triggered by ischemia–reperfusion injury, inflammatory cytokines, and immune cell attachment and migration.
- Vascular damage is caused by ischemia–reperfusion. Endothelial injury and further microcirculatory impairment aggravates tubular cell damage and increases inflammation.
- Tubular cell injury is caused by hypoxia and by the generation of reactive oxygen species during reperfusion



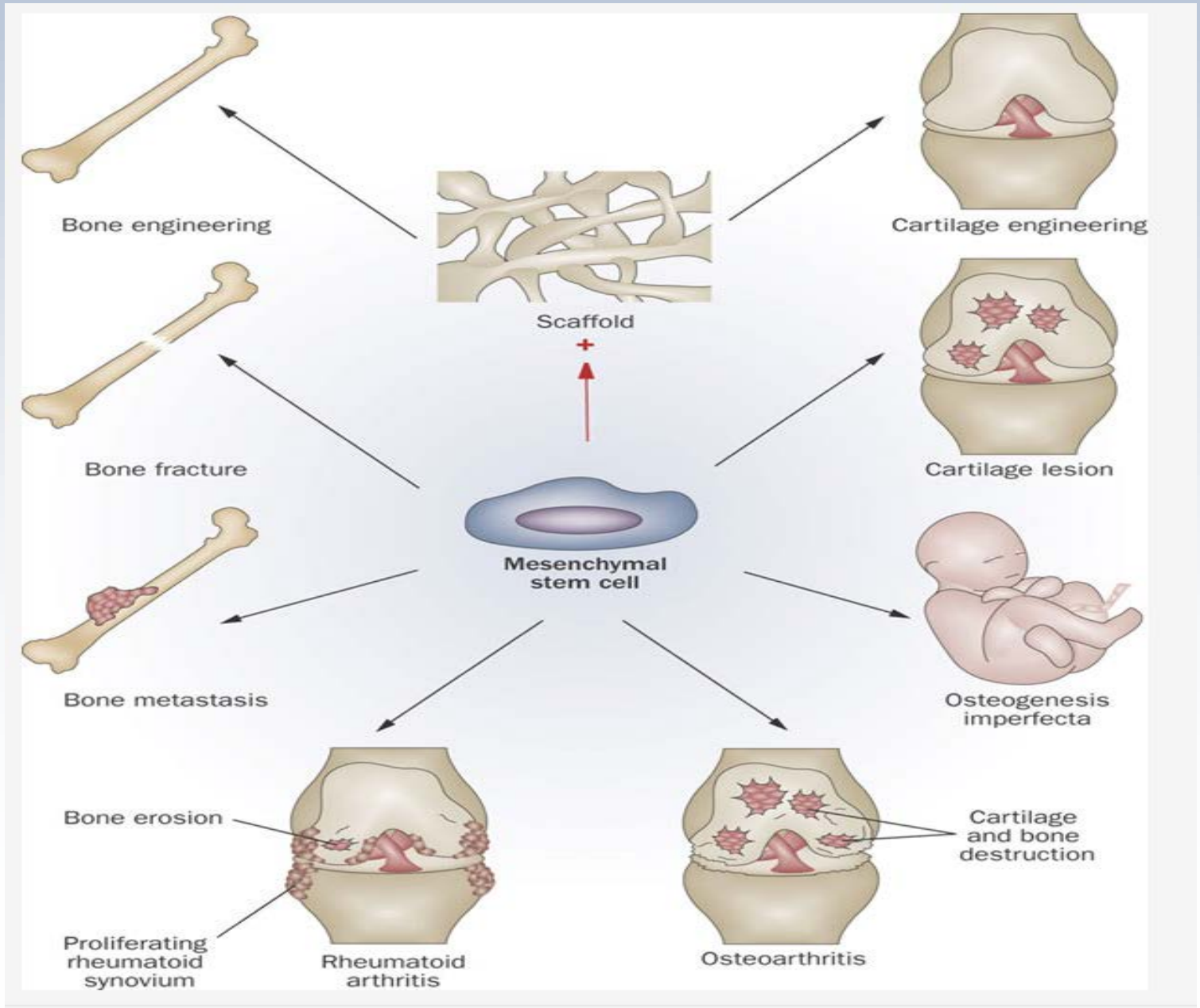
Nat. Rev. Nephrol. **doi:10.1038/nrneph.2009.229**

Intrarenal actions of MSCs in acute kidney injury

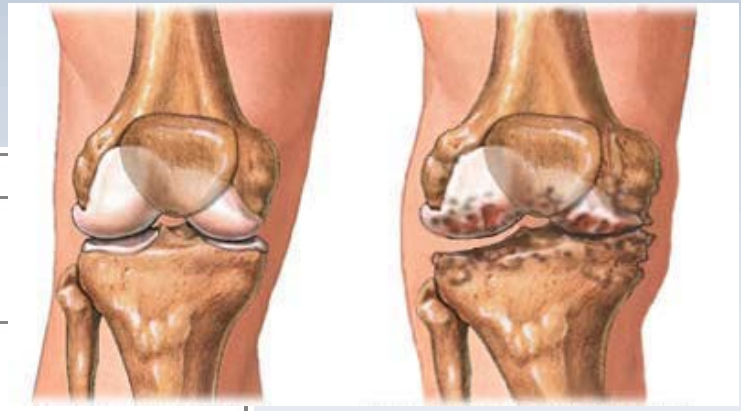


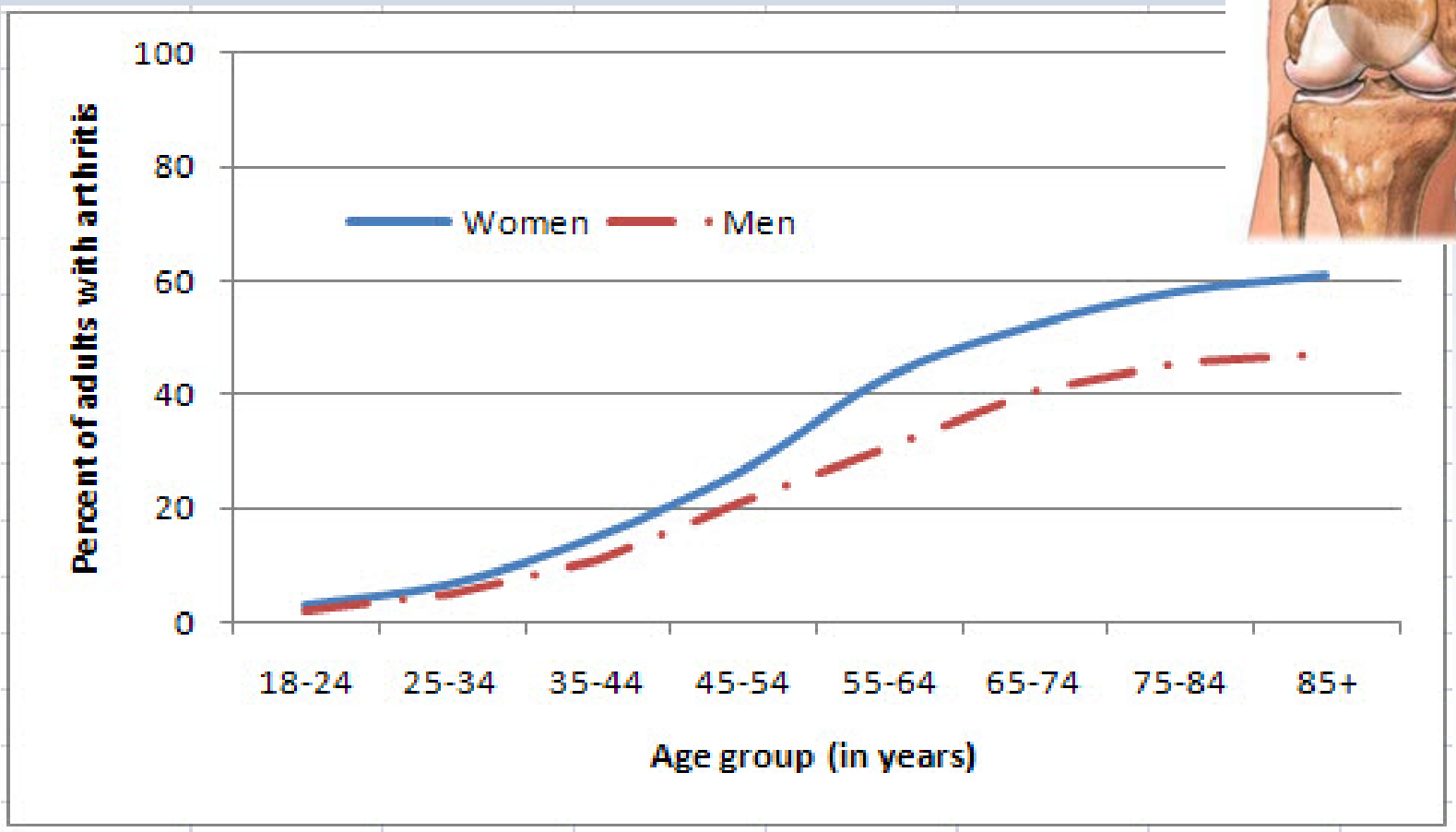
Tögel, F. E. & Westenfelder, C. (2010)

Orthopaedic Disorders and Mesenchymal Stem Cell Therapy



Arthritis in the United States





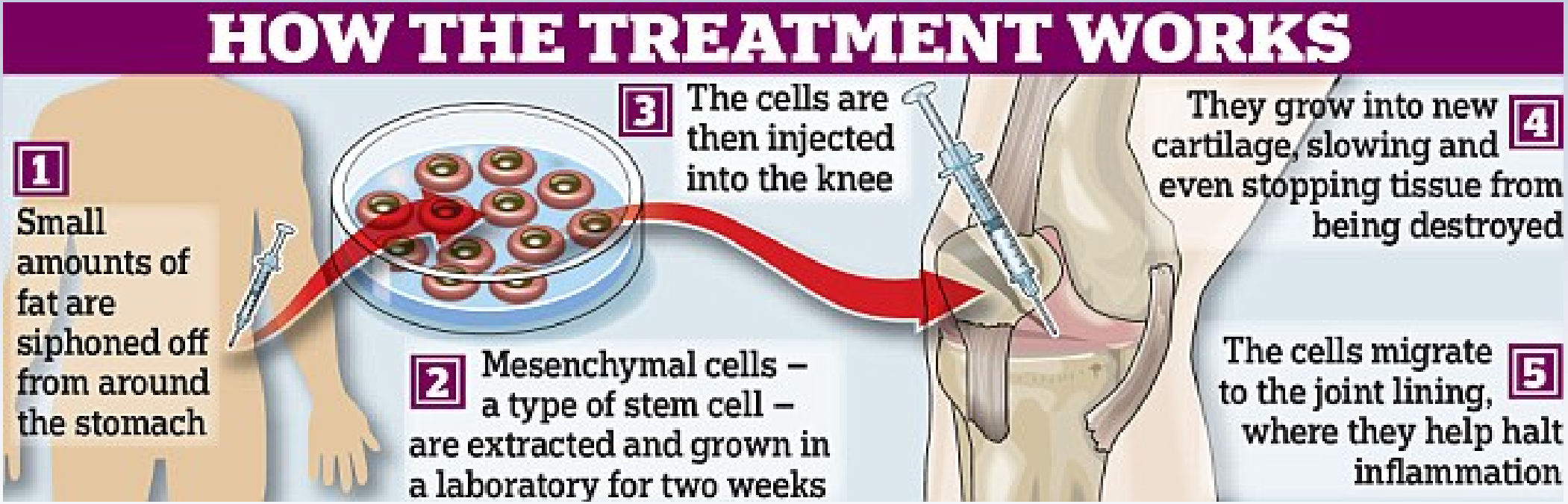
Current Treatment Options

- **Drugs**
- NSAID (Ibuprofen, Naproxen)
- Painkillers (Narcotic and Non-Narcotic)
- Corticosteroids

- **Joint Surgery**
- Knee replacement, hip replacement

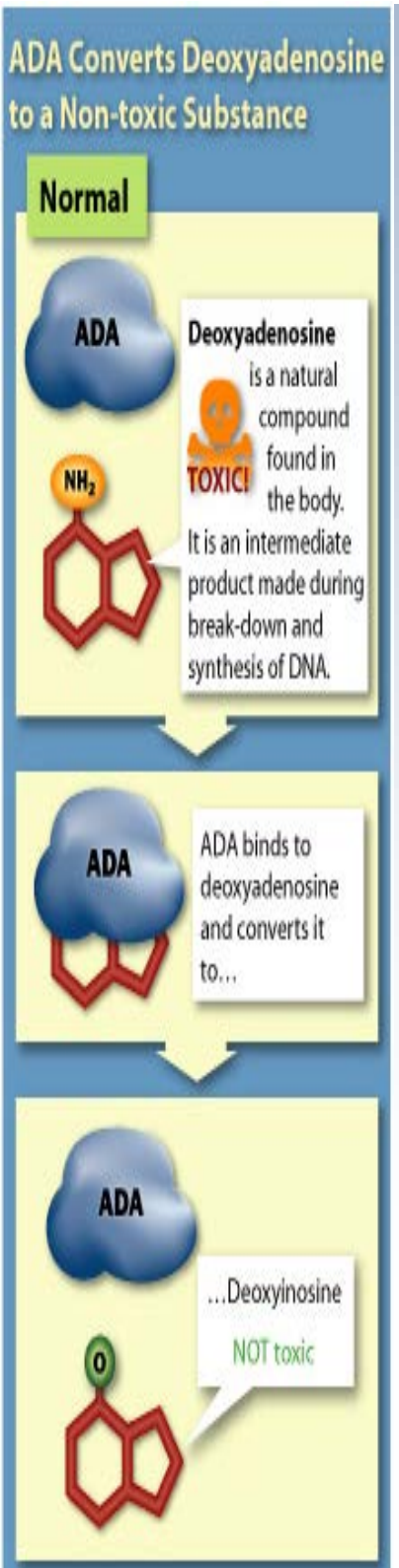
Perpetual or Extremely Invasive

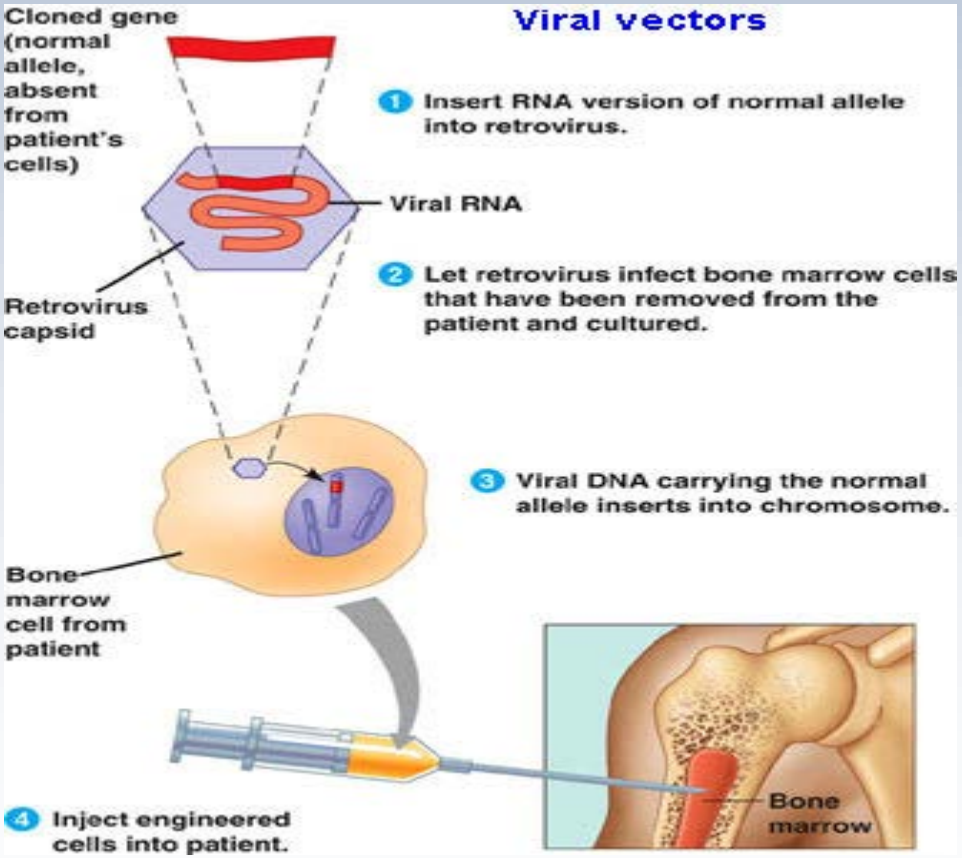
Future Treatment Options

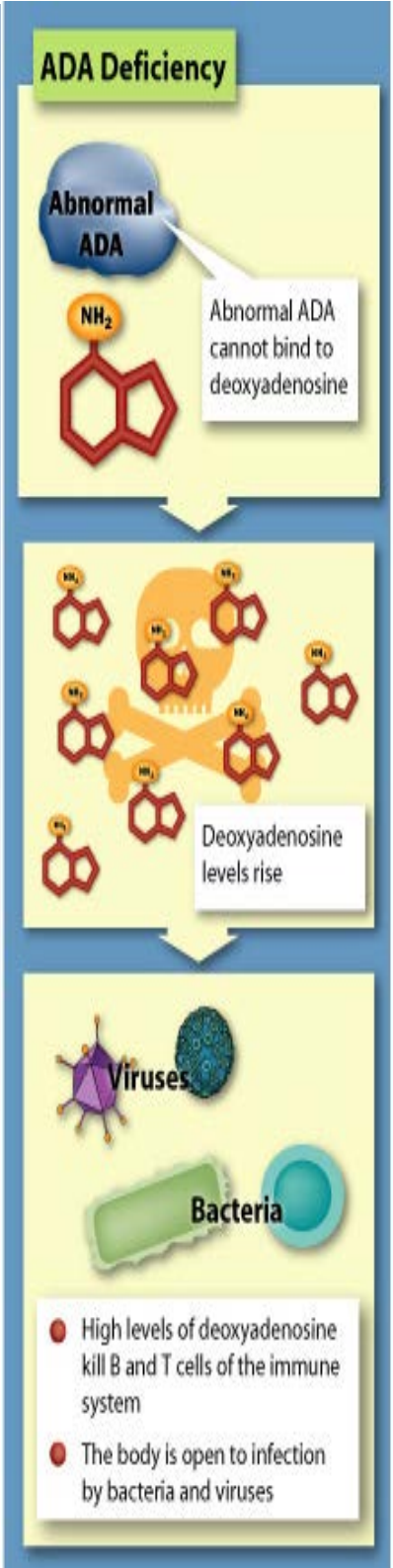


- Minimally Invasive without the daily dose of drugs
- **We are almost there!**

ADENOSINE DEAMINASE DEFICIENCY



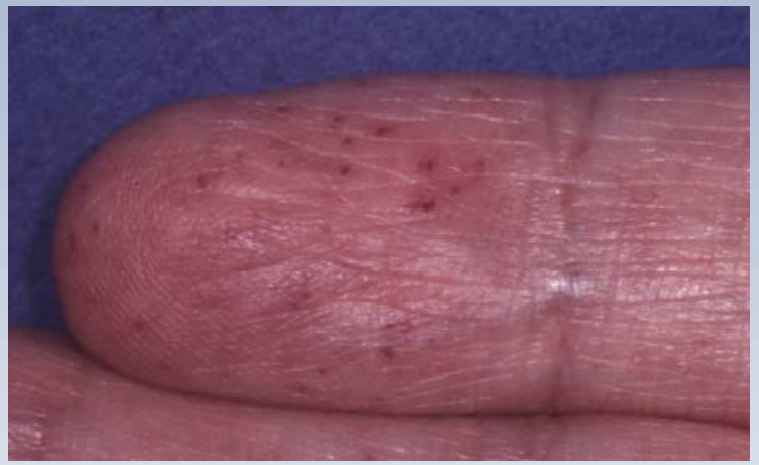


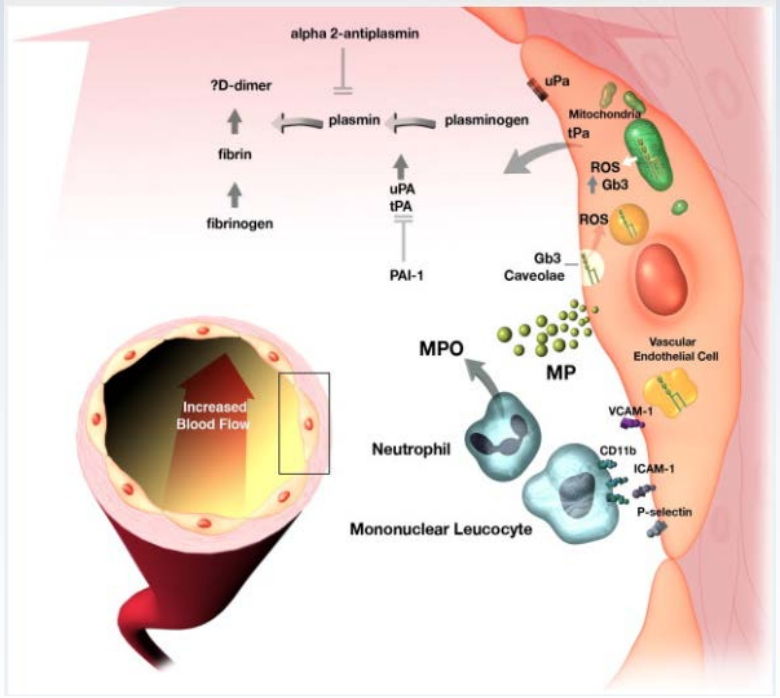


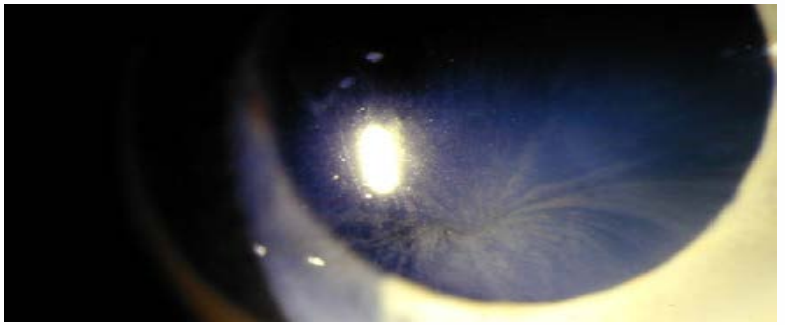
Gerson et al 1997 implanted subcut MSC graft transduced with a functional adenosine deaminase gene

FABRY'S DISEASE

- X-linked genetic disorder - deficiency of lysosomal enzyme alpha-galactosidase
- Using patient's own MSC
- Transduced with a functional galactosidase gene
- Return MSC to the patient
- Correction of deficiency (Osiris, 2000)

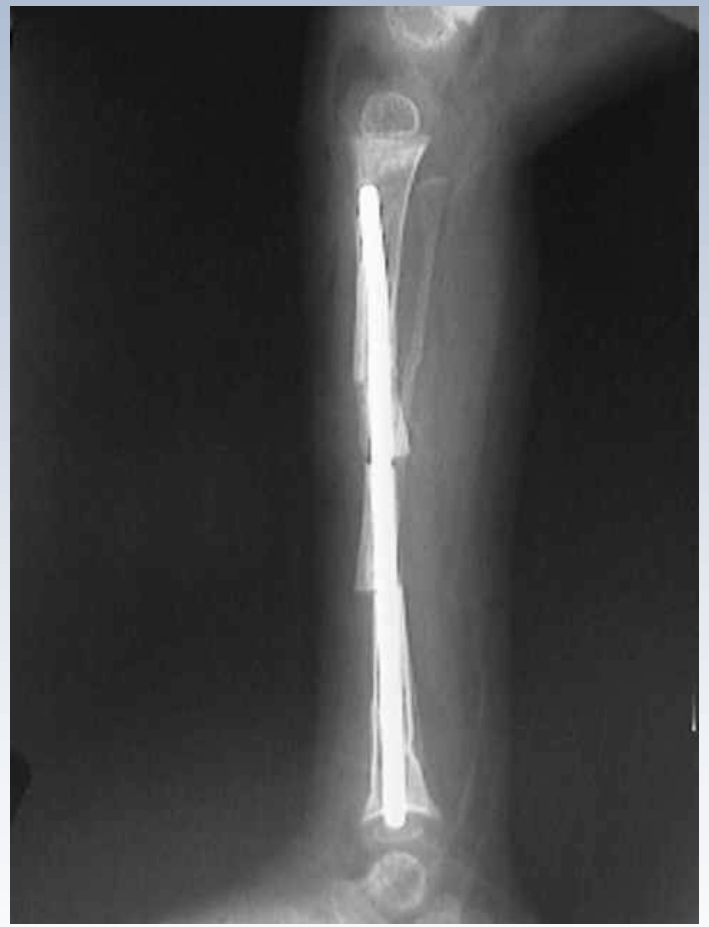


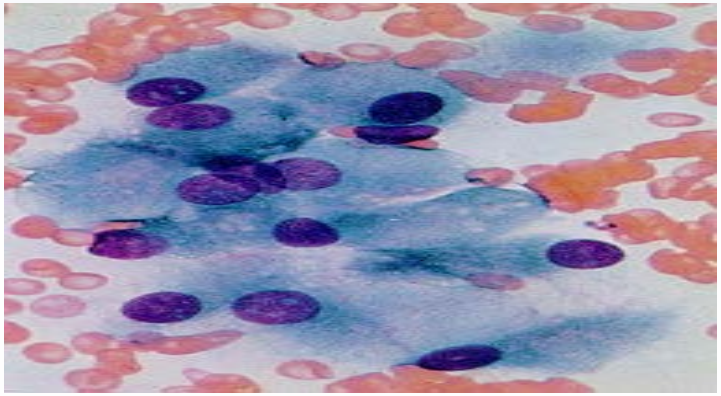




OSTEOGENESIS IMPERFECTA

- Horwitz et al 1999 reported 3 children transplanted with allogeneic MSC from HLA-compatible siblings
- New lamellar bone formation, improved osteogenesis with fewer fractures
- Engrafted MSC were shown to differentiate into osteoblasts





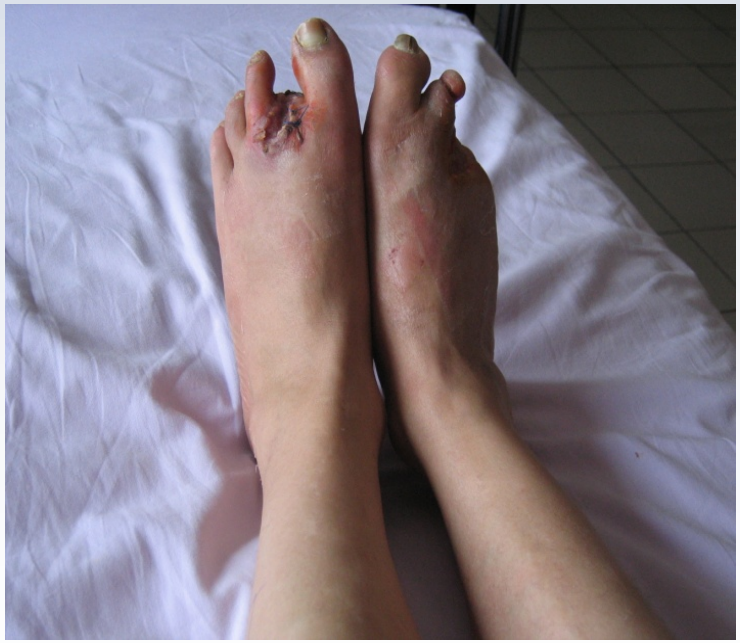
E. M. Horwitz, D. J. Prockop, A. Lorraine et al., “Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta,” *Nature Medicine*, vol. 5, no. 3, pp. 309–313, 1999

Burger Hastalığı (Tromboangiitis obliterans)' da Mezenkimal Kök Hücre Deneyimi

Ali Ünal , Leylagül Kaynar , Naci Emiroğulları , , Mustafa Çetin .....

- Küçük ve orta çaplı arter ve venleri tutan nonaterosklerotik, segmental, inflamatuar,

  obliteratif bir damar hastalığıdır.

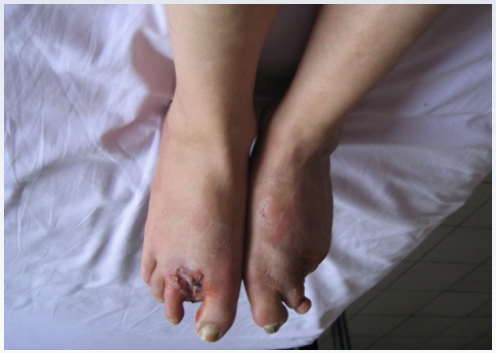


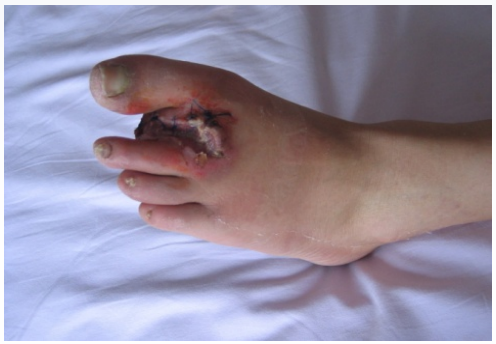
- Çoğu vakada standart tedavi ile semptomlar ilerlemekte ve amputasyonla sonuçlanmaktadır.

Burger Hastalığı (Tromboangiitis obliterans)' da Mezenkimal Kök Hücre Deneyimi

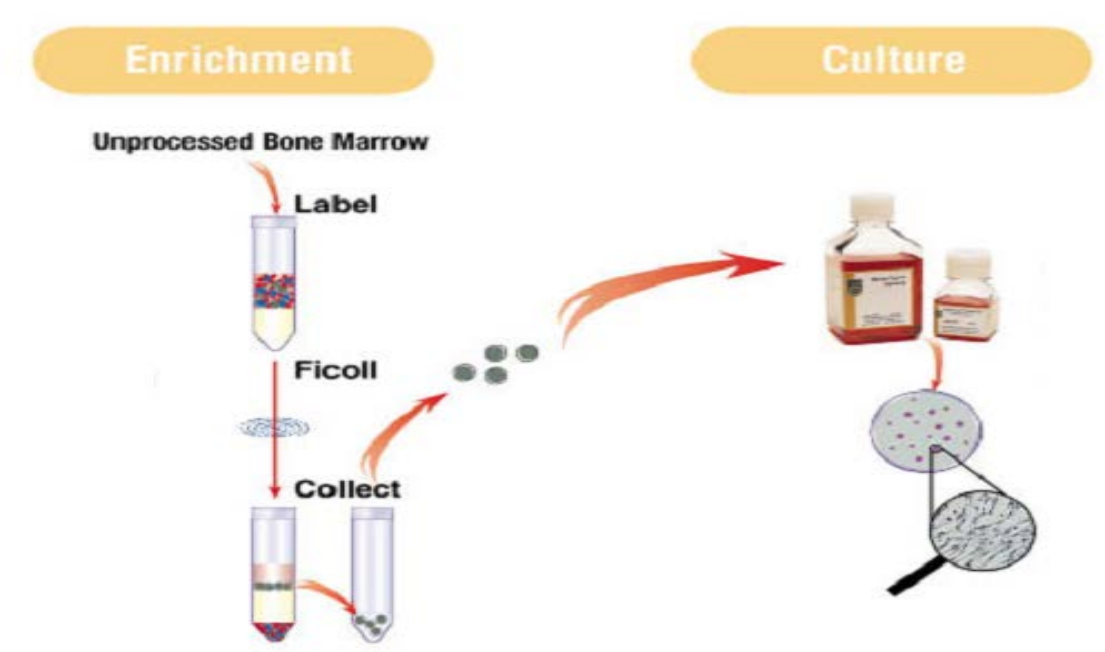
.

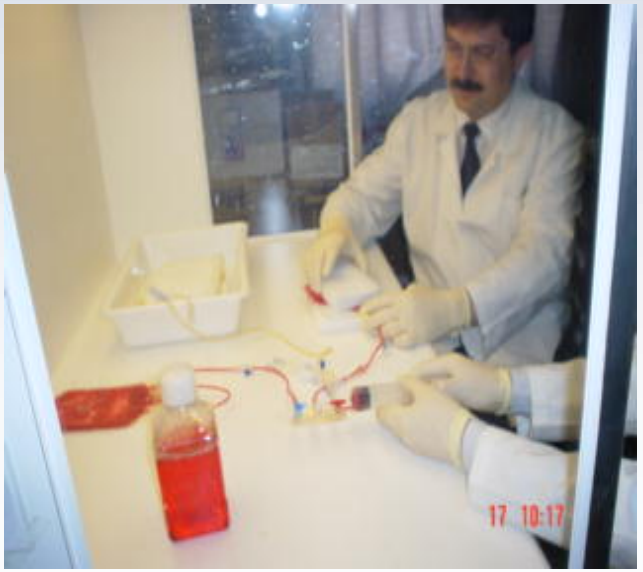
- 34 yaşında erkek hasta.
- Altı yıl önce Burger Hastalığı tanısı konulmuş ve vasküler yetersizlik nedeniyle gelişen kangren sonucu 4 yıl önce sağ ayak 3,4 ve 5. parmakları ile sol ayak 2. parmağı ampüte edilmişti.
- Tıbbi tedavi olarak aspirin, heparin ve dipridamol tedavisi almış
- İki yıl önce her iki bacaktaki, Femoral ve popliteal arterlere By Pass operasyonu uygulanmış.
- Bu tedavilere rağmen, klinik ve laboratuar olarak yeterli sonuç elde edilememiş.





Burger Hastalığı (Tromboangiitis obliterans)' da Mezenkimal Kök Hücre Deneyimi





- Her iki bacak ve ayaklarında ülserasyonları olan hastaya, mezenkimal kök hücre tedavisi uygulandı.
- Mezenkimal kök hücreler, kemik iliği kök hücrelerinden elde edildi.

Burger Hastalığı (Tromboangiitis obliterans)' da Mezenkimal Kök Hücre Deneyimi

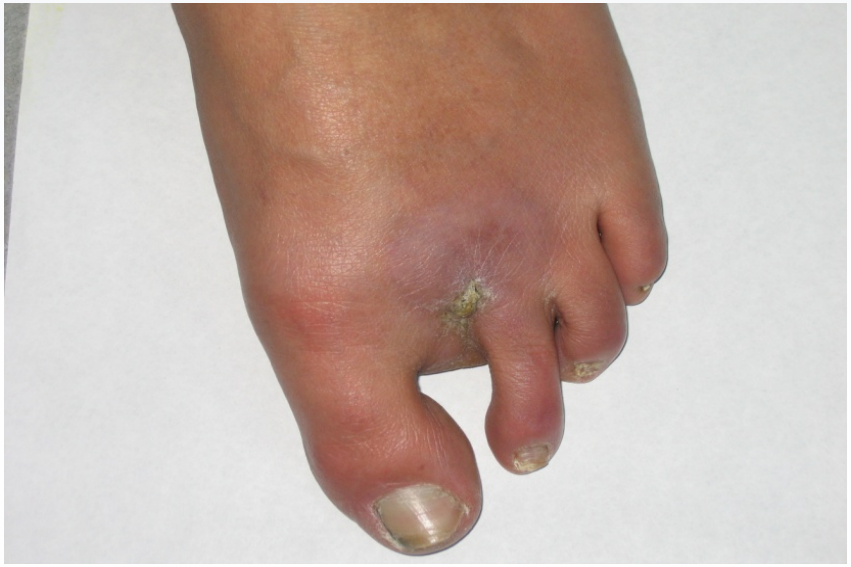
- ATİ teknoloji laboratuarında, , hasta serumu ve sitokinler içeren kültür ortamında, kemik iliği kök hücrelerinden, mezenkimal kök hücreler üretildi.
- Mezenkimal kök hücreler, anestezi altında sol bacak gastreknemius kası içerisine enjekte edildi.
- Üretilen mezenkimal kök hücre sayısı ancak bir bacak için yeterli olduğundan, sol bacağa tedavi uygulandı,
- sağ bacağa ise tedavi uygulanamadı.

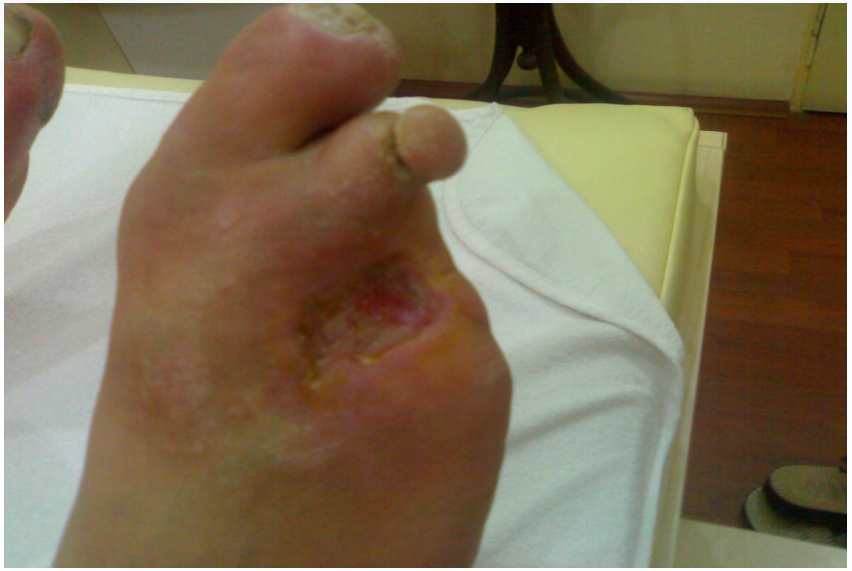
Burger Hastalığı (Tromboangiitis obliterans)' da Mezenkimal Kök Hücre Deneyimi

.

Mezenkimal kök hücre tedavisinden sonra; Sol bacaktaki ülserasyonların kaybolduğu gözlendi. Tedavi yapılmıyan sağ bacak ve ayakta, ülsere lezyonlar devam ediyordu.

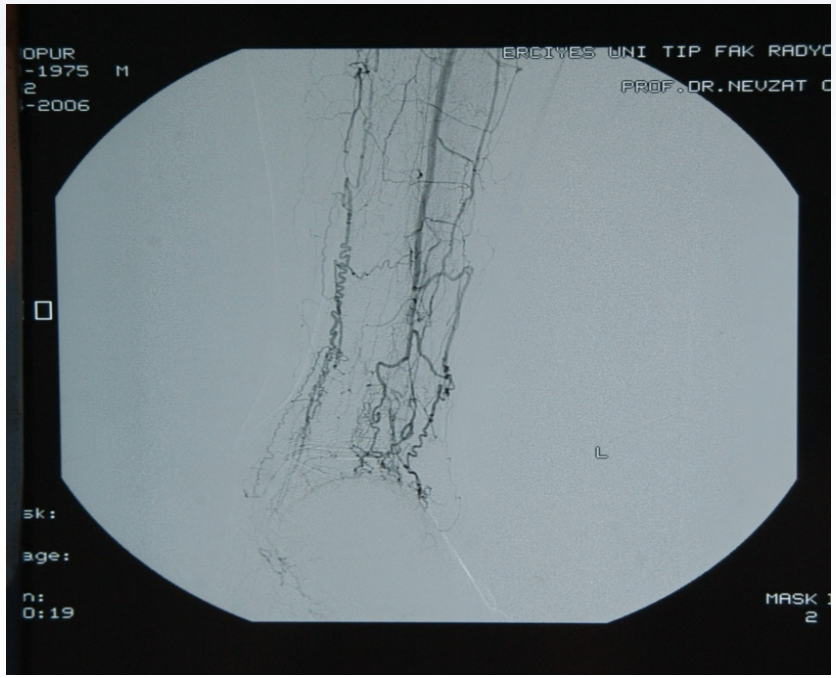
Klinik olarak karşılaştırıldığında; Mezenkimal kök hücre tedavisi uygulanan sol bacakta, yürüme ile gelişen ağrı ve krampların azaldığı tesbit edildi. Sağ bacakta ağrı, kramp ve yürüme güçlüğü devam ediyordu.

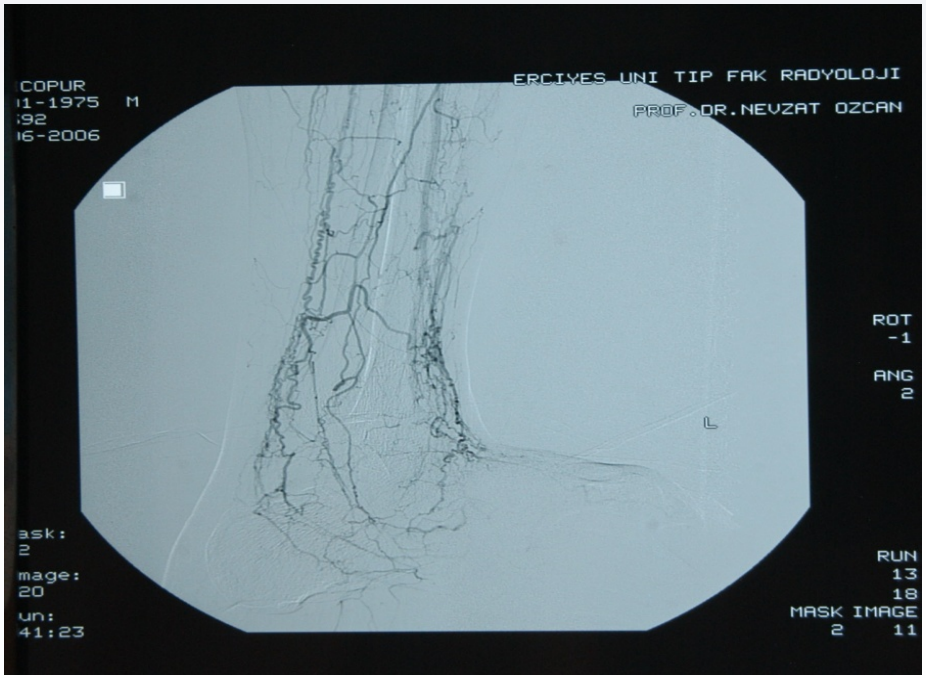




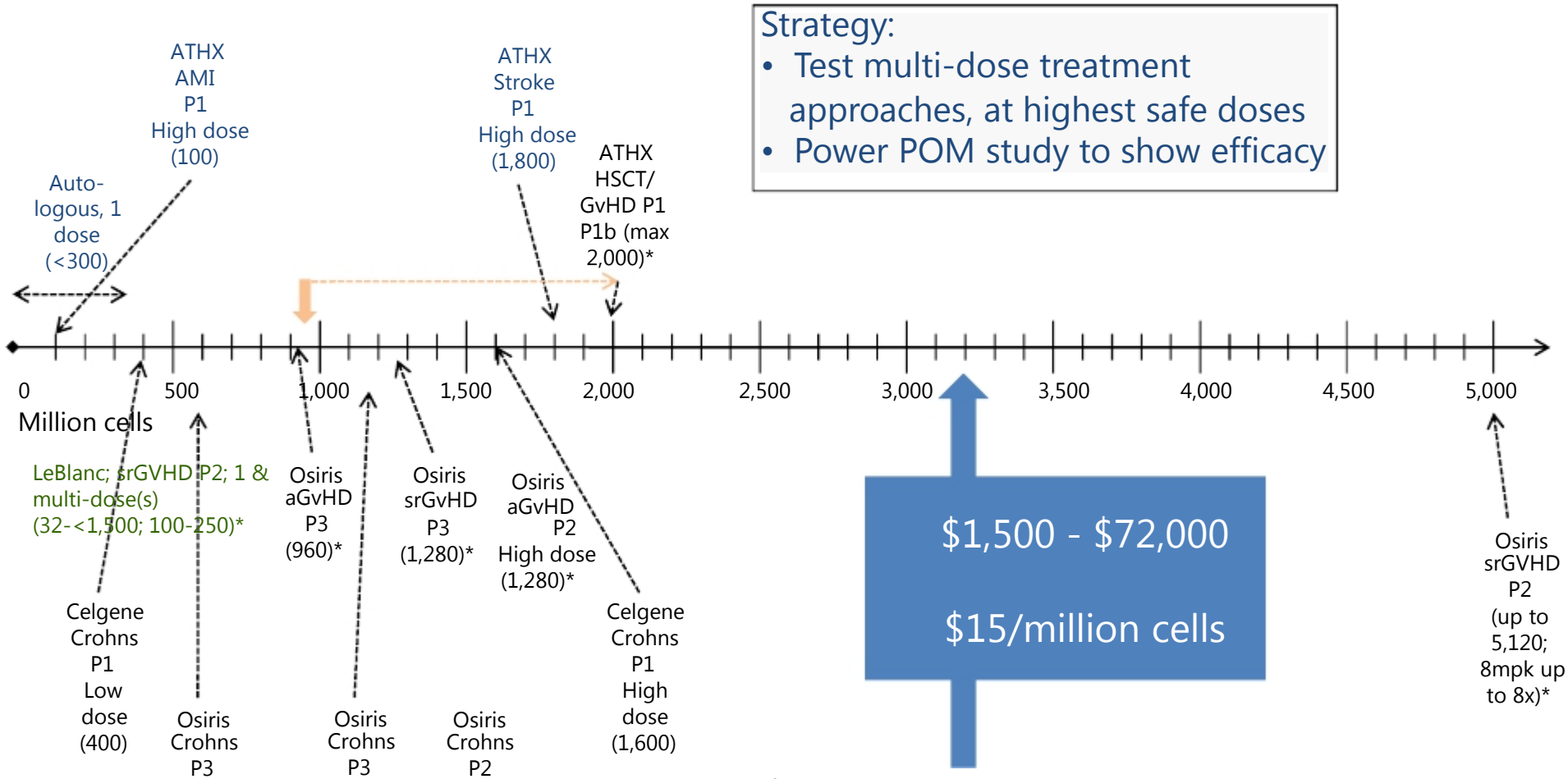
Burger Hastalığı (Tromboangiitis obliterans)' da Mezenkimal Kök Hücre Deneyimi

Kök hücre tedavisi sonrası çekilen anjiografi ile sol bacakta yeni damar oluşumları tesbit edildi.





Cumulative Dose per Patient – Selected Clinical Studies
Wide Range for Treatment COGS: Reimburseable?

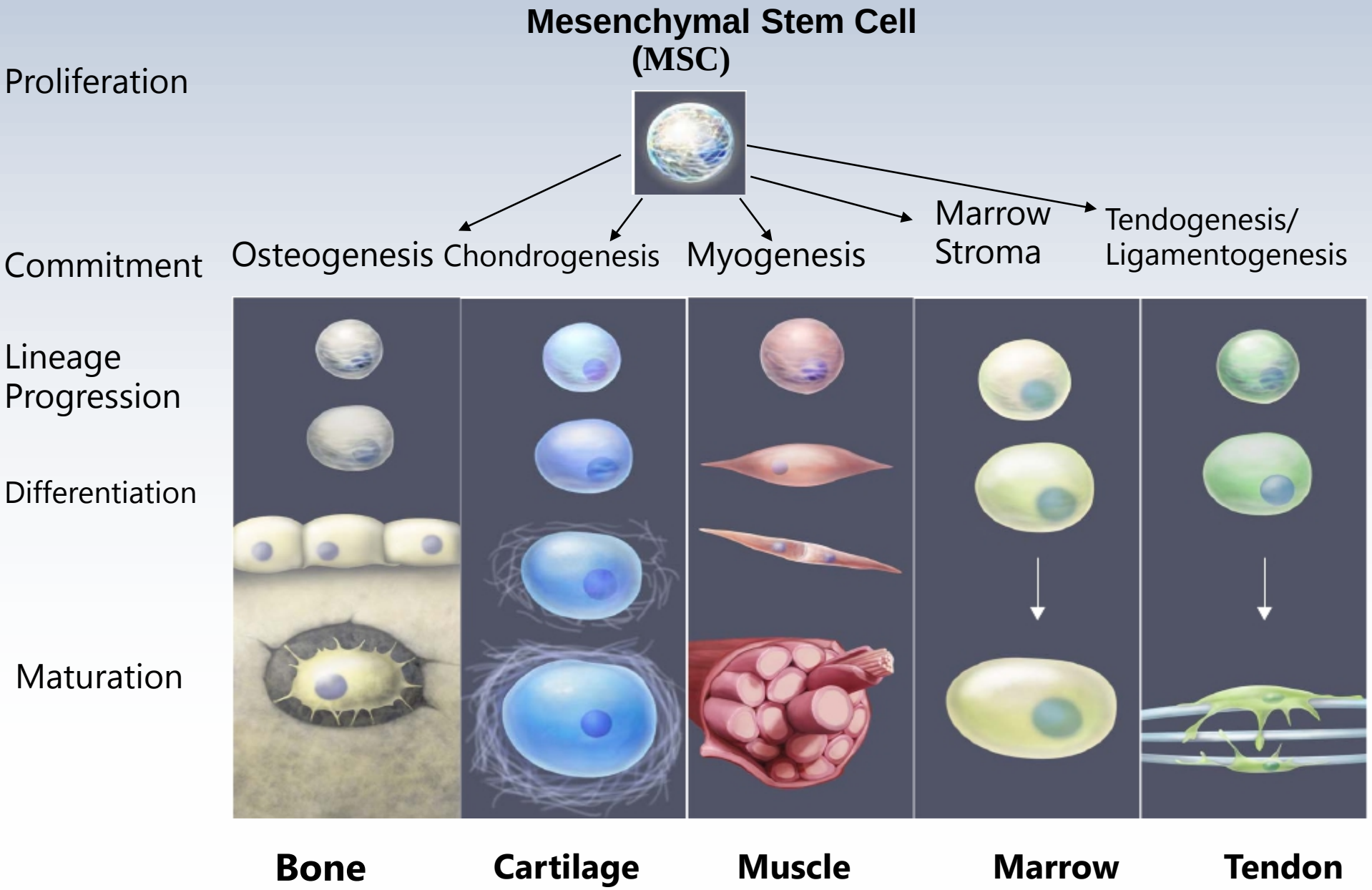


$10 million for 200 patient trial

$50.000 /patient

* Assumes 100 kg patient

The Mesengenic Process



What Are Our Biggest Development Challenges?

- Clinical product characterization and potency
  - – Lack of standards and clearing house for comparability
    - How does a physician select between products?
    - How does a physician determine comparability between sites?
- Regulatory agencies are asking for potency measurements including institutional patient designated products
- Improving dose and treatment regimen decisions
  - – Need for new technologies and approaches to determine PK/PD profile
- Bringing development experience and investment capital in from pharma and healthcare
  - – Investments guarded to date

Summary

- MSC therapies extending rapidly and globally in new indications
  - General consensus on Regulatory standards through ISCT, EBMT
- Safety profile good, clinical proof of concept still lacking

- Key Phase III approval trials launched(ing)
  - GVHD treatment (EBMT, Osiris)
  - Crohn's (Osiris, Cellerix)
  - PVD (Aastrom)
  - CHF (Mesoblast)
- Critical investment in late stage clinical development still lacking from pharma and healthcare industry

- Fundamentals underlying dose selection and treatment regimens need attention
  - Need for stronger science in PK/PD (**Pharmacokinetic/pharmacodynamic)** profiling of therapies

ERCIYES UNİVERSITY, CAPPADOCCIA BONE MARROW TRANSPLANT CENTER

CAPPADOCCIA BONE MARROW TRANSPLANT CENTER

- **Kayseri, Erciyes University Hospital (BMT), CIC 627, A (140 142) 77/63)**
- **3th at the list of European Bone Marrow Numbers.**





JACIE
joint accreditation committee
isct ebmt






Thank you for your attention