



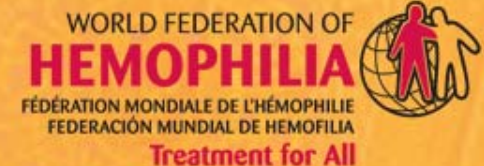
Cell-based treatment strategies for hemophilic arthropathy

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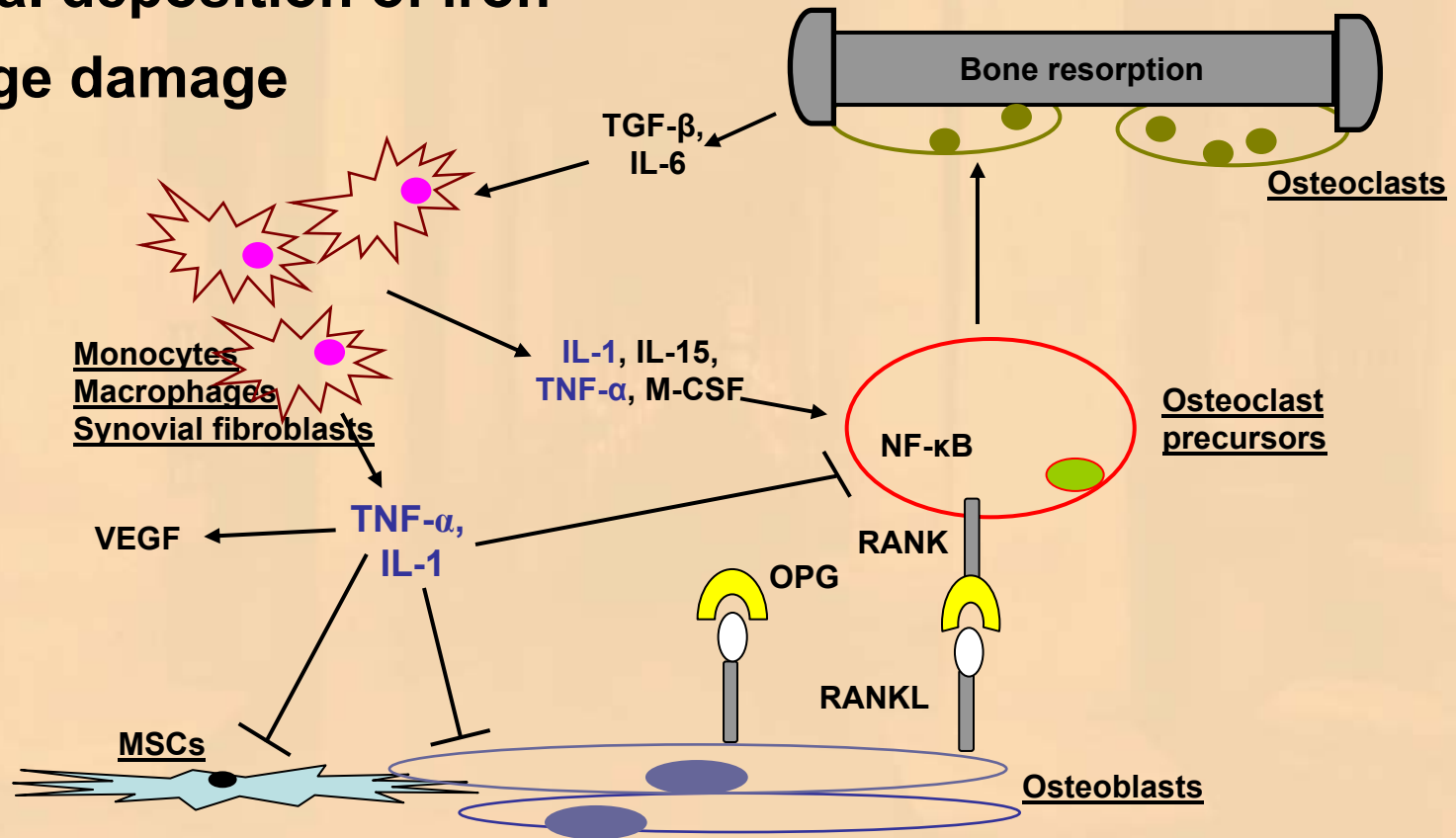
Medical and Cancer Research Center





Rodriguez-Merchan EC, Haemophilia 2006;12:337-44
Raffini L. BJH 2007;136:777-87

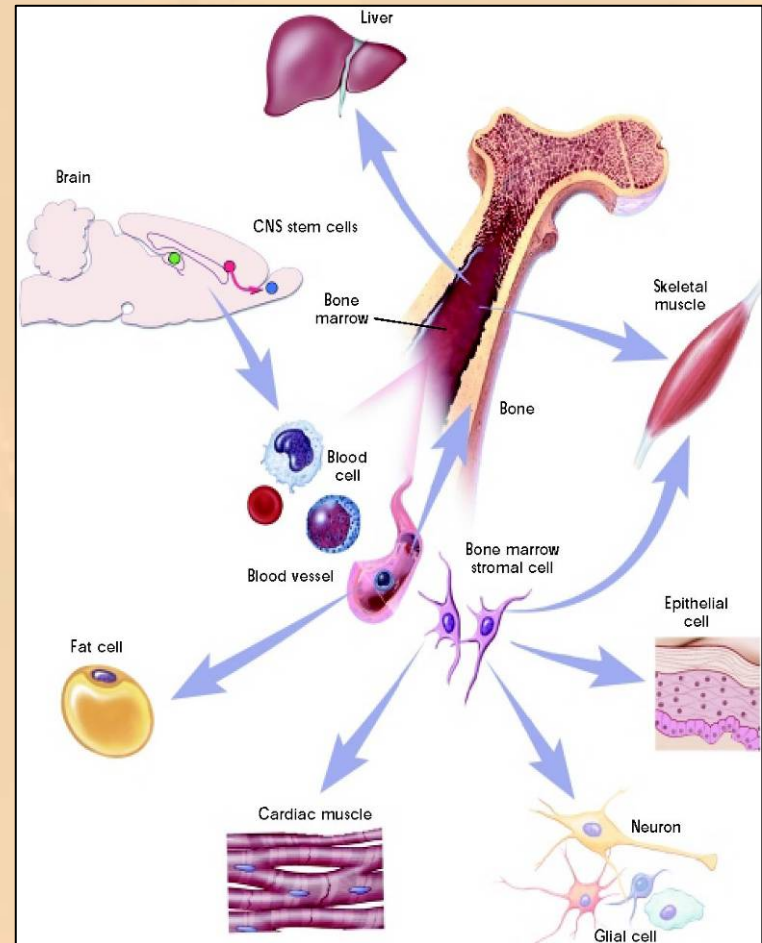
- ✓ Upregulation of inflammatory cytokines
- ✓ Synovial cell transformation
- ✓ Synovial deposition of iron
- ✓ Cartilage damage

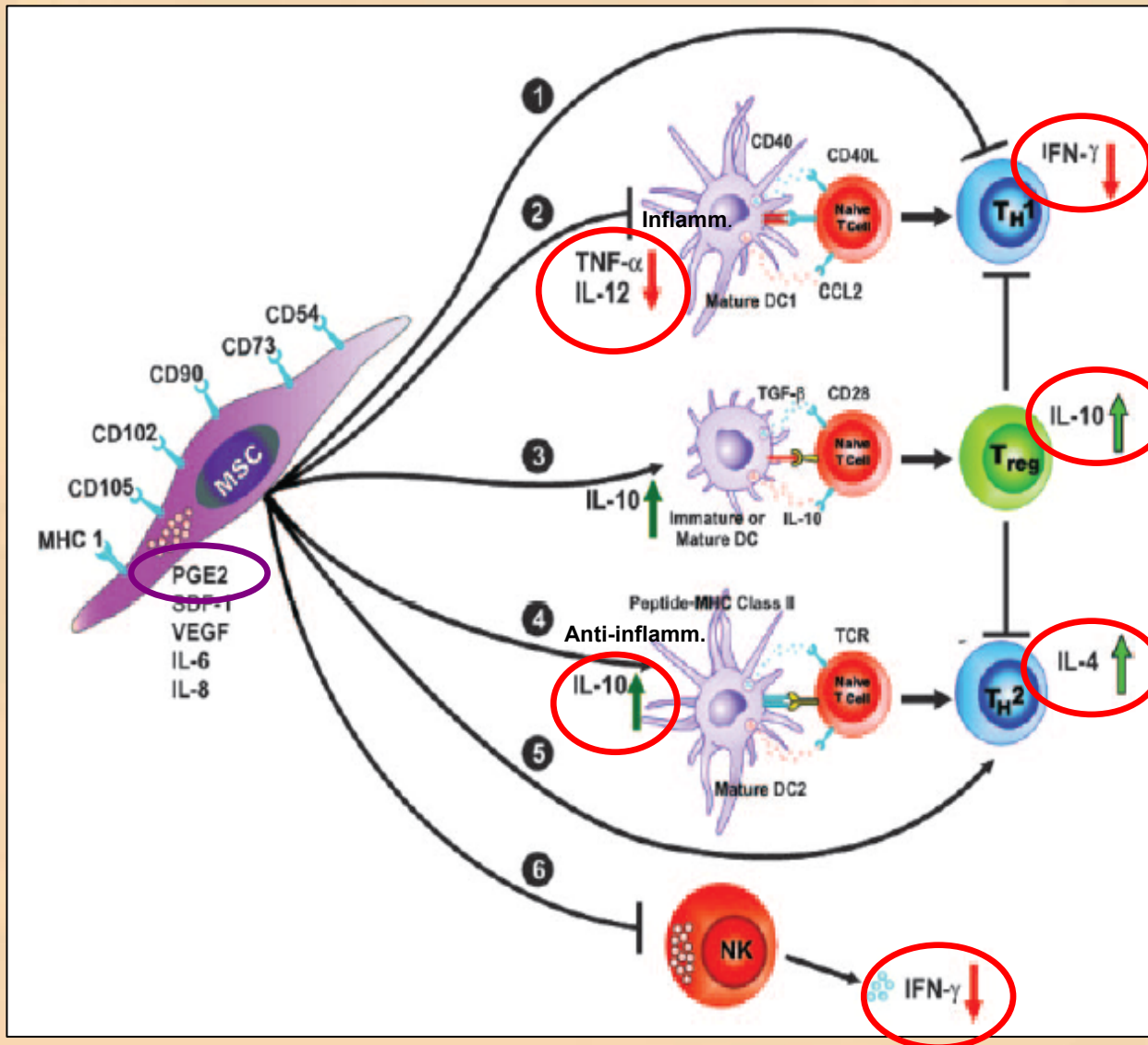


Ural AU, et al. Med Oncol, 2008 [Epub ahead of print]

Mesenchymal Stem Cells (MSCs)

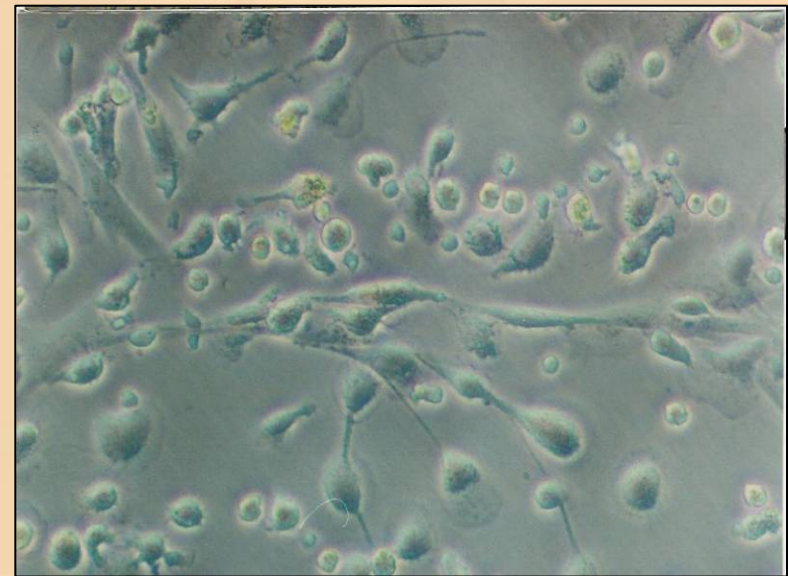
- ✓ Nonhematopoietic
- ✓ Lack of CD45, CD34
- ✓ Positive for CD105, CD73
- ✓ *Ex vivo* expansion
- ✓ *In vitro* differentiation



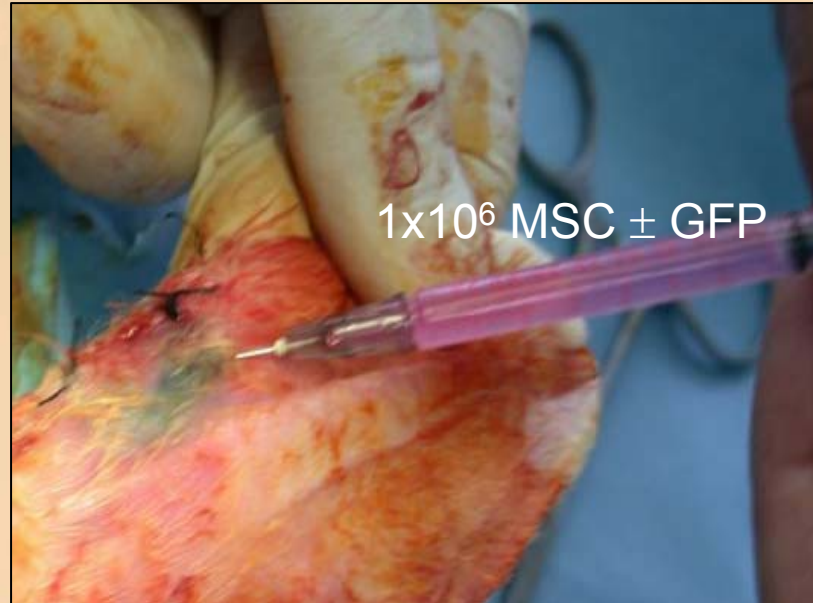
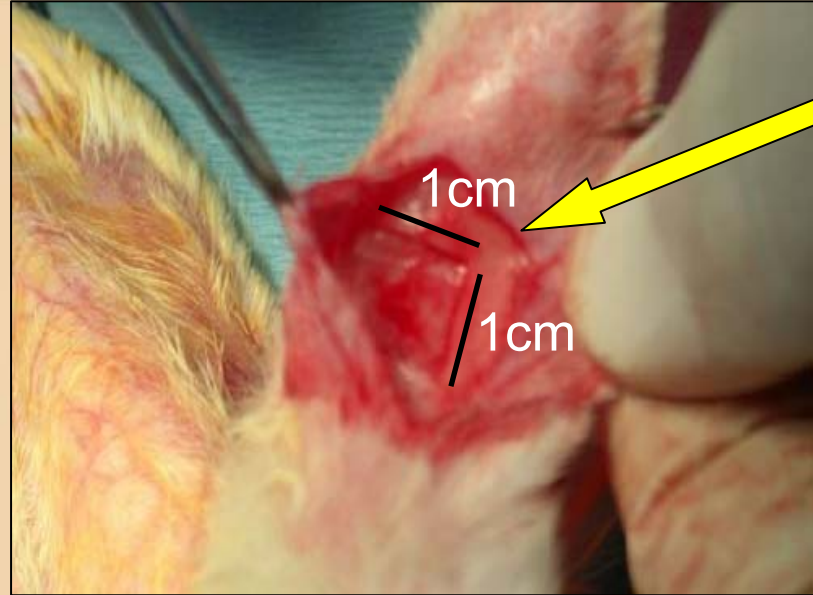
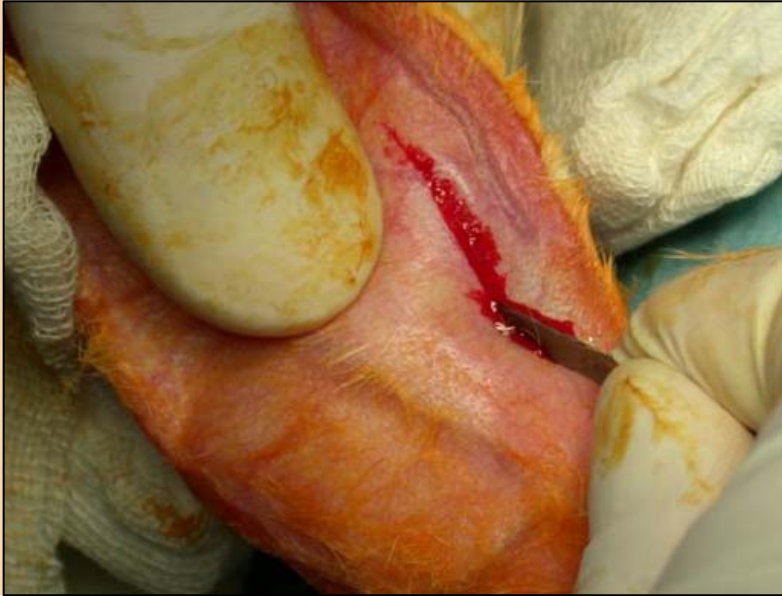


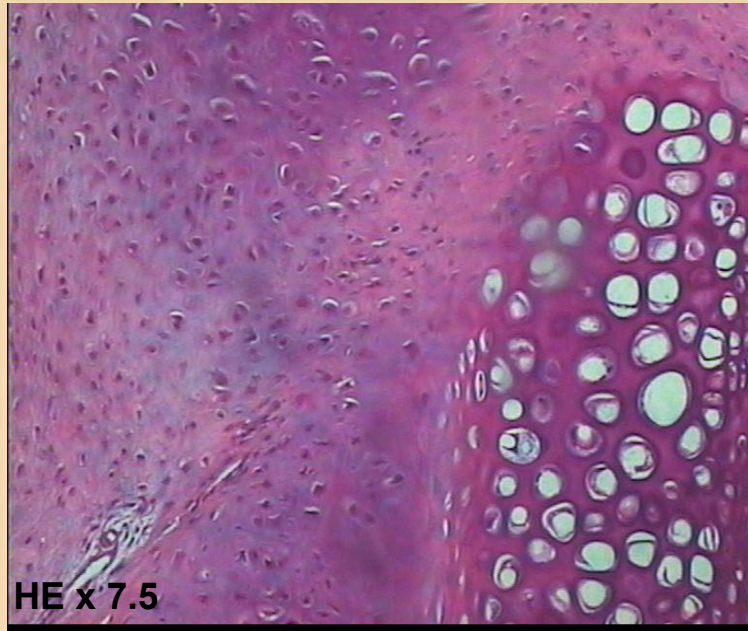
Aggarwal S, et al. Blood 2005;105:1815-22

Repair of Cartilage Defects by Using *in vitro* Differentiated MSCs in Rabbits

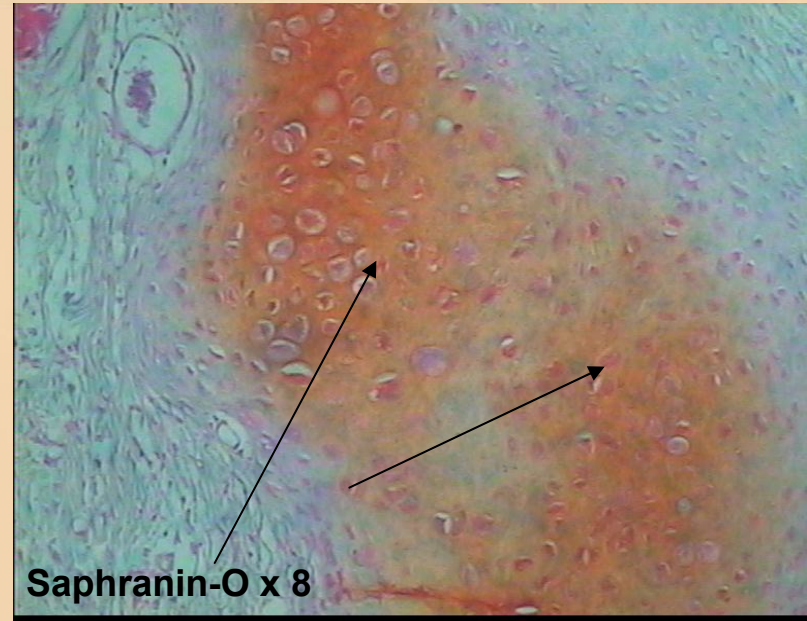


Ural AU, et al. Blood 2005, abst. 268

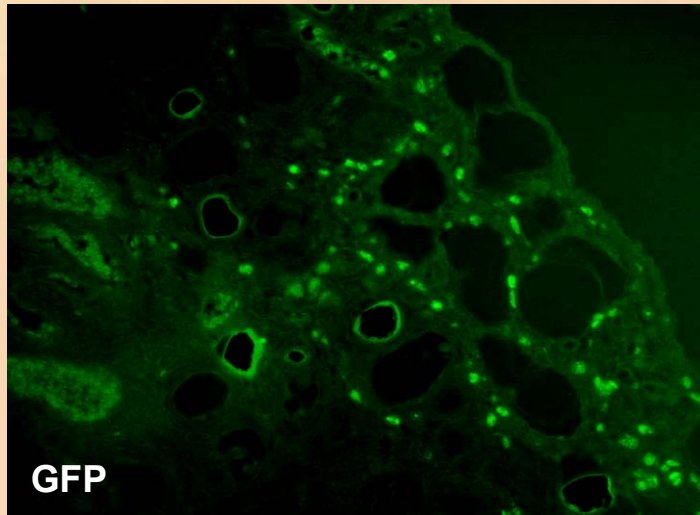




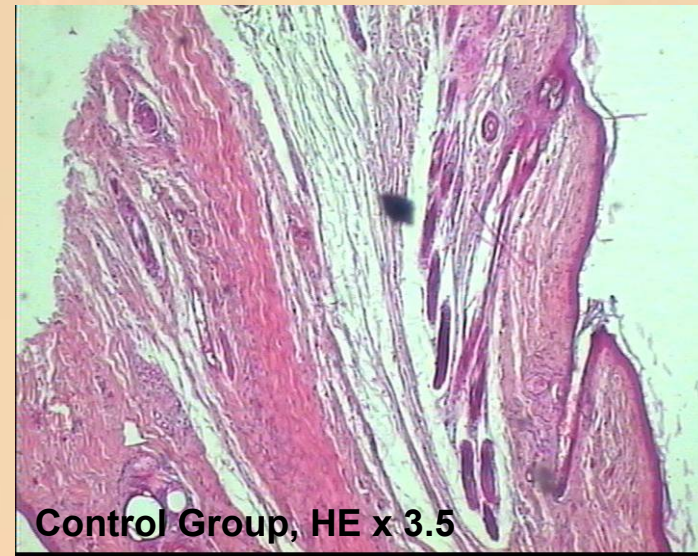
HE x 7.5



Saphranin-O x 8

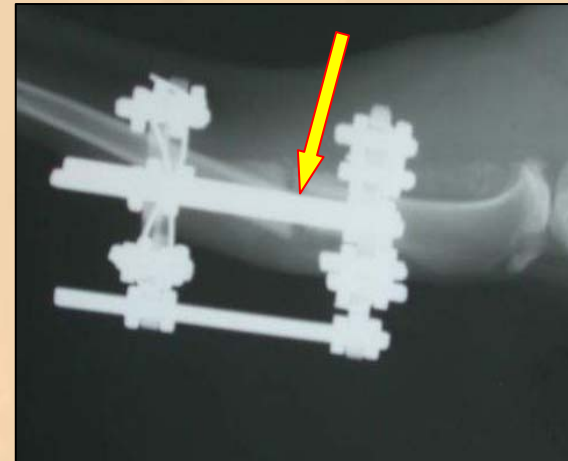
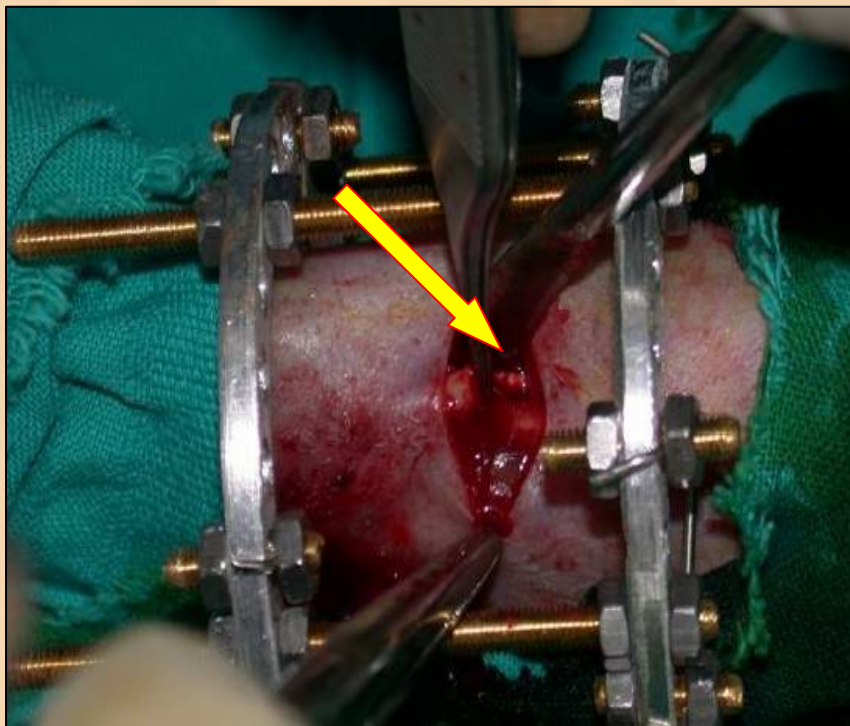


GFP

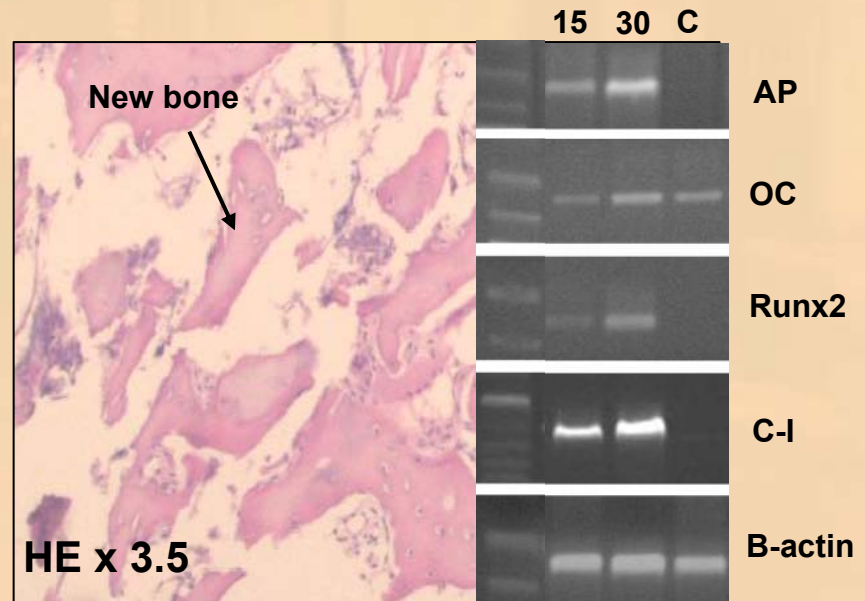
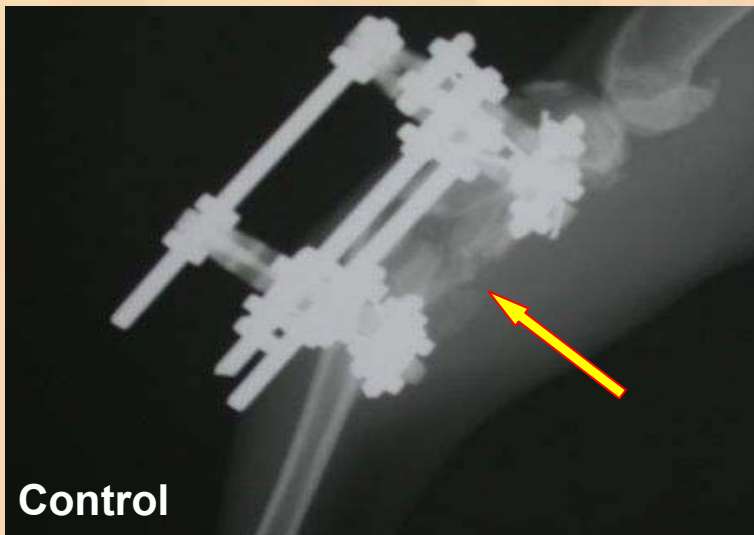
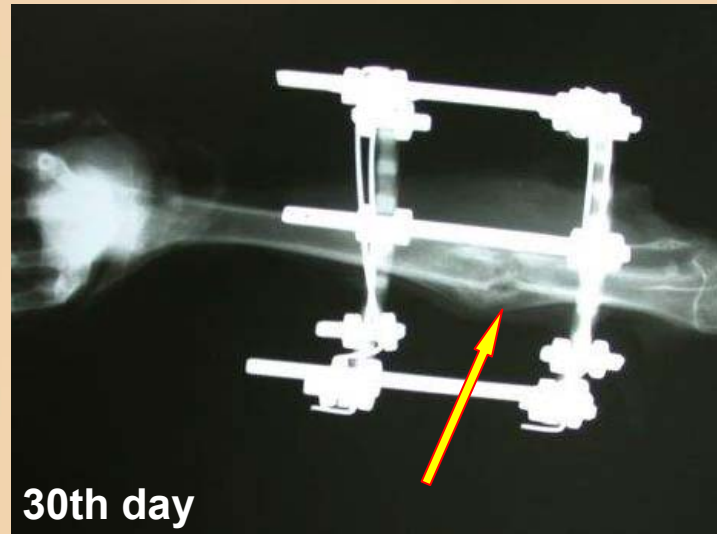
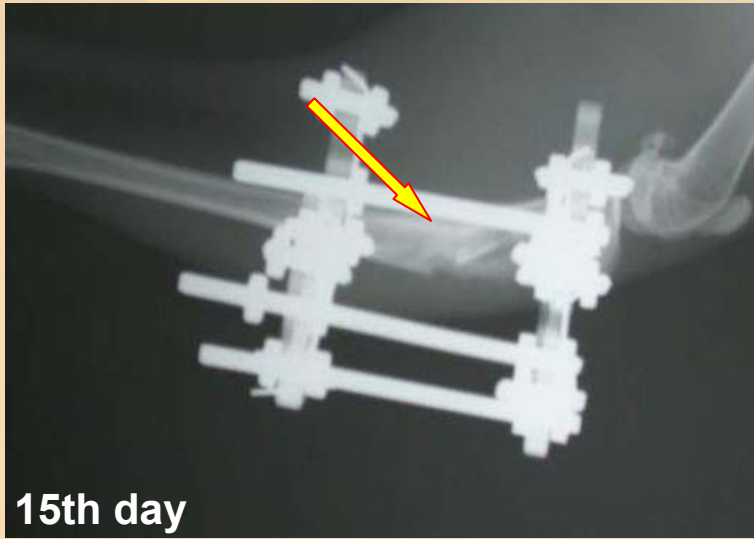


Control Group, HE x 3.5

Repair of Tibial Segmental Bone Defects by Using *in vitro* Differentiated MSCs in Rabbits



Ural AU, et al. Turkish J Hem 2004, 21(Suppl.1), abst.17



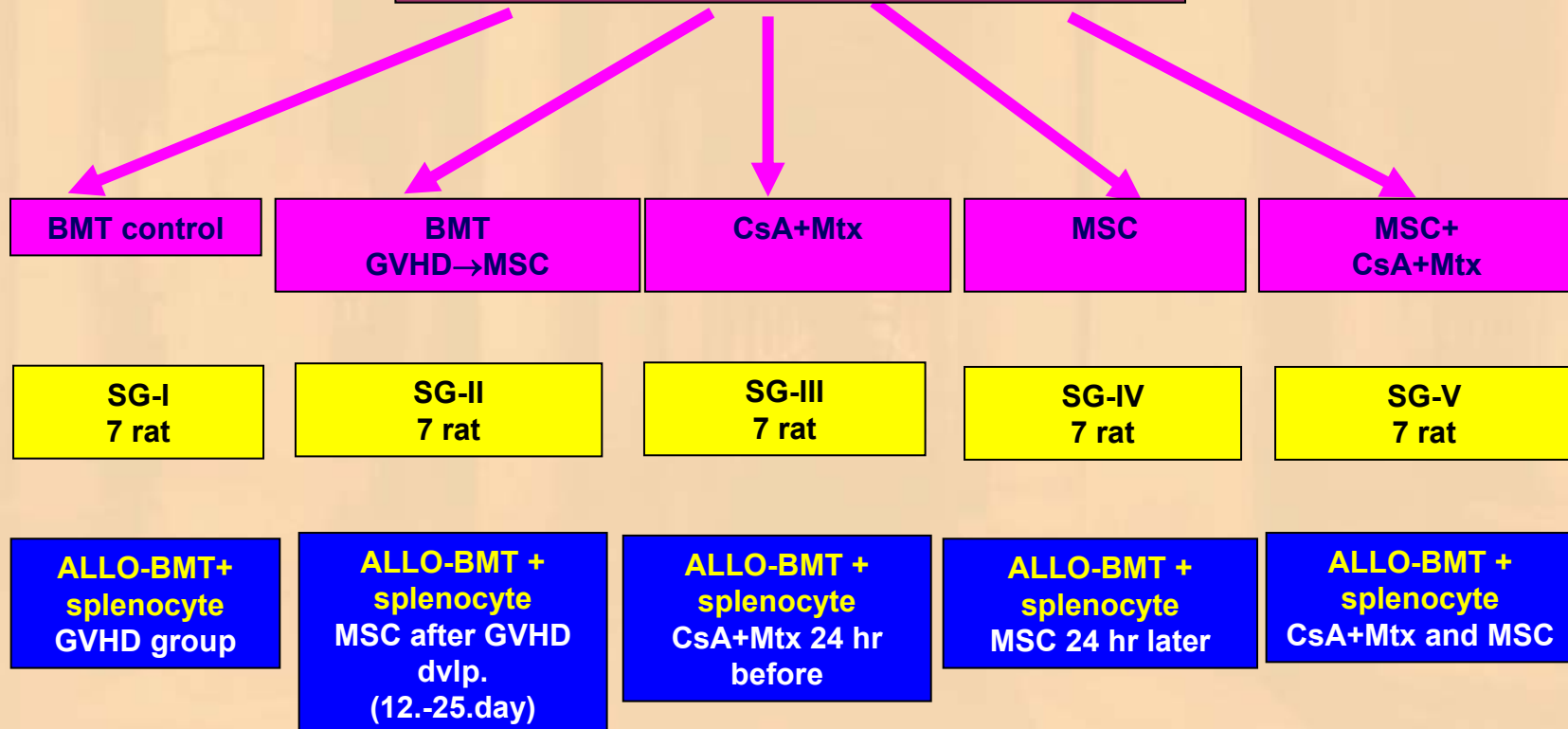
Immunosuppressive effects of MSCs on GvHD in rats following alloBMT



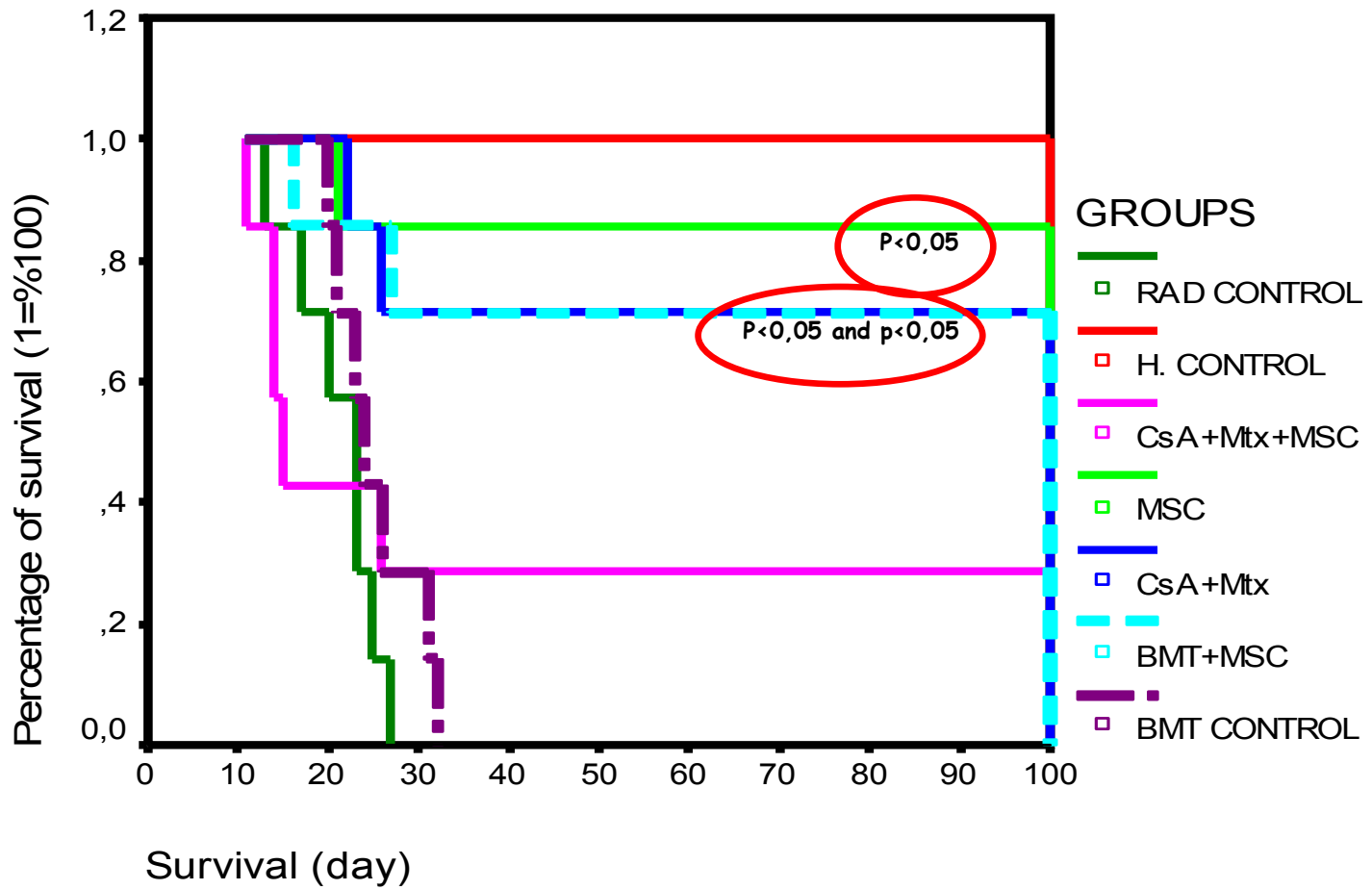
Nevruz O, et al. Blood 2007, abst. 467

Study Groups

35 wistar female rat



Kaplan-Meier



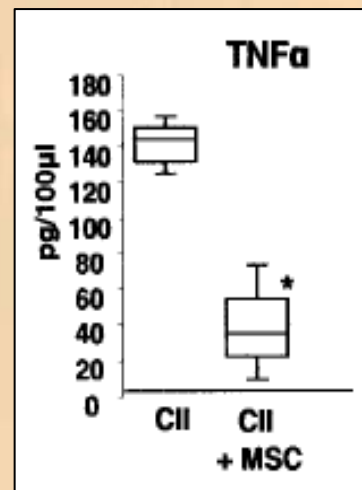
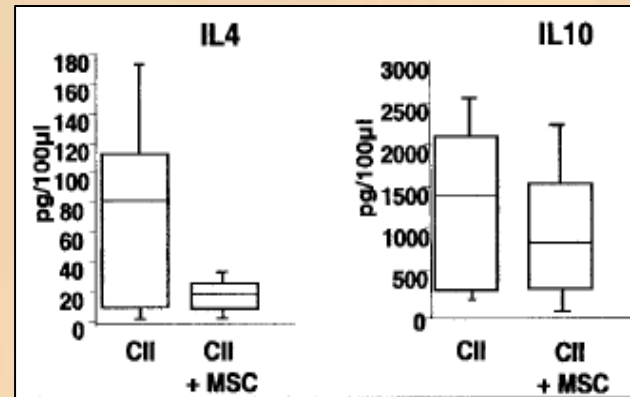
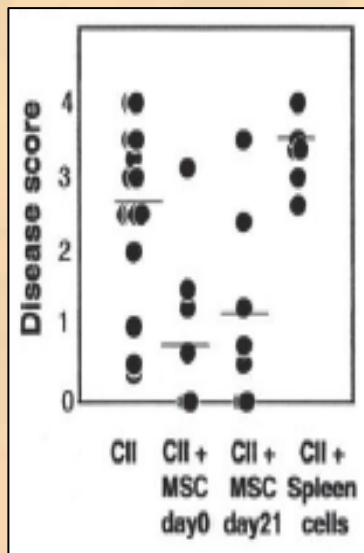
GROUPS	Liver	Intestinal	Skin
BMT GvHD→ MSC	Bile ductus damage Periportal inflammation	Cryptit GI: +; GII: ++ GIII: +	G I: Focal/diffuz vacuolization of basal layer G II: Subepidermal infiltration of lymphocytes
CsA+Mtx	Mild portal inflammation	Cryptit GI: ++; GII: ++ GIII: +	GI: Focal/diffuz vacuolization of basal layer
MSC	Mild portal inflammation	Cryptit GI: +; GII: ++	G I: Focal/diffuz vacuolization of basal layer
CsA+Mtx+ MSC	Mild hepatocyte damage Periportal inflammation	Cryptit GI: +++	G I: Focal/diffuz vacuolization of basal layer
BMT CONTROL	Bile ductus damage Stoplazmic vacuolization Hepatocyte necrosis Periportal inflammation	Cryptit GI: +; GII: ++ GIII: +++ GIV: +	G I: Focal/diffuz vacuolization of basal layer G II: Spongiose+dyskeratotic keratinocyte, lymphocytic infiltration G III: Subepidermal seperation

TNF- α and IL-1

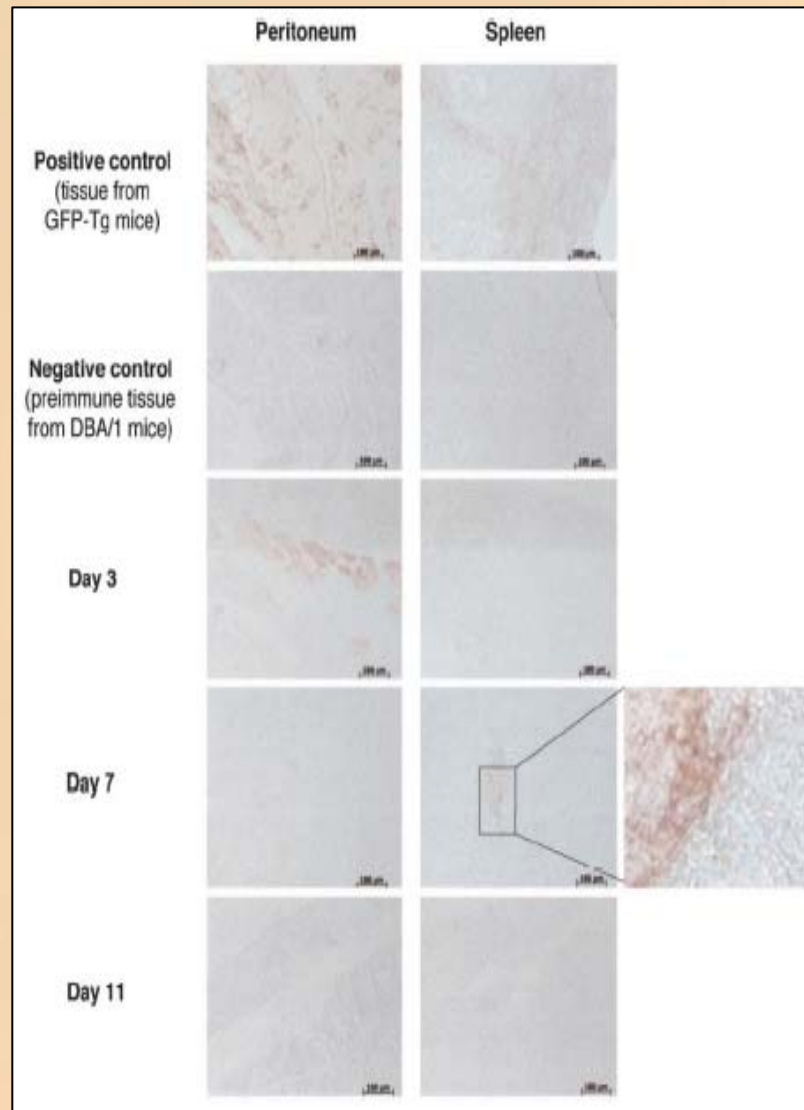
- ✓ Functional suppression of MSCs
- ✓ Synovial VEGF expr.
- ✓ OB apoptosis
- ✓ Stimulation of OC precursors
- ✓ Cartilage destruction

MSCs

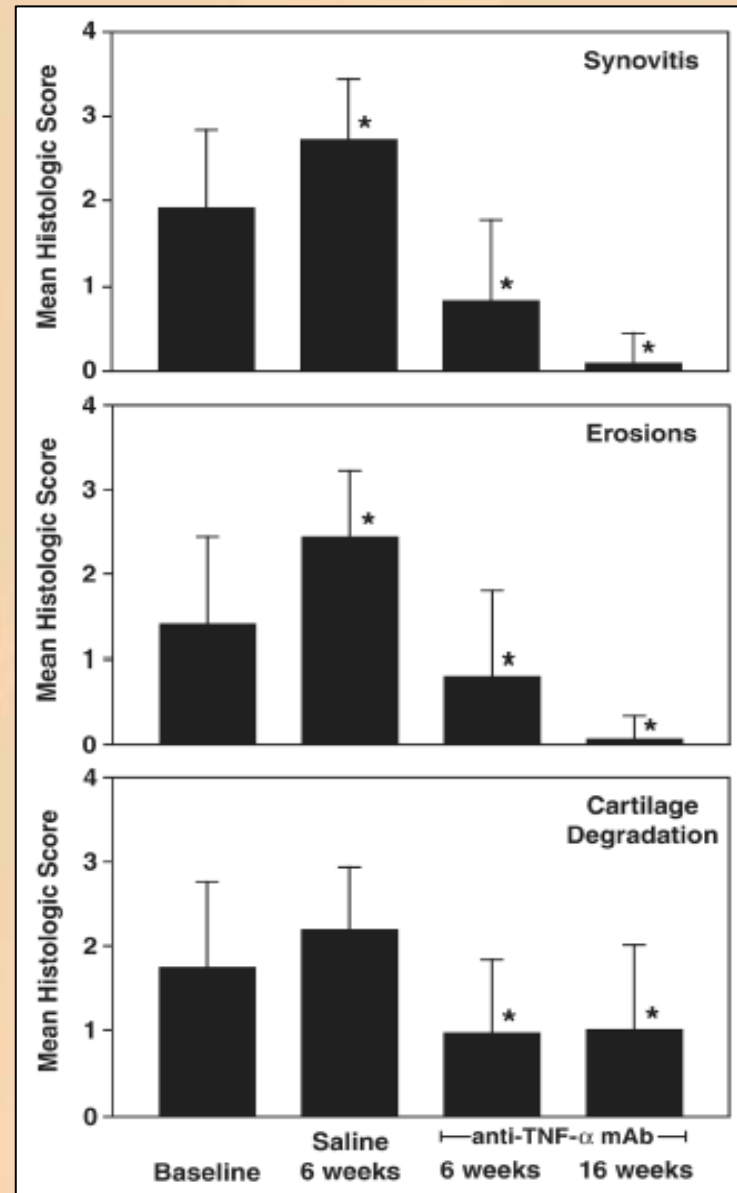
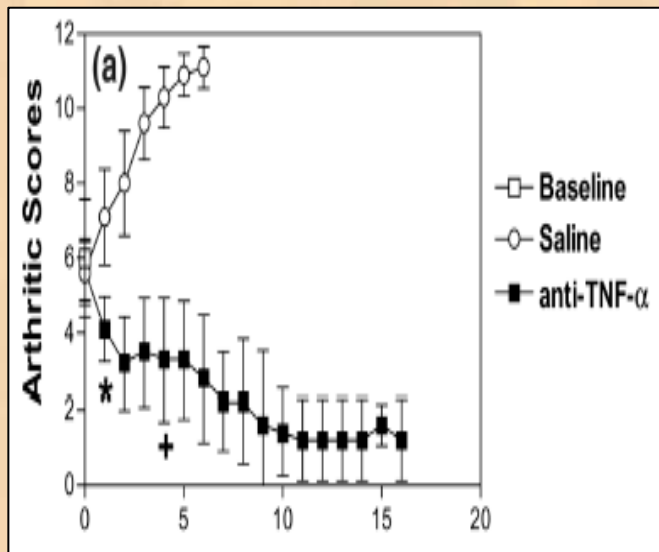
- ✓ Mesodermal differentiation
- ✓ Inhibition of TNF- α secr.
- ✓ Promotion of IL-10 and IL-4 secretion
- ✓ Inhibition of T_H1 and NK sign.
- ✓ Promotion of T_{reg} and T_H2 signaling
- ✓ Promotion of TGF- β 1 sign.



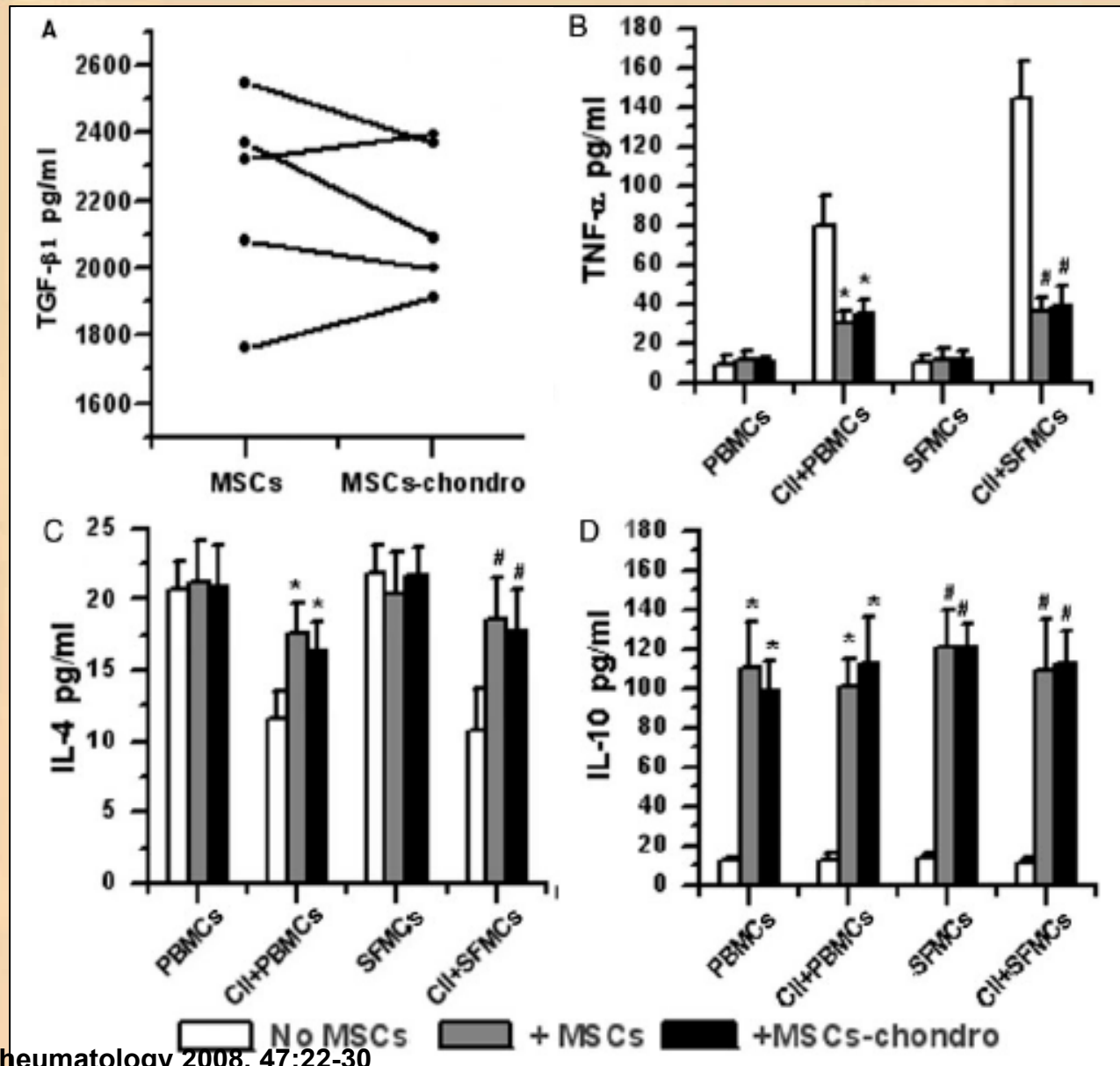
Augello A, et al. Arthritis & Rheumatism 2007, 56:1175-86



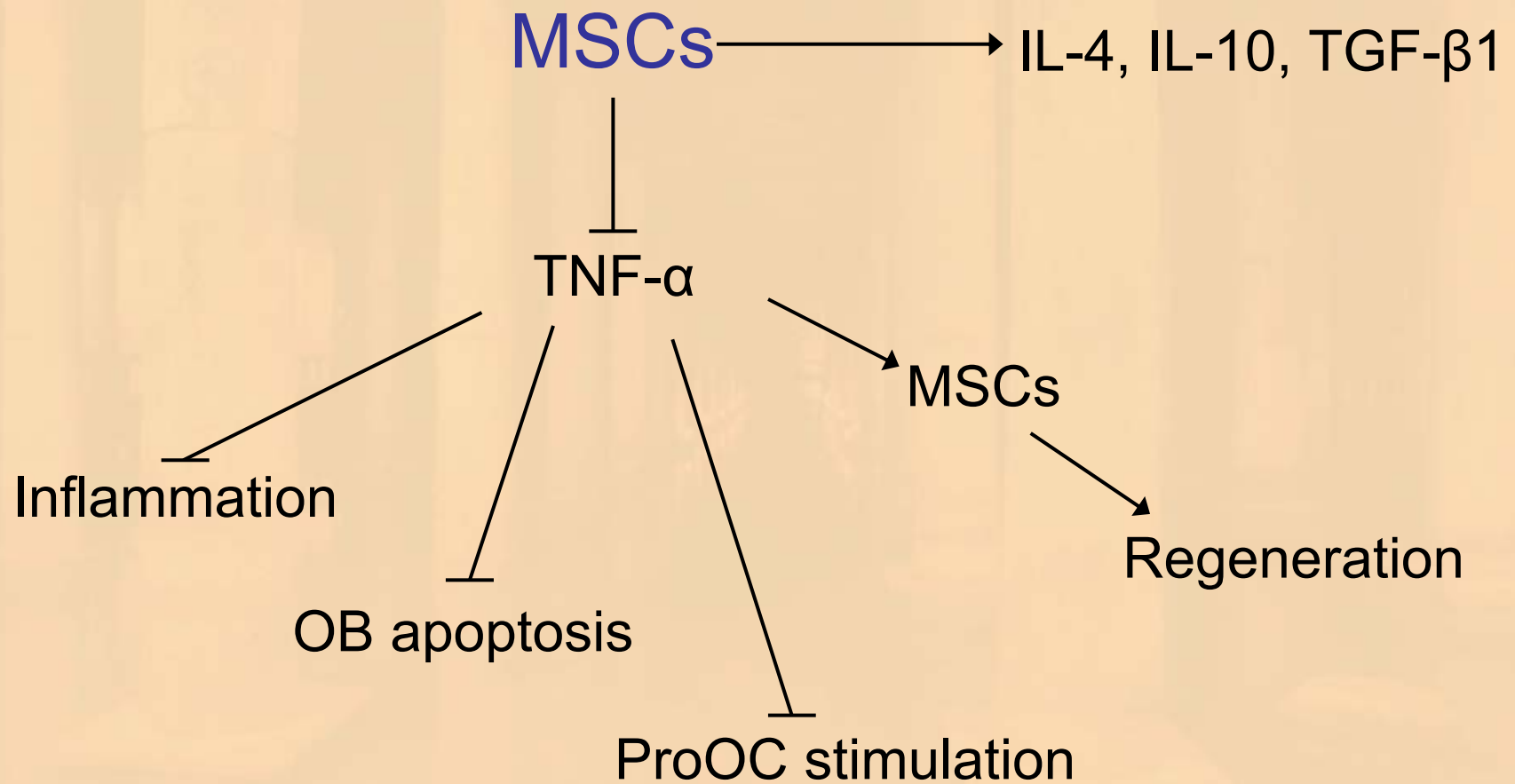
Augello A, et al. Arthritis & Rheumatism 2007, 56:1175-86



Shealy DJ, et al. Arthritis Res 2002, 4(5):R7



Zheng ZH, et al. Rheumatology 2008, 47:22-30



Ambiguous effects of MSCs

- ✓ Angiogenic effect
- ✓ Cartilage hypertrophy
- ✓ Bone formation
- ✓ Initiation or progression of arthritis
- ✓ Tumor growth facilitation in mice
- ✓ Long-term fate of MSCs?

