THE ROLE OF TISSUE ENGINEERING IN OSTEOARTHRITIS

H. Seda VATANSEVER MD, PhD

Manisa Celal Bayar University, Faculty of Medicine, Department of Histology and Embryology, Manisa Turkey

Near East University, DESAM Research Institute, Nicosia, North Cyprus

COST Istanbul School
Articular Cartilage Engineering Training School
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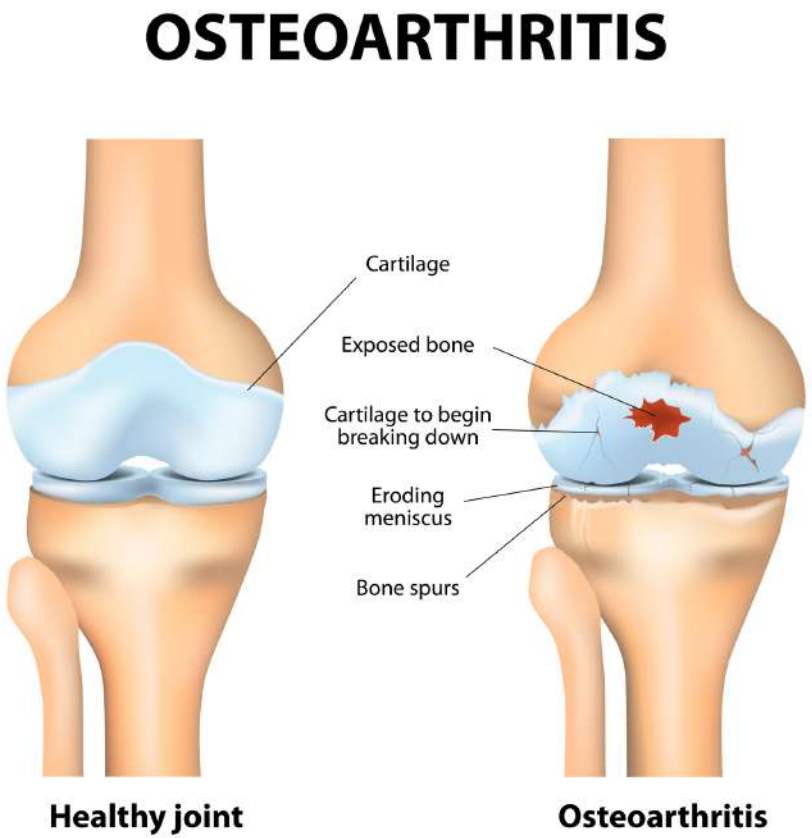
Osteoarthritis

- Osteoarthritis is defined as a whole joint disease

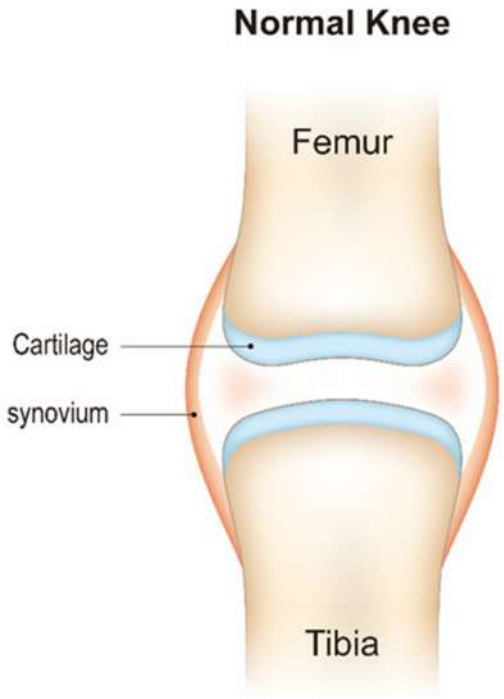
- cartilage destruction
- subchondral bone change
- osteophyte formation
- alterations of ligaments
- meniscuses

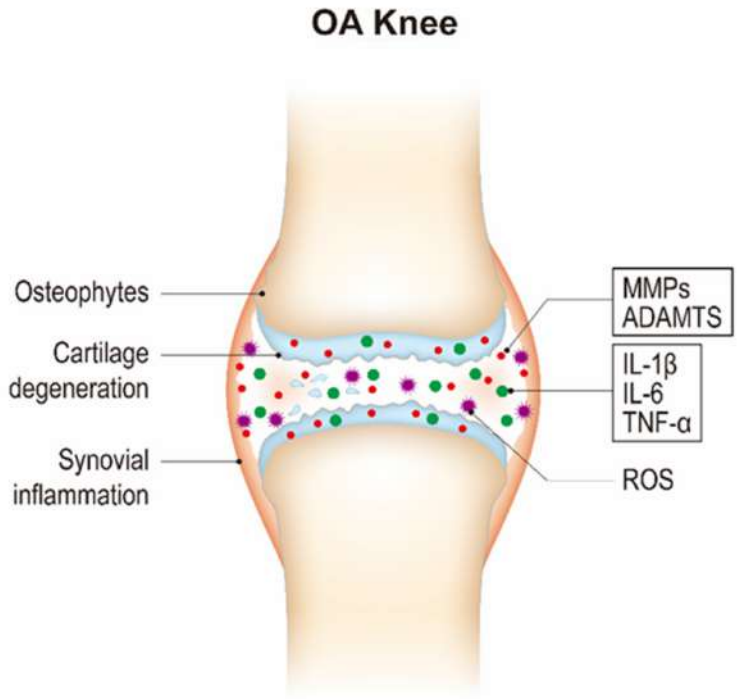


Osteoarthritis

- The three major biological factors including

- proteolytic enzymes
- proinflammatory cytokines
- reactive oxygen species (ROS)

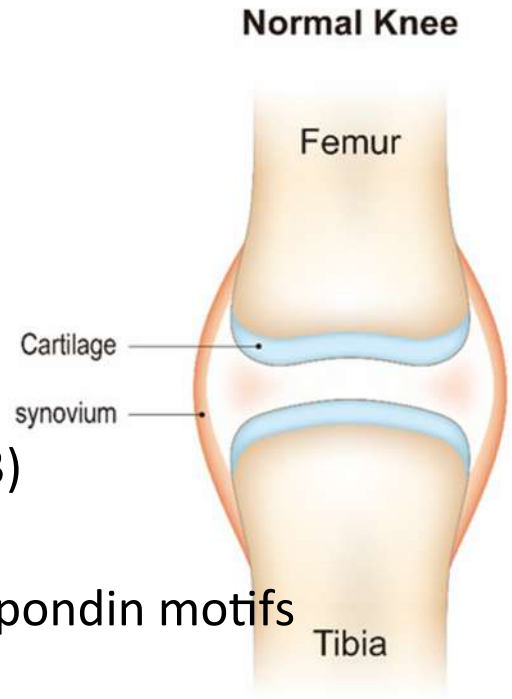


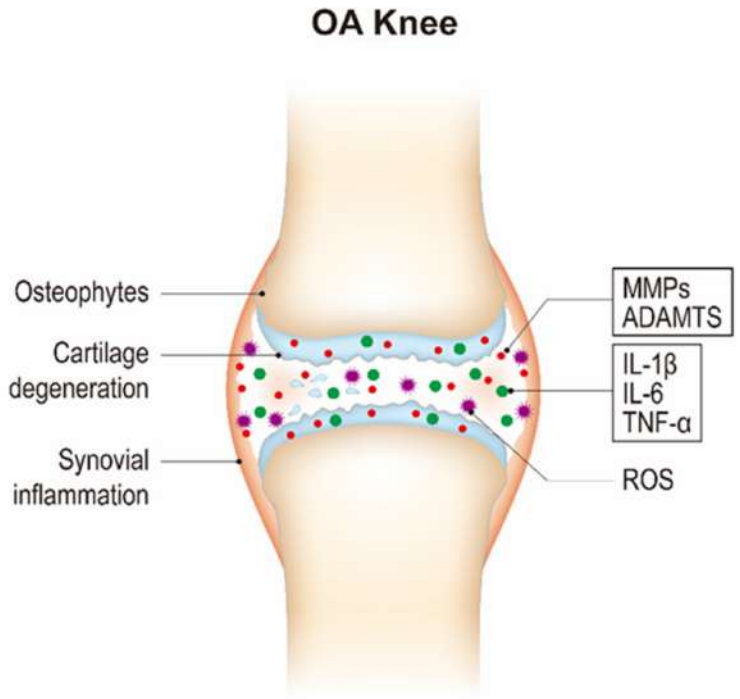


response the cartilage degredation

Osteoarthritis

- It is postulated that there is an imbalance between chondrocyte
- anabolism by
  - growth factors
- catabolism by
  - decomposing enzymes such as
    - matrix metalloproteinases (MMPs, e.g., MMP-3 and MMP-13)
    - a disintegrin
    - metalloproteinase with thrombospondin motifs (ADAMTS)

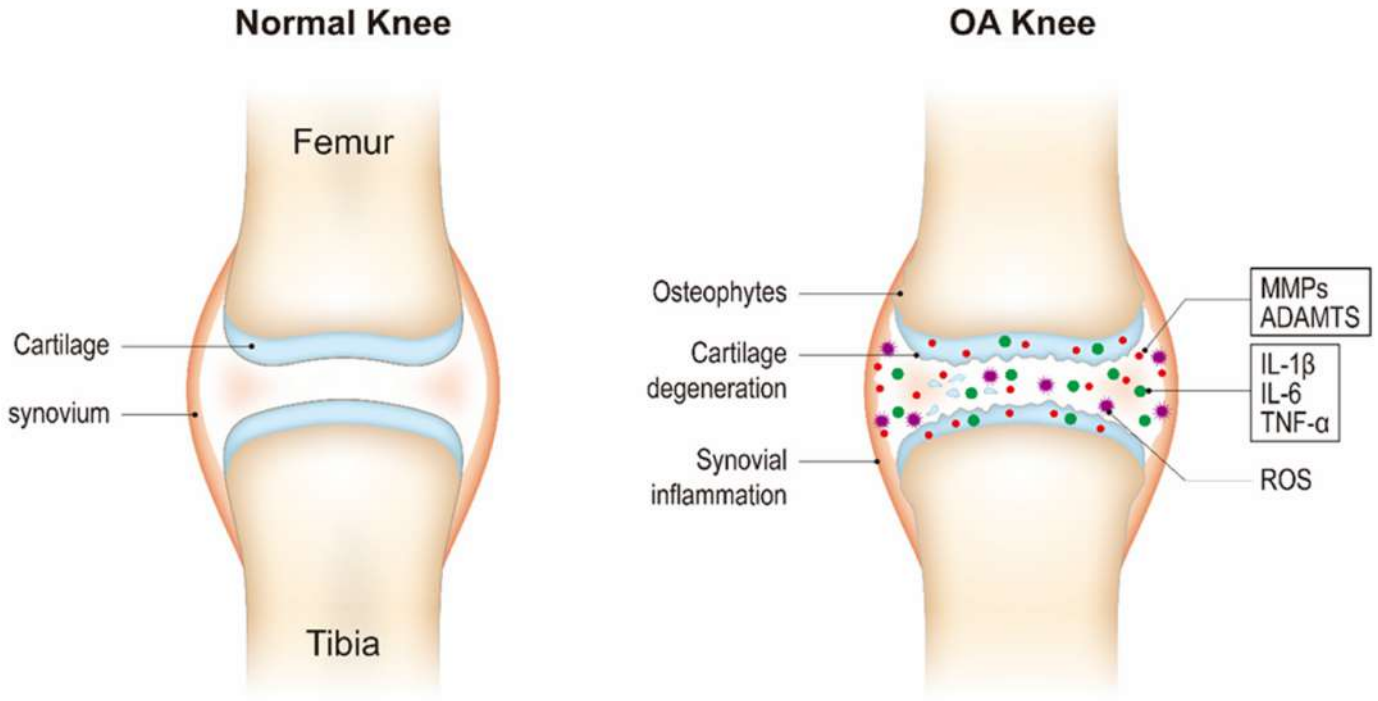




These enzymes are generated by chondrocytes

Osteoarthritis

- Inflammatory cytokines (e.g., **IL-1β, IL-6, and TNF-α**) secreted by chondrocytes and synovial cells in synovial fluid are critical mediators in OA development

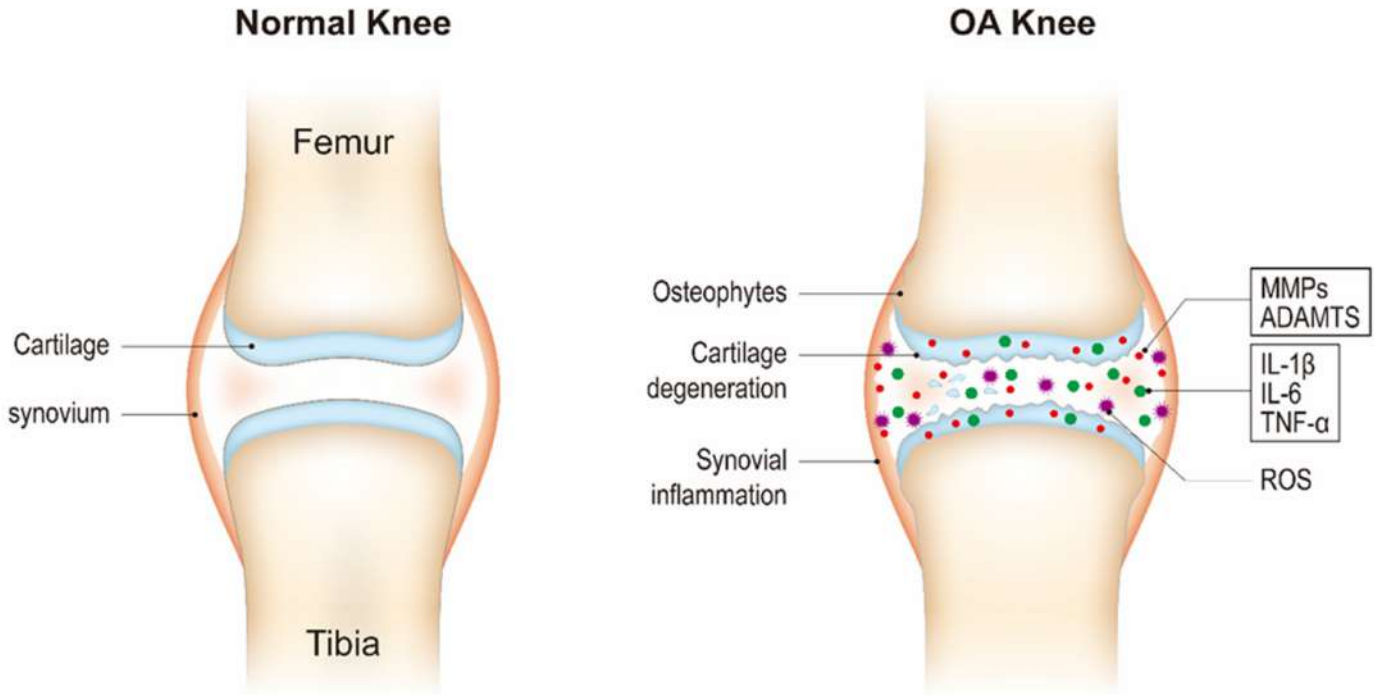


Kapoor, M.; Martel-Pelletier, J.; Lajeunesse, D.; Pelletier, J.P.; Fahmi, H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat. Rev. Rheumatol.* 2011, *7*, 33–42

Osteoarthritis

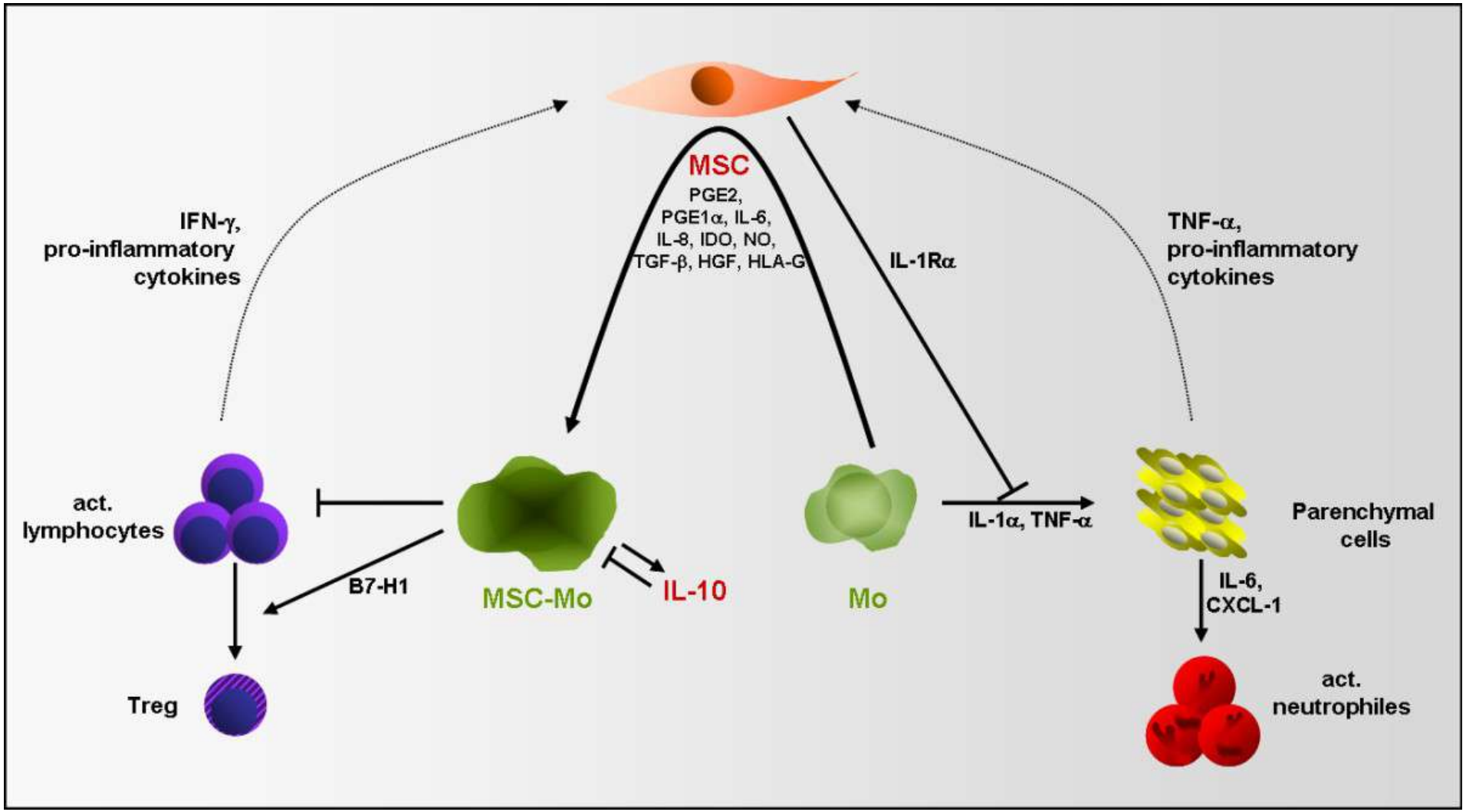
- Recent studies have shown that OA progression is closely related to oxidative stress, which refers to increased levels of intracellular ROS.

- ROS can up-regulate proinflammatory cytokine expression in OA, and the cytokines also induce ROS production, thereby accelerating OA development

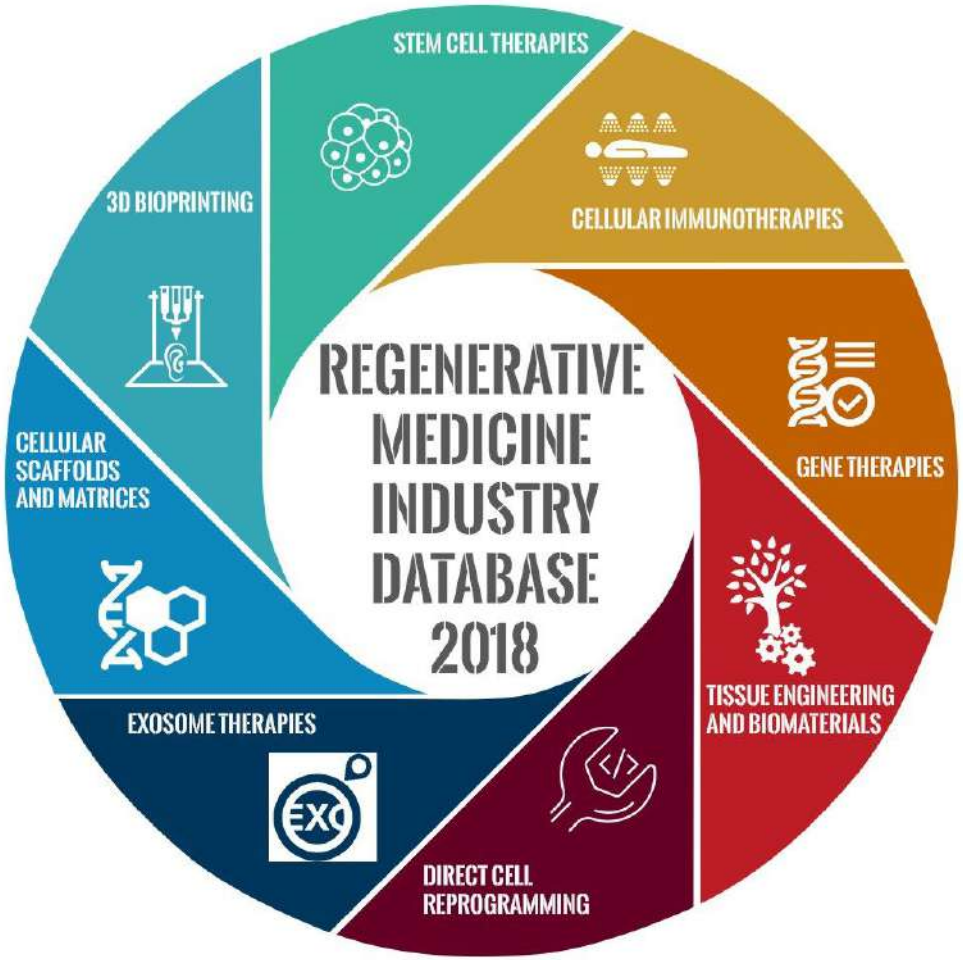


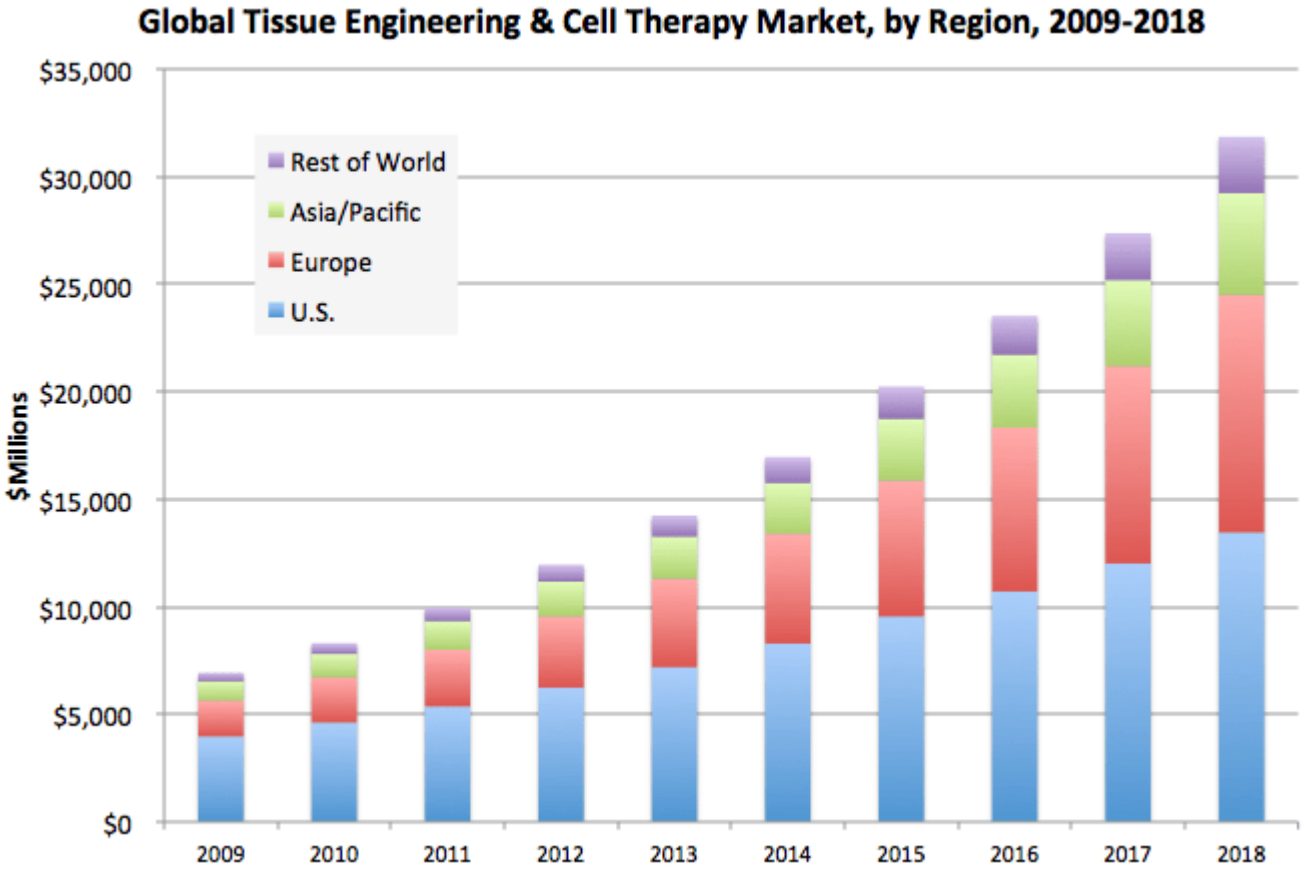
López-Armada, M.J.; Caramés, B.; Lires-Deán, M.; Cillero-Pastor, B.; Ruiz-Romero, C.; Galdo, F.; Blanco, F.J. Cytokines, tumor necrosis factor-alpha and interleukin-1beta, differentially regulate apoptosis in osteoarthritis cultured human chondrocytes. *Osteoarthr. Cartil.* 2006, *14*, 660–669

Mesenchymal Stem Cells

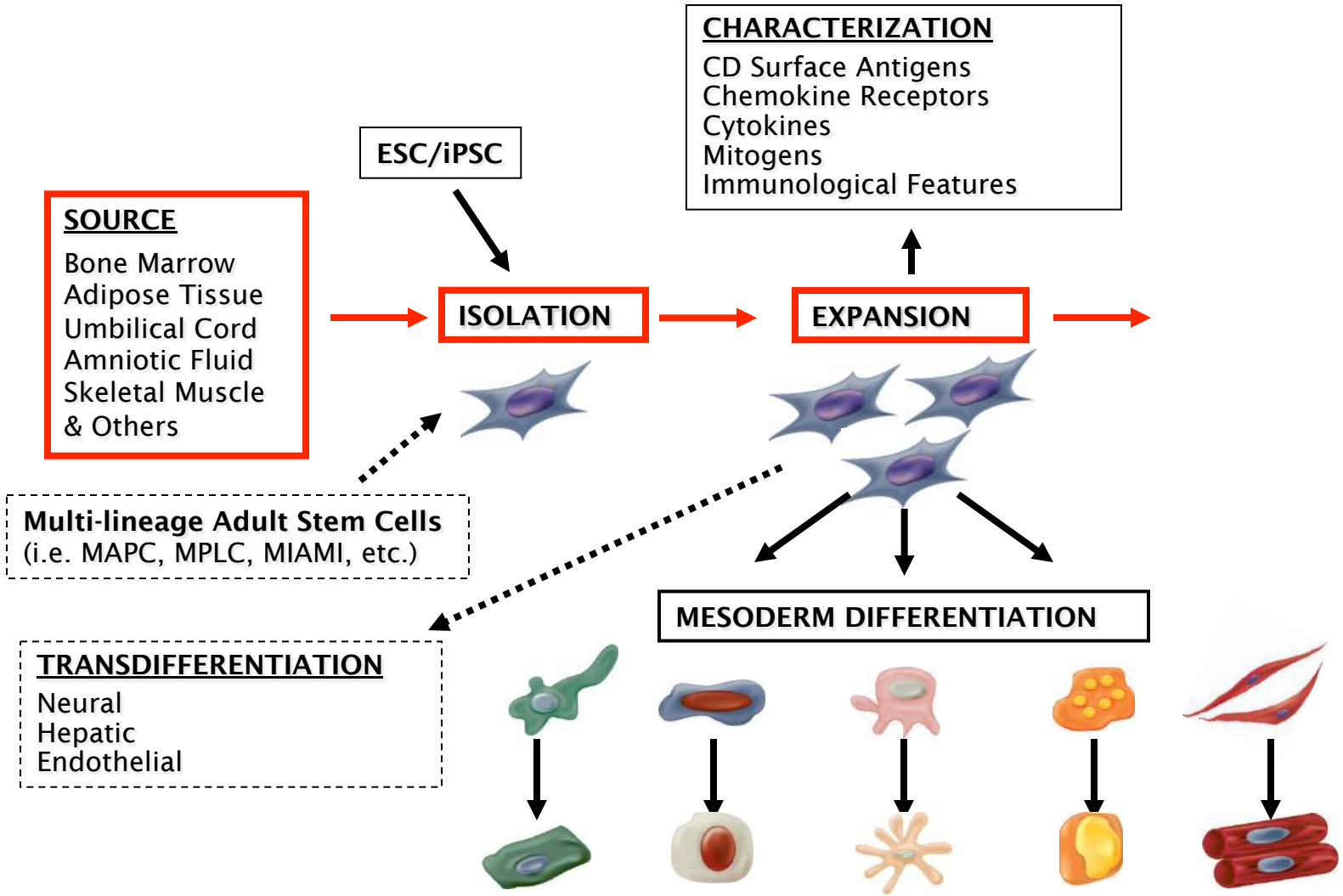


Marketing

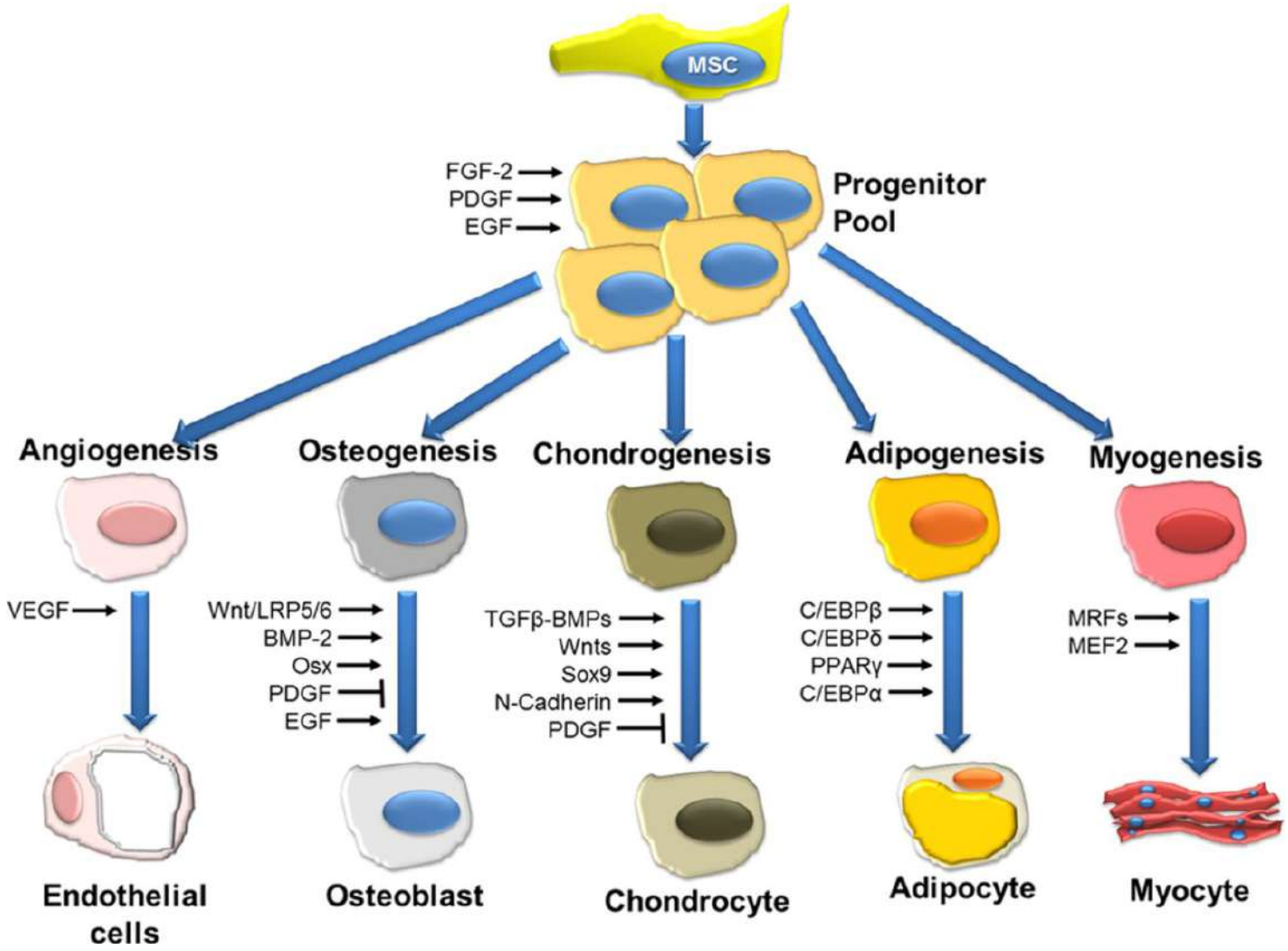

STEM CELL THERAPIES
CELLULAR IMMUNOTHERAPIES
GENE THERAPIES
TISSUE ENGINEERING AND BIOMATERIALS
DIRECT CELL REPROGRAMMING
EXOSOME THERAPIES
CELLULAR SCAFFOLDS AND MATRICES
3D BIOPRINTING
REGENERATIVE MEDICINE INDUSTRY DATABASE 2018


Global Tissue Engineering & Cell Therapy Market, by Region, 2009-2018
$Millions
$35,000
$30,000
$25,000
$20,000
$15,000
$10,000
$5,000
$0
Rest of World
Asia/Pacific
Europe
U.S.
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

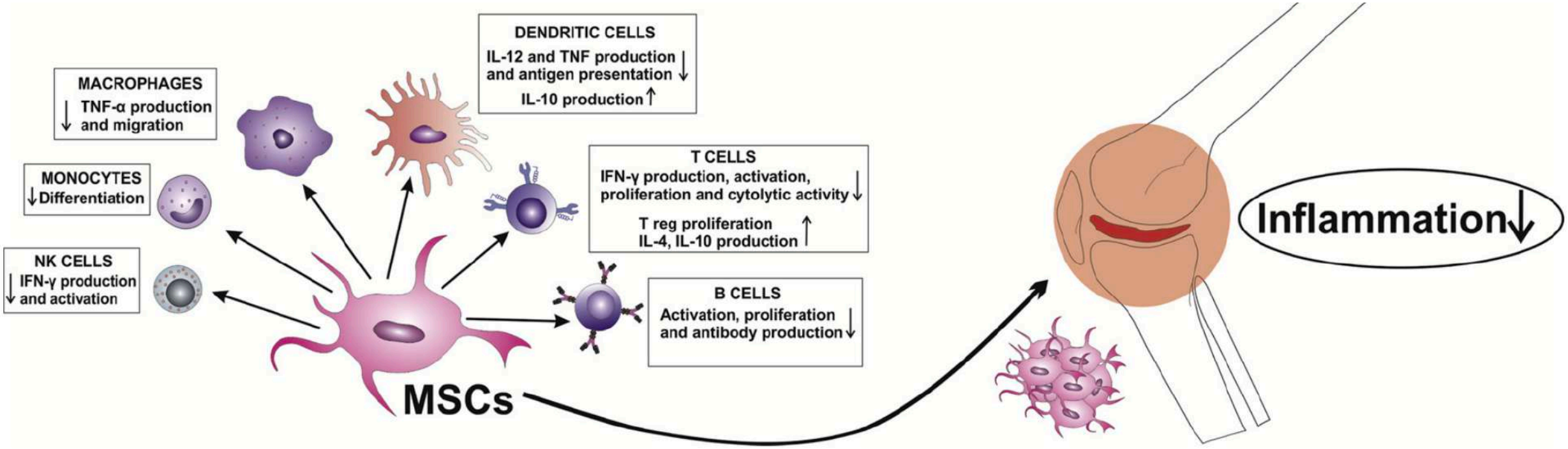
MESENCYHMAL STEM CELLS DIFFERENTIATON



MESENCYHMAL STEM CELLS DIFFERENTIATON



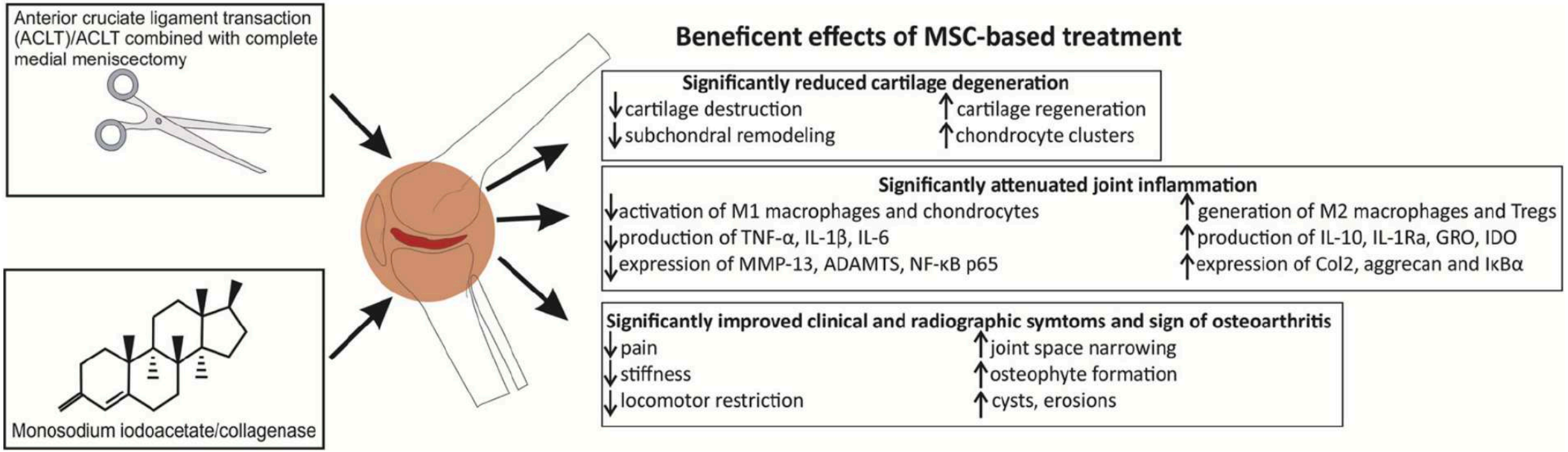
Osteoarthritis and MSC



- Repeated intraarticular injection of allogeneic MSCs results in an adverse clinical response and aggravation of OA.

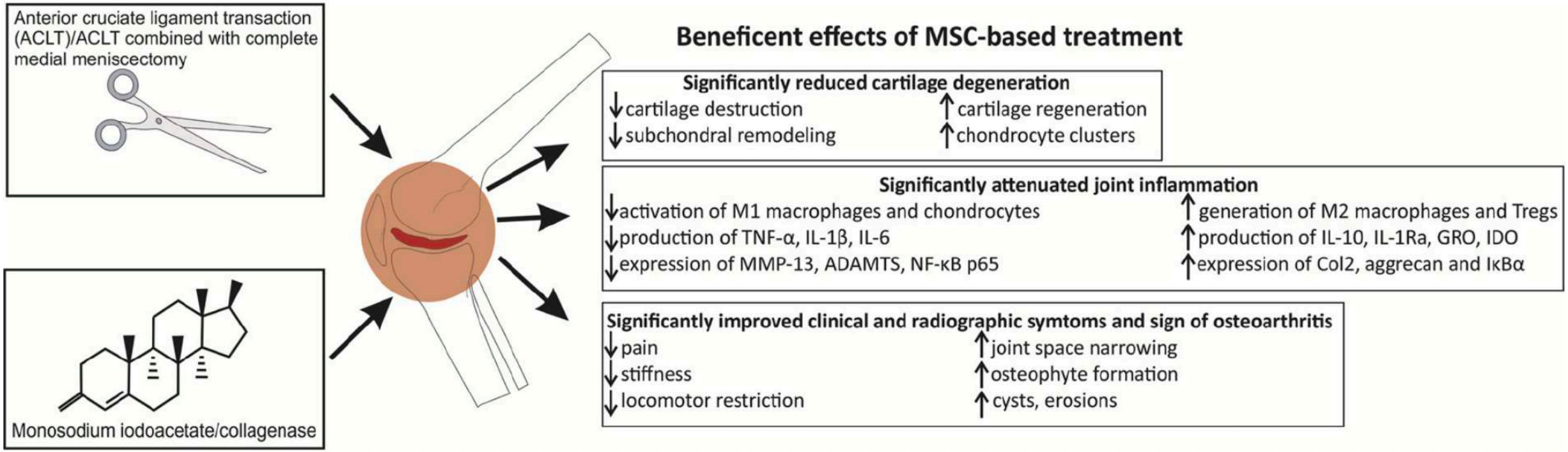
Osteoarthritis and MSC

- MSCs successfully attenuate clinical and radiographic symptoms and signs of osteoarthritis in experimental animals by promoting cartilage regeneration and by attenuating joint inflammation

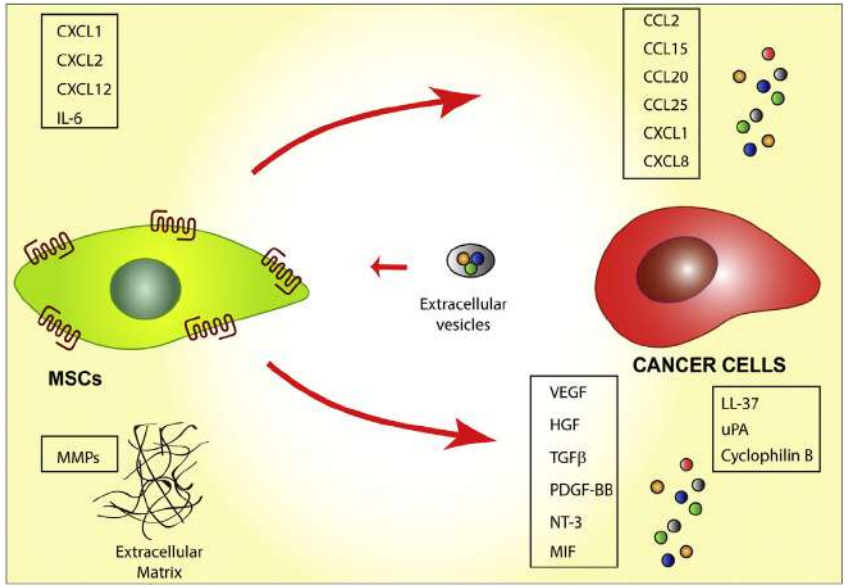


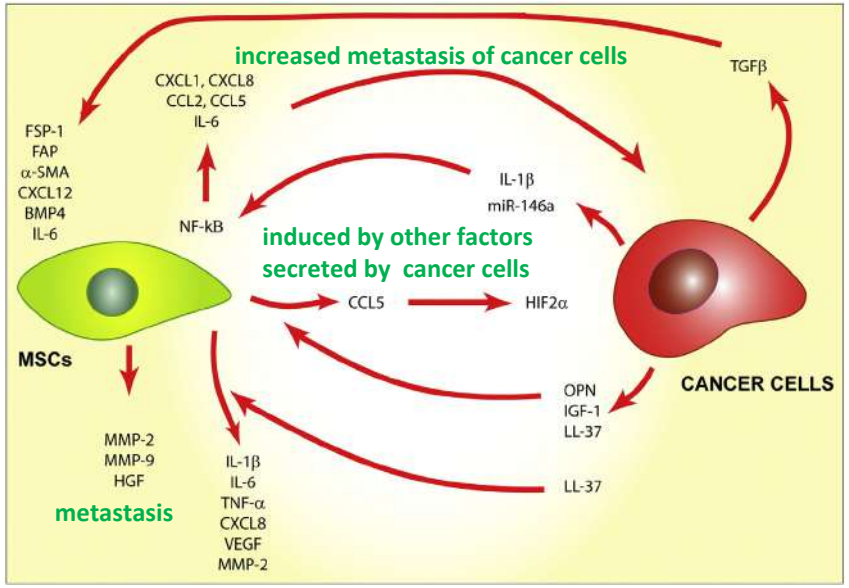
Osteoarthritis and MSC

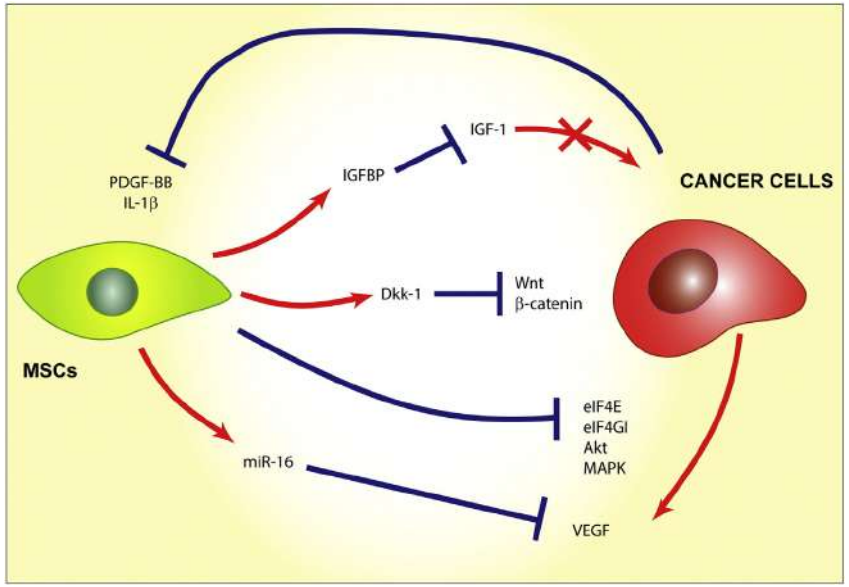
- Long-term persistence of allogeneic MSCs induces cellular and humoral immune response manifested by the increased infiltration of effector T cells and increased allo-antibody production after allogeneic MSCs administration



Crosstalk between Stem Cells and Cancer



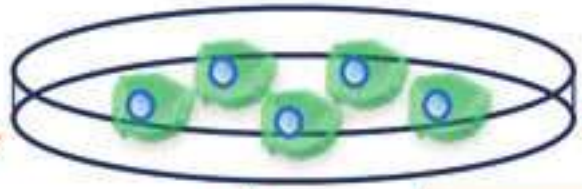




In particular, mesenchymal stem cells are recruited to the sites of developing tumors, thus promoting metastasis formation.

Their fate and function inside the tumor is still not clear: the crosstalk between stem cells and cancer cells is still controversial.

In vitro expansion of stem cells



2D culture

Natural biomaterials

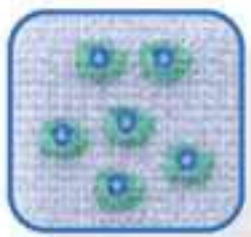
Synthetic biomaterials

3D culture

Modifications of biomaterials

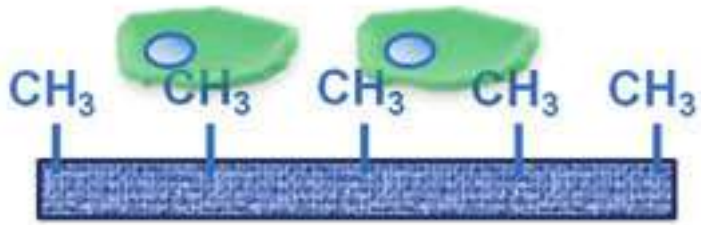
Topography/architecture

Stiffness



Cell encapsulation

Cellular spheroids



Biochemical modification

Crosstalk between ASCs and Chondrocytes

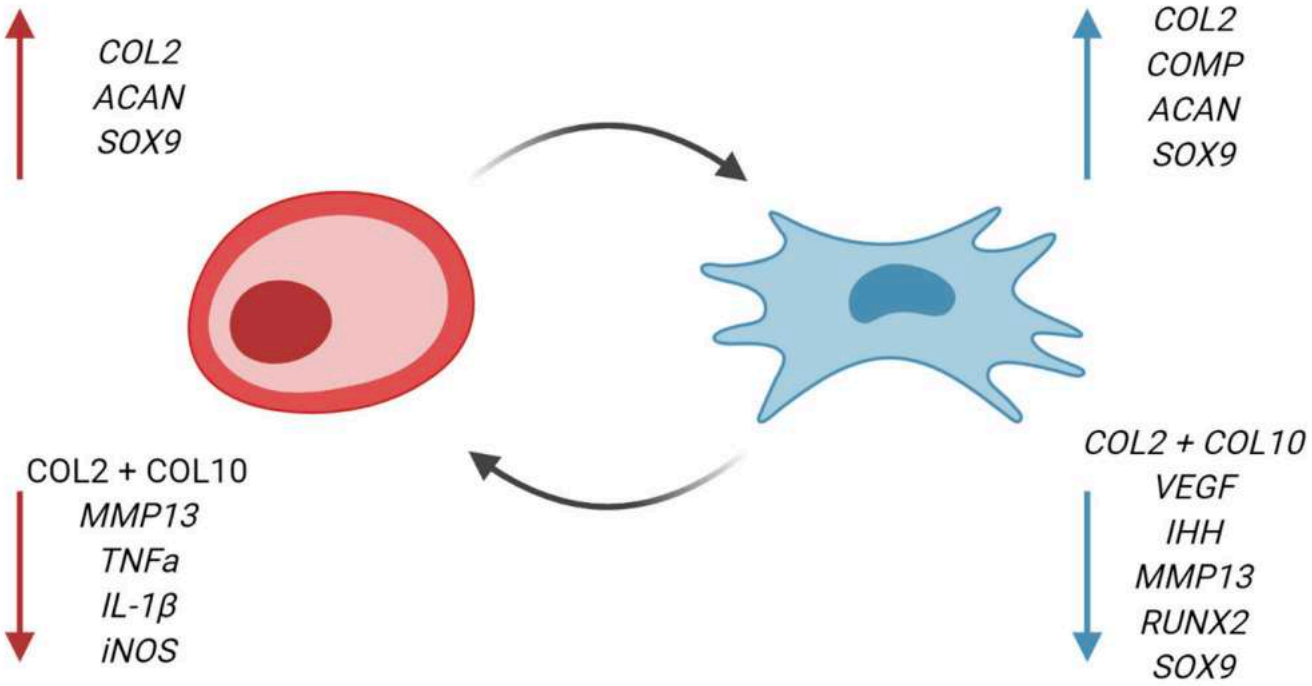
- After co-culture **significantly increased**
  - Bone morphogenetic protein 2 (BMP-2)
  - Vascular endothelial growth factor B (VEGFB)
  - Hypoxia inducible factor-1a (HIF-1a)
  - Fibroblast growth factor-2 (FGF-2)
  - Transforming growth factor-β1
- Unexpectedly, **significantly down-regulated**
  - Collagen II
  - Aggrecan

- **Crosstalk between ASCs and chondrocytes is a pathway through the regulated growth factors that might have potential in cartilage repair and regeneration and could be useful for tissue engineering.**

Zhong J, Guo B, Xie J, Deng S, Fu N, Lin S, Li G, Lin Y, Cai X. Crostalk between adipose-derived stem cells and chondrocytes: when growth factors matter.Bone Research (2016) 4, 15036

Crosstalk between MSCs and Chondrocytes

- Co-culture of chondrocytes and MSCs influence the reciprocal expression of genes associated with chondrogenic phenotype and inflammation with some genes being upregulated and others downregulated



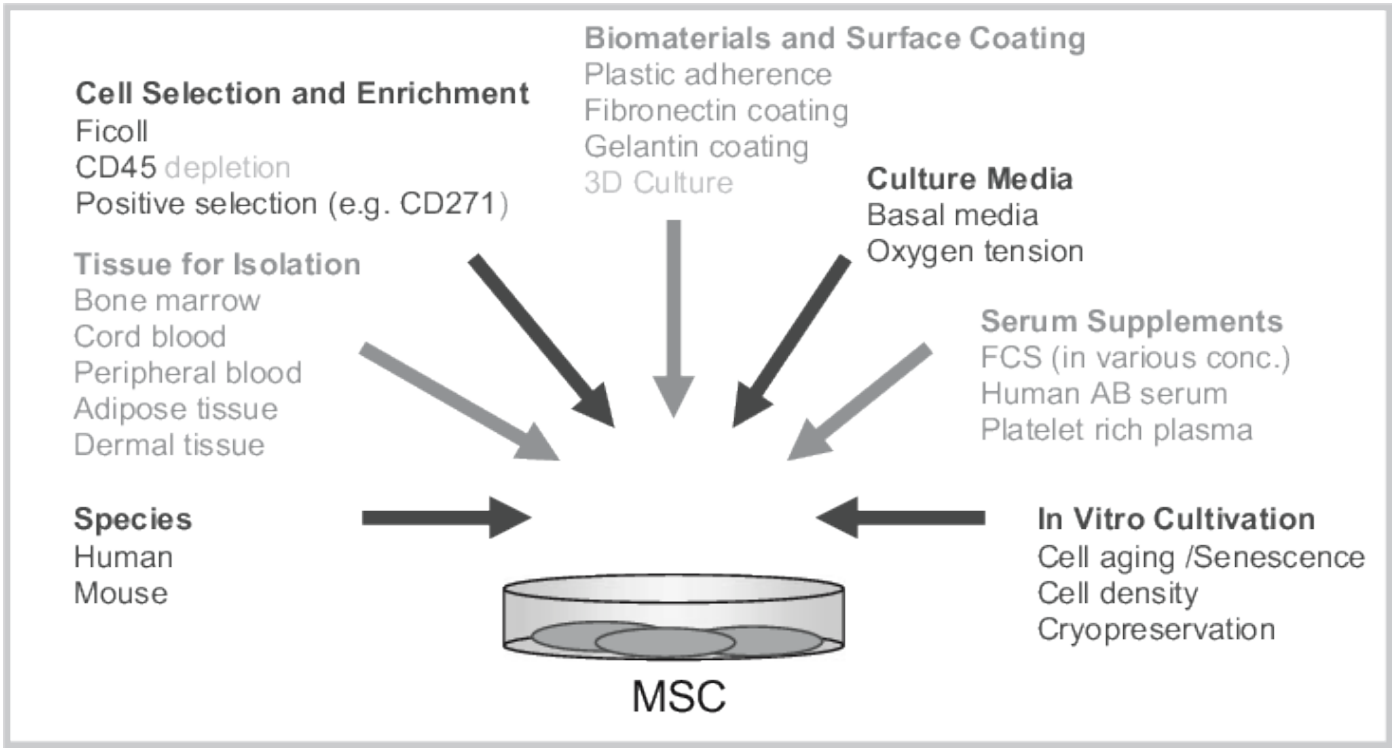
Brose TZ, Kubosch EJ, Schmal H, Stoddart MJ, Armiento AR. Crosstalk Between Mesenchymal Stromal Cells and Chondrocytes: The Hidden Therapeutic Potential for Cartilage Regeneration. Stem Cell Rev and Rep (2021) 17:1647–1665

Crosstalk between MSCs and Chondrocytes

- A downregulation of TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) is observed, also when chondrocytes are cultured in MSC-conditioned medium
- EV prevent TNF-α mediated upregulation of cyclooxygenase-2 (COX2) and proinflammatory interleukins and inhibit TNF-α-induced collagenase activity
- These results demonstrate that the antiinflammatory effect of MSCs on chondrocytes occurs via paracrine secretion, as well as cell-cell contact.

Critical parameters for MSC isolation

- Various different culture isolation protocols for MSC preparations have been described in different studies.
- Each of these parameters has impact on the composition of cell preparations and needs to be taken into account



W Wagner, AD. Ho. Mesenchymal Stem Cell Preparations—Comparing Apples and Oranges. Stem Cell Reviews and Reports 3(4):239-48, 2008

Stem Cells /biomaterials

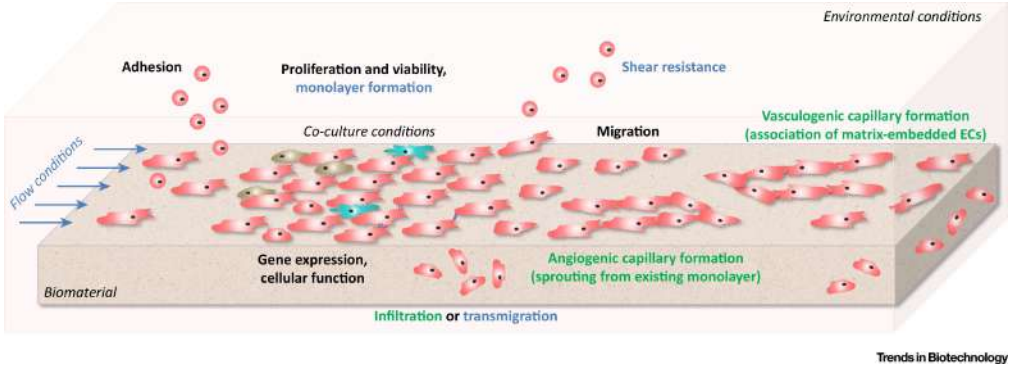
It has been reported that inhibition of the phosphatidylinositol 3-kinase Akt/mTOR pathways could provide an environment to maintain MSCs in their immature undifferentiated state during long-term culture expansion

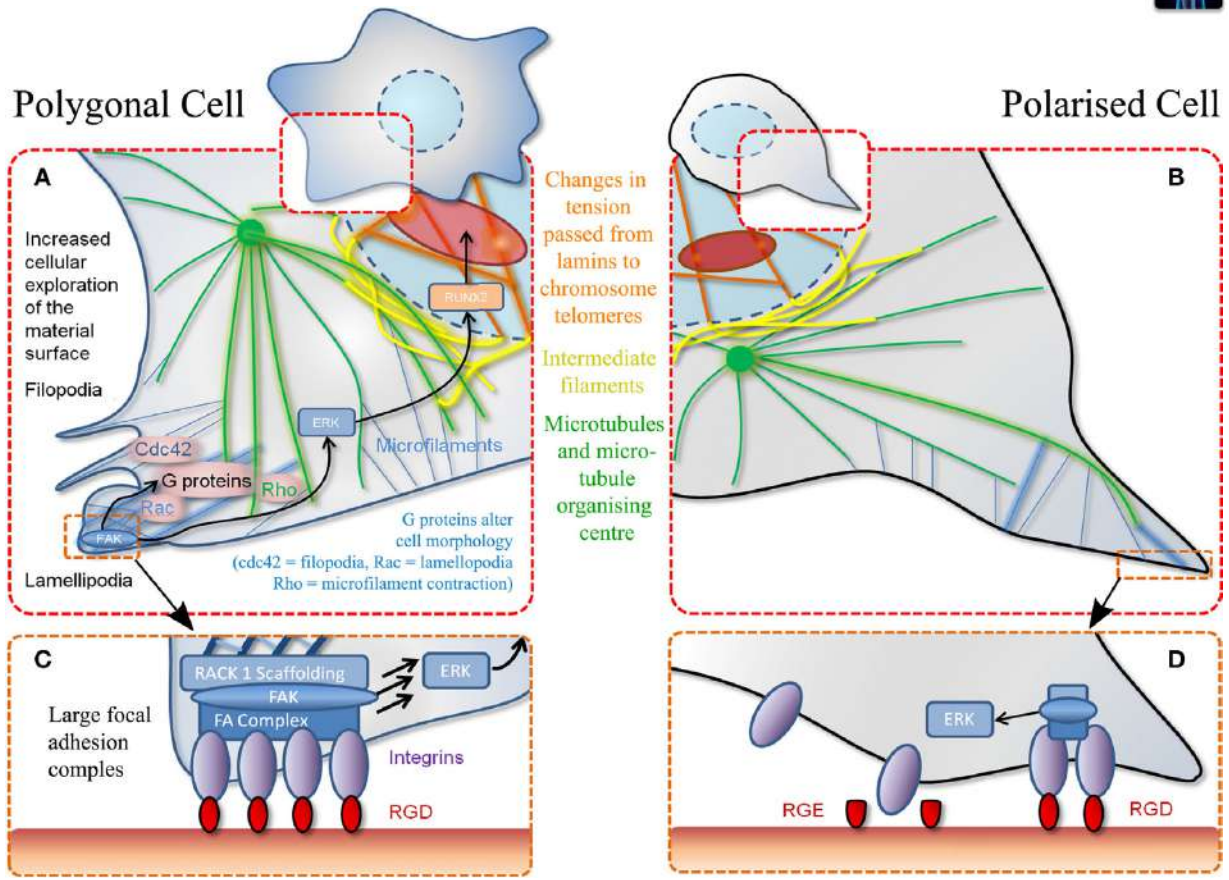
Biomaterial description	Model	Effect on cell survival
Collagen and laminin-derived cell adhesive peptide	*In vitro* cell culture, embryonic rat NSCs	Increase in cell number
Collagen gel with diffusible NGF	*In vitro* cell culture, PC-12 cells	Increase in cell number and decrease in number of apoptotic cells
Electrospun PCL nanofibers immobilized with BDNF	*In vitro* culture, NSCs	Increase in cell number
Chitosan/glycerophosphate salt hydrogels coated with PDL	*In vitro* cell culture, foetal mouse cortical cells	Increase in cell number
Elastin-like polypeptides modified with RGD	*In vitro* cell culture, PC-12 cells	Cell number comparable to collagen films
P(HEMA-*co*-AEMA) modified with YIGSR and IKVAV	*In vitro* cell culture, DRG cells	Increase in cell number
Dextran modified with RGDS or YIGSR and IKVAV	*In vitro* cell culture, DRG cells	Increase in cell number
Methyl cellulose modified with laminin	*In vitro* cell culture, cortical neurons	Increase in cell viability
Laminin coated glass coverslips	*In vitro* cell culture, oligodendrocyte progenitor cells	Decrease in number of apoptotic cells
Fibronectin coated glass coverslips	*In vitro* cell culture, oligodendrocyte progenitor cells	Decrease in number of apoptotic cells
Agarose	*In vitro* cell culture, rat cortical neurons	Complete cell death by 14 days
Collagen	*In vitro* cell culture, rat cortical neurons	Increase in percentage live cells over agarose
Fibrin, Fibronectin and Fibrin/ Fibronectin	*In vivo* scaffold for spinal cord knife cut lesion cavity	Increase in cell number
Outer PLGA scaffold, inner PEG/ PLL hydrogel	*In vivo* transplantation in a rat hemisection model	Increase in cell number
Chitosan channels/tubes	*In vivo* transplantation in rat complete spinal cord transection	Increase in cell number
Chitin/Chitosan films	*In vitro* cell culture	Increase in cell number
Methyl cellulose	*In vivo* transplantation in rat spinal cord moderate thoracic (T8) contusion injury	Decrease in cell number
ECM gel (laminin and collagen)	*In vivo* transplantation in rat spinal cord moderate thoracic (T8) contusion injury	Increase in cell number
Fibrin	*In vivo* transplantation in rat spinal cord hemisection model	Increase in cell number
Growth factor reduced Matrigel	*In vivo* transplantation into brain	Increased in graft size
Matrigel	*In vivo* transplantation into brain	Decrease in infarct size
Matrigel	*In vivo* transplantation in rat spinal cord moderate thoracic (T8) contusion injury	Increase in cell number
Ultrafoam (Collagen I)	*In vivo* transplantation into brain	Increase in cell number
Hyaluronic acid hydrogel with BDNF	*In vitro* cell culture	Increase in culture viability
Aragonite matrix	*In vitro* cell culture	Increase in cell number

MSC adhesion

(A) Binding to material surface by lamellipodia stimulates a signaling cascade. This results in transcription factor expression (RUNX2) that stimulates differentiation via other G-proteins and effectors.

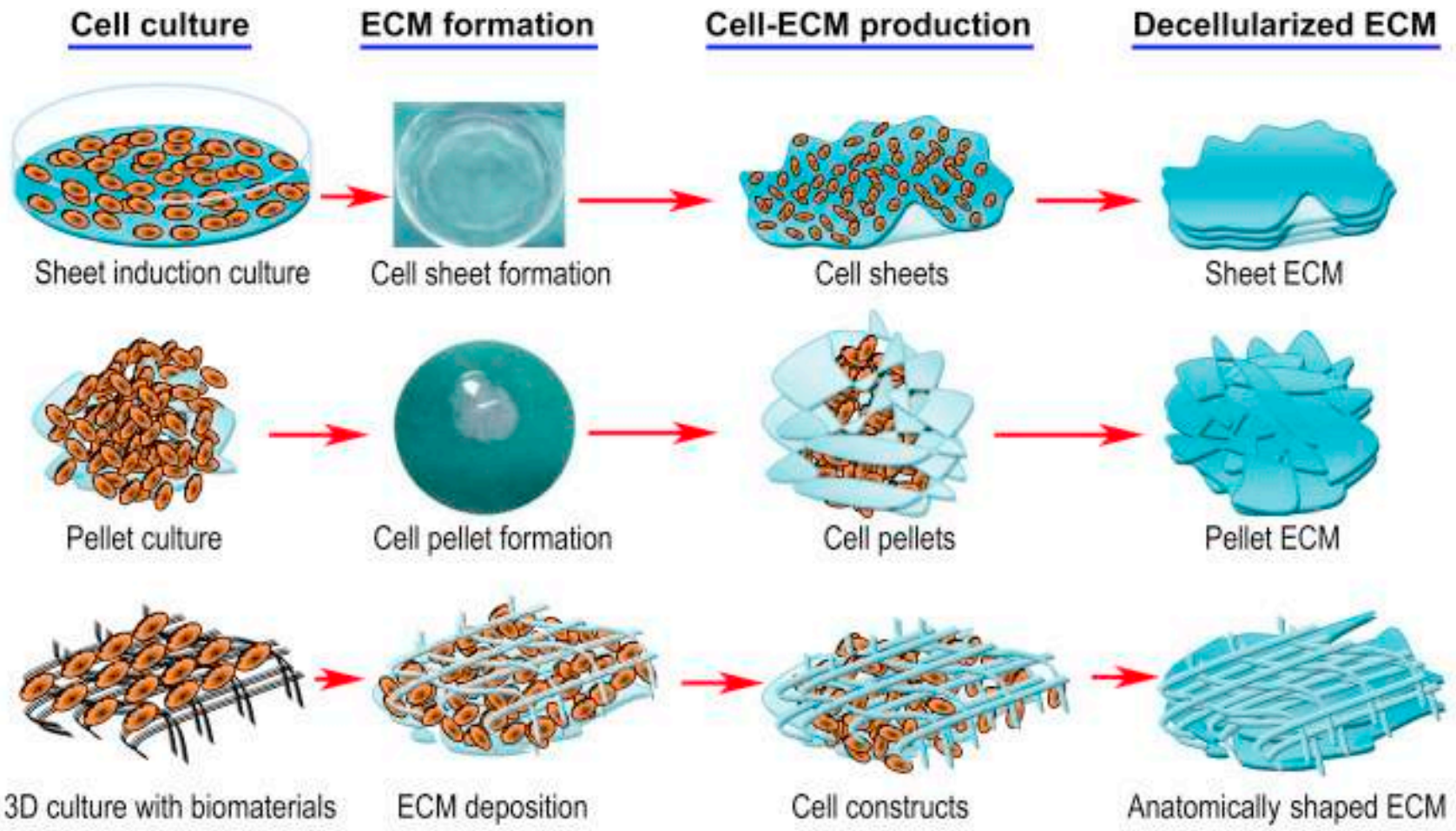
(B) Polygonal cells adhere to a material at various positions encouraging cell spreading and decreasing motility. (B) Polarized cells refer to adhesion at a single point through the same mechanisms described in (A).



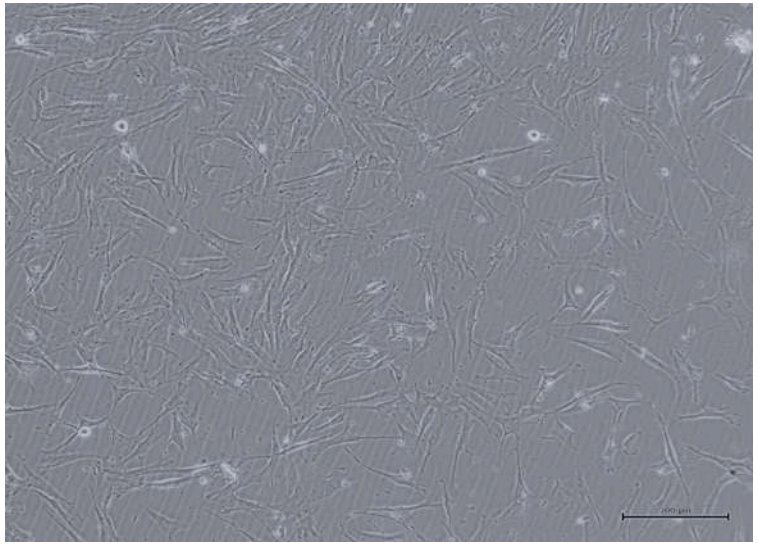


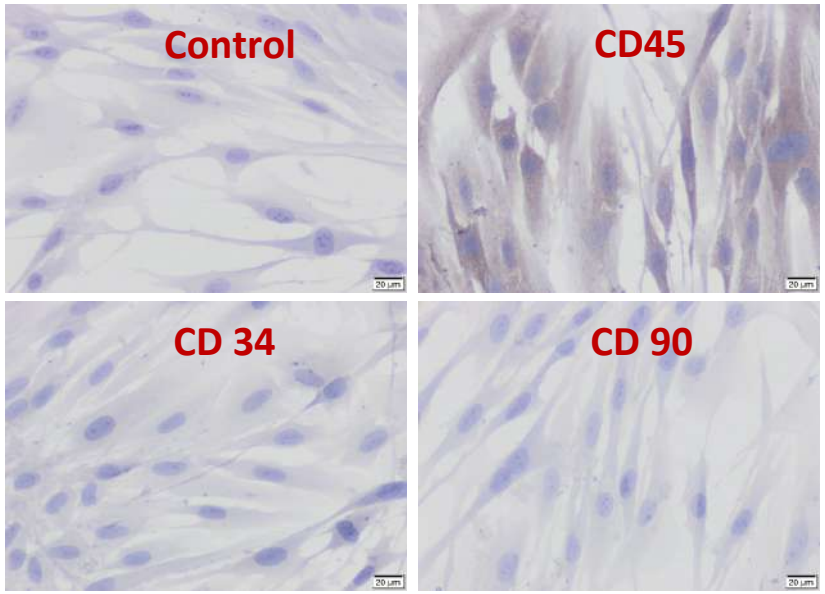
HJ Anderson, J K Sahoo, RV.Ulijn, MJ Dalby. Mesenchymal Stem Cell Fate: Applying Biomaterials for Control of Stem Cell Behavior. Front. Bioeng. &Biotech., 4:38, 1-14, 2016

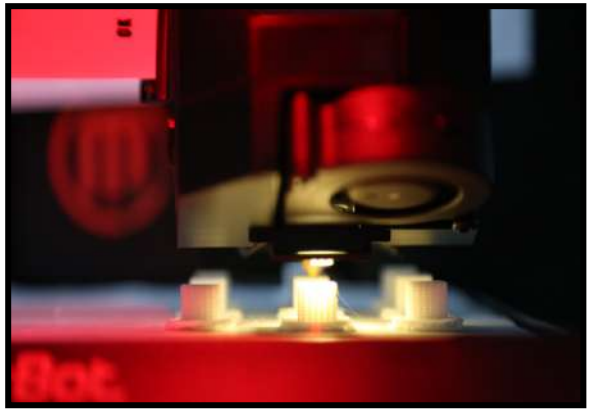
Culture

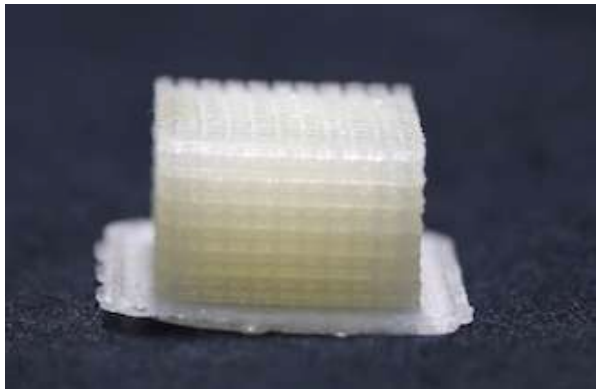

Cell culture
ECM formation
Cell-ECM production
Decellularized ECM
Sheet induction culture
Cell sheet formation
Cell sheets
Sheet ECM
Pellet culture
Cell pellet formation
Cell pellets
Pellet ECM
3D culture with biomaterials
ECM deposition
Cell constructs
Anatomically shaped ECM

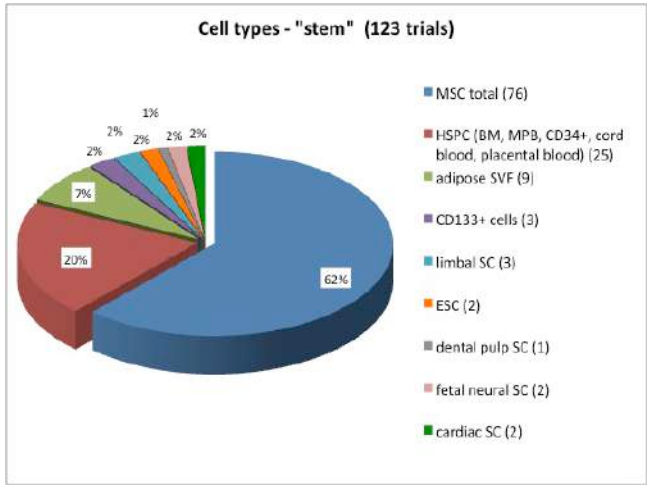
Stem Cells + Scaffold

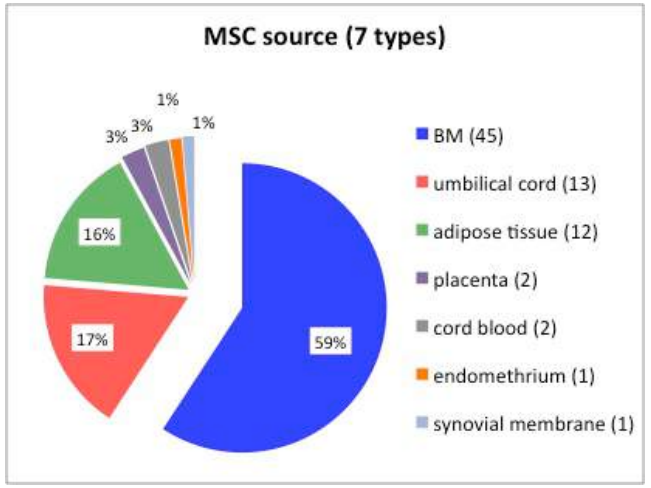


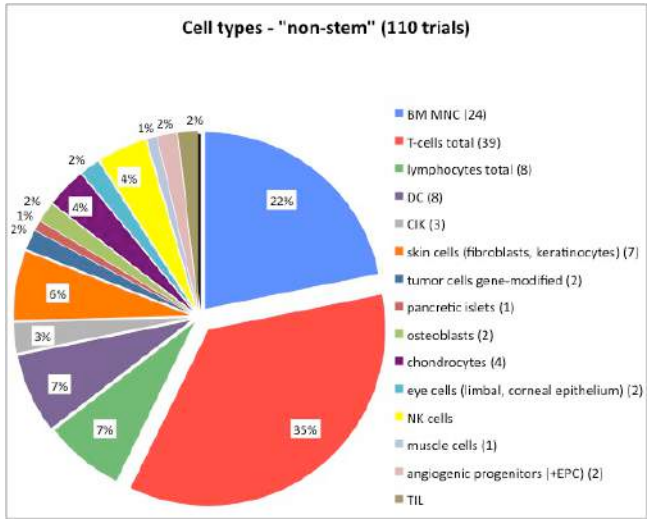


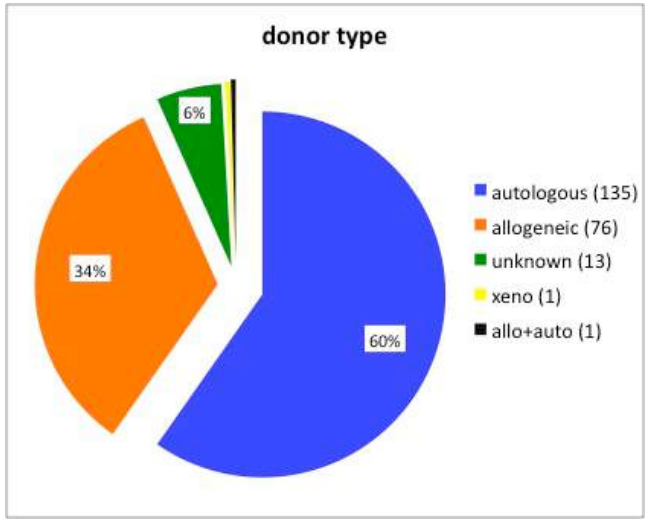


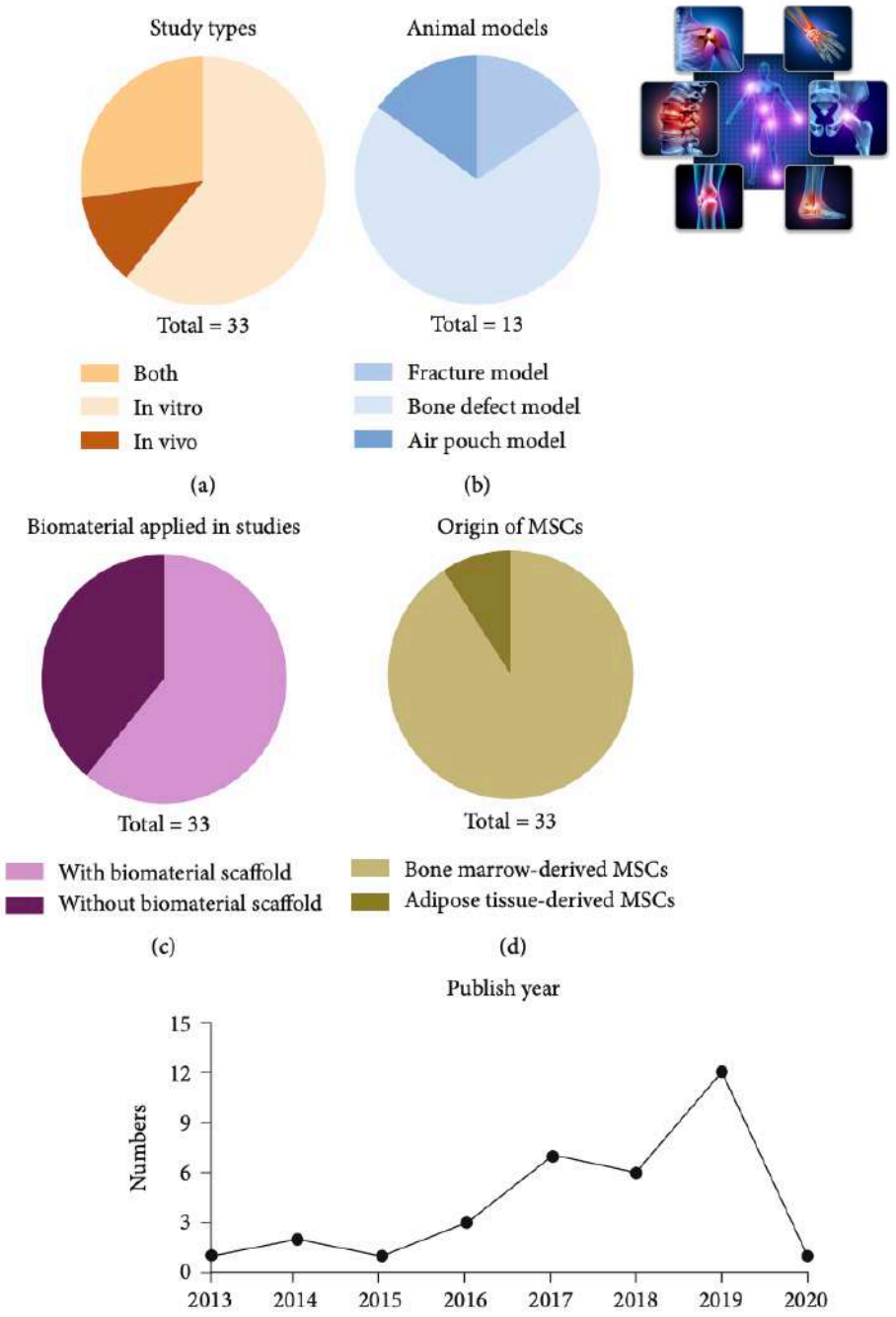












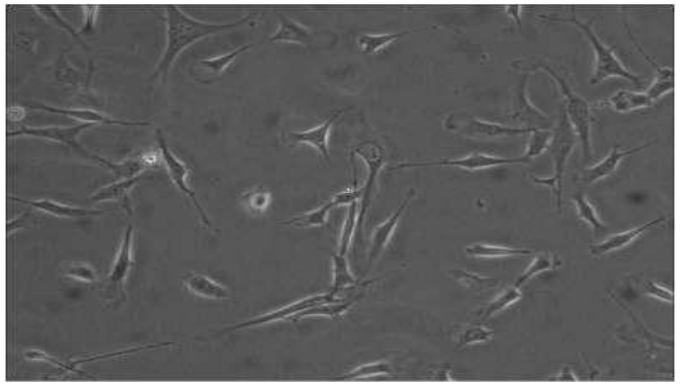
A. Bersenev . Cell Therapy Clinical Trials – 2012 Report On January 8, 2013 · 10 Comments, İn Annual Reports Cell Trials, Current Trends İn Cell Therapy

Stem Cells Studies

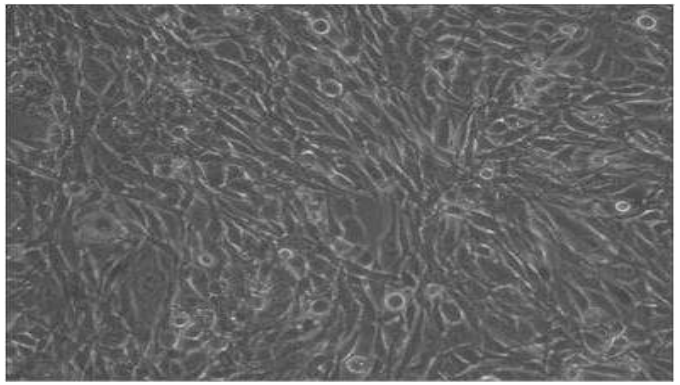
- Embryonic Stem Cells (Mouse, Human)
- Bone Marrow Mesencyhmal Stem Cells (Mouse, Rat, Human)
- Adipogenic Mesencyhmal Stem Cells (Mouse, Rat, Human)
- Dental Pulp Stem Cells (Human)
- Foreskin Mucosal Stem Cells (İHuman)
- Spermatogonial germ stem cell culture (Human)

Embryonic Stem Cells-Culture and Differentiation

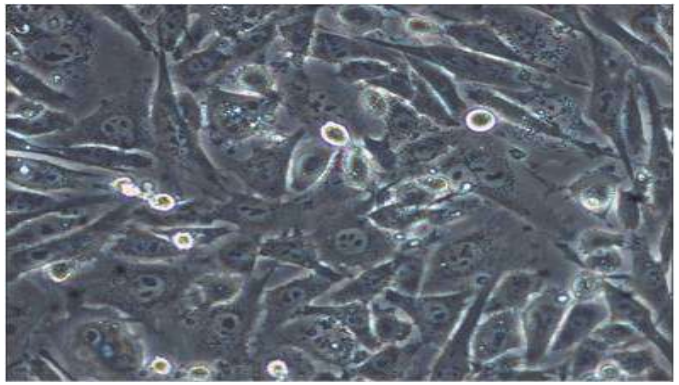
STO-2. day

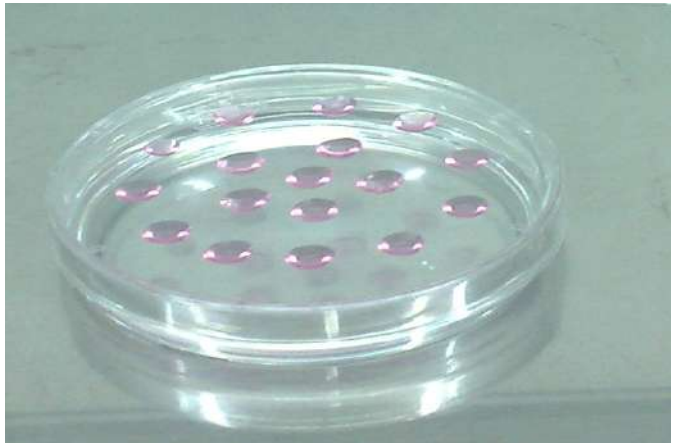


STO-7. day

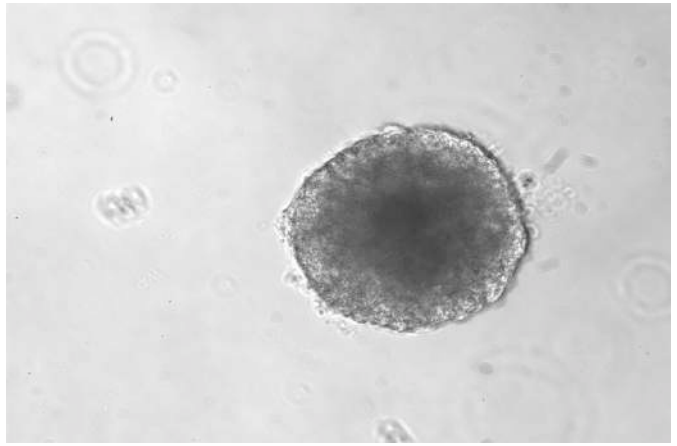


ES Cells on mit-C treated STO

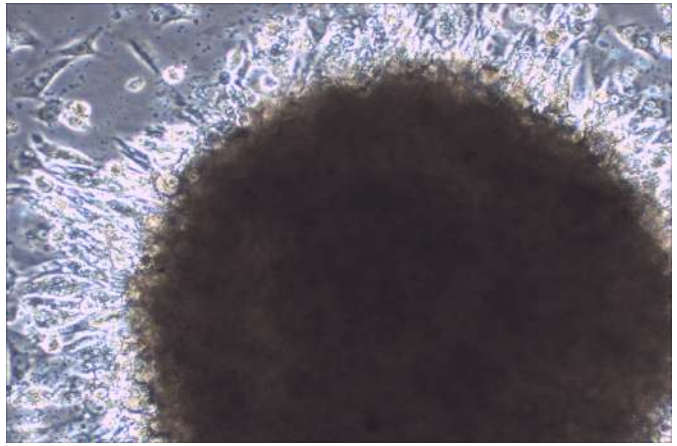




Hanging Drop

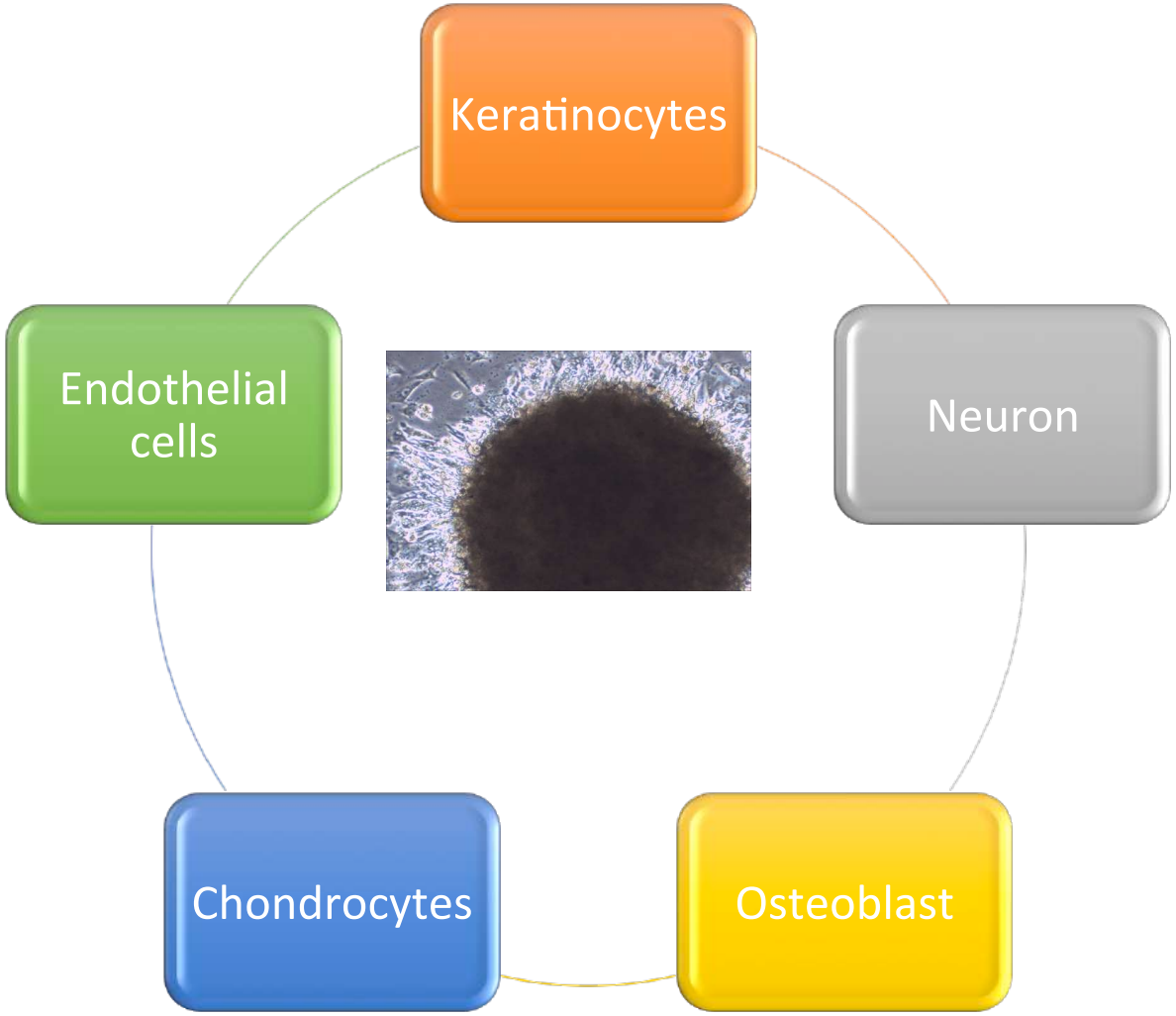


Embryoid Body

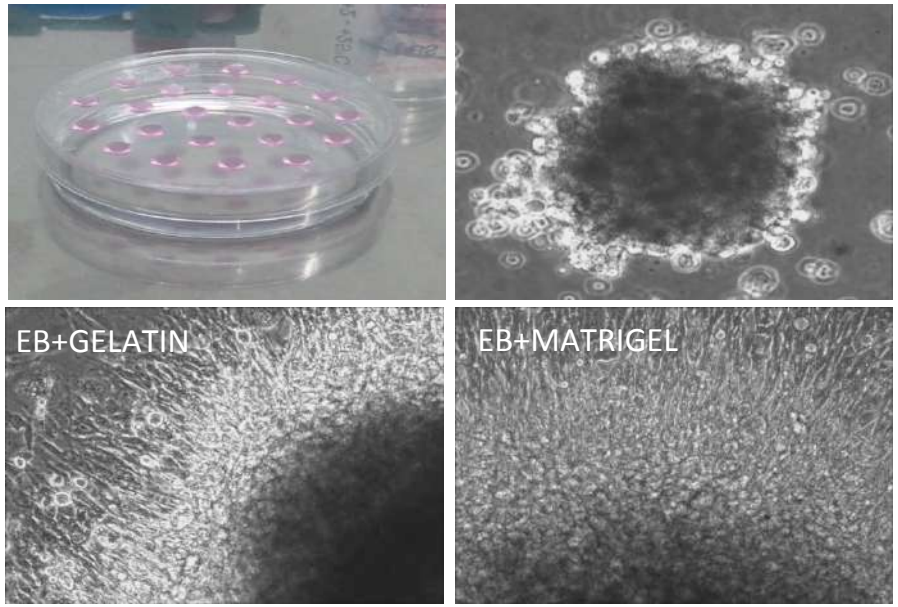


Differentiation

Embryonic Stem Cells-Culture and Differentiation



Embryonic Stem Cells- Osteogenic Differentiation



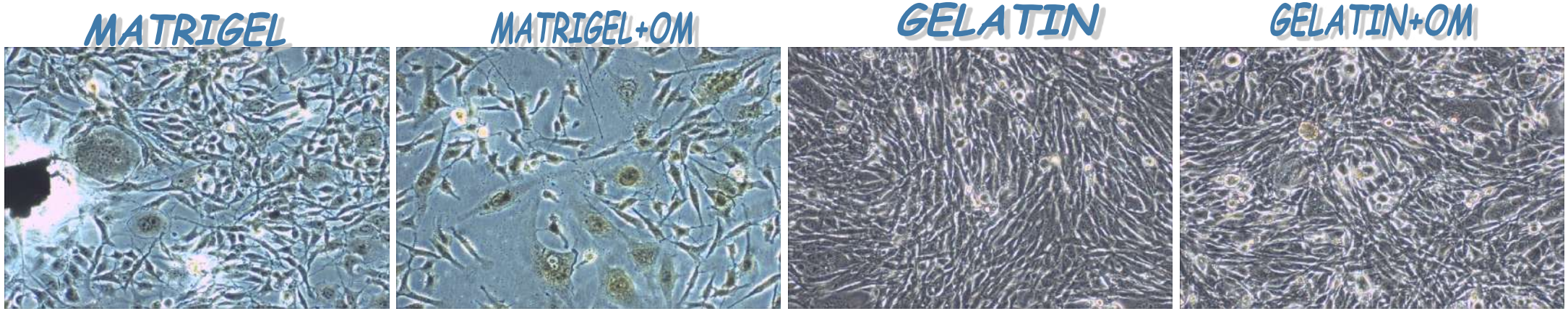
Matrigel	• Control Medium
Matrigel	• Osteogenic Medium
Gelatin	• Control Medium
Gelatin	• Osteogenic Medium

Osteogenic Medium

-10 mM Na-ß-glycerophosphate

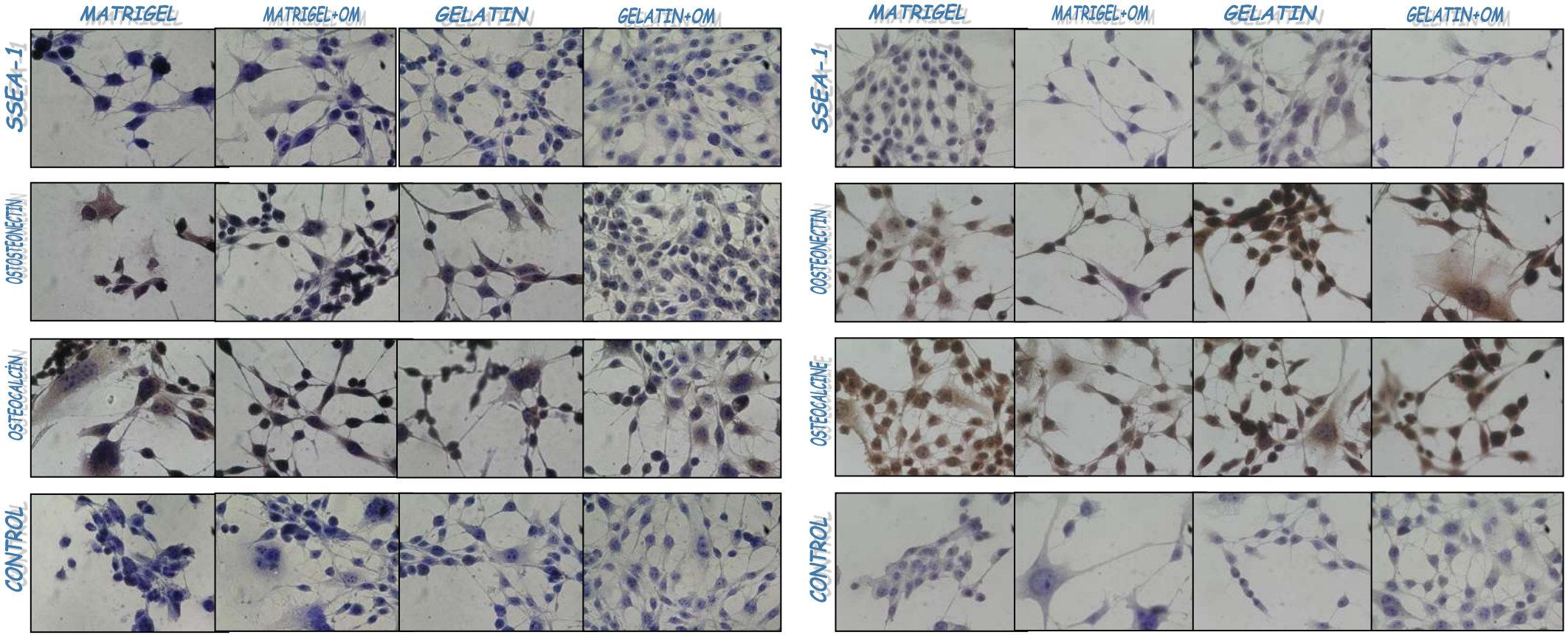
- 50 µg/ml ascorbicacid

- 10^{-8}M dexamethasone



F. Özdal-Kurt, E. Turköz-Uluer, D. Gözüaçık, İ. Deliloğlu-Gürhan, H. S. V atansever, Potential differentiation of mouse embryonic stem cells to osteblast. Regenerative Medicine Congress, Cesme, 2011. (A part of them published Cell & Tissue, 2017)

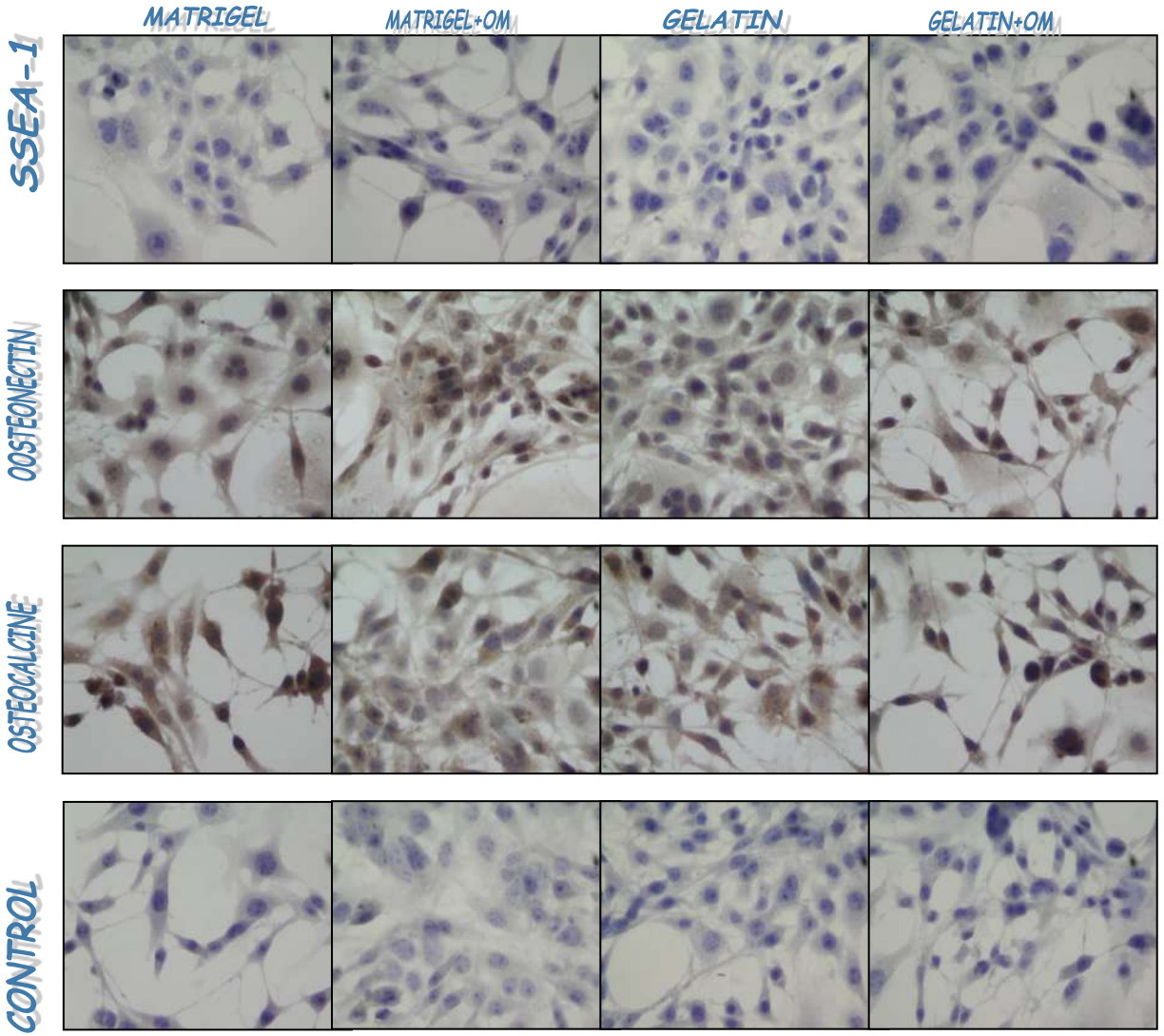
Embryonic Stem Cells- Osteogenic Differentiation-Osteoblast



15. Days **30. Days**

F. Özdal-Kurt, E. Turköz-Uluer, D. Gözüaçık, İ. Deliloğlu-Gürhan, H. S. Vatansever, Potential of mouse embryonic stem cells to osteblast. Regenerative Medicine Congress, Cesme, 2011.

Embryonic Stem Cells- Osteogenic Differentiation-Osteoblast

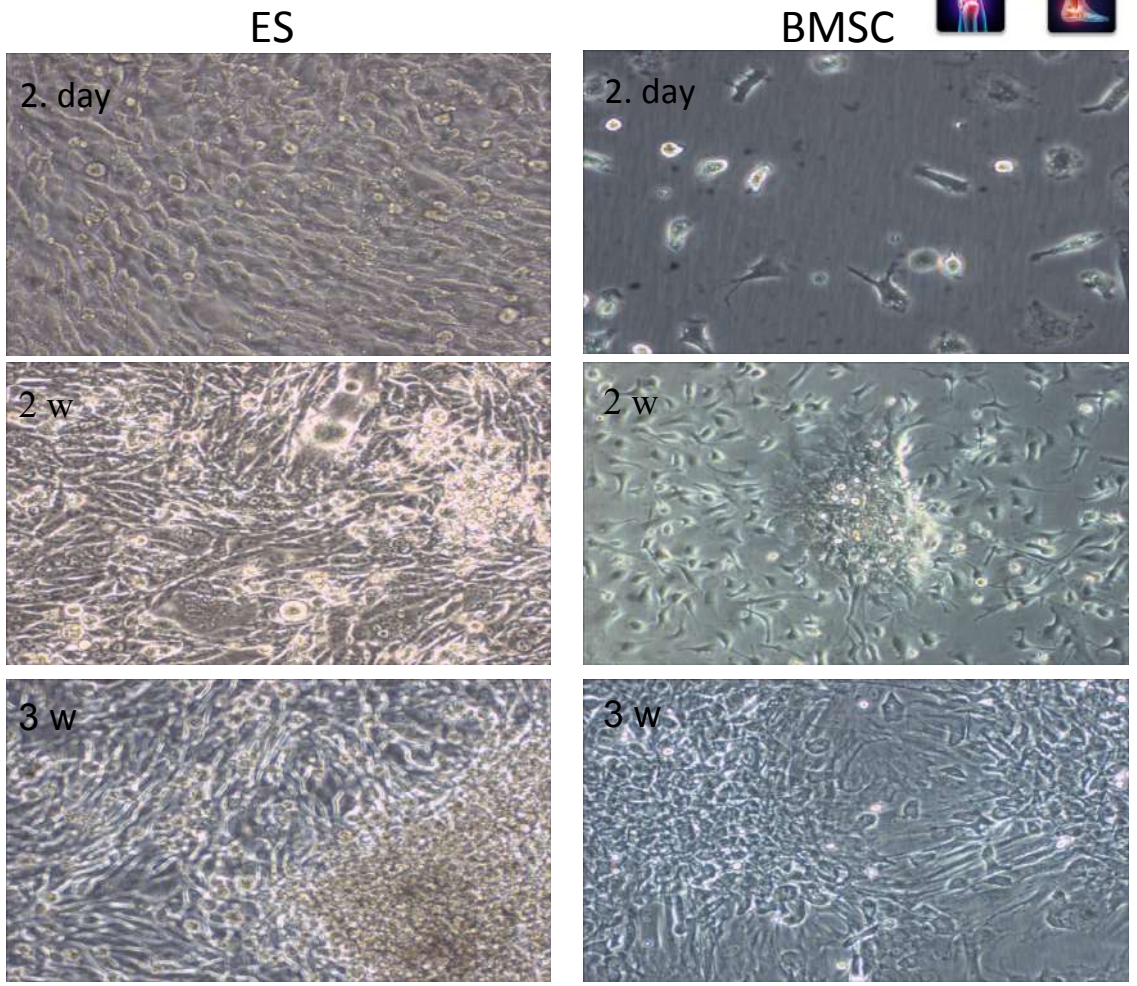


45. Days

F. Özdal-Kurt, E. Turköz-Uluer, D. Gözüaçık, İ. Deliloğlu-Gürhan, H. S. Vatansever, Potential of mouse embryonic stem cells to osteblast. Regenerative Medicine Congress, Cesme, 2011.

Embryonic Stem Cells- Chondrogenic Differentiation

Matrigel	• BMSC+CM
Matrigel	• ES+CM
Gelatin	• BMSC+CM
Gelatin	• ES+CM

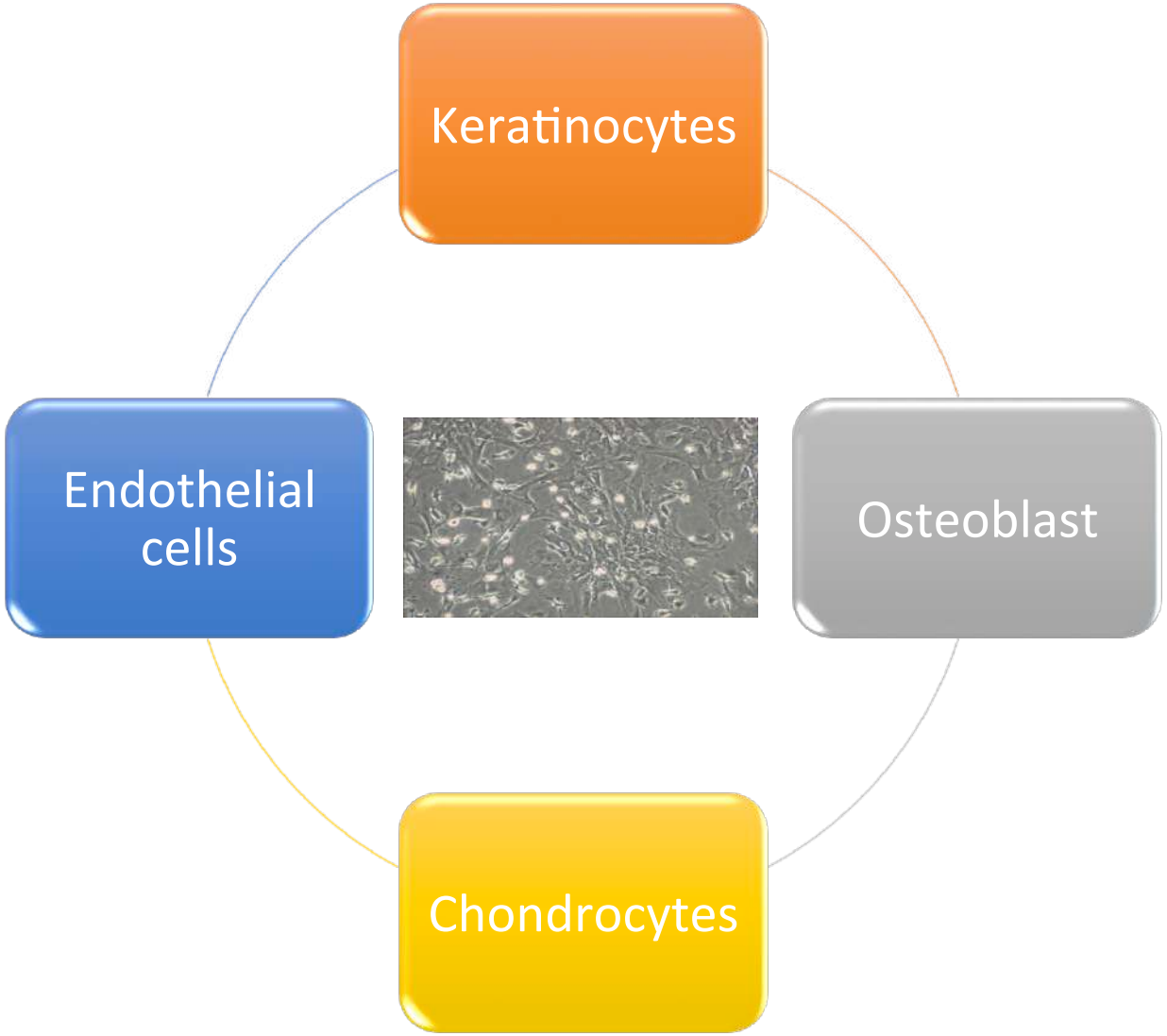


Chondrogenic Medium

- 10ng/ml TGF-β1
- 50µg/ml ascorbic acid 2 fosfat
- 100nM dexametazon,
-10% ITS (Insülin- Transferrin-Selenium)

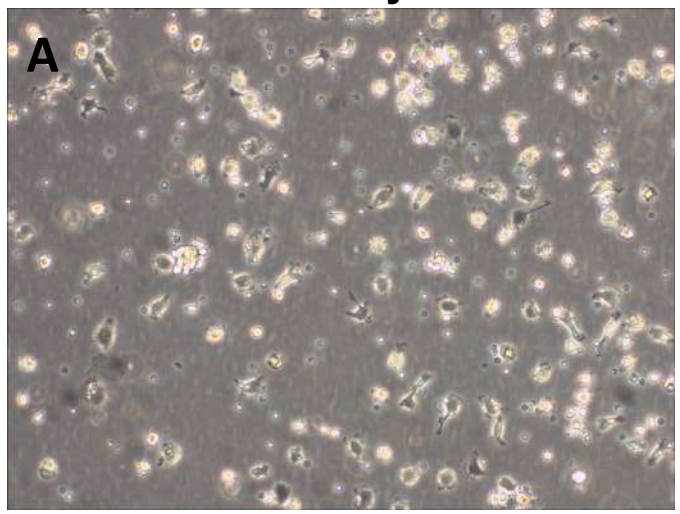
G. Kürkçü, S. i. Deliloğlu Gürhan, H.S. Vatansever, Comparion of chondrocytes derived from either mouse embryonic or mouse bone marrow mesencymal cells, Ege BAP. (A part of them published Cell & Tissue, 2017)

Bone Marrow Mesencyhmal Stem Cells-Culture and Differentiation

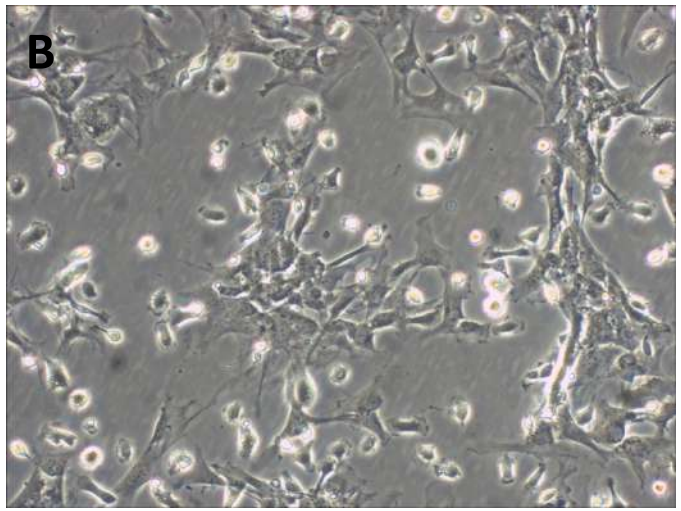


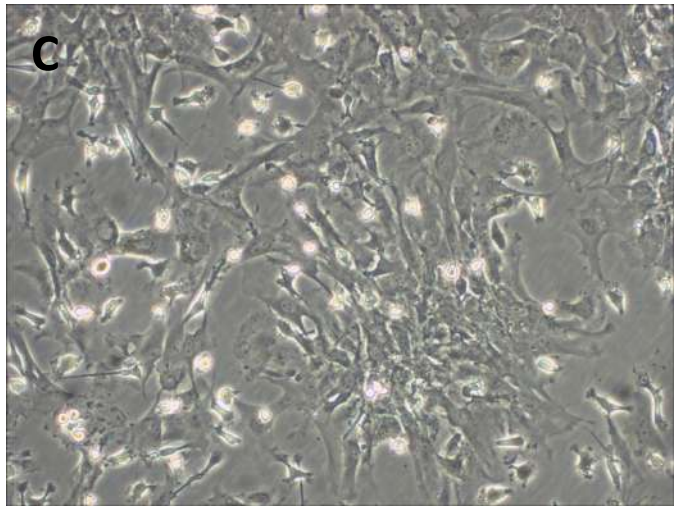
Bone Marrow Mesencyhmal Stem Cells-Culture and Differentiation

3. day



6. day

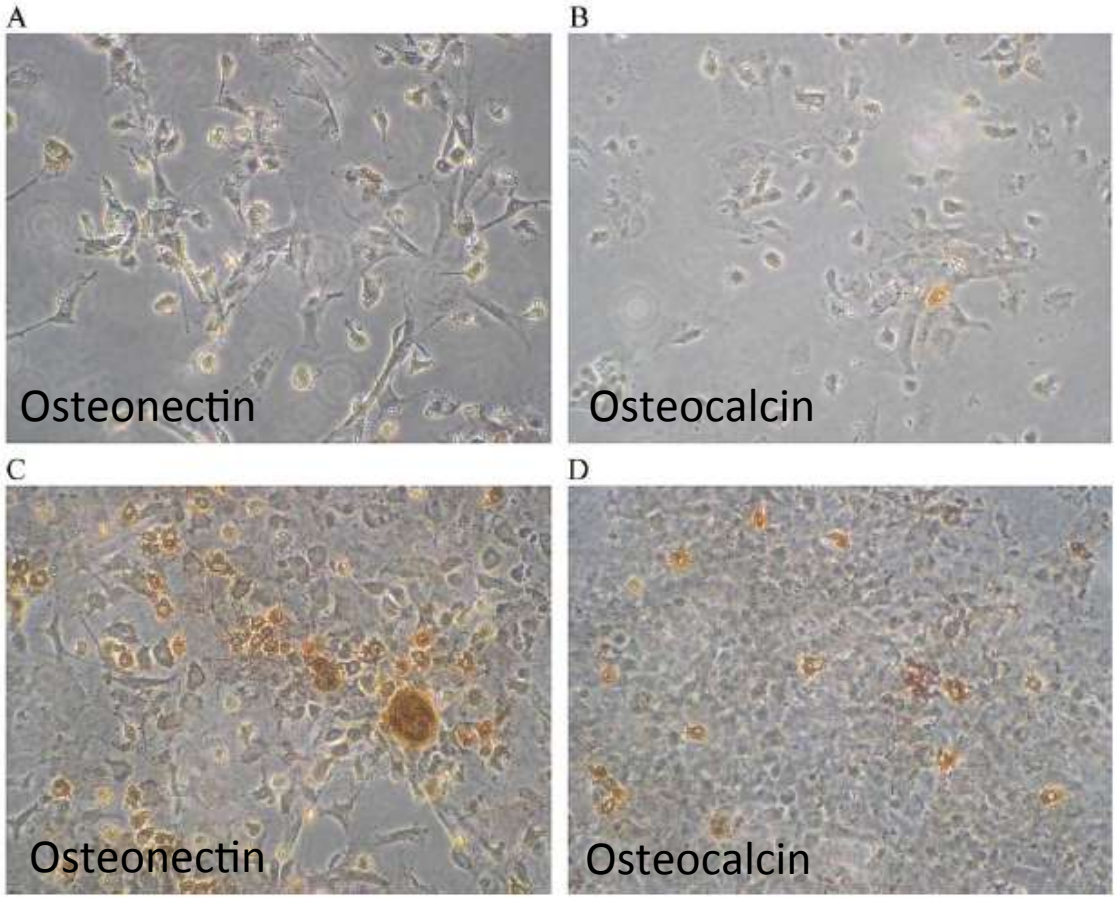




9. day

Bone Marrow Mesencyhmal Stem Cells- Osteoblast

CONTROL MEDIUM



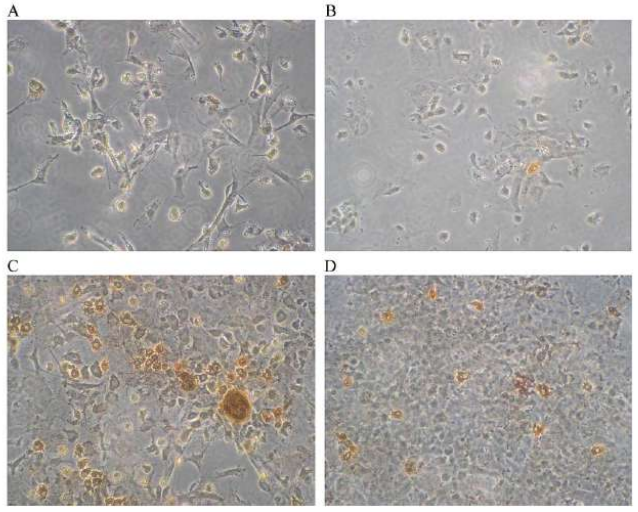
OSTEOGENIC MEDIUM

7 day of culture

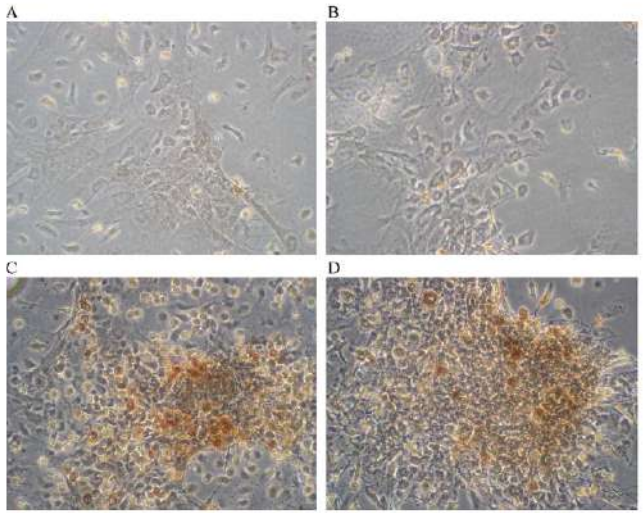
S.I. Deliloglu-Gurhan, H.S. Vatansever,, F. Ozdal-Kurt, I. Tuglu, Characterization of osteoblasts derived from bone marrow stromal cells in a modified cell culture system. Acta Histochemica, Acta Histochem. 108(1):49-57, 2006 Jan 27.

Bone Marrow Mesencyhmal Stem Cells- Osteoblast

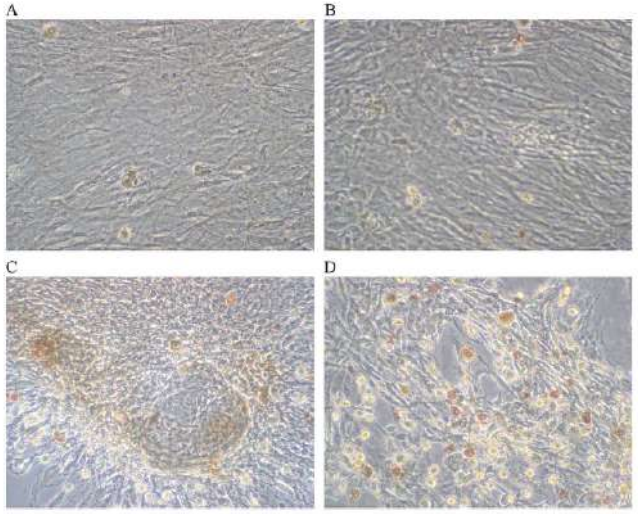
7 day



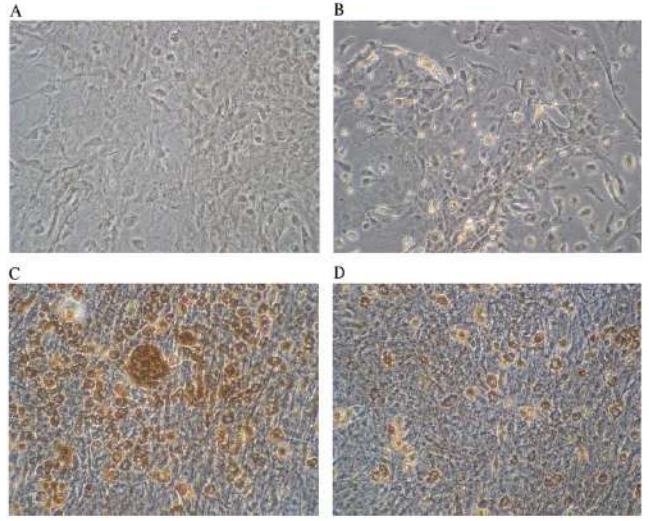
10 day



14 day

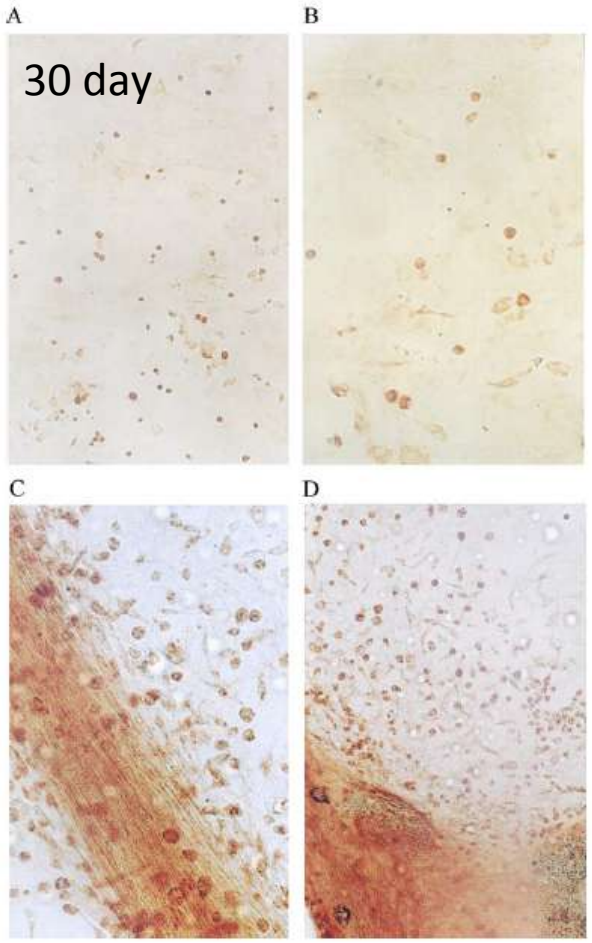


21 day

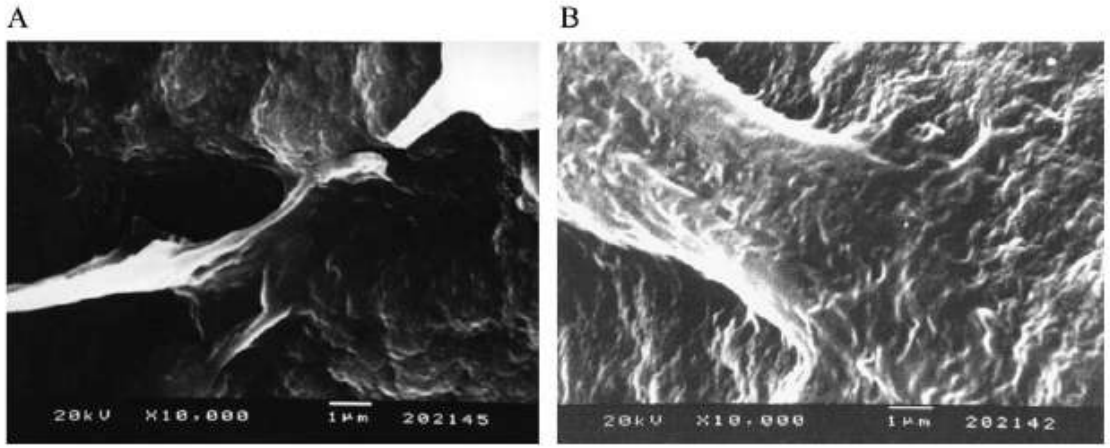


S.I. Deliloglu-Gurhan, H.S. Vatansever,, F. Ozdal-Kurt, I. Tuglu, Characterization of osteoblasts derived from bone marrow stromal cells in a modified cell culture system. Acta Histochem. 108(1):49-57, 2006.

Bone Marrow Mesencyhmal Stem Cells- Osteoblast



Mineralization and matrix formation



BMSCs cultured in OM on the HA-gel spread more and were more adhesive with a more epithleoid morphology giving a greater area of cytoplasm and longer cytoplasmic protrusion.

S.I. Deliloglu-Gurhan, H.S. Vatansever,, F. Ozdal-Kurt, I. Tuglu, Characterization of osteoblasts derived from bone marrow stromal cells in a modified cell culture system. Acta Histochem. 108(1):49-57, 2006.

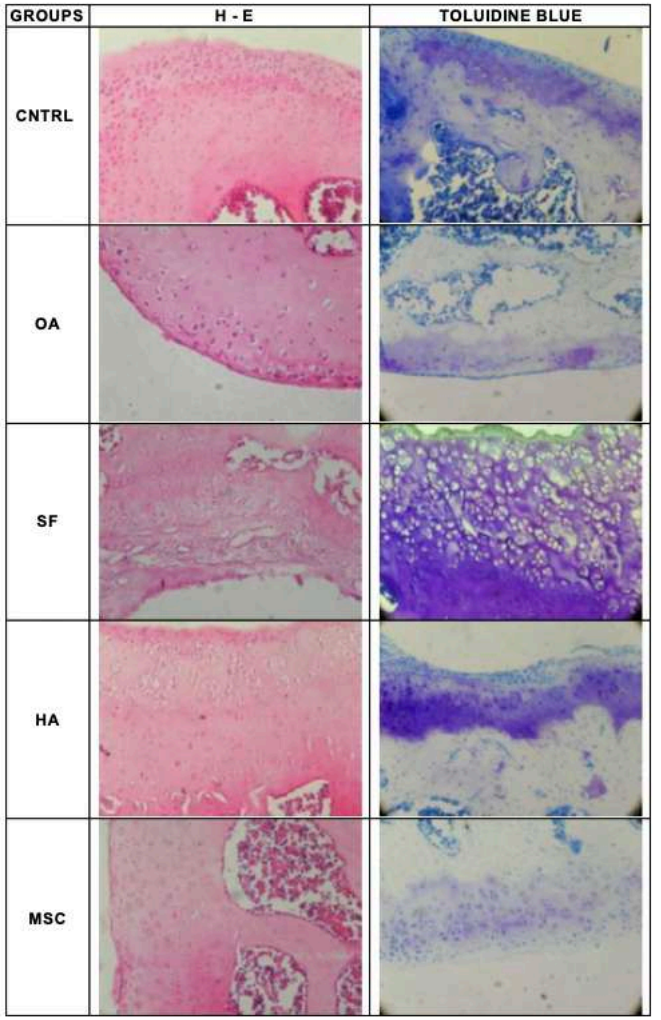
Osteoarthritis Experimental Model

- Pathogenesis and pathophysiology of disease processes are typically studied using small animal models.
- Although tiny animals have smaller joint sizes, thinner articular cartilage, and a greater cartilaginous defect regeneration rate than humans, small animal models offer the advantages of being relatively inexpensive, growing more quickly, and being easier to create

Osteoarthritis Experimental Model

- Experimental chronic OA model
  - Control group
  - OA group
  - SF group
  - HA group
  - MSC group

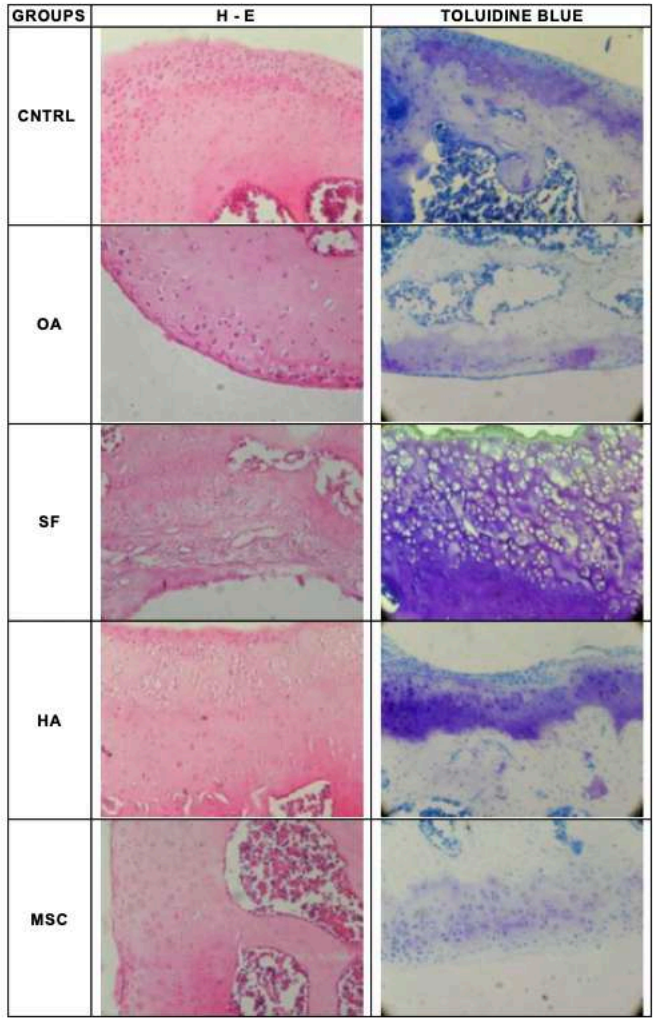
The hypertrophic condrocytes were more abundant in both SF and HA groups, however, the number of these cells were less in MSC group with hyaline-like cartilage matrix synthesis



G. Mete, F. Ozdal Kurt, H. S. Vatansever, B. Kahraman, M. Çapkın, I. Deliloglu Gurhan, İ. H. Gunal, O. A. Bora. Improved Cartılage Regeneratıon Transferring Mesenchymal Stem Cells From Bone Marrow On Osteoarthritis Model In Rat

Osteoarthritis Experimental Model

- **Control (CNTRL) group:** Less mineralization at the joint surface and intense mineralization in the proliferative zone were detected. Normal cells, hypertrophic and picnotic nucleated cells were observed.
- **OA group:** Mineralization density was more intense at the proliferation zone, it was lesser in joint and bone surface. But this mineralization was much less in both SP and HA group, however, it was similar with MSC group. Rare hypertrophic hypertrophic and picnotic nucleated cells were observed.
- **SF group:** While mineralization and proteoglycan has a lot more intense in SF group after Toluidine blue staining, this intensity continued into the articular surface. In addition, the number of hypertrophic cells were much more in this group when compared to the MSC and control groups. Picnotic nucleated cells were also observed in some places.



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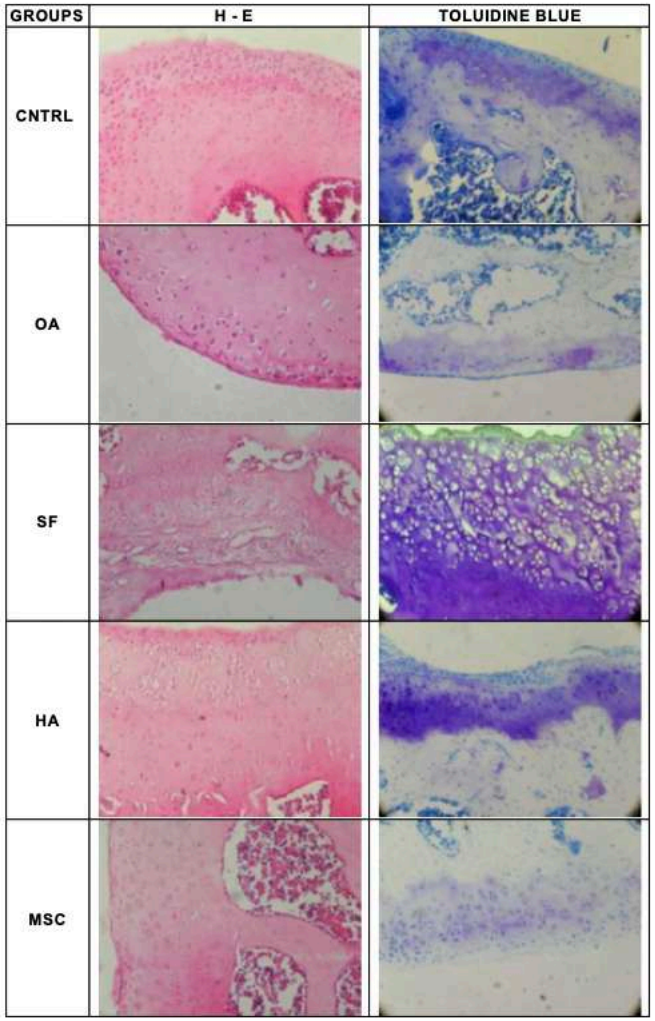
Osteoarthritis Experimental Model

- **HA group:** Mineralization at the bone place were more in than at the joint surface and proliferation zone. This intensity was lesser than MSC and control groups, but it was similar with SF group. However, hypertrophic cells were more than other groups.
- **MSC group:** Less mineralization at the joint surface, intense minerilization at the zone of proliferation region were detected. But this intensity was less than in SF and HA groups. Rare hypertrophic and picnotic cells were observed**.**



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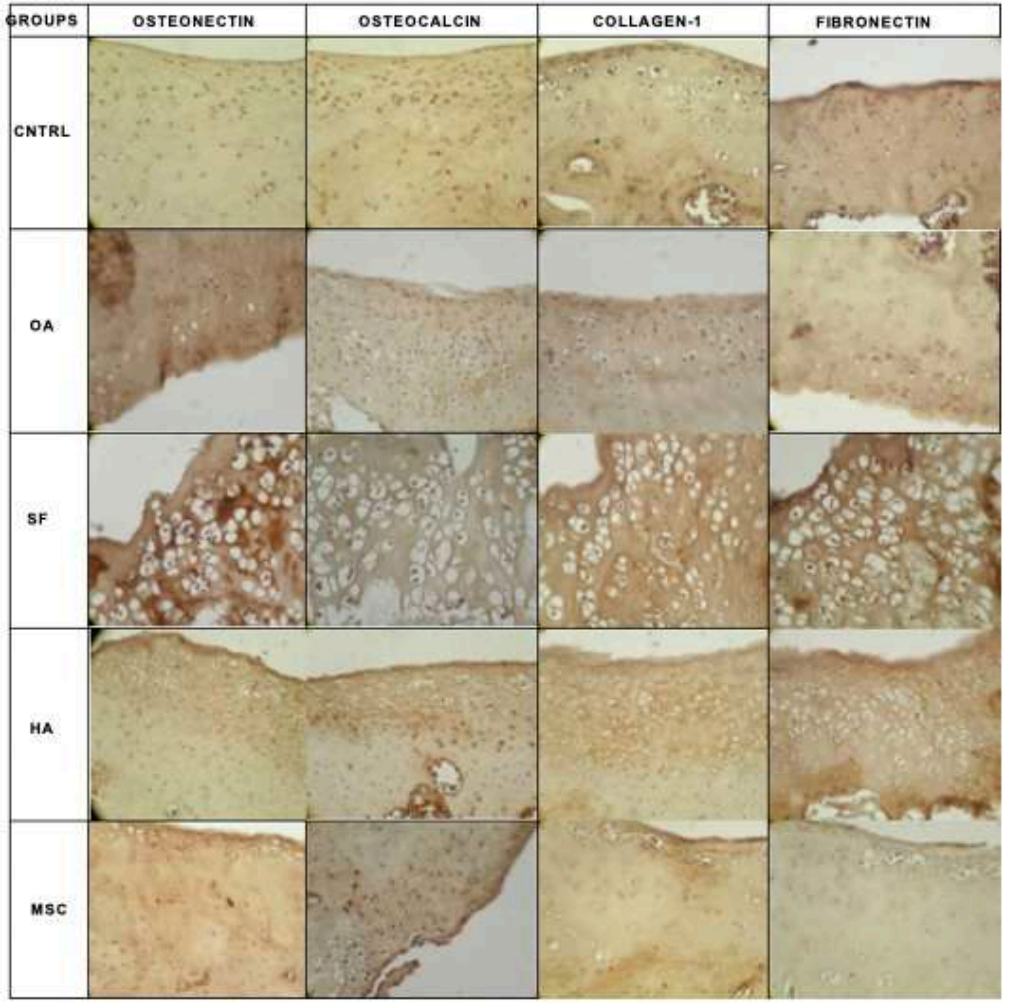
Osteoarthritis Experimental Model

- While fibronectin immunoreactivity was similar in all groups, the positive immunoreactivities of collagen-1, osteonectin and osteocalcin were observed in MSC group.
- This study demonstrates that **MSC cells transplanted into cartilage defects stimulate the repair process to promote better organization than other group.**



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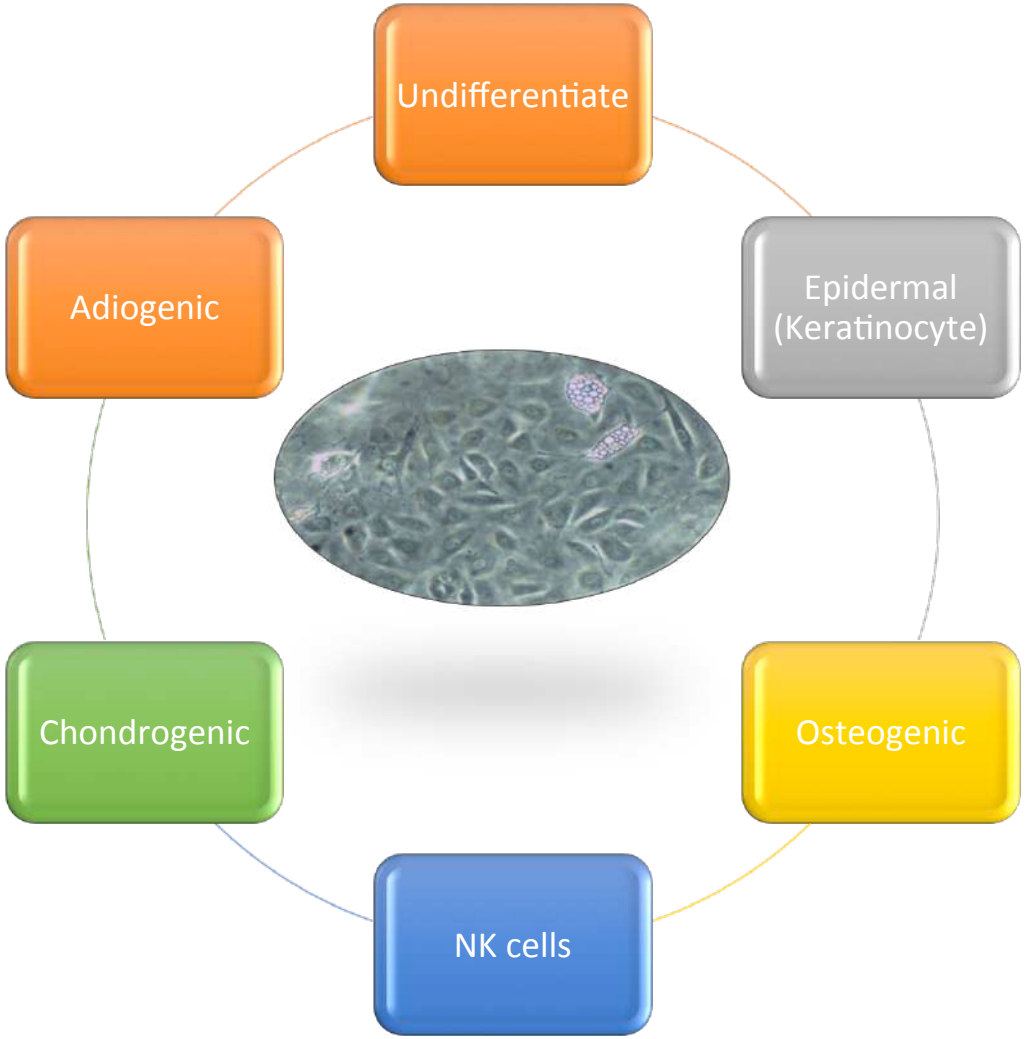
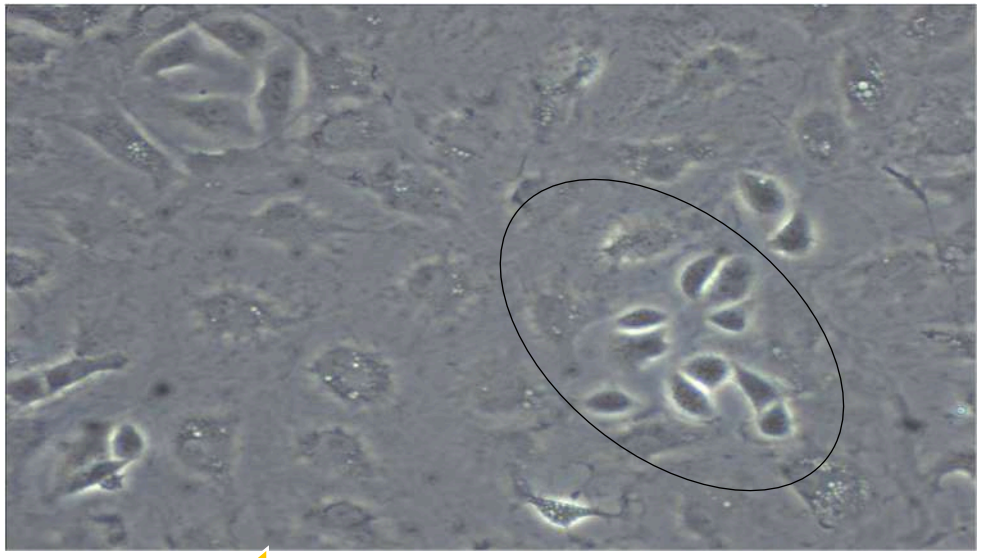
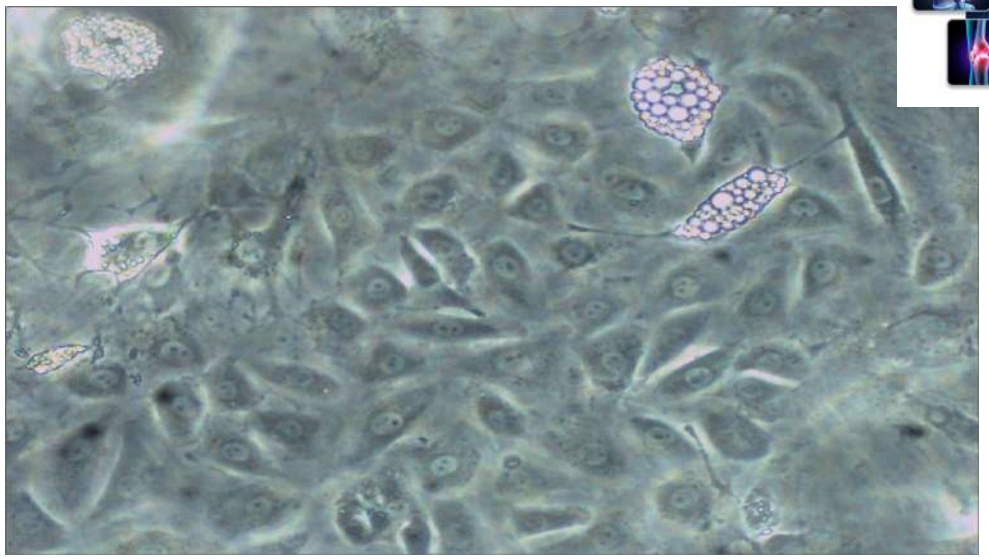
Adipogenic Mesencyhmal Stem Cells-Culture and Differentiation



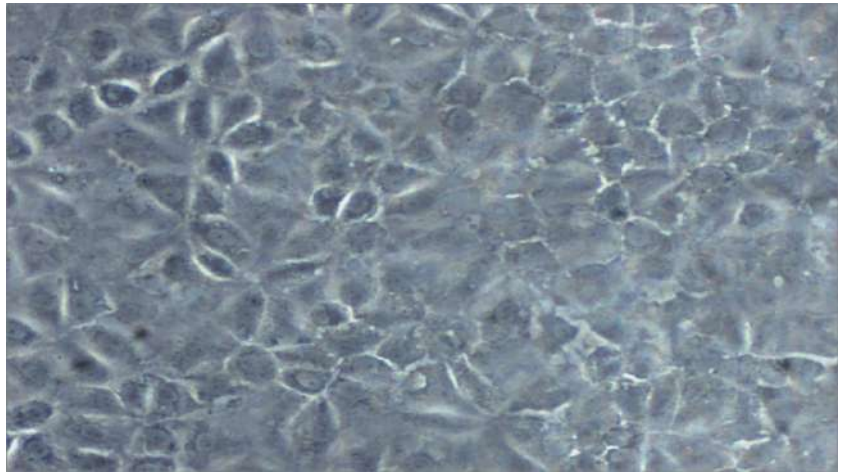
Adipogenic Mesenchymal Stem Cells- Chondrogenic Differentiation

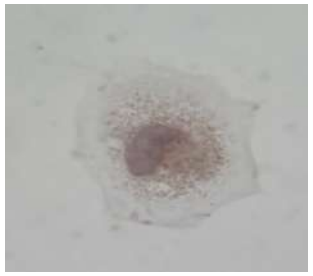




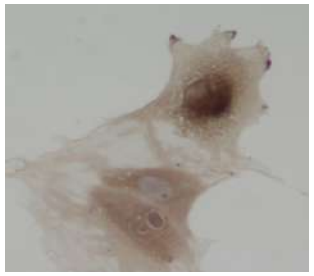
0.075 % Collagen 1

Chondrogenic Differentiation Media





Collagen-II

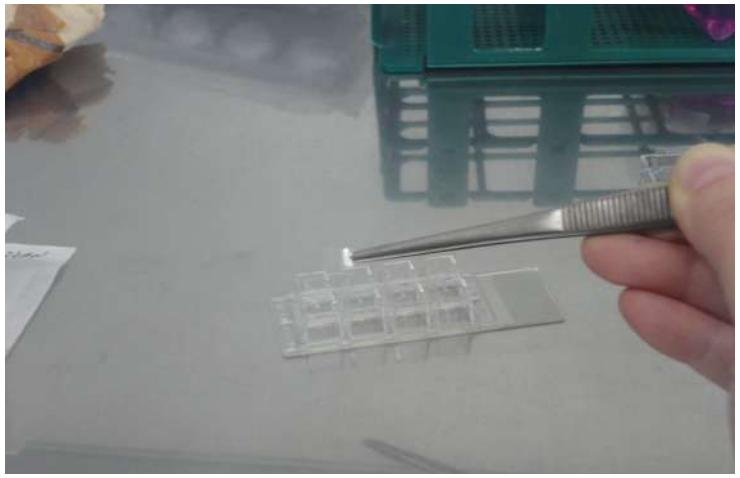


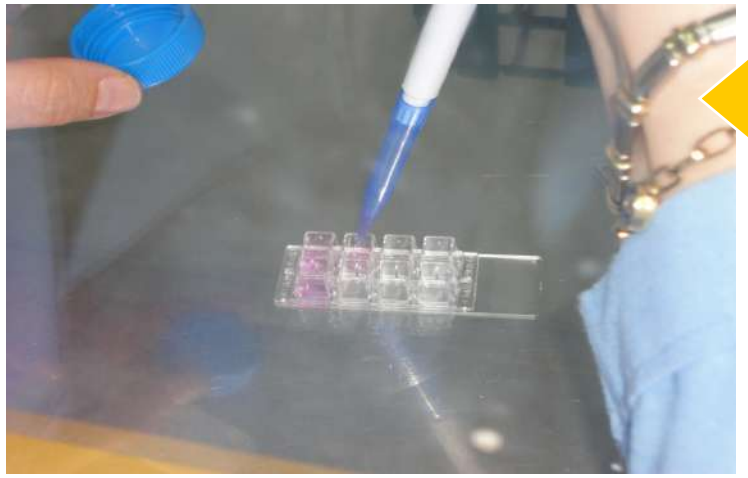
Aggrekan

Sox-9

Uz U, Gunhan K, Vatansever HS, Kıvanç M., Yuceturk AV. Novel simple strategy for cartilage tissue engineering using stem cells and synthetic polymer scaffold. Journal of Craniofacial Surgery 30(3), 940-943, 2019

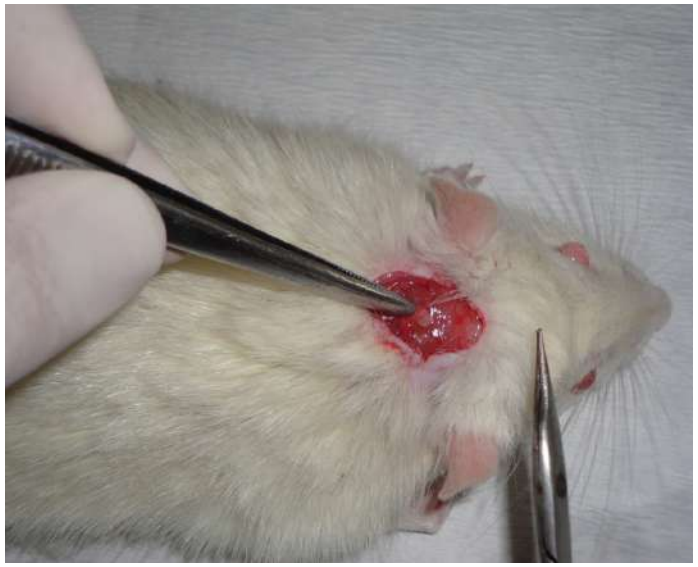
Adipogenic Mesenchymal Stem Cells- Chondrogenic Differentiation

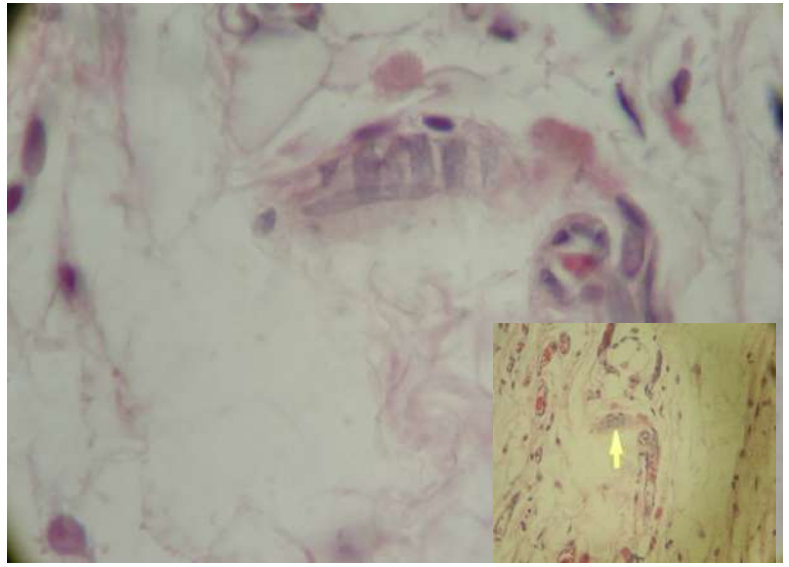




Vivosorb

Differentiated cells

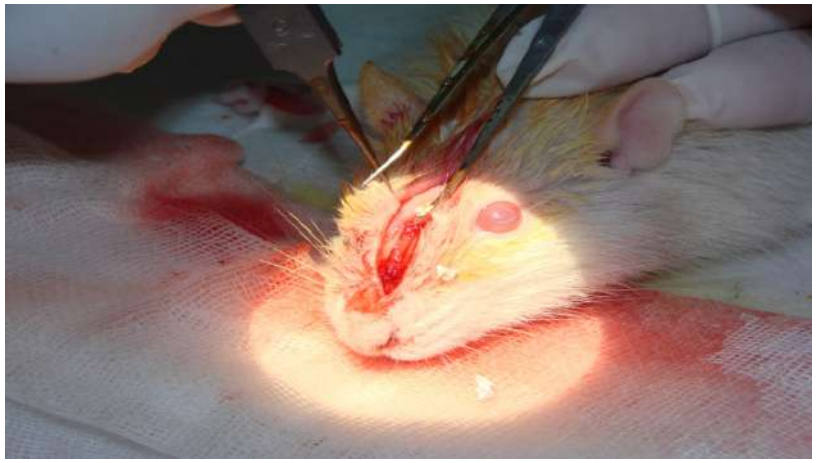
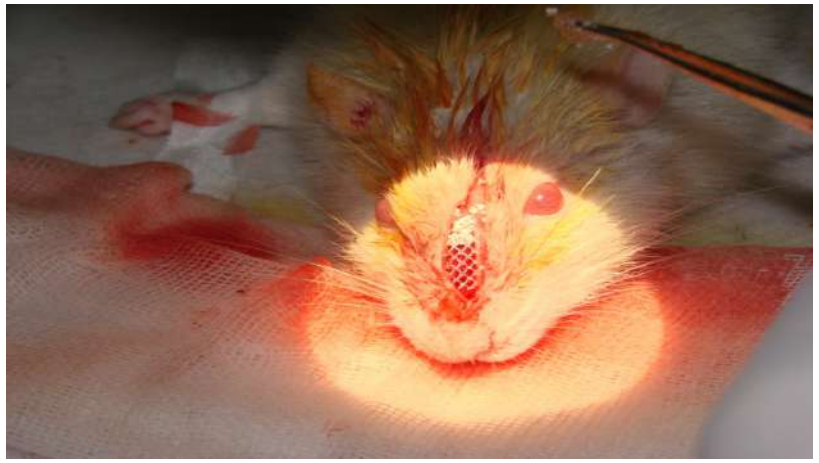
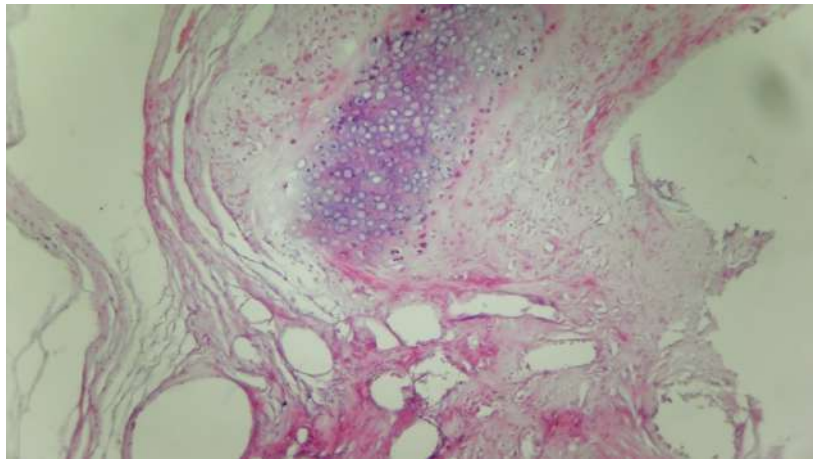
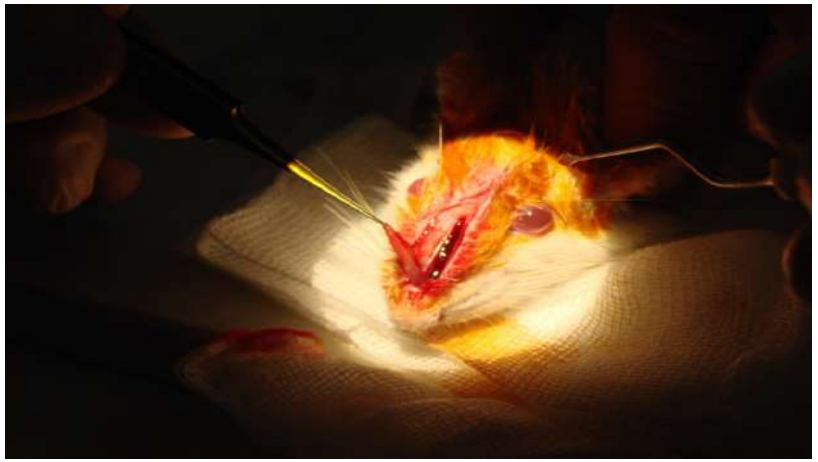
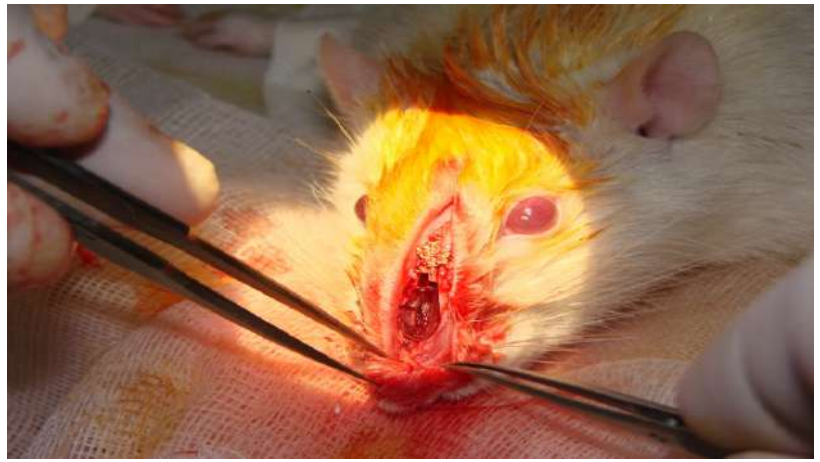
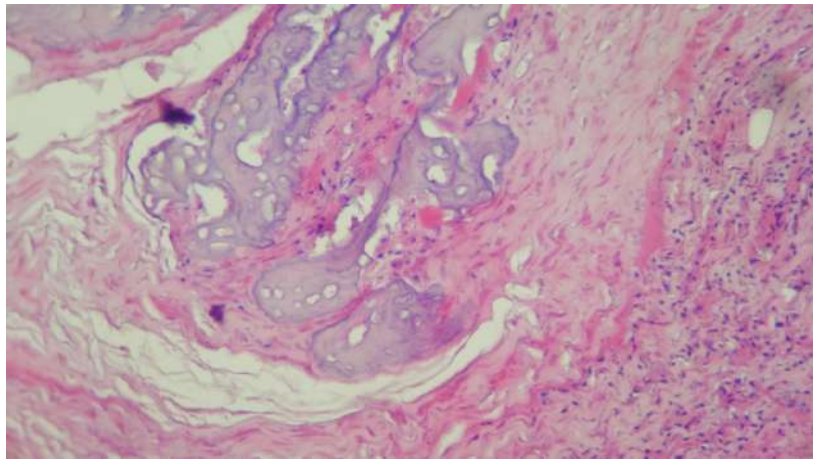




H-E Staning

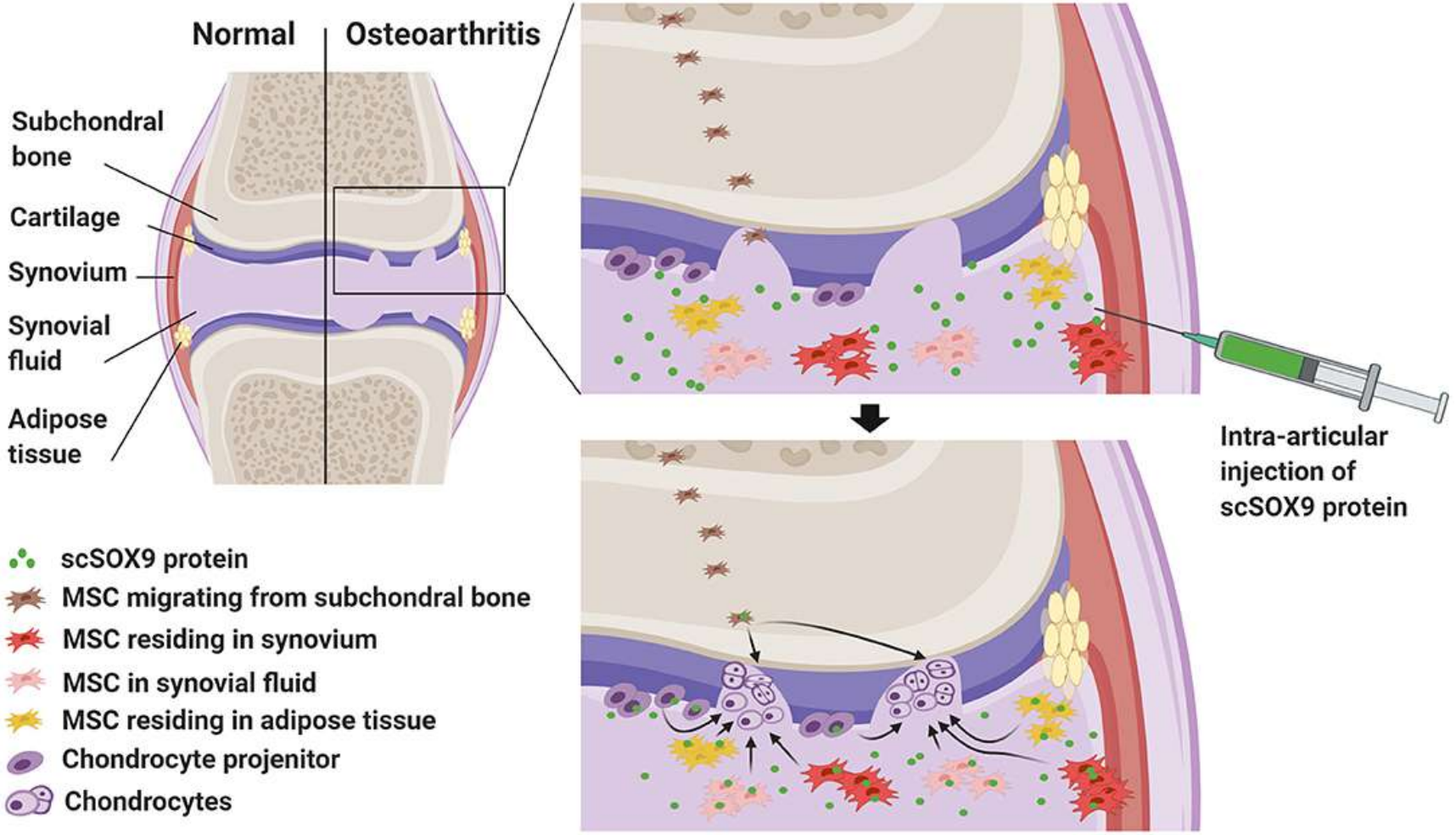
Uz U, Gunhan K, Vatansever HS, Kıvanç M., Yuceturk AV. Novel simple strategy for cartilage tissue engineering using stem cells and synthetic polymer scaffold. Journal of Craniofacial Surgery 30(3), 940-943, 2019

Adipogenic Mesenchymal Stem Cells-Chondrogen Nose Septal Defects

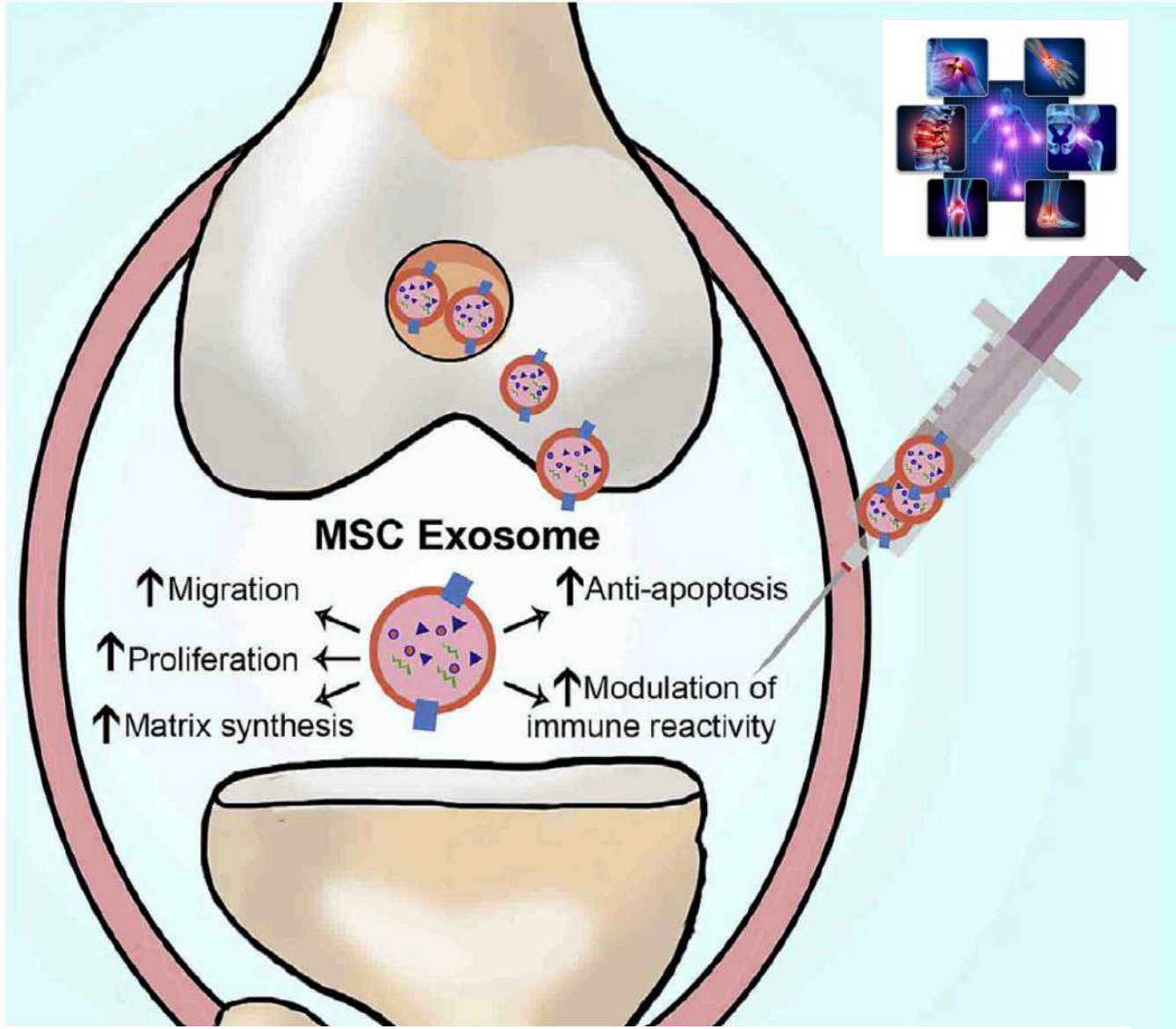
K Gunhan, S Guven, S Gökalp, A Aslan, H. Seda Vatansever. Using nasal mucosa and chondrocytes derived from adipogenic stem cells as a nasal septum. CBU BAP 2013-2015.

- MSC-mediated chondrogenesis since elevated concentrations of IL-1β suppress expression of SOX9, an essential transcription factor involved in early chondrogenesis.



BM-MSC-derived exosomes

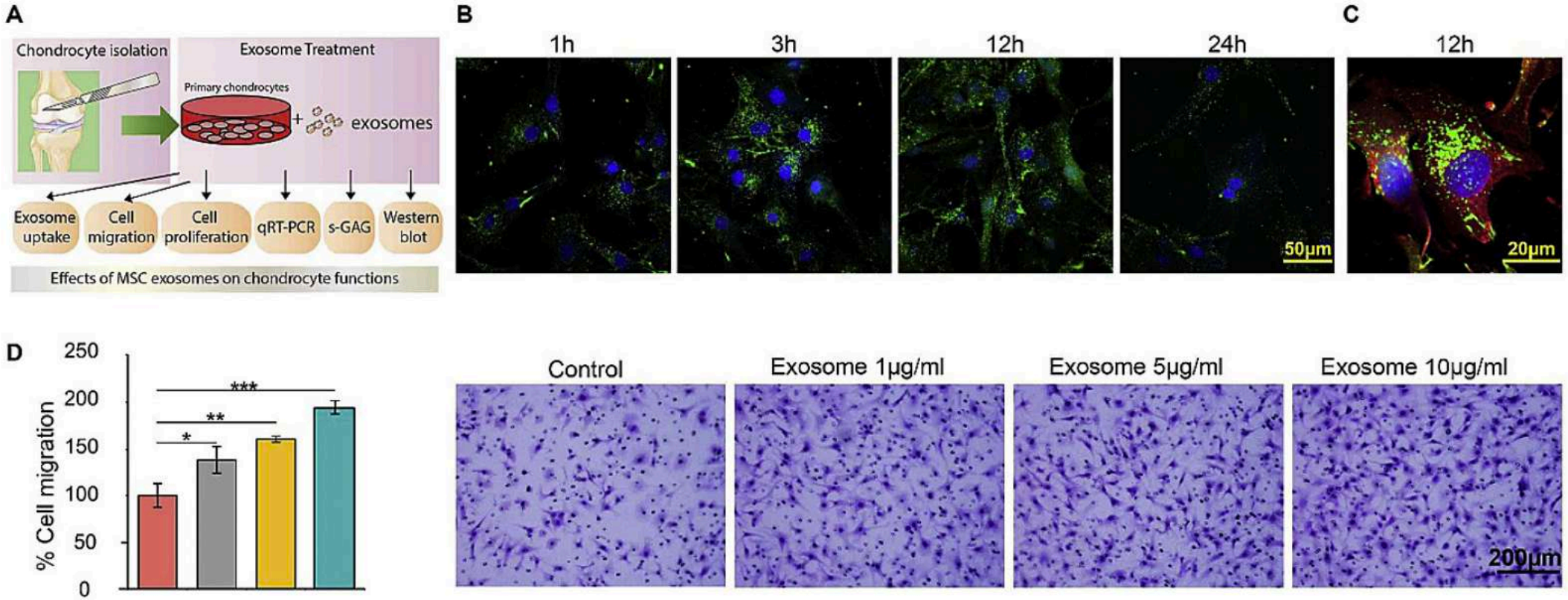
- Up-regulated expression of 35 exosomal miRNAs
  - miR-1246,
  - miR-1290,
  - miR-193a-5p,
  - miR-320c,
  - miR-92
- down-regulated expression of 106 miRNAs
  - miR-377-3p and miR-6891-5p



promoted chondrogenesis, induced chondrocyte proliferation suppressed cartilage degradation

H. Sun, S. Hu, Z. Zhang, J. Lun, W. Liao, Z. Zhang, Expression of exosomal microRNAs during chondrogenic differentiation of human bone mesenchymal stem cells, J. Cell. Biochem. (2018)

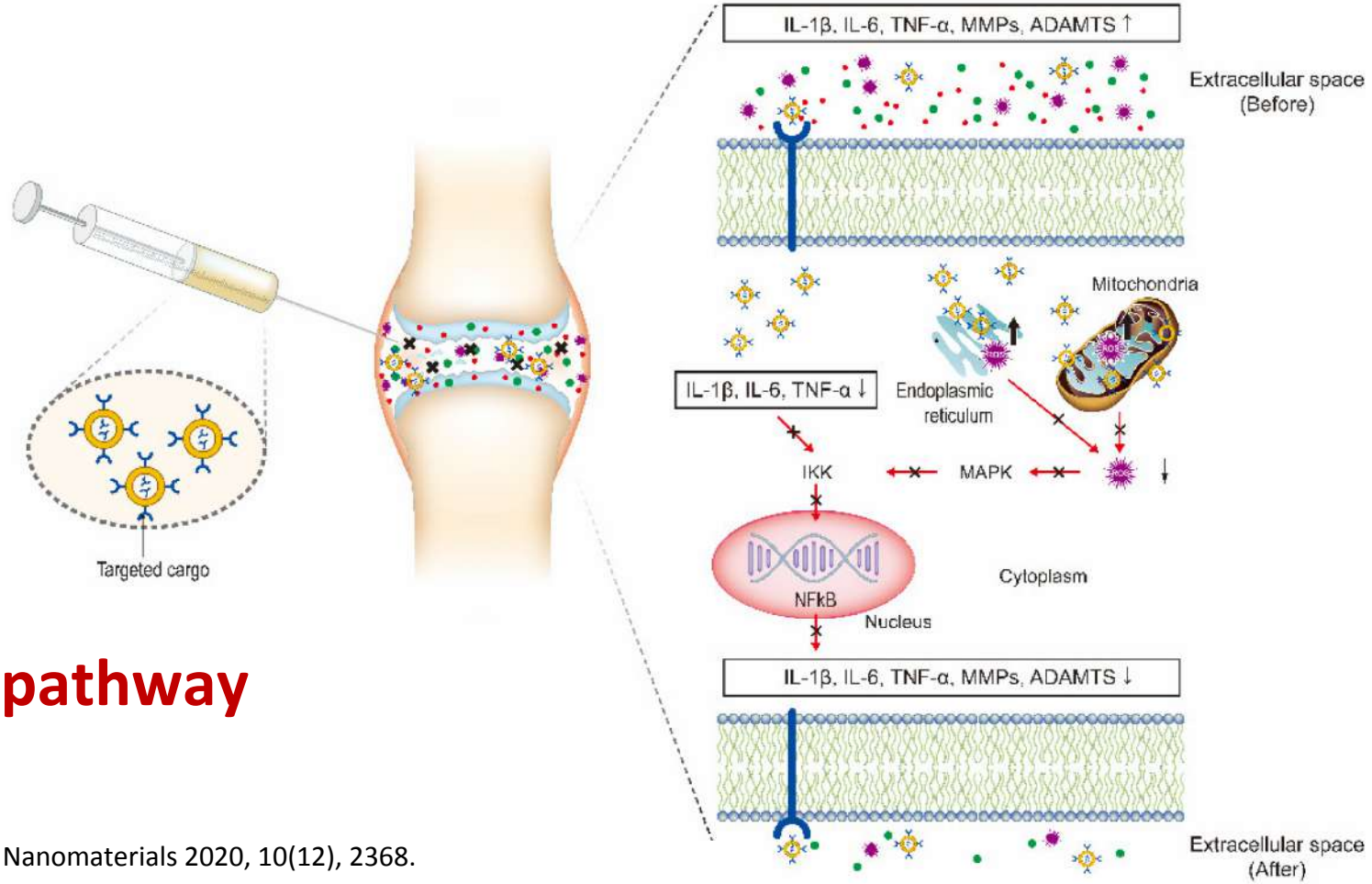
Engineering MSCs and MSC-EVs



H. Sun, S. Hu, Z. Zhang, J. Lun, W. Liao, Z. Zhang, Expression of exosomal microRNAs during chondrogenic differentiation of human bone mesenchymal stem cells, J. Cell. Biochem. (2018)

- **Intra-articular (IA) delivery of cargo-loaded nanoparticles for the treatment of OA.**

- The therapeutic effects are obtained by the NPs targeting the three major factors including;
  - inflammatory factors,
  - proteolytic enzymes,
  - reactive oxygen species (ROS)



to inhibit NF-κB signaling pathway

Jin G-Z. Current Nanoparticle-Based Technologies for Osteoarthritis Therapy. Nanomaterials 2020, 10(12), 2368.

MSC- Autophagy in injured chondrocytes

- Autophagy is activated in early stage of OA as an adaptive response to cell stress that protects chondrocytes from cell death and maintains homeostasis within cartilage tissue
- ADMSCs alleviated osteoarthritis and inhibited cartilage degeneration in Hulth rat model. These results are in line with the previous studies.
- ADMSCs reduced the secretion of proinflammatory cytokines and protected against apoptosis through autophagy inducing.

How Can Be Induce Cartilage Restoration ?

- Widely used for cell-based therapy in various medical fields, mesenchymal stem cells (MSCs) show capacity for anti-inflammatory effects, anti-apoptotic activity, immunomodulation, and tissue repair and regeneration.
- As such, they can potentially be used to treat osteoarthritis (OA).
- However, MSCs from different sources have distinct advantages and disadvantages, and various animal models and clinical trials using different sources of MSCs are being conducted in OA regenerative medicine.

How Can Be Induce Cartilage Restoration ?

- It is now widely believed that the primary tissue regeneration impact of MSCs is via paracrine effects, rather than direct differentiation and replacement.

- Cytokines and molecules produced by MSCs, including extracellular vesicles with mRNAs, microRNAs, and bioactive substances, play a significant role in OA repair.

Osteoarthritis

- While the etiology of OA remains poorly understood, it is well recognized that OA is a complex and multifaceted disease with a hallmark of articular cartilage degradation that is resulted from chondrocyte degeneration and destruction of cartilage matrix

- It has been generally believed that cartilage lacks intrinsic capacity of self-regeneration once it is damaged.

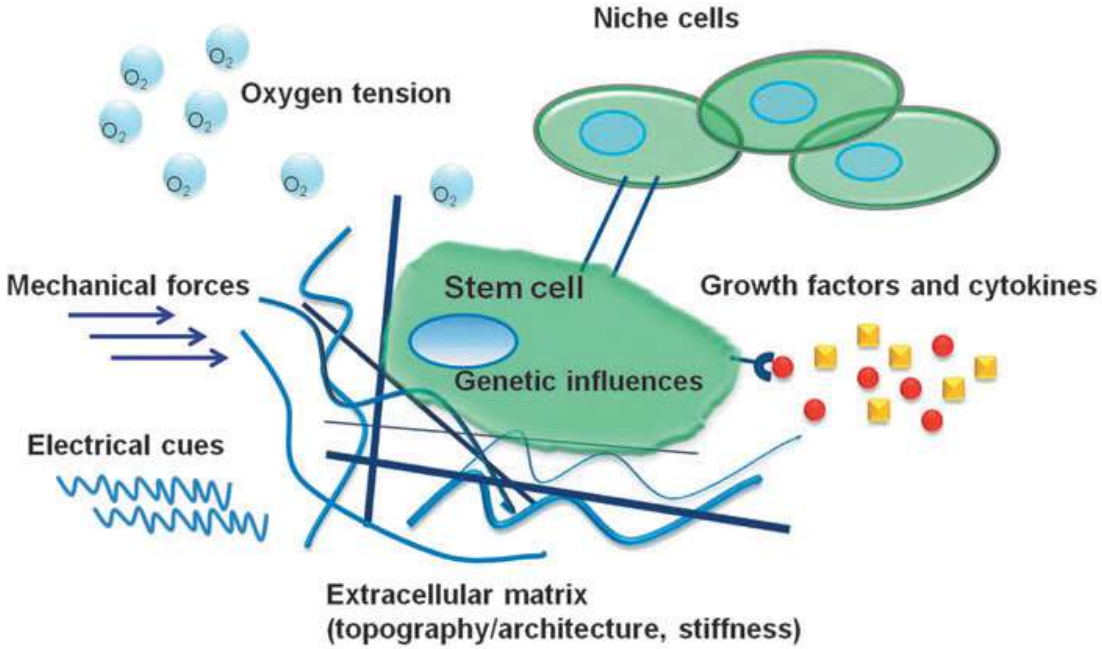
Osteoarthritis

- The lack of effective treatment options for osteoarthritis is mostly due to the very limited regenerative capacity of articular cartilage.

- **Restoration of chondrocyte population is critical in cartilage regeneration**

How Can Be Induce Cartilage Restoration ?

- It is necessary to develop new therapeutic strategies using tissue engineering techniques with or without cells.



How Can Be Induce Cartilage Restoration ?

- MSCs administered directly into synovial fluid vanished within a few days, and cell retention was approximately 3%.

- It was now widely believed that paracrine might be the primary therapeutic impact of MSCs promote cartilage regeneration in OA in part by secreting cytokines, including growth factor, tumor necrosis factor-α-induced protein 6 (TNFAIP6/TSG-6), prostaglandin-E2 (PGE2), and indoleamine 2, 3-dioxygenase (IDO).

How Can Be Induce Cartilage Restoration ?

- Under hypoxic culture conditions, MSC-secreted TGF-β1 suppressed the hypertrophic chondrocyte marker COL1 expression.

- TGF-β1 also induces the regulation of immunological response in T cells.110, 111 TGF-β1 secreted by MSCs stimulated chondrogenic proliferation

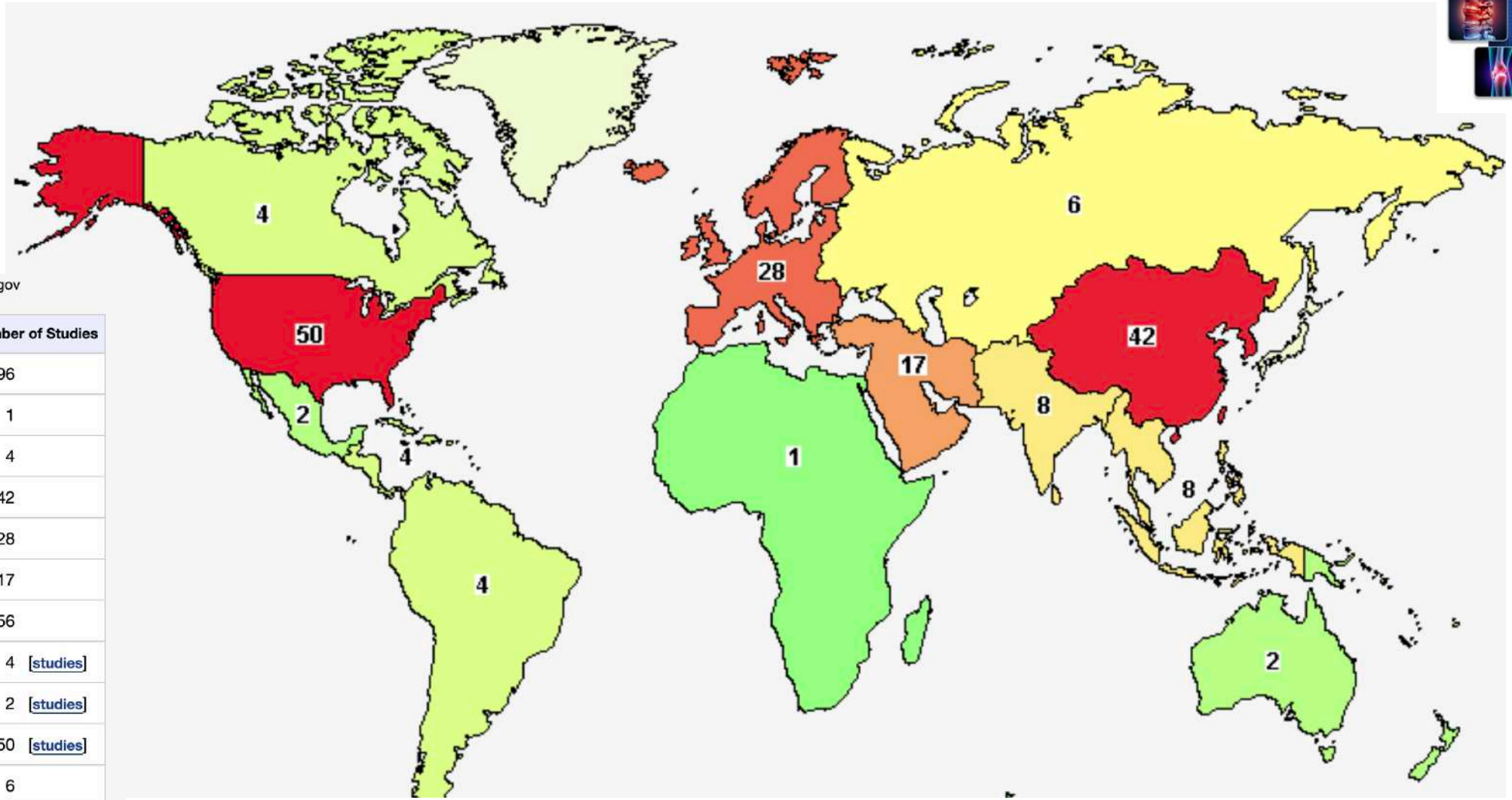
How Can Be Induce Cartilage Restoration ?

- Both biomaterials and stem cells including mesenchymal and induced pluripotent stem cells can provide a good source for tissue engineering.
- These two type of stem cells can be obtain as autologous which is important advantages for cellular therapy. Mesenchymal stem cells can be differentiating under suitable culture condition to other type of cells such as osteoblast, chondroblast etc.
- Secreted proteins, microvesicules or exsomes form stem cells are also detected.
- Therefore, rather than stem cells, the products secreted by stem cells may be alternate direction for OA treatment.

How Can Be Induce Cartilage Restoration ?

- Because of regulating of local microenvironment through paracrine nutritional factors and control of immune regulation during OA, it should be main aim for regeneration and repair and subsequently delaying cartilage degradation and improving joint function.

- Therefore, future studies on stem cells or their secreted products aim for therapeutic mechanisms in OA.



Source:https://ClinicalTrials.gov

Region Name	Number of Studies
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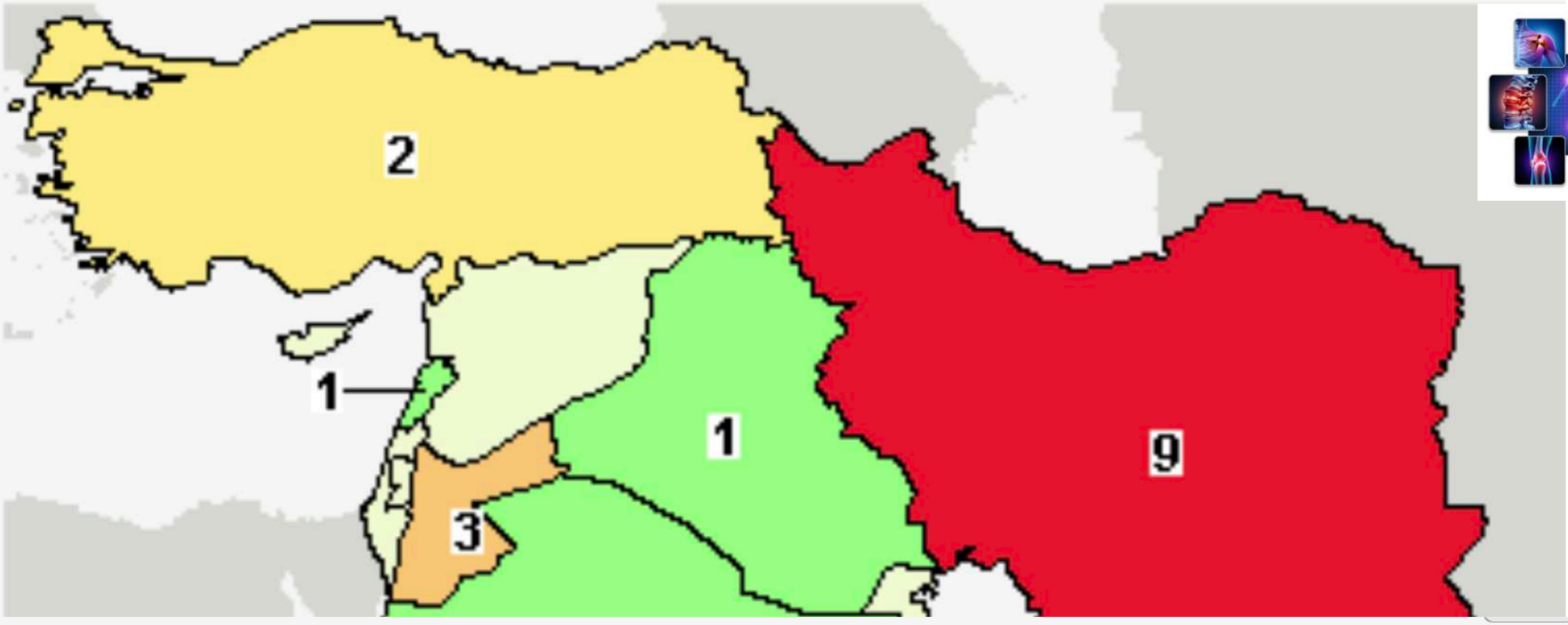
Africa [map]	1
Central America [map]	4
East Asia [map]	42
Europe [map]	28
Middle East [map]	17
North America	56
Canada [map]	4 [studies]
Mexico	2 [studies]
United States [map]	50 [studies]
North Asia [map]	6
Pacifica [map]	2
South America [map]	4
South Asia [map]	8
Southeast Asia [map]	8



Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Unknown †	WHARTON JELLY ORIGINATED MESENCHIAL **STEM CELL** in GONARTHROSIS	• **Stem Cell** • Gonarthrosis	• Biological: Wharton Jelly Originated Mesencimal **Stem Cell**	• Erciyes University Faculty of Medicine Melikgazi, Kayseri, **Turkey**
2	☐	Recruiting	**Stem Cells** and Stromal Vascular Fraction for Temporomandibular Joint Disease	• Temporomandibular Joint Disorders • Temporomandibular Disorder • Temporomandibular Joint **Osteoarthritis** • (and 2 more...)	• Biological: **Stem Cells**	• Erciyes University Kayseri, **Turkey**

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http://tip.cbu.edu.tr/temel-tip-bolumu/histoloji-embriyoloji.11713.tr.html