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Cellular Therapy and Stem Cell Production,
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ESTEM

Mesenchymal Stem Cell Treatment for Osteoarthritis

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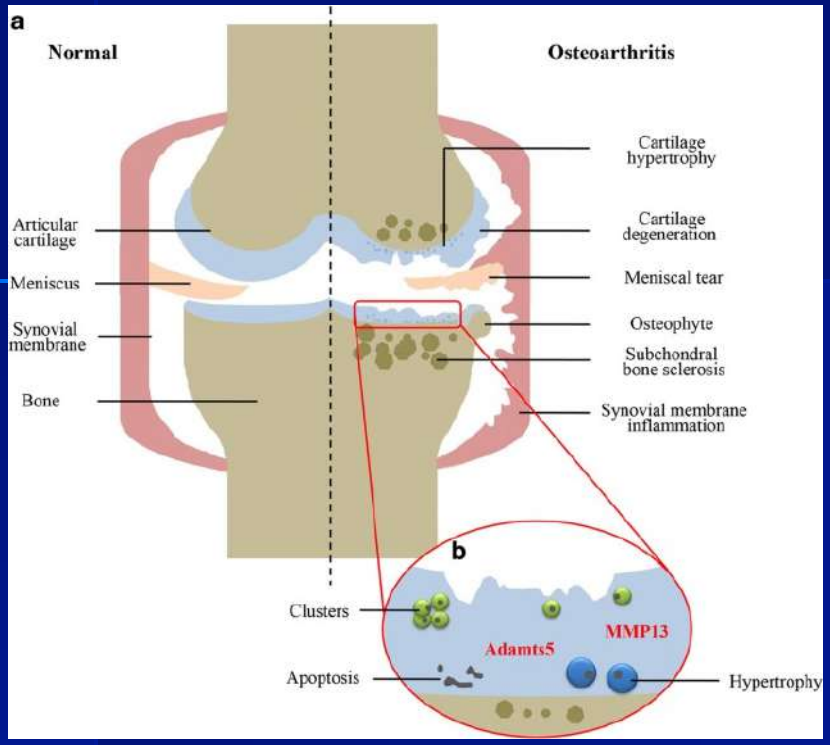
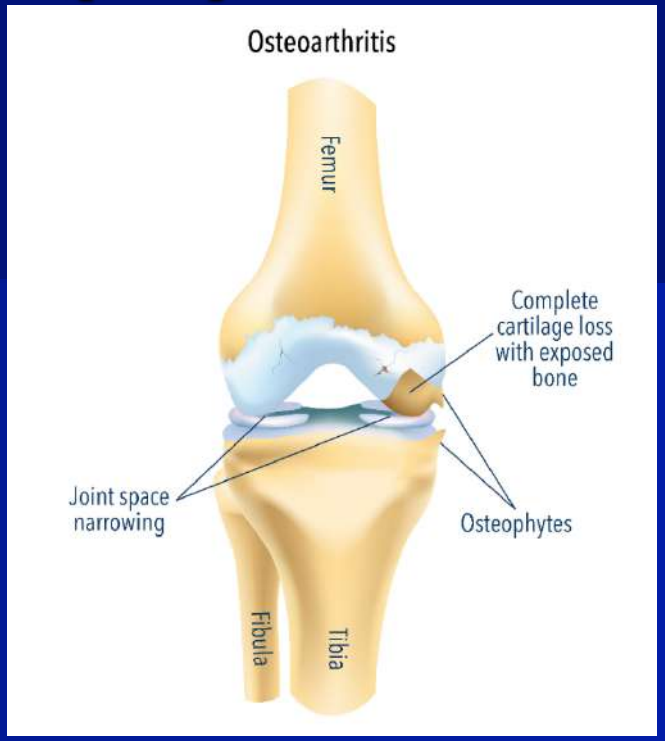
OSTEOARTHRITIS (OA)





- Osteoarhritis (OA) is the most common joint disease worldwide.
- OA is a joint disease characterized by degeneration of cartilage and inflammatory disease.
- OA is not an inactive degenerative disease; on the contrary, it is a dynamic disease caused by the imbalance between restoration and destruction of joints.
- Previously, known as a disease of elderly, but nowadays it has unfortunately been extended to youth and even childhood.

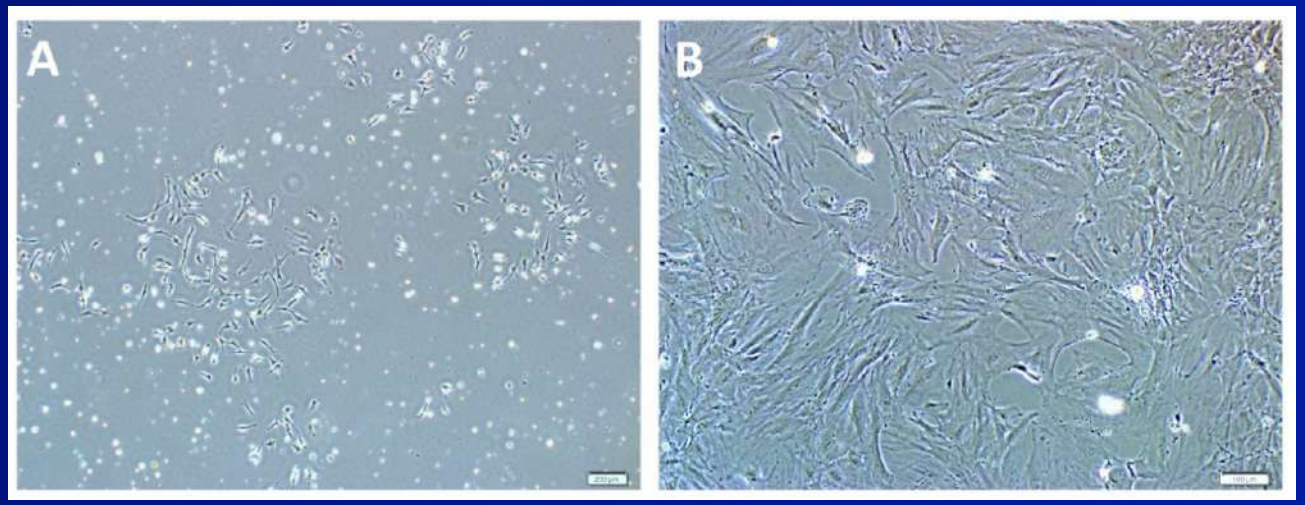
TREATMENT OF OA

- Current treatment options for OA:
  - Non-pharmacological therapy (Self-management, regular exercise, strength training, and weight control)
  - Pharmacological therapy (acetaminophen, non-steroidal anti-inflammatory drugs, and opioid analgesics, glucosamine and chondroitin, intra-articular steroids, hyaluronic acid and platelet-rich plasma)
  - Surgical Therapy (joint arthroplasty)
- Unfortunately, these options do not have an effective treatment.
- Therefore, the primary treatment goals for OA are to reduce pain and slow or halt the progression of the disease.
- **As a result, there is no gold standard treatment option for OA !!!**

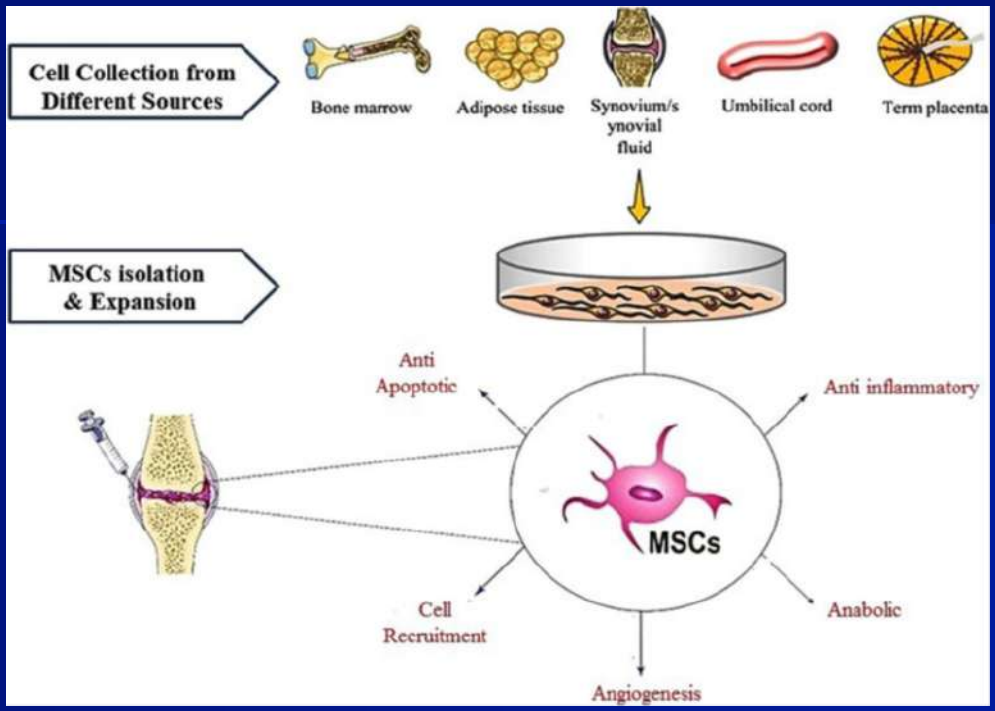
MESENCHYMAL STEM CELL-BASED THERAPY FOR OA

- **As a result, there is no gold standard treatment option for OA !!!**

- Therefore, stem cells have come to the forefront as an effective alternative treatment, especially with their regenerative and anti-inflammatory abilities.

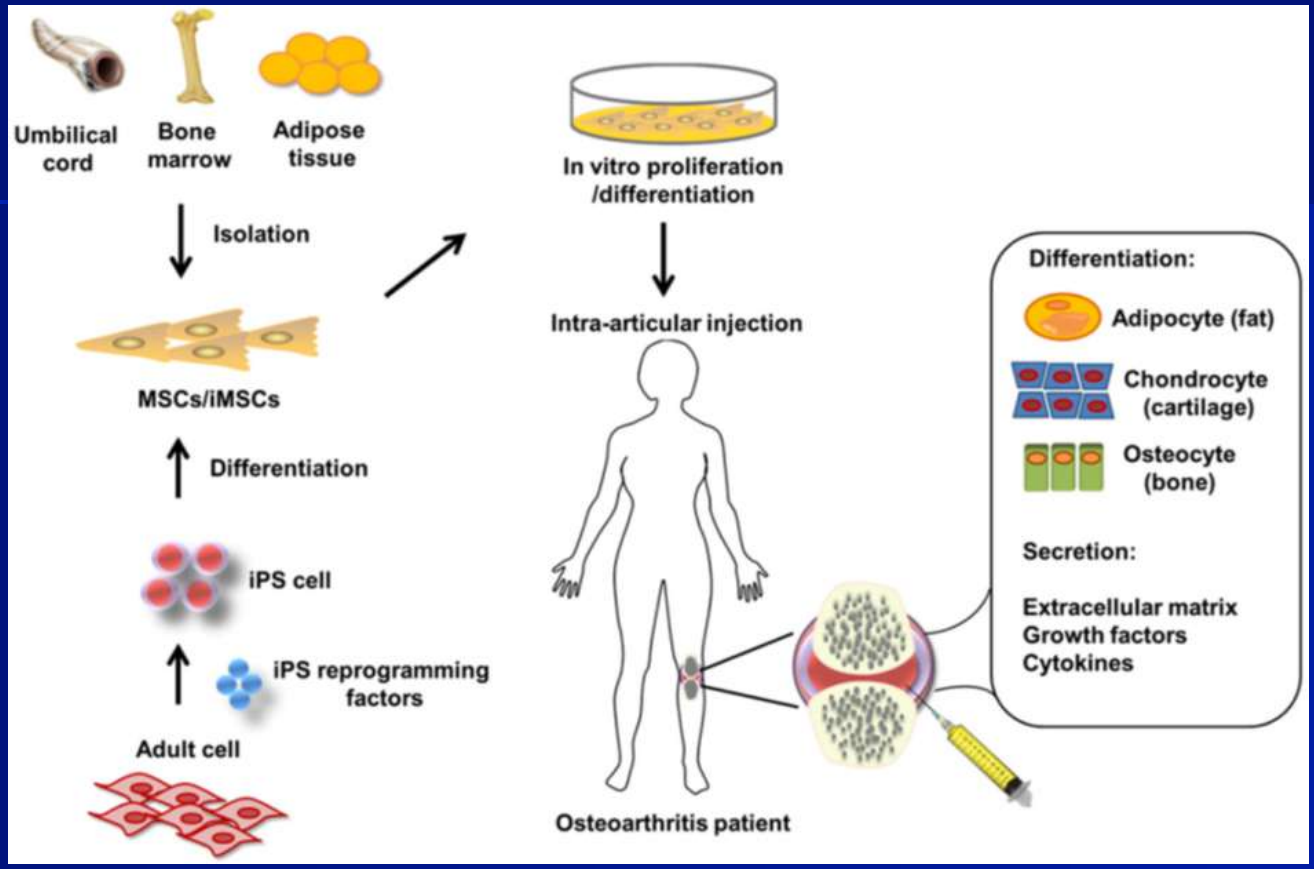


MESENCHYMAL STEM CELLS (MSCs)



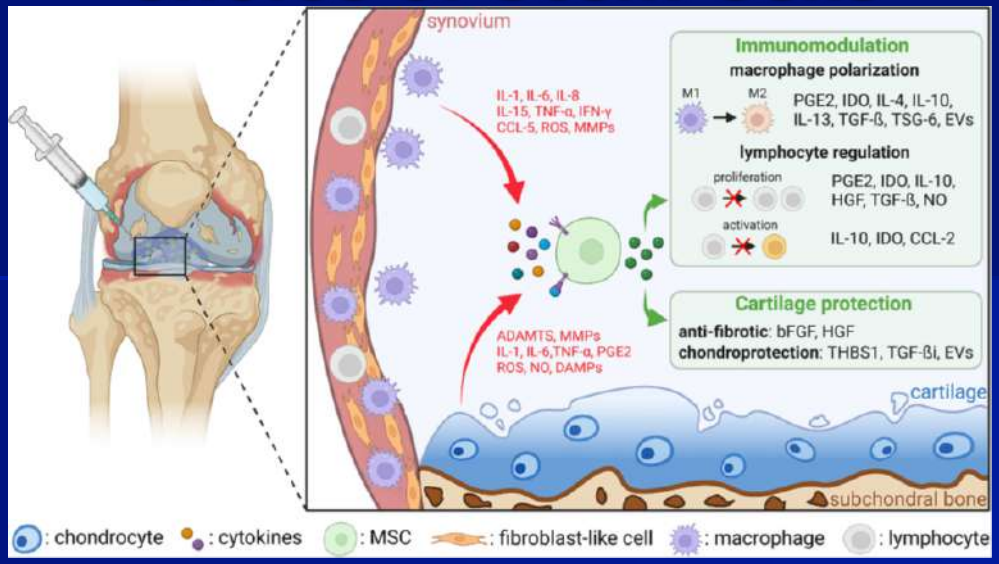
- The principal objective of regenerative medicine is to repair defectives or aged tissues by preserving their morphology and function.
- What should be considered is;
  - **which type is the most suitable stem cell population** for cartilage repair and anti-inflammatory effect.

Choice of Stem Cells



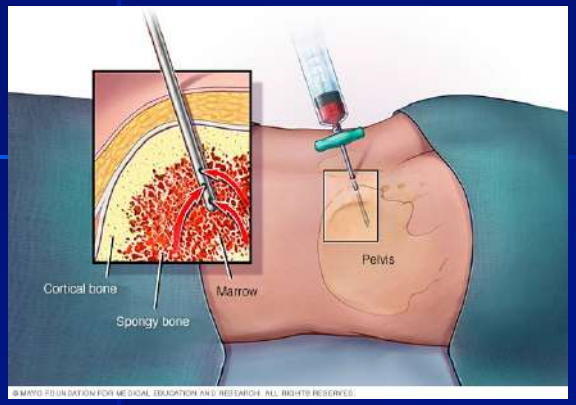
- Different sources of MSC have different characteristics and have their own advantages and disadvantages.

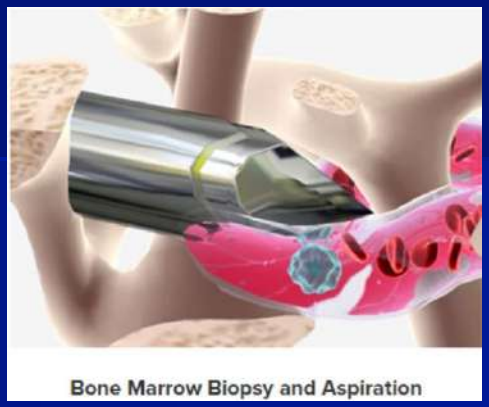
Choice of Stem Cells



- With respect to the MSC density at the source tissue, the umbilical cord has the highest, followed by the amniotic fluid and adipose tissue.
- With respect to proliferative capacity, umbilical cord and amniotic fluid have definite advantages, followed by adipose tissue and bone marrow.
- In terms of immunomodulatory capacity, umbilical cord, amniotic fluid and adipose tissue have superior immune regulation over bone marrow, while placental-MSCs have the lowest immunomodulatory capacity.
- When compared to cytokine secretion profiles, umbilical cord secrete more cell growth factor than bone marrow.

Bone Marrow Derived-Mesenchymal Stem Cells (BM-MSCs) for OA Therapy




Bone Marrow Biopsy and Aspiration

- Bone marrow-MSCs are the first discovered MSC type and bone marrow is the most widely used source of MSCs.
- The first clinical study of BM-MSC transplantation for articular cartilage defect was conducted almost 20 years ago.
- The most commonly used stem cell source in clinical phase studies is bone marrow.

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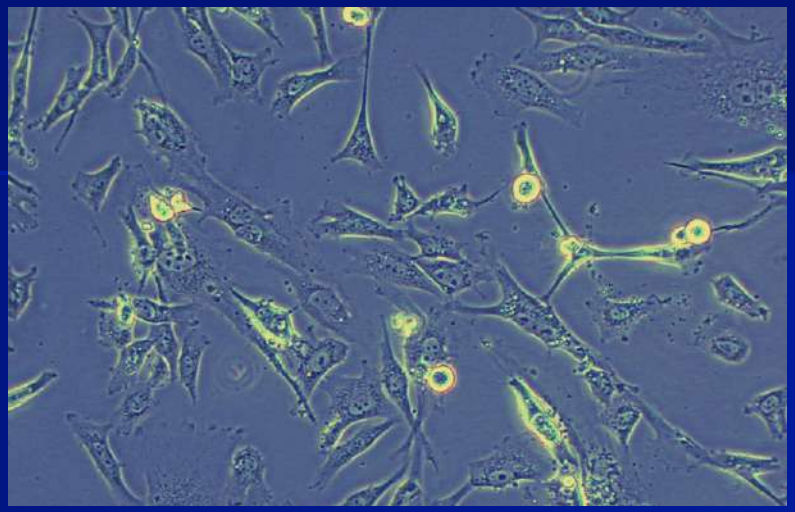
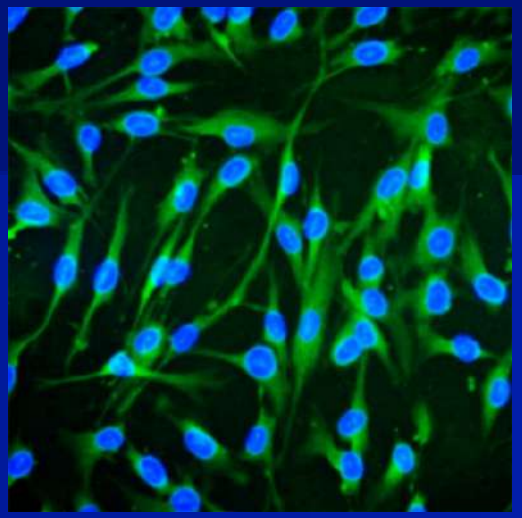
- However, they cannot be easily obtained since the donor must undergo a painful and invasive procedure.

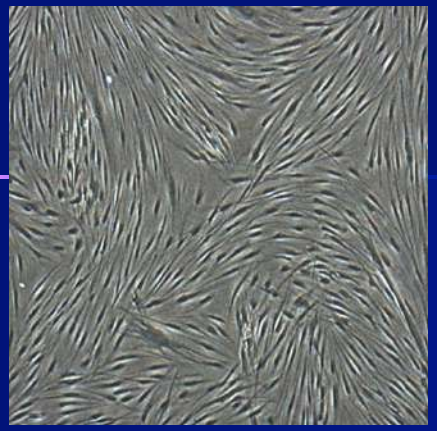
Bone Marrow Derived-Mesenchymal Stem Cells (BM-MSCs) for OA Therapy

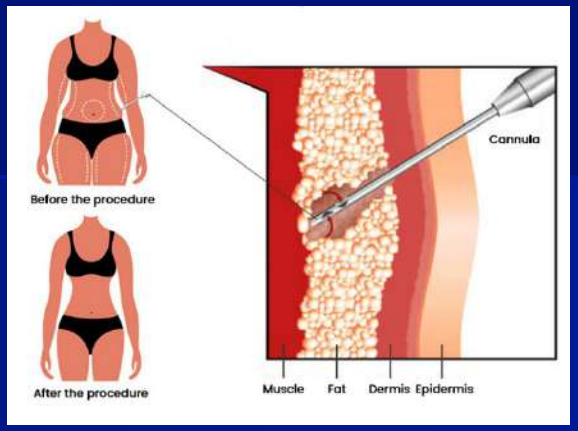


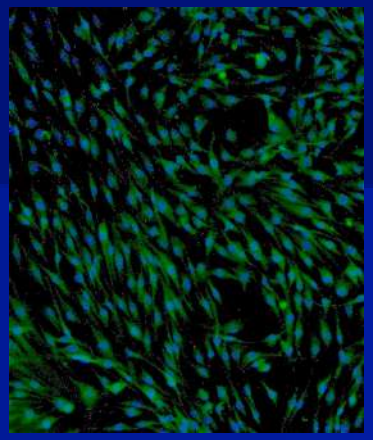


- Although this tissue is common for MSCs isolation, it does not contain the largest number of MSCs and their number decreases with age.
- The phenotype of MSCs varies depending on the patient's systemic diseases.
- This situation has encouraged researchers to search for alternative sources.

Adipose Tissue Derived-Mesenchymal Stem Cells (AT-MSCs) for OA Therapy

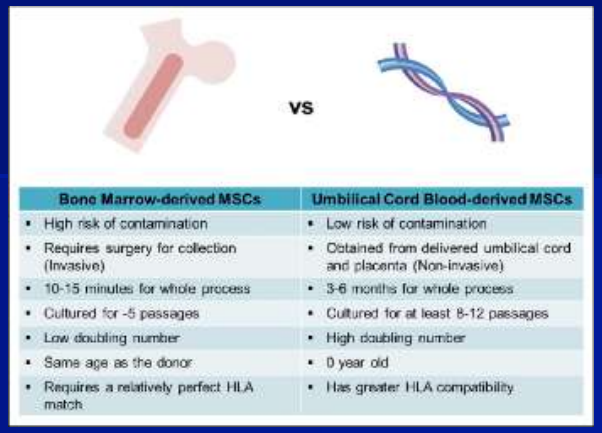




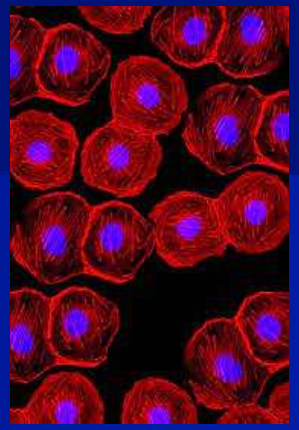


- Adipose tissue is another source of MSCs
- AT-MSCs have similar characteristics to BM-MSCs in terms of stemness,
- Moreover they have advantages compared to BM-MSCs due to their
  - easy accessibility/less invasive,
  - stem cell density, and
  - easy cell differentiation characteristics.

Umbilical Cord Blood Derived-Mesenchymal Stem Cells (UCB-MSCs) for OA Therapy

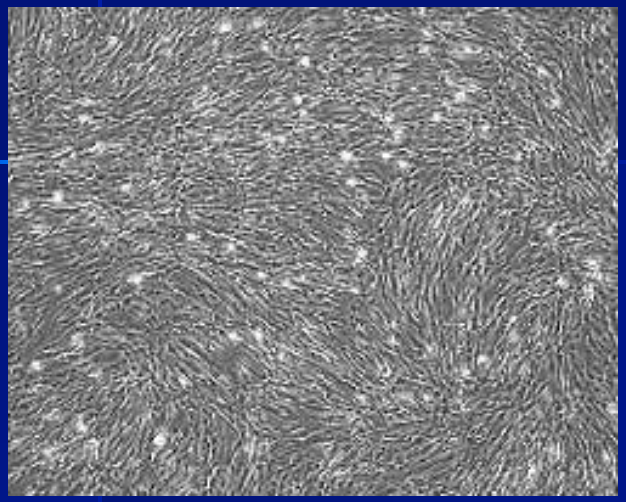


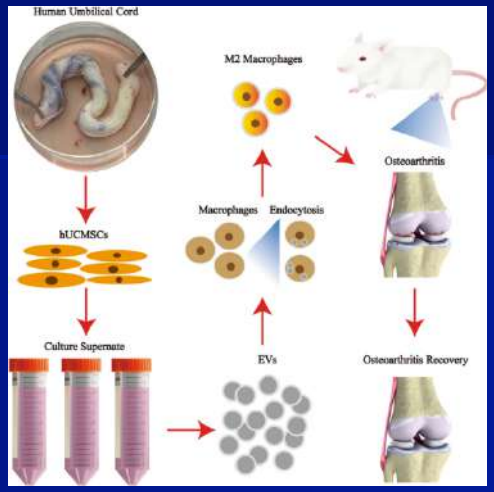
Bone Marrow-derived MSCs	Umbilical Cord Blood-derived MSCs
• High risk of contamination	• Low risk of contamination
• Requires surgery for collection (Invasive)	• Obtained from delivered umbilical cord and placenta (Non-invasive)
• 10-15 minutes for whole process	• 3-6 months for whole process
• Cultured for ~5 passages	• Cultured for at least 8-12 passages
• Low doubling number	• High doubling number
• Same age as the donor	• 0 year old
• Requires a relatively perfect HLA match	• Has greater HLA compatibility

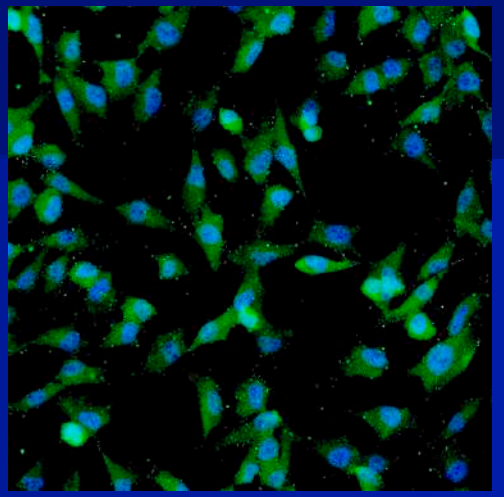


- Another alternative source of MSCs is umbilical cord blood.
- Umbilical cord blood-MSCs have similar characteristics to BM-MSCs in terms of immunophenotype and morphology,
- But they have disadvantages compared to BM-MSCs due to their
  - lower colony frequency
  - no adipogenic differentiation
  - isolation efficiency is low
- Advantages of UCB-MSCs compared to BM-MSCs due to their
  - can be cultured for a longer time,
  - easily harvested and
  - have a higher proliferation capacity.

Umbilical Cord Derived-Mesenchymal Stem Cells (UC-MSCs) for OA Therapy

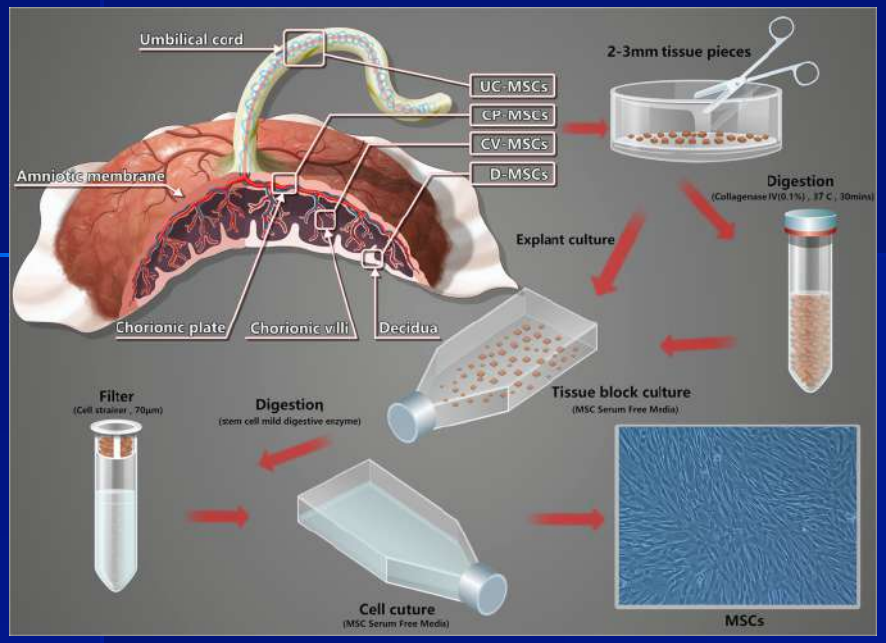


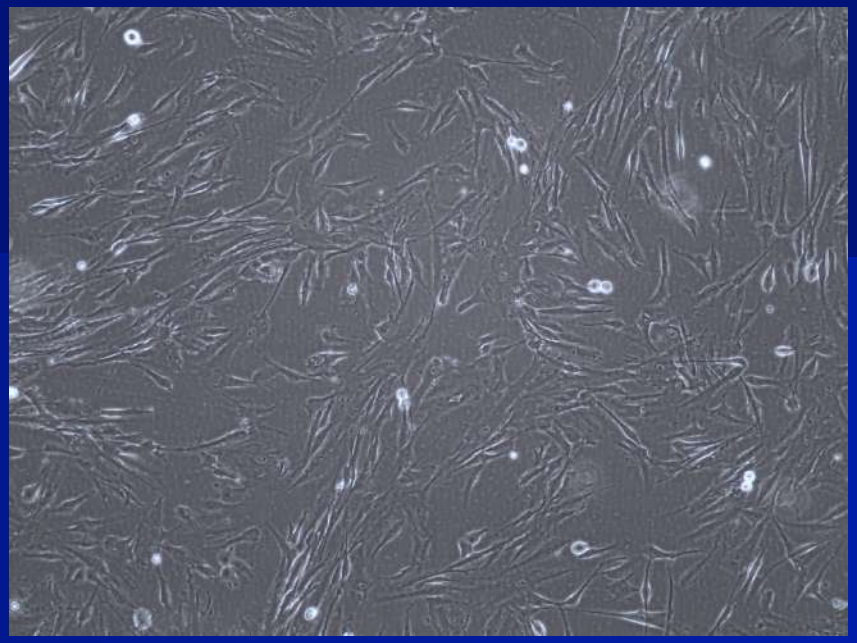




- Another alternative source of MSCs is umbilical cord.
- Umbilical cord-MSCs have similar characteristics to BM-MSCs in terms of immunophenotype and morphology,
- But they have advantages compared to BM-MSCs due to their
  - easily harvested and
  - higher capacity to proliferate
  - higher differentiation ability and
  - superior immunomodulatory capacity.

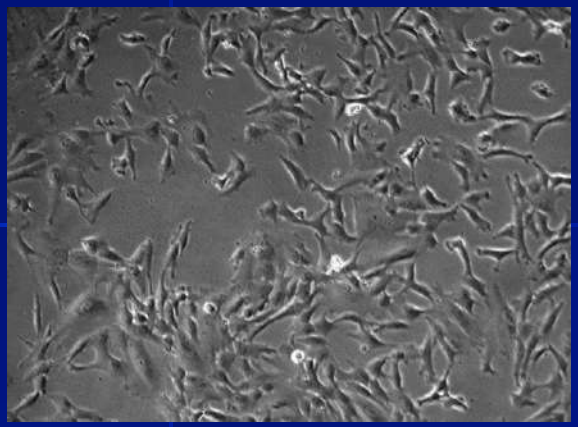
Placenta Derived-MSCs (P-MSCs) for OA Therapy

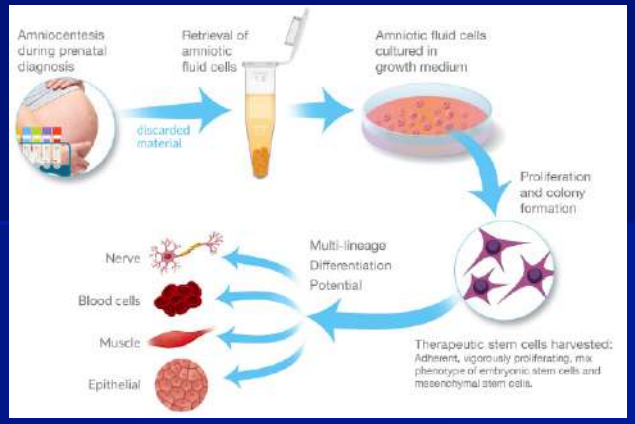


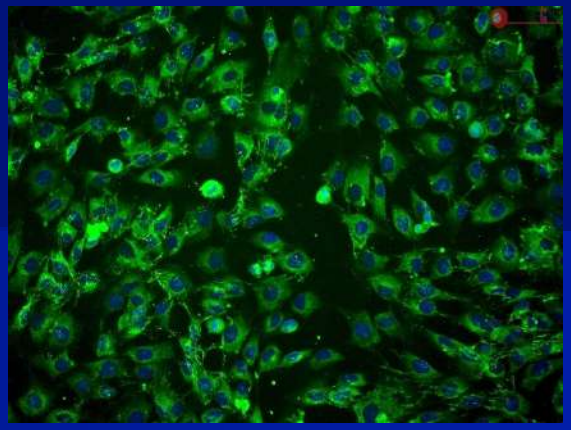


- Another alternative source of MSCs is placental tissues.
- Placenta-MSCs have advantages compared to BM-MSCs due to their
  - readily sourced and available in abundance.
  - differentiated into multiple cell types successfully.
- However, due to the fact that the placenta is a large organ containing numerous tissue types, the proliferative capacity of MSCs isolated from different placental regions is heterogeneous.

Amniotic Fluid Derived MSCs (AF-MSCs) for OA Therapy

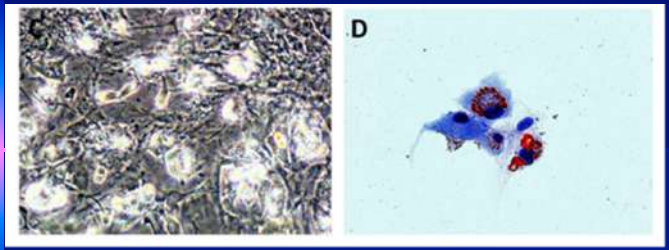


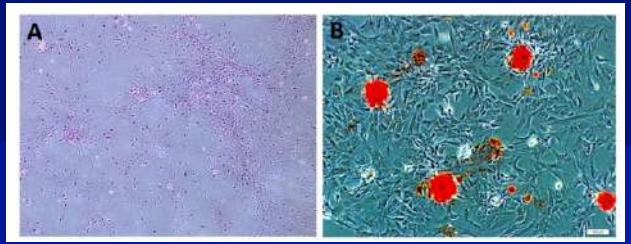


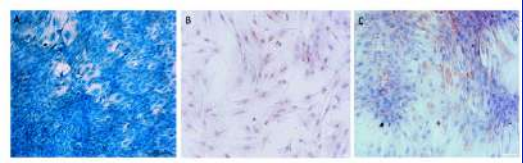


- Another suitable alternative source of MSCs is human amniotic fluid.
- MSCs have similar characteristics to BM-MSCs in terms of gene stability and immunophenotype,
- Moreover AF-MSCs have advantages compared to BM-MSCs due to their
  - better self-renewing and
  - higher and faster proliferative capacity.

Synovial Fluid Derived Mesenchymal Stem Cells (SF-MSCs) for OA Therapy

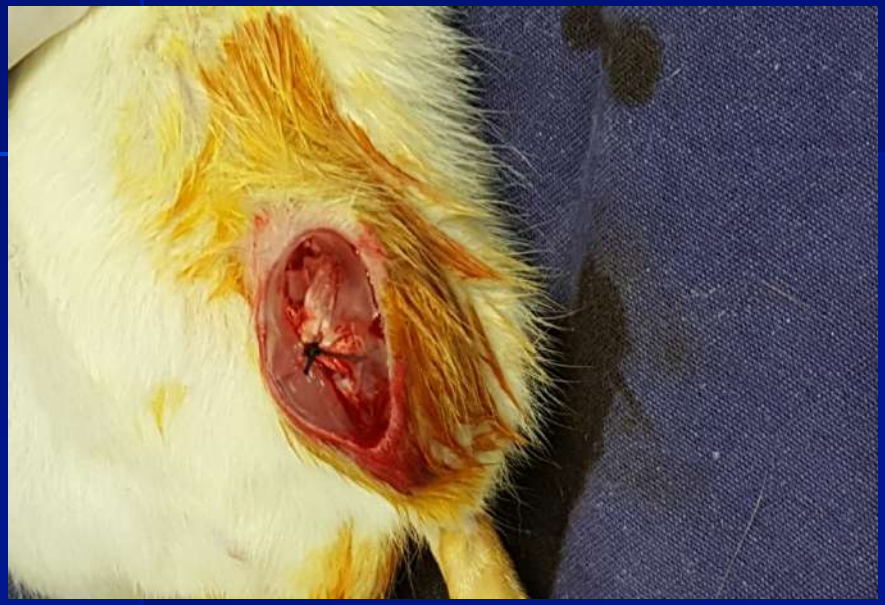


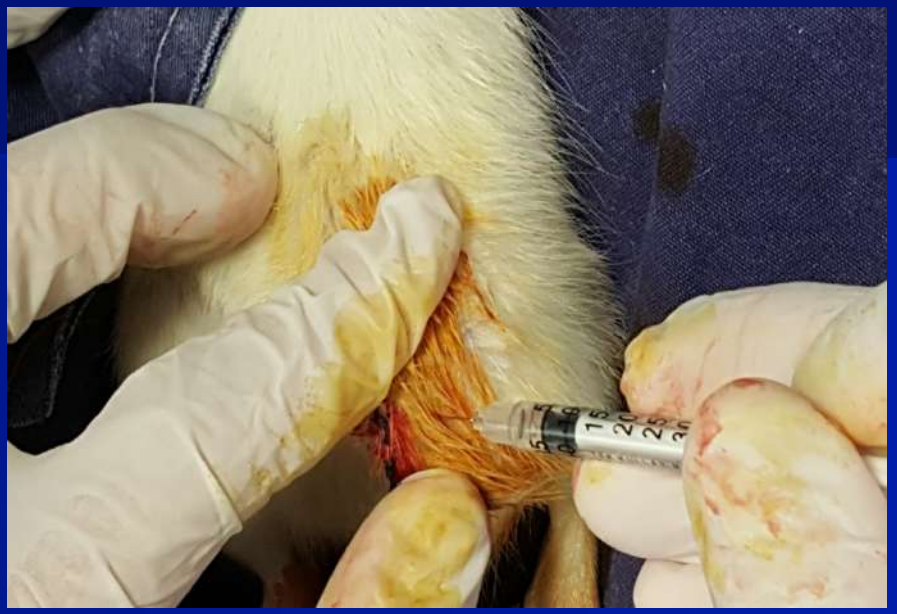




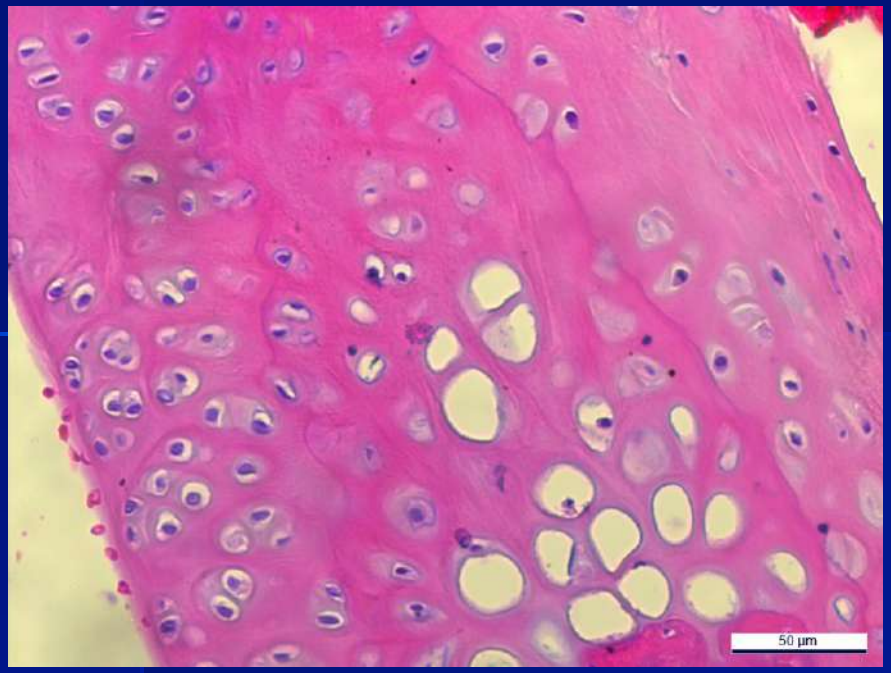
- Another suitable alternative source of MSCs is synovial fluid.
- Synovial fluid-MSCs have similar characteristics to BM-MSCs.
- Moreover they have advantages compared to other MSCs due to their
  - stronger chondrogenic differentiation abilities,
  - easily harvesting during arthrocentesis, arthroscopy, or knee surgery,
  - allowing to autologous therapies,
  - ability to differentiate more easily into damaged joint cells due to their joint origin,
  - resistance to conditions such as hypoxia and mechanical stresses arising from the healthy or unhealthy joint itself.
  - Finally they could be cultured for a longer time compared to other MSCs.

AIM

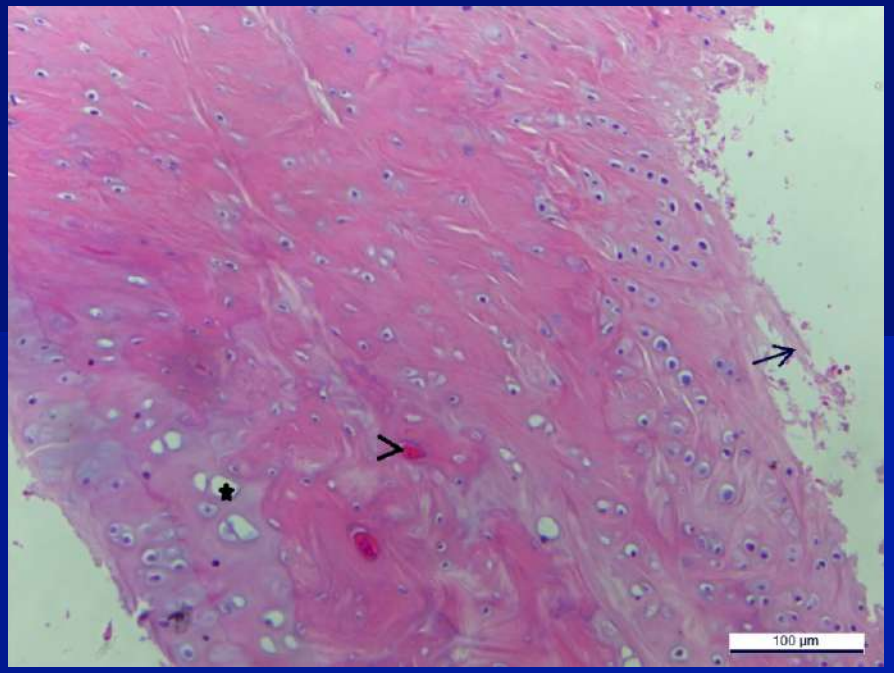




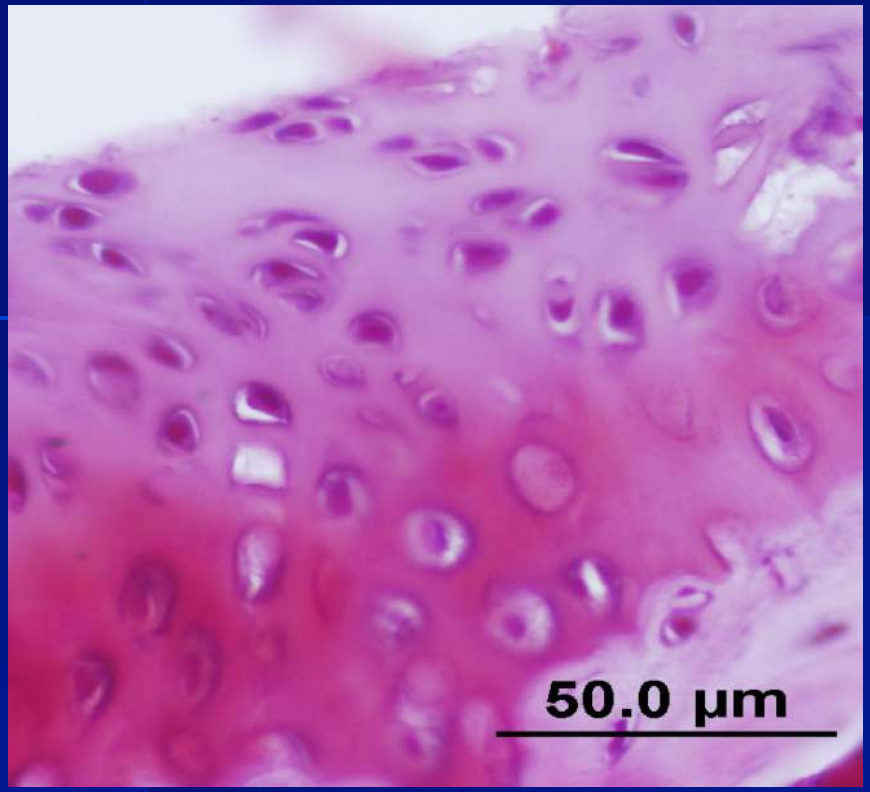
- The therapeutic effect of exosomes obtained from synovial fluid-MSCs on meniscal damage and OA model.



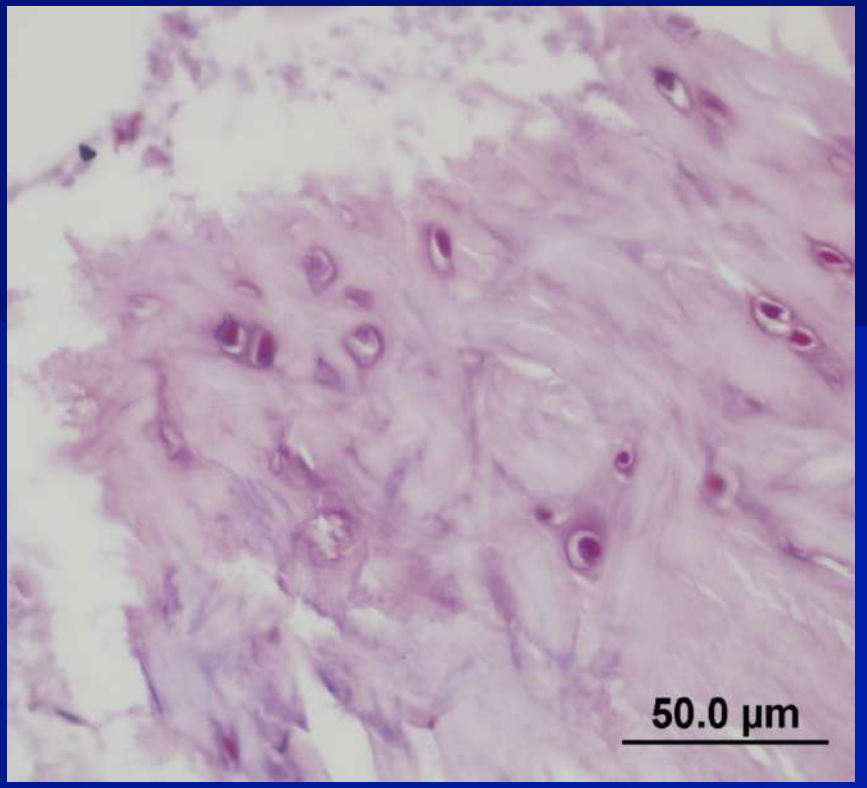
Meniscal cartilage morphology of control group. Structure of the tissue surface is smooth, and the distribution of cells appear normal. H-E (Scale bar 50 µm).



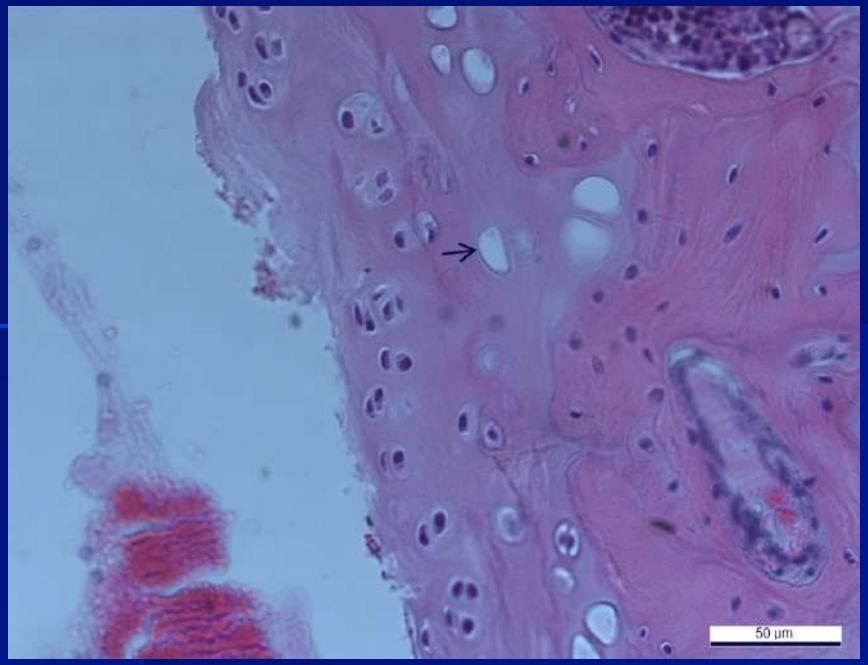
Meniscal cartilage morphology of meniscal injury group. Severe fibrillation on tissue surface (arrow), cyst (arrow head) and empty lacuna (star). H-E (Scale bar 1000 µm)



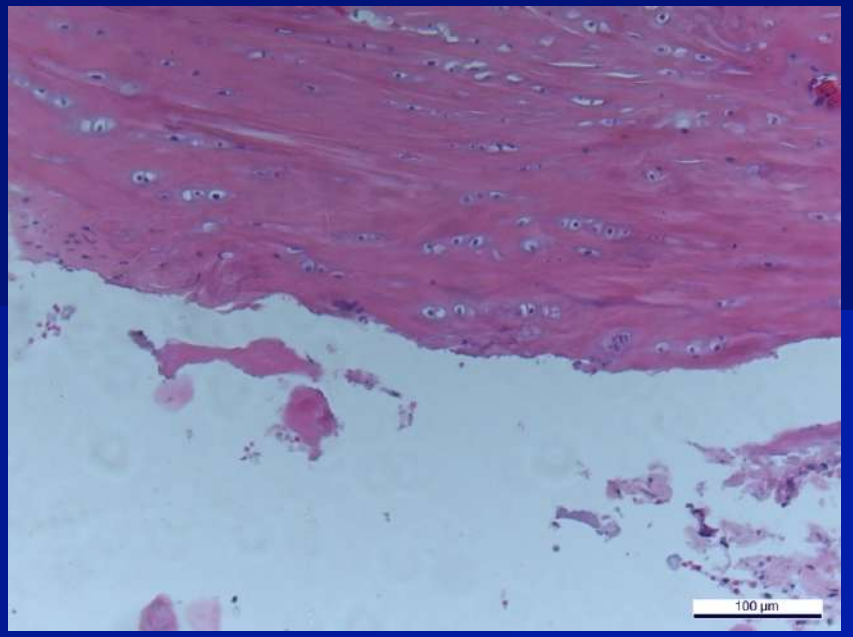
Control group meniscus cartilage with Safranin O. Normal, homogen matrix staining. Safranin O (Scale bar 50 µm).



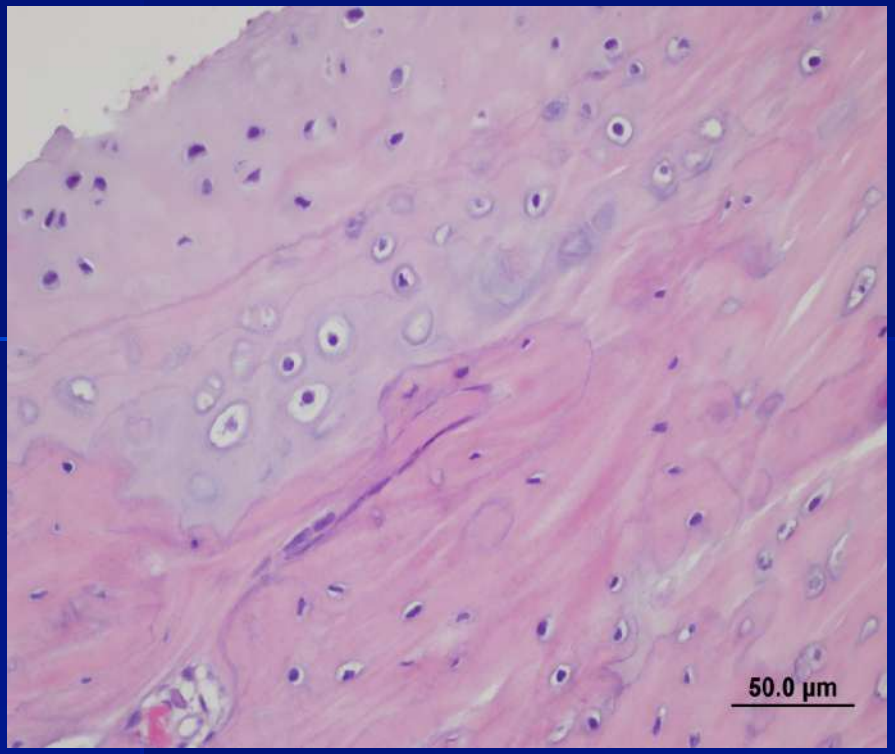
Meniscal injury group meniscus cartilage with Safranin O. Less staining and loss of Safranin O. Safranin O (Scale bar 50 µm).



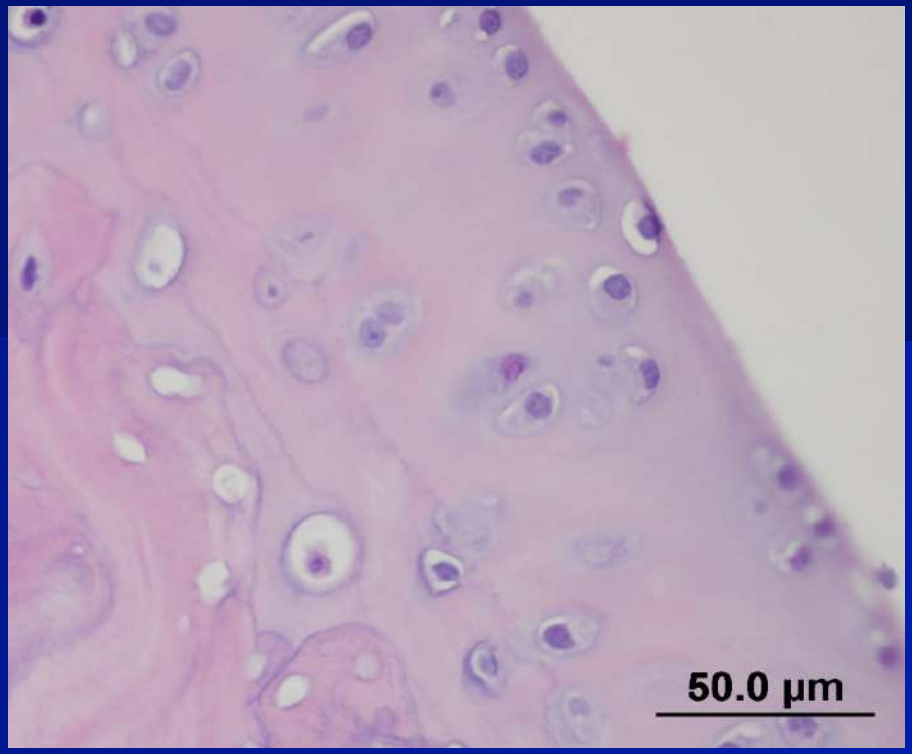
Meniscal cartilage morphology after 4 weeks of injection with SF-MSC. Slight fibrillation, few empty lacuna (arrow). H-E (Scale bar 50 µm).



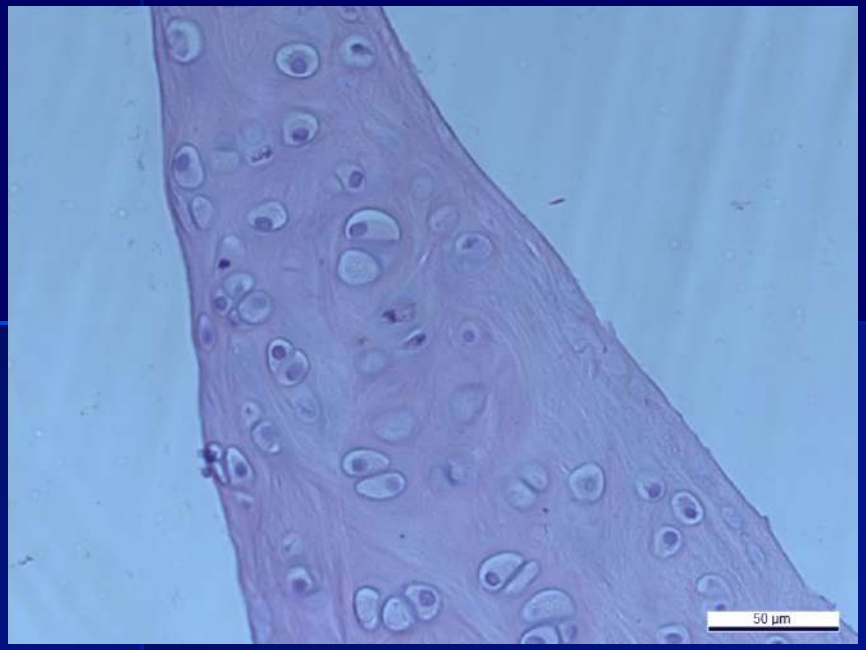
Meniscal cartilage morphology after 8 weeks of the injection with SF-MSC. Slight fibrillation, hypercellularity. H-E (Scale bar 100 µm).



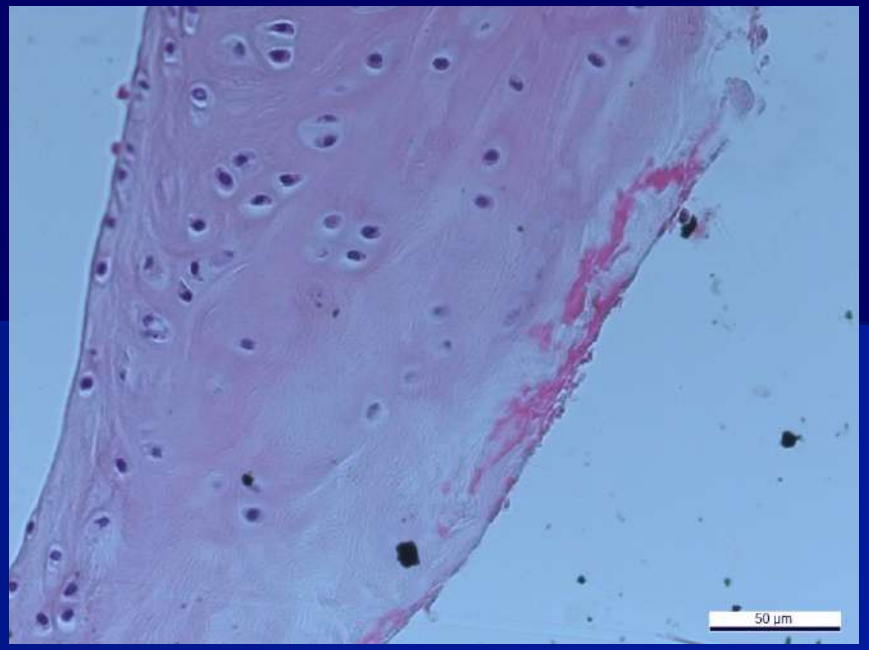
Meniscal cartilage after 4 weeks of the injection with SF-MSC. At less intensity and heterogen staining. Safranin O (Scale bar 50 µm).



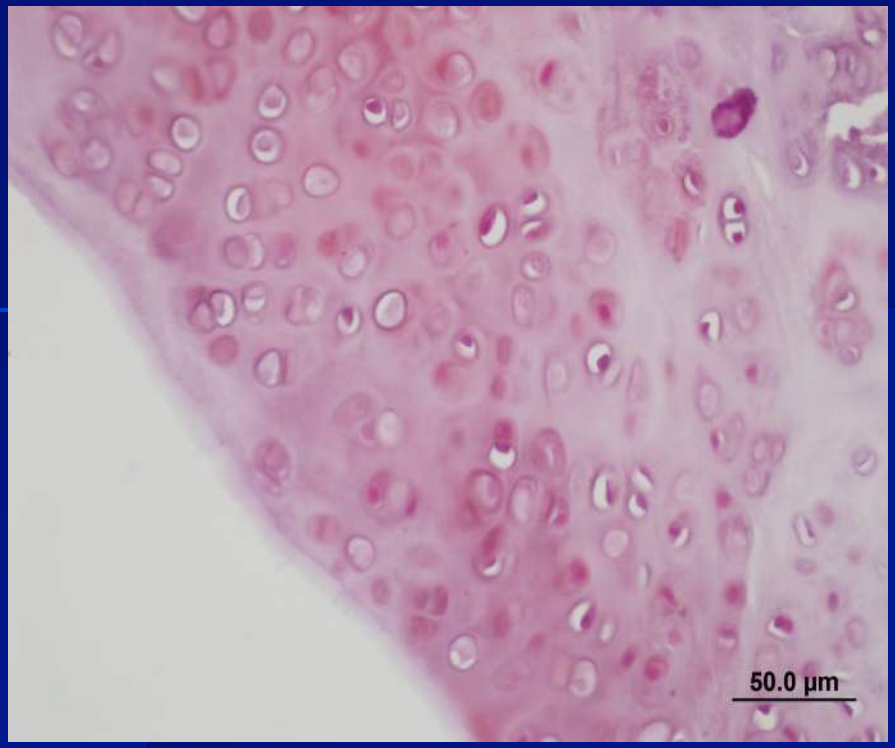
Meniscal cartilage after 8 weeks of the injection with SF-MSC. At less intensity and heterogen staining. Safranin O (Scale bar 50 µm).



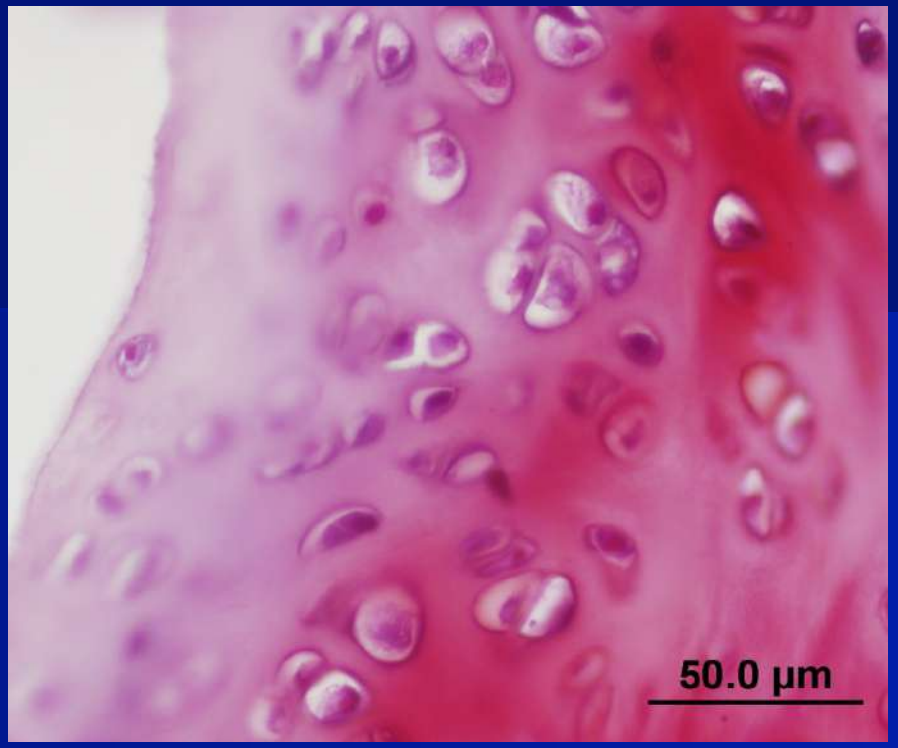
Meniscal cartilage morphology after 4 weeks of the injection with exosomes. Structure of the tissue surface is smooth and the distribution of cells appear normal. H-E (Scale bar 50 µm).



Meniscal cartilage morphology after 8 weeks of the injection with exosomes. Structure of the tissue surface is smooth and the distribution of cells appear normal. H-E (Scale bar 50 µm).

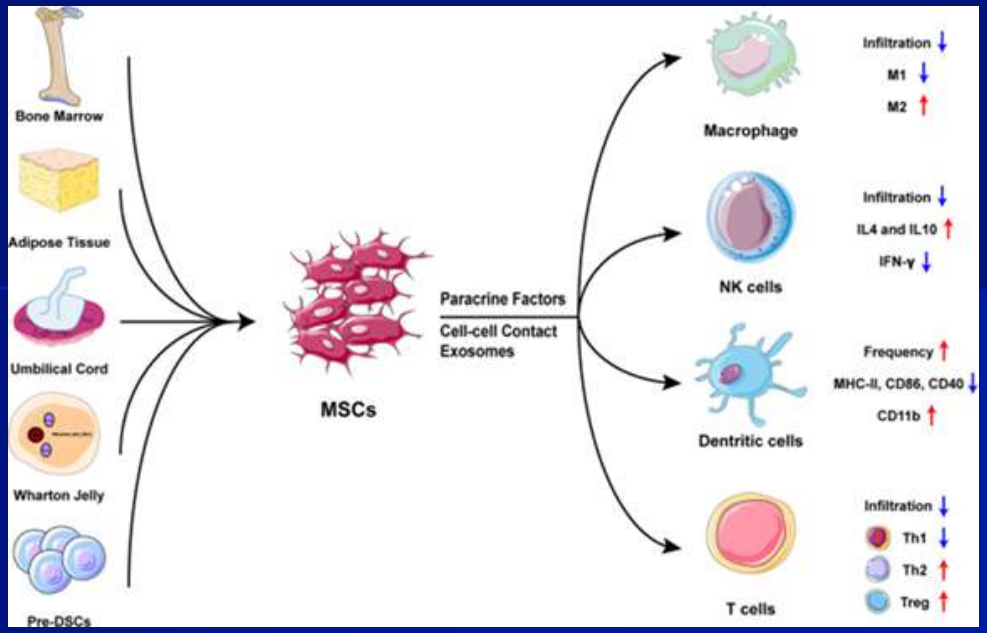


Meniscal cartilage morphology after 4 weeks of the injection with exosomes. Normal, moderately staining. Safranin O (Scale bar 50 µm).



Meniscal cartilage morphology after 8 weeks of the injection with exosomes. Normal, moderately staining. Safranin O (Scale bar 50 µm).

MSC Mechanisms for the Management of OA



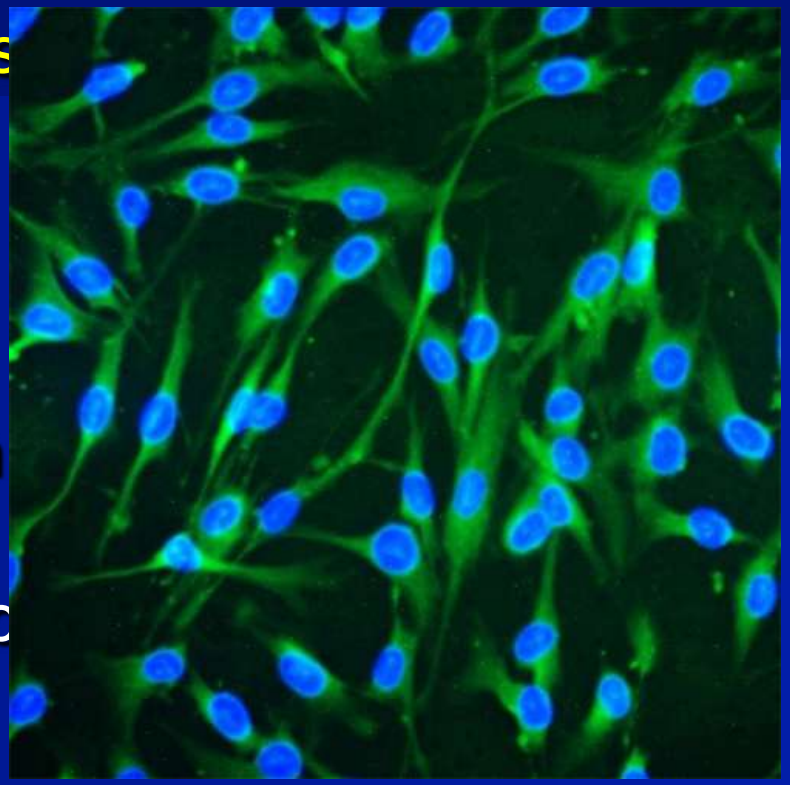
- In summary, MSCs exert their effects on OA:
  - They differentiate the aggressive and undesirable pro-inflammatory microenvironment of OA towards an anti-inflammatory phenotype with their chemokines and cytokines secretions.
  - In addition to their anti-inflammatory properties, the anti-apoptotic, anti-fibrotic, anti-hypertrophic and immunomodulatory properties of MSCs are highly effective in the treatment of OA.

Conclusions and Future Perspective

- Preclinical and clinical studies demonstrate that MSCs reduce inflammation and regenerate cellular damage in OA.
- However, the most important limitation to the use of MSCs in the treatment of OA is that a safe and effective treatment protocol has not yet been developed.
- Therefore, well-designed clinical trials with sufficient patient numbers are required.
- The key points of these clinical trials can be summarised as follows.
  - Considering the stages of OA, it is necessary to determine at which stage the treatment will be applied.
  - It is necessary to determine the stem cell dose/number of cells to be used for treatment in OA.
  - It is necessary to determine the number of stem cell doses to be used for OA treatment.
  - It is necessary to determine the stem cell source to be used for the treatment of OA.
  - New methods should be developed to reduce the cost of stem cells used for the treatment of OA.
  - All these factors also apply to cell-free therapy with stem cell exosomes.

Conclusions and Future Perspective

- MSCs are a good candidate to meet the challenge in treating OA.
- They can repair the damaged tissues or provide immunomodulatory function to reduce inflammation in OA.
- Since OA is a degenerative joint disease likely involving the depletion of endogenous MSCs,
- and adult MSCs have the potential to differentiate into cells of chondrogenic lineage,
- investigation into MSCs-based therapy should be supported for potential articular cartilage repair and regeneration.



ESKİŞEHİR

Thank You..