Orthopaedic Biologics and Stem Cells - 2018

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When and where should we be using intra-articular injections?

- Osteoarthritis/ Chondral defects
- Meniscal repair/healing
- Ligament reconstruction/ healing

Osteoarthritis (OA)

- Primary
- Chondral defects

Osteoarthritis

- Important cause of pain, disability, and economic loss
- 10 fold increase with joint injury

Post-traumatic OA

- Impact joint injuries initiate a sequence of biologic events causing joint degeneration

OA Risk Factors

- Abnormal loading on normal cartilage
- Normal loading on abnormal cartilage

Cyclic Fatigue Damage

- Damage to subchondral bone
- Loss of support or release of cytokines

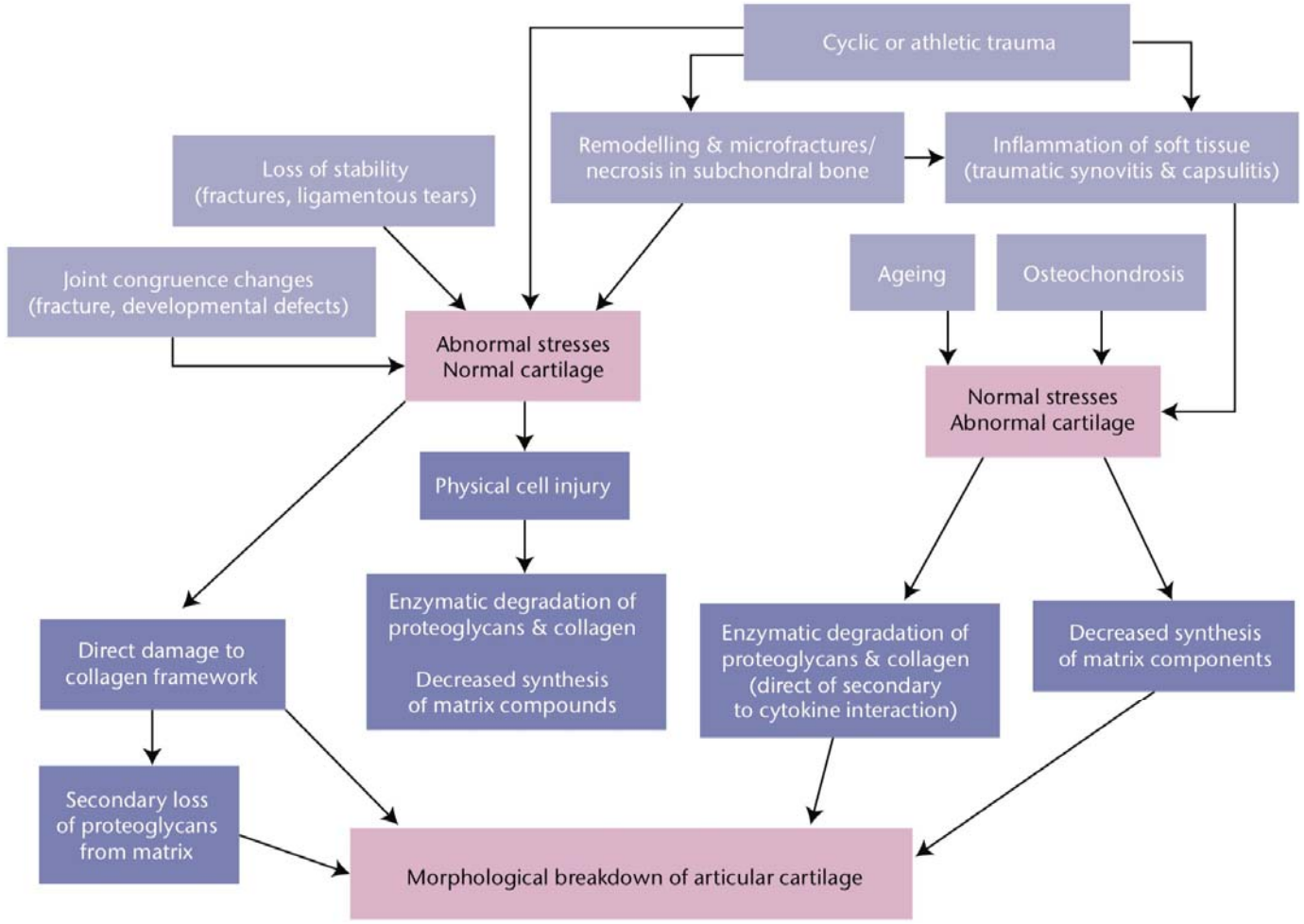


Fig. 1

Diagram showing the possible pathways for degradation of articular cartilage secondary to joint trauma in the horse (reproduced with permission from **McIlwraith CW**. Frank Milne Lecture: from arthroscopy to gene therapy: 30 years of looking in joints. *Am Assoc Equine Pract* 2005;51:65–113).

Role of Acute Synovitis/ Capsulitis

- Release of enzymes
- Release of inflammatory mediators
- Release of cytokines

Synovitis

- Loss of glucosaminoglycans (GAG)
- Increase in mediators contributing to OA

Interleukin – 1 B (IL-1)

- Master cytokine in human OA
- Remains high throughout all OA stages

Tumor Necrosis Factor- a (TNFa)

- Most prominent cytokine in acute stages of human OA

Equine studies demonstrate inhibition of OA production by gene therapy with IL- 1ra

Low innate production of IL-1 and IL-6 is associated with absence of OA at old age

Role of Synovitis

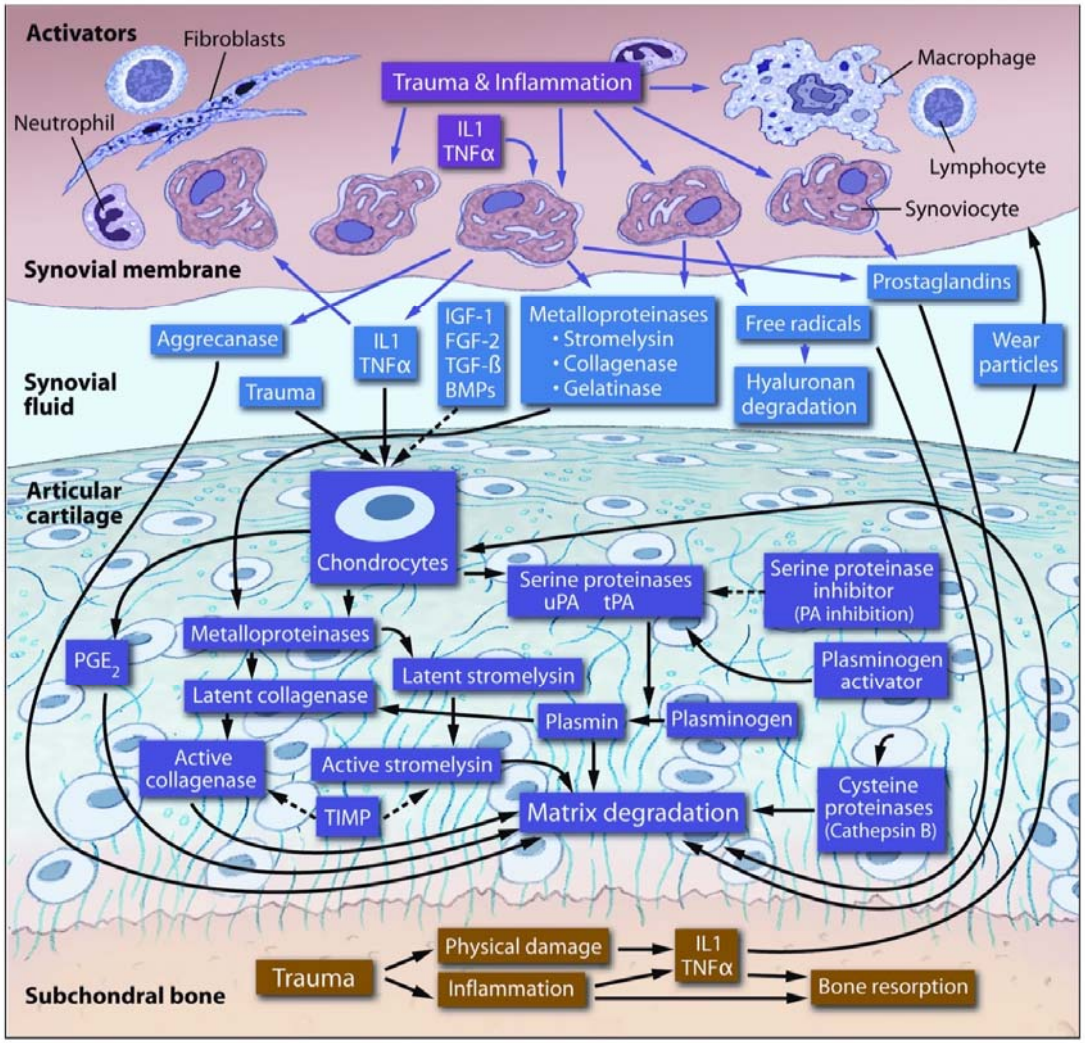
- Disrupts balance of anabolic/catabolic activities

Equine IL-1ra gene therapy has clearly demonstrated anticatabolic effects and prevents and/or decreases development of OA

Factors that Produce Environment Conducive to OA

- Trauma
- Synovitis
- Increase levels of IL-1/ TNF

C. W. MCILWRAITH, D. D. FRISBIE, C. E. KAWCAK



Ideal Therapeutic Agent for Treatment of OA

- Relieve symptoms
- Produce disease modifying effects

Corticosteroids

Beneficial ?

Harmful ?

- Betamethasone
- Methylprednisone (Depomedrol)
- Triamcinolone (Kenalog)

Betamethasone

- Articular cartilage neutral
- Decreases synovitis

Methylprednisone

- Harmful to articular cartilage

Triamcinolone

- Beneficial to articular cartilage
- Crystaline form may produce crystal production

Hyaluronan (HA)

- Decrease vascularity
- Decrease fibrillation of articular cartilage at 70 days
- ? Increase in IL-1ra

Autologous Conditioned Serum (Orthokine)

- Increase production of anti-inflammatory cytokines and growth factors using human blood
- Increase IL-1ra

ACS Production

- Incubation of venous blood in presence of medical grade glass beads

ACS Produces:

- Increased endogenous anti-inflammatory cytokines (including IL-1ra)

ACS Use:

- 6 injections over 3 weeks
- Prohibited by FDA

Endogenous wound healing mechanisms activated by the exposure of blood cells to “Alien” surfaces.

ACS

- Products released are from intracellular reservoirs & synthesis De Novo
- Numerous list of cytokines present in ACS
- Effects appear to be synergistic action of numerous cytokines

Injections appear to increase IL-1ra levels in non-injected joints

ACS injections into injured muscle appear to increase rate of healing

ACS injections for OA has shown effect on major symptoms at 6 months. Superior to HA and placebo ?

Platelet Rich Plasma (PRP)

- Whole blood is spun in centrifuge to isolate platelets

Platelets carry with them a host of growth factors/ cytokines

Potential improvement in tissue healing in tissues with limited biologic resources.

- tendinopathy

Role of PRP in OA

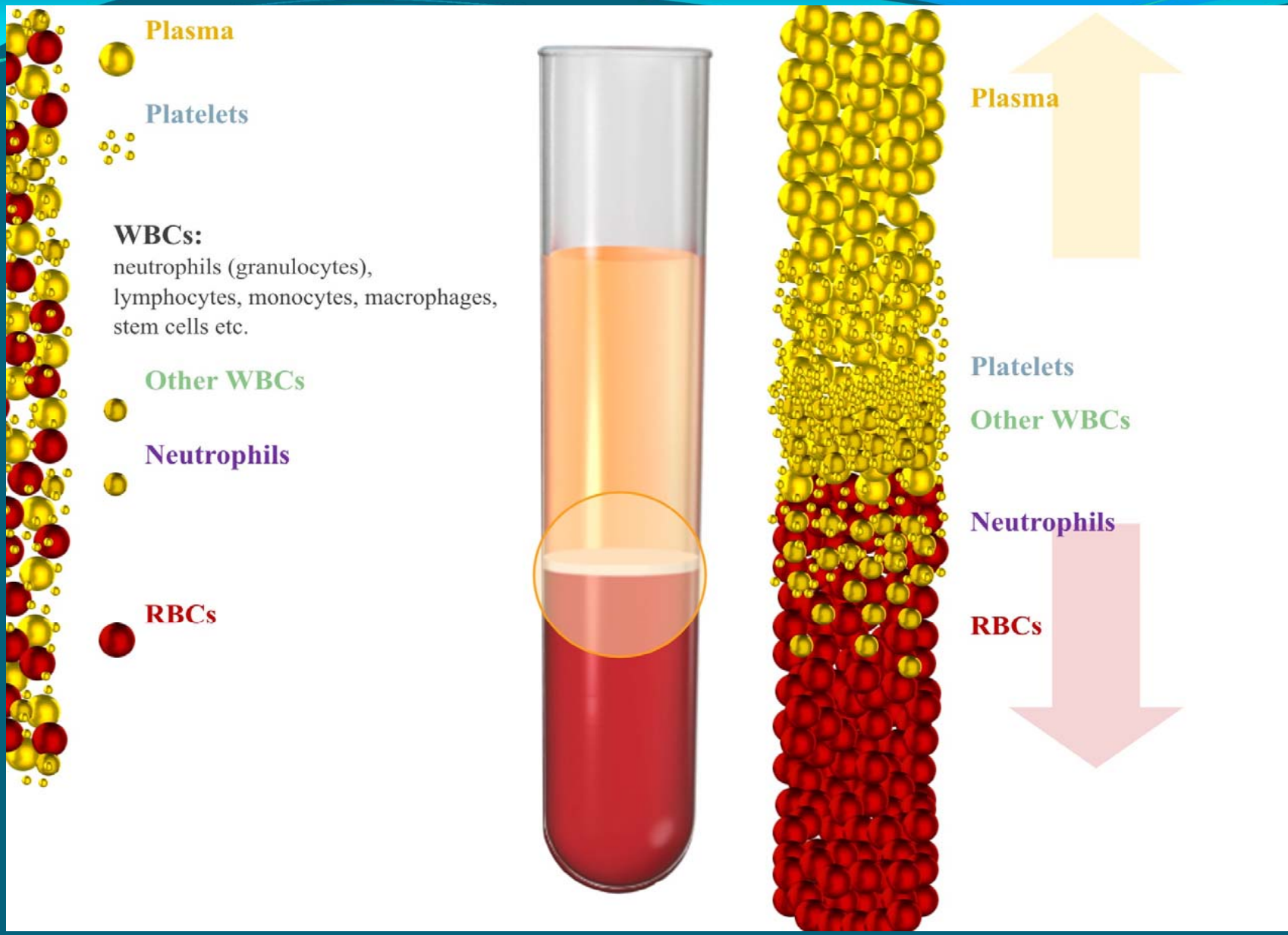
- Better than HA?

Role of white blood cells ?

Leukocyte Poor

vs

Leukocyte Rich


Plasma
Platelets
WBCs:
neutrophils (granulocytes),
lymphocytes, monocytes, macrophages,
stem cells etc.
Other WBCs
Neutrophils
RBCs
Plasma
Platelets
Other WBCs
Neutrophils
RBCs

Author	Diagnosis	Formulation	Outcome
Patel, AJSM 2013	Knee OA	Leukocyte poor	Significant difference
Filardo, Musk. Disord 2012	Knee OA	Leukocyte rich	No difference
Cerza, AJSM 2012	Knee OA	Leukocyte poor	Significant difference
Sanchez, Arthro 2012	Knee OA	Leukocyte poor	Significant difference
Spakova, Am J Phys Med Rehab 2012	Knee OA	Leukocyte poor	Significant difference
Filardo, KSSTA 2012	Knee OA	Leukocyte rich	No difference

2014 TOBI, PRP Symposium Jason Dragoo, MD

PRP

- Increase in TGF (transforming growth factor)
- Pro-fibrotic

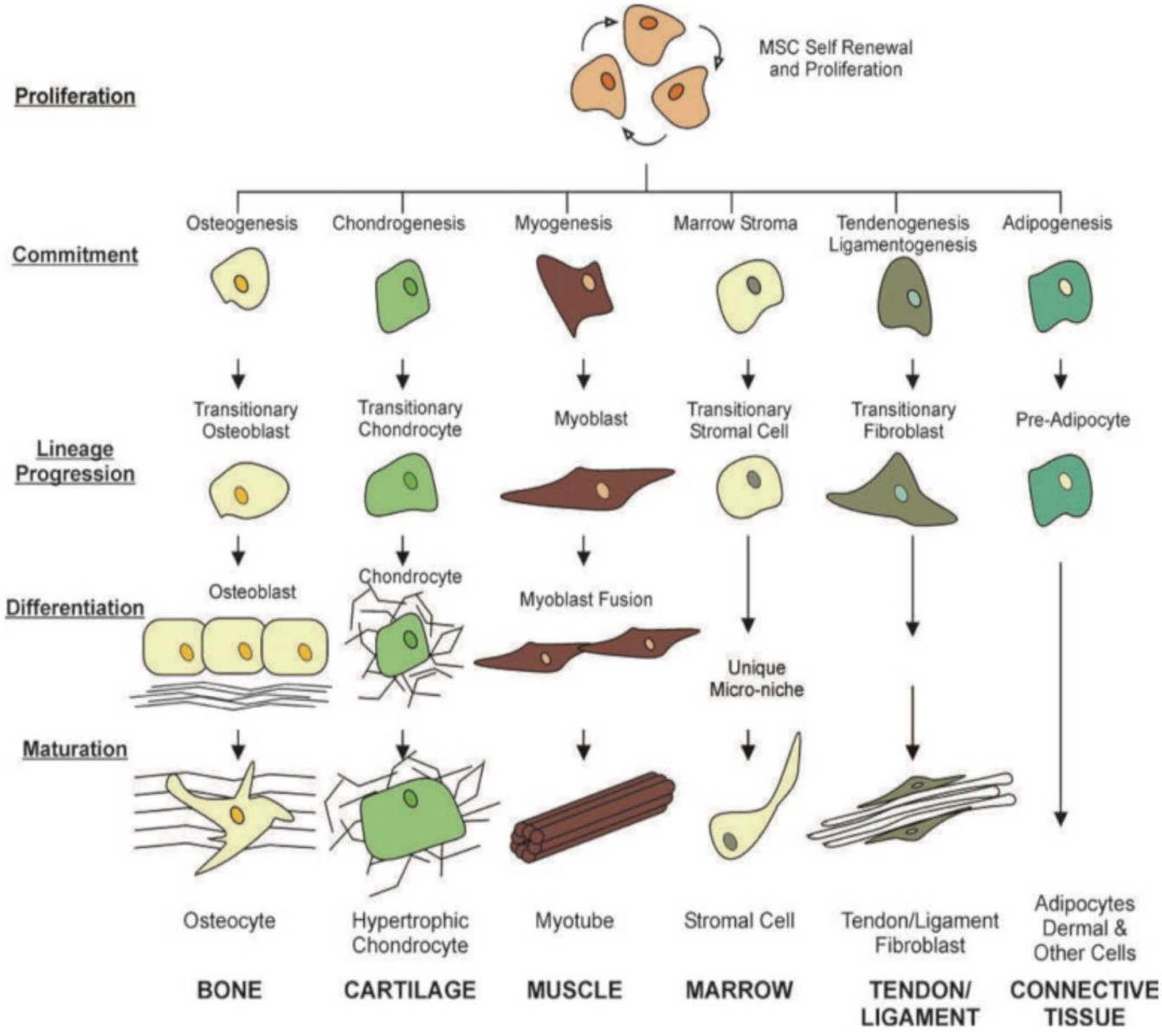
Stem Cells !!!

Stem Cells

- Progenitor cells
- Precursors of bone, cartilage, fat, tendon, and ligament

Stem Cells

- Differentiate into multiple cell lines
- Influence cells around them


Proliferation
MSC Self Renewal and Proliferation
Commitment
Osteogenesis
Chondrogenesis
Myogenesis
Marrow Stroma
Tendenogenesis Ligamentogenesis
Adipogenesis
Lineage Progression
Transitionary Osteoblast
Transitionary Chondrocyte
Myoblast
Transitionary Stromal Cell
Transitionary Fibroblast
Pre-Adipocyte
Differentiation
Osteoblast
Chondrocyte
Myoblast Fusion
Unique Micro-niche
Maturation
Osteocyte
Hypertrophic Chondrocyte
Myotube
Stromal Cell
Tendon/Ligament Fibroblast
Adipocytes Dermal & Other Cells
BONE
CARTILAGE
MUSCLE
MARROW
TENDON/ LIGAMENT
CONNECTIVE TISSUE

Mesenchymal Stem Cells (MSC)

- Iliac crest bone marrow
- Adipose tissue
- Peripheral blood

MSC

- Produce growth factors/cytokines
- Influence progenitor cells

In vivo therapeutic mechanisms of MSC's still unclear

How many stem cells are needed ?

Intra-articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee

A 2-Year Follow-up Study

Chris Hyunchul Jo,* MD, Jee Won Chai,† MD, Eui Cheol Jeong,‡ MD, Sohee Oh,§ PhD, Ji Sun Shin,* BS, Hackjoon Shim,‖ PhD, and Kang Sup Yoon,*¶ MD
Investigation performed at the Seoul Metropolitan Government–Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Republic of Korea

Background: The intra-articular injection of mesenchymal stem cells (MSCs) into the knee has shown a potential for the treatment of generalized cartilage loss in osteoarthritis (OA). However, there have been few midterm reports with clinical and structural outcomes.

Purpose: To assess the midterm safety and efficacy of an intra-articular injection of autologous adipose tissue–derived (AD) MSCs for knee OA at 2-year follow-up.

Study Design: Cohort study; Level of evidence, 3.

Methods: Eighteen patients with OA of the knee were enrolled (3 male, 15 female; mean age, 61.8 ± 6.6 years [range, 52-72 years]). Patients in the low-, medium-, and high-dose groups received an intra-articular injection of 1.0×10^7, 5.0×10^7, and 1.0×10^8 AD MSCs into the knee, respectively. Clinical and structural evaluations were performed with widely used methodologies including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and measurements of the size and depth of the cartilage defect, signal intensity of regenerated cartilage, and cartilage volume using magnetic resonance imaging (MRI).

Results: There were no treatment-related adverse events during the 2-year period. An intra-articular injection of autologous AD MSCs improved knee function, as measured with the WOMAC, Knee Society clinical rating system (KSS), and Knee injury and Osteoarthritis Outcome Score (KOOS), and reduced knee pain, as measured with the visual analog scale (VAS), for up to 2 years regardless of the cell dosage. However, statistical significance was found mainly in the high-dose group. Clinical outcomes tended to deteriorate after 1 year in the low- and medium-dose groups, whereas those in the high-dose group plateaued until 2 years. The structural outcomes evaluated with MRI also showed similar trends.

Conclusion: This study identified the safety and efficacy of an intra-articular injection of AD MSCs into the OA knee over 2 years, encouraging a larger randomized clinical trial. However, this study also showed potential concerns about the durability of clinical and structural outcomes, suggesting the need for further studies.

Clinical Trial Registration: NCT01300598

Keywords: osteoarthritis; mesenchymal stem cell; intra-articular injection; knee

2 year follow up for treatment of OA

- Best results with high cell counts
- Clinical outcomes deteriorated at 1 year follow up
- Safe

MSC

- 100 million msc's provided best results for OA
- Results in veterinary medicine indicate best results with 20-30 million msc's

Bone Marrow Aspirate Concentrate (BMAC)

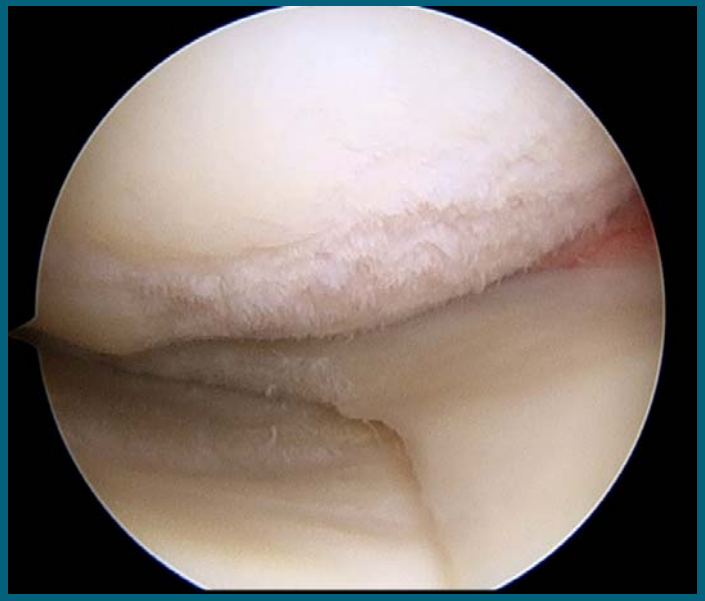
- 200k – 1.2m msc's

Stem cells can easily be enhanced or cultured

Cellular manipulation of MSC's is prohibited by FDA

BMAC

- Decreased cell counts with increasing age !
- Role on joint environment positive?
- Role in treating OA limited ?



Embryonic Stem Cells

- Living stem cells are absent!
- Role of extracellular matrix on joint environment ?

Summary

Corticosteroids

- Decreases inflammatory environment
- Choose the right one !
- Used for OA

Hyaluronan (HA)

- Increase in IL-1ra?
- Good for articular cartilage?
- Decrease in inflammation?
- Used for OA

Autologous Conditioned Serum (ACS)

- Increase good cytokines
- Decrease inflammation
- Influence on other joints
- Superior to HA
- Role in treatment of OA and muscle injury
- Limited by FDA !

Platelet Rich Plasma (PRP)

- Increases healing growth factors
- Pro-fibrotic?
- Role in OA?
- Role in tissue healing?

Stem Cells

- Produce positive growth factors
- Influence progenitor cells
- Easily enhanced/cultured
- Best results with high cell counts (100m)

Stem Cells

- Enhancement controlled by FDA

BMAC

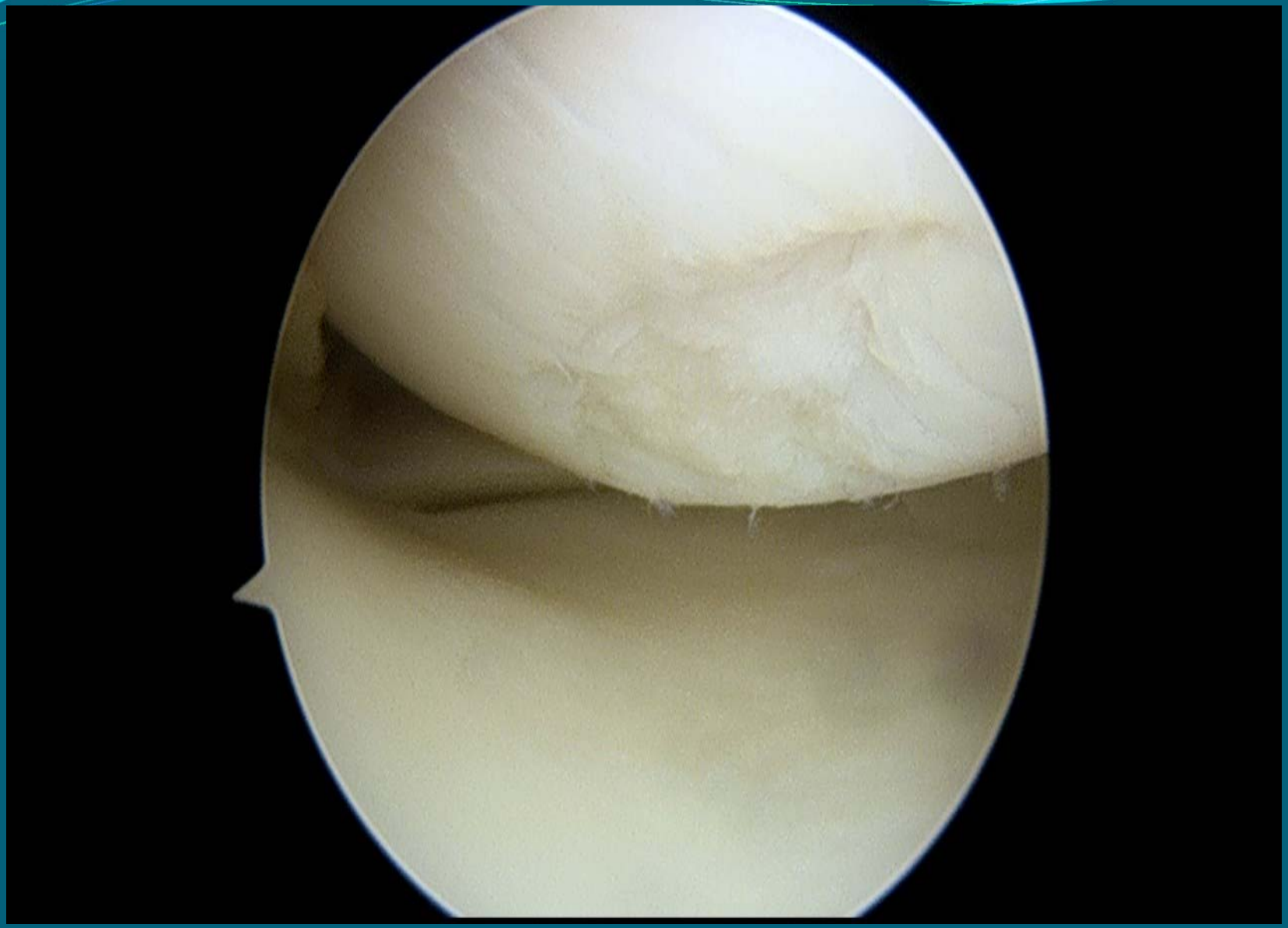
- Limited msc available
- Improves biologic environment?

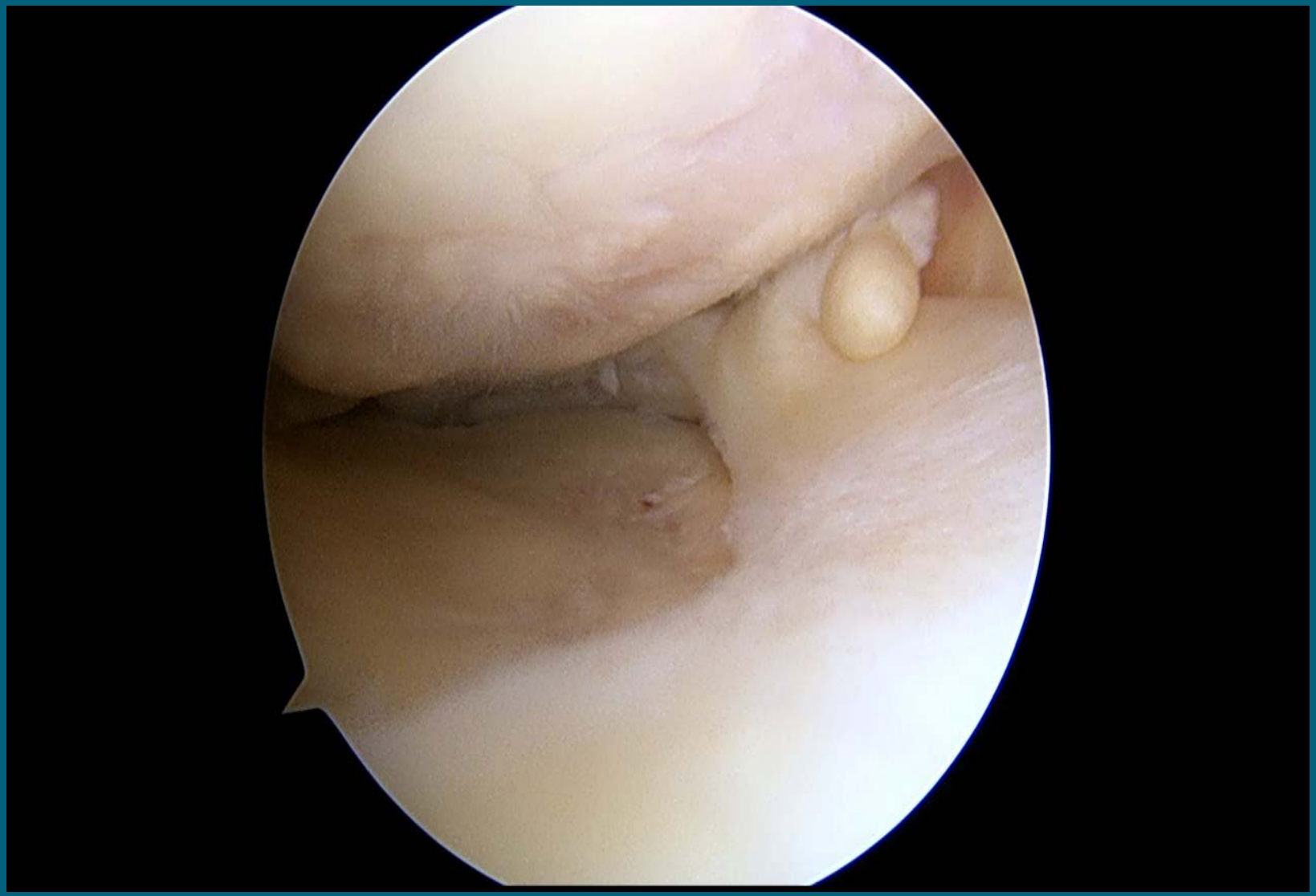
Embryonic Stem Cells

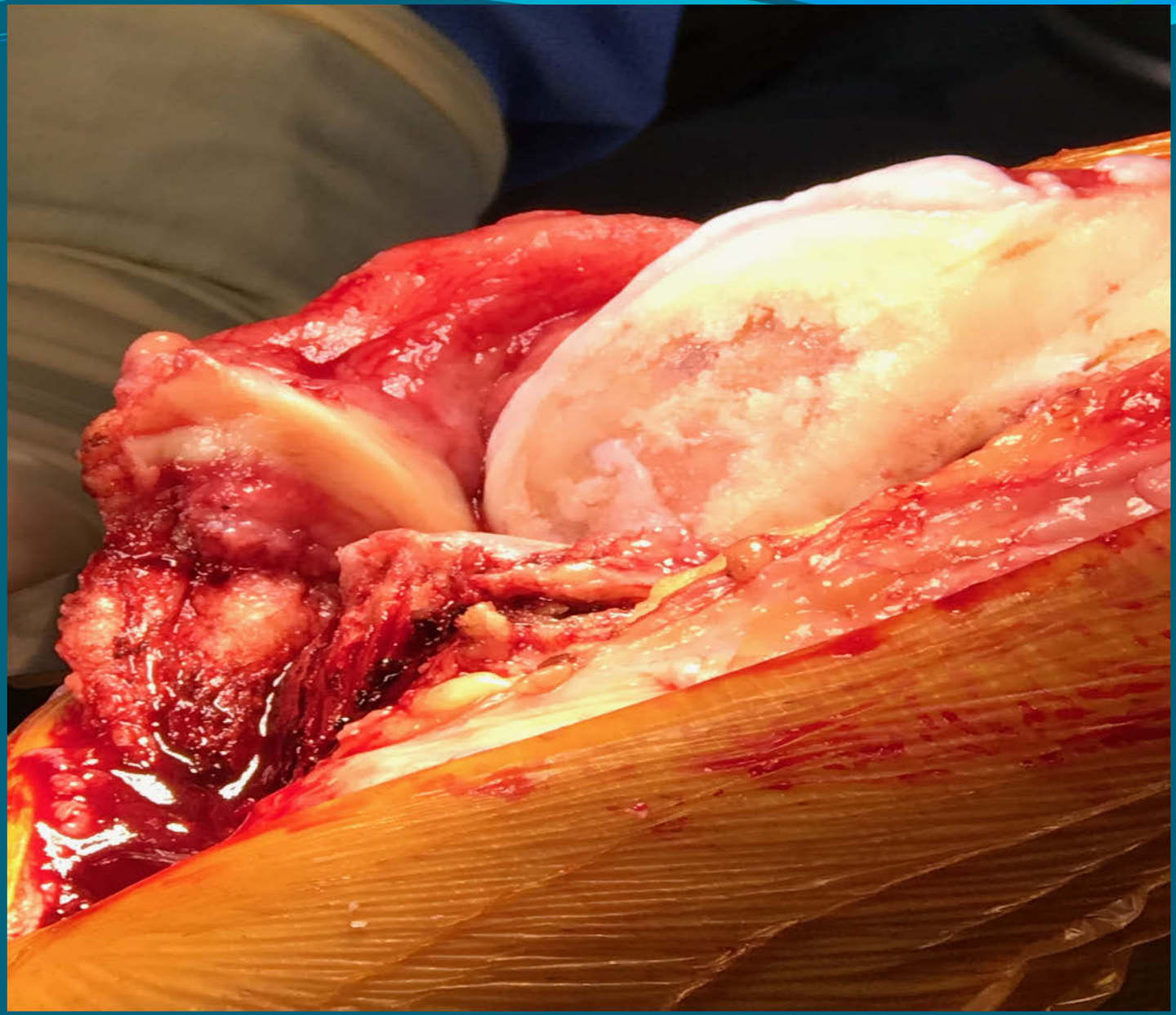
- ? Role

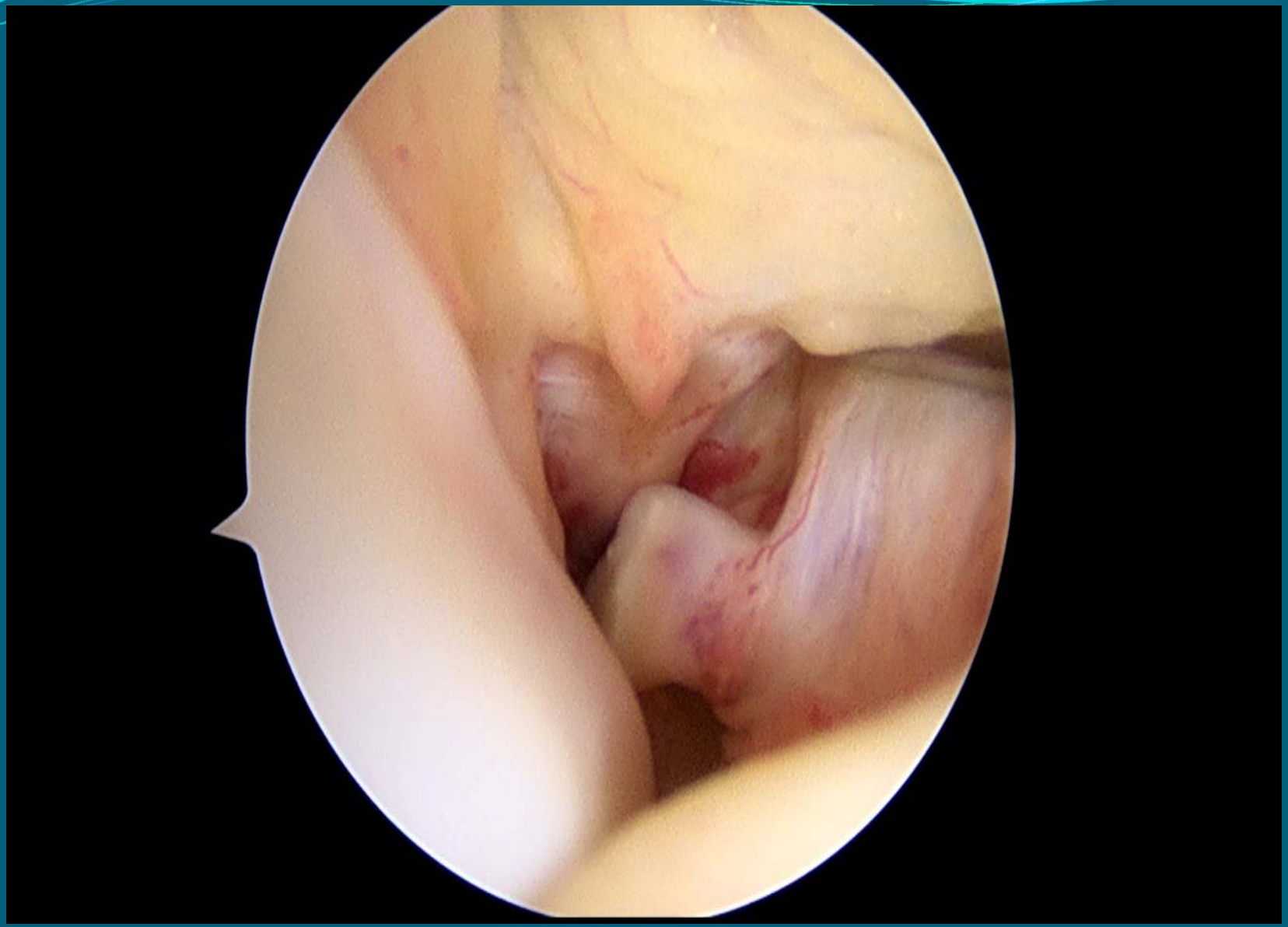
Mesenchymal Stem Cells / BMAC

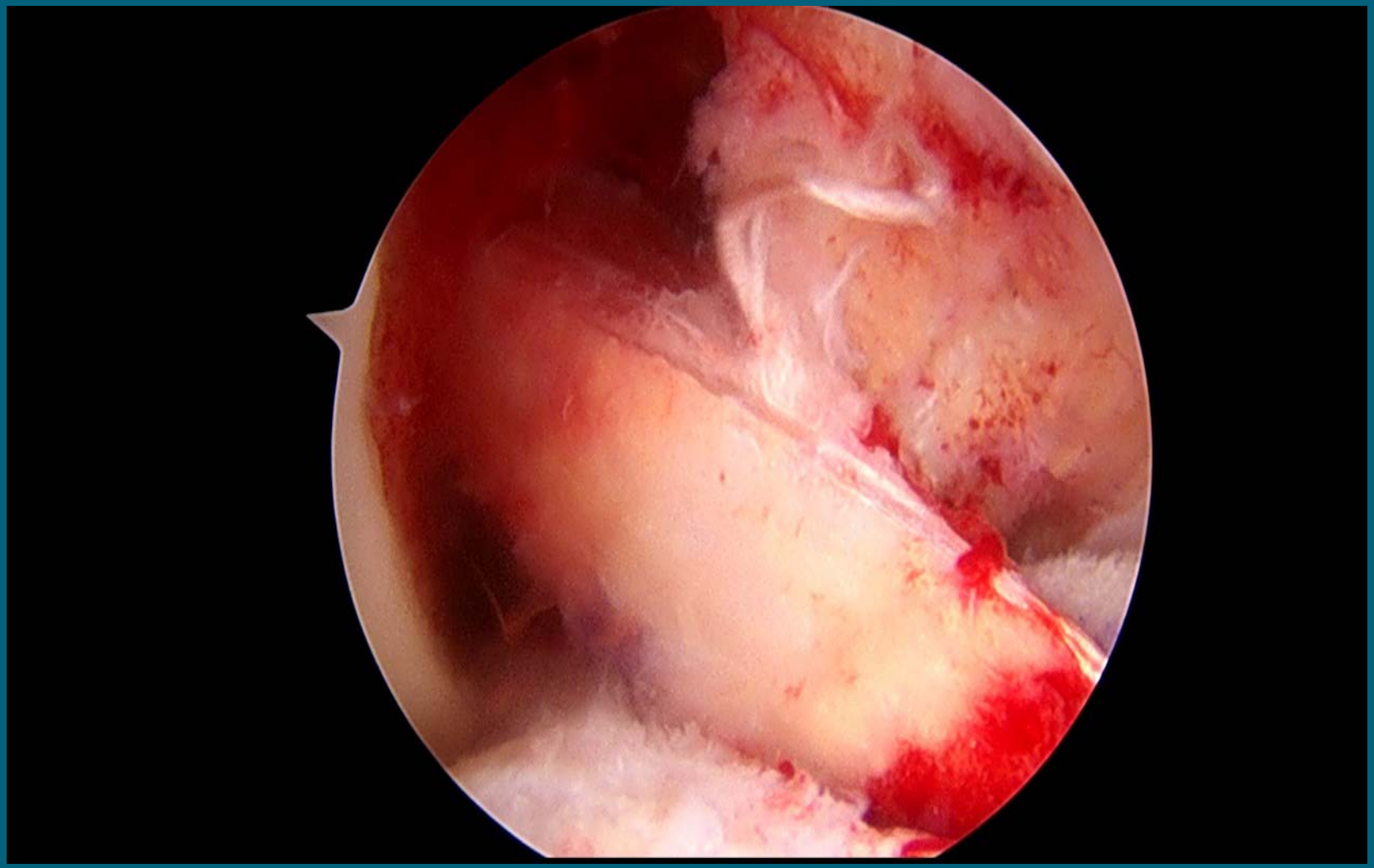
- OA?
- Ligament healing?
- Ligament reconstruction?
- Meniscal repairs?
- Post menisectomy?

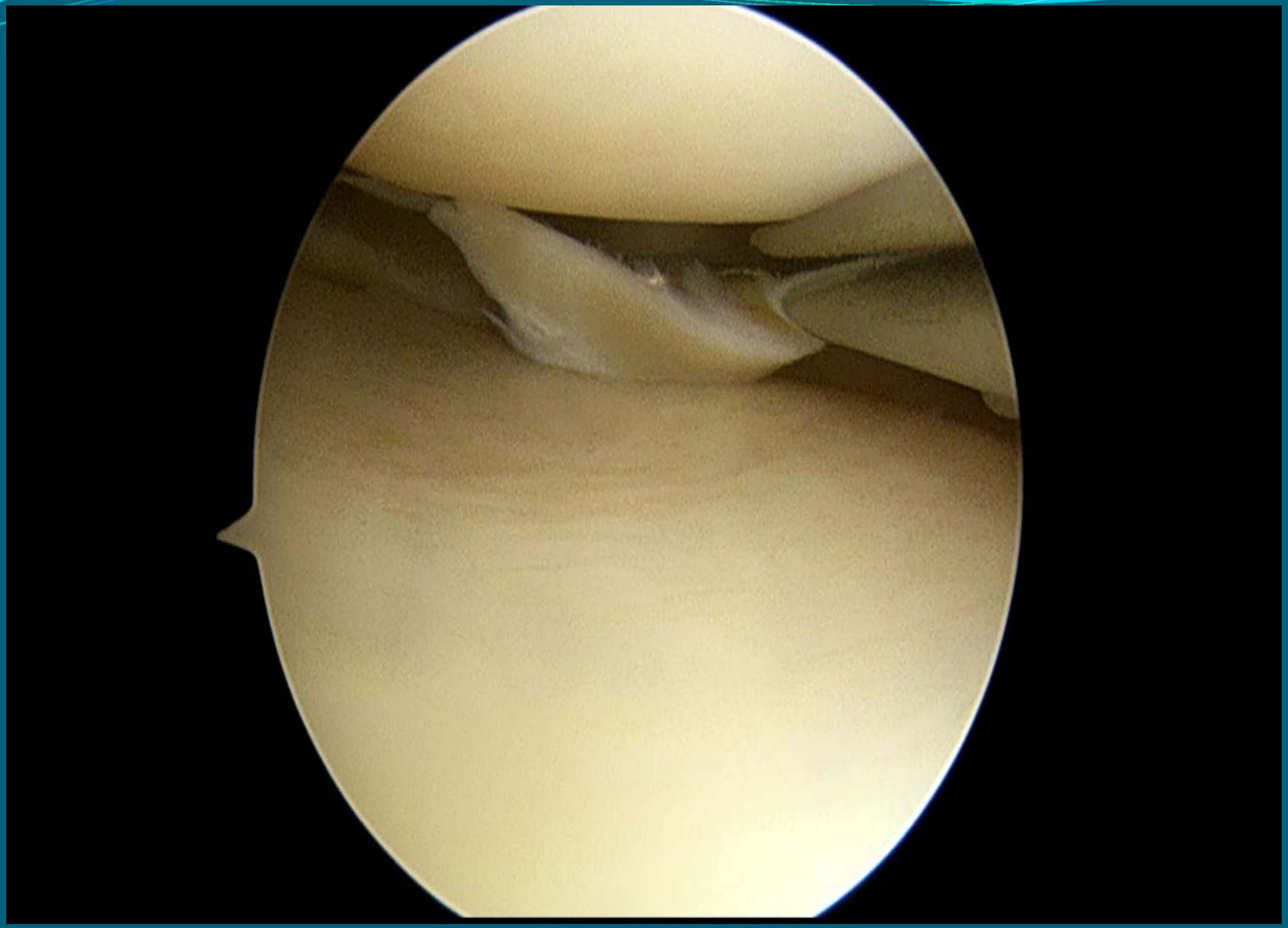


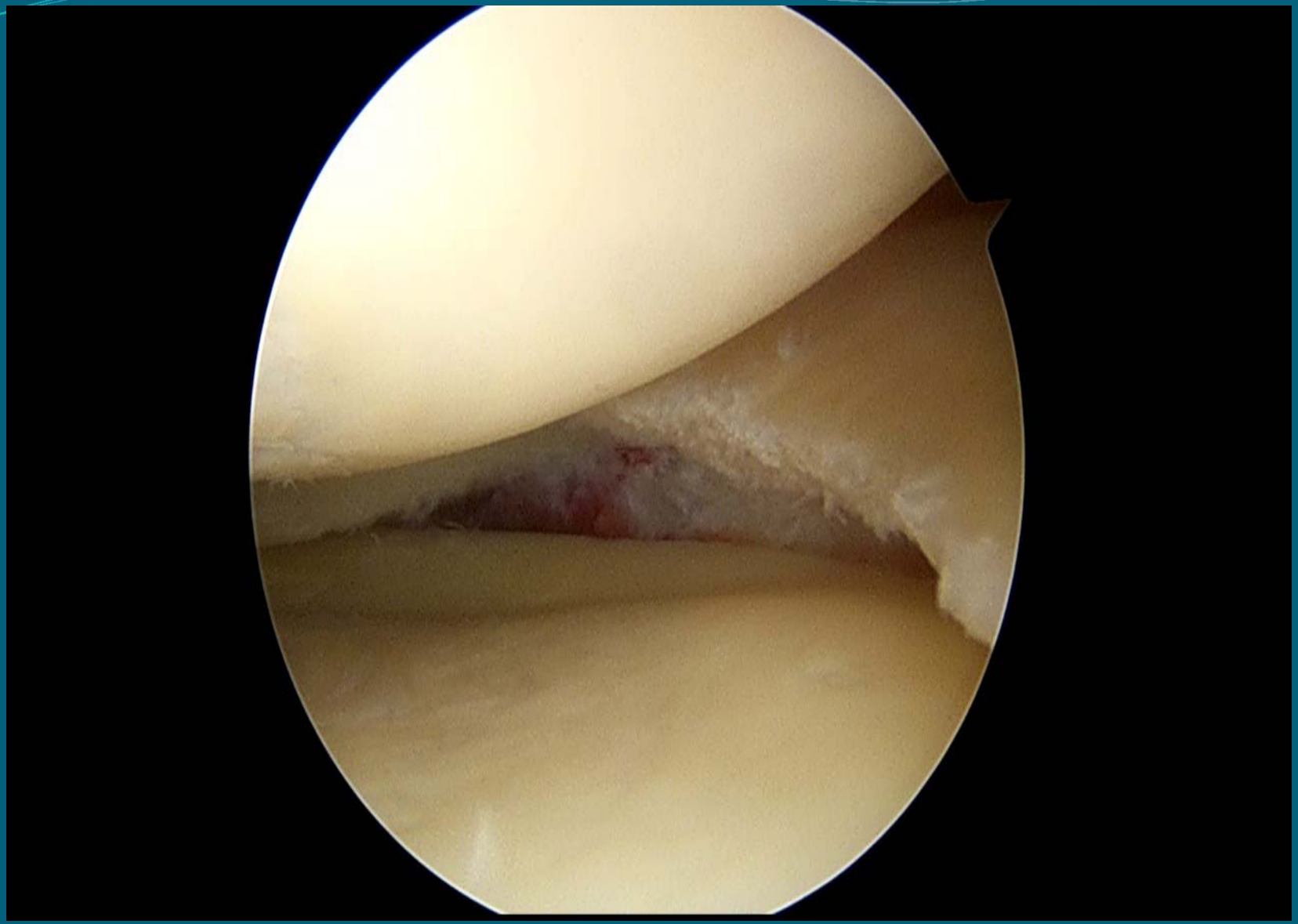


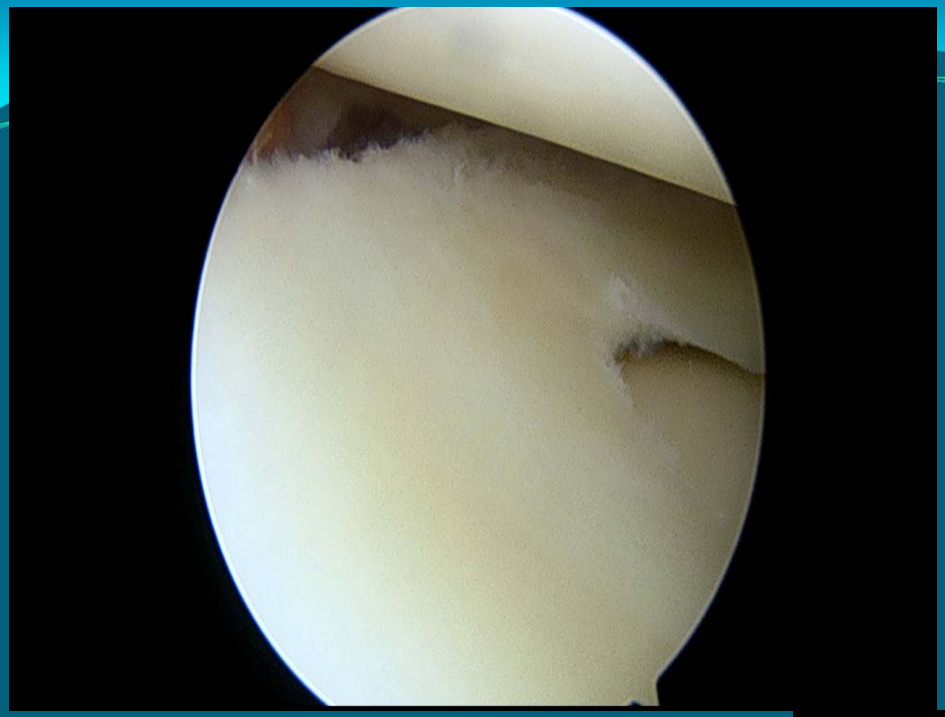


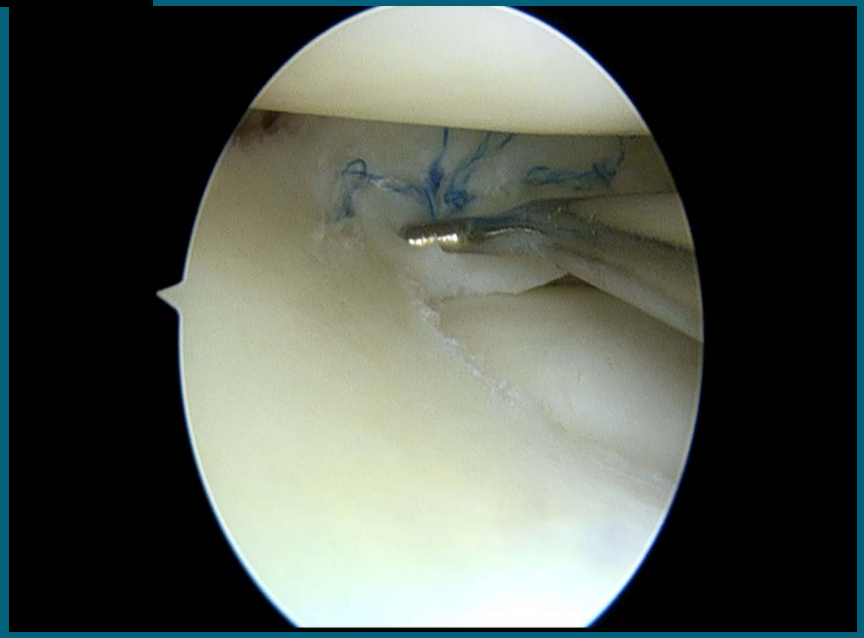


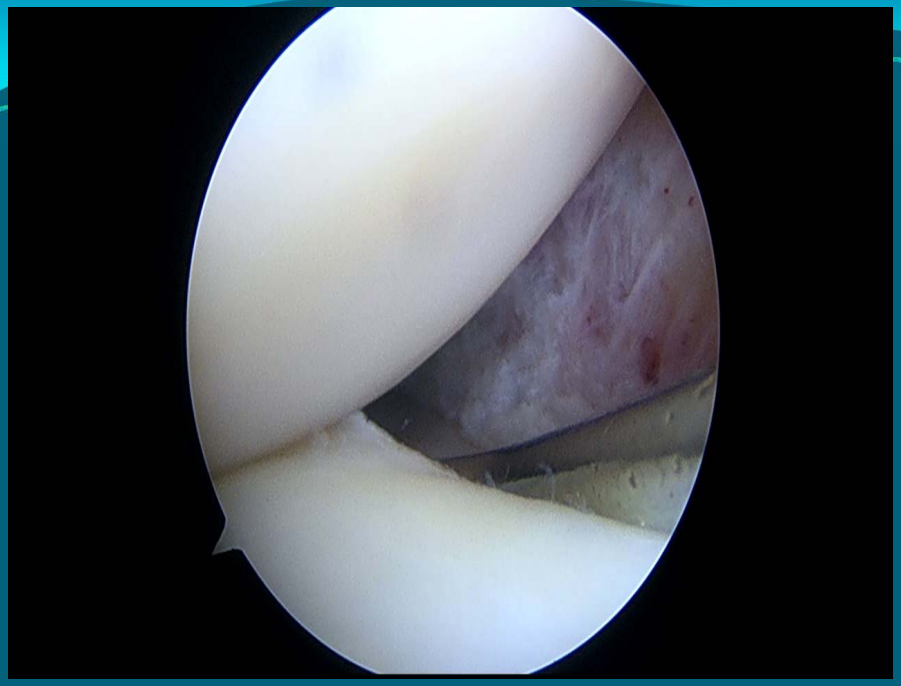


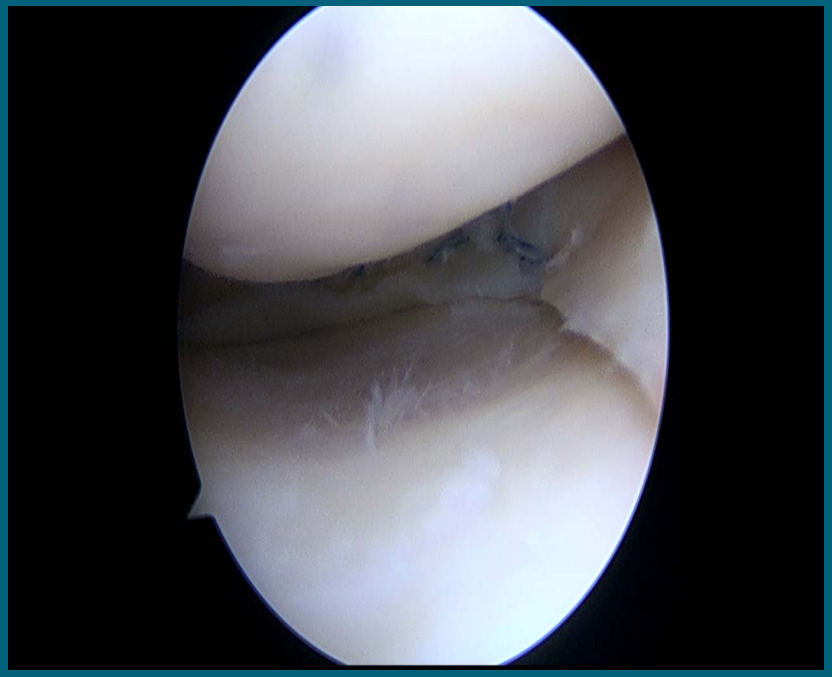












Timing of injections ?

- Intra-operative injections most likely influence inflammatory phase
- Consider injections 5 to 6 weeks post-op

Thank You !