
WORLD INSTITUTE OF PAIN®
28th Annual Gabor Racz Advanced Interventional Pain Conference and Workshop
Budapest, Hungary August 25-27, 2025
MSK Subchondral - Biologics : BMAC
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Conflict of interests

None to declare

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Editorial Board

- **Matrix Modulation of Stem Cell Phenotypic Behaviour Applied to Musculoskeletal Tissue Regeneration**

PDF Call for Papers | HTML Call for Papers

Guest Editors: Seok J. Kim, Asode A. Shetty, Akihiro Umezawa

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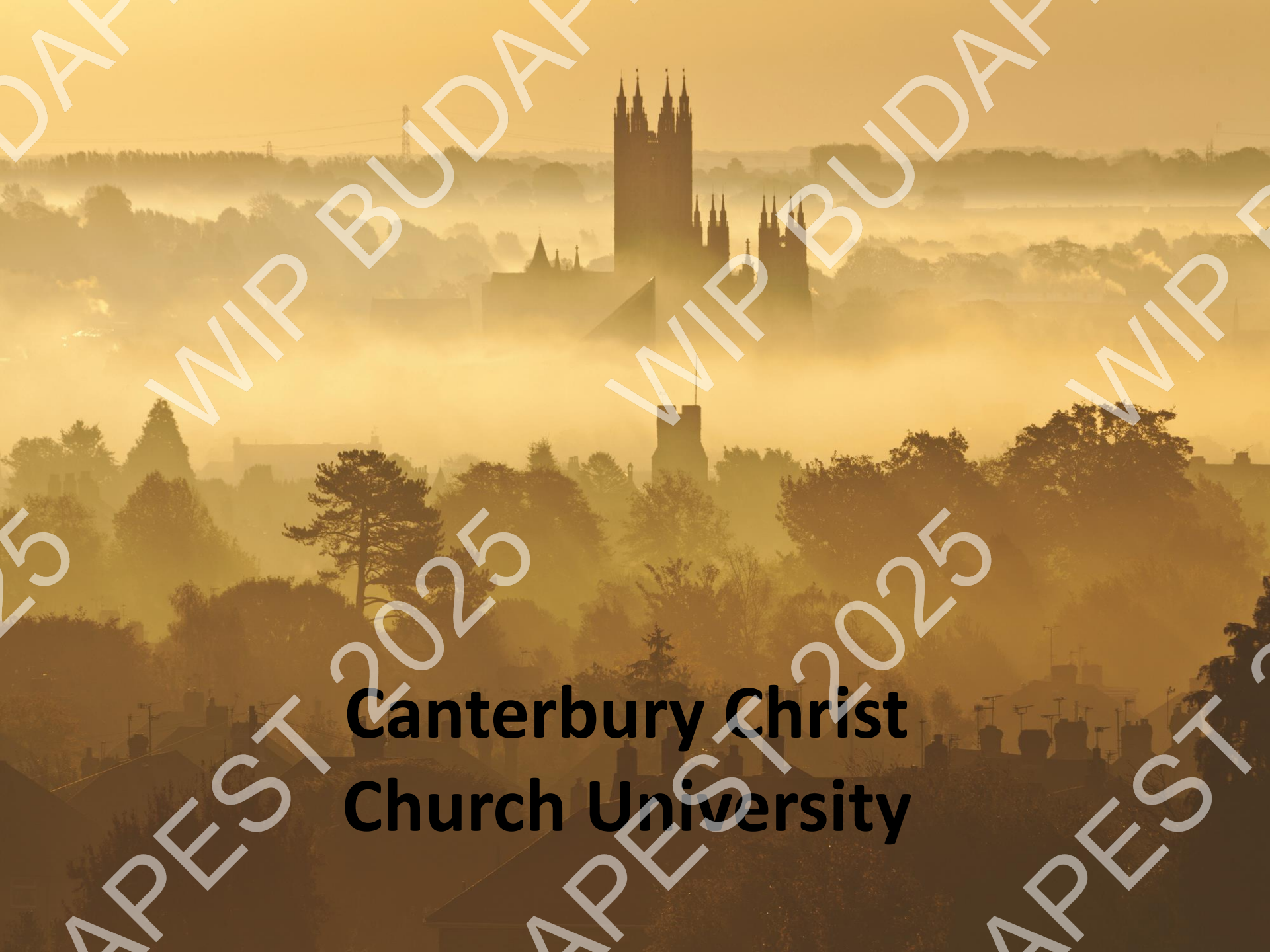


Canterbury Christ Church University

Good morning.

Greeting from CCCU

Canterbury Christ Church University

Post Doc- My first regenerative medicine conference 30 years ago…..

Orthopaedic Senior Resident :
30 years ago UKR for Cartilage defect

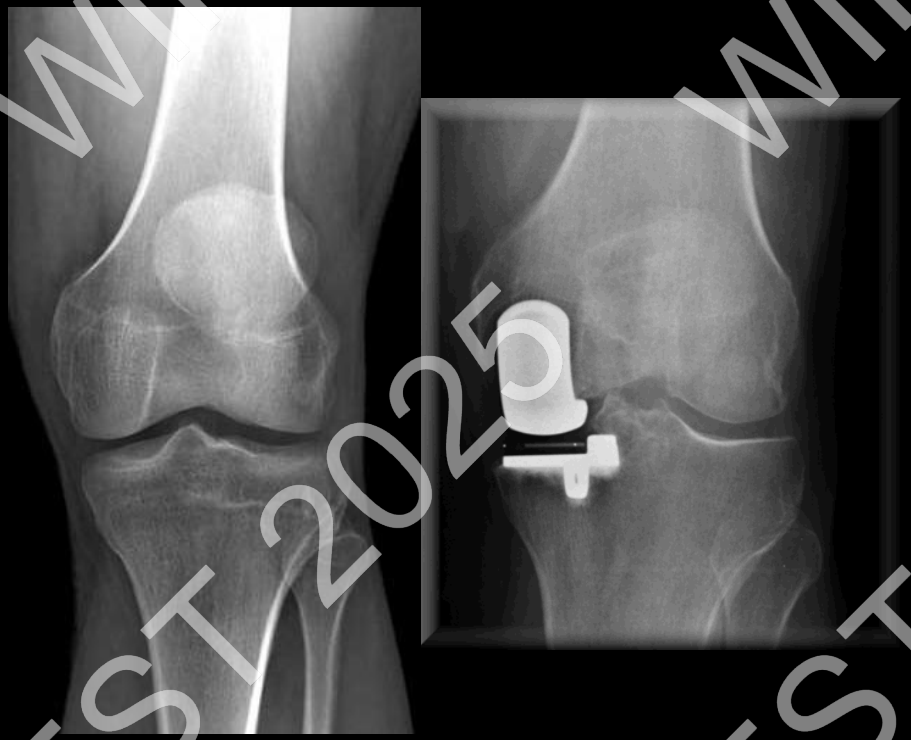
Uni-compartmental joint Replacement ?

- Universally bad result in Chondral defects

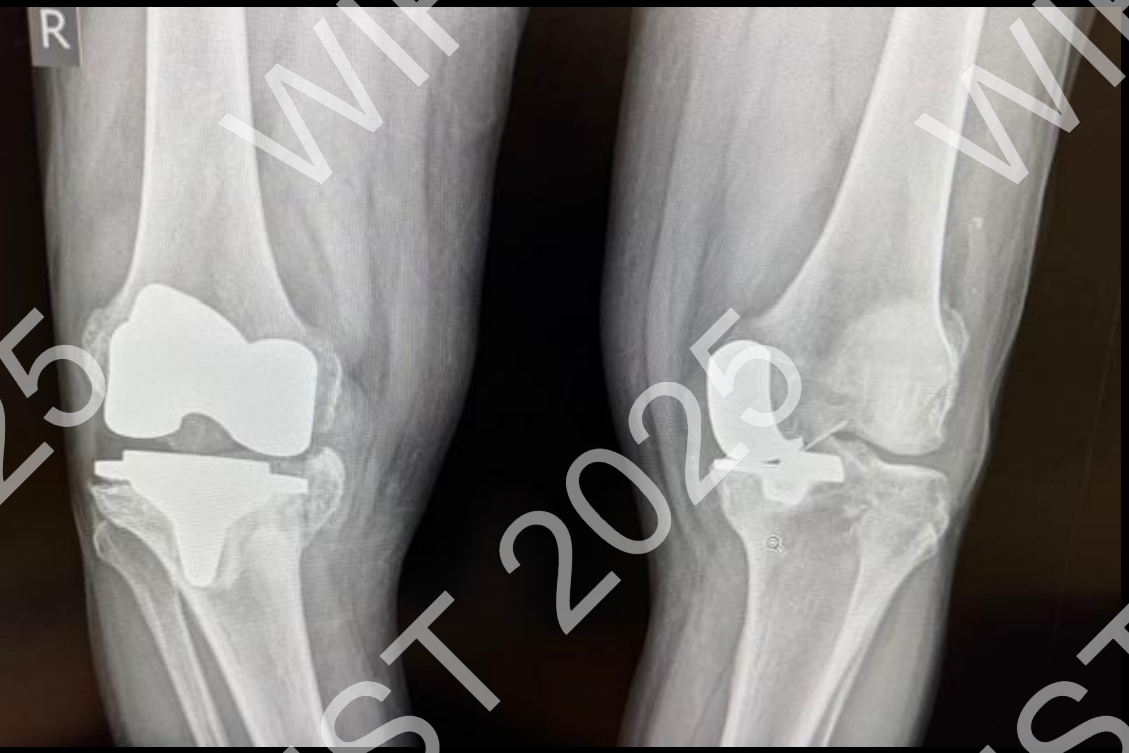
Oxford Group

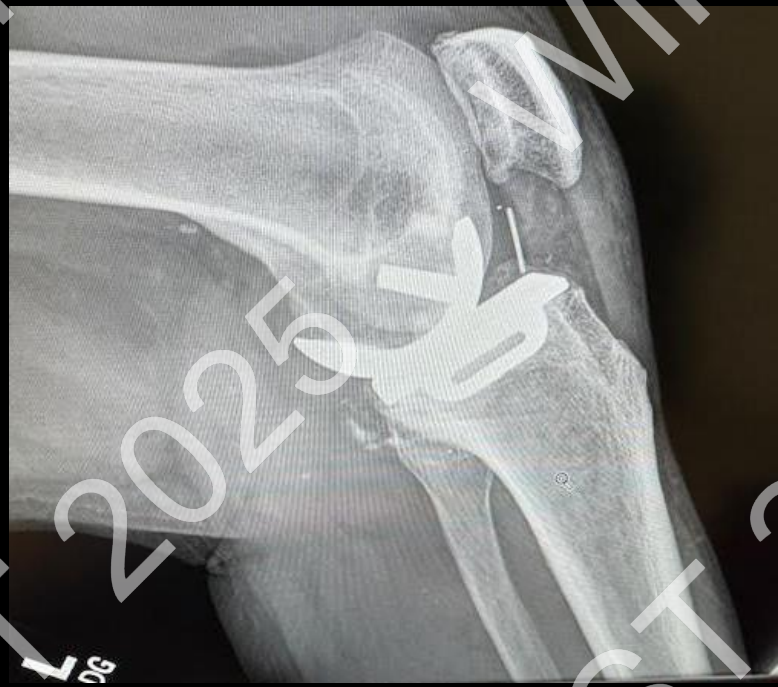
Pandit et al

The Knee 18(2011) 168-171



Consultant :25 years ago
Joint Replacement-Failure
Is it the time to change ?





Yes.

Price of not changing !.

(Professor-20 years ago)

Basic Science, Concepts & Terminology

Ortho – biologics: BMAC (Bone Marrow Aspirate Concentrate) - Subchondral Injection

Sub Chondroplasty or Intra Osseous Bio-Plasty (IOBP)

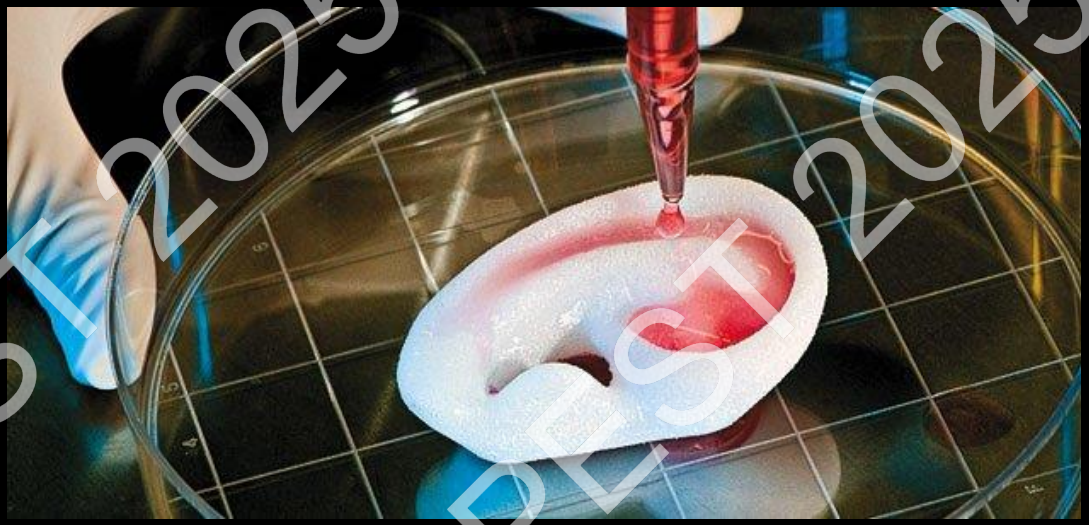
Ortho biologics are <u>therapies developed from biologic (natural) substances</u>

e.g., Cells, BMAC, Collagen Scaffolds, HA, PRP , Exosomes and Gene therapy

Tissue Engineering: Cells and Scaffolds

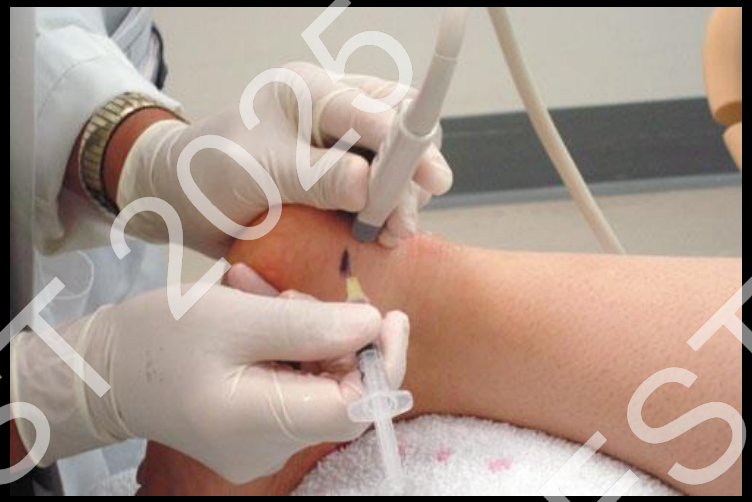
- Tissue engineering specifically uses biological and engineering principles to create new tissues and organs in a lab setting

  -*The term "tissue engineering" was officially coined at a National Science Foundation workshop in 1988*



Regenerative Medicine

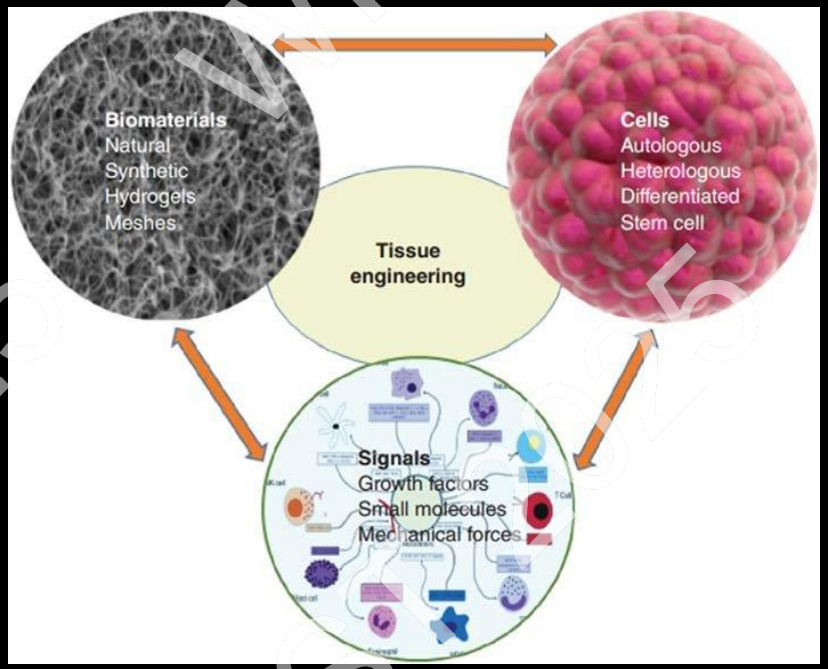
- Regenerative medicine is a field focused on repairing or replacing damaged tissues and restore normal function
- Cells, Tissues, and Organs



Stem Cells / PRP

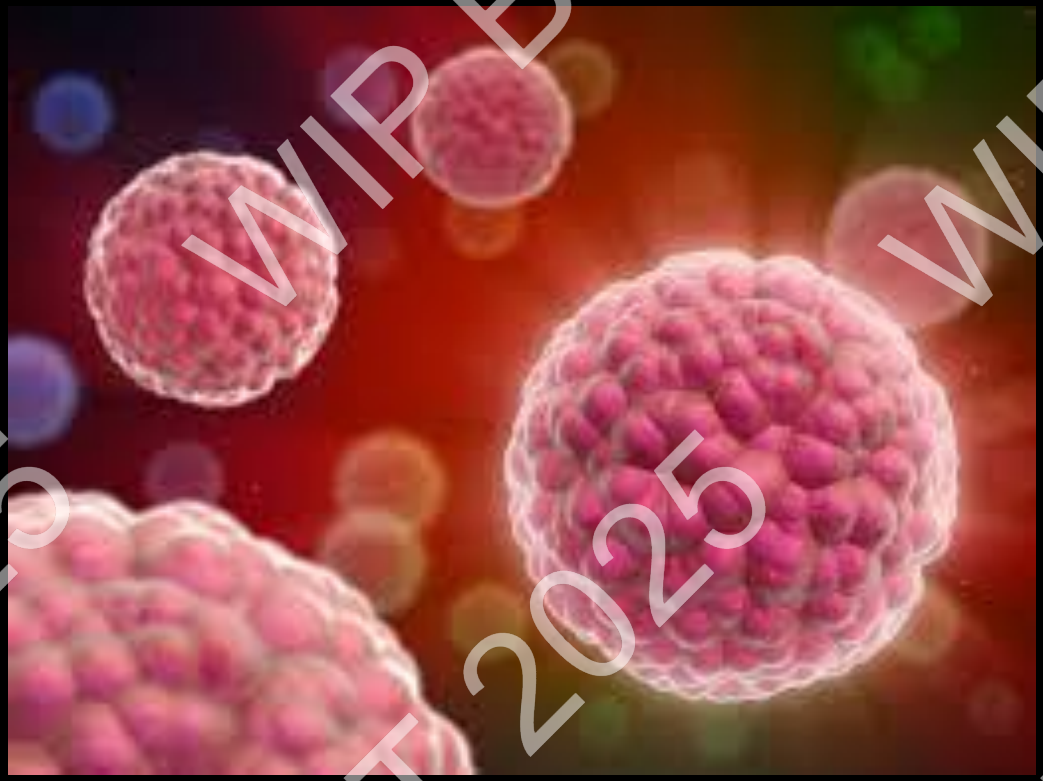
Regenerative Medicine: Triads

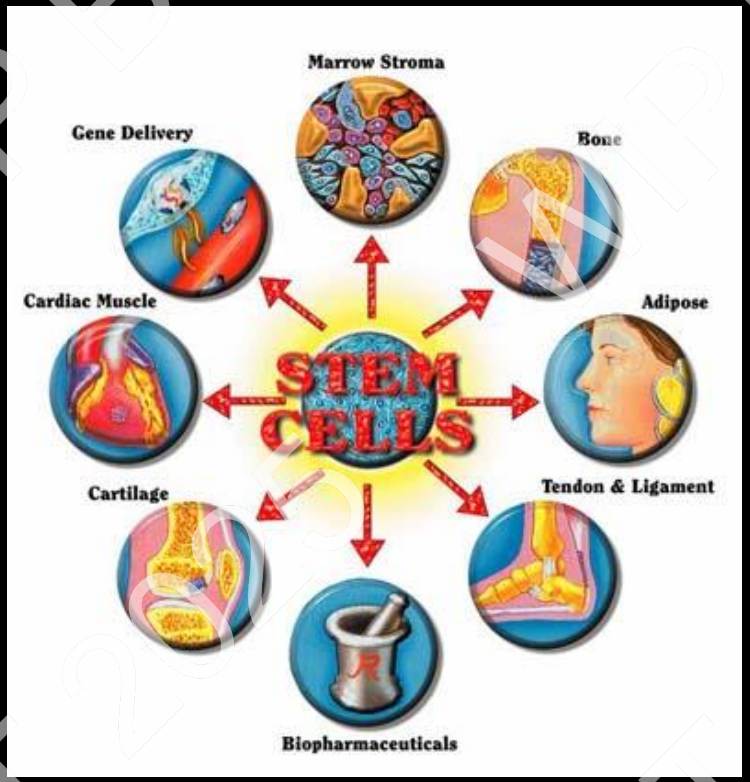
Cells, Signals, Scaffold



- Cells: Productive-
  Seed (e.g., Stem Cells, BMAC)
- Signals: Inductive-
  Fertilizer (eg.,GF, Exosomes)
- Scaffolds: Conductive-
  Soil (e.g., Atelocollagen, HA)

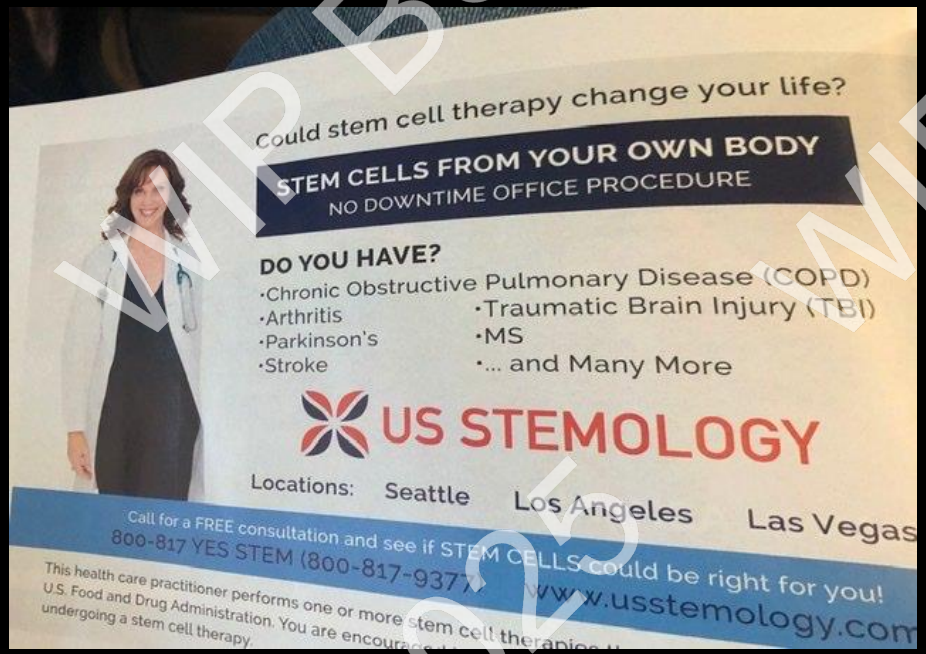
Cells: Stem cells

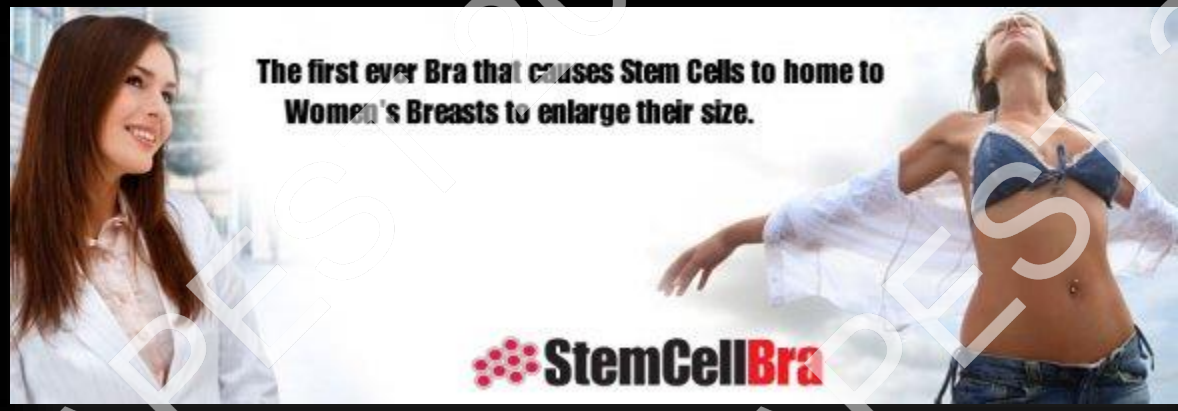




Stem Cell Injection- Hoax claim !

World's new fashion trend

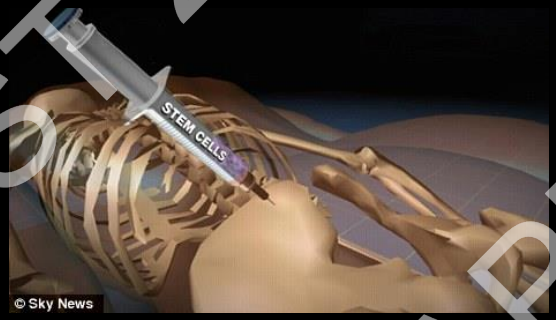


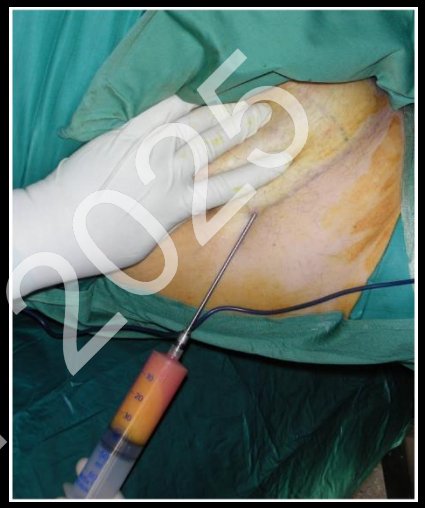


Stem Cells : Misleading terminology

BMAC: MSCs (Mesenchymal Stromal Cells) and CTPs (Connective Tissue Progenitor Cells)

- There is growing concern that uncharacterized, minimally manipulated cellular preparations from different sources are being misrepresented as stem cells





ADSCs-Adipose Derived Stromal Cells(SVF-Stromal Vascular Fragments)
MFAT-Micro Fragmented Adipose Cells

Mesenchymal Stem Cells-

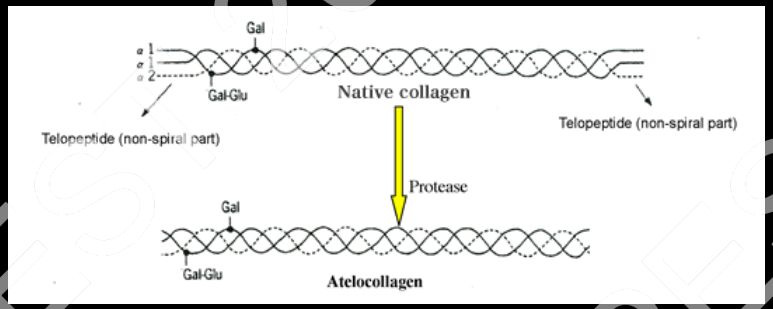
Criteria used to identify mesenchymal stem cells - As proposed by the International Society for Cellular Therapies

- Culture-expanded cells
- Adherence to plastic in standard culture condition
- Phenotype positive: (> 95% CD105, CD73, CD90
- Phenotype negative: (≤ 2%) CD45, CD34, CD14 or CD11b, CD79a or CD19 HLA-DR

BMAC - Minimally manipulated cells: Connective tissue progenitors (CTPs)

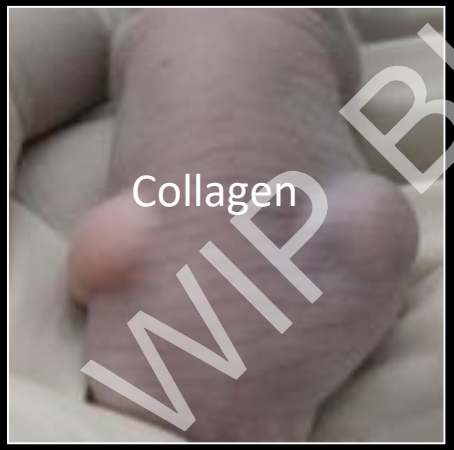
- Bone marrow cells 15 - 150 million cells /ml
- In human bone marrow, a mean of one in 20,000 cells may be CTPs
- CTPs - 30-45 Thousand Cells/ml
- Under normal conditions, connective tissue progenitors (CTPs) are not detectable in human blood

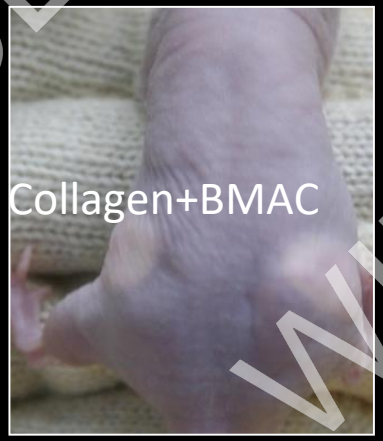
Scaffolds:
Atelocollagen-Coltrix® /HA

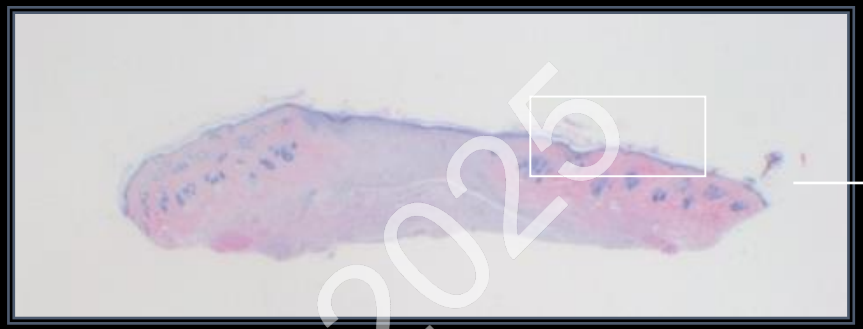


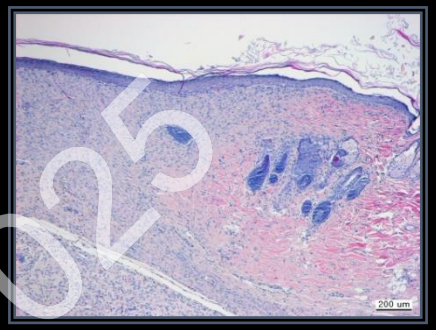
Signals-Growth factors
PRP-Plasma /Exosomes

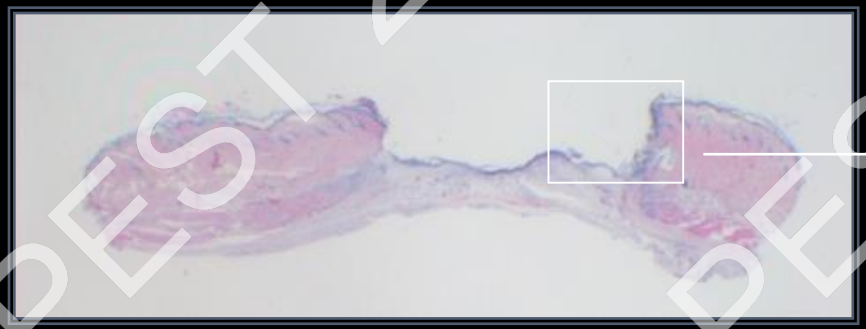
Animal Study : Rat
(Shetty-Kim : Scaffold + Cells + Signals)

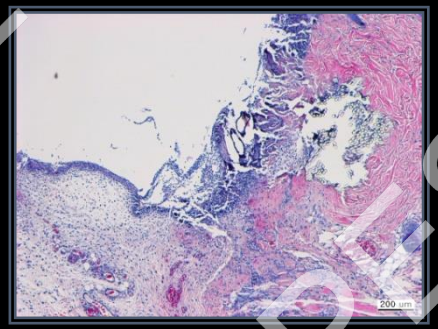




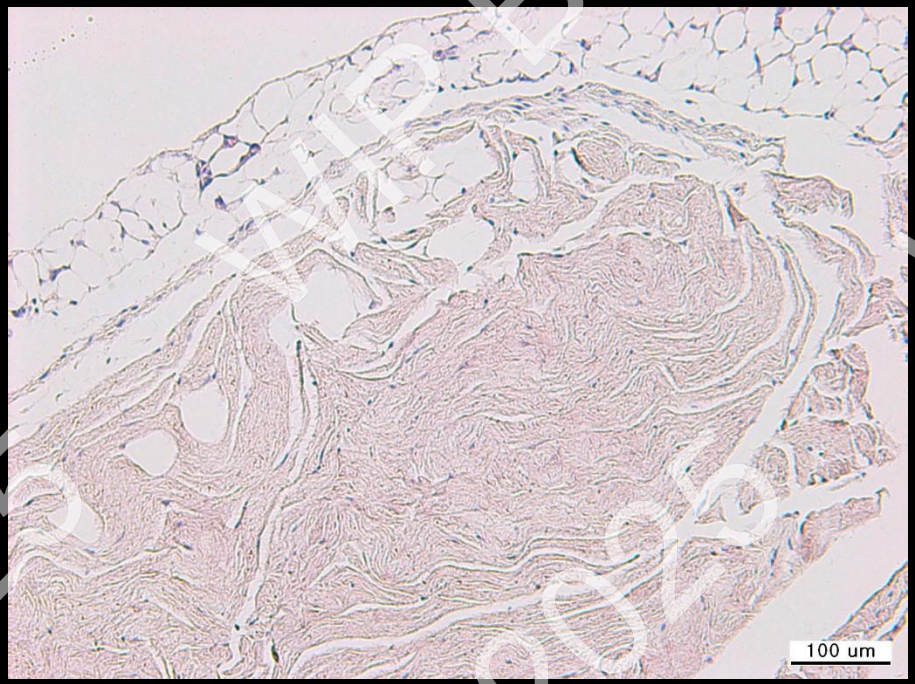




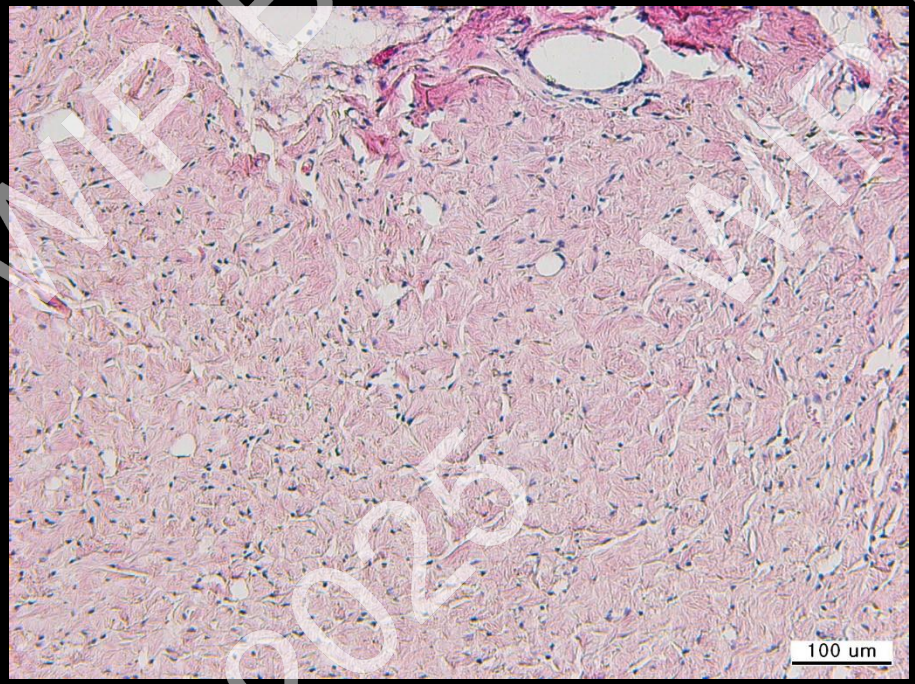




Tissue Regeneration-Cells, Scaffold and Signals

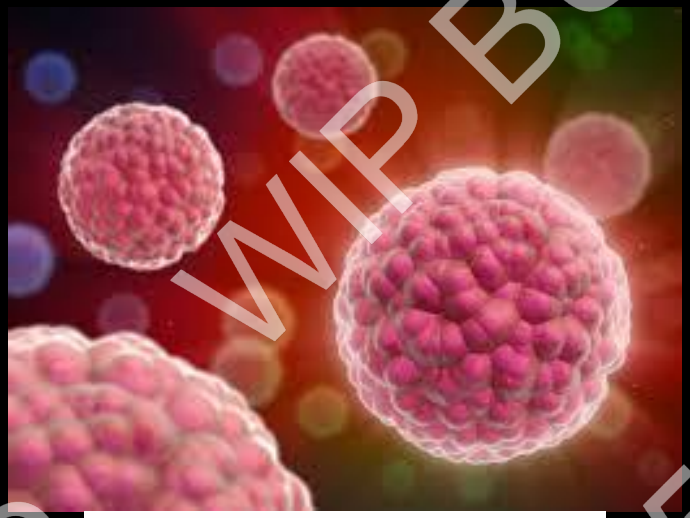


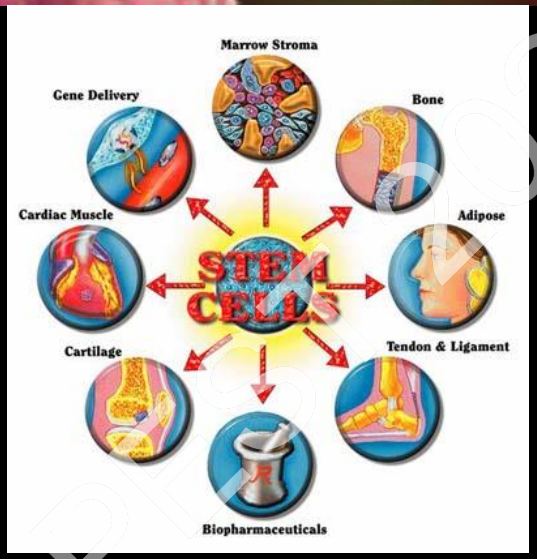
Scaffold-Atelocollagen



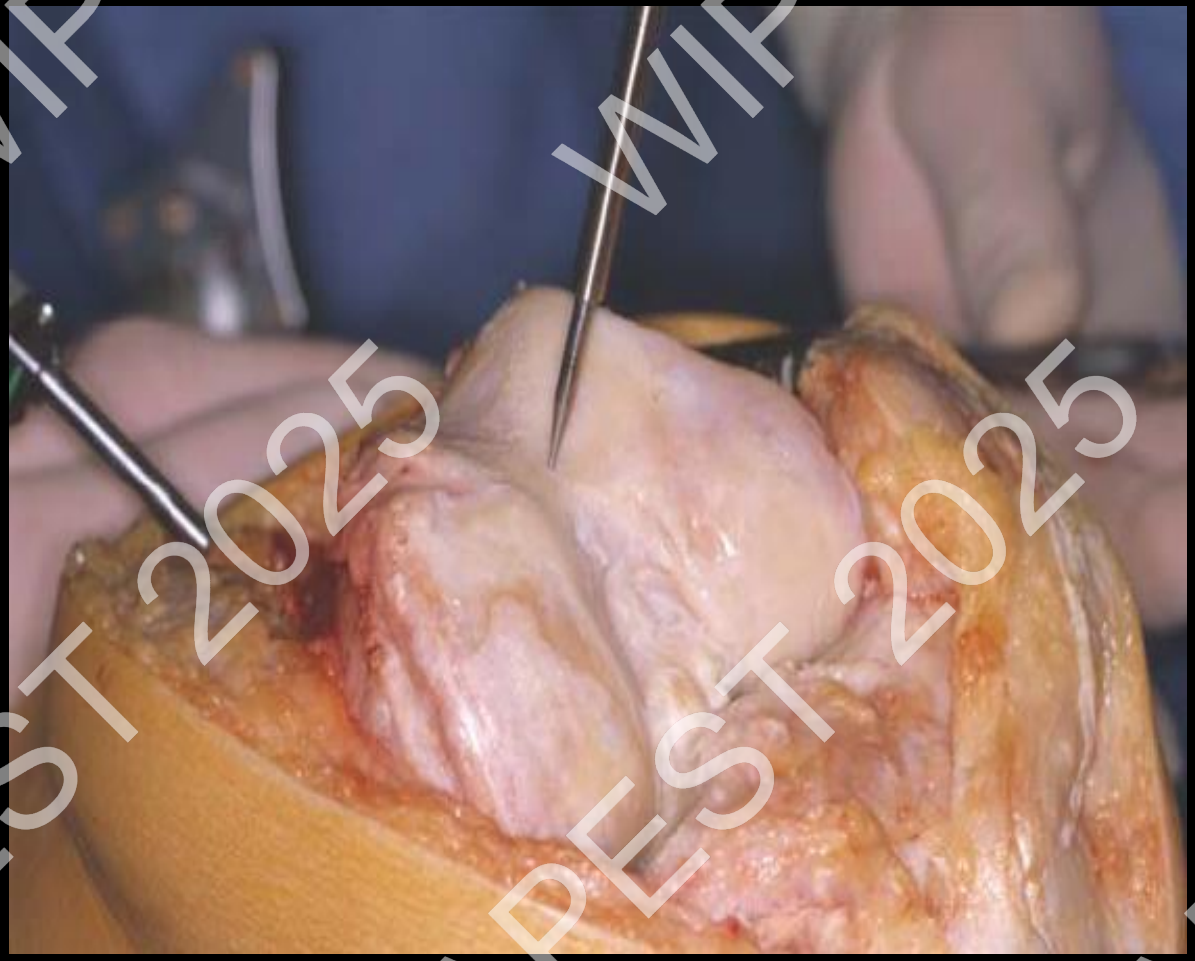
Scaffold + BMAC + Signal
(Atelocollagen + BMAC +Plasma)

Stem cells-New frontiers in Medicine
Big promise of a tiny cell….





OA Knee:
Can we grow a joint ?



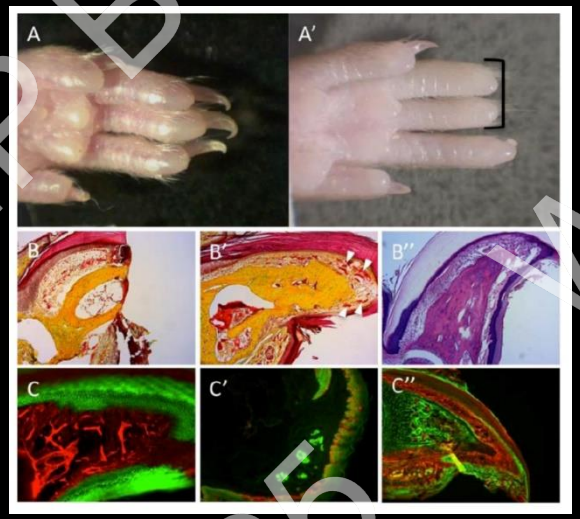
Nature -Stem Cells

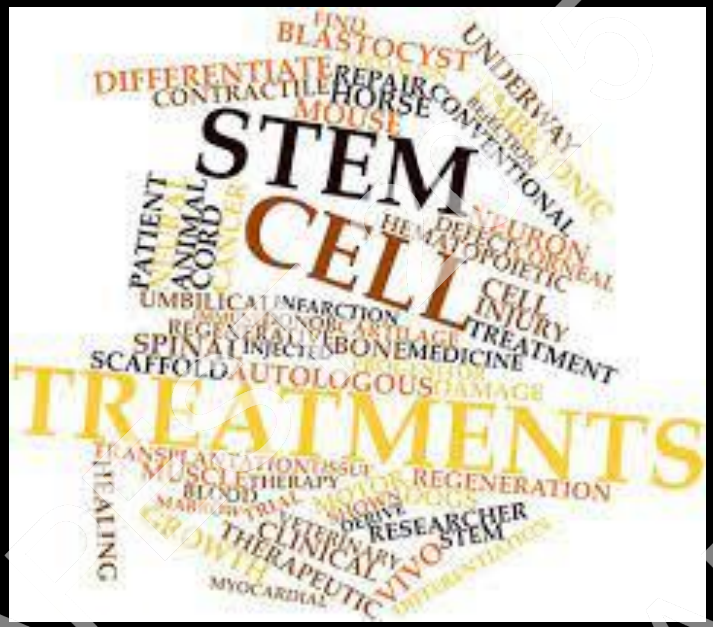
Regeneration of organs in animal kingdom

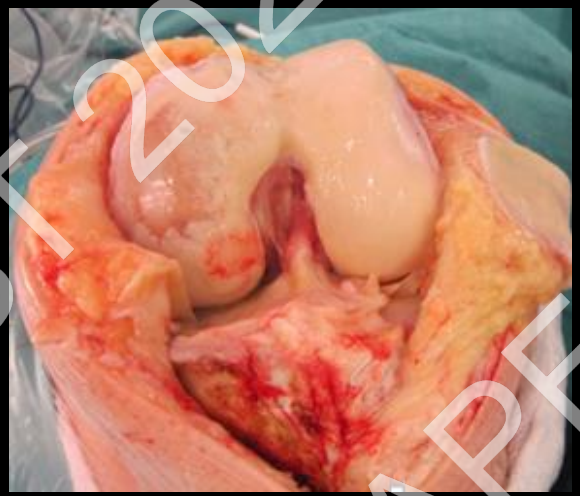
Salamander Limb regeneration

Why not in humans ?
Mouse fingertip regeneration

- Complex interplay of genes Fgf and immunolgy





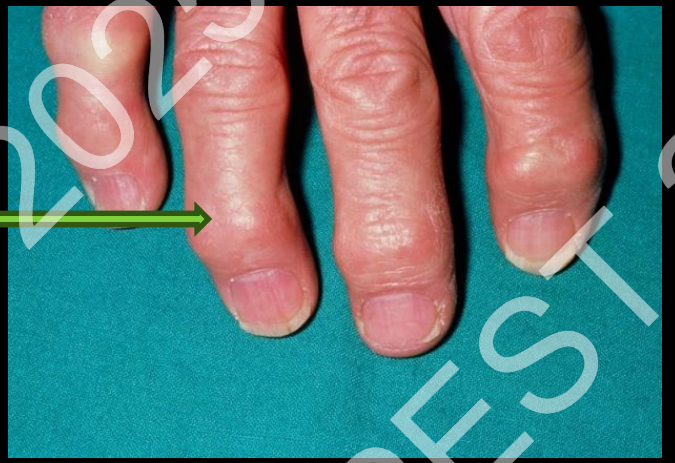


OA-Pathology and Chondral Defects:

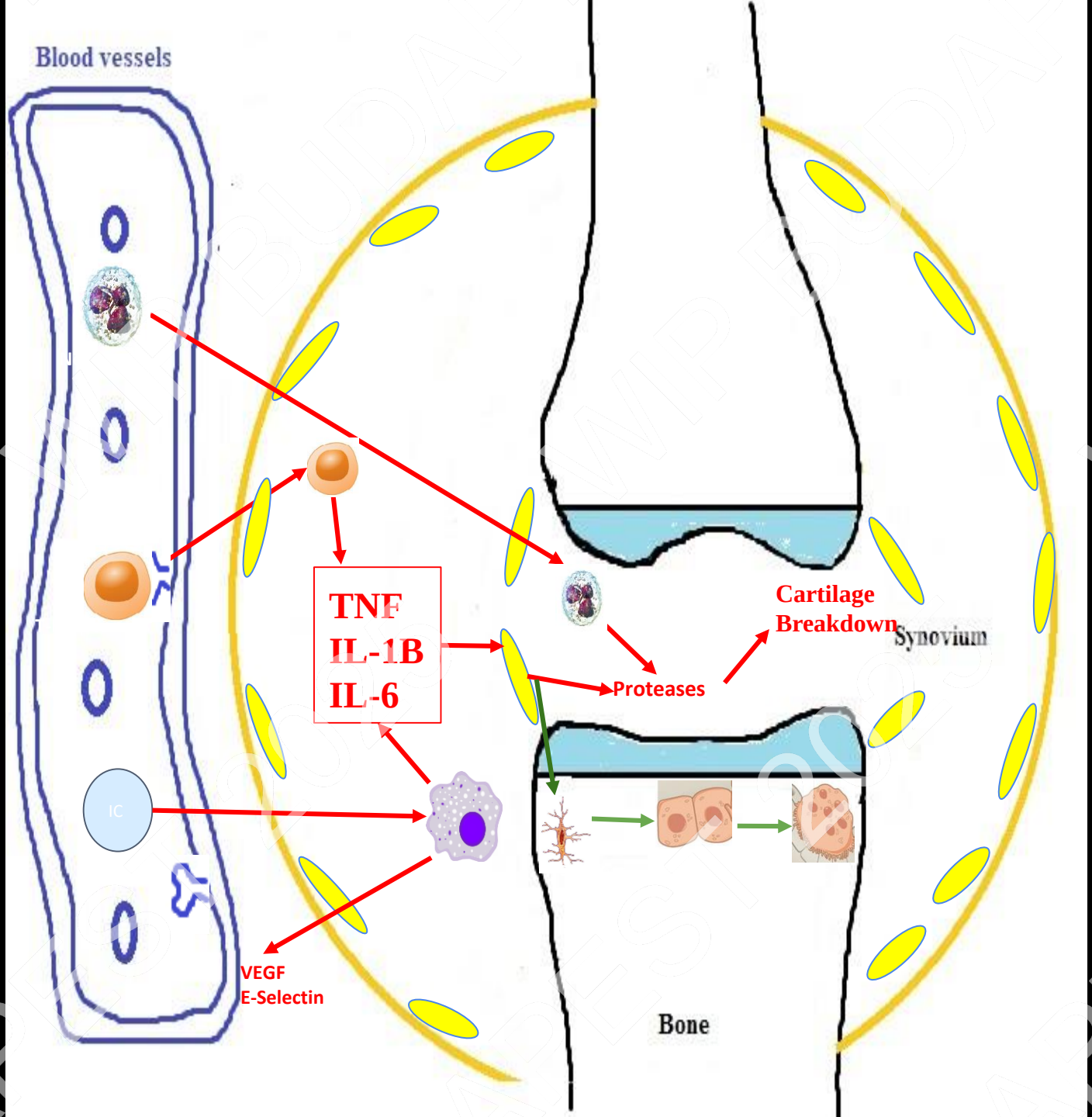
RISK FACTORS

- AGE ~ long period of time
- INFLAMMATION
  - IL-1
  - IL-6
  - TNF

  → CATABOLISM++ or ANABOLISM-
- JOINT INJURY
- MECHANICAL STRESS & OBESITY
- OTHER
  - neurologic disorders
  - genetics
  - medications



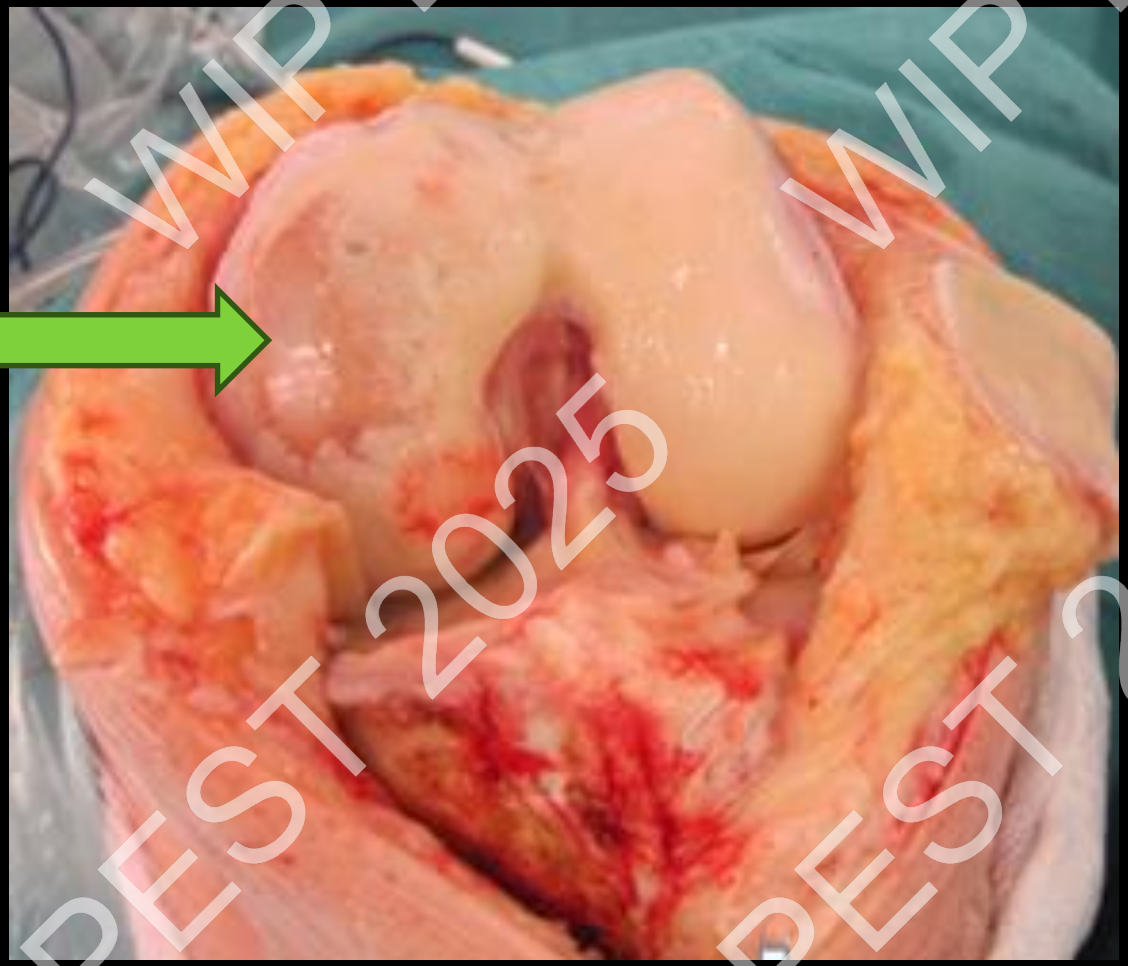
Heberden's Nodule

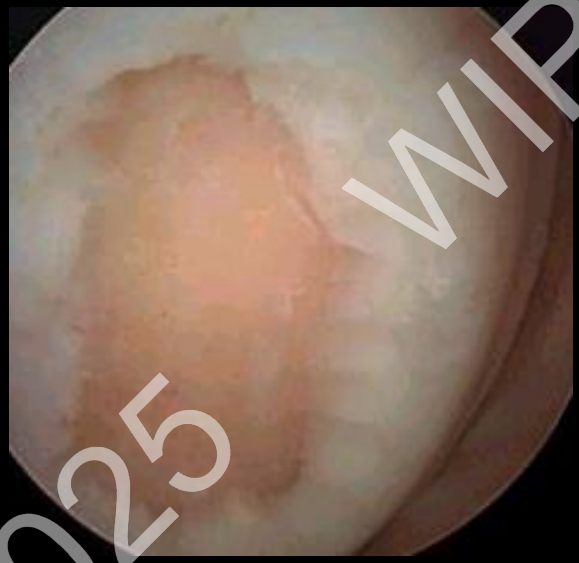

Blood vessels
TNF
IL-1B
IL-6
Cartilage
Breakdown
Synovium
Proteases
IC
VEGF
E-Selectin
Bone

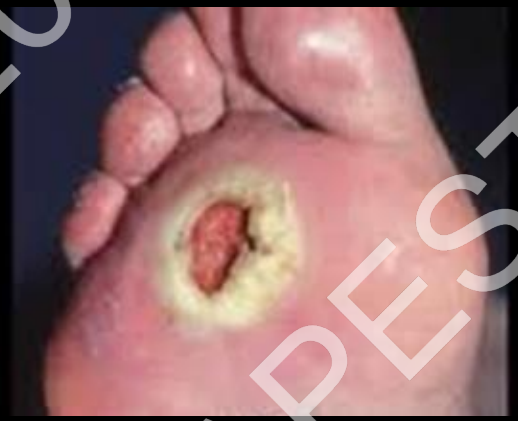
Shetty-Kim's Concepts: Cartilage Repair Surgery

Concept : Ulcer Concept

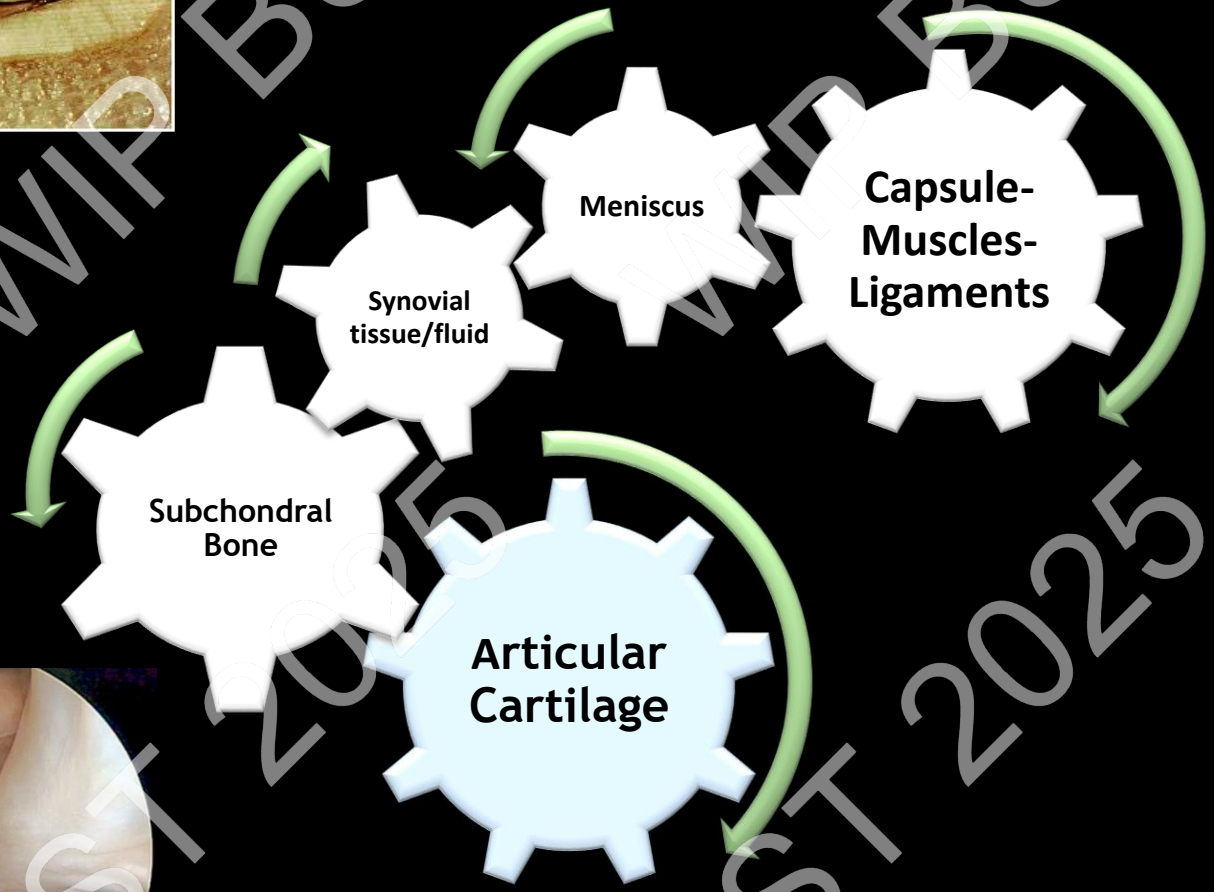
(Not wear and tear - Chronic Inflammatory condition- Resulting in ulcer)

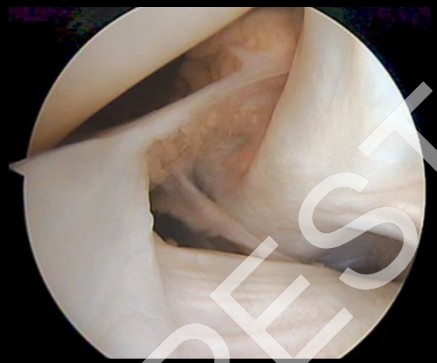






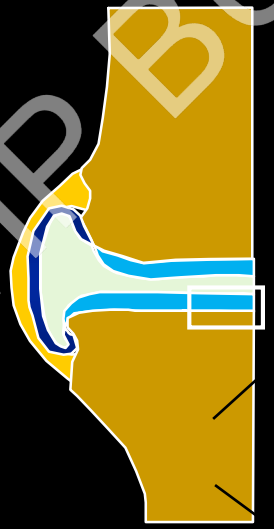
Concept :
Knee - A Synovial Organ

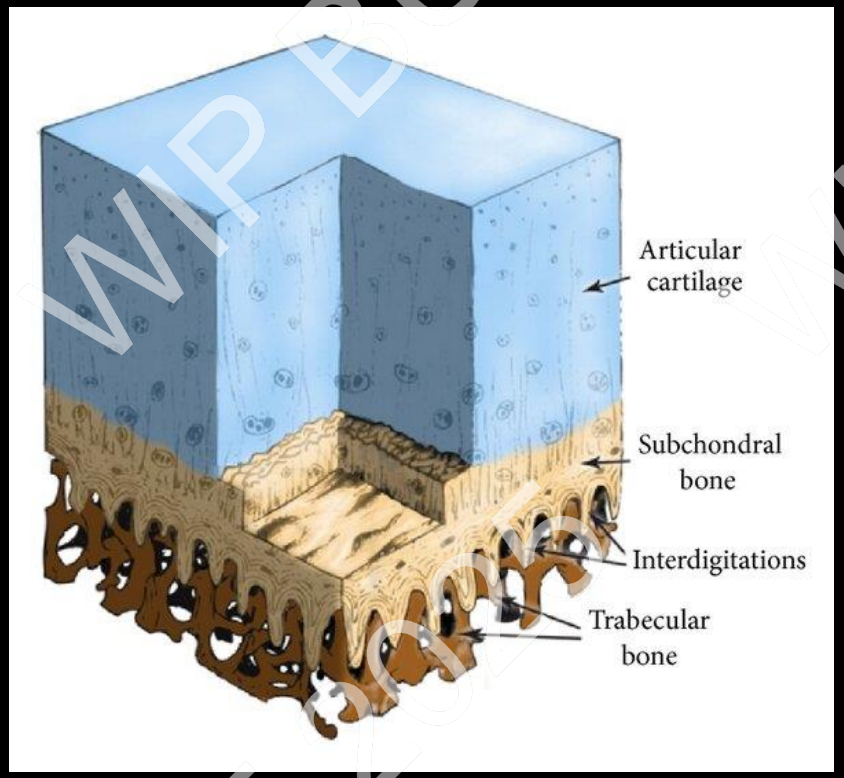


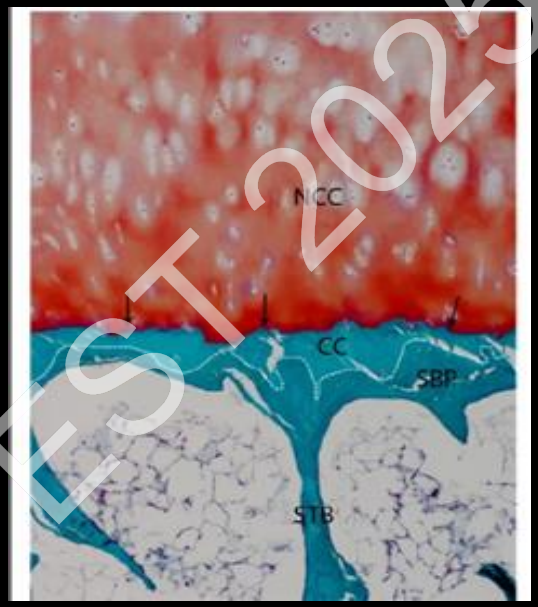


This “system” is called a Synovial Organ
We used to name it as “joint”

Subchondral Bone: A single unit (Osteo-Cartilaginous tissue)







Tide mark

Bone plate (Calcified layer CC)

Spongiosa (Subchondral bone SBP)

Subchondral Bone

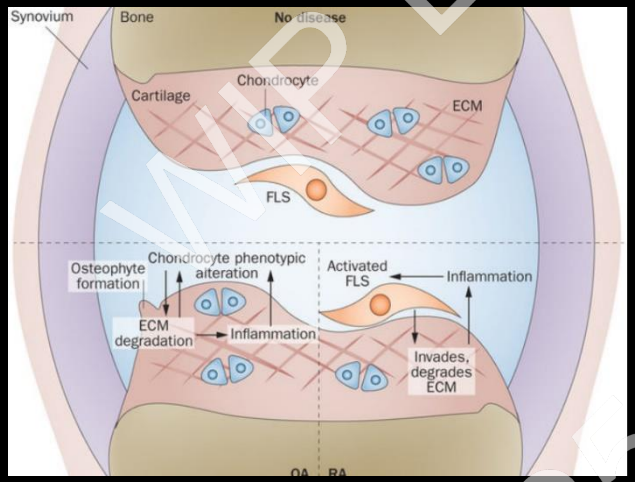
- Subchondral bone provides both mechanical and nutritional support for cartilage

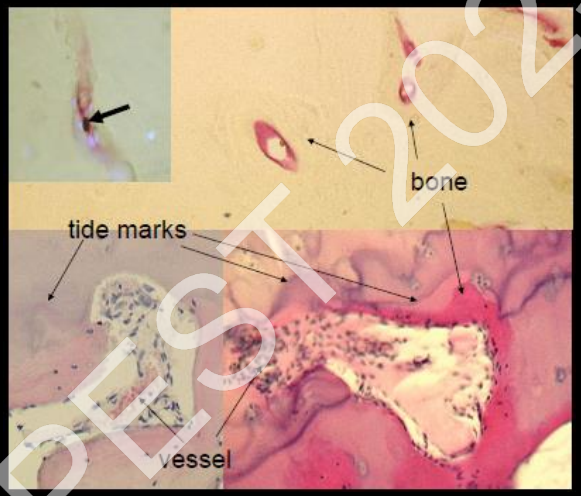
- The blood flow rate is 3 to 10 times higher than that in cancellous bone

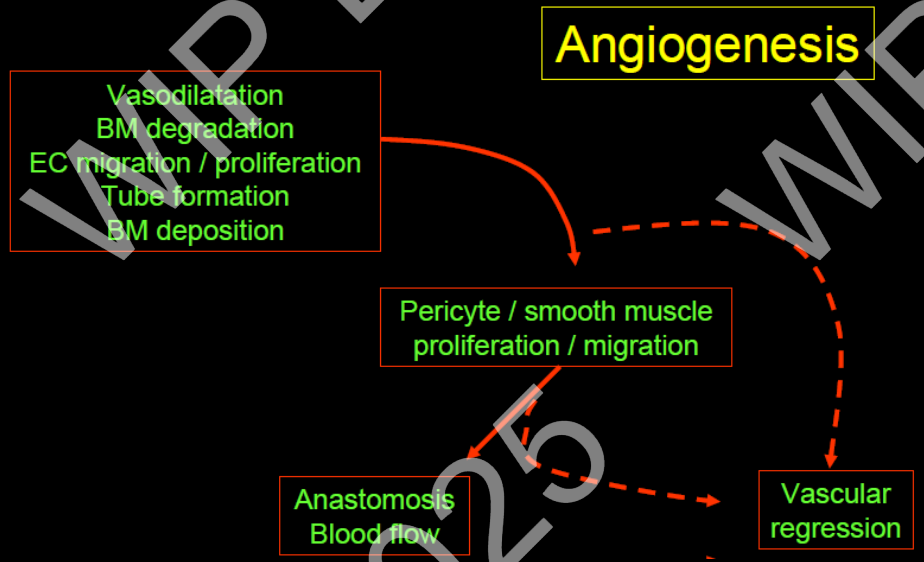
> "The role of subchondral bone in the etiology and progression of cartilage disease has likely been underestimated, although the earliest scientific reports appeared in the 1920s"

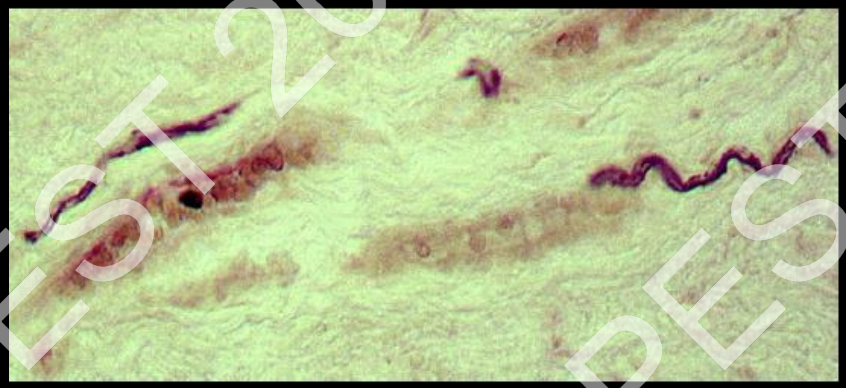
Subchondral changes results in-

Angiogenesis and Neural invasion of cartilage









Walsh et al

Articular Cartilage Repair:

Mesenchymal cell Induced Chondrogenesis : MCIC®

(BMC-Stromal cells and HA Scaffold) : Translational Clinical study - Landmark paper(NICE Approved)

Royal College of Surgeons
ADVANCING SURGICAL CARE

KNEE SURGERY

Ann R Coll Surg Engl 2018; **100:** 240–246
doi 10.1308/rcsann.2017.0223

A cost-effective cell- and matrix-based minimally invasive single-stage chondroregenerative technique developed with validated vertical translation methodology

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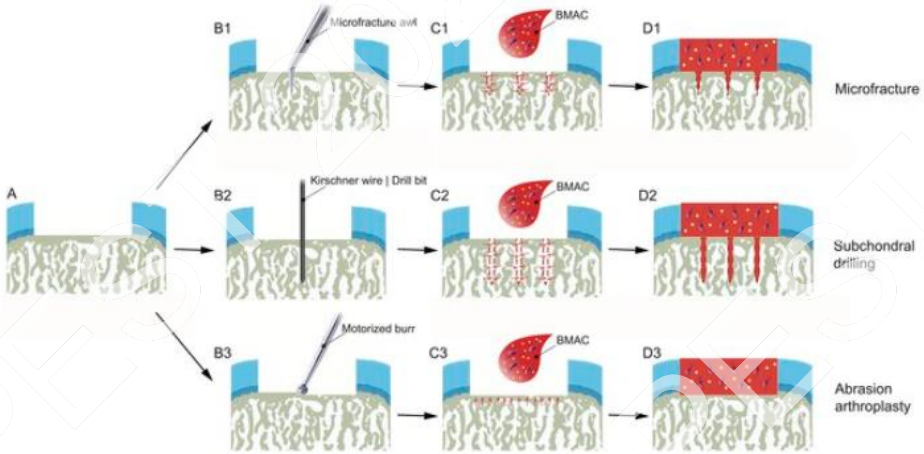
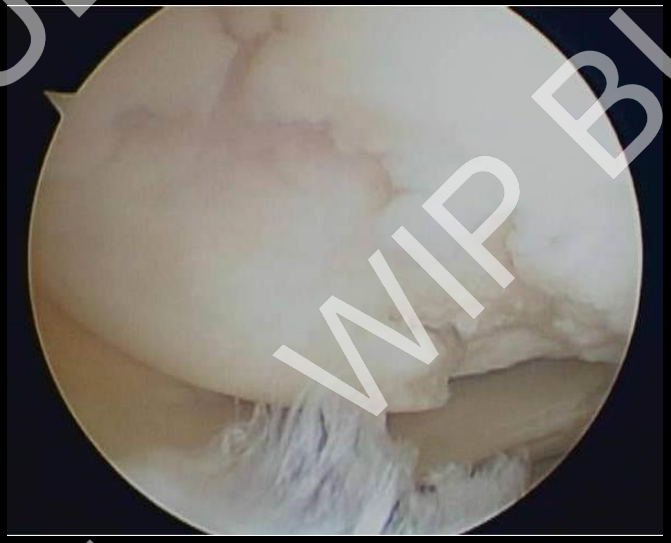
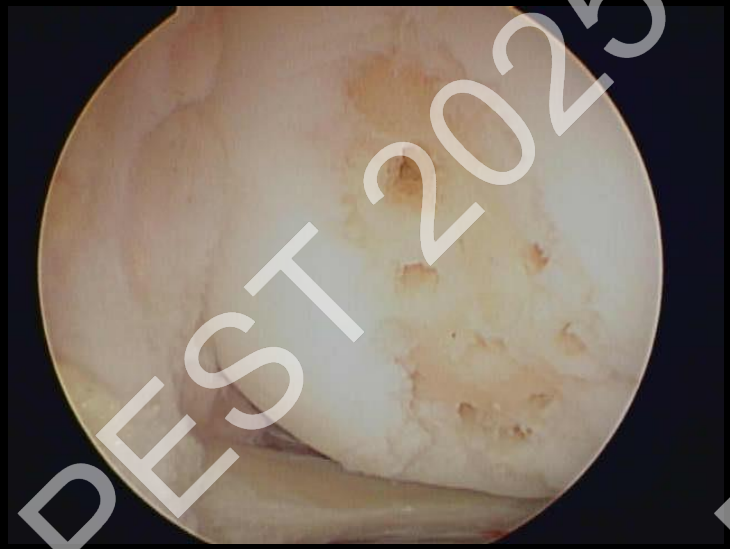
[3]MR Centre – High-field MR, Department of Radiology, Medical University of Vienna, Vienna



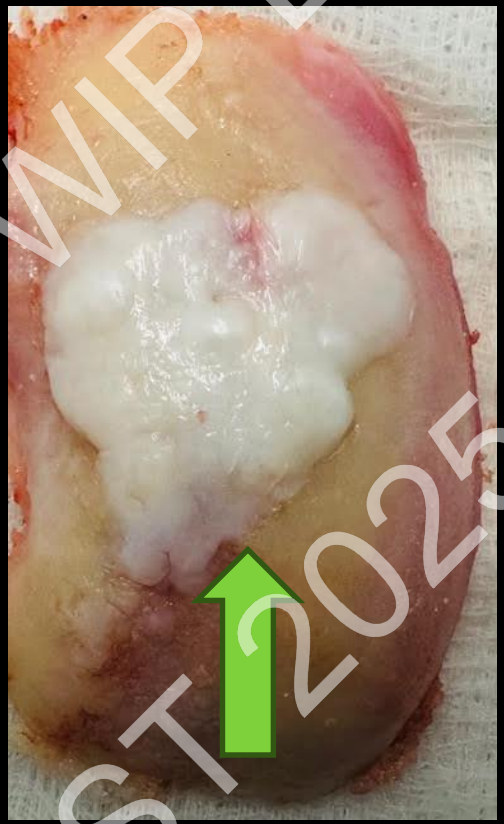
Cartilage Repair: Results

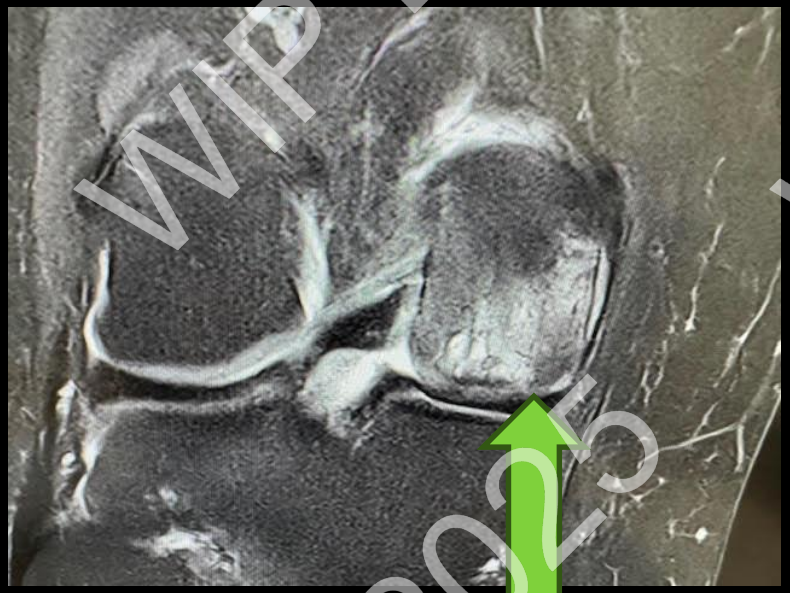


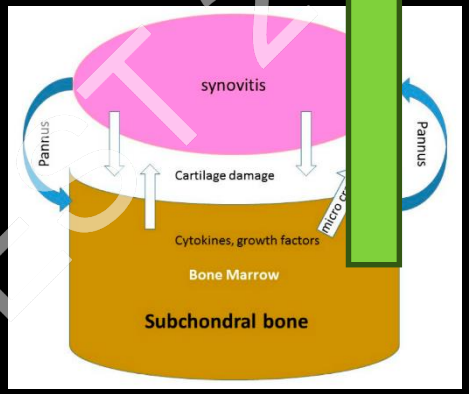


Hunterian Medal and Professorship,
Royal College of Surgeons of England, 2017

Focal Cartilage lesion- Post Cartilage repair- Bone Marrow Lesions (BML)

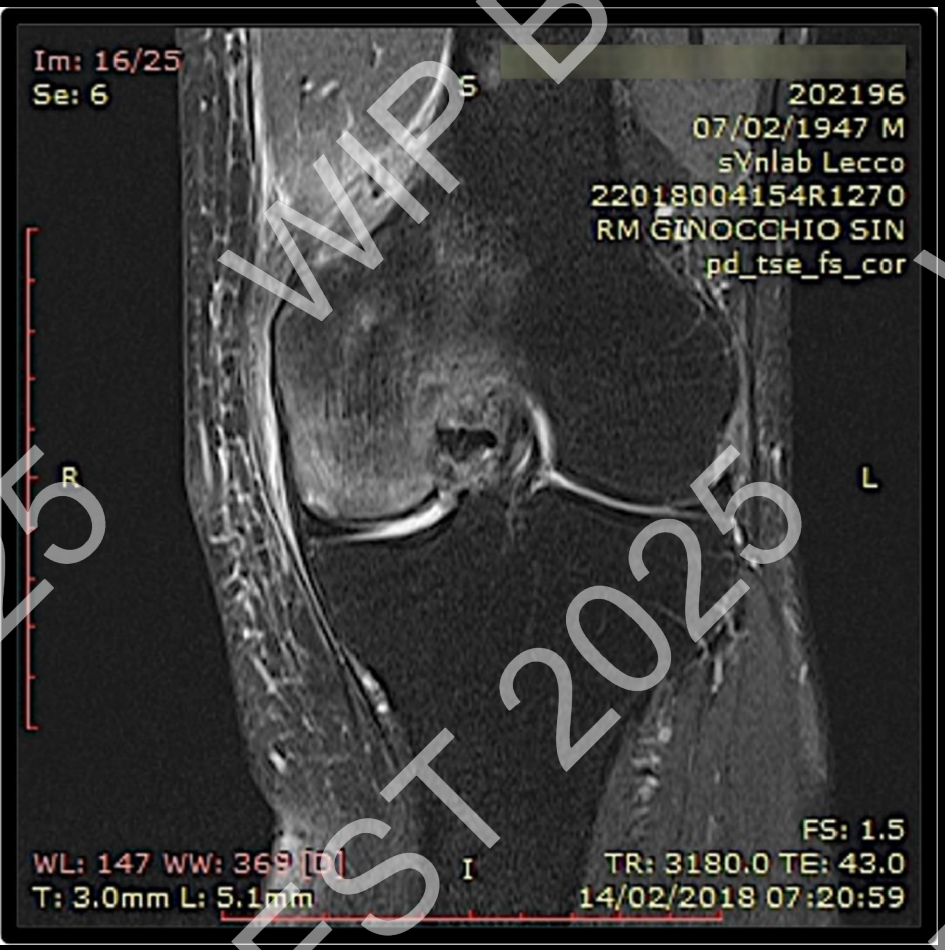


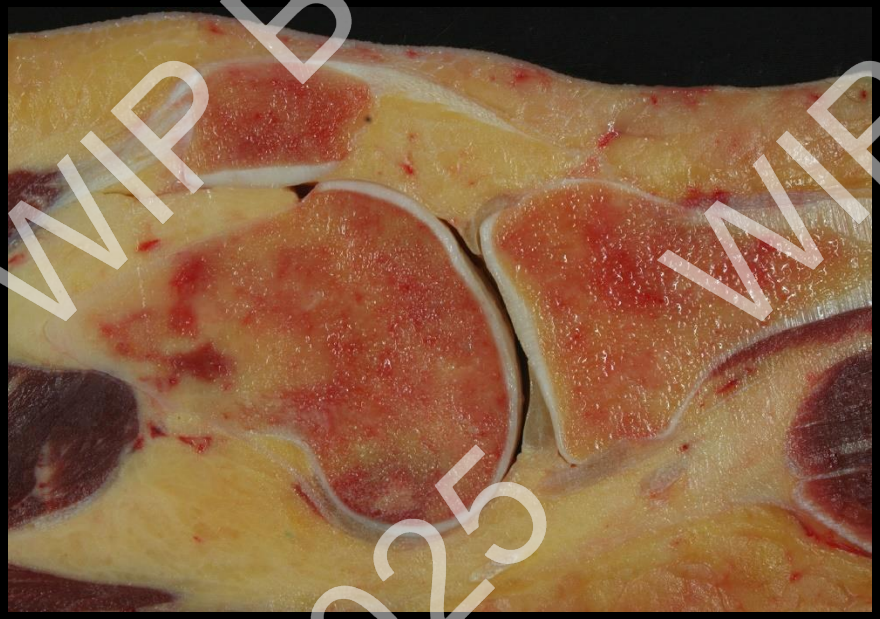


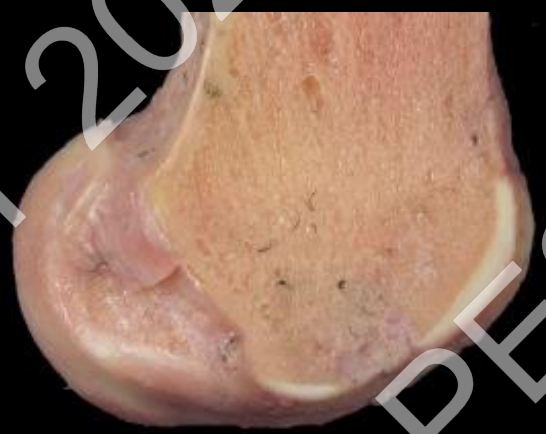


Bone Marrow Lesion (BML-MRI)

BML-Medial femoral Condyle

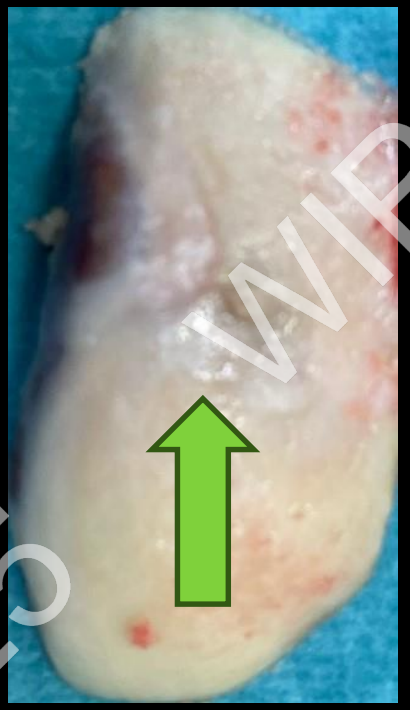


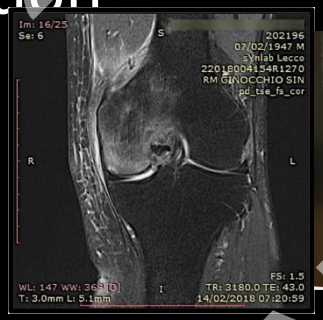


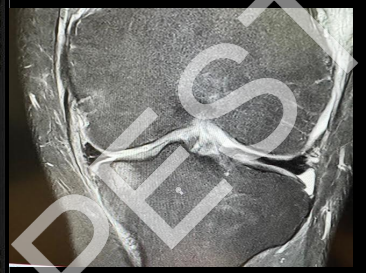


Focal Cartilage lesion-BML

- Focal changes in the subchondral bone, termed as bone marrow lesions (BMLs)
- These are features detected by magnetic resonance imaging (MRI)
- In patients with knee osteoarthritis(OA), BMLs can correlate with faster joint degeneration and increased pain (70%,Tibial progressive OA)

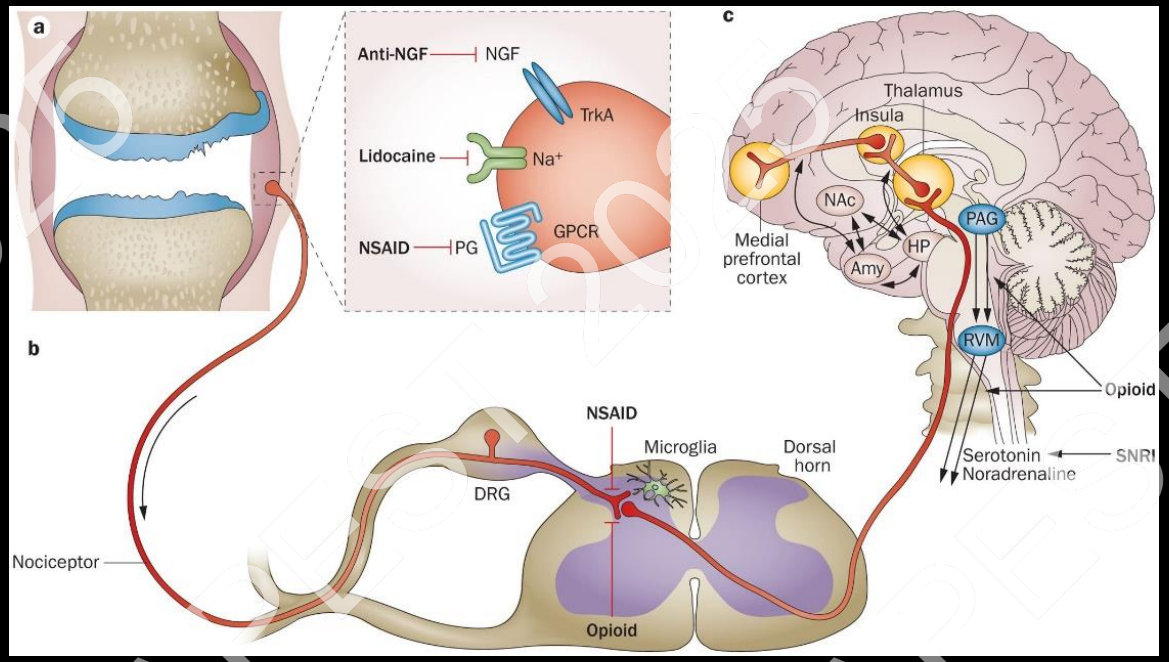






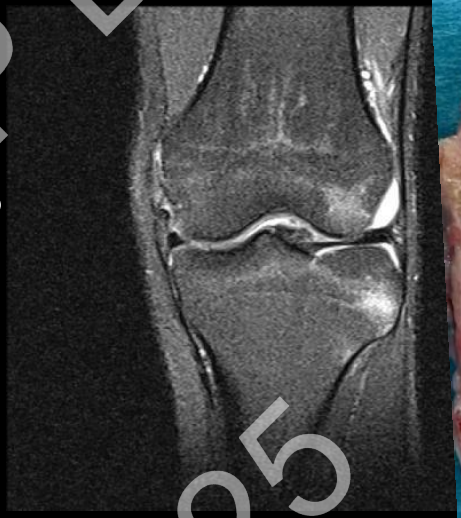
The Sources of pain in Osteoarthritis

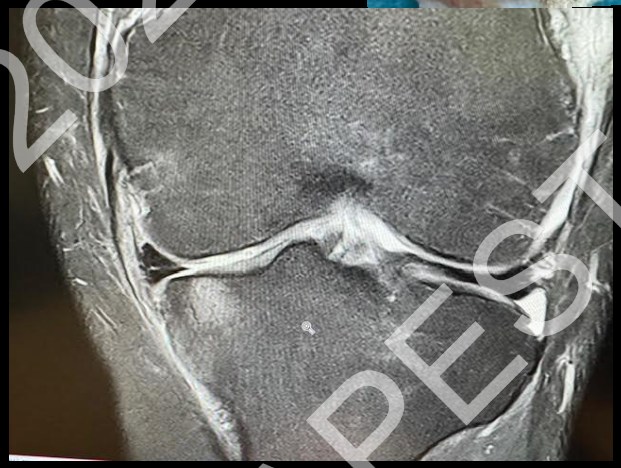
- Has multifaceted aetiologies within and outside the joint
- It is believed to be driven by both nociceptive and neuropathic mechanisms



The sources of pain in osteoarthritis

- The bone-related causes of pain in OA include subchondral microfractures
- Increased intra-osseous pressure
- Soft Tissue- Ligament instability ,Meniscal pathology

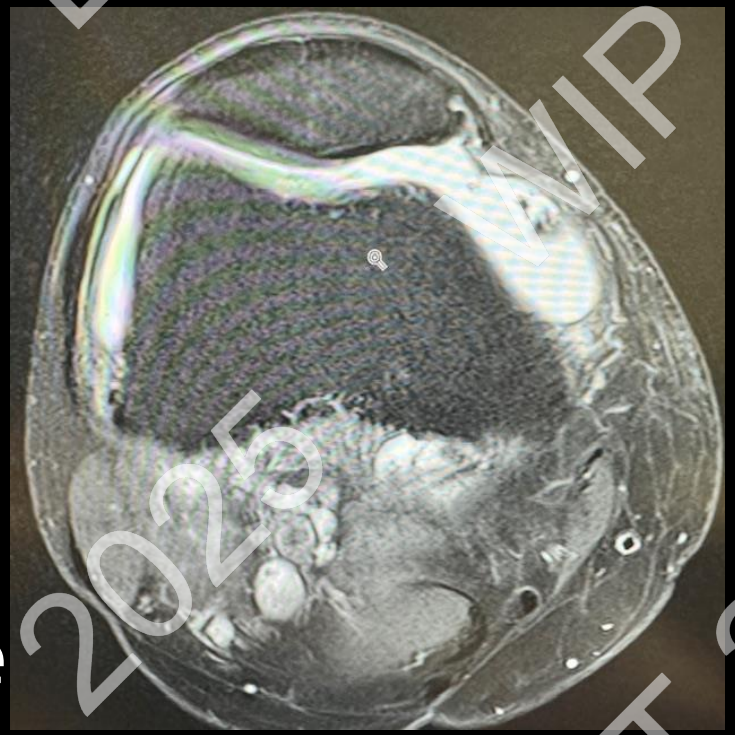




osteoarthritis

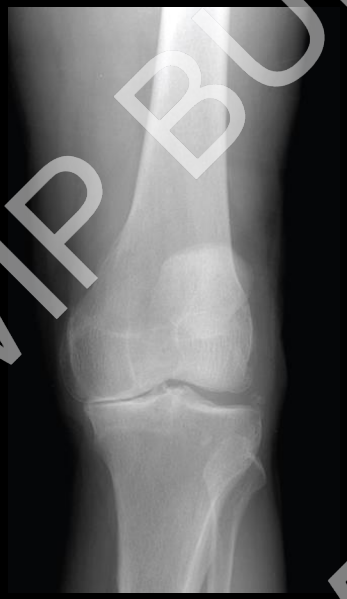
Inflammation: Synovitis & Effusion

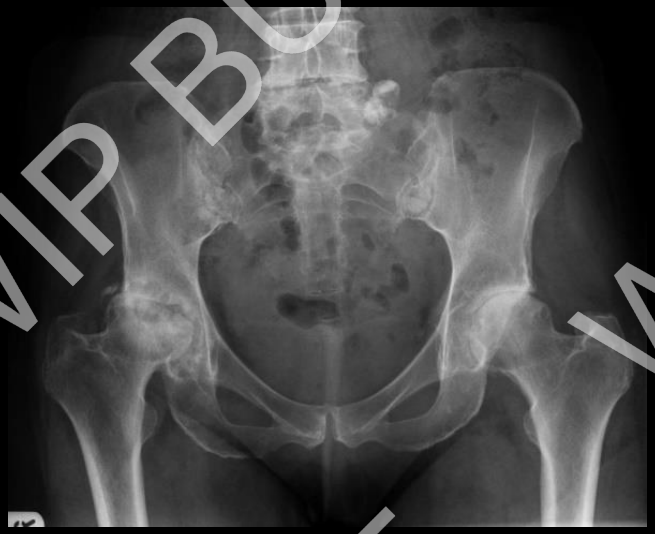
- Inflammation in the joint triggers a cascade of events
- Leads to peripheral sensitization and hyperexcitability of the nociceptive neurons in the central nervous system

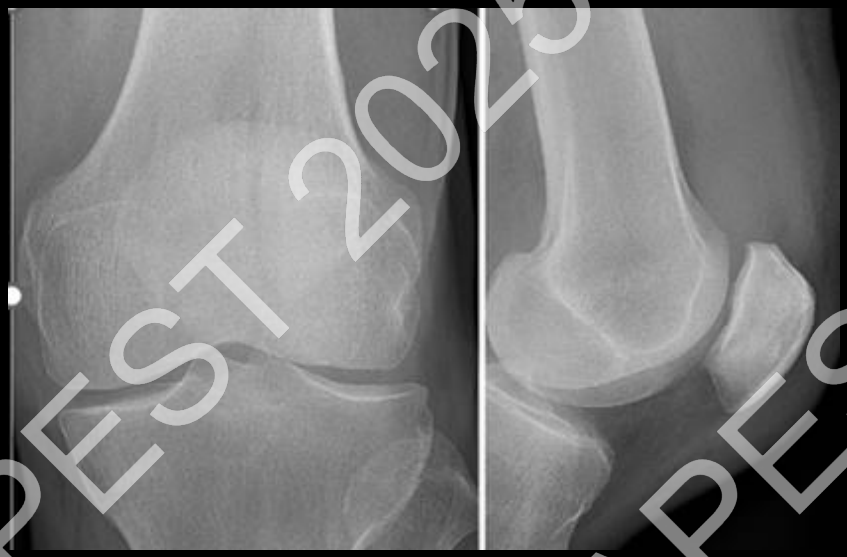


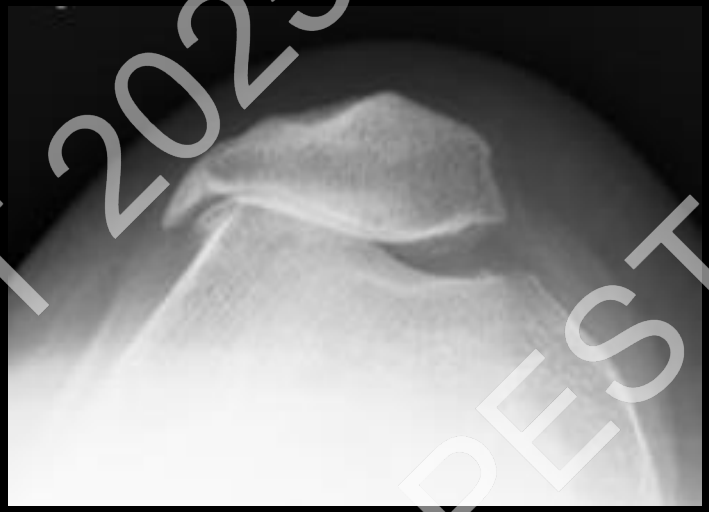
Nocturnal Pain

OA Knee: KL3-4



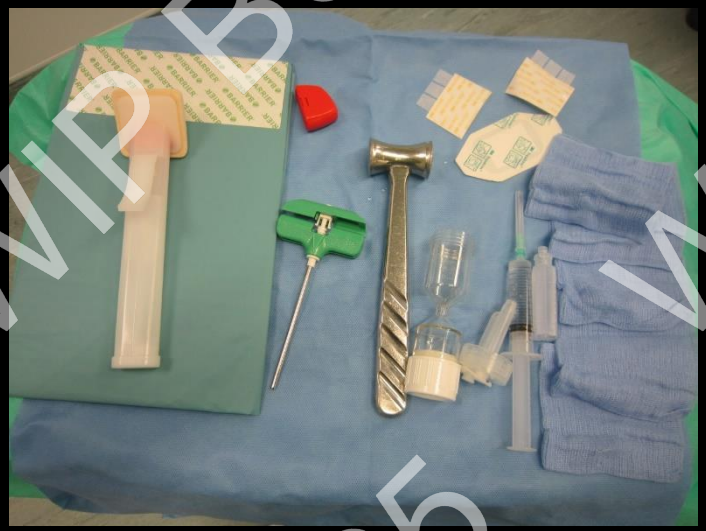






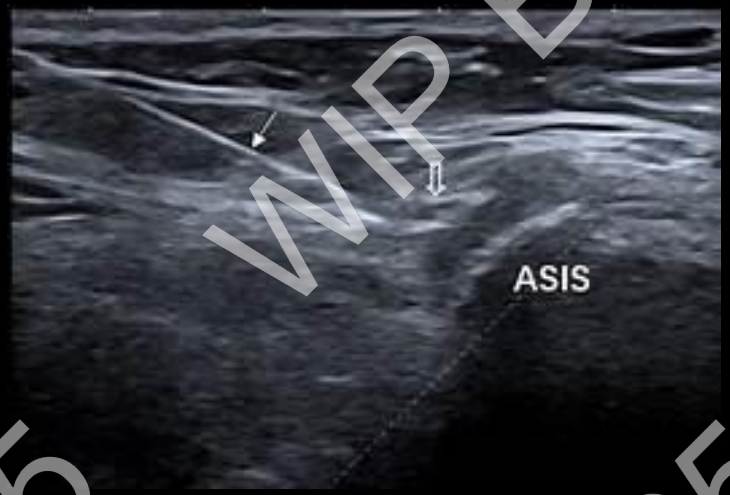
Surgical Technique:
BMAC Aspiration ,Preparation
&
Injection

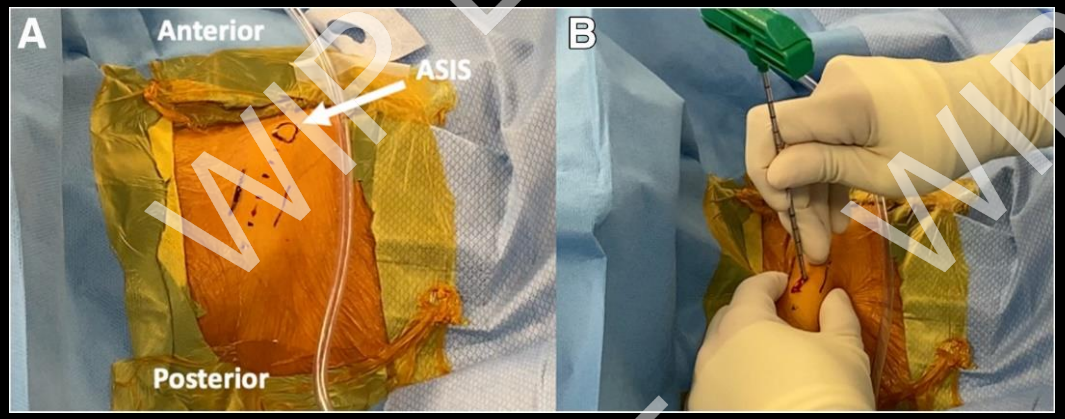
Bone marrow aspiration-Preparation(Anticoagulant-ACDA)

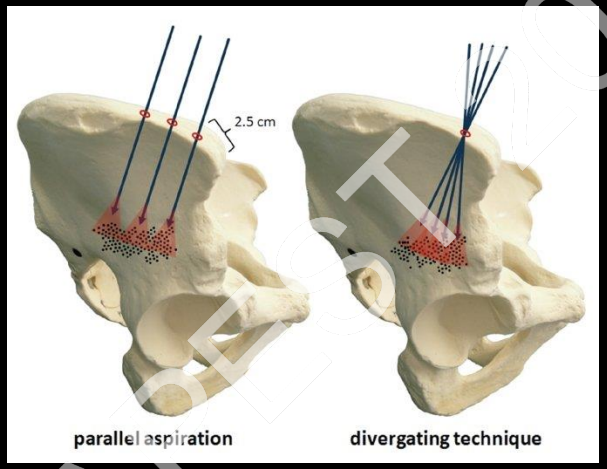


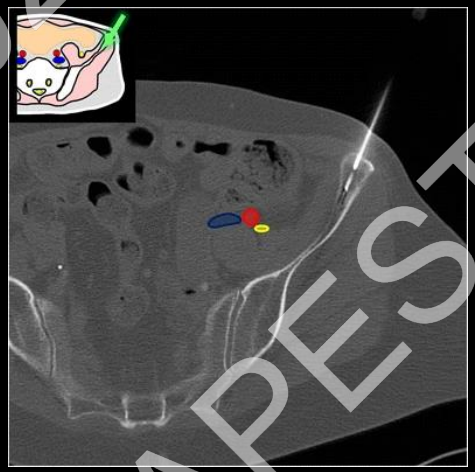
Jamshidi needle
(Colex L=110mm ,OD=3mm)

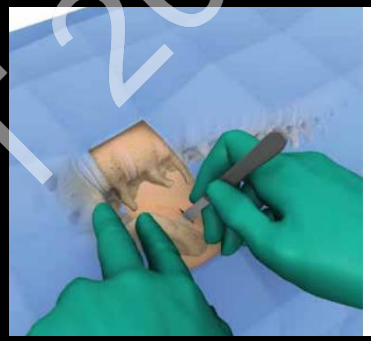
Bone marrow Aspiration- Anterior Iliac Spine

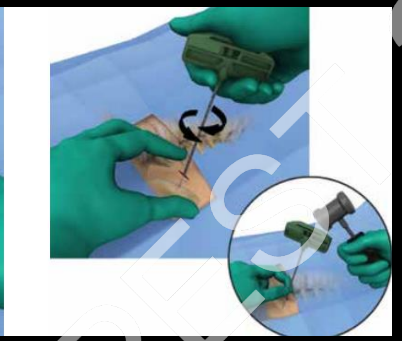




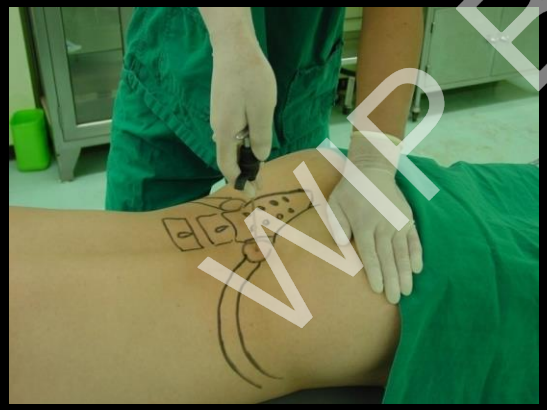


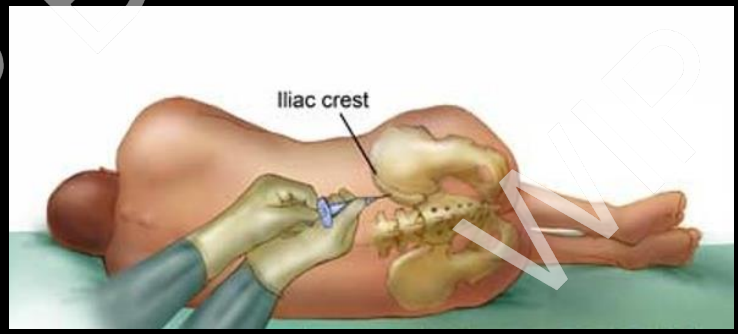


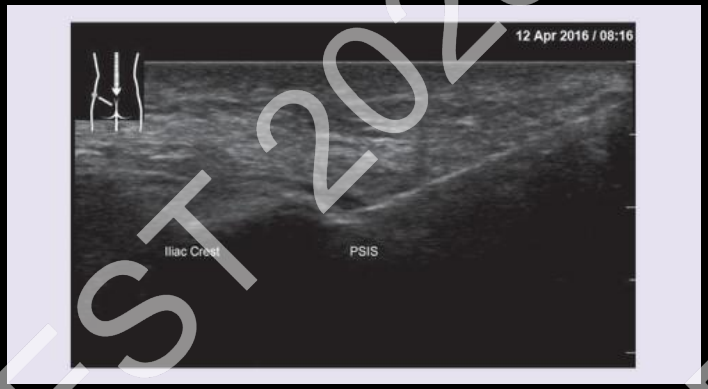


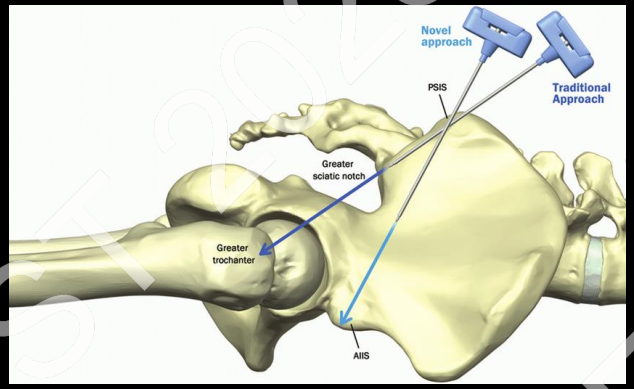


BMAC - Harvesting









Bone Marrow Aspiration Video

BMAC- Extraction:ACDA (Acid Citrate Dextrose)Separation and Concentration TriCeLL BMAC kit - Major Advantages

- Closed system
- 3 Chambers in one tube
- Double spin –
  1.Separation and
  2.Concentration
- Adjust BMAC density
  1ml~5ml

TriCeLL BMC Kit Preparation: Loading and Centrifugation- 40 ml Bone marrow with ACDA

TriCeLL Preparation-Separation

BMAC Kit
After the 1st centrifuge
3500 RPM/6minutes

TriCeLL Preparation-Push the Buffy Coat to middle Chamber (Plasma)

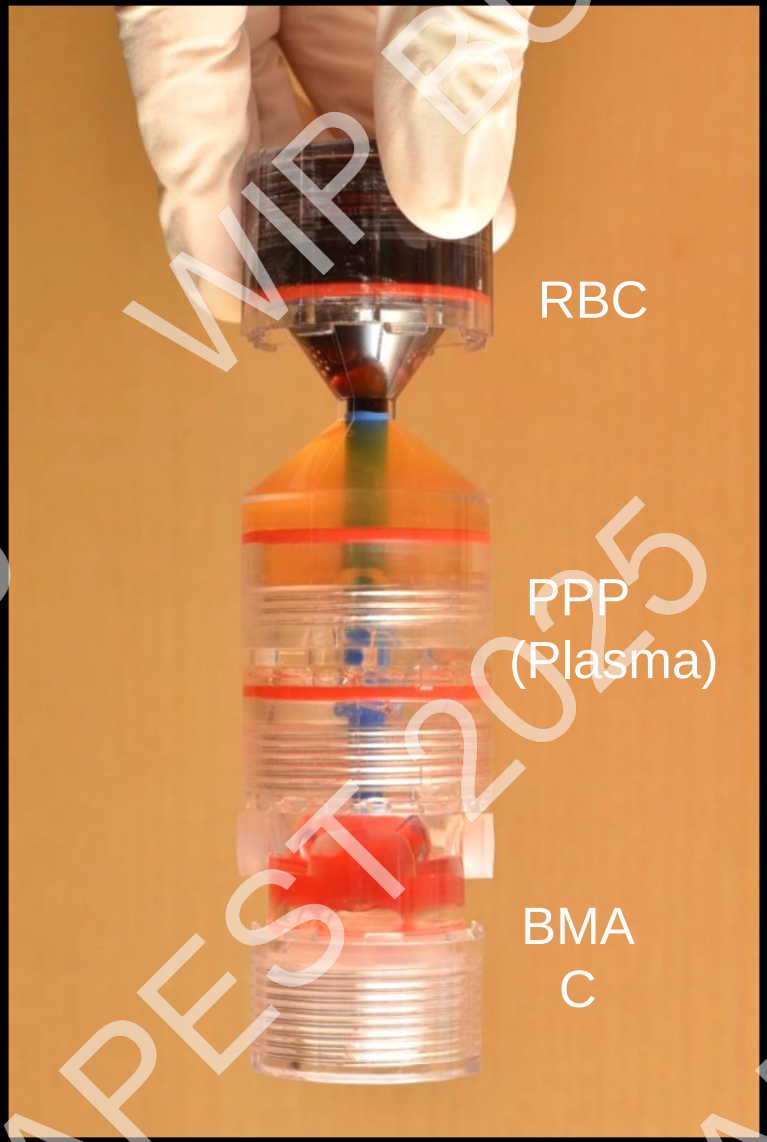
Turn the RBC chamber cap in the left direction to move buffy coat to the plasma chamber

TriCeLL Preparation –Lock RBC Chamber

Hold upper body of TriCeLL and Turn the lower part of TriCeLL right, to isolate RBC with interlocking bar

* Lock it tight as strong as you can

TriCeLL 2nd Centrifuge : Concentration

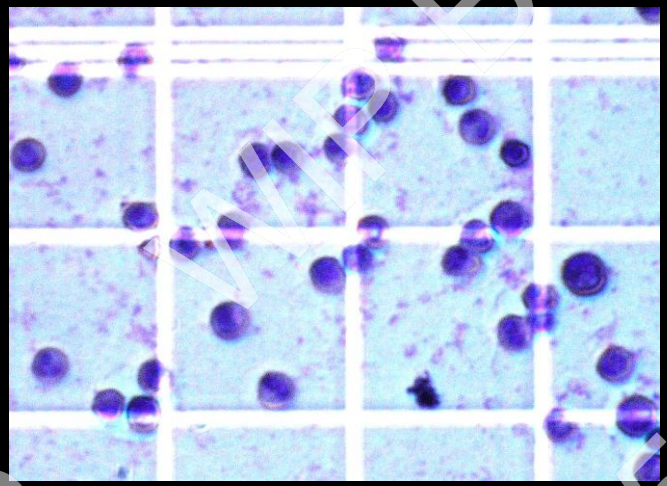


BMAC Kit
After the 1st centrifuge
3530 RPM/5minutes

BMC Kit

MSCs in Bone Marrow Aspirate

GEORGE F. MUSCHLER, et al JBJS VOL. 79-A, NO. 11, NOVEMBER 1997



- Mean No. of Nucleated cells
  15 - 150 million cells /ml
- CTPs : 150 - 460 Cells/million cells
- 30-45 Thousand Cells/ml

FRACTION AND CONCENTRATION OF BONE-MARROW-DERIVED CELLS IN DIFFERENT ASPIRATION VOLUMES*

	Total Nucleated Cells *(Millions)*	Total Bone-Marrow Cells *(Millions)*	Total Blood Cells *(Millions)*	Per Cent Bone-Marrow Cells	Per Cent Blood Cells	Concentration of Bone-Marrow Cells per ml *(Millions)*
Experiment 1						
1-ml aspirates	40	32.5	7.5	81	19	32.5
2-ml aspirates	60	45	15	75	25	22.5
Experiment 2						
2-ml aspirates	72	57	15	79	21	28.5
4-ml aspirates	100	70	30	70	30	17.5

*All data are given as geometric means.

BMC-Procedure:Image guided

- Ultrasound Guided Injection
- Do not mix with local anaesthetics Steroid
- Can use local for skin infiltration
- Avoid NSAID for 6 weeks

Injection Protocol

BMAC VIA SUBCHONDRAL INJECTION PROTOCOL

PRE- & POST-INJECTION PROTOCOLS FOR BONE MARROW ASPIRATE CONCENTRATE (BMAC) VIA SUBCHONDRAL INJECTION

In an effort to optimize your outcomes following a BMAC procedure via subchondral injection, TCO has developed the following pre- and post-injection protocols for you to follow. These are general guidelines. Your physician will discuss any restrictions or modifications that may apply specifically to you.

PRE-INJECTION PROTOCOL:

- Complete pre-procedure forms from Oberd.
- Stop smoking for 90 days (strongly recommended).
- Avoid steroids (e.g. Cortisone, Prednisone, Medrol Dose Pack), including steroid injections in the involved joint, for 90 days.
- Reduce alcohol to 2 or less drinks/day for 90 days (strongly recommended).
- Avoid NSAIDS (e.g. Advil, Motrin, Ibuprofen, Aleve, Celebrex) for 2 week the procedure.
- Off-load malaligned joint (heel wedges or off-loader brace, if necessary
- Exercise for joint mobilization:
  - Stationary bike 10-15 min per day, 6 days/week
  - Isometric exercises for quad and gluteal

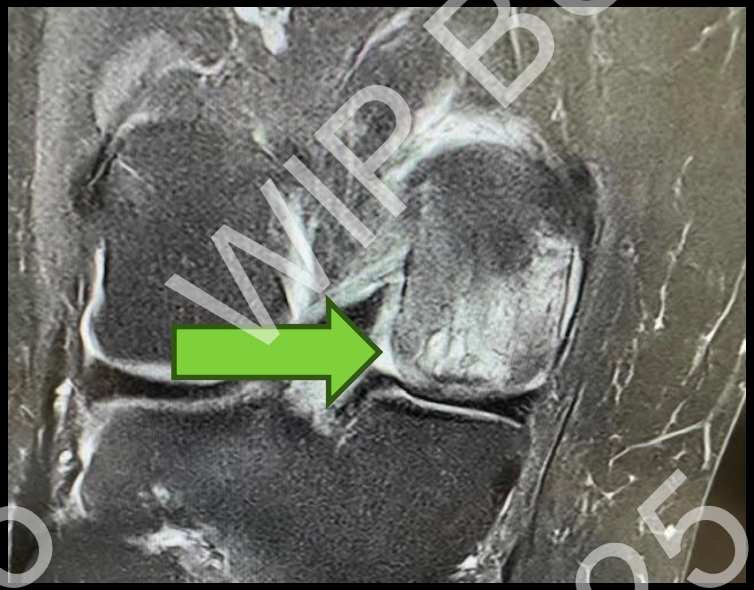
POST-INJECTION PROTOCOL:

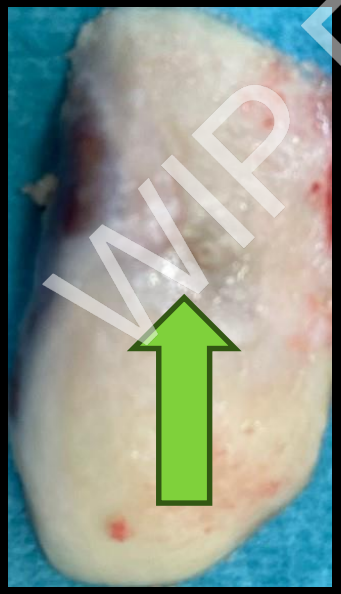
- Complete post-procedure forms from Oberd.
- Avoid NSAIDS (e.g. Advil, Motrin, Ibuprofen, Aleve, Celebrex) for 2 weeks following the procedure. If indicated, pain medication may be prescribed for 2-7 days post-surgery.
- Avoid kneeling, squats, lunging activities, running, jumping or other high-impact activities (e.g. running or stop-and-go sports) for up to 3 months. Most patients are able to return to normal activities, including light running, at 3 months. Competitive sports are allowed after 6 months.
- Ride a stationary bike with low tension for 10-12 minutes per day, 6 days per week, for 4-6 weeks.
- Patients are restricted to protected weight bearing for 1 week. Weight-bear as tolerated, but use a walker or crutches for protection.
- If tolerated, use an off-loading brace for up to 8 hours per day for 2 months post-surgery. Patients should wean themselves off the brace over a 2-4 week period.
- Follow-up visits should be done at 2 weeks and 3 months.

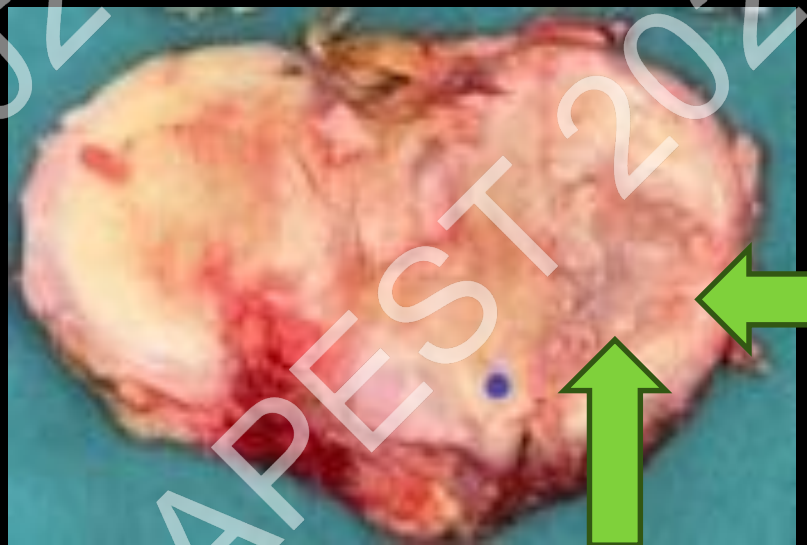
BMAC(MSCs) +Atelocollagen (Coltrix®)

Image Guided:

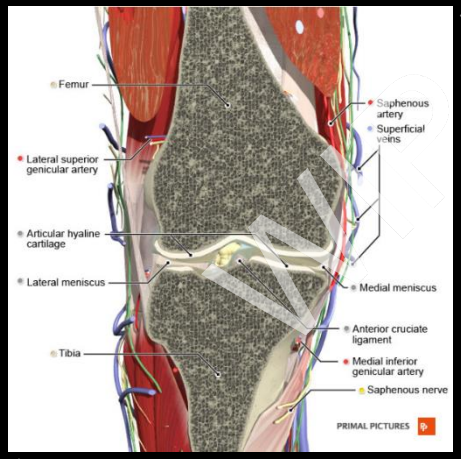
Tibia-Anteromedial lesion

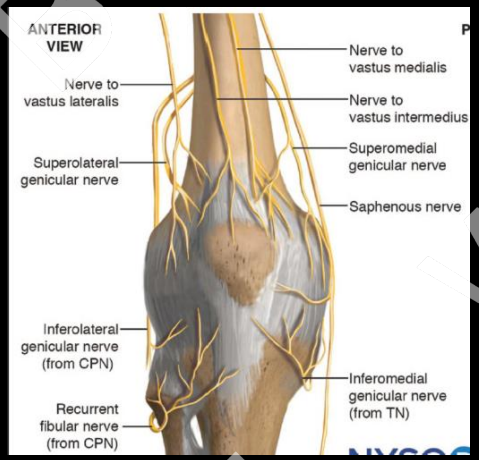




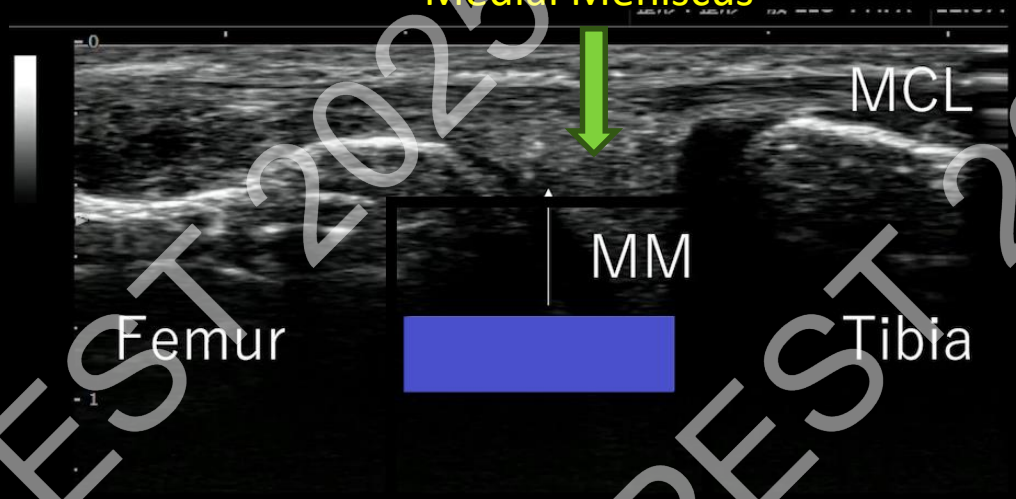


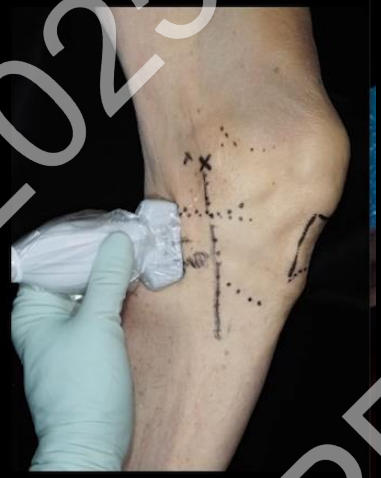
BMAC-Subchondral injection
Image Guided- US



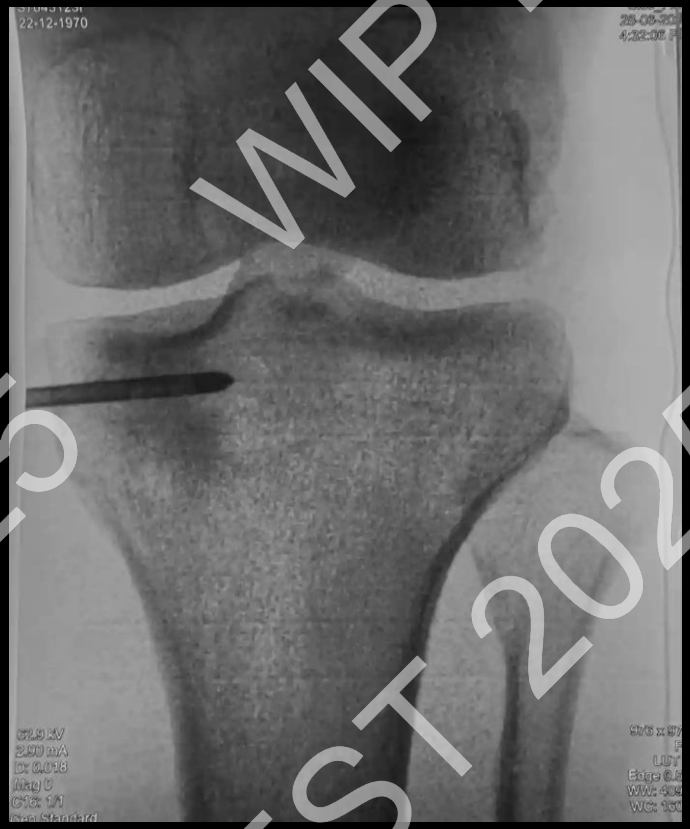


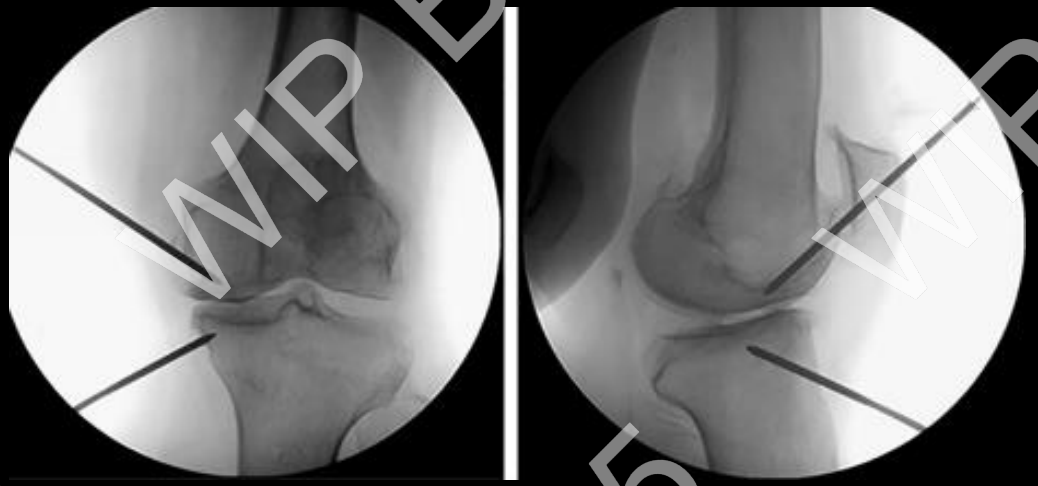
Medial Meniscus

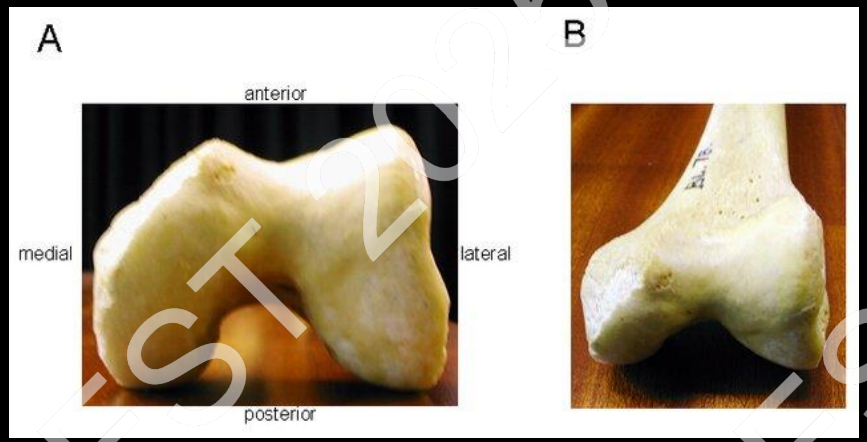




BMAC-Subchondral injection
Image Guided- Image Intensifier

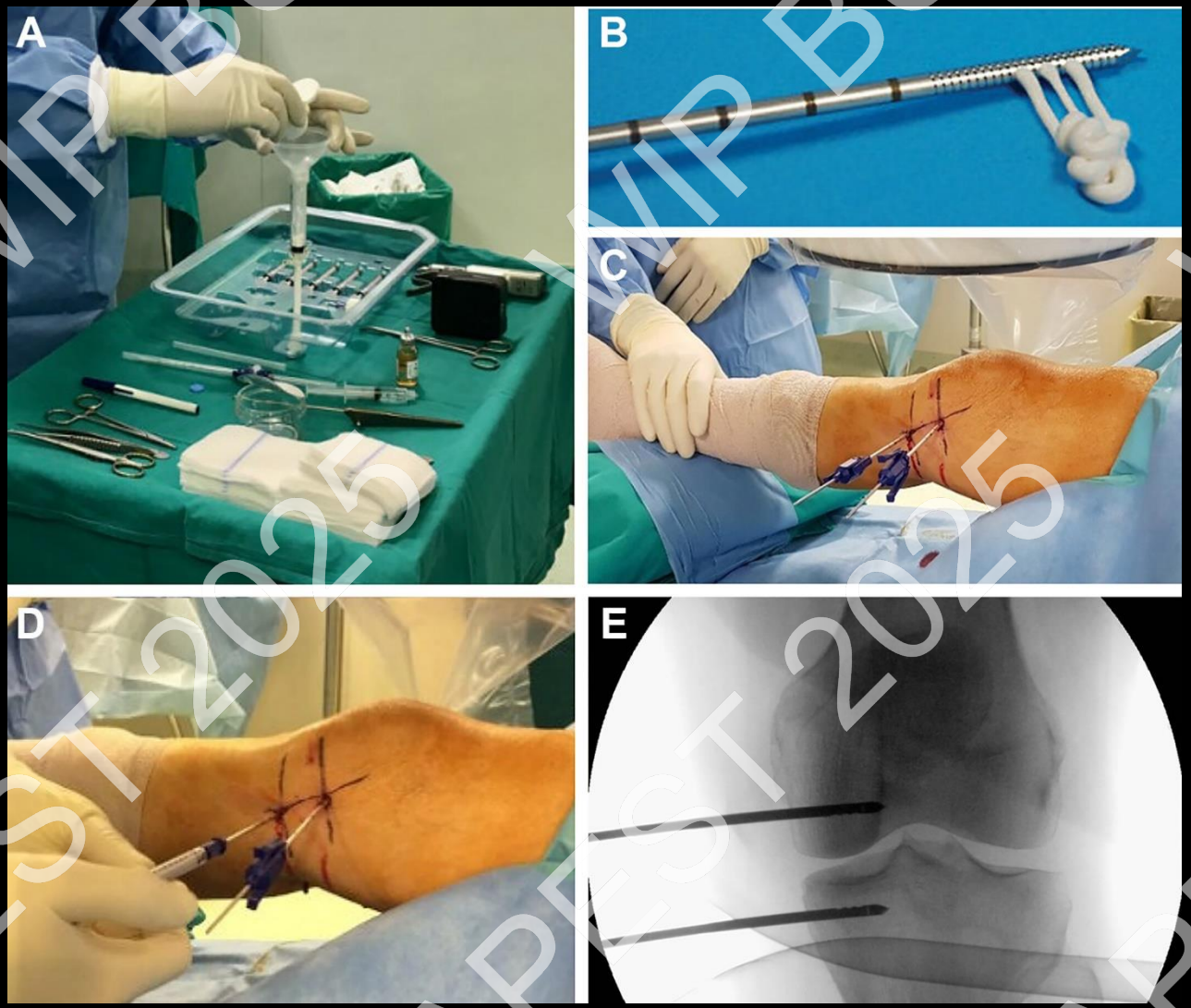






Blumensaat line, also known as the **intercondylar line**, is the line drawn along he roof of the intercondylar notch of the femur on a sagittal view of the k knee.

Subchondral Injection- Special Instruments



Results – Evidence

BMAC Injection Results: Review Article

Subchondral versus intra-articular Ortho biologic injections for the treatment of knee osteoarthritis: A review

Regen Med. 2022 Jun;17(6):389-400. James E Gardner *et al.*

- Recent data suggest that injections of orthobiologics into the subchondral bone may be superior to intra-articular injections for the management of OA

- This review highlights the rationale and current evidence for intra-articular and subchondral bone injections of Ortho biologics for the treatment of OA

BMAC Intraarticular Vs Subchondral injection

Role of Scaffolds, Subchondral, Intra-Articular Injections of Fresh Autologous Bone Marrow Concentrate Regenerative Cells in Treating Human Knee Cartilage Lesions: Different Approaches and Different Results

Int J Mol Sci. 2021 Apr 8;22(8):3844, Jacques Hernigou *et al.*

- Use of intra-articular injections resulted in a significant relief of pain symptoms in the short term and was maintained in 12 months

A review of bone marrow lesions in the arthritic knee and description of a technique for treatment

Journal of Cartilage & Joint Preservation, Volume 1, Issue 3, September 2021, Alberto Gobi et al .

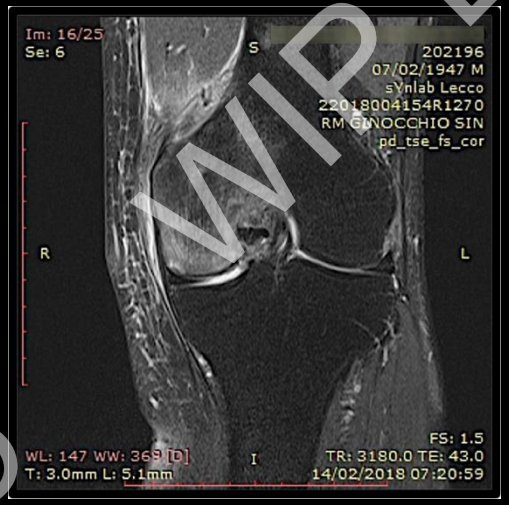
- BMAC in combination with scaffolds is better (Shetty-Kim)

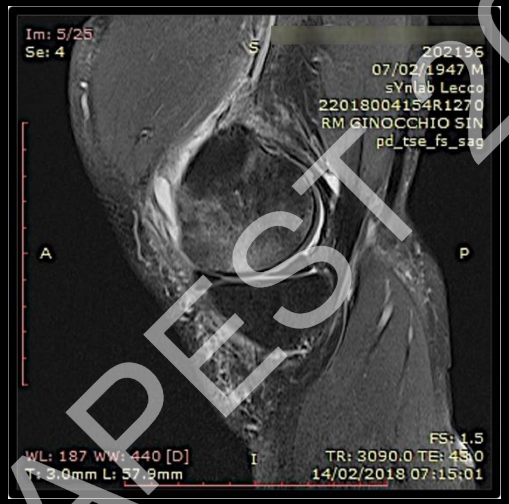
- The review also suggests a that both implantation of subchondral BMAC and scaffolds loaded with BMAC could reduce the need for further surgery

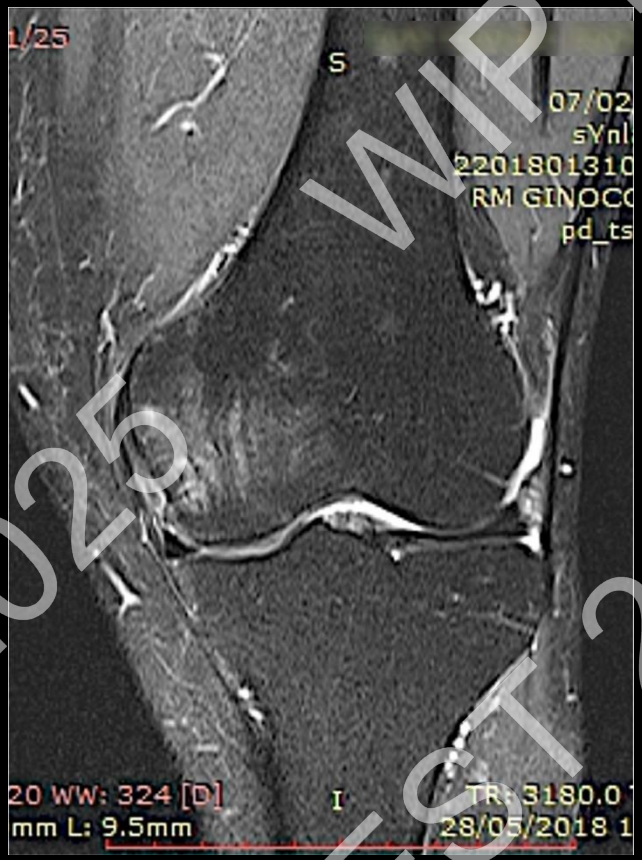
- The tendency of MSCs to differentiate into fibrocartilage affecting the outcome was a common issue faced by all the studies when biopsies were performed, except for with scaffolds implantation in which predominantly hyaline cartilage

BMAC- Subchondroplasty:

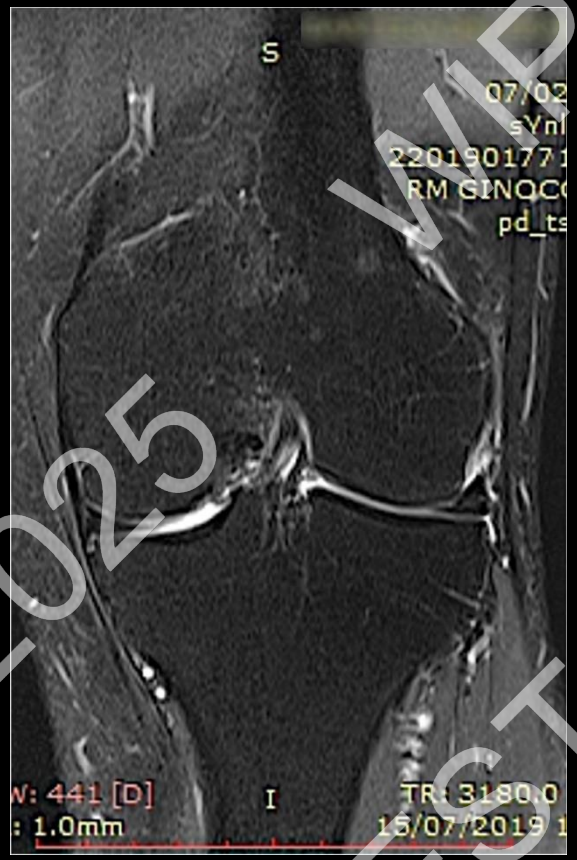
MRI follow up - Result







3 months post injection

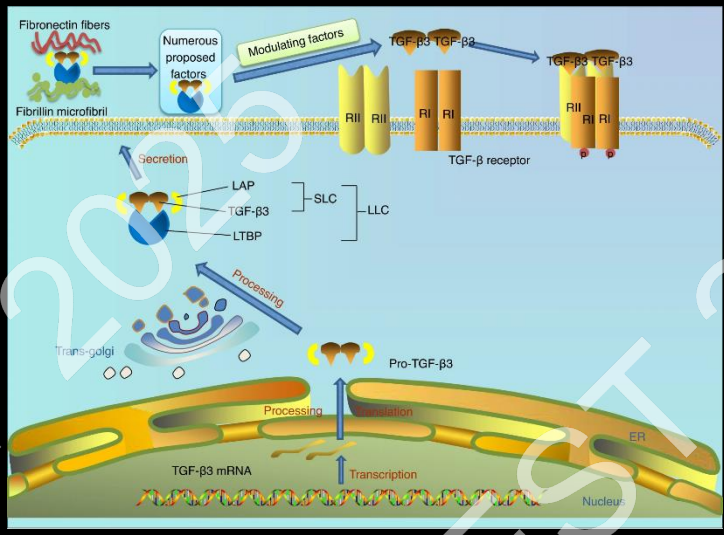


6months post injection

BMAC- Cartilage Repair: How does it work?

- Cartilage Regeneration
  Extracellular matrix (ECM) synthesis and promote chondrocyte differentiation

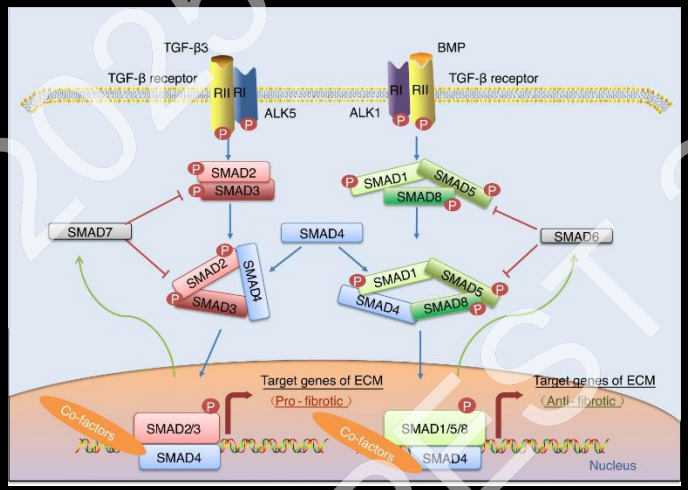
- Immunomodulation
  by suppressing synovial inflammation and preventing chondrocyte apoptosis and matrix degradation



BMAC-How does it work?

- **Inflammation Modulation**
  Bioactive factors suppress pro-inflammatory cytokines such as IL-1β and TNF-α, mitigating joint inflammation

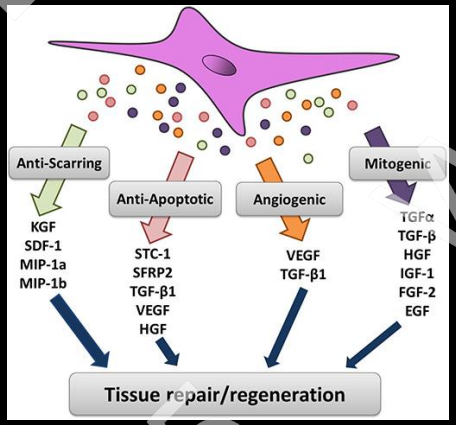
- **Subchondral Bone Remodelling**
  BMAC may enhance the osteochondral interface and OA progression, a critical factor in OA pathophysiology



How Does it Works ? :Tissue Regeneration:
Trophic effects and Paracrine effects

- "Trophic effect" :

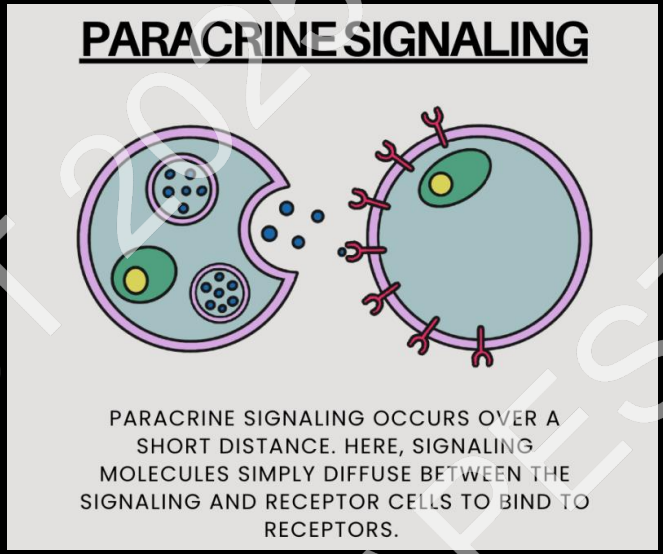
Capability to produce large variety of "Bio-active" trophic factors that stimulate neighboring parenchymal cells to start repairing damaged tissue



- "Paracrine signaling":

Allows cells to communicate with each other by releasing signaling molecules that bind to activate surrounding cells, contributing directly to the new tissues

Number of cell count is not important



Intra-articular BMAC Injection :

The American Journal of Sports Medicine 2022

Clinical Sports Medicine Update

Bone Marrow Aspirate Concentrate for the Treatment of Knee Osteoarthritis

CME

A Systematic Review

Laura E. Keeling,*† MD, John W. Belk,‡ BA, Matthew J. Kraeutler,§ MD, Alexandra C. Kallner,‖ BS, Adam Lindsay,‡ MD, Eric C. McCarty,‡ MD, and William F. Postma,† MD

Investigation performed at MedStar Georgetown University Hospital, Washington, DC, USA

Background: Bone marrow aspirate concentrate (BMAC) has emerged as a therapeutic option for symptomatic knee osteoarthritis (OA).

Purpose: To systematically review the literature to evaluate the efficacy of isolated BMAC injection in the treatment of OA of the knee joint.

Study Design: Systematic review; Level of evidence, 4.

Methods: A systematic review was performed by searching the PubMed, Embase, and Cochrane Library databases up to July 2020 to identify human studies that assessed the clinical outcomes of isolated BMAC injection for the treatment of knee OA. The electronic search strategy used was "bone marrow aspirate concentrate knee osteoarthritis."

Results: Eight studies met the inclusion criteria, including a total of 299 knees with a mean follow-up of 12.9 months (range, 6-30 months). Of all patient-reported outcomes assessed across studies, 34 of 36 (94.4%) demonstrated significant improvement from baseline to latest follow-up ($P < .05$). Five studies evaluating numerical pain scores (visual analog scale and Numeric Rating Scale) reported significant improvements in pain level at final follow-up ($P < .01$). However, 3 comparative studies evaluating BMAC in relation to other therapeutic injections failed to demonstrate the clinical superiority of BMAC.

Conclusion: The BMAC injection is effective in improving pain and patient-reported outcomes in patients with knee OA at short- to midterm follow-up. Nevertheless, BMAC has not demonstrated clinical superiority in relation to other biologic therapies commonly used in the treatment of OA, including platelet-rich plasma and microfragmented adipose tissue, or in relation to placebo. The high cost of the BMAC injection in comparison with other biologic and nonoperative treatment modalities may limit its utility despite demonstrable clinical benefit.

Keywords: bone marrow aspirate concentrate; knee osteoarthritis; injection; platelet-rich plasma

BMAC Injection-
Subchondral or Intraarticular

Randomized Controlled Trial > Int Orthop. 2021 Feb;45(2):391-399.
doi: 10.1007/s00264-020-04687-7. Epub 2020 Jul 2.

Subchondral bone or intra-articular injection of bone marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis: what better postpone knee arthroplasty at fifteen years? A randomized study

Philippe Hernigou [1], Charlie Bouthors [2], Claire Bastard [3], Charles Henri Flouzat Lachaniette [3], Helene Rouard [4], Arnaud Dubory [3]

Affiliations + expand

PMID: 32617651 DOI: 10.1007/s00264-020-04687-7

Abstract

Purpose: There is an increasing number of reports on the treatment of knee osteoarthritis (OA) using mesenchymal stem cells (MSCs). However, it is not known what would better drive osteoarthritis stabilization to postpone total knee arthroplasty (TKA): targeting the synovial fluid by injection or targeting on the subchondral bone with MSCs implantation.

- Implantation of MSCs in the subchondral bone of an osteoarthritic knee is more effective to postpone TKA than injection of the same intra-articular dose in the contralateral knee with the same grade of osteoarthritis

BMAC –Systematic Review :
The Journal of Arthroscopic and Related Surgery 2018

Systematic Review

Reporting Standards in Clinical Studies Evaluating Bone Marrow Aspirate Concentrate: A Systematic Review

Iain R. Murray, M.R.C.S., Ph.D., Patrick G. Robinson, M.R.C.S., Christopher C. West, M.R.C.S., Ewan B. Goudie, M.R.C.S., Li Y. Yong, M.R.C.S., Timothy O. White, F.R.C.S., and Robert F. LaPrade, M.D., Ph.D.

Purpose: To perform a systematic review of clinical studies evaluating bone marrow aspirate concentrate (BMAC) in the treatment of musculoskeletal pathology to compare levels of reporting with recently published minimum standards. **Methods:** A systematic review of the clinical literature from August 2002 to August 2017 was performed. Human clinical studies published in English and involving the administration of BMAC for musculoskeletal applications were included. Studies evaluating non-concentrated preparations of bone marrow aspirate or preparations of laboratory cultured cells were excluded. Studies evaluating the treatment of dental or maxillofacial conditions were excluded. Similarly, in vitro studies, editorials, letters to the editor, and reviews were excluded. Levels of reporting were compared with previously published minimum standards agreed on through an international Delphi consensus process. **Results:** Of 1,580 studies identified on the initial search, 46 satisfied the criteria for inclusion. Considerable deficiencies in reporting of key variables including the details of BMAC preparation and composition were noted. Studies reported information on only 42% (range, 25%-60%) of the variables included within established minimum reporting standards. No study provided adequate information to enable the precise replication of preparation protocols and accurate characterization of the BMAC formulation delivered. **Conclusions:** We found that all existing clinical studies in the literature evaluating BMAC for orthopaedic or sports medicine applications are limited by inadequate reporting of both preparation protocols and composition. Deficient reporting of the variables that may critically influence outcomes precludes interpretation, prevents other researchers from reproducing experimental conditions, and makes comparisons across studies difficult. We encourage the adoption of emerging minimum reporting standards for clinical studies evaluating the use of mesenchymal stem cells in orthopaedics. **Level of Evidence**: Level IV, systematic review of Level I through IV studies.

BMAC Vs PRP:
BMAC is Better

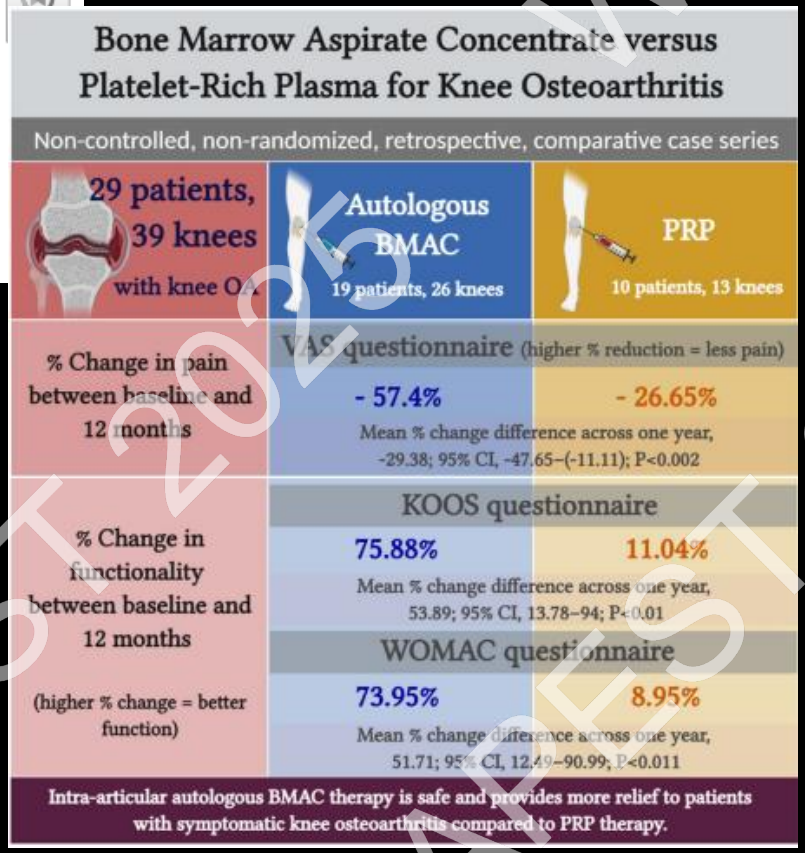
El-Kadiry *et al. BMC Musculoskeletal Disorders* (2022) 23:23
https://doi.org/10.1186/s12891-021-04910-5

BMC Musculoskeletal Disorders

RESEARCH Open Access

Bone marrow aspirate concentrate versus platelet-rich plasma for treating knee osteoarthritis: a one-year non-randomized retrospective comparative study

Abed El-Hakim El-Kadiry[1,2], Carlos Lumbao[3], Natasha Salame[2], Moutih Rafei[4,5,6,7*] and Riam Shammaa[3,8*]



PRP Vs BMAC Vs HA
BMAC is better -
BMAC with HA is much better

medicina MDPI

Medicina (Kaunas). 2021 Nov; 57(11): 1193.
Published online 2021 Nov 2. doi: 10.3390/medicina57111193

PMCID: PMC8623697
PMID: 34833411

Bone Marrow Aspirate Concentrate versus Platelet Rich Plasma or Hyaluronic Acid for the Treatment of Knee Osteoarthritis

Oliver Dulic,[1,2,3,4,5,*] Predrag Rasovic,[2,3] Ivica Lalic,[2,3] Vaso Kecojevic,[2] Gordan Gavrilovic,[4] Dzihan Abazovic,[6] Dusan Maric,[3,5] Mladen Miskulin,[7,8] and Marko Bumbasirevic[1,9]

Francesco De Francesco, Academic Editor, Veronica Romano, Academic Editor, and Arman Saparov, Academic Editor

▸ Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Abstract

Go to: ▸

Background: In the last decade, regenerative therapies have become one of the leading disease modifying options for treatment of knee osteoarthritis (OA). Still, there is a lack of trials with a direct comparison of different biological treatments. Our aim was to directly compare clinical outcomes of knee injections of Bone Marrow Aspirate Concentrate (BMAC), Platelet-rich Plasma (PRP), or Hyaluronic acid (HA) in the OA treatment. *Methods:* Patients with knee pain and osteoarthritis KL grade II to IV were randomized to receive a BMAC, PRP, and HA injection in the

Complications of PRP/BMAC Injection

- Discomfort
- Pain
- Bruising
- Bleeding
- Reactive Synovitis

(Intra-articular Injection)

Contents lists available at ScienceDirect

Journal of Orthopaedic Reports

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-reports

Catastrophic complication after intra-articular injection of platelet-rich plasma – Case report

Vijay Shetty [a,b], Clevio Desouza [a,*]

[a] Saanvi Orthopaedics, 2003, Sorrento High Street, Hiranandani Gardens, Powai, Mumbai, 400076, India
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ARTICLE INFO

Keywords:
Platelet-rich plasma
Synovitis
Knee joint
Arthroscopy
Synovectomy

ABSTRACT

Background: To report an unusual complication of a modern and popular treatment choice for early osteoarthritis of the knee.
Case presentation: A 49-year-old female patient presented to our clinic with a history of knee pain for 6 months. She was treated conservatively with physical therapy and non-steroidal anti-inflammatory drugs, despite which her pain did not resolve. The patient, after a proper discussion about the modalities of further treatment, opted to go for an intra-articular platelet-rich plasma injection. After proper counseling, both knees were given intra-articular injections of platelet-rich plasma. Eight hours after receiving intra-articular platelet-rich plasma injection the patient was admitted to the hospital with symptoms of pain and inflammation of the left knee alone. The symptoms persisted even after conservative management. Magnetic resonance imaging was done which showed changes in synovitis with bone marrow edema in both the tibia and femoral condyles. Since her symptoms deteriorated, she was advised to undergo an arthroscopic left knee debridement with a synovectomy. Laboratory and histopathological studies did not reveal any sign of infection. Once the clinical picture was resolved, the patient was able to resume an earlier activity level.
Conclusions: Although intra-articular platelet-rich plasma injections have been reported to be safe and have a few reports of minor adverse effects such as temporary increasing pain, this case proves the need for further research into published and hidden complications of this, otherwise "safe" procedure.

1. Introduction

infiltration, such as local infections, nerve damage, pain around the

Conclusion:

OA -Subchondral BMAC Injection Has both Preclinical and Clinical Evidence

International Orthopaedics (2021) 45:525–538
https://doi.org/10.1007/s00264-020-04703-w

REVIEW ARTICLE

Check for updates

Bone marrow concentrate injections for the treatment of osteoarthritis: evidence from preclinical findings to the clinical application

Carola Cavallo[1] · Angelo Boffa[2,3] · Luca Andriolo[2] · Simone Silva[2,3] · Brunella Grigolo[1] · Stefano Zaffagnini[2,3] · Giuseppe Filardo[4]

Received: 30 April 2020 / Accepted: 3 July 2020 / Published online: 13 July 2020

Abstract

Purpose To investigate the available literature on the use of bone marrow aspirate concentrate (BMAC) and summarize the current evidence supporting its potential for the injective treatment of joints affected by osteoarthritis (OA).

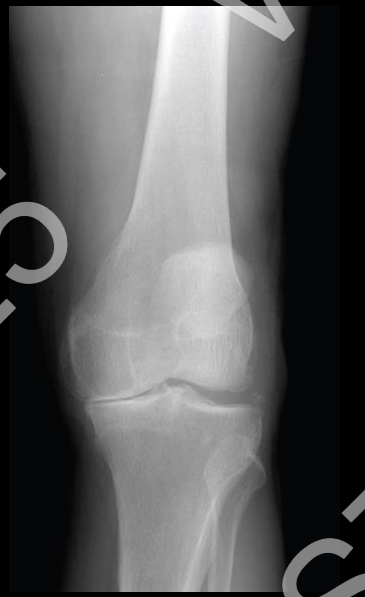
Methods A systematic literature search was conducted on three electronic databases (PubMed, Embase, and Cochrane Library) in April 2020, using the following string: "((bone marrow concentrate) OR (BMC) OR (bone marrow aspirate concentrate) OR (BMAC)) AND (osteoarthritis)", and inclusion criteria: clinical and preclinical (animal) studies of any level of evidence, written in English language, and evaluating the intra-articular or subchondral use of BMAC for the injective treatment of OA joints.

Results The publication trend remarkably increased over time. A total of 22 studies were included in the qualitative data synthesis: four preclinical studies and 18 clinical studies, for a total number of 4626 patients. Safety was documented by all studies, with a low number of adverse events. An overall improvement in pain and function was documented in most of the studies, but the clinical studies present significant heterogeneity, few patients, short-term follow-up, and overall poor methodology.

Conclusion There is a growing interest in the field of BMAC injections for the treatment of OA, with promising results in preclinical and clinical studies in terms of safety and effectiveness. Nevertheless, the current knowledge is still preliminary. Preclinical research is still needed to optimize BMAC use, as well as high-level large controlled trials to better understand the real potential of BMAC injections for the treatment of patients affected by OA.

Conclusion:

OA Treatments : K-L Grade 1 to 4
Intra-articular and Subchondral BMAC Injection is safe and effective



OA KL-3

Knee Surgery, Sports Traumatology, Arthroscopy (2021) 29:4232–4240
https://doi.org/10.1007/s00167-021-06530-x

KNEE

Check for updates

Subchondral and intra-articular injections of bone marrow concentrate are a safe and effective treatment for knee osteoarthritis: a prospective, multi-center pilot study

Elizaveta Kon[1,2] · Angelo Boffa[3] · Luca Andriolo[3] · Alessandro Di Martino[3] · Berardo Di Matteo[2,4] · Nicola Magarelli[1] · Maurilio Marcacci[1,2] · Francesco Onorato[1] · Nicoletta Trenti[1] · Stefano Zaffagnini[3] · Giuseppe Filardo[5]

Received: 13 November 2020 / Accepted: 4 March 2021 / Published online: 27 March 2021

Sustained 2 Year Results : KL 3 and 4

translational-medicine.biomedcentral.com/articles/10.1186/s12967-018-1736-8

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Journal of Translational Medicine

Home | About | Articles | Submission Guidelines | Submit manuscript

Research | Open access | Published: 13 December 2018

A specific protocol of autologous bone marrow concentrate and platelet products versus exercise therapy for symptomatic knee osteoarthritis: a randomized controlled trial with 2 year follow-up

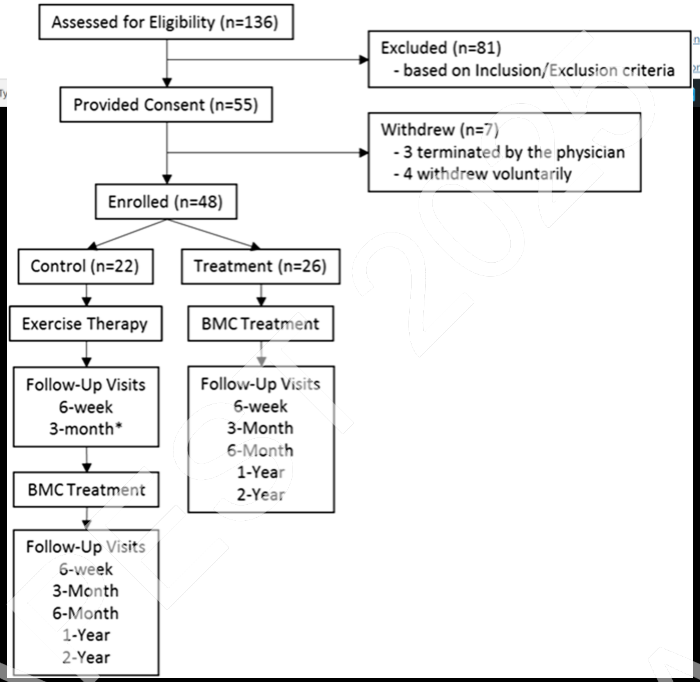
Christopher Centeno, Mitchell Sheinkop, Ehren Dodson, Ian Stemper, Christopher Williams, Matthew Hyzy, Thomas Ichim & Michael Freeman

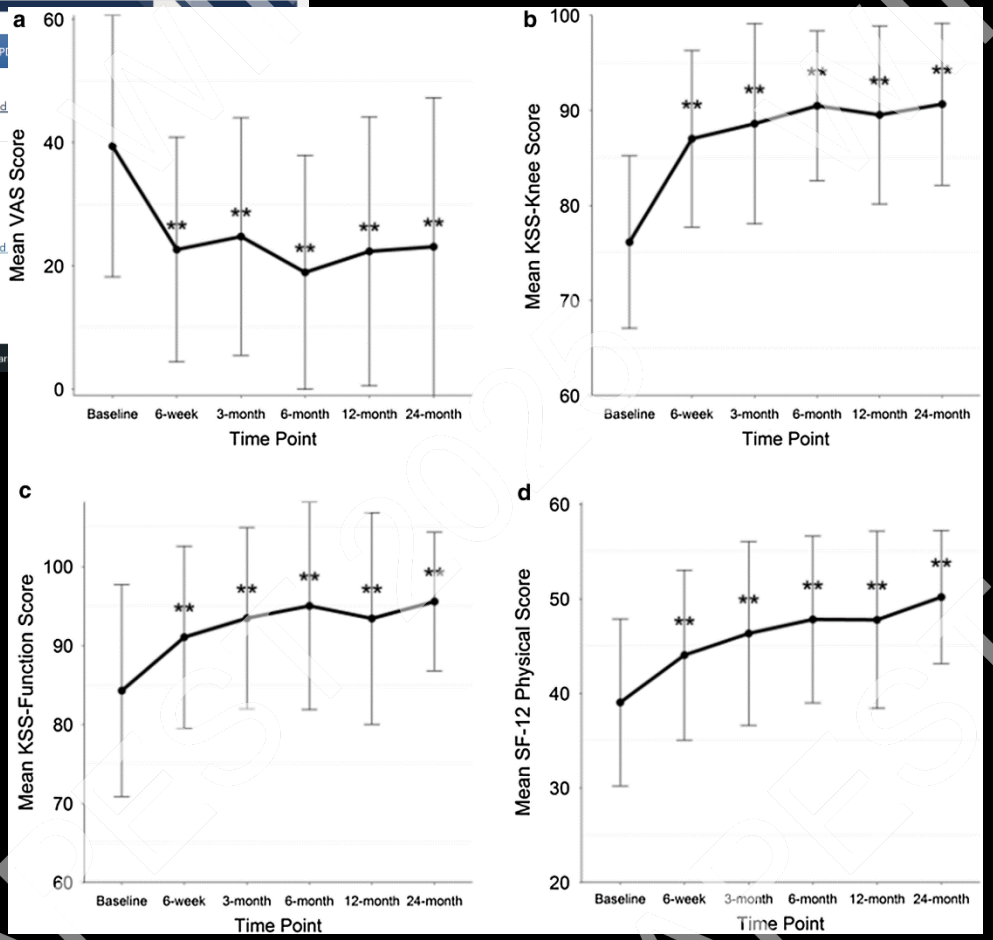
Journal of Translational Medicine **16**, Article number: 355 (2018) | Cite this article

Download PDF

Section
Cell, tissue and

Sections
Abstract
Background
Materials and





Challenges

Bone Marrow Aspirate Concentrate (BMAC) for Knee Osteoarthritis: A Narrative Review of Clinical Efficacy and Future Directions

Medicina (Kaunas). 2025 May 6;61(5):853.

Dojoon Park et al

- Variability in BMAC preparation methods
- optimal administration strategies, injection protocols
- Single vs. repeated administration, intra-articular vs. subchondral delivery
- Patient selection criteria and standardized guidelines.
- Additionally, economic feasibility and cost-effectiveness concerns limit its widespread adoption.
- Future directions for improving treatment standardization and patient-specific therapy

Where are we now & The future .....?

1980's 1990's 2000 2012 2012-20 2020-25

ACI

Tissue Engineering (MACI)

GelACI (Shetty-Kim)

New scaffolds

New Bio-materials (Shetty-Kim)

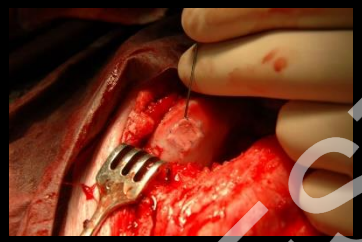
Stem Cell Manipulation

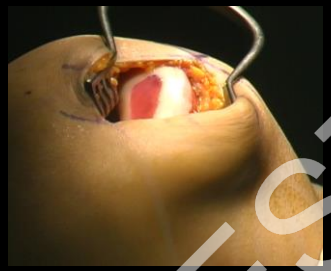
BMAC/Exosomes injection

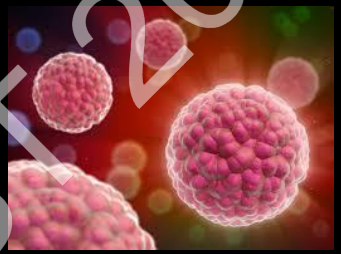
UC-Cord blood Stem cells

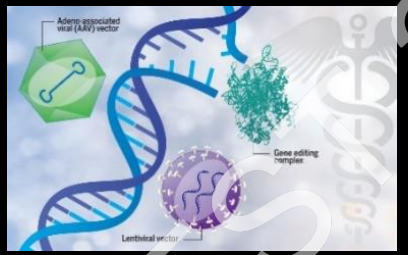
Growth factors

Gene Therapy (Shetty-Kim)

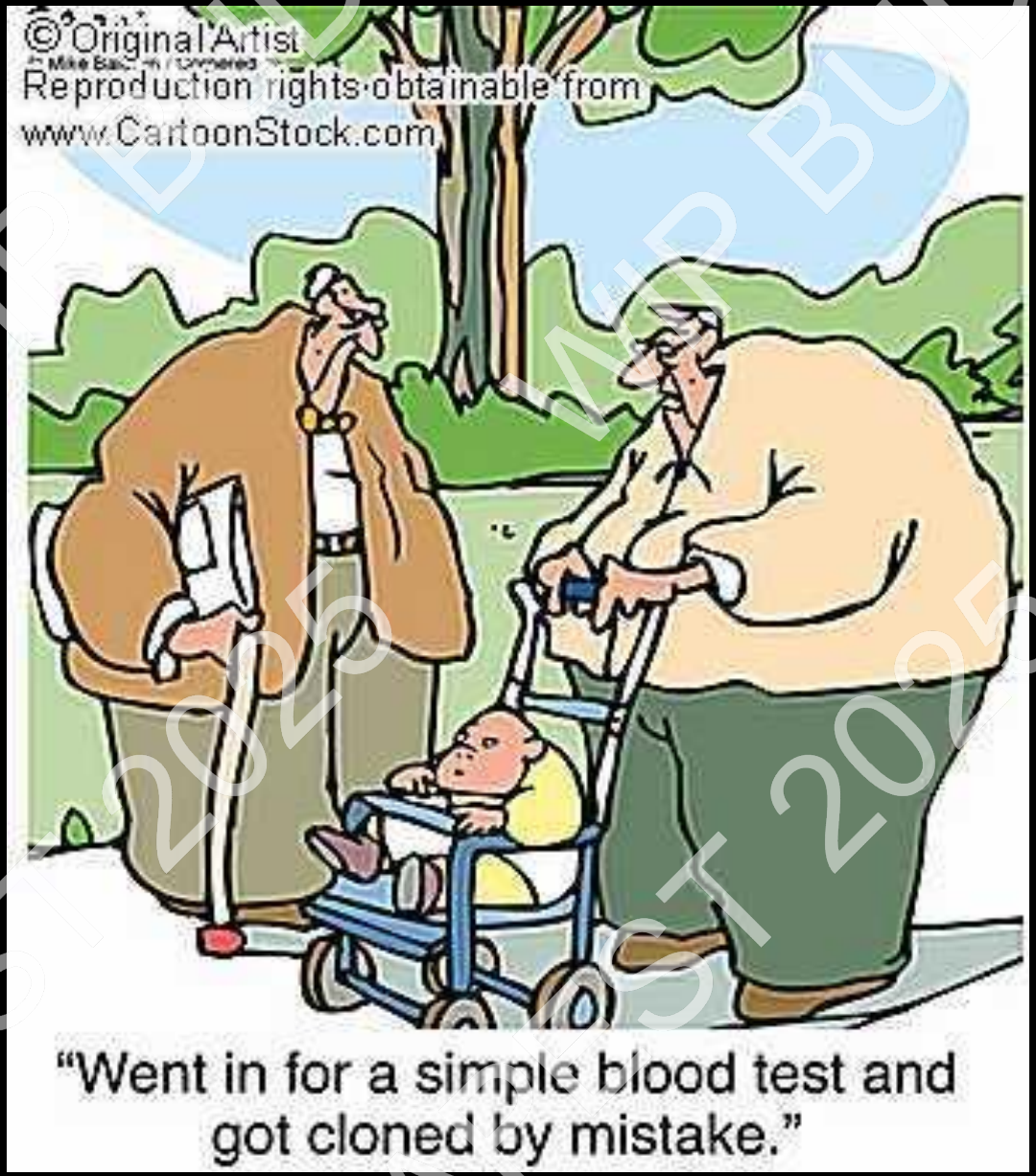








Keep it Simple

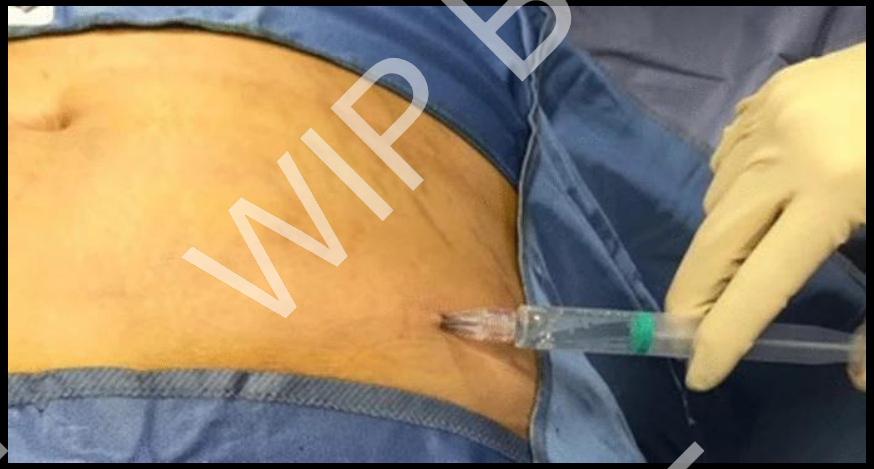


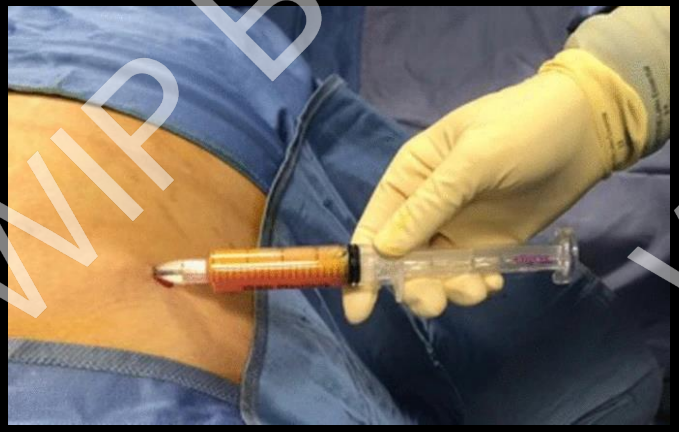
“Life can only be understood backwards, but it must be lived forwards” —

Soren Kierkegaard

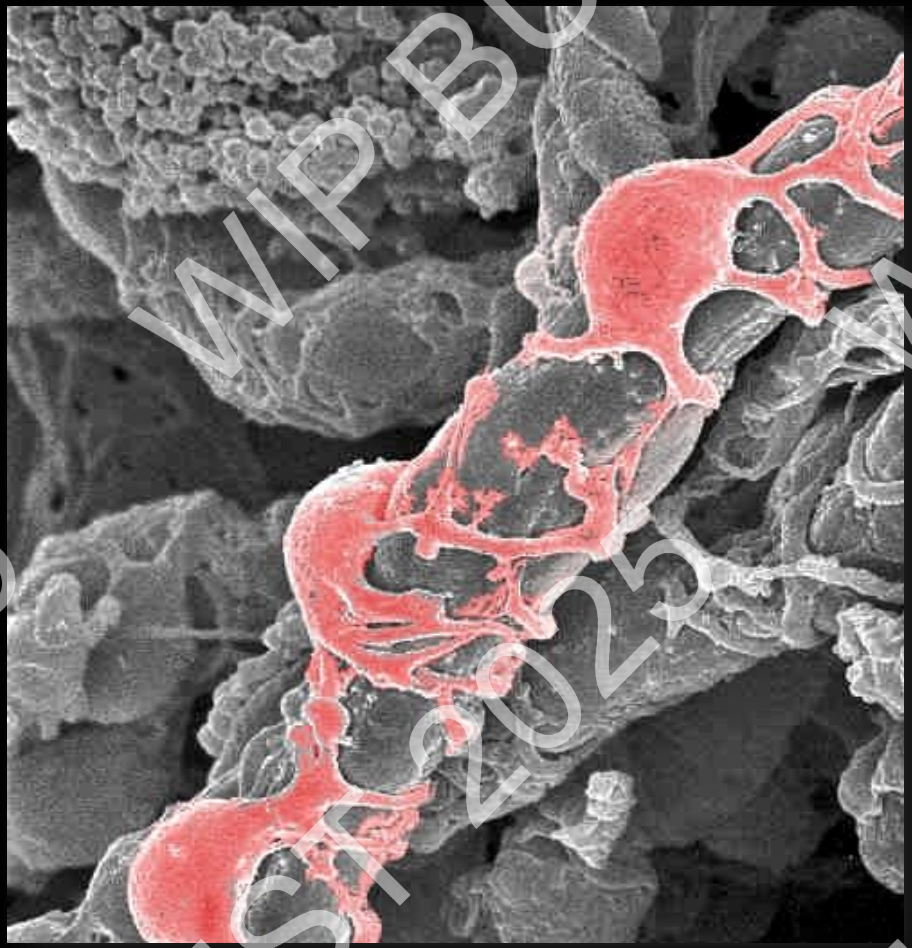
Question Time

ADSCs (Adipose Derived Stem Cells)





Where can we locate MSCs:
SVF (Stromal Vascular Fractions)

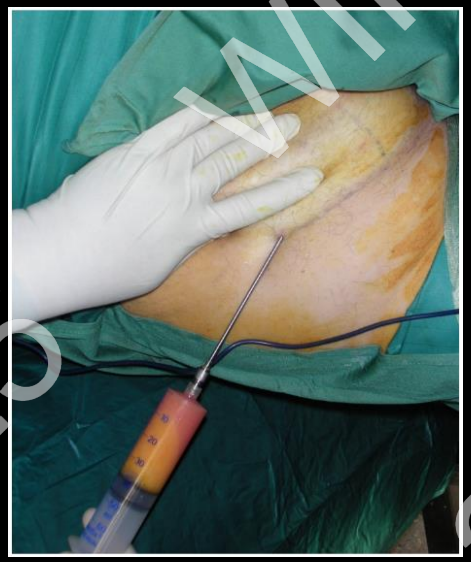


Courtesy by Al Caplan

PERICYTES
Cells on Capillaries and Micro-vessels

NOT THE STROMAL CELLS

Adipose-derived stromal cells (ADSCs) SVF or Stromal Vascular fraction



- ADSCs were reported to have a reduced potential for chondrogenic differentiation that may be a result of a lack of TGFβ1-receptor expression and reduced expression bone morphogenetic proteins (BMPs)
- The expression of hypertrophic chondrocyte markers, such as Runx2, Osterix and type X collagen, was observed in ADSCs

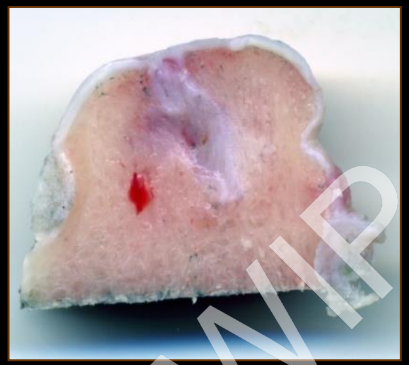
ANIMAL STUDY- Sheep:Shetty -Kim 16 SHEEP – 32 LESIONS

Scaffold+BMAC

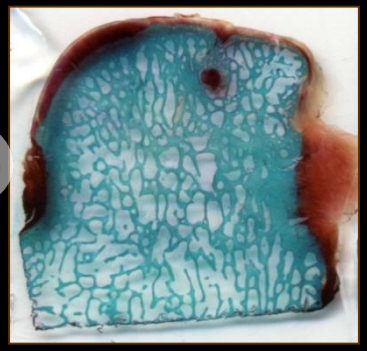
Scaffold

Scaffold + ADC

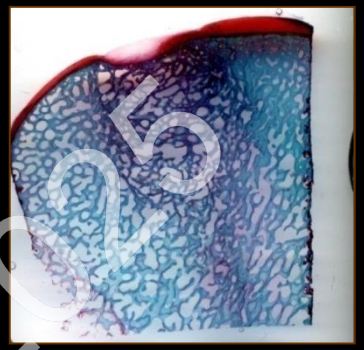
Empty control



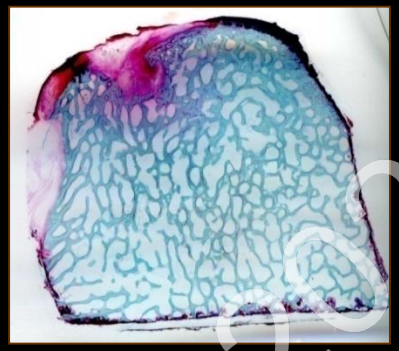
Scaffold+BMAC



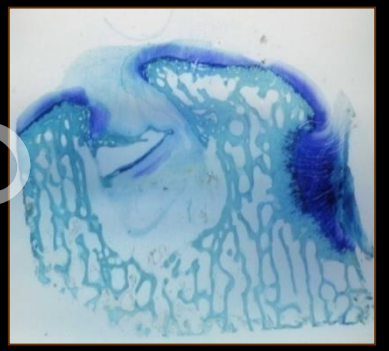
Scaffold



Scaffold + ADC

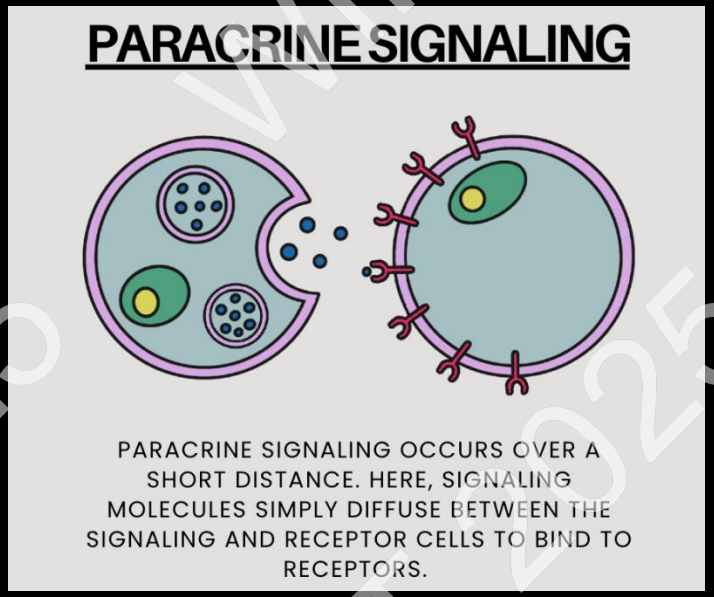


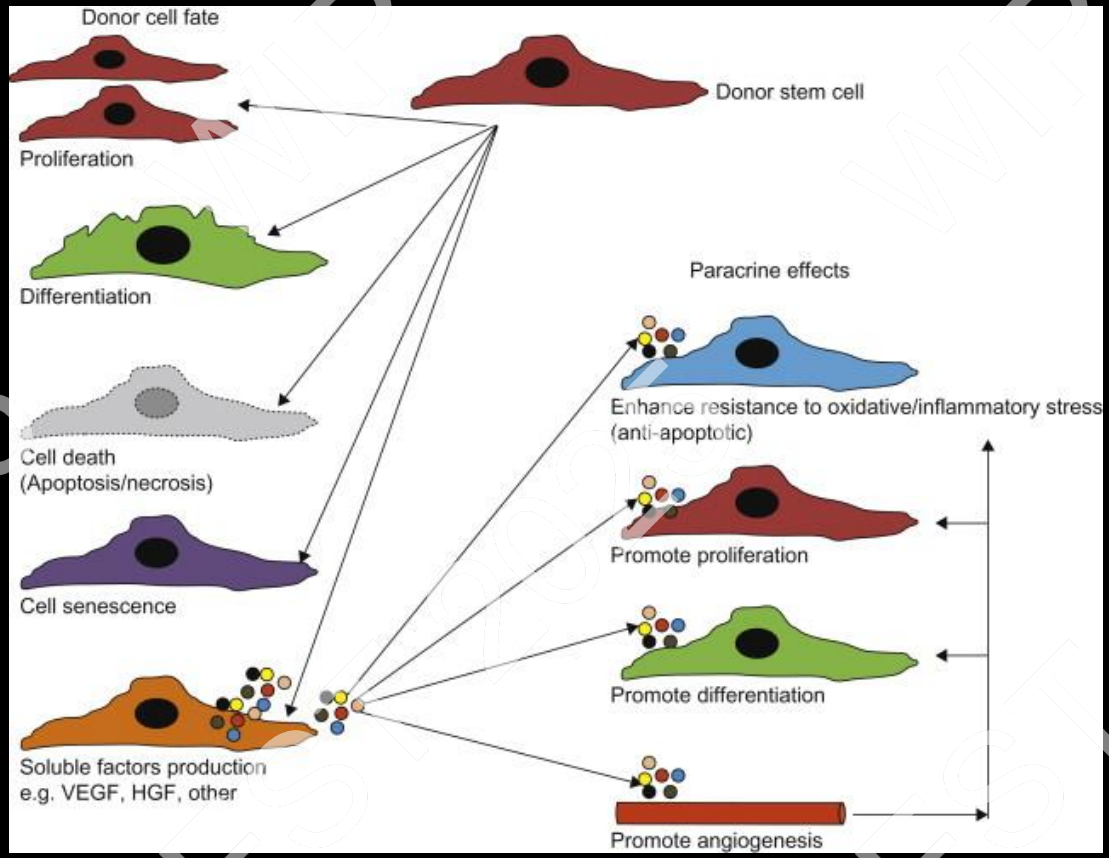
Empty control



Setty-Kim et al., *significant difference between atelocollagen cell-seeded with BMAC ,ADC Scaffold and control groups)*

Engrafting


PARACRINE SIGNALING
PARACRINE SIGNALING OCCURS OVER A SHORT DISTANCE. HERE, SIGNALING MOLECULES SIMPLY DIFFUSE BETWEEN THE SIGNALING AND RECEPTOR CELLS TO BIND TO RECEPTORS.


Donor cell fate
Donor stem cell
Proliferation
Differentiation
Cell death
(Apoptosis/necrosis)
Cell senescence
Soluble factors production
e.g. VEGF, HGF, other
Paracrine effects
Enhance resistance to oxidative/inflammatory stress
(anti-apoptotic)
Promote proliferation
Promote differentiation
Promote angiogenesis

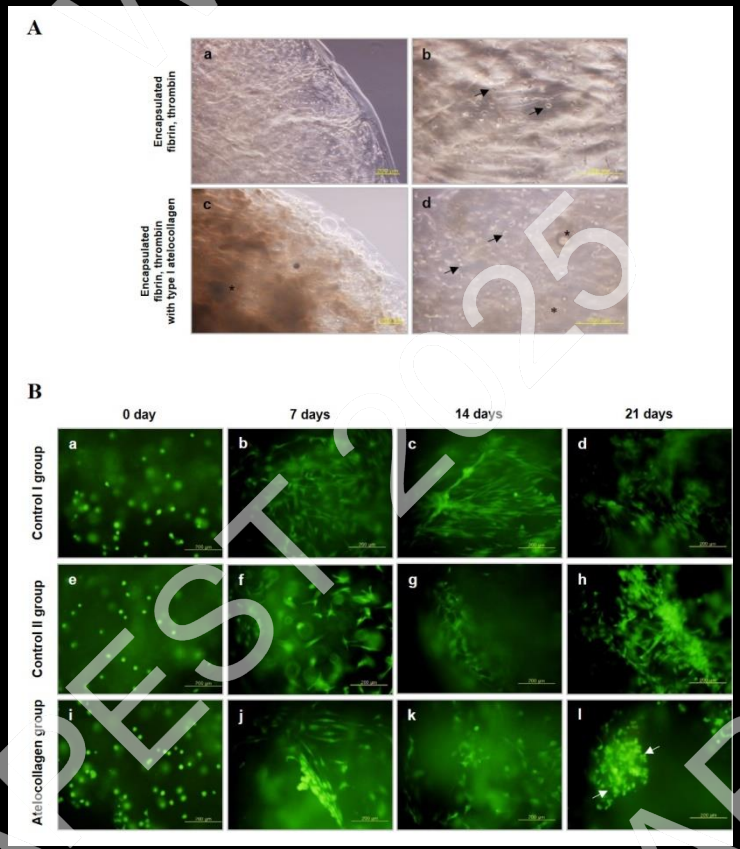
SCIENTIFIC REPORTS
nature research

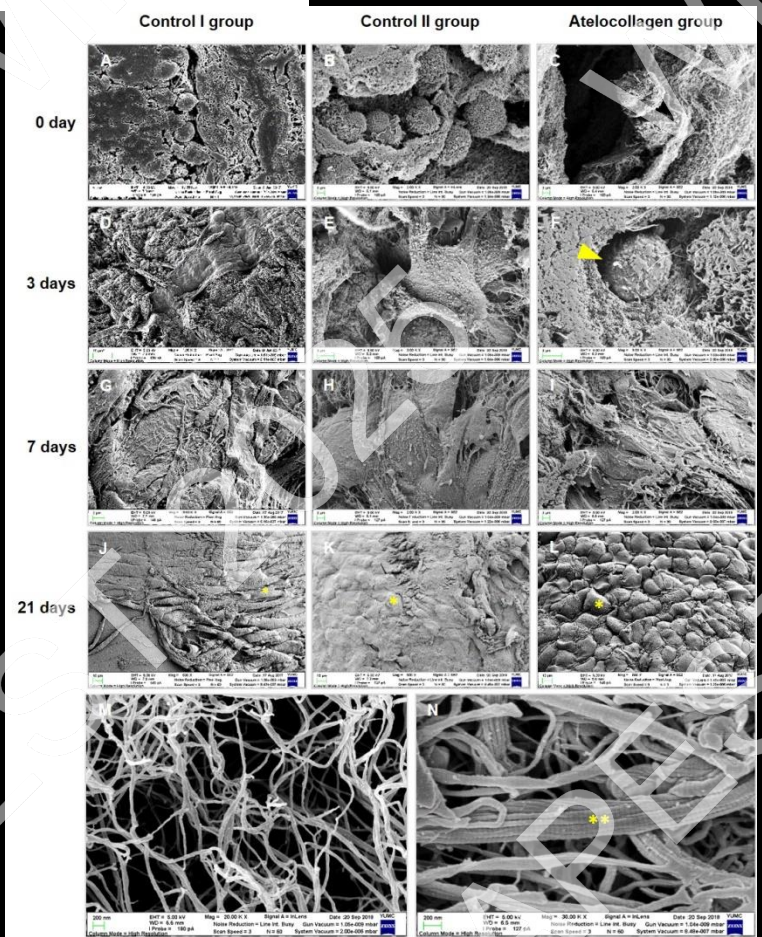
Sci Rep. 2020; 10: 10678.
Published online 2020 Jun 30. doi: 10.1038/s41598-020-67836-3

PMCID: PMC7327030
PMID: 32606308

Atelocollagen promotes chondrogenic differentiation of human adipose-derived mesenchymal stem cells

Seon Ae Kim,[1] Yoo Joon Sur,[1] Mi-La Cho,[2] Eun Jeong Go,[1] Yun Hwan Kim,[1] Asode Ananthram Shetty,[3] and Seok Jung Kim[1]

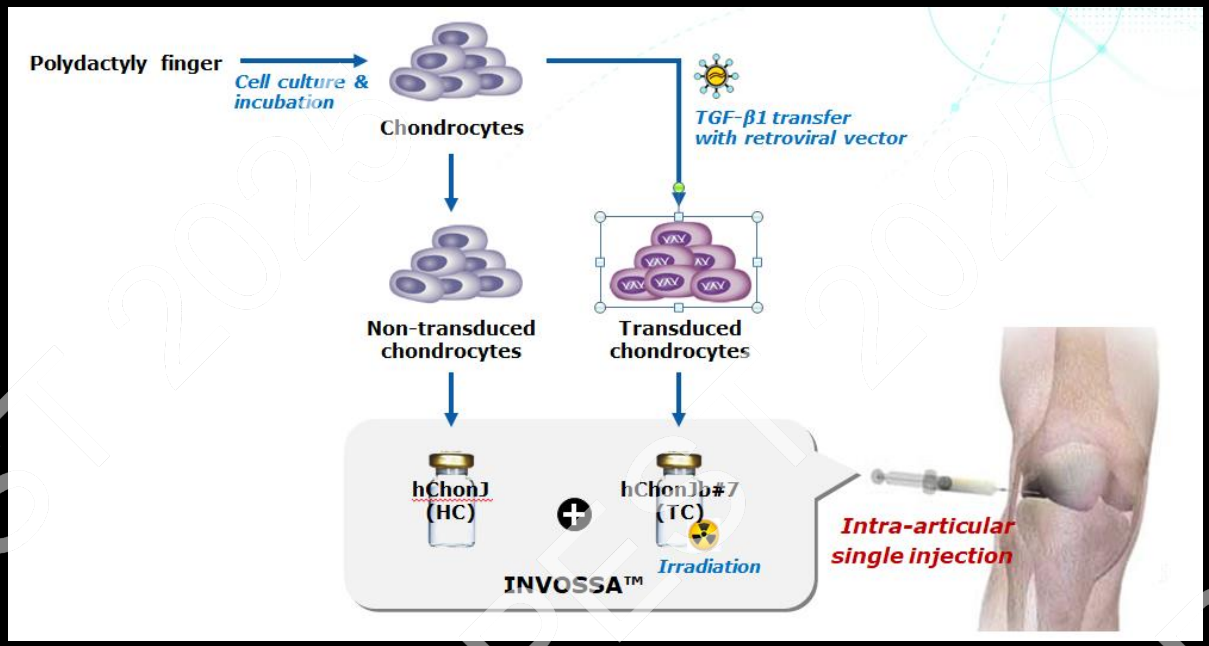




New Zealand Rabbit: Shetty-Kim

Gene Therapy

- Uses allogeneic human cartilage cells engineered to express transforming growth factor TGF-ß1.
- Invossa platform technology involves transducing the cells with a retroviral vector engineered to express TGF-ß1 at a specific therapeutic level and duration of time.



Publications- INVOSSA

TGF-ß1 (BMP) Transduction/Retroviral Vector-Adenovirus)

KR Phase **2a and** KR Phase 2b

Hum Gene Ther Clin Dev. 2015 Jun;26(2):125-30

Bone Joint J. 2015 Jul;97-B(7):924-32

A Multicenter, Single-Blind, Phase IIa Clinical Trial to Evaluate the Efficacy and Safety of a Cell-Mediated Gene Therapy in Degenerative Knee Arthritis Patients

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Abstract

Osteoarthritis leads to articular cartilage wear, and newer therapies are aimed at slowing this degeneration. Growth factors and cytokines influence cartilage formation, and researchers are studying their use on cartilage regeneration in osteoarthritis. One method uses genetically engineered cells to deliver growth factors to damaged cartilage. This technique utilizes transforming growth factor-β proteins in modified chondrocytes to stimulate cartilage growth via an intra-articular injection. We evaluated the efficacy and outcomes of this injection on patients who had International Cartilage Repair Society grade 4 knee osteoarthritis. We evaluated 27 patients (6 men, 21 women) who had late-stage knee osteoarthritis. Patients were randomized to receive genetically engineered chondrocytes doses of 6×10^6 cells (group 1) or 1.8×10^7 cells (group 2) at a 1:1 ratio. Primary endpoints were subjective and functional evaluations, assessed by the International Knee Documentation Committee (IKDC) score. Secondary endpoints were pain severity and physical function, using the Western Ontario and McMaster osteoarthritis (WOMAC) index and the 100 mm visual analog scale (VAS). Patients were followed at 2, 4, 12, and 24 weeks postinjection. Both groups had significant improvements in outcomes. Scores improved at 12 and 24 weeks from baseline in IKDC (+10 and +14 points in group 1; +11 and +13 points in group 2), WOMAC (−12 and −13 points in group 1; −10 and −12 points in group 2), and VAS (−19 and −24 points in group 1; −20 and −20 in group 2) scores. Additionally, there were no serious adverse events, and no significant difference in adverse event incidence between the groups. Both groups expressed a mean improvement in pain, function, and physical ability following treatment injection. This modality appears to be a promising treatment for cartilage degeneration. However, further larger, multicenter, randomized studies are needed to truly evaluate the efficacy of this novel approach.

THE BONE & JOINT JOURNAL

■ KNEE

A placebo-controlled randomised trial to assess the effect of TGF-ß1-expressing chondrocytes in patients with arthritis of the knee

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The aim of this study was to assess the effect of injecting genetically engineered chondrocytes expressing transforming growth factor beta 1 (TGF-β1) into the knees of patients with osteoarthritis. We assessed the resultant function, pain and quality of life.

A total of 54 patients (20 men, 34 women) who had a mean age of 58 years (50 to 66) were blinded and randomised (1:1) to receive a single injection of the active treatment or a placebo. We assessed post-treatment function, pain severity, physical function, quality of life and the incidence of treatment-associated adverse events. Patients were followed at four, 12 and 24 weeks after injection.

At final follow-up the treatment group had a significantly greater improvement in the mean International Knee Documentation Committee score than the placebo group (16 points; -18 to 49, *vs* 8 points; -4 to 37, respectively; p = 0.03). The treatment group also had a significantly improved mean visual analogue score at final follow-up (-25; -85 to 34, *vs* -11 points; -51 to 25, respectively; p = 0.032). Both cohorts showed an improvement in Western Ontario and McMaster Osteoarthritis Index and Knee Injury and Osteoarthritis Outcome Scores, but these differences were not statistically significant. One patient had an anaphylactic reaction to the preservation medium, but recovered within 24 hours. All other adverse events were localised and resolved without further action.

This technique may result in improved clinical outcomes, with the aim of slowing the degenerative process, leading to improvements in pain and function. However, imaging and direct observational studies are needed to verify cartilage regeneration. Nevertheless, this study provided a sufficient basis to proceed to further clinical testing.

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OA- Treatment:
Other Current Therapies

- PRP
  High variability in preparation; inconsistent long-term efficacy
- HA
  Effectiveness varies based on OA severity
- Corticosteroids
  Potential cartilage degradation with repeated use

Effusion and Nocturnal pain- Treat differently (MRI Vs US Examination)