


Innovative and Orthobiological Approaches to Bone Marrow Lesions

Bert R. Mandelbaum MD DHL (hon)


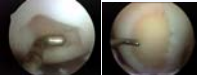

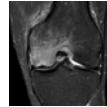
FIFA Medical Committee
 CONCACAF Medical Committee
 Asst Medical Director MLS
 F-MARC Member
 Team Physician US Soccer, LA Galaxy, Pepperdine University



Disclosures

- ▶ Consultant
 - Arthrex (Royalties)
 - Johnson and Johnson and Depuy Mitek
 - Exactech
 - Geistlich
 - Regen
 - Vericel
 - Alter G

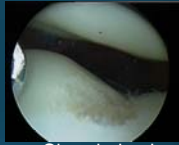
Biologic Spectrum of approaches to the Knee

• Synovium and joint	JOINT	
• Articular Cartilage Resurfacing	ARTICULAR ONLY	
• Osteochondral defects	CARTILAGE/BONE	
• Bone Marrow Lesions	BONE /CARTILAGE	

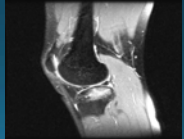
- cytokines, factors, hormones,
- < 2 cm2 > 2 cm2 size matters!
- < 7 mm deep
- > 7 mm
- **Subchondral Edema (SCE)**
- **Osteonecrosis (AVN)**
- **Insufficiency Fractures (ISFX)**
- **SONK**

Static and Dynamic Malalignment, Instability, Meniscal Pathology must managed!

Overview Bone Marrow Lesions



Chondral only

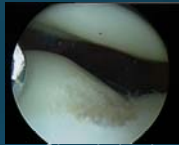


Osteochondral

Overview Bone Marrow Lesions



Black tip reef 7 ft



Chondral only



Osteochondral

Overview Bone Marrow Lesions



White Shark 16 ft

They are all sharks. but treat differently!

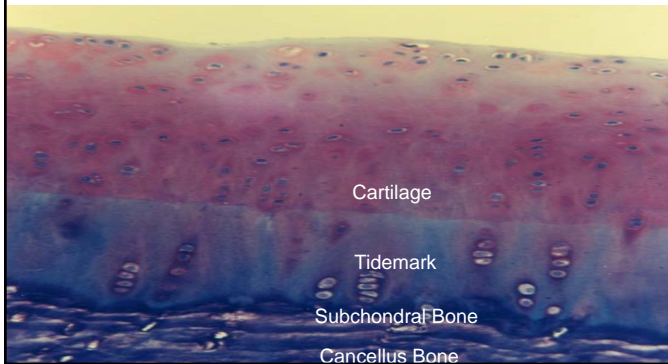


Chondral only

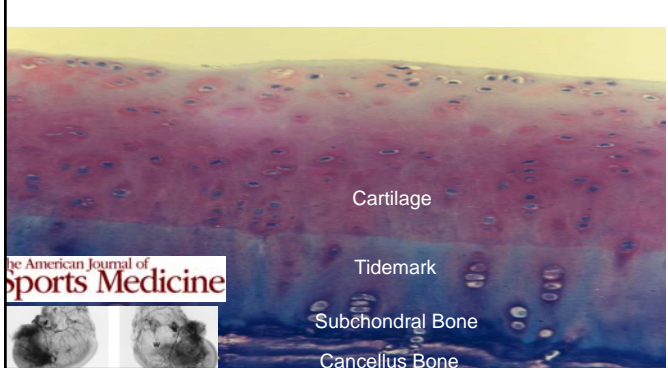


Bone/ Cartilage

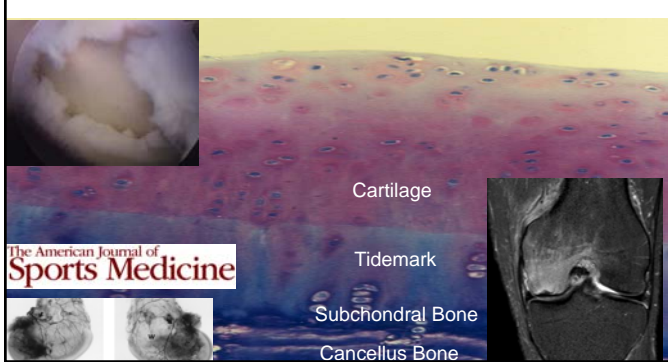
Cartilage
1995- 2000



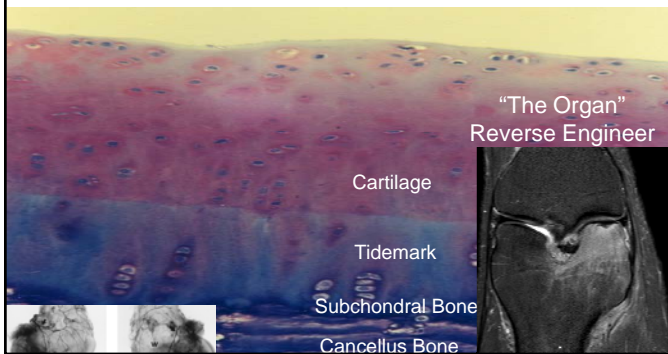
Cartilage
1995- 2000



Cartilage
1995- 2000



2000-2015 Cartilage Repair.....



50 y/o male recreational tennis player who presented with knee pain after flying he developed severe knee pain, He had begun using androgen gel 4 weeks previously for low testosterone.

Case

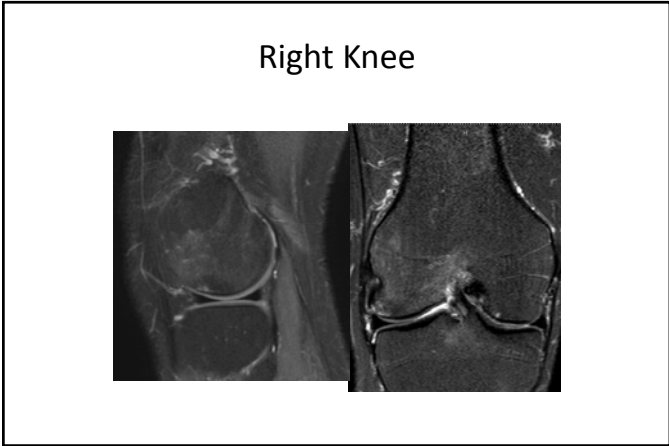
- PMHx:Low testosterone
- Meds: Vyvance 20mg BID, Lipitor 10mg qday, Prevacid 30mg daily, Vitamins, Propecia, ASA EC 81 mg po qday, Testosterone 200mg shot q month



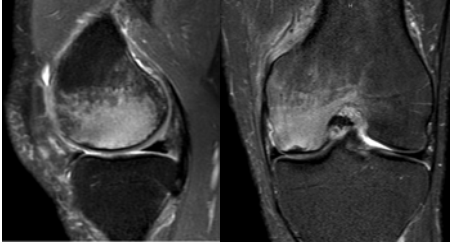








Left Knee



Case Options?
Natural course?
Timing?



50 y.o. aerobics instructor



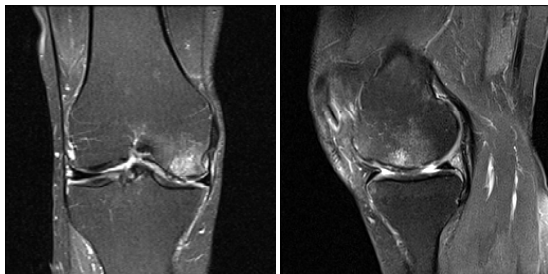
Microfracture



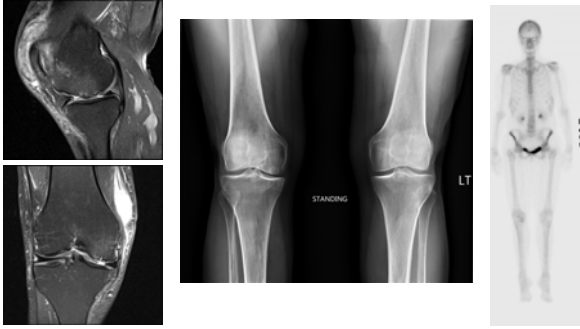
6 months later



3 years later



8 years later

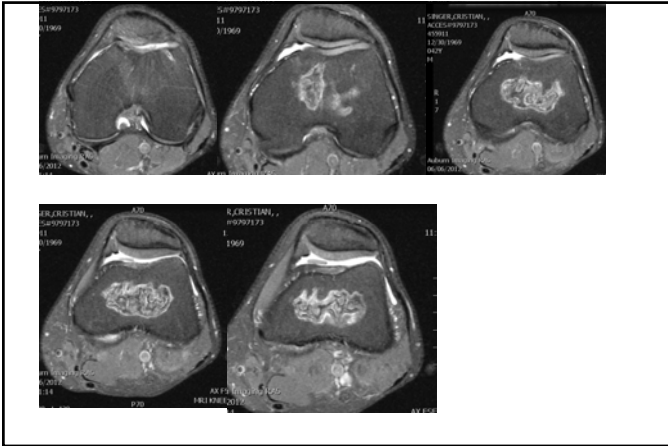


Case

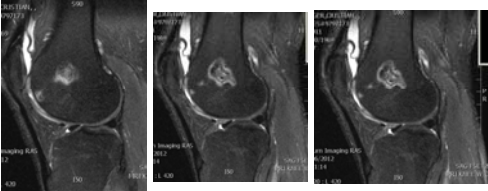
- 42 yo male, botanist, fell directly on his left knee while hiking in 6.2009. Underwent a KA, MFX of trochlea (anterior femoral condyle) in 11.2010. Has had persistent anterior pain. Failed viscosupplementation.







42 y/o botanist



What to for the chondrofacilitation, cartilage repair? The bone? All?

22 y/o professional soccer player



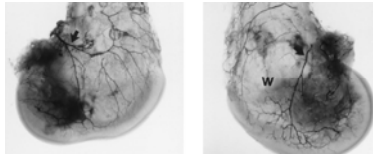
60 year old high level skier



Supporting literature Reddy et al 1998

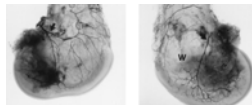
- Pathogenesis-- **Blood flow problem--**
Propensity for MFC lesions
 - Blood Flow in MFC
 - Extraosseous---superior medial genicular artery
 - Intra-osseous--- a single nutrient artery
 - **Leaves a watershed area**

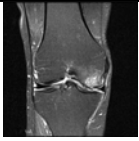
The American Journal of
Sports Medicine



Essence of subchondral bone

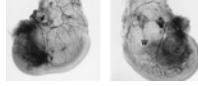
- role underestimated
- shock absorber
- highly **vascularized and vulnerable**
- terminal vessels have, in part, **direct contact** with the deepest hyaline cartilage layer
- perfusion of these vessels accounts for more than **50% of the glucose, oxygen, and water requirements of cartilage**
- Bony structure, local metabolism, hemodynamics, and vascularization of the **subchondral region differ**
- **repetitive, chronic overloading or perfusion abnormalities** may result may lead to osteonecrosis, osteochondritis dissecans, or degenerative changes





Bone Marrow Lesions

SCE

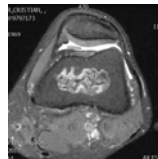


- Pathogenesis- controversial entity etiopathological processes
BML **disequilibrium between stimulus and bone to remodel and restore the physiological condition.**
- MRI finding alteration of the signal intensity of the bone
- multiple pathological conditions
 - **traumatic** (bone contusion, osteochondral fracture, insufficiency and stress fractures, etc.)
 - **atraumatic** (avascular necrosis, spontaneous osteonecrosis, osteoarthritis-associated)

Osteonecrosis.. physiology

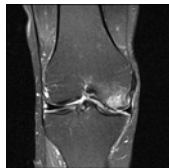
Uchio et al CORR. 2001

- 11 knees with ON vs 11 knees with OA.
- Measured intraosseous pressure and venograms
 - **intraosseous pressure elevation** of the MFC of the knees with ON
 - (62.8 +/-27.3 mm Hg)
 - **significantly higher** than both condyles of the knees with OA
 - (medial, 31.6+/-17.4 mm Hg; lateral, 29.5+/- 11.0 mmHg).
 - Venography showed **a marked capacitance disturbance of venous drainage in all patients with osteonecrosis**
- Avg Clearance time of contrast was **significantly slower** in knees with ON than knees with OA
 - (17.7 +/-6.1 minutes) vs (5.5 +/-1.6 minutes).



BME and ACI Niethammer 2015

- observed after third-generation ACI
- 38 knees by a standardized MRI up to 36 months.
- seen in **78.9% of defects** over the postoperative course
- more common in **femoral** than patellar defects
- **no correlation with the clinical outcome** could be found in this series



The American Journal of
Sports Medicine

Clinical outcome affected by subchondral bone edema
Filardo 2014.



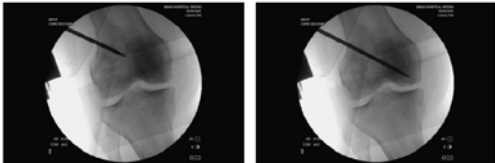
- 116 pts treated with HA ACI, performed from 6 to 108 months postoperatively
- BML was present in early phases, markedly **reduced by 3 years** then increased mid/long-term follow-up
- The initial reduction may be explained by a **maturation phase**
- **no correlation was found between BML and the clinical outcome**
- BML is a **common finding** after cartilage surgery, the **interpretation of MRI abnormalities remains to be clarified.**

Core decompression—small diameter

Marulanda et al. JBJS 2006



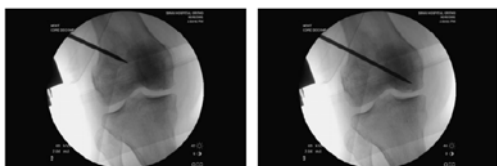
- 16 pts stage I, II secondary ON
- Small diameter (3.2mm)
- Multiple passes (2 for small lesions, 3 for large)



Short-Term Outcomes of the Subchondroplasty Procedure for the Treatment of Bone Marrow Edema Lesions in Patients with Knee Osteoarthritis Davis et al 2015



50 pts
 VAS (pre-SCP 8.3, post-SCP 3.6). Eighty-eight percent (44 of 50) of patients experienced improvement in their pain and 72% (36 of 50) experienced improvement in pain-free walking distance



Subchondral Calcium Phosphate is Ineffective BMLs with OA

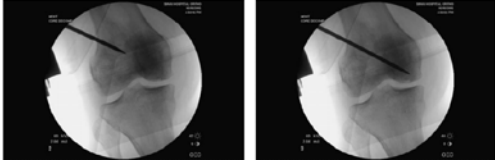
Chatterjee 2015

33 pts

7/22 poor result

Conclusions: Do not recommend

CLINICAL ORTHOPAEDICS
AND RELATED RESEARCH



CD + BMAC

Hernigou et al. CORR. 2002

- Authors had disappointing results with CD alone in hips
- Developed CD and introduced BMAC
- 189 hips with >5 years FU
- 3mm diameter trephine and BMAC injection

TABLE 2. Preoperative Stage of the Hips at the Time of Treatment and Number of Hips With Total Hip Replacement at the Most Recent Followup

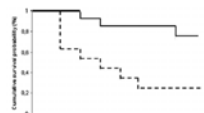
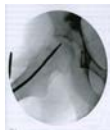
Hips (Number)	Preoperative Stage	Arthroplasty (Number; %)
59	Stage I	2 (3%)
66	Stage II	7 (8%)
12	Stage III	5 (41%)
52	Stage IV	20 (63%)



CD + BMAC

Gangji et al. Bone. 2011

- Prospective cohort
- 24 hips
- Stage I, II ON of femoral head
- CD vs CD and BMAC
- FU 60 months
 - CD = 8/11 deteriorated
 - CD + BMAC = 3/13 deteriorated



TREATMENT OF OSTEOARTRITIS OF THE FEMORAL HEAD WITH IMPLANTATION OF AUTOGRAFT BONE-MARROW CELLS

Some fundamental definitions

The 4 R's

- Regenerative therapy - broad definition for innovative therapies to **repair, replace, restore and regenerate** damaged or diseased cells, tissues and organs

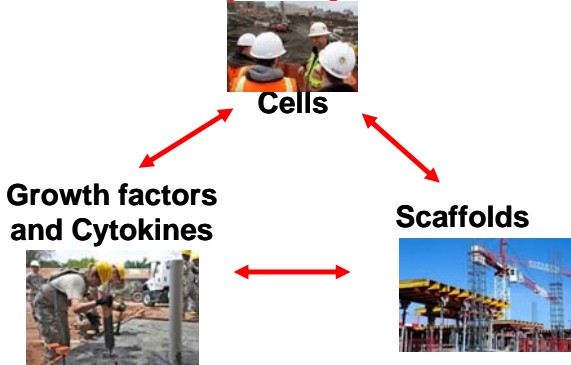


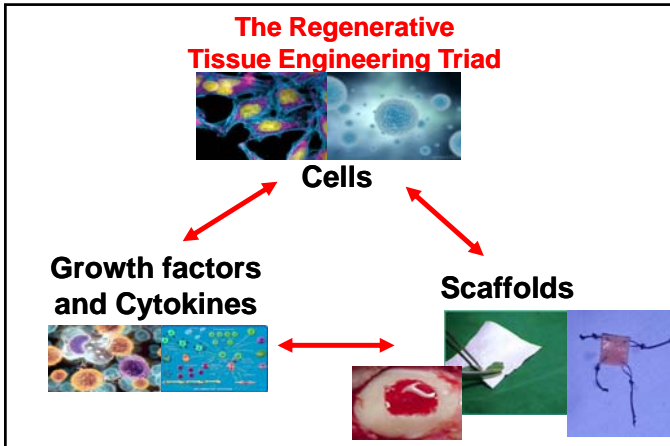
Restoration / Regeneration

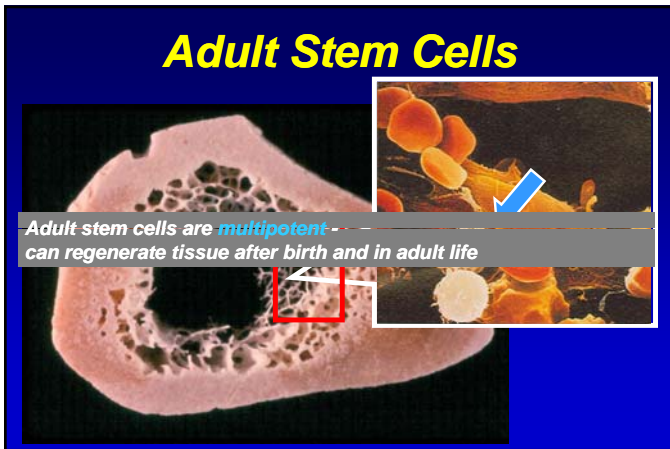


- Regeneration is the restoration of injured tissue properties **Non-distinguishable from original tissue**
- goal is to regenerate a tissue, not to repair it
- Rebuild the shape and restore the function... form and function

The Engineering Triad

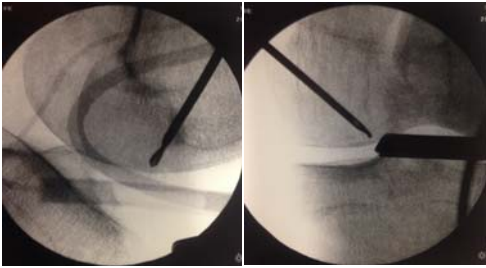






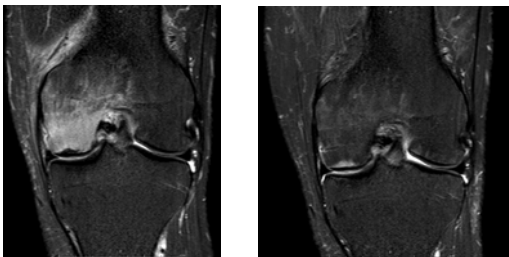
Case
50 y/o Tennis player on Testosterone
 L knee Arthroscopy with CD and BMAC

Three circular arthroscopic images showing the interior of a knee joint. The first image shows a normal-looking joint surface. The second image shows a dark, irregular area, likely a lesion or tear. The third image shows a different view of the joint surface.

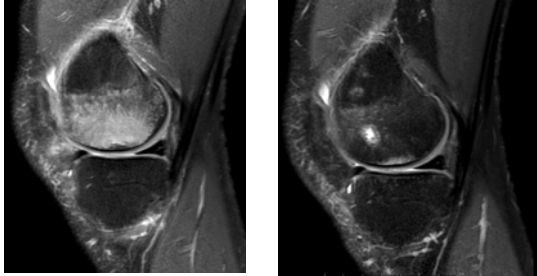




Side by Side Comparison at 3 months



Side by Side Comparison at 3 months



Clinical Case - BMAC

- 28 year old female martial arts with progressive pain, disability in lateral aspect of knee. MRI showed progressive OCD with cartilage injury



LTP OCD

Clinical Case - BMAC

- 28 year old female martial arts with progressive pain, disability in lateral aspect of knee. MRI showed progressive OCD with cartilage injury

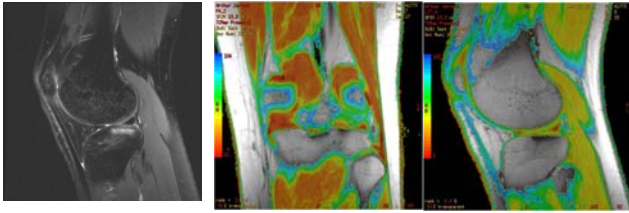


LTP OCD

Packing ICBG/BMAC

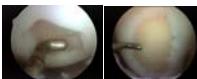
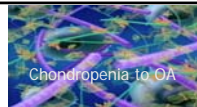
BMAC clot applied

BMAC/LTC @ 3 months with T2 Mapping



Biologic Spectrum of approaches to the Knee

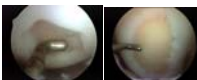
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- **Bone Marrow lesions** BONE /CARTILAGE
 - Subchondral Edema (SCE)
 - Osteonecrosis (AVN)
 - Insufficiency Fractures (ISFX)
 - SONK



Static and Dynamic Malalignment, Instability, Meniscal Pathology must managed!

Bone Marrow Lesions Conclusions


- Complicated etiopathology JOINT
- Some resolve and heal others refractory ARTICULAR ONLY
- Regeneration of bone requires cells, growth factors and scaffold and blood flow in and out CARTILAGE/BONE
- BMAC and core decompression seems to address all issues concurrently BONE /CARTILAGE
- We need to stratify lesions and the organ joint and do long term studies

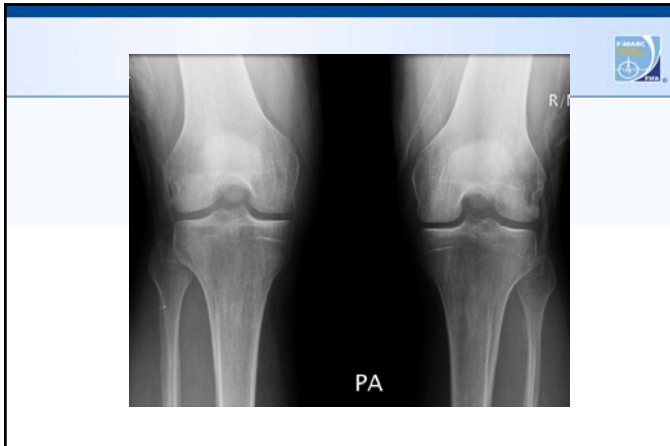




Chondrofacilitation Conclusions

- Major frontier in orthopaedic surgery and sports medicine **will be lead by molecular biology** and our ability to utilize these techniques clinically.
- Think as an adjuvant "Ideal cocktail"... HA + PRP+Toradol+ MSC+ Estradiol+ Stanizol???
- Our present understanding of and maximizing the desired effect on the native tissue **is at it's infancy.. Good steps so far!**
- basic and clinical science is essential to discover the complexities of **optimal regeneration**
- Need to be precise in not **overstating the impact!..it is the TRIAD**







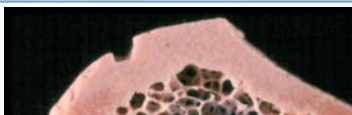


High risk of Osteonecrosis with inherited hypercoagulable disorders

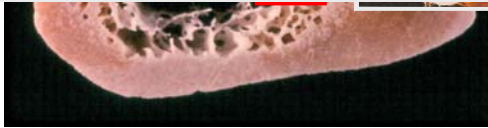


Jones et al. J Rheumatol. 2003.
 Korompilias et al. Orthop Clin North Am. 2004
 Gluek et al. JBJS Am. 2008.

Adult Stem Cells



Adult stem cells are multipotent - they can give rise to a limited number of tissues during fetal development and can regenerate tissue after birth and in adult life
Bone vs Adipose Derived



GROWTH FACTOR CONTENT OF BONE MARROW



	Plt Ct x10 ⁹ /µL	TNC x10 ⁹ /µL	PDGF-AB ng/mL	TGFB-1 ng/mL	VEGF pg/mL	Plt Ct x10 ⁹ /µL	TNC x10 ⁹ /µL	PDGF-AB ng/mL	TGFB-1 ng/mL	VEGF pg/mL
Mean	103.3	18.9	16.4	33.4	114	752	114.4	86.8	124.6	687
± SD	19.2	4.3	7.3	11.2	49.1	509	20.1	8.1	70.2	322

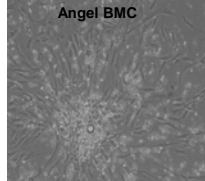
N=6

BMA = Bone marrow aspirate
BMAC = Bone marrow concentrate
Plt Ct=Platelet count
TNC = Nucleated cell count
PDGF-AB = Platelet-Derived Growth Factor Alpha/Beta
TGFB-1 = Transforming Growth factor Beta
VEGF = Vascular Endothelial Growth Factor

Technology Changes Everything

Arthrex Angel BMC	Platelet Concentration (K/ μ l)	Nucleated Cell Concentration (K/ μ l)	Hematopoietic Cell Concentration (K/ μ l)	Total Neutrophil ($\times 10^6$)
BMA	87.7 \pm 6.4	24.5 \pm 15.6	0.002 \pm 0.001	612.1
BMC	787.0 \pm 317.6	240.5 \pm 186.6	0.081 \pm 0.056	132.9
Increase Above Baseline	-9x	-10x	-33x	+80%

>80% recovery of the hematopoietic cell lines with an 80% reduction in the undesirable neutrophil cell content.



Bone Marrow Aspirate Concentrate™ (BMAC)

Aspirate bone marrow
 1. Aspirate bone marrow from donor
 2. Filter and separate plasma
 3. Concentrate cells using a centrifuge
 4. Resuspend in saline
 5. Filter again
 6. Store at 4°C

Aspirate
 1. Aspirate bone marrow from donor
 2. Filter and separate plasma
 3. Concentrate cells using a centrifuge
 4. Resuspend in saline
 5. Filter again
 6. Store at 4°C

Concentrate
 1. Aspirate bone marrow from donor
 2. Filter and separate plasma
 3. Concentrate cells using a centrifuge
 4. Resuspend in saline
 5. Filter again
 6. Store at 4°C

Resuspend
 1. Aspirate bone marrow from donor
 2. Filter and separate plasma
 3. Concentrate cells using a centrifuge
 4. Resuspend in saline
 5. Filter again
 6. Store at 4°C

Filter
 1. Aspirate bone marrow from donor
 2. Filter and separate plasma
 3. Concentrate cells using a centrifuge
 4. Resuspend in saline
 5. Filter again
 6. Store at 4°C

Store
 1. Aspirate bone marrow from donor
 2. Filter and separate plasma
 3. Concentrate cells using a centrifuge
 4. Resuspend in saline
 5. Filter again
 6. Store at 4°C

Statistics:
 ANCx = 376,000,000
 CD133+ = 16,000,000
 CFU_s/cm² = 3,000
 Progenitor = 63,000
 Cells Delivered = 5x

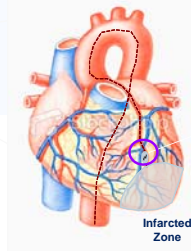
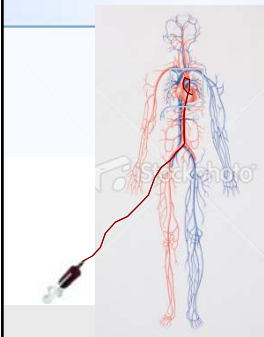
Concentrated bone marrow contains with 100% efficiency cells in less than 15 minutes

Resuspend in saline
 Resuspend in saline
 Resuspend in saline
 Resuspend in saline

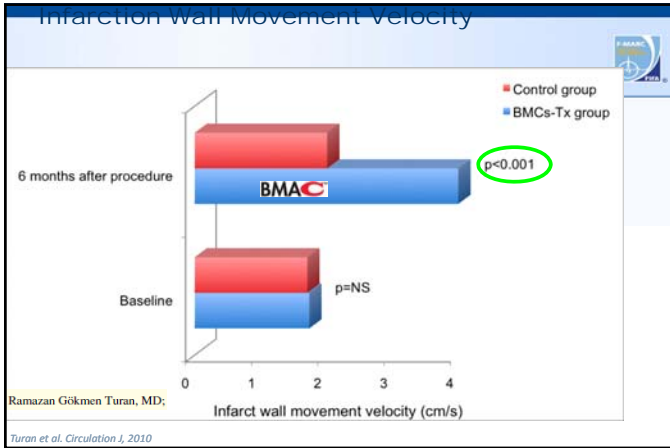
Filter again
 Filter again
 Filter again
 Filter again

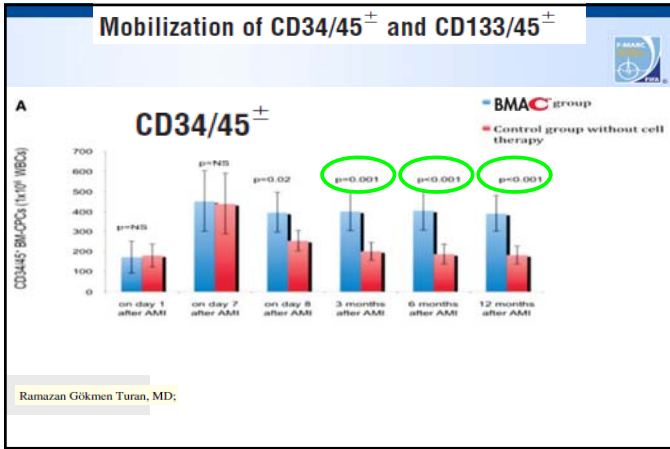
Store at 4°C
 Store at 4°C
 Store at 4°C
 Store at 4°C

Mode of Delivery



Strauer et al., Circulation 2002;106:1913-1918





Autologous Bone Marrow-Derived Mesenchymal Stem Cells Versus Autologous Chondrocyte Implantation

An Observational Study

Mehmet Nettekci, MD, PhD, and Serdar Çelebi, MD, PhD, from the Department of Orthopedics, University of Cumhuriyet Medical Faculty, Sivas, Turkey

The American Journal of Sports Medicine

"Using BMSCs in cartilage for articular cartilage repair surgery, reduced costs, and knee stability"

Abstract: The purpose of this study was to compare the clinical and radiographic outcomes of autologous bone marrow-derived mesenchymal stem cell (BMSC) implantation and autologous chondrocyte implantation (ACI) in the treatment of articular cartilage defects. The study included 20 patients who were randomized to either BMSC or ACI. The BMSC group showed significantly better clinical and radiographic outcomes compared to the ACI group. The BMSC group also had significantly lower costs and better knee stability compared to the ACI group.

Gobbi et al Cartilage 2011

We prospectively evaluated a group of patients with Large Chondral Defect treated with One-Step Surgery.

BMAC implantation

One-step Cartilage Repair with Bone Marrow Aspirate Concentrated cells and Collagen Matrix in Full-thickness Cartilage Lesions: Results at 2year follow up

Biologic arthroplasty can be defined as the surgical reconstruction of the joint using biological solutions

Biologic Spectrum of approaches to the Knee

- Synovium and joint** (JOINT)
 - cytokines, factors, hormones
- Articular Cartilage Resurfacing** (ARTICULAR ONLY)
 - < 2 cm2 > 2 cm2 size matters!
- Osteochondral defects** (CARTILAGE/BONE)
 - < 7 mm deep
 - > 7 mm
- Hyper-intense Signals (HIS)** (BONE /CARTILAGE)
 - Subchondral Edema (SCE)
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 - SONK

Static and Dynamic Malalignment, Instability, Meniscal Pathology must managed!

Exogenous use of steroids

Glueck et al. Transl Res. 2011

- 6 patients with thrombotic events after testosterone
 - testosterone patch, gel, or intramuscular
- 2 developed bilateral hip osteonecrosis 5 and 6 months
- 3 developed pulmonary embolism 3, 7, and 17 months
- 1 developed amaurosis fuga x 18 months
- All were found to have previously undiagnosed thrombophilia
 - 5 factor V Leiden heterozygosity,
 - 1 man had high factor VIII (195%), factor XI (179%), and homocysteine (29.3 umol/L).

Exogenous use of steroids

Glueck et al. Clin Appl Thromb Hemost. 2013

- Evaluated all DVT-PE events at 1 institution over 3 years for most likely cause of thrombosis (596 total)
- 7 men found to have started testosterone within 3 months of event
- 5/7 had testing and all 5 showed undiagnosed familial or acquired thrombophilia or hypofibrinolysis.



Exogenous use of steroids

Glueck et al. Clin Appl Thromb Hemost. 2014

- 14 patients who had a thrombotic event
- 5 developed ON
 - 1 of bilateral knees @2 months and 3 months
 - 4 of bilateral hips (1-60 months)
- 3 factor V Leiden heterozygotes,
- 3 had high factor VIII
- 3 had plasminogen activator inhibitor 4G4G homozygosity
- 2 had high factor XI
- 2 had high homocysteine
- 1 had low antithrombin III
- 1 had the lupus anticoagulant
- 1 had high anticardiolipin antibody Immunoglobulin G
- 1 had no clotting abnormalities



**Take Home message Rx Testosterone...
check for coagulopathic factor variations!!!!**
