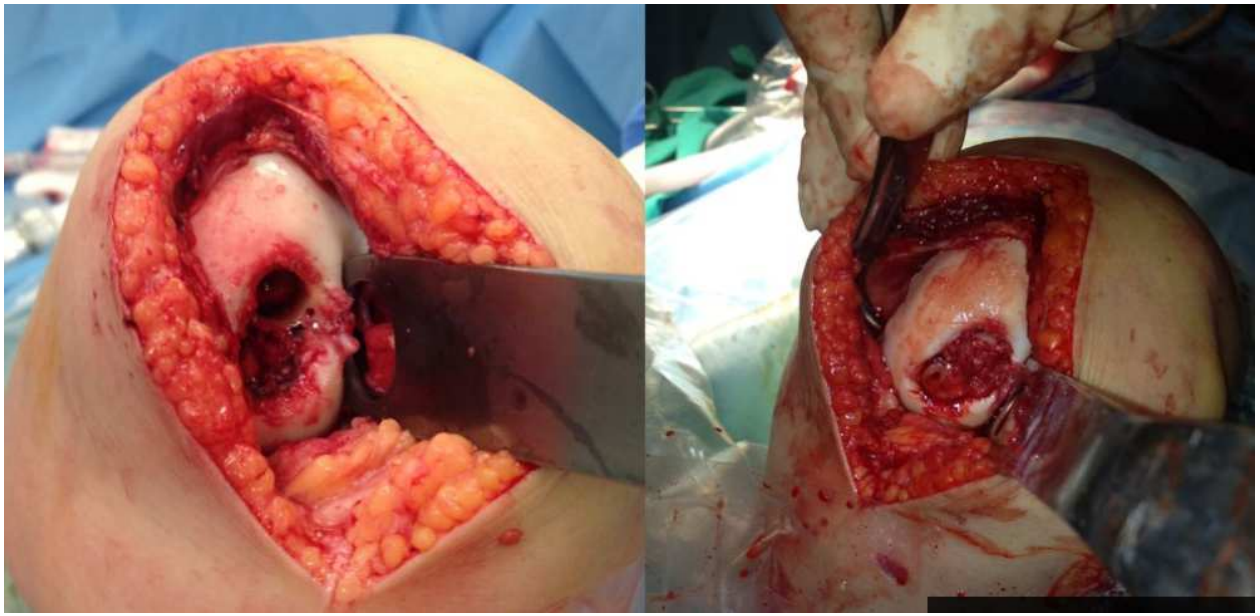
TISSUE ENGINEERING IN ORTHOPAEDIC SPORTS MEDICINE: CURRENT CONCEPTS, SURGICAL ASPECTS AND FUTURE DIRECTIONS



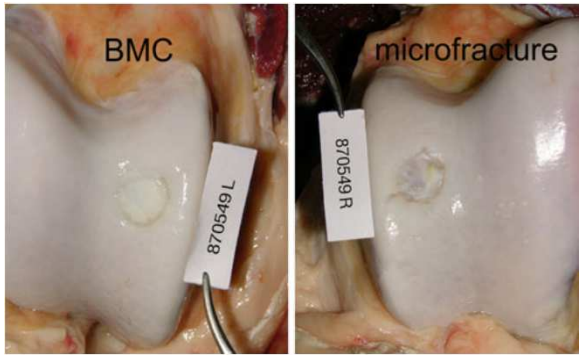
Andreas Panagopoulos, MD, PhD

Upper Limb & Sports Medicine Surgeon

Assistant Professor in Orthopaedics, University Hospital of Patras

Outline

- an overview of tissue engineering to orthopaedic sports medicine
- how these principles are being applied with examples from current studies
- to discuss future directions to translate tissue engineering strategies from the laboratory to the operating room

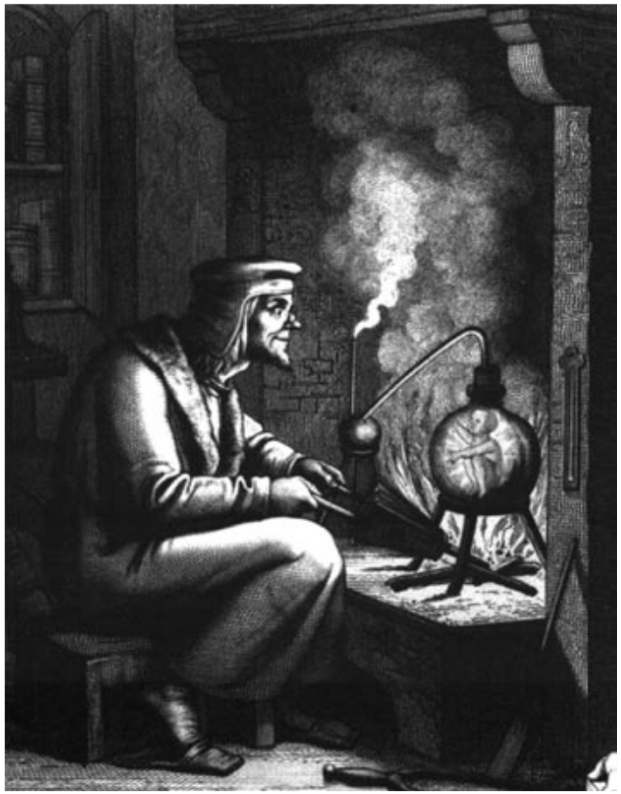


Definition

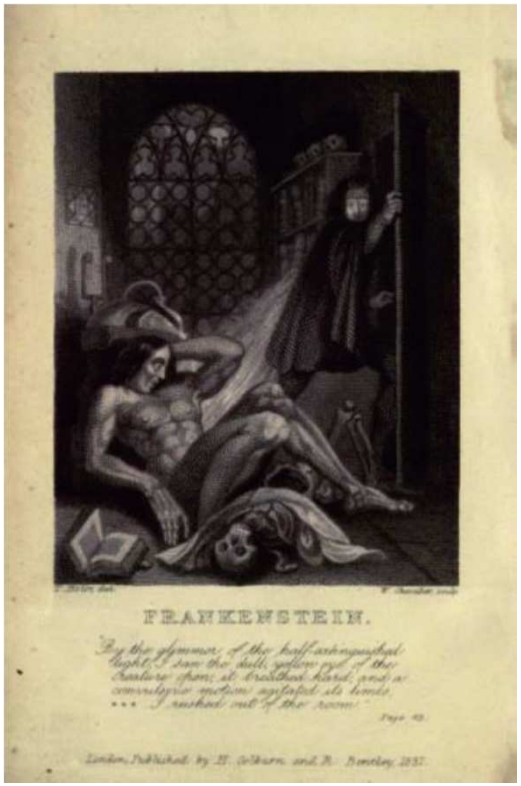
Tissue engineering can be **defined** as the use of a combination of cells, **engineering** materials, and suitable biochemical factors to improve or replace biological functions in an effort to improve clinical procedures for the repair of damaged **tissues** and organs

Historical perspective

Healing of Justinian



Depiction of Dr. Faustus and his Homunculus



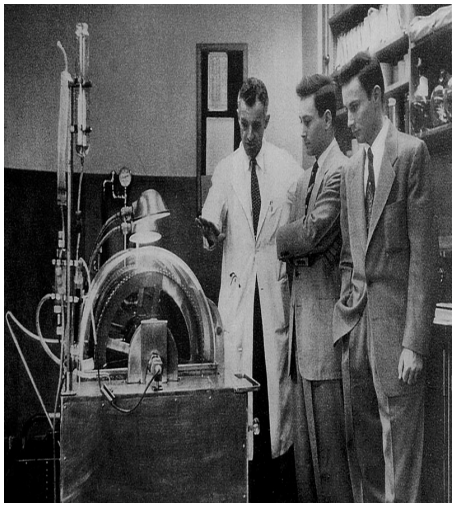
Book cover of Frankenstein (Edition 1831)

Historical perspective

- R.G. Harrison (1870–1959) : active growth of cells in culture

- A Carrel (1873–1944) methods of vascular anastomosis (microsurgery)

- W.T. Green (early 1970s) chondrocyte culture technique in combination with a “bone scaffold.”



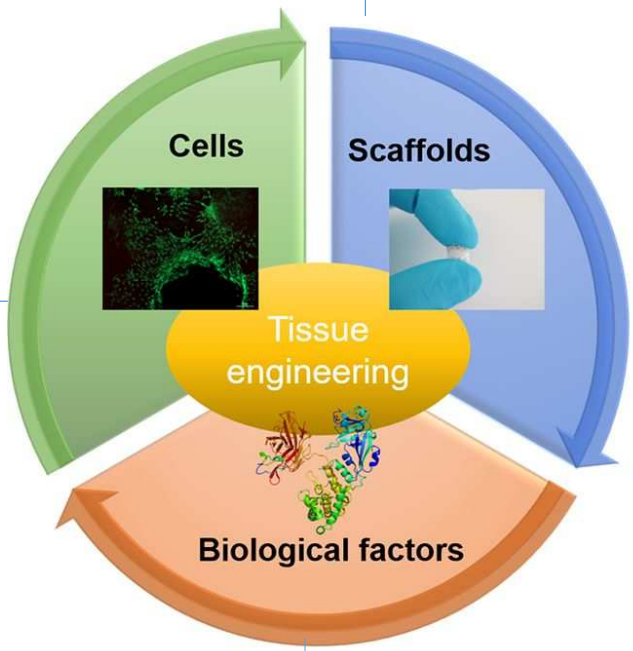
- J.P Merrill - First to attempt kidney transplantation in identical twins

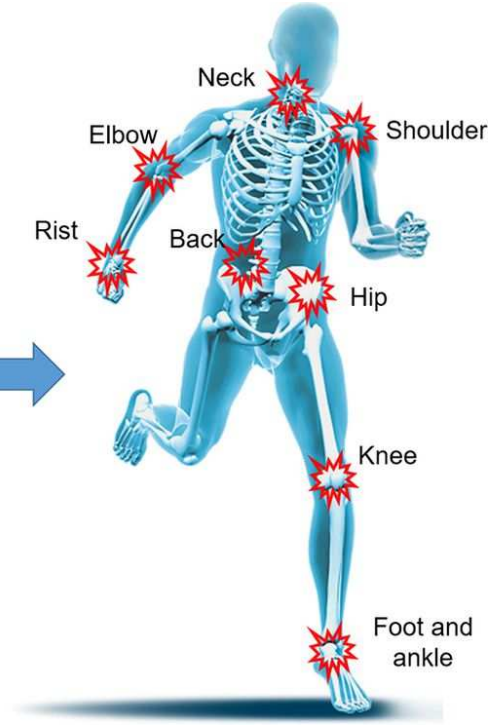
- **J. Vacanti and R. Langer** (1993) described the new technology

Harrison RG (1910) The outgrowth of the nerve fiber as a mode of protoplasmic extension. J Exp Zool 9:787–846
Carrel A, Burrows MT (1911) Cultivation of tissues in vitro and its technique. J Exp Med 13:387–398
Langer R, Vacanti JP (1993) Tissue Engineering. Science 260:920–926

Basic Concept in Sports Med

gellan gum, alginate, silk fibroin, chitosan, hydroxyapatite, collagen, hyaluronic acid and poly(glycolic acid)





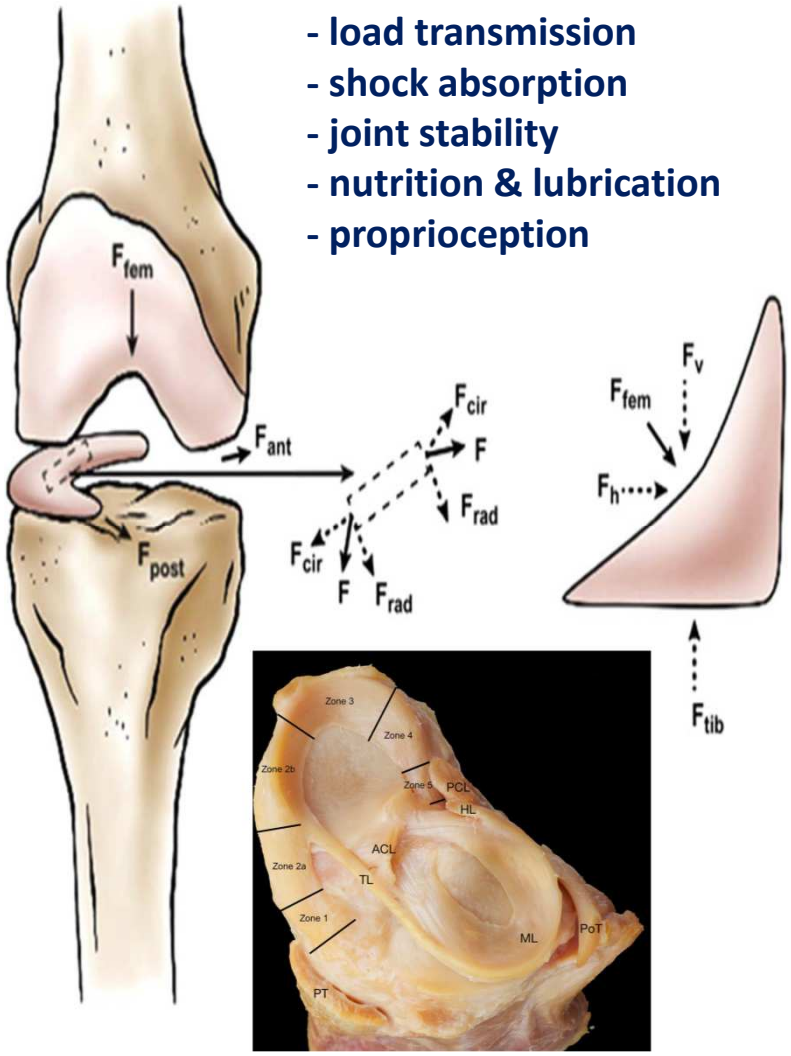
Fibroblasts,
Chondrocytes,
Stem cells
- marrow derived
- adipose tissue derived…

Platelet-rich plasma,
autologous-conditioned serum,
bone marrow concentrate
Physical stimuli

Current facts

- Living tissues are **non-homogenous entities**, composed of biologically and functionally different layers
- Growth factors, cell-based therapy and scaffolds have already shown **value for clinical application**
- There is still **low evidence** level to support current TE clinical applications mainly due to methodological limitations of published trials
- Using the 3-components of TE a **multifactorial approach** must be considered under the light of each specific tissue and physiopathological entity.

- load transmission
- shock absorption
- joint stability
- nutrition & lubrication
- proprioception



Epidemiology of cartilage damage

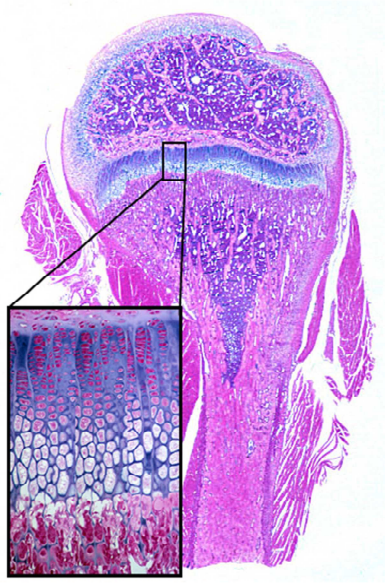
- Curl et al. described 53,569 hyaline cartilage lesions in 19,827 patients undergoing knee arthroscopy[1]
- A survey of 993 consecutive knee arthroscopies demonstrated evidence of articular cartilage abnormality in 66%[2]
- Articular cartilage defects of the femoral condyles have been observed in up to 50% of athletes undergoing ACL reconstruction[3]

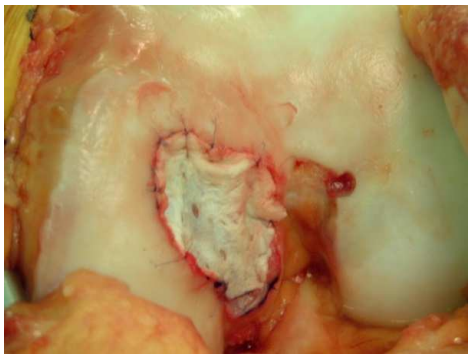
1. Curl WW, et al. Arthroscopy. 1997
2. Aroen A, et al. Am J Sports Med. 2004
3. Piasecki DP, et al. Am J Sports Med. 2003

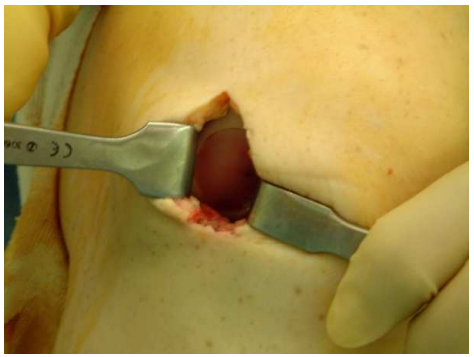
Two major problems

The **first** is to fill the defect void with a tissue that has the same mechanical properties as articular cartilage.

The **second** is to promote successful integration between the repair tissue and the native articular cartilage.

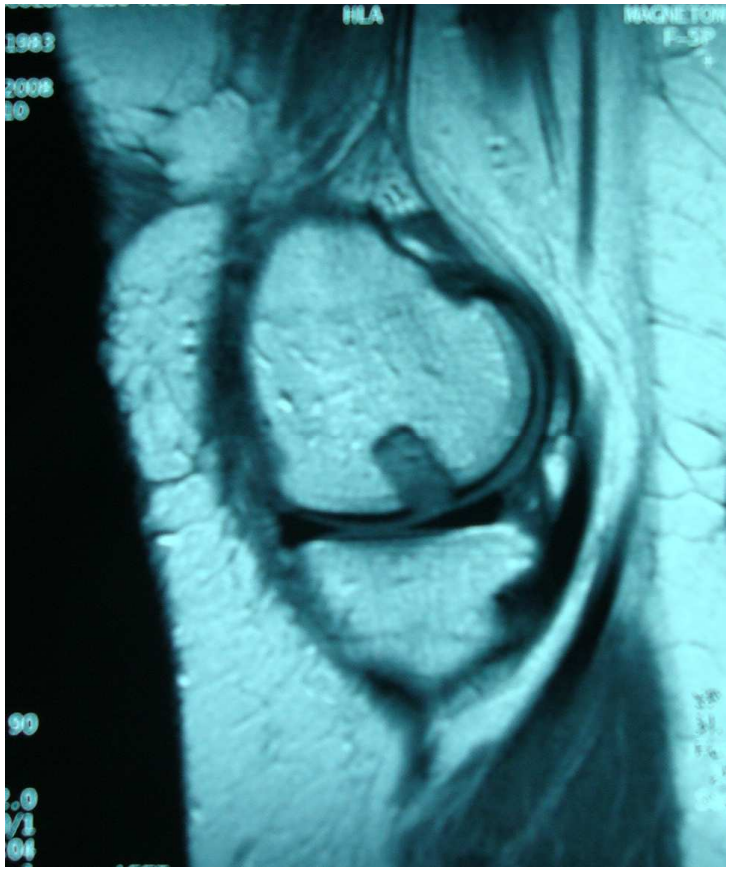






Trufit

poly DL-lactide-co-glycolide,
calcium sulfate,
polyglycolide fibers
and surfactant



2 years postoperatively

Mosaic plasty

Clinical Experiences With Autologous Osteochondral Mosaicplasty in an Athletic Population : A 17-Year Prospective Multicenter Study

László Hangody, Jozsef Dobos, Eszter Baló, Gergely Pánics, Laszlo Rudolf Hangody and Istvan Berkes

Am J Sports Med 2010 38: 1125 originally published online April 1, 2010

DOI: 10.1177/0363546509360405

The average size of the chondral defects in treated knees was **2.0 cm**

Problems in the **harvesting site** of the knee

ACI


2A


2B


3A


2C


2D

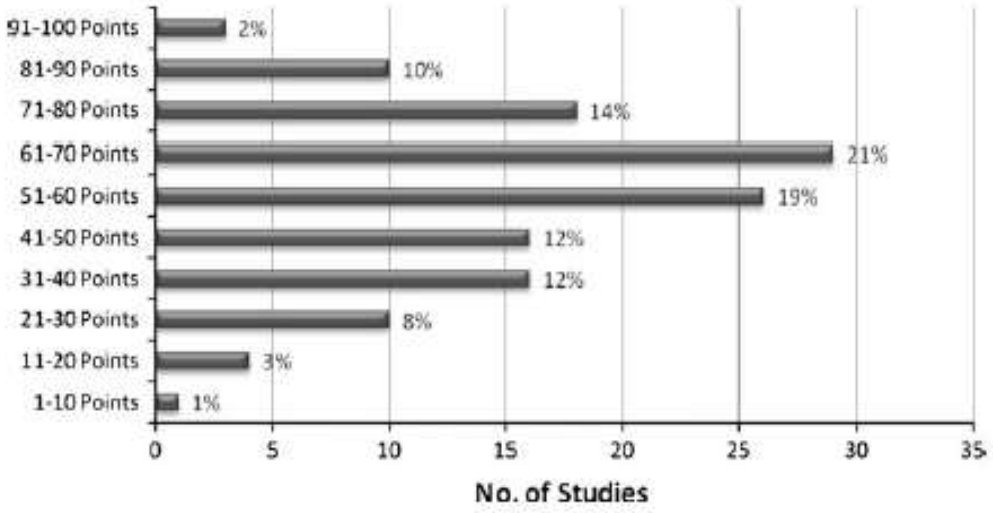

3B

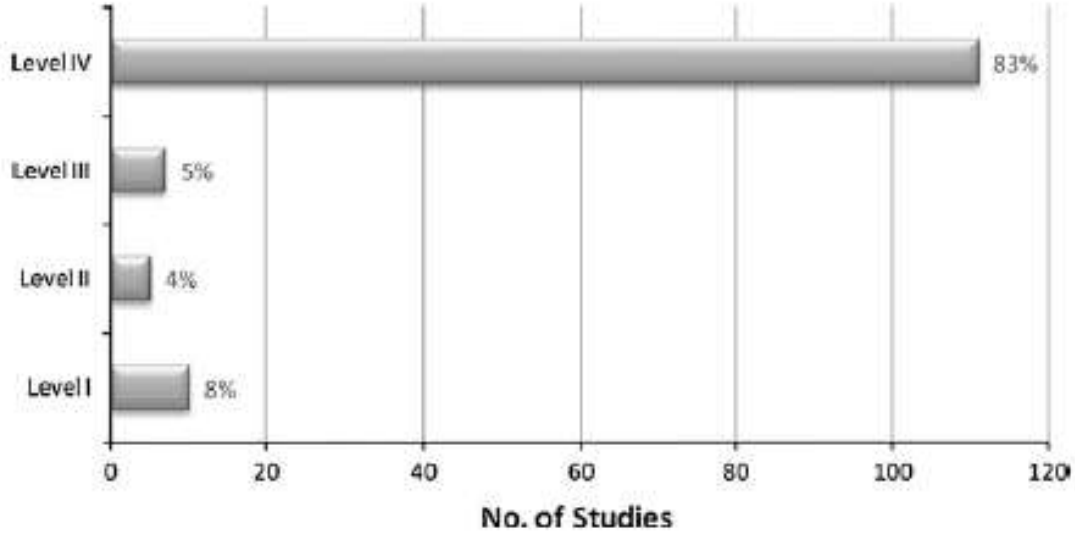
Knee Surg Sports Traumatol Arthrosc (2011) 19:543–552
DOI 10.1007/s00167-010-1271-5

KNEE

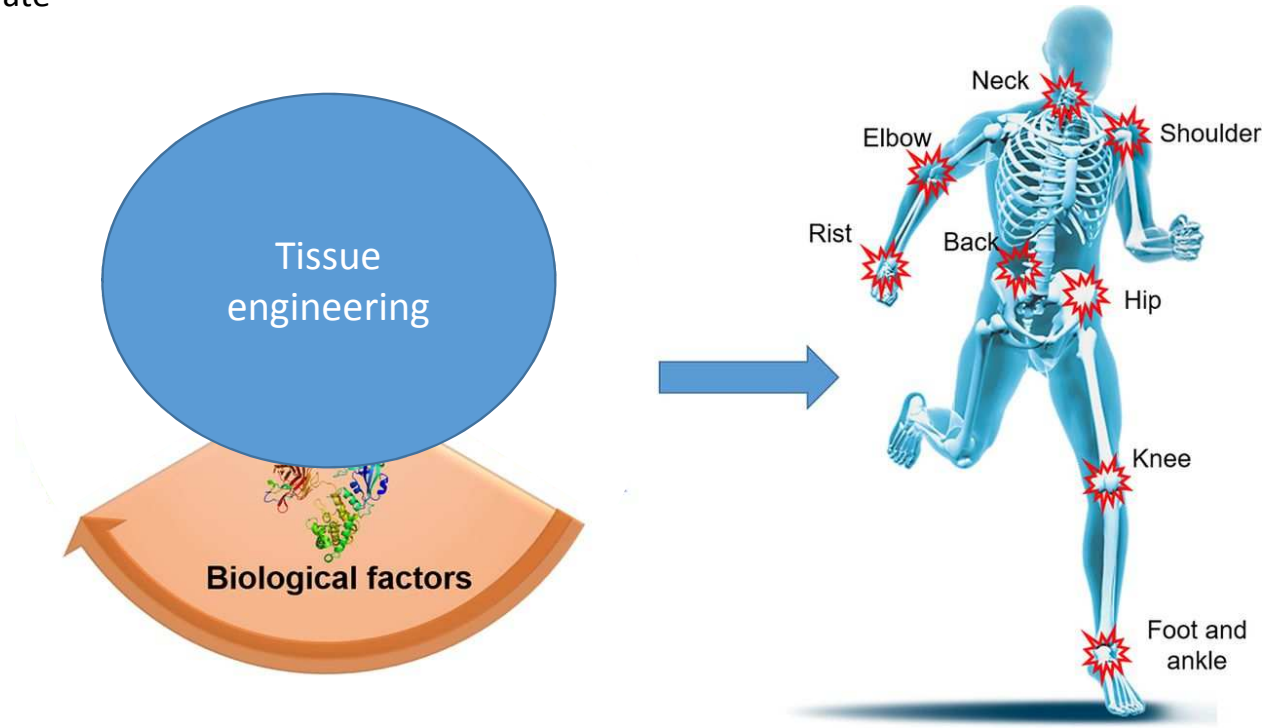
We do not have evidence based methods for the treatment of cartilage defects in the knee

Jan P. Benthien · Manuela Schwaninger · Peter Behrens





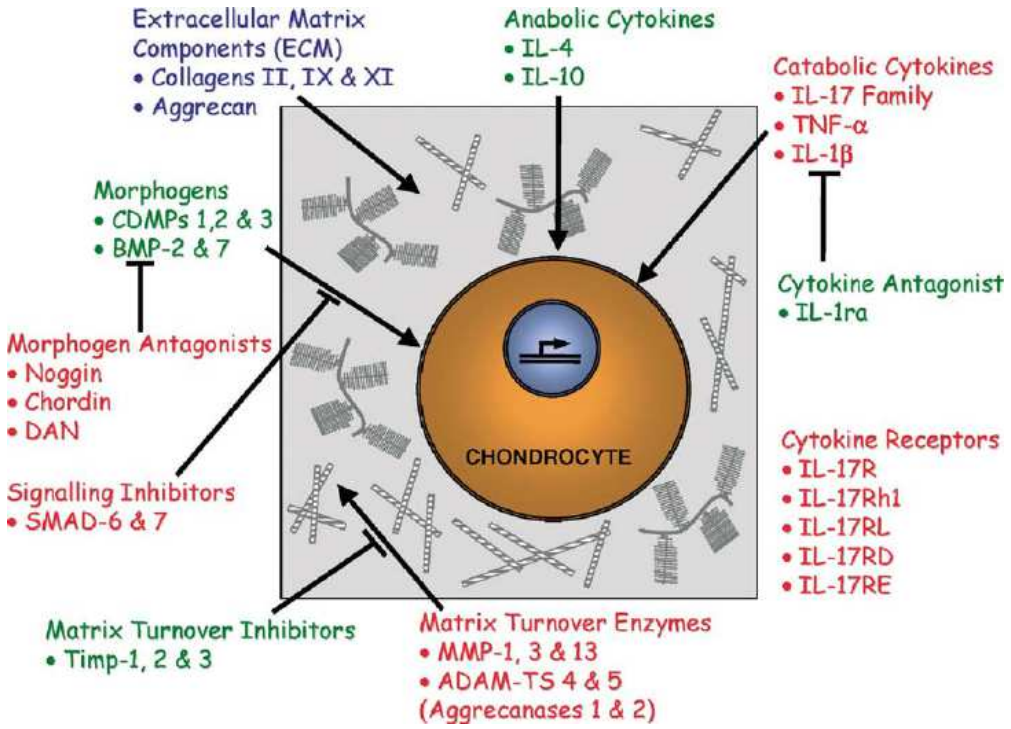
Platelet-rich plasma,
autologous-conditioned serum,
bone marrow concentrate
Physical stimuli



Biological factors

Growth factors are a group of biologically active polypeptides that can stimulate **cellular division**, **growth**, and **differentiation**

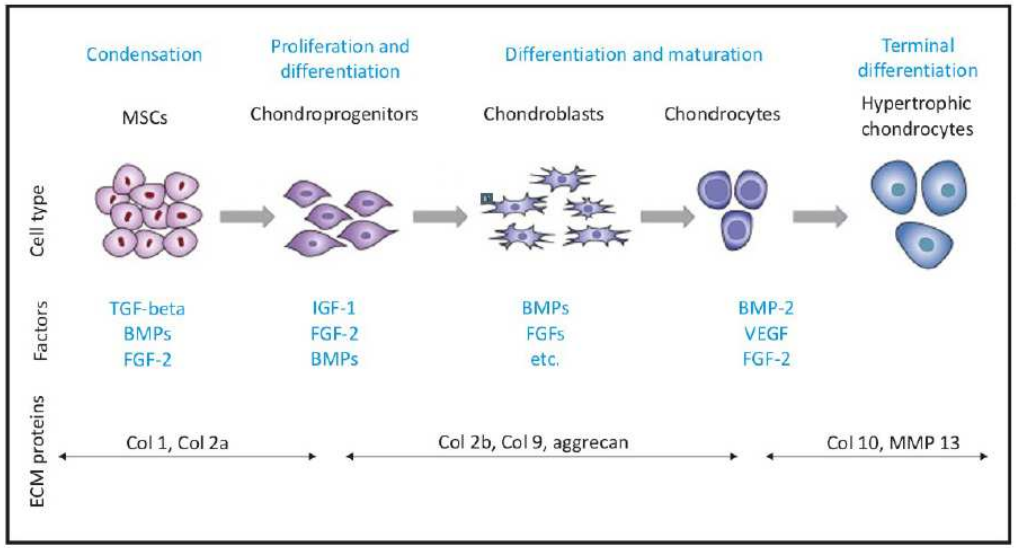
Complex relationship between anabolic growth factors and catabolic cytokines involved in extracellular matrix maintenance



Goldring MB, Tsuchimochi K, Ijiri K. The control of chondrogenesis. J Cell Biochem. 2006;97:33–44.

Growth factors types

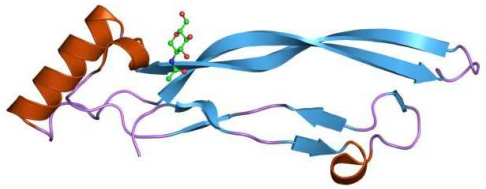
- **Transforming growth factor-b superfamily,**
  - Transforming Growth Factor-b1 and -b3
  - Bone Morphogenetic Protein-2
  - **Bone Morphogenetic Protein-7/Osteogenic Protein-1**
  - Growth differentiation factor 5 (GDF5)
- **Insulin-like growth factor-I,**
- **Fibroblast growth factor family,**
- **Platelet-derived growth factor**
- **Combined growth factor delivery** (mostly used)



Bone Morphogenetic Protein-7/Osteogenic Protein-1

(the gold standard growth factor for cartilage repair)

- Stimulates ECM synthesis
- Decreases cartilage degradation
- Decreases expression of aggrecans
- Does not cause osteophyte formation



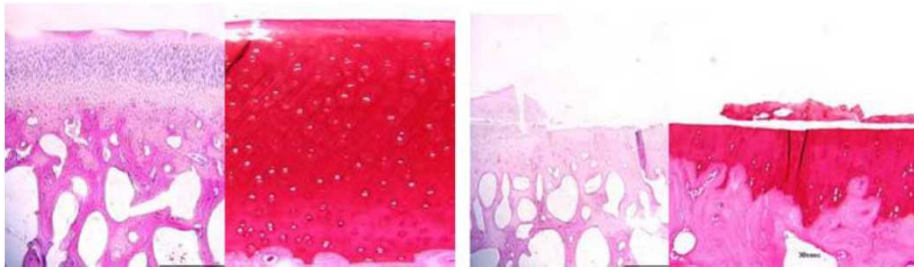
BMP-7 decrease with aging and cartilage degeneration, but degenerate cartilage is still able to **respond** to its anabolic effect

International Orthopaedics (SICOT) (2007) 31:773–781
DOI 10.1007/s00264-007-0423-9

REVIEW

OP-1/BMP-7 in cartilage repair

Susan Chubinskaya · Mark Hurtig · David C. Rueger



Histological sections of the impact area of OP-1 treated (left) and control sheep (right) femoral condyles 12 weeks after injury

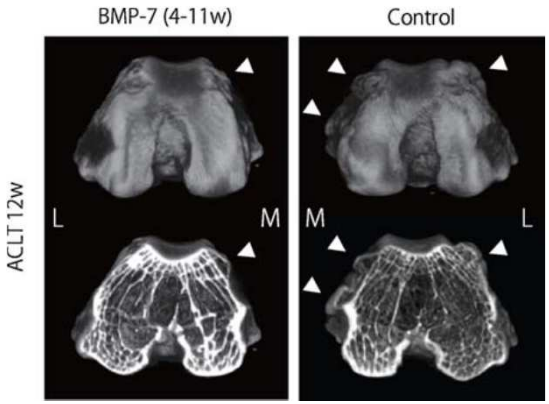
Animal studies have demonstrated that OP-1 has the ability to repair cartilage in vivo in various models of articular cartilage degradation, including focal osteochondral and chondral defects and osteoarthritis

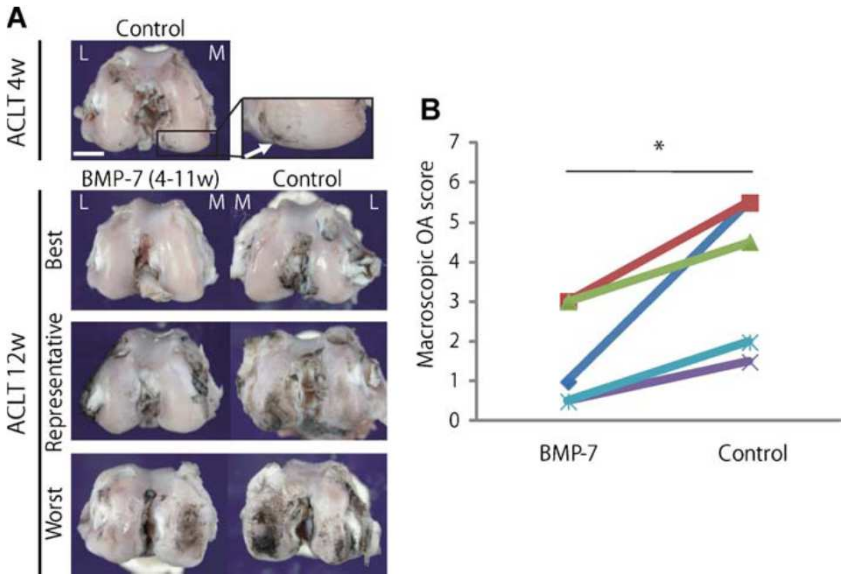
Intra-Articular Injections of Bone Morphogenetic Protein-7 Retard Progression of Existing Cartilage Degeneration

Masaya Hayashi,[1] Takeshi Muneta,[1] Toru Takahashi,[1] Young-Jin Ju,[1] Kunikazu Tsuji,[2] Ichiro Sekiya[3]

[1]Section of Orthopaedic Surgery, Graduate School of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan, [2]Global Center of Excellence (GCOE) Program, International Research Center for Molecular Science in Tooth and Bone Diseases, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan, [3]Section of Cartilage Regeneration, Graduate School of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

Received 28 October 2009; accepted 17 March 2010
Published online 7 May 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jor.21165





Weekly intra-articular injections of BMP-7 inhibited progression of existing cartilage degeneration

Hunter *et al. BMC Musculoskeletal Disorders* 2010, **11**:232
http://www.biomedcentral.com/1471-2474/11/232

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Phase 1 safety and tolerability study of BMP-7 in symptomatic knee osteoarthritis

David J Hunter[1,2*], Marilyn C Pike[3], Beth L Jonas[4], Eugene Kissin[5], Julie Krop[6], Tim McAlindon[7]

Double-blind, randomized, multi-center, placebo-controlled, single-dose escalation safety study consisting of 4 dosing cohorts in participants with knee OA

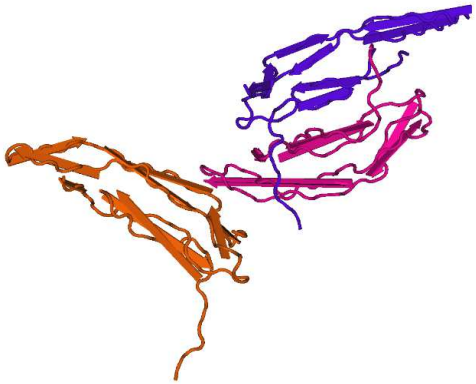
By week 12, **most participants in both the BMP-7 and placebo groups** experienced a 20% improvement in pain

Platelet-derived growth factor

Increases chondrocyte proliferation

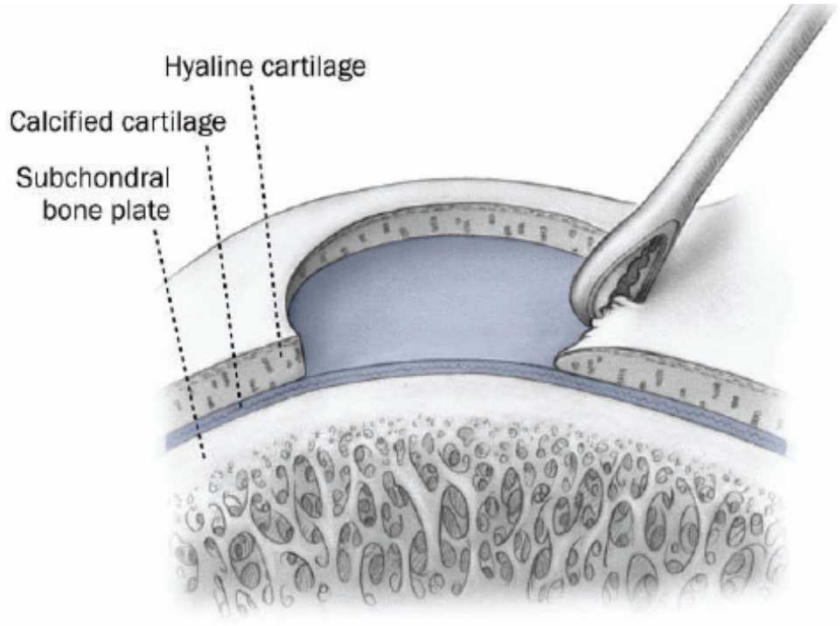
Upregulates proteoglycan synthesis

Increases meniscal cell proliferation and migration

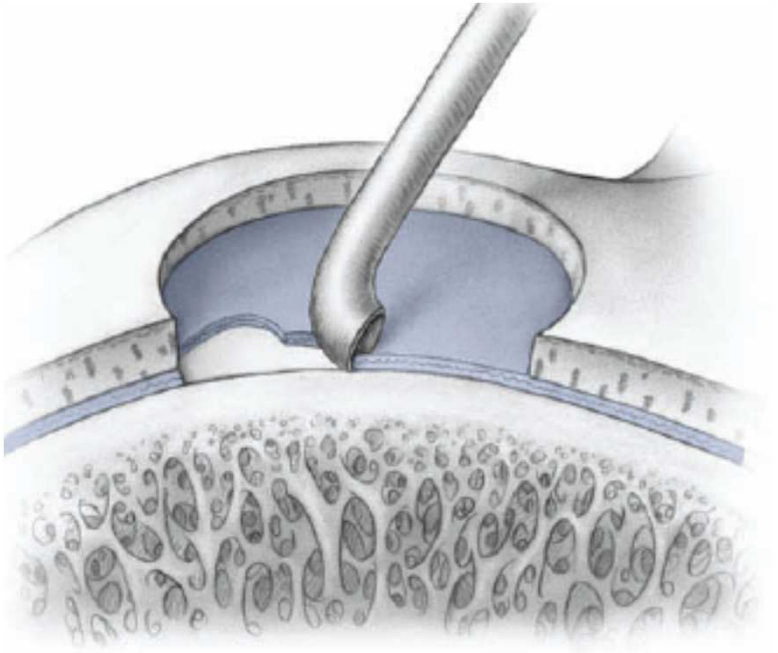


Microfracture

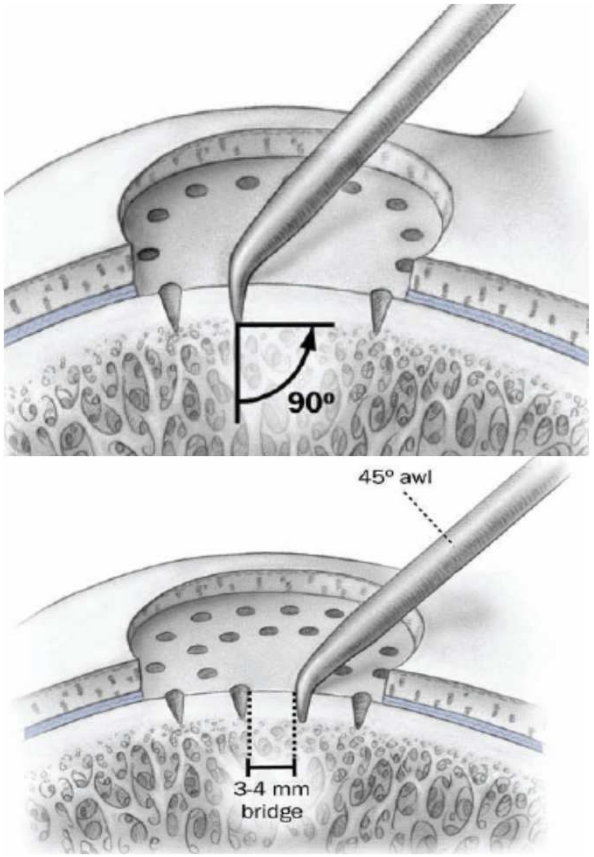
Debridement, with use of an arthroscopic shaver, of any loose cartilage flaps to create a stable peripheral cartilage margin



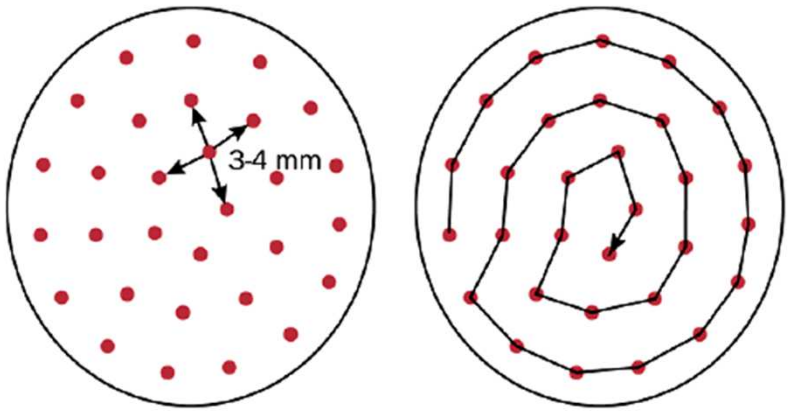
débridement of the calcified cartilage layer with use of a curet to provide manual feedback control

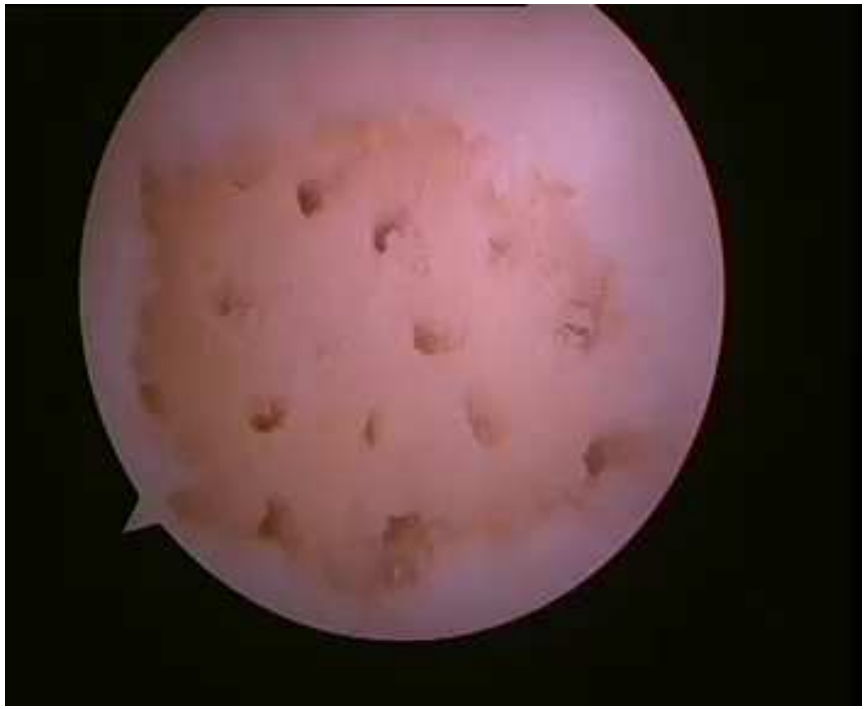


adequate depth of subchondral bone penetration and width of osseous bridges between the individual microfracture holes

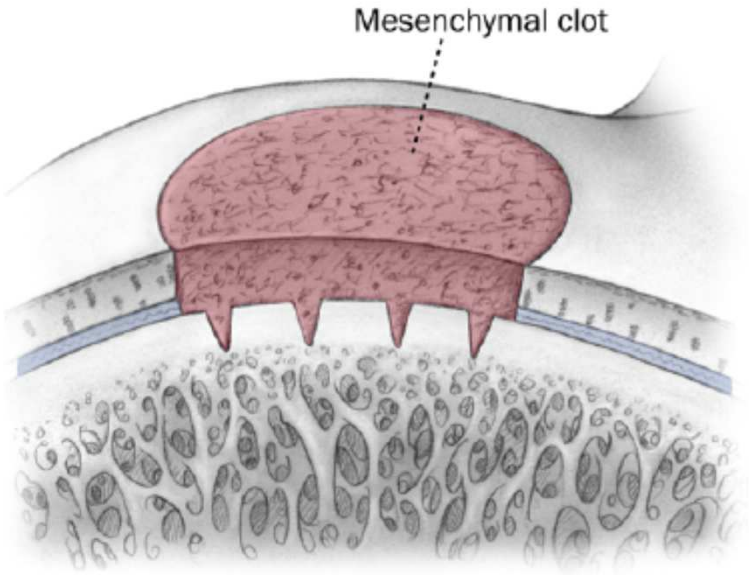


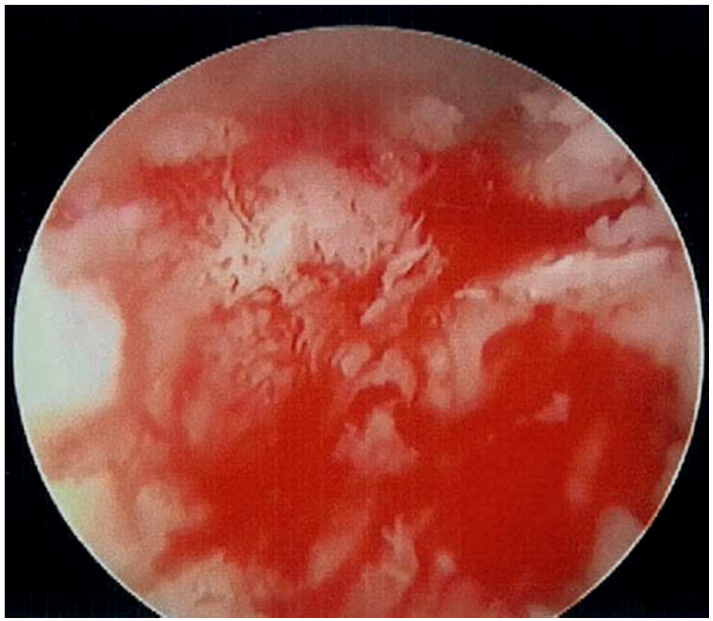
Configuration of microfracture holes





adequacy of the microfractures by noting the release of fat droplets and blood from the individual holes





Clinical studies of microfracture

The overall clinical results of the microfracture arthroplasty have shown improved knee function in 70% to 95% of patients for **a short period of time**

1. Steadman JR, et al Oper Tech Orthop. 1997;7:300-4.
2. Steadman JR, et al Knee Surg. 2003;16:83-6.
3. Steadman JR, et al Arthroscopy. 2003;19:477-84.
4. Kreuz PC, et al. Osteoarthritis Cartilage. 2006;14:1119-25.

Combined growth factor delivery

- **autologous-conditioned serum**

- **bone marrow concentrate**

- **platelet-rich plasma**

Autologous-conditioned serum (ACS)

Is generated by incubation of venous blood with glass beads, which results in increased concentration of **growth factors** and in some reports increased concentration of **IL-1 receptor antagonist protein**, which blocks the catabolic cytokine IL-1

Is injected into the affected joint in a series of **six** intra-articular injections given twice a week for 3 weeks

Meijer H, Reinecke J, Becker C, Tholen G, Wehling P. The production of anti-inflammatory cytokines in whole blood by physico-chemical induction. Inflamm Res 2003;52(10):404e7

Osteoarthritis and Cartilage (2009) **17,** 152–160

doi:10.1016/j.joca.2008.06.014

Osteoarthritis and Cartilage

International Cartilage Repair Society

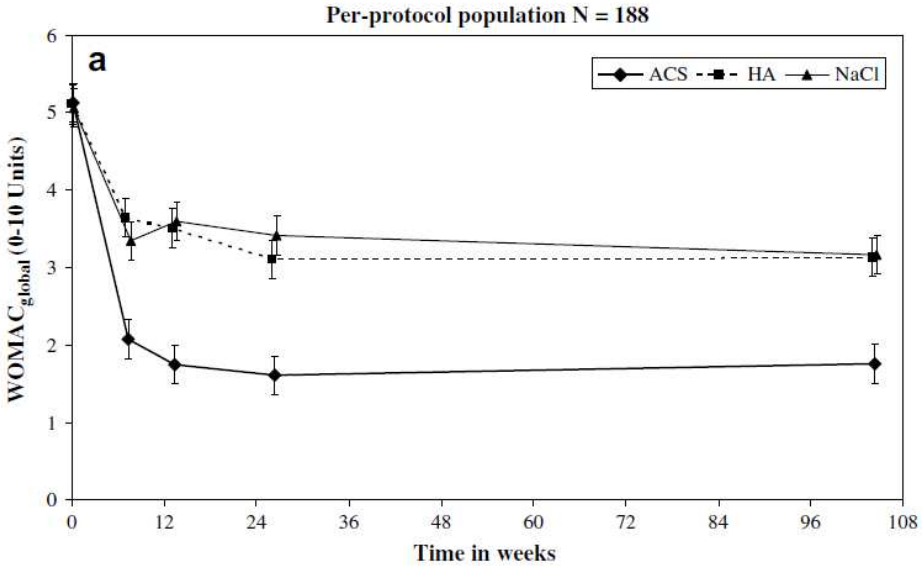
OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis

A. W. A. Baltzer M.D.†, C. Moser M.D.‡*, S. A. Jansen M.D.§ and R. Krauspe M.D.‡

376 patients with knee OA in a prospective, randomized, patient- and observer-blinded, placebo-controlled trial

… the effects of ACS were **significantly superior** to those of **HA** and **saline** for all outcome measures and time points, and improvements were clinically relevant



Rutgers *et al. Arthritis Research & Therapy* 2010, **12**:R114
http://arthritis-research.com/content/12/3/R114

arthritis research&therapy

RESEARCH ARTICLE Open Access

Cytokine profile of autologous conditioned serum for treatment of osteoarthritis, *in vitro* effects on cartilage metabolism and intra-articular levels after injection

Marijn Rutgers[1], Daniël BF Saris[1], Wouter JA Dhert[1,2] and Laura B Creemers*[1]

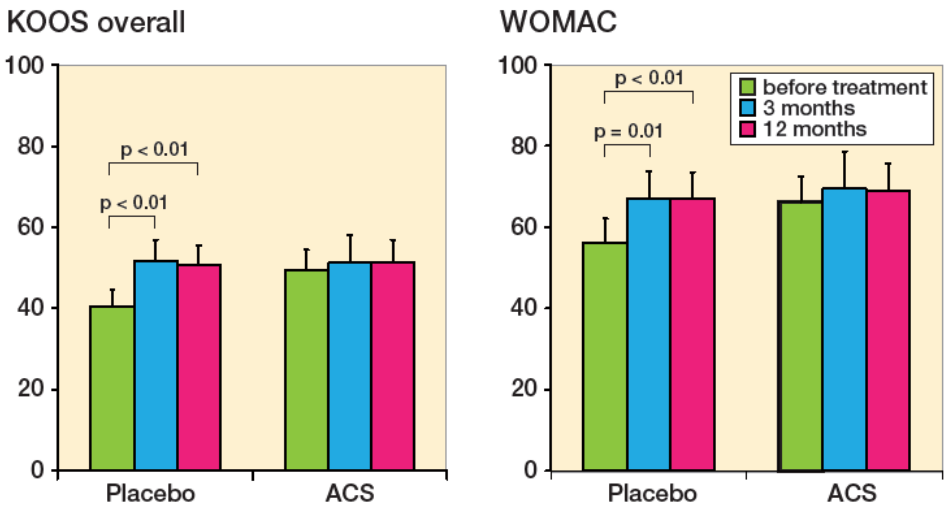
In conclusion, ACS is a mix of counteracting growth factors and cytokines that **does not have a direct effect** on cartilage metabolism and probably has a minimal influence in the joint space, given the fast disappearance of cytokines from the synovial fluid after injection

Osteoarthritis treatment using autologous conditioned serum after placebo

Patient considerations and clinical response in a non-randomized case series

Marijn RUTGERS[1], Laura B CREEMERS[1], Kiem Gie Auw YANG[2], Natasja J H RAIJMAKERS[1], Wouter J A DHERT[1,3], and Daniel B F SARIS[1,4]

In a self-selected group of 20 placebo-treated patients from an earlier RCT, ACS treatment **did not improve OA symptoms** further relative to previous placebo treatment



Bone marrow concentrate

- The advantage of BMC over PRP is that it contains MSCs
- Also, like PRP, BMC contains platelets and therefore is a rich source of growth factors
- These growth factors are also secreted by MSCs and can induce chondrogenesis

Concentrated Bone Marrow Aspirate Improves Full-Thickness Cartilage Repair Compared with Microfracture in the Equine Model

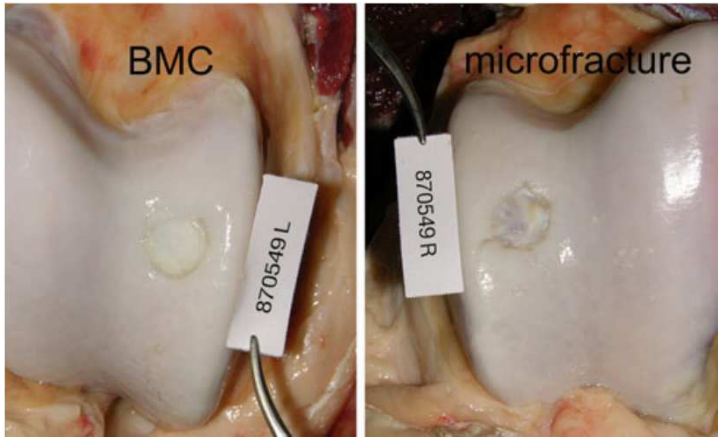
Lisa A. Fortier, DVM, PhD; Hollis G. Potter, MD; Ellen J. Rickey, DVM; Lauren V. Schnabel, DVM; Li Foong Foo, MD; Leroy R. Chong, MD; Tracy Stokol, BVSc, PhD; Jon Cheetham, VetMB, PhD; Alan J. Nixon, BVSc, MS

J Bone Joint Surg Am, 2010 Aug 18; 92 (10): 1927 -1937 . http://dx.doi.org/10.2106/JBJS.I.01284

JBJS The Journal of Bone & Joint Surgery

In an equine model of extensive (15-mm) **full thickness cartilage defects**, BMC resulted in improved cartilage repair compared with microfracture using both short-term arthroscopic inspection as well as in longer-term macroscopic, histologic, and quantitative MRI analyses

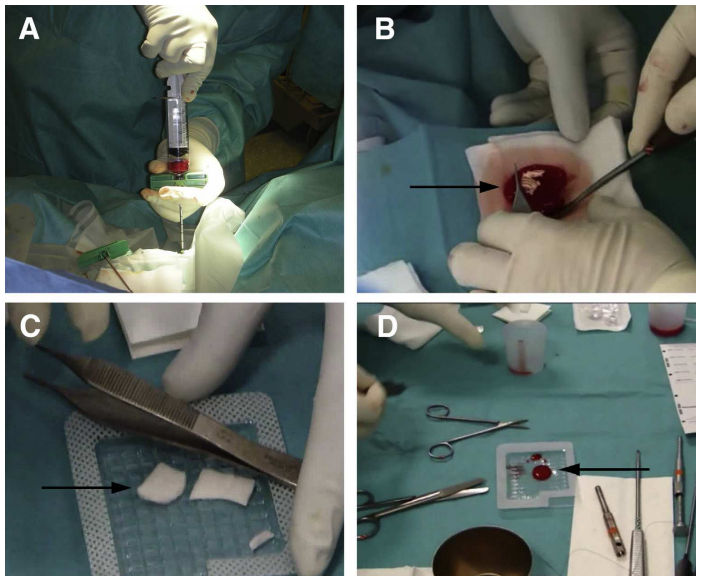
Repair tissue in BMC-treated defects was much better integrated into surrounding normal cartilage

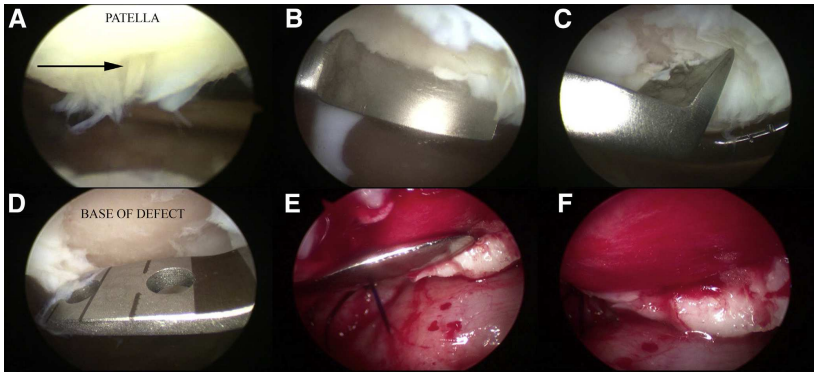


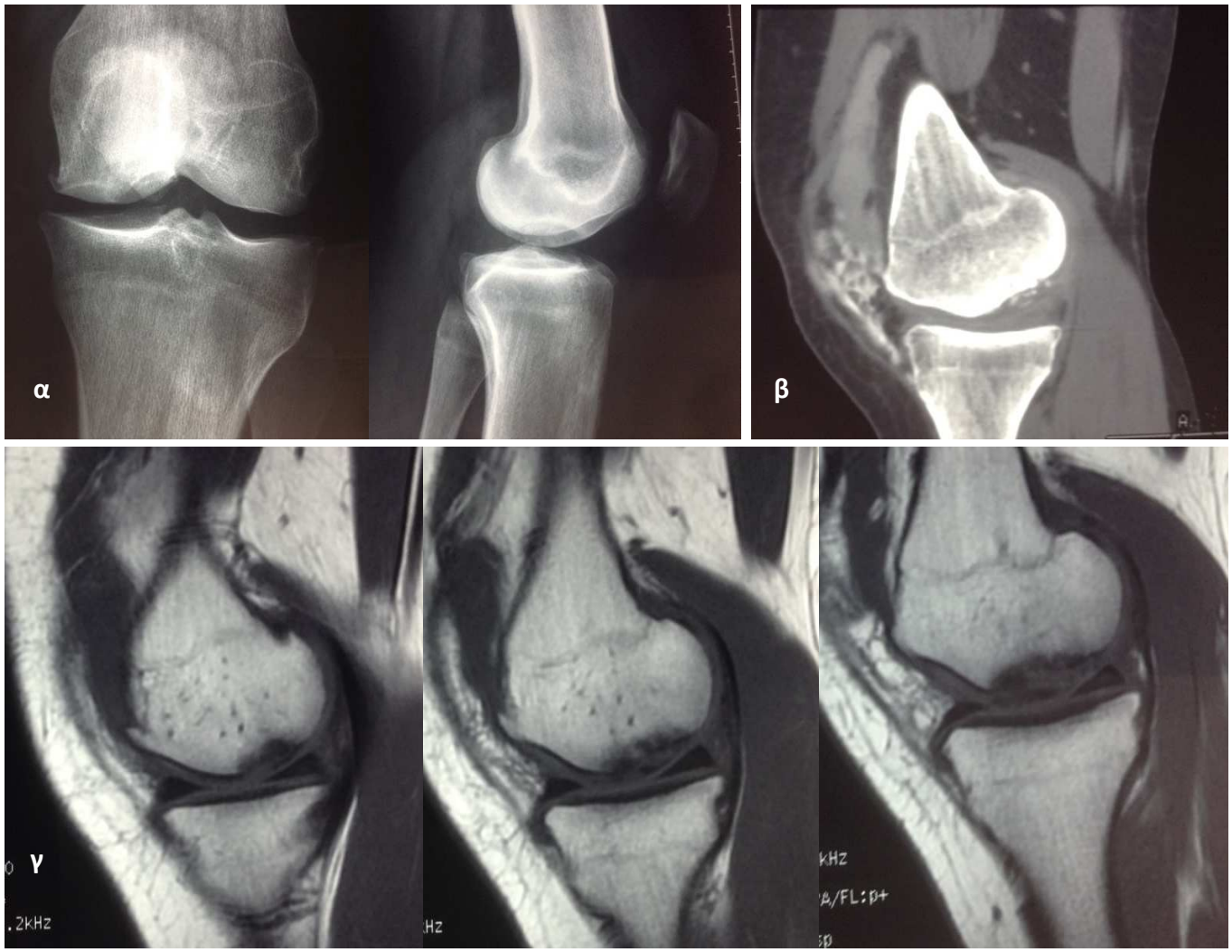
Arthroscopy Techniques, Vol 5, No 4 (August), 2016: pp e913-e918

Dry Arthroscopic Single-Stage Cartilage Repair of the Knee Using a Hyaluronic Acid-Based Scaffold With Activated Bone Marrow-Derived Mesenchymal Stem Cells

Graeme P. Whyte, M.D., M.Sc., F.R.C.S.C., Alberto Gobbi, M.D., and Boguslaw Sadlik, M.D., Ph.D.



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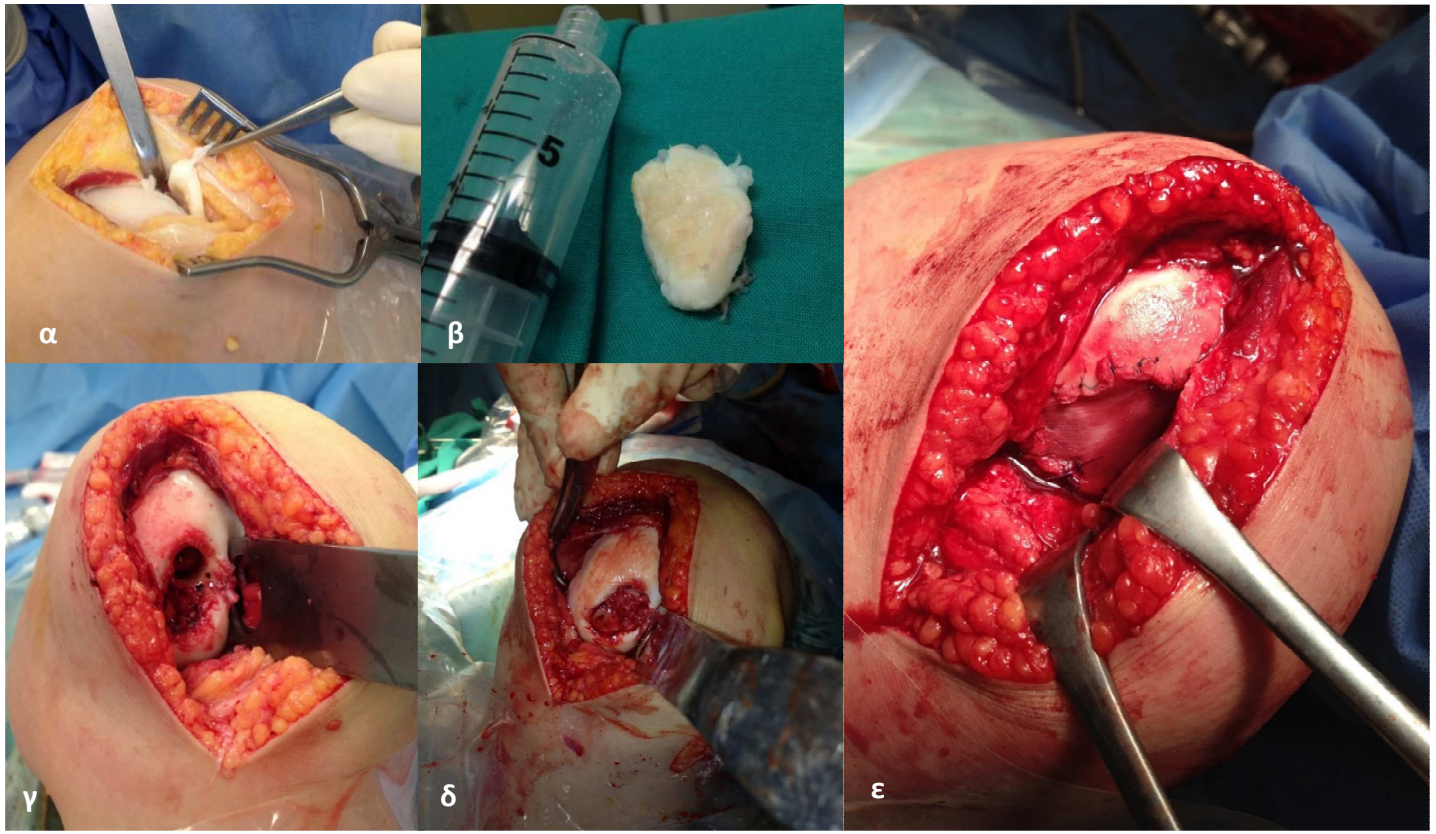
β
γ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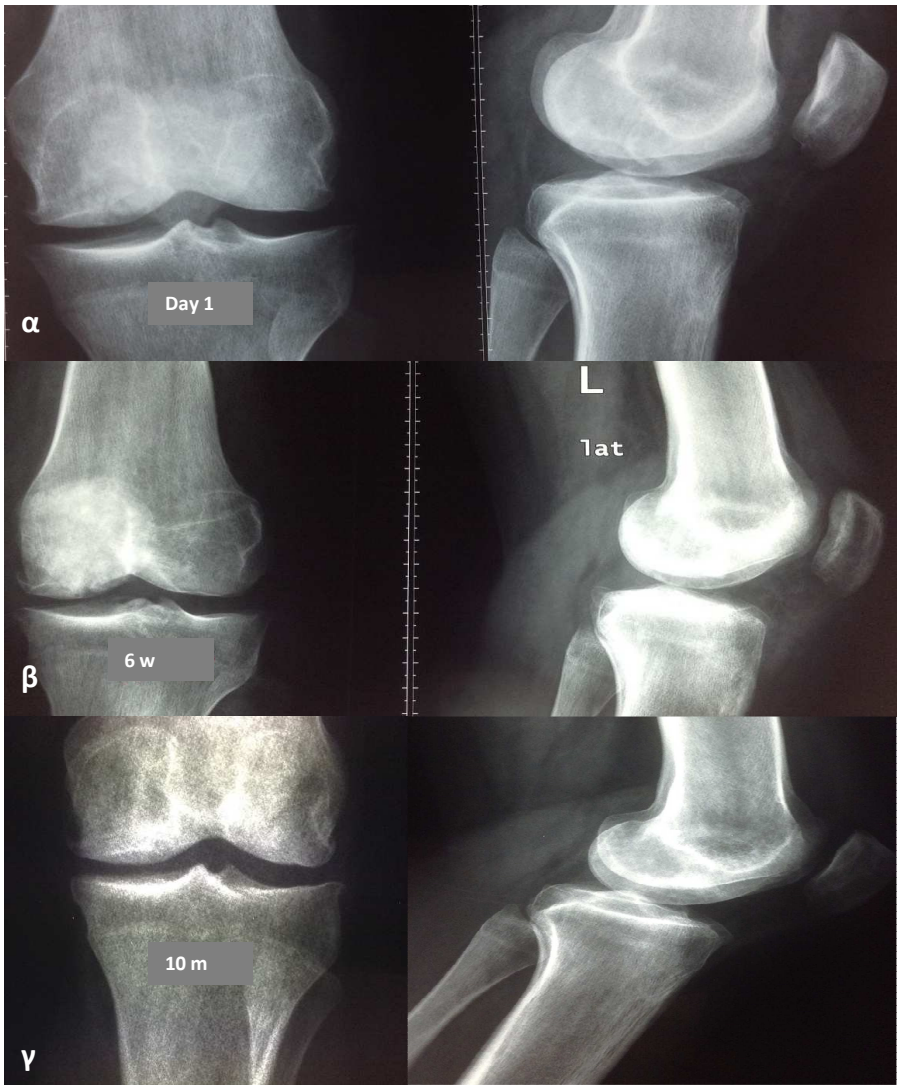
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but …

Concentrated Bone Marrow Aspirate for the Treatment of Chondral Injuries and Osteoarthritis of the Knee

A Systematic Review of Outcomes

Jorge Chahla,* MD, Chase S. Dean,* MD, Gilbert Moatshe,*† MD, Cecilia Pascual-Garrido,‡ MD, Raphael Serra Cruz,*§ MD, and Robert F. LaPrade,*||¶ MD, PhD

11 studies
5 prospective
1 retrospective
2 case series
3 case reports

3 studies investigated the clinical efficacy of BMAC in the treatment of **osteoarthritis**, and 8 studies on **focal cartilage injuries**

All reported **good to excellent overall outcomes** with the use of BMAC

but …

A Prospective, Single–Blind, Placebo–Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis

Am J Sports Med August 26, 2016 ; published online before print August 26, 2016,

The American Journal of Sports Medicine

Prospective, single-blind, placebo-controlled trial, **25 patients with bilateral knee pain** from bilateral osteoarthritis were randomized to receive BMAC into one knee and saline placebo into the other.

Early results show that BMAC is safe to use and is a reliable and viable cellular product.

Study patients experienced a **similar relief of pain** in both **BMAC-** and **saline**-treated arthritic knees

Platelet-Rich Plasma

There are over **1500** proteins within platelets and various growth factors including PDGF, VEGF, TGF-b, FGF, and EGF

Mechanism of action

- modulation of the inflammatory response,
- promotion of local angiogenesis,
- attraction of fibroblasts and local stem cells
- induction of autocrine growth factor production

Applications in SM

Patellar tendinitis

Achilles tendinitis

Plantar fasciitis

Elbow epicondylitis

Rotator cuff disorders

Cartilage regeneration

Osteoarthritis

Meniscal repair

ACL reconstruction

……

Review

Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF)

David M. Dohan Ehrenfest, Lars Rasmusson and Tomas Albrektsson

Department of Biomaterials, Institute of Clinical Sciences, The Sahlgrenska Academy at University of Gothenburg, Sweden

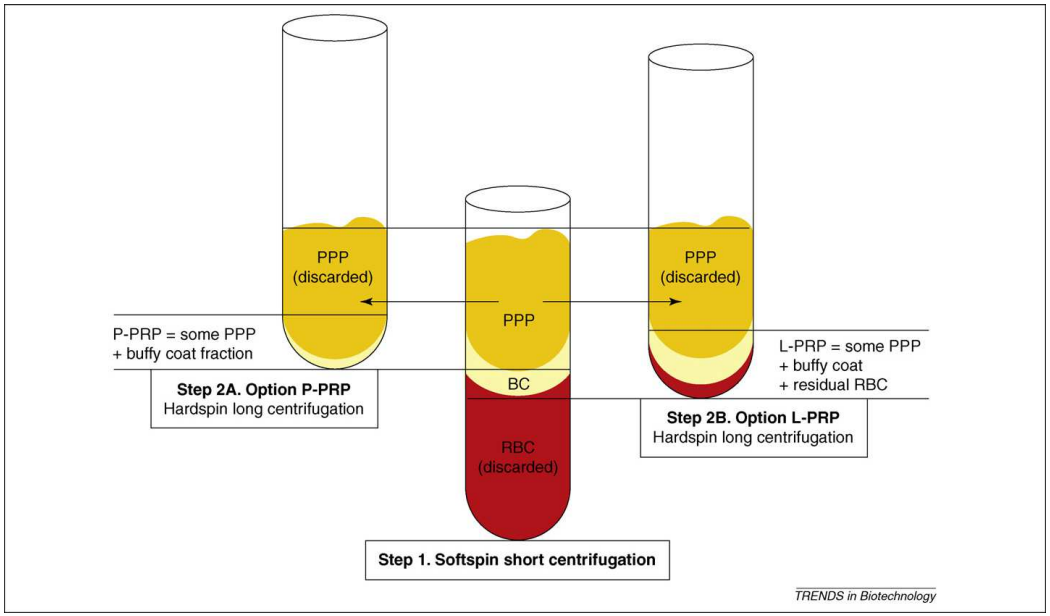
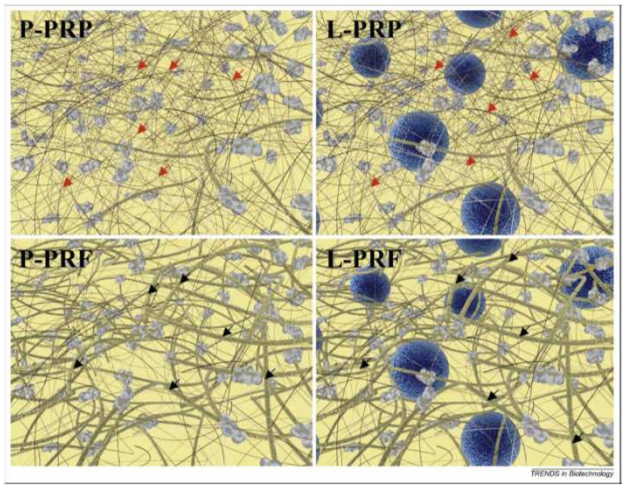


Table 2. Classification of different platelet concentrates into four broad categories depending on leukocyte and fibrin content alone [14]

Category	Example
Pure platelet rich plasma	Cell separator PRP, Vivostat PRF or Anitua's PRGF
Leukocyte and platelet rich plasma	Curasan, Regen, Plateltex, SmartPReP, PCCS, Magellan or GPS PRP
Pure platelet rich fibrin	Fibrinet
Leukocyte and platelet rich fibrin	Choukroun's PRF

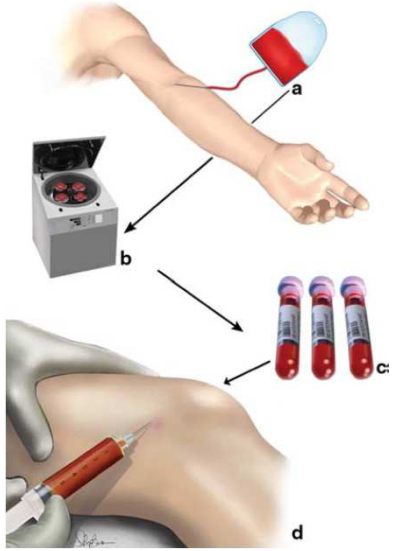


Knee Surg Sports Traumatol Arthrosc
DOI 10.1007/s00167-009-0940-8

KNEE

Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions

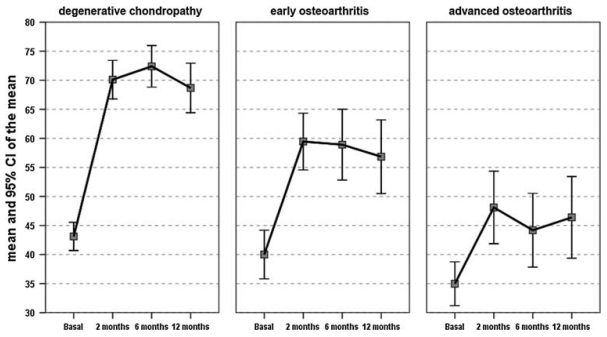
Elizaveta Kon · Roberto Buda · Giuseppe Filardo · Alessandro Di Martino · Antonio Timoncini · Annarita Cenacchi · Pier Maria Fornasari · Sandro Giannini · Maurilio Marcacci



115 knees with 4 intraarticular PRP injections given every 21 days and followed for 12 months

58 with chondral lesions (Kellgren-Lawrence 0),
33 with early OA (Kellgren-Lawrence I–III),
24 with advanced OA (Kellgren-Lawrence IV).

A **substantial improvement** in IKDC and EQ-VAS scores was noted at the end of therapy and at both the 6- and 12-month time points



Am J Sports Med. 2015 Jul;43(7):1575-82. doi: 10.1177/0363546515582027. Epub 2015 May 7.

Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial.

Filardo G[1], Di Matteo B[2], Di Martino A[1], Merli ML[1], Cenacchi A[3], Fornasari P[3], Marcacci M[1], Kon E[4].

A total of 443 patients were screened, and 192 of them were enrolled inclusion criteria

3 weekly intra-articular injections of either PRP or HA

Both treatments proved to be effective in improving knee functional status and reducing symptoms

PRP **does not provide a superior clinical improvement** with respect to HA, and therefore it should not be preferred to viscosupplementation as injective treatment of patients affected by knee cartilage degeneration and OA

Joint Bone Spine 83 (2016) 31–36

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Review

Does platelet-rich plasma have a role in the treatment of osteoarthritis?

Paul Ornetti[a,b,*], Geoffroy Nourissat[c,d], Francis Berenbaum[d,e], Jérémie Sellam[d,e], Pascal Richette[f], Xavier Chevalier[g], under the aegis of the Osteoarthritis Section of the French Society for Rheumatology (*Société Française de Rhumatologie*, SFR)

The available evidence **does not support** the use of PRP as a first- or second-line treatment for lower-limb osteoarthritis

Most of the randomized trials in patients with knee osteoarthritis support a slightly better symptomatic effect compared to hyaluronic acid, at least in patients with early disease and within the limited study follow-ups(usually 6 months).

Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
May 2016, Volume: 8, Issue: 5, Pages: 2325-2332, DOI: http://dx.doi.org/10.19082/2325

A systematic review and meta-analysis of the application of platelet rich plasma in sports medicine

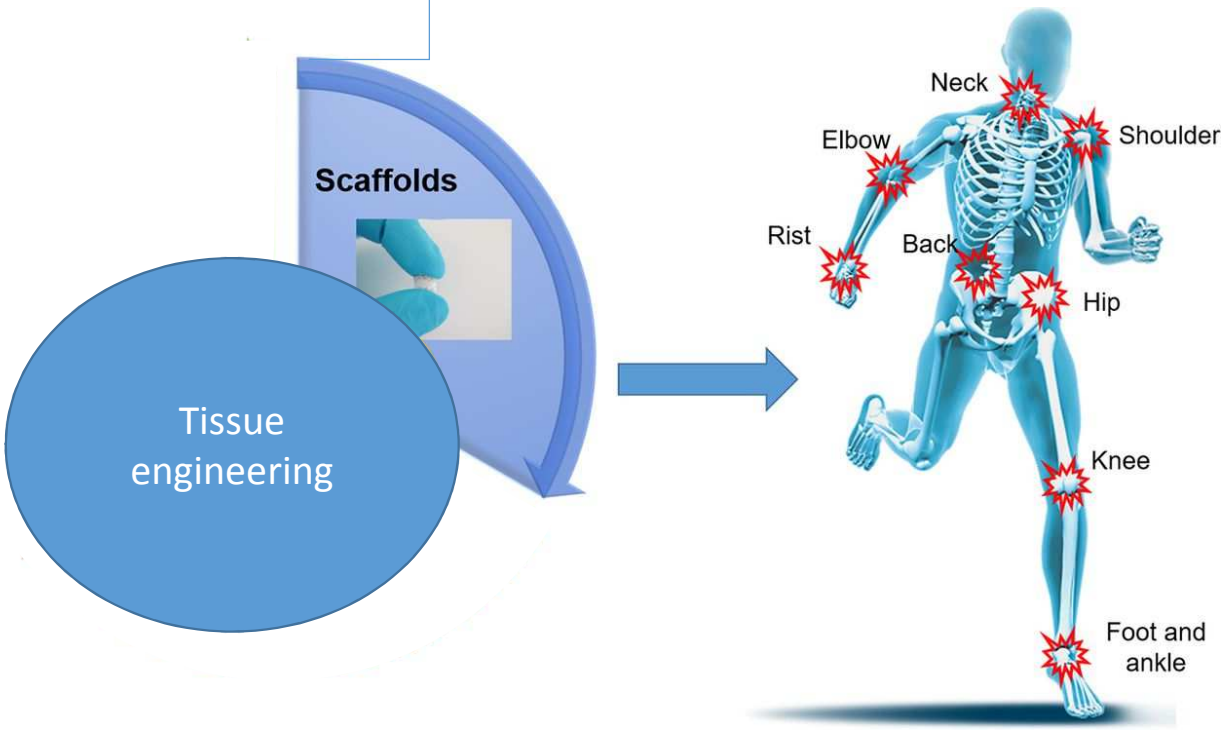
Masoomeh Gholami[1], Hamid Ravaghi[2], Masoud Salehi[3], Amirhosein Abedi Yekta[4], Shila Doaee[5], Ebrahim Jaafaripooyan[6]

Our search retrieved 905 studies, of which **13 randomized control** trials (RCT) met our inclusion criteria for systematic review and meta-analysis

The meta-analysis showed **no more effectiveness** for PRP application in sports-related injuries in terms of physical function improvement and pain relief.

Therefore, the extensive use of PRP for such injuries should be limited. Well-designed RCTs are needed to support the findings

gellan gum, alginate, silk fibroin, chitosan, hydroxyapatite, collagen, hyaluronic acid and poly(glycolic acid)



Scaffolds

Scaffolds can play two different roles; they can be used as a **mechanical support** or as a **support vehicle** for transportation of growth factors and/or cells.

gellan gum,
alginate,
silk fibroin,
chitosan,
hydroxyapatite,
collagen,
hyaluronic acid,
poly(glycolic acid) in a solid form or as a hydrogel

Three Generations of polymers

During the last 60 years, three different generations seem to be clearly marked:

- **bioinert materials** (1st generation),
  silicone rubber, PE, acrylic resins, polyurethanes, polypropylene (PP) and PMMA.

- **bioactive and biodegradable materials** (2nd generation),
  Polyglycolide (PGA), polylactide (PLA), polydioxanone (PDS), poly(3-caprolactone) (PCL), polyhydroxybutyrate (PHB), chitosan, poly(2-hydroxyethyl-methacrylate) (PHEMA), hyaluronic acid

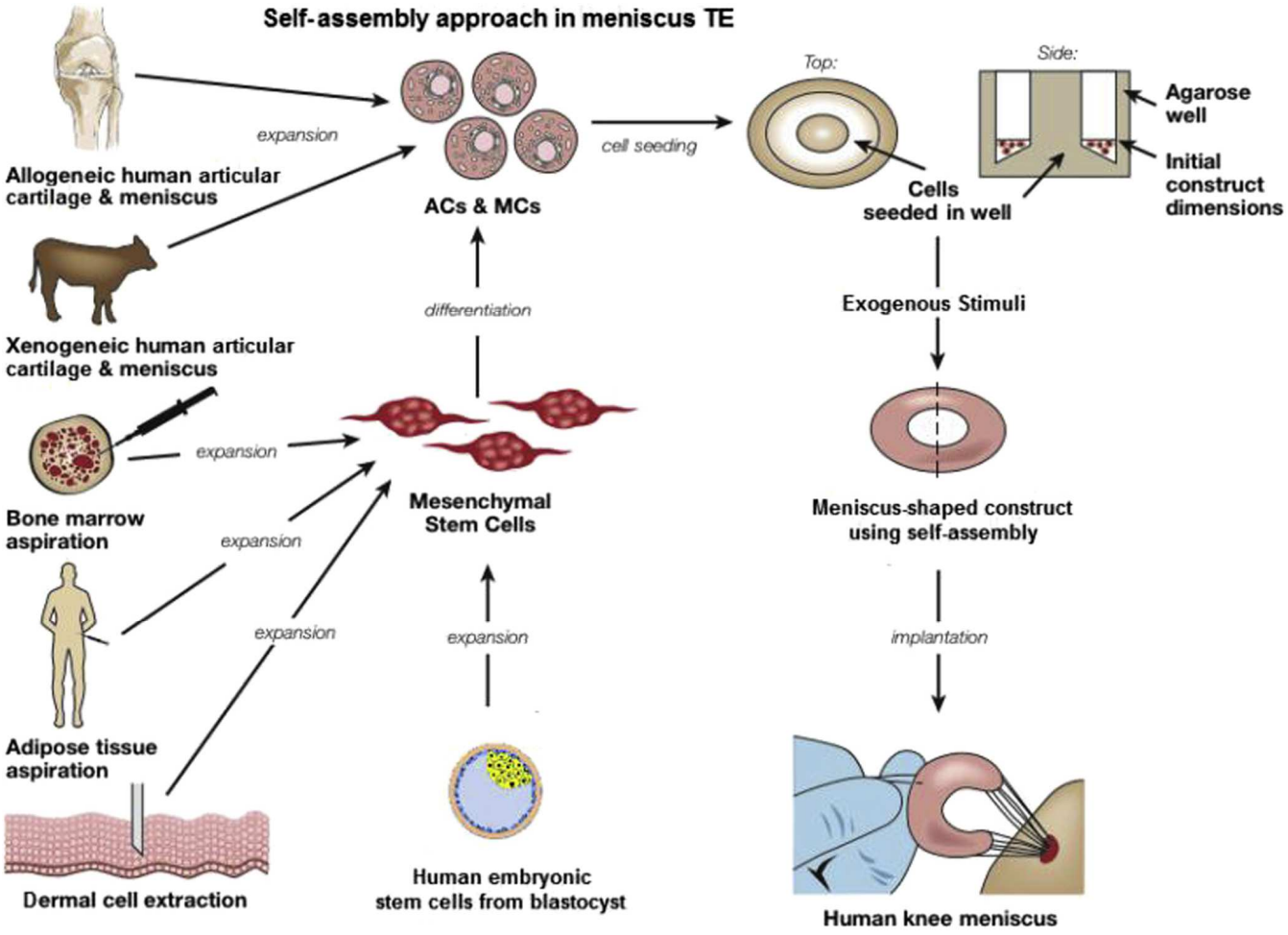
- materials designed to stimulate **specific cellular responses** at the molecular level (3rd generation)

Basic 3rd generation concept (for meniscus)

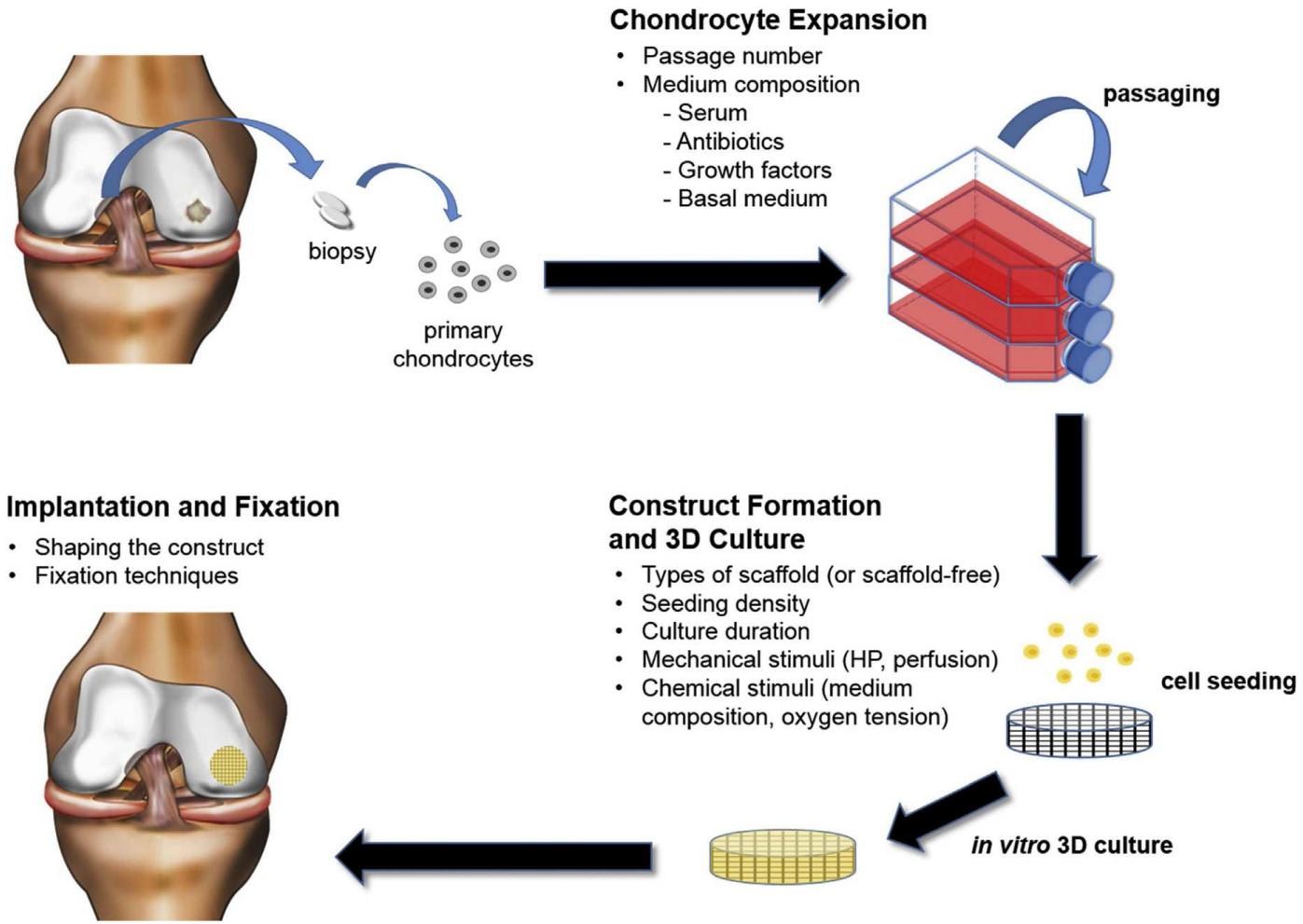
Systematic Review

Biological Augmentation and Tissue Engineering Approaches in Meniscus Surgery

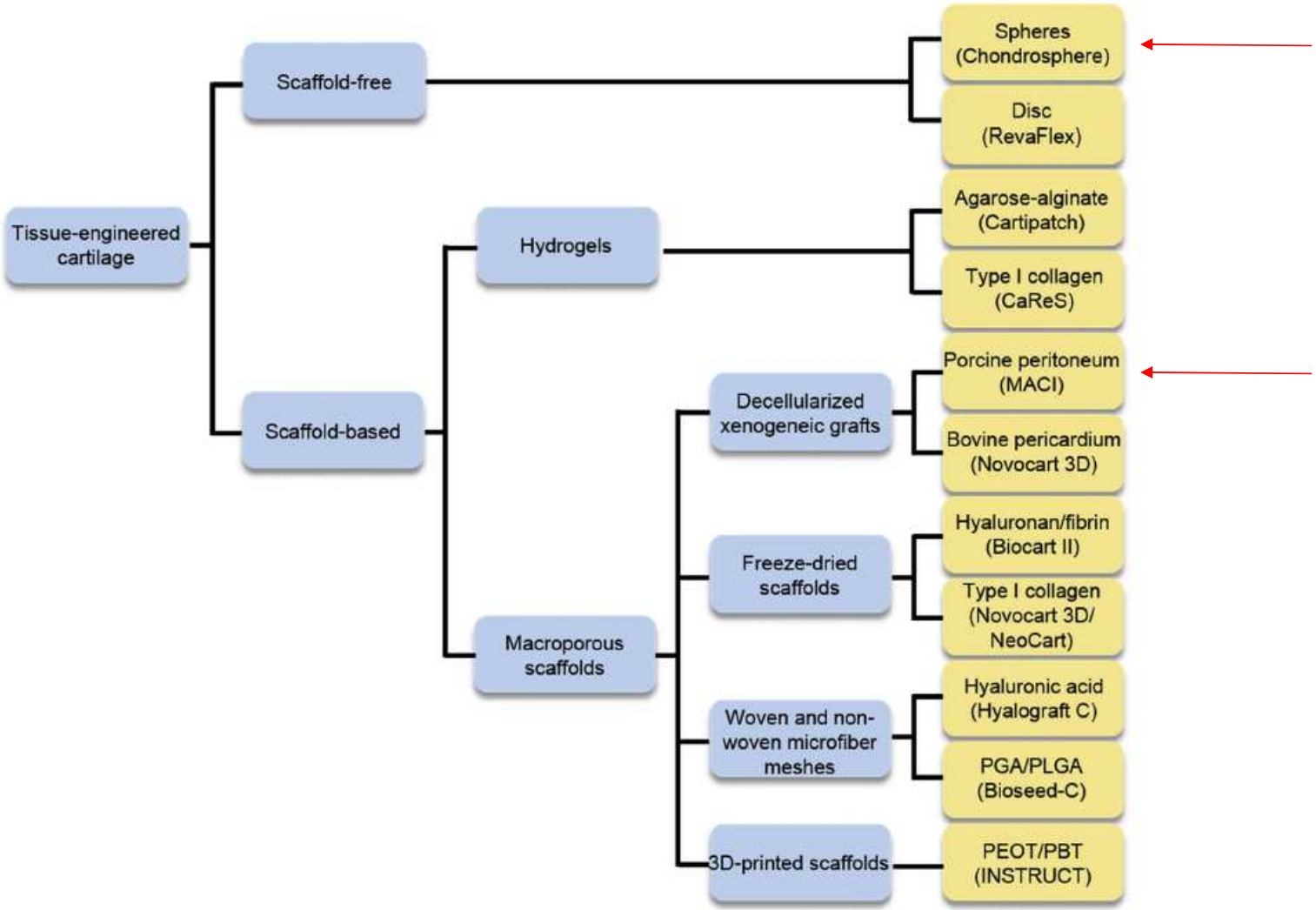
Cathal J. Moran, M.D., F.R.C.S.(Orth), Alberto Busilacchi, M.D., Cassandra A. Lee, M.D., Kyriacos A. Athanasiou, Ph.D., and Peter C. Verdonk, M.D., Ph.D.



Basic 3rd generation concept (for cartilage)



Scaffold Types



BST-CarGel

Soluble polymer scaffold containing chitosan is mixed with Bone Marrow Concentrate and applied over microfractured cartilage defects

Article

BST-CarGel® Treatment Maintains Cartilage Repair Superiority over Microfracture at 5 Years in a Multicenter Randomized Controlled Trial

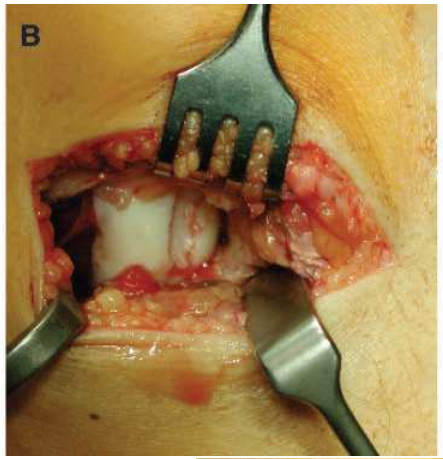
Cartilage
2015, Vol. 6(2) 62–72

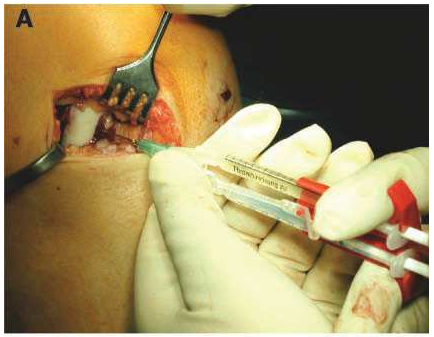
DOI: 10.1177/1947603514562064
cart.sagepub.com
SAGE

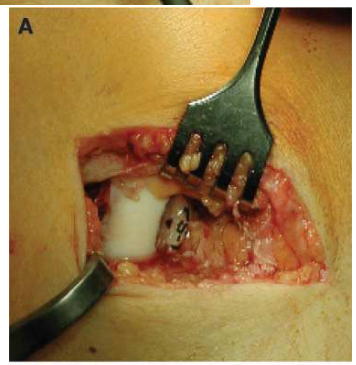
Matthew S. Shive[1], William D. Stanish[2], Robert McCormack[3], Francisco Forriol[4], Nicholas Mohtadi[5], Stéphane Pelet[6], Jacques Desnoyers[7], Stéphane Méthot[1], Kendra Vehik[8], and Alberto Restrepo[1]

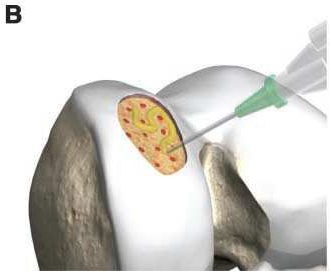
BST-CarGel was shown to be an effective midterm cartilage repair treatment that resulted in a sustained and significantly **superior repair tissue quantity** and quality over microfracture alone.

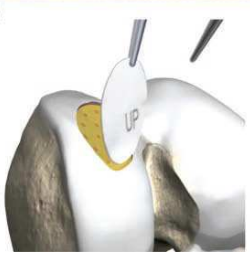
A = Autologous **M** = Matrix **I**= Induced **C** = Chondrogenesis





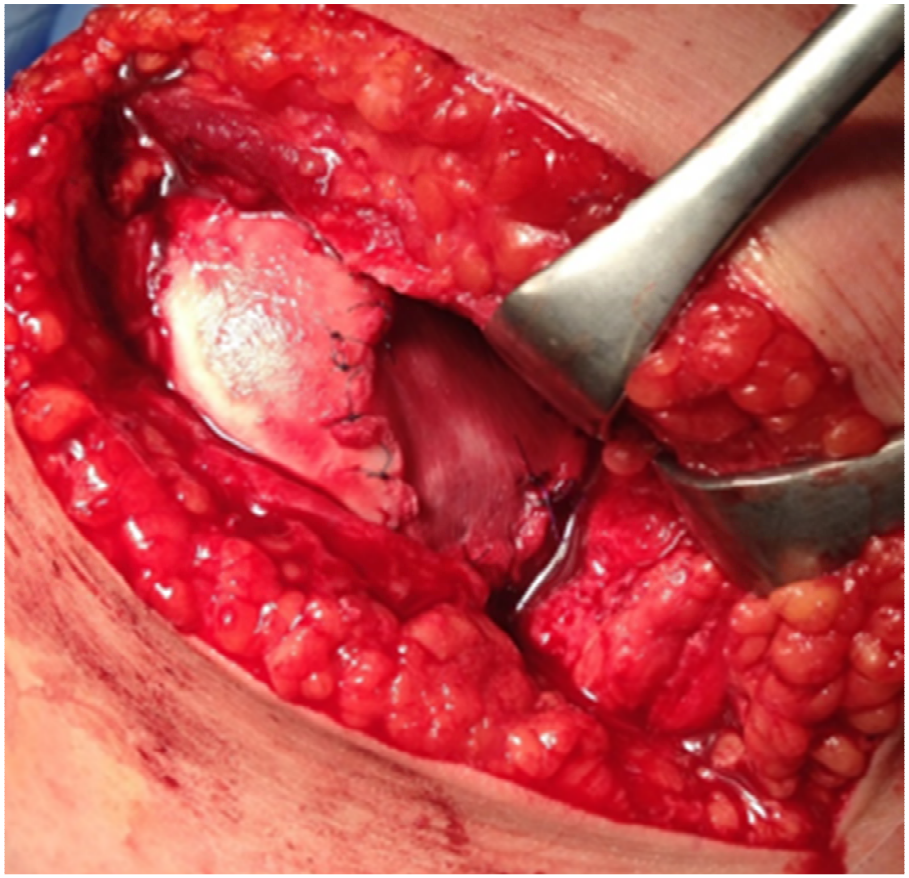






Why AMIC?

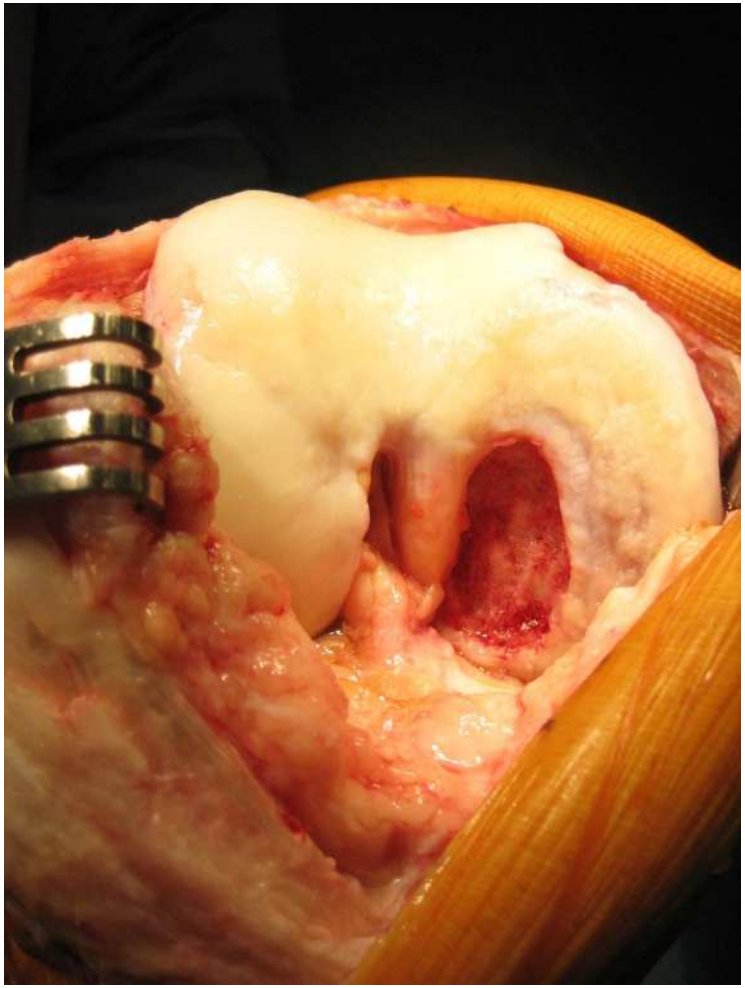
- Single stage procedure
- Provides a matrix to form fibrocartilage
- **Protects and stabilizes the blood clot**
- Promotes **migration** and adhesion of progenitor cells
- Prevents bleeding into the joint
- No donor site morbidity, no cell culture
- Costs are moderate



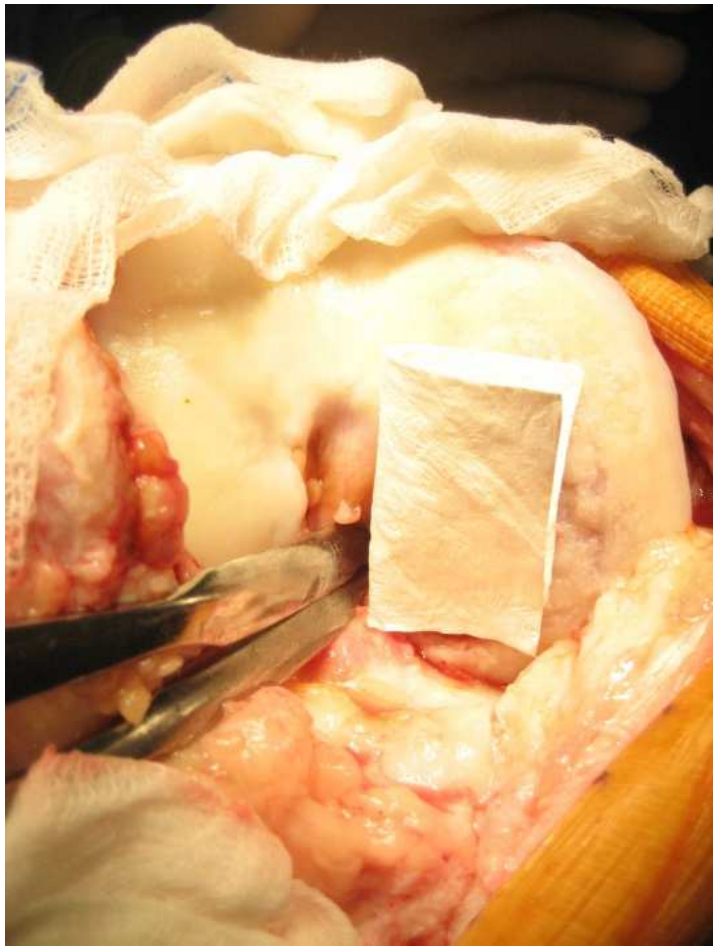
AMIC technique for cartilage regeneration

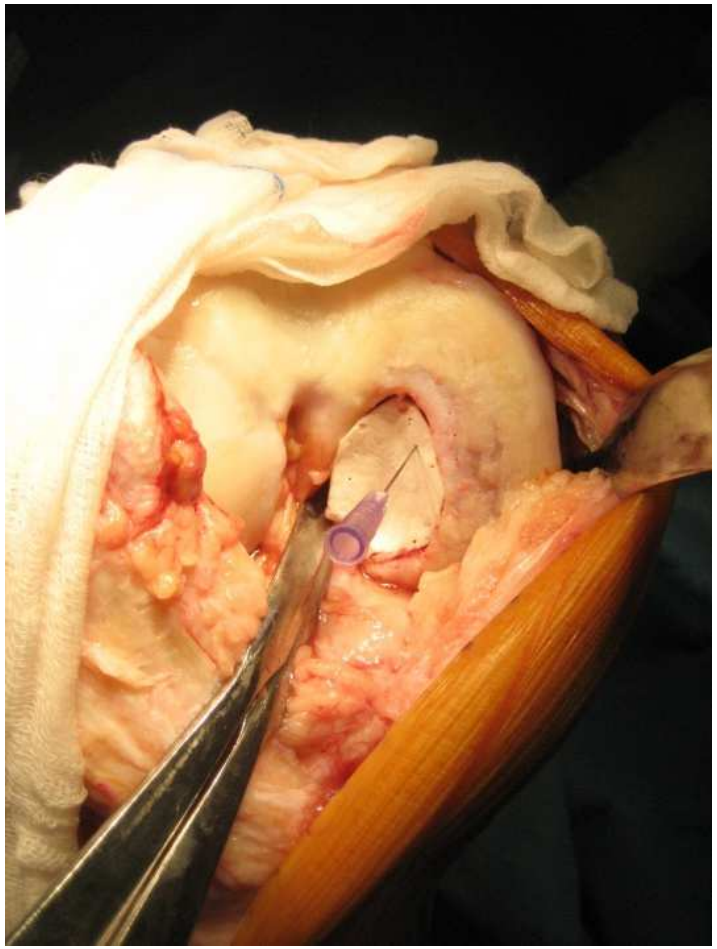
44 year old male, Large Osteochondral Defect on MFC

4 weeks later



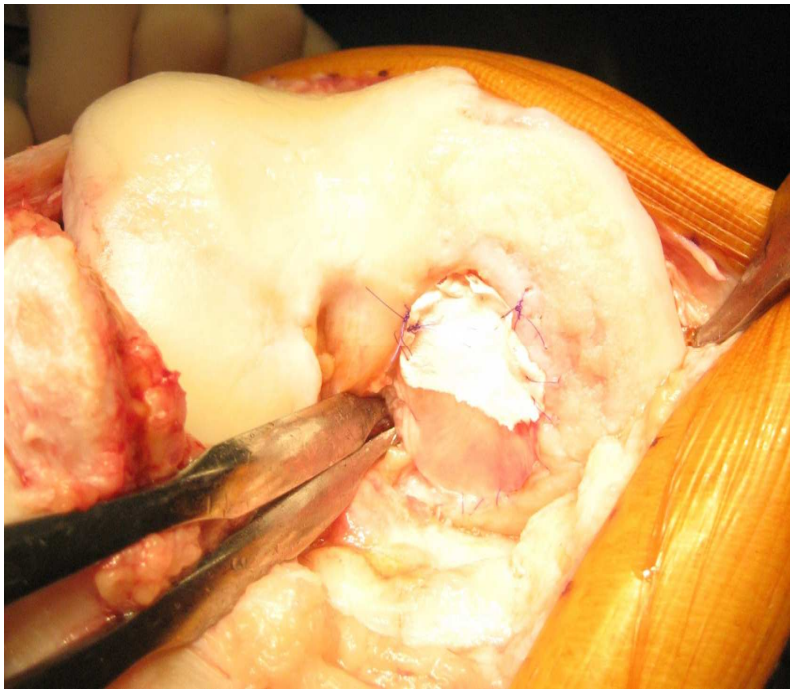
Preparation of Chondro-Gide Matrix



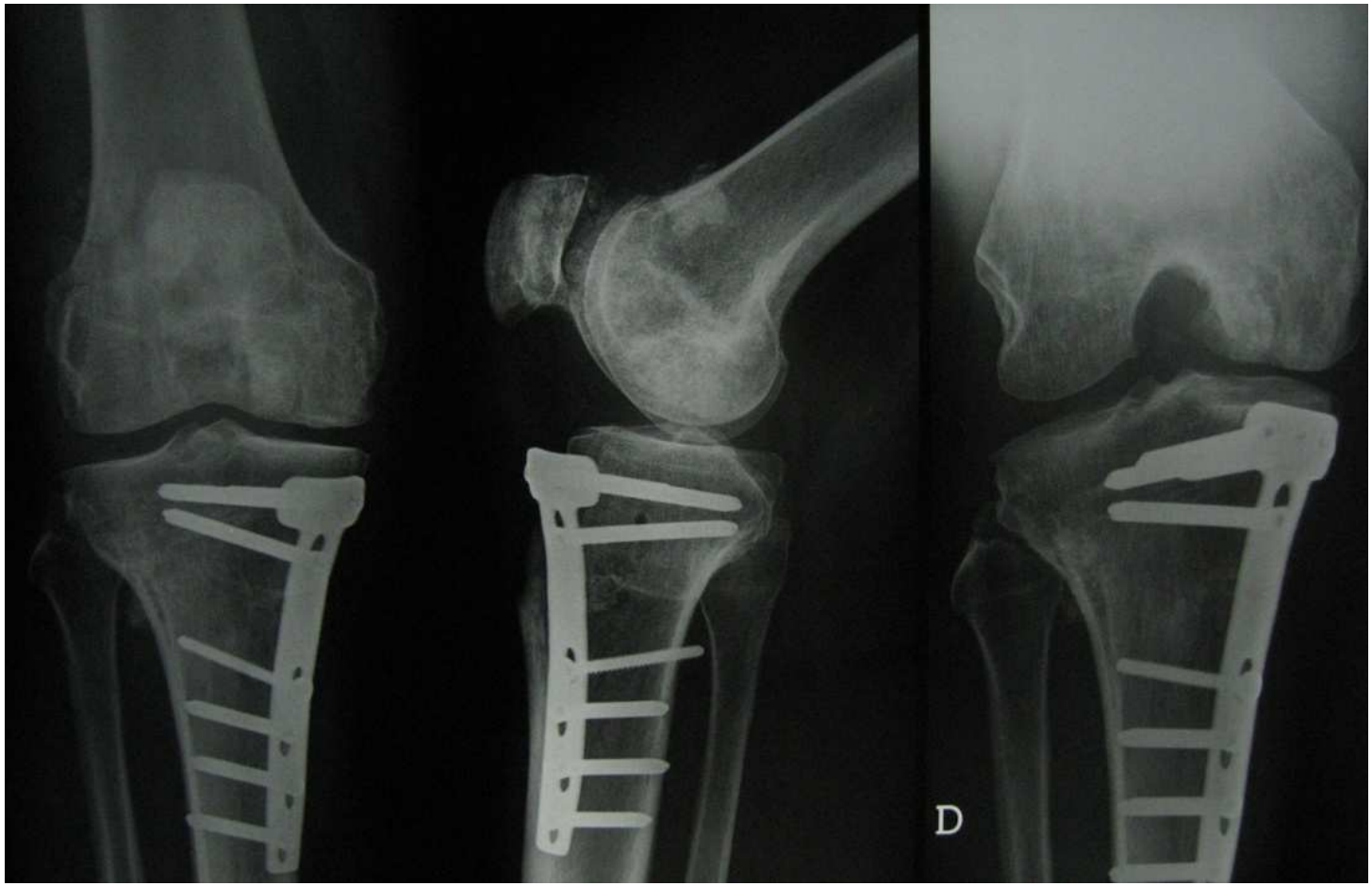


Spongiosa + Hydroxyappatite + Serum + Fibringlue

Filling of the defect and membrane suture



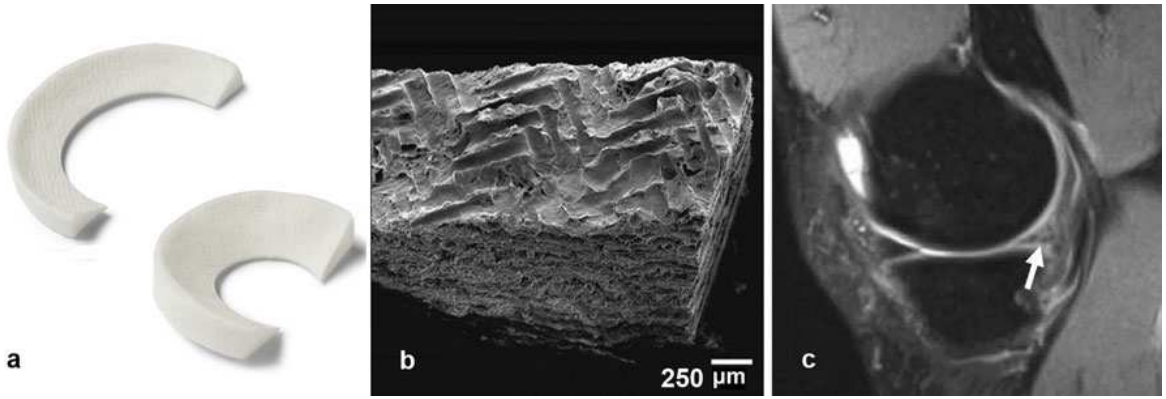
3 months later



Synthetic meniscus replacement

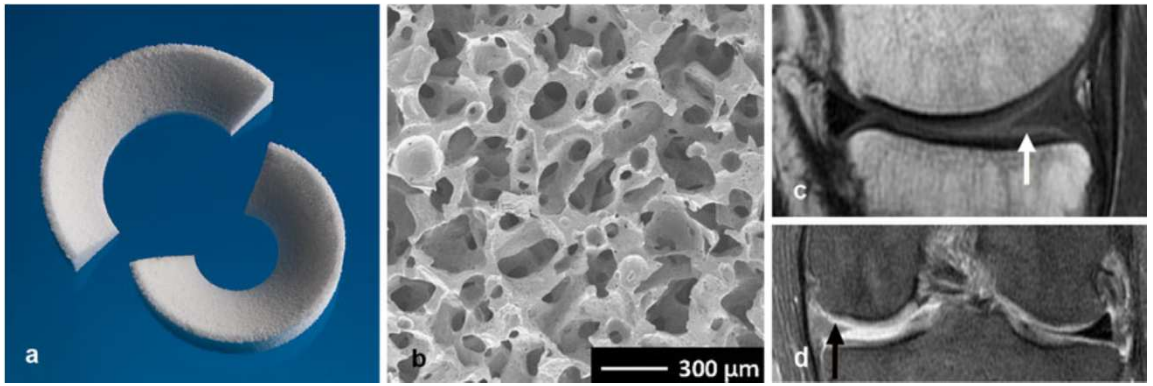
Collagen meniscus implant (CMI®)

- highly porous scaffold made of type I collagen fibres from purified bovine Achilles tendon which is supplemented with glycosaminoglycans



Actifit® implant

- Interconnected porous structure from polyurethane polymers that consist of biodegradable polyester segments combined with semi-degradable stiff segments



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OTSR-1728; No. of Pages 6
ARTICLE IN PRESS
Orthopaedics & Traumatology: Surgery & Research xxx (2017) xxx–xxx
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Original article

Actifit® polyurethane meniscal scaffold: MRI and functional outcomes after a minimum follow-up of 5 years

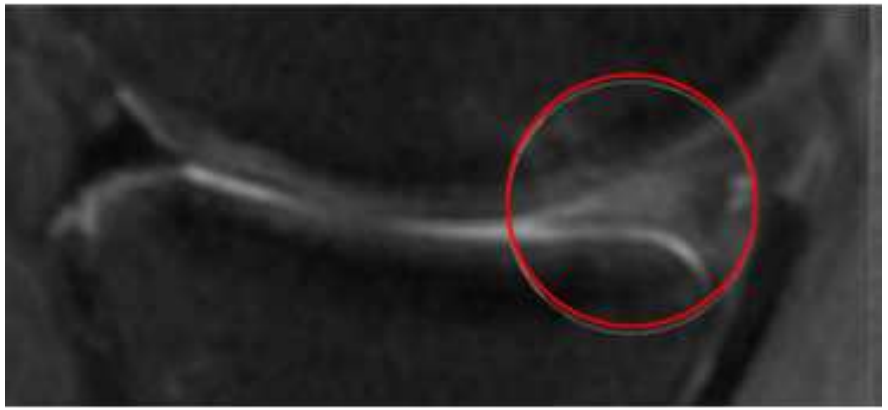
A. Leroy*, P. Beaufils, B. Faivre, C. Steltzlen, P. Boisrenoult, N. Pujol

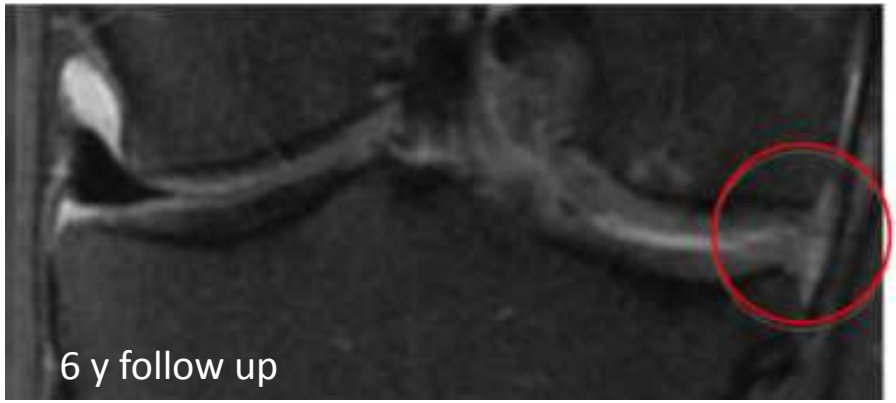
Centre hospitalier de Versailles, 177, rue de Versailles, 78150 Le Chesney, France

The Actifit® scaffold provides a comfortable knee, but **sports activities** may be limited.

The functional outcomes are stable after a mean follow-up of 6 years.

However, the **failure rate** remains high



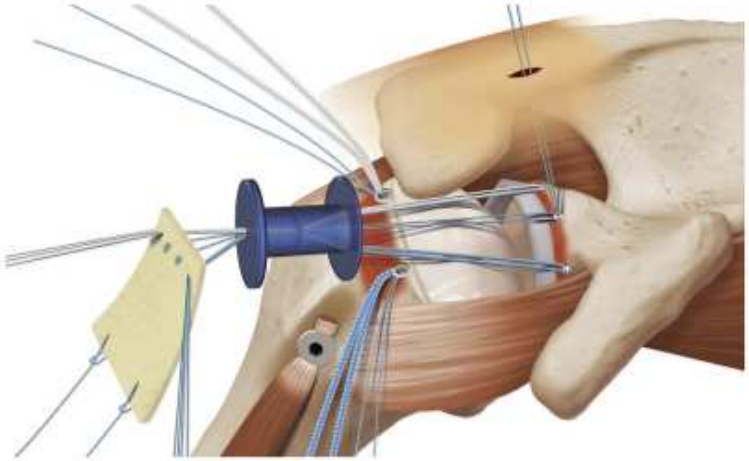


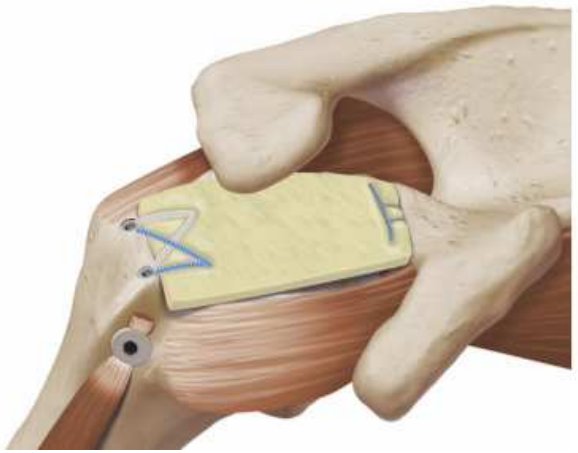
Arthroscopy Techniques, Vol 5, No 6 (December), 2016: pp e1407-e1418

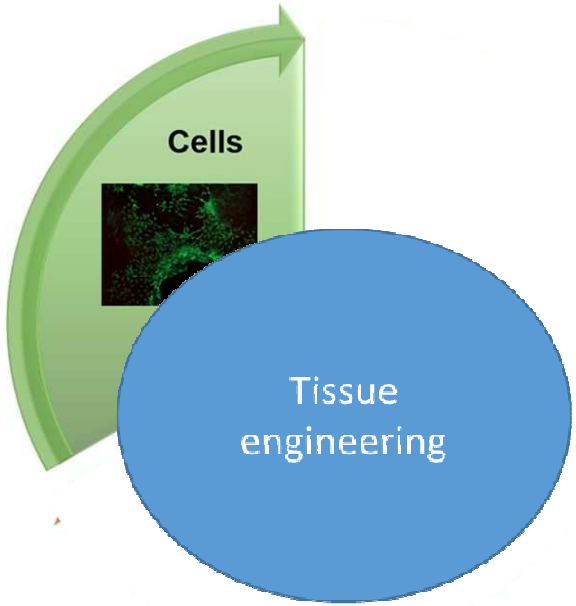
Arthroscopic Superior Capsular Reconstruction for Massive Irreparable Rotator Cuff Repair

Stephen S. Burkhart, M.D., Patrick J. Denard, M.D., Christopher R. Adams, M.D., Paul C. Brady, M.D., and Robert U. Hartzler, M.D.

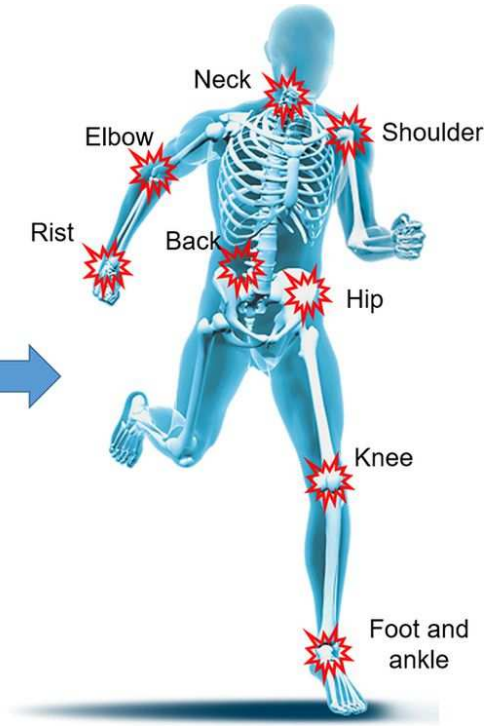
3 mm **ArthroFLEX® SCR** human dermal containing extracellular matrix molecules, growth factors, and cytokines







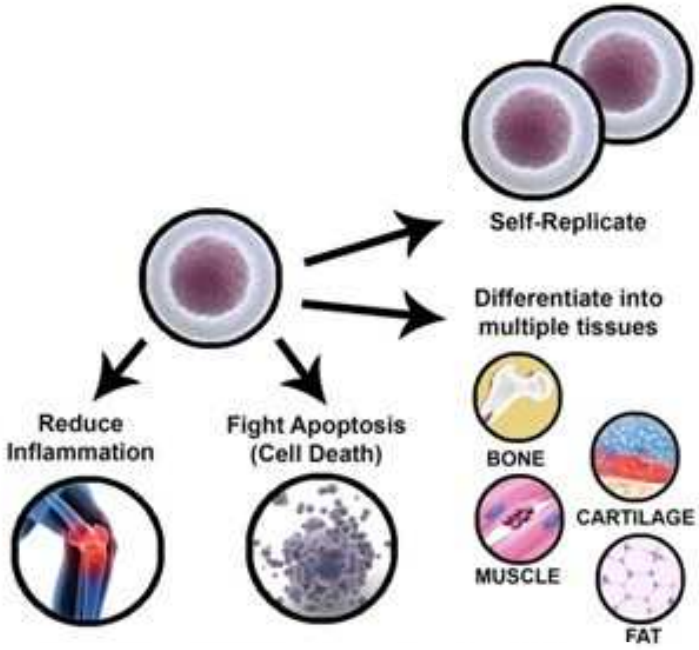
Fibroblasts,
Chondrocytes,
Stem cells
- marrow derived
- adipose tissue derived…



Stem cells

Special group of cells that have **three main features**:

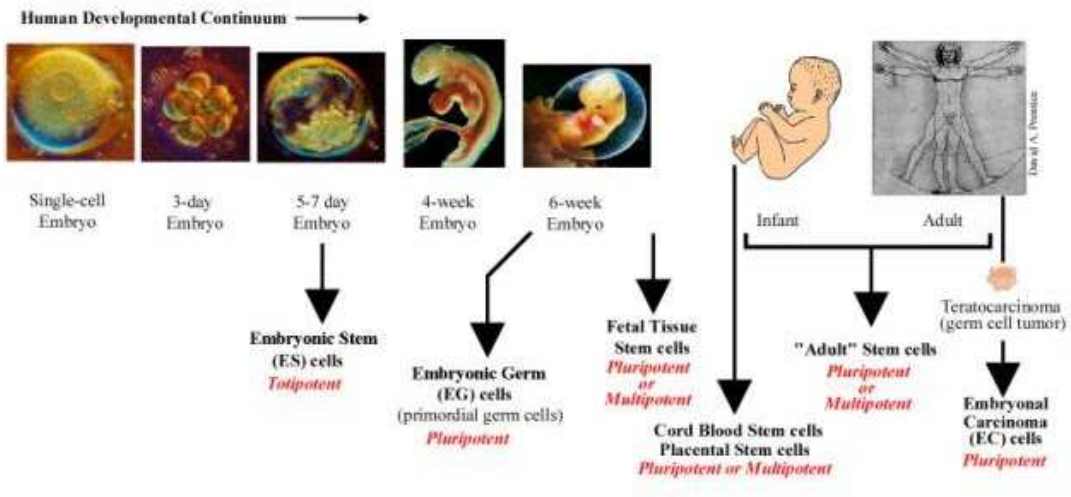
- the capacity to remain in a quiescent, undifferentiated state until stimulated
- the ability to differentiate into multiple tissue lineages (multilineage differentiation)
- the ability to undergo more replicative cycles (self-renewal).



Can reduce inflammation and fight apoptosis

Ethical issues

Stem cells types



totipotent (can differentiate into all types)

pluripotent (can differentiate into various cell types)

multipotent (limited type of specialized cells)

unipotent (strain of differential cells)

Meniscus injury repair

Cell-Based Meniscus Repair and Regeneration: At the Brink of Clinical Translation?

A Systematic Review of Preclinical Studies

Jasmijn V. Korpershoek,* BSc, Tommy S. de Windt,* MD, PhD, Michella H. Hagmeijer,* MD, Lucienne A. Vonk,* PhD, and Daniel B. F. Saris,*†‡ MD, PhD

Investigation performed at the Department of Orthopeadics, University Medical Center Utrecht, Utrecht, The Netherlands

The Orthopaedic Journal of Sports Medicine, 5(2), 2325967117690131
DOI: 10.1177/2325967117690131

The studies (53) are **heterogeneous** in animal models, cell types, and scaffolds used, and there are limited *comparative studies* available

The use of **cell-scaffold combinations** was found to be superior to the use of empty scaffolds.

Efficiency should be measured by a universal method of **biomechanical testing,** preferably with a minimum 6-month follow-up

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 436029, 10 pages
http://dx.doi.org/10.1155/2014/436029

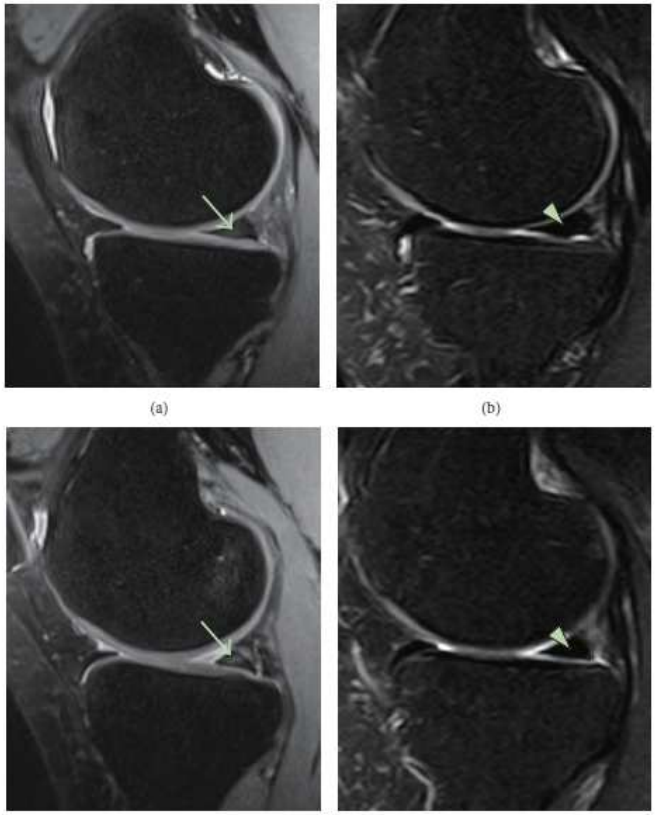
Review Article

Regenerative Repair of Damaged Meniscus with Autologous Adipose Tissue-Derived Stem Cells

Jaewoo Pak,[1] Jung Hun Lee,[1,2] and Sang Hee Lee[2]

[1] *Stems Medical Clinic, 32-3 Chungdam-dong, Gangnam-gu, Seoul 135-950, Republic of Korea*
[2] *National Leading Research Laboratory, Department of Biological Sciences, Myongji University, 116 Myongjiro, Gyeonggido, Yongin 449-728, Republic of Korea*

Three months after the treatment, the patient's symptoms improved and repeated MRI showed almost complete disappearance of the torn meniscus



Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy

JBJS , 2014

A Randomized, Double-Blind, Controlled Study

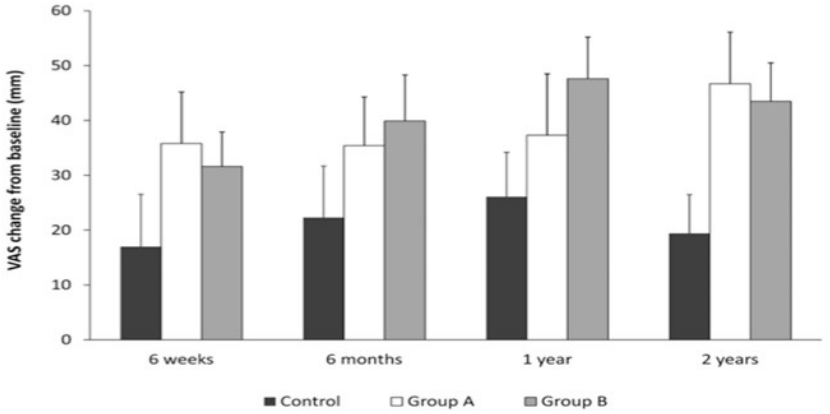
C. Thomas Vangsness Jr., MD, Jack Farr II, MD, Joel Boyd, MD, David T. Dellaero, MD, C. Randal Mills, PhD, and Michelle LeRoux-Williams, PhD

55 patients underwent a partial medial meniscectomy.
A single superolateral knee injection was given

Group A, 50 × 10^6 allogeneic mesenchymal stem cells;

Group B, 150 × 10^6 allogeneic mesenchymal stem cells;

Control group, hyaluronic acid/hyaluronan) vehicle control



There was evidence of **meniscus regeneration** and **improvement in knee pain** following treatment with allogeneic human mesenchymal stem cells.

Cartilage repair

Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 29, No 4 (April), 2013: pp 684-694

Articular Cartilage Regeneration With Autologous Peripheral Blood Stem Cells Versus Hyaluronic Acid: A Randomized Controlled Trial

Khay-Yong Saw, M.Ch.Orth., F.R.C.S.(Edin), Adam Anz, M.D., Caroline Siew-Yoke Jee, Ph.D.(Lond), Shahrin Merican, M.B.B.Ch., F.R.C.R., Reza Ching-Soong Ng, M.D., Sharifah A. Roohi, M.S.Orth., F.R.C.S.(Edin), and Kunaseegaran Ragavanaidu, M.B.B.S., M.Path.

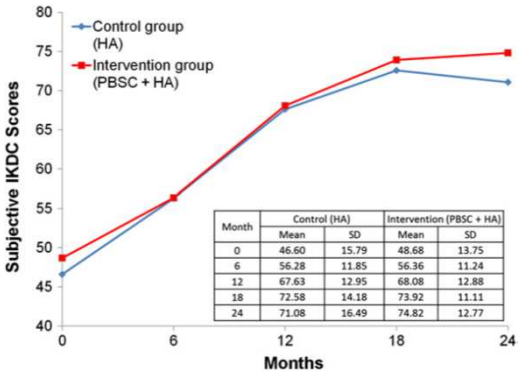
50 pt (18 - 50 years) ICRS grade 3 and 4 lesions arthroscopic **microfracture**
25 patients to the control (HA)
25 intervention (PBSC & HA)

5 weekly injections 1 week after surgery

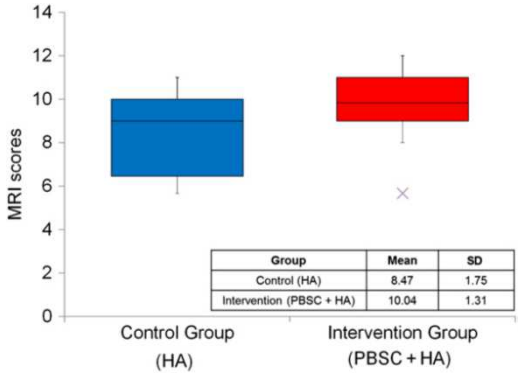
3 additional injections of either HA or PBSC & HA at weekly intervals 6 months after surgery.

Outcome scores and MRI plus biopsies

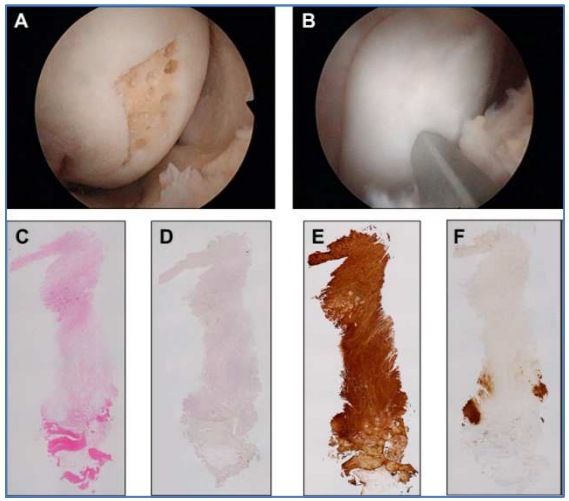
HA



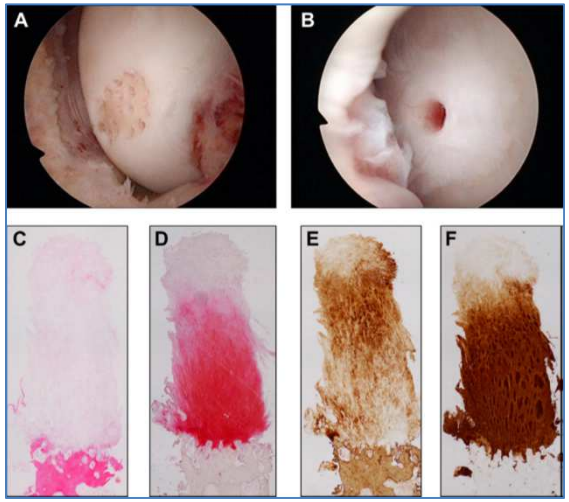
Month	Control (HA)		Intervention (PBSC + HA)	
	Mean	SD	Mean	SD
0	46.60	15.79	48.68	13.75
6	56.28	11.85	56.36	11.24
12	67.63	12.95	68.08	12.88
18	72.58	14.18	73.92	11.11
24	71.08	16.49	74.82	12.77



Group	Mean	SD
Control (HA)	8.47	1.75
Intervention (PBSC + HA)	10.04	1.31



PBSC & HA



Tendon healing

Knee Surg Sports Traumatol Arthrosc (2014) 22:66–71
DOI 10.1007/s00167-012-2279-9

KNEE

Is there a role for adult non-cultivated bone marrow stem cells in ACL reconstruction?

Alcindo Silva · Ricardo Sampaio · Rui Fernandes · Elisabete Pinto

Adult non-cultivated bone marrow stem cells do not seem to accelerate graft-to-bone healing in ACL reconstruction

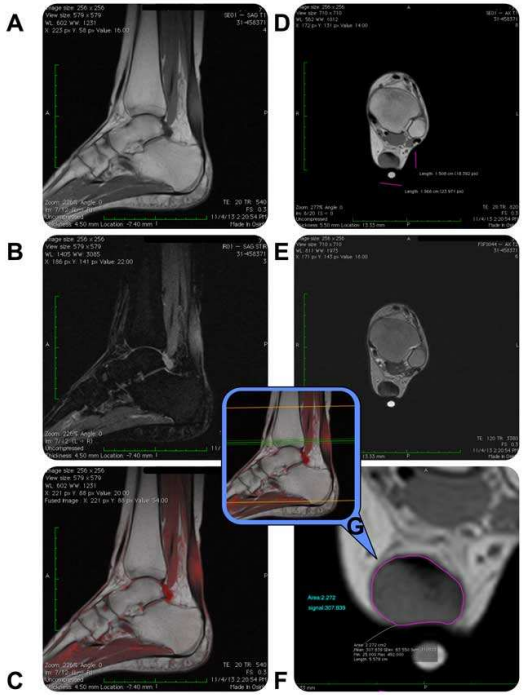
Other uses

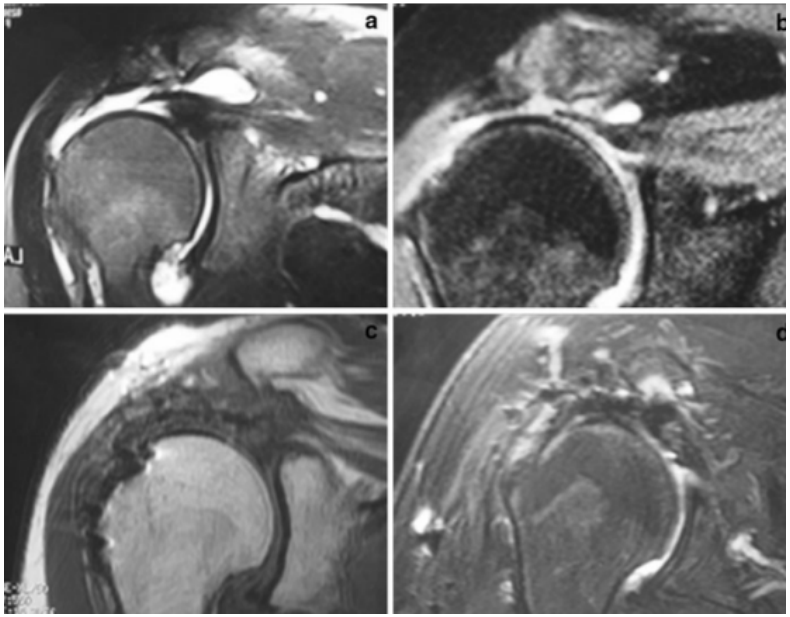
Achilles tendinopathy

Lateral Epicondylitis

Osteoarthritis

Rotator cuff repair





Conclusions

- Tissue engineering has created a **revolution** in several sports medicine conditions
- Current clinical practice already includes use of **cell, growth factors and scaffolds**.
- However, **major research and development** are still required
- Currently there is **scarce clinical evidence** supporting most of the proposed methods; this relies on methodology of most published clinical trials.

Future perspectives

- Controlled research protocols with **multidisciplinary teams** and careful follow-up
- Besides the classical triad of tissue engineering, the development of biomaterials, bioreactors, nanotechnology, gene therapy, three-dimensional bioplotter printing et al envision future perspectives for:

  - **enhancing repair** of damaged tissues (cartilage, tendon).

  - developing 'intelligent' strategies in which biomaterials, proteins and cells can be **'prepared/manipulated'** to present **different properties or behaviours in different layers**

  - development of functional and mature tissues for subsequent clinical implantation that might even be **patient specific and/or injury specific**

Future research

Sailaja *et al. Journal of Biomedical Science* (2016) 23:77
DOI 10.1186/s12929-016-0284-x

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REVIEW Open Access

Biomimetic approaches with smart interfaces for bone regeneration

G. S. Sailaja[1*], P. Ramesh[2], Sajith Vellappally[3], Sukumaran Anil[4] and H. K. Varma[2*]