Overview of mesenchymal stem cells & scaffolds for cartilage repair

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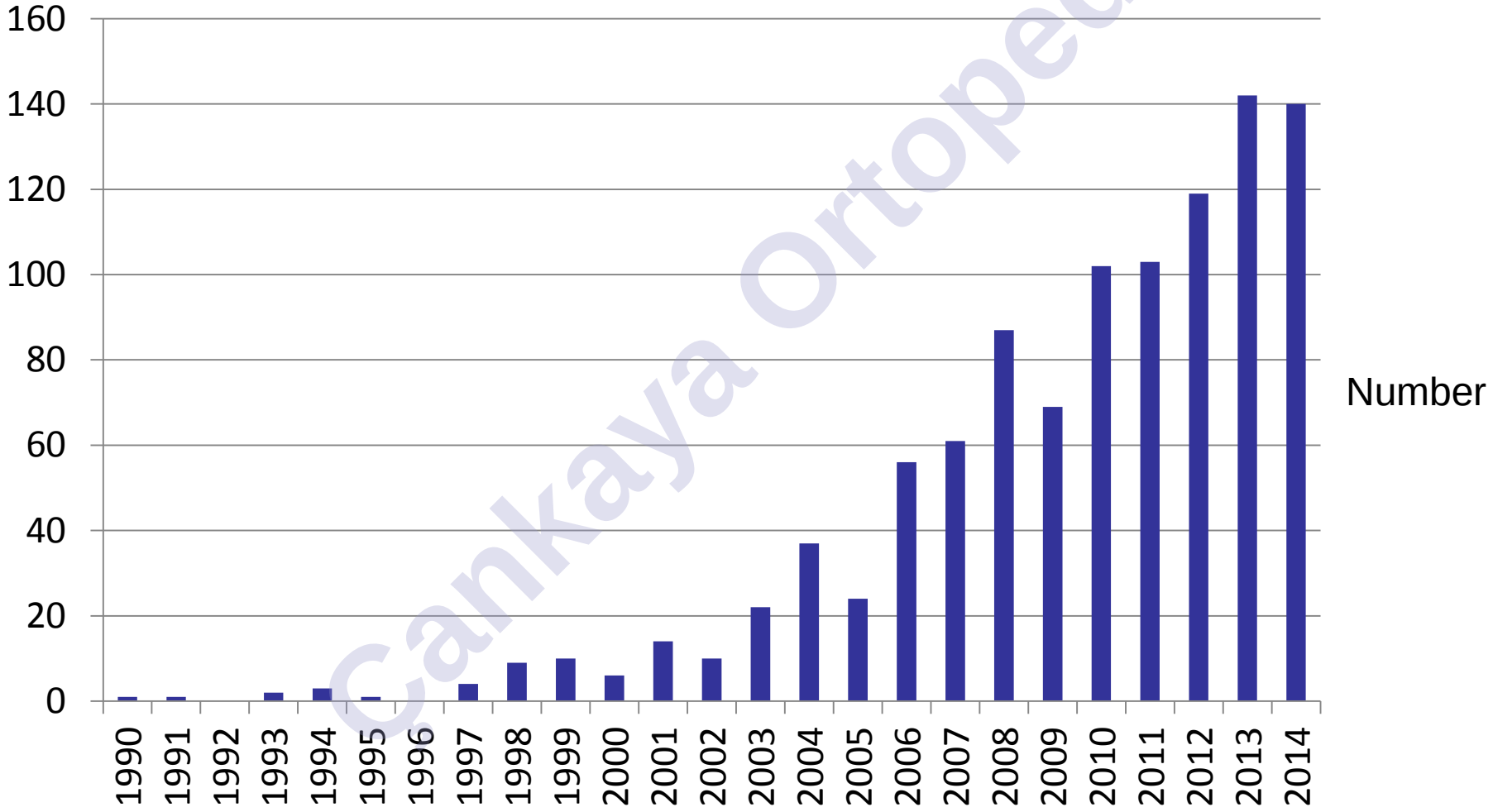
Articles on “mesenchymal stem cells in cartilage repair”



Now Available for Public Comment: Notice of Proposed Rulemaking (NPRM) for FDAAA 801 and NIH Draft Reporting Policy for NIH-Funded Trials

33 studies found for: mesenchymal stem cell AND cartilage

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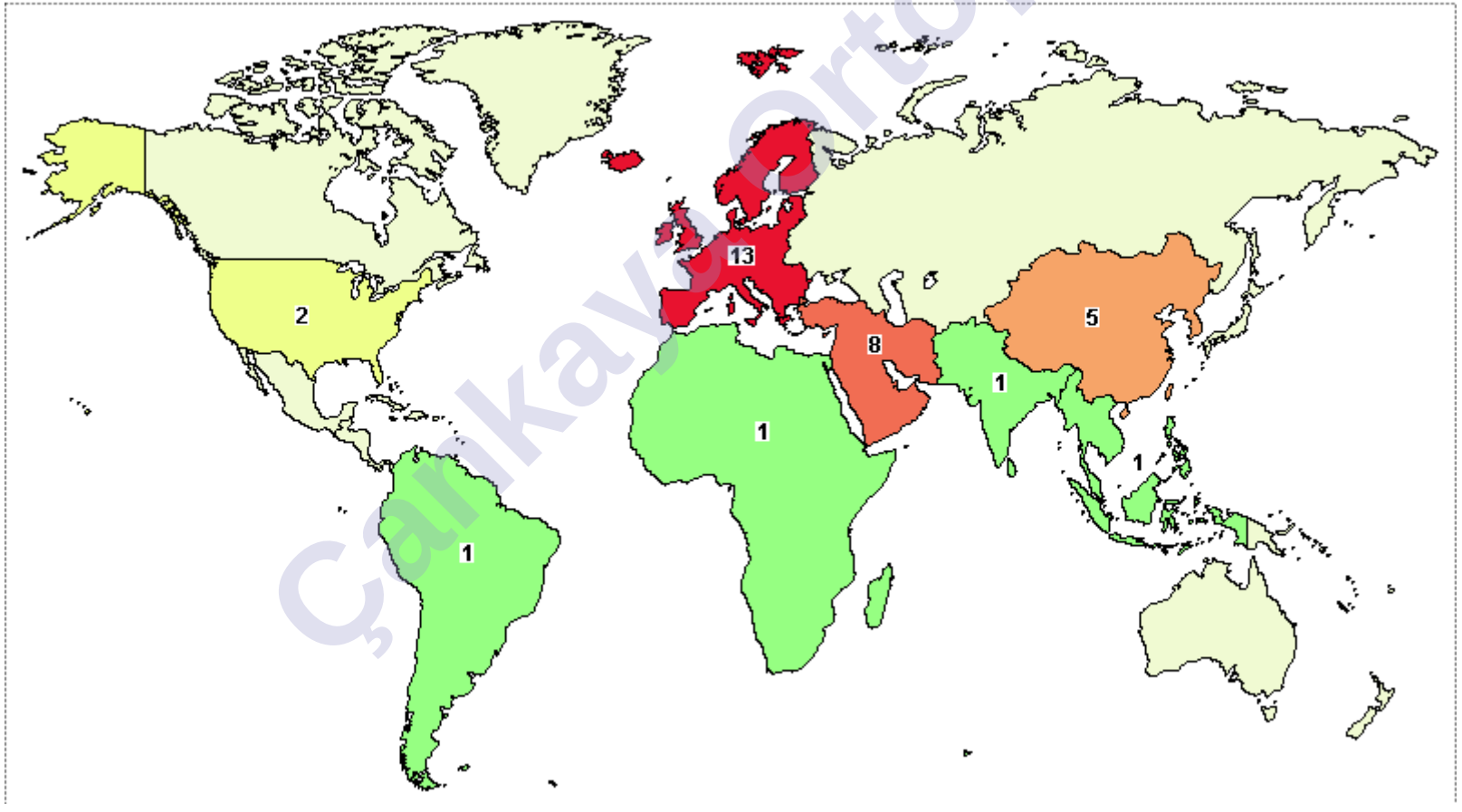
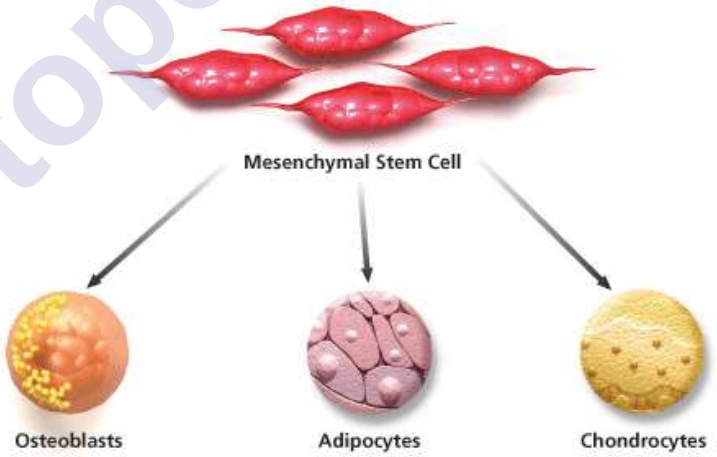


Mesenchymal stem cells

- Embriyonic
  - Immunogenic & Tumorigenic
  - Ethical concerns
- Adult
  - Bone marrow
  - Adipose tissue
  - Synovium
  - Peripheral Blood
- Scarce & scattered pericytes : % 0.001 of mononuclear cells in bone marrow
  - *Richter W. J Intern Med. 2009; 266(4):390-405.*



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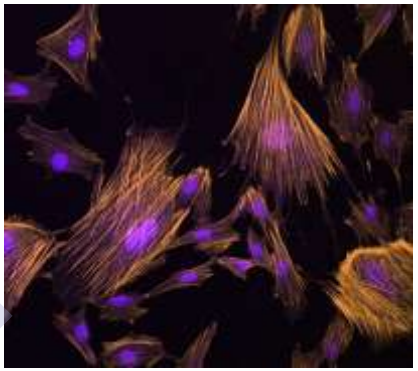
Mesenchymal stem cells



- Capacity for self-renewal & self-maintenance
- Potential for differentiation into cells forming multiple mesodermal tissues including chondrocytes
- Migrate toward injured tissues (homing/ trafficking) where they display trophic effects
- Anti-inflammatory, angiogenic, anti-apoptotic & immunomodulating effects
  - *Filardo G,(2013), Myers KR (2013), Strioga M(2012)*

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Grassel S. Tissue-Engineering Strategies to Repair Chondral and Osteochondral Tissue in Osteoarthritis: Use of Mesenchymal Stem Cells. *Curr Rheumatol Rep (2014) 16:452*

- **Preclinical studies**
  - Traumatic lesions
    - Chondral defects
      - BMSC
        - 1x ovine, 1x porcine, 1x equine studies
    - Osteochondral defects
      - BMSC
        - 2x ovine, 3x porcine, 1x equine studies
  - Chronic lesions
    - Osteochondral defects
      - BMSC
        - 3x ovine studies
- **Clinical studies**
  - Traumatic lesions
    - Chondral defects
      - BMC
        - 4x case series
      - BMSC
        - 4x case series, 1x comparative study
    - Osteochondral defects
      - BMC
        - 1x case series, 1x comparative study
  - OA-induced lesions
    - BMC
      - 1x case series, 1x comparative study
    - BMSC
      - 5x case series
    - ADSC
      - 3x case series, 1x comparative study

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MSC for Cartilage Repair

Traumatic defects & OCD

Osteoarthritis

Immunosuppresive & Anti-inflammatory Role in Rheumatoid Arthritis

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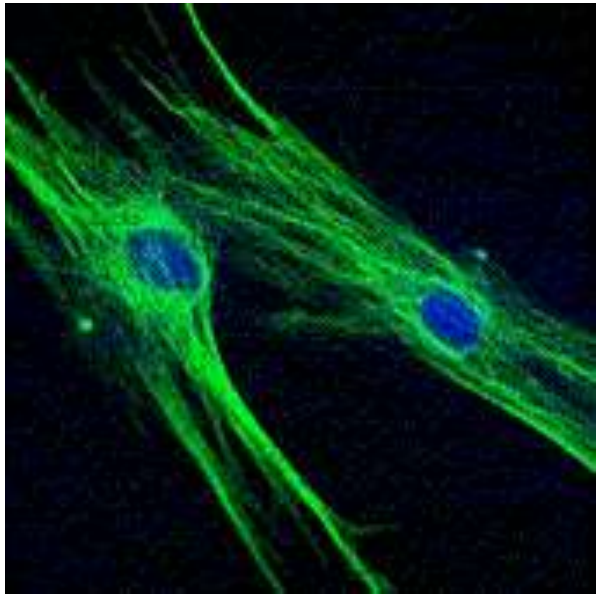
Preparation

- **Cell culture & expansion**
  - 2 step procedure
  - Requires GMP labs
  - Regulatory problems
  - Expensive
- **Cell concentration**
  - One step procedure
  - Can be performed in OR
  - Less regulatory problems

Growth factors/mechanical factors that promote chondrogenesis

- **TGF-B 1 & 3**
- BMP- 2 & 7
- FGF-2
- IGF-1
- Kartogenin
- Chondroitinase A,B,C
- Hypoxia /Heat shock
- Hydrostatic pressure

- Dexamethasone
- PRP
  - *Fortier LA .CORR 2011; 469(10): 2706*
  - *Montoya Biol Res 46, 2013, 441*



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Delivery

- Surgical implantation with or under a scaffold
  - Direct & targeted application
  - Can be combined with concommittant procedures
  - … but invasive

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Delivery

- Intra-articular injection
  - Less invasive but imprecise and not targeted
  - Autocrine and paracrine effects
  - Mostly for OA
  - Augmentation of primary surgery

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Wong KL: Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. ***Arthroscopy. 2013;29(12):2020-8.***

- 56 patients undergoing HTO & microfracture
  - 28 underwent HA injection 3 weeks post-op
  - 28 underwent cultured BMSC 3 weeks post-op

- Both groups improved
- MSC group had significantly better IKDC Lysholm, Tegner & MOCART scores

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Kim YS. Does an injection of a stromal vascular fraction containing adipose-derived MSC influence the outcomes of marrow stimulation in osteochondral lesions of the talus? A clinical and magnetic resonance imaging study.

Am J Sports Med. 2014;42(10):2424-34.

- 50 ankles underwent arthroscopic microfracture for talus OCL
- 26 received adipose derived MSC injection

- Both groups improved, but a-MSC had better VAS, AOFAS,Tegner & MOCART scores
- a-MSC injection group had better outcomes in older patients & larger lesions

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Vehicle

- Pure cell suspension/Spheroids
- Carbohydrate based scaffolds
  - Agarose, alginate
  - Chitosan/chitin
  - Hyaluronate
  - Fibrin glue
- Protein based scaffolds
  - Collagen membrane/gel
  - Fibrin
  - Gelatin
- Synthetic polymers
  - (PLA,PGA, Polycaprolactone
- Hydroxyapatite /TCP
- Amniotic membrane

Bioactive

Biodegradable

İnert

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Clinical reports of cultured/concentrated MSC for focal cartilage defects

Author	Number of patients	Cell origin	Follow up	Year
Haleem	5	BMSC+fibrin glue scaffold	12	2010
Centeno	1	BMSC	2	2008
Kuroda	1	BMSC+ collagen gel	12	2007
Wakitani	2	BMSC+ collagen gel	17-27	2007
Wakitani	2	BMSC+ collagen gel	60	2004

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Gopal K. Advances of human bone marrow-derived mesenchymal stem cells in the treatment of cartilage defects: A systematic review.

Exp Biol Med 2014;239(6):663-669.

- 996 studies on BM-MSC for cartilage repair
- 6 clinical studies
  - Cohort observational trials 2
  - Case series 3
  - Case report 1
- Good cartilage repair, minimal complications
- Better than cell free scaffolds, similar to ACI
- Hyaline like cartilage ?

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Clinical reports of cultured/concentrated MSC for OA

Author	Number of patients	Cell origin	Follow up	Year
Emadedin	6	BMSC	12	2012
Kasemkijwattana	2	BMSC	31	2011
Davatchi	4	BMSC	12	2011
Wakitani	24	BMSC	16	2002
Wong	56	BMSC	12	2013
Koh	50	ADMSC + PRP	16	2012
Koh	30	ADMSC + PRP	24	2013
Koh	18	ADMSC+PRP	26	2013

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Koh YG. Second-Look Arthroscopic Evaluation of Cartilage Lesions After Mesenchymal Stem Cell Implantation in Osteoarthritic Knees.

Am J Sports Med. 2014; 42(7):1628-1637.

- Clinical results not correlated with anatomical results
- 2nd look arthroscopy in 34 patients after MSC implantation for OA
- % 94 patient satisfaction
- %76 abnormal or severely abnormal cartilage repair (ICRS)

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Nejadnik H. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study.

Am J Sports Med. 2010;38(6):1110-6.

- 36 ACI vs. 36 cultured BMSC
- No difference in clinical scores at 24 months
- BMSC better in older patients
- Better results in younger patients and smaller lesions

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Giannini S. Cartilage repair evolution in post-traumatic osteochondral lesions of the talus: from open field autologous chondrocyte to bone-marrow-derived cells transplantation. ***Injury. 2010 ;41(11):1196-203.***

- Comparison of 10 open ACI, 46 arthroscopic ACI & 25 BMC in talar dome OCL
- 2nd look at arthroscopy 1 year
- Similar clinical improvement
- “Hyaline like” cartilage in biopsies

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Bone marrow concentrate

- One-step procedure
- Contains: mesenchymal stem cells (MSCs), hematopoetic stem cells, platelets (containing growth factors), and cytokines
- Chondrogenic potential in the articular environment
  - *Cavallo c. J Biomed Mater Res A. 2013;101(6):1559-70.*
- Usually combined with a matrix & PRP


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MAGELLAN
ARTERIOCYTE
Çankaya Ortaneli


Sankaya Ortopedi

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Basic science

- Better quality of cartilage regeneration in animal experiments
  - *Betsch M. PLoS One. 2013 Aug 12;8(8):e71602.*
  - *Fortier LA: J Bone Joint Surg Am. 2010;92:1927–1937.*
  - *Zhao Q. J Mater Sci Mater Med. 2013;24(3):793-801.*
- No effect of BMC on cartilage repair
  - *Jagodzinski M. Tissue Eng Part C Methods. 2014;20(3):215-26.*

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Clinical reports of Bone Marrow Concentrate for focal cartilage defects

Author	Number of patients	Cell origin	Follow up	Joint
Gigante	5	BMC+Collagen membrane	12	Knee
Enea	9	BMC+PGA-HA matrix	24	Knee
Giannini	48	BMC+HA membrane	24-35	Talus
Skowronski	54	BMC+Collagen membrane	12-60	Knee
Buda	20	BMC+HA membrane	24	Knee

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Problems

- In vitro/in vivo phenotype maintenance
  - *Shen Y . Current Stem Cell Research & Therapy, 2014, 9, 254-267*
- Hypertrophy
  - *Giannini S: Injury. 2010 ;41(11):1196-203.*
- Ossification
  - *Somoza RA: Tissue Eng Part B Rev. 2014*

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Safety

- Spontaneous malignant transformation of adult MSC in long term in vitro cultures
  - *Rubio D. Cancer Res. 2005;65(8):3035-9.*

- No tumors or infections in 41 patients at 75 months (range 5-137)
  - *Wakitani S: J Tissue Eng Regen Med. 2011;5(2):146-50.*

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MSC: Take home messages

- Many preclinical studies reporting benefit
- Few clinical studies have promising results but: small number of patients, short follow-up, lack of control group
- Repair tissue is still more fibrocartilage than hyaline cartilage

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Unknown..

- Best source of cells ?
- Optimal number of cells ?
- Which method of delivery is superior ?
- Are cultured cells better than BMC ?
- Which type of scaffold ?
- Should we add growth factors ? Mechanical stimulation ?
- Is the repair tissue durable ?

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Cell Free Scaffolds

Autologous Matrix Induced Chondrogenesis (AMIC)

Matrix Assisted Chondrogenesis

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What is wrong with microfracture ?

- Not durable, results deteriorate after 5 years
  - *Goyal D. Arthroscopy. 2013;29(9):1579-88.*
  - *Mithoefer K. Am J Sports Med. 2009;37(10):2053-63.*
- Regenerate is always fibrocartilage
- Worse results in large & uncontained defects,
- Worse results in older patients & high BMI
  - *Mithoefer K. J Bone Joint Surg Am. 2005; 87(9):1911-20.*

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Post-op 1 year microfracture

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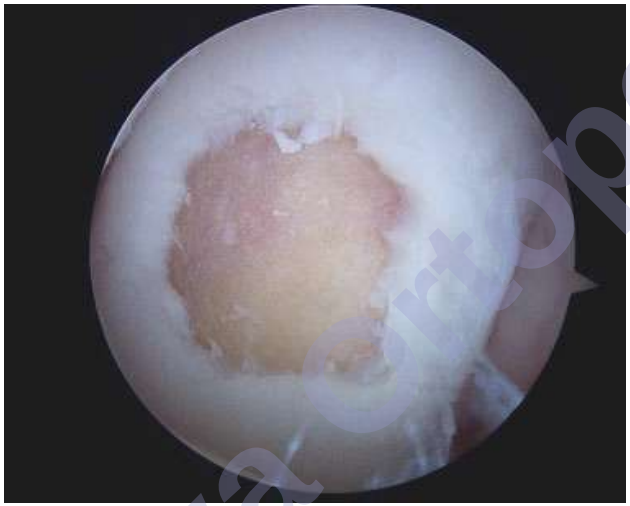
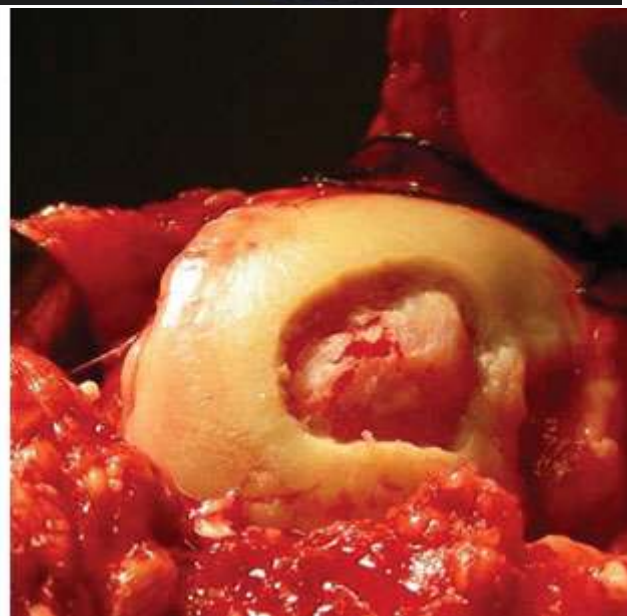
Ossification

Andreas H. Gomoll

Knee Surg 2012;25:9–16





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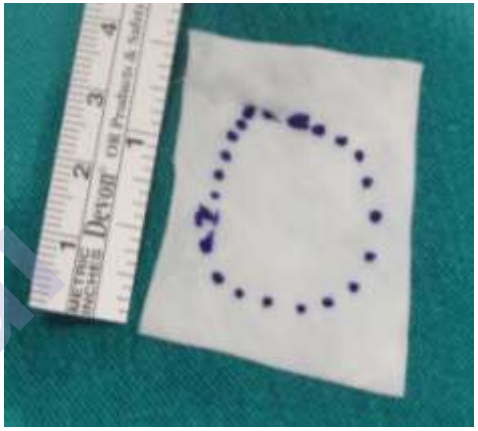
Cell free scaffolds



- Collagen
  - Chondroguide :Type I/III porcine collagen
  - Novocart : Collagen 3D matrix
- Hyaluronan based
  - Chondrotissue : PGA polymer-Hyaluronan
  - Hyalofast : Hyaff
- Hydrogels
  - Cart-Patch: Agarose-alginate
- Synthetic
  - Alpha Chondroshield: PGA
  - CAIS : Polycaprolactone-PGA
- Composite
  - BST Cargel: Chitosan, Collagen, HA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Matrix induced chondrogenesis

- Better histological & immunohistochemistry results compared to microfracture alone in sheep
  - *Erggelet C. J Orthop Res. 2009; 27(10):1353-60.*
  - *Gille J. Cartilage. 2010;1:29–42.*
- Matrix serves as a bioreactor, promotes cell migration & chondrogenesis, protects the repair tissue
  - *Erggelet C. Biomaterials. 2007 ;28(36):5570-80.*
  - *Kramer J. Cell Mol Life Sci. 2006;63(5):616-26.*

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Clinical results of AMIC using Chondrogide

Author	Number of patients	Follow-up	Results
Gille J	27	37	87% good clinical results
Gille J	57	24	Continued benefit at 2 years Defect size not important
Schiavone Panni A	17	36	77% good results
Kusano T		29	Incomplete & inhomogenous MRI filling

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Clinical results of AMIC using Chondrotissue

Author	Scaffold	Number of patients	Follow-up Months	Results
Siclari A	Chondro tissue	52	60	Significant clinical improvement 20/21 complete MR coverage
Siclari A	Chondro tissue	52	24	Sustained 2 year good results Biopsies in 4 pts hyaline like cartilage
Patrascu JM	Chondro tissue	1	24	Excellent clinical result & 2nd look arthroscopy hyaline like cartilage in biopsy

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v5.i4.444

World J Orthop 2014 September 18; 5(4): 444-449
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (5): Knee

Enhanced microfracture techniques in cartilage knee surgery: Fact or fiction?

Stefan Bark, Tomasz Piontek, Peter Behrens, Sabreen Mkalaluh, Deike Varoga, Justus Gille

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Stanish WD. Novel scaffold-based BST-CarGel treatment results in superior cartilage repair compared with microfracture in a randomized controlled trial.

J Bone Joint Surg Am. 2013;95(18):1640-50

- 41 scaffold+microfracture
- 39 microfracture alone
- 12 months follow-up
- Clinical results equal
- Greater lesion filling and superior repair tissue quality in MOCART scores in the scaffold group

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Anders SA. Randomized, Controlled Trial Comparing Autologous Matrix-Induced Chondrogenesis (AMIC®) to Microfracture: Analysis of 1- and 2-Year Follow-Up Data of 2 Centers. ***Open Orthop J. 2013;7:133-43.***

- 38 patients
- Continued improvement at 1 & 2 years
- KOOS & Cincinnati scores similar in all groups
- No difference seen in MOCART scores & MRI characteristics

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Matrix induced chondrogenesis

- Advantages
  - One step procedure
  - Cheaper than ACI/MACI
- Can be combined with BMC, PRP or MSC injections
  - *Dhollander AA: Knee Surg Sports Traumatol Arthrosc. 2011 ;19(4):536*
  - *Steinwahcs MR:Arthrosc Tech. 2014 Apr 21;3(2):e279-82.*
- Problems
  - Regenerate is still more fibrocartilage than hyaline
    - *Gigante A: Int J Immunopathol Pharmacol. 2011;24(1 Suppl 2):69.*
  - Ossification still a problem

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Unknowns ..

- What size of the lesion is appropriate ?
  - Small – medium ?
- Which scaffold is better ?
- When should we add cells ?
- What growth factors are helpful ?
- Is it durable ?

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Turkish Society of Sports Traumatology Arthroscopy & Knee Surgery

Cartilage Repair Committe

Thank you …

www.ortoklinik.com

www.cankayaortopedi.com