

Université Claude Bernard  Lyon 1

Overview about scaffold

Pr E Servien, MD PhD

Hôpital de la Croix-Rousse
Val d'Isère 14

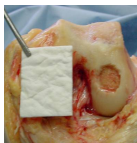
   Hôpitaux de Lyon

Cartilage scaffold

- Many studies (basic science)
- Level 1 studyare missing
- ACIMACI

Cartilage scaffold

- History ?
- Start 20 y ago ...



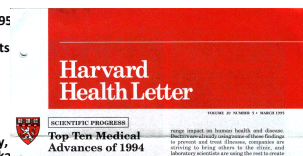
1994

N Engl J Med 1994 Oct 6;331(14):889-95

Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation.

Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L.

Department of Orthopedic Surgery, University of Göteborg, Sahlgrenska University Hospital, Sweden.

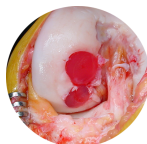
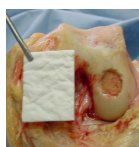


Cartilage repair



- Scaffolds / Matrix 3D
- Cells (cultures?)

- ➔ Chondrocytes (phenotype)
- ➔ Stem cells
- ➔ 1 vs 2 steps

- Growth fact.
- Gene therapy



ACI versus OCG

		Clinical	Repair
OCG		69%	34%
ACI		88%	82%

Bentley, JBJS, 2003

ACI vs Microfracture

- ❖ **Randomized trial 80 patients Level 1**
- ❖ **2 groups improvement @ 2 & 5 years**
(ICRS, Lysholm, SF 36, Tegner)
- ❖ **9 failures (22%) in each group @ 5 Y**
- ❖ **Failures occurred earlier in ACI**
- ❖ **84% biopsies histological evaluation**
- ❖ **No correlation with clinical outcome**

« [...] no significant difference, although there were a tendency that ACI results in more hyaline repair cartilage than microfracture.»

G. Knutsen, JO Drogset, L. Engebretsen & col 2006

Autologous Chondrocyte Implantation

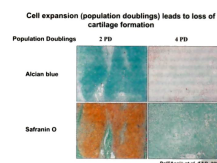
- ❖ **Osteochondral defect**
- ❖ **Cells distribution**
- ❖ **Cells differentiation**
- ❖ **Delamination**
- ❖ **Technically demanding**



Abandoned for "MACI"

scaffold

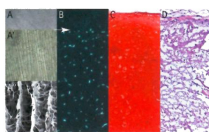
TIGENIX
DEFINING THE CUTTING EDGE IN REGENERATIVE MEDICINE



"[...] incorporate identity characterization based on in vivo biological function."

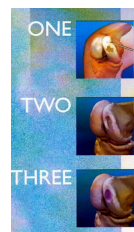
chondroselect

Aesculap Orthopaedics
Novocart 3D



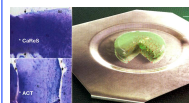
B. BRAUN
SHARING EXPERTISE

MACI



genzyme
Biosurgery

CaReS®



"[...] 3D cell cultivation directly in the transplant without further processing."

ARS ARTHRO
THE ART OF MOBILITY

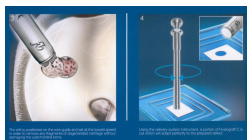
Geistlich®
Biomaterials



Leading Regeneration in Cartilage Repair

Geistlich®
Biomaterials

Hyalograft® C : arthroscopy



- Benzyle ester of hyaluronic acid (HYAFF®)
- Multicentric, 175 patients @ 2 – 4 Y
- 93% improvement @ 46 months
- Adhesive properties, no patch, MIS
- No histology

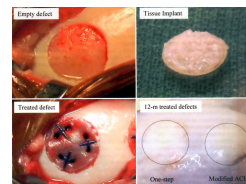
AMIC

Autologous Matrix Induced Chondrogenesis

Autologous Matrix Induced Chondrogenesis (AMIC) for focal Chondral defects of the knee. First clinical & MRI results.

- 43 patients – 6 to 24 months
- Stem cells from μ -fracture +
- Bilayer I-III collagen matrix (Geistlich® biomaterials)
- **63.7% improved**
- Pain reliefe (VAS) 5.7
- **No histology**

DePuy Mitek



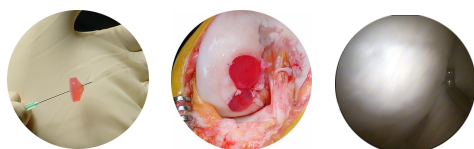
In vivo evaluation of OA one step autologous cartilage resurfacing technique (CAIS) compared to a modified ACI technique in a long term equine model.

- Morcelized cartilage fragment
- vs pre-seeding cells / scaffold
- Collagen membrane (SIS)
- 15 mm defects in 16 horses
- Assessment 4, 8 & 12 months
- Histology, immunohistochemistry

"There were areas of hyaline-like tissue present with both cell-based treatment technique, but were better with the one-step procedure"

Cartipatch®

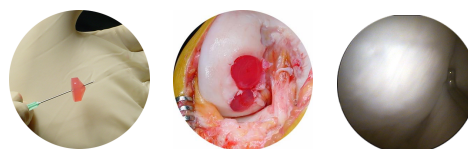
A french history



Cartipatch®

Implantable device

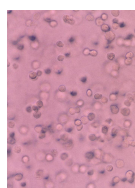
- ❖ 3D Matrix
- ❖ Solid implant
- ❖ Chondral defects
- ❖ Osteochondral defects



Cartipatch®

Cells seeded in a gel

- ❖ Autologous cell culture
- ❖ Distribution
- ❖ Differentiation
- ❖ Viability (90%)

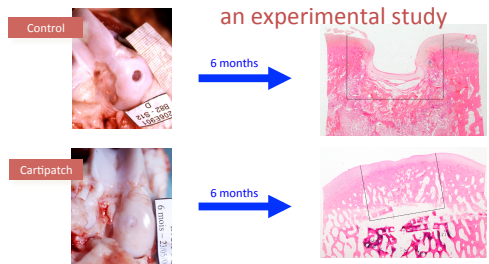


VIABILITY & PHENOTYPES
STUDY OF HUMAN
CHONDROCYTES SEED
IN A NEW GEL FOR
CARTILAGE REPAIR
Poster n° 583
ICRS Gent 2004

Cartipatch®

Sheep model

Before our clinical trial we leaded an experimental study



ICRS Toronto 2002

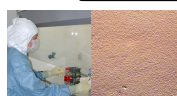
Cartipatch®

TBSF



Harvesting : 200 mg
Autologous serum 200 mL

Culture P3...
>10.10⁶ per mL



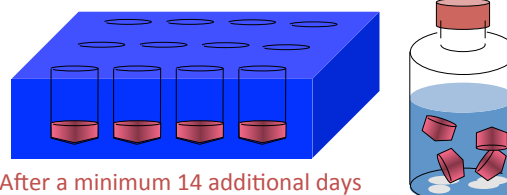
Autologous chondrocytes
were multiplied
in monolayer culture
during 3 or 4 weeks



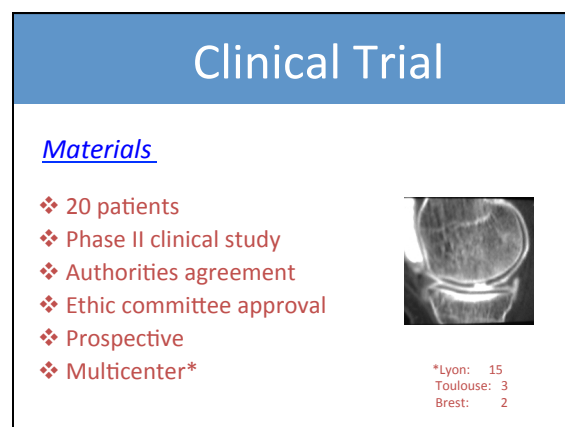
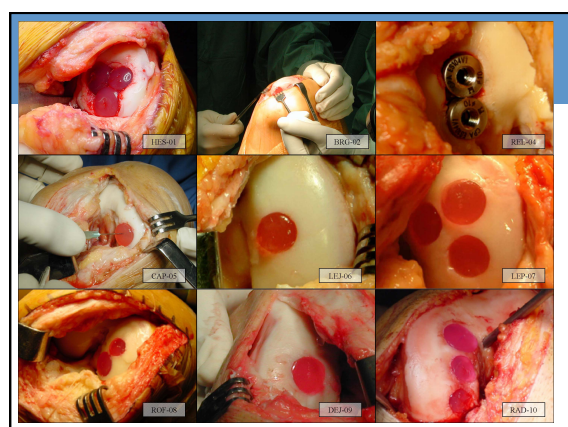
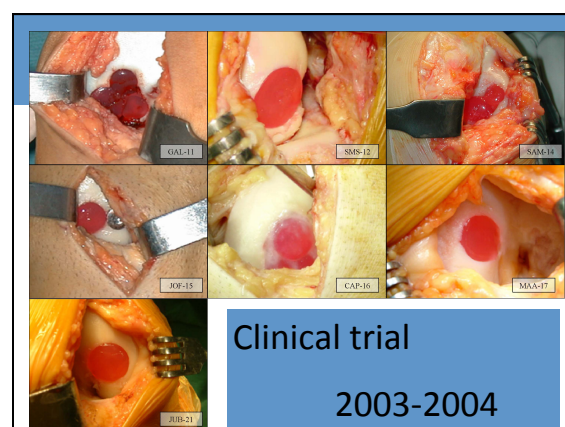
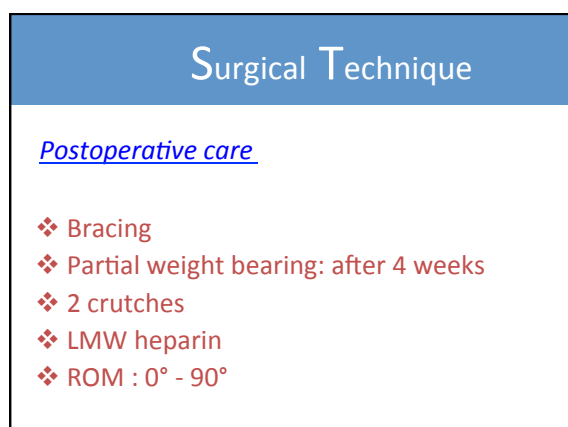
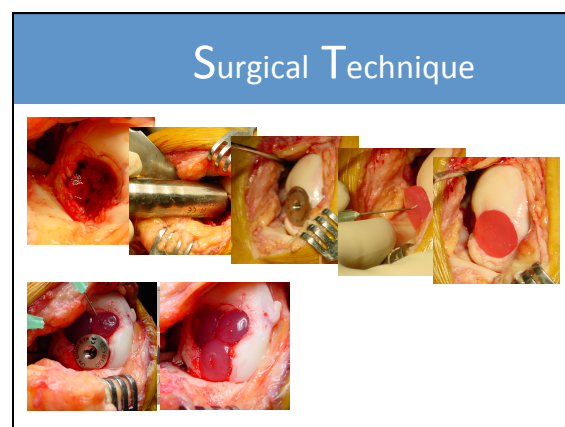
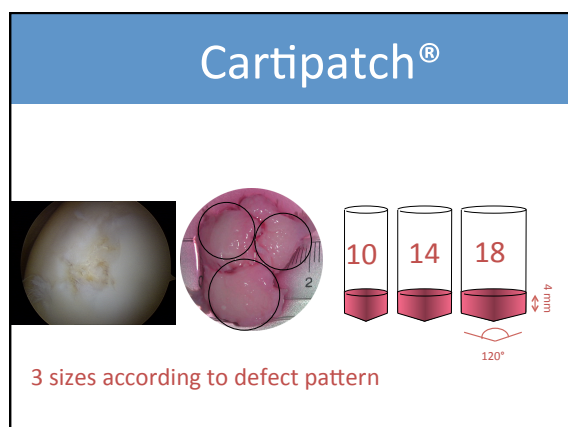
Gel matrix
Incub. >14 d

Cartipatch®

Cells are seeded in hydrogel matrix to provide cylindrical grafts of 10, 14 and 18 mm diameter.



After a minimum 14 additional days incubation, grafts were implanted in a mosaic in press-fit to fill the lesion



Clinical Trial

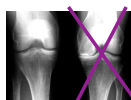
Inclusion

- ❖ < 50 years old
- ❖ Subjective IKDC < 55
- ❖ Condyle
- ❖ ICRS grade 3 or 4



Exclusion

- ❖ Kissing lesion
- ❖ ACL or meniscal tear
- ❖ Malaligned limb ($\pm 5^\circ$)



Clinical Trial

Assessment

- ❖ ICRS evaluation package (3, 6, 12, 24 months)
- ❖ X-ray (Rosenberg view)

- ❖ MRI
- ❖ Arthroscopy
- ❖ Biopsy - Histology

Year 2

Clinical Trial

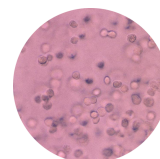
20 patients involved —→ 17 implanted

- ❖ Jan. 2003 —→ Feb. 2004
- ❖ Age: 28.9 (17 – 42)
- ❖ 15 males / 5 females
- ❖ OCD : 11 / Traumatic : 8 / ON : 1
- ❖ Previous mosaicplasty : 2
- ❖ Lesions : 3.2 cm² (1.0 to 6.7)

Clinical Trial

Patient	Culture + incubation (days)
HES-01	50
BRG-02	54
AUB-03	38
REL-04	40
CAP-05	44
LEJ-06	49
LEP-07	48
RDF-08	56
DEJ-09	55
RAD-10	43
GAL-11	42
SMS-12	48
JOF-15	40
CAP-16	54
MAA-17	57
JUB-21	62
mean	48 (7 weeks)

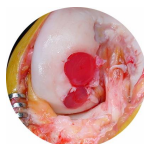
Control



Phenotype
Viability
Cell Density

Clinical Trial

Patient	10 mm graft	14 mm graft	18 mm graft
HES-01	1	2	0
BRG-02	1	1	0
AUB-03	1	0	0
REL-04	2	0	0
CAP-05	0	1	0
LEJ-06	1	0	0
LEP-07	3	0	0
RDF-08	1	1	0
DEJ-09	0	1	0
RAD-10	2	1	0
GAL-11	2	1	0
SMS-12	0	0	1
JOF-15	1	1	0
CAP-16	2	1	0
MAA-17	0	1	0
JUB-21	0	0	1
mean	1.1	0.7	0.1



Clinical Trial

- ❖ Procedure < 1 hour
- ❖ 1.9 implant / lesion
- ❖ Full coverage
- ❖ No shrinkage or lose implant
- ❖ No local complication
- ❖ No clinical inflammatory response
- ❖ No reoperation
- ❖ 2 deep venous thrombosis

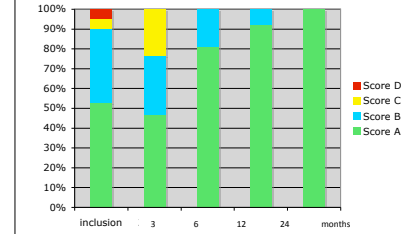
Clinical Trial

IKDC subjective score

Score	Inclusion	3 months	6 months	12 months	24 months
Number	20	16	17	13	5
Mean (Evolution)	36.6	54.3 (+17.1)	69.5 (+32.8)	71.7 (+36.5)	85.2 (+51.6)

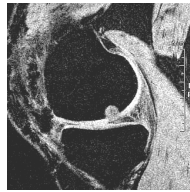
Clinical Trial

Objective IKDC score



Clinical Trial

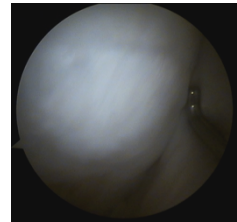
- ❖ MRI
- ❖ Arthroscopy
- ❖ Histology @ Y2



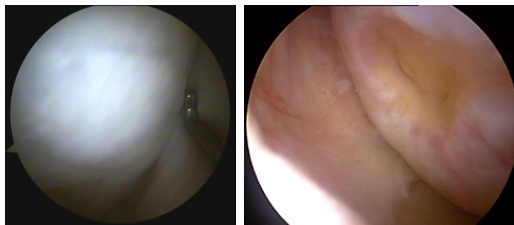
T1 weighted gradient echo

Clinical Trial

- ❖ MRI
- ❖ Arthroscopy
- ❖ Histology @ Y2



Cartipatch®

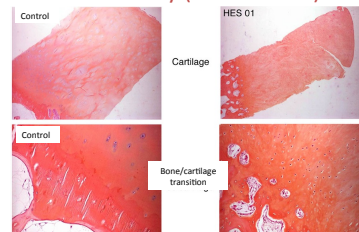


HES-01 : score = 12

SMS-12 : score = 0

Clinical Trial

Histochemistry (Biomatech®)




Biposies confirmed a well integrated cartilage tissue in the subchondral bone


Clinical Trial

Immunology (Novotec®)

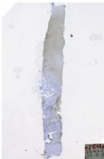
Collagène I



Collagène II

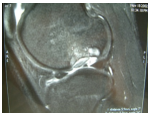


Agrécannes

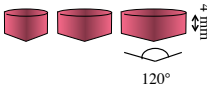


Immunohistochemistry showed collagen 2 and aggrecan impregnation of cartilage.

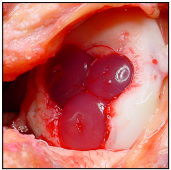
Patient 1 (HES-01)

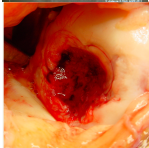
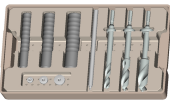


10 14 18



4 mm
120°



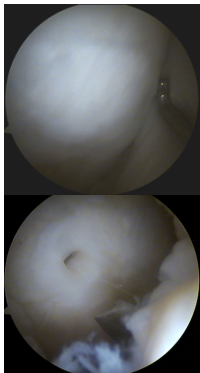



Osteochondritis dissecans
(implantation)

Patient 1 (HES-01)

Arthroscopy (2 years)

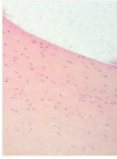
Biopsy (2 years)



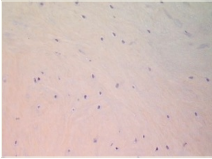
Patient 1 (HES-01)

Histology (2 years)

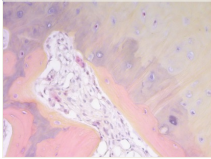
Surface




Intermediate zone





bone/cartilage transition





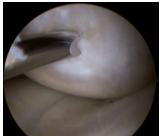
Patient 2 (BRG 02)

Failure of mosaicplasty (implantation)





Patient 2 (BRG 02)

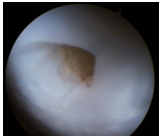
Biopsy (2 years)



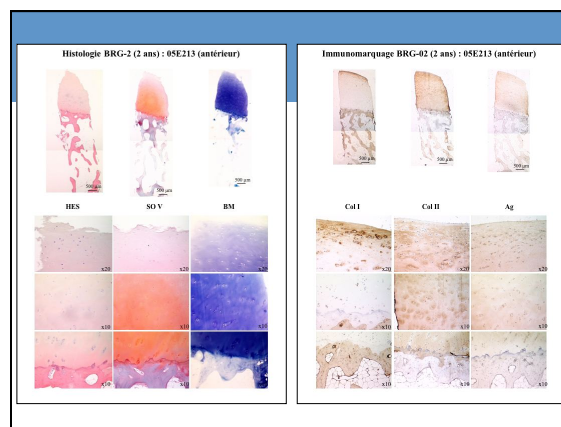
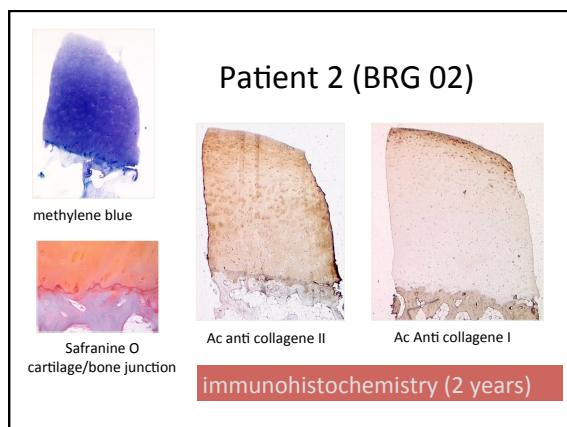
Site of biopsy



Biopsy



After biopsy



Relevances

- ❖ Accurate coverage
- ❖ Easy implantation
- ❖ No related complication
- ❖ Clinical short term improvement
- ❖ Promising histological aspect

Autologous chondrocyte implantation in a novel alginate-agarose hydrogel
OUTCOME AT TWO YEARS

T. A. S. Schell, P. Verdonk, P. Chambat, E. Delamont, J.-E. Prid, L. Rattmann, P. Neyret

Autologous chondrocyte implantation is an established method of treatment for symptomatic articular defects of cartilage. CARTIPATCH is a monolayer-expanded cartilage cell product which is combined with a novel hydrogel to improve cell phenotypic stability and ease of surgical handling. Our aim in this prospective, multicenter study on 12 patients was to investigate the clinical, radiological, arthroscopic and histological outcome at a minimum follow-up of two years after the implantation of autologous chondrocytes embedded in a three-dimensional alginate-agarose hydrogel for the treatment of chondral and osteochondral defects.

62% (n=8) with hyalin cartilage ingrowth

Follow-up at 5y

- ❖ MRI

- What next ?
- Cartipatch II Study
- Randomized Control Trial (2008-2010)
- Multicenter
- Cartipatch versus mosaicplasty
- N=60...
-

- What next ?
- Cartipatch II Study

- Femoral condyle defect
- IKDC & MRI at 2y fu
- first results ...
-

•

- What next ?
- Cartipatch II Study

- Femoral condyle
- IKDC & MRI at y fu
- first results ...
-BUT no more financial support

•

- What next ?
- Cartipatch II Study

- 15000 - 20000€ for Cartipatch
- Need more evidence based medicine
- Cartipatch® ABANDONED

•

CONCLUSION

Future ?
decellularized extracellular matrix (ECM) scaffolds
Need more level 1 STUDY for treatment support