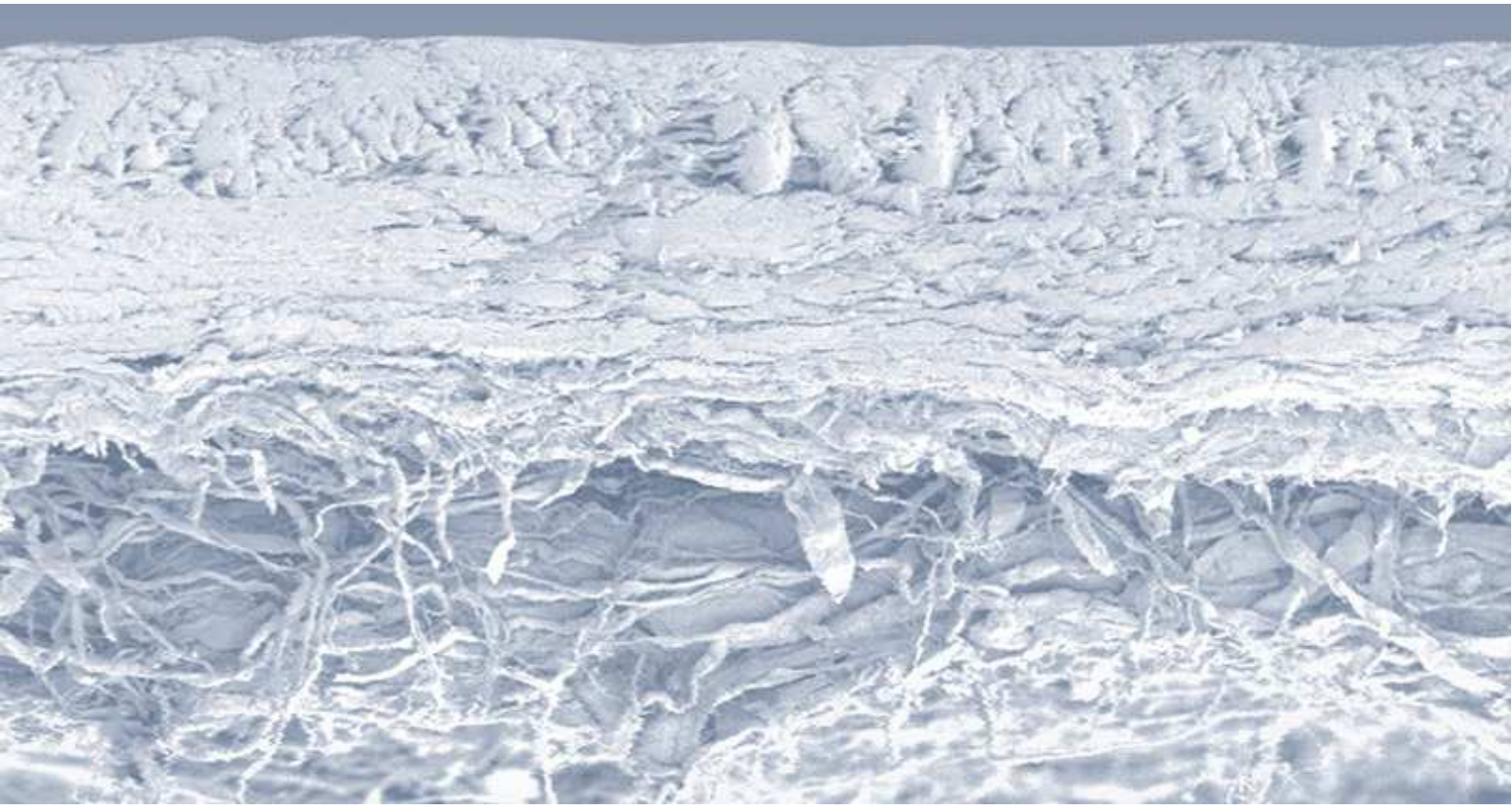
Cartilage Regeneration Newsletter



Content:

Geistlich Biomaterials
leading regeneration

Introduction

Up until the last century, the goal of medicine and surgery was twofold, **firstly to prevent the loss of health, while the second was to recover health that had been lost.**
Both goals, together with development of medical science and growing affluence in some countries, have helped to increase longevity dramatically. While the life expectancy in the first half of the last century was 50 years, reaching an average of 80 years nowadays is normal.
Longer life expectancies, combined with greater desire to maintain an "ideal body" through a balanced diet and regular exercise, have led to a new goal: achieving a long and high-quality life.

Biology and biologic solutions are playing an increasingly important role in tissue regeneration. Using a more natural biologic approach, hopefully we will abandon the notion that we should substitute a degenerative joint with a prosthetic one.

In light of recent research, it seems clear that we should pay closer attention to the role biologic interventions can play in the treatment of various orthopaedic problems.
During the ICRS many speakers emphasized the positive effect tissue engineering technology will have years from now: **"The potential of biologics in orthopaedics is not only to manage devastating congenital or traumatic problems but also to prevent or slow degenerative processes in order to maintain the activity and function of our aging population."**

This newsletter provides information about the presence of Geistlich Biomaterials in the cartilage repair area with special focus on recently published scientific and clinical papers.

Geistlich Biomaterials
March 2006

Review of the 6th ICRS Meeting

The ICRS is the main international scientific meeting for cartilage repair. Approx. 650 scientists and surgeons attended this well focused, biannual event from 9-11 January, 2006 in San Diego, US.

Traditional ACT (now referred as to ACI) as described by Lars Peterson and Matts Brittberg remains a much debated technique more that 11 years after it was first described. Recent variations include the replacement of the periosteal patch with a collagen membrane and the implantation of cells seeded within a matrix (MACI – Verigen/Genzyme, CACI). To avoid harvesting cartilage, thus creating a further area of damage, bone marrow derived stem cells have been investigated to provide an alternative to culture expanded chondrocytes.

Therefore most of the scientific contributions evolved around the above mentioned and closely related topics.
The majority (approx. 68) of presentations involved ACI (Autologous Chondrocyte Implantation) and MACT/MACI (matrix associated chondrocyte transplantation). MACI and it's derivatives was directly mentioned in about a third of those abstracts, **some authors (Bentley group) presented good long term follow up results, which included early data with Chondro-Gide® (not mentioned) but have named the package ACI-C (C for collagen covered).**
An Australian group led by Dr. T. Ackland also conducted MACI as well as ACI trials with Chondro-Gide®, later called "CACI".

An important presentation was Dr. Gunnar Knutsen's – 5 year follow up results of ACI vs. Microfracture. This showed that there appears to be no difference in outcome between the two procedures in patients with defects primarily on the femoral condyle. This generated much discussion regarding the role of expensive cell based technologies in the future.

Interesting as well were the debates about clinical outcome and how to measure and evaluate the success of an operation.
Keenly debated topics included the measurement of the quality of cartilage repair (Histology vs. MRI) and the use of a variety of knee scores (Lysholm, Cincinnati, SF-36) to evaluate the functional and most important, subjective outcome, in order to accurately reflect the patient's progress and well-being.

Also note, the ICRS plans to host a central ICRS score database in the future.

Other topics included scaffold engineering, rehabilitation as key for a successful intervention, treatment of osteochondral defects and lectures on osteoarthritis.

Geistlich Presentations/Seminars

a. Jan 10th, 2006: Geistlich Workshop: "Modern Biological Cartilage Repair Methods" (Speaker: Dr. Behrens – Overview, Dr. Steinwachs – ACT, Dr. Anders – AMIC – first results, Dr. Gellissen – MRI evaluation)

b. Key Note Lecture Prof. Jakob, Fribourg: "Autologous Membrane Induced Chondrogenesis after Marrow Stimulation" – critical evaluation of AMIC case reports

c. Presentation Dr. Bhosale, Oswestry: "Autologous Chondrocyte Implantation: 2-To-9 Year Oscell Experience"

Geistlich was one of the Silver Sponsors of the ICRS 2006. The booth attracted scientists and surgeons from all over the world.

Posters/Abstracts

Autologous Matrix Induced Chondrogenesis (AMIC) for focal chondral defects of the knee - first clinical and MRI results

S. Anders [1], J. Gellissen [2], W. Zoch[4], P Lobenhoffer4, J. Grifka [1], P. Behrens[3]

Dept. Of Orthopaedic Surgery, University Of Regensburg, Asklepios Klinikum, Bad Abbach, Germany [1], Dept. Of Radiology, University Of Lübeck, Lübeck, Germany [2], , Dept. Of Orthopaedic Surgery, University Of Lübeck, Lübeck, Germany [3], Dept. Of Trauma And Reconstructive Surgery, Henriettenstiftung, Hannover, Germany[4]

Introduction: Focal chondral defects of the knee joint can be dealt with by bone-marrow stimulating techniques like microfracturing (MF). By penetrating the subchondral layer emerging Mesenchymal stem cells are used for the repair process. Microfracturing shows good results for smaller defects up to 2 cm^2 while in larger defects early secondary degeneration has been observed. Autologous Matrix Induced Chondrogenesis (AMIC) combines MF with the application of a collagen matrix for covering the defect, hosting of the stem cells and mechanically stabilizing the blood clot.

Methods: 43 patients (30m, 13f, mean age 37y (18-53y)) with focal chondral defects of the knee joint (ICRS III-IV) of condyle, trochlea or patella were treated by standardized MF and application of a porcine collagen type-I/III bilayer matrix (Geistlich Biomaterials, Wolhusen, Switzerland). Clinical
Scores and MRI scans were evaluated with a follow-up of 6 to 24
months. 33 patients had at least one intervention (1-4) of the knee before. The mean defect size was 3.2 cm^2 (1.3-7.5cm^2).19 defects were caused by trauma.

Results: All patients considered their knee as abnormal (78%) or severely abnormal (22%) pre-operatively in comparison to the contra-lateral knee. The ICRS functional status showed an improvement from 100% ICRS III/IV to 66.7 % ICRS II/I. For 63.7% of all patients knee function was perceived as improved, for 27.2% unchanged and for 9.0% worsened after self-evaluation.
Pain decreased considerably from 5.7 to 1.9 (10=max.) on the visual analogue scale. The MRI follow-ups showed a reasonable filling of the defect with no prolonged effusion.

Conclusion: Microfracturing in combination with a collagen matrix (AMIC) can be considered feasible as a minimally invasive single step procedure for the repair of focal cartilage defects without using cultured chondrocytes. The first results concerning clinical functional improvement, pain reduction and patient satisfaction as well as defect filling in MRI are promising.

Comments: Despite the small cohort of patients; limited follow-up (6 months in some cases) and a variety of chondral injury sites including the patella, the improvement in pain relief is very promising.
We know from experience with previous publications that repaired and regenerated cartilage may take up to two years to mature, and so would expect to see these functional and subjective scores improve over the next 12 to 18 months.
This is one of the first presentations of the new AMIC (Autologous Matrix Induced Chondrogenesis) technique, which is a logical evolutionary step on from microfracture. By trapping the first few millilitres of bone marrow blood in the Chondro-Gide® membrane, a higher concentration of Mesenchymal stem cells is stabilised in the defect than with the traditional microfracture technique.

MR imaging protocols for optimized visualization of a collagen matrix used for cartilage repair

J Gellissen [1], NO Wendler [2], TK Helmberger [1], P Behrens [2]

Department Of Radiology, University Of Luebeck, Germany, Luebeck, Germany [1], Department Of Orthopaedic Surgery, University Of Luebeck, Germany, Luebeck, Germany [2]

Objective: To compare the performance of different MR pulse sequences for high-contrast and high-spatial-resolution imaging of collagen matrices.

Material and Methods: Chondral resection 2cm² in size was carried out resembling a grade- IV defect of a porcine femoral condyle. A bilayer matrix consisting of collagen I/III (Chondro-Gide®, Geistlich Biomaterials, Switzerland) was dissected and fixed with fibrin glue. MR-imaging was conducted using a 1.5T device (Siemens, Germany). 27 pulse sequences were varied with regard to their main properties (T1- and T2-weighted spin-echo or gradient echo), mode of volumetric data acquisition (2D, 3D), image matrix, slice thickness (1.3–2mm) and the choice of fat saturation techniques. Signal intensities were measured in the subchondral layer, collagen matrix, adjacent cartilage and fluid. Contrast-ratios were computed.

Results: Contrast-ratios of the matrix vs. adjacent fluid/subchondral layer were calculated with values 0.05- 0.88±0.04 and 0.03-0.99±0.05 respectively. While highest contrast was achieved using PD-weighted TSE-sequences with low echo-time, high image matrix and thin sections without fat saturation, T1-weighted IR-sequences yielded an intermediate contrast-ratio with optimal depiction of the defect depth. 5 sequences were unable to differentiate between subchondral layer and matrix.

Conclusion: Appropriate MR imaging parameter selection is crucial for optimized visualization of the matrix and has the potential to provide information about matrix integrity and success of cartilage repair.

Comments: As cartilage repair and regeneration procedures emerge from the realm of research and into everyday clinical practise, we need to develop efficient and accurate non-invasive means of monitoring the repair tissue in-vivo.
MRI has emerged as the modality of choice for visualising soft tissues, including cartilage. Unfortunately the T1 and T2 images routinely used do not give the optimum information and detail we now routinely demand. This has led radiologists to explore and describe alternative protocols such as FSE (Fast Spin Echo) and the PD-weighted TSE-sequences described above.
As not every patient is willing or suitable for dGEMRIC contrast scanning and 3T scanners are still a long way off for most hospitals, it is vital that we are able to achieve the best resolution and contrast from the current technology.

Autologous Chondrocyte Implantation Compared With Microfracture In The Knee (Five Year Follow Up)

G Knutsen [1], JO Drogset [3], L Engebretsen [2], T Grøntvedt [3], V Isaksen [1], TC Ludvigsen [2],S Roberts5, E Solheim4, T Strand 4, O Johansen [1]

University Hospital North Norway, Tromso, Norway [1], Oslo Orthopaedic University Clinic, Oslo, Norway [2], , University Hospital Trondheim, Trondheim, Norway [3], Deaconess University Hospital Bergen, Bergen, Norway[4], Robert Jones And Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire, United Kingdom[5]

Introduction: New methods have been used, with promising results, to treat full-thickness cartilage defects, but no method has been judged superior. The objective of the present study was to compare autologous chondrocyte implantation (ACI) to microfracture in a randomized trial of knees with chondral and osteochondral lesions.

Methods: 80 patients with symptomatic single chronic cartilage defects on the femoral condyle in stable knees without general osteoarthritis were included. We used the ICRS, Lysholm, SF- 36 and Tegner forms to collect data. Results from clinical follow-up including arthroscopy and biopsy at two years postoperatively, are published. This abstract presents an update with clinical results at five years.

Results: At two and five years both groups had significant clinical improvement. According to the SF-36 physical component (PCS), the improvement in the microfracture group was significantly better than the ACI group. At two years there were two failures in the ACI group, and one in the microfracture group. Five years postoperative each group had nine failures (22%). Failures occurred earlier in the ACI group. Biopsies were obtained from 84% of the patients at two years and histological evaluation of repair tissues showed no significant difference between the two groups, although there was a tendency that ACI results in more hyaline repair cartilage than microfracture. We did not find any correlation between histological quality and clinical outcome.

Conclusions: In our trial, we found that ACI and microfracture procedures yielded similar clinical results in patients with cartilage lesions of the femur. Nine failures occurred in both groups. Among the failures those in the ACI group occurred earlier. There was no significant difference in macroscopic or histological results between the two treatment groups and no correlation between histology and clinical outcome.
Level of Evidence: Therapeutic study, Level I-1a Randomized controlled trial.

Comments: Whilst this is an excellent study and we eagerly await the publication of all the results, it is clear that neither simple Microfracture nor ACI utilising a periosteal cover are the solutions to our Chondral repair and regenerative needs.
It is for these reasons that Geistlich has developed innovative materials and techniques for the treatment of cartilage lesions. The AMIC technique, improving microfracture, and Chondro-Gide® ACI, improving periosteal ACT, procedures utilise the latest tissue bioengineering technology to help nature give your patients the best possible outcome.

Microfracture as Treatment for Full Thickness Chondral Lesions in a Group of Athletes

AW Gobbi [1], RA Francisco [1], P Nunag [1], K Malinowski [1]

Orthopaedic Arthroscopic Surgery International, Milan, Italy [1]

Purpose: Prospectively investigate the outcome of microfracture technique when applied to full thickness chondral lesion of the knee in a group of athletes.

Methods: From 1991 to 1999, 109 patients were treated with microfracture technique. We prospectively followed up 53 athletes that satisfied our inclusion criteria. Average age was 38 years (range19 to 55) and mean follow up was 72 months (range: 36 to 120 months). Aetiology, clinical signs, symptoms and activity level were noted pre-operatively and at final follow up. Lysholm, Tegner, IKDC and functional tests were utilized. Intra-operatively location, size of the lesions and associated pathologies were recorded. Roentgenograms, MRI or CT scan were done before the treatment and at final follow up.

Results: Etiologic factors were mostly related to sports micro trauma (37.5%) and macro trauma (21%), while 37,5% of our patients did not report any traumatic aetiology and 4% showed patellar malalignment. The most common location was medial femoral condyle (61%). Knee pain and swelling improved in 70%, tibio-femoral crepitus in 60%. Hop test was normal in 70% at final follow up. Subjective evaluation was 40/100 preoperatively and 70/100 at final follow up. Lysholm was 56.8 pre-op. and 87.2 final. IKDC revealed: 0 A, 3 B, 40 C and 10 D preoperatively while at final follow up 70% scored A or B. Tegner improved at 2 years from 3.2 to 6 however at final follow-up 80% showed a decline in sport activity level (Tegner 5).

Conclusion: Microfracture technique can offer clinical, functional and subjective improvement in athletically active patients. However because of the decline in sports participation over time, microfracture may not be the definitive procedure for the athlete's knee and other procedures may be indicated in the future.

Comments: Microfracture is often quoted by many authors as being the most cost-effective treatment modality for an isolated chondral lesion. This paper highlights some of the weaknesses with simple microfracture in an active, sporting sub-population. Possible reasons for the noted decline in sporting activity at the final post-op follow up include the high percentage of fibrocartilage which forms after microfracture. With the greater stresses placed on chondral repairs during sporting activities, a less stable repair tissue, such as fibrocartilage is less likely to stand up to the demands placed on it. The aim of the AMIC technique is to create the ideal biological environment by trapping the first and most important 'super-clot' formed during the microfracture stage in the defect where the Mesenchymal stem cells are able to differentiate into chondrocytes and so form a healthy hyaline cartilage repair. This will be stiffer, stronger and more stable the fibrocartilage generated from simple microfracture.

Autologous Matrix Induced Chondrogenesis – A One Year Follow-Up With Clinical And MRI Results *

M Barrow [2], P Behrens [1], R Posner [1], I M Rogan [1]

Morningside Medi-Clinic, Johannesburg, South Africa [1], University of The Witwatersrand, Johannesburg, South Africa [2]

Introduction: The technique of microfracturing is well described and is shown to provide a clinically acceptable outcome in terms of pain relief and function for the majority of patients. Microfracture is however known to generate a high percentage of fibrocartilage which is well documented as being inferior to hyaline cartilage in terms of stiffness and stress resistance.
We describe a novel method of chondral repair using Mesenchymal stem cells released into the defect following microfracture. The cells are then stabilised by and within a Chondro-Gide® collagen I/III bilayer membrane (Geistlich biomaterials, Wolhusen, Switzerland).
Materials & Method: Between March 2002 and December 2003 eleven (11) patients were operated on for traumatic chondral defects using the AMIC technique and followed prospectively. The mean age was 29 years (19-40 years) and all patients had undergone at least one previous surgical procedure for the chondral defect (range: 1-9). Lesions were located on the patella (1); MFC (4); LFC (3); Trochlea (1) and Tibial Plateau (2). 10 Patients were available for follow-up and MRI scanning at 12 months.
Results: At 12 months post-op the mean subjective functional score had improved from 3.5 to 6.6 (max 10) and the pain had decreased from 6 to 2 on a 10 -point VAS. MRI demonstrated: No marrow oedema (8 patients); normal graft-host interface (7); full -thickness graft integration (10); smooth contour of articular surface (7); remaining effusion (4); sub-chondral sclerosis (5) and 75-100% graft fill in 7 patients.
Discussion: AMIC (Autologous Matrix Induced Chondrogenesis) is an exciting new technique utilising the bodies own Mesenchymal stem cells supported by a Chondro-Gide® matrix to repair a chondral defect. This study has shown a clear improvement in both pain and function, even at 12 months post-op when repair tissue is still remodelling.
This cohort of patients will continue to be followed prospectively.

Comments: It always takes a leap of faith to begin using any new technique or product, and this does not usually happen unless you are satisfied with the scientific principles underlying this. The AMIC (Autologous Matrix Induced Chondrogenesis) technique certainly has a strong heritage. Microfracture is clinically well proven to generate healthy fibrocartilage, while the Chondro-Gide® membrane has been extensively used in ACI and is the original collagen I/III membrane with an excellent track record, having been utilised in all of the ACI trials reporting medium to long term results, including those by Bentley et al and Ackland et al. It was from these two seemingly opposed repair technologies that AMIC was born.
When considering the results of this cohort of patients it is worth noting that each patient had undergone not only previous surgery for their chondral lesion, but also for numerous other pathologies such as ACL reconstruction, meniscectomy, re-alignment procedures and ORIF. These patients were all desperate to regain a pain-free functional knee. It has been postulated that all of the previous chondral surgeries failed due to the multiple intra-articular pathologies generating such forces that the repair fibrocartilage could not stand up to them and broke down. Despite the lack of histology in this cohort, the MRI scans demonstrate that the chondral repairs are solid and stable, even at this early stage. There is no reason to think they will not continue to improve as the repairs mature.

- (This abstract was revised after the ICRS by Dr. Kili)

The first prospective clinical outcome study to ACT by use serum-free medium for cell cultivation

MR Steinwachs [1], PC Kreuz [1], C Huber [1]

Cartilage Transplantation Unit, Dept. Of Orthopeadic And Trauma Surgery, University Hospital Freiburg, Freiburg, Germany [1]

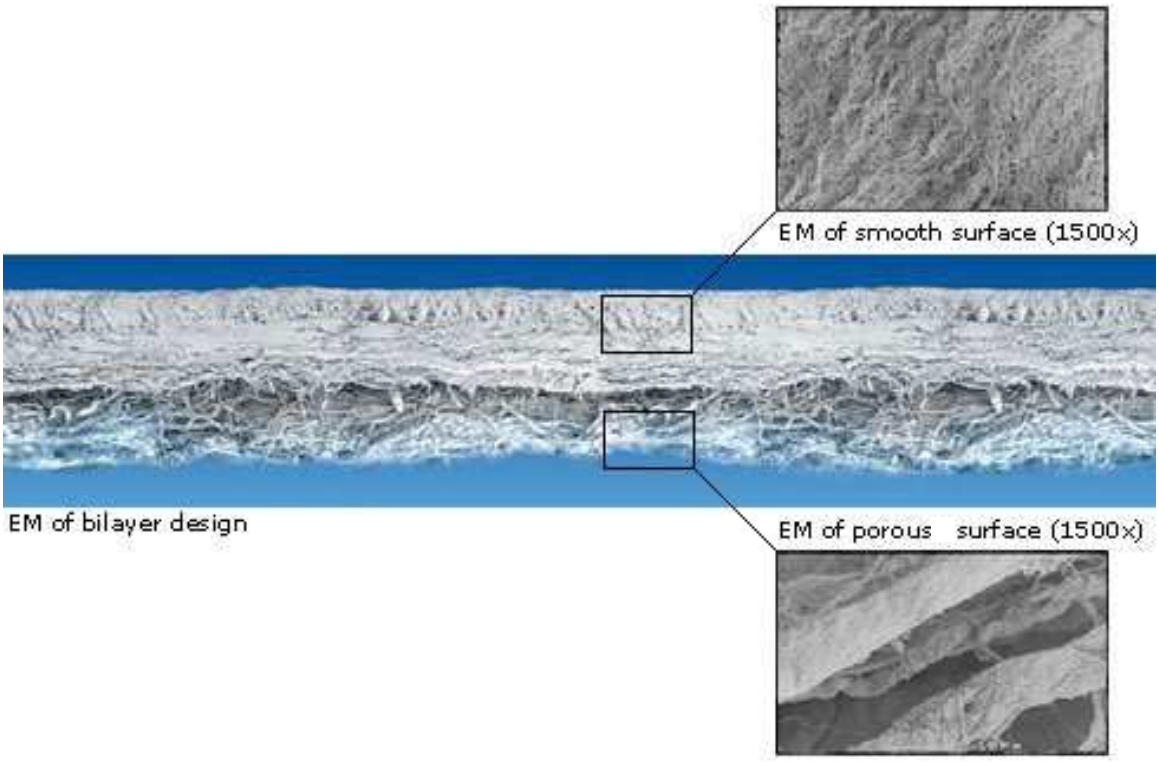
Introduction: The cartilage repair with the ACT in combination with a Chondro-Gide® collagen membrane is based on the abilities of the transplanted chondrocytes. Mitotic activity and biochemical synthesis rates are adjusted by cytokines and growth factors in the serum compounds. In the present study the clinical outcome was compared to ACT with serum expansion (BS) and serum-free cell expansion by means of 4 different clinical scores prospectively more than 1 year post OP.

Method: In the year 2003 and 2004 sixty-eight patients became because of a symptomatic grade III / IV cartilage defect in the knee joint a ACT in combination with a Chondro-Gide® collagen membrane surgically. Only 56 patients (82,4%) could be documented completely. All patients were given a further checkup preeoperativ, 6 months and 12 months postoperative clinically with ICRS-, Cincinnati, Lysholm and Tegner score. In group A were 28 patients (age: 34.4 ±8.4 years, defective size 5.7 ± 2.0 cms ^{2}, BMI 24,1 ± 2.7)) their cells with bovine serum have been cultivated. In group B became with 28 patients (age: 34,9 ± 8.8 years, defective size: 5.0 ± 1.4 cms ^{2}, BMI 24,0 ± 2.8) a serum-free cell cultivation applied.

Results: Over all conditions the 56 patients profited significantly from the applied therapy ($p \leq 0,05$). No significant differences could be proved between the groups A and B post surgically in all 4 clinical scores. By evaluation depends on the defect localizations in group A significant differences compared to the patients with a defect in the femur condyle could be observed for patellafemoral joint. In the group B with serum-free cell cultivation these differences dependent on defect localization were not found. Serum-free expansion of autologous chondrocytes allows a standardized cell expansion with good clinical outcome one year post OP.

Cartilage Regeneration with Chondro-Gide®

Bi-Layer Collagen Type I/III Membrane for Articular Cartilage Repair

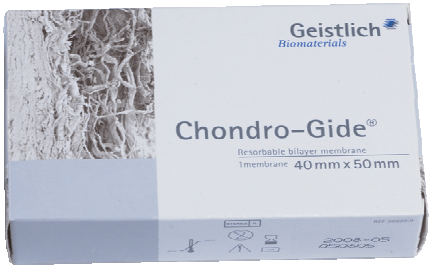


Chondro-Gide® is a ready-to-use matrix suitable for different Cartilage Repair Methods:

***ACT** (Autologous Chondrocyte Transplantation)*
Chondro-Gide® eliminates the harvest process of a periosteal flap, provides a stimulus for re-differentiation of the autologous cultured cells and reduces the risk of hypertrophy.

***AMIC®** (Autologous Matrix Induced Chondrogenesis)*
Chondro-Gide® provides a matrix to support and stabilize the super-clot following Microfracturing and therefore, allows the Mesenchymal Stem cells to differentiate and to develop hyaline-like neo-cartilage.

Product Portfolio Chondro-Gide®



Chondro-Gide® Collagen Membrane
40 x 50 mm, Reference No. 30939.9

Chondro-Gide® Collagen Membrane
30 x 40 mm, Reference No. 30915.5

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Links:

www.cartilage.org
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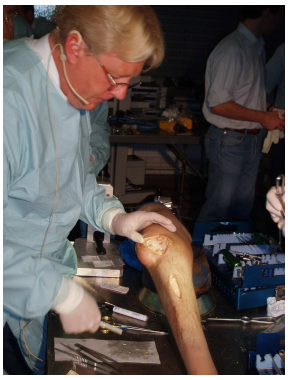
Dr. Jürgen Gallas

Italy:
Mr. Massimo Dona

UK:
Mr. (Dr.) Sven Kili, Senior Medical Advisor- Orthopaedics

Congresses & Events in 2006

April 27-30, 2006 Baden-Baden, Germany	Süddeutscher Orthopädenkongress www.vso-ev.de/texte/frame54.html
May 12-14, 2006 Munich, Germany	GOTS www.gots.org
May 24-27, 2006 Innsbruck, Austria	ESSKA www.esska2006.com/
June 15-17, 2006 Hamburg, Germany	Norddeutscher Orthopädenkongress www.norddeutsche-orthopaeden.de/
June 26-29, 2006 Davos, Switzerland	ECM VII www.ecmjournal.org/ecm_meetings
September 29-30, 2006 Salzburg, Austria	AGA www.aga2006.de
September 20-22, 2006 Lucerne, Switzerland	SGO/SSO www.sgosso.ch
September 27-29, 2006 Glasgow, UK	BOA www.boa.ac.uk/
October 2-6, 2006 Berlin, Germany	DGU/DGOOC www.orthopaedie-unfallchirurgie.de/2006/index.html
November 12-16, 2006 Rome, Italy	SIOT www.siot.it/pagine/index.html



Geistlich will provide theoretical and/or surgical skills workshops at these congresses and events. Additionally presentations related to the clinical outcome of our different products and methods will be presented.

Prof. Dr. M. Steinwachs demonstrates the ACT-Technique at the ICRS Skills Workshop 2005 in Vienna.

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