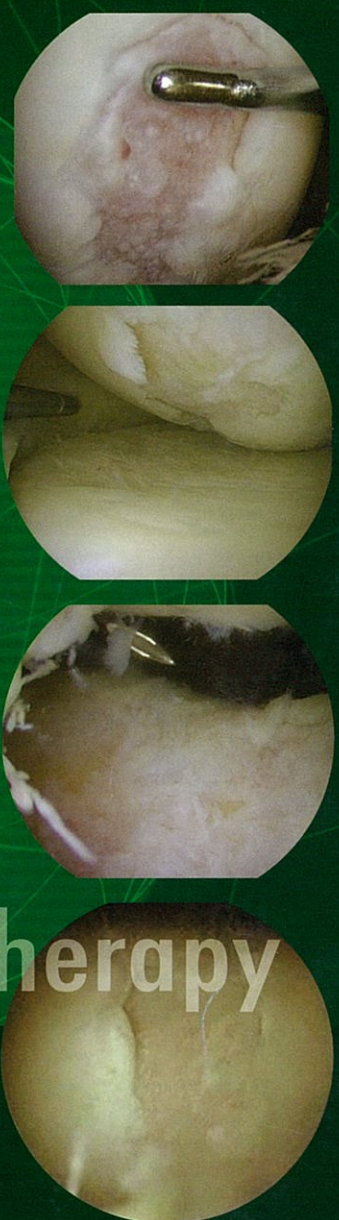
Tokyo Medical and Dental University
The 5th Global COE International Symposium

グローバルＣＯＥプログラム
歯と骨の分子疾患科学の国際教育研究拠点
デント・メドミクスのインテリジェンスハブ



Clinical Researches and Experiences for Cartilage Regeneration Therapy

東京医科歯科大学
第５回 GCOE 国際シンポジウム

臨床経験からみた軟骨再生研究

── 国際比較と近未来 ──

2011年2月3日㈭
東京医科歯科大学 M&Dタワー大講堂

第５回ＧＣＯＥ国際シンポジウム

臨床経験からみた軟骨再生研究

― 国際比較と近未来 ―

抄録集

The International Symposium of Global Center of Excellence Program
Clinical Researches and Experiences for Cartilage Regeneration Therapy

日時：2011年2月3日（木）
Date : 3rd February, 2011

会場：東京医科歯科大学 M&D タワー大講堂
Place : Tokyo Medical and Dental University

世話人 宗田 大
東京医科歯科大学大学院運動器外科学
Organizer : Takeshi Muneta
Section of Orthopedic Surgery Graduate School of Medicine
Tokyo Medical and Dental University

主催
東京医科歯科大学グローバルＣＯＥプログラム
歯と骨の分子疾患科学の国際教育研究拠点
デント・メドミクスのインテリジェンスハブ
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事務局
東京医科歯科大学大学院運動器外科学／軟骨再生学
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The International Symposium of Global Center of Excellence Program
Clinical Researches and Experiences for Cartilage Regeneration Therapy

February 3rd (Thursday), 2011

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09:35 - Opening Remarks by **Takeshi Muneta** (Symposium Coordinator)

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10:50 - 11:50 **Dennis Crawford** (Moderator : Takeshi Muneta)
"Two year clinical outcomes and T2 mapping MRI findings of a 3rd generation autologous treatment for cartilage injury.
A prospective randomized clinical trial vs. microfracture"

12:00 - 13:00 **Shigeyuki Wakitani** (Moderator : Dennis Crawford)
"Cartilage repair with autologous bone marrow mesenchymal cells"

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14:00 - 15:00 **James Hui Hoi Po** (Moderator : Ichiro Sekiya)
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"Next generation cartilage solution"

17:20 - 17:30 Closing Remarks by **Masaki Noda** (GCOE Program Leader)

Address from President

Takashi Ohyama
Tokyo Medical and Dental University

I am delighted to welcome you to this international symposium "Clinical Researches and Experiences for Cartilage Regeneration Therapy." This is managed by Global Center of Excellence (GCOE) Program. To promote education and research programs, Japanese government started GCOE Program, which has been awarded to 14 universities out of 72 candidates in medical field and our Tokyo Medical and Dental University has been awarded at the top of them.

Our GCOE program, "International Research Center for Molecular Science in Tooth and Bone Diseases" is designed to form a world-top class research center in the field of tooth and bone diseases for 3 areas; (1) elucidation of basic molecular mechanisms in pathology of the diseases leading to loss of tooth and bone, (2) fundamental clinical research for diagnosis and therapeutic treatments, and (3) advancement of functional genomic studies on tooth and bone diseases based on genomic and epigenomic science. Also, we will further develop the "international research network."

Regularly our GCOE program organizes international symposiums such as "Strategies to the create super tooth" and "Frontiers in bone biology." This time, we organize the first symposium for cartilage regeneration. The purposes of this symposium are (1) to understand current situation of cartilage regeneration therapy from clinical view, and (2) to communicate among top researchers in this field. We invited 3 international speakers from Italy, USA, and Singapore, and 2 Japanese speakers from Hiroshima and Osaka. One doctor in this hospital also has a presentation. All speakers are orthopaedic surgeons and experts in regenerative medicine for cartilage. I hope this symposium is exciting and valuable for both speakers and audiences.

Address from GCOE Program Leader

Masaki Noda
Department of Molecular Pharmacology
Medical Research Institute
Tokyo Medical and Dental University

It is our great pleasure to welcome the experts in the field of cartilage regeneration to the 5th international symposium of our Global Center of Excellence Program. Arthritis is a major concern in our modern society as our aging correlates well with loss of locomotor function that has a significant relevance to whole body health issues including cardiovascular and neuronal diseases. Osteoarthritis is characterized by the degeneration of articular cartilage that is scarcely regenerated. Challenges to restore full joint function through regeneration of articular cartilage are hot topics in the field of orthopaedic surgery and that is not only to cure patient locomotive function but also overall function of the whole body. We will be hearing the cutting edge science form the invited speakers including Drs. Ochi, Wakitani, Gobbi, Crawford, Hui and Sekiya. We very much look forward to the presentation and discussion that will provide the opportunity for us to understand the world top class and will evoke discussions for the new idea and collaborations to open novel directions for the research in this field.

Address from Symposium Coordinator

Takeshi Muneta
Section of Orthopedic Surgery
Graduate School of Medicine
Tokyo Medical and Dental University

It is honorable and a great pleasure for me, out of 27 professors in charge, to host the 5th International Symposium of Global Center of Excellence directly related clinical subject. The ultimate goal of the GCOE program is to realize clinical progress in the field of tooth and bone diseases. In the sense of program policy, this symposium is very important and significant to reach the point.

Twenty four million people are estimated to have an abnormality in their radiograph of the knee joint. Among them, 10 million people are suffering from knee pain. It is an important national subject to maintain the healthy life when Japan faces an aging society. Knee pain ranks second as a chief complaint in an outpatient clinic of the orthopedics in Japan. Considering knee pain treatment, to maintain articular cartilage health is a fundamental target. Articular cartilage damage is divided into two aspects of osteoarthritic change and cartilage damage due to sports related injuries. It will be appropriate for us clinicians to have sports related cartilage injuries as a treatment target first. Osteoarthritic change is thought to have genetic and medicosocial problems which lie under a huge background of bone joint disease.

The paper of autologous chondrocyte implantation (ACI) by Brittberg et al. in New England Journal of Medicine in 1994 has opened the door of time of curing articular cartilage. Regenerative medicine of cartilage became realistic in clinical field. Now, over 15 years passed after the publication. Estimated more than 30 thousand of ACI have been experienced all over the world, however, the therapeutic position of ACI is not well established. There still a lot of clinical subjects in respect to efficacy, safety and invasiveness remained to be resolved regarding cartilage regeneration therapy. Safety, low cost, technical easiness and low invasiveness are primary requirements for a better therapeutic procedure.

Six prominent clinicians who have a lot of clinical experiences on articular cartilage treatment with sufficient scientific background gathered at this international symposium. The symposium will hopefully give us suggestive hints on the unanswered subject of cartilage regeneration therapy with fruitful discussion, consequently leading to a better clinical outcome.

Mitsuo Ochi

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Professor Mitsuo Ochi graduated from Hiroshima University School of Medicine and entered the Department of Orthopaedic Surgery in 1977. In 1995, he moved to the Shimane Medical University as a professor and chairman, and since 2002 to present, he has been the professor and chairman of Department of Orthopaedic Surgery, Hiroshima University. He additionally has been taking the roles of the director of Hiroshima University Hospital since 2007, the executive of Hiroshima University since 2008 to the present.

Professor Ochi has had a lot of clinical experience on knee surgery and basic researches on cartilage, ligament and meniscus, leading to receiving J. Joyce Award in 1993, and 2005. In 1996, he successfully performed the world-first "clinical trial to transplant three-dimensional cultured autogeneous chondroytes embedded in atelocollagen gel". His recent focus is on less invasive technique to treat the cartilage defects using magnetic beads-stem cell complex and external magnetic force.

He has received international invitations 24 times for the last three years to give lectures including the guest lecturer at Harvard Medical School in Massachusetts in May 2009. Currently, he also serves as the society president of Japanese Orthopaedic Society of Knee Arthroscopy and Sports Medicine.

Publications (recent 3 years):

Articular cartilage repair using an intra-articular magnet and synovium-derived cells.
Hori J, Deie M, Kobayashi T, Yasunaga Y, Kawamata S, Ochi M.
J Orthop Res. 2010 Nov 9.

Bone-marrow-derived mononuclear cells with a porous hydroxyapatite scaffold for the treatment of osteonecrosis of the femoral head: a preliminary study.
Yamasaki T, Yasunaga Y, Ishikawa M, Hamaki T, Ochi M.
J Bone Joint Surg Br. ;92(3):337-41.

Atelocollagen-associated autologous chondrocyte implantation for the repair of chondral defects of the knee: a prospective multicenter clinical trial in Japan.
Tohyama H, Yasuda K, Minami A, Majima T, Iwasaki N, Muneta T, Sekiya I, Yagishita K, Takahashi S, Kurokouchi K, Uchio Y, Iwasa J, Deie M, Adachi N, Sugawara K, Ochi M.
J Orthop Sci. 2009;14(5):579-88.

Forefront of cartilage regeneration

Several surgical approaches to repair cartilage defects have been reported such as reattachment of a detached osteochondral fragment to the lesion, microfracture, mosaicplasty and ACI. We treated eight cartilage defects with autogeneic or allogeneic meniscal transplantation from 1990 to 1995. Then we started to perform transplantation of tissue-engineered cartilage made ex vivo for the treatment of osteochondral defects of the joints (110 cases) as a second generation of chondrocyte transplantation from 1996. Sixty knees who had received transplantation of tissue-engineered cartilage for cartilage defects were followed up for at least 5 years. Although the clinical results were satisfactory, we need the surgical approaches to treat large cartilage defects with minimally invasive technique. One of the less invasive surgical procedures to treat large cartilage defects is microfarcture or drilling. However, these techniques under arthroscopy are not sufficient to repair cartilage defects with hyaline cartilage. I think that there are two weak points such as insufficient number of mesenchymal stem cells and early overloading on the treated area.

1) One recent strategy is by the implantation of mesenchymal stem cells (MSCs). MSCs are the cell population of undifferentiated cells isolated from adult tissue that have the capacity to differentiate into mesodermal lineages, such as bone, cartilage, fat, muscle or other tissues. MSCs from bone marrow can be cultured and differentiated into the desired lineage in vitro with the application of specific growth factors or bioactive molecules.Intra-articular injection of too many MSCs, however, can generate free bodies of scar tissue (Agung, Ochi et al KSSTA 2006). We therefore developed a novel stem cell delivery system for cartilage repair using magnetically labeled MSCs and an external magnetic device to accumulate a relatively small number of MSCs to a desired area. Ferumoxides are dextran-coated superparamagnetic iron oxide nanoparticles approved by the US Food and Drug Administration as a magnetic resonance contrast agent for hepatic imaging of humans. By use of this ferumoxides, it is easy to make magnetically labeled MSCs. Recently we demonstrated the ability to deliver magnetically labeled MSCs to a cartilage defect that is a desired place under arthroscopy in rabbit and swine knee joints using external magnetic device (0.6T) (Kobayashi, Ochi et al. Arthroscopy 2008). This result indicates that this minimally invasive system under arthroscopy can be applicable for a focal osteochondral defect in the knee joint. The next step is to examine if this external magnetic system is effective for osteoarthritis.

We investigated if we could successfully regenerate a cartilage layer on degenerated human cartilage in vitro using this external magnetic system (Kobayashi, Ochi et al. Arthroscopy 2009). MSCs from human bone marrow were cultured and magnetically labeled. Degenerated human cartilage was obtained during total knee arthroplasty. The osteochondral fragments were attached to the sidewall of tissue culture flasks, and magnetically labeled MSCs were injected into the flasks. Using an external magnetic device, a magnetic force was applied for 6 hours to the direction of the cartilage, and then the degenerated osteochondral fragment was cultured in chondrogenic differentiation medium for 3 weeks. In the control group, a magnetic force was not applied. The specimens were evaluated histologically. A cell layer was formed on the degenerated cartilage as revealed by hematoxylin and eosin staining. The cell layer was also stained in Toluidine blue and Safranin O, and with anti-collagen type II immunostaining, indicating that the cell layer contained an abundant extracellular matrix. In the control group, a cell layer was not observed on the cartilage. In conclusion, we could demonstrate that our system could deliver MSCs onto degenerated human cartilage, and then form an abundant extracellular matrix on the degenerated cartilage in vitro.

2) Another technique is to reduce the load to the repaired area in the knee joint after bone marrow stimulation to protect immature tissue regenerated at the repaired area against destruction caused by overloading. We made a new distraction arthroplasty device (meira, Japan) which allows the range of motion with knee joint distraction(Deie ,Ochi et al. Arthroscopy 2007). After drilling or microfracture under arthroscopy, the new external device was fixed with four 6-mm pins drilled into the distal femur and the proximal tibia. After the appropriate distractive tension was applied, the ROM and the postdistraction and predistraction tibiofemoral joint spaces at 30° of flexion were measured. Although this device is usually applied for 3 months, full weight bearing is allowed one month after surgery. Until now, this device has been demonstrated to function well to repair cartilage defects.

I would like to show my techniques using an external magnetic field to deliver precisely injected cells with magnetic beads to an articular defect and articulated distraction device for reducing the load for a large osteochondral defects or osteoarthritis.

Dennis C. Crawford

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Education

Degree: Boston University School of Medicine 1995
Residency: Orthopaedic Surgery, Brown University, 2000
Fellowships:
Orthopaedic Trauma, Brown University, 2001
Orthopaedic Sports Medicine, Knee and Shoulder Surgery, University of California San Francisco, 2002.
Dr. Crawford is sub-specialty Fellowship trained in both Orthopaedic Fracture Surgery (Brown University) and Arthroscopy and Sports Medicine (University of California San Francisco).
Certifications:
Board Certified in Orthopaedic Sports Medicine; American Board of Orthopaedic Surgeons, 2010
Board Certified in Orthopaedic Surgery; American Board of Orthopaedic Surgeons, 2004

Publications (recent 3 years):

An autologous cartilage tissue implant NeoCart for treatment of grade III chondral injury to the distal femur: prospective clinical safety trial at 2 years.
Crawford DC, Heveran CM, Cannon WD Jr, Foo LF, Potter HG.
Am J Sports Med. 2009;37(7):1334-43.

Cartilage Repair: 3rd Generation Cell-Based Technologies - Basic Science, Surgical Techniques, Clinical Outcomes.
Hettrick K, Crawford DC, Rodeo S.
Sports Medicine and Arthroscopy Review. 2008;16(4):230-235.

Subtalar Release in Clubfeet: A Retrospective Study of Ten Year Outcomes.
Henn RF, Crawford DC, Eberson CP, Ehrlich M.
Foot & Ankle International. 2008 (4):390-5.

Two year clinical outcomes and T2 mapping MRI findings of a 3rd generation autologous treatment for cartilage injury. A prospective randomized clinical trial vs. microfracture

Oregon Health Sciences University
Dennis C. Crawford

Objectives: Report clinical outcomes of a novel ACTI in comparison to MF technique for treatment of grade III ICRS distal femoral cartilage injury.

Methods: A multi-site FDA phase II clinical trial comparing safety and efficacy of ACTI v. MF as primary treatment of chondral injury is reported. Thirty patients were randomized (2:1;ACTI:MF) at arthroscopic confirmation of ICRS Grade III femoral condyle lesion(s). MF or hyaline biopsy was performed at the randomization procedure. ACTI, produced by seeding a collagen I matrix with chondrocytes and bioreactor treatment, was implanted via arthrotomy and sutureless fixation at approximately 6 weeks post-biopsy. MF rehabilitation (Toe touch WB, CPM for 6 weeks) was standard for each group. Evaluations at 3, 6, 12 and 24 months included KOOS, IKDC, SF-36 and VAS pain. Responder analysis was applied using a dual threshold criteria based on previously reported MPCI (minimal perceptible clinical improvement) thresholds for both the KOOS pain and IKDC outcomes measures.

Results: A minimum of 2 year data is reported for 28 of 30 enrolled patients (19ACTI:9MF). Mean age (40 ± 9yrs), BMI (28 ± 4), injury acuity (3 ± 5yrs) and lesion size (MF252 ± 135mm2 v. ACTI287 ± 136 mm2) were comparable between arms. For both ACTI and MF, SF-36 Physical and IKDC improved from baseline ($p<0.025$) at 1 and 2 years. Improvement for ACTI v. baseline was significant, $p<0.025$ for all additional measures: KOOS pain, KOOS symptoms, KOOS ADL, KOOS QOL, SF-36 Role and VAS pain at both 1 and 2 years. Using a paired t-test, ACTI had significantly greater change from baseline than MF in IKDC ($p<0.05$) and KOOS pain ($p<0.05$) at both one and two years. ANCOVA analysis of the two groups at one year, indicated KOOS pain score change from baseline between ACTI and MF was significant ($P=0.016$), with a difference in adjusted means (ACTI-MF) of 12.06 with a 95% CI (2.388, 21.74). The difference in IKDC changes from baseline between ACTI and MF was significant, $p=0.028$, with a difference in adjusted means. Similarly, more patients ($P=0.0125$, Fischer's exact test) in the ACTI arm were therapeutic responders at 6 (43% v. 25%), 12 (76% v. 22%) and 24 months (81% v. 44%).

Conclusions: ACTI significantly improved knee pain, symptoms and function in comparison to baseline. In pain and function scores, ACTI was associated with significantly greater improvement compared to MF. This preliminary prospective randomized trial reports ACTI treatment is more effective for femoral chondral injury treatment in comparison to MF.

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Education:

1976-1983 MD, School of Medicine, Osaka University
1986-1990 PhD, Graduate School of Medicine, Osaka University

Professional Background:

1983/June-1986/March Orthopedic Surgery at 3 hospitals in Japan
1990/September-1992/April Skeletal Research Center, Case Western Reserve University, Cleveland USA
1992/April-1994/June Osaka University
1994/July-2001/June Osaka-Minami National Hospital
2001/July-2005/December Shinshu University
2001/January- Osaka City University

Publications (recent 3 years):

Highly sensitive ELISA for determining serum keratan sulphate levels in the diagnosis of OA.
Wakitani S, Okabe T, Kawaguchi A, Nawata M, Hashimoto Y.
Rheumatology (Oxford). 2010;49(1):57-62.

Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with
45 joints followed for up to 11 years and 5 months.
Wakitani S, Okabe T, Horibe S, Mitsuoka T, Saito M, Koyama T, Nawata M, Tensho K, Kato H, Uematsu K, Kuroda R,
Kurosaka M, Yoshiya S, Hattori K, Ohgushi H.
J Tissue Eng Regen Med. 2010 Jul 5.

Articular cartilage repair with autologous bone marrow mesenchymal cells.
Matsumoto T, Okabe T, Ikawa T, Iida T, Yasuda H, Nakamura H, Wakitani S.
J Cell Physiol. 2010 Nov;225(2):291-5.

Cartilage repair with autologous bone marrow mesenchymal cells

Osaka City University Graduate School of Medicine
Department of Orthopaedic Surgery **Shigeyuki Wakitani**

It has been reported that the mesenchymal stem cells in bone marrow (BMSC) contain progenitor cells of some mesenchymal tissues, such as bone, cartilage, fat, and muscle. We have reported that autologous BMMC transplantation promoted the repair of full thickness articular cartilage defects in rabbit knee (J Bone Joint Surg Am 1994). This procedure is easy to perform clinically because the autologous BMSC are easy to obtain and can be culture expanded without losing their capacity for differentiation.

We transplanted autologous BMSC for the repair of full-thickness articular cartilage defects in the patellae of a 26-year-old female and a 44-year-old male (Cell Transplantation 2004). BMSC were culture expanded, embedded in collagen gel, transplanted into the articular cartilage defect and covered with autologous periosteum. Six months after the transplantation, clinical symptoms had improved dramatically, the improvement has remained in effect (13 years in one case, and 12 years and 2 months in the other).

We transplanted BMSC to repair large articular cartilage defects in 12 knees of 12 patients with knee osteoarthritis who underwent a high tibial osteotomy (Osteoarthritis Cartilage 2002). Twelve patients served as cell free controls. Although the clinical improvement was not significantly different 16 months after surgery, the arthroscopic and histological grading score was better in the cell-transplanted group than in the control group 8 months after the surgery. We investigated the clinical score for middle follow-up period (63 months), but there was no significant difference.

We transplanted BMSC into 9 full-thickness articular cartilage defects of the patello-femoral joints (including 2 kissing lesions) in the knees of three patients (J Tissue Eng Regen Med 2007). Six months after transplantation, the patients' clinical symptoms had improved significantly and the improvements have been maintained over the follow-up periods (17 months to 27 months).

We transplanted BMSC into osteochondral defects in 4 patients (13-14 year-old) with osteochondritis dissecans of the elbow. The mean follow up period was 48 months (33-65). Clinical symptoms have improved significantly and they can play recreational sports. MRI revealed that repair cartilage showed the same intensity as normal cartilage. Arthroscopy performed in 2 patients showed that articular surface was smooth like normal articular surface. Histology of one patient 12 months after the transplantation revealed that the defect had been repaired with cartilaginous tissue.

Autologous BMMC transplantation can be expected to become an effective method for the repair of articular cartilage defects. Safety of the procedure is important. From 1998 to 2008, we transplanted BMSC into 45 joints of 41 patients. Because neither tumors nor infections were observed between 5 and 137 months (mean 75 months) of follow-up, we concluded that BMC transplantation is a safe procedure.

James Hui Hoi Po

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Academic Qualifications:

MBBS National University of Singapore, 1990
FRCS Edinburgh, 1994
MD Orthopaedic Surgery, Singapore, 2008

Publications (recent 3 years):

Comparative Study of Bone Marrow Derived Stem Cells Versus Autologus Chondrocytes in Repair of Articular Cartilage - Observational Cohort Study.
Nejadnik H, Hui JH, Choong PC, Tai BC, Lee EH.
Am J Sports Med. 38(6):1110-6, 2010

Enhancement of Meniscus Repair in the Avascular Zone using Mesenchymal Stem Cells in a porcine model.
Dutton A, Choong PF, Goh CH, Lee EH, Hui JH.
J Bone Joint Surg Br. 92 (1):169-175, 2010

The evaluation of a phasic osteochondral implant coupled with an electrospun membrane in a large animal model.
Ho S T B, Hutmatcher DW, Ekaputra AK, Hitendra D, Hui JH.
Tissue Eng Part A. 16(4):1123-41, 2010

Cartilage repair: pitfall and challenges

Director of Cartilage Repair Program
Associate Professor and Senior Consultant
Department of Orthopedic Surgery
National University Health System

James Hui Hoi Po

Various attempts in cell-based therapy were available to treat cartilage injuries since 1994, but no method has been judged superior as articular cartilage injuries have a limited potential to heal. However, the ultimate goal of treatment is not only to restore normal knee function by regenerating hyaline cartilage in the defect and complete integration of the regenerated cartilage, but also to delay the primary end point of total joint replacement.

To date, 200 cases of Autologous Chrondrocyte and Bone Marrow stem cells (BMSCs) Implantation had been performed in the author' s institution. At the last review, 87% of the patients had good and excellent results in terms of relief of symptoms and knee activities. Injectable intra-articular mesenchymal stem cells (BMSCs) suspended in hyaluronic acid as an alternative to the much more invasive methods had been commenced in clinical trial following good experimental results in porcine models. The cell-treated groups show improved cartilage healing both histologically and morphologically at 6 and 12 weeks compared to both controls. This injectable method can be performed as an out-patient procedure.

Recent literature had also argued on the different cell sources, growth factors and their reproducible efficacy. The challenge is that for clinicians and Basic Scientists to translate their superiority over traditional control methods.

Ichiro Sekiya

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Education:

1984-1990 MD, School of Medicine, Tokyo Medical and Dental University
1996-2000 PhD, School of Medicine, Tokyo Medical and Dental University

Professional Background:

1990/June-1996/March Orthopedic Surgery at 10 hospitals in Japan
2000/July-2002/June Center for Gene Therapy, Tulane University, New Orleans, USA
2002/July- Tokyo Medical and Dental University

Publications (recent 3 years):

Magnesium enhances adherence and cartilage formation of synovial mesenchymal stem cells through integrins.
Shimaya M, Muneta T, Ichinose S, Tsuji K, Sekiya I.
Osteoarthritis Cartilage. 2010;18(10):1300-9.

Horie M, Sekiya I, Muneta T, Ichinose S, Matsumoto K, Saito H, Kobayashi E.
Intra-articular Injected synovial stem cells differentiate into meniscal cells directly and promote meniscal regeneration without mobilization to distant organs in rat massive meniscal defect.
Stem Cells. 2009;27(4):878-87.

Koga H, Shimaya M, Muneta T, Nimura A, Morito T, Suzuki S, Ju YJ, Mochizuki T, Sekiya I.
Local adherent technique for transplanting mesenchymal stem cells as a potential treatment of cartilage defect
Arthritis Res Ther. 2008;10(4):R84.

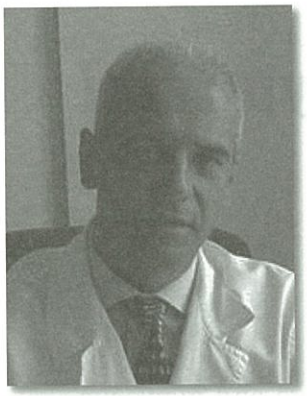
Cartilage regeneration with synovial stem cells

Tokyo Medical and Dental University
Section of Cartilage Regeneration **Ichiro Sekiya**
Section of Orthopedic Surgery **Takeshi Muneta**

Mesenchymal stem cells (MSCs) are attractive cell source for cartilage and meniscus regeneration. Our in vivo chondrogenic assay demonstrated that synovial and bone marrow MSCs had a higher chondrogenic ability than adipose and muscle MSCs. Human synovial MSCs expanded more in human serum than in FBS, and the opposite results were obtained in bone marrow MSCs. Our strategy for cartilage regeneration is transplantation of synovial MSCs.

Current cell therapy for cartilage regeneration requires invasive procedures. We have developed a novel implantation procedure with synovial MSCs. (1) Knee is positioned so that the cartilage defect is faced upward. (2) Synovial MSC suspension is slowly dripped onto the cartilage defect. (3) The knee is held stationary for several minutes or hours until most cells adhere to the cartilage defect. According to our in vitro and vivo studies, more than 60% cells adhered to the cartilage defect in 10 minutes, and promoted cartilage regeneration.

We are currently doing clinical trial for cartilage defects. All patients have their cartilage defects filled with synovial MSCs arthroscopically. Favorable results are obtained by MRI imaging in many cases, by second look arthroscopies, and by biopsies though patients undertaken these invasive examinations are still limited. Our method has such advantages that no periosteal coverage or scaffold were required and that transplantation is possible arthroscopically.



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Dr. Alberto Gobbi, founder and director of Orthopaedic Arthroscopic Surgery International (OASI) in Italy, was born in Milan on the 14th of October 1956. His father was a University Medicine professor; he obtained his doctoral degree in medicine and surgery from the State University of Milan in 1983 and presented his thesis on traumatic injuries in motorcycle sports.

He completed his specialty training in Orthopaedics and Traumatology at the University of Milan in 1982 and presented a thesis on the functional treatment of leg fractures in athletes. He also completed his second Specialty in Sports Medicine at the University of Genova.

He served as physician for the Italian Motorcycle Federation for the sport of motocross, learned arthroscopic techniques in the USA in the early 80's and he was one of the first Italian surgeons becoming member of American Academy of Orthopaedic Surgeons and Arthroscopy Association of North America and he was elected as Honorary Member. He served ISAKOS and ESSKA as member of Arthroscopy, Education and Cartilage Committee.

Member of International Cartilage Research Society since the last 8 years, he served the society as member of the General Board, program chair of the World Congress in Miami USA and co-chair of the Educational Committee. He has been elected in the Board of Directors of ISAKOS in 2009 and member of Educational Committee.

He is currently practicing in Milan as an Orthopaedic Surgeon and Sports Doctor, he is the Director of Orthopaedic Arthroscopic Surgery International and founded OASI Bioresearch Foundation a no profit organization in favour of the globalization of culture, sharing of knowledge and technological know-how. Dr Gobbi created a network of doctors from all over the world who conduct research in biotechnology and believe that the improvement of knowledge in the medical field can be a path to world peace. The International fellowship program for young doctors from developing countries, or affected by war, was the starting point of the Foundation.

O.A.S.I. Bioresearch Foundation N.P.O. has been recognized as an International teaching center from ISAKOS.

O.A.S.I.
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Publications (recent 3 years):

Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years.
Kon E, Gobbi A, Filardo G, Delcogliano M, Zaffagnini S, Marcacci M.
Am J Sports Med. 2009;37(1):33-41.

Patellofemoral full-thickness chondral defects treated with second-generation autologous chondrocyte implantation: results at 5 years' follow-up.
Gobbi A, Kon E, Berruto M, Filardo G, Delcogliano M, Boldrini L, Bathan L, Marcacci M.
Am J Sports Med. 2009;37(6):1083-92.

Primary repair combined with bone marrow stimulation in acute anterior cruciate ligament lesions: results in a group of athletes.
Gobbi A, Bathan L, Boldrini L.
Am J Sports Med. 2009;37(3):571-8.

Next generation cartilage solution

Articular cartilage has a limited intrinsic healing potential due the presence of few specialized cells with low mitotic activity; furthermore, cartilage is avascular and there is a lack of source of undifferentiated cells that can promote tissue repair. Therefore trauma and chronic irritation may lead to progressive damage, joint degeneration and early osteoarthritis. New generation of tissue-engineered strategies have been developed for the repair of complex lesions involving cartilage; Mesenchymal stem cells (MSC), platelet rich plasma (PRP) and tissue engineering could represent a new solution for cartilage repair.

In our institution we prospectively followed up 15 patients for 2 years operated for grade IV extensive cartilage lesions (average size 9.2 cm^2) of the knee, using Bone Marrow Aspirate Concentrated (BMAC) combined with a biologic scaffold (Chondro-Gide®Geistlich Wolhusen, CH). The porous structure of the scaffold facilitates adhesion, proliferation and differentiation of MSC. Bone marrow was harvested from ipsilateral iliac crest and subjected to concentration (Harvest Smart PreP2 System® - Harvest Technologies, Plymouth, MA) and activation with Batroxobin solution (Plateltex®act-Plateltex S.R.O. Bratislava, SK). X-rays and MRI as well as VAS, IKDC, KOOS, Lysholm, Marx, SF36 and Tegner scores were collected at pre-op and at 6-12 months and final follow up at 2 years. Six patients gave their consent for second look arthroscopy and five of them for a concomitant biopsy. Nonparametric statistical analysis was performed with the Wilcoxon rank test. Patients showed significant improvement in all scores at final follow-up ($p < .005$). Mean preoperative values were: VAS 5.2, IKDC subjective 43.6, KOOS Scores P=66.2/ S=68.2/ ADL=70.0/ SP=41.6/ QOL=37.2 and Tegner 2.0 while at final follow up mean scores were: VAS 0.7, IKDC subjective 80.7, KOOS P=94.0/ S=90.1/ ADL=95.1/ SP=71.3/ QOL=77.5 and Tegner 4.9. MRI showed good coverage of the lesion and tissue quality in all patients. Good histological findings were reported for all the specimens analysed who presented hyaline-like features. The good clinical outcome showed that autologous bone marrow derived and collagen I/III matrix in a one-step procedure could represent an improvement on the currently available techniques for the treatment of grade IV knee chondral lesions.

We also prospectively followed up 50 patients (mean age 47.7 years) with degenerative lesions of the knee, with a minimum follow up of 12 months. All patients were treated with 2 intra-articular injections (1 monthly) with autologous plasma rich in growth factors (PRGF) utilizing the kit provided by RegenLab-PRP®. KOOS, VAS, Tegner, IKDC and MARX scores were collected at pre-injection and at 6 and12 months. Nonparametric statistical analysis was performed with the Wilcoxon rank test. Patients showed significant improvement in all scores at final follow-up ($p < .005$). Mean pre-treatment values were: KOOS Scores: P=73.6/ S=72/ ADL=77.8/ SP=42.3/ QOL= 41.3, VAS 4.1, Tegner 3.6, IKDC 53.4 and Marx 3.8 while at final follow up mean scores were: KOOS Scores: P=88.1/ S=86.0 / ADL=94.8/ SP=64.2 /QOL=67.8, VAS 1.3, Tegner 5.2, IKDC 68.5 and MARX 9.4.Use of PRP can act as a preventive agent in patients with chronic and degenerative disease of the knee by diminishing pain and improving symptoms and quality of life.

Preliminary results are encouraging but further studies on clinical efficacy will clarify if simultaneous use of MSC and PRP could represent a real solution for regenerative medicine in cartilage repair.