

ICRS Focus Meeting

Stem Cells and Scaffolds

December 5 – 6, 2013

Bologna, Italy

Congress Centre – Rizzoli Orthopaedic Institute

*”STEM CELLS & SCAFFOLDS: A NEW FRONTIER
FOR JOINT REGENERATION”*

Final Programme



International Cartilage Repair Society

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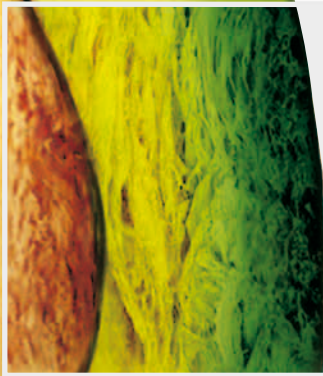


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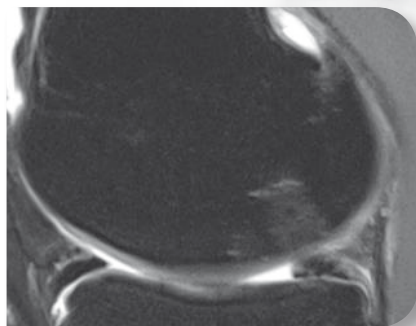
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ICRS Focus Meeting – The Knee

July 3–5, 2014 | FIFA Auditorium Sonnenberg
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Acknowledgement

The ICRS would like to thank all industry partners for their important support and participation in this unique event.

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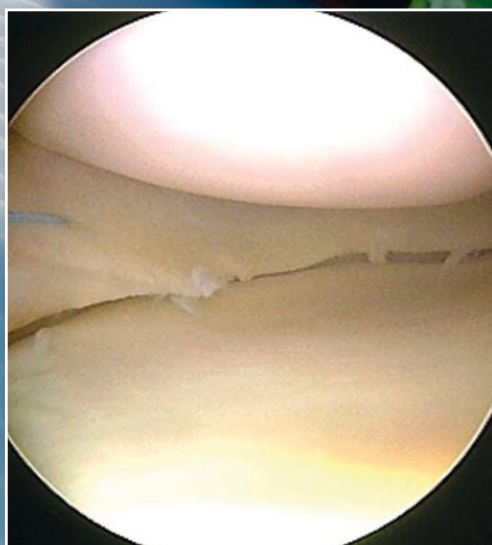
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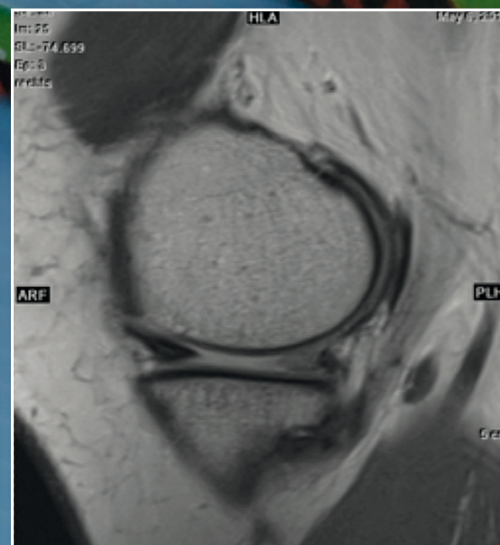
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*Photo courtesy
of Prof J. Bellemans*



**MRI at 48 months post Actifit®
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cartilage from baseline.**

Photo courtesy of Prof P. Verdonk

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FOCUS MEETING – STEM CELLS & SCAFFOLDS



Welcome Address

The intense research about tissue regeneration has led to some amazing achievements in recent years. Starting from autologous chondrocyte transplantation, firstly applied in the middle 90ties, it has been a long run to enhance our knowledge about cartilage physiopathology and to develop new therapeutic strategies. One of the current main focus is the application of hi-tech biomaterials and cell-based approaches to stimulate joint regeneration. It seems that orthopaedic practitioners, basic scientists and biomaterialists have joined their force to achieve the best results possible. The necessity of summarizing the current “state of the art” in this field is the reason behind this Focus Meeting, which is devoted to stimulate debate on the application of chondral/osteochondral scaffolds, meniscal scaffolds and stem cells for joint regeneration. The topic is really wide and attracts different scientific figures who need to work together: this is why, in the present Meeting, we will discuss both basic science aspects and the most recent clinical findings, with the aim of providing new ideas to be applied in the future. We will start from cell cultures and biomaterials but we will arrive directly to the operating theatre.

The venue of the Focus Meeting is the Rizzoli Orthopedic Institute in Bologna, one of the most historical and prestigious orthopedic centers in Europe: International renowned specialists and opinion leaders in the field will share their knowledge, allowing better understanding of the potentials and limits of these regenerative approaches and their future applications. The Focus meeting will be also enriched by LIVE SURGERY DEMOS, where innovative osteochondral and meniscal scaffolds implantation and stem cells/bone marrow-concentrate techniques will be displayed, to underline that these fascinating biological approaches are truly a tangible clinical option today.

The Christmas period in Bologna is also the perfect moment to discover interesting historical sites and truly savor some of the most attractive Italian Christmas Traditions. So it is my hope that each participant could really enjoy the best from the Scientific Sessions and also from the Italian hospitality,

Elizaveta Kon
 Scientific Programme Chair

This course is endorsed by:



SCIENTIFIC PROGRAMME

Thursday, December 05, 2013

11:00 – 13:30	Optional Guided Tour of Rizzoli Institute and Library (Umberto I Library & Putti Donation)
11:00 – 13:45	Registration
11:30 – 13:00	Welcome Reception invited by the ICRS (snacks and drinks included)
13:15 – 13:30	Welcome Francesco Antonio Manzoli – Scientific Director IOR, Prof. Maurilio Marcacci – Course Director
13:30 – 14:30	Module 1: Basic Science Perspective and Translational Development (Chair: Anthony Hollander, UK)
13:30 – 13:45	Stem Cell Applications: Will they become a Reality? (Anthony Hollander, UK)
13:45 – 14:00	Stem Cells: Expand or Not Expand? (Andrea Facchini and Brunella Grigolo, IT)
14:00 – 14:15	Stem Cells: Look into the Future (Henning Madry, DE)
14:15 – 14:30	Discussion
14:30 – 16:50	Module 2: Clinical Perspective: Smart Scaffolds for Cell Recruitment (Chair: Massimo Berruto, IT)
14:30 – 14:42	MaioRegen: indications and results (Elizaveta Kon, IT)
14:42 – 15:20	MaioRegen Live Surgery (Maurilio Marcacci, Francesco Iacono and Maria Pia Neri, IT); Discusser (Massimo Berruto, IT)
15:20 – 15:35	Return to sport after cartilage surgery (Stefano Della Villa, IT)
15:35 – 16:50	Discussion
16:50 – 17:15	Coffee Break / Industry Exhibition / Poster Viewing
17:15 – 18:55	Module 2 (Continuation): Clinical Perspective: Smart Scaffolds for Cell Recruitment (Chair: Mario Ronga, IT)
17:15 – 17:27	AgilC - CartiHeal (Andrew Levy, USA)
17:27 – 17:39	ACS-Swissbiomed Orthopedics (Christoph Erggelet, CH)
17:39 – 17:51	AMIC-Technique, Geistlich Surgery (Matthias Steinwachs, CH)
17:51 – 18:03	CellCoTec (Konrad Slynarski, PL)
18:03 – 18:15	Arthrex BioCartilage (Jason Scopp, USA)
18:15 – 18:27	BST-CarGel, Piramal (Matthias Steinwachs, CH)
18:27 – 18:39	GelrinC – Regentis Biomaterials. (Ron Arbel, IL)
18:39 – 18:55	Discussion
20:30 – 23:00	Course / Faculty Dinner at Palazzo Isolani

Take this unique opportunity to enhance your professional network with your colleagues and invited faculty in a relaxed and informal atmosphere. *Limited Vacancies. Rate: 70 Euros (Apero + 3 course Dinner with drinks included)



SCIENTIFIC PROGRAMME

Friday, December 06, 2013

08:30 – 10:20	Module 3: Smart Scaffolds & Bone Marrow Concentrate (Chair: Paolo Adravanti, IT)
08:30 – 08:42	Scaffold + BMAC: Ankle (Sandro Giannini & Francesca Vannini, IT)
08:42 – 08:54	Scaffold + BMAC: Hip (Dante Dallari, IT)
08:54 – 09:06	Scaffold + BMAC: Knee (Alberto Gobbi, IT)
09:06 – 09:18	Meniscus (Peter Verdonk, BE)
09:18 – 09:30	AMIC + BMAC (Piero Volpi & Laura De Girolamo, IT)
09:30 – 09:45	Discussion
 09:45 – 10:45	 Actifit + BM Live Surgery (Peter Verdonk, BE & Stefano Zaffagnini, IT) Discusser: Vincenzo Condello, IT
10:45 – 11:00	Cartilage surgery and osteotomy (Stephan Nehrer, AT)
11:00 – 11:10	Discussion
11:10 – 11:30	Coffee Break / Industry Exhibition / Poster Viewing
11:30 – 12:15	Module 4: Cultured MSC (Chair: Giorgio Maria Calori, IT)
11:30 – 11:45	Cartilage Treatment with MSC (Norimasa Nakamura, JP)
11:45 – 12:00	Meniscus Repair with MSC (Peter Angele, DE)
 12:00 – 12:15	 Honorary lecture: The NEW MSC: Drugs, Antibiotics and the Management of Innate Regenerative Potential (Arnold Caplan, USA)
 12:15 – 13:00	 Mini Battle: Allogenic Stem Cells - An Alternative? (Chair: Ken Zaslav, USA)
12:15 – 12:45	Pro: Daniel Saris (NL), Contra: Frank Barry (IE)
12:45 – 13:00	Discussion
13:00 – 13:45	Lunch
13:45 – 14:30	Module 5: Stem cells: open questions (Chair: Giuseppe Peretti, IT)
13:45 – 14:00	Stem Cells vs. Chondrocytes (Mats Brittberg, SE)
14:00 – 14:15	Injective Treatment with Stem Cells for OA -Scientific Basis (Elizaveta Kon, IT)
14:15 – 14:30	Discussion
14:30 – 15:30	Module 6: Early Clinical Experience (Chair: William Murrel, UAE)
14:30 – 14:45	ADIPOA European Project (Christian Jorgensen, FR)
14:45 – 15:00	The Singapore Experience (James Hui, SG)
15:00 – 15:15	The Korean Experience (Yong Gon Koh, KR)
15:15 – 15:30	The Malaysian Experience (Khay-Yong Saw, MY)
15:30 – 15:45	The Orthohealing Center Experience- Early Results with Intra-Articular Bone Marrow Concentrate (Steven Sampson, USA)
15:45 – 16:00	Allogeneic Mesenchymal Stem Cell Drug from Cord Blood (Antonio S. Lee, USA)
16:00 – 16:15	Discussion
16:15 – 16:30	Coffee Break / Industry Exhibition / Poster Viewing
16:35 – 18:05	Module 7: Joint Homeostasis (Chair: Ken Zaslav, USA)
16:35 – 16:50	Growth factors (Susan Chubinskaya, USA)
16:50 – 17:05	PRP-Platelet-rich plasma (Giuseppe Filardo, IT)
17:05 – 17:20	Serum and synovial biomarkers in early OA (Christian Lattermann, USA)
17:20 – 17:35	Hyaluronic Acid (Pascal Richette, FR)
17:35 – 17:50	Physical Stimulation (Giacomo Zanon, IT)
17:50 – 18:05	Discussion
18:05	Meeting ends

INTERNATIONAL FACULTY



Peter Angele, Prof., MD
University Hospital Regensburg, Regensburg, Germany

After his residency in the Department of Trauma and Reconstructive Surgery at the University Hospital of Regensburg, Germany, he became a consultant in the Department of Trauma Surgery with focus on regenerative knee surgery. Since July 2010, he has been fulfilling a professorship position for "Regenerative Joint Therapy" at the University Hospital Regensburg.

In addition, he extended his focus on regeneration of the knee joint by becoming a partner in a highly specialized institution "Sporthopaedicum" in 2008. Every year, he performs approximately 1000 knee surgeries with the focus on ligament reconstruction, cartilage and meniscus regeneration.

Cartilage regeneration has also been his main research interest. From 1997 to 1999, he spent a DFG sponsored research fellowship at Case Western Reserve University, USA. His research focus was stem cell based chondrogenic differentiation and mechanobiology. After his return to the University Hospital Regensburg, he continued with basic and translational research by establishing an own research group. Over the last 10 years this group could achieve grant money of more than 2 Million Euro and they published more than 60 peer reviewed, MEDLINE listed papers with the focus on stem cell based cartilage and meniscus regeneration. Since 2010, he has been the director of the FIFA Excellence Centre in Regensburg. The research focus within this responsibility is the prevention and the optimized treatment of cartilage and ligamentous injuries of the athletes.



Paolo Adravanti, MD
Casa di Cura Città di Parma, Chief of the Orthopaedic Department, Parma, Italy
President SIGASCOT

From 1980 to 1985 Teaching of Orthopaedics and Traumatology students of the School Nurses of Parma USL n. 4. Since 2006 Professor of the School of Specialization in Orthopaedics and Traumatology, University of Pavia.

Contact the office of Parma Teaching Centre dell'ESSKA (European Society of Sports, Traumatology, Knee Surgery and Arthroscopy) and SIGASCOT (Italian Society of Arthroscopy Knee Cartilage Sports Orthopaedic Technologies)

Since 2004, the annual operating My case is composed of approximately n. 1200-1300 knee surgery as the first operator of about 500 for the treatment of simple and complex ligamentous injuries, about 400 and about 350 arthroscopies of prosthetic surgery (unicompartmental, and total revisions). The number of interventions prosthetic knee is on the increase since 2007.



Ron Arbel, MD
Tel Aviv Surasky Medical Center, Tel Aviv, Israel

Dr. Arbel got his degree at Tel Aviv university medical school. Finished his residency at Tel Aviv Surasky medical centre (Ichilov hospital). Practiced in arthroscopic surgery and sports medicine in Austria, Germany, Belgium, Holland, Italy and USA (California, Mississippi and Utah). He is an Honorary Member of Arthroscopic Association of North America- AANA and a fellow in the ICRS as well as an international member in AAOS. He served as the president of the Israeli society of sports medicine 2003-2009. He is the director of sports medicine and arthroscopic surgery service in Tel Aviv Surasky

medical centre. His main work is meniscus surgery, ligaments surgery of the knee and ankle and various treatments to cartilage problems. Involved now in some researches about treatments to cartilage lesions including cartilage implantations- 2nd generation special techniques in cartilage treatments and new device- artificial meniscus ("Nusurface") for people who suffer from pain due to early degenerative cartilage lesions of the knee.

INTERNATIONAL FACULTY



Frank Barry, Prof., MD
National University of Ireland, Scientific Director, Galway, Ireland

Frank Barry is Professor of Cellular Therapy at the Regenerative Medicine Institute (REMEDI), National University of Ireland Galway. Here he directs a large group of researchers who focus on the development of new repair strategies in stem cell therapy and gene therapy in orthopaedics. Previously he was Director of Arthritis Research at Osiris Therapeutics in Baltimore, MD and a Research Fellow at Shriners Hospital for Children, Tampa, FL. He has contributed to the fields of tissue engineering and regenerative medicine by developing innovative and successful cellular therapies for the treatment of acute joint injury and arthritic disease. This has included the generation of a large body of new data in groundbreaking preclinical studies, and has led to the first phase of clinical testing of mesenchymal stem cells in clinical trials for joint injury.

In a career that has spanned both industry and academic research, he has been a driver in the development of cellular therapy as a biological repair strategy. It is his belief that the application of new technologies in regenerative medicine, including cellular therapy, gene therapy, growth factor augmentation, implantable scaffolds and nanomaterials, will have a profound impact in Orthopaedics. Frank Barry was the recipient of the 2012 Marshall Urist Award for excellence in tissue regeneration research from the Orthopaedic Research Society.



Mats Brittberg, Ass. Prof., MD, PhD
Kungsbäck Hospital, Göteborg University, Cartilage Research Unit,
Kungsbäck, Sweden

Associate Professor Mats Brittberg is a member of the Cartilage Research Unit, Department of Orthopedics Surgery, at University of Gothenburg and an orthopedic surgeon at the Kungsbäck Hospital, Kungsbäck, Sweden. He received his MD at the University of Gothenburg in 1978 and completed a specialization in orthopedics in 1985. In 1992, he passed the Swedish Orthopedic Board Exam (S.O.B.E.), and in 1996, he earned a PhD. In 2002, he became Associate Professor of orthopedics at the Sahlgrenska Academy at University of Gothenburg. Mats Brittberg is now also Gothenburg university lecturer. Mats Brittberg's research has been focused on cartilage repair and with focus on cartilage regeneration with in vitro expanded autologous chondrocytes. Today the main interest is the recent started European Connective Tissue Engineering centre (ECTEC) which is research collaboration between the Sahlgrenska Academy at University of Gothenburg with the institution of Polymer Technology, Chalmers Technical University. He has also had research collaboration with Virginia Tech in USA on biotribology in cartilage and osteoarthritis as well as research collaborations with other centers in Europe and North America. Mats Brittberg has been on the board of TESI (Tissue engineering Society International) and has been chairing the Cartilage Committee of ESSKA 2006-08. Since the start 1997, he has been working with ICRS, as a secretary, Vice-president and President (2006-2008) and finally Past-President (2008-2009). He is editor for the recently started Sage journal "CARTILAGE" and associate editor with ESSKA journal as well as being in the editorial board of Osteoarthritis and Cartilage. In September 2010, Mats Brittberg received the ICRS Genzyme Lifetime Achievement Award in cartilage research.



Massimo Berruto, MD, Prof.
Istituto Ortopedico Gaetano Pini, Milan, Italy

Orthopaedic Surgeon Chairman of Knee Surgery Dept. Of Istituto Ortopedico Gaetano Pini -Milan-Italy. Chairman of Cartilage Committee of Sigascot and Member of Board of Sigascot

INTERNATIONAL FACULTY



Arnold Caplan, Prof., PhD,
Case Western Reserve University, Director Skeletal Research Center, Cleveland, USA

Arnold I. Caplan, Professor of Biology and Director of the Skeletal Research Center at Case Western Reserve University. He received his PhD from The Johns Hopkins University School of Medicine. Dr. Caplan is a national and international scholar focusing on experimentation in the area of musculoskeletal and skin development. He has published over 400 papers and manuscripts and has long been supported by the NIH and other non-profit and for-profit agencies for his efforts in trying to understand the development, maturation and aging of cartilage, bone, skin and other mesenchymal tissues and for his pioneering research on Mesenchymal Stem Cells.



Susan Chubinskaya, Prof., PhD
Rush University Medical Center, Biochemistry and Section of Rheumatology, Chicago, United States of America

Susan Chubinskaya, PhD, The Ciba-Geigy Professor of Biochemistry; has a primary appointment as Professor of Biochemistry with secondary appointments as Professor of Internal Medicine (Section of Rheumatology) and Orthopedic Surgery at Rush University Medical Center. She is also Associate Provost for Academic Affairs at Rush. Susan was born in Kiev, Ukraine and received her PhD in 1990 from the Department of Metastasis, Institute of Oncology Problems, Ukrainian Academy of Sciences, Kiev, Ukraine. In 1992, she immigrated with her family to the United States. From 1993 to 1996 she was a postdoctoral fellow at the Department of Biochemistry at Rush. In 1996, she joined the faculty at Rush Medical College. She is an internationally recognized expert in the field of growth factors/bone morphogenetic proteins in cartilage repair and regeneration. The focus of her current research is post-traumatic osteoarthritis and biologic approaches to cartilage repair. She is a co-recipient of William J. Stickel Gold award, Am. Pod. Med. Assn., 1997; Eugene T. Nordby MD Research Award, Internat. Intradiscal Therapy Soc., 2005; 2012 Jacquelin Perry Resident Research Award. She is a holder of the Ciba-Geigy Endowed Chair, Rush University Medical Center. Her research is continuously sponsored by the NIH/NIA, NIH/NIAMS, pharmaceutical and biotech companies. She is a member of the ICRS since 2000. She served on the ICRS General Board and Executive Board as a Treasurer and currently she is a chair of the AdHoc ICRS committee on basic science. Susan published 8 book chapters, 75 peer-reviewed articles, and more than 170 peer-reviewed abstracts.



Vincenzo Condello, MD
Center for Knee Surgery and Sports Traumatology, Orthopaedic Department "Sacro Cuore" Hospital, Negrar - Verona Italy

He graduated at Medical School University "La Sapienza" in Rome in 1993 and passed the exam as Orthopedic Surgeon in 1999. Six months fellowship in Sports Medicine at Karolinska Hospital, Stockholm, in 1999. Actually responsible of the Sports Medicine Section of the Sacro Cuore Hospital, he is vice president of the Cartilage Committee of the Sigascot Association in Italy. He is currently involved in international studies on the use of scaffolds for Osteochondral repair and Menisci Substitute. Member of the ICRS since 2012.

INTERNATIONAL FACULTY



Stefano Della Villa, MD,
Physiatrist. Isokinetic Medical Group, Bologna, Italy

Stefano Della Villa received his MD from the University in Bologna in 1985 and completed his residency in Orthopaedic and Sport Rehabilitation at the Rizzoli Orthopaedic Institutes in 1988. As part of his training he worked in 1987 and 1988 with Professor Michael Dillingham, Director of Sports Medicine Programme, at Stanford University (California, US) and with Rick Eagleson, Physical Therapist of the Stanford Swimming Team.

He founded in Bologna the Isokinetic Sport Rehabilitation Centre in 1987 and since then he is the President of the company. In 1992, he organized the first edition of the International Congress of Sport Rehabilitation and Traumatology, which in 2014 will celebrate its 23rd anniversary. In 2000 he founded, together Dr Giulio Sergio Roi, the Educational and Research Department of the company focused on prevention, treatment and rehabilitation of sports injuries. In 2001, the Isokinetic Medical Group opened a new clinic in Milan and in the next years in Cortina d'Ampezzo, Turin, Verona, Rome and Rimini. From 2006 to 2010, he has been the President of the Rehabilitation Committee of the Italian Scientific Society SIGASCOT and in 2008; he became a member of the Sports Injury and Rehabilitation Committee of ICRS. Since October 2009, the Isokinetic Medical Group was accredited as FIFA Medical Centre of Excellence thanks to his long experience in the management of soccer player injuries. In November 2012, Isokinetic Medical Group opened a new clinic in London.



Laura de Girolamo, PhD,
IRCCS Galeazzi Orthopaedic Institute, Milano, Italy

Laura de Girolamo received her B.S. in Biology in 2002. She worked for three years at the Institute of Orthopaedic Sciences of the Università degli Studi di Milano in the cartilage regeneration field. In 2008, she got the PhD in Medical Pharmacology and Toxicology at the same University. During this period, she was involved in a research project about the use of adipose-derived stem cells for bone and cartilage regenerative medicine. Then she started working at the IRCCS Galeazzi Orthopaedic Institute of Milan, where she is

currently the head of the Orthopaedic Biotechnology Lab. Her main research interests include the study of mesenchymal stem cells and growth factors in musculo-skeletal regenerative medicine. She also coordinates the clinical trials of the Institute involving the use of biological products, such as cell-scaffold constructs and autologous bioactive factors. She is member of the executive committee of the Italian Mesenchymal Stem Cells Group (GISM) and Vice-President of the Research Committee of the Italian Knee Surgery Arthroscopy Sports and Cartilage Society (SIGASCOT). She is author of several peer-reviewed papers, she has been speaker at national and international congresses and she collaborates with some peer-reviewed journals as reviewer.



Dante Dallari, MD
Istituto Ortopedico Rizzoli, Bologna, Italy

From November 2011, he is Head of S.D. Conservative Orthopaedic Surgery and Innovative Techniques. He is a member of the American Academy of Orthopaedic Surgery and the of the International Cartilage Repair Society, International Society of Hip Arthroscopy. Specialist in biomedical technology with knowledge of materials (synthetic and biologic) used in prosthetic and reconstructive surgery. Author of 150 scientific publications, participated in 72 Rizzoli research projects. Currently Head of the research projects "Treatment

of osteoarthritis of the knee with Regenerative Medicine Techniques", "Comparative assessment of Regenerative Medicine and/or viscosupplementation treatment in osteoarthritis of the hip," "Biological joint reconstruction in severe cases of Osteonecrosis of the hip". Scientific Activities: Prosthetic and revision surgery of hip and knee. Hip arthroscopy. Arthroplasty in severe secondary osteonecrosis of the hip. Treatment of nonunion of long bones. Treatment of osteochondral injury.

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**Christoph Erggelet, MD, Prof., PhD,
Center for Biologic Joint Surgery, Zürich, Switzerland**

Christoph Erggelet is an orthopaedic surgeon in Zurich/ Switzerland affiliated with the Department for Orthopaedic Surgery and Traumatology, University Medical Center, University of Freiburg/Germany. He received his MD in 1986 and passed the board exam for Orthopaedic Surgery in 1993. A PhD was granted by the University of Essen/Germany in 1987. Since 2002, he is faculty member of the University Medical School, University of Freiburg Germany. Research interests focus on biologic regeneration of joint function, e.g. culture of autologous chondrocytes, meniscus regeneration and ligament repair.

He served as a founding board member of the Bio Valley initiative, a trinational tissue-engineering group, which enabled the setup of a licenced GMP laboratory at the University of Freiburg. International collaborations included board membership of the EU-funded EUROCELL program and the international Cartilage Repair Registry. Recent research has been done on stress loading of cartilage defects and stability of biodegradable scaffolds in collaboration with the Swiss Federal Institute of Technology Zurich/Switzerland. Christoph Erggelet is a member of the ICRS since the foundation in 1997 and served as a board member. He is currently the President of ICRS for the term office 2013 – 2015.



**Andrea Facchini, Prof., MD,
Istituti Ortopedici Rizzoli /Università di Bologna, Director, Italy**

Director of the laboratory of Immunoreumatology and tissue regeneration; director of the Rizzoli RIT-Research, Innovation & Technology Department. Title of qualification awarded: 1973 Medical degree, cum laude, University of Bologna, Italy. 1976 Specialist qualification, cum laude, in Clinical and Laboratory Haematology, University of Bologna, Italy. 1978 Specialist qualification, cum laude, in Internal Medicine, University of Bologna, Italy. 1982 Specialist qualification, cum laude, in Allergology and Clinical Immunology, University of Firenze, Italy. 1980 - present Professor of Clinical Immunology Faculty of Medicine and Surgery, Bologna University, Italy. 1995 - present Professor of post-graduate courses in Health and preventive Medicine, Internal Medicine, Rheumatology; Bologna University, Italy. 2002 - 2005 Director of the post-graduate school in Rheumatology Bologna University, Italy. 2003 – 2005 Italian FIRB, MIUR: Development of a normal human immortalized chondrocyte line for tissue engineering use. 2004 – 2006 Italian PRIN, MIUR: Molecular mechanisms for chondrocyte activation from cytokines and chemokines in Osteoarthritis. 2005 – 2007 Italian Health Ministry: Use of stem cells in tissue engineering for preventing cartilage damages 2006-2009 Carisbo Foundation: Identification of molecular targets of therapeutic interest in osteoarthritis. 2007-2009 Strategic Project of the University of Bologna: Common molecular targets among inflammatory and antinflammatory pathways in Osteoarthritis. 2008-2011 Project of the Emilia-Romagna Region – University of Bologna: Regenerative medicine in osteo-articular diseases 2008-2010 Italian Health Ministry: Tissue engineering in osteoarticular disease: basic and clinical evaluation.

2003 – 2008 President of commission for the management of Fundamental Oriented Research funds of Medical and applied Biological Science Committee, University of Bologna, Italy. 1999 - present Peer-reviewer of European Union FP5, FP6 and FP7 projects, CIVR, PRIN. 385 “in extenso” (199 on SCI), 21 book chapters, 560 Abstracts. Arthritis and Rheumatism, Biomaterials, Clinical and Experimental Immunology, Clinical Orthopedic & Related Researches, Gastroenterology, Journal of Immunology, Osteoarthritis and Cartilage, Tissue Engineering.

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Giuseppe Filardo, MD, PhD,
Rizzoli Orthopaedic Institute, Bologna, Italy

Graduated Summa Cum Laude (GPA 30/30 with 27 honors) in Bologna, Faculty of Medicine and Surgery, 3-time winner of the Dr. Rino Fiorini prize for “best university student” and winner of the Rotary Prize for the best graduates at the University of Bologna. Research fellow at Rush Cartilage Restoration Center in Chicago (IL), USA, with Prof. Brian Cole and Prof. Susan Chubinskaya.

Specialized in Orthopedics and Traumatology at the Rizzoli Orthopaedic Institute (Bologna, Italy) with 70/70 Cum Laude. Since 2005, member of the II Orthopaedic and Traumatology Clinic - Biomechanics Laboratory, Rizzoli Orthopaedic Institute, led by Prof. M. Marcacci, focusing on clinical and basic research in the musculoskeletal tissue engineering and regenerative medicine. Since 2011 research student in a PhD Program on regenerative medicine in the Bologna University. Investigator of several research projects on biotechnology applications in orthopaedics funded by the Rizzoli Orthopaedic Institute, the Italian government and European Community. In the 4 years after completing the Residency program focused on research on regenerative medicine, publishing a total of 106 articles on international journals (86 with impact factor), 18 articles on national journals, 17 book chapters, 20 published abstracts, and presenting the researches at 64 national and international meetings.



Sandro Giannini, Prof., MD,
Rizzoli Orthopaedic Institute, University of Bologna, Italy

Prof. Sandro Giannini is the Director of the Department of Complex Orthopaedic and Traumatologic Pathology at the Rizzoli Institute, Bologna. He is also the head of the Laboratory of Analysis of movement at the Rizzoli Institute. Currently, he is Director of the School of Specialization in Physical and Rehabilitative Medicine. He got his degree in 1971 at the University of Pisa and completed a specialization in Orthopaedic and Traumatology at University of Pisa in 1977. Other specialization he achieved: Physical Medicine and Rehabilitation in 1977 at Firenze University and Sports medicine in 1978 at

University of Rome. His principal scientific activities regard: Foot and Ankle, Shoulder; Fresh Joint Transplantations, minimally – invasive prosthesis, regenerative treatment of cartilage and bone with stem cells.



Alberto Gobbi, MD
Orthopaedic Arthroscopic Surgery International, Sport and Medicine,
Milano, Italy

Dr. Alberto Gobbi, born in October 1956, in Milan, Italy, is a Board certified surgeon and specialist in the field of orthopaedics, traumatology and sports medicine. He has been performing highly skilled surgeries for decades, which coupled with his scientific and research oriented mind, have led to a tremendous growth in the field of arthroscopy and cartilage repair worldwide. He chairs OASI Bioresearch Foundation Gobbi Onlus, a Non-Profit Organization, accredited by the Italian Ministry of Health and recognized as an International Teaching Center by International Society of Arthroscopy, Knee Surgery & Orthopaedic Sports Medicine (ISAKOS) and International Cartilage Repair Society (ICRS). The OASI Foundation promotes research on cartilage, joint aging and sports lesions and collaborates with surgeons from across the globe. He has innumerable publications to his name. In 2012, he was awarded the Best International Publication in an American Journal (AOSSM). He is the Associate Editor of ‘Cartilage’ since 2010 and is the education chair of ISAKOS. He is currently the Secretary elect of the ICRS. A talented sportsman himself, he is doctor to the Italian National Olympics Committee since 1983. He served the Medical Committees of the Italian Motorcycle Federation and the Motor-boating Federation for over 10 years. Dr. Gobbi’s office is located in Milan.

INTERNATIONAL FACULTY



Anthony Hollander, Prof., PhD
University of Bristol, School of Cellular and Molecular Medicine, Bristol, United Kingdom

Anthony Hollander is the Arthritis Research UK Professor of Rheumatology and Tissue Engineering at the University of Bristol. He has been working in the field of cartilage biology and arthritis research for two decades. Three of those years were spent at the internationally recognised cartilage laboratory at McGill University in Montreal. More recently he has focused on tissue engineering and stem cell biology for cartilage repair. Professor Hollander has received extensive peer-reviewed funding from The UK government, medical charities, the EU framework programmes and from biotechnology companies. He has been the named inventor on several patents. He is co-founder and Scientific Director of a University of Bristol spin-out company, Azellon Cell Therapeutics.

His work includes studies on the regulation of stem cell differentiation for cartilage repair and he has pioneered the development of new assays and methodological approaches for the measurement of repair tissue quality in very small biopsies of cartilage from patients with knee injuries. In 2008, Professor Hollander and a team of scientists and surgeons successfully created and then transplanted the first tissue-engineered trachea (windpipe), using a patient's own stem cells. The bioengineered trachea immediately provided the patient with a normally functioning airway, thereby saving her life. Professor is the immediate past-president of The International Cartilage Repair Society (he was President for the period 2012-2013). He has been a member of grant review boards for the UK Medical Research Council (translational stem cell committee) and the California Institute for Regenerative Medicine.



James Hui, Ass. Prof., MD,
National University Hospital, Director, Therapeutic Tissue Engineering laboratory, Singapore

A/Prof James Hui received his MBBS degree from National University of Singapore in 1990. He received his FRCS (Royal College of Surgeons, (Edinburgh UK)) in 1994, FAMS (Academy of Medicine, Singapore) in 1999 and Doctor of Medicine (National University of Singapore) in 2008. Dr Hui is currently an Associate Professor at the Department of Orthopaedic Surgery, National University of Singapore. He is heading Division of Paediatric Orthopaedics and is Director of Clinical Services for Department of Orthopaedic Surgery, National University Hospital. He is also appointed as Director for Tissue Engineering and Cell Therapy (GMP) Laboratory, National University Health System, Singapore and is a Group Leader for Cartilage Division of National University of Singapore, Tissue Engineering Programme (NUSTEP). His main research interests are on musculoskeletal tissue engineering and reconstructive surgery in paediatric orthopaedics.



Christian Jorgensen, Prof., PhD,
CHU Lapeyronie University Hospital, Montpellier, France

Pr Christian Jorgensen, specialist in Therapeutics and Rheumatology, is head of research INSERM unit U844 ("mesenchymal stem cells, joint environment and immunotherapy of Rheumatoid arthritis") Hôpital Saint Eloi – INM (Montpellier – France). Since the beginning of the unit in 2007, he animates this group composed by 11 permanent researchers dedicated to therapeutic innovation in the field of arthritis and diseases of cartilage. C Jorgensen is head of the clinical unit, "Immuno-therapy Rheumatology", University Hospital "Lapeyronie" (Montpellier). He leads the service with 30 beds dedicated to biotherapy applied to Rheumatoid Arthritis and other autoimmune diseases. C Jorgensen is a professor in the Faculty of Medicine Montpellier-Nîmes (responsible teacher of DES Rheumatology). He is also responsible for teaching the Master Pro "Evaluation & methodology of therapeutic trials. He is former member of Transparency commission at HAS. C Jorgensen has coordinated a program of 2004-2007 FP6

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integrated project Genostem : Adult mesenchymal stem cells engineering for connective tissue disorders. He is also principal investigator in the Integrated Project 6th FP-healing: Post-genomic Approaches for inflammatory rheumatic disease, Leading to the development of Improved therapy, coordinator L. Klareskog. Finally, today it coordinates the FP7 project, large scale project adipocytes: adipose-derived mesenchymal stem cells in osteoarthritis therapy, since 2009.



Elizaveta Kon, MD
Rizzoli Orthopaedic Institute, Bologna, Italy

Orthopaedic surgeon member of the II Orthopaedic Clinic led by Prof. Marcelli and Director of Nano-Biotechnology Laboratory of Rizzoli Orthopaedic Institute. Assistant Professor of Motor Sciences School, University of Bologna. President of Educational and Meeting Committee and member of the General Board of International Cartilage Repair Society (ICRS). Past-President of Fellowship Scholarships and Grants Committee of ICRS. Co-founder and past president of the Young Surgeons and Orthopedic Surgeons (YSOS) club under patronage of ICRS. Past-President of Cartilage Committee of European Society of Sports Traumatology Knee Surgery and Arthroscopy (ESSKA). Past-President of the Cartilage Research Board of Italian Society of Knee, Arthroscopy, Sport, Cartilage and Orthopaedic Technologies (SIGASCOT).

Orthopaedic surgeon and researcher focusing on clinical and basic research in the musculoskeletal tissue engineering and carrying on personally numerous research projects and clinical trials regarding biotechnology applications in orthopaedics (from pre-clinical studies to clinical trials), into the framework of Italian and European research projects. Elizaveta Kon has authored over 100 peer-reviewed scientific articles and over 20 chapters in textbooks in orthopedic surgery. She has presented at over 400 society meetings all over Europe, Asia and North America. Member of the Editorial Board of the European Journal of Sports Traumatology and Chirurgia Kolana Artroskopica Traumatologica Sportiva, and Associated Editor of BMC Musculoskeletal Disorders Journal and Advances in Orthopaedics. Winner of several awards: ICRS Travelling Fellowship in 2004 and the ESSKA- AOSSM travelling fellowship in 2009; Scientific Exhibit Award of Excellence "How to treat Osteochondritis Dissecans of the Knee: Surgical Techniques and New Trends" at the AAOS Annual Meeting 2011; Best scientific presentation at the ORTOMED Meeting 2012; Award Cum Laude at the ICRS Meeting 2013, and the Leading article Knee Surgery Sports Traumatology Arthroscopy Journal (KSSTA): "Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics", 2013.



Yong Gon Koh, MD
Department of Orthopaedic Surgery, YonseiSarang Hospital

Dr. Koh is a managing director at Yonsei SarangHospital, Seoul, South Korea. He is specialized Total Knee Arthroplasty, SportMedicine and Cartilage Regeneration. He is also the instructor at Dept. of Orthopedic surgery in Yonsei University Hospital, South Korea and a member of Korean Arthroscopy Society, Korean Knee Society, Korean Orthopedic Association and Korean Medical Association.

Dr. Koh began his training at Yonsei University School of Medicine in Korea and finished his internship at YonseiUniversity Hospital in 1994. Then Dr. Koh finished an Orthopaedic Residency in 1997 and Arthroscopy Fellowship at Yonsei University Hospital in 1998. Since 2002, he is a managing director at Yonsei Sarang Hospital and has built a strong clinical research program. He has published over 16 clinical papers through international journals and many local clinical papers. Also he displayed over 41 posters in Korea and internationally.

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Christian Lattermann, Ass. Prof., PhD
University of Kentucky, Orthopaedic Surgery, Lexington, USA

Dr. Lattermann is Vice Chairman for Orthopaedic Research and Associate Professor for Orthopaedic Surgery and Sports Medicine at the University of Kentucky. He is the Founder and Director of the Center for Cartilage Repair and Restoration at UK and is the Team Physician for two NCAA Division one colleges (University of Kentucky, Eastern Kentucky University). Dr. Lattermann began his training at Hannover Medical School in Germany and subsequently did a 2 1/2 year research and clinical fellowship in Sports Medicine at the University of Pittsburgh, USA. Dr. Lattermann decided to continue his career in the USA and finished an Orthopaedic Residency and a subsequent Sports Medicine and Cartilage Repair fellowship at the University of Pittsburgh and Rush University. He worked with Drs. Freddie Fu, Christopher Harner, Chris Evans, Bernhard Bach and Brian Cole during this time. Since 2006, he is at the University of Kentucky and has built a strong clinical research program. He is an expert in cartilage repair, outcomes research and clinical trials. He has published over 70 peer-reviewed papers, over 20 book chapters and currently holds grant funding from the National Institute of Health, Arthritis Foundation of America, NFL charities and the Physical Therapy Association of America.



Andrew Levy, MD, Prof.,
Center for Advanced Sports Medicine, Millburn, USA

Dr. Levy is a board certified orthopaedic surgeon who completed his fellowship training in Sports Medicine and Shoulder at Duke University Medical Center. Dr. Levy is not only a clinician and surgeon, but is a teacher and researcher. He has published extensively on cartilage injuries, ligament reconstruction, shoulder arthroscopy, fractures, soccer injuries, football injuries, and injuries in women's sports. He is an assistant professor of Orthopedics at the New Jersey Medical School and has received awards from the American Orthopedic Association, the American Fracture Association, and The International Olympic Committee. Dr. Levy is listed in "The Best Doctors in America", "New Jersey's Best Doctors", and "How to find the best doctors in the New York Metro region."



Henning Madry, MD, PhD,
Saarland University, Chair of Experimental Orthopaedics, Homburg, Germany

Henning Madry, a native of Germany, studied Medicine at the Charité Medical School in Berlin, Germany, with electives at the Universities of Southampton, Jerusalem, Geneva, Nice and the Baylor College of Medicine, Houston, TX, USA. He received his MD in 1996 from Humboldt University in Berlin. Resident at the Department of Trauma Surgery, Charité, Berlin from 1996-98 with Norbert Haas, MD. His postdoctoral research fellowship was at the Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston with Stephen B. Trippel from 1998-2000 and also at the Department of Chemical Engineering at the Massachusetts Institute of Technology with Gordana Vunjak-Novakovic, PhD and Bob Langer, PhD. In 2000, he founded the Laboratory for Experimental Orthopaedics and continued his residency with Dieter Kohn, MD at the Department of Orthopaedic Surgery, Saarland University, Homburg, Germany. In 2004 board-certified in Orthopaedic Surgery, since 2006 Attending Clinician. Since 2009 he holds the Endowed Chair of Experimental Orthopaedics and Osteoarthritis Research at the Saarland University. He also continues to provide advanced regenerative surgical treatments for cartilage defects.

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Giorgio Maria Calori, MD, Prof.,
Istituto Ortopedico Gaetano Pini, Head of the Division of Reconstructive
Orthopaedic Surgery and Risk Managements, Milan, Italy

He graduated in Medicine and Surgery at the University of Milan in 1982. He specialized and perfected in Hand Surgery and Microsurgery at the University of Louisville Kentucky USA in 1983/84; also he has specialized in Orthopaedics and Traumatology at the University of Milan in 1987, in Physical Therapy and Rehabilitation at the 'University of Milan in 1990, in Hand Surgery at the University of Florence in 1994. He has performed more than 8000 surgeries in the field of Orthopaedics and Traumatology, of which 40% with high DRG cluster. The time now is Chief of the Division of Orthopaedic Surgery, Restorative Gaetano Pini Orthopaedic Institute in Milan.



Maurilio Marcacci, MD, Prof.
Istituti Ortopedici Rizzoli, Bologna, Italy

Maurilio Marcacci was born in Livorno on 1.05.48. He graduated in Medicine and Surgery at the University of Pisa in 31-10-1972 and specialized in Orthopaedics and Traumatology, in Medicine of the Sport, in Physiotherapy. Maurilio is full professor of University of Bologna in the "Medicine and Surgery" Faculty, head of IX Orthopaedic Division and Biomechanics Laboratory at the Rizzoli Orthopaedic Institute and university teacher at the Specialization School in: Orthopaedics and Traumatology, Sport Medicine, Physical Medicine and Rehabilitation.

Maurilio is member of the following national and international scientific societies: EFORT, ESSKA, ISK, EORS, ISAKOS, CAOS, SIOT, SIRT, SICORMed, and SIGASCOT. Member of Editorial Board of: Journal of Sports Traumatology, Technique Knee Surgery; Member of Educational Committee ISAKOS, ExComm EFORT and Past-President of Italian Society of Orthopaedic and Traumatology, Italian Society Knee Arthroscopy Sport Cartilage and Orthopaedic Technologies (SIGASCOT). He published 6 monographs, 14 monograph's chapter, 148 articles in international papers, 104 articles in national papers, 226. International abs., 97 national abs, 12 audiovisual and attended more than 300 national-international congresses as a speaker and/or chairman. Clinical work involves the general field of orthopedics and traumatology, with particular focus on sports medicine (articular capsulo-ligament lesions, tendon and cartilaginous lesions, with transplantations of autologous chondrocytes for the repair of cartilaginous and bone defects), reconstruction of the lower limb (hip, knee), and regenerative osteo-articular diseases. The main research subjects are computer and robot assisted surgery, biotechnologies, clinical biomechanics, roentgen stereophotogrammetry analysis (RSA), innovative surgical techniques.



William D. Murrell, Jr. MD, M.Sc.,
Dubai Bone and Joint Center, Dubai, United Arab Emirates

William D. Murrell, Jr. MD, M.Sc., is a specialist orthopaedic surgeon sub-specialized in orthopaedic sports medicine. He is the President of the American Musculoskeletal Wellness Institute, Bethesda, Maryland, USA, and formerly served as the Director of Sports Medicine at the Dubai Bone and Joint Center, Dubai Healthcare City, Dubai, UAE. He completed medical school Temple University School of Medicine, Philadelphia, Pennsylvania, USA His internship and residency at the Tulane University Health Sciences Center, New Orleans, Louisiana, USA, where he was chosen as Surgical Intern of the Year, and recipient of the Orthopaedic Overseas-Orthopaedic Research Educational Fund (OO-OREF) Travelling Fellowship. He completed Fellowship in shoulder and knee at The Orthopaedic Specialty Hospital (TOSH), Salt Lake City, Utah, USA. A Fellow of the American Academy of Orthopaedic Surgery, Diplomate of the American Board Orthopaedic Surgery-Orthopaedic Sports Medicine, and selected as member of the American Orthopaedic Society Sports Medicine (AOSSM). Bill is an internationally recognized clinician and researcher, who lectures frequently at international and

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national congresses and symposia, and has authored several publications in peer review journals, books, and industry magazines for musculoskeletal medicine and biological treatments. Is the Principal Investigator-Clinical Trial investigating adjuvant stem cells in treatment of articular cartilage defect(s). He is on the Technical Advisory Board for the Foundation of Orthopaedic Reconstruction (FOR), Holyoke, MA, USA; Member AUC Voting Committee American Academy of Orthopaedic Surgeons, Rosemont, IL, USA; International advisory board Bone and Joint Journal (BJJ), London, U.K.; Review Board American Journal of Sports Medicine, Rosemont, IL, USA; Chief Medical Officer for the Dubai Duty Free Tennis Championship, Dubai, UAE; Consultant for the Al Wasl Sports Club, Dubai, UAE and the Al Merrikh Football Club, Khartoum, Sudan; former member of sports medicine committee-Dubai Sports Council, Dubai, UAE



Norimasa Nakamura, Prof. PhD, MD
Osaka Health Science University, Institute for Medical Science in Sports,
Osaka, Japan

Dr. Norimasa Nakamura is an orthopaedic surgeon and the professor of the Institute of Sports Science at Osaka Health Science University and the center for the advanced medical engineering and informatics at Osaka University. He is an orthopedic surgeon at the Osaka University Hospital, Osaka, Japan. He received his MD at the Osaka University in 1988 and completed a specialization in orthopedics in 1992. In 1994, he received a PhD. In 1995, he became

Assistant Professor of Orthopedics at the Osaka University and in 2009, moved to the current position. Norimasa Nakamura research has been focused on joint tissue repair with main focus on the regeneration of cartilage, ligament, and meniscus with stem cells. Today the main interest is the development of three-dimensional stem cell-based bio-implant for musculoskeletal tissue regeneration, whose feasibility to cartilage repair is now under the clinical trial with the permission by the Ministry of Health and Labor of Japan. Norimasa Nakamura is currently the Vice president of the ICRS.



Jason M. Scopp, MD
Peninsula Orthopaedic Associates, P.A., Center for Joint Preservation,
Salisbury, USA

Dr. Scopp is a board certified orthopaedic surgeon and a pioneer in the field of cartilage restoration, a procedure for joint pain available in only a handful of medical centers across the country. In addition to his biotechnology research on joint preservation, Dr. Scopp specializes in the treatment and prevention of sports-related injuries. Fellowship trained in Sports Medicine and a lifelong athlete himself, Dr. Scopp has been team physician for the

United States Soccer Team, University of Maryland Eastern Shore, Salisbury University and the Delmarva Shorebirds (a Baltimore Orioles organization), among others. Dr. Scopp received his medical degree from the Hahnemann University School of Medicine in Philadelphia. His residency in orthopaedic surgery was completed at University of Maryland Medical Systems, and his fellowship in sports medicine, arthroscopy and articular cartilage restoration at the Santa Monica Orthopaedic and Sports Medicine Group in California.



Steven Sampson, MD
The Orthohealing Center, (TOBI) The Orthobiologic Institute, Los Angeles, USA

Steven Sampson, D.O. is an internationally recognized expert in non-surgical orthopedics and regenerative medicine and is a Diplomat of the American Board of Physical Medicine and Rehabilitation. Dr Sampson was among the first United States authors to publish research on platelet rich plasma (PRP) that continues to lay a foundation for further biologic based therapies. He has created educational materials and hands on training of musculoskeletal ultrasound which educates thousands of physicians. Dr Sampson founded the

Orthohealing Center in Los Angeles, CA a comprehensive state of the art facility specializing solely on non-surgical orthopedics and sports medicine. Dr Sampson created the Orthobiologic Institute (TOBI), and chairs and moderates a world-class annual regenerative medicine symposium featuring

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the foremost experts in tendon and cartilage disease. Dr Sampson maintains a balanced evidence based practice and has published many peer reviewed articles and textbook chapters on orthopaedic regenerative medicine. Dr. Sampson is a clinical instructor of medicine at David Geffen School of Medicine at UCLA, Assistant Professor, Western University of Health Sciences Medical School, Adjunct Clinical Professor at Touro University, guest faculty at Loyola Marymount University, and is on staff at St. John's Health Center of Santa Monica, CA.



Stefan Nehrer, Prof., MD, PhD,
Donau University Krems, Center for Regenerative Medicine, Krems, Austria

Univ.-Prof. Dr. Stefan Nehrer is an orthopaedic surgeon at Department for Orthopaedic Surgery at the hospital in Krems, Professor for Tissue Engineering at Center for Regenerative Medicine and he is also Dean of Faculty Health and Medicine at Danube University Krems. Since 2013, he is the Head of the Department Health Sciences and Biomedicine. He studied at the Medical University Vienna where he obtained his MD in 1984 and his PhD in 1999. From 1995 to 1996, he was at the Harvard Medical School in Boston, USA, at Prof. Myron Spector where he started his scientific work in cell-based therapies in cartilage regeneration. From 2000 to 2006, he was head of orthopaedic research at the Medical University Vienna and leading surgeon in sports medicine and paediatric orthopaedic. In 2007, he was appointed Professor for Tissue Engineering at Danube University Krems. Over the years, he has continued his research on experimental and clinical applications of chondrocyte transplantation and formed a group for tissue engineering research. Furthermore, his interests focused on mesenchymal cell differentiation and design/implementation of tissue culture bioreactors for automated and controlled manufacturing of cartilage, bone and osteochondral grafts, based on autologous cells and 3D porous scaffolds. He has published more than 52 peer reviewed and 81 other articles in national and international journals and 14 book chapters. Prof. Nehrer has presented at many national and international meetings and he is member of 10 national and international societies. Furthermore, he is since 2012 president of the Austrian Society of Orthopaedics and Orthopedical Surgery.



Giuseppe Peretti, Prof., MD,
Hospital San Raffaele, Orthopaedics and Traumatology, Milan, Italy

Giuseppe Peretti received his MD degree and his Specialization in Orthopaedic and Traumatology by the University of Milan, Italy. He is currently Associate Professor in Orthopaedics and Traumatology by the University of Milan. His main research interests include the study of strategies for the repair of the cartilage, meniscus and tendon tissue. In particular, his recent studies have demonstrated the potential of the tissue engineering for the development of biological substitutes for the osteochondral and tendon repair. His work has also demonstrated the potential of the cell-based therapy for the repair of the avascular zone of the meniscus. He is chair of the Research Committee of the Italian Society SIGASCOT; vice-Chair of the Cartilage Committee of ESSKA, Chair of the Endorsement Committee of the TERMIS.



Pascal Richette, Prof., MD, PhD
Lariboisière Hospital, Paris, France

Pascal Richette is Professor of Rheumatology (Department of Rheumatology, Lariboisière Hospital, University Paris 7, in Paris, France). He is president of the OA Section of the French Society of Rheumatology (SFR), member of the scientific committee of the French Society of Rheumatology (SFR) and member of the OARSI (communication committee)

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**Mario Ronga, Ass. Prof.,
University of Insubria, Varese, Italy**

Associate Professor - Orthopaedics and Traumatology - Department of Biotechnology and Life Sciences (DBSV) - University of Insubria (Attending Orthopaedic Surgeon Ospedale di Circolo, Varese - Italy).

Clinical outcome studies in knee and ankle surgery, with particular interest in cartilage, meniscus and ligament repair for both traumatic and degenerative disease. Prevention and treatment of osteoarthritis. Application of tissue engineering techniques for the treatment of joint diseases.

Biochemical changes and gene expression in the tendon tissue and blood during tendon diseases. Author of 28 publications on PubMed indexed journals. 2004, Best paper award 9th Congress Italian Residents in Orthopaedics. 2004, Best paper award 28th Congress of the Italian Society of Foot Medicine and Surgery (SIMCP). 2004, Best paper award 5th Meeting "Giovani Leoni" Italian Society of Arthroscopy (SIA). 2004, Best residency thesis award Society Piemonte-Liguria-Lombardia of Orthopaedics and Traumatology (SPLLOT). 2005, Aircast Europe Fellowship GOTS (Gesellschaft für orthopädisch-Traumatologische Sportmedizin). 2006 "Progetto Fellowship 2006" SIA (Italian Society of Arthroscopy). 2007, Aircast (DJO) Basic Science Prize, BASEM (British Association of Sports Exercise Medicine). 2007, Second Prize for Best Poster Presentation. BOFAS (British Orthopaedic Foot & Ankle Society) Annual Conference. 2013, EAF (European Arthroscopic Fellowship). SIGASCOT (Italian Society of Knee, Arthroscopy, Sport, Cartilage, Orthopaedics Technology).



**Daniël Saris, Prof., PhD, MD
University Medical Center, Utrecht, Orthopaedics, Utrecht, Netherlands**

Daniël Saris (1966) Past president of ICRS. Graduated University of Amsterdam Medical School in 1992. During orthopedic residency he did a fellowship at the Mayo Clinic in Rochester MN USA under Prof. Shawn O'Driscoll of the Cartilage and Connective Tissue Research Laboratory and Prof. Kai-Nan An of the orthopaedic biomechanics laboratory. His PhD thesis completed in 2002 at the University of Utrecht was titled "Joint Homeostasis in Tissue Engineering for Cartilage Repair". It first introduced the now generally

accepted concept of joint homeostasis.

In 2000, Daniël joined as staff member in the department of Orthopaedics at the UMC Utrecht. In March of 2010, Dr Saris was appointed as Professor of Reconstructive Medicine at the University of Twente. Prof Dr Saris is director of the Biological Joint Reconstruction research program and head of the orthopaedic residency program at the University of Utrecht. His goal and driving force is the wish to satisfy natural curiosity into optimizing the regenerative biological capacity of the musculoskeletal system, to improve treatment and understanding of knee afflictions and to help in building an international network for ICRS with high potential and productive group dynamics.



**Khay Yong Saw, M. D.
Kuala Lumpur Sports Medicine Centre, Kuala Lumpur, Malaysia**

Dr Khay Yong Saw is a Consultant Orthopaedic Surgeon at the Kuala Lumpur Sports Medicine Centre in Kuala Lumpur, Malaysia. He graduated from Liverpool University Medical School in 1984, obtained his FRCS in Edinburgh in 1989 and went on to his chosen field which was Orthopaedic Surgery. In 1993, he completed his Masters in Orthopaedic Surgery (MCh Orth) at Liverpool University Medical School, UK. His specialisation in orthopaedic sports medicine includes knee joint arthroscopic surgery with application of stem cells

for chondrogenesis together with bone and soft tissue regeneration. In Year 2005, he started his research work in Articular Cartilage Regeneration with the use of stem cells. He has received numerous awards in the field of regenerative medicine for knee cartilage injuries. Other than his publications in the field of peripheral blood stem cells for musculoskeletal regeneration, he regularly shares his experience and knowledge at local and international conferences and events as an invited speaker. He has also organized and conducted many arthroscopic courses, some of which included live surgery.

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Konrad Slynarski, MD, PhD,
Lekmed Clinic, Head of private Sports Medicine Center Warsaw, Poland

Dr Konrad Slynarski completed his MD and PhD degrees at The Medical University of Warsaw, Poland, and completed research fellowships at Skeletal Research Center of Case Western University in Cleveland, USA, with Dr Arnold Caplan PhD (funded by the Polish-American Kosciuszko Foundation). He was a principal investigator in several worldwide clinical studies including iBalance Medical, Genzyme and CellCoTec.



Matthias Steinwachs, MD, Prof. h.c, PhD
Schulthess Klinik, Orthobiologics and Cartilage Repair, Zurich, Switzerland

Consultant Orthopaedics, Traumatology & Sports Medicine, Head of the Center of Orthobiologics & Cartilage Repair, Schulthess Klinik, Zürich, (FIFA Medical Centre of Excellence, Swiss Olympic Base, and Member of ISOC). Study of Medicine, University of Heidelberg & Göttingen, 1990 Research study at the Dept. of Pharmacology and Toxicology, University of Göttingen, 1/1991-3/1992 Ass. Doctor Dept. of Trauma Surgery, Bernward-Hospital Hildesheim, 1992 Dissertation MD/PhD University of Göttingen, 1997 Specialist education, Dept. for Orthopaedic Surgery, University of Freiburg, 1995 Training by Prof. L. Peterson, GMC Gothenburg, Sweden, 1997 Specialist exam for Orthopaedic Surgery, University of Freiburg, 1997-2007 Specialist for Cartilage Repair and Tissue Engineering, Knee Surgery, Dept. of Orthopaedic and Trauma Surgery, University Hospital Freiburg, 1998 - 2007 Member of the Steering Committee Valley Tissue Engineering Centre University Freiburg, 1998 - 2007 Head of the Cartilage Research Group, Valley TEC Freiburg, 12/2004 „Privatdozent“ (Habilitation), Venia legendi for Orthopaedic Surgery, University Freiburg, 2003-2007 Head of the first Cartilage Transplantation Unit, Dept. of Orthopaedic and Trauma Surgery, University Hospital Freiburg, 2003- Expert of “Bundesausschuss Krankenhaus (G-BA), Methodenbewertung ACT”, 2005- Member of the Expert board BMBF Project „Regenerative Medizin“, 2006 Professional Development for Sports Medicine, 2006 Honorary Professor Inst. of Sports medicine, Peking University 2007, 2008 Specialist for Orthopaedic & Traumatology 2008 Member of Expert board EMEA, London and Paul Erlich-Inst. (PEI, Langen), Congress President AGA 2012, Zürich. ICRS Board Member 2004-2008, Chair of the outcome committee of the ICRS 2008.



Francesca Vannini, MD
Istituti Ortopedici Rizzoli, VI, Bologna, Italy

Orthopedic Surgeon at the Rizzoli Orthopedic Institute in Bologna completed in Bologna her medical school with full marks. Completed her PhD in Biotechnologies (Cartilage repair) in 2004 at the University of Bologna. She was awarded with the European Foot & Ankle Society Travelling Fellowship, with the AOFAS Travelling Fellowship AOFAS, with the ICRS Travelling Fellowship and with the ESSKA travelling fellowship and she was fellow team doctor in the ESSKA program at the Chelsea Football Club in 2012. From 2004, she was appointed as a tutor at the Podiatrist University of Bologna and university lecturer at the Podiatrist University of Bologna and still give courses in this program.

She presented over 200 podium, posters and scientific exhibits at international and national meetings and authored or co-authored over 100 scientific book chapters, papers published in Science Citation Index journals and papers published in other national or international scientific journals. She is member of 6 scientific societies and she is actively involved as a committee member. She is moreover Vice president to be of SICP for the next year. She is also a reviewer of national international journals, among them Foot and Ankle International and American Journal Sports Medicine. Her main field of research and clinical practice are Cartilage repair and Foot & Ankle.

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Peter Verdonk, Prof., MD, PhD
University Hospital Ghent, Orthopaedics, Gent-Zwijnaarde, Belgium

Professor Dr Peter Verdonk, MD, PhD is a Consultant in Orthopaedic Surgery at the Antwerp Orthopaedic Center (Monica Hospitals) and Researcher at the Ghent University and the MoRe Institute. His clinical and research interests are knee surgery and Arthroplasty with a particular focus on meniscus substitution and cartilage repair. He has obtained his PhD degree at the Ghent University in 2006 on 'The Human Meniscus: characterization, transplantation and tissue engineering'. He received his orthopaedic training in Ghent University, and was a fellow of Prof. Bellemans in Leuven and of Prof. Neyret in Lyon. He has been an international traveling fellow of the International Cartilage Repair Society in 2004 and of the European Society of Sport Traumatology Knee Surgery and Arthroscopy in 2007. He is author of more than 70 peer-reviewed papers and has lectured internationally. He is also involved in a number of national and international scientific organization. For more info www.verdonk.be



Piero Volpi, Prof., MD,
Istituto Ortopedico Galeazzi, Milan, Italy.

Piero Volpi is a medical doctor and specialist in Orthopaedic Surgery & Sport Medicine. As the Director of Knee Surgery and Sport Traumatology Unit, Humanitas Clinical Research IRCCS, in Milan, Italy, he directs a team of orthopaedic surgeons, resident physicians and research fellows who mainly work on knee, shoulder, ankle surgery, arthroscopic surgery and sport traumatology as well as on development of new strategies for cartilage repair using stem cells and growth factors. He is teaching professor at the specialty school of Orthopaedics and Traumatology and Tutor for Board examination at University of Milan and he was teaching Professor at the specialty school of Sport Medicine at University of Milan. He authored 200 publications and over 500 contributions, including book chapters, articles and presentations to National and International meetings. In the field of Sport Medicine, he is responsible physician of Italian Association Football Player (AIC) from 2000 to present and he is responsible physician of a major Italian Football team F.C. Internazionale Milan from 1995 to 2000. From 1999, he is Instructor of medical matters FIFA (Federation International Football Association) and Vice-President of anti-doping committee FIGC (Federazione Gioco Calcio) and member SLA committee FIGC. He is Vice-President of SIA (Società Italiana Artroscopia) from 2013.



Giacomo Zanon, MD,
IRCCS Policlinico San Matteo, Orthopaedics and Traumatology, Pavia, Italy

He obtained the degree in Medicine and Surgery in 1996 in Milan and then the Specialization in Orthopaedics and Traumatology in 2001 in Pavia with the vote of 50/50 cum laude. In 2011 he also obtained a University Master in "Degenerative Pathology of the Knee", Università del Molise. In 2012, he gained the European Travelling Fellowship Sigascot- ESSKA. Research activity: In 1995 he performed some studies about in vitro chondrocytes growth and cartilage transplantation in rat models and published an experimental thesis: "Models of chondrocytes growth in biological tissue: experimental results" with Prof. G. Peretti, Milan. Professional activity: From 2001 he works in Clinica Ortopedica e Traumatologica, Università degli Studi di Pavia, IRCCS, Policlinico San Matteo, Pavia. His fields of expertise are knee arthroscopy, and ankle arthroscopy and open surgery, tendons pathologies and surgery and muscles pathologies and surgery, sports traumatology. He is the referee for the FIDAL consults in the Centro Studi e Ricerche in Medicina e Traumatologia dello Sport, Policlinico San Matteo, Pavia. From 1998 to 2002 he was member of the Medical Commission of the Italian Federation of Winter Sports (FISI) as orthopaedic consultant of the National Teams of Ski. From 2002 to 2012, he was the orthopaedic consultant of Volley Belgioioso, Edimes Basket Pavia, Piacenza Football Club, Serie A, Italy, Genoa Football Club, Serie A, Italy, SIGASCOT. Member of: SIOT, SIGASCOT, ISAKOS. Authors of many scientific publications in Italian, European and American journals regarding research and clinical studies about knee pathologies and sports traumatology.

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Kenneth Zaslav, Prof., MD,
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Ken Zaslav is an Orthopaedic Surgeon and the founding director of Advanced Orthopaedic Centres: Sports Medicine and Cartilage Regeneration Centres, in Richmond, Virginia in the U.S.A. He is a Clinical Professor of Orthopaedic Surgery at Virginia Commonwealth University and has published and lectured worldwide on Cartilage Repair, and non-operative treatments for Articular Cartilage injury over the past 10 years. Dr. Zaslav performed the first Articular Cartilage Transplant in Virginia in 1996 and since then articular cartilage has been his prime clinical research interest. He has been a fellow of the ICRS since 1999 and has served on its Executive Committee and Board of Directors. He is currently the Treasurer of The ICRS. He is a member of the AOSSM, AAOS and AANA and has served on its research, education and membership committees. He has spoken as an invited speaker at The FDA's Cellular, Tissue and Gene Therapies Advisory Committee meeting and was the lead author of The STAR Study of Articular Cartilage repair published in AJSM in 2009. He serves on the Scientific Advisory Boards of several Biologics companies in the United States and Israel and has previously served as The Chief Science Officer of The Virginia Bio-commercialization Center at Virginia Commonwealth University and now serves on The Board of Directors of The Virginia Life Science Investment Fund. He has been the Company Physician for The Richmond Ballet for the past 20 years.



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He received his MD degree from the University of Bologna on October 17th, 1987, final mark 110/110 cum laude. He works as first assistant orthopaedic surgeon in the Sports Traumatology Dept. of the Rizzoli Orthopaedic Institute since July 24th, 1997. He was ESSKA AOSSM travelling fellow from (June 1st-26th, 1997) in the U.S.A, visiting Sports Medicine medical centres of New York, London Ontario, Richmond, Memphis, Atlanta, Cincinnati, San Francisco. He performed a 6 months Fellowship in Sports Medicine and Orthopaedic Research at the University of Pittsburgh (USA), under the direction of Professor F. Fu and Professor S. Woo. He performed 8000 surgical operations as first surgeon up to August 31st, 2011. He is one of the 4 Italian members of the "ACL Study Group", the most important scientific society on ACL reconstruction. He is active member of many scientific societies: SIOT, SIGASCOT, SIA, IORS, AAOS, AOSSM, ESSKA, ICRS, Magellan Society, ISAKOS, ACL Study Group. He is vice-president of the SIGASCOT society (Italian Society of Knee Surgery and Sports Medicine). He was member of the cartilage committee of ESSKA (European Society of Shoulder and Knee Arthroscopy) from 2006 to 2008, and was the chairman of the arthroscopy committee of ESSKA from 2008 to 2010. He is deputy chair of the scientific committee of ISAKOS (International Society of Arthroscopy, Knee surgery and Orthopaedic Sports medicine) from 2011 to 2013. Scientific Chairman of the 15th ESSKA congress 2012. Scientific Chairman of the 16th ESSKA congress 2014. He attended as invited speaker 193 International Meetings and 195 Italian National Meetings. He is reviewer for many international journals: Am Journal Sports Medicine, Tissue Engineering, British Medical Bulletin, JOSPT, Musculoskeletal Surgery, Cartilage, Acta Orthopaedica Scand, Clinica Anatomica. Associated Editor of Knee Surg Sports Traumatol Arthrosc (ESSKA journal) from 2012.

MODULE 1: BASIC SCIENCE PERSPECTIVE AND TRANSLATIONAL DEVELOPMENT

Stem Cell Applications: Will they become a Reality?

Anthony P. Hollander¹ (UK)

Multi-potent mesenchymal stem cells (MSCs) are being widely investigated for use in tissue engineering strategies for a range of diseases and target tissues. Some attempts have been made to implant MSCs into articular cartilage lesions in patients. We have recently embarked on an MSC therapy for torn meniscal cartilage. However, translation of this biological knowledge and early clinical experience into effective and easily useable clinical protocols is limited by the fact that MSCs are a mixed population of cells, resulting in highly unpredictable results when they are used to generate daughter lineages or to generate a specific tissue. Therefore, predictive functional MSC markers are critical for ensuring improved therapeutic outcomes and meeting regulatory demands when implanting MSC-derived tissue engineering products into patients. It is widely recognised that the available MSC markers are not predictive of functional capacity and that new markers relating to subsets of this heterogeneous stem cell population will be required to move the field forward. In order to investigate this problem we generated clonal human MSC populations with varying capacities for chondrogenic differentiation. We found that each MSC clone formed chondrocytes with a defined capacity for cartilage formation and this capacity varied within an almost 400-fold range between the most and least chondrogenic progeny. We utilised some of these clones to map those differentially expressed genes that are associated with a high chondrogenic capacity. Subsequent screening of these genes led us to identify ROR2, the receptor for Wnt5a, as a cell surface marker that is up-regulated at the protein level on those MSCs with an enhanced capacity for cartilage formation. When isolated from un-cloned populations, ROR2+ve MSCs were significantly more chondrogenic than either ROR2-ve or unfractionated MSCs. In cartilage tissue engineering they produce 30% more cartilage with 60-70% higher quality. MSCs expressing ROR2 therefore provide a defined population capable of predictably enhanced cartilage production. This cell subset could be used for improved tissue engineering in vitro or to increase the chances of a successful regeneration of cartilage when implanted into cartilage lesions in patients. In this way, they might be used to improve the management of patients with focal cartilage injuries or those in the early stages of osteoarthritis.

MODULE 2: CLINICAL PERSPECTIVE: SMART SCAFFOLDS FOR CELL RECRUITMENT

MaioRegen: indications and results

Elizaveta Kon (IT)

Several lesions, such as osteochondritis dissecans (OCD), osteonecrosis, and traumatic osteochondral defects lead to changes of the entire osteochondral unit, affecting both the bone and the cartilage, two tissues characterized by different intrinsic healing capacities. Therefore, the treatment of osteochondral lesions represent a great challenge for orthopedic surgeons. Among the numerous approaches proposed to treat osteochondral lesions, biphasic scaffolds were found to be a powerful tool for their skills to reproduce the different biological and functional requirements and guide the growth of the two tissues. We performed a pilot clinical trial evaluating the result of an osteochondral nanostructured biomimetic scaffold - MaioRegen® (Fin-Ceramica Faenza S.p.A., Faenza - Italy) that has a porous 3-D composite tri-layered structure to reproduce the original anatomy of the structure.

Twenty-nine patients (9 women, 20 men, mean age 35 ± 11 years) affected by knee chondral or osteochondral lesions (average size 2.3 ± 1.3 cm², range 1-6 cm²) were treated with the osteochondral scaffold. Patients were clinically evaluated up to 6 years of follow-up using the IKDC and Tegner scores. Moreover, an MRI evaluation were performed after 2 and 5 years from the surgery.

Statistical analysis demonstrated a significant improvement of all clinical scores from the basal evaluation to the final follow-up. The IKDC subjective score improved from 39.8 ± 14.3 to 77.7 ± 13.7 and 78.8 ± 15.3 , at 1, 2, and 6 years, respectively. The Tegner score improved markedly from the baseline evaluation (2.0 ± 1.1) to the 1, 2 and 6 year of follow-up ($p < 0.0005$), with stable results over time (4.0 ± 1.6 , 4.0 ± 1.9 and 4.2 ± 2.1 , respectively). The MRI evaluation of 23 lesions significantly improved in both MOCART score and subchon-

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dral bone status from 2 to 5 years; however, some abnormalities persisted, even though images were not correlated to the clinical outcome.

This one-step surgery with the implantation of biomimetic osteochondral scaffold has a great potential for the treatment of the osteochondral lesions. The results of this technique are encouraging and underline the safety and great effect of the Maioregen, which offered a wide satisfaction of the patients and good clinical outcome with stable results up to a midterm follow-up. In particular, clinical outcome significantly improved from the baseline to the 1 year of follow-up, and from 1 to 2 years of follow-up; the improvement remain stable then up to 6 years of follow-up. Recent studies have investigated this approach for the treatment of more complex osteochondral lesions, such as patients with previous history of intra-articular fracture, tibial plateau lesions, concurrent knee axial realignment procedure, meniscal scaffold or allograft implantation, and unicompartmental osteoarthritis. For these challenging lesions the surgical approach includes, beside the osteochondral scaffold implantation, the assessment of comorbidities, such as axial malalignment or meniscal transplantations. Results were very encouraging, with clinical improvements for short-term of follow-up, thus suggesting the potential of this osteochondral scaffold not only for patients affected by OCD or little size articular cartilage defects, but also for big size defects and the abovementioned complex lesions.

Return to sport after cartilage surgery

Stefano Della Villa (IT)

Despite the improvement in the treatment procedures, articular cartilage lesions remain affected by long recovery time that preclude the athlete competition for long time.

Postoperative rehabilitation is a critical component of the treatment process for athletic articular cartilage injury and should take into consideration the biology of the cartilage repair technique, cartilage defect characteristics, and each athlete's sport-specific demands to optimize functional outcome. Systematic, stepwise rehabilitation with criteria-based progression is recommended for an individualized rehabilitation of each athlete to achieve not only initial return to sport at the pre-injury level but to allow for continued sports participation and to reduce risk for re-injury or joint degeneration under the high mechanical demands of the athletic activity.

A thorough understanding of the biological and biomechanical factors to consider and principles of cartilage repair is important and close communication between surgical and rehabilitation teams is essential for successful recovery and return to sport. Independent of the inherent differences between cartilage repair techniques, the process of rehabilitation and returning the athlete to sport after knee articular cartilage repair can be divided into three sequential phases: an initial protection and joint activation phase, a second progressive joint loading and functional joint restoration phase, and final activity restoration phase.

During the first phase the cells contained in the defect (mesenchymal stem cells or chondrocytes) start differentiating and producing a primitive, unorganized and soft initial repair cartilage tissue. During this phase the soft, putty-like repair tissue is vulnerable to mechanical overload and requires protection to avoid limited integration of the repair tissue to the defect base and surrounding normal articular cartilage. High compressive and shear stresses during this period can decrease chondrocyte metabolic rate thereby negatively affecting the process of repair tissue development and integration. In contrast, low mechanical forces may promote repair cartilage formation and nutrition. Due to the differences introduced by different cartilage repair techniques, lesion characteristics, and concomitant adjuvant procedures, the initial limit and progression of weight bearing activities should be individually determined by the surgical and rehabilitation teams for each athlete. Consequently, the duration and activities of the protection phase may be variable based on the unique situation of the individual athlete.

During the second phase, controlled gradual increase of the mechanical stress on the primary repair tissue stimulates cellular metabolism leading to production of proteoglycans and collagen deposition. This strengthens the cartilage repair tissue and makes it more resilient to increasing mechanical stress and more complex joint loading patterns.

During the final rehabilitation phase further organization and maturation of the cartilage repair tissue occurs by adapting to the even more demanding joint stresses associated with athletic impact and pivoting activi-

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ties. Gradually increasing impact and sport-specific movement patterns during this phase prepare the athlete to return to the high mechanical stresses associated with sports without overloading the repair tissue and potential repair tissue deterioration.

An important principle in cartilage repair rehabilitation is to progress the athlete on an individual basis without firm adherence to specific time guidelines but rather using a criteria-based approach. Clinical symptoms should be used to guide the progress of the athlete through rehabilitation. Pain and particularly joint effusion following the rehabilitation exercise should be avoided as they can lead to quadriceps inhibition with its negative effect on neuromuscular joint control, joint biomechanics and resultant increase in joint reaction force in the area of the cartilage repair. Neuromuscular and proprioceptive re-education has important implications for dynamic joint alignment and has been shown to play an important role in preventing injury or re-injury.

On-field rehabilitation (OFR) presents the final and very important component of the return to sport pathway following cartilage repair. The OFR is designed to gradually bring back the athlete to competition while preventing the risk for re-injury. On-field rehabilitation is organized into gradually increasing sport-specific exercises which progress from in line running and jumping to acceleration and deceleration drills, progressive pivoting and cutting maneuvers at increasing speeds, and gradual incorporation of sport-specific equipment and movement patterns. Progression is always criteria-based requiring the absence of pain, swelling, and limited ROM with the increasing activity.

In conclusion postoperative rehabilitation is a quintessential component of the treatment process for cartilage defects in the athlete. To optimize functional outcome and the ability to return to sport, rehabilitation has to be adapted to the biology of the utilized surgical repair technique, individual cartilage defect specifications, and each athlete's sport-specific demands. Using these principles and close communication between surgical and rehabilitation teams, return to even demanding high-impact sport and continued sports participation can be successfully achieved.

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Agili-CTM Induced Hyaline Cartilage Regeneration: Mechanism of Action, In-vitro and In-vivo data along with Early Clinical Results

A.S. Levy¹ (USA)

Introduction

Regeneration of true hyaline cartilage is the coveted holy grail of orthopedics. To date four major approaches for treating focal cartilage defects dominate the clinical arena: 1. Osteochondral grafting (autografts or allografts), 2. Bone marrow stimulation, 3. Acellular scaffolds and 4. Cell-based technologies. Clinical experience has outlined several drawbacks using each technique: osteochondral grafting is limited by source tissue availability, or morbidity of donor sites; Microfracture and acellular scaffolds often result in an inferior fibrocartilage tissue; Cell-based technologies, in most cases, are prohibitively expensive and complicated. A common observation in failed microfractures or technologies that target only the superficial cartilage layer is a thickened subchondral bone plate with osteophytes forming within the repaired tissue. Recent data indicates that bone marrow lesions observed in MRI imaging of focal cartilage defects may act as pain generators¹. If bone marrow lesions are related to pain generation - possibly due to fatigue failure² - then replacement of the subchondral bone plate as well as the subchondral cancellous bone seems to be of great importance. An ideal solution could be an acellular scaffold, capable of attracting stem cells, that guides a regenerative process.

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The process culminates in the formation of true hyaline-cartilage covering a regenerated bone-plate. The Agili-CTM is a first-in-class acellular implant that has been designed to allow regeneration of hyaline cartilage and subchondral bone³. The current work describes the scientific evidence as well as early clinical results.

Methods and Materials

In-vitro experimentation:

[A] Effect of the Agili-CTM implant on human mesenchymal stem cells (Lonza) was studied in an osteogenic growth medium. The cells were cultivated first in either Osteogenic medium (Lonza) or in low glucose DMEM (PAA) supplemented with 10% Fetal Calf Serum. The cells were cultured in a 30 mm Petri dish for up to 28 days. FACS analysis of cells pluripotency markers was performed. Histology was performed using H&E stain and Alizarin red stain.

[B] Human Embryonic Palatal Mesenchyme (HEPM) cells, ATCC#CRL-1486, were seeded on top of Agili-C discs (D=6mm, L=2mm) at a density of 1.6×10^4 per disc. Cells were grown in HEPM growth medium for up to 7 days, in 48 well plates. Cell growth was followed using an alamarBlue® metabolic assay, at day 1 and 7 days post-seeding. Cell attachment and morphology was observed by SEM analysis at days 1, 3, and 7 post-seeding.

[C] Chondrocyte migration and cartilage formation assay was performed using cadaveric human cartilage tissues, taken from knees and ankles in which the chondral phase of the Agili-CTM implant was placed inside the tissue in the presence of 10% and 20% FBS. Tissues were cultured for up to 120 days and then histological evaluation was performed.

In-vivo experimentation:

[A] Several designs of Aragonite and Aragonite-hyaluronic composites were evaluated in the regeneration of osteochondral defects in a caprine model (mature, female, 55-60kg). Bi-phasic aragonite-based osteochondral scaffolds were prepared with drilled channels in the cartilage phase or in the bone phase, and compared to unmodified aragonite and empty control defects. The goats were followed for 6 months. Macroscopic, histological and immunohistochemistry evaluations were performed by NAMSA in a GLP manner.

[B] A long term study was conducted on twenty four, mature, female, 55-60 kg, Saanen goats. A critical sized focal osteochondral defect (6mmx10mm) was created in the medial femoral condyle. In sixteen of the goats Agili-CTM implants were inserted into the defect. Eight goats served as empty defect control. The goats were followed for six and twelve months after which they were sacrificed. Following sacrifice the following examinations were performed: macroscopic evaluation by independent blinded experts (according to Fortier et al. and ICRS), micro CT, synovial fluid analysis, 7 Tesla MRI utilizing T2 mapping and blinded histology and immunohistochemistry according to modified ICRS II-2010 and O'Driscoll et al (by NAMSA).

Post-marketing Clinical Study:

The Agili-CTM implant is CE marked for cartilage and osteochondral regeneration. It is currently being evaluated in a post-marketing multicenter study across Europe. Currently, over 50 patients were implanted with very promising clinical and radiograph results. Results of the first patient who completed the study are described.

Results:

In-vitro experimentation:

[A] Cell culture in the implant-containing dish indicated accelerated expansion and proliferation. Aggregation and differentiation was observed with HE staining and SEM. The cell structure changed from spindle-shape to polygonal shape. The cells maintained their pluripotency markers. By day 7, an increase in the expression of Runx2 and osteopontin was detected with RT-PCR indicating differentiation of the stem cells. [B] Cell attachment to the Agili-CTM was noted 3 hours after seeding. The Agili-CTM topography is nano-rough. This feature may account for cell attachment and formation of multiple podia (Figure 1a). Polygonal cell shape transformation is noted at 14 days. The shape of mesenchymal cells is correlated to the phenotype. Polygonal cell shape transformation may indicate expression of bone and cartilage phenotype (Figure 1b). [C] Migration of cartilage cells into the implant is observed in in-vitro cultured human cartilage implanted with Agili-CTM. The migrating cells formed extracellular matrix stained with Safranin O and fast green inside the 3D structure of the scaffold suggesting for a potential of forming a hyaline-like cartilage (Figure 2).

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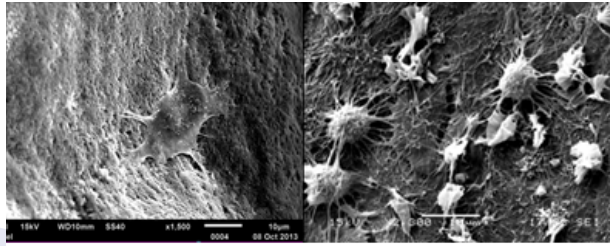


Fig. 1a: At day 1 the cells are attached to the nano-rough surface of the Agili-C implant

Fig. 1b: At 14 days the cells demonstrate a polygonal morphology and matrix synthesis

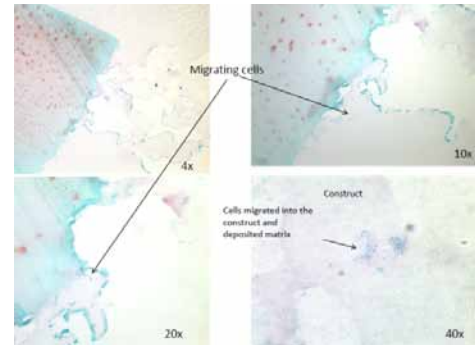


Fig. 2: Demonstration of chondrocyte migration and cartilage formation within the 3D structure of the Agili-CTM (human cadaver cartilage tissue taken from a 75 yr old male femoral condyle)

In-vivo experimentation:

The unique drilled-channels of the Agili-CTM implants appear to be crucial for hyaline cartilage regeneration. Only implants with Aragonite-hyaluronate composite and the drill-channels facing the articular space reliably induced articular cartilage formation. These implants appear to induce cartilage flow as well as cartilage colony formation from CD-90 positive cells found in the synovial fluid (Figure 3). Hyaline Cartilage and bone regeneration was found in the Agili-CTM implanted goats (Figure 4) but not in the controls. Results of Gross Appearance Macroscopic Evaluation (Fortier et al. Max=15) at six months after implantation (n=9) were 12 ± 2 vs. 5 ± 2 in the control group (n=5, $p < 0.05$) and at twelve months (n=7) 13 ± 1 vs. 9 ± 1 in the control group (n=3, $p < 0.01$) (Figure 2). Agili-CTM histological specimens at 6 months were associated with formation of articular hyaline cartilage and subchondral bone, resulting in a total score of 31 (max=38) vs 16 in the control group. Agili-CTM histological result scored 33/38 at 12 months, while control group was 18. New MOCART score average of the Agili-CTM treated animals was 32 ± 1 (max= 34) vs. 17 ± 1 in the untreated control group.

Post-marketing Clinical Study:

An active 47 year old male was injured playing volleyball. The original knee injury, which occurred 5 years prior to this implantation procedure, was defined as a rotational injury. A MRI scan revealed a full thickness chondral lesion of about 2 square centimeters in the weight-bearing area of the medial femoral condyle (Figure 5a). During arthroscopy a grade IV lesion was identified on the medial femoral condyle (Figure 5b), together with a smaller degenerative medial meniscal tear. The latter was partially resected, while the former (Figure 5c) was filled in a mini-invasive manner with two Agili-CTM implants. Both implants were introduced

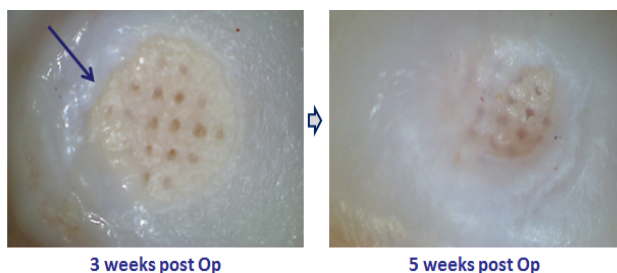


Fig. 3: Cartilage flow phenomenon from the implant periphery towards the center, enhanced by cartilage formation from within the implant (caprine model)

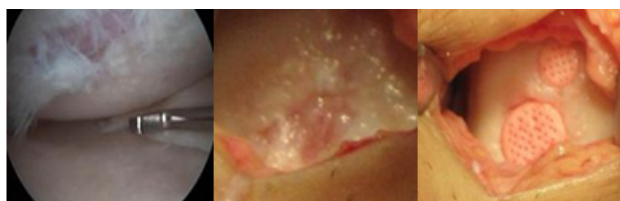


Fig. 5: A 2 sq cm² cartilage defect (Grade 4) on the MFC as observed arthroscopically (left) and during miniarthrotomy (middle). The lesion was repaired using two implants (right)

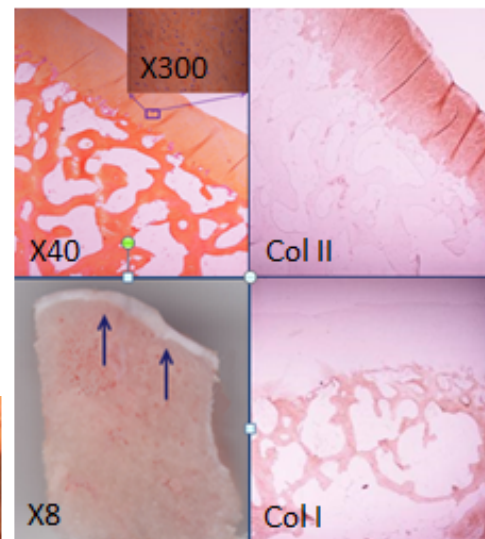


Fig. 4: Cartilage regeneration in caprine model 6 months post op (macroscopic and histologic results)

MODULE 2: CLINICAL PERSPECTIVE: SMART SCAFFOLDS FOR CELL RECRUITMENT

in a press-fit manner slightly below the native cartilage. A 3mm cartilaginous-bone bridge was intentionally left between the implants to provide mechanical stability and to facilitate biological ingrowth from the adjacent region. The rehabilitation treatment was based on the Ebert accelerated protocol approach. Six months post-operation the patient was skiing, nine months after the procedure the patient began to jog and at 12 months the patient participated in a 160-kilometer cycling race. At 18 months the patient returned to his pre-injury sports including ball-games. Twenty-four months post-operation, imaging studies appear to indicate complete regeneration of a tissue layer similar in thickness and signal properties to native hyaline cartilage, at the articular phase of the implants, good bone integration and remodeling of the bony phase of the implants (Figure 6). A sequential review of radiographs during the follow-up period indicates implant biodegradation that is suggestive of bone and cartilage formation, replacing the implant.

Discussion:

The Agili-CTM implant is an example of smart nanomaterial, directing stem cell migration into it and differentiation into either hyaline cartilage or bone, depending on material modifications. The regenerated tissue is true hyaline cartilage due to several parameters: collagen type II expression, lack of collagen type I expression, proteoglycan aggregation with typical zonation phenomenon at the 12 month follow-up time point, as well as subchondral bone plate regeneration, lack of intra-cartilaginous osteophyte formation and self-reconstructing of the articular contour. It appears that the Agili-CTM implant, in contrast to empty defects, prevents interleukin 1 expression and deterioration of surrounding articular cartilage.

In summary, the Agili-CTM is a first-of-a-kind acellular scaffold capable of inducing hyaline cartilage and subchondral bone regeneration. It appears to be useful in the treatment of focal articular cartilage defects and might also prevent deterioration of the surrounding articular surface acting to prevent progression to osteoarthritis.

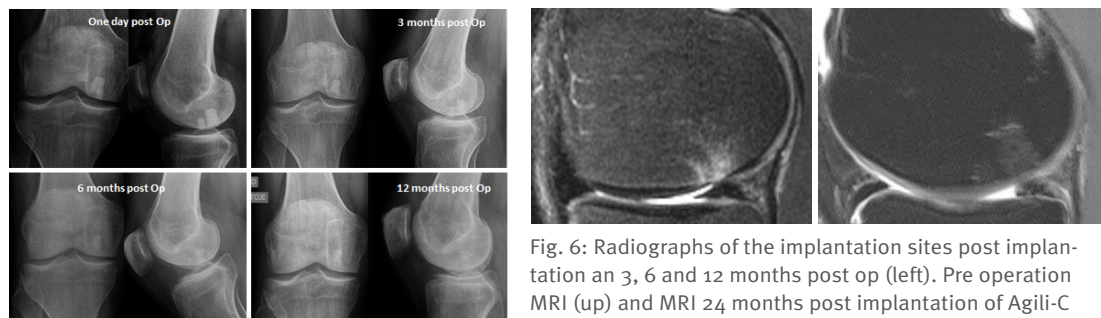


Fig. 6: Radiographs of the implantation sites post implantation at 3, 6 and 12 months post op (left). Pre operation MRI (up) and MRI 24 months post implantation of Agili-C implants (left right)

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MODULE 2: CLINICAL PERSPECTIVE: SMART SCAFFOLDS FOR CELL RECRUITMENT

AMIC-Technique, Geistlich Surgery

Matthias Steinwachs (CH)

Small scaffolds for cell recruitment:

The conservative treatment of cartilaginous lesions in young adults is dominated by two major procedures aimed to replace the anatomy and the function of the injured cartilage. Since the pioneer work of Brittberg, the two step procedure involving an autologous chondrocytes graft with or without coverage by a periosteal flap or a collagen membrane, several procedures have been evaluated in RCT's, some of them being still under evaluation. The recent review by Goyal D et al. 2013 has confirmed a good level of evidence for the ACT technique. The second procedure developed according to Steadman, is a single step autologous stimulation of the cartilage repair process through microfracture which is aimed to stimulate bone marrow stroma cells to colonize and differentiate in the debrided chondral lesion. At short-term follow-up Goyal et al 2013 could observe in his review good clinical outcomes of small lesions $< 2 \text{ cm}^2$ in patients with low postoperative demands for the microfracture treatment. But the results of microfracture are not homogeneous (Miethöfer K 2009). Beyond 5 years postoperatively, treatment failure after microfracture could be expected regardless of lesion size. Limitations for the long run of microfracture are the formation of intralesional osteophytes and a defect filling with fibrous mixed tissue. In order to further extend the indications of microfracture to larger lesions, and to enhance the efficacy of the procedure, the adjunction of a membrane covering the bioreactor induced by bleeding and bone marrow stroma cells was developed almost 10 years ago. The first clinical use was done by Steinwachs at the University Hospital Freiburg, Germany. Steinwachs et al. 2008 The AMIC procedure, autologous matrix induced chondrogenesis, was developed using a bioresorbable collagen membrane, fully biocompatible. The membrane, Chondro-Gide (Geistlich Pharma AG, Switzerland), is a bilayer membrane of collagen I and III fibers with a compact and a porous side. The porous side is in contact with the microfractured lesion, able to be colonized by cells and blood; the compact, cell occlusive superficial surface preventing cells from diffusing into the joint space and protecting them from mechanical stress. In vitro studies have demonstrated the capacity of bone marrow stroma cells to proliferate and differentiate into the membrane. The membrane can be cut to fit exactly into the defect, and to fill it restoring also a regular joint surface. The membrane is fixed through sutures or in smaller lesions using fibrin glue. A very precise physiotherapy program is used for at least 6 months with progressive recovery to physical and sports activities.

Although initially developed to treat chondral and osteochondral knee lesions, the technique has been also developed for osteochondral talus lesions and for head and acetabular lesions in the hip. Arthroscopic, or minimally invasive techniques can be used depending on the location of the lesions.

The results obtained since more than 7 years with the AMIC technique can be summarized as follows, through consecutive case series, prospective trials, comparative RCT or registry case collections:

- One step procedure of cartilage repair, with no associated morbidity
- Extended indications for the treatment of lesions of a mean size of more than 4 cm^2
- Stable improvement of the functional and clinical status of these patients after 2 and 3 years follow-up

(knee, talus, hip) and no evidence of clinical impairment after 5-7 years in the knee registry data. In the hip indications, no significant differences in clinical scoring was observed between ACL and AMIC after 5 years follow-up (Fontana et al.)

Although the AMIC procedure was initially described in association with microfractures, the “bioreactor concept” within the debrided chondral lesion can also be achieved without microfracturing the subchondral plate by local administration of bone marrow aspirate concentrate (BMAC), PRP, fibrin glue and superficial closure of the lesion with the Chondro-Gide membrane (Matrix Associated Chondroplasty (MACH© by Steinwachs)). This technique is particularly indicated in areas where bone marrow is scarce, as in patellar chondral lesions.

The present results of the AMIC procedure allow to consider it as an alternative technique to microfracture alone, particularly for lesions over the recommended size limit of 2 cm^2 allowing to extend the one step conservative treatment to lesions for which alternatives procedures do not exist or at much higher cost/benefit ratio.

MODULE 2: CLINICAL PERSPECTIVE: SMART SCAFFOLDS FOR CELL RECRUITMENT

CellCoTec

Konrad Slynarski (PL)

INSTRUCT combines autologous, freshly and rapidly isolated primary chondrocytes and bone marrow cells, in a cell mixture with a porous scaffold. The potency of the combination of primary chondrocytes with multipotent cells to support cartilage tissue regeneration, without the need for cell culture, was first demonstrated in 2001. By combining freshly isolated primary chondrocytes (non-cultured chondrocytes) with a large number of autologous cells that exhibit stem cell activity such as bone marrow cells, it is possible to achieve better and faster formation of hyaline cartilage than the existing microfracture and ACI method.

The INSTRUCT scaffold is comprised of the polymer PolyActive. PolyActive is a biocompatible, biodegradable and elastomeric polyether ester comprised of the building blocks poly(ethylene glycol) teraphthalate (PEGT) and poly(buthylene teraphthalate) (PBT).

This lecture presents the results of clinical trial - a prospective, multi-centre, open-label, single-arm study to treat cartilage lesions in the knee with the INSTRUCT.

40 patients have been implanted and will be followed-up for 2 years. The results originate from an interim analysis for all patients. Clinical experience showed that the ease of use of the scaffold was rated as excellent (77%) or good (23%). Patients showed a statistically significant ($p < 0.05$) mean improvement at 3, 6 and 12 months on VAS pain score (up to $\Delta 33$) and at 6 and 12 months on most KOOS domains (up to 23) and on IKDC (up to 21). Changes from baseline at 18 and 24 months were clinically significant on all parameters. On average, lesion filling on MRIs was consistently greater than 90% at all time-points. Hyaline cartilage was found consistently in more than 65% of 12 month biopsies. Out of the total patient cohort, 12.5% had device-related AEs and 5% experienced a treatment failure.

Intermediate results for INSTRUCT show a high potential for excellent tissue repair and clinical outcome, with INSTRUCT also offering the significant benefit of a single surgical procedure compared with existing cartilage therapies that apply chondrocytes.

The INSTRUCT is aimed to respond to the individual current treatment drawbacks by providing:

- A one-step procedure thereby reducing significantly (surgical) risks to the subject.
- Additional mechanical support provided by the scaffold.
- Optimized rehabilitation time.

Unique cell-processing procedure which is developed to intend to lead to long term hyaline like cartilage formation, expected to be a more viable long term healing solution for subjects.

BST-CarGel®: A Scaffold for Improved Cartilage Regeneration

Matthias Steinwachs (CH)

BST-CarGel® is a medical device presented as a liquid bio-scaffold which promotes hyaline cartilage regeneration when used in conjunction with bone marrow stimulation (BMS) techniques, such as microfracture or drilling. It is a one-step procedure which can be performed either by mini-arthrotomy or by arthroscopic delivery. When mixed with fresh autologous whole blood, it makes the blood clot in the cartilage lesion more voluminous than a normal clot (preventing its retraction), more adherent (due to its cationic nature), and in doing so it enhances the natural healing processes. BST-CarGel® is presently indicated for the repair of symptomatic articular cartilage lesions Grade 3 and 4, up to 7cm², located on the femoral condyles in the adult knee. Treatment with BST-CarGel® is administered through a mini-arthrotomy or by arthroscopic delivery.

The preclinical work showed that when mixed with fresh untreated autologous whole blood, BST-CarGel® stabilizes and reinforces the blood clot in the cartilage lesion, impeding its retraction [1, 2]. Furthermore, increased clot adhesivity within the lesion due to chitosan's cationic properties ensures prolonged activation of tissue repair processes by maintaining critical blood components above marrow access holes. These processes results in the enhancement of biological healing events such as: 1) increased inflammatory and bone marrow-derived

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stromal cell recruitment, 2) increased transient vascularisation of the provisional repair tissue, and 3) increased intramembranous bone formation and subchondral bone remodeling [3]. These enhanced biological events resulted, in different animal models, in a greater volume of repair tissue with improved hyaline characteristics [1-3].

An international randomized controlled trial (80 patients, aged 18 to 55, BMI ≤ 30) was conducted comparing microfracture alone to microfracture + BST-CarGel® [4]. The trial used quantitative MRI measurements for its co-primary structural endpoints, which were conducted by a third party in a blinded fashion. It was demonstrated with Level 1 evidence that the use of the bio-scaffold BST-CarGel® resulted in a consistently greater volume of repair tissue with highly improved hyaline characteristics, corroborating the previous findings from the pre-clinical work. Blinded quantitative MRI analysis at 12 months demonstrated statistical superiority for BST-CarGel® in greater % Lesion Fill ($p=0.0105$), and more cartilage-like repair tissue T2 values ($p=0.0330$). Also, BST-CarGel® treatment resulted in a significant clinical improvement (pain, stiffness and function by WOMAC) over baseline, similar to microfracture alone. Safety was similar for both groups. Additional supportive data from 38 biopsies obtained at a second look arthroscopy at an average of 13 months post-surgery were also analyzed in the same blinded fashion by a third party. BST-CarGel® showed improved ICRS macroscopic grading ($p=0.0002$) at the second look arthroscopy, superior collagen organization by polarized light microscopy (PLM; $p=0.0003$), and improvements in most histological parameters (4/6 ICRS-I and 10/14 ICRS-II, with 8 at ($p<0.05$) or near significance ($p<0.11$)). A longer term follow-up study at 3, 4 and 5 year post-surgery is actually ongoing. Preliminary data (still to be confirmed by the final analysis) from an interim analysis shows that the structural superiority found for the BST-CarGel® group persists over time. The clinical benefits for microfracture alone starts declining at an average of 2.5 years post-op, while the BST-CarGel® group improves from 1 to 4 years (unpublished data).

BST-CarGel® proves to be a treatment of choice for superior cartilage regeneration. It results in a consistently greater volume of repair tissue with highly improved hyaline characteristics at 12 months. Furthermore, preliminary data shows that the improved structural characteristics at 12 months translate into durability of the repair tissue and long-term clinical benefits.

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GelrinC® - A Novel, acellular, Single-step Treatment for Cartilage lesions on the Femoral Condyle: Self Experience, Clinical and MRI outcome

Ron Arbel (IL)

Background: GelrinC® is a unique, CE marked, “of the shelf” biodegradable hydrogel matrix composed of polyethylene glycol (PEG-DA) and denatured fibrinogen. It is applied to a microfractured cartilage defects as a liquid and then photo-cured in-situ to create an elastomeric solid. This single-step procedure leads to complete defect filling regardless of shape, depth and size. The procedure is facilitated by a delivery device that enables easy and smooth implantation and photo-curing when the knee is vertically positioned. GelrinC mode of action is based upon four principles:

- a) In-situ curing - The liquid nature of GelrinC allows complete filling of and intimate contact with the defect walls regardless of the geometry of defect. Once cured into a solid implant, a dense hydrogel matrix is formed.
- b) Sustained mechanical support - The dense matrix provides sustainable mechanical support to defect walls preventing collapse into the subchondral bone. The implant prevents uncontrolled bone marrow cells infiltration and formation of fibrous tissue as observed after microfracture procedure.
- c) Surface mediated erosion - the combination of PEG-DA and fibrinogen creates unique surface mediated erosion. The fibrinogen provides cleavage sites for proteolysis, while supporting cell adhesion and tissue recognition,

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and the PEG-DA is subjected to hydrolysis. Complete biodegradation occurs within 6-12 months post implantation. d) Gradual build-up of hyaline-like cartilage - the biodegradation of the implant through surface erosion together with micro environmental cues such as adhesion sites and material stiffness allow the migration of mesenchymal stem cells to the lesion and their differentiation into the cell-type consistent with the surrounding tissue and for gradual build-up of hyaline-like cartilage.

Purpose: To evaluate the safety, performance and efficacy of GelrinC as a treatment for articular cartilage lesions located on the femoral condyle

Study design: Pilot, single arm, open label, multi-center study

Method: Study was approved by by Ethic committee at participating centers and by local competent authority. GelrinC was successfully implanted in mini arthrotomy procedure following a standard microfracture procedure in lesions ranging from 1-6cm² amongst 25 male and female patients, age 18-65, with grade III to IVA symptomatic lesions to the femoral condyle, minimum pain of 4 in the VAS scale and no other major co-morbidities to the knee. Additional two patients were enrolled into the study but GelrinC could not be successfully implanted due to the morphology of the lesion. These patients were considered as treatment failures and were followed up for safety only. All Patients were enrolled in 8 investigational sites in Israel and Europe over a period of 3 years. Patients follow a standard rehabilitation program and complete the following self-reported questionnaires; Knee injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC) score, pain score (visual analog scale [VAS]), the IKDC functional status and SF-36 score. The SF-36 survey includes a Physical Component Summary (PCS) and a Mental Component Summary (MCS) on a scale from 0 (bad condition) to 100 (optimal condition). MRI scans were performed periodically and MOCART and T2 mapping were evaluated. Patients were followed up at 1 week and 1,3,6,12,18 and 24 months post operatively.

Personal experience: I have become a site investigator of the GelrinC clinical study in the early stages of the experience in Humans. GelrinC procedure is an augmentation to a standard microfracture and the main challenge initially was to inject the GelrinC solution to lesions that are not positioned horizontally. Over the course of the study, Regentis developed a designated delivery device that enhances and simplifies the application of GelrinC, and I personally gained more experience with the procedure. Initially the procedure required some efforts but with the delivery device it became much easier to perform, allowing treatment of lesions in different locations, adding about 15 min to the standard microfracture. We are now a few steps away from performing the procedure arthroscopically.

Results: The average age of treated patients was 37.8 and the average lesion size is 2.5cm². Results demonstrate that GelrinC is safe; 3 SAE were reported during the study none of which was related to GelrinC and no "Definitely Related" Adverse Events were observed. GelrinC was successfully implanted in a single one step procedure. Procedure lasts 10-15 minutes and includes three implantation components; in situ liquid application, 90-seconds photo-curing and confirmation of implant retention by joint cycling before suturing the knee. Follow-up demonstrated substantial improvement of all observed parameters compared to baseline: overall KOOS score (excluding sports) shows improvement of 18.9 points at 12 months (n=21, p<.001), 24.5 points at 18 months (n=14 p=0.001) and 28.5 points at 24 months (n=6, p=0.031); IKDC shows improvement of 20.5 (p<.001) points at 12 months, 30.1 at 18 months (p=0.001) and 41.6 at 24 months (p=0.031). Average VAS at baseline was 6.3 and 2.8 at 12 months (p<.001), 1.3 at 18 months (p<.001) and 1.9 at 24 months (p=0.031); SF-36 shows improvement from baseline in the PCS component but no change in the MCS component as expected. MRI MOCART score demonstrates an average improvement at 24 months of 16 points compared to 6 months. T2 mapping ratio shows that in most patients, a good ratio of 0.8-1.2 is seen for both deep and superficial tissues at 12, 18 and 24 months, furthermore, a strong improvement of the T2 signal intensity ratio is observed over time.

Conclusion: While patients are still being enrolled to the study and follow up of patient is not completed, GelrinC demonstrated significant and sustainable improvement over time. It is a promising, safe and effective novel technology for the treatment of femoral cartilage lesions. Long-term follow up and a larger sample size are required to confirm these findings compared to microfracture treatment.

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Collagen + BMAC: Ankle

Sandro Giannini (IT) & Francesca Vannini (IT)

Osteochondral lesions of the ankle joint are defects of the cartilaginous surface and underlying subchondral bone, typically affecting the talus, most frequently traumatic in origin. Osteochondral lesions are often asymptomatic and may usually be treated conservatively, taking care to follow the patient over time. Bigger lesions, or higher grade lesions, especially in adult patients, are usually painful and hardly respond to a conservative treatment, furthermore osteoarthritis may develop. So that, surgical treatment is frequently indicated. Thanks to technical advancements, regenerative techniques are quickly moving from traditional periosteum based autologous chondrocyte implantation (ACI) to bone marrow derived cell transplantation (BMDCT). The introduction of a biodegradable scaffold based on the benzylic ester of hyaluronic acid for cell support and proliferation represented a first advancement toward a full arthroscopic procedure and significantly decreased the morbidity of ACI procedure in the ankle joint. Still two surgeries were required.

Recently, BMDCT has been proposed as a technique capable to provide a repair of the lesion by hyaline cartilage in a one step procedure. Mesenchymal stem cells have the ability to differentiate into osteoblasts and chondroblasts. The rationale of the “one-step technique” is to transplant the entire bone-marrow cellular pool instead of isolated and expanded mesenchymal stem cells. The BMDCT in fact allows the implantation of MSC together with all the mononuclear cells and high regenerative potential present in the bone marrow. Furthermore, autologous bone marrow contains not only stem cells and precursor cells, but also accessory cells that support angiogenesis by producing several growth factors. This ability is particularly useful in the treatment of osteochondral lesions, where the possibility to regenerate the subchondral bone is strictly dependent on angiogenesis. According to this rationale, it is possible to implant into the defect the entire regenerative potential of the niche, without the need to select and expand the MSC in a lab phase making a one step procedure possible.

With a dedicated kit a total amount of 60 ml of bone marrow aspirate is harvested from the posterior iliac crest, with the patient in prone decubitus. A collagen scaffold and the instrumentation previously used for ACI are then used for an entirely arthroscopic implantation. Autologous platelet-rich fibrin (PRF) is added in order to provide a supplement of growth factors. The results of this procedure have been confirmed by biopsies and T2 mapping MRI and are clinically encouraging at mid term.

Bone marrow-derived cell transplantation resulted in AOFAS scores similar to those reported for other widely used techniques. Histologic and immunohistologic results by bioptic samples indicated a good quality of the regenerated tissue. T2 mapping MRI has proven capable, even in osteochondral defects of the talus, to give a qualitative assessment of the cartilage in terms of percentage of water quantity. The advantage of T2 mapping is to evaluate non invasively the presence, in articular surface, of hyaline cartilage, fibrocartilage or tissue remodeling phase. T2 mapping MRI results demonstrate the presence of a hyaline like tissue regeneration and also that the presence of a high percentage of hyaline regenerated tends to correlate to the maintenance of a high clinical score at mid term of follow-up.

Although a long term follow-up is needed, the arthroscopic “one-step” BMDCT represents may be an improvement in osteochondral repair, achieving high clinical scores with the formation of repair tissue and without the limits of previous techniques.

Biological reconstruction in high grade osteonecrosis of the femoral head: results to a minimum of 2 years of follow-up

Dante Dallari (IT)

Introduction

We present our results at a minimum of 2 years follow-up in patients with severe osteonecrosis of the femoral head (ARCO 3b, 4) treated with a new femoral epiphysis biological reconstruction procedure developed by us.

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Method

The technique involves the surgical dislocation of the femoral epiphysis and removal of chondromalacia and necrotic area, followed by the reconstruction of the epiphysis with bio-ceramic cylinder (TruFit), lyophilized bone chips soaked with concentrated stromal cells (Bone Marrow Stromal Cells) and platelet gel (Platelet Rich Fibrin) with a membrane with engineered autologous chondrocytes in covering.

Between September 2006 and September 2009 we treated 20 hips in 18 patients. Sixteen patients were males and 4 females, mean age at the time of surgery was 30,9 year (15 - 44). The follow-up includes clinical (evaluation by Harris Hip Score) and radiological (X-rays, CT and MRI of the pelvis) examination at 6 weeks and 3, 6, 12, 24 months. The cases that have had a subsequent need for prosthetic treatment and cases with HHS <75 at last follow-up were judged as clinical failures. The cases that showed progression of the degree of necrosis (ARCO classification) were judged as radiological progressions.

Objectives

In advanced cases of osteonecrosis of the femoral head, the intervention of choice is total hip arthroplasty to eliminate the pain and to restore function of the joint. Especially in young patients would be very useful to be able to use surgical techniques that allow to preserve the femoral epiphysis.

Results

At a mean follow-up of 36.7 months (24 to 59.8) we had a clinical failure in 37% of treated cases (7 patients, 2 of which were undergoing hip replacement). Radiographic progression has had in 50% of cases. The pre-operative mean HHS was 56,1 (42 - 73) and at the last follow-up it was 79,7 (60,7 - 95). The clinical failure-free patients group has a mean HHS of 85,1 (77,9 - 95).

Discussion

In advanced grades of osteonecrosis of the femoral head (ARCO Grade 3b - 4), the treatment of choice to control pain and restore function of the joint is hip replacement. In the case of young subjects that may subject the patient to significant disability and the need for subsequent treatment of revision. A number of conservative surgical solution are historically described but with poor outcome. The technique we propose aims to reconstruct the morphology of the femoral epiphysis, in order to avoid or delay the need for replacement surgery. Our results with a minimum follow-up of 2 years show that biological reconstruction of the femoral epiphysis may be a non-prosthetic alternative treatment in a high percentage of patients.

Collagen + BMAC: Knee

Alberto Gobbi (IT)

Introduction

Articular cartilage is a highly specialized tissue responsible for load bearing function as well as in providing a smooth gliding interface of a joint. Due to the presence of few specialized cells, low mitotic activity and its avascular nature, however it has a very limited potential to heal [1]. Following injury, cartilage regeneration cannot be expected, and a surgical treatment may become necessary in order to prevent the development of osteoarthritis (OA) [2].

Traditional techniques that are palliative or reparative in nature have demonstrated variable results. These include lavage and chondroplasty which can provide symptomatic pain relief but no actual hyaline tissue formation at the injured site and creates a cartilage tissue, which is functionally and mechanically inferior. Bone marrow stimulation techniques, such as subchondral plate drilling or microfracture produce hyaline-like tissue with variable properties and durability, which in many cases produces fibrocartilaginous tissue which degenerates with time [3, 4, 5]. Osteochondral autologous transplantation and mosaicplasty can restore normal cartilage tissue but their application is restricted to small defects and concerns arise regarding donor site morbidity and the need for two surgical procedures [6, 7, 8, 9, 10, 11]. Although many of the short-comings of first generation ACI are dealt with by second generation ACI, it still remains a two stage procedure, which is potentially more expensive. Hence, there has been a growing interest in establishing a one step procedure to address chondral lesions, to provide a cost effective and ideal repair tissue.

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Materials and Methods

From 2006 we prospectively followed up for 3 years 25 patients (25 knees) operated for grade 3b and 4a cartilage lesions of the knee (ICRS classification); these patients were transplanted using Bone Marrow Aspirate Concentrate (BMAC) covered with a collagen-based membrane. 18 patients had co-existing knee pathologies including tibio-femoral or patello-femoral malalignment and ligamentous insufficiency, which were treated at the same time as Mesenchymal Stem Cell (MSC) transplantation. Bone marrow was harvested from ipsilateral iliac crest and subjected to concentration and activation with Batroxobin solution (Plateltex®act-Plateltex SRO Bratislava, SK) in order to produce a sticky clot, which was implanted into the prepared cartilage defect. The patients followed the same specific rehabilitation program for a minimum of 6 months.

Results

Average age was 46.5 years (range 32-58 years). The average lesion size was 8.3 cm² (2.5-22 cm²). All the patients showed improvements in evaluation scores. Mean pre-op values were: VAS 5.4, IKDC subjective 41.73, KOOS Scores P=61.04/ S=55.64/ ADL=70/ SP=41.8/ QOL=37.2, Lysholm 65 and Tegner 2.07. At final follow up mean scores were: VAS 0.64, IKDC subjective 75.5, KOOS P=89.8/ S=83.6/ ADL=89.6/ SP=58.9/ QOL=68, Lysholm 87.9 and Tegner 4.1. No adverse reactions or post-op complication were noted. MRI showed good coverage of the lesions. Four patients gave their consent for second-look arthroscopy but only 3 for a concomitant biopsy. Good histological findings were reported for all the specimens analyzed which presented with many hyaline-like features.

Discussion

One-Step Surgery: Bone marrow derived mesenchymal stem cells

BMAC, which contains MSCs and growth factors, can present a viable single step, cost effective treatment option. The easy availability coupled with a self renewal capacity and multi-lineage differentiation potential of MSCs leading to generation of chondrogenic tissue, offers a promising option in cartilage surgery. Isolation of MSC's does not require the harvest of healthy cartilage tissue and can thereby bypasses the first surgery required for cartilage biopsy as in the case of ACL. [12-18]

These cells are present in various tissues such as bone marrow, synovial membrane, adipose tissue, muscles, tendons and umbilical cord blood; and they can be characterized by their differentiation potential into adipogenic, osteogenic and chondrogenic cells once cultured in the appropriate microenvironment [19-25]. Animal and laboratory studies have demonstrated that MSC's have chondrogenic potential [26-31]. When BMAC is used in conjunction with a collagen scaffold for the treatment of full-thickness cartilage defects of the knee, the porous structure of the scaffold facilitates adhesion, proliferation and differentiation of stromal cells obtained from the BMAC. [32] Grigolo et al [19] transplanted a hyaluronan scaffold seeded with in vitro expanded bone marrow-derived MSCs in chondral lesions of the knee in a rabbit model: they performed histological, histomorphometric and immunohistological evaluation, showing a better quality of the regenerated tissue between the implants with scaffolds carrying MSCs compared to the scaffold alone or non treated lesions in the control group at 6 months.

Hui et al [31] compared MSCs transplants to cultured chondrocytes, osteochondral autograft and periosteal grafts in animal models of osteochondritis dissecans. Based on histological and biomechanical evaluation, the authors found the stem cells transplants to be comparable to cultured chondrocytes and superior to periosteum and osteochondral autograft in their ability to repair chondral defects. Wakitani et al [30] first described the use of expanded bone marrow derived mesenchymal stem cells to repair cartilage defects in osteoarthritic knees in a clinical study: they concluded that MSCs were capable of regenerating a repair tissue. Nejadnik et al [35] compared the clinical outcomes of patients treated with first generation ACL with those treated by BMSCs injection in a prospective study: at the end of 2 years, patients from both the groups had comparable results with better results in patients in MSCs group.

Conclusions

The use of BMSCs to repair full-thickness articular cartilage lesions can be a promising option for the treatment of knee cartilage defects. This procedure shows less morbidities and complications inherent to traditional cartilage-repairing surgical techniques by lowering surgical procedure time and multiplicity of interventions in the patient.

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Continuing our research on these concepts of conservative biological approach to OA with the aim of salvaging the joint, especially in relatively young patients, we introduced the new concept of “Biologic Arthroplasty” [33, 34] for the treatment of large osteochondral lesions measuring even up to 22cm² in size.

However, carefully conducted prospectively randomized studies for each of these innovations should be carried out to validate their efficacy for cartilage regeneration.

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AMIC + BMAC

Piero Volpi (IT)

AMIC technique (Autologous Matrix Induced Chondrogenesis), which combines microfractures with the use of a type I/III porcine collagen matrix (Chondro-Gide, Geistlich Pharma), is able to stabilize and protect the blood clot coming from the microfractures of the subchondral bone. Although recently introduced, satisfactory results have been already reported at medium follow up. However, since all marrow stimulation techniques collect only a poor number of mesenchymal stem cells (MSCs) and this number is variable among patients, it could be useful to enhance these techniques with progenitor cells harvested from bone marrow of the iliac crest, in order to provide a larger number of cells that can participate to the defect regeneration. Moreover, a wide variability in terms of presence of MSCs, radically affecting the clinical outcome between individual patients or surgeons, has been reported.

Basing on these observation, a prospective randomised clinical study with the aim to evaluate and compare the efficacy of AMIC® with AMIC® enhanced by bone marrow aspirate concentrated (BMAC) for the treatment of knee chondral defects was performed.

Twenty-four patients (range 18-50 y/o) with grade II or IV chondral lesions of the knee (ICRS classification) comprised between 2-8 cm² were randomly assigned either to the standard AMIC® (group A) or to the BMAC-enhanced AMIC® technique (group B). A sample of 30 ml of bone marrow was harvested from the iliac crest of the patients of group B; the sample was then centrifuged for 15 minutes in the surgical room using the kit Marrow Stim (Biomet, Warsaw, USA); at the end of the process a phase enriched in mononuclear cells was achieved. The matrix was then embedded in the BMAC prior implantation (only for group B). Small amounts of bone marrow samples were also evaluated in vitro to assess the presence of mesenchymal progenitor cells and their chondrogenic ability. Patients were evaluated pre- and postoperative by IKDC, Lysholm Knee Score and VAS pain scale at 6, 12 and 24 months. MRI was also performed at the same time point. Population background (age, weight, lesion size) was similar for the two groups, as well as pre-operative scores (both p>0.05). All the defects were grade IV located at medial femoral condyle (n=13), lateral condyle (n=5) and patella (n=6) with equal distribution. In vitro analysis revealed a difference in terms of cell concentration and surface marker expression with a higher enrichment in group B. In both groups clinical outcome significantly improved already after 6 months from intervention (p<0.05). All scores were further improved significantly until 24 months follow-up. After 12 months significant best results were found in group B (p<0.05), whereas at 24 months the groups were comparable. MRI showed satisfactory results after 12 months in both groups with further improvement over time.

MODULE 3: SMART SCAFFOLDS & BONE MARROW CONCENTRATE

These findings seem to indicate that the use of a larger number of mesenchymal progenitor cells enhances the clinical outcome in the first phase of the healing process. This is probably due to the paracrine activity of MSCs which, by the release of anti-inflammatory and trophic molecules, are able to create an intense cross talk with the surrounding resident cells and thus to probably ameliorate the healing process. In conclusion our study allowed us to demonstrate that both AMIC® and AMIC® with BMAC are effective treatments for chondral lesions of the knee. AMIC® with BMAC had better short-term clinical outcome which could be due to higher presence of progenitor cells in the beginning of the regeneration process, thus allowing to consider this treatment for patients requiring to come back to sport activities earlier. Longer follow-up and a higher patient number are needed to confirm these findings.

Cartilage surgery and osteotomy

Stephan Nehrer (AT)

Biomechanics of joints of the lower limb is the determining factor for the development of degenerative changes especially in the knee joint. The restoration of an orthograde anatomic alignment represents the basis for every recovery of the joint function. The ligament stability, meniscal injuries and the cartilage damage are important factors for the knee joint but the biomechanics of the entire lower limb is the most important factor of progression joint diseases; therefore, osteotomies are crucial operative corrective actions, to restore correct alignment.

In the last years, osteotomies have become more important, after years of being almost out of fashion. The reasons for the positive trend are the development of angle stable screw fixation of the implant, which enables to initiate an immediate mobilization after osteotomy and by the use of the open wedge technique, which allows a more physiological adjustment of joint axis: the angle of rotation of correction is closer to the actual rotation center of deformity and no leg length is lost.

The open wedge technique of the tibia is characterized by spreading of the osteotomy gap by chisels or spreader and intraoperative correction according to intraoperative measurements. Closing wedge osteotomies do not allow corrections after cutting out the bone wedge, especially in overcorrection and lead to an asymmetric deformity of the tibial head. However, open wedge techniques need a high experience in step-wise spreading the osteotomy, otherwise your risk a fracture of the opposite corticalis. In more severe cases of correction and osteoarthritis as well as in overlength closing wedge osteotomy is still preferable.

Especially patients between 40 and 60 years with early onset osteoarthritis in a joint compartment are candidates for an osteotomy. The selection of the right patients and a detailed planning of the osteotomy before surgery are the most important factors for an optimal clinical result.

For the planning longleg-standing X-rays to evaluate the mechanical axis are mandatory on which the mechanical axis of the whole extremity is determined by drawing a line from the hip center to the center of the ankle joint (Mikulic line). Then the joint line is created and the angles between mechanical axis and joint line are measured to determine whether the deformity is in the femur or in the tibia. About 30% of varus deformities also have some amount of femoral deformity. Femoral corrections are nowadays performed as closing wedge osteotomies on the medial side with angle stable implants.

Intraoperative control of correction angles and alignment is key to successful surgery. Navigation systems or an image intensifier are used for confirmation of the achieved correction.

An arthroscopy to directly assess the intraarticular structures and address concomitant pathology is performed in all cases. Meniscus tears, ACL ruptures and cartilage defects have to be addressed at the same time, furthermore it has to be secured that the lateral compartment and the femoropatellar joint is free of severe degenerative diseases. In the case of cartilage defect we either perform a two-stage procedure with a biopsy for cell transplantation and the second surgery with osteotomy and cell transplantation. For this surgery we take a straight parapatellar incision on the medial aspect to implant the open wedge plate within an incision. First we do the arthrotomy with preparation of the cartilage defect for implantation and then we perform the osteotomy and after we have achieved a stable correction we implant the cell graft. In these mo-

MODULE 3: SMART SCAFFOLDS & BONE MARROW CONCENTRATE

stly osteochondral lesions it is also crucial to restore the bone stock adequately with bone grafting from the iliac crest preferable. With the use of cell-free membranes it is possible to use a one-step approach, however there is still a debate on what the outcomes are after both procedures. Due to the stable conditions of the osteotomy rehabilitation can be started immediately postoperatively. Restricted range of motion is provided by the use of a brace. Partial weight bearing is started early with gradual increasing ROM, after 4-6 weeks after surgery full weight bearing can be started if the joint has no effusion or pain.

With the biological treatment options in cartilage repair on the affected side osteotomies have become a wider indication in early onset osteoarthritis and are in our hands competing with hemiprotheses or partial joint replacement. However the ongoing studies and controlled trials will clarify the role of osteotomy in cartilage repair.

MODULE 4: CULTURED MSC

Scaffold-free synovial mesenchymal stem cell-based cartilage repair

Norimasa Nakamura (JP)

Philosophy

Scaffold-free stem cell-based approach is feasible to cartilage and meniscal repair with advantages in various aspects such as safety issues, cost effectiveness, minimal surgical invasion and quick surgical time, with comparable repaired tissue quality with other cell-based therapies in cartilage repair.

Background

Immune-tolerance of MSCs

Safety issues regarding the implantation of animal-derived or chemical materials in clinical settings

High medical cost with the use of scaffold

Trends in promoting minimally invasive surgery

Risk of complications by long surgery

***In vitro* characterization of the TEC -human study-**

The purpose of this study was to characterize a tissue engineered construct (TEC) generated with human synovial mesenchymal stem cells (MSCs). MSCs were cultured in medium with ascorbic acid 2-phosphate (Asc-2P) and were subsequently detached from the substratum. The detached cell/matrix complex spontaneously contracted to develop a basic TEC. The volume of the TEC assessed by varying initial cell density showed it was proportional to initial cell densities up to 4×10^5 cells / cm^2 . Assessment of the mechanical properties of TEC using a custom device showed the load at failure and stiffness of the constructs significantly increased with time of culture in the presence of Asc-2P, while in the absence of Asc-2P the constructs were mechanically weak. Thus, the basic TEC possesses sufficiently self-supporting mechanical properties in spite of not containing artificial scaffolding. TEC further cultured in chondrogenic media exhibited positive alcian blue staining with elevated expression of chondrogenic marker genes. Based on these findings, such human TEC may be a promising method to promote cartilage repair for future clinical application.

Large animal studies on cartilage repair

The objective was to *in vitro* generate a mesenchymal stem cell (MSC)-based tissue-engineered construct (TEC) to facilitate *in vivo* repair in a porcine chondral defect model. Porcine synovial MSCs were cultured in monolayer at high density and were subsequently detached from the substratum. The cell/matrix complex spontaneously contracted to develop a basic TEC. Immunohistochemical analysis showed that the basic TEC contained collagen I and III, fibronectin, and vitronectin. The basic TEC exhibited stable adhesion to the surface of a porcine cartilage matrix in an explant culture system. The TEC cultured in chondrogenic media exhibited elevated expression of glycosaminoglycan and chondrogenic marker genes. The TEC were implanted *in vivo* into chondral defects in the medial femoral condyle of 4-month-old pigs, followed by sacrifice after 6 months. Implantation of a TEC into chondral defects initiated repair with a chondrogenic-like tissue, as well as secure biological integration to the adjacent cartilage. Histologically, the repair tissue stained positively with Safranin O and for collagen II. Biomechanical evaluation revealed that repair tissue exhibited similar properties similar to those of normal porcine cartilage in static compression test but the TEC-repaired tissue

MODULE 4: CULTURED MSC

had lower micro-friction properties than normal articular cartilage. We also conducted the same surgical model study using mature (12m-old-) pigs and there was no significant difference in the modified ICRS histological scoring and biomechanical properties except for lubrication properties.

This technology could potentially be a unique and promising method for stem cell-based cartilage repair.

Large animal study on meniscal repair

The meniscus is not entirely vascularized and has limited healing capacity. When the lesion involves the avascular region, complete reparative process cannot be expected. Recent studies revealed that the mesenchymal stem cells (MSCs) from synovial membrane have the potential to differentiate into a variety of connective tissue cells. With the synovial MSCs, we have developed a novel scaffold-free tissue engineered construct (TEC). Although scaffold-free, in vitro study demonstrated that the TEC possesses sufficiently self-supporting mechanical properties to withstand surgical handling. Moreover, the TEC is adhesive to the cartilage matrix and have chondrogenic differentiating capacity. Further, we have reported the feasibility of the TEC to repair partial thickness cartilage defect in a porcine model. Likewise, the TEC might also be applicable to incurable meniscal lesions. The purpose of this study is to test the feasibility of the TEC to meniscal repair. The synovial MSCs were isolated from the synovial membrane of the skeletally matured Crown miniature pig's knee, and cultured to be confluent with 0.2mM ascorbic acid-2 phosphate (Asc-2P). The monolayer cell-matrix complex was detached from the substratum at confluent condition as reported. The detached complex actively contracted to develop a thick, three-dimensional tissue (the TEC), which was implanted to 4mm diameter cylindrical defect at the anterior horn of medial meniscus. All animals were put a cast on bilateral legs for 1 week and then back to the free-caged activity. The implanted menisci were evaluated grossly and microscopically

The meniscal defects treated with the TEC were securely filled with fibrous tissue with good tissue integration. In contrast, there were none, or only partial, repair observed in the untreated defects. Histomorphometrical evaluation revealed that the meniscal defects was significantly better filled when treated with TEC (79% vs 33%) and integration ratio to adjacent meniscal tissue was also significantly better in the treated defects with the TEC (83% vs 51%). Furthermore, SO staining was decreased in 70% of the untreated menisci at the central portion, while SO staining was preserved in the TEC-treated menisci. Notably, focal articular erosions as mirror changes were observed at both the femoral and tibial articular surfaces in the 30% of the untreated knees (n=3), while no mirror lesion was developed in any TEC-treated knee. The present study demonstrated that the TEC implantation resulted in secure filling and repairing the incurable meniscal defect with good integration to the adjacent meniscal tissue. Moreover repair of the defect resulted in the prevention of body degeneration of meniscus as well as of chondral damage facing the meniscal lesion. Taking into account that the TEC does not require any extrinsic (biological or chemical) material for scaffold, this unique implant could be a promising therapeutic tool for the repair of incurable meniscal lesions.

Clinical Experiences

Clinical Trial has started in March, 2013 at Osaka University Hospital and 4 patients has been enrolled in this study.

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MODULE 4: CULTURED MSC

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Meniscus Repair with MSC

Peter Angele (DE)

Meniscus integrity is the key for joint health. Therefore, the main goal of every meniscus treatment should be the maintenance of as much meniscus tissue as possible. Repair of meniscus tears can be achieved by meniscus suture. However, in a recently published meta-analysis, the long-term outcome of meniscus repair showed a mean failure rate of 24%. Meniscus defects can be treated with porous cell free biomaterials, which revealed in mid-term results variable outcome from complete failure to regeneration with meniscus-like tissue.

In several studies with different critical-size defects in the meniscus, we could establish meniscus regeneration with cell based regenerative approaches: Combined vascular and avascular defects in the lateral meniscus of New Zealand White Rabbits was created by resection of the complete pars intermedia and treated with mesenchymal stem cells and hyaluronan collagen composite scaffolds. The results showed meniscus like defect filling in these full size meniscal defects. In another animal model, avascular meniscal punch defects were inserted in the rabbit's lateral meniscus and filled with a combination of mesenchymal stem cells and hyaluronan collagen based scaffolds. These critical avascular defects were successfully repaired with a differentiated meniscus-like tissue after 3 months in vivo. In our model, we could give, in part, answers to the underlying mechanism with the persistence of living mesenchymal stem cells over a follow-up period of 6 weeks. However, it is still not clear, whether the MSC effect is a direct action of the mesenchymal-based cells or is rather mediated by secretion of certain stimulating factors.

Recently, promising healing potential of stem cell/carrier combinations could be achieved in a clinically more relevant model. 4mm long meniscal tears in the avascular zone in the lateral meniscus of New Zealand White Rabbits were treated with a suture in combination with cell-free hyaluronan collagen matrices or stem cell/carrier composites. After 3 months in vivo the treatment by suture in combination with a cell-free carrier showed no healing response so that this can be regarded as a non-union model. However, the treatment with a stem cell/carrier combination resulted in meniscal repair with differentiated meniscus-like tissue. Thus, mesenchymal-based cells harvested from the bone marrow seem to enhance meniscus healing in critical-size meniscus defects.

Despite the fact, that meniscus regeneration seems to be feasible by growth factors and mononucleated cells, none of the cell-based strategies has entered clinical practice to date. The implementation of cell-based strategies is mainly limited by the necessity to expand cells prior to transplantation resulting in high treatment costs.

In our talk I will also focus on alternative treatment modalities, which use growth factors concentrated from peripheral blood aspirates or mononucleated cells concentrated from bone marrow aspirates as an attractive one-step procedure without the need for cell expansion in cultures and thus lower efforts and costs. The aim would be the regeneration of meniscus tears with a one-step, arthroscopically applicable procedure in order to reduce failure rate of meniscus sutures and allow meniscus regeneration in meniscus defects.

In summary, Tissue Engineering of meniscus with mesenchymal based cells seems to be a promising approach to treat meniscal tears and defects and to restore as much native meniscal tissue as possible.

Honorary Lecture: The NEW MSC: Drugs, Antibiotics and the Management of Innate Regenerative Potential

Arnold Caplan (USA)

Marrow derived adult Mesenchymal Stem Cells (MSCs) can be isolated and culture expanded. Although these cells are capable of differentiating into lineages that result in the fabrication of bone, cartilage, muscle, marrow stroma, tendon/ligament, fat and other connective tissues, MSCs have recently been shown to be

MODULE 4: CULTURED MSC

intrinsically therapeutic. Such culture expanded adult/MSCs are immuno-modulatory especially in muting T-cells and, thus, allogeneic MSCs have been used to mute or cure graft-versus-host-disease and Crohn's disease and are now being tested in certain autoimmune diseases. Furthermore, these allo-MSCs set-up a regenerative micro-environment which is anti-apoptotic, anti-scarring, mitotic for tissue intrinsic progenitors and angiogenic. These immuno and trophic activities result from the secretion of powerful bioactive molecules that, in combination, support localized regenerative events. The MSCs reside in every tissue of the body and function as perivascular cells (pericytes) until a focal injury occurs. At sites of injury, the pericyte is released and functions as a MSC that provides molecular assistance in activities leading to tissue regeneration. It is expected that MSCs that arise from pericytes from different tissues location or anatomical sites of injury will not be equivalent. Thus, adipose-derived and marrow-derived MSCs naturally reside as pericytes and have different functional capacities. The fact that uncultured, freshly isolated autologous "stromal vascular fraction (SVF)" from fat has been shown to be therapeutically effective in horses and dogs, strongly argues that the MSCs in the SVF are a potent multi-drug and site-specific delivery vehicle. There are now over 350 clinical trials listed on the clinicaltrials.gov website and these have the potential of changing the way disease and tissue injury are medically approached. This full thesis that adult MSCs are potent therapeutic agents is the theme of this lecture.

Intraarticular Use of Mesenchymal Stem Cells

Frank Barry Regenerative Medicine Institute, National University of Ireland Galway, Ireland

Adult mesenchymal stem cells (MSCs) isolated from bone marrow and a variety of connective tissues have been extensively tested in the treatment of bone and cartilage repair and in osteoarthritis (OA). In addition, fully allogeneic transplantation of human MSCs is tolerated in the immunocompetent host and allogeneic therapy has been effective in the treatment of graft-versus-host disease. However, there are many aspects of the biology of MSCs that are poorly described and a more exhaustive characterization is necessary to exploit these cells fully in the context of tissue repair. Adequate translation of MSC therapy will only be successful if the following are addressed: (1) development of new cell-specific markers, (2) deciphering the therapeutic mechanism of action and unraveling the paracrine signals that contribute to tissue repair, (3) understanding clonal heterogeneity in cultured populations, (4) ensuring that batch variability is controlled and (5) understanding the nature of host immunomodulation by transplanted MSCs and allogenicity. Further studies are also necessary to gain a comprehensive understanding of how MSCs may contribute to cartilage repair and how they may impede the progression of OA. This review will address aspects of the characterization of MSCs and the development of new markers and will also discuss their use in cartilage repair models.

Characterization of MSCs

While the preclinical and clinical testing of MSCs has advanced rapidly over the last few years, the development of efficient and standardised methods for their isolation and characterization has not. Most attempts to isolate these cells depend on adherent culture systems with a significant risk of preparing heterogeneous or poorly characterized populations. There is evidence that MSCs isolated by current methods are not homogenous and in fact consist of mixtures of progenitors and other cells. The uncertain nature of primary isolates of MSCs, the possibility of culture-induced heterogeneity and the lack of highly specific markers raise issues of regulatory compliance that may impede clinical testing. There is a risk that emerging clinical data will be compromised by this lack of standardization and that current methods of cell isolation may not result in the most therapeutically effective cells. The lack of MSC-specific markers has also made it difficult to construct meaningful hierarchical models of multilineage differentiation and to probe the *in vivo* antecedents of cultured cells.

Presently there are several antibodies that are routinely used to characterize MSCs from human bone marrow by flow cytometry and other methods and some have been adopted as release tests for clinical grade cells. These include CD105, CD73, CD90, STRO-1 and CD271. None of these represents a canonical marker of MSCs and therefore the homogeneity, reproducibility and consistency of isolated populations is not assured.

MSCs in Cartilage Repair

There are several factors which influence the selection of cells for cartilage repair therapy. These include ease of isolation, differentiation potential, evidence of engraftment and tissue repair and the absence of a host immune response. Chondrocytes represent one type of repair cells that are cultured *ex vivo* and then delivered to the cartilage surface, but it is not clear that these are the best choice. Stem cells with chondrogenic potential may represent a more effective and more readily available cellular therapeutic for this purpose.

MODULE 4: CULTURED MSC

Several tissue-engineering approaches have been used for cartilage repair, for example the fixation of implanted chondrocytes beneath a sutured flap of ectopic tissue or a collagen membrane. Other approaches have centered on the use of cells loaded on a scaffold and delivered to a lesion site. These methods are applicable to the repair of focal defects of defined dimensions but not to the treatment of complex lesions that cover a large surface area of the joint that may be associated with severe and progressive inflammatory conditions such as OA. It is attractive to hypothesize that MSCs could have a role in cartilage protection by direct resurfacing of the articular cartilage. However, it seems more likely, based on low levels of engraftment, that transplanted MSCs are effective mediators of repair by virtue of their capacity to deliver to the host a cascade of cytoprotective, antiapoptotic, immunomodulatory or proangiogenic factors. Based in this principle, the capacity of MSCs to enhance tissue restoration in the complex degenerate environment of the OA joint may be high.

Despite this, cell-based cartilage repair remains a challenging objective. Most efforts to date have relied on the local delivery of undifferentiated cells to the cartilage surface, often in association with a biocompatible scaffold. It is useful now to consider newer approaches, including the application of cells which are predifferentiated to match the tissue target, and to devise new approaches that will ensure optimal engraftment and retention at the site of injury. In the case of articular cartilage engraftment and retention of delivered cells is difficult to achieve.

MODULE 5: STEM CELLS: OPEN QUESTIONS

Stem Cells vs. Chondrocytes

Mats Brittberg (SE)

1. Chondrogenesis:

To start chondrogenesis in a repair of a cartilaginous tissue you will need a large number of chondrogenic cells and implant those cells in high densities [2]

2. Cell implantation:

The repair of an injured mesenchymal tissue is dependent on the local availability of cells with the ability to regenerate a new tissue. The goal for the orthopaedic surgeon is to try to deliver as many of the acquired cell-types as possible into the cartilage lesion in order to achieve some sort of repair.

3. Cell origin:

All current cartilage repair methods depend on an introduction of chondrogenic cells into the defect area. Which cells that should be used and from what donor tissue they are to be harvested from can be discussed but in general, there are more chondrogenic cells in younger patients.

When comparing articular chondrocytes with mesenchymal stem cells from iliac crest in the same patients, chondrocytes and MSCs behaved different and differentiated and formed different subtypes of cartilage, the hyaline and a mixed cartilage phenotype, respectively [5].

The choice:

A living tissue needs living cells. An injured tissue needs cells for the restoration. Cartilage has a very low cell to matrix quota and cartilage has no blood circulation. Within the cartilage matrix, cell recruitment is subsequently not possible via the vessel support as seen in other tissues. Cells need to be recruited with external help, either as a direct internal source, bone marrow derived or externally handled or externally manipulated cells. The cells to be used could be divided into four subgroups;

- 1. True committed autologous chondrocytes**
- 2. True committed allograft chondrocytes**
- 3. Chondrogenic autologous progenitor cells**
- 4. Chondrogenic allograft progenitor cells.**

Furthermore, the cells could be free cells in suspension, cells, in scaffolds as immature grafts or fully developed mature grafts, chondral or osteochondral and finally cells on carriers.

MODULE 5: STEM CELLS: OPEN QUESTIONS

Acellular approaches aim to facilitate the repair activity of native cell populations.

They may consist just of an empty matrix, or of a matrix containing biological signalling agents that will recruit and trigger the differentiation of local stem cell populations resulting in the formation of a functionally repair tissue.

Up till today, external cellular technologies include laboratory isolation and in vitro expansion of the cells. Cellular approaches could also be direct isolation of cells in the OR, use of crushed cartilage fragments in gels and with the cells used either alone or in conjunction with matrices.

Bone marrow mesenchymal stem cells (MSCs) are of interest as those cells can produce both the cartilaginous part as well as the chondral part when to repair osteochondral defects.

However, as mentioned above chondrocytes and MSCs differentiate and form different subtypes of cartilage. Subsequently, I believe that to be successful in tissue engineering of cartilage injuries, one has to pay attention to both the osseous and cartilaginous part; use of chondrocytes for the cartilage layers and bone marrow stem cells for the bony part[6]. At the same time, increased knowledge is needed of which type of matrices that permits the cells used to differentiate the way that the different layers of cartilage can be produced including the important calcified layer in between the chondrocyte repaired area and the subchondral bone. The aim is to tune the cells by cell recruitment, better cell to cell communication and finally cellular synergy to produce a tissue as near to regeneration as possible.

Real chondrocytes or fake chondrocytes that is the difficult question !? My choice would be chondrocyte progenitor cells within the cartilage instead of bone marrow or adipose derived chondrogenic cells.

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Injective Treatment with Stem Cells for OA - Scientific Basis

Elizaveta Kon (IT)

Articular cartilage lesions are a debilitating disease resulting in fibrillation and subsequent degradation which can also involve the subchondral bone and lead to the development of osteoarthritis (OA). One limiting factor in the repair of these defects is the well-known low intrinsic regeneration potential of cartilage. Mesenchymal stem cell (MSC) strategies are emerging as a powerful tool for cartilage repair, thanks to their marked ability to differentiate into a variety of connective tissues including cartilage. The regenerative effects of MSCs are due to their structural contribution to tissue repair and their immunomodulatory and anti-inflammatory action, through direct cell-cell interaction or secretion of bioactive factors. They can migrate toward injured tissues (homing/trafficking) where they display trophic effects (synthesis of proliferative, proangiogenic, and regenerative molecules). MSCs in cartilage regeneration represent a promising new approach with preliminary interesting findings, although many aspects are still controversial, and they have to be clarified. The optimal MSC source has not yet been identified: MSCs can be isolated from various human sources, such as adipose tissue, umbilical cord blood, synovial membrane, synovial fluid, periosteum, dermis, trabecular bone, infrapatellar fat pad, and muscle, but they present various differentiation abilities. Besides these cell properties, the yield of cells obtained by extraction might also be a limiting factor and contributes to the choice of cell source for clinical application. The continually emerging field of experimental stem cell

MODULE 5: STEM CELLS: OPEN QUESTIONS

research and cartilage repair, particularly with the help of preclinical large animal models, will provide some new solutions to this issue. The most appropriate cell source is not the only controversial aspect. For example, many important biological pathways that determine the fate of transplanted MSCs in cartilage defects, particularly with the view to hypertrophic differentiation, are unknown. Controlling the chondrogenesis of MSCs in this environment is not understood, as well as the interplay of MSCs with the adjacent osteochondral unit.

Some researchers have investigated the possibility to improve MSCs injective approach by using therapeutic agents (growth, transcription, or signalling factors) provided as peptides or genetic sequences. Nevertheless, so far a complete regeneration of the cartilage lesions has not yet been achieved even with these systems, thus showing the need for further development and for a better understanding of the intrinsic repair processes in this highly specialized tissue.

Despite this growing interest in MSCs approach for cartilage regeneration, knowledge on this topic is still preliminary, as shown by the prevalence of preclinical studies and, among the clinical findings, by the presence of studies of low quality due to weak methodology, small number of patients, and short-term follow-up. Nonetheless, the studies available suggest a potential for these cell-based treatments to be developed in many directions, with different available cell sources, the possibility to use them concentrated or expand them in vitro, alone or augmented with growth factors, and many other improvements are being developed. Many aspects have to be optimized, and randomized controlled trials are needed to support the potential of this biological treatment for cartilage repair and to evaluate advantages and disadvantages with respect to the available treatments.

MODULE 6: EARLY CLINICAL EXPERIENCE

ADIPOA Project: Adipose Serived Stroma Cells for Osteoarthritis.

Christian Jorgensen (FR)

Osteoarthritis (OA) is a degenerative joint disease, with loss of matrix, fibrillation, formation of fissures, and ultimately complete loss of the cartilage surface, for which no efficient therapy is available. OA is a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life, with strong impact on quality of life of healthy aging population in European countries. Cartilage is known to be populated by chondrocytes but also in a limited number of cells with characteristics of mesenchymal stromal cells and side population. Culture expanded adipose derived stromal cells CD73/CD90/CD105 triple positive subpopulation had multipotency for chondrogenic, osteogenic and adipogenic differentiation. We have shown that stromal cells, in particular adipose derived stromal cells have an immuno-modulatory and anti-fibrotic activity, protect cells for oxidative stress through secreted growth factors. We have shown that Intra-articular injections of mesenchymal stromal cells prevent the development of osteoarthritis in two large animal models, but the mechanism are unknown, and the role of endogenous stem cells present in the cartilage is elusive.

The **objectives** of this collaborative FP7 project are to establish stem cell based regenerative medicine in Rheumatology. For this, we have performed preclinical experiments and toxicology studies using increasing dose of ADSC and we propose to validate new concepts for OA therapy in open phase 1 dose escalating clinical trials using autologous ASC focusing on symptomatic OA according to EMEA guidelines. We demonstrate that autologous ASC are optimal candidates to stimulate the regeneration of injured cartilage.

The Singapore Experience

James Hui (SG)

Autologous Human Mesenchymal Stem Cells for Cartilage Repair: From Bench to Bedside

Abstract: Mesenchymal stem cells (MSCs) research demonstrated therapeutic potential of the cells. They can be used to treat diversified clinical conditions, from immune modulation to tissue regeneration. We have focused on the translational development of using MSCs clinically for cartilage repair. Earlier, we have demonstrated through in vitro research that human bone marrow (BM) is better source of MSCs than adipose

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tissue (Tissue Eng 2007). In the study, BM and adipose MSCs were cultured from the same sets of donors. Results showed that BM MSCs produced significantly more collagen II and s-GAG. We further demonstrated, in small and large animal, that MSCs were capable of enhancing cartilage repair (Am J Sports Med 2007, Stem Cells 2007, IJBS 2010). Especially in porcine, biomechanical testing showed that meniscus repaired with the addition of MSCs was significantly stronger than that of the control animals. A clinical trial comparing MSCs and chondrocytes (Am J Sports Med 2010) showed that both cell types were capable of improving cartilage repair. However, MSCs appeared to be superior in longer term follow up, work just as well in older patients (> 45 yr) and require 1 less knee surgery (cost saving with lower risk potentially). Clinical trials (IRB approved) are now open and accruing patients at the National University Hospital in Singapore to evaluate the safety and efficiency of autologous BM MSCs in cartilage repair. Harvested bone marrow samples (during knee surgery) are processed in clean room environment (cGMP cell processing facility recently re-modeled and upgraded) and cultured for 3 weeks. The cells are injected locally in the knee with hyaluronic acid. Preliminary results showed that MSCs injection is a safe procedure (in terms of serious adverse events during administration of MSCs) and the rate of microbial contamination is low (1 in 218 processes during a 6-year span from 2006 to 2012). Our research and development has demonstrated that, in the setting of cartilage repair, it is feasible to translate longitudinally from laboratory to clinical studies using animal models (small and large) to validate in vitro results prior to design and initiation of human trials. Recent completion of patient accrual and final analysis of the trials demonstrated efficacy of autologous MSCs in cartilage repair. (Arthroscopy 2013).

The Korean Experience

Yong Gon Koh (KR)

Osteoarthritis (OA) is a degenerative process of the cartilage involving the immune system, wherein local inflammatory reactions occur through the production of proinflammatory cytokines. Currently, no treatment is available to improve or reverse the process. Current treatment options for articular injury and OA itself only aim to relieve inflammation and pain but do little to delay disease progression. Various surgical methods have been proposed to regenerate articular cartilage, but they all are associated with complications, leaving many patients with inadequately treated cartilage lesions. These consequences are the driving forces behind the numerous ongoing efforts to develop new tissue engineering-based strategies for the treatment of OA. Because of their multilineage potential, immunosuppressive activities, limited immunogenicity, and relative ease of growth in culture, mesenchymal stem cells (MSCs) have attracted attention for potential clinical use. Additionally, MSCs have been suggested for use in the cell-based treatment of cartilage lesions. In Korea, there are 3 accessible sources of stem cells in humans for cartilage repair. The first source is bone marrow. Bone-marrow-derived MSCs have been identified as a new option for the treatment of osteochondral defects, and a new one-step technique for bone marrow-derived MSC transplantation has been proposed by Buda. After encouraging results were obtained in the ankle and knee, bone-marrow-derived MSC transplantation is now being permitted for osteochondral lesions of the knee in Korea. The second source is cord blood. Intraarticular transplantation of allogenic human umbilical cord blood-derived mesenchymal stem cells (CAR-TISTEM®) is already being used on a commercial scale in Korea. CARTISTEM® is a novel stem cell therapy for the treatment of cartilage defects caused by degeneration (such as in osteoarthritis) or repeated traumatic injuries, resulting in the regeneration of cartilage. Through a single surgical procedure, allogenic human umbilical cord blood-derived mesenchymal stem cells mixed with a viscous biopolymer are transplanted. CAR-TISTEM® is an MSC therapy that is cultured and prepared according to the good manufacturing practice standard of the Korea Food and Drug Administration (KFDA). The third source is adipose tissue. The MSC source is very important, and it is determined based on the ease of harvesting, population density, and differentiation potential. Unfortunately, bone marrow harvesting is painful for the donor and is associated with donor-site morbidities. Furthermore, with increasing age, there is a decrease in the number, lifespan, proliferation, and differentiation potentials of MSCs. In this respect, MSCs extracted from adipose tissue have been induced to exhibit the chondrogenic, adipogenic, and osteogenic phenotypes by using appropriate media. In addition, compared with the bone marrow, the adipose tissue is reported to give a higher yield of MSCs. In some reports, adipose tissue-derived stem cells (ADSCs) represent 6–10% of stem cells in the normal stromal vascular fraction of adipose tissue, a much higher percentage than that in adult human bone marrow, where MSCs represent only 0.001% of bone marrow nucleated cells. It is for this reason that adipose tissue was chosen as the source of stem cells. Over the last few years, ADSCs have been widely used in Korea by plastic surgeons as a semi-permanent volume expander. In June 2009, the KFDA allowed ADSCs to be used in autologous cell transplants when they are obtained and processed through a medical clinic with minimal processing (enzy-

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matic treatment, but no culture or plating). Data from 3 published studies on adipose tissue-derived stem cell therapy that were performed in our institute will now be presented. The first study, published in “The Knee” in 2012, includes 25 cases of knee OA treated with intra-articular injections of autologous MSCs. Autologous MSCs were separated from the infrapatellar fat pad of OA patients, isolated in vitro, and then injected into the patients’ knee joints. The short-term results were positive and showed that infrapatellar fat pad-derived MSC therapy with intra-articular injections is safe, provides assistance in reducing pain, and improves function in patients with knee OA. Through this first study, it was shown that stem cell therapy is safe, but its effectiveness was not yet confirmed. The second study, published in “Arthroscopy” in 2013, included clinical and MRI results collected over a longer follow-up period to indicate long-term effectiveness of the stem cell therapy. Thus, it is believed that this second study supersedes the previous work and is much more important. Additionally, in the second study, results of both clinical assessments and MRI showed that MSC therapy, with MSCs intraarticularly injected into the knee, is an effective way to reduce pain and improve function in patients with knee OA. Furthermore, treatment outcomes appear to be positively related to the number of cells injected, and 2-year results were better than short-term results. The third study, entitled “Clinical outcome of injection of mesenchymal stem cells with arthroscopic treatment in osteochondral lesion of the talus,” was published in the “American Journal of Sports Medicine” in 2013. In the previous 2 studies, patients with knee osteoarthritis were included; however, in the third study, patients with ankle cartilage lesion were included. The aim of this study was to compare the clinical outcomes of MSC injection and arthroscopic marrow stimulation with those of arthroscopic marrow stimulation alone for the treatment of OLTs in older patients. This study concluded that in patients older than 50 years, injection of MSCs with marrow stimulation showed results that were more positive as compared to those for the marrow stimulation treatment alone, especially when the lesion size was larger than 109 mm² or a subchondral cyst existed.

The results of these studies propose a new option for the treatment of OA and are an important first step in its development. However, several challenges still need to be overcome, which include identifying the optimal source of stem cells, scaffolds, and growth factors. Nonetheless, the positive clinical and radiologic outcomes obtained support further randomized controlled clinical trials of this treatment modality with a large number of patients and a long follow-up period.

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The Malaysian Experience

Khay-Yong Saw (MY)

Stem Cell Therapy for the Musculo-Skeletal System

One of the most common and challenging injuries for physicians to treat is cartilage damage in joints. The structure and function of articular cartilage leads to non-healing lesions or the formation of fibrocartilage after injury occurs. Well-established arthroscopic methods utilize controlled healing with marrow stimulation or transferring of non-injured cartilage to areas of injury. Historically, these arthroscopic methods as well as open and two-stage methods have shared common marginal outcomes. Recent study has investigated synthetic and biologic adjuncts to current methodology, including the use of: hyaluronic acid (HA), platelet rich plasma, mesenchymal stem cells (MSC) and peripheral blood progenitor cells (PBPC). Cell therapy has produced exciting results in animal models and has been shown to regenerate hyaline cartilage clinically in the knee joint. Our current method utilizes arthroscopic subchondral drilling of cartilage lesions in combination with a postoperative adjunct treatment involving: stimulation of the release of PBPC with filgrastim, harvest of PBPC with apheresis, and postoperative intraarticular injection of PBPC in combination with HA. Our early results lead us to the conclusion that cell therapy will have an integral part in the future treatment of cartilage damage as well as other components of the musculo-skeletal system.

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The Orthohealing Center Experience- Early Results with Intra-Articular Bone Marrow Concentrate

Steven Sampson (USA)

Incorporating orthobiologics is an appealing option to young adults to address a void in the range of treatments between hyaluronic acid (HA) and Total Joint Arthroplasty (TJA). The first generation biologic injectables of HA, have been successful in the treatment of pain for osteoarthritis of the knee. PRP represented the second generation of biologic injectables, the first of which that are autologous. While both generations of injections have been shown to provide relief with cartilage disorders of the knee, they are ideally better suited for early intervention in active individuals. PRP has demonstrated superior results when compared to HA. There is likely a synergistic role of combining PRP with HA with their overlapping properties. However limitations of PRP may include its non-differentiated blend of anti-inflammatory, pro-inflammatory, anabolic and catabolic mediators. While the replication of the body's natural balance of growth factors used synergistically may work best; recent studies have shown that isolating or blocking particular cytokines may be optimal for particular conditions. The third generation of patient bed-side injectables is Bone Marrow Concentration (BMC). While sufficient human safety and efficacy data is mounting; there is sparse data for the intra-articular application of same day BMC therapy in OA. Along with advanced orthobiologic therapies, MR imaging of cartilage must improve in order to demonstrate regenerative tissue quality.

This presentation will provide an overview of the Orthohealing Center's osteoarthritis treatment protocols incorporating biologics from HA, PRP, BMC, and Ozone with cutting edge adjuncts to facilitate recovery. We will briefly discuss our experience with "quantitative biologics" to count platelets and monocytes from PRP & BMC in the office setting before injecting back into the patient. We believe this may shed light on post injection flares and rapid responders. Questions raised include not only variability of baseline platelet count but more importantly, why do some patients platelets concentrate well and others not? Additionally this quantitative approach may protect the physician & patient by screening for blood abnormalities (increased WBC, Platelets at baseline etc). Understanding baseline biologic profiles may explain why some patients respond favorably and others do not.

We will present preliminary outcomes data for various applications of BMC from our clinic. We will also share retrospective data that compares outcomes of TKA & THA to BMC injection with 1 year follow up. This comparative data is courtesy of our colleague, Dr Mitchell Sheinkop and was presented at the Orthobiologics Institute (TOBI) in June 2013 in Los Angeles, CA. We believe that the greatest potential of biologics in cartilage repair; combines minimally invasive arthroscopic surgery (debridement, microfracture, meniscus transplant, meniscus repair, osteochondral allograft, subchondroplasty etc) with intra-operative and post operative cellular injections. Lastly, we will present a case report of arthroscopic debridement of chondral surfaces, medial meniscectomy and Subchondroplasty (SCP) with post operative BMC injection with follow up imaging.

Further research is needed to better understand the cellular makeup of BMC including progenitor cells and exosomes. Early experimental trials of BMC have demonstrated positive results in treating OA; however, most studies are non-randomized, void of a control group and sufficiently powered sample size. Further studies are needed to better understand the role of BMC in reducing pain and increasing function in cartilage disease.

MODULE 7: JOINT HOMEOSTASIS

Growth factors

Susan Chubinskaya (USA)

Post-traumatic or early osteoarthritis (PTOA) occurs as a result of joint overuse or joint injury and primarily affects young people, actively involved in various sports. They are eager to return to regular physical routines as soon as possible, which may lead to re-injury or more severe traumas. In acute joint injuries, cartilage damage likely occurs at the time of the initial trauma or soon after. Therefore, understanding how to prevent cartilage damage before irreversible progression begins may provide a window of opportunity for the evaluation of risk and diagnosis of early PTOA, which takes years to develop. By the time it becomes symptomatic, only surgical interventions remain as a viable treatment option. There is a critical need to develop strategies for improving the outcomes after surgical interventions that would delay or prevent the subsequent development of PTOA.

This lecture will provide the latest developments in the application of growth factors, one of the most advanced biologic approaches, for the treatment of cartilage defects in PTOA. Amongst the mainly studied in vitro and in vivo growth factors are the members of the Transforming Growth Factor- β (TGF- β) superfamily, especially bone morphogenetic proteins (BMPs), Fibroblast Growth Factors (FGF)-2 and 18, and Insulin-Like Growth Factor-1 (IGF-1). BMP-2 and BMP-7 appear to be extremely potent in cartilage and bone repair. Furthermore, Tissue Gen. Inc has recently developed TG-C (cartilage), which consists of allogeneic chondrocytes cells that have been genetically modified to produce the therapeutic growth factor (TGB1). At the moment there is a Phase II study in the US being conducted for the treatment of knee OA with the use of this product (@clinical trials.gov/NCT 01221441). BMP-7, also known as osteogenic protein-1 (OP-1), has been studied most extensively in vitro in our laboratory using human cartilage as well as in OA and PTOA animal models. The results suggest that BMP-7 may be the best candidate so far for a disease-modifying OA drug and also for PTOA due to its pro-anabolic and anti-catabolic properties. Unlike TGF- β and other BMPs, BMP-7 up-regulates chondrocyte metabolism and protein synthesis without creating uncontrolled cell proliferation and formation of osteophytes. BMP-7 prevents chondrocyte catabolism induced by pro-inflammatory cytokines or fragments of cartilage matrix components. It can induce synergistic anabolic responses with other growth factors, IGF-1, in normal and OA, young and old chondrocytes. It also regulates production of other growth factors (stimulates IGF-1 expression and inhibits BMP-2 expression) and their signaling pathways. In terms of IGF-1, BMP-7 restores the responsiveness of human chondrocytes to IGF-1 lost with ageing through the regulation of IGF-1, its receptor IGF-R1, binding proteins and downstream signaling mediators. BMP-7 has been also extensively studied in various PTOA animal models in dogs, sheep, goats and rabbits. In all these PTOA models (ACL transaction, osteochondral defect, and impaction), BMP-7 regenerated articular cartilage, increased repair tissue formation and improved integrative repair between new cartilage and the surrounding articular surface. In the impaction model, a window of opportunity for BMP-7 treatment has been identified. BMP-7 was most effective in arresting progression of cartilage degeneration if administered twice at weekly intervals either immediately after trauma or delayed by three weeks. If delayed by three months, the treatment was ineffective, suggesting that the development and progression of PTOA could be arrested and maybe even prevented if the right treatment is administered at the right time. Phase I OA clinical study produced very encouraging results by showing tolerability to the treatment, absence of toxic response, and a greater symptomatic improvement in patients that received a single injection of BMP-7.

Members of the FGF family, FGF-2 and 18, have been also tested as potential disease modifying drugs. There is no consensus on the role of FGF-2 in cartilage homeostasis and responses greatly depend on the cell type, species and experimental model. FGF-2 can stimulate cartilage reparative responses, but its potent mitogenic effects may lead to chondrocyte cluster formation resulting in poor extracellular matrix organization due to a relatively low level of type II collagen. Another member of the same family, FGF-18, appears to be a more attractive choice as pro-anabolic agent in PTOA. It has been shown to induce anabolic effects in chondrocytes and chondroprogenitor cells and to stimulate cell proliferation and type II collagen production. At this point only two growth factors, FGF-18 and BMP-7, have been tested for cartilage repair in phase I clinical studies in patients with established OA. A clinical trial with FGF-18 on patients with PTOA is completed, however results are not available as of yet.

In conclusion, considering growth factor therapy, there are a number of issues that need to be taken into account: choice of the growth factor, its formulation and dose, carriers and scaffolds, delivery methods (local via injections vs systemic vs gene delivery), time of intervention, and of course, possible adverse effects.

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Another important issue is that growth factors are expressed endogenously and production of many of them is elevated in response to injury. Therefore, their autocrine levels have to be considered in determining the dose and timing of growth factors administration. Yet, taken together the literature suggests that growth factors whether as recombinant proteins or as part of other emerging therapies, for example plasma rich platelets, remain the most viable disease modifying option for the treatment of cartilage defects in post-traumatic and maybe even broader, idiopathic, osteoarthritis.

PRP-Platelet-Rich Plasma

Giuseppe Filardo (IT)

A healthy joint requires a fine-tuned balance between molecular signals regulating homeostasis, damage, restoration, and remodeling. Different factors are able to impair the maintenance of homeostasis in a joint that has been damaged or strained, and they may progressively lead to osteoarthritis (OA). The search for a minimally invasive solution to improve the status of a damaged joint surface and allow a fast return to full activity is therefore highly desirable. In this landscape, a novel promising injective treatment is Platelet-rich Plasma (PRP), a blood derivative that has a higher platelet concentrate than whole blood. When activated, platelets release a group of biologically active proteins that bind to the trans-membrane receptors of their target cells, thus leading to the expression of gene sequences that ultimately promote cellular recruitment, growth, and morphogenesis, and modulating inflammation as well. Thus, PRP is a fashionable treatment, minimally invasive and with low costs. This explains the wide application of this blood derivative to several tissues and heterogeneous pathologies in different fields of medicine. The rationale for using platelets for the treatment of different tissues is that they constitute a reservoir of growth factors that are critical to regulate the tissue healing process, which is quite similar in all kinds of tissues. However, whereas the rationale for PRP use in other tissues is clear, since platelets represent the first response to a tissue damage where they participate in stopping the vessel bleeding and trigger the healing cascade, less intuitive is the rationale for PRP use in cartilage, which is a physiologically vessel-free tissue. Moreover, whereas some molecules such as TGF β might justify its use in cartilage, PRP also contains other molecules such as VEGF that do not take part or might even jeopardize cartilage homeostasis and regeneration.

Thus, we performed a systematic literature review to understand the biological rationale and the clinical evidence for the use of intra-articular PRP injections.

This systematic review showed an increasing interest on this PRP application with an increasing number of published studies over time: 61 articles met the inclusion criteria. The analysis of in vitro studies shows an overall positive effect of PRP on cartilage tissue. Besides some controversial results, most of the findings supported the role of PRP in increasing chondrocyte proliferation, without affecting chondrogenic phenotype and with an increase in the production of matrix molecules. These properties of PRP have provided positive results also in different animal models from focal lesions to OA. Clinical studies on PRP injective treatment for joint degeneration also showed overall good results. Nonetheless, both the rapid clinical benefit and the limited effect over time are in contrast with the timing required by a hypothetically induced cartilage regeneration process. Despite the wide majority of studies focusing on cartilage tissue, it is actually likely that the clinical benefit reported after PRP injection is attributable to other action mechanisms.

An intra-articular injection does not just target cartilage, instead PRP might influence the entire joint environment, and some in vitro studies confirm the effects of PRP on other cell sources. PRP has several potential effects by enhancing the cell signaling cascade in all joint tissues and inducing positive changes in the whole joint environment through a milieu of actions. Among these, tissue regeneration is actually not the only and maybe not the most important PRP mechanism of action, and increasing evidence supports the complex role of PRP in modulating inflammation. PRP might not lead to hyaline cartilage regeneration and might not change the clinical history with significant disease-modifying properties, but it still might offer a clinical benefit with symptoms and function improvement and possibly a slowdown of the degenerative processes. Some controversial findings reported underline the limits of preclinical studies, which do not exactly represent the peculiar human pathophysiology, and several other variables complicate this field and have to be considered, such as the heterogeneous preparation methods and the consequent presence of other cells, storage modalities, application protocols, and many other aspects that might not be of secondary importance for determining PRP properties and clinical efficacy.

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With the limits of a complex field still in its infancy, the preclinical literature shows an overall support toward PRP application for the injective treatment of cartilage lesions and OA. Moreover, some conclusions can be drawn also with regards to clinical application. The first one is the safety of PRP injections, with no major adverse events reported in the literature and only some reports of self-limiting immediate pain and swelling reaction. All studies seem to agree on an overall clinical benefit of PRP. Better results with respect to saline have been shown, and some studies suggest a slight superiority of PRP with respect to viscosupplementation.

However, among the available techniques none clearly seemed to offer superior clinical results, and it appears clear that there is room for a better targeting of this PRP application. Several aspects still need to be studied to understand the mechanism of action of PRP and give better treatment indications, and possibly to optimize the procedure and improve the potential of this biological minimally invasive approach for the treatment of cartilage degeneration and OA.

Serum and Synovial Biomarkers in early OA

Christian Lattermann (USA)

It is increasingly recognized that biochemical abnormalities of the joint precede radiographic abnormalities of primary or secondary OA by as much as decades. A growing body of evidence strongly suggests that the progression from ACL injury to osteoarthritis is multifactorial, involving the interplay between biomechanical disturbances and biochemical homeostasis of articular cartilage. However, unlike primary OA, post-traumatic secondary OA (PTOA) is initiated by intra-articular pathogenic processes with a known date of onset, namely the date of joint injury. This makes it much more amenable to early intervention than primary OA whose onset is not clearly definable at this time. A widely accepted clinical model for early PTOA are patients who suffered from ACL injuries.

For many years, however, it was believed that the biomechanically and anatomically correct reconstruction of the ACL would restore near normal joint kinematics. Biomechanically the knee joint can be restored to near normal knee kinematics using the latest anatomic ACL reconstruction techniques. However, the considerable variation in response to surgical treatment even in well-controlled studies and several recent systematic reviews have suggested that reconstructive surgery of the ACL or meniscus fails to protect against OA development. When abnormal joint stressors and abnormal joint physiology occur together, the outcome is potentially even more severe. This is illustrated by the fact that severe meniscal damage to the knee is more likely to cause eventual knee OA in patients with hand OA (evidence for a genetic predisposition to OA) compared with patients without hand OA.

Numerous research efforts have been made to identify biomarkers for established or active osteoarthritis. Some progress has been made to identify reliable biomarkers that predict or identify active osteoarthritis. Various cartilage breakdown products (e.g. serum Keratan sulfate (KS), serum hyaluronic acid (HA, serum Osteocalcin, SC1,2C sC2CC-propeptide of Type II collagen chondroitin sulfate 846 epitope)) have been studied in patients with established OA. While most of the studied markers have alone or in combination been moderately successful to determine disease progression in patients with established OA^{4,5,8,36}, to date only few serum markers have been shown to correlate well with early development of OA and acute knee injury. Hunter et al. ,for example, showed that sCOMP levels are up to 6-fold higher in patients with established knee osteoarthritis using MRI criteria and not radiographs, when compared to age matched controls¹⁷. Kuhne et al. showed that in patients with intra-articular knee injuries (average age 25) sCOMP levels are elevated up to eight times over age-matched controls²¹. Wislowska et al. found that sCOMP levels correlated directly with Western Ontario MacMasters Osteoarthritis Index (WOMAC) scores in patients with OA³⁶. In addition to these findings Sharif et al ³¹ showed that sCOMP level may be an indicator of increased bone turnover making it an attractive target for us to follow bone bruises. Just recently Caterall et al. have performed a comprehensive analysis of various serum, urine and synovial fluid markers in patients with ACL injury after injury and prior to surgery. They reported synovial fluid versus serum concentrations of 12 biomarkers identifying 7 biomarkers that showed significantly higher synovial fluid concentration than serum concentrations suggesting that the serum biomarker expression stems from the injured knee joint. This presentation will provide an overview of the current state of the science regarding biomarkers in early PTOA.

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Hyaluronic Acid

Pascal Richette (FR)

Osteoarthritis (OA) is the most common type of arthritis and the major cause of disability in elderly populations worldwide. Knee OA is the most frequent form of OA affecting a large joint, and its prevalence ranges from 20 % to 40 in populations older than 35 years. Current treatments for knee OA include a combination of non-pharmacologic and pharmacologic treatments. Viscosupplementation is an intraarticular therapeutic modality that is based on the physiologic importance of hyaluronic acid (HA) in synovial joints. Its therapeutic goal is to restore the viscoelasticity of synovial fluid and the natural protective functions of HA in the joint. In vitro and in vivo studies have also suggested that HA could have protective effects on cartilage extracellular matrix and could reduce the production and activity of proinflammatory mediators and matrix metalloproteinases. Viscosupplementation as treatment for knee OA has been the focus of numerous controlled trials and the subject of several meta-analysis. In the last meta-analysis, the ES for pain relief was around 0.2-0.3, showing a modest efficacy, but that is more important than the one computed with acetaminophen (ES 0.14), which is the first line recommended therapy by several international societies. Overall, the safety profile of HA is good.

Physical Stimulation

Giacomo Zanon (IT)

The catabolic and anabolic processes in the articular cartilage are mediated by soluble factors (cytokines, chemokines, enzymes, growth factors) released by the cells present in the various joint tissues (synovial membrane, cartilage, bone). The main molecules provoking intraarticular inflammation are IL-1 β , IL-6 and TNF- α . They are mainly produced and released by neutrophils and stimulate chondrocytes to produce catabolic enzymes as metalloproteinases (MMPs), nitric oxide (NO), prostaglandins. They also stimulate mesenchymal cells to develop a fibroblastic phenotype, less specialized, so with negative consequences on the quality of the repair tissue, which tends towards fibrocartilage. On the opposite side, adenosine is recognized as an anti-inflammatory molecule linking to its A2A receptors on the membrane of neutrophils and down-regulating the pro-inflammatory cytokines. The main soluble factors involved in the anabolic processes are the transforming growth factor (TGF- β), the insulin-like growth factor (IGF-1), the bone morphogenetic protein (BMPs), the cartilage-derived morphogenetic protein (CDMPs), IL-4, IL-13, IL-10.

Many in vitro studies demonstrated that pulsed electromagnetic fields (PEMFs) could alter this cytokines cascades, promoting the proliferation of chondrocytes, stimulating the synthesis of proteoglycans and limiting the catabolic effects of pro-inflammatory cytokines through their agonist activity of the A2A adenosine receptor. The activation of this receptor inhibits the synthesis and release of pro-inflammatory cytokines such as IL-1 β , TNF- α and the enzyme cyclooxygenase 2 (COX-2), responsible for the production of prostaglandin E2.

PEMFs also showed anabolic effects: they are synergistic with IGF-1 in stimulating the production of cartilage matrix components. Moreover, PEMFs stimulated the proliferation of mesenchymal cells, the production of extracellular matrix and induced an increase in TGF- β synthesis, an anabolic cytokine for cartilage.

Animal models have clarified the actions of PEMFs on the complex interrelations between subchondral bone, bone marrow, synovial cells and chondrocytes. They showed that biophysical stimulation could modify the evolution of a joint towards osteoarthritis, maintaining the thickness of the cartilage and preventing subchondral bone sclerosis. They also demonstrated that PEMFs can accelerate the healing of cartilage lesions of the femoral condyles treated with osteochondral implants, preventing the formation of bone resorption areas.

Some clinical prospective, randomized, double blind studies definitively confirmed the effectiveness of biophysical stimulation in cartilage protection. A trial involving patients with degenerative cartilage lesions subjected to various arthroscopic treatments (chondroabrasions, microfractures, radiofrequency) demonstrated better functional outcomes in patients treated with PEMFS compared with placebo at 90 days postoperatively. The need for NSAIDs was also significantly lower.

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Another study evaluated the functional outcomes in patients undergoing arthroscopic anterior cruciate ligament reconstruction with hamstring. The patients PEMFs-treated demonstrated a faster resolution of edema and a faster recovery of the full range of motion compared to the placebo group. Postoperative pain was significantly lower, as well as the use of NSAIDs. Comparing only the patients underwent associated meniscectomy, the difference in results between the two groups became even more noticeable.

The previous studies showed that biophysical stimulation has only local effects on the articulation on which it is applied; it acts on all the joint structures: synovial membrane, cartilage, ligaments, subchondral bone. Unlike drugs has no documented side effects but, like them, has a specific dosage regimen. The effectiveness of treatment is strictly dependent on the physical features of the stimulus applied: amplitude, frequency and duration. Several studies documented that 4 hours of application of a magnetic field of 1.5 mT intensity and 75 Hz frequency gives the widest response and the biggest anabolic effects on the cartilage. In conclusion, biophysical stimulation with pulsed electromagnetic fields allows treating all the articular tissues with a local, home-administered therapy with no side effects. It has proven analgesic and anti-inflammatory effects and reduces the recovery time after trauma or surgery. PEMFs preserve the proper structure and function of the articular cartilage and promote the engraftment and the proper development of the various methods of cartilage repair.

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HANDS ON COURSE IN CARTILAGE REPAIR

www.cartilage.org

Highlights

- Basic Science in Cartilage Repair
- Treatment Options for Cartilage Repair
- Stem Cells & Cartilage Lesions
- Cartilage in Osteoarthritis
- Microfracture, ACI, OATS
- Osteotomies
- Tissue Engineering

ICRS

International Cartilage Repair Society



UNIVERSITY OF THESSALIA
SCHOOL OF MEDICINE
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& MUSCULOSKELETAL TRAUMA

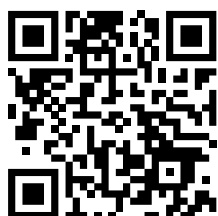
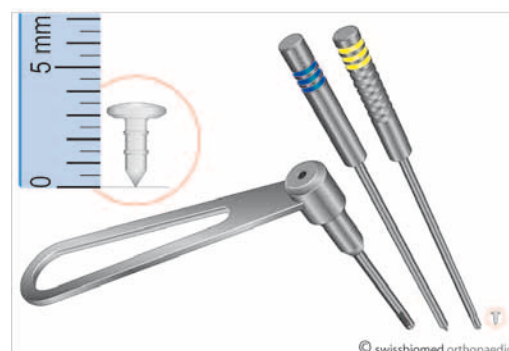
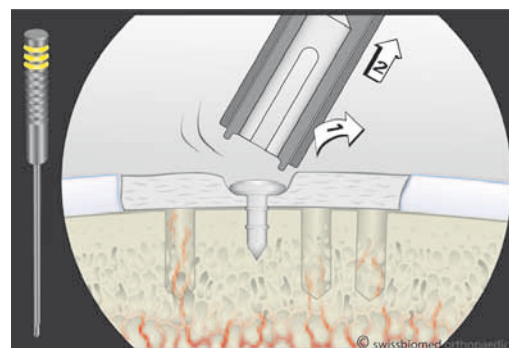
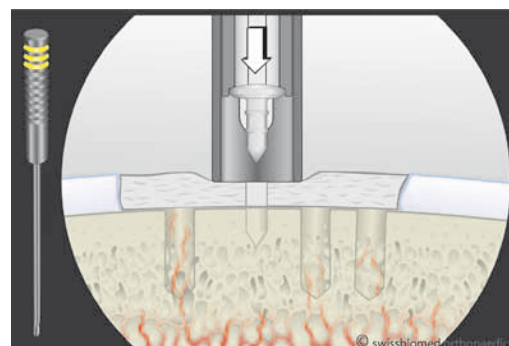
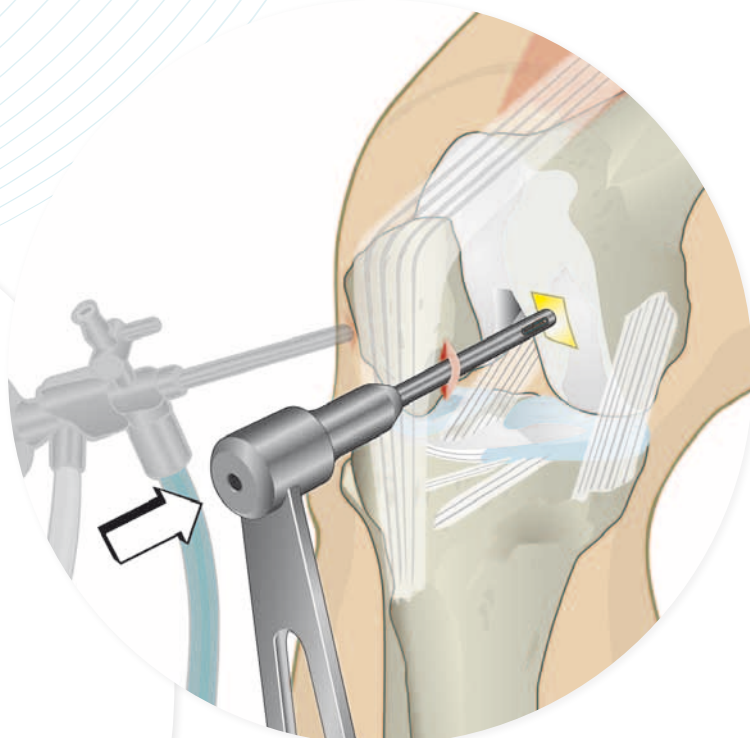
"HIPPOCRATES" AUDITORIUM & THE ANATOMY SUITES | Biopolis, Larissa - Greece

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ACS[®] -MATRIX FIXATION BY ARTHROSCOPY WITH BIOABSORBABLE PINS

ICRS Focus Meeting
Bologna, December 5, 2013

Session: Smart Scaffolds for Cell Recruitment
Thursday: 16:45 – 17:00
Christoph Erggelet (CH)



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International Cartilage Repair Society

Cartilage Repair - “A Merging of Basic Research and Clinical Applications”

ICRS is a unique forum for international collaboration in cartilaginous tissue research by bringing together clinicians, clinical researchers and basic scientists, engaged or interested in the field of cartilage biology, imaging, cartilaginous tissue engineering and translational clinical approaches to treatment of cartilage pathologies. The link between laboratory work and the daily treatments of patients in a clinical setting is extremely important to the Society.

The Society supports scientific research and the exchange of knowledge among physicians, scientists & patients of the industry in the field of Cartilage Repair. To serve its purpose, the society organizes international congresses and events, publishes journals and provides a universal internet discussion-platform. Furthermore the society provides an outstanding scientific database, financially supports research projects and pays for scholarships / fellowships which are available for members only.

Join ICRS Now!

Benefits for ICRS Members

- 2 Issues of the ICRS Newsletter
- 4 Issues of the new official ICRS Journal **Cartilage**, published by SAGE
- 4 issues of the Musculoskeletal Report (US & Europe reports)
- Highly reduced registration fees for **all ICRS educational events**
- Eligibility for ICRS Scholarships
- Eligibility for ICRS Travelling Fellowships
- Reduced price of the ICRS database software **SOCRATES™**
- Access to the “**Member Only**” section of the ICRS Website (incl. Membership Database and access to the Cartilage Knowledge Database, Electronic Posters, Abstracts and selected Symposia presentations)
- Free advertising of your cartilage meeting / course in the ICRS Newsletter and online event calendar

The Annual Membership Fees are:

Ordinary Members: € 180.00
Junior Members: € 90.00
Corporate Members: € 2800.00

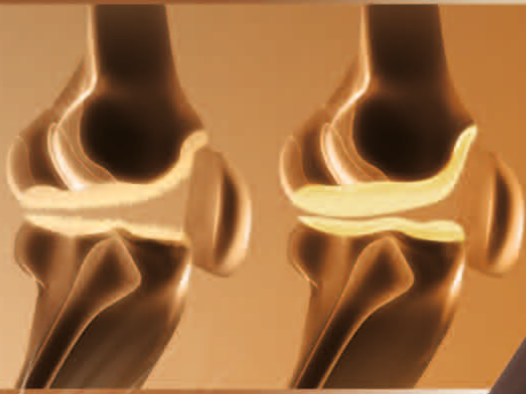
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I C R S 2015

International Cartilage Repair Society

Chicago – USA

May 8 – 11, 2015

**12th World Congress
of the International
Cartilage Repair Society**



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Mark your agenda!