20th Anniversary of the ICRS

ICRS

International Cartilage Repair Society

www.cartilage.org

ICRS Heritage Summit

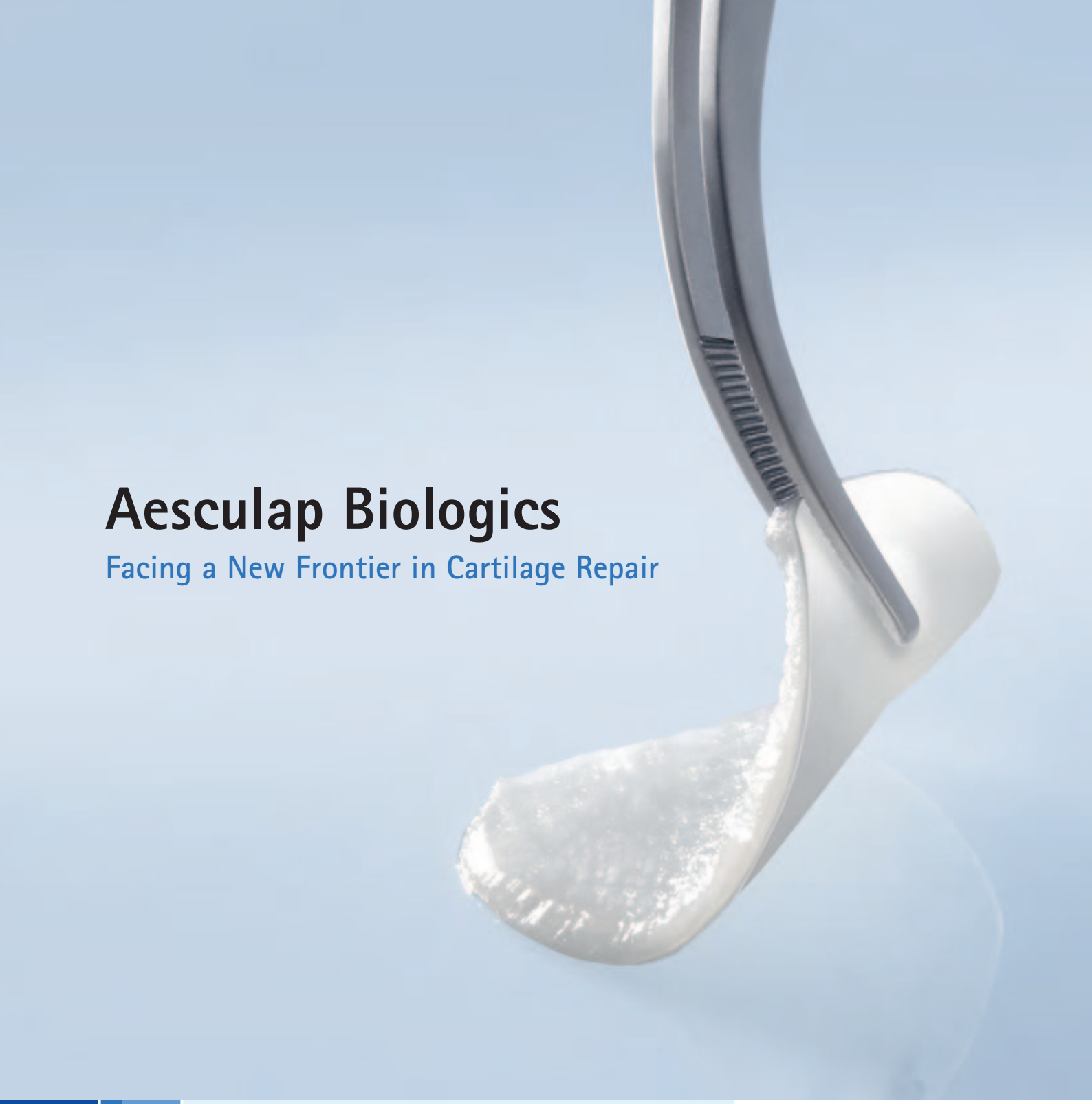
June 29 – July 01, 2017

Gothia Towers, Gothenburg, Sweden

Final Programme & Abstract Book

#ICRSSUMMIT

www.cartilage.org



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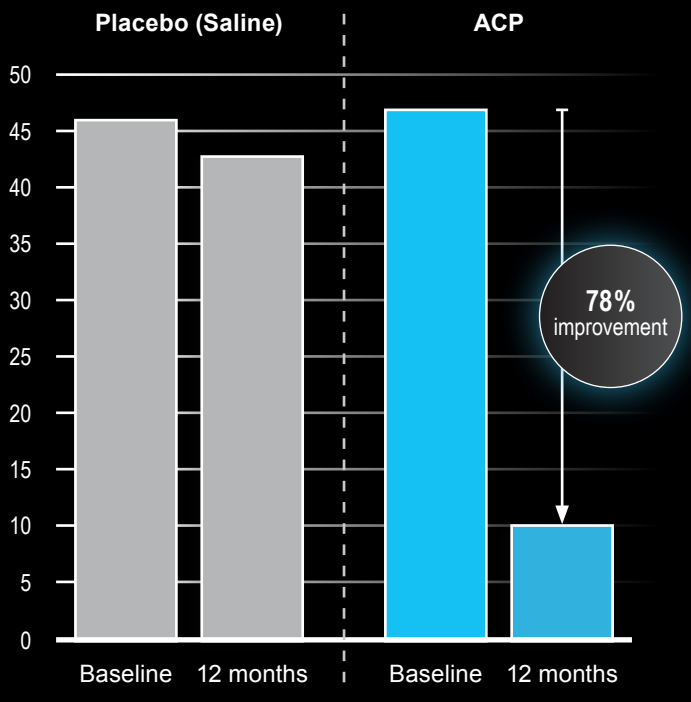

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1) Smith PA. Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis: An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial. Am J Sports Med. 2016 Apr;44(4):884-91.

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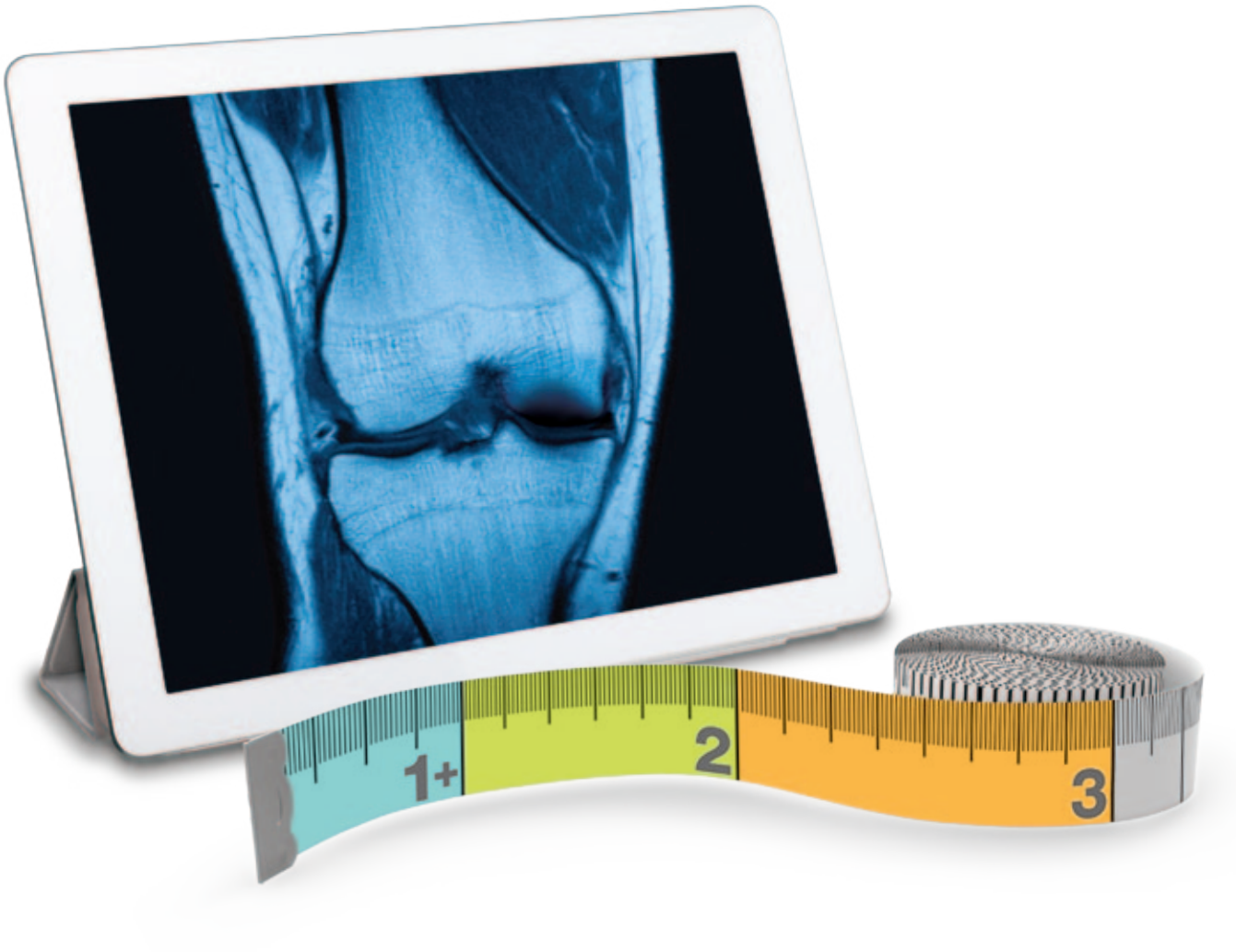

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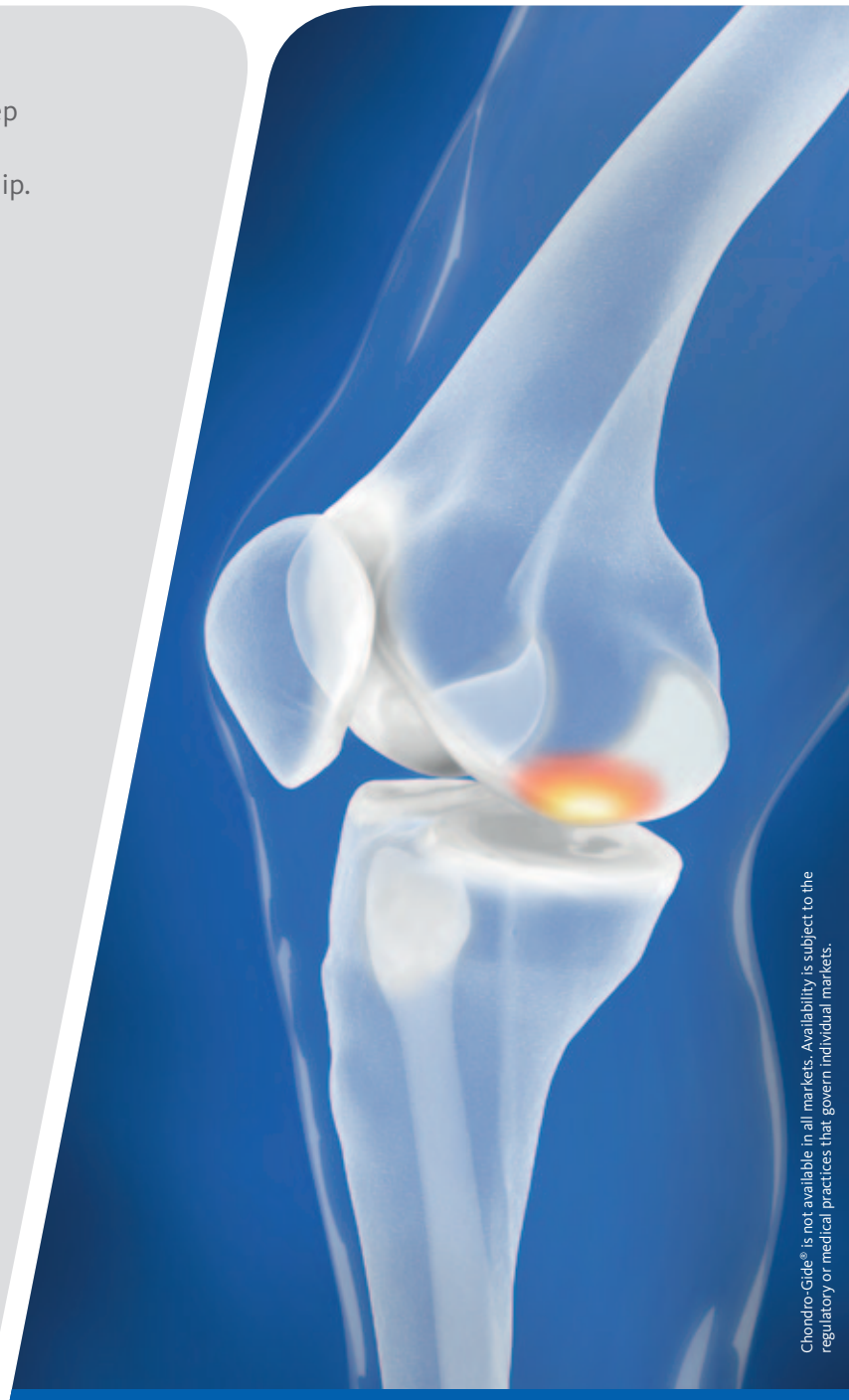

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Bone Marrow and the Subchondral Bone

Welcome

Ken Zaslav

Mats Brittberg

It is our great pleasure to welcome you to the 4th ICRS Presidential summit, this year our Heritage summit, celebrating two seminal events: the founding 20 years ago of this great society, The ICRS, and the first in man implantation of cultured chondrocytes by our esteemed members Drs. Lars Peterson, Mats Brittberg and Anders Lindahl. The summits began under the Presidency of Anthony Hollander, first held in Tallinn, as a unique small venue meeting where scientists and surgeons can meet for two days of in depth lectures and interactive discussions on an important scientific topic related to our work. This year is a little different as we celebrate these two wonderful anniversaries and take time to both congratulate ourselves on what we have achieved in the last 20 years, acknowledge our failures and look forward to what the members of this society can achieve in the next two decades.

Our first day will concentrate on where we have been and celebrate the great work done by our early leaders in the field and those that have come behind them. The roster of speakers is a virtual who's who of the cartilage world. The final half of the meeting will look to the future: what is new today, what our young researchers and surgeons are working on, and where we are headed both in cartilage research, the treatment of Osteoarthritis and use of Regenerative medicine techniques in the future.

The meeting is being held in the home of Lars, Anders and Mats, and we will honour their seminal contributions by attending this great party in the land of the midnight sun in the beautiful city of Gothenburg Sweden. Goteborg, the beautiful port city on the Kattegat at the mouth of the Gota Alv, where the river drains into the sea was the home of the great ocean explorers of earlier centuries. The Viking spirit lives on in the physicians and scientists that push the boundaries of our existing knowledge to make a better world.

We look forward to hosting you on this very special occasion to learn debate and prophesize about the future of our field.

Ken Zaslav & Mats Brittberg, Summit Chairs

Mark your Agenda

ICRS Focus Meeting – Osteoarthritis in the Athletes
Sept 28 – 29, 2017, Schulthess Clinic – Zurich, Switzerland

ICRS Surgical Skills Course – See it – Understand it – Do it
Feb 01 – 03, 2018, INR – Mexico City, Mexico

Advancing Science & Education of the Prevention & Treatment of Cartilage Disease Worldwide

Final Programme

Thursday, June 29, 2017

13:00–15:30 Module 1: Historical Look at Cartilage Repair
Moderator: Anders Lindahl (SE) & Lars Peterson (SE)

13:00–13:15 **Welcome & Introduction**
Kenneth Zaslav (US), Lars Peterson (SE) and Mats Brittberg (SE)

13:15–13:45 **Key Note Lecture, My 25 Years of Cartilage Repair (First ICRS President)**
Roland Jakob (CH)

13:45–14:00 **Marrow Stimulation for Cartilage Repair: A Historical Perspective**
William Rodkey (US)

14:00–14:15 **The Origins of Modern Cartilage Repair Technologies and Autologous Chondrocyte Transplantation**
Daniel Grande (US)

14:15–14:30 **Articular Cartilage Implantation: Taking it to the first in Man & Beyond**
Lars Peterson (SE)

14:30–14:45 **Technical Improvements & Expansion of Indications for ACI**
Tom Minas (US)

14:45–15:00 **Cells used for Cartilage Repair: The Rational & The Choice**
Mats Brittberg (SE)

15:00–15:30 **Discussion**

15:30–16:00 **Coffee Break**

16:00–18:15 Module 2: Historical Look at Cartilage Repair – Continued
Moderators: Thomas Vangsness (US) & Marcel Karperien (NL)

16:00–16:15 **Autologous Osteochondral Grafting – Historical Perspective**
Vladimir Bobic (UK)

16:15–16:30 **Fresh Osteoarticular Allografts for the Knee and Hip: History, Technique & Results**
Alan Gross (US)

16:30–16:45 **Minced Autologous/Allograft Cartilage Technologies**
Jack Farr (US)

16:45–17:00 **History of Scaffold Use for Cartilage Regeneration – From Periosteum to Biomaterials**
Chris Erggelet (CH)

17:00–17:15 **Biomechanics Matters: History & Role of Ostetomies in Cartilage Repair**
Stefan Nehrer (AT)

17:15–17:30 **Biomaterials for a One Stage Cartilage Repair**
Matthias Steinwachs (CH)

17:30–17:45 **Overview of the Progression of the Orthobiologic Surgeon & Cartilage Injury Prevention in Sports Medicine**
Bert Mandelbaum (US)

17:45–18:15 **Discussion**

18:45–20:00 Welcome Reception offert by the City of Gothenburg

Final Programme

Friday, June 30, 2017

07:30–10:00 **Module 3: Historical Perspective**
Moderators: Ken Zaslav (US) & Tim Spalding (GB)

07:30–07:45	**Welcome & Morning Announcements**
07:45–08:00	**Long Term Clinical Studies of ACI/MACI: A 25 Year Retrospective** *Brian Cole (US)*
08:00–08:15	**Long Term Data on Microfracture/Marrow Stimulation** *Kai Mithoefer (US)*
08:15–08:30	**Osteochondral Allograft Transplantation: Scientific Basis and Clinical Outcome** *William Bugbee (US)*
08:30–08:45	**Technical Enhancements & Long Term Clinical Outcomes OATS/Mosaicplasty** *Laszlo Hangody (HU)*
08:45–09:00	**Long Term Results of Combined ACI & Meniscal Transplants** *Wayne Gersoff (US)*
09:00–09:15	**Long Term Outcomes of Approved Scaffold induced Repair** *Elizaveta Kon (IT)*
09:15–09:30	**Measuring Relevant Results in Knee Repair & Regenerative Medicine** *Daniel Saris (NL)*
09:30–09:45	**A Philosophical Look-Back at how Chondrocyte Transplantation began and what has been achieved** *George Bentley (UK)*
09:45–10:00	**Discussion**

10:00–10:45 **Coffee Break**

10:45–12:30 **Module 4: New Advances In Regenerative Medicine - Basic Research**
Moderators: Dan Grande (US) & Anthony Hollander (UK)

10:45–11:00	**How to Improve the Biomechanics of our Repairs** *Darryl D' Lima (US)*
11:00–11:15	**Chondrocytes & MSCs: A Nice Couple for Cartilage Repair: True or False?** *Lucienne Vonk (NL)*
11:15–11:30	**Cartilage Repair: Assessment of the Quality and Composition** *Susan Chubinskaya (US)*
11:30–11:45	**MSCs Are Not Stem Cells** *Arnold Caplan (US)*
11:45–12:00	**Acellular Matrix Based Cartilage Regeneration in China** *Ao Yingfang (China)*
12:00–12:15	**Update on the Treatment of Cartilage Lesions in the Equine Athlete** *Wayne McIlwraith (US)*
12:15–12:30	**Discussion**

12:45–13:45 **Geistlich Lunch Industry Symposium**
Role of Biomaterials in Cartilage Repair, Current Results & Future Perspectives

- **Overview of Biomaterials for Tissue Engineering in Cartilage Repair** – *M Steinwachs (CH)*
- **Stem Cell Behavior on Different Biomaterials and Clinical Results in the Knee** – *M. Snow (UK)*
- **Clinical Use of Biomaterials in the Ankle Joint** – *M. Walcher (DE)*
- **How a bio-derived collagen membrane supports the generation of articular carti lage from nasal cartilage cells** – *M. Mumme (CH)*

Final Programme

14:00–16:00 Module 5: New Advances in Cartilage Repair – Clinical

Moderators: Daniel Saris (NL) & Leela Biant (UK)

14:00–14:15 **3D Printing for Cartilage Repair & Organ Reconstruction**
Jos Malda (NL)

14:15–14:30 **First-in-Human Clinical Study of Scaffold-Free Tissue-Engineered**
Norimasa Nakamura (JP)

14:30–14:45 **Bone Marrow and other MSC Choices for Clinical Repair of Cartilage Injury**
Alberto Gobbi (IT)

14:45–15:00 **Stem cell therapy for cartilage repair in Asia: 2012-2017**
James Hui (SG)

15:00–15:15 **Meniscus Substitution: From Allografts to Synthetic Substitutes**
Peter Verdonk (BE)

15:15–15:30 **Single stage Cartilage Repair: Health Economic**

Modeling Guiding Implementation of Regenerative Medicine
Tommy de Windt (NL)

15:30–15:45 **A health technology assessment of Autologous Chondrocyte Implantation**
Norman Waugh (UK)

15:45–16:00 **Discussion**

16:00–16:30 **Coffee Break**

16:30–18:30 Module 6: Early OA & Meniscus; Basic/Clinical

Moderators: Christian Lattermann (US) & Susan Chubinskaya (US)

16:30–16:45 **Genome wide Expression Profiling of Genes Associated with OA**
Anders Lindahl (SE)

16:45–17:00 **Mouse Models of Knee Injury and Osteoarthritis**
Linda Sandell (US)

17:00–17:15 **OA Disease Modulation by DMOADS: Possible**
Anthony Hollander (UK)

17:15–17:30 **Meniscal, Osteochondral, Grafts and Knee Reconstruction: Can they be considered effective OA Prevention?**
Alan Getgood (CA)

17:30–17:45 **The MMA of Orthopedics! A Personalized Mini Metal Implant as an Alternative to Local Biological Repair?**
Leif Ryd (S)

17:45–18:00 **Functional Cartilage MRI: Current Status & Future Outlook**
Siegfried Trattnig (AT)

18:00–18:15 **Histology & Grading in Cartilage Repair**
Pierre Mainil (CH)

18:15–18:30 **Discussion**

19:30–23:00 ICRS Heritage Anniversary Dinner

Final Programme

Saturday, July 01, 2017

08:00–10:00 Module 7: New Advancements in The Treatment Of Articular Cartilage Generation Next Presentations: Basic & Clinical (Free Paper Session)
Moderators: Andreas Gomoll & Emanuel Papacostas

08:00–08:10 **Announcements & Welcome**

08:10–08:20 **Clinical comparison of Matrix-encapsulated autologous chondrocyte implantation (MECI) to treat chondral defects in the knee with versus without other previous treated lesion**
Arredondo-Valdés Reynaldo (MX)

08:20–08:30 **Chondrogenic differentiation of whole fat tissue: A novel approach to Cartilage Regeneration**
Eder Claudia

08:30–08:40 **Development of scaffold-free tissue-engineered construct (TEC) with chondrogenic differentiation capacity using rabbit embryonic stem cell-derived mesenchymal stem cells**
Moriguchi Yu (JP)

08:40–08:50 **Mechanical compression enhances cartilage matrix synthesis of the expanded osteoarthritic chondrocytes**
Chong Pan Pan (ML)

08:50–09:00 **Effects of Micronized Cartilage Matrix on Cartilage Repair in Osteochondral Lesions of the Talus**
Lee Cassandra (US)

09:00–09:10 **Articular Cartilage Repair with Mesenchymal Stem Cells following Chondrogenic Priming in Normoxic and Hypoxic Conditions: A Preclinical Pilot Study**
Bornes Troy (CA)

09:10–09:20 **Peptidomic Analysis of Cartilage and Subchondral bone from OA patients**
Gatenholm Birgitta (SE)

09:20–09:30 **Four Years Follow-up of Arthroscopic Meniscal Allograft Trasplantation: the chondroprotective effect evaluated by T2-Mapping**
Olivos Meza Anell (MX)

09:30–09:40 **Metabonomic profiling of early and late stage knee osteoarthritis synovial fluid**
Khatib Nidal (UK)

09:40–10:00 **Judging and presentation of winning prize**

10:00–10:30 **Coffee Break**

10:30–12:30 Module 8: Panel Discussion The Disease Continuum: When is a Focal Defect OA and Is OA a Curable Disease?
Moderators: Mats Brittberg (SE) & Kenneth Zaslav (US)
Panellists: Tom Minas, Christian Lattermann, Anders Lindahl, Lars Petersen, Nori Nakamura, William Bugbee, George Bentley, Anthony Hollander

11:15–11:30 **Is it Time for Joint Preservation/Cartilage Repair Surgery to have a place in traditional OA Treatment Algorithms?**
William Bugbee (US)

11:30–12:30 **Module 9: Lunch Panel Discussion The Next 20 Years...**
Moderator: Ken Zaslav
Panelists: Alberto Gobbi, Elizaveta Kon, Tom Minas, Dan Grande, Jos Malda

12:30 **Official Meeting Adjourn**

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ICRS Heritage Summit 2017

Role of Biomaterials in Cartilage Repair
Current Results and Future Perspectives

Lunch included

FRIDAY, 30 JUNE 2017
12.45–13.45

CHAIR
Prof. Dr. Matthias Steinwachs

SPEAKERS
Prof. Dr. Martyn Snow
«Stem cell behavior on different biomaterials and clinical results in the knee»

Dr. Matthias Walcher
«Clinical use of biomaterials in the ankle joint»

Dr. Marcus Mumme
«How a bio-derived collagen membrane supports the generation of articular cartilage from nasal cartilage cells»

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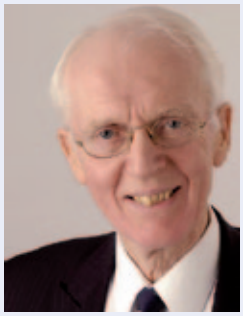
Invited Faculty (in alphabetical order)

Ao Yingfang, Prof., MD
Peking University 3rd Hospital Institute of Sports Medicine Beijing, China

Ao Yingfang has been the Principal Investigator of many national competitive grants such as National Natural Science Foundation of China, China National Science & Technology Pillar Program, etc. He has been honored with a number of national awards for outstanding scientific & technological achievement such as National Science & Technology Progress Award, the 9th Wu Jieping Medical Research Award-Paul Janssen Pharmacy Research Award (Sports Medicine), etc. Prof. Ao has published more than 120 papers including papers in indexed international journals in the fields of orthopedic surgery, arthroscopy & sports medicine. He is also the editor-in-chief of many books in Sports Medicine, Arthroscopy, Orthopaedic Traumatology such as Knee Arthroscopic Surgery; Techniques of Sports Injury Surgery; Chinese Orthopaedics (Sports Injury) which are now considered as standard textbooks in China He is also on the standing editorial board of Chinese Journal of Minimally Invasive Surgery, Chinese Journal of Orthopaedic Injury, Chinese Journal of Sports Medicine, Chinese Journal of Surgery, Chinese Journal of Orthopaedics and The Journal of Practical Orthopaedics. For his great contribution to sports medicine and arthroscopy in China, the State Council of China has honored him with the special government allowance.



Bentley George, Prof., MD
University College London Hospitals Institute of Orthopaedics & Musculo-Skeletal Science Stanmore, United Kingdom

George Bentley trained in Sheffield, Oswestry and Oxford being the first clinical reader in Orthopaedics at in the University department of Orthopaedics, Oxford. He was then Professor of Orthopaedics and Accident Surgery in the University of Liverpool, before moving to London as Director and Professor of the Institute of Orthopaedics and Musculoskeletal science of University College London as well as being Consultant Orthopaedic Surgeon at the Royal National Orthopaedic Hospital, Stanmore, London. As a Lecturer in the University of Pittsburgh. He performed the first transplantation of isolated cartilage cells into the articular surface of the knee joint (Nature, 1971). Since then he has published over 120 papers on articular cartilage and transplantation and has pioneered the basic science and clinical applications of ACI and MACI. He became a member of the IC RS shortly after its formation which conferred upon him the “Lifetime Achievement Award of the ICRS” in 2015. George has held many prestigious positions including Presidency of the British Orthopaedic Research Society, and of the British Orthopaedic Association, Vice-Presidency of the Royal College of surgeons of England, and Presidency of EFORT. His Mastership Thesis was on the “Degradation, Repair and Replacement of Articular Cartilage”. He has lectured worldwide on Orthopaedics and Trauma and education, training and Research including an Hunterian lecture, Robert Jones lecture and guest lectures of all the major Orthopaedic associations and Universities worldwide. His current work on the Stanmore Stem Cell Project(SSCP) follows the unit’s 15 year experience in the use of ACI and MACI in over 1000 patients(JBJS,Am,2014). By this project, he and his colleagues have established the patient criteria required for success in the use of ACI/MACI. He will summarize the origin of the cartilage cell transplantation procedure and what progress has been achieved over 15 years, together with a look at the future prospects in the exciting area of stem cell engineering.

Biant Leela, MD
The University of Manchester Academic Trauma and Orthopaedic Surgery Manchester, United Kingdom

Leela Biant is Academic Head of Dept Trauma & Orthopaedic Surgery at University of Manchester and Honorary Consultant Trauma and Orthopaedic Surgeon, Central Manchester University Hospitals. She is lead Clinician for Cartilage Repair and Regeneration. Leela Biant trained in London and completed specialist fellowships in Sydney and London. Her thesis was entitled ‘Articular Cartilage Injury and Repair in the Young Adult Knee’. She has undertaken research into the best techniques of clinical cartilage repair and the potential of the use of stem cells in articular cartilage repair. Research prizes include Best Paper by a Clinician at the British Orthopaedic Research Society, Presidents’ Prize Paper at The Royal Society of Medicine, Short-listed for Technical Advancement Awards at the British Orthopaedic Association and the William Little Medal twice. Dr Biant was awarded the ABC Travelling Fellowship in 2010, BASK Fellowship 2014. She is a Senior Fellow of the ICRS, BASK Treasurer, Chair of the ICRS Registry Committee

Invited Faculty

Bobic Vladimir Prof., PhD
Nuffield Health, The Grosvenor Hospital Chester, Chester, United Kingdom

Vladimir Bobic is a Consultant Orthopaedic Knee Surgeon in full-time clinical and surgical practice. He is the director and founder of Chester Knee Clinic and Cartilage Repair Centre. The clinic, founded in 1996, is based at the Grosvenor Hospital in Chester, UK, where it is recognised as an ISAKOS-approved teaching centre. Professor Bobic has over twenty-three years of extensive experience in all aspects of knee surgery, including arthroscopic surgery, ligament reconstruction, knee arthroplasty, and particularly in articular cartilage repair. He is involved in national and international collaborative clinical and basic science research related to knee articular cartilage imaging, repair, rehabilitation and functional outcomes. His clinical and surgical practice includes all contemporary articular cartilage repair technologies, including stem cell therapies. He organised one of the first UK seminars on the use of Autologous Stem Cell Therapies in Orthopaedics which was held in Chester in June 2013. He has over twenty years of experience in clinical and arthroscopic imaging, including digital image and video editing, and over sixteen years of experience in clinical and MR digital imaging of articular cartilage and subchondral bone. Prof Bobic introduced the first web-based MRI Teleradiology units at the Grosvenor Nuffield Hospital in Chester in 2004, in collaboration with Dr David Ritchie, Consultant Musculoskeletal Radiologist, Kodak and Alliance Medical. He is one of the founding members of the ICRS and a founder and former chairman of the ICRS Articular Cartilage Imaging and Rehabilitation Committees. He continues to focus on articular cartilage repair and autologous biological treatment options, which are his main clinical, imaging and research interests.

Brittberg Mats, Ass. Prof., MD, PhD
Kungsbacka Hospital, Gothenburg University, Sweden

Mats Brittberg is a member of the Cartilage Research Unit, Department of Orthopedics Surgery, at University of Gothenburg and an orthopedic surgeon at the Kungsbacka Hospital, Kungsbacka, 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 main 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. Mats Brittberg 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. In September 2010, Mats Brittberg received the ICRS Genzyme Lifetime Achievement Award in cartilage research and in 2012, the Shett- Kim Foundation (SKF) Scientific award. 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 since january 2013 Editor-in-Chief for the Sage journal ¨CARTILAGE. He is also associate editor with ESSKA journal as well as being on the editorial board of Osteoarthritis and Cartilage.

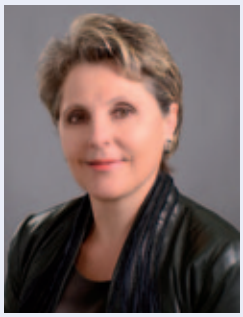
Bugbee William, Ass. Prof., MD
Scripps Clinic Medical Group Orthopaedics La Jolla, United States of America

William Bugbee is an attending physician at Scripps Clinic, La Jolla and Professor, department of Orthopaedics, university of California, San Diego. His clinical interests are in arthritis surgery of the hip, knee and ankle, joint replacement, osteochondral allograft transplantation and cartilage restoration. Research interests include biologic response to implants, innovation in knee replacement technique and design, Osteochondral transplantation, cartilage tissue engineering and biologic joint repair.

Invited Faculty

Caplan Arnold, Prof., MD, PhD
Case Western Reserve University Skeletal Research Ctr./Biology Cleveland, OH, United States of America

Arnold Caplan is a Professor of Biology and the Director of the Skeletal Research Center at Case Western Reserve University. Dr. Caplan received his B.S. in Chemistry at the Illinois Institute of Technology, Chicago, Illinois; and his Ph.D. from The Johns Hopkins University School of Medicine, Baltimore, Maryland. Dr. Caplan did a Postdoctoral Fellowship in the Department of Anatomy at The Johns Hopkins University, followed by Postdoctoral Fellowships at Brandeis University, Waltham, Massachusetts with Dr. N. O. Kaplan and Dr. E. Zwilling. He came to Case Western Reserve University as Assistant Professor of Biology in 1969 and rose through the ranks to become Professor in 1981. He has taken three sabbatical leaves: one in 1973 as a Visiting Professor in the Department of Biochemistry and Biophysics at the University of California at San Francisco Medical School with Brian McCarthy and William Rutter; one in 1976 in the Institute de Chimie Biologique at the Faculty of Medicine de Strasbourg in the Laboratory of Pierre Chambon; and lastly, the Edna and Jacob Michael Visiting Professor of the Department of Biophysics with Nathan Sharon at the Weizmann Institute of Science in Rehovot, Israel in 1984. He has received a number of awards including the Elizabeth Winston Lanier Award given by the American Academy of Orthopaedic Surgeons as part of their 1990 Kappa Delta Awards Program, the 1999 Marshall R. Urist Award for Excellence in Tissue Regeneration Research given by the Orthopaedic Research Society, the Genzyme Lifetime Achievement Award given by the International Cartilage Repair Society in 2007, the Tissue Engineering and Regenerative Medicine International Society Inaugural Lifetime Achievement Award in 2010 and is an Inaugural Member of the Pioneers of Innovation chosen by the Advocacy Committee of the Orthopaedic Research Society, March 2014. He has trained over 150 researchers, has over 400 published papers and manuscripts and has long been supported by the National Institutes of Health and other non-profit and for-profit agencies for his efforts in trying to understand the development, maturation and aging and regeneration of cartilage, bone, skin and other mesenchymal tissues.



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

Susan Chubinskaya, the Ciba-Geigy endowed professor, is the Associate Provost for Faculty Affairs at Rush University and Vice-Chair, Research and Faculty Development, Department of Pediatrics. She also holds joint appointments as Professor in the Departments of Biochemistry, Internal Medicine, and Orthopedic Surgery at Rush University Medical Center. Susan holds leadership positions in various professional societies within the field. For five years Susan was the member of the Board of the ICRS and for three years she was a Treasurer and Executive Board member of the society. Now she continues her service to the ICRS as the member of basic science committee and as an inspirational and organizational leader of this first collaborative summit between the ICRS and OARSI. She also chaired 2016 ORS Annual Program Committee and Award and Recognition Committee. Currently Susan serves as the Board member for the ORS and the chair of the ORS Annual Meeting and Educational Councils. As a researcher, 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 multiple awards and her research is continuously funded by the NIH, foundations and pharmaceutical and biotech companies. As a Principal Investigator, she secured more than $5M (direct cost) of extramural funding, presented more than 160 invited and podium lectures, published 87 peer-reviewed manuscripts, 10 book chapters, and more than 200 peer-reviewed abstracts.

Invited Faculty

Cole Brian, Prof., MD, MBA
Rush Medical College Orthopaedic Surgery Chicago, United States of America

Brian Cole is an orthopedic surgeon specializing in sports medicine at Midwest Orthopaedics at Rush and a Professor of Orthopedics and Anatomy and Cell Biology at Rush University Medical Center. He is the Associate Chairman of the Department of Orthopedics at Rush and the Section Head of the Cartilage Research and Restoration Center. Since 2011, he has served as Chairman of Surgery at Rush Oak Park Hospital and as the head of the Rush Orthopedic Master's Program. Dr. Cole's research interests include cartilage restoration, therapeutic biologics, and minimally invasive surgical techniques for the treatment of the knee, elbow, and shoulder. He has published more than 1,000 articles and 8 textbooks on orthopedic surgery and sports medicine. He received an MD and MBA from the University of Chicago, completed his orthopedic residency at the Hospital for Special Surgery at Cornell Medical Center, and a Sports Medicine fellowship at the University of Pittsburgh. His professional career outside of academia includes serving as team physician for the Chicago Bulls, co-team physician for the Chicago White Sox and team physician for DePaul University. He also co-hosts a weekly sports-medicine talk-show on ESPN radio.

de Windt Tommy, MD, PhD
University Medical Center Utrecht Orthopedics Utrecht, Netherlands

Tommy de Windt obtained is PhD (cum laude) at the department of orthopedics, University Medical Center Utrecht in the group of professor Daniel Saris. His work focuses on one-stage cartilage repair using the unique crosstalk between cartilage cells and MSCs. He has worked in Gothenburg together with professor Mats Brittberg and Professor Anders Lindahl on patient profiling in cartilage repair. He has received several grants and awards including a young investigator grant to support his PhD work and the AOSSM systematic review award. While continuing his research on one-stage cartilage repair, he is currently an orthopedic surgeon in training.

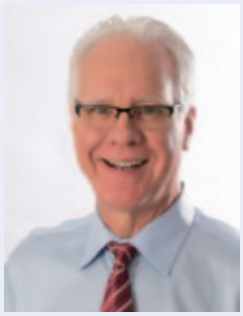
DLima Darryl, MD, PhD
Scripps Orthopaedics La jolla, United States of America

Darryl D'Lima, trained as an orthopaedic surgeon in India, and as a fellow in Adult Reconstruction at Scripps Clinic, CA. He received his PhD in Bioengineering at UC San Diego, CA. He is Professor of Orthopaedics, Director of Orthopaedic Research at Scripps Health, CA; and Chair of Musculoskeletal Research, at Scripps Clinic. He has multidisciplinary expertise in orthopaedics, biomechanics, and bioengineering. His major interests include musculoskeletal biomechanics, cartilage injury, and stem cell-based tissue regeneration. He is currently developing pluripotent stem cell derived treatment of arthritis and techniques for direct 3D printing of live repair tissue in osteochondral defects. He has published over 200 papers in peer reviewed journals. He has received academic funding from the NIH, CIRM, OREF, Knee Society, and the Aircast Foundation. In 2005 he received the Kappa Delta award from the American Academy of Orthopaedic Surgeons for his work on chondrocyte apoptosis following cartilage injury. He has received two Knee Society awards, the HAP Paul award from the International Society of Technology in Arthroplasty, and the Nicolas Andry award for the development of the world's first œsmart knee prosthesis. He is a reviewer for several international orthopaedic, bioengineering, and tissue engineering journals. He is the Chair of the Musculoskeletal Tissue Engineering (MTE) NIH study section.

Invited Faculty

Erggelet Christoph, Prof., MD, PhD
Alfaclinic Zurich, Switzerland

Christoph Erggelet is an orthopaedic surgeon in Zurich/Switzerland affiliated with the Department for Orthopeadic Surgery and Traumatology, University Medical Center, University of Freiburg/Germany. He received his MD in 1986 and passed the board exam for Orthopeadic 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, eg culture of autologous chondrocytes, meniscus regeneration and ligament repair. He served as a founding board member of the Bio Valley initiative, a tri-national 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 member of ICRS since the foundation in 1997 and served as a board member. He was President of ICRS for the term office 2013-2015.



Farr Jack, MD
Cartilage Restoration Center of Indiana OrthoIndy Greenwood, United States of America

Jack Farr received his undergraduate degree in biological engineering from Rose Hulman Institute of Technology in 1975, where he also was awarded an honorary doctorate of biological engineering. He earned his medical degree from Indiana University in 1979. He completed his orthopedic surgery residency at Indiana University Medical Center in 1986. Dr. Farr has a subspecialty practice in knee and cartilage restoration. His numerous appointments and affiliations include a voluntary clinical full professorship in orthopedic surgery at Indiana University Medical Center, a board position with the Cartilage Research Foundation, the International Cartilage Repair Society general board (Meetings and Education Committee Chair) and Patellofemoral Foundation vice president. For more information, please go to www.Cartilage Restoration.org. As a leader in U.S. cartilage restoration advances, Dr. Farr has written numerous articles, book chapters and has completed and edited two cartilage books published in 2013. He serves as associate editor for the journals Cartilage and American Journal of Orthopedics. For a full listing of publications, please visit www.Cartilage Restoration.org. He lectures both nationally and internationally and participates in several ongoing articular and meniscal cartilage clinical trials. He also was a design surgeon for a meniscal allograft transplant system and two knee patellofemoral osteotomy systems. For patients with knee changes too far advanced for restoration, Dr. Farr worked as a design surgeon for a current partial knee replacement system (Sigma High Performance Partial Knee Replacement). Dr. Farr is actively affiliated with the OrthoIndy Hospital and Community Hospital South. He is a member of the American Academy of Orthopaedic Surgeons, the American Orthopaedic Society of Sports Medicine, Arthroscopy Association of North America, the International Cartilage Repair Society, International Patellofemoral Study Group, International Society of Arthroscopy, Knee Surgery & Orthopaedic Sports Medicine and the European Society of Sports Traumatology, Knee Surgery & Arthroscopy.

Gersoff Wayne, Ass. Prof., MD
Advanced Orthopedics and Sports Medicine Orthopedics Denver, United States of America

Wayne Gersoff is an orthopedic surgeon specializing in sports medicine and cartilage restoration in Denver, Colorado. After completing his residency in Orthopedic Surgery at Yale University in 1986, he went on to complete a fellowship in Sports Medicine at the University of Wisconsin in 1987. From 1987 - 1994, he was an Assistant Professor at the University of Colorado Health Sciences Center where he also served as Director of Sport Medicine and Head Team Physician for the University of Colorado. Upon leaving the university for private practice, Dr. Gersoff has maintained his active involvement in sports medicine and cartilage restoration of the knee. He continues to serve as team physician for professional, collegiate, and high school athletes. His expertise in articular cartilage restoration and meniscal transplant has allowed him to lecture and write on these areas. He is on the general board of the ICRS and is president of the Major-League Soccer physicians group.

Invited Faculty

Getgood Alan, MD
London, Canada

A native of Northern Ireland, Dr. Al Getgood moved to Scotland where he qualified from the University of Edinburgh Medical School in 2000. A move south to the University of Cambridge followed where he completed his orthopaedic residency and doctoral research in 2011, submitting a thesis entitled 'Articular Cartilage Tissue Engineering', which was awarded the prestigious Sir Lionel Whitby medal. Sports orthopaedic fellowships followed in London, Ontario, at the Fowler Kennedy Sport Medicine Clinic and Banff Sport Medicine (Alberta) and complex knee reconstruction in Coventry (UK). Following a term as Associate professor at the University of Warwick, he returned to Canada in September 2012 to take up a new position at the Fowler Kennedy Sport Medicine Clinic, where he specializes in complex knee reconstruction. His research interests include ligament reconstruction and biological solutions to joint repair, leading a translational research laboratory at the University of Western Ontario and serving as director of the London Joint Preservation Centre specializing in cartilage and meniscus transplantation. He has authored numerous peer-reviewed articles and book chapters and currently serves on the General Board of the ICRS, the educational committee of ISAKOS and is a member of the ACL Study group, ESSKA and AOSSM. Away from work, Dr. Getgood enjoys family time with his wife and two young boys, and running.

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

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 No-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 Chair of the Education Committee for the ICRS as well as ISAKOS. 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.

Gomoll Andreas, Ass. Prof., MD
Brigham and Women's Hospital Cartilage Repair Center Boston, United States of America

Born and raised in Germany, Dr. Gomoll attended Ludwig-Maximilians-Medical School in Munich prior to spending 2 years at Brigham and Women's Hospital as a research fellow. He then completed his residency training at the Harvard Combined Orthopaedic Residency Program in Boston, MA, and a Sports Medicine Fellowship at Rush University in Chicago, IL. After his return to Boston, he joined Dr. Tom Minas at the Cartilage Repair Center at Brigham and Women's Hospital, where he specializes in biologic knee reconstruction, such as cartilage repair, meniscal transplantation and osteotomy. Dr. Gomoll has an academic appointment as Assistant Professor of Orthopaedic Surgery at Harvard Medical School. His main research interests are clinical outcome studies of existing, as well as the investigation of new cartilage repair procedures.

Invited Faculty

Grande Daniel, Prof., MD, PhD
Feinstein Institute North Shore-Long Island Manhasset, United States of America

Daniel Grande is associate investigator and director of orthopaedic research at the Feinstein Institute for Medical research. He is also associate professor at the newly accredited Hofstra School of Medicine. He completed his PhD at New York University and his post-doctoral fellowship ion biomechanics at the Hospital for Special Surgery. He has worked extensively in the area of regenerative medicine and tissue engineering. His early work developed the first use of cell based therapy for cartilage repair, currently known as autologus chondrocyte transplantation. He has served on committees with the Orthopaedic Research Society as spine topic chair and the basic science committee. Dr. Grande is significantly involved in mentoring and teaching of orthopaedic residents for his department. He has been a reviewer for a number of journals including: Journal of Orthopaedic Research, Clinical Orthopaedics, Osteoarthritis and Cartilage, American Journal of Sports Medicine, Nature Reviews Rheumatology and Applied Biomaterials. He has been awarded eight patents and helped found two companies in the orthopaedic surgery field of use. He has served as a member of several companiesâ™ scientific advisory boards. He completed a five-year rotation with OREF to assist in grant reviews. He also regularly serves on NIH study sections for RO1, R21, and SBIR/STTR grants specific to musculoskeletal applications.

Gross Allan, Prof., MD
Mount Sinai Hospital, University of Toronto Orthopaedic Surgery Toronto, Canada

Allan E. Gross received his M.D. from the University of Toronto in 1962, interned at Mount Sinai Hospital in Toronto, and then entered the Surgical Training Programme of the University of Toronto. As part of his orthopaedic training, he did one year of research under the supervision of Dr. Robert B. Salter, developing an animal model for cortisone arthropathy. He was the Duncan Fellow at the Toronto General Hospital working under Dr. F.P. Dewar. During this year, he developed an interest in bone and cartilage transplantation. In September 1970, he went to the Royal National Orthopaedic Hospital in Stanmore England, where he continued his work on the immunogenicity of cartilage. He returned to the Orthopaedic Division of the University of Toronto, Mount Sinai Hospital in July 1971, where he along with Dr. Fred Langer developed a clinical and research programme in bone and cartilage transplantation. The first osteochondral allograft was performed on New Year's Day in 1972, for a traumatic defect of a knee. A limb salvage tumour programme was initiated a few years later, because of the advances in chemotherapy. A Bone Bank was then established at Mount Sinai so that preserved tissue could be used for the tumour surgery. In the early 1980's, revision arthroplasty of the hip arrived on the scene, and it soon became apparent that some revisions required restoration of bone stock. The transplant programme continues to flourish for post-traumatic joint defects, revision arthroplasty of the hip and knee, and limb salvage following excision of bone tumours. Dr. Gross became Head of the Division of Orthopaedic Surgery at Mount Sinai in 1973 and Chief of Surgery in 1975. He became Head of the Combined Orthopaedic Unit of the Toronto General Hospital and Mount Sinai Unit in 1982, and the A.J. Latner Professor and Chairman of the Division of Orthopaedic Surgery, University of Toronto, on July 1, 1986 to July 1996. Presently, he is a full time orthopaedic surgeon in the Division of Orthopaedic Surgery at Mount Sinai Hospital.

Hangody Laszlo, Prof., MD, PhD
Uzsoki Hospital Orthopedic & Trauma Department Budapest, Hungary

Laszlo Hangody is a Clinical Professor at the Debrecen Medical School. He is Senior Consultant in the Orthopaedic Department at Uzsoki Hospital and at the Sanitas Private Clinic, also in Budapest. Dr. Hangody completed his medical degree (1982) at Semmelweis University of Medicine; received his PhD (1994) and DSc (2000) degrees from the Hungarian Scientific Academy. His specialties are orthopaedics and traumatology. Dr. Hangody's research focuses primarily on the cartilage repair, revision surgery of anterior cruciate ligament deficient knees, and minimal invasive total hip and knee replacement. He has written a number of chapters and articles for the medical press and has been an invited lecturer at over 300 international scientific meetings. He serves on the editorial boards of The Knee; Endoscopy and Minimal Invasive Therapy; Arthrocopy and Joint Surgery; Hungarian Journal of Orhopaedics and Trauma. He is an instructor of the PhD program of the Semmelweis Medical School and the Debrecen Medical School. Dr. Hangody is the past president of the Hungarian Orthopaedic Association, the elect president of the Hungarian Arthroscopic Society and a Honorary Member of the Arthroscopy Association of North America. He is a member of the SICOT, AAOS, ESSKA, ISAKOS and ICRS.

Invited Faculty

Hollander Anthony, Prof., PhD
University of Liverpool Institute of Integrative Biology Liverpool, United Kingdom

Anthony Hollander is Head of The Institute of Integrative Biology at The University of Liverpool. He has many years of experience in cartilage biology and his research is particularly focused on osteoarthritis. He also has a more general expertise in the wider fields of stem cells and tissue engineering. His work includes a study on the regulation of stem cell differentiation for cartilage repair. 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. His research into meniscal cartilage repair has led to a Phase I/IIa trial of the Cell Bandage technology that is being developed by his spin out company, Azellon Cell Therapeutics. In 2010 the Times newspaper ranking of Britain's 100 most important scientists included him at 39th on the list. Professor Anthony Hollander has been working in the field of cartilage biology and arthritis research for two decades. Three of those years were spent at the internationally recognized 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 funding in excess of £5 million of peer-reviewed funding over the past 10 years 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 a study on the regulation of stem cell differentiation for cartilage repair and has pioneered the development of new assays and methodological approaches.

Hui James, Prof., MD, PhD
National University Hospital Department of Orthopaedic Surgery Singapore, Singapore

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 a 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 was also appointed as Director for Tissue Engineering and Cell Therapy Laboratory, National University Health System, Singapore and is a Group Leader for Cartilage Division of National University of Singapore, Tissue Engineering Programme (NUSTEP). He is also currently the vice-president of Asian Cartilage Repair Society. Editorial activities: Associate Editor of JBJS (USA) Essential Surgical Techniques Journal of Tissue Engineering (Official publication of Tissue Engineering and Regenerative Medicine Society) Sub-section editor, Journal of Orthopedic Surgery (Official publication of Asia Pacific Orthopedic Association) Cartilage (Official publication of the International Cartilage Repair Society)

Jakob Roland, Prof., MD
Orthopeadische Klinik Orthopaedie Motier, Switzerland

Former Chairman of Orthopaedic Surgery of Cantonsspital, Fribourg (1995-2007), Founding President of ICRS 1997-98, Past President of Swiss Orthopaedic Society (1994-96), ISAKOS (1999-2001), AO Switzerland (2002-09). Dr. Jakob has Passed Activity as Member in Editorial Boards of Scientific Journals such as, Journal of Bone and Joint Surgery, British Volume, the Journal of Knee Surgery, Sports Traumatology and Arthroscopy, KSSTA (Board of Trustees) and La chirurgia degli organi di movimento. He has also been the Author/co- author of over 200 scientific articles and 4 text books, which include; "The Knee and the Crucial Ligaments", R.P. Jakob and H.U. Stäubli, Springer, 1991, "Planning and Reduction Technique in Fracture Surgery", J. Mast, R.P. Jakob, R. Ganz, Springer, 1989, "European Instructional Course Lectures", R.P. Jakob, P. Fulford, F. Horan, The British Editorial Society of Bone and Joint Surgery, 1999 and Osteotomies around the Knee, Ph. Lobenhoffer, R. Heerwarden, A. Staubli, R.P. Jakob (Thieme, AO Publication, 2008) Dr. Jakob has also a list of achievents and honours which include, Corresponding member Austrian AO-Chapter (2000), Godfather Herodicus Society USA (2000), Surgeon in Chief pro temp. The Hospital For Special Surgery New York (2002), Honorary Member of ANA (American Society of Arthroscopy, 2004), Honorary Member of ISAKOS (International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine, 2007), Honorary Fellow of ICRS (International Cartilage Repair Society, 2007), Honorary Member of Swiss Society of Accident Surgery and Insurance Medicine (2008) and Honorary Member of Swiss Orthopaedic Society (2009).

Invited Faculty

Karperien Marcel, Prof., MD, PhD
University of Twente Developmenal BioEngineering Enschede, Netherlands

Marcel Karperien studied biology at the University of Utrecht in the Netherlands. After a PhD in developmental biology in which he studied the molecular mechanisms underlying skeletal development, he worked 12 years at the Leiden University Medical Center on various aspects of endochondral ossification. In 2007 he moved to the University of Twente, to combine developmental biology of the skeleton with technology to improve strategies for cartilage regeneration. In 2012 he founded the department of Developmental BioEngineering (DBE) and became a full professor. The Department of Developmental BioEngineering (www.utwente.nl/tnw/dbe) is part of the MIRA institute for Biomedical Technology and Technical Medicine, which is ranked as the 7th best bioengineering institute worldwide. Currently the DBE group comprises 14 PhD students. Research focuses on i) developing injectable hydrogels for cartilage repair, ii) elucidating molecular mechanism underlying chondrocyte homeostasis, iii) improving cartilage formation, iv) the role of stem cells in cartilage regeneration, and v) exploring novel technologies for improved cartilage repair strategies. Prof. dr. Karperien is PI and participant in (inter)national projects focusing on cartilage repair including the Biomedical Materials Program, the Smartmix TeRM program, the National Initiative for Regenerative Medicine and projects funded by the Dutch Arthritis Association.

Kon Elizaveta, Ass. Prof., MD,
Universitat Humanitas, Milan, Italy

Secretary General of International Cartilage Repair Society (ICRS). Coordinator of numerous research projects and clinical trials regarding biotechnology applications in orthopaedics, into the framework of Italian and European research. Author of over 135 scientific articles in peer-reviewed and over 25 chapters in textbooks in orthopedic surgery (H-index 51). Faculty of more than 400 society meetings all over Europe, Asia and America. Associated Editor of BMC Musculoskeletal Disorders Journal and Advances in Orthopedics. Reviewer for more than 20 Orthopaedics Journals Winner of several awards: ICRS Travelling Fellowship in 2004 and the ESSKA- AOSSM travelling fellowship in 2009; Scientific Exhibit Award of Excellence at the AAOS Annual Meeting 2011; Best scientific presentation at the ORTOMED Meeting 2012; Article included in Cartilage top-cited articles published in the Arthroscopy Journal 2011-2012; Award Cum Laude at the ICRS Meeting 2013 for the electronic poster and the Leading article Knee Surgery Sports Traumatology Arthroscopy Journal in 2013.Award Cum Laude at the ICRS Meeting 2015 for the electronic poster and oral presentation.

Lattermann Christian, Ass. Prof., MD
University of Kentucky Orthopaedic Surgery Lexington, United States of America

Christian Lattermann is Vice Chairman for Orthoapedic 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 ½ 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.

Invited Faculty

Lindahl Anders Prof., MD, PhD
Sahlgrenska University Hospital Institute of Biomedicine
The Sahlgrenska Academy Gothenburg, Sweden

Anders Lindahl was appointed Professor in 2000 at the Institute of Biomedicine at The Sahlgrenska Academy at University of Gothenburg. He is the Laboratory Director of the Clinical Chemistry Laboratory of Sahlgrenska University Hospital since 2005 and he is the medical director of the cell transplantation unit and leading a research group focused on cartilage repair and chondrocyte differentiation. Anders Lindahl graduated at the Medical Faculty of the University of Gothenburg in 1979, completed his internship in 1982 and received his Board certificate in clinical chemistry in 1992. He received his Ph.D. degree in 1986. He was a research fellow in the laboratory of Dr Howard Green at the Department of Cell Biology, Harvard Medical School, Boston, MA US 1987 1988 with a work focused on gene therapy. His research on human chondrocytes commenced in 1985 and he and Professor Lars Peterson and Associate Professor Mats Brittberg performed the pioneering work introducing autologous chondrocyte transplantation (ACT) for the treatment of cartilage defects in the knee. The article in New England Journal of Medicine (331:889-895, 1994) was by Harvard Health Letter nominated as one of the ten most important scientific papers that year and is one of the 10 most cited papers in cartilage research worldwide. He has written over 100 articles in the field of chondrocyte research and has been main supervisor for 8 graduated PhD students and co-supervisor for 4 graduated PhD students. He is currently supervising 4 PhD students in training. Professor Lindahl and collaborators have treated over 1500 patients with ACT and the technology is spread worldwide with over 30000 treated patients.

Mainil-Varlet Pierre, Ass. Prof., MD, PhD
AGINKO Research AG Clinical Research Marly, Switzerland

Pierre Mainil-Varlet is a founder and active member of the International Cartilage Repair Society. Among others, he is a member of the European Society of Pathology, the Orthopaedic Research Society, the Osteoarthritis Research Society International and the Society for Biomaterials (USA). Formerly serving as CEO and co-founder of Allevia AG, Chief Medical Director of MyoPowers SA, Associate Professor of Pathology and the University of Bern, Dr. Mainil-Varlet is a board member at Aginko Research AG. Dr. Mainil-Varlet earned a Master of Business Administration Degree at the London Business School, a PhD Degree at the University of Groningen, a MD Degree at the University of Brussels. Dr. Mainil-Varlet has 15 years of experience creating successful clinical development strategies and directing all aspects of trials. He leverages his deep pre-clinical background to interface closely with regulatory authorities and translate results into clinical trial designs that consistently gain rapid approval. He provides key input in the development of clinical documentation and is the author of more than 60 publications and 150 lectures at international conferences.

Malda Jos, Ass. Prof., PhD
University Medical Center Utrecht Orthopaedics Utrecht, Netherlands

Jos Malda is Head of Research at the Department of Orthopaedics, University Medical Center Utrecht and the Department of Equine Sciences, University of Utrecht. He also leads the Utrecht Biofabrication Facility. He is a long-standing Board member of the ICRS and President of the International Society for Biofabrication. He received his MSc degree in Bioprocess Engineering from Wageningen University in 1999 and completed his PhD on Cartilage Tissue Engineering in 2003 (University of Twente and IsoTis bv). He subsequently accepted a research fellowship at the Institute of Health and Biomedical Innovation, (Queensland University of Technology, Brisbane, Australia), where he still holds an adjunct position. In 2007, Dr Malda was awarded a fellowship that allowed him to establish his research group in Utrecht, which focuses on biofabrication and biomaterials design, in particular for the regeneration of (osteo)chondral defects. He has published over 70 articles in peer reviewed international journals and was recently awarded an ERC Consolidator grant.

Invited Faculty

Mandelbaum Bert, MD
Orthopedic & Sports Medicine Group Santa Monica, United States of America

Bert Mandelbaum is a medical graduate of Washington University Medical School in St. Louis in 1980, which completed his residency in Orthopaedic Surgery at The Johns Hopkins Hospital and fellowship in Sports Medicine from UCLA. He served on the faculty at UCLA from 1986-89 and subsequently joined the Santa Monica Orthopaedic and Sports Medicine Group. He presently practices there and serves as the Director of the Sports Medicine Fellowship Program and the Research and Education Foundation and Medical Director for the FIFA Medical Center of Excellence in Santa Monica. He is currently the Co-director of Medical affairs for the Institute of Sports Sciences with Cedars Health System. He is also the Director of Research for Major League Baseball (MLB) and serves on the USOC National Medical Network Advisory Group. He also was appointed as Chief Medical Officer for the World Special Olympic Games 2015 in LA. Academically, he is well published including multiple journal articles (90) and five books. He has received five national awards for Excellence in Research in the Field of Sports Medicine. Since 1995 he has been on the editorial board of the American Journal of Sports Medicine and associate editor for Current Concept Reviews. He also served 1999-2001 as executive board member for the American Orthopaedic Society for Sports Medicine. Presently, he is Past President of the International Cartilage Repair Society (2008-09). He has also has been awarded a NIH Grant on Prevention of ACL Injuries in Children and Adolescents in collaboration with Chris Powers PhD of USC. He was honored in a distinguished fashion in 2009 with an Honorary Doctorate of Humane Letters (DHL) from the State University of New York. As a team physician Dr. Mandelbaum, has worked with UCLA Athletics (1985-1989) and Pepperdine University (1990-present, LA Galaxy and Chivas USA MLS teams. He was the Chief Medical Officer for Women's World Cup Soccer 1999 and 2003, US Soccer Men's National Teams Physician since 1991, and the assistant Medical Director for Major League Soccer since 1996, and served as USA Team Physician for Soccer World Cups '94 in the USA, '98 in France, 2002 in Japan and Korea, Germany in 2006 and South Africa in 2010. He also served as a FIFA Medical officer for World Cup 2014 in Brazil and on the USA Gymnastics Sports Medicine Advisory Board. In 2002 he was appointed to FIFA Medical Assessment and Research Committee (F-MARC) and in 2007 to FIFA's Sports Medicine Committee. He also served on the Sports Medical Committee and Olympic Medical Officer for the Sydney 2000, Athens 2004 and Beijing 2008 and London 2012 games.

McIlwraith Wayne, Prof., MD, PhD
Colorado State University Orthopaedic Research Center Fort Collins
United States of America

Wayne McIlwraith has been a faculty member at Colorado State University since 1979. Currently he is a University Distinguished Professor, holds the Barbara Cox Anthony University Endowed Chair in Orthopaedics and is Director of the Orthopaedic Research Center. He also directs the Musculoskeletal Research Program which is a CSU Program of Research and Scholarly Excellence. He obtained his veterinary degree from Massey University, New Zealand, did an internship at the University of Guelph, Canada, a surgical residency at Purdue University and has MS and PhD degrees from Purdue University. He is a Diplomate of the American College of Veterinary Surgeons, the American College of Veterinary Sports Medicine and Rehabilitation and the European College of Veterinary Surgeons, as well as, a Fellow of the Royal College of Veterinary Surgeons (UK). In addition to leading the Orthopaedic Research Center and Musculoskeletal Research Program at CSU, Wayne has a referral equine orthopaedic practice in Southern California and is a consultant and surgeon for clients internationally. The Orthopaedic Research Center has focuses of articular cartilage repair, early diagnosis of traumatic arthritis and osteoarthritis in equine athletes using novel imaging and fluid biomarker techniques, studies of the pathogenesis of intraarticular fracture and osteoarthritis, development of novel biological therapies for joint trauma and osteoarthritis and, more recently, rehabilitation therapies. He is the primary author of the only text books on diagnostic and surgical arthroscopy in the horse (four editions) and joint disease in the horse (in 2nd edition). He was Co-Program Chair of the 2012 ICRS meeting and is currently an Assistant Editor of Cartilage. He has received multiple honors including most recently the Markowitz Award from the Academy of Surgical Research 2013 and the Marshall R. Urist MD Award for Excellence in Tissue Regeneration Research from the Orthopaedic Research Society 2014.

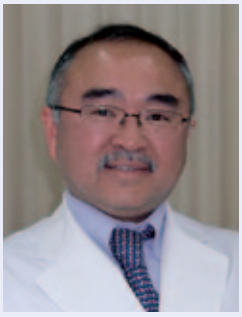
Invited Faculty

Minas Tom, Ass. Prof., MD
Brigham and Women's Hospital Harvard Medical School Chestnut Hill
United States of America

Tom is an Attending Orthopaedic Surgeon at Brigham and Women's Hospital in Boston, MA, an Associate Professor of Orthopaedic Surgery at Harvard Medical School, and Director of the Cartilage Repair Center. Tom Minas received his medical degree from the University of Toronto and his Masters in Epidemiology from the Harvard School of Public Health. He completed his fellowship in Trauma and Joint Reconstruction at the Sunnybrook Medical Centre in Toronto, Canada and a Total Joint Arthroplasty fellowship at Brigham and Women's Hospital. Tom Minas is an internationally recognized leader in joint preservation approaches to treating knee OA. He performs surgery of the knee; arthroscopy, joint preserving osteotomies, partial and total joint replacements. He is also an expert in cartilage repair and autologous chondrocyte implantation (ACI), having served on the Board and Education Committees of the International Cartilage Repair Society as well as the Chairman of the Cartilage Research Foundation. He is a member of the Knee Society, and in 2013, his team was honoured with the Insall Award for his work on Long Term Outcomes assessment of ACI in the knee. He is involved in the development of tissue preserving implants and instrumentation for knees targeted at joint resurfacing. His work in patient-specific knee replacement has led to the introduction of a family of tissue preserving, customized implants based on patient-specific imaging data to restore native articulating geometry. (International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine, 2007), Honorary Fellow of ICRS (International Cartilage Repair Society, 2007), Honorary Member of Swiss Society of Accident Surgery and Insurance Medicine (2008) and Honorary Member of Swiss Orthopaedic Society (2009).

Mithoefer Kai, MD
Brookline, United States of America

Kai Mithoefer is currently the Director of Cartilage Repair and Regeneration at Harvard Vanguard Medical Associates in Boston and a Clinical Instructor in Orthopedic Surgery at Harvard Medical School. He received his medical degree from Heinrich-Heine University in Düsseldorf Germany in 1991. He obtained his residency training in Orthopedic Surgery at Harvard Medical School and completed a fellowship in Shoulder and Sports Medicine at the Hospital for Special Surgery in New York. Dr. Mithoefer is board certified in Orthopedic Surgery and Sports Medicine in both the USA and Germany. He has been a member of the ICRS since 2003 and is currently serving as the co-chair of the ICRS Rehabilitation and Sports Committee. His research interest is in the clinical application and evaluation of novel tissue engineering techniques for articular cartilage repair with a special focus on their use in the high-demand athletic population.



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

Norimasa Nakamura is professor of the Institute for Medical Science in Sports 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, specializing in arthroscopic surgery. 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. His 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 osteochondral bio-implant using pluripotent stem cells in combination with biomaterials, by the collaboration with the iPS cell research center, the Kyoto University, and the Division of Tissue Engineering, the University of Tokyo. He serves as the President of the International Cartilage Repair Society (ICRS).

Invited Faculty

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

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 since 2011 he is also Dean of Faculty Health and Medicine and since March 2013 he is Head of Department for Biomedicine and Health Sciences at Danube University Krems. 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 73 peer reviewed articles and numerous other articles and book chapters in national and international journals. Prof. Nehrer has presented at many national and international meetings and he is member of national and international societies. Currently, he is the president of the German-Austrian-Swiss Society for Orthopaedic Traumatologic Sports Medicine (GOTS).

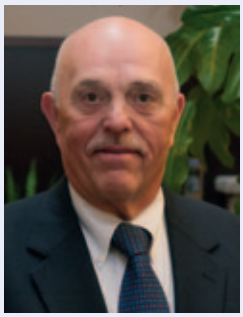
Papacostas Emmanuel, MD, PhD
TheMIS Orthopaedic Center Sports Orthopaedics Kalamaria, Thessaloniki, Greece

Emmanuel Papacostas is the founder of SportsClinic Thessaloniki and co-founder of TheMIS Orthopaedic Center in Thessaloniki, leading private institutes in the field of Sports Orthopaedics in the country. He studied medicine in the Aristotle University of Thessaloniki receiving his medical degree in 1993. He received his orthopaedic specialization diploma in 2004 and works in the private sector ever since. During and after residency he attended several international meetings in the field of sports orthopaedics and cartilage repair being awarded with several national and international fellowships. His work as a young investigator on ankle ligament injuries was awarded with the Einjar Ericsson FIMS Award in 2002. Dr Papacostas is a PhD student in the University of Thessaly since 2012, working on treatment of large chondral and osteochondar knee lesions with Autologous Chondrocyte Implantation. He became an ICRS (International Cartilage Repair Society) full member in 2005 (one of the first two Greeks), being a committee member (Publication & Communication committee 2010-2014 and Fellowship, Scholarship & Research Grand 2015). He is also a member of the International Ski Federation (FIS) Medical Committee, European Society of Sports orthopaedics Knee surgery and Arthroscopy (ESSKA) Cartilage Committee (2016) and member of several societies in the field of Sports Medicine and Sports Orthopaedics. His sports background (national and international level athletics) made him focus on sports injuries prevention and treatment and especially cartilage defects having being inspired by the ICRS, attending Surgical Skills Courses (Vienna, Miami, Rostock). He serves as head team physician of professional football teams and consultant surgeon for several clubs and national associations, having being actively involved in 2004 and 2008 Olympics. He is currently the leading researcher in the arthroscopic clinical application of CartiONE the first cartilage repair techonology that uses autologous chondrocytes to generate hyaline cartilage in one step surgical procedure. During the last 20 years Dr Papacostas wrote chapters in Sports Medicine and Sports Orthopaedics books (7), published papers in peer reviewed journals (6) and presented more than 150 papers and lectures in national and international congresses as an invited speaker.

Invited Faculty

Peterson Lars, Prof., MD, PhD
Billdal, Sweden

Lars Peterson is a professor emeritus in Orthopaedic Surgery at Gothenburg University, Sweden. Graduated from Medical School, Gothenburg University 1966, became specialist in General Surgery 1972 and Orthopaedic Surgery 1973. Defended 1974 his PhD thesis on Fracture of the neck of the talus, appointed Associate Professor 1980, Assisting Professor and Chief at the Orthopaedic Department 1974- 1988. Been head physician for the Swedish National Teams in football and icehockey. Member FIFA Medical Committee and founding member of F-MARC.Published over 200 articles in orthopaedics, several textbooks and chapters in international textbooks. Pioneered the treatment of articular cartilage injuries using autologous chondrocyte transplantation first cell therapy in orthopaedics, was one of the founders of ICRS and president 2001-02. Received many international awards. In 2007 the first European elected member of The Hall of Fame of the American Orthopaedic Society of Sports Medicine. Received 2010 The Duke of Edinburgh Prize for Outstanding contribution to international education in Sports Medicine. In 2010 awarded Doctor Honoris Causa at the University of Helsinki, Finland. In 2011 awarded Doctor Honoris Causa at Universidad Catolica San Antonio, Murcia, Spain.



Rodkey William, MD
Edwards, United States of America

Rodkey is formerly the Chief Scientific Officer and Director of the Center for Translational and Regenerative Medicine Research at the Steadman Philippon Research Institute in Vail, Colorado. He currently serves as Chairman of the Scientific Advisory Committee and is the Senior Scientist in the Center for Regenerative Sports Medicine. Dr. Rodkey's research is focused on tissue regeneration with scaffolds and cellular therapy with an emphasis on articular cartilage, meniscus, and ligaments. He has authored nearly 200 published works and has made about 500 presentations at national and international meetings. Dr. Rodkey has received numerous awards including the Excellence in Research Award from AOSSM, the Cabaud Memorial Award from AOSSM twice, the Albert Trillat Award from the International Knee Society (now ISAKOS), and GOTS-Beiersdorf Research Award 2000. He received undergraduate and Doctor of Veterinary Medicine degrees from Purdue University in his native state of Indiana and completed medical education and surgical and orthopaedic residency training in the US Army and at University of Florida. He is a member of AAOS, AOSSM, ISAKOS, ESSKA, ICRS, OARSI, EFORT, and is an Affiliate Professor of Clinical Sciences at Colorado State University.

Ryd Leif, MD
Karolinska Institute LIME Malmo, Sweden

I have a 30+ year experience as a clinically active orthopedic surgeon and clinical researcher involved primarily in joint disease of the knee. My research interests have involved the full-blown osteoarthritic (OA) knee and its treatment, i.e. prosthetic replacement. These prostheses have been studies using RSA as well as histological studies on retrieved prosthetic specimens. Further, these interests have involved the early development of OA in the young, athletic knee where chondral fractures, meniscal and ligament injuries need to be treated in order to avoid future OA many years down the line. In recent years, these interests have converged into a commercial endeavor and the development of a Focal resurfacing implant.

Invited Faculty

Sandell Linda, Prof., MD
Washington University in St. Louis Orthopaedic Surgery St. Louis, United States of America

Linda Sandell is the Mildred B. Simon Professor and Co-Director of Research in the Department of Orthopaedic Surgery and Director of the Core Centers for Musculoskeletal Biology and Medicine at Washington University in St. Louis. She has been a leader in the field of orthopaedic research, pioneering the use of molecular biologic techniques, large screening technologies, microscopy, computational biology and genetics to study cell responses to cartilage cell injury, the regulation of gene expression and osteoarthritis. Dr. Sandell was President of the Orthopaedic Research Society in 1999-2000, and was co-founder of the Women's Leadership Forum. She was recently President of the Osteoarthritis Research Society International (President 2010- 2012). Dr. Sandell has been awarded the Kappa Delta Award for Basic Science Research by the American Association for Orthopaedic Surgeons (1999), the Women's Leadership Forum Award (2010) and the Alfred R. Shands Jr, MD Award (2015) by the Orthopaedic Research Society.

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

Daniel BF Saris, Professor of Orthopedics UMC Utrecht, Professor of Reconstructive Medicine, University Twente, The Netherlands. Daniel Saris (Past President of ICRS) is a specialized knee surgeon. He graduated from University of Amsterdam Medical School. During orthopedic residency dr. Saris did a fellowship at the Mayo Clinic in Rochester MN USA and subsequently completed a PhD at the University of Utrecht in the Netherlands that introduced the now generally accepted concept of joint homeostasis. As staff member in the department of Orthopaedics at the UMC Utrecht he started The Mobility Clinic. An academical expert clinic for Musculoskeletal care and research. Prof dr Saris is management team member of the RM & stem cells focus at the UMC Utrecht and head of the orthopaedic residency program there. Patient centered progress is the central motif in his vision and work.

Spalding Tim, Ass. Prof., MD
Leamington Spa, United Kingdom

Tim Spalding is a specialist knee surgeon at University Hospitals Coventry and Warwickshire NHS Trust, in Coventry, UK, and Honorary Associate Professor at the University of Warwick. He treats all aspects of knee problems from sports related injuries to arthritis. His sub-specialist interest is in reconstructive knee surgery including meniscal transplantation, articular cartilage repair, osteotomy and ligament reconstruction. In 2015, he was the co-chairman of the program committee for ICRS 2015 conference in Chicago. Training took place in Oxford and at Royal Hospital Haslar, prior to an arthroscopy and knee surgery fellowship in Toronto, Canada in 1994-1995. He qualified in 1982 from Charing Cross Hospital, London and spent the first part of his medical career with the Royal Marines and the Royal Navy looking after service knees and seeing active service abroad. He joined Coventry in 2000 after 5 years as a Consultant in the armed forces. He has a busy sports knee surgery practice, runs a knee fellowship program and continues to be very active in teaching and research, pioneering several new techniques. Through his hobby of sailing he was the medical advisor for the Volvo Ocean Race until 2012 and now sits on the Medical advisory committee for the RNLI.

Invited Faculty

Trattnig Siegfried, Prof., MD, PhD
Medical University of Vienna MR Center, Department of Radiology Wien, Austria

Siegfried Trattnig graduated from the University of Vienna Medical School in 1985. He trained in Radiology and subsequently served as Assistant Medical Director and Acting Medical Director for the Section of Neuroradiology in the Department of Radiology, Medical University of Vienna. He was appointed as an Associate Professor in Radiology 1993 becoming the Acting Medical Director at the Clinical Magnetic Resonance Institute at the University of Vienna. Since 2003 Prof Trattnig has the position of the Medical Director of the Centre of Excellence in high-field MR at the Medical University of Vienna. In 2010, he was appointed as a full Professor for Radiology with special focus on High field MR. Prof. Trattnig has pioneered the field of multi parametric or biochemical MR imaging of cartilage. He is currently the lead researcher on the clinical 7T & 3T projects at the Medical University in Vienna. Based on the results of clinical comparison studies between 3 and 7T his Center of Excellence for High Field MR was appointed as the international Reference Center for 7 Tesla by Siemens Healthcare, the leading vendor in the ultra-high field MR. He is editorial board member of 8 scientific journals, member of 35 committees and working groups within the ISMRM, ESR, ESMRMB and the ICRS among the Executive Board member of the ESMRMB, member of the ESR Research Committee Board and Chairperson of the ESR European Imaging Biomarker Alliance (EIBALL) and Director of the School of MRI of the ESMRMB. He is an author of 431 articles in peer reviewed scientific journals and contributed to 25 scientific books. Additionally, he has held 26 peer reviewed scientific grants with a total of funding money of 13.5 Mio, received 12 scientific awards and is a reviewer for 34 scientific journals.

Vangsness, Jr. C. Thomas, Prof., MD
University of Southern California Orthopaedic Surgery Los Angeles, United States of America

Thomas Vangsness is a professor in the Department of Orthopaedic Surgery at the Keck School of Medicine of USC. He specializes in the treatment, prevention, and surgery of orthopaedic and sports-related injuries, including ACL reconstruction, meniscus surgery, cartilage repair and restoration, rotator cuff surgery and shoulder instability. Dr. Vangsness has conducted and published extensive research with a focus on such topics as shoulder and ligament biomechanics, molecular biology, allograft transplantation and stem cell biology in sports medicine. He is a team physician for USC Athletics. Dr. Vangsness received his medical degree from the University of Minnesota School of Medicine and completed fellowships in bioengineering at the Hospital for Joint Diseases, Orthopaedic Institute in New York and a sports medicine fellowship at the Kerlan-Jobe Orthopaedic Clinic in Los Angeles.

Verdonk Peter, Prof., MD, PhD
Gent-Zwijnaarde, Belgium

Peter Verdonk, is a full-time Consultant Orthopaedic Knee Surgeon at the Antwerp Orthopaedic Center (Monica Hospitals) and Researcher at the Antwerp University and the Monica Research Institute. He is also a Visiting Surgeon at the Aspetar Hospital in Doha, Qatar and an Attending Surgeon at the Antwerp University Hospital. His clinical and research interests are knee surgery and arthroplasty with a 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 90 peer reviewed papers and has lectured internationally. He is also involved in several national and international scientific organization (ICRS, ISAKOS, ESSKA, ABA, BVOT, BKS). For more info www.verdonk.be

Invited Faculty

Vonk Lucienne, PhD
UMC Utrecht Orthopaedics Utrecht, Netherlands

Lucienne Vonk studied life sciences at HU University of Applied Sciences Utrecht, The Netherlands. She worked as a research technician for two years on the production of recombinant human collagens by yeast and fungi for tissue engineering purposes at Leiden University. In 2006, she started as a PhD student at the Academic Centre for Dentistry Amsterdam under the supervision of Professor Vincent Everts and Professor Ruud Bank on the use of chondrocytes and chondrons for tissue engineering of cartilage. After completing her PhD in 2010, she joined the department of Orthopaedics at the UMC Utrecht as a postdoctoral researcher, where she is currently appointed as an assistant professor. Her research interests include cocultures with mesenchymal stromal cells (MSCs), trophic signaling by MSCs and signaling by microRNAs for cartilage repair.

Waugh Norman, Prof.
University of Warwick Medical School Coventry, United Kingdom

Norman Waugh graduated from Edinburgh Medical School, and did general training in anaesthetics (DA), general medicine (MRCP UK), geriatrics and general practice before doing specialist training in public health medicine (MPH and MFPHM). He became a consultant in public health Medicine in Tayside 1986 and then Grampian 1993. Several spells as acting DPH, Tayside January to April 1993, Grampian and Shetland most of 1999. While in Grampian, set up and directed the first Scottish HTA centre, SHPIC. Moved to Southampton in 2000 where directed the Southampton Health Technology Assessments Centre from set-up in 2000, to departure in November 2002. Appointed prof of PHM in University of Aberdeen December 2002, and led the Aberdeen HTA Group till end March 2011. Member of NICE Appraisal Committee 2001 to 2005. Joined Warwick Evidence in June 2011. Professor Waugh's research interests are mainly in diabetes including studies of incidence of type 1 in children, through to mortality studies. Other interests include: – Audit studies, such as of diabetic keto-acidosis – Trials, including the REPOSE trial of insulin pumps and structured education – Health technology assessments, mainly for NICE but also for National Screening Committee and Department of Health. Recent work has included screening for hyperglycaemia in pregnancy; self-monitoring of blood gulose in people with type 2 diabetes; NICE appraisal of liraglutide for type 2, newer drugs for type 2 diabetes, ranibizumab for diabetic macular oedema. Past research experience includes cervical screening, notably the TOMBOLA trial in mild and borderline lesions

Zaslav Kenneth, Prof. MD
Advanced Orthopedic Centers Sports Medicine and Cartilage Restoration Center Richmond, United States of America

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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1. Shive M, Stanish W, McCormack R, et al. "BST-CarGel® Treatment Maintains Cartilage Repair Superiority over Microfracture at 5 Years in a Multicenter Randomized Clinical Trial," *Cartilage*. 2015; 6(2):62-72.
2. M. Steinwachs, MD. Arthroscopic Treatment of Cartilage Lesions With Microfracture and BST-CarGel. *Arthroscopy Techniques*. 2014 Vol. 3(3): 399-402.
3. K162074 ArthroCare 510(k) Summary.
4. Data on file at Smith & Nephew, report 52918-01. The results of in-vitro simulation testing have not been proven to predict clinical performance.
5. Smith & Nephew FLOW 50 IFU (P/N 65994).

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Extended Abstracts

My 25 years of Cartilage Repair – Roland Jakob (CH)

It took me almost 20 years to learn to become what I define as a *Comprehensive Knee Surgeon and* to be able to theoretically understand the principles of pathology of injury, inflammation and degeneration, including biomechanics of overload and apply the treatment of ligament, meniscus and cartilage lesions, as well as reconstructive surgery in Osteoarthritis (OA). Out of this intensive study and practice, I would call it devotion to the topic of my heart, resulted a number of papers and publications, today some of them still worth while reading, some to a lesser extent, I would say. While many cartilage surgeons grow into Cartilage Repair through Research in a Basic Science Institution where they concentrate on one specific experimental technique that they then, at later date, hopefully are able to apply and practice in their clinical work, I devoted a lot of my time to learn to perform a good, safe and efficacious osteotomy, difficult reconstructions in posterolateral instability and secure meniscal sutures and to fix comminuted fractures of the knee. By doing this I understood that only when all the involved structures were intact and worked in sound concert, the knee function could be expected to be restored to near normality.

What techniques were around for a damaged Cartilage surface which we utilized during my early clinical activity at the University Hospital, Inselspital in Berne, Switzerland and later in Fribourg?
In the 1980s, *Pridie Drilling (1959)* was utilized and *Spongiolisation by Ficat* (1979), by which the chronically thickened subchondral plate under a cartilage defect of the patella was excavated and left empty allowing to fill in with fibrocartilage- we applied those methods mainly for naked, worn down patellae. Later, *Abrasion Chondroplasty (1986),* developed by *L. Johnson,* was introduced and in parallel *Microfracturing by R. Steadman,* developed in the late 1980s and early 1990s followed. All those 4 methods were surgically open or arthroscopic techniques, the two mentioned first had been described before arthroscopy was generally established in Europe. Today, the fact is interesting that arthroscopic drilling other than with a wire has not received further attention for a long time; although meanwhile it has been shown that it might be advantageous. These methods mentioned were all utilized because they represented the only means available.

Earlier since 1985, L. Peterson seconded by *M. Brittberg* had studied and clinically applied Autologous Chondrocyte Transplantation which later turned out to become the firm leg of modern cartilage repair following with their publication of 9 year results in *1994*.

In the early 1990s I visited my friend I. Berkes in Budapest in his Sports Medicine Institute to speak about posterolateral capsuloligamentous knee instability which at that time received great attention and to which I had devoted quite a bit of time and study. After leaving the OR where we operated on one patient with difficult varus instability, my friend showed me on his desk the thesis of a young colleague from a public hospital in Budapest on a new method to treat cartilage defects, including studies in animal experiments. His name was *Laszlo Hangody*. I browsed through his thesis and Istvan asked me for my opinion. I found it very interesting. Laszlo had developed the idea in *1991* and did his first case in *February 1992*. This greatly influenced me in the upcoming years and it influenced Cartilage Repair in general. But before that, consider this. In 1992 I was exposed to a case of a 40 years old female lab technician of our hospital whose knee presented in arthroscopy a 2 cm^2 OCD of the medial femoral condyle while X rays had not clearly identified the lesion prior to surgery. It was the time when MRI was not yet available as standard method and a CT was not done. During open arthrotomy, I was somewhat taken by surprise and did not immediately how to deal with this situation. I applied general orthopaedic principles, emptied the scar tissue in the defect and so to fill the defect I decided to retrieve a slightly oversized plug from the medial tibial plateau. But what to do for the cartilage? Having heard that in Sweden they carefully removed the periosteum and turned it upside down on a cartilage defect so that the *"Cambium layer"* was now facing the joint cavity, I sutured it back on the plug that I had meanwhile firmly impacted into the defect after shaping it to a nearly perfect fit. I had learnt that the periosteum consists of an inner "osteogenic" layer and an outer fibrous layer, the cambium layer containing mesenchymal progenitor cells that develop into osteoblasts and, after a fracture into both osteoblasts and chondroblasts which are essential to the healing process. *Lorentzon and Alfredson* and independently *O'Driscoll* had experimented with this principle.

My patient then showed a nice evolution but she remained my only "experience" with this technique. I saw her regularly during the first years; then I left Berne to move to Fribourg and only 22 years later, I succeeded to call her back for follow up, 2 years ago mainly to satisfy a certain curiosity. She was happy to come and told me she felt only minimal pain; X-rays showed a well maintained joint line on weight bearing views and an aligned limb, despite her having gained a lot of weight. On MR we found some irregularity of the Neo-cartilage surface on the grafted medial femoral condyle. She was happy that the formerly young surgeon had chosen this way of treatment and so was I. One may ask why I did not go on with this way of treatment.

Extended Abstracts

After 1995, Mosaicplasty had become the method for those who did not think "cellular" and we developed our own autologous osteochondral grafting technique with Sulzer Medica, the "Soft Delivery System" (SDS System) that definitely allowed to reduce the impaction force on the cartilage caps of the plug during extrusion out of the cannula and during the seating in the bone which we thought was an unnecessary added damage as observed in studies using confocal microscopy in comparison with the standard commercially available instruments. During the following years we performed nearly 300 mosaicplasties, carefully followed our results and published them in CORR in 2002 *(Jakob; Mainil; Whiteside)*. Right from the beginning we applied the principle to always correct an axial malalignment and compartmental overload, even with slight deformities and we pushed the indication for mosaicplasty even for larger defects, sometimes using up to 12-16 plugs and surfaces of up to 10 cm2. Patient satisfaction was good, though with relatively short follow up of up to 3 years.

The main advantage was that this technique was readily available, permitted a single step surgery and that it was autologous. This appealed to surgeons and patients and still does today in some countries and a theoretical "caveat" of late OA changes at the retrieval sites did not turn the proponents of this technique off this way of treatment. But as years went by and reoperations became necessary, the sentence became true once again: *„Nothing destroys results as much as follow up",* attributed to J. Hughston. Why so? In major grafted lesions we frequently recognized cysts at the base of the plugs indicating lack of osseous integration. On reoperations necessary because of pain we found loose pseudarthrotic plugs that could be removed simply with a tooth. Horizontal osseous and cartilaginous integration was frequently non-existing. The cartilage surface remained uneven due to incomplete filling between the plugs or lack of filling. And on top of all of that, the retrieval sites turned into a "moon-like" crater surface with only incomplete filling of the defects below the level of the healthy neighboring cartilage surface. It was also disturbing to observe thin cartilage capped plugs of 2 mm thickness from the condylar periphery when those were transplanted to the thick central location of the patellar cartilage measuring 5-6 mm with funny looking CT's. Further on, when transplantation of the knee cartilage was used for the talus it was said to be a problem because talar cartilage was different in microstructure from knee cartilage.

It was in 1997 that we proposed to a selected group of international clinicians and scientists that we felt it was time to unite the spirits and discuss techniques and results of "cartilage repair". A First International Cartilage Repair Meeting was put up in Fribourg, Switzerland for which we asked Ernst Hunziker, renowned cartilage researcher from the University of Berne, Switzerland to propose names from the World of Basic Science and together with Pierre Mainil-Varlet, at that time my Research Fellow and spirit behind the idea at Cantonsspital Fribourg, Switzerland where I worked as a Head of the Department of Orthopaedics and Traumatology, we proposed names of clinicians.

We gathered 170 participants, scientists, clinicians and representants of industry present at that first meeting. We showed Live Surgery: Lars Peterson did a Sandwich Periosteum-Chondrocyte technique for a big OCD of the femoral condyle. We did a mosaicplasty of the femoral condyle and my partner, E. Gautier performed a talar OCD repair using mosaicplasty. It happened to become a very fruitful four days exchange that united in friendship single step advocates of mosaicplasty with two-steps cellular ACI proponents which at that time presented the "en vogue" methods besides of course Microfracturing that everyone practiced. One Basic Scientist, a Biology Professor from Germany, mentioned at the end of the meeting with a smile that he had profited a lot of this event in company of Clinicians because "he had not known that cartilage was so close to bone!"

I was proposed First and Founding President; we gave the name to the Society and a friend of mine, graphic artist from Berne created the logo. It was agreed upon that as a rule, researchers and clinicians should alternate as Presidents and many of those initially present have later become Presidents. As the first task, following up during a next working-meeting that we subsequently had only one year later in the Monastery of Villars les Moines, in the same area next to Murten, we reassembled the Core of the New Society and we were able to create the first accepted Clinical an Radiological Cartilage Classification System named "According to ICRS", including MRI grading and we also attempted to define Recommendations for Basic Cartilage Research!

Today, ICRS has developed to a stimulating healthy, blooming and active Society. Three years after my 2-years Presidency I became President of ISAKOS and the two Societies since then began to collaborate well with each other, with ICRS taking the role of the younger sister. But good relations were also created and maintained with OARSI. Coming back to our field of discussion and regarding my personal attitude towards cartilage repair and as years went by, the above mentioned reasons regarding complications of Mosaicplasty slowly motivated me to turn away from that technique and made me "cellular" as well! In around 2003, we looked for a way to maintain the blood clot created by Pridie drilling or by Microfracturing within the lesion by the creation of a "house and hold principle" *(quote L. Johnson),* by

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suturing a I/III collagen matrix around a given cartilagineous defect or OCD. We used for this purpose the Chondro-Gide membrane of Geistlich Surgical from Switzerland, and it was at a meeting in Zürich shortly after I proposed that technique to Dr. Peter Geistlich, the owner of the Company. He liked it but he told me that a Surgeon from Hamburg had just proposed the same technique to him. His name was Peter Behrens who had so well studied and introduced the technique that was then given the name of "AMIC", Autologous Matrix Induced Chondrogenesis *(Benthien)*. In this way we got initiated to that idea and from then on started our "AMIC" experience, using mosaicplasty less and less, reasoning that it would be a pity to sacrifice healthy cartilage when it could reform virtually by itself which of course was the argument also represented by the ACI proponents.

Different to Behrens, when we remember well, we already started early to treat big OCD lesions by filling the debrided and drilled the defect with fresh cancellous bone, covering it with a collagen I/III matrix and we saw that it worked! We did the same on the talar OCD's and realized there that sometimes the transplanted cancellous graft had a shrinking tendency so that we supplemented it in a proportion of 1:1 with Hydroxyapatite (Orthoss, Geistlich Biomaterials) that resorbed extremely slowly and thus allowed laying down of new bone on it. We had been proposed this idea by F. Clémence, researcher with Geistlich Company. He shared with us the experience from dental surgeons who had observed prior to dental implant anchorage cancellous graft shrinkage after filling up mandibular and maxillar defects with cancellous bone. Mixing it with HA solved that problem.

In the knee, different groups of indications were prospectively established: First, pure cartilage lesions of the femoral condyles. Second, osteochondral lesions of the femoral condyles, mostly chronic OCD's; Third, posttraumatic lesions of the femoropatellar joint with or without malalignment and fourth, lesions of the same location, often kissing lesions, following chronic patellar subluxation, often presenting as OA above the age of 40. In case of the involved compartment being overloaded in frontal plane, osteotomy was performed simultaneously or in a staged procedure.

After a few years we came to realize that the best and most constant results in terms of fibrocartilage regenerate were found in lesions where fresh cancellous bone had been grafted into a chronic osteo-chondral defect and where, if needed, frontal plane alignment osteotomy was associated and in femoropatellar lesions that had at the same time been treated with combined measures for realignment *(Kusano et al 2011)*.

Today, we are able to present the 10 year AMIC results and compare them with those obtained in the same group after 2 years of follow-up. In a study of *Kaiser et al*., 34 patients having received an AMIC procedure between 2003 and 2006 have been included. 27 Patients (79%) were available at final 10 yrs. follow-up with an average age of 47 (range of 24-74 years). All patients completed a Lysholm Score and a VAS after 2 and 10 years postoperatively.

Results. Preoperative Lysholm Score prop. was of 55.76 (SD 17.73) with an average VAS of 5.64 (SD 2.22). At 2 year, the average Lysholm score was of 83.78 (SD 17.74) with an average VAS of 2.12 (SD 2.28). At 10 year follow-up, the average Lysholm Score is of 84.72 (SD 12.76) with an average VAS of 2.00 (SD 1.63). Two of the 27 patients had meanwhile received implantation of a total knee arthroplasty because of advanced femoropatellar OA. Thus the authors observed a significant improvement ($p<0.001$) in the Lysholm Score and VAS comparing the pre-operative values with the 2 and 10 years postoperative results. There was no significant difference between results at 2 and 10 years follow-up (p-value: VAS 0.82 Lysholm 0.898). In conclusion, this study shows constant good results at 10 year of follow-up after AMIC procedures in the knee and a good match with the 2 years of follow-up values. This let us conclude that the AMIC procedure overall is an enduring treatment for cartilage lesions of the knee in the long term. The study however has some limitations. Of the 34 initial cases we lost 7 for follow up. Of the group of pure condylar cartilage repairs using the AMIC Technique, only 3 could be followed while the majority of the patients reaching follow up concerned osteochondral reconstructions of the femorotibial and femoropatellar joint. Undoubtedly, the good healing property in the osteochondral group might therefore influence the overall result. A number of patients of the femorotibial group had received an osteotomy as well which by itself might favorably influence the result.

These results are in agreement with *Schiavone-Panni's* recent study on 7 year results with good patient satisfaction in 76% and good MR appearance in 66% of the 21 cases treated.

The conclusion out of 10 years' experience is that cancellous bone has not only proven to be the excellent material to fill osseous defects but also is an interesting substance as carrier of MSC's which sit on its trabecula. Cancellous bone samples contain similar numbers of nucleated cells relative to bone marrow aspirates of the same size. However according to *Sakaguchi et al*, the trabecular configuration of cancellous bone is better able to form signi-

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ficantly more nucleated cell colonies, suggesting the presence of more mesenchymal stem cells. Further on, according to a study out of the group of *P. Giannoudis (Baboolal, Kouroupis)*, 1 g of cancellous iliac crest bone equals 45 ml of iliac crest aspirate. We can assume that those stem cells can also be useful in chondroblastic differentiation if they are placed in the correct surrounding as in an osteochondral defect where they have to lay down bone covered by a cartilage layer. In fact, in our experience the best fibrocartilagineous layer of all the AMIC's achieved as judged by thickness and regularity of surface was in the OCD Group but also including histologic analysis in individual cases with partially hyaline like cartilage reformation. This experience has not only been made by us but mainly by *L. Johnson* in his remarkable collection of deep osseous defects grafted with cancellous bone alone. For some time now, we have been interested in applying and extending such reasoning to the treatment of pure chronic cartilage lesions. We argue that if the involved area shows chronicity with thickening of the subchondral plate recruiting of mesenchymal stem cells by microfracturing is difficult. We therefore decided to transform the chondral lesion in an osteochondral defect by removing the thickened subchondral plate with a burr to a depth of 3-4 mm beneath it, to drill 1-2 cm deep canals from the depth of the defect using 1,1-1,5 mm diameter drill bits *(Chen et al)*, to then suture a Chondro-Gide Matrix to the borders of the intact cartilage, leaving a "kangaroo pocket" hole open and to finally insert through this window fresh and gently crushed cancellous bone retrieved locally from the distal femur or proximal tibia or probably better, from the iliac crest. (Fig. 1, 2, 3)

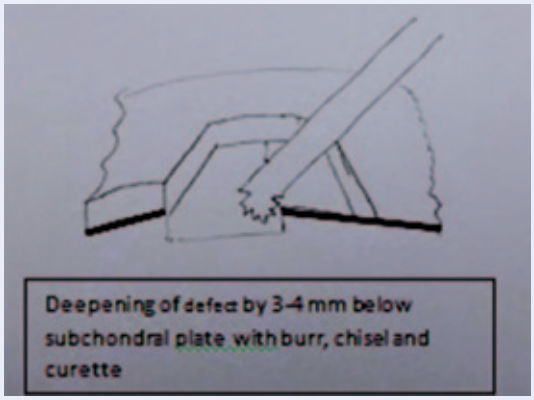

Figure 1

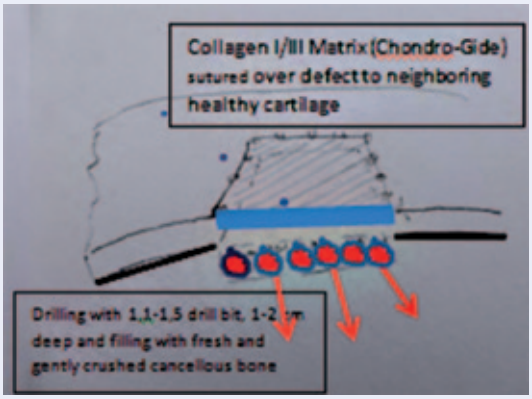

Figure 2

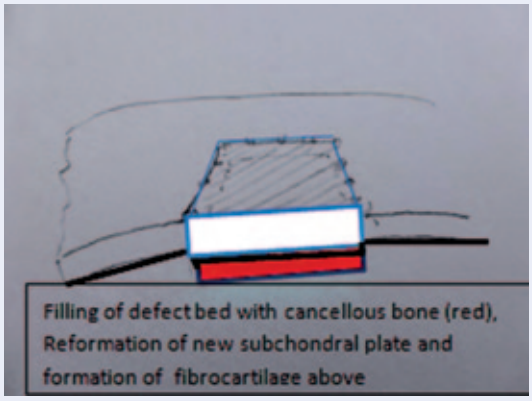

Figure 3

We hypothesize that the transplanted and released MSC's shall follow their inherent *Homing Mechanism* to work in 2 rows providing an osteoblastic and chondroblastic differentiation. A small series of 12 cases with chondral lesions has been treated over the past 3 years in different institutions accordingly by what we termed ***"Osteochondroisation"*** and results are in fact promising. *Credit to R. Martin, CHUV, Lausanne for the clinical case material (Fig. 4 a-h)*

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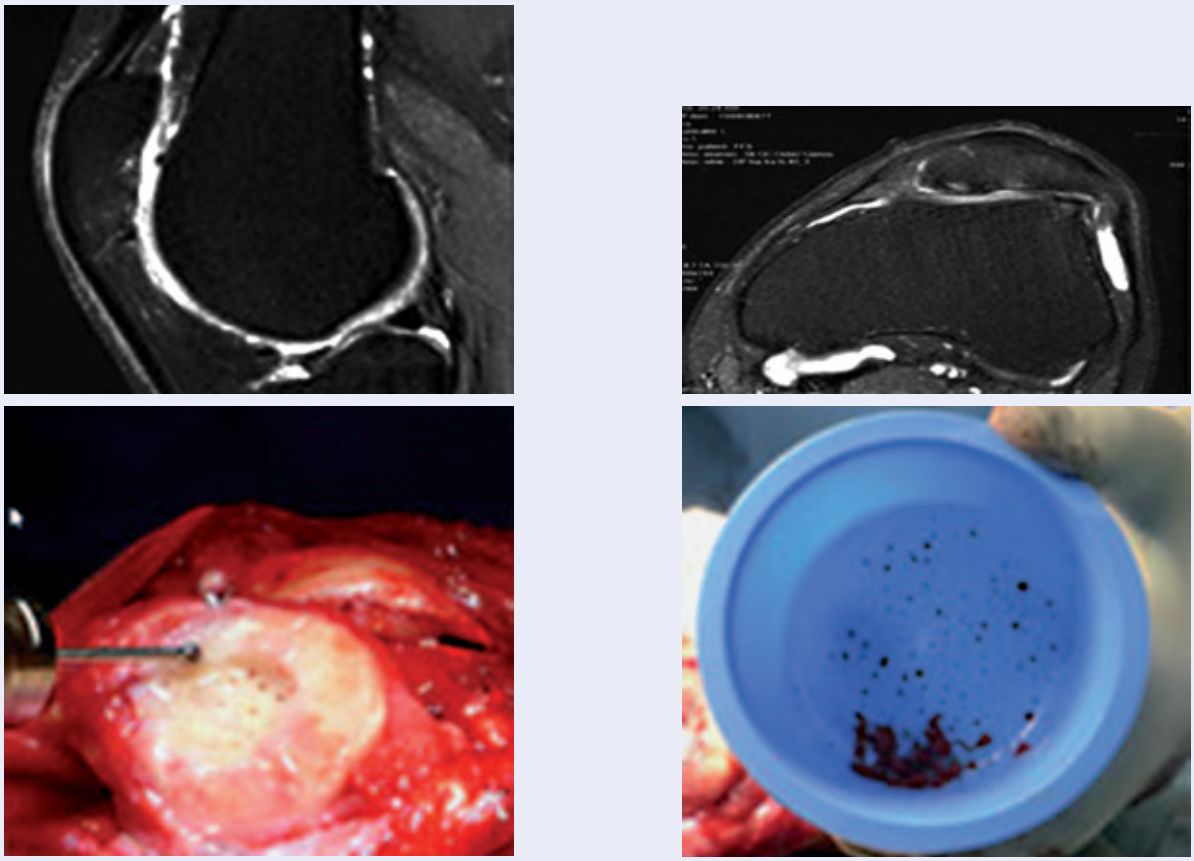

Fig. 4 a-d. Clinical Example. Severe chondral damage on the patella, resulting from chronic instability in a 27 yo man. (Trochlear dysplasia type B, MPFL insufficiency, TT-TG at 24 mm). a,b. Preoperative MRI demonstrates an extensive ICRS stage 4 chondral lesion, 20 mm diameter, with thickened subchondral bone. c. Deepening of cartilagineous defect with burr below subchondral plate and drilling. d. Fresh cancellous bone harvested from proximal tibial metaphysis.

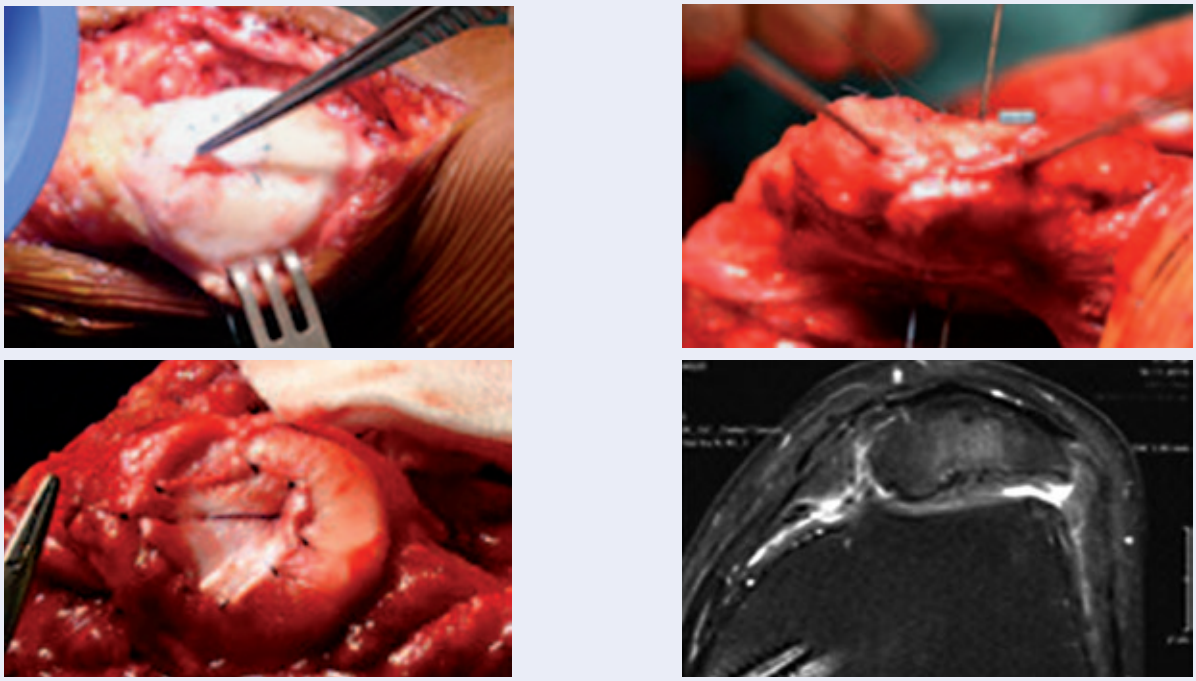

Fig. 4 Cont. e-h.: e. suturing of matrix with resorbable suture material 5.0, creating the kangaroo pocket. f,g. Adding one transfixion, transpatellar suture to improve primary stability of membrane. h. One year postoperative MRI demonstrates excellent defect filling with new "undulated" subchondral plate.

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So, the hypothesis that fresh cancellous bone is able to re-create fibro-cartilage can in a preliminary clinical way be positively answered! But animal experiments are needed to confirm our clinical observation. In future, innovative research may identify the best way to combine "gently crushed" cancellous bone chips as MSC's release agent with endogenous biochemical mediators to initiate and accelerate cartilage repair. Certainly, a similar and long standing experience has been collected by *K. Stone* without the utilization of fresh but local bone grafts in his *"Pasting"* technique. To summarize this idea, which has been initiated by Pridie in 1959, carried on by Ficat in 1979 and Steadman and by Johnson in the 1990s is now developed one step further with our hypothetic idea by which the mesenchymal stem cells sitting on fresh cancellous bone trabeculae are recommended as an economic and readily available source for fibrocartilage regeneration. This method is humbly presented and proposed here as the result of a small observational study. Future shall show whether the way proposed here is valid or if there are any drawbacks.

How has Cartilage Repair developed in general during the last 10 years? Have we been able to advance in this science?
While during the turn of the millennium OATS and ACT were the most discussed methods they were world-wide seen not the most practiced! 80% of cartilage repair gestures were "microfracturing" because of at least initially, promising results, easiness of technique, availability and economics, making it affordable in every spot of the world. OATS, mosaicplasty slowly became less utilized because of the previously mentioned reasons with the exception of a singular thick plug for a smaller defect which then allowed rapid weight bearing in an athletic patient.

Many companies offering ACI or similar chondrocyte culturing techniques of a second generation (MACI) avoiding one of its complications, e.g. hypertrophy, induced by the periosteum came and disappeared after a few years with frustrated investors because the policy of health insurance companies in most of the European countries denied reimbursement despite the positive results gained with this technique. During the past year in the US, Genzyme only implanted 1500 ACI's. In Scandinavia and Germany, Spain and Belgium it still has its applicants but in many countries the numbers have been steadily decreasing and no changes are visible regarding reimbursement policy.

How is a cartilage lesion treated in Europe today? Among 205'000 procedures/year, according to MRG 2014 Soft Tissue Solution Report Europe Top 5 Countries, 88% of the interventions are microfracturing, 6% are one step procedures, 3% are OATS, 3% are ACI, and 1% is osteochondral allografts. Although these "use" percentages are easily interpreted, less obvious is the rationale that supports them. Perhaps we use the procedure that has limited effectiveness because it is readily available. Perhaps we use it because it is affordable. Perhaps some surgeons use it because it is the only cartilage-focused procedure that they know. Perhaps we rely on this procedure because we have not as yet identified another method that although more costly, may lead to somewhat better outcomes.

Because of the disadvantage with two-step procedures, research has oriented towards single step possibilities like MSC's research and many others. Stem cells of various origins like fat tissue are under investigation and in clinical trials. PRP is utilized to bring in growth factors- its clear benefit has not yet been established. Those techniques still wait for clearance. Matrices have replaced periosteum as a carrier because of their easiness and biologic capabilities. Meanwhile not to forget in the US, allogenic materials gain easy and direct access to the market, which are not under the scrutiny of FDA clearance. Their potential needs to be looked at.

Other methods
Finally, a handful of elaborate acellular semisynthetic osteochondral implants, consisting of collagen and hydroxyapatite, and/or coral bone and other materials have been proposed. We refer to the excellent overview of *AJ Krych et al*. Such an approach to cartilage restoration has the advantage that donor site morbidity would be little or absent and that it enables a single-stage treatment thanks to an off the shelf procedure. As compared to a two-step cell culture technique it would be of relatively low cost. You would not have to fear reactions from immune response, although you might observe foreign body reactions, and the target would be to restore by biphasic implants a physiological cartilage-subchondral bone structure. Seeding by progenitor cells would allow for a lasting result enhancing production of cartilage matrix, supporting differentiation of progenitor cells to hyaline cartilage including production of chondrocytes. Some of these materials would be biodegradable; some would allow incorporation in bone. Some of them are under clinical investigation; some have again disappeared because of undesired side effects or because of non-convincing results or because of the delayed biological incorporation of the plug associated with reported failures expressed by persistent symptoms and joint effusion. Quite regularly, initial studies with author participation show promising results and only after a few years' unbiased studies then demonstrate incomplete regeneration of the cartilage and poor subchondral bone repair, with those later authors urging caution for future use.

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Here I would like to mention that after the "Symposium on Side Effects" at the Chicago ICRS Congress in 2015 which was under the initiative of the Emeritus Committee it was brought to the attention of the general board that in the future a caption should regularly be integrated in the Newsletter or on our website named "Caveat" where such unfavorable side effects should be brought to the user's attention without any delay. Unfortunately, too often I observe that a group of surgeons, investigators and authors of a new technique propose this technique repeatedly during several meetings and years, and then suddenly they leave that technique and start to talk about something totally different without ever letting us know their rationale why they gave up that technique. Only later do we hear by honest clinicians about the true reasons why this project had been given up. That is too bad and does not show us to behave as responsible clinicians towards patients and clinician-colleagues.

Methods that stood the test of time
Despite of certain soberness, regarding the milestones in our field, some methods and materials seem to show efficacy and usefulness over time! What should they fulfill? Let us try to define the criteria:

The methods should be single step techniques because of economic reasons and because of simplicity; they should show a clear and distinct benefit and advantage over existing techniques; they must not be potentially harmful; and finally, they should be affordable [including not requiring an abundance of new instrumentation and extra hands in the operating theatre]! We have to come back to the issue of economics, because today, health system money is less available. Is it that this money must be used for "more relevant" diseases than cartilage injury? I have no answer to this very critical issue of what is relevant and what is not. Clearly, or understandably, it is what is closest to your neck that counts! But a cell transplant in Leukemia is without doubt more relevant than for a hole in the cartilage. Despite the vast majority who continue to use microfracturing, literature's evidence regarding its limitations is unfortunately overwhelming:

Many clinical studies report deterioration of MFx-results over time (Steadman JR et al. 2003; Gobbi et al. 2005; Kreuz et al.2006; Mithoefer et al. 2006, 2009; Knutsen et al. 2007). That does not mean that the basic idea behind has no value; it just needs to be further developed until it shall even have more use over time. Among the techniques and tools for Cartilage Repair I should like to mention *established matrices* like *Chondro-Gide* because it is practical in handling, it allows cells to grow in rapidly and it is affordable. Understandable that it is the most utilized membrane world-wide.

Matrices using in part *Hyaluronic Acid* are liked by the users and seem to have a beneficial effect for cell growth and intercellular matrix deposition. *Cancellous bone* is not only an excellent material to fill osseous defects but also an interesting carrier of MSC's which sit on its trabecula. A number of newer techniques use a principle by which a pure cartilagineous lesion is transformed into an osteo-chondral lesion to solidly fix the implant. Although for some time the subchondral plate was deemed untouchable, for those who bring these implants on the market this does not seem to be an argument against anymore. In fact mosaicplasty was working according to the same principle-a cartilage hole is deepened into an osteochondral hole and filled with a cartilage capped osteochondral graft. Its disadvantage would be that the retrieval process of a plug might create thermal damage and be harmful for the cells and that the best source for stem cells would represent the iliac crest. But locally retrieved bone from the distal femur or proximal tibia seems to work almost as well.

Is cancellous bone able to re-create cartilage? Who had thought that? Only those who are patient and believe in the fantastic regenerative potential of human biology! Perhaps the true value that innovative research methods may provide is to identify the best way to combine endogenous biochemical mediators with cancellous bone chips to accelerate cartilage repair.

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To summarize this idea, what has been initiated by Pridie in 1959 and carried on by Ficat in 1979 and Steadman and by Johnson in the 1990s is now developed further on by an idea where the mesenchymal stem cells sitting on the cancellous trabeculae are recommended as a cheap, easily available source for fibrocartilage regeneration. The future shall reveal whether this recommendation that is for the first time proposed by our group so far in the science of cartilage repair is good enough and valid and equal or even better than other methods or if it creates other drawbacks not known by now. Maybe it shall be "too cheap" to be applied on a broader scheme. The surgeon must constantly weigh the perceived value of any procedure with the likelihood for achieving successful patient outcomes given the costs and evidence base that supports its use. All too often the basic science community does not truly understand how important it is that any cartilage restoration innovation that is developed needs to translate directly into patient treatment approaches, given the limits of the tools that the surgeon and physiotherapists have to work with. Likewise, both basic scientists and surgeons need to appreciate how strongly patient compliance with rehabilitation and psycho-behaviors contribute to the ultimate success or failure of any intervention.

Conclusion

To date, no method has been able to consistently recreate hyaline cartilage. We have learned that efforts to repair deficient cartilage is also a hopeless undertaking when the meniscus in this compartment is missing or when the ligaments are deficient, when the ipsilateral compartment is overloaded, or when there is inflammatory disease. Femoropatellar repair usually must be combined with alignment procedures as well if that seems to be the underlying cause of cartilage damage. The more efficient and successful the basic mechanical problem is addressed the less extensive cartilage repair measures can be applied. If these essential factors remain untreated not even the most elaborate cartilage repair technique can solve the problem.

Cartilage repair continues to evolve. However, we still lack clear criteria as to how much deformity is tolerable, how to effectively monitor and interpret biological markers or how to identify the ideal candidate for a given isolated or combined cartilage reconstruction based on inflammatory or degradatory joint environmental factors. We also need to establish better correlative links between surgical and patient outcomes. What if the MRI or CT looks bad, but the patient is doing great, and have returned to work or sports? Most of the present cartilage treatment options have pro's and con's; a patient specific approach is needed based on expectations and the surgeon's experience. It seems clear that a cost-effective, single stage technique has a better chance than other options to become adopted by health insurance companies. Whether this is an arthroscopic, a mini-invasive procedure or not is a secondary concern and in my opinion this factor should not influence patients as they decide to undergo a surgical treatment or not! The surgeon who takes care of this patient should be able to apply all registers of a comprehensive knee surgery and not blend the patient and promise success thanks to an "endoscopic" technique.

Finally, another serious and definite aspect is economics. When we want to avoid that cartilage repair is only performed by a few "elite surgeons" in a few "elite clinics" for a small number of "elite patients" we miss the chance to remain or to become doctors who are genuinely concerned for the topic and the field of cartilage repair. We should focus our attention on potential solutions that will be readily available to all patients who might benefit from the procedure, particularly residents of medically underserved countries. To accomplish this, future cartilage repair methods should be easy to learn, and those who learn them should to be encouraged to perform and present long-term follow-up results.

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Module 1: Historical Look at Cartilage Repair

Marrow Stimulation for Cartilage Repair: A Historical Perspective
William Rodkey (US)

Full-thickness articular cartilage defects in the knee are common, and the lesions may present in a variety of clinical settings and at different ages. A single event, the shearing forces of the femur on the tibia, may result in trauma to the articular cartilage, causing the cartilage to fracture, lacerate, and separate from the underlying subchondral bone or separate with a piece of the subchondral bone. Alternatively, chronic repetitive loading in excess of normal physiological levels may result in the fatigue and failure of the articular surface, especially in the face of meniscus deficiency or axial malalignment. The single events are usually found in younger groups, whereas chronic degenerative lesions are seen in the middle age or older groups. It has been shown that repetitive impacts can cause cartilage swelling, an increase in cartilage fiber diameter, and an alteration in the relationship between collagen and proteoglycans. Thus, acute events may not result in full-thickness cartilage loss but rather start a degenerative cascade that can lead to chronic full-thickness loss.

Articular cartilage defects that extend full thickness to subchondral bone rarely heal without intervention. Some patients may not develop clinically significant problems from acute full-thickness chondral defects, but most eventually suffer from degenerative changes that can be debilitating. It has recently been estimated that just in the United States that cartilage injuries affect about 900,000 patients annually, and more than 200,000 will undergo some type of cartilage restoration procedure (1). Techniques used to treat chondral defects include bone marrow stimulation, osteochondral allografts, osteochondral autografts, and autogenous cell transplantation. The focus of this presentation is on marrow stimulation, including the historical aspects and the evolution that has led to today's techniques.

More than 70 years ago, as early as 1946, Magnusson (2) first described open debridement of chondral lesions, removing friable inflammatory tissue from arthritic lesions to reduce mechanical symptoms. In 1959 Pridie (3) described a technique of drilling through the subchondral bone in the areas of cartilage loss to stimulate formation of a repair tissue in the areas devoid of cartilage. Ten years later Insall (4) published the clinical follow-up results of Pridie's patients. In the mid 1970's, animal studies confirmed the formation of a fibrocartilage repair tissue using Pridie's technique (5). In 1979 Ficat (6) described "spongialization" of chondral defects in the patella. In 1986 Johnson (7) published his technique and the clinical results of using a motorized shaver/burr to perform abrasion arthroplasty by removing a small amount (1 to 3 mm) of subchondral bone to stimulate formation of a repair tissue to cover the abraded area. A decade later, Steadman (8) led our group to first publish the technique and initial results of the "microfracture" technique.

The microfracture technique was developed by Steadman in the early 1980s as a new method for cartilage restoration. The primary goal of surgery was to make a series of controlled "microfractures" perpendicular to the base of the defect using a combination of specially-designed 30°, 45° and 90° awls (or "pics") which were able to reach all areas of the joint surface. This procedure is thought to augment the healing process by stimulating an inflammatory response as a result of subchondral bone fracture, making access channels that cross the subchondral plate, disrupting subchondral capillaries to allow blood and marrow-derived multipotent progenitor cells to travel through these access channels into the base of the defect, producing small fracture fragments that promote both clot formation and its adherence, and using a minimally-invasive, single-stage technique. Over time, the resulting fibrin-rich "superclot" is reorganized and remodeled into a scaffold upon which recruited undifferentiated progenitor cells can differentiate and proliferate until a new articular surface is formed. In contrast to previous methods, this technique was designed to be coupled with individualized and customized postoperative rehabilitation protocols with specific emphasis on the basic science of cartilage nutrition (9,10). The Steadman microfracture technique, or some variant of it, is today the most commonly used marrow stimulation technique.

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Module 1

The Origins of Modern Cartilage Repair Technologies and Autologous Chondrocyte Transplantation – Daniel Grande (US)

Lesions in articular cartilage are difficult to treat and cause considerable musculoskeletal morbidity, with significant economic and social implications. It is generally well accepted that such lesions eventually result in osteoarthritis (OA). OA has a significant impact on human health, particularly in populations who are at higher risk for cartilage trauma over the course of their lifetimes. These include patients who have sustained sports injuries, have biomechanical aberrations, or repetitive micro trauma to their joints. Although cartilage has a relatively simple structure compared with other tissues, cartilaginous injuries can be extremely unforgiving. The limited blood supply in cartilage is thought to be responsible for the inadequate repair post injury. A substantial fraction (~12%) of the overall burden of OA arises secondary to joint trauma, where the risk of post traumatic OA (PTOA) ranges from 20% to 50%.[1,2] Currently, 9% of the U.S. population aged 30 years and older has OA of the hip or knee, costing an estimated $28.6 billion dollars with >400,000 primary knee replacements currently being performed each year in the United States alone.[3] Thus, methods for successful cartilage repair still remain a largely unmet clinical need.

The well referenced 1743 quote from the British anatomist Hunter in which he states "Cartilage injury is a troublesome thing and once injured is seldom repaired" was the general axiom for thinking about cartilage repair for the next 200 years. Despite such negativity, there were pioneers such as William Green, MD,[4] who performed seminal experiments investigating the reparative potential of autologus and homologous chondrocyte transplantation in the 1970s. He used decalcified bone as a type of scaffold for cell transplantation. He was also the first to use the rabbit as a model to study cartilage repair. Although his success was hampered by the technology of the times, his work was a cornerstone for the future of cartilage repair as well as a pioneer in what was to become the field of tissue engineering.

Later, his colleagues George Bentley and Robert Greer[5] experimented with epihyseal and articular chondrocyte allografts in rabbits. By the early 1980s, the concept of healing cartilage with predominantly hyaline tissue was still largely considered a myth. Popular procedures at the time included Pirdie drilling and abrasion arthroplasty, which resulted in largely fibrous to fibrocartilaginous tissue. Based on the combined works of Green, Bentley, and Sokoloff,[6] an intrepid multidisciplinary group of orthopedic researchers at the Hospital for Joint Diseases in New York City, hypothesized that hyaline cartilage repair could be achieved by a cell based approach to the problem. This began a collaboration to try and develop a new method for achieving the goal of hyaline cartilage repair. The clinical motivation for pursuing this project were patients who had sustained cartilage injury but were still deemed too young for total joint arthoplasty and which resulted in pain and disability for young active individuals. The concept of a cellbased strategy was explored and determined to be a viable option. After several experiments, it was concluded that articular chondrocytes exhibited several intrinsic properties of the tissue that were deemed key to repair. First, they were already programmed to synthesize type II collagen and aggrecan. The clinical strategy was developed to first obtain a biopsy of cartilage, which would then be used to isolate free chondrocytes and expanded in culture followed by a second transplant procedure. Based on earlier work by Benya and Shaffer,[7] it was hypothesized that chondrocyte phenotype was plastic and a limited culture time in monolayer 2dimensional culture could then be reestablished by return to a 3-dimensional environment. Optimizing cell delivery and a technique for maintaining the chondrocytes within a defect was problematic as suitable biomaterial membranes were scarce at that time. The decision to use periosteum was based on its anatomical proximity to the surgical site as well as its historical use in many orthopedic applications such as interpositional arthroplasty procedures. The first results of rabbit experiments were decidedly superior then expectations and the realization that a new chapter in orthopedic research had been opened. The first report of the technique were presented at the annual meeting of the Orthopaedic Research Society in 1985 by Lars Peterson, MD and co-workers, and were promptly met with skepticism as the promising results were in conflict with current thinking as well as more than 200 years of dogma. This was followed up by 2 seminal publications, 1 in the Journal of Orthopedic Research in 1989 received significant attention.[8] The other published in the Anatomical Record[9] as part of one of the author's thesis. The procedure is now known as autologous chondrocyte implantation (ACI).

Module 1

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Articular Cartilage Implantation: Taking it to the first in Man & Beyond – Lars Peterson (SE)

The father of medicine HERODICUS stated more than two thousand years ago “that ulcerated cartilage is a troublesome thing and once destroyed it does not heal”. For over two millenniums ulcerated cartilage was considered untreatable and ending in osteoarthritis with a total loss of joint function. Modern medicine and technology created in our time the artificial joint replacement for the hip and knee osteoarthritis which have been great mechanical solutions for the older and crippled patients but is not acceptable for the young athletic population or the active middle aged patients with posttraumatic articular cartilage lesions.

Early biological attempts to treat cartilage lesions in young patients used in some cases tissue from the patient such as perichondrium or periosteum but ended up with no acceptable results. In 1965 Smith reported the first successful culture in the laboratory of rabbit chondrocytes. Injection of the cultured chondrocytes into small defects in the rabbit knee was however not successful. The first successful implantation(transplantation) with cultured autologous rabbit chondrocytes into a cartilage defect in the patella was reported in 1984(Peterson,Grande et al). Further animal studies confirmed hyaline like tissue and were reported with 1 year follow up in 1986. The transfer of animal culture technique into human cell culture technique was started in collaboration with Anders Lindahl in 1984 and the technique using human autologous serum in the culture medium was approved 1987 and the same year the Ethical Committee of the University of Gothenburg approved the treatment in human knee cartilage lesions . The first autologous chondrocyte transplantation(implantation) in Man was performed in Gothenburg, October 1987. The first clinical results were published in NEJM (1994) supported by histology of biopsies taken from the implanted area. The Food and Drug Administration in USA approved the ACT/ACI treatment in 1997 on the basis of our animal studies, approved cell culture technique using autologous human serum and autologous cell implantation using autologous periosteal membranes sutured to the defect.

The FDA approval opened up for the second step in MAN and BEYOUND to test the ACI in larger and uncontained lesions , in multiple and bipolar lesions,in unstable knees and the importance of correcting background factors for the short and long term survival of the repair area(s)Other joints were explored for the ACI treatment i.e. the ankle, hip, shoulder. elbow and others.

Important factors for good long term results in cartilage surgical treatment are the use of proven techniques based on animal studies with approved cell culture technique, the introduction of degradable biomaterials or synthetics . The first ACI using an collagen I sponge with and without the cells in the rabbit model was presented 1984 showing hyaline cartilage in the cell group.

Module 1

Right indication for the adequate treatment of the actual lesion related to defect size, depth,containment , numbers, bipolarity and correction of background factors. Available treatments have different aims fex. ACI –regeneration, Microfracture –repair, Mosaicplasty (osteo- chondral cylinders)-replacement, and others. In the end an optimal surgical technique- performed by well-trained surgeons capable of addressing background factors such as reconstructions of different types of ligament instability, osteotomies for correction of varus or valgus deformities, or reconstruction of patellofemoral instability, maltracking). Meniscus insufficiency after total or subtotal meniscus resection need restoration of the compartmental anatomy and biomechanics by meniscus transplants where there is a great need for a biologic replacement. Bone pathology OCD- defects, cyst formation, bone bruise, edema, sclerosis are demanding specific attention in restoring the bone-cartilage functional unit.

Tissue Maturation. During rehabilitation, it is extremely important with guide lines forpatient, physiotherapeut and physician to follow the 4 phases of maturation. Phase I: Proliferation and Protection (1-6weeks). Early matrix production, soft and vulnerable. ROM and Partial WB for protection. Phase II: Transition and Progression (7-12 weeks) Increased volume of cotton like tissue. Gradually increase WB for stimulation of matrix and progress in functional training. Phase III: Remodeling and Function (3-6months). Matrix undergoes gradual remodeling and adaptation to increased functional activities. Phase IV:Maturation and Optimizing (7-12-18 months) Maturation is an ongoing process and size, depth need different times for full filling and maturity fex patella versus femoral condyles . Back to training and competitive sports is possible during this period as the concentration of proteoglucans at 9 months has reached 80% of normal values and in most cases 100% at12-15 months as an indicator of maturation and normal metabolic turnover and function.

Long term result after ACI. The results at 36 months follow up of ACI have been published in 1994 (NEJM). The latest and longest follow up 10-20 years showed an overall result in femoral condyle, femoral condyle and ACL, OCD and patellar lesions of 84 % G/E. Objective data support the results. Ninetytwo % of the patients when asked would have the ACI surgery again.

Future trends are emerging with improved cell population, arthroscopic approach and tissue engineered matrix support (TEMS) where the new materials are safe like MACI, CHONDROGIDE and Hyalograft from hyaluronic acid have proven to function. Cartilage grafts, meniscus, ligaments produced in bio chambers may create a future possibility to restore joint function. Here we need interdisciplinary teams with ICRS members from basic science, engineering and clinics. These teams will be the most important result of “taking the ACI to the first step in MAN and BEYOUND by solving the cellular pathology behind osteoarthritis and other diseases for future cure.

In summary, the future seems promising. The cell-chondrocyte and ACI seem to work in cartilage lesions. The key to progress and success is the interdisciplinary research team. More importantly and BEYOND is that ACI has opened great opportunities to understand parts of the different cellular functions in cartilage. This knowledge may stimulate to future research of cellular mechanisms in pathologic conditions and injuries and the regeneration/healing in all musculoskeletal tissues in MAN. That is why continued research within ICRS on cellular, molecular, biomaterial and clinical level is so important to all of us and to Man and Beyond.

Module 1

Technical Improvements & Expansion of Indications for ACI – Tom Minas (US)

The landmark paper introducing the clinical outcomes of ACI [1] noted the best results were in isolated femoral condyles, with the transplantation of the patella being troublesome. This led to focusing on the treatment of isolated femoral condyles and evaluating the cause failures in the patella. It was felt that without correcting maltracking of the patella, newly developed cartilage would continue to undergo the same abnormal mechanics on to the regenerating tissue and lead to failure. This led to a focus on patellar realignment with ACI of the patella [2] and marked improvement in the clinical outcomes [3-7]. Mechanical symptoms after ACI were often secondary to periosteal hypertrophy necessitating evaluation by MRI scan to determine whether the symptoms were arising from the transplanted surface or another intra-articular source and lead to the understanding of the maturation of ACI by MRI scan [8].

Deep cartilage defects secondary to osteochondritis dissecans or osteonecrosis were also successfully treated by ACI. When defects were relatively shallow, i.e. less than 5-8 mm deep with a shallow profile isolated ACI demonstrated excellent clinical results. [9] when defects were relatively steep in their profile with a depth of 8-10 mm either a staged bone grafting technique followed by ACI or a newly developed single staged, "Sandwich" ACI technique also produced excellent clinical results. [10-12]

Throughout the world eliminating the use of periosteum seemed to reinvigorate the procedure of ACI by eliminating the troublesome problem of periosteal related harvesting during surgery and hypertrophy afterwards ranging anywhere from 10-50%. [13-15]

Recognizing that the subchondral bone of articular cartilage defects was altered with chronic lesions or those treated by marrow stimulation techniques including Pridie drilling, abrasion arthroplasty, and microfracture, we sought to evaluate those knees treated by ACI for virgin chondral defects versus those treated by a previous cartilage repair techniques. It was discovered that the failure rate was increased some 3 times [16] if prior cartilage repair procedures were performed before ACI and that these techniques did in fact "burn bridges". Arbitrary age limits were also imposed upon by third parties excluding children and those over 45 years of age. However, these artificial boundaries having also been proven to be untrue and excellent outcomes in the longterm have been demonstrated. [17, 18]. Pushing the limit to bipolar lesions and early OA [19-22] was also pursued. This often combined ACI with osteotomy, meniscal transplantation and ACL reconstruction. These patients also avoided knee arthroplasty in 91% of cases up to 15 years after surgery demonstrating the promise of joint preservation through biological reconstruction to include ACI.

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Module 1

Cells used for Cartilage Repair: The Rational & The Choice – Mats Brittberg (SE)

There are many possible choices of cells to use for cartilage repair. Cells are used as internal or external sources and sometimes in combination. The dream scenario when handling a cartilage lesion is to induce a regeneration of the defect cartilage area. Regeneration is a complete restoration of the defect area with a tissue identical to the surrounding native cartilage. Such regeneration is possible in amphibian animals like the axolotl and can be seen in fetus mammals. However, so far clinically no one has achieved cartilage regeneration instead different degrees of good quality repair have been presented in clinical studies. The cell responsible for the cartilage matrix, the chondrocyte, is the natural choice to use when to repair traumatized cartilage. Everyone agrees on that cells are a must if you want to make a biological repair either you go the internal way attracting chondrogeneic cells from the bone marrow for the repair or introduce minimal to maximal external manipulation of chondrogeneic cells, chondrocytes or MSCs with or without scaffolds. Still most of the cells used are autologous but an increasing use of allogeneic cells is seen.

Whatever cells are used is of less importance for the patients. For them, the technique that give them pain relief and functional recovery with long-term durability is the treatment of choice. There are responders and non-responders for all repair techniques and many patients should be informed that when a patient comes with a painful cartilage lesion, a treatment package will be offered including one or several operations and a strict rehab protocol. Cartilage lesion treatment in 2017 is still a difficult treatment and the researchers are still trying to learn the difficult language of the chondrogeneic cells; the chondrocytish and its neighboring dialects spoken but a variation of different mesenchymal stem cells. It is all about communication of how to get the used cells to go into the chondrogeneic lineage and to stabilize and produce the final dream tissue....

Regeneration; We are not there yet but since the first ACI in 1987, a lot of new research has been done and contributed to an increased knowledge about the ¨troublesome¨cartilage. It is obvious that cells are fundamental for the living organism and the future in biological repair is how to better domesticate the chondrogeneic cells in order for them to replicate the embryonic cartilage formation into full regeneration of the traumatized cartilage.

This presentation will give an analysis of the different cell choices. Some suggestions will be given for future research based on up-to-date knowledge on chondrogenic cells and .....some linguistics for the difficult spoken Chondrocytish....

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Module 2: Historical Look at Cartilage Repair Continued

Autologous Osteochondral Grafting – Historical Perspective – Vladimir Bobic (UK)

In selecting methods of restoring a damaged articular surface, it is important to distinguish articular cartilage repair from articular cartilage regeneration. Repair refers to the healing of injured tissues or replacement of lost tissues by cell proliferation and synthesis of new extracellular matrix. Unfortunately, the repaired articular cartilage generally fails to replicate the structure, composition, and function of normal articular cartilage. Regeneration in this context refers to the formation of an entirely new articulating surface that essentially duplicates the original structure of articular cartilage. Therefore, the best we can do at present is to repair the articular defect with "functional tissue", with very variable results and unknown long-term outcomes.

Unfortunately, our obsession with damaged articulating surface was focused on numerous ways of repairing articular surface only and this has led to long clinical and surgical neglect of equally important subchondral bone and its extremely important metabolic and structural role. Fortunately, it is now universally accepted that articular cartilage and subchondral bone form inseparable osteochondral unit which set the bar even higher when it comes to "cartilage" repair. We still do not seem to care much about one more possibly important layer, which is the uppermost layer of articulating surface, known as Lamina Splendens.

The closer the cartilage repair comes to hyaline cartilage, it is reasonable to assume that the end result would be a more appropriate and durable repair tissue. The choice of surgical techniques that can restore and maintain hyaline cartilage is very limited. At present, the osteochondral autograft transplantation seems to be the only surgical technique that can simultaneously restore the height and the shape of the articulating surface in osteochondral defects, with composite autologous material that contains all the necessary ingredients in the right sequence: hyaline articular cartilage, intact tidemark and a firm carrier in the form of its own subchondral bone.

However, like many orthopedic procedures which require the use of autologous tissues, this is a "rob Peter to pay Paul" situation. Consequently, the main limitation of this technique is the availability of autologous grafts. The size and depth of defects are other significant limiting factors. The dead spaces between several small circular grafts, integration of donor and recipient hyaline cartilage and cancellous bone, different position, thickness and mechanical properties of donor and recipient hyaline cartilage are further sources of clinical concern, and possible explanation for some failures in the long run.

As the inventor of OATS methodology and instruments I will discuss the development of this technology and present my surgical experience, which extends over twenty years of continuous use. The concept was based on early recognition of the existence of structurally and metabolically inseparable osteochondral unit. I prefer relatively large OATS grafts, usually 10mm in diameter and at least 15mm long. I have used OATS grafting for many years mainly for the repair of relatively small chondral defects but now I am using OATS instruments increasingly frequently for complex femoral osteochondral reconstructions and the treatment of various subchondral deficiencies and abnormalities, including SONK, OA, etc., in combination with deep intra-osseous drilling and implantation of autologous bone marrow aspirate.

Fresh Osteochondral Allografts for the Knee and Hip: History, Technique and Results Alan Gross (US)

The parameters to be considered in the selection of a cartilage repair strategy are: the diameter of the chondral defect; the depth of the bone defect; the location of the defect (weight bearing); alignment.[1] A chondral defect less than 3cms in diameter can be managed by surface treatment such as microfracture, autologous chondrocyte transplantation, mosaicplasty, or periosteal grafting.[1] An osteochondral defect less than 3 cms in diameter and less than 1cm in depth can be managed by autologous chondrocyte transplantation, mosaicplasty or periosteal grafting.[1] An osteochondral defect greater than 3cms in diameter and 1cm in depth is best managed by an osteochondral allograft.[1] A Fresh Osteochondral Allograft Transplant Programme was started at the Mount Sinai Hospital, University of Toronto in 1972. As of February 2017, 507 fresh osteochondral allografts primarily of the knee have been performed.

If there is an associated knee deformity, then an osteotomy was performed. In our series of osteochondral allografts for large post traumatic knee defects realignment osteotomy is performed about 60% of the time in order to off load the transplant. To correct varus we realign the proximal tibia with an opening wedge osteotomy. To correct valgus, we realign the distal femur with a closing wedge osteotomy.

Module 2

Our results with osteochondral allografts for the large osteochondral defects of the knee both femur and tibia, have been excellent in 85% of patients at an average follow-up of 10 years. [2,3] The Kaplan-Meier survivorship at 15 years is 72%.[2,3] At an average follow-up of 22 years in 58 patients with distal femoral osteochondral allograft, 13 have been revised (22%). The 15 year survivorship was 84%.[4]

Retrieval studies of 24 fresh ostechondral grafts obtained at graft revision or conversion total knee replacement at an average of 12 years (5 – 25) revealed the following. In the areas where the graft was still intact, the cartilage was of normal thickness and architecture. Matrix staining was normal except in the superficial and upper mid zones. Chondrocytes were mostly viable but there was chondrocyte clusters and loss of chondrocyte polarity. Host bone had extended to the calcified cartilage but variable remnants of dead bone surrounded by live bone persisted.[3] With a stable osseous base the hyaline cartilage portion of the graft can survive for up to 25 years.

The results for the hip are early. To date we have performed this procedure on 16 patients. Surgical dislocation of the hip is carried out via a trochanteric osteotomy and the defect defined and trephined out. A press-fit fresh osteochondral allograft is inserted using the trephine technique. We have published our early results on a series of 8 patients with 5 good to excellent results, 1 fair result and 2 failures.[5]

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Minced Autologous/Allograft Cartilage Technologies – Jack Farr (US)

While particulated articular cartilage to treat focal chondral defects is relatively new to the English speaking literature, Albrecht reported in the German literature in 1983 that particulated cartilage autograft implantation without bone can lead to cartilage defect healing if the cartilage is cut into small pieces.[19,] Ed Lu and Francois Binette separately replicated these findings in vitro experiments and then in the mouse, goat, and finally horse model.[20,21] All these studies together demonstrated that autograft cartilage, when mechanically minced into cubes of 1-2 mm, could affect cartilage repair as the chondrocytes escape from their lacunae, migrate, multiple and form matrix.[19,21] During this process the chondrocytes from the minced cartilage retain the standard chondroctye spheroid shape.[21]

Independently, scientist Dr. Jian Q. Yao studied particulated juvenile cartilage allograft (DeNovo NT; ISTO St. Louis MO, USA; distributed by Zimmer, Warsaw IN, USA at that time; now ZimmerBiomet) in place of autograft.[1,2] He noted the potential advantages that allograft allows no limit to the amount of harvested tissue and that juvenile cartilage has the potential of more robust cellular activity than older cartilage tissue.[13,22-25] In the equine animal model particulated juvenile articular cartilage xenografts healed chondral defects on the trochlea.[1] As the company considered DeNovo NT as a minimally manipulated human tissue allograft, regulated as a 361 HCT/P product it did not require a FDA approval pathway and thus was available for clinical use immediately.[2] A prospective study of 25 patients in a multi-center study supported by Zimmer reported good defect filling and patient reported outcome improvements.[2,26] During a similar timeframe, Cole et al. demonstrated that particulated autograft is safe to use, with risks comparable to those of MFX. In that study, autograft particulated cartialge had consistent and progressive improvement during the second year after surgery, when compared with the microfracture group.[3] The autograft project in the US was discontinued because of return on investment concerns, but there is renewed interest in particulated/minced/chipped autograft with a recent study by Foldager in Denmark (Cartilage 2015) and initiation of a new US clinical study using an automated mincer (Reveille® by Exactech, Gainsville, Florida USA).

Module 2

Biomechanics Matters: History & Role of Osteotomies in Cartilage Repair
Stefan 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 ligamental 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 decade 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 bonewedge, especially in overcorrection and lead to an asymmetric deformity of the tibial head. However, openwedge techniques need a high experience in stepwise 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). Than 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. Mensicustears, ACL ruptures and cartilage defects have to be addressed at the same time, furthermore is has to be secured that the lateral compartment and the femoropatellar joint is free of sever degenerative diseases. In the case of cartilage defect we either perform two-stage procedures with a biopsy for cell transplantation and the second surgery with osteotomy or cell transplantation. 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.

Biomaterials for a One Stage Cartilage Repair – Matthias Steinwachs (CH)

Untreated symptomatic full thickness cartilage defects of the knee may lead to degenerative osteoarthritis, knee pain, and ultimately loss of function. The early diagnostic and the treatments of those defects is complicated due to the fact that the natural history of these lesions is not entirely understood and in the early phase not all articular cartilage lesions generate symptoms. The most frequently used bone marrow based cartilage restoration technique is the microfracture technique introduced by Steadman. In studies after an initial improvement of 47-80%, the deterioration in function and pain can be observed after 18-36 month. In athletes, the return to sport of the pree-injur Level is 45-67% with this technique. The limitations of this technique are a high rate of intralesional new bone formation or progressive ossification of the regenerate tissue and limited biomechanical tissue properties, i.e. formation of fibrous cartilage with limitation in the mid-and long-term durability. To improve standard techniques by using matrices and scaffolds recent biomaterials have attempted to stabilize the bloot clot formation after marrow stimulation and to improve the stem cell differentiation into a better repair tissue quality. In recent years, different biomaterials were tested in preclinical and clinical studies. Here the 3- dimensional structure of the biomaterials determine cell contact, cell migration, and cell differentiation. Optimal biomaterials are characterized by a good availability, biocompatibility, biodegradability, adhesive properties, and low toxicity. For clinical use in conjunction with microfracture appear suitable collagens, chitosan and hyaluronic acid. Enhanced microfracture techniques are performed in the same general way as traditional microfracture, using a single-stage, minimally invasive approach.

Module 2

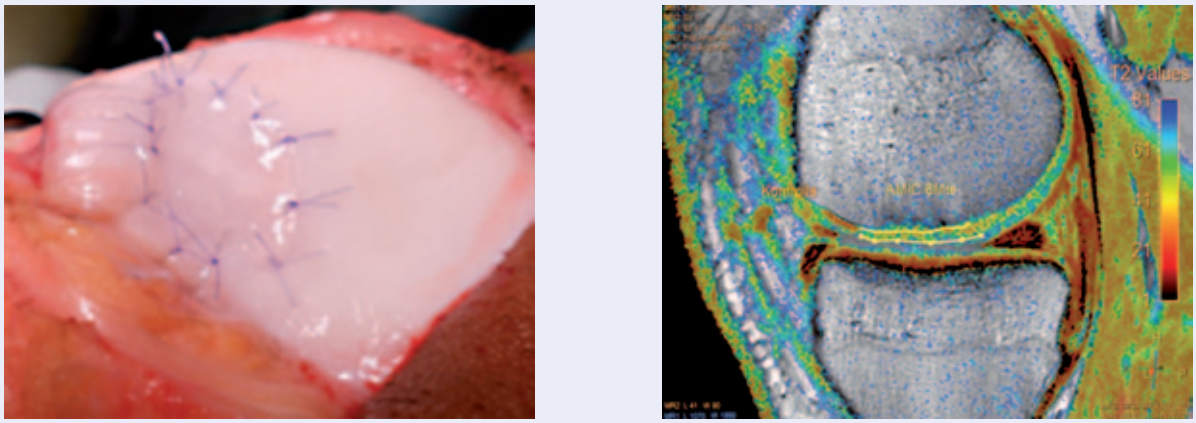

Fig.1: Sutured ChondroGide® membrane and 6 month follow up MRI with T2 mapping after AMIC®

AMIC was the first technique which combines the one step technique microfracture with the use of a porcine collagen (type I/III) membrane (ChondroGide®, Geistlich Pharma AG, Wolhusen, Switzerland). After bone marrow penetration with k-wire drilling ore microfracture instruments the button of the defect will be covered by fibrin glue to support the natural environment for stem cell differentation. To create the appropriate matrix form, an aluminium template can be used. The collagen membrane covered the defect area and has to fixed with 6/0 sutures ore fibrin glue. In recent years a variety of preclinical and clinical studies Lev. I-IV has been published which successful clinical outcome for application of the knee, talus and hip.

BST-CarGel® (Smith&Nephew, London,UK) is a Chitosan based bioscaffold derived from shrimps. Chitosan is a glucosamine polysaccharide which is naturally present in the extracellular matrix of cartilage. After dissolving chitosan into glycerophosphate buffer for 10 minutes, autologous whole blood must be added. If the clotting function is starting by 37°C the gel can have inserted via a separate arthrotomy or a dry arthroscopy (Fig.2) into the prepared defect area following microfracture. Level I multicenter study demonstrated clinical improvement over baseline with superiority over Microfracture in consistency, defect filling, tissue quality and quantity over 5 years.

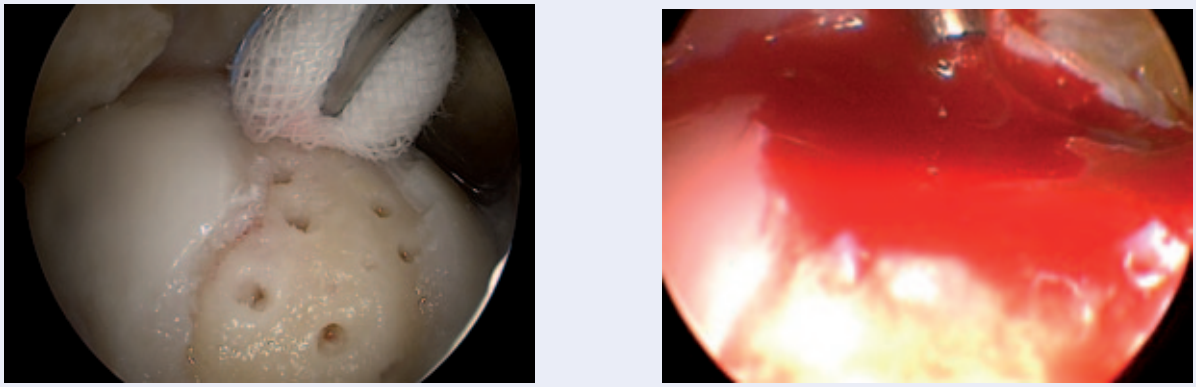

Fig.2: Dry arthroscopy of the knee, defect is dried after MF and filled with coagulating BST-CarGel®

Majoregen® (Finceramica, IT) is a nanocomposite three-layered collagen-hydroxyapatite scaffold, which was developed specially for the treatment of osteochondral defects in combination with marrow stimulation. A statistically significant improvement in all clinical scores was observed from the initial evaluation to the 2- and 5-year follow-ups in a Lev IV case series. Contraindications for advanced microfracture techniques are similar to contraindications for traditional microfracture and include allergies to collagen or seafood, bipolar lesions underlying inflammatory arthritis, diffuse degenerative osteoarthritis, and untreated instability, axial malalignment and subtotal resected meniscus. Rehabilitation is an important part of treatment. We recommend a 6-week discharge with a maximum body weight of 15 KG. In addition, the ROM is limited according to the defect localization. The use of a CPM-machine for max. 6 h / d is recommended.

Module 2

Overview of the Progression of the Orthobiologic Surgeon & Cartilage Injury Prevention in Sports Medicine – Bert Mandelbaum (US)

The role of the physician, surgeon and scientist has undergone a significant evolution in the last 20 years. Articular cartilage defects of the knee are common among athletes where the physical demands of sport result in significant acute and chronic stresses on joints. Chondral defects are associated with pain and functional impairment that limit sporting participation and may progress to joint degeneration and frank arthritis. These lesions have limited intrinsic healing ability due to the avascular nature of cartilage and the unfavorable mechanical environment for spontaneous repair within joints. The ultimate goal is prevention of injury, chondropenia and the progression of arthritis. Management of established chondral lesions aims to allow athletes to return to high-impact sports and can be considered in terms of protection of existing cartilage, chondrofacilitation and resurfacing. Repaired and/or regenerated cartilage must closely resemble and function like normal hyaline cartilage, and this ability may be the most significant factor for the return to sport. The Clinical Scientist must be able to understand and implement the recent advances that includes in epidemiology, classification, pathoanatomy and clinical assessment in athletes with chondral defects, and compare the relative merits and outcomes of established and emerging forms of treatment. The treatment of chondral lesions continues to evolve as there is no one technique or procedure that has clear superiority. There are a huge number of established and new Orthobiologics strategies aimed at preventing chondropenia, protecting chondral surfaces, and treating established lesions. This reflects the fact that chondral lesions represent a wide spectrum of disorders for which there for which there can be single satisfactory all-encompassing treatment, other than prevention. We therefore advocate an individualized or algorithmic approach to treatment considering which aspects of injury prevention, chondroprotection, chondrofaciliation and resurfacing may give athletes have the best chance to return to full sporting activity, prevent re-injury and minimize the progression to osteoarthritis under the high mechanical demands of athletic activity.

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Module 3: Historical Perspective

Long Term Data on Microfracture/Marrow Stimulation – Kai Mithoefer (US)

Focal defects of articular cartilage remain a frequent cause of pain and functional limitation often resulting in surgical intervention. As early as 1959 Pridie proposed drilling of the defect as a method to promote bleeding and recruit bone marrow elements to reconstitute cartilage in the lesion. Another frequently used technique included abrasion chondroplasty when the subchondral bone is abraded with an arthroscopic shaver to gain access to the subchondral bone mesechymal stem cells. In the 1990's Steadman introduced the microfracture, technique which still remains the most commonly performed cartilage repair technique to date because of its technical simplicity, limited patient morbidity, and satisfactory overall results. Using the principle of marrow stimulation, the microfracture technique includes debridement of the defect, removal of the calcified cartilage, and penetration of the subchondral bone with specifically designed awls. To date, microfracture is still the "gold-standard" technique against which new cartilage repair technologies are compared. However, it is well recognized that microfracture is not a panacea, as the repair cartilage formed is biomechanically and histologically different than normal hyaline articular cartilage. Recent studies have shown that the durability of the clinical improvement observed after microfracture may be limited and that some patients may show declining knee function after 18-24 months postoperatively. Several studies have shown that this is also associated with a decline in athletic activity over time. However, while some functional deterioration is observed frequently, several mid- to long-term studies have shown that joint function is still improved over baseline even 10-15 years after the index procedure. Several studies have shown long-term outcomes 10-15 years after microfracture comparable to other techniques such as autologous chondrocyte transplantation or mosaicplasty.

Several reasons have been proposed for this functional deterioration after microfracture. The limited quality of the fibro-hyaline repair cartilage has been suggested as one factor responsible for the functional deterioration seen in some patients after initial improvement following microfracture. Other factors include the limited repair tissue quantity that can be observed in some patients as well as often limited integration to the surrounding normal articular cartilage tissue. Besides the cartilage repair tissue, changes to the subchondral bone plate including cysts, edema, and more recently subchondral osseous overgrowth have been described and are considered as potential risk factors for the observed functional deterioration after microfracture. The phenomenon of bony overgrowth, also referred to as intralesional osteophyte or elevation of subchondral bone plate, is being identified in an increasing number of studies and has recently been shown to affect failure rate after microfracture. Subchondral overgrowth may also play an important role in why secondary cartilage repair procedures such as chondrocyte transplantation may have an increased failure rate after microfracture.

Despite all the limitations of the microfracture technique the principles and efficacy of cartilage repair using marrow stimulation and marrow-derived mesenchymal stem cells are increasingly recognized. Recognizing the limitations of first-generation microfrature technique has been important and has led to the development of second-generation technologies that can help to improve the shortcomings of the first-generation microfracture technology. Several studies have shown that using tissue engineering technology can be very useful in improving tissue quantity and quality after microfracture. Large scale and randomized studies have shown that by using scaffold augmentation with materials such as collagen scaffolds, hydrogels, or allograft cartilage not only consistently increase the amount of repair cartilage fill and peripheral integration but also can produce a more hyaline-like repair tissue quality and were associated with is improved clinical results in randomized controlled comparison to first-generation microfracture with improved durability of the functional improvement. Besides improvements derived from tissue engineering, the development of new subchondral drilling techniques or nanofracture have helped to reduce the subchondral bone necrosis and sealing effect associated with the use of the traditional microfracture awls. Modification of the calcified cartilage removal technique can reduce subchondral bone stimulation and overgrowth and thereby reducing failure rate. Importantly, a better understanding for the optimal indications for second-generation microfracture or marrow stimulation technology is helpful to improve both short- and long-term outcomes from this evolving cartilage repair technology and can help to reduce the need for secondary procedures or improve their efficacy.

Module 3

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Osteochondral Allograft Transplantation: Scientific Basis and Clinical Outcome
William Bugbee (US), Scripps Clinic, LA Jolla CA

Fresh osteochondral allograft transplantation (OCA) has over a hundred year clinical history. Many clinical and basic scientific studies have been performed with the result that allografting is now part of the cartilage repair paradigm for the treatment of chondral or osteochondral lesions. Allografting has also been successfully used in complex joint reconstruction for the treatment of osteonecrosis, fracture malunion and selected cases of osteoarthritis, not only in the knee but the ankle, shoulder, hip and elbow. Unlike many other cartilage repair techniques, osteochondral allografts have the ability to restore mature, hyaline articular cartilage to the affected area. By virtue of their composite structure (cartilage and bone) allografts also can restore diseased or damaged bone often present in large or complex lesions. The surgical techniques of allografting are relatively straightforward and numerous clinical studies have shown excellent results for a variety of diagnoses. Osteochondral allografts do present the surgeon with unique and important differences from other cartilage repair techniques, such as limited allograft tissue availability and the potential for transmission of infectious disease from the graft or immunologic response by the recipient. Careful evolution of tissue recovery, processing and storage protocols have resulted in more widespread availability of safe and effective osteochondral tissue, and adoption of osteochondral allografting as an important option for cartilage repair worldwide.

Our experience spans over two decades and 1000 clinical cases and represents an exemplary collaboration between basic scientists and clinicians leading to rapid translation from bench to bedside. Ongoing investigations continue to answer fundamental scientific questions and clarify the indications, surgical techniques, and clinical outcomes of fresh osteochondral allografts.

Module 3

Technical Enhancements & Long Term Clinical Outcomes OATS/Mosaicplasty
L. Hangody (HU)

Autologous osteochondral transplantation is one of the possible cartilage repair options supported by experimental data and 25 years clinical experiences. Initial experimental results of autogenous osteochondral grafting have shown consistent survival of the transplanted hyaline cartilage, but special rehabilitation program seemed to be essential for a successful clinical outcome.

In 1991 a series of cadaver studies and animal trials was carried out to check this new operative techinque. Instead of transplantation of a single big osteochondral block mosaic like transplantation of multiple small sized cylindrical osteochondral grafts was promoted. Initially, the mosaicplasty concept was tested in German Shepherd dogs and horses and in cadaver studies. Macroscopic and histological evaluations of the resurfaced areas and the donor sites showed:

1. consistent survival of the transplanted hyaline cartilage
2. formation of a composite cartilage layer consisting of »80% transplanted hyaline cartilage and »20% fibrocartilage ingrown from the bony base of the defect
3. deep matrix integration of the graft to the host tissue at the recipient site
4. donor tunnel filling to the surface with cancellous bone capped by fibrocartilage by 6-10 weeks. Fibrocartilage coverage of the donor holes seemed to be acceptable gliding surface for these less weight bearing areas.

Clinical application was begun on February 6, 1992. During the following 25 years, clinical results by various authors matched the animal results, and since 1995, the procedure has been used with similar success at numerous clinics throughout the world. Preclinical experimental results and increasing number of clinical experiences modified step by step the original rehabilitation protocol. Necrosis of subchondral cancellous bone structure caused by immediate weight bearing of operated dogs indicated postoperative non-weight bearing period in the human practice. Later this non-weight bearing period was reduced and partially substituted by partial loading based on control arthrocopy findings. Second looks after long lasting non-weight bearing represented “soft fibrocartilage” formation in the donor sites and between the grafts. Experimental data and clinical follow up results indicated to reduce the non-weight bearing period and promote partial loading relatively early after the surgery.

In the last two decades, several reports has been published about medium term and long term clinical outcomes of OAT and mosaicplasty. Short and medium term evaluations reported nearly 90% good and excellent clinical outcome and tolerable donor site morbidity. Increased donor site morbidity had a close relationship to extended graft harvest. Recently Pareek et al published a review of 10 long term evaluation. According to their evaluation on 610 patients a 72% long term success rate was reported. Further publications confirmed similar long term results.

Longer Term Results of Combined ACI and Meniscal Allograft Transplantation
Wayne Gersoff (US)

There exists a symbiotic relationship between the meniscus and the articular cartilage of the knee. The loss of meniscal tissue and its function can result in damage to the articular cartilage. While techniques have been developed to restore the articular cartilage, the success of these techniques will be compromised in the absence of functional meniscus tissue. The placement of a meniscal allograft in the presence of a significant articular cartilage defect will similarly compromise the integrity of the allograft tissue.

The combined procedures of ACI and MAT allows for both pathologies to be addressed. AS with each of these individual procedures, the knee must have ligamentous stability and be in proper alignment. There have been several reports of short and midterm results of combined articular cartilage restoration and meniscal allograft transplantation. This presentation will report the longer-term results of these combined procedures and review the surgical techniques and postoperative rehabilitation.

Module 3

Long Term Outcomes of Approved Scaffold induced Repair – Elizaveta Kon (IT)

Regenerative scaffold-based procedures have emerged as a potential therapeutic option for the treatment of chondral and osteochondral lesions. The use of scaffolds has been introduced into clinical practice to improve the results obtainable with the first-generation cell-based approach, autologous chondrocyte implantation (ACI), by overcoming its drawbacks and simplifying the procedure [1]. However, the drawbacks related to the need of a double surgical procedure promoted the development of a new treatment approach involving the implantation of various biomaterials for "in situ" cartilage repair exploiting resident bone marrow stem cells differentiation induced by the scaffold properties, thus favouring the self-regenerative potential of the body. Different new biomaterials were recently claimed to induce "in situ" cartilage regeneration after direct transplantation onto the defect site both in research and in clinical practice. The one-step approach involves the use of biomaterials able to stimulate the differentiation of resident cells and support tissue regeneration. These materials can be combined with marrow stimulation to stabilize the blood clot, thus allowing ingrowth and differentiation of cell precursors from the bone marrow [2]. At the same time, the strict correlation between cartilage and subchondral bone pathology has been acknowledged, and specific constructs were developed to address the whole osteochondral unit. Most of these procedures showed the ability to exploit the self-regenerative potential, regardless of any cell-augmentation [2].

Several biomaterials with chondro-inductive properties have been applied into clinical practice: autologous matrix-induced chondrogenesis (AMIC) was introduced using a collagen-based matrix (ChondroGide®, Geistlich Biomaterials, Switzerland) with the rationale to favor an homogenous distribution of an heterogeneous cell-population coming from the bone marrow onto a microfractured defect [3]. Most of the reports showed satisfactory results at short-term follow-up, even if incomplete filling or subchondral bone edema was frequently observed at MRI. A recent RCT study showed AMIC outperformed MFx at 5 years after surgery in 47 patients [4]. Other authors also reported good mid-term results by augmenting the procedure with one-step bone marrow concentrate (BMC) for the treatment of large size lesions [3]. The only report at long-term follow-up showed positive and stable results in 14/18 patients out of 57 treated, at 16 years after surgery [5]. However, the high rate of patients lost at follow-up strongly limits the reliability of these positive results, and of them failed undergoing arthroplasty.

A further option to augment marrow stimulation for chondral defects involves the use of chitosan hydrogel mixed with autologous whole blood after microfractures (BST-CarGel®, Piramal, Quebec, Canada). A multicenter RCT on 80 patients showed comparable short-term clinical improvement with respect to microfractures, but better filling with hyaline-like tissue. These clinical and MRI results were later confirmed at 5 years of follow-up [6], with better macroscopic and histologic appearance of the graft [7].

Also, multilayered constructs have been applied into clinical use in recent times, with the rationale for treating the entire osteochondral unit. A polymeric PLGA-PGA and calcium sulfate bi-layer scaffold (Trufit CB™, Smith & Nephew, USA), was the first introduced. After promising preclinical findings with no cell augmentation, the scaffold was then implemented in clinical practice with the indication to backfill autologous grafts donor sites with limited [8]. This procedure was also applied for direct implantation into cartilage defects, with promising short-term results [8]. However, later reports showed controversial results. Whereas a study on 57 patients observed significant mid-term clinical improvement but abnormalities at MRI [9], most of the authors reported poor clinical results [9,10], lower then mosaicplasty [11], and a high failure rate of 20-70% in the short-term [9,10].

In summary, this scaffold produced unpredictable clinical outcomes, showing some strong limitations for certain indications (i.e. patellar lesions), coupled with rather unsatisfactory tissue quality both at imaging and histology evaluations [8].

The second acellular osteochondral scaffold reported into clinical use is a three-layered collagen-hydroxyapatite nanocomposite (Maioregen®, Fin-Ceramica S.p.A., Faenza, Italy). After promising short-term findings, it was later investigated for a variety of indications, ranging from large or complex knee lesions, to osteoarthritic patients or OCDs [2,12]. The positive short-term results obtained in these demanding patient populations promoted an extensive use of this scaffold, even though some issues emerged regarding the quality of the regenerated tissue induced by the scaffold, as seen by CT or MRI scans at short-term follow-up [13]. However, a mid-term prospective evaluation of the tissue progression showed subchondral features steadily improved over time, and no correlation was found with the clinical improvement, which was stable up to final follow-up [14]. However, these findings underline the need to further improve the biomaterial characteristics for a better healing.

Module 3

A further osteochondral scaffolds, based on aragonite, has been reported for clinical use, but only positive short-term results have been published yet (Agili-C™, CartiHeal (2009) Ltd, Israel) [15].

Research in recent years is moving towards “one step” surgical and for this reason the ideal scaffold from both practical and commercial points of view should be product from the shelf and ready to use. Among several scaffolds developed for one-step implantation, only a few of them have been currently reported for the clinical use. Besides the promising short- to mid-term results in most cases, to date longer follow-up times and high-level study are mandatory to testify the effectiveness and reliability of these procedures over time.

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Module 3

Measuring Relevant Results in Knee Repair & Regenerative Medicine
Daniel Saris (NL)

Regenerative medicine is a rapidly developing field of interest in orthopedic surgery. However, there is the need for determining good outcome measures after (knee) repair surgery to compare the results of the different treatment options. Coming from radiographic and doctor oriented outcome measures we are now moving more towards patient centered outcome measures, focused on patient specific care. In cartilage repair a strong correlation between MRI outcome in predicting clinical outcome is lacking.[1] Therefore combining newly developed tools for measuring patient-based functional measurements with patient reported outcome measures (PROMs) will lead to better evaluation of relevant results after surgery.

PROMs are used extensively in orthopaedic surgery for measuring daily functionality and quality of live after surgery or trauma. However PROMs have neither been designed nor approved by patients themselves. The Patient Approved Knee Assessment (PAKA) developed at the UMCU is the first patient approved outcome tool for patients with sports related surgery of the knee.

At the outpatient clinic it is possible to extend the physical examination with movement measurements recorded by Virtual Reality Technology and use these tools for patient specific rehabilitation programs.[2] The Microsoft Kinect v2 was shown to have potential as an inexpensive tool for gait analysis for the hip and knee joint in healthy volunteers.3

Assessment of functional outcome has developed from measurements only during hospital stay and visits of the outpatient clinic to continuous patient-based outcome measures.[2] New technology, and especially the use of the smartphone and smartwatches accelerated the development of wearable and wireless devices to measure functional outcomes after knee surgery. Easy to use wearable devices as pedometer or heart rate monitor can be used to measure the activity and physical condition of the patient before and after surgery in an objective and standardized manner.[4] Biofeedback devices as SmartStep and OpenGoScience, wireless sensor insoles, can provide feedback on weight bearing in patients after lower limp surgery.[5] With these outcome measures comparing the function of the operated and non-operated knee is possible.

Different wearable sensors have been validated for measuring daily activities, gait analysis and body segment movements in osteoarthritis rehabilitation.[6,7] These sensors showed good results in monitoring the activity performance in healthy volunteers.[6] The internal measurement system showed the possibility of potentially identifying the patients who might benefit from an extra rehabilitation program.[7] These analysis can be extended to knee repair surgery, providing patient individual care.

Combining the outcome of MRI, a patient-valued PROM (the PAKA) and performance-based outcome measure, not only during hospital stay/visit but also during daily living activities using wearable and wireless devices will provide the most relevant results for patients after knee surgery and will improve the rehabilitation programs.

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Module 3

A Philosophical Look-Back at how Chondrocyte Transplantation began and what has been achieved – George Bentley (UK)

Cellular repair of articular cartilage was made possible by the isolation of living chondrocytes by Dr Audrey Smith in 1965 in London. The first successful cartilage cell transplantation was performed by Bentley and Greer in the University of Pittsburgh and reported in Nature in 1971. Bentley had previously created a model of osteoarthritis in rabbit joints and explored the possibility of transplanting cells into a cartilage defect in normal joints and in joints which had papain-induced osteoarthritis. The cells were isolated by enzymatic digestion of the matrix and were transplanted fresh by pipette into 3 mm diameter holes in the articular surface of the tibia. Controls were made in the opposite knee by simple drilling.

After three months, the joints were examined and it was found that in a high proportion of cases the holes were filled with Hyaline cartilage confirmed by matrix staining of proteoglycans, and polarised light microscopy to show the orientation of the collagen fibres. This was a novel discovery. In the following years in Liverpool and Oxford the isolated cells in culture were studied extensively and and it was found that they tended to de-differentiate unless they were cultured at high density Consequently further experiments were carried out which showed that the results were reproducible and that it was possible to grow cartilage even on the denuded bony surfaces of joints with papain-induced arthritis.

It was realised that to retain cells in the articular surface of human joints it would be necessary to create a support matrix and the first matrix tested was carbon fibre. Following some elegant work by Professor Charlie Archer, it was shown that isolated chondrocytes could form a matrix, with Type II collagen and Chondroitin sulphate and Keratin sulphate proteoglycans ,using immunofluorescence, within a carbon fibre matrix

The carbon fibre had been applied in joints without cells and the next logical step was to incorporate cells into the matrix which would act as a carrier for the cells. At this point, in 1994, Brittberg, Peterson and Lindahl developed a clinical method of transplanting isolated cartilage cells from the same patient behind a membrane of periosteum covering an osteochondral defect, and thus described the ACI(Autologous Chondrocyte Implantation) method which became the preferred cellular repair procedure for the knee. In 2003, Bentley and colleagues, after a Prospective randomised clinical trial, demonstrated that using a collagen type I/III membrane to enclose and retain cells was a comparable and simpler method with negligible problems of hypertrophy of the membrane, so that the use of periosteum was abandoned. This technique became known as the ACI© method.

The ICRS was created by Lars Peterson and Roli Jakob with interested colleagues in Fribourg in 1997 and many studies were performed using ACI(C) and MACI. These studies confirmed the good and excellent results reported by Brittberg and Petersen and this led to the concept of selecting cells which had the highest potential for producing normal hyaline cartilage repair by Saris et al, named the “Characterised Chondrocyte Imlantation” technique.

In the meantime, Tom Minas, in Boston pioneered the use of ACI in the treatment of established early-onset OA and these studies continue. Good results in 85% of patients have been reported but others have not so far achieved equal success. Apart from the study by Petersen and Brittberg et al. in Gothenburg, follow-up has often been short and numbers of patients have been relatively few, leading to problems of interpretation of results. It has become increasingly apparent that 10-year follow-up of large series of patients is required to give reliable results.

Bentley et al completed a mid-and long-term review of 950 + patients treated for up to to 12 years (Mean 7 years) in 2014 which indicated that good results could be achieved if the patients had no evidence of OA, had no previous procedures on the joint and no evidence of mal-alignment or a history of obesity or smoking habit.

The ACI/MACI procedure is now accepted scientifically but not yet by some regulatory authorities. It is also time-consuming, intricate and needs I year for rehabilitation to normal activities as well as being relatively expensive, which has produced problems with some Health-Care planners.

Consequently, attention has switched to the exciting concept of use of autogenous stem cells which has been made possible by the pioneer basic science studies of Arnold Caplan. These can be used employing a one-step procedure after the work of Gianini and Gobbi and others. Further clinical long-term trials will be needed to produce the “perfect” technique and to extend management for patients with extensive Osteochondral defects and Osteoarthritis, which will have an enormous impact on future patient care and surgical practice.

Module 4: New Advances in Regenerative Medicine – Basic Research

How to Improve the Biomechanics of our Repairs – Darryl D' Lima (US)

Osteochondral tissue has complex biomechanical properties. The tissues are heterogeneous, have variable response in tension, compression, and shear, and demonstrate significant viscoelastic and creep behavior. This complexity is due in part to the distinct zonal differences; due in part to the interactions between fibrillar protein networks and small and large glycosaminoglycans; and due in part to ionic forces and fluid flow. While the biomechanical properties of natural healthy cartilage have been well characterized, we have not yet recapitulated these properties through *in vitro* or *in vivo* tissue engineering or synthetic approaches.

At the level of matrix composition, the glycosaminoglycans complexed with aggrecan provide largely compressive stiffness, while the fibrillar collagen provide tensile stiffness. The ionic interactions, osmotic tension, and poroelastic fluid flow contribute to viscoelastic behavior. The subchondral bone provides a stiffer foundation for articular cartilage, while the calcified cartilage serves as an interface and generates a mechanical gradient between the less stiff deep zone.

The challenges facing cartilage repair are replicating the depth-dependent variation in mechanical properties and generating integration with host tissue in the radial direction. Last but not least, is the importance of long-term maintenance of biomechanical homeostasis after repair or reconstruction. For example, microfracture is reasonably successful in the short to intermediate term in relieving symptoms and enhancing function. However, the repair tissue generated after microfracture is less durable in the longer term. This has been attributed to the largely fibrocartilaginous nature of the repair tissue. While this is likely to be true, little is known about how much the difference in matrix proteins and fibrillar organization between fibrocartilage and hyaline articular cartilage is related to specific reductions in durability. Osteochondral grafting is successful in replacing tissue defects with grafts that match the native properties of cartilage and bone. However, a major disadvantage is lack of integration with the host tissue, which does not generate an intact articulating unit that is important for a durable reconstruction.

Advances are being made in developing Invasive and non-invasive measurements of cartilage repair biomechanics. This quantification will be valuable in quantifying thresholds for biomechanical properties needed during the implantation and early rehabilitation and the final properties needed for full function. In addition, more research is needed to quantify the relative importance of cells in generating tissue, the assembly and turnover of matrix molecules, and the dynamic balance between anabolic and catabolic factors contributing to tissue regeneration and integration.

Chondrocytes & MSC's: A Nice Couple for Cartilage Repair: True or False? Lucienne Vonk (NL)

Mesenchymal stromal cells (also known as mesenchymal stem or signaling cells (MSCs)) are nonhematopoietic adult cells with stem cell-like properties that can be isolated from various tissues such as bone marrow and adipose tissue. They are multipotent, meaning that they have the ability to differentiate into the lineages of mesenchymal tissues, including osteogenic, adipogic and chondrogenic and others. The capability to differentiate MSCs into different lineages of mesenchymal tissues *in vitro* has given rise to a new era in regenerative medicine, which aims at regenerating tissues and organs through stem cell differentiation. In addition, it incited the use of cocultures in which MSCs are cultured with another cell type. Cocultures of articular chondrocytes and MSCs have shown to be a viable option for cartilage repair[1]. We have recently executed a first-in-man clinical study in which a combination of autologous chondrons (chondrocytes with their native pericellular matrix) and allogeneic MSCs were used to treat large (> 2 cm^2) cartilage defects[2]. The advantage is that a cell combination eliminates the need for chondrocyte expansion and can therefore be applied in a single treatment leading to a patient friendly and more cost-effective cell therapy[2].

There has been considerable debate regarding the mechanisms and interactions that lead to cartilage regeneration in cocultures. While a considerable number of studies have reported MSCs to differentiate towards the chondrogenic lineage, others have found that they disappear and stimulate the chondrocytes to proliferate and deposit cartilage tissue (chondroinduction)[1]. Currently, the evidence towards chondroinduction is growing. However, the underlying mechanisms explaining this effect are still elusive. Several growth factors such as fibroblast growth factor (FGF), transforming growth factor-beta (TGF-β, insulin-like growth factor 1(IGF1) and bone morphogenetic protein 2 (BMP2) and extracellular vesicles have shown to be involved in the paracrine-mediated chondroinduction[1], while direct cell-cell contact with functional gap-junction development can play a considerable role in chondroinduction[3].

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Although the vast majority of studies on cocultures of chondrocytes and MSCs showed equal or even superior effects of this cell combination compared to monocultures, decreased cartilage regeneration of cocultures has also been reported[4]. This shows the need for standardization and proper quality controls for cocultures. Again, here the challenge lies in the complete understanding of the underlying mechanisms.

So while MSC induced chondroinduction through cocultures and co-implantation is a promising and exciting new technique in cartilage repair and tissue engineering, there is need to develop quality controls and standardization for these techniques. The cross talk of chondrocytes and MSCs has proven to be a reliable source for cartilage repair, even in the human being. Unfolding the mechanisms behind these cellular interactions and exploring the MSC as signaling cell will allow us to continuously improve the co-implantation technique, recently introduced in clinical single-stage cartilage repair.

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Cartilage Repair: Assessment of the Quality and Composition – Susan Chubinskaya (US)

It is widely accepted that mature human articular cartilage has a limited innate ability to repair and regenerate. While early data focused on more basic outcomes such as percentage of defect fill, the tissue formed was a “cartilage scar” or hyaline-like tissue. With more advanced technologies, it is clear that to date, no procedure has been able to reconstitute the native structure and function of true hyaline cartilage. As research advancement has somewhat plateaued in this regard, it has become clear that a multifactorial approach is required that treats the joint as an organ (Yanke & Chubinskaya, 2015).

Formation and development of hyaline cartilage takes many years and depends upon multiple factors including weight bearing, motion, cells, growth and differentiation factor, appropriate environment, etc. Thus, it is almost impossible to re-create true hyaline cartilage. Therefore, using an approach that already contains the appropriate structure (scaffold or graft) may be beneficial along with a cell source capable of coordinating its maintenance and integration. This integration will always be in two main directions: peripheral and deep. Peripheral integration involves cartilage to cartilage healing, however deep integration can either be cartilage to bone (microfracture or autologous chondrocyte implantation) or bone to bone (osteochondral allograft or autograft). While structurally this would be ideal for long term benefit in preventing further deterioration, restoration of true hyaline cartilage may not be necessary to impart short term benefits. Competing views would argue that restoration of true native articular structure and function is not necessary for *symptomatic improvement*.

State and quality of cartilage repair are always among key outcome measures used in assessing the efficacy of cartilage restoration approaches. Hyaline cartilage has a unique molecular organization and highly specialized structure and biochemical composition, which makes the task of cartilage repair extremely challenging. It contains only one cell type, the chondrocyte, responsible for synthesis and degradation of an abundant avascular and aneural extracellular matrix. The biochemical composition of cartilage matrix provide the cartilage with its remarkable biomechanical properties (Chubinskaya, Malfait, Wimmer, 2015). Most methods used for cartilage repair have the ultimate goal to stimulate the production of a hyaline-like extracellular matrix that is capable of bearing load and fulfilling the various functions of normal articular cartilage (Mainil-Varlet et al, 2003). The quality of cartilage repair is assessed by a variety of imaging techniques, including magnetic resonance imaging (MRI), computerized tomography (CT), and optical computerized tomography (OCT), morphological appearance of the joint and the repaired tissue, polarized microscopy for collagen arcades, histological studies, biochemical, immunohistochemical and biomechanical analysis of the repaired tissue as well as biomarkers released in to synovial fluid. It is thought that the morphological appearance of the re-

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pair tissue is likely to be predictive of its functionality and durability (Mainil-Varlet et al, 2003). A number of scoring systems have been used to assess the state of cartilage repair (Mankin score, O'Driscoll score, two ICRS scores, and others). The ICRS has produced a consensus paper that described a visual histological assessment scale (ICRS I) and provided specific recommendations on the types of histological stains and fixation approaches to be used. To avoid confusions with the term "hyaline-like" cartilage this grading system differentiates between normal articular cartilage and different types of repair tissue across a broad spectrum, from minimally to completely unstructured tissue. The scale considers the appearance of cartilage surface and matrix, cell distribution and viability, subchondral bone integrity and cartilage mineralization (Mainil-Varlet et al, 2003). In addition, the quality of cartilage repair is assessed clinically via arthroscopy and evaluation of clinical outcomes including pain and function. ICRS II scoring system was developed to improve reproducibility of two established histological scoring systems, the Modified O'Driscoll Scale (MODS) and ICRS I (Mainil-Varlet et al, 2010). ICRS II scale has expanded upon ICRS I and O-Driscoll score to become a 14-point scale and to provide a more in depth assessment of not only the repaired tissue, but also its integration with surrounding matrix and subchondral bone. It is based on tissue morphology (viewed under polarized light), matrix staining, cell morphology, chondrocytes clustering, surface architecture, basal integration, formation of tidemark, subchondral bone abnormalities and marrow fibrosis, the level of inflammation, the evidence of abnormal calcification/ossification, vascularization within the repaired tissue, assessment of the surface and superficial, mid/deep layers, as well as overall assessment. Each criterion is evaluated based on the visual analog scale and graded from 0 to100.

In assessing repaired tissue it is also important to recognize that biochemical constituents of the extracellular matrix undergo changes with aging and thus, the quality and functionality of repaired tissue and its appearance can be largely affected (Lee et al, 2014; Dejica et al, 2012). In addition to described scores, cartilage repair in animal models is assessed morphologically with histomorphometry by measuring the percentage of cartilage degeneration and average depression or cartilage defect in mm in the control vs experimental joints (Badlani et al, 2008). Many laboratories perform a detailed gene expression and protein analysis with immunohistochemistry of repaired cartilage including human cartilage biopsies to verify that the right constituents are synthesized, for example, aggrecan, collagen type II, and not type I, or that pro-inflammatory mediators and proteolytic enzymes are inhibited, as for example, MMP-3, MMP-13, aggrecanase, etc.

In conclusion, there is a plethora of outcome measures used to assess cartilage repair including imaging, clinical, functional, visual, and molecular. It was recommended by Hoemann et all (2011) that five variables should be controlled: 1) location of biopsy/sample section, 2) timing of biopsy/sample recovery, 3) histoprocessing, 4) staining, and 5) blinded evaluation with a proper control group. Thus, standardized methodology and identification of key outcome measures predictive of long-term clinical outcomes will help interpret and cross-compare different pre-clinical and clinical studies.

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Module 4

MSCs Are Not Stem Cells – Arnold Caplan (US)

In the late 1980's, I called a group of cells that could be isolated from human bone marrow by their adherence to cell culture dishes in serum containing medium, Mesenchymal Stem Cells, MSCs. The reason for naming them "stem cells" was that following culture expansion, we could drive the cells into the bone, cartilage, muscle, marrow stroma, fat, etc. lineages in cell culture. As was the dogma of the day, we accepted the proposition that these multipotent progenitors were housed in the "stroma" of bone marrow or periosteum. Fast-forward to today, we know that this is not correct and indeed, most, if not all MSCs arise from the differentiation of perivascular cells, pericytes. Thus, the multipotency of MSCs can only be observed in cell culture and the functioning of MSCs in vivo has nothing whatsoever to do with multipotency.

Pericytes surround every blood vessel in the body. When blood vessels are broken, or inflamed, the pericytes come off and differentiated into local MSCs. The MSCs secrete a curtain of molecules from their faces that inhibit the immune system from interrogating the injured tissue. From the back of the MSCs, molecules are secreted that affect the regeneration of the injured tissue. Given the above, I propose that MSCs name be changed to Medicinal Signaling Cells because they serve as localized "drugstores" for injured tissue.

MSCs can still be used to tissue engineer replacement cartilage, but not without their careful induction in culture into the proper articular cartilage lineage pathway. The details of this approach using human MSCs to fabricate articular cartilage in culture will be covered in this lecture. Supported by NIH and the L. David and E. Virginia Baldwin Fund.

Acellular Matrix Based Cartilage Regeneration in China – Ao Yingfang (CN)

The acellular tissue matrix(ACTM) have the advantages of good histocompatibility, low immunological rejection, three-dimensional spatial structure, and capacity to retain cytokine components, which can provide an optimal microenvironment for adherence, proliferation and differentiation of stem cells, and promote tissue repair and regeneration. ACTM have been the focus of regenerative medicine and is promising in clinical applications.

Research on tissue repair using acellular matrix material in China can be dated back to the 1990s. Back then, acellular dermis matrix, acellular blood vessels and acellular bladder were studied as substitutions of corresponding tissues in animal experiments and clinical studies which showed good prospect. In 1999, researchers in China used rabbit auricular cartilage derived acellular matrix scaffold for in vitro culture of chondrocytes. It showed good chondrogenic effect and for the first time proposed that acellular cartilage matrix scaffold may be utilized as a natural scaffold material in cartilage engineering. In 2002, some researchers used allogeneic acellular auricular cartilage matrix for cartilage defects repair in rabbit ear in vivo, and results were good. Those works laid the foundation for further study of the application of acellular cartilage matrix material in articular cartilage regeneration. In 2005, Professor Shibi Lu established an effective method for the preparation of three-dimensional human articular cartilage acellular matrix scaffold by decellularization. In 2006, Xuefeng Han showed good compatibility of porcine-derived acellular cartilage matrix and rabbit-derived chondrocytes using gross observation and proliferative activity detection, suggesting the possibility of xenogeneic acellular matrix scaffold in cartilage repair. In the same year, Professor Yingfang Ao used acellular bone matrix material and Microfracture technique to repair articular cartilage injury in rabbit and proposed the concept of a single-step in situ repair of articular cartilage injury. In 2008, Professor Quanyi Guo studied the chondrogenesis of hBMSCs combined with human acellular cartilage matrix scaffold in vitro and in vivo. In 2008, Professor Xiaochun Wei prepared heterogeneous scaffolds by decellularizing porcine cartilage for articular cartilage repair in rabbit. In 2009, Professor Hua Feng used bovine derived xenogenic acellular dermis matrix combined with autologous chondrocytes for rabbit articular cartilage repair. In 2010, Professor Yanlin Li cultured autologous bone marrow stem cells in allogeneic acellular bone matrix for chondrogenesis in vitro, then implanted it into rabbit articular cartilage defect and yielded good result.

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Since then, researches have been focused on improving the preparation process, optimizing the acellular matrix-based scaffolds, and application in clinical trials. The team led by Professor Yingfang Ao from Peking University Institute of Sports Medicine used human allogeneic acellular bone matrix material as a scaffold combined with Microfracture technique to repair articular cartilage injury in situ. 15 cases in the experiment group all yielded satisfactory evaluation. In another clinical trial, they compared Microfracture with porcine peritoneum-derived acellular matrix and Microfracture alone for knee cartilage repair. Until now they have completed 20 cases (10 from each group), and interim analysis revealed that arthroscopic cartilage repair using acellular bone matrix material and Microfracture yielded good results. The team led by Professor Shibi Lu implanted human allogeneic acellular cartilage matrix seeded with autologous chondrocytes cultured into cartilage defect and achieved good clinical results.

The acellular matrix-based scaffolds have shown great clinical prospect in cartilage tissue engineering because of their unique biological properties. The mechanical properties of acellular matrix-based scaffolds for cartilage repair is yet to be improved. And research revolves around the fields of: 1) Understanding the biological response of acellular matrix-based scaffolds within the joint environment and optimizing the preparation method of acellular matrix; 2) Improving the biomechanics, spatial structure and biological functions of acellular matrix with the application of 3D bio-printing, hydrogels and artificial synthetic materials. 3) Using non-cartilage-specific acellular matrix for cartilage repair. 4) Designing of a biphasic construct which mimics the structure of cartilage and the underlying subchondral bone for cartilage and subchondral repair.

Update on the Treatment of Cartilage Lesions in the Equine Athlete
Wayne McIlwraith (US)

Introduction Arthroscopic surgery revolutionized equine orthopaedics as it did human orthopaedics and enabled the return of many equine athletes back to full athletic activity. However limitations were quickly recognized including acute articular cartilage loss, soft tissue injury, and progressive degeneration leading to osteoarthritis (OA). This led to increasing the quest for better regenerative therapies. The goal is regeneration of articular cartilage. While a laudable goal this is not yet achieved although considerable progress has been made enhancing the quality of repair. This paper summarizes both pre-clinical research and results in clinical patients. With regard to the goal of regeneration there are a number of techniques used to try and achieve this including: 1) Transplantation of cartilage tissue, 2) Microfracture and its augmentation, 3) Gene therapy, 4) Chondrocyte implantation, 5) Mesenchymal stem cells (direct in situ implantation or intra-articular administration) and, 6) the use of scaffolds in hydrogels with and without cells.

1. Transplantation of cartilage: Early attempts of transplanting cartilage included grafting with sternal cartilage that while looking good at four months failed at 12 months. The one technique that has proven useful in cases of severe osteochondritis dissecans (OCD) in the horse is reattachment with PDS (OrthoSorb® pins).1
2. Microfracture: A desire to validate microfracture in humans led to development of the first model of articular cartilage repair in horses simulating femorotibial articular cartilage damage in humans. A number of equine models of articular cartilage healing have now been developed and this has been reviewed.2 In the first study in the horse, arthroscopic subchondral bone plate microfracture was shown to augment the healing of large chondral defects in the medial femoral condyle in horses which led to clinical adoption in equine patients. Further studies showed significant upregulation of type II collagen expression 8 weeks after microfracture and that the removal of calcified cartilage was critical for best healing of chondral defects treated with microfracture in the horse.3 Microfracture has become regularly used to promote repair of articular cartilage defects and clinical studies have been reported in humans including a systematic analysis supporting that microfracture effectively improved knee function in all studies during the first 24 months4 but reports on durability of the initial functional improvement were conflicting.
3. Gene Therapy: Pre-clinical evidence is good for the augmentative value of gene therapy in cartilage repair. In one study with an adenoviral IL1-Ra/adenoviral IGF1 combination in a single intra-articular injection showed significant increase in both aggrecan and type two collagen levels in the repair of full defects cartilage tissue.5

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4. Chondrocyte implantation: Autologous chondrocyte implantation (ACI) is the only technique licensed in humans in the US. Equine studies have shown that MACI®-like techniques can promote articular cartilage repair in experimental defects in the horse. However the caveat of two surgeries being needed remain. The use of autologous cartilage fragments (CAIS) minced and placed into defects showed good repair in defects on the medial trochlear ridge of the femur in horses, and translation to a human phase 1 study reported. Most recently the use of particulated allograft articular cartilage (biocartilage) plus PRP in microfracture defects showed superior repair compared to microfracture alone.6
5. Mesenchymal Stem Cells (MSCs): There has been considerable use of MSCs in horses to promote articular cartilage repair with clinical reports on: 1) Cartilage resurfacing, 2) Osteoarthritis, 3) Damaged intra-articular soft tissue structures (meniscus and meniscotibial ligaments). Most injured joints, at least in femorotibial articulations in the horse, have components of all three.

Pre-clinical studies with direct implantation of MSCs in fibrin or fibrin and PRP mixtures have not shown very good results and lack of superiority compared to fibrin or fibrin and PRP alone. The use of concentrated bone marrow aspirate however improves full thickness cartilage repair compared to microfracture in experimental defects on the lateral trochlear ridge of the femur.[7] Autologous articular cartilage progenitor cells from the superficial layer of articular cartilage in fibrin have also shown good results with full thickness articular defects in the horse.[8]

Better results with articular cartilage repair in pre-clinical studies and in clinical studies have been shown with intra-articular administration of bone marrow-derived MSCs. In a clinical study with average follow-up of 24± 2.6 months available there was a high return to full athletic activity in horses with femorotibial joint injuries.[9] With regard to articular cartilage damage 73.1% of horses with small areas of damage returned to work. Surprisingly 85.7% of a sub-group with severe damage including eburnation of subchondral bone treated with microfracture returned to work and 71.4% of these horses were at the same or a better level. Similarly horses with severe meniscal injury had superior return to work compared to what can be achieved with arthroscopic debridement alone. The use of an intra-articular injection of 20 million bone marrow-derived MSCs in HA four weeks after creation of a microfractured full thickness defect showed improved firmness of repair tissue arthroscopically at six months and 12 months and significant augmentation of aggrecan content compared to HA alone.[10]

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Module 5: New Advances in Cartilage Repair – Clinical

3D Printing for Cartilage Repair and Organ Reconstruction – Jos Malda (NL)

The introduction of 3D printing in the field of orthopaedics has enabled the generation of patient-matched positioning guides and custom-designed plastic and metal implants. It may, however, also provide opportunities for the generation of cell-containing constructs. This shift towards 3D bioprinting does hold potential to advance the field of cartilage regeneration and to further reproduce the intricate organisation of the joint. Thus, enabling the introduction of novel surgical treatments, regenerative therapies and providing a new set of tools to enhance our understanding of joint physiology and pathology.

The combination of multiple materials, biological cues and cells in a layer-by-layer fashion, can assist the reproduction of both the zonal organisation of cartilage and the gradual transition from resilient cartilage towards stiffer subchondral bone in engineered osteochondral grafts. In this way, optimal integration of an engineered construct with the natural surrounding tissues can potentially be obtained. Mechanical characteristics, including the smoothness and low friction that are hallmarks of the articular surface, can be tuned controlling architecture and spatial patterning of printed structures with multi-head or hybrid printers. Moreover, biofabrication can use digital medical images as blueprints for printing advanced and patient-specific implants

Nonetheless, some significant challenges need to be addressed to prompt the shift from non-living implants towards living 3D bioprinted cartilage constructs in the clinic. The bio-inks and required cartilage construct architecture need to be further optimized. The bio-ink and printing process need to meet the sterility requirements for implantation. Finally, standards are essential in order to ensure a reproducible quality of the 3D printed constructs. Once these challenges are addressed, 3D bioprinted living articular cartilage implants may find their way into daily clinical practice.

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First In-human Clinical Study of Scaffold-free Tissue-engineered Construct generated from Synovial Mesenchymal Stem Cells for Treatment of Chondral Lesions Norimasa Nakamura (JP)

Introduction

Scaffold-free tissue engineered construct (TEC) is feasible to cartilage 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

1. Immune-tolerance of MSCs
2. Safety issues regarding the implantation of animal-derived or chemical materials in clinical settings
3. High medical cost with the use of scaffold
4. Trends in promoting minimally invasive surgery
5. Risk of complications by long surgical duration

Pre-clinical studies in 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 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 paroperties. This technology could potentially be a unique and promising method for stem cell-based cartilage repair.

First in human clinical trial

Methods
In a first-in-human trial, five patients with symptomatic, chondral lesions were treated at Osaka University Hospital in Japan. Synovial MSCs isolated from 1mg arthroscopic biopsy specimen were expanded and cultured to develop a TEC that matched the lesion size. The TEC was then implanted into chondral defects (average 2.5 cm2) on femoral groove, medial condyle or lateral condyle by mini-arthrotomy or arthroscopy without any reinforcement for fixation and assessed up to 24 months after surgery. Primary outcomes were safety of the procedure. Secondary outcomes were feasibility including self-assessed clinical scores, arthroscopy, tissue biopsy and MRI-based estimation of morphological and compositional quality of the repair tissue. This study was registered at University hospital Medical Information Network (UMIN) Clinical Trial Registry (http://www.umin.ac.jp/ctr/ ; No.000008266).

Findings
No adverse reactions were recorded and self-assessed clinical scores for pain, symptom, activity of daily living, sports activity, quality of life were improved significantly from before surgery to 24 months after surgery. Secure defect filling was confirmed by second look arthroscopy and MRI. Histological assessment of biopsy specimen indicated repair tissue approaching the composition of native cartilage.

Interpretation
The scaffold-free TEC could be clinically used for regenerative repair of chondral lesions. Further study will be expected to warrant the feasibility by the assessment of large populations (cohort) and with longer follow-up.

Bone Marrow and other MSC Choices for Clinical Repair of Cartilage Injury
Alberto Gobbi (IT)

Introduction
Mesenchymal stems cells (MSCs) are multipotent in nature and are capable of differentiating into cells that constitute a number of tissues including cartilage, bone, muscle, adipose, and connective tissue. Recent evidence suggests that MSCs are derived from perivascular cells named “pericytes” that are closely associated with blood vessels, and reside at this location in a quiescent state [1]. Once activated, it has been proposed that pericytes acquire an MSC phenotype, which are capable of releasing a wide range of trophic and anti-inflammatory factors, and stimulate proliferation and differentiation of tissue specific proginator cells [2].

The capacity of these cells to repopulate areas of injured articular cartilage has been examined in vitro and in vivo. Cartilage injuries have limited healing potential, and progressive degenerative cartilage change may result from such lesions, often leading to joint pain, dysfunction, and eventual joint failure. Treating cartilage injury in the early stages of this disease process has the potential to restore joint function and to slow or prevent progression of degenerative joint change. Therapeutic protocols that make use of the regenerative qualities of MSCs are evolving rapidly, and there is great potential for these cells to be used to enhance reparative processes in numerous musculoskeletal conditions, including cartilage restoration.

Content
Mesenchymal stem cells may be sourced from a variety of autologous tissues and applied therapeutically to treat cartilage injury. Bone marrow concentrates have been shown to be a particularly dependable source of MSCs, and they have been examined for clinical use in a variety of forms, from injectable isolates to surgical application of clot-activated implants. These cellular therapies are used to provide a source of multipotent cells for chondrocyte repopulation and cartilage restoration. Encouraging short- and medium-term clinical outcomes have been demonstrated by combining bone marrow concentrates with biocompatible scaffolds to create composites that assist delivery of multipotent cells to the site of cartilage injury [3-5]. Cartilage repair using this technique has demonstrated comparable outcomes to procedures that utilize autologous chondrocytes [6], is performed as a single-stage procedure, and may be used arthroscopically [7].

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More recently, there has been increasing use of adipose tissue as a source of MSCs for clinical applications. Mesenchymal stem cells are easily sourced from adipose tissue in the form of adipose-derived stem cells (ASCs). These cells can be harvested and concentrated for immediate use in the outpatient setting, without further tissue manipulation. ASCs sourced from abdominal lipoaspirates have been shown to induce chondrocyte proliferation and extracellular matrix deposition, without need for autologous cell expansion prior to implantation [8]. Recently, published data has examined the ability of ASCs sourced from lipoaspirate to promote the outgrowth of cells capable of restoring chondrocyte cell lines, and to impart trophic paracrine effects on chondrocytes.

Summary

Understanding of stem cell biology continues to develop and there have been important clinical advances in the treatment of cartilage injury with cellular therapies that take advantage of mesenchymal stem cells and various growth factor isolates. The capabilities of mesenchymal stem cells to promote chondrogenesis and restoration of articular cartilage continues to be studied extensively. Treatment of high-grade cartilage injury with single-stage surgery using scaffolds embedded with bone marrow aspirate concentrate has demonstrated good to excellent medium-term clinical outcomes. More recently, adipose-derived stem cells have been increasingly used to treat cartilage injury, and early investigations have been promising.

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Stem Cell Therapy for Cartilage Repair in Asia: 2012-2017 – James Hui (SG)

Introduction

Clinics offering stem cell therapy have mushroomed across Asia, offering a bewildering array of treatments for medical-related issues, literally from the head to the toe. Stem cell therapy's popularity, heavily contingent on its image of one with tremendous regenerative potential, is a superb candidate for repairing cartilage, an avascular tissue which possesses poor self-healing properties. This paper aims to provide a comprehensive review of advances made in stem cell therapy for cartilage repair in Asia, over the past 5 years.

Methods

A pubmed search was performed using the keywords "Asia, stem cell, cartilage repair, clinical trial, 2012-2017" in March 2017.

Results

Over the span of these 5 years, Asian countries have collectively published 4(level 2), 8(level 3), 13 (level 4) studies, including 1 meta-analysis. The number of cohort studies and case series outnumber randomized controlled trials, at a 5:1 ratio. A vast majority of the studies investigated the efficacy of stem cells, both in its homogeneous form or heterogeneous mixture, in ameliorating the effects of osteoarthritis (23 out of 26 studies). Korea is the foremost Asian country paving the way in clinical research utilising stem cells for application in cartilage repair, with a particularly focused approach towards harnessing the full potential of adipose tissue and stromal vascular fraction (Pak J et al, Koh YG et al, Kim YS et al, Jo CH et al). Investigators from other countries used MSC types included bone marrow stem cells (Wong KL et al), umbilical cord blood MSCs (Park YB et al), peripheral blood (Saw KY et al) and synovial fluid MSCs (Sekiya I et al). The application of autologous cells was noted in all the studies except for 1 study which used allogeneic umbilical cord blood MSCs. 65% of

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the studies applied less than 10 million MSCs for cartilage treatment. All the studies consisted of single administration of MSCs with the exception of 1 study which involved multiple injections of peripheral blood stem cells (Saw KY et al). Some studies included additional PRP and hyaluronic injections to further optimize the repair process. The number of studies whereby MSC administration was done through injection doubles that of implantation. The average follow-up period is 28 months, with the longest record being 7 years currently. Outcomes were usually measured in terms of functional scores, pain scores, with some including MRI and histological analyses. The findings made so far have been encouraging. The implantation of umbilical cord blood MSCs was observed to result in improved VAS and IKDC scores in osteoarthritic patients by 6 months, and these improved clinical outcomes remained stable over 7 years of follow-up (Park YB). MRI data also revealed that osteoarthritic patients subjected to arthroscopic microfracture followed by an injection of adipose stromal vascular fraction, were observed to have a thicker layer of regenerated cartilage at 12 months (Nguyen et al). A recently conducted meta-analysis (Cui GH et al) concluded that MSC treatment led to significantly improved pain and functional status in knee OA, with a long-lasting effect stretching up to two years after treatment, without any deterioration observed over time. An interesting point to note is that the meta-analysis has also confirmed a long-held suspicion of many healthcare professionals- that MSC efficacy has an inversely proportional relationship with disease severity. None of the abovementioned studies have reported any adverse effects arising from the usage of MSCs.

Conclusion

Stem cell therapy performed in the Asian region has been consistently observed to result in an improved outcome for osteoarthritis. Over the next decade, we can anticipate more high-quality data to emerge from the ongoing clinical trials, and provide greater insight on MSC's effectiveness for cartilage repair. As important as large randomized controlled trials are due to their translational value, small series and case reports should not be underestimated and overlooked, as these undeniably provide proof-of-concept data, for better-designed clinical trials.

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Module 5

Meniscus Substitution: From Allografts to Synthetic Substitutes – Peter Verdonk (BE)

In the last decades, the surgical treatment of meniscal injury or damage has shifted from a total meniscectomy towards a partial meniscectomy or repair. Recently, attempts have been made to promote meniscal healing, as well as the replacement of damaged menisci with allografts, scaffolds, meniscal implants, or substitutes. The correct approach to the chronic painful meniscectomised knee joint also requires consideration of other pathologies including alignment, stability, and cartilage degeneration.

Meniscus allograft transplantation (MAT) is a viable solution for the younger patient with chronic pain in the meniscectomised knee joint. Current long-term term data demonstrates that MAT yields good to excellent results in terms of improvements pain, function and activity levels. While there is still limited evidence to suggest that the procedure alters the natural history of degenerative change within the affected compartment, there are reasons to believe that meniscus replacement may have the potential to delay or prevent the possible need for traditional knee arthroplasty in affected patients. The complications are not severe and comparable to meniscal repair. The overall failure rate at final follow-up is acceptable and the allograft heals well in most cases. Progression of osteoarthritis is acceptable at mid-term evaluation. Increased signal on MRI is a common finding without clinical complaints. Meniscal substitutes based on synthetic or natural polymers have been described. Most of these implants are based on biodegradable materials, which form temporary scaffolds that degrade in the body over time and are replaced gradually by newly formed tissue. Potential shortcomings of this approach include the lack of durability, associated with most biodegradable materials under in vivo knee loading conditions, as well as the variability in the individual patient's biological response to the implant, limited age of the target population and the quality of the tissue formed. Nevertheless, midterm clinical data shows significant improvement in knee function and pain in patients with segmental meniscus defects treated by such scaffolds. More recently, a non-anchored, self-centering discoid-shaped, polycarbonate-urethane meniscus implant, reinforced circumferentially with UHMWPE fibers is proposed for the treatment of post-medial-meniscectomy pain in the middle-aged patient with limited medial OA. Early clinical experience provides proof of principle that such prosthetic, flexible implants result in clinical improvement and increased knee function. In conclusion, loss of meniscus function results in progressive cartilage degeneration and OA. Substitution of lost meniscus tissue with biological implants such as scaffold and allografts, or prosthetic medial implants result in proven clinical improvement. However, its chondroprotective effect is still debated.

Single-stage Cartilage Repair: Health Economic Modeling to Guide Implementation of of new technologies in Regenerative Medicine – Tommy de Windt (NL)

Market competition, increasing healthcare costs and insurance policies are forcing a shift in focus from two-stage to single-stage interventions for cartilage repair and tissue engineering. While cost-effectiveness should be one of the primary drivers in this development, the field primarily has its focus on research and development. Thus, it remains unclear whether cost-effective single-stage cartilage repair will find its way in the near future. An important reason for this uncertainty is that traditionally, cost-effectiveness is measured after a prolonged period of time. However, implementing early health economic modelling in our field may allow us to gain essential insight in the parameters driving the cost-effectiveness of new interventions before they are introduced into clinical practice.1 Prior to initiating a first-in-man trial exploring a single-stage procedure (IMPACT), we estimated the likely incremental cost-effectiveness ratio (ICER) of this investigator-driven treatment compared to both microfracture and ACI, and identified those parameters that affect the cost-effectiveness.2 A decision tree with clinical health states was constructed. The ICER was calculated by dividing the incremental societal costs by the incremental quality adjusted life years (QALYs). Costs were determined from a societal perspective. A headroom analysis was performed to determine the maximum price of IMPACT compared to both ACI and microfracture, assuming a societal willingness to pay (WTP) of €30,000/QALY. One-way sensitivity analysis was performed to identify those parameters that would drive the cost-effectiveness. The societal costs of IMPACT, ACI, and microfracture were found to be approximately €11,797, €29,741, and €6,081, respectively. After our initial model, a phase I (first-in-man) clinical trial was launched to study single-stage application of allogeneic mesenchymal signalling or stromal cells (MSCs) mixed with 10% or 20% recycled autologous chondrons for the treatment of large (> 2 cm2) cartilage defects in 35 patients.3 With a follow-up of 18 months, we were able to update our early health economic Models to better understand the impact this single-stage procedure has on cost-effectiveness. Indeed, the first-in-man trial showed no treatment-related serious adverse events and statistically significant improvement in clinical outcome. MRI and second-look arthroscopies showed consistent newly formed cartilage tissue. A biopsy taken from the center of the repair tissue was found to have hyaline-like features with a high concentration of proteoglycans and type II collagen. MSCs were found to be a safe cell source to augment or facilitate tissue regeneration in a clinical setting and instead of engraftment or differentiation as previously suggested, allogeneic MSCs

seem to stimulate tissue regeneration through paracrine mechanisms and cellular communication. Thus, the results of this study indicate that using a mixture of autologous chondrons and allogeneic 'signaling' cells can be a feasible and safe strategy. Such a single-stage procedure, with 'off-the-shelf' use of allogeneic MSCs would have major benefits for patients, payers and providers alike as they would not need two separate surgical treatments. In addition, patients are allowed to start rehabilitation immediately following surgery, instead of having to wait on a cell expansion period. Compared to ACI, IMPACT is less costly, which is largely attributable to the cell expansion procedure that has been rendered redundant.4 We found non-inferior and even superior clinical outcome compared to ACI and mirofracture in comparison to previous randomized controlled trials. While microfracture can be considered the most cost-effective treatment option for smaller defects, our models show a single-stage tissue engineering procedure can replace ACI to improve the cost-effectiveness for treating larger defects, especially if clinical non-inferiority can be achieved. Long term follow-up will allow us to continuously update the models to monitor cost-effectiveness.

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A Health Technology Assessment of Autologous Chondrocyte Implantation
Norman Waugh (UK)

HTA reports address three questions;

- Does it work? – At what cost? – Is it worth it?

In order to help policy-makers and health care funders answer a fourth question;

- Should we provide it?

In the UK, the National Institute for Health and Clinical Excellence (NICE) has appraised autologous chondrocyte implantation (ACI) three times. The first two appraisals concluded that ACI could not be recommended outwith research studies. The third appraisal is underway, with guidance from NICE expected in Autumn 2017. The final scope from NICE was: "To appraise the clinical and cost effectiveness of autologous chondrocyte implantation within the applicable licensed indications for repairing symptomatic articular cartilage defects of the knee." The patient group was defined as: "Adults with symptomatic defects in the cartilage of the knee with no advanced osteoarthritis." Each appraisal has been supported by an HTA report commissioned from an independent academic group. The first report[1] found no randomised trials. The second[2] found a few trials but with short-term follow-up. This presentation summarises the findings of the third HTA report[3].

HTA reports include systematic reviews of clinical effectiveness, and cost-effectiveness analysis, usually requiring an economic model. This report also included exploratory survival analysis [4], and critiques of submissions by manufacturers of the three ACI products identified by NICE (ChondroCelect, then from TiGenix; MACI from Sanofi; and OsCell from Oswestry).

One problem in evaluating ACI is that the technology is evolving, and the longest follow-up comes from superseded forms of ACI, namely first generation ACI with periosteal caps (ACI-P), and second generation with collagen caps (ACI-C). The third generation uses chondrocytes loaded into a collagen matrix – MACI.

We made an assumption that results of ACI-C and MACI would at least be no worse than those of ACI-P, and probably better in some ways (including cost – trimming of hypertrophy being required less often).

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The main comparator, for all but small defects, was microfracture. The cost-effectiveness analysis was driven by short-term improvements in symptoms and hence quality of life, by longer-term outcomes and in particular the need for knee arthroplasty, and by the costs, which were dominated by the cost of the cells. We reported cost-effectiveness using costs per quality adjusted life year (QALY), the "common currency" used by NICE and others. Costs per QALY under £20,000 are usually considered good value, depending on the strength of evidence.

The evidence problems encountered included;

- A lack of long-term follow-up on newer methods of ACI. This is a common problem in assessment of non-pharmacological treatments. Devices and procedures often evolve over time.
- A shortage of good long-term data on microfracture results. We found no long-term data on newer forms of "enhanced microfracture" such as with collagen caps.
- Hence a need for survival analysis going beyond the timescale of observed results, involving some speculative predictions
- There was a shortage of long-term data on quality of life data, though the ACTIVE trial 5 will provide that, with 10 years of follow-up.
- Uncertainties over the costs of cells. The commercial cells were much more expensive than those from the NHS facility in Oswestry. However we were aware of confidential discounts.
- Problems with success and failure data from older studies in which many/most patients had had previous repair attempts. We think the older studies therefore under-estimate the benefits of ACI.

We carried out a range of sensitivity analyses to address uncertainties, for example applying different costs of cells.

Our conclusions were that;

- ACI was cost-effective compared to microfracture because long-term outcomes seemed better. Microfracture was less expensive but gave fewer QALYs.
- ACI was best done as first procedure. We did not think an approach which might appear less expensive, by using microfracture first, then ACI when microfracture failed, was as cost-effective as primary ACI.
- ACI became highly cost-effective when the price of cells was reduced

Uncertainties include;

- Whether ACI should be used in patients with asymptomatic chondral lesions, which may progress to OA. We note the guidance from the Dutch Orthopaedic Association 6 that asymptomatic ICRS grade 5 should be treated.
- ACI did not appear cost-effective in patients with Kellgren-Lawrence grades indicating advanced osteoarthritis, but might be cost-effective in early OA (KG grade 1). Further research is required.

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Module 6: Early OA & Meniscus; Basic/Clinical

Genome wide Expression Profiling of Genes Associated with OA – Anders Lindahl (SE)

Cartilage injuries leading to secondary osteoarthritis (OA) have been an enigma for doctors since the age of Hippocrates. Primary OA is one of the most common forms of musculo-skeletal disease throughout the world with over 80 million patients affected and nearly 1 million patients are hospitalized each year in the U.S alone with a cost estimated to $60 billion. Currently no early diagnostic marker for primary OA is available and no disease modifying treatment exists. Cartilage defects due to trauma could initiate a localized OA (secondary OA) in the young active individual due to the low capacity of cartilage regeneration and subsequent repair. This fact is still a challenge for cartilage researchers and orthopedic surgeons and was the driving force behind the autologous chondrocyte transplantation (ACT) technique developed in Gothenburg Sweden over 25 years ago. In recent decades the ACT technology have triggered research in cell and matrix technology since cartilage is a good target for clinical tissue engineering based on the fact that the cell population is homogenous and the perception is that the tissue structure is relatively simple. Although treatment of focal lesions is promising also in long term follow up over 15 years a cell therapy treatment for primary OA is far away.

The sequencing of the human genome 15 years ago and the development of high throughput sequencing in recent years with a dramatic cost reduction per genome in combination with new proteomics technology and computer technology has enabled researchers to gather and analyze enormous amount of data that was impossible only a decade ago. Monogenetic diseases in cartilage e.g. collagen II mutations with distinct phenotypes in the growth plate causing dwarfism and osteoarthritis combined and collagen IX mutations cause epiphyseal dysplasia and vitreoretinopathy indicate that the collagen matrix is critical for the OA disease. The logical consequence has thus been to search for genetic polymorphisms or mutations in the molecular components of cartilage. However, a comprehensive analysis of polymorphisms in the collagen IX gene failed to link the changes to osteoarthritis. In contrast, the combined evidence today from genome wide association studies and cell biology experiments points in a different direction than defect matrix molecules and a wear and tear hypothesis. Several of loci associated with OA contain genes encoding key regulatory genes controlling skeletogenesis and endochondral ossification. Genes responsible for direct or indirect gene transcription is important in OA in contrast to genes encoding structural proteins of the extracellular matrix.

The conclusion is that the susceptibility genes for OA operate on the regulatory level of tissue regeneration and maintenance and not on a structural level. The genes connected to OA are related to chondrocyte development and differentiation, regulation of apoptosis, cell proliferation and differentiation, transcriptional regulation and skeletal development and morphogenesis. These data combined suggests that active control of cell regeneration is central to cartilage maintenance and dysfunctional regeneration mechanism is central to the OA disease. The most promising candidates in this context are the master transcriptional regulator RUNX2, the PTH like hormone and GDF5 - a member of the BMP subgroup of TGF-beta superfamily that is central in fetal development and joint formation.

The induced pluripotent stem cell technology combined with gene editing provides a unique opportunity to simulate early human mesoderm development and elucidate the functional role of susceptibility genes for OA. In such an experiment, we have demonstrated that a one allele knock down of GDF5 give rise to a distinct defect phenotype and influences several important cartilage formation mechanisms.

The start of the cell therapy era in cartilage regeneration by the pioneering work with ACT 25 years ago triggered the scientific field towards studies of cartilage regeneration and stem cells. As a consequence, the knowledge in the field has increased significantly as indicated by he numbers of publications in the field. The cellular focus in the transplantation technology has revealed new understanding of the degenerative mechanisms behind the OA disease where we now have implications that the disease is basically a cell regenerative dysregulation and not a consequence of wear and tear, a knowledge that gives hope for future disease modifying treatments in patients.

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Mouse Models of Knee Injury and Osteoarthritis – Linda Sandell (US)

Small animals provide a reproducible model system in which to test the effects of injury in the short term and the long-term pathobiology of the development of osteoarthritis (OA). In addition, the effects of potential various treatments for events occurring during injury and OA can be tested. In this talk, I will focus on two models of osteoarthritis, (1) the destabilization of the medial-tibial meniscal ligament (DMM) and (2) a non-invasive impact injury. The DMM model has become the standard for many laboratories investigating the impact of specific gene mutations or knock out of specific molecules on the development and severity of OA. Many laboratories have used common inbred strains as OA models such as C57BL/6, DBA and MRL. We have taken an approach that allows us to inquire about the genetics of OA, through using recombinant inbred strains (RI) of mice and the advanced intercross (AI) of the strains LG/J and SM/J. The LG/J strain is a close relative of the MRL super healer mouse and heals its ear wounds well. The SM/J strain is a "non-healer" mouse that does not heal ear wounds within a month. The RI and AI lines have members that are at the extremes of ear wound healing and span the range in between healing and non-healing. Using these genetic models, we have demonstrated that healing of articular cartilage has a significant genetic component that is related to the ability to heal ear wounds in a positive manner (1). In contrast, the ability to heal cartilage is inversely related to the development of OA, thus individuals that heal poorly have a higher tendency to develop degenerative disease (2). These findings indicate that there are healing processes active in cartilage that likely to protect the cartilage from degeneration.

In the model of non-invasive cartilage injury in the mouse, we show early events that can be manipulated to potentially protect the joint from a degenerative response to the injury (3). Two important events are found to occur at these early times (1 to 14 days), apoptosis in the cartilage at the site of impact and a variable degree of proliferation in the synovium. We have also identified a different response in cells surrounding the direct impact zone. There is a significant difference in response of the synovium and cartilage if the impact forces are high enough to rupture the anterior cruciate ligament (ACL): the cartilage is damaged throughout the joint and ectopic calcifications form in the synovium. Recently, we have been able to abrogate the effects of injury by inhibiting inflammation and increasing autophagy by the inhibition of the transcription factor, NF-kB (4).

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OA Disease Modulation by DMOADS: Possible? – Anthony Hollander (UK)

Osteoarthritis (OA) is a disease of the whole joint with obvious changes in the subchondral bone and articular cartilage but probably also involving other joint structures. OA therapies can be broadly divided into those which treat symptoms (analgesics and anti-inflammatories) and those which, in theory, are disease modifying anti-arthritic drugs (DMOADS). Whilst the earliest pathological changes to be observed in OA are subchondral sclerosis and osteophytosis, it is the gradual loss of cartilage that has received most attention with respect to the development of DMOADs.

It has been known for decades that degradation of the Type II collagen component of cartilage is caused by metalloproteinases. Both collagenase 1 and collagenase 3 have been implicated in this destructive process. Identification of the proteinase that is responsible for cleavage of aggrecan was more challenging but led eventually to the discovery of aggrecancases 1 and 2, members of the ademolysin family. Numerous attempts have been made to selectively inhibit collagenases and aggrecanases as a method of treatment for OA but invariably those molecules with any potency also lead to serious side-effects, including severe musculoskeletal pain. Some neutraceuticals have been widely used to control the disease. These include glucosamine and chondroitin, which can be bought over the counter as oral tablets. However, there is limited evidence of any long-term benefit from these approaches. OA patients therefore remain at the mercy of aggressive pain inhibition to delay the probable outcome of arthroplasty.

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Mesenchymal stem cells (MSCs) have been investigated in many labs for their chondrogenic capacity that is most easily demonstrated using tissue engineering protocols. Stimulation of MSCs with TGFbeta under the right culture conditions can lead to the formation of a cartilage extracellular matrix that is rich in Type II collagen and aggrecan. Whilst this approach might one day be of use in the treatment of small traumatic lesions, it is very hard to see how it can be scaled up for the treatment of idiopathic OA in the ageing population. Recent attempts to inject MSCs into the OA joint have demonstrated some degree of efficacy with respect to analgesia and limited evidence of disease modification as judged by MRI. Do these early studies provide the basis for developing an effective cell-based DMOAD for OA?

If undifferentiated MSCs that are injected into the joint are to have any chance of inhibiting or reversing cartilage damage, they will need to overcome numerous obstacle. First they need to migrate into the articular cartilage, ideally accumulating at the sites of greatest damage. Then they need to engraft into the damaged tissue and communicate with the endogenous chondrocytes. Through this process, they need to initiate cartilage synthesis either by driving the resident chondrocytes or by themselves differentiating into new chondrocytes and then elaborating an extracellular matrix. They also need to be able to survive the ravages of on-going inflammatory processes in the diseased joints and if they are allogeneic cells they must avoid immune rejection.

Given these huge hurdles, it seems likely that an injectable MSC DMOAD will need to be targeted at patients at a relatively early stage of disease, before the cartilage degradation has progressed too far. This will require careful stratification of patients, which in turn is likely to mean the development of new biomarkers of OA.

In summary, there are currently no DMOADs for OA and the path to developing one is hugely challenging but not impossible. An MSC-based therapy offers a significant opportunity, if some of the major hurdles to success can be overcome.

Meniscal & Osteochondral Grafts & Knee Reconstruction: Can They Be Considered Effective OA Prevention? – Alan Getgood (CA)

Osteoarthritis (OA) is one of the leading causes of disability in the Western world with epidemiological data suggesting that it costs between 1-2.5% of the GDP of many industrialized[1] countries. The numbers of patients who will require joint replacement is on the rise exponentially and as such will continue to be a significant socioeconomic burden for decades to come[2].

Unfortunately, we still have not found treatment strategies that are able to prevent OA. Surgeons are often faced with young patients who have sustained joint injuries at an earlier age, now presenting with early signs of OA associated with pain, loss of motion and disability. Traumatic injuries such as anterior cruciate ligament (ACL) ruptures can progress to post traumatic OA. ACL injuries are one of the most common sports and activity related injuries in the younger age demographic, with approximately 10% of isolated ACL reconstructions progressing to PTOA by 10 years; this increases to approximately 50% with concurrent meniscal or cartilage injury [3,4]. Potter et al. showed progression of size and grade of chondral lesions at the time of ACL reconstruction, particularly in the lateral femoral condyle[5]. Whilst there are surgical procedures to treat ligament instability, meniscal deficiency and cartilage loss, there is very limited data to suggest that these procedures have a significant impact on the natural history of OA progression.

Most non-invasive treatments such as oral anti-inflammatories and analgesics, oral nutraceuticals, injections and physiotherapy are focused on symptom palliation. This, in combination with weight loss and activity modification forms the basis of early treatment. Unfortunately, the spectrum of surgical treatment options available is somewhat limited. Arthroscopic debridement has been shown to be no better than physiotherapy in many randomized clinical studies[6-8]. More invasive options such as realignment osteotomy have shown good 10-15 year results prior to, or instead of, full joint replacement[9]. However, the question remains as to whether the addition of cartilage restoration procedures such as fresh osteochondral allograft (OCA) and/or meniscal allograft transplantation (MAT) can change the natural history of the disease.

The introduction of biological joint replacement focused on addressing primarily biomechanical anomalies with the hope of establishing a more favorable biological environment in the knee. Mechanical alignment, ligament laxity, meniscal deficiency are all assessed prior to thinking about procedures to restore the articular surface of the joint. Papers have been published documenting the results of these complex surgeries[10,11], yet it is difficult to draw conclusions, as the patients are so heterogeneous on presentation.

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Whilst the short-term results of these procedures can be good, and have shown excellent improvement in patient reported outcomes, none of the studies have shown that these procedures prevent OA. Indeed, in most series of fresh OCA and MAT, failure rates are higher in patients who already have existing OA[11,12]. Thus, it is a good argument to perform these procedures in knees that do not have OA.

Unfortunately, the present evidence does not necessarily support this approach. There is some weak evidence that MAT can reduce the progression of OA[13]. Fresh OCA to date has not been shown to prevent degenerative change, although has shown excellent medium and long-term outcomes[14]. Cell based cartilage repair has also not shown to be efficacious in the prevention of OA. The only procedure that has shown any potential of a reduction in OA is realignment osteotomy, which in some cases has even shown regeneration of cartilage in the short term[15].

As such, the decision to perform 'biological reconstruction' should not be taken with the goal to prevent OA. It should be utilized to treat the patient's current debilitating symptoms and has the potential to provide good results in the medium to long term. However, patients should be counselled that OA will likely still be an issue in the future.

Based on the current literature, it is clear that a combined mechanical and biological approach is required to limit the development and progression of OA. It is highly unlikely that biology alone will be able to address the needs of the biomechanically challenged joint. Equally, providing the ideal mechanical environment will likely be the first step in introducing adjuvant biological treatments to successfully address OA.

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Module 6

The MMA of Orthopaedics! A Personalized Mini Metal Implant as an Alternative to Local Biological Repair? – Leif Ryd (MD)

Introduction: After 30 years of "cell" treatments, advances have been made and it is now an accepted mode of treatment for local articular cartilage lesions. Also, however, the weaknesses of various biological treatments have been delineated: Cell treatment is less effected in the somewhat elderly patients and repetitive attempts are not indicated (1). Hence, for the "treatment gap patients" (2) alternative methods are sought and a "mini metal" implant may be an alternative.

Methods: The Episealer implant is a patient specific devise, where the articulating surface is a replica of the original cartilage surface at the defect site, manufactured from MR-images through a CAD/CAM process. After segmentation of the MR images, the femoral knee is digitally reconstructed and a damage report, where lesions in the cartilage and BMLs in the subchondral bone are delineated, is sent to the surgeon through a proprietary digital platform. After approval of a suggested implant position and size, a surgical kit including the implant and surgical tools, is delivered "just in time" for surgery. Patient specific guide instruments ascertaining an exact positioning of the implant just slightly recessed beneath the surrounding healthy cartilage, are included in the surgical kit. The implant is manufactured in cobalt-chrome and surfaces facing bone/cartilage are coated with hydroxyapatite (HA) on top of a layer of titanium, both approximately 60 µm thick. The implant is inserted through a mini arthrotomy and incorporates into the bone tissue in about 4 weeks, necessitating only a short rehabilitation period (3).

Results: At the time of this writing about 175 implants have been inserted in the femoral condyles or in the trochlea over a > 4-year period. Clinical results have been satisfactory with an aggregated KOOS score increasing from about 35 preoperatively to 75 after 12 months. There have been 2 revisions, the first, 16 months after surgery due to opposing cartilage wear in a compromised patient and the second, after 28 months due to hematogenous infection. Apart from the first patient here, no patient having passed 24 months has shown any signs of wear of the opposing cartilage on standing x-rays.

Discussion: While the cartilage lesion, in the early years identified by arthroscopy, forms but a superficial evidence of a possible primary process occurring in the subchondral, where modern MRI technology readily identifies a plethora of findings, a hard implant addressing also bony processes may make sense. The Episealer operation excises floppy cartilage edges into healthy cartilage and, also, opens up the subchondral BML. This is from where the pain emanates. Should the BML extend deep into the bone, the implant can, up to certain limitations, be made thicker to comply 3-dimensionally with the lesion.

Clinical experience, so far, supports this idea, for the GAP-patient, aged 35-65 years, as a primary procedure and, for the younger patients, possible as a salvage procedure.

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Module 6

Functional Cartilage MRI: Current Status & Future Outlook – Siegfried Trattnig (AT)

Osteoarthritis (OA) changes in hyaline articular cartilage are characterized by important changes in the biochemical composition of cartilage. The macromolecular network of cartilage consists mainly of collagen and proteoglycans. Normally, the collagen network is highly organized, serves as the tissue's structural framework, and is the principal source of tensile and shear strength. Glycosaminoglycans (GAGs) are repeating disaccharides with carboxyl and sulfate groups attached to the larger aggrecan molecule (proteoglycan) that is part of the extracellular matrix network of cartilage. GAG molecules possess considerable net negative charge and confer compressive strength to the cartilage. Loss of GAGs and increased water content represent the earliest stage of cartilage degeneration, while the collagenous component of the extracellular matrix still remains intact. Several MR imaging techniques are available that enable detection of biochemical changes that precede the morphologic degeneration in cartilage. All of these techniques attempt to selectively demonstrate the GAG components and/or the collagen fiber network of the extracellular matrix and are usually summarized as "compositional imaging" of cartilage.

After cartilage repair surgeries, a regeneration of cartilage in the defect area should be visualized and quantified in the follow-up. While morphological imaging can only assess the filling of the defect by repair tissue, its integration and surface as well as structure of repair tissue and the subchondral bone using the semiquantitaive scoring system (MOCART), only compositional imaging can provide quantitative information of the biochemical status of the repair tissue in the follow up.

Delayed Gadolinium enhanced MRI of Cartilage (dGEMRIC)
The dGEMRIC and sodium (23 Na) MR imaging techniques are based on similar principles, with positive sodium ions being attracted by the negatively fixed charged density of the GAG side chains. These electrostatic forces are responsible for a direct relationship between the local sodium concentration and fixed charged density with a strong correlation between fixed charged density and GAG content. dGEMRIC is based on the fact that GAGs contain negatively charged side chains, which lead to an inverse distribution of negatively charged contrast agent molecules (eg, gadolinium) with respect to GAG concentration. Drawbacks of this technique are the need to use a double dose of a gadolinium-based contrast agent (0.2 mmol per kilogram of body weight) and the requirement for a delay between intravenous administration of the agent and the start of the MR examination (usually 60–90 minutes) to allow complete penetration of the contrast agent into the cartilage. Varus malalignment is associated with a lower dGEMRIC index on the medial side, while the opposite trend is evident in valgus malalignment. Correlations between dGEMRIC index and pain, as measured by the Western Ontario and McMaster Universities Arthritis Index, were evident in patients with hip dysplasia. dGEMRIC studies have demonstrated that moderate exercise can improve knee cartilage GAG (estimated by T1 in the presence of gadopentetate dimeglumine) in patients at high risk for OA. In patients with an injury to the anterior cruciateligament, lower GAG concentrations were found in the medial compartment of the femoral and tibial articular cartilage of the injured knee when compared with the contralateral (uninjured) knee. In patients with femoroacetabular impingement, correlations were observed between dGEMRIC index, pain, and a angle, suggesting that hips with more femoral deformity may show signs of early OA. Using dGEMRIC in several studies the maturation of cartilage repair tissue after different types of repair surgery with respect to the development of GAG could be monitored.

T2 and T2* mapping
T2 mapping has been used to describe the composition of hyaline articular cartilage in the knee joint on the basis of collagen structure and hydration. In addition to the transverse relaxation time (T2) of articular cartilage, T2* relaxation measures have recently been investigated for depiction of the collagen matrix. In healthy articular cartilage, an increase in T2 values from deep to superficial cartilage layers can be observed; this is based on the anisotropy of collagen fibers running perpendicular to cortical bone in the deep layer of cartilage. Therefore, zonal evaluation of articular cartilage is important in T2 analyses. Analyses of T2 relaxation times in the knee have been performed previously, usually at 1.5 T or, more recently, 3.0 T, demonstrating the ability to depict abnormalities before there is evident morphologic change. In vivo MR imaging studies have demonstrated that cartilage T2 values are related to age. Cartilage T2 values seem to be associated with the severity of OA, and there are variations between tibial and femoral cartilage T2. A significant correlation between patellar cartilage T2 and the severity and grade of cartilage and meniscus lesions has been demonstrated. Subjects with high activity levels had significantly higher prevalence and grade of abnormalities and higher T2 values than did subjects with low activity levels.

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In cartilage repair tissue with a mean value of one year after surgery the T2 values in repair tissue were similar to normal cartilage and it could be demonstrated that the visualization and quantification of zonal T2 was a good marker for an organization of the collagen fiber network of repair tissue in the follow up.

Sodium imaging

The major advantage of sodium MRI in musculo-skeletal applications is that it is highly specific to glycosaminoglycan content and, since the sodium from surrounding structures in the joint is low (<50mM), articular cartilage can be visualized with very high contrast without the requirement for any exogenous contrast agent such as that in dGEMRIC. The recent proliferation of 7 T whole-body MRI scanners in clinical research centers offers a significant impact on sodium MRI and its potential for clinical use. Since SNR scales linearly with increasing field strength and the lack of B1 penetration and Bo susceptibility that pose problems with proton imaging, sodium MRI can be particularly advantageous at higher fields. The low gyromagnetic ratio of sodium also means significantly lower power deposition compared with proton imaging and thus reducing SAR problems at 7T. Although sodium MRI has high specificity and does not require any exogenous contrast agent, it does require special hardware capabilities (multinuclear) and specialized RF coils.

With the application of a 7T whole body system and a modified 3D GRE optimized for sodium imaging and dedicated multi-element sodium coils several clinical studies could be performed: In a small group of 12 patients after matrix-associated autologous chondrocyte transplantation (MACT) sodium imaging allowed to differentiate between sodium content and hence GAG in the transplants compared to native, healthy cartilage. In all patients, the sodium SNR was lower in the repair tissue compared to healthy cartilage. A good correlation between sodium imaging and dGEMRIC in the quantification of GAG content was found in patients after MACT.

In another study 18 patients after different cartilage repair surgery (9 bone marrow stimulation (BMS) and 9 MACT patients) matched with age, postoperative interval and defect location were examined with sodium imaging. Sodium SNR was significantly lower in BMS and MACT repair tissue, compared to reference cartilage. Sodium SNR was significantly higher in MACT than in BMS repair tissue. Similar studies in patients after long term autologous osteochondral transplantation (AOT) in which hyaline cartilage is transplanted and in patients after patella dislocation have demonstrated the potential of sodium imaging in the detection of early stages of cartilage degeneration.

Chemical Exchange Saturation Transfer (gagCEST)

Chemical exchange saturation transfer (CEST) imaging have recently been presented as a technique with the potential to measure PG content in cartilage. These technique exploits the biochemical properties of GAG, i.e., the chemical exchange of labile protons with bulk water (gagCEST). It was shown that labile –NH (δ=3.2 ppm offset from the water resonance) and –OH (δ=0.9 to 1.9 ppm) protons of GAG can be used as CEST agents through selective saturation of their resonance signals (16). This selectivity is also the fundamental difference between gagCEST and T rho relaxation, with the latter being caused by a sum of non-distinguishable exchange effects.

Recent studies aimed mostly at general optimization of gagCEST imaging techniques, but also the feasibility of gagCEST imaging in patients was demonstrated at 7 Tesla. In the latter study, a strong correlation was found between gagCEST results and sodium imaging, which is a sensitive and highly specific method to determine cartilage GAG content at 7 Tesla.

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Module 7 – ICRS Generation Next Free Paper Session

7.1 *Clinical comparison of Matrix-encapsulated autologous chondrocyte implantation (MECI) to treat chondral defects in the knee with versus without other previous treated lesion.*

Presenter: Reynaldo Arredondo-Valdés, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra", Sports Orthopedics and arthroscopy, Mexico Reynaldo H. Arredondo-Valdés, Anell Olivos-Meza, F. Enrique Villalobos-Córdoba, Socorro Cortés-González, Francisco J. Pérez-Jimenez, J. Clemente Ibarra_Ponce de León

Purpose: To compare the clinical and image effect of MECI to treat knee chondral defects isolated and associated to another previous-treated lesion. **Methods:** Prospective cohort. Patients underwent to MECI without any other associated lesion (Only-Chondral Defect Group or OCDG) and them which lesion were diagnosed in a previous treatment of another lesion (Previous-Treated Lesion Group or PTLG). Follow-up was performed with clinical scores and T2-Mapping-MRI before surgery and 6, 12, 24, 36, 48 and 60 months post-op. **Results:** Fifty-two patients were included with an average age of 35±9.01 years. 20 patients included to OCDG and 32 patients included to PTLG. Average Tegner activity score of OCDG compared to PLG was 7.11±1.56 vs 7.09±1.93 before lesion (P=0.983), 3.00±2.59 vs 3.66±2.68 before surgery (P=0.420), ascending to 5.71±2.21 vs 5.00±2.45 at 60 months (P=0.887). Average Lysholm knee scoring was 57.33±21.54 vs 51.34±21.05 before surgery (P=0.343) ascending to 78.17±20.31 vs 86.33±18.33 at 60 months. Carti-Gram miliseconds relaxation time for native cartilage was 36.88±6.19 vs 37.41±8.74 (P=0.373) at 3 months post-op and for implant was 52.92±6.78 vs 55.41±15.55 (P=0.361). At 60 months post-op native cartilage was 40.72±6.60 vs 39.02±5.55 (P=0.550), implant was 40.02±10.07 vs 44.27±8.69 (P=0.338). **Conclusion:** MECI produces clinical and MRI-image improvement both as a single treatment and in conjunction with another previous treatment.

7.2 *Chondrogenic differentiation of whole fat tissue: A novel approach to cartilage regeneration*

Presenter: Claudia Eder, Orthopaedic Hospital Speising, Spine Center / Spine Surgery Department, Austria Eder C., Schildboeck S., Klughofer J., Ogon M.

Purpose: Despite tremendous in vitro achievements, the clinical breakthrough towards a routine application of cartilage tissue engineering is still missing. Scaffold materials available so far have not been able to produce sufficiently long lasting hyalinous cartilage. As adipose tissue contains stem cells in a collagen and glycosaminoglycan-containing matrix, the chondrogenic differentiation of total fat tissue might pose an alternative to scaffold development. **Materials & Methods:** Fat tissue biopsies were cultured either in chondrogenic differentiation medium or in control cell culture medium without previous isolation of stem cells. Histology, Collagen and glycosaminoglycan synthesis and mechanical strength were evaluated. **Results:** The chondrogenic grafts showed a smooth surface remodelling. Histology resembled the morphology of articular cartilage with positive Alcian Blue and Safranine O staining. Average glycosaminoglycan content was 16,92 µg/mg tissue versus 1,92µg/mg in the control samples (p<0,0001). Total collagen content was 8,76 µg/mm versus 0,27 µg/mm in the controls (p<0,0001), and durometrical hardness was 5 Shore versus 0,25 Shore in the controls (p<0,0001). **Conclusion:** Total adipose tissue can be successfully differentiated towards a tissue of a chondrogenic phenotype and shows a potential to create a fully autologous, scaffold free cartilage transplant.

Module 7

7.3 Development of scaffold-free tissue-engineered construct (TEC) with chondrogenic differentiation capacity using rabbit embryonic stem cell-derived mesenchymal stem cells

Presenter: Yu Moriguchi, Osaka University Graduate School of Medicine, Orthopaedic Surgery, Japan
Yu Moriguchi1, Kazunori Shimomura1, Takeshi Teramura2, Ryota Chijimatsu1, Morito Sakaue1, Norihiko Sugita1, Akira Myoui1, Hideki Yoshikawa1, Norimasa Nakamura1, 3 1Osaka University Graduate School of Medicine 2Kinki University Faculty of Medicine 3Osaka Health Science University, Osaka, Japan

Purpose: The purpose of the present study is to develop a scaffold-free three-dimensional tissue-engineered construct (TEC) from embryonic stem cells (ESCs) and to investigate its feasibility to facilitate cartilage repair, in comparison with that of prior art TEC derived from mesenchymal stem cells (MSCs). **Materials & Methods**: Rabbit ESC-based TEC (eTEC) was generated by hypoxic stepwise differentiation via ESC-derived MSCs (eMSCs). Quantitative PCR, glycosaminoglycan assay, and histological assessment were performed in pre- and post- chondrogenic conditions. Gene expression of eMSCs was further assessed based on microarray analysis. The rabbit synovial MSCs and TEC derived from them (sTEC) served as control. TECs combined with beta-TCP were implanted into 5 mm diameter, 6mm deep osteochondral defects created on the femoral grooves of skeletally mature rabbits, which were sacrificed at 4, 8, and 24 weeks postoperatively. **Results**: The in vitro results demonstrate the analogy between both TECs except that eTEC has a significantly higher chondrogenic potential than sTEC. Microarray analysis showed that tumor-related genes were attenuated over time in chondrogenic differentiation of eMSCs. Implantation of the composite of eTEC leads to cartilage repair superior to that of sTEC both in quality and speed. **Conclusion**: TEC can be an applicable local deliver system with efficacy and safety in ESC-based cell therapy for cartilage repair.

7.4 Mechanical compression enhances cartilage matrix synthesis of the expanded osteoarthritic chondrocytes

Presenter: Pan Pan Chong, University of Malaya, Department of Orthopaedic Surgery, Malaysia
Pan Pan Chong1, Ponnurajah Panjavarnam1, Wan Nor Hanis Wan Ahmad1, Chee Ken Chan1, Belinda Pingguan-Murphy2, Tunku Kamarul1 1National Orthopaedic Centre of Excellence for Research and Learning (NOCERAL), Department of Orthopaedic Surgery, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. 2Department of Biomedical Engineering, Faculty of Engineering Building, University of Malaya, Kuala Lumpur 50603, Malaysia

A study was conducted to evaluate of the biosynthesis of isolated osteoarthritic chondrocytes to varying dynamic compressive strain and loading duration. The proximal tibial was resected as a single osteochondral unit during total knee replacement surgery from patients (N=20). Scanning Electron Microscope (SEM) and atomic force microscopy (AFM) were used to measure the microstructure of cartilage interface. The isolated osteoarthritic chondrocytes were seeded with 3% agarose, subjected to 10% and 20% uniaxial dynamic compression for 4- and 8-days using bioreactor system. The deformed cellular lacunae in the osteoarthritic cartilage was detected by SEM. AFM analysis demonstrated that collagen fibrils in the extracellular matrix region of normal cartilage were denser and shorter while in osteoarthritic cartilage, they were longer and less dense. The compressed osteoarthritic chondrocytes showed more intense and broader deposition of collagen type VI compared to control. The expression of collagen type VI was directly proportional to the duration of compression in which 8 days compression was significantly higher than 4 days compression. The 20% compression showed significantly higher intensity compared to 10% compression in 4- and 8-days. It is apparent that the biosynthetic activity of human chondrocytes from osteoarthritic joints can be enhanced using selected compression regimes.

Module 7

7.5 Metabonomic profiling of early and late stage knee osteoarthritis synovial fluid

Presenter: Nidal Khatib, Cardiff University, Pathophysiology and Repair, United Kingdom
Nidal Khatib, Andreas Papageorgiou, Stephen Fairhurst, Christopher Wilson, Rhys Williams, Cathy A Holt, Deborah J Mason

Purpose: The purpose of this study was to use Nuclear Magnetic Resonance (NMR) spectroscopy to generate multiparametric metabolite concentration profiles of knee joint synovial fluid from chondral lesion and severe osteoarthritic (OA) patients, ultimately to identify diagnostic and prognostic metabolic biomarkers of lesion progression. **Materials & Methods:** Joint fluid was aspirated from 9 patients with focal cartilage lesions (ICRS grade II/III), and 9 patients with severe OA (KL grade III/IV). 1H 500MHz NMR spectroscopy was performed and relative intensities of spectral signals of glutamate, glutamine, creatine, glucose, alanine, lactate, phenylalanine, leucine, isoleucine, citrate, and valine were compared. Students t-tests and principle least squares discriminant analysis was used to identify strongest discriminatory metabolites between cohorts. **Results:** T-tests revealed there was significantly higher ($p<0.05$) levels of glutamate in severe OA fluids compared to chondral lesion fluids. Discriminant analysis revealed the strongest significant ($p<0.05$) discriminators between groups were glutamate, citrate and creatine. **Conclusions:** These results suggest glutamate, a neurotransmitter responsible for joint pain and inflammation, is the strongest candidate for a metabolic biomarker of joint lesion progression to OA. Changes in citrate and creatine levels may be due to energy dysregulation of joint tissues, and they could potentially be candidates if investigated further.

7.6 Effects of Micronized Cartilage Matrix on Cartilage Repair in Osteochondral Lesions of the Talus

Presenter: Cassandra Lee, University of California at Davis, Orthopaedic Surgery, United States
Sohni Singh, Connor Nathe, Evan Lian, Jeff Lu, Alvin Shieh, Dominik Haudenschild PhD, Cassandra A. Lee MD, Eric Giza MD, Christopher Kreulen MD

Introduction: A promising technique for treatment of osteochondral lesions of the talus (OLT) uses an acellular micronized cartilage matrix (MCM), BioCartilageâ to fill the lesion. Marrow cells from microfracture are thought to repopulate MCM and form hyaline-like cartilage. The effect of MCM on bone marrow cells remains untested. We hypothesized that adding bone-marrow derived stem cells to MCM would result in chondrogenic differentiation. Verifying combination of matrix and cells resulting in cartilage regeneration would affirm a reliable, one-step treatment of OLTs. **Methods:** Human bone marrow-derived stem cells were expanded in monolayer culture. Stem cells were mixed with MCM at the manufacturer recommended ratio for reconstitution. 2x106 Cells were well-cultured with MCM in chondrogenic media. Cell viability, gene expression, and histology were performed after 3 weeks. **Results:** Rehydrating MCM prior to addition of cells was required for cell viability. The combination of stem cells and MCM produced a cohesive structure, with 98% cell viability. Stem cells alone did not form viable constructs. **Discussion:** MCM is a suitable scaffold for the chondrogenic differentiation of bone marrow-derived stem cells, given that the matrix is first rehydrated before adding cells. Preliminary results suggest cartilage matrix deposition occurred surrounding the cells after 3 weeks of chondrogenic culture.

Module 7

7.7 Articular Cartilage Repair with Mesenchymal Stem Cells following Chondrogenic Priming in Normoxic and Hypoxic Conditions: A Preclinical Pilot Study

Presenter: Troy Bornes, University of Alberta, Division of Orthopaedic Surgery, Canada
Troy D. Bornes, Adetola B. Adesida, Nadr M. Jomha

Purpose: This study assessed a novel protocol that involved transplantation of bone marrow mesenchymal stem cells (BMSCs) into articular cartilage defects in sheep following a short period of chondrogenic priming. The impact of oxygen tension during pre-implantation culture was also investigated. **Methods:** Ovine BMSCs were isolated, expanded, seeded within a hyaluronic acid scaffold, primed ex vivo in chondrogenic medium for 4 days under normoxia (21% oxygen) or hypoxia (3% oxygen), and implanted within full-thickness cartilage defects in the femoral condyles of 5 sheep. Pre-implantation priming was evaluated using RT-qPCR. Six months after implantation, histological assessment was performed on tissues. **Results:** Priming of pre-implantation BMSCs resulted in increased expressions of collagen II and aggrecan in comparison to unprimed BMSCs ($p<0.05$). BMSC-seeded scaffolds produced proteoglycan-rich cartilaginous tissues. Defects implanted with BMSC-seeded scaffolds had larger repair tissue areas, percentages of defect fill and O'Driscoll histological scores than cell-free controls ($p<0.05$). A difference in histological scores was not found between tissues derived from hypoxia- and normoxia-cultured BMSC-seeded scaffolds ($p=0.90$). **Conclusion:** We demonstrate that priming for a short period (4 days) improves the chondrogenic gene expression profile of BMSCs, chondrogenically primed BMSCs produce superior cartilaginous tissue to cell-free controls, and oxygen tension during pre-implantation culture does not consistently modulate repair tissue formation in this model.

7.8 Peptidomic Analysis of Cartilage and Subchondral bone from OA patients

Presenter: Birgitta Gatenholm, Clinical Sciences, Orthopedics, Sweden
Birgitta Gatenholm, Johan Gobom, Tobias Skillbäck, Kaj Blennow, Henrik Zetterberg, Mats Brittberg

Purpose: In patients with cartilage lesions and osteoarthritis, pain is one of the major reasons for seeking medical care, yet the knowledge on the pain origin is very limited. Studies suggest pain is affected both by mechanisms involving neuropeptide signaling, peripheral and central sensitization but also psychological factors altering the pain perception. The purpose of this study was to develop a method for directly analyzing bone samples and enablingidentification of peptides that may play a role in pain development. **Materials and Methods:** Femur condyle bone samples from zones with manifest cartilage damage and macroscopically healthy zones were collected from 6 patients undergoing total knee arthroplasty. The samples were demineralized, marked with Tandem Mass Tag labeling and analyzed using liquid chromatography coupled with tandem mass spectrometry. **Results:** Using peptidomics, 6,292 endogenous peptides were identified. 248 peptides differed significantly from damaged zones compared to macroscopically healthy zones. None of the neuropeptides identified differed significantly. However the findings of SHANK2 and TENASCIN-R were interesting with their special connections to chronic pain and neuron protections. **Conclusions** This pilot study shows promising results for the usage of peptidomics to identify endogenous peptides that may play a role in the pain mechanisms involved in OA.

7.9 Four Years Follow-up of Arthroscopic Meniscal Allograft Trasplantation: the chondroprotective effect evaluated by T2-Mapping

Presenter: Anell Olivos-Meza, Instituto Nacional De Rehabilitacion, Orthopedic Sports Medicine And Arthroscopy, Mexico Olivos-Meza Anell, Cruz-López Francisco, Llano-Rodríguez Tomas, Almazán-Díaz Arturo, Ibarra Clemente.

Purpose: to evaluate quantitatively by T2-mapping the chondroprotective effect of MAT at 4-years follow-up. **Material & Methods:** Twenty-one patients with medial post-meniscectomy syndrome with ages 18 to 50 years. Fresh frozen (FF) and gamma irradiated (GI) grafts were used. All MAT were performed arthroscopically. Clinical evaluation was performed pre-op and at 12, 24, & 48 post-op. T2-mapping to evaluate the chondroprotective effect was done. **Results:** A total of 21 patients were included with 22 MAT procedures (12 FF & 10 GI); mean age 31 years. Clinical scores improved significantly from pre-op to 4 years follow-up: IKDC (0.001), Lysholm (0.001), Tegner (0.001); KOOS: symptoms (0.001), pain (0.002), sports (0.001), & Quality of life (0.001). T2-mapping evaluation in femur and tibia at pre-op (35.41, 36.55) compared to 12m (37.17, p=0.110 & 34.33, p=0.488) and 24m (38.47, p=0-098 & 38.47, p=0-169) were not significant different; pre-op values compared to 36m (39.95, p=0.002 & 41.35, p=0.013) and 48m (40.33, p=0.003 & 41.49, p=0.003) had significant increase. **Conclusions:** Although T2-mapping values showed significant increase after 4 years of meniscal allograft transplantation those values can not be considered as cartilage degenerative changes due to are still into the range of healthy cartilage.

Module 8 – Panel Discussion: The Disease Continuum

Is it Time for Joint Preservation/Cartilage Repair Surgery to have a place in traditional OA Treatment Algorithms? – William Bugbee, D'Arcy Roche

As we enter the third decade of the existence of the International Cartilage Repair Society, there is an opportunity to reflect on how the field of cartilage repair has evolved. We have made tremendous scientific and technical advances in clinical and surgical application of our treatments and it may be argued that many interventions have moved from "niche" to "standard of care". Furthermore, we now have long-term clinical outcome data on many "joint preserving" procedures lending ever more support to the validity of cartilage repair surgery.

We have also made great progress in the understanding of the implications and natural history of injuries and diseases we are treating. Better understanding of the epidemiology and pathophysiology of articular cartilage (and meniscal) injury and disease has led to a reappraisal of the disease continuum extending from cartilage/joint injury to "advanced" osteoarthritis.

While many of us are enthusiastic scientists and practitioners of cartilage repair, championing its efficacy, we are also humbled by the complexity and difficulty of effectively treating a synovial joint afflicted with degenerative arthritis, like so many of our colleagues in other specialties have found.

So, as the field of "cartilage repair" inexorably merges with the treatment of "osteoarthritis" it is time to examine whether or not cartilage repair and restoration merits a place in current standard treatment (practice) guidelines of osteoarthritis? Using the knee as a model example, the answer requires a thoughtful analysis of many potentially controversial questions:

1. Is the current definition of osteoarthritis adequate and does it help characterize the natural history of cartilage and meniscal deficiency. Should all cartilage injuries be considered "early OA"? Will a redefinition allow for more comprehensive treatment guidelines to be developed?
2. What are the indications and efficacy of cartilage repair procedures both in symptom management and effect on natural history? Is cartilage repair superior to (palliative) medical management? And in which patients?
3. Are current knee osteoarthritis practice guidelines incomplete or even biased against surgical treatment of arthritis? Why?
4. Does the ICRS have a mandate to fundamentally restructure the discussion around management of osteoarthritis and provide leadership on the role of early (surgical) intervention?

A brief review of representative knee OA treatment guidelines is instructive:
Feuerstein, in a systematic analysis of the quality of scientific evidence and conflicts of interest in knee practice guidelines reported that 211 of the 214 OA treatments listed were palliative (symptom management) while only 3 directly treated the condition and provided long-term efficacy. OARSI recommends 25 treatment options divided into 4 groups: general, non pharmacological, pharmacological and surgical. The surgical options include only lavage/debridement, joint fusion, and osteotomy, partial and total joint replacement. There is no mention of cartilage restoration. 20/22 (87%) of the OARSI guideline authors were rheumatologists, only 2 were orthopaedists. The AAOS guidelines (91% of authors were orthopaedists) were developed from an analysis of the OARSI guidelines. The AAOS endorsed 5, judged 8 as inconclusive, rejected 6 (including HA, glucosamine and joint lavage and debridement). Of the 5 surgical treatments only osteotomy was given a limited "yes" endorsement (joint replacement was not addressed).

The ICRS is the preeminent organization devoted to cartilage repair and joint preservation. As such we have an obligation to participate in the important discussion about the management of cartilage injury and subsequent osteoarthritis. The decades long work of scientists and clinicians associated with the ICRS has led to advances in the treatment of cartilage injury and early arthritis that are valuable treatments for patients, yet not reflected in the standard of care guidelines published by other medical organizations. It is suggested by the authors the ICRS support an initiative to identify and promote the role of cartilage repair in the management of OA.

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- Stimulates Cartilage Cell Proliferation[4^]
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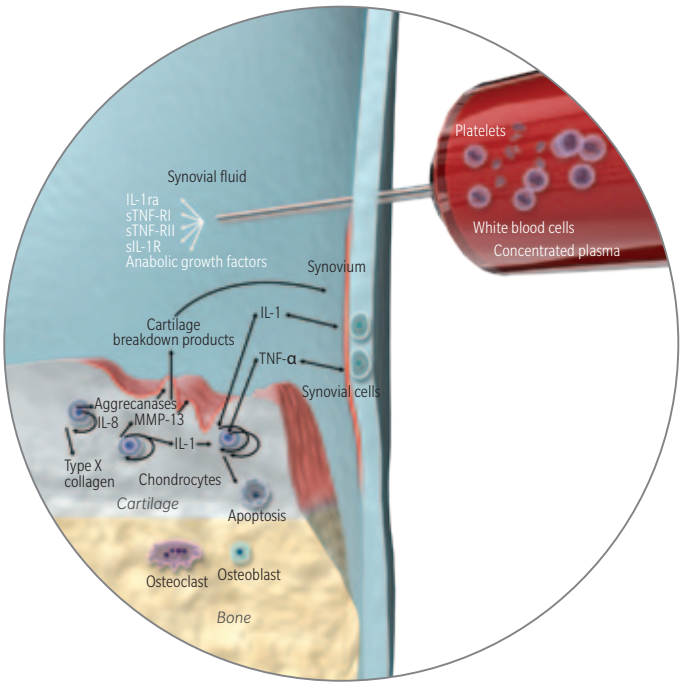

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^ Cell culture assays are not necessarily indicative of clinical outcomes.

ICRS Summit Poster Presentations

P1 – Recovery Effect of Normal Synovium in Response to Cartilage Insult

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Purpose This study aimed to investigate the effect of normal synovium on the healing response of damaged cartilage, which remains unknown. Methods Fresh human tali and femoral condyles with normal gross morphology were used. Cartilage explants from both joints and grossly normal synovium from the knee joint were harvested and randomly assigned to one of four treatment groups: (1)non-treated cartilage without synovium; (2)non-treated cartilage with synovium; (3)IL-1ß-treated(10ng/ml) cartilage without synovium; (4)IL-1ß-treated(10ng/ml) cartilage with synovium. Samples from cartilage explants and synovium were collected at 0, 2, and 14 days and assessed for Live-Dead assay and histology. Results There were no significant differences in the %Live cells between non-treated cartilage with or without synovium. While neither IL-1ß-treated group fully returned to the baseline %Live cells in Group-1's superficial zone(86.7±4.5 %), Group-4 explants exhibited a significantly greater %Live cells within the superficial zone than Group-3 explants after two days(74.0±4.4 %, 48.7±7.9 %, $p<0.01$). Group-4 explants continued to trend towards greater viability than Group-3 explants at day 14(77.4±8.9 %, 59.2±18.4%, $p=0.17$). On histological analysis, Group-3 explants revealed pronounced hypocellularity and reduced matrix staining when compared to Group-4 explants. Conclusion When applied to damaged cartilage, healthy synovium improves both cell viability and histological features, suggesting a potential recovery mechanism for damaged cartilage.

P2 – Adipose-derived stem and chondrocytes share some stemness features and a similar behavior after an inflammatory stimulus but showed a better anti-inflammatory/-catabolic potential

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Purpose: to investigate stemness and anti-inflammatory features of articular chondrocytes (ACs) in comparison with adipose-derived stem cells (ASCs). Materials & Methods: Pair matched ACs and ASCs from hip joint (n=8) were characterized for their clonogenic ability, immunophenotype, differentiation potential, and stem cell marker expression. After IL-1b stimulation, the release of IL-6, IL-1Ra, TNFa and expression of VEGFA, TGFB1, MMPs (1-3-13) and TIMPs (1-3) were evaluated. Results: ACs showed a very similar expression to ASCs in term of immunophenotype, stem cell markers and clonogenic ability. However, they showed no appreciable ability to differentiate into adipogenic lineage, lower osteogenic-, but higher chondrogenic-differentiation in comparison with ASCs. Higher basal levels of TIMP1-3 and IL-1Ra but lower of TNFa were observed in ASCs in comparison with ACs. Upregulation of MMP1-3-13, VEGFA and IL-6 and downregulation of TGFB were observed after IL-1b treatment in both types of cells. Moreover, ASCs showed an upregulation of IL-1Ra. Conclusion: ACs show several stemness features, demonstrating the presence of a subpopulation of tissue specific progenitors that could be stimulated in situ to promote a more physiological healing process. On the other side the natural anti-inflammatory/anti-catabolic behavior of adipose tissue stem cells could be exploited to further favor tissue homeostasis restoration.

P3 – Evaluation of different commercial hyaluronic acid as vehicle injection for human adipose derived mesenchymal stem cells

Camila Cohen Kaleka Pedro Debieux da Silva Mário Ferretti Eder Zucconi Mariane Secco Moisés Cohen

Purpose: The main purpose of this study is to evaluate, in vitro, the cytotoxicity activity of different commercial brands of hyaluronic acids to be used as vehicle injection for human adipose derived mesenchymal stem cells (AD-MSCs). Material & Methods: AD-MSCs were divided into 7 groups: one control group where AD-MSC where cultivated with phosphate-buffered saline (PBS) and 6 other groups where AD-MSC were cultivated with different commercial brands of hyaluronic acid. AD-MSC viability analysis was performed after 4, 24 and 48 hours in contact with each treatment using trypan staining method on countess automated cell counter (Thermo Fisher Scientific). Results: The results clearly demonstrated a significant difference in cell viability when AD-MSC were exposed to different hyaluronic acids compared to control group. Conclusion: Our data suggest that hyaluronic acid can be used as a vehicle injection for human AD-MSC but caution is needed to choose the best product aiming its future therapeutic application.

ICRS Summit Poster Presentations

P4 – Arthroscopic Cartilage Lesion Preparation Using Standard Curette Technique is Associated with Qualitative Differences About the Defects that are Clinically Relevant

Graeme P. Whyte, Boguslaw Sadlik, Adrian Matlak, Adrian Blasiak, Wojciech Klon, Mariusz Puszkarz

Purpose: To examine the quality of arthroscopic cartilage debridement using curette technique by comparing variations within cartilage lesions prepared in human cadaveric knee specimens. A secondary aim is to determine the effects of surgeon experience on prepared defect characteristics. Methods: Standardized cartilage lesions located to the medial/lateral condyle and trochlea were created within human cadaver knees. Histologic specimens were prepared to examine the verticality of surrounding cartilage walls and the morphologic characteristics of the prepared defects. Characteristics of prepared defects were compared among surgeons of varying experience. Results: Thirty-three specimens were analyzed. There was no association of cartilage lesion wall verticality and surgeon experience. Mean cartilage wall verticality was superior at the rear aspect of the lesion compared to the front aspect ($p<0.001$). Significant variability of prepared defects was identified with respect to the morphology of surrounding cartilage ($p<0.001$), cartilage wall profile ($p=0.016$), debrided lesion depth ($p=0.028$), bone sinusoid access ($p=0.009$), and bone surface profile ($p=0.040$). Conclusions: Arthroscopic cartilage lesion preparation using standard curette technique results in inferior perpendicularity of surrounding cartilage walls at the front aspect of the defect, compared to the rear aspect. There is significant variability of debridement depth using standard curette technique. Surgeon experience did not impact morphologic properties of cartilage lesions prepared arthroscopically using curettes.

P5 – Ageing of the murine and bovine intevertebral disc induces a chondrocyte-like transition in the inner annulus fibrosus that correlates with increased BMP2/GDF5 expression

G.G.H. van den Akker, M. Bakx, A. Rorije, E. Vitters, E.N. Blaney Davidson, P.M. van der Kraan

Purpose: To map age-related changes in histology, cell phenotype and growth factor expression in the intervertebral disc. Materials & methods: Mice (4, 8, 12, 16 and 20 months old, n=20/group) and bovine tail IVDs (1, 3 and 5 years old, n=6/group) were used for histological, biochemical and gene expression analyses. Results: Proteoglycan content of NP and AF tissue peaked in 12 months old mice. The integrity of lamellar AF tissue was decreased in 12 and 20 months old mice. Gene expression was analyzed separately in three anatomical regions of the bovine IVD. COL5A1 and COL12A1 expression was decreased by ageing in NP, iAF and oAF tissue. A reduction in COL2A1, but not ACAN, was found in ageing NP tissue, while the ageing AF showed increased COL2A1 and ACAN expression. Age-related differences were maintained when cells were cultured in vitro. TGFB2 and BMP2 expression were increased in the ageing NP. However, both genes were decreased in the ageing outer AF, which only showed increased GDF5 expression. Conclusion: IVD ageing has opposite effects on NP and AF cell biology. Growth factor expression is differentially regulated in ageing NP and AF tissues. This study has important implications for growth factor mediated IVD repair.

P6 – Interposition of a Cell-Seeded Slow-Degrading Membrane Generates a Stable Osteochondritis Dissecans-Like Lesion in a Large Animal Model

James M. Friedman MD, Mackenzie L. Sennett BS, Marcelo B. Bonadio MD, Blair Ashley MD, Robert L. Mauck PhD, James L. Carey MD

Introduction: The purpose of this study was to assess the durability of a surgically created osteochondritis dissecans (OCD) lesion at 5 and 10 weeks, as well as the impact of fibrous cell delivery on this process. Methods: Osteochondral fragments were created bilaterally in the medial femoral condyles of 16 juvenile Yucatan mini-pigs. Membranes were placed into the defect and the fragment was secured with transchondral sutures. Membranes included collagen (CM), fenestrated poly(ε-caprolactone) (fenPCL), tenocyte-seeded CM, and tenocyte-seeded fenPCL. Defects were analyzed by gross inspection, X-ray, micro-computed tomography (μCT), and histology. Results: Grossly, clear demarcation between fragment and surrounding cartilage was noted in all cases. Tenocyte-seeding significantly increased the degree of non-union at 10 weeks, with a hypercellular fibrous border surrounding the fragment. Tenocyte-seeded CM defects showed subsidence, whereas tenocyte-seeded fenPCL defects remained flush. Discussion: Tenocyte-seeded collagen and fenPCL membranes generated a higher degree of non-union at 10 weeks than acellular membranes. The addition of tenocytes may have resulted in continuous generation of fibrous matrix that eventually replaced the degradable membranes. This study demonstrates that a tenocyte-seeded fenPCL membrane generates an OCD-like lesion in a mini-pig. This animal model will provide a platform to evaluate interventional therapies for OCD treatment.

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P7 – Microarray Analysis of Human Mesenchymal Stem Cells Differentiated to Osteoblasts and Chondrocytes, the role of the small molecule Y-27632
Julio Granados-Montiel, Clemente Ibarra.

Purpose To understand the role of ROCK inhibition using the small molecule Y-27632 during bone and cartilage differentiation using primary human mesenchymal stem cells. Materials & Methods We used a commercially available bone-marrow-derived mesenchymal stem cell line. The cell line was purchased from ATCC® and the catalogue number is PCS-500-012. For chondrocyte induction, Kartogenin was added at a 100-nM final concentration. The ROCK inhibitor Y-27632 was used in the experimental condition at a 10-µM final concentration. For Osteoblast induction, Dexamethasone was added at 1 x 10-6 M final concentration, The ROCK inhibitor Y-27632 was used in the experimental condition at 10-µM final concentration. Results There are two genes that are highly up or down regulated, depending on the culture conditions. These genes are Leptin and DKK1. The former is involved in adipose tissue metabolism, and the latter in the well-known Wnt signalling pathway.Interestingly CXCL super family of Chemokines were up regulated in the cartilage groups. Conclusion After differentiation of mesenchymal stem cells towards bone or cartilage, there are many genes that must be tightly regulated in order to obtain pure populations if the main aim is regenerative medicine.

P8 – Suppression of sterol regulatory element-binding protein-2 ameliorates high-fat diet-induced deterioration of knee cartilage
*Ke Tao, Rujun Li, Chenxi Cao, Ke Yan, Hu Li, Jianhao Lin**

Purpose: To investegate the functional expression of transcription factor of lipid metabolism (SREBP-2) in cartilage from high-fat diet induced obese mouse models. Materials & Methods: Baseline expression of SREBP-2 was detected in the normal and DMM-induced osteoarthritic lesions in the knee joint, while overexpression and suppression effects of SREBP-2 was separately delivered via adenovirus to mice fed with chow or high-fat diet. Results: 1 of 14 normal, 1 of 12 DMM-induced OA mice were increased SREBP-2 compared with 6 of 14 and 9 of 12 littermates treated high-fat diet, while expression of SREBP-2 related genes was measured in 2 of 14, 1 of 14, and 2 of 14 normal, 1 of 12, 1 of 12, and 2 of 12 DMM models, and 6 of 14, 6 of 14, 5 of 14 and 7 of 12, 10 of 12, 10 of 12 to their corresponding models (up to 3.00-, 6.00-, 2.50-, 7.00-, 10.00-, and 5.00- fold difference, respectively, $p \leq 0.010$). Overexpression of the SREBP-2 downregulated the expression of extracellular matrix markers of normal cartilage, while enhanced the type X, I collagen in vitro and in vivo, a finding in the contrary with the suppression of SREBP-2. Conclusion: These findings demonstrate that suppression of SREBP-2 might contribute bio-protective effects upon chondrocytes.

P9 –Relationship between osteoarthritis progression and Vasoactive Intestinal Peptide
Munekazu Kanemitsu, Tomoyuki Nakasa, Yoshiko Shirakawa, Masakazu Ishikawa, Shigeru Miyaki, Nobuo Adachi

INTRODUCTION: Osteoarthritis (OA) is a progressive joint disorder. Subchondral bone plays an important role in cartilage metabolism, and the sensory nerve plays an important role in bone remodeling. Vasoactive Intestinal Peptide (VIP) is one of the neuropeptide and affects bone metabolism. The purpose of this study is to analyze the expression of VIP and evaluate the relation between VIP and OA progression. METHODS: Human's tibia was obtained at the time of total knee arthroplasty. The expression pattern of VIP and the relationship between OA progression and VIP expression were evaluated with histological and micro CT analysis. DMM model mice (control group and VIP antagonist injection group) were scarified at 4 and 8 weeks. These samples were analyzed as the human's sample. RESULTS: In human, a positive correlation was found between BV/TV of subchondral bone and OARSI Grade. Expression of VIP in articular cartilage decreased and in subchondral bone increased as OA progression. Subchondral bone of sever OA, blood vessel and nerve fiber penetrated the tidemark. VIP expressed along with blood vessels and expressed in nerve fiber. In mice, VIP antagonist significantly inhibited OA progression and of subchondral bone sclerosis. Conclusion: VIP is involved in subchondral bone sclerosis and OA progression.

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P10 –The TMSB4 pseudogene lncRNA functions as a competing endogenous RNA to promote cartilage degradation in human osteoarthritis
Qiang Liu, Xiaoqing Hu, Xin Zhang

Purpose Mechanical stress plays a key role in the development of cartilage degradation in osteoarthritis (OA). Nevertheless, the role of long noncoding RNAs in mechanical stress induced regulation of chondrocytes remains unclear. The aim of this study was to explore the function of mechanical stress-related long noncoding RNAs in cartilage. Methods and Materials OA cartilage was isolated from the knee joints of patients undergoing total knee arthroplasty. Microarray hybridization were performed based on the lncRNA Arraystar protocols. Tissue samples were collected from 50 patients and chondrocytes were exposed to cyclic tensile strain (CTS). Results A total of 107 lncRNAs were differentially expressed in damaged cartilage versus intact cartilage. Of these lncRNAs, 51 were up-regulated and 56 were down-regulated in the damaged tissue. The TMSB4 pseudogene, lncRNA-MSR, was up-regulated in the damaged cartilage and was activated in response to mechanical stress. Furthermore, lncRNA-MSR regulated the expression of TMSB4 by competing with miRNA-152 in chondrocytes. Conclusion Our results demonstrated that up-regulation of lncRNA-MSR initiates pathological changes that lead to cartilage degradation, and the inhibition of lncRNA-MSR could represent a potential therapeutic target for OA.

P11 – Changes in cartilage defect and subchondral bone after bone marrow stimulating technique on full thickness articular cartilage defect
Seiju Hayashi, Tomoyuki Nakasa, Masakazu Ishikawa, Shigeru Miyaki, Nobuo Adachi

Purpose This study elucidated the pathological mechanism of cartilage repair after bone marrow stimulating techniques. We also focused on time-course changes in subchondral bone condition. Materials & Methods 2mm x 2mm of full thickness cartilage defect was prepared at the patella groove in 10 week aged rats, and subchondral drilling was applied. The time-course changes in subchondral conditions including diameter of the drilled holes and mineral density were assessed by 3-dimentional micro-computed tomography at 0, 3, 7, 14, and 28 days postoperatively. Osteoclast density was analyzed by counting the number of TRAP positive cells surrounding the drilled holes. Cartilage repair response at the defect was also assessed using Pineda score. Results Diameter of the drilled hole continuously expanded by day-14, and disappeared at day-28. Bone mineral density temporally decreased at day-3, and then increase by day-28. The number of TRAP positive cells increased at day-3, and then returned to normal level. Although blood clot or repair tissue was not detected at the defect by day-3, cartilage repair process started from deep inside the drilled holes. Pineda score showed gradual improvement after day-7. Conclusion Cartilage repair started from drilled holes with simultaneous remodeling of subchondral bone.

P12 – 3D bioprinting of iPSCs to generate cartilage like tissue using chemically modified bio-ink
Alma Forsman, Rocio Castro Viñualas, Erdem Karabulut, Erik Romberg, Duong Nguyen, Daniel A Hägg, Josefine Ekholm, Puwapong Nimkingratana, Camilla Brantsing, Theodoros Kalogeropoulos, Samantha Zaunz, Sebastian Concaro, Mats Brittberg, Anders Lindahl, Paul Gatenholm, Annika Enejder and Stina Simonsson

Purpose: Cartilage lesions can develop into secondary osteoarthritis (OA) and are a worldwide burden. As a prospective treatment for such lesions and the objective of this study is to develop a cartilage prototype by 3D bioprinting of human induced pluripotent stem cells (iPSCs). The benefits by using an established iPSC line are an unlimited cell source with regeneration capacity and OA protective genotype. Materials & Methods: Here we 3D bioprinted iPSCs in alginate/nanocellulose bio-ink and comparing chemically modified nanocellulose bio-ink, to resemble the micro environment found in cartilage tissue. Designing protocols that generates hyaline cartilage from pluripotent cells in vitro is still a challenge, due to that joint formation are late in development and far from the pluripotent state. Toward this end, we used protocols for hyaline-like cartilage generation from iPSCs using combinations of growth factors or co-culture with irradiated chondrocytes. Results: Increased cell density were detected by 2-photon-fluorescence-microscopy within the cartilaginous-like tissue, indicating the importance for good cell survival after printing. Collagen type II could be detected and the pluripotency-marker Oct4 was lost in the cartilage mimics. Improved cartilage generation was achieved in the modified bio-ink. Conclusion: We were able to form cartilage-mimics by 3D bioprinting iPSCs.

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P13 – Osteochondral regeneration using a scaffold-free construct of adipose tissue-derived mesenchymal stem cells made by bio three-dimensional printer with needle-array in pigs.
Daiki Murata, Yoshihiro Kunitomi, Kaori Harada, Dandan Song, Takafumi Sunaga, Koichi Nakayama, Takeshi Sogawa, Makoto Fujiki, and Kazuhiro Misumi

Background: We examined the regeneration of articular cartilage and subchondral bone using scaffold-free constructs consisting of AT-MSCs and fabricated using bio 3D printer with a needle-array. Methods: AT-MSCs were isolated from minipigs and expanded until a sufficient number of cells was obtained. A 3D-printed construct consisting of absolutely 2,900 spheroids that each contained 1.3 x 10^4 autologous AT-MSCs was implanted into an osteochondral defect (diameter 5.2 mm and depth 4 mm) created in the right femoral trochlear groove of each pig. The left femoral defect was the control. At three and six months post-operation, healing was assessed by histology, CT, and MR imaging. Results: The percentages of radiolucent volumes (mm3) at three months compared with those immediately after the surgeries were significantly decreased in the implanted defects compared with the controls. The total scores of a modified 2D-MOCART grading system were significantly increased in the implanted defects comparing to the controls. And also, the average of ICRS histological scores were significantly higher in the implanted defects than in the controls. Conclusions: This is the first report suggesting that implantation of a scaffold-free 3D-printed construct consisting of autologous AT-MSCs regenerates cartilage and subchondral bone within six months in pig.

P14 – Proliferative capacity of human chondrocytes in 3D bioprinted cartilage in vivo – a quantitative analysis
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Abstract. Cartilage repair and replacement is a major challenge in plastic reconstructive surgery. The development of a process, able to create patient specific cartilage framework, would be a major breakthrough. Objective. To quantitatively evaluate, in vivo, the proliferation capacity and cartilage formation ability in mono- and cocultures of human chondrocytes and human mesenchymal stem cells in a 3D bioprinted hydrogel scaffold. Methods. 3D bioprinted constructs (5 x 5 x 1.2 mm) were produced using nanofibrillated cellulose and alginate in combination with human chondrocytes and human mesenchymal stem cells with a 3D extrusion bioprinter. Immediately following bioprinting, the constructs were implanted subcutaneously on the back of 48 nude mice and explanted after 30 and 60 days, respectively and examined morphologically and immunohistochemically. Results and conclusion. After implantation the constructs retained their mechanical properties and were easy to handle. Constructs with human nasal chondrocytes only showed good proliferation abilities and after 60 days 17.2 % of the surface area was covered with proliferating chondrocytes. In constructs with a mix of chondrocytes and stem cells an additional proliferative effect was observed. The chondrocytes produced glucosaminoglycans and collagen type 2. This study shows a technique to create 3D bioprinted cartilage in a clinically relevant setting with human cells in vivo.

P15 – Covalent incorporation of heparin improves chondrogenic tissue formation for 3D bioprinting of photo-curable thiol-ene gelatin based hydrogel bioinks
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3D bioprinting is driving personalised cartilage repair strategies forward. A major challenge in the field lies in designing hydrogel-based materials with both relevant bioink- and chondrogenic properties. This study aimed adopted two different platforms to biofabricate and co-polymerise gelatin and heparin. We investigated the effect of methacryloylation (GelMA) and allylation (GelAGE) of gelatin on physico-chemical properties, shape fidelity, heparin retention, and ability to promote chondrogenic differentiation. Hydrogels were photo-polymerised (30mW/cm2-3min, Ru/SPS, DTT), and mechanical, rheological and biofabrication properties were characterised. Thiolated heparin was incorporated into human articular chondrocyte-laden gelatin hydrogels (15x106cells/ml) and cultured (5w) in chondrogenic differentiation media to assess cell viability, GAG, DNA, matrix deposition, mechanical properties and RNA (collagen I/II, aggrecan, Sox9). GelMA and GelAGE were successfully synthesised for 3D bioprinting of cell-laden hydrogel constructs, displaying high fidelity, viability (>75%) and tailorable stiffness (5-140 kPa). GelAGE displayed significantly

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higher heparin retention (~90%) compared to GelMA (~25%) hydrogels, reflecting the potential advantages of the step-growth thiol-ene polymerisation. Furthermore, all constructs supported long-term viability, with incorporation of heparin yielding significantly greater differentiation capacity compared to gelatin hydrogels alone. In conclusion, GelAGE can be applied as a cell-instructive bioink to enhance chondrogenesis, with tunable properties adaptable to different bioprinting platforms, as compared to commonly used gelatin-based bioinks.

P16 – Arthroscopic Treatment of Patellar and Trochlear cartilage lesions with Matrix Encapsulated Chondrocyte Implantation versus Microfracture: Quantitative Assessment with T2-Mapping at 4-years follow-up
Olivos-Meza Anell, Arredondo-Valdés Reynaldo, Villalobos Enrique, Almazán Díaz Arturo, Pérez-Jiménez Francisco, Ibarra Clemente

Purpose: To compare T2-mapping results over a 4-year period of patients with cartilage lesions in patella and trochlea comparing two arthroscopic techniques in a randomized clinical trial. Material and Methods: Seventeen patients (ages 18-55 yo) with symptomatic full-thickness cartilage lesions on either patella or trochlea were randomized into Matrix Encapsulated Chondrocyte Implantation (MECI) or Microfracture (MF). Both procedures combined cartilage restoration procedures with unloading/realigning techniques. Clinical assessment and T2-mapping-MRI were evaluated at 3, 12, 24 and 48 months. Results: T2-mapping values improved significantly over time in MECI compared to MF at 24-months (39.35 vs 50.44, p=0.007) & 48-months (36.54 vs 48.37, p=0.005). However, when comparing control values to MECI no significant difference was found at 12 (p=0.714), 24 (p=0.175) and 48-months (p=0.097). MF values never reach control T2-mapping values. Clinically no significant difference was observed between groups for any score at 3, 12, 24 & 48-months follow-up (p>0.05). Conclusions: Clinically both techniques improved significantly over the time. However, quantitative assessment showed that only new-formed tissue with MECI technique improves significantly since 12-months post-operatively and maintain stable values compared to native cartilage until 48 months follow-up. MF results never were comparable to those native values.

P17 – Platelet-Rich Plasma Intra-articular Knee Injections Versus Viscosupplementation: Long-term Results of A Randomized Controlled Trial.
Giuseppe Filardo, Berardo Di Matteo, Francesco Tentoni, Filippo Selleri, Alessandro Di Martino, Maurilio Marcacci, Elizaveta Kon.

PURPOSE: To compare the long-term clinical outcome of intra-articular injections of either Platelet Rich Plasma (PRP) or Hyaluronic acid (HA) to treat knee degenerative pathology. METHODS: 167 patients with unilateral symptomatic knee with history of chronic pain or swelling and imaging findings of degenerative changes underwent 3 weekly injections of either PRP or HA and were prospectively evaluated basally and then at 2, 6, 12, 24 and mean 64.3 (+- 7.8) months of follow-up using IKDCsubj, KOOS, EQ-VAS, and Tegner scores. RESULTS: Both treatments were effective in function and symptoms: IKDCsubj score in PRP rose from 52.4±14.1 to 66.2±16.7 at 12m (p<0.0005), in HA group from 49.6±13.0 to 64.2±18.0 at 12m (p<0.0005). Stable results were documented up to 24 months, a slight not significant decrease was observed in both treatments at the final 64.3 months' evaluation. The comparative analysis showed no significant inter-group difference at any follow-up evaluation in any of the clinical scores, except for the rate of re-intervention at 24m which was significantly higher in HA group (38.2% vs 21.5%, p=0.034). CONCLUSIONS: PRP does not provide a superior clinical improvement with respect to HA, and therefore it should not be preferred to viscosupplementation as a first line injective treatment of patients affected by knee cartilage degeneration and osteoarthritis.

P18 – Treating Osteoarthritis with an Autologous Anti-Inflammatory Protein Solution Yielded a Favorable Safety Profile and Significant Pain Relief in an Open-Label Pilot Study
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Purpose: The objective of this study was to assess the safety of the output of the Autologous Protein Solution (APS) kit in patients with knee osteoarthritis. Secondarily, APS effectiveness was evaluated using the Western Ontario and McMaster Universities Arthritis Index(WOMAC). Materials and Methods: This study was conducted under an Investigational Device Exemption (https://clinicaltrials.gov/ct2/show/NCT02262364). APS was prepared using the nSTRIDE® APS Kit (Zimmer Biomet) and injected intra-articularly immediately after preparation. Safety was assessed by adverse events (AEs), injection-site assessments, and knee examinations. Effectiveness was assessed by WOMAC questionnaires. Results: 11 patients were enrolled in this study. Sufficient blood could not be drawn from one patient and they were withdrawn. Minor AE were experienced by 7 subjects(63.6%). There was one severe AE (diverticulitis) unrelated to the device or procedure. One subject had one AE that was judged 'likely' to be procedure related (arthralgia / musculoskeletal discomfort). All other AE were unrelated to the device or procedure. WOMAC pain scores improved

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significantly over the study(ANOVA, p < 0.0001, 12.0 ± 1.2 - before injection, 3.3 ± 2.9 1 - year post-treatment, 72.5% WOMAC pain improvement). Conclusions: A single APS injection yielded a safety profile that compares favorably to other intra-articular therapies.

P19 – Quality of Arthroscopic Cartilage Defect Preparation in the Human Knee is Dependent on Technique and Instrumentation
Graeme P. Whyte, Boguslaw Sadlik, Adrian Matlak, Mariusz Puszkarz, Wojciech Klon, Martin Wiewiorski

Purpose: To compare the morphologic properties of cartilage defects in the human knee prepared by standard curette technique to a modified technique using specialized instruments. Methods: Cartilage defects were prepared arthroscopically in fresh human knee cadavers using either a standard curette technique (ST), or a technique using specialized instruments (CT). Osteochondral blocks containing prepared lesions were harvested and a comparative histologic analysis of cartilage defect morphologic properties was performed. Results: There were 69 cartilage lesions prepared by either ST or CT technique that were analyzed. Mean angle deviation from vertical of the cartilage wall at the rear aspect of the lesion for the ST group was 12.9°, compared to 9.3° in the CT group (p=0.219). Mean angle deviation from vertical at the front aspect of the prepared lesions was 29.2° in the ST, compared to 7.1° in the CT group (p<0.001). Objective debridement depth was more likely to be achieved using the CT technique compared to ST (p<0.001). Conclusions: The perpendicularity of surrounding cartilage walls of arthroscopically prepared cartilage defects is superior using a specialized angle-specific instrument technique, compared to standard curette technique at the front aspect of the lesions. Preparing cartilage lesions to the level of subchondral bone is more consistently achieved using specialized instruments compared to standard curettes.

P20 – Cartilage Repair Using Hyaluronic-Acid Based Scaffold Embedded with Multipotent Mesenchymal Stem Cells Sourced from Bone Marrow Aspirate Concentrate: A Multicenter Experience
Graeme P. Whyte, Alberto Gobbi, Boguslaw Sadlik, Marc Castro

Purpose: To examine clinical outcomes of cartilage repair in the knee using hyaluronic-acid based scaffold embedded with bone marrow aspirate concentrate (HA-BMAC) performed at multiple centers and to determine the impact of age, body mass index (BMI), lesion size, and compartment involvement on outcomes. Methods: Forty-six patients (mean age 41.9 years) with grade IV cartilage injury were treated with HA-BMAC at three centers specialized in orthopaedic surgery. IKDC subjective, VAS, and KOOS instruments were used preoperatively and at final follow-up to assess outcome. Comparative analysis of cases categorized by age, BMI, lesion characteristics, and compartment involvement was performed. Results: Clinical improvement was demonstrated at final follow-up according to all outcome instruments (p<0.001), after a mean follow-up of 28.3 months. Mean lesion size was 8.7 cm2 (range 1-27 cm2). Outcomes were not affected by age less than or greater than 45 years, lesion size less than or greater than 4 cm2, treatment of multiple lesions, or multicompartment treatment. There was no association between clinical outcome and BMI. Conclusions: Cartilage repair of the knee using hyaluronic acid-based scaffold embedded with bone marrow aspirate concentrate demonstrated good to excellent clinical outcomes at multiple treatment centers. These outcomes were not affected by age, BMI, lesion size, treatment of multiple lesions, or multicompartment involvement.

P21 – Integrins α10β1 and α11β1 control quality and predict potency of chondrocytes
Katarzyna Masoumi, Martina Johannesson, Grit-Carsta Bulwin, Giulietta Roël, Jan F. Talts, Caroline Ehrencrona, Carl-Magnus Högerkorp and Evy Lundgren-Åkerlund

Purpose: To validate integrins α10β1 and α11β1 as markers of identity, purity and potency of chondrocyte preparations. Materials and Methods: Human chondrocytes isolated from knee cartilage were expanded in medium containing human serum or platelet lysate. Expression of integrins α10β1 and α11β1 on chondrocytes and synovial fibroblasts was analysed by flow cytometry using specific antibodies. Subsequently, the chondrocytes were subjected to pellet mass cultures to analyse redifferentiation capacity as assessed by collagen type II expression using immunohistochemistry. Results: We found that integrin α10β1 expression on expanded chondrocytes correlated with redifferentiation capacity in pellet mass cultures. We also found that platelet lysate, in comparison to human serum, increased both expression of integrin α10β1 and the redifferentiation capacity of the chondrocytes. In addition, analysis of integrin α11β1, specifically assessed cellular contamination of synovial fibroblasts, which occurs commonly in chondrocyte preparations. Conclusion: Our results demonstrate that integrins α10β1 and α11β1 are important biomarkers for the identification of chondrocytes and fibroblasts, respectively, and thus provide a way to control the purity of chondrocyte preparations and to be a quality read-out for optimising culture conditions. Furthermore, since integrin α10β1 can predict the redifferentiation capacity of chondrocyte preparations, this suggests its suitability as a potency marker in cell therapy of cartilage.

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P22 – Hexagonal Mosaicplasty in Talar Dome Osteochondral Lesions
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Purpose:To present the early clinical and radiologic results of mosaicplasty with the new osteochondral graft system in the treatment of talar dome chondral lesions. Methods and Materials:Between years 2015 and 2017, hexagonal mosaicplasty procedures were carried out in 13 consecutive talar dome osteochondral lesion cases.Among them 11 patients with a minimum follow-up of 6 months were included the study.There were 5 male and 6 female patients. The mean age of the patients was 42.5(±10.3). the clinical assessments were standardized with an initial AOFAS scoring. The radiological diagnosis was based on the magnetic resonance imaging.All patients were treated with hexagonal autograft mosaicplasty following medial malleolar osteotomy.One patient had a hardware removal for the broken screw and the other excluded case did not reached the 6 month follow-up.In postoperative 4th week weight bearing was allowed to all patients.The clinical outcomes of the patients were evaluated with score of AOFAS in the postoperative 6th month. Results:The mean defect area was 90.4(±30.0) mm2.The mean preoperative AOFAS score was 41(±11.5). The mean postoperative AOFAS score was 87.5(±6.0),showing significant amelioration. Conclusion:The new hexagonal osteochondral graft system has promising outcomes. we hope that the study would bring a new point of view for mosaicplasty in talar osteochondral lesions.

P23 – Autologous tendon graft for treatment of osteochondritis dissecans of the knee. 10 year follow-up
Orkun Gul, Sezgin Acil, Muhammet Salih Ayas, Ahmet Ugur Turhan,

Purpose: Since tendon is resistant to overloads and acts as scaffold, it was planned for osteochondral defect (OCD) repair. It is preferred because it is both solid and flexible material and adaptable to all kinds of defect and the geometry of the joint. Method: Defect treatment with autologous tendon graft was planned for 15 OCD patients between 1999-2005. Peroneus longus tendon was taken from the same leg, globed according to the size of the defect and placed in the defect. The knee was extended and the graft kept in place. it was kept in cylinder cast, knee exercises were started. Results: Average follow-up time was 10 years. None of the patients had pain. Knees were able to move freely. All of the patients were pleased. Degeneration was not advanced in radiograms. Magnetic Resonance Imaging showed the tendon defected. The posterior side of the graft had bone marrow edema. No complications were seen after surgery. No cases underwent revision. Conclusion: According to ten-year results, tendon autograft can be used in osteochondral defect repair. No complications were seen and the patients continued their previous activities. Tendon autograft can be recommended in osteochondral defect treatment, it is biological, easily applicable and safe.

P24 – Treatment of cartilage lesions in the knee with all arthroscopic technique of Matrix-Encapsulated Chondrocyte Implantation: 6 years follow-up with T2-mapping MRI.
Reynaldo H. Arredondo-Valdés, Anell Olivos-Meza, F. Enrique Villalobos-Córdoba, Socorro Cortés-González, Francisco J. Pérez-Jimenez, J. Clemente Ibarra-Ponce de León

Purpose: To evaluate clinical and imaging results of all arthroscopic technique of Matrix-Encapsulated Chondrocyte Implantation (MECI) Methods: Prospective cohort. Patients with symptomatic focal cartilage lesions in the knee underwent to all arthroscopic MECI. Follow-up was performed with clinical scores and T2-mapping-MRI. Results: A total of 52 patients with a mean age of 35±9.01 years were operated. Tegner score was 3.42±2.64 before surgery, increased since 24 months to maximal levels of 5.54±2.33 at 36 months (P=0.001). Lysholm score was 53.50±21.21 at pre-op, improving since 6 months reaching maximum values at 48 months 87.10±10.83 (P<0.001). IKDC-subjetive score was 43.00±14.70 at pre-op, improved since 3 months with maximal values of 74.22±16.11 at 24 months (P<0.001). At 3 months, CartiGram® relaxation time were 37.24±7.95 (native cartilage) and 54.61±13.36 (MECI) (P<0.001), 38.64±6.35 vs. 47.06±8.13 at 6 (P<0.001), 38.2±16.55 vs. 40.45±5.26 at 12 (P = 0.020), 37.23±4.89 vs. 38.96±6.20 at 18 (P = 0.187), 36.21±7.70 vs. 38.98±8.91 at 24 (P=0.049), 38.04±7.44 vs. 39.87±6.30 at 36 (P=0.331), 38.86±6.44 vs. 40.28±11.56 at 48 (P=0.910), 40.19±6.15 vs. 43.72±7.84 at 60 (P=0.134) and 36.52±3.79 vs. 40.30±8.13 at 72 (P=0.282) Conclusion: MECI technique shows significant improvement in clinical scores and T2-mapping since 3 follow-up months. Those results remain at 6 years follow-up.

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P25 – Retrograde Funnel Drilling Technique: A Study on accuracy, adequacy, safety and reproducibility in treating OCD
Sahanand S K, Rajan D V, Bansal R G, Benny J E

Objectives: To devise an accurate, safe, adequate and easily reproducible technique of retrograde drilling for treating OCD with regular arthroscopic equipments and image intensifier. Methods: Technique involves drilling a pilot guide pin under image intensifier and arthroscopic zig . Cannulated reamer followed by kwire passed adjacent to pilot guide pin in 8 different directions around pilot guide pin. Depth and diameter of cannulated reamer determines the area covered. Variations reconstructed in computer simulated 3D reconstructions. Reproducibility, Accuracy and Adequacy assessed by 3 different surgeons performing on bone models.In our study, 10 joints (7 Knees + 3 Ankles) with grade II & III OCD underwent this procedure performed by a single surgeon. Follow up ranges from 1 to 3 years. Results: Short term follow up results of 7 patients (10 lesions) showed good outcome. None had cartilage damage intra-operatively or progression of lesion stage on follow up indicating safety and efficacy. Bone model drilling by 3 surgeons proved to be accurate and reproducible. Conclusion: Retrograde Funnel drilling is accurate, adequate, safe, efficacious and easily reproducible technique for treating OCD. Templates designed will aid surgeons plan and perform this technique easily.

P26 – Poster:Retrograde bone grafting for cystic type of symptomatic OCLT: New Technique
Sahanand S K, Rajan D V,

Objectives: To develop a minimally invasive technique in treating symptomatic cystic type of osteochondral lesion of talus. Methods: Technique involves retrograde percutaneous drilling a pilot guide pin under image intensifier till the cyst followed by cannulated reamer. Cylindrical autologous bone graft harvested from ipsilateral proximal tibia using OATS instrumentation. The cylindrical graft was passed retrograde into the cyst using OATS cannula and trocar. Two patients who underwent this technique was followed up for 1 year. Results: Both the patients showed good outcome as per AOFAS scores at 1 year follow up with moderate filling up of defect on MRI. Conclusion: Retrograde bone grafting is a minimally invasive technique with good outcome on short term follow up.

P27 – Osteochondral Allografts for Osteochondritis Dissecans of the Knee: Do Outcomes Differ by Age?
Eric J. Cotter BS, Rachel M. Frank MD, Kevin C. Wang BS, Trifon Totlis MD, PhD, Sarah Poland BA, Max A. Meyer BS, Brian J. Cole MD, MBA

Purpose: To report mid-term clinical outcomes of osteochondral allograft transplantation (OCA) for patients with knee osteochondritis dissecans (OCD) lesions, investigate age-based differences in outcomes and describe return-to-sport (RTS) rates. Materials & methods: Forty-six patients with OCD (48 knees) who underwent OCA (minimum 2-year follow-up) were included. They were separated into two groups; A. 20 years of age or older and B. less than 20 years old at the time of OCA. Preoperative and final follow-up patient reported outcomes (PROs), RTS, and satisfaction were reported. Results: Thirty-eight patients (40 knees) were available for clinical follow-up (average 7.36±3.29 years). There were significant improvements in all PROs overall and for both groups ($P<0.05$) other than SF-12 Mental. There were no significant differences between the 2 groups in terms of preoperative, postoperative or magnitude of change for all PROs. Thirty-six patients (92.3%) would have the procedure again. Eighteen patients (81.8%) RTS at an average 14.0 months. Ten patients (43.5%) in Group A and 7 patients (33.3%) in Group B underwent reoperation. Group A had 2 failures. Conclusions: OCA for OCD of the knee leads to clinically meaningful improvements in PROs, high satisfaction and RTS rates regardless of patient age. While reoperation may be common following OCA, failure rate is low at mid-term follow-up.

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P28 – Age-related changes in the knee meniscus.
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Purpose: Aging is a prominent risk factor for the development of osteoarthritis (OA), which affects knees and causes major health burdens. Meniscal dysfunction mostly based on degeneration contributes to its development. Meniscal degeneration is caused by various extrinsic factors, such as repetitive trauma or leg malalignment, while meniscal aging is considered as internal changes, such as molecular or cellular changes. Little is known about age-related changes in the meniscus. Therefore, we reviewed the understanding of the aging meniscus. Design: There are few articles about aging in the meniscus, because most reports only demonstrate the effects of OA on the meniscus. We searched PubMed to identify and summarize all English-language articles evaluating aging in the meniscus. Results: There is evidence of compositional changes in the meniscus with aging, involving cells, collagens, and proteoglycans. In addition, as recent reports on the aging of cartilage have indicated, senescence of the meniscal cells may also lead to disruption of tissue homeostasis. Due to the low turnover rate of collagen, accumulation of advanced glycation end products largely contributes to tissue stiffness and vulnerability, and finally results in degenerative changes or tears. Conclusion: Age-related changes induce meniscal tissue vulnerability and finally lead to meniscal dysfunction.

P29 – The effect of severity and duration of osteoarthritis on postoperative outcome in total hip arthroplasty
Arkan Sayed-Noor Associate Professor

Purpose To evaluate the radiographic degree of osteoarthritis (OA) and the duration of symptoms on the postoperative functional outcome and quality of life after a Total Hip Arthroplasty (THA). Material & Methods 286 patients with primary hip OA were investigated preoperatively and 12-15 months postoperatively with two questionnaires, WOMAC and EQ-5D. The degree of OA was assessed according to the Kellgren-Lawrence (KL) classification system while the preoperative OA symptom duration was divided to < 3 years and > 3 years. A linear logistic regression analysis was used to investigate the influence after adjusting for possible confounders. Results 222 patients completed the study. 73 patients had KL grade 1-2 and 149 patients KL grade 3-4. There were 92 patients with symptoms < 3 years and 130 patients with symptoms > 3 years. All patients, regardless groups, improved significantly after the operation. Unadjusted analysis showed a relation between symptom duration > 3 years and better outcome. When using regression, both KL classification and symptom duration had not effect on the functional outcome or quality of life. Conclusion Preoperative radiographic severity and duration of symptoms did not influence the outcome after THA and therefore should not affect the timing of operative intervention.

P30 – Surgical Correction of Patella Maltracking - Midterm, Clinical Follow up
Keltz Eran, Ofir Dror, Beer Iftach, Nierenberg Gabriel

Purpose: Mid-term clinical outcome of Fulkerson distal realignment operation of the patella with the various associated procedures such as lateral release, medial plication and microfracture of the patella. Methods: 21 patients were prospectively evaluated for 22 Fulkerson distal realignment and associated procedures. The average follow up time was 48 month (12-156). Clinical outcome reported by self administered subjective International Knee Documentation Committee (IKDC) score and Tegner-Lysholm knee scoring scale. Associated procedures were reported individually. Results: Preoperative, average subjective IKDC score was 50.2. Tegner-Lysholm score was 68.3. The average score postoperatively, at a mean follow up time of 48 month, was 72.6 and 80.5 respectively. The number of various associated procedures included 4 microfracture of patella for full thickness cartilage lesion, 3 lateral releases and 2 medial augmentations. One patient with Elhers Danlos disease required excessive medialization of the tibia tuberosity. 3 patients had surgery related complications. Conclusion: Fulkerson distal realignment with selective individualized associated procedures demonstrate an overall increase in subjective and functional clinical scores at medium term follow up with valid correlation to the reported literature. Special attention should be given to associated pathologies secondary to patella mall traction.

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P31 – Short term results from a prospective study of bone marrow derived stem cells in the treatment of osteochondral defects in the knee employing an optimised rehabilitation protocol (Stanmore Stem Cell Project- SSCP).
A.D. Iliadis, J. Donaldson, J. Miles, T.W.R. Briggs, R.W.J Carrington, G. Bentley

Purpose: A prospective study to evaluate a single stage procedure employing autologous bone marrow derived stem cells in articular cartilage repair and a 6-month rehabilitation protocol. We present our initial short-term results. Materials and Methods: Eligible patients with knee osteochondral lesions underwent autologous stem cell transplantation surgery. An optimised 6-month rehabilitation regime is employed. Validated assessments using the visual analogue scale, modified Cincinnati knee score, Bentley functional outcome score and EQ-5D scores are collected at regular intervals. Cross sectional imaging is performed pre-operatively and at 6 months. Results: Short-term (6 month) data for 25 patients (mean age 29yrs, 18 males and 7 females) were collected. Mean VAS score for pain improved from 3.24 pre-operatively to 6.64 at 6 months ($p<0.05$). Mean modified Cincinnati scores improved from 60.40 to 47.92 ($p<0.05$) and the mean Bentley functional outcome score improved from 2.87 to 2.20 ($p<0.05$). Substantial graft integration and cartilage regeneration was reported in 13 out of 20 interval scans. Conclusion: Early short-term results from our study demonstrate favourable outcomes in terms of pain and function. These are comparable to our previous experience with autologous chondrocyte implantation. High definition cross sectional imaging confirms high rate of integration for this novel, time and cost-effective approach.

P32 – Improper regeneration after stem cell therapy in degeneration of cartilage
Assistant professor in orthopedic surgery Joint specialisty

Purpose To classify improper regeneration after stem cell therapy in degeneration of cartilage. Materials & Methods 50 patients treated with adipose or bone marrow derived stem cell were evalated in terms of secondary arthroscopy and histology. Kellgrene-Lawrence 1 to 3 grade osteoarthritis of the knee was included. Stem cell was isolated from autologous fatty tissue of abdomen or bone marrow of iliac bone. Minimally treated autologous adult stem cell was used. MRI was checked at baseline, postoperative 3 and 12 months. Secondary arthroscopy was performed at postoperative 9 to 18 months. Regenerative cartilage biopsy was done in consent informed patients. Results On secondary arthroscopy, improper regenerations are classified to incomplete, uneven, hypertrophic, softening patterns. Overall MRI regeneration scores were 2 points(good) in hypertrophy pattern. ICRS II scores were average 70 points in all patterns. Conclusion To enhance stem cell therapy, improper regeneration should be elaborately evaluated. These patterns are supposed to be meaningful method to evolute stem cell therapy.

P33 – Biomimetic Collagen-Hydroxyapatite Scaffold Versus Bone Marrow Stimulation For Chondral And Osteochondral Lesion: A 2-Year Randomized Controlled Trial.
Filardo Giuseppe, Kon Elizaveta, Brittberg Mats, Busacca Maurizio, Condello Vincenzo, Engebretsen Lars, Marlovits Stefan, Niemeyer Philipp, Platzer Patrik, Posthumus Mike, Van Der Merwe Willem, Verdonk Peter, Verdonk Renè, Victor Jan, Widuchowski Wojciech, Zorzi Claudio, Marcacci Maurilio.

PURPOSE: To assess the benefit provided by a collagen-hydroxyapatite (coll-HA) multilayer scaffold for the treatment of chondral and osteochondral knee lesions. METHODS: The coll-HA scaffold was compared to bone marrow stimulation (BMS) in a multicenter randomized controlled trial: 100 patients affected by symptomatic grade III-IV lesions were evaluated for up to 2 years (51 study group, 49 control group). Primary efficacy measurement was IKDCsubj score at 2 years; secondary were: KOOS, IKDC, Tegner and VASpain scores at 6, 12 and 24 months. Tissue regeneration was evaluated with MRI Mocart score at 6, 12 and 24 months. An external independent agency ensured data correctness and objectiveness. RESULTS: A significant improvement of all clinical scores was obtained in both groups, although no overall significant differences were detected between treatments. The subgroup of patients affected by deep osteochondral lesions (i.e. Outerbridge IV and OCD) showed a significantly better IKDCsubj outcome ($p=0.036$) in the coll-HA group. Severe adverse events were documented in 3 patients in the coll-HA group and in 1 in the BMS group. The Mocart score showed no statistical difference between groups. CONCLUSIONS: This biomimetic implant showed no benefit compared to BMS for chondral lesions, but this procedure can be considered safe and a suitable option for the treatment of osteochondral lesions.

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P34 – Autologous Chondrocyte Implantation as Treatment for Unsalvageable Osteochondritis Dissecans: 10- to 25-year Follow-up

James L. Carey, MD, MPH, Kevin G. Shea, MD, Anders Lindahl, MD, PhD, Haris S. Vasiliadis, MD, PhD, Carl Lindahl, PhD, Lars Peterson, MD, PhD

Introduction: The purpose of this study was to assess the long term outcomes 15 to 25 years following autologous chondrocyte implantation (ACI) as treatment for unsalvageable osteochondritis dissecans (OCD). Methods: All Swedish and Norwegian patients (59 patients with 67 OCD lesions) that underwent ACI for OCD between 1990 and 2005 were identified through manual chart review and were sent questionnaires with patient-oriented outcome measures. In addition, patients were asked whether they had to undergo further surgery, including knee replacement, of the knee that underwent ACI. They were asked whether they would have the surgery again if in the same situation. Results: Fifty-five patients (93%) with 63 OCD lesions responded. Current mean Lysholm and Tegner scores were 75.1 and 4.2, respectively. Current mean KOOS Pain scores were 79. With respect to prior surgery, 17 knees (27%) underwent any additional surgery, but only 2 knees (3%) underwent knee replacement. Forty-seven patients (86%) would undergo ACI again if in the same situation. Discussion: ACI as treatment for OCD provides enduring results after 10- to 25-year follow-up. In the setting of few other long-term studies following cartilage repair, ACI remains a lead treatment option for unsalvageable OCD lesions.

P35 – A Single Stage Arthroscopic Treatment Of Articular Cartilage Defects – Autologous Collagen Induced Chondrogenesis (Acic: Shetty-Kim Technique) Five Year Results

Karan Alva, Asode Anantharam Shetty, Seok-Jung Kim, David Stelzeneder, Siegfried Trattnig

Introduction: We describe five results of a novel single stage arthroscopic technique for the treatment of articular cartilage defects of the knee. This involves micro drilling and application of Atelo-collagen (Coltrix) and fibrin gel scaffold. Materials and Method: The preclinical study involved two groups of rabbits treated with micro-drilling, and micro-drilling with Atelo-collagen and fibrin gel. New cartilage were subjected to staining, immunohistochemistry and scanning and transmission electron microscopy to analyse the microstructural morphologies. The micro-drilling with Atelo-collagen, fibrin gel scored better than the micro-drilling alone. The surgical procedure involved micro-drilling and application of Atelo--collagen and fibrin gel under CO_2 insufflation. Patients underwent morphological evaluation with MRI (T2*-mapping and d-GEMRIC scans). Clinical assessment was done with Lysholm, IKDC and KOOS scores. Radiological assessment was performed with MOCART score. Results: At five years, Lysholm score was 74, compared to 49 pre operatively ($p<0.05$). KOOS (symptomatic) improved to 92 from 62 ($p<0.05$). IKDC (subjective) went to 78 from 40 ($p<0.05$). The mean T2* relaxation-times for the repair tissue and native cartilage were 26 and 29.9 respectively. Average MOCART score for all lesions was 70. Conclusion: This technique shows encouraging clinical results at five year follow-up. The morphological MRI shows good cartilage defect filling and the biochemical MRI suggests hyaline like repair tissue.

P36 – Integrin α10β1-selected equine MSCs have increased chondrogenic differentiation and cartilage adhesion capacity

Linda Larsson, Kristina Uvebrant, Matilda Thorén, Paolo Alberton, Attila Aszodi, Jan F. Talts, Evy Lundgren-Åkerlund

Purpose: In order to develop a safe and effective MSC therapy for cartilage damage we selected equine MSCs based on the chondrocyte cell surface marker integrin α10β1. We here evaluated chondrogenic differentiation and cartilage adhesion capacity of integrin α10β1-selected MSCs. Materials & Methods: MSCs were isolated from equine adipose tissue and selected for integrin α10β1 expression with integrin α10-antibodies. Selected and unselected cells were evaluated by differentiation assays and ex vivo cartilage adhesion assays. Results: Both selected and unselected MSCs expressed stemness markers CD44, CD90 and CD105 and did not express CD45 or MHC class II and were able to differentiate into osteocytes and adipocytes. However, integrin α10β1-selected MSCs showed higher chondrogenic differentiation capacity compared to MSCs with no/low expression of integrin α10β1 or unselected MSCs. Furthermore, integrin α10β1-selected MSCs, to a larger extent, adhered to cartilage defects in ex vivo osteochondral explants. Conclusion: We demonstrate that integrin α10β1 can be used to identify and select MSCs with high chondrogenic differentiation potential and increased adhesion to damaged cartilage. These results demonstrate that integrin α10β1 is an important marker for quality control and potency prediction of equine MSCs for cartilage repair.

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P37 – Low frequency of subchondral bone barrow edema after high-density autologous chondrocyte implantation (HD-ACI) *Lucia Aboli, Elena Rodriguez-Iñigo, Isabel Guillén-Vicente, Juan Manuel López-Alcorocho, Marta Guillén-Vicente, Steve Abelow, Pedro Guillén-García*

Purpose Subchondral bone marrow edema (BME) is frequent after an autologous chondrocyte implantation (ACI). The aim of this work was to study the frequency of BME after HD-ACI. Materials & Methods In this study 40 patients with focal chondral lesions (>1cm in diameter) in the knee were included. All the patients were treated with HD-ACI: 5 million autologous chondrocytes per cm2 of chondral lesion on a type I/III collagen porcine membrane. After 12 and 24 months, the presence of subchondral BME was assessed by magnetic resonance imaging. Functional and clinical knee outcomes were studied by the International Knee Documentation Committee (IKDC). Results A significant subchondral BME was observed in 10 (25%) at 12 months and in 11 out of the 40 patients (27.5%) after 24 months post-implantation. The improvement of the IKDC score from the baseline was 27.3 (95% CI: 17.3-32.2) and 32.1 (95% CI: 23.2-35.4) points at 12 and 24 months, respectively. No correlation was observed between the presence of subchondral BME and IKDC score at any time period. Conclusion The percentage of subchondral BME is relatively low after HD-ACI and it does not correlated with the functional and clinical knee outcomes.

P38 – Modern OCA Transplantation: The Gold Standard for Cartilage Repair? An analysis of 200 osteochondral allografts of the femoral condyle
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Purpose: Purpose of this study was to evaluate outcome, failure rate and long-term survivorship of fresh osteochondral allografts (OCA) of the femoral condyle performed for "typical" cartilage repair indications using contemporary allografting techniques. Material & Methods: This study comprised 200 knees treated with OCA for isolated femoral condyle lesions from 1999 to 2014 with a 2-year minimum follow-up. Mean age was 31.1 ± 11.6 years. Mean graft area was 6.26 cm^2 (range, 2.25 to 13.0 cm^2). Mean International Knee Documentation System (IKDC) scores and satisfaction with the procedure were recorded. Clinical failure was defined as OCA removal (revision OCA or arthroplasty). Graft survivorship was determined. Results: Mean follow-up was 6.7 years (range, 1.9-16.5). At latest follow-up, mean IKDC pain, function and total score were 2.76, 7.31 and 75.73, respectively. OCA failure rate was 8%. Graft survivorship was 95.6% at 5 years and 91.2% at 10 years. Patient satisfaction was 89.0%. Conclusion: OCA was associated with significant clinical improvement, high patient satisfaction, low failure rate and excellent long-term survivorship when used for isolated femoral condyle lesions of the knee. Outcome with OCA for femoral condyle lesions is equal or better than other currently available cartilage repair treatments.

P39 – Mesenchymal stem cells for articular cartilage repair: cell tracking and characterization using a novel immunocompetent in vivo model
María Satué1, Daniela Zwolanek1, Verena Proell1, José R. Godoy1, Kathrin I. Odörfer1, Magdalena Flicker1, Sigrid Hoffman2, Thomas Rülicke1, and Reinhold G. Erben1 1Department of Biomedical Sciences, University of Veterinary Medicine, Vienna, Austria. 2Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany.

Purpose. Mesenchymal stem cells (MSCs) promote cartilage regeneration but their therapeutic role remains unclear. Here, we used a novel in vivo cell tracking system based on a transgenic donor and corresponding immunocompetent marker-tolerant recipient rat line to track and evaluate the fate of intra-articularly injected MSC in a focal cartilage defect model. Materials & Methods. A dual transgenic rat model based on the human placental alkaline phosphatase protein (ALPP) was established. Donor lines express heat-resistant ALPP and recipient lines express heat-sensitive ALPP. Full-thickness cartilage defects were created in the knee of recipient animals and donor ALPP MSCs were intra-articularly injected. ALPP-labeled MSCs were tracked in the defects and chondrogenic differentiation was evaluated by histochemical and immunofluorescence staining. Results. Donor ALPP MSCs were found at the bottom of the cartilage lesions, where they formed aggregates which highly expressed SRY-box 9 (SOX9) protein. Collagen type II (COLII) formation and a more regular cartilage oligomeric matrix protein (COMP) distribution were observed in the defects of MSC-injected rats. Conclusion. This immunocompetent in vivo model allows to track and to characterize genetically labeled MSCs within defined cartilage lesion in the absence of immune-mediated rejection. We found that intra-articularly injected MSC facilitated cartilage regeneration.

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P40 – A Chondrogenic Fibrin-HA Hybrid Proteoglycan for OA Pain Relief and Cartilage Preservation: from Bench to Clinic
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Purpose: A novel approach for knee OA treatment providing global joint preservation and early onset pain relief by intraarticular injection of a synthetic, biomimetic proteoglycan composed of Hyaluronic acid (HA) uniquely cross linked to human Fibrinogen. Materials and Methods: HA-Fibrinogen conjugate prepared by pre-activating high molecular weight HA coupled to either autologous human plasma or purified Fibrinogen and characterized by SEC, ELISA, IHC, qPCR, DMMB and AlamarBlue. Results, Preclinical: Early exposure of 3D cultures of human articular chondrocytes to distinct HA-Fibrinogen conjugates lowers proliferation rates and significantly increases chondrocyte differentiation markers including type 2 Collagen, FGFR3, GAG deposition and secretion in a dose dependent manner, supporting previously described results in OA animal models. Clinical: More than 100 people suffering from mild to severe knee OA were treated by intra articular injections with the Fibrin-HA hydrogel marketed in Israel under the brand names RegenoGel (shelf product) and RegenoGel-OSP (autologous plasma based). An unprecedented early onset pain relief of 90% was observed in a post marketing survey of the first 50 patients. Conclusions: Strong chondrogenic effect was exhibited by a particular synthetic HA-Fibrinogen conjugate in 3D human chondrocyte cultures. Preliminary clinical assessment demonstrates unprecedented early onset pain relief. Long term efficacy is being assessed in a placebo-controlled clinical trial.

P41 – Integrin α10β1+ Mesenchymal Stem Cells Mitigate the Development of Posttraumatic Osteoarthritis
Michelle L. Delco, DVM, PhD, Jan F. Talts, PhD, Margaret Goodale, Sarah Pownder, DVM, PhD, Matthew Koff, PhD, Evy Lundgren-Åkerlund, PhD, Lisa A. Fortier, DVM, PhD

Purpose To investigate the safety and efficacy of integrin α10 1-selected mesenchymal stem cells (MSCs) in prevention of the development of posttraumatic osteoarthritis. Materials & Methods Equine MSCs positive for integrin α10 1 were selected (Uverbrant, ICRS 2015). Focal cartilage impacts were arthroscopically delivered on both tali (Delco, ORS 2017). Joints were treated with 20 x 106 MSCs or vehicle 4 days post-injury. Synovial fluid was serially collected for ELISAs. Second look arthroscopy was performed at 6 weeks, horses were euthanized at 6 months. Radiographs were obtained at surgeries and euthanasia. Joints were imaged using 3T MRI. Synovial membrane and osteochondral histology was performed on impacted and control samples. Results No off-target effects were observed. At study end, treated limbs had less radiographic subchondral bone sclerosis. Histologically, treated joints had less cartilage fibrillation and fissuring. Type II collagen immunohistochemistry was stronger in treated limbs. Synovial fluid ELISA results indicated increased collagen synthesis (CPII) and diminished collagen degradation (C2C) in treated joints. PGE-2 concentration was increased in MSC treated joints, suggesting immunomodulation of MSCs. Conclusion This study supports the use of α10 1+ MSCs for the treatment of post-traumatic osteoarthritis. The treatment is safe and there is strong evidence to suggest the cells may mitigate the effects of joint trauma.

P42 – Return to Work after Articular Cartilage Repair Intervention
Puwapong Nimkingratana MD PhD, Mats Brittberg MD PhD.

Purpose Several papers deal with athletes' return to sports after cartilage repair. However, since most people spend more time at non-sports related occupations than they do participating in sports, investigation of patients returning to work is an important area for research. Materials-Methods A systematic review of relevant medical databases using MEDLINE/PUBMED/EMBASE during January 1966 to June 2016 was performed to obtain information related to returning to work after cartilage repair. Data are presented as MEAN±SEM with a 95% confidence interval. Results Only 5 studies were identified describing 283 patients. ACI was the most common intervention. The average return to work time post treatment was 3.87 months. Time to return to pre-injury level was positively correlated with ACI and associated with good-excellence clinical outcomes. Time to return to work was associated with the physical workload in each occupation ($p<0.05$). However, no significant correlation with age, gender or BMI was identified. Conclusions Cartilage repair in general provides a high rate of return to work; however, only a few studies report data in contrast to the extensive data on return to sports. A prognostic return to work score could be useful for prospective studies. A high/fast degree of return would provide added justification for the increased costs of effective new cartilage repair treatments.

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P43 – Treatment of cartilage lesions in the knee with all arthroscopic technique of Matrix-Encapsulated Chondrocyte Implantation: 6 years follow-up with T2-mapping MRI.
Reynaldo H. Arredondo-Valdés, Anell Olivos-Meza, Félix Enrique Villalobos-Córdoba, Socorro Cortés-González, Francisco Javier Pérez-Jiménez, J. Clemente Ibarra-Ponce de León

Purpose: To evaluate clinical and imaging results of all arthroscopic technique of Matrix-Encapsulated Chondrocyte Implantation. Methods: Prospective cohort. Patients with symptomatic focal cartilage lesions in the knee underwent to all arthroscopic Matrix-Encapsulated Chondrocyte Implantation. Follow-up was performed with clinical scores and imaging with T2-mapping. Results: A total of 52 with a mean age of 35±9.01 years were operated. Tegner score was 3.42±2.64 before surgery, increased since 24 months to maximal levels of 5.54±2.33 at 36 months (P=0.001). Lysholm score was 53.50±21.21 before surgery, increased since 6 months with maximal values at 48 months 87.10±10.83 (P<0.001). IKDC-subjetive score was 43.00±14.70 before surgery, increased since 3 months with maximal value of 74.22±16.11 at 24 months (P<0.001). CartiGram® relaxation time values was 37.24±7.95 for native cartilage and 54.61±13.36 for implant at 3 months (P<0.001), 38.64±6.35 vs. 47.06±8.13 at 6 (P<0.001), 38.2±16.55 vs. 40.45±5.26 at 12 (P = 0.020), 37.23±4.89 vs. 38.96±6.20 at 18 (P = 0.187), 36.21±7.70 vs. 38.98±8.91 at 24 (P=0.049), 38.04±7.44 vs. 39.87±6.30 at 36 (P=0.331), 38.86±6.44 vs. 40.28±11.56 at 48 (P=0.910), 40.19±6.15 vs. 43.72±7.84 at 60 (P=0.134) and 36.52±3.79 vs. 40.30±8.13 at 72 (P=0.282) Conclusion: MECI technique shows significant improvement in clinical scores and T2-mapping MRI since 3 to 24 follow-up months and those results remain at 6 years follow-up.

P44 – Hematopoietic-mesenchymal signal regulates MSC properties
Sanshiro Kanazawa1,2, Atsuhiko Hikita1, Tsuyoshi Takato1,2, Kazuto Hoshi1, 2 1, Department of Cartilage and Bone Regenerative Medicine, Graduate School of Medicine, The University of Tokyo, Japan. 2, Department of Oral and Maxillofacial Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[Purpose] It is well known that stemness of hematopoietic stem cells (HSCs) is maintained through interaction with mesenchymal cells, although the identity of mesenchymal cells remains a subject of dispute. We speculate that the stemness of mesenchymal stem cells (MSCs) may also be maintained by interaction with hematopoietic cells. In this study, we examined the effect of HSCs on MSC properties. [Methods] Bone marrow-derived MSCs and HSCs from mice were subjected to co-culture, and the change of MSC properties by co-culture was analyzed. We also co-cultured MSCs and c-Mpl deficient mice derived-HSCs, which exhibit impaired stemness. Lastly, we transplanted wild-type and c-Mpl deficient mice-derived MSCs into a mouse skull defect model. [Results] We revealed that MSCs co-cultured with HSCs maintained their properties better than MSCs cultured alone. In mesenchymal induction, MSCs co-cultured with HSCs were equally differentiated and matured as monocultured MSCs. Meanwhile, we observed alteration of MSC properties by co-culturing with c-Mpl deficient mice-derived HSCs. Furthermore, in vivo transplantation experiments revealed that c-Mpl deficient mice-derived MSCs showed a change in osteogenic ability compared to those from wild-type mice. [Conclusion] These results suggest that hematopoietic-mesenchymal signal plays pivotal roles in the maintenance of stemness of MSCs.

P45 – Autologous Chondrocyte Implantation for Bipolar Chondral Lesions in Tibio-femoral Compartment
Takahiro Ogura MD, Tim Bryant BSN, RN, Brian A. Mosier MD, and Tom Minas MD, MS

Purpose: To evaluate clinical outcomes after autologous chondrocyte implantation (ACI) for the treatment of bipolar chondral lesions in tibio-femoral (TF) compartment. Methods: We evaluated 57 patients who had ACI for the treatment of symptomatic bipolar chondral lesions in TF compartment. One patient did not return for follow-up. Thus, 56 patients (58 knees) were included with a minimum of 2 years follow-up. Bipolar lesions were present in the medial (32 knees) and lateral (26 knees) compartment. Patients were evaluated with the modified Cincinnati Knee Rating Scale, Visual Analogue Scale, Western Ontario and McMaster Universities Osteoarthritis Index, the Short Form 36, a satisfaction survey and standard radiographs. Results: Survival rate was 80% at 5 years and 76% at 10 years. Of 46 knees with retained grafts, all functional scores significantly improved postoperatively with high satisfaction at a mean of 7.2 years postoperatively. At last follow-up, 24 of 46 successful knees were radiographically assessed (average, 5.5 years postoperatively), with no significant osteoarthritis progression. Outcomes for 12 patients were considered as failures at a mean of 4.1 years. Conclusions: ACI for the treatment of bipolar chondral lesions in TF compartments provided successful clinical outcomes and could possibly prevent or delay rapid OA progression over mid- to long-term follow-up.

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P46 – Avoidance of Total Knee Arthroplasty in early osteoarthritis of the knee with intra-articular implantation of Autologous Activated Peripheral Blood Stem Cells versus Hyaluronic Acid: a randomized controlled trial with differential effects of Growth Factor
Thana Turajane, Ukrit Chaweewannakorn, Jongjate Aojanepong, Warachaya Fongsarun, Konstantinos I Papadopoulos

Aim: In this randomized controlled trial, in early OA that failed conservative intervention, the need for total knee arthroplasty (TKA) and WOMAC scores were evaluated, following a combination of arthroscopic micro-drilling mesenchymal cell stimulation (MCS) and repeated intra-articular (IA) autologous activated peripheral blood stem cells (AAPBSC), growth factor addition (GFA) and hyaluronic acid (HA) versus IA-HA alone. Methods: AAPBSC harvested via leukapheresis were administered IA in Group 1 along with MCS combined with HA and GFA (platelet rich plasma (PRP) and Granulocyte Colony Stimulating Factor (hG-CSF)); as in Group 2 but without hG-CSF while Group 3 received IA-HA alone. Each group of 20 patients received three weekly IA injections and was evaluated at baseline, 1, 6, and 12 months. Results: At 12 months, all patients in the AAPBSC groups were surgical intervention free compared to three patients needing TKA in Group 3 ($p<0.033$). Total WOMAC scores showed statistically significant improvements at 6 and 12 months for the AAPBSC Groups vs. controls. There were no notable adverse events. Conclusion: We have shown avoidance of TKA in the AAPBSC groups at 12 months and potent, early and sustained, symptom alleviation through the addition GFA vs. HA alone. Differential effects of hG-CSF were noted with earlier onset of symptom alleviation throughout.

P47 – Cartilage regeneration in a rat model of knee OA by SM04690, a potential disease modifying Wnt pathway inhibitor *Vishal Deshmukh, Charlene Barroga, Haide Hu, Sunil KC and Yusuf Yazici*

Introduction: Increased Wnt signaling in osteoarthritis (OA) leads to cartilage thinning and bone remodeling. SM04690, a small-molecule Wnt pathway inhibitor, was evaluated for its potential to induce chondrogenesis, protect cartilage, limit inflammation, and improve joint health. Methods: SM04690-induced chondrogenesis from human mesenchymal stem cells (hMSCs) was evaluated by qPCR and histology. In vivo efficacy was measured in a rat knee surgical OA model by histology (OARSI score) and biomarkers, and in the rat monosodium iodoacetate (MIA) injection-induced OA model by histology, ELISA for pro-inflammatory cytokines, and pain by paw withdrawal threshold using Von Frey apparatus. Results: In vitro, SM04690 induced differentiation of hMSCs into mature, functional chondrocytes. In rat OA models, a single SM04690 intra-articular injection resulted in therapeutic concentrations >180 days, without detectable systemic exposure or toxicity. Compared to vehicle, SM04690 regenerated cartilage, decreased OARSI score ($p<0.05$), inhibited proteases ($p<0.05$) and improved OA biomarkers ($p<0.05$). In the MIA model, SM04690 inhibited inflammatory cytokine production ($p<0.05$) and increased paw withdrawal threshold ($p<0.05$). Conclusions: Preclinically, SM04690 induced chondrogenesis, regenerated cartilage, inhibited protease release, improved cartilage health, and reduced inflammation and pain compared to vehicle. SM04690 has potential as a disease modifying therapy for OA.

ICRS Summit Poster Presentations

P48 – Mesenchymal stem cell exosomes and mechanisms of action in cartilage repair

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Purpose: We had previously reported that human mesenchymal stem cell (MSC) exosomes effectively repair critical-sized osteochondral defects in immunocompetent rats. Here, we investigate the mechanisms of action underlying this repair. Materials & Methods: In 36 rats, osteochondral defects were created and given weekly intra-articular injections of exosomes (100µg/ml) or saline vehicle for over 12 weeks. Cartilage repair was assessed by gross examination, histology and synovial fluid analysis. Cell-based assays were performed to determine the cellular processes activated by exosomes. Results: We observed in our rat model that exosome treatment rapidly initiated cellular proliferation and infiltration followed by an orderly cartilage and subchondral bone regeneration. This was further reflected by significant improvements in histological scores by exosome treatment ($p<0.01$). In chondrocyte cultures, MSC exosomes were rapidly internalized and elevated chondrocyte survival, migration, proliferation, and matrix synthesis, in part through activation of AKT and ERK signalling. Additionally, exosome-treated defects displayed a higher infiltration of CD163+ regenerative M2 macrophages and lower infiltration of CD86+ M1 macrophages, with a concomitant reduction in synovial pro-inflammatory cytokines such as IL-1 and TNF-α. Conclusion: MSC exosomes exert its potent therapeutic efficacy through a coordinated mobilisation of multiple cell types and activation of cellular processes that are critical to cartilage repair and regeneration.

P49 – Peripheral blood derived MSC could maintain phenotype and enhance matrix formation of meniscal cells in the coculture system

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Purpose The aim of this study was to established the culture system of peripheral blood mesenchymal stem cells (PB-MSC) and meniscal fibrocartilage cells (MFC) under both 2D monolayer culture and 3D micromass pellet culture conditions. Methods The coculture system of peripheral blood MSC and MFC was established with different composition ratios. The general morphological changes of cells and pellet were observed under microscope. The labeling efficiency and the proportion of the two kinds of cells were detected by FCM and microscopy. The matrix formation and meniscal cells phenotype characteristics were analyzed. Results Our results demonstrate that MFC/MSC coculture at the ratio of 50/50 could enhance matrix formation and maitain meniscal phenotype in terms of ECM expression under 2D monolayer culture condition. But under 3D micromass pellet culture condition, the optimal meniscus ECM production was positively correlation to the percentage of MFC. Conclusion This study aims to establish a co-culture system of peripheral blood MSC and MFC, in which MFC could be reversed by the paracrine secretion which is the trophic effects of MSC, thereby restoring the phenotypic characteristics of MFC.

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