ICRS 2013

International Cartilage Repair Society

Izmir – Turkey

September 15 – 18, 2013

11th World Congress of the International Cartilage Repair Society

Main Programme & Extended Abstracts

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2013
ICRS, IZMIR, TURKEY

17/09
TUESDAY 17TH SEPTEMBER
13.00-14.00
MEETING ROOM SMYRNA 2

Chair:
Tim Spalding, MBBS. (LOND), FRCS(Ed), FRCS Orth.
Specialist Knee Surgeon, University Hospitals Coventry and Warwickshire NHS Trust
Honorary Associate Professor, Warwick Medical School, University of Warwick

Presenters:
Peter Verdonk, MD, PhD
Orthopaedic Surgeon at AZ Monica, Antwerp; Professor in Orthopaedics and Traumatology at Ghent University, Belgium

Philipp Niemeyer, MD, PhD
Department of Orthopaedic Surgery and Traumatology, Freiburg University Hospital, Germany

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Sept. 15 – 18, 2013
Izmir / Turkey

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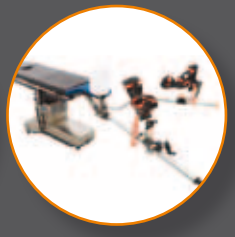

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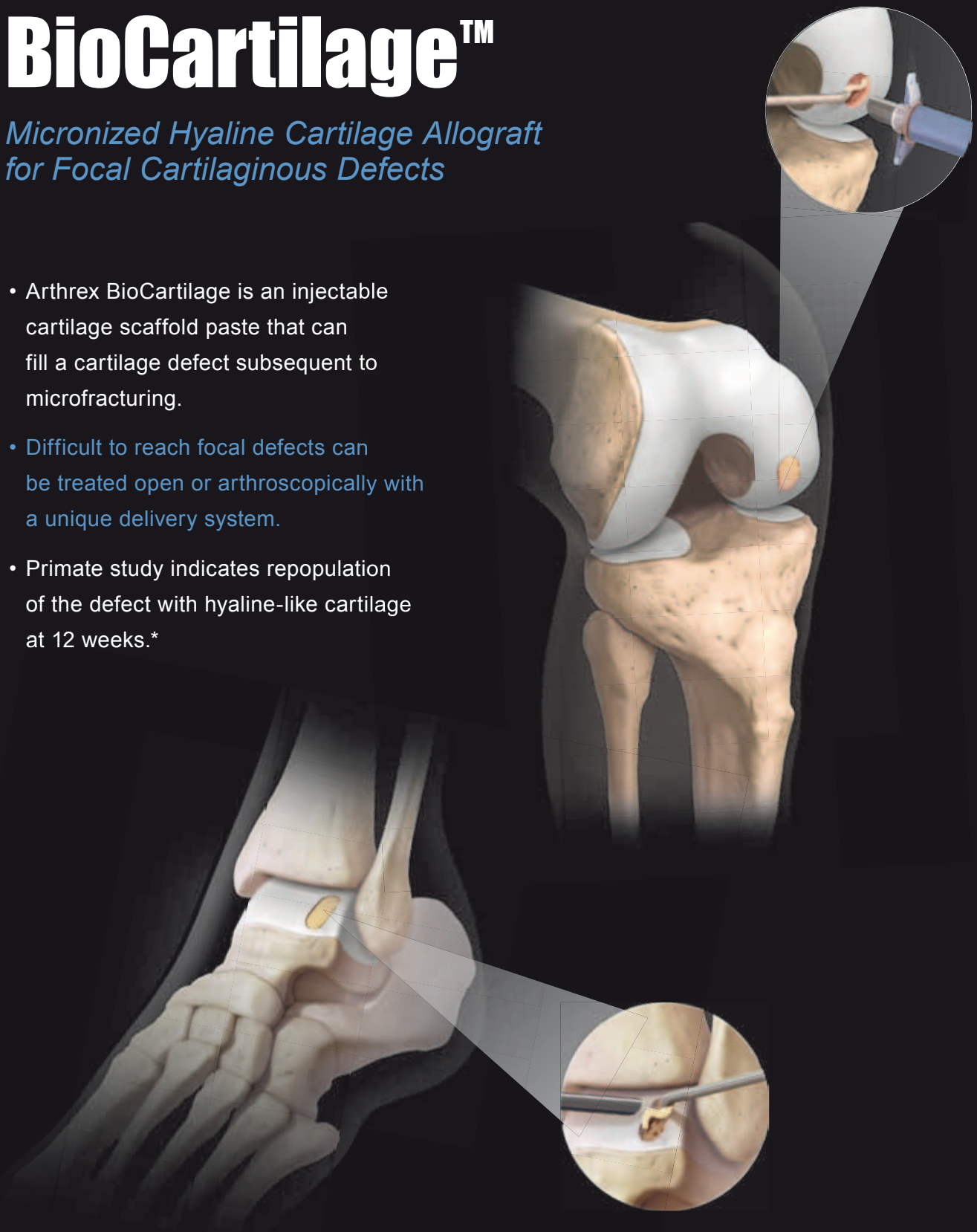

Malinin T, et al, Induction of regeneration of articular cartilage defects by freeze-dried particulate cartilage allografts, ICRS, 2009 Meeting; poster presentation.

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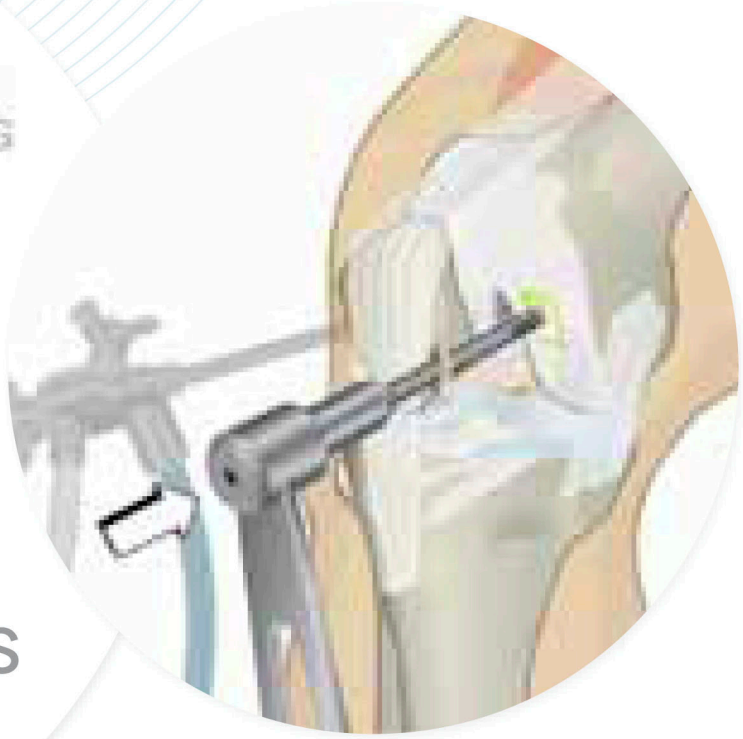

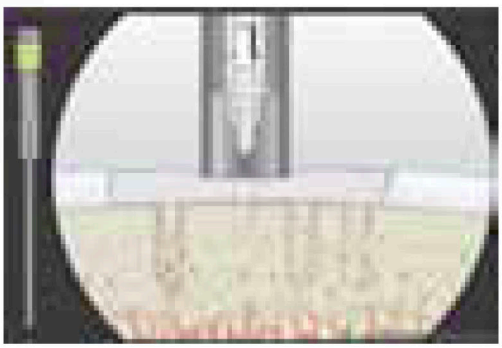

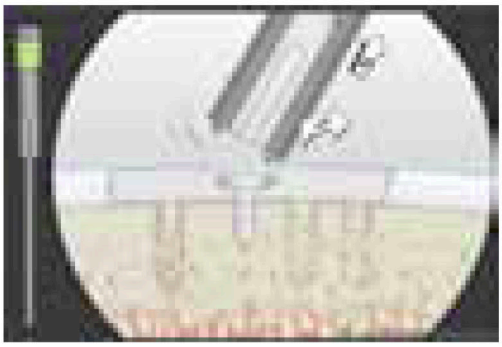

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Sunday, 15 Sept 15.15–15.45:	**AMIC® Knee,** Matthias Steinwachs
Monday, 16 Sept 10.45–11.15:	**AMIC® Knee,** Roland Jakob
Tuesday, 17 Sept 10.45–11.15:	**AMIC® Talus,** Martin Wiewiorski
Wednesday, 18 Sept 09.45–10.15:	**AMIC® Talus,** Markus Walther

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Symposium Invitation

The Future of Chondral & Osteochondral Regeneration with the One-Step Procedure Approach

Monday, 16 September, 2013

Location: Smyrna 2

Time: 13:00 - 14:00

(Certificate of Attendance Provided)

Lunch Provided

Moderator:

Dr. Mahmut Nedim Doral, Hacettepe University, Turkey

Speakers:

Dr. Nurettin Heybeli, Trakya University, Turkey

Dr. Marco Spoliti, San Camillo Hospital, Italy

Dr. Konrad Slynarski, Lekmed Szpital, Poland

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Programme Overview

Sunday, Sept. 15

09:00 – 18:00

Registration

10:00 - 12:00 Plenary Session 0.0
Cartilage Restauration in Turkey - A Clinical & Scientific Update Page 64
Room: Didim

13:00 – 14:00 Plenary Session 1.0
Cartilage & Sports (ICRS-FIFA) Page 65
Room: Smyrna 1

14:15 – 15:15	14:15 – 15:15	14:15 – 15:15
Session 2.1 **Cartilage Injury to Osteoarthritis** Page 65 Room: Smyrna 1	Session 2.2 **Biomaterials in Cartilage Repair** Page 65 Room: Grand Efes II	Session 2.3 **Minimally Invasive CR** Page 66 Room: Smyrna 2

15:15 – 15:45
Coffee Break/Industry Exhibition

15:45 – 16:45	15:45 – 16:45	15:45 – 16:45
Session 3.1 **Cartilage Rehabilitation** Page 66 Room: Smyrna 1	Session 3.2 **Cartilage Development** Page 66 Room: Grand Efes II	Session 3.3 **Intervertebral Disk** Page 67 Room: Smyrna 2

17:00 – 17:45 Plenary Session 4.0
Opening Ceremony & Awards Session Page 67
Room: Smyrna 1

17:45 – 18:45 Plenary Session 5.0
Honorary Lectures Page 67
Room: Smyrna 1

19:00 – 20:30
Welcome Reception
Gardens Swissôtel

Monday, Sept. 16

07:30 – 08:15	07:30 – 08:15	07:30 – 08:15
Session 6.1 **Patellofermoral Cartilage Injury** Page 68 Room: Smyrna 2	Session 6.2 **Tissue Quality & Outcome** Page 68 Room: Grand Efes II	Session 6.3 **How to write, submit or review for the JC** Page 68 Room: Didim

08:30 – 09:30 Plenary Session 7.0
The Subchondral Bone & Cartilage Repair Page 69
Room: Smyrna 1

09:45 – 10:45	09:45 – 10:45	09:45 – 10:45
Session 8.1 **Why is Cartilage Repair Unsuccessful?** Page 69 Room: Smyrna 1	Session 8.2 **Immunology Cytokines Regenokine** Page 69 Room: Grand Efes II	Session 8.3 **Understanding & Managing Pain in CR** Page 69 Room: Smyrna 2

10:45 – 11:15
Coffee Break/Intermission/Exhibition/Poster Viewing

11:15 – 12:45 Free Paper Sessions
9.1 Animal Models Page 70
Room: Didim
9.2 Cell-based Cartilage Repair Page 71
Room: Smyrna 2
9.3 Stem Cells & Cartilage Regeneration Page 72
Room: Smyrna 1
9.4 Biomaterials & Scaffolds Page 73
Room: Grand Efes II

13:00 – 14:00 Industry Symposia
10.1 Sanofi Biosurgery Page 74
Room: Smyrna 1
10.2 Anika Therapeutics Page 74
Room: Smyrna 2
10.3 Synthes Page 74
Room: Grand Efes II
10.4 Karl Storz Page 74
Room: Didim

14:15 – 15:45 Free Paper Sessions
11.1 Outcome, Sport & Rehabilitation Page 75
Room: Grand Efes II
11.2 Cartilage & Meniscus Page 76
Room: Smyrna 2
11.3 Chondrocyte Biology Page 77
Room: Smyrna 1
11.4 Growth Factors & Cytokines Page 78
Room: Didim

16:00 – 17:15
General Assembly (For Members only)
Room: Smyrna 1

16:00 – 18:00
Poster Viewing Cocktail
Room: Poster Area

18:45 – 23:30 (Meeting Point: 18:30 Lobby Convention Center)
President's Dinner at the World Famous Celsius Library

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Programme Overview

Tuesday, Sept. 17

07:30 – 08:15	07:30 – 08:15	07:30 – 08:15
Session 14.1 **Management of Cartilage Injury** Page 79 Room: Smyrna 2	Session 14.2 **Animal & Culture Models** Page 79 Room: Grand Efes II	Session 14.3 **Chondroprotection** Page 79 Room: Didim

08:30 – 09:30 Plenary Session 15.0
Stem Cells Page 80
Room: Smyrna 1

09:45 – 10:45	09:45 – 10:45	09:45 – 10:45
Session 16.1 **Joint-Specific Cartilage Injury and Repair** Page 80 Room: Smyrna 2	Session 16.2 **Systemic Effect of Cartilage Repair** Page 80 Room: Grand Efes II	Session 16.3 **Molecular Regulation of Cartilage Repair** Page 80 Room: Smyrna 1

10:45 – 11:15
Coffee Break/Intermission/Exhibition/Poster Viewing

11:15 – 12:45 Free Paper Sessions
17.1 Imaging & Biomarkers Page 81
Room: Didim
17.2 Marrow Stimulation/Osteochondral Allografts Page 82
Room: Smyrna 1
17.3 Stem Cell Biology Page 83
Room: Grand Efes II
17.4 Osteoarthritis Page 84
Room: Smyrna 2

13:00 – 14:00 Industry Symposia
18.1 Arthrex Page 85
Room: Smyrna 1
18.2 Tigenix Page 85
Room: Smyrna 2
18.3 Regentis Page 85
Room: Grand Efes II
18.4 Episurf Page 85
Room: Didim

14:15 – 15:15 Plenary Session 19.0
The Cartilage Odyssey Page 86
Room: Smyrna 1

15:30 – 16:30	15:30 – 16:30	15:30 – 16:30
Session 20.1 **Cartilage Imaging & Functional Testing** Page 86 Room: Smyrna 2	Session 20.2 **Mesenchymal Stem Cells** Page 86 Room: Smyrna 1	Session 20.3 **Biomakers** Page 86 Room: Grand Efes II

16:30 – 17:30
Poster Viewing/Coffee Break/Industry Exhibtion

17:30 – 18:30	17:30 – 18:30	17:30 – 18:30
Session 21.1 **Meniscus Update** Page 87 Room: Grand Efes II	Session 21.2 **New Horizons in Tissue Engineering** Page 87 Room: Smyrna 1	Session 21.3 **Culture Models** Page 87 Room: Smyrna 2

19:00 – 23:30 (Meeting Point: 19:00 Lobby Convention Center)
ICRS 1001 Turkish Nights at Sultan's Place

Wednesday, Sept. 18

07:30 – 08:15	07:30 – 08:15	07:30 – 08:15
Session 22.1 **Regulatory Aspects of Cartilage Research** Page 88 Room: Didim	Session 22.2 **Current Patient Selection for Cartilage Repair** Page 88 Room: Grand Efes II	Session 22.3 **Cartilage Imaging** Page 88 Room: Smyrna 2

08:30 – 09:00 Plenary Session 23.0
ICRS Vision an Development Page 89
Room: Smyrna 1

09:00 – 09:30 Plenary Session 23.1
YSOS & ICRS Fellowship Report Page 89
Room: Smyrna 1

09:30 – 10:15
Coffee Break/Intermission/Exhibition/Poster Viewing

10:15 – 11:15	10:15 – 11:15	10:15 – 11:15
Session 24.1 **Lessions from Animal Models** Page 90 Room: Smyrna 2	Session 24.2 **Biomechanics-Joint Distraction Arthroplasty** Page 90 Room: Grand Efes II	Session 24.3 **Chondropenia and Early Osteoarthritis** Page 90 Room: Smyrna 1

11:30 – 13:00 Free Paper Sessions
25.1 Joint-specific Cartilage Repair, IVD Page 91
Room: Smyrna 2
25.2 Miscellaneous Clinical Science Page 92
Room: Didim
25.3 Cartilage Cell Transplantation Page 93
Room: Grand Efes II
25.4 Biomechanics/New Cartilage Technologies Page 94
Room: Smyrna 1

13:00 – End of Meeting

Programme at a Glance

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I would like to thank you all for preferring Izmir and wish the conference great success. Hoping that you will allow time to get to know our city and I wish you a pleasant and memorable stay in Izmir.

Yours Sincerely,

Hakan Tartan

Dr. Hakan Tartan
Mayor of Konak Municipality

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Dear Friends, Dear Colleagues

Anthony Hollander

I am delighted to welcome you to Izmir for the 11th ICRS World Congress. This is the first time we have held the congress in Turkey and I know that for many of you this is your first visit to the country. I know that you will find it a warm and friendly place to meet with colleagues in a fascinating destination. The conference agenda is also fascinating with the scientfic, clinical and industry perspectives carefully blended so that there is something for everyone to enjoy and a many opportunities for all of us to learn from each other.

I invite you to approach the meeting in an open-minded way and to go to some sessions outside your normal range so that you can expand your horizons and find new areas of interest. We will all benefit from learning in this way, which is uniquely possible at the ICRS Congress because of the diversity of our membership. Finally, I hope that you will all make an effort to meet new colleagues and expand your network. If you are a younger delegate please don´t be shy of approaching the most famous scientists and clinicians to ask a question or just chat. If you have been coming to ICRS a little longer then please be as open and friendly as you always are. I hope personally to talk with as many of you as possible so please come and say hello during the meeting. I wish you all a pleasant stay in Izmir and a memorable World Congress.

Anthony Hollander
ICRS President 2012 – 2013

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http://bit.ly/Cart2013-4SPreface

Norimasa Nakamura and Rocky S. Tuan

Preface

Cartilage 2013 4: S

http://bit.ly/Cart2013-4S-12

Tommy S. de Windt, Lucienne A. Vonk, Mats Brittberg, and Daniel B.F. Saris

Treatment and Prevention of (Early) Osteoarthritis Using Articular Cartilage Repair—Fact or Fiction? A Systematic Review

Cartilage 2013 4: S -12.

http://bit.ly/Cart2013-4S-21

Susan Chubinskaya and Markus A. Wimmer

Key Pathways to Prevent Posttraumatic Arthritis for Future Molecule-Based Therapy

Cartilage 2013 4: S -21.

http://bit.ly/Cart20134S26

Robert A. Magnussen, Victoria Duthon, Elvire Servien, and Philippe Neyret

Anterior Cruciate Ligament Reconstruction and Osteoarthritis: Evidence from Long-Term Follow-Up and Potential Solutions

Cartilage 2013 4: S -26.

http://bit.ly/Cart2013-4S-37

Christopher D. Murawski, Megan R. Wolf, Daisuke Araki, Bart Muller, Scott Tashman, and Freddie H. Fu

Anatomic Anterior Cruciate Ligament Reconstruction: Current Concepts and Future Perspective

Cartilage 2013 4: S -37.

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Dear ICRS Members, Colleagues and Friends

We have the great pleasure of welcoming you to the 11th Word Congress of the International Cartilage Repair Society in Izmir, Turkey. This meeting of our society will provide another exciting and comprehensive update on the basic science of cartilage as well as the newest clinical research on cartilage injury and cartilage repair. It provides a wonderful opportunity for basic scientists, surgeons, rehabilitation specialists, and industry partners to share the rapidly advancing knowledge in cartilage biology and regenerative medicine. Besides providing our members and guests with an update on the latest developments, a specific goal of the 2013 program is to provide a unique forum for interdisciplinary education and to inspire a creative translational exchange between clinical and preclinical scientists in this exciting field. Accordingly, the scientific sessions have been designed to combine both basic science and clinical aspects of each individual topic to facilitate translational scientific exchange, education, and collaboration.

The basic science (preclinical) perspective includes new stem cell and tissue engineering topics, research areas (ECM derived scaffolds, lessons from cartilage development, molecular regulation of repair) as well as world class speakers who will provide in-depth presentations on the specific topics that promise to become the sources for next generation musculoskeletal tissue regeneration and repair technologies.

From a clinical perspective, the most recent, up-to-date information on current treatment approaches will be presented as well as emerging clinical technologies and concepts that will provide the basis for the future diagnosis of cartilage injury, cartilage restoration and rehabilitation. Specifically, the role of the subchondral bone in cartilage pathology and restoration, immunological aspects of joint injury and function, and new clinical applications of recent tissue engineering approaches, novel biomaterials, and modern molecular biology and cellular technologies for cartilage restoration will all be presented during the Izmir meeting. Practical issues like cartilage rehabilitation, lessons from failed cartilage repair, and management of the broad spectrum of cartilage injury and degeneration will be discussed by international clinical leaders. In addition, comprehensive instructional courses and new “Current Concept Lectures” will offer unique learning opportunities from experienced clinical experts on clinically relevant topics.

The 11th World Congress is the first ICRS meeting held in the world’s Eastern hemisphere bringing state-of-the-art cartilage science and technology closer to the doorstep of many active members and cartilage scientists from Asia, India, and the Middle East. We look forward to an open and stimulating scientific and cultural exchange that will give all participants the opportunity to learn from each other’s unique experiences and approaches to cartilage science and will further promote the active ongoing international collaboration in our steadily expanding society.

Kai Mithoefer & Wiltrud Richter
Scientific Co-Chairs ICRS 2013

Wiltrud Richter

Kai Mithoefer

Didem Kozaci

Mehmet Binnet

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Past World Congresses

- 1997 – 1st World Congress
  Freiburg, Switzerland; Roland Jakob
- 1998 – 2nd World Congress
  Boston, USA; Alan Grodzinsky
- 2000 – 3th World Congress
  Gothenburg, Sweden; Lars Peterson
- 2002 – 4th World Congress
  Toronto, Canada; Shawn O'Driscoll
- 2004 – 5th World Congress
  Gent, Belgium; Rene Verdonk
- 2006 – 6th World Congress
  San Diego, USA; Bert Mandelbaum, Bill Bugbee
- 2007 – 7th World Congress
  Warsaw, Poland; Jaroslaw Deszczynski,
  Jacek Kruczynski, Konrad Slynarski
- 2009 – 8th World Congress
  Miami, USA; Jack Farr, Tom Minas
- 2010 – 9th World Congress
  Sitges / Barcelona, Spain; Ramon Cugat, Pedro Guillen
- 2012 – 10th World Congress
  Montreal, Canada; Michael Buschmann, Patrick Lavigne

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1997	Roland Jakob, Switzerland
1998	Roland Jakob, Switzerland
1999	Alan Grodzinsky, USA
2000	Lars Peterson, Sweden
2001	Lars Peterson, Sweden
2002	Shawn O'Driscoll, USA
2003	Shawn O'Driscoll, USA
2004	Ernst Hunziker, Switzerland
2005	Ernst Hunziker, Switzerland
2006	Mats Brittberg, Sweden
2007	Mats Brittberg, Sweden
2008	Bert Mandelbaum, USA
2009	Lisa Fortier, USA
2010	Lisa Fortier, USA
2011	Daniël Saris, NL
2012	Anthony Hollander, UK
2013	Anthony Hollander, UK (current)

Honorary Fellows

2007	Alan Grodzinski, USA
2007	Roland Jakob, Switzerland
2007	Lars Peterson, Sweden
2009	Mats Brittberg, Sweden
2012	Tom Minas, USA
2012	Stefan Nehrer, Austria

Award Winners

- **Genzyme – ICRS Award for Excellence in Cartilage Research**

2004	Ronald Dorotka et al, Austria
2006	Mark Randolph et al, United Kingdom
2007	Gerjo Van Osch et al, The Netherlands
2009	Avner Yayon et al, Israel
2010	Attila Aszody et al, Germany
2012	Xiaofeng Cui et al, USA

- **Genzyme – ICRS Lifetime Award**

2004	Lars Peterson, Sweden
2006	Allan Gross, Canada
2007	Arnold Caplan, USA
2009	Richard Steadman, USA
2010	Mats Brittberg, Sweden
2012	Joseph Buckwalter, USA

Best Rated Abstracts

2007	K. Nakagawa et al, Japan
2007	C. Moser et al, Germany
2009	J.F. Harrington et al, USA
2010	S. D'Arcy et al, Ireland
2012	G. Van Den Akker, NL
2013	N. Nakamura et al, Japan

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Zaslav Kenneth, Richmond, USA

Invited Faculty Members

Please find the “who is who” of our distinguished invited faculty members on pages 28 to 50.

(Only invited faculty members, who have sent us their biosketch and portraits by July 30, could be included in this book and therefore it does not represent an complete listing.)

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Phone +41 44 503 73 70
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office@cartilage.org

Congress Dates

Start: Sunday, Sept. 15 at 10.00
End: Wednesday, Sept. 18 at 13.00

Language

The official language of the congress is English. No simultaneous translation will be provided.

Congress Registration

- Pre-Registration

Until Sept. 05, only internet online registrations are accepted at www.cartilage.org. After that date, only onsite registration at the Swissôtel congress registration desk will be possible.

- On-Site Registration

The registration desks are located on the ground level of the Swissôtel conference centre.

Attention: ICRS-Members who are not in good standing with their membership dues 2012/2013 will automatically be charged with the non-member fee by the registration system.

Congress Registration Fees

Early, until July 08

ICRS Members	€ 390.00
Non-Members	€ 550.00
Industry Representatives	€ 650.00
Junior-Members/Residents/Nurses*	€ 290.00*
Acc. Persons**	€ 90.00**

Late, July 9 to August 20

ICRS Members	€ 490.00
Non-Members	€ 650.00
Industry Representatives	€ 750.00
Junior-Members/Residents/Nurses*	€ 390.00*
Acc. Persons**	€ 100.00**

On-Site, as from August 21

ICRS Members	€ 550.00
Non-Members	€ 690.00
Industry Representatives	€ 850.00
Junior-Members/Residents/Nurses*	€ 450.00*
Acc. Persons**	€ 110.00**

** to be accompanied by a certificate signed by the head of department, if not a Junior Member of ICRS*

*** accompanying persons do not have access to attend scientific sessions but are cordially invited to attend the Welcome Reception and the Opening Ceremony*

Payment – Registration Fees

Registration fees must be paid to ICRS within 10 days after the date of registration or latest until the end of the registration period of the respective fee type. Payments can be made as follows:

- **By Credit Card**

VISA, Euro/Mastercard and American Express

- **Cash (onsite only)**

TL, US$ & € Euros are accepted

General Information

Regular Registration Fee includes

- Access to all Scientific Sessions (except Instructional Courses)
- Access to the Technical Industry Exhibition
- Access to the Scientific Poster Exhibition with wine & cheese
- 17 CME Credits (for the whole congress attendance)
- Welcome Reception & Coffee Breaks
- Congress Bag with Main Programme
- Personal Badge and Certificate of Attendance

On-site Registration Desk Opening Hours

The secretarial office and the registration desk will be open as follows:

Saturday	Sept 14	16.00 – 18.00
Sunday	Sept 15	09.00 – 18.30
Monday	Sept 16	07.15 – 18.30
Tuesday	Sept 17	07.15 – 18.30
Wednesday	Sept 18	07.15 – noon

On-site Check-in Procedures

Delegates must personally check-in at the appropriate registration desk at the main entrance with a valid ID. An express lane for check-in of pre-registered and prepaid delegates will be available.

Participants are requested to bring the confirmation letter or a copy of the invoice with them. This will facilitate an efficient congress check-in.

Cancellations of Congress Registrations & Name Changes

Written notification is required for all registration cancellations and name changes. Cancellation of registration should be sent to the ICRS Congress Office in Zurich. Name changes will be charged with € 100.00 each.

Refunds for registration cancellations are as follows

- 80% for cancellations before June 15
- 50% for cancellations from June 16 to August 20
- No refund can be made thereafter

In case of cancellation due to the rejection of abstracts or refuse of entry visa to Turkey, the full amount of the registration fee will be refunded.

Cancellation of the Congress by the Organizer

In case of cancellation of the congress by the organizer, congress fees will be refunded in case of cancellation due to other reasons than war, war-like events, acts of terrorism or epidemics, in which case only a proportional part would be refundable.

Badges

All participants should pick-up their badges at the registration desk. The personalized badge is not transferrable and it is your admission card to the congress.

Badge Replacement: Please do not forget or lose your badge. In case of loss, a replacement badge will only be provided against an administrative charge of € 50.00.

Security Checks

For organizational and security reasons, badges have to be worn all the time at the congress venue. A lanyard will be given to you with the congress bag. ID-checks may occur at any time.

Final Programme

Participants will find a copy of the "Final Programme & Abstract book" in the congress bags. The bags will be handed out upon congress check-in. The congress abstracts will be available well in advance of the congress in a searchable database on our website as well as in pdf format. New this year will be that congress abstracts and the programme of interest can be downloaded to your IPhones.

Additional copies may be purchased at the rate of € 15.00 per book, at the registration desk.

Information for Authors & Presenters

Speaker's Ready Room / AV Centre

The Speaker Ready Room is located on Level 3 at Room Konak 2. All presentations must be in English and must be provided on CD-ROM or USB-Memory Stick to be placed on the central server on-site. It is mandatory that the data carriers are delivered to the Speaker Ready Room at least 3 hours prior to the respective session. The computers in the server room are equipped with Microsoft Windows 7 and Microsoft Office 2010. If you use Macintosh, please convert your Keypoint presentation or your PowerPoint Presentation for MAC into PowerPoint for PC Windows format. In case of using QuickTime movies into your presentation, please take care to convert the movies into a standard video codec like MPEG 2. If you have any doubt, please contact the AV Centre 4 hours before your presentation. Our technicians will have enough time to verify and adapt your presentation if needed.

Important:
It will not be possible to use your own laptop or your memory stick for your presentation in the session rooms. If a presenter has included videos into the PPT presentations, she/he should make sure that the movies run on the most commonly used video software with Windows compatible codec. Example: MPEG 2.

The material remains the property of the speakers and will only be re-used by ICRS with the speaker's permission. Without this formal permission, your data will be definitely deleted after the congress.

Financial Disclosure Statement:

All Presenters must include a Financial Disclosure Statement. We request all presenters to cooperate in this by declaring any commercial role or conflicts of interests in the related research on the first slides of their presentations or on the posters for poster presentations.

Opening hours Speaker's Ready Room / AV Centre:

Saturday	Sept 14	16.00 – 18.30
Sunday	Sept 15	08.00 – 18.30
Monday	Sept 16	07.00 – 18.30
Tuesday	Sept 17	07.00 – 18.30
Wednesday	Sept 18	07.00 – 13.00

Podium Presentations / Free Papers

Speaking Time: 7 Minutes
Discussion Time: 3 Minutes

It is absolutely necessary that all podium presenters respect the given speaking time in order not to delay the entire congress schedule. Session Moderators are instructed to interrupt a presentation in case of exceeding the speaking time of 7 Minutes.

Scientific Poster Sessions

Monday Sept 16 from 16.00 – 18.00 (Wine & Cheese)
Tuesday Sept 17 from 16.30 – 17.30 (Coffee Break)

In addition to the electronic poster exhibit, the authors where asked to bring a traditional paper poster and reserving in advance a poster wall with ICRS. All congress participants are strongly encouraged to join both poster sessions. Specific poster tours during these sessions on Monday and Tuesday will be organized. To facilitate discussions and networking, all wall poster presenters are required to stay near their poster boards during both poster session time. Authors should encourage a lively discussion with interested participants. The presenters should introduce themselves as poster presenters and be well prepared to answer questions and initiate discussions. Approximately 250 wall posters are located in the foyers of the congress center and the electronic posters stations are located at level 5. The abstracts of the posters can be found on our website and in the electronic poster viewing system onsite.

Wall Poster Certificates:

A jury will select the best wall posters, who will be awarded with a certificate.

Electronic Poster Exhibition

(Partly sponsored by Geistlich Surgery)

14 Workstations will be available for viewing about 250 electronic scientific exhibits. To facilitate communication between authors and participants, all users can leave a message to any author of any electronic poster in the system. The authors are required to answer these questions during and after the congress. Participants are requested to make intense use of this facility to enhance communication with the authors of the electronic posters.

The system offers great flexibility and provides enhanced opportunities for communication. The ability to use moving images, to link to related websites, to search quickly the whole of the scientific exhibition for specific topics in minute detail, to e-mail entire exhibits to one's-self or

General Information

to a colleague and to access the exhibit from any internet-linked computer in the world are amongst its many advantages besides the post congress availability of the presentations during many years.

Users have also the possibility to informally score/rate the electronic posters by clicking on the "stars" in the system, besides to bookmark important ones.

Our onsite staff will be happy to introduce you to the system and assist you during these hours.

E-Poster Certificates:

- 2 Awards "Magna cum Laude"
- 2 Awards "Cum Laude"
- 2 Awards "Certificate of Merit"

Publication – Supplement Journal "Cartilage"

Congress abstracts are citable and will also be published electronically in the congress supplement of our official Journal "Cartilage", published by Sage ISSN 1947-6043.

We strongly encourage all authors to submit their full manuscripts to our peer reviewed journal "Cartilage" which publishes full length original manuscripts on all types of cartilage including articular, nasal, auricular, tracheal/bronchial, and intervertebral disc fibrocartilage. Manuscripts on clinical and laboratory research are welcome. Instructions to authors for submissions are available at http://cart.sagepub.com

General Assembly / Business Meeting (for members only)

Monday, Sept. 16, 2013, 16.00 – 17.15 - Smyrna 1

All ICRS members are kindly invited to attend our General Assembly. Retired Members and Corporate Members have no right to vote, but are most welcome to attend the Business Meeting.

CME – Credits (17 Hours)

The ICRS 2013 is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.net The ICRS 2013 - 11th World Congress of the International Cartilage Repair Society is designated for a maximum of, or up to **17 European CME credits** (ECMEC).

Each medical specialist should claim only those credits that he/she actually spent in the educational activity. The EACCME credit system is based on 1 ECMEC per hour with a maximum of 3 ECMECs for half a day and 6 ECMECs for a full-day event.

Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME credits to an equivalent number of AMA PRA Category 1 Credits™. Information on the process to convert EACCME credit to AMA credit can be found at www.ama-assn.org/go/internationalcme.

Live educational activities, occurring outside of Canada, recognized by the UEMS-EACCME for ECMEC credits are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada.

Certificate of Attendance / CME Credits

To obtain your confirmation of attendance and your CME Credits, you may choose one of two options

- **Print your certificate onsite at the Congress**

Please use one of the dedicated workstations to print out your certificate. After having identified yourself by means of your badge number and your last name, the personalized certificate of attendance will be printed automatically.

- **Print your certificate at your home**

Upon your return from Turkey, please visit www.cartilage.org. After having identified yourself online by means of your badge number and last name you can print-out at home your personalized certificate of attendance.

Time Zone

Standard time zone daylight saving: UTC/GMT +2 hours. Time zone abbreviation: EEST – Eastern European Summer Time.

Language

The official congress language is English. No simultaneous translation will be provided. The official country language, Turkish, is the first language in the country. However many people in the city centres and resort areas also speak English, to some degree.

Climate

The Aegean type Mediterranean climate of Izmir can be easily characterised by its lengthy, sunny summer months and mild, winter weather. Many tourists favour visiting Izmir during the spring or fall seasons, when the climate is pleasantly warm and dry. Between September and October, temperatures in Izmir regularly exceed 25°C / 76°F and can often top 30°C / 85°F

General Information

Clothing

Smart casual wear is recommended. For visiting mosques, dress neatly as you would to visit a church (no shorts or sleeveless tops, and wear socks to walk on the carpets).

Credit Cards / Cash Machines

All major credit cards are widely accepted. Bank cash machines (ATM) can be found easily and debit cards are also widely used. If you are using a foreign card at a bank machine, your money will be disbursed in Turkish funds. There is also an ATM machine in the lobby of the Swissôtel.

Currency

The currency in Turkey is Turkish Lira. 1 € Euro 2.50 TL (Date of printing, July 2013). Euros and US dollars are also accepted in many hotels and tourist awreas, but you will save money by converting some funds into Turkish liras at one of the many exchange offices or banks in the city. They typically offer competitive rates and charge no fees.

Tipping

Service charges are typically not included in the bills in Turkey. Please add 10 % for restaurants and bars or add the equivalent of 1–5 US$ for a friendly service. This applies to waiters, barbers and hairdressers, taxi drivers, etc. Tips should rather be given in cash Turkish liras and not be added to the credit card charge on the bills.

Health Care

Special Vaccinations are not required for entry into Turkey but an individual travel & health insurance is highly recommended because health insurance plans often do not extend full coverage for medical services received outside the country of residence

Entry Formality / Visa

We strongly recommend that all participants needing a visa to attend the Congress in Turkey start their application process as soon as possible by contacting the local Turkish Consulates to obtain and follow instructions.
www.mfa.gov.tr/visa-information-for-foreigners.en.mfa.

Disclaimer

ICRS and the congress organizer cannot accept any liability for the acts of any suppliers to this meeting nor the safety of any attendee while in transit to or from this event. All participants are strongly advised to carry proper travel and health insurance as the ICRS cannot accept liability for any accidents or injuries that may occur. The information in this programme is subject to change without prior notice. For updated information please visit frequently our congress online programme on our website.

Cancellation of the Congress by the Organizer

Congress fees will be reimbursed if the congress is cancelled for other reasons than war, warlike events, and acts of terrorism or sickness epidemics. In the latter circumstances only a proportion of the congress fee would be refundable.

Technical Industry Exhibition

A technical industry exhibition with will take place at the Swissôtel convention centre. It will be open every day throughout the meeting and exhibitors will present a wide range of orthopaedic- and cartilage repair related products. Participants are encouraged to take advantage of this unique opportunity to be updated with the most recent advances and latest news from our industry partners. Interested companies may contact the ICRS Executive Office for further exhibit- and sponsoring information.

Intermissions

During intermissions, coffee, tea and refreshments will be served in the exhibition area as a courtesy from the ICRS.

Services for Persons with Disabilities

Please inform the ICRS office or indicate on the accommodation online booking form any special requirements you may have to allow us to best serve you. The Swissôtel has international-standard facilities for the physically challenged, including access ramps, elevators and toilets for people with special needs.

Security / Badges

The safety of all congress attendees is of utmost importance to our society. ICRS and the Swissôtel have taken security precautions to ensure the maximum possible safety for all participants. Identity check controls may occur at any time by the security staff. Congress badges are personalized, not transferable and guarantee individual access to different section of the event. For organizational and security reasons, badges have to be worn all the time at the congress venue.

General Information

Electricity, Weights and Measures

- Electricity: 220 volts 60 hz
- Weights: Kilo/Gramm system
- Measures: Metric system

Water

Turkish tap water is generally not safe to drink. We recommend drinking bottled water.

Internet/WLAN

As a special courtesy, ICRS will provide free WLAN Hot Spots and a public Internet corner to all attendees and exhibitors.

Meals, Snacks & Refreshments

The Restaurant & Bar in the Hotel Lobby will be at your disposal during the opening hours. Delegates may purchase light meals, snacks, sandwiches, salads, sweets and soft drinks against payment. No lunch or lunch boxes will be provided by the ICRS. However, most Industry Satellite Symposia organizers will offer exclusive lunch boxes during their symposia at lunch time.

During morning intermissions, coffee, tea and refreshments are served in the exhibition area. The coffee breaks are offered by ICRS to all delegates and company representatives.

Mobile Phones

Please turn-off or put your mobile phone to the "silent-modus" during all scientific sessions.

Photos/Recording

Taking photos or video/ audio recording during the scientific presentations or from the poster area is strictly prohibited. Note that the majority of the Presentations, posters and many officially audiorecorded sessions will become available online after the congress at the ICRS website in the members' area. Therefore there is no need to take pictures during the sessions or from the poster exhibits.

Security

The safety of all congress attendees is of the utmost importance to the ICRS meeting. The conference centre and ICRS have taken security precautions to ensure the maximum possible safety for all the participants. Identity check controls may occur at any time.

Smoking

The ICRS World Congress is a non-smoking congress. Smoking is not permitted at the conference centre except in designated smoking areas outside of the building.

Opening Ceremony, ICRS Awards

Sunday Sept. 15, 2013, 17.00 – 17.45
Room: Smyrna 1

Awards

The following offical ICRS honors will be awarded:

- ICRS – Lifetime Award
- ICRS – Sanofi Award for Excellence in Cartilage Research (US$ 5000.00)
- ICRS / FIFA Award (US$ 1000.00)
- Best Rated Abstract
- 6 Electronic Poster Awards
- Wall Poster Certificates

Travel and Transportation

Swissôtel Buyuk Efes, Izmir is conveniently located in the centre of Izmir's commercial district, steps away from the heart of the city. Adnan Menderes Airport is less than 15 km away. The cost of taxi is of around US$ 28 from the airport to downtown hotels.

Official Airline Network – Convention Code: TK06S13

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The Star Alliance member airlines are pleased to be appointed as the Official Airline Network for ICRS 2013 Izmir, Turkey.

To obtain the Star Alliance Conventions Plus discounts and for booking office information please visit www.staralliance.com/conventionsplus and: Choose "For delegates" - Under "Delegates login" enter the conventions code **TK06S13.** Choose one of the participating airlines listed or call the respective reservation contact listed and quote the conventions code **TK06S13** when booking the ticket. Registered participants plus one accompanying person travelling to the event can qualify for a discount of up to 20%, depending on fare and class of travel booked.

Discounts are offered on most published business and economy class fares, excluding website/internet fares, senior and youth fares, group fares and Round the World fares. Please note: For travel from Japan and New Zealand special fares or discounts are offered by the partici-

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No matter where you are travelling from, the Star Alliance™ network offers you a wide choice of flights to Izmir.

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You can also save money when you book your flights. Simply quote the Convention Code TK06S13 and you plus one travelling companion will receive a special discount. Better still, no matter which Star Alliance member airline's frequent flyer programme you belong to, you can earn and redeem miles across all 28 airlines.

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www.staralliance.com

Information correct as of 06/2013

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Hotel Information/Accomodation

Swissôtel Grand Efes (Congress Venue)
Gaziosmanpasa Bulvari No:1
35210 Alsancak, Izmir, Turkey
izmir@swissotel.com
www.swissotel.com/izmir

The Swissôtel Grand Efes is prominently located in the heart of Izmir's commercial hub and set in 12,000 m2 of landscaped gardens overlooking the spectacular Kordon on the Aegean Sea. The hotel is within walking distance of the city centre and the airport is less than 15 km away. 402 luxuriously appointed guest rooms including 55 spacious suites feature state-of-the-art technology.

Special Courtesy: As a special courtesy, the hotel offers exclusively to ICRS congress attendees, complimentary health club access and free high speed internet access in the hotel rooms. Children under 12 years, sharing the room with their parents are free of charge.

Room Rates
(incl. Breakfast buffet and Service Charges, VAT excl.)

• Classic & Swiss Advantage Room:
SGL € 150.00 / DBL € 170.00

• Business Suite Room
SGL € 300.00 / DBL € 320.00

• Executive Suite Sea View Room:
SGL € 450.00 / DBL € 450.00

Hilton Izmir
Gazi Osmanpasa Bulvari No:7
35210 Izmir, Turkey
derya.ficici@hilton.com
www.izmir.hilton.com

Enjoy the dramatic setting with staggering views of Izmir Bay and the surrounding mountains from the Izmir Hilton hotel. Spanning 34 floors, the hotel is one of the tallest buildings in the region, offering superior views in every single guest room and suite. Located in the heart of the city, near to the old town, the hotel is within walking distance of shopping, entertainment and dining.

Special Courtesy: Early Check-in and Late Check-out upon availability. Free Health Club and WLAN access for ICRS participants. Fitness center, heated indoor pool, squash and tennis courts, etc.

Room Rates
(incl. Breakfast buffet and Service Charges, VAT excl.)

• Hilton Superior Room
SGL € 110.00 / DBL € 130.00

• Hilton Sea View Room
SGL € 130.00 / DBL € 150.00

• Hilton Executive Floor Sea View
SGL € 144.00 / DBL € 155.00

Credit Card Guarantee / Payment
A credit card guarantee for the entire reservation period is required to confirm and secure your hotel room reservation. Please note that your Hotel invoice shall be settled directly to the hotel upon your check-out.

Hotel Room Cancellation
Cancellations are to be addressed to the Hotels directly in writing. The following cancellation fees will apply:
For cancellations until August 12, charge of 1 night. For cancellations after August 12 and No-Shows, charge of the entire reservation period.

Hotel Reservation Changes
Hotel reservation changes must be directed to the individual hotels in written. Room night reductions of existing reservations are subject to the cancellation conditions as described above.

Social Networking Opportunities

ICRS supports compliance with international ethical standards and therefore emphasizes that participants who would like to attend social events shall bear all related costs themselves.

Sunday, September 15

Welcome Cocktail
19.00 PM – 20.30 PM
Participants, industry representatives and accompanying persons are invited to join the opening ceremony and welcome cocktail at the Swissôtel Grand Efes. This reception is offered to you by the ICRS. After the cocktail, participants have free time for their own leisure to discover Izmir and enjoy one of the many nice restaurants / bars at the harbour promenade right in front of the Swissôtel.

Monday, September 16

ICRS Fun Run for Healthy Joints (3-4 km)
06.15 AM– 07.00 AM
ICRS and the Hotel Swissôtel Grand Efes understand that maintaining a fitness routine while traveling is difficult. Congress participants wanting to get off the treadmill and take their workout outside can join the complimentary ICRS Fun Run led by members of the ICRS & Swissôtel Grand Efes management teams. Runners meet at 6:00 a.m. in the Lobby for a four-mile beachside jog returning by 6:45 a.m.

Fun Run 2010, Spain

Monday, September 16

ICRS 2013 President's Dinner
20.00 PM

SOLD OUT

The President's Dinner 2013 **will be held at the World Famous Celsius Library in Ephesus, one of the great cities of the Greeks in Asia Minor and home to the Temple of Artemis, one of the Seven Wonders of the World.** The venue is located around 70 KM South of Izmir or a 1 hour drive away from the Swissotel (Meeting Point at 18.30 hs at the Foyer of the Convention Center, Bus departure at 18.45)
Fee: 140 Euros

Tuesday, September 17

1001 Turkish Nights
19.30 PM – 23.00 PM
Great Turkish style entertainment for everyone! Join us for a magic evening with mouth watering oriental cuisine, drinks and assist amazing folkloric presentations such as belly dancers, whirling dervishes and much more. Let you be immersed in a magical 1001 night atmosphere together with your colleagues from all around the world. Here, you can look forward to delicious specialties, regional beverages and enjoy typical music and cultural show acts. Price per person: (incl. dinner, drinks & entertainment) Individual Participants: 75.00 (partly sponsored by ICRS) Industry Representatives: € 95.00

Invited Faculty 2013 in alphabetical order (not complete)

Akgun Isik, Prof. MD
Gayrettepe Florence Nightingale Hospital,
Orthopaedics & Traumatology,
Esenyurt Istanbul, Turkey

Prof. Isık Akgun was working at Cerrahpasa School of Medicine ,department of orthopaedics and traumatologia in Istanbul-Turkey until 2011 and has now his own practice. He received his MD at Istanbul university in 1980 and completed a specialization in orthopadica in 1986.He became Associated Professor of orthopaedics at Istanbul University - Cerrahpasa School of Medicine in 1993 and became Professor i n 1999 .He is interested in sports medicine ,knee surgery and cartilage repair.He has papers about microfractures,and he has research about tru-fit and culture of mesenchymal stem cells. He studied at various clinic, USA, Germany, England. He gave also many lectures in many foreign countries. He is now the president of Istanbul Turkish association of sports injuries, arthroscopic surgery and knee surgery. He is member of ESSKA ,ISAKOS, ICRS and AAOS.

Alini Mauro, Dr.
AO Research Institue, Biomaterials and
Tissue Engineering,
Davos, Switzerland

Mauro Alini graduated in Chemistry from the University of Lausanne (Switzerland) in 1983. Since then he has been involved in connective tissue research, starting form his Ph.D. research work, done at the Laboratory of Cellular Pathology in Locarno (Switzerland), which focused on the isolation and characterization of proteoglycans extracted from both normal human mammary gland and carcinomas thereof. In September 1988, he joined the Joint Diseases Laboratory (under Dr. A. R. Poole's direction) at the Shriners Hospital in Montreal to work on quantitative and qualitative changes in extracellular matrix proteins (particularly proteoglycans and collagens) of the growth plate tissue before and at the time of cartilage matrix calcification during endochondral bone formation. In January 1995, he was appointed as an Assistant Professor at the Division of Orthopaedic Surgery of the McGill University (Chair Prof. M. Aebi) and head of the Biochemistry Unit of the Orthopaedic Research Laboratory, working to develop new biological approaches to treating intervertebral disc damage. Since July 2000, he is in charge of the Musculoskeletal Regeneration Program at the AO Research Institute (Davos, Switzerland), focusing on cartilage, bone and intervertebral disc tissue engineering. Since September 2009 is also the Vice-Director of the same Research Institute.

Angele Peter, Prof.
University Hospital Regensburg,
Department of Trauma Surgery,
Regensburg, Germany

After my residency in the Department of Trauma and Reconstructive Surgery at the University Hospital of Regensburg, Germany, I became a consultant in the Department of Trauma Surgery with focus on regenerative knee surgery. Since July 2010 I have been fulfilling a professorship position for " Regenerative Joint Therapy" at the University Hospital Regensburg. In addition, I extended my focus on regeneration of the knee joint by becoming a partner in a highly specialized institution "sporthopaedicum" in 2008. Every year, I perform approximately 1000 knee surgeries with the main focus on ligament reconstruction, cartilage and meniscus regeneration. Cartilage regeneration has also been my main research interest. From 1997 to 1999 I spent a DFG sponsored research fellowship at Case Western Reserve University, USA. My research focus was stem cell based chondrogenic differentiation and mechanobiology. After my return to the University Hospital Regensburg I continued with basic and translational research by establishing an own research group. Over the last 10 years this group could achieve grant money of more than 2 Million Euro and we published more than 60 peer reviewed, medline listed papers with the focus on stem cell based cartilage and meniscus regeneration. Since 2010 I have been the director of the FIFA Excellence Centre in Regensburg. The research focus within this responsibility is the prevention and the optimized treatment of cartilage and ligamentous injuries of the athletes.

Årøen Asbjørn, MD, PhD
Oslo University Hospital, Department
of Orthopaedic Surgery,
Oslo, Norway

Asbjørn Årøen MD, PhD is researcher at the Oslo Sports Trauma Research Center and Orthopedic surgeon at the Department of Orthopedic Surgery at Akershus University Hospital. Asbjørn is a specialist in general surgery and orthopedic surgery and has been in clinical practice since 1995 and his clinical practice is focusing knee and shoulder injuries. He is also an appointed member of Regional Ethical committee from 1st July 2013. In 1997 he spent one year as a research fellow at the University of Pittsburgh with Professor Freddie H. FU where he focused his research on cartilage and PCL injuries additional to clinical work. Asbjørn served as a team physician for a local soccer club during a 2 years period with special attention to prevention of injuries. He has published twenty nine research papers concerning the topic cartilage injuries rehabilitation, Achilles tendon ruptures, posterior cruciate ligament, posterolateral corner of the knee and ankle problems. Asbjørn has published additional review papers about cartilage injuries, book chapters in addition to instructional courses and DVD.

Invited Faculty 2013 in alphabetical order (not complete)

His PhD degree, "Cartilage Injuries and the Repair Process", considering the prevalence, injury mechanisms and treatment options for cartilage was defended by the University of Oslo in October 2005. Asbjørn was one of 4 selections for the ESSKA-ASIAN-PACIFIC FELLOWSHIP; March-April 2008, and at the moment, as a KSSTA Editorial Member. He received as the senior author the prestigious Hughston award for the best study in the American Journal of Sports Medicine in 2011. From 2012, Asbjørn has been a reviewer in 6 major orthopedic journals. He is supervising 3 PhD students focusing on diagnosis and treatment of cartilage injuries, treatment of PCL injuries, and on fracture care and prevention in children. He also serves as the leader of the Orthopedic Research Group at Akershus University Hospital. Asbjørn's new projects are related to the natural history of the combination of cartilage injury and anterior cruciate ligament rupture and the use of mesenchymal stem cells for treatment of cartilage injury in the knee. He has recently completed an international fellowship to take part in a biomechanical study on posterior cruciate ligament surgery with the Steadman Phillippon Research institute.

Aszodi Attila, Dr. PdD
Ludwig-Maximilians-University (LMU),
Department of Surgery,
Munich, Germany

Attila Aszódi studied biology and chemistry at the Eötvös Lorand University, (Budapest, Hungary) and received his PhD at the Agricultural Biotechnology Center (Gödöllö, Hungary) in cell biology. After a postdoc period in the Max Planck Institute for Biochemistry (Martinsried, Germany, 1995-97) he was a group leader at the Department of Experimental Pathology of Lund University Hospital (Lund, Sweden, 1998-2001) where he received his Habilitation in Experimental Pathology. In 2002-2010, he was a group leader at the Department of Molecular Medicine of the Max Planck Institute for Biochemistry, Martinsried, Germany. In 2011, he has joined to the Laboratory for Experimental Surgery and Regenerative Medicine (Experimed) at the Department of Surgery, Ludwig-Maximilians University of Munich and leads the Cartilage Research unit. Since 2013 he is a co-chair of Experimed. Attila Aszodi´s research interest is focusing on the understanding of common molecular and cellular processes acting in embryonic, adult and healing cartilaginous tissues. His group is applying an interdisciplinary strategy that combines mouse genetics, cell biology and tissue engineering in order to study normal, pathological and regenerative skeletal tissue biology. He is a board member of the International Matrix Biology Society and has joined to ICRS in 2011.

Bekkers Joris, MD
UMC-Utrecht, Orthopaedic Surgery,
Utrecht, Netherlands

Dr. Joris Bekkers is an orthopedic resident with special interest in translational cartilage repair and imaging. He currently works at the orthopedic department of the University Medical Center Utrecht, the Netherlands. He followed a student research fellowship at the Mayo Clinic at the lab of prof. O'Driscoll and prof. K-N An studying the biomechanics of in vitro cultured cartilage. In 2007 he obtained his Medical Degree at the University of Utrecht following which he started a PhD program on translational cartilage research. This resulted in his thesis entitled: 'Towards one-stage cell-based treatment and non-invasive evaluation of cartilage defects' which can be downloaded at http://www.e-pubs/?epub=jorisbekkers. His research focused on the preclinical development of the one-stage IMPACT cartilage repair procedure as well as non-invasive imaging modalities for cartilage regeneration. In 2012 he was awarded the ICRS Stryker clinical scientist travelling fellowship.

Bentley George, Prof.
Royal National Orthopaedic Hospital,
Sarcoma unit,
Stanmore, United Kingdom

Professor George Bentley is the Lead Investigator for the ACI/MACI cartilage clinical trial at the RNOH, Stanmore, UK. In addition he is an Honorary Orthopaedic Surgeon at the Royal National Orthopaedic Hospital, London.

He carried out his orthopaedic training in the Universities of Sheffield, Birmingham and Oxford and became Professor of Orthopaedics in Liverpool in 1976. In 1982 he became Professor and Director of the Institute of Orthopaedics in University College London.

He was the first person to transplant successfully cartilage cells, a study that was published in Nature in 1972. Since then he has continued to carry out translational research with cartilage cells, including a recent 10 year follow-up study of 800 patients who had undergone ACI or MACI. This study not only showed the success of the method over a long period of time, but also the factors that were important in achieving good results.

He has been President of the British Orthopaedic Research Society, the British Orthopaedic Association and the European Federation of National Associations of Orthopaedics and Traumatology (EFORT). He has been Chairman of the Scientific Committee of the British and EFORT Orthopaedic Societies and has extensive experience in both clinical and laboratory cartilage transplantation. He is an active member of the ICRS and the ORS and has published over 300 papers in peer-reviewed journals and made 500 presentations at Universities and to Learned Societies. In 2012 he was awarded the Life Time Achievement Award of the UK/ICRS Cartilage Club.

Invited Faculty 2013 in alphabetical order (not complete)

Binnet Mehmet, Prof., MD
Ankara University - İbni Sina Hospital,
Orthopeadic Surgery,
Ankara, Turkey

Mehmet S.Binnet is an Orthopaedic Surgeon and the Professor of Department of Orthopaedic and Traumatological Surgery at Ibni Sina Hospital, Ankara . As a Professor, he is responsible for academic formations at the University of Ankara, Turkey. Mehmet S.Binnet received his initial training with Prof.Dr.F.Fu and being a former pupil of Prof.Dr.Werner Müller, it was quite natural that in 1989 he devoted his activity on knee surgery. Mehmet S.Binnet was nominated Professor at the University of Ankara in 1995 . His main activity is clinical. Academically, he is well published including multiple journal articles (62) and five boks chapter.

He has been a member of the ICRS since 2000 and is currently serving as the chair of the ICRS 11 th World Congress in Izmir. His research interest is in the clinical application and evaluation of with tissue engineering techniques for large cartilage defects . He also served 2001-2003 as executive board member for the Turkish Socitey of Orthopaedics and Traumatology. Presently, he is Past President of the Turkish Society of Sports Traumatology, Arthroscopy and Knee Surgery.

As a team physician Dr. Binnet has worked with Turkish National Football Team and he was the Chairman Medical Commitee of Turkish Foootball Association . Since 1992 he was Medical Commitee Member of UEFA and served as UEFA Medical Officer for EURO 96 in England, EURO 2000 in Belgium -Holland, EURO 2004 in Portugal, EURO 2008 in Switzerland -Austria and EURO 2012 in Poland-Ukraine. In 2006-2008 he was appointed to FIFA Medical Assessment and Research Project (F-MARC).

Brittberg Mats, Ass. Prof., MD
Kungsbacka Hospital, Göteborg University,
Cartilage Research Unit,
Kungsbacka, 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.

Burdick Jason A., Prof., PhD
University of Pennsylvania, Department
of Bioengineering,
Philadelphia, USA

Jason A. Burdick, PhD is Professor of Bioengineering at the University of Pennsylvania in Philadelphia, PA, USA. Jason has his PhD in Chemical Engineering from the University of Colorado and was a postdoc at MIT. Dr. Burdick's research involves the development of hydrogels for various biological applications and his laboratory is specifically interested in understanding and controlling polymers on a molecular level to control overall macroscopic properties. These hydrogels include photocrosslinkable systems based on natural polymers that exhibit spatially and temporally distinct properties and can be processed into fibrous structures, as well as self-assembled materials designed from non-covalent chemical interactions that are useful as injectable hydrogels. The applications of his research range from controlling stem cell differentiation through material cues to fabricating scaffolding for regenerative medicine and tissue repair. Jason currently has over 125 peer-reviewed publications and has been awarded a K22 Scholar Development and Career Transition Award through the National Institutes of Health, an Early Career Award through the Coulter Foundation, a National Science Foundation CAREER award, and a Packard Fellowship in Science and Engineering. He is on the editorial boards of Tissue Engineering, Biomedical Materials, Biomacromolecules, Journal of Biomedical Materials Research A, ACS Applied Materials and Interfaces.

Invited Faculty 2013 in alphabetical order (not complete)

Buschmann Michael, Prof., PhD
École Polytechnique de Montréal,
Génie Chimique,
Montréal, Canada

Michael Buschmann received a B. Engineering Physics from the University of Saskatchewan in 1984, and a Ph.D. in Medical Engineering and Medical Physics from the Division of Health Sciences and Technology at the Massachusetts Institute of Technology and Harvard University in 1992. His postdoctoral training in cartilage microscopy and histology was then completed at the University of Bern in Switzerland in 1994. Since 1994, Dr. Buschmann has established a multidisciplinary research program as Professor of Biomedical Engineering and Chemical Engineering at Ecole Polytechnique. The program focuses on the use of biomaterials to repair joint tissues including articular cartilage and on the discovery and development of polymer-based gene and drug delivery systems for Diabetes, Cancer and Inflammatory diseases. (http://www.polymtl.ca/tissue/). He is one of the primary inventors of the BST-CarGel™ technology now in Pivotal clinical trial evaluation, and has been involved in transferring technology to founding BioSyntech (acquired by Piramal Healthcare Canada) and Biomomentum Inc, another Canadian start-up. Dr. Buschmann has published 115 articles, 241 conference proceedings and 15 patented or patent pending inventions. He is Director of the FRSQ Group in Biomedical Science and Technology and has received the Innovator Prize from the Quebec Association for Industrial Research (ADRIQ), the Melville Medal from the American Society of Mechanical Engineers (ASME), and an Award of Merit of the Canadian Arthritis Network of Centres of Excellence.

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

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

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

Dr. Cole is a Professor in the Department of Orthopedics with a conjoint appointment in the Department of Anatomy and Cell Biology at Rush University Medical Center in Chicago, Illinois. In 2011, he was appointed as Chairman of Surgery at Rush Oak Park Hospital. He is the Section Head of the Cartilage Research and Restoration Center at Rush University Medical Center, a multidisciplinary program specializing in the treatment of arthritis in young active patients. He also serves as the head of the Orthopedic Master's Program and trains residents and fellows in sports medicine and research. He lectures nationally and internationally, and through his basic science and clinical research has developed several innovative techniques for the treatment of shoulder, elbow and knee conditions. He has published more than 1,000 articles and has published 5 widely read textbooks in orthopedics.
Dr. Cole was chosen as one of the Best Doctors in America" each year since 2004 and as a "Top Doctor" in the Chicago Metro area each year since 2003. In 2006, he was featured as "Chicago's Top Doctor" and placed on the cover of Chicago Magazine. Dr. Cole is the team physician for the Chicago Bulls NBA Basketball team, co-team physician for the Chicago White Sox Major League Baseball team and DePaul University in Chicago. In 2009, Dr. Cole was chosen as the "NBA Team Physician of the Year". Dr. Brian J. Cole is a member of Midwest Orthopaedics at Rush, the regional leader in comprehensive orthopaedic services.

Diego Correa, MD, MSc, PhD
Cleveland, United States of America

MD from Universidad Javeriana (Bogotá-Colombia); MSc in Mechanical Engineering from Universidad de Los Andes (Bogotá-Colombia); PhD in Cellular and Molecular Physiology from Yale University (2004-2008) / Harvard University (2008-2009). Currently, appointed as Sr Research Associate at the Skeletal Research Center - Case Western Reserve University (Cleveland, OH – USA), where he leads the projects related with the use of MSCs in the areas of Articular Cartilage repair and their role during the establishment of skeletal cancer

Invited Faculty 2013 in alphabetical order (not complete)

metastasis, where he holds a patent (along with Dr Arnold Caplan). Dr Correa is an expert in Cell Biology, with special interest on adult stem cells and their clinical application in Regenerative Medicine. Author and co-author of numerous papers, and recipient of various distinctions and fellowships, such as the Young Investigator Award from OARSI (Osteoarthritis Research Society International); special delegate for the Academy of Achievements 46th International Summit; the George Robert Pfeiffer Fellowship from the Gustavus and Louise Pfeiffer Research Foundation during graduate school at Yale University, and the Engineering School Research Fellowship from Universidad de Los Andes. Dr Correa also participates in entrepreneurial activities, such as the creation of successful private start-up companies in the areas of Regenerative Medicine and adult stem cell-based therapies.

Dell'Accio Francesco, MD, PhD, FRCP
Centre of Experimental Medicine and Rheumatology, William Harvey Reserarch Institute, London, United Kingdom

Dr Dell'Accio is a clinical rheumatologist and a scientist whose interest is focused in cartilage biology. He has been active in the field of cartilage repair by and autologous chondrocyte transplantation. Moving to the UK in 2003 he unveiled the molecular cascade activated by injury to the articular cartilage. His current research aims at understanding the role that individual signaling molecules in cartilage wound healing and homeostatic responses, with the ultimate goal to develop pharmacological interventions to restore cartilage integrity.

Dr Dell'Accio and his group investigate the molecular mechanisms that preside to the healing of skeletal tissues, and in particular to cartilage, with the ultimate aim of identifying possible therapeutic intervention to promote cartilage healing/supporting cartilage homeostasis in diseases such as isolated cartilage defects and osteoarthritis. Dr Dell'Accio's group identified a distinct signalling response of adult human articular cartilage to mechanical injury. Individual signalling molecules and signalling pathways identified by this screening are being tested in vitro and in vivo for their function in cartilage biology and joint surface repair. In vivo models include surgical models of osteoarthritis (destabilization of the medial meniscus (DMM) or a novel model of mechanical cartilage injury and regeneration developed in our laboratory. His group have recently discovered that WNT molecules can signal simultaneously through multiple, reciprocally inhibitory pathways, with distinctive outcomes (Nalesso et al. J Cell Biol 2011). He is now exploring on one hand the biological function of such mechanism for cartilage homeostasis, and on the other hand how we can exploit it to protect cartilage from degradation in arthritis.

Diederichs Solvig, PhD
Orthopaedic University Hospital Heidelberg, Research Centre for Experimental Orthopaedics, Heidelberg, Germany

Solvig Diederichs studied biochemistry at Hannover University, Germany, and received her PhD in 2008 on dynamic cell cultivation for bone tissue engineering. She focused her postdoctoral research at the Research Center for Experimental Orthopaedics at the Heidelberg University Hospital, Germany, on adult stem cell biology with application in tissue engineering and regeneration of bone and cartilage. Currently, she works on adult and pluripotent stem cell differentiation into mesenchymal lineages, bioreactor techniques and application of physical strain, and functionalization, designing and testing of biological scaffolds. Her first postdoctoral assignment was at the Heidelberg University Hospital, where she worked on mesenchymal stem cell chondrogenesis in bioactivated scaffolding materials. As a research fellow she joined Prof. Dr. Tuan's group at the University of Pittsburgh School of Medicine for two years, where she worked on induced pluripotent stem cell differentiation into the mesenchymal lineage. She returned to Heidelberg in January 2013 where she is presently building her own research group focusing on induced pluripotent stem cells for regenerative orthopaedics in the Research Center for Experimental Orthopaedics.

Erggelet Christoph, Prof. PhD
Center for Biologic Joint Surgery, Zürich, 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 a member of the ICRS since the foundation in 1997 and served as a board member. As a member of the education comittee he initiated the ICRS Surgical Skills Course series together with Prof. Dr. Stefan Nehrer from Vienna/Austria.

Invited Faculty 2013 in alphabetical order (not complete)

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

Dr. Farr received his undergraduate degree in Biological Engineering from Rose Hulman Institute of Technology in Terre Haute, Indiana in 1975, where he also was awarded an honorary doctorate of Biological Engi¬neering. He earned his medical degree from Indiana University in 1979. He completed his Orthopaedic Surgery residency at Indiana University Medical Center in 1986.

Over the past 25 years, Dr. Farr has continued to focus his practice in sports medicine and knee restoration. His numerous appointments and affiliations include a voluntary clinical professorship in Orthopaedic Surgery at Indiana University Medical Center, a board position with the Cartilage Research Foundation (treasurer) the International Cartilage Repair Society (Industry Liaison Committee Chair) and Patellofemoral Foundation.

As a leader in US cartilage restoration advances, Dr. Farr has written numerous articles, book chapters and is completing a car¬tilage book to be published in 2013. He lectures both national and internationally and participates in several ongoing articular and meniscal cartilage clinical trials. He also was a design surgeon for a Meniscal Allograft Trans¬plant System and two knee patellofemoral osteotomy systems (T3 with Arthrex and Tracker with DePuy/Mitek). For patients with knee changes too far advanced for restora¬tion, Dr. Farr worked as a design surgeon for a new/current partial knee replacement system (Sigma High Performance Partial Knee Replacement). Dr. Farr is actively affiliated with the Indiana Orthopaedic Hospital, Community Hospital South and St. Francis Hospital Center. He also has courtesy affiliations with other Indianapolis area hospitals.

He is a member of the American Academy of Orthopaedic Surgeons, the American Orthopaedic Society of Sports Medicine, the International Cartilage Repair Society and numerous other professional organizations.

Feng-Huei Lin, Distinguished Professor
National Taiwan University, Institute of Biomed. Eng., Taipei

Dr. Feng-Huei Lin was born in 1957 in Taiwan. He obtained his BS degree in Department of Earth Sciences, National Cheng Kung University (NCKU), Taiwan, in 1980. After served in army for 2 years, he was invited to be a teaching assistant in Department of ES, NCKU, in 1982. In 1983, he joined the Functional Ceramics Lab in Institute of Materials Sciences and Engineering, NCKU, Taiwan. He was assigned to do the research in Bio-ceramic and Composite for Orthopaedics; where he received the training both in Materials Technology and Medical Science. During the PhD training, he was not only to take course in engineering school, but also in medical school; that included biochemistry, cell biology, physiology, pathology, anatomy... He was honoured as PhD degree with 12 SCI publications in November, 1989. In early 1990, He was recruited as an associate professor in Centre for Biomedical Engineering, College of Medicine, National Taiwan University (NTU); where he started his academic career. In 1997, he promoted to the full professor. He organized to setup the institute of biomedical engineering in NTU and served as acting director in the institute during 1997-1999. He was invited to be the first Engineering background director in Department of Biomedical Engineering, NTU-hospital (2003-2005). In 2005-2008, he back institute of biomedical engineering, NTU, as director. During 2006-2009, National Science Council, Taiwan, asked his help to be the Convenor of Biomedical Division to allocate the budget and to make the future planning in the next 10 years. In 2008-2012, he temporarily transferred to Biomedical Engineering Division, National Health Research Institute, as director and took in charge of Development of Biomaterials and Tissue Engineering. Now, he is the distinguished professor in NTU, Chair professor in National Taipei University of Technology, Executive editor of Journal of Biomedical Engineering (SCI) and International Fellow of International College of Biomaterials Sciences and Engineering.

Dr Lin served as standing committee member in many international societies since 1996. He was permanent international advisory board in Ceramic, Cell and Tissue (CCT) (1998-2010); and served as the President in 2010. He was one of the standing committee members in WACBE (2005-) and council member in TERMIS-AP Chapter (2009-2011). He also served as editorial board members in many SCI journals, for instance, Biomaterials, International Journal of Biomaterials, International Journal of Biomater Resear and Eng, Journal of Musculoskeletal Research etc..

Since 1990, Dr Lin has published over 220 SCI papers, joined 6 book chapters, awarded 47 patents and transferred 14 technologies to industry to be product. He expanded his research interests by discussion with clinical doctors 4 hours every week. His research is in scaffold for tissue engineering, nano-technology for drug and gene delivery, bio-nano-science for cancer hyperthermia, biomaterials for stem cell research, and hydrogel for vitreous body substitute. He is willing to cooperated with different kinds of researchers and scientists; and very happy to help young blood to do the research by sharing the knowledge, experience and lab tools. He is very experience both in academic research and industry to push the research fruits to the commercial product.

Invited Faculty 2013 in alphabetical order (not complete)

Frondoza Carmelita, Assoc. Prof., PhD
Johns Hopkins University, Orthopaedic Surgery, Balto, United States of America

Carmelita G. Frondoza, Ph.D., currently holds appointments as Associate Professor in the Department of Orthopaedic Surgery, School of Medicine at the Johns Hopkins University, and as Professor in the Department of Clinical Science, College of Veterinary Medicine, Mississippi State University. Her area of interest is the biology of joints in health and disease with a focus on cartilage.

Dr. Frondoza obtained her PH.D degree in Immunology at Johns Hopkins University and did her postdoctoral training at the Johns Hopkins Oncology Center. She subsequently became Director of Research at the Johns Hopkins Arthritis Division, Department of Orthopaedic Surgery with joint appointments in the School of Public Health, Department of Molecular Immunology and The Oncology Center. She later served as Senior R&D Director at Nutramax Laboratories. She has published extensively in the field of Orthopaedics, lectured at universities and scientific meetings. She is a peer reviewer for several journals and is on editorial boards. In addition to her research activities, she has mentored predoctoral, medical and veterinary students as well postgraduate fellows.

Gelse Kolja, MD
Univesity Hospital Erlangen, Orthopaedic Trauma Surgery, Erlangen, Germany

Kolja Gelse studied Medicine at the University of Erlangen-Nuremberg, Germany, and the DUKE University Medical Center, USA, from 1996 –2003. In 2004 he received the degree "summa cum laude" for his MD thesis at the Department of Experimental Medicine, University of Erlangen. He performed his clinical education as Resident at the Department of Orthopaedic Trauma Surgery and the Department of Orthopaedic Rheumatology at the University of Erlangen-Nuremberg from 2003-2010. Since 2007, he is the leader of the Laboratory for Cartilage and Osteoarthritis Research at the University Hospital Erlangen. In 2010 he certified as a specialist for Orthopaedic and Trauma Surgery and finished his "Habilitation" on the subject "Cellular and molecular therapeutic approaches for cartilage defects and osteoarthritis". Since 2010 he is Attending Clinician at the Department of Orthopaedic Trauma Surgery at the University Hospital Erlangen. He has received international and national awards, including the Dr. Fritz Erler Junior Price for Operative Medicine and the Karl-von-Frisch Price. He has published over 44 peer-reviewed publications and book chapters. His basic scientific interests include the mechanisms of chondrocyte differentiation and cellular as well as molecular approaches for cartilage repair and treatment of osteoarthritis.

Gerhardt Michael, MD
Santa Monica Orthopaedic and Sports Medicine Group, Santa Monica, USA

Dr. Gerhardt is a board certified orthopaedic surgeon who joined the Santa Monica Orthopaedic and Sports Medicine Group in 2003 as the group's Director of Hip and Groin Disorders, in addition to seeing patients with all other types of musculoskeletal injuries. Dr. Gerhardt has completed subspecialty training in hip arthroscopy, and is one of the leading physicians in the country with extensive experience in new, minimally invasive techniques for hip procedures. Dr. Gerhardt is also active in sports medicine, serving as Team Physician for US Soccer Federation, Pepperdine University, and Chivas USA of Major League Soccer, among others.

Dr. Gerhardt graduated from the Medical College of Pennsylvania, and performed his internship and residency at the University of Southern California, before completing a Sports Medicine Fellowship with the Santa Monica Orthopaedic and Sports Medicine Group.

Getgood Alan, MD
University of Western Ontario, Fowler Kennedy Sport Medicine Clinic, London, Canada

Alan is Associate Professor of Trauma and Orthoapedic Surgery at the University of Warwick, UK. His clinical interests include sports injuries of the knee and shoulder, and the treatment of young arthritics, with a particular focus on osteotomy, articular cartilage repair and meniscal reconstruction. His research includes both a clinical and basic science focus, with an emphasis towards combination biological products, which can potentially enhance tissue regeneration.

Following graduating from the University of Edinburgh in 2000, Alan moved to Cambridge to complete his orthopaedic training. In 2009 he completed his Doctor of Medicine thesis entitled 'Articular Cartilage Tissue Engineering' from the University of Cambridge. A one-year fellowship in orthopaedic sports medicine followed at both the Fowler Kennedy Sport Medicine Clinic (London, Ontario, Canada) and Banff Sport Medicine (Alberta, Canada), where he was involved in the medical care for Alpine Canada ski team. On returning to the UK, he then completed a further knee reconstruction fellowship in Coventry. In September this year he will return to the Fowler Kennedy Clinic to take up a faculty position at the University of Western Ontario and continue his clinical and research interests. When away from work Alan enjoys skiing, climbing and running marathons.

Invited Faculty 2013 in alphabetical order (not complete)

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

Dr. Alberto Gobbi, born in October 1956, in Milan, Italy, is a Board certified surgeon and specialist in the field of orthopaedics, traumatology and sports medicine. He has been performing highly skilled surgeries for decades, which coupled with his scientific and research oriented mind, have led to a tremendous growth in the field of arthroscopy and cartilage repair worldwide. He chairs OASI Bioresearch Foundation Gobbi Onlus, a 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.
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.

Görtz Simon, MD
University of California, San Diego,
Orthopaedic Surgery,
San Diego, United States of America

Simon Görtz received his medical degree from the Julius-Maximilians-Universität Würzburg, Germany in 2004, before completing a post-graduate research fellowship at the University of California, San Diego. There, he served as the Secretary of the Organizing Committee of the 6th ICRS World Congress in San Diego in 2006. In 2008, he was awarded the ICRS Lars Peterson - Genzyme Traveling Fellowship. Simon is past president of the ICRS Young Scientists and Orthopaedic Surgeons group, has served the ICRS as an abstract reviewer, and on the ICRS Education & Meeting as well as Regulatory & Industry Liaison committees. He has co-authored over ten book chapters and 75 peer-reviewed articles and abstracts related to articular cartilage repair. He currently is a resident physician in the Department of Orthopaedic Surgery at the University of California, San Diego. His clinical and research interests include sports medicine and lower extremity reconstruction, with a focus on cartilage repair.

Grässel Susanne, Prof.
University of Regensburg,
Orthopaedic Surgery,
Regensburg, Germany

Susanne Grässel is an APL-professor at the Dept. of Orthopedic Surgery, Experimental Orthopedics, University of Regensburg in Germany. She received her doctoral degree in Biology at the Westfälische Wilhelms-University of Münster 1992 and went as a postdoctoral fellow first to the Dept. of Pathology and after two years to the Dept. of Dermatology and Cutaneous Biology, Thomas –Jefferson-University, Philadelphia, USA where she started to work on molecules of the extracellular matrix (Perlecan and Collagen XVI). 1997 she went back to Münster as an Assistant Professor where she obtained her habilitation in Physiological Chemistry and Pathobiochemistry on a Lise-Meitner-Habilitationsfellowship. In 2003 she started as an Associate Professor at the Dept. of Orthopedic Surgery where she founded the Laboratory of Experimental Orthopedics. In 2010 she was awarded with the Apl-Professorship for Experimental Orthopedics. She is board member of the "Division Basic Research" of the DGOU and the German Society of Matrix Biology and was awarded with several orthopedic prices (Wilhelm-Roux-award, Albert Hoffa-award, Themistokles-Gluck award). Her basic scientific research interests are cartilage biology and pathology, bone and cartilage degeneration and regeneration, chondrogenic and osteogenic differentiation of MSC, peripheral nervous system in cartilage and bone pathology, collagens and tumorigenesis.

Henrotin Yves, Prof.
University of Liège, Motricity Sciences,
Liège, Belgium

Yves Henrotin is Professor of Pathology, Physical Therapy and Rehabilitation and director of the Bone and Cartilage Research Unit at the University of Liège (Belgium) www.bcru.be. He is also an administrator of the Centre of Immunology (CIL) and the Centre for Oxygen Research and Development (CORD). He has been head of the Physical Therapy and Rehabilitation department at the

Invited Faculty 2013 in alphabetical order (not complete)

Princess Paola Hospital, Marche-en-Famenne, Belgium, since 1991. He is the member of the American College of Rheumatology, the Osteoarthritis Research Society International, the French Society of Rheumatology and the International Cartilage Repair Society. Since 2006, he is member of the board of directors the Osteoarthritis Research Society international (OARSI), the premier organization focused on the prevention, diagnosis and treatment of osteoarthritis. He was elected treasurer in 2010. He has been elected permanent chairmen of the world BMJD debate and consensus congress since 2010. Further, he was chairman of the 2010 OARSI world congress. He is also the vice-president of the Spine section and the osteoarthritis section of the French Society of Rheumatology since 2008, board member of the French Society of Rheumatology since 2011, president of the Belgium Back Society since 2000 and president of the Belgium Scientific Society of Physical Therapy since 2008. He was the Belgium delegate and board member of the COST B13 action "Low back pain: guidelines for its management" organized by European Commission Research Directorate General. He is Co-President of the board of the National Council of Physical Therapy and Rehabilitation for the Belgium Health Ministry. He serves the editorial board of several scientific reviews including "Osteoarthritis and Cartilage". He is a section editor of the BMC musculoskeletal disorders since 2009. He is also member of international Faculty of F1000 section rheumatology and immunology which consists of experts who are highly respected in their chosen fields and nominated to the Faculty of 1000 (F1000) by their peers. He has published over 200 scientific peer-reviewed papers and 10 chapters of book. He is the co-editor of the book "Osteoarthritis: clinical and experimental aspects" (Springer), co-editor of "Primer in OA" (edited by the OARSI) and editor of the book "Nonpharmacological modalities for the management of osteoarthritis" (Bentham). In 2005, he received a prestigious national prize (De Cooman Prize) for his contribution in the better understanding of osteoarthritis pathophysiology. He is also the founder and the chairman of the board of Artialis SA, a spin-off of the University of Liège specialized in the research and development of biological markers of musculoskeletal disorders www.artialis.be

Hoemann Caroline, Prof. PhD
Ecole Polytechnique, Dept Chemical Engineering, Montreal, Canada

Dr. Hoemann (PhD, MIT, 1992), spent 5 years as an R&D director, in a Montreal-based biomedical device company, where she co-invented a novel medical device for articular cartilage repair, BST-CarGel®. The product was recently tested in an 80-patient controlled randomized clinical trial, with promising interim data at 1 year post-treatment. Dr. Hoemann is an associate professor of Chemical Engineering and Biomedical Engineering, has over 40 publications, 6 patents, and serves on the editorial board of Cartilage, and The Open Orthopaedics Journal. Her translational research program aims to understand the mechanisms of cartilage repair, in order to bring new treatment options to patients with arthritis.

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

Anthony Hollander is the Arthritis Research UK Professor of Rheumatology and Tissue Engineering at the University of Bristol and current President of the International Cartilage Repair Society. He has many years 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.

Hoshi Kazuto, Associate Prof., PhD
Graduate School of Medicine,
The University of Tokyo,
Tokyo, Japan

Kazuto Hoshi MD, PhD graduated from Faculty of Medicine, the University of Tokyo in 1991. He worked in the University of Tokyo Hospital as a clinical fellow of orthopaedic surgery. He obtained PhD from the University of Tokyo in 1998. Since 2001, he has been an associate professor of Department of Cartilage & Bone Regeneration, Graduate School of Medicine, the University of Tokyo, and has been engaged in the research and develop for clinical application of cartilage tissue engineering. His laboratory focus on the application of cell biology on chondrocytes and stem cells for cartilage regenerative medicine, the fabrication of tissue-engineered cartilage with greater firmness and a 3D-structure, and the clinical trials of the tissue-engineered cartilage. He has received Young Investigator Award of Japanese Society for Bone Morphometry (1999), Young Investigator Award of Japanese Association of Anatomist (2000), Young Investigator Award of Japanese Society for Bone and Mineral Research (2001), Young Investigator Award of Japanese Society of Electron Microscopy (2002), Outstanding Paper Award of Japanese Society for Regenerative Medicine (2004) and The Johnson & Johnson Innovation Award of Japanese Society for Regenerative Medicine (2013).

Invited Faculty 2013 in alphabetical order (not complete)

Hurtig Mark, Prof. DVM
University of Guelph, Clinical Studies,
Guelph, Canada

Professor Mark Hurtig is the director of the Strategic Research Resource Laboratory for the Canadian Arthritis Network at the University of Guelph in Canada. He received a DVM at Guelph in 1978, an MVSc from the University of Saskatchewan in 1983, and completed American College of Veterinary Surgeon Diplomate status in 1989. While working 15 years as a staff surgeon for the Ontario Veterinary College at the University of Guelph he developed a career interest in joint injuries and sports medicine that has led to collaborations in cell & molecular biology, biomechanics, engineering, biochemistry, and biophysics. He has been an ICRS member since 1998 and served as an ICRS board member, chairing the animal models subcommittee during 2005-2008. His working group on risk factors that predict osteoarthritis after knee injury includes faculty and clinician-scientists from hospitals across Canada with collaborations in many other countries. His laboratory encourages graduate students from many other disciplines who wish to focus their career on articular injuries and tissue repair.

Kandel Rita, MD
Mount Sinai Hospital, Laboratory Medicine & Pathobiology,
Toronto, Canada

Dr. Rita Kandel is a clinician-scientist and Chief of Pathology and Laboratory Medicine at Mount Sinai Hospital, Toronto, Canada. She is a Professor in the Department of Laboratory Medicine and Pathobiology at the University of Toronto, cross-appointed to both the Department of Surgery and the Institute of Biomaterials and Biomedical Engineering at the University of Toronto. She is the Director of the Bioengineering of Skeletal Tissues Team, which consists of a multidisciplinary group of investigators, including engineers, biologists, stem cell biologists, and clinicians whose work focuses on regenerative medicine. Her research interest is in the bioengineering of tissues for articular cartilage repair and intervertebral disc replacement. She has been active in many organizations including International Cartilage Repair Society (ICRS). She is the Program Chair for the 2014 World Congress on Osteoarthritis (OARSI). She is currently an Associate Editor of Cartilage and a member of the Editorial Board of Osteoarthritis and Cartilage. She has published over 190 papers and has or applied for 6 patents.

Karperien Marcel, Prof., Dr., PhD
University of Twente, Tissue Regeneration,
Enschede, Netherlands

Prof. Dr. Marcel Karperien (h.b.j.karperien@utwente.nl) 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.

Knutsen Gunnar, Ass. Prof. PhD
University Hospital North-Norway,
Orthopedic Dept.,
Tromsoe, Norway

Present: Consultant Orthopaedic Surgeon University Hospital North Norway and Associate Professor University of Tromso. Specialist registration 1990 in general surgery and 1994 in orthopaedic surgery

Since 1994 I have been consultant orthopaedic surgeon at the University Hospital North Norway. In 2010 I had the position as Head of orthopaedic department, however, after one year I decided to spend more time again in clinic and research. PhD University of Tromso 2008: Cartilage repair: The use of chondrocytes and bone-marrow cells in cartilage repair.

Main interests are osteochondral repair, arthroscopic surgery, sports traumatology, osteoarthritis and knee replacements. I have been working clinically and scientifically with cartilage injuries and repair since the mid nineties and I am the leader of a Norwegian randomized trial comparing ACI and microfracture. Recently we started a new cartilage RCT comparing AMIC and ACI-C, and I am supervising new PhD candidates. I had a sabbatical year from my post in Norway 2002-2003 working with Prof James Richardson in Oswestry UK (Robert Jones and Agnes Hunt Orthopaedic and Hospital). For more than 10 years I have been consultant orthopaedic surgeon for a top level soccer club in Norway.

Invited Faculty 2013 in alphabetical order (not complete)

Kon Elizaveta, MD
Instituti Ortopedici Rizzoli, Biomechanics Laboratory, Bologna, Italy

Elizaveta Kon, MD was born in Moscow. Degree in Medicine in 1994 and Specialization in "Orthopaedics and Traumatology" at the University of Bologna 1999. Since 1993 carry out surgical, clinical, and research activities at the Rizzoli Orthopaedic Institute in Bologna, Italy.

Staff member of the III Clinic Orthopaedic and Traumatology and Biomechanics Laboratory (leaded by Prof. Maurilio Marcacci), orthopaedic surgeon and researcher focusing on clinical and basic research in the musculoskelal tissue engineering. Assistant Professor of Motor Sciences Faculty of the University of Bologna, held the course of "Bioengineering applying to the locomotor apparatus pathology" (2000-2005). Since 2010 Director of Nano-Biotecnology Laboratory and carry on personally numerous research projects and clinical trials regarding biotechnology applications in orthopaedics (from pre-clinical studies to clinical trials). Principal investigator of numerous research projects funded by the Italian Government and European Community.

President of Cartilage Committee of European Society of Sports Traumatology Knee Surgery and Arthroscopy (ESSKA). President of Fellowship Scholarships and Grants Committee and member of the General Board ICRS. Co- founder and past president of Young Surgeons and Orthopedic Surgeons (YSOS) club of International Cartilage Repair Society (ICRS). President of the Cartilage Committee and Board Member of the Italian Society of Knee, Arthroscopy Sport Cartilage and Orthopaedic Technologies (SIGASCOT).

Elizaveta Kon has authored over 1000 peer-reviewed scientific articles and over 20 chapters in textboooks in orthopedic surgery. She has presented at over 200 society meetings all over Europe, Asia and North America. Awards: ICRS Travelling Fellowship in 2004 and ESSKA - AOSSM travelling fellowship in 2009. She is a member of the Editorial Board of the BMC Musculoskeletal Disorders Journal and European Journal of Sports Traumatology, reviewer for many Orthopedic journals including American Journal of Sports Medicine (golden reviewer), Cartilage, Journal of Arthroscopy, Clinical Orthopaedics and Related Research, Knee Surgery Sports Traumatology Arthroscopy Journal, Journal of Tissue Engineering, Biomaterials ect.

Kreuz Peter Cornelius, Dr. PhD
Uniklinik Rostock, Klinik und Poliklinik für Orthopädie, Rostock, Germany

PD Dr. med. habil. Peter Cornelius Kreuz is orthopaedic surgeon at the university medical center Rostock, Germany. After his medical eduction in Munich (Germany), Sanct Gallen (Switzerland) and Washington (USA), he received his MD at the Ludwig Maximilian university of Munich in 2001 with the title: Biomechanical investigation of different intramedullary nails (PFN) in unstable pertrochanteric fractures. During his residency at the Ludwig Maximilian university of Munich, Germany (1999-2001), at the university medical center Freiburg, Germany (2001-2008) and at the Technical university of Munich, Germany (2009-2010), he completed additional specializations in Tissue engineering, sports medicine, advanced trauma life support, chiropractic and medical radiation protection. In 2006 he completed his specialization in orthopedics and in 2008 in orthopedic and trauma surgery. He received numerous prizes for his posters (ICRS 2004, GOTS 2005, GOTS 2006) and medical lectures (Freiburg 2005, 2006, 2007; Stolberg 2007; Science in Rostock 2011) in the field of cartilage repair. He developed a new score for tissue hypertrophy and was involved in the development of a new approach to posterior osteochondral lesions of the talus. Since 2002 he is member of the ICRS. In January 2009 he earned a PhD with his research in the field of cartilage regeneration in the knee and ankle. Since 2010 he works in the department of orthopedic surgery in the university medical center Rostock. In 2011 he was director of the first german ICRS surgical skills course in Rostock, in 2012 he was organizer of the annual congress of the german society for orthopedic and trauma surgery and performed the ICRS Zimmer fellowship in Boston and Los Angeles and in 2013 he was selected for the AGA Hip arthroscopy fellowship. He has research collaborations with different centers in Europe and America.

Lattermann Christian, Dr.
University of Kentucky, Orthopaedic Surgery,
Lexington, United States of America

Dr. 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 1/2 year research and clinical fellowship in Sports Medicine at the University of Pittsburgh, USA. Dr. Lattermann decided to continue his career in the USA and finished an Orthopaedic Residency and a subsequent Sports Medicine and Cartilage Repair fellowship at the University of Pittsburgh and Rush University. He worked with Drs. Freddie Fu, Christopher Harner, Chris Evans, Bernhard Bach and Brian Cole during this time.

Since 2006 he is at the University of Kentucky and has built a strong clinical research program. He is an expert in cartilage repair, outcomes research and clinical trials. He has published over 70 peer-reviewed papers, over 20 book chapters and currently holds grant funding from the National Institute of Health, Arthritis Foundation of America, NFL charities and the Physical Therapy Association of America.

Invited Faculty 2013 in alphabetical order (not complete)

Leung Victor Y. L., Ass. Prof. PhD
The University of Hong Kong,
Dept. Orthopaedics & Traumatology,
Hong Kong, China

Victor Leung is a Research Assistant Professor of Department of Orthopaedics & Traumatology at The University of Hong Kong. He obtained his bachelor's degree in Biochemistry and subsequently PhD in Molecular and Developmental Genetics from The University of Hong Kong in 2003. After graduation he received training in the Department of Orthopedic Surgery and Biochemistry, Rush Medical College in Chicago, and later in University of Pittsburgh School of Medicine, specializing in musculoskeletal regeneration and bioengineering. Since 2011, he has been appointed as the Director of the Intervertebral Disc Biology & Regenerative Engineering Program in the department and has been a member of the Stem Cell and Regenerative Medicine Consortium and Centre for Reproduction, Development and Growth of the institute. His research interests are in understanding of the spine and regenerative medicine for the associated degenerative disease. Special focus includes molecular and cell biology of the intervertebral disc and strategies for treating disc degeneration in particular using stem cell-based engineering or therapies. He is also interested in utilizing chemical genetics to search for molecules that promote functional restoration. He is the recipient of 2010 ICHTS Webster Jee Young Investigator Award for his contribution to the musculoskeletal research.

Lohmander Stefan, Prof., MD, PhD
Lund University, Orthopedics,
Lund, Sweden

Stefan is senior professor at the Department of Orthopedics at Lund University, Sweden, and professor at the Institute of Sports Science and Clinical Biomechanics, and the Department of Orthopedics and Traumatology, University of Southern Denmark. He received his training and degrees at the Karolinska Institute. After serving as a visiting scientist at the NIH in Bethesda USA, he moved to Lund University. His research focuses on basic and clinical aspects of cartilage and osteoarthritis. Stefan Lohmander has served as Visiting Professor at the Department of Orthopaedics, University of Iowa, the Department of Orthopaedics and Sports Medicine, University of Washington, Seattle, USA, and at the Departments of Rheumatology and Orthopedics, and Kolling Research Institute, University of Sydney, Australia.

He is the editor-in-chief of 'Osteoarthritis and Cartilage' and past president of the Osteoarthritis Research Society International. He has received the OARSI Award for Clinical OA Research, the ORS Steindler Award for significant international contributions to the understanding of musculoskeletal disease and injury, the Marshall Schiff Award from the American College of Rheumatology for 'research in the interface between rheumatology and orthopedics in musculoskeletal medicine', and the Bone and Joint Decade 2000-2010 Award for Research in Osteoarthritis.

Lotz Martin, Prof. Dr.
The Scripps Research Institute in La Jolla, California
La Jolla, United States of America

Martin Lotz is a Professor in the Department of Molecular and Experimental Medicine and Head of Arthritis Research at The Scripps Research Institute in La Jolla, California. He received his MD degree from University of Heidelberg in 1981 where he trained in internal medicine. In 1983 he moved to San Diego for a research fellowship at The Scripps Research Institute and a rheumatology fellowship at UCSD. His research in the areas of joint biology and arthritis pathogenesis led to more than 250 publications. For almost 20 years he directed a program on joint aging and osteoarthritis, which advanced understanding of the regulation of chondrocyte activation and differentiation, cell death in cartilage and the role of stem cells in cartilage homeostasis and disease. Some of these findings are currently undergoing evaluation in clinical trials.

Martin Lotz is a Professor in the Department of Molecular and Experimental Medicine and Head of Arthritis Research at The Scripps Research Institute in La Jolla, California. He received his MD degree from University of Heidelberg in 1981 where he trained in internal medicine. In 1983 he moved to San Diego for a research fellowship at The Scripps Research Institute and a rheumatology fellowship at UCSD. His research in the areas of joint biology and arthritis pathogenesis led to more than 250 publications. For almost 20 years he directed a program on joint aging and osteoarthritis, which advanced understanding of the regulation of chondrocyte activation and differentiation, cell death in cartilage and the role of stem cells in cartilage homeostasis and disease. Some of these findings are currently undergoing evaluation in clinical trials.

MacLeod James N., VMD, PdD
John and Elizabeth Knight Chair,
Gluck Equine Reserach Center,
Kentucky, United States of America

Dr. MacLeod is a veterinarian and scientist at the University of Kentucky, with joint appointments in the Gluck Equine Research Center and the College of Medicine. He holds the John and Elizabeth Knight Chair in musculoskeletal sciences. Dr. MacLeod has been a leader in developing genomic strategies to study equine gene expression. He conducts research on synovial joints, with a focus on osteoarthritis, articular cartilage repair, intra-articular medications, and Wobbler Syndrome. Dr. MacLeod's research has been widely published in leading scientific journals and is funded by the National Institutes of Health, the National Science Foundation, the Grayson-Jockey Club Foundation, the Morris Animal Foundation, the Kentucky Horse Racing Commission, and the Lourie Foundation.

Invited Faculty 2013 in alphabetical order (not complete)

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

Associate Professor Jos Malda is affiliated to both the Department of Orthopaedics, University Medical Center Utrecht (The Netherlands) and the Department of Equine Sciences, University of Utrecht. 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). He subsequently accepted a research fellowship at the Institute of Health and Biomedical Innovation, (QUT, Brisbane, Australia), where he still holds an adjunct position. In 2007, he was awarded a prestigious Veni Grant by STW/NWO for the engineering of articular cartilage with biomimetic zones using bioprinting technologies. His research has a particular focus on implants for regeneration of osteochondral defects. He has published over 60 peer-reviewed publications and book chapters and has been actively involved in the organisation of international conferences in the field of regenerative medicine. He is currently a board member of the ICRS and an editorial board member of Biofabrication. He currently involved in a number of European Union funded projects, e.g. as coordinator of PrintCart, and as steering committee member of SkelGen and HydroZones.

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

Dr. 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 also the Director of Research for Major League Baseball (MLB) and also is Co-director of The USOC CSS National Medical Center of excellence 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 serves on the USA Gymnastics Sports Medicine Advisory Board. In 2002 he was appointed to FIFA Medical Assessment and Research Committee (F-MARC). In 2007 he was appointed 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. He serves as a consultant to several companies including: Depuy Mitek J and J, Zimmer, Smith and Nephew, Arthrex, Exactech, Alter G, Game Ready, Genzyme Sanofi and RTI. He is married to Ruth a Family Physician with 3 children Rachel 22, Jordan 20 and Ava 16.

Marlovits Stefan, Prof.
University of Vienna, Department of Traumatology, Vienna, Austria

Stefan Marlovits is Professor of Traumatology at the Medical University of Vienna. During his career he has been involved in most major activities of traumasurgery and orthopaedics. He is experienced in the treatment of multiple injured patients and major orthopedic trauma. Furthermore he has great experience in arthroscopic procedures especially in the knee. Main focuses in the operative procedures are mini-invasive techniques especially for the treatment of joints disorders. Special interest of his clinical work is the knee joint, with injuries to the meniscus, ligaments and cartilage. He was the Head of Research at the Department of Traumatology at the Medical University of Vienna. He has worked extensively in the area of biological cartilage repair procedures and has published extensively in this field. He is member of different national and international scientific societies.

Martin Ivan, Prof. PhD
Institute for Surgical Research and Hospital Management, University Hospital Basel,
Basel, Switzerland

Prof. Dr. Ivan Martin studied Biomedical Engineering at the University of Genova where he obtained his PhD in 1996. Between 1996 and 1999 he was a postdoctoral associate at Harvard/MIT. He joined the Departments of Surgery and of Biomedicine at the University of Basel in 1999 as Director of the Tissue Engineering Research Group. In 2007

Invited Faculty 2013 in alphabetical order (not complete)

he was appointed Professor for Tissue Engineering. From 2004 to 2009 he was the first president of the European section of the Tissue Engineering Regenerative Medicine International Society (TERMIS). He is currently member of the editorial boards of 5 international journals and of the 'Mesenchymal stem cell committee' of the International Society for Cellular Therapy (ISCT). His group includes scientists from the biological, engineering and clinical fields, dedicated to develop solid scientific basis for innovative translational strategies in regenerative medicine. In this field he is author of more than 160 peer-reviewed papers on international journals and inventor on 10 patent applications, accounting for an H-index of 47. The developed science and technology have been translated into three clinical trials for cell-based cartilage and bone repair, and into the founding of a spin-out company for the commercialization of tissue culture bioreactors (Cellec Biotek AG).

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

Prof. 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.

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 book 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 and Assistant Editor of 'Cartilage'.

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

Dr. Minas is an Attending Orthopedic Surgeon at Brigham and Women's Hospital in Boston, MA, an Associate Professor of Orthopedic Surgery at Harvard Medical School, and Director of the Cartilage Repair Center. Dr. 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.

Dr. 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 honored 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.

Mithoefer Kai, MD
Harvard Vanguard Medical Associates,
Harvard Medical School,
Cambridge, United States of America

Kai Mithoefer is currently an orthopedic surgeon at Harvard Vanguard Medical Associates in Boston and clinical faculty member 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. Kai Mithoefer has served as an active member of the Scientific Program Committee for the 2010 ICRS Meeting in Sitges/Barcelona. He is a member of the editorial board of the journal "Cartilage" and has co-edited the 2012

Invited Faculty 2013 in alphabetical order (not complete)

FIFA/ICRS Supplement on Articular Cartilage Injury in the Football (Soccer) Player as well as the 2011 ICRS Newsletter on Cartilage Rehabilitation. He is serving as the scientific program co-chair for thr ICRS Meeting 2013 in Izmir.

Moroni Lorenzo, Assist. Prof., PhD
University of Twente, Tissue Regeneration Department,
Enschede, The Netherlands

Dr. Lorenzo Moroni studied Biomedical Engineering at Polytechnic of Milan, Italy, and Nanoscale Sciences at Chalmers Technical University, Sweden. In 2001, he visited the lab of Professor Luke Lee at University of California Berkley, where he worked on microfabrication technologies for tissue engineering applications. After receiving his Ph.D in 2006 at University of Twente with Professor van Blitterswijk's group on 3D scaffolds for cartilage and osteochondral regeneration, he worked at Johns Hopkins University as a post-doctoral fellow focusing on hydrogels and stem cells. In 2008, he was appointed the R&D director of the Musculoskeletal Tissue Bank of Rizzoli Orthopaedic Institute in Bologna, Italy, where he investigated the use of stem cells from alternative sources for cell banking, and the development of novel bioactive scaffolds for bone and cartilage regeneration. He joined again the Tissue Regeneration department in 2009 as an assistant professor. Currently, his research interests aim at generating new libraries of bioactive scaffolds to recruit and deliver stem cells in situ and control their differentiation. He is also a co-founder of the biotech company Screvo B.V., which is committed to the production of animal implantable 3D high through-put screening systems.

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

Dr. Norimasa Nakamura is an orthopaedic surgeon and the professor of the Institute of Sports Science at Osaka Health Science University and the center for the advanced medical engineering and informatics at Osaka University. He is an orthopedic surgeon at the Osaka University Hospital, Osaka, Japan. He received his MD at the Osaka University in 1988 and completed a specialization in orthopedics in 1992. In 1994, he received a PhD. In 1995, he became Assistant Professor of Orthopedics at the Osaka University and in 2009, moved to the current position. Norimasa Nakamura research has been focused on joint tissue repair with main focus on the regeneration of cartilage, ligament, and meniscus with stem cells. Today the main interest is the development of three-dimensional stem cell-based bioimplant for musculoskeletal tissue regeneration, whose feasibility to cartilage repair is now under the clinical trial with the permission by the Ministry of Health and Labor of Japan. Norimasa Nakamura has been the Secretary General (Executive Board) of the ICRS since 2010 and the chair of the scientific committee of ISAKOS since 2013.

Niemeyer Philipp, Prof., MD
Universitätsklinikum Freiburg, Department of Orthopedic Surgery and Traumatology,
Freiburg i.Br., Germany

Professor Philipp Niemeyer is member of the Department of Orthopedic Surgery and Traumatolgy oft he Freiburg University Hospital (Germany, Director: Prof. Dr. N. P. Südkamp) and head of the divsion of knee surgery and cartilage repair. After graduating from the University of Freiburg in 2002, he began his clinical training at the Department of Orthopaedics at the University of Heidelberg (Germany, Prof. Dr. V. Ewerbeck), which he continued in the Department of Orthopedics and Traumatology at the University of Freiburg. Since that time, he conducts research into preclinical and clinical aspects of the regeneration of cartilage tissue. In addition to publishing various scientific papers in this area he was awarded in 2005 with the Kurt Steim Award of the University of Freiburg in 2012 and the Research Prize of the German Society for Orthopaedics and Orthopaedic Surgery (DGOOC). In 2013 he became Associate Professor at the Freiburg University.

Noeth Ulrich, MD
University of Wuerzburg, Department of Orthopaedic Surgery,
Wuerzburg, Germany

Omlor Georg, MD,
Universitätsklinik Heidelberg, Department Orthopädie, Unfallchirurgie und Paraplegiologie, Heidelberg, Germany

Dr. Omlor is an Orthopaedic and Trauma surgeon at the Orthopaedic University Hospital at the University of Heidelberg, Germany. His subspecialties are Spine surgery and Orthopaedic Oncology.

He received his MD at the University of Heidelberg in 2005 and made his additional Basic Research Doctoral Thesis in 2007. Since 2006 he works in the Orthopaedic University Hospital at the University of Heidelberg, where he completed his specialization in Orthopaedic surgery and Trauma surgery in 2012. Dr. Omlor´s research is focused on the intervertebral disc with special emphasis on animal models to analyze molecular mechanisms of disc degeneration and disc regeneration by the administration of therapeutic biomaterials and mesenchymal stem cells. Since 2009, he is the leader of the research group: "Experimental Disc Degeneration and Regenerative Therapies" at the Department of Experimental Orthopaedics at the University of Heidelberg.

Invited Faculty 2013 in alphabetical order (not complete)

Pelletier Jean-Pierre, Prof. MD
University of Montreal, Dept. of Arthritis & Rheumatology
Montreal, Canada

Jean-Pierre Pelletier, M.D. is a Professor of Medicine, Accredited Member of the Department of Pharmacology, Head of the Arthritis Centre of the University of Montreal, Chief of the Division of Rheumatology and Director and Co-founder of Osteoarthritis Research Unit at the University of Montreal Hospital Centre (CHUM). He is also co-titular head of the Chair in Osteoarthritis at the University of Montreal.

His principal research interest lies in understanding the mechanisms involved in the pathophysiology of osteoarthritis, as well as in investigating and developing new therapeutic strategies to counteract the disease through basic, preclinical and clinical research. He also developed, with his team, new imaging technology to quantify structural joint tissue alterations in osteoarthritis of the knee and hip. Targeted tissues include cartilage, bone osteophytes, suchondral bone lesions, synovial fluid and synovial membrane. His works have led to a large number of landmark studies and major breakthroughs and discoveries. Winner of several international and national awards and prizes, he has an impressive number of publications (over 415) in world-renowned, peer-reviewed journals, and has made numerous guest speaker appearances.

Ranga Adrian, PhD
Swiss Federal Institute of Technology (EPFL), Laboratory of Stem Cell Bioengineering - LSCB, Lausanne, Switzerland

Adrian Ranga is a Post-Doctoral Fellow in the Laboratory of Stem Cell Bioengineering at the Swiss Federal Institute of Technology Lausanne (EPFL), Switzerland. He received his PhD at EPFL in 2013 with Prof.Matthias Lutolf, and his Masters degree from McGill University, Canada. Adrian Ranga's research focuses on developing innovative bioengineering technologies and deploying them to investigate basic and translational questions in stem cell biology and tissue engineering. His work focuses primarily on the high throughput generation of combinatorial hydrogel arrays, which are used to investigate the role of extrinsic cues in specifying stem cell fate. Adrian Ranga has been supported by grants from the National Science and Engineering Research Council of Canada (NSERC), as well as by a BD Biosciences Research Grant.

Richter Wiltrud, Prof. PhD
Orthopaedic University Heidelberg,
Research Department,
Heidelberg, Germany

Prof. Dr. W. Richter is a Full Professor and Director of the Research Centre for Experimental Orthopaedics at Heidelberg University, Germany. She has been a leader in the field of cellular and molecular cartilage research pioneering the use of mesenchymal stroma cells for cartilage and intervertebral disk repair and the application of high throughput screening technologies for cartilage assessment.

As a molecular biologist she received her Ph.D. at Ulm University, Germany and gained her post-doctoral experience at the University of California San Francisco and University of Ulm, where she completed her Habilitation in Experimental Medicine. She is a faculty member of Heidelberg University since 1998 and holds a chair for Experimental Orthopaedics since 2004. She has been President of the Basic Research Association of the German Society for Orthopaedic Surgery from 2005-2010, was a Board Member of EORS (2006-2011) and is member of ICRS since 2005. She is the scientific program director together with Kai Mithoefer at the ICRS 2013 conference.

Wiltrud Richter´s research has been focused on molecular and cellular aspects of stem cell and chondrocyte biology, mesenchymal stroma cell differentiation, tissue engineering, biomaterials and growth factor development and testing. She has been awarded several prices including the Wilhelm-Roux-Award of the German Orthopaedic Research Society, the Sandoz price for therapeutic research and the Mario Boni Award.

Riminucci Mara, Assoc. Prof. MD, PhD
University of Rome La Sapienza,
Roma, Italy

Mara Riminucci is currently Associate Professor of Pathology at the University La Sapienza of Rome where she received her MD and PhD degrees. She spent several periods of work at the National Institutes of Health in Bethesda, where she also played the activity of Expert Consultant as part of a clinical Protocol on Fibrous Dysplasia of the skeleton. Mara Riminucci has a long-standing interest and experience in bone cell biology and skeletal diseases. Since 1994, her research activity is especially focused on the cellular and molecular pathology of Fibrous Dysplasia (FD) and other GNAS-related human disorders. She received awards from national and international scientific societies (Italian Society of Anatomic Pathology , NIDCR; American Society for Bone and Mineral Research; International Bone and Mineral Society) and participated as invited speaker at several national and international meetings including Gordon Research Conference, European Pediatric Orthopedic Society; International Academy of Pathology

Invited Faculty 2013 in alphabetical order (not complete)

Roberts Sally, Prof.
RJAH Orthopaedic Hospital, Centre for Spinal Studies,
Shropshire, United Kingdom

Sally Roberts works in the Robert Jones & Agnes Hunt Orthopaedic Hospital, Oswestry, and Keele University, UK. She is a research scientist investigating cartilaginous tissues, particularly the intervertebral disc and articular cartilage, both the aetiopathogenesis of their degeneration and also ways in which they can be repaired or treated. Sally has been a member and fellow of the ICRS as well as a Board member for many years and has an active interest, particularly in developing histological outcome measures for cartilage repair techniques.

Rodeo Scott, Prof. Dr.
Hospital for Special Surgery,
Orthopedic Surgery,
New York, United States of America

Dr. Scott Rodeo is Professor of Orthopaedic Surgery at Weill Medical College of Cornell University and is an Attending Surgeon at the New York-Presbyterian Hospital and the Hospital for Special Surgery, where he is Co-Chief of the Sports Medicine and Shoulder Service. He is Associate Team Physician for the New York Giants Football Team. Rodeo served as a Team Physician for the United States Olympic Team in 2004, 2008, and 2012. Rodeo graduated cum laude from Stanford University, where he completed his undergraduate work while on an athletic scholarship. He completed medical school graduating with honors from Cornell University Medical College.

Sah Robert, Prof. MD, B.S, M.S
University of California, San Diego,
Bioengineering, MC0412,
La Jolla, United States of America

Robert L. Sah is Professor of the Department of Bioengineering, Adjunct Professor of the Department of Orthopaedic Surgery, and co-director of the Center for Musculoskeletal Research at UCSD. He received the B.S. and M.S. in Electrical Engineering and the Sc.D. in Medical Engineering from M.I.T., and the M.D. from Harvard. He joined UCSD Bioengineering in 1992 and was promoted to Professor in 2001. Dr. Sah has contributed to the Tissue Engineering and Regenerative Medicine International Society as a North America council member, to the International Cartilage Repair Society as a member of the Executive Board, to a number of journals including Arthritis and Rheumatism, Cartilage, Journal of Orthopaedic Research, Osteoarthritis and Cartilage, and Tissue Engineering in editorial roles. His research interests are the biomechanics, mechanobiology, and tissue engineering of articular cartilage, synovial fluid, and synovial joints with the ultimate goal of improving the treatment, diagnosis, and prevention of osteoarthritis. He is recipient of the Van C. Mow medal, a fellow of the American Institute for Medical and Biological Engineering, and a Professor of the Howard Hughes Medical Institute.

Santambrogio Laura, Prof. MD. PhD
Albert Einstein College of Medicine,
Jack and Pearl Resnick Campus,
New York, United States of America

Dr. Santambrogio is an M.D. Ph.D who graduated from Padua University in Italy in 1993 and trained as a postdoctoral fellow at Harvard University. She was recruited in 2003 at Albert Einstein College of Medicine in New York City where she is currently a Professor of Pathology, Microbiology and Immunology. A major focus of her research is the analysis of how oxidative post-translational modifications affect cartilage structure and functionality. Using redox proteomic analysis and illustrative MS/MS mapping her laboratory determined that oxidative post-translational modifications are a hallmark of aging in intervertebral discs. Increased protein carbonylation favor fragmentation and aggregation of matrix structural proteins, affect cartilage structural integrity and ultimately its mechanical functions.

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

Daniël Saris (1966) Amsterdam The Netherlands. Graduated University of Amsterdam Medical School in 1992. During orthopedic residency he did a fellowship at the Mayo Clinic in Rochester MN USA under Prof. Shawn O'Driscoll of the Cartilage and Connective Tissue Research Laboratory and Prof. Kai-Nan An of the orthopaedic biomechanics laboratory.
His PhD thesis completed in 2002 at the University of Utrecht was titled "Joint Homeostasis in Tissue Engineering for Cartilage Repair". It first introduced the now generally accepted concept of joint homeostasis. In 2000 Daniël joined as staff member in the department of Orthopaedics at the UMC Utrecht. In March of 2010 dr Saris was appointed as Professor of Reconstructive Medicine at the University of Twente. Prof dr Saris is co director of the Biological Joint Reconstruction research program and head of the orthopaedic residency program at the University of Utrecht. He describes his goal and driving force as a wish to satisfy natural curiosity into optimizing the regenerative biological capacity of the musculoskeletal system, improve treatment and understanding of knee afflictions and to help in building an international network for ICRS with high potential and productive group dynamics.

Invited Faculty 2013 in alphabetical order (not complete)

Scanzello Carla R., Ass. Prof., PhD
Rush University, Dept of Rheumatology,
Chicago, United States of America

Carla Rose Scanzello, M.D., Ph.D. is Assistant Professor in the Division of Rheumatology at the University of Pennsylvania. She received her MD and PhD from Temple University, completed residency in Internal Medicine at New York Presbyterian Hospital (Weill Cornell), and fellowship in Rheumatology at the Hospital for Special Surgery in New York. She is a member of the American College of Rheumatology, the Orthopedics Research Society and the Osteoarthritis Research Society International, and serves on editorial boards for Osteoarthritis and Cartilage and Arthritis and Rheumatism. She has received research funding from the National Institute of Health, and has published in peer-reviewed journals including Nature Medicine and Arthritis and Rheumatism.

Dr. Scanzello investigates the consequences and molecular stimuli of synovial inflammation in patients with meniscal injury and osteoarthritis, with the goal of identifying prognostic markers and improving current therapy. With a group of interdisciplinary collaborators, she studies the impact of synovitis on post-surgical outcomes in patients after arthroscopic partial meniscectomy. In these patients she has identified a set of inflammatory mediators specifically associated with synovitis and knee symptoms. Her current laboratory efforts are aimed at understanding how these mediators contribute to osteoarthritis progression, using both in vitro and in vivo models.

Schmal Hagen, Prof. PhD
University of Freiburg Medical Center,
Department of Orthopedic Surgery,
Freiburg, Germany

Hagen Schmal is an orthopaedic surgeon affiliated with the Department for Orthopaedic Surgery and Traumatology, University Medical Centre, University of Freiburg/Germany. He is the assistant medical director, experienced in general surgical fracture treatment, surgery of the knee including cartilage regeneration, and specialized in pelvic, foot and paediatric trauma surgery. He has a strong record of scientific activity in the field of cartilage tissue engineering and received funding during the Valley Tissue Engineering Centres program (1998-00), grants of the competence network biomaterials Baden Wuerttemberg (2003-06), Deutsche Arthrose-Hilfe e.V. (2007/08), AO Foundation (since 2009), from the Department of Education and Research Germany (since 2011), and the research commission the University of Freiburg (2011/12). His clinical studies were focused on pelvic fractures (pelvic working group of the German Society of Traumatology) and pediatric fracture treatment. He works as reviewer for a variety of journals as Tissue Engineering and Cytotherapy, and organizations (grant applications) as the AO Foundation International (Switzerland). A Ph.D. was granted by the University of Freiburg/Germany in 2008, the appointment as Professor started 2012. He passed the board exam for General Surgery in 2004, for Orthopaedic Trauma Surgery in 2006, and for Special Orthopaedic Surgery in 2012. Hagen Schmal is member of the ICRS, the AO Trauma, and the German Society of Traumatology.

Sekiya Ichiro, MD, PhD
Tokyo Medical and Dental University,
Cartilage Regeneration,
Tokyo, Japan

Professor Ichiro Sekiya is a director of Center for Stem Cell and Regenerative Medicine at Tokyo Medical and Dental University, Japan. He received his MD at Tokyo Medical and Dental University in 1990. He completed a specialization in orthopedics and passed the Japan Orthopedic Association (JOA) Exam in 1996. He earned a PhD at Tokyo Medical and Dental University in 2000. He worked as a postdoctoral fellow with Dr. Darwin J. Prockop in the US in 2000-2002. Ichiro Sekiya became a professor of Department of Cartilage Regeneration at Tokyo Medical and Dental University in 2011. He is now also professor of Department of Applied Regenerative Medicine at Tokyo Medical and Dental University. Ichiro Sekiya's research has been focused on cartilage and meniscus repair and with main focus on cartilage and meniscus regeneration with autologous synovial stem cells. Since the start 2012, he has been working with ICRS, as a member of scientific committee. He is now in the editorial board of "Stem Cells", "Journal of Orthopaedic Science", and "Stem Cell Research & Therapy". He received New Investigator Research Award at Orthopaedic Research Society in 1998, New Investigator Research Award at Japan Orthopaedic Association in 2002, and New Investigator Research Award at Tokyo Medical and Dental University in 2002.

Shive Matthew, Dr. PhD
Piramal Healthcare, Laval, Canada

Dr. Matthew Shive is a consultant in medical device and pharmaceutical product development, as well as medical marketing and education. Dr. Shive received his B.S. from the Johns Hopkins University, and his M.Sc. and Ph.D. from Case Western Reserve University, all in Biomedical Engineering with a focus on Biomaterials. His scientific expertise relates to the interactions between implanted biomaterials and biological systems supported by over 125 publications, scientific articles and conference proceedings in the fields of tissue and cartilage repair and biomaterials. From 2000-2009, Dr. Shive oversaw product development at BioSyntech, a device company in Montreal that developed and manufactured regenerative products including those for cartilage, bone and wound repair. Notably, Dr. Shive designed and implemented the clinical development program for BST-CarGel, a device for cartilage repair, which recently received CE Mark approval following the completion of a first-of-its-kind multicenter RCT in Canada, Spain and Korea. He continues to

Invited Faculty 2013 in alphabetical order (not complete)

advance the clinical science behind BST-CarGel as a Senior Advisor to Piramal Healthcare (who acquired BioSyntech in 2010). Currently, Dr. Shive also provides strategic guidance to other multinational biotechnology firms, offering a number of support services during their pre-clinical, clinical, regulatory and marketing activities.

Silvers Holly, MPT
Velocity Physical Therapy,
Los Angeles, United States of America

Holly J. Silvers is a board certified Physical Therapist specializing in sports orthopaedic rehabilitation in Santa Monica, CA. She is a graduate of Western University of Health Sciences with a Masters Degree of Physical Therapy and of Rutgers University (BS: Biological Sciences and Communications). She is a current member of United States Soccer Federations Men's and Women's National Medical Team, a member of FIFA's F-Marc Medical Research Committee, and a member of the International Cartilage Research Society's Rehabilitation Committee. She is also the spokesperson for the American Physical Therapy Association's taskforce on ACL Prevention. In addition, she is the director of rehabilitation for Major League Soccer's Chivas USA, the Los Angeles Galaxy, and the Amgen Tour of California pro-tour cycling race.

Currently, she is the director of research at the Santa Monica Orthopaedic and Sports Medicine Research Foundation with a primary focus on ACL Prevention, articular cartilage injury prevention and rehabilitation, sports hernia prevention and head injury prevention in athletes. Ms. Silvers also presides on the editorial board of the British Journal of Sports Medicine and has published several peer reviewed articles on the prevention of ACL injury, cartilage implantation rehabiliation, groin injury and patellofemoral disorders.

Snyder-Mackler Lynn, Prof.
University of Delaware, ,
Newark, United States of America

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

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

Trattnig Siegfried, Prof. Dr.
Medical University of Vienna, MR Center,
Department of Radiology,
Vienna, Austria

Univ. Prof. Dr. 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 multiparametric or biochemical MR imaging of

Invited Faculty 2013 in alphabetical order (not complete)

cartilage. He is currently the lead researcher on the clinical 7T & 3T projects at the Medical University in Vienna. He is editorial board member of 6 scientific journals, member of 15 committees within the ESR, ESMRMB and the ICRS among the Executive Board member of the ESMRMB and Member of the ESR Research Committee Board. He is an author of 336 articles in peer reviewed scientific journals and contributed to 23 scientific books. Additionally he has held 23 peer reviewed scientific grants, received 8 scientific awards and is a reviewer for 26 scientific journals.

Tuan Rocky, Dr. PhD
University of Pittsburgh, Orthopaedic Surgery,
Pittsburgh, United States of America

Dr. Rocky S. Tuan is the Director of the Center for Cellular and Molecular Engineering, Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine. He also serves as the Executive Vice Chairman for Orthopaedic Research at the University of Pittsburgh, and the Associate Director of the McGowan Institute for Regenerative Medicine.

Dr. Tuan earned his BA in Chemistry from Berea University, where he was a member of Phi Kappa Phi Honor Society and the recipient of the Austin Scholar Award. From there he went to Rockefeller University in New York, where he earned his PhD in Life Sciences (Biochemistry and Cell Biology). He continued his postdoctoral research at Rockefeller until he won a Research Fellow from first the Department of Orthopaedic Surgery and then the Department of Medicine, both at Harvard Medical School. Dr. Tuan served as a professor in the Department of Biology at the University of Pennsylvania, where he was awarded an honorary MA in 1987. He was also a professor at Thomas Jefferson University, where he became the Director of the Orthopaedic Research Laboratory (1988-2001), the Academic Director of the MD-PhD Program (1992-1995), and the Vice Chairman of the Department of Orthopaedic Surgery (1996-2001). In 2001, Dr. Tuan became the Chief of Cartilage Biology and Orthopaedics Branch of the National Institute of Arthritis, Musculoskeletal and Skin Diseases. In both 2006 and 2007 he was given the Special Recognition Award, NIH Undergraduate Scholars Program.

Dr. Tuan's research focuses on the development, growth, function, and health of the musculoskeletal system, the biology of adult stem cells, and the utilization of this knowledge to develop technologies that will regenerate and/or restore function to diseased and damaged musculoskeletal tissues. He is a member of several professional societies, including the Society for Physical Regulation in Biology and Medicine, the Osteoarthritis Research Society International, and the Tissue Engineering Regenerative Medicine International Society. He is the Editor-in-Chief of Birth Defects Research; Part C – Embryo Today and Stem Cell Research and Therapy.

Van Assche Dieter, PhD
UZ KULeuven, Rheumatology,
Leuven, Belgium

Dieter Van Assche was born on January 24th 1972. He holds Master degrees in the Physical Education (1994) and in Physical Therapy (1996), both at the KU Leuven, Belgium. Thereafter he graduated as Master of Science in Manual Therapy. From 1997 to 2013 he worked at the University Hospitals Leuven consecutively on outpatient rehabilitation, orthopedic department and the last ten years as senior physical therapist at the department of Rheumatology. He combined this with scientific work at the Faculty of Kinesiology and Rehabilitation. Between 2002 and 2008 he coordinated physical therapy and functional outcome assessments in the multi-centre randomized clinical trial comparing characterized chondrocyte implantation to microfracture in treatment of patients with of local full thickness cartilage defects on the femur condyle of the knee. In 2010 he finalized his PhD research on objective functional outcome after cartilage repair in the knee. Since 2011 he is assistant professor at the Department of Rehabilitation Sciences with main research focus on rehabilitation following joint disorders.

Van Osch Gerjo, PhD
Erasmus MC, University Medical Center Rotterdam, Orthopaedics & Otorhinolaryngology, Rotterdam, Netherlands

Gerjo van Osch (1967) studied medical biology at the University of Utrecht (MSc 1990) and received her PhD in 1994 at the University of Nijmegen on animal models for osteoarthritis. Since then she became involved in cartilage tissue engineering and especially the use of different cell types and growth factors. She is currently appointed as full professor at the Erasmus MC, University Medical Center in Rotterdam the Netherlands where she is leading a research group of approx. 12 people that is part of the departments of Orthopaedics and Otorhinolaryngology. Her research focuses on cellular aspects of connective tissue degeneration and regeneration (www.erasmusmc.nl/orthopaedie/research/labor/CTCRgroup).

Gerjo van Osch has been working in the field of cartilage since 1990. She is co-author on over 130 international peer-reviewed publications.She has been active in various committees of the International Cartilage Repair Society (ICRS). She served as council member of the European chapter of the TERMIS and chaired the TERMIS-EU meeting in Rotterdam in 2006. She is associate editor of Cartilage and editorial board member of Tissue Engineering and Journal of Tissue Engineering and Regenerative medicine.

Invited Faculty 2013 in alphabetical order (not complete)

Van Roermund Peter, Prof. Dr.
University Medical Center Utrecht,
Orthopaedics,
Utrecht, Netherlands

Peter van Roermund was born on 30 April 1949 in Kokkengen, The Netherlands. His Professional experience: 1985 – today staff member, department of orthopaedics ,UMC Utrecht. 2001 -2003: President Dutch Orthopaedic Society, 2005-present: President Bone and Joint Decade the Netherlands. Reports and documents written: Thesis in 1994: Tibial lengthening by distraction epiphysiolysis. Clinical and experimental studies. University of Utrecht, Award 2002: The Kenneth A.Johnson Memorial Award and Lecturer AOFAS winter meeting Dallas USA: joint distraction as treatment of OA ankle joints

Vannini Francesca, Dr.
Istituti Ortopedici Rizzoli, VI,
Bolgona, Italy

Born in Lugo (RA), Italy.15/04/1973, graduated full marks in medicine in 1998 (Bologna University), Italy. 1998 – 2003- Appointed permanent resident of Orthopedics and Traumatology, Orthopedic Clinic of Bologna University at Rizzoli Orthopedic Institute. 2003-February to July: Residency rotation at the Department for Foot&Ankle Surgery of Union Memorial Hospital, Baltimore, MD, USA to expand on Foot & Ankle Surgery and research. Completed her PhD in Biotechnologies (Cartilage repair) in November 2006, at the University of Bologna. Was awarded with the European Foot & Ankle Society Travelling Fellowship, with the AOFAS Travelling Fellowship AOFAS, and with the ICRS Travelling Fellowship. In November 2004 was appointed as a tutor at the Podiatrist University of Bologna. In June 2005 appointed as orthopedic consultant at the Rizzoli Orthopedic Institute II Clinic. From 2006 was appointed as university lecturer at the Podiatrist University of Bologna.

Main field of research and clinical practice are Cartilage repair and Foot &Ankle surgery. Participated in National and International study groups. Participated in National and International meetings organization as part of the scientific committee. Participated with presentations in national and international meetings, among them presented podium, posters and scientific exhibits at the “American Academy of Orthopaedic Surgeons”.

Authored or co-authored scientific book chapters, papers published in Science Citation Index journals and papers published in other national or international scientific journals. Is member of AOFAS (American Foot&Ankle Society), ICRS (International Cartilage Repair Society),ESSKA (European Society of Sports Traumatology, Knee Surgery and Arthroscopy) member,EFAS (European Foot & Ankle Society),SIOT (Società Italiana di Ortopedia e Traumatologia),SICP (Società Italiana della Caviglia e del Piede), SIGASCOT (Società Italiana di Chirurgia del Ginocchio, Artroscopia, Sport, Cartilagine e Tecnologie Ortopediche).

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

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

von Rechenberg Brigitte, Prof. Dr. med. vet.
University of Zurich, Equine Hospital,
Vetsuisse Faculty,
Zurich, Switzerland

Prof. Dr. med.vet. Brigitte von Rechenberg, is a veterinarian and Diplomate of the European College of Veterinary Surgeons (ECVS). She is specialized in small animal surgery with focus on orthopedic surgery and traumatology. She is the founder and head of the Musculoskeletal Research Unit (MSRU) and the official Competence Center for Applied Biotechnology and Molecular Medicine at the University of Zurich, where preclinical animal studies can be conducted according to GLP including a reference histology laboratory. Experience with cartilage resurfacing in sheep and goats are among her expertise.

Wakitani Shigeyuki, Prof. PhD
Mukogawa Women's University,
School of Health & Sports Sciences,
Nishinomiya, Japan

Professor Shigeyuki Wakitani belongs to the School of Sports and Health Sciences, Mukogawa Women’s University. He is also a visiting professor of Osaka City University, Yokohama City University, Shinshu University, Institute of Medical Science the University of Tokyo, and Matsumoto Dental University. He received his MD at Osaka University in 1983 and in 1990 he earned a PhD. Between 1990 and 1992, he studied in Dr. Arnold I. Caplan’s labo in Case Western Reserve University, Cleveland, Ohio, USA. He investigated in Osaka University from 1992 to 1994, in Osaka-minami National Hospital from 1994 to 2001, in Shinshu University from 2001 to 2005, in Osaka City University from 2006 to 2011, and from 2011 in Mukogawa Women’s University.

Invited Faculty 2013 in alphabetical order (not complete)

S. Wakitani's research has been focused on cartilage repair with cell transplantation, especially with autologous bone marrow mesenchymal stem cells. Today the main interest is automatic cell culture machine that can reduce the necessity of cell processing facilities. The machine is installed in Osaka University and will be installed in Chulalongkorn University in Bangkok, Thailand next month, and S. Wakitani is planning to perform clinical research of cell transplantation that are cultured by the machine. S. Wakitani is also planning a multicenter randomized control clinical study of autologous bone marrow mesenchymal cell transplantation in Japan. S. Wakitani received the Johnson & Johnson Innovation Award of the Japanese Society for Regenerative Medicine in 2011.

Walsh David, Prof.
University of Nottingham Clinical Sciences Building, Arthritis Research UK Pain Centre, Academic Rheumatology,
Notthingham, United Kingdom

David Walsh is Professor of Rheumatology at the University of Nottingham and Consultant Rheumatologist at Sherwood Forest Hospitals NHS Foundation Trust. In 2010 he established the Arthritis Research UK Pain Centre in Nottingham, together with a multidisciplinary research team including preclinical neurosciences, psychology, neuroimaging, orthopaedics and evidence synthesis. The Centre aims to develop new and improved treatments through a translational research programme into the mechanisms by which changes within the joint and in the nervous system interact with psychosocial factors to produce arthritis pain. His preclinical research has focused on structural changes that contribute to joint pain, in particular angiogenesis, nerve growth and inflammation in the synovium and subchondral bone. His clinical research is defining the spectrum of pain phenotypes in people with arthritis based on underying pain mechanisms, in order to better target treatments to those most likely to benefit. He is Clinical Director of the Back Pain Unit at King's Mill Hospital, providing diagnositic assessment and multidisciplinary Pain Management Programmes for people with chronic low back pain. The Back Pain Unit benefits from clinical psychologists, physiotherapists, occupational therapists and pain nurse specialists working in close partnership with anaesthetists and spinal surgeons.

Wehling Peter, Prof. MD.
Center for Orthopaedics and Molecular Medicine,
Düsseldorf, Germany

Prof. Dr. med. Peter Wehling (1955) studied Medicine in Cologne, Montpellier,Düsseldorf and London, Ontario during the years of 1977 until 1983. The following year in 1984, he accomplished his residency at the Neurophysiology Institute at the University of seldorf, which was then followed by his residency in trauma surgery in Düsseldorf in 1985. During the years of 1986 until 1989 Prof. Dr. Wehling successfully completed his residency in orthopaedics at the University Hospital in Düsseldorf. In 1989 he was certified as a specialist in orthopaedics. In 1990 he was an attending surgeon at the Orthopaedic Clinic at the University Hospital in Düsseldorf. During the years of 1991 until 1992 he completed his Professorial thesis about neurophysiological and neuropathological research in nerve regeneration at the University of Düsseldorf and was also chief surgeon at the Neurosurgery Clinics in Osnabrück in the same years.His first own medical practice was established in 1992 in Düsseldorf. The following year he founded a biotech company, which was called Orthogen. In 2002 Prof. Dr. Wehling became an adjunct professor at the University of North Carolina, Chapel Hill, USA. In 2006 he founded and became the CEO of the Centre for Molecular Orthopaedics in Düsseldorf. Since 2009 Prof. Dr. Wehling successfully runs a joined group practice with Dr. med. Jens Hartmann in Düsseldorf, focusing on molecular orthopaedics and molecular medicine

Welsch Goetz, Ass. Prof.
University of Erlangen-Nuremberg,
Department of Trauma Surgery,
Vienna, Austria

Dr. Goetz H. Welsch is Assistant Professor at the University of Erlangen, Germany. He is German board certified orthopaedic and trauma surgeon with the speciality of knee surgery and sports medicine. Furthermore he is team physician of a professional German soccer team. His clinical and scientific focus is since more than 10 years regenerative cartilage therapy including different techniques of cartilage repair procedures. Besides this, Dr. Welsch is a well known musculoskeletal imaging expert in close collaboration with the Medical University of Vienna, Austria. He has been involved in several studies mainly concerning advanced MR imaging technologies in cartilage repair. In this field he has published many studies about the MOCART score and recently the 3D MOCART score. Furthermore he works very intensely in biochemical cartilage imaging techniques like T2 mapping, dGEMRIC, T1rho and Diffusion Weighted Imaging. Especially within the field of quantitative T2 mapping, Dr. Welsch published many studies and is one of the most active researchers world-wide.

Dr. Welsch is member of different orthopaedic and radiological societies, authored more than 60 peer-reviewed papers and about 20 book chapters, is an active reviewer for more than 15 journals and in the advisory board of Archives of Orthopaedic and Trauma Surgery (AOTS). He leads grants of the German and the Austrian Research Society and works together with various international groups in the field of cartilage imaging. In the International Cartilage Repair Society (ICRS) he is co-chair of the imaging group and was on of the Lars Peterson - Genzyme Travelling fellows 2010. Dr. Welsch lectures regularly at scientific and medical congresses around the world.

Invited Faculty 2013 in alphabetical order (not complete)

Williams Riley, MD
Hospital for Special Surgery, ,
New York, United States of America

Dr. Riley J. Williams III is a specialist in the field of shoulder, knee and elbow surgery at Hospital for Special Surgery. Dr. Williams holds a dual appointment in both the Department of Orthopedic Surgery, as a full-time member of the Sports Medicine & Shoulder Service, and as a Clinician-Scientist in the Research Division. He is also an Associate Professor at Weill Cornell Medical College. Dr. Williams attended college at Yale University and the Stanford University School of Medicine. His clinical and research interests include: cartilage repair and transplantation, arthroscopic shoulder repair (rotator cuff tears, labrum tears), arthroscopic shoulder stabilization, anterior cruciate and posterior cruciate ligament reconstruction, and elbow ligament reconstruction. Dr. Williams is the Director of the Institute for Cartilage Repair at Hospital for Special Surgery.

Dr. Williams has worked with the Brooklyn Nets professional basketball team for many years. In addition, he is the head team physician for the New York Red Bulls professional soccer team, and the Iona College Department of Athletics. He has also served as Associate Team Physician for both the New York Mets professional baseball and New York Giants professional football teams. Dr. Williams is an active member of the New York Road Runners Club

Wondrasch Barbara, Dr.
Medical University, Department for Traumatology,
Vienna, Austria

Barbara Wondrasch is Physical Therapist and she is working as a lecturer and researcher at the Department for Health and Science at the University of Applied Sciences in St.Poelten (Austria). The main focus of her clinical and scientific work is Sports Medicine, Traumatology and Orthopedics. She is an expert in the area of rehabilitation after cartilage injuries and after cartilage repair and was part of the author team publishing the first paper about rehabilitation after chondrocyte implantation in the knee (American Journal of Sports Medicine, 2006). Since 2010 she is doing her PhD studies at the Norwegian School of Sport Sciences under the supervision of Prof. May Arna Risberg, PT, PhD. The topic of her PhD studies is "A new approach to rehabilitation for patients with articular cartilage lesions in the knee. Recently, Barbara and the research group in Oslo published a paper, "The feasibility of a 3-Month Active Rehabilitation Program for Patients With Knee Full-Thickness Articular Cartilage Lesions: The Oslo Cartilage Active Rehabilitation and Education Study", in the Journal of Orthopaedic and Sports Physical Therapy.

Zaslav Kenneth, 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.

Situation Plan - Find Your Way

Level 5
- Session Room Smyrna 1
- Session Room Smyrna 2
- Poster Area
- ICRS Lounge

Level 3
- Session Room Didim
- ICRS Meeting & Board Rooms
- Speaker Ready Room
- AV Center
- ICRS Office
- Poster Area

Level 1
- Industry Exhibition
- Tour Desk (Venus Tourism)
- Session Room Grand Efes 2
- Free Internet Corner

Level 0
- Registration
- Congress Bag Hand-out
- Congress Certificate Stations

Industry Exhibition & Sponsoring

Technical Exhibit Opening Hours

Sunday	12.00 - 17.30 hrs.
Monday	09.30 - 17.30 hrs.
Tuesday	09.30 - 17.30 hrs.
Wednesday	09.30 - noon.

Sufficient time during intermissions is reserved for visiting the booths of leading manufacturers which present the latest achievements and give competent information. For detailed information on the exhibiting companies, please consult the exhibit guide on the following pages.

ICRS 2013 and the ICRS Society express their gratitude to all collaborators and volunteers for this meeting. Particularly the participation of the following companies is much appreciated and gratefully acknowledged:

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  Piramal Healthcare, Laval, Canada
  Regentis Biomaterials, Or Akiva, Israel
  Swissbiomed, Zurich, Switzerland

Exhibitors (Alphabetical Order)

Company	Booth Nr.
Acibadem	2
Arthrex	10
Arthrosurface	21
Biomet Europe	5
Biomomentum	9
BMI Biomedical Implants	7
CellCoTec	19
Depuy Synthes	4
Episurf Medical	13
Fin-Ceramica Faenza	22
Geistlich Surgery	3
Karl Storz	11
Mobileturk	8
Orteq	23
Orthogen	1
Piramal Healthcare	17
Regentis Biomaterials	14
Sanofi Biosurgery	16
SERVA Electrophoresis	6
Soylu Medical	15
Tigenix	18
Vertebral Technologies	24

Exhibitors (Numerical Order)

Company	Booth Nr.
Orthogen	1
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Arthrex	10
Karl Storz	11
Episurf Medical	13
Regentis Biomaterials	14
Soylu Medical	15
Sanofi Biosurgery	16
Piramal Healthcare Canada	17
Tigenix	18
CellCoTec	19
Arthrosurface	21
Fin-Ceramica Faenza	22
Orteq	23
Vertebral Technologies	24

2013 ICRS WORLD CONGRESS
SEPTEMBER 15-18, 2013
GRAND EFES SWISSOTEL
LEVEL 1

Exhibitor	Lenght	Width	Area	Booth Nr.
Acıbadem	3	2	6 m^2	2
Arthrex Inc.	6	4	24 m^2	10
Arthrosurface	3	3	9 m^2	21
Biomet	6	2	12 m^2	5
Biomomentum	3	2	6 m^2	9
BMI	3	2	6 m^2	7
Cellcotec	3	2	6 m^2	19
Depuy Synthes	4	4	16 m^2	4
Episurf Medical	3	3	9 m^2	13
Finceramica	3	3	9 m^2	22
Geistlich	6	4	24 m^2	3
Karl Storz	4	3	12 m^2	11
Mobileturk	3	2	6 m^2	8
Orteq	3	3	9 m^2	23
Orthogen	3	2	6 m^2	1
Piramal	5	5	25 m^2	17
Regentis Biomaterial	3	3	9 m^2	14
Sanofi Biosurgery	5	5	25 m^2	16
Serva Electrophoresis	3	2	6 m^2	6
Soylu Medikal	3	3	9 m^2	15
Vertebral Tech	3	3	9 m^2	24
Tigenix	5	5	25 m^2	18

Exhibitor's Guide (A – Z)

Acibadem Healthcare Group **Booth Nr. 2**
Fahrettin Kerim Gökay cad.49 Altunizade 34662
İstanbul / Turkey
direnc.saribas@asg.com.trmpany
Direnç Sarıbaş
www.acibadem.com.tr

The Leading Hospitals Group of Turkey
Leading provider of health services in Turkey, Acıbadem Healthcare Group offers highest quality diagnosis and treatment in the most comfortable, safe and patient-oriented environments, employing the latest and best medical technologies. Consistent growth since the foundation of its first hospital in 1991 has today rendered Acıbadem the best known and most valuable brand in health in Turkey and an internationally recognized and respected name.

Acıbadem is unique in its integrated delivery model, offering services beyond its wide network of hospitals and outpatient clinics: Acıbadem Project Management designs, constructs and equips turn-key hospital projects in Turkey and abroad. Acıbadem Insurance provides health and life insurance and policy advisory. Acıbadem Mobile provides urgent care, ambulance, home health and telemedicine services. A Plus provides catering, laundry and cleaning services geared specifically for clinical facilities of all sizes. Acıbadem Labmed provides the largest spectrum of laboratory services including genetics, pathology, stem cell, cord blood and food and hygiene. Acıbadem University represents transfer of Acıbadem's experience in deliveryto the academic platform and to training of future generations of healthcare professionals.

As the first healthcare institution publicly listed in the Istanbul Stock Exchange, Acıbadem takes pride in re-investing in Turkey and the healthcare industry. Acıbadem's international growth vision is not only limited to serving an increasing number of patients from foreign countries, but runs the gamut from offering clinical and administrative education programs, training cases in collaboration with local physicians, affiliation and co-branding agreements, consulting engagements, outsourcing of reference laboratory, tele-medicine and facilities management services, insurance policy and systems advisory, management partnerships and direct investment opportunities.

Anika Therapeutics, Inc. **Satellite Symposium**
32 Wiggins Avenue
Bedford, MA 01730, USA

Contact: Hadi El Heneidi
helheneidi@anikatherapeutics.com
www.anikatherapeutics.com

Headquartered in Bedford, Mass., Anika Therapeutics, Inc. develops, manufactures and commercializes therapeutic products for tissue protection, healing, and repair. These products are based on hyaluronic acid (HA), a naturally occurring, biocompatible polymer found throughout the body. Anika's products range from orthopedic/joint health solutions led by Orthovisc® and MonoviscTM, treatments for osteoarthritis of the knee; as well as therapeutics in new areas such as advanced wound treatment and ear, nose and throat care; to surgical aids in anti-adhesion. The company also offers aesthetic dermal fillers for the correction of facial wrinkles. Its regenerative tissue technology advances Anika's vision to offer therapeutic products that go beyond pain relief to protect and restore damaged tissue.

Arthrex GmbH **Booth Nr. 10**
Liebigstr. 13
85757 Karlsfeld / Munich, Germany

Tel +49/8131/5957-0
Fax +49/8131/5957-245
info@arthrex.de | www.arthrex.de

Arthrex has been improving surgical techniques in orthopaedics and traumatology since 1981. With over 6,000 developed products, Arthrex stands for innovation and quality in the field of arthroscopy, sports medicine and orthopaedics. Working with renowned orthopaedists and surgeons, solutions are continuously developed and improved to make even complex procedures evermore simple and safe.

Our product range comprises electronic equipment for arthroscopy, reconstruction instruments and implants for sports medicine and traumatology, joint prosthetics, and orthobiologic products. Arthrex is an independent, privately held corporation headquartered in Naples, FL, USA, with currently over 1,400 employees in 13 subsidiaries throughout the world.

Arthrex is a Diamond Partner of the ICRS.

Arthrosurface **Booth Nr. 21**
28 Forge Parkway
Franklin, MA 02038, USA

aarnone@arthrosurface.com
www.arthrosurface.com

Arthrosurface® develops surface implants and mesenchymal stem cell delivery technology. The implants provide an active alternative to joint replacement and the cell delivery system provides a simple, standardized reproducible way of accessing bone marrow stem cells. By tailoring the implant to match the patients' unique joint surface the native biomechanics remain intact. Unlike a total joint replacement which removes all the cartilage and significant amounts of bone, Arthrosurface® implants only replace the damaged surface. The implants are available as a hemi or as bipolar devices depending on the indication. The implant is placed into the damaged area of the joint where the cartilage has worn away. The exposed and painful bone is covered and the remaining structures are left untouched, allowing the patient to move naturally again without pain. The procedure lets patients resume full activity without restrictions and may be performed as an outpatient procedure.

Exhibitor's Guide (A – Z)

Biomet Healthcare **Booth Nr. 5**
Bridgend UK
www.biomet.com

Biomomentum Inc. **Booth Nr. 9**
970 Michelin, Suite 200
Laval, Quebec, H7L 5C1
Canada

Tel:+1 (450) 667-2299
www.biomomentum.com
info@biomomentum.com

Biomomentum specializes in providing solutions for the biomechanical evaluation of biomaterials and cartilage. The Arthro-BST™ is a hand-held medical device used in conjunction with arthroscopic procedures for the non-destructive measurement of compression-induced streaming potentials of articular cartilage. The instrument measures streaming potentials generated during gentle compression of the articular cartilage and calculates a quantitative parameter reflecting its electromechanical properties. Scientific literature has indicated that streaming potentials are not only a function of the stiffness of cartilage, but also of its composition, structure, and thickness. In addition to its clinical applications, the Arthro-BST™ offers a vast array of research opportunities in the field of cartilage repair. The company also develops and commercializes the Mach-1™, a modular, multiple-axis mechanical tester capable of performing compression, tension, shear, and torsion tests for the precise characterization and mechanical stimulation of cartilage and other soft tissue or materials. This innovative device can be used to automatically map the mechanical properties of full articular cartilage surfaces in indentation. Biomomentum also offers biomechanical testing services using its unique instrumentation.

BMI Biomedical Implants GmbH **Booth Nr. 7**
Langenstücken 11
D 21271 Hanstedt, Germany

Phone: 0049 4184 895775
info@biomedicalimplants.de
www.biomedicalimplants.de

BMI is producer of Carbonfibre Pins CHOPIN® and the instruments for implanting them. We are selling our pins on an exclusive base all over the world. Due to the increasing number of Cartilage Defects of the people the interest is enormous. There is no alternative to preserve the own joint, but with that Carbonfibre Pins CHOPIN® it is possible to safe it. The product is established since more than ten years. As you can see studies and the literature confirms the big success (more than 80% of the treated patients) of that method. A lot of patients are happy to get that treatment and they can take part in very short time on their normal life again, with the own joint. Even they are doing their sports after a very short period without a long time of rehabilitation. So we can make that people happy and on the other side we safe a lot of costs.

Please visit our homepage – www.biomedicalimplants.de - and our booth No. 7 at ICRS Congress in Izmir 15th – 18th of September, to get more information.

CellCoTec B.V. **Booth Nr. 19**
Prof. Bronkhorstlaan 10, Building 48
3723 MB Bilthoven, The Netherlands
Contact: fergus.macleod@cellcotec.com
www.cellcotec.com

CellCoTec has developed and markets a breakthrough, cell based technology for regenerating damaged articular cartilage in the knee. Using a unique patented technology, CellCoTec's lead product, INSTRUCT, offers orthopaedic surgeons a reliable and high quality repair for grade III and grade IV lesions in a single surgical procedure. Interim results from our European multi centre clinical study are showing consistent cartilage regeneration, and excellent patient outcomes. The procedure involves taking freshly isolated autologous chondrocytes, harvested from the lesion site and healthy non-weight bearing parts of the knee ,and combining them with bone marrow cells, as aspirated. This cell combination is then seeded onto a biocompatible and biodegradable co-polymer scaffold implant with a similar dynamic stiffness to that of native cartilage. The scaffold provides immediate mechanical support and achieves full integration and defect filling of the lesion.

CellCoTec's INSTRUCT scaffold is CE marked and regulated as a class III medical device in Europe. INSTRUCT is available for use by certified orthopaedic surgeons following in-hospital training by CellCoTec. If you would like to know more about INSTRUCT please visit us on Stand 19.

DePuy Synthes Mitek Sports Medicine **Booth Nr. 4**
Ivan Holzner (EMEA Marketing Manager)
Gubelstrasse 34
6300 Zug, Switzerland

T. +41 58 231 5959, C. +41 79 176 0309
Email: iholzner@its.jnj.com
Website: www.DePuySynthes.com

DePuySynthes Mitek Sports Medicine offers minimally invasive and arthroscopic surgical solutions that address the challenges of soft tissue repair in the knee, shoulder and other joints.

Our suture anchoring implants are used worldwide to reattach damaged ligaments and tendons in the hand, wrist, thumb and ankle, while our wide array of innovative surgical products for knee joint repair helps surgeons who are attempting to restore natural movement to their patients. By improving upon and creating new, technologically advanced materials, instruments and techniques, we look

Exhibitor's Guide (A – Z)

to open the range of treatment options up to new possibilities. And by advancing procedural solutions in the field of sports medicine, we will continue to provide physicians with the instruments needed to make extraordinary patient outcomes a reality.

Episurf Medical **Booth Nr. 13**
Stora Skuggansväg 11
11542 Stockholm, Sweden

per.möller@episurf.com
www.episurf.com

Episurf Medical is dedicated to help people (with painful joint injuries) by providing fully customized solutions for treatment of human joints. With the help of the µiFidelity ™ system Episurf has developed, Episurf is able to design and create implants which are tailored to each person's unique anatomy. This increases surgical precision and optimizes the fit of the implant.

Our aim is:
- To improve lives by providing patient-specific treatment solutions.
- To enable people to never stop moving
- To make pain-free motion a given right by providing people with troubled joints an effective and patient-specific treatment

During 2013 we have started the sales of our first product EPISEALER knee for the treatment of cartilage injuries in the femoral condyle. EPISURF MEDICAL is a young orthopaedic company, traded on the Swedish stockmarket.
EPISURF -INDIVIDUALY CUSTOMIZED

Fin-Ceramica Faenza S.p.A. **Booth Nr. 22**
Via Granarolo 177/3
48018 Faenza (RA), Italy

Contact: Daniela Donati – Mkt & Sales, Event Manager
ddonati@finceramica.it
www.finceramica.com

Finceramica (Italy) operates worldwide with the aim of developing, producing and marketing proprietary bone and cartilage substitutes, including custom-made solutions for particular clinical needs. Research activity focuses on innovative bioceramic materials, ceramic-polymer composites and a new generation of biological joint replacements and knee resurfacings.

Maioregen®, the company's lead product designed for osteochondral regeneration, is a biomimetic, nanostructured multilayer scaffold obtained through a unique, patented process, result of the cooperation between Finceramica and internationally recognized research centres.
Stop by our booth no. 23 for more information on our products.

Geistlich Pharma AG **Booth Nr. 3**
Business Unit Surgery
Bahnhofstrasse 40
6110 Wolhusen, Switzerland

Phone: +41 41 492 55 55
Fax: +41 41 492 56 39
Email: surgery@geistlich.com
Website: www.geistlich-surgery.com

Geistlich Surgery develops premier global solutions for the formation of bone and cartilage in the rapidly advancing field of regenerative medicine.

Chondro-Gide® is the leading natural collagen matrix in cartilage regeneration. This standardised, easy to handle matrix can be used to treat cartilage defects using the innovative AMIC® technique or using ACI. AMIC® is a single-step, cost efficient and effective procedure for treating traumatic cartilage defects. Chondro-Gide® provides a suitable cell carrier and positively influences chondrogenic differentiation of mesenchymal stem cells to form a mostly hyaline-like cartilaginous repair tissue.

Orthoss® is a natural bone graft substitute. Its inorganic bone matrix has a macro- and microporous structure similar to human spongeous bone. It is structurally integrated into the surrounding bone and incorporated into the natural remodelling process. As a result of the excellent biofunctionality, Orthoss® is an ideal bone graft substitute which can be used alone or during composite bone grafting using autologous bone or bone marrow aspirate when treating large defects. This includes the repair of defects following trauma, reconstruction in orthopaedics and in spinal surgery. Over 25 years of clinical experience show a high degree of safety and efficacy.

Karl Storz GmbH & Co KG **Booth Nr. 11**
Mittelstraße 8
78532 Tuttlingen, Germany

Contact:
Sigrid.Lanzillotti@karlstorz.com
www.karlstorz.com

KARL STORZ is a renowned manufacturer that is well established in all fields of endoscopy and can be considered as market leader in rigid endoscopy. The still family held company was founded in 1945 in Tuttlingen, Germany, and has grown to one with a worldwide presence and 5800 employees. KARL STORZ offers a range of both rigid and flexible endoscopes for a broad variety of applications. Today's product range also includes fully integrated concepts for the OR and servicing.

Exhibitor's Guide (A – Z)

Mobileturk Saglik **Booth Nr. 8**
Mmobileturk sağlık ürünleri imalat sanayi ve tic.ltd.şti.
aziziye mahallesi cinnah cad.
kuloğlu sokak no : 15/2 çankaya / Ankara

Contact:
Telefon: 0 312 440 85 75
Fax: 0 312 440 85 92
www.mobileturksaglik.com.tr
koray.gurbuz@mobileturk.com.tr
info@mobileturk.com.tr

Firmamız ortopedi ve beyin cerrahi alanlarında faaliyet göstermektedir. Travma, kıkırdak, spinal ve greft distribütörlüklerimiz mevcuttur. Yeni bir kuruluş olmamıza rağmen sektörde çok tecrübeli ortaklarımız bulunmaktadır ve piyasada iyi bir yer edinmeye başlamış bulunmaktayız. Bu kongrede tanıtımını yapacağımız kıkırdak impanltı ürünümüz bizim için çok önemlidir.

Orteq Sports Medicine **Booth Nr. 23**
10 Greycoat Place, London, UK

Contact:
Simon Coles, VP Sales & Marketing
scoles@orteq.com
www.orteq.com

Orteq Sports Medicine with offices in London, UK and Chicago, US was established in 2005 to develop and commercialize solutions for orthopaedic/sports medicine injuries. Orteq's first product Actifit,® is a biodegradable, biocompatible polymer scaffold, specifically designed to facilitate tissue ingrowth and regeneration in the meniscus, a fibrocartilage cushion in the knee. Actifit® is indicated for irreparable meniscus tears and over 2000 have been implanted in Europe since CE mark approval. Actifit®'s one and two year EU clinical study results have been published in the American Journal of Sports Medicine. Based on it's EU safety and efficacy data, Orteq® has also recently gained FDA IDE approval to start an Actifit® clinical study in the USA. For further information please visit: www.orteq.com or visit booth 23 at ICRS.

Orthogen Lab Services GmbH **Booth Nr. 1**
Graf-Adolf-Strasse 41
40210 Düsseldorf, Germany

www.orthokine.com
Julio.Reinecke@orthogen.com

ORTHOGEN Lab Services GmbH, a subsidiary of ORTHOGEN AG. ORTHOGEN Lab Services GmbH is focused on the treatment of musculoskeletal system diseases. ORTHOGEN Lab Services GmbH offers two medical devices:
EOT® II- syringe is used to generate Autologous Conditioned Serum from patients own blood for the innovative Orthokine®-therapy. The conditioned serum is prepared at site of care and contains clinically effective anti-inflammatory and regenerative signalling proteins. It is used for the treatment of joint, spine, tendon and muscle injuries.

Osteokine®-PRP is used for the processing of platelet rich plasma (PRP) at site of care. The high concentration of thrombocytes supports and accelerates the natural tissue healing process through release of growth factors. The use of autologous PRP is well established for the treatment of tendon and ligament lesions and slow-to-heal injuries.

Orthogen AG is dedicated to the development of new techniques for tissue regeneration. Both in the animal and in the human health markets Orthogen has successfully made a difference to what was available before.

Piramal Life Sciences **Booth Nr. 17**
475, Boul. Armand-Frappier
Laval, QC H7V 4B3, Canada

bdbioorthopaedics@piramal.com
bst-cargel.piramal.com
www.piramal.com

Piramal | Life Sciences Bio-Orthopaedics is a Piramal Group Company. Piramal Group Company is a diversified global conglomerate with operations in over 30 countries and brand-presence across 100 markets around the world.

Piramal | Life Sciences Bio-Orthopaedics is dedicated in joint tissues regenerative therapies to improve patients quality of life and delay/prevent definitive surgery. BST-CarGel®, our unique and advanced biopolymer technology, is a medical device intended to promote hyaline cartilage regeneration when used in conjunction with a bone marrow stimulation technique for the repair of articular cartilage. BST-CarGel® is a first line treatment suited for most cartilage lesion cases. An international, multicenter, randomized controlled trial with the highest standards has demonstrated that BST-CarGel® was a safe and effective cartilage repair treatment. Taken together, the trial data strongly supports a positive risk-benefit analysis for BST-CarGel® and a solution for consistent, high quality cartilage regeneration.

BST-CarGel® is manufactured in Canada under a certified manufacturing process that meets the highest safety and quality standards. BST-CarGel® received European Regulatory approval which enabled its commercialization in all the European Union countries in 2012.

Exhibitor's Guide (A – Z)

Regentis Biomaterials Ltd. **Booth Nr. 14**
2 Ha'Ilan Street, Northern Industrial Zone
P.O.Box 260, Or-Akiva 30600, Israel

Livnat@regentis.co.il
www.regentis.co.il

Regentis Biomaterials is a tissue repair company developing innovative biodegradable hydrogels for local repair of soft and hard tissue. Our platform technology is a family of hydrogels called Gelrin™. These gels can be injected or applied to a specific local site and offer beneficial properties for the local repair of damaged tissue such as cartilage and bone.

The Gelrin™ technology offers off-the-shelf products that are designed to be suitable for both open surgery and minimally invasive procedures. An ideal solution for physicians and their patients, the products are easy to implant and have been shown to stimulate the regeneration of healthy cartilage and bone tissue.

Regentis' flagship product is GelrinC, a biodegradable hydrogel for articular cartilage regeneration, providing a controlled environment for gradual tissue repair and formation of hyaline-like cartilage. GelrinC is comprised of polyethylene glycol diacrylate (PEG-DA) and denatured fibrinogen, a natural substrate for tissue regeneration. These materials form a matrix for tissue repair – combining the stability and versatility of a synthetic material with the bio-functionality of a natural material. GelrinC has recently received CE mark in Europe. CAUTION: GelrinC is an investigational product, not available in the US

Sanofi Biosurgery **Booth Nr. 16**
55 Cambridge Parkway
MA 02142 Cambridge, USA

www.sanofi.com

Sanofi Biosurgery is a global strategic business unit of Sanofi, which develops and markets unique, innovative devices, biologics and cell therapies which meet unmet needs in a variety of areas including osteoarthritis and cartilage repair.

Sanofi Biosurgery is a Diamond Partner of the ICRS.

SERVA Electrophoresis GmbH **Booth Nr. 6**
Carl-Benz-Str. 7
69115 Heidelberg, Germany

collagenase@serva.de
www.serva.de

Collagenase NB GMP and research grades. SERVA offers Collagenase NB products for high-yield isolation of viable cells. In addition to research grades SERVA is a worldwide supplier of Collagenase NB and Neutral Protease NB products manufactured according to GMP guidelines.

Collagenase NB 6 GMP Grade is especially suitable for isolation of a broad variety of cells, including chondrocytes and stem cells from adipose tissue, which can be used for clinical applications such as cell therapy, tissue engineering and regenerative medicine. Excellent performance, high safety standards and reliable lot-to-lot consistency are ensured by high manufacturing standards. All SERVA Collagenase NB products are produced by the German pharmaceutical company Nordmark.

SERVA Electrophoresis GmbH is a German life science company founded in 1953. Its unique and comprehensive product portfolio includes also electrophoresis and laboratory devices, fine biochemicals, and enzymes.

Smith & Nephew Inc. **Platinum Sponsor**
150 Minuteman Road
Andover, Massachusetts, USA

www.smith-nephew.com

Smith & Nephew is a global medical technology business dedicated to helping improve people's lives. With leadership positions in Orthopaedic Reconstruction, Advanced Wound Management, Sports Medicine and Trauma, Smith & Nephew has around 11,000 employees and a presence in more than 90 countries. Annual sales in 2012 were more than $4.1 billion. Smith & Nephew is a member of the FTSE100 (LSE NYSE: SNN).

Exhibitor's Guide (A – Z)

SOYLU MEDİKAL SAN. VE DIŞ. TİC. LTD. ŞTİ. **Booth Nr. 15**
Mimar Sinan Caddesi Merkez Mahallesi
Piri Reis Caddesi Ayça Sokak Şana Sitesi E Blok No:20
Büyükçekmece/İstanbul, Turkey

Tel: +90 212 863 12 99
Fax: +90 212 863 65 43
www.soylumedikal.com
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Founded in 2004, Soylu Medical began his career by selecting the branch of orthopedics. Soylu Medical has attained a place in these fields. As of 2006, company has added his product range Hyalonect is used as perios implant in the field of orthopedic which is produced by previously Italian Fidia and now Anika Therapeutics. Continuing to increase his product portfolio Soylu Medical at 2011 has added to his product range Hyalofast (Anika Therapeutics) which is used in surgery of the cartilage. With his nearly 80 employees and logistic offices in seven regions of Turkey, in Turkey market company distributes the products of Anika Therapeutics.

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B-3001 Leuven, Belgium

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Clinical data shows superior structural repair versus microfracture after 12 months and durability of clinical benefit after 5 years, especially when treatment is performed 3 years after onset of symptoms. ChondroCelect is manufactured in a state-of-the-art European facility utilizing a robust, consistent & reproducible manufacturing process according to GMP standards.

Tigenix is a Diamond Partner of the ICRS.

Vertebral Technologies Inc. (VTI) **Booth Nr. 24**
5909 Baker Road Suite 550
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Telephone: 952-979-9353
Email: jwilliams@vti-spine.com
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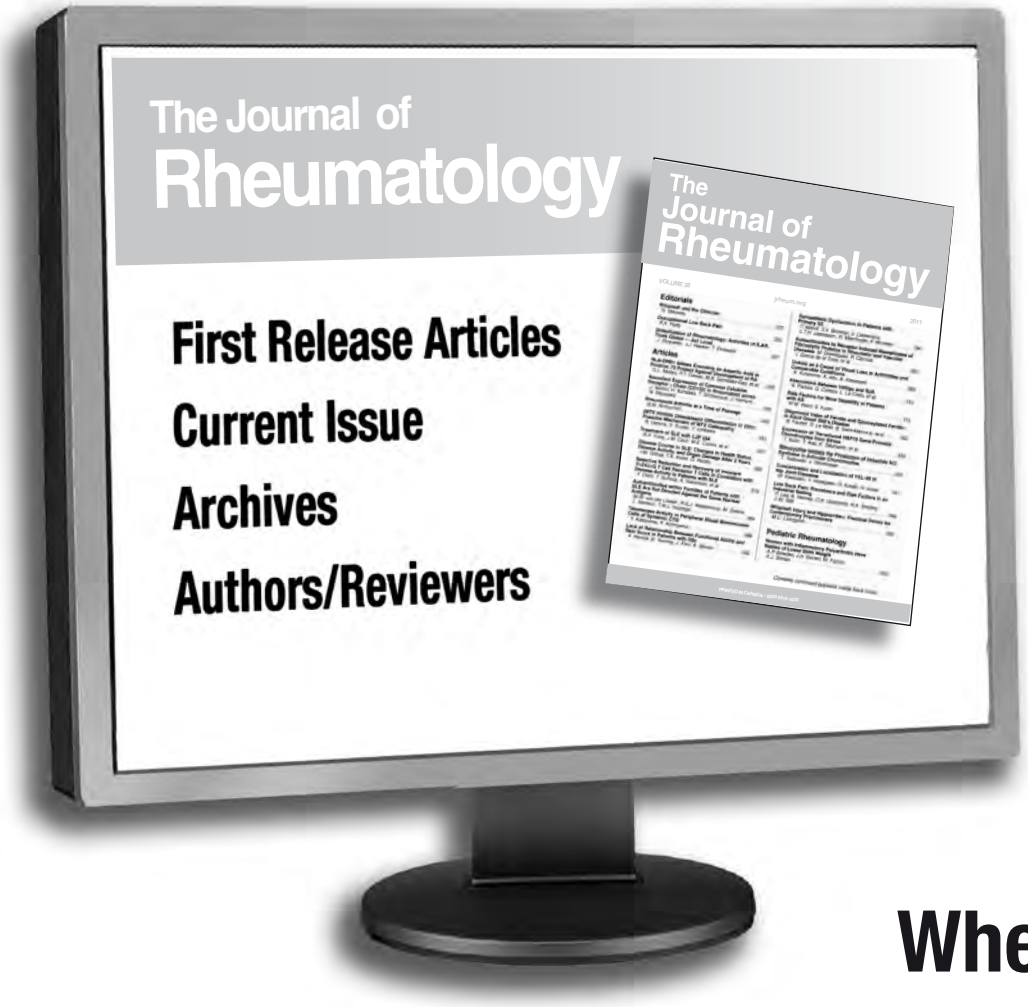

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11th World Congress of the International Cartilage Repair Society ICRS 2013

Sept. 15 – 18, 2013

Agenda

Scientific Programme

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Programme: Sunday, September 15, 2013

07:30 - 09:00 **Room: Petek Board Room**
ICRS Editorial Board Meeting
Chair: Mats Brittberg/SE

09:00 - 10:00 **Room: Bayrakli Board Room**
ICRS Executive Board Meeting
Chair: Anthony Hollander/UK

10:15 - 12:00 **Room: Bayrakli Board Room**
ICRS General Board Meeting
Chair: Anthony Hollander/UK

Session: 0.0 **Special Session in Turkish Language**
10:00 - 12:00 **Room: Didim**

Cartilage Restauration in Turkey - A Clinical & Scientific Update
Moderators: Didem Kozaci/TR, Tahsin Beyzadeoglu/TR

0.01 The Effect of MACI for Deep Osteonecrotic Femoral Condyle Defect
M. Binnet Ankara/TR

0.02 Stem Cell-Based Cartilage Repair in Isolated Articular Cartilage Lesions and Arthritic Conditions
I. Akgun[1], M.C. Unlu[1], O.A. Erdal[1], M. Erturk[2], T. Ogut[1], F. Kantarci[1] [1]Istanbul/TR, [2]Trabzon/TR

0.03 Micro/nano scale structural and elemental investigation of bone-cartilage interface
K. Memisoglu[1], O. Gundogdu[1], D.A. Bradley[2], M. Bailey[2], C. Jeynes[2], O. Bunk[3] [1]Kocaeli/R, [2]Guildford/UK,[3]Villigen/CH

0.04 A Comparison Of The Effects Of Neuronal Oxide Synthase And Inducable Nitric Oxide Synthase Inhibition On Cartilage Damage
N.S. Gokay[1], I. Yilmaz[1], A.S. Demiroz[2], A. Gokce[1], S. Dervisoglu[2], B. Vural Gökay[2] [1]Tekirdag/TR, [2]Istanbul/TR

0.05 The effect of platelet rich plasma on osteochondral defects treated with mosaicplasty technique
E. Altan[1], K. Aydin[2], H. Senaran[2], O.F. Erkocak[2], M.A. Acar[2] [1]Istanbul/TR, [2]Konya/TR

0.06 The ideal Timing of siRNA Plasmid transfection on Primer Chondrocyte Cultures
I. Yilmaz, N.S. Gokay, A. Gokce, R. Bircan Tekirdag/TR

0.07 Bilayer-Matrix Autologous Chondrocyte Transplantation in Treatment of Deep OsteoChondral Lesions of Knee
M. Bozkurt[1], C. Isik[2], S. Gürsoy[2], O. Algin[2], N. Cay[2], G. Kartal[2] [1]Gölbaci -Ankara/TR, [2]Ankara/TR

0.08 The efficacy of microfracture technique for the treatment of knee articular cartilage lesions
S. Tasci[1], S. Unlu[2], M.F. Catma[2], B. Tunc[2], M. Altay[2], M. Bozkurt[2] [1]Hakkari/TR, [2]Ankara/TR

0.09 The compatibility of the evaluation methods of cartilage repair patients
U.Z. Koçak, A. Nalbant, B. Ünver, M. Erduran Izmir/TR

0.10 The Clinical Utility of Accelerated and Delayed Weightbearing Approaches to Postoperative After MACI: A Systematic Review
A. Nalbant, U.Z. Koçak, B. Ünver, M. Erduran Izmir/TR

Programme: Sunday, September 15, 2013

Session: 1.0 **Plenary Session**
13:00 - 14:00 **Room: Smyrna 1**

Cartilage & Sports (ICRS-FIFA)
Moderators: Lars Peterson/SE, Marcy Zenobi-Wong/CH

1.1 Effect of Sport on the Athlete's Joint: The Scientific Perspective
K. Mithoefer Chestnut Hill/US

1.2 Treatment and Prevention of Articular Cartilage Injury in the Athlete
B. Mandelbaum[1], K. Mithoefer[2] [1]Santa Monica/US, [2] Chestnut Hill/US

1.3 Return to Sport after Cartilage Repair: Opportunities and pitfalls for rehabilitation
D. Van Assche Leuven/BE

1.4 Emerging Scientific Approaches for Management of Athletic Cartilage Injury
S. Chubinskaya Chicago/US

Session: 2.1 **Special Session**
14:15 - 15:15 **Room: Smyrna 1**

Cartilage Injury to Osteoarthritis: Spectrum of Disease; Spectrum of Treatment
Moderators: Alberto Gobbi/IT, Stefan Lohmander/SE

2.1.1 Basic Science of Cartilage Injury and Degeneration
R.L. Sah La Jolla/US

2.1.2 Clinical Spectrum of Cartilage Injury
D.B.F. Saris Utrecht/NL

2.1.3 Adapting Therapeutic Concepts to Cartilage Injury Severity
P. Angele Regensburg/DE

Session: 2.2 **Special Session**
14:15 - 15:15 **Room: Grand Efes II**

Biomaterials in Cartilage Repair
Moderators: Jason Burdick/US, Caroline Hoemann/CA

2.2.1 In situ Forming Oxidized Hyaluronic Acid Hydrogel for Nucleus Pulposus Regeneration
F.-H. Lin Taipei/TW

2.2.2 Hydrogels versatile Scaffolds for Cartilage Repair
J. Malda Utrecht/NL

2.2.3 Engineering Developmental Signals into Hydrogels for Cartilage Repair
L. Bian, M. Guvendiren, W. Gramlich, R. Mauck, J.A. Burdick Philadelphia/US

Programme: Sunday, September 15, 2013

Session: 2.3 **Special Session**
14:15 - 15:15 **Room: Smyrna 2**

Minimally Invasive Cartilage Repair
Moderators: Elizaveta Kon/IT, Matthias Steinwachs/DE

2.3.1 Evolution of Minimally Invasive Cartilage Repair
A. Getgood London/CA

2.3.2 Reducing Invasiveness of Adjuvant Procedures
B.J. Cole Chicago/US

2.3.3 Arthroscopic Transplantation of Synovial MSCs for Cartilage Regeneration
I. Sekiya, T. Muneta Tokyo/JP

15:15 - 15:45 **Coffee Break / Intermission / Exhibition / Poster Viewing**

Session: 3.1 **Special Session**
15:45 - 16:45 **Room: Smyrna 1**

Cartilage Rehabilitation: Current & Developing Concepts
Moderators: Dieter Van Assche/BE, Kai Mithoefer/US

3.1.1 Current Principles and Challenges of Cartilage Rehabilitation
D. Van Assche Leuven/BE

3.1.2 Useful Equipment and Modalities for Cartilage Rehabilitation
H.J. Silvers Santa Monica/US

3.1.3 Promoting Muscle Recovery after Cartilage Repair
B. Wondrasch St. Poelten/AT

Session: 3.2 **Special Session**
15:45 - 16:45 **Room: Grand Efes II**

Lessons from Cartilage Development
Moderators: Ernst Hunziker/CH, Rocky Tuan/US

3.2.1 Cartilage Repair in Axolotl Salamanders
J.N. Macleod Kentucky/US

3.2.2 Chondrocyte Proliferation and Differentiation in Cartilage Development
A. Aszodi Munich/DE

3.2.3 Developmental Engineering of Cartilage from Stem Cells
W. Richter Heidelberg/DE

Programme: Sunday, September 15, 2013

Session: 3.3 **Special Session**
15:45 - 16:45 **Room: Smyrna 2**

Intervertebral Disk
Moderators: Georg Omlor/DE, Rita Kandel/CA

3.3.1 Comparison of Intervertebral Disc and Articular Cartilage
R. Kandel Toronto/CA

3.3.2 Towards intervertebral disc repair: insights from stem cell studies
V.Y.L. Leung Hong Kong/CN

3.3.3 Regeneration of intervertebral discs: Lessons from large animal models
G. Omlor Heidelberg/DE

Session: 4.0 **17:00 - 17:45** **Room: Smyrna 1**

Opening Ceremony, Awards & Honorary Lectures
Moderators: Anthony Hollander/UK, Norimasa Nakamura/JP

Session: 5.0 **17:45 - 18:45** **Room: Smyrna 1**

Honorary Lectures

5.1 The Joint 'Organ': Comprehensive Concepts for Cartilage Restoration
B.J. Cole Chicago/US

5.2 From matrices and cells to biomechanics and clinical benefit - challenges and paradigms in cartilage repair
M. Buschmann Montreal/CA

19:00 – 20:30 **Welcome Reception** **Gardens Swissôtel**

Participants, industry representatives and accompanying persons are invited to join the opening ceremony and welcome cocktail at the Swissôtel Grand Efes. This reception is offered to you by the ICRS. After the cocktail, participants have free time for their own leisure to discover Izmir and enjoy one of the many nice restaurants / bars at the harbour promenade right in front of the Swissôtel.

Programme: Monday September 16, 2013

Session: 6.1 **Instructional Course (Pre-Registration required)**
07:30 - 08:15 **Room: Smyrna 2**

Patellofermoral Cartilage Injury
Moderators: Jack Farr/US, Tom Minas/US

6.1.1 Diagnostic Workup of Patellofemoral Cartilage Injury
A. Gobbi, G. Karnatzikos, D.G. Lad, S.R. Sukesh Milano/IT

6.1.2 Treatment Options, Surgical Indications & Outcome in the Patellofemoral Cartilage Repair T. Minas, A. Von *Keudell, T. Bryant, R. Han Chestnut Hill/US*

6.1.3 Rehabilitation for Patellofemoral Cartilage Injury & Repair
L. Snyder-Mackler Delaware/US

Session: 6.2 **Current Concept Lecture (Pre-Registration required)**
07:30 - 08:15 **Room: Grand Efes II**

Tissue Quality & Outcome
Moderators: Ivan Martin/CH, Sally Roberts/UK

6.2.1 Does cellular graft quality affect cartilage repair outcome?
I. Martin Basel/CH

6.2.2 Use of Histology, Biomarkers & Proteomics to determine Tissue Quality and Outcome S. Roberts, H. Fuller, K. *Wright, H.S. McCarthy Shropshire/UK*

6.2.3 MRI Assessment of Tissue Quality & Outcome
S. Marlovits Vienna/AT

Session: 6.3 **Instructional Course (Pre-Registration required)**
07:30 - 08:15 **Room: Didim**

How to write, submit or review for the Journal Cartilage
Moderators: Mats Brittberg/SE, Gerjo Van Osch/NL

6.3.1 How to write a Cartilage Article
G.J.V.M. Van Osch Rotterdam/NL

6.3.2 Submitting Manuscripts to the ICRS Journal ‹Cartilage›
M. Brittberg Kungsbacka/SE

6.3.3 Reviewing for the ICRS Journal ‘Cartilage’
W. McIlwraith Fort Collins/US

Programme: Monday September 16, 2013

Session: 7.0 **Plenary Session**
08:30 - 09:30 **Room: Smyrna 1**

The Subchondral Bone & Cartilage Repair
Moderators: Brian Cole/US, Wayne McIlwraith/US

7.1.0 Basic Science of the Subchondral Bone in Healthy, Diseased & Repaired Cartilage
C.D. Hoemann Montreal/CA

7.2.0 Clinical Spectrum and Relevance of Subchondral Bone Changes for Cartilage Injury and Repair G.
Knutsen Tromsoe/NO

7.3.0 Treatment of Subchondral Bone Pathology
J. Farr Greenwood/US

Session: 8.1 **Special Session**
09:45 - 10:45 **Room: Smyrna 1**

Lessons from Failure: Why is Cartilage Repair Unsuccessful?
Moderators: Haris Vasiliadis/GR, Stefan Nehrer/AT

8.1.1 Definition and Epidemiology of Failed Cartilage Repair
A.H. Gomoll Boston/US

8.1.2 Why does Cartilage Repair Fail?
P. Niemeyer Freiburg/DE

8.1.3 Strategies to Improve Failure Rate
M. Steinwachs, B. Waibl, M. Mumme Zürich/CH

Session: 8.2 **Special Session**
09:45 - 10:45 **Room: Grand Efes II**

Immunology, Cytokines, Regenokine
Moderators: Elizaveta Kon/IT, Hari Reddi/US

8.2.1 Immunological Aspects of Cartilage Science
A.P. Hollander, S. Zang, S. Dickinson, S. Pang, K. Brady, W. Kafienah, D.C. Wraith Bristol/UK

8.2.2 Value of single Cytokines & Factor Cocktails for Cartilage Repair
M.K. Lotz La Jolla/US

8.2.3 Clinical Experience with Regenokine
P. Wehling Düsseldorf/DE

Session: 8.3 **Special Session**
09:45 - 10:45 **Room: Smyrna 2**

Understanding & Managing Pain in Cartilage Injury and Repair
Moderators: Alan Getgood/CA, Felix Enrique Villalobos Córdova/MX

8.3.1 Basic Science of Joint Pain
D.A. Walsh Notthingham/UK

8.3.2 Why is Cartilage Injury Painful?
M. Brittberg Kungsbacka/SE

8.3.3 Treatment Principles and Approaches
P.C. Kreuz Rostock/DE

Programme: Monday September 16, 2013

10:45 - 11:15 **Coffee Break / Intermission / Exhibition / Poster Viewing**

Session: 9.1 **Free Paper Session**
11:15 - 12:45 **Room: Didim**

Animal Models
Moderators: Mark Hurtig/CA, Wayne McIlwraith/US

9.1.1 Interspecies comparison of subchondral bone properties important for cartilage repair
A. Chevrier[1], A.S.M. Kouao[1], M.B. Hurtig[2], M. Buschmann[1] [1]Montreal/CA, [2]Guelph/CA

9.1.2 Early Response of Cartilage and Synovium to Controlled Non-invasive Joint Injury in Vivo Suggests Treatment Options
L.J. Sandell, P. Wu, N. Holguin, M.J. Silva St. Louis/US

9.1.3 Deletion of Gangliosides Enhances Cartilage Degradation in Murine Models of Osteoarthritis
F. Sasazawa[1], T. Onodera[1], T. Yamashita[2], N. Iwasaki[1] [1]Sapporo/JP, [2]Sagamihara/JP

9.1.4 Sprifermin increased joint space width and reduced subchondral bone sclerosis as translational primary outcome measures in a rat OA model
K. Kleinschmidt[1], S. Lindemann[1], M.J. Heneka[2], H. Guehring[1] [1]Darmstadt/DE, [2]Karlsdorf Neuthard/DE

9.1.6 A scaffold-free tissue-engineered construct (TEC) derived from rabbit embryonic stem cells in osteochondral repair
Y. Moriguchi[1], R. Chijimatsu[1], M. Sakaue[1], K. Shimomura[1], Y. Yasui[2], K. Koizumi[2], N. Sugita[1], Y. Yonetani[2], H. Yoshikawa[3], N. Nakamura[2] [1]Suita City/JP, [2]Osaka/JP, [3]Suita/JP

9.1.7 Comparison of hydroxyapatite and beta-tricalcium phosphate-based biphasic implant for osteochondral repair
K. Shimomura[1], Y. Moriguchi[1], W. Ando[2], R. Nansai[3], H. Fujie[3], S. Horibe[1], K. Shino[1], H. Yoshikawa[1], N. Nakamura[11]Osaka/JP, [2]Hyogo/JP, [3]Tokyo/JP

9.1.8 The intra-articular injection of alginate-chitosan beads in an hydrogel prevents the development of osteoarthritis in ACLT rabbit model
F. Oprenyeszk[1], M. Chausson[2], V. Maquet[2], J.-E. Dubuc[3], Y. Henrotin[1] [1]Liege/BE, [2]Herstal/BE, [3]Brussels/BE

9.1.9 Chondroprotective effect of an intra-articular Adipose derived Stromal Cell injection for the management of osteoarthritis in rabbit
G. Desando, C. Cavallo, F. Sartoni, L. Martini, A. Parrilli, F. Veronesi, M. Fini, R. Giardino, A. Facchini, B. GrigoloBologna/IT

Programme: Monday September 16, 2013

Session: 9.2 **Free Paper Session**

11:15 - 12:45 **Room: Smyrna 2**

Cell-based Cartilage Repair (Clinical)

Moderators: Lars Peterson/SE, Daniel Grande/US

9.2.1 Improved health-related quality of life in patients treated with MACI implant compared with microfracture for chondral defects of the knee

A. Price[1], M. Brittberg[2], N. Mehin[3], F. Dehle[4], D. Dowton[4], S. Kili[1], D.B.F. Saris[5] [1]Oxford/UK, [2]Kungsbacka/SE,[3]Paris/FR, [4]Sydney/AU, [5]Utrecht/NL

9.2.2 Transplantation of Adipose-Derived Mesenchymal Stem Cells for Knee Articular Cartilage Focal Lesions

M.I. Iosifidis[1], T. Kyriakidis[1], I. Melas[1], E. Michalopoulos[2], A. Mpintoudi[1], K. Stavropoulou[2], A. Kyriakidis[11]Thessaloniki/GR, [2]Athens/GR

9.2.3 ACI in the patella - a multi-center experience.

A.H. Gomoll[1], B.J. Cole[2], J. Farr[3], S.D. Gillogly[4], R.M. Arnold[4], K. Hussey[2], T. Minas[1] [1]Boston/US, [2]Chicago/US,[3]Indianapolis/US, [4]Atlanta/US

9.2.4 Osteochondral lesions of the femoral condyles: is One step repair technique with bone marrow derived cells keeping promises?

R. Buda, F. Vannini, L. Ramponi, M. Cavallo, A. Ruffilli, M. Baldassarri, F. Castagnini, S. Giannini Bologna/IT

9.2.5 Clinical improvement with MACI implant versus microfracture in SUMMIT: Effects of lesion size and acute trauma

D.B.F. Saris[1], A. Price[2], J.O. Drogset[3], A. Pod kubka[4], A.I. Tsuchida[1], S. Kili[2], M. Brittberg[5] [1]Utrecht/NL,[2]Oxford/UK, [3]Trondheim/NO, [4]Prague/CZ, [5]Kungsbacka/SE

9.2.6 Graft Hypertrophy after Matrix Based Autologous Chondrocyte Implantation (mb-ACI) - 3 year follow up

P. Müller, T. Niethammer, A. Horng, A. Ficklscherer, V. Jansson, M.F. Pietschmann Munich/DE

9.2.7 Trends in the Surgical Treatment of Articular Cartilage Lesions: An Analysis of a Large Private Payer Database Over 8 years

F.M. McCormick, J.D. Harris, R.M. Frank, K. Hussey, H. Wilson, A.K. Gupta, G.D. Abrams, B.R. Bach, Jr, B.J. Cole Chicago/US

9.2.8 Recurrence rate of intralesional osteophytes removed during Autologous Chondrocyte Implantation

M.K. Demange[1, 2], A. Von Keudell[2], T. Bryant[2], S. Sodha[2], T. Minas[2], A.H. Gomoll[2] [1]Sao Paulo/BR, [2]Boston/US

9.2.9 Arthroscopic Matrix Encapsulated Autologous Chondrocyte Implantation for cartilage lesions in the knee. Randomized Clinical Trial.

E. Villalobos Jr, C. Ibarra, A. Izaguirre, C. Velasquillo, I. Alba-Sanchez, V. Martinez, S. Cortes, C. Trueba, G. Franco,A. Vargas, V. Guevara, A. Olivos Meza, L.G. Ibarra Mexico City/MX

Programme: Monday September 16, 2013

Session: 9.3 **Free Paper Session**

11:15 - 12:45 **Room: Smyrna 1**

Stem Cells & Cartilage Regeneration

Moderators: Anthony Hollander/UK, Ichiro Sekiya/JP

9.3.1 Identification of MSC affinity peptide and its application in tissue engineering cartilage repair
Z. Shao, Y. Ao Beijing/CN

9.3.2 Survival rate of adipose mesenchymal stem cells is related to route of administration and antigen compatibility in arthritic mouse models
K. Toupet[1], M. Maumus[1], J.A. Peyrafitte[2], P. Bourin[2], C. Jorgensen[1], D. Noel[1] [1]Montpellier/FR, [2]Toulouse/FR

9.3.3 Adipose mesenchymal stromal cells protect chondrocytes from degeneration associated with osteoarthritis
M. Maumus[1], C. Manferdini[2], K. Toupet[1], J.A. Peyrafitte[3], A. Piacentini[2], E. Gabusi[2], A. Facchini[2], P. Bourin[3], G. Lisignoli[2], C. Jorgensen[1], D. Noel[1] [1]Montpellier/FR, [2]Bologna/IT, [3]Toulouse/FR

9.3.4 Weekly intraarticular injections of synovial mesenchymal stem cells delay cartilage degeneration in a rat osteoarthritis model
N. Ozeki[1], I. Sekiya[1], K. Tsuji[1], T. Saito[2], T. Muneta[1] [1]Tokyo/JP, [2]Yokohama/JP

9.3.5 Combinatorial gene-therapy approaches to OA control using stem cells overexpressing TGF-β3 combined with IL-1β and TNF-α RNA silencing
A.E. Watts[1], L. Begum[1], W. McIlwraith[2], A.J. Nixon[1] [1]Ithaca/US, [2]Fort Collins/US

9.3.6 Survival rate of adipose mesenchymal stem cells is related to route of administration and antigen compatibility in arthritic mouse models
K. Toupet[1], M. Maumus[1], J.A. Peyrafitte[2], P. Bourin[2], C. Jorgensen[1], D. Noel[1] [1]Montpellier/FR, [2]Toulouse/FR

9.3.7 One step implantation of activated mesenchymal stem cells in knee osteochondral lesions: results at 2 years of a 37 prospective cases
M. Assor Marseille/FR

9.3.8 Arthroscopic Finding After Intra-Articular Injections of Adipose-Derived Stem Cells with Knee Osteoarthritis Y.J.
Choi, O.R. Kwon, Y.G. Koh, S.-B. Jo, D.-S. Suh Seoul/KR

9.3.9 The contribution of dynamic compression to integrin-TGFbeta crosstalk during chondrogenesis
T. Zhang, Z. Yang, J.H.P. Hui Singapore/SG

Programme: Monday September 16, 2013

Session: 9.4 **Free Paper Session**

11:15 - 12:45 **Room: Grand Efes II**

Biomaterials & Scaffolds

Moderators: Jos Malda/NL, Ulrich Noeth/DE

9.4.1 Failed Osteochondral Repair by MayoRegen® Scaffolds in Patients with Ostochondritis Dissecans
B. Christensen, C.B. Foldager, C. Bünger, M. Lind Aarhus/DK

9.4.2 The Treatment of Cartilage Defects of the Knee with Microfracture augmented with a Biodegradable Scaffold: outcomes at 12 months.
K.F. Almqvist[1], B.J. Cole[2], J. Bellemans[3], R. Arbel[4], E. Basad[5], S. Anders[6], S. Trattnig[7], A. Korner[3] [1]Gent/BE,[2]Chicago/US, [3]Or Akiva/IL, [4]Tel Aviv/IL, [5]Giessen/DE, [6]Bad Abbach/DE, [7]Wien/AT

9.4.3 Treatment of massive osteochondral lesions of the knee with implant of acellular scaffold: a multicenter prospective study
M. Berruto[1], M. Delcogliano[2], G. Carimati[1], F. De Caro[2], C.F. De Biase[2], F.M. Uboldi[1], P. Ferrua[1], A. Delcogliano[3][1]Milano/IT, [2]Parma/IT, [3]Rome/IT

9.4.4 Combining Intra-articular Injection of PTHrP with Collagen-silk Scaffold Effectively Promotes Osteochondral Defect Repair
W. Zhang, J. Chen, J. Tao, C. Hu, L. Chen, J. Ji, H.W. Ouyang Hangzhou/CN

9.4.5 Decellularized cartilage scaffolds do not lock MSCs in a chondrogenic state
D. Gawlitta, K.E.M. Benders, J. Visser, A.S. Van Der Sar, D.H.R. Kempen, L.F.H. Theyse, W.J.A. Dhert, J. MaldaUtrecht/NL

9.4.6 Tailored hyaluronic acid-based hydrogels for cartilage regeneration
T. Böck, V. Schill, M. Krähnke, A. Steinert, J. Tessmar, T. Blunk, J. Groll Würzburg/DE

9.4.7 Sulfated, acrylated hyaluronan hydrogels for cartilage tissue engineering
E. Öztürk[1], J. Becher[2], M. Schnabelrauch[2], M. Zenobi-Wong[1] [1]Zurich/CH, [2]Jena/DE

9.4.8 Photochemical Crosslinking Stabilizes Protein Hydrogels for Articular Cartilage Regeneration
M. Randolph, M.A. Omobono, X. Zhao, S. Jang, R.W. Redmond, T.J. Gill Boston/US

9.4.9 Computational Design of Tissue Scaffolds for Cartilage Repair via the Level-Set Method
O.S. Aslan, G. Kiziltas-Sendur Istanbul/TR

Programme: Monday September 16, 2013

Session: 10.1 **Industry Sponsored Satellite Symposium**
13:00 - 14:00 **Room: Smyrna 1**

Sanofi Biosurgery - The MACI® Implant – Setting New Standards in Cartilage Repair
Moderator: D.B.F. Saris Utrecht/NL

10.1.1 Results of SUMMIT: MACI® Implant vs. Microfracture, A Prospective, Randomized Controlled Trial - Meeting the New Standards in Cartilage Repair
D.B.F. Saris Utrecht/NL

10.1.2 Long-Term Follow-Up and Health Economic Value Implications of the MACI Implant
G. Bentley Stanmore/UK

Session: 10.2 **Industry Sponsored Satellite Symposium**
13:00 - 14:00 **Room: Smyrna 2**

Anika Therapeutics - The Future of Chondral & Osteochondral Regeneration with the One-Step Procedure Approach"
Moderator: Mahmut Doral/TR

10.2.1 Background and advantages of HYAFF-11 (scaffold of hyaluronic acid), including cost-effectiveness comparisons between multiple chondral lesion treatment options
N. Heybeli Edirne/TR

10.2.2 Comparing clinical efficacy of 1-step regeneration versus 2-step
M. Spoliti Roma/IT

10.2.3 Arthroscopic cases using HyaloFast in combination with microfracture & other techniques
K. Slynarski Warszawa/PL

Session: 10.3 **Industry Sponsored Satellite Symposium**
13:00 - 14:00 **Room: Grand Efes II**

Synthes - Mitek Sports Medicine
10.3.1 Anatomical Approach in ACL Surgery
M. Bozkurt Gölbaci -Ankara/TR

10.3.2 RIGIDFIX® Curve – New Cross Pin Fixation Technique for an Anatomic ACL Reconstruction
A. Lelli Bologna/IT

Session: 10.4 **Industry Sponsored Satellite Symposium**
13:00 - 13:30 **Room: Didim**

Karl Storz - Update in Cartilage Repair
10.4.1 „One step bone & cartilage repair"
M. Steinwachs, Zurich/CH

Programme: Monday September 16, 2013

Session: 11.1 **Free Paper Session**

14:15 - 15:45 **Room: Grand Efes II**

Outcome, Sport & Rehabilitation

Moderators: Barbara Wondrasch/AT, Holly Silvers/US

11.1.1 Biomechanical Knee Cartilage Analysis in Young Professional Soccer Players by a T2 Mapping Unloading Algorithm

G.H. Welsch[1], L. Waldenmeier[1], C. Evers[1], S. Trattnig[2], A. Mauerer[1], R. Janka[1], M. Lochmann[1] [1]Erlangen/DE,[2]Wien/AT

11.1.2 Long-term results after microfracture treatment of full-thickness knee chondral lesions in athletes

A. Gobbi, G. Karnatzikos, S.R. Sukesh, D.G. Lad Milano/IT

11.1.3 ACT versus MSCs reconstruction technique in athletes knee and ankle coin cartilage defect

S. Zanasi, G. Maci, M. Pastina Bologna/IT

11.1.4 The Basic Science of Continuous Passive Motion in Promoting Knee Health: A Systematic Review

D.M. Knapik[1], J.D. Harris[2], G. Pangrazzi[1], M.J. Griesser[1], R. Siston[1], S. Agarwal[1], D. Flanigan[1] [1]Columbus/US,[2]Chicago/US

11.1.5 ACI for knee cartilage injuries: Moderate functional outcome and performance in patients with high-impact activities

A. Panagopoulos[1], L.V. Niekerk[2], I. Triantafillopoulos[3] [1]Patras/GR, [2]Northallerton/UK, [3]Athens/GR

11.1.6 Early resumption of impact sports leads to poorer clinical outcome after mb-ACI in the knee

M.F. Pietschmann, T. Niethammer, A. Horng, A. Ficklscherer, V. Jansson, P.E. Müller Munich/DE

11.1.7 Failures in Matrix-assisted ACI: analysis on 193 patients and systematic review

G. Filardo, E. Kon, L. Andriolo, F. Balboni, A. Roffi, M. Marcacci Bologna/IT

11.1.8 Comparison of Measures of Patellofemoral Alignment and Patient Reported Outcomes among ACI Patients with Gradual vs Sudden Symptom Onset

N.A. Kenney, J.S. Howard, B. Noehren, S. Duncan, C. Lattermann Lexington/US

11.1.9 Does sex matter in cartilage surgery? Analysis of clinical results after MACT in a large cohort of patients at 5 years follow-up

L. Andriolo, G. Filardo, E. Kon, F. Perdisa, B. Di Matteo, M. Marcacci Bologna/IT

Programme: Monday September 16, 2013

Session: 11.2 **Free Paper Session**
14:15 - 15:45 **Room: Smyrna 2**

Cartilage & Meniscus
Moderators: Jason Burdick/US, Tommy S. De Windt/NL

11.2.1 Treatment of post-meniscectomy syndrome with a free-floating meniscus implant: a prospective, open label, single-arm trial
P. Verdonk[1], A.A.M. Dhollander[2], R. Verdonk[3] [1]Antwerp/BE, [2]Gent/BE, [3]Ghent/BE

11.2.2 Clinical symptoms does not reflect early articular cartilage degeneration in short-term periods after subtotal/total meniscectomy
S.-I. Bin[1], S.-S. Seo[2], D. Sohn[1], B.-S. Lee[2] [1]Seoul/KR, [2]Busan/KR

11.2.3 Meniscus allograft transplantation: Survival analysis of 217 cases up to 24 years
P. Verdonk[1], S. Herregods[2], A. De Kock[2], R. Verdonk[2] [1]Antwerp/BE, [2]Gent/BE

11.2.4 Clinical results of polyurethane scaffold in lateral meniscus segmental defects
R. Verdonk[1], H. Bouyarmane[1], P. Beaufils[1], J. Bellemans[1], S. Roberts[1], T. Spalding[1], S. Zaffagnini[2], M. Marcacci[2], P. Verdonk[3] [1]Gent/BE, [2]Bologna/IT, [3]Antwerp/BE

11.2.5 Meniscal Allograft Transplantation Reoperation Rates, Operative findings, and Survival Curve
F.M. McCormick, J.D. Harris, R.M. Frank, K. Hussey, H. Wilson, A.K. Gupta, G.D. Abrams, B.R. Bach, Jr, B.J. ColeChicago/US

11.2.6 In vitro evaluation of streaming potentials with respect to micro and macroscopic cartilage scoring systems
R. Abedian Dehaghani, M. Ricklefs, M. Ettinger, A. Drazidis, C. Hurschler, C. Becher Hannover/DE

11.2.7 Vertical versus beveled walls in full-thickness articular cartilage defects - Should we be creating vertical walls?
J.D. Harris[1, 2], K. Hussey[1], H. Wilson[1], A. Espinoza-Orias[1], R. Stanley[1], R. Rames[1], B.J. Cole[1] [1]Chicago/US,[2]Houston/US

11.2.8 Lipid composition, ultrastructure and tribological behaviour of synovial fluid in healthy equine intercarpal joints
C.I. Matei, C. Boulocher, M. Schramme, M. Sava, T. Roger, J. Bodennec, Y. Berthier, M.-G. Blanchin, A.-M. SfarghiuLyon/FR

11.2.9 Evaluation of a Novel Technique to Map the Biomechanical Properties of Entire Articular Surfaces Using Indentation
S. Sim[1, 2], E. Quenneville[2], M. Garon[2], C.D. Hoemann[1], M.B. Hurtig[3], M. Buschmann[1] [1]Montreal/CA, [2]Laval/CA,[3]Guelph/CA

Programme: Monday September 16, 2013

Session: 11.3 **Free Paper Session**

14:15 - 15:45 **Room: Smyrna 1**

Chondrocyte Biology & Extracellular Matrix

Moderators: A. Robin Poole/CA, Ernst Hunziker/CH

11.3.1 Validation of the ICRS Osteochondral Histology Score (ICRS-OCHS)

A. Getgood[1], G. Bradica[2], E. Castiglione[2], D. Bryant[1], R. Kandel[3], S. Frenkel[4], L.A. Fortier[5] [1]London/CA, [2]Exton/US,[3]Toronto/CA, [4]New York/US, [5]Ithaca/US

11.3.2 Fibrillar collagens in engineered cartilage studied by second harmonic generation and focused ion beam/scanning electron microscopy.

M.Ø. Olderøy[1], M. Lilledahl[2], M. Sandvold[2], F.P. Reinholt[1], J.E. Melvik[3], P. Sikorski[2], J.E. Brinchmann[1] [1]Oslo/NO,[2]Trondheim/NO, [3]Sandvika/NO

11.3.3 Extracellular matrix domain formation as an indicator of chondrocyte dedifferentiation and hypertrophy

L. Wu, F.A. Petrigliano, D. McAllister, J.S. Adams, D. Evseenko Los Angeles/US

11.3.4 Topographical microstructures increase proliferation of human primary chondrocytes in vitro.

N. Joergensen, A.B. Nielsen, O.Z. Andersen, M. Foss, M. Lind, H. Lysdahl Aarhus C/DK

11.3.5 Expression of TGFβ receptors and collagen type II in bovine chondrocytes during prolonged monolayer culture

A. Tekari[1], R. Luginbuehl[2], S. Dolder[1], W. Hofstetter[1], R.J. Egli[1, 2] [1]Bern/CH, [2]Bettlach/CH

11.3.6 Improved biomechanical function of cartilage tissue engineering constructs by stimulation with BMP-4/-7 heterodimer

A. Krase[1], R. Abedian Dehaghani[2], C. Hurschler[2], W. Richter[1] [1]Heidelberg/DE, [2]Hannover/DE

11.3.7 Overexpression of hsa-miR-148a promotes type II collagen synthesis by osteoarthritic chondrocytes

L.A. Vonk, A.H.M. Kragten, W.J.A. Dhert, D.B.F. Saris, L.B. Creemers Utrecht/NL

11.3.8 A Novel Use For Acid Ceramidase In Cell-Based Therapies For Degenerative Joint Diseases

M. Frohberg, S. Sachot, Y. Ge, X. He, V.A. Deangelis, E.H. Schuchman, C.M. Simonaro Ny/US

11.3.9 Immature costal chondrocytes share mutipotent differentiation potential and immunosuppressive effect with mesenchymal stem cells

S. Zhang, D.C. Wraith, A.P. Hollander Bristol/UK

Programme: Monday September 16, 2013

Session: 11.4 **Free Paper Session**
14:15 - 15:45 **Room: Didim**

Growth Factors & Cytokines
Moderators: Charles Archer/UK, Laura Santambrogio/US

11.4.1 Effects of different Platelet Rich Plasma preparations on cultured human chondrocytes
C. Cavallo, G. Filardo, E. Mariani, A. Roffi, E. Kon, M. Marcacci, A. Facchini, B. Grigolo Bologna/IT

11.4.2 Comparison of growth factor release from Leukocyte/Platelet-Rich Fibrin (L-PRF), Leukocyte/Platelet-Rich Plasma (L-PRP) and blood clot
M. Schär, J. Diaz Romero, S. Kohl, M. Zumstein, D. Nesic Bern/CH

11.4.3 Anti-inflammatory Effect of Platelet Rich Plasma via S1P Receptor in Human Osteoarthritis Synovial cells and Chondrocytes
S. Lee, J.K. Lee, S.A. Han, S.C. Seong, M.C. Lee Seoul/KR

11.4.4 Negative Effect of Platelet Rich Plasma on the Differentiation of Synovium-derived Mesenchymal Stem Cells
J.K. Lee, S. Lee, S.C. Seong, M.C. Lee Seoul/KR

11.4.5 Synovial fluid: a promising cell source for immuno-modulation therapy in osteoarthritis.
N. Maillard, A. Cikankowitz, G. Grimandi, O. Gauthier, S. Brouard, J. Guicheux, N. Degauque, C. Vinatier Nantes/FR

11.4.6 Endoglin regulates TGF-beta signaling and collagen production in chondrocytes
A. Philip, Y. Chi, K. Finnson Montreal/CA

11.4.7 Microfracture and platelet rich plasma application in the focal osteochondral defect of the knee
N. Elmalı, M.E. Mirel, M. Karakaplan, N. ahin Malatya/TR

11.4.8 Autologous Platelet Enhanced Fibrin (APEF) Scaffold Supports In Situ Repair in an Equine Model
L. Goodrich[1], A. Chen[2], N. Werpy[1], J.D. Kisiday[1], P. Morley[1], W. McIlwraith[1], R.L. Sah[2], C. Chu[2] [1]Fort Collins/US,[2]California/US

11.4.9 The efficacy of intra-articular injection of autologous conditioned plasma after microfracture for the treatment of cartilage lesions.
P. Schaeferhoff, P. Klein, H. Dewitz Köln/DE

16:00 - 17:15 **General Assembly (For Members Only)** **Room: Smyrna 1**

16:00 - 18:00 **Poster Viewing Session (Wine & Cheese)** **Poster Area**

18:45 – 23:30 **President's Dinner at the World Famous Celsius Library in Ephesus**

18:30 **Meeting Point:** Registration Area **Swissôtel Convention Center**

18:45 **Bus Departure** (the bus ride to Ephesus takes approx. 70 minutes)
Dress Code: Smart Casual (Gentlemen: no tie - **Ladies:** as this is an ancient site, please do **not** use high heels...)

23.00 **Return** by Bus to Swissôtel
Fees: 140 Euros (incl. Transport, Entrance Fee, Dinner, entertainment)

Programme: Tuesday September 17, 2013

Session: 14.1 **Instructional Course (Pre-Registration required)**
07:30 - 08:15 **Room: Smyrna 2**

Management of Cartilage Injury in the Competitive Athlete
Moderators: Kai Mithoefer/US, Joris Bekkers/NL

14.1.1 Epidemiology of Cartilage Injury in Athletes
J.E.J. Bekkers Utrecht/NL

14.1.2 Treatment Options and Considerations in Competitive Athletes
K. Mithoefer Chestnut Hill/US

14.1.3 Optimising rehabilitation for the competitive athlete
L. Snyder - Mackler Newark/US

Session: 14.2 **Current Concept Lecture (Pre-Registration required)**
07:30 - 08:15 **Room: Grand Efes II**

Animal & Culture Models
Moderators: L.J. Sandell/US, Mauro Alini/CH

14.2.1 Culture Models under loading and non-loading conditions
M. Alini, S. Grad, M.J. Stoddart Davos/CH

14.2.2 Models in small animals for cartilage research
L.J. Sandell St. Louis/US

14.2.3 Cartilage defects in the stifle joints of sheep and goats – the “pro’s and con’s - and the do and don’ts”
B. Von Rechenberg Zürich/CH

Session: 14.3 **Current Concept Lecture (Pre-Registration required)**
07:30 - 08:15 **Room: Didim 1**

Chondroprotection
Moderators: Carmelita Frondoza/US, Jos Malda/NL

14.3.1 The Role of Biomarkers in Chondroprotection
Y. Henrotin Liège/BE

14.3.2 Animal & In Vitro Models for Chondroprotection Research
C. Frondoza Baltimore/US

14.3.3 Clinical Overview of Chondroprotection
H.S. Vasiliadis Ioannina/GR

Programme: Tuesday September 17, 2013

Session: 15.0 **Plenary Session**
08:30 - 09:30 **Room: Smyrna 1**

Stem Cells
Moderators: Ivan Martin/CH, Wiltrud Richter/DE

15.1 A critical appraisal of mesenchymal stroma cells regarding their nature, identity, and significance
M. Riminucci Roma/IT

15.2 Cartilage repair with autologous bone marrow mesenchymal stem cells
S. Wakitani Nishinomiya/JP

15.3 New Frontiers
R.S. Tuan Pittsburgh/US

Session: 16.1 **Special Session**
09:45 - 10:45 **Room: Smyrna 2**

Joint-Specific Cartilage Injury and Repair
Moderators: George Bentley/UK, Rodrigo Mardones/CL

16.1.1 The Shoulder
B.J. Cole Chicago/US

16.1.2 The Hip
M. Gerhardt Santa Monica/US

16.1.3 A minimum 10-year outcome study of Autologous Chondrocyte Implantation in the knee
T. Minas, A. Von Keudell, G. Arvind, A.H. Gomoll, T. Bryant Chestnut Hill/US

16.1.4 The Ankle
F. Vannini Bologna/IT

Session: 16.2 **Special Session**
09:45 - 10:45 **Room: Grand Efes II**

Systemic Effect of Cartilage Repair
Moderators: Gerjo Van Osch/NL, Martin Lotz/US

16.2.1 Systemic Effect of Cartilage Repair: Overview of Systemic Effects on Cartilage Repair – Basic Science in Crosstalk with Clinics
H. Schmal Freiburg/DE

16.2.2 Melanocortin and Destruction of Articular Cartilage
S. Grässel[1], J. Lorenz[1], G. Hackmayer[1], N. Schäfer[1], C. Baier[1], W. Richter[2], M. Böhm[3] [1]Regensburg/DE,[2]Heidelberg/DE, [3]Münster/DE

16.2.3 Cartilage Regeneration And Usefulness of Medication
K. Hoshi, T. Saito, T. Takato Tokyo/JP

Session: 16.3 **Special Session**
09:45 - 10:45 **Room: Smyrna 1**

Molecular Regulation of Cartilage Repair
Moderators: Attila Aszodi/DE, Francesco Dell'Accio/UK

16.3.1 The role of miRNA in chondrogenesis and osteoarthritis
W. Richter Heidelberg/DE

16.1.2 Oxidative Stress in Cartilage
L. Santambrogio New York/US

16.3.3 Growth Factors and PRP: Clinical Application
E. Kon, G. Filardo, A. Di Martino, B. Di Matteo, G. Tesei, M.L. Merli, M. Marcacci Bologna/IT

Programme: Tuesday September 17, 2013

10:45 - 11:15 **Coffee Break / Intermission / Exhibition / Poster Viewing**

Session: 17.1 **Free Paper Session**
11:15 - 12:45 **Room: Didim**

Imaging & Biomarkers
Moderators: Christian Lattermann/US, Goetz Welsch/DE

17.1.1 Correlation between the histological grading score and T2 mapping after implantation of tissue-engineered cartilage
N. Adachi, M. Ochi, G. Kamei, M. Deie, A. Nakamae Hiroshima/JP

17.1.2 Comparison of clinical, quantitative and qualitative MRI results 10 years after ACI-P in the knee joint
B. Erdle[1], S. Porichis[1], M. Uhl[1], M. Steinwachs[1, 2], C. Erggelet[1, 3], N.P. Südkamp[1], P. Niemeyer[1], G.M. Salzmann[11]Freiburg/DE, [2]Zürich/CH, [3]Zurich/CH

17.1.3 High-resolution diagnostics of cartilage thickness and lesions in clinical work.
J. Salo, A. Joukainen, J. Töyräs, H. Kokkonen, J.S. Jurvelin, H. Kröger Kuopio/FI

17.1.4 Is there a correlation between traumatic Bone Bruise in acute ACL lesions and cartilage defects during follow – up?
F. Figueroa, D. Figueroa, X. Ahumada, R. Calvo, A. Vaisman Santiago/CL

17.1.5 Edema in Matrix-assisted Autologous Chondrocyte Transplantation: MRI Evaluation at Different Follow-up Times.
G. Filardo, A. Di Martino, E. Kon, F. Perdisa, F. Tentoni, A. Roffi, M. Marcacci Bologna/IT

17.1.6 Comparison of MRI T1rho mapping and histology for normal and torn menisci in a pig model.
Y. Nakagawa, I. Sekiya, S. Kondo, T. Nagata, T. Tabuchi, M. Obara, T. Okuaki, H. Koga, K. Tsuji, T. MunetaTokyo/JP

17.1.7 Lumican is a potential biomarker for osteoarthritis
H. Quasnichka[1], P. Jones[2], A. Morgan[3], J. Tarlton[1], N. Avery[1], D. Kozaci[4], C. Hughes[3], C. Jackson[1], A.P. Hollander[1],S. Roberts[2], B. Caterson[3] [1]Bristol/UK, [2]Ag/UK, [3]Cardiff/UK, [4]Aydin/TR

17.1.8 Cartilage damage biomarkers are increased after a joint bleed; an explorative human and canine in vivo study
L.F.D. Van Vulpen, M.E.R. Van Meegeren, G. Roosendaal, S.C. Mastbergen, F.P.J.G. Lafeber Utrecht/NL

17.1.9 Synovial cytokine expression in ankle osteoarthritis depends on age and stage
H. Schmal, R. Henkelmann, G. Bode, N.P. Südkamp, G.M. Salzmann, P. Niemeyer Freiburg/DE

Programme: Tuesday September 17, 2013

Session: 17.2 **Free Paper Session**

11:15 - 12:45 **Room: Smyrna 1**

Marrow Stimulation & Ostechondral Allografts

Moderators: Peter Behrens/DE, Rocky Tuan/US

17.2.1 Smoking Inhibits Cartilage Repair after Microfracture but not BST-CarGel® Treatment in a Randomized Controlled Trial

M. Shive[1], W.D. Stanish[2], R. McCormack[3], F. Forriol Campos[4], N. Mohtadi[5], S. Pelet[6], J. Desnoyers[7], A. Restrepo[11]Laval/CA, [2]Halifax/CA, [3]Vancouver/CA, [4]Madrid/ES, [5]Calgary/CA, [6]Quebec City/CA, [7]Greenfield Park/CA

17.2.2 Clinical and MRI Outcomes Following Arthroscopic Microfracture of Osteochondral Lesions of the Distal Tibial Plafond

K.A. Ross, N.A. Smyth, C.P. Hannon, T. Deyer, J.G. Kennedy New York/US

17.2.3 Microfracture Clinical Outcomes Are Not Influenced by Lesion Size: A 2 to 8 Year Follow-up Study

W.G. Rodkey, K.K. Briggs, J..R. Steadman Vail/US

17.2.4 Dry arthroscopy for cartilage defect repair on the patella using AMIC procedure enhanced with BMCA - 2 years follow-up

B. Sadlik, A. Blasiak, T. Trzaska Bielsko-Biala/PL

17.2.5 Microfracture treatment elicits only limited intra-lesional bony overgrowth in a multicenter RCT

M. Shive[1], W.D. Stanish[2], R. McCormack[3], F. Forriol Campos[4], N. Mohtadi[5], S. Pelet[6], J. Desnoyers[7], J. Tamez-Pena[8], S.M. Totterman[9], E. Schreyer[9], A. Restrepo[1] [1]Laval/CA, [2]Halifax/CA, [3]Vancouver/CA, [4]Madrid/ES, [5]Calgary/CA, [6]Quebec City/CA, [7]Greenfield Park/CA, [8]Monterrey/MX, [9]Rochester/US

17.2.6 Surgeon Reliability in Calcified Cartilage Layer Removal: Open Versus Arthrosopic Technique

A. Yanke[1], J. Harris[1], A.S. Lee[1], V. Karas[1], M. Riccio[2], G. Abrams[1], B. Forsythe[1], S.J. Nho[1], N.N. Verma[1], C. Bush-Joseph[1], B.R. Bach, Jr[1], B.J. Cole[1] [1]Chicago/US, [2]New York/US

17.2.7 Implant-guided bone plate resorption and woven bone repair is coupled to hyaline cartilage regeneration from microdrill holes in aged knees

J. Guzman-Morales, C.-H. Lafantaisie-Favreau, G. Chen, C.D. Hoemann Montreal/CA

17.2.8 Osteoarthritis grade affects subchondral bone properties after microfracture

M. Hurtig[1], J. Steeds[1], K.D. Gordon[1], C.D. Hoemann[2], J. Theodoropoulos[3], P. Marks[3] [1]Guelph/CA, [2]Montreal/CA, [3]Toronto/CA

17.2.9 Single staged, arthroscopic treatment of chondral lesions with microfracture, bone marrow aspirate cells and fibrin gel: two year results.

A.A. Shetty[1], S.J. Kim[2], V.A. Shetty[1], P. Bilagi[3] [1]Chatham/UK, [2]Seoul/KR, [3]Gillingham/UK

Programme: Tuesday September 17, 2013

Session: 17.3 **Free Paper Session**

11:15 - 12:45 **Room: Grand Efes II**

Stem Cell Biology

Moderators: Solvig Diederichs/DE, Diego Correa/US

17.3.1 Identification of distinct signalling mechanisms for chondrogenesis in fetal compared with adult human bone marrow mesenchymal stem cells
K. Brady[1], S.C. Dickinson[1], P.V. Guillot[2], J. Polak[2], W. Kafienah[1], A.P. Hollander[1] [1]Bristol/UK, [2]London/UK

17.3.2 Human developmental chondrogenesis as a basis for the engineering of chondrocytes from pluripotent stem cells
L. Wu, F.A. Petrigliano, D. McAllister, J.S. Adams, K.M. Lyons, D. Evseenko Los Angeles/US

17.3.3 Chondrogenic cell population derived from human embryonic stem cells by density gradient separation
N. Joergensen, A. Gabrielsen, M. Lind, H. Lysdahl Aarhus C/DK

17.3.4 Maturation of chondrocytes derived from human induced pluripotent stem cells
A. Owaidah[1], I.M. Khan[2], S.C. Dickinson[1], L. Carpenter[3], S.M. Watt[3], N. Avery[1], A.P. Hollander[1], W. Kafienah[11]Bristol/UK, [2]Swansea/UK, [3]Oxford/UK

17.3.5 Directed induction of hyaline chondrogenic cells from dermal fibroblast culture by defined factors
N. Tsumaki[1], K. Hiramatsu[2], H. Outani[2], M. Okada[1], A. Yamashita[1], H. Yoshikawa[2] [1]Kyoto/JP, [2]Suita/JP

17.3.6 Wnt3a enhances proliferation and chondrogenic potential of adult mesenchymal stem cells
R. Narcisi[1], M. Cleary[1], P.A. Brama[2], M.J. Hoogduijn[1], D. Ten Berge[1], G.J.V.M. Van Osch[1] [1]Rotterdam/NL,[2]Dublin/IE

17.3.7 SOX8 - a new key player in chondrogenesis?
S. Herlofsen, T. Høiby, J.E. Brinchmann Oslo/NO

17.3.8 Safety of mesenchymal stem cell application for regenerative therapy: Functional role of c-Myc for expansion and cell differentiation
N. Werth[1], S. Boeuf[1], J. Brocher[1], E.-M. Maurer[1], M. Anton[2], W. Richter[1] [1]Heidelberg/DE, [2]Munich/DE

17.3.9 microRNA-140 regulates chondrogenic differentiation of human MSCs by post-transcriptional enhancement of chondrogenic molecules
R.B. Jakobsen[1], T.A. Karlsen[1], T.S. Mikkelsen[2], J.E. Brinchmann[1] [1]Oslo/NO, [2]Cambridge, Massachusetts/US

Programme: Tuesday September 17, 2013

Session: 17.4 **Free Paper Session**

11:15 - 12:45 **Room: Smyrna 2**

Osteoarthritis

Moderators: Bruce Caterson/UK, Linda Sandell/US

17.4.1 The biochemical interaction between subchondral bone and cartilage in OA
M. Pustjens[1], S.C. Mastbergen[1], W.H. Noort Van Der Laan[2], R.J. Van Heerwaarden[2], F.P.J.G. Lafeber[1] [1]Utrecht/NL,[2]Woerden/NL

17.4.2 The infrapatellar fat pad is an active joint adipose tissue with modulatory effects on articular cell functions.
D. Mainard, C. Guillaume, J.-B. Gross, P. Gegout-Pottie, N. Presle Vandoeuvre Les Nancy/FR

17.4.4 Regulation of Rac1 activity in chondrocytes ameliorates cartilage destruction of osteoarthritis in vivo
S. Zhu Hangzhou/CN

17.4.5 PPARgamma-deficient mice exhibit severe surgically-induced osteoarthritis associated with defective autophagy and mTOR signaling
F. Vasheghani Farahani, Y. Zhang, M. Blati, M. Kapoor Montreal/CA

17.4.6 Targeted delivery of anti-HIF-2α siRNA can prevent cartilage degeneration in arthritic mouse model
Y. Ao, Y. Pi Beijing/CN

17.4.7 Hydros-TA Joint Therapy for Osteoarthritis in the Knee: A Prospective, Multicenter, Randomized, Double-blind Study
R. Petrella, P. Emans, J. Alleyne, D. Gill, M. Maroney Maastricht/NL

17.4.8 Comparison between PRGF and Hyaluronic acid intra-articular knee injections for degenerative osteoarthritis
E. Iliopoulos, A. Panagiotou, E. Vlachou, C. Zidrou, M.I. Iosifidis, A. Kyriakidis Thessaloniki/GR

17.4.9 Clinical Outcomes Of Intra-Articular Injections Of Crespine®Gel In Patients With Hip Osteoarthritis: A Retrospective Clinical Study
G. Skog Gräddö/SE

Programme: Tuesday September 17, 2013

Session: 18.1 **Industry Sponsored Satellite Symposium**
13:00 - 14:00 **Room: Smyrna 1**

Arthrex - Promising Treatment Options For Different Types of Cartilage Lesions
Moderators: Bert Mandelbaum/US, Brian Cole/US

18.1.1 BioCartilage - the new treatment option for cartilage
B.J. Cole Chicago/US

18.1.2 BioMatrix CRD - The Product, Preclinical and Clinical Experiences
L. Bös Pforzheim/DE

18.1.3 PRP / ACP for Chondropenia and OA in the Athlete
B. Mandelbaum Santa Monica/US

Session: 18.2 **Industry Sponsored Satellite Symposium**
13:00 - 14:00 **Room: Smyrna 2**

Tigenix - Science & evidence in knee cartilage therapy "Mind the Gap": Quick Fix vs. Durable Repair
Moderator: Tim Spalding/UK

18.2.1 Debate & Presentation of Clinical Cases 1
P. Verdonk Gent-Zwijnaarde/BE

18.2.2 Debate & Presentation of Clinical Cases 2
P. Niemeyer Freiburg/DE

Session: 18.3 **Industry Sponsored Satellite Symposium**
13:00 - 13:30 **Room: Grand Efes 2**

Regentis - GelrinC – Novel solution for cartilage repair
Moderator: Alastair Clemow/IL

18.3.1 Introduction to GelrinC
A. Clemow Or Akiva/IL

18.3.2 GelrinC treatment for cartilage lesions - Clinical experience and outcome
R. Arbel Hod Hasharon/IL

18.3.3 GelrinC treatment for cartilage lesions - Radiological outcome
S. Trattnig Wien/AT

Session: 18.4 **Industry Sponsored Satellite Symposium**
13:00 - 13:30 **Room: Didim**

Episurf - Episealer® customized Femoral condyle resurfacing implant

18.4.1 Episealer® customized femoral condyle resurfacing implant
L. Ryd Malmö/SE

Programme: Tuesday September 17, 2013

Session: 19.0 **Plenary Session**
14:15 - 15:15 **Room: Smyrna 1**

The Cartilage Odyssey
Moderators: Daniël Saris/NL, Rocky Tuan/US

19.1 Landmarks of Cartilage Science Evolution
G.J.V.M. Van Osch Rotterdam/NL

19.2 Opportunities for Translational Cartilage Science
M.B. Hurtig Guelph/CA

19.3 Quo Vadis Cartilage Repair?
C. Erggelet Zurich/CH

Session: 20.1 **Special Session**
15:30 - 16:30 **Room: Smyrna 2**

Cartilage Imaging & Functional Testing
Moderators: Stefan Marlovits/AT, Giuseppe Filardo/IT

20.1.1 Imaging Options for Cartilage Injury, Repair & Subchondral Bone
G.H. Welsch[1, 2] [1]Erlangen/DE, [2]Vienna/AT

20.1.2 Functional Cartilage MRI: Current Status and Future Outlook
S. Trattnig Wien/AT

20.1.3 Recent Advances in Biomechanical and Electromechanical Assessments of Cartilage
M. Buschmann Montréal/CA

Session: 20.2 **Special Session**
15:30 - 16:30 **Room: Smyrna 1**

Mesenchymal Stem Cells
Moderators: Ichiro Sekiya/JP, Wiltrud Richter/DE

20.2.1 Better MSC by Reprogramming of iPS?
S. Diederichs[1], R.S. Tuan[2] [1]Heidelberg/DE, [2]Pittsburgh/US

20.2.2 Engineering of Cartilage from Stem Cells
D. Correa Cleveland/US

20.2.3 Intraarticular injection of mesenchymal stem cells for osteoarthritis therapy
U. Noeth Wuerzburg/DE

Session: 20.3 **Special Session**
15:30 - 16:30 **Room: Grand Efes II**

Biomarkers
Moderators: Philipp Niemeyer/DE, Susan Chubinskaya/US

20.3.1 Soluble Biomarkers to evaluate Chondroprotection: The Revolution is underway!
Y. Henrotin Liège/BE

20.3.2 The role of biomarkers in Human Clinical Trials
C. Lattermann Lexington/US

20.3.3 Early joint changes after injury: destruction or repair?
S. Lohmander Lund/SE

16:30 - 17:30 **Poster Viewing / Coffee Break / Industry Exhibition**

ICRS
International Cartilage Repair Society

Programme: Tuesday September 17, 2013

Session: 21.1 **Special Session**
17:30 - 18:30 **Room: Grand Efes II**

Meniscus Update
Moderators: Peter Cornelius Kreuz/DE, Roland Jakob/CH

21.1.1 Biomarkers in Meniscal Injury: Focus on Inflammation
C. Sanzello Chicago/US

21.1.2 Meniscus Repair & Transplantation: Results & New Frontiers
S. Rodeo New York/US

21.1.3 Meniscal Substitution: Inducations, Outcomes & Future Developments
P. Verdonk[1, 2] [1]Gent/BE, [2]Ghent/BE

Session: 21.2 **Special Session**
17:30 - 18:30 **Room: Smyrna 1**

New Horizons in Tissue Engineering
Moderators: Michael Buschmann/CA, Norimasa Nakamura/JP

21.2.1 Microtechnologies to Construct the Extracellular Microenviroment
A. Ranga Lausanne/CH

21.2.2 High Throughput Tools for Tissue Engineering
C.A. Van Blitterswijk, J. De Boer, P. Habibovic, R. Truckenmüller, L. Moroni Enschede/NL

21.2.3 Evolution and Implementation of Clinical Cartilage Tissue Engineering Strategies
N. Nakamura Osaka/JP

Session: 21.3 **Special Session**
17:30 - 18:30 **Room: Smyrna 2**

Culture Models
Moderators: Carmelita Frondoza/US, Susanne Grässel/DE

21.3.1 Stimulation of superficial zone protein: lessons from explant culture models
H. Reddi Sacramento/US

21.3.2 Co-culture of MSC and Chondrocytes: What Cells teach each other
M. Karperien Enschede/NL

21.3.3 A tissue therapy model using nasal chondrocytes and bioreactor
I. Martin Basel/CH

19:30 **ICRS 1001 Turkish Nights at Sultan's Place** (Saime Sultan Yalisi)

19:00 **Meeting Point:** Registration Area **Swissôtel Convention Center**

19:15 **Bus Departure** (the bus ride to Sultan's Place takes approx. 20 minutes)
Dress Code: Casual

23:30 **Return** by Bus to Swissôtel
Fees: Participants = € 75 Euros – Industry Representatives = € 95 Euros
(incl. Transport, Entrance Fee, Dinner, Entertainment)

Programme: Wednesday September 18, 2013

Session: 22.1 **Instructional Course (Pre-Registration required)**
07:30 - 08:15 **Room: Didim**

Regulatory Aspects of Cartilage Research
Moderators: Kenneth Zaslav/US, Matthew Shive/CA

22.1.1 Regulatory Developments in Cartilage Repair in the USA
K.R. Zaslav Richmond/US

22.1.2 Update on Cartilage Research Regulation in Europe
M. Brittberg Kungsbacka/SE

22.1.3 Key Points to consider when planning a Cartilage Repair Study
M.S. Shive Laval/CA

Session: 22.2 **Current Concept Lecture (Pre-Registration required)**
07:30 - 08:15 **Room: Grand Efes II**

Patient Selection for Cartilage Repair
Moderators: Joris Bekkers/NL, Riley Williams/US

22.2.1 How do Patient Criteria Affect Cartilage Repair
J.E.J. Bekkers Utrecht/NL

22.2.2 Achieving Clinical Success following Cartilage Repair: Considering the Patient and the Lesion
R.J. Williams New York/US

22.2.3 Patient Profiling & Treatment Algorithm for Cartilage Repair
D.B.F. Saris Utrecht/NL

Session: 22.3 **Current Concept Lecture (Pre-Registration required)**
07:30 - 08:15 **Room: Smyrna 2**

Cartilage Imaging
Moderators: Goetz Welsch/DE, Siegfried Trattnig/AT

22.3.1 Current Principles for Imaging of Cartilage Injury and Repair
S. Trattnig Wien/AT

22.3.2 Use of Quantitative MRI in Assessing Cartilage Lesions and Structural Changes in Osteoarthritis and Related Conditions
J.P. Pelletier, J. Martel-Pelletier Montreal/CA

22.3.3 Subchondral Bone Imaging
G.H. Welsch Erlangen/DE

Programme: Wednesday September 18, 2013

Session: 23.0 **Plenary Session**
08:30 - 09:00 **Room: Smyrna 1**

ICRS Vision and Development
Moderators: Anthony Hollander/UK, Christoph Erggelet/CH

23.1 ICRS Strategic Outline
C. Erggelet Zurich/CH

23.2 ICRS Meets the Middle East
M. Binnet Ankara/TR

Session: 23.1 **Plenary Session**
09:00 - 09:30 **Room: Smyrna 1**

YSOS & ICRS Fellowship Report
Moderators: Alan Getgood/CA, Simon Görtz/US

23.1.1 Sanofi Fellowship Report 2012
H.S. Vasiliadis Ioannina/GR

23.1.2 Sanofi Fellowship Report 2013
F.M. McCormick Chicago/US

23.1.3 Young Cartilage Investigator Report: YSOS
D. Stelzeneder Vienna/AT

09:30 - 10:15 **Coffee Break / Intermission / Exhibition / Poster Viewing**

Programme: Wednesday September 18, 2013

Session: 24.1 **Special Session**
10:15 - 11:15 **Room: Smyrna 2**

Lessons from Animal Models
Moderators: Caroline Hoemann/CA, Kerstin Kleinschmidt/DE

24.1.1 Small Animal Models
F. Dell'Accio London/UK

24.1.2 Large Animal Models
W. McIlwraith, D.D. Frisbie Fort Collins/US

24.1.3 Anti-Angiogenesis in Cartilage Repair Models
K. Gelse Erlangen/DE

Session: 24.2 **Special Session**
10:15 - 11:15 **Room: Grand Efes II**

Biomechanics-Joint Distraction Arthroplasty
Moderators: Tim Spalding/UK, Floris P.J.G. Lafeber/NL

24.2.1 Progress in Biomechanical Testing
R.L. Sah La Jolla/US

24.2.2 Current Concepts of Joint Biomechanics in Articular Cartilage Injury & Repair
A. Gobbi, G. Karnatzikos, D.G. Lad Milano/IT

24.2.3 Distraction Arthroplasty: Scientific Principles and Clinical Experience
P.M. Van Roermund Utrecht/NL

Session: 24.3 **Special Session**
10:15 - 11:15 **Room: Smyrna 1**

Chondropenia and Early Osteoarthritis
Moderators: Andreas Gomoll/US, Peter Cornelius Kreuz/DE

24.3.1 Epidemiology of Cartilage Injury & Early Osteoarthritis
A. Årøen[1], S. Løken[2], L.P. Granan[2], E.A. Sivertsen[1] [1]Lørenskog/NO, [2]Oslo/NO

24.3.2 Chondropenia: Concept and Quantification
B. Mandelbaum, S. Pro, T. McAdams Santa Monica/US

24.3.3 Treatment Options for Early Osteoarthritis
G. Bentley Stanmore/UK

Programme: Wednesday September 18, 2013

Session: 25.1 **Free Paper Session**

11:30 - 13:00 **Room: Smyrna 2**

Joint-specific Cartilage Repair, IVD

Moderators: Isik Akgun/TR, Martin Wiewiorski/CH

25.1.1 "One step" arthroscopic bone marrow derived cells transplantation: a novel solution for early degenerative ankle disease?
F. Vannini, R. Buda, M. Cavallo, A. Ruffilli, A. Parma, F. Castagnini, G. Pagliazzi, E. Sebastiani, S. Giannini Bologna/IT

25.1.2 3-year results after cartilage reconstruction with autologous matrix induced chondrogenesis (AMIC)
M. Walther, S. Altenberger, S. Kriegelstein, C. Volkering, F. Dreyer, A. Röser München/DE

25.1.3 Bipolar fresh total osteochondral allograft in the ankle trhough anterior approach: what's influencing the survivorship?
S. Giannini, R. Buda, G. Pagliazzi, A. Ruffilli, M. Cavallo, L. Ramponi, S. Maraldi, F. Vannini Bologna/IT

25.1.4 Comparison of Cartilage Repair Techniques in the Human Cadaveric Hip Joint: A Biomechanical study.
A.J. Cassar Gheiti, D.P. Byrne, K.J. Mulhall Dublin/IE

25.1.5 Microfracture or AMIC for arthroscopic repair of acetabular cartilage defects in femoroacetabular impingement.
D. Mancini[1], A. Fontana[2] [1]Napoli/IT, [2]Lanzo d'Intelvi (co)/IT

25.1.6 Fresh-stored osteochondral allografts for the treatment of femoral head defects: surgical technique and preliminary results
O. Safir[1], P. Kuzyk[1], Y. Kosashvilli[2], O. Ban Lulu[1], A. Gross[1] [1]Toronto/CA, [2]Petah Tiqwa/IL

25.1.7 Percutaneous treatment of lumbar discogenic back pain with allogeneic juvenile chondrocytes: 24-month follow-up of 15 patients
D. Coric[1], K.A. Pettine[2], A. Sumich[1], M.O. Boltes[1], H.D. Adkisson[3] [1]Charlotte/US, [2]Loveland/US, [3]St. Louis/US

25.1.8 Can quantitative T2 mapping predict lumbar intervertebral disc herniation? Which evaluation approach is best?
D. Stelzeneder[1], G.H. Welsch[1], S. Trattnig[1], S. Domayer[1], M. Brix[1], K. Pieber[1], R. Windhager[1], S. Trattnig[2][1]Vienna/AT, [2]Wien/AT

25.1.9 Mechanobiology of the nucleus pulposus: the effect of osmotic loading in nucleus pulposus cell sub-populations
T. Saggese, P. Redey, S. McGlashan Auckland/NZ

Programme: Wednesday September 18, 2013

Session: 25.2 **Free Paper Session**

11:30 - 13:00 **Room: Didim**

Miscellaneous Clinical Science: Allograft, Medication, Others

Moderators: William Bugbee/US, Alan Getgood/CA

25.2.1 The Effect of Platelet-rich Plasma on Autologous Osteochondral Transplantation: An in vivo Rabbit Model
N.A. Smyth, A.M. Haleem, C.D. Murawski, H.T. Do, J.T. Deland, J.G. Kennedy New York/US

25.2.2 Bone Cysts after Osteochondral Allograft Repair of Cartilage Defects in Adult Goats
A.L. Pallante-Kichura, E. Cory, W.D. Bugbee, R.L. Sah La Jolla/US

25.2.3 The Regenerative Potential of Multi-Layer Collagen-Based Scaffolds in a Caprine Osteochondral Defect Model
T.J. Levingstone[1], R.T. Brady[1], A. Ramesh[1], P.A. Brama[1], F.J. O'Brien[1], J.P. Gleeson[2] [1]Dublin/IE, [2]Cork/IE

25.2.4 Greater axial trough obliquity increases the risk of graft extrusion in lateral meniscus allograft transplantation
D.-H. Lee[1], S.-I. Bin[1], S.-S. Seo[2], J.-M. Kim[1], B.-S. Lee[3], D. Sohn[1] [1]Seoul/KR, [2]Busan/KR, [3]Incheon/KR

25.2.5 Cell-free biomimetic scaffold for osteochondral defects: a prospective clinical study at 72 months of follow-up.
E. Kon, G. Filardo, A. Di Martino, F. Perdisa, S. Patella, G. Venieri, M. Marcacci Bologna/IT

25.2.6 Fresh Osteochondral Allograft Transplantation for Osteochondritis Dissecans of the Knee
K. Sadr, P.A. Pulido, J.C. McCauley, W.D. Bugbee La Jolla/US

25.2.7 Clinical and MRI evaluation of medium- to long-term results after Autologous Osteochondral Transplantation (OCT) on the knee joint
L. Zak, I. Krusche-Mandl, S. Aldrian, S. Trattnig, S. Marlovits Wien/AT

25.2.8 Agili-C Implant Induced Articular Hyaline Cartilage Regeneration in a Caprine Osteochondral Defect Model
E. Kon[1], D. Robinson[2], A.S. Levy[3], K.R. Zaslav[4], G. Filardo[1], J. Shani[5], V. Condello[6], N. Altschuler[2] [1]Bologna/IT,[2]Kfar Saba/IL, [3]Millburn/US, [4]Richmond/US, [5]Beit Berl/IL, [6]Negrar Vr/IT

25.2.9 MRI and Clinical Evaluation of Patellofemoral Chondral Lesions Treated with Juvenile-Derived Allograft Cartilage (De Novo NT)
C. Pascual Garrido[1], R.J. Williams, Iii[2], S. Gold[2], H.G. Potter[2], R.F. Warren[2], S. Rodeo[2] [1]Denver/US, [2]New York/US

Programme: Wednesday September 18, 2013

Session: 25.3 **Free Paper Session**

11:30 - 13:00 **Room: Grand Efes II**

Cartilage Cell Transplantation (Basic Science)

Moderators: Dobrila Nesic/CH, Norimasa Nakamura/JP

25.3.1 Chondrogide® Results in a Better Quality of Repair Tissue than Periosteum during Autologous Chondrocyte Implantation

H. McCarthy, J.B. Richardson, S. Roberts Gobowen/UK

25.3.2 Elevated aggrecanase type 1 (ADAMTS-4) activity in synovial fluid may predict autologous chondrocyte implantation failure.

K. Wright[1], K. Firth[1], S. Wainwright[2], J.B. Richardson[1], S. Roberts[1] [1]Shropshire/UK, [2]Cardiff/UK

25.3.3 Influence of Interleukin-1β expression on cartilage regeneration after matrix-associated autologous chondrocyte transplantation

C. Albrecht, C.A. Reuter, D. Stelzeneder, L. Zak, B. Tichy, S. Marlovits, S. Trattnig, S. Aldrian Vienna/AT

25.3.4 Gene expression of transplanted chondrocytes from ACI may reveal new markers predicting the quality of the repair tissue

T. Paatela[1], J. Stenberg[2], A.I. Vasara[1], H. Nurmi[3], L. Peterson[2], I. Kiviranta[1], A. Lindahl[2] [1]Helsinki/FI, [2]Gothenburg/SE,[3]Jyväskylä/FI

25.3.5 Abnormalities in the superficial zone of repair cartilage using a tissue engineered construct (TEC) derived from mesenchymal stem cells

W. Ando[1], Y. Moriguchi[1], R. Nansai[2], R. Chijimatsu[1], K. Shimomura[1], H. Yoshikawa[1], H. Fujie[2], N. Nakamura[1,3] [1]Suita City/JP, [2]Tokyo/JP, [3]Osaka/JP

25.3.6 In vitro chondrogenesis by fusion of precultured scaffold-free cell aggregates

M. Lehmann[1,2], F. Martin[1,2], K. Mannigel[1], K. Kaltschmidt[1], U. Sack[2], U. Anderer[1] [1]Senftenberg/DE, [2]Leipzig/DE

25.3.7 One-stage cell-based cartilage regeneration using a combination of chondrons and mesenchymal stromal cells; comparison to microfracture

J.E.J. Bekkers, A.I. Tsuchida, M.H.P. Van Rijen, L. Vonk, W.J.A. Dhert, L.B. Creemers, D.B.F. Saris Utrecht/NL

25.3.8 The influence of joint damage to regenerative capacities of caprine articular chondrons

L.A. Vonk, A.H.M. Kragten, W.J.A. Dhert, S.C. Mastbergen, F.P.J.G. Lafeber, L.B. Creemers, D.B.F. Saris Utrecht/NL

25.3.9 Success of articular cartilage implants is dependent upon anatomic location and graft-based immune reaction

G.D. Duraine[1], B. Arzi[1], D.J. Huey[1], D.L. Borjesson[1], B. Murphy[1], C.A. Lee[2], J. Hu[1], K. Athanasiou[1], N. Baumgarth[1] [1]Davis/US, [2]Sacramento/US

Programme: Wednesday September 18, 2013

Session: 25.4 **Free Paper Session**
11:30 - 13:00 **Room: Smyrna 1**

Biomechanics & New Cartilage Technologies
Moderators: Kenneth Zaslav/US, Stefan Nehrer/AT

25.4.1 Use of Pulsed Electromagnetic Fields in Cartilage Lesions of the Knee: Results After 2-year follow-up in a Group of Active Patients
A. Gobbi, G. Karnatzikos, S.R. Sukesh, M. Petrera, D.G. Lad Milano/IT

25.4.2 Arthroscopic spraying of cartilage defects using chondron laden fibrin glue: a feasibility study in cartilage tissue engineering
T.S. De Windt[1], J.K. Buskermolen[1], L. Vonk[1], M. Karperien[2], W.J.A. Dhert[1], D.B.F. Saris[1,2] [1]Utrecht/NL, [2]Enschede/NL

25.4.3 Translamellar Dynamics of the Surface Active Phospholipid Layer: Proton Wave Propagation through Sphingomyelin Raft Channels
W.K. Augé Fall River/US

25.4.4 Methodological quality of knee articular cartilage studies
J.D. Harris[1,2], B.J. Erickson[1], G.D. Abrams[1], G.L. Cvetanovich[1], F.M. McCormick[1], A.K. Gupta[1], B.R. Bach, Jr[1], B.J. Cole[1] [1]Chicago/US, [2]Houston/US

25.4.5 Arthroscopic optical coherence tomography provides detailed information on articular cartilage lesions in horses
N. Te Moller[1], H. Brommer[1], J. Liukkonen[2], T. Viren[2], M. Timonen[2], P. Puhakka[2], J.S. Jurvelin[2], R. Van Weeren[1], J. Töyräs[2] [1]Utrecht/NL, [2]Kuopio/FI

25.4.6 Intra and inter-observer reliability of ten major histological scoring systems used for the evaluation of in vivo cartilage repair
D.E. Bonasia, A. Marmotti, A.D.F. Massa, A. Ferro, D. Blonna, F. Dettoni, M. Bruzzone, F. Castoldi, R. RossiTorino/IT

25.4.7 Can articular cartilage be saved after loss of subchondral bone
A.M. Shaheen Shebin Elkom/EG

25.4.8 The Role of Patient Metrics in a Novel Autologous Therapy Preparation
K. O'shaughnessey[1], A. Matuska[1], J. Hoeppner[1], J. Farr[2], M. Klaassen[3], C. Kaeding[4], C. Lattermann[5], W. King[1], J. Woodell-May[1] [1]Warsaw/US, [2]Greenwood/US, [3]Elkhart/US, [4]Columbus/US, [5]Lexington/US

25.4.9 Can we predict the health economic value of single-stage cartilage repair prior to implementation? An innovative financial approach.
J.C. Sorel[1], T.S. De Windt[1], M.J. Ijzerman[2], D.B.F. Saris[1,2] [1]Utrecht/NL, [2]Enschede/NL

13:00 **End of Meeting**

13:00 - 14:00 **ICRS General Board 2013 - 2015 Meeting** **Room: Petek Board Room (26)**
Moderators: Christoph Erggelet/CH, Anthony Hollander/UK

Poster Sessions (Electronic & Traditional)

Monday, Septemeber16, 2013 from 16.00 – 18.00
Tuesday, September 17, 2013 from 16.30 – 17.30

Poster presenters are required to stay near their poster boards during both poster sessions. Authors should encourage discussions with participants. The poster presenter should introduce themselves and be prepared to answer questions and initiate discussions. This year we will organize poster tours during the poster sessions.

A jury will select the best poster presenters, who will be awarded with a certificate.

Basic Science / Allografts

P1 Human meniscal fibrochondrocytes inhibit the proliferation of allogeneic lymphocytes exposed IL-2
S. Abe, H. Nochi, H. Ito Asahikawa/JP

P2 Viability and chondrogenic markers from cadaveric cartilage donor for clinical application in cartilage repair.
A. Olivos Meza[1], C. Ortega-Sanchez[2], A. Izaguirre[2], C. Velasquillo[2], J. Granados-Montiel[2], V. Martinez[1], C. Ibarra[21]Mexico City/MX, [2]Coatepec/MX

Basic Science / Animal Models

P0 Medial meniscal release, a new model of osteoarthritis in rabbits: a pilot study
C. Boulocher, C. Chenu, N. Saulnier, E. Pillet, E. Chereul, L. Magnier, T. Roger, S. Maddens, E. Viguier Marcy l'Etoile/FR

P3 Expression of PPARa, b, g, and H- and L-PGDS During Osteoarthritis in the Spontaneous Hartley Guinea Pig and the Experimental Dog Models
F.E. El Mansouri, F.E. El Mansouri, H. Afif, M. Kapoor, M. Benderdour, J.P. Pelletier, J. Martel-Pelletier, H. FahmiMontreal/CA

P4 The TNFα-induced apoptosis is inhibited by COX-2 selective blocker in isolated rabbit articular chondrocytes
K. Kumagai, S. Imai, M. Kubo, T. Maeda, F. Toyoda, H. Matsuura, Y. Matsusue Otsu/JP

P5 Evaluation of a rat arthritis model induced by various doses of monoiodoacetic acid
M. Udo, I. Sekiya, K. Tsuji, T. Muneta Tokyo/JP

Basic Science / Biomarkers

P6 Development of a S100 cell-based ELISA for screening of stimuli inducing redifferentiation of human articular chondrocytes
J. Diaz Romero, E. Schoenholzer, D. Nesic Bern/CH

P7 Cartilage biomarkers C2C and CTX-II do not respond to moderate intensity physical activity in healthy subjects
R. Gransier, P. Emans, T. Vanalphen, T.J.M. Welting, L. Van Rhijn, K. Meijer Maastricht/NL

P8 Chondrocytes in cultures for cell therapy- Validation of identity, purity and potency.
M. Hagman, C. Brantsing, J. Van Der Lee, C. Concaro, M. Leander, E. Skiöldebrand, A. Lindahl Gothenburg/SE

P9 Inhibition of Asporin Signaling is Critical in the Prevention of Cartilage Damage by Physiotherapies
D.M. Knapik, P. Perera, J. Nam, D. Flanigan, S. Agarwal Columbus/US

Poster Sessions (Electronic & Traditional)

Basic Science / Biomaterials and Scaffolds

P10 Chondrogenic differentiation of Mesenchymal Stem Cells in the sponges and hydrogels
Z. Ge[1], J. Zhang[1], J. Lin[1], Z. Yang[2] [1]Beijing/CN, [2]Singapore/SG

P11 Collagen-based microspheres for differentiation of mesenchymal stem cells: a potential strategy for cartilage engineering
M. Mathieu, E. Belamie, S. Benth, S. Vigier, C. Jorgensen, D. Noel Montpellier/FR

P12 Report on a custom-made implant for Focal Knee Resurfacing
N. Martinez-Carranza[1], A.-S. Lagerstedt[2], H. Nurmi-Sandh[2], H. Berg[1], P. Schupbach[3], L. Ryd[1] [1]Stockholm/SE,[2]Uppsala/SE, [3]Horgen/CH

P13 Cartilage regeneration in novel supramolecular hydrogels
L.M. Kock[1], M. Comellas-Aragonès[2], G. Pawar[2], S. Kheyrrooz[2], R. Sijbesma[2], W.J.A. Dhert[1], K. Ito[2], P.Y.W. Dankers[2], D. Gawlitta[1] [1]Utrecht/NL, [2]Eindhoven/NL

P15 A Porous Non-Degradable Implant for Osteochondral Defects: Evaluation in an in vivo Rabbit Model
A.J. Krych[1], F. Wanivenhaus[2], S.B. Doty[2], R.F. Warren[2], S. Maher[3] [1]Rochester/US, [2]New York/US, [3]New York City/US

P16 A modified pellet culture model for studying tissue-implant interactions: Application for cartilage repair biomaterials
S. Cohen, Y. Shachaf, O. Nadir, R. Wechsler Or Akiva/IL

P17 A new scaffold to cultivate human chondrocytes
E. Antonioli[1], A.O. Lobo[1], F.R. Marciano[2], M. Cohen[3], E.J. Corat[2], V.J. Trava-Airoldi[2], M. Ferretti[1] [1]Sao Paulo/BR,[2]Sao Jose Dos Campos/BR, [3]São Paulo/BR

P18 Reinforcement of gelatin methacrylamide hydrogel with a poly(-caprolactone) melt-electrospun fiber network for cartilage repair
J. Visser[1, 2], F.P.W. Melchels[1, 2], P. Dalton[2], W.J.A. Dhert[1], D.W. Hutmacher[2], J. Malda[1, 2] [1]Utrecht/NL, [2]Kelvin Grove/AU

P21 Evaluation of small molecule delivery from a hydrogel in a simulated knee joint environment
T.W. Spitters[1], M. Karperien[1], A. Petit[2], M. De Leeuw[2], D. Stamatialis[1] [1]Enschede/NL, [2]Groningen/NL

Basic Science / Biomechanics

P23 A Novel Syntetic Meniscus Implant: Similiarity in terms of Viscoelastic Behavior and response to long-term soaking
M. Shemesh[1], R. Asher[1], E. Zilberberg[1], F. Guilak[2], E. Linder-Ganz[1], J.J. Elsner[1] [1]Netanya/IL, [2]Durham/US

P24 Dynamic Stability of a Non-Fixed Meniscus Implant: In-vitro Study Using a Novel Robotic Knee System
J.J. Elsner[1], T.F. Bonner[2], A. Greene[1], J. Halloran[2], G. Agar[3], E. Hershman[4], R.W. Colbrunn[2], E. Linder-Ganz[11]Netanya/IL, [2]Cleveland/US, [3]Beer Yaakov/IL, [4]New York/US

P25 Plowing Forces – as Occuring in Articular Joints – Modulate Lubricin Biosynthesis on Cartilage Surfaces
O.R. Schätti, L.M. Gallo Zurich/CH

P26 Correlation of Non-destructive Electromechanical Probe (Arthro-BST) Assessment with Histological Scores and Mechanical Properties in Human Knee Joints
S. Sim[1, 2], A. Chevrier[1], E. Quenneville[2], M. Garon[2], M. Buschmann[1] [1]Montreal/CA, [2]Laval/CA

P27 Novel unconfined compression test using Jamshidi osteochondral biopsies couples biomechanical properties with histological structure
A. Bell[1], G. Chen[2], E. Quenneville[3], M.B. Hurtig[1], C.D. Hoemann[2] [1]Guelph/CA, [2]Montreal/CA, [3]Laval/CA

Poster Sessions (Electronic & Traditional)

Basic Science / Cartilage /Cell Transplantation

P28 Cross-linked hyaluronic acid as a scaffold for the treatment of cartilage defects
C. Bauer[1], R.R. Baumgartner[2], M. Hornof[2], F. Halbwirth[1], E. Niculescu-Morzsa[1], H. Zwickl[1], S. Nehrer[3] [1]Krems/AT,[2]Leobendorf/AT, [3]

P29 The Use of Human Amniotic Membrane for Cartilage Repair: A Sheep Study
S.K. Tabet[1], D.M. Conner[1], D. Thal[2] [1]Albuquerque/US, [2]Santa Fe/US

P30 Title: Evaluation of repair cartilage by bone marrow-derived mesenchymal stem cells for osteochondral defect in a non-human primate.
S. Araki, S. Imai, M. Kubo, T. Mimura, K. Nishizawa, H. Ueba, K. Kumagai, Y. Matsusue Otsu/JP

P31 Tracking Chondrocytes within the Extracellular Matrix with Fluorescent Probes
A.J. McNally, K. Sly, C. Chapman, S. Lin Gainesville/US

P32 Cell viability in matrix-assisted autologous chondrocyte implantation
L.C. Biant, P. Hindle, A.C. Hall Edinburgh/UK

P33 Ropivacaine and Fentanyl for post-operative intra-articular analgesia: cytotoxic on human fibroblasts and mesenchymal stem cells?
A. Ficklscherer, M.F. Pietschmann, V. Jansson, P.E. Müller Munich/DE

P34 Characterisation of repair cells isolated from the site of autologous chondrocyte implantation (ACI): a novel report of two clinical cases.
K. Wright[1], C. Mennan[1], H. Fox[2], J.B. Richardson[1], R. Banerjee[1], S. Roberts[1] [1]Oswestry/UK, [2]Cambridge/UK

P35 Long-term results of cartilage repair after allogeneic transplantation of cartilaginous aggregates for osteochondral defects in rabbits
T. Yoshioka[1], H. Mishima[1], S. Sakai[2], T. Uemura[1] [1]Tsukuba/JP, [2]Inashiki/JP

P36 Additional surgical procedure rate after use of a bilayer collagen membrane in autologous chondrocyte implantation.
S.K. Tabet, L.M. James Albuquerque/US

P37 The effect of low intensity pulsed ultrasound for scaffold-free cartilage: The trial of implantation for partial-thickness defect
K. Uenaka, K. Oda, K. Mori, M. Kubo, S. Imai, Y. Matsusue Otsu/JP

P38 Infant hip chondrocytes for tissue engineering of scaffold-assisted cartilage grafts
P.C. Kreuz[1], M. Endres[2], C. Gentili[3], J.P. Krueger[2], R. Cancedda[3], C. Kaps[2] [1]Rostock/DE, [2]Berlin/DE, [3]Genova/IT

P39 Ex vivo Comparison of a Novel Tapered Osteochondral Allograft Transplantation System with Standard Cylindrical Insertion Techniques
S.L. Sherman[1], F. Pfeiffer[2], A. Stoker[1], J.L. Stannard[1], J.L. Cook[1] [1]Columbia/US, [2]Boonville/US

P40 Not all the loose body fragments are a good source for cell culture
P. Guillen-Garcia[1], E. Rodriguez-Iñigo[1], I. Guillen-Vicente[1], R. Caballero-Santos[1], M. Guillen-Vicente[1], M. Casqueiro-Abad[1], T. Fernandez-Jaen[1], S.P. Abelow[2], D. Val[1], J.M. Lopez-Alcorocho[1] [1]Madrid/ES, [2]SouthLake Tahoe, California/US

Poster Sessions (Electronic & Traditional)

Basic Science / Cartilage and Meniscus

P42 Nanosecond Pulsed Electric Fields (nsPEFs) Enhance Proliferation of Chondrocytes through Wnt Signaling Pathway
Z. Ge, K. Zhang, J. Lin Beijing/CN

P43 A novel organ-slice-culture model for meniscal repair
N. Shintani, F. Bourquin, K.A. Siebenrock, E.B. Hunziker Bern/CH

P44 Atomic force microscopy allows to quantify spatially elastic responses of engineered cartilage tissues to IL-1 exposure
L. Penuela[1], F. Wolf[2], D. Wendt[2], I. Martin[2], R. Raiteri[1], A. Barbero[2] [1]Genova/IT, [2]Basel/CH

P45 Meniscal Glycosaminoglycan Coverage Twelve Weeks Post Injury in a Traumatic Loading Model of the Knee Joint
K. Fischenich[1], G.A. Coatney[1], J. Haverkamp[1], K.D. Button[2], C. Decamp[2], R.C. Haut[2], T.L. Haut Donahue[1] [1]Fort Collins/US, [2]East Lansing/US

P46 New Therapeutic Approach for Meniscus Repair Combination with Infrapatellar Fat Pad and Type I Collagen Scaffold
S. Oda, S. Otsuki, Y. Hoshiyama, Y. Kurokawa, M. Nakajima, M. Neo Takatsuki-city/JP

P47 Toward scaffold-based meniscus repair: effect of human serum, hyaluronic acid, TGF-ß3 and PRP on cell recruitment and re-differentiation
U. Freymann, S. Metzlaff, M. Endres, M. Sittinger, C. Kaps, W. Petersen Berlin/DE

P52 In Vivo Toxicity of Local Anesthetics and Corticosteroids on Cartilage and Synovium
S.L. Sherman, C. Linville, A. Stoker, D. Flood, J.L. Cook Columbia/US

P53 Meniscal Regeneration Using a Bovine Dermal Collagen Matrix
M. Randolph, S. Hammoud, K. Cornwell, T.J. Gill Boston/US

P54 Intraarticular Contact Pressures after Anterior Horn Lateral Meniscus Tear, Repair and Meniscectomy
H. Goitz, A. Esquivel, M. Prince, A. Andre Detroit/US

P55 Definitive Molecular Signatures Identified in Human Injured Meniscus are Segregated Largely with Age and Not with Cartilage Damage
M.F. Rai, D. Patra, L.J. Sandell, R.H. Brophy St. Louis/US

Basic Science / Cartilage Imaging and Functional Testing

P57 Reliability of in-vitro evaluation of compression-induced cartilage streaming potentials
C. Becher, M. Ricklefs, M. Ettinger, A. Drazidis, C. Hurschler, R. Abedian Dehaghani Hannover/DE

P58 T2 – What Does it Mean in Cartilage Repair and How Best to Use it in a Multi-Center Clinical Trial
J. Riek, V. Shah, E. Ashton, M.W. Tengowski Rochester/US

Basic Science / Culture Models

P60 The bio-mechano-reactor: design and development of a new tool for Osteoarthritis research.
T. Struik, S.C. Mastbergen, H. Weinans, F.P.J.G. Lafeber Utrecht/NL

Poster Sessions (Electronic & Traditional)

Basic Science / Extracellular Matrix

P61 Characterization of cell metabolic changes in osteoarthritic labrum cells
A. Dhollander[1], N. Juchtmans[1], S. Lambrecht[1], D. Elewaut[1], P. Verdonk[2], J. Victor[1] [1]Gent/BE, [2]Gent-Zwijnaarde/BE

P62 Effect of hyaluronic acid and chondroitin sulfate in extracellular matrix of chondrocytes
C.-H. Hsieh, J.-J. Tsai-Wu, H. Chiang, S. Chen, C.-C. Jiang Taipei/TW

P63 Differential Effects of Cyclooxygenase-1 and -2 specific NSAIDs on Chondrogenic Differentiation
M.M.J. Caron, P. Emans, D.A.M. Surtel, A. Cremers, D. Ophelders, K. Sanen, L.W. Van Rhijn, T.J.M. WeltingMaastricht/NL

Basic Science / Growth factors, PRP and Cytokines

P64 Synergıstıc Effect Of Tgf- 1 And Bmp–7 On Chondrogenesıs And Extracellular Matrıx Synthesıs
A. Gokce, I. Yilmaz, R. Bircan, N.S. Gokay Tekirdag/TR

P65 Toward the identification of bone formation factors in BMA and peripheral blood for spinal fusion by flow cytometry and TOF mass spectrometry
S.-S. Lin[1], C.-C. Niu[2], L.-J. Yuan[2], C.-Y. Yang[2], W.-J. Chen[2] [1]Kweishan/TW, [2]Taoyuan/TW

P66 Soluble mediators in health, cartilage defects and osteoarthritis; Differential expression in synovial fluid, tissue and cell culture.
A.I. Tsuchida[1], M. Beekhuizen[1], M.M.C. 't Hart[1], G.J.V.M. Van Osch[2], T.R. Radstake[1], W.J.A. Dhert[1], D.B.F. Saris[1,3], L.B. Creemers[1] [1]Utrecht/NL, [2]Rotterdam/NL, [3]Enschede/NL

P67 Leukocyte-depletion in PRP decreases the proliferative effects of human chondrocytes
M.L. Olesen[1], M. Lind[1,2], H. Lysdahl[1], C.B. Foldager[1,3] [1]Aarhus C/DK, [2]Aarhus/DK, [3]Boston/US

P68 Intra-articular Injection of rhFGF18 (Sprifermin) Improves Microfracture Treated Chondral Defects in Sheep
A. Getgood[1], J. Power[2], R. Brooks[2], H. Guehring[3], N. Rushton[2], F.M. Henson[2] [1]London/CA, [2]Cambridge/UK,[3]Darmstadt/DE

P69 The role of bFGF in tissue engineered cartilage
M. Wilke, D. Wittek, V. Methner, J.J. Smink Teltow/DE

P70 The Effect of Platelet Rich Plasma on Articular Cartilage during the Development of Osteoarthritis in an ACL Transection Rabbit Model
M.C. Lee, J.K. Lee, S. Lee, S.C. Seong Seoul/KR

P71 The Effect of Platelet Rich Plasma on the Chondrocyte Apoptosis after Mechanical Injury
J.K. Lee, S. Lee, S.C. Seong, M.C. Lee Seoul/KR

P72 Preparation of Platelet-rich plasma (PRP) changes the composition of white blood cells in platelet-rich plasma
M.L. Olesen, M. Lind, H. Lysdahl, C.B. Foldager Århus C/DK

P73 Platelet lysate (PL) maintains human articular chondrocytes phenotype and regulates inflammation process
R. Pereira[1,2], M. Scaranari[2], R. Benelli[2], P. Strada[2], R. Reis[1], R. Cancedda[2], C. Gentili[2] [1]Caldas Das Taipas – Guimarães/PT, [2]Genova/IT

P74 Platelet-rich Plasma composition affects sinoviocytes behavior: an in vitro comparative study
E. Assirelli, L. Pulsatelli, V. Canella, E. Mariani, G. Filardo, E. Kon, M. Marcacci, A. Facchini Bologna/IT

P75 Fibroblast synovial stem cells and platelet lysate: the potential modulation of phenotype for engineering cartilage
R. Pereira[1,2], D. Martinelli[1], M. Scaranari[1], R. Benelli[1], R. Ruggeri[1], R. Cancedda[1], C. Gentili[1] [1]Genova/IT, [2]Caldas Das Taipas – Guimarães/PT

Poster Sessions (Electronic & Traditional)

Basic Science / Histology

P77 Woven bone-lining cells and proliferating chondrocyte progenitors induced by bone marrow stimulation express alpha smooth muscle actin
C. Mathieu[1], G. Chen[1], H. El Gabalawy[2], A. Calderone[1], C.D. Hoemann[1] [1]Montreal/CA, [2]Manitoba/CA

P78 Morphology of sheep articular and nasal septum cartilage harvested for tissue engineering in bioreactor
A. Vukasovic, P. Kostesic, V. Gusak, D. Maticic, D. Jezek, D. Hudetz, M. Pecina, A. Ivkovic Zagreb/HR

Basic Science / Intervertebral Disc

P79 Early intervertebral disc degeneration involves a decrease in caveolin-1: ready to translate?
L. Smolders, B. Meij, D. Onis, F. Riemers, N. Bergknut, G. Grinwis, R. Wubbolts, M. Groot-Koerkamp, D. Van Leenen, F. Holstege, H.A.W. Hazewinkel, L.B. Creemers, L. Penning, M.A. Tryfonidou Utrecht/NL

P80 Effects of Hyperbaric Oxygen on MAPK Signaling and Mitochondrial Apoptotic Pathway in Degenerated Human Intervertebral Disc Cells
C.-C. Niu[1], S.-S. Lin[2], L.-J. Yuan[1], W.-J. Chen[3], C.-Y. Yang[3] [1]Kweishan, Taoyuan/TW, [2]Kweishan/TW,[3]Taoyuan/TW

P81 Assessing the potential of autologous cells for intervertebral disc tissue engineering.
S. Turner, K. Wright, P. Jones, J. Trivedi, S. Roberts Oswestry/UK

P82 Intervertebral disc regeneration in - vivo using Mesenchymal Stem cells combined with the chondrogenic agent, Pentosan polysulfate
P. Ghosh, D. Oehme, S. Shimmon, J. Wu, I.P. Ghosh, T. Goldschlager, G. Jenkin Brookvale, Nsw/AU

P83 First Steps towards biological annulus fibrosus repair
M. Endres, U. Freymann, M. Cabraja, C. Woiciechowsky, C. Kaps Berlin/DE

P84 A new strategy for regeneration of nucleus pulposus tissue
M. Endres, J.P. Krueger, C. Woichiechowsky, C. Kaps Berlin/DE

P85 A novel nucleotomy model with intact anulus fibrosus to test intervertebral disc regeneration strategies
G. Vadalà[1], F. Russo[1], G. Pattappa[2], M. Peroglio[2], S. Grad[2], V. Stadelmann[2], M. Alini[2], V. Denaro[1] [1]Rome/IT,[2]Davos/CH

P86 The role of Diabetes type I in Intervertebral Disc Degeneration
F. Russo[1], V. Denaro[1], G. Vadalà[1], K. Ngo[2], Q. Dong[2], Y. Fan[2], M. Trucco[2], G. Sowa[2], J. Kang[2], N. Vo[2] [1]Rome/IT,[2]Pittsburgh/US

Basic Science / Microfracture/Bone Marrow Stimulation

P87 Bone Marrow Access in Cartilage Repair: Comparison of Microfracture, Nanofracture, K-wire, and Drill in the Adult Ovine Model
P. Behrens[1], D. Schaffner[2], N. Bertollo[2], R. Oliver[2], C. Christou[2], W.R. Walsh[2] [1], [2]Sydney/AU

Poster Sessions (Electronic & Traditional)

Basic Science / New Cartilage Technology

P88 In Vitro Evaluation of Minced Adult and Juvenile Articular Cartilage: A Time Course Analysis
S. Chubinskaya, K. Wepking, A.A. Hakimiyan, A. Margulis, L. Rappoport, B.J. Cole Chicago/US

P89 DNA demethylation is involved in regulating chondrocyte specific and pluripotency genes in c-iPSCs during TGF signaling
C. Brantsing, L. Enochson, C. Boreström, N. Bigdeli, A. Forsman, A. Lindahl, S. Simonsson Gothenburg/SE

P90 Cartilage fragments in a composite scaffold for one-step cartilage repair: hypoxia as a model of joint microenvironment. An in vitro-study
A. Marmotti[1], S. Mattia[1], D.E. Bonasia[1], M. Bruzzone[1], S. Terrando[1], C. Tarella[1], E. Ponzo[1], F. Castoldi[1], G.M. Peretti[2] [1]Torino/IT, [2]Milan/IT

Basic Science / Osteoarthritis

P91 Differences of Danger signal receptors in large and small Osteoarthritic joints
G. Barreto[1], E. Waris[1], E. Kaivosoja[1], A. Soininen[2], T. Sillat[2], P. Ylinen[2], Y. Konttinen[1] [1]Hus/FI, [2]Helsinki/FI

P92 Role of ultra-high-molecular-weight hyaluronic acid as a chondroprotective agent in a rabbit knee osteoarthritis model
S. Elmorsy, T. Funakoshi, F. Sasazawa, M. Todoh, S. Tadano, N. Iwasaki Sapporo/JP

P93 Therapeutic Effects of Intra-articular Ultra-purified Low Endotoxin Alginate Administration on A Dog Osteoarthritis Model.
Y. Tsukuda[1], M. Ito[2], Y. Izumisawa[2], T. Onodera[1], Y. Kasahara[1], T. Igarashi[1], N. Ohazawa[3], N. Iwasaki[11]Sapporo/JP, [2]Ebetsu/JP, [3]Tokyo/JP

P94 H3K9 demethylation by LSD1 contributes to IL-1-induced mPGES-1 expression in OA chondrocytes
F.E. El Mansouri, H. Fahmi Montreal/CA

P95 Effects of hyperbaric oxygen on nitric oxide-induced apoptosis via enhancement of the expression of Hsp 70
L.-J. Yuan[1], S.-S. Lin[2], S.W.N. Ueng[3], C.-C. Niu[1], Y.-S. Chan[1], C.-Y. Yang[1], W.-J. Chen[1] [1]Taoyuan/TW,[2]Kweishan/TW, [3]Kweishan, Taoyuan/TW

P96 Silencing of microRNA-101 prevents extracellular matrix degradation in chondrocytes and cartilage degradation in MIA rats
L. Dai, Y. Ao Beijing/CN

P97 Expression and function of Leukotriene B4 receptors in human articular chondrocytes
A.K. Hansen, I. Martinez, B. Sveinbjörnsson Tromsø/NO

P98 Low levels of Vitamin D effect on Cartilage and subchondral bone in a Rat Model
C. Pascual Garrido[1], M.E. Angeline[2], R. Ma[2], R.F. Warren[2], S. Rodeo[2] [1]Denver/US, [2]New York/US

P99 Aberrant expression of autophagy markers during osteoarthritis
Y. Zhang, F. Vasheghani Farahani, M. Blati, M. Kapoor Montreal/CA

P100 Inducible Cartilage-specific mTOR knockout mice are resistant to cartilage degradation in mice model of OA
Y. Zhang, M. Blati, M. Kapoor Montreal/CA

P101 Intra-articular Injection of Heparan Sulfate Endosulfatases (Sulf) Suppresses Cartilage Degeneration
Y. Kurokawa, S. Otsuki, Y. Hoshiyama, S. Oda, M. Neo Takatsuki City/JP

Poster Sessions (Electronic & Traditional)

P102 Anti-inflammatory effects of hydrophilic and lipophilic statins with hyaluronic acid in articular chondrocytes
C.-H. Chang[1,2], Y.M. Hsu[1,2], F.-H. Lin[3] [1]Taoyuan/TW, [2]New Taipei City/TW, [3]Taipei/TW

P103 Lithium reduces severity of experimental osteoarthritis through autophagy
Y. Wu, S. Zhu, H.W. Ouyang Hangzhou/CN

P104 Development and re-translational validation of an in vitro model for acute infections in human joints
H. Schmal, I.H. Pilz, G.M. Salzmann, N.P. Südkamp, P. Niemeyer Freiburg/DE

P105 Inhibition of Rac1 activity in chondrocytes effectively ameliorates cartilage destruction of osteoarthritis in vivo
S. Zhu, Y. Wu, H. Liu, P. Chen, Y. Zhou, H.W. Ouyang Hangzhou/CN

P106 Resveratrol decreases cartilage formation by osteoarthritic chondrocytes
L.A. Vonk, A.H.M. Kragten, W.J.A. Dhert, D.B.F. Saris, L.B. Creemers Utrecht/NL

P107 Agrin: a new endogenous chondrogenic molecule for tissue engineering
S. Eldridge, K. Vincente-Greco, G. Nalesso, C. Pitzalis, M. Perretti, P. Kabouridis, F. Dell'Accio London/UK

P108 Location dependent progression of traumatic and post-traumatic lesions of the knee cartilage in a rat model of osteoarthritis
D.M. Knapik, R.K. Harrison, R. Siston, S. Agarwal, D. Flanigan Columbus/US

P109 Clinical benefits in compensation of synovial fluid viscosity in gonarthrosis treatment by injectable polyacrilamide viscoprosthesis
M. Ayas[1], V. Zar[2], V. Voloshin[2], A. Martynov[2] [1]Izmir/TR, [2]Moscow/RU

P110 platelet derived growth factor (PDGF) can promote matrix synthesis by chondrocytes in high density culture
A. Montaseri[1], L. Roshangar[1], J. Soleimani Rad[1], M. Shakibaei[2], H. Jarolmasjed[1], A.M. Navali[1] [1]Tabriz/IR, [2]Munich/DE

P111 Identification of Novel AGE Receptors in Osteoarthritic Cartilage
S. McGlashan, L. Yu, B. Uy, S. Shaikh Auckland/NZ

Basic Science / Osteochondral Grafts

P112 Feasibility of an Osteochondral Allograft for Biologic Glenoid Resurfacing
G.L. Cvetanovich, P.N. Chalmers, A.B. Yanke, A.K. Gupta, E. Klosterman, N.N. Verma, A.A. Romeo Chicago/US

P113 Protocols for human osteochondral fragments preservation
E. Sousa, F. Marques, D.P. Aguiar, M.E. Duarte, B. Olej Rio De Janeiro/BR

P114 Osteochondral Allograft for the treatment of great condylar lesion of the knee
D. Codina Grañó, A. Dalmau Coll, J. Barrachina, S. Sánchez Navarro, A. Seculi Palacios Sant Cugat Del Vallès/ES

Basic Science / Others

P115 The IL4-10 synerkine is equally effective in protecting cartilage from blood-induced damage compared to the individual components
L.F.D. Van Vulpen, M.E.R. Van Meegeren, S.A.Y. Hartgring, C. Steen-Louws, C.E. Hack, J.A.G. Van Roon, S.C. Mastbergen, F.P.J.G. Lafeber Utrecht/NL

P116 Effect of preservation conditions of human synovial MSC derived tissue engineer construct (TEC) on its chondrogenic differentiation.
M. Sakaue, Y. Moriguchi, N. Sugita, H. Hasegawa, R. Chidimatsu, K. Koizumi, Y. Yasui, H. Yoshikawa, N. Nakamura Osaka/JP

Poster Sessions (Electronic & Traditional)

Basic Science / Stem cells

P117 Comparative characterization of bone marrow, subcutaneous adipose tissue, synovium, and infrapatellar fat pad derived MSCs
M.Y. Cho, Y.J. Choi, J.E. Yeo, Y.H. Jung, S.B. Jo, O.R. Kwon, D.-S. Suh, Y.G. Koh Seoul/KR

P118 Is Chondrogenic differentiation of bone marrow mesenchymal stem cells influenced by donor age? Importance for cartilage engineering
J.-F. Stoltz[1], N. De Isla[2], Y. Li[2], N. Charif[2], V. Decot[1], D. Mainard[3] [1]Vandoeuvre Les Nancy/FR, [2]Vandoeuvre-les-Nancy/FR, [3]Nancy/FR

P119 Mesenchymal stem cells modulate synthesis of inflammatory cytokines by chondrocytes from osteoarthritis patients
E. Antonioli[1], L. Sardinha[2], C. Janovsky[1], M. Cohen[2], A.C. Goldberg[1], M. Ferretti[1] [1]Sao Paulo/BR, [2]São Paulo/BR

P120 In vitro Co-culture of Adipose Synovium- and Fibrous Synovium- derived Stem Cells Enhances Proliferation
M.Y. Cho, J.E. Yeo, Y.H. Jung, Y.J. Choi, S.-B. Jo, O.R. Kwon, D.-S. Suh, Y.G. Koh Seoul/KR

P121 Survival rate of adipose mesenchymal stem cells is related to route of administration and antigen compatibility in arthritic mouse models
K. Toupet[1], M. Maumus[1], J.A. Peyrafitte[2], P. Bourin[2], C. Jorgensen[1], D. Noel[1] [1]Montpellier/FR, [2]Toulouse/FR

P122 Integrating Non-viral Sleeping Beauty Vector Delivery of Sox Transcription Factors Enhances MSC Chondrogenesis
A.J. Nixon, L. Begum Ithaca/US

P123 Self-renewal and Environmental Plasticity of Neural Crest-derived, Hox-negative Adult Human Chondrocytes
K. Pelttari[1], B. Pippenger[1], S. Feliciano[1], C. Scotti[2], P. Mainil-Varlet[3], M. Jakob[1], C. Cillo[4], I. Martin[1], A. Barbero[1] [1]Basel/CH, [2]Milano/IT, [3]Marly/CH, [4]Napoli/IT

P124 The effect of chondrogenic differentiation of co-cultured Human Synovium-derived Stem Cells and Chondrocytes
J.E. Yeo, O.R. Kwon, M.Y. Cho, Y.H. Jung, Y.I. Kim, Y.J. Choi, Y.G. Koh Seoul/KR

P125 A High-Throughput Screen For Factors That Modulate In Vitro Chondrogenesis
R.B. Jakobsen[1], S.R. Herlofsen[1], E. Østrup[1], X. Zhang[2], T.S. Mikkelsen[2], J.E. Brinchmann[1] [1]Oslo/NO, [2]Cambridge, Massachusetts/US

P126 Human mesenchymal stem cells in synovial fluid increase in knee after harvest of synovium
M. Ojima, I. Sekiya, K. Tsuji, T. Muneta Tokyo/JP

P127 Inhibition of TAK1 and/or JAK can rescue impaired chondrogenic differentiation of human mesenchmal stem cells in OA-like conditions.
H.M. Van Beuningen[1], M.L. De Vries - Van Melle[2], E. Vitters[1], W. Van Den Berg[1], G.J.V.M. Van Osch[2], P. Van Der Kraan[1] [1]Nijmegen/NL, [2]Rotterdam/NL

P128 Human mesenchymal stem cells derived from synovial fluid in patients with osteochondral lesion of the talus
Y.S. Kim, Y.G. Koh, Y.J. Choi Seoul/KP

P129 Chondrogenic differentiation of mesenchymal stem cells in a simulated osteochondral environment is hydrogel dependent
M.L. De Vries - Van Melle[1], M.S. Tihaya[1], N. Kops[1], W. Koevoet[1], J.A.N. Verhaar[1], M. Alini[2], D. Eglin[2], G.J.V.M. Van Osch[1] [1]Rotterdam/NL, [2]Davos/CH

Poster Sessions (Electronic & Traditional)

P130 Identification of a novel mesenchymal stem cell surface marker that is predictive of cells with a high chondrogenic potential
S.C. Dickinson, C.A. Sutton, K. Brady, W. Kafienah, A.P. Hollander Bristol/UK

P131 Characterization of Progenitor Cells Isolated from the Subchondral Bone of Rabbit Trochlea and Condyle
G. Dwivedi, A. Chevrier, C.D. Hoemann, M. Buschmann Montreal/CA

P132 Evaluation on chondrogenic maturity of proliferated MSC by mesenchymal-hematopoietic interaction
S. Kanazawa, T. Takato, K. Hoshi Tokyo/JP

P133 Minced umbilical cord fragments as an effective cell source for cartilage and bone tissue engineering. An in vitro tridimensional study.
A. Marmotti[1], S. Mattia[1], D.E. Bonasia[1], M. Bruzzone[1], D. Gioia[1], L. Mazzuchelli[1], C. Tarella[1], F. Castoldi[1], R. Rossi[1], G.M. Peretti[2] [1]Torino/IT, [2]Milan/IT

P134 Modulation of Hyaluronic Acid synthesis by Mesenchymal Stem Cells in osteoarthritic chondrocytes
C. Janovsky[1], E. Antonioli[2], S.D.S. Benedito[2], H.B. Nader[2], M. Ferretti[1] [1]São Paulo/BR, [2]Sao Paulo/BR

P135 Chondrogenic differentiation of human synovium-derived stem cells encapsulated in the injectable Transglutaminase 4-hydrogel
S. Lee, J.K. Lee, H.J. Min, S.C. Seong, M.C. Lee Seoul/KR

P136 Characterisation of Mesenchymal Stem cells from the human umbilical cord for allogenic cell therapy
C. Mennan, K. Wright, A. Bhattacharjee, S. Turner, J.B. Richardson, S. Roberts Oswestry/UK

P137 A comparison of culture expanded stem cells versus freshly isolated cells in 3 dimensional scaffolds for cartilage repair
N. Kohli, W.E.B. Johnson, M. Snow Birmingham/UK

P138 Optimization of the number of Bone Marrow-Mesenchymal Stem Cells (BM-MSCs) induced to Chondrocytes seeded in a collagen matrix membrane
J. Berendsen, F. Las Heras, L. Hoyos, C. Jofre, A.I. Basagoitia, R. Mardones Santiago/CL

Clinical Research / Allografts

P139 Morphologic changes in fresh-frozen meniscus allografts over 1 year
B.-S. Lee[1], S.-I. Bin[2], S.-S. Seo[3], J.-M. Kim[2], D. Sohn[2] [1]Incheon/KR, [2]Seoul/KR, [3]Busan/KR

P140 Osteochondral Allograft Transplantation of the Knee in the Pediatric and Adolescent Population
R.T. Murphy[1], A.T. Pennock[2], W.D. Bugbee[3] [1]Irvine, California/US, [2]San Diego, California/US, [3]La Jolla/US

P141 Standards of procurement, processing and utilization of fresh osteochondral allografts in Brazil
L.E. Tirico, L.A. Santos, M.K. Demange, R. Gobbi, F.J. Angelini, M.U. Rezende, J.R. Pécora, A.T. Croci, G.L. Camanho São Paulo/BR

P143 Treatment of Large Full-thickness Chondral Defects of the Knee with Bone Marrow Aspirate Concentrate (BMAC) in One-Step Surgery
A. Gobbi, G. Karnatzikos, S.R. Sukesh, D.G. Lad Milano/IT

Poster Sessions (Electronic & Traditional)

Clinical Research / Biomaterials and Scaffolds

P144 Cartilage repair in a rabbit model: Development of a subchondral defect
M. Neary, V. Barron, G. O'Malley, F. Shannon, N. Rooney, F. Barry, M. Murphy Galway City/IE

P145 Treatment of knee osteochondral lesions with a biomimetic scaffold: medium term follow-up results.
M. Berruto, F.M. Uboldi, P. Ferrua, L. Gala, E. Usellini, G. Carimati Milano/IT

P146 Evaluation of kinematic behavior of an artificial medial meniscus implant: a pilot study using open-MRI
T. De Coninck[1], J.J. Elsner[2], M. Shemesh[3], E. Linder-Ganz[3], R. Verdonk[4], P. Verdonk[4, 5] [1]Ghent/BE, [2]Cambridge/US, [3]Netanya/IL, [4]Gent/BE, [5]Antwerp/BE

P147 Arthroscopic AMIC® for the treatment of FAI in the hip
D. Mancini[1], A. Fontana[2] [1]Napoli/IT, [2]Lanzo d'Intelvi (co)/IT

P148 Clinical efficacy of synthetic biphasic scaffolds compared to microfracture for articular cartilage defects of the knee
D.H. Nawabi, K.J. Jones, J.T. Nguyen, R.F. Warren, R.J. Williams New York/US

P150 Use of a fibrin gel prepared from snake-venom in chondral defects : a sheep model
A.L.M. Yamada, C.N. De Barros, R.S.F. Junior, C.A. Hussni, M.J. Watanabe, C.A. Rodrigues, A.L.G. Alves Botucatu/BR

P151 The use of nanostructured biomimetic scaffold in the treatment of the advanced osteochondral lesions of the knee: clinical and MRI results
C. Zorzi[1], V. Condello[2], V. Madonna[3], F. Cortese[3], R. Giovarruscio[1], D. Screpis[2] [1]Verona/IT, [2]Negrar/IT, [3]Negrar, Verona/IT

P152 Arthroscopic meniscal scaffold implantation: early clinical results at 24 months of follow-up
R. Giovarruscio, V. Condello, V. Madonna, D. Screpis, C. Zorzi Negrar/IT

Clinical Research / Cartilage /Cell Transplantation

P153 Human rib perichondrial transplantation: a 20-year follow-up
M.P.F. Janssen[1], J.A. De Bruin[1], E.J.P. Jansen[2], S.K. Bulstra[3], P.J. Emans[1] [1]Maastricht/NL, [2]Sittard-Geleen/NL, [3]Groningen/NL

P154 Treatment of Cartilage Defects of the Knee: Expanding on the Existing Algorithm
O. Behery, R. Siston, J. Harris, D. Flanigan Columbus/US

P155 Two years results after Matrix-associated autologous chondrocyte transplantation using the Novocart(R)3D saffold
L. Zak, C. Albrecht, H.K. Widhalm, G. Vekszler, S. Trattnig, S. Marlovits, S. Aldrian Wien/AT

P156 Revision of Recurrent Osteochondral Lesions of the Talus with Autologous Matrix - Induced Chondrogenesis (AMIC)
M. Wiewiorski, M. Miska, V. Valderrabano Basel/CH

P157 Revision Cartilage Cell Transplantation for failed Autologous Chondrocyte Transplantation in Chronic Osteochondral Defects of the Knee
S. Vijayan, J. Rahman, G. Bentley, T. Briggs, J. Skinner, R. Carrington Stanmore/UK

Poster Sessions (Electronic & Traditional)

P158 Long-term Results of Autologous Chondrocyte Implantation for Knee Osteochondritis Dissecans in Adults with Juvenile Onset Disease
S. Vijayan, G. Bentley Stanmore/UK

P159 Osteochondral regeneration with scaffold free 3D-structure of swine adipose tissue-derived mesenchymal stem cells
D. Murata[1], S. Tokunaga[1], T. Tamura[2], H. Kawaguchi[1], M. Fujiki[1], N. Miyosi[1], K. Nakayama[3], K. Misumi[1] [1]Kagoshima/JP, [2]Fukuoka/JP, [3]Saga/JP

P160 Scaffold-free cell-matrix bead-type autologous chondrocyte implantation, CartiLifeTM for cartilage repair: Early clinical results
K.-H. Park[1], S. Lee[1], J. Lee[1], J.-Y. Lee[1], B.C. Chae[1], Y. Son[2], K.H. Yoon[1], M.C. Lee[1] [1]Seoul/KR, [2]Yongin/KR

P161 The preclinical road to IMPACT: An investigator driven first in man trial exploring single-stage cartilage repair using chondrons and MSCs.
T.S. De Windt[1], L. Vonk[1], I.C. Slaper-Cortenbach[1], J.E.J. Bekkers[1], W.J.A. Dhert[1], D.B.F. Saris[1, 2] [1]Utrecht/NL, [2]Enschede/NL

P162 Minimally invasive implantation of autologous chondrocytes transduced with rAAV5-IGF-I improves cartilage repair in the equine model
K. Ortved, L. Begum, A.J. Nixon Ithaca/US

P163 Matrix-induced autologous chondrocyte implant (MACI®) improves healing of full thickness cartilage defects in the equine model
A.J. Nixon[1], H. Sparks[1], L. Begum[1], N. Moran[2], G. Matthews[2] [1]Ithaca/US, [2]Framingham/US

P164 One step technique with bone marrow derived cells in osteochondral lesions of the patello-femoral joint. Does it work?
M. Cavallo, F. Vannini, R. Buda, A. Ruffilli, L. Ramponi, G. Pagliazzi, F. Castagnini, S. Giannini Bologna/IT

P165 Treatment of osteochondritis dissecans of the knee with bone marrow-derived cells transplantation: results and T2 mapping evaluation
F. Vannini, M. Battaglia, R. Buda, S. Natali, M. Cavallo, M. Baldassarri, A. Olivieri, S. Giannini Bologna/IT

P166 Autologous Chondrocyte Implantation In The Cartilage Repair
M. Handl Prague/CZ

P167 Gender-specific differences of patients with cartilage defects
B. Blutsch, L. Zak, C. Albrecht, D. Stelzeneder, S. Marlovits, P. Platzer, S. Hajdu, S. Aldrian Vienna/AT

P168 Molecular and Functional MRI Evaluation of the Continuous Re-differentiation Process of Implanted Autologous Chondrocytes.
I. Alba-Sanchez, A. Lopez-Reyes, F.E. Villalobos Jr, A. Izaguirre, C. Ibarra, A. Olivos Meza, C. Velasquillo Mexico City/MX

P169 Use of Chondroguide® membrane with autologous expanded pre-differentiated MSC in the treatment of full tickness knee lesions. 6 m to 7 y f.u.
R. Mardones, A. Orizola, A.I. Basagoitia, J. Berendsen Santiago/CL

Poster Sessions (Electronic & Traditional)

Clinical Research / Cartilage Imaging and Functional Testing

P170 Cartilage Delamination in Cam FAI: Diagnostic Accuracy of MR Arthrography with and without Leg Traction in Comparison to Arthroscopy.
E. Schmaranzer, M. Kogler, M. Reichkendler St. Johann In Tirol/AT

P171 Early tibiofemoral osteoarthritis treated with platelet-rich plasma
R. Hart, A. Safi, M. Komzák, P. Jajtner, M. Puskeiler, P. Hartová Znojmo/CZ

P172 Longitudinal Evaluation of Cartilage Repair after Osteochondral Defects with Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC)
T. Shirai[1], M. Kobayashi[1], S. Nakamura[1], R. Arai[1], K. Nishitani[1], T. Satake[1], T. Okada[1], K. Togashi[1], L.E. Dahlberg[2],H. Kuroki[1], Y. Nakagawa[1], T. Nakamura[1], S. Matsuda[1] [1]Kyoto/JP, [2]Malmö/SE

P173 Reconstruction of osteochondral defects by combined bone grafting and the Chondrogide™ membrane as a sandwich technique
M. Petri[1], C. Von Falck[1], N. Hawi[1], E. Liodakis[1], M. Ettinger[1], S. Brand[1], T. Stübig[1], C. Krettek[1], M. Jagodzinski[1], C. Haasper[2] [1]Hannover/DE, [2]Hamburg/DE

P174 Acetabular Cartilage Delamination in Cam-FAI: Diagnostic Accuracy of MR Arthrography in Correlation to Arthroscopy.
E. Schmaranzer, M. Kogler, M. Reichkendler St. Johann In Tirol/AT

P175 dGEMRIC of Cartilage After AMIC - Aided Reconstruction of Osteochondral Lesions of the Talus
M. Wiewiorski, M. Miska, M. Kretschmar, U. Studler, O. Bieri, V. Valderrabano Basel/CH

P177 Modified MOCART scoring system for cartilage repair: validity and usefulness in comparative trials for osteochondral repair
I. Van Breuseghem, I. Carruet Sint-Niklaas/BE

P178 Pre-Operative Evaluation for Knee A C Repair: MRI 3D Thickness Maps Derived from a Validated, Automated Segmentation Platform
J. Farber[1], J. Tamez-Pena[2], S.M. Totterman[3], K. Baum[3], E. Brandser[4], B. Holladay[4], J. Larkin[4], F. Heis[4] [1]Cincinnati, Oh/US, [2]Monteray/MX, [3]Rochester/US, [4]Edgewood/US

P179 Preoperative MRI Underestimates Articular Cartilage Defect Size Compared With Findings at Arthroscopic Knee Surgery
A. Campbell, M.V. Knopp, G.P. Kolovich, W. Wei, G. Jia, R. Siston, D. Flanigan Columbus/US

P180 3D FSE FS of Knee AC at 3T for Clinical Use and Quantitative Analysis, and T2 Maps: A single MR Data Set for Morphology and Quantification
J. Farber[1], S.M. Totterman[2], K. Baum[2], J. Tamez-Pena[2, 3], H. Lejay[4] [1]Cincinnati, Oh/US, [2]Rochester/US,[3]Monterrey/MX, [4]Milwaukee/US

P181 Feasibility of Glycosaminoglycan (GAG) Chemical Exchange Saturation Transfer (CEST) Imaging of the ankle at 3 Tesla
M. Brix, B. Schmitt, M. Willegger, S. Trattnig, R. Windhager, S. Domayer Vienna/AT

P182 Gadolinium Uptake by DeNovo Chondral Repair In Situ: Robust Graft Uptake After Arthrography May Mimic Chondral Defect on MRI
J. Farber[1], J. Larkin[2], E. Brandser[2], S.M. Totterman[3] [1]Cincinnati, Oh/US, [2]Edgewood/US, [3]Rochester/US

Poster Sessions (Electronic & Traditional)

P183 Patello-Femoral Cartilage Kinematics in Adolescent Professional Soccer Players assessed by Biochemical T2 Mapping
G.H. Welsch[1], L. Waldenmeier[1], C. Evers[1], S. Trattnig[2], A. Mauerer[1], R. Janka[1], M. Lochmann[1] [1]Erlangen/DE,[2]Wien/AT

P184 High resolution patient case - symptomatic TC-joint with a flap like cartilage lesion.
J. Salo Kuopio/FI

Clinical Research / Chondrocytes

P185 Matrix assisted autologous chondrocyte transplantation: long term results at 10 years of follow-up
B. Di Matteo, G. Filardo, E. Kon, L. Andriolo, G. Tesei, S. Ali Ahmad, M. Marcacci Bologna/IT

P186 Biomolecular characterization of chondrocytes embedded in a collagen I-matrix (CaReS®) at the time of transplantation
F. Halbwirth[1], E. Niculescu-Morzsa[1], H. Zwickl[1], C. Bauer[1], S. Nehrer[2] [1]Krems/AT, [2]

Clinical Research / Clinical outcome

P187 First clinical experience with INSTRUCT - a single surgery, autologous cell based technology for cartilage repair
J. Hendriks[1], P. Verdonk[2], W. Widuchowski[3], M. Snow[4], T. Dolata[5], J. Kruczynski[6], K. Slynarski[7] [1]Bilthoven/NL,[2]Antwerp/BE, [3]Katowice/PL, [4]Birmingham/UK, [5]Bydgoszcz/PL, [6]Poznan/PL, [7]Warsaw/PL

P188 HA/PLLA pin fixation of osteochondral fragment for osteochondritis dissecans of the knee
M. Kubo, K. Uenaka, S. Araki, K. Kumagai, Y. Matsusue Otsu-city/JP

P189 Contoured metallic resurfacing for grade IV articular cartilage lesions of the femoral condyle
P. Behrens[1], J. Benthien[2], J. Gelließen[3] [1], [2]Davos Platz/CH, [3]Hamburg/DE

P190 Autologous chondrocyte implantation on the femoral condyles – Ten-year clinical and radiographic results
M. Drobnič, D. Martinčič, D. Radosavljevič Ljubljana/SI

P191 Fixation of osteochondral lesions of the talus using bone pegs: a report of two cases
N. Kanzaki, T. Fujishiro, S. Hayashi, S. Hashimoto, R. Kuroda, M. Kurosaka Kobe/JP

P192 Clinical Outcome of Internal Fixation of Unstable Juvenile Osteochondritis Dissecans Lesions of the Knee
A.J. Krych, J.E. Webb, L.W. Lewallen, A.L. McIntosh Rochester/US

P193 Grade 4 Patellofemoral Chondral Defects Result in Increased Patient Disability
K.K. Briggs, W.G. Rodkey, J..R. Steadman Vail/US

P194 Development of a valid and reliable knee articular cartilage study methodological quality questionnaire
J.D. Harris[1, 2], B.J. Erickson[1], G.D. Abrams[1], B.J. Cole[1] [1]Chicago/US, [2]Houston/US

P195 Safety and efficacy of chondrotissue® for the treatment of knee cartilage defects: clinical results after 12 and 24 months
M. Herbort[1], D. Fritschy[2], R. Verdonk[3], C. Castelli[4], G. Zappala[4] [1]Muenster/DE, [2]Geneva/CH, [3]Gent/BE, [4]Bergamo/IT

P196 Combined osteotomy, meniscal transplantation, and articular cartilage surgery in young patients with unicompartmental arthritis
J.D. Harris[1, 2], K. Hussey[1], H. Wilson[1], A.H. Gomoll[3], B.J. Cole[1] [1]Chicago/US, [2]Houston/US, [3]Boston/US

ICRS International Cartilage Repair Society

Poster Sessions (Electronic & Traditional)

P197 Matrix Autologous Chondrocyte Transplantation in Treatment of Wide Osteochondral Lesions of Knee
M. Bozkurt[1], C. Isik[2], S. Gürsoy[2], O. Algin[2], N. Cay[2], M. Dogan[2] [1]Gölbaci -Ankara/TR, [2]Ankara/TR

P198 Predictors of long-term treatment success with autologous chondrocyte implantation in the knee joint
M.N. Dugard, J.C. Parker, E. Robinson, J.H. Kuiper, S. Roberts, J.B. Richardson Oswestry/UK

P199 Short-term results of a cell free collagen type I matrix for the treatment of cartilage defects - clinical and magnetic resonance imaging
T. Efe[1], B. Pfister[1], D. Malcherczyk[1], P.P. Roessler[1], A. Getgood[2], J. Struewer[1], M.B. Rominger[1], K.F. Schuettler[11]Marburg/DE, [2]London/CA

P200 Should we still talk about "patellofemoral" cartilage lesions? A comparative study
G. Filardo, E. Kon, L. Andriolo, A. Di Martino, S. Zaffagnini, M. Marcacci Bologna/IT

P201 Femoral cortical index as a spy of bone fragility in patients with hip fracture
M. Feola, V. Tempesta, C. Rao, M. Celi, E. Gasbarra, U. Tarantino Rome/IT

P202 New biomimetic ostechondral scaffold to treat Osteochondritis dissecans of the knee: prospective clinical study at 24 months of follow-up.
E. Kon, G. Filardo, A. Di Martino, L. Andriolo, F. Tentoni, G. Altadonna, M. Marcacci Bologna/IT

P203 Polyurethane synthetic scaffold for meniscal regeneration: prospective clinical study at 3 years' follow-up.
F. Perdisa, E. Kon, G. Filardo, A. Di Martino, S. Patella, S. Zaffagnini, M. Marcacci Bologna/IT

P204 X-Ray joint degeneration after arthroscopic mosaicplasty. Results at 12 years' follow-up.
G. Filardo, E. Kon, F. Perdisa, M.L. Merli, A. Di Martino, M. Marcacci Bologna/IT

P205 Osteochondritis dissecans: comparison of different surgical approaches
F. Vannini, E. Kon, G. Filardo, R.E. Buda, L. Andriolo, S. Natali, F. Balboni, S. Giannini, M. Marcacci Bologna/IT

P207 Autologous osteochondral graft in the treatment of chondral and osteochondral knee lesions: clinical evaluation at 3 years of follow-up.
A. Di Martino, E. Kon, G. Filardo, S. Ali Ahmad, G. Tesei, M. Marcacci Bologna/IT

P208 Patient profiling in cartilage regeneration: mid-term results and prognostic factors of MACT. A multicenter study
G. Filardo, F. Vannini, E. Kon, A. Di Martino, L. Andriolo, R. Buda, A. Ferruzzi, S. Giannini, M. Marcacci Bologna/IT

P209 Defect size Normalized to Tibial Width is more Highly Correlated to Patient Reported Outcomes following ACI than Raw Defect Size, BMI, or Age
J.S. Howard[1], A.M. Carpiaux[1], R. Royalty[2], C. Lattermann[1] [1]Lexington/US, [2]Prestonsburg/US

P210 Two years clinical results of MACI for the treatment of knee cartilage lesions
I. Terzidis[1], A. Sideridis[1], E. Papacostas[1], K. Epaminontidis[1], V. Goyrgoylis[2], M. Hantes[3], K.N. Malizos[3] [1]Pylaia, Thessaloniki/GR, [2]Komotini/GR, [3]Larisa/GR

Poster Sessions (Electronic & Traditional)

Clinical Research / Histology

P212 A novel combination of zonal collagen typing and histological scoring reveals hyaline cartilage repair mechanism in clinical biopsies
C.D. Hoemann, N. Tran-Khanh, G. Chen, A. Chevrier, M. Buschmann Montreal/CA

Clinical Research / Intervertebral Disc

P213 Effects of controlled release of celecoxib from an LDH-pNIPAAM hydrogel in a canine disc degeneration model
N. Willems, M.A. Tryfonidou, G.C.M. Grinwis, N.E. Papen-Botterhuis, M. Langelaan, S.G.M. Plomp, W.J.A. Dhert,L.B. Creemers, B.P. Meij Utrecht/NL

Clinical Research / Joint Specific Cartilage Repair

P214 Biological resurfacing of unicompartmental knee and ankle OA (Kissing lesions)
S. Zanasi, G. Maci, M. Pastina Bologna/IT

P215 Joint distraction results in clinical and structural improvement of hemophilic ankle arthropathy: a series of three cases
L.F.D. Van Vulpen, M.E.R. Van Meegeren, K. Van Veghel, P. De Kleijn, P.M. Van Roermund, D.H. Biesma, G. Roosendaal, S.C. Mastbergen, F.P.J.G. Lafeber Utrecht/NL

P216 Clinical and functional outcomes of RevaFlex, a tissue-engineered cartilage implant derived from allogeneic juvenile chondrocytes
B.J. Cole[1], J. Farr[2], K. Bonner[3], G. Gold[4], H.D. Adkisson[5] [1]Chicago/US, [2]Indianapolis/US, [3]Virginia Beach/US,[4]Stanford/US, [5]St. Louis/US

P217 Surgical Treatment of Isolated Lateral Compartment Chondral Defects
J.D. Harris[1, 2], K. Hussey[1], B. Saltzman[1], H. Wilson[1], G.D. Abrams[1], B.J. Cole[1] [1]Chicago/US, [2]Houston/US

P219 Bone marrow-derived cells and biophysical stimulation for talar osteochondral lesions: a prospective, randomized, controlled study
R. Buda, M. Cadossi, M. Cavallo, L. Ramponi, A. Parma, S. Natali, M.C. Bulzamini, S. Giannini Bologna/IT

P220 Molecular Insight into the Association Between Cartilage Regeneration and Ear Wound Healing in Genetic Mouse Models
M.F. Rai, A. McAlinden, E. Schmidt, J.M. Cheverud, L.J. Sandell St. Louis/US

Clinical Research / Medication and Cartilage

P221 Orthokine-Therapy for high-pain knee OA may delay surgery. Independent 2 year prospective clinical observational study.
J. Baselga García-Escudero, P.M. Hernández Trillos Madrid/ES

P222 Intra-articular local anesthetic showed no chondrotoxic effect in cartilage biopsies assigned for autologous chondrocyte cultivation
M. Drobnič[1], K. Ravnihar[2], N. Kregar-Velikonja[1], A. Barlič[1] [1]Ljubljana/SI, [2]Jesenice/SI

P223 “Theracurmin” has anti-inflammatory effects on knee osteoarthritis in randomized controlled study.
S. Mukai[1], Y. Nakagawa[1], S. Yamada[1], M. Matsuoka[1], E. Tarumi[1], T. Hashimoto[2], C. Tamura[2], A. Imaizumi[2], J. Nishihira[3], T. Nakamura[1] [1]Kyoto/JP, [2]TOkyo/JP, [3]Ebetsu/JP

Poster Sessions (Electronic & Traditional)

Clinical Research / Meniscus

P224 Osteoarthritis development after medial meniscectomy in long-term follow-up (20 years at least)
R. Hart Znojmo/CZ

P225 Risk Factors for end-stage osteoarthritis after Meniscectomy in the Radial Tears of Medial Meniscus Posterior Horn
B.-S. Lee[1], S.-I. Bin[2], S.-S. Seo[3], J.-M. Kim[2], D. Sohn[2] [1]Incheon/KR, [2]Seoul/KR, [3]Busan/KR

P226 Comparing meniscal scaffold. Short-term results.
E. Bulgheroni[1], P. Bulgheroni[1], A. Grassi[2], P. Cherubino[1] [1]Varese/IT, [2]Bologna/IT

P227 Outcomes of meniscal repair combined with anterior cruciate ligament reconstruction
T. Matsushita, R. Kuroda, K. Nagai, Y. Nishizawa, T. Matsumoto, T. Matsuzaki, S. Oka, A. Uefuji, M. KurosakaKobe/JP

P228 Outcome of meniscal allograft transplantation related to chondral wear: Advanced degenerative change should not be a contraindication.
P. Kempshall, H. Standell, A. Getgood, C. Robb, P. Thompson, T. Spalding Coventry/UK

P229 A novel polycarbonate-urethane meniscus implant for the treatment of middle aged patients: First experience from 30 patients
R. Arbel[1], S. Israeli[2], Y. Beer[3], Z. Ben-Haim[2], N. Blumberg[1], N. Shabshin[1], J.J. Elsner[4], E. Nocco[4], R.W. Treharne[4], E. Linder-Ganz[4], G. Agar[3], N. Rozen[2] [1]Tel Aviv/IL, [2]Afula/IL, [3]Zeriffin/IL, [4]Netanya/IL

P231 All-inside technique for meniscal repair in high level athletes. Back to sports and failure.
A. Sideridis[1], I. Terzidis[1], N. Koukoulias[2], E. Papacostas[1] [1]Pylaia, Thessaloniki/GR, [2]Thessaloniki/GR

P232 Combined ACL reconstruction and medial Collagen Meniscus Implant. Clinical and radiographic results at long-term follow-up.
E. Bulgheroni[1], P. Bulgheroni[1], P. Cherubino[1], A. Grassi[2], G.M. Marcheggiani Muccioli[2], S. Zaffagnini[2], M. Marcacci[21]Varese/IT, [2]Bologna/IT

P233 Allograft meniscus transplantation: results at minimum of 48 months
R. Giovarruscio, V. Condello, V. Madonna, D. Screpis, C. Zorzi Negrar/IT

Clinical Research / Microfracture/Bone Marrow Stimulation

P235 Functional and T2 Mapping Outcomes after Microfracture with Concentrated Bone Marrow Aspirate for Osteochondral Lesions of the Talus
C.P. Hannon, K.A. Ross, C.D. Murawski, T. Deyer, N. Smyth, H. Do, J.G. Kennedy New York/US

P236 Talonavicular Arthroscopy: A Novel Technique and Early Clinical Results
K.A. Ross, C.M. Seaworth, N. Smyth, J. Ling, J.G. Kennedy New York/US

P238 Validity of T2 mapping in characterization of the regeneration tissue by microfractures in osteochondral lesions of the ankle
M. Battaglia, F. Vannini, G. Rossi, C. Monti, R. Buda, M. Cavallo, E. Ferranti, S. Giannini Bologna/IT

Poster Sessions (Electronic & Traditional)

Clinical Research / Osteoarthritis

P239 An international multicentre prospective study on the efficacy of a polyacrylamide hydrogel in horses with osteoarthritis
A. Tnibar[1], H. Schougaard[2], L. Camitz[3], J. Rasmussen[4], M. Koene[5], W. Jahn[6], B. Markussen[7] [1]Taastrup/DK,[2]Them/DK, [3]Næstved/DK, [4]Morud/DK, [5]Luesche/DE, [6]Bargteheide/DE, [7]Copenhagen/DK

P240 Effectiveness and safety in treatment of osteoarthritis with Synvisc.
T. Mae[1], K. Nakata[1], M. Hamada[1], T. Mitsuoka[1], S. Nakagawa[1], Y. Toritsuka[1], Y. Tanaka[2], Y. Yamada[1], K. Yoneda[1], Y. Yonetani[1], H. Yoshikawa[1] [1]Suita/JP, [2]Osaka/JP

P241 Femoral-tibial subchondral surface area ratio (FSTAR) is predictive of knee osteoarthritis symptoms and progression
J. Everhart, R. Siston, D. Flanigan Columbus/US

P242 The relationship between external knee adduction moment, internal loading and T1Rho MRI in early stage knee OA patients
K. Meijer, R. Garcia Van Der Westen, P. Oomen, R. Gransier, P. Emans, L. Van Rhijn Maastricht/NL

Clinical Research / Osteochondral Grafts

P243 Microfracture versus OAT for High-Grade Osteochondral Lesions of the Talus: A Ten-year Prospective Comparative Clinical Experience.
B. Dierckman, R. Shani, S. Labib Atlanta/US

P244 Optimization of Osteochondral Graft Surgical Instrumentation
A.S. Levy[1], P.A. Davidson[2], D. Robinson[3], E. Kon[4], K.R. Zaslav[5], J. Shani[6], M. Drobni [7], N. Altschuler[3] [1]Millburn/US,[2]Park City/US, [3]Kfar Saba/IL, [4]Bologna/IT, [5]Richmond/US, [6]Beit Berl/IL, [7]Ljubljana/SI

P245 Autogenous Osteochondral Graft Transplantation for Osteonecrosis of the Knee; A Novel Method of Eyeglass-Plasty
Y. Matsusue[1], M. Kubo[2], K. Uenaka[2] [1]Otsu/JP, [2]Otsu-city/JP

P246 Cyst Formation Following Autologous Osteochondral Transplantation; A Post-Operative MRI Evaluation
I. Savage-Elliott, N. Smyth, C.D. Murawski, C.P. Hannon, T. Deyer, H. Do, J.G. Kennedy New York/US

P247 Combined Meniscus and Osteochondral Allograft Transplantation: Minimum Two-Year Follow-up with an Analysis of Failures
G. Abrams, K. Hussey, J.D. Harris, B.J. Cole Chicago/US

P248 Factors affecting the Outcome of Autologous Osteochondral Transplantation for the Focal Cartilage Lesion of the Patella
Y. Yonetani[1], Y. Tanaka[2], K. Nakata[1], S. Horibe[2] [1]Suita/JP, [2]Osaka/JP

Clinical Research / Others

P249 Treatment of osteochondritis dissecans of the knee in skeletally immature athletes by fixation with bioabsorbable implants
I. Melas, M.I. Iosifidis, D. Metaxiotis, D. Alvanos, A. Kyriakidis Thessaloniki/GR

Poster Sessions (Electronic & Traditional)

Clinical Research / Platelet Rich Plasma and Growth factors

P250 Platelet rich plasma in the management of articular cartilage pathology: a systematic review.
A. Dold, M. Zywiel, D. Taylor, T. Dwyer, J. Theodoropoulos Toronto/CA

P252 PRP treatment for knee chondropathies grade I-III: results at 1 year
F.M. Uboldi, M. Berruto, G. Carimati, P. Ferrua, W. Albisetti Milano/IT

P253 PRP injections in the treatment of refractory proximal patellar tendinopathy: results at 4 years of follow-up
G. Filardo, E. Kon, B. Di Matteo, A. Di Martino, M.L. Merli, A. Roffi, M. Marcacci Bologna/IT

P254 Platelet-Rich Plasma vs Hyaluronic Acid to treat knee degenerative pathology: a randomized double blind controlled trial
G. Filardo, E. Kon, B. Di Matteo, A. Di Martino, M.L. Merli, A. Roffi, G. Venieri, M. Marcacci Bologna/IT

P255 Platelet-rich plasma immersed polymers scaffolds improve cartilage repair in the knee
A. Siclari[1], G. Mascaro[1], C. Gentili[2], C. Kaps[3], R. Cancedda[2], E. Boux[1] [1]Biella/IT, [2]Genova/IT, [3]Berlin/DE

Clinical Research / Rehabilitation and Sport

P256 Iatrogenic cartilage lesion during hip arthroscopy: peripheral first technique avoids this complication
A. Nogier, T. Boyer Paris/FR

Clinical Research / Stem Cells

P259 Reconstruction by MSCs of knee and ankle coin cartilage defects: preliminary results at 2 yrs f.up
S. Zanasi, G. Maci, M. Pastina Bologna/IT

P260 Use of autologous peripheral blood progenitor cells for articular cartilage regeneration afther subchondral drilling in the knee
C. Rafols, J.E. Monckeberg, J. Numair, B. Capurro, B. Morales Santiago/CL

P261 Tri-Therapy treatment for partial to full-thickness chondral defects in the knee. Evaluation of clinical results in 36 to 54 months. *F. Bascunan Santiago/CL*

P262 Clinical outcome of Autologous Bone Marrow Aspirates Concentrate (BMAC) Injection in Degenerative Osteoarthritis of the Knee *J.D. Kim Busan/KR*

P263 Knee Osteoarthritis: Quality of Life (QoL) Measures Following Autologous Stem Cell Therapy D.
Lox Clearwater/US

P264 Adipose-derived mesenchymal stem cell implantation for cartilage regeneration in osteoarthritic knees
Y.S. Kim, Y.J. Choi, Y.G. Koh Seoul/KP

P265 Characterization of stem cells from equine dental pulp
M. Hidalgo De La Garma[1], M. Masri[1], E. Diaz[1], J. Granados-Montiel[1], C. Landa[1], C. Ortega-Sanchez[1], R. Gomez-Garcia[1], C. Ibarra[2] [1]Mexico City/MX, [2]Mexico/MX

P266 Selected and Cultured Bone Marrow Stromal Cells in Bone Formation: A Randomised Controlled Study
A. Bhattacharjee, S. Bajada, J.H. Kuiper, P. Harrison, B.A. Ashton, S. Roberts, J.B. Richardson Oswestry/UK

P267 Abstract 5805 Autologous mesenchymal stem cells in treatment of chondral and osteochondral lesions of the knee: results at 1 year follow up
R. Giovarruscio, V. Condello, D. Screpis, C. Zorzi Negrar/IT

Clinical Research / Subchondral Bone

P268 Treatment for osteochondral lesion of talar dome with subchondral bone cyst
T. Nakasa, N. Adachi, T. Kato, M. Ochi Hiroshima City/JP

Notes

Extended Abstracts & Index

1. Abstract Book

The abstracts of all Free Papers and Posters can be found in a searchable database as well as in a pdf-format for your print-out or download on our website www.cartilage.org (ICRS 2013 – Final Programme & Abstracts)

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0.02

Stem Cell-Based Cartilage Repair in Isolated Articular Cartilage Lesions and Arthritic Conditions

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Introduction: It is widely accepted that lesions of articular cartilage from trauma or any other cause cannot be repaired spontaneously because of absence of vascular, lymphatic or neuronal supply and very low metabolic activity of the tissue. Therefore after disruption of integrity of the cartilage, pain, restriction of motion and eventually osteoarthritis ensues. Different treatment modalities have been designed to relieve pain and improve loss of function, slow or cease progression of osteoarthritis and possibly restore articular cartilage in young active patients with isolated cartage lesions or osteoarthritis. However, only a few methods including microfracture, mosaicplasty, osteochondral allograft and autologous chondrocyte implantation (ACI) are used widely with different indications. As ACI is becoming a major treatment choice in cartilage lesions, especially for those larger than 2 cm^2 in the knee and larger than 1,5 cm^2 in the ankle, its potential weaknesses are becoming more of concerns. Especially concerns about histology of the newly formed tissue which is hyaline-like cartilage and difficulties in culturing chondrocytes to obtain large amount of cells to fill a large defect, have led to studies that search for a novel alternative under the scope of tissue engineering.

Adult autologous mesenchymal stem cells (AMSCs), with their multipotency and much higher proliferation capacity relative to chondrocytes make them ideal cells for tissue engineering, not only because of their regenerative capacity but also because of their trophic effects.

We conducted a prospective study to evaluate the effect of AMSC implantation (AMSCI) or AMSC injection on cartilage healing in 26 patients with isolated cartilage lesions or degenerative joint diseases as a cell based treatment.

Content

Materials and Methods: We applied AMSC implantation with open arthrotomy technique to full thickness isolated cartilage lesions in 7 knees, 5 ankles and 2 hips of 14 patients. AMSC injections were done to 17 knees and 2 ankles of 13 patients for degenerative joint diseases. The mean size of isolated lesions was 3,57 cm^2 (range 1,5 to 8cm^2). MSCs were cultured from synovium or bone marrow. The mean age of patients was 41,9 (range 21-59).

Patients were followed in third, sixth, twelfth months and after every six months, using KOOS, Lysholm, HSS and Hokkaido knee scores, Tegner activity scale, VAS pain scale, AOFAS score and Harris hip score. T2 MRI mapping was done to 20 patients in average 21,1 months (range 14-36). Second look arthroscopy was done to three patients and histological examination to only one.

Results: The mean follow-up was 25 (range 13 to 41) months. AMSCI to isolated cartilage lesions of the knee and ankle or AMSC injection into the knee for degenerative arthritis showed statistically significant clinical improvement from the preoperative period to the end of the first year and follow-up. AMSC implantation to isolated cartilage lesions of the hip showed remarkable improvement in clinical scores, as well. We did not detect any relation between duration of production and cell counts or viability of the cells.

T2 MRI mapping was done to 21 patients in average 21,1 months (range 14-36). T2 mapping MRI in isolated cartilage lesion group showed more than 75% filling of the defects with the new tissue which had similar T2 times to intact cartilage T2 times. In AMSC injection groups MRI T2 mapping showed some decrease in bony edema but did not detect any new tissue formation. On the other hand, there was not any deterioration of the condition.

Second look diagnostic arthroscopies showed fair integration of the scaffold to the surrounding with visible borders, less consistency than native cartilage, complete filling of defects and good joint surface congruence. Histological examination of one case detected hyaline-like cartilage inside the new tissue.

Conclusion: AMSC application for isolated cartilage lesions is a promising method to heal cartilage lesions in knee, hip or ankle. Intraarticular injections of AMSCs into knees or ankles have promising effect to stop or slow the progression of degenerative joint diseases. However, there is still need for larger scale long term studies supported by histological analyses, which compare MSC application with control groups and other methods of cartilage repair.

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1.1

Effect of Sport on the Athlete's Joint: The Scientific Perspective

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Introduction: Articular cartilage injuries in athletes can result from acute traumatic injury, or can develop from chronic pathologic joint loading patterns in high-impact athletes such as joint instability or axis deviation. It has been shown that normal knee articular cartilage becomes conditioned to loading and to a large number of repetitive cycles of loading that occur during low impact activities with a healthy cartilage homeostasis that is maintained as long as there are no changes to the normal patterns of locomotion, the structure of the knee joint, or cartilage biology.

Content: In fact, both clinical and basic science studies have demonstrated that intact articular cartilage adjusts to the increasing weightbearing activity like it can usually be seen in the athletic population by increasing articular cartilage volume and cartilage thickness in a linear dose-response relationship. However, several recent studies indicate that this dose-response curve can reach a threshold and that activity beyond this threshold can result in maladaptation and injury of articular cartilage. Various experimental studies have presented data supporting the conclusion that individual variations of joint loading and joint kinematics, such as with meniscal deficiency or ligamentous instability can have a profound influence on the initiation of articular cartilage injury and progression of joint degeneration. High-impact joint loading above the injurious threshold has been shown to decrease articular cartilage proteoglycan content and to increase levels of degradative enzymes and chondrocyte apoptosis. Experimental studies have shown that high-intensity and repetitive movement may induce loss of articular cartilage thickness particularly in the superficial zone. Synovial and serum biomarkers such as MMP-1, MMP-3, TIMP-1, and COMP have been found to be reflective of the extent of the articular cartilage pathological changes. These biomarkers not only detected changes of metabolism in articular cartilage but were also useful in monitoring change of disease course and articular cartilage repair. Clinical studies in runners and soccer players detected increased synovial levels of aggrecan, keratin-sulfate, procollagen II C-propeptide and TIMP-1 indicating that high-impact loading can induce a catabolic response and increased cartilage matrix turnover even after only 60-90 minutes of running or even a single game of soccer. Prolonged high-impact joint loading above the injury threshold can lead to breakdown of the joint surface by decreasing cartilage metabolism, death of cartilage cells, and

destruction of the tissue components that provide the typical shock-absorbing features of articular cartilage. Biomechanical studies have shown that not only does the loading phase of impact compression play a role in introducing substantial damage and deformation to articular cartilage, but that the unloading phase also contributes to overall cartilage damage by exacerbating articular surface lesions. With continued repetitive loading and unloading activity such as running or jumping over time the integrity of the functional weight bearing unit is then lost and a chondropenic response is initiated that can include loss of articular cartilage volume and stiffness, elevation of contact pressures, and development or progression of articular cartilage defects and osteoarthritis. This is also supported by the experimental finding of significant increases in the subchondral bone thickness after repetitive impact activity. Development of joint inflammation and accumulation of inflammatory cytokines such as IL-1 and TNF-a have also been found to synergistically deplete cartilage proteoglycan content and aggravate joint degradation.

Besides chronic overload, acute traumatic overload can cause cartilage injury. Acute impact injury associated with rupture of the anterior cruciate ligament (ACL) have been found do produce a load dependent joint surface injury. Traumatic joint loading forces of less than 20 MPa have been associated with so called "bone bruising". Even though no acute cartilage defects result at these loads, this contusion-type injury of the joint surface has been shown to result in significant apoptotic chondrocyte cell death and chronic decrease of proteoglycan content and aggrecan that is detectable even 2 years after the initial impact injury. With joint forces greater than 25-30 MPa acute cartilage defects occur, particularly with a combination of shear and compression loading. Besides acute cartilage defect often subchondral compression fractures can be observed with these acute injuries.

Due to the high functional specialization of articular cartilage tissue it has lost its ability to repair itself when injured. Recent reports demonstrated that the lack of spontaneous healing of hyaline articular cartilage defects in athletes resulted in significant pain and swelling and were associated with marked life-style changes and limitation of athletic activity. Some long-term data in athletes with isolated severe chondral or osteochondral damage in the weightbearing condyles showed a 75% initial return to sport initially, but a significant decline of athletic activity was observed over time with development of radiographic evidence of osteoarthritis in the 45-60% of athletes 14-34 years after the injury. These results are supported by the up to 12 fold increased risk of knee osteoarthritis in high-impact athletes established by the National Institute of Health (NIH) and other independent studies. Untreated articular cartilage defects have been shown to result in significantly worse long-term joint function. The high demands on the joint surfaces in athletes make treatment of articular cartilage injuries and the restoration of the injured joint surfaces critically important to facilitate continued athletic participation and to maintain a physically active lifestyle. The documented detrimental effect of high-impact articular loading in the athletic population requires cartilage surface restoration that can effectively withstand the significant mechanical joint stresses generated during high-impact, pivoting sports. Besides reducing pain, increasing mobility and improving knee function, the ability to return the athlete to sport and to continue to perform at the pre-injury athletic level presents one of the most important parameters for a successful outcome from articular cartilage repair in this challenging population. A thorough understanding of the basic science of the pathophysiology and molecular biology of articluar cartilage injury and repair specifically in athlete is critical for the medical staff attending to the athlete presenting with acute or chronic articular cartilage injury. The combination of a thorough basic science and clinical understanding of athletic cartilage injury will allow for optimization of the athlete's evaluation, treatment, rehabilitation, and ability to return to competition.

1.3

Return to Sport after Cartilage Repair: Opportunities and pitfalls for rehabilitation

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Introduction: In the athlete's perspective 'Return to sport participation after cartilage repair' is a key concern from onset of symptoms, surgery and throughout the full rehabilitation. Sport is their life and the sport is probably the 'heart' of the intimate social environment. Healthcare professionals should pay attention and open, appropriately communicate these concerns after cartilage repair. To strengthen counseling of the sometimes hard-to-handle expectations of athletes the following issues are highlighted: background on prevalence and injury mechanism, the current evidence on return to sport participation and opportunities and pitfalls for rehabilitation.

Content: Prevalence and injury mechanism. The prevalence of cartilage lesions in general population is estimated between 5 to 11%. In contrast, for recreational and professional athletes the prevalence of cartilage lesions is 35% [1]. Most cartilage defects (70%) are non-isolated. In the over 2 million sport participants injuring annually the anterior cruciate ligament (ACL) meniscal tears (60–70%), cartilage lesions (20%) and subchondral bone lesions (>80%) are common associated injuries. Subchondral bone lesions are recently associated with cartilage loss when repetitively highly loaded[2]. Chondrocyte apoptosis and production of catabolic factors affecting matrix structure may lead to early cartilage breakdown. Resulting, years later, in first signs of early joint degeneration. Also for isolated knee cartilage defects (30%) poor healing capacity is well documented. In a long-term study of Messner and Maletius, in athletes with severe isolated chondral knee injury, 75% of these athletes initially returned to sport. However a significant decline of athletic activity level and sports participation were observed 14 years after the initial injury. Although most patients continued to engage in individual fitness activities and were satisfied with their knee function, radiographic evidence of osteoarthritis was present in 57% of these athletes[3]. Similar results on increased risk for knee osteoarthritis are reported in high-demand, pivoting athletes[4],[5].

Prevalence figures after cartilage injury are more than double in subjects participating in high demanding sports compared to normal population. Although this points at direct biomechanical onset of cartilage injury it does not imply that overload or macro trauma with total joint involvement is the only possible start of local cartilage lesions. Genetic predisposition, improper motor control and training errors can result in cartilage to be more susceptible for injury. In vivo studies show increased concentrations of inflammatory cytokines and mediators in the joint in mechanically induced models of osteoarthritis and in vitro studies confirm that mechanical load is a powerful regulator of matrix metabolism, cell viability, and the production of pro-inflammatory mediators[6].

Current evidence on return to sport participation. Mithoefer and colleagues reported on 'Return to sports participation after articular cartilage repair in the knee ' in 2009[7]. Summarized, **average rates on return-to-sports activity** in the athletic population have been reported after microfracture (68%)[8], autologous chondrocyte transplantation (ACT) (74%)[9],[10],[11], osteochondral autologous transfer (91%)[12], and osteochondral allograft transplantation (88%)[13]. Overall return rates reported are superior for competitive athletes (71%-100%) than for recreational athletes (16%-29%). Return to competitive or professional football was observed in 100% after microfracture and 83% after ACI[9,14]. Irrespective of the surgical techniques the **return to play at pre-injury level** is 65% after cartilage repair. In contrast **timing to return** to sports depends in the cartilage repair techniques and rehabilitation. Time to return to sports was shortest after osteochondral autograft (7 months) and longest after ACI (17 months). In football, competitive players returned to play faster than recreational athletes (12 v. 22 months). Della Villa and colleagues showed that intensive, sports-specific rehabilitation was able to reduce the time to return to play after ACI. The rehabilitation included criteria based progression, isokinetic training and sport-specific on-field rehabilitation. The authors reported a faster recovery of previous activity level (8.6 months) and an earlier return to competition (10.6 months) compared with the controls (10.6 and 12.4, respectively). In cartilage repair the effect of histological tissue quality on return to play remains inconclusive, but a macroscopic superior repair tissue grade was associated with better rate of return to sport7,12,14,[15] ,[16] ,[17],[18],[19] . Next generation techniques, such as Matrix-associated (MACI) and scaffold-enhanced microfracture show similar rates for return to sports compared with the first-generation techniques7, 9,18,[20].

Opportunities and pitfalls for rehabilitation. An important window of opportunity for rehabilitation sets before surgery. In consistency with rehab after ACL reconstruction the functional status and restoration of local joint homeostasis before surgery is reflected in early postoperative recovery. "A good start is very valuable." For local knee cartilage lesions, depending on localization and size, exercising and consequently triggering local muscle power output, neuromuscular control and lower limb stability is frequently possible. Movement ranges, which involve no local stress on injured cartilage, are preferred to gain functionality. Often one can focus on possible compensatory mechanisms or movement disorders accompanying the onset of symptoms or lesion.

A typically pitfall is setting unrealistic goals in rehabilitation. Some factors have been shown to affect the ability return to sports after cartilage repair positively: age (<25yrs), duration of symptoms (<12months), lesion size (<2cm²), lesion type (contained), number of previous surgeries (low), athlete's skill level (high), concomitant procedures (no) and repair tissue morphology (good)[21]. Since 70% of cartilage lesions are non-isolated the 'average' patient starts often from a suboptimal initial situation. Representative a recent MRI study, focusing on morphological and biochemical cartilage changes after ACL reconstruction, showed reduced quality and resiliency of cartilage at 6 months after surgery compared to controls. In this study, patients were operated at 2,5 months (median) after injury and had no cartilage lesions at time of arthroscopy. Interestingly, the sooner surgery was performed, the more cartilaginous functional decline was apparent at 6 months after surgery. Surgery performed within a 2.5- to 6-month window led to recovery comparable with the control group [22]. So reports on fast recovery after cartilage repair should be viewed in a broader perspective.

Compliance to rehabilitation after cartilage repair is challenging to achieve in recreational athletes[23]. Dealing with the patient's coping strategy leads to another opportunity. Since knee pain persists longer than 3 months, chronicity of pain emerges. Occasionally pain-avoidance or a pain-persistence pattern can be observed. For the latter the athlete is active despite the pain, ignores limits, is non-accepting and demands cognitions about limitations. Both patterns require different approaches. Therefore it is helpful to recognize behavioral patterns to achieve realistic goals.

Few authors reported on the ability to continue to play after cartilage repair. Although durability of athletic activity was observed in 87% of athletes treated with ACT after 52 months, continued sports activity was only 53% after treatment using microfracture in athletes7,9,18. Mithoefer and Della Villa reported the best durability after ACI with 77% of athletes continued playing sports at the pre-injury level at 3 years after ACI[24].

Summarized sports participation years after cartilage repair can differ extensively. To rephrase the words of Neuman and colleagues on risk of OA after ACL reconstruction[25]: "Some individuals not able to participate in sports because of a knee injury may be more affected in their quality of life than affected by degenerative changes at radiography." By analogy of the previous, we need to look for ways to decrease the risk of OA after cartilage injury and repair; we should strive to provide our patients with the highest-quality surgery and rehabilitation available. Alongside optimizing functional outcome postoperatively, we must tackle as much as possible all possible factors leading to cartilage breakdown. Cartilage disorders can stay below subjects' perception. Therefore one should consider optimal strategies for better long-term outcomes. Luckily on the short-term, fitted sport participation yields both mental and physical health benefits of its own.

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1.4

Emerging Scientific Approaches for Management of Athletic Cartilage Injury

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

Content: Current surgical tactics for the treatment of symptomatic articular cartilage defects include palliative (arthroscopic debridement and lavage), reparative (marrow stimulation techniques), and restorative (osteochondral grafting, autologous chondrocyte implantation, etc.) approaches. The major challenge for all of them is the regeneration of normal functional mature hyaline cartilage that can sustain the load, resist compression, and most importantly, integrate with the host tissue. If the tissue is spontaneously repaired it usually fails to reproduce original structure and function, thus, making it more susceptible to re-injury. It is important to understand the underlying mechanisms of cartilage repair in order to create novel molecular mechanism-based treatment algorithms to promote chondral and/or osteochondral repair. For many years, our laboratory was involved in the biologic characterization of chondrocytes and cartilage tissue used for various surgical interventions, with the goal to identify means for their optimization and improvement. Here we will present our findings on cells and tissues sampled prior to autologous chondrocytes implantation (ACI), osteochondral allografting, and DeNovo neo-cartilage formation. Chondrocytes and cartilage specimens from these three surgical applications were tested for cell viability, metabolic activity, responsiveness to active agents (growth factors and cytokines), as well as the ability to form articular cartilage and maintain its structural integrity. In all these studies, the results were compared to fresh primary chondrocytes or cartilage tissues obtained from normal human donors within 24 hours of death.

Chondrocytes prepared for ACI transplantation were used for our studies after an initial 2-week expansion right before implantation. They were cultured either in monolayers or alginate beads and treated with insulin-like growth factor-1 (IGF-1), osteogenic protein-1 (OP-1), or a combination of the two. In monolayer culture unlike fresh primary chondrocytes, ACI cells changed their morphologic appearance within the first 4 hours and became elongated regardless of culture conditions, cell density, the presence or absence of serum, serum concentrations or the presence of growth factors. However, in alginate, they were able to maintain chondrocytic phenotype. Similarly to primary chondrocytes, growth factors, especially combined, promoted ACI cells survival (that was otherwise reduced in un-stimulated cells) and induced chondrocyte proliferation. Major differences between primary and ACI chondrocytes were found in their ability to respond to growth factors and produce an extracellular matrix. The largest extracellular matrix was laid out by the primary chondrocytes and especially when stimulated by the combination of OP-1 and IGF-1. This matrix was enriched in collagens type II and VI, aggrecan, decorin, and fibronectin. However, the same combination of growth factors or IGF-1 alone did not stimulate any noticeable matrix deposition by the ACI cells. Contrary, these cells only responded to the OP-1 treatment and synthesized some collagen type II and fibronectin, though, an overall amount of synthesized matrix by autologous chondrocytes determined by the size of matrix was much smaller than those produced by normal chondrocytes. Interestingly, the levels of proteoglycan synthesis were comparable between the two types of chondrocytes. The results obtained from this study point towards weaker phenotypic stability and reduced anabolic potential of ACI cells as compared to primary chondrocytes. The clinical implications of our findings might be a significant promise for anabolic growth factors in cartilage repair as a potential modifying therapy for the enhancement of chondrocytic phenotype of autologous chondrocytes.

The second study was aimed at understanding the survival potential and metabolic activity of refrigerated, prolong stored osteochondral allografts (OCA) in comparison to fresh cartilage (FC) grafts. Both types of tissues were subjected to impaction used for graft insertion and the catabolic cytokines present within an intra-articular environment. The following are the major findings of this study: 1) refrigerated, prolong stored allograft cartilage contains less viable cells and more apoptotic cells than fresh cartilage; 2) impaction that mimics surgical insertion revealed a stronger effect on cell survival than on cellular metabolism; this effect also predominated over the effect of cytokines and was evident for both OCA and FC; 3) on the contrary, cytokines tested in this study had no significant effect on chondrocyte viability but influenced chondrocytes' synthetic activity as measured by PG synthesis; 4) both insults resulted in the depletion of cartilage matrix; and 5) finally, storage for more than three weeks led to changes in the macroscopic appearance and integrity of allograft cartilage matrix, which may contribute to potential allograft failure. These studies added to our understanding of the biology of OCA and identified the most critical areas of concern: length of storage, impaction forces, and reduced chondrocyte viability. It appears that the state of the intra-articular environment, specifically, the presence of acute inflammation is not too big of an issue for this particular treatment option.

A third study was assessing the migratory and metabolic activity of juvenile cartilage prepared to be used for DeNovo method of neo-cartilage formation. Comparing juvenile cartilage with adult tissue of different ages no significant differences were identified in migratory and metabolic activities between juvenile and adult chondrocytes obtained from donors younger than 50 years old. Ability to migrate and form an extracellular matrix was reduced in cartilage from donors of older age. Knee chondrocytes revealed a higher migration rate than the ankle chondrocytes. In both juvenile and young adult cartilage tissues chondrocytes migration was initiated between 11 and 14 days of culture and the time of initiation was independent of the presence or absence of fibrin glue or serum concentrations. However, fibrin glue and high serum concentrations (20%) induced more massive migration from a greater number of cartilage pieces (about 3-fold difference in comparison to samples cultured without the glue and 10% serum; $p \leq 0.05$). It took about 40 to 45 days for a new matrix to cover the entire surface of the well from a 48-well plate. The majority of migrated cells remained viable and maintained a chondrocytic phenotype (round shape) throughout the culture. Newly formed tissue was very cellular and the appearance was similar between juvenile and adult samples. The levels of cumulative PG synthesis (original and neo-cartilage together) were comparable between juvenile and adult cartilage as well.

In conclusion, studies on clinical samples used for three surgical approaches enhanced our understanding of the biology of tissues and cells used to treat cartilage defects. We were able to unravel some underlying mechanisms responsible for the reparative ability of these tissues and cells. We also characterized the changes they undergo as a result of preparatory modifications. Furthermore, our findings identified specific technical parameters that need to be optimized in order to improve the outcomes of surgical interventions. Finally, the obtained results have broadened our understanding of cartilage tissue's potential, which should permit the development of strategies for targeted therapeutic treatments that in combination with surgical interventions could promote long-lasting cartilage repair, arrest or slow the subsequent development of PTOA.

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2.1.2

Clinical Spectrum of Cartilage Injury

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Introduction: It is well known that articular cartilage defects can cause pain, limitations in function and be a burden to the patient, possibly resulting in a impaired quality of life. But what is the spectrum of a cartilage injury? To understand this we should define the spectrum of a disease. Isaac Newton first used the term spectrum ('spectre', literally 'image apparition') in the 17th century to indicate a distinction arising from a quantitative continuum of distinct colours when a beam of white light is dispersed. A spectrum is defined by the Oxford dictionary as: 'a band of colours, as seen in a rainbow, produced by separation off the components of light by their different degrees of refraction according to wavelength' or 'a wide range'. As an illustration, Philips described a spectrum of disease for urinary tract infections (UTIs).[1]If a study is undertaken in an acute setting in children with similar alternative diagnosis and conditions (e.g. viral infections, avoiding school and symptoms of the urinary tract one could call this the disease spectrum of UTIs. In terms of pain, different characteristics such as types of pain (e.g. nociceptive, neuropathic, psychogenic), location and magnitude can form the spectrum of pain. In psychiatry a spectrum is a range of linked conditions with either a similar appearance or a syndrome composed of subgroups (e.g. autistic spectrum). Finally, and coming back to our field, osteoarthritis (OA) represents a disease spectrum of disease affecting different joints with a gradual increase in severity and a variety of symptoms such as pain, stiffness and loss of function.

Content: What about a cartilage injury? Is this a simple defect in an otherwise healthy joint or is it part of a disease continuum? In the past decades we have learned that cartilage defects are often associated with comorbidities of the joint such as meniscal injury, ligamentous instability and malalignment.[2]Indeed, patients with a ACL rupture have an increased risk of developing cartilage defects and OA.[3, 4]Recently it was found that ACL deficiency leads to early scaffold instability in an ex-vivo model.[5]This continuum of disease, could be a manifestation of a disturbed joint homeostasis.[6]In a cartilage injury, this disturbance is illustrated by an increase in markers such as interleukin-6[7]metalloproteinase-3 (MMP-3) and insukine like growth-I (IGF-1)[8], and mesenchymal stromal cells in the synovial fluid.[9]MMP-3 and IGF-I were still found to be elevated one year after cartilage repair.[10]Using a microarray, we have found sixty-six miRNAs that were differentially expressed between normal and OA cartilage. Modulating the expression of several of these miRNAs in defect derived chondrocytes resulted in more collagen type II and a higher proteoglycan content in the regenerated tissue. In addition, the synovial fluid of injured knee joints was found to impair chondrogenesis.[11]Schmal et al.[10]found aggrecan levels not to change in knee lavage fluids after cartilage repair while concentrations of bFGF, IL-1beta and IGF-I significantly increased. The observation that early treatment has an influence on clinical outcome also tells us that we are possibly influencing joint homeostasis.[12, 13]

What exactly is causing these changes to the joint homeostasis following a knee injury? This is a question we and many research groups ask and will keep asking. It is a highly relevant question as the patients referred to our specialized knee clinic generally do not have a single local defect in an otherwise perfectly healthy joint. Indeed, Engen et al. found that the heterogeneity of referred patients is not represented by randomized controlled trials in cartilage repair.[14]Earlier studies have shown the tendency of cartilage defects to progress to OA in time.[15, 16]The increased axial compression in the defect rim and shear in the opposing tissue underline the iomechanical changes following cartilage injury.[17, 18]In truth, we may not always realize that we are treating a disease spectrum, not a local cartilage defect. Again, the multiple approaches we and many others use in daily practice such as a combined ACL reconstruction or osteotomy and cartilage repair treatment, corroborate this view. Can a cartilage repair procedure influence the disease spectrum by itself? We should acknowledge that while it seems there is an increased risk of developing OA after a cartilage injury, it is not yet clear if we can prevent OA. In a recent review, albeit limited, we did find evidence that cartilage repair can be used in early OA with short-term success delaying the need for a total knee arthroplasty.[19]More recently, Bae et al.[20]found a survivorship of 88.8% at five years and 67.9% at 10 years after microfracture in patients with a mean age of 61 (range 40-75). The size of the cartilage defect and the severity of preoperative varus deformity seemed to influence clinical outcome. Undoubtedly, if we could transpose the success of cartilage repair to (early) OA treatment, it would have a great impact on our field. New research models targeting the joint homeostasis before and after treatment may help in this quest. The acknowledgement that a cartilage injury is part of a spectrum, could make it easier for us when assessing our patients and designing our research models. The road ahead of us is long, but ever more exciting and could eventually provide a treatment for the entire spectrum of an articular cartilage injury.

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2.1.3

Adapting Therapeutic Concepts to Cartilage Injury Severity

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Introduction: The hyaline cartilage fulfills important function of the knee joint. Cartilage injuries, which can occur during car accidents or sport injuries, have the potential to degenerate further with the onset of osteoarthritis.

For many years, due to absent treatment options, cartilage injuries were left untreated and patients had to deal with the endogenous degeneration process of the cartilage layer leaving a painful bone-bone interface in the osteoarthritic knee joints. A huge number of patients were taught that they have to wait getting old enough for a total knee replacement.

This has completely changed. In the last 20 years, a variety of successful treatment options for local cartilage defects were developed, which allow early regeneration of the cartilage and, therefore, delay or prevention of the endogenous osteoarthritic degeneration process.

The selection of the most promising treatment procedure for a specific patient depends on the cartilage injury itself (defect size, defect depth), the demand of the patient and on additionally existing joint injuries like ligament instabilities, meniscus tears, defects to the subchondral bone and/or axis deformation of the leg (e.g. varus, valgus). These additional joint injuries or joint deformations have to be addressed in a multimodal regenerative joint therapy in order to achieve successful treatment of the cartilage lesion.

Content:

No treatment of cartilage lesions

Not all cartilage injuries need treatment. According to the ICRS classification, cartilage injuries grade I and II, partial thickness injuries to the cartilage, can mainly left untreated without progression to osteoarthritis in long-term. From the literature we learned that not all cartilage injuries progress to osteoarthitis, however the risk increases significantly with cartilage defect size. Therefore, especially cartilage defects grade I, II and even grade III with a defect size smaller than 1cm² don´t need surgical treatment. Another important aspect for treatment necessity should be the presence of symptomatic cartilage defects. Knowing that cartilage is a tissue without nerval structures this aspect seems to be abstruse. However, the cartilage injury, which is combined with marked reduction in cartilage function will result in symptomatology through inflammation of the surrounding tissue (synovium) and increased mechanical load to the subchondral layer (oedema, bone bruise, fracture).

Conservative treatment of cartilage lesions

For conservative treatment of cartilage lesions physiotherapy, a variety of intraarticular or orally administered drugs and orthotics, e.g. insoles and braces are available. Physiotherapy have shown to significantly reduce symptoms of cartilage damage and osteoarthritis. Physical therapy (cold-, heat application, lymph drainage, ultrasound) can reduce significantly inflammation of the joint capsule, of tendons and their insertions. Non steroidal antiphlogistic drugs, e.g. diclophenac, reduce joint pain and joint inflammation. They can be used as a good therapeutic additive acutely after trauma or after surgical treatment. A variety of intraarticular or orally administered cartilage drugs and nutritional supplements are available on the market. In small case series a modulation of clinical symptoms was recorded. However they have not proven significant impact on efficacy in randomized trials. Nevertheless they seem to fail to achieve regeneration of the cartilage defects.

Refixation of hyaline cartilage

Patella luxations are often accompanied with osteochondral flakes due to shear load to the joint surface during luxation and reposition of the patella. In the acute case, these fragments can be placed into the defect and fixed with resorbable pins. The successful cartilage regeneration is dependent on the solid connection of the cartilage bone interface in the defect. In the subacute and chronic case, the osteochondral flakes are deformed and solid placement of the flakes in the defects cannot be achieved. Successful refixation is dependent on the osseous part of the flake, however refixation of chondral flakes with minimal osseous layer can be achieved.

Tissue Response method

During joint arthoscopy, cartilage defects can be treated with tissue response procedures, e.g. microfracture. For sucessfull application of the microfracture technique, the surgeon has to create stable cartilage defect rims and has to remove the calcified subchondral layer at the bottom of the cartilage defect side. Then, with drills or chisels, the subchondral bone plate is penetrated in 3-4 mm distance from each other. This leads to the outflow of blood, which brings regeneration cells (stem cells) and growth factors to the defect area. It is important to control successful penetration of the subchondral plate during arthroscopy. Microfracture is especially suitable for small chondral defects (<2cm²). The technique allows the creation of fibrocartilaginous repair tissue, which has minor biomechanical stability compared to native cartilage. After initial clinical improvement, the clinical scores show a moderate reduction after 3-5 years after microfracture. Microfracture was used ubiquitary for cartilage defects of different size because of its easy, cheap and arthroscopic application and its low risk for complication. However, recently, a complication rate of up to 50% was recorded with intralesional osteophytes, subchondral sclerosis and subchondral cysts. In order to increase the cell number in the defect, Tissue Response technology, e.g. microfracture, can be combined with the use of biomaterials, which cover the cartilage defect. Whether this will improve the results of microfracture in terms of tissue quality, clinical outcome and reduction of complications has still to be proven in randomised clinical trials. In the follow-up treatment, load has to be reduced in the treated cartilage defect. Cartilage defects in the weight bearing zone are treated with 15kg of partial weight bearing commonly for 6 weeks. For microfracture application in the patellofemoral compartment the knee flection is restricted to 60° for 6 weeks postoperatively. Improved regeneration of neocartilage has been reported after the postoperative use of continuous passive motion (CPM), which is administered for 4-6 weeks postoperatively.

Osteochondral transplantation (OCT)

In OCT, osteochondral transplantation, cartilage-bone-cylinders were taken from destinct areas and transplanted in the defect area. The cylinder requires a sufficiently large bone component in order to consolidate in the defect. This cartilage treatment method allow the transfer of high-value hyaline cartilage in the defect. However, the spaces remaining between the cylinders are covered with an inferior scar tissue. The results are good with this procedure, however healthy cartilage areas are destroyed at the donor side. In order to reduce donor side morbidity, the OCT should be used only in cartilage defects smaller than approximately 3cm². Especially for small **osteochondral** defects this method allows a successful treatment option of the osseous and chondral defect with one technique. Recently, cell-free plugs are available in order to treat chondral or osteochondral defects without donor side morbidity, however the sucess- and complication-rate is not yet available.

Chondrocyte transplantation (ACT)

For more than 15 years, autologous chondrocyte transplantation is used successfully for reconstruction of full thickness cartilage or osteochondral defects larger than 3-4cm². A localized cartilage damage and not osteoarthritic joint surfaces must exist for successful treatment with ACT. Especially suitable is the ACT method for patients between 18 and 50 years. The chondrocyte transplantation can be combined with biomaterials, e.g. NOVOCART® 3D procedure (TETEC, Aesculap). A small quantity of cartilage is taken during a knee arthroscopy from the patient. In certified laboratory the chondrocytes are removed out of the cartilage and then amplified. After the necessary cell number is reached, the cartilage cells are loaded into three-dimensional biomaterials in order to keep the chondrogenic morphology of the chondrocytes. Inside the biomaterials, the cells begin already with the production of new cartilage extracellular matrix. Before the chondrocyte-biomaterial construct is implanted in the patient`s cartilage defect, a thorough analysis for vitality, sterility of the cells and the capacity of the chondrocytes to form hyaline cartilage is performed. Three to six weeks after the cartilage harvest, the chondrocyte-biomaterial construct is transplanted into the cartilage defect in a minimally invasive surgery. The rehabilitation after chondrocyte transplantation includes a long-term partial weight bearing period of up to 10 weeks and the use of "continuous passive motion" (CPM). The regeneration of the cartilage takes place over several years.

Multimodal joint therapy – reason for successful cartilage therapy

Successful cartilage therapy is to be expected only with simultaneous handling of the concomitant injuries (ligament tears, meniscus tears, subchondral defect). Unstable knee joints increase the shear forces in a knee joint dramatically leading to a failure of the cartilage procedure. Also pathological load due to deformities in the leg axis (valgus or varus deformity) has to be corrected with osteotomies in order to lead the cartilage regeneration to success. Varus or valgus deformity of more than 5° should be addressed. Subchondral bone defects, e.g. in osteochondritits dissecans, has to be treated prior to chondrocyte transplantation. Bone grafts, mainly from the iliac graft will be implanted in the osseous defect prior or together with the chondrocyte transplantation.

Late stage cartilage treatment – Osteotomy and knee replacement

The treatment options during late stage cartilage treatment are osteotomies and knee replacement procedures. After onset of osteoarthritis, cartilage regeneration cannot be achieved. Osteotomies can reduce clinical symptoms by load reduction in a osteoarthritic knee compartment. Especially for active patients younger than 60 years this treatment procedures seems to be promising. The alternative is part or total knee replacement depending on the amount and location of the degeneration. In summary, modern cartilage therapy has a variety of conservative and surgical treatment options available. The selection of the most promising treatment procedure for a specific patient depends on the cartilage injury itself, the demand of the patient and on additionally existing joint injuries. These additional joint injuries (e.g. ligament injury) or joint deformations (e.g. deformation of leg axis) have to be addressed in a multimodal regenerative joint therapy in order to achieve successful treatment of the cartilage lesion. The biologic cartilage treatment of localized has to be performed as early as possible in order to regenerate cartilage and delay or prevent osteoarthritis. After onset of osteoarthritis, osteotomies and knee replacement allow treatment options for pain reduction and increase in quality of life.

References:

Cartilage literature last 20 years

2.2.1

In situ Froming Oxidized Hyaluronic Acid Hydrogel for Nucleus Pulposus Regeneration

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Introduction: Encapsulation of nucleus pulposus (NP) cells within in situ forming hydrogels is a novel biological treatment for early stage intervertebral disc degeneration. The procedure aims to prolong the life of the degenerating discs and to regenerate damaged tissue. In this study, we developed an injectable oxidized hyaluronic acid-gelatin–adipic acid dihydrazide (oxi-HAG-ADH) hydrogel. High molecular weight (1900 kDa) hyaluronic acid was crosslinked with various concentrations of gelatin to synthesize the hydrogels and their viscoelastic properties were analyzed. Interactions between the hydrogels, NP cells, and the extracellular matrix (ECM) were also evaluated, as were the effects of the hydrogels on NP cell gene expression. The hydrogels possess several clinical advantages including sterilizability, low viscosity for injection, and ease of use. The viscoelastic properties of the hydrogels were similar to native tissue, as reflected in the complex shear modulus (11~14 kPa for hydrogels, 11.3 kPa for native NP). Cultured NP cells not only attached to the hydrogels but also survived, proliferated, and maintained their round morphology. Importantly, we found that hydrogels increased NP cell expression of several crucial ECM-related genes, such as COL2A1, AGN, SOX-9, and HIF-1A.

Content:

Materials Preparation: HAG polymers were prepared by EDC/NHS chemical crosslinking (Tang et al., 2007). A series of 0.025, 0.25, and 0.5 mg/mL gelatin solutions were prepared by dissolving gelatin in 400 mL double-distilled water (DDW) at 60°C. HA at 5 mg/mL was then added to the solutions, which were stirred overnight at room temperature to generate HAG1 (5 mg/mL HA, 0.025 mg/mL gelatin), HAG2 (5 mg/mL HA, 0.25 mg/mL gelatin), and HAG3 (5 mg/mL HA, 0.5 mg/mL gelatin) solutions. Crosslinking was performed by adding EDC and NHS at a molar ratio of 2:1 to the HAG solutions for 30 min. The reactions were terminated by the addition of 5 mL glycine (40 mg/ml). The solutions were dialyzed to remove byproducts, and the final HAG1, HAG2, HAG3 polymers were obtained by lyophilization (FDU-1200, EYELA, Tokyo, Japan). Spectrum 100™ FT-IR (PerkinElmer, Massachusetts, USA) with a universal attenuated total reflectance accessory (UATR) was used to identify the functional groups of the polymers. HA and HAG polymers were dissolved in DDW at room temperature and oxidized with sodium periodate as previously described (Su ***et al.***, 2010). Briefly, 400 mL of 5 mg/mL polymer solution was gently mixed with 10 mL of sodium periodate (2.67%) and kept in the dark for 24 h. Ethylene glycol was added to stop the oxidation reaction. The final oxidized HA or HAG polymers (oxi-HA, oxi-HAG1, oxi-HAG2, and oxi-HAG3) were obtained by dialysis and lyophilization. Spectrum 100™ FT-IR with UATR was used to confirm the oxidation results.

Results & Discussion: Gene expression was measured in NP cells cultured in hydrogels for 7 days (Fig. 1). The mRNA levels of HIF-1A and SOX-9 were increased significantly in hydrogel-cultured cells compared with monolayer-cultured cells ($p < 0.05$). There was no significant difference in HIF-1A gene expression among the hydrogel-cultured groups. Levels of SOX-9 mRNA were significantly lower in the cells cultured in oxi-HA-ADH and oxi-HAG3-ADH than in oxi-HAG1-ADH hydrogel (12.76 ± 0.1, $p < 0.05$). The highest SOX-9 mRNA level was found in cells cultured in the oxi-HAG2-ADH hydrogel (20.82 ± 3.36, $p < 0.05$). Fig. 1B shows the expression of small leucine-rich protein (SLRP)-related genes. BGN and DCN mRNAs were increased significantly in

the hydrogel-cultured cells compared with the monolayer-cultured cells ($p < 0.05$). NP cells cultured in oxi-HAG1-ADH, oxi-HAG2-ADH, and oxi-HAG3-ADH hydrogels expressed much more DCN mRNA that those cultured in the oxi-HA-ADH hydrogel ($p < 0.05$). Moreover, the level of BGN was significantly higher in the oxi-HAG2-ADH hydrogel-cultured group (65.04 ± 12.83) than in other groups ($p < 0.05$). Fig. 1C shows the expression of ECM-related genes. AGN and COL2A1 mRNA levels were increased significantly in the hydrogel-cultured cells compared with monolayer-cultured cells ($p < 0.05$). Among the hydrogel groups, the highest AGN expression was observed in NP cells cultured in the oxi-HAG2-ADH hydrogel. AGN is the major proteoglycan of the IVD and is responsible for maintaining tissue hydration through osmotic pressure. The level of COL1A1 mRNA was decreased significantly in cells cultured on the hydrogels compared with monolayer-cultured cells ($p < 0.05$).

Conclusion: Encapsulation of NP cells in in situ forming hydrogels is a novel biological treatment for early stage IVD degeneration. In the present study, oxi-HAG2-ADH in situ forming hydrogel was developed using high molecular weight hyaluronic acid and gelatin. The hydrogel possesses several advantages such as sterilizability, low viscosity for injection, and ease of use. The shear modulus of the hydrogel was

similar to native NP tissue. The hydrogel was biocompatible; encapsulated NP cells not only survived but also proliferated well. Importantly, the oxi-HAG2-ADH hydrogel also activated NP cell synthesis of COL2A1, AGN, SOX-9, BGN, DCN, and HIF-1A mRNA. Taken together, these results indicate that oxi-HAG2-ADH is a promising hydrogel for future application in the treatment of early stage IVD degeneration.

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2.2.2

Hydrogels versatile Scaffolds for Cartilage Repair

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Introduction: Whilst durable repair of articular cartilage defect still remains a challenge, hydrogel materials do offer a unique opportunity to provide an extracellular matrix-like environment with the opportunity for restoration of articular cartilage defects. Since hydogels are hydrophilic polymer networks with high water content (>80%), they can mimic the native chondrocyte environment and induce the typically spherical appearance of these cells even when they have been expanded (1). However, the design of optimal hydrogel biomaterials to fully restore the chondrocyte phenotype and guide cartilage regeneration is still a challenge in the field (2, 3). A suitable hydrogel obviously must be biocompatible, foster abundant matrix accumulation that resembles the original hyaline cartilage, i.e. a tissue rich in collagen type II and aggrecan and matrix should be spread throughout the hydrogel, rather than concentrated in the pericellular regions. It should degrade at an appropriate rate, and through appropriate mechanisms. Moreover the hydrogel must be sufficiently strong to withstand the stresses within the mechanically challenging environment of the joint, which can be 5 MPa or higher (4, 5). Also, it should ideally facilitate the regeneration of the complex zonal organization of native cartilage. Finally, and critically, it must be practical to use it in a clinical setting: it must be sterilizable, easy to handle, and crosslink relatively rapidly.

Content: Hydrogels can be fully synthetic, allowing for the tailoring of their physical characteristics. These hydrogels provide embedded cells with an inert environment without active binding sites, often resulting in low cell viability. In order to improve control over cellular differentiation in these gels, bioactive compounds have to be added or grafted to the network, like peptide sequences and growth factors. Peptide sequences can modulate cellular behavior by providing binding sites in otherwise inert hydrogels, whereas growth factors can further direct cellular differentiation in order to regenerate a specific tissue type. However, historically, hydrogels used in cartilage tissue engineering applications are predominantly based on naturally derived polymers, including alginate, gelatin, collagen, chitosan, fibrin and hyaluronic acid. Cells benefit from the abundance of chemical signals present in these hydrogels, resulting in high viability and proliferation rates. These signals can also be used to induce the formation of specific neo-tissues, but due to batch-to-batch variation and the sensitivity of cells these variations, reproducibility of constructs can remain complicated.

Gelatin is a naturally derived hydrogel and is produced by the hydrolysis of ECM-derived collagens, predominantly type I. Chemical modification can produce gelatin methacrylamide (Gel-MA), which can be crosslinked in the presence of a photoinitiator and light. Gel-MA hydrogels are gaining popularity as biomaterials, since they are enzymatically degradable, support the formation of new ECM, can be produced at low cost, are potentially injectable, and are easily crosslinked under physiological conditions. In previous work, Gel-MA hydrogels have been identified as a potentially useful biomaterial for cartilage tissue engineering (6, 7). Gel-MA hydrogels support the deposition of new matrix, however the composition of the new matrix is more akin to fibrocartilage than articular cartilage, consisting of both collagen types I and II. Functionalization with specific cartilage ECM components can enhance the chondrogenic differentiation of cells embedded within hydrogels. For example, we observed that chondrocyte behaviour in Gel-MA-based was influenced by the by the incorporation of two of the most abundant glycosaminoglycans (GAGs) into the hydrogels: hyaluronic acid (HA) and chondroitin sulfate (CS), to generate biomimetic hydrogels for cartilage tissue engineering. We have shown that with the addition of small quantities of photo-crosslinkable HA-MA, and to a lesser extent CS-MA, chondrogenesis and mechanical properties of the tissue engineered constructs can be enhanced. The addition of HA-MA resulted in more rounded cell morphologies, enhanced chondrogenesis, and increased distribution of the newly synthesised matrix throughout the construct. Compressive moduli also increased and were further in enhanced for constructs containing CS-MA.

The combination of hydrogels that can direct specific differentiation of embedded cells with biofabrication approaches offer the opportunity to address the specific zonal organization of native (osteo)chondral tissue (8). With biofabrication three-dimensional tissue-like structures composed of materials and cells can be manufactured in a single manufacturing procedure. Cell-laden hydrogels are commonly used in biofabrication and are termed “bio-inks”. However, while advances have been made in modifying these hydrogel-based systems for enhanced bioactivation, cell survival and tissue formation, little attention has so far been paid to optimize hydrogels for the physico-chemical demands of the biofabrication process. Although hydrogels are intrinsically weak biofabrication allows for the simultaneous deposition of reinforcing fibers to improve overall implant mechanical properties (9). Nevertheless, biofabrication is still in its infancy and multiple issues, including the lack of specific hydrogel bioinks (10), still need to be addressed in order to bring this technology from the bench to the bedside.

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2.2.3

Engineering Developmental Signals into Hydrogels for Cartilage Repair

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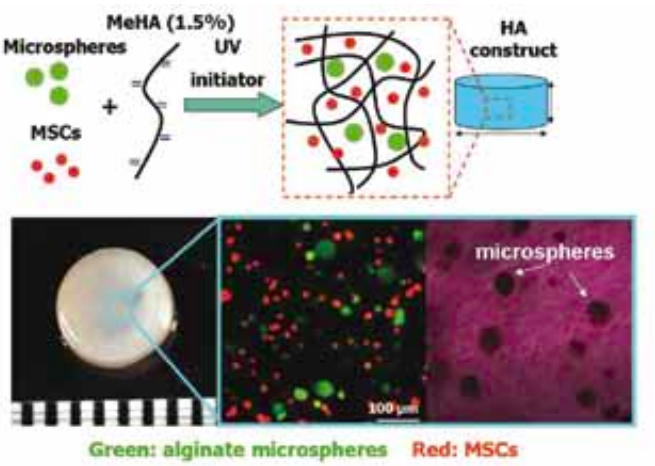
Introduction: Articular cartilage lines the surfaces of joints and transmits the forces generated with loading. Erosion of articular cartilage as a consequence of injury or degenerative diseases is extremely prevalent, causing considerable pain and loss of mobility in a wide segment of the adult population [1]. Limited by its poor healing capacity, and given the increasing incidence of osteoarthritis, there exists a growing demand for cell-based strategies for repair. Cartilage tissue engineering (TE) has emerged as an alternative to these current clinical approaches. In cartilage TE, chondrocytes (or a chondrogenic cell source) are combined with a scaffolding material to sequester cells and capture accumulated ECM, forming a cartilage-like replacement tissue. A wide variety of scaffold approaches have been investigated (for review, see [2,3]). Further work has shown that inclusion of anabolic growth factors normally found in the maturing and mature synovial fluid (such as IGF-1, TGF beta family members, and FGF) can further improve cartilage-like tissue development in engineered constructs [4-5].

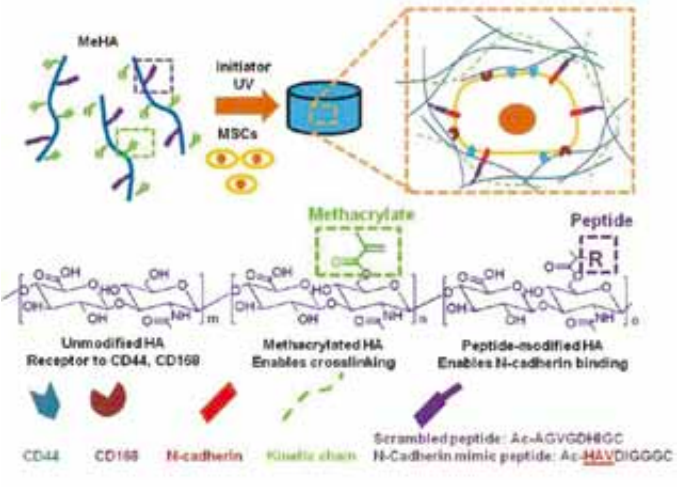
Our laboratory is interested in the creation of developmental microenvironments to foster the initial differentiation and the subsequent functional maturation of these engineered constructs, using mesenchymal stem cells (MSCs) and hydrogels derived from the cartilage extracellular matrix (ECM) constituent, hyaluronic acid (HA). The most common method to fabricate HA gels is to add a methacrylate group to the HA backbone and use a photopolymerization process to encapsulate cells. These gels also provide initial receptor-matrix binding as well as controlled mechanics and degradation. Our governing hypothesis is that such materials can promote the initial commitment to phenotype, and the culture environment can be further tuned to enable and advance maturation. Three major areas that we are investigating are (1) the delivery of growth factors (i.e., TGF beta 3) that stimulate MSC chondrogenesis, including as implantable constructs, (2) the influence of culture environments, such as cell density and mechanical loading on chondrogenesis, and (3) the importance of gel chemistry and inclusion of biological signals on chondrogenesis. With respect to this final topic, we have now begun to consider the introduction of additional cues present in the microenvironment during cartilage development. For example, during early cartilage formation in the limb bud, cell-cell interactions are mediated by N-cadherin signaling rather than through the ECM [6]. As with soluble cues, N-cadherin mediated signaling is present only over a short time, and is replaced as accumulated ECM begins to mediate biophysical signaling from the microenvironment. Thus, this represents a viable target for material modification to alter MSC response.

Content: Due the recognition of MSCs as a viable cell source for cartilage repair and members of the transforming growth factor-beta (TGF-β) superfamily being a key mediator of MSC chondrogenesis, we developed delivery systems for TGF-ß [7]. While TGF-β mediated MSC chondrogenesis is well established with in vitropellet or hydrogel cultures, clinical translation will require effective delivery of TGF-βs in vivo. In this first study, we investigated the co-encapsulation of TGF-ß3 containing alginate microspheres with human MSCs in HA hydrogels towards the development of implantable constructs for cartilage repair (see Figure). TGF-β3 encapsulated in alginate microspheres with nanofilm coatings showed significantly reduced initial burst release compared to uncoated microspheres, with release times extending up to 6 days. HA hydrogel constructs seeded with MSCs and TGF-ß3 containing microspheres developed comparable mechanical properties and cartilage matrix content compared to constructs supplemented with TGF-β3 continuously in culture media, whereas constructs with TGF-β3 directly encapsulated in the gels without microspheres had inferior properties. When implanted subcutaneously in nude mice, constructs containing TGF-β3 microspheres resulted in superior cartilage matrix formation to groups without TGF-ß3 or with TGF-ß3 added directly to the gel. However, calcification was observed in implanted constructs after 8 weeks of subcutaneous implantation. This study demonstrates that the controlled local delivery of TGF-β3 is essential to neocartilage formation by MSCs and that further optimization is needed to avert the differentiation of chondrogenically induced MSCs towards a hypertrophic phenotype. There is growing evidence that mechanical signals play a critical role in the regulation of MSC chondrogenesis and in cartilage development. In this second study, we investigated the effect of dynamic compressive loading on chondrogenesis, the production and distribution of cartilage specific matrix, and the hypertrophic differentiation of human MSCs encapsulated in HA hydrogels during long term culture [8]. After 70 days of culture, dynamic compressive loading increased the mechanical properties, as well as the GAG and collagen contents of HA hydrogel constructs in a seeding density dependent manner. The impact of loading on HA hydrogel construct properties was delayed when applied to lower density (20 million MSCs/ml) compared to higher seeding density (60 million MSCs/ml) constructs. Furthermore, loading promoted a more uniform spatial distribution of cartilage matrix in HA hydrogels with both seeding densities, leading to significantly improved mechanical properties as compared to free swelling constructs. Using a previously developed in vitro hypertrophy model, dynamic compressive loading was also shown to significantly reduce the expression of hypertrophic markers by human MSCs and to suppress the degree of calcification in MSC-seeded HA hydrogels. Findings from this study highlight the importance of mechanical loading in stem cell based therapy for cartilage repair in improving neocartilage properties and in potentially maintaining the cartilage phenotype.



With regards to the gel chemistry, HA hydrogels provide a backbone polymer to which MSCs can interact through several cell surface

receptors that are expressed by MSCs, including CD44 and CD168 (see Figure). Previous studies [9] showed that this 3D hydrogel environment supports the chondrogenesis of MSCs, and here we demonstrate through functional blockade that these specific cell-material interactions play a role in this process. Beyond matrix interactions, cadherin molecules, a family of transmembrane glycoproteins, play a critical role in tissue development during embryogenesis, and N-cadherin is a key factor in mediating cell-cell interactions during mesenchymal condensation and chondrogenesis [6]. In this third study, we functionalized HA hydrogels with N-cadherin mimetic peptides and evaluated their role in regulating chondrogenesis and cartilage matrix deposition by encapsulated MSCs [10]. Our results show that conjugation of cadherin peptides onto HA hydrogels promotes both early chondrogenesis of MSCs and cartilage specific matrix production with culture, compared to unmodified controls or those with inclusion of a scrambled peptide domain. This enhanced chondrogenesis was abolished via treatment with N-cadherin specific antibodies, confirming the contribution of these N-cadherin peptides to chondrogenesis. Subcutaneous implantation of MSC-seeded constructs also showed superior neocartilage formation in implants functionalized with N-cadherin mimetic peptides compared to controls. This study demonstrates the inherent biologic activity of HA-based hydrogels, as well as the promise of biofunctionalizing HA hydrogels to emulate the complexity of the natural cell microenvironment during embryogenesis, particularly in stem cell-based cartilage regeneration. Most recently, we have recognized the importance of the temporal properties of the cadherin signal and have designed hydrogels where the peptide is linked through a sequence that is cleavable by the enzyme ADAM-10, which cells use to cleave N-cadherin during development.



These three studies illustrate the importance of the hydrogel environment to regulate features of MSC chondrogenesis and the development of neocartilage using tissue engineering principles. Next steps are to assess the utility of such approaches in large animal studies in clinically relevant animal models.

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2.3.1

Evolution of Minimally Invasive Cartilage Repair

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Introduction: Advances in device technology, materials science and cell and molecular biology have helped improve the delivery of articular cartilage repair into clinical practice. This presentation will summarize how articular cartilage repair strategies have evolved since the early days of Pridie drilling and abrasion arthroplasty, to the latest technological advances utilizing the paradigm of tissue engineering as a working platform.

Content: One can look at the evolutionary process of minimally invasive cartilage surgery meaning either that pertaining to the surgical approach, or alternatively in terms of the morbidity incurred to the patient. If you take autologous chondrocyte transplantation as an example, the technique has evolved quite considerably since the first case in 1987. Following arthroscopy and biopsy, the second stage involved harvesting a periosteum patch from the anteromedial tibia, requiring a more extensive surgical exposure, and improved access to the joint surface to allow easy suturing of the patch to the perilesional cartilage. Currently, 3rd generation ACI techniques can be performed arthroscopically, utilizing 3D matrices, which have been cultured with chondrocytes in-vitro, implanted under inert gas arthroscopy, and held in place using fibrin glue or similar[1;2].

Bone marrow stimulation techniques have also evolved. Abrasion arthropasty and Pridie drilling have largely given way to microfracture. Possibly the ultimate in minimally invasive procedures, this cheap, relatively technically easy to perform procedure has had problems with maintenance of long term clinical outcome, often related to the inferior tissue quality which it produces[3]. As a result, it has evolved in an effort to improve on tissue composition and clinical outcome. The so-called augmented microfracture techniques such as autologous matrix induced chondrogenesis (AMIC)[4], which were mostly performed in an open fashion, can now be performed in arthroscopic manner much the same as matrix assisted chondrocyte implantation (MACI; Sanofi, Paris). However, newer technological advances in materials such as the chitosan based BST Cargel (Piramal Healthcare, Mumbai, India) have allowed for the ability to implant a scaffold again under gas arthroscopy, with no further fixation device being required. This has resulted in improvements in tissue quality over microfracture alone, as assessed by biopsy and MRI in a large multicenter randomized clinical trial[5]. Similar delivery techniques have been developed for Biocartilage (Arthrex Inc. Naples FL), a micronized allograft cartilage matrix which can be injected over a microfractured defect. However, as yet only preclinical animal data exists, with clinical results awaited in the future. To date, no randomized clinical trials of augmented microfracture compared to cell based therapies such as ACI has been performed.

Osteochondral autograft transplant (OATS) has witnessed the development of new single use devices, with improved methods to assist in arthroscopic harvest perpendicular to the joint surface and

subsequent delivery. However, multiple plugs for larger defects, such as is the case in mosaicplasty, often require a greater exposure and have the unwanted side effects of donor site morbidity. A number of manufacturers have developed off the shelf osteochondral scaffolds, which can be implanted arthroscopically. Unfortunately, in some cases the material properties have not been optimal, and some published results have been poor[6]. It is therefore important to choose your treatment modality not on ease of use or minimal exposure, but on clinical outcome.

In an attempt to lesson the morbidity incurred by patients, a number of cell based therapies have been refined to patient side, one-stage procedures. Bone marrow aspirate concentrate has been utilized as a patient sided treatment, but this one stage cell based therapy may be minimally invasive from a standpoint of the surgical approach, however the bone marrow aspiration has the potential of increasing perioperative morbidity. Although this has been studies extensively in horses[7], minimal long term data exist as to its efficacy in man[8]. Further results are awaited. Novel treatments such as that delivered by CellCoTec (Netherlands) are currently under investigation in Europe. This patient side co culturing system of chondrocytes and bone marrow aspirate are added together on a proprietary osteochondral scaffold in the operating room then implanted. This reduces the need for two stage treatments, therefore reducing patient morbidity, however it remains to be seen if good quality repair tissue results. Ultimately, these procedures require large multicenter clinical trials to prove efficacy, an area which is fraught with difficulty. Cartilage Autograft Implantation System (CAIS, Johnson & Johnson) showed promise in preclinical animal studies[9] and clinical case series[10]. However, its development was abandoned due to financial constraints of running a large multicenter study to gain FDA approval, which highlights the difficulties of bringing similar cartilage repair technologies to the market.

With all of these new techniques, which have appeared on the market over the last two decades, it is of utmost importance that we strive to improve cartilage repair and patient clinical outcome. However, this should not be affected by a growing search for easier, less invasive ways to implant new technology. In many cases of articular cartilage disease, there is significant co-morbidity such as ligament instability, malalignment and meniscus deficiency. It is widely accepted that these should be corrected prior to any biological articular cartilage repair strategy performed, and done so in as an invasive manner as is required to achieve optimal results.

It is therefore likely that in the future, the most minimally invasive articular cartilage repair process will be one of prevention of disease, particularly in the filed of post traumatic osteoarthritis and development of degenerative disease. New disease modifying drugs are on the horizon and are being tested worldwide. It is likely that a combination of procedures which correct biomechanical abnormalities augmented with a novel biologic, administered in the early phase of disease will be the key to success for long term successful treatment. However, significant financial hurdles remain meaning novel methods of navigating the regulatory pathways are required, to ensure patient safety, procedure efficacy and cost effective manufacture and delivery.

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2.3.2

Reducing Invasiveness of Adjuvant Procedures

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Introduction: Surgical treatment of symptomatic articular cartilage lesions in the knee requires concomitant strategies to address malalignment, meniscal deficiency, and/or ligamentous instability. Innovations and improvements in surgical techniques and implants now permit minimally-invasive surgery with significant improvements in clinical outcomes. Further, single-staged all-arthroscopic and/or mini-arthrotomy proce-dures are now being used for marrow stimulation techniques and cell-based therapies with the use of various augments and scaffolds.

Content: Surgical decision-making for symptomatic chondral and osteochondral defects in the knee is multifactorial and controversial. Surgeons treating these lesions must avoid linear reasoning and "treat the patient" and not just the presence of a defect on MRI or arthroscopic picture. All concomitant injuries must be addressed either simultaneously during treatment of the articular cartilage or sequentially in a staged fashion: Meniscal repair or transplantation in the setting of meniscal tear or deficiency; realignment osteotomy in the setting of malalignment (tibial tubercle anteromedialization Fulkerson osteotomy for patellofemoral compartment; valgus-producing high tibial osteotomy for varus or varus-producing distal femoral osteotomy for valgus); and ligamentous reconstruction (e.g. ACL) in the setting of instability.

Advancements in articular cartilage surgical techniques now permit minimally-invasive access to most areas within the tibiofemoral and patellofemoral compartments. Augmented marrow-stimulation techniques such as autologous matrix-induced chondrogenesis (AMIC) and juvenile micronized allograft cartilage matrix may enhance microfracture biology. These techniques may be performed with use of a scaffold and via mini-arthrotomy or all-arthroscopically. Osteochondral autograft techniques may be performed all-arthroscopically. Osteochondritis dissecans fragments may be internally fixed with arthroscopic techniques and bioabsorbable screw fixation to avoid a second surgery for hardware removal. Juvenile minced articular cartilage cell therapies may be placed through a mini-arthrotomy, as can traditional and newer chondrocyte- and stem cell-based therapies. All-inside meniscal repair devices now preclude larger accessory incisions for inside-out repair and the associated potential risks. Meniscal transplantation is now commonly performed using an arthroscopic-assisted anterior mini-arthrotomy technique. Tibiofemoral unloading osteotomy techniques may now be performed with minimal incisions and smaller, lower-profile locking plate technologies. Ligamentous reconstruction and patellofemoral osteotomies utilize traditional open strategies. Utilization of both validated patient-reported and surgeon-measured outcome measures, the addition of concomitant procedures improves cartilage restoration outcomes.

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2.3.3

Arthroscopic Transplantation of Synovial MSCs for Cartilage Regeneration

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Introduction: See Content.

Content: [Comparison of human stem cells derived from various mesenchymal tissues] Mesenchymal stem cells (MSCs) are a fascinating source for regenerative medicine for cartilage. There are increasing reports that MSCs can be isolated from various adult mesenchymal tissues. We performed a patient-matched quantitative comparison of the properties of human MSCs isolated from bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue. Human mesenchymal tissues were obtained from 8 donors during knee surgery for ligament injury. After collagenase digestion or gradient-density separation, nucleated cells were plated at an appropriate density for expansion at the maximum rate without colony-to-colony contact. Yield, expandability, chondrogenic potential were compared among MSCs from the 5 different tissue sources. Colony number per 1000 nucleated cells was lower, and cell number per colony was higher, in bone marrow than in other mesenchymal tissues. When the cells were replated at low density every 14 days, bone marrow–, synovium-, and periosteum-derived cells retained their proliferation ability even at passage 10. In chondrogenesis studies in which the cells were pelleted and cultured in vitro, pellets from bone marrow–, synovium-, and periosteum-derived cells were shown to be larger and stained more extensively for cartilage matrix. Synovium-derived cells, in particular, had the greatest ability for chondrogenesis. Superiority of synovium as a potential source of MSCs for cartilage regeneration was demonstrated.

[Comparison of MSCs for in vivo chondrogenesis] Synovial MSCs had the best expansion and chondrogenic ability in vitro in humans. However, one drawback is that the evaluation of in vitro chondrogenesis may not represent the chondrogenic potential of MSCs transplanted into cartilage defect. We compared the in vivo chondrogenic potential of rabbit MSCs. MSCs were isolated from bone marrow, synovium, adipose tissue, and muscle of adult rabbits. Proliferation potential and in vitro chondrogenic potential were compared. Synovial and muscle MSCs had a higher proliferation potential than other cells. After transplantation into cartilage defects, synovial and bone marrow MSCs produced much more cartilage matrix than other cells. Synovial and bone marrow MSCs had greater in vivo chondrogenic potential than adipose and muscle MSCs, but synovial MSCs had the advantage of a greater proliferation potential.

[Increased proliferation of human synovial MSCs with autologous human serum]For clinical safety, autologous human serum should be used instead of fetal bovine serum (FBS). We compared the 2 types of serum for their enhancement of the proliferation of synovial and bone marrow MSCs. Synovium, bone marrow, and peripheral blood were obtained from 18 donors. Synovial and bone marrow MSCs were cultured with autologous human serum or FBS and analyzed. Human synovial MSCs expanded more in human serum than in FBS, and the opposite results were obtained with bone marrow MSCs. Hierarchical clustering analysis showed that the cell source, rather than the type of serum, affected the gene expression profile. Human serum contained high levels of platelet-derived growth factor (PDGF), synovial MSCs expressed higher levels of PDGF receptor α than did bone marrow MSCs, and neutralizing PDGF decreased the proliferation of synovial MSCs with autologous human serum. Autologous serum predominated in increasing the proliferation of synovial MSCs through PDGF signaling.

[Local adherent technique for transplanting MSCs to cartilage defect.] Current cell therapy for cartilage regeneration requires invasive procedures, periosteal coverage and scaffold use. We have developed a novel transplantation method with synovial MSCs to adhere to the cartilage defect. For ex vivo analysis in rabbits, the cartilage defect was faced upward, filled with synovial MSC suspension, and held stationary for 2.5 to 15 minutes. The number of attached cells was examined. For in vivo analysis in rabbits, an autologous synovial MSC suspension was placed on the cartilage defect, and the position was maintained for 10 minutes to adhere the cells to the defect. For the control, either the same cell suspension was injected intra-articularly or the defects were left empty. Ex vivo analysis in rabbits demonstrated that the number of attached cells increased in a time-dependent manner, and more than 60% of cells attached within 10 minutes. The in vivo study showed that a large number of transplanted synovial MSCs attached to the defect at 1

day, and the cartilage defect improved at 24 weeks. The histological score was consistently better than the scores of the two control groups (same cell suspension injected intra-articularly or defects left empty) at 4, 12, and 24 weeks. Ex vivo analysis in humans provided similar results to those in rabbits. Placing MSC suspension on the cartilage defect for 10 minutes resulted in adherence of ~60% of synovial MSCs to the defect, and promoted cartilage regeneration. This adherent method makes it possible to adhere MSCs with low invasion, without periosteal coverage, and without a scaffold.

[Cartilage repair after a minimally invasive method of transplantation of synovial MSCs into cartilage defects in pigs] We examined the usefulness of the local adherent technique with synovial MSCs in pigs. Cartilage defects were created in both knees of seven pigs, and divided into MSCs treated and non-treated control knees. Synovial MSCs were injected into the defect, and the knee was kept immobilized for 10 min before wound closure. To visualize the actual delivery and adhesion of the cells, fluorescence-labeled synovial MSCs from transgenic green fluorescent protein (GFP) pig were injected into the defect in a subgroup of two pigs. In these two animals, the wounds were closed before MSCs were injected and observed for 10 min under arthroscopic control. The defects were analyzed sequentially arthroscopically, histologically and by magnetic resonance imaging (MRI) for 3 months. Arthroscopic observations showed adhesion of synovial MSCs and membrane formation on the cartilage defects before cartilage repair. Quantification analyses for arthroscopy, histology and MRI revealed a better outcome in the MSC-treated knees than in the non-treated control knees. Leaving a synovial MSC suspension in cartilage defects for 10 min made it possible for cells to adhere in the defect in a porcine cartilage defect model. The cartilage defect was first covered with membrane, then the cartilage matrix emerged after transplantation of synovial MSCs.

[Clinical study of arthroscopic transplantation of synovial MSCs for cartilage regeneration] We started clinical study of arthroscopic transplantation of synovial MSCs for cartilage regeneration. First of all, peripheral blood was collected to prepare autologous serum. Approximately 0.5 mg synovial tissue was harvested arthroscopically. After enzyme digestion, nucleated cells derived from synovial tissue were cultured with 10% autologous serum in our cell processing center certified by ISO 9001. At 12 days, we performed bacterial, virus, endotoxin tests. At 14 days, colony forming cells derived from synovium, referred to synovial MSCs, were harvested. Approximately 500 million synovial MSCs were suspended in 0.2 ml. The cartilage defect was faced upward, and its position was held manually. A suspension of prepared MSCs was placed into the defect through an 18-gauge needle. After 10 min, the arthroscopic portals were closed without washing the inside of the knee joint. The patients started ROM exercise at 1 day, partial weight bearing at 2 weeks, and full weight bearing at 6 weeks. Favorable results are obtained by MR imaging in most patients with femoral condyle cartilage defects, in addition by second look arthroscopies, and by biopsies though patients undertaken these invasive examinations are still limited. Our method has such advantages that no periosteal coverage or scaffold are required and that transplantation is possible arthroscopically.

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3.1.3

Promoting Muscle Recovery after Cartilage Repair

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Introduction: While designing a rehabilitation program for patients after cartilage repair, several issues have to be addressed. The aim of the rehabilitation after cartilage repair is to ensure an optimal healing of the repair site by local adaptation and remodelling of the repair and return the patient to an optimal level of function. That means that patients are able to do several activities of daily life without great complaints and limitations and that he is able to do low impact sport activities.

Optimal healing of the graft means to avoid forces, especially high shear and compressive forces which might be deleterious for the transplanted area. Unloading and immobilization reduces high compressive and shear forces, however the disadvantages of unloading and immobilization one joints structures are well investigated and documented. Therefore it is a challenge to optimise the achievement of these two controversial goals – graft protection and return to function - within rehabilitation. In order to fulfil these demands the rehabilitation protocol includes three main components, which should be individualized to each patient: progressive weight bearing, restoration of range of motion (ROM) and enhancement of muscle control and strengthening. The modalities of these three main components (progressive weight bearing, restoration of ROM and enhancement of muscle control and strengthening) are based on the physiology of cartilage, biomechanics of the knee joint and the biology of the healing repair site – which is mainly depending upon the sort of cartilage repair procedure.

Content: The development of muscle strength and endurance after cartilage repair is important both on a structural and on a functional level. Structurally muscle strength may protect the healing repair site by dissipating forces acting on the knee and functionally muscle strength and endurance provide the ability to participate in activities of daily life in the early postoperative phase and in addition sport activities in the later postoperative stage.

Pain and effusion have been observed frequently in early postoperative stages and have been reported to be responsible for the inhibition of the quadriceps muscle leading to reduced quadriceps muscle function. Restoration of quadriceps muscle function cannot be emphasized enough as a lack of this function is frequently reason for an extension lag which may lead to an increased pressure within the patellofemoral joint and to altered knee joint kinematics. Hence, the quadriceps muscle needs to be addressed particularly by several therapeutic modalities such as therapeutic exercises, muscle stimulation and biofeedback. Muscle stimulation can be used alone or it can be incorporated with therapeutic exercises to facilitate the active contraction of the quadriceps muscle in the early postoperative phase. Several studies have examined the use of electrical stimulation and biofeedback indicating that electrical stimulation and biofeedback facilitate the return of muscle activation. Electrical stimulation is generally used when patients present the inability to activate muscles with the aim to recruit a maximum amount of muscle fibers during active contraction. Therefore, electrical stimulation may also be used throughout the rehabilitation process.

Muscle strength exercises have to be performed in a manner which minimizes shear loading across the defect area, especially shear forces combined with compression. To protect the healing repair site, size and location of the lesion should be considered when implementing muscle strength exercises. Certain types of muscle contraction and, as isometric, concentric and eccentric muscle work, are important tools in rehabilitation after cartilage repairing Especially eccentric muscle work act as sort of shock absorber of forces acting on the repair site.

In the early postoperative phase isometric exercises, especially of the quadriceps muscle and the hamstrings, should be emphasized as they produce no shear forces and prevent further damage. Isometric exercises have to be performed in positions – angels of knee flexion – which are not engaging the repaired site.

The next phase of strengthening will involve concentric and eccentric exercises which can be done in open (OKC) or closed kinetic chain (CKC) systems. To protect the repair site, an understanding of the applied clinical biomechanics should be considered. Furthermore, the knowledge of the biomechanics in terms of contact area (distribution and magnitude), contact load and contact pressure helps to find positions and movements which can support the healing process by stimulating the repair site physiologically in harmless positions. Starting with exercises in closed chain systems prevent damaging shear forces over the repair site. A gradual progressive loading in closed chain systems is possible and open chain exercises within a limited arc of motion can be implemented.

Approximately (depending on the surgical procedure and the cartilage repair procedure) after 2 to 4 weeks postoperatively concentric strengthening exercises in closed-kinetic chains and in partial weight bearing positions with small arc movements and out of the repair zone can be initiated. After 6-8 weeks postoperatively these exercises can be performed in full weight bearing positions with respect to the transplanted area. In general, within the first 8 postoperative weeks, CKC exercises should be preferred, because studies reveal lower shear stress within the joint and more functional joint compression. Additionally CKC exercises result in muscular co- contraction which is more functional and leads to higher joint stability.

After 9 weeks postoperatively concentric exercises can be implemented over the full range of motion, as the repair site has to get used to these forces which are similar to that of daily life´s activity. This phase is characterized by eccentric exercises of the quadriceps as the eccentric function of the quadriceps helps to absorb shock and dissipate forces on the knee during high activity. To increase the muscle torque of the quadriceps and the hamstrings isolated strengthening is necessary, which can be completed by exercises in open kinetic chain systems. By reason that this kind of strengthening increases critical shears forces, the exercises should be instructed in small ranges out of the repair zone.

Resisted exercises should be resumed not before 6 weeks after surgery as within this time the healing tissue is not matured and therefore very susceptible for damage. In general strengthening exercises after cartilage repairing should be performed in pain-free range with low resistances so that high numbers of repetitions are possible to stimulate remodelling of the repair. Resistance should be gradually and slowly increased and should be dependent on patient´s symptoms.

The dynamic stability of the knee relies largely on the proprioception and strength, endurance, and power provided by the quadriceps, hamstrings and the pelvis muscles during ADL and sport activities. So strengthening exercises targeting the entire lower extremity should be included in the later phases when strengthening exercises with relevant doses are tolerated. Core stability is also shown to be important in reducing load within the knee as good core stability assists in controlling the production and distribution of forces in the knee during activities.

Further components of dynamic knee stabilization strategies are neuromuscular drills of the lower extremity. A few studies have also shown that including neuromuscular exercises prior to strengthening exercises seems to improve muscular strength more than only including traditional strengthening exercises. As neuromuscular exercises produce less joint loading than strength training and are also often tolerated better by the patients than only strengthening exercises, neuromuscular training should be part of the rehabilitation program after cartilage repair.

The neuromuscular system involves the detection of afferent inputs via proprioceptors, the response to this stimulus in the central nervous system and the initiation of an efferent reaction (sensomotoric system) to maintain balance, stability and mobility.

Proprioception is the body´s ability to realize joint position in space. These mechanoreceptors – proprioceptors - are found in joint capsule, in menisci and in several ligaments forming a complex system for articular joint proprioception with spinal and cortical projections[19. A good proprioceptive function is necessary to stabilize a joint both in static positions and during dynamic activity allowing positioning and controlled joint movement. Therefore proprioception is an important component in the restoration of functional joint stability. A lot of studies describe a loss of proprioceptive deficits after joint injuries, in connection with common articular pathologies and after surgical interventions.

To promote the healing process of the repair site and to prevent jeopardizing forces across the joint rehabilitation should address proprioceptive deficits in a functional and dynamic manner. This should be considered in every phase of rehabilitation progression and is traditionally trained by exercises that stress balance with and without vision, in loaded or unloaded positions at varying joint angles and in the full available ROM.

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Hambly, 2006 Van Assche, 2010 Reinold, 2006 Wondrasch, 2009 Wondrasch, 2013

3.2.1

Cartilage Repair in Axolotl Salamanders

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Introduction: The intrinsic repair capacity of articular cartilage in mammals is extremely limited, making therapeutic treatment of large joint surface lesions challenging and the prognosis guarded. Despite recent advances in surgical and pharmacological treatment options, damaged adult articular cartilage is never fully restored. Instead, a structurally different and functionally deficient "hyaline-like" scar tissue forms in place of pre-existing articular cartilage. Across phylogeny, however, certain species have the potential for regeneration of injured tissues that far exceeds that which occurs in mammals. Even some vertebrates, most notably certain salamander and newt species within the order Urodela, have the capacity for near complete limb regeneration that includes the cartilaginous elements of their skeleton. What can the cellular and molecular mechanisms of cartilage regeneration in these animals teach us about variables that limit articular cartilage repair in mammals? Are any of these mechanisms latent and potentially still accessible in mammals such that they become potential targets for improved therapies?

Content: Studies in Ambystoma mexicanum, the Mexican axolotl mole salamander, demonstrate the ability to repair even large cartilaginous lesions in the femorotibial joint that include the joint surface.[1] Surgical resection of the medial condyle from the distal femur to the level of the metaphysis heals completely by 24 weeks (Figure 1) even in sexually mature individuals at one to two years of age. Histological assessment of the healing process indicates the participation of cells from an interzone-like tissue that is retained in the intra-articular space.

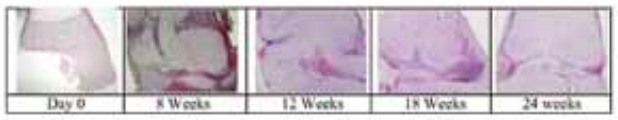

Figure 1. Healing of epiphyseal and articular cartilage in the axolotl following resection of the medial femoral condyle to the level of the metaphysis. H&E stained sections are shown at the indicated time points post surgery.

Interestingly, the interzone-like tissue is present in axolotl salamanders from the carpus through distal joints in the forelimb and the knee through distal joints in the hind limb. Cavitation, with the formation of a joint space and joint capsule, is restricted to the large proximal limb joints - shoulder, elbow, and hip.[2] Location, structural features, and the expression of biomarker genes including growth and differentiation factor 5 (GDF5) and Brother of CDO (BOC) suggest homology of interzone-like tissue in axolotls to the interzone tissue present transiently during fetal development of diarthrodial joints in mammals (Figure 2).

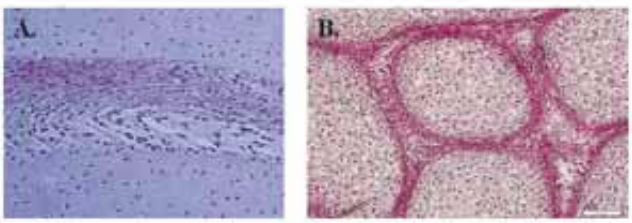

Figure 2. Interzone tissue in the intra-articular space of (A) the knee joint in an adult axolotl, and (B) the developing carpus of an equine fetus.

These data suggest two future directions for research that may advance cell-based and tissue engineering therapies in mammals. The first is whether the presence of interzone tissue within a joint can provide a requisite cell population that enables articular cartilage repair. In a developmental context, the interzone is a progenitor of several joint tissues including articular cartilage. It is unknown, however, whether interzone cells will retain this potential in an adult mammalian synovial joint and achieve the repair of joint surface lesions. The Mexican axolotl salamander is neotenic and maintains aquatic larval characteristics such as external gills and a dorsal tail fin into sexual maturity. Unlike other urodele amphibians such as frogs and toads, individual axolotls only rarely enter and proceed through metamorphosis spontaneously to a terrestrial form. As such, perhaps the femorotibial joint of an adult axolotl more closely models the knee joint of a mammalian fetus, with the observed ability of interzone cells to facilitate cartilage repair being restricted to this developmental context. Nonetheless, the biology of interzone cells may provide insights into gene expression profiles or epigenomic chromatin features that can be used to optimize the selection or efficacy of mesenchymal stem cell or autologous chondrocyte transplantation strategies.

A second direction for additional research is the identification and characterization of important regulatory mechanisms. Removal of the femoral condyle in the axolotl salamander model initiates a regenerative process that stimulates the proliferation of interzone cells and their movement to the resected area through both growth and migration. Regulatory and patterning mechanisms must be present to limit cell division and growth when repair tissue fills the lesion, to direct cellular differentiation and tissue morphogenesis, and to enable integration of newly regenerated tissues into the surrounding normal structures to achieve the full restoration of joint structure. Identity of these regulatory processes and their mechanisms of action are largely unknown, as well as the extent to which they parallel developmental events. Is the potential for differentiation of interzone tissue into articular cartilage and other joint structures restricted to a skeletal microenvironment, or will it also occur if interzone tissue is transplantated into a soft tissue site? How do signaling gradients achieve proximal/distal, dorsal/ventral, and anterior/posterior tissue patterns and what exactly forms the regulatory gradients? To what extent is the ability to generate regulatory signals retained in cavitated synovial joints of postnatal mammals and does this potential change with maturity and aging? In general, enhanced tissue regeneration occurs at earlier developmental stages, younger ages, and smaller sizes. Indeed, there is some evidence to suggest that fetal or very young mammals have the potential to heal partial thickness articular cartilage lesions without scar formation, but that this ability is lost with ambulation and cartilage maturation in the postnatal period.

Studies in different animal species and across taxonomic groups that compare the potential for limb regeneration and the intrinsic ability to repair skeletal tissue lesions can provide novel medical insights for both human and veterinary patient populations, especially as they relate to emergent strategies in regenerative medicine. The increasing breadth of whole genome sequence data, together with improvements in the extent and quality of structural and functional genome annotation greatly enhance these analyses. Experiments in my laboratory center on the interzone tissue and derived primary cell lines from horses and axolotl salamanders. We are trying to investigate the differentiation potential of interzone cells, determine if interzone cells have tissue lineage differentiation preferences in comparison to other multipotent progenitor cells, define patterns of interzone-restricted gene expression, assess the phenotypic stability of interzone cells in tissue culture, and identify parameters that influence or regulate all of these processes.

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3.2.2

Chondrocyte Proliferation and Differentiation in Cartilage Development

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Introduction: Hyaline cartilage is a connective tissue of mesenchymal origin with a specialized extracellular matrix (ECM) composed of a fibrillar compartment of collagens filled with an extrafibrillar compartment, rich in proteoglycans. Chondrocytes are responsible for the production, arrangement and maintenance of the ECM, and therefore ultimately determine the physical properties of the tissue such as tensile and compressive resilience. Cartilage moulds form during embryogenesis via the sequential steps of mesenchymal cell proliferation, chondroprogenitor commitment and chondrocyte differentiation under the control of multiple mechanisms including systemic and local modulation, cell-cell and cell-matrix interactions, cellular signalling, transcriptional and translational regulation. Most fetal cartilages are transient and, along the endochondral ossification pathway, gradually replaced by bone following chondrocyte hypertrophy, apoptosis, cartilage matrix mineralization, vascularization and degradation. Oppositely, in articular cartilage, the permanent, load-bearing tissue of diarthrodial joints, the chondrocytes acquire a stable phenotype that resists hypertrophy and vascular invasion, thus maintain a mechanically adequate ECM throughout the life. Osteoarthritis (OA) is an age-related and/or trauma-induced degenerative disorder of the synovial joints culminating in the irreversible destruction of the articular cartilage. Current therapeutic strategies seek to ameliorate pain and increase mobility, however, to date, none of them halts disease progression or regenerates damaged cartilage. Thus, there is an ultimate need for the development of new, non-invasive treatments that could substitute joint replacement for late- or end-stage patients. Although OA is the most common musculoskeletal condition that causes significant health and social problem worldwide, its exact aetiology is still unclear. Besides metabolic imbalance, activation of the endochondral ossification program through articular chondrocyte hypertrophy and apoptosis has been identified as important determinants of OA progression. Understanding of regulatory mechanisms governing chondrocyte proliferation and differentiation during development should provide a better insight into the pathomechanism of osteoarthritis and may facilitate the development of therapeutic approaches aiming to repair cartilage defects. Furthermore, recent cartilage tissue engineering applications utilizes the concept of "developmental engineering", emphasizing that "in vitro biomimetics of in vivo tissue development" should be a prerequisite for engineering functional articular cartilage either from chondrocytes or stem cells.

Content: Major part of the mammalian skeleton is laid down by a multi-step process called endochondral bone formation. During embryogenesis, first structures that prefigure the future bones are formed by the condensation of skeletogenic mesenchymal stem cells (MSCs) (phase I). Precartilaginous condensations require the stop of MSC proliferation and the expression of specific matrix and adhesion molecules allowing cell aggregation. This event is primarily under the control of TGF-beta and Wnt/beta-catenin signalling. The next step is the determination of the MSCs to the chondroprogenitor fate and chondrocyte early differentiation (phase 2). Chondrogenesis spread out from the central core region of the precartilaginous condensation. The cartilaginous moulds are surrounded by a mesenchymal sheet (perichondrium) and consist of immature, proliferative chondrocytes which synthesize cartilage ECM molecules including collagen II and aggrecan. Chondrocyte early differentiation is tightly controlled by transcription factors such as the Sox genes trio (Sox5, 6 and 9), growth factors (BMPs, FGFs and TGF-beta) and sonic hedgehog (Shh). In the next step, fully differentiated chondrocytes produce a vast amount of cartilage-specific matrix (phase 3) than centrally located cells stop to proliferate, mature and differentiate into hypertrophic chondrocytes which typically express collagen X instead of collagen II (phase 4). Terminal differentiation of hypertrophic chondrocytes is accompanied by expression of osteoblast marker genes and matrix remodelling enzymes (e.g. matrix metalloproteinase 13, MMP13), ECM mineralization and invasion of blood vessels, chondroclasts and osteoblast precursors leading to the replacement of cartilage scaffold by bone. The program of proliferation, maturation and remodelling takes place within a specialized structure, called growth plate. Growth plate chondrocytes form horizontal zones reflecting their differentiation stage (resting, proliferative, prehypertrophic and hypertrophic), undergo characteristic shape changes (round, flat, prehypertrophic, hypertrophic) and arranged into vertical columns. Proliferation, matrix production and hypertrophy of growth plate chondrocytes are the major factors, which are essential to achieve longitudinal elongation of endochondral bones. The maturation program and proliferation of chondrocytes within the growth plate are spatially and temporary tightly controlled by numerous signalling pathways. One of the pivotal regulators is Indian Hedgehog (Ihh), secreted by prehypertrophic chondrocytes, which directly stimulates both chondrocyte proliferation and maturation. Furthermore, Ihh induces the expression of parathyroid hormone-related peptide (Pthrp) in subarticular chondrocytes. Pthrp signals through its Prp receptor in proliferating and prehypertrophic chondrocytes to prevent the differentiation of Ihh expressing cells, thus, the onset of hypertrophic differentiation. In addition to this this negative feedback loop which is essentially regulates the pool of proliferative chondrocytes and delays prehypertrophy, BMP, FGF and the canonical Wnt/beta-catenin signalling pathways modulate the formation and/or proliferation of distinct chondrocyte population. The switch from prehypertrophy to hypertrophy is driven by the Runt-domain transcription factors Runx2 and Runx3 and the Runx2 downstream target MADS-box transcription factor Mef2c, and is negatively modulated by the histone deacetylase Hdac4.

Diarthroidal joints unite different type of tissues to ensure load transmission within skeletal structures and coordinate their movements. The opposing bones are covered with articular cartilage (AC) and are separated by a joint cavity enclosed in a capsule linking the skeletal elements. The capsule is lined by a synovial membrane that secretes synovial fluid, which lubricates the AC surface and provides nutrition to the joint's components. AC is a permanent, specialized type of hyaline cartilage that functions as a load bearing tissue and can resist shearing forces and friction. The AC, similar to the growth plate, characterized by a high degree of anisotropy and is divided into four zones (Fig. 3B) with distinct organization of the matrix and cells: superficial (or tangential), intermediate (or transitional), deep (or radial) and calcified. The superficial zone is the thin, outermost layer of the AC which contains elongated cells and densely packed collagen fibrils arranged parallel of the surface. The intermediate zone contains individual spherical chondrocytes and a relatively disorganized collagen network, whereas in the deep zone the cells tend to organize into columns with radially oriented collagen fibril bundles between them. The calcified zone is separated from the upper zones by the tidemark and its main function is to anchor the AC to the subchondral bone. Synovial joints develop through two main processes called joint specification and joint morphogenesis. In the step of joint specification, skeletogenic MSCs expressing the Sox trio are directed to the articular fate under the control of Tgfb2, canonical Wnt and growth differentiation factor-5 (Gdf5) signalling cascades. During joint morphogenesis a cavity forms in the interzone between articulating skeletal elements driven by a not fully-understood mechanism involving high-level synthesis of hyaluronan, shift in ECM composition and skeletal movement. Next, specific articular cells differentiate and form the joint tissues. The continued expression of the Sox trio is pivotal for articular chondrocyte differentiation, while it seems that Wnt/beta-catenin signalling prevents chondrocyte differentiation at sites not destined for articular cartilage. The development of the AC progresses by appositional growth driven by a progenitor/stem cell population at the articular surface. Important to note that although many signalling pathways operating in the growth plate cartilage (Ihh, Pthrp, Bmp, Tgf-beta) are also important for maintaining the postnatal AC, articular chondrocytes normally quiescent, express an early phenotype and do not terminally differentiate. Under pathological conditions, such as primary OA and cartilage injuries, chondrocytes may regain proliferation potential and activate the terminal hypertrophic differentiation program contributing to metabolic imbalance and progressive degradation of the articular cartilage.

Cartilage resident matrix proteins interact with each other in a complex manner to define the physical framework for cells and to control the availability, activity and cell surface presentation of bioactive molecules. Almost all ECM proteins, directly or indirectly, bind to and activate cellular receptors such as integrins, which in turn stimulate intracellular signalling pathways regulating cellular behaviour such as proliferation, survival and differentiation. Chondrocytes express several integrin receptors for cartilage matrix ligands such as $\alpha1\beta1$, $\alpha2\beta1$ and $\alpha10\beta1$ (for collagen II), $\alpha5\beta1$, $\alpha v\beta3$ and $\alpha v\beta5$ (for fibronectin) and $\alpha6\beta1$ (for laminin). The roles of integrins in cartilage development were first studied in culture systems. In high density micromass culture, which recapitulates several steps of chondrogenesis, β_1 integrin blocking antibodies were shown to prevent the formation of cartilaginous nodules implying that integrins may be important for the transition of mesenchymal precursors to chondrocytes. In chicken sternal organ culture, blocking $\beta1$ integrin resulted in reduced growth, increased apoptosis and abnormal organization of the actin cytoskeleton. Other experiments highlighted the importance of $\beta1$ integrins in hypertophic chondrocyte differentiation: signalling via

α1β1 and α5β1 integrins was required for transglutaminase-induced hypertrophy of cultured AC chondrocytes; a β1 integrin-blocking antibody impaired collagen X deposition in sternal organ culture; while missexpression of α5β1 in embryonic chick legs resulted in joint fusion and initiation of the hypertrophic differentiation program. To investigate the in vivo function of β1 integrins during endochondral bone formation, the floxed β1 integrin gene was conditionally inactivated in the entire cartilaginous skeleton using a transgene driving the expression of the cre recombinase under the control of the collagen II promoter (Col2a1cre). Mutant mice (β1fl/fl-Col2a1cre+) develop perinatal lethal chondrodysplasia, characterized by the lack of columnar growth plate, reduced chondrocyte proliferation, abnormal cell shape and distorted collagen fibrillar network in the ECM. These results show that β1 integrins-mediated cell matrix interactions are essential for chondrocyte geometry, motility and cytokinesis, essential mechanisms necessary for the proper formation and function of the growth plate. To assess the impact of β1 integrins on the function of adult knee joints, the β1 integrin gene was also inactivated in early limb mesenchyme using the Prx1-cre transgene. Mutant mice developed short limbed dwarfism and had joint defects due to β1 integrin deficiency in articular regions. The AC was structurally disorganized, accompanied by accelerated terminal differentiation evidenced by collagen X missexpression, altered shape, and disrupted actin cytoskeleton of the chondrocytes. Defects in chondrocyte proliferation, cytokinesis, and survival resulted in hypocellularity. Taken together, the data imply that integrins-mediated signaling pathways are crucial regulators of chondrocyte proliferation and differentiation both in growth plate and articular cartilage.

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3.2.3

Developmental Engineering of Cartilage from Stem Cells

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Introduction: Growth and differentiation are tightly linked during embryonic development, and when cartilage develops from mesenchymal progenitors, cells undergo extensive proliferation followed by condensation, a process which increases the cell density and leads to enhanced cell-cell contacts. When the cell-per-volume ratio is high enough, cells located centrally of the condensed structure withdraw from the cell cycle, stop proliferation, and establish cartilaginous nodules. These contain the chondro-progenitor cells which, after a transient exit from the cell cycle, resume cell division and produce components of the extracellular cartilage matrix, especially proteoglycans and collagen type II. In permanent articular cartilage, chondrocytes differentiate terminally into mature chondrocytes with column formation. In contrast to this, in the transient cartilage formed during endochondral bone formation, these cells undergo a hypertrophic development where they increase in size and up-regulate markers like collagen type X and alkaline phosphatase (ALP).

Content: Mesenchymal stroma cells (MSC) subjected to in vitro chondrogenesis by standard protocols up-regulate, beside the desirable proteoglycans and collagen type II, hypertrophic markers as well, an unwanted behaviour for the formation of stable articular cartilage. The question is whether the same linkage of proliferation and differentiation found in natural chondrocyte development is recapitulated during in vitro chondrogenesis of MSC and will allow to influence the outcome and improve developmental engineering of cartilage from MSC. This work will outline that while in vitro expansion of MSC may correspond to the initial proliferation of mesenchymal progenitors before condensation, the natural condensation step is imitated upon switching to the high density pellet system. It will be demonstrated that better growth during the expansion phase will result in better differentiation results. Indeed, cell proliferation stops after condensation until cells are designated chondroblasts, as suggested for mesenchymal progenitors in vivo, and restarts during pellet growth and cartilage matrix deposition. Dividing chondroblasts appear in pellet areas turning positive for collagen type II which in some pellets were organized like primitive growth plates moving through the pellets. Irreversible growth arrest of cells before initiation of differentiation completely prevented successful chondrogenesis.

In conclusion, growth and differentiation were closely coordinated during chondrogenesis of MSC and resembled the multiple stages known from embryonic cartilage development. Knowledge on the proper regulation of cell proliferation during cell determination and chondrogenesis and the relevance of growth for the success of differentiation of articular chondrocytes will thus be important for better in vitro guidance of MSC in order to produce larger constructs of a stable chondrocytic phenotype for MSC-based tissue engineering approaches.

3.3.1

Comparison of Intervertebral Disc and Articular Cartilage

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Introduction: Both the articular cartilage and intervertebral disc are involved in weight bearing and movement. As both tissues are prone to degeneration, identifying a biological repair therapy would have a significant clinical impact.

Content: Articular cartilage is an avascular connective tissue covering the articulating ends of bones in synovial joints[1,2]. It is a load-bearing tissue that absorbs and distributes compressive and shear forces applied to the joint while permitting low friction articulation. Articular cartilage fulfills these functions through a complex depth-dependant zonal architecture[1,2]. Although all zones contain aggrecan (proteoglycan), collagen type II and water, each zone is characterized by a distinct composition and extracellular matrix organization resulting in four zones: superficial, mid, deep and calcified.

In contrast the intervertebral disc is a specialized structure consisting of interdependent tissues, the annulus fibrosus and the nucleus

pulposus which are sandwiched between two cartilage endplates that are integrated to the adjacent vertebral bodies[3-5]. The outer annulus fibrosus is responsible for withstanding circumferential tensile forces while the nucleus pulposus and inner annulus fibrosus resists compressive forces. Together these can handle more load than each tissue alone stressing the importance of intact properly integrated structures. Intact cartilage endplates are also necessary[6]. The cartilage endplates contributes to maintenance of nucleus pulposus cell viability, absorbs the water that extrudes from the nucleus pulposus during loading and prevents protrusion of the nucleus pulposus into the adjacent vertebral body. The organization of the IVD allows the disc to rotate, flex and resist tensile and shear forces and is critical for proper disc function.

Although compositionally very different these two tissues have several features in common. They are both weight bearing tissues, with a soft tissue-bone interface, have limited vascularity (cartilage has none) and they rely on diffusion for distribution of oxygen and nutrients and removal of degradation products. Not surprisingly they both commonly undergo degradation. In an autopsy study, 97% of individuals 50 yrs or older showed IVD degeneration whereas osteoarthritis affects approximately 10% of the population[7,8]. Both diseases are very common and manifest with pain and limitation of mobility. The etiology for these diseases has not been fully elucidated and is likely multi-factorial but genetics play a large role[8-12]. Additional contributing factors for osteoarthritis are body habitus, aging, hormonal status, and trauma. For the intervertebral disc, aging, the relative avascularity of the tissue, mineralization of or trauma to the cartilage endplate, mechanical factors, vertebral body microfractures, and/or loss of notochordal cells likely also contribute to this degenerative process.

Interestingly as much of the weight bearing in cartilage and the intervertebral disc is supported by tissue rich in proteoglycans, collagen and water (cartilage: joint and nucleus pulposus: intervertebral disc) the mechanisms contributing to the progression of these two diseases are similar. Both diseases are characterized by a gradual loss of proteoglycans and continuing damage to the collagen network as a result of upregulation of proteases (matrix metalloproteases (MMP) and ADAM-TSs (disintegrin and metalloproteinase with a thrombospondin

domain)). These negatively impact the stiffness of the cartilage and nucleus pulposus and contribute to abnormal loading and progressive damage of the tissues. In addition there are changes in the calcified cartilage and bone. Interestingly both cartilage and the intervertebral disc have little if any capacity for repair because of the lack of vascularity and the development of a blood clot with injury, presence of few stem cells, and the presence of dense matrix that limits cell migration. As a result the approach to treatment in both entities is similar. Interventions such as exercise, weight loss and anti-inflammatory medications are used as first line treatments. The medications do not inhibit tissue destruction and in a proportion of patients the disease process progresses. Failure of these approaches culminates in surgical intervention and for both diseases this is not an optimal outcome. As a result there has been great interest in developing biological repair approaches to overcome the limitations of surgical treatments. Approaches such as the use of hyaluronate injections, and implantation of cells with or without scaffolds have been evaluated in animal studies in both diseases. However both osteoarthritis and disc degeneration suffer from a common problem- the lack of a good animal model. More recently stem cell injections into the affected joint or disc are being evaluated in human clinical trials. Although the disc and cartilage compositionally are very different, they have some commonality in the processes leading to degeneration. It should be possible to apply what we learn from each disease to fast track the research into treatment options for the other disease.

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3.3.2

Towards intervertebral disc repair: insights from stem cell studies

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Introduction: The intervertebral discs (IVD) have an important role in the motion of the spinal column, contributing to various body postures and force coordination in daily activities. Along with its role in spinal motion, the disc has a major function in providing cushioning effects to the spine against axial load. Unlike cartilage engineering, the engineering of the disc confronts many challenges because of its complexity and presence of extraordinary stresses related to its anatomy and function. Similar to articular cartilage in appendicular joints, intervertebral disc suffers from degeneration. The causes of IVD degeneration are not clear, although it is thought to be multifactorial with a large contribution from both genetic and environmental components (1, 2). Current treatments predominantly aim not to correct the degeneration, but alleviate symptoms such as back pain and sciatica which are often manifested by severe IVD degeneration or radiculopathy caused by the degenerated disc. For a decade, various studies have attempted to treat disc degeneration with stem cell-based approaches. How far have we achieved in using stem cells to regenerate or bioengineer a functional intervertebral disc, and how do we extrapolate their use in future?

Content: The disc core, or nucleus pulposus (NP), functions to withstand the compressive load so as to maintain disc height and range of motion of spinal segment. The loss of integrity of the NP is in fact amongst the earliest events of this progressive process. These imply that the NP plays pivotal roles in IVD homeostasis and function. Rebuilding the NP or preventing a loss of its function is an important goal in treating disc degeneration. There are two distinct ways of using stem or stem-like cells in NP engineering. One of the available sources under in-depth research are mesenchymal stromal/stem cells (MSCs) (3). On one hand, MSCs have been used to engineer into NP-like cells directly for de novo disc engineering or implantation into the disc to recover the authentic NP function by promoting matrix maintenance. On the other, MSCs may also be delivered directly into the disc to

modulate the microenvironment and disc cell activities, or to acquire a differentiated phenotype in situ that may benefit NP function. Although there are shortcoming of patient selection and inadequate definition of standards to evaluate efficacy, pilot clinical trials suggest disc repairing and alleviation of symptoms by intradiscal implantation of MSCs (4, 5).

Studies of MSC-based disc regeneration have been investigated in various animal models, from mouse to mini-pig and sheep. While parameters such as approaches for inducing disc degeneration, dosages and injection protocols of MSCs vary, the results of these animal studies have laid important foundation to our understanding in the effects and mechanism of action of MSCs in vivo. MSCs can differentiate into collage II- and proteoglycan-producing cells in the degenerated discs and that growth factors such as TGF-beta, GDFs, and BMPs may induce MSCs to differentiate into NP-like cells in vitro (*6*). However, data have also shown that MSCs and NP cells can mutually exchange biological information. Co-culturing with MSCs may promote NP cell activities through cell-cell contact or paracrine action. Conversely, NP cells may also induce NP cell-like phenotype in MSCs, possibly via transfer of membrane-bound micro-vesicles (*7*). This suggests MSCs can have activities other than self-differentiation that contribute to disc regeneration.

MSCs also have other unidentified activities that may alleviate disc degeneration. Fibrosis is common to chronic inflammatory conditions and is related to excessive tissue remodelling as a result of disrupted wound healing. Abnormal deposition and/or cross-linking of the collagen matrix ultimately lead to defective cellular homeostasis and repair, thence to hardening and scarring of tissues. Anatomical studies on autopsy and surgical specimens show evidence of fibrosis in the majority of degenerated discs. Study has shown abnormal collagen fibril bundling in mechanically compromised discs, suggesting abnormal collagen matrix meshwork is one of the major factors for reduced elastic and viscous behaviors of the disc that ultimately leads to altered kinematics of the joint under load. We recently show that human disc degeneration exhibits features of fibrosis and that a rabbit disc degeneration model shows similar features. Further in vivo study shows that implantation of bone marrow-derived MSCs can inhibit fibrosis in the degenerating NP and effectively preserves its mechanical characteristics and the overall motion segment function. At the nano-scale, collagen aggregation and fibril stiffening were found to be reduced in the NP matrix of discs treated with MSCs compared to those treated with a placebo. Along with their activity in anti-fibrosis, MSCs achieves this by suppressing abnormal deposition of collagen I and actively repressing the profibrotic mediators that are implicated in mediating the collagen anomalies in fibrotic diseases.

Interestingly, studies suggest that cells derived from human degenerated discs have multi-differentiation potential and possess in vitro characteristics of MSCs. These observations implicate that the disc may contain stem-like cells which possibly responds to stimuli and becomes activated in the degeneration or induced-repair processes. Remarkably, a recent study reported that human NP contains progenitor cells which exhibit self-renewal capacities in vitro and in vivo and express both tyrosine kinase receptor (Tie2) and disialoganglioside 2 (GD2) (*8*). A cognate Tie2 ligand can activate these NP progenitor cells. Such progenitor cell activity was found reduced in degenerated discs. Our recent study has further revealed a group of cells from normal Rhesus monkey discs possesses characteristics of progenitor cells including clonogenicity as well as a tendency to differentiate into multiple cell lineages and retain differentiation potential after extended expansion in vitro and in vivo. The small leucine-rich proteoglycans (SLRPs) may act as a unique niche component to regulate the activities of these disc progenitors through hypoxia induced factors (HIFs), implying that regulation of HIFs activation or stabilization may be a key element that governs the homeostasis of disc progenitors under hypoxic stress (*9*). Because collagen fibrils can regulate stem cell activities (*10*), the findings of the association of disc degeneration with abnormal fibril meshwork provide a new angle to explain the limited self-repair in degenerated intervertebral discs. Altogether, these support a capacity of MSCs in potentiating resident progenitor activities and ultimately tissue repair or regeneration through a regulation on microenvironment, providing mechanistic basis for MSC-based therapies.

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5.0.1

From matrices and cells to biomechanics and clinical benefit - challenges and paradigms in cartilage repair

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Introduction: The multifaceted and multidisciplinary nature of cartilage repair provides this area of research with many exciting avenues to pursue and also many difficult challenges that need to be addressed. Surgeons and scientists from numerous scientific disciplines have been pursuing bone marrow stimulation techniques, cell implantation, biomaterials and tissue implants in people, animal models, and in vitro models. The guiding principle has always been to intervene in some fashion in order to promote the regeneration of the natural structure and function of adult articular cartilage. Healthy adult articular cartilage arises from a development process that has many similarities to endochondral ossification although terminal chondrocyte differentiation to hypertrophy is impeded in the articular zone in contrast to the growth plate. Recent work in this area of articular cartilage development has been very enlightening for cartilage repair since it further details how the very particular and functional structure of adult articular cartilage is biologically produced and has led to the identification of particular cell types in articular cartilage with regenerative properties. Equally enlightening has been recent developments in understanding the biomechanics of articular cartilage where the triumvirate of collagen, proteoglycan and interstitial water are responsible for strain and strain rate dependent stiffness allowing cartilage to be relatively soft under gentle loading conditions but approaching the stiffness of subchondral bone under aggressive loading conditions. From a fundamental point of view the basic question remains “given a symptomatic cartilage lesion requiring treatment, how can we recapitulate natural developmental processes to regenerate structurally and biomechanically sound articular cartilage”.

Content: Prior to proposing particular technologies and techniques that could provide the answer to this question, one should delineate the clinical context in which the treatment will be implemented and the requirements for such a treatment to be accepted. In terms of clinical context, progress has been recently made in understanding the influence of patient specific parameters such as age, lesion location, lesion size, and prior surgery, however the influence of these factors and their interactions need to be more completely understood. There is a need for more well controlled and randomized

studies on tightly defined patient populations. The constraints involved in these types of studies may appear onerous but they lead to very helpful insights that are needed to guide our progress. Further standardization of patient and lesion characteristics would also be very beneficial. In terms of the requirements for acceptance of a new treatment, the overarching theme of clinical benefit versus current standard of care is central for most regulatory agencies. It is important for scientists developing new technologies to understand that perfect structural repair of articular cartilage may not translate to an easily measurable clinical benefit and thus may not be accepted by regulatory or reimbursement authorities. For example simple knee pain scores at 1 or 2 years post treatment may not be influenced by high versus low quality of cartilage repair. Longer times or possibly different clinical benefit outcomes may be needed. The second aspect of demonstrating clinical benefit is the definition of a reference point or a comparator. Often microfracture is used as the bar to which new treatments are compared. This may be a natural choice, however the technique of microfracture still needs to be standardized and such a standard adhered to in order to permit a valid reference comparison to be made. The implementation of this standardized comparator would be of great benefit to the field and to patients.

On the background of cartilage developmental and biomechanics and the clinical context in which treatments for cartilage lesions are to be implemented, the use of biomaterials, cells, bioactive factors and surgical techniques for cartilage repair can be pursued. Some key factors in such studies are the residence, degradation and biological effects of implanted biomaterials, and their influence on natural repair from subchondral bone and effects on opposing cartilage and synovium. Similarly, for implanted cells, it is paramount to follow their fate and understand how they influence repair since recent studies from our field and from other fields suggest delivered cells may have an indirect paracrine effect on tissue regeneration. Any of the proposed treatments will have outcomes that depend on the patient and lesion characteristics (age, location, subchondral bone health...) and also depend upon the type of surgical technique used to prepare the lesion for treatment. Thus the design of studies that test and develop new cartilage treatments is a complex process that needs input from many different disciplines in order to achieve the goal of improvements compared to current treatments. Fortunately the field has benefited from a critical mass of high quality basic and clinical research and there is a rich body of literature upon which we can design new solutions for cartilage repair.

5.0.2

The Joint 'Organ': Comprehensive Concepts for Cartilage Restoration

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Introduction: The natural history of a chondral defect in the knee is currently unknown. Lesion progression to osteoarthritis is both mechanical and biological. If the patient's defect corresponds to their location of symptoms, then surgical treatment may be selected. The surgical goal should aim to not only fill the articular cartilage defect on a stable subchondral base, but also normalize the intra-articular synovial fluid environment homeostasis. Treatment of symptomatic articular cartilage lesions is complex and multifactorial. Surgical decision-making must account for all concomitant patient-, limb-, and knee-specific pathologies. The characterization of long-term surgical "success" is based on patient- and surgeon-based outcome measures.

Content: Management of symptomatic chondral and osteochondral defects in the knee is multifactorial and controversial. Surgeons treating these lesions must avoid linear reasoning and "treat the patient" and not just the presence of a defect on MRI or arthroscopic picture. All concomitant injuries must be addressed including menisco-ligamentous status and alignment. Evidence in the field of articular cartilage restoration is proliferating rapidly, with an emphasis on the knee joint as a whole "organ." The surgical goal is to optimize the cellular and extra-cellular components as close as possible to that of normal hyaline articular cartilage. Single-stage, minimally-invasive procedures utilizing enhanced marrow-stimulation, scaffolds, and autologous and/or allograft cell-based (both chondrocyte and non-chondrocyte [stem cell]) are available options. There is also recent emphasis on the subchondral bone as an important component of the osteochondral unit and its influence on outcomes. Treatments that address both the articular cartilage and subchondral bone include osteochondral autograft/mosaicplasty, osteochondral allograft, and subchondroplasty. Understanding the intra-articular biological inflammatory milieu is of utmost importance as the anabolic, catabolic, and nociceptive constituents of the synovial fluid may alter the outcome of cartilage surgery in the knee. The natural history of a full-thickness chondral defect and the long-term outcomes of biological joint restoration as to the prevention and/or progression of osteoarthritis are currently unknown. Outcome assessment should be based on both validated patient-reported and surgeon-measured outcomes. The quality of articular cartilage research is improving with greater numbers of high-quality randomized trials. There is significant room for development in public and private research funding to improve availability and accessibility of these potentially costly advanced techniques to patients.

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6.1.1

Diagnostic Workup of Patellofemoral Cartilage Injury

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Introduction: High grade focal chondral defects are seen in 11% to 20% of knee arthroscopies: 11% to 23% in the patella, and 6%-15% in the trochlea.[1,2] A detailed history and physical evaluation of the entire kinetic chain from pelvis to foot is essential before attributing a patient's symptoms solely to the presence of a chondral defect. The key to successful treatment lies in the correct diagnosis of a chondral defect, and also, in the accurate identification of associated pathomechanical factors, such as patella alta, trochlea dysplasia, increased lateral position of the tibial tubercle and secondary soft-tissue problems.

Content:

History

Symptoms: Record the onset, duration and progress of the problem with effect on activities of daily living. Identify anterior knee pain with or without patellar instability; Is the pain more troublesome or instability?

Pain: Associated trauma, exact location and timing of pain (activity related), quality, radiation, exacerbating and relieving factors should be noted. The commonest history is of anterior knee pain. Sometimes, pain is retropatellar, peri-patellar, or in the instance of trochlear defects, posteriorly in the popliteal fossa. Ask for increased pain with prolonged flexed knee (movie-theatre sign) and stair climbing, or difficulty getting up from a low chair. Rule out pain referred from the hip.

Instability: Often the mechanism of patellofemoral (PF) chondropathy is unknown. Trauma is the commonest initiating factor. Ascertain the amount of energy associated with the first dislocation-higher the energy greater is the incidence of chondral pathology. Patellar dislocation is associated with damage to the articular surface in up to 95% of patients.[3] Record the most recent dislocation-interval pain and effusion may suggest chondral damage.

Feeling of giving away: due to quadriceps weakness, meniscal tear, ligament deficiency, or other disorders around the knee.

Locking: catching sensation that occurs on extension under load (staircase climbing or chair rising) unlike meniscal pathology where the knee locks up.

Crepitus: common symptom which should not be over treated. It may occur due to malalignment, synovial impingement, quadriceps tendon, or chondrosis. Large defects can cause clicking or popping

Past History:

Rule out medial patellar instability after a lateral release or realignment surgery. Failure to consider this might lead to a misdiagnosis of persisting lateral instability and lead to unnecessary surgery leading to further exacerbation of the problem.

Physical Examination

Gait Anatalgic or not

Symmetry

Stride length

Patellar orientation

Alignment of the knee

Pelvic tilt.

Single leg knee bend test: the patient is asked to bend his leg bringing the knee close to the thorax. Which helps assess the quadriceps as well as evaluate the core stability at the hip and pronation of foot and ankle.[4]

Standing examination

With the patient barefoot in the bipodal position, feet together pointing ahead, look for:

Alignment of the limb

Orientation of the patellae

Patellar height

Patients with a valgus angulation are predisposed to lateral subluxation; those with squinting patellae have a higher incidence of PF pain, while out-facing patellae are associated with habitual subluxation or dislocations.

From the side and back, the inclination of the pelvis, spinal curvatures and the position of the body with respect to the pelvis and foot rotation anomalies can be assessed.

Q angle: gives an idea of the tracking of the knee. It is measured in the standing position by drawing a line between the center of the patella and the anterior superior iliac spine and a second line between the center of the patella and the center of the tibial tubercle (average 14° in men, 17° in women). Anatomic variants (in facing patellae or lateral displacement of the tibial tubercle) result in an increased Q angle which increased tendency for patellofemoral pain.[5,6]

Seated examination

Inspection

Swelling of the tibial tuberosity or inferior pole of the patella: osteo-chondrosis, insertional tendinitis or a partial rupture of the patellar tendon. Muscular atrophy: especially Vastus medialis Patellar height:Patella alta, the high riding patella faces upwards towards the ceilingPatella baja, the patella is lower than the normal side, drawn into the sulcus between the femoral condyles.

Patellar tracking: In the presence of instability, the patella undergoes

subluxation near full extension constituting the J-sign.[7]

Tubercle-sulcus angle: Assessed at 90° knee flexion, it is a variation of the Q angle[8], measured by drawing a line passing through the centre of the patella and the centre of tibial tubercle and a second line drawn perpendicular to the transepicondylar axis. Normally ≤ 8° in women and ≤ 5° in men

Supine examination

Inspection: Rotation of the extremities Lateral patellar tracking with movement of the knee

Palpation: Patellar facet tenderness[9]: The patella is shifted medially to expose the medial facet and is palpated for tenderness, then repeated for the lateral facet.

Excessive lateral pressure syndrome: tenderness is localized to the PF ligament. Anteromedial knee pain may be due to an inflamed medial patellar plica[10] palpable as a fibrous cord between the patella and medial femoral condyle.

Extensor mechanism: In case of quadriceps or patellar tendon rupture, a gap is palpated along with tenderness on attempted straight leg raise test.

Jumper's knee: tenderness and spongy crepitus at proximal patellar tendon just inferior to the tip of patella

Special tests

Passive patellar grind test

The patella is pressed with the palm of one hand against the femoral groove and the knee is passively flexed. In the presence of degeneration or irregularity of the articular surface, a crunching sensation is transmitted along with pain.[11]

Step-Up-Step-Down test

Pain and crepitus are felt for; intense pain on early step down suggests a distal articular lesion. An unloading operation of the distal pole such as an anterior or anteromedial tibial tubercle transfer is indicated.

Patellar glide test

With the knee at 20°-30° flexion along with a relaxed quadriceps, this test estimates passive patellar mobility. Translation is estimated between the centre of patella and the medial and lateral epicondyles. In the presence of a tear of the medial or lateral structures, it is increased. Translation is decreased in case of arthrofibrosis.[12]

Passive patellar tilt test

With the knee extended and quadriceps relaxed, it is used to evaluate the lateral retinaculum. Normal tilt is 0°; In case of excessive surgical release of the lateral retinaculum, the tilt is increased and the patellar plane may be rotated internally.[13]

Engagement sign

To assess the tracking and engagement of the patella over the proximal trochlea; usually abnormal in cases of dysplastic trochlea, patella alta or recurvatum leading to patellofemoral pain. Pain is felt at the inferior pole of the patella when the patella engages the trochlea as the knee is flexed with pressure over the distal tip of patella; a bump can also be felt in case of dysplastic trochlea.[14]

Apprehension test (Fairbanks sign)

Pathognomonic of symptomatic patellar instability; simulates an episode of patellar dislocation under controlled conditions.[15] Apprehension manifesting as expressions of anxiety or quadriceps contraction to prevent knee flexion suggests a positive test.

IMAGING FOR PF JOINT

RADIOGRAPHS

AP view (monopodal stance when possible) supplemented with a hip to ankle alignment film is used to determine the extent of varus or valgus alignment and joint space narrowing.[3]

30 or 45 degree flexion Rosenberg/ Shuss view: better to detect joint line narrowing.

True lateral view (superimposed posterior condyles) monopodal in 15-20° flexion will show Patella alta/baja. Dejour et al. have shown that the true lateral radiograph provides more information to assess trochlear dysplasia (crossing sign between the sulcus line and lateral condyle) while Maldague and Malghem evaluated patellar tilt.[16,17] Patellar height is to be measured with indices (Caton-Deschamps, Insall-Salvati ratio or Blackburne-Peel index)

Low flexion angle axial view (Merchant view): sulcus angle, congruence angle, joint space narrowing, subchondral sclerosis and shape of the patella can be assessed

Stress radiographs: only objective measure of PF joint instability.

CT SCAN

Ordinary CT scans do not provide much information about cartilage status, unless intra-articular contrast is injected (CT arthrogram). This allows identification of Stage I to IV chondral lesions, cartilage thickness and allows detailed assessment of lesion position and dimensions.

This is a useful tool when a tibial tubercle osteotomy is being considered. The tibia tubercle-trochlear groove (TT-TG) distance can be measured and can be a guide towards decision making. Multiple flexion angles may provide more information where cartilage lesions are associated with a malpositioned patella relative to the trochlea.

MRI

Superior sensitivity and specificity for articular cartilage has made it an essential investigation for evaluating osteochondral lesions. Due to thickness of patellar cartilage, it can be visualized in both axial and sagittal cuts. Geometry and thinner cartilage of trochlea make it harder to assess.

Short-tau inversion recovery (STIR) sequences are an example of a fat-suppression technique used for imaging cartilage defects.

T1-weighted series: illustrate anatomic features of articular cartilage well

T2-weighted series: better demonstrate contrast between cartilage and joint fluid

3D FISP (fast imaging with steady procession): when effusion is present

3D Flash sequences: very sensitive for PF lesions.

Emerging sequences:

3T 3D DESS (double echo steady state) and 3T 3D SPGR (spoiled gradient echo): These permit volumetric analysis.

Gadolinium enhanced MRI can quantify the content and distribution of glycosaminoglycan (GAG) in articular cartilage. T2 mapping is more sensitive to collagen structure.[18]

DIAGNOSTIC ARTHROSCOPY

Chondral lesions may be classified as per the International Cartilage Repair Society (ICRS) System

Grade 0: Macroscopically Normal cartilage

Grade 1a: Cartilage with intact surface with fibrillation and/or slight softening

Grade 1 b: Grade 1 a with additional superficial lacerations or fissures

Grade 2: defects that extend deeper but involve less than 50% of the cartilage thickness

Grade 3: Defects that extend more than 50% of the cartilage thickness, but not through the subchondral bone plate

Grade 4: Cartilage lesions that extend into the subchondral bone

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6.1.2

Treatment Options, Surgical Indications & Outcome in the Patellofemoral Cartilage Repair

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Introduction: Patello-femoral chondomalacia remains one of the most troubling conditions for an orthopedist to treat. A careful assessment with physical examination and clinical history is the basis for assessment and management. Muscle imbalance, soft tissue contractures and patellar maltracking are easily discovered by physical exam. Physical therapy to relieve these conditions remains the mainstay of primary treatment, as is successful in the majority of patients.

Content: Specialized testing to localize background factors are only necessary when therapy fails to produce improvement. Plain films are very useful to identify patella alta or infera, trochlea dysplasia by Dejours lateral "crossing sign", as well as radiographic joint space narrowing and eary osteoarthritis. CT scan with intra- articular contrast agent with the knee in extension with the qudriceps relaed and the contracted is a powerful test which can localize articular cartilage location, dyspasia, bone cysts and sclerosis as well as TT_TG distance (Tibial Tubercle – Tibial Groove distance normally ⟨ 18mm) for maltracking as well as direct view of tilt and subluxation or maltracking. MRI scan offers accurate assessment of cartilage fissuring, swelling and subchondral bone marrow edema.All this information is necessary prior to recommending a treatment plan to restore normal mechanics and the possibility of cartilage repair.

Fulkerson [1] demonstrated that when there was articular damage to the inferior pole or lateral facet of the patella in combination with an increased TT_TG or lateral maltracking that an antero-medialization of the tibial tubercle in combination with a soft tissue realignment of the extensor mechanism could produce good and excellent clinical improvements in 85% of patients for up to 10 years. However defects in other locations of the patella would result in poor outcomes.

Initial results of ACI in the patella were poor when maltracking was not addressed but improved to almost 80% good and excellent when realignment was added [2]. Our results [3], mirrored those of Peterson and noted that the lesions were substantial ($5cm^2$) and localized to those areas that would not do well with isolated osteotomy alone proving that cartilage repair was necessary to get a good outcome with pan – patellar disease or medial facet disease of the patella.

Bentley[4] demonstrated that ACI in the patella was preferable to mosaicplasty for the patella and recommended that maosaicplasty be abandoned in the patella based on the uniformly poor outcomes in his series and that ACI be the treatment of choice.

Kreuz et al.[5], noted that microfracture did demostrate improvements in the first 18 months after treatment in the patellofemoral jont but these results deteriorated from 18-36 momnths and were shorth lived and did not recommend this in this location.

Our longterm results in the isolated patella have just been reviewed and are as follows.

A Comprehensive Assessment of Autologous Chondrocyte Implantation to Isolated Patella Defects: a two- to fifteen year follow-up

by Keudell A, Bryant T, Han R, Minas T

Background: Autologous Chondrocyte Implantation has been proven to be a lasting treatment option for patients with chondral defects. Up to now, there has been limited evidence of the efficacy of ACI to single defects in the patella.

Methods: Between May 1995 and May 2009, 510 patients were treated with ACI at our institution. Among those were 30 symptomatic focal chondral patella (4 Type II, 7 Type III, 7 Type IVa, 12 Type IVb) defects that we treated with autologous chondrocyte implantation and 22/30 underwent additional Tibial Tubercle Osteotomy (20/22 Fulkerson and 2/22 McKay TTO). 24/30 patients experienced either sports-, motor vehicle- or fall- related trauma. The defect size averaged at 4.7± $2.1cm^2$. M/F ratio was 12/18, Ø BMI=27 and Ø age at time of surgery was 32±10 years. Prospective evaluation of patients with a series of validated clinical assays and subjective clinical rating (Patient Satisfaction, modified Cincinnati, Knee Society Score, WOMAC, SF36) was performed at a minimum of twenty-four months and up to hundred-and-seventy five months. Magnetic resonance imaging using the MOCART score was performed at a mean of thirty-one months.

Results: At the time of last follow-up, knee function was rated good to excellent in twenty-five patients (83%), fair in four patients (13%) and poor in one patient (3%). Three patients failed after a mean of 75 months. Failures were defined as ⟩25% delamination, revision cartilage repair surgery or prosthesis implantation. Significant increases in all clinical and health utility outcome scores were seen. Age was positively correlated with higher clinical scores(r= -0.6, p=0.0009). Magnetic resonance imaging at 31±25 months postoperative in twenty-four knees demonstrated good repair-tissue fill in the defect in eighteen patients (75%), moderate fill in five (21%), and poor fill in one patient (4%). The fill grade, surface and integrity of the repair tissue correlated with clinical scores (r=-0.43, r=-0.48, p=-0.44, respectively; p⟨0.05). All knees with good fill demonstrated improved knee function and pain, whereas poor fill

grade was associated with limited improvement and decreasing functional scores after twenty-four months.

Conclusion: Autologous chondrocyte implantation to isolated patella defects results in significant functional improvement at a minimum of 24 months. The best outcome was seen with good fill grade, surface and integration of the graft.

In summary, treatment of patellofemoral disease demands a thorough evaluation of the background factors necessary for the cartilage loss and then localizing damage on the patella, trochlea or both. Boney realignment is frequently required and when cartilage repair is necessary to those large lesions that are pan – patellar, medial patella facet or central trochlea, then ACI provides durable and predictable results that appears to be supported in the literature as the best technique. This is the author's favored technique in this problematic location in the knee.

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6.2.1

Does cellular graft quality affect cartilage repair outcome?

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Introduction: A recent study proposed a correlation between the symptomatology of patients treated with ACI and the quality of the repair tissue, suggesting that the persistence of symptoms, e.g. pain or swelling, after surgery is reflected by the presence of non-hyaline cartilage repair tissue [1]. These observations underline the importance to improve the quality of the generated repair tissue following treatment of cartilage defects and in turn prompt to address in which way the properties of the implanted graft regulate the quality of tissue repair.

In the absence of more stringent experimental models, the field is currently driven by the assumption that the potency of implanted cells in a joint can be predicted by their in vitro or in vivo (ectopic implantation in nude mice) cartilage forming capacity. However, very little knowledge has been generated in the attempt to correlate the clinical outcome of ACI with the properties of the implanted cells.

Similar considerations hold in the related area of tissue engineered cartilage. The regeneration of a hyaline-like tissue could be facilitated by the implantation of a pre-engineered, functional cartilage tissue, as opposed to the delivery of a chondrocyte suspension. This would imply that autologous cells are cultured within an environment permissive of or supporting chondrogenesis (e.g., a porous three-dimensional – 3D – biomaterial of pre-defined size and shape), generating a graft approaching the biochemical and biomechanical properties of native cartilage. Indeed, the presence of extracellular matrix (ECM) around cells was reported to enhance donor cell retention at the repair site [2] and possibly protect the cells from environmental factors such as inflammatory molecules [3]. Furthermore, pre-cultivation under conditions inducing cell differentiation was shown to support enhanced ***in vivo*** development of engineered cartilage at ectopic sites in mice as well as orthotopically [4] and improved cellular response to a compressive deformation conditioning resembling a mild rehabilitation regime. Importantly, from a clinical point of view, the improved mechanical stability of the more mature and stable engineered graft would also allow easier surgical handling, application even in critically sized defects and possibly earlier post-operative loading.

Content: One often underestimated critical factor in cartilage tissue engineering is the quality of the starting material, namely the chondrocytes isolated from different cartilage biopsies. The capacity of isolated cartilage cells to proliferate and – most importantly – to regenerate a tissue is in fact not only dependent on the health state of the joint and on the age of the donor, but is also extremely variable between individuals in the same age range and with no history of joint disease. The use of specific growth factors during cell expansion, in conjunction with low percentages of serum, can reduce the variability in proliferation and re-differentiation capacity, but is not sufficient to guarantee a reproducible quality of the resulting engineered cartilage. This challenge poses the critical question of whether autologous cell-based grafts will ever be considered as suitable for clinical use if their quality cannot be standardized within a rather narrow range.

In this context, several groups have strived to identify markers to predict and possibly control the chondrogenic capacity of chondrocytes. But despite interesting studies targeting expression of a discrete set of genes [5], of surface molecules [6] or of secreted proteins [7], markers reliably capable to distinguish cell populations with specific degrees of cartilage forming ability have yet to be identified.

In order to translate the opportunities of cell-based cartilage repair into effective therapeutic options (e.g., for the treatment of traumatic cartilage injuries), it will be essential to understand which signals should be delivered at what stage into a joint to promote durable cartilage regeneration. Only with this fundamental knowledge will it be possible to design cellular grafts with a defined mode of action and supported by suitable quality controls for predictable potency. Ultimately, we have to admit that - although the first clinical report of autologous chondrocyte implantation is now dated about 20 years ago – it is not yet established which factors play which role in the cartilage healing processes.

Is cartilage regeneration dependent upon the quality of the delivered cells, which play an active role in producing a suitable repair tissue? Or are the functional properties of the developed extracellular matrix in the graft the key regenerative signal, possibly by supporting appropriate transduction of mechanical loading? Or is the profile of cytokines released by the transplanted cells the essential component to manage local inflammation and stimulate tissue repair? Until these crucial questions find scientifically grounded answers, it will not be possible to define whether a quality control for engineered cartilage products should rely on the chondrogenic capacity of the implanted cells, on the mechanical tests of the developed matrix, or on the pattern of factors produced and released during culture. And without a clearly identified mode of action, combined with predictable potency factors, it will not be realistic or sound to introduce a product which is not easily standardized and reproducible for a widespread clinical use.

Thus, the field critically requires to perform hypothesis-driven experiments aiming at the definition of mechanistic relationships between specific cellular graft properties and the resulting clinical outcome. At this stage, the gained knowledge and understanding will be crucial to design alternative, smarter ways to deliver the defined cues in an injured joint. This could be addressed for example by using drug delivery vehicles, cell-free intelligent scaffolding materials or intra-operative cell processing procedures, combined with appropriate surgical techniques and post-operative rehabilitation regimes.

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The text of this extended abstract has been liberally adapted from [8]

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6.2.2

Use of Histology, Biomarkers & Proteomics to determine Tissue Quality and Outcome

S. Roberts, H. Fuller, K. Wright, H.S. McCarthy
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Introduction: Many tools can be used to assess the health status of an individual, or more specifically for this society, the health of articular cartilage. Histology, biomarkers and proteomics are all such techniques and can be used not only to determine the disease state of cartilage but also to monitor the success of repair techniques used in its treatment. They can contribute to the evaluation of therapies but can also further our understanding of the biology and processes leading to clinical success and good quality repair. All have advantages and also limitations which will be described briefly.

Content: Histology provides information on the structure of the repair tissue, the molecules present in the matrix and the way they are organised; it can therefore provide information on the expected functioning of the tissue, for example, its ability to resist compressive loading. Depending on the orientation and manner in which the sample is obtained and how it is processed subsequently, it can also provide a whole raft of other information. The use of antibodies specific to different molecules can identify the extracellular matrix molecules, whilst using antibodies to signalling molecules or those on the cell membrane can inform on different cellular pathways or processes such as senescence, apoptosis or necrosis. It can also be combined with other physical techniques, such as fourier-tranformed infra red spectroscopy (FT-IRIS) to provide a sophisticated mode of analysis (Hanifi et al 2012).

Histology is often assessed qualitatively and as such can be very helpful. However for it to be a useful outcome measure in preclinical or clinical trials (Hoemann et al 2011), some means of scoring and rendering it more quantitative is required. Several scoring systems have been developed, for both diseased and more recently repair cartilage (reviewed by Rutgers et al 2010). The ICRS II score, developed by the histological endpoint committee of the ICRS, has now been used in several clinical trials; it assesses 14 different parameters using a visual analogue score for each, to improve discrimination (Mainil-Varlet et al 2010).

Limitations of histology as an outcome measure for patients relate primarily to it being invasive and necessitating removal of some of the repair tissue itself. This makes the use of histology for longitudinal study unattractive. Also histological study of a necessarily small biopsy represents only a fraction of the whole repair region so cannot assess total lateral integration, for example, as imaging modalities could do (Roberts et al 20013).

Biomarkers, measuring levels of biochemicals in body fluids, such as synovial fluid (SF), urine and plasma or serum, may also assist in assessing cartilage tissue quality and repair. There are numerous groups world-wide exploring the potential of several known osteoarthritis (OA) related biomarkers, including enzymes associated with matrix degradation, such as matrix metalloproteinases, or matrix components such as hyaluronan, cartilage oligomeric matrix protein (COMP) and glycosaminolgycans (eg chondroitin sulphates (CS)). Their use in screening or monitoring patients treated for cartilage repair, however, is limited. Nganvongpanit et al (2009) monitored serum levels of CS and hyaluronan (HA) in dogs following ACI and drilling, with CS levels showing some promise as a biomarker. Vasara et al (2009) have followed patients pre-treatment and 1 year post-ACI, monitoring MMP3 and IGF-1, and see increased levels of both of these a year after treatment.

In our centre ACI has a success rate of ~80% (as indicated by a post-operative increase in Lysholm score). We are seeking biomarkers in this patient group which could either predict pre-operatively the success or failure of ACI or could also be used to monitor the injury site post-operatively. We have measured aggrecanase activity, hyaluronan (HA), COMP, CD14 and lipid levels in the SF and where possible, in the blood plasma of 97 ACI patients. This patient group was composed of 28 ACI 'non-responders' and 67 ACI 'responders'. All assay results in synovial fluid were normalised to urea content.

HA, COMP and CD14 levels were significantly higher in the SF of ACI responders post-operatively compared to ACI non-responders. Lipid levels increased in the SF of all patients following ACI treatment. No significant differences were observed between patient groups for any of the biomarkers tested in blood plasma. Aggrecanase activity was elevated in the SF of those ACI patients that did not respond to treatment, both before and after cell implantation, compared to those for which the procedure was deemed a success. This suggests that aggrecanase activity in the SF of joints with cartilage defects may be used to identify patients that will not respond to standard ACI treatment. Elevated levels of HA, COMP and CD14 in the SF of ACI patients that respond well to treatment may be indicative of functional cartilage remodelling and beneficial prolonged inflammatory processes in ACI treated joints. Lipid levels may increase in the SF of ACI treated joints as a consequence of blood and marrow infiltration following surgery.

The attraction of biomarkers is that they can often be measured quickly, in an automated and usually quantitative form. It is relatively non-invasive to obtain the samples and they can be performed longitudinally. Limitations may relate to the stability of the molecule and possibly their metabolism. Blood markers are usually measured per millilitre of plasma or serum. For urine or synovial fluid, however, this is not so convenient. With urine, a decision needs to be made as to whether to measure the 24 hour output (providing logistics problems for the laboratory and patient) or if not, should it be normalised to creatinine or urea? In synovial fluid, markers will need to be normalised to another molecule due to difficulties of volume control and sampling.

Proteomics, in contrast, is a technique which determines the presence of the 'whole' protein population, rather than individual molecules. Characterisation of proteomic changes associated with disease often helps to shed light on disease mechanisms and identify biomarkers for therapeutic target and disease prognosis. It is rarely the case that such proteins are either "present" or "absent", but more likely that they vary in abundance to different degrees. It is therefore important to have a sensitive and accurate method to measure these changes using an unbiased approach. Shotgun proteomic approaches enable identification of proteins that are up-regulated or down-regulated under specific conditions and this can be studied in a range of patient samples (e.g. cell and tissue lysates, serum, urine, CSF and synovial fluid). Isobaric tags for relative and absolute quantification (iTRAQ) make it possible to both identify and quantify proteins simultaneously, and can easily be multiplexed, enabling analysis of up to 8 different samples within the same experiment.

Our own research on a cartilage repair technique can be used to illustrate the application of iTRAQ for a clinically-relevant problem. Again, seeking to understand why 20% of patients treated in our centre do not respond so well, we aimed to determine if there is a protein biomarker in the synovial fluid that could predict the success of ACI and aid patient selection. Using iTRAQ labelling and MALDI TOF-TOF mass spectrometry (Comley et al 2011; Fuller et al 2010,2012), we performed an unbiased and quantitative proteomic comparison of synovial fluid, with and without albumin and Ig

depletion, pooled from 4 patients who had responded well to ACI with synovial fluid from 4 pooled samples from patients who did not respond well to ACI. (Responders were identified by a Lysholm clinical score increase of 55 points compared to the pre-operative value, at an average of 13 months post ACI, and non-responders were identified by a mean decrease in Lysholm score of 26 points post-ACI).

Following strict filtering of the data and statistical analysis, 20 out of the 175 proteins identified (without albumin and Ig depletion) and 17 out of the 125 proteins identified (with albumin and Ig depletion) appeared to be significantly altered between non-responders and responders. Notably, numerous lipid and haemoglobin binding and carrier proteins appeared to be elevated in the responder group, whilst matrix molecules appear to be highest in the non-responder group. Lipids are likely to be associated with lipid binding proteins and so perhaps lipid rich synovial fluid provides an optimal environment for ACI joint repair by reducing friction or shear on fragile repair tissue. In contrast, matrix proteins were markedly increased in the pooled SF from non-responders, including fibronectin, lubricin, lumican and cartilage oligomeric matrix protein. This may indicate severe osteoarthritic changes in patients where joint destruction may be too advanced to respond to ACI treatment. Although further validation work is needed, this preliminary study shows that iTRAQ-labelling and mass spectrometry is a useful technique for highlighting potential biomarkers worthy of follow-up study.

Whilst mass spectroscopy and proteomics is a hugely powerful technique, like all methods it too does have limitations. One of these is cost, with a detailed analysis perhaps costing thousands of euros per sample (hence the rationale for pooling samples above, but which is not an ideal approach). It also creates a mountain of data which requires careful and skilled analysis. These different methods each have their forté and the appropriate method should be chosen depending on the design of the individual study and the question being asked.

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6.2.3

MRI Assessment of Tissue Quality & Outcome

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Introduction: Articular cartilage is important in providing a low-friction gliding surface in joints, to acting as a shock-absorber, and to minimizing peak pressures on the subchondral bone. Its defects are one of the most common results of injuries in the knee joint. The inability of cartilage to heal has led to the development of treatment options to reduce symptoms and to prevent osteoarthritis. These include marrow stimulation techniques like microfracturing, osteochondral transplantation, autologous chondrocyte transplantation in different variations and other techniques.

Content: To evaluate not only the results of surgical cartilage repair procedures, but also the presurgical cartilage situation, Magnetic Resonance Imaging (MRI) is the method of choice for its non-invasivness, multi-planar capability and high soft tissue contrast. Different morphological and biochemical cartilage specific sequences are therefore available to assess the repair tissue in comparison to its surrounding healthy cartilage. A helpful tool is the semiquantitative evaluation of scores with variables, which make the results comparable between patients and during the course of follow up. One of the most often used, adapted and enhanced scores is the MOCART (Magentic resonace Observation of CArtilage Repair Tissue) score.

The score and evaluation parameters give the opportunity to compare patients and studies even in multi-center trials, as well as to show the maturation of repair tissue in the follow-up, with statistically significant correlations between different parameters and different clinical scores. Furthermore, a new score has been introduced, adapted to the requirements of isotropic sequences, giving the possibility to observe the repair tissue in the axial, coronal and sagittal plane - this score is called 3D-MOCART. Regarding the MRI evaluation, MOCART as well as 3D-MOCART are designed not only for the assessment of cartilage repair tissue after matrix-associated autologous chondrocyte transplantation (MACT), but also to evaluate the radiological outcome after OCT-procedures. MRI classification system – MOCART (Magnetic resonance Observation of CArtilage Repair Tissue)

MRI as a method for the observation and assessment of cartilage repair tissue is widely available, and a practical point scoring system like the MOCART (Magnetic resonance Observation of CArtilage Repair Tissue) or the 3D MOCART is beneficial. Based on the standard 2D MOCART score, the 3D MOCART uses the capabilities of increasingly available isotropic 3D MR sequences to better grade the repair tissue and its adjacent structures after multiplanar reconstruction (MPR) of this 3D MR data set.

The 2D MOCART score evaluates nine pertinent parameters the degree of the defect repair and filling of the defect, the integration to border zone, the surface of the repair tissue, the structure of the repair tissue, the signal of the repair tissue, the integrity of the subchondral lamina and the subchondral bone and the appearance of adhesions and effusion. The 3D MOCART is based on the 2D MOCART and includes the evaluation of the degree of defect fill in a more detailed graduation, the cartilage interface in two planes, the bone interface, the surface, the structure, the signal intensity, the subchondral lamina, the chondral osteophytes, the bone marrow edema, the subchondral bone and effusion. **2D MOCART Score**

1. Degree of defect repair and filling of the defect
Complete (on a level with adjacent cartilage) 20
Hypertrophy (over the level of adjacent cartilage) 15

Incomplete (under the level of adjacent cartilage)
⇢50% of adjacent cartilage 10
⇠50% of adjacent cartilage 5
Subchondral bone exposed (complete delamination or dislocation and/or loose body 0

2. Integration to border zone
Complete (complete integration with adjacent cartilage) 15
Incomplete (incomplete integration with adj. cartilage)
Demarcating border visible (split-like) 10
Defect visible
⇠50% of the length of the repair tissue 5
⇢50% of the length of the repair tissue 0

3. Suface of the repair tissue
Surface intact (lamina splenders intact) 10
Surface damaged (fibrillations, fissures and ulcerations)
⇠50% of repair tissue depth 5
⇢50% of repair tissue depth 0

4. Structure of the repair tissue
Homogenous 5
Inhomogenous or cleft formation 0

5. Signal intensity of the repair tissue
Dual T2-FSE
Isointense 15
Moderate hyperintense 5
Markedly hyperintense 0
3D-GE-FS
Isointense 15
Moderate hypointense 5
Markedly hypointense 0

6. Subchondrale lamina
Intact 5
Not intact 0

7. Subchondral bone
Intact 5
Non-intact (edema, granulation tissue, cysts, sclerosis 0

8. Ahesions
No 5
Yes 0

9. Effusion
No 5
Yes 0

Max 100 **3D MOCART Score** Variables Points

1. Defect-fill (degree of defect repair and filling of the defect in relation to the adjacent cartilage)
0 % 0
0-25 % 0
25-50 % 5
50-75 % 10
75-100 % 10
100 % 15
100-125 % 15
125-150 % 5
150-200% 0
⇢ 200% 0
Lokalisation
Whole area of cartilage repair ⇢50% ⇠50%
Central Peripheral Weight-bearing Non weight-bearing

2. Cartilage Interface(Integration with adjacent cartilage to border zone in two planes)
Sagittal Coronar (Patella, Trochlea: Axial) 15
Complete Complete
Demarcating border Demarcating border 10
Defect visible ⇠ 50% Defect visible ⇠ 50% 5
Defect visible ⇢ 50% Defect visible ⇢ 50% 0
Lokalisation
Whole area of cartilage repair ⇢50% ⇠50%
Central Peripheral Weight-bearing Non weight-bearing

3. Bone Interface (integration of the transplant to the subchondral bone; intefration of a possible periosteal flap)
Complete 5
Partial delamination 0
Complete delamination 0
Delamination of periosteal flap 0
Lokalisation
Weight-bearing Non weight-bearing

4. Surface (constitution of the surface of the repair tissue)
Surface intact 10
Surface demaged ⇠50% of depth 5
Surface demaged ⇢50% of depth 0
Adhesions 0
Lokalisation
Whole area of cartilage repair ⇢50% ⇠50%
Central Peripheral Weight-bearing Non weight-bearing

5. Stucture (constitution of the repair tissue)
Homogeneous 5
Inhomogeneous 0
Cleft formation 0
Lokalisation
Whole area of cartilage repair ⇢50% ⇠50%
Central Peripheral Weight-bearing Non weight-bearing

6. Signal-Intensity (Intensity of MR signal of the repair tissue in comparison to the adjacent cartilage)
Normal (identical to adjacent cartilage) 15
Nearly normal (slight areas of signal alteration) 10
Abnormal (large areas of signal alteration) 0
Lokalisation
Central Peripheral Weight-bearing Non weight-bearing

7. Subchondral Lamina (Constitution of the subchondral lamina)
Intact 5
Not Intact 0
Lokalisation
Whole area of cartilage repair ⇢50% ⇠50%
Central Peripheral Weight-bearing Non weight-bearing

8. Chondral Osteophyts (Osteophytes within the cartilage repair area)
Absent 5
Osteophyt with ⇠50% of the thickness of the cartilage transplant 5
Osteophyt with ⇢50% of the thickness of the cartilage transplant 0
Lokalisation
Size: _____mm (plane:_____) x _____mm (plane:_____)
Central Peripheral Weight-bearing Non weight-bearing

9. Bone marrow edema (Maximum size and localization in relation to the cartilage repair tissue and other alterations assessed in the 3D MOCART Score)
Absent 5
Small (⇠1cm) 0
Medium (⇠2cm) 0
Large (⇠4cm) 0
Diffuse 0
Lokalisation
Size: _____mm (plane:_____) x _____mm (plane:_____)
Whole area of cartilage repair ⇢50% ⇠50%
Central Peripheral Weight-bearing Non weight-bearing

10. Subchondral Bone (Constitution of the subchondral bone)
Intact 5
Not Intact 0
Granulation tissue
Cyst
Sclerosis
Lokalisation
Whole area of cartilage repair ⇢50% ⇠50%
Central Peripheral Weight-bearing Non weight-bearing

11. Effusion (Approx. size of joint effusion visualized in all planes)
Absent 15
Small 10
Medium 10
Large 0
Max 100

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7.1.0

Basic Science of the Subchondral Bone in Healthy, Diseased & Repaired Cartilage

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Introduction: The subchondral bone is a mineralized and porous structure that bridges the ends of long bones and the articular cartilage. As the injured knee adapts to altered load-bearing and inflammatory changes, osteoarthritis, a disease of both bone and cartilage, can progress along with cartilage loss, thickening of the calcified cartilage layer, and sclerosis and stiffening of the subchondral bone plate. Due to the complexities of treating partial-thickness cartilage lesions, cartilage repair therapies normally begin with complete debridement of all non-calcified lesional cartilage. Therapeutic treatments are subsequently applied not to cartilage, but to the exposed calcified cartilage or subchondral bone. Recent advances have been made in understanding how surgically-induced damage of subchondral bone leads to repair responses tied to hyaline cartilage regeneration.

Content:

The bone plate exhibits striking anatomical changes in disease.

Below healthy cartilage with normal loading patterns, the subchondral bone trabeculae are arranged as ordered "spokes" that fan outward from the bone plate, which allows an even transmission of load. Rabbit models of cartilage repair have shown that the contours of the bone plate adapt to the biomechanical environment. Forced articulation of a displaced knee patella can create new trochlear groove on the lateral facet[1]. In normal human joints, the bone plate can be very thin, around 1 trabeculae[2] (~70 µm), while in animal joints the bone plate may be as thick or thicker than the articular cartilage layer (up to 500 µm) [3, 45]. Damaged articular cartilage can develop into a lesion with an unpredictable rate, and may take years to become a full-thickness lesion. During this time, the subchondral bone is changing. With increasing cartilage lesion severity, the subchondral bone develops an abnormal trabecular structure and most frequently becomes sclerotic[6]. A sclerotic bone plate can be up to 2000 µm to 3000 µm thick. Bone plate sclerosis fills the region below a cartilage region with bone matrix and diminishes the number and proximity of bone marrow mesenchymal stem cells in the vicinity of the lesion. Bone plate sclerosis also diminishes microfracture-induced marrow access, the physical communication between the cell-rich marrow cavities and the cartilage lesion [6]. Treatment of cartilage lesions by microfracture leads to unpredictable levels of tissue fill, and greater fill is associated with improved outcomes[7].

Bone plate structure is altered by subchondral bone damage.

Once surgically removed, by drilling, microfracture, or coring, subchondral bone is very slow to regenerate in skeletally mature joints. In a sheep model, subchondral bone defects created by Jamshidi biopsy persist at 3 months post-operative as mainly non-mineralized tissues[8]. Deep drilling in sheep condyles can lead to osteolysis and subchondral cyst formation [9]. At 6 months post-operative, in a rabbit model of microdrilling, the perforated bone plate is incompletely restored, and the surrounding bone plate exhibits signs of sclerosis[10]. Treatment of the microdrilled defect with a chitosan/blood implant led to a more porous regenerated subchondral bone plate[11], fewer residual drill hole voids, and a more integrated cartilage repair tissue with higher levels of glycosaminoglycan[10]. Porous subchondral bone arises from a more robust subchondral angiogenesis response during early stages of subchondral bone repair which favors woven bone synthesis [12], and in later stages of cartilage repair, when the deep zone hypertrophies and becomes invaded by blood vessels during endochondral ossification.

Studies on subchondral bone damage leading to hyaline articular cartilage repair suggest a role for bone remodeling

The highest quality articular cartilage repair tissue is frequently observed along with a remodeling and regenerating bone plate, following bone marrow stimulation[8, 13] or cell-assisted therapy [14, 15]. Occasionally, hyaline repair cartilage is formed above subchondral cysts that develop deeper in the bone, below the initial defect [16,17]. Hyaline cartilage repair is believed to arise from bone marrow mesenchymal stromal cells (MSCs), which normally synthesize collagen type I, the major matrix component of bone and fibrous tissue. Therefore, commitment of stromal cells to the chondrocyte lineage is needed to initiate hyaline cartilage repair from subchondral bone. This phenotypic switch involves repression of collagen type I, which may be partly mediated by miRNA[18, 19], and induction of collagen type II expression, which depends on Sox9 [20]. These factors are known to be under the control of bone morphogenetic proteins (BMP) and transforming growth factors (TGF-β).

In vitro, MSC pellet cultures can be induced to form chondrogenic foci when the media is supplemented by chondrogenic factors (BMP-2, TGF-β1, TGF-β3) [21, 22], known components of demineralised bone matrix [23,24]. Several studies have shown that repair cartilage can arise from the surfaces of remodeling woven bone, through the induction of chondrogenic foci, most notably at the bone plate[8,25]. Treatments that guide osteoclast activity to the bone plate[26] could therefore promote the release of endogenous chondrogenic factors through transient matrix demineralization. The first stages of chondrogenic foci show an appositional growth mechanism from the surfaces of remodeling woven bone[12]. Because woven bone synthesis depends on angiogenesis[27], these observations explain how treatments of damaged subchondral bone with angiogenic factors can have therapeutic effects on repairing articular cartilage, a normally avascular tissue.

The kinetics of chondrocyte terminal differentiation and hypertrophy, naturally promoted by BMP and TGF-β[21, 22], is also an important component of successful hyaline cartilage repair. When pre-hypertrophic hyaline growth cartilage is invaded from the epiphyseal bone by blood vessels capped with a thin layer of osteoid [4], close proximity of subchondral blood vessels and proliferating chondrocytes can have an anabolic effect on repair. Conversely, premature hypertrophy of repair cartilage in the subchondral bone area can lead to persistence of subchondral cartilage[28], or to limited vascular invasion of calcified cartilage, a dense non-porous calcified subchondral bone plate[10], and lower volume of articular soft repair tissue [29]. Treatments that stimulate early angiogenesis and bone remodeling without accelerating chondrocyte hypertrophy have the potential to improve bone-driven cartilage repair.

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7.2.0

Clinical Spectrum and Relevance of Subchondral Bone Changes for Cartilage Injury and Repair

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Introduction: Over the last two decades we have witnessed an enormous increase in the interest in biological repair of articular ostochondral defects. The 1994 NEJM paper from the Gothenburg group, introducing autologus chondrocyte implantation for repair of cartilage defects, had huge impact in the development and overall interest in this field(1). After the initial breakthrough, the focus in the following years was mainly on achieving hyaline or hyaline-like cartilage in the treated defect. Going back to the first ICRS meeting in Fribourg Switzerland I remember the enthusiasm and hope for the tissue engineering of normal hyaline cartilage. Since then we have learned that we still not are able to reproducibly regenerate hyaline cartilage in adults, however, we have a myriad of techniques that are being steadily refined. Over the last few years we are again focusing more on the role of subchondral bone in both the clinical spectrum of osteochondral pathologies and also the importance of subchondral bone and the interface between cartilage and bone in the repair process. In a way, we could say that the circle is closing. In the pre-biological repair era, focus was on subchondral bone and bone healing – the general opinion was that cartilage was not possible to heal in adults. In 2007 I attended a meeting in Luxemburg as a

member of The ESSKA Cartilage Committee. The topic of the meeting was "The subchondral bone in articular cartilage repair". The meeting also resulted in 4 papers in the KSSTA journal (2-5). The enthusiastic attendees had lively discussions around the fundamental role played by the subchondral bone in context of cartilage physiology and repair. Perhaps we could call the running decade "the subchondral bone and stem cells decade" as well as the nineties could be called "the decade of articular cartilage". However, to be able to solve the existing problems in osteochondral pathologies and hopefully also delay disabling osteoarthritis, scientists and clinicians agree that we need to focus on both cartilage and subchondral bone including the interface between them. Not only that, we also have to keep in mind the role of the ligaments, menisci and synovium. Genetics and biomechanics also will always play a role in these pathologies.

In my lecture I will outline the different clinical pathologies regarding subchondral bone, and will discuss the relevance of subchondral bone changes for cartilage injury and repair.

Content: 1. Traumatic disorders

a. Subchondral fractures: Includes avulsion of bone and cartilage fragment(s), non displaced fissures and fracture lines or depressed (lowered and compressed) part(s) of a joint. In this setting I do not discuss displaced joint related fractures involving not only cartilage and the subchondral bone. b. Bone bruise and oedema of the subchondral bone:

This is often seen following joint injuries and is linked to the severity of the impact/shear force. Bone bruise was often not detected in the pre MRI era. It has also been called the occult fracture because mostly not seen on conventional x-rays. Normally the bone bruise will disappear after 12 weeks, but have been seen up to two years following the knee injury. Bone bruise could be an important reason for knee pain and arthroscopic surgery may not help or could even in some cases make the pain worse. c. Stress fracture of subchondral bone:

-Fatigue type: Normal bone following abnormal load

-Insufficiency type: mainly in older osteoporotic patients, can be atraumatic 2. Osteochondritis dissecans (OCD):

a. Juvenile

b. Adult

The ethiology of OCD is still not well known. Micro trauma and ischemic events are often mentioned as factors that could be involved in the development of the process. Today we use the ICRS (International Cartilage Repair Society) classification system. The most frequent location of the defect is the posterolateral part of the medial femurcondyle in the knee. It is also common in the ankle, but can bee seen in other joints as elbow, hip, shoulder and even in smaller joints.

Juvenile OCD has a good prognosis if treated conservatively or operatively. Adult onset of OCD has been shown to increase risk of OA. 3. Avascular necrosis

It has also been called secondary osteonecrosis of the knee (SON), but is also seen in other joints. In contrast to bone infarct in the bone marrow avascular necrosis is located subchondral.

a. Anabolic steroid use and corticosteroid use

b. Alcoholism

c. Systemic lupus, HIV, Sickle-cell-, Gaucher- and Caisson-disease (decompression sickness)

d. Avascular necrosis of caput femoris, caput humeri or caput radii following a fracture (could in principle be subchondral area of any bone). 4. Idiopathic spontaneous osteonecrosis of the knee (SPONK or SONK) or also called Ahlback disease:

Typical is a sudden onset of unilateral medial knee pain in an elderly patient (more women). The ethiology is not clear, however, some abnormal loading and or minor trauma are being discussed. The same picture in the subchondral bone has been seen following arthroscopic surgery, and the surgery itself could have been the trauma initiating the osteonecrosis. 5. Osteoarthris (OA):

Osteoarthritis always includes involvement of subchondral bone. Stiffening and thickening of the subchondral bone plate/calcified cartilage; changes in the trabecular bone and osteophytes are typical. Bone marrow lesions and subchondral cysts are seen. It is not known what comes first – cartilage or subchondral bone changes. Subchondral bone changes and reduction of joint space are the main focus in radiographic OA classification systems. OA knees having subchondral bone marrow lesions including bone bruise had significantly more pain than dose without(6). 6. Pathologic subchondral fractures or micro fractures following malign primary tumours or metastasis.

It can have the same picture as osteoporotic insufficiency fractures

7. Benign cysts:

Synovial cysts are often diagnosed in rheumatoid arthritis and following other inflammatory joint diseases. It is also seen following osteochondral trauma and haemodialysis associated subchondral bone cysts. 8. Postoperative changes:

It is common to observe changes in the subchondral bone following chondral and osteochondral repair. Stiffening and thickening of the subchondral bone plate and or calcified cartilage, elevation of the tidemark and intralesional osteophytes have been found and could probably be related to failure of the repair(7;8). All of these subchondral bone changes may influence the affected articular joint and needs to be evaluated. Imaging diagnostic tools are standard radiographs, CT, MRI and scintigraphy. Moreover, the interface between cartilage and subchondral bone is also extremely important and needs to be addressed in osteochondral pathologies and repair. We have mainly two biomechanical issues: Collapse or insufficiency of the structures under the hyaline cartilage or stiffening of the tissue. Even after healing of the bone the cartilage degradation may progress and end up in a full blown osteoarthritis. In an OA animal model an increase in the thickness of the calcified cartilage and decrease in the thickness of the overlying hyaline cartilage has been found(9). Thickening of the calcified cartilage elevates the tidemark. When should we operate? Radiographic or MRI findings often do not correlate to pain and functional disability of the patients, and we should not recommend extensive surgery if the patient has little symptoms. Some diagnosis, however, needs operative treatment to avoid further progress of the symptoms or more damage to the joint. Loose bodies or unstable osteochondral fragments provoking catching, locking and synovitis requires surgery. Also patients having radiographic OA or also acute cartilage injuries can respond to a conservative rehabilitation program and should not be rushed into surgery to early. SPONK patients in general do not benefit from arthroscopic surgery, however some of them end up with a unicondylar knee or TKA.

Some differences exist between different joints and location within the joint. In the upper extremity the mechanical load does not play the same role as in the lower extremity and e.g. the patello-femoral joint needs special considerations in knee surgery. It is interesting to observe that symptomatic OA following osteochondral injuries and pathologies are less frequent in the congruent ankle joint compared to the knee joint. In a recent paper presenting long term results of patients having arthroscopic debridement and marrow stimulation in the ankle, it was concluded that the initial success of this treatment was maintained over time (10).

I believe that in some locations and defects it could be more important to address and treat the pathology in the subchondral bone than in the cartilage. Conclusions

Subchondral bone changes are common and often associated with cartilage pathologies. They can be traumatic or atraumatic and should always be considered in the evaluation of a painful or dysfunctioning joint. We should bear in mind that in many cases operative intervention is not indicated, and for some patients, time and a rehabilitation program is the best prescription. When an operation is needed we should think on cartilage, bone and the interface between them. In the forthcoming years I believe that the subchondral bone (including its stem cells and growth factors) and the interface will be even more important and studied than today. We and others have already identified stem cells in the subchondral area underneath cartilage defects and evaluated their chondrogenic potential (11).

In the context of tissue engineering, proper integration of implants or the regenerated tissue in to surrounding tissue margins is and will be one of the cornerstones in the field of chondral and osteochondral repair.

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7.3.0

Treatment of Subchondral Bone Pathology

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Introduction: It has been long recognized that the functional unit of mammalian diarthrodial joints is osteochondral and not just articular cartilage in isolation. The "chicken and egg" argument regarding the etiology of osteoarthritis continues; that is, does it begin at the subchondral bone level or is it due to a malfunction of the cartilage at a genetic/epigenetic level possibly exacerbated by trauma/microtrauma. With most of today's cartilage specific repairs/restorations reporting some percentage of bone/cartilage interface problems (e.g., intralesional osteophytes, delamination, etc.), there is a renewed interest in how subchondral bone and articular cartilage interact.[1]

Content: When considering cartilage restoration intervention before classic osteoarthritis is present, it is recognized that not only does subchondral bone influence the type of cartilage restoration that may be optimal, but certain treatments of the subchondral bone may adversely affect/limit future treatment options (e.g., chondrocyte implantation is less effective after marrow stimulation).[2,3]

To fully appreciate subchondral bone, some review of the bone/cartilage interface is useful. The anatomy of this interface is complex. From a biomechanical standpoint, just as Sharpey's fibers serve both as anchors of tendon to bone and at the same time serve to modulate the stress riser at the junction of two structures with vastly different mechanical properties, the calcified cartilage serves to not only to stress modulate/relieve, but also to allow modulate chemical communication between bone and cartilage. The area of interest begins at the interface of the articular cartilage and calcified cartilage. This junction is termed the***tidemark***. The interlock between the articular cartilage and calcified cartilage is undulating. The calcified cartilage layer is between 20 µm and 250 µm in cadaver femurs without arthritis while the tidemark is only 5 µm thick.[4] The other interface is between this calcified cartilage and the subchondral (lamellar) bone plate and is termed the ***cement line*** and is even rougher (1.99 compared to 1.14). Deep to the lamellar subchondral bone plate is cancellous bone contained peripherally by cortical bone in the metaphyseal area.

Damage to the subchondral bone may be initially subtle and only be in the form of overload as described by Dye who used bone scans to show focal areas increased uptake in subchondral bone.[5] The bone scan changes precede MRI changes in many cases. Over a (sometimes short) time frame, MRI positive bone marrow lesions (BMLs) may then develop. These BMLs have been shown to be related to pain,[6] potentially speed cartilage damage,[7] and in the end, potentially increase the likelihood of total knee reconstruction.[8] Prescient work by Dr. Radin suggested a mechanism for the contribution of subchondral bone to progressive cartilage damage: damage to the subchondral micro-architecture could cause increased shearing stress on cartilage resulting in the bone bed provided inadequate support during loading.[9] Additionally, stiffening of the subchondral plate with increasing necrotic tissue (fat necrosis and fibrous tissues is noted histologically[10,11]) would cause horizontal splits in overlying cartilage.[12]

A growing understanding of subchondral bone highlights the interconnected nature of the subchondral bone and cartilage. Hwang et al. showed that there was an elevated flow of chemicals/fluids between cartilage and subchondral bone in osteoarthritis.[13] On the other hand, Arkill noted a 5-fold decrease of small molecule penetration of cartilage versus calcified cartilage.[14] This "cross-talk" may be further influenced by changes to microstructure of subchondral bone from localized stresses including an increase in microcracks and microfractures of the trabeculae.[15,16] Bonde reported that nonarthritic patella had one penetrating vessel across the tidemark in 75-90 year olds compared with 9 per subject in arthritic knee patellae.[17] Finally, it has been suggested that the flow of growth factors via communicating channels during remodeling and repair of subchondral bone may initiate a feedback loop which between cartilage and bone which leads to OA progression.[18]

As the transition zone appears of key importance, researchers have focused on this area. On the other hand, cartilage surgeons have focused on the articular aspects, yet all clinicians have witnessed either advancement of the tidemark, intralesional osteophytes, or tidemark duplication. These are probably all inter-related and expressions of a common underlying mechanism—to be determined. While the calcified cartilage largely blocks blood vessels from the cartilage it does modulate the messaging between the bone and articular cartilage. Note that undulating nature of the tidemark makes impossible to distinguish by the naked eye. That is, for the surgeon who is treating cartilage lesions, the clinical truth is either they remove all the cartilage and leave the calcified cartilage or remove all the calcified cartilage and expose microscopic vessels.

As noted above, the range of changes in subchondral bone varies from overload with remodeling of bone (only noted on bone scan), to intense frank stress fracture, to more chronic bone marrow lesions in which histology demonstrates some adipose necrosis and interstitial fibrosis, to those associated with frank osteoarthritis with hydraulic creation of subchondral cysts. When there are "stress only changes", these may be reversible with activity modification to allow the bone to reenter its "envelope of function" as per Dye.[19] The more established lesions with interstitial changes may not have adequate healing potential with decreased loading alone. In these case, if there is associated articular cartilage damage, there may be a role for an osteochondral repair, such as synthetic constructs (e.g.,MaioRegen: Fin-Ceramica, Faenza S.p.A[20]) or biologics, e.g., autograft osteochondral plugs, or allograft osteochondral transplants. (Obviously, this is a complex multifactorial process and all contributing factors must be identified and managed, e.g., malalignment, meniscal deficiency, ligament stability, etc.)

Within the scope of the complete treatment algorithm, there is an option of treating specifically the subchondral bone. Frank cysts may be bone grafted with cancellous bone or bone substitute. For the symptomatic BML (osteochondritis dissecans drilling fixation and avascular necrosis drilling, bone grafting and pluripotential cell injections are outside the scope of these lesions), a relatively new option of treatment is stabilizing the area of abnormal bone using low viscosity calcium phosphate. The low viscosity allows the injectant to flow around the cancellous trabeculae (Subchondroplasty®: Knee Creations, West Chester, PA or Injectionoplasty®: Skeletal Kinetics, Cupertino, CA).[21] This is different from earlier highly viscous forms of calcium phosphate that, at times, displaced trabeculae and formed a solid mass. The current injectant cures endothermically (avoiding thermal necrosis) with resultant porosity that allows bony replacement as the subchondral bone lesion heals. The notion of treating more advanced chondrosis (frank osteoarthritis) at the subchondral bone level may be considered strange by many yet early study results suggest this is a viable option[21]. (Note that Felson established a strong correlation between BML and patients with osteoarthritis who had pain in 2001.[22])

While articular cartilage repair has been the primary focus of this society and orthopaedics as a whole, the osteochondral unit cannot be underestimated. Given the significant body of research showing that cartilage relies on healthy subchondral bone, and how persistently damaged or remodeling subchondral bone aggravates cartilage loss, a solution that seeks to heal subchondral bone and turn-off the damaging feedback cycle is an intriguing option.

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8.1.1

Definition and Epidemiology of Failed Cartilage Repair

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Introduction: Cartilage repair remains an imprecise academic and clinical endeavor with failure rates ranging between 5 and 40%. Elucidation of failure mechanisms would be a crucial first step that could lead to improvements in techniques, and technologies, to improve outcomes.

The cartilage literature has reported various failure rates based on the specific technique. However, in addition, many confounding factors have been described that influence outcomes, including the number, size and location of defects; the patient's age, gender and BMI; and the condition of subchondral bone.

Content: Steadman et al[1] published their midterm results with microfracture, reporting that 7 years after surgery, 80% of patients rated their knee as improved. Only patients younger than 45 years with traumatic defects and without ligamentous or meniscal injury were analyzed. Other mid- to long-term outcome studies using inclusion criteria that are more applicable to clinical practice suggest a deterioration of functional outcome scores after 2 years [2-7]. Several studies also demonstrated decreased survival in lesions larger than 2 to 3cm^2.[8-10]

Outcomes for osteochondral autograft transfer [11-13] have been promising with good to excellent results in 92% of patients with femoral condylar defects, 87% in tibial resurfacing, and 74% in patellar and/or trochlear procedures [14]. Marcacci et al [15] reported their midterm followup with comparable results but demonstrated inferior results in larger lesions such as the ones treated in our study with ACI.

Osteochondral allograft transplantation [16,17]has been used for the treatment of large osteochondral lesions: Gortz et al [18] reported a 89% survival rate at 5½ years for the management of steroid-induced osteonecrosis of femoral condyles in patients that on average were 24.3 years of age. Similar and better rates have been reported for the treatment of OCD lesions and focal chondral defects.[19,20]

Peterson et al. evaluated the long-term outcome of ACI with more than 10 years follow-up [21]. Patients in this cohort concluded that they were better than before the surgery in 74%, whereas 92% were satisfied with the procedure and would repeat it, findings that are comparable with ours.

Only few articles report have focused on the important subject of subchondral bone integrity but show striking evidence that suggest that prior subchondral surgery, especially microfracture, increases the failure rate of subsequent ACI [22,23]. Extensive pre-operative subchondral edema was found to be a negative predictor for subsequent cell-based therapy[24], as was defect chronicity.[25]

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8.1.2

Why does Cartilage Repair Fail?

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Introduction: Independent of the type of therapy applied, success rates following treatment of cartilage defects of the knee vary between 75 and 95 percent. While during the initial years following introduction of new technologies such as arthroscopic microfracturing or autologous chondrocyte implantation (ACI), the major focus has been put on technical and methodological aspects in order to improve clinical outcome and success rates, in recent years, the focus has stronger been put on the factor of patient selection in terms of the identification of the ideal patient for cartilage repair. There have been numerous studies dealing with the issue of positive as well as negative prognostic factors that help to anticipate the outcome following cartilage repair. Nevertheless, those factors are heterogeneous and widespread. In order to systematically categorize prognostic parameters, these can be grouped under different categories.

Content: Factors that influence clinical outcome following ACI for treatment of cartilage defects of the knee include patient-specific parameters on the one hand, such as body mass index (BMI), nicotine abuses, patients age, prior surgical treatment, duration of symptoms, etc. and defect specific characteristics such as containment of the defect, defect location, defect size, number of defects treated, on

the other hand. While age alone does not significantly influence clinical outcome, an increased BMI represents a negative prognostic factors for the incidence as well as the progress of gonarthritis, recent study also reveal that an increased BMI is associated with an inferior outcome following cartilage repair. Analogous has been found for the use of nicotine, while interestingly ex-smokers to not perform better after giving up smoking in context of the cartilage repair. Prior surgical treatment and a long duration of symptoms prior to cartilage repair have also been described as negative prognostic factors. Although it remains unclear, if those factors influence prognosis independently, this observation leads to the recommendation that an early and definite treatment of symptomatic cartilage defects should be recommend. Nevertheless, the specific reason for this clinical observation remains unclear. Concerning defect location, patellofemoral cartilage lesions are still associated with inferior outcome, several hypothesis trying to explain this observation with is independent of the kind of cartilage repair. Since concomitant treatment of preexisting deformities and biomechnical abnormalities has been proven to be essential for outcome in the femorotibial joint, most likely the limited understanding of the etiology of the patellofemoral cartilage defects might be the reason for still inferior outcome.

In addition to these parameters recently, some new aspects have been evaluated concerning their influence on clinical outcome. With regard to this, surgical technique, cell quality and rehabilitation also seem to significantly influence the clinical outcome following autologous chondrocyte implantation but also other cartilage repair techniques. While the first generation of ACI is clearly associated with an increased risk of transplant hypertrophy and therefore with increased risk for revision surgery, the aspect of cell quality and its influence of clinical outcome is new. Expression of cartilage specific proteins and cell viability of the time of transplantation seem to affect mid-term clinical outcome and might also be a target for further improvement of the clinical outcome rates concerning ACI.

Among all factors identified as relevant for clinical outcome, some of these factors are given and fixed and cannot be changed by either the surgeon nor the patient, while others can be influenced and even changed during the treatment and rehabilitation of a patient who underwent ACI, arthroscopic microfracturing or any other kind of surgical cartilage repair. Nevertheless, knowledge and careful consideration of these factors is essential for clinical success and in order to achieve an optimal and best possible clinical outcome in patients with cartilage defects of the knee., although the majority of these factors could be identified only by studies with low evidence level, they play an important role in clinical practice.

This paper presents a review of the scientific literature available which focuses on the questions as to what parameters influence the outcome of a patient following ACI, arthroscopic microfracturing or other types of surgical cartilage repair for treatment of cartilage defects of the knee. No isolated factors could be identified that influence the outcome following, but it seems that clinical outcome is influenced by many different parameters. These parameters should be considered carefully, at the time of decision about what kind of treatment is applied. Scoring systems that provide a quantitative assessment of the chances of success for the individual patient in the future facilitate the decision for or against a therapy. Nevertheless, not all responsibility in order to optimize the chances for clinical success are in the hands of the surgeon; the patient should also be informed especially about those parameters which can be influenced by him-/herself in order to create good prerequisites for the surgical treatment.

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8.1.3

Strategies to Improve Failure Rate

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Introduction: The treatment of cartilage lesions requires an integrative therapeutic approach. To accomplish this, it is essential to understand the damage as either a mechanical as well as a biomechanical one. In this context, cartilage defects of the knee joint have to be seen as part of an impaired function of the organ "knee". The symptomatic has to be consecutively interpreted as a disturbed joint homeostasis. Improvement in failure rate is additionally based on respecting individual patient characteristics. Ongoing pain or impaired function is often interpreted as a treatment failure. There are nevertheless no cartilage specific scores, which would be differentiating between the different causes of pain. In numerous cases, the origin of symptoms likely has not been identified.

Content: Indication Specific Problems

Patient's Symptoms

It has proved to be very valuable to thoroughly investigate patient's complaints. "Pain" is the main parameter to keep in mind. To achieve a satisfying result, pain eliciting movements as well as pain characteristics have to be investigated. Cleary localized, mechanically reproducible pain at motion (active) and / or passively inducible pain (passive) and / or pain at rest (inactive) are to be distinguished. If a localized sharp pain is denoted, it's likely a local mechanical problem e.g. meniscus, cartilage. A more diffuse pain pattern is more often a sign of an irritation of the Hoffa fat pad. Burning sensations, found regularly at the arthroscopy portals in previously operated patients, are a sign of damage to superficial sensory nerves. The latter quite often lead to reinterventions, which, independently of the content, lead to unsatisfactory results. A stress dependent joint swelling is occurring in accordance with cartilage defects.

Timing of Surgery

Isolated cartilage defects often lead to pain and concomitant joint effusion under intensive stress in a well-defined flexion angle. Patients therefore tend to modify their sports activity. This avoidance leads to chronify of pain complicating a sufficient, early treatment. Without adequate treatment, a slow biomechanical / biochemical process is initiated starting locally but then involving the whole joint. When the localized process is passed, only the dynamics of the degenerative process can be modified. Several studies have proved that significant differences in the outcome after cartilage repair can be found depending on the duration of symptoms. Athletes, for example, show a significant higher return to sport when the symptoms where present less than 12 months (Steinwachs et al. 2011). In a non-athletic population a similar effect was found for different treatment algorithms after 3 years of symptoms (Saris et al. 2009).

Diagnostics

As cartilage lesions often comprise concomitant meniscal tears, damage to the cruciate and collateral ligaments, the clinical examination should involve all joint functions. Additionally, senso-motoric and muscular deficits as axis deviations shall be noted. Functional x-rays and orthoradiographs are standard diagnostic tools. The MRI (⟶ 1.5 T) allows not only for the detection of cartilage defects but the additional pathologies of menisci, ligaments and the subchondral bone. The imaging should allow for the differentiation of chondral and osteochondral defects with or without subchondral osseous pathology (cyst, necrosis, edema, bone bruise) and detection of concomitant pathologies. Not noticing concomitant pathologies is one of the most frequent causes for a treatment failure.

Therapeutic regimen

To establish an individual therapeutic regimen, the different origins of pain and pathologies have to be considered. The treatment of the cartilage lesion is combined with the one of the concomitant pathologies, e.g. cruciate ligament reconstruction, correction of axis deviations, meniscal interventions, to minimize rehabilitation time. A healthy bone stock is essential for sufficient cartilage therapy. Persistent osseous pathologies often require the treatment of the osseous defect. Cell therapies on pathologic bone often lead to ongoing symptoms and failure of the cartilage reconstruction. Previous bone-marrow stimulating interventions lead to damage of the subchondral bone at the defect site and not rarely induce a chronic osseous pathology negatively determining future interventions.

The choice of the adequate cartilage reconstructive procedure involves the size and localization of the defect. Necessary treatment of side pathologies and patient's age play an important role as well.

In traumatic lesions, the joint has to be stabilized initially and, whenever possible, the meniscus has to be preserved. The result of this part of the intervention is determining the success of cartilage reconstruction more than the cartilage repair itself. The best results are obtained in small, traumatic cartilage lesions in young patients who have not been previously operated. In these cases, a complete reconstitution of the cartilage defect on a level of 80 to 90% is possible, if concomitant pathologies are adequately treated. As a general rule, the longer an untreated cartilage defect exists, the worse the results and long-term outcome will be.

Therapy specific problems

Due to the fact that cartilage defects have a very limited, age-dependent, self-healing capacity, a surgical approach is required in adults with symptomatic ICRS grade III/IV defects of the knee joint. Cartilage Repair techniques have been developed over more than 20 years for the treatment of articular cartilage defects. The Microfracture, Autologous Chondrocyte Implantation and Osteochondral Transplantation were investigated extensively. A sufficient number of validated studies on an acceptable level of evidence are available especially for these methods. The best histological repair cartilage and the best durability were found for the ACI technique. The Microfracture technique by R. Steadman is a well proven technique and indicated in small lesions ⟵ 2 cm² on femoral condyles in young and active patients. The Microfracture promotes the formation of fibrous tissue with a histologic range from primitive scar tissue up to fibrous-hyaline mixed cartilage under local biochemical and biomechanical factors. In patients ⟶ 40 years and in OA joints the results are limited.

Numerous studies have proved that the Microfracture is not able to solve the problem of cartilage regeneration in the medium term. Up to now it is unclear whether bone marrow cells in the joint form rather bone (intralesional osteophytes) than high-quality cartilage. For this purpose a better control of the maturation of bone marrow cells is necessary.

The combination of Microfracture and biomaterial allows for the treatment of larger defects in the knee, hip and ankle joint. Different biomaterials like gels, membranes and scaffolds of different compositions are in clinical use. In some cases, the cell biologic properties are so bad that they are withdrawn from the market later. Patients treated with one of these methods often require further surgery. The choice of the right AMIC procedure type helps to limit treatment failures.

Osteochondral reconstruction via transplantation of autologous cartilage-bone cylinders has proved to be apt for the treatment of osteochondral defects. In the past, the lesion sites have been filled with multiple cylinders of small diameters. Surface congruency and integration of the cylinders was limited leading to treatment failure. Limiting the number of cylinders in combination with a minimally traumatizing harvesting leads to better results. Synthetic implants did lead to non-convincing results.

The ACI has the advantage of high tissue quality in the treatment of large (⟶ 2cm²) defects. Multiple alternative methods with many different biomaterials have been thrown on the market in the past years. Tissue hypertrophy was a main problem of first generation ACI. Cleft formation and integration problems are observed more with the MACI techniques. Pathology of the subchondral bone is often seen in treatment failures.

Conclusion The number of treatment failures in cartilage repair can be minimized with an optimal examination and an individual treatment respecting concomitant pathologies and integrating them into the treatment algorithm. Choosing the right repair technique bases on size, depth and localization of the defect as well as on the professional requirements and sport activity, prognostic factors like age, BMI, smoking, gender, previous operations and concomitant pathologies. New therapeutic strategies should have passed scientific investigation before being implemented in clinical routine to avoid treatment failures.

Quite often, the essential postoperative rehabilitation protocol is followed inconsequently or incompletely, consequently leading to a treatment failure. An extensively accepted rehabilitation protocol should be integrative part of the therapeutic algorithm.

8.2.1

Immunological Aspects of Cartilage Science

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Introduction: Autologous chondrocyte implantation has been in use in one form or another for over 20 years (1) and it remains the primary approach to cartilage regeneration in patients. The use of autologous cells is attractive to patients because it eliminates the need to manage the risk of immune rejection. However from a socioeconomic perspective a personalised medicine procedure of this sort is a significant problem as it impacts heavily on health care budgets and limits the numbers of patients who can access the therapy. An allogeneic cartilage repair therapy would allow many patients to be treated using cells from a single donor. These cells could be donated chondrocytes or adult mesenchymal stem cells or it could be pluripotent stem cell lines derived from embryos or generated through reprogramming of somatic cells. But any allogeneic therapy will need to have developed alongside it a clear strategy for the prevention of immune rejection. It is very unlikely that treatments requiring immunosuppression would be tolerated by orthopaedic patients and therefore alternative methods of immunoregulation must be considered.

Content: In 2001, Devine et al (2)showed that MHC-mismatched MSCs could survive for up to 76 days in one recipient in a baboon model. They went on to show that Baboon MSCs could not stimulate allogeneic lymphocyte proliferation in vitro showing that they were hypoimmunogenic. They also demonstrated third party immune suppression in vitro and prevention of skin graft rejection in vivo. The mechansims of MSC-mediated immunoregulation have been extensively studied (3, 4). They modulate cytokine production by lymphocytes with different effects on different subsets of lymphocytes and in this way they create an anti-inflammatory environment when they are co-cultured with lymphocytes. These immunoregulatory properties of MSCs make them very attractive as a potential allogeneic cell source for cartilage repair. However there remains uncertainty around the effects of MSC differentiation on their immunoregulatory capacity with some studies showing that immune suppression is retained upon differentiation (5)and others showing it is lost (6). There is certainly a risk that the differentiated progeny derived from MSCs will lose the ability to prevent immune rejection and this must be taken into account when developing allogenic MSC therapies.

Pluripotent stem cells have been considered for many years as an ideal cell type for use in regenerative medicine strategies. Embryonic stem (ES) cells lack expression of MHC class II antigens and are both immunogenic and potentially immunoregulatory, but

the assumption is that their differentiated progeny will be rejected by the recipient immune system (7). Induced pluripotent stem cells (iPS cells) offer a potential way around the immune rejection of pluripoitent stem cell derived transplants because they can be used in an autologous fashion. This solution however has two flaws. The first is that it fails to deal with the prohibitive cost of autologous therapies. The second is that there is some evidence that autologous iPSCs may nevertheless be rejected by the aptient's immune system because of the reactivation of embryonic antigens for which the host has no immune tolerance, as shown recently by Zhao et al (8). Other studies, however, continue to suggest that both iPS and ES cells and their progeny can be implanted without immune rejection (9, 10). This problem remains to be resolved and may determine the success or otherwise of pluripotent stem cell therapies.

An alternative approach to providing an allogeneic cartilage repair therapy may be to rely on the immune privilege that is inherent in mature articular cartilage because of its physical structure. In particular, the high concentration of aggregated aggrecan is thought to provide a block to the infiltration of immune cells and antibodies into the cartilage matrix. A careful study by Langer et al reported in 1974 (11)described the key mechanism involved. They concluded that transplantation of intact cartilage does not elicit an immune response whereas transplantation of cartilage shavings or chondrocytes may do so. Their evidence suggested that the cartilage extracellular matrix blocks exposure of chondrocytes to the immune cells and conversely blocks the infiltration of anti-chondrocyte lymphocytes or antibodies into the cartilage. These observations provide strong support for the idea of transplantation of intact cartilage from donors or for the production of allogeneic tissue engineered cartilage. A cartilage tissue engineering approach (12)would rely on the new tissue reaching a high level of maturation during the in vitro phase of development in order to have the capacity to provide a physical barrier between implanted cells and the host immune system. Alternatively, a temporary immunosuppression could be provided for a few weeks after implantation of allogenic tissue engineered cartilage to allow the implant to integrate and mature to a point where it has acquired immune privilege. Preliminary evidence from our laboratory in sheep studies suggests that tissue engineered cartilage can indeed survive implantation across immunological barriers, even in the xenogeneic setting.

It is probable that a range of strategies will be needed in order to provide safe allogeneic cartilage repair therapies and careful attention to understanding the various methods of avoidance of immune rejection will provide important routes to the clinic for cheaper, more effective regenerative medicine strategies.

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8.3.1

Basic Science of Joint Pain

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Introduction: Musculoskeletal pain is a major source of disability and distress, and an important drain on world economies. Much musculoskeletal pain is associated with joint disease, in particular osteoarthritis (OA) and rheumatoid arthritis (RA). The mechanisms by which arthritis causes joint pain are complex, and include structural, cellular and biochemical changes within the joint, together with alterations in peripheral and central pain processing. Pain is `an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (1). Its psychological meaning and impact are therefore integral to the pain experience. Recent advances in the understanding of arthritis pain help explain why what patients describe is often not closely related to what is seen on radiographs. Novel treatment strategies offer substantial hope for the future.

Content: Structural abnormalities within the joint are associated with arthritis pain, although it is less certain which precise structural changes may cause pain. Structural pathology in the cartilage, synovium and subchondral bone occur concurrently, such that each may be acting as a surrogate marker for other pathological processes associated with pain. Although cartilage integrity and osteophytosis have been associated with OA pain, Magnetic Resonance Imaging studies have identified subchondral bone marrow lesions and synovitis as being most strongly associated with pain in OA.

Osteoarthritis has traditionally been considered a disease of articular cartilage, and yet normal adult cartilage contains no nerves and cannot therefore be a source of pain. Joint pain may be associated with the mildest of cartilage changes, and may be experienced from joints in which the articular cartilage appears normal. Despite this, arthritis pain is associated with cartilage defects observed macroscopically, and with loss of integrity of the articular cartilage observed under the microscope. Even mild loss of joint space on radiographs (KL grade 1 or 0) predicts progression of painful OA. Despite not being a source of pain itself, cartilage pathology may contribute to OA pain by either driving synovial inflammation, or by compromising the normal mechanical and biochemical barrier that shields nociceptive nerves in the subchondral bone from events within the joint.

Loss of integrity of the osteochondral junction occurs early in OA, first by invasion of the articular cartilage by blood vessels and nerves from the underlying subchondral bone, and later by fissuring or cleavage of articular cartilage through the tidemark. Loss of osteochondral integrity increases hydrolic conductance between synovial and subchondral compartments, with subchondral nerves exposed to mechanical and biochemical factors from which they are normally protected. Bone marrow lesions are associated with

cartilage defects detected by MRI, and their histological correlates (fibrovascular infiltration of the subchondral bone marrow) are associated with both fissures and with increased numbers of osteochondral vascular channels.

Bone marrow lesions are also associated with increased subchondral bone turnover. Bone remodelling results in the classical morphometric characteristics of OA, with marginal osteophytes, and increased thickness of the subchondral bone plate, overlying bone with reduced trabecular density. Subchondral osteoporosis and altered biomechanical stresses predispose to trabecular fractures, which may contribute to the development of bone marrow lesions and bone pain. Furthermore, the increased osteoclastic activity which accompanies bone remodelling may activate or sensitise subchondral nerves by creating an acidic environment and activating pH sensitive ion channels such as TRPV1. Bone marrow lesions contain abundant macrophages, that generate nerve growth factor (NGF) and other chemicals, thereby activating or sensitising subchondral nerve endings, and driving nerve growth into abnormal locations such as the articular cartilage.

Synovial inflammation, detected by MRI, ultrasound or histopathology, is associated with OA pain. Synovitis is the predominant cause of pain in active rheumatoid arthritis (RA), particularly in early disease prior to joint damage. Common molecular pathways may link synovitic pain in OA and RA, although cellular and biochemical differences may also indicate that discrete treatment strategies may be useful in each. Cyclo-oxygenase inhibitors relieve both OA and RA pain more successfully than does paracetamol, and NGF is upregulated in the synovium in both diseases. Intra-articular glucocorticosteroid injections similarly provide benefit in both OA and RA. However, RA synovitis has a greater drive from specific immune responses, indicated by more intense lymphocyte infiltration and activation. A broad portfolio of immunomodulatory biologic agents reduce pain in RA, although early studies with anti-tumour necrosis factor alpha have suggested limited benefit in OA.

Recent research has highlighted how nociceptive inputs from the arthritic joint are moderated by the central nervous system. Peripheral nerves in arthritic joints become more sensitive to factors such NGF, and central sensitisation results in amplification of pain signals as they pass through the spinal cord. Central sensitisation is mediated by complex changes in gene expression by neuronal cells, as well as activation of neuroimune pathways involving astrocytes and microglia.

Pain transmission may be further enhanced, or inhibited, by descending signals from the brain. Abnormalities of central pain processing are common and widespread in people with arthritis, affecting not only inputs from the arthritic joint, but more broadly augmenting pain experienced in other body regions. Severe abnormalities of central pain processing may be recognised in people diagnosed with fibromyalgia, but similar mechanisms interact with pain originating in the joint to augment arthritis pain in people who do not satisfy fibromyalgia classification criteria. Central pain augmentation may normalise after the peripheral source of pain has been removed, for example by joint replacement surgery, indicating that continued nociceptive input and/or biochemical factors produced by the arthritic joint are required to maintain abnormalities of central pain processing.

Central mechanisms may also reduce pain signalling, as may be utilised by psychological pain management techniques. The potential magnitude of central modulatory effects on pain processing can be suggested by placebo effects in randomised controlled trials (RCTs). In RCTs of drugs used for OA pain, placebo analgesic effects are of similar magnitude to pharmacological effects. Placebo analgesia involves specific neurological and molecular pathways within the central nervous system which offer potential as pharmacological targets.

OA progression can be seen as a staged sequence through which progressive structural changes introduce additional pain mechanisms that synergise to produce the severe, unremitting pain too often associated with end stage disease. Cellular and molecular changes in the joint, including inflammation and bone turnover may be episodic or persistent, contributing to flares or sustained OA pain. Recognition of this complexity within the pain pathways is important in selecting novel therapeutic targets, and for defining patient subgroups in which specific treatments are most likely to be successful and establishing appropriate recruitment criteria for clinical trials.

Stratifying care for patients with OA, based on pain mechanisms in addition to symptom severity, has potential to improve patient outcomes, ensure efficient healthcare provision, and identify novel treatments that may be of particular benefit to subgroups of people with OA. Such a stratified approach has long been practiced with joint replacement surgery, suitable for late stage disease, where higher degrees of structural damage predict better post-operative outcomes. Other treatments are needed for pain in early OA. Clinical trials of bisphosphonates which target increased bone turnover have focused on patient subgroups with pain associated with bone marrow lesions. Drugs targeting synovial inflammation are most likely to be successful in people whose pain is associated with synovitis. Treatments that retain or repair osteochondral integrity may prevent pain progession, where osteochondral lesions are the primary source of symptoms. Mechanisms of arthritis pain overlap between diagnoses, and treatments effective for inflammatory joint disease may also have some benefit in OA, while treatments found effective in OA may hold potential for improved management of RA.

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8.3.2

Why is Cartilage Injury Painful?

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Introduction: Our extremities are articulated and the nervous system controls our movements. The soft tissue components have a sensory innervation. There is no nerves in cartilage and menisci are poorly innervated. Contrary, the synovial capsule is reachly innervated. Sensory endings are innervated by axons of different sizes and they are distributed throughout the joint. Nerves are also found in the ligaments. When the joint is damaged subsequently many structures could be responsible for pain development. Why is then cartilage painful or is it not ?

Pain development in a joint with isolated cartilage lesions is maybe different compared to pain in an organ disease like osteoarthritis. However, the pain mechanisms could partly use the same channels of information, the nerves and neural peptides.

Content: Our extremities are articulated and the nervous system controls our movements. The soft tissue components have a sensory innervation. There is no nerves in cartilage and menisci are poorly innervated. Contrary, the synovial capsule is richly innervated. Nerves are also found in the ligaments. When the joint is damaged subsequently many structures could be responsible for pain development. Pain development in a joint with isolated cartilage lesions is different compared to pain in osteoarthritis. However, the pain mechanisms could partly use the same channels of information, the nerves and neural peptides.

Elevated stress in the subchondral bone has been discussed as being a pain cause (Draper et al, 2011). Elevated subchondral stresses also induce an increased metabolic activity (Draper et al, 2011). Such an activity could be identified by scintigraphic examination as well as by MRI.

Possible sources of pain in patients with OA include the synovial membrane, joint capsule, periarticular ligaments,periosteum, and subchondral bone (Grubb et al, 2004). The subchondral bone related causes of pain include periostitis associated with osteophyte formation, subchondral micro fractures, bone angina due to decreased blood flow and elevated intraosseous pressure, and bone marrow lesions detected on magnetic resonance imaging (MRI). Such sources of pain could possibly also be part of the pain in isolated cartilage lesions.

Walsh et al. (2007) looked at OA patients subchondral bone and synovial linings. Blood vessels breached the tidemark in 60% of patients with OA and 20% of post mortem controls. Osteochondral vascular density increased with increasing cartilage damage severity and clinical disease activity scores, but not with synovitis. Synovial angiogenesis indices increased with increasing histological synovitis, but were not related to osteochondral vascular density or other indices of OA disease severity. Osteochondral vascularity seems to be associated with the severity of OA cartilage changes and clinical disease activity (Walsh et al, 2007).

The synovial lining could also produce pain by a pain irritation of sensory nerve endings within the synovium from osteophytes and synovial inflammation caused by to the release of prostaglandins, leukotrienes, and cytokines. (Wong et al, 1993, Dirmeyer et al, 2008)

The subchondral bone involvement is possibly much more important in the success of cartilage repair techniques and such bone involvement could be part of the development of OA and the following pain situation.

Bone cells are under the influence of different systemic and local auto/paracrine factors. One such regulatory factor that can play both a sensory/ afferent and a regulatory/efferent role consists of neuro-peptide-containing nerves. In particular, the calcitonin gene-related peptide (CGRP)

(Brain et al. 1985, Kruger et al, 1999), substance P (Bjurholm et al, 1988, Halliday et al, 1993) and vasoactive intestinal peptide (VIP) (Rahmann et al. 1992) have been suggested to be involved in such regulatory loopes. Furthermore, the chondrocytes have receptors for substance P (Millward-Sadler et al. 2004).

In 1969, Greenwald and Hayes found that a pathway for dye from the medullary cavity to the articular cartilage in the human femoral head does exist. In 1994 Milz and Putz demonstrated also the existence of several channels between the subchondral region and the uncalcified cartilage into the cartilage. Early subchondral changes include redistribution of blood supply with marrow hypertension and bone marrow oedema. The chock absorption properties of articular cartilage depend on the combined unit of the cartilage layer and the subchondral bone layer giving the articular cartilage its visco elastic properties. Disturbances of the unit in isolated lesions as well as in widespread OA may elicit disturbances in the subchondral bone signalling system with a increased stiffness and subsequent pain development.

When the fine homeostatic balance is disturbed, secretions of neuropeptides in the subchondral region may occur and could be transported via special channels to the cartilage and subsequently direct influence receptors on the chondrocytes (Suri et al, 2007).

Angiogenesis in bone under the cartilage layer is dependent on these channels from subchondral bone spaces into noncalcified articular cartilage. Proangiogenic factors might stimulate nerve growth, and molecules produced by vascular cells could both stimulate nerve growth (Mapp and Walsh, 2008). As sensory nerves grow along new blood vessels, they may eventually penetrate noncalcified articular cartilage, osteophytes and the inner regions of menisci.

Angiogenesis could subsequently be the cause of structural damage and pain in cartilage defects (Mapp and Walsh, 2008).

Future research on cartilage repair has to be focused also on the subchondral bone metabolic activity. The vascularity involvement is of great interest with subsequent neural ingrowth with possible effect on pain appearance (Neugebauer et al. 1995).

Treatment focus of interest is the nerves and the vascularity.

Central nervous system control:

Wager et al. has developed what they have named a functional MRI (fMRI). It is a fMRI-based measure that predicts pain intensity at the level of the individual person. They used machine-learning analyses to identify a pattern of fMRI activity across brain regions--a neurologic signature--that was associated with heat-induced pain. The pattern included the thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the anterior cingulate cortex, the periaqueductal gray matter, and other regions. With the measurement, they were able to assess pain elicited by noxious heat in healthy persons. The next step is to evaluate if also their signature predicts clinical pain such as from a cartilage lesion or an OA joint. Gwilim and co-workers (2010) used Voxel-based morphometry (VBM), a method of assessing brain gray matter volume related to various chronic pain conditions. Areas of the thalamus in patients with chronic OA pain exhibited decreased gray matter volume. However, when these preoperative changes were compared with the brain morphology of the patients 9 months after surgery, the areas of reduced thalamic gray matter volume were found to have "reversed" to levels seen in healthy controls (Gwilim et al, 2010).

With new tools (Target specific SPECT-CT) for identifying nerve involvement in the cartilage tissue, one may in the future correlate such local pain inducing centres and their central nervous system engagement and by such findings follow more exact the effect of local or generalized treatments.

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8.3.3

Treatment Principles and Approaches

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Introduction: Circumscribed cartilage lesions are considered an initial event in the progression of osteoarthritis. Clinical and animal studies have shown, that even small lesions may be associated with impaired knee function and pain [Cicuttini F, Schinhan M]. However pain may have also a lot of other possible sources including the synovial membrane, the joint capsule, periarticular ligaments, periosteum and the subchondral bone [Grubb BD]. High threshold nociceptive afferents terminate primarily in the synovium and periosteum, and normally respond only to movement of the joint beyond the working limits. Following joint damage, two factors combine to alter the mechanical sensitivity of articular nociceptors. Firstly, physical changes (joint effusion and tissue edema) alter the resting and movement-induced forces exerted on the joint tissues and secondly, inflammatory mediators released within the damaged tissue sensitize articular nociceptive afferents by binding to receptors on the nerve endings. These factors result in a reduction of the mechanical threshold for activation of articular nociceptors such that manipulation of the joint within the normal range is easily sufficient to activate them [Grubb BD].

Content: However also extraarticular nociceptors are stimulated just by the surgical approach. Problems can be scars and adhesions within and around the joint. Especially adhesions of the Hoffa fat pad and the patella tendon lead to altered biomechanics with increased patellofemoral joint reaction force [Ahmad CS]. Furthermore the parapatellar approach is associated with a detachment and refixation of the vastus medialis muscle as well as the neurovascular bundles, that run to the distal border of the muscle. In this context electromyographic studies have shown, that a VMO detachment leads to an altered electromyographic pattern and clinical symptoms with pain [Kreuz PC]. Even long term biomechanical evaluations after autologous chondrocyte implantation with isokinetic strength measurements, comparing healthy and operated knee showed significantly reduced maximum strength capacities for knee flexion and extension of the treated knee [Kreuz PC]. If these results are attributed to the treated chondral lesion, the approach or other joint-related neurological or biochemical factors is still unclear. However the mentioned factors support an arthroscopic over an open treatment of chondral lesions of the knee.

In this context different arthroscopic techniques have been developed for autologous chondrocyte implantation of the knee. The scaffolds are inserted through small cannulas and fixed with fibrin glue or resorbable pins. Other techniques work without any scaffold by using chondrospheares, conglomerates of chondrocytes or injectible solutions of chondrocytes and other matrix specific molecules. In a prospective study open ACI with periosteum was compared with arthroscopic ACI using Hyaff C. The arthroscopic procedure was associated with less complications such as hypertrophy, delamination and less failure. Furthermore clinical results were significantly different after twelve months in favor of arthroscopic ACI, which improved more rapid, while the findings at the other intervals were comparable [Ferruzzi A]. Similar results were shown in another study comparing open and arthroscopic ACI using Chondrospheares [Schreyer T]. Furthermore some arthroscopic techniques can be used also for chondral defects of the patella with the patient in prone position, to keep the implated cells within the prepared defect site.

Besides the arthroscopic approach there are three important factors to be considered for cartilage repair. First the patient should be treated as early as possible, since randomized controlled trials have shown, that patients with a long duration of symptoms of more than 3 years have significantly worse results compared to patients with a short onset of symptoms [Vanlauwe J]. Main reason for this phenomenon may be the altered homeostasis of the joint with increased numbers of catabolic and inflammatory cytokines, chemokines and growth factors, that lead to a worse response of the implated chondrocytes, which have to rely on a favorable environment for tissue regeneration [Beekhuizen M]. Second marrow stimulation techniques such as microfracture or drilling should be used only within their indication spectrum, since failures with need for revision surgery have a strong negative effect on subsequent cartilage repair with autologous chondrocyte implantation and therefore should be used judiciously in larger cartilage defects that could require future treatment with autologous chondrocyte implantation [Minas T]. Third pathologies of the subchondral bone have to be addressed in every treatment by separate repair of the osseous and chondral compartment. This includes diagnoses such as osteochondritis dissecans and bone edema, which can be visualized by MRI or diseases with an increased bone turnover p.e. in biomechanically overloaded regions, which can be seen in SPECT/CT imaging. Treatment of these pathologies is crucial, since altered bone with its huge amount of nerve fibers is one of the main sources for joint pain and intact bone is the basis for a successful cartilage repair [Hirschmann MT].

A perfect perioperative management should try to avoid the development of a hematoma, which promotes the formation of scars and adhesions. This can be accomplished by limited synovectomy, intraarticular drain insertion if necessary, compressive dressing and

cooling after surgery as well as blood pressure control. Furthermore all cartilage debris should be removed from the joint, since studies have shown, that debris are associated with the expression of inflammatory biomarkers such as TNF α with subsequent synovitis, effusion, pain and impared cartilage repair [Cameron-Donaldson M]. Finally a perfect cartilage repair and pain management includes also a perfect postoperative care, which has to be adapted individually to each patient with his age, gender, compliance, environment as well as to the cartilage defect with its depth, location and size.

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14.1.2

Treatment Options and Considerations in Competitive Athletes

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Introduction: The incidence of articular cartilage injuries in the athletic population has been found to be more than twice as high as in the general population. Participation in high-impact, pivoting sports such as football or basketball in particular has been associated with an increasing number of sports-related articular cartilage injuries with higher injury rates at the competitive and professional level. The exact frequency with which these injuries occur in specific sports is still not exactly known but clinical experience shows that these injuries are still often underreported. One recent survey has shown that 20% of professional American football players have articular cartilage injuries in the knee even at the beginning of their careers. Acute injuries of the articular cartilage surface of the knee often occur together with other acute joint injuries and have been described in up to 50% of knee with acute ligament tears, meniscal injuries, or dislocations of the knee cap. For the competitive athlete articular cartilage injury presents a significant concern since these injuries can be associated with significant symptoms and affecting the athlete's ability to perform. In addition, treatment can be associated with prolonged rehabilitation and absence from competition. Once a cartilage defect has been diagnosed, a individualized treatment approach should be developed that is tailored to the individual cartilage injury characteristics, associated joint pathology, and sport-specific demands of each competitive athlete. Careful consideration is also given to the stage of the player's career when surgical and non-surgical treatment options are discussed. Before treatment is initiated, detailed discussions and counseling between player, team staff, and medical team are critically important to assure optimal compliance and outcome of the patients and facilitate return to competition.

Content: Non-operative treatment should always be considered in highly competitive athletes, particularly for small defects, low-grade defects or defects associated with no or minimal symptoms. Treatment is focused on optimizing muscular support for the joint, reducing joint inflammation, and temporary activity modification. Viscosupplementation, PRP, or anti-cytokine injections can be used on an individual basis but limited systematic data is available on their efficacy in the athletic population with articular cartilage injury.

If articular cartilage restoration is required, the minimal goals include reducing joint pain, increasing mobility, and improving knee function with unrestricted participation in the low-demand regular daily activities. For high-level activity patients, the ability to return to pre-injury level sports and to continue playing at this activity level over time presents one of the most important parameters of a successful outcome from articular cartilage repair. This goal is more challenging since the detrimental effect of high-impact articular loading requires a cartilage surface restoration that is able to withstand the increased mechanical joint stresses generated during high-impact, pivoting activities such as during sports participation. Several surgical techniques have created considerable clinical and scientific enthusiasm for articular cartilage repair in athletes. Based on the source of the cartilage repair tissue, these surgical techniques can generally be categorized into three groups: marrow stimulation based techniques, osteochondral transplantation techniques and cell-based repair techniques.

The microfracture technique is the most frequently used marrow stimulation technique and has been studied specifically in the sports population. Several studies have evaluated the activity levels after microfracture with up to 11 year follow-up after surgery. Activity levels and knee function improved significantly after microfracture in all these studies. Besides improving activities of daily living, patients that had undergone microfracture were able to successfully return to high-impact, pivoting sports including football, soccer, alpine skiing, basketball, rugby, and tennis. Functional improvement was described in 45-72% and return to sport after microfracture was seen in 38-80% of patients. The ability to return to athletics at the pre-injury level was 57-76%. Return to professional and high-level competitive sports was better than to recreational athletics. A recent study showed that while return to sports participation after microfracture can be achieved rapidly, performance and playing time will increase gradually over time until full participation is achieved. Return rate to high-impact activites after microfracture tends to be higher in younger patients with small cartilage defects, shorter times between injury and surgery, and without prior surgical intervention. A long-term decline of the initial improvement of postoperative knee function and sports participation was observed in some studies

after microfracture in athletes and occurred between 24-37 months postoperatively. However, despite the decline in activity levels the functional level was still better than before surgery.

Osteochondral autograft transfer (OATS, mosaicplasty) has been shown to result in 78-95% good or excellent knee function. Return to daily activities was reported in 61-93% of patients and full, unrestricted athletic activity at the pre-injury level was reported in 84-94% of patients after this cartilage repair technique. The time to return to daily activities ranged from 4-8 weeks and return to sports was reported at an average of 4-10 months after surgery. Longer times between injury and surgery and increased patient age were associated with a delayed return to demanding activities such as sports. If radiographic studies prior to surgery showed that arthritis was already present, this predicted lower activity levels after this surgical technique. One comparative study of this mosaicplasty with microfracture demonstrated that knee function improved after both surgical techniques. Ten years after surgery, the rate of patients playing sports at the pre-injury level was higher after mosaicplasty. Long-term studies show that the improvement of knee function can be maintained up to 10 years after surgery with this technique. Osteochondral allograft can also be used with good success in athletes. The use of allograft reduces the operative injury and pain and accelerates postoperative recovery. Up to 3 years after surgery similar improvement of knee function can be found with the use of allograft and autograft. The time to return to activity after donor graft transplantation was also found to be similar to that after autograft transplantation. However, long-term results on allograft transplantation are still pending and systematic information about ability to return to high-impact sports is limited. One recent study found that at an average of 2.5-years, return to sport was possible in 88% at an average of 10 months after surgery. Return at pre-injury level of sports was achieved in 79%. Age ≥25 years and preoperative duration of symptoms greater than 12 months negatively affected the ability to return to sport.

Autologous chindrocyte transplantation has been shown to produce significant postoperative improvement of knee function and increased activity levels in 82-100% of patients. The ability to return to high-level activities including sports varied between 33-96%. Best results were obtained with isolated cartilage lesions located on the inside compartment of the joint. Better postoperative activity levels were achieved in younger patients and with shorter duration between injury and surgical treatment. Return rate was better for competitive athletes compared to patients returning to recreational sports. Importantly, postoperative participation in sports has been shown to significantly improve overall knee function after cartilage cell transplantation and is therefore encouraged. The average time to return to activities of daily living was 2-4 months and return to demanding activities, including high-impact sports ranged between 12-24 months. The time to return to sport was shorter in competitive level athletes. Following cartilage cell transplantation, athletes returned to the same skill level in 60-80% and 87-96% of returning athletes maintained their ability to play sports at the same level more than 4 years after surgery attesting to the excellent durability of the functional improvement from this technique even under high demands. Return to high activity levels was better with fewer prior surgeries but high activity levels were also frequently reached if cartilage cell transplantation was used as a secondary procedure following failure of other cartilage repair methods.

Combined pathology such as malalignment, ligamentous instability, or meniscal injury and deficiency is frequently encountered by the surgeon treating articular cartilage defects in the athletic knee. Surgically addressing these concomitant pathologies is critical for an effective and durable articular cartilage repair. Recent data demonstrated that isolated or combined adjuvant procedures have no significant negative effect on the ability to return to athletics after microfracture, mosaicplasty, or autologous chondrocyte transplantation.

In summary, articular cartilage injury is a potentially career ending injury for competitive athletes. Health care providers treating injured athletes are frequently required to make decisions regarding treatment options, the timing of exercise progression, the resumption of functional activities and return to competitive play. Treatment should be individualized to the specific athlete's demands and can include surgical and non-surgical options. If needed, articular cartilage repair procedures can successfully improve knee function and return patients to demanding postoperative activities, often at the pre-injury level. Besides repairing articular cartilage injuries, surgically addressing associated injuries such as ligament or meniscal injuries has been shown to be critical for an effective and durable articular cartilage repair and has no negative effect on the ability to return to demanding activities. The success of all available surgical techniques has been shown to be dependent on several factors including patient age, size of the cartilage defect, time between injury and surgical treatment, and the athletic activity and skill level of the treated patient. The choice of repair technique should be tailored to each individual athlete by a surgeon that is specialized in the treatment of articular cartilage injuries and who regularly uses the complete spectrum of cartilage repair procedures. The decision when the athlete can safely return to sport after recovering from a performance-limiting injury often presents a particular challenge to the athlete's physician, physical therapist, and athletic trainer. Quickly and safely returning the athlete to sport can be achieved by adopting an outcomes-based approach to treatment progression, in which the athlete must reach specific benchmarks before advancing activity levels. Subjective and objective outcome parameters provide complementary information and are best used in combination to provide the most comprehensive assessment of the athlete's functional ability. Return to sports after injury in the athletic population presents a critical but complex issue that requires a systematic and individualized approach to assure the safe return of the athlete to competition at pre-injury performance level and successful continued participation without re-injury.

14.2.1

Culture Models under loading and non-loading conditions

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Introduction: The influence of dynamic versus free swelling culture is becoming increasingly apparent. Using chondrocytes, we have demonstrated that cells isolated from different areas within the knee cartilage behave differently with respect to mechanical loading. We have also shown that complex multiaxial load can mature a tissue engineered construct such that it develops a similar histological appearance to native tissue. Bone marrow derived mesenchymal stem cells (MSCs) offer great promise in the repair of defects of the musculoskeletal system. Classical tissue engineering incorporates a source of cells, a scaffold to retain them, and biochemical cues. Increasingly mechanical force is being shown to regulate the phenotypic fate decisions in these cells and this may be a mechanism by which the behaviour of MSCs may be optimised for the tissue of interest. Mechanical stimuli are of crucial importance for the development and maintenance of articular cartilage. While a number of studies have shown a beneficial effect of load for chondrogenesis of MSCs there is some controversy as other studies have indicated an inhibitory effect.

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For the conditioning of cartilaginous tissues, various bioreactor systems have been developed that have mainly aimed to produce cartilaginous grafts for tissue engineering applications. Emphasis has been on in vitro pre-conditioning, whereas the same devices could be used to attempt to predict the response of the cells in vivo or as a pre-screening method before animal studies. As a result of the complexity of the load and motion patterns within an articulating joint, no bioreactor can completely recreate the in vivo situation. Using a custom built loading device, it is possible to apply compression, shear or a combination of both stimuli onto fibrin/polyurethane composites in which human cells with chondrogenic potential can be embedded. One major advantage of this device is the possibility to carry out reproducible multiaxial loading ***in vitro.***

This enables the work to be performed directly on human cells, and such studies would be difficult to reproducibly carry out in animal models.

In this study, bovine chondrocytes were seeded into polyurethane scaffolds and subjected to dynamic compression, applied by a ceramic ball, for 1 h daily [loading group 1 (LG1)]. In loading group 2 (LG2), the ball additionally oscillated over the scaffold, generating sliding surface motion. After 3 weeks, the surfaces of the engineered constructs were analysed by friction force and indentation-type AFM (IT-AFM). Results were complemented and compared to immunohistochemical analyses. We observed that the loading type significantly influenced the mechanical and histological outcomes. Constructs of LG2 exhibited lowest friction coefficient and highest micro- and nano-stiffness. Collagen type II and aggrecan staining were readily observed in all constructs and appeared to reach deeper areas in loaded (LG1, LG2) compared to unloaded scaffolds. Lubricin was specifically detected at the top surface of LG2. In conclusions, this study proposes that sliding-type biomechanical stimuli may favour (re-)generation and maintenance of functional articular surfaces and support the development of mechanically competent engineered cartilage.

To simplify the system, and more accurately mimic the in vivo situation, it is possible to perform studies where no exogenous growth-factors are added to the culture medium. Using the same custom built loading device as above we applied compression, shear or a combination of both stimuli onto fibrin/polyurethane composites in which human mesenchymal stem cells were embedded, no exogenous growth-factors were added to the culture medium. Compression alone was insufficient for the chondrogenic induction of human mesenchymal stem cells. However, the addition of shear led to significant increases in chondrogenic gene expression. Compared to the mRNA levels of the free swelling control, mechanical compression alone did not show a significant effect on mRNA expression of the genes analysed. Shear alone only showed a significant up-regulation for the COMP gene. However, exposure to a sliding motion, superimposed on mechanical compression, led to a significant up-regulation of Sox9, Col 2, AGG and COMP.

At the histological level, where compression alone or no mechanical input was provided (free-swelling), the surface was unorganized and more of a fibro- cartilaginous nature. Furthermore, in the free swelling group, the main accumulation of tissue appears to have occurred on top rather than within the scaffold. Accumulation of proteoglycan-rich ECM was only observed in constructs where compression and shear was applied as indicated by the metachromatic staining. A pronounced metachromatic stain could be observed in the upper region of the scaffold. The other loading groups showed barely any sulphated matrix deposition indicated by a lack of metachromatic staining.

Thus any observed chondrogenic induction was purely a result of the loading protocol applied. These effects would not have been observed in static culture and indicate the application of dynamic load is required to accurately determine cellular responses in vivo. These recent data would suggest that under these conditions, shear is a critical component when inducing chondrogenesis in human mesenchymal stem cells by mechanical means. In agreement with other groups, uniaxial load in isolation does not appear sufficient to induce chondrogenic differentiation. This may play a role in natural healing within the musculoskeletal system, whereby the same cell type (MSCs) initiates bone repair (uniaxial load) and cartilage repair (multiaxial load) resulting from different mechanical cues.

Taking this new information into account, it may be possible to develop novel cartilage regeneration therapies which utilise rehabilitation protocols to optimise cartilaginous differentiation of MSCs. Translation of MSCs into a clinical therapy has been challenging, in part due to the complex manipulations required within a laboratory setting. Transferring these steps to the patient in an “in vivo bioreactor” approach would reduce the complexity of the external manipulations and increase the potential for these cells to be used in a clinical setting.

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14.3.2

Animal & In Vitro Models for Chondroprotection Research

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Introduction: Despite a great deal of basic research using animal and in vitro models, effective treatments of cartilage lesions is still not at hand. It is generally accepted that cartilage has a limited capacity to heal which implies an intrinsic ability of this tissue for self-repair. Understanding the early events leading to cartilage damage and identification of molecular mechanisms involved in its repair is likely to pave the way for the development of effective treatment strategies. The central players in cartilage biology are chondrocytes and their role in cartilage repair has been the focus of nearly all chondroprotection studies. Chondrocytes produce and degrade the extracellular matrix (ECM) that constitutes cartilage. Injury to chondrocytes disrupts the balance between ECM synthesis and breakdown thus compromising the structural integrity of cartilage. As a consequence, the mechanical function of articular cartilage as the load bearing tissue in the joint is impaired. Moreover, chondrocytes have restricted ability to proliferate and dead cells are not replaced. One of the major debilitating joint disorders in adult man and animals that is characterized by focal cartilage lesions is osteoarthritis (OA). Earlier studies suggested that OA solely involves articular cartilage. However, it is now acknowledged that all tissues forming the joint are involved including synovium, subchondral bone, capsule, ligaments, meniscus, and muscles. Their participation in the destruction of cartilage is suspected to involve inflammatory mediators, reactive oxygen species and degradative enzymes (1). This expanded view of cartilage pathology requires the use of both animal and in vitro models to build a comprehensive understanding of how cartilage responds to injury following trauma or in disease. This presentation aims to provide an overview of animal and in vitro models for chondroprotection research, particularly in the study of OA.

Content: Animal Models

Several animal models have been used to study the biology of cartilage with the goal of mimicking some aspects of pathology. They are instrumental in identifying potential agents that could be used for treatment as well as provide information regarding safety and efficacy. Use of in vivo models has the advantage of addressing biomechanical issues that are important in articular cartilage function in the joint. Animal models also facilitate analysis of the role of genetics in the evolution of cartilage degeneration. In spite of the array of available animal models, questions have been raised as to which animal model would be most appropriate. Caution has been raised that cartilage tissue from animals may differ from humans which could limit inferences from these studies. There is also a debate whether these models could reliably be used to screen for therapeutic agents. The current thought is that there is no single animal model that ideally portrays human OA. However, several models have been reported to exhibit important features of the disease (2). There is the notion that new models may need to be developed to more fully study all aspects of human OA. They could clarify the relationships between structure, function and disease symptoms. For example, only animal models allow studies of all joint tissues in their natural environment. Unfortunately, currently used animal models have not been successful in defining these relationships.

The animal models that have often been used to study cartilage degeneration following trauma or in OA include mice, rats, guinea pigs, rabbits, sheep, goats and horses. Species such as Dunkin-Hartley guinea pigs that display naturally occurring OA are touted to more closely simulate the slow onset and progression of the disease (2). This advantage is hampered by limited availability of animals thus restricting their routine use in screening for therapeutic agents. The more practical approach is to experimentally induce cartilage damage surgically, chemically or by physical impact. However, the resulting cartilage degeneration is deemed to be too acute or too extensive to reflect the slow progression characteristic of OA. Nevertheless, they may be useful for studying other forms of cartilage disorders (2). Regardless of the models, a critical factor that has been identified in the use of animals is the age-dependence of the response. Studies showed that cartilage response to injury and ability to heal in adult man and animals differ from the young. This has been attributed to differences in metabolism during growth.

Mouse knockout and transgenic models serve as important research tools to study the role of genetics in predisposition to disease. It has been suggested that genetically engineered mouse models may offer clues to prevention of OA (3). A major drawback is that the mouse model does not recapitulate the mechanical loading of articular cartilage in the human joint. Another small animal for the study of joint injury is the rat model. Studies in rats suggested that the method used for induction of joint injury (chemically or surgically) plays a role in response to analgesics used in OA. There could be distinct nociceptive mechanisms requiring appropriate models to study pain in OA (3). The ACL resected rabbit model has been instrumental in identifying chondroprotecive agents as assessed by histology. Treatment with compounds such glucosamine and chondroitin sulfate restored the appearance of normal cartilage (4). Similarly, dogs have been useful in analysis of cartilage injury and in evaluating agents that could minimize cartilage degeneration (5). Sheep, goats and horses being larger animals offer the advantage of more closely approximating the orthopaedic biomechanics of the human joint (6). The size of their joints is amenable for collection of synovial fluid, imaging, histological and biochemical analyses thus facilitating assessment of outcome measures. Horses are attractive animal models as they spontaneously develop OA which recapitulate many features of the human disease. Experimental induced OA-like cartilage defects in horses are used to assess structure modifying compounds (7).

Consensus guidelines are being developed on the use animal models for the study of cartilage and OA with the goal of reducing the number of animals as well as refine the efficiency of protocols. These guidelines will help define appropriate outcome assessment measures and facilitate discovery of potential therapeutic strategies for chondroprotection.

In Vitro Models

In vitro models including tissue explants, isolated cells and cell clusters have significantly contributed to the understanding of cartilage and chondrocyte biology. They can be designed to study individual as well as complex biological pathways. Transfection and RNAi technologies are also providing new information on chondrocyte function. In vitro models offer the opportunity to study entire physiologic pathways. These models have provided critical information on the role of growth and differentiation factors exemplified by TGF-β, IGF, and BMPs in the synthesis of cartilage ECM. They have helped elucidate regulation of ECM synthesis and degradation by transcription factors such as SOX, NF-kB. The linkage between inflammation and oxidative stress, and their impact on chondrocyte metabolism were discovered with the help of in vitro models thus offering clues for targeting multiple intervention points. These models have become an important tool in discovery of potential therapeutic agents as they provide a platform for functional screens. They enable the search for compounds that minimize chondrocyte death and destruction of cartilage ECM. These models also screen for compounds that would boost ECM production. An extensive list of candidates for disease modifying, chondroprotective agents for human OA has been generated initially using in vitro models. Some examples include inhibitors of iNOS, MMPs, aggrecanases, ROS but yet to be approved for man. A few are currently used in veterinary medicine (2, 8, and 9). However, a major limitation of in vitro models is that they do not provide any information about system effects that depend on multiple organs, tissue and cell-cell interactions.

Tissue explants usually from large animals such as bovine, equine and human cartilage are thought to approximate the joint environment. Chondrocytes are maintained in their three dimensional collagenous scaffold where their production of ECM components could be easily monitored. Explants are particularly useful to evaluate cartilage degeneration in an impact trauma model (10). One drawback of using explants is that survival and metabolic activity is limited to several weeks which restricts the time for evaluation of test agents. A more common alternative is the use of monolayer culture since chondrocytes can be propagated sequentially over time and be readily available in ample numbers. However, there is a concern that chondrocytes in monolayer culture undergo a phenotypic shift (11).

To more closely recapitulate the physiological condition in the joint, alternative in vitro models have been developed. Studies in man and in animals demonstrate that articular cartilage in the joint detect, process, and transduce mechanical signals. In conditions where these mechanical signals are absent or reduced, cartilage undergo pathologic changes. Excessive or aberrant mechanical stress to cartilage has been associated with progression of OA. In vitro models were designed to support the notion that chondrocytes sense and respond to mechanical signals by changes in morphology, proliferation, and production of ECM components. Chondrocytes recognize their biomechanical environment as they are subjected to load, compression, stretch, and shear. It is thought that detection of mechanical signals triggers a series of molecular events that determine whether chondrocytes divide, differentiate, or continue to maintain their phenotype. Several culture apparatus have been used to study chondrocytes under conditions of mechanical stress. Explants, chondrocytes seeded as monolayers, in microcarriers, or in a scaffold are cultured in an apparatus where they are subjected to mechanical forces. These culture models attempt to simulate conditions in the joint where chondrocytes are exposed to (a) static or dynamic compression, (b) cyclic strain and; (c) fluid induced-shear. There is also a wide variety of materials for scaffolds or microcarriers used for chondrocyte culture. Examples of these scaffolds are natural materials such as collagen, fibrin and synthetic polymers such as polyglycolic acid, polyurethane. Major advancement in cartilage and chondrocyte culture technology has led to critical information about its metabolism and function. However, currently available scaffold designs could only capture some biomaterial features of cartilage. Similarly, available culture systems are not able to completely recapitulate the biomechanical environment in the joint. The search for the appropriate culture design and apparatus remains a challenge. Conclusion

Advances in developing chondroprotective strategies require an understanding of all mechanisms suspected to contribute to cartilage pathology. Such understanding necessitates the use of multiple approaches to evaluate the role and contribution of different joint tissues. Animal and in vitro models will remain critical tools in the ongoing effort to identify and optimize strategies for chondroprotection.

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15.2

Cartilage repair with autologous bone marrow mesenchymal stem cells

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Introduction: Osteochondral defects are not thought to be quite a few. Such lesions are clinically important because they can be symptomatic and disabling, with pain and/or locking of the joint, and can predispose to further cartilage loss and development of OA. One of the largest problems associated with osteochondral defects is the limited capacity of articular cartilage for repair. Reasons for limited repair capacity are not elucidated; however, insufficient progenitor cells or growth factors are thought to contribute to this limitation to some extent. Thus, we thought it might be effective to transplant progenitor cells of bone and cartilage into articular cartilage defects.

Obtaining cells for transplantation is a major issue in tissue engineering and regenerative medicine. It is possible to transplant allogeneic cells, but these are not widely used in clinical practice because of the likelihood of immunologic reactions and disease transmission. Autologous cell transplantation is better suited to clinical practice because there is neither immunologic reaction nor disease transmission, but an important problem is the limited amount of tissue that can be collected from the patient because of donor site morbidity. Among the types of autologous cells that may be used in transplantation, somatic stem cells are the most suitable because of their simultaneous capacity for proliferation and differentiation. We were interested in autologous bone marrow mesenchymal stem cells (BMSC), which were one of somatic stem cells. When bone marrow blood is cultured in a plastic tissue, adherent cells appear and proliferate. These cells were first described 40 years ago as progenitor cells of bone and cartilage. We speculated that these cells might be useful in repairing osteochondral defects in joints because these cells differentiated into both cartilage and bone. We have reported that transplantation of autologous BMSC promoted the repair of osteochondral defects in rabbit knees in 1994. This procedure is easy to perform clinically because autologous BMSC are easy to obtain and can be culture expanded without losing their capacity for differentiation.

Content: In 1998, we transplanted autologous BMSC to repair of human articular cartilage defects for the first time in the world. Two patients with cartilage defects in patella were the objective patients. We collected autologous bone marrow blood, cultured adherent cells, and embedded them in collagen gels. At surgery, we opened the knee joint through para-patellar medial approach. Then, we abraded the defect area, put the cells in gels in the defects and covered with autologous periosteum. Six months after the transplantation, clinical symptoms had improved dramatically, the improvement has remained in effect (15 years in one case, and 13 years in the other), and both patients have been satisfied with the outcome. One year after the transplantation, we performed arthroscopy and biopsy, and found that the defects were covered with fibro-cartilage.

As a next procedure, we planned to transplant them into medical uni-compartmental OA knee joints. 12 patient received cell transplantation as described above, 12 received collagen gel transplantation without cells. One year after the transplantation, the repair was better in cell transplanted group, but there were no significant differences of the improvement of clinical symptoms between them. 10 years after the transplantations, there were no significant differences of clinical symptoms between them.

We transplanted autologous BMSC in non-OA knee joints, in patello-femoral joint in three cases involving 9 defects in 5 knees. For non-OA knees, the clinical results are better than those for OA knees. It may be because the environments of OA knee are bad for transplanted cells, and/or because non-OA patients are younger

We also transplant them into non-weight bearing joints. We transplanted autologous BMMC into osteochondral defects in 5 patients with osteochondritis dissecans of the elbow. Mean age was 14 years-old. The mean follow up period was 40 months (24-56). Clinical symptoms have improved significantly. MRI revealed that repair cartilage showed the same intensity as normal cartilage. Arthroscopy performed in 2 patients showed that articular surface was smooth like normal articular surface. Histology of the third patient 12 months after the transplantation revealed that the defect had been repaired with the hyaline-like cartilage. For elbow joints, the results are better, presumably because the patients were much younger, and/or because elbow is not weight bearing joint.

Autologous BMSCs are thought to be safe because of the absence of immunologic reaction and disease transmission. However, it is possible that they will form tumors during long time follow-up. We transplanted autologous BMSCs to repair articular cartilage in 1998, which was the first such trial ever reported. Subsequently we performed this procedure in about 40 patients. Demonstration that neither partial infections nor tumors appeared in these patients would provide strong evidence for the safety of autologous BMSC transplantation. Thus, we checked these patients for tumor development and infections. From 1998 to 2008, we transplanted BMSC into 45 joints of 41 patients. Clinical symptoms improved in most patients. In some patients, we confirmed that defects had been repaired with tissue that looked like fibrous to hyaline like cartilage histologically. Because neither tumors nor infections were observed between 5 and 137 months (mean 75 months) of follow-up, we conclude that BMSC transplantation is a safe procedure.

Autologous BMMC transplantation can be expected to become an effective method for the repair of osteochondral defects. However, some investigators might think that BMSCs should not be used to repair articular cartilage because they will undergo hypertrophy and this may lead to chondrocalcification. In our animal experiments, consecutive histology showed that replacement of cartilage by bone had stopped at the level of tidemark. We have never observed calcification above the tidemark in clinical data. From these data, we conclude that autologous BMSC respond to the mechanical environment in an appropriate way when they are implanted into a joint.

As we showed that this procedure is safe and effective, it has a problem that the surgical invasion is large. To explore a less invasive procedure, we are planning to perform multi-centre randomized non-blinded comparative study of injection of autologous BMSC to repair cartilage defects in Japan.

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15.3

New Frontiers

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Introduction: Development of Adult Stem Cells and Novel Biomaterials for Skeletal Tissue Regeneration and Disease Modeling Rocky S. Tuan, PhD Director, Center for Cellular and Molecular Engineering, and Professor and Executive Vice Chairman, Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Content: The intrinsically low capacity of cartilage for tissue repair and regeneration is a clinical challenge to effective treatment of degenerative joint diseases, such as osteoarthritis, the main cause of physical disability. Tissue engineering and regenerative medicine represents a potentially promising approach. The principal requirements are cells, scaffolds, and biological signals. Adult stem cells, such as mesenchymal stem cells (MSCs), may be harvested from autologous tissues sources, including bone marrow and adipose. MSCs have the ability to undergo multi-lineage differentiation, including chondrogenesis, and are actively being investigated as a candidate cell type for cartilage repair. Critical to successful cell-based tissue engineering is the use of a biocompatible biomaterial scaffold that ideally also enhances proliferation and differentiation of the seeded cells. Biomimetic scaffolds that simulate the structure of native extracellular matrix, e.g., the nanoscalar fibrous nature of collagen, have shown promise in skeletal tissue engineering using MSCs both in vitro and in vivo. Recent work on the use of custom-designed, photo-crosslinked hydrogel scaffolds, which allows cell encapsulation during fabrication, demonstrates high fidelity reproduction of internal structure and excellent cell retention, viability, and differentiation. Specifically, we are currently applying a 3D printing approach and a custom-designed microbioreactor to construct a microtissue analogue of the osteochondral junction, based entirely on MSC-derived components, to model the pathogenesis of osteoarthritis. Taken together with their differentiation potential and recently discovered trophic activities, adult stem cells thus present a powerful platform for regenerative, therapeutic, and disease modeling applications in biomedicine.

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16.1.3

A minimum 10-year outcome study of Autologous Chondrocyte Implantation

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Introduction: Background: Autologous chondrocyte implantation (ACI) has demonstrated good and excellent results in over 75% of patients up to 10 years after surgery. Reports of longer-term outcomes, however, remain limited.

Several cartilage repair procedures are in current clinical application, including microfracture, osteochondral autograft transfer, osteochondral allograft transplantation, and autologous chondrocyte implantation (ACI). Given the economic challenges facing our healthcare system, it appears prudent to choose procedures that provide the most durable long-term outcome. Comparatively few studies have examined long-term outcomes, an important factor when considering the substantial differences in cost and morbidity among the various treatment options.

Content: Questions to be answered:

The purposes of this study were to describe the (1) survivorship of ACI grafts, (2) the long-term functional outcomes using validated scoring tools after ACI, and (3) provide an analysis of potential predictors for failure. We performed our analyses at a minimum of 10 years after treatment of symptomatic chondral defects of the knee.

Patients and Methods: 210 patients treated with ACI were followed for more than 10 years. Mean age at surgery was 36±10 years; mean defect size measured 8.4± 5.5cm^2. Outcome scores were prospectively collected pre- and postoperatively at the last follow-up.

Articular comorbidities such as malalignment, patellar maltracking, and meniscal or ligamentous deficiency were corrected in a staged or concurrent procedure. Patients with more than 3° of malalignment were corrected through a neutralizing osteotomy of the tibia or femur. Concomitant procedures included high tibial osteotomy (HTO) in 33 (15.7%), tibial tubercle osteotomy (TTO) in 49 (38 Fulkerson, 11 Maquet) (23.3%), combined HTO/TTO in 15 (7.1%), and distal femoral osteotomy in three patients (1.4%). Anterior cruciate ligament (ACL) repair was performed in 10, lateral collateral ligament (LCL) in one, and combined ACL/LCL in another patient.

Eighty-nine of 210 (42.2%) patients had previously undergone attempts at cartilage repair, including microfracture in 13 of 210 (6.2%), abrasion arthroplasty in 30 (14.2%), and drilling in 46 (21.9%) patients.

Definition of Failure

Failure rates were reported in three categories: graft failure with revision using partial knee arthroplasty or TKA; graft failure with revision cartilage repair; and graft survival but development of new defects elsewhere in the same knee necessitating additional surgery (progression of disease).

Outcome Evaluation

Functional outcomes were evaluated with five validated, generic- and disease-specific instruments measuring changes in symptoms, function, and sports activity level to avoid ceiling and floor effects. Data were routinely collected preoperatively, at 1 and 2 years post-operatively, and then biennially; only the preoperative and final followup data for each patient were analyzed for this study.

Lastly, the Patient Satisfaction Questionnaire asked patients (1) to rate the operated joint compared with before surgery; (2) to assess their overall satisfaction with their surgery; (3) to assess if they would have the surgery again; and (4) to rate the results of their surgery (all on scales of 1 [best] to 5 [worst]).

Results: At a mean of 11.8± 1.6 years follow-up, 53 of 210 patients had at least one failed ACI graft. 19 of these patients went on to arthroplasty, 27 patients were salvaged with revision cartilage repair and 7 patients declined further treatment; 3 patients were lost to follow-up. The modified Cincinnati increased from 3.9±1.5 to 6.4±1.5, SF-36 increased from 32.7±13.6 to 49.0±18.1 and from 45.7±13.7 to 51.9±15.0 for PCS and MCS, respectively. WOMAC improved from 39±21 to 23±16, KSS knee score rose from 54±18 to 79±19 and KSS function from 65±23 to 78±17 (all p<0.0001). Kaplan-Meier survival demonstrated higher graft survival for patients with complex versus salvage type lesions (p=0.03), with primary ACI versus ACI after prior marrow stimulation (p=0.004), and with concomitant HTO versus no HTO (p=0.01).

Conclusions: ACI provided durable outcomes and significantly improved function in 75% of patients a minimum of 10 years after surgery. A history of prior marrow stimulation, as well as the treatment of very large defects(⇢ 15 cm²) predicted increased risk of failure.

While many studies have demonstrated short-term success after various cartilage repair procedures, relatively few have provided information on long-term durability of 10 years and beyond. Such information, however, is essential for the appropriate selection of repair technique. Most patients presenting with cartilage defects are quite young; transient improvement in pain and function in the short-term is therefore not adequate in a patient population that measures its remaining period of life and gainful employment in decades. Especially autologous chondrocyte implantation has to demonstrate superior outcomes in the long-term to justify its high up-front investment of cost and morbidity compared with other treatment options.

"***Level of Evidence*** Level II, Prognostic study

16.2.1

Systemic Effect of Cartilage Repair: Overview of Systemic Effects on Cartilage Repair – Basic Science in Crosstalk with Clinics

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Introduction: There are a variety of different systemic effects, influencing the development of cartilage defects as well as the outcome following cartilage repair. In order to analyze the issue systematically the main categories epidemiology, biomechanics and biochemistry were defined, knowing that the different factors may have sequential or simultaneous effects on more than one category.

Content: The main epidemiological parameters are sex and age, which have an impact on cartilage metabolism by a changed biochemistry and are associated with varying hormone levels and cell senescence. Consequently, several studies have shown differences dependent on sex, demonstrating that male patients achieved significantly better clinical results following cartilage regenerating surgery compared with female patients (1). Although increased age and cell senescence has been associated with decreased regeneration potential in chondrocytes and mesenchymal stem cells (MSC), several studies dealing with cartilage repair have shown that patient age (except juveniles) was not associated with a poorer outcome (2). This might be caused by the limited age window usually applied for patients undergoing this kind of surgery. Furthermore, chronologic and biologic age may differ. On the other hand, it is certain that production of growth hormones, cytokines, and connective tissue proteins changes with age and predisposes for degenerative diseases, e.g. correlations of cytokine expression with age were found for BMP-2 and IGF-1, proteins with decisive roles in cartilage repair (3).

Another epidemiological parameter with significant effects on biomechanics and biochemistry is the body mass index (BMI). Generally, obesity correlates with a poor clinical outcome. This seems not only to be caused by the higher biomechanical loading seen mainly in the joints of the lower extremity, but also by different biochemical reactivity of the joints compared with people with normal weight. Pain of patients with knee osteoarthritis (OA) was associated with synovial fluid adiponectin–leptin ratio, and adiponectin promotes insulin sensitivity and fat β-oxidation (4). In addition to its metabolic effects, adiponectin is an important local and systemic modulator of cartilage biology, involving direct and indirect mechanisms and a large set of downstream molecular signals. Available data about actions on cartilage are controversial, showing both pro- and anti-inflammatory actions.

A further systemic parameter with potential influence on cartilage biology is smoking (5). Although the association between smoking and knee articular cartilage is still under discussion, the literature suggests an overall negative effect on clinical outcome following cartilage regenerating measures. This might be caused by the negative influence of smoking on synovial biochemistry with reduced cytokine expression of IGF-1 and bFGF, mediators related to cartilage metabolism (3).

In persons with different forms of rheumatic diseases as rheumatoid arthritis the balance of anabolic and catabolic activities is compromised, and the extent of tissue degradation predominates over the capacity of tissue repair. This mismatch eventually results in cartilage loss and diminishes the chances for a successful cartilage repair. Tissue homeostasis is controlled by coordinated actions and crosstalk among a number of pro-anabolic and anti-anabolic and pro-catabolic and anti-catabolic factors. In all inflammatory diseases, an elevation of anti-anabolic and catabolic factors occurs (6). This biochemical disturbance is usually accompanied by a destruction of the whole joint, making cartilage regenerating surgery inapplicable in these patients. Interestingly, with regard to acute forms of inflammation anabolic activity as overexpression of BMP-7 is also increased with a delay (7). This may support cartilage regeneration, but fails to repair the tissue in chronic forms of inflammation because of both quantitative and qualitative insufficiency. Similarly, cartilage repair techniques have not as yet been used in haemophilia as the lesions afflicting these patients tend to be extensive rather than focal. In the future, these techniques – and others currently under investigation – may be able to play some role in the treatment of articular cartilage lesions in persons with haemophilia (8).

Animal studies suggest that antibone-resorptive drugs used for treatment of osteoporosis could have benefit on OA by preventing periarticular bone loss, decreasing cartilage degradation, in parallel with the suppression of MMP-13, IL-1β, and RANK ligand expression (9). These effects certainly could be beneficial in cartilage regeneration as well. Thus, although there is a high level of evidence for considering the subchondral bone as a relevant therapeutic target in OA and cartilage repair, until now there is no reliable evidence for the efficacy of anti-osteoclastic drugs fighting structural deterioration of cartilage. At this point the impact of Vitamin D and parathyroid hormone (PTH) should be discussed with their potential effect on cartilage repair. The response of chondrocytes to vitamin D metabolites seems to depend on the zone from which the cells were originally derived. Effects cover inhibition of proliferation, increases of membrane fluidity, and stimulation of alkaline phosphatase activity, collagen synthesis or proteoglycan synthesis, but do not clearly support cartilage repair (10). In contrast, several studies suggested that the transient activation and release from PTH/PTHrP signaling during the early stages of the cartilage repair process facilitates the induction of regenerative chondrogenesis in full-thickness articular cartilage defects (11). The effects of systemically applied COX-inhibiting drugs on differentiation and metabolism of cartilage and in cartilage repair are still under discussion. Data suggest that apoptosis may be reduced by COX-inhibition, but downregulation of specific cartilage markers as collagen type II or aggrecan induced by pro-inflammatory stimuli as IL-1β remained unchanged.

Inflammatory-like reactions may be induced by traumatic injuries leading to the typical cascade of biochemical and cellular reactions. This may impair an intact joint possibly causing besides cartilage damage also arthrofibrosis, bone deformity or instability followed by OA (12). In contrast to chronic systemic inflammations, the impact is occasional, increasing the chances for a successful treatment of cartilage damages when joint symmetry, stability and the correct axis may be restored. The importance of these factors has been shown in numerous studies also in association with constitutional axis deviations. Correction of varus deformity by high tibial osteotomy even leads to a reduced rate of reinterventions and longer survival rates of cartilage implants, when deviation was less than 5° (13).

Controlled mechanical stimulation and strain appears to enhance the supply of nutrients and improve the synthesis of extracellular matrix (ECM) via mechano-transduction pathways of chondrocytes. This has been shown on the basis of in vitro studies, when application of mechanical stimulation to the construct increased the mechanical properties of cartilage constructs, enhancing the ECM network. These data are in concordance with the clinical success of functional treatment and early physiotherapy after cartilage regenerating surgery.

Systemic, chronic diseases as diabetes mellitus are also known to have influence on cartilage repair. Application of diabetic metabolic conditions increased chondrocyte apoptosis through a mechanism that involved enhanced production of TNFα (14). But these effects could be reversed by insulin application, generally promoting chondrocyte differentiation and stabilizing the cellular phenotype.

Besides the perception that the overview of the mentioned systemic factors influencing cartilage repair is not complete, one further aspect should be considered. Why is it important to know all this? If a cartilage lesion is going to be successfully treated, at first an individual analysis has to be performed recognizing all local and systemic conditions that might influence the outcome. This leads to the idea of personalized medicine in connection with cartilage repair. E.g. deviation of axis and ligament instability should be treated together with the cartilage lesion or one might speculate

that treatment of cartilage defects related to chronic inflammatory diseases might rather utilize MSC because they possibly exhibit beneficial immunmodulatory properties.

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16.2.2

Melanocortin and Destruction of Articular Cartilage

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Introduction: Proopiomelanocortin (POMC)-derived peptides such as melanocortins exert their pleiotropic effects via binding to melancortin receptors (MCRs). There is now compelling evidence for the existence of a functional POMC system within the osteoarticular system. Accordingly, distinct cell types of the synovial tissue and bone have been identified to generate POMC-derived peptides like adrenocorticotropin (ACTH) or α-melanocyte stimulating hormone (α-MSH). MCR subtypes, especially MC1R, MC2R (the ACTH-receptor), MC3R and MC4R have been detected in various cells of the synovium, cartilage and bone. The respective ligands of these POMC-derived peptide receptors mediate an increasing number of newly recognized biological effects in the osteoarticular system. These include bone mineralization and longitudinal growth, cell proliferation and differentiation, extracellular matrix synthesis, osteoprotection, and immunomodulation. Importantly, bone formation is also regulated by the central melanocortin system via a complex hormonal interplay with other organs and tissues involved in energy metabolism. Among the POMC-derived peptides examined in cell culture systems from osteoarticular tissue and in animal models of experimentally induced arthritis, α-MSH, ACTH and MC3R-specific agonists appear to have the most promising anti-inflammatory actions. The effects of these melanocortin peptides may be exploited in future for the treatment of patients with inflammatory and degenerative joint diseases (Bohm and Grassel, 2012).

Content: Recently, we demonstrated that melanocortin-1 receptor (MC-1R) is expressed in human articular chondrocytes. Furthermore, chondrocytes are target cells for α melanocyte-stimulating hormone (α-MSH), a prototype of MCs, which is capable of regulating a number of genes involved in extracellular matrix composition and inflammation in chondrocytes. We could recently demonstrate the presence of MC1R, MC2R and MC5R transcripts and the MC1R-protein in human articular chondrocytes derived from patients with OA (Fig. 1). Treatment of these chondrocytes with a-MSH was associated with functional coupling as shown by cAMP assays but not with a Ca^{2+} response. The induction pattern of regulatory and structural ECM components such as collagens as well as Sox9 and anabolic and catabolic cytokines points towards a function of a-MSH as a trophic factor in skeletal development during endochondral ossification. (Grassel et al., 2009). Compared to synovium, less is known about production of POMC peptides by chondrocytes. We and others detected truncated forms of POMC mRNA (transcripts related to exon 2) in human articular chondrocytes obtained from patients with end-stage OA. However, POMC transcripts related to exon 2-3 were not detectable suggesting that articular chondrocytes cannot make POMC protein (Andjelkov et al., 2006; Grassel et al., 2009). In addition, an increased level of α-MSH was detected in osteoarthritic synovial fluid (Catania et al., 1994). In the presence of MC-1R, α-MSH shows anti-inflammatory and cytoprotective effects in many different cell types (Brzoska et al., 2008). Based on these findings, we suggest a chondroprotective role of α-MSH and its receptor MC-1R in cartilage physiology.

To identify the role of MC-1R-signaling for the progression of osteoarthritis (OA), a surgically induced OA-model was applied in MC-1R signaling-deficient mice (MC1Re/e): the destabilization of the knee joint by incision of the medial menisco-tibial ligament (DMM) (Glasson et al., 2007). To determine the progression of OA, animals were sacrificed after 2, 4, 6, 8 and 12 weeks post surgery. Knee joints were embedded in paraffin and 5 µm frontal sections were cut through the entire joint at 80 µm intervals and stained with Safranin-O and Fast green. Sections were evaluated by morphometric analysis and by a histological scoring system for murine OA (Glasson et al., 2010). Collagens II and X were analyzed by immunohistochemistry and subchondral bone structure was analyzed with ***in vivo*** µCT.

4 and 8 weeks post surgery, the area of degenerated articular cartilage in MC1Re/e was significantly increased compared to wild type (WT), shown by both, morphometric analysis and histological scoring of Safranin-O stained sections **(Fig.2)**. 12 weeks post surgery, difference with respect to cartilage destruction between Mc1Re/e and WT disappeared. In addition, gender specific differences affect cartilage destruction during progression of OA and occur earlier in signal – deficient MC-1R-mice as in WT-mice indicating that MC-1R signalling modulates the effects of female sex hormones in OA. Collagen II and X staining pattern was similar in both mouse strains. ***In vivo*** µCT analysis demonstrates alteration in subchondral bone structure.

Our data suggest that degeneration of articular cartilage in MC1Re/e mice progresses faster than in WT which point towards a more severe OA-progression. Hence, the melanocortin system could play a chondroprotective role in early OA-development. It is conceivable that inflammatory reactions can be mitigated by the induction of endogenous MCs or administration of a-MSH to the affected joints.

The data obtained so far highlight a significant number of biological effects of POMC-derived peptides via MCR expressed by the majority

of non-neuronal resident cell types within the osteoarticular system. From our data and from reports of other groups, we propose several possible modes of actions of POMC peptides in bone and cartilage. Inflammatory processes originated from diseases such as OA and RA increase bone and cartilage turnover and promote degradation of these tissues. The osteoarticular system responds to this with an evolutionary conserved stress response in analogy to the classical HPA axis, that is increased synthesis of POMC-derived peptides. The release of such POMC peptides will subsequently not only modulate the activity of immune cells in the osteoarticular system but also of resident cells as osteoclasts, osteoblasts, chondrocytes, synoviocytes and their progenitor cells. In line with such a local endocrine stress response of the osteoarticular system is also the newly discovered osteoprotective effect of ACTH on osteonecrosis of the femoral head. ACTH produced either locally within the hip joint or released into the circulation by induction of the classical endocrine HPA axis appears to promote osteogenic-chondrogenic differentiation of multipotent precursor cells. Supported by studies on mice with ablated genes of the POMC system (Ahn et al., 2006; Cawley et al., 2010) a complex interplay further appears to exist between the central melanocortin system, bone and additional organs involved in energy metabolism such as adipose tissue or pancreas. The effects of these melanocortin peptides may be exploited in future for the treatment of patients with inflammatory and degenerative joint diseases.Understanding precisely the functional role of POMC-derived peptides in cells of the osteoarticular system should finally help to better tailor more efficient future therapies against inflammatory or degenerative joint diseases (Bohm and Grassel, 2012).

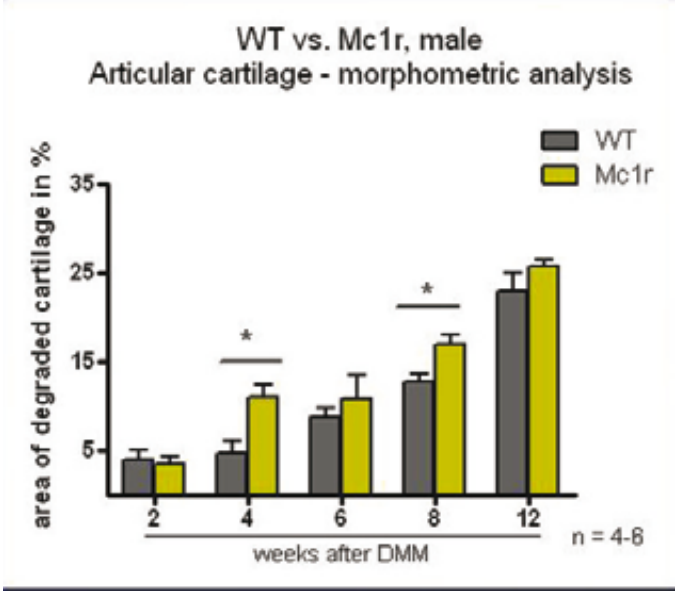

Fig.1 MC-1R immunoreactivity in articular chondrocytes in situ.

Chondrocytes stained for expression of MC-1R in cryostat sections of articular cartilage. The articular surface is marked at the top of the picture (A). Staining for MC-1R was detected in all cells of the middle (C) and deep zones (D) of the articular cartilage, whereas markedly reduced or no staining was observed in the superficial zone (B). Sections incubated without the primary antibody or with pre-immune serum served as a negative control. No sections showed any staining in such control experiments (data not shown). N = 3; all bars = 100µm. **Fig.2: Cartilage destruction after OA-induction**

Knee joint articular cartilage of WT (grey bars) and MC1Re/e (yellow bars) mice was morphometrically evaluated after surgical induction of OA and compared to sham operated leg. 4 and 8 weeks after OA induction, progression of cartilage destruction was more severe in WT than in MC1Re/e mice. After 12 weeks the differences disappeared. *=p≤0.05

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16.2.3

Cartilage Regeneration And Usefulness of Medication

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Introduction: Cartilage is widely present throughout the body, including joint, intervertebral disc, nose, ear, and trachea. This tissue plays an important role in maintaining the body shape, daily movement, and exercise. However, cartilage is affected by various diseases including ageing-related diseases such as osteoarthritis, inflammatory diseases such as rheumatoid arthritis, trauma to joint, congenital anomalies such as cleft lip and palate, and large deficits after surgery for tumors or cancers. Once the cartilage tissues are damaged due to those disorders, it becomes difficult to maintain the morphology of body or face, as well as resulting in deterioration of daily activities, such as walking and mastication, which significantly interferes with the patient’s quality of life. As the cartilage tissues have limited capacity for self-repair, those that are once damaged are not likely to be repaired from natural healing. Thus, the methods, to maintain the healthy cartilage or to regenerate the damaged one, by some medications including growth factors, antibodies and low molecular weight compounds are anticipated to be developed.

Content: Regarding the methods to maintain the healthy cartilage, some molecules have recently been focused on. Syndecan-4 enhanced ADAMTS5 activation mediated by MMP3 activation, leading to cartilage degeneration. Both syndecan-4–deficient mice and syndecan-4–specific antibody–treated mice showed a marked decrease of ADAMTS5

activation and the cartilage degeneration, suggesting that the inhibition of syndecan-4 will be of great value for the treatment of cartilage damage in osteoarthritis (Echtermeyer 2010). Hedgehog signal may be also the target. Hedgehog pharmacological blockade prevented cartilage degradation (Lin 2009). Notch signal is known to inhibit the early differentiation of cartilage (Fujimaki 2006). Our collaborator found that the Notch transcriptional effector, recombination signal binding protein for Ig kappa J (RBPjκ) inactivation in adult articular cartilage using type II collagen (Col2a1)- re(ERT);Rbpj(fl/fl) mice caused resistance to osteoarthritis development in the knee joint. Moreover, intraarticular injection of N-[N-(3,5-diflurophenylacetate)- l-alanyl]-(S)-phenylglycine t-butyl ester (DAPT), a small compound Notch inhibitor, to the mouse knee joint prevented cartilage degradation (Hosaka 2013). Those results suggested the Notch signaling in chondrocytes may be an extracellular therapeutic target of osteoarthritis.

On the other hand, once the cartilage is impaired, we should attempt to regenerate this tissue. We had established an "implant-type" tissue-engineered cartilage with a greater firmness and a 3D-structure. For that, we developed 1) a proliferation medium for chondrocytes to realize a more than 1000-fold increase in number without using fetal bovine serum that has been restricted to clinical application, and 2) a scaffold system that effectively preserves chondrocytes in the engineered tissue and provides the adequate 3D shape to the tissue.

For the proliferation medium, we examined the optimal combination from 12 putative soluble chondrocyte regulators including FGF-2, IGF-I, insulin, BMP-2, PTH and others. Using the statistical method that is termed "analysis of variance by fractional factorial design", the effects of the individual factors and the synergy of the combinations were evaluated. As a result, the combination of FGF-2 and insulin with 5% human serum showed a 10-12-fold increase in number within one week and provided an approximate 1000-fold increase around 3 weeks. (Takahashi 2005)(Tanaka 2008)

In addition, we fabricated the scaffold system, to realize;1) sufficient mechanical strength mimicking native cartilage: 2) preservation of seeded cells and their even distribution: 3) good biocompatibility/biodegradability. To meet with these requirements, we decided to use the combination of hydrogel and porous scaffolds (Yamaoka 2010). Considering biological effects and clinical availability, atelocollagen may be accessible for hydrogel (Yamaoka 2006). Next, we investigated the structure and composition of porous scaffolds. We prepared ones of a classical polymer PLLA or PLGA with various kinds of porosity and pore sizes. The porous scaffolds possessed sufficient strength even with high porosity (⋯›95%) and good interconnectivity, which showed favorable cartilage regeneration when transplanted in the subcutaneous space of nude mice with chondrocyte/atelocollagen mixture (Tanaka 2010). In order to examine the biocompatibility, we conducted a canine model for autologous transplantation of the tissue-engineered cartilage, and compared between such scaffolds of PLLA and PLGA. The tissue-engineered constructs using PLLA contained abundant cartilage after transplantation, although the PLGA constructs did not show the cartilage and could not maintain their shapes (Asawa 2012). The PLLA scaffolds were suitable for cartilage tissue engineering under the immunocompetent conditions, because of the retard at degradation properties and the decrease in the severe tissue reactions during the early stage of transplantation.

With these technologies, we applied the implant-type tissue-engineered cartilage for treatment of a nasal deformity in patients with cleft lip/palate (Hoshi 2013). As the next step, we would make the size of tissue-engineered cartilage larger or further promote the maturation of the regenerative cartilage, which enables to widen the indication range of the tissue-engineered cartilage to the treatment of trachea or joints. For the purpose to improving the properties of the regenerative cartilage, our group found that a new disease-modifying osteoarthritis drug (DMOAD) candidate, TD-198946 regulated RUNX1 expression and induced chondrogenic differentiation without promoting hypertrophy. The DMOAD candidate strongly regenerated the cartilage, when used in vivo, implying that TD-198946 is regarded useful for the enhancement of cartilage regeneration (Yano 2012). Moreover, we have the choice to use iPS cells instead of conventional cell sources. iPS cells are accessible because they are produced by the reprogramming of somatic cells, while those pluripotent cells can be harvested without quantitative limitation. These characteristics are very advantageous to make a large-sized regenerative tissue, like the tissue-engineered joint. Now, we have established the porcine iPS cells, and attempted to use them in large-sized joint defects of miniature pings. We hope these tissue-engineered constructs will alleviate the problems concerning the present treatment of cartilage diseases.

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16.3.3

Growth Factors and PRP: Clinical Application

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Introduction: The fascinating perspective of applying biological strategies for the management of cartilage pathology has led to a growing interest in the field of growth factors and stem cells: the most recent discoveries in this particular area of pre-clinical and clinical research were at the basis for the creation of a new figure, the "orthobiologist", who is an orthopaedic practitioner specializing in biological and bio-engineered treatments, both conservative and surgical.

The preeminent role is played by blood derivatives, and in particular Platelet-rich Plasma (PRP). Platelet-derived GFs contained in PRP are the most exploited way to administer a biological stimulus to several different damaged tissues, such as cartilage, tendons and muscle, that might benefit from this particular approach [1, 2]. Being able to treat patients with a product derived directly from their own blood is an attractive proposition due to the theoretical reduced risks of intolerance and side effects than those commonly ascribed to traditional commercial drugs.

The biological rational behind this kind of treatment is the topical administration of several important molecules normally involved in joint homeostasis, healing mechanism and tissue regeneration. First of all platelet-derived GFs, which are a group of polypeptides playing important roles in the regulation of growth and development of several tissues, including cartilage. Platelets contain storage pools of GFs [1, 2, 3] such as: platelet-derived growth factor (PDGF); transforming growth factor (TGF-β); platelet-derived epidermal growth factor (PDEGF); vascular endothelial growth factor (VEGF); insulin-like growth factor 1 (IGF-1); fibroblastic growth factor (FGF); epidermal growth factor (EGF) etc...

Alpha granules are also a source of cytokines, chemokines and many other proteins [1,2] involved in stimulating chemotaxis, cell proliferation and maturation, modulating inflammatory molecules and attracting leukocytes [1,2]. Besides alpha granules, platelets also contain dense granules, which store ADP, ATP, calcium ions, histamine, serotonin and dopamine, that also play a complex role in tissue modulation and regeneration. Finally, platelets contain lisosomal granules which can secrete acid hydrolases, cathepsin D and E, elastases and lisozyme, and most likely other not yet well characterized molecules, the role of which in tissue healing should not be underestimated.

Content:

CLINICAL APPLICATION OF PRP

PRP has been applied both as a conservative approach and as a biological augmentation during surgical procedures. In the latter application, there are just a few studies that, in most cases, combine PRP with other biological strategies, such as autologous mesenchymal stem cells or membranes. Furthermore, these trials lack any control group and therefore the clinical evidence is poor and no assessment can be made about the exact role of PRP and its real contribution to a better healing and clinical outcome with respect to the bare surgical procedure.

Looking at conservative management, we have more data to rely on: intra-articular clinical application of PRP has been tested in several studies to date. The majority of the papers deals with knee application, whereas just two studies focus on hip and only one on tibio-talar joint. A fundamental distinction should be made between case reports/case series and comparative/randomized trials: this reflects the different quality of the papers and the reliability of the results reported in current literature.

In 2008 Sanchez et al. firstly reported the injective application of a platelet concentrate (PRGF) in a retrospective observational study on 60 patients [4], 30 treated with intra-articular injections of PRGF and 30 with injections of HA. Patients from both groups underwent 3 injections one week apart and were evaluated basally and at 5 weeks of follow-up focusing in particular on “stiffness”, “pain”, and “function”. The results were encouraging, showing better efficacy in pain control, even though the short follow-up is a major weak point of the study.

In 2010, Sampson et al. published a study [5] on 14 patients with knee OA who received 3 PRP injections 1 month apart. Inclusion criteria were clinical and radiographical OA signs in patients with previous unsuccessful conservative management. Evaluation was carried out for up to 52 weeks using the Brittberg-Peterson Visual Analog Pain, Activities and Expectation score, VAS for pain, and KOOS score. The authors found a statistically significant improvement in the scores examined, with a reduction of pain at rest and during physical activity. After one year, 8 patients were completely satisfied with the treatment received. In 2010 Wang-Saegusa et al. [6] published a prospective study on a large cohort of 261 patients treated for mono- or bilateral knee OA, who received 3 injections of PRP 2 weeks apart. Statistical analysis revealed significant results with an improvement in all the scores adopted.

In the same year Kon et al. also published a prospective study [7] on 91 patients (a total of 115 knees) treated with 3 injections of 5 mL PRP (1 every 3 weeks). Inclusion criteria were: clinical history of knee pain or articular swelling lasting more than 4 months, radiographic or MRI signs of OA. Patients underwent clinical evaluation at basal level and at 2, 6, and 12 months of follow-up through IKDC objective, IKDC subjective, and EQ-VAS (general health status evaluation) scores. No major complications were seen, except for a case of marked post-injective pain and swelling which resolved spontaneously after 2 weeks. Eighty percent of the patients treated expressed satisfaction with the treatment received. The clinical improvement in all the variables at 2 months was later confirmed at 6 months of follow-up, whereas a tendency to worsen was reported at 12 months of follow-up. Some factors were also identified to influence the clinical efficacy: young male patients were the best responders to PRP application, and also the grade of articular cartilage degeneration was correlated with clinical outcome. Patients with chondropathy alone, without signs of OA, presented better and more lasting results compared to patients with early or severe OA. A subsequent evaluation [8] at 24 months of follow-up confirmed the trend that emerged after the 12 months follow-up: a further and marked decrease in the clinical outcome was evident, thus confirming the time-dependency of intra-articular therapy with platelet-derived GFs. The authors estimated the median duration of the PRP effect to be 9 months.

Napolitano et al. [9] treated 27 patients, either affected by simple chondropathy or initial OA, with 3 injections of 5 ml PRP performed one week apart from each other. Significant results were obtained after treatment without the occurrence of adverse events. Similar findings were also reported by Gobbi et al. [10] who treated 50 patients with 2 monthly injections of PRP and evaluated them up to 1 year, showing a positive outcome both in patients who had undergone previous cartilage surgery and those who had not. In more recent times, a case report and 3 case series were published by Freitag [11], Torrero [12], Harpern [13], and Jang [14], respectively. These studies confirmed the safety of the procedure and the encouraging clinical results obtained by previous authors. In particular, Freitag et al. employed, for the first time, photo-activated PRP and Jang et al. pointed out a poorer outcome in patients affected mainly by patello-femoral degeneration.

Looking at comparative or randomized trials, the first one was published by Kon et al. [15] in 2011. PRP was tested against low molecular weight hyaluronic acid (LW-HA) and high molecular weight HA (HWHA) in 3 homogeneous groups of patients. The results showed a better performance for the PRP group at 6 months of follow-up. In particular the biological approach produced superior results than HA in the bare chondropathy group. Conversely, in the early OA group the gap with HA was not significant and in the severe OA group no difference in clinical outcome was observed. Another interesting finding was that patients aged up to 50 yy had a greater chance to benefit from PRP approach. The same authors were the first to compare two different PRP preparations: high concentrate leukocyte-rich PRP vs low concentrate leukocyte-free PRP. 144 patients were treated and evaluated up to 6 months revealed, reporting comparable positive results with both treatments; the PRP-leukocyte group suffered from more swelling and pain reaction immediately after the injections [16]. Also Spakova et al. [17] compared the efficacy of PRP versus viscosupplementation in 120 patients. An increase in the clinical scores was reported in both groups but statistically superior results were found in the PRP group.

Recently, four randomized controlled trials have been published. Sanchez et al. [18] investigated the efficacy of single-spinning leukocyte-free PRP compared to HA in 153 patients evaluated up 6 months of follow-up. The only aspect where a clear superiority of PRP was demonstrated was the percentage of responders (patients with at least 50% of pain reduction), which was significantly higher in PRP group. Besides this finding, the study went on confirming that PRP in moderate/severe OA is not more effective than HA. Similar considerations were raised by Filardo et al [19], according to the preliminary results (109 patients) of their randomized double blind trial comparing PRP and HA: no statistical inter-group difference was reported and just a tendency toward better results for the PRP group at 6 and 12 months follow-ups was found in patients affected by low grade cartilage degeneration (Kellgren Lawrence up to 2).

Conversely, Cerza et al. [20] treated 120 patients by either Autologous Conditioned Plasma (ACP) or HA. Surprisingly, ACP group showed a significantly better performance than HA in all groups of treatment, including patients affected by grade 3 knee OA. Furthermore the clinical gap between treatments increased over time in favor of ACP. Lastly, a recent randomized trial by Patel et al [21] was the first to test PRP versus saline. 78 patients affected by Kellgren grade I-III OA were included and treated bilaterally with one injection of PRP,

two injection of PRP (three weeks apart) or one injection of saline. Despite the low number of patients included, a significant difference was observed between PRP and saline solution in term of clinical outcome. Interestingly, no difference was reported among patients who received one or two PRP injections.

Regarding hip application, the first clinical studies were conducted by Battaglia et al. [22], and Sanchez et al. [23] on 20 and 40 patients respectively. Similar conclusion were reached by the authors: PRP is a safe treatment, capable of improving articular function, reducing pain during daily activities and delaying more invasive solutions. However, time-dependent effect was showed also in this case, with results worsening over time.

Just one paper investigated the efficacy of PRP vs HA in osteochondral talar lesions, on 30 patients [24]. At short term evaluation a superior clinical performance was documented in PRP group.

CONCLUSIONS

According to current evidence, there is no clear indication for the use of PRP in cartilage pathology, due to the fact that only a few high quality, randomized trials have been published, mainly about knee pathology. PRP has not been proved to be superior with respect to other traditional approaches such viscosupplementation, and the great enthusiasm about biological treatments, initially justified by encouraging preliminary results, now needs real support. For the moment PRP cannot be considered as first line treatment for cartilage pathology, and its application should be reserved to patients who, basing on the current scientific evidence, can obtain the best results from this approach.

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19.1

Landmarks of Cartilage Science Evolution

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Introduction: We know for centuries, even millennia, that cartilage does not heal well after damage but we are still searching for the perfect solution to this problem. Although cartilage consists of one tissue and one cell type, it remains difficult to heal defects. This is partly due to the avascularity of the tissue and partly due to its high physical demands. Much progress has been made, though, in the last century.

Content: For me the first milestone in cartilage science is probably the theory of the structure of cartilage by Benninghoff in 1925. In the '60-'70 large progress was made by the research on proteoglycans in cartilage. Important contributors were Helen Muir (started in the 50s and later her students Tim Hardingham, Mike Bayliss, Cahir McDevitt), Dick Heinegard, Vincent Hascall, Klaus Kuettner and Bruce Caterson. Also in this period the structure of collagens in cartilage became known. Important contributors here were Darwin Prockop, Klaus von der Mark and David Eyre (collagen crosslinks). Moreover in this period, our basic knowledge of osteoarthritis was founded. Henry Mankin was of great importance for description of the changes on tissue level as well as metabolic changes in cartilage during the development of osteoarthritis. The ideas and concepts of his research are still valid now.

In the '80s (actually starting late 70's and running into the '90s) much progress was made in research on the mechanical properties and function of cartilage by Van Mow and Alan Grodzinsky. The models by Dennis Carter (based on theory of Pauwels 1940) were instrumental for our understanding of the role of mechanical loading in the development and regeneration of cartilage.

Parallel to the basic science, progress was made in clinical science. The earliest recorded hip replacement is probably performed by T. Gluck in Germany in 1891, using ivory to replace the femoral head. In the '40s metal became popular in the US. The clinical success of hip replacements was probably largely due to the design of Charnly in the '60s.

But apart from replacements of worn cartilage by biomaterials, people were intrigued by the possiblility of the use of transplants or body's own materials. The first cartilage transplants were performed in the early 1900s. In 1959, Pridie introduced the drilling of holes in damaged cartilage through the subchondral bone to stimulate the healing process of the body. In the '90s the idea of making wholes through the subchondral bone was popularized by J. Richard Steadman to the gold standard of cartilage repair today.

Chondrocytes were isolated and cultured in monolayer already since the '20s, since relatively pure population of cells could be isolated from embryonic cartilage anlangen. In the '60s Holzer H. noticed that chondrocytes lose their specific phenotype when cultured in monolayer later confirmed in adult human chondrocytes by Klaus VonderMark and Paul Benya, who demonstrated that culturing chondrocytes in a gel preserved the phenotype. This allowed many subsequent studies on cartilage matrix assembly.

In 1965 Audrey Smith published a paper in Nature describing for the first time that chondrocytes can be frozen and thereafter cultured. This might be seen as an important milestone in the development of articular chondrocyte implantations as we have them available now.

A milestone for cartilage repair is definitely the paper by Daniel Grande in 1987 were he described chondrocyte transplantation in rabbits. Although this paper was hardly noticed these days, it was noticed by Anders Lindahl and Lars Peterson and led to the first in man chondrocyte transplantation, published in 1994 by Mats Brittberg et al.

Next to the use of chondrocytes in transplantation, progenitor or stem cells form an alternative cell source. Perichondrium was recognized as potential source by Engkvist O and Skoog V in the '70s, and similarly periosteum in the '80s by O'Driscoll S. This idea was used in a series of clinical studies by George Homminga in the late '80s. Although the results were promising yet not optimal, the use of periosteum flap was used in the first autologous chondrocyte implantation. But a real milestone occurred In the '60s when Alexander Friendenstein isolated colony forming cells from bone marrow. These cells were called Mesenchymal Stem Cells by Arnold Caplan since they could differentiate into multiple mesenchymal lineages. He and Brian Johnstone demonstrated the chondrogenic potential of these cells in the late '90s. Mary Murphy et al. injection of MSCs in goat joints after meniscectomy (a model for osteoarthritis) with the idea to repair articular cartilage defects at the start of the 21st century. Surprisingly they found regeneration of the meniscus and a delay in the development of osteoarthritis. Later on the pleiotropic effects of MSCs, being able to differentiate into chondrocytes but also secrete trophic factors that can stimulate tissue repair or anti-inflammatory factors to allow tissue repair or to inhibit tissue degeneration became clear.

Over the last years, it has become clear that the joint has local stem cells. The role of these endogenous stem cells in cartilage repair is not clear yet. There are strong indications that cartilage in osteoarthritic joints can repair by applying joint distraction, as introduced by Floris Lafeber and Peter van Roermund. The removal of shear forces while still allowing hydrostatic pressure in the joint might stimulate the endogenous healing process. These data might proof that the dogma that cartilage cannot heal itself should be rejected.

It appears hard to label milestones in the most recent year, since milestones can only be called milestones in retrospect. We seem to have two episodes of concentrations of milestones in cartilage science evolution: One in the '60-70s on characterization of cartilage matrix and culture of isolated chondrocytes. And a second episode late '80-90s related to autologous chondrocyte implantation and the chondrogenic differentiation of adult mesenchymal stem cells. In the past years we have benefitted from the technological developments and innovation such as in the field of genetics and genetically modified and knock-out mice; RNA technologies such as PCR and microarray; immunohistochemistry, in situ hybridisation and FACS to characterize tissues and cells; and more recently induced pluripotent stem cells (iPS) and miRNA. But despite the progress many of the basic questions are not yet answered. It is not so much the question ***if***, but rather ***how*** we will find the perfect way to regenerate cartilage that is damaged. Should we organize the cartilage repair society in this quest or leave it up to the individual adventurer's motivation, insight and creativity?

Disclaimer: I realize that this is not a complete nor a specific overview of the evolution of cartilage science. The selected milestones are just my personal choice at the moment.

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20.1.1

Imaging Options for Cartilage Injury, Repair & Subchondral Bone

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Introduction: Magnetic resonance imaging (MRI) is intensively used to assess the cartilage injuries as well as structural changes in the cartilage repair tissue and the adjacent structures post-operatively. Due to its strength to visualize all different tissues, MRI has been recognized as an excellent tool to define the exact conditions in the joint. Concerning cartilage repair, with the given tissue contrast and sensitivity to tissue composition, MRI has a very high potential in the description of joints before and after different cartilage repair procedures. Specifically it may a) help estimating the size, nature and location of lesions preoperatively, in order to optimize surgical planning, b) provide in vivo data on the mechanical strains in the target environment that the repair tissue needs to withstand, c) help to evaluate the quality and success of tissue repair processes after surgical treatment and d) allow to monitor degenerative changes in the whole joint after cartilage repair.

Significant advances have been made in characterizing, quantifying and standardizing the specific morphological as well as biochemical changes in patients before and after cartilage repair. Besides the exact evaluation of the cartilage defect respectively the cartilage repair tissue, also the surrounding tissues can be assessed in best possible fashion non invasively [1-3]. Concerning bony irregularities, MRI depicts calcified bone as a signal void, comparably to radiography; furthermore structural changes, especially bone marrow edema can be assessed very precisely [4]. The role of the subchondral bone plate before and after different cartilage repair surgeries is of enormous interest. Pre-operatively the specific surgical treatment option is not only based on the character and size of the cartilage defect but even more dependent

on the formation of the underlying bone. Comparably in the follow-up after cartilage repair surgery, the characterization of the subchondral bone is of utmost importance to measure the success of the specific surgical technique. Besides the evaluation of cartilage and bone, all other structures within the joint have to be visualized and to be taken into consideration. Hence the joint where cartilage repair takes place has to be seen as a "whole organ" and whole organ scores will be important not only in osteoarthritis but also in cartilage repair [5].

Concerning articular cartilage, MRI can visualize morphological alterations such as reduction in cartilage volume, cartilage contour irregularities, fissures and cartilage thinning [6]. As structural cartilage damage is preceded by biochemical alterations such as proteoglycan loss, or changes in the collagen matrix, there is a substantial interest in detecting such changes in the course of cartilage disease/injury or after cartilage repair [7-9]. The biochemical MRI techniques most often reported to visualise cartilage ultra-structure are delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) and T2 mapping [10, 11]. Using dGEMRIC, biochemical MRI has the ability to quantify functionally relevant macromolecules within articular cartilage such as glycosamnioglycans (GAG).

Recent advances in MR sequences together with the implementation of high-resolution MRI due to high-field MR systems as well as sophisticated coil technology have overcome existing limitations and led to promising ***in-vivo*** approaches in morphological and biochemical MRI in cartilage repair [12-14].

The aim of this talk is to review the current literature and present own ideas of our working group, on MRI in cartilage repair with the focus on advanced morphological and initially biochemical MR imaging techniques. Hence the existing cartilage defect/injury can be assessed in detail, enabling for decision making in the specific therapeutical pathway. After cartilage repair the repair tissue as well as the surrounding structures can be assessed non-invasively and possible complications can be depicted.

Content:

Pre-requirements for cartilage imaging

When working on an optimal protocol for cartilage imaging, the first question is which MR system to use. Commonly available systems are of different vendors and have field strengths of 1.0 Tesla, 1.5 Tesla or 3.0 Tesla. There are different studies available to compare different field strengths in there ability to diagnose knee pathologies as well as providing information on the benefits of higher field strengths [15-17].

Although at 1.0 or 1.5 Tesla, MRI is able to detect cartilage irregularities in high quality, the 3.0 Tesla examinations provided a better visibility especially of smaller structures and cartilage was better delineated [17].This is usually based on an increased average signal-to-noise and contrast-to-noise ratio at higher fields. Concluding, at 3.0 Tesla, imaging of the knee is faster and/or a higher visibility (and resolution) of anatomic structures can be reached [16, 17]. In cartilage injury or repair, the highest available field strength should be used to provide the best available quality of the MR protocol.

Besides the field strength however, the selection of a dedicated, multi-channel coils is possibly even more important [16, 17]. Most available MR scanner today come with an eight or fifteen channel knee coil. To use these coils in cartilage patients will improve the image quality and provides also in 1.0 or 1.5 Tesla the ability to end up in high-resolution MR protocols in an acceptable acquisition time [18].

The pre-requirement of an optimal MR scan is using the right sequences and plan the sequences on the localizer (initial landmark scan of the knee) in the right direction. Hence in a standard 2D MR evaluation, to gain high-quality, high-resolution images, the anatomical curvature and localisation of e.g. the femoral condyles have to be taken into consideration. This is especially important after cartilage repair when the area where the repair has taken place is known. By e.g. adapting the sequence-slab (orientation) exactly on the respective femoral condyle, the repair tissue and the adjacent structures can be assessed in best possible quality and resolution.

Diagnosis of cartilage injury – Pre-operative MRI

The quality of the diagnosis is naturally one of the most important parts when treating patients. Hence the pre-operative MRI needs to be of high quality, especially as existing studies show that radiologic reports based on standard morphological MRI frequently underestimate the actual size of a lesion (which were then found intra-operatively) [19, 20]. In the study of Gomoll an co-workers, cartilage lesions where underestimated up to 300% in the patello-femoral joint [20]. Based on a high quality MRI, this should not be the case and cartilage lesions should be graded better. For sure it will never be possible that a 100% match is reached between non-invasive diagnosis and the following surgery, nevertheless for preparing a tailored surgical approach, the match has to be in the range of the real defect. Reasons for the pre-operative under-estimation of the cartilage lesion are based on different reasons. First a standard MRI usually consists of 2D sequences with a slice thickness in between 3 to 5 mm and an existing interslice gap. Hence the borders of the cartilage defect are not exactly depicted. Furthermore there are regions in the knee (e.g. the trochlea) where the assessment of the anatomy is nearly not possible by 2D MR sequences. Possible better results can be reached by exploiting isotropic MR sequences [14, 21]. With these sequences, a 3D data set can be acquired (e.g. 0.5x0.5x0,5 mm) without any gap between the slices. Using 3D viewing tools the observer can navigate three-dimensionally within the knee joint and all anatomical regions can be graded adequately.

Besides morphological MRI, also biochemical MR sequences, such as dGEMRIC, T2 mapping or others, can be used in pre-operative imaging. Although a full thickness cartilage defect cannot be evaluated, biochemical MRI is a very promising tool to i) assess the borders of the cartilage defect regarding to their quality, to ii) assess the cartilage defect itself if there is not a full-thickness defect, and iii) to assess the cartilage quality of the surrounding tissue. Although nearly no studies are available on this topic, all given examples will be topics of future research and will help in clinical decision making. To assess the "real" border of the deteriorated cartilage is very important and although this decision is done intra-operatively, as mentioned above, more knowledge has to be acquired pre-operatively that a better planning of the surgical procedure is possible. To evaluate a more chronic and not full-thickness cartilage defect in its quality of the thin remaining cartilage layer is another possible option for the pre-operative use of biochemical MRI. Hence the biochemical and biomechanical quality of these cartilage areas can be assessed. This is roughly comparable to the evaluation of overall cartilage quality of the joint. Especially in older patients, based on these possibilities, it might be easier to know in advance if a patient will benefit form a surgical cartilage repair procedure or not. Concluding pre-operative MRI (respectively optimal cartilage diagnosis) should contain of a set of cartilage sensitive MR sequences, and if possible a 3D-isotropic MR sequence and as well as (if possible) a biochemical MR sequence. Moreover the rest of the joint has to be diagnosed in comparably high quality.

Post-operative MRI

An optimal MRI protocol after a cartilage repair procedure, should in principle contain the same set of sequences than the pre-operative MRI. However as the area where the repair procedure has taken place is now known, this area can be depicted in more detail in highest possible resolution. The planning of such a sequences slab is mentioned above; by exploiting high resolution in the limited area of cartilage repair, early changes like beginning delimitation, subtle split like lesions, or underlying bony changes can be diagnosed and possibly treated with the aim to prevent the patient from a failure of the repair procedure.

In the post operative follow-up, the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system is claimed to allow subtle and suitable assessment of the articular cartilage repair tissue [22, 23]. This MR assessment of the MOCART score is based on standard 2D MR sequences, depending on the locality of the area of cartilage repair, the MR evaluation of the cartilage repair tissue is performed on sagittal, axial or coronal planes using high spatial resolution together with a slice thickness of 2-4 mm. However, also this MOCART scoring system can now be performed in more detail and with additive variables, enabling for a more precise depiction of the repair tissue as well as the surrounding structures. This new MOCART score [14] can be still assessed by 2D standard MR sequences, however also the new and above mentioned 3D isotropic MR sequences can be used and their potential benefits are incorporated into this new score. In recent literature, this score seems to be reproducible and can be achieved by different MR protocols and in different joints besides the knee joint [14, 21].

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20.1.2

Functional Cartilage MRI: Current Status and Future Outlook

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Introduction: 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.

Content: 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.

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 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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20.2.1

Better MSC by Reprogramming of iPS?

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Introduction: Mesenchymal stromal cells (MSCs) have a high potential for therapeutic efficacy in cartilage regeneration and are presently under clinical investigation as potential substitute for autologous chondrocytes in cartilage repair strategies. Their postulated capacity of in vitro and in vivodifferentiation along mesodermal cell lineages, including cartilage, bone, ligament, and tendon, makes them especially valuable for musculoskeletal tissue engineering (Caplan, 2005). When compared with autologous chondrocytes, MSC isolation is less invasive and cells are available in higher amounts. However, the number of MSCs that can be obtained from a single donor is still limited and although the ex vivo expansion of MSCs can be considerable, it is nonetheless finite. In addition, MSCs are adult somatic cells with a limited life span and after a number of passages in culture undergo cellular senescence (Bruder et al, 1997). Their proliferative potential and differentiation capacity decline even more with increasing age and in patients with skeletal or metabolic diseases (Stolzing et al, 2008), which impedes autologous applications for those patients who are especially in need for regenerative medicine. Limited availability and declining capacity critically compromise MSC applicability for regenerative medicine and tissue engineering approaches that require substantial cell quantities.

Unlimited proliferative capacity is an inherent property of pluripotent stem cells (PSCs). Consequently, both embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have been investigated intensely for regenerative medicine purposes. Pluripotent stem cells comprise, in addition, the ability to differentiate into virtually any cell type derived from the three embryonic lineages (i.e., ectoderm, mesoderm, and endoderm). However, ***in vitro*** differentiation of such developmentally immature cells into specific tissue forming cells is inevitably a highly complex process that requires the coordinated development of a number of well-defined intermediate cell types (Wu and Hochedlinger, 2011). Interestingly, intermediate cells with properties surprisingly similar to MSCs have been described as transient populations during differentiation into mesodermal offsprings, including chondrocytes, osteoblasts, and cardiomyocytes (Barberi et al, 2005; Lian et al, 2007).

The potential derivation of MSC-like progenitors from pluripotent stem cells would be most intriguing, since this approach combines the advantage of unlimited proliferative capacity of PSCs with the well-known properties of MSCs and might open the possibility to generate large amounts of highly uniform MSC batches. Such PSC-derived MSC-like progenitor cells (PMPs) have been reported to be immature cells in a transitional state of development (between stem cells and terminally differentiated cells) (Barbet et al, 2011). Their restricted capacity to self-renew and differentiate possibly reduces tumorigenicity, making them therefore attractive with regard to safety aspects and therapeutic applicability. PMPs derived from both ES as well as iPS cells have been reported to express MSC-typical surface markers and to comprise mesodermal tri-lineage ***in vitro*** differentiation capacity (i.e., chondrogenic, osteogenic, and adipogenic). What is more important, these cells did not show tumorigenicity when transplanted into immunodeficient mice (Karlsson et al, 2009; Lee et al, 2010) (de Peppo et al, 2010; Hwang et al, 2008; Olivier and Bouhassira, 2011; Trivedi and Hematti, 2007). Using iPS cells rather than ES cells as the starting cell type opens the possibility of developing autologous cells and tissues. The potential capability to generate readily expandable, patient specific multipotent human MSC-like cell lines from well-characterized iPS cell lines represents a promising endeavor in the field of regenerative medicine.

However, methods that are currently used to derive PMPs are highly variable, which might crucially limit inter-study comparability. Differentiation of PSCs into MSC-like populations has been accomplished by forced differentiation of PSC colonies (Trivedi and Hematti, 2008) or single cells (Karlsson et al, 2009), by intermediate generation of embryoid bodies (Hwang et al, 2008), and via co-culture with mesenchymal cell lines (Barberi et al, 2005). Despite incongruent methods, results seem to suggest that PMPs are developmentally younger than bone marrow MSCs and exhibit a higher proliferative potential (de Peppo et al, 2010). Although they seem to possess the MSC-typical tri-lineage potential, differentiation outcomes appear to be inferior to bone marrow MSCs. Direct comparison between PMPs and MSCs, however, has so far been limited by the cells originating from different donors. Well-known donor-dependent MSC heterogeneity thus impedes specific conclusions when cells were derived from different donors.

Content: Our strategy was therefore to reprogram in a first step human bone marrow MSCs back to pluripotency and to subsequently re-derive PMPs from these MSC-derived iPSCs. This allowed for the first time a direct side-by-side comparison of PMPs with the originating MSCs from the same donor. The value of this system is that the comparison would not be hampered by any donor-dependent variances so that conclusions concerning efficiency of derivation protocols as well as PMP properties and differentiation may be specifically defined. For PMP derivation we used three different protocols: (1) embryoid body formation, (2) indirect co-culture with MSCs, or (3) forced differentiation of colonies, and compared PMPs directly with the originating MSCs. All generated PMP lines exhibited typical MSC/fibroblastic morphology, exhibited the MSC-typical surface marker profile and were able to differentiate in vitro along the osteogenic, chondrogenic, and adipogenic lineages. However, in direct comparison to MSCs from the same donor, PMPs displayed a unique expression pattern of mesenchymal and pluripotency genes and were less responsive to traditional MSC differentiation protocols. In accordance with previous reports on ESCs, our data on iPSCs strongly suggest that mesenchymal progenitor cells generated from PSCs via spontaneous differentiation are not identical to primary mesenchymal stem cells but are rather at a more primitive developmental stage. Implications of these results will be discussed.

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20.3.1

Soluble Biomarkers to evaluate Chondroprotection: The Revolution is underway!

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Introduction: OA is a disease affecting the metabolism of all joint tissues leading to structural changes visible by imaging techniques. Unfortunately, features visible by imaging are in most cases irreversible and progressively moving towards worsening. One challenge for the next decade will be disease detection at the early stage when the first molecular/metabolic changes appear in joint tissues. Another challenge is to develop tools to assess the efficacy of OA treatment on the natural history of the disease. At this time, joint space narrowing measurement on standard X-ray remains the goal standard. This method has some important limitations: lack of reproducibility and sensitivity, confounded by meniscal lesions and extrusion, poorly correlated with joint function and pain. Therefore, there is an acute need for reliable biological markers that can facilitate earlier diagnosis of OA, predict the progression of the disease and evaluate the efficacy of therapeutic modalities (1).

Content: A recent literature review resulted in the identification of 16 biochemical markers investigating cartilage matrix turnover. Nine concerned collagen type II degradation (Coll2-1, Coll2-1NO_2, CTX-II, Helix-II, C2C, TIINE, CIIM) and synthesis (PIIANP, PIICP). Keratan sulphate, chondroitin sulphate 846 (CS846) and ARGS-aggrecan fragment investigate proteoglycans degradation. Serum cartilage oligomeric matrix protein (COMP), deaminated-COMP (D-COMP), fibuline-3 fragments (Fib3-1 and Fib3-2) were the other biochemical markers that are considered as markers of cartilage matrix metabolism (2).

At this time, none of the current OA pharmacological treatment can significantly modify the natural course of OA. A significant decrease of knee joint space narrowing after a 3-year follow-up has been reported for glucosamine and chondroitin sulphate. Risedronate and strontium ranelate, two drugs currently used to treat osteoporosis decreased urinary CTX-II levels suggesting that they can modulate cartilage metabolism, even if they did not alter radiological progression. However, recently, it was demonstrated that CTX-II was more strongly associated with bone markers (i.e. uNTXI, uCTXI, serum PINP, and osteocalcin) than with other cartilage markers (PIIANP, sCS846, sCOMP), while the "other" cartilage marker markers were not so strongly associated with the bone markers (3). These data indicate that CTX-II might reflect bone rather than cartilage metabolism. In a exploratory study investigating the effects of three intra-articular injections of hyaluronic acid (Hylan GF-20) on the evolution of 10 biochemical markers, we have demonstrated that uCTXII, sColl2-1 and sColl2-1NO_2 levels were significantly affected by treatment suggesting that these markers are sensitive to metabolic change occurring in one single joint (4, 5). More recently, we have observed that three months treatment with bio-optimized curcumin significantly decreased sColl2-1 level in 24 patients with knee OA, suggesting that sColl2-1 could be a companion marker to assess curcumin efficacy at a individual level and in the next phases of its clinical development (7).

Although many OA-related biomarkers are currently available they exist in various states of qualification and validation. At this time, none of the existing biomarker can be considered as a surrogate marker of joint space width measurement. The biomarkers that are likely to have the earliest beneficial impact on clinical trials fall into two general categories, those that will allow targeting of subjects most likely to either respond and/or progress (prognostic value) within a reasonable and manageable time frame for a clinical study, and those that provide early feedback for preclinical decision-making and for trial organizers that a drug is having the desired biochemical effect (6). In this context, the recent development of large cohort designed to qualify biomarker will accelerate biochemical marker implementation in clinical research.

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21.1.2

Meniscus Repair & Transplantation: Results & New Frontiers

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Introduction: The important role of the meniscus in the knee joint is well established. Given these important roles, methods to either repair or replace the meniscus are critical. In this lecture I will review current techniques as well as future horizons for meniscus repair and meniscus replacement.

Content:

Meniscus Repair: Current Status

Various meniscal repair techniques have been developed over the years, including suture based repairs as well as various implants and fixators. However, it is well-established that healing of the meniscus is a slow and imperfect process. The basic cell biology of the meniscus, such as relatively poor vascularity and low cellularity, limits the tears that can be repaired and makes healing unpredictable.

The clinical results of meniscus repair of suitable tears have been relatively good. Most series demonstrate good outcomes in 60-80% of patients. However, there is a distinct rate of incomplete and failed healing of the meniscus following repair, with failure rates as high as 15-25% using objective imaging studies. The fate of the incompletely healed meniscus is also not well-established. Furthermore, the function of the "healed" meniscus is not well known. Even though an imaging study may demonstrate apparent healing of the meniscus repair site, it is not known if the healed tissue restores the normal biomechanical function of the meniscus. These considerations make clear the need for techniques to improve meniscal healing. Work in this area is based on improved understanding of the basic cellular and molecular mechanisms of meniscus biology and meniscus healing. Specifically, information about the behavior of meniscal cells and their ability to synthesize appropriate matrix proteins is needed in order to lead to new techniques to improve meniscal healing.

Meniscus Repair: New Frontiers

New frontiers for improving meniscus healing will come from further understanding of basic meniscal cell biology. Cytokines, pluripotent cells, and scaffolds may all be used to improve meniscus healing. The

current challenge is to identify the specific cytokines that are most effective in various phases of the healing process. Another important challenge is to identify the appropriate carrier vehicle(s) for a given growth factor. Platelet rich plasma has tremendous potential as a source of autologous growth factors, but further information is required to identify the specific components of platelet rich plasma that are effective in meniscus healing. In the future more refined uses of platelet rich plasma may be useful for improving meniscus healing. The combination of platelet rich plasma with stem cells may present a method to improve meniscus healing.

Cell-based approaches also have tremendous potential for the improvement of meniscus healing. Multi-potent cells can be harvested from bone marrow, adipose tissue, and even from the synovium. Further advances in basic stem cell biology will likely suggest improved methods to use cell-based approaches to improve meniscus healing. Furthermore, techniques such as use of embryonic stem cells and induced pluripotent cells, which involves reprogramming adult differentiated cells to make these cells pluripotent, have great promise. However, at this time these techniques are limited by ethical and safety concerns, and thus further research is needed.

It is also known that the inflammatory environment in the postoperative knee joint may adversely affect healing, and thus techniques to modulate the inflammatory milieu in the postoperative knee joint may be effective to improve meniscus healing. For example, inflammatory mediators increase the expression of matrix metalloproteases, which may have adverse effects on meniscus healing and matrix remodeling. Modulation of the levels of pro-inflammatory mediators and matrix metalloproteases present another avenue to improve meniscus healing.

Meniscus Transplantation: Current Status

Meniscus transplantation has a well-defined role in complex knee reconstruction. It is now well-established that meniscus transplantation is effective in treating symptoms due to early arthrosis, including pain and swelling. However, there is currently no evidence that meniscus transplantation can change the long-term natural history of the meniscus-deficient knee. There are distinct limitations to the use of human allograft meniscus tissue, including tissue availability, cost, the need for precise sizing, the risk of disease transmission from the transplanted tissue, and the potential for an immune response against the transplanted tissue to negatively affect graft incorporation and remodeling. Fresh frozen tissue has been used most commonly due to the simplified logistics of transplantation and storage. Furthermore, frozen tissue has diminished immunogenicity. However, frozen tissue is acellular and thus requires cellular repopulation by host cells. This process of cellular repopulation can weaken the tissue due to the need for the repopulating cells to digest the matrix in order to migrate into the dense meniscal tissue.

The limitations of frozen, acellular tissue has led to the use of viable tissue which contains live cells. The obvious advantage of viable tissue is the presence of a cell population to repair microscopic matrix damage. However, the process of at least partial repopulation of the transplanted tissue with host cells still occurs following transplantation of viable meniscal tissue. It is known that donor cells in viable meniscal transplants do survive long-term; however, the function of these cells as far as matrix synthesis and repair of microscopic matrix damage is unknown. All of these considerations point out the need for new techniques for replacement of lost meniscus function.

Meniscus Transplantation: New Frontiers

The use of human meniscus allograft tissue may be improved using techniques that can improve the biologic environment following transplantation. For example, in the future it may be possible to seed the allograft tissue with a specific cell type or to use gene therapy techniques to transfect the meniscal cells with a gene (or genes) that will have a positive effect on healing.

The meniscus transplantation field clearly needs an "off-the-shelf" implant that is available to use at the time of index meniscectomy. It is well-established that the optimal time to replace the meniscus is as early as possible, in order to prevent the degenerative changes that ensue following meniscectomy. There are currently 3 synthetic meniscus replacement devices that have been used in humans. These include:

1. collagen-glycosaminoglycan composite (Collagen Meniscus Implant, Menaflex, ReGen Biologics, New Jersey)

2. resorbable porous polyurethane implant (Actifit, Orteq Ltd., London)

3. Kevlar-reinforced polycarbonate-urethane (Nusurface, Active Implants, Israel).

The advantages of these materials are their availability "off the shelf", sterility, and the ability to have available implants of various sizes. Furthermore, there is currently promising early clinical outcomes data available using these implants. As further clinical experience is gained with these implants, the design, materials, and techniques for implantation should continue to improve.

Materials continue to be developed that may have application for meniscus replacement. For example, hydrogels are a promising class of materials that can mimic the material properties of meniscus tissue and also support cell viability and cellular function. Continued advancements in the area biomaterials will likely lead to the identification of new materials that can be used for meniscus replacement. Ultimately, these materials can be combined with pluripotent cells in a tissue engineering paradigm for replacement of the meniscus.

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21.2.2

High Throughput Tools for Tissue Engineering

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Introduction: As the human body holds more than 200 cell types that synthesize a multitude of both soluble and solid actives in addition to a diversity of components that provide various means of mechanical support, it is clear that extremely complex interactions stand at the basis of the proper functioning of all tissues. Evolutionary processes resulted in intricate biological systems, with robust and adaptable redundancies, as well as multifunctional and multiscale components, which set a hampering factor in compatible materials research – there are no material "standards" that all of biology must follow. This intrinsic complexity impedes full understanding and concomitantly limits developments in materials research for biological applications.

With the increase of complexity, certainly when this is associated with only a partial understanding of the underlying mechanisms, superior strategies need to be applied to unravel or direct processes that result from such complex interactions. Rather than striving for a full understanding of the underlying mechanisms upon which to base ones actions, it might be more productive to rapidly screen a multitude of approaches and select the one with the most promising result for scale up. High throughput based methods allow simultaneous synthesis/processing and evaluating of a multitude of system variations (***e.g.***, material, molecular) (***1***) to isolate desired behavior/responses. Such methods were commonly applied within the field of pharmacology for drug discovery (***2***), the successful genetic screening of fruit flies and zebra fish (***2***), and variegated applications in systems biology (***3***), as examples. Building on these past successes (also including proteomics or genomics (***4, 5***)), modern approaches have accelerated the discovery process

and analytical methods, and have likewise extended insights and potential applications. Far from autonomous improvement, successful studies rely on the technological advancements of many fields, as every step involved in this approach requires high throughput methods; from synthesis characterization (***e.g.***, from a chemical or structural perspective) to analysis and characterization of the desired outcome (***e.g.***, at cellular or tissue level). Surprisingly, in tissue engineering this approach is still largely unexplored.

Content: Here, we will discuss the production, characterization, and use of a set of tools that enable high throughput screening of a multitude of experimental conditions in two- (2D) and three dimensions (3D). The platform is based on five pilars. Similarly to what is done in drug discovery, we first introduce the use of high throughput assessment of biologically active agents for our cells. As the pharma industry is forced in this direction with a frequently much better biological fundamental knowledge base, it is bound to be useful in our much smaller field with technologically more complex applications. Although, the hit compounds may still fail in the following process, at least we will now be testing the most powerful among many instead of the best of few. Second, as our systems are so complex we will frequently have to use multiple compounds simultaneously. As these tend to interact, routine lab protocols will not suffice to obtain the optimal combination of factors which is why we now invest in lab on a chip platforms to allow the testing of multifactorial combinations in the shape of multiplex arrays. Screening of soluble and surface-bound chemical as well as surface topography parameters on cell behavior is now possible with this platform through microfluidic technologies. Four stable, independent and perpendicular diffusion-based concentration gradients can be created in a square chamber, where cells are cultured, enabling a combinatorial investigation of four soluble compounds in a single assay. Furthermore, surface chemistry and topography of the cell culture chamber can be modified to increase its relevance for regenerative medicine research that includes biomaterials. Third, as we see the rise of instructive, smart, scaffolds and/or biomaterials and also here lack most of the fundamental knowledge on the driving mechanism(s), we have implemented array technology to assess the instructive abilities of libraries with millions of surface topographies in an approach referred to as materiomics. These libraries are built on several biomaterial chemistrie by random computed-generated combinatorial permutations of elementary shapes, which we call primitives. High content imaging and bioinformatic tools further complement the platform, consenting the generation and analysis of desired readouts. Fourth, we have embarked on developing platforms that allow us to generate complex tissues in the meso to macro range in a high throughput version. These tissue building blocks are built by controlling the size of homogeneous and heterogeneous cell aggregates in geometrically defined shapes. By introducing instructive microparticles at specific ratios during cell aggregation, we can control the degree of cell condensation and foresee to be able to steer cell activity. This approach will create possibilities to assemble such pre-defined microtissues into larger structure which may mimic the complex structure of organs or parts thereof. Finally, by exploitng our know-how on biofabrication technologies we have developed a 3D platform enabling screening to happen directly in vivo. Experimental conditions include biomaterial formulations, biomolecules, and cell aggregates. This allows us to improve correlation between in vitro and in vivo findings, at the same time reducing the amount of animals and abating associated costs that would be needed to test the same amount of experimental conditions with conventional technologies.

The combination of the above technologies will now offer us a toolbox that is better fit for dealing with tissue engeering complexity than most conventional techniques applied today. These tools allowed us to screen thousands to millions of conditions, which led to the discovery of smart surfaces and cell co-culture conditions instructive for musculoskeletal tissue regeneration.

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21.2.3

Evolution and Implementation of Clinical Cartilage Tissue Engineering Strategies

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Introduction: It is widely accepted that chondral injuries usually do not heal spontaneously. Therefore, a variety of approaches have been tested to improve cartilage healing. Among them, chondrocyte-based therapies have been extensively studied since the successful report of autologous chondrocyte implantation. However, this procedure may have limitations including the sacrifice of undamaged cartilage within the same joint. To overcome such potential problems, stem cell therapy has been investigated to facilitate regenerative tissue repair. Multipotent cells including mesenchymal stem cells (MSC) may be well suited for cell-based therapies for cartilage repair.

In addition to the selection of a cell source, it is

important to establish an appropriate environment for cell proliferation and differentiation. For this purpose, many studies have focused on the development of scaffolds [8]. Scaffolds generally contain synthetic polymers such as poly (l-lactide) (PLLA), poly (glycolide) (PGA), poly (dl-lactide-co-glycolide) (PLGA), and alginate or biological materials such as collagen, fibrin hyaluronan, and chitosan; however, their long-term side effects still remain unclear. Various scaffolds have been approved for clinical use. However, there are still several issues associated with their long-term safety. In order to avoid unknown risk, a scaffold-free cell delivery system could be an excellent alternative.

Due to its unique matrix organization, articular cartilage has anti-adhesive properties and therefore integration of implanted tissue into an adjacent cartilage matrix has been an issue in the treatment of chondral injuries.

To overcome this problem, most implantation procedures have required enzyme treatment of the surface of the cartilage matrix, reinforcement of the initial fixation by suturing, or the use of absorbable pins. However, an animal study revealed that a suture track in the surrounding articular cartilage remains unhealed, and is a defect that could potentially be a trigger site for subsequent degradation of matrix. Therefore, an implantable tissue that possesses adhesive properties to cartilage tissue would be optimized for secure tissue integration.

Based on these requirements, a scaffold-free threedimensional tissue-engineered construct (TEC) composed of human mesenchymal stem cells (MSCs) derived from synovium and extracellular matrices (ECMs) synthesized by the cells has been generated in vitro. In the present lecture, the feasibility of this unique scaffold-free implant will be introduced followed by the discussion regarding future tissue engineering towards cartilage regeneration.

Content:

Development of the Basic TEC

When synovium-derived MSCs were cultured to confluence in the presence of ⟶0.1 mM ascorbic acid-2 phosphate (Asc-2P), collagen synthesis significantly increased with time in culture. Subsequently, the monolayer cellmatrix complex cultured in Asc-2P became a stiff sheetlike structure, which could be easily detached from the substratum by exerting mild shear stress at the cell-substratum interface using gentle pipetting. After detachment, the monolayer sheet immediately began to actively contract and evolved into a thick 3D tissue. Histology and scanning electron microscope (SEM) assessment of the 3D tissue showed that the cells and the ECM were three-dimensionally integrated together at high cell density. Immunohistochemical analysis showed that the TEC was rich in collagen I and III. In contrast, there was no expression of collagen II within

the TEC. Fibronectin and vitronectin were also abundant in the TEC. Notably, all the molecules were diffusely distributed throughout the matrix and there was no overt polarity in matrix organization within the TEC. When the TEC was folded within the matrix, it was apparent that the layers were integrated into each other and a series of foldings led to development of one spherical body several millimeters thick. This ontracted tissue was termed a tissue engineered construct (TEC) derived from MSCs.

The basic human TEC has adhesive properties which facilitate association and adhesion to cartilage matrix.

To test the adhesive property of the TEC to an established intact cartilage matrix, basic human TECs were placed on the injured surface of a fresh-frozen human chondral fragment. Within 5 min, the TEC had adhered to the chondral fragments. When the TEC-chondral complexes were further cultured for 7 days, they remained stably associated for the entire time. Histology at day 7 showed close adhesion of the TEC to the injured surface of the chondral fragments. Immunohistochemistry showed that fibronectin and vitronectin were localized at the interface between the TEC and the injured surfaces of chondral fragments. C**hondrogenic Differentiation Capacity of TEC.** Human TEC cultured in a chondrogenic medium containing BMP-2 showed increased glycosaminoglycan (GAG) synthesis and deposition as evidenced by intense Alcian Blue staining. The quantification of GAGs indicated that GAG synthesis was significantly higher in the TEC exposed to the chondrogenic medium compared to those generated in the absence of such components. Detection of cartilage-specific markers, collagen II (Col2a1), aggrecan, and sox9 messenger RNA (m-RNA) by semiquantitative RT-PCR confirmed the cartilage phenotype of the treated TEC. Untreated TEC, as well as monolayer cell cultures, showed only weak expression of cartilage-specific markers.

In order to assess the efficacy of the TEC in an in vivo model, a porcine model was chosen as the physiology of the pig is similar to that of humans in many respects, and porcine articular cartilage of the knee is sufficiently thick as to allow creation of a chondral defect without damaging the subchondral bone. Prior to performing such studies, a preliminary characterization of the ability of porcine-derived MSC from synovium to generate a TEC comparable to that discussed above for the human MSC was undertaken. To test the feasibility of using a porcine TEC without chondrogenic manipulation to repair a chondral injury, a juvenile porcine chondral injury model was used. After implantation, the TEC firmly adhered to the injured joint surface without suture. To confirm the early adhesion mode of the TEC to the injured surface, histology at day 7 was examined. The TEC was tightly adhered to the injured chondral surfaces. Higher magnification revealed that the adhesion was mediated by matrix-to-matrix interaction and, as shown in the in vitro culture study, fibronectin was localized to the interface between the TEC and the surface of the defects. At 6 months postimplantation, 50% of defects in animals treated with the TEC were completely covered with repaired tissue, while in the remaining defects, majority of the lesions were covered with the repair tissue with minimal failure of tissue integration. Without the TEC treatment, 75% of the lesions had no tissue coverage and there was evidence of extensive erosion of subchondral bone, while 25% of the lesions were only partially covered with repair tissue. The mean macroscopic score for the TEC-treated group (0.25 ± 0.50) was significantly lower than that for the untreated group (1.50 ± 0.50), where a higher score is suggestive of a failure to resolve and progression toward osteoarthritis. Histologically, the chondral lesions in the non-treatment control group showed evidence of osteoarthritic changes with loss of cartilage and destruction of subchondral bone. Conversely, when treated with the TEC, the defects were filled with repair tissue exhibiting good integration to the adjacent cartilage and the restoration of a smooth surface. At higher magnification, spindle-shaped fibroblast-like cells were dominant at the surface of repaired tissue, while majority of the cells were round-shaped in lacuna in the deeper areas of the repair tissue.

The Safranin O positive area of this repair tissue also stained for collagen II. In histological scoring, all criteria of the TEC-treated group were significantly better than those for the untreated group, indicating better repair of the defects. At no point following implantation was there any histological findings that suggested central necrosis of the implanted TEC.

The mechanical properties of porcine chondral defects treated with a porcine-derived TEC approximates those of normal cartilage 6 months postimplantation.

It is accepted that the articular cartilage is a biphasic viscoelastic material which indicates a strain-rate dependent mechanical behavior [17]. It means that the viscoelasticity of cartilage which retains interstitial water might be mainly reflected in faster compression test, while the matrix viscoelasticity without interstitial water could be mainly reflected in slower compression test. In the repair tissue of the untreated group, the tangent modulus (defined as the slope of the curve at 5% of strain) was significantly lower than that for normal cartilage. In contrast, there were no significant differences detected between the tangent modulus for the repair tissue in the TEC implant group and that of normal cartilage. This result suggested that the viscoelastic properties of tissue repaired with the chondrogenic TEC construct, either with or without interstitial water, are likely similar to those of control or normal cartilage. Digital microscopy revealed that the surface of the repair tissue in the TEC group was smooth, and similar to normal cartilage. In addition, coefficient of friction of the resulting repair tissue in this group was not significantly different from that of normal cartilage. **The Next Generation Cell-Based Strategy to Regenerate Cartilage** The feasibility of a unique scaffold-free three-dimensional TEC generated from MSCs for effective cell-based cartilage repair in an allograft model has been demonstrated.

The TEC can be developed without any exogenous scaffold, and implantation of the TEC would have minimal risk of potential side effects induced by artificial or extrinsic biological materials contained in the scaffold. Therefore, with the use of autologous serum, it should be technically possible to develop the TEC in a xeno-free system, a factor that could minimize the risk of immune reactivity developing to the TEC. The TEC also has been shwon to facilitate cartilage repair with good integration to the adjacent cartilage matrix and the repair tissue exhibited chondrogenic differentiation without any evidence of central necrosis up to 6 months after implantation. Biomechanical analysis also revealed that the tissue repaired with the in vitro generated TEC implants exhibited modulus and frictional properties similar to the properties of normal porcine cartilage. To our knowledge, this study was the first demonstration of a successful animal model of MSC-based therapy for repair of a clinically relevant chondral injury that does not breach the subchondral plate. The basic TEC originally does not express chondrogenic marker molecules such as collagen II, instead is rich in collagen I and III. However, when basic TECs were subsequently cultured in a chondrogenic medium, the cells began to synthesize a cartilage-like matrix including expression of aggrecan and collagen II. These results suggest that the basic TEC also could have the potential to generate a matrix composition similar to that of articular cartilage by responding to endogenous growth factor signals after implantation in vivo.It is notable that implantation of TEC without anypretreatment to promote a specific differentiation pathway resulted in tissue repair associated with an active chondrogenic differentiation response, although the repair sites still contained fibrous tissue at the surface. This suggests that the local in vivo environment might have stimulated chondrogenic differentiation of the TEC. While the mechanisms underlying the chondrogenic repair obtained thus far are still not clearly delineated, it should be noted that the animal model used in the present study involves a chondral injury that does not breach the subchondral plate, and thus the relatively bleeding-free environment at the site of the lesion might be involved in such specific chondrogenic differentiation in vivo rather than the development of

a fibrocartilage response. However, to attain a more optimal or extensive chondrogenic differentiation response, some biological manipulation of the TEC may be required before implantation to further optimize the rate and extent of repair, and this approach is one of our next steps.

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21.3.2

Co-culture of MSC and Chondrocytes: What Cells teach each other

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Introduction: The current procedure for Autologous Chondrocyte Implantation (ACI) requires two surgical interventions interrupted by a few weeks. This interruption is required to expand the limited number of chondrocytes isolated during the first intervention in vitro to obtain sufficient cells for filling up the defect in the second intervention. Despite clear clinical benefit, this two-step procedure has a number of disadvantages: Chondrocyte expansion in vitro is associated with loss of the cell's phenotype which may hamper neocartilage formation once reimplanted in the patient. It has the risk of infection and cell transformation and is a timely and therefore costly procedure. Hence there is a clear clinical and societal need to bring back cell based cartilage repair strategies to a one-step surgical procedure. This immediately poses a challenge: How to obtain sufficient cells for peroperative implantation? It has been proposed that the number of chondrocytes needed in an ACI procedure could be reduced by replacing a substantial part of the cells by mesenchymal stromal cells (MSCs) (1). MSCs have stem-cell like characteristics and can readily differentiate into chondrocytes under appropriate culture conditions, at least in vitro. They can be isolated from various tissues such as bone marrow, adipose tissue and synovium. The ease of isolation and their multilineage potential has raised considerable interest in the use of MSCs in cartilage repair strategies (1).

Content: Indeed when primary chondrocytes are mixed with MSCs in pellet co-cultures cartilage formation exceeds matrix production in pellet mono-cultures of MSCs or primary chondrocytes, providing a rational for co-implantation of primary chondrocytes and MSCs (2). Furthermore this observation suggests the existence of cell communication between the primary chondrocytes and the MSCs. Improved cartilage formation in pellet co-cultures has been explained by the ability of the primary chondrocytes to orchestrate chondrogenic differentiation of MSCs. It has been shown that chondrocytes secrete growth factors like Bone Morphogenic Proteins, which are known to stimulate chondrogenic differentiation of MSCs. Alternatively, MSCs may also instruct the chondrocytes to produce more cartilage. The latter explanation is in line with a proposed trophic role of the MSC in tissue repair as has been described in for example the infarcted heart. To distinguish between these two possibilities, my lab set out to perform xenogeneic pellet co-cultures of bovine primary chondrocytes and human bone marrow derived MSCs. In such assays the contribution of each cell type to matrix production can be studied using species specific PCR. In addition, the fate of each cell population can be followed over time (2).

When primary bovine primary chondrocytes (bPCs) are mixed with human MSCs in a 20:80% ratio and cells are allowed to form a pellet, a clear segregation of the two cell populations due to self-organization is observed. The MSCs invariably end up in the centre of the pellet, while the bPC localize in the outer layers of the pellet. After 4 weeks of differentiation, either in chondrogenic differentiation medium (serum free medium plus additives and TGFβ) or in serum containing proliferation medium, pellets homogenously stained positive for glycosaminoglycans indicative for efficient cartilage matrix production. Remarkably, species specific PCR demonstrated a near exclusive bovine origin of the extracellular matrix. This coincided with our observation that after 4 weeks species specific genomic PCR demonstrated an almost complete absence of human MSCs in the pellet co-cultures. This suggests that the bovine cells have taken over despite the fact that they are seeded at a much lower density than the MSCs. This observation is explained by the fact that in pellet co-cultures only, the MSCs potently stimulate chondrocyte proliferation while simultaneously undergoing cell death most likely via apoptosis (2). When MSCs and primary chondrocytes are mixed in an alginate gel in which both cell types are physically separated similar observations were made. The bovine chondrocytes started to proliferate while the MSCs started to die indicating that direct physical contact is not necessary for improved cartilage formation in mixtures of chondrocytes and MSCs. Furthermore, our data suggests that the beneficial effect on cartilage matrix production in pellet co-cultures are caused by a trophic effect of the MSCs on the primary chondrocytes rather than differentiation of the MSCs themselves into chondrocytes, although we cannot completely exclude that some MSCs may have actually undergone chondrogenic differentiation, albeit a minority (2).

Subsequently we were able to show that this trophic role of the MSCs in stimulating cartilage formation was not intrinsic to the xenogeneic culture method employed by us. Similar data were found in fully human pellet co-cultures. In the latter cultures we showed the specific disappearance of the MSCs from the pellets over time using the analysis of donor specific short tandem repeats (2,3).

We next examined whether the trophic role of the MSC in pellet co-cultures with human primary chondrocytes (hPCs) is restricted to bone marrow MSCs or is a more generalized feature of MSCs. To test this we performed pellet co-cultures of hPCs with the MSC fraction from adipose tissue and synovium. Similar observations were made clearly indicating that observed trophic role is not depending on the origin of the MSC population (3). Interestingly, cartilage formation in pellet co-cultures of freshly isolated stromal fraction of adipose tissue which contains amongst others the MSC fraction was increased compared to the cartilage formation in enriched MSC fractions. These enriched MSC fractions are obtained after selection based on plastic adherence and cell culture. We then examined whether the trophic role of the MSC in the pellet co-cultures was related to the chondrogenic potential of the MSCs. MSCs are well known for their heterogeneity which is reflected in a large donor to donor variation in chondrogenic potential in differentiation assays in vitro. In this experiment we determined the chondrogenic potential of 20 MSC donors and studied the role of each of these MSCs in pellet co-cultures. Remarkably, in each of these co-cultures, the MSCs gradually disappeared over time, despite a broad range in chondrogenic potential. Even donors which did not differentiate into chondrocytes in vitro effectively stimulated cartilage matrix formation in pellet co-cultures as effective as donors with very high chondrogenic potential. Our data showed that improved cartilage formation in pellet co-cultures of primary chondrocytes and MSCs is not related to the chondrogenic potential of the latter.

To elucidate the molecular mechanism underlying the stimulation of chondrocyte proliferation in pellet co-cultures with MSCs we first showed that this effect was partly mimicked by using MSC conditioned medium. This suggested that this effect was mediated by an MSC secreted factor(s). To identify this factor we performed genome wide expression profiling of pellet mono-cultures and pellet co-cultures. Detailed comparison identified acidic Fibroblast Growth Factor (FGF1) as an MSC secreted factor stimulating chondrocyte proliferation. Remarkably, FGF1 is only secreted by MSCs in pellet co-cultures suggesting that an interaction with the primary chondrocytes is necessary for efficient induction of FGF1 expression by MSCs. Experiments with neutralizing antibodies subsequently demonstrated that blocking FGF1 activity also inhibited chondrocyte proliferation in pellet co-cultures (4).

In conclusion, in pellet co-cultures of primary chondrocytes and MSCs extensive communication between both cell types occurs. This results in increased cartilage formation by a profound stimulation of chondrocyte proliferation while simultaneously MSCs start to die. In the pellet co-culture model, MSCs have a trophic role and over time disappear from the cultures, rather than differentiating into chondrocytes. The MSC secreted factor FGF1 is instrumental in stimulating chondrocyte proliferation in pellet co-cultures. Our study provides a rational for replacing part of the primary chondrocytes with MSCs. These MSCs could be derived from various tissue sources. Exploiting the trophic role of MSCs could be an efficient strategy to boost cartilage regeneration in situ.

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21.3.3

A tissue therapy model using nasal chondrocytes and bioreactor

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Introduction: Autologous chondrocyte implantation (ACI) has been well-established in the clinic for the repair of cartilage injuries for nearly two decades. Although good clinical results are generally reported in short-term follow-up, the technique does not reproducibly support durable regeneration in the long-term. Moreover, due to the high costs, long rehabilitation time, large inter-patient variability of the chondrocyte quality and a lack of sound cost versus benefit data, ACI has failed to gain acceptance by the health care sector and therefore suffers from very limited reimbursement coverage. As an alternative, a three-dimensional cartilage tissue graft, engineered in vitro to possess functional properties (i.e., to biochemically and mechanically mimic native cartilage), could reduce the initial rehabilitation time and result in a more durable repair in the long-term. To reduce the variability in the quality of the engineered tissue grafts, a cell source with more reproducible function such as nasal chondrocytes could be used. As compared to articular chondrocytes, nasal chondrocytes have a higher and more reproducible capacity to generate functional cartilaginous tissue, which is less dependent of the donor age, and show a similar response to physical forces resembling joint loading.

The central bioprocesses for engineering cell-based grafts have traditionally been, and continue to be, based on conventional manual benchtop techniques, which due to the large number of manual and labor-intensive manipulations required, possess inherent risks of contamination, potential high intra- and inter-operator variability, limited scale-up opportunity, and high manufacturing costs in the long-term. Bioreactors have the potential to overcome these limitations by: i.) providing a controlled physico-chemical culture environment, which tightly regulates the bioprocesses, minimizing process and product variability, ii.) including monitoring and data management systems which offer a high level of traceability and increased compliance to regulatory guidelines, and iii.) introducing automation which facilitates safe and standardized production methods and maximizes prospective scale-up and cost-effectiveness in the long-term. Thus, the bioreactor-based implementation of automated, controlled, and streamlined manufacturing processes, similar to other biotech sectors (e.g., the pharmaceutical industry), will be instrumental to facilitate the broad utilization and commercialization of tissue grafts as therapeutic solutions.

Content: This presentation will first present the scientific data substantiating the use of nasal chondrocytes as a source of autologous cells for the generation of functional cartilage grafts. In contrast to articular chondrocytes, nasal chondrocytes can continuously revert from differentiated to de-differentiated states across serial cycles of cloning, while conserving the ability to generate cartilage tissue in vitro and in vivo. The compatibility at an articular site of implantation will be discussed based on the capacity to respond to physical loading and inflammatory conditions, as well as to modify the constitutive gene expression profile, associated with the embryonic derivation. Indeed, adult human mesectoderm-derived nasal chondrocytes can be constitutively distinguished from mesoderm-derived articular chondrocytes by their lack of expression of specific HOX genes (e.g., HOXC4, HOXD8). However, nasal chondrocytes can adopt the HOX-positive profile of a mesoderm environment upon subcutaneous implantation or in articular cartilage defects. Validation of the principles will be discussed in light of a pre-clinical study which demonstrated safety and feasibility of tissue engineered (TE) cartilage grafts based on autologous NC for the repair of articular defects in goats. Also based on the here presented findings, the Basel University Hospital has recently started a first-in-man phase I clinical study to treat traumatic knee joint defects with cartilaginous constructs generated from autologous NC (http://clinicaltrials.gov Identifier: NCT01605201; status: 3rd patient treated).

The presentation will then describe a streamlined, bioreactor-based manufacturing system, whereby the phase of cell expansion in monolayers is bypassed and all cell and tissue culture processes are performed within a single perfusion bioreactor chamber, under monitoring of the relevant culture parameters. Regulatory bodies have recently outlined stringent quality control guidelines for the production of engineered tissue products for clinical applications (European Medicines Agency, 2008, FDA, 2008, ICH PIC7S Guide to Good Manufacturing Practice for Medicinal Products, 2009, ICH guidelines). The manufacturing system is being designed to be compatible with regulatory compliance by a thorough graft characterization during the production and at the time of release, including quantitative measurements of the tissue's most relevant biological attributes (e.g., cell number, amount of specific extracelluar matrix components). Validation of the paradigm in a de-centralized production setting is ongoing, with graft implantation in an autologous goat model.

The lecture will discuss the clinical, scientific and socio-economic impact of the proposed approach, which is currently being pursued in the context of a European project consortium (BIOreactor-based, Clinically Oriented Manufacturing of Engineered Tissues, http://www.biocomet.eu/). The ultimate goal is to produce cartilage tissue grafts, engineered to possess functional properties, with the aim of establishing a tissue therapy to reduce initial rehabilitation time and support a durable repair in the long-term. Moreover, the program targets the development of a safe and scalable production system to standardize the production of the functional cartilage grafts, which will be key to reach cost-effectiveness.

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22.2.1

How do Patient Criteria Affect Cartilage Repair

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Introduction: We should be thorough in knowing the patient that surrounds the cartilage defect instead of only focussing on the defect itself as patient characteristics are major factors that could influence the clinical improvement measured after cartilage repair. Therefore identification of patient criteria that influence the course of cartilage treatment is of paramount importance in the process

from diagnostic workup to treatment follow-up. Increasing work, knowledge and enthusiasm of such factors will facilitate adequate timing and selection of suited treatments and thereby improve patient and provider satisfaction.

Content: Improved diagnostic modalities and availability of articular cartilage repair techniques have increased the population of patients seeking help for an articular cartilage defect. In addition, the heterogeneity of patients presenting with a defect has increased, ranging from young active adults to middle aged patients with multiple degenerative lesions. Little studies are designed to provide prognostic information on how patient criteria affect cartilage repair. Therefore most identified factors are derived from secondary outcome measures and analysis.

Several studies have shown an influence of patient age on the clinical improvement (measured with validated questionnaires) following cartilage surgery.(1-4)Whether these studies handle 30 or 40 years of age as the cut-off point above which results become less satisfactory, they all show the same trend; increasing age negatively influences clinical improvement from cartilage surgery. This phenomenon could be related to the effects of ageing on the senescence of cells and tissues and thus the extent of the regenerative response. Also, older patients have, in general, a less active life-style compared to younger patients. Development of articular cartilage follows patterns of physiological loading during development.(5) Therefore, such loading patterns could also be important during cartilage regeneration and be a reason for less clinical improvement with increasing age. The patients' activity level, before onset of cartilage-defect-related symptoms, also influences clinical outcome following defect surgery. Knutsen et al showed that more active patients have improved clinical scores, regardless of treatment(6), whereas in other hands the influence of activity level seems treatment-type specific. Deterioration in sports activity has been noticed following microfracture(7;8) treatment while ACI was found more durable in active patient.(7-10) On the other hand, microfracture also shows acceptable results in several cohorts of professional athletes.(11;12) Overall, active patients seem to benefit more from cartilage surgery compared to less active patients.

Defect size is also a frequently mentioned factor that could influence outcome of cartilage surgery. However, this effect seems more treatment-type specific instead of size-dependent. Clinical outcome seems not to be influenced when lesions are treated with ACI whereas this effect tends to deteriorate when larger lesions are treated using microfracture.(6;10;13) Gender differences only showed to influence cartilage formation in vitro but not in clinical trials.(14)

Already 10 years ago the concept of joint homeostasis was introduced showing that the environment of a cartilage lesion at start of the treatment influenced its outcome.(15) Biological mechanisms underlying this phenomenon are currently developed and increasing knowledge on influencing cytokines, interleukines and other proteins have moved this field forward. Symptom duration, also referred to as defect age, describes the time from first defect-related symptom to diagnosis and treatment. Increasing defect age has, in several studies, been related to worse outcomes after cartilage surgery.(2;10;16) With treatment delay, and thus ongoing defect degeneration, the conditions for cartilage regeneration become worse as the intraarticular environment will be increasingly disturbed. Also genetic properties of the reimplanted chondrocytes in ACI have shown to influence clinical outcome. Patients with a higher CC-score (a score based on genetic markers for chondrogeneicity) showed more clinical improvement compared to those with lower scores.(10)

Conclusion: Several patient-related criteria have been revealed to influence clinical outcome following cartilage surgery which could aid optimizing the timing and treatment selection of cartilage defects. However, until studies remain underpowered and not designed for such patient-criteria-related subanaysis, conflicting evidence will steer the application of patient factors in daily practise from evidence-based to expert-opinion-based.

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22.2.3

Patient Profiling & Treatment Algorithm for Cartilage Repair

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Introduction:

Nowadays the physician faces a difficult challenge to select the right treatment for the increasing heterogeneity and number of patients seeking help for their cartilage defects. Timing and selection of the correct treatment fitted to the needs of the patient and possibilities of the physician influences eventual outcome and bilateral satisfaction. Identification of influencing factors that could steer the physician into the correct direction could serve as landmarks in the diagnostic

and therapeutic process. Moreover, decision trees, based on such factors, would make life even easier. The concept of patient profiling has been introduced several years ago and covers the identification of patient-related parameters that influence the outcome of cartilage defect treatment. Based thereon, several treatment algorithms have been presented. Unfortunately, global application of such algorithms remains a challenge as treatment selection is still driven by the health care availability, insurance coverage and expert opinion.

Content: Factors like duration of symptoms (also referred to as defect age), activity level and age of the patient have been related to influence the clinical outcome of cartilage defect treatment unaware of type of treatment.(1-6)Such factors are therefore not helpful in the treatment selection process but rather inform the physician on overall outcome regardless of treatment type. The influence of defect size on clinical outcome is dependent on what cartilage treatment is applied which makes defect size a discriminating factor for treatment selection. For example, the clinical improvement decreases with increasing defect size in microfracture cohorts. This effect was not reported for ACI.(1;7)Also for larger defects ACI and OAT were found to be superior to MF in several randomized trials(8-11)while larger defects seem to respond better to ACI compared to OAT.(7)A size threshold is difficult to determine, although literature suggests to apply ACI on lesions ⇢2.5 cm². For lesions ⇢2.5 cm² and involvement of the subchondral plate and/or bone the ACI procedure should be combined with a sandwhich technique. Also for lesions ⇠2.5 cm² involvement of the subchondral bone is a discriminating factor in treatment selection. In osteochondral lesions ⇠2.5 cm² (single plug) OAT is preferred whereas for small chondral lesions MF is a good treatment option.(1)For professional athletes ACI resulted in a better clinical improvement compared to MF.(12;13)Therefore, surgical debridement and cartilage biopsy for a later off season ACI should also be considered in such special cases.(1)

Little attention is paid to the characteristics of intraarticular tissues while, as presented, the subchondral bone is an example of such a characteristic that discriminates the one treatment from the other. Next to patient profiles increasing knowledge on such tissue typing could further fine-tune the already designed treatment algorithms.

The demands on the physician and applied treatment increases with increasing heterogeneity of patients seeking help for their cartilage defect and the wish to be active up to a higher age. Several studies already showed adequate clinical results following ACI and OAT in early OA.(14-16)With this change in treatment paradigm the question arises whether the indication of ACI should be adjusted according to the spirit of time or adequate treatments for early OA, such as joint distraction, are to be considered for such patients.

Conclusion: Current evidence-based treatment algorithms are based upon the size of the lesion and involvement of the subchondral bone. General patient profiles like duration of symptoms activity level and age of the patient can be used to discuss realistic expectations from surgery with your patient. Additional knowledge and typing of intraarticular tissues could be helpful in further fine-tuning the treatment algorithms while the increased heterogeneity of cartilage patients makes the development of one single treatment algorithm difficult. Finally, future clinical trials comparing two or more cartilage repair procedures should be sufficiently powered to perform additional subanalysis that take the effects of treatment specific as well as patient and tissue specific characteristics on clinical outcome into account

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22.3.2

Use of Quantitative MRI in Assessing Cartilage Lesions and Structural Changes in Osteoarthritis and Related Conditions

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Introduction: Osteoarthritis (OA) and cartilage lesions are the most common form of musculoskeletal disorders. New technologies are needed that can allow reliable and sensitive assessment of joint structural changes over time to follow disease progression and study treatment effects. Such development is challenging in diseases known to be very often of insidious onset and slow progression. For decades, the technical means were limited to conventional radiographs, which have low sensitivity even though there have been improvements with computer assisted methods and new imaging protocols. Moreover, the reliability of the radiographic measurement of joint space narrowing (JSN) is compromised by a number of factors, including the positioning of the joint, meniscal extrusion, and a very small annual change [1,2].

Content: The introduction of magnetic resonance imaging (MRI) to the field of OA allowed direct, precise, and reliable assessment of

cartilage and other joint structures and their changes over time. Several different semi-quantitative scoring systems using different acquisition protocols have been developed and proposed to assess structural changes in patients with knee OA and related conditions, including the Whole-Organ Magnetic Resonance Imaging Score (WORMS) [3], the Knee Osteoarthritis Scoring System [4], the Boston Leeds Osteoarthritis Knee Score [5], the system published by Ding et al [6], and the recently published MRI Osteoarthritis Knee Score [7]. These scoring systems were used for the understanding of the pathophysiology of OA and the relationship between joint tissue structural changes and disease symptoms. They can assess cartilage defects in a number of subregions of the joint using a grading scale. Quantitative cartilage assessments have also been developed [8-10] and successfully applied in clinical trials [11-13]. However, there is discussion about which method is optimal to assess cartilage changes, semi-quantitative (scores) or quantitative (continuous values), particularly in the context of disease modifying OA drug (DMOAD) trials. Advances in MRI technology have led to significant improvement in spatial resolution and contrast, enabling researchers to evaluate anatomical damage of all the joint structures across both cross-sectional and longitudinal planes. The quantification of these changes has been the real challenge for many years. The recent improvements in image analysis have led to the reliable quantitative measurement of cartilage volume and thickness in both normal and disease conditions such as in OA. Cartilage volume quantification is now used for determining changes in this tissue over time using specific MRI acquisitions combined with computer software to obtain valuable information on cartilage volume in normal and OA subjects [14-17], allowing for the reliable evaluation of cartilage volume and thickness in anatomical subregions as well as specific focal defects [8] and the assessment of change in cartilage volume of the knee over time [11-17]. The risk factors identified to be associated with faster progression are female gender, high body mass index, reduced range of movement of the study knee, greater knee circumference, and higher knee pain and stiffness scores as assessed by the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) questionnaire, and structural damage such as meniscal damage or joint malalignment [15,18-21]. A study comparing patients who had undergone surgical meniscectomy with controls, showed that cartilage volume loss over time as assessed by quantitative MRI was greater in patients who underwent partial meniscectomy [15]. In another study looking at the risk factors for progressive cartilage loss in knee OA patients using MRI, data showed that meniscal and anterior cruciate ligament tears were associated with a more rapid cartilage loss [20] as well as the presence of a severe medial meniscal extrusion [19]. The importance of other structural changes such as bone marrow hypersignal (lesions) in assessing knee OA has been demonstrated [18,21].

A non-invasive scoring system for synovial thickness using MRI and semi-automated technology was recently developed [11]. It accurately and reliably assesses the severity of synovitis in knee OA patients. The first ever published clinical research trial using quantitative MRI was a two-year randomized multicentre trial exploring the effects of licofelone, a lipoxygenase and cyclooxygenase (LOX/COX) inhibitor, for disease modifying properties in OA patients 11. Quantitative MRI was used to assess changes in cartilage volume and X-rays (Lyon-Schuss) were used to measure changes in joint space width (JSW) over 24 months. MRI data demonstrated that cartilage volume loss was significantly less in the licofelone group compared to the control group at 12 and 24 months. In this study, the reduction in the JSW in the licofelone group did not reach significance. These findings clearly demonstrate the important limitation of standard radiographs compared to quantitative MRI in investigating DMOAD treatment effects.

With regard to the sensitivity to detect treatment effect using the semi-quantitative versus the quantitative method, a recent study [22] showed a statistically significant difference in the percentage of cartilage volume loss between the two treatment groups, whereas for the cartilage defects, a close to significant difference was observed only in the medial plateau. In addition, the semi-quantitative assessment demonstrated a lower sensitivity to change than the quantitative evaluation of the cartilage volume loss indicated by lower SRM values (4.3 to 6-fold for the global knee and subregions). This is well in line with the sensitivity to change of the current gold standard, JSN, which was shown to be inferior to cartilage volumetry, and consistent with a recently published study using 3T MRI that demonstrated the superiority of quantitative measurements over semi-quantitative scores to assess change over time [23]. Moreover, the assessment of cartilage loss performed in subregions, including the weight-bearing regions of condyles and plateaus, was much less sensitive with regard to the assessment of changes over time and response to treatment. This finding was mainly related to the greater inter-patient variability and could likely apply to the semi-quantitative scoring system. Comparison between treatment groups in a cohort of patients with knee OA demonstrated that assessing cartilage volume loss provides a much greater sensitivity to treatment response globally than the semi-quantitative scoring method. This study has provided information that has helped to answer two very important questions that are relevant not only to longitudinal studies but, more importantly, to DMOAD clinical trials involving the assessment of cartilage changes over time between treatment groups and, therefore, response to treatment.

To address the question of the benefit of a DMOAD, a "hard" outcome such as preventing the occurrence of total knee replacement (TKR) could be targeted. In this line of thought, a number of recent studies were performed to identify predictive factors for TKR. Data revealed that baseline score of bone marrow lesions in the medial compartment, medial JSW, presence of severe medial meniscal tear, medial meniscal extrusion, and C-reactive protein level were strong predictors of TKR.

MRI-based quantitative knee joint structure assessments are and will be increasingly used for evaluation of the efficacy of a DMOAD. To date, semi-automated quantitative MRI assessment methods have shown enough stability to produce cohort-scaled results. A new generation of tools, which are fully automated, will enhance stability and reproducibility of MRI reading. In recent years, our group has developed such fully automated segmentation systems for knee OA bone contours [24], as well as quantitative volume evaluation of cartilage [25] and synovial fluid [26], which showed excellent reproducibility.

The concentration of glycosaminoglycan (GAG) in articular cartilage is also known to be an important determinant of the mechanical properties of this tissue. Concentrations of GAG have been explored using delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). The assessment of cartilage degeneration through GAG can be performed with the same efficiency as the dGEMRIC approach, but with a completely non-invasive technology. This technology uses a spin-lock pulse sequence allowing evaluation by T1p parameter, comparable with the T1 or T1Gd [27]. Another MRI acquisition technique, T2-mapping, was further shown to detect changes in cartilage water content [28]. The detection of small physiological changes in water content may help in the early diagnosis of OA.

T2 imaging was also suggested to be relevant for collagen variation assessment [29], in establishing the relationship between T2 cartilage imaging and the cartilage water content, proteoglycan concentration, collagen concentration, or tissue anisotropy. Alternatively, the MR diffusion tensor imaging (DTI) could also be useful for detecting early changes in collagen fibre alignment, as DTI allows determination of the degree of diffusion anisotropy and the direction of local diffusion in tissues, as well as identification of the orientation of collagen fibres.

In conclusion, the quantitative assessment of cartilage thickness and volume and other joint structure changes is primarily to objectively evaluate the disease course as well as treatment that may slow down joint tissue damage. Semi-automated, and now fully automated, technologies to assess and quantify joint structure have opened the door to intensive and autonomous computation, enabling images from large scale studies to be reliably analyzed in a shorter time frame with high accuracy. Quantification of cartilage loss and the other changes in joint structure observed in OA and related conditions over time will improve the disease monitoring and help to develop and test new interventions to prevent the progression of these extremely prevalent musculoskeletal disorders. MRI technology should therefore be included in clinical trials and used for the detection of OA or cartilage defects, as well as treatment follow-up and the prediction of long term outcomes.

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24.1.1

Small Animal Models
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Introduction: Animal models are essential for testing several aspects of cell/molecular preparations, constructs, or devices for osteochondral repair before these can be tested into humans. Large animal models have been traditionally used to study aspects related to retention of cells, efficacy of procedures, and biomechanical outcomes such as stiffness (Breinan et al., 2001; Hunziker, 2002; Aigner et al., 2010; Chu et al., 2010; Little and Zaki, 2012; Johnstone et al., 2013). In large animals, cartilage thickness and biomechanics better approach those of the human species and allow not only a better comparability of results, but also the performance of procedures that are more similar to those used in humans: for instance, in a large animal models such as the goat it will be possible to perform autologous chondrocyte implantation in a way that is very similar to that used in humans, including the retention of the cells under a synthetic membrane or a periosteal flap (Hunziker, 2002; Dell'Accio et al., 2003; De Bari et al., 2006). The same procedure cannot be performed in the mouse or in the rat.

Some issues, however, cannot be resolved with large animal models. For instance, in the majority of the large animal models there is a very high rate of delamination (Driesang and Hunziker, 2000; Vasara et al., 2004)which makes these models of limited use for potency studies. Species specificity is an additional problem, particularly when testing the function of molecular treatment which may differ in different species.

Small animal models can tackle some of these issues.

Content: The cartilage of mice and rats is much thinner than that of humans, is subjected to very different biomechanics, and its architecture is also somewhat different (Hunziker, 2002; Mainil-varlet et al., 2009; Little and Zaki, 2012), nevertheless small animal models have a number of features that make them invaluable in modern regenerative medicine.

1) Amenability to genetic manipulation.

Modern regenerative medicine relies ever more on molecular approaches either to improve cellular preparations, or to harness the host environment and its inherent healing capacity. In these contexts small animal models offer the opportunity to test specific hypotheses using homologous recombination to delete genes or transgenics to deliver genes. The recent technological improvements in conditional knockout or overexpression, together with the detailed knowledge of mouse biology and availability of reagents has allowed an expanding range of opportunities and spectacular results (Sampson et al., 2011; Johnson et al., 2012; Waller et al., 2013).

2) Chimeric models.

The availability of nude mice and nude rats has offered the opportunity to test human cell preparations for their capacity to form cartilage in vivo by generating chimeric systems in which human cells are implanted in such animals, often in ectopic sites

One such model was used to generate a biomarker-based surrogate potency score and quality control for chondrocytes to be implanted in autologous chondrocyte implantation (ACI) (Dell'Accio et al., 2001). After validation in goats (Dell'Accio et al., 2003), such potency assay was used in a controlled clinical trial to generate quality-controlled chondrocytes for ACI in humans (Saris et al., 2008; Vanlauwe et al., 2011). Remarkably, at 3 years follow up, this quality control score correlated with the clinical outcome (pain and disability) (Saris et al., 2009)thereby confirming its predictive value and clinical relevance in humans. The same assay is being used to test the effect of bioactive molecules such as WNTs on expanded human chondrocytes in a clinically relevant assay (Nalesso et al., 2011). Finally, a similar assay is being used to test and optimize the use of mesenchymal stem cells for tissue engineering (Scotti et al., 2010, 2013).

3) Genetic screening.

Small animal models of joint surface injury and healing have demonstrated that there is a genetic component to repair (Eltawil et al., 2009). Similar animal models are being used to screen the mouse genome for genes or loci that are associated with the capacity to heal cartilage defects (Rai et al., 2012)in the hope that such molecules may yield new bioactive factors that can be used to support endogenous healing.

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24.1.2

Large Animal Models

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Introduction: From a clinical point of view there are two distinct goals of cartilage repair: 1) restoration of joint function (which includes pain relief) and 2) prevention or at least delay of the onset of osteoarthritis.[1] These goals can potentially be achieved through replacement of damaged or lost articular cartilage with a substance capable of functioning under normal physiological environments for an extended period but the limitations of this repair process have long been recognized[1] and regeneration is not achieved. Methods of assessing putative repair techniques have not been developed in vitro and therefore screening of potential procedures for human clinical use is done by preclinical studies using animal models of articular defects.

In 2007 the Food and Drug Administration (FDA) issued a draft guidance to the industry on steps that could be taken towards obtaining an investigational device exemption (IDE) or investigation on new drug (IND) application for new products intended to repair or replace damaged articular cartilage.[2] It was stated that animal models should be used to evaluate the biological response to the product, the durability of the response, toxicology and dose response. Published animal cartilage repair models and guidelines for preclinical cartilage repair studies have been recently published.[3] Due to financial and time limitations model conditions are often selected for a specific application rather than an overall examination. Simpler models in rodents, guinea pigs or rabbits to solve specific problems such as retention or fixation, survival

of implanted cells, dose response or modulation of the biologic response. Once proof of principle for the cartilage repair procedure or product is established, pilot studies with large animal species, including the dog, pig, sheep, goat and horse are conducted and finally pivotal studies from six months up to a year or longer are required. The authors' have used the horse for these latter studies and there are advantages that will be discussed. In some situations we have used a pilot study to evaluate comparison of techniques in rabbits and then with the superior technique defined, a 12 month study in horses ensues.

Early studies of cartilage repair in the horse most commonly involve surgically created defects of the carpus and these have been recently reviewed.[1] The carpus is a frequent site of articular cartilage injury in racehorses and, therefore, a large body of literature regarding cartilage injury at this site is available to provide clinical relevance to the research finding. Currently the joints of horses with anatomic equivalence to the human knee and ankle are used for cartilage repair studies. Equine models for cartilage repair have been performed using the medial femoral condyle (MFC), the lateral trochlear ridge (LTR) of the femur and the medial trochlear ridge (MTR) of the femur. The tibiotalar joint is potentially useful when investigating specific repair techniques with indications related to the ankle joint of humans. In domestic animals, the ankle joint is also called the hock.

Content: Lessons learned from animal models - Any novel therapy aimed at treating adult patients should ideally be tested in experimental animals that have achieved skeletal and articular cartilage maturity. Skeletal maturity has often been defined by growth plate closure but may be difficult to characterize because individual growth plates and secondary centers of ossification may remain radiographically evident for some time after exponential growth of long bones have ceased.[3] The more orthodox approach that has been recognized is that articular cartilage maturity is reached when chondrocyte growth and proliferation are completely arrested, a continuous layer of calcified cartilage separates the articular cartilage from subchondral bone, and the subchondral bone plate is minimally vascularized.[3] At this point, mature articular cartilage also demonstrates a degree regional, biochemical and biomechanical properties associated with a history of functional demands that are not found in juvenile tissue.[3] Goats and sheep are readily available from commercial and agricultural suppliers as 2-year-old or older animals. Animals of this age are considered mature based on the previously mentioned criteria of zonal architecture, lack of spontaneous intrinsic repair response and continuous calcified cartilage layer. Domestic and mini pigs have closed distal femoral growth plates and most of the characteristics of mature cartilage by 18 months although vascular penetration through the calcified cartilage is often present and slightly older animals would be preferred. Osteochondritis and cartilage growth deformities are also common and pigs older than 18 months are more difficult to handle. In the horse the metaphyseal growth plate activity is variable from site to site. There is full maturation of the distal femoral cartilage including formation of a tide mark by 24 months of age. Horses 2 years or older should be screened for naturally occurring disease including osteochondritis dissecans and subchondral bone cysts in the femorotibial and femoropatellar joints before being admitted into a study.

Choice of animal species **-** In the FDA guidance document contains many references to the utility of large animal species such as the goat, sheep and horse in cartilage repair models.[2] However, as mentioned before smaller laboratory animal models can be valuable tools in the early stages of development for cartilage repair therapies and products. Goats and sheep are frequently used in cartilage repair models because the knee joints are large enough to create lesions as large as those treated in patients (0.5-1cm^2). These species are also popular models for osteochondral grafting and meniscal repair. Both sheep and goats share similar characteristics although the goat has slightly thicker cartilage.[4] Domestic and mini pigs have been used as models because of the thick cartilage in this species particularly in the domestic pig. However, fast growing domestic pigs commonly present with subchondral bone abnormalities and a very soft, thin and irregular subchondral bone plate due to osteochondritis dissecans and similar developmental lesions. In many cases domestic pigs are used in short-term studies before they are mature because pigs older than 2 years of age are larger and difficult to handle. Mini pigs are more tractable and although critically sized osteochondral defects more often published chondral defects have also been created successfully and are also more representative of human cartilage repair. The main advantages of the horse model are the large joints size and thick articular cartilage layer[4] with easy arthroscopic joint access.[1]

Critically sized defect models have been developed in both the equine femoral trochlear ridges and medial femoral condyles.[1] Various studies have document critical sized defects in the medial femoral condyle and initially defined as 9mm or greater but typically 15mm^{2}has been preferred for definitive studies.[1]

Microfracture, osteochondral grafting and single step and multiple cell-based cartilage repair have been successfully evaluated in this species. Horses can be monitored with respect to clinical response after cartilage repair by assessment of lameness and more recently more sophisticated gait analysis. The thickness of the non-calcified and calcified cartilage together is closely equivalent to human with calcified cartilage being thicker and non-calcified cartilage thinner. While it has been pointed out that subchondral bone layer is thicker in large animal species than human,[3] this has not been considered a significant caveat because of subchondral sclerosis in many human clinical cases.

Femoral condyle (weight bearing) models **-** The medial femoral condyle (MFC) model was initially developed to evaluate the effect of subchondral bone microfracture on articular cartilage repair and has since been used to look at early events in cartilage repair after subchondral bone microfracture as well as the effect of removal or retention of calcified cartilage, the value of augmentative gene therapy, the repair of full thickness defects treated with microfracture and, most recently, evaluate the effect of intraarticular bone marrow-derived mesenchymal stem cells (MSCs) injected four weeks after defect creation.[5]

Equine femoral trochlear models **-** Use of the lateral trochlear ridge in the horse as a model was developed by Alan Nixon at Cornell University. It was first reported as a 12mm diameter defect in 1994 and a modified 15mm defect reported in 1995. This latter model has been reported in a number of studies.[1]

In the medial trochlear ridge, initial work created multiple 4mm defects for gathering pilot data. These model studies were short-term and it is recognized that a 4mm defect is less than what is considered to be critically sized. Presently, two 15mm defects on the MTR of the femur is the standard to test cartilage transplantation techniques. Randomization of the defect sites needs to be considered ***a piori*** in the study design because there is variation between proximal and distal defects depending on the exercise regimen and time of evaluation. Most recently, two 15mm defects on the MTR model have been used to evaluate both an autologous chondrocyte implantation (ACI) technique and an autologous fragment transplantation technique (CAIS).[1]

Postoperative care and exercise **-** Hand walking is commenced at two weeks and at four months an exercise regimen of 2 minutes trot, 2 minutes gallop and 2 minutes trot on a high speed treadmill is implemented. In this fashion, between 4-12 months the repair technique is subjected to athletic exercise.

Number of horses to sufficiently power a study **-** The ability to use each horse as its own control by performing a repair procedure in one limb and using the opposite limb as a control or having two defects on the same trochlear ridge allows for the investigator to use statistical evaluations that account for interpatient variability and therefore fewer animals are required to achieve sufficient power. Specific numbers in these previous studies have been based on power calculations.

Study duration **-** The length of a study will be dependent on the type of repair being evaluated and the goals of the study. Pilot studies will obviously be shorter than definitive preclinical studies. These authors generally use 12 or 18 months depending on both wishes of the company (in the case of industry grants) and budget.

Outcome parameters **-** The extensive number of outcome parameters that can be utilized is a significant strength of using the equine model. Potential assessments include: clinical examination for lameness and synovial effusion as well as response to flexion; pretreatment or post-treatment radiographs; MRI (terminal); synovial fluid and serum biomarkers; routine synovial fluid analysis; sequential arthroscopies; optical coherence tomography; gross postmortem examination; histopathological, histochemical and immunohistochemical analyses; biochemical analysis for type II collagen/type I collagen as well as aggrecan and glycosaminoglycan content, real-time quantitative PCR evaluation for mRNA expression in the tissue; and biochemical evaluation.

Advantages of equine femoropatellar and femorotibial models in the horse – Advantages include an ability to use an arthroscope to create lesions and perform second look arthroscopies, the large lesion size allowing for more tissue for evaluation, the ability to have controlled exercise and test the ability of the repair to cope with athletic exercise as well as institute rehabilitation regimens, the ability to selectively leave the entire calcified cartilage layer or on the other hand completely remove it with certainty, horses get similar orthopaedic clinical diseases as humans so clinical evaluation in naturally occurring diseases can be additive to the preclinical research studies. Disadvantages include the requirement of special animal care capabilities as well as expertise. Subchondral cystic lesions can follow violation of the subchondral plate when creating the lesions but it seems less of a problem than that reported in the goat.

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24.1.3

Anti-Angiogenesis in Cartilage Repair Models

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Introduction: Articular cartilage is an avascular, bradytrophic tissue in which the chondrocytes physiologically maintain their unique differentiation status throughout life. In contrast to chondrocytes of the fetal growth plate, articular chondrocytes physiologically retain their stable differentiation status. They do not undergo terminal differentiation and their extracellular matrix does not calcify above the tide mark. Bone marrow stimulating techniques such as microfracturing of the subchondral bone plate are simple, minimally-invasive, and cost-effective cartilage repair approaches that are frequently applied in clinical settings. Unfortunately, the ingrowing osteochondral progenitor cells often fail to undergo complete chondrogenic differentiation, which leads to the formation of inferior fibrocartilage. In addition, this technique is associated with matrix calcification, vascular ingrowth and inadvertent endochondral ossification (1, 2). These negative side effects do not only interfere with the clinical outcome but are also considered as negative predictors for potential secondary salvage procedures, including autologous chondrocyte transplantation (3).

Physiologically, healthy articular cartilage contains considerable amounts of anti-angiogenic proteins, including Chondromodulin-I (Chm-I) and Thrombospondin-1 (TSP-1) (4, 5). Instead, we could demonstrate a significant lack of these factors in microfracture-induced cartilage repair tissue. Interestingly, the lack of these factors coincided with the ingrowth of CD31-positive capillary structures and hypertrophy of the subchondral bone plate (6).

The aim our work was to investigate if the application or overexpression of such anti-angiogenic factors within cartilage repair tissue would retain the avascularity of cartilage tissue and thus prevent endochondral ossification. The knee joint of miniature pigs seems to be an adequate model to test this hypothesis, since this established animal model is confronted with poor endogenous cartilage repair response and also with significant endochondral ossification within microfracture-treated defects, which provides a situation comparable to human joints (6, 7).

Content: We either focussed on the gene transfer of Chm-I and TSP-1 using self-complementary Adeno-Associated Virus (AAV) vectors or we applied the factors as recombinant proteins. The functionality of overexpressed or recombinant Chm-I and TSP-1 was confirmed in angiogenesis assays in which the formation of capillary-like structes of endothelial cells was significantly inhibited by these two factors (8, 9).

In vivo, the effects of Chm-I or TSP-1 were investigated in articular cartilage lesions in the femoral trochlea of miniature pigs. To evaluate the potential effects of Chm-I overexpression within the cartilage lesions, we performed two different treatment schemes: Chm-I gene transfer was either combined with the microfracture technique to capture its effects on ingrowing osteochondral progenitor cells, or osteochondral progenitor cells were infected ***ex vivo*** by AAVChm-I and subsequently transplanted into chondral lesions with an intact subchondral bone plate to focus on the effect of Chm-I on transplanted osteochondral progenitor cells without the interference by invading cells from the bone marrow.

Since TSP-1 is not a chondrogenic stimulus by itself, its effects on the formation of cartilage repair tissue were also investigated in combination with stimulation by the established chondrogenic factor osteogenic protein-1 (OP-1). The lesions were treated by the microfracture technique and either received no further treatment or were treated by additional application of recombinant OP-1, recombinant TSP-1, or a combination of both proteins.

Six and 26 weeks after surgery, the repair tissue and the degree of endochondral ossification were assessed by histochemical and immunohistochemical methods detecting collagen types I, II, X, Chm-I, TSP-1 and CD31.

In order to further investigate the mechanisms exerted by Chm-I and TSP-1, we performed genome-wide expression analyses (Affymetrix U133 Plus 2.0 Array) and quantitative RT-PCR of stimulated cells.

Comparable to the repair response in human joints, microfracture treatment in this animal model merely induced the formation of inferior fibrocartilaginous repair tissue with significant ossification in deeper layers of the defects which resulted in significant hypertrophy of the subchondral bone plate and formation of intralesional osteophytes after 26 weeks (8, 9).

In contrast, direct application of AAVChm-I vectors into microfractured cartilage lesions stimulated chondrogenic differentiation of ingrowing precursor cells that was characterized by a proteoglycan-rich matrix positive for type II collagen. Simultaneously, overexpression of Chm-I also significantly inhibited terminal chondrocyte hypertrophy, the invasion of vessels structures and excessive endochondral ossification, which was otherwise observed in non-treated lesions. Thus, Chm-I stabilizes the phenotype typical for articular chondrocytes by both inducing chondrogenic differentiation and inhibiting terminal differentiation. Indirect gene transfer, with infection of osteochondral precursor cells by AAVChm-I ***ex vivo***, also supported chondrogenic differentiation of these transplanted cells. AAVChm-I-infected cells maintained a chondrocyte-like phenotype and formed a hyaline-like matrix which was superior to that formed by non-infected or AAVGFP-infected cells (8). The mechanism of action of Chm-I is still largely unknown. Expression analyses demonstrated that Chm-I upregulated the expression of the cell cycle inhibitor $p21^{cip/waf}$ in chondrocytes and mesenchymal stem cells. Furthermore, Chm-I also increased the expression of Stanniocalcin-1 (STC-1) and S100P, two factors involved in the calcium homeostasis. Interestingly, Chm-I also significantly stimulated the expression of Superoxidismutase-2 (SOD-2), an enzyme protecting against oxidative stress.

In the same cartilage repair model, the application of TSP-1 inhibited terminal differentiation of ingrowing repair cells and excessive endochondral ossification. However, in contrast to Chm-I, the application of TSP-1 as a single stimulus failed to induce chondrogenesis by itself. Instead, chondrogenesis could be effectively be induced by application of OP-1 (= BMP-7), but this factor induced significant chondrocyte hypertrophy, characterized by synthesis of collagen type X, and excessive bone formation. Interestingly, a simultaneous application of both TSP-1 and OP-1 induced and maintained a permanent, non-hypertrophic chondrocyte-like phenotype within cartilage repair tissue. In this combined application, TSP-1 could effectively inhibit the terminal differentiation promoted by OP-1, while TSP-1 did not interfere with chondrogenic effect of OP-1 (9). The genome-wide expression analysis revealed that TSP-1 inhibits the expression of GADD45ß which is a factor that promotes chondrocyte hypertrophy.

In summary, both Chm-I and TSP-1 efficiently inhibited the terminal chondrocyte differentiation and ossification within the cartilage repair tissue and, thus contributed to the stability of the permanent phenotype of articular chondrocytes. These therapeutically valuable effects may not merely be directly ascribed to anti-angiogenic properties and resulting tissue hypoxia, but may also involve cell cycle control and cell differentiation.

Since the stabilization of the chondrocyte phenotype and the inhibition of inadvertent ossification within cartilage repair tissue is of central clinical importance, it is worthwhile that future studies optimize the kinetics and mode of application of these factors (gene transfer vs. recombinant protein). Additionally, it will be interesting to identify further anti-angiogenic factors, as well as their specific target genes, binding partners, receptor molecules and signalling cascades in order to gain further insight into the mechanisms that are responsible for the maintenance of the permanent chondrocyte phenotype.

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24.2.2

Current Concepts of Joint Biomechanics in Articular Cartilage Injury & Repair

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Introduction: Cartilage defects are challenging because of its avascular and hypo-cellular nature. Several factors maintain the internal milieu and affect the quality of the repair- patient age, size of the lesion, its depth, associated ligament laxity or meniscus loss and angular malalignment.

Content: Factors affecting the Biomechanics of the knee

1. Menisci

Menisci absorb at least 50% of the compressive load on the tibiofemoral joint between 0 and 90º of flexion and nearly the entire load is absorbed by the posterior horns of the menisci in flexion beyond 75º. They also participate in shock absorption, lubrication and passive stabilization of the joint. [1] Total and even partial meniscectomy gradually results in radiographic and symptomatic degenerative changes in the knee.[2]

2. Patellofemoral (PF) joint

PF compression force is the result of compression of the patella into the trochlear groove resulting from a combination of quadriceps and patella tendon forces. Maximum contact force occurs at 70º to 80º of knee flexion[3], beyond which, patella forces decrease as the quadriceps tendon begins to directly articulate with the trochlea. Static bony anatomy contributing to PF stability includes the depth and shape of the trochlea, shape of the patella, femoral anteversion, tibial rotation and alignment of the tibiofemoral articulation. The dynamic factors include muscular interaction and change in anatomical relationships related to range of motion of the knee. A 10º increase in Q angle causes a 45% increase in peak contact pressure on the lateral aspect of the PF joint.[4] Although PF contact forces increase with flexion, so does the total contact area, which distributes the forces more widely, resulting in a less significant increase in contact pressure. If the PF contact area is decreased, the cartilage is subjected to abnormally high joint reaction force, and is at risk of developing defects and subsequent osteoarthritis. The PF compressive forces may range from 0.5 times body weight while walking to as much as 7.6 times the body weight while squatting.[5] Weak hip musculature results in excessive adduction and internal rotation at the hip causing increased knee valgus, which in turn can lead to PF and ACL injury.[6,7]Chondromalacia is a function of the process of cartilage loss and time. With an acute injury to the joint, biochemical and biomechanical changes take place; repetitive insult (athletes and with increasing age) leads to progressive deterioration in the volume of cartilage. Hormones, weight and local joint factors also play an important role in this cascade of articular cartilage break down. Once local contact pressure is reduced due to articular cartilage wear there will be a concomitant increase in adjacent contact pressure, resulting in rapid progression of chondromalacia to chondropathy.

3. Ligaments

There is documented synergism between the MCL and ACL and a possible role in articular cartilage protection. [2] The tibiofemoral articular compression combines with tensile forces in the ACL to resist an internal rotation force at the knee joint. The MCL is the primary restraint to valgus injury. Maximum restraining force is described at 25º flexion, decreasing with extension, when the ACL and posteromedial corner (posterior oblique ligament) increase their contribution.[8] Injury to either of these structures might lead to the development of early OA due to either increased tibiofemoral contact stress and/or valgus instability / increased translation. The PCL is the primary restraint to posterior tibial translation at all flexion angles beyond 30 degrees.[9] The posterolateral corner structures resist varus stress, posterior tibial translation near full extension and external rotation of the tibia relative to the femur.[10]

4. Angular Deformities

Limb mal-alignment, varus or valgus accentuates the stress on the articular surface within the involved compartment. This will result in further loss of the articular surface cartilage and increased stress on the subchondral bone, leading in turn to further progressive increase in the mal-alignment.

CARTILAGE REPAIR

1. MARROW STIMULATION-MICROFRACTURE

Delivery of cells from the bone to the articular surface, resulting in neo-chondrogenesis through the formation of a clot of fibrin and precursor cells.[11]

Disadvantages:

Inferior mechanical tissue properties[12]

Possibility of formation of intralesional osteophytes limiting tissue durability.[13,14]

Of 170 patients operated between 1991 and 2001, 67 athletes were included in a study (in press) and prospectively followed up. 61 were available at final follow-up at 15 years. All evaluation scores improved at 2 years, but deteriorated at long term; however average scores were better than baseline at final follow-up. Patients with smaller lesions and age ≤ 30 years showed better results. Radiographs at final follow-up showed OA changes in 40% of the knees.

2. AUTOLOGOUS CHONDROCYTE IMPLANTATION

1st generation ACI involved healthy cartilage harvest from non weight bearing zone in the knee, culture and expansion of the chondrocytes, and their reinjection into the defect underneath a periosteal patch securely sutured so as to be watertight.[15]

In 2nd generation ACI, to reduce the morbidity, natural or synthetic scaffolds have been used. These should be biocompatible, biodegradable, bioactive and permeable.[16]

A primary tissue evolves over approximately 2 years which matures to histologically superior repair cartilage with characteristics of fibrous–hyaline mixed to hyaline-like tissue.[17]

34 patients with PF lesions treated with 2nd generation ACI were studied at 5-year follow-up.[18] A significant improvement was noted in all scores. A decline in scores was found in patients with multiple lesions and concomitant patellar lesions at the end of 5 years. Relook arthroscopy (7 cases) revealed the repaired surface to be nearly normal and biopsy samples showed hyaline-like tissue. While comparing 2nd generation ACI with microfracture long term results of return to sport were better for the ACI group.[19]

Disadvantages:

Prolonged rehabilitation

High cost for cell cultivation

2 surgeries

Advantages:

Technically easier

Mini-open arthrotomy / arthroscopic

Histologically superior repair tissue,

Suitable for defects larger than 2 cm^2

3. OSTEOCHONDRAL TRANSPLANTATION

Osteochondral cylinders (5 to 12 mm diameter and 15 to 20 mm length) are harvested from low stress areas of the joint to address small- and medium-sized chondral and osteochondral defects in a press-fit technique.[20]

The rehabilitation protocol is similar to that of fracture healing.

Advantages:

Better tissue quality

Predictable integration

Relatively short rehabilitation

Disadvantage:

Donor site morbidity

Insufficient vertical integration of the cartilaginous component of the graft

Open procedure

Defects ⇦3 cm^2.

4. BONE MARROW ASPIRATE CONCENTRATE (BMAC)

Multipotent stem cells (MSCs) and growth factors are easily available and when coupled with a renewal capacity and multi-lineage differentiation potential can generate chondrogenic tissue.[21,22]

Their isolation is devoid of the need to harvest healthy cartilage tissue for biopsy and subsequent chondrocyte cell cultivation. This technique maximizes cell-to-cell contact and provides a strong chondrogenic environment utilizing a collagen I/III matrix promoting chondrogenic differentiation of MSC and hyaline cartilage regeneration.

From 2006, we have been using BMAC combined with different scaffolds. In a study published in 2011, at 2 years follow up with 15 patients it was concluded that 1-step surgery with BMAC and collagen I/III matrix could be a viable technique in the treatment of grade IV knee chondral lesions.[23] We recommend it for patients aged ⇦60 years, BMI ⇦ 30, with a stable or stabilized and aligned knee.

CORRECTION OF MALALIGNMENT

Tibiofemoral malalignment, PF maltracking, and ligamentous insufficiency, should be addressed to avoid extreme mechanical joint stresses and repetitive micro-trauma, which are detrimental to articular cartilage repair and increase the risk of early OA.[24,25] Malalignment should be corrected at the time of the cartilage repair as full thickness chondral defects rarely heal without a direct intervention. In our experience, together with the newer techniques of articular cartilage repair, an open wedge high tibial osteotomy (HTO) can fully complement the surgical treatment. The rationale is to correct the angular deformity at the knee, and thus decrease the excessive weight bearing load across the affected compartment.

INDICATIONS:

Physically active individual usually ⇦60 years

Thin individual; good general health

Range of Motion: 0-120º.

Unicompartmental (medial) OA, intact lateral compartment

CONTRAINDICATIONS:

Rheumatoid arthritis

A very unstable knee

Severe bone loss of the medial tibia or femur

Patella baja

Subluxation ⇨1 cm

Deformity ⇨15º

Allogeneic meniscal transplantation should be considered in young patients because HTO alone can be associated with poor functional outcomes.[26]Proximal or distal realignment and bony procedures may be needed to treat patellofemoral maltracking which may be contributing to cartilage defects and affecting their treatment.

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24.2.3

Distraction Arthroplasty: Scientific Principles and Clinical Experience

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Introduction: Treatment of osteoarthritis in the knee-or ankle joint may be difficult, especially in young patients. The traditional options of treatment involve joint replacement and arthrodesis meaning that patients will lose not only pain but also their joint. Moreover, long term effects following these procedures may be deleterious such are the need for repeated revision surgery and the development of osteoarthritis in adjacent joints. In an attempt to avoid or postpone these options of treatment including their effects, joint distraction is being used for almost 20 years . The rationale for joint distraction is related to the Ilizarov method. In the 1980`s, the Ilizarov method of limb lengthening became popular based on the discovery that growth and remodeling of bone and soft tissues could be induced by subperiosteal corticotomy following by gradual distraction with the use of a ring fixator [1]. The idea was that gradual distraction of an osteo-arthritic joint may induce growth and remodeling in damaged cartilage and bone as well, allowing surgeons to postpone removal of the original joint.

Content: The first report of joint distraction was treatment of the hip [2]. In 80 patients (age 9-69) with several different indications of joint degeneration (e.g. osteoarthritis, osteonecrosis and chondrolysis) a hinged frame was applied for 1.5 – 2.5 months. Pain levels decreased and function and mobility improved, supported with an increase in JSW on X-ray. In 2005 and 2009, another two studies on hip joint distraction were published with only adolescent patients, again showing improvement in pain and function and increased JSW [3,4] . Probably due to the difficulty in placing the external fixation pins in the pelvic bone and the satisfactory outcome of total hip joint replacement, hip distraction has not been implemented broadly despite the satisfactory clinical results.

Literature regarding clinical trials with osteoarthritic ankle joint distraction revealed 13 retrospective, prospective or randomized controlled trials studies. All studies reported significant clinical improvements in pain and mobility. Cartilage growth had been analysed indirectly by measuring an increase of the JSW on weight-bearing X-rays as established in 7 out of 12 studies with a modest [5-7] to significant [8-12] result even in a 7 years follow up[13]. Lack of standardized X-rays hampers comparison of such measurements. Increase of cartilage tissue in the joint had been confirmed with MRI evaluation in some studies. [10,12] Similar remarks can be made on the reported decrease in bone density, as measured on X-rays. [9,11, 12] A decrease in peri-articular bone density have been found in high density areas following OA ankle joint distraction using standardized radiographs in the AIDA (Ankle Images Digital Analysis) method [15] .The group from Iowa showed a decreased bone density and improvement of bone cysts on serial standardized CT measurements of OA ankle joints s after distraction [14]. These decrease in bone cysts appeared to correlate with a decrease of pain. [14] Adding ankle motion during distraction with a hinged external fixation frame showed an early and sustained beneficial effect on outcome [16]. Joint distraction in three cases of hemophilic ankle arthropathy showed a similar remarkably positive effects on subchondral bone structure and function [12]. Although the studies were well documented, they are still of limited quality. Only three randomized controlled trials are described, two on ankle joint distraction and one on knee joint distraction. All with limited number of patients included. Furthermore, these studies have modest follow-up periods of 1, 2 and 5 years and function [25]. Therefore, more RCT studies are needed to evaluate the use of joint distraction in treatment of OA joints. [24]

Encouraging short term effects have been reported also following distraction of severely painful OA knee joints in relatively young patients. An increase in joint space width has been found in a number of patients following distraction of an OA knee joint [17]. Similar findings have been reported after OA knee joint distraction using the KIDA (Knee Images Digital Analysis) method .[27] MRI is able to quantify cartilage and to show changes in its morphology, volume and even composition.[28]. Following a two months OA knee joint distraction period, MRI revealed a significant increase in cartilage thickness and a decrease of denuded bone areas [17]. Biomarker levels showed a trend towards increased collagen type II synthesis and a decreased breakdown. [8] Further studies are needed to evaluate the exact value of MRI measurements.

Unfortunately, actual repair of articular cartilage remains difficult to study in humans.

Several models of inducing OA in canine or rabbit knee joints with subsequent distraction have been developed in literature such are by ACL transection [18], or in combination with total meniscectomy,[19] papain injection[20], or by making osteochondral defect in the femur [21] or tibia [22], or by damaging the weight bearing cartilage of both femoral condyles: the groove model.[23] The characteristics of the experimentally induced canine knee joint OA in ACLT/ medial meniscectomy - and Groove model reflect greatly those of human OA making these models suitable for studying human OA.[18]

An 8 weeks joint distraction of an OA knee joint in beagles induced by ACLT resulted in a normalization of the proteoglycan (PG) turnover of the articular cartilage directly after treatment. [18] However, histology did not show cartilage repair. The study was repeated using the groove model. A significant less loss of PG content and collagen damage was found in the distracted OA canine knee joints compared to the not treated OA group. In addition, both the macroscopic and histological grade of cartilage damage was found to be less in the distraction group. [24]

Further research and analysis will be necessary to understand the pathophysiological changes which may occur in OA joints during and following joint distraction.

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24.3.1

Epidemiology of Cartilage Injury & Early Osteoarthritis

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Introduction: A cartilage injury in a joint is potential disabling and occurs at all ages. Causes of a cartilage injury include the start of degenerative process, Osteochondritis Dissecans (OCD) and the chondral fracture as a result of a traumatic joint injury.

Content:

Knee articular cartilage

In a large study by Widuchowski and co-authors involving 25,124 knee arthroscopies, OCD was found in 2% of all the knee arthroscopies. This illustrates that the majority of cartilage lesions seen in knee arthroscopy are associated with other injuries. A cartilage lesion might also be diagnosed in early degenerative changes in which only one anatomical location is affected, as in early osteoarthritis. Arthroscopically, it can be difficult to differentiate between an isolated chondral injury of the femoral knee cartilage and the initiation of degenerative changes of the articular cartilage, as these in early stages might present a similar arthroscopic view. Often the prior knee history in addition to the period of knee symptoms must be accounted for in order to differentiate between these two conditions. It is almost impossible to estimate how often a focal degenerative lesion is accounted for as a pure cartilage lesion, however this probably represents a minority of the lesions seen. The study by Årøen and co-authors in 2004 found that full thickness cartilage lesion of more than 2 cm^2 was found in 62 patients of 993 knee arthroscopies and 50 % of these had cartilage lesion as the only pathology of the knee. Furthermore it was found that 10 of these 31 patients were classified as OCD. Hjelle et al demonstrate the increasing number of cartilage injury with increasing age as well as the fact that most of the lesions are rather small in area might therefore not be suitable for a cartilage repair surgery. Furthermore, a systematic review found that half of the full-thickness cartilage lesions in athletes diagnosed were asymptomatic, further emphasizing the fact that not all full-thickness cartilage defects diagnosed needs to end with a cartilage repair surgery.

Cartilage injury of the knee and associated injuries

The two conditions which are most thoroughly studied with respect to concomitant cartilage injuries conditions that are most thoroughly studied with respect to concomitant cartilage injuries are patellar dislocations and rupture of the anterior cruciate ligament (ACL).

Patellar dislocations put stress on the retropatellar joint and lead to cartilage injuries. As a consequence osteoarthritis (OA) can develop, and Mäenpää et al. found an incidence of patellofemoral OA in 22% of the patients in a study with mean follow up period of 13 years. Depending on the modality by which cartilage injuries have been investigated after primary or recurrent patellar dislocation, the incidence varies. In studies where patients underwent surgery, it varied from 32% to 96%. In MRI studies incidences from 30% to 75% have been recorded.

Just as after patellar dislocations, the presence of an articular cartilage lesion in ACL–injured knees is considered a predictor of OA. In a study from NKLR Røtterud et al found an incidence of 6.4% full-thickness cartilage lesions in 15,783 knees undergoing ACL reconstructions. In this study it was found that male patients with ACL rupture had an increased risk for full-thickness cartilage injuries, compared to female patients. Moreover, acquiring the ACL injury during team handball was found to be a risk factor for male patients as well. No other sports was found to have an impact on the risk of acquiring full-thickness cartilage lesions, however for racket sports, the authors found a trend towards higher risk.

Hip

The epidemiology of hip osteoarthritis has been extensively investigated. However there is lack of knowledge about the prevalence of focal cartilage injuries in the hip joint. Over the last decade femoro-acetabular impingement has been recognized as a cause of cartilage injuries, labral injuries at later OA in the hip. The number of open and later arthroscopic procedures to treat these conditions has increased rapidly. With the development of arthroscopic treatment we have obtained increased knowledge also about cartilage injuries in the hip joint. Lesions following developmental conditions similar to OCD in the knee also exist in the hip. Osteochondral lesions are most common on the femoral head. Femoral head lesions may be related to Calvé-Legg-Perthes disease (Freeman et al 2013) and are rarely due to acute or chronic injuries in sports. However in a few cases high-energy injuries in sports may cause acute hip dislocations with fractures including osteochondral fractures of the femoral head. Avascular necrosis of the femoral head is also seen after hip dislocations.

The most common cartilage injury in the hip joint is located in the acetabulum and is usually seen together with a labral injury in which in most cases are probably caused by femoroacetabular impingement. The development of cartilage injuries in the acetabulum seems to follow a typical pattern in many cases. First there is a development of a so called wave sign with an intact chondrolabral junction. Then a fissure in the chondrolabral junction develops. The next step is chondral flap, and finally a complete detachment of this flap. This pattern does not fit into the ICRS classifications system and thus an alternative classification system has been proposed for the acetabulum. These injuries are often not detected at MRI and are first seen at arthroscopy.

There are few MRI studies reporting on hip abnormalities in asymptomatic subjects. Aydingöz et al found abnormal signal intensity of the labrum in 1,5 Tesla MRI increasing from 18% in patients under 20 years to 55 % in patients older than 50.Lecouvet found (also 1,5 T) absence of labrum in 14% and this increased significantly with age. Round and flat labra were found in 11 % and 9% of subjects, respectively. Intralabral areas of high signal intensity communicating with the free surface increased with age. Even higher findings were obtained in a recent study with a prevalence of labral tears in more than 80% of and paralabral cysts in more than 20% (Schmidt et al 2012). In an MRI 3 Tesla investigation of 39 asymptomatic elite and collegiate hockey players labral tears was found in 56% and osteochondral lesions in 18%. Thus, it is reason to believe that both labral and chondral lesions are common in asymptomatic individuals particularly in sports with a high risk of hip injuries. The frequency of these abnormalities also seem to increase with age.

In a cadaver study of 54 hips (age 48-78), 28 of the hips had a labral lesion. All of the cadaveric specimens had some degree of articular degeneration. 68% had a small area of fissuring. 26% had areas of full-thickness erosion with exposure of subchondral bone (McCarthy et al 2001).

There are several case series on the prevalence of these injuries at hip arthroscopy showing that they are very common in the acetabulum, and that injuries of the femoral head are less common. In a series of 45 professional athletes all had labral tears, 21 had a grade IV acetabular chondral defect, 3 had a grade IV femoral head lesions, 17 had grade I-III acetabular lesions and 14 had a grade I-III femoral head lesions. 2 had exensive OA (Phillipon et al 2007). In a similar study of 47 high level athletes 46 had a labral tears, the chondrolabral junction was abnormal in all cases, but the rest of the cartilage was normal in 41 of the athletes (Nho et al 2011)

OA and hip replacement probably represents the end stage of impingement, labral injuries and cartilage injuries in the hip joint. In a study of former Swedish elite athletes (age 50-93 years old) the relative risk for having a hip replacement for former soccer, team handball and ice-hockey players compared to a control group was between 2.48 and 2.95. Also non-impact sports carried a higher relative risk (1.87) (Tveit et al 2012).

Ankle

Ankle injuries are very frequent in sports medicine and constitute approximately 15%-20% of all sports injuries, out of which 75% are ankle sprains. Whereas the diagnosis of ligamentous tears after such injuries can be done by clinical evaluation, the symptoms and signs of associated cartilage injuries are unspecific. However, the reliability of MRI to detect isolated cartilage injuries in the ankle is

poor due to the thin cartilage that measure only 0.4–2.1 mm. The indications for surgery may be chronic instability or pain, and the time from the initial trauma varies from study to study, which can to some degree explain differencies in incidence of cartilage injuries, i.e. exertional pain.after an ankle trauma: In a study from Taga et al 31 patients suffering from lateral ligament injuries and unstable ankles were operated. 89% of the acutely injured ankles and 95% of chronic injured ankles had chondral injuries. In contrast to this Komenda et al found chondral injuries in a frequency of 25 %. when assessing chronic unstable ankle joint by arthroscopy. Schäfer et al also studied unstable ankles and found cartilage lesions of the talus in 54% of the joints .

Takao et al found that 40.3 % of patients with residual symptoms after ankle sprain, had osteochodral injuries detected by arthroscopy. In 27.6% of the patients with osteochondral lesions, ankle arthroscopy was the only method that could reveal the cause of the persistant pain. Persistent pain after ankle sprain, with or without, ankle instability is however common. Arthroscopic studies in this population of patients reveal cartilage injuries from 40-95% though the estimation of the area of the cartilage lesion by arthroscopic examination involves over and underestimation.

Future perspectives

The incidence and prevalence of cartilage injuries in the different joint is not well described and there is definitely an area which needs to be further explored. However as the Knee Ligament Registries only records the combination of ligament and cartilage injuries the need for a Cartilage Registry is clear and would expand our knowledge on all surgically treated patients. Such a registry needs a simple scoring form and evaluation of cartilage injury with clear inclusion criteria is the lesson learned from the ACL-registry. Furthermore long-term financial support is needed and a steering board which is independent from the medical industry. A weakness of such a registry would be that only those injuries diagnosed arthroscopically would be included in the registry.

Clinical trials has demonstrated that the variation in the outcome increases with longer follow-up making a serious challenge for both performing and interpreting the statistical analyses. This would be solved in a registry design since a large number of patients would be followed, and in addition these data could be combined with arthroplasty registries. Arthroplasty is considered the final surrogate endpoint in all evaluation of the joints subjected to these injuries. Another question to be outlined is the diversity of treatment options available to treat these injuries. The variation of eligible patients in the different RCTs in cartilage repair, as shown by Engen and co-authors, make the need for a national or regional cartilage registry evident.

Conclusion

“Epidemiology of cartilage injury is listed as key word in PubMed in 494 publications indicating that this should be fairly well described. This might be partly true for the knee but for other joints the information is spare and improved registration through registries for the different joints or in cartilage injury registry would be one way forward in order to assess a better evidenced based numbers for this injury. The most severe disability of cartilage injury is caused in the knee where the symptoms are at the same level as those scheduled for TKA, however these patients are 30 years younger. Full thickness cartilage lesions are found frequently at knee arthroscopy in percentage of 5-10 %, however not all are symptomatic and there is frequent associations with other knee injuries especially meniscus and ligament injuries. Increasing age and specific sports activities increase the risk for this injury. There is a lack of knowledge on the natural history of cartilage lesion and the assumption that this will result in degenerative changes in the knee joint requiring a TKA might not be true.

References:

Listed in text

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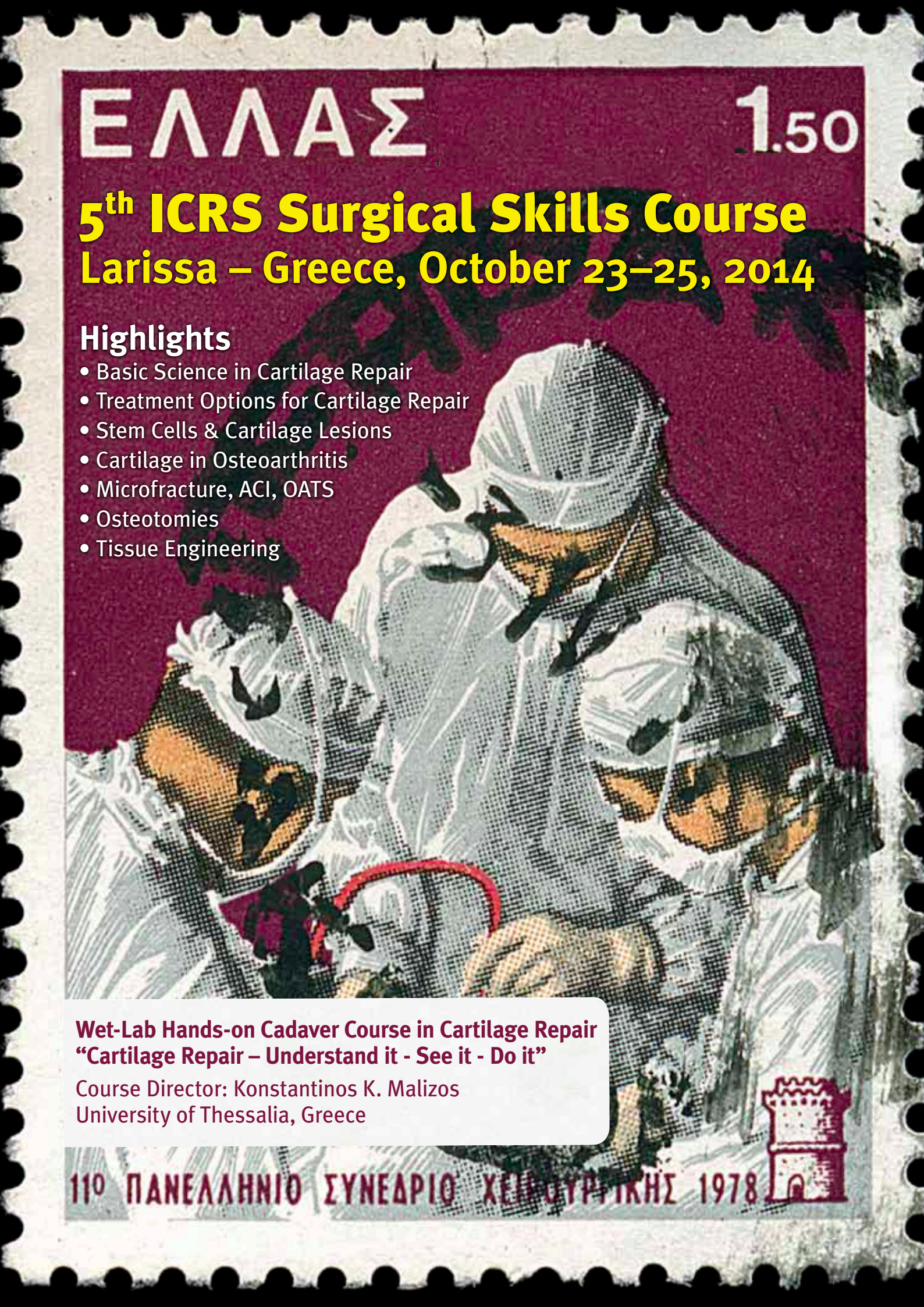
This author index lists the names of all authors and co-authors of the all congress abstracts (Podium Presentations, Poster Presentations & submitted Extended Abstracts by the invited faculty). The numbers in the index refer to the final programme number and the letter "P" before the final programme number refers to the poster section.



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