AO Foundation

AO Research Institute Davos

Activity Report 2013

Table of contents

1 Introduction

The AO Foundation remains fortunate to have its own independent research institute which brings academic credibility to the Foundation and opens the Foundation to other academic Institutes and Societies. The immense collective knowledge within the ARI in research in the field of musculoskeletal trauma is again on the world map through international societies naming ICRS, ORS and TERMIS as three world-wide society examples, where ARI members sit in various committees and boards, elected on academic merit.

In 2013 the AO Research Institute Davos (ARI) maintained an excellent production of focused (musculoskeletal trauma clinical problems) preclinical research data. The scientific results were published in top journals (46 papers with an average impact factor of 2.58) within the field and presented at the leading international society congresses (70 presentations with a 97% acceptance rate). The ARI maintained its excellent results in extramural funding acquisition (CHF 2.4 million) from national and international funding sources along with maintaining its AAALAC accreditation status and ISO accreditation status. The ARI hosted 10 medical and 2 non-medical Research Fellowships in 2013. ARI Research Fellowships are an excellent possibility to strengthen the AO network, with many of the leading surgeons in our network having performed a Research Fellowship in Davos at the beginning of their careers.

I wish to thank the whole team of the ARI (including our medical research Fellows, interns and guests) for their high motivation and passion for solving clinical problems through detailed, high level translational research, for their dedication to the ARI and the AO Foundation in Davos and when representing the ARI and AO at national and international congresses, symposia and AO events. This dedication to high level academic work to solving musculoskeletal clinical problems is rewarded through the many accolades (from grants, high level publications, keynote lectures, awarded symposia and workshops to positions on national and international society committees and boards) ARI now has. I wish to thank the clinical division (CD's) research commissions and the AO Technical Commission (TK) for their medical advice / guidance of many of the ARI projects. All ARI projects funded by the CD's and TK are monitored with regards to their clinical relevance by the surgeons in the respective research committees, keeping the ARI projects focused on relevant musculoskeletal clinical problems. I also would like to thank Claas Albers (Director AO Technical Commission) for collaborative efforts during the year, our CFO/COO Lukas Kreienbühl for all his collaborative joint projects with me (to support ARI, Davos and Graubünden) where we make a strong team and finally our CEO and my boss Rolf Jeker for putting up with me and keeping me in the right direction.

On a very sad note, Matthias Forte, a highly valued member of ARI died on April 14, 2013 at the age of 33. Matthias started as a Project Leader at the ARI in July 2011, having recovered from cancer. He quickly became a highly-valued member of the Biomedical Services and ARI team. Unfortunately Matthias acquired secondary cancer and had further aggressive treatment. After having fought the disease a second time, Matthias restarted his work in November 2012 and continued to be extremely positive and a good motivator of his fellow team members. Unfortunately in January a medical examination revealed that the cancer had spread and was no longer treatable and Matthias spent his last few months of life with his close family. Matthias was truly inspirational to all of us here at ARI and he will be sorely missed.

Within this report you will see our achievements from 2013 and I would also like to invite you to regularly look at the ARI website for updates http://www.aofoundation.org/ari

Sincerely

Prof Dr R Geoff Richards, Director AO R&D

2 Mission / Goals / Outlook

Mission

Excellence in applied Preclinical Research and Development within trauma and disorders of the musculoskeletal system and translation of this knowledge to achieve more effective patient care worldwide.

Goals

- Contribute high quality applied Preclinical Research and Development (exploratory and translational) focused towards clinical applications/solutions.
- Investigate and improve the performance of surgical procedures, devices and substances.
- Foster a close relationship with the AO medical community, academic societies, and universities.
- Provide research environment / support for AO clinicans.

All ARI projects are Applied Preclinical Research or Applied Preclinical Development projects focused towards clinical applications.

- **Exploratory Applied Preclinical Research** is fundamental research, to solve major clinical problems over an extended timeframe (over 10 years).
- **Translational Applied Preclinical Research** aims at developing a clinical applicable result in around 5 years and builds upon the fundamental applied preclinical research. This research is usually not possible without the previous fundamental applied preclinical research.

Rolling Outlook ARI (3 years start)

- Develop productive potential of ARI innovation technology portfolio and create an ARI intellectual property strategy.
- Enabling the environment to foster competitive Innovation within the ARI collaborative research consortia.
- Exploitation of diverse innovative ARI translational research bringing more economic sustainability to the AO Foundation.

Providing research environment / support for AO Fellows.

3 Funding Summary

Income Statement	2012 Actual		2013 Actual	
in CHF '000	abs	%	abs	%
AO Foundation Contribution	6'718	58%	6'718	59%
3rd party Income	2'492	22%	2'400	21%
AO Intercompany	2'276	20%	2'261	20%
Total Income	**11'486**	**100%**	**11'378**	**100%**
AOTrauma*	3'987	35%	3'995	35%
AOSpine*	464	4%	414	4%
AOCMF*	625	6%	681	6%
AOVET	36	0%	66	1%
AOTK	563	5%	606	5%
AOER*	1'920	17%	2'027	18%
AO Foundation*	1'273	11%	1'100	10%
3rd party projects	2'492	22%	2'400	21%
Total Expenses	**11'359**	**100%**	**11'289**	**100%**
Net Result	**127**		**89**	

* incl. AO Intercompany

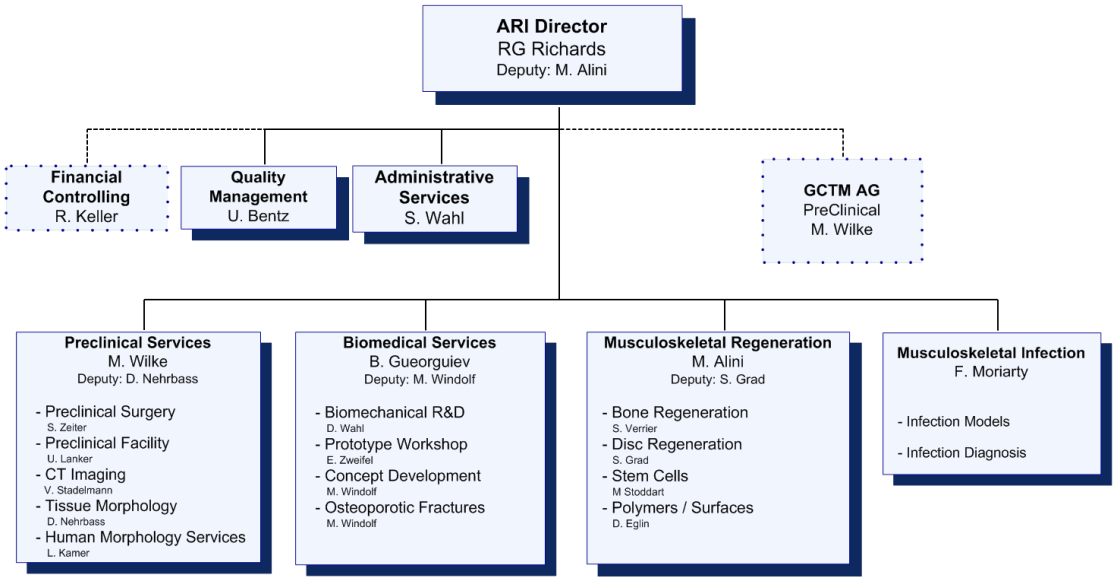
'3rd Party Income' amounted to CHF 2'400 K and remained 14% (CHF 391 K) below budget and 4% (CHF 92 K) below previous year. The main reason for the decrease versus budget was lower than expected activities with commercial partners through GCTM (CHF -542 K) which however could partially be compensated with higher grant and other '3rd Party Income' (CHF +151 K).

From a cost type point of view, the main categories were 'Personnel Expenses' with 70%, followed by 'Material Expenses' with 14% and 'Building Expenses' with 3%.

Overall, a positive 'Net Result' of CHF 89 K was achieved compared to a balanced budget, mainly caused by a policy of reduction of holiday / worktime accruals.

4 Structure

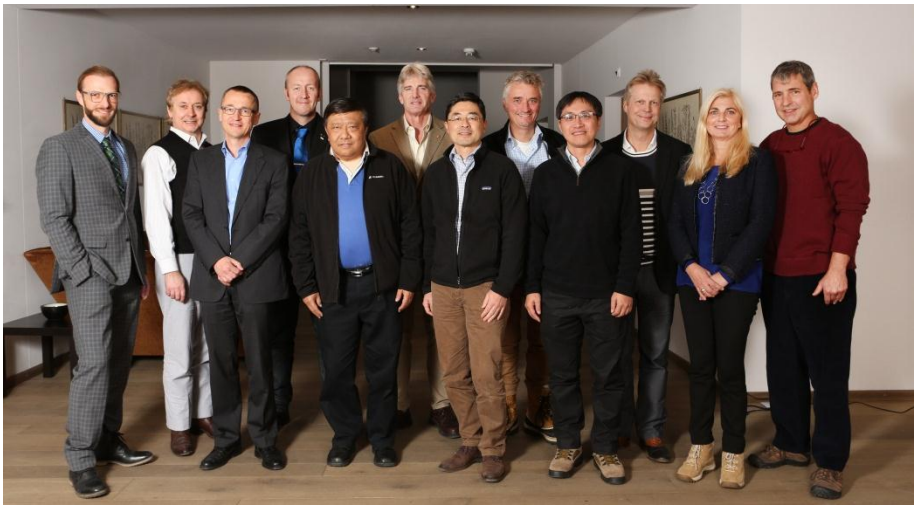
4.1 ARI Structure (as of 2013)



4.2 AO R&D Platform

The newly formed AO R&D Platform is supporting and advising the AO Foundation Board (AOFB) in all R&D related topics - clinical and pre-clinical. The R&D Platform agreed on their charter and work plan for 2014 as follows:

- Draft an AO R&D strategy paper
- Monitor R&D internal and external fund allocation
- Utilize R&D Management & Information Platform IT database to collect information for strategic considerations and outcome measurement
- Define and monitor metrics to assure target attainment
- Coordinate research transition:
  a) Increase priority focus, reduce project numbers
  b) Support and align strategy to attract and create more IP
  c) Support and align AO CID initiatives



from left to right: Peter Langer, Carl Kirker-Head, Lukas Kreienbühl, R. Geoff Richards, Suthorn Bavonratanavech, Mark Markel, Keita Ito, Michael Schütz, Frankie Leung, Risto Kontio, Beate Hanson, Mark Vrahas

Note: The AcC (Academic Council) was dissolved, because it became too large and inefficient. The AcC's main duties were to set the medical and scientific goals of the AO Foundation.

4.3 ARI Advisory Committee

ARI now has a new Advisory Committee (ARI AC), which had its first meeting in December 2013. The AO Research Institute Davos Advisory Committee gives operational and strategic scientific advice and guidance to the AO Research Institute Davos (ARI) and helps assure the efficient deployment of the AOF infrastructure with respect to the service provision activities to Clinical Divisions and CPPs (Clinical Priority Programs). The ARI AC monitors/controls the ARI output on behalf of the AO Foundation Board (AOFB) and is a group with expertise relevant to the R+D objectives of the AO Foundation and acts as both a sounding board and sparring partner for the management of the AO Research Institute Davos. The ARI AC has no funds available for own projects, i.e. no budget authority.

The ARI AC's tasks and responsibilities in detail are to:

- Give advice and guidance to the AO Research Institute Davos in the fields of:
  - Portfolio of competences (skills of personnel and type of equipment).
  - Strategy and priority setting for direct funds of the AO Research Institute Davos
  - Exploratory research Collaborative Research Program(s).
  - Business development and initial advice on technology transfer
  - Regulatory issues
- Monitor/control the ARI output of direct funding on behalf of the AOFB.
- Support the advancement of the capabilities of the AO Research Institute Davos to assure the efficient deployment of the infrastructure.

The chair of the ARI AC will represent the ARI AC at the new AO R&D Platform.

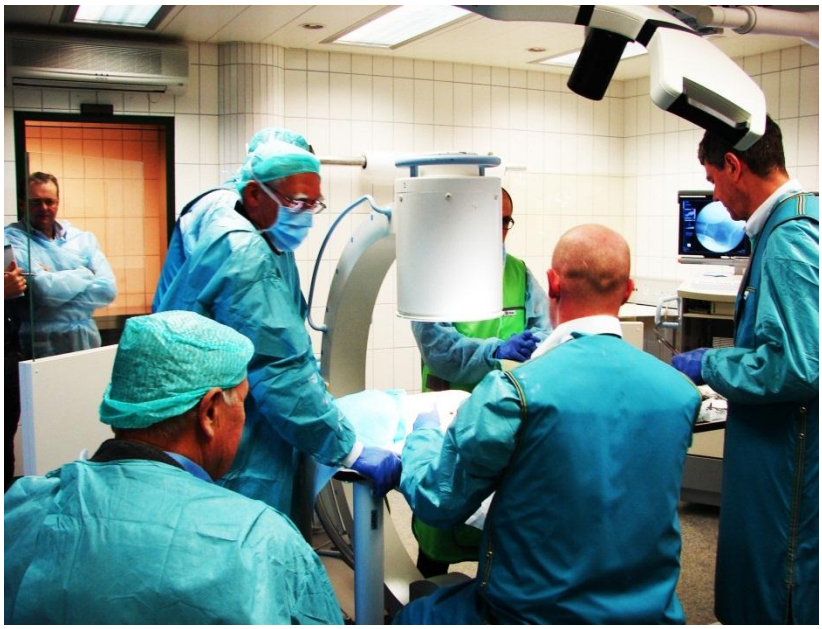
ARI Advisory Committee (ARI AC), since December 2013
R. Geoff Richards, Brian Johnstone, Joost de Bruijn, Michael Schütz, Robert Frigg

4.4 Biomedical Services

Program Leader: Boyko Gueorguiev-Rüegg, Deputy: Markus Windolf
Team Members: Nando Adank, Yash Agarwal, Jan Caspar, Benno Dicht, Manuela Ernst, Ladina Hofmann-Fliri, Matthias Forte, Kevin Frey, Prisca Lemm, Claudia Münch, Walter Ocampo, Ronald Schwyn, Philipp Steinmetz, Ulf Viehöfer, Dieter Wahl, Daniel Widmer, Christoph Wolfrum, Noel Wyss, Ivan Zderic, Erich Zweifel
Fellows: Gaston Camino, Michael Götzen, Niklas Grüneweller, Rukmanikanthan Shanmugam, Miguel Triana
Guests: Mark Lenz, Charlotte Newton, Sascha Rausch, Uwe Wolf, Kerstin Schneider, Hristo Skulev

The Biomedical Services Program performs research and development within the areas of Biomechanical Research, Concept Development, Osteoporotic Fractures and a Prototype Workshop. The focus areas are technically oriented and work in close collaboration with clinical, scientific and industrial partners to improve patient care. The activities include biomechanical and computational studies to investigate fracture fixation with special emphasis on osteoporotic bone conditions, development and analyses of new concepts and technologies of potential relevance to solve clinical problems.

Biomechanical Research
The process of finding the optimal solution to clinical questions is enhanced by biomechanical modeling and testing, aiming to establish integrated experimental and computational investigation methods for research in fracture fixation and joint reconstruction. The capabilities range from in silico methods to more classical anatomy within the state-of-the-art anatomical labs, where two workplaces are equipped with radiolucent OR tables, C-arms and balanced LED operation room lights to mimic surgical conditions. A high resolution camera system, integrated into the OR lights, is available for documentation and educational purposes. Advanced biomechanical studies are performed with material testing machines using tailored test protocols with physiological load patterns, supplemented with X-rays, video and interfragmentary motion tracking systems. Analyses based on finite elements methods help to design, optimize and test existing, as well as newly developed implants and endoprostheses on bone models.



AO Technical Commission practical at ARI anatomical labs

Concept Development and Osteoporotic Fractures
Clinical relevance, simplicity and efficiency are directives to develop innovative solutions affecting musculoskeletal healthcare. With special reference to osteoporotic fractures, the team aims to improve various steps of operative fracture treatment involving advanced surgical decision making, simplified implant positioning, systematic implant optimization, reinforcement techniques with bone cement and assessment of healing. The goals are pursued in strong cooperation with medical and technical collaborators worldwide in order to achieve the highest standards during the whole concept development process from the idea through proof-of-concept to a clinically applicable solution.

New biofeedback concept for fracture monitoring

Prototype Workshop
With its highly trained CNC polymechanics and toolmakers the ISO 13485 certified Prototype Workshop facilitates complete machining of sophisticated pieces and guarantees a high quality precision work. Specialized for the production of medical devices in close collaboration with the project partners, it is involved in the prototype development processes from the very beginning.

4.5 Preclinical Services

Program Leader: Markus Wilke, Deputy: Dirk Nehrbass
Team Members: Daniel Arens, Mauro Bluvol, Karin Camenisch, Iska Dresing, Ursula Eberli, Peter Erb, Jacqueline Faoro, Pierina Faoro, Andrea Furter, Nora Goudsouzian, Thomas Heldstab, Lukas Kamer, Katharina Kluge, Urban Lanker, Reto Müller, Angela Nehrbass, Hansrudi Noser, Dominic Perren, Tanja Schmid, Sonam Sharma, Christoph Sprecher, Vincent Stadelmann, Sandra Thöny, Stephan Zeiter
Fellows: Tobias Helfen, Bronislaw Nowicki, Sarah Peters, Philipp Poxleitner, Daniel Wagner, Viktor Varjas
Student Externs: Silke Baer, Annick Baur, Linda Freitag, Heike Janssen, Andrea Nies, Eva Nordemann

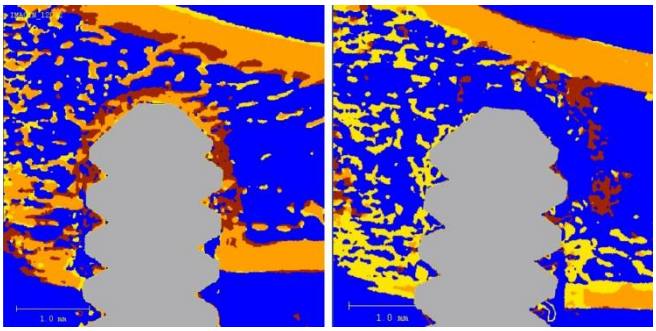
The Preclinical Services Program consists of five Focus Areas (FA): FA Preclinical Surgery and FA Animal Care conduct all ARI (internal/external/commercial) *in vivo* studies – often in close collaboration with FA CT Imaging and usually followed by *ex vivo* analysis in FA Tissue Morphology. FA Human Morpholgy Services has the closest relation to CT Imaging however frequently collaborates beyond the ARI.

The Focus Area Human Morphology Services is a computer laboratory for advanced medical image processing and analysis. The services comprise an infrastructure to run and maintain a database of Computed Tomography (CT) scans and 3D statistical bone models. In 2013 the database has been extended to more than 2000 CTs and 300 High Resolution Peripheral Quantitative CTs as well as bone computer models. Moreover new computer tools are available to generate and analyze 3D statistical bone models in order to visualize major bone shape variations, to investigate on bone stock distribution, to design averaged plate shapes, or to design virtual bones according to user criteria.
Using these technologies and competences collaborations have been established with network partners of AOTrauma and TK System with the objective to create standardized 3D bone models for Finite Element Simulation to allow new implant constructs to be efficiently tested. Within AOCMF a focus was on developing computer algorithms to improve computer visualization of the skull.

The Focus Area Tissue Morphology performs routine histological processing and staining but is specialized in hard tissue evaluation techniques including resin embedding for bone samples with implants, hard tissue microtome sectioning, modified stainings for thicker resin sections, and subsequent qualitative, semiquantitative or quantitative analysis. Custom set up for immunhistological staining are routinely performed, immunofluorescence microscopy and surface evaluation by electron microscopy (SEM) and profilometry complete the spectrum of available techniques.

The Focus Area Surgery together with the FA Animal Care has performed research in the fields of bisphosphonate related osteonecrosis of the jaw (BRONJ), bone infection, bone healing and cartilage regeneration. Several studies addressing clinically relevant problems have been conducted. In particular, models to investigate different aspects (diagnosis, treatment, applied research) of bone infection have been standardized and characterized such as infected intramedullary nail models in sheep and rabbits and infected implant models in rabbits and rodents. Studies are performed with highly qualified staff specialized in laboratory animal medicine (ECLAM), anesthesia (ECVAA) and surgery (ACVS / ECVS) in order to keep up to date with new technologies and developments. One particular achievement has been receipt of accreditation by the "Association for Assessment and Accreditation of Laboratory Animal Care" (AAALAC).

The Focus Area CT Imaging is an interdisciplinary team to investigate bone quality by means of computed tomography and image analysis. The core competences are micro Computed Tomography (microCT), CT, image analysis and image based biomechanics.



Bone reactions to a sterile screw (left) and an infected screw (right) analyzed via time-series of in-vivo microCT scans. (orange=quiescent, yellow=resorbed and red=new bone)

4.6 Musculoskeletal Regeneration Program

Program Leader: Mauro Alini, Deputy: Sibylle Grad
Team Members: Jennifer Bara, Marco Bruderer, Stephanie Caprez, Ewa Czekanska, David Eglin, Matteo D'Este, Oliver Gardner, Markus Glarner, Marietta Herrmann, Milena Janki, Laura Kyllönen, Patrick Lezuo, Zhen Li, Claudia Löbel, Ursula Menzel, Alexander Neumann, Girish Pattappa, Marianna Peroglio, Robert Peter, Dalila Petta, Priyanka Pravincumar-Makwana, Adriano Rucci, Jason Ryan, Gian-Marco Semadeni, Ana-Maria Stanciuc, Martin Stoddart, Gert-Jan ter Boo, Sophie Verrier
Fellows: Xu Chen, Marc Anton Füssinger, Jagoda Jalowiec, Tatiana Pirvu
Guests: Andreas Binder, Sebastien Blanquer, Nicolas Broguiere, Andrea Cochis, Arita Dubnika, Rahul Gawri, Martina Glück, Li Jin, Matti Kesti, Catarina Pereira, Adrian Perez, Olga Rozhnova, Fabrizio Russo, Ryan Seelbach

The program develops biological approaches addressing pathologies of the musculoskeletal system, with a particular focus on bone, intervertebral disc and cartilage tissues. The ultimate goal is to identify strategies for prevention of skeletal degenerative disorders and to re-establish functionality.

Polymers and Surfaces Focus Area
Biomaterials for skeletal repair can provide structural and mechanical features for the filling of defects, but also be carrier for drugs, cells and biological factors. One of our goals is the development of highly porous 3D structures for bone and cartilage tissue engineering, using tailored polymers and composites. Our experience lies in the design of biocompatible, biodegradable polyurethanes and their processing with controlled architecture. A second field of research investigates the preparation of hyaluronan, a natural occurring biopolymer, based biomaterials which can be used to deliver drugs and cells. These injectable biodegradable materials have considerable potential in infection prophylaxis and tissues repair.

Stem cell Focus Area
The area aims to investigate the role of mechanical and soluble factors in the activation of mesenchymal stem cells, and the promotion of differentiation and tissue repair. We are particularly interested in stem cell therapies for bone and cartilage which could be applied within a clinical setting. Mechanical forces are one way stem cell fate could be manipulated by way of rehabilitation protocols. A greater understanding of the role of strain applied to cells would also improve fracture healing outcomes. We are also becoming increasingly interested in the activation of mesenchymal stem cells and their capacity to secrete factors which promote endogenous healing. Activation of this pathway, rather than a differentiation pathway, might provide an additional mechanism by which healing can be promoted in a more natural way.

Disc repair/regeneration Focus Area
Novel therapies for intervertebral disc (IVD) regeneration that are currently under investigation in translational and pre-clinical research include the application of functional biomaterials used for structural support, as cell carrier and drug delivery system. Furthermore, improved knowledge of underlying mechanisms of tissue failure and of the natural tissue repair capacity may lead to new approaches for preventing or activating endogenous responses. The disc focus team is utilizing *in vitro* and *ex vivo* cell and organ culture models aiming to test hydrogels, scaffolds and membranes to be used for delivery of cells and bioactive factors for both nucleus pulposus and annulus fibrosus repair. Our IVD culture techniques are continuously improved in order to optimize the delivery routes of therapeutics and the mechanical loading conditions to approach a physiological response. Furthermore, mechanisms of tissue degeneration and cellular repair capabilities, such as stem/progenitor cell homing, are studied.

Bone regeneration Focus Area
Bone has regenerative capabilities that often lead to spontaneous bone regeneration in form and function. Bone healing and fracture repair involves an efficient sequence of dynamic events due to an important vascularization network supplying the damaged tissue with oxygen, nutrients, growth factors and precursor cells. However, the cases of large bone defects (more than 1.5 times larger than the bone diameter) remain to be a major challenge for the trauma surgeon and bone reconstructive surgery. In addition to significant bone loss (usually treated using autologous bone implant when available) the blood supply is also generally damaged. The aim of the Bone Regeneration Focus area is to create an alternative to the actual gold standard (autologous bone graft). These tissue engineered bone implants are based on the association of autologous cells with biodegradable scaffolds (polyurethane, PU) under autologous biological stimulation able to restore vascularization, bone integrity and biomechanical properties.

4.7 Musculoskeletal Infection

Leader: Fintan Moriarty
Team Members: Pamela Furlong, Iris Keller, Virginia Post, Inga Potapova, Marina Sabate Bresco
Fellows: Christoph Erichsen, Simon Hackl
Guests: Charlotte Newton

The Musculoskeletal Infection team performs research to develop improved preclinical models of bone infection and various laboratory based studies into biomaterials associated infection.

Goal 1: Much research has been focused on ways to further reduce the incidence of infection associated with fracture fixation devices, such as basic design modifications or antibiotic loaded coatings. In the Musculoskeletal Infection team, we aim to develop clinically relevant standardized preclinical models of infection that may be used to test the performance of any such new implant design or active coating.

Goal 2: Infections associated with implanted fracture fixation devices can be difficult to diagnose and treat. This is because the clinical presentation of the infections may be subtle and similar to sterile inflammation, delayed healing or aseptic non-unions. Improved understanding of the pathogenesis of bone infections, improved therapeutics (local delivery vehicles, coatings, passive immunizations) and improved diagnostic tools are the second goal of the musculoskeletal Infection team.

Second annual meeting of the AO Trauma Clinical Priority Program (CPP) Bone Infection in Venice, 11-12 October 2013.

4.8 ARI Administrative Service Group

Manager: Sonia Wahl
Q-Manager & Purchasing: Ulrich Bentz
Team Members: Nadine Abegglen, Isabella Badrutt, Claudia Barblan, Carla Escher, Gregor Müller, Monika Schneider, Daniela Schraner, Marisa Vivalda

The main goal of the ARI Administrative Services team is to provide an excellent service in all administration and organization fields of the AO Research Institute Davos (ARI) and to numerous AO Partners.

- Organize the ARI Directors office
- Professional office management in English and German
- Correspondence
- Organization of meetings and minute taking
- Preparing presentations
- Organize expense accounts
- Hotline and main contact for ARI
- Time management and control of ARI projects
- Travel organization for ARI employees and AO Partners
- Organization of congresses and events for ARI and part of the organization where ARI is represented at major AO events. This service is also offered to our AO Partners
- Supply the internal AO Research community (ARI, CID, Knowledge Services) with peer reviewed papers, book chapters, and books from sources all over the world
- Collation of all AO Research publications
- Purchasing for the ARI
- ARI personnel management (support hiring, organization, etc.)
- ARI Fellowship organization and support

2013 the ARI Administrative Service Group has organized for:

AO Research Institute (ARI)

08.-09.01.2013	AO Frakturenkurs für Medizinstudenten von Schweizer Universitäten, Davos, Switzerland
10.-11.01.2013	Cours AO pour étudiants en médicine des Universités Suisse: Traitement des fractures, Davos, Switzerland
05.-06.04.2013	AO Traumakurs für ETHZ und ZHAW Studenten 2013, Davos, Switzerland
23.-25.06.2013	eCM XIV Stem & Progenitor Cells for Musculoskeletal Regeneration Congress, Davos, Switzerland
25.-26.06.2013	19th Swiss Conference on Biomaterials (SSB), Davos
09.-10.12.2013	First ARI Advisory Committee (ARI AC) Meeting, Davos

AO Exploratory Research (AOER)

07.05.2013	AOER Board Meeting, Zürich, Switzerland
03.09.2013	AOER Board Meeting, Davos
03.-04.09.2013	AOER Collaborative Research Program Meetings, Davos
05.-07.09.2013	"Where Science meets Clinics" The symposium of AO Exploratory Research, Davos, Switzerland

AOTrauma Research Commission (AOTRC)

17.03.2013	AOTRC Meeting, Paris, France
05.04.2013	Augmentation Meeting, Dübendorf, Switzerland
01.06.2013	AOTRC Meeting New York, USA
11.10.2013	AOTrauma Meeting, Venice, Italy
12.10.2013	AOTrauma Annual CPP Meeting Bone Infection, Venice, Italy

5 Institutional and Professional Relations

Geoff Richards has appointments as honorary Professor at Cardiff School of Biosciences, Cardiff University, Wales, GB and at the Institute of Biological Sciences, Aberystwyth University, Wales, GB. He is a Fellow of Biomaterials Science and Engineering (FBSE). He is cofounder and Editor-in-Chief of the eCM Journal. He has Life Honorary Membership of the Swiss Society of Biomaterials (president in 2007-2009). Geoff is an executive committee member for EORS (European Orthopedic Research Society). Geoff is a member and Director of the Board of the Foundation of the AO Research Institute Davos. He has been invited as a "Swiss Personality" to the World Economic Forum Annual Meeting 2012, 13 and 14. Since 2013, Geoff is an Associate Editor of the Journal of Orthopaedic Translation; Member at Large TERMIS-Europe & European representative of the world council Tissue Engineering and Regenerative Medicine International Society (TERMIS); Member of the WOA (World Orthopedic Alliance) organizing Committee for 1st World Congress of WOA in Beijing; Member of executive committee of Academia Raetica (umbrella organisation for the most highly qualified research institutes and the different clinics within the Canton of Grisons and its closer geographical regions); Member of executive committee of Science City Davos. He was a member of the AO Foundation Academic Council until it was dissolved in July 2013 and the board of directors AOGCTM until the end of 2013.

Mauro Alini is an adjunct Professor at the Division of Surgery of the McGill University, Montreal, Canada. He is President of The Swiss Bone and Mineral Society (2011-13). He serves as a member of the Award Committee for The GRAMMER European Spine Journal Award. He is a member of the Scientific Editorial Board of the eCM Journal. He is Deputy Editor Section (Pathophysiology) of the BioMed Central Musculoskeletal Disorders and a member of the Editorial Board of the Open Orthopedic Journal, both online journals. He is also on the Editorial Board of the Open Orthopedic Journal, both online journals. He is also on the Editorial Board of the Biomedical Material Journal and on the Assistant Editorial Board of the European Spine Journal. He is also in the international Editorial Board of the Journal of Orthopaedic Translation.

Boyko Gueorguiev-Rüegg was appointed as honorary lecturer at the Technical University of Varna, Bulgaria in the fields of biomedical engineering and biotechnology. He also acts as journal reviewer for J Orthop Trauma, Clin Biomech, J Orthop Res, eCM Journal, Arch Orthop Trauma Surg and BMT Biomed Eng.

Markus Wilke is a Diplomate of the American and European College of Veterinary Surgeons since 2003 and a member of the ECVS Credentials Committee.

Fintan Moriarty is a member of the eCM Journal International Editorial Review Board. He was invited to join the Scientific Committe of the Asia Pacific Orthopaedic Association, Infection Section and Award Committe for the Best Musculoskeletal Infection Paper Prize. He also acts as a journal reviewer for Journal of Orthopedic Trauma, Materials Chemistry and Physics, Veterinary and Comparative Orthopedics and Traumatology, Antimicrobial Agents and Chemotherapy, BioMed Research International, Journal of Biomedical Materials Research part A, Journal of Clinical Microbiology, Plos One.

David Eglin is a member of the Executive Committee of the Swiss Society for Biomaterials and maintains responsibility of Web-editor. He has been appointed as member of the International Editorial Board of Journal of Orthopaedic Translation (JOT) for 5 years. He is also a member of the eCM Journal International Editorial Review Board.

Sibylle Grad is a member of the eCM Journal International Editorial Review Board and a co-organizer of the yearly eCM conference. She is also a co-organizer of the Research Interest Group (RIG) named The Spine Research Community at the ORS. She is an Associate Faculty Member of the Faculty of 1000 Medicine.

Hansrudi Noser acts as an examiner at the University of Fürstentum Liechtenstein.

Vincent Stadelmann lectures at The Swiss Institute of Technology Lausanne.

Martin Stoddart is a Scientific Editor for eCM Journal, an editor of BioMed Research International Orthopedics and a member of the Review Editorial Board of Frontiers in Craniofacial Biology. He is also the Co-ordinator of the yearly eCM conference and a webeditor of eCM. He is a member of the Orthopeadic Research Society Basic Science Education committee. He is an Associate Faculty Member of the Faculty of 1000 Medicine. Also he was appointed for a three-year term as a member of the Basic Science Education Committee (BSEC) of the Orthopaedic Research Society (ORS).

Sophie Verrier is a member of the eCM Journal International Editorial Review Board and a co-organizer of the yearly eCM conference.

Markus Windolf acts as journal reviewer for J Biomech, Clin Biomech, J Orthop Trauma, J Orthop Res, Injury, Med Eng Phys, Vet and Comp Orthop Trauma and Arch Orthop Trauma Surg.

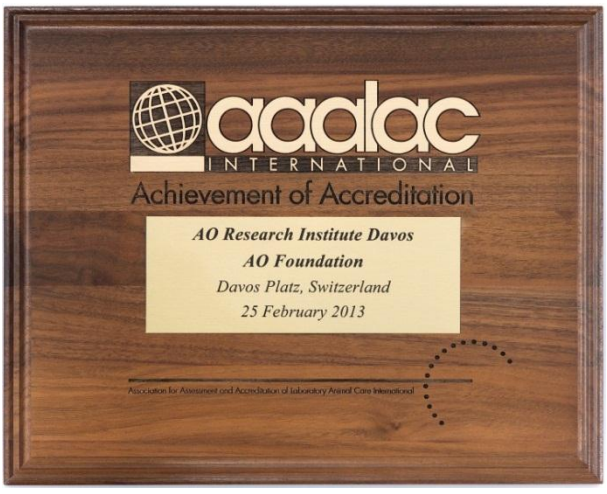
Stephan Zeiter is a member of the education committee of the Swiss Laboratory Animal Science Association. He has reviewed for the following journals: Journal of Biomedical Materials Research: Part A, Journal of Tissue Engineering and Regenerative Medicine and Laboratory Animals.

Marianna Peroglio is a member of the eCM Journal International Editorial Review Board.

Yash Agarwal acts as a journal reviewer for Vet and Comp Orthop Trauma, International Journal of Computer Assisted Radiology and Surgery and Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization. He is a member of the ISO 150 technical committee (implants for surgery, mechanical testing and standards) and a member of ASTM International Technical Committee for F04 Medical and Surgical materials and devices (voting member) and for E08 Fatigue and Fracture (non-voting member). He is also a consultant and reviewer on ISO Technical Advisory Groups (TAGs) for medical devices and implants.

6 Good News

The Preclinical Facility of the AO Research Institute Davos has received full accreditation of by AAALAC in March 2013 completing a two year application process. AAALAC International stands for the "Association for Assessment and Accreditation of Laboratory Animal Care" (http://www.aaalac.org/) and is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs – undertaking one of the internationally highest recognized accreditation programs. The AO Research Institute is one of only three accredited institutions in Switzerland and one of the few academic Research Institutes in Europe. AAALAC endorses the use of animals to advance medicine and science when there are no non-animal alternatives, and when it is done in an ethical and humane way. By fulfilling AAALAC requirements we can guarantee one of the highest possible international animal welfare standards. The accreditation is proof of our continuing ambition to improve animal welfare at the ARI's Preclinical Facility.



Stephan Zeiter successfully passed his board exams to become a Diplomate of the European College of Laboratory Animal Medicine (ECLAM). ECLAM is a veterinary speciality organisation established for the speciality of laboratory animal medicine (http://eslav-eclam.org/eclam). The status of Diplomate of the ECLAM represents the highest level of certification in laboratory animal medicine. Currently, there are only 3 other ECLAM Diplomates within Switzerland.

Extramural funding

The Musculoskeletal Regeneration Program has been granted a 3 year SNF grant (CHF 356'250). The project is entitled "The effect of spatial, temporal and mechanical cues on the modulation of human mesenchymal stem cell chondrogenesis and hypertrophy" and Martin Stoddart is the Principal Investigator. The ARI application co-authors were Mauro Alini and Sibylle Grad.

The Swiss National Science Foundation (SNSF) is Switzerland's foremost institution in the promotion of scientific research. One of its core tasks is the evaluation of research proposals and, every year, the SNSF awards funding to the best applications. By distributing public research money based on a competitive system, the SNSF contributes to the high quality of Swiss research.

The AO Research Institute Davos has been awarded the first ever EU-China Biomaterials Research Project. David Eglin (scientific coordinator), Prof RG Richards and Prof M Alini, together with renowned European and Chinese partners, have successfully entered the first joint European-Chinese research call on biomaterials. The four-year-long RAPIDOS project (ARI part EUR 713'720 for 4 years) is aimed at patient specific bone-forming tissue engineering constructs. More specifically, the project targets the repair of large blow-out orbital floor fractures and the reconstruction of large bone defects in proximal femur or proximal tibia.

An EU-FP7 grant for 4 years (EUR 275'000 for 4 years) has been awarded to Marianna Peroglio and Mauro Alini to fund a PhD student that will work on the project starting 2013. The aim of the BIOBONE (Bioceramics for Bone Repair) project is to offer multidisciplinary training in the field of bioceramics, bioactive glasses and composites for bone repair, in collaboration with industries and universities. The scientific goals are to develop advanced knowledge on a range of bioceramics, bioactive glasses, hybrids and composites focusing on new processing strategies, biodegradation optimization and cell-material interactions. In total, 12 PhDs and 3 Post-docs will be involved in the BIOBONE ITN in 5 academic institutions and 4 industrial partners, all at the cutting-edge of their fields. BIOBONE will offer a unige training framework, including hands-on training at the maint host institution, exchanges with other partners of the network and regular seminars.
BIOBONE Initial Training Network (ITN) is a project funded by the Marie Curie actions under the FP7 People Programme from the European Commission (partners listed under abstracts at page 81).

The AO Research Institute Davos (Mauro Alini, David Eglin, Matteo D'Este and Sophie Verrier) has been the successful recipient of a European FP7 grant (EuroNanoMed II call) for the project Nanoforesto ("Multifunctional injectable nano HAp composites for the treatment of osteoporotic bone fractures"). The action aims are the development of new design, processing, characterization, and modeling techniques of biomaterials from the nano to macro level and their applications to stem cells, regenerative orthopedics. Within this framework of 4 European partners, our 3 year project (CHF 235'000 for 3 years) will focus on the preparation of injectable composites including thermoresponsive hyaluronan hydrogels containing nanohydroxypaptite and drug loaded microcapsules. These compositions will be then characterized for their injectability, viscoelasticity, cytocompatibility and the effect of sterilization processes on the biological efficiency of encapsulated drugs will be assessed.

Other grants
An SRN (Spine Research Network) Exchange Award has been granted to Sibylle Grad by the AOSpine Research Commission. This allowed her to spend 4 weeks in the laboratory of Daisuke Sakai, Tokai University School of Medicine, Kanagawa, Japan.

The AO Research Institute Davos (Fintan Moriarty) has been successful in applying for the EU COST proposal "Improved Protection of Medical Devices Against Infection (iPROMEDAI)". The COST Action (TD1305) will support international networking and inter-institutional work placements on the problem of the device infection, and will commence activities in 2014.
Amount: Travel and networking costs only, Duration: 2014 – 2017
Partners:

- Luginbühl R, RMS Foundation, Bettlach, Switzerland
- Textor M, ETH Zurich, Switzerland
- Malmsten M, Uppsala University, Uppsala, Sweden
- Zaat S, Academic Medical Center, Amsterdam, Netherlands
- Sarasua J, University of the Basque Country Bilbao, Spain
- Pandit A / Wang W, National University of Ireland, Dangan, Ireland
- Reimhult E, University of Natural Resources and Life Sciences, Vienna, Austria
- Moriarty F, AO Research Institute Davos, Switzerland
- Lee G, University College, Dublin, Ireland
- Haycock J, Kroto Research Institute, University of Sheffield, UK

Dagmar Vos, successfully defended her PhD (Implant removal after fracture healing: fact and fiction) at Utrecht University on September 17, 2013, performed part of her research presented in her thesis at the AO Research Institute in Davos.

Prof Chris van der Werken handing the thesis diploma to Dr Dagmar Vos in the hall of Utrecht.

Dagmar Vos, a trauma surgeon at Amphia Hospital Breda, the Netherlands, was also financially supported by a research grant from the AO Foundation, Davos Switzerland. Prof Chris van der Werken, AO Foundation Past-President (her promoter) and Prof R Geoff Richards (Director of AO Research Institute Davos) her co-promoter attended as members of the jury, both wearing the traditional gowns, colours and beret. Prof Richards was very proud of Dagmar's achievement as this was his first promotion of a medical PhD from the Netherlands (after the invite to co-promote Dagmar several years earlier from Prof van der Werken).

Should implants be removed? A question frequently asked of trauma and orthopaedic surgeons is whether an implant will be removed, and if yes, when? Although implant removal after fracture healing is daily practice, a clear scientific basis for this practice does not exist. The studies in this thesis were performed to unpick the facts and fiction of implant removal since there is still a debate about the indications, complications and clinical outcome of implant removal. Indications for implant removal after fracture healing are diverse and most publications present retrospective studies, case reports or expert opinions. Opinions and habits vary between surgeons (eg, differences between countries), patients (eg, children and adults) and implants (eg, plates versus nails). Accepted indications for removal used to be the assumed risk of metal corrosion, allergic reactions, bone atrophy and carcinogenesis. But the lack of proof that implants damage health, and the observed technical problems along with the introduction of titanium alloy implants, made surgeons less enthusiastic to remove implants. Currently, the main indications are generally ‘relative’ and driven by patient’s complaints and symptoms. The results of a national survey among all members of the Dutch Trauma Society and Dutch Orthopaedic Trauma Society, confirm that the opinion and attitude towards implant removal after fracture healing is diverse, even in a small country such as the Netherlands. Also in children implant removal is topic of a discussion. Pediatric fracture treatment differs because of rapid fracture healing and the nature of the growing skeleton. Implants preferably used are Kirschner-wires, elastic stable intramedullary nails and/or screws. The results of a retrospective study in 298 children showed that standard removal resulted in less than 10 % complications. As within literature, most complications were minor and transient. Only four refractures (1 %) appeared. Titanium alloy implants have become popular due to their better biocompatibility and mechanical properties under dynamic load. Unfortunately, removing titanium implants can be very difficult due to bone adherence. In a sheep model the ease of removal of stainless steel, standard titanium alloy and polished titanium alloy nails was compared. Surface polishing significantly reduced pull-out forces required to remove standard titanium alloy nails, comparable to forces observed for stainless steel.
A prospective clinical cohort study was performed in five hospitals to describe the main complications and clinical outcome of implant removal after fracture healing. Most patients (n=287) had symptoms related to the implant and expected them to improve after removal. The main complaints were ‘pain’ and ‘limited joint mobility’. The overall complication rate was 30 %. The percentage was higher in the lower extremity (37 %) than in the upper extremity (22 %; p=0.005), resulting in a 2.8 times higher complication odds (95 % CI: 1.57–5.06). The main complications in the upper extremity were sensory nerve injuries (6 %) and wound infections (6 %). In the lower extremity postoperative bleeding (19 %) – especially after nail removal (femur nail 21 %, tibia nail 22 %) – and wound infections (10 %) were seen. A significant improvement of pain, limited joint mobility and muscle weakness was observed. The overall satisfaction with the outcome was very high for both surgeon and patient, since 97 % would decide for the same procedure again.

ARI hosts consortium meeting for the FP7 project NPMimetic

On March 11–12, 2013, the consortium meeting of the partners of the FP7 funded European project NPMimetic was organized at the AO Research Institute Davos (ARI). Twenty scientists from the ten partner institutions participated in this meeting which was already the fifth get-together of the complete consortium in 24 months. Urszula Narkiewicz from the European Commission and Hans Jörg Meisel, the clinical/scientific project advisor also attended the meeting and obtained insight in the status and progress of the work.

NPMimetic with its full title "Biomimetic nano-fiber-based nucleus pulposus regeneration for the treatment of degenerative disc disease" is a four year project run under the FP7–NMP Theme Nano-sciences, nanotechnologies, materials and new production technologies. Its aim is to develop a novel treatment for intervertebral disc degeneration based on synthetic nanofibers combined with a bioactive polymer hydrogel. NPMimetic is coordinated by Marco Helder from the University of Amsterdam (Holland) and includes the partner companies Nicast (Israel), ProCore (Israel), OsmDan (Israel), and Melab (Germany), the partner universities of Minho (Portugal), Sheffield (England) and Zürich (Switzerland), and the partner institutions CM Development (France) and ARI. This brings together expertise in degradable and non-degradable synthetic and bio-polymer processing, injection technology, mathematical modeling, structural and chemical analysis, protein delivery, biomechanics, in vitro, ex vivo and in vivo preclinical methods for intervertebral disc research, complemented by project management and spine surgery.

The role of the ARI within the consortium is to perform cell and organ culture experiments to assess the in vitro and ex vivo performance of the newly developed materials and techniques. ARI staff Mauro Alini, Sibylle Grad, Marianna Peroglio and Zhen Li from the Musculoskeletal Regeneration Program are involved in conducting and supervising these studies. In particular, collaboration with ProCore has resulted in the publication and presentation of abstracts at the World Biomaterials Conference, the TERMIS World Congress, and the Swiss Society for Biomaterials Meeting in 2012, while close interactions with the partners Nicast and University of Zürich are also continuing. NPMimetic is funded by the EU Commission by a total of EUR 4,000,000, of which EUR 532,000 is granted to the ARI. This meeting was successful and gave rise to stimulating discussions among the partner clinicians and scientists. Importantly, the consortium demonstrated that the project is well on-track.

Combined Meeting of Orthopedic Research Societies 2013

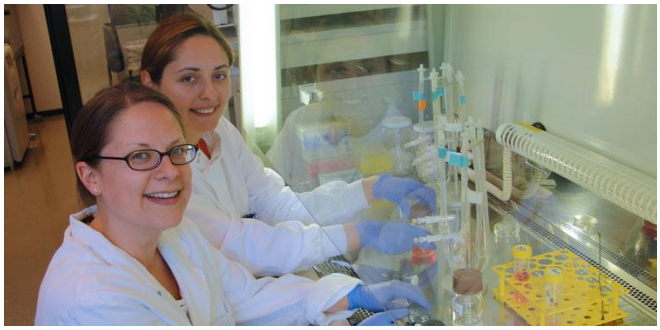
CORS is a global network of national and regional societies sharing a strong dedication to orthopedic research. Nine societies from around the globe are currently active within CORS, which aims to promote orthopedic science and education on a global basis. CORS representatives regularly meet at the annual Orthopedic Research Society (ORS) meeting and once every three years CORS organizes a big scientific meeting, such as the recent CORS 2013 which took place at the Congress Center of San Servolo in Venice.

In the opening day of the CORS meeting, the ARI and AOTRAUMA co-hosted a symposium entitled "Bone Infection, an AO Trauma Clinical Priority Program for Research". Prof R Geoff Richards and Dr Edward Schwarz (Rochester, USA) were the session chairs, which showcased the latest achievements of the AOTrauma CPP Bone Infection, and presentations by CPP members. This symposium followed on from the second annual meeting of the AOTrauma Clinical Priority Program on Bone Infection, which also took place in Venice (picture right).

The opening symposium presentation was by Prof Stephan Kates (Rochester, USA), who gave an overview of the clinical problem of bone infection as faced in daily surgical practice, and briefly presented an overview of projects included in the CPP Bone Infection. Prof Volker Alt (Giessen, DE) outlined the different preclinical in vivo models used for bone infection research, with special focus on clinical relevance. Dr Fintan Moriarty (ARI) presented the influence of implant materials on the development of infection, giving an insight to foreign-body reaction and the interplay between the foreign body and biomechanics with regard to osteomyelitis. Finally, Dr Edward Schwarz (Rochester, USA) reported the latest achievements of a passive immunization strategy for staphylococcal bone infection. This particular passive immunization strategy has already shown efficacy in murine models and has recently been shown to be efficacious in a diabetic mouse model, which is another important clinically relevant model.

Prof Volker Alt addresses the attendees of the CORS meeting during the AO symposium on Bone Infection.

Furthermore, this years' CORS program included two infection sessions for submitted abstracts. "Infection I" was chaired by ARI's Prof Richards and Dr Fintan Moriarty. The first infection session included six papers dealing with a broad spectrum of new methods for preventing orthopedic implant related infections. Included in the speaker rostrum for this session was Dr Julia Blackburn (Bristol, UK), who was a recipient of a European Orthopaedic Research Society travel grant to visit ARI in summer 2013. Dr Blackburn reported on her approach to support human osteoblast maturation while deterring bacterial surface attachment by using coated titanium surfaces with the bioactive lipid, lysophosphatidic acid (LPA).



European Orthopaedic Research Society (EORS) Exchange Travel grant winner's visit to the AO Research Institute, Davos. From August 7 to September 3, 2013, Dr Julia Blackburn visited the AO Research Institute Davos (ARI) as part of a European Orthopaedic Research Society (EORS) Exchange Travel Grant.

The Infection II session was moderated by ARI's Dr Inga Potapova. ARI was well represented at this session and presented the following four talks covering their most recent activity in bone infection research. From the Imaging Focus area: Dr Vincent Stadelmann presented Computed tomographic (CT) monitoring of bone around an infected implant. From the Musculoskeletal Infection Group: Dr Potapova presented a paper on intra-vital imaging of infection using click chemistry-generated imaging probes; Marina Sabaté Brescó, talked about immune responses in osteomyelitis after osteosynthesis in a murine model; Dr Virginia Post, presented a paper on biofilm and molecular characterization of S. aureus isolated from orthopedic implant related infections and correlations of the characterization with type of device.

In addition to infection, CORS 2013 covered a broad spectrum of topics and ARI was also well represented throughout, with Prof Mauro Alini (Vice-Director, ARI), Dr Marianna Peroglio, Dr Boyko Gueorguiev and Ivan Zderic also presenting their papers and posters. Many ex-ARI medical fellows were present at the congress including, Ted Miclau (San Francisco, past ORS president and in the presidential line for OTA), Henk Eijer (Bern) and Kirsten Schneider (St Gallen). Numerous ex non-medical ARI fellows and team members were also present such as Kelvin Yeung (Hong Kong), Samantha Chan (Bern), Jerome Noailly (Barcelona), Hans Van Oosterwyck (Leuven) Melissa Knothe Tate (Sydney), Terry McIff (Kansas).

Overall, CORS 2013 was a successful global conference, attended by many of the organizing committees of the respective independent societies, and marked the official formation of the International Combined Orthopaedic Research Society (ICORS). The AO Foundation was well represented with symposia and numerous presentations by the researchers at ARI and has been invited to be a Associate Scientific member of the ICORS.

The next CORS shall take place in Xian, China October 21-25, 2016, hosted by the Chinese ORS.

Relocation Prototype Workshop

The governing board of the AO Foundation gave a green light for relocation of the Prototype Workshop in a new building at the AO Center areal. The preparation work for the new building started in autumn 2013. The new premises will lead to a better integration in the ARI, shorter communication channels, closer collaboration and more flexibility of the activities, keeping all workshop capacities via optimal use of personnel resources.

Picture depicting the planned new location of the Prototype Workshop at the AO Center area.

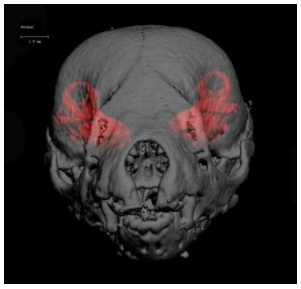
Conference Awards

Yash Agarwal won the prize for best podium presentation at the Orthopaedic Product News Hip & Knee Conference: Brigstocke G, Agarwal Y, Bradley N, Frehill B, Crocombe A. Finite element analysis of cement shear stresses in augmented total knee replacement, London, UK, 27.06.2013.

Mark Lenz has been awarded the 3rd Posterprice at ESTES 2013, Lyon, France with the title "The concept of point contact fixation – interface mechanics of cerclages" Lenz M, Perren SM, Gueorguiev B, Richards RG, Fernandez dell'Oca A, Höntzsch D, Hofmann GO, Windolf M. 14th ESTES, Lyon, France, 4-7 May 2013.

Timo Schmid won the International Federation of Foot and Ankle Societies (IFFAS) award for the best international paper at the Annual Meeting of American Orthopaedic Foot and Ankle Society: Schmid T, Zurbriggen S, Zderic I, Gueorguiev B, Weber M, Krause F, Ankle joint pressure changes in a pes cavovarus model: supramalleolar valgus osteotomy versus lateralizing calcaneal osteotomy, AOFAS, Hollywood, Florida, USA, 17-20 July 2013.

Ursula Eberli won the best microCT image competition at the SCANCO user meeting in Appenzell with a 3D rendering of the internal ear of a bat after a peer vote. Appenzell, Switzerland, October 2013.



Florian Schmidutz won the 2013 Young Researcher Award ("Nachwuchsförderpreis") for his presentation about Bone integration in Hemi-Resurfacing Shoulder Prosthesis ("Die knöcherne Integration von Hemi-Resurfacing Implantaten der Schulter") at the annual meeting from the Association of Orthopeadic and Trauma surgeons of south Germany (Vereinigung Süddeutscher Orthopäden und Unfallchirurgen e.V.).

Organized Student Courses / Meetings

AO Research Institute Davos hosted 150 Medical Students from Swiss Universities

From January 8-11, 2013 150 medical students from Swiss Universities joined one of the two fracture courses held in German and French at the AO Center Davos. These popular two-day courses are organized annually to give interested 4th-6th year medical students a first insight into the principles of osteosynthesis. The students from the Universities of Bern, Basel, Zurich, Lausanne and Geneva were instructed and supported by the experienced surgeons Dr. Christian Ryf from the hospital Davos, Dr. Raphael Jenni from the Cantonal hospital in Chur, Dr. Stefan Hefer from the hospital Chablais in Monthey, as well as additional qualified AO surgeons. Besides basic theoretical knowledge, practical aspects were addressed, while particular emphasis was put on the treatment of common snow sports injuries. In the popular hands-on trainings, all participants could practice the different osteosynthesis techniques using various plates, screws and nails on synthetic bone models. The correct handling of the surgical instruments requires manual skills and concentration but was tackled with great enthusiasm.

During the tour through the labs of the ARI, different projects from the fields of basic and applied science were presented, which initiated stimulating discussions about future treatment options of injuries and diseases of the musculoskeletal system. The stations of the "skill training lab" provided again the opportunity to test the participants' practical skills and experience the pitfalls of surgical practice. The strong interest and motivation of the students suggest that some of them will most likely be participating at the well-established AO Courses in a couple of years. This is also corroborated by Dr. Markus Loibl, a former ARI medical research fellow who has supported the courses as instructor for many years: *"The transition from university life to practicing medicine or surgery is a very challenging task for medical students. With this course the AO offers assistance with this task and gives an introduction to AO philosophy of patient care. Taking the time to explain the key steps of an operation with hands-on training, thereby experiencing AO philosophy of sharing knowledge, may excite the fascination for surgical disciplines. After graduation from university, once a preliminary residency decision has to be made, this will bring back many of the students as young residents to take the AO basic principles course."*

AO Trauma Course for Engineering Students from ETHZ and ZHAW

On April 5-6, 2013 more than 50 engineering students from the Swiss Federal Institute of Technology Zürich (ETHZ) and the University of Applied Sciences Winterthur (ZHAW) gathered at the AO Center Davos for the annual Trauma course. As every year this 2-day course was once more fully booked, highlighting its great popularity.

Osteosynthesis training

Particularly attractive were the hands-on osteosynthesis exercises, whereby the use of metal implants for fracture treatment was explained and demonstrated. Utilizing artificial bone models the future engineers could attempt to fix different fractures using common surgical instruments and devices such as plates, screws, nails and fixators. Importantly, this raised awareness that besides expert knowledge special manual skills are required by every surgeon. The students were supported and instructed by Dr. Raphael Jenni from the Cantonal hospital in St. Gallen, Dr. Christian Ryf from the hospital Davos, and a qualified instructor team. A presentation of the AO Surgery Reference complemented the surgery-related part of the course.

Insight into AO Research

Guided tours through the laboratories of the ARI and instructive lectures given by ARI scientists provided insight into current research projects. Every project aims at solving a relevant clinical problem, whereby interdisciplinary teamwork is indispensable.

The “skill training lab” offered again the opportunity to test the participants' manual capabilities, while the respective underlying biomechanical and biological mechanisms were demonstrated and explained.

The goal of the Trauma course was not to give a surgical education to the engineers, but to provide basic knowledge in skeletal repair and regeneration. Computer-assisted biomechanical analysis, bioreactors for cell and tissue cultures, and bioresorbable implants were only few examples demonstrating the close connection between medical and technical sciences. Basic understanding in biology and medicine is particularly important for engineers who will focus on medical technology, which is a fast growing sector. The high motivation of the participating students and the favorable feedback suggests that some of them may envisage a career in the medical technology or biomedical engineering field.

Engineering students practice at the Skill Training station.

RAPIDOS Project

The ARI has been awarded the first ever EU-China Biomaterials Research Project in 2013. David Eglin (scientific coordinator), Prof RG Richards and Prof M Alini, together with renowned European and Chinese partners, have successfully entered the first joint European-Chinese research call. This innovative project and consortium initiated in Davos was ranked first in a very competitive field of more than 25 consortiums and 150 research groups. The team formed is partly the result of the endeavours of ARI to educate and instil the AO Davos spirit in young surgeons and scientists for many years. Two of the Chinese partners - Prof L Qin and Prof TT Tang - were fellows in 1993 and in 2004, respectively. Prof Grijpma from Twente has been connected to ARI for the last few years through the AO Exploratory collaborative research program for intervertebral disc and Prof Joost de Bruijn (also Twente) has been connected for many years to ARI throught the eCM journal, where he is a scientific editor. Today, along with Prof Richards, Prof Grijpma, Prof Qin and Prof Tang, have become directors of their respective institutes. Based on their long-trusted relationship, it was a matter of minutes for each individual partner to agree to work together and initiate this venture.

RAPIDOS project partners kick off meeting in Davos, June 21, 2013.

The four-year-long RAPIDOS (Rapid Prototyping of Custom-Made Bone-Forming Tissue Engineering Constructs) project is aimed at patient specific bone-forming tissue engineering constructs. More specifically, the project targets the repair of large blow-out orbital floor fractures and the reconstruction of large bone defects in proximal femur or proximal tibia. In line with the clinical priorities of the AO Foundation, the goal of this European and Chinese consortium is to apply rapid-prototyping technologies to create patient specific tissue engineered implants made of resorbable polymer and calcium phosphate ceramic composites specifically designed by integrating imaging and information technologies; biomaterials and process engineering; and

biological and biomedical engineering for novel and truly translational bone repair solutions. The use of Chinese medicine extracts combined with the most recent fabrication techniques reunites the millennial knowledge of Chinese medicine with cutting-edge biomaterials science in this venture. The RAPIDOS activities and progresses can be followed on the web through the RAPIDOS portal http://rapidos-project.eu

The RAPIDOS Consortium

The European partners - Prof DW Grijpma from the University of Twente, Netherlands; Prof T Peijs from Queen Mary College of London, UK; Prof J de Bruijn from Xpand Biotechnology AG based in the Netherlands, and ARI - will receive a funding of Euros 1.7 million from the EU commission. The Chinese partners in this consortium will be financed by the Natural Science Foundation of China. The Chinese partners include Prof L Qin from Translational Medicine Research and Development Center of the Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences; Prof TT Tang from the Shanghai Key Laboratory of Orthopaedic Implant at Shanghai Jiao Tong University; and Prof SB Lu and Dr J Peng from The Institute of Orthopaedics of Chinese People's Liberation Army General Hospital in Beijing.

The RAPIDOS project objectives were presented at the 4th China-European Symposium on Biomaterials and Regenerative Medicine in Sorrento this July and have already gathered interest from the community. The planned scientific exchanges and scientific workshops are truly exciting opportunities for the ARI to exchange with leading scientists and surgeons in Europe and China.

RAPIDOS project partners in Davos, June 21, 2013. left to right: Prof TT Tang, Prof RG Richards, Dr L Kamer, Dr D Eglin, Prof J de Bruijn, Dr Z Li, Dr H Yuan, Prof M Alini, Prof DW Grijpma and Prof L Qin.

RAPIDOS Project partners in Beijing, China on November 10, 2013.
Upper left to right: Dr Wang Xinjiang, Dr Peng Zhang, Dr Jiang Peng, Prof Ting-Ting Tang, Dr Huipin Yuan, Dr Yuxiao Lai, Dr Xinluan Wang; Lower left to right: Dr Mei Yuan, Prof Dirk Grijpma, Prof Joost de Bruijn, Prof Geoff Richards, Prof Shi-bi Lu, Prof Ling Qin, Dr David Eglin.

The RAPIDOS project meeting took place in Beijing China on November 10, 2013 at the prestigious Institute of Orthopedics at the Chinese PLA (People's Liberation Army) General Hospital (301 Hospital), Beijing. Director of the PLA Orthopedic Institute and member of the Chinese Academy of Engineering Prof Shi-Bi Lu, was the guest of honor.

19th Swiss Conference on Biomaterials

The 2013 SSB (Swiss Society for Biomaterials) Annual Meeting and General Assembly took place at the Congress Centre in Davos, Switzerland on June 25-26, 2013 and was organized by David Eglin and Matteo D'Este from the ARI. The topic of the meeting was Polymers & Biomaterials and brought together scientists, clinicians and industry. International keynote speakers shared the podium with students and scientists from Switzerland.

During the General Assembly of the SSB in Davos on June 26, 2013, the members accepted to integrate Tissue Engineering research and development in its purpose and activities and formed a new name The Swiss Society for Biomaterials and Regenerative Medicine.

David Eglin welcomes the participants.

Prof Bert Müller, University of Basel.

AO Exploratory Research Annual CRP Meetings 2013, Davos

Annual Meetings are dedicated to bringing together research partners from the three AOER-funded Collaborative Research Programs (CRPs) and discuss together with the Program Committees the progress and future directions of the program. For the first time, the Annual Meetings also included a workshop on 'Product Development' held by Elliott Gruskin and his team from De PuySynthes.

From September 3-5, 2013 the AO Exploratory Research (AOER) Annual CRP Meetings were held at the AO Foundation headquarters in Davos, Switzerland. This report provides an outline of the presentations and activities covered in these three days and an outlook to the Annual Meetings 2014.

The Meetings started with a welcome address from the AOER Board (AOERB) Chair Prof Michael Schütz (Queensland University, Australia) and the Head of AOER Sandra Steiner (AO Foundation, Switzerland) at the AO Center Auditorium. This was followed by the progress reports from the research partners including ample time for discussions after each presentation.

Audience at the CRP partner presentation

CRP Partners and Committees

Where Science meets Clinics symposium

ARI, AO Exploratory Research and AOTK System hosted a successful three-day symposium, September 5-7, 2013 at the Congress Centre in Davos. Well over one hundred scientists and clinicians travelled to Davos to attend the second international symposium "Where Science meets Clinics 2013".

Presentation sessions

M. Schütz (Brisbane), S. Steiner (Davos), N. Südkamp (Freiburg)

This event provided an open platform to foster exchange and networking between the research and clinical communities so as to stimulate successful clinical translation of innovative science. Prof Michael Schütz and Dr Sandra Steiner welcomed the participants to this year's symposium, which brought together scientists and clinicians from a multidisciplinary environment to discuss current issues and novel strategies for bone, intervertebral disc and articular cartilage repair and regeneration. This was followed by a brief introduction to the AO Foundation by the Foundation's current President, Jaime Quintero (Colombia).

Global experts shared this platform to talk about the current procedures, achievements and challenges regarding the latest repair strategies on the Symposium's core topics: 1) Cell Therapy and Responsive Materials in Bone, Intervertebral Disc and Articular Cartilage Repair. 2) Barriers and Strategies for Translation of New Tissue-Engineered Materials to the Clinic. The symposium format also had plenary and parallel breakout discussion groups to encourage participants to contribute actively.

Impressions from the second international symposium "Where science meets Clinics" 2013.

Workshop "Animal models in bone regeneration research"

Research using animals is rightly under high public and scientific scrutiny and is cost- and time-intensive. Therefore, it is both ethically and scientifically crucial to design, execute, analyse and interpret experiments properly. This workshop organized by Markus Wilke, Vincent Stadelmann and the preclinical team was held on September 26-27, 2013 at the ARI. In total, 40 scientists from Switzerland (Geneva, Lausanne, Basel, Zurich, Winterthur, Davos), Austria (Graz) and Singapore participated in the workshop. This was an exciting opportunity to exchange experiences, techniques and to network. The core topics were the choice of animal models, surgical techniques and anesthesia and imaging and biomechanical assessment. Each session was followed by practical demonstrations at the Preclinical Services building.

This workshop was accredited as 1.5 days of continuing education in Switzerland for experimenters and study directors in animal experimentation, and was sponsored by RISystem and SCANCO Medical.

Practical demonstrations during the Sept. 2013 workshop
left photo: rodent surgery; right photo: biomechanical stimulation.

OrthoNose project at the Davos Courses 2013

Over 1,200 surgeons enrolled in the collaborative OrthoNose study at the Davos Courses 2013. The OrthoNose project was a collaborative AOTrauma study involving the AO Research Institute Davos (ARI) and AO Clinical Investigation and Documentation, with clinical partners from BGU Murnau (DE) and the University of Rochester (US). As part of the AOTrauma CPP Bone Infection, OrthoNose is a study investigating nasal colonization in orthopedic surgeons with multi-resistant bacteria. The study targeted participants and faculty at the Davos courses; this large scale event offered a unique opportunity to generate data from a sizable international collection of active surgeons from the fields of trauma, spine, CMF and veterinary surgery. Stephen Kates (Principal Investigator of the AOTrauma CPP Bone Infection) and Geoff Richards (ARI Director) supported the team effort which was managed by the ARI Musculoskeletal Infection leader Fintan Moriarty.

Throughout the two weeks of the courses, more than 1,200 surgeons provided anonymous, voluntary nasal swabs to project leader Mario Morgenstern (BGU Murnau) and his team. The swabs have since been transported to the hospital laboratory, where the bacterial growth, identification and antibiotic resistance profile has already been completed. The results of this study will shed light on an under investigated issue of significant clinical relevance. Patient colonization has been the subject of a large number of studies, however, the colonization of surgeons, and healthcare workers in general, has been largely underreported. The results of OrthoNose—coming as it does from such a large and geographically diverse population—will ensure that a modern snapshot of the global colonization of surgeons will soon be available. The project team aim to produce the results of the study in spring 2014.

Left photo: Project team members at the ARI booth: Left to Right Fintan Moriarty (ARI), Julia Mily (University of Munich), R. Geoff Richards (Director ARI), Stephen Kates (CPP BONE Infection Principal Investigator, University of Rochester), Mario Morgenstern (BGU Murnau).

Right photo: Participation in OrthoNose.

7 eCM Journal, symposia and annual Conference

eCM Journal
eCM is extremely proud that it was one of the first open access scientific journals world-wide initiated in 1999. eCM also started immediately with a transparent review process (now known as open peer review) including a transparent route to becoming a member of the Review Board. Now these logical steps to us at the time are seen as being well ahead of their time.

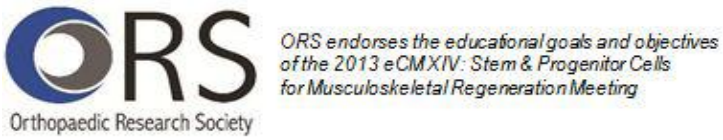
eCM Impact factor categories were re-examined in 2011/12 through a prism of a citation analysis by Thomson Reuters. They examined the fields reflected in the journal's content, the cited references in that content, and those fields citing eCM journal, as reflected by the Web of Science. The analysis supported the following conclusions which took effect in 2013
(1) Addition to "Engineering Biomedical" and "Cell & Tissue Engineering" categories.
(2) Maintenance of the title in the field of "Material Science, Biomaterials"
(3) Removal from "Biochemistry & Molecular Biology".

In June 2013 the 2012 impact factors were released. For eCM the following was awarded:
Five-year Impact Factor 2012- 5.7 - 2nd in MATERIALS SCIENCE, BIOMATERIALS,
3rd in CELL & TISSUE ENGINEERING, 4th in ENGINEERING, BIOMEDICAL
Yearly Impact Factor: 2012 4.558 3rd in MATERIALS SCIENCE, BIOMATERIALS, 4th in CELL & TISSUE ENGINEERING, 5th in ENGINEERING, BIOMEDICAL.

eCM Founded by scientists for the benefit of Science rather than profit, published by AO Research Institute Davos.

eCM Symposium at CORS 2013
eCM Journal hosted a symposium at the Combined Meeting of Orthopedic Research Societies in Venice in October 2013. The symposium entitled Producing the Stable Chondrocyte Phenotype—Considerations for In Vitro Stem Cell Differentiation was organized by Prof Brian Johnstone (Portland, USA) and Prof R Geoff Richards and at which Prof Mauro Alini, Prof Charlie Archer (Cardiff, UK) and Brian Johnstone spoke. CORS is a global network of national and regional societies sharing a strong dedication to orthopedic research. Nine societies from around the globe are currently active within CORS, which aims to promote orthopedic science and education on a global basis. CORS representatives regularly meet at the annual Orthopedic Research Society (ORS) meeting and once every three years CORS organizes a big scientific meeting, such as the recent CORS 2013 which took place at the Congress Center of San Servolo in Venice.

eCM Conference
2013 eCM XIV: Stem & Progenitor Cells for Musculoskeletal Regeneration was held between June 23-25. 2013. This year was special since it was the first time ORS (Orthopedic Research Society) endorsed the educational goals and objectives of an external conference and we are very proud that this ebndorsement was given to eCM.



It was also the first year where the conference was organised by a new ARI team, consisting of Dr. Martin Stoddart, Dr. Sophie Verrier, Dr Sibylle Grad and Dr. David Eglin. The previous 13 eCM conferences had been organised by the ARI Director, Prof. Geoff Richards and ARI Vice Director, Prof. Mauro Alini, in combination with Prof. Charlie Archer, University of Cardiff, Wales.

While holding great promise, the use of stem and progenitor cells for musculoskeletal regeneration has still not become a clinical reality. Though stem cell research has moved on over the last 20 years, there are still some significant hurdles to overcome to make the use of these cells a clinical reality. Understanding the mechanisms that control cell proliferation, differentiation and integration is essential to achieve clinical treatment methods. Their potential to regulate the endogenous response and modulate inflammation is only just beginning to be explored.
In addition, the regulatory constraints and safety issues must be taken into consideration. This meeting firstly gave introductions to the stem cell area and then moved onto where we are with stem cell research and how far we have to go to get to safe clinical treatments.
This was an extremely successful meeting. Turnout was high and the discussions after talks were extensive and thought provoking. This year in particular, the number and high standard of student presenters was a source of pride for the organisers and is something we hope will continue. Choosing the winners of the Robert Mathys student prizes was incredibly challenging with Elisabeth Seebach being a worthy winner with her talk Mesenchymal stroma cells implanted in fibrin hydrogel trigger attraction of M1 macrophages, endothelial cells and early immune modulation stimulating long bone healing without long-term engraftment (Research Centre for Experimental Orthopaedics, Orthopaedic University Hospital Heidelberg, Germany).

All abstracts from this conference can be found at
http://www.ecmjournal.org/journal/supplements/vol026supp03/ecm14.htm

8 AO Research Institute Davos Fellows

The ARI's Research Fellowship program again attracted resident and senior surgeons from around the world. Some of the many benefits to a surgeon of undertaking an ARI Fellowship are:

- Actively participating in research projects and generating tangible research results
- Possibility of co-authoring publications in medical journals
- Learning how to approach future research challenges
- Inspiration from being part of an world renowned international multidisciplinary R&D team
- Enlarging personal networks for future R&D activities
- Having access to research colleagues and mentors

In 2013 a total of 12 fellows started their fellowships in one of the ARI research labs, whereby all research groups/programs were involved in hosting a fellow for a time period of 6 to 12 months.

Gaston Camino Willhuber, Italian Hospital of Buenos Aires, Argentina

ARI Project: Biomedical Services Program; Influence of reduction & screw orientation on stability of sacroiliac joint stabilization. I came to the ARI for my 6 month period as a Medical Research Fellow. I am interested in different projects related to percutaneous techniques and augmentation in pelvis and hip. Since the beginning of my studies, I have been interested in research activities, experimental designs and clinical research. I was very happy to work at ARI and to have the opportunity to learn more about research, education, language and social life in Davos.

Xu Chen, Shengjing Hospital affiliated China Medical University, China

ARI Project: Musculoskeletal Regeneration Program; Intervertebral disc repair/regeneration (Nano-fiber-based nucleus pulposus regeneration for the treatment of degenerative discs). Occasionally I think back the moment that I met the the AO principles during my internship in China, yet now working in an outstanding group within the ARI, what a pleasant feeling! Instead of simply taking it into practice, it's very meaningful and interesting to explore the principle between the science and clinical work. The experienced staff can help you to broaden your horizon, especially in your topic of interest. And the well-equipped facilities and excellent management will leave you quite a deep impression. I have really appreciated the golden opportunity to learn from the best.

Christoph Erichsen, Trauma Center Murnau, Germany

ARI Project: Musculoskeletal Infection Group (Implant related infections with S.epidermidis / S.aureus). I had the chance to gain research experience in the field of implant associated infections. It was a pleasure working in such a friendly and helpful environment in a professional team. Together we were able to keep up and even intensify the ongoing collaboration between the Trauma Center Murnau and the ARI. Besides that the intercultural exchange and beautiful nature of Davos made my stay here an unforgettable time.

Marc-Anton Füssinger, Craniomaxillofacial Surgery, University of Freiburg, Germany

ARI Project: Musculoskeletal Regeneration Program; Project Homecell (Osteogenic differentiation of mesenchymal stem cells). I finished my medical studies in 2011, I continued with the study of dentistry in Freiburg, Germany. Since I am really interested in research concerning bone regeneration in the field of cranio-maxillo-facial surgery, I was happy to get the opportunity for a one-year-medical fellowship at the ARI. Besides the deep insight in the field of research, working and living in a multidisciplinary and international group in a wonderful environment is a great experience which I will never forget. The main focus of my work was the stimulation of mesenchymal stem cells in direction to osteogenic lineage for the treatment of bone defects.

Niklas Grüneweller, University Hospital Münster, Department for Trauma and Reconstructive Surgery, Münster, Germany

ARI Project: Biomedical Services Program; Biomechanical comparison of augmented versus non-augmented iliosacral screws in a fracture model. I came to the AO Research Institute Davos (ARI) already having an idea about the excellence of scientific research and equipment. On my first day at the ARI, I was even more impressed: Among high-end scientific equipment, the multi-lingual team with colleagues from all over the world was most fascinating. The team structure is different to German clinics, and you get much more easily in contact with people. This makes the work in ARI and the stay in Davos very pleasant. In my project, we try to answer biomechanical questions from a multi-disciplinary viewpoint. So I worked together with engineers, technicians and other physicians, who helped a lot to detect and to manage the problems we faced in my project. Besides the positive qualities of the ARI with its friendly employees, I liked the Swiss hospitality and of course the beautiful countryside at Landwassertal with its surrounding valleys Dischma, Sertig and Flüela.

Simon Hackl, Trauma Center Murnau, Germany

ARI Project: Musculoskeletal Infection Group; Development of a large animal model to study the biology of two-stage hardware exchange due to implant related osteomyelitis. During my residency in trauma surgery at the Trauma Center Murnau I had to the opportunity to do a Medical Research Fellowship in the Musculoskeletal Infection Group at the ARI. Thereby I gained further experience in research work. In addition to gaining practical skills in working with large animal models I also learned how to process the resulting samples in the bacteriology laboratory. From the beginning I was surprised by the number and variety of projects that were running concurrently. Furthermore I have really appreciated the intercultural exchange at work and spending my free time in a beautiful natural environment. So I would recommend a medical research fellowship in the ARI to every surgeon with an interest in science.

Jagoda Jalowiec, Wroclaw University of Environmental and Life Sciences, Faculty of Veterinary Medicine, Poland

ARI Project: Musculoskeletal Regeneration Program; bone regeneration: PRP-Gel as a delivery system for tissue engineering. After graduation from veterinary school in Wroclaw, Poland, I worked for two years as an equine veterinarian focusing on orthopedic surgery and regenerative medicine. As a Research Fellow I work in a unique interdisciplinary team of cell biologists, engineers and clinicians which broadened my knowledge in cutting edge orthopedic research. I appreciate the very friendly atmosphere, exchanging ideas and chance to discuss relevant problems.

Bronislaw Nowicki, University of Veterinary Medicine, Equine Hospital, Vienna, Austria

ARI Project: Preclinical Services Program; preclinical surgery. As a Veterinary Research Fellow I am predominantly working in the animal facility with laboratory animals. My job is to prepare surgical aspects of ongoing projects, take part in anesthesia, surgery and postoperative care. However as a Research Fellow I also have the opportunity to visit Laboratories where projects are prepared and attend meetings where they are planned – so I have full overview of our research projects, from the beginning to the end. It is a great and rewarding job, and good start for a research career.

Walter D. Ocampo (non-medical fellow), Universidad de Costa Rica, San José, Costa Rica

ARI Project: Biomedical Services Program; FE Modeling of osteoporotic bone. The time spent here has helped me to gain knowledge in the area of bone numerical modeling, with a very practical approach and working alongside very experienced, knowledgeable, and talented professionals. As an engineer, it has been a very enriching experience to be able to interact and collaborate with medical research fellows as well as with fellows from various other disciplines. Everything happens within a very friendly and motivating international environment.

Philipp Poxleitner, Oral & Maxillofacial Surgery, University Hospital Freiburg, Germany

ARI Project: Preclinical Services Program; Large animal models for Bisphosphonate related Osteonecrosis of the jaws (BRONJ). I worked on a project that focuses on the development and progression of BRONJ, a major issue in Oral and Maxillofacial Surgery. ARI has provided me with a fantastic environment to gain insight into planning and conducting experimental studies. Working in a multidisciplinary team with so many experts in one place was a unique experience. All the different cultures and people combined with the beauty of Davos made it an exciting and inspirational time for me.

Rukmanikanthan Shanmugam, University of Malaysia, Malaysia

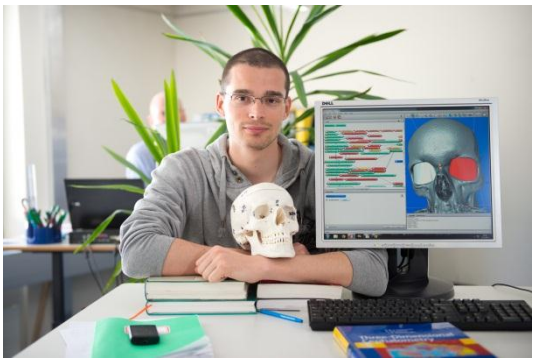
ARI Project: Biomedical Services Program; Comparison of lateral phalangeal locked plating versus standard non-locked dorsal or lateral plating. I am a senior lecturer in orthopaedics and practising orthopaedic surgeon in the University of Malaya (UM), Malaysia. I obtained my undergraduate medical degree from the Science University of Malaysia and masters in Orthopaedic surgery from UM. My subspecialty is foot and ankle surgery and deformity correction surgery using internal and external fixators. Being a lecturer in a teaching institution with a research portfolio in biomechanics, I am excited and happy to get a chance to work with the AO family through ARI, which is an excellent opportunity to establish contacts and future research collaborations.

Miguel Triana, Fundacion Cardioinfantil and Hospital Infantil San José-Universidad Ciencias de la Salud and Universidad el Bosque Bogotá, Colombia

ARI Project: Biomedical Services Program; A new concept for fracture fixation using locking implants. I am an orthopaedic trauma surgeon from Bogotá, Colombia and did my AOTrauma Fellowship in Marseille in 2004. Now I have the opportunity to work on a project proving a new concept of using locking implants for fracture fixation. With its great team the ARI is an excellent place to work and gain international experience. I am very glad with my fruitful stay in Davos and the fulfillment of my objectives.

I recommend this thrilling experience to new young orthopedic surgeons and would like to encourage them to apply for a Fellowship at the ARI.

Viktor Varjas (non-medical research fellow), University of Szeged, Hungary



ARI Project: Human Morphology Services; Workflow for improving 2D & 3D skull visualization – a novel iterative voxel/mesh based approach. Just after finishing my MSc studies as a Software Engineer specializing on Image Processing, I got the opportunity to work on an interesting project at the ARI. The main goal is to improve the 3D visualization of the skull generated from CT image to facilitate precise virtual surgery planning and diagnosis. We are focusing on the orbital (intact and fractured case) and the dental region, where current standard techniques fail to generate an appropriate 3D model because of partial volume averaging (pseudo holes) and the presence of metallic objects (streak artifacts). I really enjoy working in a wonderful place like Davos.

9 Project Abstracts by Specialties

9.1 AOCMF

Workflow for improving 2D and 3D skull visualization - a novel iterative voxel/mesh based approach (3DSkullVis) (L. Kamer)

Adequate skull visualization is essential for many diagnostic or therapeutic applications in craniomaxillofacial surgery. Two- and three-dimensional (2D/3D) image data generated from Computed Tomography (CT) and Cone Beam Computed Tomography (CBCT) scanners have become a mainstay in the pre-, intra- and postoperative assessment, as well as for planning of craniomaxillofacial surgery procedures. The quality of the 2D image data stack and 3D computer model obtained from these X-ray based tomographic imaging modalities is fairly good. However, there are still system immanent limitations and there is a need to improve 2D/3D image data of the skull. The problem zones are the orbit and dental occlusion. Even though well-known problems are well documented, they are not sufficiently addressed in today's software solutions. Currently, the surgeon and the researcher have to accept, what has been generated by the imaging workstation and/or visualized by the planning software. Additional manual adjustments are very time consuming or not feasible.

Technically, there are several shortcomings associated with CT and CBCT. Image quality may be significantly compromised by beam hardening, photon starvation, undersampling, patient motion, filtering effects or limited image resolution. For craniomaxillofacial surgery, mainly metal artifacts created by metallic dental restorations, partial volume averaging and stair steps due to limited image resolution and insufficient 3D meshing techniques significantly compromise adequate 2D and 3D data assessment in the surgeon's daily practice. They hamper proper visualization of the teeth. Metal artifacts create image streaks even affecting adjacent structures such as the mandible, maxilla, soft tissue or cervical spine. Both, partial volume averaging and insufficient meshing, compromise 3D skull visualization, mainly the bony orbit at its thinnest bone parts. Other regions such as the infraorbital and mastoid region or temporalis fossa may be affected in a similar but to less marked extent.

We would like to bring in new thoughts into 2D and 3D skull visualization and to computer modeling. We propose developing a workflow for enhanced post-processing of routine clinical CT and CBCT data to improve 2D and 3D image data quality and visualization of the skull. It will include computer tools for significant metal artifact reduction, for improved 3D mesh generation and for the repair of thin bony parts such as the orbit. A novel approach will be implemented to optimize the visualization of the dental occlusion in CT and CBCT data. It will hopefully allow for automated integration of high precision laser data taken from the dental occlusion. In a second phase, the workflow will be tested in a series of clinical data.

We hope this to set a new standard in skull visualization to enhance craniomaxillofacial diagnostic, preoperative planning and treatment. The computer tools developed might be used for clinical application, for research and development or education.

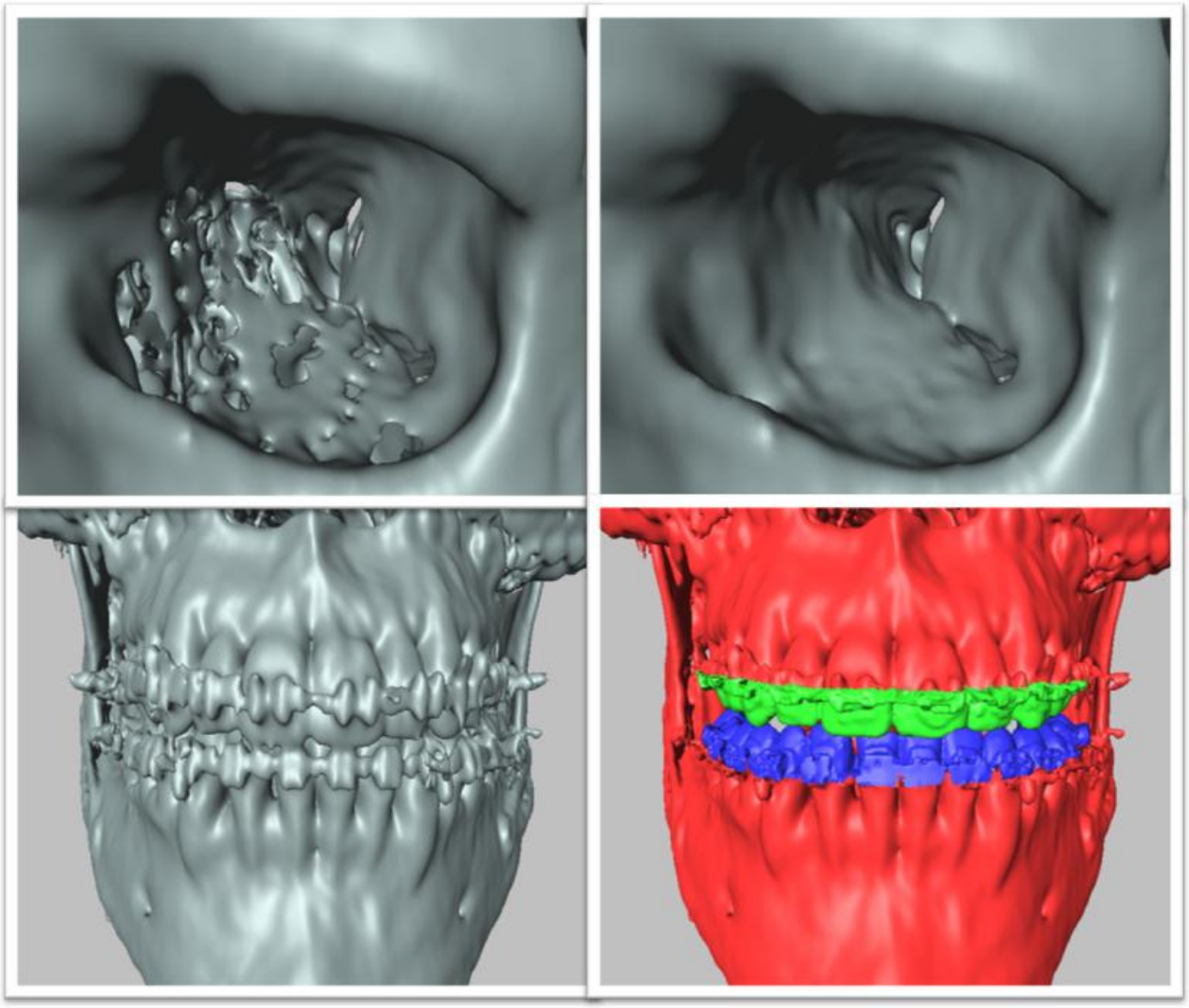


Figure 9.1.1: An automated computerized worklow has been developed with the objective to improve 3D visualization of the orbit and dental occlusion.

Development of a Preclinical model of Bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Ongoing) (M. Stoddart)

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a side effect of bisphosphonate therapy. It mainly occurs in patients receiving nitrogen-containing bisphosphonates with a prevalence reported of up to 19% in cancer patients, with cases in osteoporotic patients also reported. If diagnosis or treatment is delayed, BRONJ can develop to a severe and devastating disease. However, little progress has been made in understanding the pathophysiology of BRONJ. Therefore the aim of this study was to investigate, in collaboration with partners from the AOCMF community, the induction of BRONJ using Zoledronic acid in three different preclinical models, with the aim to establish a suitable preclinical test model to allow for detailed investigations into the development of BRONJ. Two different large animal models of BRONJ were developed, one in sheep and one in minipig. Reproducible BRONJ developed upon a physical injury trigger, in this case tooth extraction. BRONJ was confirmed using both CT and histology. The project will now look further into preventative measures.

Partners:

- Otto S (MD), Ludwig-Maximilians-University of Munich, Munich, Germany
- Voss P (MD), University Hospital Freiburg, Freiburg, Germany
- Lindhorst D (MD), Hannover Medical School, Hannover, Germany

9.2 AOSpine

Survival and Differentiation of Bone Marrow Derived Mesenchymal Stem Cells into Disc Cells when Injected into an Intervertebral Disc Organ Culture System (DISCFREQ) (Completed) (S. Grad)

For cell-based intervertebral disc (IVD) regeneration, mesenchymal stem cells (MSCs) are promising candidates, since they have the ability to differentiate into various lineages, potentially including IVD cells, and to stimulate disc cells in situ. However, open questions remain regarding the choice of the cell carrier, the injection method, and the fate of implanted MSC populations. The objective of this project was to evaluate and optimize the fate of injected MSCs in an IVD maintained in our *in vitro* organ culture system under defined loading conditions. Carrier material, cell preconditioning, and mechanical parameters were evaluated.

The main parameter used to define the physiological loading in nucleotomized discs was considered the disc height; we targeted a maximum disc height loss of 10%. Sinusoidal loading regimes were tested, with a mean load varying from 0.04 to 0.3 MPa. It was found that the mean load leading to such disc height losses should be <0.1 MPa. Moreover, to implement a complete disc height recovery, discs were maintained free swelling after loading, leading to full disc height recovery also for partially nucleotomized discs.

The behavior of human MSCs embedded in a thermoreversible hyaluronan hydrogel and implanted in an IVD in organ culture was investigated. We found that MSCs differentiated towards an IVD-like phenotype without pre-conditioning or growth factor supplementation, when cultured in hydrogel in the IVD cavity. Since there was a high hydrogel loss under loading, fibrin was tested as an alternative MSC carrier. MSCs suspended in fibrin were applied to IVDs through an endplate approach. Discs were kept unloaded for one week and then loaded at 0.06 ± 0.02 MPa for 2 weeks. Fibrin was stable in the chosen experimental conditions, as shown by histological staining of the IVD (Figure). No significant cell loss or decrease in cell viability was found in the fibrin gel after 2 weeks of loading. Combinations of these two materials (hyaluronan and fibrin) may represent an interesting future perspective and need to be checked.

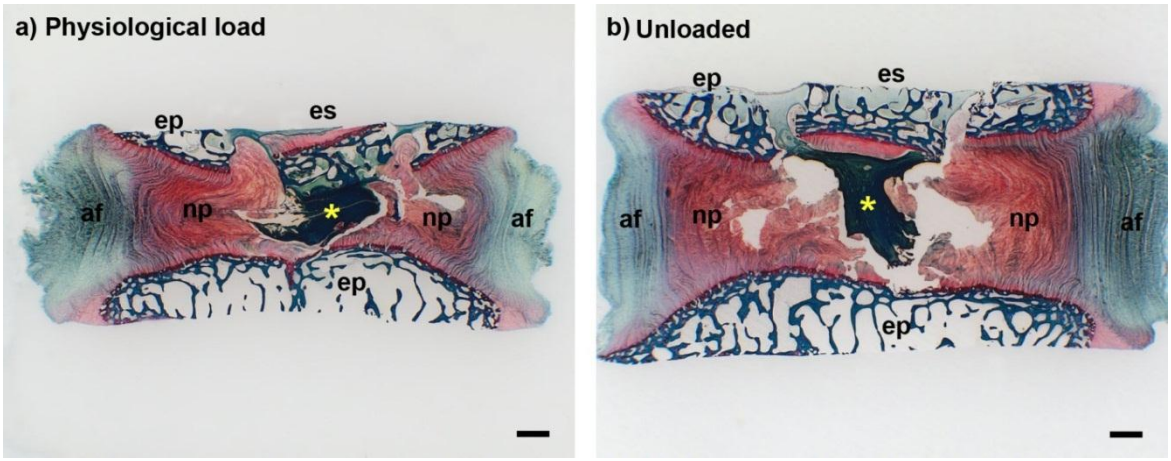


Figure 9.2.1: Safranin O/Fast-Green stained methacrylate section of partially nucleotomized intervertebral discs using an endplate approach and refilled with a fibrin gel carrier containing MSCs. a) disc following one week without load and one week of physiological load; b) unloaded control cultured for 14 days. Scale bar = 1 mm. Red: proteoglycans, blue: collagens. Yellow asterisk = fibrin gel with MSCs, af = annulus fibrosus, np = nucleus pulposus, ep = endplate, es = endplate stopper.

Pres:

Li Z, Peroglio M, Lezuo P, Pattappa G, Alini M, Grad S. An endplate approach improves the mechanical response of nucleotomized intervertebral discs. 59th Annual Meeting of the Orthopaedic Research Society, San Antonio (Texas, USA), 26-29 Jan. 2013.

Peroglio M, D'Este M, Eglin D, Grad S, Benneker LM, Alini M. *Hyaluronan hydrogel supports human mesenchymal stromal cells (hMSCs) differentiation toward the disc phenotype without growth factor supplementation.* 2013 International Society for Hyaluronan Sciences, Oklahoma City, Oklahoma (USA), 2-7 June 2013.

Pub:
Peroglio M, Eglin D, Benneker LM, Alini M, Grad S. Thermoreversible hyaluronan-based hydrogel supports *in vitro* and *ex vivo* disc-like differentiation of human mesenchymal stem cells. Spine J 13(11):1627-39, 2013.

Vadalà G, Russo F, Pattappa G, Schiuma D, Peroglio M, Benneker LM, Grad S, Alini M, Denaro V. The transpedicular approach as an alternative route for intervertebral disc regeneration. Spine 38(6):E319-24, 2013.

Partners:
- Benneker LM (PD Dr med), Inselspital, University of Bern, Switzerland
- Vadala G (MD, PhD), Department of Orthopaedics and Trauma Surgery, University Campus Biomedico Rome, Italy

Stem cell based intervertebral disc regeneration – evaluation of cell carrier and delivery strategy for pre-clinical application (TRANSDISC) (Ongoing) (S. Grad)
The aim of this project is to optimize the application of mesenchymal stem cells (MSCs) for intervertebral disc (IVD) regeneration. An IVD organ culture system is used to investigate the effect of physiological or degenerative loading. Fibrin and hyaluronan based cell carrier materials are evaluated *ex vivo* in organ culture*;* finally, the trans-pedicular delivery approach will be tested in a pilot *in vivo* study.
An initial organ culture study was undertaken to assess fibrin and MSCs contribution to IVD regeneration in under loading. Bovine IVDs with endplates were dynamically loaded in a bioreactor under "physiological" (0.1 Hz) or "degenerative" (10 Hz) conditions for 3 h/day for 7 days. Then, nucleotomies were performed and cavities filled with fibrin, MSCs in fibrin, MSCs in PBS, or PBS. Discs were physiologically loaded for additional 7 days. Results demonstrate that the implanted fibrin gel could preserve the disc height of nucleotomised IVDs following dynamic loading (Figure). Importantly, the chosen fibrin composition could withstand sustained physiological loads and maintain both disc height and viability of implanted MSCs. Future work will focus on assessing the behavior and regenerative effects of implanted MSCs in the IVD.

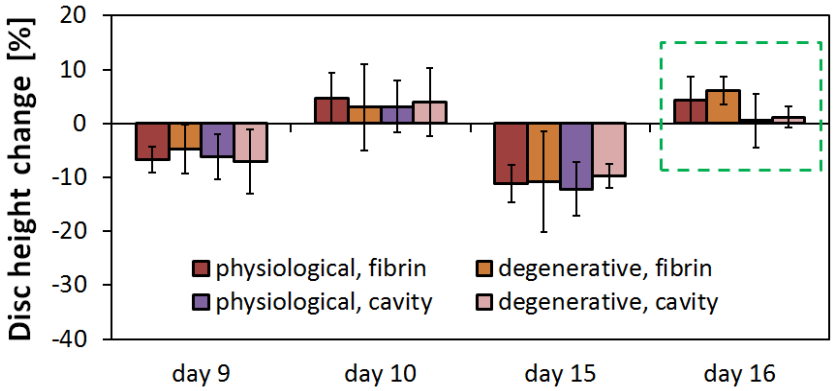


Figure 9.2.2: Disc height change (compared to disc height after dissection) in nucleotomized IVDs after loading and recovery. Red and orange are fibrin groups, purple and pink the groups without fibrin. Dashed rectangle highlights that fibrin promotes recovering of disc height.

Pres:
Janki M, Peroglio M, De Wild M, Benneker LM, Alini M, Grad S. *Effects of mechanical load and mesenchymal stem cells on bioreactor cultured intervertebral discs.* Where Science Meets Clinics Symposium, Davos (Switzerland), 5-7 Sept. 2013.

Peroglio M, Eglin D, Benneker LM, Alini M, Grad S. *Loading and carrier determine the success of stem cell delivery into degenerative discs.* 8th Combined Meeting of Orthopaedic Research Societies, San Servolo (Venice, Italy), 13-16 October 2013.

Peroglio M, Pattappa G, Lezuo P, Grad S, Alini M. *A bioreactor-based evaluation of intervertebral disc repair.* Swiss-Japanese Symposium on Musculoskeletal Research, Zürich (Switzerland), 25 Nov. 2013.

Partners:

- Benneker LM (PD Dr med), Inselspital, University of Bern, Switzerland
- Vadala G (MD, PhD), Department of Orthopaedics and Trauma Surgery, University Campus Biomedico Rome, Italy

Mesenchymal Stem Cell Chemo-Attractive Scaffolds for Intervertebral Disc Regeneration – In Vitro Studies using a Whole Organ Culture System (DISCHOME) (Completed) (S. Grad, M. Alini)

Studies have suggested that trafficking of native mesenchymal stem cells (MSCs) to injured tissue occurs in a natural healing response. Recent data indicate that homing of MSCs to damaged areas within the intervertebral disc (IVD) may also occur. Here we hypothesized that specific soluble factors are released by cells of the IVD in response to damage and that these factors are able to recruit human MSCs to the site of injury. Furthermore, injection of chemotactic factors into the nucleus pulposus may increase MSC migration into IVDs in an organ culture system.

Conditioned medium from IVD cultured under “degenerating” conditions was subjected to large scale proteomics analysis to identify potential chemo-attractants. Proteomic analysis revealed the presence of CCL5/RANTES and CXCL6 within conditioned media. Higher concentrations of CCL5 were found in the degenerative media, and chemokine immunoprecipitation showed that MSCs had a significantly reduced chemotactic migration towards CCL5-immunoprecipitated and CCL5/CXCL6 co-immunoprecipitated media. Furthermore, CCL5 was identified in bovine (Figure 9.2.3) and human disc tissue by immunohistochemistry. Hence, CCL5 may be a key chemoattractant that is produced and released by the intervertebral disc cells. These factors could be used to enhance stem/progenitor cell mobilization in regenerative therapies for early stages of disc degeneration.

The capability to induce migration of MSCs through the disc tissue towards the center of the disc was assessed by delivering chemotactic factors into the disc space. The delivery method was optimized using a hyaluronan based hydrogel carrier and release system. The aim was to develop a novel system that promotes endogenous MSC recruitment through biomaterial-based chemo-attractant delivery, as an alternative to conventional MSC-scaffold applications. MSCs recruitment was evaluated in an *ex vivo* IVD organ culture by the delivery of Stromal Cell Derived Factor-1 (SDF-1) using a thermoreversible hyaluronan-based system composed of hyaluronan-poly(N-isopropylacrylamide) (HA-pNIPAM) as a carrier. SDF-1 containing HA-pNIPAM gels were injected in a bovine *ex vivo* model in a cavity created in the nucleus pulposus. MSCs were then seeded on the top of the cartilaginous endplate. MSCs were recruited from the endplate towards the cavity created in the IVD. This recruitment was significantly enhanced by SDF-1-HA-pNIPAM hydrogels. This study demonstrated that the thermoreversible HA-PNIPAM hydrogel is a suitable carrier for CXCL12/SDF-1 delivery in the IVD, being able to recruit MSCs towards an injured disc.

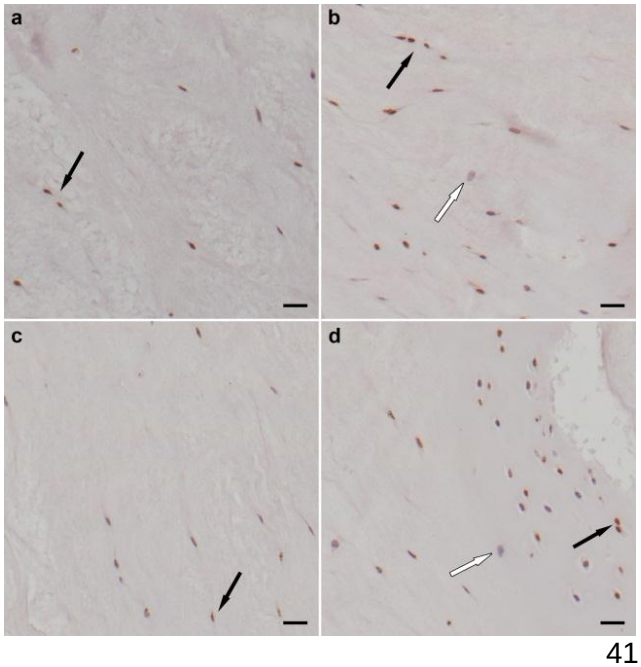


Figure 9.2.3: CCL5 immunolabelling of bovine intervertebral disc sections. (a) AF and (b) NP regions of discs cultured under degenerative (HF) conditions; (c) AF and (d) NP regions of discs cultured under physiological (LF) conditions. Black arrows indicate CCL5 positive cells; white arrows indicate CCL5 negative cells. Scale bar = 20 µm.

Pres:
Leite Pereira C, Peroglio M, Pattappa G, D'Este M, Eglin D, Goncalves R, Grad S, Barbosa M, Alini M. *Development of chemoattractant delivery system for mesenchymal cells recruitment to intervertebral disc.* 26th European Conference on Biomaterials, Madrid (Spain), 8-12 Sept. 2013.

Pattappa G, Peroglio M, Sakai D, Mochida J, Benneker LM, Alini M, Grad S. *Mesenchymal stem cell homing into the intervertebral disc: a chemotactic induced response.* European Cells & Materials Annual Conference, Davos (Switzerland), 23-25 June 2013.

Grad S et al. *Role of chemokines in stem cell homing into the degenerative disc*. 2nd International Philadelphia Spine Research Symposium, November 6-8, 2013, Philadelphia. Invited lecture.

Partners:
- Barbosa M (Prof), Instituto de Engenharia Biomédica (INEB) and Universidade do Porto, Portugal
- Sakai D (Prof), Tokai University School of Medicine, Kanagawa, Japan

Role of the intervertebral disc in the development and progression of spinal deformities (DISCFORM) (Ongoing) (S. Grad)
The etiology of spinal deformity in idiopathic scoliosis is still unclear to date, both with respect to initiation and progression of the disease. It is thought that asymmetric loading is involved in the disorder, although there is little information about the cause of these inappropriate forces acting on the spine. While the influence of genetic factors has been partially identified, the role of the intervertebral disc in the development of idiopathic scoliosis is not obvious. The aim of this project is to elucidate molecular differences between disc cells from patients with idiopathic scoliosis in comparison with cells from healthy individuals. In collaboration with the Hadassah Medical Center in Israel and the Novosibirsk Institute of Traumatology and Orthopaedics, annulus fibrosus and nucleus pulposus cells were obtained from patients undergoing surgery for scoliosis correction. RNA was isolated from the cells in order to gain microarray gene expression profiles that are then compared to the profiles of cells from healthy individuals. Molecules with different gene expression pattern are also evaluated at the protein level using immunohistochemistry on sections from scoliotic and healthy discs. Finally, the effect of asymmetric loading will be investigated in an organ culture model. Variations in the expression of structural or regulatory molecules may provide insight in underlying mechanisms of spinal deformities and may identify new targets for early therapeutic intervention.

Partners:
- Schroeder J (MD), and Kaplan L (Prof), Hadassah Hebrew University Medical School, Jerusalem, Israel
- Mamonova E (PhD), Innovative Medical Technology Center, Novosibirsk, and Mikhail Sadovoy (Prof), Novosibirsk Research Institute of Traumatology and Orthopaedics, Russia
- Haglund L (Prof), McGill Scoliosis and Spine Group, Montreal, Canada

9.3 AOTrauma

Development of a biofeedback system for bone healing and its application for mechano-biological research (ImpCon 2) (Ongoing) (M. Windolf)

Problem: Flexible internal fixation aims at improving induction of callus by imposing confined, reversible displacement at the fracture site. One of the main issues to be addressed is still related to the exact role of implant stiffness and adjustment of the structural flexibility to create an optimal environment for fracture repair. Improving the technology for internal fixation by necessity relies on improved understanding of the mechano-biology of fracture repair. Creating defined mechanical conditions at the fracture site with continuous data collection shall provide valuable information.

Goal: This follow-up study of the previous project 'ImpCon' aims at refining a recently introduced implant system for research with biofeedback technology and its in-vivo application in an ovine model in order to extent the current mechano-biological knowledge on fracture repair.

Results: Issues from in-vivo pilot trials revealed the necessity to further optimize the system. Several modifications and improvements were implemented in the electronic modul and on the fixation hardware. The system design was verified in bench testing. To study the impact of fixation stiffness on the course of fracture healing, six sheep were operated with either high- or low-axial plate stiffness. Promising first results become obvious and are currently under evalutation. In parallel, the development of a prototype implant capable to actively change its axial stiffness was successfully accomplished.

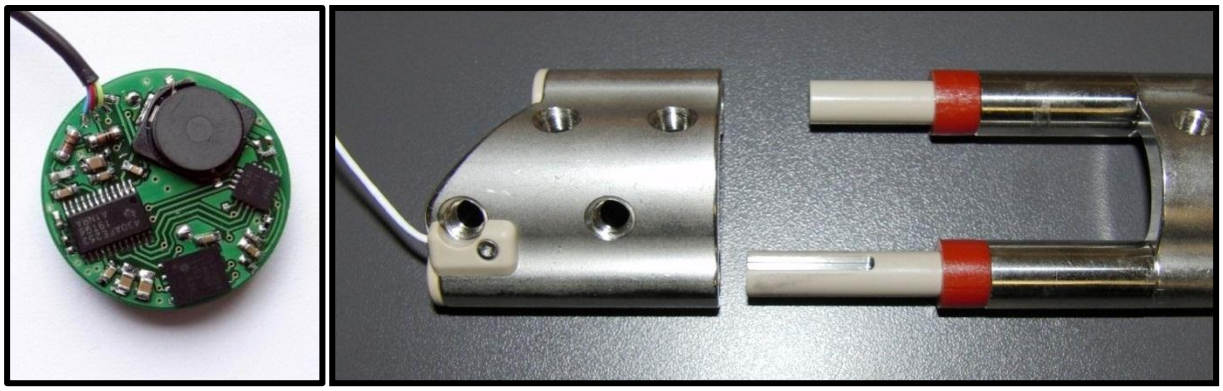


Figure 9.3.1: Implant system for research with biofeedback technology: Implantable electronics (left) and instrumented internal fixator (right).

Theses:

Viehöfer U. Aktive Anpassung der mechanischen Eigenschaften eines Osteosyntheseimplantats zur Förderung der Knochenheilung. 2013. RWTH Aachen (Diplom / Radermacher K, Dietz-Laursonn K, Windolf M).

Partners:

- Mathis H (Prof, PhD), Institute for Communication Systems, Hochschule für Technik, Rapperswil, Switzerland
- Radermacher K (Prof, PhD), RHTW Aachen University, Aachen, Germany

AO Implant Positioning Assistance (SimpCAS X-in-one) (Ongoing) (M. Windolf)
Problem: Current solutions for computer aided surgery lack of wider acceptance due to considerable disadvantages regarding complexity, costs and effectiveness.

Goal: A simplified Computer Aided Surgery system shall be developed utilizing a conventional C-arm as imaging and navigation means rendering additional tracking and imaging equipment unnecessary. The concept aims to improve a variety of surgical routine interventions in trauma and orthopedics.

Results: Besides PFNA (DepuySynthes Inc.) application, distal interlocking and adjustment of femoral anteversion, the system was further enhanced to aid in general anatomical plating (e.g. PHILOS, DepuySynthes Inc.) or Dynamic Hip Screw insertion. Hardware requirements were consequently reduced to increase efficiency and simplicity. A comprehensive accuracy and performance analysis was carried out. A first approach for providing additional real-time feedback was developed and successfully tested.

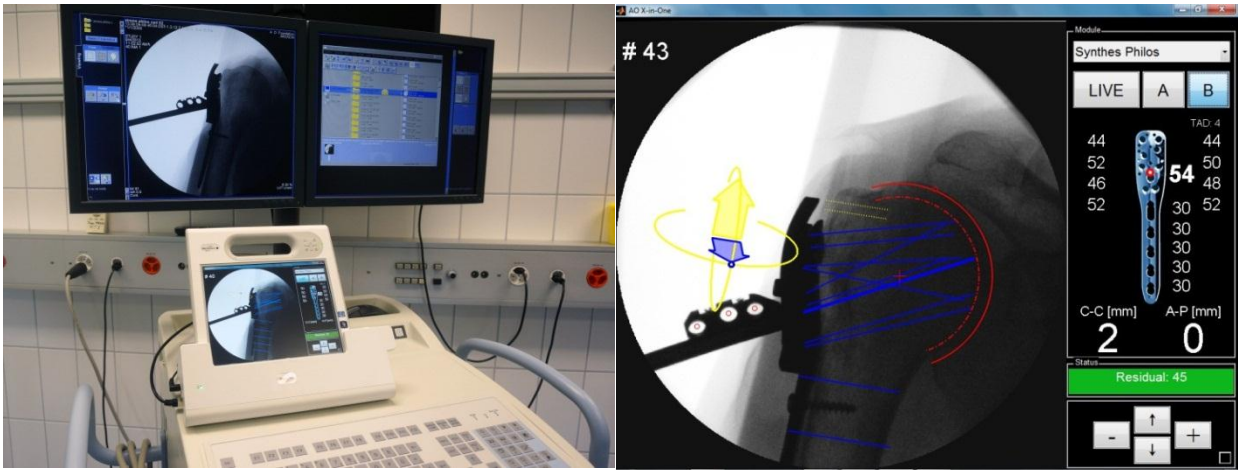


Figure 9.3.2: Left: Medical tablet computer with X-in-One software connected to a standard C-arm.
Right: Software screenshot. Screw trajectories of a PHILOS plate (blue lines) projected into an X-ray image.

Theses:
Wolfrum C. Entwicklung eines röntgenbasierenden chirurgischen Navigationskonzepts mit Echtzeit Feedback. 2013. Hochschule Ansbach (Bachelor / Boger A, Windolf M).

Partners:
- Blauth M (Prof, MD), University Hospital Innsbruck, Austria
- Mosheiff R (Prof, MD), Hadassah University Hospital, Jerusalem, Israel
- Liebergall M (Prof, MD), Hadassah University Hospital, Jerusalem, Israel
- Boger A (Prof, PhD), University of applied Sciences, Ansbach, Germany

Cement augmentation methods for improved fracture fixation in osteoporotic bone (ImplantAug) (M. Windolf)

Problem: The landscape of trauma surgery will significantly shift towards geriatric patients. Despite improvements in implant design, one major complication, namely failure at the bone implant interface (cut-out), remains in the treatment of fragility fractures throughout various anatomical regions. To reduce the cut-out risk, cement augmentation at the bone-implant interface is a potential method to strengthen the implant purchase. Furthermore, it allows early and confident mobilization of elderly patients, which in turn can decrease morbidity and mortality rates. From an economic standpoint, not only direct costs for re-operations, but also aftercare and rehabilitation periods may be significantly reduced by augmentation approaches.

Goal: The overal goal of this project was to evaluate potential implant augmentation procedures at several anatomical key locations in terms of biomechanical benefits and related risks. It was also aimed to support the development process of new augmentation related fixation devices and cement injection procedures to optimize and establish the concept in clinics.

Results: An extensive amount of sub-studies have been carried out under the umbrella of this large frame project (former AugTech) in the last 5 years (see ARI Activity Reports 2009-2012). The studies can be grouped in three main topics: 1) General studies delivering base-line data concerning the behaviour of cement in bone; 2) Classical biomechanical studies comparing augmented with non-augmented implants in terms of implant stability; 3) Studies focusing on potential risk factors and biological aspects associated with cement augmentation.

1) General studies

Several basic studies delivered important base-line data which were used in further experiments focusing on osteoporotic anatomical key regions. One *in vitro* study, for example, investigated injectability and distribution of different cements. This helped in the development of optimal injection methods and instruments. Most recently, two studies have been carried out investigating cement flow behavior. In one of the studies, a time-lapsed CT approach was developed to visualise precisely the cement flow distribution within the bone structure at incremental injection steps. Combined with microFE modeling, this approach allows assessment of the mechanical properties of the augmented bone during injection. The second study focused on analysing the allocation of bone cement in artificial inhomogeneous cancellous bone structures. The results of both studies can help in developing a procedure for pre-operative planning of the cement flow. Such a procedure could for example help in predicting cement leakage.

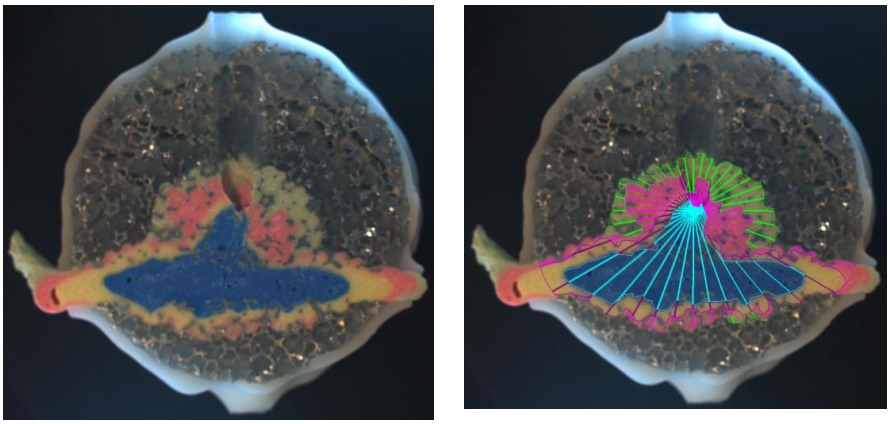


Figure 9.3.3: Allocation of bone cement in surrogate osteoporotic trabecular bone structures visualized by stepwise injection of bone cement colored with acrylic powder (left) together with evaluaton of the cement flow direction (right).

2) Biomechanical studies

A clear biomechanical potential of augmentation procedures was demonstrated in various applications, namely at the hip (Dynamic Hip Screw, Proximal Femoral Nail Antirotation), at the foot (Expert Hindfoot Arthrodesis Nail, HCS screws for calcaneous fractures) at the proximal humerus (PHILOS plate), at the distal femur (LCP DF plate) and at the proximal tibia (LCP PLT plate). However, recent studies have also shown that augmentation cannot be applied as a routine concept to every implant.

For three cannulated hip screws, for example, augmentation did not show an improvement in terms of stability in a femoral neck fracture model. Most recently, a study comparing augmented versus non-augmented SI-screws in cadaveric pelvices was performed. Augmentation improved screw purchase in the sacrum significantly. The stability of the whole construct, however, was not improved due to sintering of the washer into the ilium. For some of the above mentioned studies, sophisticated computer models were developed, allowing rapid and systematic pre-evaluation of several test parameters (eg. which screws to augment, how much cement to inject, cement location).

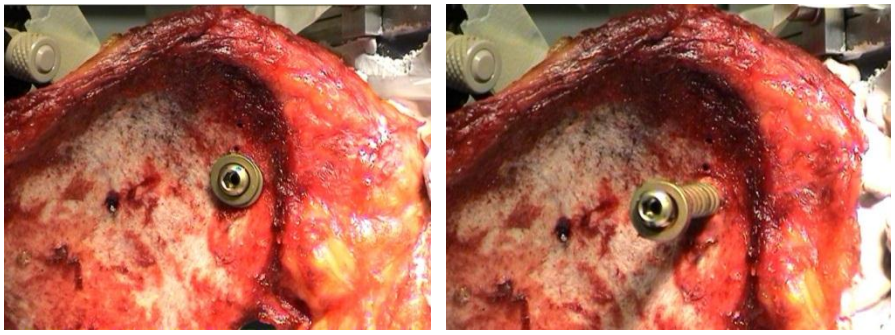


Figure 9.3.4: Cadaveric pelvis before (left) and after (right) biomechanical testing. The typical failure mode as seen in clinics (screw turnout) was reproduced.

3) Studies focusing on potential risk factors
Aside from biomechanical aspects, it was aimed to continuously improve and optimize augmentation techniques in terms of safety and efficacy. Associated risks can be diminished by reducing the required amount of cement and optimizing the cement properties and locations. Adverse side effects of implant augmentation such as thermal necrosis were critically investigated. Studies revealed, for example, negligible heat generation for augmentation of hip implants and the PHILOS plate if properly applied—important base line knowledge for clinical application.

Invited Pres:
Windolf M, Experimentelle Überlegungen zu Augmentationstechniken. 2013. DKOU.

Pres:
Blankstein M, Widmer D, Götzen M, Fliri L, Richards RG, Gueorguiev B, Windolf M. Cement augmentation of the Perforated Proximal Femur Nail Antirotation (PFNA) blade does not cause critical femoral head intra-osseous pressure elevation. 2013. SICOT.

Blankstein M, Widmer D, Hofmann-Fliri L, Götzen M, Richards RG, Gueorguiev B, Windolf M. Messung des intraossären Drucks im Femurkopf während der Zementaugmentation von Klingenimplantaten. 2013. DKOU.

Blazejak M, Windolf M, Nicolino T, Büchler L, Gueorguiev B, Hofmann-Fliri L. In-vitro temperature evaluation during cement augmentation of proximal humerus plate screw tips. 2013. ECTES.

Eberli U, Fliri L, Lorenzetti S, Windolf M, Stadelmann V, Gueorguiev B. Decreased cement stiffness does not improve the anchorage of augmented implants in osteoporotic bone. 2013. SBMS.

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Klos K, Rausch S, Mückley T, Wolf U, Windolf M, Gueorguiev B. Biomechanischer Vergleich zwischen einer winkelstabilen Platten- und einer zementaugmentierten Schraubenosteosynthese zur Versorgung von Kalkaneusfrakturen. 2013. ISF.

Nicolino T, Götzen M, Hofmann-Fliri L, Gueorguiev B, Blauth M, Windolf M. Implant augmentation in osteoporotic femoral neck fractures: No biomechanical advantage in a cadaveric model. 2013. ECTES.

Nicolino TI, Götzen M, Barla J, Gueorguiev B, Windolf M, Hofmann-Fliri L. Aumentación de implantes en fracturas osteoporoticas de cuello femoral: No se observan ventajas biomecánicas en un modelo cadavérico. 2013. 50° Congreso Argentino de Ortopedia y Traumatología.

Röderer G, Scola A, Hofmann-Fliri L, Schmölz W, Gebhard F. Cement augmented locked plating of a proximal humerus fractures model in consideration of local bone quality. 2013. FFN.

Röderer G, Scola A, Schmölz W, Fliri L, Gebhard F. Screw augmentation in locked plating of proximal humerus fractures. A biomechanical *in vitro* study. 2013. EFORT.

Röderer G, Scola A, Schmölz W, Fliri L, Gebhard F. Biomechanische *in vitro* Untersuchung der Zementaugmentation am proximalen Humerus basierend auf der lokalen Bestimmung der Knochenqualität. 2013. VBC.

Röderer G, Scola A, Schmölz W, Hofmann-Fliri L, Gebhard F. Die zementaugmentierte winkelstabile Plattenosteosynthese am proximalen Humerus. Eine biomechanische *in vitro* Studie. 2013. DKOU.

Röderer G, Scola A, Schmölz W, Hofmann-Fliri L, Gebhard F. Einfluss der Zementaugmentation auf die Primärstabilität einer winkelstabilen Plattenosteosynthese am Modell der proximalen Humerusfraktur. 2013. DGfB.

Wähnert D, Hofmann-Fliri L, Kösters C, Raschke MJ, Richards RG, Gueorguiev B, Windolf M. Das Potential der Implantataugmentation bei der Versorgung osteoporotischer distaler Femurfrakturen. 2013. DKOU.

Wähnert D, Hofmann-Fliri L, Raschke MJ, Richards RG, Windolf M. Implant augmentation as a new concept in the treatment of osteoporotic distal femur fractures. A biomechanical study. 2013. ECTES.

Zderic I, Unholz C, Windolf M, Gueorguiev B, Stadelmann VA. Cement flow monitoring and assessment of injection forces during vertebroplasty. 2013. DKOU.

Zderic I, Windolf M, Gueorguiev B, Stadelmann V. Monitoring of cement distribution in vertebral bodies during vertebroplasty. 2013. CORS.

Pub:

Blazejak M, Hofmann-Fliri L, Büchler L, Gueorguiev B, Windolf M. In vitro temperature evaluation during cement augmentation of proximal humerus plate screw tips. Injury 2013 Oct;44(10):1321-6.

Götzen M, Nicolino T, Hofmann-Fliri L, Blauth M, Windolf M. Metaphyseal screw augmentation with PMMA oft he LISS-PLT plate improves angular stabiltiy in osteoporotic proximal third tibia fractures a biomechanical study in human cadaveric tibiae. J Orthop Trauma 2013; Epub Sept 26.

Röderer G, Scola A, Schmölz W, Gebhard F, Windolf M, Hofmann-Fliri L. Biomechanical *in vitro* assessment of screw augmentation in locked plating of proximal humerus fractures. Injury 2013 Oct;44(10):1327-32.

Sermon A, Hofmann-Fliri L, Richards RG, Flamaing J, Windolf M. Cement augmentation of hip implants in osteoporotic bone: How much cement is needed and where should it go? J Orhtop Res 2014 Mar;32(3):362-8. Epub 2013 Nov 20

Theses:
Münch C. Entwicklung eines standardisierten Testmodells für den proximalen Humerus am Beispiel einer neuen Zementaugmentations-Technik. 2013. Technische Universität Hamburg-Harburg. (Diplom / Morlock M, Estorff O, Windolf M, Hofmann L).

Partners:
- Blauth M (Prof, MD), Medical University Innsbruck, Austria
- Röderer G (MD), Ulm University, Germany
- Raschke M (Prof, MD), University Hospital Münster, Germany
- Boger A (Prof, PhD), University of applied Sciences, Ansbach, Germany
- Weber A (PhD), DePuy Synthes GmbH, Solothurn, Switzerland
- Morlock M (Prof, PhD), TU Hamburg-Harburg, Germany

Prophylactic reinforcement of the proximal femur to prevent secondary hip fractures (ProphylacticAug) (Ongoing) (M. Windolf)
Problem: After an osteoporotic hip fracture, the risk of sustaining a second fracture at the contralateral hip increases significantly. An invasive prophylactic reinforcement of the contralateral limb during operation of the primary fracture could be justified for high-risk patients.

Goal: To develop an effective procedure for prevention of secondary hip fractures by reinforcing the intact contralateral femur mechanically.

Results: For designing a fixation solution, a test model was developed consisting of dynamic numerical simulations as pre-evaluation tool and of a cadaveric free-fall setup. The model was applied to a first potential fixation approach consisting of a V-shaped implant-cement system with a small plate and two cannulated locking screws. The developed dynamic simulations showed good correlation with the biomechanical test results in terms of failure load, energy uptake and stiffness. Even though the tested fixation approach has not offered a clinically relevant solution yet, it can be used as starting point for future developments.The combination of finite element simulations as a pre-evaluation tool together with biomechanical tests provide a powerful tool to systematically investigate possible solutions for the prophylactic reinforcement of the proximal femur.

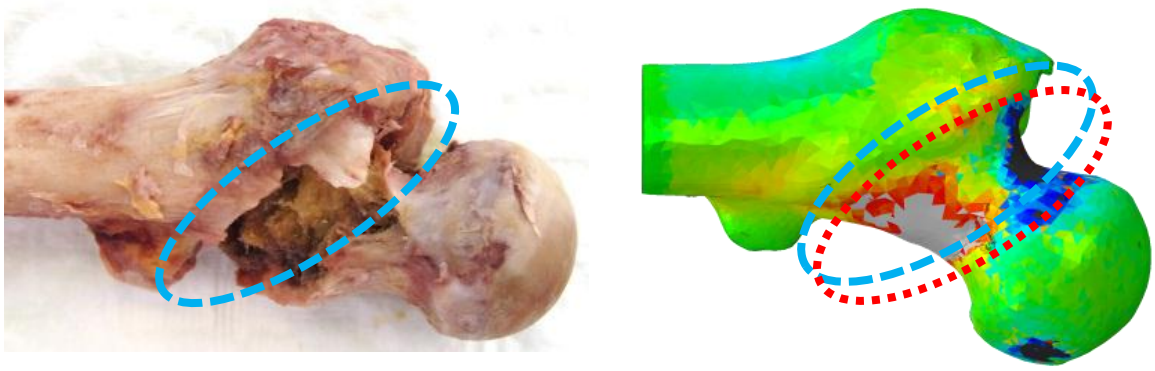

Figure: 9.3.5: Visual comparison of experimental and virtual fracture pattern of a proximal femur.

Pres:
Widmer D, Hofmann-Fliri L, Blankstein M, Blauth M, Zweifel E, Gueorguiev B, Windolf M. Prophylaktische Verstärkung des proximalen Femurs im porotischen Knochen. 2013. DKOU.

Partners:
- Blauth M (Prof, MD), Medical University Innsbruck, Austria
- Schmölz W (Prof, PhD), Medical University Innsbruck, Austria

The effect of subchondral cement augmentation on the overlying cartilage (CartAug) (ongoing) (L. Hofmann-Fliri)

Problem: When bone cement is placed around an implant close to a joint, there is a risk of harming the subchondral bone, which is an important region for nutrition and remodeling of the overlying cartilage. In contrast to other biological impacts, the effect of cement augmentation on the overlying articular cartilage is still poorly understood.

Goal: To investigate the potential effects in presence of bone cement in the subchondral region on the adjacent articular hyaline cartilage in an ovine preclinical model.

Results: Placement of a metal screw in the subchondral bone of proximal sheep tibiae did not lead to pathologic changes in the overlying cartilage after a follow-up of 2 months. In addition, subchondral injection of polymethylmethacrylate (PMMA) in the proximal tibiae and the distal ovine femora does not seem to affect the viability of the hyaline cartilage after a follow-up of 2 months. Macroscopic (ICRS) as well as microscopic histological arthritis scores (modified Mankin) were very low for both groups and did not differ from the untreated contralateral control joints. Evaluation of 4 months follow-up groups is currently ongoing.

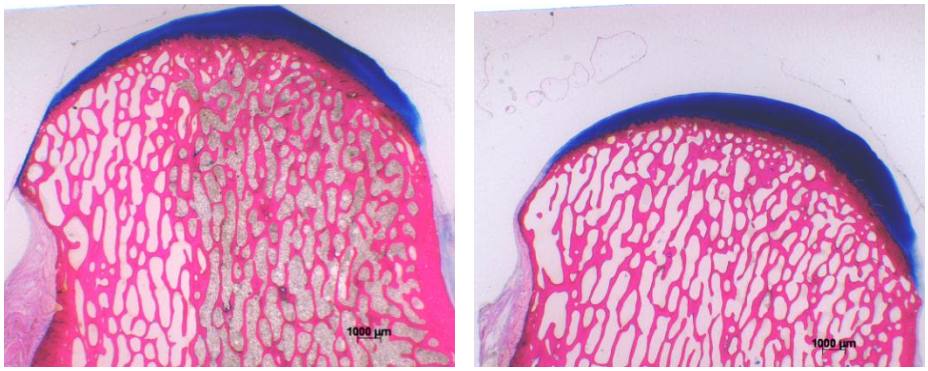

Figure 9.3.6: Histological sections (Giemsa-Eosin) of a subchondrally augmented ovine femur condyle (left) and the corresponding contralateral control (right) after a follow-up of 2 months. No pathologic changes in the cartilage and subchondral bone are visible dispite a large amount (2.3 ml) of subchondrally injected PMMA.

Partners:

- Blauth M (Prof, MD), Medical University Innsbruck, Austria
- Fairclough J (Prof, PhD), Spire Cardiff Hospital, Wales
- Von Rechenberg B (Prof, DVM), University of Zurich, Switzerland

Influence of reduction and screw orientation on stability of sacroiliac joint stabilization (SiStab) (I. Zderic)

Problem: Posterior pelvic ring injuries are common in high energy trauma accidents. Internal screw fixation allows early rehabilitation and decrease of mortality rate. However, there is little knowledge regarding the influence of screw orientation on stability. Moreover, there are controversies whether the quality of reduction has an effect on functional outcomes.

Goal: To investigate the biomechanical stability in an artificial pelvic model simulating sacroiliac dislocation stabilized with two screws in the S1 corridor, comparing thereby oblique to parallel screw orientation and anatomical to non-anatomical reduction.

Results: Significant lower stability was detected in the models with non-anatomical sacroiliac joint reduction compared to the anatomically reduced pelvises. No significant differences in terms of stability were observed between the models with different screw orientations.

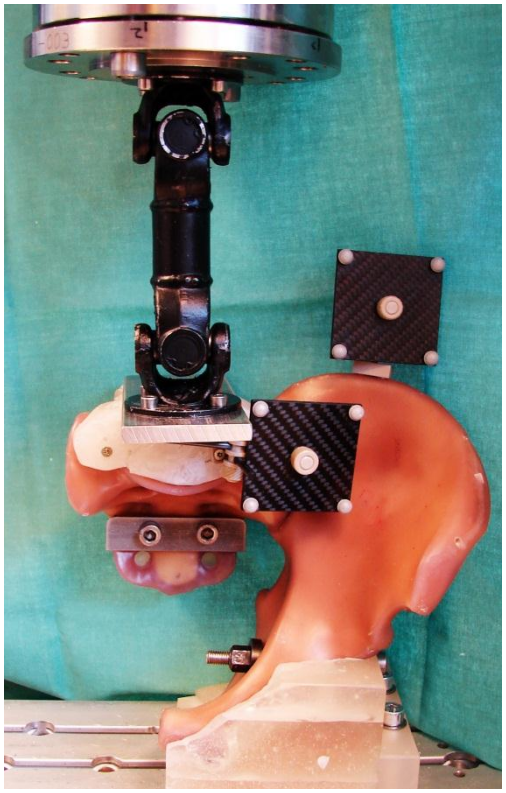

Figure 9.3.7: A hemi pelvis mounted for mechanical testing with attached markers for motion tracking.

Partners:

- Sancineto C (Prof, MD), Italian Hospital, Buenos Aires, Argentina
- Barla J (MD), Italian Hospital, Buenos Aires, Argentina

Comparison of lateral phalangeal locked plating versus standard non-locked dorsal or lateral plating (PhalFix) (M. Ernst)

Problem: Early mobilization following hand injuries is recommended to prevent stiffening and loss of range of motion. In some fractures of the proximal phalanx, adequate surgical stabilization is required. The current standard procedure is dorsal plate fixation. However, it carries the risk of adhesion or even rupture of the extensor tendon. Although considered mechanically inferior, lateral plating is less disruptive to the extensor mechanism. With the recent availability of locking plates, it might become a valid alternative to the conventional technique.

Goal: This biomechanical study investigated the stability of dorsal versus lateral plating in the proximal phalanx using a novel anatomical lateral locking plate and a standard non-locking plate currently used for treatment of phalangeal fractures.

Results: Instrumentation with the locking plate provided at least as good stability as the conventional non-locking implant and under certain loading conditions showed even higher construct stiffness. Predominant mode of failure was cortical breakage and usually occurred through the most dorsal screw hole of the proximal bone fragment into the fracture line. Along with its beneficial aspects regarding interference with the surrounding soft tissue, lateral locked plating can be considered as a genuine alternative to the conventional technique.

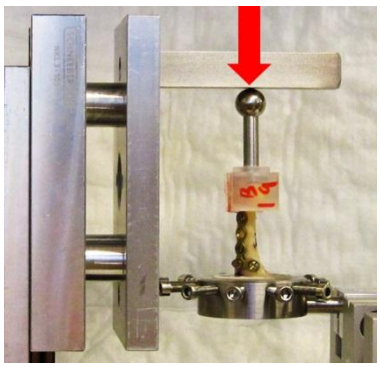

Figure 9.3.8: Biomechanical testing of a proximal phalanx instrumented with a dorsal non-locking plate.

Pres:

Ernst M, Kanthan SR, Wahl D, Windolf M, Gueorguiev B. Is locked lateral plating biomechanically superior to conventional plate fixation in the proximal phalanx? 2014. ECTES.

Ernst M, Kanthan SR, Wahl D, Windolf M, Gueorguiev B. Angular Stable Lateral Plating Is A Valid Alternative To Conventional Plate Fixation In The Proximal Phalanx. 2014. EFORT.

Partner:

- Haag R (MSc), DePuy Synthes, USA

Human Morphology Service Center (database of CT scans, 3D virtual bone models and 3D statistical shape and grey value models) (H. Noser)

It forms a sustainable umbrella project for collecting medical image data, mainly Computed Tomography (CT) data of unaffected bone, Peripheral Quantitative CT (pQCT) data, and know how in image processing and analysis for efficient use in related projects. Currently more than 2000 CT data and bone computer models are available. Moreover, computer tools have been developed for creating statistical shape models (SSM) of bones and for applying them in many related projects. Based on SSMs the software tools enable us to efficiently visualize major bone shape variations, to measure semi-automatically distances and angles on bones, to investigate bone stock distributions, to design averaged pre-shaped plates shapes, or to design virtual bones with specific bone shapes containing particular bone stock distributions (e.g. osteoporotic women).

3D statistical bone density distribution at anatomical key regions and its application for osteosynthesis optimization in osteoporotic bone (SynPorOpti) (L. Kamer)

Fragility fractures involve all kinds of bones. Apart from spinal fractures predominantly metaphyseal areas of long bones are affected. Fracture fixation may be compromised by a reduced bone mass and altered bone structure which may result in an increased number of complications and fixation failures. Clinical outcome could be improved by increasing the anatomical knowledge about the statistical spatial distribution of the local amount of bone available in osteoporotic key regions and about its intra- and inter-individual variations. Transferring these data to computer simulations might be useful for systematically improving implant anchorage in osteoporotic bone. The objectives of the study are to perform a three-dimensional (3D) anatomical study of metaphyseal sites of osteoporosis relevant regions based on peripheral quantitative CT (pQCT) scanning, creating 3D statistical anatomical computer models of osteoporosis key regions (=3D BMD maps), to demonstrate the inter- and intra-individual spatial variations of the bone mineral density (BMD), and to identify potential anatomical sites showing invariable, good bone stock with regard to BMD. Secondly a standardized interface to incorporate 3D BMD maps into existing Finite Element approaches to virtually test implant designs and locations in terms of fixation strength have to be defined. Thirdly the feasibility of the concept on a representative region (proximal Femur) has to be assessed.

The biomechanical relevance of a statistical model of the proximal humerus was investigated by transferring the model into a Finite-Elements environment and comparing it against individual bones. The study was carried out on the example of PHILOS (DepuySynthes Inc.) plating at the proximal humerus.

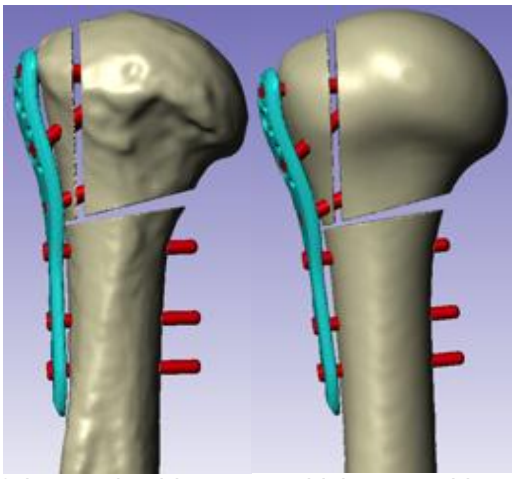

Figure 9.3.9: Computer model of the proximal humerus which was subjected to Finite Elements simulation; the results of the contributing single models were compared with the corresponding statistical mean model.

Partners:

- Blauth M (Prof, MD), Department of Trauma Surgery and Sportsmedicine, Medical University of Innsbruck, Austria
- Popp AW (MD), Department of Osteoporosis, Inselspital Bern, University Hospital and University of Bern, Switzerland
- Lenz M (MD), University Hospital Jena, Department of Trauma, Hand and Reconstructive Surgery, Germany
- Röhrle O (Prof, PhD), University of Stuttgart, Germany

Cortical and trabecular bone remodeling of the proximal humerus - impact on the fracture zones (PorOsHum) (ongoing) (C. Sprecher)

Fractures of the proximal humerus are directly related to osteoporotic bone remodeling processes in elderly people. Studies at the distal radius and the tibia recently have shown that beside the trabecular bone loss, also the microstructural bone remodeling processes at the cortical bone have a critical impact on the fracture risk. Despite the high incidence of proximal fractures in the humerus of elderly people, little is known about the microstructural bone remodeling processes of the cortex at the fracture sides of the humerus. Evaluation of the microstructural bone remodeling processes is performed in a representative collective with a wide range of bone mineral density [BMD]). The cortical thickness and cortical porosity are analyzed by HR-pQCT (resolution 82 µm) and histological sections (Figure 9.3.10).

The current results show overall a decreasing cortical thickness and an increasing porosity in comparison to the BMD values.

Osteoporotic bone remodeling processes highly affect the cortical microstructure of the proximal humerus. The cortical thickness is highly reduced with a concurrent increase of the cortical porosity (Figure 9.3.10). As the cortex at the surgical neck has a high influence on the stability, the microstructural bone remodeling processes are very likely to highly contribute to the fracture risk in elderly people.

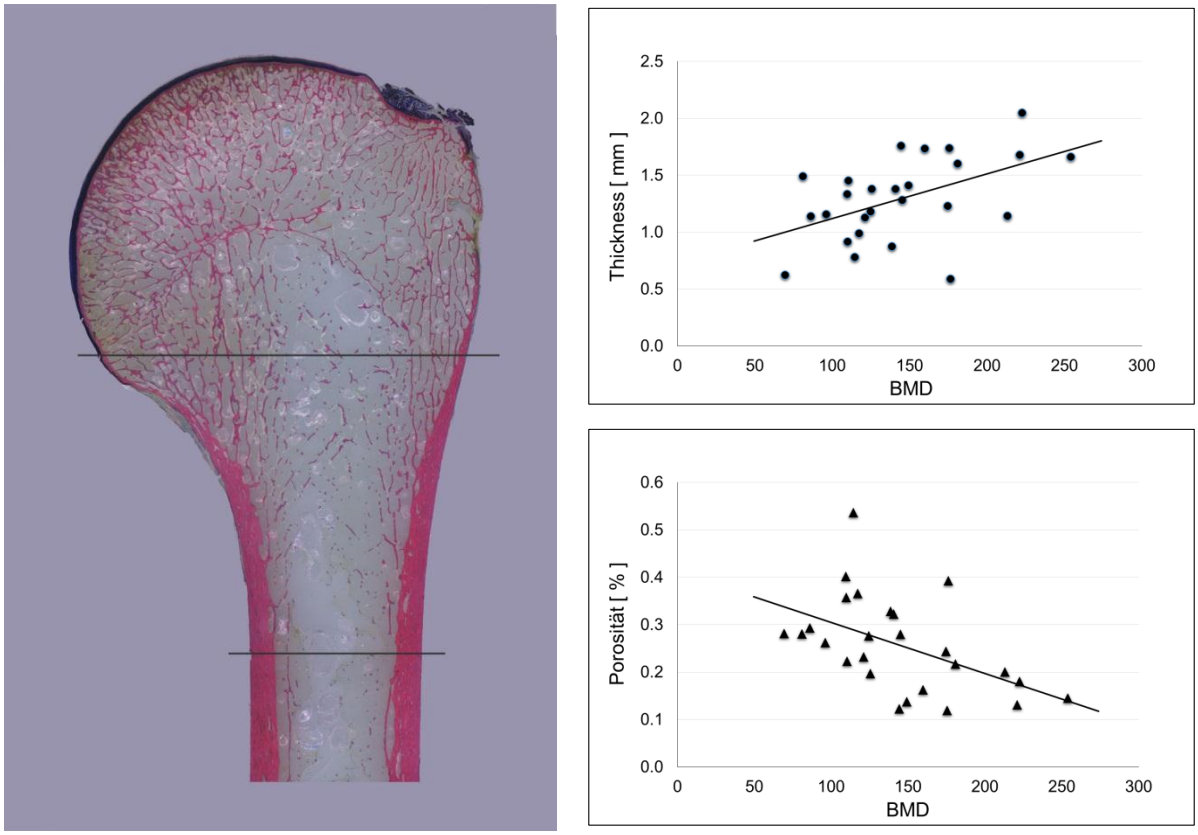

Figure 9.3.10: Giemsa-Eosin stained histological section through a proximal humerus (left) and the cortical thickness and porosity versus BMD in scatter plots determined by HR-pQCT (right).

Partners:

- Blauth M (Prof, MD), Department for Trauma Surgery, University of Innsbruck, Austria
- Oh CW (Prof, MD), Department of Orthopedic Surgery, Kyungpook National University Hospital, South Korea
- Schmidutz F (MD), Helfen T (MD) and Milz S (Prof), Department of Orthopedic Surgery, University of Munich (LMU), Germany

Pre-activation of bone cells for faster healing after surgery (BonePrep) (V. Stadelmann)

Rapid patient mobilization after surgery has been proven to reduce patients' morbidity. Since numerous bone surgeries are planned more than a week in advance, the waiting time between planning and surgery could be used to activate the bone metabolism so it reaches its maximal healing potential immediately post-op. Our aim was to test if pre-activating stem cells ahead of surgery could accelerate healing. In this study, we tested the effect of pre-mobilization of mesenchymal stem cells with granulocyte colony stimulating factor (G-CSF) in rats with a femoral critical size defect. In short a PEEK plate was used to stabilize 4.5mm segmental defect in three groups of F344 Fisher rats (10µg human recombinant G-CSF daily for five days pre-operatively (group1), post-operatively (group2) or postoperative saline control (group 3). Defect healing was monitored with *in vivo* micro computed tomography for 210 days post-op. The contralateral femurs were scanned post-mortem to compute their cortical thickness and bone density. White blood cells (WBC) from blood samples collected at -5, 0, 5 and 60 days were sorted for CD34+ and CD45+ populations and quantified using FACS. CONTROL rats displayed a slow healing with 2.16±0.49mm^3 of new bone at 210 days post-op. In the POST and PRE groups new bone volume was 4.0±2 and 3.3±2.3mm^3, respectively. Surprisingly, in PRE and POST groups, individual responses were very non-uniform: some rats of both groups showed more than 6.5mm^3 new bone (+280% vs best CONTROL) and some just 1.5mm^3 (equivalent to slowest CONTROL). Differences between groups were not significant. WBC numbers were significantly higher after injections in PRE and POST. No changes were detected in CONTROL. At 60 days, CD34+ and CD45+ populations were significantly larger in PRE and POST. The very large individual differences in defect healing did not correlate with FACS results. No effect was observed on the contralateral femur.

Although not consistant (in some other individuals the treatment had no effect), the results suggest that in certain individuals the pre-treatment with G-CSF can accelerate healing by almost 300% compared to no treatment.

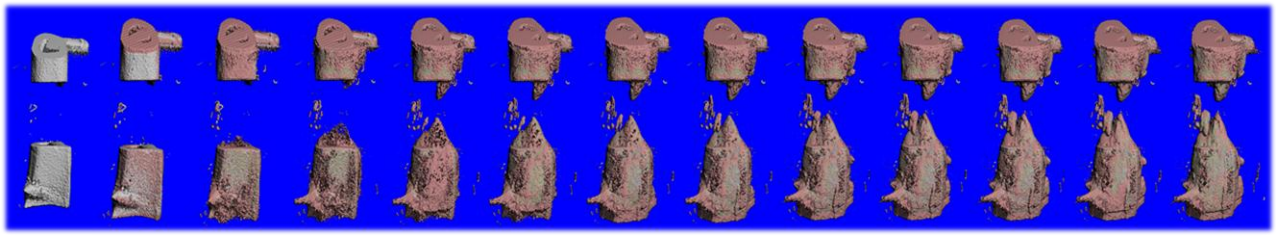

Figure 9.3.11: Incomplete healing of a critical size defect shown with time-series of *in vivo* microCT scans.

Development of a novel flexible antimicrobial local delivery platform for infection prophylaxis (HYDROBAC) (Ongoing) (D. Eglin)

In orthopaedic surgery, infections associated with medical devices are still one of the critical cause of failure and complications. The prevention of these infections may be improved by local placement of antibiotic containing and releasing materials. A biodegradable antibacterial carrier that displays controlled delivery of antibiotic would serve as an adjunct to systemically administered antibiotics without requiring subsequent surgical removal. Hyaluronan derivatives have been combined with antibiotics to form nano-complexes particles (Figure 9.3.12). The resultant compositions have been characterized with respect to antibiotic release and handling. They have shown to have a sustain release of antibiotic for several days and that the antibiotic release was increase upon degradation by hyaluronisdase.

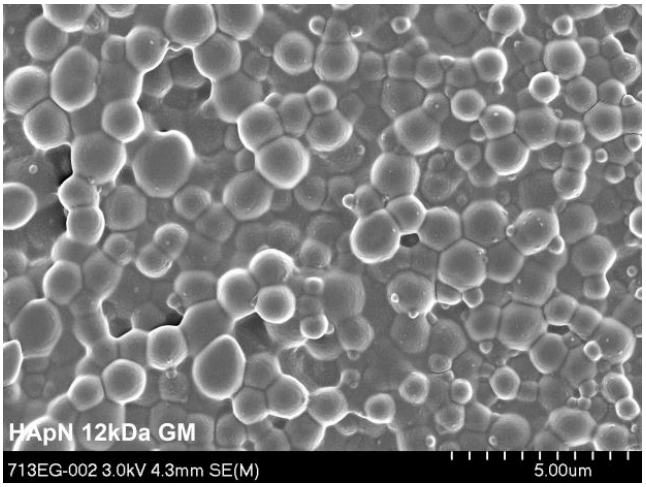

Figure 9.3.12: Scanning electron microscopy image of nano-complex of hyaluronan derivative with gentamycin.

Pres:

ter Boo GJ, Grijpma DW, Moriarty TF, Eglin D.Thermoresponsive hyaluronan compositions for local infection prophylaxis. 2013. ESB.

Pub:

ter Boo GJ, Grijpma DW, Moriarty TF, Eglin D. Hyaluronic acid conjugates and their complexation with gentamicin for local infection prophylaxis. Eur Cell Mater 2013;26 S4:50 SSB.

Partner:

- Grijpma DW (Prof), University of Twente, The Netherlands

Biodegradable putty-like antibiotics loaded hydrogel for implant infection treatment (AOTGEL) (Ongoing) (D. Eglin)

Bacterial infection in orthopaedic surgery and especially in polytraumatic patients is a main cause of failure with a high burden and associated cost. After debridement of the infected site, poly(methyl methacrylate) beads or cement are the most common delivery materials put in place to fill temporally the bone defect and release antibiotic locally. However, such materials are still sub-optimal.

Improved delivery systems that can be injected to easily fill up complex shape, be transparent to clinical imaging, have a long lasting release while being fully degradable and providing release of antibacterial agents targeting intracellular bacteria are needed. In this project microspheres made of biodegradable polymers (poly(ε-caprolactone), polylactide and poly(trimethylcarbonate)) have been prepared and loaded with gentamicin salts with different solubility and ability to target intracellular bacteria. The microspheres prepared are being characterized for their ability to sustain the relase of antibiotic for several weeks and to degrade in parallel to avoid the presence of residual material in the absence of antiobiotic.

Partner:

- Grijpma DW (Prof), University of Twente, The Netherlands

Injectable hydrogel for releasing osteogenic factors in osteoporotic bone fracture (OSTEOGEL) (Ongoing) (D. Eglin)

Osteoporosis has been recognized as an escalating cause of fractures, implants loosening, failures and also an increase in contralateral fracture in the ageing population. Treatment of osteoporotic fractures is challenging due to the decreased bone strength and sub-optimal bone healing. Therefore, an off-the-shelf anabolic therapy that would stimulate bone healing locally and increase implant stability could be a step toward a better fracture management in osteoporotic and ageing patients (Figure 9.3.13). This project aims at developing an injectable drug release system for the local delivery of osteogenic factors. The release from hyaluronan hydrogel carrier and activity of osteogenic drugs such as recombinant human bone morphogenetic protein-2 (rhBMP-2), strontium ranelate (SrRa) and icariin have been compared. SrRa is a dual action drug with bone anabolic and anti-resorptive effects. Icariin is an osteopromotive and bone protective plant-derived molecule. An injectable thermoresponsive hyaluronan hydrogel was able to modulate the release of the different osteogenic factors studied. Varying the total polymer concentration and thermoresponsive chain length should allow further tailoring the drugs release. The preliminary cell studies indicated that rh-BMP-2, SrRa and icariin were able to enhance the osteogenic differentiation of hMSCs under osteogenic conditions, although acting through different mechanisms.

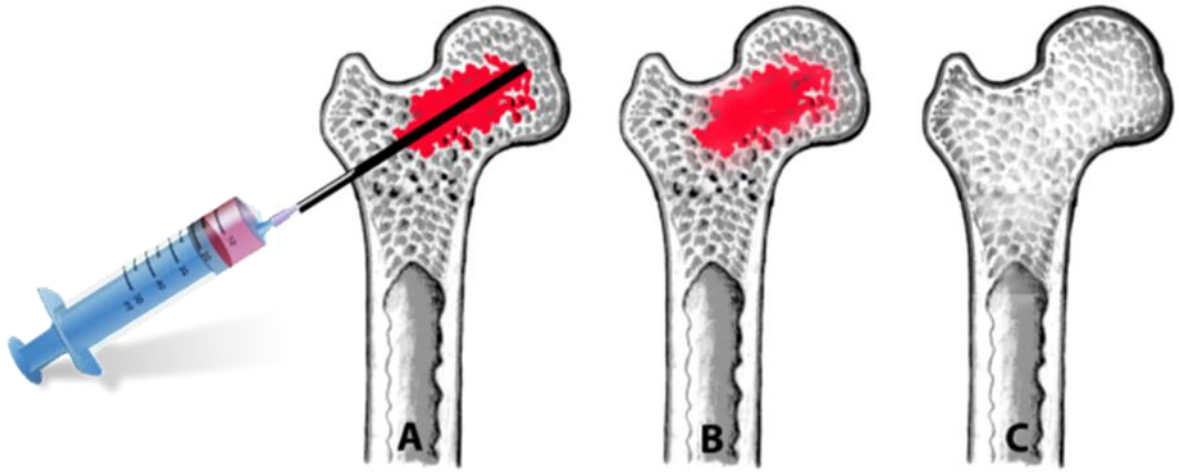

Figure 9.3.13: Osteogel; local injection and delivery of osteogenic drug into fracture site of osteoporotic patient for enhancing repair capacity.

Mechanisms of Mesenchymal Stem Cell Homing and Differentiation (HomeCell) (Ongoing) (M. Stoddart)

The homing mechanism of MSCs is of particular interest for clinical applications aimed at applying a more noninvasive systemic cell administration to treat inflammation and injury. During the natural repair of an injury, cells experience homing signals. Cells involved in tissue engineering would not have seen this homing signal. Additionally, on reaching an injured site the cells would receive inflammatory signals which are also likely to greatly affect their response. We sought to ask whether these signals play a role in priming the cells to affect a repair. In this project, we are exploring how factors, which are known to be involved in the homing of MSCs to sites of injury, modify the behavior and performance of the cells. In this study we analysed the influence of two hour stimulation of MSCs with interleukin 1β (IL1β), granulocyte-colony stimulating factor (GCSF), stromal cell-derived factor 1 (SDF1) and stem cell factor (SCF). Our results demonstrated that the short stimulation exerts pronounced effects on multiple cytokines genes and proteins expression in MSCs cells 48 and 72 hours later. The stimulation with certain factors regulated the expression of cytokines involved in various processes during fracture healing, including callus formation, remodelling, angiogenesis and bone cells differentiation. Moreover, the expression pattern of Wnt signalling pathway components suggested the differential regulation of this pathway by IL1β and SCF. Altogether, the robust paracrine action of MSCs can be achieved within just 2 hours treatment. These results suggest that integrating inflammatory modulation in bone tissue engineering would provide more powerful strategy to enhance bone regeneration processes.

Pres:

Stem cells in Biomedical Engineering - Today and Tomorrow. Biomedical Engineering day, University of Bern, 24th May 2013 – Stoddart MJ. Keynote

Benefits of Chemotactic and Inflammatory Modulators in Bone Regeneration. 2013 TERMIS. Czekanska E, Ralphs JR, Alini M, Stoddart MJ.

MSC-Osteoblast Crosstalk in Osteogenesis. 2013 TERMIS. Glück M, Gardner OF, Czekanska E, Salzmann GM, Alini M, Stoddart MJ.

Effect of Il-1beta during osteogenic differentiation of human MSCs Swiss Bone and Mineral Society, Bern, Switzerland 2013. Loebel C, Czekanska E, Staudacher J, Alini M, Stoddart MJ.

The RunX2 - Sox9 "see-saw": A balance for MSC osteogenesis Orthopeadic Research Society 2013 San Antonia, USA. Loebel C, Czekanska E, Alini M, Stoddart MJ.

Analysis of Staphylococcal nasal colonization in orthopaedic surgeons attending AO Courses Davos 2013 (OrthoNose) (M. Morgenstern)

Staphylococcus aureus and *Staphylococcus epidermidis* are two of the most common pathogens causing diseases, especially orthopaedic device related bone infections. Previous studies have found nasal colonization rates of *Staphylococcus aureus* up to 37% in the general population. It has been shown that asymptomatic colonized health-care workers are capable of transmitting Methicillin-resistant Staphylococcus aureus (MRSA) to others.The aim of OrthoNose is to determine the prevalence and antibiotic resistance patterns of *S.aureus* and *S.epidermidis* nasal colonization in a large cohort of global orthopaedic-, CMF-, and veterinarian surgeons at the AO Davos Courses 2013.

Throughout the two courses weeks, more than 1'200 surgeons provided anonymous, voluntary nasal swabs. The demographics of the enrolled surgeons followed the overall participant profile, with Trauma, CMF, Spine and veterinary surgeons included from over 40 countries. Detailed results are expected to be available in early 2014.

Partners:

- Kates S (Prof, MD), University of Rochester, USA
- Morgenstern M (MD), BGU Murnau, Germany
- Erichsen C (MD), BGU Murnau, Germany
- Hackl S (MD), BGU Murnau, Germany

Development of clinically relevant animal models for investigating musculoskeletal Infections; their treatment, prevention and diagnosis (Infect-fx) (F. Moriarty)

Musculoskeletal infection is one of the most common complications associated with surgical fixation of bones fractured during trauma. In order to more accurately mimic the clinical situation observed in infection after osteosynthesis, the infect-fx project is developing a rabbit fracture model that will allow assessment of the impact of infection on fracture healing and allow evaluation of novel interventional strategies in a clinically relevant model.

A custom-made humeral nail was developed in 2012 in collaboration with RISystem AG and the preclinical testing programme. The osteotomy model was successfully developed, whereby a 100% healing rate was observed in rabbits receiving the new nail, and in a plate group utilizing a commercially available locking plate. The rabbit osteotomy model has since been further developed to incorporate osteomyelitis. In the osteomyelitis model, we have performed a dose response curve for *S. aureus*. The model displays signs of localised infection, without systemic effects. With this model established, it will allow us to reduce the number of animals required in future studies.

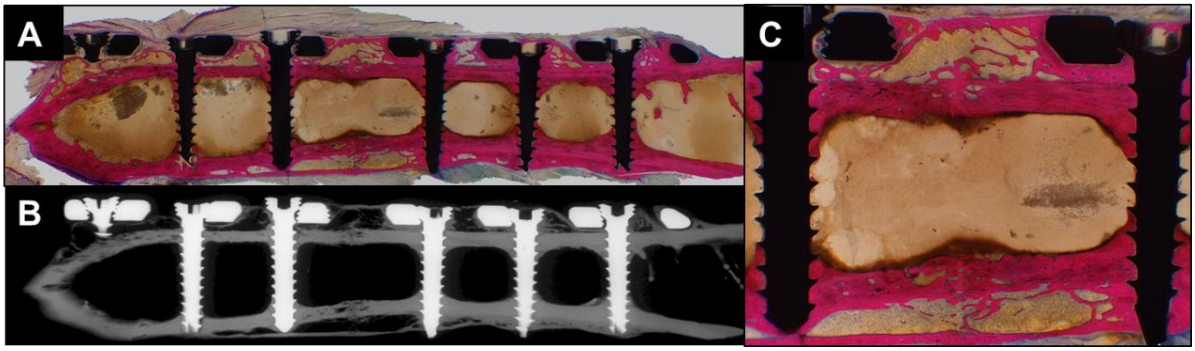

Figure 9.3.14: Healing in the rabbit humeral plate model revealed by light microscopy (A & C) and contact radiography (B).

Pres:

Influence of material on the development of device-associated infections, Moriarty TF, CORS Venice, Italy, 13th - 16th October2013.

Can we Influence the risk of infection by implant design? Moriarty TF, European College of Veterinary Surgeons (ECVS) annual scientific conference in Rome, Italy, July 2013.

Pub:

Bone infection. Moriarty TF. Vet Comp Orthop Traumatol. 2013;26(4).

Animal Models of Orthopedic Implant-Related Infection. Calabro L, Lutton C, Fouad Seif El Din A, Richards RG, Moriarty TF, in: Biomaterials Associated Infection: Immunological Aspects and Antimicrobial Strategies. Moriarty TF, Zaat SAJ, Busscher HJ (Eds.)

Partner:

- RISystem AG

Investigating the molecular epidemiology of Staphylococcal isolates from musculoskeletal infections associated with internal fracture fixation devices (StaphTyp) (V. Post)
The aim of this study is to identify the key virulence factors retained by S*taphylococcus aureus* isolated from infections surrounding fracture fixation devices and survey the most prevalent virulence factors possessed by this organism. Over 350 bacterial isolates have been collected from Hospitals and University departments in Liestal, Luzern, Geneva and Freiburg in Switzerland and from two hospitals from Nantes and Lille in France. In collaboration with the Trauma center from Murnau Germany, the collection of prospective *S. aureus* as well as *S. epidermidis* isolates continues with increasing number of isolates (over 250 isolates as of End of 2013). Whole genome sequencing has been performed on the isolates. This study has highlighted significant trends regarding the virulence requirements displayed by *S. aureus* isolates associated with implant related infections in comparison to non-implant related infections. Ongoing whole genome sequencing will be required to examine genomic differences among the different infection cases.

Pres:
Biofilm formation & molecular characterization of *Staphylococcus aureus* isolated from orthopaedic implant related infections depends on type of device. Post V, Wahl P, Uckay I, Zimmerli W, Corvec S, Loiez C, Ochsner P, Moriarty TF. CORS Venice, Italy, 13th - 16th October 2013.

Basic Science of Infection, T Fintan Moriarty, Asia Pacific Orthopaedic Association, Annual meeting Kuching Malaysia, August 2013.

Partners:
- Wahl P (MD), Fribourg, Switzerland
- Zimmerli W (MD), Liestal, Switzerland
- Ochsner P (MD), Luzern, Switzerland
- Ilker U (MD), Geneva, Switzerland
- Corvec S (MD), CHU de Nantes, France
- Loiez C (MD), CHR Lille, France
- Militz M (MD), Murnau, Germany

Development of new agents for the specific diagnostic imaging of infections associated with orthopedic devices (Imagin) (V. Stadelmann)
Our infection imaging project aims to improve the understanding of the progression of bone infection and improve the diagnosis of infection by combining newly developed infection probes with functional imaging modalities. Current clinical gold standard methods target both septic (infectious) and aseptic conditions. Together with the CT Imaging focus area, we have followed the dynamic changes occurring in bone in a rat infected screw model using micro CT, which were verified postmortem by bacteriology, histology, and mechanical testing. This technique enables differentiation between infected and non-infected implants as early as three days, which is significantly shorter than conventional radiography. Furthermore, different species of bacteria have been shown to result in different patterns of bone loss: for example, *S. aureu*s displays rapid osteolysis, which differs significantly from *S. epidermidis,* which results in slower and less significant bone loss. Therefore, this model follows clinical observations whereby *S. aureus* is an agent of acute infection, and *S. epidermidis* causes less acute, more chronic style infections.

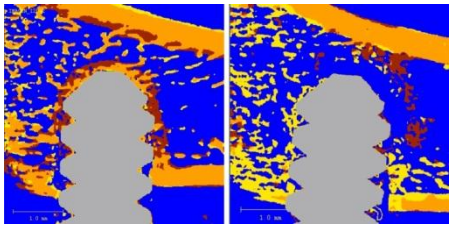

Figure 9.3.15: Bone reactions to a sterile screw (left) and an infected screw (right) analyzed via time-series of in-vivo microCT scans. (orange=quiescent, yellow=resorbed and red=new bone)

Pres:
Click chemistry for imaging of infection: two-step labeling of Staphylococcus aureus with lysostaphin. Potapova I, Eglin D, Laschke MW, Bischoff M, Richards RG, Moriarty TF. CORS, Venice, Italy, 13th - 16th October 2013.

In-vivo monitoring of bone around an infected implant. Stadelmann V, Potapova I, Camenisch K, Eberli U., Richards RG, Moriarty TF. CORS ,Venice, Italy, 13th - 16th October 2013.

Partners:
- Laschke MW (MD), University of Saarland, Homburg/Saar, Germany
- Bischoff M (PhD), University of Saarland, Homburg/Saar, Germany

Pub:
Potapova I, Eglin D, Laschke MW, Bischoff M, Richards RG, Moriarty TF. Two-step labeling of Staphylococcus aureus with Lysostaphin-Azide and DIBO-Alexa using click chemistry. 2013, JMM 92, 90 – 98.

Assessing the Role of the Implant Material and stability on the Development of Infection (Immunobact) (M. Sabaté Bresco)
An important factor for bone healing is the biomechanical stability of the fixed construct. Different mechanisms of healing have been observed in unstable fractures, which suggest different molecular and cellular events through the entire bone healing process. It is also known that instability of an implanted device increases the risk of developing an infection. However, little is known about the mechanisms underlying this phenomenon.
We have developed a murine femur osteotomy model with rigid and flexible internal fixators to study the influence of implant stability on the development of infection. A clinical *S. epidermidis* isolate has been used to contaminate the operative field. The immune response is being characterized in the different contexts (stable vs unstable, not-infected vs infected) to better understand the influence of biomechanics on infection susceptibility.

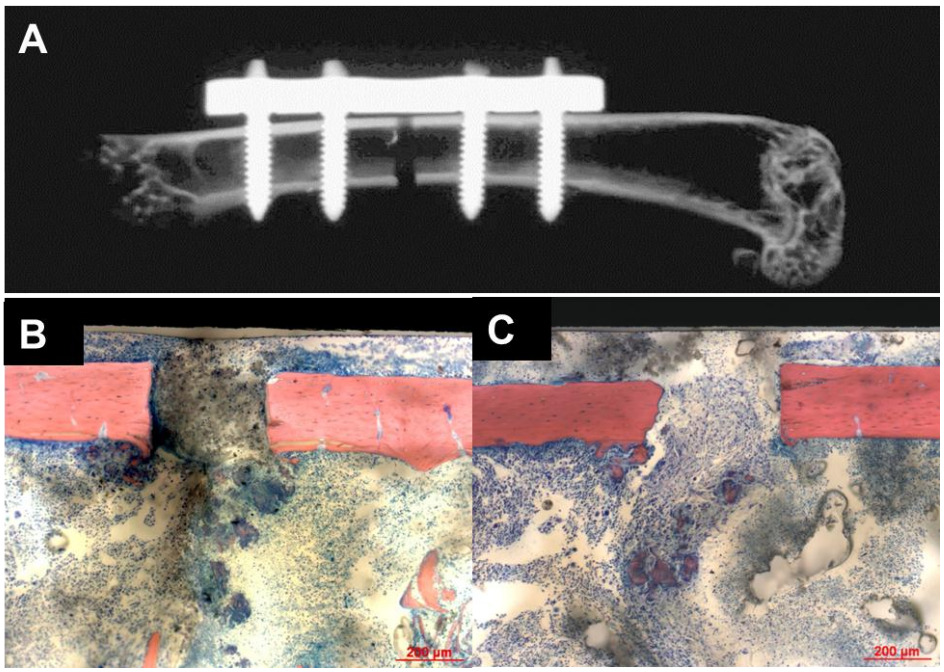

Figure 9.3.16:
A: Contact radiograph of *S. epidermidis* infected mouse at day 7. Early signs of osteolysis are observed.
B: H&E section of osteotomy gap indicating early cellular infiltration at day 3.
C: Osteotomy gap at day 7 showing extensive cellular infiltration and signs of osteolysis at fracture ends.

Pub:
Bacterial adhesion to orthopaedic implant materials and a novel oxygen plasma modified PEEK surface. Rochford ET, Poulsson AH, Salavarrieta Varela J, Lezuo P, Richards RG, Moriarty TF. Colloids Surf B Biointerfaces.;113:213-22. Epub 2013.

Pres:
Assessing the role of implant associated immune response on the development of infection *in vivo*. Rochford ETJ, Sabaté Brescó M, Ziegler M, O'Mahony L, Richards RG, Moriarty TF. CORS, Venice, Italy, 13th - 16th October2013.

PEEK vs Titanium: Evidence of Infection Risk in Preclinical Studies ,Moriarty TF, Asia Pacific Orthopaedic Association, Annual meeting Kuching Malaysia, August 2013.

Partners:
- O'Mahony L (PhD), Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland
- RISystem AG

Development of a large animal model to study the biology of two stage hardware exchange due to implant related osteomyelitis, and determine the efficacy anti-glucosaminidase (Gmd) passive immunization (StaphAb) (V. Post)
Both one and two stage replacement of infected total joint replacements (TJRs) and fracture fixations have an unacceptably high reinfection rate. This is commonly attributed to "dormant" bacteria present in the vicinity of the implant that survived debridement and antibiotic administration (systemically and local) at each stage of the two stage exchange. A major limitation towards the development of superior prevention strategies and therapies (i.e. vaccines, antibiotics, implant coatings) in these cases is the lack of a standardized large animal model of reinfection. Thus, the overall aim of this project is to generate a large animal model that recapitulates the salient features of one and two stage hardware exchange, as may occur for a TJR or infected fracture non-union. In the past year, we have successfully established a localised implant related ostemyelitis. The infection remained localised and allowed an observation period of 8 weeks with out any signs of systemic infection. The osteomyelitis was visualised by radiography at approximately 5 weeks, and post mortem CT scans also revealed characteristic bone changes at 8 weeks. Infusion trials of the passive immunization strategy, in collaboration with University of Rochester, have also been performed.

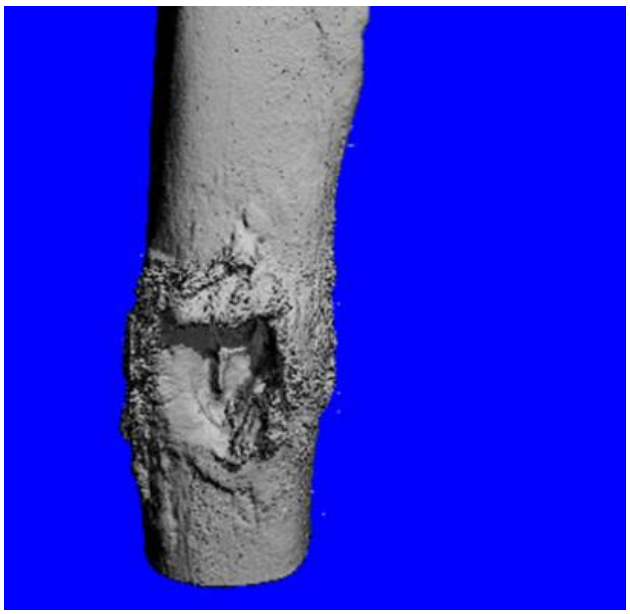

Figure 9.3.17: Post mortem CT scan of sheep tibia with obvious signs of osteomyelitis surrounding the inoculation point.

Pres:
Development of a Passive Immunization Strategy for *Staphylococcus aureu*s Moriarty TF, Asia Pacific Orthopaedic Association, Annual meeting Kuching Malaysia, August 2013.

Animal models of Implant Related Infection Moriarty TF European College of Veterinary Surgeons (ECVS) annual scientific conference in Rome, Italy, July 2013.

Partners:
- Kates S (Prof, MD), University of Rochester, Rochester, USA
- Schwarz E (Prof, PhD), University of Rochester, Rochester, USA

9.4 AOVET

Development of an external fixator for large animals (EquiCastSleeve) (Ongoing)
(D. Widmer)
Problem: The currently used transfixation pin cast system can be associated with severe pin loosening in horses.

Goal: To develop a new transfixation pin-sleeve system for reduced strain at the bone implant interface.

Results: Next generation prototype pin-sleeve system developed and biomechanically tested.

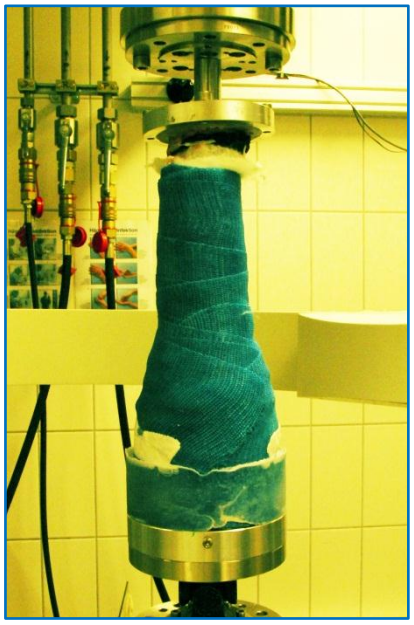

Figure 9.4.1: Biomechanical setup with an equine specimen mounted for testing.

Partners:
- Watkins J (Prof, DVM), College of Veterinary Medicine, Texas A&M University, Texas, USA
- Fürst A (DVM), Equine Hospital, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland
- Lischer C (Prof, DVM), Equine Clinic, Department of Veterinary Medicine, Freie Universität Berlin, Berlin, Germany

9.5 TK System

Development of a supplementary device for the external fixator to monitor the course of fracture healing using a novel data collection concept (SmartFix) (Ongoing) (M. Windolf)
Problem: The course of fracture healing after surgical intervention is difficult to clinically assess. All too often healing complications are detected too late. Scientifically the influence of mechanical environment on fracture consolidation is widely described. However, information on healing and load-bearing progression in fracture patients is only barely tapped due to the inaccessibility of a confined biological region.

Goal: To develop a biofeedback data collection concept, allowing continuous monitoring of the healing progress over several months, to be used as supplementary device with an external fixator. This approach minimizes patient risks and is hence predestinated for early collection of clinical data.

Results: Mechanical improvements were implemented to the previously developed prototype, resulting in enhanced sensitivity and reliability of the system. Pilot test data verified the system functioning. In collaboration with the BGU Tübingen, a clinical trial is currently in planning and will follow in 2014 to evaluate feasibility and validity of the proposed approach.

Figure 9.5.1: Measurement device with strain gauge sensor and electronic unit, attachable to external fixators.

Partners:

- Pohlemann T (Prof, MD), UK Homburg, Germany
- Höntzsch D (Prof, MD), BG Unfallklinik Tübingen, Germany
- Mathis H (Prof, PhD), Institute for Communication Systems, Hochschule für Technik, Rapperswil, Switzerland

Cerclages for osteosynthesis augmentation (Cerclage) (M. Windolf)
Problem: The stability of cerclage fixation depends on the lasting tension. Up to now, there was only a little insight in the cerclage fixation mechanics. Moreover, the belief of a strangled blood supply owing to cerclage application is still present.

Goal: To investigate systematically various aspects of cerclage fixation, involving tightening techniques, cerclage types and configurations, circumferential cerclage-bone contact and performance in periprosthetic fracture fixation in order to draw a comprehensive picture of the cerclage technique.

Results: Cerclage-bone contact is dependent on the bone surface geometry. The cerclage provides a point contact fixation which installs non-loaded, spanned zones where the periosteum is not compressed, rendering a strangulation of the blood supply unlikely. Cortical damage and bone resorption underneath the cerclage have to be attributed to micromotion and not to weakness of the cortex itself. Cable cerclages provide increased fixation strength compared to wire cerclages. Double looped cerclages provide better fixation stability in comparison to single looped cerclages.
Cerclage-screw combination is a valuable alternative to bicortical screw anchorage especially in osteoporotic bone. When cerclages are used, they should be combined with at least one screw to achieve a stable fixation. Although providing a good fixation against lateral load, even well tightened cable cerclages are susceptible to axial compression and torsion.

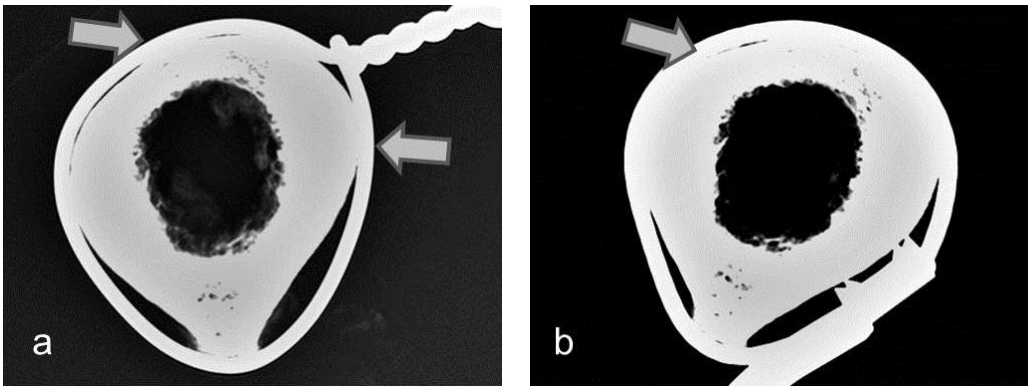

Figure 9.5.2: Point contact fixation of wire (a) and cable (b) cerclages.

Partners:
- Lenz M (MD), UK Jena, Germany
- Perren SM (Prof, MD, PhD), AO Foundation, Davos, Switzerland
- Höntzsch D (Prof, MD), BG Unfallklinik Tübingen, Germany
- Fernandez Dell'Oca A (Prof, MD), British Hospital, Montevideo, Uruguay

Pres:
Lenz M, Perren SM, Gueorguiev B, Richards RG, Fernandez Dell'Oca A, Höntzsch D, Hofmann GO, Windolf M. The concept of point contact fixation – interface mechanics of cerclages. 2013. ECTES.

Lenz M, Gueorguiev B, Richards RG, Mückley T, Hofmann GO, Höntzsch D, Perren SM, Windolf M. Optimierung der Dauerbeanspruchbarkeit von Cerclagen – eine biomechanische Studie. 2013. NOUV.

Pub:
Lenz M, Perren SM, Gueorguiev B, Höntzsch D, Windolf M. Mechanical behavior of fixation components for periprosthetic fracture surgery. Clin Biomech 2013 Nov-Dec;28(9-10):988-93.

Lenz M, Perren SM, Richards RG, Mückley T, Hofmann GO, Gueorguiev B, Windolf M. Biomechanical performance of different cable and wire cerclage configurations. Int Orthop 2013 Jan;37(1):125-30.

Pressure investigation in transverse patellar fracture fixation with two different tension band wiring techniques (PatBand) (I. Zderic)

Problem: Tension band wiring is the most common treatment for transverse patellar fracture fixation. Its main principle in all modifications is fracture reduction and possible conversion of tensile into compression forces acting in the fracture gap. The latter should stabilize the fracture and improve bone healing. However, some experimental data do not support the theoretical principles behind it. In addition, no supporting clinical data are available and moreover, in no study pressure distribution in the patellar fracture gap has been investigated during the early mobilization phase with regard to flexion/extension of the knee joint.

Goal: To investigate biomechanically pressure distribution in transverse patellar fractures fixed with two different tension band wiring techniques using either K-wires or cannulated screws.

Results: Fixing transverse patella fractures with both tension band wiring techniques provided compression at the articular fracture region. The higher initial compression observed with cannulated screws seemed to be compromised after the settling phase. A possible reason for that could be poor bone quality or high distraction forces acting on the patella during the extension of the knee.

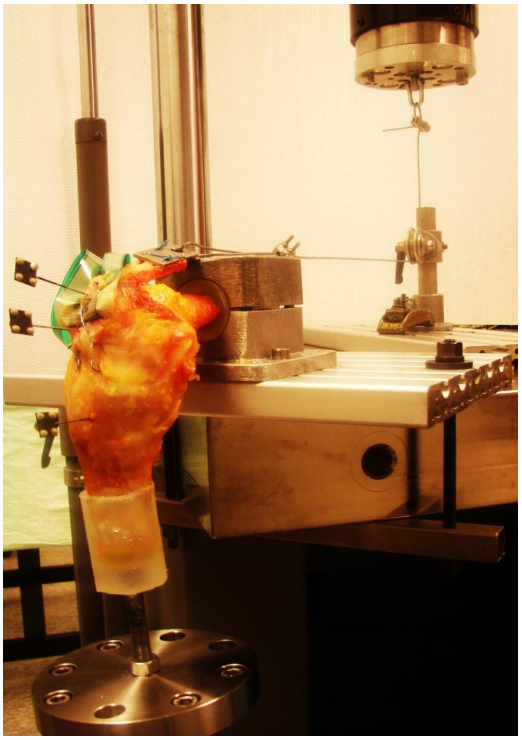

Figure 9.5.3: Biomechanical setup with a specimen mounted for testing.

Partner:

- Höntzsch D (Prof, MD), BG Unfallklinik Tübingen, Germany

Pres:

Zderic I, Nicolino T, Windolf M, Gueorguiev B. Pressure investigation in transverse patellar fracture fixation with two different tension band wiring techniques. A biomechanical study. 2013. CORS.

Anatomical evaluation for new trans-sacral fixation concepts for sacral insufficiency fractures. CT based 3D statistical modeling and analysis of the sacrum in Asians and European Caucasians (3DSacroMorph) (L. Kamer)

Within the rapidly growing population of elderly people, osteoporotic fractures, and among them sacral insufficiency fractures, are getting common. However, their treatment is a clinical challenge. Conservative treatment often ends with fracture displacement and nonunion. For earlier mobilization and pain relief, internal fixation is sometimes required. Fixation with a trans-sacral positioning bar has been advocated recently, but the space available for this kind of fixation of the S1 body is limited. The purpose of this study is to evaluate the sacral morphology and bone stock available in the Asian as well as in the European Caucasian ethnicity in order to develop efficient and safe fixation methods for sacral insufficiency fractures.

In the sacrum there exists a large inter-individual variation in the morphology and bone quality, significantly influencing sacral fixation concepts such as trans-sacral fixation. In this project application we propose Computed Tomography (CT) based three-dimensional (3D) statistical computer modeling and analysis of the sacrum to study these variations. In CT samples of Asians and Europeans a statistical model of the entire sacrum, and submodels of S1 and S2 (i.e. models of safe zones for safe screw positioning at S1 and S2 level) including the corresponding ilium parts will be computed. In a first phase a technical feasibility study will be performed to assess the different technical steps required for the image processing workflow. Then a final evaluation will be made in a sufficiently large series of CT data of elderly Asians and of European Caucasians.

Partners:

- Sawaguchi T (Prof, MD), Department of Orthopaedics & Joint Reconstructive Surgery, Toyama Municipal Hospital, Toyama, Japan
- Rommens PM (Prof, MD), Department of Trauma Surgery, Center for Musculoskeletal Surgery, University Medical Center, Mainz, Germany
- Uesugi M (PhD), Department of Orthopaedic Surgery, Tsukuba Medical Center, Tsukuba, Japan

CT imaging, processing and analysis (HumFE CTI) (L. Kamer)

Fixation of proximal humerus fractures, especially in elderly patients, remains a surgical challenge. Fracture fixation is compromised by a reduced bone mass and altered bone structure which may result in an increased number of complications and fixation failures. It is expected that complications will increase due to a rising incidence of osteoporosis. Currently the failure rate of plate and screw fixations of proximal humeral fractures is high.

Fixation concepts are traditionally evaluated based on biomechanical testing. This technique is, however, time consuming, requires anatomical specimens to be used and is still not standardized. In future computational approaches might offer an alternative solution as technology evolves. They could be advantageous over traditional experimental testing offering reproducible conditions, reduced testing effort and the ability of taking specific bone and fracture patterns into account. Further on better anatomical knowledge about the morphological variation of a bone, i.e. about its size and shape variation, and about the bony content would mean valuable information. It would permit for systematic design optimization for maximizing the implant anchorage.

Thus a standardized, validated virtual testing workflow would be a powerful alternative to react on the rising need for implant evaluation. It would be helpful in optimizing implant geometries, or parameters like screw directions, screw length or simply the number of inserted screws could be systematically investigated to involve the regions with the best available bone stock and at the same time to minimize the amount of fixation hardware.

We propose developing a standardized workflow using FE modeling and a set of three-dimensional standardized bone models that cover the varying morphology and bone stock of the proximal humerus. Up to now such technical workflow does not exist and suitable anatomical data for the proximal humerus have to be generated.

To goal of this project is the design and test a Finite Element workflow based on three-dimensional bone models generated from Computed Tomography scans.

Partner:

- Weber A (PhD), DePuy Synthes, Solothurn, Switzerland

9.6 AO Exploratory Research

Cement flow monitoring and assessment of injection forces during vertebroplasty (Feasibility InCemVert) (V. Stadelmann)

In the first part of this research, the goal was to generate experimental data of cement flows into bone. We developed time-lapsed computed tomography (CT) as a novel approach to capture the penetration of cement within bone. This was performed in vertebral bodies, since the surgical protocols are well established there. In brief, vertebrae were first microCT scanned at high resolution, then placed inside a clinical CT where bone cement was injected one milliliter at a time. After each injection, a scan was rapidly acquired. The scans were co-registered to obtain composite images with the cement distribution merged with the bone structure, producing time-lapsed recording of the cement flow. The leakage time and locations were evaluated by visual inspection of the 3D rendered images. Image data for each incremental step was then prepared for micro finite element modeling (microFE). The endplates were virtually embedded to apply the boundary conditions of a uniaxial compression. The models were solved for stiffness, failure load and Von Mises stress (VMS) distribution. The bones were mechanically tested in compression until failure.Cement leakage occurred in all vertebrae, whereby in 4 cases the cement leaked into the spine channel. FE simulations correlated ($R2 = 0.778$, $p<0.05$) with mechanical tests. As expected, an elevated stress concentration between the endplate and the cement was observed unless the endplate was in direct contact with the cement (Figure 9.6.1).

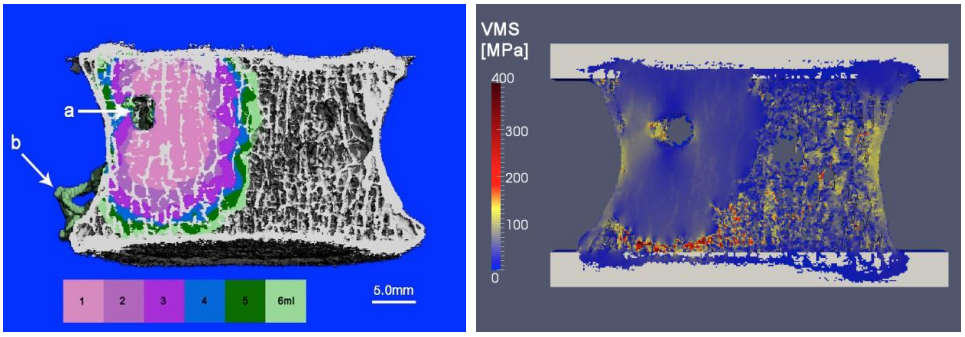

Figure 9.6.1: (Left) Cement distribution at each increment of injected volume within the bone structure. (a: point of entry, b: leakage of cement); (Right) VMS distribution within bone structure with 4ml cement. High VMS are concentrated under the cement mass.

Flow simulations. Finally the bone geometries were used to simulate cement flow in collaboration with FlowKit Ltd. Given the complex nature of bone structure, the hydrodynamics equations were solved at pore scale using a Lattice Boltzmann Method (LBM) with some simplifying assumptions (e.g. Newtonian flow, constant cement properties, no gravitational effects and no surface tension). Only the bone structure and the initial conditions (injection point and flow rate) were introduced in the models. So far, four models were solved on supercomputers and validated against those obtained with time-lapsed CT. The most striking result of the simulations was the excellent power of prediction for leakage locations, as shown in (Figure 9.6.2) (Manuscript in preparation).

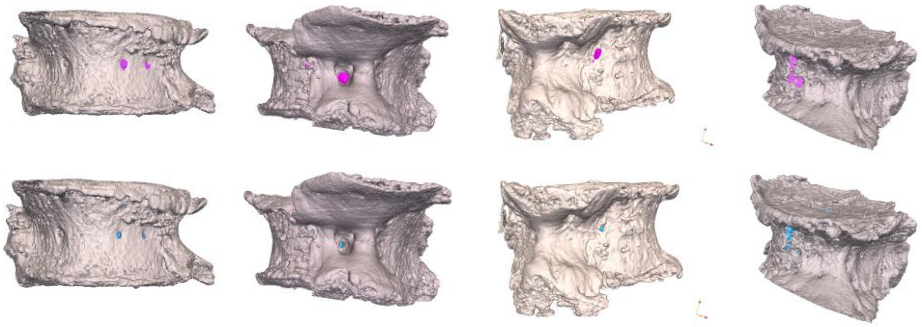

Figure 9.6.2: Visualization of leakage locations: Upper row shows experimental data with cement leakage in pink and lower row shows numerical data of the same bone with cement leakage in blue.

Arthroscopic anatomy and approaches to the rabbit stifle joint (Feasibility Kneescope) (S. Peters)

In both human and veterinary medicine, minimally invasive surgical techniques are becoming the standard of care wherever possible. One of the most prevalent minimally invasive techniques is the use of arthroscopic procedures to replace open arthrotomies. As orthopedic research continues to advance, it is important for commonly available animal models to keep pace with the current clinical standard of care. Current rabbit models for orthopedic research, such as the creation of osteochondral defects in non-weight bearing surfaces, are all performed via open arthrotomies. Additionally, the routine use of arthroscopy in laboratory medicine will reduce the animal burden and decrease the effects of the surgical approach on the study outcome. This study describes the arthroscopic approaches and intraarticular anatomy of the rabbit stifle joint with the aim that a standardized arthroscopic approach can then replace open arthrotomies in various lapine orthopedic investigations. Twenty cadaveric stifles from female New Zealand White rabbits were examined arthroscopically, the instrumentation, the optimal surgical technique has been developed and the rabbit knee arthroscopic anatomy has been described. A manuscript is in preparation.

Non-invasive biomechanical monitoring of bone healing in a dynamized bone defect in sheep (Feasibility Bonemonit) (U. Eberli)

Nowadays clinicians do not have a quantitative tool to evaluate the stability of healing bone. Computed tomography (CT) provides structural information about calcified tissues. However, in presence of fixation devices the occurrence of metallic artefacts limits the image quality. A radiolucent implant with inbuilt displacement sensor developed in ARI to monitor bone healing both visually and mechanically during the healing of a small defect in the sheep tibia was used. Since several studies have also shown that mechanical stimulation influences bone healing, the implant was designed to be axially dynamizable in compression[1]. The implant consists of two metallic ends which are connected by two carbon rods providing the radiolucency and sliding capacity. The aim was to assess and to evaluate temporal patterns of bone healing in a dynamized large bone defect in two adult Swiss white alpine sheep over a period of 7 months.

At surgery, the implant was fixed to the medial aspect of the left tibia and a 6 mm defect was created using an oscillating saw. Thirteen CT scans were acquired during the healing period at a resolution of 0.63 mm. A phantom was used to convert CT units into bone density values. Regions of interest (ROI) were defined in the post-op scans. Scan data of the following time points were registered to the post-operative scan. Interfragmentary motion was monitored continuously with on-board data processing over the first four months. The two sheep showed very different defect healing, with one specimen forming proper callus and showing bone densification; but the second specimen showing no visible callus formation and poor bone densification. Data analysis of the displacement sensor is still on going.The difference may originate from several factors such as diverse anatomical constitutions, variable sliding capacity of the implants and so forth (work in progress). So far our custom radiolucent implant allows the acquisition of perfect CT images without any artefacts in the ROI.

Reporter driven isolation of osteogenic and endothelial progenitors from mesenchymal stem cells (Comstem) (Complete) (M. Stoddart)

The use of human mesenchymal stem cells as source material for cell based therapies for bone repair is hindered by the heterogeneous populations normally obtained. Reliable identification and selection of MSCs is still problematic due to lack of suitable markers. Even markers which are sometimes used, such as CD105, CD90 or CD73, are not cell specific. Often attachment to tissue culture plastic is the only selection performed. This results in a heterogeneous cell population which will not behave in a uniform manner during induction to a specific cellular. We have taken the approach that potentially there are no specific CD markers and have looked for an alternative solution to identify functional cell types. We have developed a simple adenoviral based reporter system which is responsive to active Runx2 transcription factor, the factor responsible for osteoblast differentiation. Using this reporter system, and in combination with other projects within the group, we have established the Runx2 alone is a poor indicator of osteoblastic differentiation.

A dual reporter system, also monitoring the expression of Sox9, will be required to more accurately establish osteogenic potential on the cellular level. Results from this project should dramatically alter the development of future online reporter monitoring systems for all cell types.

Pres:
Monitoring Human Osteogenesis *in vitro*, LBIT Vienna

Pub: Bruderer M, Alini M, Stoddart MJ. Role of HOXA9 and VEZF1 in endothelial biology. J Vasc Res 2013;50:265-278

Partner:
- Vogel V (Prof), Department of Materials Science, ETH Zurich, Switzerland

Chondrogenesis of human bone marrow mesenchymal stem cells in fibrin-polyurethane composites (Stemload) (Ongoing) (M. Stoddart)
Tissue engineering is believed to be the future of articular cartilage repair due to the unsatisfying results of the current clinical procedures. MSCs derived from bone marrow (BMSCs) have demonstrated the potential to differentiate into several cell lineages, including chondrocytes. We have been investigating mechanical stimulation in a multiaxial load bioreactor on the fate of human bone marrow derived stem cells in the absence of exogenous chondrogenic growth factors. We have demonstrated that the application of shear, superimposed over compression, leads to an autoinduction of chondrogenic differentiation. This would imply that redistributing the cells by increasing the concentration at the upper surface where the shear is applied, would lead to a more robust response. Our studies have demonstrated that asymmetric seeding of tissue engineered cartilage implants not only leads to an improved chondrogenic response, but also reduces donor variability by improving the response from cells harvested from donors previously considered to be poor. This provides invaluable information when considering rehabilitation protocols post intra-articular surgery.

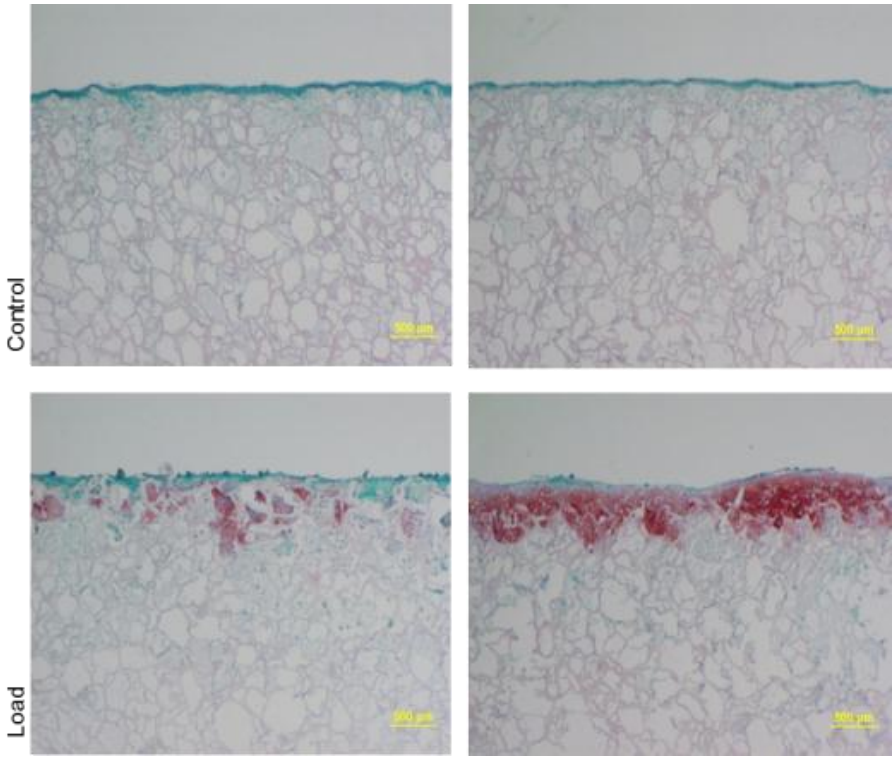

Figure 9.6.3: Safranin O Stain for cartilaginous matrix molecules (Glycosaminoglycan- orange) Unloaded (Top), loaded (bottom). Even cell distribution (left) asymmetrical cell distribution (right)

Pres:
The role of asymmetrical cell distribution during mechanically induced chondrogenesis of human bone marrow derived stem cells. Gordon Conference, Musculoskeletal Biology and Bioengineering, New Hampshire. Gardner O, Musumeci G, Archer CW, Alini M, Stoddart MJ.

Mechanically induced chondrogenesis of mesenchymal stem cells can be improved by manipulating the location of cells within a tissue engineering scaffold. Where Science Meets Clinics, Davos. Gardner O, Musumeci G, Archer CW, Alini M, Stoddart MJ.

Pub:
Neumann AJ, Schröder J, Alini M, Archer CW, Stoddart MJ. Enhanced adenovirus transduction of hMSCs using 3D hydrogel cell carriers. Mol Biotechnol. 2013 Feb;53(2):207-16.

Neumann A, Alini M, Archer CW, Stoddart MJ. Chondrogenesis of human bone-marrow derived mesenchymal stem cells is modulated by complex mechanical stimulation and adenoviral-mediated overexpression of BMP 2. Tissue Eng A. 2013 Jun;19(11-12):1285-94.

Wang N, Grad S, Stoddart MJ, Niemeyer P, Südkamp N, Alini M, Chen J, Salzmann G. Bioreactor-induced chondrocyte maturation is dependent on cell passage and onset of loading. Cartilage January 9, 2013 as doi:10.1177/1947603512471345

Petrou M, Niemeyer P, Stoddart MJ, Grad S, Bernstein A, Mayr H, Bode G, Südkamp N, Alini M, Salzmann G. Mesenchymal Stem Cell Chondrogenesis: Composite Growth-Factor-Bioreactor Synergism for Human Stem Cell Chondrogenesis. Regen Med. 2013 Mar;8(2):157-70.

Neumann AJ, Alini M, Archer CW, Stoddart MJ. Retroviral-mediated overexpression of human bone morphogenetic protein 2 affects human mesenchymal stem cells during monolayer proliferation: A Cautionary note. Electronic Journal of Biotechnology. 2013 Feb;53(2):207-16

Hilz FM, Ahrens P, Grad S, Stoddart MJ, Dahmani C, Wilken FL, Sauerschnig M, Niemeyer P, Zwingmann J, Burgkart R, von Eisenhart-Rothe R, Südkamp N, Weyh T, Imhoff AB, Alini M, Salzmann GM. Influence of extremely low frequency, low energy electromagnetic fields and combined mechanical stimulation on chondrocytes in 3-D constructs for cartilage tissue engineering. Bioelectromagnetics. 2013 Nov 6. doi: 10.1002/bem.21822.

Wang N, Grad S, Stoddart MJ, Niemeyer P, Reising K, Schmal H, Südkamp N, Alini M, Salzmann GM. Particulate cartilage under bioreactor-induced compression & shear. Int Orthop. 2013 Nov 28.

Randau TM, Schildberg FA, Alini M, Wimmer MD, Haddouti el-M, Gravius S, Ito K, Stoddart MJ. The effect of dexamethasone and triiodothyronine on terminal differentiation of primary bovine chondrocytes and chondrogenically differentiated mesenchymal stem cells. PLoS One. 2013 Aug 16;8(8):e72973

Gardner O, Archer CW, Alini M, Stoddart MJ. Chondrogenesis of mesenchymal stem cells for cartilage tissue engineering. Histology and Histopathology 2013 28:23-42.

Johnstone B, Alini M, Cucchiarini M, Dodge GR, Eglin D, Guilak F, Madry H, Mata A, Mauck R, Semino CE, Stoddart MJ. Tissue engineering for articular cartilage repair – the state of the art. eCM Journal 2013 May 2;25:248-67

Book Chapters:
Salzmann GM, Stoddart MJ. Bioreactor Tissue Engineering for Cartilage Repair. ICRS book. Developing insights in cartilage repair. Springer. Emans, Pieter J., Peterson, Lars (Eds.) 2014.
p 79-97

Partners:

- Archer CW (Prof), School of Biosciences, Cardiff University, Wales, United Kingdom
- Salzmann G (PD Dr med), Department of Orthopaedic and Trauma Surgery, University Medical Center, Albert-Ludwigs University Freiburg, Germany
- Acute Cartilage Injury Collaborative Research Programs Consortium

Investigation of bone marrow stem cells in the bone marrow niche in an *in vitro* system (Stemcart) (Ongoing) (M. Stoddart)

The aim of this project is to use a bioreactor system to culture whole marrow in a quiescent state. The reactor could then be used to investigate stem cell activation and migration, as well as providing a source of early cells which could be more clearly defined. This would able investigations into the role of soluble factors on more clearly defined naïve populations, which will reduce ambiguities caused by working with populations of cells which have been heavily expanded. The hypothesis is that by re-creating the *in vivo* stem cell niche, we can carry out studies that are currently not possible using standard MSC isolation techniques. Using this knowledge, we will further develop clinically applicable protocols for bone and cartilage repair by investigating the role of soluble factors and gene therapy vectors on the osteogenic and chondrogenic potential of freshly isolated cells. Within this system we have developed protocols to monitor cell proliferation and cell behavior of naïve freshly isolated marrow mononuclear cells and then attribute the behavior to either the mesenchymal or hematopoietic cell population. We have also been investigating the potential cross talk between the two cell types and whether this is modified when the cells are cultured in isolation. The rationale being that most *in vitro* work is performed with mesenchymal cells, whereas single procedures are likely to use fresh cells which are a mixed population. The normally absent hematopoietic fraction will likely influence any response via paracrine signaling. This study intends to provide more information on the fundamental biology of freshly isolated mononuclear cells. This is critical as in a single surgical procedure it is freshly isolated cells, not monolayer expanded cells, which will be available.

Pres:

Bara JJ, Menzel U, Lezuo P, Alini M, Stoddart MJ. Modelling the mesenchymal stem cell niche in bone marrow, FIRM Symposium, Girona, Spain.

Bara JJ, Menzel U, Lezuo P, Alini M, Stoddart MJ. Modelling the mesenchymal stem cell niche in bone marrow, eCM XIV Conference, Davos, Switzerland.

Partner:

- Acute Cartilage Injury Collaborative Research Programs Consortium

Elucidation of pathways involved in annulus fibrosus failure by mRNA profiling and subsequent protein assessment (DISCPHEN) (Ongoing) (S. Grad)

Intervertebral disc (IVD) degeneration is often associated with annulus fibrosus (AF) rupture and subsequent nucleus pulposus (NP) protrusion/prolapse. New therapies, both stimulating anabolic processes and inhibiting catabolic and inflammatory processes, are likely to be most effective. Essential for the development of such therapies is the elucidation of mechanisms leading to IVD degeneration and in particular to AF failure. The aim of this study is to elucidate the pathways involved in processes leading to AF rupture in order to identify new treatment targets.

Towards this aim, large scale phenotype comparison between AF cells from healthy and degenerated discs were performed. Cells were isolated from healthy and degenerated human IVDs obtained at autopsy. Gene expression profiles were analyzed by microarray expression mapping and results corroborated by real-time PCR. There were 237 genes found differentially regulated between degenerative and healthy AF (Figure 9.6.4). Of these, 119 genes were up-regulated, whereas 118 genes were down-regulated in the degenerative AF. Up-regulation was found for growth factors, inflammatory and angiogenic genes, while enzymes involved in proteoglycan metabolism were down-regulated. Degeneration-matched IVD sections are used for localization of the respective proteins by immunohistochemistry.

Furthermore, the functional role of differentially expressed proteins will be assessed *in vitro*. This allows identifying new molecules with regenerative or anti-degenerative functions.

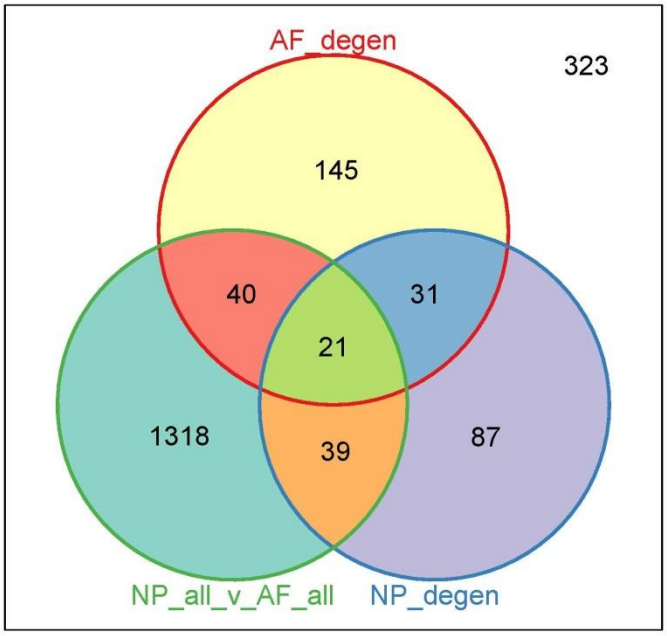

Figure 9.6.4: Three-way Venn diagram demonstrating that in total 237 genes are differentially regulated in degenerative versus healthy annulus fibrosus (AF), while 178 genes are differentially regulated in degenerative versus healthy nucleus pulposus (NP). Of these, 52 genes are differentially regulated in both tissues.

Pub:

Cunningham C, Srivastava A, Collin E, Grad S, Alini M, Pandit A, Wall JG. Isolation and characterisation of a recombinant antibody fragment that binds NCAM1-expressing intervertebral disc cells. PLoS One 8(12):e83678, 2013.

Partners:

- Annulus Fibrosus Repair Collaborative Research Programs Consortium
- Haglund L (Prof), McGill Scoliosis and Spine group, Montreal, Canada
- Mwale F (Prof), McGill University, Lady Davis Institute, Montreal, Canada
- Gallagher WM (Prof), UCD Conway Institute, University College Dublin, Ireland
- O'Gaora P (Prof), UCD Conway Institute, University College Dublin, Ireland

Synthesis of a biodegradable scaffold to improve the integration in osteochondral defects (JANUSCAF 2) (Ongoing) (D. Eglin)

Regeneration of articular cartilage after a trauma is still highly limited and often the only acceptable method is through surgical replacement. Our main objective is to address the issue of the functional integration and stabilization of cartilage tissue engineered implant into the subchondral bone.

Our initial goal has been the development of a press-fitted biphasic construct directly implanted in a critical size osteochondral defect in a rabbit model. The second stage consisted in assessing the combination of the elastomeric scaffold which role is to provide mechanical stability with a hyaluronan hydrogel which can be infiltrated into the scaffold and serve as cells and drug carrier. A first *in vivo* study has shown that the hydrogel envisioned is biocompatible and bioresorbable (Figure 9.6.5). The best combinations of hard and soft biomaterials are being currently tested.

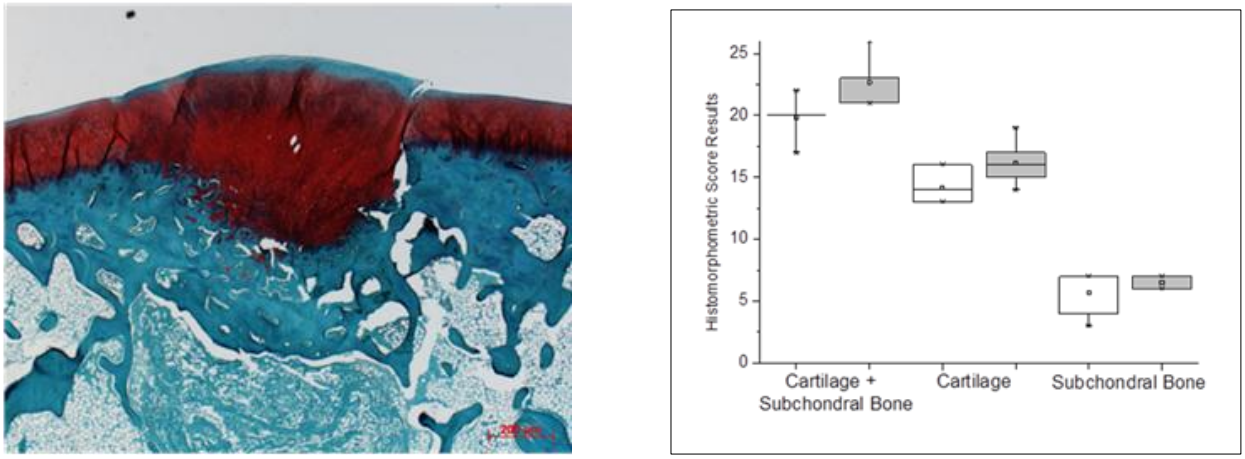

Figure 9.6.5: Representative Safranin-O Fast green stained histological image of the osteochondral defect filled with hyaluronan hydrogel at 12 weeks post op and histomorphometric score results.

Pres:

Dresing I, Zeiter S, Alini M, Eglin D. Press-fit Osteochondral Poly(ester-urethane) Scaffolds in a Rabbit Model. 2013. ESB.

Pub:

Galea L, Peroglio M, Eglin D, Graule T, Bohner M. Recrystallization and polymer impregnation improve strength and toughness of calcium phosphate ceramics. Eur Cell Mater 2013;26 S4:1 SSB.

Laschke MW, Schank TE, Scheuer C, Kleer S, Schuler S, Metzger W, Eglin D, Alini M, Menger MD. Three dimensional spheroids of adipose-derived mesenchymal stem cells are potent initiators of blood vessel formation in porous polyurethane scaffolds. Acta Biomater. 2013 Jun;9(6):6876-84.

Partners:

- Laschke M (PD Dr med), University Saarland, Homburg, Germany
- Bohner M (Prof), RMS Foundation Switzerland
- Acute Cartilage Injury Collaborative Research Programs Consortium

Thermoresponsive hydrogels based on natural polysaccharide (CARTHA) (Ongoing) (D. Eglin)

Regeneration of articular cartilage after a trauma is still highly limited and often the only acceptable method is through surgical replacement. This research project proposes to develop a novel approach to create bioactive, biomimetic, multifunctional, and biodegradable tunable hydrogels that can be designed to specifically stimulate cells and biological repair processes in a controlled manner.

A major motivation for this work is the potential to generate a simple material platform that can be used in minimally invasive procedures where they can be injected as liquids and form into solid gels upon crosslinking at the site of injury while displaying multiple desired biomolecular and physical signals.
To date, preliminary cell culture data reporting the influence of decoration of the 1st hydrogel platform with biofunctional dendrimers decorated with binding epitope (RGD peptide) indicated the ability to create injectable resorbable 3D matrices directing cell behavior (Figure 9.6.6).

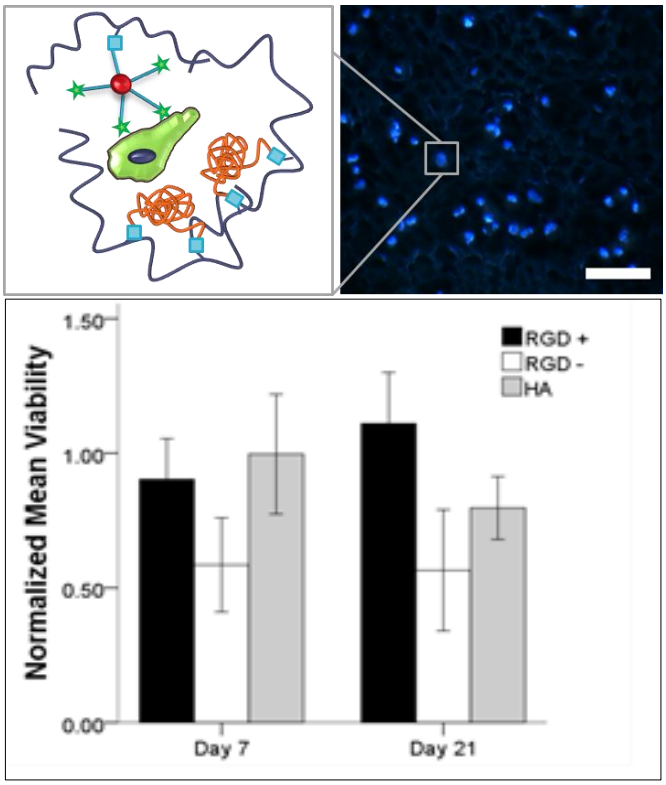

Figure 9.6.6:
Top: Schematic representation of the hMSC in HA-PNIPAM/HA-RGD and a fluorescent micrograph of DAPI stained hMSC nuclei showing homogenous cell distribution in the hydrogel (scale bar 50 µm).
Bottom: hMSC viability relative to HA at day 7

Pres:
D'Este M, Eglin D, Alini M. Synthesis and Characterization of Thermoresponsive Hyaluronan Hydrogels. 2013. ISHAS.

Seelbach R, Peroglio M, Fransen P, Royo M, Albericio F, Alini M, Eglin D, Mata A. Modulating the biochemical environment of a hyaluronan-based thermo-reversible hydrogel with integrin binding dendrimers. 2013. ESB.

Pub:
D'Este M, Eglin D. Hydrogels in calcium phosphate moldable and injectable bone substitutes: Sticky excipients or advanced 3-D carriers? Acta Biomater 2012;9:5421-30 (epub 2012 Nov 28).

Johnstone B, Alini M, Cucchiarini M, Dodge GR, Eglin D, Guilak F, Madry H, Mata A, Mauck RL, Semino CE, Stoddart MJ. Tissue engineering for articular cartilage repair--the state of the art. Eur Cell Mater. 2013 May 2;25:248-67.

Malonzo C, Chan SC, Kabiri A, Eglin D, Grad S, Bonél HM, Benneker LM, Gantenbein-Ritter B. A papain-induced disc degeneration model for the assessment of thermo-reversible hydrogel-cells therapeutic approach. J Tissue Eng Regen Med. 2013 Jan 9. [Epub ahead of print].

Partner:
- Acute Cartilage Injury Collaborative Research Programs Consortium

Fibrous polymeric patch for annulus fibrosus repair (AFEPATCH) (Ongoing) (D. Eglin)
Low back pain is a major public health problem in our society and the cause of significant morbidity. While the aetiologies are many, intervertebral disc (IVD) degeneration is recognized to be the leading cause for chronic low-back pain. The major aim of this study was to prepare a cellularized biodegradable polymeric patch which combines first a plug mimicking the annulus fibrosus tissue architecture and guiding new tissue repair and secondly a membrane closing the annulus defect and providing some mechanical stability. Membranes were prepared using a slow resorbable polymer capable to retain its mechanical integrity under complex load for an extended period of time (e.g. poly(ester-urethane)).
The design of these flexible and elastic degradable membranes was optimized. In organ culture study, sutured poly(ester-urethane) patch was able to retain the scaffold in discs under mechanical load without protrusion of nucleus pulposus (Figure 9.6.7). *In vivo* study will be performed to assess the safety and efficacy of the biomaterial devices developed.

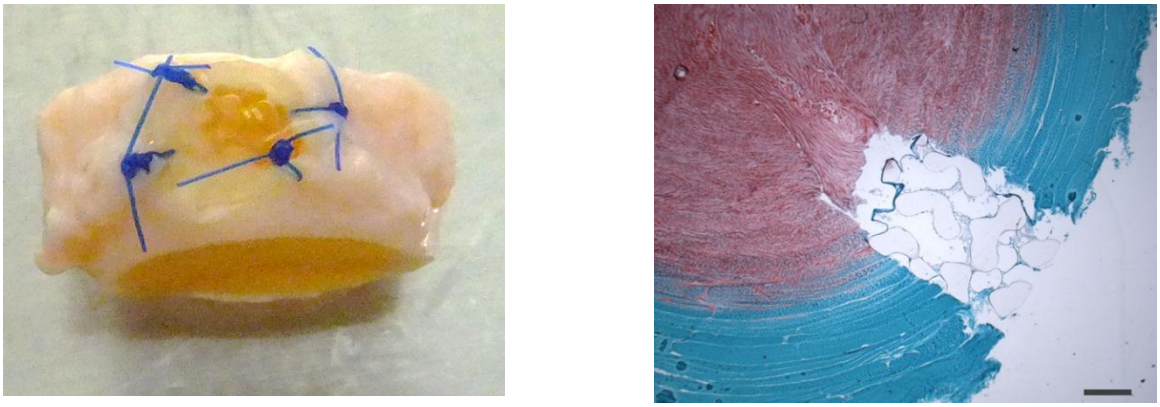

Figure 9.6.7: Images of an explanted IVD with a scaffold inserted in the annulus fibrosus and closed with a poly(ester-urethane) patch (left) and histology image of IVD disc after 1 week physiological load showing the retention of the scaffold and nucleus pulposus.

Pres:
Li Z, Pirvu T, Blanquer SBG, Grijpma DW, Alini M, Eglin D, Grad S. Mesenchymal stem cells encapsulated poly(trimethylene carbonate) implants for annulus fibrosus defect repair - an organ culture study under dynamic load. Philadelphia spine research symposium, Nov 6-8, 2013, Philadelphia, US. Oral presentation.

Pub:
Guterl CC, See EY, Blanquer SB, Pandit A, Ferguson SJ, Benneker LM, Grijpma DW, Sakai D, Eglin D, Alini M, Iatridis JC, Grad S. Challenges and strategies in the repair of ruptured annulus fibrosus. Eur Cell Mater. 2013 Jan 2;25:1-21.

Li Z, Pirvu T, Blanquer SB, Grijpma DW, Grad S, Alini M, Eglin D. Polyurethane membrane for annulus fibrosus rupture closure. Eur Cell Mater 2013;26 S4:55 SSB 2013

Li Z, Privu T, Blanquer SB, Grijpma DW, Grad S, Alini M, Eglin D. Polyurethane membrane for intervertebral disc annulus rupture closure - feasibility under dynamic loading in an organ culture study. Eur Cell Mater 2013;26 S8:43 (AOER Symposium).

Partner:
- Annulus Fibrosus Ruptures Collaborative Research Programs Consortium

Promotion of vascularization in large size bone defect implants (NEOVASC) (S. Verrier)

The repair of large bone defects still constitutes a major challenge for trauma and orthopedic surgeons. To date most of the efforts have been focused on the filling of the gap with autologous bone grafts, or various bio-active materials associated or not with cells. However, an active blood vessel network is an essential factor for cells to survive and integrate to the surrounding tissues. In previous work, we developed an *in vitro* pre-vascularized 3D polyurethane (PU) bone implant based on the association of human Endothelial Progenitor Cells (EPC) with human Mesenchymal Stem Cells (MSC). Both cell populations were obtained from human bone marrow aspirates (Ref.-Nr. KEK-BE: 188/10), and seeded in scaffolds in different relative ratios, and in the presence of platelet rich plasma (an autologous source of growth factors). We showed the formation of luminal tubular structures in the co-seeded scaffolds as early as day 7 in culture. In the present study we investigated the potential of these pre-cellularized constructs to promote *in vivo* the implants' neo-vascularization. EPCs were co-seeded with MSCs 3D PU scaffolds and either directly implanted subcutaneously in nude mice, or after one week of in-vitro pre-culture. Eight weeks post implantation, the mice were euthanized, the scaffolds removed, and embedded for histological analysis (Figure 9.6.8). In the pre-culture scaffolds, the highest and deepest neo-vascularization degree was obtained with the constructs containing MSC and EPC in a 50-50 ratio. Interestingly, when the constructs were implanted directly after cell-seeding, the best neo-vascularization was obtained for the scaffolds seeded with EPC only. An explanation could be that in pre-cultured scaffolds, the *in vitro* culture phase allows the formation of stabilized tubular structures prior to implantation (Duttenhoefer et al eCM 2013), accelerating the *in vivo* vascularization. In the direct implantation cases, and given the limited rate of the natural oxygen diffusion, the MSCs might not survive, while EPCs may adapt to this hypoxic environment and secrete factors attracting cells from the surrounding, fostering vascularization. In both cases, we could detect vascularization in the center of the scaffolds that was partly perfused, proving a connection with the host vasculature. EPCs that can be isolated in an autologous way proved their high angiogenic potential when implanted *in vivo*. Thus, BM-derived EPCs are a promising source of cells to promote neovascularization in tissue engineered constructs.

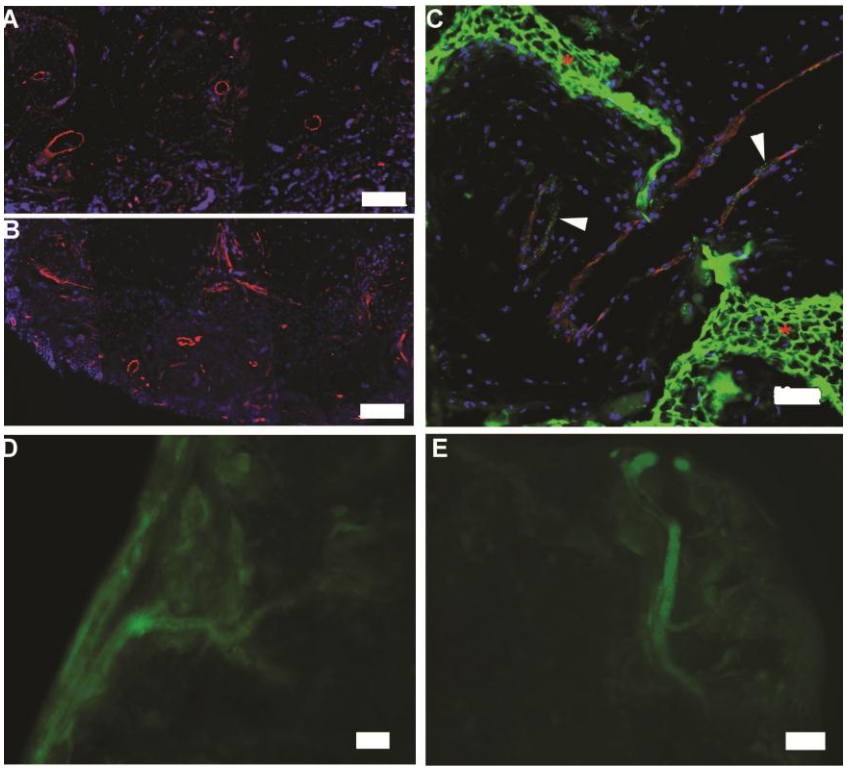

Fig 9.6.8: In vivo neovascularization and anasthomosis of vessels in implanted scaffolds. Cryosections stained for αSMA (red) showing micro-vessels (A-C). MMA embedded sections (D, E). Prio to euthanasia, some mice received an intravenous injection of FITC-lectine to dected the anasthomosis between the scaffold neo-vascularstructure and host vessels (green) (C-E). White arrow heads on the thin sections (C) underlines the FITC-lectin labeling of the micro-vessels' lumen. On the thick sections (D, E), the green fluorescence shows the perfusion of the scaffolds. Scale bars depict 200 µm (A, B), 100 µm (E), 50 µm (C, D). Red star (C) scaffolds' autofluorescence.

Pres:

Herrmann M, Binder A, Menzel U, Alini M, Verrier S. "Optimal autologous culture of Endothelial Progenitor Cells for Tissue Engineering of Vascularized Implants". EU TERMIS, 17-20 June 2013, Istanbul, Turkey.

Herrmann M, Duettenhöfer F, Loibl M, Binder A, Zeiter S, Peters S, Alini M, Verrier S. "Endothelial Progenitor Cells promote neovascularization of tissue engineered implants *in vivo*". EU TERMIS, 17-20 June 2013, Istanbul, Turkey.

Binder A, Herrmann M, Loibl M, Alini M, Verrier S. "Origin of Pericyte-like Cells in Co-cultures of Mesenchymal Stem Cells and Endothelial Progenitor Cells". EU TERMIS, 17-20 June 2013, Istanbul, Turkey.

Pub:
Loibl M, Binder A, Herrmann M, Duttenhöfer F, Richards RG, Nerlich M, Alini M, Verrier S. Originin of pericyte-like cells in co-culture of mesenchymal stem cells and endothelial Progenitor cells. J. BioMed Research International. 2013.

Duttenhöfer F, Lara de Freitas R, Meury T, Loibl M, Benneker LM, Richards RG, Alini M, Verrier S. 3D scaffolds co-seeded with Human Endothelial Progenitor and Mesenchymal Stem Cells: Evidence of prevascularization within 7 days. eCM journal, Aug 29.;26:49-64 2013.

Partners:
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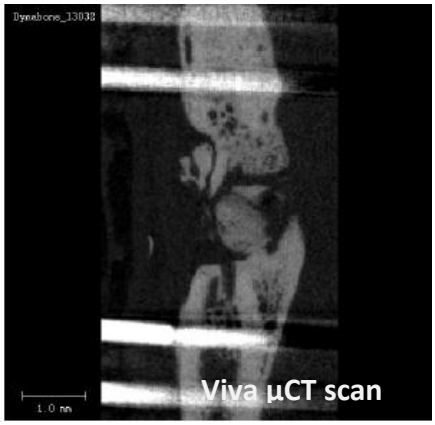
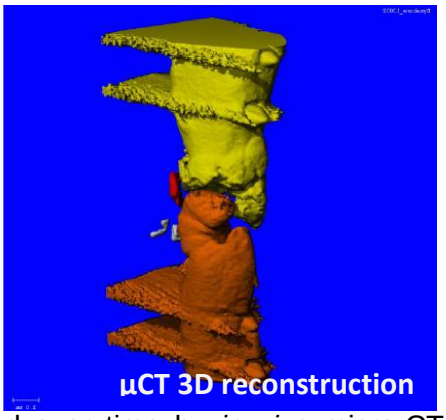
- Benneker L (PD Dr med), University Hospital Bern, Switzerland

Effect of dynamization on critical size bone defect healing (DynaBone) (S. Verrier)





Critical size bone defects are defined as those being more than 1.5 times larger than the bone diameter and do not heal if left untreated. This constitutes a major challenge for trauma surgeons, and to date, the gold standard treatment resides in the gap filling with autologous bone graft. Because of the low amount available, and the need of a 2nd place of surgery associated with increased pain and risk of infections for the patient, alternative methods are under investigation since about 2 decades that involve structural scaffolds associated with biological active components (cells, growth factors). Presently, rigid fixations are widely used for the management of all kind of fractures. However, over the past few years, increasing amount of experimental and clinical evidence report that the fracture healing can be influenced by mechanical loading. Yet, most of the data available are concerning small fracture gaps (≤2mm), simple osteotomies or distraction osteogenesis cases. Thus very little is known about the effect of mechanical stimulation when applied to a critical size bone defect. Questions concerning the timing, the amount, and the length of stimulation are still open. In the present study we aim to investigate the effect of axial mechanical loading on the healing of a critical size bone defect in the rat femur. In order to establish a favorable stimulation protocol, the large bone defects are treated with autologous/syngeneic bone graft (gold standard, positive control) to which different loading protocols are applied. The bone formation process is assessed over time by *in vivo* micro-CT imagining (Figure 9.6.9). Once the optimal stimulation conditions will be determined, we will then move to a more complex but also clinical relevant model in which the defect will be treated with tissue engineered constructs aiming to promote bone formation and implant's neo-vascularization in parallel.

Figure 9.6.9: Viva-micro-CT scan (upper figure). 3D reconstruction of the micro-CT (lower figure). Elements that are interconnected appear in the same color.

Partner:
- Matthys R, RISystem, Davos, Switzerland

9.7 Extramural project abstracts

Healing of Segmental Defects of Bone by Gene Transfer (Gendef2) (Ongoing) (S. Zeiter)
NIH Grant Number: 2R01AR050243-06A1, 5 years for $667'311, Ending: July 2015
The aim of this NIH-funded study is to assess efficacy of bone healing of segmental defects by genetically modified muscle grafts in a large animal model. Ad.BMP-2 transduced autolgous muscle grafts will be used to fill a created diaphyseal segmental defect in the sheep tibia. The defects will be stabilized with a locking compression plate (LCP Quarter pipe with window). The healing will be compared to positive control autologous cancellous bone graft group (gold standard), and to a negative control group (left empty). *In vivo* evaluation is performed with digital radiography followed by *post mortem* examination (computed tomography, histology and/ or mechanical testing). The first step of establishing both the negative and positive control groups is complete. The muscle adenovirus construct is currently being tested.

Partner:
- Christopher H. Evans (PhD), Mayo Clinic, Rochester, Minnesota, USA

Rational Bioactive Materials Design for Tissue Regeneration (Biodesign) (Ongoing)
(M. Stoddart, M. Alini), FP7-NMP-2010-Large-4 (nr. 262948), ARI Funding: EUR 573'000,
Period: 01.01.2012 – 31.12.2016
The development of functional materials for tissue regeneration is today mostly based on perceived and limited design criteria often using a single point approach with lengthy animal trials. The outcome after in-vitro and in-vivo evaluation is often disappointing resulting in a tedious iteration process. The main objective of this project is to achieve radical innovations in state-of-the-art biomaterials and to design highly performing bioinspired materials learning from natural processes. By this outcome driven project comprising first class academic and industrial participants the project will create scientific and technical excellence and through links with these SMEs will strengthen the technological capacity and their ability to operate competitively on an international market. BIODESIGN will (i) perform a careful retrospective-analysis of previous outcomes from clinical studies performed with humans through preclinical modeling in a reverse engineering approach applied to an in-vitro to the molecular design level, (ii) develop new strategies for a more rational design of ECM mimetic materials serving both as gels and load carrying scaffolds, (iii) link novel designs to adequate and more predictive in-vitro methods allowing significant reduction in development time and use of preclinical models and (iv) evaluate these concepts for musculoskeletal and cardiac regeneration. By the development of safe, ethically and regulatory acceptable, and clinically applicable materials this project will promote innovations to improve the health and quality of life of the patients. BIODESIGN will stimulate technological innovation, utilization of research results, transfer of knowledge and technologies and creation of technology based business in Europe. ARIs part within this consortium is the analysis of materials for bone regeneration.

Pub:
A phenotypic comparison of osteoblast cell lines versus human primary osteoblasts for biomaterials testing. Czekanska EM, Stoddart MJ, Ralphs JR, Richards RG, Hayes JS. J Biomed Mater Res A. 2013 Aug 24. doi: 10.1002/jbm.a.34937.

Partners:
- Uppsala Universitet, Sweden
- Eidgenössische Technische Hochschule, Zurich, Switzerland
- Ludwig Botzmann Gesellschaft, Österreichische Vereinigung zur Förderung der Wissenschaftlichen Forschung, Austria
- Universitätsklinikum Hamburg-Eppendorf, Germany
- University College, London, UK
- Technion Israel, Institute of Technology, Israel
- The University of Nottingham, UK
- University of Keele, UK
- University of Southampton, UK

- Regentis Biomaterials Ltd., Israel
- Baxter Innovations GmbH, Austria
- Termira AB, Sweden
- Regentec Ltd., UK
- Ecole Polytechnique Fédérale de Lausanne, Switzerland
- University of Nottingham in Malaysia, Malaysia
- King's College London, UK

Biomimetic nano-fiber-based nucleus pulposus regeneration for the treatment of degenerative disc disease (NPMimetic) (Ongoing) (S. Grad, M. Alini)
FP7-NMP-2009-small-3 (nr. 246351), ARI Funding: EUR 532'000, Period: 01.02.2011 – 31.01.2015

The golden standard for treatment of degenerative disc diseases is still the spinal fusion, an extensive surgery, which impairs spinal motion. Clinicians and scientists are searching for new technologies allowing motion preservation and a favorable long-term outcome. Based on electrospinning technology and a chemically modified extracellular matrix-based biopolymer, the NPmimetic consortium is developing a biomimetic nano-polymer based gel for minimally invasive treatment. Electrospinning is applied to design and develop a nano-fiber based, biocompatible, biodegradable, synthetic scaffold that will mimic mechanical properties of native nucleus pulposus (NP) for immediate and short term treatment. Anabolic agents are conjugated to the biodegradable polymer to be gradually released *in situ*. Ultimately, the synthetic scaffold is integrated with a bioactive polymer that is highly potent in supporting cell activity for long-term cure. The role of the ARI is the extensive *in vitro* and *ex vivo* testing of all biomaterials and their combinations, using cell and organ cultures. Specifically, the feasibility of implantation of the fibrin-hyaluronan based nano-biopolymer into the IVD was confirmed in an organ culture model (Figure 9.7.1). This project is funded by the European Union's 7th Framework Program NMP-2009-2.3-1.

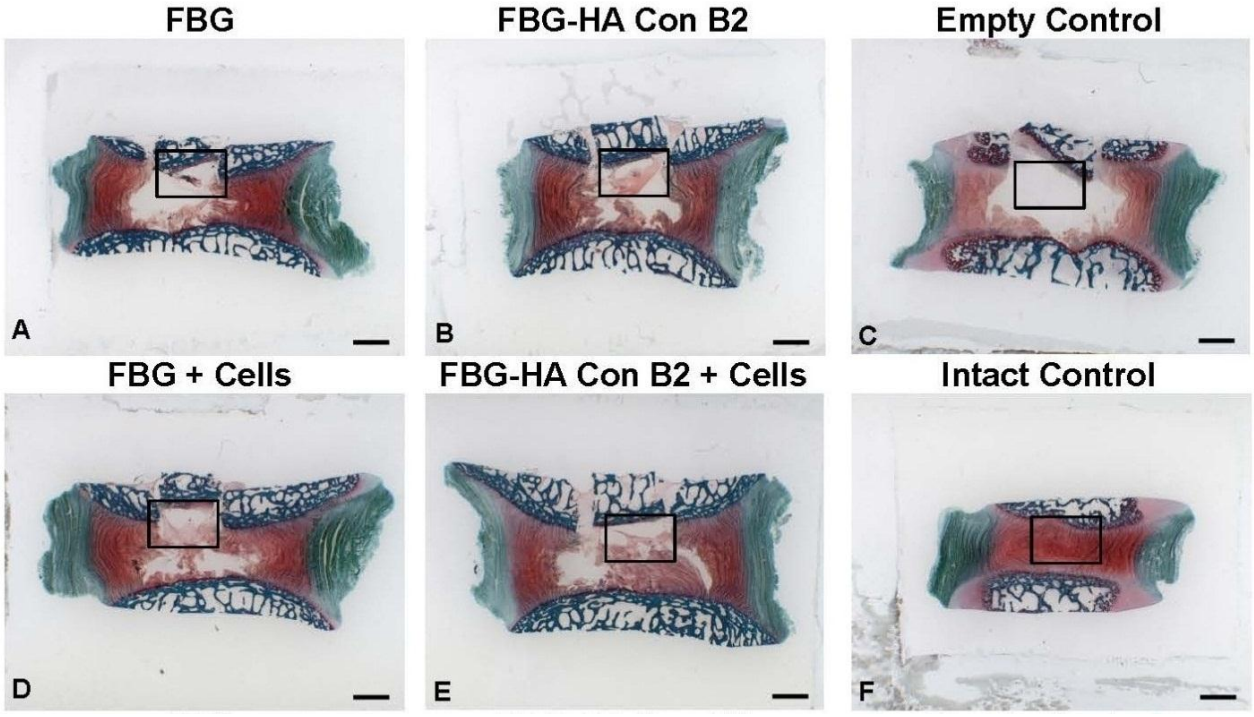


Figure 9.7.1: Representative images of bovine caudal discs stained with Safranin O/Fast Green, 14 days after nucleotomy. (A) nucleotomized disc refilled with fibrin gel, (D) nucleotomized disc refilled with fibrin gel with embedded NP cells, (B) nucleotomized disc refilled with FBG-HA conjugate B2 based hydrogel, (E) nucleotomized disc refilled with FBG-HA conjugate B2 based hydrogel with embedded NP cells, (C) nucleotomized disc as negative control, (F) intact disc as positive control. Scale bar 2 mm.

Partners:
- Nicast Ltd., Lod, Israel
- CM Développement, Paris, France
- ProCore BioMed Ltd., Ness Ziona, Israel
- Vrije Universiteit medisch centrum (VUmc) Amsterdam, The Nederlands
- University Hospital Zurich, Switzerland
- Centro de Tecnologias Mecanicas e de Materiais (CT2M), Minho University, Portugal
- Melab GmbH, Stuttgart, Germany
- Sheffield Hallam University, UK
- OSM-Dan Ltd., Rehovot, Israel

Gene Activated Matrices for Bone and Cartilage Regeneration in Arthritis (GAMBA) (Completed) (D. Eglin, M. Alini), FP7-NMP-2009-small-3 (nr. 245993),
ARI Funding: EUR 457'800, Period: 2010 – 2013

The GAMBA project had four major objectives: 1) Establishing GAMBA, creating the construction kit – matching materials science and gene vector development to achieve hierarchies of spatiotemporal control of bioactivity on command and demand; 2) Validating GAMBA – matching biophysics and cell biology in order provide proof of concept in cell culture models and eventually in animal models; 3) Linking GAMBA to society through innovative outreach methods including teaching students, discussing chances and risks in patient and citizen panels and raising awareness for gender equality within and outside the consortium; 4) Disseminating and exploiting project results through publications, public relations efforts and eventually through commercial product developments. After having established the components and modules for spatio-temporal control of bioactivity in a composite matrix during the first reporting period, the focus in the second reporting period was on assembling the modules and on characterizing such assemblies in terms of biophysical properties and in terms of biological function. As far as justifyable from an ethics point of view, individual modules or module assemblies were to be tested in small and large animal models. In parallel to the scientific objectives, the public outreach objectives were to be concluded with a final report while continued dissemination efforts were in place and project management would establish the final plan for the use and dissemination of foreground. The research receives funding from the European Union's 7th Framework Program under grant agreement n° NMP3-SL-2010-24.

Pres:
Eglin D, D'Este M, Borget P, Daculsi G, Mykhaylyk O, Plank C, Anton M, Alini M. Multiphasic Gene Activated Matrices for Osteochondral Regeneration in Osteoarthritis. 2013. ISACB6

Pub:
de Vries-van Melle ML, Tihaya MS, Kops N, Koevoet WJ, Murphy JM, Verhaar JA, Alini M, Eglin D, van Osch GJ. Chondrogenic differentiation of human bone marrow-derived mesenchymal stem cells in a simulated osteochondral environment is hydrogel dependent. Eur Cell Mater. 2014 Feb 3;27:112-23.

Partners:
- Klinikum rechts der Isar, Germany
- National University of Ireland, Ireland
- OZ Biosciences SA, France
- Biomatlante SA, France
- Erasmus Universitair Medisch Centrum Rotterdam, The Netherlands
- Instituto Nazionale per la Ricerca sul Cancro, Italy
- Institut National de la Santé de la Recherche Médicale, France
- Science Dialogue SRG, Germany

Bioceramics for bone repair (BIOBONE) (Started) (M. Peroglio, M. Alini)
FP7-PEOPLE-2011-ITN (nr. 289958), ARI Funding: EUR 275'010, Period: 2012 – 2016

The continuous advances in the treatment of damaged and diseased bone will lead to a strong demand for new treatments and the qualified professionals able to develop and implement them. Due to their unique properties, the use of ceramics for bone substitution and engineering is expanding fast. Ceramics are currently making inroads in high volume applications such as dental or orthopedic implants. However, much work is still needed for them to reach their full potential. This work will demand scientists and engineers with multidisciplinary backgrounds incorporating fields as diverse as materials science and engineering, orthopedics, tissue engineering, biology, chemistry and biomedical engineering. The final objective of this network is to train young researchers to fill this demand in the strategic area of bioceramics for bone repair.

The aim of the BIOBONE (Bioceramics for Bone Repair) project is to offer multidisciplinary training in the field of bioceramics, bioactive glasses and composites for bone repair, in collaboration with industries and universities. The scientific goals are to develop advanced knowledge on a range of bioceramics, bioactive glasses, hybrids and composites focusing on new processing strategies, biodegradation optimization and cell-material interactions. In total, 12 PhDs and 3 Post-docs will be involved in the BIOBONE ITN in 5 academic institutions and 4 industrial partners, all at the cutting-edge of their fields. BIOBONE will offer a unique training framework, including hands-on training at the main host institution, exchanges with other partners of the network and regular seminars.

BIOBONE Initial Training Network (ITN) is a project funded by the Marie Curie actions under the FP7 People Programme from the European Commission.

Partners:

- Imperial College of Science, London, UK
- Universitat Politècnica de Catalunya, Spain
- INSA-Lyon, France
- University of Erlangen-Nuremberg, Germany
- AO Research Institute Davos, Switzerland
- University of Mons, Belgium
- CeramTec, Germany
- Noraker, France
- Lucideon, UK
- Keramat, Spain

Biofunctional hyaluronan hydrogel for critical sized bone defect regenerative therapy (NAMABIO) (Started) (D. Eglin), NAMABIO COST MP1005, ARI Funding: CHF 180'000, Period: 2012 – 2015

Large bone defects are still representing a challenge for regeneration and surgical treatments. Autologous cancellous bone grafting is still the gold standard for restoration of segmental bone defects. Due to a large spectrum of donor site morbidity, a general approach to enhance bone regeneration is the implantation of osteoconductive scaffolds, most commonly the ceramic materials β-tricalcium phosphate and hydroxyapatite. However, this procedure, where a bone matrix is directly deposited by osteoblasts (intramembraneous ossification), has not achieved optimal results yet. The alternative route is bone formation through an intermediate cartilage template, known as indirect (endochondral) ossification. This novel developmental approach mimics the natural fracture healing process and promising results were shown recently. Regarding the mechanical properties of healing bone we propose that a soft material would rather support developmental bone regeneration.

The aim of our work is to develop a mechanical tunable material that can promote endochondral bone tissue engineering *in vitro* and *in vivo*.

The research receives funding from the Swiss National Funding under COST action number MP1005.

Partners:

- Zenobi-Wong M (Prof), ETH Zurich, Switzerland
- NAMABIO COST Action Partners

Rapid Prototyping of Custom-Made Bone-Forming Tissue Engineering Constructs (RAPIDOS) (Started) (D. Eglin, M. Alini), FP7-NMP-2013-EU-China (nr. 604517), ARI Funding: EUR 713'720, Period: 2013 – 2017

In cranio-maxillofacial surgery, large blow-out orbital floor fractures have still mitigated outcomes and improved scaffold solutions are needed. The reconstruction of large bone defects in proximal femur or proximal tibia in orthopaedic surgery is also an enormous challenge due to the requirements for both complex shape and partial load bearing ability. This is the goal of this European and Chinese consortium to apply technologies to create custom-made tissue engineered constructs made of resorbable polymer (PTMC or PLGA) and calcium phosphate ceramic composites specifically designed by integrating 1) imaging and information technologies, 2) biomaterials and process engineering, and 3) biological and biomedical engineering for novel and truly translational bone repair solutions. Advanced solid free form fabrication technologies; precise stereolithography and low melt temperature rapid prototyping will provide the necessary control to create such innovative high resolution medical devices. The use of Chinese Medicine extract, bone anabolic Icaritin which has shown to promote osteogenic differentiation of stem cells and enhance bone healing *in vivo*, will be a safe and technologically relevant alternative to the intensely debated growth factors. These challenges will advantageously be confronted by a strong Eastern -Western biomaterials collaborative effort. The synergistic collaboration envisioned will allow; 1) comparison and exchange of advanced and commercially relevant biomaterials developed; 2) parallel development of two precise technologies, stereolithography and low temperature rapid prototyping allowing for preparation of custom-made composite scaffolds loaded with unique biologics effectors. The planned personal exchanges, the scientific workshops, the use of a unique IT platform connecting trauma surgeons worldwide with the scientists of the consortium will insure that the flow of knowledge and exchange of exciting findings.

This joint project is funded by EU-NSFC under the European Union's 7th Framework Program, NMP-2013-EU-China proposal, project n°604517 and from the NSFC-DG-RTD, project registration n°512111203. The RAPIDOS activities and progresses can be followed on the web through the RAPIDOS portal http://rapidos-project.eu

Pres:

Eglin D, Richards RG, Qin L, Tang TT, de Bruijn J, Peng J, Lu S, Peijs T, Alini M, Grijpma DW. RAPIDOS: Rapid Prototyping of Custom-Made Bone-Forming Tissue Engineering Constructs. 2013. CESB.

Partners:

- University of Twente, The Netherlands
- Xpand Biotechnology BV, The Netherlands
- Queen Mary, University London, United Kingdom
- Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, China
- Shanghai Jiao Tong University, China
- General Hospital of People's Liberation Army – Beijing 301 Hospital, China

Development of tools to control microbial biofilms with relevance to clinical drug resistance (BALI) (Started) (F. Moriarty), FP7-HEALTH.2011.2.3.1-5 (nr. 278890),
ARI Funding: EUR 317'928, Period: 2012 – 2015

Infections by biofilm-forming microorganisms on indwelling medical devices such as catheters, prosthetic joints and internal fracture fixation devices often cause severe, chronic infections. Current strategies to prevent biofilms are based on conventional systemic antibiotic treatment, which often fails due to low local concentration and short release duration. However, improved prevention of infection could be achieved by coating of a medical device with a controlled release coating, ensuring that the antibiotic remains attached after the device is inserted and enable predetermined constant antibiotic release for prolong duration.

The specific formulation used in this study consists of biodegradable polyester: poly lactic-co-glycolic acid (PLGA), dipalmitoyl phosphatidyl choline (DPPC) and distearoyl phosphatidyl choline (DSPC), cholesterol.

The coating enables protection of the drug reservoir from hydration and enzymatic degradation, and allows predetermined and constant release of antibiotic for up to several months.

In an *in vivo* study, twelve skeletally mature New Zealand White rabbits received an inoculum of a clinically isolated *Staphylococcus aureus* strain direct into the medullary cavity of the humerus. Immediately after inoculation, animals received either a PolyPid doxycycline nail, or an uncoated control nail. Quantitative bacteriology revealed the presence of a biofilm infection and colonization of surrounding bone in all animals receiving uncoated nails. None of the animals receiving the coated nail displayed any radiographic signs of infection, and were completely culture negative for biofilm on the implant, and in the bone samples.

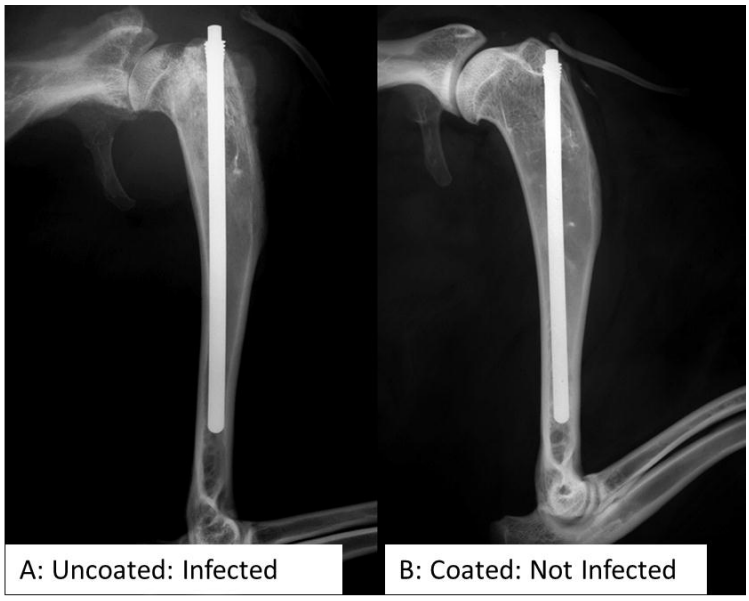


Figure 9.7.2: Contact radiograph of (left) rabbit receiving an uncoated implant with obvious signs of infection and a rabbit (right) reeiving a coated implant where the infection was cleared and normal bone appearance is observed.

Pres:

Controlled Release Polymers for Infection Prophylaxis. Moriarty TF, Asia Pacific Orthopaedic Association, Annual meeting Kuching Malaysia, August 2013.

Partners:

- Zaat S (PhD), AMC, Amsterdam, Netherlands
- Emanuel N (PhD), PolyPid Ltd, Tel Aviv, Israel
- Nibbering P (PhD), Leiden University Medical Centre (LUMC), Netherlands
- AO Foundation Clinical Investigation and Documentation (AOCID), Davos, Switzerland
- Lohner K (PhD), Austrian Academy of Sciences (AAS), Austria
- van Leuwen R (MD), MADAM Therapeutics (MADAM Tx), Netherlands

10 Operations standards and safety

Successful 2013 renewal audit of AO Research Institute

From April 10 to 11, 2013, two external auditors from the SQS (Swiss Association for Quality and Management Systems; www.sqs.ch) visited ARI two full days for the renewal audit of the institute.
ARI has received the renewal of the certification for 3 years without any non-conformities requiring immediate actions. Having held several open discussions with staff members and management, the auditors were impressed by the levels of commitment and knowledge. The entire AO Research Institute is certified according to the international standard ISO 9001:2008.

The Biomedical Services Program is additionally certified as a medical device manufacturer according to ISO 13485:2003.
ARI is one of the very few academic research organizations to have achieved this certification.

AAALAC certification of Preclinical facility

The Preclinical Facility was accredited by AAALAC in early 2013. The Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. AO Research Institute Davos is one of 3 accredited institutions in Switzerland, and the only accredited academic Research Institute in Switzerland.

GLP accreditation

The aim to get GLP accreditation in 2015 was put on hold, after the first meeting of the ARI Advisory Committee in December 2013. The following main reasons led to this decision. Firstly our main industrial partner has not started any new study in the Preclinical area since 2 years. Secondly all related FDA guidance and regulation documents are only in draft status and not yet binding. Last but not least, most of the studies we conducted until today would not fall under the new regulations.

Nevertheless a first study is currently still running and will be finished GLP-like.

11 Team Members

Director

Richards R. Geoff	Prof, Prof, PhD, MSc	01.10.91

ARI Management

Alini Mauro	Prof, PhD	01.07.99
Bentz Ulrich	Dipl Ing HTL Mikrotechnik	01.08.07
Grad Sibylle	Dr sc nat, PhD	03.08.00
Gueorguiev Boyko	PhD, MSc (01.03.03 – 30.09.09)	01.07.10
Keller Rolf	Technischer Kaufmann	17.06.96
Moriarty Fintan	PhD, BSc	19.03.07
Stoddart Martin	PhD, MPhil, BSc	01.07.05
Wahl Sonia	Dipl DH Ökonomin HFP	01.12.95
Wilke Markus	Dr med vet, Dipl ACVS/ECVS	22.08.11

Scientific & Technical Staff

Abegglen Nadine	Administrative Assistant (40%)	01.09.09
Agarwal Yash	MEng, PhD Cand	07.10.10
Arens Daniel	Dr med vet (01.06.03 – 30.09.06)	01.11.07
Badrutt Isabella	Administrative Assistant	16.07.12
Bara Jennifer	PhD, BSc	01.02.13
Barblan Claudia	Administrative Assistant (70%)	15.11.10
Bluvol Mauro	Chemielaborant (Eidg FA[1])	01.06.03
Camenisch Karin	MSc (80%)	07.04.08
Caspar Jan	Poly mechanics	01.01.09
Czekanska Ewa	PhD Cand, MPhil, MSc	07.10.08
D'Este Matteo	PhD	01.04.11
Dicht Benno	Mechaniker (Eidg FA[1])	01.01.78
Dresing Iska	Dr med vet	01.05.11
Eberli Ursula	MSc ETH (80%)	01.02.11
Eglin David	PhD	01.06.06
Erb Peter	Animal Care (Eidg FA[1])	03.05.93
Ernst Manuela	MSc, Human Movement Science	01.10.11
Escher Carla	Administrative Assistant (40%)	01.01.95
Faoro Pierina	Arztgehilfin (MPA), Animal Care (Eidg FA[1])	01.12.07
Furlong-Jäggi Pamela	Chemikerin FH, BSc (40%)	01.02.04
Furter Andrea	Animal Care (Eidg FA[1])	24.04.06
Gardner Oliver	PhD Cand	27.10.11
Glarner Markus	Chem Messtechniker (Eidg FA[1])	01.11.97
Goudsouzian Nora	BSc	01.02.02
Heldstab Thomas	Zeichner / Konstrukteur	04.02.91
Herrmann Marietta	Dr rer nat, PhD	01.11.12
Hofmann-Fliri Ladina	MSc ETH	01.10.09
Kamer Lukas	Dr med, Dr med dent (80%)	21.05.07
Keller-Stoddart Iris	MTL Technician (60%)	21.10.09

[1] Eidg FA = Eidg Fähigkeitsausweis

Kluge Katharina	Dr med vet (60%)	01.02.12
Kyllönen Laura	PhD, MSc	13.02.13
Lanker Urban	Animal Care (Eidg FA[1])	16.06.86
Lezuo Patrick	Dipl Eng	01.08.03
Li Zhen	PhD	01.08.11
Löbel Claudia	PhD Cand, Dr med	01.01.12
Menzel Ursula	PhD, Dipl Biol	01.07.11
Müller Gregor	Lic phil, Librarian (50%)	17.01.05
Müller Reto	Animal Care (Eidg FA[1])	13.11.01
Nehrbass Dirk	Dr med vet, FTA Pathol + Toxicopathol	01.10.10
Noser Hansrudi	PD Dr ès science EPFL	18.10.04
Peroglio Marianna	PhD	01.03.09
Perren Dominic	Animal Care	01.02.83
Peter Robert	Dipl Laborant HFP	15.09.84
Post Virginia	PhD	20.09.10
Pravincumar Makwana Priyanka	Dr phil	01.11.13
Sabate Bresco Marina	PhD Cand, MSc	17.01.13
Schmid Tanja	Dr med vet, Dipl ECVS	07.01.13
Schneider Monika	Administrative Assistant (50%)	06.02.06
Schraner Daniela	Administrative Assistant (40%)	15.04.10
Schwyn Ronald	Dipl Medizintechniker HF	01.11.92
Sharma Sonam	MSc, Biomedical Engineering	15.07.11
Sprecher Christoph	Dipl Ing FH	01.02.00
Stadelmann Vincent	PhD, Bioengineering EPFL	24.01.11
Stanciuc Ana-Maria	PhD Cand, MSc	20.01.13
ter Boo Gert-Jan	PhD Cand, MSc, Biomedical Engineering	15.01.12
Thöny Sandra	MSc, Human Biology	07.11.11
Verrier Sophie	Dr sc nat	01.08.04
Vivalda Marisa	Administrative Assistant	01.05.03
Wahl Dieter	Dipl techn Werkzeugspezialist HFP	01.11.93
Widmer Daniel	MSc, Biomedical Engineering	23.04.12
Windolf Markus	Dip Ing TU	01.11.04
Wyss Noel	Poly mechanics	01.08.08
Zderic Ivan	MSc ETH	01.02.11
Zeiter Stephan	Dr med vet, PhD (01.02.00 – 12.05.02)	01.06.03
Zweifel Erich	European Industrial Engineer EIE	30.11.92

Apprentice

Adank Nando	Apprentice	01.08.11
Frey Kevin	Apprentice	01.08.11

Internship

Caprez Stephanie	Internship	05.08.13
Petta Dalila	MSc, Biotechnology	04.02.13
Ryan Jason Dean	Internship IAESTE Student	03.06.13

Medical Research Fellows

Füssinger Marc Anton	Dr med	11.02.13
Jalowiec Jagoda	Med vet	01.09.13
Nowicki Bronislaw	Med vet	15.04.13

Non Medical Research Fellows

Baur Annick	EPFL Student	18.02.13 – 12.04.13
Ocampo Walter David	MSc, Mechanical Engineering	01.05.13 – 30.11.13
Steinmetz Philipp	BSc, Engineering	01.03.13 – 31.08.13
Wolfrum Christoph	BSc Student, Werkzeugmechaniker	01.03.13 – 31.08.13
Varjas Victor	MSc, Software Engineer	04.02.13 – 31.12.13

Employees left 2013

Scientific & Technical Staff

Bruderer Marco	PhD Cand	01.10.08 – 31.12.13
Faoro Jacqueline	Reinigungskraft Animal Facility	22.08.11 – 30.06.13
Forte Matthias	Dipl Ing	15.07.11 – 14.04.13
Lemm Prisca	Poly mechanics	01.01.10 – 31.07.13
Nehrbass Angela	Dr med vet (60%)	08.11.10 – 30.10.13
Neumann Alexander	PhD Cand, Dipl Biol	01.05.09 – 30.04.13
Pattappa Girish	PhD	01.07.10 – 31.03.13
Potapova Inga	PhD	01.01.10 – 31.12.13
Semadeni Gian-Marco	Apprentice	01.08.11 – 30.10.13

Internship

Baer Silke	Vet Internship	18.03.13 – 10.05.13
Freitag Linda	Vet Internship	30.09.13 – 29.11.13
Janki Milena	Internship, BSc Cand	22.04.13 – 30.11.13
Janssen Heike	Vet Internship	13.05.13 – 08.06.13
Rucci Adriano	Internship	08.07.13 – 31.12.13
Nies Andrea	Vet Internship	01.12.12 – 01.02.13
Nordemann Eva	Vet Internship	15.07.13 – 13.09.13

Medical Research Fellows

Camino Wilhuber Gaston	Dr med	01.04.13 – 30.09.13
Chen Xu	Dr med	01.07.13 – 31.12.13
Erichsen Christoph	Dr med	01.01.13 – 31.08.13
Götzen Michael	Dr med	01.05.12 – 30.04.13
Grüneweller Niklas	Dr med	01.07.13 – 31.12.13
Hackl Simon	Dr med	01.07.13 – 31.12.13
Helfen Tobias	Dr med	01.09.12 – 31.05.13
Peters Sarah	Dr med vet	01.08.12 – 30.06.13
Pirvu Tatiana	Dr med	01.07.12 – 30.06.13
Poxleitner Philipp	Dr med	01.01.13 – 30.09.13
Triana Miguel	Dr med	08.10.13 – 07.12.13
Rukmanikanthan Shanmugam	Dr med	15.10.12 – 31.03.13
Wagner Daniel	Dr med	01.05.12 – 17.02.13

Non Medical Research Fellows

Münch Claudia	MSc Cand, Medical Engineering	01.06.12 – 29.03.13
Viehöfer Ulf	MSc Cand, Medical Engineering	01.08.12 – 17.02.13

Guests

Binder Andreas	Musculoskeletal Regeneration (S. Verrier), 6th Semester Human Medicine, University of Regensburg, Germany, 03.09.12 – 30.04.13
Blackburn Julia	Guest all Programs / Group, Winner EORS exchange visit grant (1month), 07.08.13 – 04.09.13
Blanquer Sebastien	Musculoskeletal Regeneration, University of Twente, Netherlands, 02.09.13 – 06.09.13
Broguiere Nicolas	Musculoskeletal Regeneration, from ETH to work on project NAMABIO, 17.06.13 – 19.06.13
Cochis Andrea	Musculoskeletal Regeneration, University of Eastern Piedmont, Novara, Italy, 12.02.13 – 05.04.13
Dubnika Arita	Musculoskeletal Regeneration, Cost Stipend, Rudolf Cimdins Riga Biomaterial Innovation and Development Center of Riga, Technical University, Riga, Latvia, 08.01.13. – 01.02.13
Gawri Rahul	Musculoskeletal Regeneration, Guest Scientist (S. Grad), McGill University, Montreal, Canada, 20.07.13 – 17.08.13
Glück Martina	Musculoskeletal Regeneration, University of Freiburg, Germany, 03.09.12 – 12.04.13
Kesti Matti	Musculoskeletal Regeneration, ETH Zurich, Switzerland, 08.07.13 – 15.07.13
Jin Li	Musculoskeletal Regeneration, Guest Scientist, University of Virginia, Charlottesville, VA, USA (S.Grad), 17.04.13 – 08.05.13
Leite Pereira Ana Catarina	Musculoskeletal Regeneration, Instituto de Engenharia Biomédica, Porto, Portugal, 16.05.13 – 29.05.13
Lenz Mark	Universitätsklinikum Jena, Germany, Project Collaboration, several times
Newton Charlotte	Biomedical Services & Musculoskeletal Infection, University of East Anglia, Norwich Medical School, Norfolk, UK, 05.08.13 – 16.08.13
Perez Adrian	Guest Scientist (D. Eglin), Fundacion CIDETEC, Donostia San Sebastian, Spain, 30.09.13 – 12.10.13
Prelipcean Flavius-Fabian	Preclinial Services, University of Agronomic Sciences and Veterinary Medicine of Bucharest, Romania, 01.07.13 – 31.07.13
Rausch Sascha	Biomedical Services, Klinik für Unfallchirurgie Jena, Germany, 08.04.13 – 12.04.13
Rozhnova Olga	Musculoskeletal Regeneration, Guest Scientist (S. Grad), Novosibirsk Institute of Traumatology and Orthopedics, Novosibirsk, Russia, 18.11.13-22.11.13
Russo Fabrizio	Musculoskeletal Regeneration, Campus Bio-Medico, University of Rome, Italy, 08.02.13 – 17.02.13
Schmidutz Florian	Preclinical Testing, Ludwig-Maximilians University, Munich, Germany, 12.10.13 – 15.10.13 / 18.10.13 – 20.10.13 / 15.11.13 – 24.11.13 / 29.11.13 – 07.12.13
Schneider Kerstin	Biomedical Services, Guest Project Work, Kantonsspital St. Gallen, Switzerland, 11.11.13 – 16.11.13
Seelbach Ryan	Musculoskeletal Regeneration, University of Barcelona, Spain, 01.01.13 – 31.12.13
Skulev Hristo	Technical University of Varna, Bulgaria, staff training according work plan under Erasmus program at the ARI (period 1week/10hours), (B. Gueorguiev), 15.07.13 – 21.07.13
Wolf Uwe	Biomedical Services, Friedrich Schiller Universität, Jena, Germany, 08.04.13 – 04.05.13

Guest Presentations at AO Center
On March 8, 2013 Iraida Loinaz from CIDETEC Resp. Unidad de Biomateriales, Biomaterialeen Unitate Arduraduna, Head of Biomaterials Unit, Spain gave a guest presentation with the title: A new family of injectable hydrogels with self healing properties with application in tissue engineering.

On March 13, 2013 Dr. Gisela Anna Kuhn from Eidgenössiche Technische Hochschule (ETH) Zurich gave a guest presentation with the title: Effect of axial loading on the murine tail. Micro-CT for determination of capillary density.

On April 5, 2013 Dr. Brandon Markway from the Oregon Health & Science University, Oregon, USA gave a guest presentation with the title: Differential effects of hypoxia and inflammatory factors on MSCs and chondrocytes.

On October 7, 2013 Prof. Tarun Goswami from the Institute of Material Science and Welding, Technical Universtiy of Graz, Austria gave a guest presentation with the title: Biomaterials and biomedical devices. Engineering materials in biomedical applications for total joint replacement and orthopaedic repair via ORIF.

On October 9, 2013 Dr. John Costi, Head of Biomechanics & Implants Laboratory, The Medical Device Research Institute, Adelaide, South Australia gave a guest presentation with the title: Multiscale biomechanical testing and computational modelling of biological tissues.

12 ARI Patents

A device for manipulating a bone or bone fragment or a surgical instrument, tool or implant and a method for positioning such a device
- First Application: PCT/CH2009/00295 filed 2009-09-02
- Case: 10.2538
- Developer / Inventors: AOR&D, M. Windolf, C. Nötzli

Biomedical Polymer Material for Tissue Repair and Engineering
- First Application: PCT/CH2006/000424 filed 2006-08-10
- Case: 10.2278
- Developer / Inventors: AOR&D, S. Gogolewski

Cannula
- First Application: PCT/CH2008/000238 filed 2008-05-27
- Case: 10.2283
- Developer / Inventors: AOR&D, A. Gisep, V. Boner, N. Suhm

Sleeve for a Transfixation Device for an External Fixator
- First Application: PCT/CH2007/000210 filed 2007-04-30
- Case: 10.2344
- Developer / Inventors: AOR&D, K. Schwieger, V. Sprenger

Cannula and Device for Liquid Jet Irrigation of Bone
- First Application: PCT/CH2008/000019 filed 2008-01-15
- Case: 10.2356
- Developer / Inventors: AOR&D, A. Gisep, P. Kuhn

Bone Fixation Device with Cover
- First Application: PCT/CH2009/000095 filed 2009-03-18
- Case: 10.2406
- Developer / Inventors: AOR&D, RG. Richards, C. Nötzli

Bone Fixation Device
- First Application: PCT/CH2008/000349 filed 2008-08-15
- Case: 10.2470
- Developer / Inventors: AOR&D, M. Windolf

Device for Processing and Transmitting Measured Signals for Monitoring and/or Controlling Medical Implants, Diagnostic Devices or Biological Processes
- First Application: PCT/CH2009/000198 filed 2009-06-11
- Case: 10.2555
- Developer / Inventors: AOR&D, M. Windolf

Cannula and Kit for Bone Cement Injection
- First Application: PCT/CH2011/000007 filed 2011-04-19
- Case: 10.2567
- Developer / Inventors: AOR&D, M. Windolf

Method for Designing and/or Optimizing a Surgical Device
- First Application: PCT/CH2010/000046 filed 2010-02-25
- Case: 10.2607
- Developer / Inventors: AOR&D, S. Brianza, D. Schuima, A. Tami

Surgical Instrument
- First Application: PCT/CH2010/000330 filed 2010-02-25
- Case: 10.2676
- Developer / Inventors: AOR&D, S. Brianza, R. Schwyn

Biocompatible Implant
- First Application: PCT/CH2008/000181 filed 2008-04-21
- Case: 10.F5001
- Developer / Inventors: AOR&D, M. Alini, S. Verrier, D. Eglin

Polymer Surface Modification
- First Application: PCT/EP2009/003744 filed 2009-05-27
- Case: 10.F5002
- Developer / Inventors: AOR&D, A. Poulsson, RG. Richards

Identification and Selection of Functionally Committed Mesenchymal Stem Cells Subpopulations
First Application: PCT/CH2006/000425 filed 2006-08-11
Case: 22.2277
Developer / Inventors: ARI, M. Alini, M. Stoddart

A Method and a Device for Computer Assisted Surgery
First Application: PCT/CH2011/000299 filed 2011-12-15
Case: 10.2799
Developer / Inventors: AOR&D, M. Windolf, C. Nötzli

Method and Device for Measuring the Local Mechanical Resistance of a Porous Body
First Application: PCT/CH2006/000611 filed 2006-10-31
Case: 10.2281
Developer / Inventors: AOR&D, R. Schwyn, M. Hänni, N. Suhm

Implant for Cementing into Bone, Method for Cementing an Implant into Bone and Package for Implant
First Application: PCT/EP97/00957 filed 1997-02-27
Case: 22.1520
Developer / Inventors: ARI, S. Tepic

Treatment of Tumors by Selective Protein Depletion
First Application: PCT/EP94/02640 filed 1994-08-09
Case: 29.1431
Developer / Inventors: ARI, S. Tepic

Hand-actuated Tool
First Application: 94114850.4 filed 1994-09-21
Case: 22.14854
Developer / Inventors: ARI, S. Tepic

Method of Bone Cement Preparation
First Application: PCT/EP98/08199 filed 1998-12-14
Case: 22.1676
Developer / Inventors: ARI, S. Tepic

Laserpointer Surgeon controlled nagivation system
First Application: PCT/CH00/00668 filed 2000-12-18
Case: 10.1802
Developer / Inventors: AOR&D, M. Hehli, N. Suhm, P. Messmer, P. Regazzoni, P. Müller

Method of Automatic Guiding a C-Arm X-ray Device
First Application: 09/658,428 filed 2000-09-08
Case: 21.1837
Developer / Inventors: ADI, N. Suhm, P. Messmer

Device for moving a Medical Apparatus in a Controlled Manner (MEPUC)
First Application: PCT/CH2000/000022 filed 2000-01-14
Case: 21.1780
Developer / Inventors: ADI, N. Suhm, P. Messmer

Pending
Thermosensitive Hyaluronic Acid Conjugates and Methods for the Preparation thereof
First Application: IP 5003 PCT E filed 2013-10-02
Case: 10.F5003
Developer / Inventors: AOR&D, M. D'Este, D. Eglin

13 Publications & Presentations

13.1 Peer reviewed publications

epub 2012 - in print 2013

Beck A, Nehrbass D, Stoddart MJ, Schiuma D, Green J, Lansdowne JL, Richards RG, Boure LP.
The use of Reamer Irrigator Aspirator (RIA) autograft harvest in the treatment of critical-sized iliac wing defects in sheep: investigation of dexamethasone and beta-tricalcium phosphate augmentation.
Bone 2013;53:554-65 *(epub 2012 Dec 27) (IF 3.823)*

Brianza S, Vogel S, Rothstock S, Thalhauser M, Desrochers A, Boure L.
Comparative biomechanical evaluation of a pin-sleeve transfixation system in cadaveric calf metacarpal bones.
Vet Surg 2013;42:67-74 *(epub 2012 Dec 05) (IF 1.242)*

Brianza S, Vogel S, Rothstock S, Desrochers A, Boure L.
In vitro Evaluation of the Torsional Strength Reduction of Neonate Calf Metatarsal Bones with Bicortical Defects Resulting from the Removal of External Fixation Implants.
Vet Surg 2013;42:75-8 *(epub 2012 Dec 05) (IF 1.242)*

Brink PR, Windolf M, de BP, Brianza S, Braunstein V, Schwieger K.
Tension band wiring of the olecranon: Is it really a dynamic principle of osteosynthesis?
Injury. 2013;44(4):518-22 (epub 2012, Oct. 09) *(IF 1.975)*

D'Este M, Eglin D.
Hydrogels in calcium phosphate moldable and injectable bone substitutes: Sticky excipients or advanced 3-D carriers?
Acta Biomater 2013;9:5421-30 *(epub 2012 Nov 28) (IF 5.093)*

Devine DM, Hahn J, Richards RG, Gruner H, Wieling R, Pearce SG.
Coating of carbon fiber-reinforced polyetheretherketone implants with titanium to improve bone apposition.
J Biomed Mater Res B Appl Biomater 2013;101:591-8 *(epub 2012, Dec 20) (IF 2.308)*

Lädermann A, Gueorguiev B, Stimec B, Fasel J, Rothstock S, Hoffmeyer P. Acromioclavicular joint reconstruction: a comparative biomechanical study of three techniques.
J Shoulder Elbow Surg 2013;22:171-*8 (epub 2012 Apr 27) (IF 2.319)*

Lenz M, Gueorguiev B, Richards RG, Muckley T, Hofmann GO, Hontzsch D, Windolf M.
Fatigue performance of angle-stable tibial nail interlocking screws.
Int Orthop 2013;37:113-*8 (epub 2012 Aug 9) (IF 2.319)*

Lenz M, Perren SM, Richards RG, Mückley T, Hofmann GO, Gueorguiev B, Windolf M.
Biomechanical performance of different cable and wire cerclage configurations.
Int Orthop 2013;37:125-30 *(epub 2012 Nov 10) (IF 2.319)*

Mendel T, Radetzki F, Wohlrab D, Stock K, Hofmann GO, Noser H.
CT-based 3-D visualisation of secure bone corridors and optimal trajectories for sacroiliac screws.
Injury 2013;44:957-63 *(epub 2012 Dec 13) (IF 1.975)*

Neumann AJ, Schroeder J, Alini M, Archer CW, Stoddart MJ.
Enhanced Adenovirus Transduction of hMSCs Using 3D Hydrogel Cell Carriers.
Mol Biotechnol 2013;53:207-16. *(epub 2012, Mar 01) (IF 2.171)*

Potapova I, Eglin D, Laschke MW, Bischoff M, Richards RG, Moriarty TF.
Two-step labeling of Staphylococcus aureus with Lysostaphin-Azide and DIBO-Alexa using click chemistry.
J Microbiol Methods 2013;92:90-98 *(epub 2012, Nov 13) (IF 2.161)*

Rausch S, Schlonski O, Klos K, Gras F, Gueorguiev B, Hofmann GO, Mückley T.
Volar versus dorsal latest-generation variable-angle locking plates for the fixation of AO type 23C 2.1 distal radius fractures: A biomechanical study in cadavers.
Injury 2013;44:523-6 *(epub 2012 Sep 20) (IF 1.931)*

Schiuma D, Plecko M, Kloub M, Rothstock S, Windolf M, Gueorguiev B.
Influence of peri-implant bone quality on implant stability.
Med Eng Phys 2013;35:82-7 *(epub 2012 Jun 08) (IF 1.779)*

published 2013

Agarwal Y, Doebele S, Windolf M, Shiozawa T, Gueorguiev B, Stuby FM.
Two-leg alternate loading model - A different approach to biomechanical investigations of fixation methods of the injured pelvic ring with focus on the pubic symphysis.
J Biomech 2013;epub Nov 15 *(IF 2.716)*

Audige L, Cagienard F, Sprecher CM, Suhm N, Muller MA.
Radiographic quantification of dynamic hip screw migration.
Int Orthop 2013;epub Oct 22 *(IF 2.319)*

Beck A, Woods S, Lansdowne JL, Arens D.
The effects of multiple high-resolution peripheral quantitative computed tomography scans on bone healing in a rabbit radial bone defect model.
Bone 2013;56:312-9 *(IF 3.823)*

Blazejak M, Hofmann-Fliri L, Buchler L, Gueorguiev B, Windolf M.
In vitro temperature evaluation during cement augmentation of proximal humerus plate screw tips.
Injury 2013;44:1321-6 *(IF 1.931)*

Borumandi F, Hammer B, Noser H, Kamer L.
Classification of orbital morphology for decompression surgery in Graves' orbitopathy: two-dimensional versus three-dimensional orbital parameters.
Br J Ophthalmol 2013;97:659-62 *(IF 2.725)*

Bruderer M, Alini M, Stoddart MJ.
Role of HOXA9 and VEZF1 in Endothelial Biology.
J Vasc Res 2013;50:265-78 *(IF 2.434)*

Cunningham C, Srivastava A, Collin E, Grad S, Alini M, Pandit A, Wall JG.
Isolation and Characterisation of a Recombinant Antibody Fragment That Binds NCAM1-Expressing Intervertebral Disc Cells.
PLoS One 2013;8:e83678 *(IF 3.730)*

Czekanska EM, Stoddart MJ, Ralphs JR, Richards RG, Hayes JS.
A phenotypic comparison of osteoblast cell lines versus human primary osteoblasts for biomaterials testing.
J Biomed Mater Res A 2013;epub Aug 24 *(IF 2.834)*

Duttenhoefer F, Lara de FR, Meury T, Loibl M, Benneker LM, Herrmann M,Richards RG, Alini M, Verrier S.
3D scaffolds co-seeded with human endothelial progenitor and mesenchymal stem cells: Evidence of prevascularisation within 7 days.
Eur Cell Mater 2013;26:49-65 *(IF 4.558)*

Gardner OF, Archer CW, Alini M, Stoddart MJ.
Chondrogenesis of mesenchymal stem cells for cartilage tissue engineering
Histol Histopathol 2013;28:23-42 *(IF 2.281)*

Goetzen M, Nicolino T, Hofmann-Fliri L, Blauth M, Windolf M.
Metaphyseal screw augmentation with PMMA of the LISS-PLT plate improves angular stability in osteoporotic proximal third tibia fractures - a biomechanical study in human cadaveric tibiae.
J Orthop Trauma 2013;epub Sept 26 *(IF 1.751)*

Guterl CC, See EY, Blanquer SB, Pandit A, Ferguson SJ, Benneker LM, Grijpma DW, Sakai D, Eglin D, Alini M, Iatridis JC, Grad S.
Challenges and strategies in the repair of ruptured annulus fibrosus.
Eur Cell Mater 2013;25:1-21 *(IF 4.558)*

Hilz FM, Ahrens P, Grad S, Stoddart MJ, Dahmani C, Wilken FL, Sauerschnig M, Niemeyer P, Zwingmann J, Burgkart R, von Eisenhart-Rothe R, Sudkamp NP, Weyh T, Imhoff AB, Alini M, Salzmann GM.
Influence of extremely low frequency, low energy electromagnetic fields and combined mechanical stimulation on chondrocytes in 3-D constructs for cartilage tissue engineering.
Bioelectromagnetics 2013;epub Nov 06 *(IF 2.021)*

Johnstone B, Alini M, Cucchiarini M, Dodge GR, Eglin D, Guilak F, Madry H, Mata A, Mauck RL, Semino CE, Stoddart MJ.
Tissue engineering for articular cartilage repair--the state of the art.
Eur Cell Mater 2013;25:248-67 *(IF 4.558)*

Kamer L, Noser H, Hammer B.
Anatomical background for the development of preformed cranioplasty implants.
J Craniofac Surg 2013;24:264-8 *(IF 0.686)*

Kubosch D, Windolf M, Milz S, Sudkamp NP, Strohm PC.
Biomechanical comparison of three types of bone graft for anterior spondylodesis.
Technol Health Care 2013;21:315-22 *(IF 0.638)*

Lenz M, Perren SM, Gueorguiev B, Höntzsch D, Windolf M.
Mechanical behavior of fixation components for periprosthetic fracture surgery.
Clin Biomech (Bristol, Avon) 2013;28:988-993 *(IF 1.869)*

Lenz M, Perren SM, Gueorguiev B, Richards RG, Hofmann GO, Fernandez DA, Höntzsch D, Windolf M.
A biomechanical study on proximal plate fixation techniques in periprosthetic femur fractures.
Injury 2013;epub Oct 29 *(IF 1.931)*

Loibl M, Baumlein M, Massen F, Gueorguiev B, Glaab R, Perren T, Rillmann P. Ryf C, Naal FD.
Sports Activity After Surgical Treatment of Intra-articular Tibial Plateau Fractures in Skiers.
Am J Sports Med 2013;41:1340-7 *(IF 4.439)*

Malonzo C, Chan SC, Kabiri A, Eglin D, Grad S, Bonel HM, Benneker LM, Gantenbein-Ritter B.
A papain-induced disc degeneration model for the assessment of thermo-reversible hydrogel-cells therapeutic approach.
J Tissue Eng Regen Med 2013;epub Jan 09 *(IF 2.826)*

Mendel T, Noser H, Kuervers J, Goehre F, Hofmann GO, Radetzki F.
The influence of sacral morphology on the existence of secure S1 and S2 transverse bone corridors for iliosacroiliac screw fixation.
Injury 2013;44:1773-9 *(IF 1.931)*

Metzger W, Schwab B, Miro MM, Grad S, Simpson A, Veith M, Zaporojtchenko V, Verrier S, Hayes JS, Bubel M, Pohlemann T, Oberringer M, Aktas C.
Induction of osteogenic differentiation by nanostructured alumina surfaces.
J Biomed Nanotechnol 2013;epub *(IF 5.256)*

Moriarty F.
Bone infection.
Vet Comp Orthop Traumatol 2013;26:IX *(IF 1.013)*

Neumann A, Alini MP, Archer CP, Stoddart MJ.
Chondrogenesis of human bone-marrow derived mesenchymal stem cells is modulated by complex mechanical stimulation and adenoviral-mediated overexpression of bone-morphogenetic protein 2.
Tissue Eng Part A 2013;19:1285-1294 *(IF 4.065)*

Neumann AJ, Alini M, Archer CW, Stoddart MJ.
Retroviral-mediated overexpression of human bone morphogenetic protein 2 affects human mesenchymal stem cells during monolayer proliferation: A cautionary note.
Electron J Biotechnol 2013;16/2 *(IF 0.827)*

Peroglio M, Eglin D, Benneker LM, Alini M, Grad S.
Thermoreversible hyaluronan-based hydrogel supports *in vitro* and *ex vivo* disc-like differentiation of human mesenchymal stem cells.
Spine J. 2013;13(11):1627-39 *(IF 3.355)*

Petrou M, Niemeyer P, Stoddart MJ, Grad S, Bernstein A, Mayr HO, Bode G, Südkamp N, Alini M, Salzmann GM.
Mesenchymal stem cell chondrogenesis: composite growth factor-bioreactor synergism for human stem cell chondrogenesis.
Regen Med 2013;8:157-70 *(IF 3.873)*

Popp AW, Schwyn R, Schiuma D, Keel MJ, Lippuner K, Benneker LM.
DensiProbe Spine: an intraoperative measurement of bone quality in spinal instrumentation. A clinical feasibility study.
Spine J 2013;13:1223-1229 *(IF 3.355)*

Potapova I.
Functional Imaging in Diagnostic of Orthopedic Implant-Associated Infections.
Diagnostics 2013;3:356-371 *(IF n.a.)*

Radetzki F, Mendel T, Noser H, Stoevesandt D, Rollinghoff M, Gutteck N, Delank KS, Wohlrab D.
Potentialities and limitations of a database constructing three-dimensional virtual bone models.
Surg Radiol Anat 2013;35:963-8 *(IF 1.130)*

Randau TM, Schildberg FA, Alini M, Wimmer MD, Haddouti el-M., Gravius S, Ito K, Stoddart MJ.
The effect of dexamethasone and triiodothyronine on terminal differentiation of primary bovine chondrocytes and chondrogenically differentiated mesenchymal stem cells.
PLoS One 2013;8:e72973 *(IF 3.730)*

Rausch S, Loracher C, Frober R, Gueorguiev B, Wagner A, Gras F, Simons P, Klos K.
Anatomical Evaluation of Different Approaches for Tibiotalocalcaneal Arthrodesis.
Foot Ankle Int 2013;epub Dec 11 *(IF 1.474)*

Richards RG.
AO Research Institute Davos within the AO Foundation: A model for translation of science to the clinics.
Journal of Orthopaedic Translation 2013;1:11-8 *(IF n.a.)*

Rochford ET, Poulsson AH, Salavarrieta VJ, Lezuo P, Richards RG, Moriarty TF. Bacterial adhesion to orthopaedic implant materials and a novel oxygen plasma modified PEEK surface.
Colloids Surf B Biointerfaces 2013;113C:213-22 *(IF 3.554)*

Röderer G, Brianza S, Schiuma D, Schwyn R, Scola A, Gueorguiev B, Gebhard F, Tami A.
Mechanical assessment of local bone quality to predict failure of locked plating in a proximal humerus fracture model.
Orthopedics 2013;36:e1134-e1140 *(IF 1.054)*

Röderer G, Scola A, Schmolz W, Gebhard F, Windolf M, Hofmann-Fliri L.
Biomechanical *in vitro* assessment of screw augmentation in locked plating of proximal humerus fractures.
Injury 2013;44:1327-32 *(IF 1.931)*

Schmid T, Zurbriggen S, Zderic I, Gueorguiev B, Weber M, Krause FG.
Ankle joint pressure changes in a pes cavovarus model: supramalleolar valgus osteotomy versus lateralizing calcaneal osteotomy.
Foot Ankle Int 2013;34:1190-7 *(IF 1.474)*

Scola A, Gebhard F, Weckbach S, Dehner C, Schwyn R, Fliri L, Röderer G.
Mechanical quantification of local bone quality in the humeral head: a feasibility study. Open Orthop J 2013;7:172-6 *(IF n.a.)*

Sermon A, Hofmann-Fliri L, Richards RG, Flamaing J, Windolf M.
Cement augmentation of hip implants in osteoporotic bone: How much cement is needed and where should it go?
J Orthop Res 2013;epub Nov 20 *(IF 2.875)*

Sprecher CM, Gahlert M, Rohling S, Kniha H, Gueorguiev B, Milz S.
Comparison of imaging methods used for dental implant osseous integration assessment.
J Mater Sci Mater Med 2013;24:2195-200 *(IF 2.141)*

Vadala G, Russo F, Pattappa G, Schiuma D, Peroglio M, Benneker LM, Grad S, Alini M, Denaro V.
The transpedicular approach as an alternative route for intervertebral disc regeneration.
Spine (Phila Pa 1976). 2013;38(6):E319-24 *(IF 2.159)*

Varga E Jr, Hammer B, Hardy BM, Kamer L.
The accuracy of three-dimensional model generation. What makes it accurate to be used for surgical planning?
Int J Oral Maxillofac Surg 2013;42:1159-66 *(IF 1.521)*

Viehöfer AF, Shinohara Y, Sprecher CM, Boszczyk BM, Buettner A, Benjamin M, Milz S.
The molecular composition of the extracellular matrix of the human iliolumbar ligament.
Spine J 2013;epub Oct 16 *(IF 3.355)*

Wähnert D, Hofmann-Fliri L, Gotzen M, Kosters C, Windolf M, Raschke MJ.
Feasibility study on the potential of a spiral blade in osteoporotic distal femur fracture fixation.
Arch Orthop Trauma Surg 2013;133:1675-9 *(IF 1.358)*

Wang N, Grad S, Stoddart MJ, Niemeyer P, Südkamp NP, Pestka J, Alini M, Chen J, Salzmann GM.
Bioreactor-induced chondrocyte maturation is dependent on cell passage and onset of loading.
Cartilage 2013;epub Jan 09 *(IF n.a.)*

Wang N, Grad S, Stoddart MJ, Niemeyer P, Reising K, Schmal H, Südkamp NP, Alini M, Salzmann GM
Particulate cartilage under bioreactor-induced compression and shear.
Int Orthop 2013;epub Nov 28 *(IF 2.319)*

13.2 Books and bookchapters

Moriarty TF, Zaat SAJ, Busscher HJ (Eds.)
Biomaterials Associated Infection. Immunological Aspects and Antimicrobial Strategies.
New York, Heidelberg, Dordrecht, London: Springer; 2013 (*)

Calabro L, Lutton C, Seif El Din AF, Richards RG, Moriarty TF.
Animal Models of Orthopedic Implant-Related Infection.
In: Moriarty TF, Zaat SAJ, Busscher HJ (Eds).
Biomaterials Associated Infection. Immunological Aspects and Antimicrobial Strategies.
New York, Heidelberg, Dordrecht, London: Springer; 2013; p. 273-304 (*)

Grad S, Stoddart MJ, Eglin D, Alini M.
Cartilage Tissue Engineering. Advances in Stem Cell-Based Approaches.
In: Ramalingam M, Vallittu P, Ripamonti U, Li WJ (Eds.)
Tissue Engineering and Regenerative Medicine. A Nano Approach.
Boca Raton: CRC Press / Taylor & Francis; 2013; p. 413-31

Schmidmaier G, Gahukamble AD, Moriarty TF, Richards RG.
Infection in Fracture Fixation: Device Design and Antibiotic Coatings Reduce Infection Rates.
In: Moriarty TF, Zaat SAJ, Busscher HJ (Eds).
Biomaterials Associated Infection. Immunological Aspects and Antimicrobial Strategies.
New York, Heidelberg, Dordrecht, London: Springer; 2013; p. 435-53 (*)

(*) Moriarty, Calabro & Schmidmaier: the book was already available in 2012 (Copyright 2013) and therefore also mentioned in the 2012 ARI acitvity report

13.3 Abstracts published in journals

Collin E, Kilcoyne M, Grad S, Alini M, Joshi L, Pandit A.
Cell surface glycosylation and glycosaminoglycan composition profiles in immature and mature intervertebral discs.
Eur Cell Mater 2013;26 S8:22 (AOER Symposium) (poster)

Galea L, Peroglio M, Eglin D, Graule T, Bohner M.
Recrystallization and polymer impregnation improve strength and toughness of calcium phosphate ceramics.
Eur Cell Mater 2013;26:1 (SSB) (oral)

Gardner OF, Musumeci G, Archer CW, Alini M, Stoddart MJ.
Mechanically induced chondrogenesis of mesenchymal stem cells can be improved by manipulating the location of cells within a tissue engineering scaffold.
Eur Cell Mater 2013;26 S8:5 (AOER Symposium) (oral)

Herrmann M, Binder A, Menzel U, Alini M, Verrier S.
Towards an autologous culture of human endothelial progenitor cells.
Eur Cell Mater 2013;26:43 (ECM) (poster)

Janki M, Peroglio M, De Wild M, Benneker LM, Alini M, Grad S.
Intervertebral disc regeneration by mesenchymal stem cells and fibrin.
Eur Cell Mater 2013;26 S8:23 (AOER Symposium) (poster)

Lenz M, Nicolino T, Hofmann GO, Gueorguiev B, Richards RG, Kojima KE.
Interfragmentary compression of different tibial plateau split fracture fixation techniques - an experimental study.
Injury 2013;44:S24-S25 (OI Küntscher Soc) (oral)

Li Z, Pirvu T, Blanquer SB, Grijpma DW, Grad S, Alini M, Eglin D.
Polyurethane membrane for annulus fibrosus rupture closure.
Eur Cell Mater 2013;26:55 (SSB) (poster)

Li Z, Privu T, Blanquer SB, Grijpma DW, Grad S, Alini M, Eglin D.
Polyurethane membrane for intervertebral disc annulus rupture closure - feasibility under dynamic loading in an organ culture study.
Eur Cell Mater 2013;26 S8:43 (AOER Symposium) (poster)

Pattappa G, Peroglio M, Sakai D, Mochida J, Benneker LM, Alini M, Grad S.
Mesenchymal stem cell homing into the intervertebral disc: A chemotactic induced response.
Eur Cell Mater 2013;26:53 (ECM) (poster)

Potapova I, Eglin D, Laschke MW, Bischoff M, Richards RG, Moriarty TF.
Bioorthogonal reaction for two-step labeling of Staphylococcus aureus with Lysostaphin.
Eur Cell Mater 2013;26:43 (SSB) (poster)

Sprecher CM, Braunstein V, Nehrbass D, Milz S, Gohlke F, Hertel R, Südkamp NP, Schmidutz F.
Hemi-resurfacing implants of the shoulder: short term osseous integration.
Eur Cell Mater 2013;26:27 (Meet Expert) (poster)

Sprecher CM, Boudrieau RJ, Suter T, Keating JH, McCarthy RJ, Milz S.
Is increased occurrence of peri-implanted osteosarcoma associated with cast stainless steel implants?
Eur Cell Mater 2013;26:3 (Meet Expert) (oral)

ter Boo GJ, Grijpma DW, Moriarty TF, Eglin D.
Hyaluronic acid conjugates and their complexation with gentamicin for local infection prophylaxis.
Eur Cell Mater 2013;26:50 (SSB) (poster)

Vadala G, Russo F, De Strobel F, Bernardini M, Eglin D, Grad S, Alini M, Denaro V.
The transpedicular approach for the study of intervertebral disc regeneration strategies: *in vivo* characterization.
Eur Cell Mater 2013;26:65 (ECM) (poster)

Wagner A, Bleiler C, Stadelmann V, Windolf M, Gueorguiev B, Köstler H, Boger A, Röhrle O, Ehlers W.
Porous-media simulation of bone-cement spreading during vertebroplasty.
PAMM 2013;13:67-8 (GAAM) (oral)

13.4 Conference proceedings

Bara JJ, Menzel U, Lezuo P, Alini M, Stoddart MJ.
Modelling the Mesenchymal Stem Cell Niche in Bone Marrow.
2013 FIRM Symposium (oral)

Bara JJ, Menzel U, Lezo P, Alini M, Stoddart MJ.
Modelling the Mesenchymal Stem Cell Niche in Bone Marrow.
2013 eCM XIV (poster)

Binder A, Herrmann M, Menzel U, Loibl M, Nerlich M, Alini M, Verrier S.
Origin of Pericyte-like Cells in Co-cultures of Mesenchymal Stem Cells and Endothelial Progenitor Cells.
2013 TERMIS (poster)

Blankstein M, Widmer D, Hofmann-Fliri L, Götzen M, Richards RG, Gueorguiev B, Windolf M.
Messung des intraossären Drucks im Femurkopf während der Zementaugmentation von Klingenimplantaten.
2013 DKOU (oral)

Blankstein M, Widmer D, Götzen M, Fliri L, Richards RG, Gueorguiev B, Windolf M.
Cement augmentation of the Perforated Proximal Femur Nail Antirotation (PFNA) blade does not cause critical femoral head intra-osseous pressure elevation.
2013 SICOT (e-poster)

Blazejak M, Windolf M, Nicolino T, Büchler L, Gueorguiev B, Hofmann-Fliri L.
In-vitro temperature evaluation during cement augmentation of proximal humerus plate screw tips.
2013 ECTES (oral)

Campbell DA, Kamer L, Windolf M, Wähnert D, Nunez Vazquez F, Noser H.
A method of 3D bone mineral density mapping for the distal radius.
2013 IFSSH & IFSHT (oral)

Czekanska E, Ralphs JR, Alini M, Stoddart MJ.
Benefits Of Chemotactic And Inflammatory Modulators In Bone Regeneration.
2013 TERMIS (poster)

D'Este M, Eglin D, Alini M.
Synthesis and Characterization of Thermoresponsive Hyaluronan Hydrogels.
2013 ISHAS (poster)

Dresing I, Zeiter S, Alini M, Eglin D.
Press-fit Osteochondral Poly(ester-urethane) Scaffolds in a Rabbit Model.
2013 ESB (poster)

Eberli U, Fliri L, Lorenzetti S, Windolf M, Stadelmann V, Gueorguiev B.
Decreased cement stiffness does not imporve the anchorage of augmented implants in osteoporotic bone.
2013 SBMS (oral)

Eglin D, Richards RG, Qin L, Tang TT, de Bruijn J, Peng J, Lu S, Peijs T, Alini M, Grijpma DW.
RAPIDOS: Rapid Prototyping of Custom-Made Bone-Forming Tissue Engineering Constructs.
2013 CESB (oral)

Eglin D, D'Este M, Borget P, Daculsi G, Mykhaylyk O, Plank C, Anton M, Alini M..
Multiphasic Gene Activated Matrices for Osteochondral Regeneration in Osteoarthritis.
2013 ISACB (poster)

Glueck M, Gardner OF, Czekanska E, Salzmann GM, Alini M, Stoddart MJ.
MSC-Osteoblast Crosstalk in Osteogenesis.
2013 TERMIS (poster)

Goetzen M, Nicolino T, Hofmann-Fliri L, Gueorguiev B, Blauth M, Windolf M.
A novel approach for extraarticular proximal tibia fracture fixation in osteoporotic bone - a biomechanical study in human cadaveric tibiae.
2013 ECTES (oral)

Gomes GS, Oliveira RG, Kojima KE, Lenz M, Nicolino T, Gueorguiev B.
Locking plates maintain applied interfragmentary compression in tibia plateau split fracture fixation. An experimental study.
Placas bloqueadas mantêm compressao interfragmentaria aplicada em fraturas cisalhamento (split) de planalto tibial. Estudo experimental.
2013 CBTO (oral)

Herrmann M, Binder A, Menzel U, Alini M, Verrier S.
Optimal Autologous Culture of Endothelial Progenitor Cells for Tissue Engineering of Vascularized Implants.
2013 TERMIS (poster)

Herrmann M, Duttenhöfer F, Loibl M, Binder A, Zeiter S, Peters S, Alini M, Verrier S.
Endothelial Progenitor Cells Promote Neovascularization of Tissue Engineered Implants *in vivo.*
2013 TERMIS (poster)

Herrmann M, Duttenhöfer F, Loibl M, Binder A, Zeiter S, Alini M, Verrier S.
Promotion of neovascularization in tissue engineered bone implants.
2013 SBMS (poster)

Herrmann M, Binder A, Loibl M, Menzel U, Alini M, Verrier S.
Endothelial Progenitor Cells for Tissue Engineering of Vascularized Bone Implants.
2013 FIRM (oral)

Kamer L, Noser H, Popp AW, Lenz M, Windolf M, Blauth M.
Analyse der Knochendichte und deren Verlustes in der distalen Tibia bei Osteoporose.
2013 DKOU (oral)

Klos K, Rausch S, Mückley T, Wolf U, Windolf M, Gueorguiev B.
Biomechanischer Vergleich zwischen einer winkelstabilen Platten- und einer zementaugmentierten Schraubenosteosynthese zur Versorgung von Kalkaneusfrakturen.
2013 ISF (e-poster)

Klos K, Loracher C, Fröber R, Gueorguiev B, Mückley T, Simons P.
Vergleichende anatomische Studie zur Evaluierung zweier verschiedener Zugänge zum lateralen Release.
2013 ISF (e-poster)

Kojima KE, Lenz M, Nicolino T, Hofmann GO, Richards RG, Gueorguiev B.
Interfragmentary compression of different tibia plateau split fracture fixation techniques.
An experimental study.
2013 CORS (oral)

Lenz M, Perren SM, Gueorguiev B, Richards RG, Fernandez dell'Oca A, Höntzsch D, Hofmann GO, Windolf M.
The concept of point contact fixation - interface mechanics of cerclages.
2013 ECTES (poster)

Lenz M, Gueorguiev B, Richards RG, Mückley T, Hofmann GO, Höntzsch D, Perren SM, Windolf M.
Optimierung der Dauerbeanspruchbarkeit von Cerclagen - eine biomechanische Studie.
2013 NOUV (poster)

Li Z, Peroglio M, Lezuo P, Pattappa G, Alini M, Grad S.
An endplate approach improves the mechanical response of nucleotomized intervertebral discs.
2013 ORS (poster)

Li Z, Pirvu T, Blanquer SB, Grijpma DW, Alini M, Eglin D, Grad S.
Mesenchymal stem cells encapsulated poly(trimethylene carbonate) implants for annulus fibrosus defect repair - an organ culture study under dynamic load.
2013 Philadelphia Spine Research Symposium (oral)

Loebel C, Czekanska E, Alini M, Stoddart M.
The RunX2 - Sox9 "see-saw": A balance for MSC osteogenesis.
2013 ORS (poster)

Loebel C, Czekanska E, Staudacher J, Alini M, Stoddart M.
Effect of Il-1beta during osteogenic differentiation of human MSCs.
2013 SBMS (oral)

Mendel T, Arlt S, Noser H, Marintschev I, Radetzki F, Culemann U, Hofmann GO.
Frakturversorgung am Azetabulum - Existiert in der infra-azetabulären Region regelhaft ein Knochenkorridor für eine 3,5 mm Schraube?
2013 NOUV (poster)

Mendel T, Radetzki F, Stock K, Hofmann GO, Noser H.
PC-gestützte 3-D Berechnung sicherer Korridore und optimaler Positionen für SI-Schrauben anhand klinischer CT-Datensätze.
2013 DKOU / DGU (oral)

Mendel T, Arlt S, Noser H, Marintschev I, Radetzki F, Hofmann GO.
Computer-assisted 3-D analysis of the safe intra-acetabular bone path for a long 3.5 mm screw.
2013 EFFORT (oral)

Nicolino T, Goetzen M, Hofmann-Fliri L, Gueorguiev B, Blauth M, Windolf M.
Implant augmentation in osteoporotic femoral neck fractures: No biomechanical advantage in a cadaveric model.
2013 ECTES (oral)

Nicolino T, Goetzen M, Barla J, Gueorguiev B, Windolf M, Hofmann-Fliri L.
Aumentación de implantes en fracturas osteoporoticas de cuello femoral: No se observan ventajas biomecánicas en un modelo cadavérico.
2013 CAOT (oral)

Peroglio M, D'Este M, Eglin D, Grad S, Benneker L, Alini M.
Hyaluronan Hydrogel Supports Human Mesenchymal Stromal Cells (hMSCs) Differentiation Toward the Disc Phenotype Without Growth Factor Supplementation.
2013 ISHAS (oral)

Peroglio M, Eglin D, Benneker L, Alini M, Grad S.
Mesenchymal Stem Cell in the Intervertebral Disc: Is There a Need for Preconditioning?
2013 SIB (oral)

Peroglio M, Eglin D, Benneker L, Alini M, Grad S.
Loading and carrier determine the success of stem cell delivery into degenerative discs.
2013 CORS (oral)

Pirvu T, Alini M, Grad S.
Does Platelet-rich plasma improve annulus fibrosus self-repair properties in-vitro?
2013 GSC (oral)

Pohlemann T, Agarwal Y, Wahl D, Windolf M, Gueorguiev B.
Residual holding strength of dynamic locking versus conventional locking head screws.
2013 ESBioMech (oral)

Post V, Wahl P, Uckay I, Zimmerli W, Corvec S, Loiez C, Ochsner P, Moriarty TF.
Biofi Im formation and molecular characterization of Staphylococcus aureus isolated from orthopaedic implant related infections depends on type of device.
2013 CORS (oral)

Potapova I, Eglin D, Laschke MW, Bischoff M, Richards RG, Moriarty TF.
Click chemistry for imaging of infection: two-step labeling of Staphylococcus aureus with lysostaphin.
2013 CORS (oral and moderator)

Poulsson AH, Eglin D, Zeiter S, Camenisch K, Sprecher C, Agarwal Y, Nehrbass D, Wilson J, Richards RG.
Investigation of Oxygen Plasma Modified PEEK Osseointegration in a Sheep Model.
2013 ESB (oral)

Rochford ET, Sabaté Bresco M, Ziegler M, O'Mahoney L, Moriarty TF.
Assessing the role of implant associated immune responses on the development of infection.
2013 CORS (oral)

Röderer G, Scola A, Hofmann-Fliri L, Schmölz W, Gebhard F.
Cement augmented locked plating of a proximal humerus fractures model in consideration of local bone quality.
2013 FNN (oral)

Röderer G, Scola A, Schmölz W, Hofmann-Fliri L, Gebhard F.
Biomechanische *in vitro* Untersuchung der Zementaugmentation am proximalen Humerus basierend auf der lokalen Bestimmung der Knochenqualität.
2013 VBC (oral)

Röderer G, Schmölz W, Hofmann-Fliri L, Gebhard,F.
Screw augmentation in locked plating of proximal humerus fractures. A biomechanical *in vitro* study.
2013 EFFORT (oral)

Röderer G, Scola A, Schmölz W, Hofmann-Fliri L, Gebhard,F.
Die zementaugmentierte winkelstabile Plattenosteosynthese am proximalen Humerus. Eine biomechanische *in vitro* Studie.
2013 DKOU (oral)

Röderer G, Scola A, Schmölz W, Hofmann-Fliri L, Gebhard F.
Einfluss der Zementaugmentation auf die Primärstabilität einer winkelstabilen Plattenosteosynthese am Modell der proximalen Humerusfraktur.
2013 DGfB (oral)

Schmid T, Zurbriggen S, Weber M, Zderic I, Gueorguiev B, Wahl D, Krause F.
Ankle joint pressure in pes cavus after supramalleolar tibial and lateralizing calcaneal osteotomy.
2013 AOFAS (oral)

Schmid T, Zurbriggen S, Gueorguiev B, Zderic I, Krause F.
Evaluation of a static pes cavus model based on changes of the osseous architeture.
2013 DKOU (oral)

Schmid T, Zurbriggen S, Weber M, Zderic I, Wahl D, Krause F.
Ankle joint pressure in pes cavus after supramalleolar tibial and lateralizing calcaneal osteotomy.
2013 DKOU (oral)

Schmidutz F, Sprecher CM, Gohlke F, Hertel R, Südkamp NP, Braunstein V.
Der zementfreie Oberflächenersatz der Schulter: Eine Analyse der sekundären Stabilität [Cementless resurfacing arthroplasty of the shoulder: An analysis of the secondary stability].
2013 AGA (oral)

Schmidutz F, Sprecher CM, Milz S, Nehrbass D, Südkamp NP, Hertel R, Gohlke F, Braunstein V.
Hemi-Resurfacing der Schulter: Analyse des Bone-Remodellings unter dem Implantat.
2013 NOUV (oral)

Schmidutz F, Sprecher CM, Nehrbass D, Milz S, Hertel R, Südkamp NP, Gohlke F, Braunstein V.
Evaluation der ossären Integration und Knochenumbauprozesse von Oberflächenersatzimplantaten der Schulter.
2013 DVSE (oral)

Schmidutz F, Sprecher CM, Nehrbass D, Milz S, Gohlke F, Hertel R, Südkamp NP, Braunstein V.
Hemi-Resurfacing der Schulter: Analyse der knöchernen Integration und Knochenumbauprozesse.
2013 DKOU (oral)

Schmidutz F, Sprecher CM, Milz S, Nehrbass D, Gohlke F, Hertel R , Jäger M, Südkamp NP, Braunstein V.
Die knöcherne Integration von zementfreien Hemi-Resurfacing Implantaten der Schulter.
2013 MSEOUMF (oral)

Schmidutz F, Sprecher CM, Gohlke F, Hertel R, Südkamp NP, Braunstein V.
Die knöcherne Integration von Hemi-Resurfacing Implantaten der Schulter.
2013 VSOU (oral)

Schneider K, Zderic I, Gueorguiev B, Richards RG, Nork SE.
What is the underlying mechanism for the failure mode observed in the Proximal Femoral Locking Compression Plate? A Biomechanical Study.
2013 CORS (oral)

Schneider K, Zderic I, Gueorguiev B, Richards RG, Nork SE.
What is the underlying mechanism for the failure mode observed in the Proximal Femoral Locking Compression Plate? A Biomechanical Study.
2013 SICOT (e-poster)

Seelbach R, Peroglio M, Fransen P, Royo M, Albericio F, Alini M, Eglin D, Mata A.
Modulating the biochemical environment of a hyaluronan-based thermo-reversible hydrogel with integrin binding dendrimers.
2013 ESB (oral)

Sharma S, Stadelmann V, Kamer L, Noser H.
Design of an image analysis workflow to access bone mineral densities using different X-ray based imaging modalities.
2013 SBMS (poster)

Stadelmann VA, Potapova I, Camenisch K, Eberli U, Richards RG, Moriarty TF.
In-vivo monitoring of bone around an infected implant.
2013 CORS (oral)

ter Boo GJ, Grijpma DW, Moriarty TF, Eglin D.
Thermoresponsive hyaluronan compositions for local infection prophylaxis.
2013 ESB (poster)

Vadala G, Russo F, Pattappa G, Schiuma D, Peroglio M, Grad S, Benneker L, Alini M, Denaro V.
The transpedicular approach as new route for intervertebral disc regeneration.
2013 ISSLS (poster)

Vadala G, Russo F, Pattappa G, Peroglio M, Grad S, Stadelmann V, Alini M, Denaro V.
A novel nucleotomy model with intact anulus fibrosus to test intervertebral disc regneration strategies.
2013 ISSLS (poster)

Wagner D, Kamer L, Sawaguchi T, Noser H, Rommens PM.
Bone stock distribution along trans-sacral corridors in the elderly and it's relevance to sacral insufficiency fractures.
2013 OTA (poster)

Wagner D, Rommens P, Sawaguchi T, Kamer L, Noser H.
Anatomical variability and its implication on trans-sacral corridors and implant positioning. Results from CT based 3D statistical modeling of the sacrum.
2013 EFORT (oral)

Wagner D, Rommens PM, Sawaguchi T, Kamer L, Noser H.
Bone stock distribution within the sacrum and its implication to the understanding and treatment of sacral insufficiency fractures.
2013 ECTES (oral)

Wagner D, Kamer L, Sawaguchi T, Noser H, Rommens PM.
It's the corridor height limiting safe trans-sacral implant positioning.
2013 OTA (poster)

Wähnert D, Hofmann-Fliri L, Kösters C, Raschke MJ, Richards RG, Gueorguiev B, Windolf M.
Das Potential der Implantataugmentation bei der Versorgung osteoporotischer distaler Femurfrakturen.
2013 DKOU (poster)

Wähnert D, Hofmann-Fliri L, Raschke MJ, Richards RG, Windolf M.
Implant augmentation as a new concept in the treatment of osteoporotic distal femur fractures. A biomechanical study.
2013 ECTES (oral)

Widmer D, Hofmann-Fliri L, Blankstein M, Blauth M, Zweifel E, Gueorguiev B, Windolf M.
Prophylaktische Verstärkung des proximalen Femurs im porotischen Knochen.
2013 DKOU (oral)

Zderic I, Nicolino T, Windolf M, Gueorguiev B.
Pressure investigation in transverse patellar fracture fixation with two different tension band wiring techniques. A biomechanical study.
2013 CORS (poster)

Zderic I, Windolf M, Gueorguiev B, Stadelmann V.
Monitoring of cement distribution in vertebral bodies during vertebroplasty.
2013 CORS (oral)

Zderic I, Unholz C, Windolf M, Gueorguiev B, Stadelmann VA.
Cement flow monitoring and assessment of injection forces during vertebroplasty.
2013 DKOU (oral)

13.5 Dissertations

Dresing IM, Zeiter S, Auer J, Alini M, Eglin D.
Evaluation of a press-fit Osteochondral Poly(ester-urethane) Scaffold in a Rabbit Defect Model.
2013 Universität Zürich, Vetsuisse (Auer J, Zeiter S) – Dr med vet

Janki M.
Effects of mechanical load and mesenchymal stem cells on intervertebral discs cultured in a bioreactor system.
2013 FHNW - Life Sciences (Grad S, Peroglio M, De Wild M) - BSc
Her degree was awarded with the highest rank (6/6). She also got an overall mark of 5.4/6 for her Bachelor degree in Life Science Technologies.

Neumann A.
The effect of mechanical stimulation and biological factors on human mesenchymal stem cell and human articular cartilage progenitor cell chondrogenesis and hypertrophy.
2013 Cardiff University, School of Biosciences (Stoddart MJ, Alini M, Archer CW, Boulter CA) – PhD

Ocampo Garcia WD.
Evaluation of a statistical humerus model through finite element analysis .
2013 Universität Stuttgart - Institute of Applied Mechanics (Röhrle O, Windolf M) - MSc

Rochford ET.
From preoperative to postoperative: Bacterial contamination of orthopaedic implant materials.
2013. Aberystwyth University, Institute of Biological, Environmental and Rural Sciences (ap Gwynn I, Richards RG, Moriarty TF) - PhD

Röhling SK.
Osseointegration von Zirkoniumdioxidimplantaten mit mikrorauer Oberflächentopografie im Vergleich zu Titan-SLA Implantaten - Eine biomechanische und histomorphometrische Untersuchung am Miniaturschwein.
2013 Ludwig-Maximilians-Universität München, medizinische Fakultät (Milz S) – Dr med dent

Steinmetz P.
Analyse des Verteilungsverhaltens von Knochenzement bei der Injektion in osteoporotische Wirbelkörper anhand von offenporigen Schaumstoffmodellen
2013 Hochschule Ansbach – Ingenieurwissenschaften (Boger A, Gueorguiev B) – BSc

Wolfrum C.
Entwicklung eines röntgenbasierenden chirurgischen Navigationskonzepts mit Echtzeit Feedback.
2013 Hochschule Ansbach - Ingenieurwissenschaften (Boger A, Windolf M) – BSc

13.6 Presentations (not in conference proceedings)

26.-29.01.2013	Richards Geoff: "Biomaterial Session", ORS 2013 Annual Meeting, San Antonio, TX, USA (Session Chair)
22.03.2013	Richards Geoff: "Implant Removal: Point - Counterpoint - When to Remove When Not to Remove", AAOS 2013 Annual Meeting, Chicago, USA (Invited Faculty)
12.-15.06.2013	Richards Geoff: "News from the AO Institutes: Q&A", Board of Trustees Meeting, Lima, Peru
23.-25.06.2013	Richards Geoff: "Clinical Perspectives", eCM XIV, Davos, Switzerland (Session Chair)
25.-26.06.2013	Richards Geoff: "Welcome to Davos", 19th Swiss Conference on Biomaterials, Davos, Switzerland (Welcome Presentation)
13.09.2013	Richards Geoff: "Basic research", Mini-Symposium Trauma Centre University Hospitals Leuven, Belgium – AO today – an update (Invited Speaker)
19.09.2013	Richards Geoff: "How does the environment impact upon risk and progression of infection in trauma?", Symposium Graubünden forscht 2013 "Gesundheit und Umwelt", Chur, Switzerland (Invited Speaker)
13.10.2013	Richards Geoff: "Bone Infection, an AO Trauma Clinical Priority Program for Research", Symposium at CORS, San Servolo, Venice, Italy (Symposium Organizer)
13.10.2013	Richards Geoff: "Infection I", Symposium at CORS, San Servolo, Venice, Italy (Session Moderator)
29.10.2013	Richards Geoff: "Learnings from the Orthopaedic Field", Cochlear Science and Research Seminar, Vienna, Austria (Invited Speaker)
29.10.2013	Richards Geoff: "Round Table Discussion – Soft Tissue and Implants", Cochlear Science and Research Seminar, Vienna, Austria (Invited Speaker)
09.11.2013	Richards Geoff: "Fracture Healing, Latest R&D to Help the Clinician", The 8th International Congress of Chinese Orthopaedic Association, Beijing, China (Invited Speaker)
09.11.2013	Richards Geoff: "Bone Formation and Regeneration", The 8th International Congress of Chinese Orthopaedic Association, Beijing, China (Moderator)
01.12.2013	Richards Geoff: "Infection and Implant Design", AOCMF Course, Davos, Switzerland (Invited Speaker)
02.12.2013	Richards Geoff: "The influence of implant surfaces", AO Hand Course, Davos, Switzerland (Invited Speaker)

09.12.2013	Richards Geoff: "The AO Research Institute", AO Basic Principles Course, Davos, Switzerland (Invited Speaker)
22.-23.03.2013	Alini Mauro: "The AO Research Institute: A Successful Story: Innovation in Medicine: Major Issues and Ways to their Solutions", Novosibirsk, Russia (Invited Speaker)
07.-08.2013	Alini Mauro: "Biomechanics and Cartilage Repair. Advance in Orthopaedic Research: East-meets-West", Shenzhen, China (Invited Speaker)
23.05.2013	Alini Mauro: "Identification of Intervertebral Disc Specific Cellular Markers and their Use for Disc Tissue Regeneration", Dept. Bioscienze, Biotechnologie and Biofarmaceutica, University of Bari, Italy (Invited Speaker)
03.-05.06.2013	Alini Mauro: "Injectable Hydrogels for the Application of Cell-Based Regenerative Approaches in Intervertebral Disc Degeneration", Annual Congress of the Italian Biomaterials Society, Baveno, Italy (Invited Speaker)
13.09.2013	Alini Mauro: "Cells Therapy for IVD Regernation: Exogenous vs. Endogenous Approaches", Mini-Symposium Trauma Centre University Hospitals Leuven, Belgium – AO today – an update (Invited Speaker)
15.10.2013	Alini Mauro: "Looking for Intervertebral Disc Specific Chemo-Attractants for the Homing of Mesenchymal Stem Cells into Degenerative IVDs, Symposium at CORS, San Servolo, Venice, Italy (Invited Speaker)
15.10.2013	Alini Mauro: "Spine II", Symposium at CORS, San Servolo, Venice, Italy (Session Moderator)
16.10.2013	Alini Mauro: "Regulating the Chondrocyte Phenotype by Complex Multiaxial Load", Symposium at CORS, San Servolo, Venice, Italy (Invited Speaker)
April & November 2013	Gueorguiev Boyko: Series of lectures on "Biomechanics of bone fracture fixation and treatment of joint disorders" and "Metals, ceramics and polymers used as biomaterials in medicine with focus on traumatology, orthopedics and dentistry". Technical University of Varna, Bulgaria (Invited Speaker)
04.-06.07.2013	Moriarty Fintan: "Animal models of implant related infection" and "Can we influence the risk of infection by implant design" at the European College of Veterinary Surgeons (ECVS) annual scientific conference, Rome, Italy (Invited Speaker)
29.-30.08.2013	Moriarty Fintan: "Basic Science of Infection", Asia Pacific Orthopaedic Association, Annual Meeting Kuching, Malaysia (Invited Speaker)
13.10.2013	Moriarty Fintan: "Influence of material on the development of device-associated infections, CORS Venice, Italy (Invited Speaker)
13.10.2013	Moriarty Fintan: "Infection I", Symposium at CORS, San Servolo, Venice, Italy (Session Moderator)
28.-29.11.2013	Moriarty Fintan: "Preclinical Research in Musculoskeletal Infection at the AO Research Institute Davos", BGU Murnau Research Day, Murnau, Germany (Invited Speaker)
01.12.2013	Moriarty Fintan: "Infection CPP", Update from AO Research Institute Davos, AO Courses Davos, Switzerland (Invited Speaker)
04.12.2013	Moriarty Fintan: "Local antibiotic delivery in the prevention and treatment of Osteomyelitis", AOTrauma Masters Course, Davos, Switzerland (Invited Speaker)
05.12.2013	Moriarty Fintan: "Local antibiotic delivery in the prevention and treatment of Osteomyelitis", AOTrauma Masters Course, Davos, Switzerland (Invited Speaker)
09.12.2013	Moriarty Fintan: "Infection CPP", Update from AO Research Institute Davos, AO Courses Davos, Switzerland (Invited Speaker)
16.10.2013	Potapova Inga: "Infection II", Symposium at CORS, San Servolo, Venice, Italy (Session Moderator)
01.12.2013	Eglin David: "Gel", Update from AO Research Institute Davos, AO Courses Davos, Switzerland (Invited Speaker)
09.12.2013	Eglin David: "Gel", Update from AO Research Institute Davos, AO Courses Davos, Switzerland (Invited Speaker)

11.06.2013	Grad Sibylle: "Behandlung von Knorpel- und Bandscheibenbeschwerden – Was bringt die Zukunft?" Aerzteverein Davos, Hospital Davos, Switzerland (Invited Speaker)
06.-08.11.2013	Grad Sibylle: "Role of chemokines in stem cell homing into the degenerative disc." 2nd International Philadelphia Spine Research Symposium, Philadelphia, USA (Invited Faculty Speaker)
24.05.2013	Stoddart Martin: "Stem cells in Biomedical Engineering – Today and Tomorrow." Biomedical Engineering Day, University of Bern, Switzerland (Keynote Speaker)
01.12.2013	Stoddart Martin: "Bone healing", AOCMF Course, Davos, Switzerland (Invited Speaker)
01.12.2013	Stoddart Martin: "Biological enhancement of impaired bone healing", AOCMF Course Davos, Switzerland (Invited Speaker)
14.10.2013	Peroglio Marianna: "Tissue Engineering II", Symposium at CORS, San Servolo, Venice, Italy (Session Moderator)
01.12.2013	Windolf Markus: "X-in-One / Fracture Monitoring Device", Update from AO Research Institute Davos, AO Courses Davos, Switzerland (Invited Speaker)
09.12.2103	Windolf Markus: "X-in-One / Fracture Monitoring Device", Update from AO Research Institute Davos, AO Courses Davos, Switzerland (Invited Speaker)
21.02.2013	Zeiter Stephan and Matthys Romano (RISystems): "Spitzenchirurgie für Mensch und Tier." Naturmuseum Luzern, Switzerland (Invited Speakers)
05.06.2013	Zeiter Stephan and Matthys Romano (RISystems): "MouseFix – Von der Idee zum Spin Off." Naturforschende Gesellschaft Davos, Switzerland (Invited Speakers)
25.-28.8.2013	Agarwal Yash: "Implant Biomechanics" at European Society of Biomechanics 2013 congress, Patras, Greece (Invited Session Chair)
06.06.2013	Arens Daniel: "Chirurgie News aus dem AO." Jubiläumskongress 200 Jahre Gesellschaft Schweizer Tierärzte, Bern, Switzerland (Invited Speaker).
20.09./27.09./ 04.10./11.10./ 18.10./25.10. 01.11./08.11. 15.11./20.12.2013	Hansrudi Noser: "Multimedia Anwendungen und Praxis". University Zurich, Switzerland (Invited Speaker)
04.-06.07.2013	Schmid Tanja: Resident training at the 22nd ECVS Annual Scientific Meeting, Rome, Italy (Invited Speaker)
01.12.2013	Widmer Daniel: "Osteoporosis CPP", Update from AO Research Institute Davos, AO Courses Davos, Switzerland (Invited Speaker)
09.12.2013	Widmer Daniel: "Osteoporosis CPP", Update from AO Research Institute Davos, AO Courses Davos, Switzerland (Invited Speaker)

ARI team 2013

Davos at dusk in December during the AO courses, inspiring innovation.
(AO Publishing / Media Production Team).