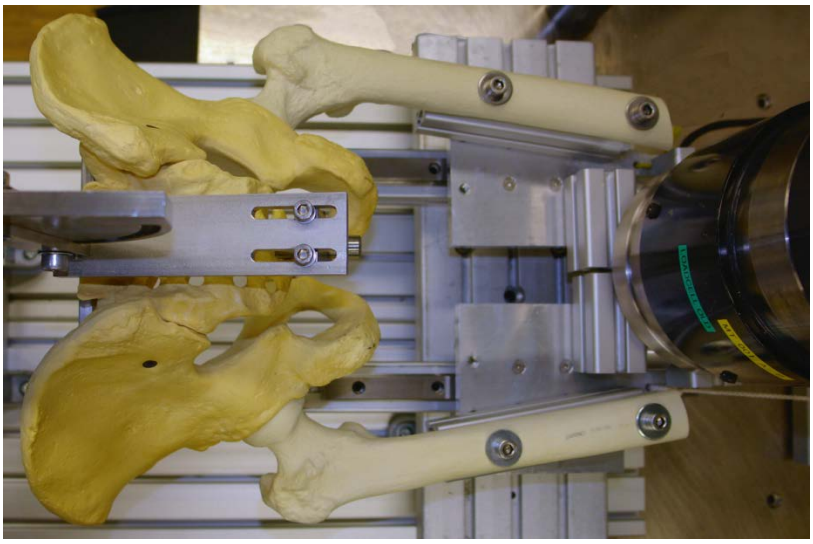
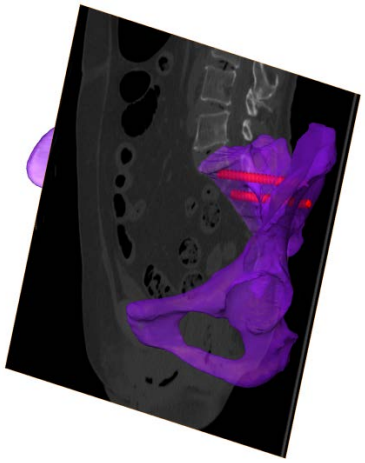
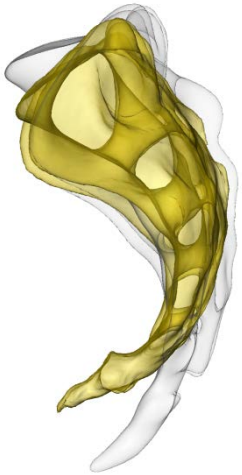
AO Foundation

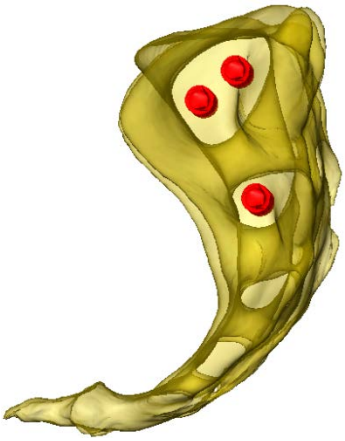
AO Research Institute Davos

Activity Report 2012









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1 Introduction

Having now completed three years as the Director of AO Research Institute Davos I have (alongside knowing our strengths) become fully aware of the perceived weaknesses from the Foundation and potential threats to this long standing internationally respected Institute. Fortunately, I am also seeing more and more opportunities of how to use our depth in knowledge and special strength in innovation and patent protection to again help the AO Foundation financially survive to and through the third jubilee (the 75th or Diamond Jubilee), assuming our current mass in the Institute which was deemed the critical mass in 2008/2009 review and current reduced budget is at least maintained.

In the 2013 the Global Competitive Report of the World economic forum, Switzerland again ranks number 1 and in relation to research and translation the report mentions " Switzerland's scientific research institutions are among the world's best, and the strong collaboration between its academic and business sectors, combined with high company spending on R&D, ensures that much of this research is translated into marketable products and processes reinforced by strong intellectual property protection. This robust innovative capacity is captured by its high rate of patenting per capita, for which Switzerland ranks a remarkable 2nd worldwide " The AO Foundation spends approximately 30% of its yearly budget on R&D, 50% of this is in extramural grants. Approximately 30% of this (approximately 10% of the AO Foundation's total annual budget) is spent within preclinical R&D at the AO Research Institute Davos from which the Foundation owns all the intellectual property.

The AO Foundation is unique compared to societies in the same field such as AAOS, ORS, EFORT, ECTES etc. in that it has its own research institute which strongly increases the academic credibility to the Foundation and scientifically supports information taught by the excellent medical education of the AO Foundation's "newly" formed Education Institute. The credibility is ensured through many avenues, such as the continuation in improvement in quality of ARI publications (maintaining the impact factor in the higher level of the musculoskeletal field); acquirement of national and high level international consortium grants; running of the true open access eCM journal (which is number one within trauma research having a 5 year impact factor of over 5 and more than 17,000 registered readers); bringing the ARI team to the forefront of high quality international conferences (such as ORS and TERMIS) and editorial boards and societies along with bringing ARI team members into national and international society committees, chairing positions at major conferences, holding keynote lectures and organizing and co-organizing important national and international scientific conferences. This international respect has also helped show the outside world that the AO Foundation is an independent Foundation at arm's length to its industrial partners and this continues to bring societies to the AO Foundation, who now wish to work with us as partners rather than distance themselves from us.

I wish to note my gratitude to the ARI team members including ARI medical research Fellows for their dedication to both the AO Research Institute Davos and to the AO Foundation within difficult times of high administration for internal (intramural) funding. Both the ARI long serving (and younger) scientists are well respected within the international musculoskeletal research field, as seen in this report.

Sincerely

Prof Dr R Geoff Richards, Director AO R&D

2 Mission and Goals

Mission

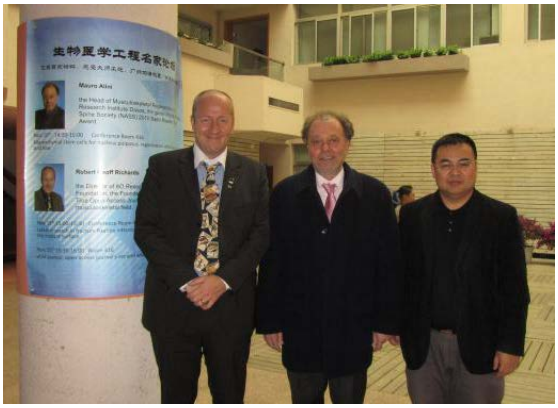
Excellence in applied Preclinical Research and Development within trauma and disorders of the musculoskeletal system and translation of this knowledge to achieve more effective patient care.

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.

1. **Exploratory Applied Preclinical Research** is fundamental research, to solve major clinical problems over an extended timeframe (over 10 years).
2. **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.



Fostering new relationships with Asian Universities (in this case Beihang University, Beijing, top left), Societies - COA (Chinese Orthopedic Association – top right), WOA (World Orthopedic alliance- bottom left and right).

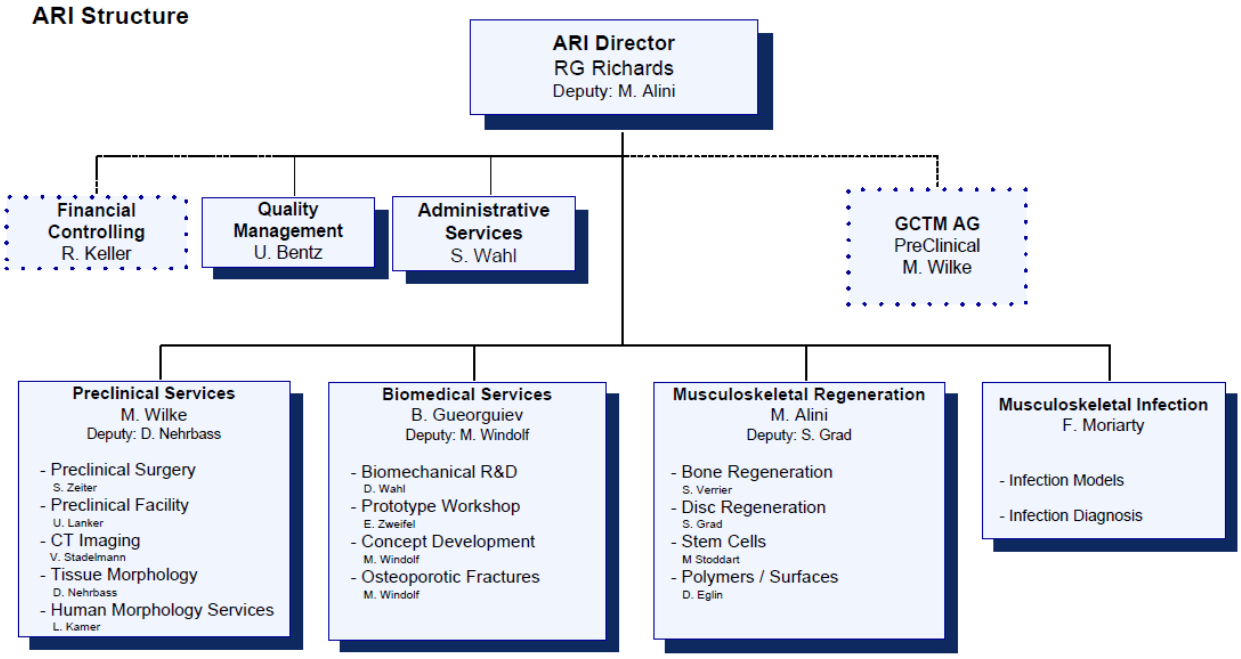
3 Funding Summary

Income Statement	2011 Actual		2012 Actual	
in CHF '000	abs	%	abs	%
AO Foundation Contribution	7'878	67%	6'718	58%
3rd party Income	2'960	25%	2'492	22%
AO Intercompany	994	8%	2'276	20%
Total Income	**11'833**	**100%**	**11'486**	**100%**
AOTrauma *	3'354	29%	3'987	35%
AOSpine*	563	5%	464	4%
AOCMF *	460	4%	625	6%
AOVET	59	1%	36	0%
AOTK	400	4%	563	5%
AOER *	2'609	23%	1'920	17%
AO Foundation *	983	9%	1'273	11%
3rd party projects	2'960	26%	2'492	22%
Total Expenses	**11'388**	**100%**	**11'359**	**100%**
Net Result	**445**		**127**	

* incl. AO Intercompany

The decrease in the 'AO Foundation Contribution' vs. previous year resulted mainly from the introduction of the new funding concept for the AO Research Institute (CHF -1'241K).
Therefore, this decrease reflects a change in reporting and not a decrease of the consolidated R&D costs.

4 Programs, Groups and Focus Areas



4.1 Biomedical Services

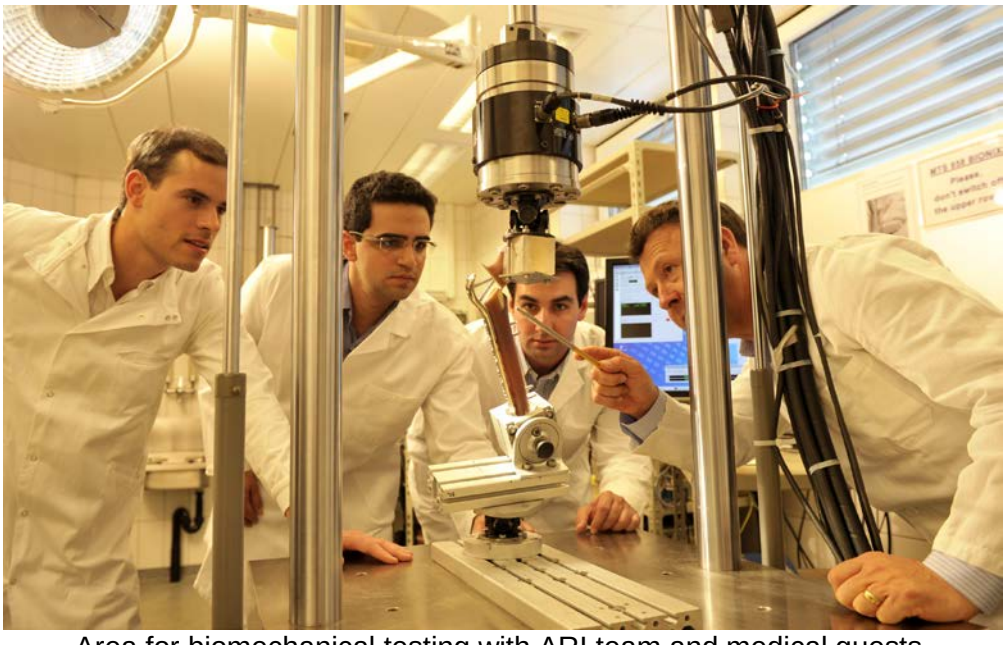
Program Leader: Boyko Gueorguiev-Rüegg, Deputy: Markus Windolf
Team Members: Nando Adank, Yash Agarwal, Fabian Berri, Jan Caspar, Benno Dicht, Manuela Ernst, Ladina Hofmann-Fliri, Matthias Forte, Kevin Frey, Prisca Lemm, Claudia Münch, Ronald Schwyn, Ulf Viehöfer, Dieter Wahl, Daniel Widmer, Noel Wyss, Ivan Zderic, Erich Zweifel
Fellows: Michael Blankstein, Marek Blazejak, Michael Götzen, Tomas Nicolino, Kerstin Schneider, Ortal Segal, Rukmanikanthan Shanmugam, Yasuyuki Shiozaki, Charles White
Guests: Mark Lenz, Dirk Wähnert

The Biomedical Services Program performs research within the areas of Biomechanical Research, Concept Development, Osteoporotic Fractures and a Prototype Workshop. The focus areas are technically oriented and work in collaboration with clinical, scientific and industrial partners to improve patient care. The activities include biomechanical and finite element 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.

Anatomical laboratory with ARI fellows.

Biomechanical Research

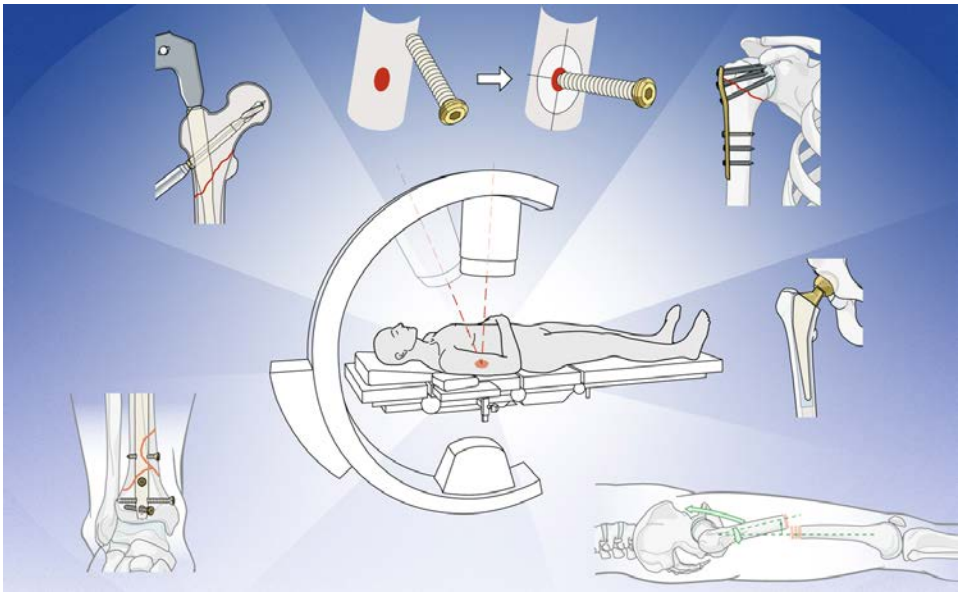
The process of finding the optimal solution to clinical questions is enhanced by biomechanical modeling and testing, aiming to establish integrated experimental and computational investigation methods for research in fracture fixation. The capabilities range from in silico methods to more classical anatomy 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 testing 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 on bone models.



Area for biomechanical testing with ARI team and medical guests.

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 the concept to a clinically applicable solution.

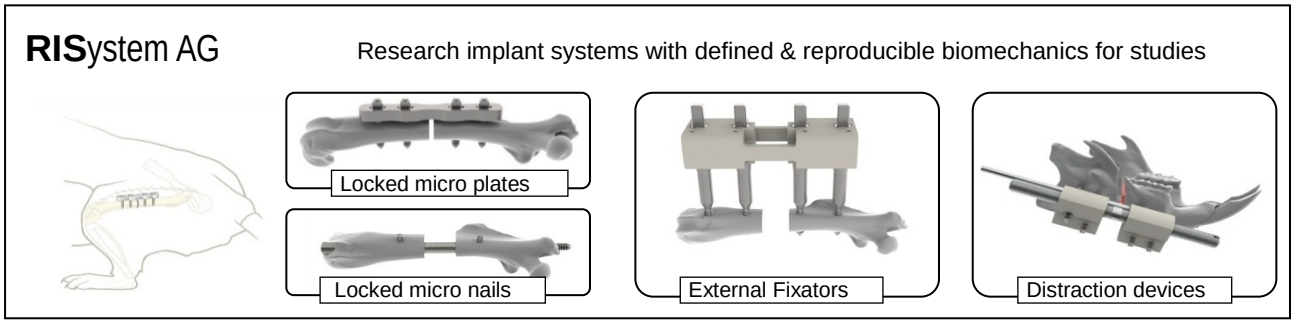


Different applications of a novel approach for simplified computer aided surgery.

Prototype Workshop

Specialized for production of sophisticated pieces and devices, the workshop is involved in the development of prototypes from the very beginning in close collaboration with our project partners. It facilitates the complete machining of prototypes including milling, turning, wire cutting EDM and finishing. Qualified CNC mechanics and toolmakers guarantee high quality of work.

Implants for research produced in the Prototype Workshop.



4.2 Preclinical Services

Program Leader: Markus Wilke, Deputy: Dirk Nehrbass
Team Members: Daniel Arens, Mauro Bluvol, Karin Camenisch, Iska Dresing, Ursula Eberli, Balazs Erdöhelyi, Peter Erb, Pierina Faoro, Andrea Furter, Nora Goudsouzian, Thomas Heldstab, Lukas Kamer, Katharina Kluge, Urban Lanker, Olga Martin, Reto Müller, Angela Nehrbass, Hansrudi Noser, Dominic Perren, Monika Schneider, Sonam Sharma, Christoph Sprecher, Vincent Stadelmann, Sandra Thoeny, Stephan Zeiter
Fellows: Joseph George, Tobias Helfen, Sarah Peters, Florian Schmidutz, Daniel Wagner, Philipp Zerbe
Student Externs: Christian Günther, Andrea Nies, Cynthia Unholz

Preclinical Facility and Animal Care Focus Area
Intense efforts have been made to increase animal welfare aspects including development of systems to more objectively evaluate the animal wellbeing and working towards standards required by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International, the highest international review body for animal experimentation. With the pending accreditation our processes are evaluated by an independent external organization to demonstrate that we not only meet the minimum standards required by law but also going the extra step to achieve excellence in animal care and use. (Accreditation was given in February 2013).

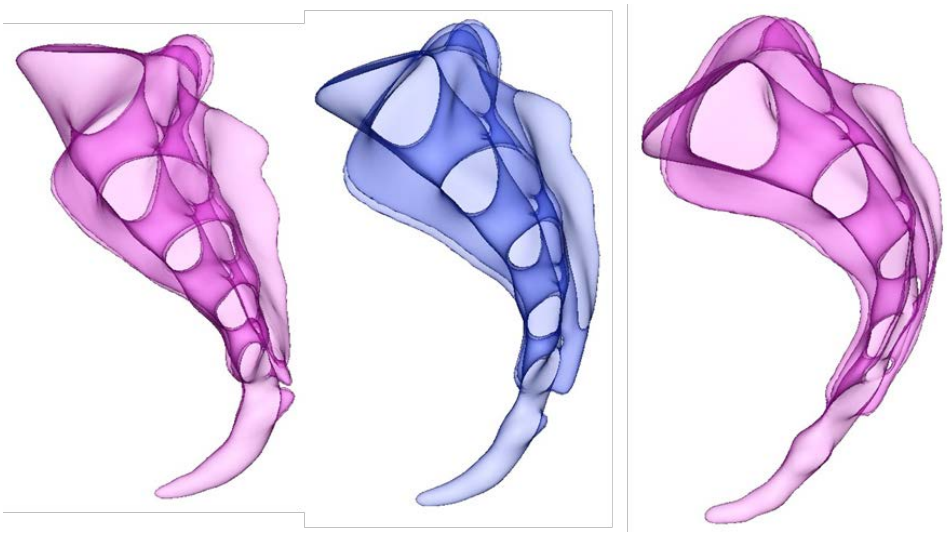
Preclinical Surgery Focus Area
Successful preclinical studies require a team effort of highly skilled and dedicated personnel: team members are specializing in laboratory animal medicine (ECLAM), anesthesia (ECVAA) and surgery (ACVS / ECVS), our veterinarians have excellent cross-training and our animal care staff is well trained and dedicated. Together, we have developed a number of new models like BRONJ (bisphosphonate related osteonecrosis of the jaw) in different species, a craniotomy model in sheep, a new treadmill and force plate exercise and monitoring unit for sheep, and a number of new osteotomy models in rabbits. New models to investigate different aspects (diagnosis, treatment, basic research) of bone infection are initiated: infected intramedullary nail models in sheep and rabbits and infected implant models in rabbits and rodents have started.

CT Imaging Focus Area

The Imaging Focus Area is an interdisciplinary team (physicist, biomechanic and bioengineer). The focus of our team is to investigate bone quality, bone healing and implant anchorage by means of computed tomography. Our daily work involves the design of image acquisition routines, development of custom image processing algorithms, and management of large image databases.
Our core competence is Computed Tomography (CT). CT produces 3D data that can be manipulated in order to visualize various bodily structures based on their ability to block the X-ray beam. Our clinical CT allows us to work with large animal models in-vivo. The XtremeCT and VivaCT allow us to scan small animals in-vivo and in-vitro specimens at very high resolution, and to analyze the finest details of their bony structures.

Human Morphology Services Focus Area

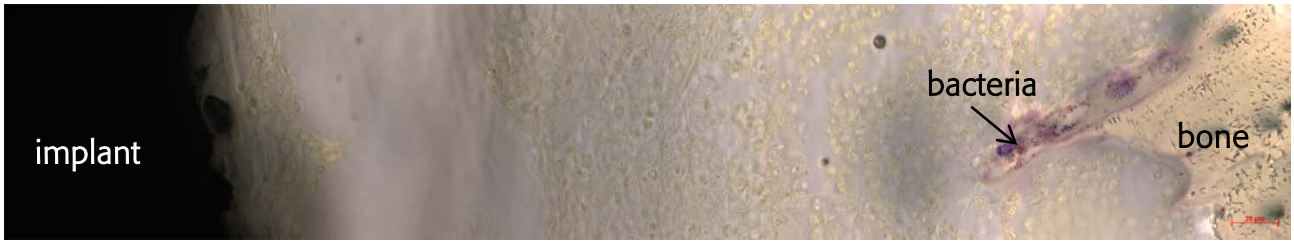
ARI Human Morphology Services is a computer laboratory for advanced medical image processing and analysis. The services comprise an infrastructure to run and maintain a database of Computed Tomography (CT) scans, three-dimensional (3D) bone models and 3D statistical bone models. Currently more than 1500 CT data and bone computer models are available. Moreover new computer tools have recently been developed for creating and analyzing 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 competences collaboration with the TK Pelvic Expert Group has been established to assess the anatomical variability of the sacrum in order to help improving fracture fixation in patients affected by sacral insufficiency fractures. Sites of special importance are the borders of the trans-sacral corridors as well as the sacroiliac joint. More than 150 pelvic CT scans of elderly Asians and Europeans are currently being processed. 3D statistical models of the sacrum is being generated to study the pathways for safe implant positioning (see figure) and to analyze the internal bone stock distribution, contributing to better understanding of the sacral anatomy and its implications on the surgical decision making process and the operative technique. A similar approach was used to support the TK Patella Task Force to establish an anatomical background for the development of new fracture fixation concepts for the patella.
In a large AOTrauma project osteoporosis key sites in long bone is studied using peripheral quantitative CT scan in order to assess the spatial variation of bone mineral density. The datasets will be merged to averaged 3D BMD maps and will then be transferred to a Finite Element environment, in order to provide a tool for systematically improving implant anchorage in the osteoporotic bone.
Within the scope of the AOCMF CPP Program "Imaging and Planning of Surgery" a project has been initiated in order to improve computer model visualization of the skull, with special emphasis on the bony orbit and the dental occlusion.



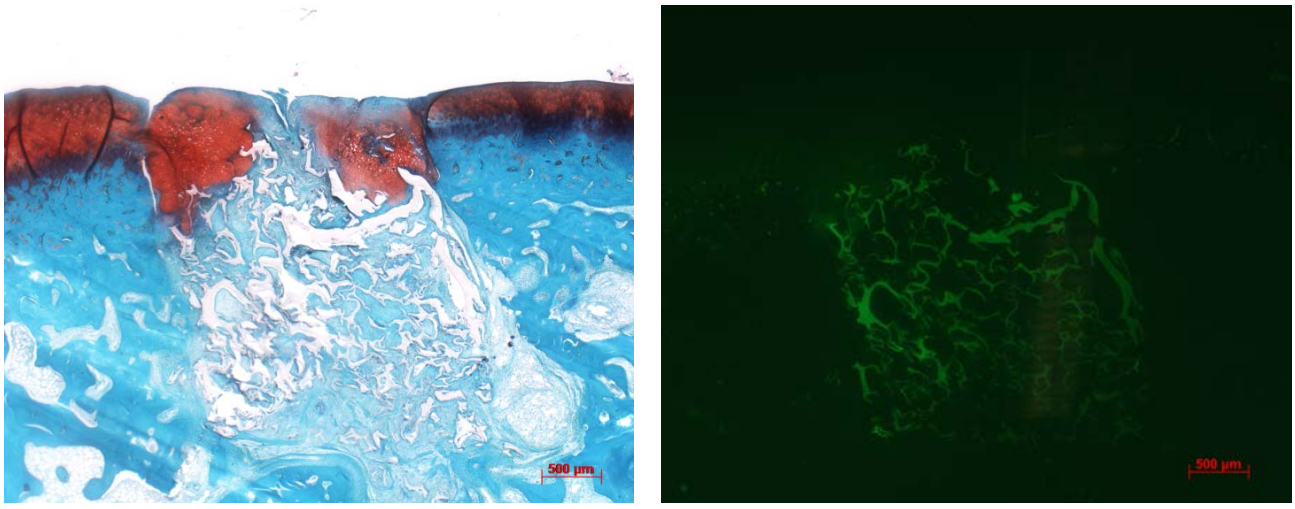
Lateral semitransparent view of a 3D statistical model of the sacrum. Mean shape (blue) and extreme shapes (purple).

Tissue Morphology Focus Area

Tissue Morphology provides collaborative research and services, which include histology of paraffin-embedded, cryofixed, and non-routine resin-embedded undecalcified hard tissue, with and without implants. For immunohistochemistry and cytochemistry, we have standard protocols for several different techniques. Microscopic investigations can either be performed descriptively by semiquantitative grading systems or quantitatively by histomorphometric image analysis on conventional transmitted as well as several reflected light methods including fluorescence and confocal microscopy. Thereby, histological routine staining as well as special staining (e.g. for bacteria) can be applied. Surface topographical characterization is performed with non-contact white light profilometry while scanning electron microscopy (SEM) is available for use in material morphological analysis as well as routine elemental determination using energy dispersive X-ray microanalysis (EDX). State of the art SEM techniques have been developed internally for biomaterial, cell, tissue and bacterial interface studies. Finally, a telepathology system enabling a remote live microscopic observation via internet supports our custom-oriented research and facilitates collaboration by discussion and teaching possibilities.



Histological section of a non-decalcified, resin-embedded bone tissue with an induced bacterial infection (osteitis). At the left side, the metallic implant can be seen. At the right side numerous colonies of coccoid bacteria (purple) are visualized by special staining (Brown-Brenn, not counter-stained).



Histological section of decalcified, paraffin-embedded hard tissue with an induced osteochondral defect (rabbit knee joint). The left picture shows the brightfield light microscopical view of the cartilage defect visualizing the advanced defect closure by special staining (Safranin O - Fast Green). The right picture shows the identical area in emitted light view visualizing the intrinsic autofluorescence of the scaffold material used.

4.3 Musculoskeletal Regeneration Program

Program Leader: Mauro Alini, Deputy: Sibylle Grad
Team Members: Marco Bruderer, Ewa Czekanska, David Eglin, Matteo D'Este Oliver Gardner, Markus Glarner, Marietta Herrmann, Matti Kesti, Patrick Lezuo, Zhen Li, Ursula Menzel, Alexander Neumann, Girish Pattappa, Marianna Peroglio, Robert Peter, Alexandra Poulsson, Gian-Marco Semadeni, Martin Stoddart, Abby Sukarto, Gert-Jan ter Boo, Sophie Verrier
Fellows: Claudia Löbel, Tatiana Pirvu
Guests: Jennifer Bara, Andreas Binder, Stephanie Bryant, Pierina Casanova, Andrea Cochis, Haddouti El-Mustapha, Martina Glück, Giuseppe Musumeci, Catarina Pereira, Tobias Reuber, Fabrizio Russo, Eugene See, Ryan Seelbach, Judith Staudacher, Gian-Luca Vadala, Houman Zahedmanesh

The program develops biological approaches addressing pathologies of the musculoskeletal system, with a particular focus on bone, 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
Scaffold and delivery system design and fabrication are major areas of biomaterials, musculoskeletal tissue engineering and regenerative medicine research.

Our main research focuses on designing polymeric biomaterials to perform several or all of the following functions: (i) promote cell-biomaterial interactions, cell adhesion, and ECM deposition, (ii) permit sufficient transport of gases, nutrients, and regulatory factors to allow cell survival, proliferation, and differentiation, (iii) resorb and release bioactive molecules and particles at a controllable rate, and (iv) provoke a minimal degree of inflammation or toxicity in vivo. Our experience lies in the design of biocompatible and biodegradable polyurethanes and their processing with controlled architecture. We also investigate the use and modification of hyaluronic acid for development of injectable solutions. These injectable biodegradable materials have important medical applications, e.g. delivering cells, drugs, and biological signals to the tissues.

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 basic science 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 group is utilizing *in vitro* and *ex vivo* cell and whole organ culture models aiming to test injectable hydrogels to be used for delivery of cells and anabolic or chemotactic molecules. Our IVD culture techniques are continuously improved in order to optimize the delivery routes of therapeutic agents and the mechanical loading conditions to approach a physiological response. Furthermore, mechanisms of tissue degeneration and cellular repair capabilities, such as cell homing, are studied using healthy and diseased cells and tissues from human and bovine sources.

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.

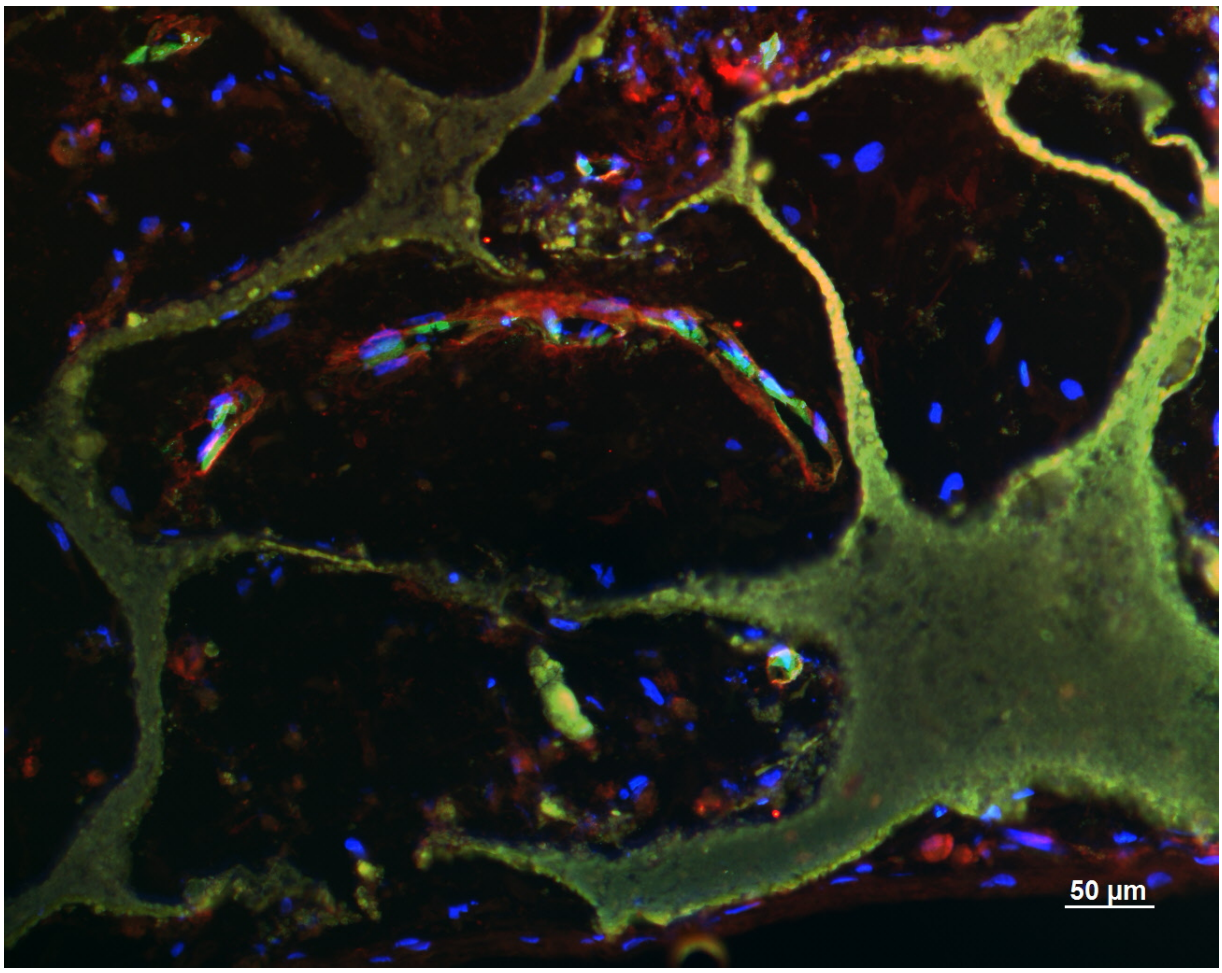


Figure: In vitro formation of vessels like structures in pre-cellularized PU scaffolds. In blue: DAPI nuclear staining. In red CD146 specific staining (endothelial/pericytes marker), in green HUVEC cells (mature endothelial cells), co-localizing with blue DAPI, and red CD146 (inside the scaffold pores). Due to strong auto-fluorescence the scaffold can be seen in dark green.

4.4 Musculoskeletal Infection Group

Group Leader: Fintan Moriarty
Team Members: Pamela Furlong, Iris Keller, Virginia Post, Inga Potapova, Edward Rochford
Fellows: Mario Morgenstern, Hayder AlSaadi, Claus Seyboth

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 group, we aim to develop clinically relevant standardized 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. This is because the clinical presentation of the infections may be subtle and similar to sterile inflammation, delayed healing or aseptic non-unions. The development of new diagnostic tools is the second goal of the musculoskeletal Infection group.

AOTrauma Clinical Priority Program (CPP) Bone Infection. The five year program has eight separate projects with the goal to improve the care of staphylococcal infections. The principle investigator of this CPP is Prof. Stephen Kates (middle) from the Department of Orthopedic Surgery at the University of Rochester, United States. Left Prof Edi Schwarz (same address) and right Dr Fintan Moriary, Group leader Musculoskeletal Infection (ARI). The CPP will host a symposium at the upcoming CORS meeting in 2013 in Venice.

4.5 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 minutes 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 AO Research Institute Davos
- ARI personnel management (support hiring, organization etc.)
- ARI Fellowship organization and support

2012 the ARI Administrative Service Group has organized for:

AO Research Institute (ARI)

10.-11.01.2012	AO Frakturenkurs für Medizinstudenten von Schweizer Universitäten, Davos
30.-31.03.2012	AO Traumakurs für ETHZ und ZHAW Studenten, Davos
24.-26.06.2012	eCM XIII Bone Fixation, Repair & Regeneration Congress, Davos

AO Exploratory Research (AOER)

21.05.2012	AOER Board Meeting, Zürich, Switzerland
05.-07.11.2012	AOER Collaborative Research Program Meetings, Homburg, Germany
07.11.2012	AOER Board Meeting, Homburg, Germany

AOTrauma Research Commission (AOTRC)

09.03.2012	AOTRC Meeting, Istanbul, Turkey
23.06.2012	AOTrauma Middle East Research Committee Meeting, Cairo, Egypt
01.-02.07.2012	AOTRC Meeting, Zürich, Switzerland
06.-07.10.2012	AOTrauma 1st Annual Meeting Clinical Priority Program (CPP) Bone Infection
17.11.2012	AOTRC Meeting, Beijing, China

5 Institutional and Professional Relations

R 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. In June 2012 Geoff was elected as a Fellow of Biomaterials Science and Engineering (FBSE). From 2004 until 2012 he was an Honorary Senior Research Fellow in the Division of Infection and Immunity, University of Glasgow, GB. He is cofounder and Editor-in-Chief of the eCM Journal. He has Life Honorary Membership of the Swiss Society of Biomaterials (where he was president in 2007-2009). Geoff is chair of the Infection Topic Committee of ORS (Orthopedic Research Society) in 2011 and 2012 and is a current executive committee member for EORS (European Orthopedic Research Society). He is a member of AO Foundation Academic Council, the board of directors AOGCTM and is a member and Director of the Board of the Foundation of the AO Research Institute Davos.

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 (2011/2012). He serves as a member of the Award Committee for The GRAMMER European Spine Journal Award. From 2010 until 2012, he has been a member of the European Council of the Tissue Engineering Regenerative Medicine International Society (TERMIS). 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 Biomedical Material Journal and on the Assistant Editorial Board of the European Spine Journal.

Boyko Gueorguiev-Rüegg acts as journal reviewer for J Orthop Res, Arch Orthop Trauma Surg and BMT Biomed Eng.

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

- 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. She is also the scientific chair of our two day fracture courses offered to medical and engineering students.

- Martin Stoddart is a Scientific Editor for eCM Journal 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 an Associate Faculty Member of the Faculty of 1000 Medicine.

- Fintan Moriarty is a member of the eCM Journal International Editorial Review Board. He is also a member of the Scientific Committe of the Asia Pacific Orthopaedic Association, Infection Section. He 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.

- David Eglin is on the executive committee of the Swiss Society for Biomaterials and is also the society Web-editor. He is also a member of the eCM Journal International Editorial Review Board.

- Hansrudi Noser is adjunct Professor at the Dept. of Informatics of the University of Zürich.

- Vincent Stadelmann lectures at The Swiss Institute of Technology Lausanne.

- Sophie Verrier is a member of the eCM Journal International Editorial Review Board.

- 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

- Yash Agarwal acts as a journal reviewer for Vet and Comp Orthop Trauma. 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).

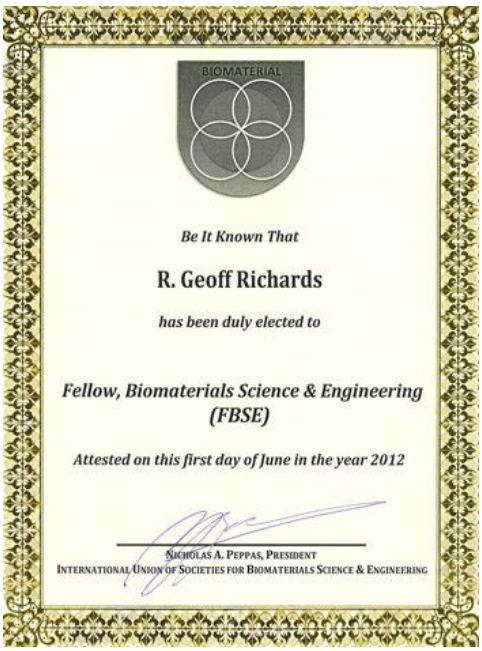
- Marianna Peroglio is a member of the eCM Journal International Editorial Review Board.

- Alexandra Poulsson is a member of the eCM Journal International Editorial Review Board.

6 Good News

Awards

Geoff Richards, Director ARI has been awarded the prestigious Fellow, Biomaterials Science and Engineering (FBSE) honor. At the World Biomaterials Congress in Chengdu, China, in June 2012 Geoff received this prestigious honor. The award was created to recognize members of world biomaterial societies who have gained excellent professional standing and high achievements in the field of biomaterials science and engineering. The FBSE award is announced every four years with approximately 40 recipients worldwide. The fellow status is awarded for life. The duly nominated, approved, confirmed, and installed fellow has the right to carry the letters FBSE. These letters indicate the national recognition and international respect of his/her comprehension of professional issues and accomplishments as a scientist or engineer in the field of biomaterials science and engineering.


BIOMATERIAL

Be It Known That

R. Geoff Richards

has been duly elected to

Fellow, Biomaterials Science & Engineering (FBSE)

Attested on this first day of June in the year 2012

NICHOLAS A. PEPPAS, PRESIDENT
INTERNATIONAL UNION OF SOCIETIES FOR BIOMATERIALS SCIENCE & ENGINEERING

Mark Lenz won the best Oral Presentation Award at the congress 'Osteosynthese International 2012': Lenz M, Perren SM, Gueorguiev B, Richards RG, Hofmann GO, Windolf M. Fracture fixation around intramedullary implants - a biomechanical study on different cerclage looping techniques, Gerhard Küntscher Society, Rostock, Germany, 19-22 September, 2012.

Mark Lenz (middle) with Prof. Georg Gradl, Congress president (left) and Hans W. Stedtfeld, President of the Küntscher Society (right) at the award ceremony.

Oliver Gardner won best presentation award at the 'Graubünden Forscht' conference in Davos, 12th – 13th September.

Positions

Daniel Arens has been elected for the Board of Directors of the Swiss Association of Veterinarians in Industry and Research (SAVIR). SAVIR provides support with its creative network of veterinarians working in the fields of business, industry, research and education. SAVIR was founded as an association in 2002 and is now a specialist branch of the Association of Swiss Veterinarians.

Extramural funding

European Commission funded research project (seventh framework program) (EU FP7) Grants
BIODESIGN: Rational Bioactive Materials Design for Tissue Regeneration. ARI personnel: Mauro Alini, Martin Stoddart, 590,000€ in total (2012–2016).

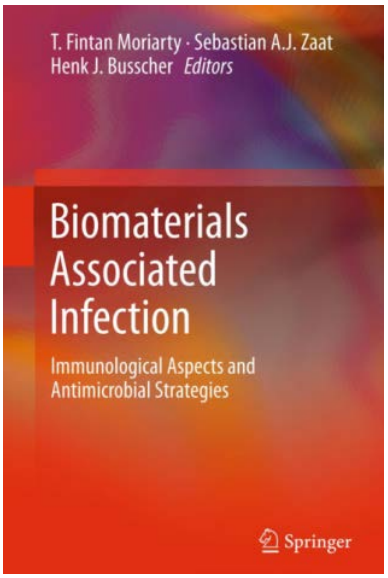
Other grants

The Musculoskeletal Regeneration Program (David Eglin and Mauro Alini) has been the successful recipient of a European COST action NAMABIO. (Funding 180'000 CHF/ 3 years Swiss State Secretariat for Education and Research). 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 and dental medicine. Within this framework, our 3 year project will focus on the development of biofunctional self-assembling hyaluronan hydrogels for rapid vascularisation and critical sized bone defect regenerative therapy.

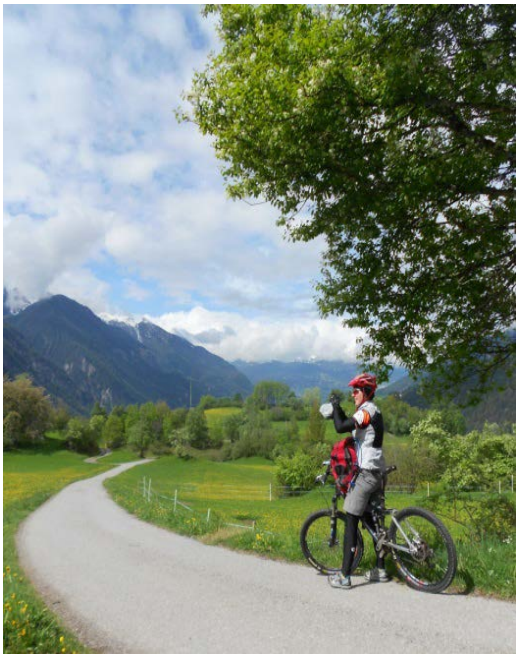
The Musculoskeletal Regeneration Program (Sibylle Grad and Mauro Alini) has been granted the second year funding of a Research Grant from the North American Spine Society (NASS) for the project "Stem cell based Intervertebral Disc Regeneration – Evaluation in Organ Culture" (USD 50'000/year). This basic research project investigating the fate of human mesenchymal stem cells after injection into an intervertebral disc in a whole organ culture system will provide important insight into the effects of the carrier and mechanical environment on cell survival and activity.

Short-Term Scientific Mission (STSM) Grants from the COST framework for European Cooperation in Science and Technology were awarded to Andrea Cochis, PhD student from University of Piemonte Orientale, Novara (I) and Dr. Houman Zahedmanesh, Katholieke Universiteit Leuven (BE). These exchange visits are aimed at strengthening the existing network by allowing scientists to go to an institution or laboratory in another COST Country to foster collaboration, to learn a new technique or to take measurements using instruments and/or methods not available in their own institution/laboratory. Both researchers spent 6-8 weeks in the Musculoskeletal Regeneration Program.

General



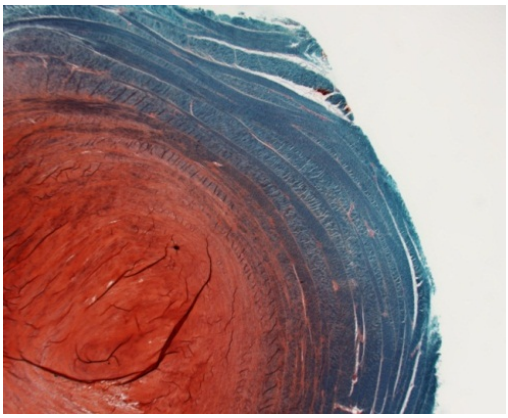
Fintan Moriarty was the main Editor alongside co-editors Sebastian A.J. Zaat and Henk J Busscher of a recently published book: Biomaterials Associated Infection: Immunological Aspects and Antimicrobial Strategies. The book was published by Springer in October 2012. AOTrauma and AOERB Medical Research fellows contributed work to the book - Lorenzo Calabro, Abhay Gahukamble, Ahmed Seif El Din and Cameron Lutton along with several of the ARI team.



Prof. Stephanie Bryant from the department of Chemical and Biological Engineering of the University of Colorado, US, was visiting Professor in the Musculoskeletal Regeneration program for 4 months. This was made possible through the successful application to a Burroughs Wellcome Fund (BWF) 2012 collaborative travel grant for the research project entitled: Decoding Biochemical and biophysical cues for engineering musculoskeletal tissues.

Prof. Stephanie Bryant enjoying the Swiss mountains during a break from the laboratory at the AO Research Institute.

The figure below, taken from the article by Pattappa et al., "Diversity of intervertebral disc cells: phenotype and function", *J Anatomy* 221, 480-496 (2012), was selected as a cover illustration for the Journal of Anatomy, volume 221, issue 6, December 2012.



Safranin O-Fast-green staining of a caudal IVD from a 6-month-old bovine calf showing the distribution of sulphated glycosaminoglycans and collagen across the disc. An outer AF region rich in collagen and a central NP region rich in glycosaminoglycans are observed in the overview of the disc.

New Hoods in Tissue Morphology labs

In autumn 2012 the Focus Area Tissue Morphology (Preclinical Services Program) acquired two new, state-of-the-art, full stainless steel hoods. These custom-made cabinets are not only built for work with volatile chemicals (whose gases go upwards) but also for trimming of formaldehyde-fixed tissue samples (whose fumes are heavier than air and go downwards). Therefore, these hoods are equipped with *two* ventilation systems whose air flow is automatically controlled by the opening width of the glass shield. By these measures a maximum of occupational safety is provided to the whole personnel.

As an important addition to the facility the Biosafety Area has been opened and the first projects studying bone infection have started. The Biosafety Area includes a surgery room, two separate animal rooms and a maintenance storage area. Two different species (infection models) can be operated and kept in parallel in this area with organisms requiring a biosafety level 2.

New in-vivo scanner in Imaging Focus Area

An in-vivo micro computed tomography scanner (VivaCT40) was acquired in January 2012. This scanner allows in-vivo scanning of small animals (mice, rats) at a resolution of 10 micrometers non-invasively. This scanner opens new perspectives in high-resolution analysis of implant integration, infections, and bone diseases in preclinical models and completes our CT imaging capabilities from small bone samples to large animal capability.

Collaboration

AO Research Institute Davos established collaboration with the Technical University of Varna, Bulgaria in the field of biotechnology, where Boyko Gueorguiev will start a program towards a Professorship title.

Organized Student Courses

The AO Research Institute Davos yearly offers interested medical and engineering students two day courses to give a first insight into the treatment methods in orthopedic and trauma surgery. In January 2012, 40 medical students from Swiss universities participated in the "fracture course", while 48 engineering students from the ETH Zurich and the ZHAW in Winterthur attended the "trauma course" in April 2012. The topics of lectures included both basic knowledge on the principles of osteosynthesis and clinical applications, such as emergency treatment for polytrauma patients. In the hands-on exercises the participants had the opportunity to practice modern techniques of osteosynthesis with surgical instruments, screws, plates and nails. They were supported by a team of expert course instructors around Raphael Jenni of the Kantonsspital Chur and Christian Ryf of the Spital Davos. The atmosphere was enthusiastic, and for some of the future surgeons and engineers this first contact may well lead to a closer relationship with the AO Foundation's network of surgeons or R&D teams.

Medical students joining the fracture course in January 2012.

Hands-on for engineering students in practical exercises.

AO Exploratory Research Collaborative Research Programs Annual Meetings took place in Homburg, Germany

These annual meetings are dedicated to bringing together research partners and clinicians involved in the Collaborative Research Programs.

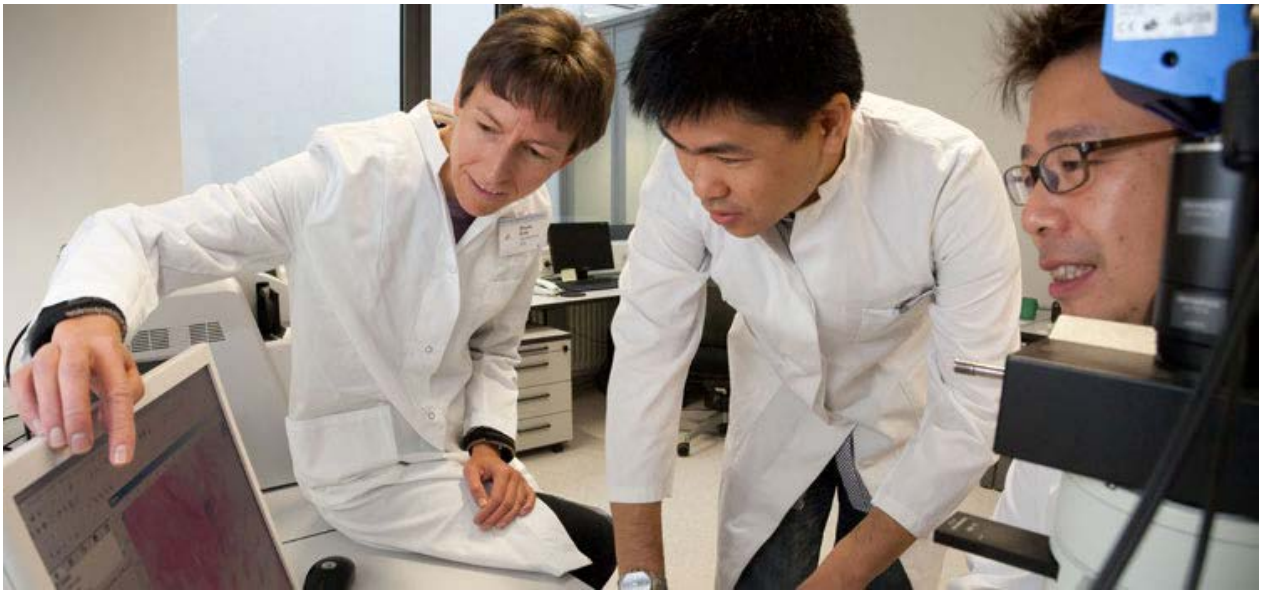
From November 5–7 2012, the AO Exploratory Research Annual Collaborative Research Program Meeting was held on the idyllic wooded campus of the University Hospital of Homburg/Saar, Germany. The meeting was hosted by the program partners Prof Michael Menger, Dean of the School of Medicine and Prof Henning Madry, Chair of Experimental Orthopedics and by Prof Tim Pohlemann, Chief of Trauma Surgery at the university.

The AO Exploratory Research Board is responsible for the governance and funding of the Collaborative Research Programs of the AO Foundation and the AO Exploratory Research Board chair Prof Michael Schütz and the Head of AO Exploratory Research Sandra Steiner welcomed the participants. Collaborative Research Programs are developed in three focused areas, each addressing a major problem in clinical musculoskeletal disease and injury. These programs are long-range programs starting with basic science research and extend over six to seven years to develop solutions that could be translated in clinical products or methodology to improve patient care. The three focused areas are: Annulus Fibrosus Rupture, Acute Cartilage Injury and Healing Problems of Bone—Large Bone Defect Healing
Each of these focused areas is supervised by three experts in their respective fields. On a yearly basis, the funded researchers meet to interact and exchange ideas and solidify collaborations that have already begun within their research consortiums. This report will review the results of the 2012 Annual Research Meeting.

Following the presentations the various groups met with their respective program steering committees. This gave the groups the opportunity to review the work that had been done, to establish further collaborations and interactive research programs for the next year and to finalize their research strategy for the entire program duration.

Workshop on Annulus Fibrosus cell isolation for Collaborative Research Program partners

The aim of the workshop was to provide all consortium members with an optimized protocol for pure annulus fibrosus cell isolation that was established by the Tokai University research team.



Organized by the Collaborative Research Program Annulus Fibrosus Rupture (CRP AFR) partners Prof. Daisuke Sakai and Sibylle Grad, and supported by the AO Exploratory Research Board, a hands-on training workshop took place at the AO Research Institute Davos (ARI) on November 9–10, 2012. The workshop provided all consortium partners with an optimized and harmonized protocol for pure annulus fibrosus cell isolation, which was established by the Tokai University research team.

Current methods for annulus fibrosus cell isolation are highly variable, making comparisons between different studies problematic. Furthermore, cell isolation from intervertebral disc tissue is challenging due to the strictness of separating the nucleus pulposus and annulus fibrosus, especially in certain species that do not present an apparent border between the two tissue types. As part of their project within the AFR program, scientists from Tokai University School of Medicine in Japan have established a new protocol for critical extraction of pure annulus fibrosus cells. It was thus of vital interest to disseminate the technique and experience to all consortium members in order to analyze and compare data from an identical viewpoint.

The laboratory demonstration in Davos was held as a “satellite event” after the CRP Annual Meeting in Homburg. Special emphasis was put on the appropriate enzymatic digestion of the annulus fibrosus tissue and on primary cell surface marker analysis for subsequent sorting and sequential culture. Under the guidance of Prof. Daisuke Sakai, Tomoko Nakai and Tadashi Nukaga from Tokai University, ten researchers from the CRP partner institutions Mount Sinai Medical Center, New York, National University of Ireland, Galway, University of Twente, The Netherlands, and the AO Research Institute Davos participated in the workshop and gained hands-on experience in the dissection of mouse tail discs, extraction of annulus cell populations, and analysis of cell surface markers by FACS (fluorescence activated cell sorting). Eventually, a population of potential annulus progenitor cells could be identified, confirming that the procedure was successful. The successful technique will also be introduced in other partners’ laboratories to assure that in the future an identical protocol will be used by all consortium members.

Meeting to share the perspectives of orthopedic surgeons and researchers on implant infections.

On June 15th 2012 a meeting to share the perspectives of orthopedic surgeons and researchers on implant infections was held at the AO Research Institute Davos. The interdisciplinary symposium was organized by the Musculoskeletal Infection Group and the Department of Septic and Reconstructive Surgery of the Trauma Center Murnau, Germany. The purpose of this meeting was to bring microbiological researchers with an expertise on the field of implant infections together with orthopedic surgeons from a well-established center for septic bone surgery. At the conclusion of the meeting is was stated that merging the knowledge of microbiologists, orthopedic surgeons and immunologists is needed and could create the basis for future interdisciplinary projects on implant infections in orthopedic and trauma surgery.

Bringing together two research centers to develop new collaborative strategies

On February 17, the AO Research Institute Davos (ARI) played host to colleagues from the Department of Trauma Surgery, University Hospital Regensburg (UKR), Germany, on the occasion of the first ARI - UKR scientific get-together. The concept, devised by Markus Loibl, (former AO Research fellow), and Mauro Alini (ARI Vice-Director, Program Leader Musculoskeletal Regeneration) was to bring together two research centers which focus on similar but complimentary research in order to develop new collaborative strategies.

After a tour of ARI's facilities in Davos to demonstrate its capabilities, a series of presentations from both groups preceded an active discussion in which it was immediately clear the potential benefits for both parties. In order to ensure an active collaboration, a visit by ARI members to Regensburg is in the offing so that the ARI team can meet more members of the Regensburg team and see the facilities available.

7 eCM Journal and Conference

eCM Journal

eCM Open Access Journal, published by AO Research Institute Davos
Journal Citation Reports® 2011 released in June (2012) listed eCM with an Impact Factor (the average number of citations to papers published during the preceding two years) for 2011of 3.028, a large drop from 2010, but still very high within the trauma field. The five-year Impact Factor# was released as 4.953. (3rd in Biomaterials) and the Article Influence Score* 1.46 (2nd in Biomaterials). The journal also had surpassed the 17000 registered readers. In 2012, eCM has also become the official Research Journal of the European Orthopaedic Research Society (EORS).

Geoff Richards the Editor-in-Chief of eCM was invited as a speaker and panel discussion at the session on "The future of Orthopaedic Journals" in May 2012 at the 13th EFORT Congress, Berlin, Germany (EFORT European Federation of National Associations of Orthopaedics and Traumatology). He was also invited along with other world leading journal editors to the plenary debate "Future of publishing" at the 3rd TERMIS, World Congress 2012, “Tissue Engineering & Regenerative Medicine”, September 5 - 8, 2012, Hofburg Congress Centre, Vienna, Austria.

Five year Impact Factors are based on cites to articles published in the previous five years. This gives a better indication of longevity of the article than the standard impact factor.
* Article Influence Score - The Article Influence determines the average influence of a journal's articles over the first five years after publication. The mean Article Influence Score is 1.00. A score greater than 1.00 indicates that each article in the journal has above-average influence.

Geoff Richards, Editor-in-Chief of eCM journal speaking at the plenary debate "future of publishing" at the 3rd TERMIS, World Congress 2012, Vienna, Austria.

eCM Conference

2012 eCM XIII: Bone Fixation, Repair & Regeneration

eCM XIII: Bone Fixation, Repair & Regeneration (Focus CMF, Spine, Trauma, Vet) was held from 24th – 26th June 2012 in the Conference Center Davos, Switzerland. Approximately 120 participants travelled to Davos for this year's eCM from as far away as China, Japan, USA, Middle East in addition to many from Europe. The scientific program was arranged by the conference organizers Martin Stoddart, Sophie Verrier, Mauro Alini and Geoff Richards from the ARI, with the assistance of Prof. Charles Archer from Cardiff University. The conference was arranged in single sessions covering the problem failed bone healing. Although bone has a remarkable propensity to repair, there are a number of situations where the repair process fails. This leads to many complications both social and economic. There are multiple challenges which must be met to overcome this situation; a complete understanding of bone biology, at the molecular, cellular and mechanical level is required. Within the active discussion sessions, these topics and the reason for failure to translate bench side approaches to the clinic were investigated further. From the numerous excellent speakers it became apparent that the vascular environment is particularly critical in bone healing. There was also demonstration that the cellular response to mechanical stimulation can be used to modulate the healing response. This is gradually starting to be modeled using computer simulations, which may ultimately lead to accurate in silico models that can faithfully mimic the healing response. All abstracts from the conference can be found at http://www.ecmjournal.org/journal/supplements/vol024supp01/vol024supp01.htm

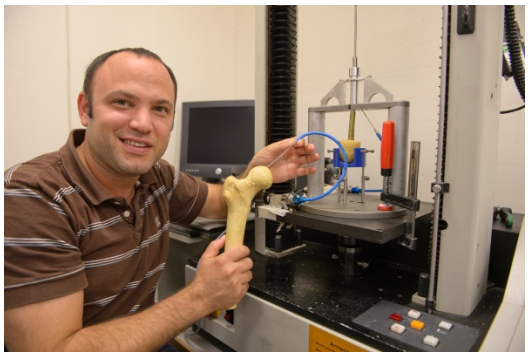
8 AO Research Institute Fellows

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

- Creating tangible research results
- Co-authoring publications in medical journals
- Learning how to approach future research challenges
- Being a member of a multidisciplinary R&D team
- Enlarging personal networks for future R&D activities
- Having access to research colleagues and mentors

In 2012 a total of 14 fellows worked 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.

Michael Blankstein, University of Toronto, Canada

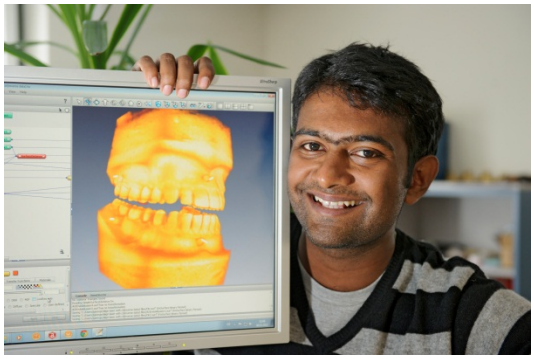


ARI Project: Biomedical Services Program. Assessment of intra-osseous femoral head pressures during cement augmentation of the perforated Proximal Femur Nail Antirotation (PFNA) blade
Over the past few months I have been working with the biomedical team at ARI. It has been an absolute pleasure to work alongside such talented international professionals from so many different disciplines. I have gained tremendous insight into the principles that drive research and development of novel implant designs. I believe this unique experience will have a very positive influence on my career as an academic

Marek Blazejak, Department of Orthopaedic Surgery, Spital Wallis, Brig, Switzerland

ARI Project: Biomedical Services Program. In-vitro temperature evaluation during cement augmentation of proximal humerus plate screws
During my fellowship in Davos I had excellent access to all resources one needs to carry out research work: highly competent and cooperative colleagues, engaged and energetic Project Managers, helpful staff from the ARI workshop, access to the library and all the equipment necessary to do the experiments - and no distraction by the hectic pace of a hospital. The project I dealt with aims to improve fracture fixation in patients with osteoporosis and offered me a unique opportunity to better understand the innovation process in trauma surgery.

Joseph George, Ernakulam General Hospital, Kerala, India



ARI Project: Preclinical Services Program. Evaluation of accuracy of CAD/CAM fabricated splints for orthognathic surgery

My fellowship at the AO entailed the development of pre-operative and post-operative analytical software tools to better augment planning and follow-up of CMF cases. We worked with CT scans and laser scans and participated in generating data which would help the surgeon in limiting the morbidity of the procedure. The interdisciplinary and international essence of ARI is extremely exciting and provides tremendous possibilities. The workplace is very friendly and encouraging to a young clinician like me. Working alongside software engineers and taking coffee breaks with molecular biologists, polymer engineers and such encourages and inspires everyone. It was truly an inspirational and exciting time for me at the ARI.

Michael Götzen, Vorarlberg, Austria

ARI Project: Biomedical Services Program. The effect of subchondral cement augmentation on the overlying cartilage

After my medical studies in Innsbruck, Tirol, I worked for two and a half years in Switzerland as a trauma and orthopedic surgeon. Doing an ARI fellowship has opened up a lot of new opportunities for me. In contrast to being trapped in the everyday clinical work, ARI offers you the occasion and time to focus on basic science. The well-equipped facilities and very experienced staff help you to investigate new methods in your specific topic of interest. AO connects scientists from all over the world, which not only promotes scientific exchange, but also leads to an intercultural network of friendships.

Tobias Helfen, Ludwig-Maximilians University, Munich, Germany

ARI Project: Tissue Morphology Group. Osteoporosis research project
I completed my studies at the Ludwig-Maximilians University in Munich, Germany. Since 2009 I have been working as a trauma and orthopedic resident at the Department of Traumatology and Orthopedic Surgery, Ludwig-Maximilians University Munich, focusing on trauma and orthopedic surgery, but as emergency doctor also in emergency medicine. In September 2012 I started my ARI fellowship, joining the Tissue Morphology group with a special focus on osteoporosis.

Claudia Loebel , Jena, Germany

ARI Project: Musculoskeletal Regeneration Program. Homecell Project: Osteogenic Differentiation of Mesenchymal Stem Cells
After I completed my medical studies in 2011 in Halle-Wittenberg (Germany) I was very pleased to get the opportunity to do a one year medical fellowship in ARI. Working in an interdisciplinary group within the Musculoskeletal Regeneration program I knew I would gain great experience in basic orthopedic research. The main focus of my work is on the differentiation of mesenchymal stem cells for the treatment of bone defects. During this year I have really appreciated the intercultural exchange at work and spending my free time in a beautiful natural environment.

Mario Morgenstern, Trauma Center Murnau, Germany

ARI Project: Musculoskeletal Infection Group. Implant associated infections
I am an AOTrauma medical research fellow in the Musculoskeletal Infection Group. I studied at the University of Munich, Germany and completed my thesis in the Department of Sport-Orthopedics at the Technical University Munich on the topic of high tibial osteotomies. Since 2008 I have been working as an orthopedic resident at the Trauma Center Murnau, Germany. The large number of polytrauma patients treated in this center and a well-established department for septic and reconstructive orthopedic surgery arose my interest in these two research issues. In preparation for my fellowship I was able to set up a research collaboration between the Murnau Trauma Center and the ARI on implant associated infections in orthopedic surgery. I appreciated the opportunity to gain research skills and to work in an interdisciplinary group of scientists on implant infections in orthopedic surgery. During my fellowship I analysed the pheno- and genotypical properties of staphylococci isolated from implant infections. My goal is to find a correlation between the clinical course of the implant infection and the bacterial pheno- and genotype. In terms of the AOTrauma Clinical Priority Program (CPP) Bone Infection I was involved in the establishment of a large animal bone infection model and was taking part as principal investigator of the Trauma Center Murnau in the worldwide CPP Bone Infection Registry. The registry is collecting bacterial specimens, blood samples and clinical information from patients with a Staphylococcus aureus bone infection.

Tomas I. Nicolino, Institute of Orthopedics and Traumatology "Carlos E. Ottolenghi", Italian Hospital of Buenos Aires, Argentina

ARI Project: Biomedical Services Program. Cannulated screw augmentation in the proximal femur
I arrived at the ARI in July 2012. From the beginning I was surprised by the number and variety of projects that were running concurrently. I joined the Biomedical Service Program to work on implant augmentation in osteoporotic bones. As a surgeon this experience gives me the opportunity to understand medical problems from different approaches. The atmosphere is great and allows you to exchange ideas with colleagues from diverse areas. During this fellowship I have also had the opportunity to make a lot of new friends, learn cultures from all around the world and spend a great time in Davos.

Sarah Peters, Chicago, IL, USA

ARI Project: Preclinical Services Program. I work on several projects, not just one, although Dynabone and StaphAB would be the main ones.
As a Veterinary Research Fellow within the Preclinical Facility, I work with mice, rats, rabbits and sheep, while helping develop new and improved ways of fixing fractures and supporting bone healing. I am especially interested in methods of increasing the rate of bone healing in order to minimize post-operative discomfort and shorten recovery times in all species, from mice to humans.

Tatiana Nataly Pirvu, Charité Universitätsmedizin, Berlin, Germany

ARI Project: Musculoskeletal Regeneration Program. Intervertebral disc repair/regeneration
After completing my medical studies at the Charité University Hospital in Berlin, I had the opportunity to do a Medical Fellowship in the Musculoskeletal Regeneration Program (Intervertebral Disc Repair) in ARI. In doing this, I have received insights into the activities of basic researchers. In addition to practical skills in working with cell cultures and tissues as well as their analysis, I have learned plenty of different viewpoints and approaches regarding exploratory focus, and how they differ from medical opinions and clinical research. After the completion of the Fellowship next year I will start my residency in orthopedics / trauma surgery and I am going to use the skills I have learned within the AO in my own clinical as well as experimental research projects.

Kerstin Schneider, Department of Orthopaedic Surgery and Traumatology, Kantonsspital St. Gallen, Switzerland

ARI Project: Biomedical Services Program. Biomechanical investigation on failure modes of proximal femoral fracture fixation with PFLCP

During my ARI fellowship in Davos, I joined the Biomedical Services Program. Right from the beginning I was overwhelmed by the number and variety of projects that were running and impressed by the well-equipped facilities and the great experience of the staff.

With my particular project, I focused on failure modes of implants (locking plates) for proximal femoral fracture fixation. I gained tremendous insight into the complex development process of novel implants based on a close collaboration directly with the implant developers.

Not only I enjoyed the scientific exchange within an international/intercultural network during the daily coffee breaks, but also I appreciated the great opportunity to make a lot of new friends and to spend a great time in Davos.

Ortal Segal, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

ARI Project: Biomedical Services Program. Implant augmentation techniques

I have done an internship from 2004 to 2005 at the Sourasky Medical Center in Tel Aviv, Israel at the Department of Int. Medicine "D", Pediatrics Surgery and Emergency Medicine. Since 2006 I have been a resident at the Orthopedic Division of the Tel Aviv Medical Center in Tel Aviv, Israel. After my fellowship I will go back there and aim to lead orthopedic trauma and to become an active faculty member in the AO courses.

Rukmanikanthan Shanmugam, University of Malaya, Malaysia

ARI Project: Biomedical Services Program. Comparison of lateral phalangeal locked plating versus standard non-locked dorsal or lateral plating

We are in the midst of setting up a biomechanics lab for the orthopedic surgery department at my university; thus, for me the opportunity to work with a multidisciplinary team where each team member is an expert in what he does is a golden opportunity to learn from the best and establish links with good mentors for future projects. So far my experience here has been pleasant; not only are the staff friendly and helpful, there is also the natural beauty of Davos to be experienced.

Daniel Wagner, Center of Musculoskeletal Surgery, University Medical Center, Johannes Gutenberg-University, Mainz, Germany

ARI Project: Preclinical Services Program. 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 (TK project)

In our computer laboratory we are currently analyzing more than 120 Computed Tomography scans of the pelvis to study the morphology of the sacrum. The project forms collaboration between ARI members and surgeons of the worldwide AO Network. Its goal is to improve fracture fixation in elderly patients. My research work is based on novel techniques for three-dimensional virtual bone modeling. It is very interesting to get new insights into the sacral anatomy and to think about how this knowledge could be transferred to become part of the daily practice of a surgeon. I am happy to be part of an interdisciplinary team consisting of engineers, clinicians and computer scientists. This helps me to think about my research in different ways and teaches me how to work scientifically, hopefully to find new clinical solutions. I would recommend a fellowship in the ARI to every surgeon with an interest in science.

Charles White, New York Downtown University, New York, USA

ARI Project: Biomedical Services Program. Biomechanical investigation of ankle and hindfoot stability and joint pressures using a cadaveric model of lateral talar process excision
I completed my medical studies at the New York Collge of Podiatric Medicine as Doctor of Podiatric Medicine in 2009. I have done a residency at the St. Vincent's Hospital in New York for 36 months, followed by a residency at the New York Downtown Hospital in the department of Podiatric Medical & Surgical with added credential for Reconstructive Rearfoot & Ankle Surgery. Afther this fellowship I will go back to the New York Downtown University and will work further in the team of Dr. Sands.

Philipp Zerbe, University of Zurich, Switzerland

ARI Project: Preclinical Services Program. Preclinical surgery
While studying at the Vetsuisse Faculty in Zurich I was already working on several scientific projects. My voluntary work with wildlife brought me to different research facilities under changing conditions. After working as assistant veterinarian in a rotating internship and at emergency duty at the small animal clinic, Vetsuisse Faculty in Zurich, I came to Davos to improve my project management skills. To be able to work in various projects within the AO facilities gave me the chance to gain further insight into a cross-linked way of thinking. I appreciated the possibility of intercultural exchange within the Fellow-family.

9 Project Abstracts by Specialties

9.1 AOCMF

Workflow for improving 2D and 3D skull visualization - a novel iterative voxel/mesh based approach

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 and 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.

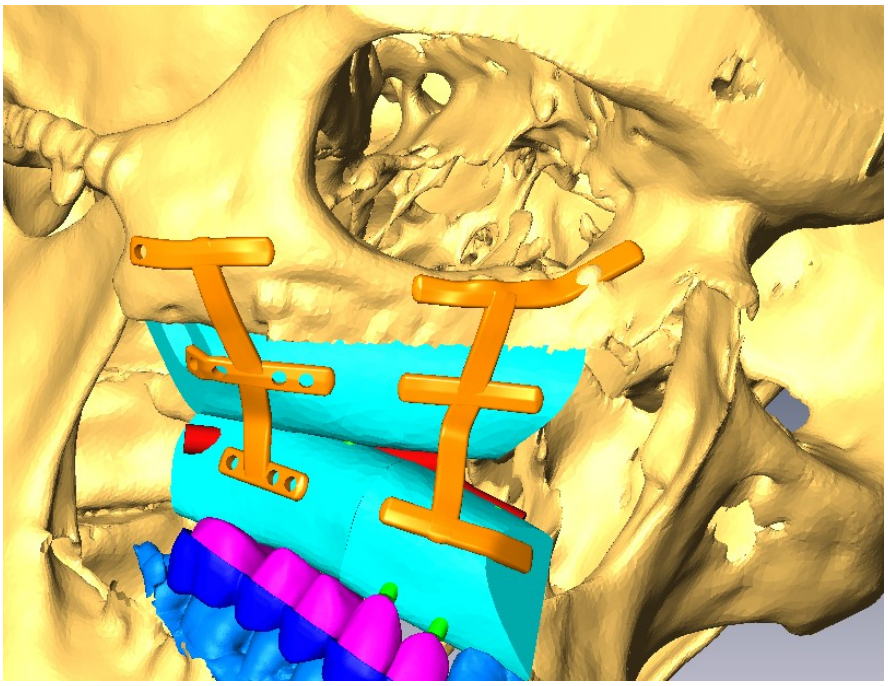
We would like to bring in new thoughts into 2D and 3D skull visualization and to computer modeling. We propose developing a workflow for enhanced post-processing of routine clinical CT and CBCT data to improve 2D and 3D image data quality and visualization of the skull. It will include computer tools 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.

Workflow for custom-made CAD/CAM titanium plates based on virtually planned maxillofacial reconstruction

Maxillofacial defects caused by trauma, tumor resection or malformation requires complex three-dimensional (3D) functional and aesthetical reconstruction. The postoperative result is dependent on the meticulous preoperative planning and its transfer to surgery. One of the latest techniques represents the prefabrication of fibula flaps, which includes reconstruction of occlusion, bone and soft tissue based on a physical 3D model planning (i.e. Rapid Prototyping models). They provide the most accurate technique allowing for complete functional reconstruction with the best fitting of drilling templates, occlusal splints, suprastructure and individual osteosynthesis plates.
Computer-assisted virtual planning could on one hand replace existing 3D planning and would on the other hand improve the adaptation and accuracy of fit of custom-made reconstruction plates. Based on our 10 year experience with prefabricated fibular flaps for the reconstruction of extended maxillofacial defects, we propose a new workflow to treat such patients. It includes preoperative image data acquisition, processing and analyzing the data and the development of surgeon driven software procedures. Then the planning procedure will then undergo Computer-Aided Design/Computer-Aided Manufacturing (CAD/CAM) processes resulting in the production of a custom-made titanium plate. This plate will act as an accurate intraoperative guidance and fixation device - thus helping the surgeon to obtain a good surgical result. The following milestones will be included in the study:

- matching of skull and fibula Computed Tomography (CT) data
- virtual planning of a new occlusion
- evaluation and determination of the size, osteotomies and alignment of the fibula flap within the defect
- planning of an individually designed reconstruction plate
- transfer of the data to a production unit

In a first attempt the feasibility will be tested on a virtual patient. It will also include the evalution of different CAD/CAM techniques. In a second attempt given clinical cases will be treated using the newly developed planning software in combination with the unit that allows for the production of custom made plates.



Together with expert surgeons a computerized planning workflow was elaborated in order to reconstruct large sized maxillofacial defects.

Pres:
Kamer L, Rohner D et al. Workflow for custom-made CAD/CAM titanium plates based on virtually planned maxillofacial reconstruction. AOCMF 1st Workshop Clinical Priority Program (CPP) Imaging and Planning of Surgery, May 5, 2011 Freiburg, Germany

Partners:
- Rohner D, Cranio-Facial Center (cfc) Hirslanden, Aarau, Switzerland
- Hammer B, Cranio-Facial Center (cfc) Hirslanden, Aarau, Switzerland

Evaluation of accuracy of CAD/CAM fabricated splints for orthognathic surgery

The clinical outcome in orthognathic surgery depends critically on accurate preoperative planning. The need for three-dimensional preoperative assessment has been documented over the past years and conventional planning has been added by a three-dimensional computerized approach. Until now, these techniques have mainly been used in single cases, i.e. in complex asymmetric cases and not in routine clinical practice.
Computer-assisted virtual planning could on one hand replace existing conventional planning and model surgery and would on the other hand improve the accuracy of the clinical outcome.
In conventional as well as in virtual approaches, surgical splints are usually used for transferring the surgical plan to the patient. Conventional splints are manufactured on the plaster cast models, whereas in computerized approaches this is achieved using CAD/ CAM (Computer-aided design/ Computer-aided manufacturing) techniques (i.e. manufactured Rapid Prototyping techniques). However, there it is still controversy concerning the best approach to manufacturing of accurate CAD/ CAM splints.
The goal of the present study is to define a suitable workflow to produce CAD/ CAM splints in orthognathic surgery. To obtain an accurate virtual model of the dental surfaces, different radiological and surface scan modalities will be assessed. The different processing steps will be evaluated and then combined with the most suitable Rapid Prototyping manufacturing technique and material respectively. Finally, these splints will be compared with conventional manufactured splints (gold standard). The best manufacturing process will be integrated into computerized planning procedures of clinical cases.

Pres:
Zizelmann C. Evaluation of accuracy of CAD/CAM fabricated splints for orthognathic surgery AOCMF 1st Workshop Clinical Priority Program (CPP) Imaging and Planning of Surgery, May 5, 2011 Freiburg, Germany.

Pub:
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 Mar 20.

Partner:
- Rohner D, Cranio-Facial Center (cfc) Hirslanden, Aarau, Switzerland

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

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. The current theories, namely the over-suppression of bone turnover, ischemia due to anti-angiogenetic effects, local infections or soft-tissue toxicity are – neither alone nor in combination – suitable to answer the questions of paramount importance: (i) why is only the jaw bone affected? (ii) why and how do the derivates differ in their potency to induce a BRONJ? and (iii) why and when is BRONJ manifested? In order to investigate these questions further, a reliable preclinical model is required. Therefore the aim of this study was to investigate 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 investiagtions into the development of BRONJ.

Partners:

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

9.2 AOSpine

Role of the intervertebral disc in the development and progression of spinal deformities (DISCFORM) (Started)

The etiology of spinal deformity in idiopathic scoliosis is 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 established, the role of the intervertebral disc in the development of idiopathic scoliosis is not clear. The aim of this project is to elucidate molecular differences between disc cells from patients with idiopathic and neuromuscular scoliosis in comparison with cells from healthy individuals. Gene expression profiles will be analyzed by microarray and quantitative RT-PCR. Molecules with different gene expression profiles will be evaluated at the protein level using immunohistochemistry on sections from scoliotic and healthy discs. Furthermore, 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, and Kaplan L, Hadassah Hebrew University Medical School, Israel
Mamonova E, Innovative Medical Technology Center, Novosibirsk, and Sadovoy M, Novosibirsk Research Institute of Traumatology and Orthopaedics, Russia

Surface modification of PEEK to improve tissue integration PEEKSURF (Completed)

Polyetheretherketone (PEEK) is a non-resorbable polymer used advantageously to replace metals in devices such as spine cages and patient specific craniomaxillofacial implants. It has high strength and good wear properties compared to other polymers such as UHMWPE. Moreover, PEEK is radiolucent allowing evaluation of the tissue integration to implant. However, PEEK has an intrinsic low surface energy, which can limit cellular adhesion and this can in turn lead to implant loosening as a result of fibrous encapsulation. The surface of PEEK can be altered by plasma modification to increase the surface energy and thereby improve cellular adhesion in order to avoid implant loosening. A study has been performed to quantify, in a relevant *in vivo* model, bone contact to PEEK surfaces and assess the translational potential of the new proprietary surface modification.

Results: Machined and moulded polyetheretherketone (PEEK) implants with or without an Oxygen Plasma treatment were prepared and implanted in sheep in the cancellous bone of the distal femur and proximal tibia and cortical bone of the tibia. After 4, 12 and 26 weeks, push-out test, fluorochrome labelling, qualitative and quantitative histomorphometric analyses were performed. In the cancellous bone, Push-out force increases with time and a trend toward higher force was observed for machined vs. moulded and Oxygen Plasma treated vs. non-treated. On-going remodelling of the bone was apparent in cancellous and cortical locations peripheral to the implants at short time point. Minimal or no inflammation was observed for all implants at all locations and time points. Bone-implant contact (BIC) was quantified at all-time points and locations for the 4 prepared surfaces. The BIC values ranges from 20% to 50 %. In the cancellous bone, no significant difference was observed while in the cortical the BIC increased significantly from 4 to 26 weeks.
This study provides a unique reference for further modifications and *in vivo*assessment of PEEK implants. Topography of PEEK implant surface influence the osseointegration of PEEK implant in vivo. Commercially relevant stable oxygen plasma modification is not detrimental to PEEK osseointegration.

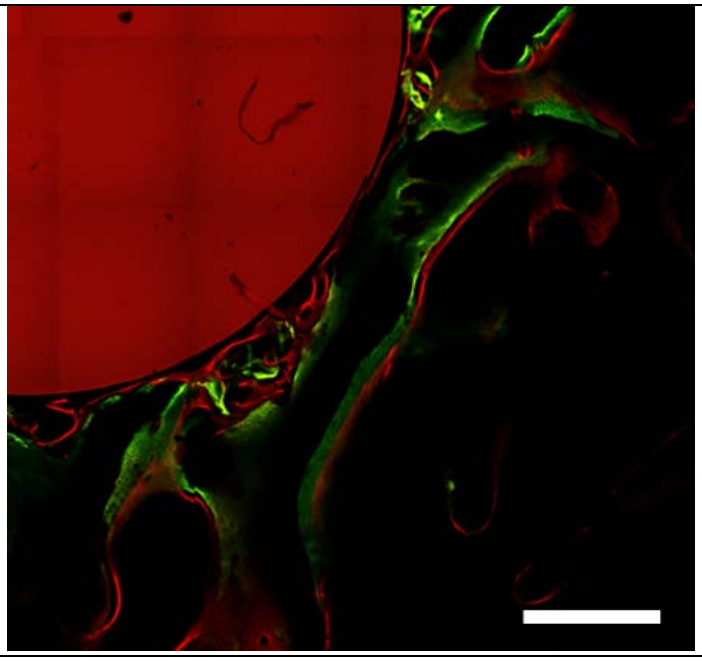


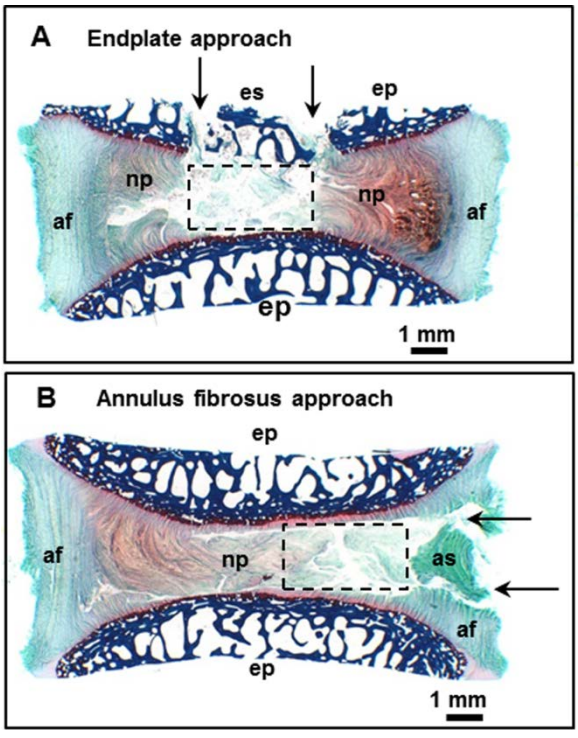
Figure: Representative fluorescence image of a PEEK implant and the surrounding cancellous bone after 4 weeks implantation. (Fluorochrome labeling with calcein green 1 week post-implantation and xylenol orange 3 weeks post-implantation. Scale bar 500 µm).

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

For cell-based intervertebral disc regeneration, mesenchymal stem cells (MSCs) appear to be ideal candidates, since they have the ability to differentiate into various cell types, potentially including IVD cells, and to stimulate host disc cells. However, there are still open questions regarding the choice of the cell carrier, the injection method, and the fate of implanted cell populations. The aims of this project are (1) to evaluate an appropriate carrier system for the injection of MSCs, (2) to study the effect of "chondrogenic" preconditioning on the survival and differentiation of MSCs injected into an IVD, (3) to establish an appropriate cell/carrier delivery route for *ex vivo* studies, and (4) to investigate the effect of dynamic compressive loading on differentiation of MSCs injected in an IVD in organ culture**.**

To study the effect of MSC pre-conditioning, discs were harvested from bovine tail and MSCs isolated from human bone marrow. MSCs were either suspended in thermoreversible hyaluronan-based hydrogel (HA-pNIPAM) and directly supplied to the IVDs or pre-differentiated with growth factors and then supplied to the IVDs. Results showed that HA-pNIPAM induced MSC differentiation toward the disc phenotype without addition of growth factors. In addition, direct combination of HA-pNIPAM with the disc environment induced a stronger disc-like differentiation of MSCs than pre-differentiation of MSCs followed by their delivery to the discs. Thus, hyaluronan-based thermoreversible hydrogel supports MSC differentiation without the need for growth factor supplementation.

The current clinical approach to deliver therapeutics, cells and/or hydrogels for IVD regeneration leads through the annulus fibrosus (AF), resulting in a potentially detrimental mechanical destabilization. We investigated whether an endplate (EP) approach might improve the mechanical response of nucleotomized discs compared to an AF approach. Bovine caudal discs were nucleotomized either through an EP or AF defect and were evaluated under dynamic load by using histological and mechanical techniques. Data indicate that the EP approach improves the mechanical response of nucleotomized IVDs through maintenance of an intact and functional AF.



Sagittal histological sections (safranin O - fast green staining) of intervertebral discs after a partial nucleotomy through (A) the endplate (EP) or (B) the annulus fibrosus (AF) after 1 week dynamic loading. The size of the nucleotomized region (dotted) is similar for both approaches; in the EP approach an EP stopper (es) was used to close the cavity, while in the AF approach an AF stopper (as) was used to close the cavity. Arrows indicate the cutting plane.

Pres:
Peroglio M, Eglin D, Benneker LM, Alini M, Grad S. Evaluation of a thermoresponsive hyaluronan hydrogel as stem cell carrier for intervertebral disc regeneration. SSB 2012, Zürich, eCM Journal 23 Suppl 2, 24, 2012.

Peroglio M, Grad S, Eglin D, Benneker LM, Alini M. Thermoreversible hyaluronan hydrogels support mesenchymal stem cells discogenic differentiation in vitro and ex-vivo. WFSR 2012, Helsinki, Global Spine Journal 2012;2 Suppl 1

Striegl B, Grad S, Eglin D, Benneker L, Bono E, Alini M, Graf-Hausner U, Peroglio M. Human disc cells and mesenchymal stem cells differentiation in a thermoreversible hydrogel: an in vitro and ex-vivo study. ORS 2012, San Francisco.

Striegl B, Grad S, Eglin D, Benneker LM, Bono E, Alini M, Graf-Hausner U, Peroglio M. In vitro evaluation of a thermoreversible hyaluronan-based hydrogel loaded with cell-seeded polyurethane particles for nucleus pulposus repair. WFSR 2012, Helsinki, Global Spine Journal 2012;2 Suppl 1

Vadalà G, Russo F, Pattappa G, Schiuma D, Peroglio M, Grad S, L. Benneker LM, Alini M, Denaro V. "The transpedicular approach as new route for intervertebral disc regeneration and biological fusion". World Forum for Spine Research, Helsinki, Finland, June 2012.

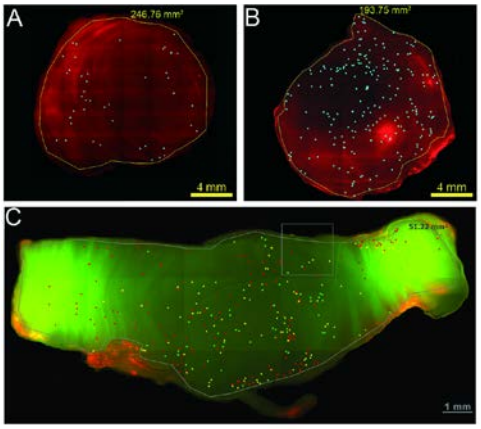
Vadalà G, Russo F, Pattappa G, Schiuma D, Peroglio M, Grad S, Benneker LM, Alini M, Denaro V. "The transpedicular approach as new route for intervertebral disc regeneration". European Orthopaedic Research Society (EORS). Amsterdam, September 2012.

Pub:
Peroglio M, Grad S, Mortisen D, Sprecher CM, Illien-Jünger S, Alini M, Eglin D. Injectable thermoreversible hyaluronan-based hydrogels for nucleus pulposus cell encapsulation. Eur Spine J 21 Suppl. 6:839-49, 2012.

Partners:
- Benneker LM, University Hospital Bern, Switzerland
- Vadala G, Department of Orthopaedics and Trauma Surgery, University Campus Bio-Medico of Rome, Italy

Mesenchymal Stem Cell Chemo-Attractive Scaffolds for Intervertebral Disc Regeneration – In Vitro Studies using a Whole Organ Culture System (DISCHOME) (ongoing)

Cell-based approaches have received increasing attention for therapy of early intervertebral disc (IVD) degeneration, with a main focus on the regenerative capacity of mesenchymal stem cells (MSCs). The disadvantage of cell implantation methods is that two invasive procedures are required; furthermore, *in vitro* expansion is associated with impaired homing and proliferative capacity of MSCs. An alternative approach implies the recognition of endogenous mechanisms that may be activated to induce an appropriate repair response. Progenitor cell populations with the potential to initiate repair mechanisms have recently been discovered in various tissues including the IVD. It is also suggested that trafficking of native MSCs to injured tissue occurs in a natural healing response. Recent data indicate that homing of MSCs to damaged areas within the IVD may also occur. We hypothesize that specific soluble factors are released by cells of the IVD in response to injury/damage and that these factors are able to recruit MSCs to the site of damage. Furthermore, injection of such specific chemotactic factor(s) into the nucleus pulposus may stimulate MSC migration into IVDs cultured under simulated-physiological conditions and enhance MSC migration into induced degenerative discs. The capability of MSCs to migrate through the disc tissue towards the center of the disc is assessed by delivering chemotactic factors into the disc space. The delivery method will be optimized by testing different hydrogel carriers and release systems. The aim is to develop a novel system that promotes MSC recruitment *in situ* through biomaterial-based chemo-attractant application, as an alternative to MSC-scaffold colonization *in vitro*.



Engraftment of bone marrow–derived mesenchymal stem cells (MSCs) into the disc cultured under (A) physiological and (B) degenerative conditions after interactive counting; yellow ring marks the region of interest and blue dots mark the counted cells. (C) Sagittal section of induced degenerative disc showing labeled MSCs (red, yellow, and green) that were administered at different time points during culture.

Pres:

Leite Pereira C, Pattappa G, D'Este M, Eglin D, Gonçalves R, Grad S, Barbosa M, Alini M. Development of a chemoattractant-delivery system for MSCs recruitment in the degenerated disc. EORS 2012.

Pattappa G, Illien-Jünger S, Peroglio M, Stoddart MJ, Benneker LM, Sakai D, Mochida J, Grad S, Alini M. Homing of IGF-1 transduced mesenchymal stem cells (MSCs) in degenerative intervertebral discs accelerates proteoglycan synthesis. ORS 2012, San Francisco.

Pub:

Illien-Jünger S, Pattappa G, Grad S, Peroglio M, Stoddart M, Sakai D, Mochida J, Alini M. Homing of Mesenchymal Stem Cells in Induced Degenerative Intervertebral Discs in a Whole Organ Culture System. Spine 37(22):1865-73, 2012.

Sakai D, Nakamura Y, Nakai T, Mishima T, Kato S, Grad S, Alini M, Risbud MV, Chan D, Cheah KS, Yamamura K, Masuda K, Okano H, Ando K, Mochida J. Exhaustion of nucleus pulposus progenitor cells with ageing and degeneration of the intervertebral disc. Nature Commun Dec 11;3:1264, 2012.

Partners:

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

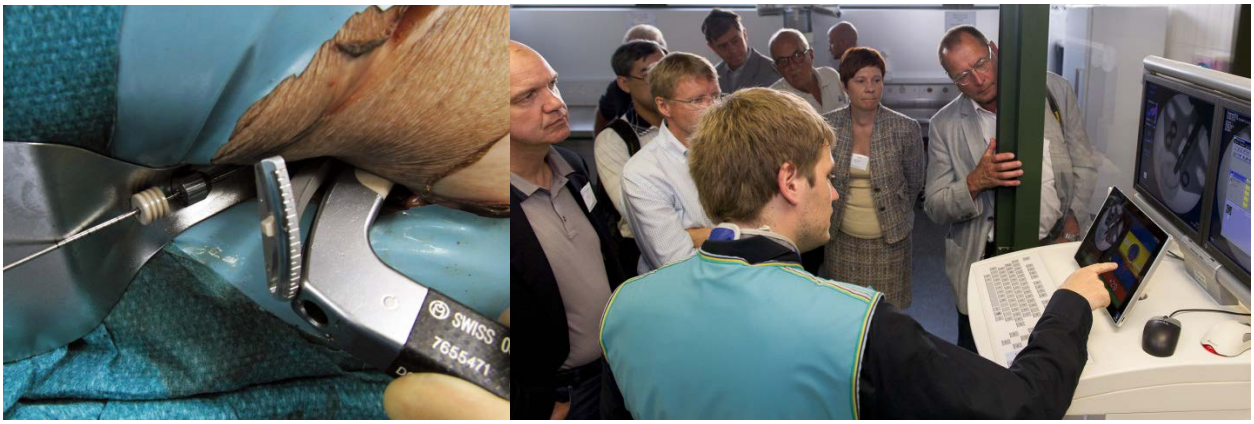
9.3 AOTrauma

A novel approach for simplified computer aided surgery, exemplified on nailing of proximal femur fractures (SimpCAS X-in-one, ongoing)

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: Proof of concept was reached for a prototype system capable of (1) placing an implant centered in the femoral head, (2) adjusting the anteversion of a femur, and (3) locking an intramedullary nail distally in place. The principle was further generalized to become a generic support system for nailing and plating procedures. Legal regulations are in process to test the system in clinics.



Demonstration of the novel approach for simplified computer aided surgery at AO Trustees Meeting in Davos where over 2/3 of the trustees showed high interest in the system.

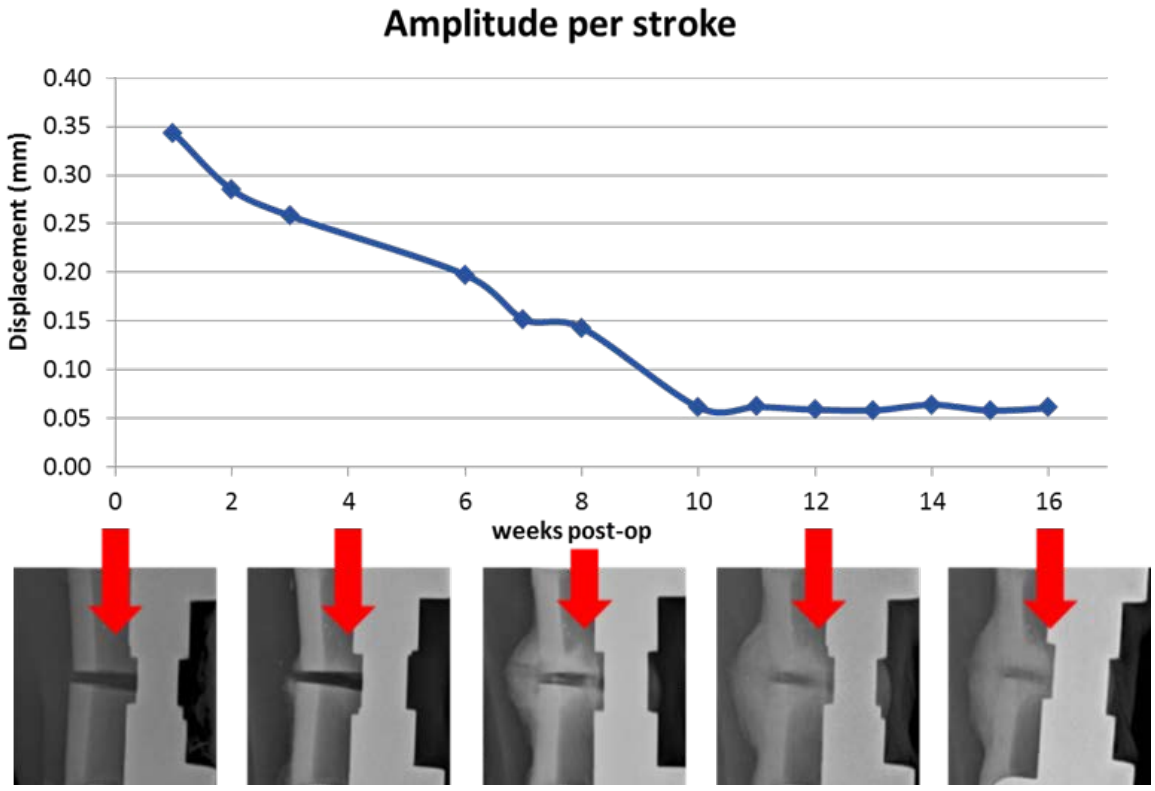
Pres:
Windolf M. A novel assistance technology for efficient implant positioning. 2012. ECTES

Partners:
- Mosheiff R, Hadassah University Hospital, Jerusalem, Israel
- Liebergall M, Hadassah University Hospital, Jerusalem, Israel

Development of a dynamizable internal fixator system for large animal bone research with biofeedback technology (ImpCon)

Problem: Various attempts have been undertaken to take clinical advantage of fostered bone formation under mechanical stimulation of the fracture. However, the phenomenon is not fully understood and requires further investigation. For this reason, research and clinical applications with biofeedback systems, characterizing the healing process are gaining importance, but feasible solutions are still missing.

Goal: To develop and extend the portfolio of a recently introduced plating concept to serve as an advanced implant system for bone research using large in-vivo models by stimulating and monitoring of the healing process in a wireless fashion.
Results: In-vivo application of an instrumented dynamizable plate at an ovine tibia was a successful proof of the concept. Data logger was developed and monitored continuously and autonomously motion in the fracture gap over 16 weeks. Ongoing bone consolidation was detected by a decreasing motion signal over time disregarding model activity and magnitude of physiological loading. Next steps became obvious to enhance the application of the system. A follow-up project application was submitted to AOTrauma.



Fracture healing progress indicated by decrease of the motion in the fracture gap (displacement) and callus formation over time.

Partner:

- Mathis H, Institute for Communication Systems, Hochschule für Technik, Rapperswil, Switzerland

Development of a biofeedback system for bone healing and its first application for mechano-biological research (ImpCon 2, ongoing)

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 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 research implant system with biofeedback technology and its in-vivo application in an ovine model in order to extent current mechano-biological knowledge on fracture repair.

Results: After conditional project approval, several electronic and mechanical improvements of the existing system were carried out in order to enhance the necessary high precision and interpretation of the collected data. Three specimens were operated to investigate the function of the revised system and to obtain first results on the effect of implant stiffness on bone healing. A concept for active modulation of implant stiffness based on actual callus formation is currently under development.

Data logger unit for on-board processing of in-vivo collected data.

Partners:

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

Cement augmentation methods for improved fracture fixation in osteoporotic bone (ImplantAug, ongoing)

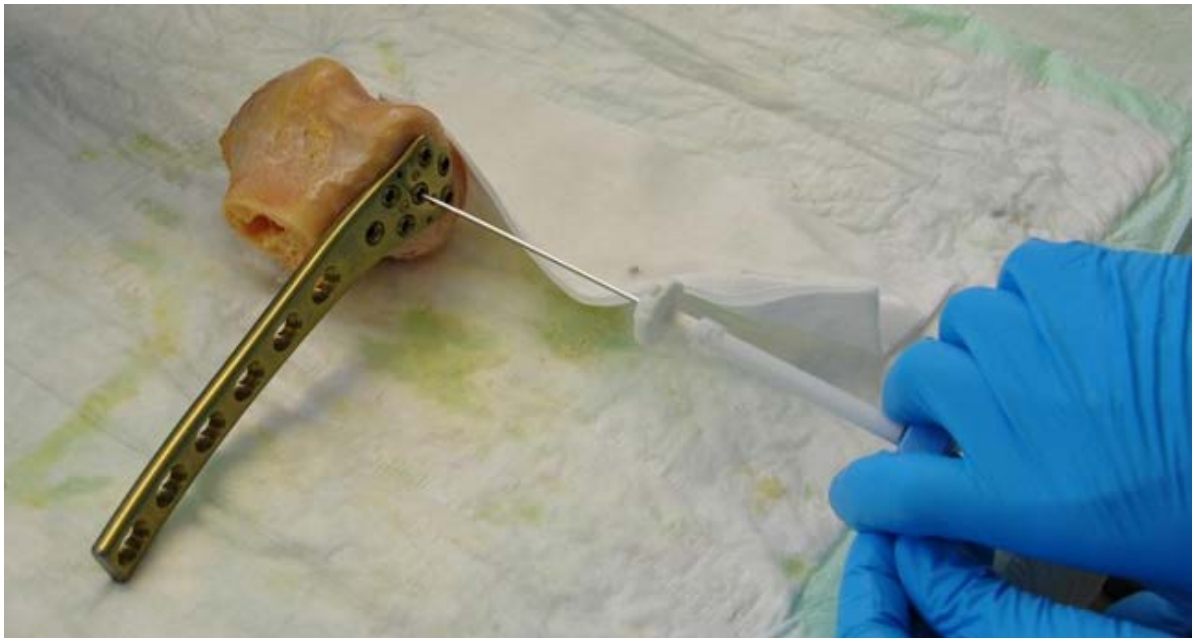
Problem: Fracture treatment in elderly patients remains a major challenge in trauma surgery. It is expected that complications will increase due to a rising incidence of osteoporosis. Despite implant design improvements mechanical complications still persist, which may have devastating consequences. Application of bone cement for improved implant purchase in osteoporotic bone is a promising option to reduce the risk of failure and to allow for early and confident mobilization of elderly patients.

Goal: To evaluate potential implant augmentation procedures at several anatomical key locations in terms of biomechanical benefits and related risks. It is 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: The project is divided into several sub-projects.

Cement localization and volume in proximal femur augmentation. The effect of the localization and amount of PMMA-based bone cement on implant purchase for augmentation of PFNA blades (Synthes GmbH) was investigated. The experiments revealed an influence of the cement location on the biomechanical competence of the bone-implant construct. There was an inverse correlation between the distance of the PMMA cloud to the apex of the femoral head and the number of load-cycles to failure. The cement amount can be reduced to 2ml if placed at a beneficial location (cranial to the tip of the blade) without compromising biomechanical stability.

Augmentation as a new concept in treatment of osteoporotic distal femur fractures. The biomechanical potential of a plate-screw augmentation in osteoporotic distal femur fractures was evaluated. The number of load-cycles to failure was significantly higher in the augmented group compared to the non-augmented one, which demonstrates the high potential of this technique to increase implant anchorage.



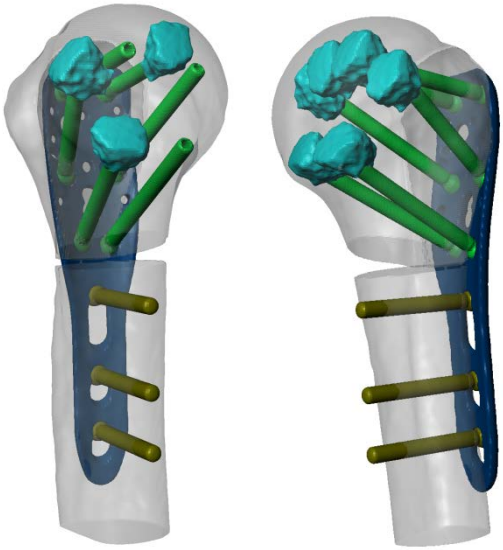
Injection of bone cement through cannulated screws in a human distal femur.

A novel approach for fracture fixation in osteoporotic extra-articular tibia fractures. The biomechanical benefit of plate augmentation in the proximal tibia was investigated using an extra-articular fracture model (AO-41-3.3) in a paired test on human bone. Varus collapse in the augmented group was significantly less compared to the non-augmented one. It was shown that cement augmentation of the LISS-PLT plate-screws (Synthes GmbH) significantly lowers secondary varus displacement in osteoporotic bone.

Screw augmentation in osteoporotic femoral neck fractures. It was assessed whether augmentation of three cannulated screws using bone cement in stable femoral neck fractures could improve implant fixation. The results of this biomechanical experiment showed no advantage of cement application at the tips of three cannulated screws in a stable femoral neck fracture model. Hence, it can be concluded that cement augmentation cannot be applied as routine concept in fracture fixation. The indication must be rigorously evaluated, taking into account fracture pattern, implant selection and failure mechanisms.

In vitro assessment of screw augmentation in locked plating of proximal humerus fractures. It was biomechanically assessed whether cement augmentation of particular PHILOS plate screws (Synthes GmbH), aiming at a region with poor bone quality, is effective in improving biomechanical stability. The augmented samples withstood significantly more load-cycles until failure compared to the non-augmented control. The augmentation of two specific screws, aiming at poor bone quality, was almost as effective as four augmented screws with twice as much amount of cement. The study showed the need for a systematic analysis of the augmentation pattern of multiple load carries at the proximal humerus.

Systematic computational evaluation of bone cement configuration for augmentation at the proximal humerus. A systematic evaluation was performed with the help of finite element simulations in order to investigate all possible cemented screw combinations of the PHILOS plate (Synthes GmbH) and achieve the best possible construct stability. Whereas complete augmentation of all 6 proximal PHILOS screws showed the highest reduction in bone strains, configurations with only 3 augmented screws were found to be with comparable strain reductions and superior results compared to configurations with 4 or 5 screws.



Example of two different cemented screw combinations of the PHILOS plate used for computer simulation.

Temperature study on the PHILOS plate. The issue of exothermic heat development during augmentation of the proximal PHILOS plate screws with PMMA-based bone cement and the risk of bone and cartilage necrosis were addressed. In an ex-vivo experiment it was shown that the augmentation led to a locally limited development of supraphysiological temperatures in the cement cloud and closely around it. However, the critical threshold values for necrosis of bone and cartilage reported in the literature were not reached.

Assessment of intra-osseous femoral head pressures during implant augmentation. The intra-osseous pressure and corresponding force necessary for bone cement injection through a perforated cephalic implant was measured to assess whether the generated pressure carries a risk for development of avascular necrosis. The ex-vivo model revealed a small transient increase in intra-osseous pressure after sequential 1ml injections of up to 6 ml of PMMA. Pressures never reached published values linked to avascular necrosis and always returned to baseline after each step of injection.

Pres:
Fliri L, Lenz M, Stucki J, Boger A, Windolf M. Ex-vivo evaluation of the polymerization temperatures during cement augmentation of PFNA blades. 2012. ESTES.

Sermon A, Fliri L, Richards RG, Boonen S, Windolf M. Augmentation of hip implants in osteoporotic bone: How much cement is needed and where should it go? 2012. ESTES.

Pub:
Wähnert D, Hofmann-Fliri L, Schwieger K, Brianza S, Raschke MJ, Windolf M. Cement augmentation of lag screws: an investigation on biomechanical advantages. Arch Orthop Trauma Surg 2012 (Epub ahead of print).

Fliri L, Lenz M, Boger A, Windolf M. Ex vivo evaluation of the polymerization temperatures during cement augmentation of proximal femoral nail antirotation blades. J Trauma Acute Care Surg 2012 Apr;72(4):1098-101.

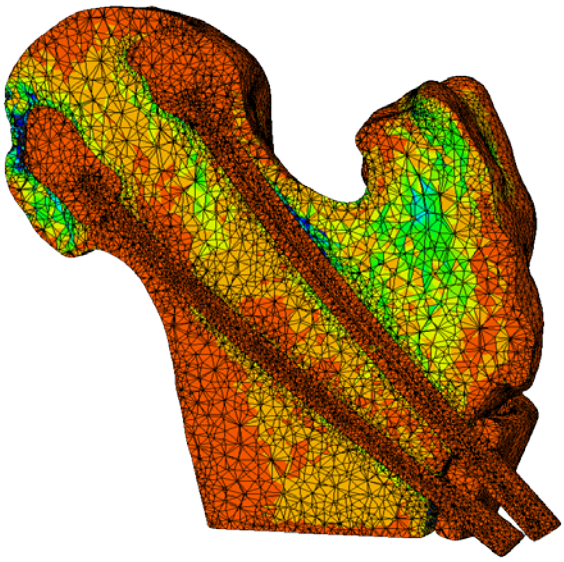
Partners:
- Blauth M, Medical University Innsbruck, Austria
- Röderer G, Ulm University, Germany
- Südkamp N, University Hospital Freiburg, Germany
- Raschke M, University Hospital Münster, Germany
- Morlock M, Technical University Hamburg Harburg, Germany
- Weber A, Synthes GmbH, Solothurn, Switzerland

Prophylactic reinforcement of the proximal femur to prevent secondary hip fractures (ProphylacticAug, ongoing)

Problem: Geriatric hip fractures are associated with a high risk of secondary fractures at the contralateral side. Mortality can be significantly increased after a secondary fracture. Hip protectors have not proven to lower the fracture risk and the effect of pharmacological treatment of osteoporosis is often too slow to reduce the fracture incidence. A prophylactic mechanical reinforcement of the contralateral limb during operation of the initial fracture could be of interest in highly osteoporotic cases.

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

Results: In a previous phase of this project a selective V-shaped bone cement configuration showed potential to increase stability of the proximal femur. A computational test model was developed and applied to systematically investigate different reinforcement materials in terms of configurations and mechanical properties. It was shown that optimal results can be achieved with an augmented metallic implant. A first promising implant design was developed and investigated in a biomechanical experiment on human bone with an established setup for fall simulation. Results showed a statistically significant increase in energy absorption until fracture of the reinforced femora. However, lack of consistency was observed with some complicated subtrochanteric fractures created during the fall simulation. Currently, the concept is further developed to find a solution for reliable reinforcement of the proximal femur, allowing revision surgery in case of a fracture occurrence.



Finite element model for evaluation of a new reinforcement concept to prevent secondary hip fractures.

Pub:
Fliri L, Sermon A, Wähnert D, Schmoelz W, Blauth M, Windolf M. Limited V-shaped cement augmentation of the proximal femur to prevent secondary hip fractures. J Biomater Appl. 2012 (Epub ahead of print).

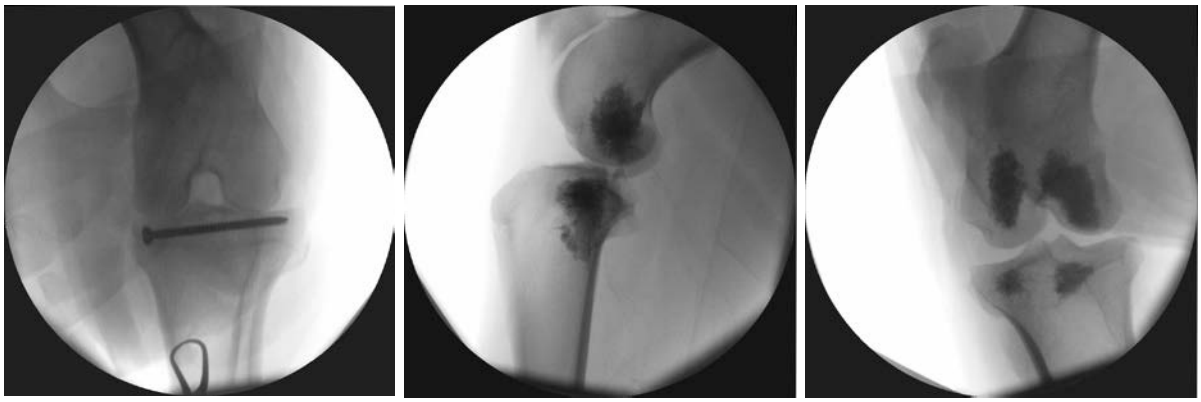
Partners:
- Blauth M, Medical University Innsbruck, Austria
- Schmölz W, Medical University Innsbruck, Austria
- Van Lenthe H, ETH Zurich, Switzerland

The effect of subchondral cement augmentation on the overlying cartilage (CartAug, ongoing)

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 effect of bone cement in the subchondral region on the adjacent articular hyaline cartilage in an ovine preclinical model.

Results: In a first phase necessary methods were developed ex-vivo. The subchondral bone area was defined, the surgical model was established and quantification of the subchondrally injected bone cement was ensured. A pilot in-vivo series with 8 specimens and a follow-up of 2 months was carried out. A metal screw was placed in the subchondral bone of the proximal tibia in order to investigate the pure effect of subchondral bone compaction on the overlying cartilage. Cement clouds with different amounts (2ml and 0.5ml) were placed in the distal femur and proximal tibia at different distances to the hyaline cartilage. Evaluation of the test results is currently in process. A second series with a follow-up of 4 months is planned.



Radiographs demonstrating implant and cement placement near the cartilage in an ovine knee.

Partners:
- Blauth M, Medical University Innsbruck, Austria
- Fairclough J, Spire Cardiff Hospital, Wales
- Von Rechenberg B, University of Zurich, Switzerland

Interfragmentary compression of different tibia plateau split fracture fixation techniques

Problem: Interfragmentary compression in tibia plateau split fracture fixation is necessary to maintain anatomical reduction and avoid post-traumatic widening of the plateau. However, its amount depends on the applied fixation technique.

Goal: To quantify the interfragmentary compression created by a reduction clamp with subsequent angle stable locking plate fixation in an osteoporotic and a non-osteoporotic synthetic human bone model in comparison to cancellous or cortical lag screw fixation.

Results: Preliminary compression applied by a reduction clamp was maintained after angle stable locking plating. Fixation technique with two 6.5 mm cancellous screws would be appropriate for young human non-osteoporotic bone, whereas four 3.5 mm lag cortical screw configuration could also be applied in osteoporotic bone.

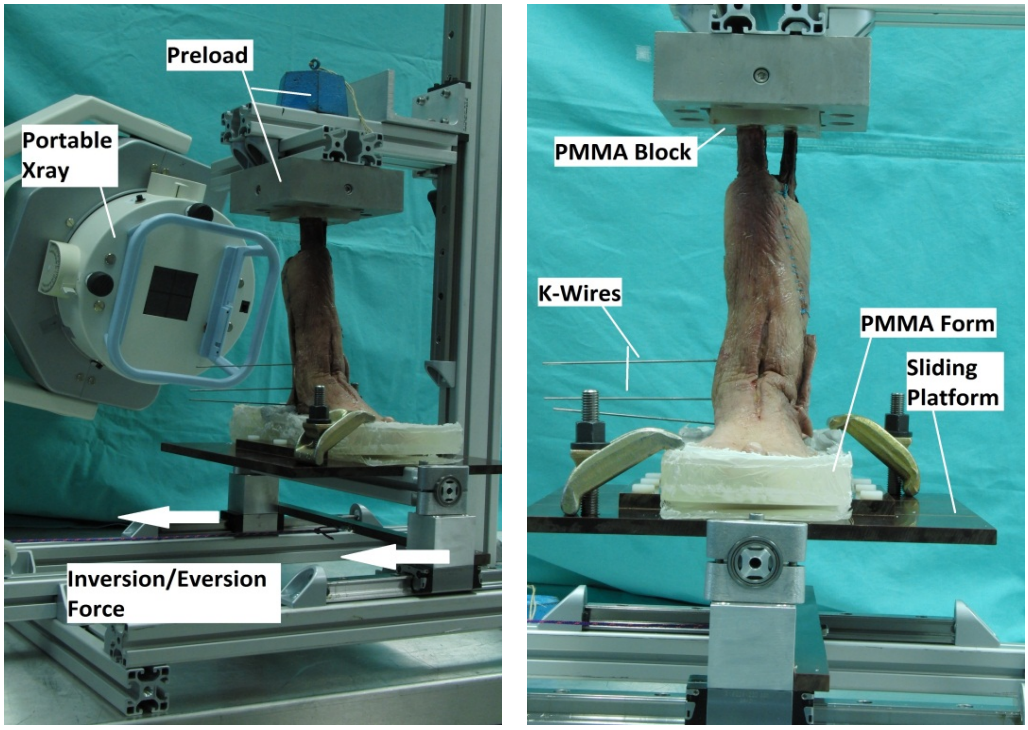
Partner:
- Kojima KE, University of Sao Paulo, Brazil
- Lenz M, Universitätsklinikum Jena, Germany

Biomechanical assessment of ankle and hindfoot stability and joint pressures using a cadaveric model of a large lateral talar process excision

Problem: Fractures of the lateral process of the talus are frequently overlooked and should be considered in the differential diagnosis of ankle pain. Lateral process fracture fragment excision may be followed by hindfoot instability and altered hindfoot biomechanics, associated with a shift of ankle and subtalar joint contact pressures. This may lead to osteochondral lesions and persisting pain originating from posttraumatic arthritis. There is controversy regarding the ideal fragment size for internal fixation versus excision and a concern that excision of a large fragment may lead to significant instability.

Goal: To assess biomechanically the effect of a simulated large lateral talar process excision on ankle and subtalar joint stability and ankle pressures.

Results: Excision of large 2-3 cm^3 fragment of the lateral process of the talus does not produce significant instability in the subtalar joint, as demonstrated by no significant angular change with forced inversion and eversion. With respect to the ankle joint, a 3 cm^3 fragment excision produced a talar tilt which was statistically significant. This could be related to the significant soft tissue dissection required to resect a large fragment.



Specimen placed in a seesaw test rig for radiographic assessment under inversion and eversion forces.

Partner:

- Sands AK, Saint Vincents Hospital, New York, USA

Influence of insertion angle on locking stability of variable and fixed angle locking screws (ongoing)

Background: Plating of epiphyseal fractures with short articular fragment requires positioning of the screws exactly within the fragment. Variable angulation of the locked screw in the LCP may avoid penetration into the articular space or missing the fragment. The new variable angle locked screws (Synthes GmbH) allow a range of 15° inclination in all directions.

Goal: To investigate locking stability of variable angle locked screws in comparison to fixed angle locked screws.

Results: Whereas variable angle locked screws provided a good locking stability at all investigated angles (0°-15°) with a slight decrease with 15° angulation, fixed angle locked screws provided such stability only at 0° angle under quasi-static loading.

Partners:
- Perren SM, AOF, Davos, Switzerland
- Fernandez A, British Hospital, Montevideo, Uruguay
- Lenz M, Universitätsklinikum Jena, Germany
- Haag R, Synthes Inc, West Chester, USA
- Dutoit C, Synthes GmbH, Solothurn, Switzerland

3D statistical bone density distribution at anatomical key regions and its application for osteosynthesis optimization in osteoporotic bone

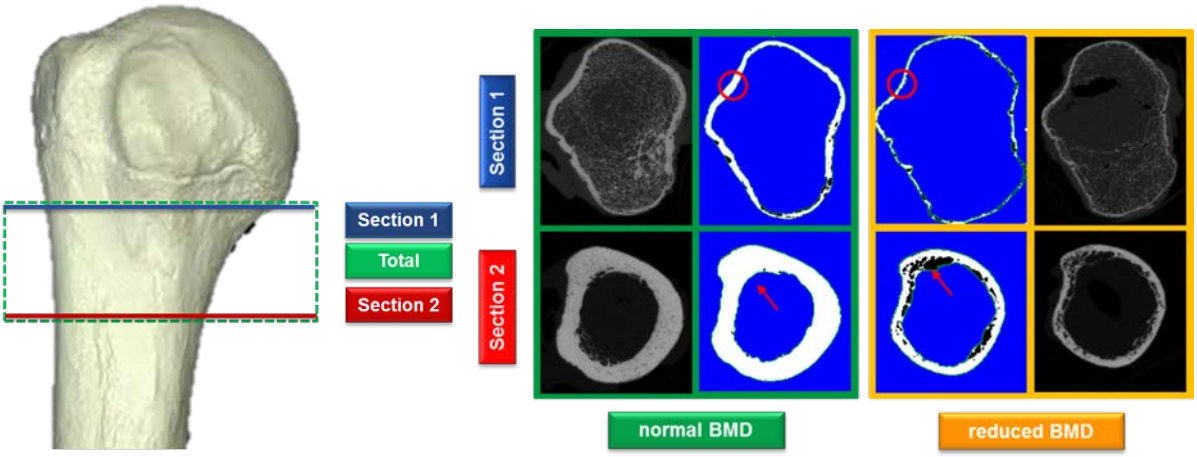
Fragility fractures involve all kinds of bones. Apart from spinal fractures predominantly metaphyseal areas of long bones are affected. Fracture fixation may be compromised by a reduced bone mass and altered bone structure which may result in an increased number of complications and fixation failures. 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 present study are:

1. based on peripheral quantitative CT (pQCT) scanning to perform a three-dimensional (3D) anatomical study of metaphyseal sites of osteoporosis relevant regions, creating 3D statistical anatomical computer models of osteoporosis key regions (=3D BMD maps), in order 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.
2. to define 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.
3. to assess the feasibility of the concept on a representative region (proximal Femur).

Partners:
- Blauth M, Medical University Innsbruck, Austria
- Popp AW, Berne University, Switzerland
- Lenz M, Jena University, Germany

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

Fractures of the proximal humerus are one of the most frequent injuries in elderly people. The predominant fracture zone at this age is the surgical neck which is probably related to osteoporotic changes of the bone. However, only little is known about the development and progression of osteoporosis at the proximal humerus. Especially the sides of the bone remodeling processes are still not completely understood.
Therefore, the cortical thickness, cortical porosity and the trabecular bone volume fraction were analyzed. Evaluation was performed in a representative collective (bone mineral density, BMD) of proximal humeri by *HRqCT* (resolution 82 µm).
The analysis revealed, that compared to individuals with a normal BMD, the trabecular bone fraction was decreased in individuals with a reduced BMD. However, also the cortical thickness clearly decreased in individuals with a reduced BMD, with a simultaneous increase of the cortical porosity.
Osteoporotic bone remodeling not only affects the trabecular bone of the proximal humerus, but also appears to have a significant impact on the cortical thickness and the porosity. Both factors are very likely to contribute to the fracture risk in elderly people.



Bone remodeling at the proximal (section 1) and distal (section 2) part of the surgical neck at the humerus. Compared to a humerus with a normal BMD, the cortical thickness is decreased and the cortical porosity is increased in a humerus with a reduced BMD.

Partners:

- Blauth M, Department for Trauma Surgery, University of Innsbruck, Austria
- Oh CW, Department of Orthopedic Surgery, Kyungpook National University Hospital, South Korea
- Schmidutz F, Department of Orthopedic Surgery, University of Munich (LMU)

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

Infections associated with implanted devices are a major problem in orthopedic surgery. The prevention and treatment 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. Thermo-responsive polysaccharide hydrogels containing antibacterial agents are being synthesized with varying degradation rates and various antimicrobial agents such as antibiotics. The resultant gels will be fully characterized with respect to chemical structure, cytocompatibility and antimicrobial release and activity.

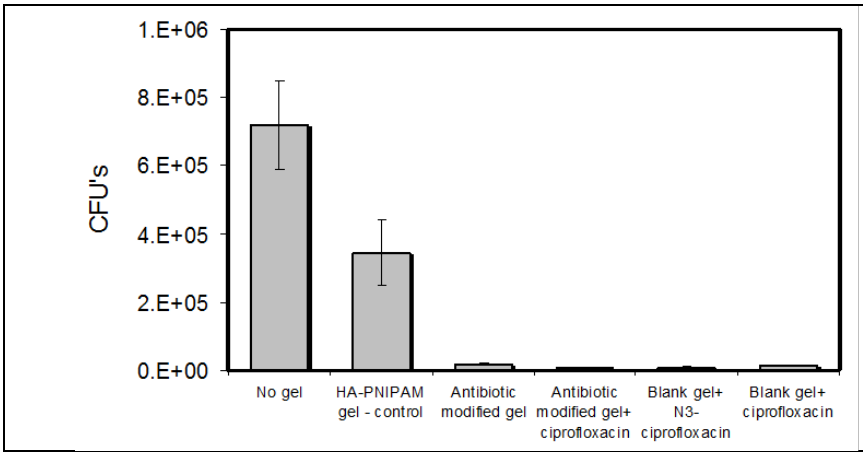


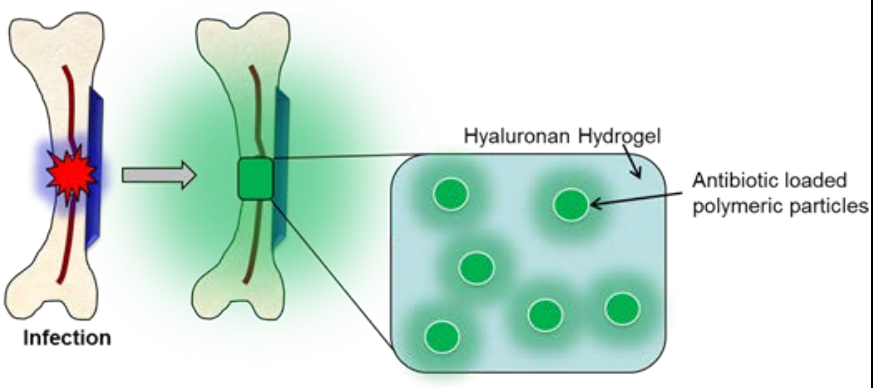
Figure: Representative antimicrobial activity of different gel compositions loaded or not with antibiotic on test implant material surfaces.

Pres:
Eglin D, Horn N, Cameron L, Richards RG, Moriarty TF. Antibacterial activity of antibiotic loaded thermo-responsive hyaluronan hydrogel. 2012. EBJIS.

Partner:
- Grijpma D, University of Twente, The Netherlands

Biodegradable putty-like antibiotics loaded hydrogel for implant infection treatment. AOTGEL (Started)

Bacterial infection in orthopedic 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 the bone defect temporally and release antibiotic locally. Alternative antibiotics loaded materials to treat infection that 1) could be administrated as a putty or injectable form to fill up space and complex zones of traumatized infected bone tissue, 2) are transparent to clinical imaging techniques, 3) provide a steady and long release of a wide range of antibiotic agents, and 4) are biodegradable after their useful life, are not yet available.
Therefore, the goal of this project is (i) to develop a putty-like biodegradable hydrogel, (ii) to develop a method to encapsulate antibiotics in biodegradable microparticles made of the poly(ε-caprolactone) that can be loaded into the gel; (iii) to study and control the antibiotic release from the particles embedded in the hydrogel *in vitro* and *in vivo*.



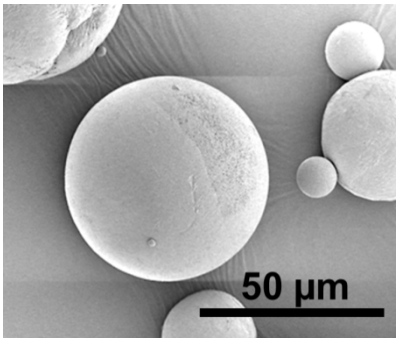


Figure: Schematic of the putty-like material for implant infection treatment and scanning electron microscopy image of polymeric carrier particles.

Injectable hydrogel for releasing osteogenic factors in osteoporotic bone fracture. OSTEOGEL (Started)

Osteoporosis has been recognized as an escalating cause of fractures, implant loosening, failures and increases in contralateral fractures in the ageing population. Treatment of fractures in patients with osteoporosis is particularly difficult. Systemic medications of anabolic drugs like bone morphogenetic proteins (BMPs), human parathyroid hormone (PTH) and teriparatide (rePTH) to increase bone formation activity in osteoporotic patients are becoming more popular in our ageing and at risk population. However, the necessary daily administration of PTH can be a burden for the patient. In this context, an off-the-shelf anabolic therapy that would stimulate locally the healing of bone and implant stability without obstruction on late surgery, in combination or without the need of repeat anabolic drug injection, could be a step toward a better solution for fracture management in osteoporotic and ageing patients. Thus, this project aims at developing a delivery system for improved and biologically relevant release of osteogenic molecules.

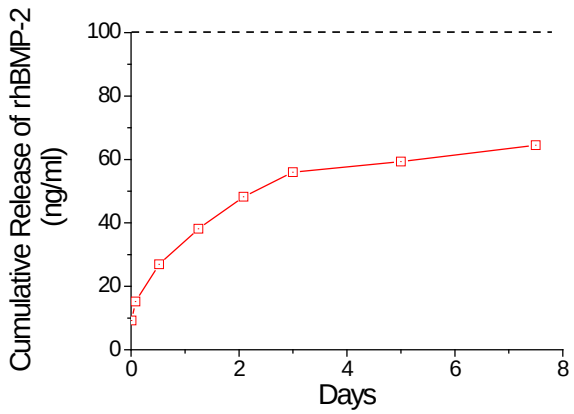


Figure: Plot of the *in vitro* cumulative release of rhBMP-2 from thermo-responsive hyaluronan hydrogel as a function of time. The inital rhBMP-2 concentration is100 ng/ml and the protein release was measured by ELISA. A sustained release for more than 1 week was achieved.

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

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 will explore 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. MSCs are prestimulated with the factor of interest and the effect of the stimulation on gene expression profiles is determined. The stimulated cells will also be co-cultured with osteoblasts or naïve MSCs. As a control, unstimulated cells are co-cultured with osteoblasts or naïve MSCs. The cells' differentiation over time will be determined. This could provide a mechanism by which MSCs could more effectively be used in fracture repair by stimulating the cells within the operating theater in order to prime them prior to implantation.

To control implant-tissue interactions through implant surface modification (Implantsurf) (Finished)

In order to accurately reproduce the clinical situation during fracture repair, more advanced *in vitro* models are required. We developed a 3 dimensional co-culture system, utilizing a collagen gel base combined with hydroxyapatite particles. This addition has eliminated the shrinkage normally associated with such culture systems, allowing for cultures to be performed over weeks. We have used this system to investigate the cross-talk signaling that occurs between human mesenchymal stem cells and osteoblast progenitors. In addition, we have produced a constitutively green fluorescing osteoblast line which enables more accurate determination of which cell (MSC or osteoblast) is producing a particular response. We have discovered that the osteoblastic response can be greatly enhanced when co-cultured with MSCs. This would suggest that MSCs have a powerful effect on osteoblast development. The response is also dependent on the stiffness of the substrate in which the cells are cultured. We aim to use this system to further investigate the effect of various soluble factors on MSC, and osteoblast, behavior and differentiation in a more natural 3D environment. This offers further insights into how these different cell types interact and how we may use this information to develop more suitable cell based strategies in the future.

Pres:

Czekanska EM, Ralphs JR, Alini M, Stoddart MJ. Interactions of MSC and bone cells during the process of in vitro mineralization. Swiss bone and mineral society, Basel, March 29, 2012.

Czekanska EM, Ralphs JR, Alini M, Stoddart MJ. Human mesenchymal stem cells stimulate in vitro mineralization of MG63 osteoblast precursors. International Society Stem Cell Research, Yokohama, Japan, June 13 - 16, 2012.

Czekanska EM, Ralphs JR, Alini M, Stoddart MJ. Investigating the factors directing the process of in vitro mineralization. 3rd TERMIS World Conference, September 5-8th 2012, Vienna Austria

Pub:

Czekanska EM, Stoddart MJ, Richards RG, Hayes JS. In search of an osteoblast cell model for in vitro research. eCM Journal 2012 (24):1 – 17.

Partners:

- Ralphs JR, Cardiff Institute of Tissue Engineering and Repair, School of Biosciences, Cardiff University, Wales, United Kingdom
- Hayes JS, Regenerative Medicine Institute, National Centre for Biomedical Engineering Science, National University of Ireland, Galway, Ireland

Investigating the molecular epidemiology of Staphylococcal isolates from musculoskeletal infections associated with internal fracture fixation devices (StaphTyp)

The aim of this study is to identify clonal structure of *Staphylococcus aureus* isolated from infections surrounding fracture fixation devices and survey the most prevalent virulence factors possessed by this organism. Over 300 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 200 isolates as of End of 2012). The identification and characterization of most prevalent strain types is beginning to provide information as to the role of specific virulence factors crucial for the pathogenesis of these infections.

Pres:

Post V, Wahl P, Uckay I, Ochsner P, Zimmerli W, Moriarty TF, Richards RG. Molecular characterization of *Staphylococcus aureus* isolated from orthopaedic device related infections. ISSSI2012, Lyon 26.-30.8. 2012.

Post V, Wahl P, Uckay I, Ochsner P, Zimmerli W, Moriarty TF, Richards RG. Molecular characterization of *Staphylococcus aureus* isolated from orthopaedic device related infections. Graubünden Forscht - Young Scientists in Contest 12.-13. 9.2012.

Post V, Wahl P, Uckay I, Ochsner P, Zimmerli W, Moriarty TF, Richards RG. Molecular characterization of *Staphylococcus aureus* isolated from orthopaedic device related infections. EBJIS, Montreux 20.-22. 9.2012.

Partners:

- Wahl P, Freiburg, Switzerland
- Zimmerli W, Liestal Switzerland
- Ochsner P, Luzern, Switzerland
- Uckay I, Geneva, Switzerland
- Corvec S, CHU de Nantes, France
- Loiez C, CHR Lille, France
- Militz M, Murnau, Germany

Development of new agents for the specific diagnostic imaging of infections associated with orthopedic devices (Imagin)

Our infection imaging project aims to improve 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. We have found that bacteriocins, which are bacteria produced molecules designed to specifically target other bacteria, display promising infection diagnostic potential. The bacteriocins have been labeled with dyes and exposed to Escherichia coli, Staphylococcus aureus, Staphylococcus epidermidis, and Pseudomonas aeruginosa and detected by Flow cytometry. Thus far we have identified bacteriocins that specifically identify Gram positive bacteria. These molecules have also been found to be non-toxic to host cells. Furthermore a two-step labeling procedure has been developed which allows an increase in signal and also allows improved delivery of probes to the target bacteria. The protocol was successfully proven to work *in vivo* in collaboration with project partners in Germany see Figure 1.
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 (Figure 2) and verified postmortem by bacteriology, histology, and mechanical testing.

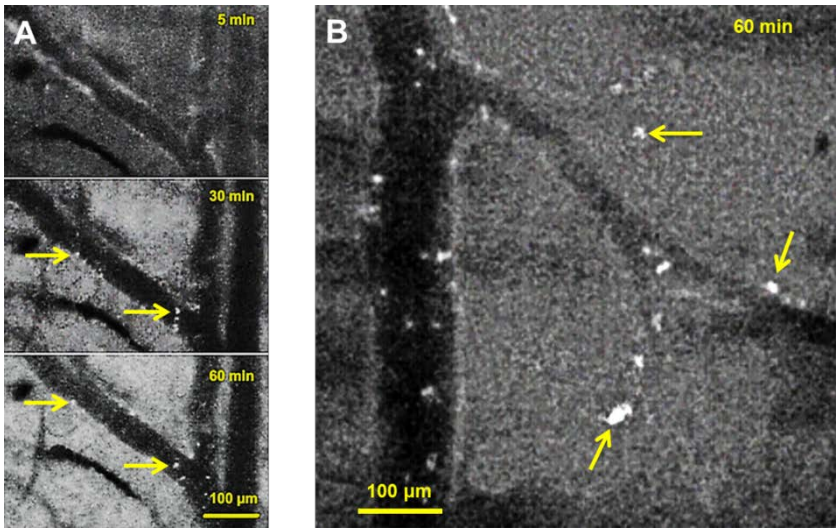


Figure 1: Intravital Fluorescence Microscopy of in vivo labeling of bacteria in an infected mouse.

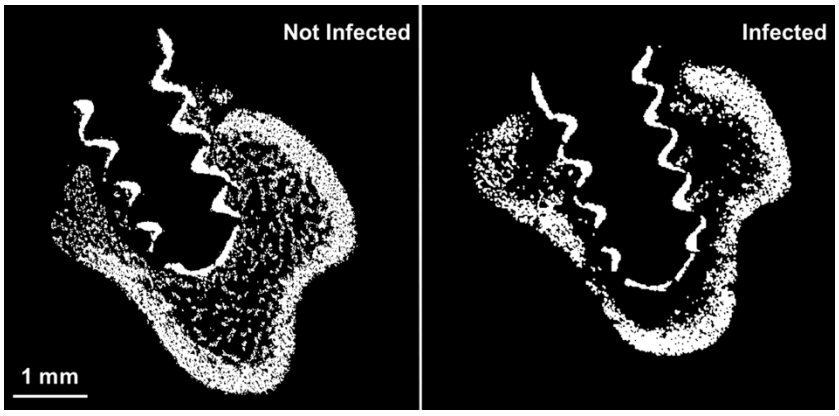


Figure 2: Micro CT of an infected and non-infected screw in a rat femur 3 weeks after implantation, showing marked loss of bone structure.

Pres:
Potapova I, Stadelmann V, Richards RG, Moriarty TF. Micro Computed Tomography for imaging Implant Associated Orthopedic Infections. EBJIS. September 20 – 22, 2012/ Montreux. Oral Presentation.

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. Publication.

Partners:
- Laschke M, Bischof M, Univeristy of Saarland, Homburg, Germany
- Signore A, University la Sapienza, Rome, Italy

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

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 (a spin off from the ARI) and the preclinical testing program. The osteotomy model was successfully developed, whereby a 100% healing rate was observed rabbits receiving the new nail, and in a plate group utilizing a commercially available locking plate. The rabbit osteotomy model will now enter a phase of establishment and characterization of staphylococcal infection, using both implant types. In parallel, in collaboration with the tissue morphology focus area, we have developed a histopathological classification scheme for implant related osteomyelitis in preclinical studies, which will increase our ability to more closely understand and identify the stage of osteomyelitis in our preclinical models.

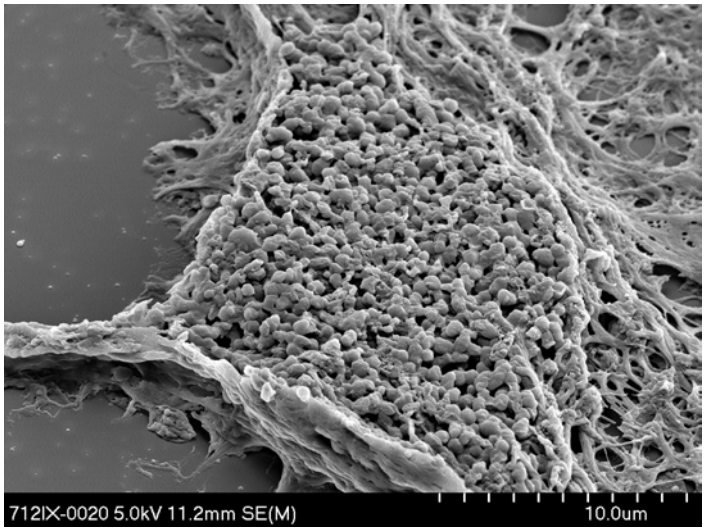


Figure 3: SEM micrograph of a bacterial biofilm growing in the intramedullary space of a rabbit.

Pres:
Moriarty TF. Animal models of implant related Osteomyelitis. European Bone and Joint Infection Society annual meeting, September 20 – 22, 2012/ Montreux. Oral Presentation.

Post V. Bacterial Infection in a rabbit intramedullary nail infection model. European Bone and Joint Infection Society annual meeting, September 20 – 22, 2012/ Montreux. Oral Presentation.

Gahukamble A. Bacterial Infection in a rabbit intramedullary nail infection model. Congress of the Asia Pacific Orthopaedic Association, New Delhi, India from 3rd to 6th October 2012.

Calabro L. Challenges in Developing a Rabbit Fracture Model for Orthopaedic Trauma Research. Australian Orthopaedic Association, October 8-11 2012.

Pub:
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; 2012; p. 273-304.

Partner:
- RISystem AG, Davos, Switzerland

The Effect of Stainless Steel Schanz Pins Topography on Bone and Soft Tissue Integration: a Loaded External Fixator Fracture Model in Sheep (ExFixSurf)

The most commonly encountered complications associated with external fixation are pin loosening and pin tract infection (PTI). Insertion techniques can be source of thermal and mechanical damage of the bone during pin insertion. Micro-motion at the pin site and formation of fibrous tissue at the tissue-pin interface have been identified as the main causes of pin loosening and infection. In this project, we are aiming to reduce infection rate by improving soft and hard tissue integration to Schanz screws by providing surfaces optimal for integration. Prototype novel microrough stainless steel Schanz screws have been prepared in collaboration between the Infection group and Tissue Morphology focus area. The Schanz screws have now been placed in both a load bearing and a non-load bearing preclinical model in the sheep. A histological scoring system was developed by the Tissue Morphology focus area, and the first two groups are now being investigated. Final results shall be presented once the third and final group specimens have completed the histologcal analysis.

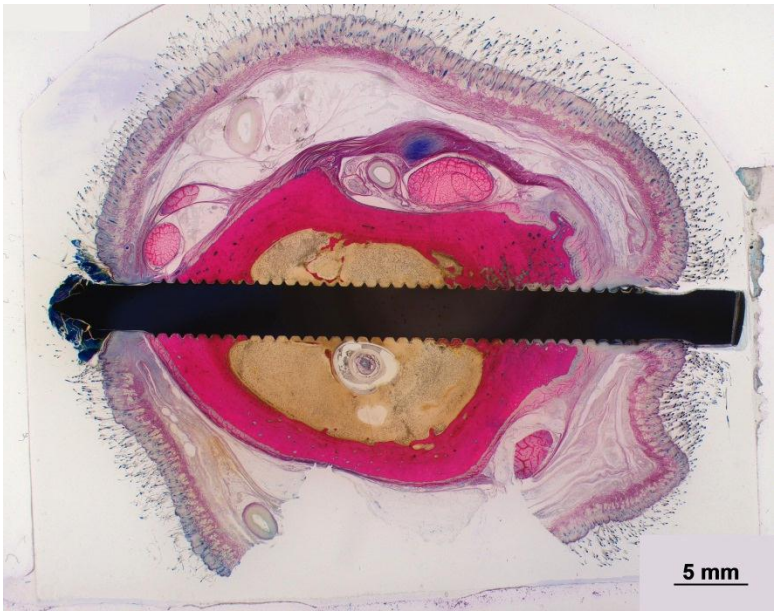


Figure 4: Cross section of Schanz screw displaying Screw: tissue interaction with both soft and hard tissues.

Assessing the Role of the Implant Mediated Immune Response on the Development of Infection (Immunobact)

Previously it has been shown that different materials can influence the immune response upon implantation. The *in vivo* reaction to an implant may then, in theory, influence infection susceptibility due to an altered immune response.
The *in vitro* immune response to a bacterial contamination of a range of orthopaedic materials including rough and electropolished metals and oxygen plasma treated PEEK was measured. A range of techniques were used, including: NF-κB activation, complement activation and cytokine secretion, all in the presence or absence of bacterial contamination of the materials. It was observed that, in general, micro-rough titanium was the least immune-stimulatory and the PEEK materials were the most. The effect of oxygen plasma treatment was diverse, depending on the immune response measured.
The immune response to titanium and PEEK was studied *in vivo* as these materials showed the greatest difference *in vitro*. Initially, the existing MouseFix internal fixation plate model of bone healing was used to measure the immune response to plates made of titanium and PEEK. This

model was then adapted to include pre-operative contamination of the implants by *S. aureus* bacteria. Using the MouseFix model (photo below) it was observed that the immune response was affected by material choice. In addition, the presence of both implant materials and an osteotomy led to a degree of immunosuppression. In the presence of bacterial contamination, the materials once again affected the immune response. However, the number of bacteria associated with the implant and host tissue were not significantly affected on day 7.

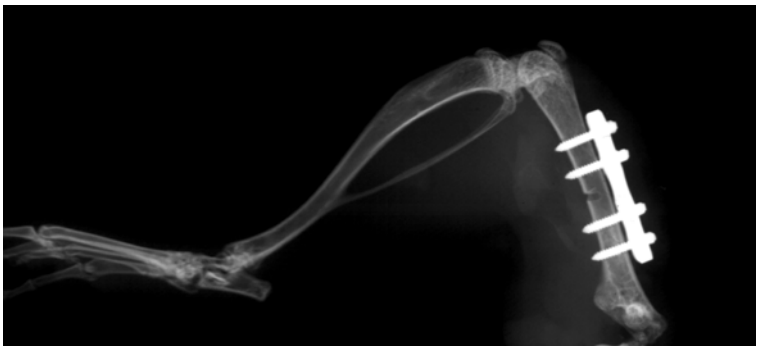


Figure 5: Contact radiograph of murine osteotomy fixed with a titanium mousefix plate.

Pub:
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Pres:
Rochford ET. The Role of Implant Assoviated Immune Response in the Development of Infection. European Bone and Joint Infection Society annual meeting, September 20 – 22, 2012/ Montreux. Oral Presentation.

Rochford ET. The Role of Orthopaedic Implant Material Choice on the Immune Response to Bacterial Contamination. Graubünden Forscht - Young Scientists in Contest 12.-13. 9.2012. Davos.

Partner:
- O' Mahony L, Swiss Institute of Allergy and Asthma Research, Davos, Switzerland

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)

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. Remnants of biofilm, intracellular survival or the presence of bacteria within micro -abscesses as well as a diminishing humoral protection may all explain the high rate of reinfection in these cases. Any novel intervention aiming to reduce this high rate of reinfection should ideally be validated in a preclinical model that replicates in as much as possible the clinically salient features of the infection. A major limitation towards the development of superior prevention strategies and therapies (i.e. vaccines, antibiotics, implant coatings) in these cases i s 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, and to use this model to provide definitive preclinical efficacy data for anti-glucosaminidase (Gm d) passive immunization.
In the early stages of this project we have performed cadaver trails to determine the optimal IM nail for use in this study and its most appropriate application. Following on from this, uninfected control sheep have been operated using the agreed upon custom made stainless steel 9.5mm IM nail. The time points for analysis have been after 3, 6 and 9 weeks. The uninfected group shall be observed into 2013 to identify the healing period required using this model, though at 3 weeks post-operative, all data shows early signs of callus formation. The first 4 infected sheep were also operated in the final quarter of 2012, whereby, *S. aureus* was inoculated via a catheter directly into the osteotomy site. As of end of December 2012, both groups remain under observation, with results available in 2013.

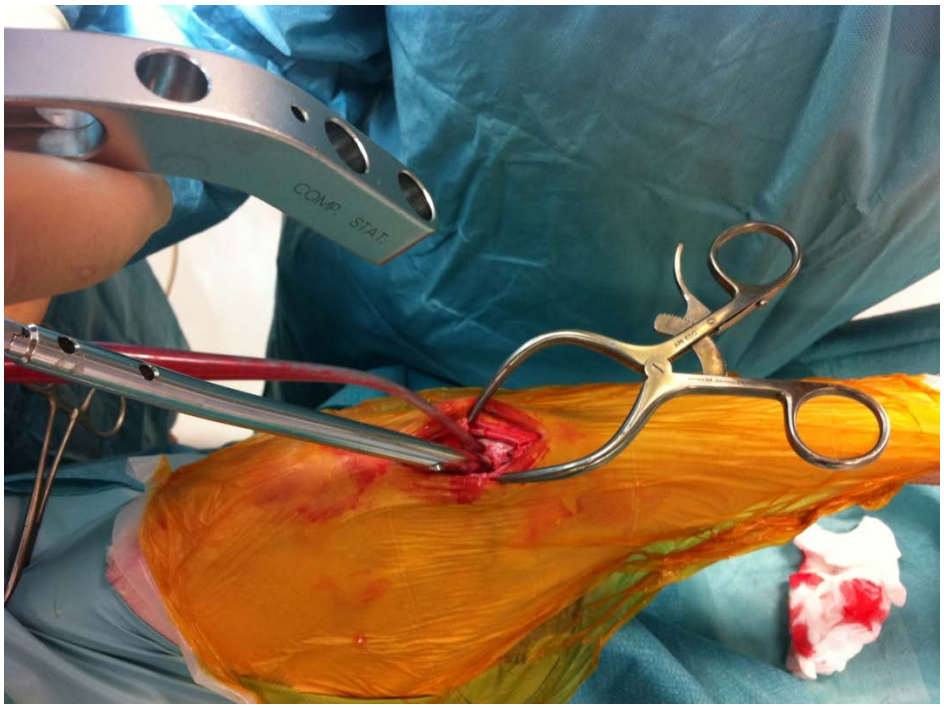


Figure 6: Intraoperative photograph showing insertion of the IM nail into the sheep tibia.

Human Morphology Services - Database of CT scans, 3D bone model and 3D statistical shape models

It forms a sustainable umbrella project for collecting medical image data, mainly Computed Tomography (CT) data of unaffected bone, and know how in image processing and analysis for efficient use in related projects. Currently more than 1500 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 (Figure). 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).

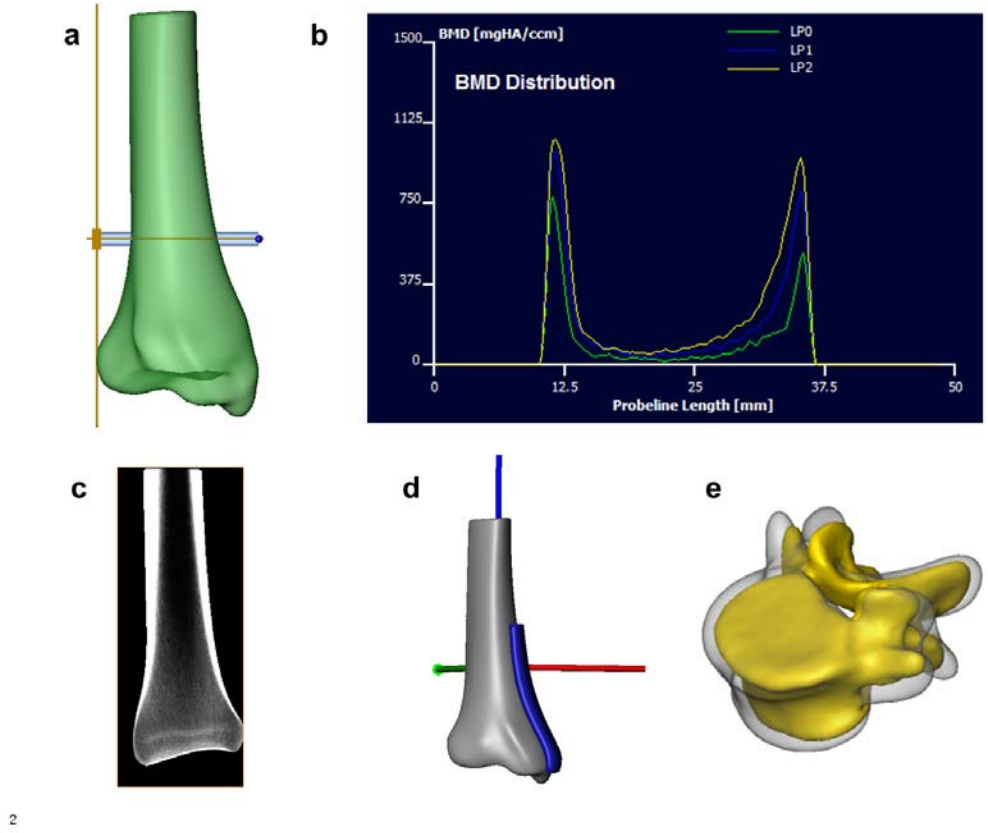


Figure: HMS developed software tools for visualizing bone stock distribution along interactively chosen screw paths in normal, osteopenic and osteoporotic bone (a + b); visualizing averaged bone mineral density (BMD) in the distal tibia (or any other bone) (c); computing automatically plate shapes for interactively determined region of interests (d), visualizing form variations of bones using Principal Components Analysis (e.g. S1 vertebra) (e).

Pre-activation of bone cells for faster healing after surgery

A large number of bone surgeries are planned more than a day in advance. This delay between planning and surgery could be used to activate the bone metabolism to reach its maximal healing potential immediately post-op. This could improve surgery outcomes, particularly in patients with weak bone metabolism, and shorten the post-operative cares in most patients.

The delay between surgery-related trauma and active bone healing accounts for the time needed to transform the trauma signal (inflammation, bleeding, …) into stem cell mobilization, cell differentiation and cells homing to the trauma site. The aim of this project is thus to test if this delay can be reduced by pre-activating bone cells ahead of surgery.

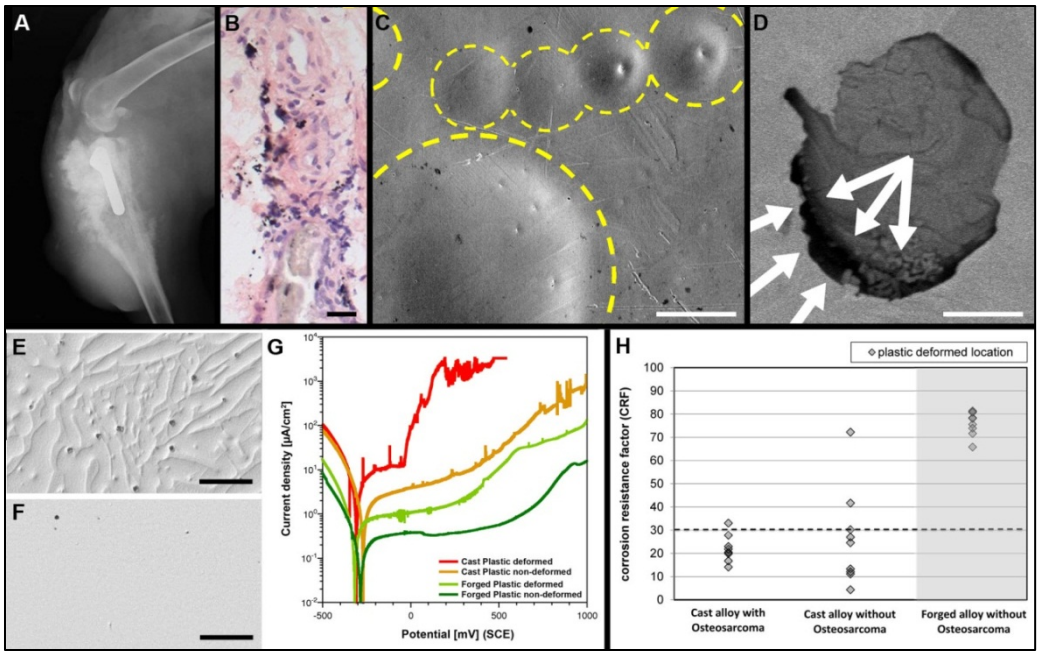
There are various ways to activate bone cells ahead of healing time: the most direct ones being administration of a pharmaceutical agent (e.g. BMP), undertaking physical activity or through direct surgical approach (such as reaming of the bone). Each probably have different delays and outcomes, and they are not all applicable in all situations. Although indirect, the method of choice, in our opinion, is to mobilize stem cells into the peripheral blood before surgery through a pharmaceutical action.

In this preliminary study, we will test pre-mobilization of mesenchymal stem cells (MSC) with a therapeutic agent in a self-healing large bone defect model in the rat. To mobilize MSCs and endothelial progenitor cells, an injection of granulocyte colony stimulating factor (G-CSF) will be given five days pre-operatively to the test animals, control animals will receive the injection for five days after surgery and SHAM animals will only receive saline injections. Healing of the defects will be monitored with in-vivo micro computed tomography (uCT) until bridging. Blood samples will be taken to monitor the blood level of MSCs. The progression of healing will be compared to that of control rats.

9.4 AOVET

Evaluation of Slocum TPLO plates retrieved from dogs with peri-implant osteosarcoma and non-affected animals (Finished)

Tibial plateau leveling osteotomy (TPLO) in veterinary surgery is commonly used to treat cranial cruciate ligament rupture in large bread dogs. An unusual accumulation of peri-implant osteosarcoma was observed in dogs treated with Slocum cast stainless steel TPLO plates. It was postulated that the metallurgical inhomogeneity of the plate surface, or the corrosion properties of the cast stainless steel material itself, were related to this observation. Metallographic investigation confirmed the inhomogeneity of the bulk material. Micro electrochemical corrosion tests were performed at randomly chosen spots located on the parts of the plate surface which had contact with the underlying bone. Local corrosion measurements showed a wide variation within each plate surface and between different plates made of cast stainless steel. Especially undesired surface alterations (i.e. artifacts created during plate contouring) reduced corrosion behavior considerably. Contouring of the cast plates clearly alters the corrosion resistance and reduces the electrochemical breakdown potential at the contoured location considerably. In contrast, explanted plates made of forged stainless steel (Synthes TPLO) showed in all locations measurement better local corrosion values than the cast stainless steel plates.



Radiograph of an operated dog knee with a large lysis zone in the tibia beneath the Slocum TPLO plate made of cast stainless steel (SS) (A). An osteosarcoma is shown histological section (HE stain, B, scale = 20 µm). C and D show findings on the surface interpreted as corrosion damages (C scale = 20 µm, D scale = 2 µm). Metallographic sections of the bulk material visualize the inclusions and inhomogeneity of the cast SS in comparison to the forged SS from a Synthes plate (scales = 50 µm). Example of micro electrochemical corrosion measurements displayed in G. Reduced corrosion behavior is documented for the cast SS which is massively decreased after contouring the plate (red lines). In contrast to the forged SS (green lines) always shows better resistance. In H the inhomogeneity of the cast SS plates corresponds to the variety of the corrosion resistance factor (CRF).

Partners:

- Boudrieau RJ, Cummings School of Veterinary Medicine, Tufts University, North Grafton, USA
- Suter T, EMPA, Swiss Federal Laboratories for Materials Science and Technology, Dübendorf, Switzerland
- Milz S, Anatomische Anstalt der Ludwig-Maximilians-Universität München, Germany

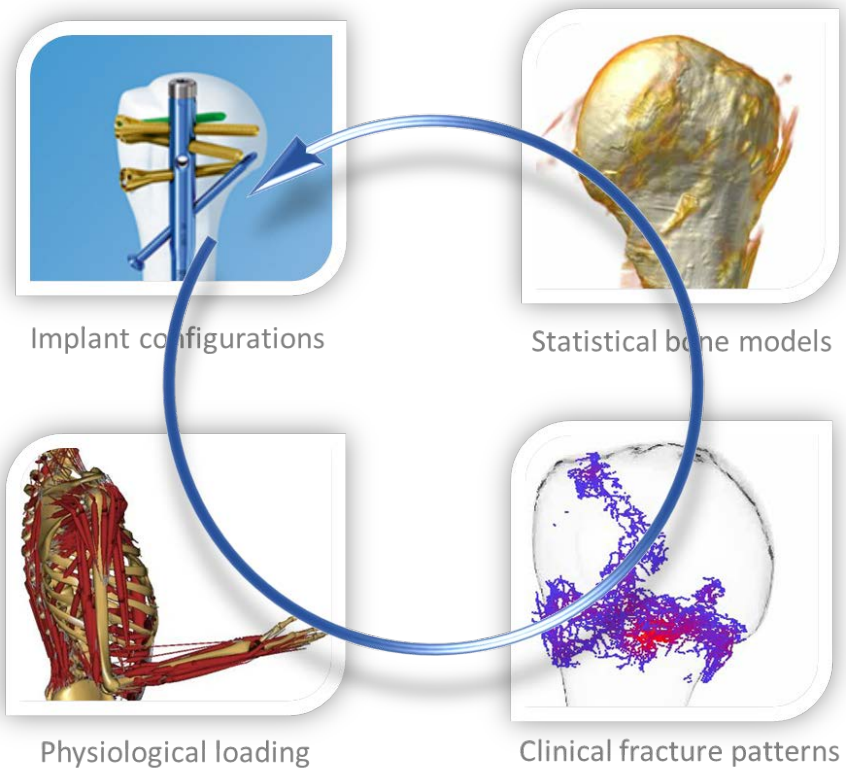
9.5 TK System

Development of a standardized computational testing model for the proximal humerus

Problem: Treatment of fragility fractures remains a major challenge at the proximal humerus. Compromised bone mass, complex loading conditions, multifragmental fractures, absent bony support and limited surgical access render the proximal humerus fixation problem.

Goal: To establish a reliable and efficient numerical simulation tool to systematically improve the of long-term fixation hardware performance and to solve the fixation problem at the proximal humerus.

Results: A computational toolkit was developed allowing for parametric analysis of proximal humerus repair constructs. The toolkit comprises a first generation statistical bone model based on CT data (bone density maps), statistical fracture patterns derived in a first approach from clinical CTs as well as a semi-automatic workflow from implant placement to evaluation of local bone tissue deformations via finite elements analysis. A database of physiological loading patterns from inverse dynamics will be included at a later stage. The model was firstly used to analyze a variety of implant configurations of the MultiLoc proximal humerus nail (Synthes GmbH).



Workflow for automatized implant optimization comprising different computational steps.

Partners:

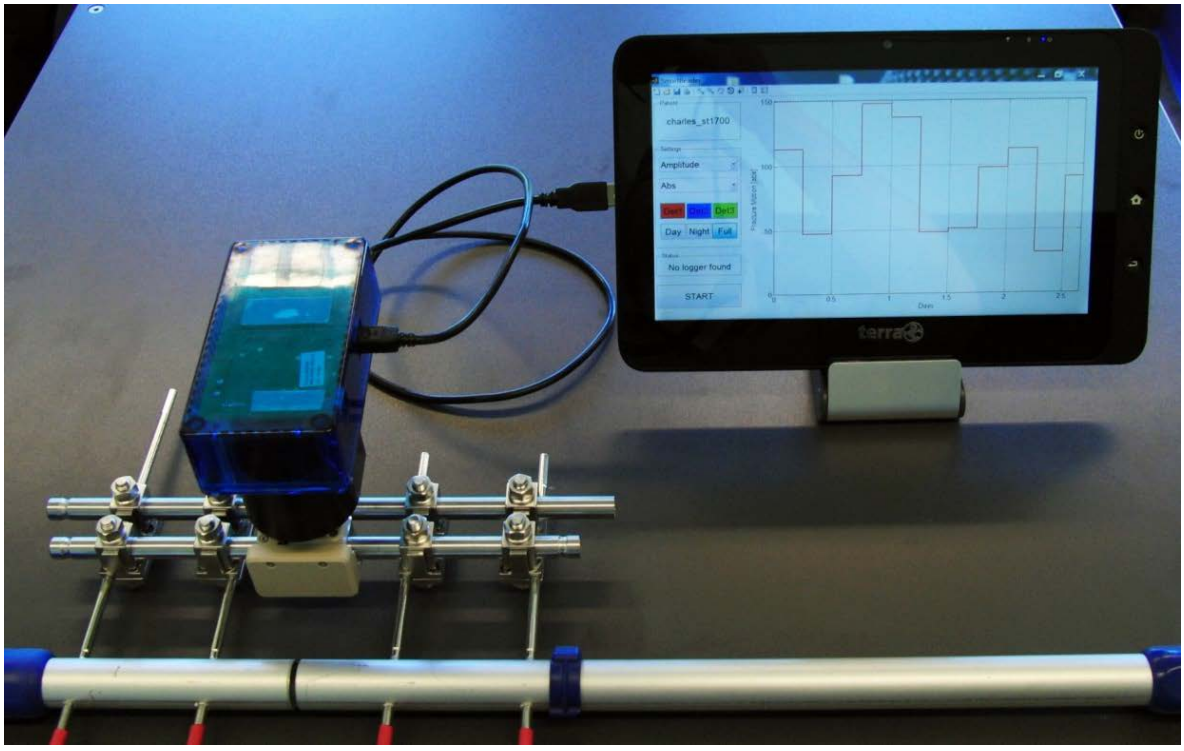
- Südkamp N, University Hospital Freiburg, Germany
- Nijs S, UZ, Leuven, Belgium
- Resch H, University Hospital Salzburg, Austria
- Thomas G, Synthes GmbH, Solothurn, Switzerland

Development of a supplementary device for the external fixator to monitor the course of fracture healing using a novel data collection concept (ongoing)

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: A prototype device was developed to be attachable to a wide range of conventional external fixator configurations. The device is capable of assessing continuous side-bar deformations and transmitting the results to the outside. Patient interaction is not required. First clinical applications are in planning.



Prototype device for monitoring of fracture healing attached to an external fixator.

Theses:
Ernst M. Development of a supplementary device for the external fixator to monitor the course of fracture healing using a novel data collection concept. 2012. ETH Zurich (MSc / Müller R, Lorenzetti S, Windolf M)

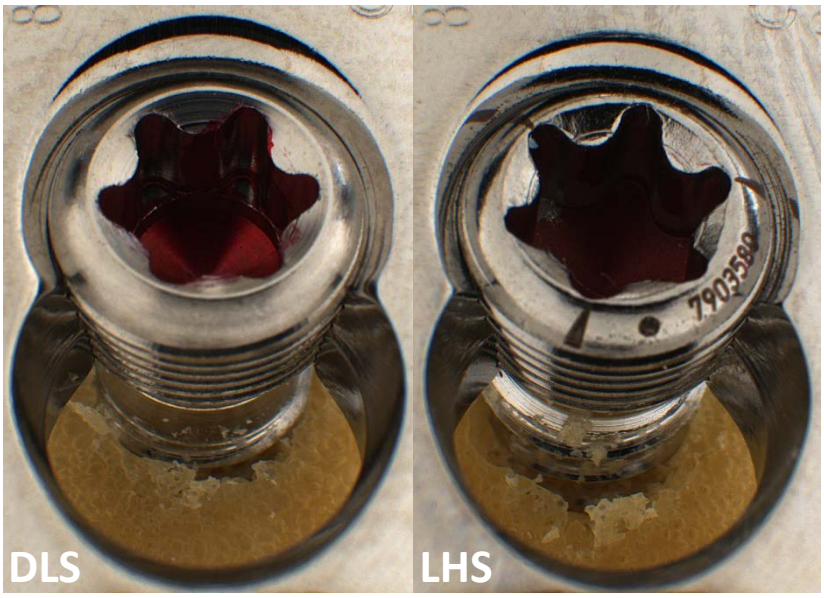
Partners:
- Pohlemann T, UK Homburg, Germany
- Höntzsch D, BG Unfallklinik Tübingen, Germany
- Mathis H, Hochschule für Technik, Rapperswil, Switzerland
- Lorenzetti S, ETH Zurich, Switzerland

Residual holding strength of dynamic locking versus conventional locking head screws (ongoing)

Background: Novel dynamic locking screws (DLS) developed for LCP plating allow increased micromotion at the ciscortex site under the plate, compared to conventional locking head screws (LHS), and are therefore believed to be beneficial for callus formation. It is hypothized that DLS is advantageous for improved screw purchase and holding strength under physiological loading. This might be beneficial in clinical situations of decreased bone quality (osteoporosis).

Goal: To investigate biomechanically the holding strength of DLS versus LHS plated constructs in surrogate diaphyseal bone model under dynamic loading.

Results: From biomechanical point of view, LCP with DLS is advantageous than LHS in terms of bone-screw holding strength and interface stability. In addition, the fixation with DLS was more flexible and with lower axial stiffness than LHS.



Degradation of bone screw interface with DLS (lefts) and LHS (right).

Partners:

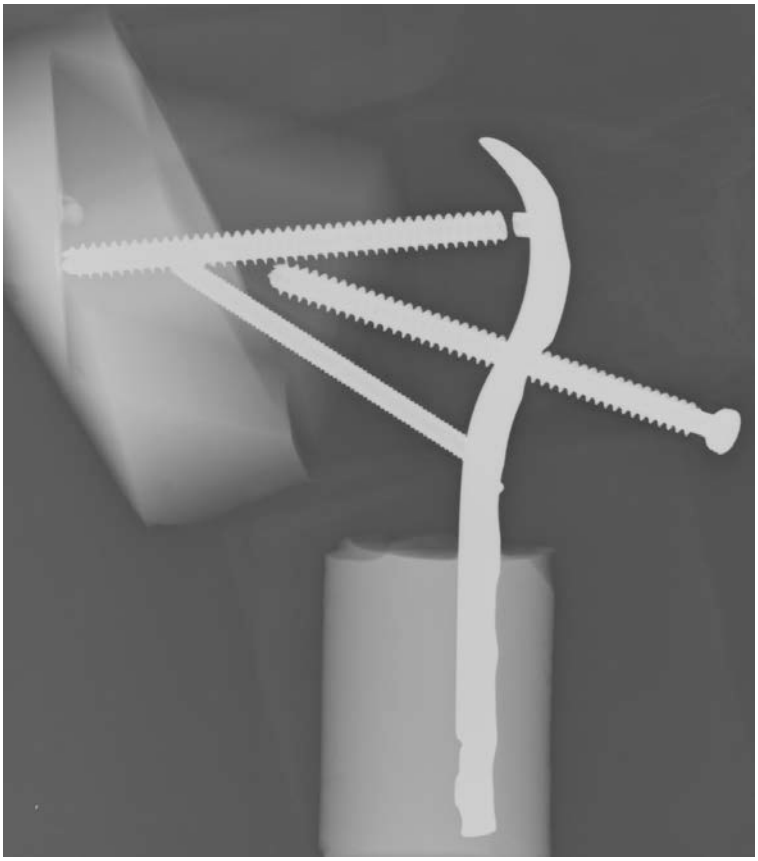
- Pohlemann T, UK Homburg, Germany
- Weber A, Synthes GmbH, Solothurn, Switzerland
- Schnider N, Synthes GmbH, Solothurn, Switzerland

Biomechanical investigation on failure modes of proximal femoral fracture fixation with PFLCP (ongoing)

Background: Biomechanical studies showed that the proximal femoral locked compression plate (PFLCP) is stronger or equivalent to other fixation methods for fractures of the femoral neck and subtrochanteric femur fractures. Testing the specimens only under axial load does not account for in vivo multivector forces acting across the hip. However, in clinical practice proximal screw failure in terms of screw loosening and migration out of the plate hole as well as screw breakage is observed in some cases. The type of failure may be the result of patient factors as well as technical factors.

Goal: To evaluate and reproduce biomechanically the failure modes seen in the clinical cases of fracture fixation with PFLCP.

Results: 2° deviation from the nominal axis of either the first or the second proximal PFLCP screw could lead to significantly earlier construct failure, consistent with the failure mode observed clinically. Based on this, particular attention should be paid on proper and exact screw insertion to minimize screw loosening and construct failure.



Failure mode of a specimen fixed with PFLCP after biomechanical testing.

Partners:

- Nork S, Harborview Medical Center, Seattle, USA
- Graves M, University of Mississippi Medical Center, Jackson, USA
- Sommer C, Kantonsspital Graubünden, Chur, Switzerland
- Stoffel K, Murdoch Orthopaedic Clinic, Australia
- Oh JK, Korea University Guro Hospital, Seoul, South Korea
- Altmann M, Synthes GmbH, Solothurn, Switzerland
- Wolf S, Synthes GmbH, Solothurn, Switzerland

Comparison of composite, porcine and human non-osteoporotic and osteoporotic foot bone properties for biomechanical testing

Goal: To compare mechanical properties of porcine and synthetic composite foot bone to non-osteoporotic and osteoporotic human foot bone and assess the suitability of these substitutes for biomechanical studies.

Results: Porcine bone exhibited a mechanical strength in axial pullout direction as well as in shear direction comparable to non-osteoporotic human bone. Porcine bone represents an appropriate substitute for young human non-osteoporotic bone within the foot.

Partners:
- Sands AK, Saint Vincents Hospital, New York, USA
- Castro M, Scottsdale Healthcare, USA
- Winson I, Southmead Hospital, Bristol, USA
- Gerstner JB, Centro Medico Imbanaco of Cali, Colombia
- Lenz M, Universitätsklinikum Jena, Germany

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 (Pelvic Expert Group)

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.

Pres.
Wagner D, Rommens PM, Sawaguchi T, Kamer L, Noser HR. 3D Morphology of the Sacrum and its Impact on Treating Sacral Insufficiency Fractures. A Workflow using CT based 3D Statistical Modeling. EORS 2012, European Orthopaedic Research Society. 20th annual meeting, Amsterdam, September 26-28, 2012.

Partners:
- Sawaguchi T, Toyama Municipal Hospital, Toyama, Japan
- Rommens PM, University Hospitals of the Johannes Gutenberg-University Mainz, Germany
- Wagner D, University Hospitals of the Johannes Gutenberg-University Mainz, Germany
- Uesugi M, Tsukuba Medical Center, Tsukuba, Japan
- Sheldon M, Altmann M, Synthes GmbH, Solothurn, Switzerland

Anatomical Background for New Fixation Concepts for Patellar Fractures. CT based 3D Statistical Modeling and Analysis of the Patella in Asians and European Caucasians (Patella Task Force)

Most of the patellar fractures show good operative results. However complex fracture patterns are still difficult to treat and associated with a high complication rate. There is still no convincing osteo-synthesis concept available. Other methods of internal fixation have to be considered to further optimize the operative outcome.
In this project application we propose Computed Tomography (CT) based three-dimensional (3D) statistical computer modeling and analysis of the patella in order to establish a scientific anatomical basis for new concepts for fracture repair of the patella. In CT samples of adult Asians and Europeans Caucasians a statistical model of the entire patella will be computed and analyzed.

Partners:
- Höntzsch D, BG-Unfallklinik, Tübingen, Germany
- Helfet DL, Cornell University Medical College, New York, USA
- König C, Synthes GmbH, Solothurn, Switzerland

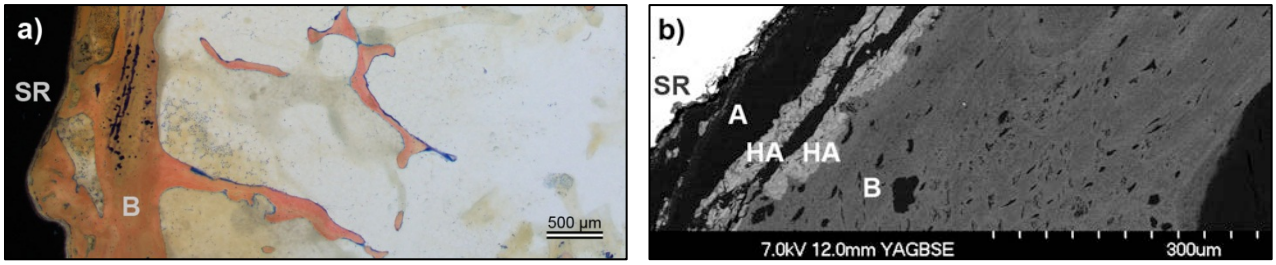
Histomorphological Analysis of Shoulder Resurfacing Arthroplasty (ShouCap) (Finished)

Shoulder resurfacing arthroplasty (SRA) is designed to restore the function of the shoulder with little trauma compared to stemmed shoulder arthroplasty. At the same time, SRA preserves a maximum of the humeral bone stock in order to ease potential revision surgeries. Currently, several cementless SRA designs from different manufactures are available. Studies have reported about good early results and sufficient initial stability. However, due to the radiopaque implant no data about the secondary stability are available. Therefore, the present study evaluates the osseous integration and bone remodeling processes of SRA.

Explanted human SRA implants were collected and evaluated by histomorphological analysis (bright field light microscopy, microradiography and scanning electron microscopy). Analysis was performed qualitatively and quantitatively with respect to the relative bone density below the implant and the bone-implant contact.

Qualitative and quantitative analysis revealed a clearly reduced bone stock under the implant. Furthermore, the bone was inhomogeneously distributed, with bone predominantly located at the stem and the outer rim. In contrast, osseous integration at the bone-implant interface was found to be good, which was confirmed by scanning electron microscopy.

In conclusion, the SRA implants showed a good bone-implant contact, which is suggestive for sufficient primary stability and good osseous integration. However, the bone density under the resurfacing implant was clearly reduced, which is probably related to stress shielding and unloading of the bone, similar as seen in hip resurfacing arthroplasty.



Good osseous ingrowths of the bone (B) at the interface of the shoulder resurfacing implants (SR): a) Giemsa-Eosin stained section and b) Scanning Electron Microscope micrograph. (shrinkage artifact (A), hydroxyl-apatite coating (HA).

Partners:

- Braunstein V, Sportsclinic Munich, Germany
- Hertel R, Lindenhofspital, Bern, Switzerland
- Gohlke F, Department of Shoulder Surgery, Klinikum Bad Neustadt, Germany
- Schmidutz F, Department of Orthopedic Surgery, University of Munich (LMU), Germany
- Südkamp NP, Department of Orthopedic and Trauma Surgery University of Freiburg, Germany

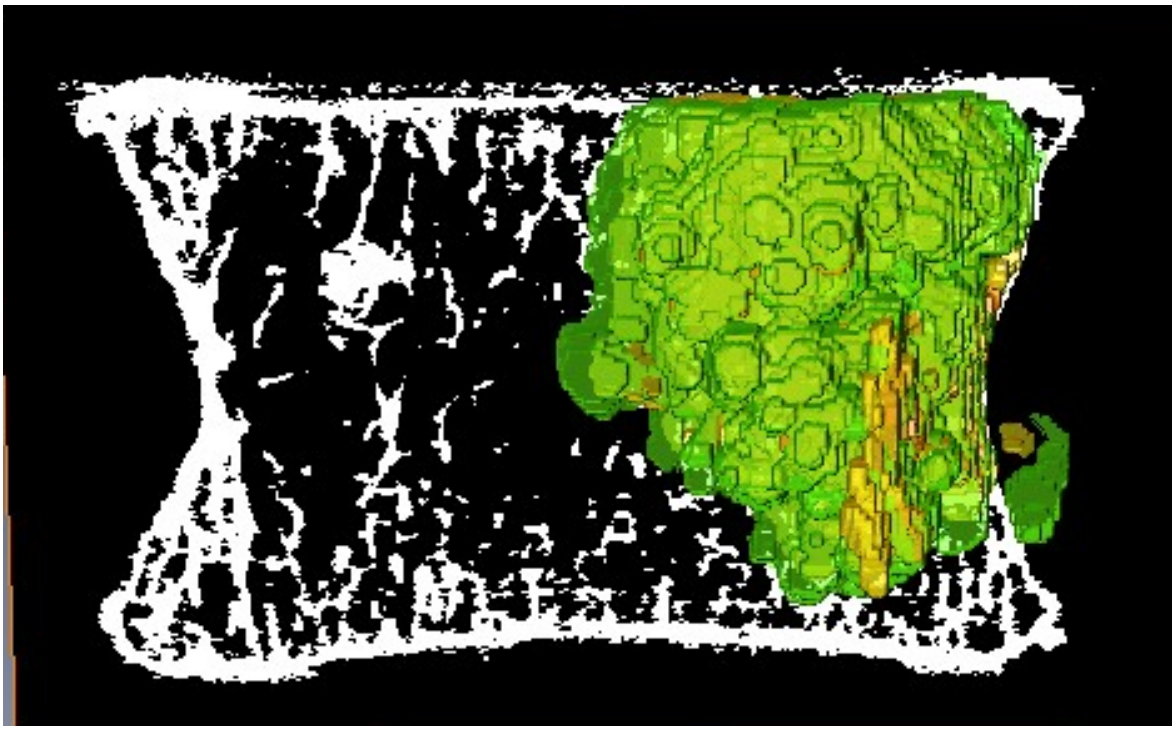
9.6 AO Exploratory Research

Cement flow monitoring and assessment of injection forces during vertebroplasty (Feasibility)

Problem: Prophylactic vertebroplasty is expected to reinforce weak vertebral bodies and possibly to minimize fracture risks. Cement leakage can cause severe complications, whereas smaller volumes of cement may reduce its occurrence. Significant mechanical benefit is only obtained when the cement filling connects both endplates inevitably increasing the leakage risk. A better understanding of the cement flow into bone is thus required.

Goal: To develop methods for cement flow monitoring and assessment of the mechanical impact during stepwise injection.

Results: Cement flow distribution within the bone structure was precisely visualized by time-lapsed CT approach at each incremental injection step. Combined with micro-finite element modeling, this approach allowed assessment of mechanical properties of augmented bone during injection. Partial cement filling would result in an increased risk of failure of the trabecular bone adjacent to the cement cloud.



Visualization of cement cloud flow in a vertebral body after incremental injection steps.

Partners:

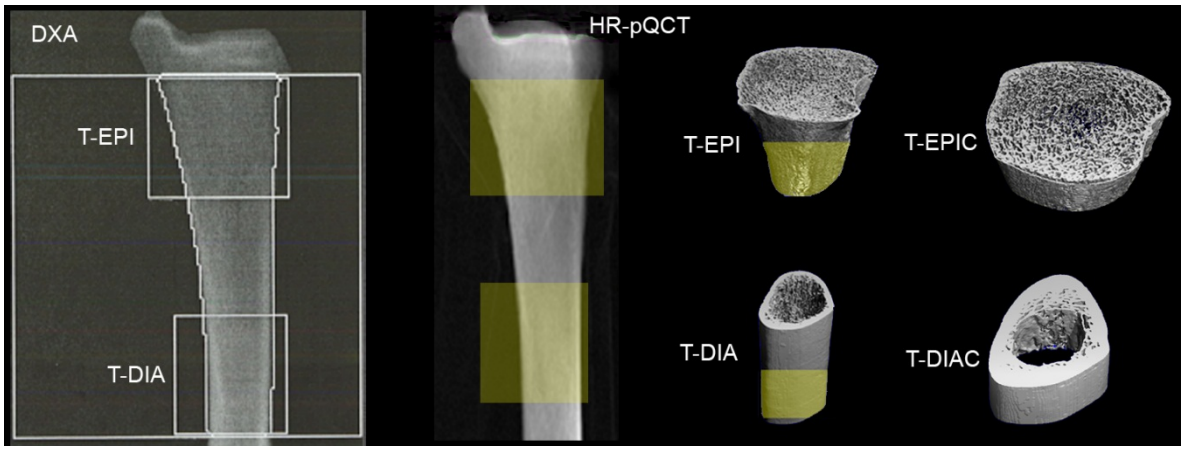
- Röhrle O, University Stuttgart, Germany
- Boger A, Hochschule Ansbach, Germany

Fracture prediction capabilities of DXA measurements at the distal tibia and establishment of a normative data base (NormTib, ongoing) (Feasibility)

Problem: Dual-energy X-ray absorptiometry (DXA) is the worldwide standard examination to identify patients with low bone mineral density (BMD) and predict the individual fracture risk. In contrast to established skeletal regions the distal tibia offers to distinguish cortical and trabecular bone in a single skeletal site. In a cohort of 700 postmenopausal women the predictive value of the BMD at the distal tibia regarding fracture risk had been demonstrated. However, a reference data set of healthy individuals does not exist yet. In a recent ex-vivo study it has been shown that BMD of the tibia diaphysis combined with structural parameters of the cortex superiorly translates into bone strength. These experimental results need to be confirmed in a clinical context.

Goal: With the overall goal to improve fracture prediction, it was aimed to quantify the tibia cortex in a standardized manner by DXA and with high resolution CT in young, healthy females to confirm recent findings and to collect normative data to establish a DXA benchmark for the distal tibia.

Results: Ethical and legal approvals were obtained to conduct the study. 72 healthy females between 20 and 40 years old from the region Davos, Switzerland were measured with DXA at the tibia and other reference locations (femur, spine, radius). Additionally the probands were scanned with HR pQCT at the tibia and the distal radius. Data evaluation is in progress.



Regions of interest in a distal tibia by DXA (left) and corresponding volumes of interest as 3D reconstructions by HR pQCT (right).

Partners:

- Lippuner K, Inselspital Bern, Switzerland
- Popp A, Inselspital Bern, Switzerland

Synthesis of a biodegradable scaffold to improve the integration in osteochondral defects and critical size defects in bone. JANUSCAF 1 (Ongoing)

Regeneration of articular cartilage after a trauma is still highly limited. Our main objective is to address the issue of the functional integration and stabilization of tissue engineered implants in the subchondral bone. The general approach is the development of a biphasic construct directly implanted in the defect. The porous construct formed should have suitable chemical and physical properties for the support of cells and for tissue formation and should allow for the controlled spatial development of functional bone and cartilage tissues. One of the issues for osteochondral defect repair is to control spatially the vascularization and bone formation. Hence, an interface between the cartilage and the bone part of the construct in the form of a micro-porous membrane, designed such that biological tissue growth occurs in the intended spaces, could possibly prevent

the unwanted cartilage ossification. Thus in this project, biphasic poly(ester-urethane) devices were prepared and characterized *in vitro* and *in vivo,* displaying successful press-fitting of the scaffolds, but also demonstrating limitation in matching complex scaffold structures with tissues morphology.

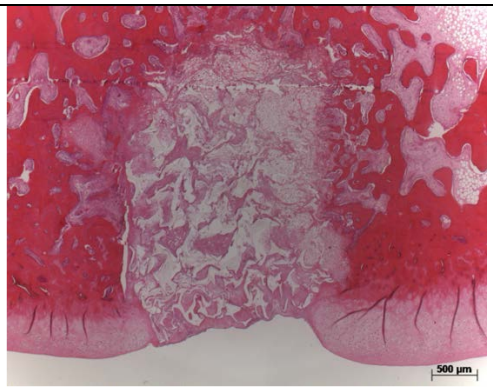


Figure: Representative H&E histology image of a biphasic poly(ester-urethane) scaffold in a osteochondral defect *in vivo* model after 12 weeks.

Pres:
Dresing I, Zeiter S, Alini M, Eglin D. Press-fit biphasic scaffolds in an osteochondral defect model in rabbits. Conference «Graubünden forscht – Young Scientists in Contest» September 12–13, 2012. Davos. (Poster).

Pub:
Laschke MW, Kleer S, Scheuer C, Schuler S, Garcia P, Eglin D, Alini M, Menger MD. Vascularisation of porous scaffolds is improved by incorporation of adipose tissue-derived microvascular fragments. Eur Cell Mater. 2012;24:266-77.

Partners:
- Laschke M, University of Sarland, Germany
- Goldberg HA, University of Western Ontario, Canada
- Acute Cartilage Injury Collaborative Research Programs Consortium

Thermoresponsive hydrogels based on natural polysaccharide. CARTHA (Ongoing)

The capacity to modulate the biochemical environment of a thermoresponsive hydrogel encapsulating human mesenchymal stromal cells (hMSCs) is a fundamental requisite for cell biology and therapeutic applications. This has been shown, for example, by functionalization with an integrin binding sequence (RGDS). However, this has rarely been achieved without further hydrogel modification.

Thus, we have further developed thermo-reversible hyaluronan compositions which provide an injectable 3D matrix platform. Furthermore, we have demonstrated the impact of biocompatible and bio-functional dendrimer grafted onto an hyaluronan backbone, combined to a thermoresponsive hyaluronan hydrogel, on hMSCs viability and osteogenic differentiation.

Pub:
Fransen P, Pulido D, Seelbach R, Mata A, Eglin D, Royo M, Albericio F. Biofunctionalization of biopolymers with peptide conjugated dendrons. J Pept Sci 2012;18:S25. (European Peptide Symposium).

Partner:
- Acute Cartilage Injury Collaborative Research Programs Consortium

Fibrous polymeric patch for annulus fibrosus repair. AFEPATCH (Ongoing)

Low back pain is a major public health problem in our society and the cause of significant morbidity. While the etiologies are many, intervertebral disc (IVD) degeneration is recognized to be the leading cause for chronic low-back pain. The major aim of this study is to prepare a cellularized biodegradable polymeric patch which combines first a plug mimicking the annulus fibrosus (AF) 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 slowly resorbable polymer capable of retaining its mechanical integrity under complex load for an extended period of time (e.g. poly(ester-urethane)). The polymeric plugs were assessed for their ability to support the regeneration of AF tissue *in vitro*. Different membrane compositions and architectures were characterized regarding their mechanical and structural properties. This work will provide the basis to develop novel biological patches for the repair of AF defects (Figure).

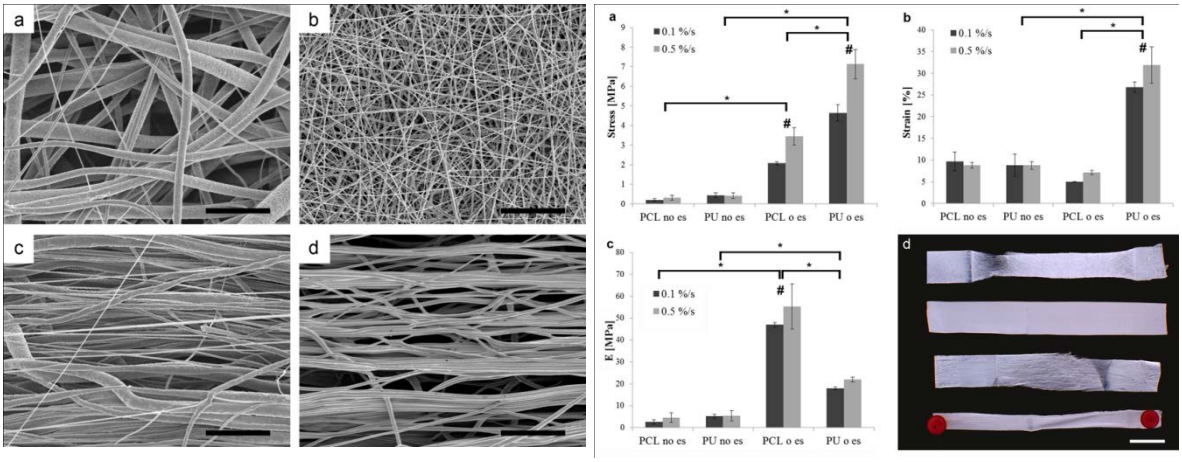


Figure: (Left a-d) Representative SEM images showing morphological structures of non-oriented PCL (a), non-oriented PU (b), oriented PCL (c) and oriented PU (d). The SEM was operated at 1.00 kV, 40-20 µA and WD=8-10 mm. Scale bar = 20 µm. (Right a-d) Mechanical properties of non-oriented PCL (PCL no es), non-oriented PU (PU no es), oriented PCL (PCL o es) and oriented PU (PU o es) scaffolds (yield stress: a; yield strain: b; Young's modulus: c). *Indicates $p < 0.05$ for marked groups, # indicates $p < 0.05$ 0.1 %/s strain vs. 0.5 %/s strain. Mean ± standard deviation (SD). For non-oriented scaffolds N = 3, for oriented scaffolds N = 2 (duplicates per batch). (d) Non-oriented PCL, non-oriented PU, oriented PCL and oriented PU (from top to bottom) scaffolds after tensile testing with a maximal applied strain of 100 %. Scale bar = 5 mm.

Pres:

Wismer N, Fortunato G, Ferguson SJ, Alini M, Grad S, Eglin D. Characterization of biodegradable electrospun scaffolds for annulus fibrosus tissue engineering: biochemical and biomechanical properties. 2012. WBC.

Pub:

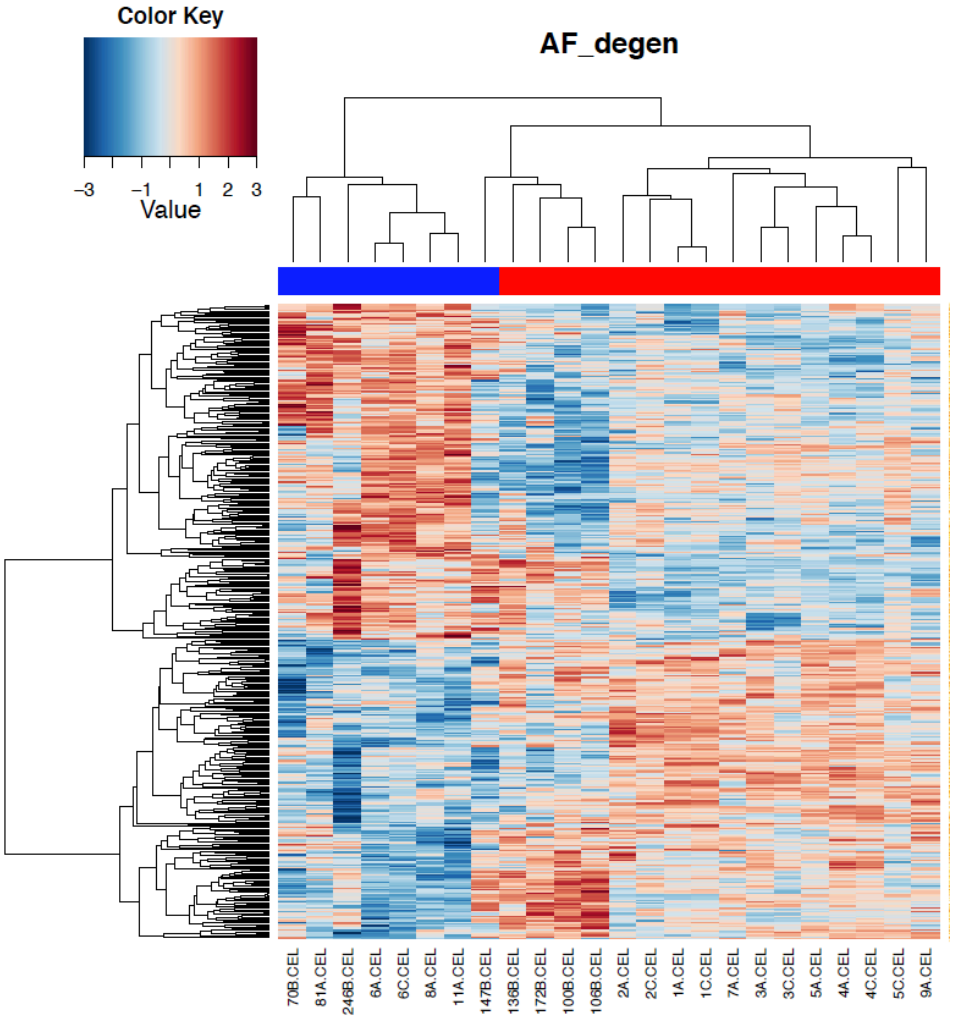
Grad S, Wismer N, Fortunato G, Ferguson SJ, Alini M, Eglin D. Biodegradable electrospun scaffolds for annulus fibrosus tissue engineering: effect of scaffold structure and composition on annulus fibrosus cells in vitro. Global Spine Journal 2012;2 Suppl 1:S37–S38 (WFSR)

Partner:

- Annulus Fibrosus Ruptures Collaborative Research Programs Consortium

Elucidation of pathways involved in annulus fibrosus failure by mRNA profiling and subsequent protein assessment (DISCPHEN) (ongoing)

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 more effective than the current anabolic therapies. 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 as well as from surgical samples with ruptured AF. Gene expression profiles were analyzed by microarray expression mapping and results confirmed by real-time PCR. Age- and degeneration-matched IVD samples will be used for subsequent quantification and localization of respective proteins by immunohistochemistry. Furthermore, the functional role of differentially expressed proteins will be assessed in AF cells in vitro. This allows identifying molecules with regenerative or anti-degenerative functions.



Map of differentially expressed genes in AF cells. Downregulated genes (in degenerated relative to healthy AF cells) appear as blue, while upregulated genes appear as red in the plot.

Pres:
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. WFSR 2012, Helsinki; Global Spine J 2, Suppl.1, S84-S85 (2012).

Collin E, Mahor S, Kilcoyne M, Hendig D, Grad S, Alini M, Pandit A. Upstream upregulation of glycosaminoglycans production by targeting synthesizing enzymes using a nonviral gene delivery method for intervertebral disc regeneration. WFSR 2012, Helsinki; Global Spine J 2, Suppl.1, S38-S39 (2012)..

Cunningham CM, Srivastava A, Collin E, Grad S, Alini M, Pandit A, Wall G. Cell targeting nanoparticles for gene delivery to nucleus pulposus cells for intervertebral disc regeneration. WFSR 2012, Helsinki; Global Spine J 2, Suppl.1, S123 (2012).

Pub:
Pattappa G, Li Z, Peroglio M, Wismer N, Alini M, Grad S. Diversity of Intervertebral Disc Cells: Phenotype and Function. J Anatomy 221(6):480-96, 2012.

Partner:
- Annulus Fibrosus Ruptures Collaborative Research Programs Consortium

Reporter driven isolation of osteogenic and endothelial progenitors from mesenchymal stem cells (Comstem) (Ongoing)

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 mesenchymal stem cells 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. Upon differentiation to osteoblasts the reporter is activated and cells express GFP allowing the responsive cells to be separated and harvested by fluorescent activated cell sorting (FACS). Using this system we have indications that different sub-populations of cells undergoing osteogenesis signal to each other, affecting the behavior of the other sub-populations. This project will investigate the cross-talk signaling further and the technology platform will be expanded into new cell types such as endothelial cells.

Pres:
Bruderer M, Stoddart MJ, Vogel V, Alini M. Characterization of osteoprogenitors functionally isolated from human mesenchymal stem cells by a runx2-responsive reporter adenovirus. International Society Stem Cell Research, Yokohama, Japan, June 13 - 16, 2012.

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

Chondrogenesis of human bone marrow mesenchymal stem cells in fibrin-polyurethane composites (Stemload) (Ongoing)

Tissue engineering is believed to be the future of articular cartilage repair due to the unsatisfying results of the current clinical procedures. Mesenchymal stem cells derived from bone marrow (BMSCs) have demonstrated the potential to differentiate into several cell lineages, including chondrocytes. We have been investigating the combinatorial effect of adenoviral BMP-2 gene therapy and mechanical stimulation in a multiaxial load bioreactor on the fate of human bone marrow derived stem cells. A combination of the two stimuli led to an increase in chondrogenic gene expression in the absence of exogenous chondrogenic growth factors. As this study utilizes unstimulated mesenchymal stem cells, does not involved the use of exogenous growth factors and combines each component in a single procedure, it can be performed within the operating theater (we have previously developed a gene therapy approach which can be performed within 3 minutes using 5% of the typical viral burden used). This offers potentially new rehabilitation protocols using intraoperative gene therapy for the repair of intra-articular fractures.

Invited Pres:

Mechanoregulation of Stem cell fate. The Orthopaedic Trauma Institute International Research Symposium on "Tissue engineering, regeneration and repair of orthopaedic tissues" San Francisco, February 3rd, 2012.

Acute cartilage injury regeneration. European Society for Trauma and Emergency Surgery. Basel, May 13th 2012. – Keynote.

MSC, growth factors and biomechanics in musculoskeletal repair and regeneration. International Mini-Symposium on Regenerative Medicine. University Hospital Zürich, June 22nd 2012 – Keynote.
Mesenchymal stem cells for cartilage repair and regeneration. Seminar- University of Pennsylvania July 31st 2012.

Mechanoregulation of Stem cell fate. 2nd International Conference on Regenerative Orthopedics and Tissue Engineering. 21st September, 2012, Opatija, Croatia – Keynote.

Mechanically induced chondrogenesis- Mimicking the in vivo environment in vitro. Belgium Symposium on Tissue Engineering. 18th September 2012, Leuven, Belgium. – Keynote.

The role of multiaxial load on mesenchymal stem cell fate. EORS 2012, 20th Annual Meeting, Amsterdam, 26-28 September – Keynote.

Pres:

Salzmann GM, Petrou M, Bernstein A, Niemeyer P, Mayr H, Grad S, Stoddart MJ, Alini M, Südkamp N. Composite Growth-Factor-Bioreactor Synergism for Human Stem Cell Chondrogenesis. EFFORT 2012.

Neumann AJ, Alini M, Anton M, Archer CW, Stoddart MJ. The effect of retroviral-mediated overexpression of BMP-2 on hMSCs during monolayer proliferation. ORS 2012, February 4-7th, San Francisco California, USA.

Neumann AJ, Alini M, Archer CW, Stoddart MJ. Combined effect of mechanical load and BMP-2 overexpression on the chondrogenesis of human bone marrow derived stem cells. International Cartilage Repair Society, Montreal, May 12-15, 2012.

Neumann AJ, Alini M, Anton M, Archer CW, Stoddart MJ. The effect of retroviral-mediated overexpression of BMP-2 on hMSCs during monolayer proliferation. International Cartilage Repair Society, Montreal, May 12-15, 2012.

Schätti O, Grad S, Goldhahn J, Alini M, Stoddart MJ. Chondrogenic induction of human mesenchymal stem cells by mechanical means. Musculoskeletal Biology and Bioengineering GRC, August 5th – 10th, 2012.

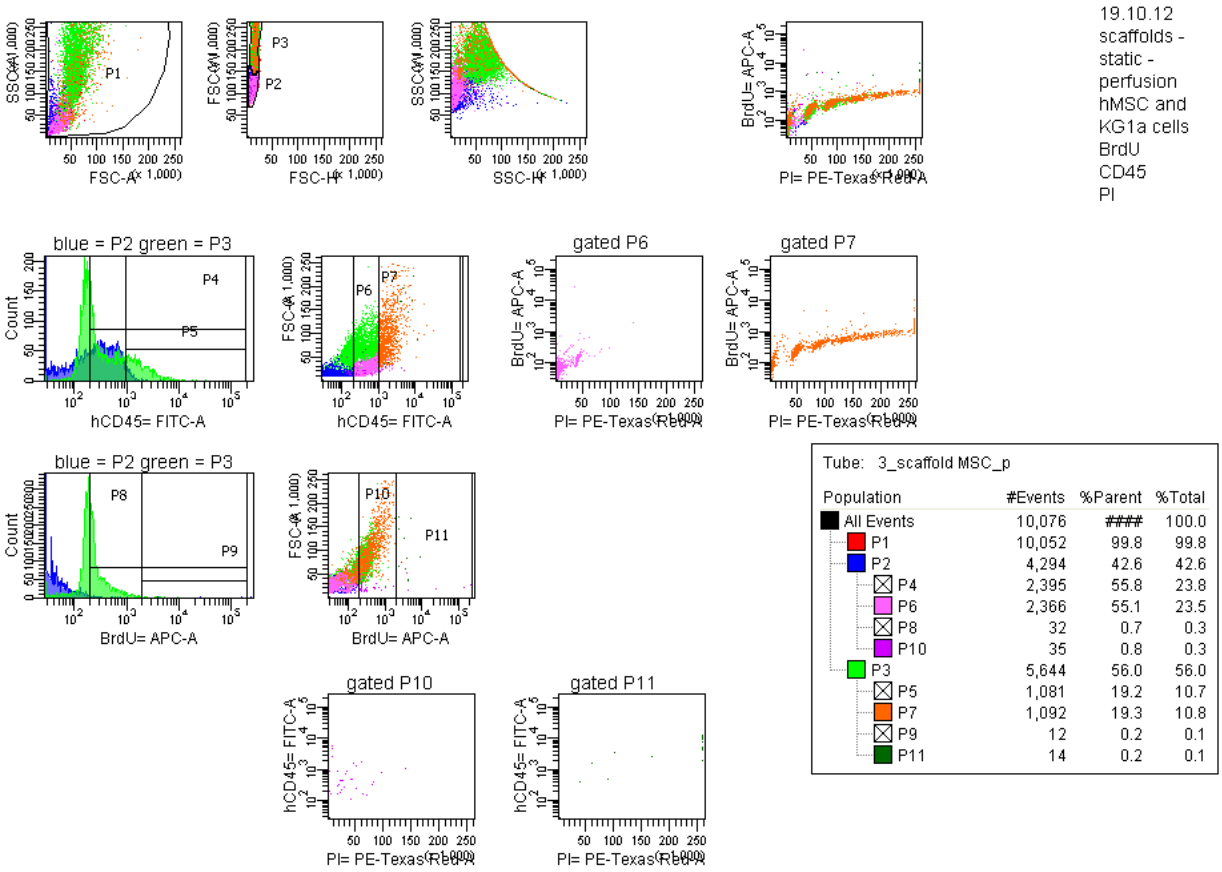
Zahedmanesh H, Stoddart MJ, Alini M, Van Oosterwyck H. Numerical quantification of cell level mechanical stimuli in fibrin-polyurethane composite scaffolds under compressive and interfacial shear loads; Implications for cartilage tissue engineering. COST Workshop in Vienna, September 4-5, 2012.

Pub:
Neumann A.J, 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.

Partners:
- Archer CW, Cardiff Institute of Tissue Engineering and Repair, School of Biosciences, Cardiff University, Wales, United Kingdom
- Salzmann G, Department of Orthopaedic and Trauma Surgery, University Medical Center, Albert-Ludwigs University Freiburg, Germany

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

Within this project, we aim to develop an *in vitro* culture system to mimic the human bone marrow stem cell niche in an artificial perfusion bioreactor environment, in order to culture human adult stem cells. With this new bioreactor system we aim to keep the viable human bone marrow stem cells in a quiescent state, as they are within the human long bone niche. We aim to use this system to investigate the behavior of freshly isolated cells and compare the behavior of the Mesenchymal stem cells alone and in combination with the hematopoietic cells (CD45+ cells) normally present in a fracture environment. This is crucial as it is freshly isolated cells, not monolayer expanded mesenchymal stem cells, which are available to surgeons and could be applied within a single surgical procedure intraoperatively. We have now established the methods for CD45+ cell separation, Brdu labeling of proliferating cells within the scaffold, release of cells from the fibrin scaffold and triple fluorescence label analysis of the cultured cells, to determine the proportion of proliferating cells, and which are CD45+ or CD45-. All these methods were established with fresh human bone marrow. We also investigated the co-culture of monolayer expanded human MSCs with KG1a, a human myeloblast cell line (Fig.).



Pres:

Lezuo P, Alini M, Stoddart MJ. Degradation of fibrin gels during monoculture of human MSC's. Swiss Society for Biomaterials, Zürich, May 3rd 2012.

Bara JJ, Lezuo P, Menzel U, Alini M, Stoddart MJ. In vitro investigation of the mesenchymal stem cell niche in bone marrow. Belgium Symposium on Tissue Engineering. 18th September 2012, Leuven, Belgium.

Promotion of vascularization in large size bone defect implants (Neovasc) (ongoing)

The repair of large bone defects still constitutes a major challenge for trauma and orthopedic surgeons, as not only bone is damaged, but also the vascular network. An active blood vessel network is an essential factor for cells to survive and integrate to the surrounding tissues. A promising approach to overcome these problems is tissue engineering, which seeks to develop a biological substitute, capable of mimicking the natural environment, and to regenerate and improve the functional state of damaged tissue. In our previous work (see Activity Report 2011, project ECPGRAFT), *in vitro* studies showed that the association of endothelial progenitor cells (EPC) with bone marrow mesenchymal stem cells (BMSC) within a polyurethane scaffold promoted the formation of PECAM-positive tubular structures. The aim of the present project is to investigate the ability of these pre-cellularized scaffolds to form tubular structures directly *in vivo* and their capacity to connect to the surrounding blood network when implanted sub-cutaneously. In parallel, the role of pericytes in the formation of these capillary like structures is further investigated.

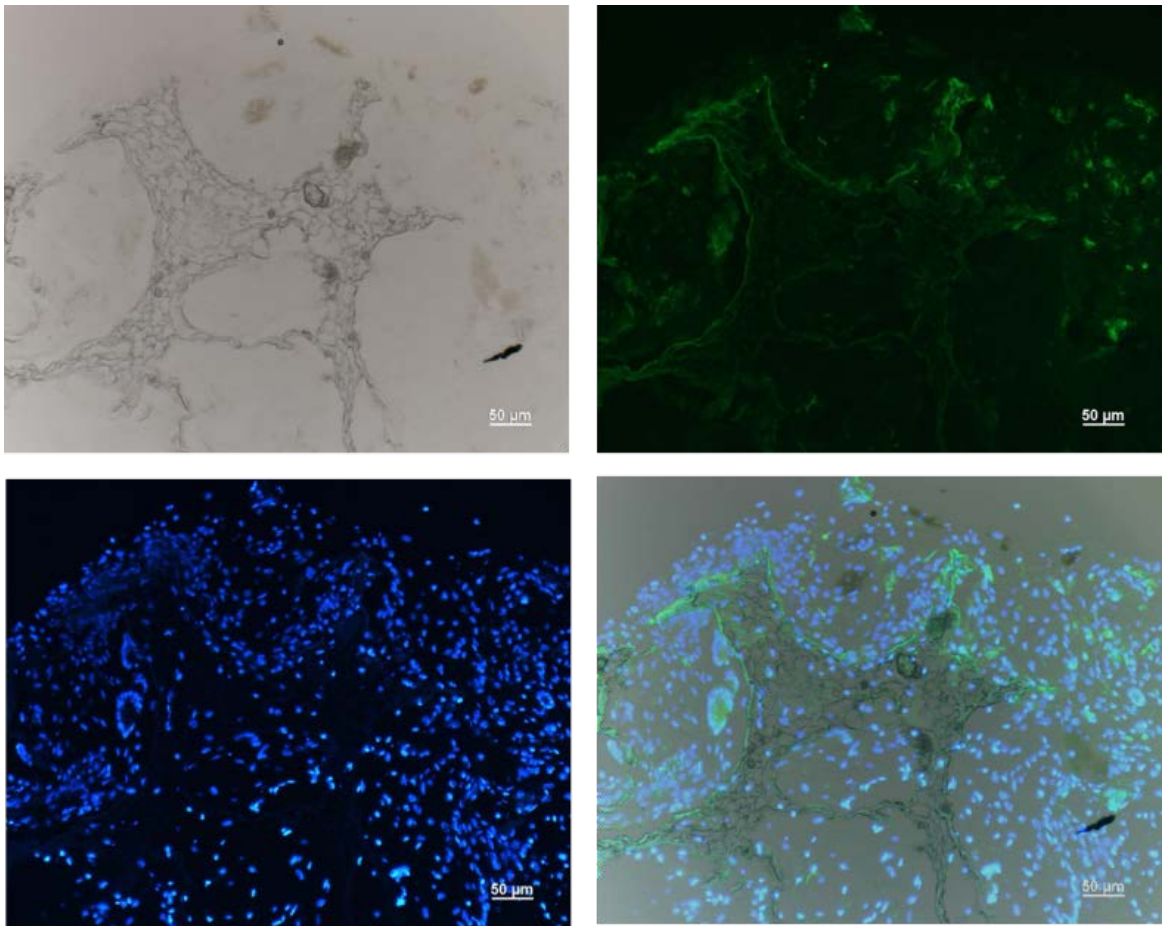


Figure: New vessels perfusion after 8 weeks implantation in the back of nude mice. Top left: Bright field image showing the scaffold (in grey). Top right shows FITC-Lectin underlining the presence of perfused vessel structure (in green well defined areas, to be differentiated from the scaffold auto fluorescence, also green). Bottom left: DAPI nuclear staining. Bottom right: merged picture of the 3 previous images.

Pub:

Laschke MW, Kleer S, Scheuer C, Schuler S, Garcia P, Eglin D, Alini M, Menger MD. Vascularization of porous scaffolds is improved by incorporation of adipose tissue-derived microvascular fragments. Eur Cell Mater. 2012 Sep 24;24:266-77.

Pres:

Verrier S, Duttenhoefer F, Richards G, Alini M. Pre-vascularized 3D constructs for bone critical size defects. EORS 2012 Amsterdam, NL.

Verrier S, Duttenhoefer F, Egli S, Benneker LM, Richards RG, Alini M. Co-seeding of EPC/MSC in 3D scaffolds (Endothelial Progenitor Cells / Mesenchymal Stem Cells) promotes implant's neovascularization: evidence of pericytes' participation. eCM 2012, Davos, CH.

Duttenhoefer F, Egli S, Benneker LM, Richards RG, Alini M, Verrier S. Coculture of Endothelial Progenitor Cells (EPC) and Mesenchymal Stem Cells (MSC) in polyurethane scaffolds (PU) promotes simultaneously implant neo-vascularization and bone neo-formation. TERMIS 2012 Vienna, AU.

Partner:

- Laschke M, Institute of Clinical & Experimental Surgery, University of Saarland, 66421, Homburg/Saar, Germany

Effect of dynamization on critical size bone defect healing (DynaBone) (ongoing)

Presently, rigid fixations are widely used for the management of all kind of fractures. However, over the past few years, an increasing amount of experimental and clinical evidence reports 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 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, we first treat the large bone defect with autologous/syngeneic bone graft (gold standard, positive control) to which different loading protocols are applied. 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 neo-vascularization in parallel. In the first year of this project and under the kind advises from Prof Steven Goldstein, we could produce an external dynamizable fixator adaptable to the mechanical loading system he provided us. Out of preliminary data, we could show the feasibility to follow bone remodeling over time using vivaCT.

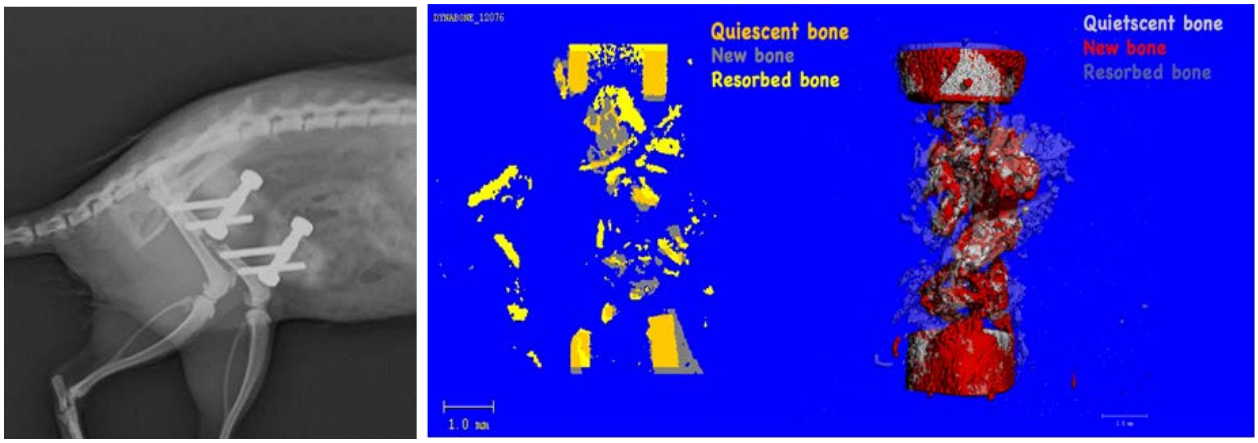


Figure: Left picture: Xray image of post-osteotomy. The bone defect was filled with trabecular bone graft (from syngenic animal) and fixed with a dynamizable radiolucent external fixator (made out of peek). Middle picture: VivaCT images showing the presence of quiescent bone in orange (both edges of the osteotomy site and chips of implanted trabecular bone), the resorbed bone (in yellow) and new formed bone (in grey) 4 weeks after surgery. The figure on the right shows a 3D reconstruction of the middle

9.7 Extramural project abstracts

Gene Activated Matrices for Bone and Cartilage Regeneration in Arthritis (GAMBA) (ongoing)

This consortium develops a novel gene-activated matrix platform for bone and cartilage repair with a focus on osteoarthritis-related tissue damage. The science & technology objectives of this project are complemented with an innovative program of public outreach, actively linking patients and society to the evolvement of this project. The GAMBA platform is implementing a concept of spatiotemporal control of regenerative bioactivity on command and demand. A biomimetic hyaluronan gel is being developed at the AO Research Institute Davos as a three-dimensional carrier in combination with a ceramic matrix, growth factor-encoding gene vector nanoparticles, magnetic nanoparticles and mesenchymal stem cells. Anatomical adaptivity is achieved with engineered thermal properties of the polymer matrix, which embeds other modules, selected according to functional requirements. The research receives funding from the European Union's 7th Framework Program under grant agreement n° NMP3-SL-2010-24.

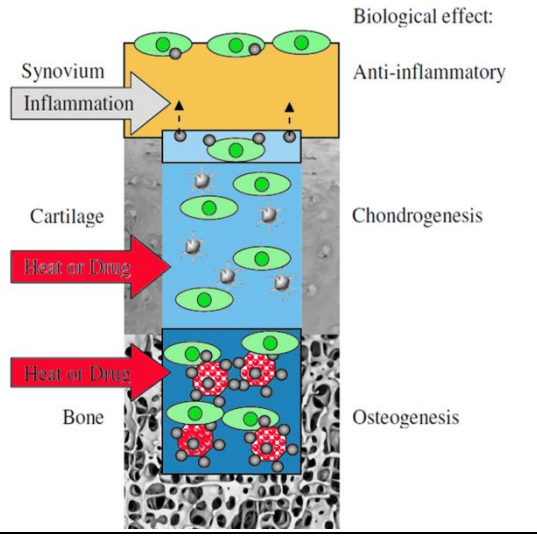


Figure: Concept of GAMBA for spatiotemporally controlled gene expression for bone and cartilage regeneration and reduction of inflammation on command and demand.

Pres:

Sukarto A, Rentsch D, Alini M, Eglin D. In situ gelation of acrylate hyaluronic acid derivatives as cell and gene delivery vehicles for osteochondral repair. 2012. WBC.

D'Este M, Borget P, Daculsi G, Mykhaylyk O, Plank C, Anton M, Alini M, Eglin D. Development of gene activated matrices for osteochondral regeneration in osteoarthritis. 2012. EORS.

D'Este M, Eglin D, Borget P, Daculsi G, Alini M. Calcium Phosphate/Thermoresponsive Hyaluronan Composites for Bone Repair. 2012. SBMS.

D'Este M, Borget P, Daculsi G, Alini M, Eglin D. Injectable osteoconductive composite displaying gelation at body temperature. 2012. WBC.

Pub:

D'Este M, Alini M, Eglin D. A new single step synthesis for thermoresponsive hyaluronan hydrogels. Eur Cell Mater 2012;23 Suppl 2:3 (SSB).

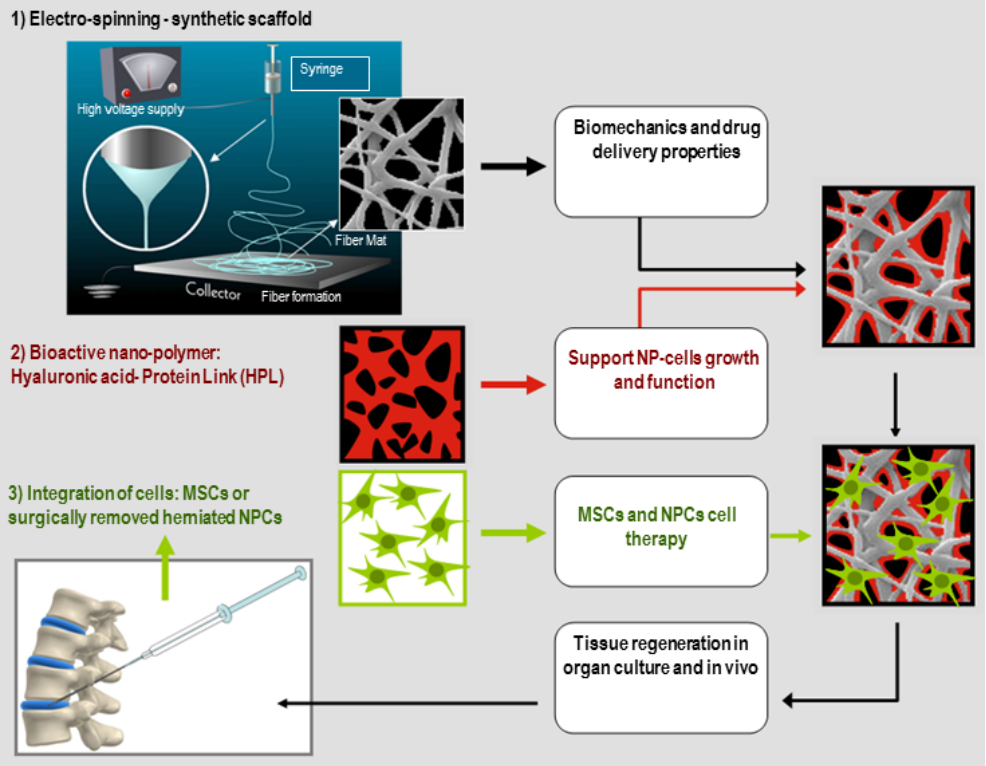
D'Este M, Alini M, Eglin D. Single step synthesis and characterization of thermoresponsive hyaluronan hydrogels. Carbohydr Polym. 2012;90(3):1378-85.

Partners:

- Klinikum rechts der Isar TUM, Munich, Germany
- National University of Ireland, Galway, Ireland
- Oz Biosciences SAS, Marseille, France
- Biomatlante SAS, Nantes, France
- Erasmus Universitair Medisch Centrum, Rotterdam, The Netherlands
- Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy
- Institut National de la Santé et de la Recherche Medicale, Nantes, France
- Science Dialogue GbR, Weilheim, Germany

Biomimetic nano-fiber-based nucleus pulposus regeneration for the treatment of degenerative disc disease (NPMimetic) (ongoing)

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 and/or anti-inflammatory drugs will be carried by biodegradable nano-fibers to be gradually released *in situ* thus, healing and/or preventing inflammation. Furthermore, 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. The multidisciplinary team is complemented by a spine surgeon to define inputs and outputs of the research from a clinical implementation point of view. The research receives funding from the European Union's 7th Framework Program NMP-2009-2.3-1.



NPmimetic concept: integrating electro-spun synthetic nano-fibers with bioactive nano polymer for generating an injectable biomimetic matrix to support nucleus pulposus cells for long-term IVD repair.

Pres:

Li Z, Sirkis R, Peroglio M, Wertzel A, Amit B, Alini M, Yayon A, Grad S. A Novel Nano-biopolymer for Nucleus Pulposus Regeneration. World Biomaterials WBC 2012, Chegdu.

Li Z, Sirkis R, Peroglio M, Wertzel A, Mevorat-Kaplan K, Alini M, Yayon A, Grad S. Biomimetic fibrinogen-hyaluronan conjugates for nucleus pulposus regeneration. SSB 2012, Zürich Eur Cell Mater 23, Suppl.2, 30 (2012).

Li Z, Sirkis R, Peroglio M, Wertzel A, Amit B, Alini M, Grad S, Yayon A. A novel nano-biopolymer for intervertebral disc regeneration: In vitro study on nucleus pulposus cells. TERMIS 2012, Vienna; J Tissue Eng Regen Med 6, Suppl.1, 43 (2012).

Partners:

- Nicast Ltd., Lod, Israel
- CM Développement, Paris, France
- ProCore BioMed Ltd., Ness Ziona, Israel
- Vrije Universiteit Medisch Centrum (VUmc), Amsterdam, The Netherlands
- 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

Rational Bioactive Materials Design for Tissue Regeneration (Biodesign) (Ongoing)

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.

Partners:

- Uppsala Universitet, Sweden
- Eidgenössische Technische Hochschule, Zurich, Switzerland
- Ludwig Boltzmann 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

Evaluation of antimicrobial peptide OP145 delivered via PolyPid coating as a prophylaxis and treatment of intramedullary nail related infection (BALI)

Orthopedic implant related infections are prototypical biofilm infections with particularly high re-infection rates after secondary revision procedures due to the difficulty in eliminating the biofilm that is present on and surrounding the implant by conventional antibiotic therapy. This study aims to test antibiotic loaded coatings on an implant to combat orthopedic infections. The coatings based on two novel entities: a novel antimicrobial agent and a novel coating system. These coated implants will serve both prophylaxis of implant related infection and treatment of infected bones. This project is in the preparation phase in 2012, with experimental work to begin in 2013.

Partners:
S.A.J. Zaat Amsterdam Medical Center, Netherlands,
Noam Emanuel, Polypid Ltd. Israel

10 Operations standards and safety

Successful 2012 routine audit of AO Research Institute Davos
From April 23 to 24, 2012, two external auditors from the SQS (Swiss Association for Quality and Management Systems; www.sqs.ch) visited ARI for the routine audit of the Institute.
ARI keeps the existing certification for another year without any non-conformities requiring immediate actions. Having held several open discussions with several staff members and management, the auditors were impressed by the levels of commitment and knowledge at both locations.
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.

QM recommendations
The SQS certification auditor/assessors of ARI specifically mentioned again in 2012 that the new review system from the AO Foundation should NOT be applied to concept development or innovation projects, since this might cause major setbacks to such sensitive projects. This issue was part of the Research Review Process and will be decided by AOVA subsequently.

AAALAC certification of Preclinical facility
In 2012 a big effort was put into the accreditation of the new Preclinical Facility.
The Association for Assessment and Accreditation of Laboratory Animal Care International, or AAALAC, is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs.
For more detailed info see under 5. focus areas preclinical surgery and preclinical facility.

GLP accreditation
Since the regulatory framework in our main customers most important market changed and requires GLP conform studies for the approval medical devices, we started investing in getting ready for a GLP accreditation for specific parts of the institute. We are aiming to get this accreditation in 2015/2016.

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	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
Nehrbass Dirk	Dr med vet, FTA Pathol + Toxicopathol	01.10.10
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

AO Senior Scientific Advisor:

Perren Stephan M.*	Prof, Dr med Dr sci (hc), Chirurg FMH	01.01.64

Scientific & Technical Staff:

Abegglen Nadine	Administrative Assistant (50%)	01.09.09
Agarwal Yash	MEng, PhD Candidate	07.10.10
Arens Daniel	Dr med vet (01.06.03 – 30.09.06)	01.11.07
Badrutt Isabella	Administrative Assistant	16.07.12
Barblan Claudia	Administrative Assistant (70%)	15.11.10
Bluvol Mauro	Chemielaborant (Eidg FA[1])	01.06.03
Bruderer Marco	PhD Cand	01.10.08
Camenisch Karin	Technical Assistant (40%)	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	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
Escher Carla	Administrative Assistant (40%)	01.01.95
Faoro Pierina	Artzgehilfin (MPA)	01.12.07
Forte Matthias	Dipl Ing	15.07.11
Furlong-Jäggi Pamela	Chemikerin FH, BSc	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
Lanker Urban	Animal Care (Eidg FA[1])	16.06.86
Lemm Priska	Poly mechanics	01.01.10
Lezuo Patrick	Dipl Eng / PhD Cand	01.08.03
Li Zhen	PhD	01.08.11
Menzel Ursula	PhD, Dipl Biol	01.07.11
Müller Gregor	Lic phil, Librarian (50%)	17.01.05
Müller Reto	Animal Care (Eidg FA[1]) (80%)	13.11.01
Nehrbass Angela	Dr med vet (60%)	08.11.10
Neumann Alexander	PhD Cand, Dipl Biol	01.05.09
Noser Hansrudi	PD Dr ès science EPFL	18.10.04
Pattappa Gisrish	PhD	01.07.10
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
Potapova Inga	PhD	01.01.10
Schneider Monika	Administrative Assistant (50%)	06.02.06
Schraner Daniela	Administrative Assistant (50%)	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
ter Boo Gert-Jan	MSc, Biomedical Engineering	15.01.12
Thöny Sandra	MSc, Human Biology	07.11.11
Verrier Sophie	D res Science	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	01.06.03
Zweifel Erich	European Industrial Engineer EIE	30.11.92

Apprentice

Adank Nando	Apprentice	01.08.11
Frey Kevin	Apprentice	01.08.11
Semadeni Gian Mario	Apprentice	01.08.11

Internship

Münch Claudia	MSc Cand, Medical Engineering	01.06.12
Nies Andrea	Vet Internship	01.12.12
Viehöfer Ulf	Student	01.08.12

Medical Research Fellows:

Götzen Michael	Dr med	01.05.12
Helfen Tobias	Dr med	01.09.12
Löbel Claudia	Med Cand	02.01.12
Peters Sarah	Dr med vet	01.08.12
Pirvu Tatiana	Dr med	01.07.12
Rukmanikanthan Shanmugam	Dr med	15.10.12
Wagner Daniel	Dr med	01.05.12

Non Medical Research Fellows:

Ernst Manuela	MSc, ETHZ	01.10.11

Employees left 2012

Scientific & Technical Staff:

Berri Fabian	CNC Mechanics (60%) (01.08.99 – 31.07.03)	01.11.07 -
Egli Sandrine	FH Biotechnologin, BSc	14.02.11
Erdhöhely Balazs	Computer Science and informatics	01.08.11 – 30.06.12
Martin Jurado Olga		09.01.12 – 30.11.12
Poulsson Alexandra	PhD, MSc, BEng	29.08.06
Rochford Edward	PhD Cand, MPhil, BSc	03.08.08 – 31.10.12
Sukarto Abby	MSc	13.10.10 – 31.08.12
Trüssel Patrick	Apprentice /Technician	01.08.09 – 30.09.12

Internship

Casanova Pierina	Trainee	05.01.12 – 20.06.12
Ernst Manuela	Master Student	01.10.11 – 31.12.12
Günther Christian	Vet Internship	08.10.12 – 30.11.12
Kesti Matti	IAESTE Student	01.07.12 – 31.12.12
Unholz Cynthia	Master Student	01.10.12 – 31.12.12

Medical Research Fellows:

Al-Saadi Hayder	Dr med	14.10.11 – 13.10.12
Blankstein Michael	Dr med	17.07.12 – 31.12.12
Blazejak Marek	Dr med	16.04.12 – 15.07.12
Georg Joseph	Dr med	01.03.12 – 31.08.12
Morgenstern Mario	Dr med	16.02.12 – 30.09.12
Nicolino Tomas	Dr med	01.07.12 – 31.12.12
Segal Ortal	Dr med	16.10.12 – 31.12.12
Shiozaki Yasuyuki	Dr med	15.08.11 – 15.02.12
Schmidutz Florian	Dr med	01.05.11 – 30.04.12
Schneider Kerstin	Dr med	02.01.12 – 16.09.12
Seyboth Claus	Dr med	01.08.11 – 17.01.12
White Charles	Dr med	01.07.12 – 30.09.12
Zerbe Philipp	Dr med vet	01.02.12 – 31.07.12

Guests:

Masumeci Giuseppe	PhD, Assistant Professor of Human Anatomy, Dep of Bio-Medical Sciences, University of Catania, Italy, Musculoskeletal Regeneration, 05.09.11 – 24.02.12
Leite Pereira Catarina	Practicum at Musculoskeletal Regeneration, 05.01.12 – 31.12.12
Reuber Tobias	Albert-Ludwigs-Universität Freiburg, Germany, Project Cell Homing Musculoskeletal Regeneration, 05.09.11 – 12.04.12
Staudacher Judith	Albert-Ludwigs-Universität Freiburg, Germany, Project Chondrogenese Musculoskeletal Regeneration, 05.09.11 – 15.04.12
Seelbach Ryan	MSc, University of Barcelona, Spain Musculoskeletal Regeneration, since 19.03.12
Zahedmanesh Houman	MD, UZ Leuven, Traumatology, Leuven, Belgium Musculoskeletal Regeneration, 05.04.12 – 30.05.12
Cochis Andrea	University of Eastern Piedmont, Novara, Italy Musculoskeletal Regeneration, 16.04.12 – 30.05.12
Bryant Stephanie	Visiting Professor, University of Colorado, USA Musculoskeletal Regeneration, 01.05.12 – 07.08.12

Da Silva Adelina Maria	Faculdade de Medicina Veterinaria, Brazil Preclinical Services, Histology, 16.05.12 – 25.05.12
Haddouti El-Mustapha	University Hospital of Bonn, Germany Musculoskeletal Regeneration, 16.05.12 – 28.06.12
Bara Jennifer	Institute for Science and Technology in Medicine, Keele University, UK Musculoskeletal Regeneration, 20.06.12 – 21.11.12
Wähnert Dirk	MD, Universitätsklinikum Münster, Project Collaboration Biomedical Services, 25.06.12 – 03.08.12
Schmid Timo	Inselspital Bern, Project Collaboration, 01.11.-30.11.12
Zurbriggen Sebastian	Inselspital Bern, Project Collaboration, 01.11-30.11.12
Lenz Mark	Universitätsklinikum Jena, Project Collaboration, several times
Katie Lehovsky	Practicum, Radlett, Herb, GB Musculoskeletal Regeneration, 09.07.12 – 20.07.12
Grossenbacher Christian	Practicum, Kantonsschule Olten, Switzerland Musculoskeletal Regeneration, 19.11.12 – 23.11.12
Mauderli David	Practicum, Kantonsschule Olten, Switzerland Musculoskeletal Regeneration, 19.11.12 – 23.11.12
See Eugene Yong-Shun	University of Galway, Ireland CRP AFR Workshop at Musculoskeletal Regeneration, 09.11.-01.12.12
Sakai Daisuke	Tokay University, Isehara, Japan CRP AFR Workshop at Musculoskeletal Regeneration, 09.11.-10.11.12
Nukaga Tadashi	Tokay University, Isehara, Japan CRP AFR Workshop at Musculoskeletal Regeneration, 09.11.-10.11.12
Tomoko Nakai	Tokay University, Isehara, Japan CRP AFR Workshop at Musculoskeletal Regeneration, 09.11.-10.11.12
Illien-Jünger Svenja	Mount Sinai School of Medicine, New York, USA CRP AFR Workshop at Musculoskeletal Regeneration, 09.11.-16.11.12
Likhitpanichkul Morakot	Mount Sinai School of Medicine, New York, USA CRP AFR Workshop at Musculoskeletal Regeneration, 09.11.-17.11.12

AO Senior Scientific Advisor:

Stephan Perren, one of the AO founding fathers, celebrated his 80th birthday.

On October 07, 2012 Stephan Perren, one of the AO Foundation's founding fathers, celebrated his 80th birthday. For many of these 80 years Stephan has been intimately involved with the AO; in addition to his role as a founder, he also chaired the AO Technical Commission and the AO Development steering committee for 16 years and for 28 years was the Director of the AO Research Institute Davos. All these tasks he performed alongside his work as a medical doctor and Honorary Professor at the Universities of Bern, Montevideo and Aberysthwyth to mention just a few of his other professional duties. He was also cofounder of the European Society of Biomechanics and International Society for Fracture Repair.

Stephan is still very committed to the AO world, giving regular presentations as well as writing and editing—he was joint editor with Peter Matter on a recently published book commemorating the 20th anniversary of the AO center—and more. In his private life Stephan is also still very active and recently bought an electric bike to cycle around the hills of Davos.

Congratulations on this milestone birthday from the AO Research Institute Davos (former Laboratory for Experimental Surgery Davos).

12 Publications & Presentations

12.1 Peer reviewed publications

epub 2011/ 2010 - in print 2012 (counted within 2011 key performance indicators, not 2012 KPI's)

Gahlert M, Roehling S, Sprecher CM, Kniha H, Milz S, Bormann K.
In vivo performance of zirconia and titanium implants: a histomorphometric study in mini pig maxillae.
Clin Oral Implants Res 2012;23:281-6 *(epub 2011 Aug 2) (IF 2.514))*

Hayes JS, Czekanska EM, Richards RG.
The Cell-Surface Interaction.
Adv Biochem Eng Biotechnol 2012;126:1-31 *(epub 2011 Oct 8) (IF n.a.)*

Ockert B, Braunstein V, Sprecher CM, Shinohara Y, Milz S.
Fibrocartilage in various regions of the human glenoid labrum. An immunohistochemical study on human cadavers.
Knee Surg Sports Traumatol Arthrosc 2012;20:1036-41 *(epub 2011 Oct 5) (IF 2.209)*

Ockert B, Braunstein V, Sprecher C, Shinohara Y, Kirchhoff C, Milz S.
Attachment sites of the coracoclavicular ligaments are characterized by fibrocartilage differentiation: a study on human cadaveric tissue.
Scand J Med Sci Sports 2012;22:12-7 *(epub 2010, June 18) (IF 2.867)*

Peroglio M, Grad S, Mortisen D, Sprecher CM, Illien-Junger S, Alini M, Eglin D.
Injectable thermoreversible hyaluronan-based hydrogels for nucleus pulposus cell encapsulation.
Eur Spine J 2012;21:S839-S849 *(epub 2011, Aug 27) (IF 1.965)*

Rathnayaka K, Momot KI, Noser H, Volp A, Schuetz MA, Sahama T, Schmutz B.
Quantification of the accuracy of MRI generated 3D models of long bones compared to CT generated 3D models.
Med Eng Phys 2012;34:357-63 *(epub 2011 Aug 18) (IF 1.623)*

Sermon A, Boner V, Boger A, Schwieger K, Boonen S, Broos PL, Richards RG, Windolf M.
Potential of polymethylmethacrylate cement-augmented helical proximal femoral nail antirotation blades to improve implant stability--a biomechanical investigation in human cadaveric femoral heads.
J Trauma Acute Care Surg 2012;72:E54-E59 *(epub 2011, Jul 15) (IF 2.478)*

Sermon A, Boner V, Schwieger K, Boger A, Boonen S, Broos P, Richards G, Windolf M.
Biomechanical evaluation of bone-cement augmented Proximal Femoral Nail Antirotation blades in a polyurethane foam model with low density.
Clin Biomech (Bristol , Avon) 2012;27:71-6 (*epub 2011 Aug 7) (IF 2.071)*

Verrier S, Hughes L, Alves A, Peroglio M, Alini M, Boger A.
Evaluation of the in vitro cell-material interactions and in vivo osteo-integration of a spinal acrylic bone cement.
Eur Spine J 2011;21:800-9 *(epub 2011, Aug 03) (IF 1.965)*

Wohlrab D, Radetzki F, Noser H, Mendel T.
Cup positioning in total hip arthoplasty: spatial alignment of the acetabular entry plane.
Arch Orthop Trauma Surg 2012;132:1-7 *(epub 2011 Aug 28) (IF 1.369)*

published 2012

Alajmo G, Schlegel U, Gueorguiev B, Matthys R, Gautier E.
Plunging When Drilling: Effect of Using Blunt Drill Bits.
J Orthop Trauma 2012;26:482-487 *(IF 2.135)*

Arora R, Milz S, Sprecher C, Sitte I, Blauth M, Lutz M.
Behaviour of ChronOS Inject in metaphyseal bone defects of distal radius fractures: tissue reaction after 6-15 months.
Injury 2012;43:1683-8 *(IF 1.975)*

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 2012; epub Dec 27 *(IF 4.023)*

Braun T, Lepper J, Heiland GR, Hofstetter W, Siegrist M, Lezuo P, Gaestel M, Rumpler M, Thaler R, Klaushofer K, Distler JH, Schett G, Zwerina J.
Mitogen- activated protein kinase 2 (MK2) regulates physiological and pathological bone turnover.
J Bone Miner Res 2012; epub Nov 20 *(IF 6.373)*

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 2012; epub Dec 05 *(IF 1.265)*

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 2012; epub Dec 05 *(IF 1.265)*

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 2012;epub Oct 09 *(IF 1.975)*

Czekanska E, Stoddart MJ, Richards RG, Hayes JS.
In search of an osteoblast cell model for *in vitro* research.
Eur Cell Mater 2012;24:1-17 *(IF 3.028)*

D'Este M, Alini M, Eglin D.
Single step synthesis and characterization of thermoresponsive hyaluronan hydrogels.
Carbohydr Polym 2012;90:1378-85 *(IF 3.628)*

D'Este M, Eglin D.
Hydrogels in calcium phosphate moldable and injectable bone substitutes: Sticky excipients or advanced 3-D carriers?
Acta Biomater 2012; epub Nov 28 *(IF 4.865)*

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 2012; epub Dec 20 *(IF 2.147)*

Fliri L, Lenz M, Boger A, Windolf M.
Ex vivo evaluation of the polymerization temperatures during cement augmentation of proximal femoral nail antirotation blades.
J Trauma Acute Care Surg 2012;72:1098-101 *(IF 2.478)*

Fliri L, Sermon A, Wahnert D, Schmoelz W, Blauth M, Windolf M.
Limited V-shaped cement augmentation of the proximal femur to prevent secondary hip fractures.
J Biomater Appl 2012; epub Apr 05 *(IF 2.082)*

Glatt V, Evans CH, Matthys R.
Design, characterisation and in vivo testing of a new, adjustable stiffness, external fixator for the rat femur.
Eur Cell Mater 2012;23:289-98 *(IF 3.028)*

Grad S, Loparic M, Peter R, Stolz M, Aebi U, Alini M.
Sliding motion modulates stiffness and friction coefficient at the surface of tissue engineered cartilage.
Osteoarthritis Cartilage 2012;20:288-295 *(IF 3.904)*

Hayes JS, Welton JL, Wieling R, Richards RG.
In vivo evaluation of defined polished titanium surfaces to prevent soft tissue adhesion.
J Biomed Mater Res B Appl Biomater 2012;100:611-617 *(IF 2.147)*

Hoppe S, Alini M, Benneker LM, Milz S, Boileau P, Zumstein MA.
Tenocytes of chronic rotator cuff tendon tears can be stimulated by platelet-released growth factors.
J Shoulder Elbow Surg 2012; epub Apr 20 *(IF 2.747)*

Illien-Junger S, Pattappa G, Peroglio M, Benneker LM, Stoddart MJ, Sakai D, Mochida J, Grad S, Alini M.
Homing of Mesenchymal Stem Cells in Induced Degenerative Intervertebral Discs in a Whole Organ Culture System.
Spine (Phila Pa 1976) 2012;22:1865-1873 *(IF 2.078)*

Kamer L, Noser H, Kirsch E, Hammer B.
Anatomy-based surgical concepts for individualized orbital decompression surgery in graves orbitopathy. II. Orbital rim position and angulation.
Ophthal Plast Reconstr Surg 2012;28:251-5 *(IF 0.691)*

Kirchhoff C, Braunstein V, Milz S, Sprecher CM, Kirchhoff S, Graw M, Imhoff AB, Hinterwimmer S.
Age and gender as determinants of the bone quality of the greater tuberosity: A HR-pQCT cadaver study.
BMC Musculoskelet Disord 2012;13:221 *(IF 1.580)*

Kirchhoff C, Kirchhoff S, Sprecher CM, Ahrens P, Imhoff AB, Hinterwimmer S, Milz S, Braunstein V.
X-treme CT analysis of cancellous bone at the rotator cuff insertion in human individuals with osteoporosis: superficial versus deep quality.
Arch Orthop Trauma Surg 2012; epub Dec 07 *(IF 1.369)*

Krause F, Blatter S, Waehnert D, Windolf M, Weber M.
Hindfoot Joint Pressure in Supination Sprains.
Am J Sports Med 2012;40:902-908 *(IF 3.792)*

Ladermann 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 2012; epub Apr 26 *(IF 2.747)*

Laschke MW, Kleer S, Scheuer C, Schuler S, Garcia P, Eglin D, Alini M, Menger MD.
Vascularisation of porous scaffolds is improved by incorporation of adipose tissue-derived microvascular fragments.
Eur Cell Mater 2012;24:266-77 *(IF 3.028)*

Lenz M, Windolf M, Muckley T, Hofmann GO, Wagner M, Richards RG, Schwieger K, Gueorguiev B.
The locking attachment plate for proximal fixation of periprosthetic femur fractures-a biomechanical comparison of two techniques.
Int Orthop 2012;36:1915-1921 *(IF 2.025)*

Lenz M, Gueorguiev B, Joseph S, Van der Pol B, Richards RG, Windolf M, Schwieger K, de Boer P.
Angulated locking plate in periprosthetic proximal femur fractures: biomechanical testing of a new prototype plate.
Arch Orthop Trauma Surg 2012;132:1437-1444 *(IF 1.369)*

Lenz M, Perren SM, Gueorguiev B, Richards RG, Krause F, Fernandez dell'Oca A, Höntzsch D, Windolf M.
Underneath the cerclage: an ex vivo study on the cerclage-bone interface mechanics.
Arch Orthop Trauma Surg 2012;132:1467-1472 *(IF 1.369)*

Lenz M, Gueorguiev B, Richards RG, Mückley T, Hofmann GO, Höntzsch D, Windolf M.
Fatigue performance of angle-stable tibial nail interlocking screws.
Int Orthop 2012;epub Aug 09 *(IF 2.025)*

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 2012; epub Nov 10 *(IF 2.025)*

Maier D, Kamer L, Noser H, Stankovic Z, Guth A, Baurle P, Südkamp NP, Kostler W.
Morphometric analysis of anatomical implant forms for minimally invasive acetabular fracture osteosynthesis.
Comput Aided Surg 2012;17:240-8 *(IF 0.296)*

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 2012; epub Dec 13 *(IF 1.975)*

Mueller MA, Hengg C, Hirschmann M, Schmid D, Sprecher C, Audige L, Suhm N.
Mechanical torque measurement for in vivo quantification of bone strength in the proximal femur.
Injury 2012; epub Jul 11 *(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 2012; epub Mar 01 *(IF 2.171)*

Pattappa G, Li Z, Peroglio M, Wismer N, Alini M, Grad S.
Diversity of intervertebral disc cells: phenotype and function.
J Anat 2012;221:480-496 *(IF 2.370)*

Plank C, Eglin D, Fahy N, Sapet C, Borget P, van Osch G, Gentili C, Miramond T, Zöller K, Anton M.
Gene activated matrices for bone and cartilage regenration in arthritis.
Eur J Nanomed 2012;4:17-32 *(IF n.a.)*

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 2012; epub Nov 13 *(IF 2.086)*

Rausch S, Schlonski O, Klos K, Gras F, Gueorguiev B, Hofmann GO, Muckley 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 2012;epub Sep 20 *(IF 1.975)*

Richards RG, Moriarty TF, Miclau T, McClellan RT, Grainger DW.
Advances in Biomaterials and Surface Technologies.
J Orthop Trauma 2012;26:703-707 *(IF 2.135)*

Rochford ET, Richards RG, Moriarty TF.
Influence of material on the development of device-associated infections.
Clin Microbiol Infect 2012;18:1162-1167 *(IF 4.540)*

Rothstock S, Plecko M, Kloub M, Schiuma D, Windolf M, Gueorguiev B.
Biomechanical evaluation of two intramedullary nailing techniques with different locking options in a three-part fracture proximal humerus model.
Clin Biomech (Bristol, Avon) 2012;27:686-91 *(IF 2.071)*

Rothstock S, Kowaleski MP, Boudrieau RJ, Beale BS, Piras A, Ryan M, Boure L, Brianza S.
Biomechanical and computational evaluation of two loading transfer concepts for pancarpal arthrodesis in dogs.
Am J Vet Res 2012;73:1687-95 *(IF 1.269)*

Sakai D, Nakamura Y, Nakai T, Mishima T, Kato S, Grad S, Alini M, Risbud MV, Chan D, Cheah KS, Yamamura K, Masuda K, Okano H, Ando K, Mochida J.
Exhaustion of nucleus pulposus progenitor cells with ageing and degeneration of the intervertebral disc.
Nat Commun 2012;3:1264 *(IF 7.396)*

Schiuma D, Plecko M, Kloub M, Rothstock S, Windolf M, Gueorguiev B.
Influence of peri-implant bone quality on implant stability.
Med Eng Phys 2012;epub Jun 07 *(IF 1.623)*

Stadelmann V, Conway CM, Boyd SK.
In vivo monitoring of bone-implant bond strength by microCT and finite element modeling.
Comput Methods Biomech Biomed Engin 2012; epub Jan 30 *(IF 1.169)*

Stoddart MJ, Richards RG, Alini M.
EDITORIAL: In vitro experiments with primary mammalian cells: To Pool or not to Pool?
Eur Cell Mater 2012;24:i-ii *(IF 3.028)*

Wähnert D, Hofmann-Fliri L, Schwieger K, Brianza S, Raschke MJ, Windolf M.
Cement augmentation of lag screws: an investigation on biomechanical advantages.
Arch Orthop Trauma Surg 2012;epub Dec 21 *(IF 1.369)*

Windolf M, Schroeder J, Fliri L, Dicht B, Liebergall M, Richards RG.
Reinforcing the role of the conventional C-arm - A novel method for simplified distal interlocking.
BMC Musculoskelet Disord 2012;13:8 *(IF 1.580)*

12.2 Books and bookchapters

Moriarty TF, Zaat SAJ, Busscher HJ (Eds.)
Biomaterials Associated Infection. Immunological Aspects and Antimicrobial Strategies.
New York, Heidelberg, Dordrecht, London: Springer; 2012.

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; 2012; p. 273-304.

Iordanova I, Antonov V, Sprecher CM, Gueorguiev B.
Plasma-Sprayed Bioceramic Coatings on Ti-Based Substrates. Methods for Investigation of Their Crystallographic Structure and Mechanical Properties.
In: Jazi H (Ed.). Advanced Plasma Spray Applications: INTECH Open Access; 2012; p. 99-122.

Perren SM, Fernandez Dell'Oca A, Regazzoni P, Windolf M.
New aspects of cerclage: improved technology applicable to MIO with special reference to periprosthetic fractures.
In: Babst R, Bavonratanavech S, Pesantez R (eds).
Minimally Invasive Plate Osteosynthesis - Second expanded Edition.
Stuttgart, New York: AO Foundation / Georg Thieme; 2012; p. 31-48.

Poulsson AH, Richards RG.
Surface Modification Techniques of Polyetheretherketone, Including Plasma Surface Treatment.
In: Kurtz SM (Ed). PEEK Biomaterials Handbook. pdl - Plastics Design Library. Elsevier.
Amsterdam et al. 2012; p. 145-61.

Rochford ET, Jaekel DJ, Hickok NJ, Richards RG, Moriarty TF.
Bacterial Interactions with Polyaryletheretherketone.
In: Kurtz SM (Ed.). PEEK Biomaterials Handbook. pdl - Plastics Design Library. Elsevier.
Amsterdam et al. 2012; p. 93-117.

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; 2012; p. 435-53.

Windolf M, Perren SM.
Basic mechanobiology of bone healing.
In: Babst R, Bavonratanavech S, Pesantez R (eds).
Minimally Invasive Plate Osteosynthesis - Second expanded Edition.
Stuttgart, New York: AO Foundation / Georg Thieme; 2012; p. 13-30

12.3 Abstracts published in journals

Collin E, Kilcoyne M, Grad S, Alini M, Joshi L, Pandit A.
Cell surface glycosylation and glycosaminoglycan composition profiles in inmature and mature intervertebral disks.
Global Spine Journal 2012;2 Suppl 1:S84-S85 (WFSR)

Collin E, Mahor S, Kilcoyne M, Hendig D, Grad S, Alini M, Pandit A.
Upstream upregulation of glycosaminoglycans production by targeting synthesiszing enzymes using a nonviral gene delivery method for intervertebral disk regeneration.
Global Spine Journal 2012;2 Suppl 1:S38-S39 (WFSR)

Cunningham CM, Srivastava A, Collin E, Grad S, Alini M, Pandit A, Wall G.
Cell targeting nanoparticles for gene delivery to nucleus pulposus cells for intervertebral disk regeneration.
Global Spine Journal 2012;2 Suppl 1:S123 (WFSR)

D'Este M, Alini M, Eglin D.
A new single step synthesis for thermoresponsive hyaluronan hydrogels.
Eur Cell Mater 2012;23 Suppl 2:3 (SSB)

Fransen P, Pulido D, Seelbach R, Mata A, Eglin D, Royo M, Albericio F.
Biofunctionalization of biopolymers with peptide conjugated dendrons.
J Pept Sci 2012;18:S25. (European Peptide Symposium)

Grad S, Wismer N, Fortunato G, Ferguson SJ, Alini M, Eglin D.
Biodegradable electrospun scaffolds for annulus fibrosus tissue engineering: effect of scaffold structure and composition on annulus fibrosus cells in vitro.
Global Spine Journal 2012;2 Suppl 1:S37-S38 (WFSR)

Lezuo P, Alini M, Stoddart M.
Degradation of fibrin gels during monoculture of human MSC's.
Eur Cell Mater 2012;23 Suppl 2:5 (SSB)

Li Z, Sirkis R, Peroglio M, Wertzel A, Mevorat-Kaplan K, Alini M, Yayon A, Grad S..
Biomimetic fibrinogen-hyaluronan conjugates for nucleus pulposus regeneration.
Eur Cell Mater 2012;23 Suppl 1:30 (SSB)

Peroglio M, Grad S, Eglin D, Benneker LM, Alini M.
Thermoreversible hyaluronan hydrogels support mesenchymal stem cells discogenic differentiation in vitro and ex-vivo.
Global Spine Journal 2012;2 Suppl 1:S124-S125 (WFSR)

Peroglio M, Eglin D, Benneker LM, Alini M, Grad S.
Evaluation of a thermoresponsive hyaluronan hydrogel as stem cell carrier for intervertebral disc regeneration.
Eur Cell Mater 2012;23 Suppl 2:24 (SSB)

Rochford ET, Poulsson AH, O'Mahoney L, Ziegler M, Richards RG, Moriarty TF.
The effect of material choice on the immune response to bacterial contamination.
Eur Cell Mater 2012;23 Suppl 2:35 (SSB)

12.4 Conference proceedings

Agarwal Y, Stuby F, Windolf M, Shiozawa T, Ochs BG, Gonser C, Stöckle U, Gueorguiev B.
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12.5 Dissertations

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Development of a supplementary device for the external fixator to monitor the course of fracture healing using a novel data collection concept.
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ARI Team 2012

Employees left 2012

Fellows & Internship 2012