AO Foundation

AO Research Institute Davos

Activity Report 2014

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1 Introduction

In September 2009 I took over as the Director of AO Research Institute Davos (ARI) in troubled times having gone through a 30% cut in funding and having re-integrated the AO Development Institute back within its structure. All ARI projects have since been reviewed and monitored with regards to clinical relevance by the surgeons in the clinical division's research committees and TK along with the ARI Advisory committee for the direct funding from the AO Foundation. The efficiency of this system improved, though one issue is for the clinical divisions to find clinicians with enough pre-clinical research experience for the committees.

The AO Research Institute Davos continues to give the academic credibility to the AO Foundation. Our highly motivated, solution oriented, knowledgeable research team are well respected in the international musculoskeletal research community. We have brought the AO Foundation closer to major international societies such as the Orthopedic Research Society (ORS), where the AO is visible through our symposia, workshops, positions on committees and boards and also major awards and the Orthopedic Trauma Society (OTA), where AO has been visible in the several Basic Science Focus Forums. The number of publications has steadily risen since 2009 along with the average impact factor (IF) of all the ARI publications and in 2014 a record of IF 4.07 for 61 papers, was achieved. The ARI Medical Fellowship program was re-launched where 69 medical fellows have spent time since 2009, to learn the basics of preclinical research at ARI to help them move forward with their careers. Two of these Fellows have even received PhD`s from their work here at their local universities in Utrecht and Leuven (Dagma Vos and An Sermon) and several non AO hospitals (in old definition terms) have got closer involved with AO through this scheme, such as Murnau in Germany with our Infection work, as part of the AOTrauma clinical priority program (CPP) on bone infection. The fellowships have even helped us to bring in major grants such as the RAPIDOS European Chinese research project coordinated by the ARI, with two of the Chinese sites being run by ex ARI fellows. Within this period, the ARI built a modern preclinical facility with two operation suites and then achieved AAALAC certification (the only academic institute currently in Switzerland with this) and has initiated the work for GLP accreditation of the facility. The old suites were converted into a very well used human cadaver lab.

2014 has been full of achievements for ARI. We have set our goals now to maintain this level of excellence despite recent further 10% cut in AO internal Funding over 2013-2015. Our future in the next few years moves again towards the original goal of ARI in the 50's to 90's to bring the created knowledge to solutions for effective patient care (the original idea for the set-up of the ADI in the mid 90's, by Professor Stephan Perren). The way we bring this created knowledge to solutions is likely to diversify more over the next few years and this leads once again to exciting times.

To maintain global respect as an independent entity, the AO Foundation must not just educate health providers, but must be at the forefront of creating knowledge through research and utilize this knowledge through development to bring solutions to clinical problems via the surgeon and operating room personnel to the patient. A recent example of this is the "playground" from the ARI which now operates through AO Education as the AO Skill training lab, teaching health providers through hands on means basic principles of fracture fixation, to improve the understanding at the operation table. Another example is the surface finish of the AO approved implants which have all recently been updated to incorporate the created knowledge from the ARI on topography to reduce boney contact, yet allow free gliding tissues to move unhindered.

I would like to invite you all to see our knowledge creation from 2014 within this ARI report and to look at the ARI website to see our latest publications http://www.aofoundation.org/ari

Sincerely

Prof Dr R Geoff Richards FBSE, Director AO R&D

2 Mission / Goals / Outlook

Mission

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

Goals

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

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

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

Rolling Outlook ARI (3 years start)

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

20 year strategy for Research focused towards clinical applications/solutions within the CMF area undertaken with the CMF R&D Committee in 2014.

3 Funding Summary

Income Statement	2013 Actual		2014 Actual	
in CHF '000	abs	%	abs	%
AO Foundation Contribution	6'718	59%	8'909	73%
3rd party Income	2'400	21%	1'738	14%
AO Intercompany	2'261	20%	1'624	13%
Total Income	**11'378**	**100%**	**12'271**	**100%**
AOTrauma *	3'995	35%	4'090	33%
AOSpine*	414	4%	431	3%
AOCMF *	681	6%	595	5%
AOVET	66	1%	70	1%
AOTK	606	5%	406	3%
AOER *	2'027	18%	1'691	14%
AO Foundation * °	1'100	10%	3'444	28%
3rd party projects	2'400	21%	1'738	14%
Total Expenses	**11'289**	**100%**	**12'465**	**100%**
Net Result	**89**		**-193**	

* incl. AO Intercompany

° incl. newly integrated Collaborative Research Programs

'3rd Party Income' amounted to CHF 1,738 and remained 30% (CHF 735 K) below budget and 28% (CHF 661 K) below previous year. The main reasons for the decrease vs. budget were lower activities in commercial projects and an impairment of income concerning mainly long term projects with European Union grants.

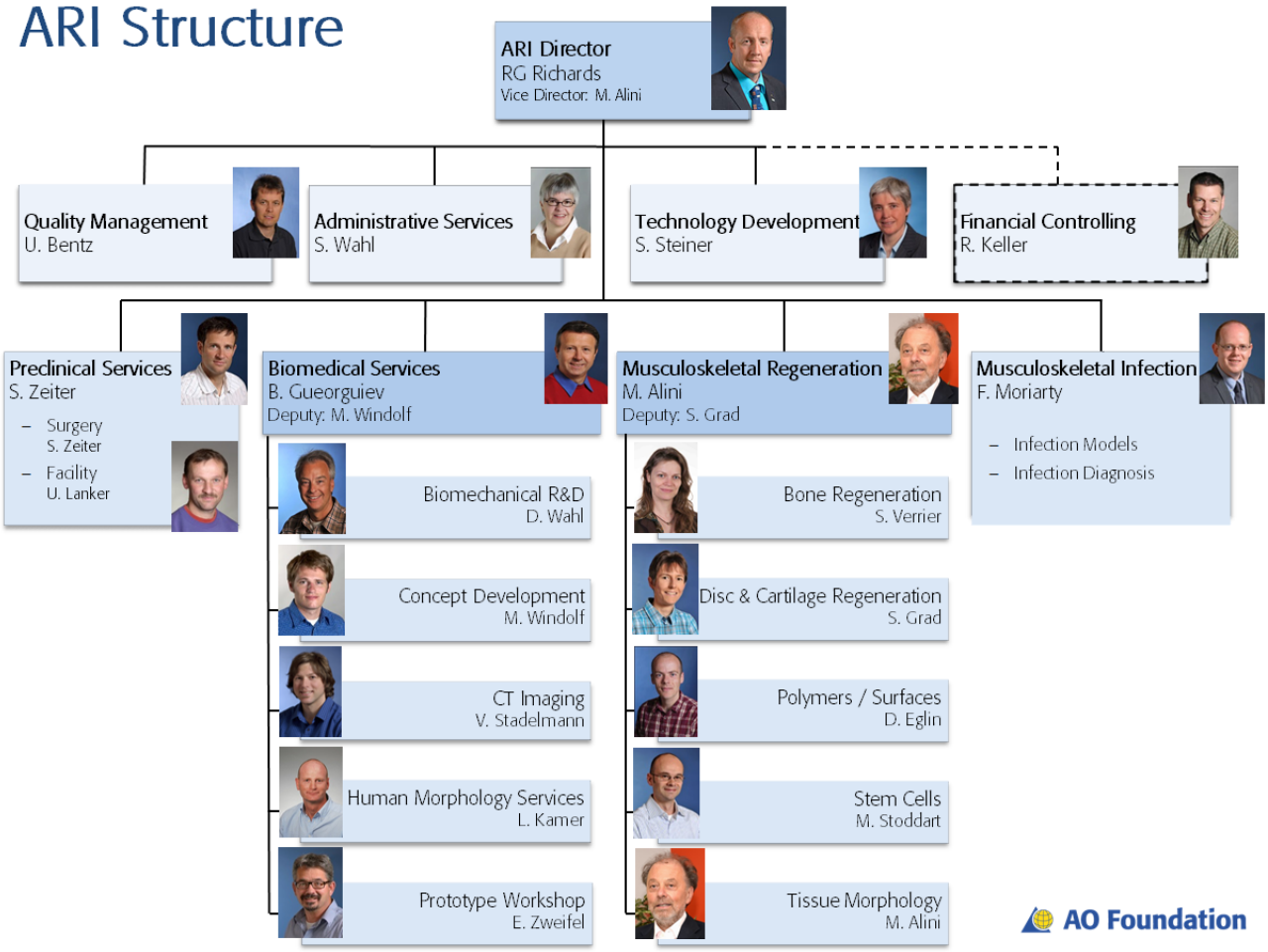
With regard to the split of the 'Total Expenses' by organizational unit, 'Musculoskeletal Regeneration' had the highest stake with 28% followed by 'Preclinical Services' and 'Biomedical Services' with 17% each. The underspend vs. budget of 'Preclinical Services', 'Tissue Morphology' and 'Medical Imaging' amounted to CHF 576 K (- 13%) and was mainly caused by the lower level of commercial projects. The overspend in 'Management' of 29% vs. Budget was mainly caused by a lower-than-budgeted absorption of indirect cost by the respective research projects due to the lower-than-budgeted project activity.

From a cost type point of view, the main categories were 'Personnel Expenses' with 64%, followed by 'Material Expenses' and 'Scientific & Regional Expenses' with 11% each.

Overall, a negative 'Net Result' of CHF 193 K was achieved compared to a balanced budget, which needs to be recovered in 2015 / 2016 within the mid term planned budget to achieve a zero net result over the three years.

4 Structure

4.1 ARI Structure (as of 2014)



4.2 AO R&D Platform

The AO R&D Platform is supporting and advising the AOFB in R&D topics for any AO Foundation money spent in this area internal at the Institutes, or external through actual funding through the AO Foundation itself or its affiliates (clinical divisions, TK and ARI). The R&D Platform agreed on their charter and work plan for 2014 as follows:

- Utilize R&D Management & Information Platform IT database to collect information for strategic considerations and outcome measurement

- Coordinate research transition:
  a) Increase priority focus, reduce project numbers
  b) Support and align strategy to attract and create more IP (focused IP incubator / IP task force)
  c) Align collaboration with ARI and CID

- Clarification Intra- & Extra-mural funding and respective AORRC (AO Research Review Commission) review. The Platform has revised the AO peer review charter for submission to the AOFB.

- Verification of the IP wording in AO Foundation standard contracts for research funding

R&D platform meeting in December 2014, Davos

4.3 ARI Advisory Committee

The ARI Advisory Committee (ARI AC) met in June and December at the AO Research Institute in Davos. The ARI AC gives operational and strategic scientific advice and guidance to the ARI. The ARI AC monitors the ARI output on behalf of the AO Foundation Board (AOFB) and is a group with expertise relevant to the R&D objectives of the AO Foundation and acts as both a sounding board and sparring partner for the management of the AO Research Institute Davos. The ARI AC has no funds available for own projects, i.e. no budget authority.

The ARI AC's tasks and responsibilities in detail are to:
- Give advice and guidance to the AO Research Institute Davos in the fields of:
  - Portfolio of competences (skills of personnel and type of equipment)
  - Strategy and priority seeting for direct funds of the AO Research Institute Davos
  - Exploratory research Collaborative Research Program(s)
  - Business development and intital advice on technology transfer
  - Regulatory issues
- Monitor/control the ARI output of direct funding on behalf of the AOFB

- Support the advancement of the capabilities of the AO Research Institute Davos to assure the efficient deployment of the infrastructure.

The current ARI Advisory Committee (ARI AC) (since December 2013) is
- Prof Dr Michael Schütz (Chair/ clinician), Queensland University of Technology, Australia
- Prof Brian Johnstone, Oregon Health & Science University, USA
- Prof Joost de Bruijn, University of Twente, Netherlands
- Prof Robert Frigg, ex Head of Synthes Global Technology and Innovation Group

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

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

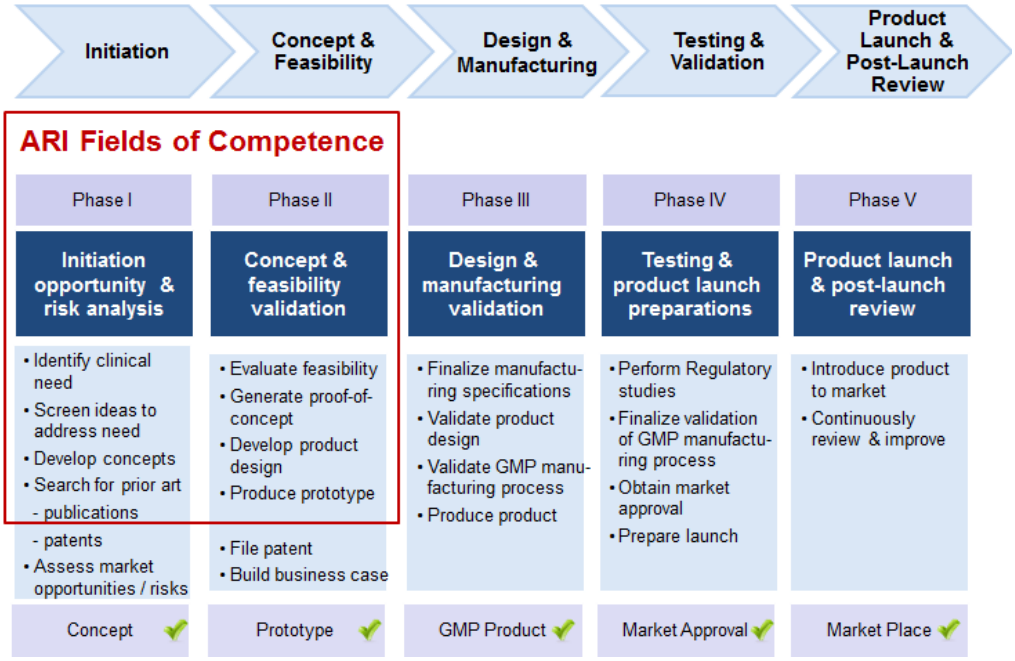
4.4 ARI Technology Development

Manager: Sandra Steiner

From clinical need to product launch

In the past years the major focus of ARI has been to strive for academic excellence as demonstrated by invitations for scientific presentations at expert meetings and publications in high class peer reviewed journals. More recently, the ARI strategy has been further extended to reinforce in addition the development of products with commercial potential.

As a first step towards this expansion of the ARI activities the current ARI fields of competence were reviewed and an outline of the additional expertise that would be required for successful product development and launch was prepared, as shown below:



Before drafting ARI product development strategies, a thorough review of the current ARI patent portfolio was initiated. At the time of review the portfolio included 24 active ARI and ex ADI patents. Several of those will be expiring in the next 2-3 years and for some (e.g. imaging patents) exploitation is already ongoing under AOF guidance. Of the remaining 17 patents five are related to "X-in-One" or "Densiprobe" and their development is well advanced. The remaining 12 patents were subjected to a review in order to decide on their value and potential for exploitation.

During an ARI retreat, each patent was presented by one of the participants and in subsequent breakout sessions four patents were identified with potential for exploitation which include:

- Bone fixation device (WO 2010/017649)
- Cannula and kit for injection of Bone Cement (WO 2011/082499)
- Identification and selection of stem cells being committed to differentiate to a specific type for obtaining a homogeneous population of stem cells (WO 2008/017171)
- Thermosensitive hyaluronic acid conjugates and methods for the preparation thereof (WO 2015/048988)

Subsequently, follow-up studies to strengthen these four patens and to move towards tailored product development strategies were discussed. For the remaining patents the value for ARI and AOF was evaluated and decisions on next steps for each of them were taken.

4.5 Biomedical Services

Program Leader: Boyko Gueorguiev-Rüegg, Deputy: Markus Windolf
Team Members: Nando Adank, Stefan Aeberhard, Yash Agarwal, Jan Caspar, Benno Dicht, Ursula Eberli, Manuela Ernst, Kevin Frey, Thomas Heldstab, Ladina Hofmann-Fliri, Martin Hristov, Lukas Kamer, Prisca Lemm, Hansrudi Noser, Ronald Schwyn, Sonam Sharma, Vincent Stadelmann, Peter Varga, Viktor Varjas, Deyan Veselinov, Daniela Vögtli, Dieter Wahl, Daniel Widmer, Noel Wyss, Ivan Zderic, Erich Zweifel

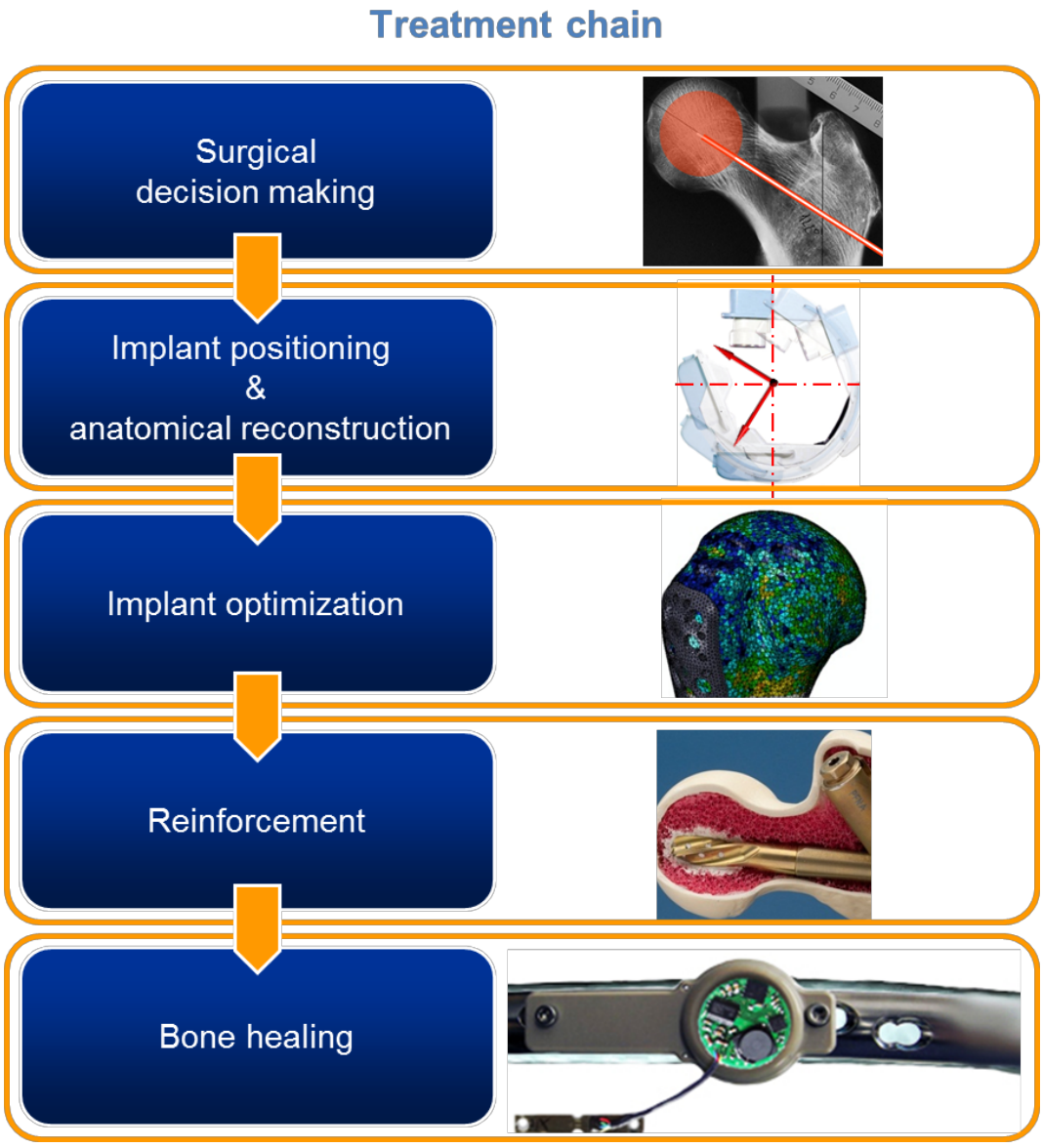
Fellows: Maren Fischer, Jennifer Hagen, Johanna Nilson, Guilherme Seva Gomes

Guests: Mitko Alexandrov, Ariane Barandun, Steven Bresina, Fabian Duttenhöfer, Julia Evers, Ovid Azarya Farhi, Dominic Gehweiler, Stephan Grechenig, Niklas Grüneweller, Kajetan Klos, Mark Lenz, Michael Neuhaus, Walter Ocampo, Sabine Ochmann, Albrecht Popp, Thomas Remmele, Timo Schmid, Paul Schmitz, Jana Schwinn, Paul Simons, Hristo Skulev, Andres Stricker, Daniel Wagner, Dirk Wähnert

The Biomedical Services Program performs research, development and service work in close collaboration with clinical, scientific and industrial partners to improve patient care. The activities are structured and organized in five technically oriented focus areas: Biomechanical R&D, Concept Development, CT Imaging, Human Morphology Services and Prototype Workshop.

The process of finding the optimal solution to clinical questions is enhanced by biomechanical modelling and testing, aiming to establish integrated experimental and computational investigation methods for research in fracture fixation and joint reconstruction. Advanced biomechanical studies are performed using tailored testing protocols with physiological load patterns, supplemented with X-rays, video and motion tracking systems. 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. Analyses based on finite elements methods help to design, optimize and test existing, as well as newly developed implants and endoprostheses on bone models. 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 and anatomical reconstruction, systematic implant optimization, reinforcement techniques with bone cement and assessment of bone healing.



A variety of methods and procedures are developed to meet the demand of the increasingly sophisticated experimental designs for investigation of bone quality, bone healing and osseointegration by means of CT and medical image processing and analysis. A CT database is maintained and computer knowledge is used to develop 3D virtual and statistical bone models and to elaborate fitting project workflow in order to obtain an optimal result. With its highly trained CNC polymechanics and toolmakers the prototype workshop facilitates complete machining of sophisticated tools and guarantees a high quality precision work. Specialized for the production of medical devices, it is involved in the prototype development processes from the very beginning. The program works very closely with the AO Foundation Technical Commission Institute (AOTK – German abbreviation) and it's various medical Expert Groups who provide the clinical questions to be answered and the clinical advice during the projects.

4.6 Preclinical Services

Leader: Stephan Zeiter (previously Markus Wilke until end of February 2014)
Team Members: Daniel Arens, Karin Camenisch, Iska Dresing, Peter Erb, Pierina Faoro, Andrea Furter, Katharina Kluge, Urban Lanker, Reto Müller, Dominic Perren, Tanja Schmid,
Fellows: Bronislaw Nowicki, Christian Günther
Student Externs: Tatjana Harting, Annegret Lucke, Karolina Roscak, Teo Boon Han, Claudia Windhövel, Kinga Wojtczak

Preclinical Services conduct all ARI (internal/external/commercial) *in vivo* studies – often in close collaboration with other Focus Areas. We are an AAALAC International accredited institution. AAALAC International stands for the "Association for Assessment and Accreditation of Laboratory Animal Care" (http://www.aaalac.org/) and is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment program. Staff are highly qualified and specialized in laboratory animal medicine (ECLAM), anesthesia (ECVAA) and surgery (ECVS).

Together with the Focus Area Infecion and CT Imaging we have developed infection models in mice, rats, rabbits and sheep enabling us to investigate different aspects (diagnosis, treatment, applied research) of bone infections. Another focus has been on bisphosphonate related osteonecrosis of the jaw (BRONJ) and on bone as well as cartilage regeneration. For this either standardized models have been used or new models tailored to the research questions have been developed. New projects aiming to refine the surgical and analgesic technique of existing preclinical models have been iniated.

4.7 Musculoskeletal Regeneration Program

Program Leader: Mauro Alini, Deputy: Sibylle Grad
Team Members: Jennifer Bara, Mauro Bluvol, Stephanie Caprez, Ewa Czekanska, David Eglin, Matteo D'Este, Oliver Gardner, Markus Glarner, Nora Goudsouzian, Marietta Herrmann, Laura Kyllönen, Patrick Lezuo, Bojun Li, Zhen Li, Claudia Löbel, Ursula Menzel, Dirk Nehrbass, Marianna Peroglio, Robert Peter, Dalila Petta, Priyanka Pravincumar-Makwana, Jason Ryan, Gian-Marco Semadeni, Christoph Sprecher, Ana-Maria Stanciuc, Martin Stoddart, Lukas Straumann, Gert-Jan ter Boo, Sophie Verrier
Fellows: Marc Anton Füssinger, Jagoda Jalowiec, Gernot Lang, Jan Voss
Guests: Lorin Benneker, Ana-Iulia Blajan, Emma Cavalli, Sakai Daisuke, Marta Dias, Sven Hoppe, Pascal Kaiser, Zepur Kazezian, Elena Littmann, Rose Long, Gil Costa Machado, Robert Ossendorff, Adrian Perez, Lourdes Recha Sancho, Fabrizio Russo, Philipp Sedlaczek, Ryan Seelbach, Tino Stauber, Martin Stefanic, Sandra Thöny, Shan Tian, Gian Luca Vadala, Kalan Violin, Wu Wei, Michael Wirth, Hongji Yan

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

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.

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

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

Stem cell Focus Area
The Stem Cell Focus area is particularly interested in stem cell therapies for bone and cartilage that could be applied within a clinical setting. We aim to investigate the role of mechanical and soluble factors in the activation of mesenchymal stem cells, and the promotion of differentiation and tissue repair. 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. This is the concept that the implanted cells direct the response, rather than become the tissue of interest. 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.

Tissue Morphology Focus Area
Performing histological processing and staining is daily routine in the Focus Area Tissue Morphology. Hard tissue evaluation techniques, including resin embedding for bone samples with implants, is one of the core competences. Others are hard tissue microtome sectioning, modified stainings for thicker resin sections, and subsequent qualitative, semiquantitative or quantitative analysis. Custom immunohistological staining is routinely performed. Fluorescence microscopy and scanning electron microscopy (SEM), equipped with an Energy-dispersive X-ray spectroscope (EDX) to identify chemical elements for e.g. surface evaluation and profilometry, complete the spectrum of available techniques.

4.8 Musculoskeletal Infection

Leader: Fintan Moriarty
Team Members: Pamela Furlong, Iris Keller, Virginia Post, Marina Sabate Bresco, Barbara Stanic
Fellows: Julian Fischer, Willem Metsemakers, Eleftheria Samara

The Musculoskeletal Infection team performs research focussed upon the clinical challenges of post-traumatic osteomyelitis. The goals are to develop improved preclinical models of bone infection that provide a more accurate representation of the clinical situation, and subsequently use these models to study the factors that play a role in the progression of these infections.

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 preclinical models of infection that may be used to test the performance of any such new implant design or coating. In collaboration with ARI colleagues, we have established mouse, rat, rabbit and sheep models of implant related osteomyelitis.

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

4.9 ARI Administrative Service Group

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

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

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

In 2014 the ARI Administrative Service Group has organized for:

AO Research Institute Davos (ARI)

21.02.2014	TUHH-ARI Scientific Exchange Meeting
02.-03.04.2014	ARI Retreat, Pontresina, Switzerland
25.-26.04.2014	AO Traumakurs für ETHZ und ZHAW Studenten 2014, Davos, Switzerland
22.-23.05.2014	CERL/ARI Meeting, Davos, Switzerland
28.-29.06.2014	Collaborative Meeting ARI – Technical University Varna, Bulgaria
16.-18.06.2014	eCM XV Cartilage & Disc: Repair and Regeneration Congress, Davos, Switzerland
19.-20.06.2014	Collaborative Research Program Meetings: Acute Cartilage Injury (ACI) and (Annulus Fibrosus Rupture (AFR), Davos, Switzerland
04.03.2014	ARI Advisory Committee (ARI AC) Video Conference Meeting
20.06.2014	ARI Advisory Committee (ARI AC) Meeting, Davos, Switzerland
16.12.2014	ARI Advisory Committee (ARI AC) Meeting, Davos, Switzerland

AO Foundation (AOF)

21.06.2014	AOF IP Task Force Meeting, Davos, Switzerland
04.09.2014	AOF IP Task Force Meeting, Berlin, Germany

AOTrauma Research Commission (AOTRC)

30.03.2014	AOTRC Meeting, Fort Lauderdale, USA
26.07.2014	AOTRC Meeting, London, United Kingdom
18.10.2014	AOTrauma Annual CPP Meeting Bone Infection, Rochester NY, USA
19.11.2014	AOTRC Meeting, Beijing, China

5 Institutional and Professional Relations

Geoff Richards has appointments as honorary Professor at Cardiff School of Biosciences, Cardiff University, Wales, GB and a second at the Institute of Biological Sciences, Aberystwyth University, Wales, GB. He is a Fellow of Biomaterials Science and Engineering (FBSE). He is cofounder and Editor-in-Chief of the eCM Journal. He has Life Honorary Membership of the Swiss Society of Biomaterials (president in 2007-2009). Geoff Richards is a member and Director of the Board of the Foundation of the AO Research Institute Davos.
Geoff Richards is an executive committee member for the European Orthopedic Research Society. Since 2013, Geoff Richards is an Associate Editor of the Journal of Orthopaedic Translation; elected Member at Large TERMIS-Europe & European representative of the world council Tissue Engineering and Regenerative Medicine International Society (TERMIS); Member of executive committee of Academia Raetica and Vice President of Science City Davos. In 2014 Geoff Richards became a member of International Combined Orthopaedic Research Societies (ICORS) Steering Committee. He has been invited as a "Swiss Personality" to the World Economic Forum Annual Meeting each year since 2012.

Mauro Alini is an adjunct Professor at the Division of Surgery of the McGill University, Montreal, Canada. He serves as a member of the Award Committee for The GRAMMER European Spine Journal Award. He is a member of the Scientific Editorial Board of the eCM Journal and on the Assistant Editorial Board of the European Spine Journal. He is also in the international Editorial Board of the Journal of Orthopaedic Translation and Associate Editor of Tissue Engineering and Regenerative Medicine (Frontiers in Bioengineering and Biotechnology). He is representative to the AOSpine R&D Commission from ARI and in 2014 became chair of the AOSpine research network.

Boyko Gueorguiev-Rüegg is honorary lecturer at the Technical University of Varna, Bulgaria in the fields of biomedical engineering and biotechnology. He was appointed as Associate Editor and Editorial Board Member of the Journal of Orthopaedic Trauma (four-year term), Academic Editor at the Editorial Board of *Medicine* and Editorial Board Member of *International Journal of Orthopaedics*. He also acts as journal reviewer for Arch Orthop Trauma Surg, BMC Musculeskeletal Disorders, BMT Biomed Eng, Clin Biomech, eCM Journal, Engineering Failure Analysis, J Forensic Biomech, J Orthop Res.

Stephan Zeiter is the representative to the AOVET R&D Commission from ARI and a member of the education committee of the Swiss Laboratory Animal Science Association. He has been a member of the scientific committee of the combined ESLAV/ ECLAM meeting 2014 in Athens. He has reviewed for the following journals: eCM, Acta Biomaterialia, Journal of Biomedical Materials Research Part A, Journal of Tissue Engineering and Regenerative Medicine as well as Laboratory Animals.

Fintan Moriarty was invited onto the board of associate editors of the journal of orthopaedic trauma for four years. He is is a member of the eCM Journal International Review Panel.

David Eglin is a member of the Executive Committee of the Swiss Society for Biomaterials and regenerative Medicine and the Tissue Engineering and Regenerative Medicine International Society (TERMIS) EU Chapter. He is also a member of the International Editorial Board of Journal of Orthopaedic Translation (JOT) and a member of the eCM International Review Panel.

Sibylle Grad is a member of the eCM Journal International Review Panel 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 Orthopaedic Research Society (ORS). In addition she is a member of the ORS Program Committee. She is an Associate Faculty Member of the Faculty of 1000 Medicine.

Martin Stoddart is the representative to the AOCMF R&D Commission from ARI. He is a Scientific Editor for eCM Journal, Journal Editor for Tissue Engineering Parts A, B, C, an editor of BioMed Research International Orthopedics and a member of the Review Editorial Board of Frontiers in Craniofacial Biology. He is also the Co-ordinator and organiser of the yearly eCM conference and a webeditor of eCM. He is a member of the Basic Science Education Committee (BSEC) of the Orthopaedic Research Society (ORS). He is an Associate Faculty Member of the Faculty of 1000 Medicine. He was a member of the ORS New Investigator Reccognition Award Committee at the annual meeting in New Orleans.

Sophie Verrier is a member of the eCM International Review Panel and a co-organizer of the yearly eCM conference. She also acts as a reviewer for research journals such as Tissue Engineering (part A, B and C), Stem Cell Research, Bone, Injury, Journal of Orthopedic Research and she evaluates research project applications for funding (INSERM, France).

Daniel Arens is a member of the board of directors of the Swiss Association of Veterinarians in Industry and Research.

Marietta Herrmann is a member of the eCM International Review Panel.

Hansrudi Noser is a lecturer at the University of Zürich, Switzerland and acts as a member of the high school graduation committee of Liechtenstein.

Marianna Peroglio is a member of the eCM International Review Panel.

Vincent Stadelmann lectures at The Swiss Institute of Technology Lausanne.

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.

6 Good News

Positions

Dr Martin Stoddart has been appointed to serve a four year term as a Journal Editor for Tissue Engineering Parts A, B, C starting 1st Janurary 2014.

Dr Sibylle Grad was appointed to serve a two year term in the ORS Program Committee.

Dr David Eglin has been elected as member of the Executive Committee of the European Chapter of the Tissue engineering and Regenerative Medicine Society (TERMIS) for 3 years.

Dr med vet Stephan Zeiter was appointed as member of the education committee of the European College of Laboratory Animal Medicine (ECLAM).

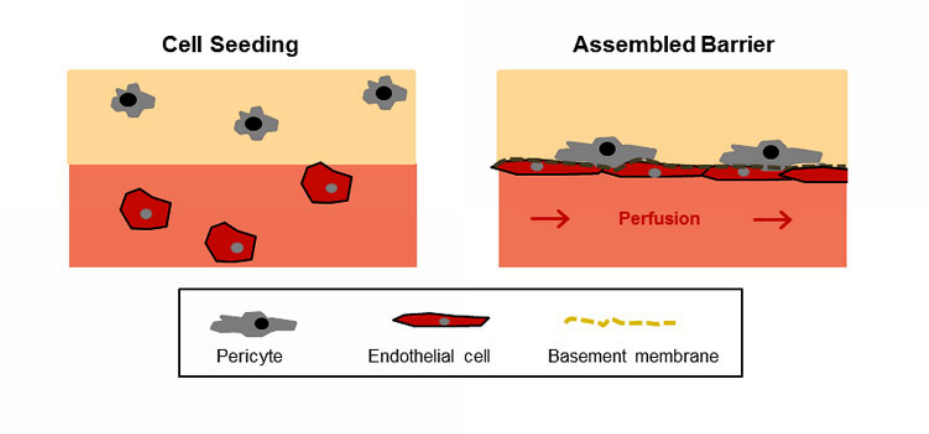
In 2014, Professor Geoff Richards was elected vice president of Science City Davos (previously executive committee) and a member of International Combined Orthopaedic Research Societies (ICORS) Steering Committee.

Extramural funding

3R Grant:

Dr Marietta Herrmann, in collaboration with Dr Laurent Barbe from CSEM, Landquart, Switzerland, has been awarded 3R funding for a project entitled 'An *in-vitro* micro-vascular model mimicking the endothelial barrier' (part of the Perivasc project, see page 84). The project will investigate cell-cell interactions and cell migration of endothelial cells and pericytes in their physiological context. Both cell types are important players in the process of bone regeneration supporting neovascularization and new bone formation at the same time. The novel microfluidic culture system will address major parameters of the 3D environment of endothelial cells and pericytes. Thus, the model will provide new insight on phenotypic and functional characteristics of pericytes, which are thought to be a physiological reservoir of mesenchymal stem cells.

The model is built of two compartments (i) a hydrogel with encapsulated pericytes mimicking the perivascular tissue (beige) and (ii) a perfused microchannel containing endothelial cells (light red). In the assembled barrier endothelial cells cover the micro-channel, produce components of the basement membrane and prompted pericytes to migrate towards the endothelial layer.



The 3R Foundation is a cooperative institution with members of the public and pharmaceutical industry involved. It is dedicated to support alternative research methods following the principles to reduce, refine and replace animal experimentation.

Dr Martin Stoddart, in collaboration with Prof Yubo Fan of the Beihang University, Beijing, has been awarded a Sino Swiss Science and Technology cooperation Exchange Grant. Effects of mechanical load on Chondrogenic differentiation capacity of bone marrow-derived mesenchymal stem cells in hydrogels. CHF 30'000 for one year.

Preclinical Services have successfully applied with a project to the AO Foundation strategy fund aiming to strengthen preclinical research through three approaches: generation of a more uniform, globally available AO sheep; education and training, and Good Laboratory Practice (GLP) accreditation. Preclinical research has made important contributions throughout AO history and it is important to continue to raise standards for how preclinical research is done. This project will help to decrease the burden on animals used while maximizing research output in the future.

Marianna Peroglio received the AO Spine Research Network Exchange Award, which enabled her to visit Prof. Lisbet Haglund laboratory at Montreal General Hospital in Canada. During her one month stay, a protocol for the application of thermoreversible hydrogel in human discs was developed and training was conducted about different analytical techniques for the characterization of proteoglycans in intervertebral disc tissue.

The ARI is proud to have been awarded the TERMIS2017 annual meeting, which they will organize in Davos.

Conference Awards

Dr Markus Windolf was awarded the best oral presentation award (1st price) at the 15th ECTES & 2nd World Trauma Congress in Frankfurt, Germany, 24-27 May (2014): D.Widmer, L.Hofmann-Fliri, E.Zweifel, M.Blankstein, B.Gueorguiev-Rüegg, M.Blauth, M.Windolf. Prophylactic reinforcement of the porotic proximal femur. A systematic approach to find a valid solution.

Best poster award: K.Klos, S.Rausch, U.Wolf, M.Windolf, B.Gueorguiev, Biomechanischer Vergleich zwischen einer winkelstabilen Platten- und einer zement- augmentierten Schraubenosteosynthese zur Versorgung von Kalk-aneusfrakturen, 20. Jahrestagung D.A.F. (Deutsche Assozation für Fuss- und Sprunggelenk e.V.), Münster, Germany, 28-29 March (2014).

M.Ernst, R.Shanmugam, D.Wahl, M.Windolf, R.G.Richards, B.Gueorguiev, *Is angle-stable locked lateral plating biomechanically superior to conventional plate fixation in the proximal phalanx?*, 7th World Congress of Biomechanics (WCB), Boston, USA, 6-11 July (2014)
was nominated for the ESB Clinical Biomechanics Award at the WCB together with 3 other abstracts.
http://www.esbiomech.org/?page_id=42

Florian Schmidutz and coauthors won the 2nd Prize in the poster competition for their poster about Bone integration in Hemi-Resurfacing Shoulder Prosthesis ("Oberflächenprothesen führen auch an der Schulter zu einem Stress-Shielding und Verlust von Knochensubstanz") at the endoprothetic congress ("Endoprothetik 2014") in Berlin.

Claudia Loebel, PhD student at the ARI, is the successful recipient of the Swiss Society for Biomaterials and Regenerative Medicine poster award of the 2014 society meeting with her poster entitled "Precise tailoring of hyaluronan-tyramine hydrogels using DMTMM conjugation". Supervisors Prof Marcy Zenobi-Wong (ETH) and Dr David Eglin (ARI).

Claudia Loebel won Best Oral Award for her presentation "A mechanical tunable Hyaluronan hydrogel for endochondral bone tissue engineering", at the EORS 2014, Nantes, France.

Claudia Loebel from ARI presents at EORS 2014 and was awarded the prize of best overall presentation

The paper "Effekt einer Kombination von Biomaterialien und Zellen zur Erhaltung der Bandscheibe nach Annulotomie" by L. Benneker, Z. Li, T. Pirvu, S. Blanquer, D. Grijpma, M. Alini, D. Eglin, and S. Grad was selected to be presented in the "Best of" session of the 9th German Spine Conference 2014 in Leipzig.

Marina Sabaté Bresco won the Agean Conference Travel Award (USD 1000) for best poster presentation at the 5th International Conference on Osteoimmunology, Kos, Greece (15th-20th June 2014).

Marina Sabaté Bresco won an award for best oral presentation in Clinical Sciences at the Graubünden forscht 2014: Young Scientists in Contest, Davos. Switzerland (10th-11th September 2014).

Organized Student Courses / Meetings

ORS Research Interest Group: “Translation of Cell-Based Therapies“:
ARI actively contributed to the 2014 ORS annual meeting in New Orleans, by hosting a research interest group addressing the challenges facing the translation of cell-based therapies in orthopaedics. Organised by Jennifer Bara & Marietta Herrmann and chaired by Geoff Richards, the meeting was very successful, attracting an international group of scientists, surgeons and industry representatives. The meeting included presentations from experienced clinicians James Richardson (RJAH Orthopaedic Hospital, UK) and George Muschler (Cleveland Clinic, US) together with scientific and industry expert, Anthony Ratcliffe (Synthasome, US). Translation proved to be a pivotal theme of the conference.

Dr Sibylle Grad was co-organizer of the Spine Research Interest Group session at the Orthopedic Research Society 60th Anniversary annual meeting in New Orleans. The expert discussions of this session on "Nucleus pulposus phenotype" resulted in a position paper published in the Journal of Orthopedic Research:
Risbud MV, Schoepflin ZR, Mwale F, Kandel RA, Grad S, Iatridis JC, Sakai D, Hoyland JA. Defining the Phenotype of Young Healthy Nucleus Pulposus Cells: Recommendations of the Spine Research Interest Group at the 2014 Annual ORS Meeting. J Orthop Res. 2014 Nov 20. doi: 10.1002/jor.22789. [Epub ahead of print]

Dr Sibylle Grad and Dr James Iatridis successfully also organized a workshop at the same conference entitled "Cell and Tissue Engineering for Annulus Fibrosus Repair: AO Foundation Collaborative Research Project" involved all partners of the Collaborative Research Program Annulus Fibrosus Repair, including lectures given by Dr Stephen Ferguson, Dr Abhay Pandit, Dr Daisuke Sakai and Dr Dirk Grijpma.

AOTrauma Course in Fracture Treatment and Musculoskeletal Repair for Engineering Students from ETHZ and ZHAW

On April 25-26, 2014, approximately 40 engineering students and supervisors from the Swiss Federal Institute of Technology Zürich (ETHZ) and the University of Applied Sciences Winterthur (ZHAW) met at the AO Center Davos to join the annual AOTrauma course. The goal of this popular two-day course, organized by Dr Sibylle Grad and Christoph Sprecher from the ARI under Director R Geoff Richards, is to provide insight into both the principles of fracture treatment and recent activities within the ARI.

After some statistical insight into the types and frequency of winter sports injuries, PD Dr Jan Benthien from the Davos hospital provided a general overview of the principal fracture treatment methods, which served as an optimal introduction to the topic. In the following hands-on osteosynthesis training, the accurate application of metal implants for fracture treatment was explained and demonstrated by a team of experts led by Dr Raphael Jenni and additional qualified surgeons from the cantonal hospitals of Chur and St Gallen. Operating on artificial bone models, the future engineers created and treated different fractures using typical surgical instruments and devices such as plates, screws, nails and fixators. These osteosynthesis exercises proved to be a highlight of the AOTrauma course, combining surgeon's expertise, biomechanical understanding and manual skills. Proud of their achievement, many students took photographs of their fixed bone models.

The hands-on osteosynthesis training implies concentrated work and lively discussions.

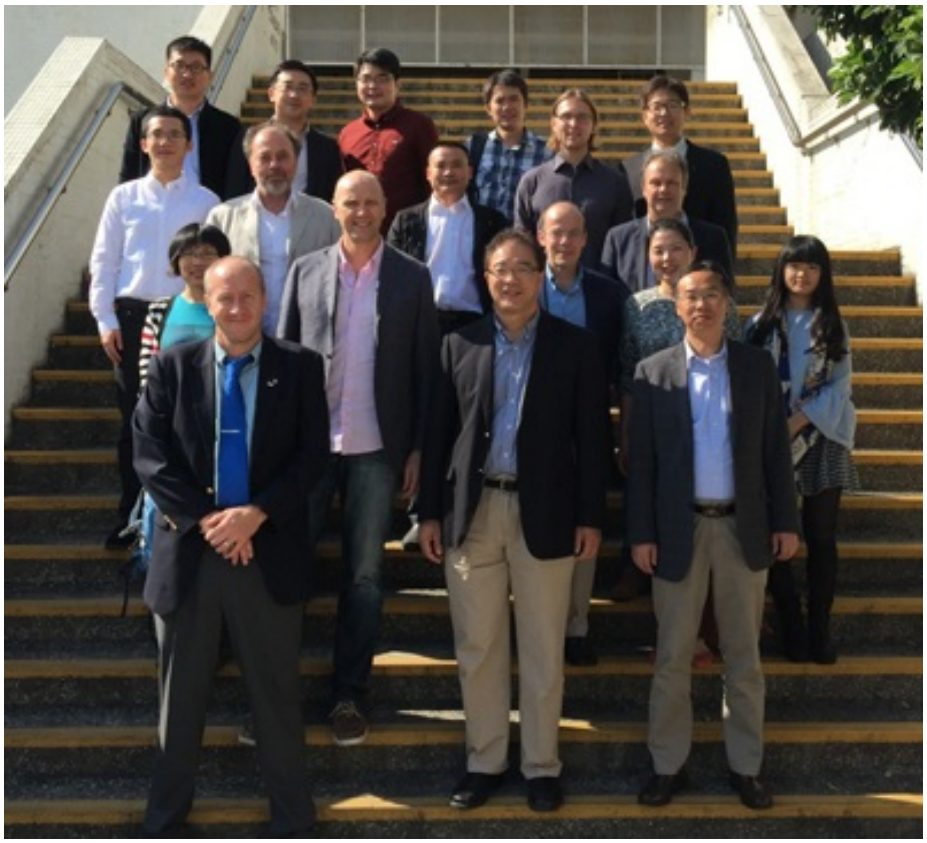
The second part of the course consisted of guided tours through the ARI laboratories and instructive lectures conducted by ARI scientists. The aim was to provide an overview of ARI research activities in general and current research projects in particular. Topics included: *in vivo* models in orthopedic research, bioreactors for cell and tissue culture, infection prevention and treatment, and bioresorbable implants, among others. The ARI principle that every project aims at solving a relevant clinical problem was communicated to the participants, and the importance of interdisciplinary teamwork was emphasized. Stations of the "skills training lab" were also integrated into the ARI tour. Besides the osteosynthesis training, this offered participants' an opportunity to test their manual skills; while the fundamental biomechanical and biological mechanisms were demonstrated and explained by experienced ARI employees.

The course also demonstrated the essential connections between biomedical and technical sciences. Basic understanding in biology and medicine is of particular importance to engineers with a focus on medical technology. The participating students were highly motivated and provided favorable feedback suggesting that some of them may pursue a career in biomedical engineering. The superviors, as each year, were very happy with the course.

The third official joint Chinese-European RAPIDOS meeting took place in Hong Kong, in November 2014, almost one year after the kick-off meeting held in Beijing.

The RAPIDOS Partners meeting at the Prince of Wales Hospital in Hong Kong.

On the 15th of November 2014, the RAPIDOS partners were guests of the Prof Ling Qin, who welcomed the team at the Prince of Wales Hospital, the Chinese University of Hong Kong. The day started with the scientific reports from all the RAPIDOS partners. Prof Tang from SJTU presented the last studies on the antimicrobial activity of the magnesium containing scaffold developed at SIAT. This was followed with the very comprehensive report of Dr Wang from 301 Hospital on microstructure and mechanical properties of femoral head with osteonecrosis, which is one of the clinical problem targeted by the RAPIDOS consortium. The SIAT team gave several reports on the progress in the low temperature rapid prototyping fabrication of scaffolds, their osteogenicity and antibacterials activities and finally recent findings on the biological action of icariin. Mike Geven, PhD student at UT, reported the first successful creation of consortium shaped composite implant using Stereolithography, while Xi Zhang, PhD student at QMUL, reported the incorporation of icariin into electrospun-fibers intended to be used at drug delivery system and reinforcement material. Finally, Dr Yuan presented a preclinical study showing the enhanced osteoinduction of icariin loaded calcium phosphate particles.



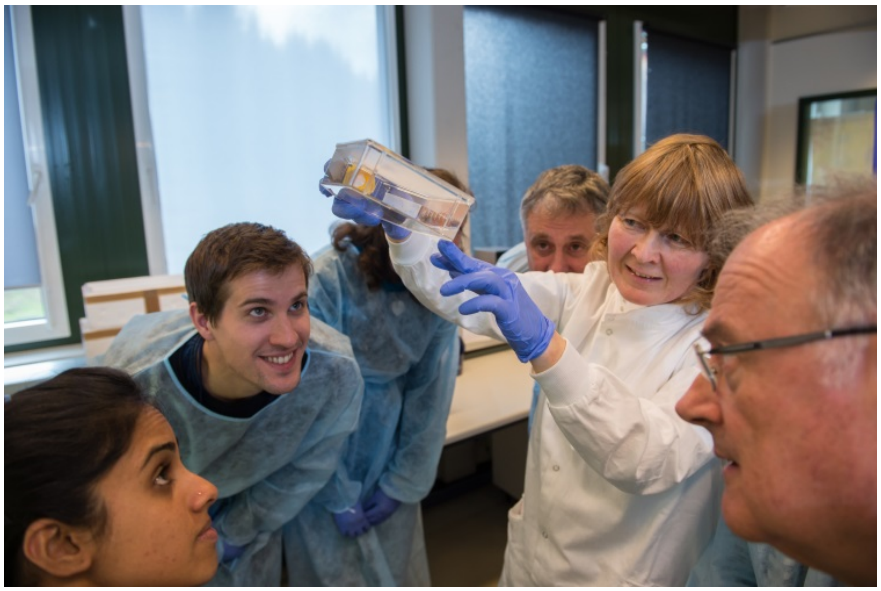
Biobone workshop

The workshop was organized by the ARI from April 27-30, 2014 as part of the European project "Biobone" (www.bioboneitn.eu). The project Biobone, which stands for bioceramics for bone repair, is funded by the initial training network (ITN) Marie Curie Actions of the European Research Program FP7. The goal of this workshop was to give students with an engineering background the basis to understand the biological of biomaterials. The workshop brought together researchers from all over Europe from fields as diverse as materials science and engineering, orthopaedics, biology and chemistry.

The balance of lectures and practical exercises made this workshop special in the words of the participants and the students could directly apply osteosynthesis principles to synthetic bones and follow cell biology concepts through demonstrations in cell culture laboratories. Prof R Geoff Richards gave a very inspiring talk on the influence of implant surface in trauma and additional lectures were covered by members of the ARI. Renowned invited speakers - Dr Rainer Detsch from the University of Erlangen-Nuremberg (Germany), Dr Marcy Zenobi-Wong from ETH Zürich (Switzerland) and Dr Daniel Hartmann from University of Lyon (France) - shared their views on bone cells, stem cell differentiation and bone extracellular matrix.

Participants at the BioBone workshop on "Cell-material interactions" in front of the AO Center in Davos.
Prof Geoff Richards, Director of ARI (stands most left), Prof Eduardo Saiz, Coordinator of the BioBone-ITN FP7 project (second row, sixth from right), Dr Marianna Peroglio, organizer of the workshop (second row, fifth from right), Prof Mauro Alini, Biobone project coordinator at ARI (first row, second from left).

Clinical and industrial perspectives were essential parts of the workshop. PD Dr Jan Benthien, specialist in Orthopaedics and Trauma Surgery at Davos Hospital, introduced the participants to the principles of osteosynthesis with lectures and practical exercises. Dr Alan Porporati (Ceramtec, Germany) gave a comprehensive lecture on the evolution of bioceramics for hip implants and an overview of the current applications. The workshop was organized by Dr Marianna Peroglio, Christoph Sprecher and Daniela Schraner from the ARI. Ana-Maria Stanciuc and Elena Littmann, respectively PhD student at ARI and visiting PhD student from Imperial College London in the Biobone project, took an active part in the workshop by leading the young scientist events.



Dr Ursula Menzel from the ARI shows cells in a cell culture flask to the Biobone workshop participants.

Successful 20th Swiss Society for Biomaterials & Regenerative Medicine Meeting (SSB+RM)
The meeting, hosted by the osteosynthesis devices company Medartis AG in Basel (CH) on May 7-8, 2014, was an opportunity for ARI scientists to present their work to their peers in Switzerland.

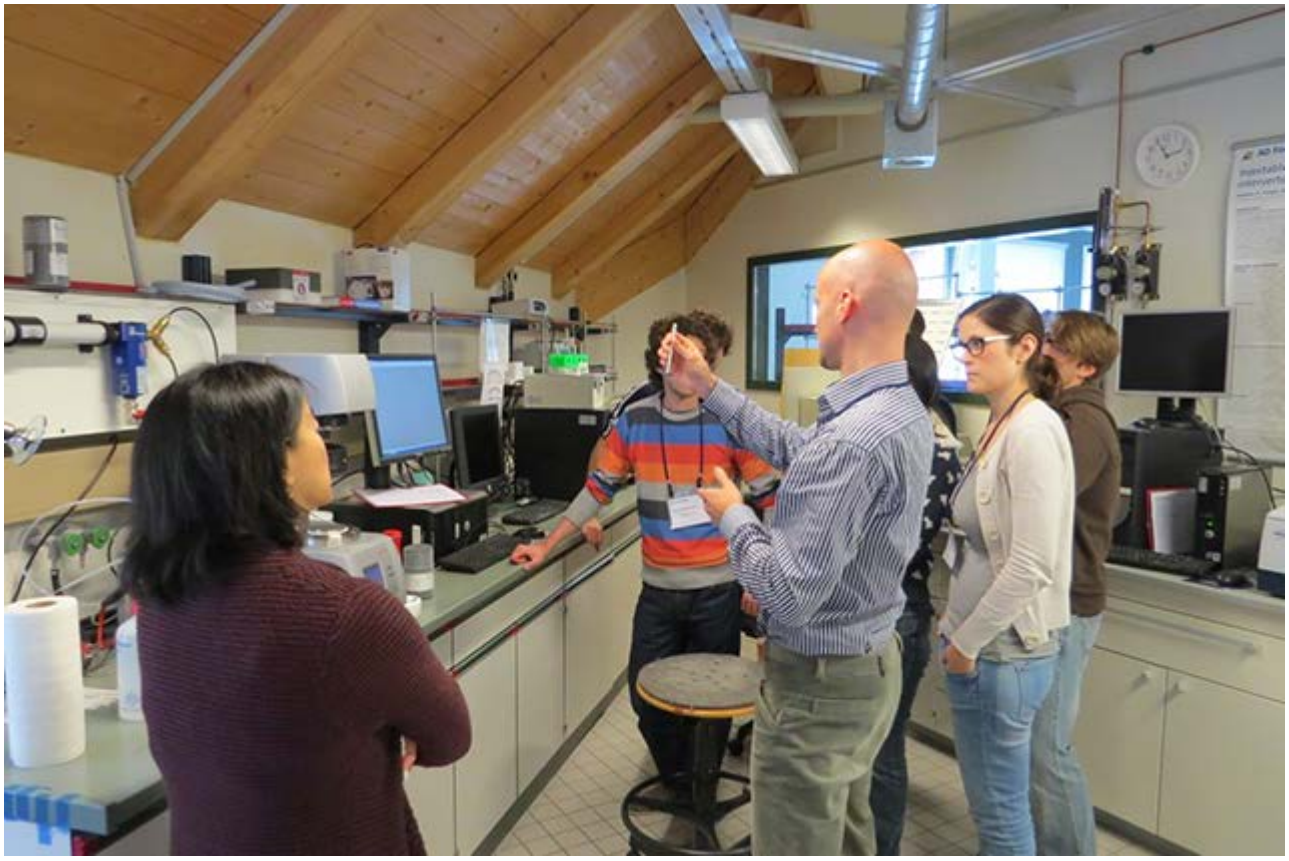
Young scientists attending the Swiss Society for Biomaterials and Regenerative Medicine (SSB+RM) meeting 2014 in front of the Medartis Building in Basel.

The 20th edition 2014 special topic was on ions and molecule release from biomaterials with several keynote speakers and notably Dr Kathrin Scherer giving a compromised overview of metal sensitization in dermatologic patients with metal implants from a clinical point of view. ARI was well represented by the oral and poster presentations of three scientists of the Musculoskeletal Research Program. The highlight of the day was the best poster presentation award given to Claudia Loebel from ARI for her work on the precise tailoring of hyaluronan-tyramine hydrogels for cell therapy applications.

CERL/ARI 2nd Joint Meeting
On May 22-23, 2014, the second joint meeting between the ARI and the Cartilage Engineering and Regenerative Medicine (CERL) Research Group at ETH Zürich (lead by Prof Marcy Zenobi-Wong) took place in Davos (CH). The event was organized by Claudia Loebel and Dr David Eglin of the Musculoskeletal Regeneration Program.

Group photo of the participants of the 2nd CERL/ARI Joint Meeting with Prof Marcy Zenobi-Wong (first row, third from right) and Dr David Eglin (most left).

The aim of this joint meeting is to bring together the two research groups investigating musculoskeletal repair, tissue engineering and regenerative medicine solutions in order to improve understanding and develop innovative collaborative strategies.
One emphasis of the meeting was to actively encourage the communication and collaboration of young scientists and members of both groups. A series of presentations on research projects from both groups preceded an active and inspiring discussion which continued until late evening. A workshop on rheology, an important tool for the biomaterials developed in both laboratories, enriched the meeting with lectures and practical demonstrations. Matteo D´Este from ARI and Mischa Mueller from ETH Zurich introduced students and scientists to the basics and the applications of rheological measurements.



Matteo D´Este, Research Scientist at ARI, demonstrating the practical use of rheological instrument to the meeting participants.

AO Research Institute (ARI) Annual CRP Meetings

The Annual Collaborative Research Project (CRP) Meetings were held at the AO Foundation headquarters in Davos (CH) from June 19-20, 2014. The meetings began with a welcome address and a short introduction on the goals of the six year programs from Sandra Steiner (ARI). This was followed by progress reports from the research partners and post-presentation discussions.

Peter Roughley and Mats Brittberg in a lively conversation.

CRP Acute Cartilage Injury (ACI) Session
The CRP ACI session was moderated by Prof Mats Brittberg (Kungsbacka Hospital, SE) and Prof Peter Roughley (Shriners Hospital for Children, CA) who together with Prof Brian Johnstone (Oregon Health Science University, US) are the expert members of the CRP ACI Committee.

Prof Farshid Guilak (Duke University, US) started with the progress update on the multifunctional 3D woven scaffolds for osteochondral repair. Following interesting discussions, David Eglin (ARI, CH) gave an update on his elastomeric scaffolds and on controlling the degradation of hyaluronan hydrogel for cartilage repair. Then, prior to the coffee break, Carlos Semino (Ramon Llull University, ES) spoke about bioactive and biomimetic scaffolds for cartilage regeneration.

The session continued with the report on the gene transfer of chondrogenic factors combined with mechanical loading of MSCs to enhance articular cartilage repair, by Prof Henning Madry and Prof Magali Cucchiarini (University of Saarland, DE). After that, Martin Stoddart (ARI, CH) gave his update on in vitro recapitulation of the in vivo stem cell niche and on the effect of mechanical stimulation and biological factors on human mesenchymal stem cell chondrogenesis and hypertrophy. Prof Rob Mauck and Prof George Dodge (University of Pennsylvania, US) then spoke about a novel platform for optimizing material design for cartilage tissue engineering and enabling drug discovery for cartilage restoration. Prof Peter Roughley and Prof Mats Brittberg once again thanked the presenters and highlighted the issues that would require further in depth discussions at the CRP ACI breakout session the next day. The aim of this program is to develop a single step repair technique for acute cartilage injury that can be used in the operating room.

CRP Annulus Fibrosus Rupture (AFR) Session
In the afternoon the CRP AFR session was moderated by Prof Gunnar Andersson (Rush University, US) and Prof Peter Roughley (Shriners Hospital for Children, CA) who together with Prof Brigitte Vollmar (University of Rostock, DE) are the expert members of the CRP AFR Committee.

The session commenced with a presentation by Prof Abhay Pandit (National University of Ireland, IE) who reported on the use of hollow spheres for bioactive molecule delivery. This was followed by Prof James Iatridis (Mount Sinai School of Medicine, US) report on adhesive biomaterial and novel mechanical analyses to enhance annulus fibrosus repair. Prof Dirk Grijpma (University of Twente, NL) then took the podium to present his update on the preparation of designed flexible biodegradable scaffolds by stereo lithography for use in intervertebral disk repair.

In the latter part of the afternoon, David Eglin reported on the development of a fibrous polymeric patch for annulus fibrosus repair. This was followed by an update on the characterization of annulus fibrosus cells and the identification of a suitable cell source for efficient tissue regeneration by Prof Daisuke Sakai (Tokai University, JP). After interesting discussions, Sibylle Grad (ARI, CH) spoke on the elucidation of pathways involved in intervertebral disc failure by gene expression profiling and protein assessment. Prof Stephen Ferguson (ETH Zurich, CH) and Lorin Benneker (University of Bern, CH) presented the final report for the day on the determination of target morphological and biomechanical properties for an annulus repair implant.

This session was concluded with the remark that the CRP breakout sessions on the following morning would be important for discussions on the preclinical proof of concept studies to be planned for the final funding period April 2015 to December 2016.
CRP ACI and AFR Parallel Breakout Sessions

The CRP breakout sessions took place at the Hotel Grischa in Davos. These sessions are crucial for the research partners as they provide them with the opportunity for face-to-face discussions with the program committee experts. In these sessions the consortia achievements are reviewed, further collaborations and interactions are established and the research plans for the following year are discussed and finalized. By December 2016, each CRP team will need to have completed a pre-clinical proof of concept study with its consortium developed repair device.

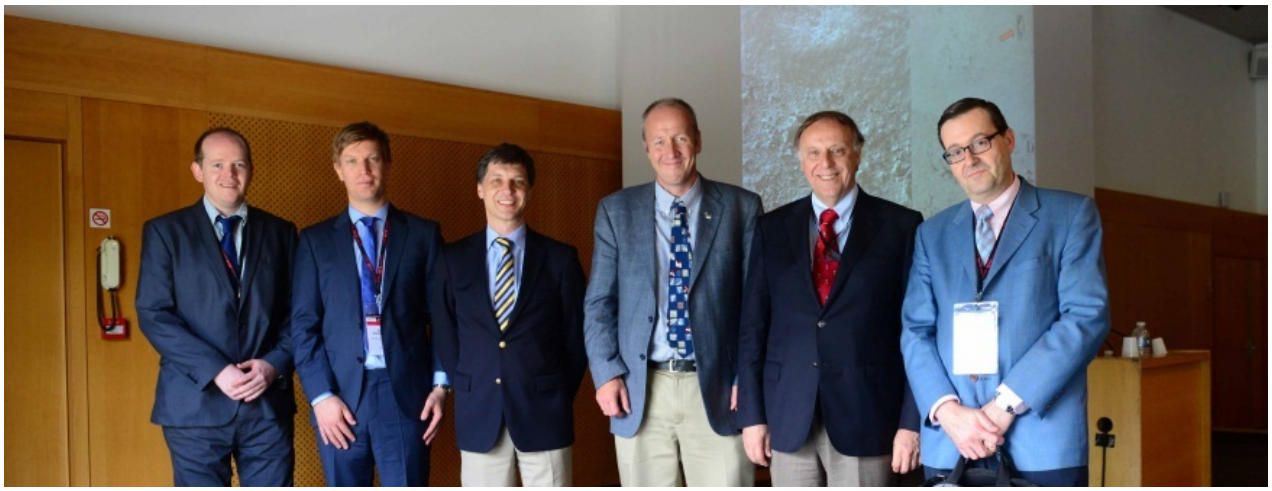
Conclusions and outlook

The overall feedback on the Annual CRP Meetings 2014 was very positive. The ample discussion time that was scheduled after the progress presentations and at the breakout sessions were extremely valuable and gave many new insights to the participants. There was also ample opportunity for networking between researchers and clinicians which produced many new ideas for ways forward.

ACI and AFR Partners in discussions

AO symposium at EORS

On July 2–4, 2014 the Annual Meeting of the European Orthopaedic Research Society (EORS) was held in Nantes (FR). This twenty-second meeting of the EORS was a great success, bringing together over 300 delegates from 43 countries. The mission of EORS is to promote research and development in orthopedic surgery and related sciences in Europe through interdisciplinary coordination, exchange of scientific and technical experience, and education. The AO Foundation was prominent at this year's meeting, with a dedicated symposium covering AOTrauma's CPP Bone Infection and numerous oral and poster presentations from members of the AO Research Institute Davos (ARI).



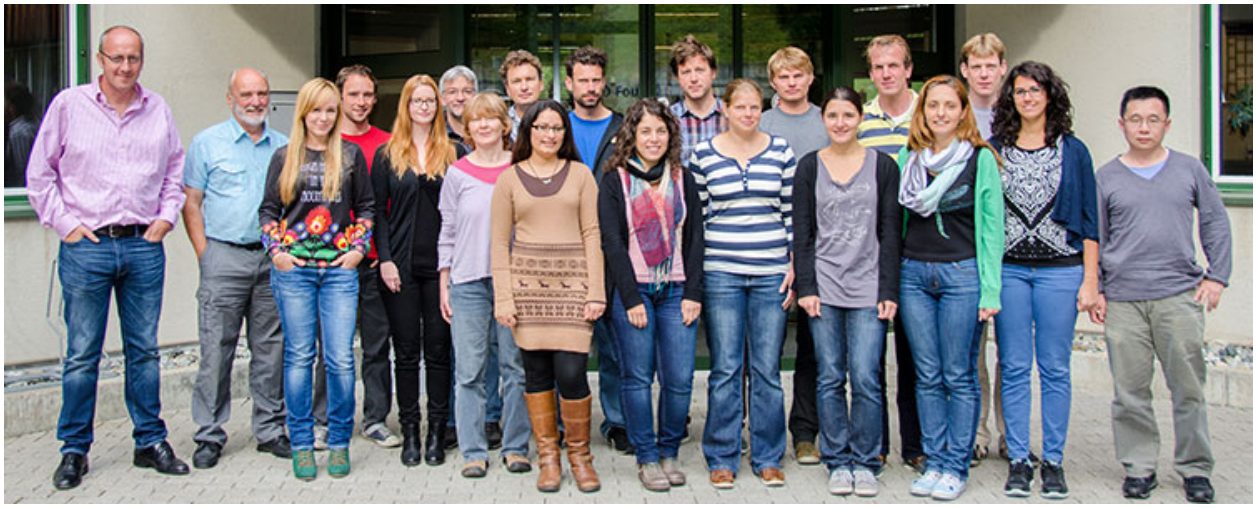
Attending the AOTrauma CPP Bone Infection symposium at EORS 2014 in Nantes (L-R) Fintan Moriarty (ARI), Mario Morgenstern (BGU Murnau, DE), Volker Alt (University of Giessen, DE), Geoff Richards, (ARI), Pierre Hoffmeier (University Hospital Geneva, CH), and Enrique Gómez-Barrena, EORS President (University of Madrid, ES).

On July 4, 2014 the AO Foundation hosted a symposium entitled Clinical Priority Program on Bone Infection. ARI director, Prof R Geoff Richards (Davos, CH) and Prof Pierre Hoffmeyer (Geneva, CH) were the session chairs, which showcased the latest achievements of the AOTrauma CPP Bone Infection. The opening presentation was by Prof Volker Alt (Giessen, DE), on the clinical problem of bone infection faced in daily surgical practice, and presented an overview of the CPP, with a focus on clinical research. The ongoing Bone Infection registry project was described in detail and the contribution of the AO network of clinical partners was highlighted. Dr Fintan Moriarty from ARI provided an update on preclinical studies in ARI in the CPP. Cited projects included the development of murine models to better understand the role of fracture stability on infection risk, and also a project on in vivo monitoring of infection-induced osteolysis at high resolution. Dr Mario Morgenstern (Murnau, DE) gave an update on the OrthoNose project, which was run at the AO Davos Courses 2013. Upon completion of his presentation, Dr Morgenstern fielded many questions from the audience, indicating the high interest and relevance of his work to the assembled audience. Prof Hoffmeyer drew the symposium to a close with a keynote address summarizing the highlights of a career of research and clinical experience in the problem and developments of bone infection.

Mario Morgenstern and Geoff Richards performing a nasal swab of "the Great Elephant", a creation inspired by the works of French novelist Jules Verne at the EORS 2014 conference dinner.

Scanning Electron Microscopy Course (SEM)

A two-day course on Scanning Electron Microscopy (SEM) took place at the ARI on September 15–16, 2014. Nineteen participants from ARI and collaborative institutions such as the Swiss Institute of Allergy and Asthma Research in Davos (SIAF), the University of Fribourg and the University Ramon Llull, Barcelona, Spain, were able to learn from the experienced lecturers. The course was given by Prof Dr Geoff Richards in collaboration with his University mentor, Dr Iolo ap Gwynn of the University of Wales, Aberystwyth, Wales. They provided the attendees with entertaining and very intensive lectures describing the physical basics of SEM, the methodological approach to SEM sample preparation and analysis, and showed many examples demonstrating the importance of specimen preparation and imaging parameters on the produced images quality. Furthermore, questions on reported results and ideas could be exchanged.



SEM Course 2014 participants with lecturer Prof R Geoff Richards (left) and Dr Iolo ap Gwynn (2nd left) in front of the AO Center in Davos.

Dr Iolo ap Gwynn during his presentation in the lecture room.

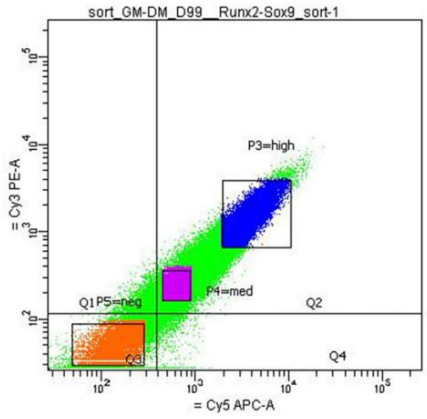
General
Daniel Arens has been accredited for the European College of Laboratory Animal Medicine (ECLAM) examination - he is now ECLAM eligible.

Marco Bruderer successfully defended his PhD thesis entitled "Transcription factor-specific reporter constructs – basis for the functional identification and isolation of subpopulations of human mesenchymal stem cells and tool for live cell approaches". ETH Zürich. Supervisors Prof Viola Vogel (ETH) and Dr Martin Stoddart (ARI).

Ewa Czekańska successfully defended her PhD thesis entitled "In vitro cell and culture models for osteoblasts and their progenitors" at the Cardiff University in Wales, UK. Supervisors: Dr Martin Stoddart (ARI), Dr Jessica Hayes, Regenerative Medicine Institute, NUI Galway, Ireland & Dr Jim Ralphs, School of Biosciences, Cardiff University, Wales, UK.

Markus Windolf successfully earned his PhD (Dr. biol. hum.) from the University of Ulm, Germany on July 17, 2014. His thesis "Fracture fixation in osteoporotic bone" summarizes a part of the experimental work performed in the ARI over the past 10 years in 20 selected peer-reviewed publications. The aim of the work was to provide surgeons with biomechanical evidence for application of surgical concepts such as implant augmentation in the elderly population to encounter the problem of fixation failure in reduced bone mass. Prof Anita Ignatius, head of the Institute of Orthopaedic Research and Biomechanics in Ulm as well as Markus' supervisor Prof Lutz Dürselen kindly provided the opportunity for this doctorate which, again, reinforces the long-lasting friendship between both research groups.

Work which is being performed at the ARI was chosen for the highly successful series of Science/AAAOS webinars. On August 27, 2014 Dr Martin Stoddart presented the webinar on work being done at the ARI on methods to investigate mRNA expression within cells. More specifically, he highlighted a recent ARI publication in Tissue Engineering Part A, which established the ratio of Runx2/Sox9 mRNA expression as an early marker of mesenchymal stem cell differentiation into bone or cartilage. This, combined with live cell sorting, can be used to improve isolation and characterisation of cell populations for the repair of bone and cartilage. (http://webinar.sciencemag.org/webinar/archive/techniques-rna-detection)



Cell sort plot showing expression of Sox9 (for cartilage) and Runx2 (for bone) expression based on fluorescence intensity.

ARI Research highlighted in Materials Today:
Recent published collaborative work between the ARI and ETH-Zurich on new bioprinting technology (Matti Kesti, Michael Müller, Jana Becher, Matthias Schnabelrauch, Matteo D'Este, David Eglin, Marcy Zenobi-Wong, A versatile bioink for three-dimensional printing of cellular scaffolds based on thermally and photo-triggered tandem gelation, Acta Biomaterialia, Available online September 23, 2014) was highlighted in Materials Today, an open access journal which reports the latest trends and advances to all the materials community worldwide.
(http://www.materialstoday.com/biomaterials/news/versatile-bioink-prints-tissue-scaffolds-in-3d/)

David Eglin was a guest scientist for one month in July 2014 at the Orthopaedics Research Laboratory at Montreal General Hospital (McGill University), Montreal, Canada (Prof Lisbet Haglund).

On November 27, 2014 Dr An Sermon, a trauma surgeon at University Hospital Leuven and former medical research fellow at the ARI, successfully defended her PhD thesis to obtain the degree of Doctor in Biomedical Sciences from the Catholic University of Leuven. Her thesis title was *Addressing the challenge of hip fracture fixation and prevention in old age – Preclinical and clinical studies assessing the osteoporotic femoral head*. The preclinical part of the research presented in her thesis was carried out at the ARI, under the directorship of Prof R Geoff Richards within the program of Dr Boyko Gueorguiev.

The public presentation was held in the beautiful and ancient Promotion room located in the University Hall. This is the oldest building of the Catholic University of Leuven in Belgium which was founded in 1425 by Pope Martin V. KU Leuven is the oldest surviving Catholic university in the world and the oldest university in the low countries of Europe. An's defense took place in a traditional way with the eight members of the jury (who agreed unanimously to pass her), including Prof Richards (a co-promoter of Dr Sermon) dressed in the Faculty of Medicine's black and pink robes. Dr Sermon presented on the meta-analysis of the long-term effects of clinical pathways for older hip fracture patients and the development, implementation and the evaluation of a traumatologic-geriatric fracture prevention program. In the second part of her talk she presented three biomechanical studies that she performed at the ARI between 2009 and 2011. All three studies were dealing with the concept of implant augmentation and substantially contributed to the establishment of this technique in clinics. Dr Sermon worked very closely each time she was at ARI with many of the team of Dr Gueorguiev's, especially with Ladina Fliri-Hoffman who both attended the defense. After the thirty minute public lecture and one hour interrogation by the jury members, the jury left for a short discussion before returning to the hall to the candidate where Dr Sermon was officially awarded the degree of Doctor in Biomedical Sciences.

New Facilities

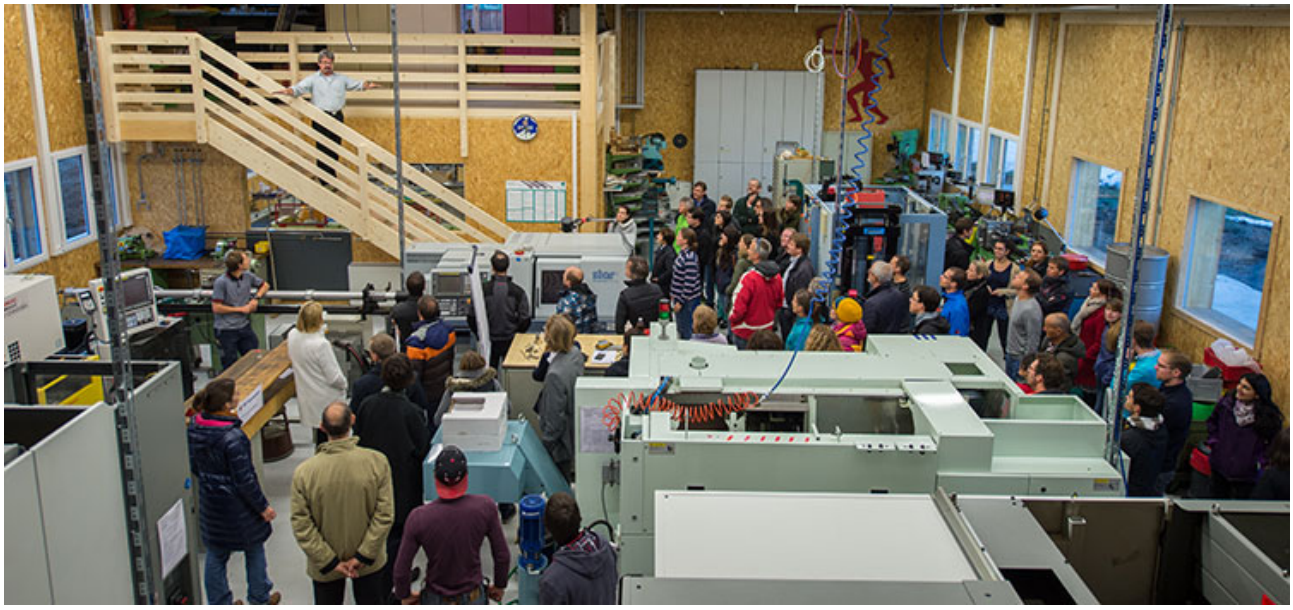
In the middle of 2013 the AO decided that it should construct a dedicated building on the grounds of the AO Center to house the ARI Prototype Workshop - which up until this point had been housed in nearby rented accommodation. So on October 29, 2014 the ribbon was cut on a new purpose-built workshop at the AO Foundation headquarters in Davos.

Set up in 1992 the workshop produced prototypes of new implants, surgical instruments and innovative high-quality tools for the ARI in close collaboration with the network of AO surgeons and AO's industrial partners. The workshop also worked on projects with AO spin-off companies (Synbone AG, Malans and RISystem AG, Davos).

Before the building project began it was decided that the architecture of the workshop should reflect that of the AO's main building. Preparation work started in autumn 2013, the main phase of construction in April 2014 and the project was completed in October 2014. ARI staff members Erich Zweifel (Workshop Manager) and Rolf Keller (Financial Controller of ARI) managed the building construction and relocation work. The new workshop was operational, as planned, on November 1, 2014.

Although it is a smaller than the old rented building, the new building is much more convenient and spacious to work in because it has been specifically designed for our needs. It is much brighter and, thanks to the double height of the building, the atmosphere is much more comfortable for the team. The motivation to move the workshop was that this would save long-term running costs and that by having our own purpose built facility at the AO Center itself shows real commitment from the AO Foundation to ARI's development strategy and to the location of Davos as our headquarters.

Alongside its high-quality prototype building work, twelve local apprentices have so far been educated as polymechanics in the workshop. In addition to his role as workshop manager Zweifel is a certified apprenticeship-teacher. This sort of collaborative effort by the ARI is highly appreciated among the community in Davos and Graubünden.

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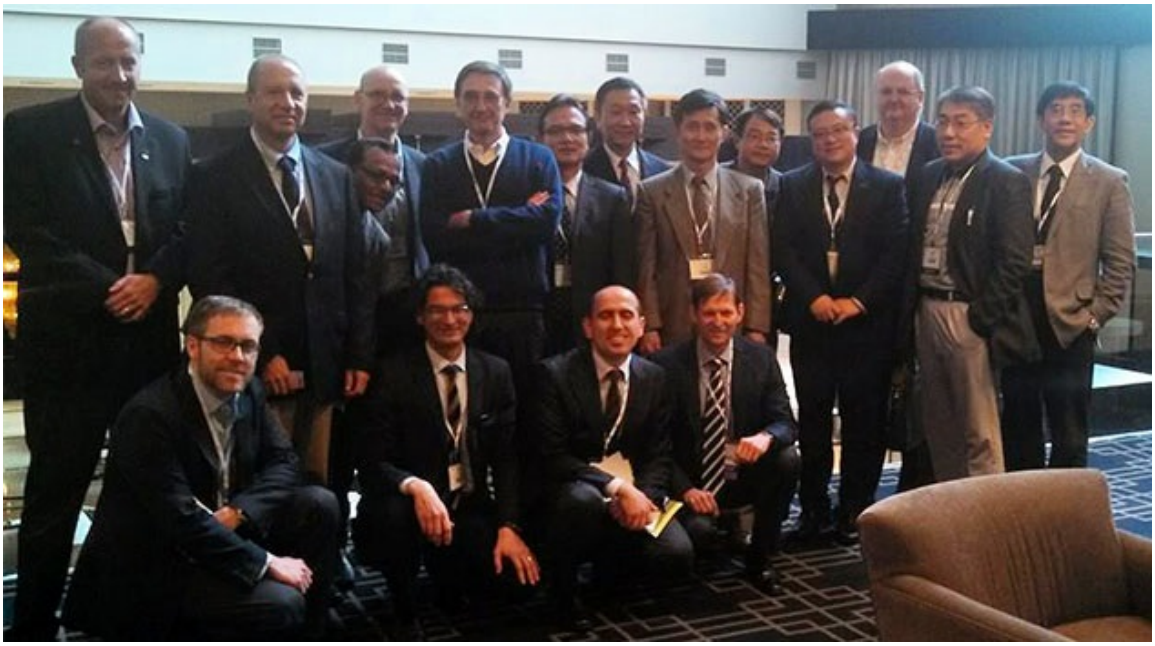
Collaboration
AO Research Institute Davos (ARI) hosted scientific get together with the Institute of Biomechanics from the Technical University Hamburg-Harburg, Germany in February 2014.

A meeting to share perspectives of researchers and developers in the fields of orthopedic and trauma biomechanics was held at the AO Center Davos. The workshop was organized by ARI's Biomedical Services Program and the Institute of Biomechanics from the Technical University Hamburg-Harburg, Germany (TUHH). The concept was to bring together two research centers with focus on similar but complimentary topics in order to develop new collaborative strategies between joint replacement and trauma care to achieve force multiplication in the field. Considering the long lasting relation between both groups with continuous staff exchange over the past decades, the importance of maintaining a close collaboration was highlighted by both institute heads, Prof Michael M Morlock (Director Institute of Biomechanics, TUHH) and Prof R Geoff Richards (Director ARI).

At the second official meeting of the ICORS (International Combined Orthopaedic Research Societies) council - which took place during the 60th Annual Meeting of the ORS (Orthopaedic Research Societies) in New Orleans (US) in March 2014 - the AO Foundation was accepted as an Associate Scientific Member of ICORS. Associate Scientific Members have the same rights as members, with the exception of voting rights, and both AO Research Institute Davos (ARI) and the AO Foundation are proud to be the first non-society member of this global federation of societies. ARI director Prof Geoff Richards will be the official AO representative with Prof Mauro Alini as the deputy.



Geoff Richards was actively involved in drawing up the founding ICORS charter together with past ORS president Ted Miclau (former ARI Medical Research Fellow) before the last ORS meeting, in Venice (IT) in October 2013, where the society was established. The first ICORS meeting will be in Xian, China in 2016, followed by Montreal, Canada in 2019.

The Constituent Societies of ICORS are: Australia-New Zealand Orthopaedic Research Society (ANZORS); British Orthopaedic Research Society (BORS); Canadian Orthopaedic Research Society (CORS); Chinese Orthopaedic Research Society (CORS); European Orthopaedic Research Society (EORS); Japanese Orthopaedic Association (JOA); Korean Orthopaedic Research Society; Orthopaedic Research Society (ORS); Taiwan Orthopaedic Research Society.

The purposes and responsibilities of the ICORS are to:

- Promote orthopedic and musculoskeletal research, including the fields of engineering, biology, and clinical research.
- Allocate venues for tri-annual International Combined Orthopaedic Research Society (ICORS) Meeting.
- Monitor organizational progress and educational content and success of the tri-annual meetings.
- Organize a face-to-face meeting at each tri-annual meeting and each Orthopaedic Research Society (ORS) Annual Meeting.
- Interface with the ORS and other member organizations to enhance international collaboration and programming, including the Annual ORS meeting.
- Support the development of new Orthopaedic Research organizations globally.

Prof R Geoff Richards presenting the AO Foundation at ORS 2014, New Orleans (US).

Prof Mauro Alini elected to the ORS International Committee

Prof Mauro Alini, Vice Director of the ARI has been elected to the new ORS International Committee as one of only four European members. This demonstrates the progress ARI has made in being internationally recognized on its academic merit. The ORS has always been an international society, with members from around the world who are engaged in musculoskeletal research. Approximately 25 % of the ORS membership is international, with members in more than 46 countries. The Board of Directors established the ORS International Committee in March 2014 in New Orleans. At this inaugural meeting, committee members discussed ways that the ORS can better serve our international members. A number of excellent suggestions were provided, many of which will be introduced to our international membership over the next few years.

On 11th April 2014, members of the University Clinic Freiburg, Germany, visited ARI, to describe running projects and exchange ideas on future collaborations. The symposium, organised by Dr Fabian Duttenhoefer from Freiburg (presenting Clinical Application of MSC in Hard Tissue Regeneration) and Dr Martin Stoddart from ARI (Presenting Paracrine signalling), was an ideal opportunity for clinical and translational researchers to meet and determine how their complementary skill sets can be best utilized.

After introductory presentations from Prof Geoff Richards (ARI) and Prof Rainer Schmelzeisen (Freiburg), the morning session was dedicated to speakers from Freiburg who detailed the clinical problems they face, and the projects they are running to overcome these issues. This is the continuation of long standing links between the two Institutes and plans for future work together are already underway. It was particularly satisfying to see three past ARI Fellows return. Such links between clinicians and bench based scientists are crucial in realising the translation of novel therapies into the clinic.

Participants of the research symposium from ARI and Freiburg.

ARI hosted a delegation from the Technical University Varna, Bulgaria in May 2014 in the framework of a collaboration agreement signed between the two institutes. During the presentation session, the institutes detailed current and past activities in order to explain their respective capabilities. A protocol for further collaborative steps was signed as extension to the existing collaboration agreement.

7 eCM Journal, symposia and annual Conference

eCM Journal

eCM started as a concept in 1999 of free science publication. eCM was one of the first open access scientific journals in the world and initiated the transparent review process (now known as open peer review) including a transparent route to becoming a member of the International Review Panel. eCM always has had rigorous peer revieing and the novel discussion with named reviewers (as would happen in a conference) included as an integral part of accepted publications. eCM was set up and remains as a not-for-profit journal. eCM was and is a pioneer with many of its innovative ideas leading the way for major publishing companies to follow. This was disruptive to the research publishing industry and is now seen as best practice.

In June 2014 the 2013 impact factors were released. Five-year Impact Factor 2013- 5.991 (3rd in Materials Science, Biomaterials, 3rd in Cell & Tissue Engineering, 4th in Engineering, Biomedical). Yearly Impact Factors: 2013 4.887 (4th in Materials Science, Biomaterials, 3rd in Cell & Tissue Engineering, 4th in Engineering, Biomedical), the leading Journal of musculoskeletal research.

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

Front page of eCM journal

eCM Conference

The fifteenth eCM Conference, held at the Congress Center Davos from June 16–18, 2014, was dedicated to Cartilage & Disc: Repair and Regeneration. The conference was organized by Martin Stoddart, Sibylle Grad and David Eglin from the ARI, who have been organizing the conference since 2013 with support from the Scientific Advisory Committee of the eCM Journal. Since their inception in 1999, until 2012, the eCM conferences were organized by Geoff Richards and later also with Mauro Alini of ARI Davos, and Charlie Archer from the University of Cardiff (later Swansea). On the fifteenth anniversary their work in establishing eCM Conference as a highly-anticipated annual event was highlighted with a special thank you presentation.

Martin Stoddart presents Charlie Archer, Mauro Alini and Geoff Richards with a thank you from eCM Conferences.

As a special feature of eCMXV, the opening session was devoted to the extensive and fascinating work of Peter Roughly and Charlie Archer, two invaluable and long-time connections to ARI and Charlie a long time member of the eCM Scientific Advisory Committee. Peter Roughley gave an indepth introduction to the detailed molecular structure, turnover and function of aggrecan, the key proteoglycan in cartilage and disc, sharing both his extensive knowledge and the still unresolved questions. Ilyas Khan then illustrated the fundamental cartilage biology and recent findings about the inherent and induced regenerative potential of articular cartilage elucidated by the Charlie Archer group over a number of decades.

Work of excellent quality was presented by a respectable number of students who competed for the annual popular Robert Mathys student prizes. In the end the prize for the best oral presentation was awarded to Angela Armiento for her talk on A mouse model of joint surface injury: contribution of functional mesenchymal stem cells to cartilage repair; with Olga Krupkova a very close second for her presentation entitled Epigallocatechin 3-gallate suppresses interleukin-1β-induced inflammatory responses in intervertebral disc cells in vitro and reduces radiculopathic pain in vivo. First prize in the poster category was awarded to Pauline Colombier for her poster Generating nucleus pulposus-like cells from human adipose stromal cells: a first step towards the regeneration of intervertebral disc with the second prize being awarded to Chris Fellows for his work Articular cartilage contains a nestin positive stem cell population. The overall F1000 Poster prize was awarded to Martin Knight for the work Lithium chloride triggers primary cilia elongation and inhibits hedgehog signalling in articular chondrocytes CL Thompson, A Wiles, CA Poole, MM Knight.

Prof Chris Little during question time.

Clinical Significance

The final session was dedicated to the clinical translation of new therapies, where Mats Brittberg emphasized the recent focus on one-stage procedures to improve the efficiency of cartilage repair techniques and Joji Mochida reported on clinical experience with transplantation of activated autologous nucleus pulposus cells. Safety and efficacy of these new treatments are promising, opening the door for further investigations into biological repair and regeneration. The scientific program was particularly special this year and was very well received by the participants.

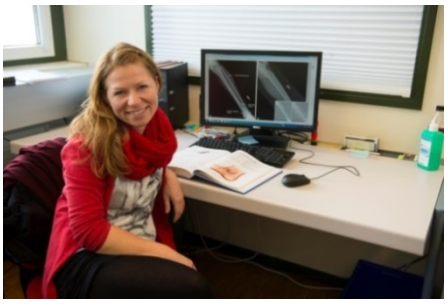
All abstracts from this conference can be found at
http://www.ecmjournal.org/journal/supplements/vol028supp02/ecm15.htm

8 AO Research Institute Davos Fellows

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

- Creation of tangible results in research
- Possibility of medical publication as a co-author (depending upon fellowship time and level of input)
- Knowledge on how to approach research challenges in future
- Inspiration from being part of a world renowned international multidisciplinary R&D team
- Inside knowledge attainment of the AO Foundation
- Enlarging personal networks for future R&D and AO Foundation activities
- Chance to have a research friend/mentor that is always easy to contact

Julian Fischer, Trauma Center Murnau, Germany
ARI Project: Musculoskeletal Infection Group; Molecular epidemiology of Staphylococcus aureus isolates from orthopaedic device related infections in multiple European countries. He previously studied at the University of Leipzig and later completed his doctoral thesis at the Institute for Nuclear Medicine at the University of Bonn. Since 2010 he has been working as a resident in trauma and orthopedic surgery at the Trauma Center Murnau, Germany where he is also part of the ongoing collaboration between the ARI and the Trauma Center Murnau.



Maren Fischer, University Hospital Münster, Germany
ARI Project: Biomedical Services Program; Fracture of the posterior malleolus: influence on ankle joint pressure and biomechanics in a trimalleolar fracture model. Maren studied medicine at Westfaelische Wilhelms University Muenster, where she earned her medical degree in 2010 and where she completed her doctoral thesis. Since 2011 she has been working as a trauma and orthopedic resident at the Dept. of Trauma-, Hand- and Reconstructive Surgery of University Hospital of Muenster.

Christian Günther, University of Veterinary Medicine, Hannover. ARI Project: Preclinical Services Program; The efficacy of local antibody delivery versus systemic administration in improving bone mass and implant mechanical stability. Christian passed his veterinary examination at the University of Veterinary Medicine Hannover in 2014. In 2012 he completed a veterinarian externship in the Preclinical Services Program within ARI. For the last 4 years he has worked as a student assistent in the night and emergency service at the clinic for small animals of the University of Hannover.

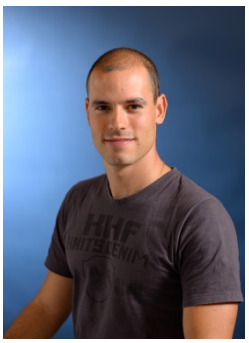
Jennifer Hagen, University of Washington, USA. ARI Project: Biomedical Services Program; Direct comparison of syndesmotic reconstructive techniques using weightbearing CT & hindfoot stability in the setting medial talar facet excision. Jennifer completed her orthopedic residency at the University of Washington and her orthopedic trauma fellowship at Shock Trauma in Baltimore, Maryland. After her research fellowship at ARI, she will begin to work as an assistant professor of orthopedic trauma at the University of Florida, Gainesville in the spring 2015.

Gernot Lang, Ruhr University, Bochum, Germany
ARI Project: Musculoskeletal Regeneration Program; Biomimetic nano-fiber-based nucleus pulposus regeneration for the treatment of degenerative disc disease. He grew up in Essen, Germany and studied at the Ruhr-University-Bochum. Attending a part of the internship at the Dept. for Orthopedic Surgery at the Inselspital in Bern he became interested in disc regeneration and now he is very happy and grateful to have the chance of joining the ARI team in Davos to gain experience in musculoskeletal exploratory research.

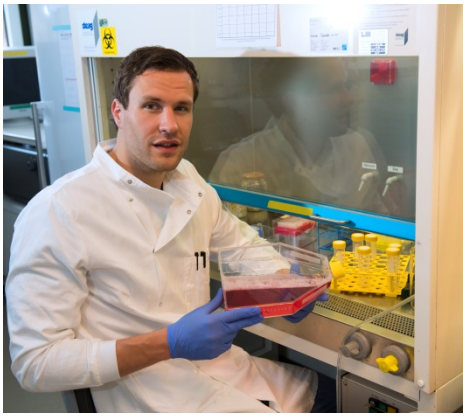
Willem-Jan Metsemakers, University Hospital, Leuven, Belgium
ARI Project: Musculoskeletal Infection Group; The development and prevention of infection in a biomechanically defined osteotomy model in the rabbit & Development of tools to control microbial biofilms with relevance to clinical drug resistance. Willem is a Trauma surgeon. He studied medicine at the Catholic University of Leuven and recently started his PhD thesis there under copromotion of Prof.RG Richards of ARI. The title of the thesis is: Long bone fractures in polytraumatised patients: risk analysis of musculoskeletal complications and strategies to prevent them.

Johanna Nilsson, University Hospital, Uppsala, Sweden. ARI Project: Biomedical Services; Virtual bite registration in 3D composite models of the jaws – How to merge Computed Tomography with laser scan data? Johanna graduated from the University of Gothenburg in 2011 as a Doctor of Dental Surgery. Currently she is a PhD student at Uppsala University Hospital in the Department of Surgical Sciences, Oral and Maxillofacial surgery. She is especially interested in virtual imaging for surgical planning and evaluation in CMF.

Eleftheria Samara, University of Thessaly, Volos, Greece
ARI Project: Musculoskeletal Infection Group;
Development of tools to control microbial biofilms with relevance to clinical drug resistance. Eleftheria finished Medical School in the University of Thessaly in Greece, she has worked as a resident in Trauma and Orthopaedics in Switzerland.



Guilherme Seva Gomes, University of Sao Paulo, Brazil
ARI Project: Biomedical Services Program; The Osteoporosis Implant & New Implant concepts for periprosthetic fracturs. Guilherme performed his medical education at University of São Paulo and graduated in 2009. He finished the General Trauma and Orthopedic Surgery Residency program in January 2014 and has been working as a Trauma Surgeon in public health care in Brazil since then. After the fellowship he will start his Residency in Hand and Microsurgery in Brazil.



Jan Voss, Charité University Medicine, Berlin, Germany
ARI Project: Musculoskeletal Regeneration Program; Mechanisms of Mesenchymal Stem Cell Homing and Differentiation. Jan finished his studies in medicine and defended his experimental doctoral thesis at the department for neurology about the influence of dendritic cells on the disease progression in an animal model of multiple sclerosis in the year 2012. In his second year of residency at the Department of Oral and Maxillofacial Surgery at the Charité - Universitätsmedizin Berlin he applied for a CMF medical research fellowship at the AO and joined the Musculoskeletal Regeneration Program at the ARI in the beginning of February 2014.

Current and past fellows who helped at the AO Courses Davos, December 2014 with the ARI Director, Prof R Geoff Richards.

9 Project Abstracts by Sponsors

9.1 AOCMF

Virtual bite registration in 3D composite models of the jaws – how to merge Computed Tomography with laser scan data (L. Kamer)

Studying the dental occlusion is a key planning step in maxillofacial surgery that usually relies on physical modeling. Up to now dental impression taking, wax bite registration, face bow transfer, plaster cast modeling and mounting the casts on an articulator is made in parallel with radiological assessment. Regularly Computed Tomography or Cone Beam Computed Tomography (CT/ CBCT) forms a part of the routine diagnostic procedure to analyze the bone of the maxillofacial region. They also offer the possibility for a three-dimensional (3D) computer model to be created. However, appropriate computer visualization of the dental occlusion cannot be obtained. Limited image resolution, creation of metal artifacts and difficult image segmentation, as well as separation of upper from lower teeth hamper accurate 3D modeling and visualization. In addition, the patient is usually scanned with the teeth in a habitual but not in a diagnostic inter-occlusal relationship as required for treatment planning.

The introduction of optical scanning technologies has made high precision occlusal modeling available. In theory CT or CBCT might be merged to optical scans to get a model of the bony jaws and dental occlusion. However, an appropriate workflow needs to be defined for exact fitting of the two different imaging modalities in order to get a 3D model of the jaws with the dental occlusion and the TMJ placed in the correct diagnostic position. This project is stimulated by the idea of incorporating all these information into a single competent model. It would form a new integrated standard in patient assessment. A computerized workflow will be developed putting CT/CBCT and optical scan data into a computer model of the maxillofacial region with a correct diagnostic jaw position. If applicable, the workflow will be tested in a series of clinical data using standard planning software.

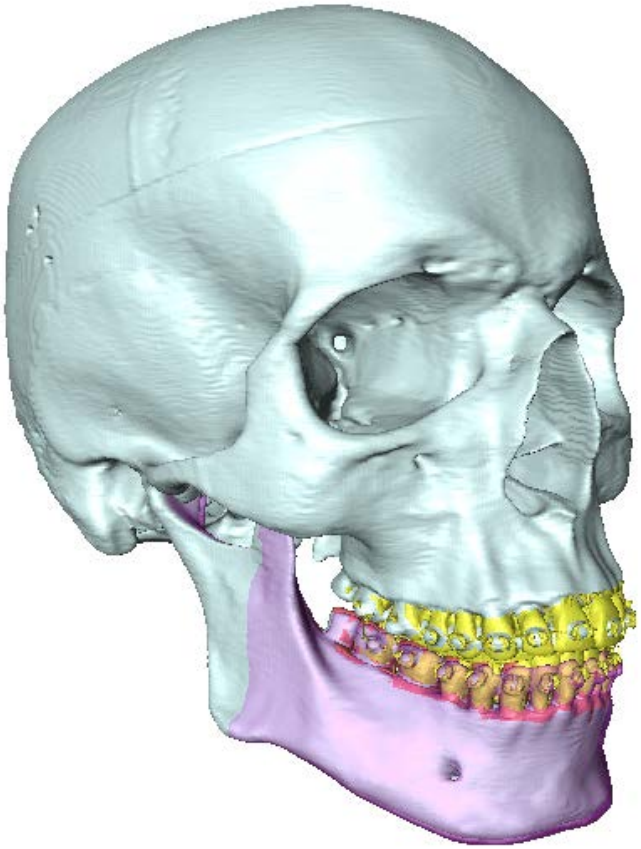


Figure 9.1.1: 3D CT model of a plastic skull (grey) merged to intraoral optical scans of the upper and lower teeth (yellow). The lower jaw is re positioned according to a diagnostic position (purple) using a virtual bite registration procedure.

Pres:

Nilsson J, Thor A, Kamer L. Virtual bite registration – a workflow for creating a 3D model for orthognathic surgery planning. 2014. SAOMS

Partners:

- Nilsson J (DDS), AO Research Institute Davos, Switzerland, Institute for Surgical Sciences, Department of Oral Maxillofacial Surgery and Plastic Surgery, Uppsala University, Sweden
- Thor A (DDS, PhD), Institute for Surgical Sciences, Department of Oral Maxillofacial Surgery and Plastic Surgery, Uppsala University, Sweden

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

Adequate skull visualization is essential for many diagnostic or therapeutic applications in craniomaxillofacial (CMF) surgery. 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 CMF 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. Currently, surgeons and researchers 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 CMF surgery, mainly metal artifacts created by metallic dental restorations, partial volume averaging and stair steps due to limited image resolution and insufficient 3D meshing techniques significantly compromise adequate 2D and 3D data assessment in the surgeon's daily practice. They hamper proper visualization of the teeth. Metal artifacts create image streaks even affecting adjacent structures such as the mandible, maxilla, soft tissue or cervical spine. Both, partial volume averaging and insufficient meshing, compromise 3D skull visualization, mainly the bony orbit at its thinnest bone parts. Other regions such as the infraorbital and mastoid region or temporalis fossa may be affected in a similar but to less marked extent.

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

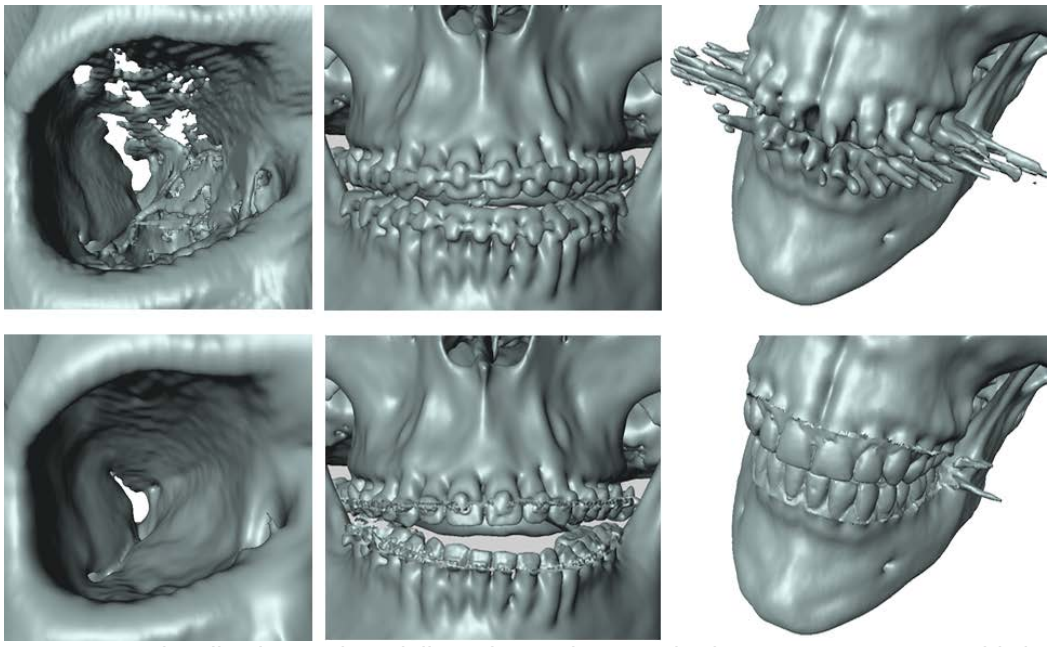


Figure 9.1.2: Poor 3D visualization and modeling when using standard CT or CBCT. Bony orbit (top row left) and dental occlusion may be affected by pseudo holes (top row right), limited image resolution and metal artifacts (top row). Study results with automatic procedures developed to reconstruct the bony orbit (bottom row left) and dental occlusion (bottom row right).

Optimization of osseointegration of dental implant by surface modification with bisphosphonates (BispImp, ongoing) (V. Stadelmann)

Problem: Implants coated with bisphosphonates (BP) have shown favorable osseointegration and superior implant stability when compared with non-coated implants, but BP-coatings are not yet used in dental implants, the main reason being the fear to cause bisphosphonate-related osteonecrosis of the jaws (BRONJ) in the neighbor bone.

We believe that the odds of inducing BRONJ as a side effect of BP-coated implants are negligible since the local dose is only a fraction of the systemic dose.

Goal: The aim of the project is to introduce BP-coated dental implants in a minipig model that is favorable for the occurrence of BRONJ and demonstrate that necrosis does not happen.

Results: In total 10 Göttingen minipigs have been operated. They randomly received two control or BP-coated implants in PM2 of left mandible and left maxilla, and left PM4s were removed. Data analysis is ongoing. Our preliminary findings show that the implants were osseointegrated (Figure 9.1.3 right) and no necrosis seemed to occur in the periprosthetic bone of either implant type nor in the defect sites.

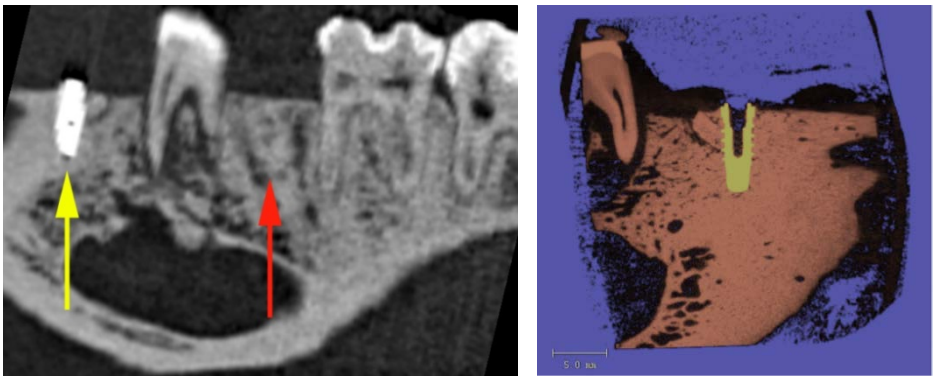


Figure 9.1.3: Left: In vivo CT showing the location of the implant (yellow arrow) and healed defect (red arrow) in the mandible. Right: high-resolution microCT of the osseointegrated implant.

Partner:

- Otto S (MD), Ludwig-Maximilians-University of Munich, Munich, Germany

Workflow for virtual fracture reduction in double mandibular fractures (V. Varjas)

Double mandibular fractures are located bilaterally in different parts of the mandible and include a diversity of fractures patterns. A majority of the fractures occur in young men. However, also elderly with an edentulous or atrophic mandible suffer from bilateral fractures. There exists a variety of treatment options for bilateral mandibular fractures due to the heterogeneity of fracture types and patterns. Adequate treatment critically relies on appropriate fracture reduction and fixation techniques to reestablish the masticatory function and to minimize the complication rate. Hence, a thorough understanding of the given individual situation is essential to define an optimal treatment strategy.

Computerized preoperative planning could be a supportive diagnostic aid to improve the preoperative assessment. The procedure usually includes three-dimensional (3D) Computed Tomography (CT). Despite technical advances, 3D planning in double mandibular fractures remains a particular challenge since limited CT image resolution and artifacts due to metallic dental restoration hamper proper 3D visualization making adequate visualization difficult to achieve. Furthermore, a computerized workflow requires a method to virtually reduce the fracture segments. Virtual fracture reduction is not a well-established technique yet and it remains a challenging task requiring specific software developments to be made with particular reference to maxillofacial reconstruction procedures.

The objective of this feasibility study is to develop a technical workflow to properly visualize and virtually reduce double mandibular fractures. Standard preoperative CT will be utilized and advanced image processing techniques and virtual reality devices will be adopted to model and reposition the bone fragments. Further on, it will be evaluated whether or not the technical developments require optical scan information of the dental surface to properly establish the inter-occlusal relationship. The ultimate goal would be to integrate the developments made into a clinical workflow and/or to use them for educational purpose to teach fracture fixation strategies.

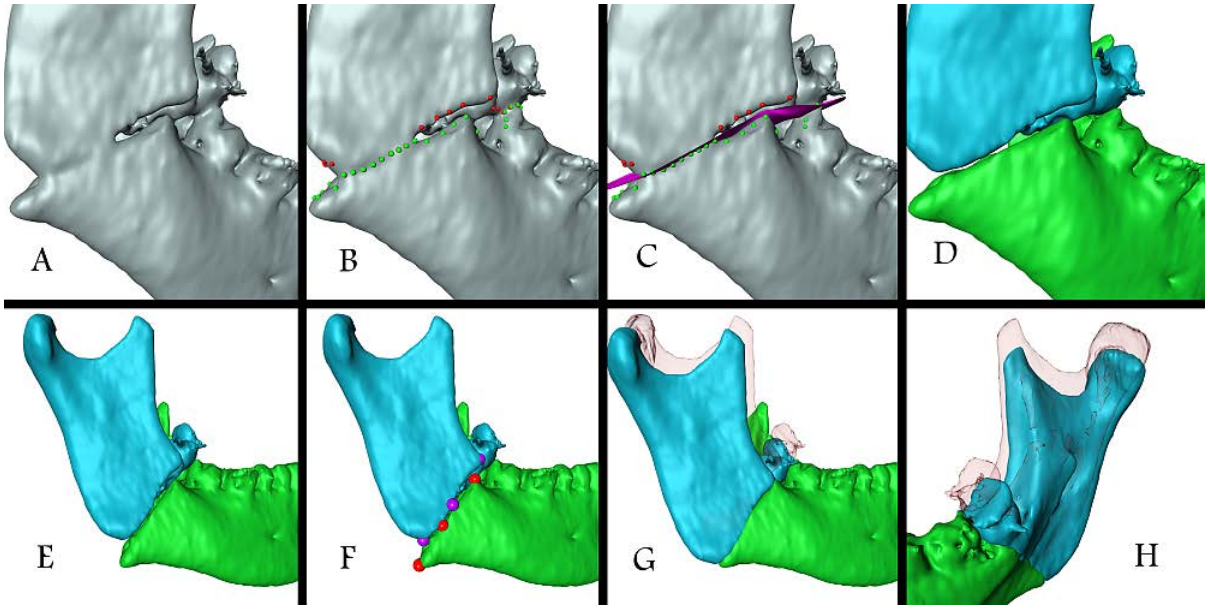


Figure 9.1.4: Illustration of the technically demanding procedure to identify, label and virtually reduce the 3D fracture segments: A) 3D fracture pattern, B) landmarks set describing the fracture, C) magenta colored separation surface, D-E) labelled 3D fracture segments, F) corresponding landmarks on each fragment, G-H) Reduction process, dislocation is visualized in semitransparent red.

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

It forms a sustainable umbrella project for collecting medical image data, mainly Computed Tomography (CT) data of unaffected bone, Peripheral Quantitative CT (pQCT) data, and know-how in image processing and analysis for efficient use in related projects. 3D statistical bone modeling and analysis represent advanced computational techniques and very precious anatomical information for studying the most important size and shape variations of given bone samples of like the mandible or cranium. Based on the study of such models averaged templates for preshaped implants can be easily produced for example. We developed and tested a technical workflow for creating such a 3D statistical model of the entire cranium based on a series of five standard CT scans. The challenge in this workflow is the definition of a sufficient number of corresponding anatomical landmarks to compute homologous triangulations representing the outer cranium's surface. These homologous surfaces represent the basis for creating a statistical model or mean model. Accordingly, a 3D model of the mandible may be computed. However, a 3D statistical model of the entire dentition cannot be obtained since the position and number of the teeth are highly variable among different individuals.

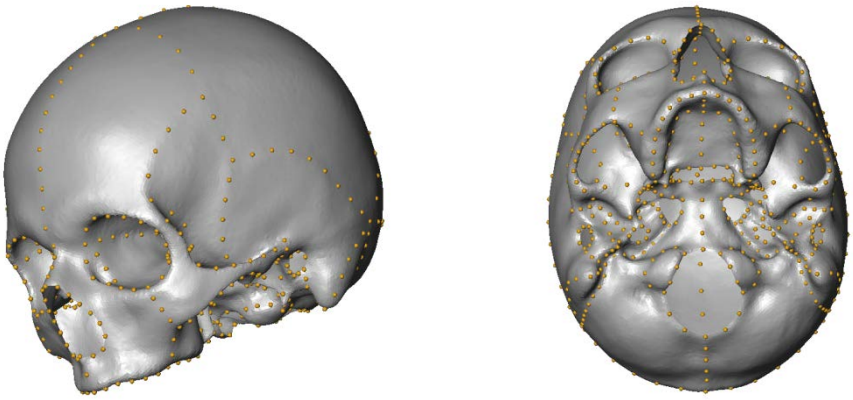


Figure 9.1.5: Mean shape computed from five craniums and 589 anatomical homologous landmarks.

Development of a Preclinical model of Bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Ongoing) (M. Stoddart)
Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a side effect of bisphosphonate therapy. 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. In collaboration with partners from the AOCMF community, two different large animal models of BRONJ were developed using Zoledronic acid and tooth extraction as a trigger, one in sheep and one in minipig. Reproducible BRONJ developed upon a physical injury trigger, in this case tooth extraction. BRONJ was confirmed using both Ct and histology. More recently we have been investigating potential preventative measures, in particular the potential benefit of bisphosphonate withdrawl on BRONJ progression after surgery. This has shown initial promising reults and this avenue of research will be investigated further.

Pres:
Antiosteoclastic drugs and their impact on maxillofacial and orthopedic bone biology, disease, diagnosis, prevention, surgery, and treatment modalities (ARONJ). AOCMF 2nd Clinical Priority Program (CPP) conference. Imaging and Planning in Surgery. 22.09.14, Prague, Czech Republic

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

9.2 AOSpine

Stem cell based intervertebral disc regeneration – evaluation of cell carrier and delivery strategy for pre-clinical application (Transdisc) (Ongoing) (S. Grad)
The project aims at optimising the application of mesenchymal stem cells for intervertebral disc regeneration. A bioreactor specifically designed for intervertebral disc whole organ cultures was used first to induce degeneration and then to investigate different cell carrier materials and delivery approaches. These studies led to the identification of a fibrin gel formulation capable of withstanding physiological loading regimes inside nucleotomised intervertebral discs. Moreover, this fibrin formulation provides an effective stem cell carrier which preserves cell viability inside the disc (Figure 9.2.1). It was found that stem cells can contribute to the restoration of degenerated discs by inducing an up-regulation of anabolic markers in disc cells. However, the disc cell response depends on their grade of degeneration. Healthy, physiologically loaded disc cells responded better to the treatment than degenerative disc cells, indicating that the state of the disc cells at the time of stem cell administration might be of key importance when developing stem cell-based therapies for disc regeneration.

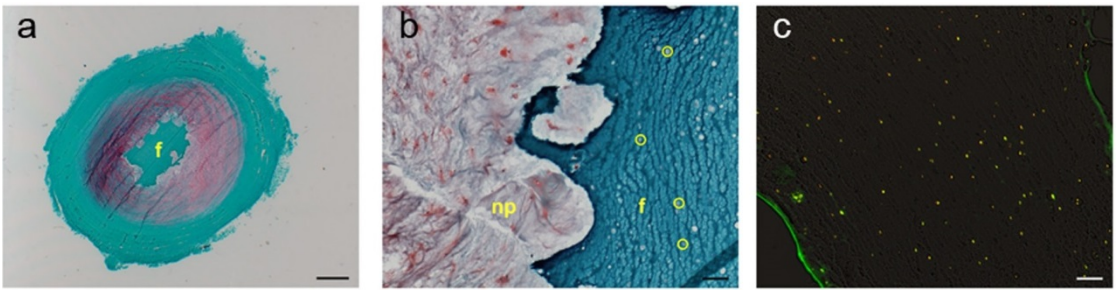


Figure 9.2.1: (a) Safranin-O/Fast stained section of a nucleotomised bovine caudal intervertebral disc treated with human stem cells encapsulated in a fibrin carrier (f), scale bar = 2 mm; (b) detailed view of the nucleus pulposus (np) tissue/fibrin interface, yellow circles = stem cells in the fibrin gel, scale bar = 50 µm; (c) calcein AM staining of PKH26 labelled human stem cells in fibrin following a two-week whole organ culture (yellow = viable MSCs), scale bar = 100 µm.

Pres:
Caprez S, Peroglio M, Janki M, De Wild M, Benneker LM, Alini M, Grad S. Stem cell effect on mechanically-loaded nucleotomised intervertebral discs. ECM 2014, Davos, Switzerland (Poster).

Caprez S, Peroglio M, Janki M, De Wild M, Benneker LM, Alini M, Grad S. Role of fibrin gel in whole intervertebral discs under loading. TERMIS 2014, Genova, Italy (Oral).

Leite Pereira C, Gonçalves RM, Peroglio M, Pattappa G, Eglin D, Barbosa MA, Alini M, Grad S. Stromal Cell Derived Factor-1-delivery system: a new approach for the recruitment of mesenchymal stem cells in degenerating intervertebral disc. World Forum for Spine Research 2014, Xi'an, China (Poster).

Pattappa G, Peroglio M, Sakai D, Mochida J, Benneker LM, Alini M, Grad S. CCL5 is a key chemoattractant in degenerative intervertebral discs. ORS 2014, New Orleans, USA (Poster).

Peroglio M, Janki M, De Wild M, Benneker LM, Alini M, Grad S. Fibrin gel contributes to the restoration of disc height in nucleotomized intervertebral discs under dynamic load. ORS 2014, New Orleans, USA (Oral).

Peroglio M, Grad S, Alini M. Stem cell based Intervertebral Disc Regeneration – Evaluation in Organ Culture. North American Spine Society (NASS) in San Francisco on November 14th, 2015. USA (Oral - Research Grant Awards Session)

Pub:
Leite Pereira C, Gonçalves RM, Peroglio M, Pattappa G, Eglin D, Barbosa MA, Alini M, Grad S. The effect of SDF-1 and thermoreversible hyaluronan hydrogel on the recruitment of mesenchymal stem cells in degenerating intervertebral discs. Biomaterials 35:8144-53, 2014.

Pattappa G, Peroglio M, Sakai D, Mochida J, Benneker LM, Alini M, Grad S. CCL5 is a key chemoattractant released by degenerative intervertebral discs in organ culture. Eur Cell Mater 27: 124-36, 2014.

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

Role of the intervertebral disc in the development and progression of spinal deformities (Discform) (Ongoing) (S. Grad)
The etiology of spinal deformity in idiopathic scoliosis is still unclear to date. The cause of this disease is assumed to be multifactorial. One of these suspected influences is the asymmetric loading condition involved in the disorder. The aim of this project is to establish an asymmetrical loading device which mimics the load bearing condition of discs in scoliotic patients, and to investigate the effect of asymmetrical loading on organ cultured discs.

Bovine caudal discs were placed on a 10˚ wedge, and loaded dynamically at 0.02-0.4 MPa, 1 Hz, 1 h/day, for 6 days (Figure 9.2.2 a). During the loading period no sliding or rotation of discs was observed, thus allowing a clear identification of the wedged side. Moreover, disc height at the wedged side was found to be lower compared to the non-wedged side after 1h of loading (Figure 9.2.2 b). Disc cell viability was maintained above 80% after 6 days of loading. Phenotypic changes of disc cells at wedged side and non-wedged side are analysed and compared with discs loaded symmetrically. In addition, molecular differences between disc cells from patients with idiopathic and neuromuscular scoliosis in comparison with cells from healthy individuals are being elucidated by microarray and immunohistochemistry. These data will then be compared to identify the key molecules initiated by asymmetrical loading and involved in scoliosis pathylogy.

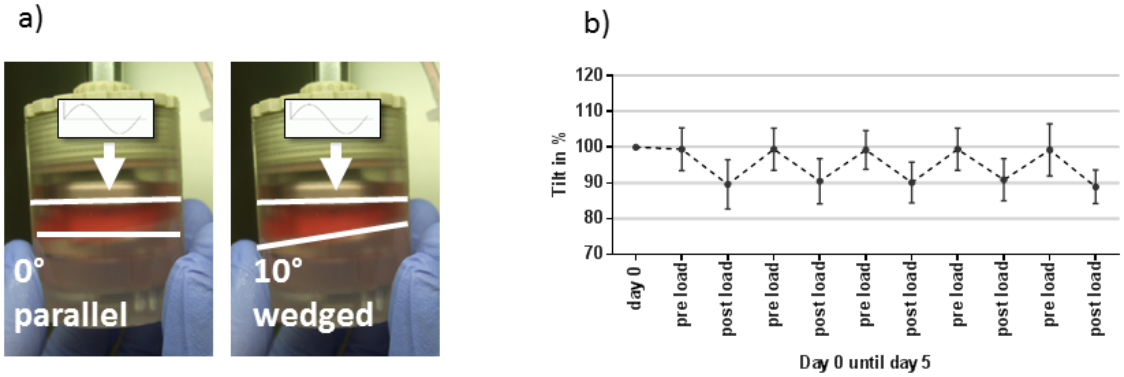


Figure 9.2.2: a) Loading chamber for symmetric load (left) or asymmetric load with a wedge inlet (right). b) Percentage of disc height at wedged side compared to non-wedged side.

Partners:

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

9.3 AOTrauma

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

Problem: Flexible internal fixation aims at improving induction of callus by imposing confined, reversible displacement at the fracture site. The exact role of implant mechanics and the potential of adjusting the structural flexibility to create an optimal environment for fracture repair are still unclear. Improving the technology for internal fixation by necessity relies on improved understanding of the mechano-biology of fracture repair. Creating defined mechanical conditions at the fracture site with continuous data collection shall provide valuable information.

Goal: This study aims exploring the mechano-biological processes of fracture repair under defined mechanical conditions in an ovine model using a recently introduced research implant system with biofeedback technology.

Results: The plate fixator was further improved to overcome remaining technical issues. Four animals were operated to investigate a new time dependent fixation protocol following the concept of inverse dynamization. Another two groups of four animals each were operated to study the effect of different load thresholds for dynamization. In the first group, interfragmentary motion (IFM) was permitted at a load of 25 kg or higher (high preload), while in the second group IFM started at a load of 12.5 kg (low preload). Maximum range of motion was limited to 0.3 mm in both groups. Mean interfragmentary motion substantially decreased in all animals over time, indicating ongoing bone healing. However, weekly radiographs as well as post mortem CT data revealed significantly enhanced callus formation in the high preload group compared to the low preload group.

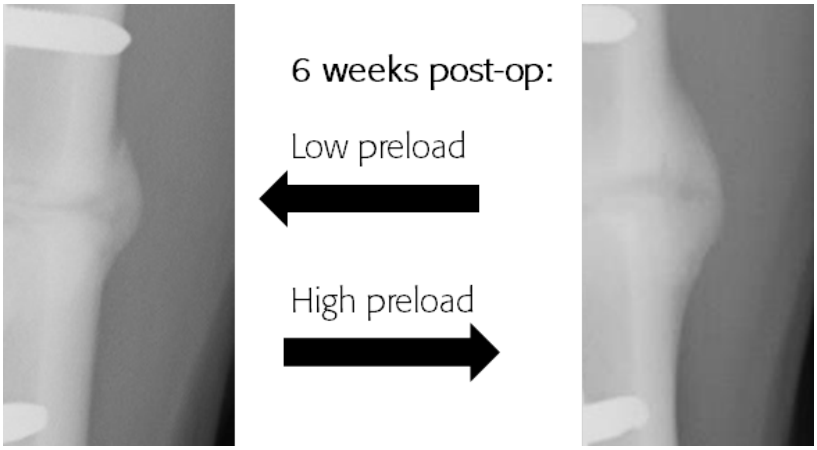


Figure 9.3.1: Anteroposterior (AP) Radiographs at 6 weeks post-op of two animals. Left: low preload (12.5 kg) applied to the spring of the fixator; right: pre-load to the spring of the fixator increased to 25 kg. A more pronounced callus formation becomes obvious for the high-preload animal.

An instrumented bridge plate was developed to measure plate deflection over time. Six animals, undergoing a large bone defect experiment at the Queensland University of Technology, Australia, delivered continuous data on limb loading and animal activity over months.

Pres:
Windolf M, Ernst M, Schwyn R, Perren SM, Mathis H, Wilke M, Richards RG.
A Biofeedback System for Continous Monitoring of Bone Healing. 2014. International Conference on Biomedical Electronics and Devices.

Pub:
Windolf M, Ernst M, Schwyn R, Perren SM, Mathis H, Wilke M, Richards RG.
A Biofeedback System for Continuous Monitoring of Bone Healing. Proceedings of the International Conference on Biomedical Electronics and Devices 2014: 243-248

Partners:
- Mathis H, Insitute for Communication Systems, Hochschule Rapperswil, CH
- Schuetz M (Prof, MD), Hutmacher D (Prof, PhD), Epari D (PhD), Institute of Health and Biomedical Innovation, QUT, Brisbane, Australia

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

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

Results: An X-in-one module for proximal humeral plating (PHILOS, DePuy Synthes Inc.) was tested in a close-to-reality setting with 6 human cadaveric specimens in a randomized left-right comparison to manual surgery. Precision of the procedure in terms of distance of the screw tips to the joint increased by 50% due to use of X-in-one. Total number of x-ray shots was reduced by 64% and total operation time by 38%. Further modules are in development. An existing module aiming at restoring anatomical anteversion of the femur after nailing was refined and improved in a master thesis. An animation video illustrating the concept was developed in the frame of another master thesis.

Theses:
Aeberhard S, Flouroscopy based measurement of bone rotation, master thesis
Veselinov D, Computer animation: Clip for presentation X-in-one, master thesis

Partners:
- Blauth M (Prof, MD), University Hospital Innsbruck, Austria
- Mosheiff R (Prof, MD), Hadassah University Hospital, Jerusalem, IL
- Liebergall M (Prof, MD), Hadassah University Hospital, Jerusalem, IL
- Albert-Ludwigs-University Freiburg, Germany
- Farhi OA (Prof, Dr Sc), Skulev HK (Doc, PhD) Technical University Varna, Varna, Bulgaria

Prophylactic reinforcement of the proximal femur to prevent secondary hip fractures (ProphylacticAug, ongoing) (P. Varga)
Problem: After an osteoporotic hip fracture, the risk of sustaining a second fracture at the contralateral hip as well as the related morbidity and mortality increase significantly. Internal prophylactic strengthening of the contralateral femur by means of surgical intervention may be able to help avoiding a secondary fracture in case of a fall. Being an invasive treatment of a not yet fractured bone, prophylactic augmentation requires strong ethical justification on the path to clinical applicability. A clear mechanical benefit of the method to be used is one of the most crucial ingredients of the gain-to-risk ratio.

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

Results: In order to expedite the development process large emphasis was put on numerical investigations. A fully automated virtual analysis framework, incorporating a state-of-the-art, previously validated nonlinear material model of bone, has been developed for the purpose of generating case-specific finite element models of proximal femora from CT images and performing a destructive test of the bone in fall configuration. In a retrospective analysis these finite element models provided an excellent prediction of the experimental fracture load and reasonably good estimate of the fracture pattern of thirteen intact femora tested experimentally in sideway fall configuration by means of a drop-tower setup in two previous studies. The framework was then used to analyze the mechanical benefit of different augmentation configurations. In a first parametric sub-study not only the volume, but also the positioning of the cement cloud was shown to significantly influence the fracture load. Moreover, a novel concept called 'Ask the bone' was developed to identify, by means of numerical bone remodeling simulations, the ideal cement location for the fall load case. This augmentation strategy was shown numerically to approximately double the fracture load compared to the intact case, however, require relatively large cement volumes.
In the frame of a master thesis, the effect of different morphological parameters on the mechanical competence of the proximal femur was investigated in a parametric numerical study.

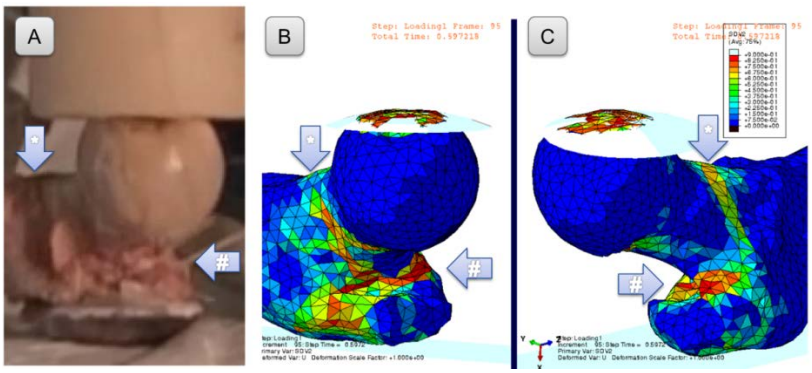


Figure 9.3.2: Proximal femur fracture in fall configuration. The experimental drop tower test (A) results in a trochanteric collapse (#), followed by the fracture of the neck (*). The finite element simulation (B and C being different views) is able to reproduce these fracture patterns (red color: high damage).

Pres:
Widmer D, Hofmann-Fliri L, Zweifel E, Blankstein M, Gueorguiev B, Blauth M, Windolf M. Prophylactic reinforcement of the porotic proximal femur. A systematic approach to find a valid solution. 2014, ECTES, Frankfurt, Germany. Best oral presentation award.

Theses:
Voegtli D, Parametric analysis of proximal femur morphology on fracture behaviour in sideways fall situations, master thesis

Partners:
- Blauth M (Prof, MD), Medical University Innsbruck, Austria
- Zysset P (Prof, PhD), ISTB, Berne, CH
- Helgasson B (PhD), Institute for biomechanics, ETHZ, Zurich, CH

Cement augmentation methods for improved fracture fixation in osteoporotic bone (ImplantAug, ongoing) (M. Windolf, L. Hofmann-Fliri)
Problem: The landscape of trauma surgery will significantly shift towards geriatric patients. Despite improvements in implant design, one major complication, namely failure at the bone implant interface (cut-out), remains in the treatment of fragility fractures throughout various anatomical regions. The application of bone cement for improved implant purchase in osteoporotic bone is a promising option to reduce risk of failure and allow for early mobilization of elderly patients.

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

Results: A comprehensive experimental picture of implant augmentation with bone cement was drawn. Augmentation reveals high biomechanical potential. However, it cannot be applied as routine concept in osteoporotic fracture treatment. The indication must be rigorously evaluated, considering fracture pattern, implant selection, failure mechanisms and cement formulation. Cement augmentation appears save when applied responsibly.

Pres:
Windolf M. Experimental basics for augmentation techniques, AO Trauma Symposium, Augmentation - the new standard in osteoporotic fracture care. 2014, EFFORT, London, UK. Invited lecture

Grüneweller N, Raschke M, Widmer D, Zderic I, Gueorguiev B, Fuchs S, Windolf M. Biomechanischer Vergleich augmentierter und nicht-augmentierter SI-Schrauben im Hemi-Pelvis - Model). 2014. DKOU.

Klos K, Rausch S, Wolf D, Windolf M, Gueorguiev B. Biomechanischer Vergleich zwischen einer winkelstabilen Platten- und einer zementaugmentierten Schraubenosteosynthese zur Versorgung von Kalkaneusfrakturen. 2014. DAF (Posterpreis).

Widmer D, Münch C, Forte M, Hofmann-Fliri L, Gueorguiev-Rüegg B, Südkamp N, Windolf M. Cement augmentation of a proximal humerus plate for osteoporotic fracture. Numerical analysis of a complex problem. Eur J Trauma Emerg Surg. 2014; 40(Suppl 1):S11 (ECTES).

Zderic I, Windolf M, Gueorguiev B, Stadelmann V. Monitoring of cement distribution in vertebral bodies during vertebroplasty. Bone Joint J 2014;96B(Suppl 11):183 (CORS).

Pub:
Blankstein M, Widmer D, Goetzen M, Hofmann-Fliri L, Richards RG, Gueorguiev B, Windolf M. Assessment of Intra-osseous Femoral Head Pressures During Cement Augmentation of The Perforated Proximal Femur Nail Antirotation (PFNA) blade. J Orthop Trauma 2014;28(7):398–402.

Goetzen M, Windolf M, Schmoelz W. Augmented screws in angular stable plating of the proximal humerus: What to do when revision is needed? Clin Biomech (Bristol, Avon). 2014;29(9):1023–6.

Rausch S, Klos K, Wolf U, Gras M, Simons P, Brodt S, Windolf M, Gueorguiev B. A biomechanical comparison of fixed angle locking compression plate osteosynthesis and cement augmented screw osteosynthesis in the management of intra articular calcaneal fractures. Int Orthop. 2014;38(8):1705-10.

Wähnert D, Hofmann-Fliri L, Richards RG, Gueorguiev B, Raschke MJ, Windolf M. Implant augmentation: adding bone cement to improve the treatment of osteoporotic distal femur fractures: a biomechanical study using human cadaver bones. Medicine. 2014;93(23):e166.

Theses:
Sermon A, Addressing the challenge of hip fracture fixation and prevention in old age, PhD thesis
Windolf M, Fracture fixation in osteoporotic bone, PhD thesis

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

The effect of subchondral cement augmentation on the overlying cartilage (CartAug)
(L. Hofmann-Fliri)
Problem: The overall response to implant augmentation in clinics is still cautious, due to the fact that possible joint cartilage violation through subchondral PMMA injection could occur. Augmentation of the proximal femur nail has been standardized as far as clinical use of the proximal femur nail antirotational (PFNA, DePuy Synthes Inc.) was launched three years ago. Sermon et al. investigated cement distribution in cadaveric human femoral heads while injecting Traumacem V+ (DePuy Synthes Inc.) into the PFNA and could not find any repeatability. In fact, cementing of the subchondral bone was a common distribution pattern.
Goal: To assure safe implant augmentation, the objective of this study was to investigate the potential negative effect of PMMA on the subchondral plate and its overlying joint cartilage in vivo. In order to characterize the etiology of possible cartilage damage through subchondral manipulation during implant augmentation, this study investigated the influence of the insertion of metalwork and bone cement on the cartilage separately in a sheep knee model.
Results: Our findings showed that within a follow-up of 2 and 4 months neither the insertion of a screw nor injection of PMMA based bone cement close to the joint line seem to damage the adjacent subchondral bone or cartilage. This study suggests that short to mid-term negative effects of a screw or PMMA on the joint cartilage are very unlikely.

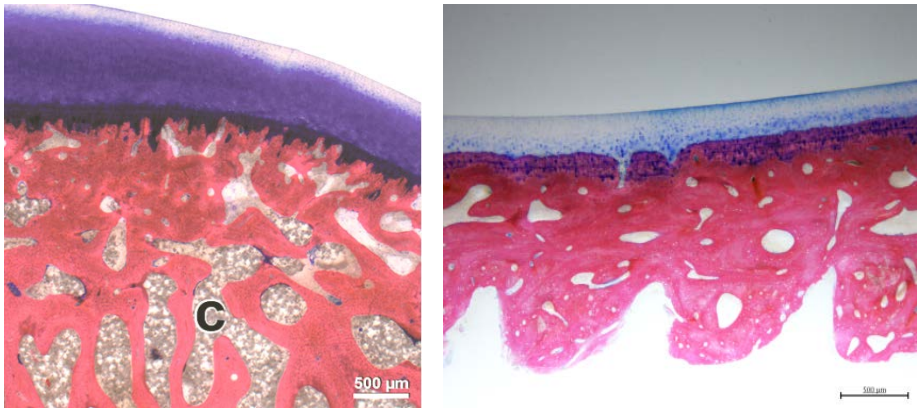


Figure 9.3.3: Giemsa-Eosin stained sections showing (left) a large amount (2ml) of subchondrally injected bone cement © and (right) a screw placed very close to the overlying cartilage: no obvious cartilage and subchondral plate changes after 4 months follow-up

Pub:
Goetzen M, Hofmann-Fliri L, Arens D, Zeiter S, Stadelmann V, Nehrbass D, Richards RG, Blauth M. Does metaphyseal cement augmentation in fracture management influence the adjacent subchondral bone and joint cartilage?: an in vivo study in sheep stifle joints. Medicine. 2015;94(3):e414

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

The osteoporosis implant (OsteoFix, ongoing) (L. Hofmann-Fliri)
Problem: The problem of osteoporosis and the related difficulties in geriatric fracture fixation are well known and described. A major technical advancement to overcome these issues is the augmentation of implants with bone cement. In highly porotic bone, where conventional metallic implants run into limits, cement still offers mechanical benefits by providing purchase to the implant. As a consequence, existing implants underwent minor modifications by adding cannulations and perforations, allowing additional injection of bone cement (Sermon et al. 2012, Unger et al. 2012).
The landscape of trauma surgery will significantly shift towards management of fragility fractures. The question must be raised whether this important patient segment should be further treated with 'line extensions' of conventional fixation hardware, or efforts should be undertaken to develop new solutions dedicated to the specific problem.

Goal: The aim of this feasibility project is to develop new fixation concepts specifically tailored to improve osteoporotic fracture care by combining the benefits of both rigid and injectable materials.

Results: Idea mining lead to several novel fixation concepts which have been judged according to specific criteria. First prototypes have been manufactured and tested. Evaluation of the experiments is ongoing.

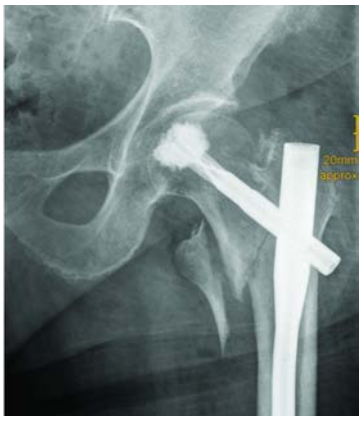


Figure 9.3.4: Example of implant augmentation in the treatment of a proximal femur fracture.

Partners:

- Blauth M (Prof, MD), Medical University Innsbruck, Austria
- Sermon A (MD, PhD), University Hospital Leuven, Belgium

Ortho Meets Trauma – New implant concepts for periprosthetic fractures (OMT, ongoing) (L. Hofmann-Fliri)

Problem: The prevalence of total hip replacements is increasing worldwide. As the number of implants placed increases along with the aging population, it is inevitable that associated fractures also become more common (Holley et al. 2007). Once a fracture occurs, treatment is complicated by osteoporosis, defects in the bone and presence of prosthesis. Recently, new implants specifically designed for periprosthetic fractures such as the locking attachment plate (Depuy Synthes Inc.) or the non-contact bridging periprosthetic femur system (Zimmer GmbH) have been introduced to the market. These systems allow placement of angle stable screws around the prosthesis stem. Nonetheless, complication rates after treatment of periprosthetic femur fractures remain high and will likely increase with the increasing number of osteoporotic patients treated with THA. In the light of the growing segment of geriatric patients, it becomes more and more apparent that a close handshake between orthopedic and trauma care could generate a major benefit in the field. Current interfaces between prosthetics and trauma are minor or inexistent.

Goal: To propose and develop new concepts for combined orthopaedic trauma care with special reference to periprosthetic fractures.

Results: Several new concepts for fixation of periprosthetic fractures were proposed. Prototyes were manufactured and are currently under evaluation by biomechanical testing.

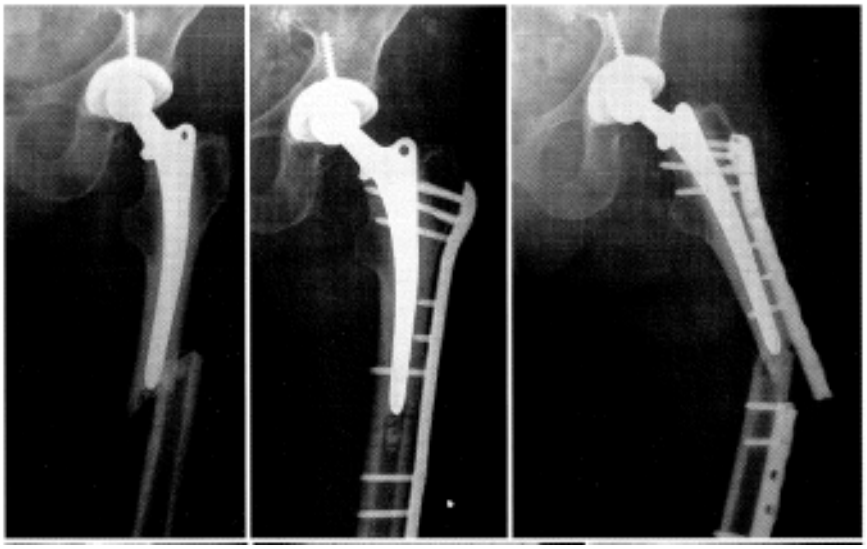


Figure 9.3.5: Example of a periprosthetic fracture and failure of the fixation 10 weeks after postoperatively (Erhardt et al. 2008).

Partners:

- Blauth M (Prof, MD), Medical University Innsbruck, Austria
- Sermon A (MD, PhD), University Hospital Leuven, Belgium

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

Goal: The objectives of present study are based on high resolution peripheral quantitative CT (HR-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 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. A standardized interface will be defined to incorporate 3D BMD maps into existing Finite Element (FE) approaches in order to virtually test implant designs and locations in terms of fixation strength. In addition, the feasibility of the concept will be tested on such a representative region as the proximal femur.

Materials & Methods. Our X-ray based 3D anatomical study will cover five metaphyseal sites of osteoporotic key regions, i.e. the distal radius, the proximal humerus, the proximal and distal femur, as well as the proximal tibia. The technique for creating 3D BMD maps was elaborated in a technical feasibility study performed on distal tibia. For each region we propose HR-pQCT scanning of 60 fresh-frozen bone specimens of human adults. If applicable, each skeletal site will be examined by dual energy x-ray absorptiometry (DXA) for classification of the specimens according to the T-score. Via the computation of statistical bone shape models, 3D BMD maps of the cortical and cancellous bone will be created using custom-made software algorithms. These maps will comprise statistical meaningful parameters, such as average values and variance, calculated and visualized for each image voxel. Subsequently, the 3D BMD maps will be transferred into an existing FE environment by directly mapping the density information.

For validation of the approach, individually scanned proximal femur specimens will be virtually instrumented with a hip screw and tested in an FE environment with regard to stress in the bone structure. Results will be compared with the statistically merged representation of the specimen collective.

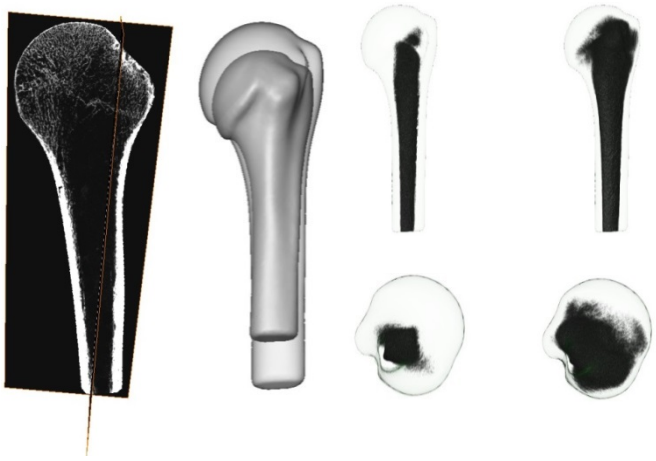


Figure 9.3.6: Approximately 60 post mortem proximal humeri were scanned using an extended HR-pQCT protocol (left). A 3D statistical bone model and averaged bone mineral density models were computed to demonstrate the mean shape, the shape and size variation (middle) and the 3D patterns of bone stock distribution in anterior and axial views (right).

Partners:

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

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

This sustainable umbrella project is formed to collect medical image data, mainly Computed Tomography (CT) data of unaffected bone, Peripheral Quantitative CT (pQCT) data, and know-how in image processing and analysis for efficient use in related projects. Currently, more than 2000 CT data and bone computer models are available. Moreover, computer tools have been developed to create statistical shape bone models (SSM) and to apply them in further projects. Based on SSMs, the software tools enable 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 (eg. osteoporotic women). Currently, 3D statistical models of the clavicle, humerus, radius, femur patella, the distal radius, the sacrum and the vertebra L5 are included in our portfolio.

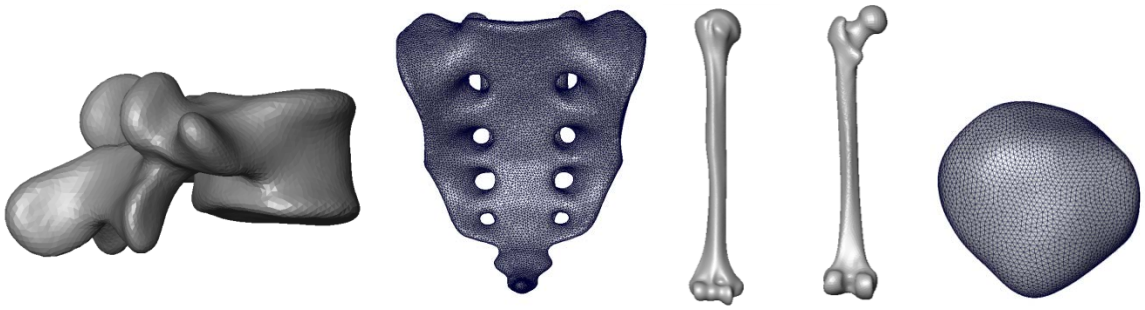


Figure 9.3.7: 3D statistical mean models of the vertebra L5, sacrum, humerus, femur, and patella.

Hindfoot stability in the setting medial talar facet excision (J. Hagen)

Problem: Talocalcaneal tarsal coalition describes a congenital fusion of a portion of the subtalar joint, a critical joint in the foot. Often these coalitions are resected when they become symptomatic, however, it is unclear how much of the medial talus can be removed before the subtalar joint becomes unstable. Often, surgeons will chose to fuse this joint, rather than risk causing instability. Fusion of the joint does not come without penalty, however. The adjoining joints of the foot and ankle must compensate for the lack of motion and many experts believe this can lead to premature arthritis.

Goal: The aim of this study is to evaluate the effect limited resection of the medial talar facet(s) has on subtalar stability. We hypothesize that up to 30% of the medial facet can be resected without evidence of subtalar instability. We utilized a novel loading frame, developed at the AO Research Institute Davos (ARI), to simulate weight-bearing in cadaveric feet before and after resection of portions of the talus.

Results: There was no gross clinical instability in any of the specimens after cutting the bone and no statistically significant differences in the measurements between the resected states and the intact state when corrected for repeated measures. There is not evidence from this study that resecting up 30% of the medial facet and antero-medial portion of the posterior facet of the talus

results in instability of the subtalar joint. Clinical investigation needs to be conducted prior to recommending resecting up to 30% of the medial facet without subsequent subtalar fusion, but this study supports the effort for joint preservation.

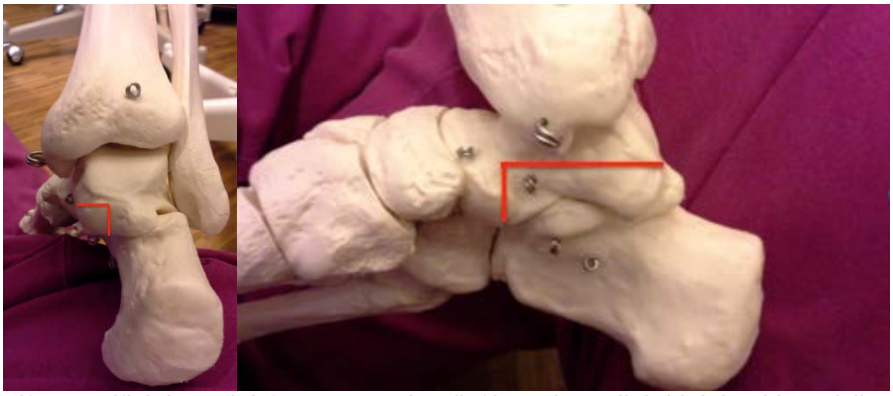


Figure 9.3.8: Hindfoot artificial model from posterior (left) and medial (right) with red lines demonstrating resection region of medial talus.

Partners:

- Sands AK (MD), New York Presbyterian - Lower Manhattan Hospital, New York, NY, USA
- Swords MP (MD), Mid-Michigan Orthopaedic Institute, East Lansing, MI, USA
- Rammelt D (MD), University Clinic Carl Gustav Carus, Dresden, Germany

Influence of different tip apex distances on failure of the helical blade (M. Lenz)

Problem: Tip apex distance is considered as one main indicator of sufficient hip screw postioning. A tip apex distance of 10mm or less in both planes with a center–center position is regarded as golden standard. The influence of larger tip apex distances as well as inferior positioning of the lag screws have been widely investigated, however, the data on a reduced tip apex distance are lacking.

Goal: To perform an ex vivo investigation on the influence of a reduced tip apex distance with respect to fixation stability of a helical blade, failure mode and correlation of the fixation stability with bone mineral density and break away torque.

Results: Tip apex distance is an important parameter for optimal helical blade positioning. Break away torque could be used as a parameter for implant fixation stability estimation in cancellous bone. Reducing the tip apex distance further on does not enhance fixation stability.

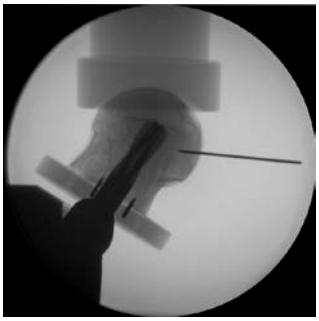


Figure 9.3.9: X-ray of a specimen instrumented with a helical blade and mounted for biomechanical testing.

Partners:

- Lenz M (MD), University Hospital Jena, Germany
- Schwinn J, University Hospital Jena, Germany
- Weber A (PhD), DePuy Synthes GmbH, Solothurn, Switzerland

Fracture of the posterior malleolus: influence on ankle joint pressure and biomechanics in a trimalleolar fracture model (M. Fischer)
Problem: Trimalleolar fractures show an increasing incidence in elderly people. They are associated with a high risk for development of posttraumatic arthritis. The reasons for this are still controversially discussed, especially the role of the posterior malleolar fragment (PMF).

Goal: To evaluate whether a small PMF of less than 25% would alter pressure distribution in the ankle joint and lead to decreased ankle stability since clinical studies showed a favorable outcome comparing patients with small reduced PMF to patients with a non-reduced PMF.

Results: Our results show that a small PMF of less than 25% does indeed alter pressure distribution in the ankle joint but also indicate that there is no overall improvement in this pressure distribution comparing reduction of the PMF to the non-reduced situation. In addition, a small surgically not addressed PMF does not reduce ankle stability in biomechanical testing.

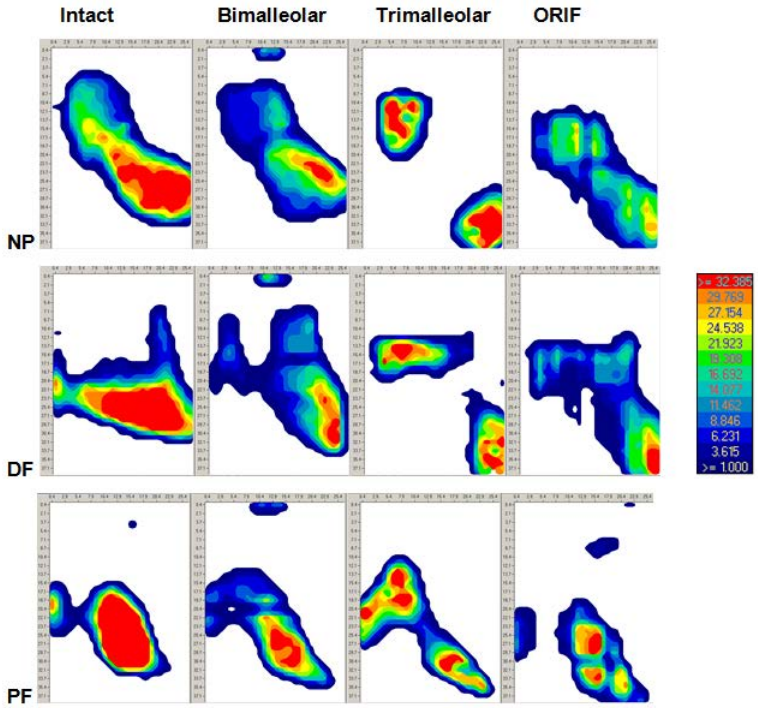


Figure 9.3.10: Images from pressure measurements of an ankle joint in intact, fractured and reconstructed condition.

Partners:
- Wähnert D (MD), University Hospital Münster, Münster, Germany
- Evers J (MD), University Hospital Münster, Münster, Germany

Biomechanical investigation of head loosening of variable angle locking screws in comparison to fixed angle locking screws under cyclic loading (M. Lenz)
Problem: The principle of variable angle (polyaxial) head-locking screws is nowadays increasingly applied in fracture fixation, especially in the distal radius. Maintenance of stable fixation under cyclic loading, preventing loss of fracture reduction, is critical for fracture treatment in general and especially for the treatment of delayed healing. Whereas locking screw head loosening is observed in non-orthogonal inserted fixed angle locking screws, head loosening of variable angle locking screws has not been investigated yet. In a previous study with destructive quasi-static mechanical tests it was able to reveal construct failure due to overloading of the fixed and variable angle locking screws such as bending, breakage or breakout. However, no information is gained about

construct endurance. Screw loosening is a continuous process requiring application of cyclic activity and gives information about construct durability.

Goal: To investigate biomechanically the head loosening of variable angle locking screws in comparison to fixed angle locking screws under cyclic loading conditions.

Results: Stainless steel and titanium variable angle and fixed angle locking screws offer a stable and lasting locking mechanism. Cyclic loading had no or only marginal effect on removal torque. Although differences in removal torque exist, when comparing the respective non-loaded groups to the cyclically loaded ones, they are less relevant, since removal torque was maintained under cyclic loading. A loosening of the locked head would implicit a nearly complete drop of the removal torque, since loosened head threads provide no torque resistance during unscrewing. Cyclic testing had no influence on removal torque of screws inserted in an inclined position.

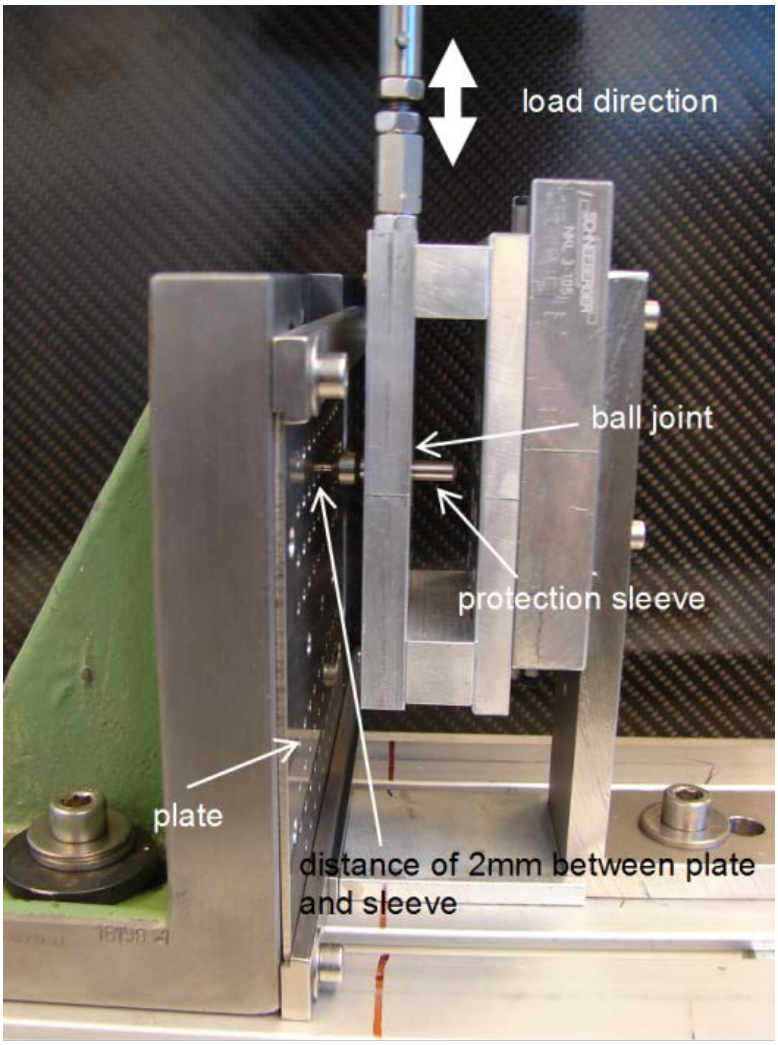


Figure 9.3.11: Test setup for biomechanical testing.

Partner:

- Perren SM (Prof, MD), AO Foundation, Davos, Switzerland

Direct comparison of syndesmotic reconstructive techniques using weightbearing CT (J. Hagen)

Problem: Injury to the syndesmosis (series of strong ligaments that create stability at the ankle joint) occurs in 10-13% of all operative ankle fractures, and there is evidence that both incomplete treatment and malreduction of the syndesmosis can lead to poor clinical outcomes. There is limited data about the intact positioning and relative motion of the native syndesmosis. Inter-person anatomy can vary drastically, making reconstruction of this joint challenging.

Goal: The aim of this study is to elucidate more detailed information on the position of the fibula in the syndesmosis during simulated weightbearing: in the intact state, with sequential sectioning of the ligaments, and following two reconstructive techniques. We will use clinical CT data to allow us to compare the individual specimens' native anatomy to the injured and reconstructed state. We hypothesize there will not be a significant difference in the techniques' ability to restore anatomy.

Results: The degree of deformity in all intact and injury states was dependent on the foot position. Neither reconstruction was clearly superior at restoring physiologic motion, and both techniques had most difficulty in the externally rotated and dorsiflexed positions. The differences between the techniques were not visible with direct comparison, only with comparison of each technique to its intact state were they revealed. This highlights the benefit of this study design and the ability to compare a reconstructed limb to its own intact state, instead of relying on a population norm. This study design can serve as a model for future ex vivo testing of reconstructive techniques.

Figure 9.3.12: Demonstration of a specimen in a CT compatible loading frame, developed at the AO Research Institute Davos.

Partners:

- Simons P (MD), Katholisches Klinikum Mainz; Mainz, Germany
- Klos K (PD, MD) Katholisches Klinikum Mainz; Mainz, Germany

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

Infectious complications occur in a minor but significant portion of the patients undergoing joint replacement surgery or fracture fixation, particularly those with severe open fractures, those undergoing revision arthroplasty or those at elevated risk because of poor health status. Once established, infections are difficult to eradicate, especially in the case of bacterial biofilm formation on implanted hardware. Local antibiotic carriers offer the prospect of controlled delivery of antibiotics directly in target tissues and implant, without inducing toxicity in non-target organs. Polymeric carriers have been developed to optimize the release and targeting of antibiotics. Passive polymeric carriers release antibiotics by diffusion and/or upon degradation, while active polymeric carriers release their antibiotics upon stimuli provided by bacterial pathogens. Additionally, some polymeric carriers gelate in-situ in response to physiological stimuli to form a depot for antibiotic release. In this project, hyaluronan derivatives have been combined with antibiotics to form nano-complexes particles and injectable thermoresponsive formulations. The resultant compositions have been characterized with respect to antibiotic release and handling. An *in vivo* study has shown the ability of a gentamicin loaded injectable formulation in preventing an infection similarly to a commercial gentamicin laoded collagen fleece (Figure 9.3.13).

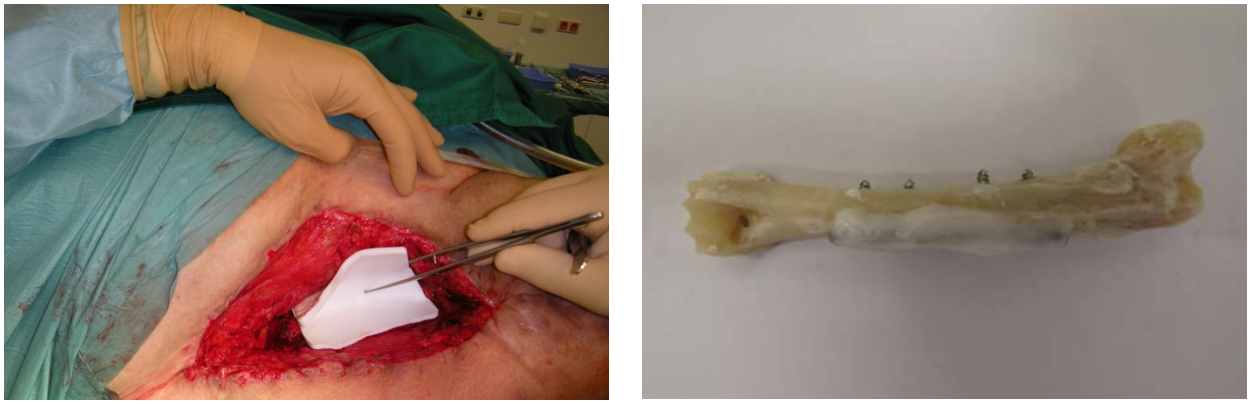


Figure 9.3.13: Antibiotic loaded collagen fleece applied at the surgical site before insertion of the implant (Image courtesy of Dr. Mario Morgenstern of BGU Murnau, Germany) and application of new thermoresponsive hydrogel formulation loaded with antibiotic.

Pub:

Gert-Jan A ter Boo, Dirk W Grijpma, Thomas F Moriarty, Robert G Richards, David Eglin. Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery. Biomaterials. Accepted.

Partners:

- Grijpma DW (Prof), University of Twente, The Netherlands
- Mario Morgenstern (Dr), BGU Murnau, Germany

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

Bacterial infection in orthopaedic surgery and especially in polytraumatic patients is a main cause of failure with a high burden and associated cost. After debridement of the infected site, poly(methyl methacrylate) beads or cement are the most common delivery materials put in place to fill temporally the bone defect and release antibiotic locally. However, such materials are still sub-optimal. Improved delivery systems that can be injected to easily fill up complex shape, be transparent to clinical imaging, have a long lasting release while being fully degradable and providing release of antibacterial agents targeting intracellular bacteria are needed. In this project, lipophilic derivative of gentamicin to reduce the antibiotic solubility and prolonge its bioavaibility was prepared. Subsequently, entrapment of this lipophilic gentamicin within poly(trimethylene carbonate) (PTMC) matrices was performed. The lipophilic gentamicin was synthesized by ion-pairing. The susceptibility of *Staphylococcus aureus* and *Staphylococcus epidermidis* for lipophilic gentamicin was tested and the viability of eukaryotic cells (fibroblasts) upon exposure assessed. The loading of the lipophilic gentamicin into PTMC films and microspheres was achieved by compression molding and emulsion techniques. The lipophilic gentamicin was successfully prepared as confirmed by FTIR-spectroscopy. Lipophilic gentamicin was bactericidal for *S. epidermidis* and *S. aureus* at 0.5 µM and 8.5 µM, respectively. At 1.1 µM no reduction in fibroblasts viability was observed. At 11 µM the reduction was ~50%.

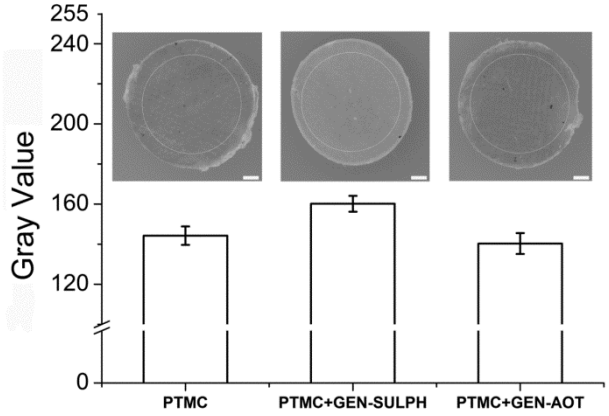


Figure 9.3.14: Gray values obtained for PTMC discs, poly(trimethyl carbonate) (PTMC) discs loaded with gentanicin sulfate (GEN-SULPH) and PTMC discs with lipophilic gentamicin (GEN-AOT) by optical microscopy in diffuse illumination mode, demonstrating the solubilisation of the lipophilic gentamicin in the PTMC compared to gentamicin sulfate.

Pres:
ter Boo GA, Grijpma DW, Richards RG, Moriarty TF, Eglin D. Delivery of gentamicin-AOT from poly(trimethylene carbonate) films. 2014 AFPM, Liege, Belgium (Poster).

ter Boo GA, Grijpma DW, Richards RG, Moriarty TF, Eglin D. Monodisperse microspheres loaded with gentamicin dioctyl sodium sulfosuccinate for the treatment of orthopaedic infections. 2014 ESB, Liverpool, UK (Poster).

Pub:
ter Boo GA, Grijpma DW, Richards RG, Moriarty TF, Eglin D. Hydrophobic gentamicin loaded poly(trimethylene carbonate) delivery system for the treatment of orthopaedic infections. Eur Cell Mater. 2014;28 (Suppl 6):13. (2014 SSB, Basel Switzerland).

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

Cortical and trabecular bone remodeling of the proximal humerus - impact on the fracture zones (PorOsHum) (ongoing) (C. Sprecher)
Fractures of the proximal humerus are directly related to osteoporotic bone remodeling processes in elderly people. Studies at the distal radius and the tibia have shown that the microstructural bone remodeling processes of the trabecular and cortical bone have a critical impact on the fracture risk. Despite the high incidence of proximal humerus fractures in elderly people, little is known about the bone remodeling processes of the cortical and the trabecular bone at the fracture sides.
Therefore defined regions of Giemsa-Eosin stained sections through the proximal humerus of donors with different bone mineral densities were performed. The histomorphological evaluation revealed significant differences between the humeral calotte (yellow) and the supporting subcapital areas (green and black) (Figure 9.3.15) and could demonstrate that osteoporotic bone remodeling processes highly affect the bone morphology of the proximal humerus.
The significant decrease of bone stock between the calotte and subcapital region might contribute to sintering and the failure of osteosynthetic fracture fixation in patients with reduced bone stock, which can regularly be observed in clinics.

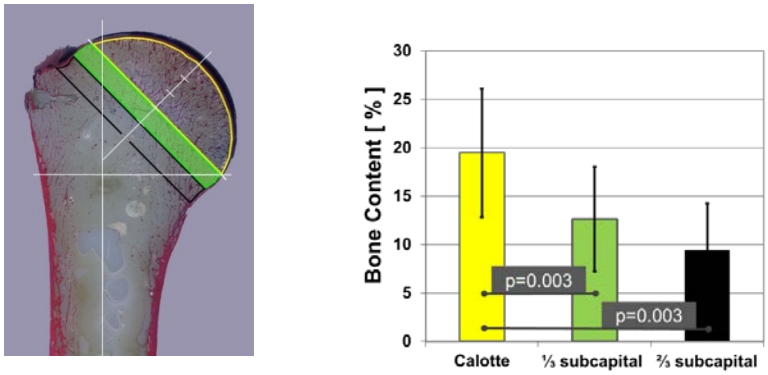


Figure 9.3.15: The relative bone content is the subcapital regions (⅓ subcaptial, green and ⅔ subcaptial, black) are significantly lower than in calotte (yellow) .

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

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

Fragility fractures can cause significant morbidity and mortality in patients with osteoporosis and inflict a considerable medical and socioeconomic burden. Moreover, treatment of an osteoporotic fracture is challenging due to the decreased strength of the surrounding bone and suboptimal healing capacity, predisposing both to fixation failure and non-union. Whereas a systemic osteoporosis treatment acts slowly, local release of osteogenic agents in osteoporotic fracture would act rapidly to increase bone strength and quality, as well as to reduce the bone healing period and prevent development of a problematic non-union. The identification of agents with potential to stimulate bone formation and improve implant fixation strength in osteoporotic bone has raised hope for the fast augmentation of osteoporotic fractures. Stimulation of bone formation by local delivery of growth factors is an approach already in clinical use for the treatment of non-unions, and could be utilized for osteoporotic fractures as well. Small molecules have also gained ground as stable and inexpensive compounds to enhance bone formation and tackle osteoporosis. The aim of this project is identifies promising new candidate molecules and innovative approaches for the local drug delivery in osteoporotic bone (Figure 9.3.16). Bone anabolic and catabolic molecules such as bone morphogenetic protein, phytomolecule and strontium ranelate, have been compared in their ability to induce human mesenchymal stromal cells osteogenicity and mineralization in vitro. Their releases from delivery vehicules (hydrogel) have been compared.

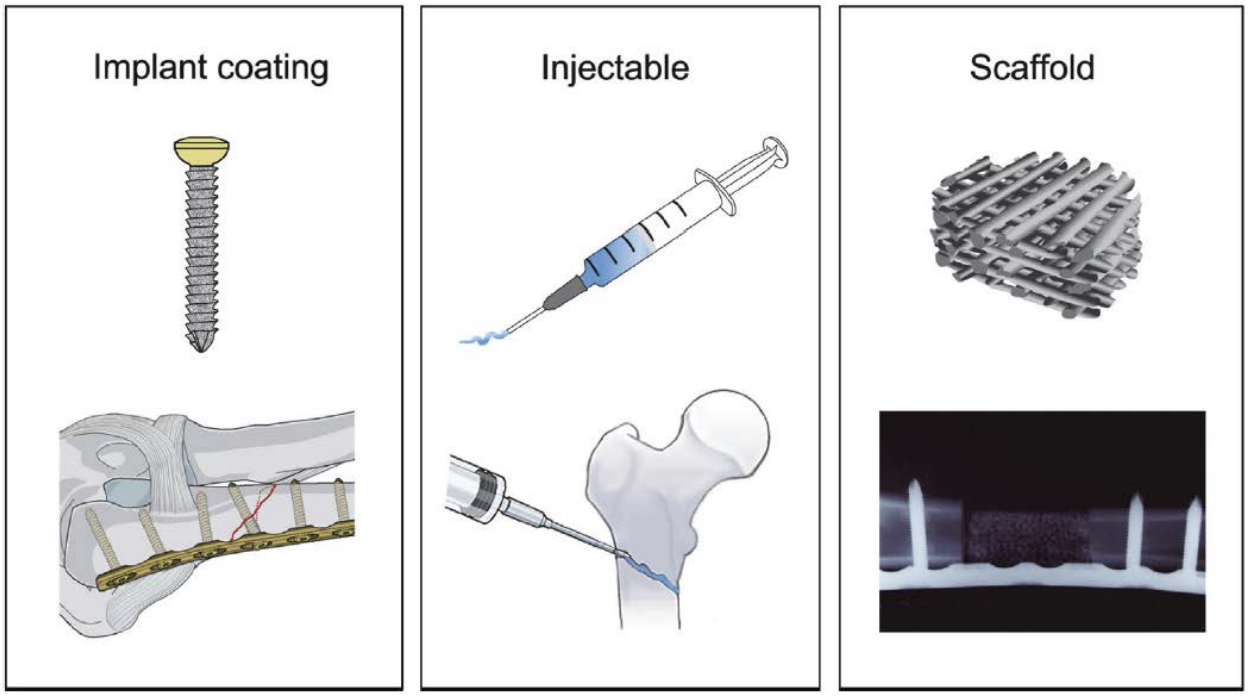


Figure 9.3.16: Schematics of potential local drug delivery strategies for osteoporotic fractures. Implant coatings, injectable bone cements and gels are considered feasible delivery approaches to target drugs for osteoporotic fractures. In case of large bone defects, delivery via scaffold structures can be considered. All images courtesy of AO Foundation, Switzerland. Left panel, lower image from AO Surgery Reference, www.aosurgery.org.

Pres:

Kyllönen L, Stoddart MJ, Alini M, Eglin D. Injectable Hydrogel Releasing Osteogenic Factors in Osteoporotic Bone Fracture. 2014 IBMS, Ghent, Belgium (Poster).

Pub:

Kyllönen L, Stoddart MJ, Alini M, Eglin D. Injectable hydrogel for the delivery of bone anabolic factors in osteoporotic bone fracture. Osteologie 2014;23/2:A6–7. SBMS Bern, Switzerland.

Kyllönen L, D'Este M, Alini M, Eglin D. Local drug delivery for enhancing fracture healing in osteoporotic bone. Acta Biomater. 2015;11:412-34.

Mechanisms of Mesenchymal Stem Cell Homing and Differentiation (HomeCell) (Ongoing) (M. Stoddart)
The homing mechanism of MSCs is of particular interest for clinical applications aimed at applying a more noninvasive systemic cell administration to treat inflammation and injury. During the natural repair of an injury, cells experience homing signals. Whereas cells used during tissue engineering approaches would not have experienced this homing signal. Additionally, on reaching an injured site the cells would receive inflammatory signals which are also likely to greatly affect their response. This project has been investiagating the secreastome of human mesenchymal stem cells, and how it can be modified in a clinically applicable approach. In this study we analysed the influence of two hour stimulation of mesenchymal stem cells (MSCs) with interleukin 1β (IL1β), granulocyte-colony stimulating factor (GCSF), stromal cell-derived factor 1 (SDF1) and stem cell factor (SCF). Our results demonstrated that a short 2 hour stimulation exerts pronounced effects on multiple cytokines genes and proteins expression in MSCs cells 48 and 72 hours later. The stimulation with certain factor regulated the expression of cytokines involved in various processes during fracture healing, including callus formation, remodelling, angiogenesis and bone cells differentiation. Altogether, the robust paracrine action of MSCs can be achieved within just 2 hours treatment. Co-culture models have also demonstartzed that the modified secreatome of the MSCs then leads to differential signals being provided to osteoblasts. These results suggest that integrating inflammatory modulation in bone tissue engineering would provide more powerful strategy to enhance bone regeneration processes.

Pres:
Preclinical Research translation to the Clinic: Towards intra-operative cell repair. 24.10.2014, TERMSTEM2014, Porto, Portugal (Invited Presentation)

Enhancing inflammatory and chemotactic signals to regulate bone regeneration. Ewa Czekanska, Jim Ralphs, Mauro R Alini, Martin Stoddart. ORS Annual meeting 2014: ORS: March 15th-18th

Pub:
Bara JJ, Richards RG, Alini M, Stoddart MJ. Bone marrow-derived mesenchymal stem cells change phenotype following in vitro culture: Implications for basic research and the clinic. Stem Cells. 2014 Jan 21. doi: 10.1002/stem.1649

Loebel C, Czekanska E, Staudacher J, Salzmann G, Richards RG, Alini M, Stoddart MJ. The calcification potential of human MSCs can be enhanced by interleukin-1β in osteogenic medium. J Tissue Eng Regen Med. 2014 Sep 4

Czekanska EM, Ralphs JR, Alini M, Stoddart MJ. Enhancing inflammatory and chemotactic signals to regulate bone regeneration. Eur Cell Mater. 2014 Oct 23;28:320-34

Analysis of Staphylococcal nasal colonization in orthopaedic surgeons attending AO Courses Davos 2013 (OrthoNose, M. Morgenstern)
Staphylococcus aureus and *Staphylococcus epidermidis* are two of the most common pathogens causing diseases, especially orthopaedic device related bone infections. It has been shown that asymptomatic colonized health-care workers are capable of transmitting Methicillin-resistant *Staphylococcus aureus* (MRSA) to others.The aim of OrthoNose is to determine the prevalence and antibiotic resistance patterns of *S.aureus* and *S.epidermidis* nasal colonization in a large cohort of global orthopaedic-, CMF-, and veterinarian surgeons at the AO Davos Courses 2013.
From a cohort of 1,166 surgeons, we found an average *S. aureus* nasal colonization rate of 28.0%. MRSA prevalence averaged 2.0%, although significant regional variations were observed. Recent use of systemic antibiotics was associated with higher rates of carriage of resistant staphylococci.
This study shows rates of nasal colonization for methicillin sensitive *Staphylococcus aureus* and MRSA in surgeons are similar to the general population.

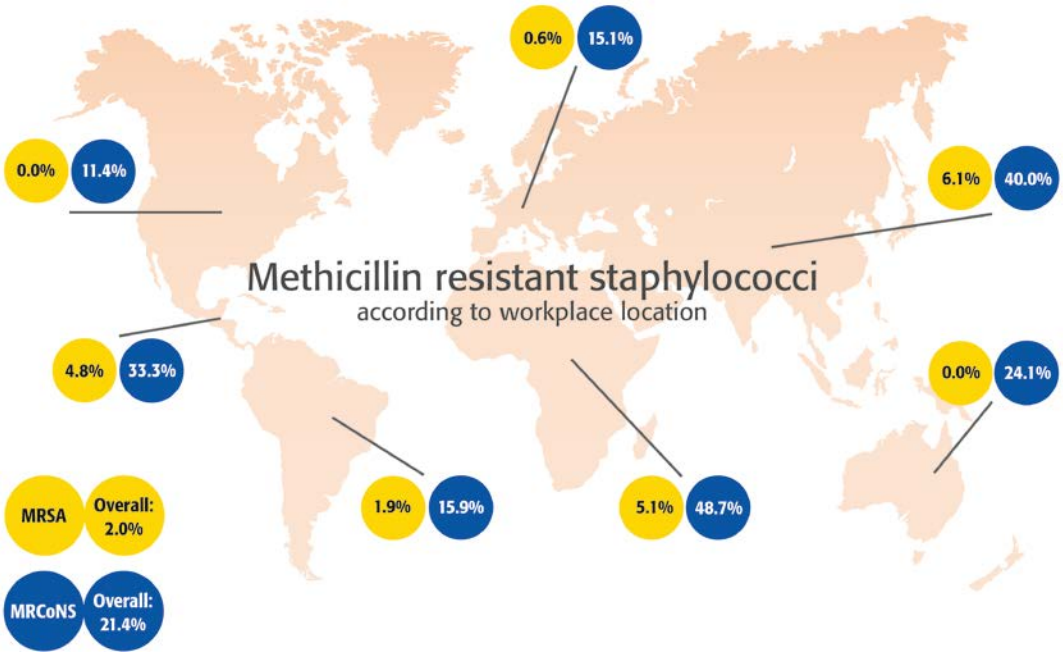


Figure 9.3.17: World map showing surgeon workplace and nasal carriage of MRSA and MRCoNS

Pres:
Morgenstern M, Post V, Moriarty TF, Richards RG, Kates SL. Nasal Colonization of Orthopedic surgeons with multi-resistant bacteria 2014 EORS (oral)

Partners:
- Kates S (MD), University of Rochester, USA
- Morgenstern M (MD), BGU Murnau, Germany

Development of clinically relevant animal models for investigating musculoskeletal Infections; their treatment, prevention and diagnosis (Infect-fx, D. Arens)
In order to more accurately mimic the clinical situation observed in infection after osteosynthesis, the infect-fx project has developed a rabbit fracture model allows assessment of the impact of infection on fracture healing and the impact of interventional strategies in a clinically relevant model.
A custom-made humeral nail was developed in collaboration with RISystem AG and the preclinical testing programme. The osteotomy model was successfully developed, whereby a 100% healing rate was observed in rabbits receiving the new nail, and in a plate group utilizing a commercially available locking plate. The rabbit osteotomy model has recently been further developed to incorporate osteomyelitis. In the osteomyelitis model, we have performed a dose response curve for *S. aureus*. The model displays signs of localised infection, without systemic effects. With this model established, it will allow us to reduce the number of animals required in future studies. Current activities are comparing the resistance against infection of titanium and steel plates, with differeing surface topographies.

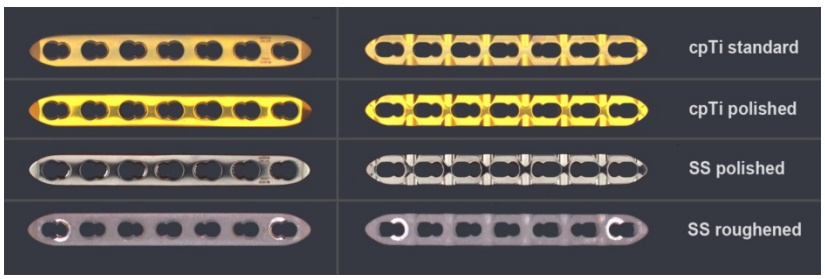


Figure 9.3.18: Implants with different materials (commercially pure Titanium (cpTi) and Stainless Steel (SS) and different topographies (polished, standard or roughened) are shown. The resistance against infection of these different implants is currently being testedin a rabbit humeral osteotomy model.

Pres:
Moriarty TF, Richards RG. Rabbit and other animal models for bone related medical device infection. 2014 iPROMEDAI

Partner:
- RISystem AG, Davos, Switzerland

Molecular epidemiology of Staphylococcus isolates from musculoskeletal infections associated with fracture fixation devices (StaphTyp, V. Post)
From the on-going AOTRC-funded project STAPHTYP, approximately 400 *S. aureus* and 150 *S. epidermidis* isolates have been collected from patients with implant-related bone infection. These isolates have been specifically selected from infections associated with fracture fixation implants, alongside prosthetic joint, osteomyelitis and numerous control groups. The results showed that *S. aureus* isolates display significant repertoire of virulence factors and a clonal nature. There are however, significant trends, which may indicate the virulence requirement between implant and non-implant related osteomyelitis do not entirely overlap.
In the most recent activity of the STAPHTYP project we complemented the laboratory analysis with clinical observation and follow up (e.g. complete healing, persisting infection etc. at 2 years). We have now performed whole genome sequencing of these isolates to provide data that surpass that feasible by conventional microbiology techniques. The data is currently being analysed, detailing the link between lab investigations such as biofilm formation and genome sequence and cross reference this data with patient outcome. A small number of patients have also suffered recurrent infections and we have isolated these sequential isolates, which offer great potential for monitoring the bacterial adaptation to bone infection, which has not been studied to date.

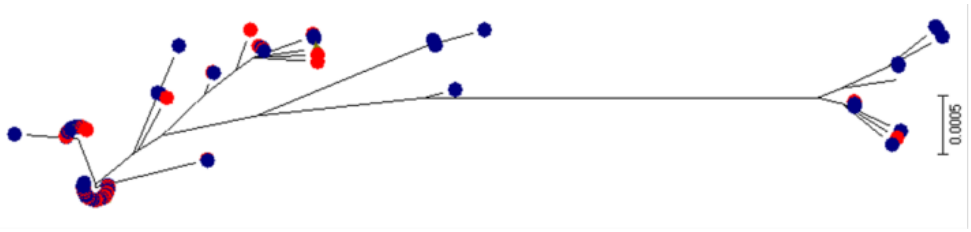


Figure 9.3.19: Phylogenetic tree of the whole genome sequenced *S. epidermids* isolates. Red dot: negative outcome (amputation persistent fistula etc.). Blue dot: healed without incident.

Pres:
Morgenstern M, Erichsen C, Post V, Hungerer S, Militz M, Moriarty TF, Richards G, Bühren. Implantat Infektionen mit *Staphylococcus epidermidis* - Korrelation zwischen klinischem Outcome und bakteriellen Eigenschaften. 2014 DKOU (oral)

Erichsen C, Post V, Morgenstern M, Hungerer S, Militz M, Moriarty TF, Richards RG, Bühren V. Correlation between bacterial phenotype and clinical outcome in orthopedic device related bone infections with *Staphylococcus aureus*. 2014 EBJIS (oral)

Pub:
Post V, Wahl P, Uckay I, Ochsner P, Zimmerli W, Corvec S, Loiez C, Richards RG, Moriarty TF. Phenotypic and genotypic characterisation of *Staphylococcus aureus* causing musculoskeletal infections. Int J Med Microbiol 2014;304(5-6):565-76

Partners:
- Mario Morgenstern (MD), BGU Murnau, Murnau, Germany
- Samuel Sheppard (Prof), University of Swansea, Swansea, UK

Micro CT for Imaging of Implant Associated Orthopedic Infections (ImagIn, F. Moriarty)
The aim of this study was to evaluate morphological changes of bone adjacent to a bacteria-colonized implant, with the aim of identifying temporal patterns that are characteristic of infection. Together with the CT Imaging focus area, we have followed the dynamic changes occurring in bone in a rat infected screw model using micro CT, which were verified postmortem by bacteriology, histology, and mechanical testing. The results follow clinical observations whereby *S. aureus* causes rapid bone loss, whilst *S. epidermidis* causes less significant bone loss. In an additional development, we have been able to calculate screw pull out force using Finite Element models, and these have been proven to be accurate based on post mortem biomechanical tets.
The most recent activities have focussed upon the comparison of different pathogens, including *S. epidermidis* and *Propionibacterium acnes*. These pathogens cause clinically diverse symptoms, and the model clearly could differentiate between these pathogens based solely upon bone loss adjacent to the implant. This model is now a proven tool for monitoring infection-induced bone changes in a living animals.

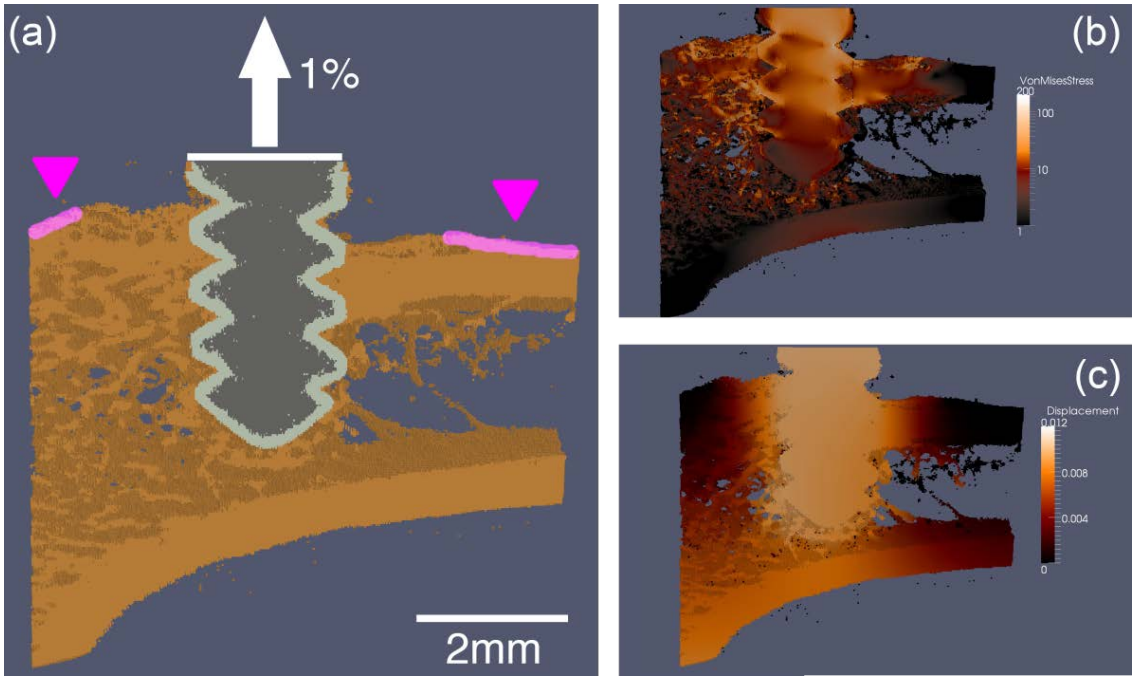
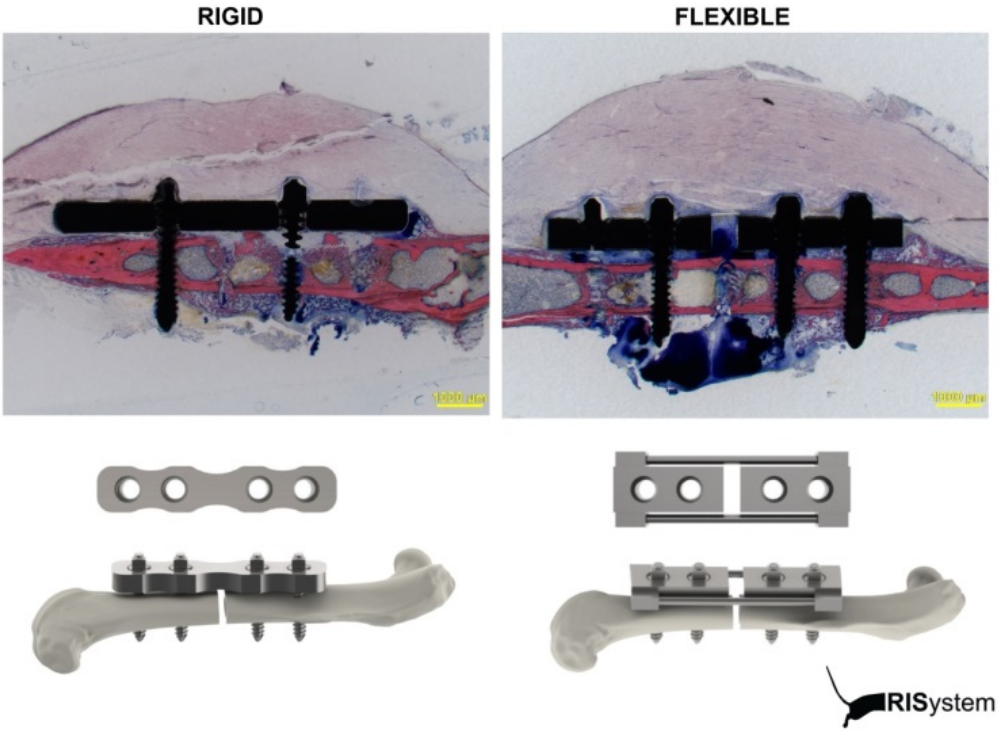


Figure 9.3.20: Illustration of teh Finite Element analysis in the rat model of implant infection: (a) Micro finite element pullout model.(b) Computed VonMises stress distribution. (c) Computed displacement field.

Pres:
Moriarty TF, Stadelmann V, Richards RG. Patterns of bone evolution near implants experimentally colonised by staphylococci and propionibacteria. 2014 EBJIS (oral)

Assessing the Role of the Implant Material and stability on the Development of Infection (Immunobact, M. Sabaté Brescó)
Clinical belief ditates that instability of an implanted device increases the risk of developing an infection. However, little is known about the mechanisms underlying this phenomenon. We have developed a murine femur osteotomy model, with rigid and flexible internal fixators, to study the influence of implant stability on the development of infection. A clinical *S. epidermidis* isolate has been used to contaminate the operative field and the progression of the infection has been assessed after several days and weeks. The results showed that, for most of the time-points, animals carrying a rigid implant could clear the infection in a higher percentage. At the same time, the immune response is being characterized in the different contexts (stable vs unstable, not-infected vs infected) to better understand the influence of biomechanics on infection susceptibility.



Pres:
Sabaté Brescó M, Kluge K, Ziegler M, Richards RG, O'Mahony L, Moriarty F. Immune response during bone healing in a murine fracture model with osteomyelitis: role of biomechanical stability. 2014 Osteoimmunology

Sabaté Brescó M, Kluge K, Ziegler M, Richards RG, O'Mahony L, Moriarty F. Assessing the role of implant stability on the development of staphylococcal osteomyelitis in a murine fracture model. 2014 Academia Raetica

Moriarty TF, Sabaté Brescó M, O'Mahony L, Kluge K, Richards RG, Zeiter S. Staphylococcus epidermidis infection increases in the presence of unstable fixation: evidence in a murine fracture model. 2014 EBJIS; 2014

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

Development of a large animal model to study the biology of two-stage hardware exchange due to implant related osteomyelitis (StaphAb, V. Post, T. Schmid)
This project involves the development of a model of two-stage hardware exchange of an infected implant. The primary aims and guiding principles of this phase of the project are to 1) mimic clinical treatment protocols, 2) avoid obvious sub-standard care to the sheep, and 3) achieve a high failure rate upon completion i.e. recurrence of the infection.
Once established, treatment of this infection involved removal of the infected nail, debridement (reaming, the use of a femoral canal brush) and insertion of a vancomycin and gentamicin loaded cement nail (spacer). Systemic antibiotics were administered for two weeks, after which time, the second stage of the revision was performed (spacer removal and definitive fixation). Experimental results show that a chronic infection is present at 8 weeks postoperatively, and that a full treatment protocol of debridement, lavage and implant exchange with a short interval antibiotic treatment is capable of clearing the infection.

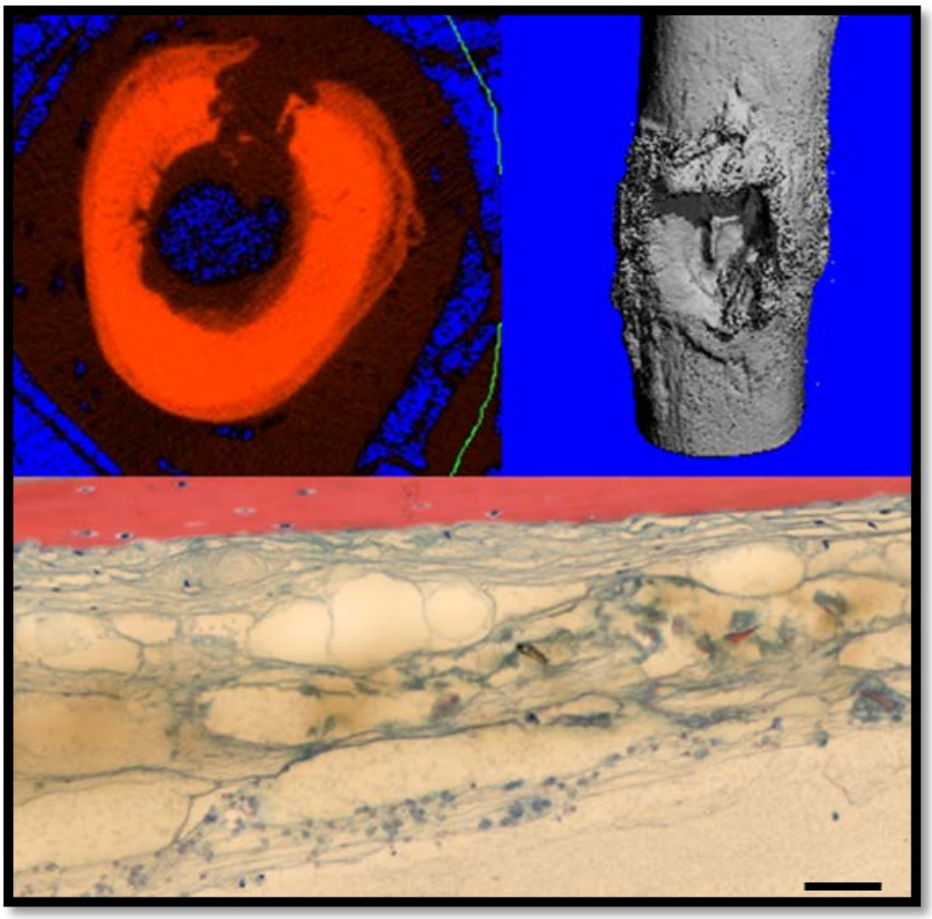


Figure 9.3.21: Eight weeks post-inoculation, the sheep display radiographic signs of infection with osteolysis around the entry point of the bacterial inoculum (upper panel). Histological sections revealed presence of a series of bacterial micro-colonies along the fibrous tissue membrane that formed adjacent to the implant (bar 100 µm).

Partners:

- Steven Kates (Prof), University of Rochester, Rochester, USA
- Edward Schwarz (Prof), University of Rochester, Rochester, USA

EpiLog: *S. epidermidis* bone infections associated with implanted medical devices in human patients (Epi-Log, B. Stanic)

Infection remains a serious problem in orthopedic and trauma surgery. Infections caused by *Staphylococcus epidermidis* are typically difficult to diagnose due to teh relatively moderate symptoms involved. A major limitation in the ability to diagnose these infections is due to the limited knowledge of the cellular and molecular mechanisms governing the immune response to *S. epidermidis* infection. In this project, we have begun collecting biological samples from with an *S. epidermidis* bone infection. In the first six months of this project, we have prepared the Clinical Investigation Plan and ethical approval has been granted. A sample processing facility has been commissioned at the hospital site, which will allow on-site, immediate processing of fresh specimens.

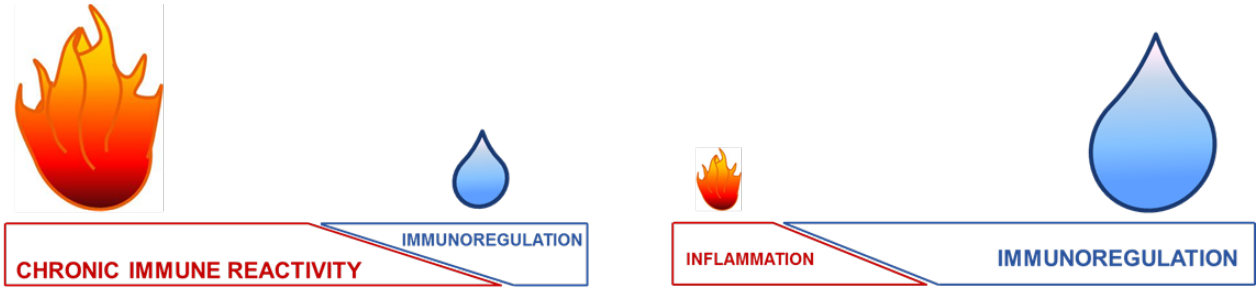


Figure 9.3.22: Simplified schematic of alternative immune responses that may be elicited by different pathogens. The Epi-Log project will investigate how *S. epidermidis* infected patients fit within this scheme.

Partners:

- Morgenstern Mario (MD), BGU Murnau, Murnau, Germany
- John L Daiss, University of Rochester, New York, USA

9.4 AOVET

Development of a novel trans–cortical fixation pin–sleeve cast system for managing unstable distal limb fractures in horses (U. Eberli)

Problem: The transfixation pin cast (TCP) is the preferred method to treat equine distal limb fractures which are contaminated, severely comminuted or associated with extensive soft-tissue trauma. However, using the TCP can lead to complications at the bone implant interface. Previously, a pin-sleeve cast system was developed at the ARI to overcome the most important issue of pin-loosening. Although peak strains could be reduced and more evenly distributed in the bone around the pins when using the pin-sleeve cast system, its dimensions were judged by experienced equine orthopaedic surgeons to be too large to be usable in practice.

Goal: To reduce the pin-sleeve cast system dimensions to meet the surgeons' requirements while still providing the necessary system stiffness and stability.

Methods: A modified pin-sleeve cast system (PSC) consisting of two separate sleeves with reduced outer diameter was tested biomechanically and by means of finite element analysis (FEA). Two cadaveric distal horse limbs were instrumented with two or three PSC systems, respectively and biomechanically tested under cyclic axial loading until failure. An FE model of this setup was built, analysed and validated via biomechanical testing. Furthermore, the gain in system stiffness by adding pin pretension was evaluated by FEA after determining the optimal pin pretension numerically. While in biomechanical testing parameters of interest were the occurrence of pin-sleeve contact as well as pin failure, in FEA the critical load was defined as the minimum of those causing pin-sleeve contact and pin yielding.

Results: The PSC system appears not to provide sufficient stability to justify its application in adult horses.

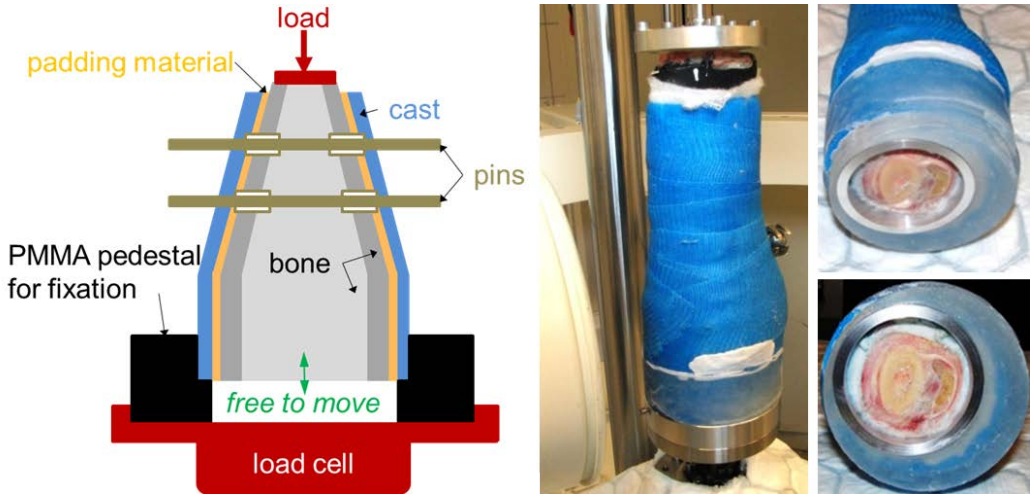


Figure 9.4.1: Schematic drawing of the test setup (left) and pictures taken from a specimen mounted for biomechanical testing on the machine with a detailed view of the distal embedding (right).

Partners:

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

9.5 TK System

Development of a supplementary device for fracture fixation implants to monitor the course of fracture healing using a novel data collection concept (SmartFix, ongoing) (M. Windolf)
Problem: Information on healing progression and load-bearing characteristics in fracture patients is only barely tapped due to the inaccessibility of a confined biological region and the limited value of radiographic methods. A novel approach to continuously assess fracture motion from implant bending and extract relevant healing parameters therefrom has been developed at the AO Research Institute Davos (ARI) within a related project (ImpCon) recently. Based on this principle, a prototype device, AO Fracture Monitor, for healing assessment in external fixation patients has been created to non-invasively prove the concept in clinics.

Goal: To develop a device for monitoring the process of bone healing via implant deflections of external and internal fixators and to prove its function in clinics.

Results: Eight prototype devices for use with external fixators, complying with CE requirements, were produced in the ARI prototype workshop. The software user interface was reworked for enhanced functionality and greater ease of use. A web platform was developed for zentralized collection, evaluation and visualization of monitoring data. A comprehensive documentation covering a detailed system description, user manual and risk analysis was prepared. Together with AOCID and Prof. D. Höntzsch as Principal Investigator, a clinical study was started after approval of the local ethics committee had been obtained. A first prototype of a bridging plate monitoring system was realized. For stepwise miniaturization and standardization of the wireless transmission protocol, another phase for electronics development was initialized with the final goal of an implantable monitoring system.

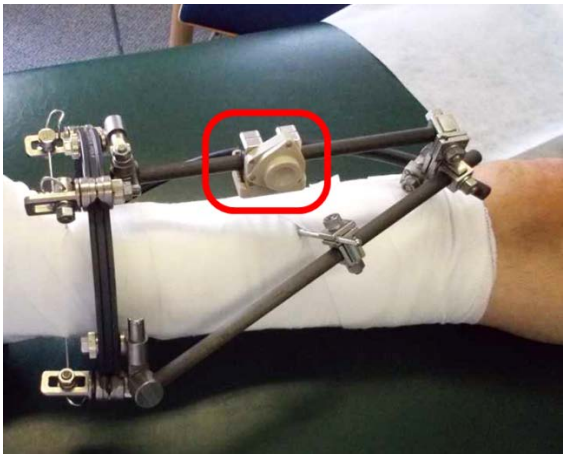



Figure 9.5.1: Prof Dankward Hoentzsch attaching the AO Fracture Monitor to a patient suffering from a tibia fracture treated with an external fixator.

Partners:

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

Biomechanical evaluation of femoral neck fracture fixation with a new less invasive implant system in comparison to Three Cannulated Screws, DHS Blade and DHS with antirotation screw (I. Zderic)

Problem: Three Cannulated Screws (3CS), a Dynamic Hip Screw (DHS) with antirotation screw (DHS-Screw) or with a Blade (DHS-Blade) are the gold standards for fixation of unstable femoral neck fractures. Compared to 3CS, both DHS systems require a larger skin incision with a more extensive soft tissue dissection while providing the benefit of superior stability. A newly designed implant system, which is under development, combines the advantages of angular stability with a less invasive surgical technique.

Goal: To evaluate the biomechanical performance of the new less invasive implant system in comparison to established methods for fixation of the femoral neck in a cadaveric model.

Results: From a biomechanical point of view, the new implant system is a valid alternative to treat unstable femoral neck fractures, representing the advantages of a minimal invasive implant with comparable stability to the two DHS systems and superior to 3CS.

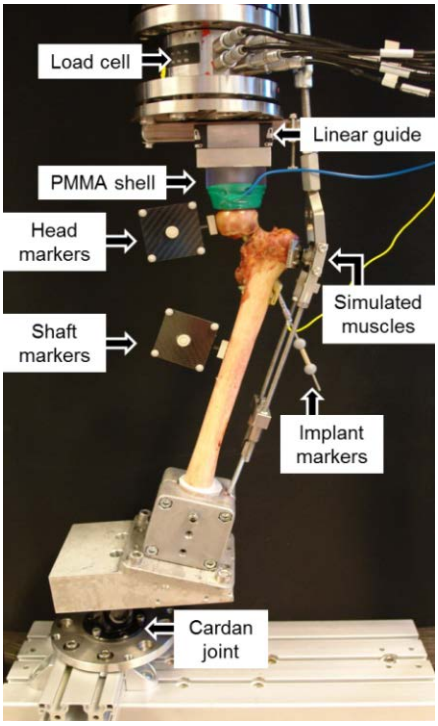


Figure 9.5.2: Setup with a specimen for biomechanical testing.

Partners:

- Stoffel K (Prof, MD), Cantonal Hospital Baselland and University Basel, Liestal, Switzerland
- Sommer C (MD), Cantonal Hospital Graubuenden, Chur, Switzerland
- Oswald M, DePuy Synthes, Suzhou, China
- Müller D, DePuy Synthes, Zuchwil, Switzerland

Biomechanical study on proximal plate fixation techniques in periprosthetic femoral shaft fractures (M. Lenz)

Problem: Treatment of periprosthetic femoral fractures gains more importance due to the increasing number of total hip arthroplasties. Plate osteosynthesis with angular stable locking screws is a preferred treatment option. Exact bicortical placement of angulated locking screws next to the prosthesis stem is difficult because of the narrow possible corridor for bypassing the prosthesis stem.

Goal: To evaluate the potential of additional plate anchorage in the greater trochanter via a hook and compare it to a fixation with subtrochanterically placed locking attachment plate in an in-vitro periprosthetic fracture model (Vancouver type B1).

Results: The potential of additional plate anchorage in the greater trochanter was evaluated. However, subtrochanterically located locking attachment plates provide high fixation stability so that additional hook plate anchorage in the greater trochanter interfering with the iliotibial tract is not necessarily needed.

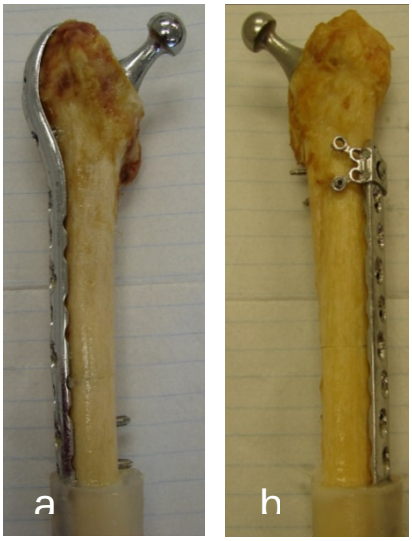


Figure 9.5.3: Specimens prepared for biomechanical testing with a hook plate (left) and LCP with locking attachment plate (right).

Partners:

- Lenz M (MD), University Hospital Jena, Germany
- Stoffel K (Prof, MD), University of Basel, Switzerland

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

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

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

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

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

To goal of this project is to design and test an FE workflow based on three-dimensional (3D) bone models generated from Computed Tomography scans. Two work packages will be defined. In the first work package a library of standardized 3D bone models will be created using techniques for 3D statistical modeling and analysis and for virtual bone design. In the second one CT scans will be acquired obtained from ten pairs of fresh frozen humerus samples in order to create 3D bone models serving as models to validate the workflow.

Performed within the framework of the TK Upper Extremity Expert Group, the project forms a collaboration between ARI Human Morphology Services (HMS) and Depuy Synthes. ARI HMS will take over the responsibility for creating the 3D bone models required in work packages 1 and 2 whereas Depuy Synthes will be responsible for designing and testing the FE workflow.

Partner:

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

In–vitro biomechanical investigation of growth plate modulation systems on surrogate bone models (Y. Agarwal)

Problem: Limb deformities, mainly leg length discrepancies and varus/valgus abnormalities of the knee, are common problems encountered daily by pediatric orthopedic surgeons. Although 'guided growth' for deformity correction harnessing the ability of a growing bone to undergo plastic deformity is an old paediatric orthopaedic principle, there are still many questions to be answered yet with regard to the guided growth.

Goal: To develop a test setup and loading protocol for biomechanical testing to investigate in–vitro growth plate modulation systems on surrogate bone models and test its feasibility with the existing implant for deformity correction.

Results: The developed test setup and loading protocol for in–vitro biomechanical investigation of growth plate modulation systems worked well for two construct types with bicortical and monocortical screw fixation.

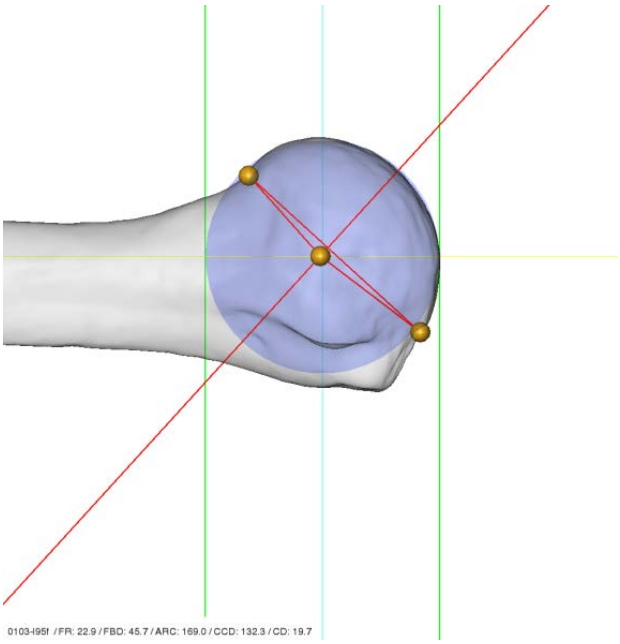


Figure 9.5.4: Development of a computer tool to assess different morphological parameters in 3D computer models of the proximal humerus.

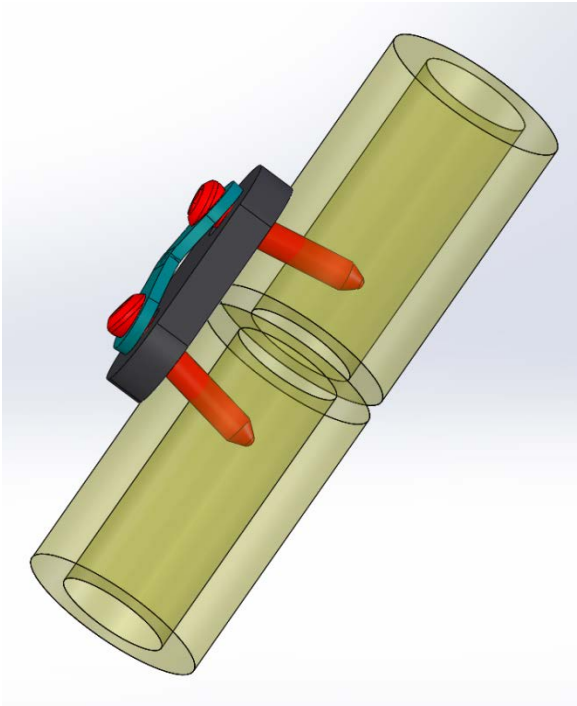


Figure 9.5.5: Model of a specimen, comprising two cylindrical fragments bridged with a bar-and-plate system using two diverging screws.

Partners:

- Slongo T (Prof, MD) University Children's Hospital, Berne, CH
- Hunter JB (MD), Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK

9.6 ARI Exploratory Research

Bone cement flow behavior analysis by injection through medical cannulas (I. Zderic)
Problem: Vertebroplasty is an established method for treatment of osteoporotic compression fractures aiming to restore mechanical strength of the affected bone and to alleviate pain. Cement leakage is one of the most serious adverse events and a well-known health risk for the patient undergoing vertebroplasty as there is a high risk of embolism or neurological damage. Pre-operative planning of the cement filling process can provide significant benefits in terms of reduced complication rates. However, to develop such in silico tools, experimental data is needed in order to validate them on a sound base. Therefore, experimental data on the cement flow behavior in each step of the injection path, including the flow within the medical cannulas need to be generated.

Goal: To investigate the initial step of an augmentation process by analyzing the flow behavior of bone cement through medical cannulas.

Results:
Subsequently injected cement portions did not intermix and no turbulent cement flow was observed. Cement flow through medical cannulas is laminar, can therefore be regarded as predictable under constant injection parameters. This fundamental study could serve for future simulations to determine the initial conditions of the cement flow before it exits the cannula.

Figure 9.6.1: Test setup with pre-filled syringe mounted for injection.

Partners:
- Boger A (Prof, PhD), University of Applied Sciences, Ansbach, Germany
- Röhrle O (Prof, PhD), Institute of Applied Mechanics and Stuttgart Research Centre for Simulation Technology, Stuttgart, Germany

Assessment of cement flow during injection within bone (V. Stadelmann, I. Zderic)
Problem: Cement distribution strongly influences the mechanical outcome of bone augmentation. To refine the augmentation procedures, a better control of cement distributions is needed. For that, one needs a better understanding of cement flows within bone. Cement flow is a dynamic process in a complex spatial structure, and standard imaging techniques cannot fully capture it.

Goal: To develop a new composite imaging approach to capture bone augmentation procedure in space and in time.

Results: Thirteen vertebrae were used and prepared for vertebroplasty. They were first microCT-scanned at high resolution. Then, time-lapsed CT scans were acquired while bone cement was injected one milliliter at a time into the vertebrae. The scans were superimposed onto the high-resolution scans to obtain composite images of the cement distribution merged within the bone structure producing time-lapsed recording of the cement flow.
In addition to composite time-lapsed CT scans, Finite Element models allow to represent evolution of strain patterns under a fixed load for each step of vertebroplasty. This gives a novel insight into the evolution of mechanical impact of cement augmentation. Prior to reaching endplate-to-endplate contact, high strains are located in the cortical shell. As cement injection progresses, high strains appear in the trabecular structure between the cement cloud and the endplates until cement-to-endplate contact is established. Finally, the high strains in the cortical shell disappear when the cement cloud finally contacts the shell on the side.

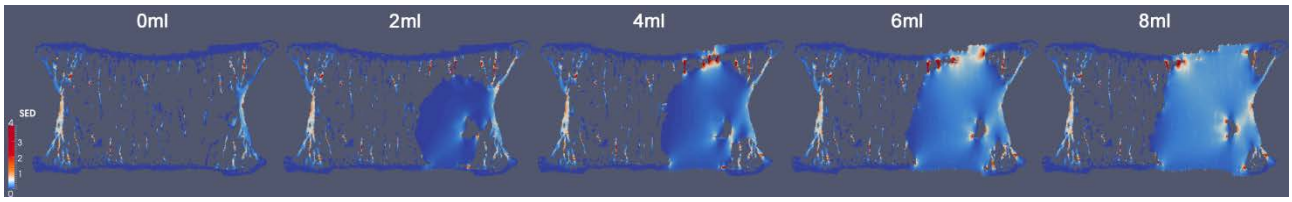


Figure 9.6.2: Progression of cement distribution with a L4 vertebrae during vertebroplasty, as captured by our composite time-lapsed CT technique. Bone and cement colors represent the strain energy density under a constant axial load simulating compression.

Pres:
Baur A, Eberli U, Zderic I, Wahl D, Windolf M, Latt J, Stadelmann VA. Time-lapsed computed tomography and numerical simulations of cement flow during verterbroplasties. Computer Methods Biomechanics and Biomedical Engineering 2014, Amsterdam

Partners:
- Boger A (Prof, PhD), University of Applied Sciences, Ansbach, Germany
- Röhrle O (Prof, PhD), Institute of Applied Mechanics and Stuttgart Research Centre for Simulation Technology, Stuttgart, Germany

Non-invasive biomechanical monitoring of bone healing in a dynamized bone defect in sheep (U. Eberli)
Problem: Nowadays clinicians do not have a quantitative tool to evaluate the stability of healing bone. Computed tomography (CT) provides three-dimensional structural information about calcified tissues, but its image quality is limited in presence of metallic fixation devices. To use CT with unrestricted image quality, we developed a radiolucent implant. Additionally, the implant incorporated displacement sensors enabling to monitor bone healing mechanically. Since several previouw studies have shown that mechanical stimulation influences bone healing, the implant was designed to be axially dynamizable in compression.

Goal: To investigate temporal patterns of bone healing and to evaluate the mechanical quality of healing bone non-invasively in vivo. Load counts from the displacement sensor as well as finite element analysis (FEA) based solely on architectural data from CT images shall be used to reach our aim.

Methods: Two adult Swiss white alpine sheep were operated and monitored over a healing period of 7 months. At surgery, the implant was fixed to the medial aspect of the left tibia and a 6 mm defect was created. Bone healing and the associated evolution of mechanical properties of the newly formed bone were monitored by means of in vivo CT and CT image-based Finite Element Analysis (FEA). Interfragmentary motion was monitored continuously with onboard data processing over the first four months.

Results: The two sheep showed very different defect healing, with the animal forming proper callus and showing bone densification, and the other animal showing no visible callus formation and poor bone densification. At week 10 post-op a first connection of the bone over the 6 mm segmental defect was observed in the CT scans of the former. From that point on, the torsional stiffness increased overall towards the end of the study.
This study shows that our model and workflow could allow assessment of bone stability during the healing process non-invasively. However, more specimens are needed to optimize the FE models and to validate them with mechanical testing. The difference in healing between the two animals may originate from several factors such as diverse anatomical constitutions, variable sliding capacity of the implants etc. Our custom-made implant has proven to be mechanically reliable and its radiolucency allows acquisition of perfect CT images without any artifacts in the region of interest. CT data acquired during the healing process can be converted easily into FE models to evaluate the bone stiffness.

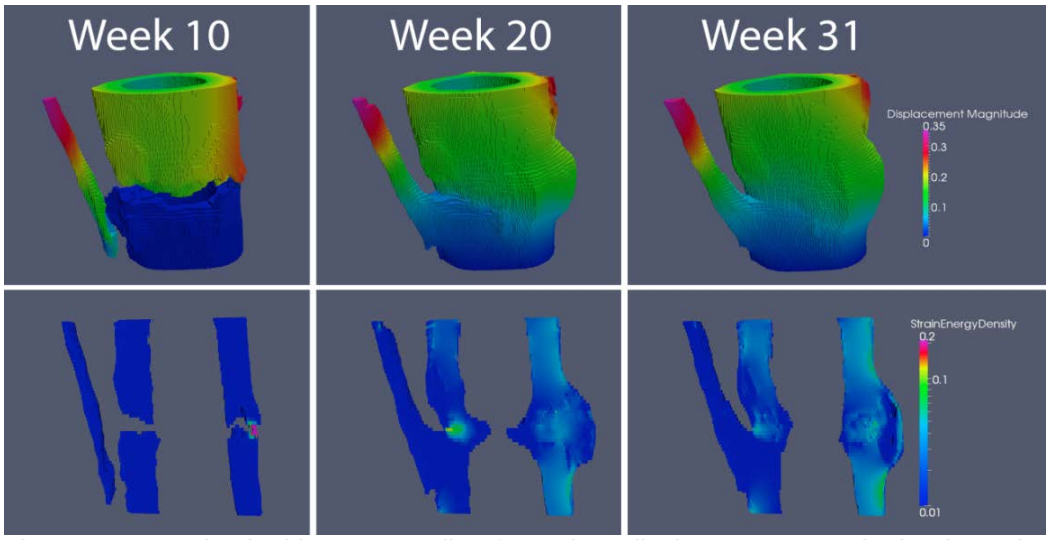


Figure 9.6.3: Animal with proper callus formation: displacement magnitudes in and around the region of interest in 3 exemplary time points (top row) and representative thick slices of the corresponding FE models showing Strain Energy Densities (bottom row).

Pres:
Eberli U, Schwyn R, Ernst M, Windolf M, Stadelmann VA. 2014. SBMS.
Eberli U, Schwyn R, Ernst M, Zderic I, Windolf M, Stadelmann VA. 2014 EORS.
Eberli U, Schwyn R, Ernst M, Windolf M, Stadelmann VA. 2014. WCB.
Eberli U, Schwyn R, Ernst M, Windolf M, Stadelmann VA. 2014. Academia Raetica.
Eberli U, Schwyn R, Ernst M, Windolf M, Stadelmann VA. 2014. CMBBE.

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

Regeneration of articular cartilage after a trauma is still highly limited and often the only acceptable method is through surgical replacement. Our main objective has evolved during this project and after addressing first hard biomaterial scaffolds, we addressed the use of soft biomaterials for cells and drug encapsulation. Hard poly(ester-urethane) scaffolds have been assessed in an osteochondral defect model *in vivo*, showing the lack of integration to the cartilage of the slow degradable biomaterial. Hydrogels are soft biomaterials which pose interesting features for cartilage regeneration strategies, such as the option for injectability and in situ gelation resulting in optimal filling of defects. *In vitro* and *in vivo* studies showed that chondrogenesis of human mesenchymal stromal cells (hMSCs) in an osteochondral environment was hydrogel-dependent (Figure 9.6.4). Finally, a thermoresponsive hyaluronan hydrogel formulation has shown to be biocompatible and biodegradable.The best combinations of hard and soft biomaterials are being currently tested.

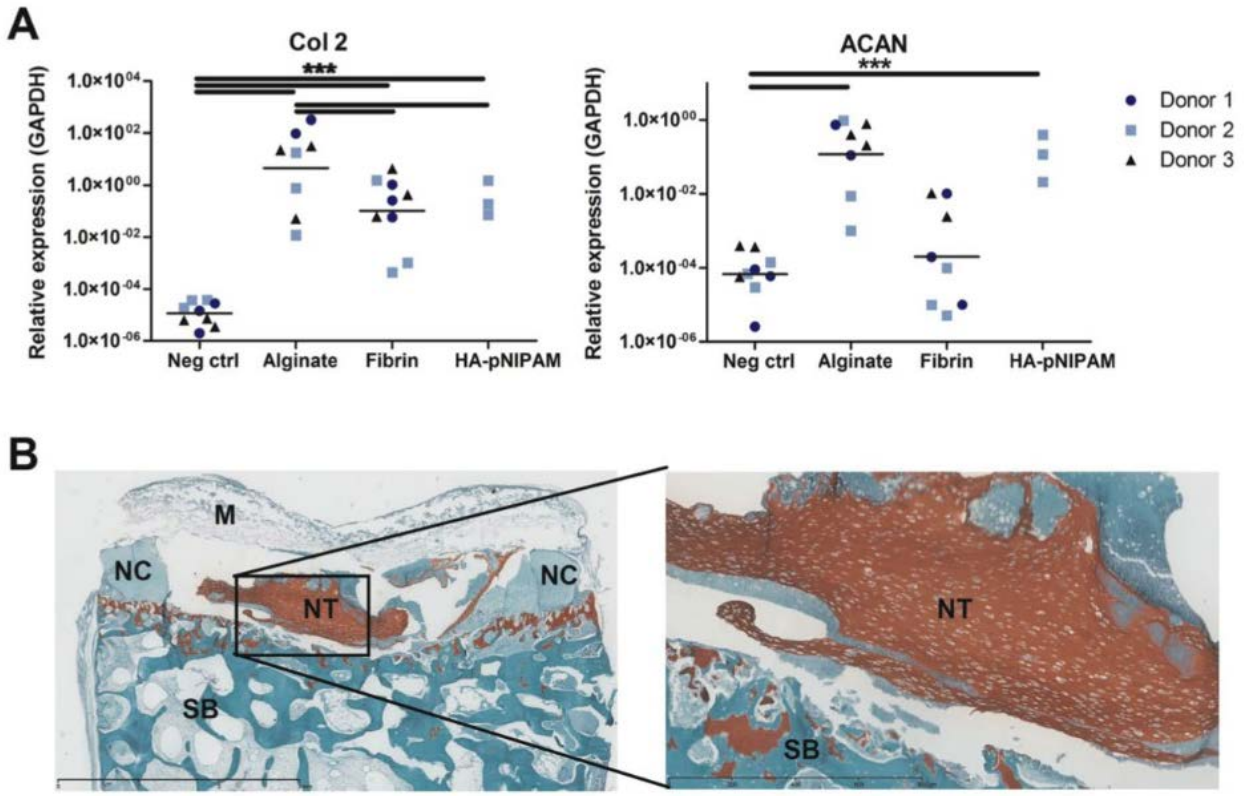


Figure 9.6.4: A) Gene expression of Col2 and ACAN relative to GAPDH of hBMSC-hydrogel constructs cultured in incomplete chondrogenic medium in simulated cartilage defects in an osteochondral biopsy model for 28 days. B) Representative safranin-O stained sections of hMSC-alginate constructs in simulated cartilage defects in an osteochondral biopsy model that were implanted subcutaneously in nude mice for 12 weeks.

Pres:

Eglin D, D'Este M, Dresing I, Alini M. Injectable Thermo-responsive Hyaluronan Hydrogel in a Rabbit Osteochondral Defect Model. 2014 ESB conference, Sept. 2014, Liverpool, UK (Poster).

Petta D, Eglin D, Dresing I, Alini M, D'Este M. Thermoresponsive hyaluronan hydrogel for osteochondral defects repair. SIB 2014, June 2014, Italy (Oral).

Soenjaya Y, Eglin D, Willett TL, Holdsworth DW, Alini M, Hunter GK, Goldberg HA. Healing of Rat Calvarial Defect with Nanohydroxyapatite/Poly(Ester-urethane) Scaffolds Loaded With rhBMP-2. 2014 ORS, March 2014, New Orleans, US (Poster).

Pub:
Laschke MW, Grasser C, Kleer S, Scheuer C, Eglin D, Alini M, Menger MD. Adipose tissue-derived microvascular fragments from aged donors exhibit an impaired vascularisation capacity. Eur Cell Mater 2014;28:287–98.

Dresing I, Zeiter S, Auer J, Alini M, Eglin D. Evaluation of a press-fit osteochondral poly(ester-urethane) scaffold in a rabbit defect model. J Mater Sci Mater Med 2014;25(7):1691–700

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

Partners:
- Laschke M (PD Dr), University Saarland, Homburg, Germany
- Goldberg HA (Prof), University of Western Ontario, Canada
- van Osch GJ (Prof), ERASMUS University, The Netherlands
- Acute Cartilage Injury Collaborative Research Programs Consortium

Thermoresponsive hydrogels based on natural polysaccharide. CARTHA (Ongoing)
(D. Eglin)
Regeneration of articular cartilage after a trauma is still highly limited and often the only acceptable method is through surgical replacement. This research project proposes to develop a novel approach to create bioactive, biomimetic, multifunctional, and biodegradable tunable hydrogels that can be designed to specifically stimulate cells and biological repair processes in a controlled manner. A major motivation for this work is the potential to generate a simple material platform that can be used in minimally invasive procedures where they can be injected as liquids and form into solid gels upon crosslinking at the site of injury while displaying multiple desired biomolecular and physical signals.
A versatile approach was demonstrated to present clustered binding epitopes in an injectable, thermoresponsive hydrogel. Well-defined multivalent dendrimers bearing four integrin binding sequences and an azido moiety were covalently grafted to propargylamine-derived hyaluronic acid using copper-catalyzed alkyne–azide cycloaddition (CuAAC), and then combined with poly(*N*-isopropylacrylamide)-modified hyaluronan. The dendrimers were prepared by synthesizing a bifunctional diethylenetriamine pentaacetic acid core with azido and NHBoc oligo(ethylene glycol) aminoethyl branches, then further conjugated with solid-phase synthesized RGDS and DGRS peptides. Rheological measurements demonstrated that dendrimers do not influence the elastic or viscous moduli of thermoresponsive hyaluronan compositions at a relevant biological concentration. Finally, human mesenchymal stromal cells were encapsulated in the biomaterial and cultured for 21 days, demonstrating the faculty of this dendrimer-modified hydrogel as a molecular toolbox for tailoring the biofunctionality of thermoresponsive hyaluronan carriers for biomedical applications (Figure 9.6.5).

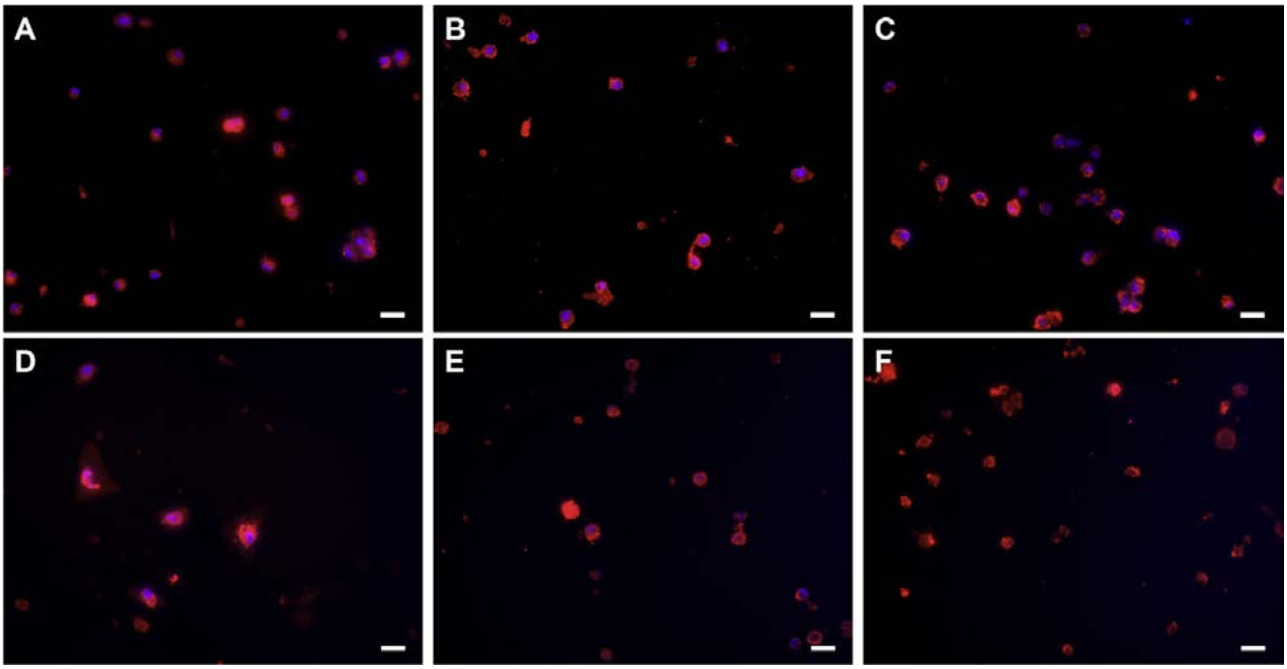


Figure 9.6.5: Fluorescent micrographs of PKH26 labeled cryosections of hMSC encapsulated in (A and D) the RGDS hydrogel, (B and E) the DGSR hydrogel and (C and F) the Hyal hydrogel after 7 (A, B, C) and 21 days (D, E, F) of culture in osteogenic medium. Scale bar: 20 µm.

Pres:
D'Este M, Alini M, Eglin D. Amidation via DMTMM: A New and Efficient Method for Hyaluronan Biomaterials Preparation. Sept 2014, ESB meeting, Liverpool, UK (Poster).

Seelbach R, Fransen P, Peroglio M, Duttenhoefer F, Alini M, Royo M, Mata A, Eglin D. Dendrimers Presenting Spatially Controlled Clusters of Binding Epitopes for Tailoring hMSCs Microenvironments. EORS 2014, Nantes, FR (oral).

Eglin D. Stimuli responsive hyaluronan materials for musculoskeletal repair. Sept 2014, eMRS fall meeting, Warsaw, PL (Invited speaker).

Pub:
D'Este M, Eglin D, Alini M. A systematic analysis of DMTMM vs EDC/NHS for ligation of amines to hyaluronan in water. Carbohydr Polym. 2014;108:239–46.

Seelbach R, Peroglio M, Fransen P, Royo M, Albericio F, Alini M, Eglin D, Mata A. Binding Epitope Decorated Dendrimers in Thermoreponsive Hyaluronic Acid Hydrogels Influence Stem Cells. J Tissue Eng Regen Med. 2014;8(S1):215 (TERMIS).

Seelbach RJ, Fransen P, Peroglio M, Pulido D, Lopez-Chicon P, Duttenhoefer F, Sauerbier S, Freiman T, Niemeyer P, Semino C, Albericio F, Alini M, Royo M, Mata A, Eglin D. Multivalent dendrimers presenting spatially controlled clusters of binding epitopes in thermoresponsive hyaluronan hydrogels. Acta Biomater. 2014;10(10):4340–50.

Partners:
- Duttenhoefer F (Dr) Universitätsklinik Freiburg, Germany
- Acute Cartilage Injury Collaborative Research Programs Consortium

Fibrous polymeric patch for annulus fibrosus repair. AFEPATCH (Ongoing) (D. Eglin)
Low back pain is a major public health problem in our society and the cause of significant morbidity. Recurrent intervertebral disc (IVD) herniation and degenerative disc disease have been identified as the most important factors contributing to persistent pain and disability after surgical discectomy. An annulus fibrosus (AF) closure device that provides immediate closure of the AF rupture, restores disc height, reduces further disc degeneration and enhances self-repair capacities is an unmet clinical need. In this project, a poly(ester-urethane) membrane was developed to cover a poly(trimethylene carbonate) (PTMC) scaffold seeded with human bone marrow derived mesenchymal stromal cells (MSCs) and assessed for AF rupture repair in a bovine organ culture annulotomy model under dynamic load for 14 days (Figure 9.6.6). The sutured membrane combined with the PTMC scaffold restored disc height of annulotomized discs and prevented protrusion of nucleus pulposus tissue. Implanted MSCs showed an up-regulated gene expression of type V collagen, a potential AF marker, indicating in-situ differentiation capability. Furthermore, MSCs delivered within PTMC scaffolds induced an up-regulation of anabolic gene expression and down-regulation of catabolic gene expression in adjacent native disc tissue, which may decelerate the degenerative process. In conclusion, the combined biomaterial and cellular approach has the potential to prevent disc re-herniation, stabilize disc height, and retard further degeneration of native disc tissue.

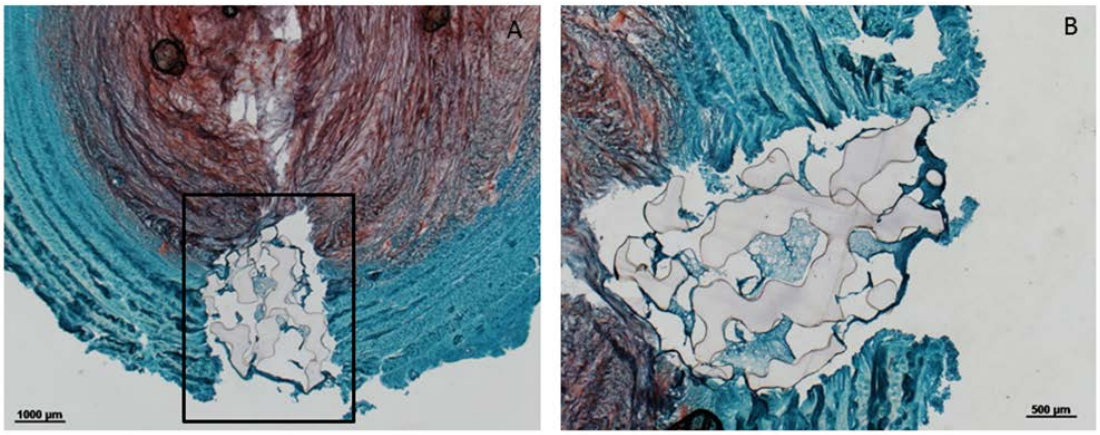


Figure 9.6.6: Representative Safranin O/Fast Green stained sections of annulotomized discs repaired with PU membrane and PTMC scaffold, cultured for 14 days. Scale bar: (A) 1000 µm, (B) 500 µm.

Pres:
Li Z, Pirvu T, Blanquer SB, Benneker LM, Grijpma DW, Alini M, Eglin D, Grad S. A combined cellular and biomaterial approach for annulus fibrosus rupture repair. 2014 Stem Cell Meeting

Pub:
Li Z, Pirvu T, Blanquer SB, Grijpma DW, Benneker LM, Alini M, Eglin D, Grad S. Transplantation of bone marrow derived mesenchymal stem cells embedded in poly(trimethylene carbonate) scaffold: mechanical and biological repair of ruptured annulus fibrosus. Eur Cell Mater 2014;28(Suppl 2):61 (ECM).

Li Z, Pirvu T, Benneker LM, Blanquer SB, Grijpma DW, Alini M, Eglin D, Grad S. A combined cellular and biomaterial approach for restoration of disc height and prevention of degeneration in annulotomized disc. Eur Spine J 2014;23(11),2501 (DWG).

Li Z, Peroglio M, Grad S, Eglin D, Alini M.Annulus Fibrosus Repair. Global Spine Journal 2014;4 S01 (WFSR).

Pirvu T, Blanquer SB, Benneker LM, Grijpma DW, Richards RG, Alini M, Eglin D, Grad S, Li Z. A combined biomaterial and cellular approach for annulus fibrosus rupture repair. Biomaterials. 2014; epub Dec 10.

Partner:
- Annulus Fibrosus Ruptures Collaborative Research Programs Consortium

The role of Pericytes in Bone Regeneration (ongoing) (Perivasc) (S. Verrier)

Pericytes are constitutive components of microvessels and present in all vascularized tissues. During angiogenesis pericyte recruitment is crucial for the stability of newly formed vessels. Our previous work revealed that in tissue engineered constructs containing mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) MSCs differentiation towards a pericyte-like phenotype is a critical step within the neovascularization process. Interestingly, it was recently suggested that pericytes represent common ancestor cells providing an in vivo source of MSCs. This combined function of pericytes is of particular interest for bone tissue engineering approaches and motivated this project to study mechanisms involved in pericyte stimulation and migration. We investigated pericytes from different tissue sources including retina, placenta, bone marrow and adipose tissue. Pericytes have been isolated from fresh human tissue by their expression of specific surface marker using FACS or magnetic-bead enrichment. Subsequently, we characterized the pericytes in respect to their surface marker expression and their ability to differentiate into osteogenic, adipogenic and chondrogenic lineage. The results showed that not all pericyte types maintain their multilineage potential suggesting that not all pericytes represent a source of MSCs. Besides, we were also interested in the angiogenic properties of pericytes. To elucidate this we used a Matrigel™ assay, in this well established angiogenesis model, endothelial cells seeded on a thin layer of Matrigel™ networks of tube-like structures within 24 hours. We have shown that pericytes participated to the formation of such networks (Figure 9.6.7). Interestingly, network formation was only seen when pericyte-endothelial cell ratios were in a physiologically relevant range. Having characterized pericytes from different tissues we are now aiming to study stimulation and migration of pericytes. For this propose, an in vitro vascular network model will be developed enabling to study pericytes in their natural environment.

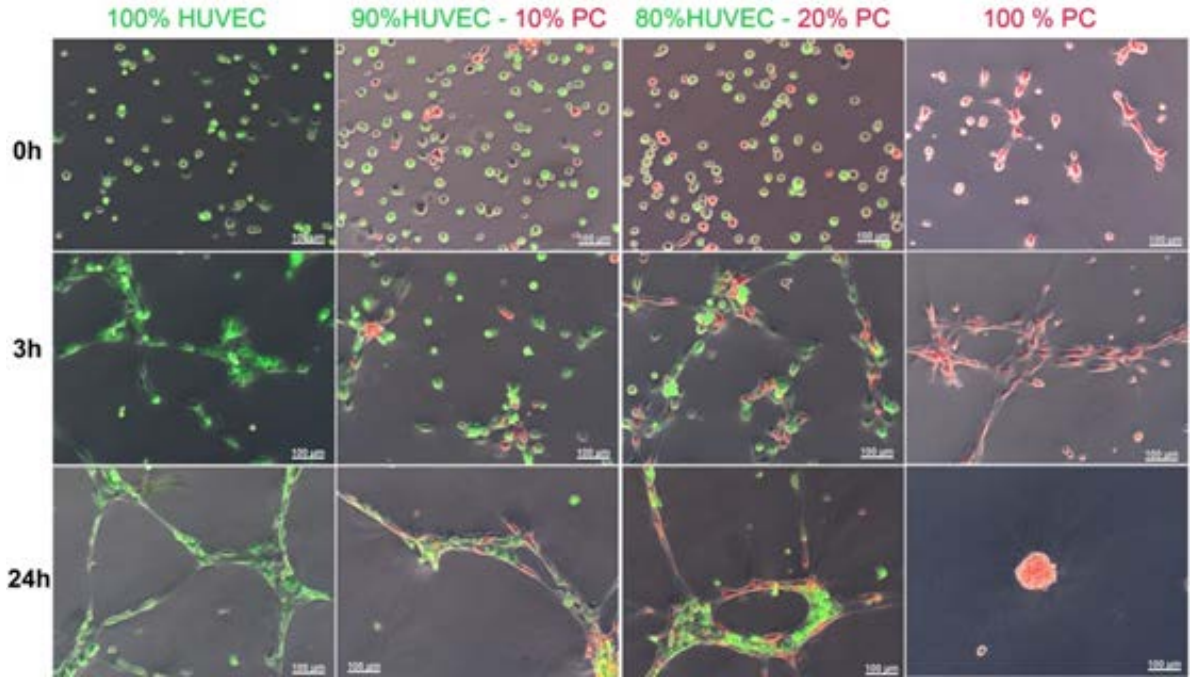


Figure 9.6.7: Pericytes (PCs) support tube-like structure formation on Matrigel™. A thin layer of growth factor reduced Matrigel™ was seeded with GFP-labeled HUVECs and/or PkH26 red labeled retinal pericytes at a density of 7500 cells/cm2 and observed directly after seeding and after 3h and 24h incubation. Scale bars depict 100 µm.

Pres:

Herrmann M, Binder A, Loibl M, Menzel U, Alini M, Verrier S. Neovascularization of Tissue Engineered Constructs for Large Bone Defects. ORS, New Orleans, USA

Verrier S, Neo-vascularization of 3D scaffolds, Inserm workshop, Bordeaux, France

Herrmann M, Verrier S, Alini M. Pre-vascularization of 3D scaffolds promotes host tissue integration. Jahrestagung AO Trauma, Kiel, Germany

Jalowiec JM, Herrmann M, Menzel U, Bara JJ, D'Este M, Alini M, Verrier S. Platelet rich plasma gel as an autologous delivery system of growth factors and cells for tissue engineering applications. TERMIS, Genova, Italy

Binder A, Herrmann M, Menzel U, Alini M, Verrier S. Direct cell-cell contact between Mesenchymal Stem Cells and Endothelial Progenitor Cells induces a Pericyte-like Phenotype in vitro. SBMS, Bern, Switzerland

Herrmann M, Bara JJ, Menzel U, Jalowiec JM, Osinga R, Scherberich A, Alini M, Verrier S. The Multilineage Potential of Pericytes Derived from Different Human Tissues. Stem Cell Meeting, Basel, Switzerland

Herrmann M, Neovaskularisation von zellbeladenen Knochenersatzmaterialen für große Knochendefekte. Unfallchirurgischen Seminar, Regensburg, Germany

Pub:
Loibl M, Binder A, Herrmann M, Duttenhoefer F, Richards RG, Nehrlich M, Alini M, Verrier S. Direct Cell-Cell Contact between Mesenchymal Stem Cells and Endothelial Progenitor Cells Induces a Pericyte-Like Phenotype In Vitro. BioMed Research International, 2014, doi:10.1155/2014/395781

Herrmann M, Binder A, Menzel U, Zeiter S, Alini M, Verrier S. CD34/CD133 enriched bone marrow progenitor cells promote neovascularization of tissue engineered constructs in vivo. Stem Cell Research, 2014, 13:465-477.

Partners:
- Barbe, L, CSEM Landquart
- Scherberich A, Department of Biomedicine, University Hospital Basel
- Laschke, M, Experimentelle Chirugie, Uniklinikum Saarland

Effect of dynamization on critical size bone defect healing (Dynabone) (S. Verrier)
Bone defects exceeding the bone diameter 1.5 times or more are referred to as critical size bone defects and do not heal spontaneously. The current gold standard therapy is autologous bone graft. This has however several limitations including donor site morbidity and a restriction in the amount of available graft material, which is the motivation to investigate alternative treatment strategies. Interestingly over the past years some studies suggested that mechanical loading may influence bone healing. While most of the results were obtained from small fracture models, little is known on the effect of mechanical loading on the bone formation in a critical size defect. This study aimed to establish a fracture model suitable to investigate the effects of axial mechanical loading on large bone defects. A 4 mm femoral defect was created in adult, male Fischer rats fixed with an external fixator, which has been modified to fit in a home-made mechanical loading device. Animals were observed over a period of 12 weeks by x-ray and CT with respect to plate stability and bone healing. The data revealed that the modification of the external fixator had no influence on plate stability. Control groups with empty defects did not show any signs of bone healing within 12 weeks. All other rats were transplanted with bone graft from syngeneic donor animals which was chipped into small fragments and mixed with fibrin glue to prevent graft displacement. We found that bone formation in these animals was only seen when animals were treated with immunosuppressive drugs (Figure 9.6.8). In contrast, syngeneic bone graft was quickly resorbed in immunocompetent animals suggesting that immunosuppression might be critical to support bone healing in this model.

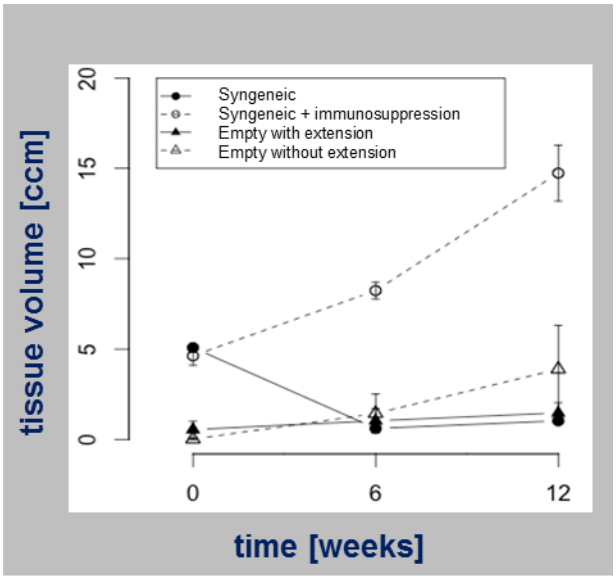


Figure 9.6.8: Bone healing of a 4 mm femoral defect in rats. Bone volume was calculated from CT scans. The graph indicated that empty defects did not heal as expected. Syngeneic bone graft was resorbed within the first six weeks while a steady increase in bone tissue volume was observed when animals were treated with immunosuppressive drugs.

In vitro assessment of osteogenesis (Ostmonit) (Ongoing) (M. Stoddart)

This project aims to develop online monitoring methodologies that can be used to reduce the experimentation required for the *in vitro* testing of osteogenic cells, materials and therapies. We have demonstrated that individual markers are often not sufficient to establish accurately cell behaviour. To provide a more accurate assessment of cell fate decisions, we have determined that ratios of mRNA messages for commonly investigated master transcription factors, such as Sox9 (chondrocyte) and Runx2 (Osteoblast) provide a more accurate assessment of cell behaviour. We have demonstrated that the ratio of Runx2:Sox9 mRNA message on day 7 can predict calcification potential of human bone marrow derived mesenchymal stem cells on day 28. The standard method to establish mRNA message on day 7 is destructive. Therefore, we have been establishing real-time fluorescent monitoring systems than can be performed on viable cells in a non-destructive way. Using transcription factor activated viral reporter constructs and fluorescent markers for messenger RNA, we aim to determine the most robust mechanism for identifying cell phenotype changes.

Pres:

Techniques for RNA Detection: Where Are We Headed? AAAS Science Webinar Series.
27.08.2014, Martin Stoddart,
http://webinar.sciencemag.org/webinar/archive/techniques-rna-detection

Pub:

Bruderer M, Richards RG, Alini M, Stoddart MJ. Role and Regulation of RUNX2 in osteogenesis. Eur Cell Mater. 2014 Oct 23;28:269-86.

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

Tissue engineering is believed to be the future of articular cartilage repair due to the unsatisfying results of the current clinical procedures. Mesenchymal stem cells derived from bone marrow (BMSCs) have demonstrated the potential to differentiate into several cell lineages, including chondrocytes. Using our unique multiaxial load bioreactor we have been able to induce chondrogenic differentiation of human BMSCs in the absence of exogenous chondrogenic growth factors. To our knowledge, we are the only group world wide with this capability. We have demonstrated that the application of shear, superimposed over compression, leads to an autoinduction of chondrogenic differentiation. This would imply that redistributing the cells by increasing the concentration at the upper surface where the shear is applied, would lead to a more robst reponse. Our more recent studies have demonstrated that asymmetric seeding of the cells within tissue enginnered cartilage implants not only leads to an improved chondrogeneic response, but also reduces donor variability by improving the response from cells havested from donors previously considered to be poor. In addition, we have discovered that interfacial shear not only increase the production of the chondrogenic factor Transforming Growth Factor β (TGFβ) it also increases activation of the protein. This provides invaluable information when considering rehabilitation protocols post intra-articular surgery.

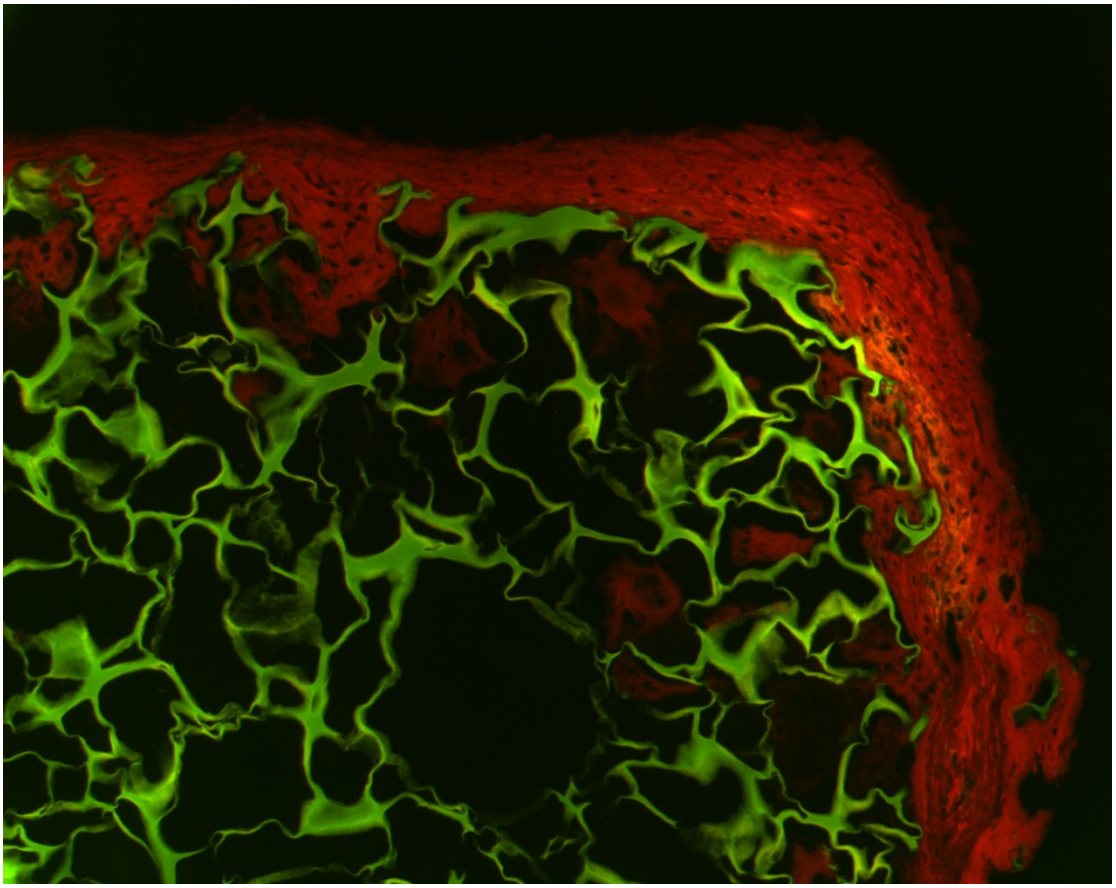


Figure 9.6.9: Chondrogenic implant subject to mechanical load. Stained with Safranin O and viewed under fluorescence. Cell matrix is orange, polyurethane scaffold is green.

Pres:
'Tribological Tissue Engineering of Cartilage'. Oliver Gardner, Charlie Archer, Mauro Alini, Martin J Stoddart. (Poster)
Stem cells in development and disease, 9-10 September 2014, Basel, Switzerland

'Asymmetric Cell Seeding Enhances the Mechano-Induction of Chondrogenesis in Human MSCs in the Absence of Exogenous Growth Factors'. Oliver FW Gardner, Giuseppe Musumeci, Charles W Archer, Mauro Alini, Martin J Stoddart (Poster)
ORS Annual meeting 2014: ORS: March 15th-18th

'Improving the deposition of cartilage-like matrix by mechanically stimulated MSCs in the absence of growth factors through the asymmetrical seeding of fibrin-polyurethane scaffolds. Oliver FW Gardner, Giuseppe Musumeci, Charles W Archer, Mauro Alini, Martin J Stoddart (Oral presentation)
TERMIS 2014: 10th-13th June 2014.

Comparing the secretomes of unstimulated and mechanically loaded MSCs. Oliver FW Gardner, Charles W Archer, Mauro Alini, Martin J Stoddart (Poster). eCM XV: Cartilage & Disc: Repair and Regeneration, 16th – 18th June 2014, Congress Center, Davos, Switzerland

'Improving the deposition of cartilage-like matrix by mechanically stimulated MSCs in the absence of growth factors through the asymmetrical seeding of fibrin-polyurethane scaffolds. Oliver Gardner, Giuseppe Musumeci, Charles Archer, Mauro Alini, Martin J Stoddart. (Poster presentation)
Academia Raetica 2014: 10th-11th September 2014.

Pub:
Cucchiarini M, Madry H, Guilak F, Saris DB, Stoddart MJ, Koon Wong M, Roughley P. A vision on the future of articular cartilage repair. Eur Cell Mater. 2014 May 6;27:12-6.

Madry H, Alini M, Stoddart MJ, Evans C, Miclau T, Steiner S. Barriers and strategies for the clinical translation of advanced orthopaedic tissue engineering protocols. Eur Cell Mater. 2014 May 6;27:17-21.

Zahedmanesh H, Stoddart MJ, Lezuo P, Forkmann C, Wimmer MA, Alini M Phd, Van Oosterwyck H. Deciphering mechanical regulation of chondrogenesis in fibrin-polyurethane composite scaffolds enriched with human mesenchymal stem cells; a dual computational and experimental approach. Tissue Eng Part A. 2014 Apr;20(7-8):1197-212. doi: 10.1089/ten.TEA.2013.0145. Epub 2014 Jan 11.

Partners:
- Archer CW, University of Swansea, Wales, United Kingdom
- Acute Cartilage Injury Collaborative Research Program Consortium

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

The aim of this project is to culture whole marrow mononuclear cells in a quiescent state. Most *in vitro* studies investigate monolayer expanded or selected cells, which would not be the cell type present during the natural repair process. We are able to investigate the role of soluble factors on more clearly defined naïve populations, which will reduce ambiguities caused by working with populations of cells which have been heavily expanded. The hypothesis is that by re-creating the in vivo stem cell niche, we can carry out studies that are currently not possible using standard MSC isolation techniques. Within this system we have developed protocols to monitor cell proliferation and cell behavior of naïve freshly isolated marrow mononuclear cells and then attribute the behavior to either the mesenchymal or hematopoietic cell population. We have also been investigating the potential cross talk between the two cell types and whether this is modified when the cells are cultured in isolation. The rationale being that most in vitro work is performed with mesenchymal cells, whereas single step, intraoperative procedures are likely to use fresh cells which are a mixed population. The normally absent hematopoietic fraction will likely influence any response via paracrine signaling. Using this new culture model, we are able to determine the effect of various growth factors on the same cell population that would be available to a surgeon. In addition, we are able to investigate how the stimulated cells then co on to influence other cells in directing a repair response. This study intends to provide more information on the fundamental biology of freshly isolated mononuclear cells. This is critical as in a single surgical procedure it is freshly isolated cells, not monolayer expanded cells, which will be available.

Pres:

'3D culture of mononuclear cells in fibrin as a model of the mesenchymal stem cell niche in bone marrow' Jennifer J Bara, Marietta Herrmann, Ursula Menzel, Mauro Alini, Martin Stoddart. 2014 TERMIS Annual congress, Genoa, Italy, 10th-13th June 2014. (Poster)

'Modelling the mesenchymal stem cell niche in bone marrow'. Jennifer J Bara, Ursula Menzel, Mauro Alini, Martin Stoddart. Orthopaedic Research Society 2014 Annual Conference, New Orleans, USA. March 15th-18th, 2014 (Poster)

'A culture system for bone marrow-derived mononuclear cells.' Jennifer Bara, Marietta Herrmann, Ursula Menzel, Mauro Alini, Martin Stoddart. 'Future Investigators of Regenerative Medicine' FIRM conference in Girona, Spain 8-11th Sept 2014. (Presentation)

Pub:

Bara JJ, Richards RG, Alini M, Stoddart MJ. Bone marrow-derived mesenchymal stem cells change phenotype following in vitro culture: Implications for basic research and the clinic. Stem Cells. 2014 Jan 21. doi: 10.1002/stem.1649

Partner:

- Acute Cartilage Injury Collaborative Research Program Consortium

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

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

Towards this aim, microarray data sets were generated from human AF cells and analysed using the ingenuity pathway analysis software. Relative gene expression values were validated by quantitative real-time RT-PCR, and dysregulated proteins were identified by immuno-histochemistry (Figure 9.6.10). Microarray analysis revealed 17 dysregulated molecular markers and various dysregulated cellular functions, including cell proliferation and inflammatory response, in the human degenerative AF. Furthermore, the most significant inflammatory pathway induced in degenerative AF was found to be the interferon signalling pathway. The observed up-regulation of interferon-induced proteins and growth factor binding protein is suggested to interfere with cell growth and proliferation. This study indicates that interferon signalling pathway activation with related gene and protein up-regulation may affect cellular function in human degenerative disc; this pathway may therefore be considered for specific therapeutic targeting.

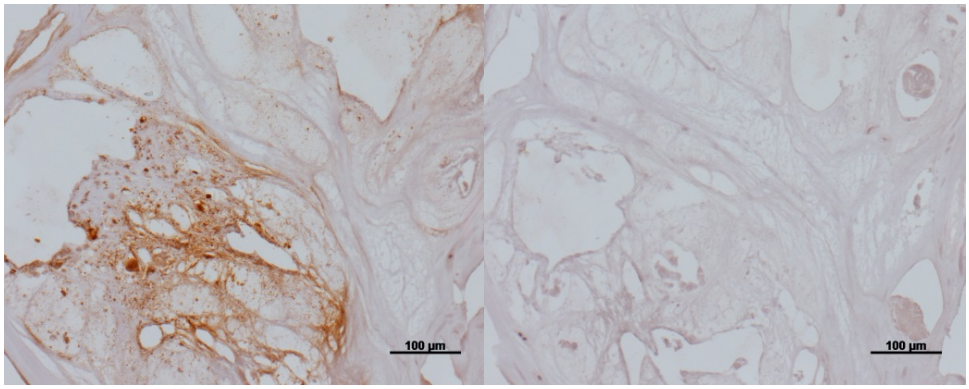


Figure 9.6.10: Intense interferon-induced protein immunolabelling was observed in a severely degenerated region in the annulus fibrosus of a human lumbar disc (left). Negative control sections (right) did not show any staining.

Pres:

S Grad, R Gawri, L Haglund, J Ouellet, F Mwale, LB Creemers, J Rutges, WM Gallagher, P O'Gaora, A Pandit, M Alini. New insight into human disc degeneration by gene expression profiling. World Forum for Spine Research WFSR, Xi'an, China, 2014.

Z Li, M Peroglio, S Grad, D Eglin, M Alini. Annulus Fibrosus Repair. World Forum for Spine Research WFSR, Xi'an, China, 2014.

Z Kazezian, R Gawri, L Haglund, J Ouellet, F Mwale, A Pandit, M Alini, S Grad. Identification of disc degeneration markers in the human AF by microarray. ECM Conference, Davos, 2014.

Pub:

Benneker LM, Andersson G, Iatridis JC, Sakai D, Härtl R, Ito K, Grad S. Cell therapy for intervertebral disc repair: Advancing cell therapy from bench to clinics. Eur Cells Mater 27s:5-11, 2014.

Sakai D, Grad S. Advancing the Cellular and Molecular Therapy for Intervertebral Disc Disease. Adv Drug Deliv Rev. 2014

Partners:

- Annulus Fibrosus Repair Collaborative Research Program Consortium
- Haglund L (Prof), McGill Scoliosis and Spine group, Montreal, Canada
- Mwale F (Prof), McGill University, Lady Davis Institute, Montreal, Canada

9.7 ARI Collaborative Research Programs

A multicomponent repair device for the treatment of acute cartilage injuries

Acute cartilage injuries are often resulting in cartilage degeneration and joint osteoarthritis which are leading causes of disability. The avascular nature of the cartilage matrix coupled with the limited proliferative activity of mature chondrocytes severely impairs the healing of cartilage lesions.

The ARI sponsored "acute cartilage injury" Collaborative Research Program (CRP ACI) aims to address this clinical need and to develop an off-the-shelf device that stimulates repair of acute cartilage injuries. A consortium of scientists and clinicians with relevant expertise embarked in 2011 on a repair strategy that combines state-of-the art material science, biomechanics, gene therapy, bioactive molecules and cells.

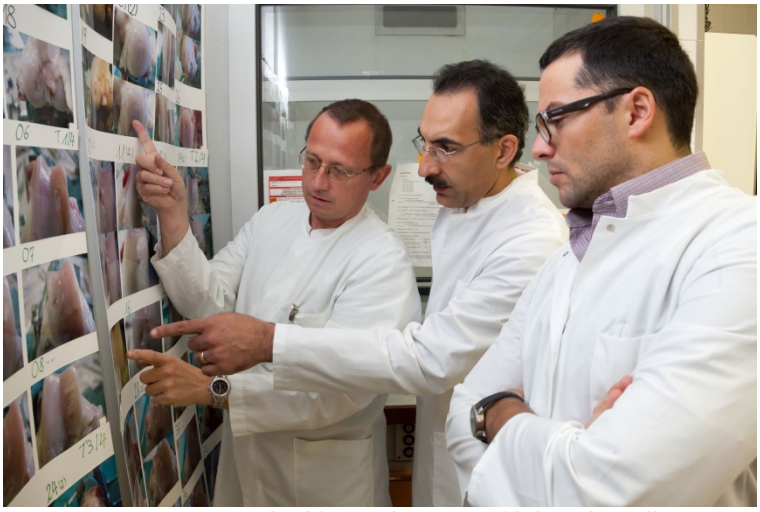
In the past years the consortium has developed novel chondrogenic hydrogel biomaterials that can encapsulate cells and viral vectors. When combined with a newly designed 3D woven scaffold the device stays within the defect, supports joint loading, and through its biologically active components induces repair. Pilot studies investigating various combinations of biomaterials, viral vectors and cells have been carried out to select the most promising candidate devices.

In the final two years of the program the consortium will test two of its most promising multicomponent repair devices, one including and one without viral vectors carrying the Sox9 gene, in a pre-clinical proof-of-concept minipig chondral defect model. Full thickness chondral defects will be created in the femoral condyles of the minipigs to enable experimental repair to be compared with the “gold standard” of microfracture. One group of animals will be used to compare the woven scaffold alone or in conjunction with peptide-based or hyaluronan-based hydrogels to facilitate chondrogenesis. All scaffold combinations will be supplemented with cells present in bone marrow aspirates as a source of mesenchymal stem cells. A second group of animals will be used for gene therapy enhanced repair studies, where cells in the aspirates will be virally transduced prior to implantation. Repaired defects will be evaluated both histologically and biomechanically to compare their properties with those of authentic articular cartilage and with repair tissue generated by microfracture.

The partners of the CRP ACI consortium include:

- Alvaro Mata, Queen Mary University of London, GB, Carlos Semino, Parc Cientific Barcelona, ES
- Robert Mauck, George Dodge University of Pennsylvania, Philadelphia, US
- Henning Madry, Magali Cucchiarini,The Saarland University, Homburg, D
- Farshid Guilak, Duke University, Durham, US
- Martin Stoddart, David Eglin, Mauro Alini, AO Research Institute, Davos, CH

The program is professionally guided and monitored by the CRP committee members Mats Brittberg (clinician), Brian Johnstone and Peter Roughley (scientists).



CRP ACI partners looking at images of injured cartilage.

Tissue engineered implants for annulus fibrosus repair

Disc herniation is the most frequent pathological conditions requiring spinal surgery and its incidence is continuously increasing in the Western world. Sustainable repair of disc lesions and of annulus fibrosus ruptures still remain a substantial challenge despite considerable advances achieved in the past decade.

The ARI sponsored "annulus fibrosus rupture" Collaborative Research Program (CRP AFR) aims to address remaining barriers and ultimately to offer to the surgeon an off-the-shelf solution for treating disc herniation in one intervention. In light of this, an international inter disciplinary consortium of experts with combined scientific and clinical expertise in this field was convened with the task to develop a repair device which restores disc mechanical properties, prevents re-herniation and stimulates repair activities.

Towards this aim the consortium has since its inception in 2011 developed several biocompatible materials with complementary functions which when combined provide closure of AF ruptures and initiate repair activities. Through its research it gained fundamental new insights into physiological and pathological characteristics of the AF including the discovery of AF-derived progenitor cells and obtained an improved understanding of the biomechanical requirements for an AF repair device.

In the remaining two years of the program the consortium is performing last optimizations of the components to be included in its repair device which in a final step will then be evaluated in a pre-clinical proof–of-concept ovine AF defect model. Initial studies will determine whether the wider cervical discs are more appropriate than the narrower lumbar discs for avoiding endplate damage while creating the repair lesion. The proof of concept study will then evaluate both inert and bioactive repair techniques. Inert repair will use a scaffold to plug the lesion, a fibrin-based glue to unite the plug and scaffold, and a polyurethane patch to externally seal the defect. Bioactive repair will utilize a hyaluronan-based hydrogel that has been activated to facilitate cell infiltration or has been supplemented with AF progenitor cells. Repair will be evaluated histologically and biomechanically to assess both its structural integrity and functional capacity.

The partners of the CRP AFR consortium include:

- Stephen Ferguson, ETH Zürich, Lorin Benneker, University of Bern, CH
- Dirk Grijpma, University of Twente, Enschede, NL
- James Iatridis Mount Sinai School of Medicine, New York, US
- Abhay Pandit, National University of Ireland, Galway, IR
- Daisuke Sakai, Tokai University School of Medicine, Kanagawa, JP
- Stephan Zeiter, Sibylle Grad, David Eglin, Mauro Alini, AO Research Institute, Davos, CH

The program is professionally guided and monitored by the CRP committee members Gunnar Anderson (clinician) and Peter Roughley (scientist).

CRP AFR partners discussing histological sections of annulus fibrosus.

9.8 Extramural Projects

Biomimetic nano-fiber-based nucleus pulposus regeneration for the treatment of degenerative disc disease (NPMimetic) (Finished) (S. Grad, M. Alini), FP7-NMP-2009-SMALL-3 (nr, 246351), ARI Funding: EUR 532'382, Period: 01.02.2011 – 31.01.2014

The golden standard for treatment of degenerative disc diseases is still the spinal fusion, an extensive surgery, which impairs spinal motion. Clinicians and scientists are searching for new technologies allowing motion preservation and a favorable long-term outcome. Based on electrospinning technology and a chemically modified extracellular matrix-based biopolymer, the NPmimetic consortium is developing a biomimetic nano-polymer based gel for minimally invasive treatment. Electrospinning is applied to design and develop a nano-fiber based, biocompatible, biodegradable, synthetic scaffold that will mimic mechanical properties of native nucleus pulposus (NP) for immediate and short term treatment. Anabolic agents are conjugated to the biodegradable polymer to be gradually released *in situ*. Ultimately, the synthetic scaffold is integrated with a bioactive polymer that is highly potent in supporting cell activity for long-term cure. The role of the ARI is the extensive *in vitro* and *ex vivo* testing of all biomaterials and their combinations, using cell and organ cultures. In the current period, the implantation of a nano-fiber based polyurethane scaffold with swelling capacity for disc replacement was tested in a whole organ intervertebral disc culture bioreactor system under relevant mechanical loading conditions (Figure 9.8.1).

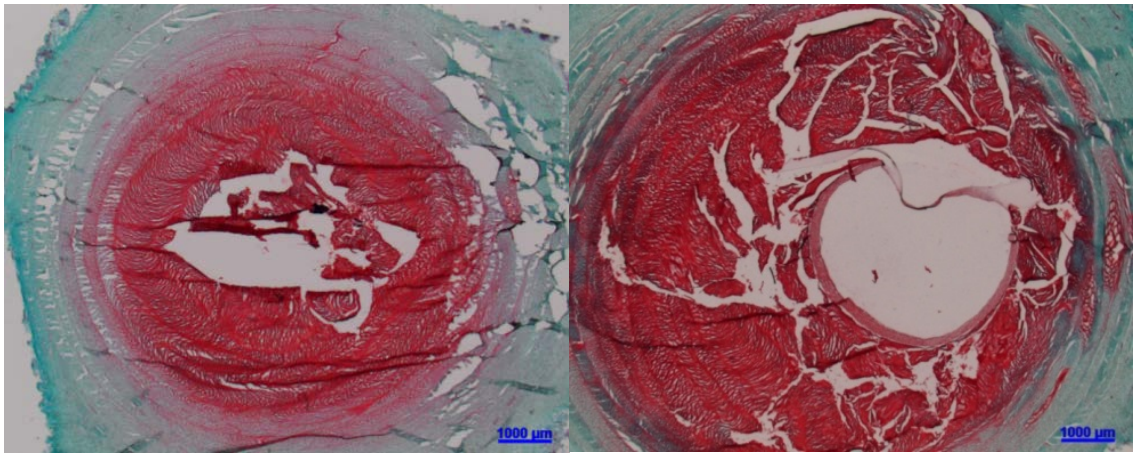


Figure 9.8.1: Representative Safranin O/Fast Green stained transverse sections of partially nucleotomized bovine discs implanted with combined biomaterials after 14 days of culture under dynamic load. Overview images of discs without (left) and with (right) implants are shown; scale bar = 1000 µm. Nano-fibrous swelling polyurethene scaffold, surrounded by fibrinogen-hyaluronan conjugate hydrogel with incorporated TG-BMP 2/7 was implanted as disc replacement strategy.

Pres:

Li Z, Chen X, Sacks H, Yayon A, Alini M, Grad S. Nucleus pulposus replacement: hydrogel or scaffold? – an organ culture study under dynamic load. World forum for spine research, May 15-17, 2014, Xi'an, China.

Li Z, Chen X, Sacks H, Yayon A, Alini M, Grad S. Polyurethane Scaffold with Swelling Capacity In Situ for Nucleus Pulposus Repair. TERMIS, Jun 10-13, 2014, Genova, Italy.

Lang G, Li Z, Chen X, Sacks H, Yayon A, Alini M, Grad S. Biomimetic nucleus pulposus replacement for the treatment of degenerative disc disease. Academia Raetica, Sep 10-11, 2014, Davos, CH.

Pub:

Zhen Li, Keren Mevorat Kaplan, Abraham Wertzel, Marianna Peroglio, Boaz Amit, Mauro Alini, Sibylle Grad and Avner Yayon. Biomimetic fibrin-hyaluronan hydrogels for nucleus pulposus regeneration. Regen. Med. 9(3):309-26, 2014.

Partners:

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

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

The continuous advances in the treatment of damaged and diseased bone will lead to a strong demand for new treatments and the qualified professionals able to develop and implement them. The aim of the BIOBONE (Bioceramics for Bone Repair) project is to offer multidisciplinary training in the field of bioceramics, bioactive glasses and composites for bone repair, in collaboration with industries and universities.

In total, 12 PhDs and 3 Post-docs are involved in the BIOBONE ITN in 5 academic institutions and 4 industrial partners, all at the cutting edge of their fields. BIOBONE offers a unique training framework, including hands-on training at the main host institution, exchanges with other partners of the network and regular seminars. BIOBONE Initial Training Network (ITN) is a project funded by the Marie Curie actions under the FP7 People Programme from the European Commission. ARI performs extensive *in vitro* evaluation of bioinert and bioactive biomaterials developed within the consortium. In 2014, ARI organised a three-day workshop on "Cell-material interactions" and hosted two PhD students from Imperial College London for their six month secondment. The students evaluated the interactions of human stem cells with new biomaterial formulations (Figure 9.8.2). Advanced training was also provided to postdocs enrolled at industrial partner institutions.

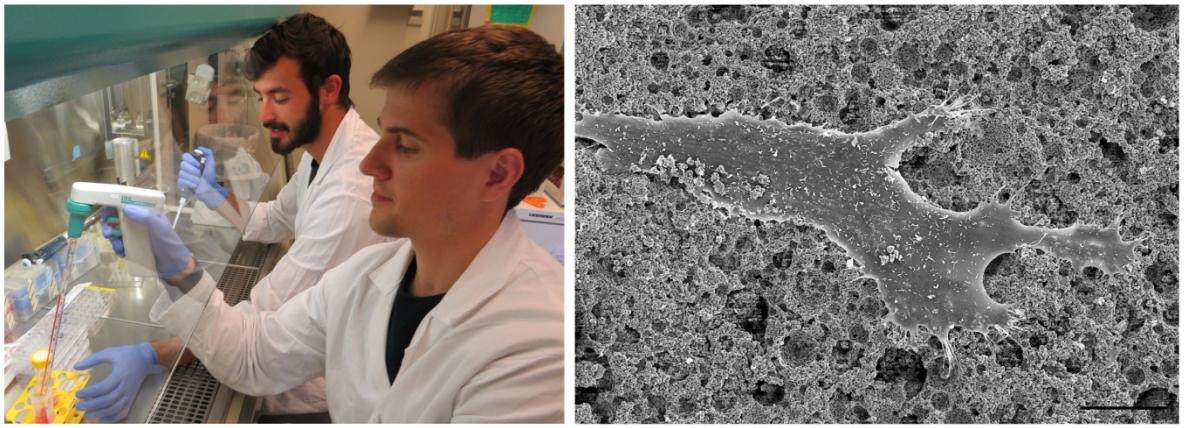


Figure 9.8.2: (left) Biobone student training in one of the ARI cell culture laboratories; (right) human stem cell on a microporous calcium phosphate substrate, scale bar = 20 µm.

Pres:

Costa Machado G, García-Tuñón E, Eslava S, Peroglio M, Alini M, Saiz E. Effect of composition and surface topography on the adhesion and differentiation of human mesenchymal stem cells on calcium phosphate materials. E-MRS 2014 Fall Meeting, Warsaw, Poland (Oral).

Littmann E, Solanki AK, Gentleman E, Erlach TV, Peroglio M, Alini M, Autefage H, Stevens MM. The response of human mesenchymal stem cells to bioactive glass ionic dissolution products. 2014 E-MRS Fall Meeting, Warsaw, Poland (Oral).

Littmann E, Solanki AK, Autefage H, Alini M, Peroglio M, Stevens MM. Hypoxia mimicking glasses for osteochondral tissue engineering. ECM 2014, Davos, Switzerland (Oral).

Littmann E, Solanki AK, Autefage H, Alini M, Peroglio M, Stevens MM. The effect of bioactive glass ionic dissolution products on chondrogenesis. FIRM 2014, Girona, Spain (Poster).

Littmann E, Solanki AK, Alini M, Peroglio M, Autefage H, Stevens MM. Bioactive glasses: a novel approach to treat osteoarthritis. SET for Britain 2015, London, UK (Poster).

Stanciuc A, Stoddart M, Alini M, Peroglio M. Characterisation of human primary osteoblasts from osteoarthritic femoral heads. SSB 2014, Bern, Switzerland (Poster).

Stanciuc A, Stoddart M, Alini M, Peroglio M. Characteristics of human primary osteoblasts from osteoarthritic femoral heads. Academia Raetica Young Scientists in Contest 2014, Davos, Switzerland (Poster).

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

Rational Bioactive Materials Design for Tissue Regeneration (Biodesign) (Ongoing)
(M. Stoddart, M. Alini), FP7-NMP-2010-Large-4 (nr. 262948), ARI Funding: EUR 573'000, Period: 01.01.2012 – 31.12.2016

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

Pres:
Techniques for RNA Detection: Where Are We Headed? AAAS Science Webinar Series. 27.08.2014 http://webinar.sciencemag.org/webinar/archive/techniques-rna-detection

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

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

Classical bone tissue engineering (TE) typically uses bone substitutes consisting of cells and a carrier matrix or scaffold, generating bone tissue by a process resembling intramembranous ossification and direct osteoblastic differentiation. Several factors such as addition of osteogenic stimuli, growth factors, and the osteogenic properties of the scaffold have shown to influence *in vivo* bone formation. However, optimal and reliable repair outcome in a large range of cases has not been achieved so far.

In the context of skeletal tissue repair, the principle of engineering processes targets the engineering of bone through endochondral ossification, the embryonic development pathway of long bones. The natural process of endochondral bone formation is associated with several advantages when translated to approaches for bone TE. It has the potential to overcome issues critical to the functioning of engineered bone grafts, such as resistance to hypoxic conditions, vascularization and mechanical stability. The promise and limitations of differentiating human mesenchymal stem cells (hMSCs) through the endochondral route for bone TE were shown recently. Though, the impact of bone process engineering has not yet been discussed in respect to biomaterials properties and design. In vivo and in vitro investigations using hypertrophic cartilage templates are principally reported in the literature with several important findings establish a central role of scaffold properties in directing developmental bone regeneration. The intention of this project is therefore to elucidate the biomaterials physical and chemical cues that could be manipulated to direct hypertrophic differentiation of different cell types and finally control endochondral bone TE process in vitro.

Tyramine based hyaluronan conjugates (HA-Tyr) able to form hydrogel upon exposure to horseradish peroxidase and hydrogen peroxide were synthesized and characterized in the first part of the project (Figure 9.8.3). Current work is focusing on the hypertrophic potential of TE constructs engineered *in vitro*. For future studies the aim is to investigate the ability of hMSCs encapsulated in HA-Tyr hydrogels to form bone through hypertrophic cartilage *in vivo*.

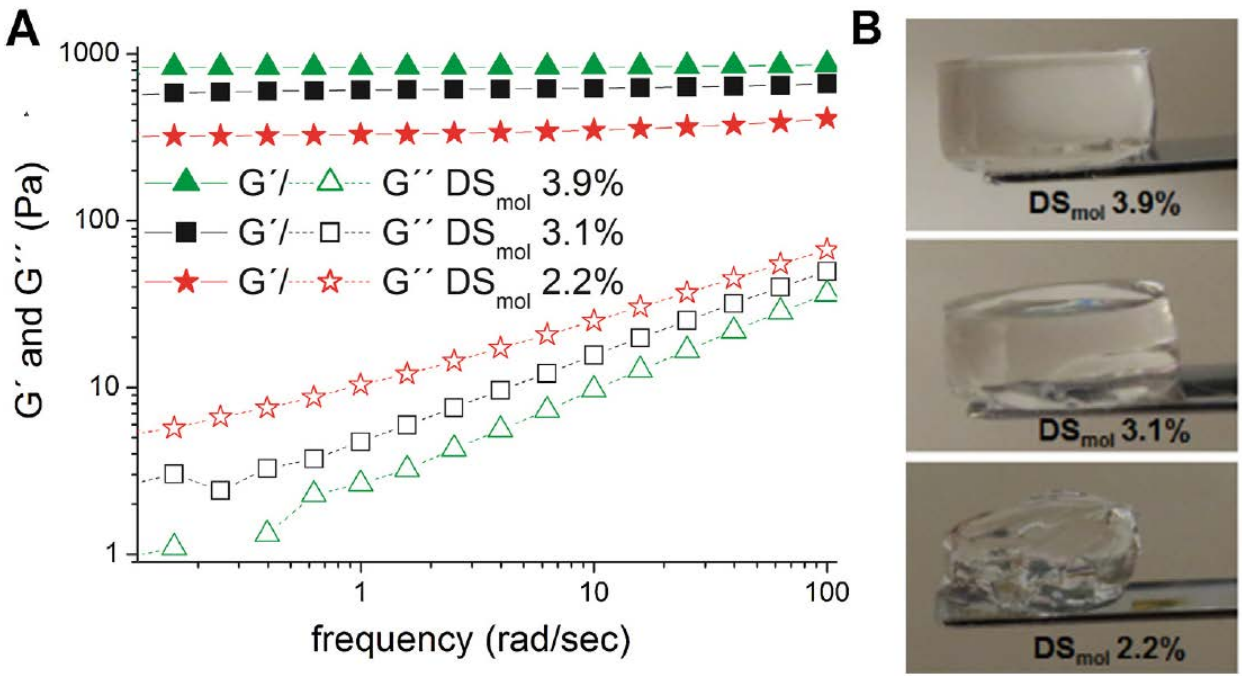


Figure 9.8.3: (A) Rheological measurement (frequency sweep): Typical frequency dependence of the storage modulus G' and loss modulus G'' of HA–Tyr hydrogels and (B) images of the corresponding samples fabricated using 1 Unit/ml HRP and 0.34 mM of H_2O_2. Rheological measurement was taken with constant deformation of 1% (linear viscoelastic range) at RT.

Pres:
Loebel C, D'Este M, Alini M, Zenobi-Wong M, Eglin D. Precise Hyaluronan-tyramine synthesis for tailored cellular microenvironments. 2014 ESB (Poster).

Pub:
Loebel C, D'Este M, Alini M, Zenobi-Wong M, Eglin D.Precise tailoring of hyaluronan-tyramine hydrogels using DMTMM conjugation. Eur Cell Mater. 2014;28(Suppl 6):31 (2014 SSB).

Loebel C, D'Este M, Alini M, Zenobi-Wong M, Eglin D. Precise tailoring of tyramine-based hyaluronan hydrogel properties using DMTMM conjugation, Carbohydrate Polymers. 2015: 115; 325-33.

Partners:
- Zenobi-Wong M (Prof), ETH-Zurich, Switzerland
- Mauck R (Prof), University of Pennsilvania, United State
- NAMABIO COST Action Partners

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

The research project entitled: "rapid prototyping of custom-made bone-forming tissue engineering constructs (RAPIDOS)" is one of the three unique projects which are the result of the first co-ordinated call for research proposals in Biomaterials launched by the European Union (EU) Commission and the National Natural Science Foundation of China (NSFC) in 2013 for facilitating bilateral translational research.

We formed the RAPIDOS European and Chinese consortium with the aim to apply technologies creating custom-made tissue engineered constructs made of resorbable polymer and calcium phosphate ceramic composites specifically designed by integrating: 1) imaging and information technologies, 2) biomaterials and process engineering, and 3) biological and biomedical engineering for novel and truly translational bone repair solutions. Advanced solid free form fabrication technologies, precise stereolithography and low temperature rapid prototyping provide the necessary control to create innovative high-resolution medical implants (Figure 9.8.4). The use of Chinese Medicine extracts, such as the bone anabolic factor icaritin which has shown to promote osteogenic differentiation of stem cells and enhance bone healing *in vivo*, is a safe and technologically relevant alternative to the intensely debated growth factors delivery strategies.

This unique initiative driven by a global consortium is expected to accelerate scientific progress in the important field of biomaterials and to foster high scientific co-operation between China and Europe.

The RAPIDOS activities and progresses can be followed on the web through the RAPIDOS portal http://rapidos-project.eu

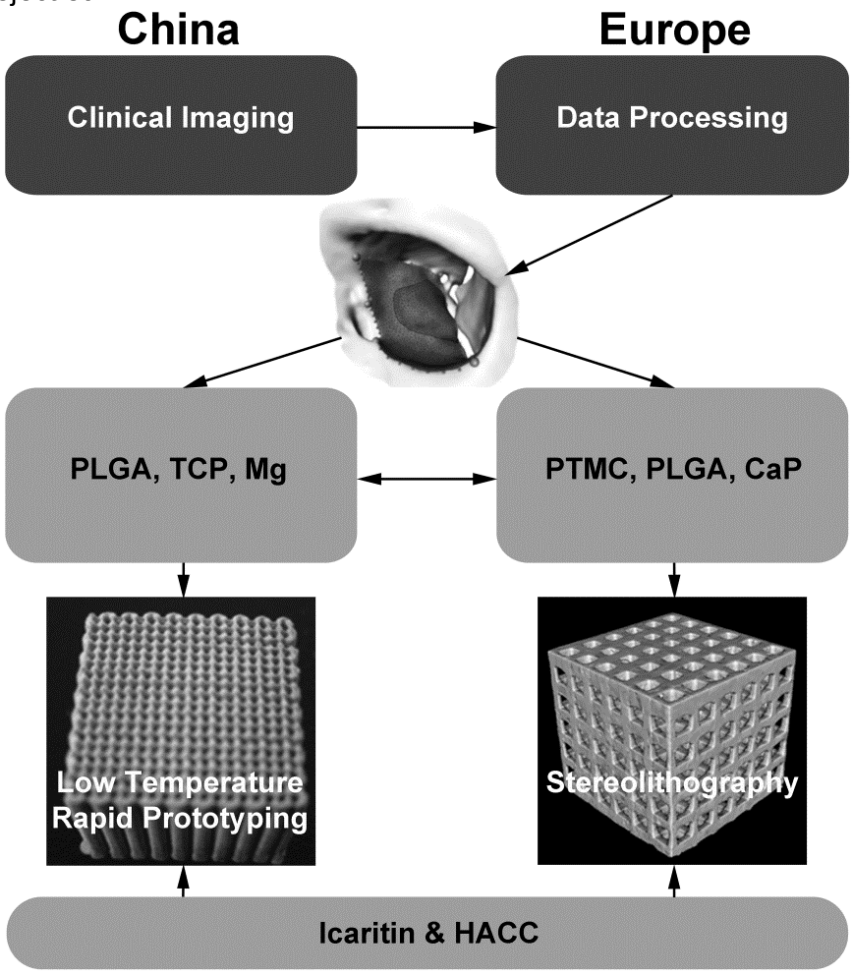


Figure 9.8.4: Scheme of the RAPIDOS approach toward custom-made scaffolds: from standard clinical computed tomography data collection and processing to create specific implant design to development of composite biomaterials for fabrication of implants using additive manufacturing technologies and inclusion of bioactive products. PLGA: Poly(L-lactide-co-glycolide); Mg: Magnesium, TCP: β-Tricalcium phosphate; PTMC: Poly(trimethyl carbonate); CaP: Calcium phosphate particles HAAC: Hydroxypropyltrimethyl ammonium chloride chitosan.

Partners:

- Grijpma D (Prof) University of Twente, The Netherlands
- De Bruijn J (Prof) Xpand Biotechnology BV, The Netherlands
- Peijs T (Prof) Queen Mary, University London, United Kingdom
- Qin L (Prof) Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, China
- Tang T-T (Prof) Shanghai Jiao Tong University, China
- Peng J (Prof) General Hospital of People's Liberation Army – Beijing 301 Hospital, China

The effect of spatial, temporal and mechanical cues on the modulation of human mesenchymal stem cell chondrogenesis and hypertrophy. (Gradiff) (Ongoing) (M. Stoddart, S. Grad, M. Alini), Swiss National Science Foundation (SNF- 31003A_146375/1.), ARI Funding: CHF 356'250, Period: 09/2013-08/2016

All joints in the human body are covered with a protective layer of cartilage. When cartilage is destroyed, movement becomes painful, this is common in an elderly population. Adult stem cells, derived from the patient's own bone marrow, can potentially be used to repair damaged cartilage and alleviate pain. However, the mechanism by which stem cells become cartilage is still not fully understood. Aim: This project aims to investigate how cartilage formation is affected by the way cell talk to each other (Paracrine signalling). We believe that there are critical growth factors for cartilage development (such as Insulin like growth factor 1 and Parathyroid hormone-related protein) and that a concentration gradient, from high to low concentration, must be present for them to work properly. We will apply physiological load to induce stem cells to become the cells of cartilage (chondrocytes) and we will use gene therapy to improve the cartilage formation. One advantage of gene therapy is that we can infect a subset of cells, such as those only on the top or only those in the bottom, and this then then be used to form a gradient within a three dimensional scaffold. The final aim is to use the data obtained to develop new treatments for cartilage injuries.

Pres:

Effects of lipids and cholesterol on the chondrogenesis of human mesenchymal stem cells
Makwana Priyanka, Alini Mauro, Gardner Oliver, Stoddart Martin. Academia Raetica 2014: 10th-11th September 2014. (Oral Presentation)

Multifunctional injectable nano HAp composites for the treatment of osteoporotic bone fractures (M. Alini; M. D'Este), ERANet EuroNanoMed2 NANOFOROSTEO (nr: 31NM30_152035), ARI Funding: CHF 235'000, Period: 2014 –2016

The failure of osteosynthesis in case of large bone defect and osteoporosis fracture repair is still a big unmet clinical in orthopaedics. While autograft is still the gold standard in many clinical circumstances, the use of synthetic bone void fillers does not present issues of amount and shape of bone tissue availability and avoids donation site morbidity. The project NANOFOROSTEO consists of the development of a new injectable void filler based on hyaluronan easily adapted to the shape of the void to fill, avoiding at the same time the particle's migration once localized at the intended anatomical location. A further novelty of this application resides in loading such hydrogel with nano-microencapsulated complexes-drug delivery system (Figure 9.8.5). Poly (lactic acid), polyglycolic acid, poly(ε-caprolactone) and their co-polymers such as poly(lactic-co-glycolic acid) have been extensively used to deliver small molecules (e.g. antibiotics, proteins) through their hydrolytic and enzymatic degradation *in vivo* and have a long history in the field of drug delivery. Furthermore, Sr, Mg and Zn substituted nano-hydroxyapatite particles will be synthesized and incorporated together with Strontium ranelate in polymer/drug formulations extending the range of compositions. The possibility of combining the above hyaluronal hydrogel features with the nano-hydroxyapatite technological platform on osteoconductive and on inhibitor of bone resorption particles has a great potentials and it is of value to explore these new line of products/approaches against osteoporosis fracture repair. Furthermore, High Pressure Processes will be used as an innovative method for sterilisation. It is well known the limitations of the present sterilisation approaches (inactivation and degradation). It is therefore, of highest commercial and clinical importance, to evaluate such new sterilisation approaches, which could lead to a better functional drugs activity.

In this project, the characterization of hyaluronan and coated hydroxyapatite particles composites has been achieved. The introduction of a "cold-sterilization" method using high hydrostatic pressure for bacterial decontamination of hyaluronan hydrogel and its composites with hydroxyapatite nanoparticles and covered hydroxyapatite nanoparticles demonstrated.

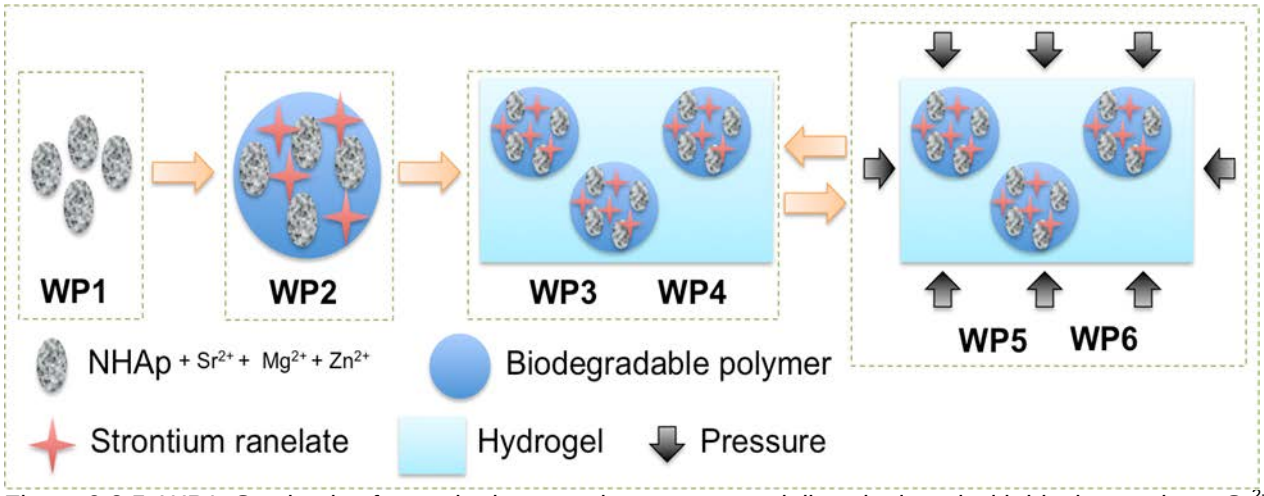


Figure 9.8.5: WP1: Synthesis of nano-hydroxyapatite, pure or partially substituted with bivalent cations: Sr^{2+}, Mg^{2+}, Zn^{2+}. WP2 Formation of microparticle complexes of biodegradable polymer + strontium ranelate + substituted nano-hydroxyapatite with sustained release of drug and nanoparticles. WP3 Preparation of microparticle/gel compositions for handling and maintaining of structural integrity at application site. WP4 *In vitro* investigations of microparticle/gel compositions on osteoblast and osteoclast behaviour, before and after sterilization. WP5 and WP6 Development of pressure sterilization processes of novel microparticle/gel compositions.

Pres:
Alini M, Locs J, Largeteau A, Demazeau G, Tomoaia-Cotisel M. Multifunctional injectable nano HAp composites for the treatment of osteoporotic bone fractures (NANOFOROSTEO). EuroNanoMed, Oslo, Sweden (Poster).

Pub:
Matteo D' Este, David Eglin, Mauro Alini and Laura Kyllönen. Bone Regeneration with Biomaterials and Active Molecules Delivery. Current Pharmaceutical Biotechnolog. *Accepted.* PMID: 25658379.

Partners:
- Locs J (Prof) Riga Technical University, Rudolfs Cimdins Riga Biomaterials Innovations and Development Center, Latvia
- Largeteau A (Prof) Centre National de la Recherche Scientifique, Institut de Chimie de la Matière Condensée de Bordeaux, France
- Demazeau G (Prof) HPBioTECH, France
- Tomoaia-Cotisel M (Prof) Babes-Bolyai University of Cluj-Napoca, Chemical Engineering, Romania

Development of tools to control microbial biofilms with relevance to clinical drug resistance (BALI, F. Moriarty, FP7-HEALTH-2011-two-stage, 2012-2016; 317'928 EUR)

Implant-associated bone infections caused by antibiotic-resistant pathogens pose significant clinical challenges to treating physicians. Prophylactic strategies that act against resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are urgently required. In the present study, we investigated the efficacy of a biodegradable Polymer-Lipid Encapsulation MatriX (PLEX) loaded with the antibiotic doxycycline as a local prophylactic strategy against implant-associated osteomyelitis. the PLEX-doxycycline coating on titanium alloy implants provided complete protection against implant-associated MSSA osteomyelitis, and resulted in a significant reduction in the number of culture positive samples when challenged with a doxycycline-resistant MRSA.

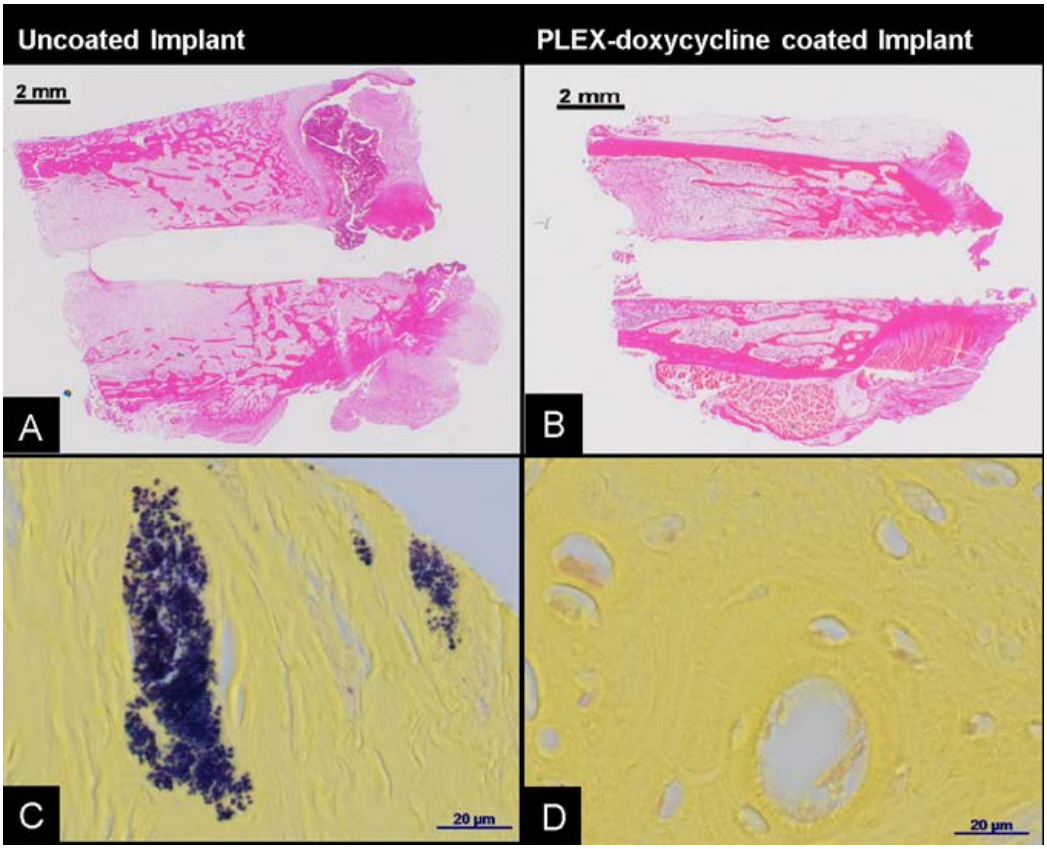


Figure 9.8.6: Microscopic images of tissues from rabbits receiving either a coated or uncoated implant. Rabbits receiving the uncoated implant displayed absces formation (A), and bacteria within the tissues (C), whilst rabbits receiving eth coated implant displayed a physiological apearance of the tissues (B) and no b acteria observed in the tissue (D).

Pres:

Emanuel N, Cohen O, Rosenfeld Y, Richards RG, Moriarty TF. Efficacy of a lipid-and-polymer-based PolyPid drug delivery coating containing doxycycline to prevent implant-related infection. 2014 EORS.

Partners:

- PolyPid Ltd, Tel Aviv, Israel
- Leiden University Medical Centre (LUMC), Netherlands
- AO Foundation Clinical Investigation and Documentation (AOCID), Switzerland

10 Operations standards and safety

Successful 2014 routine audit of AO Research Institute

On April 9th two external auditors from the SQS (Swiss Association for Quality and Management Systems; www.sqs.ch) visited ARI for the yearly routine audit of the institute.
ARI has passed the routine audit without any non-conformities. Having held several open discussions with staff members and management, the auditors were impressed by the levels of commitment and knowledge. The entire AO Research Institute is certified according to the international standard ISO 9001:2008.

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

AAALAC certification of Preclinical facility

The Preclinical Facility was accredited by AAALAC in early 2013. The Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. AO Research Institute Davos is one of 3 accredited institutions in Switzerland, and the only accredited academic Research Institute in Switzerland. In 2014 no site visit by the AAALAC was conducted. Next site visit is planned in 2016.

GLP accreditation

In 2014 we finished a first project GLP-like. After positive decision of the AO Strategy Fund to strengthen AO's preclinical research, the GLP accreditation project was relaunched with the official application for accreditation planned in Q2 2015.

11 Team Members

Director

Richards R Geoff	Prof, Prof, PhD, MSc	01.10.91

ARI Management

Alini Mauro	Prof, PhD	01.07.99
Bentz Ulrich	Dipl Ing HTL Mikrotechnik	01.08.07
Grad Sibylle	Dr sc nat, PhD	03.08.00
Gueorguiev Boyko	PhD, MSc (01.03.03 – 30.09.09)	01.07.10
Keller Rolf	Technischer Kaufmann	17.06.96
Moriarty Fintan	PhD, BSc	19.03.07
Stoddart Martin	PhD, MPhil, BSc (01.08.95 – 30.09.96)	01.07.05
Steiner Sandra	PhD	01.01.14
Wahl Sonia	Dipl DH Ökonomin HFP	01.12.95
Zeiter Stephan	Dr med vet, PhD (01.02.00 – 12.05.02)	01.06.03

Scientific & Technical Staff

Abegglen Nadine	Administrative Assistant (40%)	01.09.09
Arens Daniel	Dr med vet (01.06.03 – 30.09.06)	01.11.07
Badrutt Isabella	Administrative Assistant	16.07.12
Bara Jennifer	PhD, BSc	01.02.13
Barblan Claudia	Administrative Assistant (70%)	15.11.10
Bluvol Mauro	Chemielaborant (Eidg FA[1])	01.06.03
Camenisch Karin	MSc (80%)	07.04.08
Caspar Jan	Poly mechanics	01.01.09
D'Este Matteo	PhD	01.04.11
Dicht Benno	Mechaniker (Eidg FA[1])	01.01.78
Eberli Ursula	MSc ETH (80%)	01.02.11
Eglin David	PhD	01.06.06
Erb Peter	Animal Care (Eidg FA[1])	03.05.93
Ernst Manuela	MSc, Human Movement Science	01.10.11
Escher Carla	Administrative Assistant (40%)	01.01.95
Faoro Pierina	Arztgehilfin (MPA), Animal Care (Eidg FA[1])	01.12.07
Furlong-Jäggi Pamela	Chemikerin FH, BSc (40%)	01.02.04
Furter Andrea	Animal Care (Eidg FA[1])	24.04.06
Gardner Oliver	PhD Cand	27.10.11
Glarner Markus	Chem Messtechniker (Eidg FA[1])	01.11.97
Goudsouzian Nora	BSc	01.02.02
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%) (01.04.91-31.12.01)	21.10.09
Kluge Katharina	Dr med vet (60%)	01.02.12
Kyllönen Laura	PhD, MSc	13.02.13
Lanker Urban	Animal Care (Eidg FA[1])	16.06.86
Lezuo Patrick	Dipl Eng	01.08.03
Li Bojun	PhD	06.01.14
Li Zhen	PhD	01.08.11
Löbel Claudia	PhD Cand, Dr med	01.01.12
Menzel Ursula	PhD, Dipl Biol	01.07.11
Müller Gregor	Lic phil, Librarian (50%)	17.01.05
Müller Reto	Animal Care (Eidg FA[1])	13.11.01

[1] Eidg FA = Eidg Fähigkeitsausweis

Nehrbass Dirk	Dr med vet, FTA Pathol + Toxicopathol	01.10.10
Noser Hansrudi	Prof Dr ès sciences EPFL	18.10.04
Peroglio Marianna	PhD	01.03.09
Perren Dominic	Animal Care	01.02.83
Peter Robert	Dipl Laborant HFP	15.09.84
Petta Dalila	PhD Cand, MSc, Biotechnology	01.01.14
Post Virginia	PhD	20.09.10
Sabate Bresco Marina	PhD Cand, MSc	17.01.13
Schmid Tanja	Dr med vet, Dipl ECVS	07.01.13
Schneider Monika	Administrative Assistant (50%)	06.02.06
Schraner Daniela	Administrative Assistant (40%)	15.04.10
Schwyn Ronald	Dipl Medizintechniker HF	01.11.92
Sprecher Christoph	Dipl Ing FH	01.02.00
Stadelmann Vincent	PhD, Bioengineering EPFL	24.01.11
Stanciuc Ana-Maria	PhD Cand, MSc	20.01.13
Stanic Barbara	PhD	01.06.14
ter Boo Gert-Jan	PhD Cand, MSc, Biomedical Engineering	15.01.12
Verrier Sophie	Dr sc nat	01.08.04
Varga Peter	PhD	04.08.14
Varjas Viktor	MSc, Software Engineer	01.01.14
Vivalda Marisa	Administrative Assistant	01.05.03
Vögtli Daniela	MSc	06.01.14
Wahl Dieter	Dipl techn Werkzeugspezialist HFP	01.11.93
Windolf Markus	Dip Ing TU	01.11.04
Wyss Noel	Poly mechanics	01.08.08
Zderic Ivan	MSc ETH	01.02.11
Zweifel Erich	European Industrial Engineer EIE	30.11.92

Apprentice

Adank Nando	Apprentice	01.08.11
Frey Kevin	Apprentice	01.08.11
Hassler Andri	Apprentice	04.08.14

Internship

Straumann Lukas	Internship	10.06.14

Medical Research Fellows

Fischer Julian	Dr med	04.08.14
Günther Christian	med vet	14.04.14
Hagen Jennifer	Dr med	01.09.14
Lang Gernot	Dr med	14.01.14
Voss Jan	Dr med	10.02.14

Employees left 2014

ARI Managment

Wilke Markus	Dr med vet, Dipl ACVS/ECVS	22.08.11 – 13.02.14

Scientific & Technical Staff

Agarwal Yash	MEng, PhD Cand	07.10.10 – 30.04.14
Czekanska Ewa	PhD Cand, MPhil, MSc	07.10.08 – 28.03.14
Dresing Iska	Dr med vet	01.05.11 – 31.05.14
Heldstab Thomas	Zeichner / Konstrukteur	04.02.91 – 17.12.14
Lemm Prisca	Poly mechanics	01.07.14 – 10.09.14
Pravincumar Makwana Priyanka	Dr phil	01.11.13 – 31.10.14
Shao Jia	PhD	01.06.14 – 31.08.14
Sharma Sonam	MSc, Biomedical Engineering	15.07.11 – 28.02.14
Thöny Sandra	MSc, Human Biology	07.11.11 – 28.02.14
Widmer Daniel	MSc, Biomedical Engineering	23.04.12 – 30.04.14

Internship

Caprez Stephanie	Internship	05.08.13 – 24.07.14
Harting Tatjana	Vet Internship	03.03.14 – 28.04.14
Hristov Martin	ERASMUS Student	01.05.14 – 30.09.14
Lucke Annegret	Vet Internship	28.04.14 – 20.06.14
Roszak Karoline	Vet Internship	06.01.14 – 28.02.14
Ryan Jason Dean	Internship IAESTE Student	03.06.13 – 28.03.14
Teo Boon Han	Vet Internship	03.11.14 – 27.12.14
Windhövel Claudia	Vet Internship	20.06.14 – 15.08.14
Wojtczak Kinga	Vet Internship	18.08.14 – 31.10.14
Veselinov Deyan	ERASMUS Student	05.05.14 – 16.09.14

Medical Research Fellows

Fischer Maren	Dr med	06.01.14 – 30.06.14
Füssinger Marc Anton	Dr med	11.02.13 – 31.01.14
Jalowiec Jagoda	Med vet	01.09.13 – 31.12.14
Lenz Mark	Dr med	01.10.14 – 31.10.14
Nilsson Johanna	Dr med dent	09.01.14 – 20.05.14
Nowicki Bronislaw	Med vet	15.04.13 – 31.12.14
Seva Gomes Guilherme	Dr med	01.05.14 – 31.10.14
Metsemakers Willem-Jan	Dr med	02.04.14 – 30.09.14
Samara Eleftheria	Dr med	08.01.14 – 31.10.14

Non Medical Research Fellows

Aeberhard Stefan	MSc	01.04.14 – 30.09.14

Guests

Alexandrov Mitko	Biomedical Services (B. Gueorguiev), Technical University Varna (TUV), Bulgaria, 28.05.14 – 29.05.14
Barandun Ariane	Biomedical Services (D.Wahl), Inselspital Universität Bern, Switzerland, 10.06.14 – 30.06.14
Benneker Lorin	Musculoskeletal Regeneration (S. Grad), Inselspital Bern, Switzerland 23.06.14 – 24.06.14
Blajan Ana-Iulia	Musculoskeletal Regeneration (M. Alini), University Politehnica Bucharest, Romania 01.07.14 – 29.08.14
Bresina Steven	Biomedical Services (D. Wahl), Scyon Orthopaedics, 15.04.14
Cavalli Emma	Musculoskeletal Regeneration / Polymer Group (D. Eglin), ETH Zürich, Switzerland, 04.08.14 – 08.08.14
Daisuke Sakai	Musculoskeletal Regeneration (S. Grad), Tokai University Isehara, Japan, 21.06.14 – 24.06.14
Dias Marta	Musculoskeletal Regeneration (D. Eglin), Guest Internship, University of Minho Guimarães, Portugal, 04.08.14 – 05.09.14
Duttenhöfer Fabian	Biomedical Services (D. Wahl), MUG – Chirurgie Uniklinik Freiburg, 23.04.14, 15.05.14
Evers Julia	Biomedical Services (B. Gueorguiev) Universitätsklinik Münster, Germany, 14.04.14 – 16.05.14
Farhi Azarya Ovid	Biomedical Services (B. Gueorguiev), Technical University Varna (TUV), Bulgaria, 28.05.14 – 29.05.14
Gehweiler Dominic	Biomedical Services (B. Gueorguiev) Universitätsklinik Münster, Germany, 13.04.14 – 19.04.14
Grechenig Stephan	Biomedical Services (B. Gueorguiev), Uniklinik Regensburg, Germany, 25.08.14 – 26.08.14
Grüneweller Niklas	Biomedical Services (B. Gueorguiev) University Hospital Münster, Germany, 10.03.14 – 18.03.14, 05.05.14 – 06.05.14
Hoppe Sven	Musculoskeletal Regeneration (S. Grad), Inselspital Bern, Switzerland, 23.06.14 – 24.06.14
Kaiser Pascal	Musculoskeletal Regeneration / Tissue Morphology (C. Sprecher), Guest Doktorand Anatomische Anstalt der LMU München, Germany, 12.08.14 – 14.08.14, 23.09.14 – 25.09.14
Kazezian Zepur	Musculoskeletal Regeneration, PhD Candidate (S. Grad) National University of Ireland Galway, 23.06.14 – 15.08.14
Klos Kajetan	Biomedical Services (D. Wahl), Katholisches Klinikum Mainz, Germany, 18.09.14 – 21.09.14
Lenz Mark	Biomedical Services (B. Gueorguiev) Universitätsklinikum Jena, Germany, 01.09.14 – 30.09.14
Littmann Elena	Musculoskeletal Regeneration (M. Peroglio), Imperial College London, UK, 17.01.14 – 11.07.14, 15.12.14 – 19.12.14
Long Rose	Musculoskeletal Regeneration (S. Grad), Icahn School of Medicine at Mount Sinai NY, USA, 18.06.14 – 23.06.14
Machado Gil	Musculoskeletal Regeneration (M.Peroglio), Imperial College London, UK, 26.05.14 – 31.07.14, 23.10.14 – 31.12.14
Metsemakers Willem-Jan	Musculoskeletal Infection (F. Moriarty), UZ Leuven, Belgium, 17.11.14 – 23.11.14
Nieuhaus Michael	Biomedical Services (D. Wahl), Universitätsmedizin Mainz, Germany, 25.11.14 – 28.11.14
Nilsson Johanna	Human Morphology Services (L. Kamer), Folktandvàrden Västertorg Uppsala, Sweden, 07.07.14 – 11.07.14
Ocampo D. Walter	Biomedical Services (B. Gueorguiev), University Stuttgart, Germany, 10.03.14 – 21.03.14
Ochmann Sabine	Biomedical Services (B. Gueorguiev), Universitätsklinik Münster, Germany, 15.04.14

Ossendorff Robert	Musculoskeletal Regeneration (S. Grad / M. Stoddart), Guest Student Universität Freiburg, Germany, 13.10.14 – 31.05.15
Perez Adrian	Musculoskeletal Regenration (D. Eglin), Guest Scientist Fundacion CIDETEC, Donostia San Sebastian, Spain, 12.05.14 – 23.05.14
Popp Albrecht	Preclinical Services / HMS (L. Kamer), Inselspital Bern, Switzerland, 26.04.14
Recha Sancho Lourdes	Musculoskeletal Regeneration (D. Eglin), Institut Quimic de Sarria, Barcelona, Spain, 08.09.14 – 27.10.14
Russo Fabrizio	Musculoskeletal Regeneration (S. Grad), Campus Bio-Medico, University of Rome, Italy, 31.03.14 – 10.04.14
Schmid Timo	Biomedical Services (D.Wahl), Inselspital Universität Bern, Switzerland, 10.06.14 – 13.06.14
Schmidutz Florian	Preclinical Testing, Ludwig-Maximilians University, Munich, Germany, 30.01.14 – 02.02.14
Schmitz Paul	Biomedical Services (B. Gueorguiev), Universität Regensburg, Germany, 25.08.14 – 26.08.14
Schwinn Jana	Biomedical Services (Guest Mark Lenz), Friedrich Schiller Universität Jena, Germany, 29.09.14 – 17.10.14
Sedlaczek Philipp	Musculoskeletal Regeneration (S. Grad), SAMD Mittelschule Davos, Switzerland, Maturaarbeit während Ferien, 4 Wochen, 28.04.14 – 30.05.14
Seelbach Ryan	Musculoskeletal Regeneration (D. Eglin), PhD Candidate, University of Barcelona, Spain, 01.01.13 – 15.05.14
Simons Paul	Biomedical Services (D. Wahl), Katholisches Klinikum Mainz, Germany, 18.09.14 – 21.09.14
Skulev Hristo	Biomedical Services (B. Gueorguiev), Technical University (TUV), Bulgaria, 28.05.14 – 29.05.14
Stauber Tino	Musculoskeletal Regeneration (D. Eglin), Guest Internship, ETH Zürich, Switzerland, 22.09.14 – 23.12.14
Stricker Andres	Biomedical Services (D.Wahl), MUG – Chirurgie Uniklinik Freiburg, Germany 23.04.14
Stirnimann Patrik	Biomedical Services (B. Gueorguiev / I. Zderic), DePuy Synthes, Switzerland 05.02.14 – 07.02.14
Tian Shan	Musculoskeletal Regeneration Biomedical Engineering (M. Stoddart) Guest PhD Student, SSSTC Exchange Grant Application,School of Biological Science and Medical Engineering, Beihang University, China, 26.11.14 – 30.11.15
Vadala Gian Luca	Musculoskeletal Regeneration (M. Alini), Campus Bio-Medico, University of Rome, Italy, 29.01.14 – 30.01.14
Violin Kalan	Musculoskeletal Regeneration /Tissue Morphology (N. Goudsouzian), Energy and Nuclear Research Institute Sao Paulo, Brazil 15.06.14 – 28.06.14
Wagner Daniel	Preclinical Services / HMS (L. Kamer), Universitätsmedizin Mainz, Germany, 13.01.14 – 17.01.14, 05.03.14 – 07.03.14
Wähnert Dirk	Biomedical Services (B. Gueorguiev), Universitätsklinik Münster, Germany, 13.04.14 – 19.04.2014
Wei Wu	Musculoskeletal Regeneration, Erasmus MC - University Medical Center Rotterdam, The Netherlands, 02.09.14 – 01.10.14 Universitätsklinik Münster, Germany, 13.04.14 – 19.04.14
Wirth Michael	Musculoskeletal Regeneration (S. Grad), Universität Zürich, Switzerland, 04.08.14 – 29.08.14
Yan Hongji	Musculoskeletal Regeneration (M. Stoddart), University Uppsala, Sweden, 24.02.14 – 28.02.14, 19.03.14 – 29.03.14

Guest Presentations at AO Center

On January 14, 2014 Dr Samuel K Sheppard from Medical Microbiology and Infectious Diseases, Swansea University, UK gave a guest presentation with the title: Genome wide association studies in staphylococci.

On January 14, 2014 Dr Llinos G Harris from Medical Microbiology and Infectious Diseases, Swansea University, UK gave a guest presentation with the title: Population genomics of Staphylococcus epidermidis.

On April 1, 2014 Dr Justine J Roberts from Graduate School of Biomedical Engineering, University of New South Wales, Sydney, Australia gave a guest presentation with the title: The PEG hydrogels for cartilage tissue engineering in a mechanical environment.

On May 1, 2014 Prof Jérôme Chevalier from Université de Lyon – INSA Lyon, France gave a guest presentation with the title: The answer of bioceramics to mechanical demands: towards complex microstructure and architectures.

On May 2, 2014 Dr Dominik Haudenschild from UC Davis School of Medicine, Department of Orthopaedic Surgery, Orthopaedic Research Laboratory, Sacramento, CA/USA gave a guest presentation with the title: Early Responses to Knee Injury: Lessons from a Mouse Model.

On June 6, 2014 Dr Yuxiao Lai from Shenzhen Institute of Advanced Technology, Shenzhen, China gave a guest presentation with the title: Bioactive scaffold fabricated by 3D printing for bone regeneration.

On October 27, 2014 Prof Dieter Pahr from Technical University, Vienna, Austria gave a guest presentation with the title: Parametric Computational Biomechanics – Today and Tomorrow.

On November 28, 2014 Dr Olivier Guillaume from Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Austrian Cluster of Tissue Regeneration, Austria gave a guest presentation with the title: Injectable scaffolds for IVD regeneration to the ARI?

12 ARI Patents

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pending

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

Method for manufacturing an auxiliary device suitable for the manufacture of a patient customized implant
First Application: PCT/CH2015/000001 filed 20015-01-13
Developer / Inventors: AOR&D, L. Kamer, D. Eglin

13 Publications & Presentations

13.1 Peer reviewed publications

published papers (epub & on paper)

Bara JJ, Richards RG, Alini M, Stoddart MJ.
Bone marrow-derived mesenchymal stem cells change phenotype following in vitro culture: Implications for basic research and the clinic.
Stem Cells 2014;32(7):1713-23 *(IF 7.133)*

Benneker LM, Andersson G, Iatridis JC, Sakai D, Hart R, Ito K, Grad S.
Cell therapy for intervertebral disc repair: advancing cell therapy from bench to clinics.
Eur Cell Mater 2014;27(Suppl):5-11 *(IF 4.887)*

Bergmann CJ, Odekerken JC, Welting TJ, Jungwirth F, Devine D, Boure L, Zeiter S, van Rhijn LW, Telle R, Fischer H, Emans PJ.
Calcium phosphate based three-dimensional cold plotted bone scaffolds for critical size bone defects.
Biomed Res Int 2014;2014:852610 *(IF 2.706)*

Blankstein M, Widmer D, Gotzen M, Hofmann-Fliri L, Richards RG, Gueorguiev B, Windolf M.
Assessment of Intra-osseous Femoral Head Pressures During Cement Augmentation of The Perforated Proximal Femur Nail Antirotation (PFNA) blade.
J Orthop Trauma 2014;28(7):398-402 *(IF 1.540)*

Bleiler C, Wagner A, Stadelmann VA, Windolf M, Kostler H, Boger A, Gueorguiev-Rüegg B, Ehlers W, Röhrle O.
Multiphasic modelling of bone-cement injection into vertebral cancellous bone.
Int J Numer Method Biomed Eng 2014;epub Nov 4 *(IF 1.542)*

Bruderer M, Richards RG, Alini M, Stoddart MJ.
Role and regulation of RUNX2 in osteogenesis.
Eur Cell Mater 2014;28:269-86 *(IF 4.887)*

Compagnoni SC, Schulzki T, Thoeny S, Reinhart WH.
Influence of parenteral nutrition on blood rheology and platelet aggregation in vitro.
Biorheology 2014;51(2-3):187-96 *(IF 1.590)*

Cucchiarini M, Madry H, Guilak F, Saris DB, Stoddart MJ, Koon Wong M, Roughley P.
A vision on the future of articular cartilage repair.
Eur Cell Mater 2014;27(Suppl):12-6 *(IF 4.887)*

Czekanska EM, Ralphs JR, Alini M, Stoddart MJ.
Enhancing inflammatory and chemotactic signals to regulate bone regeneration.
Eur Cell Mater 2014;28:320-34 *(IF 4.887)*

D'Este M, Eglin D, Alini M.
A systematic analysis of DMTMM vs EDC/NHS for ligation of amines to hyaluronan in water.
Carbohydr Polym 2014;108:239-46 *(IF 3.916)*

de Vries-van Melle ML, Tihaya MS, Kops N, Koevoet WJ, Murphy JM, Verhaar JA, Alini M, Eglin D, van Osch GJ.
Chondrogenic differentiation of human bone marrow-derived mesenchymal stem cells in a simulated osteochondral environment is hydrogel dependent.
Eur Cell Mater 2014;27:112-23 *(IF 4.887)*

Dresing I, Zeiter S, Auer J, Alini M, Eglin D.
Evaluation of a press-fit osteochondral poly(ester-urethane) scaffold in a rabbit defect model.
J Mater Sci Mater Med 2014;25(7):1691-700 *(IF 2.379)*

Duttenhoefer F, Mertens ME, Vizkelety J, Gremse F, Stadelmann VA, Sauerbier S.
Magnetic resonance imaging in zirconia-based dental implantology.
Clin Oral Implants Res 2014;epub Jun 04 *(IF 3.123)*

Filipov O, Gueorguiev B.
Unique stability of femoral neck fractures treated with the novel biplane double-supported screw fixation method: A biomechanical cadaver study.
Injury. 2014;epub Nov 27 *(IF 2.462)*

Gahukamble AD, McDowell A, Post V, Salavarrieta Varela J, Rochford ET, Richards RG, Patrick S, Moriarty TF.
Propionibacterium acnes and Staphylococcus lugdunensis Cause Pyogenic Osteomyelitis in an Intramedullary Nail Model in Rabbits.
J Clin Microbiol 2014;52(5):1595-606 *(IF 4.232)*

Goetzen M, Windolf M, Schmoelz W.
Augmented screws in angular stable plating of the proximal humerus: What to do when revision is needed?
Clin Biomech (Bristol, Avon) 2014;29(9):1023-6 *(IF 1.880)*

Günther CM, Muller PE, Mutschler W, Sprecher CM, Milz S, Braunstein V.
Straight proximal humeral nails are surrounded by more bone stock in comparison to bent nails in an experimental cadaveric study.
Patient Saf Surg 2014;8:18 *(IF n.a.)*

Herrmann M, Binder A, Menzel U, Zeiter S, Alini M, Verrier S.
CD34/CD133 enriched bone marrow progenitor cells promote neovascularization of tissue engineered constructs in vivo.
Stem Cell Res 2014;13(3PA):465-77 *(IF 3.912)*

Hoppe S, Uhlmann M, Schwyn R, Suhm N, Benneker LM.
Intraoperative Mechanical Measurement of Bone Quality With the DensiProbe.
J Clin Densitom 2014;epub Jul 31 *(IF 1.603)*

Kesti M, Muller M, Becher J, Schnabelrauch M, D'Este M, Eglin D, Zenobi-Wong M.
A versatile bioink for three-dimensional printing of cellular scaffolds based on thermally and photo-triggered tandem gelation.
Acta Biomater. 2014;epub Sep 23 *(IF 5.684)*

Kyllönen L, D'Este M, Alini M, Eglin D.
Local drug delivery for enhancing fracture healing in osteoporotic bone.
Acta Biomater 2014;epub Sep 16 *(IF 5.684)*

Lansdowne JL, Devine D, Eberli U, Emans P, Welting TJ, Odekerken JC, Schiuma D, Thalhauser M, Boure L, Zeiter S.
Characterization of an ovine bilateral critical sized bone defect iliac wing model to examine treatment modalities based on bone tissue engineering.
Biomed Res Int 2014;2014:250958 *(IF 2.706)*

Laschke MW, Schank TE, Scheuer C, Kleer S, Shadmanov T, Eglin D, Alini M, Menger MD.
In vitro osteogenic differentiation of adipose-derived mesenchymal stem cell spheroids impairs their in vivo vascularization capacity inside implanted porous polyurethane scaffolds.
Acta Biomater 2014;10(10):4226-35 *(IF 5.684)*

Laschke MW, Grasser C, Kleer S, Scheuer C, Eglin D, Alini M, Menger MD.
Adipose tissue-derived microvascular fragments from aged donors exhibit an impaired vascularisation capacity.
Eur Cell Mater 2014;28:287-98 *(IF 4.887)*

Li Z, Kaplan KM, Wertzel A, Peroglio M, Amit B, Alini M, Grad S, Yayon A.
Biomimetic fibrin-hyaluronan hydrogels for nucleus pulposus regeneration.
Regen Med 2014;9(3):309-26 *(IF 3.873)*

Leite Pereira C, Goncalves RM, Peroglio M, Pattappa G, D'Este M, Eglin D, Barbosa MA, Alini M, Grad S.
The effect of hyaluronan-based delivery of stromal cell-derived factor-1 on the recruitment of MSCs in degenerating intervertebral discs.
Biomaterials 2014;35(28):8144-8153 *(IF 8.312)*

Loebel C, Czekanska EM, Bruderer M, Salzmann G, Alini M, Stoddart MJ.
In Vitro Osteogenic Potential of Human Mesenchymal Stem Cells Is Predicted by Runx2/Sox9 Ratio.
Tissue Eng Part A 2014;epub Aug 4 *(IF 4.254)*

Loebel C, Czekanska EM, Staudacher J, Salzmann G, Richards RG, Alini M, Stoddart MJ.
The calcification potential of human MSCs can be enhanced by interleukin-1beta in osteogenic medium.
J Tissue Eng Regen Med 2014;epub Sep 4 *(IF 4.428)*

Loebel C, D'Este M, Alini M, Zenobi-Wong M, Eglin D.
Precise tailoring of tyramine-based hyaluronan hydrogel properties using DMTMM conjugation.
Carbohydr Polym 2014;epub Sep 15 *(IF 3.916)*

Loibl M, Binder A, Herrmann M, Duttenhoefer F, Richards RG, Nerlich M, Alini M, Verrier S.
Direct Cell-Cell Contact between Mesenchymal Stem Cells and Endothelial Progenitor Cells Induces a Pericyte-Like Phenotype In Vitro.
Biomed Res Int 2014;2014:395781 *(IF 2.706)*

Loibl M, Lang S, Brockhoff G, Gueorguiev B, Hilber F, Worlicek M, Baumann F, Grechenig S, Zellner J, Huber M, Valderrabano V, Angele P, Nerlich M, Prantl L, Gehmert S.
The effect of leukocyte-reduced platelet-rich plasma on the proliferation of autologous adipose-tissue derived mesenchymal stem cells.
Clin Hemorheol Microcirc 2014;epub Dec 23 *(IF 2.215)*

Madry H, Alini M, Stoddart MJ, Evans C, Miclau T, Steiner S.
Barriers and strategies for the clinical translation of advanced orthopaedic tissue engineering protocols.
Eur Cell Mater 2014;27(Suppl):17-21 *(IF 4.887)*

Miclau T, Adachi N, Antoniou J, Baldini N, Blunn G, Boyd S, Chang JK, Grimm B, Guo XE, Im GI, Kim SY, Korkusuz F, Lee OK, McCaskie A, Richards RG, Shetty G, Sivananthan S, Tang TT, Xu J, Qin L.
International Combined Orthopaedic Research Societies: A model for international collaboration to promote orthopaedic and musculoskeletal research.
Journal of Orthopaedic Translation 2014;2:165-169 *(IF n.a.)*

Moriarty TF, Grainger DW, Richards RG.
Challenges in linking preclinical anti-microbial research strategies with clinical outcomes for device-associated infections.
Eur Cell Mater 2014;28:112-28 *(IF 4.887)*

Nehrbass D, Arens D, Zeiter S.
Spontaneous bilateral avulsion fracture of the tuberositas tibiae in a New Zealand White rabbit - A counterpart to Osgood-Schlatter disease in humans?
Exp Toxicol Pathol 2014;epub Nov 27 *(IF 2.005)*

Pattappa G, Peroglio M, Sakai D, Mochida J, Benneker LM, Alini M, Grad S.
CCL5/RANTES is a key chemoattractant released by degenerative intervertebral discs in organ culture.
Eur Cell Mater 2014;27:124-36 *(IF 4.887)*

Perren SM, Regazzoni P, Fernandez Dell'Oca AA.
Biomechanical and Biological Aspects of Defect Treatment in Fractures Using Helical Plates.
Acta Chir Orthop Traumatol Cech 2014;81(4):267-71 *(IF 0.415)*

Pirvu TN, Schroeder JE, Peroglio M, Verrier S, Kaplan L, Richards RG, Alini M, Grad S.
Platelet-rich plasma induces annulus fibrosus cell proliferation and matrix production.
Eur Spine J 2014;23:745-753 *(IF 2.473)*

Pirvu T, Blanquer SB, Benneker LM, Grijpma DW, Richards RG, Alini M, Eglin D, Grad S, Li Z.
A combined biomaterial and cellular approach for annulus fibrosus rupture repair. Biomaterials 2014;epub Dec 10 *(IF 8.312)*

Popp AW, Buffat H, Cavelti A, Windolf M, Perrelet R, Senn C, Lippuner K.
Cortical bone loss at the tibia in postmenopausal women with osteoporosis is associated with incident non-vertebral fractures: Results of a randomized controlled ancillary study of HORIZON.
Maturitas 2014;77:287-293 *(IF 2.861)*

Popp AW, Buffat H, Eberli U, Lippuner K, Ernst M, Richards RG, Stadelmann VA, Windolf M.
Microstructural Parameters of Bone Evaluated Using HR-pQCT Correlate with the DXA-Derived Cortical Index and the Trabecular Bone Score in a Cohort of Randomly Selected Premenopausal Women.
PLoS One 2014;9(2):e88946 *(IF 3.534)*

Poser L, Matthys R, Schawalder P, Pearce S, Alini M, Zeiter S.
A standardized critical size defect model in normal and osteoporotic rats to evaluate bone tissue engineered constructs.
Biomed Res Int 2014;2014:348635 *(IF 2.706)*

Post V, Wahl P, Uckay I, Ochsner P, Zimmerli W, Corvec S, Loiez C, Richards RG, Moriarty TF.
Phenotypic and genotypic characterisation of Staphylococcus aureus causing musculoskeletal infections.
Int J Med Microbiol 2014;304(5-6):565-76 *(IF 3.420)*

Poulsson AH, Eglin D, Zeiter S, Camenisch K, Sprecher C, Agarwal Y, Nehrbass D, Wilson J, Richards RG.
Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model.
Biomaterials 2014;35:3717-3728 *(IF 8.312)*

Radetzki F, Wohlrab D, Goehre F, Noser H, Delank KS, Mendel T.
Anatomical conditions of the posterior pelvic ring regarding bisegmental transverse sacroiliac screw fixation: a 3D morphometric study of 125 pelvic CT datasets.
Arch Orthop Trauma Surg. 2014;134(8):1115-20 *(IF 1.310)*

Rausch S, Klos K, Wolf U, Gras M, Simons P, Brodt S, Windolf M, Gueorguiev B.
A biomechanical comparison of fixed angle locking compression plate osteosynthesis and cement augmented screw osteosynthesis in the management of intra articular calcaneal fractures.
Int Orthop. 2014;38(8):1705-10 *(IF 2.019)*

Risbud MV, Schoepflin ZR, Mwale F, Kandel RA, Grad S, Iatridis JC, Sakai D, Hoyland JA.
Defining the Phenotype of Young Healthy Nucleus Pulposus Cells: Recommendations of the Spine Research Interest Group at the 2014 Annual ORS Meeting.
J Orthop Res 2014;epub Nov 20 *(IF 2.972)*

Rochford ET, Subbiahdoss G, Moriarty TF, Poulsson AH, van der Mei HC, Busscher HJ, Richards RG.
An in vitro investigation of bacteria-osteoblast competition on oxygen plasma-modified PEEK.
J Biomed Mater Res A 2014;102(12):4427-34 *(IF 2.328)*

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13.5 Conference proceedings

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Modelling the mesenchymal stem cell niche in bone marrow.
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Mechanical torque measurement to assess the bone strength of the posterior pelvic ring in human cadavers.
2014 EFORT (poster)

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Camino G, Zderic I, Richards RG, Sancineto C, Barla J, Windolf M, Gueorguiev B.
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Enhancing inflammatory and chemotactic signals to regulate bone regeneration.
2014 ORS (poster)

D'Este M, Alini M, Eglin D.
Amidation via DMTMM: A New and Efficient Method for Hyaluronan Biomaterials Preparation.
2014 ESB (oral)

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Cortical thickness and porosity of the proximal humerus correlate with osteoporotic bone remodelling: An analysis of micro-structural remodelling
2014 EORS (poster)

Eberli U, Schwyn R, Ernst M, Windolf M, Stadelmann V.
Non-invasive biomechanical monitoring of bone healing in a dynamized bone defect in sheep.
2014 WCB (poster)

Eberli U, Schwyn R, Ernst M, Windolf M, Stadelmann V.
Non-invasive biomechanical monitoring of bone healing in a dynamized bone defect in sheep.
2014 Academia Raetica (oral & poster)

Eberli U, Schwyn R, Ernst M, Zderic I, Windolf M, Stadelmann V.
Non-invasive biomechanical monitoring of bone healing in a dynamized bone defect in sheep.
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Eglin D, D'Este M, Dresing I, Alini M.
Injectable Thermo-responsive Hyaluronan Hydrogel in a Rabbit Osteochondral Defect Model. 2014 ESB (poster)

Eglin D.
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Emanuel N, Cohen O, Rosenfeld Y, Richards RG, Moriarty TF.
Efficacy of a lipid-and-polymer-based PolyPid drug delivery coating containing doxycycline to prevent implant-related infection.
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Ernst M, Shanmugam R, Wahl D, Windolf M, Gueorguiev B.
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2014 EFORT (poster)

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2014 WCB (oral)

Filipov O, Ernst M, Gueorguiev B.
Biplane double-supported screw fixation for better stability of femoral neck fractures. A biomechanical study.
2014 EFFORT (oral)

Filipov O, Ernst M, Gueorguiev B.
Unique stability of femoral neck fractures treated with the novel method of biplane double-supported screw fixation. A biomechanical study.
2014 WCB (poster)

Filipov O, Gueorguiev B.
Unique stability of femoral neck fractures treated with the novel method of Biplane Double-supported Screw Fixation. A biomechanical cadaver study.
2014 World Congress of Orthopaedics (oral)

Filipov O, Oh JK, Ernst M, Gueorguiev B.
Biplane Double-Supported Screw Fixation For Unique Stability Of Femoral Neck Fractures. A Biomechanical Study.
2014 AOTAP (oral)

Gardner O, Archer C, Alini M, Stoddart MJ.
Tribological Tissue Engineering of Cartilage.
2014 Stem Cell Meeting (poster)

Gardner OF, Musumeci G, Archer CW, Alini M, Stoddart MJ.
Improving the deposition of cartilage-like matrix by mechanically stimulated MSCs in the absence of growth factors through the asymmetrical seeding of fibrin-polyurethane scaffolds.
2014 Academia Raetica (poster)

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Asymmetric cell seeding enhances the mechano-induction of chondrogenesis in human MSCs in the absence of exogenous growth factors.
2014 ORS (poster)

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Biomechanischer Vergleich augmentierter und nicht-augmentierter SI-Schrauben im Hemi-Pelvis - Model.
2014 DKOU (oral)

Gueorguiev B, Lenz M, Perren SM, Richards RG, Fernandez Dell'Oca AA, Höntzsch D, Windolf M.
Benefit and harm of cerclages for osteosynthesis augmentation.
2014 WCB (oral)

Gueorguiev B.
Biomechanics of bone fracture fixation and treatment of joint disorder.
2014 Jubilee Int. Conference '20 Years Kinesitherapy', SW University 'Neofit Rilski' (oral)

Helfen T, Sprecher CM, Eberli U, Müller PE, Gueorguiev B, Schmidutz F.
Osteoporotischer Knochenumbau am proximalen Humerus: Analyse der kortikalen Dicke und Porosität im Hinblick auf das Frakturrisiko.
2014 VSOU (oral)

Helfen T, Sprecher CM, Eberli U, Müller PE, Richards RG, Gueorguiev B, Schmidutz F.
Kortikale Dicke und Porosität am proximalen Humerus korrelieren mit dem osteoporotischen Knochensubstanzverlust: Eine Analyse der mikrostrukturellen Umbauprozesse.
2014 Academia Raetica (oral & poster)

Herrmann M, Bara JJ, Menzel U, Jalowiec JM, Osinga R, Scherberich A, Alini M, Verrier S.
The Multilineage Potential of Pericytes Derived from Different Human Tissues.
2014 Stem Cell Meeting (oral)

Herrmann M, Binder A, Loibl M, Menzel U, Alini M, Verrier S.
Neovascularization of Tissue Engineered Constructs for Large Bone Defects.
2014 ORS (oral)

Klos K, Rausch S, Wolf D, Windolf M, Gueorguiev B.
Biomechanischer Vergleich zwischen einer winkelstabilen Platten- und einer zementaugmentierten Schraubenosteosynthese zur Versorgung von Kalkaneusfrakturen.
2014 DAF (poster)

Kyllönen L, Stoddart MJ, Alini M, Eglin D.
Injectable Hydrogel Releasing Osteogenic Factors in Osteoporotic Bone Fracture.
2014 IBMS (poster)

Lang G, Li Z, Xu C, Hagit S, Avner Y, Alini M, Grad S.
Biomimetic nucleus pulposus replacement for the treatment of degenerative disc disease.
2014 Academia Raetica (oral)

Li B, Loebel C, Menzel U, Alini M, Stoddart MJ.
Online monitoring of stem cell fate decisions.
2014 ISSCR (poster)

Li Z, Pirvu T, Blanquer SB, Benneker LM, Grijpma DW, Alini M, Eglin D, Grad S.
A combined cellular and biomaterial approach for annulus fibrosus rupture repair.
2014 Stem Cell Meeting (poster)

Littmann E, Solanki AK, Alini M, Peroglio M, Autefage H, Stevens MM.
Bioactive glasses: A novel approach to treat osteoarthritis.
2014 SET (poster)

Littmann E, Solanki AK, Gentleman E, Erlach TV, Peroglio M, Alini M, Autefage H, Stevens MM.
The response of human mesenchymal stem cells to bioactive glass ionic dissolution products.
2014 E-MRS (oral)

Littmann E, Solanki AK, Autefage H, Alini M, Peroglio M, Stevens MM.
The effect of bioactive glass ionic dissolution products on chondrogenesis.
2014 FIRM (oral)

Loebel C, Czekanska E, Alini M, Stoddart MJ.
Early prediction of osteogenic potential of human mesenchymal stem cells by Runx2/so9 ratio.
2014 ORS (poster)

Loebel C, D'Este M, Alini M, Zenobi-Wong M, Eglin D.
Precise Hyaluronan-tyramine synthesis for tailored cellular microenvironments.
2014 ESB (poster)

Makwana P, Alini M, Gardner OF, Stoddart MJ.
Effects of lipids and cholesterol on the chondrogenesis of human mesenchymal stem cells.
2014 Academia Raetica (oral)

Mendel T, Wienke A, Ullrich B, Noser H, Goehre F, Hofmann G, Radetzki F.
Vergleich der Reliabilität Röntgen- und CT-Bild-basierter Beurteilungskriterien sakraler Formvarianten in Hinblick auf eine sichere transversale SI-Verschraubung im 1. Sakralsegment.
2014 DKOU (oral)

Metzger W, Schwab B, Oberringer M, Pohlemann T, Hayes J, Verrier S, Schimmelpfennig L, Grad S, Veith M, Pütz N, Miro MM, Simpson A, Wennemuth G, Bubel M, Aktas C.
Zellselektivität von Al_2O_3 Nanostrukturen.
2014 DGBM (poster)

Morgenstern M, Post V, Moriarty TF, Richards RG, Kates S.
Nasal Colonization of Orthopedic surgeons with multi-resistant bacteria
2014 EORS (oral)

Morgenstern M, Erichsen C, Post V, Hungerer S, Militz M, Moriarty TF, Richards RG, Bühren V.
Implantat Infektionen mit Staphylococcus epidermidis - Korrelation zwischen klinischem Outcome und bakteriellen Eigenschaften.
2014 DKOU (oral)

Moriarty TF, Richards RG.
Rabbit and other animal models for bone related medical device infection.
2014 iPROMEDAI (oral)

Moriarty TF, Sabaté Brescó M, O'Mahony L, Kluge K, Richards RG, Zeiter S.
Staphylococcus epidermidis infection increases in the presence of unstable fixation: evidence in a murine fracture model.
2014 EBJIS (oral)

Moriarty TF, Stadelmann V, Richards RG.
Patterns of bone evolution near implants experimentally colonised by staphylococci and propionibacteria.
2014 EBJIS (oral)

Nilsson J, Thor A, Kamer L.
Virtual bite registration – a workflow for creating a 3D model for orthognathic surgery planning.
2014 SAOMS (oral)

Oh JK, Schneider K, Zderic I, Stoffel K, Richards RG, Nork SE, Gueorguiev B.
What is the underlying mechanism for the failure mode observed in the Proximal Femoral Locking Compression Plate? A Biomechanical Study.
2014 AOTAP (oral)

Pattappa G, Peroglio M, Sakai D, Mochida J, Benneker LM, Alini M, Grad S.
CCL5 is a Key Chemoattractant in Degenerative Intervertebral Discs.
2014 ORS (poster)

Peroglio M, Janki M, De Wild M, Benneker LM, Alini M, Grad S.
Fibrin Gel Contributes to the Restoration of Disc Height in Nucleotomized Intervertebral Discs under Dynamic Load.
2014 ORS (oral)

Peters ST, Schmid T, Wilke M.
Arthroscopic Approach and Anatomy of the Rabbit Stifle Joint.
2014 ACVS Surgery Summit (poster)

Petta D, Eglin D, Dresing I, Alini M, D'Este M.
Thermoresponsive hyaluronan hydrogel for osteochondral defects repair.
2014 SIB (oral)

Radetzki F, Wohlrab D, Göhre F, Noser H, Delank K, Mendel T.
Einfluss der Sakrumposition zwischen den Darmbeinen auf eine sichere transversale SI-Verschraubung der Sakralsegmente S1, 2 & 3. Eine computerassistierte anatomische Analyse anhand von 125 CT-Datensätzen.
2014 DKOU (oral)

Sabaté Brescó M, Kluge K, Ziegler M, Richards RG, O'Mahony L, Moriarty F.
Immune response during bone healing in a murine fracture model with osteomyelitis: role of biomechanical stability.
2014 Osteoimmunology (poster)

Sabaté Brescó M, Kluge K, Ziegler M, Richards RG, O'Mahony L, Moriarty F.
Assessing the role of implant stability on the development of staphylococcal osteomyelitis in a murine fracture model.
2014 Academia Raetica (oral)

Sands A, White C, Blankstein M, Zderic I, Ernst M, Windolf M, Richards RG, Gueorguiev B.
Beurteilung der Sprunggelenk- und Rückfußstabilität sowie des Gelenkdrucks in einem humanen Kadavermodell nach Entfernung eines Großteils des Processus lateralis tali. Eine biomechanische Studie.
2014 DKOU (oral)

Schmidutz F, Agarwal Y, Müller PM, Gueorguiev B, Richards RG, Sprecher C.
Der zementfreie Oberflächenersatz der Schulter führt zu einem deutlichen Stress-Shielding Phänomen: Eine humane Explantate und Finite-Elemente-Analyse.
2014 AGA (poster)

Schmidutz F, Sprecher C, Müller PM, Gueorguiev B, Eberli U, Helfen T.
Osteoporotische Knochenumbauprozesse führen am proximalen Humerus zu einer deutlichen Abnahme der kortikale Dicke und Zunahme der Porosität: Eine Analyse der mikrostrukturellen Umbauprozessen.
2014 AGA (poster)

Schmidutz F, Agarwal Y, Sprecher C, Müller PE, Richards RG, Gueorguiev B.
Der zementfreie Oberflächenersatz der Schulter induziert ein knöchernes Stress-Shielding: Eine humane Explantate- und Finite-Elemente-Analyse.
2014 DKOU (oral)

Schmidutz F, Sprecher CM, Nehrbass D, Milz S, Gohlke F, Hertel R, Südkamp N, Braunstein V.
Oberflächenprothesen führen auch an der Schulter zu einem Stress-Shielding und Verlust von Knochensubstanz.
2014 Endoprothetik (poster – 2nd prize)

Seelbach R, Fransen P, Peroglio M, Duttenhoefer F, Alini M, Royo M, Mata A, Eglin D.
Dendrimers Presenting Spatially Controlled Clusters of Binding Epitopes for Tailoring hMSCs Microenvironments.
2014 EORS (poster)

Soenjaya Y, Eglin D, Willett TL, Holdsworth DW, Alini M, Hunter GK, Goldberg HA.
Healing of Rat Calvarial Defect with Nanohydroxyapatite/Poly(Ester-urethane) Scaffolds Loaded With rhBMP-2.
2014 ORS (poster)

Sprecher CM, Boudrieau RJ, Suter T, Keating JH, McCarthy RJ, Gueorguiev B, Richards RG, Milz S.
Correlation between low corrosion resistance and osteosarcoma.
2014 DKOU (oral)

Sprecher CM, Schmidutz F, Agarwal Y, Müller PE, Richards RG, Gueorguiev B.
Der zementfreie Oberflächenersatz der Schulter induziert ein knöchernes Stress-Shielding: Eine humane Explantate- und Finite-Elemente-Analyse.
2014 Academia Raetica (poster)

Stanciuc A, Stoddart M, Alini M, Peroglio M.
Characteristics of human primary osteblasts from osteoarthritic femoral heads.
2014 Academia Raetica (poster)

Steinmetz P, Zderic I, Boger A, Sprecher C, Windolf M, Richards RG, Gueorguiev B.
Cement flow behaviour in artificial cancellous bone structures. A biomechanical study.
2014 EORS (poster)

ter Boo GA, Grijpma DW, Richards RG, Moriarty TF, Eglin D.
Monodisperse microspheres loaded with gentamicin dioctyl sodium sulfosuccinate for the treatment of orthopaedic infections.
2014 ESB (poster)

ter Boo GA, Grijpma DW, Richards RG, Moriarty TF, Eglin D.
Delivery of gentamicin-AOT from poly(trimethylene carbonate) films.
2014 AFPM (poster)

Vadala G, Russo F, De Strobel F, Bernardini M, Eglin D, Denaro L, Alini M, Busetto R, D'Avella D, Denaro V.
Reproducible Disc Degeneration Scale In A Large Animal Model.
2014 ORS (poster)

Voegtli D, Widmer D, Noser H, Kamer L, Windolf M.
Parametric analysis of proximal femur morphology on fracture behavior in sideways fall situations.
2014 Academia Raetica (oral)

Wagner D, Kamer L, Noser H, Sawaguchi T, Rommens PM.
Einfluss der Knochenverteilung entlang der trans-sakralen Korridore auf die Frakturmorphologie und die Behandlung von Insuffizienzfrakturen des Sakrums.
2014 DKOU (oral)

Wagner D, Kamer L, Sawaguchi T, Noser H, Rommens PM.
Die Knochenverteilung im Sakrum erklärt die Frakturmorphologie von Insuffizienzfrakturen des Sakrums und beeinflusst deren operative Behandlung.
2014 Alterstraumatologie (poster)

Wagner D, Kamer L, Sawaguchi T, Noser H, Rommens PM.
The anatomy of the cranial boarder of trans-sacral corridor S1 explains its variability.
2014 SICOT (oral)

Wagner D, Kamer L, Sawaguchi T, Noser H, Rommens PM.
Sacral insufficiency fractures in the light of the sacral bone mass distribution.
2014 SICOT (oral)

Wagner D, Kamer L, Sawaguchi T, Noser H, Rommens PM.
Limitations in virtual trans-sacral implant positioning demonstrated in 3D pelvic models.
2014 SICOT (oral)

Wagner D, Kamer L, Sawaguchi T, Noser H, Rommens PM.
Virtual trans-sacal implant positioning is critical in S1 whereas in S2 a trans-sacral corridor always is present.
2014 OTA (poster)

Windolf M, Hofmann-Fliri L, Widmer D, Richards RG, Blauth M, Gueorguiev B.
Implant augmentation with bone cement in osteoporotic bone.
2014 AOTAP (oral)

Windolf M, Lenz M, Perren SM, Richards RG, Fernandez Dell'Oca AA, Höntzsch D, Gueorguiev B.
Benefit and Harm of Cerclages for Osteosynthesis Augmentation.
2014 AOTAP (oral)

Zderic I, Camino G, Wahl D, Sancineto C, Barla J, Windolf M, Richards RG, Gueorguiev B.
Analysis of sacroiliac joint screw fixation: Do quality of reduction and screw orientation influence biomechanical stability?
2014 EORS (poster)

13.6 Dissertations

Czekanska EM
In vitro cell and culture models for osteoblasts and their progenitors:
2014 Cardiff University (Stoddart M, Ralphs J) - PhD.

Sermon A
Addressing the challenge of hip fracture fixation and prevention in old age. Preclinical and clinical studies assessing the osteoporotic femoral head.
2014 KU Leuven (Flamaing J, Richards RG) – PhD.

Varga E
Computerized treatment planning and its realization in maxillofacial surgery and in dental implantoloty
2014 Faculty of Medicine, University of Szeged Piffkó J, Varga E) supported within ARI by Kamer Lukas

Windolf M
Fracture fixation in osteoporotic bone.
2014 Universität Ulm (Richards RG, Dürselen L, Ignatius A) - PhD.

Veselinov D
Computer animation: Clip for presentation X-in-one.
2014 TU Varna (Gueorguiev B) - MSc.

Vögtli D
Parametric analysis of proximal femur morphology on fracture behaviour in sideways fall situations.
2014 ETH Zürich (Windolf M) – MSc.

13.7 Presentations (not in conference proceedings)

11.06.2014	Richards Geoff: "Hurdles in a successful example of stem cell-based regenerative medicine", TERMIS Chapter Meeting, Genova, Italy (Chair plenary lecture)
27.-30.06.2014	Richards Geoff: "Report from AO Research Institute Davos", Board of Trustees Meeting, Budapest, Hungary (Lecture)
27.-30.06.2014	Richards Geoff: "Symposium: Barriers to bringing an idea to market and the strategies of translational research", Board of Trustees Meeting, Budapest, Hungary (Moderator)
04.07.2014	Richards Geoff: "Infection and Trauma II", EORS 2014 Annual Meeting, Nantes, France (Session chair)
04.07.2014	Richards Geoff: "AO Foundation", EORS 2014 Annual Meeting, Nantes, France (Session chair)
01.09.2014	Richards Geoff: "EORS Symposium", ESB 2014 Annual Conference, Liverpool, UK (Chair)
10.09.2014	Richards Geoff: "Expectations and needs of Young Academics", Graubünden Forscht – Young Scientists in Contest 2014, Davos, Switzerland (Podium Chair)
11.09.2014	Richards Geoff: "Medical Sciences", Graubünden Forscht – Young Scientists in Contest 2014, Davos, Switzerland (Session Chair)
06.11.2014	Richards Geoff: "Why Translational Research is Important", German Society for Biomaterials, Annual Conference, Dresden, Germany (Invited Speaker)
15.12.2014	Richards Geoff: "Infection and implant design", AOCMF Course-Principles in Craniomaxillofacial Fracture Management, Davos, Switzerland (Invited Speaker)
11.04.2014	Alini Mauro: "Articular Cartilage: from Anatomy to TE. Update on anatomy and histology", Scuola di Medicina e Chirurgia, Università degli Studi di Catania, Italy (Invited Speaker)
22.-25.08.2014	Alini Mauro: "Endogenous VS exogenous repair of IVD", BioMed 2014 meeting, Köyceğiz, Turkey (Invited Speaker)
02.-05.09.2014	Alini Mauro: "Looking for a chemoattractant released by injured IVD", 10th Congress on Stem Cell Biology & Technology, Tehran, Iran (Invited Speaker)
10.09.2014	Alini Mauro: "Present and Future of Tissue Engineering", Graubünden Forscht – Young Scientists in Contest 2014, Davos, Switzerland (Invited Speaker)
17.-19.09.2014	Alini Mauro: "Hydrogel-based approaches towards minimally invasive treatment of IVD", 6th International Conference "Biomaterials, Tissue Engineering & Medical Devices" BioMedD, Constanta, Romania (Invited Speaker)
23.-24.10.2014	Alini Mauro: "Hyaluronan based hydrogel for biologicals and cells delivery for cartilage and intervertebral disc regeneration", Term Stem Symposium 2014, Porto, Portugal (Invited Speaker)
17.-18.11.2014	Alini Mauro: "Stem cell for intervertebral disc regeneration: Which cells? At which time? And how to deliver them?", 4th International Symposium on Stem Cell Biology and Regenerative Medicine, Hong Kong, China (Invited Speaker)
16.-17.5.2014	Boyko Gueorguiev-Rüegg: "Bony Anatomy and Implant Development & Paediatric Fractures", 2nd AOTrauma Asia Pacific Scientific Congress & TK Experts Symposium, Seoul, S. Korea (Session Panel)
16.-19.04.2014	Moriarty Fintan: Society for Biomaterials Annual Congress, Denver, Colorado, USA (Invited Speaker)
October 2014	Moriarty Fintan: Improved Protection of Medical Devices Against Infection (iPROMEDAI) Annual Meeting, Porto, Portugal (Invited Speaker)
21.-22.04.2014	Grad Sibylle: "Bioreactor for in vitro optimization of cartilaginous constructs", Freiburger Knorpeltage, Freiburg, Germany (Invited Speaker)
15.-17.05 2014	Grad Sibylle: "Annulus fibrosus repair" (by Zhen Li, Marianna Peroglio, Sibylle Grad, David Eglin, Mauro Alini), World forum for spine research, Xian, China (Invited Speaker)

10.05.2014	Herrmann Marietta: "Pre-vascularization of 3D scaffolds promotes host tissue integration". Herrmann M, Verrier S, Alini M. Jahrestagung AO Trauma, Kiel, Germany
19.09.2014	Herrmann Marietta: "Neovaskularisation von zellbeladenen Knochenersatzmaterialen für große Knochendefekte" Unfallchirurgischen Seminar, Regensburg, Germany
15.-17.03.2014	Stoddart Martin: "Scaffolds for Cartilaginous Tissue Engineering & Repart, Spotlight", ORS Annual Meeting, New Orleans, USA (Session Chair)
08.08.2014	Stoddart Martin: "AO Research Institute Davos Within the AO Foundation: A Model for Translation of Science to the Clinics", Gordon Research Conference on Musculoskeletal Biology & Bioengineering held at Proctor Academy in Andover, NH, USA (Invited Speaker)
22.09.2014	Stoddart Martin: "Antiosteoclastic drugs and their impact on maxillofacial and orthopedic bone biology, disease, diagnosis, prevention, surgery, and treatment modalities (ARONJ)", AOCMF 2nd Clinical Priority Program (CPP) conference. Imaging and Planning in Surgery, Prague, Czech Republic (Invited Speaker)
24.10.2014	Stoddart Martin and Richards Geoff: "Preclinical Research translation to the Clinic: Towards intra-operative cell repair", TERMSTEM2014, Porto, Portugal. (Invited Speaker)
24.-25.09.2014	Stoddart Martin: 50th Anniversary Jubilee Conference celebrating 50 years of the Orthopaedics at the University of Basel, Switzerland (Session Chair)
12.-14.04.2014	Verrier Sophie: "Neo-vascularization of 3D scaffolds", "3rd dimension bridges the gap between cell culture and live tissue" Inserm workshop, Bordeaux, France (Invited Speaker)
08.03.2014	Windolf Markus: "Biomechanische Pathophysiologie der Pseudarthrose", Symposium Pseudarthrosen in Orthopädie und Unfallchirurgie, Jena, Germany (Invited Speaker)
04.-06.06.2014	Windolf Markus: "Experimental basics for augmentation techniques", AOTrauma Collaborating Society Session at EFFORT 2014 "Augmentation – The New Standard in Osteoporotic Fracture Care?", London, UK (Invited Speaker)
19.11.2014	Zeiter Stephan: "Development of an orthopedic mouse model", Maastricht University Medical Center, the Netherlands (Invited Speaker)
10.11.2014	Lanker Urban: "Herdenschutz – der einsame Kampf", Naturforschende Gesellschaft Davos (NGD), Switzerland (Invited Speaker)