AO Foundation

AO Research Institute Davos

Activity Report 2015

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1 Introduction

I have had the honor to direct the AO Research Institute Davos (ARI) since 2009 with a very knowledgeable, motivated and dedicated multidisciplinary team. Each year we improve our deliverables from the academic side and for the research and development support of the AO Foundation's clinical network. All of our projects are dedicated to solving clinical problems with the final aim to help the patient. In 2015 the ARI continued to strengthen relations with the clinical divisions (CD's) and technical commission (TK) who clinically guide our projects. Each project receives a medical godfather, is reviewed by the respective clinical division's research committee (all clinicians) on the clinical relevance and milestones during the project's life or by the ARI advisory committee, which also includes respected international scientists.

On the academic side the ARI has achieved the level it now needs to maintain. 2015 was an outstanding year academically, with a major award, three honorary professorships, good publications, good representation at conferences and within society boards all while performing good support to the AO Foundation. In 2015 the ARI published their second highest number of publications ever with 71 peer reviewed papers, with an average impact factor of 3.28, well above the average of the musculoskeletal field (the highest ever was 74 in 2009 with a lower average impact factor of 2.46 though).

Notably, I would like to highlight the ORS Marshall R. Urist, MD Award – the highest award of the Orthopaedic Research Society to Prof Mauro Alini for his pioneering work on disc degeneration. He is only the third European based scientist to have won this award. Dr Boyko Gueorguiev, Program Leader at ARI, received an Honorary Professorship from the Technical University of Varna (TUV) which is a great reward for his excellent collaborations with TUV. Dr Martin Stoddart was awarded an honorary Professorship at the University of Freiburg, Germany for his long-term collaborations there. We currently have 5 Professors at ARI. These notable achievements strengthen our international academic reputation along with increasing the academic reputation of the AO Foundation.

On the future side, effort was put into the setup of a development incubator to support Innovation for the future of the AO Foundation. This initiative is aimed to help the development of ideas to proof of concept that can then be valorized and help improve translation to better patient outcomes.

Finally, we received an historic visit in 2015, which you can see in our good news.

I would like to thank the ARI employees for their commitment to the ARI, our collaborations with the clinical divisions and TK and to the whole AO Foundation again in 2015. Motivated hard working people, within motivated functioning teams are the key to our success and future.

Sincerely

Prof Dr R Geoff Richards FBSE, Director AO R&D, Director AO Research Institute Davos

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 focused towards clinical applications/solutions.
- Investigate and improve the performance of surgical procedures, devices and substances.
- Foster close relationships with the AO medical community, academic societies, and universities.

2016 Outlook

- Focusing resources on creating new surgical solutions such as for smart surgery
- Bringing preclinical research to the highest accreditation, retaining ISO certification, AAALAC accreditation and finalizing GLP certification
- Maintaining academic excellence with the tissue engineering and regenerative medicine program

Rolling Outlook ARI (3-5 years)

- 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.

3 Funding Summary

Income Statement	2014 Actual		2015 Actual	
in CHF '000	abs	%	abs	%
AO Foundation Contribution	8'909	73%	8'708	69%
3rd party Income	1'738	14%	2'193	17%
AO Intercompany	1'624	13%	1'651	13%
Total Income	**12'271**	**100%**	**12'552**	**100%**
AOTrauma *	4'090	33%	3'921	32%
AOSpine*	431	3%	440	4%
AOCMF *	595	5%	505	4%
AOVET *	70	1%	77	1%
AOTK *	406	3%	622	5%
AOER	1'691	14%	1'532	13%
AO Foundation *	3'444	28%	2'797	23%
3rd party projects	1'738	14%	2'193	18%
Total Expenses	**12'465**	**100%**	**12'087**	**100%**
Net Result	**-193**		**464**	

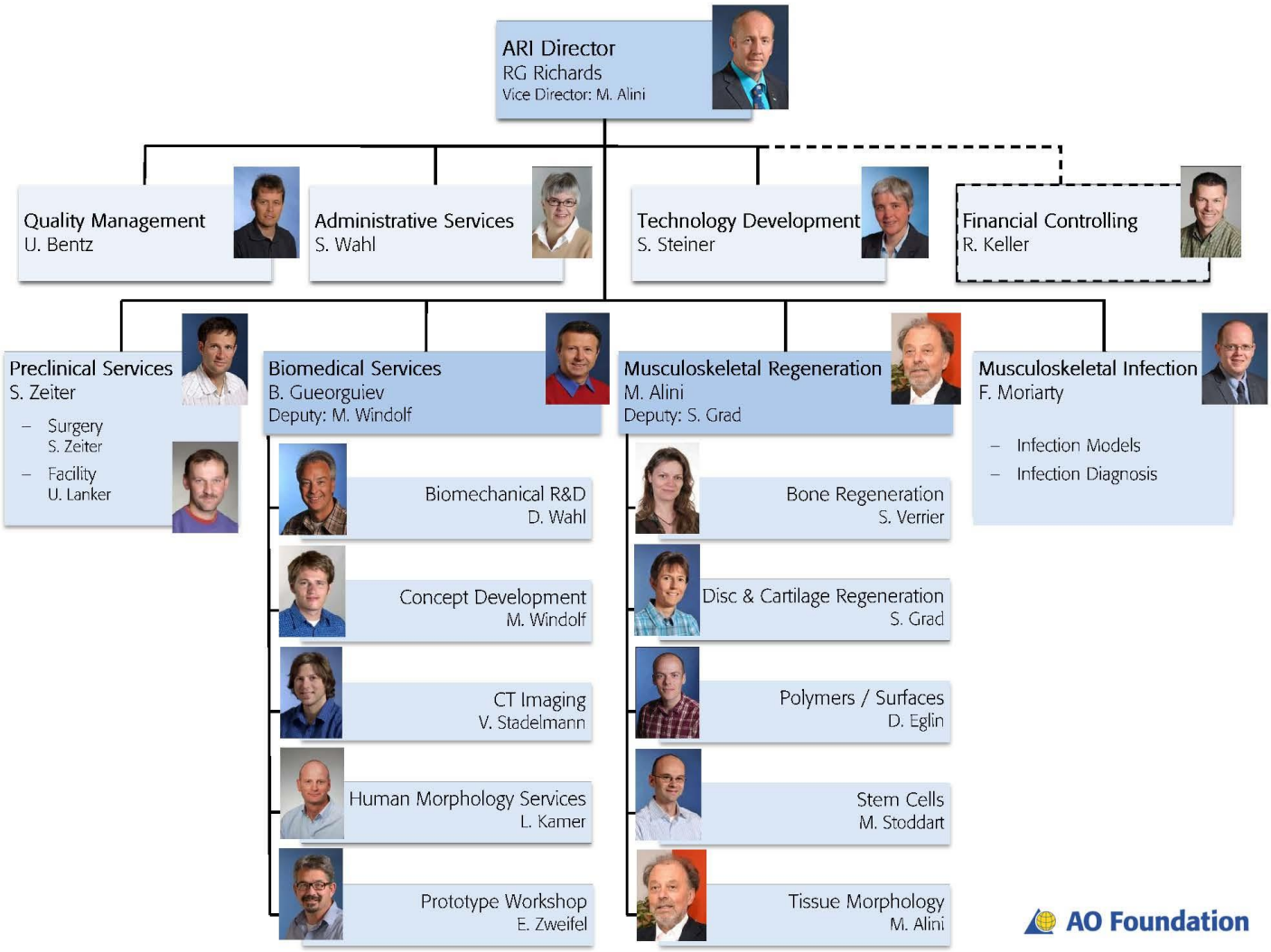
* incl. AO Intercompany

3rd Party Income' amounted to CHF 2'193 and remained 6% (CHF 115) above budget and 26% (CHF 455 K) above previous year. The main reasons for the increase vs. budget were an increased number of 3rd party paid services, research collaborations and additional grants. With regard to the split of the 'Total Expenses' by organizational unit, 'Musculoskeletal Regeneration' had the highest stake with 30% followed by 'Biomedical Services' with 17% and 'Preclinical Services' with 16%. From a cost type point of view, the main categories were 'Personnel Expenses' with 66%, followed by 'Material Expenses' with 11% and 'Scientific & Regional Expenses' with 9%.

Overall, a positive 'Net Result' of CHF 464 K was achieved compared to a balanced budget. 67K from the 2014 deficit had already been built into the reduced 2015 Budget. The remaining 126K deficit from 2014 is covered by the 2015 result. Considering these items the adjusted result amounts to 338 K.

4 Structure

4.1 ARI Structure (as of December 2015)



4.2 AO R&D Platform

The AO Research and Development Platform (AO R&D Platform) supports and advices the AO Foundation Board (AOFB) in its governing tasks, e.g. strategy definition, supervision and outcome measurement and ensures know-how and information exchange between respective stakeholders. AOFB is responsible to set the strategy, provide the funding and evaluates the outcome from research. All research stakeholders are accountable to the AOFB. The AO R&D Platform monitors, reviews and further develops the strategy defining clinical needs and implementation on behalf of the AOFB in an advisory capacity. The AO R&D Platform coordinates among research stakeholders to exchange information and develop best practice in operations and evaluation. It has no funding and decision authority.

The Chairperson of the ARI Advisory Committee is a member (ex officio, with voting rights) and the AO ARI director is a member (without voting rights)

In 2015 the main topics with relevance to the ARI were

- Monitoring the setup of the AO R&D Management and Information System (MIS)
- Monitoring and review application for AAALAC Member Organization for the AO Foundation
- Monitoring of the IP Incubator Task Force (Development Incubator) progress on the Feasibility study & implementation plan for IP management policy with the main question of Should AO include Development in future and how?

4.3 ARI Advisory Committee

The ARI Advisory Committee (ARI AC) met in June and December at the AO Research Institute Davos (ARI). 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 ARI. 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 ARI in the fields of:
  - Portfolio of competences (skills of personnel and type of equipment)
  - Strategy and priority setting for direct funds of the ARI
  - Exploratory research Collaborative Research Program(s)
  - Business development and initial advice on technology transfer
  - Regulatory issues
- Monitor/control the ARI output of direct funding on behalf of the AOFB
- Support the advancement of the capabilities of the ARI 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

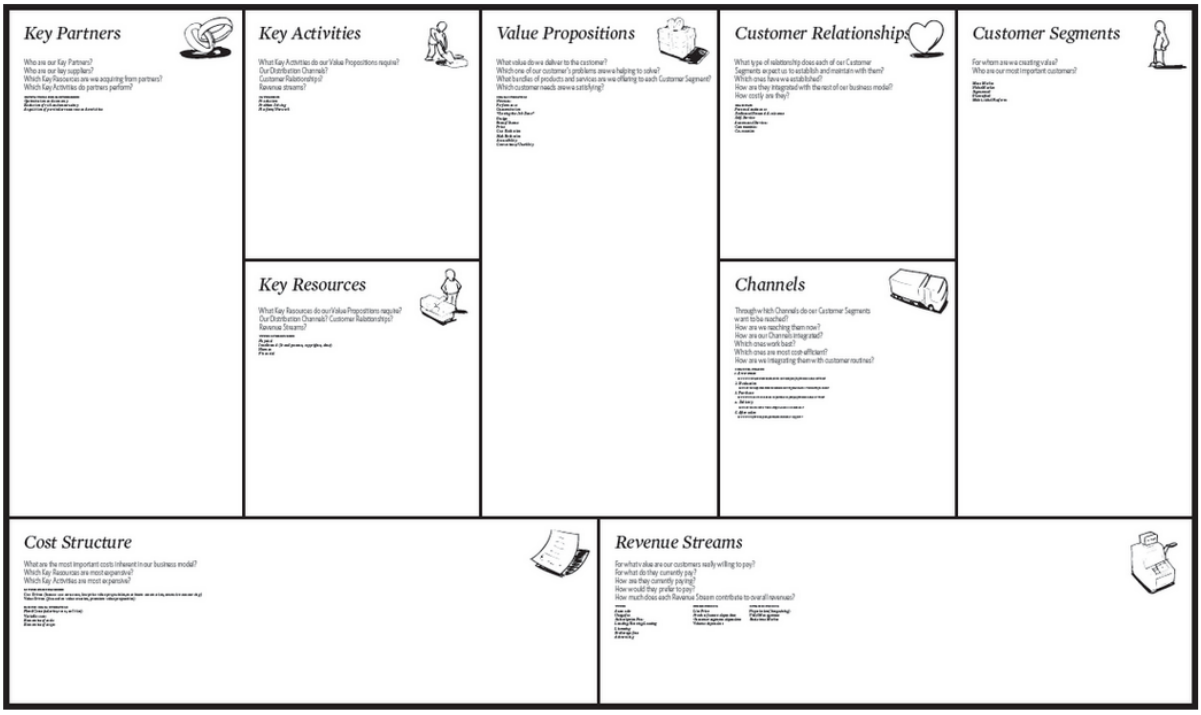
4.4 ARI Technology Development

Technology Development Officer: Sandra Steiner

The 2015 ARI retreat was focused on the generation of theoretical early business models for the most advanced ARI development projects to expand on the thorough review of all ARI patents, which was achieved the previous year.

Prof Robert Frigg, ex Head of Synthes Global Technology and Innovation Group, was the first speaker and introduced the participants to the Canvas business plan model.

A poster with the standard elements of the Canvas model is shown below:



Using this Canvas poster as a template a number of early business plans were created by the participants during breakout sessions. Some of these were generated for spontaneous product ideas developed during the retreat and others had specific ARI projects as a basis. The latter included the following projects:

- Fracture monitoring (M. Windolf)
- Patient specific implants (L. Kamer)
- Carrier and biologics (M. D'Este, D. Eglin)
- Infection and gel (F. Moriarty, D. Eglin)

To provide a flavor of the steps involved to bring a new product eventually to the market, Yvonne Bovell a consultant for GLP and regulatory matters was invited and presented an overview of the complex regulatory requirements for obtaining market approval of MedTech products. To conclude, and in order not to discourage participants from continuously trying out new ideas, Prof Joost de Bruijn shared his own experience in successfully launching his own company Progentix which emerged from a typical out-of-the box idea.

4.5 Biomedical Services

Program Leader: Boyko Gueorguiev-Rüegg, Deputy: Markus Windolf
Team Members: Nando Adank, Nicola Barchi, Jan Barcik, Jan Buschbaum, Jan Caspar, Benno Dicht, Ursula Eberli, Manuela Ernst, Kevin Frey, Ladina Hofmann-Fliri, Jason Inzana, Dominik Jenni, Lukas Kamer, Benjamin McCarl, Hansrudi Noser, Manuel Schneider, Ronald Schwyn, Flurin Spiller, Vincent Stadelmann, Peter Varga, Viktor Varjas, Daniela Vögtli, Dieter Wahl, Ivan Zderic, Erich Zweifel

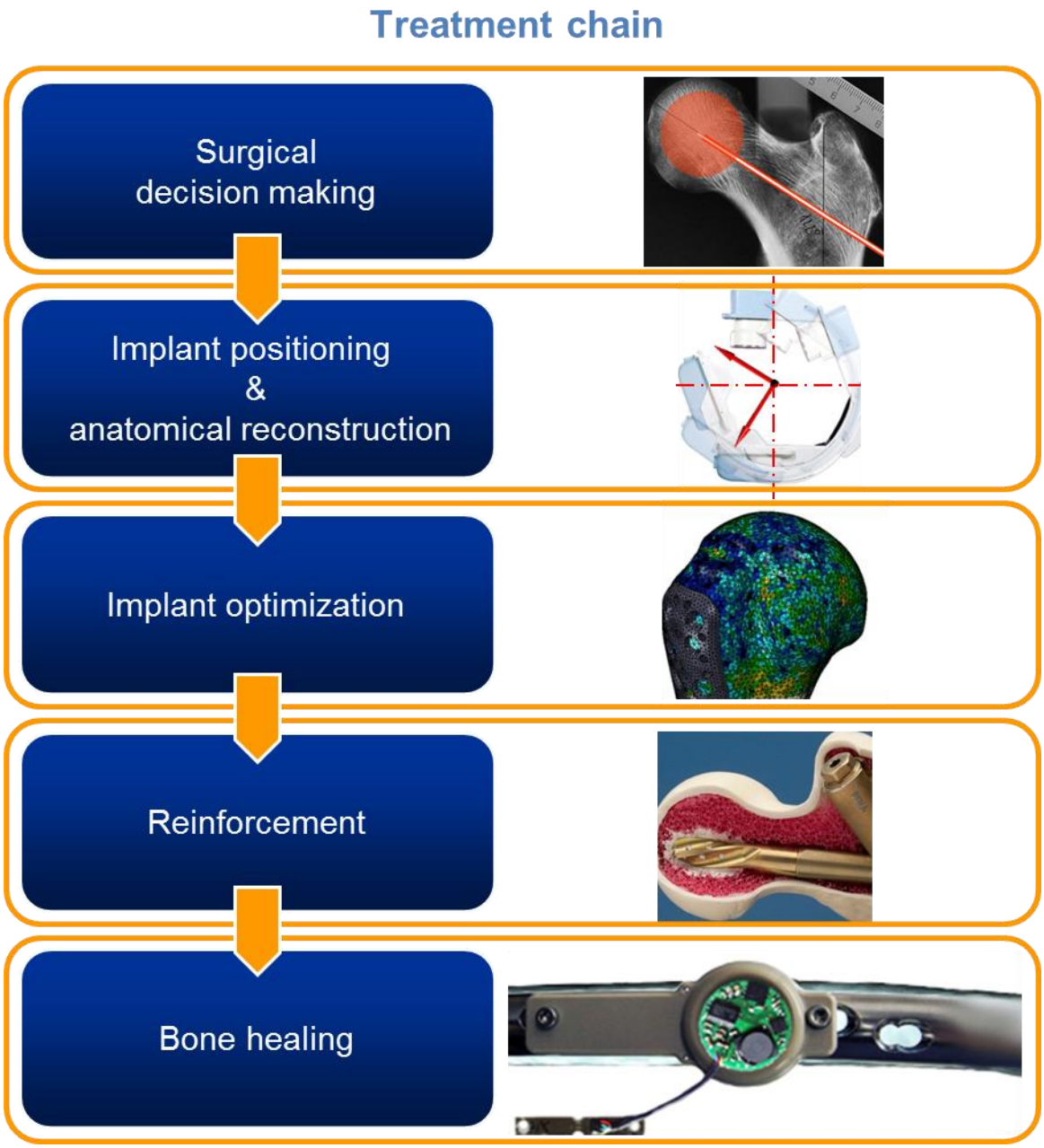
Fellows: Yves Acklin, Charlotte Arand, Koen Dullaert, Dominic Gehweiler, Jennifer Hagen, Theresia Sommerer

Guests: Marc Attinger, Ariane Barandun, Stephen Bresina, Yan Chevalier, Fabian Duttenhöfer, Craig Emms, Andreas Fösel, Janosch Häberli, Philipp Henle, Yuan Huan, Georg Klammer, Kajetan Klos, Sebastian Knell, Fabian Krause, Alexandre Ledermann, Claire Nagels-Marcon, Michael Nienhaus, Marie Reumann, Philipp Schmierer, Paul Schmitz, Paul Simons, Andrej Stricker

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 (in 2015) are structured and organized in five 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.

4.6 Preclinical Services

Leader: Stephan Zeiter and Urban Lanker
Team Members: Daniel Arens, Corina Berset (AOF), Karin Camenisch, Peter Erb, Pierina Faoro, Andrea Furter, Katharina Kluge, Jann Lanker, Urban Lanker, Reto Müller, Dominic Perren, Tanja Schmid
Fellows: Nicolo Cosmelli, Christian Günther, Linda Freitag
Student Externs: Marco Canic, Fabian Gieling, Erika Hilbold, Judit Magnusson Wulcan, Valentina Riehl, Anna Vincek, Lore Vissers

Preclinical Services conduct all ARI (internal/external/commercial) *in vivo* studies – often in close collaboration with other Focus Areas. All *in vivo* studies are conducted under the highest standards with great responsibility. Therefore, we became an AAALAC International accredited institution in 2013. 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. Reaccreditation for AAALAC took place in November as well as first inspection for the aspired GLP (Good Laboratory Practice) accreditation. GLP is gaining more and more importance in the biomedical field and is expected to be a requirement for medical devices in the near future (http://www.fda.gov).

Staff of Focus Area Surgery are highly qualified and specialized in laboratory animal medicine (ECLAM), anesthesia (ECVAA) and surgery (ECVS). Together with the Focus Area Infection, CT Imaging and Focus Area Polymers and Surfaces we have further developed preclinical infection models in mice, rats, rabbits and sheep by using those to investigate different aspects (diagnosis, treatment, applied research) of bone infections. Another focus has been on bisphosphonate related osteonecrosis of the jaw (BRONJ), where a minipig model was developed 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 conducted.

In order to reach these goals and always stay focused the team successfully performed as many surgeries (700 in total) in 2015 as never before.

4.7 Musculoskeletal Regeneration Program

Program Leader: Mauro Alini, Deputy: Sibylle Grad
Team Members: Jennifer Bara, Mauro Bluvol, David Eglin, Matteo D'Este, Luzia Douma, Niamh Fahy, Oliver Gardner, Markus Glarner, Olivier Guillaume, Nora Goudsouzian, Andri Hassler, Marietta Herrmann, Maria Hildebrand, Laura Kyllönen, Patrick Lezuo, Bojun Li, Zhen Li, Flavio Linardi, Claudia Löbel, Graziana Monaco, Ursula Menzel, Caroline Moser, Dirk Nehrbass, Marianna Peroglio, Robert Peter, Dalila Petta, Silvia Pettinelli, Fatemeh Safari, Yemane Semere, Christoph Sprecher, Ana-Maria Stanciuc, Martin Stoddart, Lukas Straumann, Gert-Jan ter Boo, Federico Urzi, Letizia Vainieri, Sophie Verrier, Reihane Ziadlou
Fellows: André Arruda, Gernot Lang, Fabrizio Russo, Jan Voss, Ying Zhang
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. The ultimate goals are to identify strategies for prevention of 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 current 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 / Cartilage Regeneration Focus Area
Novel therapies for intervertebral disc and articular cartilage regeneration that are currently under investigation in translational and pre-clinical research include the application of functional biomaterials used for structural support, as cell carriers and drug delivery systems. Furthermore, we are investigating underlying mechanisms of tissue failure and of the natural tissue repair capacity to identify new approaches for preventing adverse reactions and activating regenerative responses. The disc/cartilage focus area is utilizing *in vitro* and *ex vivo* cell and organ culture models aiming to test hydrogels and scaffolds to be used for delivery of cells and bioactive factors for both nucleus pulposus, annulus fibrosus or articular cartilage repair. Our organ 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 (such as a main interest antibiotics for infection treatment) 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 which could be applied within a clinical setting. We 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 investigating 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 themselves becoming 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. The secreted molecules and their effects can also be used as biomarkers to determine patient specific healing potential. A serum based biomarker approach may dramatically improve patient specific clinical decisions.

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, belong to the core competences. Others are hard tissue microtome sectioning, modified staining for thicker resin sections, and subsequent qualitative, semi quantitative 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 Sabaté Brescó, Barbara Stanic, Keith Thompson
Fellows: Julian Fischer, Stoyan Petkov

The Musculoskeletal Infection team performs research focused upon the clinical challenges of implant related bone infection. 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 or novel interventions aimed at preventing or treating them.

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 immunizations) 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, Vreni Geret, 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

2015 the ARI Administrative Service Group has organized for:

AO Research Institute (ARI)

05. - 06.02.2015	Cost Meeting, Davos, Switzerland
18. - 19.03.2015	ARI Retreat, Flims, Switzerland
01. - 02.04.2015	Block course: Skeletal Repair for ETHZ and ZHAW students, Davos, Switzerland
24. - 26.06.2015	eCM XVI Bone and Implant Infection, Convention Center, Davos, Switzerland
14. - 16.09.2015	Collaborative Research Program Meetings: Acute Cartilage Injury (ACI) and Annulus Fibrosus Rupture (AFR), Philadelphia, USA
23.06.2015	ARI Advisory Committee (ARI AC) Meeting, Davos, Switzerland
09.12.2015	ARI Advisory Committee (ARI AC) Meeting, Davos, Switzerland

AO Foundation (AOF)

28.05.2015	AOF IP Task Force Workshop 1, GoToMeeting
23.06.2015	AOF IP Task Force Workshop 2, Davos, Switzerland
14.07.2015	AOF IP Task Force Workshop 3, GoToMeeting
30.09.2015	AOF IP Task Force Workshop 4, Dübendorf, Switzerland

AOTrauma Research Commission (AOTRC)

04.02.2015	AOTRC Meeting, Las Vegas, USA
29. - 30.05.2015	AOTRC Meeting, HongKong, China
30.10.2015	AOTRC Meeting, Zürich, Switzerland13.03.2015 AOTrauma Annual Meeting on Fracture Fixation in Osteoporotic Bone (FFOB), Zürich, Switzerland
31.10.2015	AOTrauma Annual CPP Meeting Bone Infection, Zürich, Switzerland

5 Institutional and Professional Relations

Geoff Richards has appointment as honorary Professor at Cardiff School of Biosciences, Cardiff University, Wales, GB. In 2015 he also became Honorary Professor at the Medical Faculty of Albert-Ludwigs University, Freiburg, Germany. 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 was from 2013 until the end of 2015 a member of TERMIS-EU council and the World Council Tissue Engineering & Regenerative Medicine International Society. Geoff is a member and Director of the Board of the foundation of the AO Research Institute Davos. Geoff is an executive committee member for the European Orthopedic Research Society. Since 2013, Geoff is also an Associate Editor of the Journal of Orthopaedic Translation. He is a member of executive committee of Academia Raetica and Vice President of Science City Davos. In 2014 Geoff became a member of International Combined Orthopaedic Research Societies (ICORS) Steering Committee. He is a guest lecturer of the MSc Course Skeletal Repair at the Department Health Science and Technonogy (D-HEST) of the ETH Zurich. 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, Journal Orthopaedic Research 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 an honorary professor at the Technical University of Varna, Bulgaria in the fields of biomedical engineering and biotechnology. He is 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 a journal reviewer for Arch Orthop Trauma Surg, BMC Musculoskeletal Disorders, BMT Biomed Eng, Clin Biomech, Engineering Failure Analysis, J Forensic Biomech, J Orthop Res, J Orthop Trauma and Medicine.

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 is a member of the education committee of the European College of Laboratory Animal Medicine (ECLAM) and he has reviewed for the following journals: Acta Biomaterialia, BioMed Research International, eCM, Journal of Biomedical Materials Research Part A, Journal of Tissue Engineering and Regenerative Medicine, European Spine Journal as well as Laboratory Animals.

Fintan Moriarty is an invited lecturer at the Bern University of Applied Sciences, MSc program in Medical Technology (2015). He was also invited onto the board of associate editors of the journal of orthopaedic trauma for four years. He is a member of the eCM Journal International Review Panel. He is a lecturer of the MSc Course Skeletal Repair at the Department Health Science and Technonogy (D-HEST) of the ETH Zurich.

David Eglin is a member of the Executive Committee of the Swiss Society for Biomaterials and regenerative Medicine (SSB&RM) 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 organizer and lecturer of the MSc Course Skeletal Repair at the Department Health Science and Technonogy (D-HEST) of the ETH Zurich. She is a member of the Editorial Board of the Scoliosis and Spinal Disorders Journal. 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 member of the ORS Program Committee of the Annual ORS Meeting. She is an Associate Faculty Member of the Faculty of 1000 Medicine.

Martin Stoddart is an Honorary Professor at the Medical Faculty of Albert-Ludwigs University, Freiburg, Germany. He lectures on the Skeletal Repair MSc module at the ETH Zürich. He is the Chair of the Orthopeadic Research Society (ORS) Basic Science Education Committee, and a member of the ORS Communications Council. He is a member of the International Cartilage Repair Society Communication and Publication Committee. He is 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 the Co-ordinator and main organiser of the yearly eCM conference and a webeditor of eCM. He is the ARI representative to the AOCMF R&D commission. He is also an Associate Faculty Member of Faculty of 1000 Medicine.

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. She evaluates research project applications for funding and moderates scientific sessions at national and international conferences (e.g. DKOU, eCM or ORS). She is a member of the Women's Leadership Forum committee (WLF) of the Orthopaedic Research Society (ORS).

Markus Windolf acts regularly 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.

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

Jennifer Bara is a member of the eCM International Review Panel.

Matteo D'Este is a member of the eCM International Review Panel.

Oliver Gardner is a member of the eCM International Review Panel.

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

Zhen Li is a member of the eCM International Review Panel.

Hansrudi Noser is a professor at the ETHZ. In addition, he acts as an examiner at the University of Fürstentum Liechtenstein.

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

Vincent Stadelmann lectures at The Swiss Institute of Technology Lausanne.

Peter Varga is a reviewer for the following journals: Bone, J Biomech, Med Eng Phys, Acta Biomater, J Mech Behav Biomed, Eur Cells Mater, J Biomech Eng-T ASME, Arch Orthop Trauma Surg, Medicine. Furthermore, he has been reviewing for the Belgian funding body Research Foundation Flanders (FWO).

6 Good News

Royal visit

The ARI had the honor to have received HRH the Prince of Wales as our guest for a private visit. We highly appreciate this, especially as he took some of his valuable holiday time for us especially as his official public schedule was full after his short break in Davos-Klosters.

From left to right: Prof Thomas Rüedi (founder AO Foundation), Patty Palmer Thomkinson (long term colleague of HRH), Prof Peter Matter (founder AO Foundation and past President AO Foundation), HRH the Prince of Wales, Prof Geoff Richards (Director AO Research Institute Davos), Prof Stephan Perren (founder AO Foundation and past Director AO Research Institute Davos), Dr Rolf Jeker (vice Chair AO Foundation and CEO)

It had been a desire of Prof Richards (even before taking up the Directorship in 2009) to have HRH visit the ARI, knowing his strong connection to our local region and especially to our past president Peter Matter. Naturally being Prince of Wales the strong connection to Prof Richards' country of birth and that they both spent some time in University at Aberystwyth added to the wish. The timing was right, 25 years after HRH had fracture fixation of his shoulder from AO trained British surgeons using the AO techniques. He received the first titanium plate and titanium screws implanted in Britain that had been designed here at the ARI based upon years of innovative research concepts for better healing and care of the surrounding tissues. Prof Richards showed the overview of plate development followed by Manuela Ernst showing our developments in reducing use of X-Rays and improving accuracy of implant placement with our digital aiming device, followed by a glimpse to the near future where sensing implants inform the surgeon (through smart phones) the state of the bone healing situation, saving patient, hospital, and insurance costs. Dr Martin Stoddart originally from Manchester (and also an Aberystwyth graduate) showed our hip bioreactor which is unique to the ARI and how the team's results have already come into our local hospital in Davos to improve patient rehabilitation methods.

Manuela Ernst explains the AO fracture monitor invented and developed at ARI.

HRH demonstrates his excellent humor in relation to the Swiss Implants.

Professorships
Three professorships have been awarded to ARI staff members in 2015

From left to right: Prof Geoff Richards, Prof Hristo Skulev, Prof Boyko Gueorguiev

In the framework of the collaboration between the ARI and the Technical University of Varna (TUV), Prof Geoff Richards, Director AO R&D, and Dr Boyko Gueorguiev, Program Leader Biomedical Services at ARI, visited TUV on 20 May 2015 and participated at Boyko's promotion as an Honorary Professor of the University. Within the 53 year history of the TUV, there have been a total of only 27 honorary professors (from all over the world) at the University. Boyko is the first honorary professor from Switzerland.
The certificate award ceremony commenced after a welcome meeting with Prof Ovid Farhi, Rector of TUV, Prof Hristo Skulev, Vice-Rector of Research, and Prof Velko Naumov, Vice-Rector of International Cooperation.
The nomination for honorary professorship was initiated by the Department of Materials Science and Technology at the Faculty of Industrial Technology, where Boyko had been appointed as an honorary lecturer in the field of biomedical engineering. Following a letter of intent between ARI and TUV from 2012 and considering Boyko's scientific, publication and educational activities with the University, his candidacy for the professorship was fully supported by the University Scientific Academic Board. The Certificate of Honorary Award with the title Professor of the Technical University of Varna was handed over to Boyko by the Rector of the University Prof Farhi in a special forum of the Academic Board in the presence of university's lecturers, scientific collaborators, team members, and PhD students. Boyko thanked warmly for this highly appreciated award, expressed his strong commitment to foster further the future scientific and educational collaboration between the two institutions. He then gave his inaugural lecture on the biomechanical research and development of implants for bone fracture fixation and treatment of joint disorders. In his turn, Prof Geoff Richards lectured on the AO translational model and how this functions in collaboration with academic and industrial partners. Prof Richards welcomed the furthering of the collaboration with one of the most innovative universities in Bulgaria.

Prof Richards was highly impressed with the maritime qualification center at TUV, with their developments in software for simulations in captain training and education and believes this is an area where there is good potential for cross–fertilization of knowledge for both research and educational simulations in the trauma field.

Prof Geoff Richards, Prof Ovid Farhi and Prof Boyko Gueorguiev (from left to right) in the largest simulation complex for training of the maritime qualification, displaying the latest technologies for training which is based at the Technical University of Varna.

The three ARI professors (from left to right) Martin Stoddart, Geoff Richards, and Boyko Gueorguiev at a recent congress.

ARI is proud to announce that Dr Martin Stoddart and Prof Geoff Richards from AO Research Institute Davos have both been awarded honorary Professorships at the Medical Faculty of Albert-Ludwigs University, Freiburg, Germany. Dr Stoddart was proposed by Prof Schmelzeisen, and Prof Richards was proposed by Prof Südkamp. This further strengthens a longstanding connection between the two institutes which both parties look forward to continuing.

Positions

Dr med vet Stephan Zeiter was appointed as council member of the European College of Laboratory Animal Medicine (ECLAM) at their general assembly in September in Hannover.

First EU Horizon2020 project with ARI partner

Mobility, important for well-being, is seriously impaired in many people by chronic low back pain and osteoarthritis due to degeneration of cartilaginous tissue of the intervertebral disc and joint. The aim of the project TargetCaRe (Targeting cartilage regeneration in joint and intervertebral disc diseases) is to achieve regeneration of damaged and degenerated tissues by employing targeting strategies tailored to the pathology and the tissues involved. Towards this aim, ARI scientists collaborate with other experts in advanced drug delivery carriers with dedicated targeting tools, state of the art imaging techniques, and joint or disc biology. Regeneration of diseased tissues will be achieved by loading biologically active agents in state-of-the-art nanocarriers.

The biologically active agents should stimulate the body's own capacity to regenerate by attracting local stem cells or inhibiting degeneration. Delivery and retention will be assessed by advanced *in vivo* and molecular imaging techniques to monitor distribution of the delivered compounds at the tissue level, as well as detect biological markers of regeneration.
TargetCaRe is a 4-year European Training Network (ETN) project run by a consortium of 12 partner institutions located in 5 different countries. One major objective of the Network is to train 15 young scientists who will complete their PhD thesis in the context of TargetCaRe. As such TargetCaRe will establish a network of scientists skilled in the use of smart nanocarriers, unique approaches of targeting by disease specific molecules, and application of innovative imaging tools.

The ARI scientists Prof Mauro Alini and Dr Sibylle Grad are significantly involved in the project as leaders of the Work Package on Intervertebral Disc Regeneration. The role of the ARI is to provide advanced bioreactor systems for joint and disc in order to evaluate the newly developed nanocarriers with bioactive factors in relevant ex-vivo conditions. The project Target CaRe receives funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No 642414. Funding for ARI is CHF 530k in total, which includes two 3-year PhD positions starting in autumn 2015.

Consortium members at the kick-off meeting at Erasmus University Medical Center in Rotterdam.

Congress / Conference Attendance
The ARI ran a symposium at the EFORT congress in Prague, Czech Republic, May 27-29, 2015

The ARI was present at 16th EFORT Congress (European Federation of National Associations of Orthopaedics and Traumatology). The main topic of the congress which took place this year in Prague, Czech Republic from May 27-29, 2015 was infection. The ARI had keynotes at EORS (European Orthopaedic Research Society) and AOTrauma symposia and other oral / poster presentations. As ARI is central within the AOTrauma CPP Bone Infection, the musculoskeletal Infection group attended the meeting with four oral presentations and two poster presentations. Dr Fintan Moriarty presented an overview of the latest research on antibiotic releasing hydrogels at the AOTrauma session, and also gave an invited keynote describing the preclinical in vivo models in operation at ARI during the European Orthopedic Research Society (EORS) session. Further oral presentations included the PhD work of Marina Sabaté Brescó on the role of biomechanical stability on infection risk, and the work of Dr Virginia Post on MRSA colonization in active orthopedic surgeons. Poster presentations were given by Gert-Jan terBoo on his PhD work involving controlled release of gentamicin by hydrophobic modification, and finally, Dr Willem-Jan Metsemakers presented a poster on his ARI fellowship work involving antibacterial implant coatings. Prof Boyko Gueorguiev and Dr Ivan Zderic from the Biomedical Services program also attended and presented current work on augmented versus non-augmented sacroiliac screws in a hemi-pelvis model (poster) and on stability and joint pressures using a human cadaveric model of a large lateral talar process excision (oral).

AO Foundation innovation symposium at Swiss MedTech Expo in conjunction with the Fraunhofer Institute

Two AO Foundation Institutes (AOTK and ARI), together with the Fraunhofer Institute (DE), organized the first innovation symposium dedicated to internal and external treatment strategies for the human locomotor system "Mobilität schaffen – Innere und äussere Behandlungsstrategien am Bewegungsapparat". The symposium took place during the Swiss Medtech Expo on September 15-16 in Lucerne (CH) comprising a mixture of industry exhibition, knowledge transfer and networking with the participation of 160 international and national exhibitors and research leaders in the medtech field.

Manuela Ernst presenting at the
Innovation symposium at Swiss MedTech Expo

Prof Boyko Gueorguiev (ARI) contributed too with his talk on simulation based implant development (Simulationsgestützte Entwicklung von Implantaten). The well-attended series of lectures was completed by Manuela Ernst (ARI) talking about sensor controlled monitoring of fracture healing (Sensorgesteuerte Überwachung des Frakturheilungsverlaufs).

A Tissue Engineering—Developmental Biology Paradigm workshop was delivered at the TERMIS World Congress in Boston, US in early September 2015 by ARI researchers

Workshop participants

ARI PhD student Oliver Gardner and former ARI post-doctoral researcher Dr Girish Pattappa (currently of the University of Nantes, FR) organized a pre-conference workshop entitled "The Tissue Engineering—Developmental Biology Paradigm" at the recent TERMIS World Congress in Boston, US.

The goal of the Tissue Engineering and Regenerative Medicine International Society (TERMIS) is the worldwide advancement of both the science and technology of tissue engineering and regenerative medicine. The aim of the workshop was to show how an understanding of how developmental biology can, and is, being used to inform tissue engineering approaches for the repair of degenerating or damaged tissues. The workshop included presentations from Dr April Craft, assistant professor of orthopedic surgery and stem cell and regenerative medicine at Harvard University, Dr Atanas Todorov from the department of Biomedicine at the University of Basel (CH) and Dr Catherine Kuo associate professor of Biomedical engineering at the University of Rochester, US. The session concluded with a panel discussion on the potential that may be unlocked through developmentally minded approaches to the field of tissue engineering.

Dr April Craft's work focuses on the production of cartilage tissue from embryonic stem cell lines. A particular focus of Craft's work is the recapitulation of developmental ques in a step by step manner in vitro, in order to produce cells with a chondrocytic phenotype that can actively lay down cartilage-like matrix in the lab from embryonic stem cells. The application of these stage specific ques and signals to these cells as they develop need to be strictly controlled, and administered at the right point of differentiation in order to prevent the production of mixed lineage cultures. This work has shown that cells are capable of performing the 'heavy lifting' of tissue repair (e.g., producing suitable extracellular matrix in the case of cartilage) but in order to do so they must be given the right signals at the right time.

The focus of Dr Atanas Todorov's presentation was the use of the process of endochondral ossification of for the repair of critical sized defects in bone. Todorov's work has focused on the use of mesenchymal stem cells to produce bone tissue through a cartilage precursor. This process is made possible by the transition of mesenchymal stem cells from a chondrogenic phenotype to a hypertrophic phenotype during their differentiation, leading to the formation of calcified tissue. The bone tissue produced by in this manner can be devitalized and used as a supportive structure for bone formation in an in vivo setting providing the possibility for an 'off the shelf' product for the repair of bone defects.

Oliver Gardner presenting at the workshop.

The final presentation was given by Dr Katherine Kuo, whose work focuses on the use of developmental principles for tendon tissue engineering. The field of tendon development has received less focus that than other musculoskeletal tissues such as bone and cartilage. As a result Kuo's work has focused on unravelling the processes of tendon development as well as developing tissue engineering approaches with a developmental biology angle for tendon repair. This work has focused on the importance of mechanical stimuli and growth factors such as TGF-β in tendon development, as well as identifying potential markers of tenogenesis.

The workshop was a resounding success and ARI congratulates Oliver Gardner and Girish Pattappa on an excellent event. ARI is also happy to announce that the 2017 TERMIS-EU chapter meeting will be held in Davos and organized by them.

Conference Awards
Mauro Alini, Vice-Director ARI, 2015 Winner of the ORS Marshall R Urist, MD Award

Prof Mauro Alini was the 2015 recipient of the ORS Marshall R. Urist, MD Award – the highest award of the Orthopaedic Research Society (ORS). This is the first time an ARI member has won this award that was created in 1996. This prestigious award honors an investigator who has established him/herself as a cutting-edge researcher in tissue regeneration research and has done so with a sustained ongoing body of focused research in the area of tissue regeneration as it relates to the musculoskeletal system. Mauro presented a modified version of this talk at the AO Trustees Meeting in Thailand in June 2015.

While this is the ultimate honor within the ORS, ARI also had a strong representation in ORS, with a number of ARI members taking part in committee activities, and organizing, symposia, workshops and research interest groups. In addition to the AO Foundation being the only non-society member of International Combined Orthopaedic Research Societies (ICORS), the academic excellence of ARI is being recognized internationally at multiple levels within the field.

Reviewed and accepted ORS symposia

Improving the Translational Success of Cell-Based Therapies
Organizers: Jennifer J. Bara, Marietta Herrmann, Geoff Richards, ARI.
This workshop, addressed the clinical, scientific, and industrial requirements for the successful translation of cell-based therapies into both the clinic and market with an emphasis on educating investigators new to the translational process. By identifying current challenges and ascertaining the perceptions and needs of future investigators, suggestions were made and a white paper will be written to aim to help to improve rates of translational success in the future.

Speakers
Clinical Considerations for Translational Success Theodore Miclau, MD, University of California, San Francisco
Scientific Considerations for Translational Success Christopher H. Evans, PhD, Mayo Clinic
Industrial Considerations for Translational Success Anthony Ratcliffe, PhD, Synthasome, Inc.

Reviewed and Accepted ORS Workshops

Acute Cartilage Injury: AO Foundation Collaborative Research Project
Organizers: Martin Stoddart, ARI, George R. Dodge, PhD, University of Pennsylvania
The repair of acute cartilage injuries is still a significant challenge in orthopedics. Current methods do not reproducibly result in hyaline like repair tissue, and the repair is often short lived. A more active, yet aging, population is increasing the frequency of injury and the longer term effect of osteoarthritis is becoming more prevalent. The economic burden due to the ever increasing need is enormous. This workshop highlighted the influence of cell, materials and mechanical environment in the repair of cartilage defects. In addition, strategies for screening the large number of potential combinatorial devices were emphasized. Interdisciplinary and international collaborations are needed to bring diverse ideas and technologies to bear. In this workshop the outcome of multidisciplinary, multinational consortium with complementary expertise as a collaborative research project of the AO Foundation was described.

Speakers
Enhancing the Biology of Cartilage Regeneration Magali Cucchiarini, PhD, Saarland University Medical Center
In Vitro and In Vivo Screening of Cartilage Repair Products Robert Mauck, PhD, University of Pennsylvania
Hard and Soft Materials for Articular Cartilage Repair David Eglin, PhD, AO Research Institute Davos

Other accepted Activities

Good and Bad Animal Models for Orthopaedic Research: Scientific and Ethical Considerations
Organizer: Stephan Zeiter, ARI.
Objectives: There is a scientific and ethical imperative that clinically most relevant models are used for orthopaedic research. Scientifically, the models should mimic as much as possible the (human) clinical situation. Ethically, according to the 3R principle, the number of animals used should be kept a minimum and potential pain, suffering, or distress should be minimized in all animals used in order to enhance animal welfare.

Research Interest Group: Spine Research Community
Co-organizer: Sibylle Grad, PhD, AO Research Institute Davos
Animal Welfare in Orthopaedic Research: Focus on Refinement and Reduction
Keynote lecture: The Team Approach to Implementing the 3R's Stephan Zeiter, DVM, PhD, DipECLAM, AO Research Institute Davos

Mauro Alini and his colleagues on award night.

Dr Jennifer Bara was awarded a Travelling Scientist Fellowship by the International Cartilage Repair Society (ICRS)

This is a newly introduced ICRS award, aiming to provide promising young postdoctoral scientists with an opportunity for international exchange in a stimulating environment and to gain exposure to high quality basic research in laboratories that are world famous for their work on articular cartilage injury, repair, and regeneration. Between 30th April-10th May 2015, Jennifer, together with four other award recipients; Giovanna Desando (Rizzoli Orthopaedic Institute, Bologna, Italy), Lucienne Vonk (University Medical Center Utrecht, The Netherlands), Christophe Merceron (University of Michigan U.S.A and University of Nantes, France) and their travelling mentor, Prof Daniel Grande (The Feinstein Institute for Medical Research, New York), visited and participated in scientific exchange with several prestigious cartilage research centers in the United States. The trip was completed by presenting their fellowship experience at the ICRS World Congress in Chicago.

Research groups involved in the scientific exchange included: Gerard A. Ateshian and Clark T Hung, Columbia University, New York City; Jeremy Mao, Columbia University, New York City; Suzanne Maher, Hospital for Special Surgery, New York; Marjolein van der Meulen, Lara Estroff, Itai Cohen. Larry Bonassar, Lisa Fortier, Alan Nixon, Cornell University, New York; James Cook, University of Missouri, and Susan Chubinskaya at Rush University Medical Centre, Chicago. We congratulate Jennifer for this award.

From left to right: Gerard Ateshian, Daniel Grande, Christophe Merceron,
Lucienne Vonk, Jennifer Bara, Clark Hung, Giovanna Desando at Columbia University, New York City

30th GOTS congress (Gesellschaft für Orthopädisch-Traumatologische Sportmedizin), June 12-13, 2015 in Basel, Switzerland

For their two studies '*Modifikation der Zentrifugation zur Reduktion der Leukozytenzahl in PRP und die Auswirkung auf die Proliferation von autologen mesenchymalen Stammzellen*' and '*Klinisch-radiologischer Langzeitverlauf nach intraartikulärer Tibiakopffraktur bei Skifahrern*', both performed in collaboration with ARI, Siegmund Lang and Alexander Hanke from the University Hospital Regensburg, Germany, have been awarded with the first and the third prize 'Young Investigator Award', respectively, at the 30th GOTS congress (Gesellschaft für Orthopädisch-Traumatologische Sportmedizin), 12-13 June 2015 in Basel, Switzerland.

Organized Student Courses / Meetings

"Skeletal Repair" for MSc students from D-HEST at ETHZ and ZHAW students

On April 7-8, 2015, more than 40 students and supervisors from the Federal Institute of Technology in Zürich (ETHZ) and the University of Applied Sciences in Winterthur (ZHAW) met at the AO Center in Davos to join the practical course on "Skeletal Repair". For the first time this 2-day course was run as a part of a Masters course in Health Technologies at the Department Health Sciences and Technology (D-HEST) of the ETHZ. The goal is to complement the lecture series at the ETHZ and ZHAW with practical hands-on training.

Participants and instructors of the Block Course "Skeletal Repair"

Osteosynthesis and skills training

After a comprehensive introduction to the principles of surgical fracture repair by Dr Jan Benthien from the Hospital Davos, the participants were invited to test their surgical skills on different osteosynthesis exercises. Using artificial bone models, the correct application of common surgical instruments and the positioning of the metal implants including nails, plates, screws and external fixators were professionally demonstrated by Dr Raphael Jenni from the Cantonal Hospital in Chur. Together with a qualified team of surgeon instructors Raphael Jenni guided and supported the students throughout the surgical procedures. Four stations of the "Skill Training Lab" that were organized by Dieter Wahl, and demonstrated by Manuela Ernst and ARI fellows, complemented the exercises part with focus on bone fracture treatment. The aim is raise the awareness of translating basic biomechanical and physical principles into practical application.

On the second day Prof R Geoff Richards gave an illustrative lecture about the importance of pre-clinical translation and demonstrated some recent examples of products and procedures developed by the AO. Although the way from bench to bedside is long and the ARI is primarily involved in the first steps, translation of research findings into the clinics has always been the ultimate goal for all ARI projects.

Skill Training Lab: In the Skill Training exercise Dieter Wahl explains the importance of the optimal torque for correct placement of the screws.

The course was completed by different workshops addressing relevant topics from in vitro and in vivo studies for skeletal research to real clinical cases. Adenovirus transduction was demonstrated by Dr Martin Stoddart, adhesive polymers by Dr David Eglin, implant infection by Dr Fintan Moriarty, disc organ culture by Dr Sibylle Grad, in vivo models by Dr Stephan Zeiter, and bone microscopy by Christoph Sprecher. Bernd Heinlein and Daniel Baumgartner from ZHAW led the workshop on endoprosthetics, while Dr Raphael Jenni involved the participants in clinical case studies. Insight and participation in laboratory studies was very motivating and might have encouraged some of them to pursue an MSc thesis in the field.
The overall feedback from the course participants was extremely positive, while the intense support and high competence of all instructors was particularly appreciated.
The block course on Skeletal Repair was supported by the AO Research Institute Davos (ARI), the Hospital Davos, RISystem and DePuy Synthes.

COST Meeting
In June 2015 a meeting of the COST Action TD1305: Improved Protection of Medical Devices Against Infection (iPROMEDAI) was held at the AO Center in Davos.

General
New status for ARI
After applying to the Commission for Technology and Innovation (CTI), the ARI has been approved as a "CTI-recognized research institute".


Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Certificate

5. December 2014

The ARI is now on the official list of research facilities cleared for contributions, as a potential research partner for any Swiss company applying for grants from the Commission for Technology and Innovation CTI. As part of their evaluation, two experts from the CTI's life sciences expert group visited ARI's facilities in Q3, 2014 to confirm that it complies with their standards.
Small and medium-sized (SME) enterprises often require exactly the research infrastructure and resources which are available at ARI, and ARI will encourage industrial SME partners to work with them on research projects.
From research to market: what does the CTI do? The CTI promotes knowledge and technology transfer between research institutions, universities and companies in a unique way – paying half of the project-related research costs directly to the universities and research institutions. The other half is met by the company, the business partner.

Fellowship at Queensland University of Technology, Brisbane, Australia
Markus Windolf, PhD conducted a 12 months research fellowship at Queensland University of Technology, Brisbane, Australia upon invitation from the ARI Advisory Committee chair, Prof Michael Schütz. The goal was to approach clinical problems from an engineering perspective in order to generate surgical innovations. As a result of the fellowship experience, 6 invention records and two patents have already been filed so far and ideas continue to be developed. This research collaboration with interdisciplinary working has the potential to improve patient care in orthopaedic medicine.


Prof Michael Schütz (left), Dr Markus Windolf (right)

Members of Kanton Graubünden local government visit the ARI
On March 6, 2015 two members of Kanton Graubünden local government, Barbara Janom Steiner, Chair of the Finance Department and Christian Rathgeb, Chair of the Department of Health visited AO Research Institute Davos (ARI), under the Directorship of Prof R. Geoff Richards. The kantonal government members were accompanied by four of the local Davos government, Tarzisius Caviezel (Davos Mayor), Simi Valär, Stefan Walser and Herbert Mani.


Great weather for showing the ARI off to the local politicians.

Prof Richards initially gave an overview of the ARI and the AO Foundation and along with Irene Eigenmann (CFO/COO AO Foundation) showed how the AO has both an academic and economic impact on Davos and Graubünden, putting Davos on the world map for healthcare in the area of

trauma and orthopaedics. The ARI team took the opportunity to show the visitors the ARI's Preclinical surgery suite and animal housing (Dr med vet Stephan Zeiter and Andrea Furter). This was followed by a tour of the new prototype workshop which was built in 2014 (Jan Caspar). Further a few innovative projects in the biomedical services team under the leadership of Dr Boyko Gueorguiev were presented, which in the long term should help reduce hospital, patient and insurance costs.

Jan Caspar (on the far right) takes the politicians through the design and production process of prototypes.

Prof Richards added some local spice by introducing Manuela Ernst, as the winner of the Parsenn Derby in 2014. The Parsenn Derby Davos is the oldest downhill ski race in the world (founded 1924), ten years before the world's first T-bar tow became operational in 1934 at the foot of the Jakobshorn in Davos.

Manuela Ernst shows the ARI's X-in-One system which reduces X-Ray exposure to the patient and increases accuracy for implant placement.

Finally Dr Martin Stoddart and Dr Marietta Hermann from the Musculoskeletal Regeneration program under the leadership of Prof Mauro Alini, showed some of the innovative work with human stem cells for cartilage and bone regeneration, including a complex bioreactor system, which is unique in the world in turning human stem cells to cartilage.
The visitors were suitably impressed and will be invited to observe part of the AO Foundation Davos Courses in December 2015.

PhD Defense
Jan Buschbaum successfully defended his PhD thesis entitled "Computer-assisted fracture reduction: Development of a method for automatic planning of reduction paths using the example of femoral shaft fracture" at the Faculty of Medicine, Saarland University, Homburg with supervisors Prof Dr med Tim Pohlemann (Saarland University, Homburg) and Prof Dr- Ing Rainer Fremd (University of Applied Sciences, Kaiserslautern).

AO Foundation Davos Courses December 2015
During the AO Foundation Davos Courses 2015, ARI hosted in its anatomical labs at the AO Center main building the sessions for practical exercises of the AOTrauma Masters Course 'Current Concepts - Upper Extremity'. For this purpose the ARI facilities were specially equipped with all necessary systems for demonstration, video transfer, visualization and communication, as well as with the full amount of human material needed for the training.

Collaboration
AO strengthens its links with the ETH Zurich
A well-established relationship between the Department of Health Sciences and Technology (D-HEST) at ETH Zurich and the ARI has had a very positive impact, especially through joint research projects, in the field of the musculoskeletal system. Over the past three years, the partnership added a focus on talent development which will be further enhanced by a new collaborative agreement. A new talent program for outstanding talent at D-HEST will create value amongst the next generations of musculoskeletal scientists by offering ETH student's access to four AO fellowships and up to five AO Research Opportunity Awards each year. These awards can be used to provide financial support to students performing their master's thesis work at ARI.

Ties have been further strengthened through a new Masters course *Skeletal Repair*, which is accredited by ETHZ, and organized by ARI researchers (Drs David Eglin, Sibylle Grad, Fintan Moriarty, Martin Stoddart) over the year at ETH Zurich. This challenging and fulfilling course includes a 2-day practical course in ARI Davos with guest lectures. The students will obtain a clinically relevant education in transferring novel therapies into the clinic along with more fundamental principles within the field. ARI Director Prof Richards noted that the ARI is extremely proud to have been invited to teach this course at the highest ranking mainland European University, ETHZ (12th in world rankings in 2015), which was initiated after a visit from the then president of ETHZ, Prof Dr Ralph Eichler to the ARI in Davos.

Davos Knee Symposium - Cooperation of medicine, rehabilitation and research

Knee injuries leading to cartilage defects occur frequently, both in everyday life as well as during exercise. The most frequent surgical interventions are acute bone marrow-stimulation techniques, such as microfracture and nanofracture. The rehabilitation after such treatments is as important as the surgery itself and translational research being performed at ARI can help define evidence based physical therapy protocols. On August 19, 2015, all orthopedic surgeons, rehabilitation therapists and general practitioners from Davos were invited to the AO Center to discuss the optimal therapy for cartilage restoration with knee injuries.

The clinicians, rehabilitation therapists and scientists present were greeted by Prof R Geoff Richards, Director ARI. Prof Mauro Alini then described the importance of mechanical stress on cartilage regeneration. PD Dr med Jan Benthien, Co-Chief Orthopedic Surgery, Davos Hospital, explained very clearly the different surgical treatments for cartilage defects, but also pointed out that the complete restoration of the original cartilage remains a wishful thinking. Very promising is nanofracture, wherein relatively deep holes are punctured into the underlying bone with a thin needle. This offers advantages over the standard microfracture technique, where larger, less defined holes are produced. Then stem cells from the bone marrow are mobilized to invade the defect and initiate regeneration.

Martina Friedli, qualified physiotherapist, and Roelof van der Wijk, head of the Davos hospital physiotherapy team, extensively explained the structure and functions of the cartilage as well as numerous individual factors that influence the regeneration after surgery. The main targets after surgery are wound healing and tissue structure, which can be improved through active mobilization. Scientific studies using a world unique bioreactor began the ARI over 15 years ago. Dr Sibylle Grad (ARI) showed impressive scientific results, which targeted mechanical stress in chondrocyte derived tissue cultures, leading to the development of cartilage-like tissue and a frictionless surface.

Finally, Dr Martin Stoddart (ARI) presented exciting results from stem cell research: human patient derived stem cells from the bone marrow, encapsulated in a fibrin carrier, can be converted into chondrocytes solely by the correct mechanical load, with a combination of shear and compression providing the best results. This research can be directly related to rehabilitation protocols after marrow stimulation techniques and discussions are ongoing to bring this work to the clinic. Thus a targeted physiotherapy, based on scientific evidence, is essential for rehabilitation after marrow stimulation techniques.

The very informative lectures gave rise to lively discussions. All participants agree that in the future an even closer cooperation should be sought in order to better implement the latest findings, taking ARI preclinical studies into the clinical arena. The actual healing process takes place during the rehabilitation phase. Therefore, it will be indispensable, to standardize precisely the rehabilitation techniques and treatment protocols.

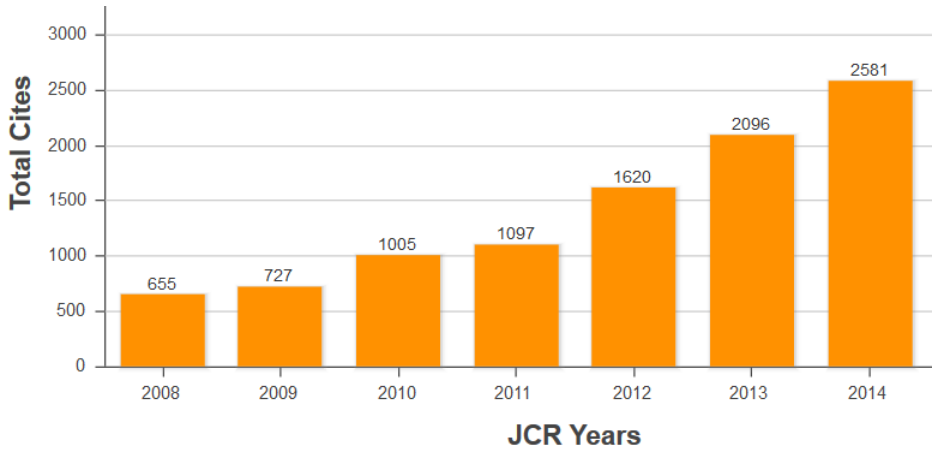
PD Dr med Jan Benthien from Spital Davos presenting at the AO Center.

7 eCM Journal, symposia and annual Conference

eCM Journal EUROPEAN CELLS & MATERIALS ISSN: 1473-2262
eCM started as a concept in 1999 of free publication of science. eCM was one of the first open access scientific journals in the world and was Not-for-profit from day 1. eCM initiated the transparent review process (now known as open peer review) including the first journal to show a transparent route to becoming a member of the International Review Panel. eCM's success has come from always having had rigorous peer reviewing and the novel discussion with named reviewers (as would happen in a conference) included as an integral part of accepted publications. eCM was and remains a pioneer with many of its innovative ideas having lead 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 2015 the 2014 impact factors were released. Five-year Impact Factor 2014 - 5.984
Yearly Impact Factors: 2014 4.486, remaining steady since 2012.

Over the years, cites (according to Journal Citation reports) are steadily increasing to eCM papers



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4. Five-year Impact Factor 2014 -5.984; Impact factor: 2014- 4.486; 2013 4.887; 2012 4.558; 2011 3.028; 2010 9.65; 2009 5.378; 2008 4.289.
5. Indexed by ISI within: Science Citation Index Expanded, "Materials Science", "Engineering Biomedical" and "Cell & Tissue Engineering" Citation Index categories. Journal Citation Reports/ Science Edition, AJC, Biosis Previews and Biological abstracts. Indexed in CAS, Index Medicus, Medline and Scopus databases and can be searched directly from Pubmed, Biomedsearch, DOAJ and Open J Gate. NLM: 100973416.
6. Over 3000 PubMed monthly linkouts & 7000 monthly visits (Google analytics).
7. Discussion with reviewers feature, which is an integral section of the paper, allows sensible arguments to be included (as would occur in our eCM conferences).
8. Speed of publication, 40 days average from submission to first decision, ~3 weeks after full acceptance, paper is online.
9. Transparent route to becoming a member of the International Review Panel.
10. Founded and run by scientists for the benefit of Science rather than profit.

eCM Conference

The sixteenth eCM Conference, the second of which dedicated to Bone and Implant Infection, was held at the Congress Center Davos, Switzerland from June 24-26, 2015. eCMXVI, was organized by Dr Fintan Moriarty, Dr Martin Stoddart and Prof Geoff Richards from the ARI.

The scientific program of involved keynote speakers presenting both the clinical problems encountered the latest findings in clinical and pre-clinical research as well as developments in materials science, microbiology and host response to infection. The conference had a significant clinical focus, with numerous clinicians presenting keynotes on the clinical problem of bone infection as faced by Trauma, Orthopaedic and Infectious Disease physicians.

Participants of eCMXVI: Bone and Implant Infection

Work of excellent quality was presented by a respectable number of students who competed for the popular Robert Mathys student prizes. In the end, the prize for the best oral presentation was awarded jointly to Nicola Kavanagh for her talk "*Staphylococcus aureus* infection causes hyper mineralization by osteoblasts in a 3D extra-cellular matrix environment"; and Payal Balraadjsing for her presentation entitled "Dendritic cell induced T-cell responses to biomaterials in presence of staphylococcal infection". First prize in the poster category was awarded to Paul Taylor for his poster "Dip and dry' micropattern-capable bioactive coatings for biomaterial surface modification in treating implant related infection and inflammation".

All abstracts from this conference can be found at
http://www.ecmjournal.org/journal/supplements/vol030supp02/vol030supp02.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

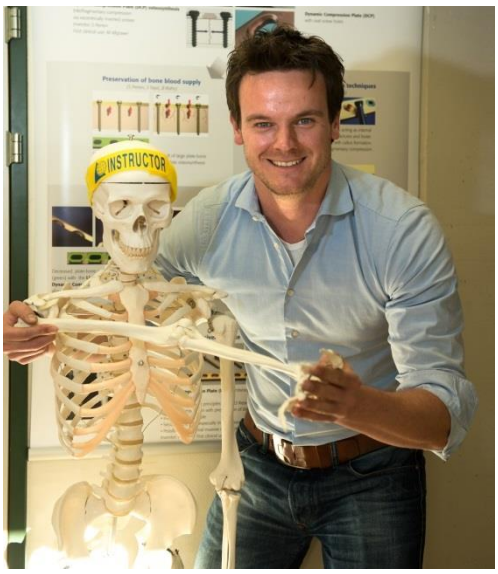
Yves Acklin, University of Basel, Basel, Switzerland
ARI Project: Biomedical Services Program; HumSlide: Biomechanics of a new gliding screw concept for proximal humerus fracture fixation / PelFix: Biomechanical investigation of posterior a pelvic ring fixation / ProxHumVal: In vitro biomechanical characterization to enable validation of computational models of proximal humerus fracture fixation.
Yves worked several years as a consultant trauma surgeon in Basel and Chur. He achieved the Swiss board certification in general surgery and orthopaedic surgery as well as EBSQ trauma surgery. After completion of a sports orthopaedic and arthroscopy fellowship at the University of Alberta, Canada, he joined the ARI Research Fellowship program. In Davos, the ARI offers an in-depth opportunity to biomechanical research. In his 7-months fellowship, he focuses on fracture treatment. The first project is to develop alternative concepts for proximal humerus fracture fixation with the help of FE models and mechanical testing. In his second project, he investigates advanced methods for anterior as well as posterior pelvic ring fixations.

Charlotte Arand, University of Mainz, Mainz, Germany
ARI Project: Biomedical Services Program; PelMorph: Anatomical evaluation for new fixation concepts in pelvic and acetabular fractures.
Charlotte is 27 years old. In 2014 she finished her studies of medicine with the internship at the University of Mainz in Germany. In July 2014 she started her residency at the Centre for Orthopedics and Trauma Surgery at the University's Hospital in Mainz. During her studies she started scientific working in the biomechanical laboratory and has just finished her doctor thesis. Now she is working on the 3DPelMorph project in the Biomedical Services program and looking forward to gain a lot of new experiences, get to know a lot of interesting people and hopefully produce some interesting results that may be useful for the treatment of injuries and degenerative changes concerning the pelvis.

André Arruda, Pontifical Catholic University of Paraná, Brazil
ARI Project: Musculoskeletal Regeneration Program; Bisphosphonate related osteonecrosis of the Jaw-Role of soft tissue healing.
Since he started his graduation course, he is involved in research in basic science, intervertebral disc degeneration and spinal cord injury, with Spine surgery team. In his year in AO Research Institute Davos, he is collaborating in the Musculoskeletal Regeneration Program / Stem Cells Group and willing to learn more about basic science,

understanding better the potential of Regenerative Medicine and its clinical future application to patients in day-by-day clinical work. In Davos, he is enjoying to be in touch with an interdisciplinary and high level group of scientists, living in a different manner and trying to learn winter sports.

Nicolò Cosmelli, Università degli Studi di Milano, Italy
ARI Project: Preclinical Services Program and Musculoskeletal Infection Group; Biofilm Alliance: Development of tools to control microbial biofilms with relevance to clinical drug resistance.
Nicolò is in his sixth year of medical studies. In the last year he has been an intern in the Dept. of Trauma Surgery, Humanitas Research Hospital of Milan. He has taken time off from Medical School for a 6 months AO Research Fellowship with the Preclinical Services Program and in the Musculoskeletal Infection Group to work on his final Thesis: Novel approaches to combat biofilm infections. Nicolò is willing to gain research skills, to work in an interdisciplinary group of scientists and to be in Davos as he loves the outdoor lifestyle, whether it is skiing in winter or biking in the summer.



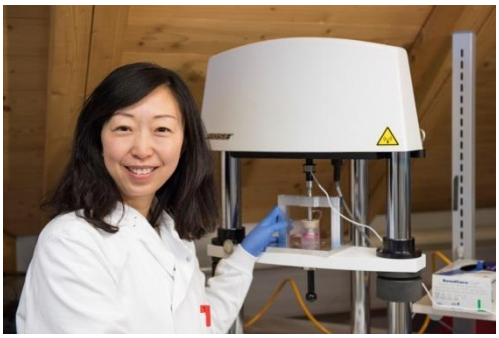
Koen Dullaert, Maastricht University, the Netherlands
ARI Project: Biomedical Services Program; FibSyn: Biomechanics of the fibula and syndesmosis and evaluation of different treatment techniques for syndesmotic ruptures / PatBand 2: Biomechanical evaluation of two different methods for transverse patellar fracture fixation.
Koen is 26 years old and studied medicine at Maastricht University, the Netherlands, where he earned his medical degree in 2013. Since 2013 he has been working as a resident not-in-training at the Department of General, Vascular and Trauma Surgery in St. Elisabeth Hospital Tilburg, the Netherlands. Koen will be completing a yearlong AOTrauma medical research fellowship in the Biomedical Services Program at the AO Research Institute Davos. Having performed prior research in the functional outcomes of scaphoid fractures, he has special interest in Biomechanics. He greatly appreciates the opportunity to gain experience in Orthopedic Trauma research and will use it as a solid base for future clinical work.

Linda Freitag, University of Veterinary Medicine, Hannover, Germany
ARI Project: Preclinical Services Program, Gellocal2: The efficacy of local Bisphosphonates and BMP-2 delivery versus systemic administration in improve bone mass and mechanical implant stability / AtypMouse: Atypical fractures under treatment with bisphosphonates.
Linda is the new research fellow in the Preclinical Services Program and will stay for one year. She is 24 years old and graduated in March 2015 at the University of Veterinary Medicine Hannover. In 2013, she already spent two months at AO for a veterinarian externship. Linda wants to gain further insight into preclinical research and project management. She has got a strong interest in anesthesia as well as orthopedic surgeries and looks forward to an exciting year with her team!

Dominic Gehweiler, Westfälische Wilhelms-Universität, Münster, Germany
ARI Project: Biomedical Services Program; 3DAxisAtlas: 3D Atlas of the Upper Cervical Spine for Fracture Fixation.
Dominic is a medical research fellow at the AO Research Institute Davos since January 2015 and he is glad to be able to collaborate for one year in the Biomedical Services Program. In 2012 he finished his doctorate at the Westfälische Wilhelms-Universität Münster on a biomechanical study of the spine and started working as resident at the Department of Trauma-, Hand- and Reconstructive Surgery of the University Hospital of Münster. In his year in Davos, he is looking forward to gain new experiences and knowledge and to meet many scientists from around the world.

Stoyan Petkov, Charité Universitätsmedizin, Berlin, Germany
ARI Project: Musculoskeletal Infection Group; StaphAB: Development of a large animal model to study the biology of two stage hardware exchange due to implant related osteomyelitis / StabhAB-X: Efficacy of gentamicin loaded thermoresponsive hydrogel in the prevention and treatment of infection in a large animal model.
Stoyan studied medicine at Charité - Universitätsmedizin Berlin, where he earned his medical degree in 2011. Since 2011 he has been working as a surgeon- and trauma-resident at Spital Emmental in Switzerland. He completed his doctoral thesis on Novel Clostridium perfringens enterotoxin suicide gene therapy for selective treatment of claudin-3- and -4-overexpressing tumors in 2012 in Berlin.

Theresia Sommerer, University of Ulm, Germany
ARI Project: Biomedical Services Program; MeCoFus: Biomechanical investigation on medial column fusion in foot.
Theresia studied medicine at University of Ulm where she earned her medical degree in 2011. Since 2011 she has been working as a trauma resident at the Department of Trauma-, Hand-, and Reconstructive Surgery of the University Hospital of Ulm, and completed her doctoral thesis on Apoptosis and Inflammation during Acute respiratory distress syndrome (ARDS) in a cell-culture model in 2014. Theresia is a medical research fellow in the Biomedical Services division at ARI for 6 months.



Ying Zhang, Shanghai Changzheng Hospital, China
ARI Project: Musculoskeletal Regeneration Program; The effect of asymmetrical loading on the intervertebral disc.
Ying worked as a spine surgeon in Shanghai Changzheng Hospital, Shanghai, China. She is going to stay in ARI for 6 months working in the Discform project. In China, there is a key laboratory in her department. She hopes to gain research experience both in performing a specific project and in managing a laboratory. She also wants to build a close connection between ARI and her laboratory and look for potential cooperation between two laboratories.

9 Project Abstracts by Sponsors

9.1 AOCMF

Computed tomography models to simulate mandibular fracture reduction to plan osteosynthesis and design surgical guides (V. Varjas, L. Kamer)

Computerized preoperative planning could potentially offer enhanced assessment and treatment options to improve and facilitate craniomaxillofacial surgery procedures. The technology might be used for clinical applications and education/teaching purposes for surgeons or medical staff. The computerized process requires three-dimensional (3D) information to be processed such as image data obtained from computed tomography (CT). A major task is to achieve virtual fracture reduction with the fracture segments properly aligned for planning of the osteosynthesis or even for designing of surgical guides. Until now there was an open question as to whether the technology could be utilized to evaluate mandibular fracture cases.

This AOCMF study investigated implementation of computed tomography-based fracture reduction and computerized planning of the osteosynthesis using surgical guides in patients affected by double mandibular fractures.

A series of nine standard, preoperative CT scans of patients affected by double mandibular fractures were post-processed using new software algorithms and a mean model of the mandible.

A computerized technique was developed that allowed for 3D modelling of the mandibular segments, separation of the mandible from the cranium, distinction of the fracture fragments, virtual fracture reduction and planning of the osteosynthesis construct and surgical guides.

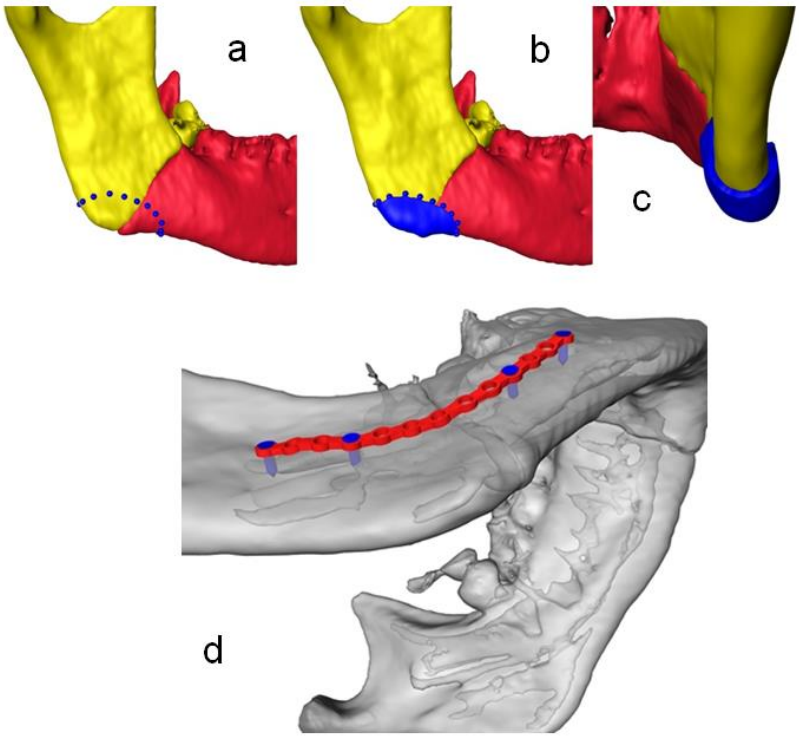


Figure 9.1.1: Planning of fracture reduction, a surgical guide template and osteosynthesis: Landmarks were manually defined (**a**) to outline the contour of a surgical guide template (**b-c**); immediate planning of the osteosynthesis (**d**) (a-d: interim results).

The technique as developed in this study was considered to be useful to assess complex mandibular fracture cases. The technology might also be utilized as a new tool to teach the principles of fixation of mandibular fractures.

Pub:
Voss JO, Varjas V, Raguse JD, Thieme N, Richards RG, Kamer L. CT-based virtual fracture reduction techniques in bimandibular fractures. J Craniomaxillofac Surg. 2016 Feb;44(2):177-85. doi: 10.1016/j.jcms.2015.11.010. Epub 2015 Dec 1.

Partners:
- Voss JO (MD), Department of Oral & Maxillofacial Surgery, Charité -Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany
- Raguse JD (MD, DDS, PhD), Department of Oral & Maxillofacial Surgery, Charité - Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany
- Thieme N (MD) Department of Radiology, Charité - Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany

Bisphosphonate related osteonecrosis of the Jaw- Role of soft tissue healing (ARIBRONJ) (Ongoing) (M. Stoddart)
As a side effect of the widespread use of bisphosphonates (BPs) for treatment of osteoporosis and in oncology treatments, bisphosphonate related osteonecrosis of the Jaw (BRONJ) has become increasingly prevalent. While there is an increasing understanding of the development of the disease, the underlying mechanism is still unclear. Until a greater understanding of the etiology can be established and attempts at prevention and treatment are speculative. While a great deal of attention has been focused on understanding the disease from a skeletal perspective, comparatively little has been done to investigate the influence of BPs on soft tissue healing. The soft tissue coverage provides protection, a source of angiogenesis and a physical block from invading microorganisms. This study aims to investigate the effects of Zoledronic acid on soft tissue biology, with the hypothesis being soft tissue healing is impaired, leading to the onset of BRONJ.

Pres:
Poxleitner PJ, Iliev K, Nelson K, Ziebart T, Stoddart M, Schmelzeisen R, Voss P. Palatinaler Defekt verursacht Sinusitis bei Zoledronatbehandelten Schafen.
2015 DGMKG

Pub:
Voss PJ, Stoddart MJ, Ziebart T, Zeiter S, Nelson K, Bittermann G, Schmelzeisen R, Poxleitner P. Zoledronate induces osteonecrosis of the jaw in sheep. Journal of Cranio-Maxillofacial Surgery. 2015. doi:10.1016/j.jcms.2015.04.020

Voss PJ, Stoddart MJ, Bernstein A, Schmelzeisen R, Nelson K, Stadelmann V, Ziebart T, Poxleitner P. Zoledronate induces Bisphosphonate-related Osteonecrosis of the Jaw in osteopenic sheep. Clinical Oral Investigations. 2015 Apr 7. [Epub ahead of print]

Partners:
- Otto S (MD), Ludwig-Maximilians-University of Munich, Munich, Germany
- Voss P (MD), University Hospital Freiburg, Freiburg, 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)

This project aims at optimizing the application of bone marrow derived mesenchymal stem cells for intervertebral disc regeneration. Using a bioreactor system specifically designed for intervertebral disc whole organ cultures, a degenerative state is induced by high frequency loading and low glucose conditions. Subsequently stem cells are delivered to the nucleus pulposus of the disc through a cavity made through the endplate, whereby different hydrogels are used as cell carriers. A fibrin gel formulation was successful for stem cell delivery and could withstand physiological loading regimes applied to the disc. Furthermore, an interaction was found between the host disc cells and the injected stem cells. In particular, stem cells may contribute to the restoration of degenerated discs by inducing an up-regulation of anabolic markers in disc cells. Furthermore, the injected stem cells can differentiate towards a disc cell phenotype. However, the cell-cell interactions and cellular responses depend on the degenerative state of the disc. This indicates that the state of the disc cells at the time of stem cell injection might determine the success of the treatment.

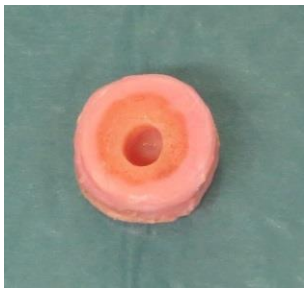


Figure 9.2.1: Reproducible nucleotomy is achieved using a bone drill and an arthroscopic shaver.

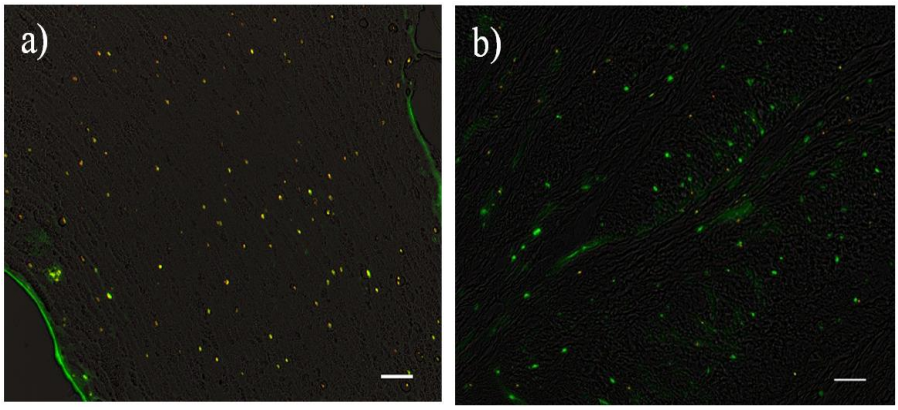


Figure 9.2.2: (a) PKH26 fluorescent labelled mesenchymal stem cells suspended in fibrin gel and injected in a nucleotomimzed disc. Cell viability is maintained after 7 days of culture. (b) Inner annulus fibrosus tissue stained with Calcein AM/ethidium homodimer 1 shows the presence of mainly viable cells (green), with only few dead cells (red).

Pres:

Peroglio M, Caprez S, Benneker LM, Alini M, Grad S. Stem Cells Contribution to the Restoration of Degenerated Intervertebral Discs Depends on their Degenerative State. ORS Annual Meeting 2015, Las Vegas.

Peroglio M, Caprez S, Benneker LM, Alini M, Grad S. Influence of disc degeneration on the efficacy of stem cell treatment: an ex-vivo study. BioSpine Annual Meeting 2015, Berlin.

Peroglio M, Li Z, Lezuo P, Alini M, Grad S. Why using bioreactors for whole organ cultures of intervertebral discs? BioSpine Annual Meeting 2015, Berlin.

Peroglio M, Caprez S, Benneker LM, Alini M, Grad S. Stem cell effect is influenced by the degenerative state of intervertebral discs. DKOU 2015, Berlin.

Pub:
Vadalà G, Russo F, Pattappa G, Peroglio M, Stadelmann V, Roughly P, Grad S, Alini M PhD, Denaro V. A nucleotomy model with intact annulus fibrosus to test intervertebral disc regeneration strategies. Tissue Eng C 21(11):1117-24, 2015.

Sakai D, Grad S. Advancing the Cellular and Molecular Therapy for Intervertebral Disc Disease. Adv Drug Deliv Rev 84:159-71, 2015.

Gantenbein B, Illien-Jünger S, Chan SC, Walser J, Haglund L, Ferguson SJ, Iatridis JC, Grad S. Organ culture bioreactors - Platforms to study human intervertebral disc degeneration and regenerative therapy. Curr Stem Cell Res Ther 10(4):339-52, 2015.

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

Role of the intervertebral disc in the development and progression of spinal deformities (Discform) (Completed) (S. Grad)
The etiology of the spinal deformity in idiopathic scoliosis is unclear to date, both with respect to initiation and progression of the disease. While the influence of certain genetic factors has been established, the role of the intervertebral disc in the development of idiopathic scoliosis has scarcely been investigated. The aim of this project was to identify molecular differences between disc cells from patients with idiopathic scoliosis in comparison with trauma patients and healthy individuals. To address this aim, cellular gene expression profiles were analyzed by microarray and quantitative gene expression analysis. Microarray results revealed that more than 50 genes were more highly expressed in scoliotic *vs*. healthy annulus fibrosus and 26 genes in scoliotic *vs*. traumatic annulus fibrosus, whereby 21 genes showed higher expression in scoliotic annulus fibrosus compared to both control groups. Quantitative gene expression analysis by real time polymerase chain reaction confirmed significantly increased levels of inflammatory markers, matrix metalloproteinases and hypertrophy markers in annulus fibrosus cells from scoliotic discs.

Results of this study reveal significant changes in the gene expression profile of disc cells from patients with idiopathic scoliosis compared to patients with traumatic disc damage or donors with no known disc disorders. Better knowledge of the dysregulation of structural or regulatory molecules may identify underlying mechanisms of spinal deformities, which will help defining new targets for early therapeutic intervention.

Partners:
- Rozhnova O (PhD), Schelkunova E (PhD), Mikhailovsky M (Prof MD), Sadovoy M (Prof MD), Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Y.L. Tsivyan, Novosibirsk, Russian Federation
- Haglund L (Prof), McGill Scoliosis and Spine Group, Montreal, Canada

9.3 AOTrauma

Development of a computational test-kit for the proximal humerus (SystemFix) (Ongoing) (J. Inzana, M. Windolf)

Background: Treatment of fragility fractures at the proximal humerus remains a major challenge in trauma surgery. Several factors such as highly compromised bone mass, complex loading conditions, multi-fragmental fractures, absent bony support and limited surgical access renders the fixation particularly complex. However, the complications listed above are difficult to model in vitro and accommodate with traditional implant design strategies, leading to limitations in each surgical solution. In contrast with laboratory experiments, computational simulations can enable a more versatile, efficient and systematic screening process for new design ideas or research questions and can provide dramatic cost savings.

Goal: The objective of this ongoing project is to develop a robust set of computational tools, algorithms, and datasets that will enable systematic biomechanical simulations of osteoporotic fracture fixation in the proximal humerus.

Results: The foundational computational algorithms and datasets for this virtual toolkit have been developed. Currently, the software is capable of efficiently modeling more than 50 virtual patients with three possible fracture patterns that are stabilized with a PHILOS plate or other implant, under six different loading configurations (3 physiological loads, 3 laboratory-based experimental loads). The PHILOS implant can be configured with any combination of standard locking screws (of any length) or cannulated screws with PMMA augmentation (with any volume of PMMA). Generalized algorithms are being developed to facilitate the simulation of new implant designs.

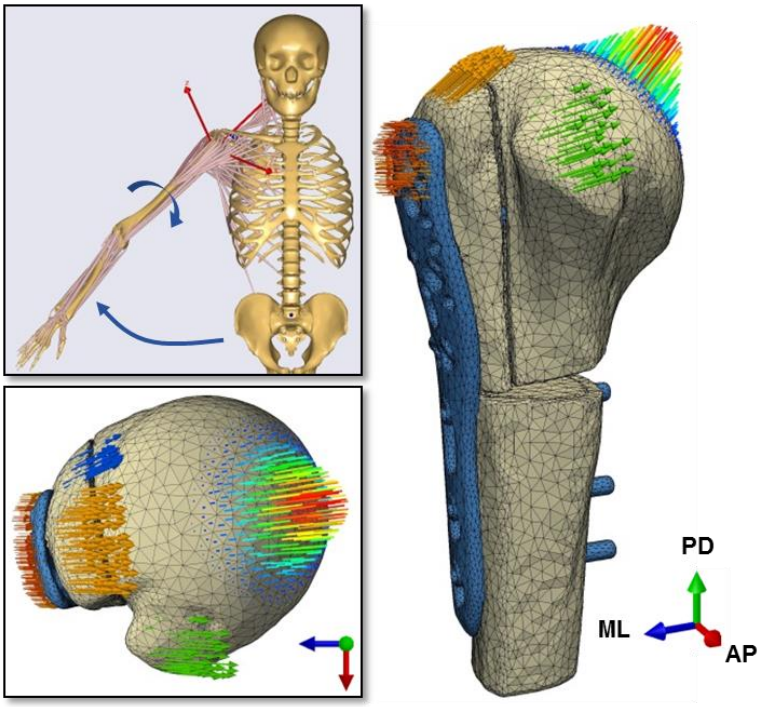


Figure 9.3.1: Physiological loading protocols developed based on inverse dynamics simulations of common shoulder motions in daily living.

Partners:

- Blauth M (Prof), Medical University Innsbruck, Austria
- Südkamp N (Prof), University Hospital Freiburg, Germany
- Nijs S, (Prof), University Hospital Leuven, Belgium

AO Implant Positioning Assistance (SimpCAS, X-in-One) (Ongoing) (M. Windolf)
Problem: The task of placing implants plays a key role in trauma and orthopedics surgery. 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: To pursue the path to clinical application, existing X-in-one algorithms were developed into a prototype but fully functioning medical software in collaboration with Mevis BreatCare (Mevis Medical Solutions AG). Two pilot modules (proximal humeral plating (PHILOS, DePuy Synthes Inc.) and hip-nail insertion (PFNA DePuy Synthes Inc.) were realized. Medical device certification is still pending. A clinical handling test for the PHILOS module is in planning as suggested by the Upper Extremity Expert Group (AOTK).

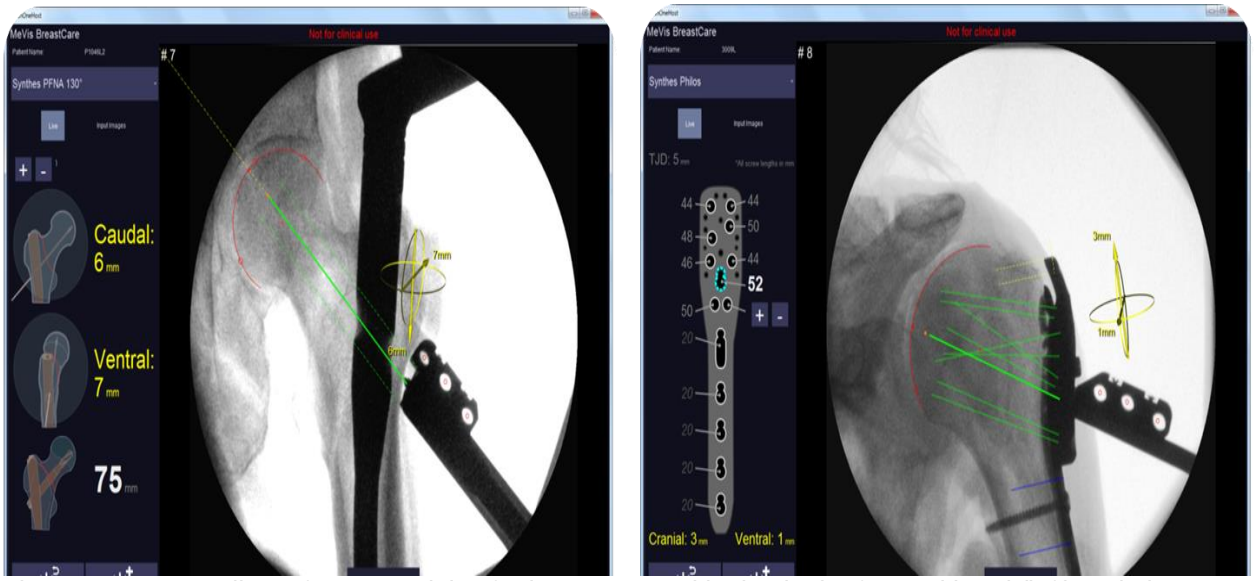


Figure 9.3.2: Two pilot software modules for lag screw positioning in the femoral head (left) and placement of a proximal Humerus plate (right) developed in cooperation with MeVis Medical Solutions AG

Partners:
- Mevis BreatCare (Mevis Medical Solutions AG), Bremen, Germany
- Blauth M (Prof MD), University Hospital Innsbruck, Austria
- Boger A (Prof), Hochschule Ansbach, Germany

Cement augmentation methods for improved fracture fixation in osteoporotic bone (ImplantAug) (Ongoing) (L. Hofmann-Fliri, M. Windolf)
Problem: The landscape of trauma surgery will significantly shift towards geriatric patients. Despite improvements in implant design one major complication, 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 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:
Grüneweller N, Raschke MJ, Widmer D, Zderic I, Wähnert D, Gueorguiev B, Richards RG, Fuchs T, Windolf M. Biomechanical Evaluation Of Augmented Versus Non-Augmented Sacroiliac Screws In A Newly Developed Hemi-Pelvis Model. 2015. EFORT.

Grüneweller N, Raschke MJ, Widmer D, Zderic I, Wähnert D, Gueorguiev B, Richards RG, Fuchs T, Windolf M. Biomechanical evaluation of augmented versus non-augmented sacroiliac screws in a newly developed hemi-pelvis model. Eur J Trauma Emerg Surg. 2015;41(Suppl 2):S62 (ECTES).

Hofmann-Fliri L, Götzen M, Zeiter S, Arens D, Richards RG, Windolf M, Blauth M. Influence of implant augmentation with bone cement on adjacent subchondral bone and cartilage. 2015. WCO-IOF-ESCEO.

Inzana J, Münch C, Varga P, Hofmann-Fliri L, Südkamp N, Windolf M. Variable Biomechanical Benefits of Screw Augmentation in Proximal Humerus Fractures. 2015. EORS.

Inzana J, Münch C, Hofmann-Fliri L, Varga P, Südkamp NP, Windolf M. Enhancing Fixation of Osteoporotic Proximal Humerus Fractures: Insights from a Systematic Evaluation of PHILOS Screw Augmentation. 2015. Whitaker International Scholars workshop.

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

Pub:
Windolf M. [Biomechanics of implant augmentation]. Unfallchirurg 2015 Sep;118(9):765-71.

Hofmann-Fliri L, Nicolino TI, Barla J, Gueorguiev B, Richards RG, Blauth M, Windolf M. Cement augmentation of implants – No general cure in osteoporotic fracture treatment. A biomechanical study on non-displaced femoral neck fractures. J Orthop Res. 2015;Epub Jul 16.

Braunstein V, Ockert B, Windolf M, Sprecher CM, Mutschler W, Imhoff A, Postl LK, Biberthaler P, Kirchhoff C. Increasing pullout strength of suture anchors in osteoporotic bone using augmentation – A cadaver study. Clin Biomech (Bristol, Avon). 2015 Mar;30(3):243-7.

Dissertations:
Wähnert D. Biomechanische Untersuchungen zur Versorgung osteoporotischer Femurfrakturen. 2015. Westfälische Wilhelms-Universität Münster (Raschke MJ, Mückley T) – Habilitation / medical fellow

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

Prophylactic reinforcement of the proximal femur to prevent secondary hip fractures (ProphylacticAug) (Ongoing) (P. Varga, M. Windolf)

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 femora by means of surgical intervention may be able to help to avoid the 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/risk ratio.

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

Results: The previously developed finite element (FE) analysis framework was further extended and utilized to investigate alternative prophylactic augmentation approaches. Based on the moderate success of the previous cement-based strategy, the strengthening effect of different combinations of metal implants, developed based on the PFNA nail and blade, with and without cement augmentation was analyzed. Different configurations of implant dimensions and positioning, cement volume and location were consistently evaluated in terms of the strengthening effect in sideways fall. The optimized cement-augmented metal implant provided, compared to the non-augmented state, a strengthening of 135 ± 40% in yield force and 345 ± 160% in yield energy for the osteoporotic sample group (N = 12). These encouraging results require experimental validation, which is planned for the next reporting period.
The CT images of sixty-five proximal femora, collected previously in frame of the SynPorOpti project, were further analyzed here. Osteoporosis status (healthy, osteopenic and osteoporotic) was determined from bone mineral density information. Failure load computed from the CT image based FE models. The subject-specific risk of fracture was then evaluated as the ratio of the loads acting during a sideways fall, estimated based on body height and weight, and the FE-based fracture load of the femur. This approach was used to determine the aimed augmentation effect for the osteoporotic samples, i.e. the one required to reach the subject-specific healthy state. Results showed that a strengthening up to 165% may be required for heavily osteoporotic individuals.

Pub:

Raas C, Hofmann-Fliri L, Hörmann R, Schmoelz W. Prophylactic augmentation of the proximal femur: an investigation of two techniques. Arch Orthop Trauma Surg. 2016 Jan 9. [Epub ahead of print]

Varga P, Schwiedrzik J, Zysset PK, Fliri-Hofmann L, Widmer D, Gueorguiev B, Blauth M, Windolf M. Nonlinear quasi-static finite element simulations predict in vitro strength of human proximal femora assessed in a dynamic sideways fall setup. J Mech Behav Biomed Mater. 2015 Dec 3;57:116-27. doi: 10.1016/j.jmbbm.2015.11.026. [Epub ahead of print]

Pres:

Varga P, Inzana J, Gueorguiev B, Blauth M, Windolf M. Prophylactic augmentation of the osteoporotic proximal femur: cement or metal? Insights from computer simulations. 2016. ECTES (accepted as oral)

Varga P, Schwiedrzik J, Zysset P, Gueorguiev B, Blauth M, Windolf M. How to augment the osteoporotic proximal femur? – Ask the bone. 2015. ESB (BioMech) (oral)

Varga P, Schwiedrzik J, Zysset PK, Sprecher C, Gueorguiev B, Blauth M, Windolf M. Optimierung der Knochencement-basierten prophylaktischen Augmentation des proximalen Femurs anhand von FEA. 2015. DKOU (poster)

Partners:

- Blauth M (Prof), Medical University Innsbruck, Austria
- Schmölz W (ass. Prof), Medical University Innsbruck, Austria
- Zysset PK (Prof), University Bern, Switzerland

Influence of cement stiffness on augmented implant stability (CEMPROP) (Ongoing) (U. Eberli)

Problem: Bone cements are widely used to enchance implant purchase in orthopaedic surgery, vertebroplasty and fracture treatment by increasing the contact area between bone and implant. It is believed that in osteoporotic bone augmentation with soft cement is superior to hard cement because the former will not induce stress concentrations at the bone-cement interface and thus less damage will occur under loading. This belief is probably a result of research in vertebral augmentation. Indeed, despite the great potential of cement injection in vertebral body to reduce pain and restore stiffness after vertebral compression, the procedure induces a high risk of fractures in the non-augmented neighbor vertebrae. Investigations to prevent such adjacent fractures led to development of bone cements with lower material elastic modulus.
In the context of implant augmentation, however, the superiority of softer cements has not been formally established yet. In contrary, our preliminary findings even suggest that harder cements would be advantageous. For example, PFNA blades augmented with unmodified cement sustained 40% more cycles until failure compared to softened cement. Also, image-based finite element (FE) modelling showed that non-augmented bone elements in proximity of augmented bone were subjected to higher stresses with soft cement augmentation compared to hard cement augmentation.

Goal: To develop a dedicated FE model, validated with mechanical testing and gain better understanding in how both cement stiffness and distribution influence implant purchase in osteoporotic bone under mechanical loading.

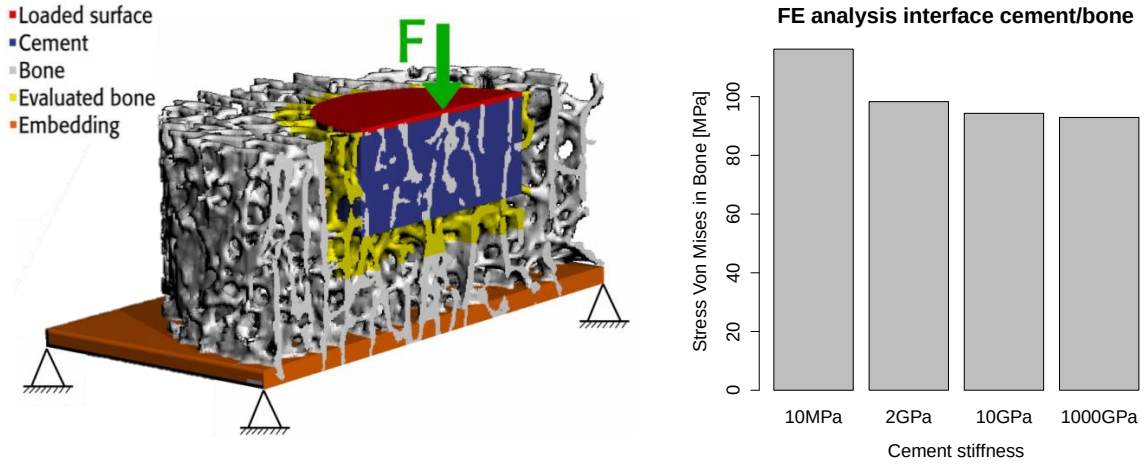


Figure 9.3.3: Visualization of a micro FE model (cut in half) with its components and boundary conditions (left). Average stresses Von Mises stresses in the bone, calculator from the micro FE models with varying cement stiffness (right).

Partner:

- Blauth M (Prof), Medical University Innsbruck, Austria

The osteoporosis implant (OsteoFix - feasibility) (L. Hofmann-Fliri, M. Windolf)
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 the additional injection of bone cement (Sermon et al. 2012, Unger et al. 2012).
The landscape of trauma surgery will significantly shift towards the 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 if efforts should be undertaken to develop new solutions dedicated to the specific problem.

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

Results: After an idea mining phase, a promising solution consisting of a flexible metallic component equipped with specific features for cement augmentation was developed. Finite Elements simulations were performed to estimate implant behavior and material stresses to optimize the design. The final version was then produced in ARI's Prototype Workshop and tested mechanically until failure. The implant showed promising results with a failure load of 3500N. Next steps would involve testing the biomechanical performance in a close-to-clinics setting with implant-bone constructs.

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

Ortho meets Trauma - New implant concepts for periprosthetic fractures (OMT - feasibility) (L. Hofmann-Fliri, M. Windolf)
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 the presence of the prosthesis. Recently, new implants specifically designed for periprosthetic fractures such as the locking attachment plate (Synthes GmbH) or the non-contact bridging periprosthetic femur system (Zimmer GmbH) have been introduced to the market. These systems allow the 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 an 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: The goal of this feasibility project was to propose and develop new concepts for combined orthopaedic/trauma care with special reference to periprosthetic fractures.

Results: From several brainstorming sessions and discussions with experts, two major ideas for an implant solution for the proximal femur which would not depend on a modification of the prosthesis stem were generated. Two docking options to attach to the stem were evaluated in terms of clinical handling and biomechanical stability. For both ideas a prototype implant was designed and produced. One was tested mechanically and compared to the golden standard (Locking Attachment Plate (LAP), DePuy Synthes Inc.). The results of cyclic testing showed that the new concept performed similarly to the LAP group with respect to bone-implant stability, but revealed that the new solution could avoid/reduce prosthesis sintering. Nevertheless, the actual clinical benefit compared to LAP remains questionable. Future optimization appears necessary.

Partners:

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

Development of a biofeedback system for bone healing and its application for mechano-biological research (ImpCon2) (Ongoing) (M. Ernst, M. Windolf)

Problem: Flexible internal fixation aims at improving induction of callus by imposing confined, reversible displacement at the fracture site. One of the main issues to be addressed is still related to the exact role of implant stiffness and adjustment of the structural flexibility to create an optimal environment for fracture repair. Improving the technology for internal fixation by necessity relies on improved understanding of 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 at 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: Previous study groups operated with the research implant system were allowed a 10% interfragmentary strain. To study the effect of axial motion on fracture consolidation, two animal groups were operated with a dynamization limit at 30% and 50% of the gap size (see figure). Furthermore, a first version of an instrumented plate was composed of an electronic unit connected to a strain gage sensor has been tested at QUT Brisbane, Australia. Six sheep operated for an experiment unrelated to this study were instrumented with the device to acquire plate bending during weight bearing.

Three publications based on the experimental data collected within this project are in preparation. The development of the biofeedback module for bridging plates is continued in a follow-up study.

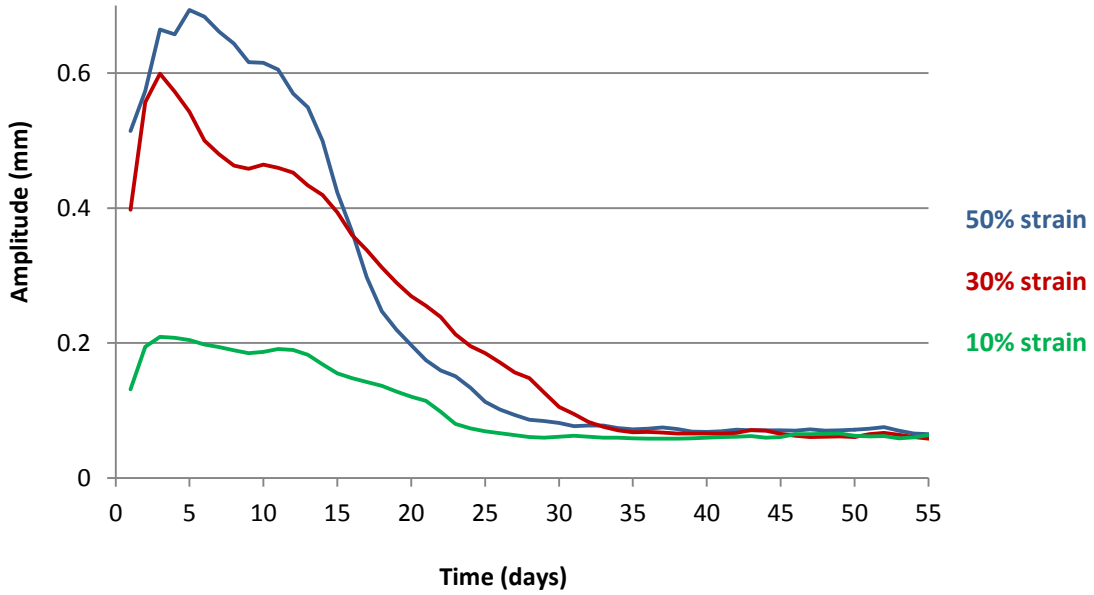


Figure 9.3.4: Mean interfragmentary motion in the fracture gap with different dynamization limits. Within 5 weeks, strain in all groups was reduced to a level allowing fracture consolidation.

Pres:
Windolf M: "Fracture monitoring sensor", DKOU 2015, Berlin (Invited Lecture).

Ernst M: "Fracture monitoring – Endeavors and obstacles", von-Behring-Röntgen-Symposium 2015, Giessen (Keynote lecture)

Ernst M: "Sensorgestützte Überwachung des Frakturheilungsverlaufs", Swiss Medtech Expo 2015. Luzern (Invited Lecture).

Pub:
Fountain S, Windolf M, Henkel J, Akbarzadeh AT, Schuetz MA, Hutmacher DW, Epari DR, 2015. Monitoring Healing progression and characterizing the mechanical environment in preclinical models for bone tissue engineering. Tissue Eng Part B Rev epub Oct 28.

Partners:
- Epari DR (PhD), Queensland University of Technology (QUT), Brisbane, Australia
- Perren SM (Prof, MD, PhD), AO Foundation, Davos, Switzerland
- Helbling Technik AG, Wil, Switzerland

Computer models to study osteoporosis relevant sites and to simulate fracture fixation (L. Kamer)
Osteosynthesis of fragility fractures is a particular clinical concern that involves fracture fixation in skeletal sites with reduced bone mass and altered bone structure. It consequently results in compromised mechanical stability of the bone-implant construct.
To assess osteoporosis relevant sites with regard to bone mass distribution, bone loss, size and shape variation and to simulate surgical fixation, a series of 358 high-resolution peripheral quantitative computed tomography (HR-pQCT) scans were acquired from six different epiphyseal sites of long bones of post mortem samples. Statistical bone models were generated, analyzed and subjected to numeric simulations.
Large anatomical variations in size, shape and with regard to bone loss were observed (Figure 9.3.5 a-c). However, each epiphyseal site displayed a distinct bone mass distribution pattern that was quantified by volumetric bone mineral density (vBMD) measurements. In presence of bone loss, the bone stock was ubiquitously decreased, whereas the bone mass distribution was maintained.
Average computer models of the proximal humerus were further evaluated using finite element simulations to investigate the mechanical behavior in the context of plate fracture fixation (Figure 9.3.5 d). The results were compared with the corresponding numerical behavior of the population of bones from which the average case was generated.
The approach was considered to be useful to establish new anatomical and biomechanical understanding and may be applied to other skeletal sites and used as benchmarking models. They may also be transferred to new analysis methods such data mining and machine learning.

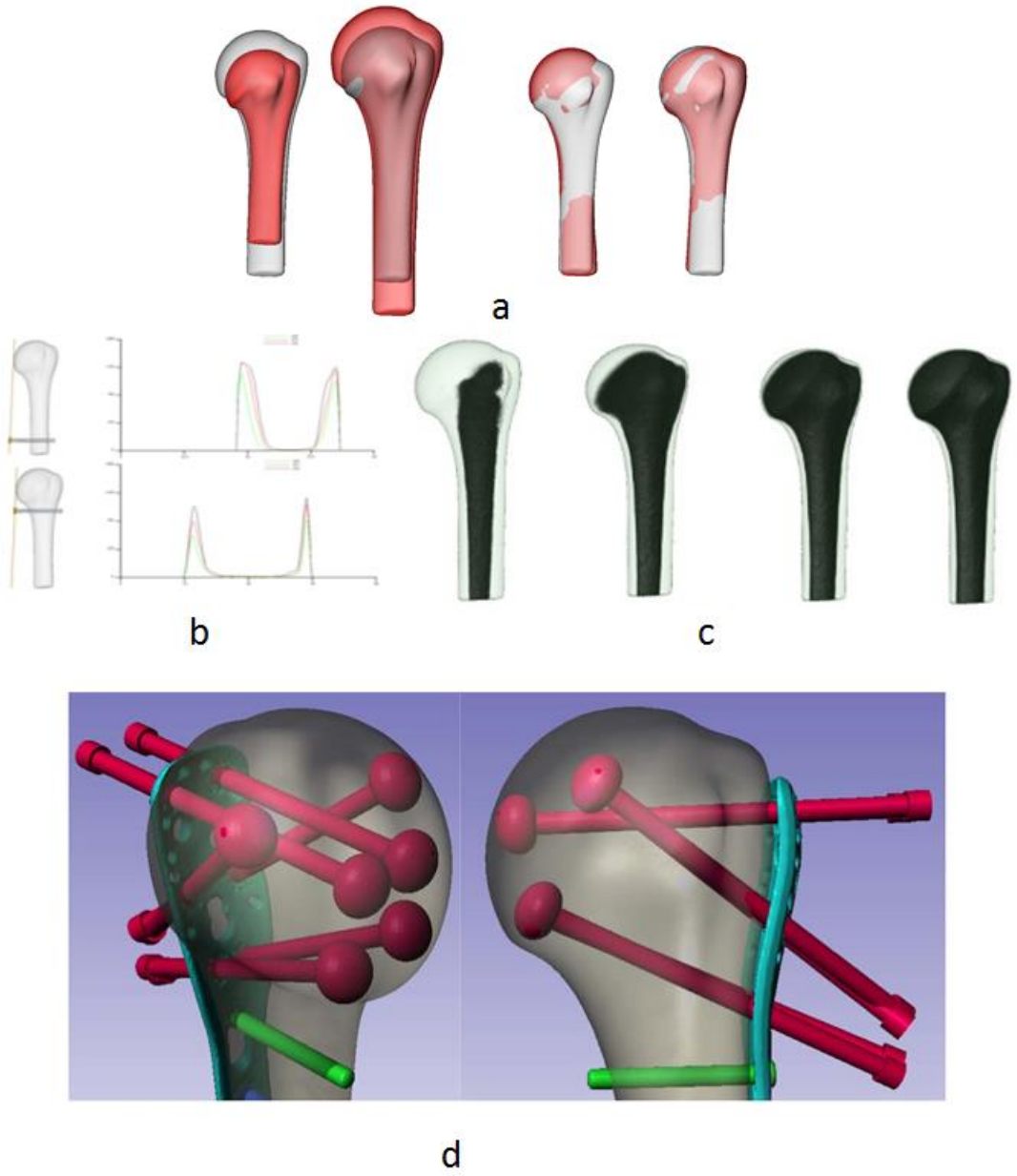


Figure 9.3.5: Computer model of the proximal humerus to demonstrate anatomical variation and finite element simulation. (a) Mean model of the proximal humerus (grey transparent) with different size and shape patterns (red transparent). (b) Examples of virtual bore probes taken at two different sites in the shaft region: The curves demonstrate the differences in vBMD between the models when averaged according to low (green), middle (red) and high (black) average vBMD values; y-axis: vBMD values in mg Hydroxyapatite /ccm; x-axis: probe length in mm. (c) Visualization of the mass distribution with low vBMD values in the medullary cavity, intermediate vBMD values in the subarticular zone, high and maximum vBMD values in the cortex. (d) Virtual placement of a Philos plate and screws. Half spheres at the screw tips were temporarily used as a positioning tool to achieve consistent distance to the cartilage.

Publication:

Kamer L, Noser H, Popp AW, Lenz M, Blauth M. Computational anatomy of the proximal humerus: An ex-vivo HR-pQCT study. J Orthopedic Translation. 2016 Jan;4 Dec 1, 46-56.

Partners:

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

Comparison of parenteral buprenorphine and sciatic nerve block for providing postoperative analgesia in a mouse model of femur osteotomy and plate fixation (Ongoing) (K. Kluge)

Problem: Effective pain management is one of the major challenges in laboratory animals. Regional anesthesia techniques, the gold standard in human medicine for orthopedic procedures, has not been described in rodent orthopedic models for the purpose of providing analgesia.

Goal: The aim of the study was to evaluate the efficacy of a sciatic nerve blockade with lidocaine and bupivacaine compared to analgesia with parenteral buprenorphine in mice undergoing experimental femur osteotomy with plate fixation.

Materials and Methods: Twelve skeletally mature female C57Bl/6N mice scheduled to undergo orthopedic surgery for an unrelated study were anaesthetized using isoflurane to effect and were randomly allocated to either receive buprenorphine (group A) subcutaneously (SC) or a sciatic nerve block (Group B) with lidocaine combined with bupivacaine before beginning of surgery at time 0 h. Postoperatively, both groups received buprenorphine SC at 6 and 12 h and had access to paracetamol for 3 days in the drinking water. At baseline, 2, 6, 9, 12, 24, 48 and 72 hours after surgery, pain was assessed with a visual analogue scale (VAS) by one observer blinded to treatment identity and gait analysis was performed using a computer-assisted, video-based, unforced walkway system (Catwalk, Noldus AG, Netherlands). Statistical analysis was carried out by using a repeated measure ANOVA with posthoc Tukey test for data analysis with a significance level of $p<0.05$.

Results: VAS was not statistically different between groups with significant changes over time ($p<0.0001$). Regularity index, a measure of interlimb coordination, was neither different between groups nor over time. Duty cycle, expressing stand as percentage of step cycle, was not different between groups with significant decreases over time ($p<0.0001$). Comparing left and right hind limb contact intensity per time point in both groups or paw print intensity of the operated leg between groups, there was no difference.

Conclusion: This technique of intraoperative perineural analgesia was not inferior to an opioid-based protocol in providing postoperative analgesia in mice for the duration of 3 days.

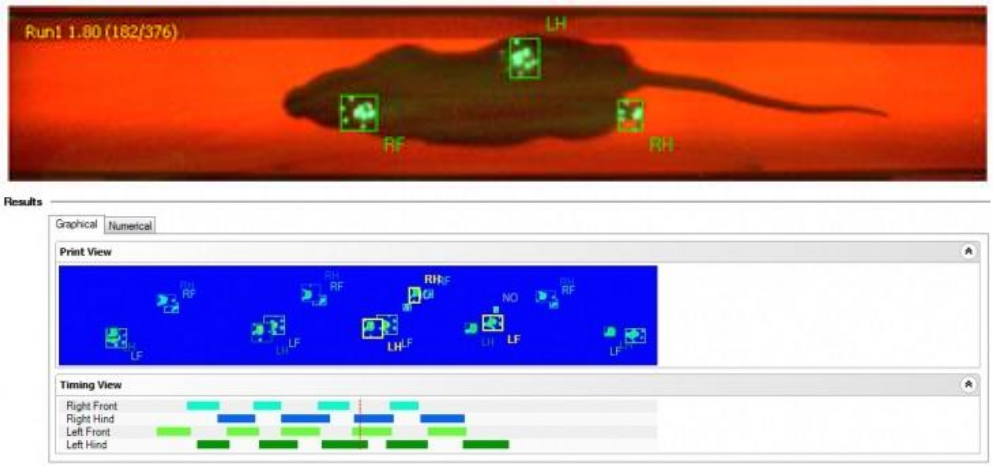


Figure 9.3.6: Gait analysis postoperatively using a computer-assisted, video-based, unforced walkway system (Catwalk, Noldus AG, Netherlands)

Partner:

- Kutter APN (Dr med vet DECVAA) Vetsuisse Faculty, University of Zurich, Switzerland

A refined and clinically more relevant, preclinical osteochondral defect model in rabbits (Ongoing) (T. Schmid)

Background: An osteochondral defect in the femoral trochlear groove of the rabbit is a well described single site defect animal model to study cartilage regeneration and repair. As orthopaedic research continues to advance, it is important for commonly available preclinical models to keep pace with the current clinical standard of care. However, current preclinical models of osteochondral defects in rabbits are all performed via open arthrotomies, diverging from clinical practice.

Goal: In this study we aim to demonstrate the feasibility to create such defects in the rabbit in vivo and to investigate, if healing of an untreated defect is affected by the surgical approach. Additionally, it is hypothesized that the use of arthroscopy will reduce the animal's burden representing a refinement of the model.

Materials and Methods: Eight skeletally mature female New Zealand White Rabbits were used for this study. In group 1 an osteochondral defect was created with arthroscopic technique. In group 2 the femoropatellar joint was approached via an open arthrotomy and a defect of the same size and depth as in group 1 was created. The effect of the surgical procedure on general condition and activity of the rabbits were monitored over 6 weeks. Movement of each rabbit was monitored with a tracking system (Ethovision, Noldus AG, Netherlands). After euthanasia and evaluation of the operated stifle joint using the macroscopic cartilage repair assessment ICRS, the distal femora were fixed for histology.

Results: With further results still pending, we can conclude that a standardized osteochondral defect in the trochlear ridge of the femur can be created arthroscopically in rabbits. With the same pain medication protocol, both rabbit groups showed the same behavior after surgery. The macroscopic cartilage repair assessment ICRS showed a better overall repair in the arthroscopic group. It will be interesting to see if histology supports this finding.

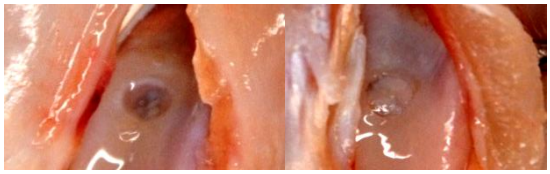


Figure 9.3.7: Images of the macroscopic assessment of cartilage repair – left side a rabbit of the arthrotomy group with an overall abnormal repair, right side a rabbit of the arthroscopic group with nearly normal appearance 6 weeks after surgery.

Mechanisms of Mesenchymal Stem Cell Homing and Differentiation (HomeCell) (Completed) (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 investigating the secreastome of human mesenchymal stem cells, and how it can be modified in a clinically applicable approach. In this study we analyzed 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, remodeling, 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 demonstrated 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:
Voss JO, Löbel C, Duttenhöfer F, Alini M, Stoddart M.Effect of IL-1β short-term stimulation on human MSCs in co-culture with MG63-GFP cells. 2015 DGMKG

Pub:
Glueck M, Gardner O, Czekanska E, Alini M, Stoddart MJ, Salzmann GM, Schmal H. Induction of osteogenic differentiation in human mesenchymal stem cells by crosstalk with osteoblasts . Biores Open Access. 2015 Jan 1;4(1):121-30. doi: 10.1089/biores.2015.0002

In vitro assessment of osteogenesis (Ostmonit) (Ongoing) (M.Stoddart)
This project has developed 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 behavior. 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 behavior. 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 established real- time fluorescent monitoring systems than can be performed on viable cells in a non-destructive way. Sorting cells based on their relative fluorescence results in population of cells that are more osteogenic than the original mixed population.

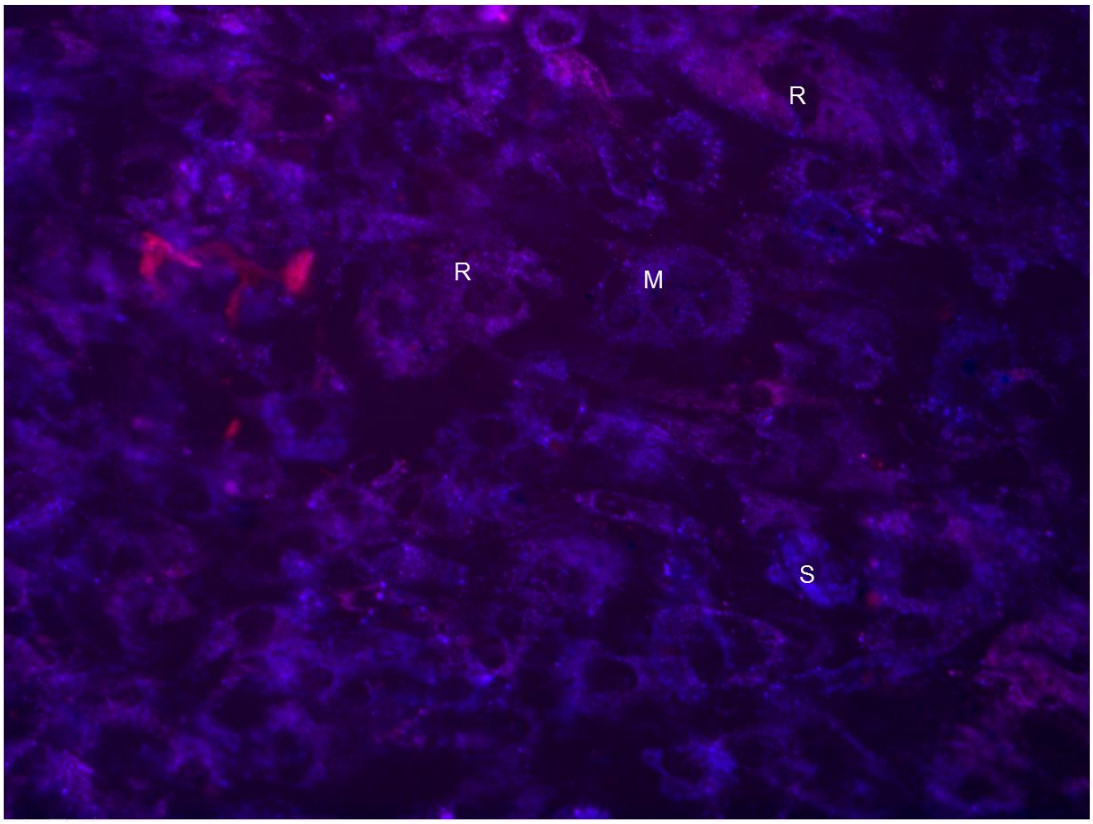


Figure 9.3.8: Mixed population of human mesenchymal stem cells at differing stages of differentiation. Blue cells (S) express higher levels of Sox9 and are undifferentiated. Pink cells (R) express more Runx2 and are more mature osteoblasts. Intermediate colored cells (M) are transitioning to osteogenic differentiation.

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:

Culture and characterization of bone marrow-derived mononuclear cells encapsulated in fibrin. Jennifer J. Bara, Marietta Herrmann, Ursula Menzel, Lorin Benneker, Mauro Alini, Martin J. Stoddart. TERMIS World Congress 2015: September 8th-11th

Pub:

Bara JJ, Herrmann M, Menzel U, Benneker L, Alini M, Stoddart MJ. 3D culture and characterization of mononuclear cells from human bone marrow. Cytotherapy. 2015 Feb 10. pii: S1465-3249(15)00007-9.

Stoddart MJ. Mesenchymal Stem Cells as a Source of Repair Cytokines: MSCs as the Conductors. Journal of the American Academy of Orthopaedic Surgeons. J Am Acad Orthop Surg. 2015 Jun 3. pii: JAAOS-D-15-00202.

Stoddart MJ, Bara J, Alini M. Cells and secretome - towards endogenous cell re-activation for cartilage repair. Adv Drug Deliv Rev. 2015;84:135-45

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

Infections occur in a minor but significant portion of the patients undergoing joint replacement surgery or fracture fixation. Once established, infections are difficult to eliminate, 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. In this project, polymeric carriers have been developed to optimize the release and targeting of antibiotics. More specifically, a thermoresponsive hyaluronan derivative combined with antibiotics to form an injectable thermoresponsive formulation which can easily flow into small spaces between tissues and implant before setting. Remarkably, the gelation temperature of the developed formulation could be modulated by the concentration of sulfate ions introduced, rendering suitable the use of the delivery system for open wound fracture of the lower extremity (Figure 9.3.9). *In vivo* studies are being completed to assess the ability of a gentamicin loaded injectable formulation in preventing an infection.

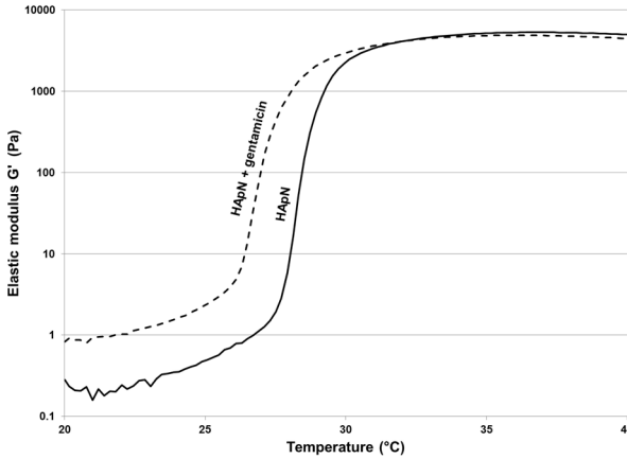


Figure 9.3.9: Rheological profile of thermoresponsive hyaluronan formulation loaded or not with gentamicin sulfate as a function of the temperature.

Pres:

ter Boo GJ, Arens D, Keller Stoddart I, Mets makers WJ, Schmid T, Zeiter S, Richards RG, Grijpma DW, Moriarty TF, Eglin D. Release of gentamicin from a thermo-responsive hyaluronan hydrogel in an in vivo contaminated fracture model. Eur Cell Mater. 2015;30(Suppl 2):76.

ter Boo GJ, Arens D, Keller Stoddart I, Mets makers WJ, Schmid T, Zeiter S, Richards RG, Grijpma DW, Moriarty TF, Eglin D. An injectable formulation of thermo-responsive hyaluronic acid-pNIPAm loaded with gentamicin for infection prophylaxis in an in vivo contaminated fracture model in rabbits. Eur Cell Mater. 2015;30(Suppl 1):13.

ter Boo GJ, Arens D, Keller Stoddart I, Mets makers WJ, Schmid T, Zeiter S, Richards RG, Grijpma DW, Moriarty TF, Eglin D. Release of gentamicin from a thermo-responsive hyaluronan hydrogel in an in vivo contaminated fracture model. Eur Cell Mater. 2015;30(Suppl 2):76.

Schmid T, Keller I, ter Boo GA, Moriarty TF, Eglin D, Zeiter S. Elevated C reactive protein level is an indicator of infection in rabbits in a contaminated fracture model. Eur Cell Mater. 2015;30(Suppl 2):70.

Pub:

ter Boo GJ, Grijpma DW, Moriarty TF, Richards RG, Eglin D. Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery. Biomaterials. 2015 Jun;52:113-125. doi: 10.1016/j.biomaterials.2015.02.020.

Partners:

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

Biodegradable putty-like antibiotics loaded hydrogel for implant infection treatment AOTGEL (Completed) (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 prolong its bioavaibility was prepared. 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. Subsequently, entrapment of this lipophilic gentamicin within continuous (e.g. films) and discrete (micro-particles) matrices made of poly(ε-caprolactone) (PCL); poly(trimethylene carbonate) (PTMC) was performed. Typically, microparticles of PTMC loaded with antibiotic were prepared using a new electrospray manufacturing technology (Figure 9.3.10). Sustain delivery of antibiotic over long period could be achieve.

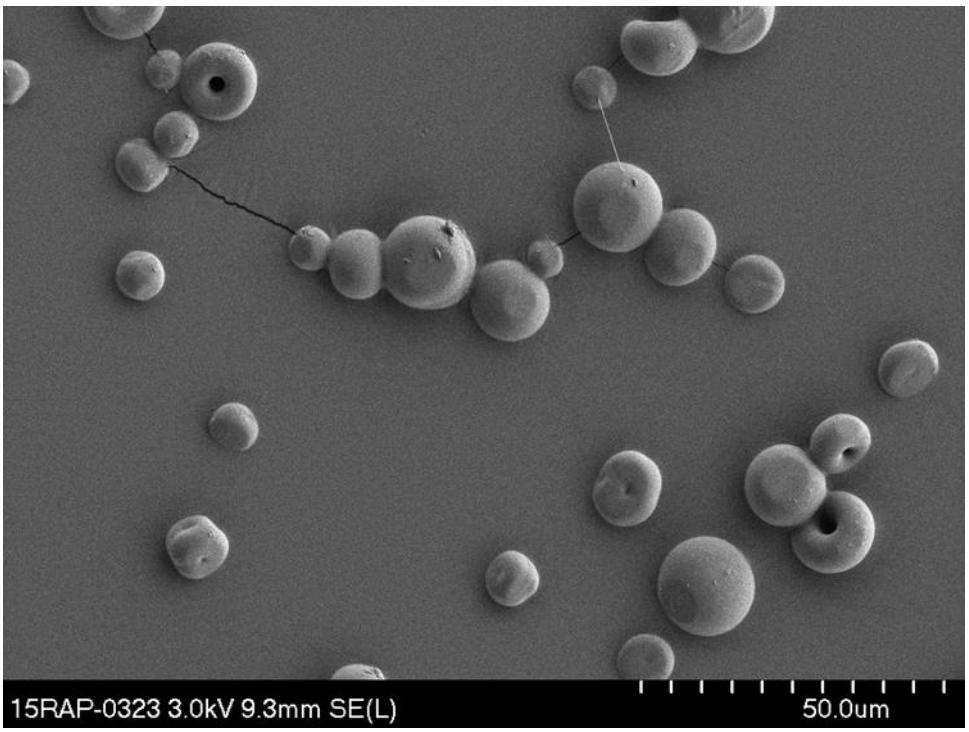


Figure 9.3.10: Scanning electron microscopy image of a PTMC microparticles prepared using electrospray manufacturing process.

Pres:

ter Boo GJ, Grijpma DW, Richards RG, Moriarty TF, Eglin D. An antibiotic delivery system based upon poly(trimethylene carbonate) loaded with a hydrophobic gentamicin. 2015 EFFORT.

Pub:

ter Boo GJ, Grijpma DW, Richards RG, Moriarty TF, Eglin D Preparation of gentamicin dioctyl sodium sulfosuccinate loaded poly(trimethylene carbonate) matrices intended for the treatment of orthopaedic infections. Clin Hemorheol Microcirc. 2015;60:89-98.

Partner:

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

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

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. 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* (Figure 9.3.11). Their releases from delivery vehicles (e.g. hydrogel, ceramic) have been compared. The local delivery of zoledronic acid and bone morphogenetic protein, in an osteoporotic animal model, enhances local bone density to the level of non-osteoporotic animal.

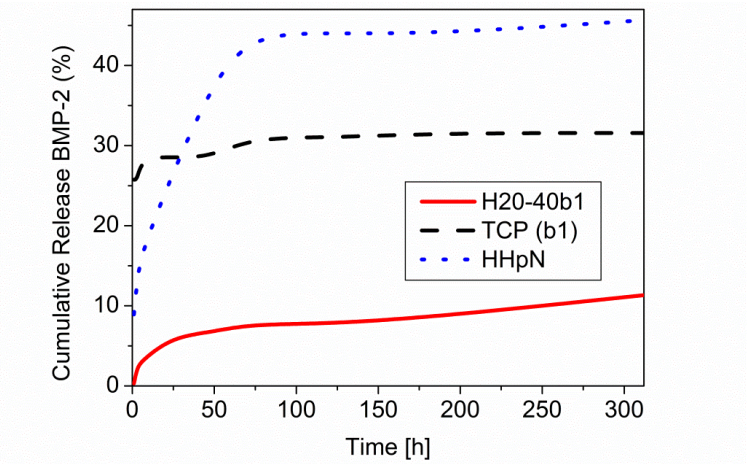


Figure 9.3.11: BMP-2 release profile from hyaluronan hydrogel (HHpN), tricalcium phosphate ceramic particles (TCP) and composite hydrogel-ceramic particles (H20-10b1) (from Petta *et al.* J Orthop Translation. 2015).

Pres:

Petta D, Fussell G, Hughes L, Buechter DD, Sprecher CM, Alini M, Eglin D, D'Este, M. A new ß-tricalcium phosphate / thermoresponsive hyaluronan hydrogel composite as injectable bone graft substitute delivering drugs. Eur Cell Mater. 2015;29(S1)39.

Kyllönen L, Stadelmann V, Alini M, Eglin D. Injectable Hydrogel for the Delivery of Bone Anabolic Factors in Osteoporotic Bone. Tissue Eng Part A. 2015;21(S1):S254.

Pub:

Kyllönen L, D'Este M, Alini M, Eglin D. Local drug delivery for enhancing fracture healing in osteoporotic bone. Acta Biomater. 2015;11:412-434.

D'Este M, Eglin D, Alini M, Kyllönen L. Bone Regeneration with Biomaterials and Active Molecules Delivery. Curr Pharm Biotechnol. 2015;16:582-605.

Petta D, Fussell G, Hughes L, Buechter DD, Sprecher CM, Alini M, Eglin D, D'Este M. Calcium phosphate/thermoresponsive hyaluronan hydrogel composite delivering hydrophilic and hydrophobic drugs. J Orthop Translation. 2015;epub Dec 31.

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

Fractures of the proximal humerus are highly related to age and osteoporotic bone remodeling. Although previous studies have highlighted the cortical bone as a major side of the bone loss, the microstructural changes of the humerus have not been evaluated entirely. The aim of the study was the investigation of the cortical bone loss at the surgical neck of the humerus as one of the major fracture sides. More than 60 fresh frozen humeri with an age range of 19-98 years were scanned with high-resolution peripheral quantitative CT (voxel size 82 µm). The mean BMD at the proximal humerus was negatively correlated to the age ($p=0.001$, figure 9.3.11). Also highly significant correlation of $p<0.001$ were found for the cortical thickness and cortical porosity. Interestingly, all correlations were significant for the subgroups of males and females ($p<0.022$).
Osteoporotic bone remodeling highly affects the humeral cortex of the surgical neck, leading to an extensively increased cortical porosity and reduced thickness. The microstructural bone loss reduces the resistance of the proximal humerus and contributes to the increased fracture risk in elderly people.

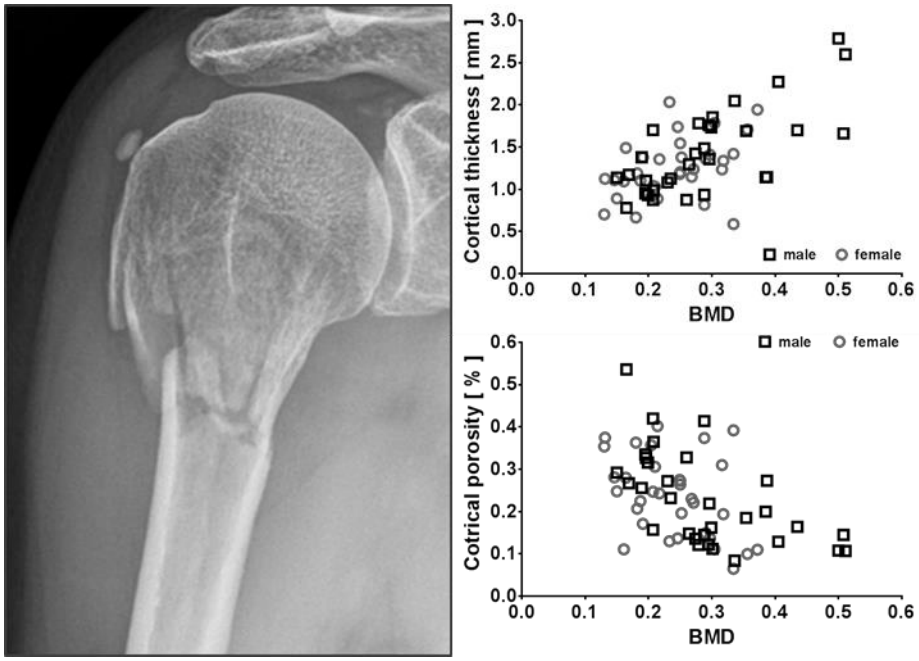


Figure 9.3.12: A fracture at the surgical neck of the humerus as one of the major fracture site shown in a clinical x-ray (left). The correlation between the BMD and cortical thickness (above) and cortical porosity (below) is highly significant and independent of the gender.

Pub:

Sprecher CM, Schmidutz F, Helfen T, Richards RG, Blauth M, Milz S. Histomorphometric Assessment of Cancellous and Cortical Bone Material Distribution in the Proximal Humerus of Normal and Osteoporotic Individuals: Significantly Reduced Bone Stock in the Metaphyseal and Subcapital Regions of Osteoporotic Individuals. Medicine (Baltimore). 2015 Dec;94(51):e2043.

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) and Helfen T (MD) (both Department of Orthopedic Surgery) and Milz S (Prof MD, Department of Anatomy II), University of Munich (LMU), Germany

Impact of risk factors on implant-related bone infections (BONSAI) (K. Thompson)
The impact of co-morbidities, such as post-menopausal osteoporosis, on both the incidence and progression of implant-related bone infection is poorly understood. To investigate this in more detail, we have developed an *in vivo* model system involving the implantation of a bacterially colonized screw into the rat proximal tibia, with which we can monitor bone changes in response to infection in real-time using microCT imaging.
Our results to date have demonstrated that microCT imaging can detect osteolysis in *Staphylococcus epidermidis*-inoculated rats as early as day 6 in the local vicinity of the screw, and that antibiotic therapy (rifampin and cefazolin) administered on day 7 following inoculation resulted in the total clearance of *S. epidermidis* in >80% of infected animals. Further studies involving the use of ovariectomised (OVX) rats, to mimic a low bone mass state characteristic of post-menopausal osteoporosis, are currently in progress to determine if osteoporotic bone has an altered capacity to defend against *S. epidermidis*-induced osteolysis.

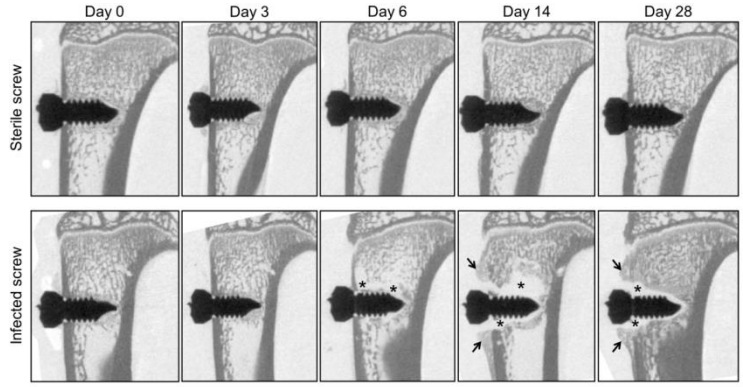


Figure 9.3.13: Loss of bone over a 28-day period following implantation of a *S. epidermidis* inoculated screw into the proximal tibia of a rat. No bone loss is observed with the sterile screw but extensive bone loss (*) occurs around inoculated screws The areas indicated by arrows also highlight a proliferative response of the periosteal tissue as the infection proceeds.

Publications (abstracts in journals):
Stadelmann VA, Camenisch K, Eberli U, Furlong P, Moriarty TF. Patterns of bone evolution near infected implants. Eur Cell Mater. 2015;30(Suppl 2):73 (eCM / poster)

Publications (papers):
Stadelmann VA, Potapova I, Camenisch K, Nehrbass D, Richards RG, Moriarty TF. In Vivo MicroCT Monitoring of Osteomyelitis in a Rat Model. Biomed Res Int. 2015;2015:587857

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 that allows assessment of the impact of infection on fracture healing and the impact of interventional strategies in a clinically relevant model.
In the past year we have compared the resistance against infection of titanium and steel plates, with differing surface topographies. No significant differences were seen in susceptibility to infection when comparing titanium and steel implants with conventional or modified topographies. Polished titanium implants, which have previously been shown in preclinical studies to reduce complications associated with tissue adherence, do not affect infection rate in this preclinical fracture model. Therefore, polished titanium implants are not expected to affect the infection rate, or influence implant stability, in the clinical situation.

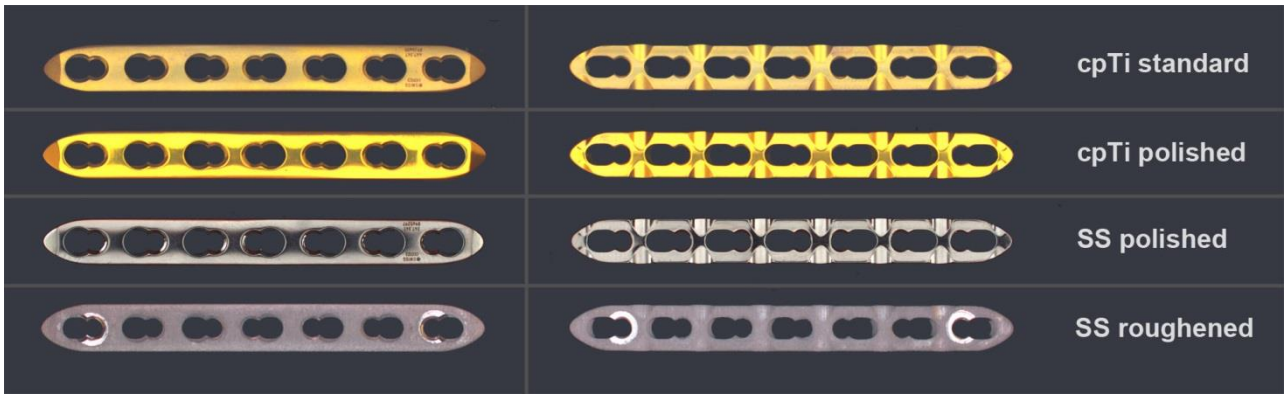


Figure 9.3.14: Implants with different materials (commercially pure Titanium (cpTi) and Stainless Steel (SS) and different topographies (polished, standard or roughened) are shown. The resistance against infection of these different implants is currently being tested in a rabbit humeral osteotomy model.

Pub:
A rabbit humerus model of plating and nailing osteosynthesis with and without Staphylococcus aureus osteomyelitis. Arens D, Wilke M, Calabro L, Hackl S, Zeiter S, Zderic I, Richards RG, Moriarty TF. Eur Cell Mater. 2015 Sep 21;30:148-61

Assessing the Role of the Implant Material and stability on the Development of Infection (Immunobact) (M. Sabaté Brescó)
Mechanical stability is one of the main factors in bone healing. It is also known that instability 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. The results to date have shown that animals carrying a rigid implant could more frequently and rapidly clear *S. epidermidis* infection. The immune response associated with infection and stability are being characterized to better understand the influence of biomechanics on infection susceptibility. It seems that IL-17-type responses may be important for infection clearance and thus is the focus of current studies.

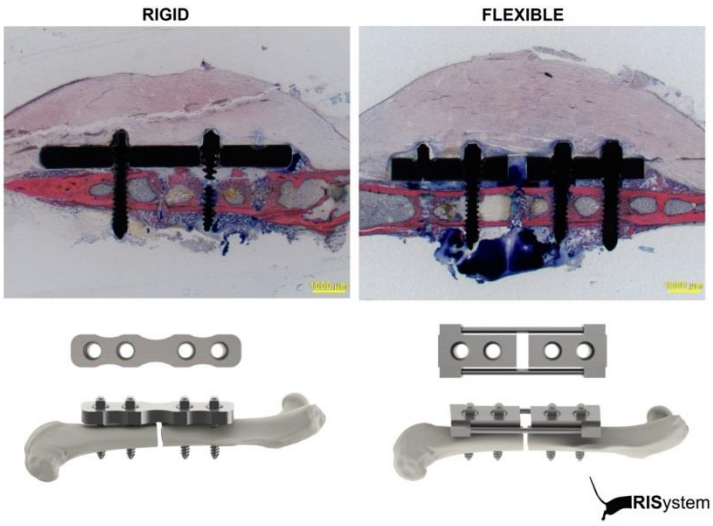


Figure 9.3.15: Rigid (left) and flexible (right) implants lead to diferencesin infection clearance in a murine model. Rigid fixation allows animals to clear infection more rapidly and in more animals.

Pub:
Sabaté Brescó M, Kluge K, Ziegler M, Richards RG, O'Mahony L, Moriarty TF
The role of biomechanical stability on Staphylococcus epidermidis osteomyelitis in a murine fracture model (oral)
Eur Cell Mater. 2015;30(Suppl 2):30

Sabaté Brescó M, Kluge K, Ziegler M, Richards RG, Moriarty TF, O'Mahoney L
Immune response during bone healing in a murine fracture model with osteomyelitis: role of biomechanical stability (oral)
9th World Immune Regulation Meeting (WIRM), 18-21 March 2015, Davos, Switzerland

Sabaté Brescó M, Kluge K, Ziegler M, Nowicki B, Richards RG, O'Mahoney L, Moriarty TF
The role of biomechanical stability on Staphylococcus epidermidis osteomyelitis in a murine fracture model (oral). 16th EFORT Congress, 27-29 May 2015, Prague, Czech Republic

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

EpiLog: *S. epidermidis* bone infections associated with implanted medical devices in human patients (B. Stanic)
Infection remains a serious problem in orthopedic and trauma surgery. Infections caused by *Staphylococcus epidermidis* are typically difficult to diagnose due to the 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 collected local (bone marrow) and systemic samples (blood) from 40 human subjects enrolled for revision surgery (septic and non-septic controls) in collaboration with clinical coordinator DrMario Morgenstern at BGU Murnau in Germany.
In addition to ongoing profiling of cellular immune responses, we have performed immune proteome analysis of an early pool of infected and non-infected patients. Twenty six specific candidate *S.epidermidis* proteins (antigens) have been identified and shown to induce production of specific immunoglobulins following bone infection in greater amounts than non-infected controls. Validation of the retrieved candidate proteins, as well as screening in the full cohort of patients, is ongoing.

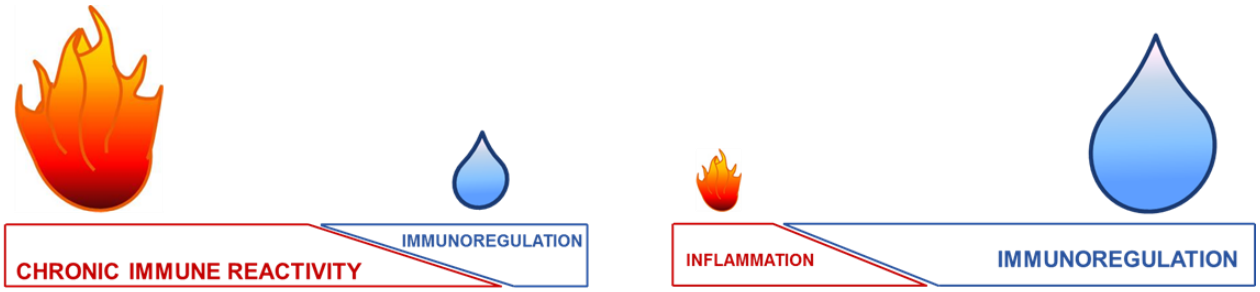


Figure 9.3.16: Simplified schematic of alternative immune responses that may be elicited by different pathogens. The Epi-Log project will investigate how *S. epidermidis* infected patients fit within this scheme.

Partners:
- Morgenstern M (MD), BGU Murnau, Murnau, Germany
- Daiss JL, University of Rochester, New York, USA

Molecular epidemiology of staphylococcal isolates from musculoskeletal infections associated with orthopaedic devices (StaphSeq) (V. Post)

In the most recent activity of the StaphSeq project we have focused on a prospective collection of 152 *S. epidermidis* and 94 *S. aureus* isolated from patients with implant related bone infection. The clinical observation and follow-upperiod has now reached our 26 month target. The patients have been categorized into good or bad outcome according to definitions developed with clinical partners. Whole genome sequencing of these isolates was performed in addition to conventional analyses such as biofilm forming ability. Using the whole genome data, we observed that the 113 clinical *S. epidermidis* isolates clustered in 3 clades (Figure 9.3.17). A trend between the distribution of clinical good outcome and bad outcome isolates and clades were observed (p= 0.051). Clade A compromised 35 of the 45 (77.8%) bad outcome *S. epidermidis* isolates while Clade B consisted of 8 (17.8%) and Clade C of 2 (2.2%) bad outcome isolates (Figure 1). There was no statistically significant correlation between further clinical outcome measurements such as FFI/PJI, acute infection, chronic immunosuppression, obesity, smoking, open fracture, diabetes, revision surgery and clustering of the isolates.

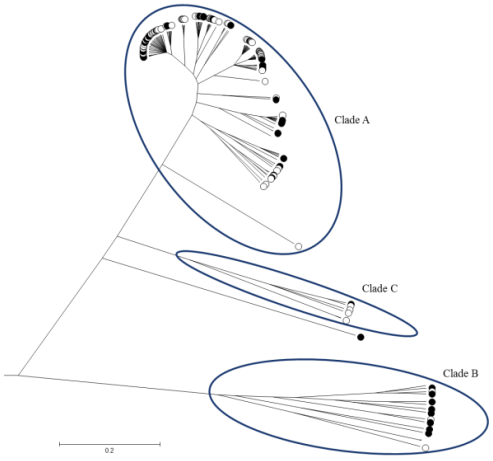


Figure 9.3.17: Population structure of 113 *S. epidermidis* isolates constructed from 123 core genes and implemented in CLONALFRAME, with the 3 clades highlighted. The scale (0.2) represents the number of substitutions per site. Isolates are labelled according to the clinical follow-up (FUP) outcome: bad outcome (filled circle) and good outcome (open circle).

Pres:

Post V, Morgenstern M, Richards RG, Moriarty TF. Characterization of nasal methicillin-resistant staphylococcus aureus from an international cohort of orthopaedic surgeons. 2015 EFORT (oral)

Post V, Morgenstern M, Richards RG, Moriarty TF. Characterization of nasal Methicillin-resistant Staphylococcus aureus from orthopaedic surgeons. Eur Cell Mater. 2015;30(Suppl 2):62 (eCM / poster)

Post V, Wahl P, Richards RG, Moriarty TF. Eradication of bacterial biofilms from titanium implants by vancomycin: beyond the reach of common local delivery. Eur Cell Mater. 2015;30(Suppl 2):63 (eCM / poster)

Morgenstern M, Erichsen C, Hackl S, Mily J, Militz M, Friederichs J, Hungerer S, Bühren V, Moriarty TF, Post V, Richards RG, Kates SL. Antibiotic Resistance of Commensal Staphylococcus aureus and Coagulase Negative Staphylococci in an International Cohort of Surgeons. Eur Cell Mater. 2015;30(Suppl 2):4 (eCM / oral)

Pub:

Morgenstern M, Erichsen C, Hackl S, Mily J, Militz M, Friederichs J, Hungerer S, Bühren V, Moriarty TF, Post V, Richards RG, Kates SL.2016. Antibiotic Resistance of Commensal Staphylococcus aureus and Coagulase-Negative Staphylococci in an International Cohort of Surgeons: A Prospective Point-Prevalence Study. PLoS One. Feb 3;11

Partners:

- Morgenstern M (MD), BGU Murnau, Murnau, Germany
- Sheppard S (Prof), University of Swansea, Swansea, UK

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. S. Zeiter, F. Moriarty)

In 2015 we have successfully established an implant related osteomyelitis model with a two-stage exchange in sheep using a methicillin-susceptible *S. aureus*. Different treatment possibilities were evaluated with a) debridement, implant exchange, local and systemic antibiotic treatment b) debridement and implant exchange, c) debridement, implant exchange and systemic antibiotic treatment and d) debridement, implant exchange and local antibiotic treatment. Only with the full standard of treatment the infection were completely eradicated (Figure 9.3.18 a-d).

Furthermore, we have proceeded to perform the two-stage hardware exchange of the infected implant with a methicillin resistant *S. aureus* (MRSA). Once established, treatment of this infection involved removal of the infected nail, debridement 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). The animals were all culture positive at implant removal, remained mainly culture positive at spacer removal, although at lower levels, and infection returned to a high bacterial count upon euthanasia (Figure 9.3.18 e).

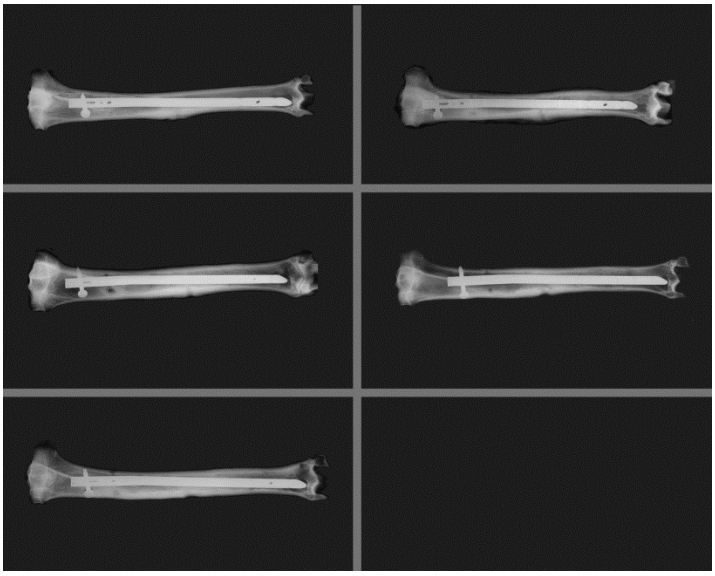


Figure 9.3.18: Representative Contact-radiographs from one sheep of each treatment group at euthanasia with UHN IM nail. a) MSSA debridement, implant exchange, local and systemic antibiotic treatment, b) MSSA debridement and implant exchange, no antibiotic treatment c) MSSA debridement, implant exchange and systemic antibiotic treatment, d) MSSA debridement, implant exchange and local antibiotic treatment, e) MRSA debridement, implant exchange, local and systemic antibiotic treatment.

Partners:

- Kates S (Prof), University of Rochester, Rochester, USA
- Schwarz E (Prof), University of Rochester, Rochester, USA

9.4 AOVET

Biomechanical evaluation of different plating techniques for feline ilial fracture stabilization (IlCat) (I. Zderic)

Problem: Ilial fractures are a common surgical problem in cats. Internal fixation using lateral plating is associated with a high incidence of complications. Strategies to decrease the risk of implant-associated complications include dorsal, locking, and orthogonal plating. However, biomechanical studies comparing plating methods for feline ilial fractures are lacking.

Goal: To biomechanically compare the stiffness and fatigue resistance of four different plating techniques for feline iliac fracture fixation, namely 1) dorsal non-locking, 2) lateral non-locking, 3) lateral locking and 4) combined lateral and dorsal non-locking double plating.

Results: Double plating resulted in a significantly higher stiffness and resistance to failure than the other fixation groups. Using a locking plate does not influence initial stiffness, but results in increased resistance to fatigue failure compared to single non-locking plating, and hence represents the best compromise between mechanical stability and invasiveness.

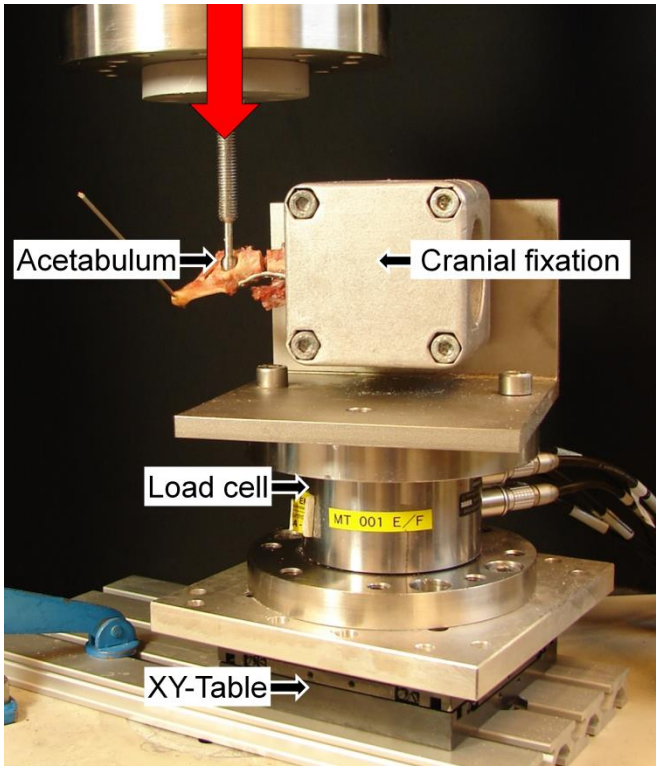


Figure 9.4.1: Setup for biomechanical testing

Partners:

- Schmierer P (Dr med vet), Clinic for Small Animal Surgery, Vetsuisse Faculty University of Zurich, Zurich, Switzerland
- Smolders L (Dr med vet), Vetsuisse Faculty University of Zurich, Zurich, Switzerland
- Pozzi A (Dr med vet), Vetsuisse Faculty University of Zurich, Zurich, Switzerland
- Knell S (Dr med vet), Clinic for Small Animal Surgery, Vetsuisse Faculty University of Zurich, Zurich, Switzerland

9.5 TK System

Computational anatomy of the cervical spine C1-C3 assessed by quantitative computed tomography and its implications for screw fixation (D. Gehweiler, H. Noser, L. Kamer)

Fracture fixation of the cervical spine represents a demanding procedure and includes accurate implant positioning close to vital structures. Both surgical approach and fixation strategy are also considered to depend on bony anatomy. Hence, anatomical knowledge about the local bony conditions is of critical importance, particularly in situations with limited space and reduced bone mass.

A total number of 120 standard clinical quantitative computed tomography (QCT) scans of the cervical spine were acquired to generate a three-dimensional (3D) statistical model of C1-C3 in order to assess the bony anatomy with regard to implant positioning.

A large anatomical variation was observed with size as the main variation pattern dominating over shape criterion. At C2 level anatomical conditions were identified that interfered with the bony pathway of the vertebral artery, thus not allowing placement of a pedicle screw. A characteristic pattern in the trabecular and cortical bone mass distribution was identified, which varied across the examined anatomical site. In the presence of bone loss, the bone mass was ubiquitously decreased, while the pattern of bone mass distribution remained constant.

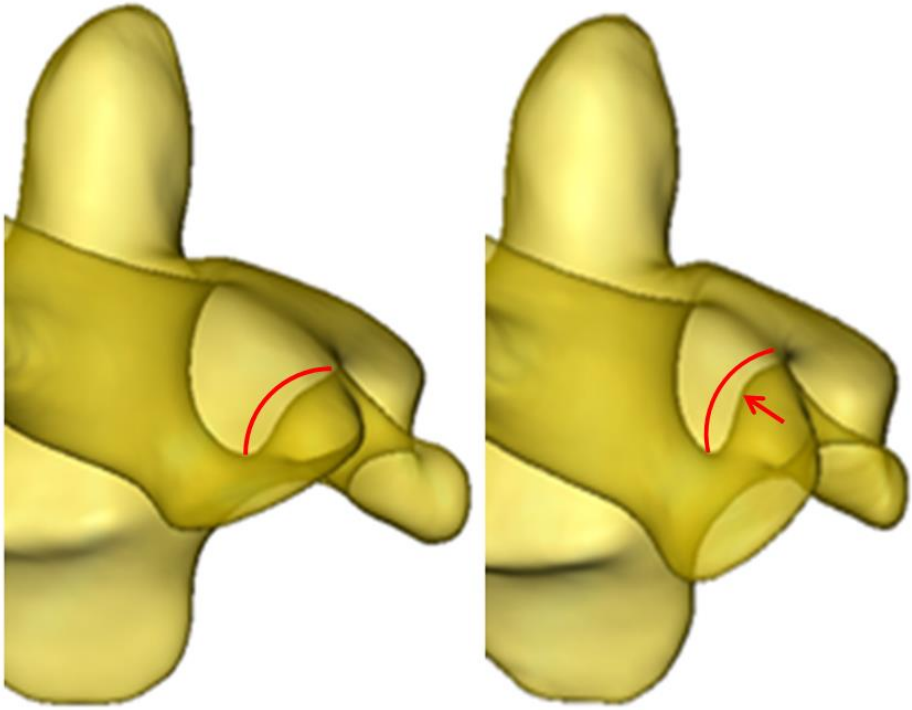


Figure 9.5.1: Statistical model of C2 and bony pathway of the vertebral artery. The computer model illustrates anatomical conditions that allow (left) or do not allow (right; arrow) for a pedicle screw to be placed through the pedicle corridor.

A new a priori understanding was established about the anatomy of C1-C3 describing the anatomical conditions that allow or do not allow for implants to be placed through the pedicle corridor. The choice of implant (type, number, size, and position of the implant) highly depends on thorough anatomical understanding and knowledge about each given individual situation. The models may also be evaluated using finite element simulation to investigate the mechanical behavior in the context of implant fixation.

Partners:

- Wähnert D (MD, PhD) Department of Trauma, Hand and Reconstructive Surgery, University Hospital Münster, Albert-Schweitzer-Campus, Münster, Germany
- Raschke MJ (MD, PhD, Professor) Department of Trauma, Hand and Reconstructive Surgery, University Hospital Münster, Albert-Schweitzer-Campus, Münster, Germany

Biomechanical testing of Patella implant prototypes (PatBand 2) (I. Zderic)
Problem: tension band wiring is the most common treatment for transverse patellar fracture fixation. Its main principle in all modifications is to neutralize muscle traction, reduce the fracture and possibly convert tensile forces into compression forces in the fracture gap. Although the tension band wiring is currently the mostly used operation technique, some experimental data do not support the theoretical principles behind it. Besides the established tension band wiring techniques, a new Intraosseous Nail solution for transverse patellar fracture fixations is currently under development.

Goal: (1) To compare the biomechanical performance of two different methods for fixation of transverse patellar fractures, namely tension band wiring through cannulated screws and intraosseous nailing; (2) to further investigate whether the principle of tension band wiring works for transverse patellar fracture fixation.

Results: from biomechanical point of view the new intraosseous nail did not outperform tension band wiring through cannulated screws in terms of relative interfragmentary movements throughout cyclic testing. Hence, only to a limited extent it can be recommended as a valuable substitute for transverse patella fracture fixation.

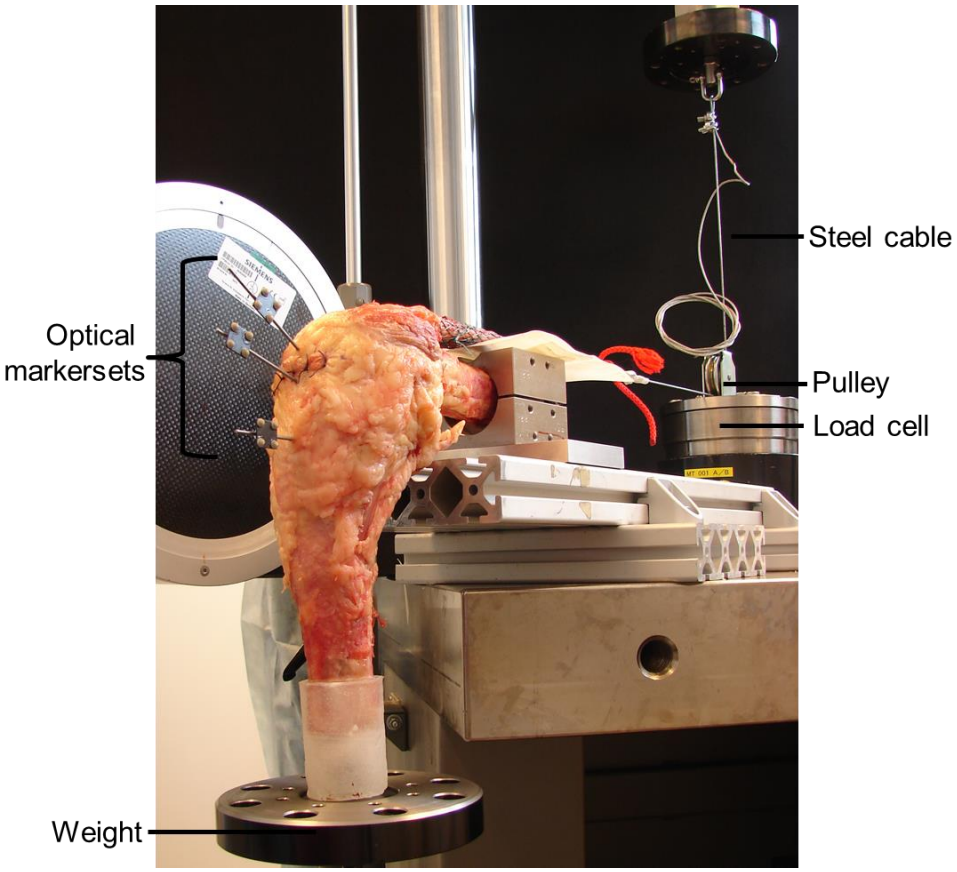


Figure 9.5.2: Test setup with a mounted specimen, ready for mechanical testing.

Partners:
- Sommer C (MD), Cantonal Hospital Graubuenden, Chur, Switzerland
- Stoffel K (Prof, MD), Cantonal Hospital Baselland and University Basel, Liestal, Switzerland
- Höntzsch D (Prof, MD), Occupational Injury Clinic Tübingen, Tübingen, Switzerland
- Perren SM (Prof, MD, PhD), AO Foundation, Davos, Switzerland
- Lee M (Prof, MD), UC Davis Health System, Sacramento, CA, USA
- Rommens P (Prof, MD), Gutenberg University, Mainz, Germany

Clinical data collection with the AO Fracture monitor on external fixator patients (SmartFix, Ongoing) (M. Ernst, 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 deflection and extract relevant healing parameters therefrom has been recently developed in the ARI within a related project (ImpCon 2). Using this system, a prototype device (AO Fracture Monitor) for healing assessment in external fixation patients has been created as a means to non-invasively prove the concept in clinics.

Goal: The AO Fracture Monitor should be applied within a clinical trial to assess the diagnostic value of the recorded parameters.

Results: Clinical data collection at BGU Tübingen (Principal Investigator: Prof D. Höntzsch) was started with the inclusion of the first patient in January 2015. By end of 2015 five patients have been enrolled in the study, four of which have completed the full monitoring period of six months. Preliminary analysis of the recorded data suggests that the monitored parameters can clearly reflect differences in individual healing progression. Hence, the concept proofs its potential for assessment of fracture healing also in a clinical setting. The development of a second generation monitoring system has been pursued further with the overall goal of creating an implantable data logger to be used in combination with conventional internal fixators.

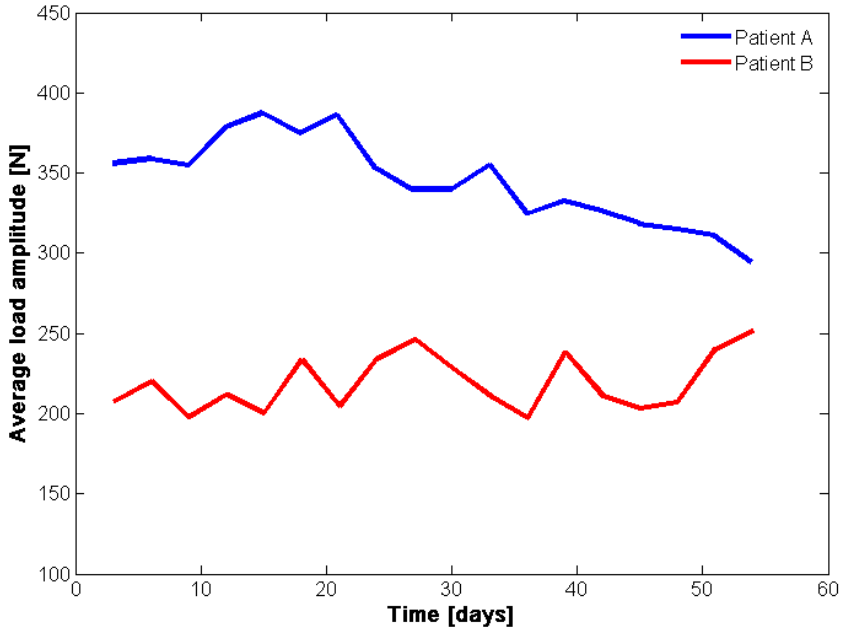


Figure 9.5.3: Average external fixator load in two patients over a period of two months. A drop of the curve over time in patient A (blue) indicates onset of fracture healing. The rather constant load level in patient B (red) suggests no signs of fracture consolidation so far.

Partners:
- Pohlemann T (Prof), UK Homburg, Germany
- Höntzsch D (Prof), BG Unfallklinik Tübingen, Germany
- Mathis H (Prof), Institute for Communication Systems, Hochschule für Technik, Rapperswil, Switzerland
- Helbling Technik AG, Wil, Switzerland

9.6 ARI Exploratory Research

3D modeling of the skull based on Magnet Resonance Imaging (BlackBone MRI) (L. Kamer)

Magnet Resonance Imaging (MRI) does not expose the patient to X-ray radiation and may be used to generate a three-dimensional (3D) computer model of the skull instead of computed tomography (CT) or cone beam computed tomography (CBCT).

A post mortem sample of the skull was subjected to MRI scanning and a computerized workflow was developed that allowed for a 3D reference model of the calvaria, orbit and mandible be efficiently adapted to the given situation of the MRI scan. In addition CT scanning was performed to generate a 3D model of the skull.

An MRI acquisition protocol with an isotropic image resolution ≤ 1mm could solely be obtained for the three single craniomaxillofacial sub regions as mentioned above. However, the protocol did not fulfill the requirements for the entire skull to be scanned at a sub millimetric scale. A specific workflow was developed for the craniomaxillofacial sub regions, as illustrated in Figure 9.6.1: The process required landmarks to be manually placed to delineate to outline the bony contour of the region of interest. According to these landmarks the reference models were positioned and adapted. Additional user interaction was required to check and to adjust it to the given situation.

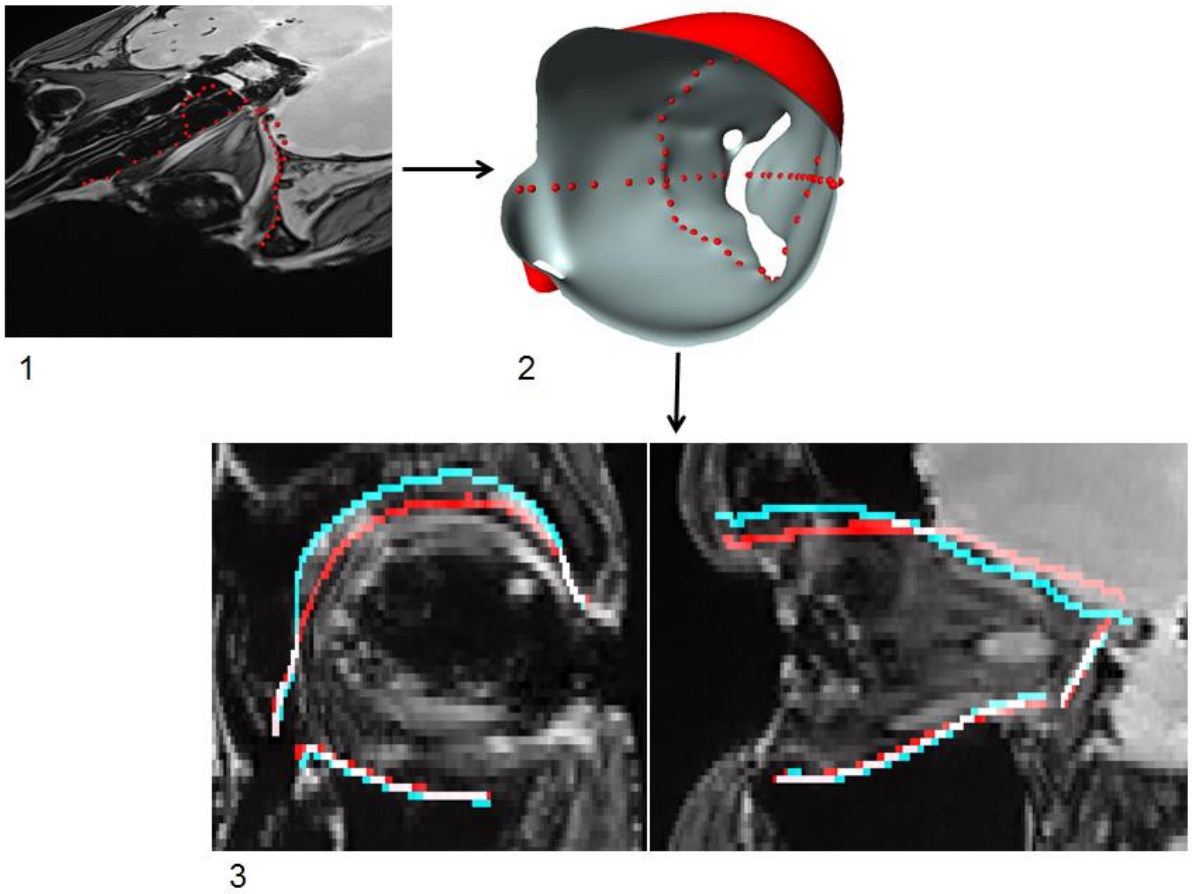


Figure 9.6.1: 3D modeling workflow as developed in the project (example orbit).

Chondrogenesis of human bone marrow mesenchymal stem cells in fibrin-polyurethane composites (Stemload) (Completed) (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 worldwide 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 robust response. Our more recent studies have demonstrated that asymmetric seeding of the cells within tissue engineered cartilage implants not only leads to an improved chondrogenic response, but also reduces donor variability by improving the response from cells harvested from donors previously considered to be poor. 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. Additionally, we have identified novel targets that are only modified during mechanically induced chondrogenesis. These are potentially new clinical targets that would not be identified during standard chondrogenic induction protocols. This provides invaluable information when considering rehabilitation protocols post intra-articular surgery.

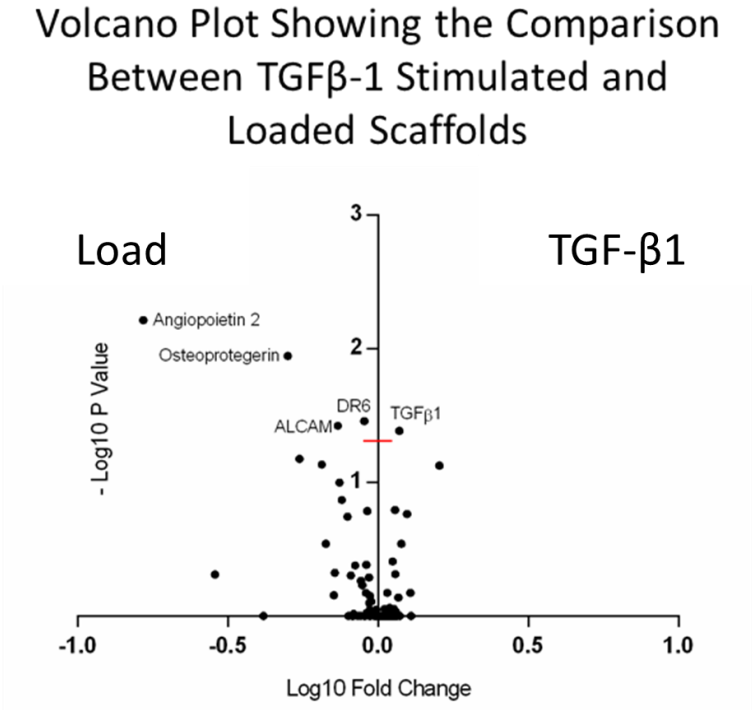


Figure 9.6.2: Volcano plot showing the results of the three sets of statistical comparisons made between groups. This plot has –Log10 p-value of the comparison on the Y-axis and Log10 fold change of the comparison for each factor on the X-axis. As a result the greater the fold change the further a factor is away from zero on the X-axis and the lower the p-value of a comparison the further away from zero on the Y-axis. Factors that underwent a significant change have been labelled. The red line on the Y-axis represents a –Log10 p-value of 1.3 this is equivalent to a p-value of 0.05, factors above this line underwent a significant change.

The plot represents TGF-β1 stimulated samples compared to loaded samples. Factors on the left had side of the Y-axis were higher in loaded samples than TGF-β1 stimulated samples and factors on the right hand side were higher in TGF-β1 stimulated samples than loaded samples.

Pres:
Effects of rAAV sox9 gene transfer upon the chondrogenic differentiation of hMSCs seeded in polyurethane scaffolds. Venkatesan J., Rey-Rico Ana, Gardner O., Eglin D., Alini M., Stoddart M., Cucchiarini Madry Magali, Madry H. DKOU, 20-23 October, Berlin Germany

Venkatesan JK, Rey-Rico A, Gardner O, Schmitt G, Eglin D, Alini M, Stoddart M, Cucchiarini .
Effects of rAAV Sox9 gene transfer upon the chondrogenic differentiation of Hmscs seeded in polyurethane scaffolds.
2015 ORS

Pub:
Neumann AJ, Gardner OF, Williams R, Alini M, Archer CW, Stoddart MJ. Human Articular Cartilage Progenitor Cells Are Responsive to Mechanical Stimulation and Adenoviral-Mediated Overexpression of Bone-Morphogenetic Protein 2. PLoS One. 2015 Aug 20;10(8):e0136229. doi: 10.1371/journal.pone.0136229. eCollection 2015.

Book Chapter:
Gardner OF, Alini M, Stoddart MJ. Mesenchymal stem cells derived from human bone marrow. Methods in Molecular Biology: Cartilage Tissue Engineering – Methods and Protocols. Pages 41-52. Humana Press. 2015. Print ISBN: 978-1-4939-2937-5

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

The role of Pericytes in Bone Regeneration (Perivasc) (ongoing) (S. Verrier)
Pericyte recruitment is essential for the stability of newly formed vessels. It was also suggested that pericytes represent common ancestor cells giving rise to mesenchymal stem cells (MSCs) in the adult. Here, we systematically investigated pericytes and MSCs from different human tissues in terms of their angiogenic and multilineage differentiation potential in vitro in order to assess the suitability of the different cell types for the regeneration of vascularized tissues.
Magnetic-activated cell sorting (MACS®) was used to enrich CD34-CD146+ pericytes from adipose tissue (AT) and bone marrow (BM). The multilineage potential of pericytes was assessed by testing their capability to differentiate towards osteogenic, adipogenic and chondrogenic lineage in vitro. Pericytes and endothelial cells were co-seeded on Matrigel™ and the formation of tube-like structures was examined to study the angiogenic potential of pericytes. MSCs from AT and BM were used as controls.
CD34-CD146+ cells were successfully enriched from AT and BM. Only BM-derived cells exhibited trilineage differentiation potential. AT-derived cells displayed poor chondrogenic differentiation upon stimulation with TGF-β1. Interestingly, osteogenic differentiation was more efficient in AT-PC and BM-PC compared to the respective full MSC population. Matrigel™ assays revealed that pericytes from all tissues integrated into tube-like structures.
We show that MACS® enriched pericytes from BM and AT have the potential to regenerate tissues of different mesenchymal lineages and support neovascularization. MACS® represents a simple enrichment strategy of cells, which is of particular interest for clinical application. Finally, our results suggest that the regenerative potential of pericytes depends upon their tissue origin.

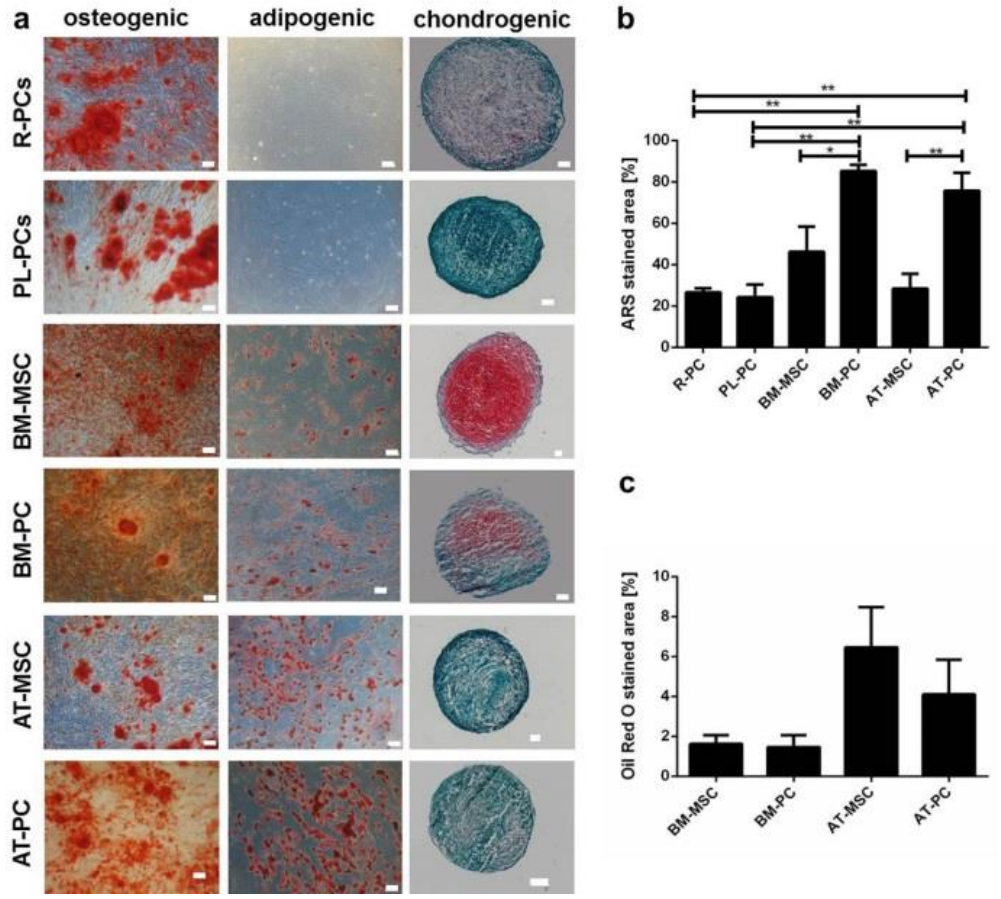


Figure 9.6.3: Multilineage differentiation potential. a) Osteogenic (left column), adipogenic (middle column) and chondrogenic differentiation (right column) of pericytes assessed by Alizarin Red S (ARS), OilRedO and SafraninO-FastGreen staining, respectively. Only BM-derived cells were able to undergo chondrogenic differentiation observed by pink staining of glycosaminoglycans. Note that R-PC and PL-PC were not able to differentiate towards the adipogenic lineage (indicated by accumulation of red-stained lipid droplets). Mineral deposition (red stain) was observed for all cell types. Pictures of the entire wells were used to quantify the area stained with Alizarin Red S (b) and OilRed O (c). Depicted are mean values +/- SEM. * $p < 0.05$; ** $p < 0.01$. Scale bars = 100 µm.

Pres:

Herrmann M, Bara JJ, Jalowiec JM, Menzel U, Sprecher C, Scherberich A, Alini M, Verrier S. The role of pericytes in bone tissue engineering - an in vitro comparison of pericytes from different human tissues. ISBR, Berlin, June 2015.

Herrmann M, Bara JJ, Menzel U, Jalowiec JM, Osinga R, Scherberich A, Alini M, Verrier S. Pericytes Support Bone Regeneration by Complementary Mechanisms - an in vitro Investigation into the Angiogenic and Osteogenic Properties of Pericytes Derived from Multiple Tissue Sources. ORS, Las Vegas, March 2015.

Herrmann M, Bara JJ, Hildebrand M, Menzel U, Sprecher C, Scherberich A, Alini M, Verrier S. The role of pericytes in bone tissue engineering – an in vitro investigation of the angiogenic and osteogenic potential of pericytes . SCGO/SBMS, Bern, May 2015.

Herrmann M, Bara JJ, Hildebrand M, Menzel U, Sprecher C, Scherberich A, Alini M, Verrier S. Pericyte Plasticity – Investigation of the Angiogenic and Multilineage Potential of Pericytes. TERMIS World congress, Boston Sept. 2015

Pub:
Herrmann M, Verrier S, Alini M. "Strategies to stimulate mobilization and homing of stem and progenitor cells for bone tissue repair." Frontiers in Bioengineering and Biotechnology: Tissue engineering and Regenerative Medicine.2015

Herrmann M, Laschke MW, Alini M, Scherberich A, Verrier S. "Vascularization, Survival, and Functionality of Tissue-Engineered Constructs", in "Tissue Engineering", Elsevier, (2015), ISBN: 978-0-12-420145-3

Jalowiec J, Menzel U, Bara JJ, D'Este M, Alini M, Verrier S, Herrmann M**.** "Platelet rich plasma gel as an autologous delivery system of growth factors and cells for tissue engineering applications." Tissue Engineering Part C, 2015

Duttenhoefer F, Lara de Freitas R, Loibl M, Bittermann G, Richards RG, Alini M, Verrier S. "Endothelial cell fraction contained in bone marrow derived mesenchymal stem cell populations impairs osteogenic differentiation." BioMed Research International, 2015

Partners:
- Barbe L (PhD), CSEM Landquart, Switzerland
- Scherberich A (PhD), Department of Biomedicine, University Hospital Basel, Switzerland
- Laschke M (Prof, MD), Experimentelle Chirugie, Uniklinikum Saarland, Germany

The role of immunosuppression in bone healing (ImmunoSup) (started) (S. Verrier)
Although, bone is an organ with high regenerative capacity, 5-10% of fractures do not heal spontaneously. Currently investigated treatment options include tissue engineered constructs containing cells. Towards clinical translation of these implants, preclinical testing is vital, and particularly for cell-based implants certain obstacles are faced. Autologous cells have the advantage that no immunological response has to be considered. Though, in case of rodents the cell number obtained in an autologous manner might be insufficient, and many tissue engineered construct are based on human cells. To avoid any xenogenous graft rejection, pre-clinical investigations of such constructs are mainly conducted in immunodeficient / immunosuppressed animals. On the other hand the immune system, including the adaptive, T-cell mediated immunity is highly involved in the bone healing process. Therefore, results obtained from immunosuppressed animal models might be biased and make a translation of results towards clinics difficult. This project aims to identify the contribution of the adaptive immune response in the healing process of xenogeneic implants in a femoral defect model by comparing the healing pattern in immunocompetent, T-cell depleted rnu rats and Fisher rats treated with immunosuppressive drugs.

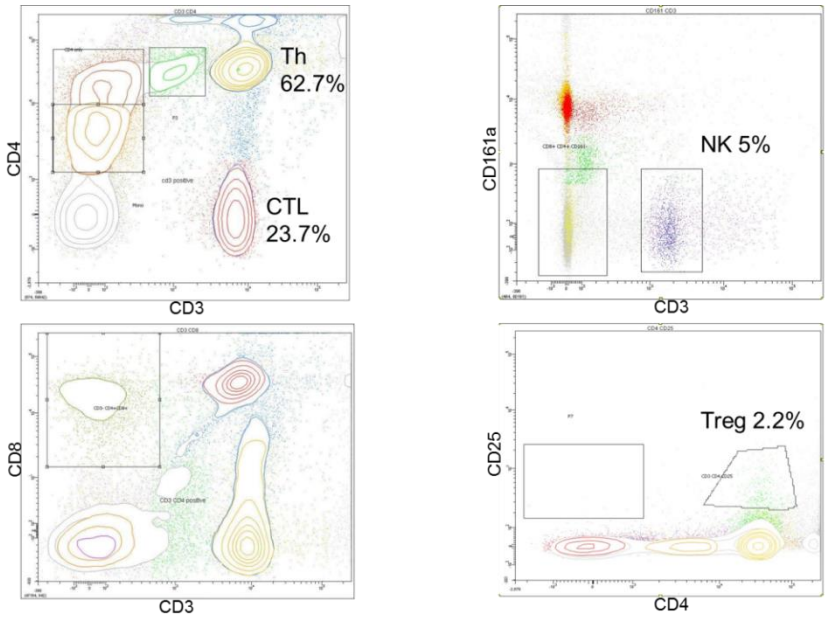


Figure 9.6.4: FACS analysis of immune cells in rat blood samples. The involvement of the immune-system during bone healing can be follow looking at the evolution of the frequency of different immune-related cell populations in the blood.

Partner:

- Akdis C (Prof), SIAF, Davos, Switzerland

Mobilization of Endothelial Progenitor Cells (BonePrep 2) (completed) (S. Verrier)

Stem and progenitor cell mobilization is a critical event in bone regeneration. Mesenchymal stem cells (MSCs) are required as osteoprogenitor cells. In addition, endothelial progenitor cells (EPCs) are required to promote neovascularization, which in turn ensures the survival of cells within the defect. Accordingly, transplantation of CD34-expressing cells, which contain EPCs, has been shown to efficiently support vascularization and bone healing. These cells can be mobilized by administration of granulocyte-stimulating factor (G-CSF). Although it has already been demonstrated that G-CSF mobilizes CD34-positive cells and to positively influencing bone healing, little is known about the exact composition of the mobilized cell population.

Furthermore, treatment with G-CSF has so far only been applied after a surgical intervention, meaning that stem cells are only mobilized several days after the intervention. Surgeries such as joint replacement, implant revisions, anatomical corrections and non-life threatening trauma surgery are however often planned in advance. In this case it would be feasible to pre-treat patients with G-CSF to ensure an increased accumulation of stem and progenitor cells immediately after the surgery during the very early stages of bone healing.

The aim of this project was to establish methods to study the composition and time-line of cell mobilization after G-CSF administration. In particular, we focused on EPCs to address the neovascularization of bone defects. Our data shows that different cell populations are upregulated by G-CSF treatment. The time course of upregulation follows a cell specific pattern and reflects the half-life of the cells; this is particularly evident for CD34+ cells which have a long life span. However, both CD34+ and CD11b+ cells might contribute to the bone formation process by promoting the neovascularization within the defect. The long survival time of CD34+ cells may also account for the observation that no significant differences were observed within the pre- and post-treatment groups. Although in this study no bridging of the critically-sized defect was reached, an improved healing was clearly shown. These results identify cell mobilization by G-CSF as a potential treatment option to facilitate the healing of large bone defects in combination with other treatment methods such as bone grafts.

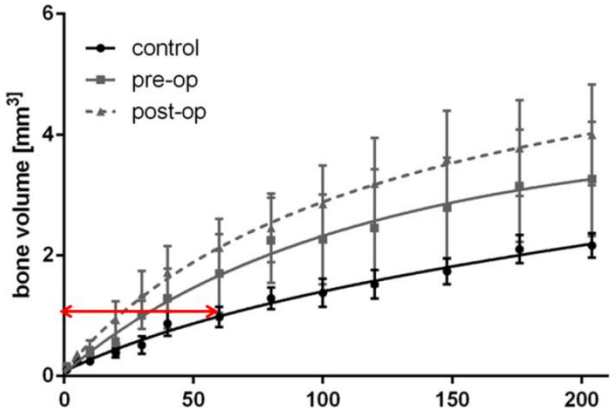


Figure 9.6.5: In vivo micro CT analysis of bone formation. Rats of each group were subjected to micro-CT at several time points over a period of 200 days. As the critical defects were left empty, as suspected no bridging could be observed. Though continuous bone formation was observed for all experimental groups, and when rats received G-CSF an acceleration of bone formation was observed (red arrow).

Pub:
Herrmann M, Zeiter S, Erbeli U, Hildabrand M, Camenisch K, Menzel U, Alini M, Verrier S, Stadelmann V. "Short-term G-CSF Treatment Accelerates Bone Healing", Submitted Journal of Orthopedic Research

Synthesis of a biodegradable scaffold to improve the integration in osteochondral defects (JANUSCAF 2) (completed) (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. Finally, an injectable hyaluronan hydrogel formulation has shown to be fully biocompatible and allow for normal healing of an osteochondral defect (Figure 9.6.6).

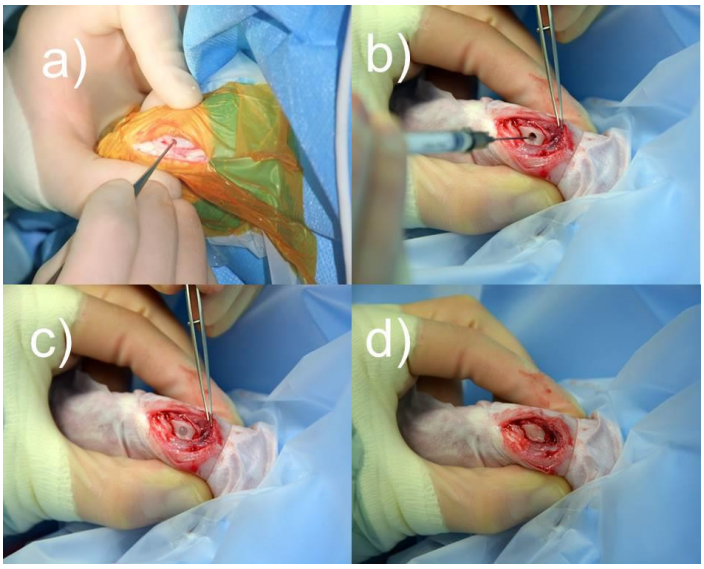


Figure 9.6.6: Intraoperative image illustrating (a) the cleaning the borders of the osteochondral defect from the debris created after drilling; (b) filling of the defect with pre-hydrogel; (c) pre-hydrogel immediately after injection; (d) gel formation one minute after injection.

Pub:
Laschke MW, Kleer S, Scheuer C, Eglin D, Alini M, Menger MD. Pre-cultivation of adipose tissue-derived microvascular fragments in porous scaffolds does not improve their in vivo vascularization potential. Eur Cell Mater. 2015;29:190-201.

Bayon Y, Bohner M, Eglin D, Therin M, Montali A, Procter P, Fisher J, Richards RG. Progressing innovation in biomaterials. From the bench to the bed of patients. J Mater Sci Mater Med. 2015;26(9):5562.

Partners:
- Laschke M (MD, PD Dr), University Saarland, Homburg, Germany
- 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 (Figure 9.6.7).

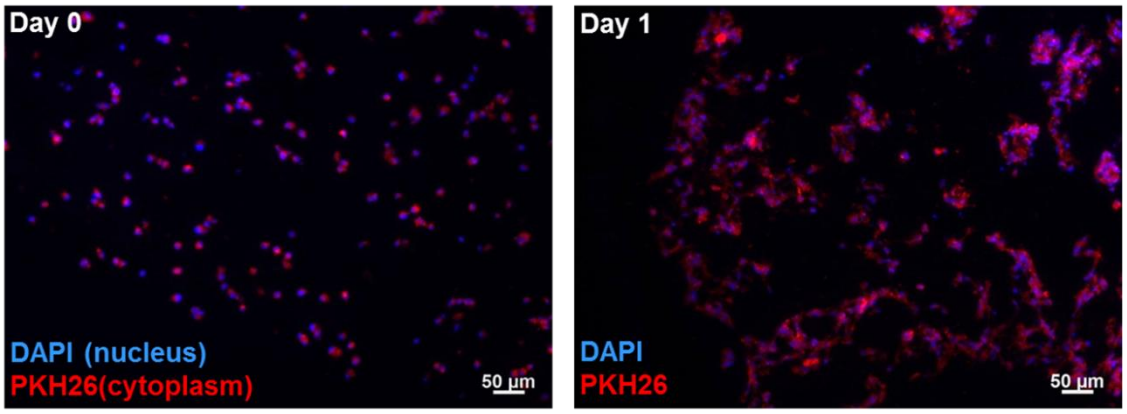


Figure 9.6.7: Fluorescent images of human mesenchymal stromal cells encapsulated in thermoresponsive hydrogel at day 0 and day 1 showing cells spreading.

Pres:
Eglin D. Hard and Soft Materials for Articular Cartilage Repair. 2015 ORS

Rosenzweig DH, Moir J, Gawri R, Eglin D, Weber M, Quellet J, Steffen T, Haglund L. Dynamic loading, matrix maintenance and cell injection therapy of human intervertebral discs cultured in a bioreactor. 2015 ORS.

Seelbach R, Fransen P, Royo M, Albericio F, Alini M, Mata A, Eglin D. Peptide Binding Dendrimer Decorated Injectable Hyaluronan Hydrogels Modulate the Controlled Release of BMP-2 and TGF-ß1. 2015 ESB.

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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. 2015;11:162-72

Seelbach RJ, D'Este M, Alini M, Mata A, Eglin D. Copper catalyst efficiency for the CuAAC synthesis of a poly(N-isopropylacrylamide) conjugated hyaluronan. Clin Hemorheol Microcirc. 2015;60:25-37

Seelbach RJ, Fransen P, Pulido D, D'Este M, Duttenhoefer F, Sauerbier S, Freiman TM, Niemeyer P, Albericio F, Alini M, Royo M, Mata A, Eglin D. Injectable Hyaluronan Hydrogels with Peptide-Binding Dendrimers Modulate the Controlled Release of BMP-2 and TGF-beta1. Macromol Biosci. 2015;2015;15(8):1035-1044

Partners:
- Acute Cartilage Injury Collaborative Research Programs Consortium
- Zenobi-Wong M. (Prof), ETH, Zurich, Switzerland

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.
Multiple annulus repair strategies were developed using sutured polyurethane membranes designed to prevent herniation, scaffolds optimized for cell delivery, fibrin-genipin adhesive and their combination. These repair strategies were evaluated for biomechanical restoration, herniation risk and failure mode using a bovine injury model in collaboration with the Annulus Fibrosus Ruptures Collaborative Research Programs Consortium (Figure 9.6.8). Fibrin-genipin was the simplest annulus fibrosus repair solution evaluated that involved an easily deliverable adhesive that filled irregularly-shaped annular defects and partially restored disc biomechanics with low herniation risk, suggesting further evaluation for disc repair may be warranted.

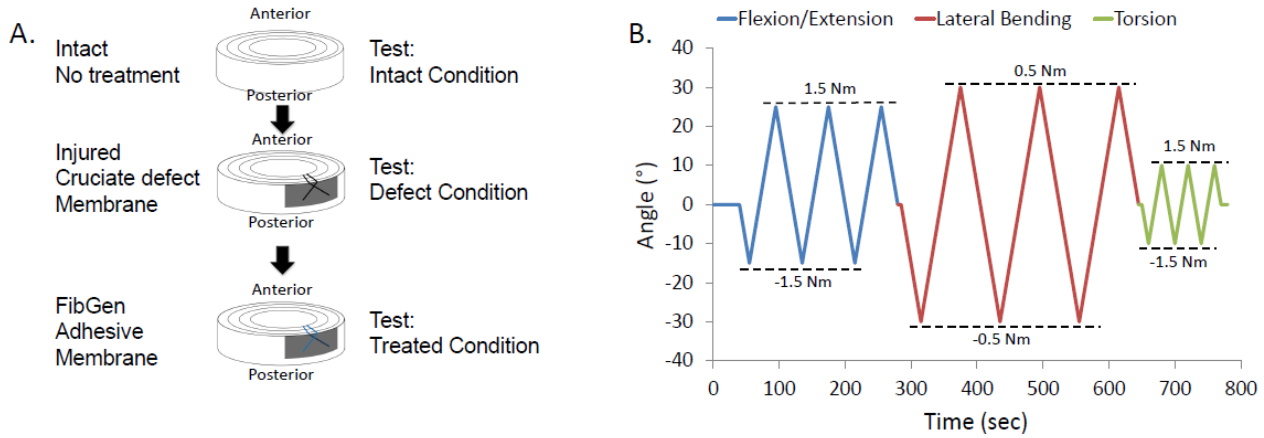

Figure 9.6.8: Example of multi-axial flexibility tests applied to determine biomechanical behaviors of AF repair strategies (from Long *et al.,* Acta Biomater. 2015).

Pres:
Long RG, Litsas DC, Eglin D, Blanquer SB, Grijpma DW, Hecht AC, Iatridis JC.Fibrin Based Annular Sealant Has Low Risk of Herniation in Bending in Bovine IVD Injury Model. 2015 ORS.

Pub:
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. 2015;42:11-19

Partner:
- Annulus Fibrosus Ruptures Collaborative Research Programs Consortium

Bio-adhesive biopolymers for integration of cartilage injury regenerative therapy (started) (D. Eglin)
The therapeutic options for cartilage repair have significantly expanded in the last decades. However, one critical issue that still remains unresolved is the integration to the native cartilage tissue. It is common to every medical intervention aiming at focal cartilage defects repair, and intrinsic to the inherent process repair. This project aims at developing a biomaterial formulation composed of an optimized bio-inspired adhesive biopolymer that could form a strong and resilient adhesive able to simultaneously bind cartilage tissue and form a hydrogel for the delivery of chemoattractant biologics and fill articular cartilage defect (Figure 9.6.9).

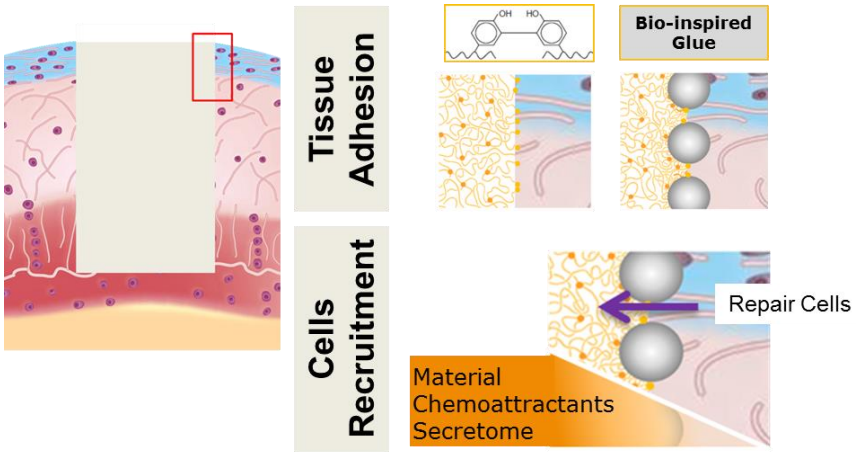

Figure 9.6.9. Scheme of the proposed approach for improved integration.

Pres:
Cavalli E, Loebel C, Eglin D, Zenobi-Wong M. Towards an Extracellular Matrix Based, In-situ Crosslinkable Scaffold for Cartilage Repair. 2015 ORS.

Cavalli E, Loebel C, Eglin D, Zenobi-Wong M. In-situ crosslinkable, extracellular matrix based scaffold for cartilage repair. Eur Cell Mater. 2015;30(Suppl 1):24.

Partner:
- Zenobi-Wong M (Prof), ETH-Zurich

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

Low back pain is a major cause of disability especially for people between 20 and 50 years of age. Current surgical therapies fail to replace the normal disc in facilitating spinal movements and absorbing load. The focus of regenerative medicine is on identifying biomarkers and signaling pathways to improve our understanding about cascades of disc degeneration and allow for the design of specific therapies. We hypothesized that comparing microarray profiles from degenerative and non-degenerative discs will lead to the identification of dysregulated signaling and pathophysiological targets. Microarray data sets were generated from human annulus fibrosus cells and analyzed using IPA ingenuity pathway analysis. Gene expression values were validated by quantitative real time RT-PCR, and respective proteins were identified by immunohistochemistry. Microarray analysis revealed 238 differentially expressed genes in the degenerative annulus fibrosus. Seventeen of the dysregulated molecular markers showed $\log_2$-fold changes greater than ±1.5. Various dysregulated cellular functions, including cell proliferation and inflammatory response, were identified. The most significant canonical pathway induced in degenerative annulus fibrosus was found to be the interferon pathway. This study indicates interferon-alpha signaling pathway activation with interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) and insulin-like growth factor binding protein 3 (IGFBP3) up-regulation, which may affect cellular function in human degenerative disc.

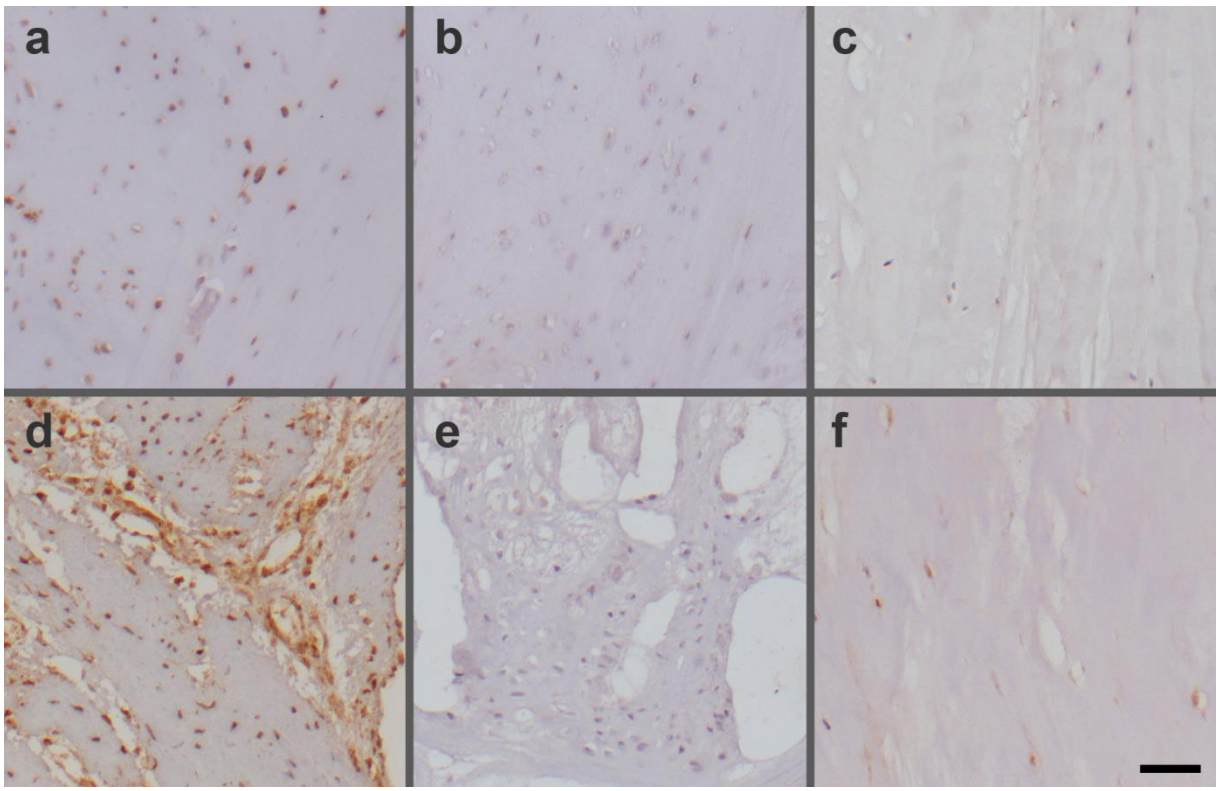

Figure 9.6.10: Immunohistochemical analysis of IGFBP3 (a-c) and IFIT3 (d-f) in sections of human degenerative and non-degenerative annulus fibrosus. Intense immunolabelling for IGFBP3 (a) and IFIT3 (d) was observed in degenerated regions of the annulus fibrosus of a lumbar disc from a 47 year old female with disc degeneration Grade III. Negative control sections for IGFBP3 (b) and IFIT3 (e) did not show any staining. IGFBP3 positive cells were absent (c), while IFIT3 positive cells were observed in the inner annulus fibrosus of a normal disc (f) (degeneration Grade I) from a 13 year old male. Scale bar: 50 µm.

Pres:

Kazezian Z, Gawri R, Haglund L, Ouellet J, Mwale F, O'Gaora P, Pandit A, Alini M, Grad S. Gene Expression Profiling Identifies Interferon Signaling and IGFBP3 as Mediators in Human Intervertebral Disc Degeneration. ORS Annual Meeting 2015, Las Vegas, US.

Kazezian Z, Li Z, Alini M, Grad S, Pandit A. Hyaluronic Acid Down-regulates Interferon Signaling Molecules in Injured Bovine Intervertebral Disc. TERMIS World Congress 2015, Boston, US.

Kazezian Z, Li Z, Sakai D, Alini M, Grad S, Pandit A. Anti-inflammatory Injectable Hyaluronic Acid for Annulus Fibrosus Repair. ORS Philadelphia Spine Research Symposium 2015, Philadelphia, US.

Pub:
Kazezian Z, Gawri R, Haglund L, Ouellet J, Mwale F, Tarrant F, O'Gaora P, Pandit A, Alini M, Grad S. Gene Expression Profiling Identifies Interferon Signaling Molecules and IGFBP3 in Human Degenerative Annulus Fibrosus. Sci Rep 5:15662, 2015.

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 33(3):283-93, 2015.

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

Cell homing in the degenerative intervertebral disc: Characterization of migrating cells and their regenerative potential (DISCREGEN) (ongoing) (S.Grad)
Degeneration of the intervertebral disc (IVD) is a major source of low back pain and a significant burden for public health. Recent research aiming at biological regeneration has focused on cell therapies using mesenchymal stem cells (MSCs) derived from different tissues. However, the ideal cell population has not been identified yet. We have shown in an organ culture model that bone marrow derived MSCs are able to migrate towards the disc in response to tissue damage. Furthermore, we identified candidate chemoattractants involved in MSC homing towards damaged discs. The present project aims to identify the cell subpopulations with superior homing potential and to investigate their regenerative capacity in an induced degenerative disc.
Conditioned medium is obtained from induced degenerative bovine discs. Human MSC subpopulations recruited by the degenerative conditioned medium are identified using cell migration assays and are characterized regarding specific surface marker expression. The effect of homed cell populations on the metabolic activity and gene expression of IVD cells in induced degenerative discs will be determined. This study will provide insight into IVD repair mechanisms in terms of participating stem and progenitor cells and their effects on the IVD. Gained knowledge on the specific cells and factors that induce and contribute to IVD repair will help to develop strategies for attenuation of disc degeneration.

Pub:
Sakai D, Nishimura K, Tanaka M, Nakajima D, Grad S, Alini M, Kawada H, Ando K, Mochida J. Migration of bone marrow-derived cells for endogenous repair in a new tail-looping disc degeneration model in the mouse: a pilot study. Spine J 15(6):1356-65, 2015.

Li Z, Peroglio M, Alini M, Grad S. Potential and limitations of intervertebral disc endogenous repair. Curr Stem Cell Res Ther 10(4):329-38, 2015.

Grad S, Peroglio M, Li Z, Alini M. Endogenous cell homing for intervertebral disk regeneration. J Am Acad Orthop Surg 23(4):264-6, 2015.

Partners:
- Benneker L (PD Dr med), Inselspital Bern, Switzerland
- Sakai D (Prof), Tokai University School of Medicine, Japan

9.7 ARI Collaborative Research Programs

The AO Research Institute Davos (ARI) Annual CRP Meetings

The Annual Collaborative Research (CRP) Meetings were held in Philadelphia, US from September 14-16, 2015. The meetings started with a welcome address from Prof R Geoff Richards, Director of the ARI, followed by progress reports from the CRP research partners, post-presentation discussions, and breakout sessions.

CRP Annulus Fibrosus Rupture (AFR)

The CRP AFR session was moderated by Prof Gunnar Andersson (Rush University, US) and Prof Peter Roughley (Shriners Hospital for Children, CA); both are members of the CRP AFR advisory Committee. The session commenced with an overview presentation by Dr Sibylle Grad (ARI, CH) summarizing the program, goals and the roles of the individual program partners in the final proof of concept (PoC) study. The final aim of the Program is to develop a functional implant for the repair of annulus fibrosus defects by using biomaterials and bioactive agents specifically designed by the consortium partners. This overview was followed by the talk of Prof Dirk Grijpma (University of Twente, NL) who presented an update on the design and optimization of his flexible PTMC scaffolds used to seal AF defects. These scaffolds can be tuned in terms of porosity, pore size and degradation behavior in order to minimize the risk of extrusion. Prof James Iatridis (Mount Sinai School of Medicine, US) then reported on their adhesive biomaterial which is applied as a sealant for restoring disc mechanics and promoting repair of the ruptured annulus. The fibrin-genipin adhesive glue has been shown to promote repair of large annular defects in organ cultures and is currently also being investigated as drug or cell carrier. Subsequently Dr David Eglin (ARI, CH) presented an update on his poly(ester-urethane) membrane used for the closure of the annulus fibrosus defect; in addition, new methods to reinforce the cohesion of the adhesive sealant using polymeric fibers were introduced. This reinforcement significantly improved the adhesion strength of the sealant. Prof Stephen Ferguson (ETH Zurich, CH) then reported on his proof testing of the implant coatings and the biomechanical verification of implant performance. Biological modification of e-spun membranes significantly inhibited cell adhesion, which will be essential to prevent dural adhesion / neural ingrowth. Furthermore, baseline biomechanical tests for ovine lumbar and cervical discs are ongoing in order to establish an optimized procedure for the PoC study analysis. Prof Ferguson's presentation was followed by an update on the delivery system of bioactive hyaluronan microgels for reducing the inflammatory reaction in the ruptured annulus developed by Prof Abhay Pandit (National University of Ireland, IE). In an organ culture annular defect model with induced inflammation, delivery of hyaluronan microgels showed significant anti-inflammatory and anti-catabolic effects. After that Prof Daisuke Sakai (Tokai University, JP) provided a final report on the implantation of the consortium biomaterials in the rat tail annulus defect model. Neither the PTMC scaffold nor the polyurethane membrane showed signs of degradation after up to 16 weeks; while the fibrin-genipin glue was mostly degraded after 16 weeks. Then he spoke on the generation of functional annulus fibrosus cells for the PoC study and for human applications. Specifically, a highly proliferative cell population with improved ability for cell contraction in collagen was described. Dr Stephan Zeiter (ARI, CH) presented the concluding report for the morning session updating the participants on the results obtained with the sheep pilot studies and the progress made with the sheep proof of concept studies in which the developed device is being tested. Two pilot studies were performed, using different combinations of fibrin-genipin glue, PTMC scaffold, and polyurethane closure membrane in lumbar and cervical AF defect models. For the main studies the consortium decided in favor of the cervical disc full thickness AF defect model, due to the larger disc height, better accessibility and better reproducibility of the procedure. While one sheep study that used the adhesive glue injected in the defect is currently ongoing, the decision on the "bioactive" implant will be made according to the results of further pilot and organ culture experiments.

CRP Acute Cartilage Injury (ACI)

In the afternoon CRP ACI session was moderated by Prof Mats Brittberg (Kungsbacka Hospital, SE) and Prof Brian Johnstone (Oregon Health Science University, US) who together with Prof Peter Roughley (Shriners Hospital for Children, CA) are the expert members of the CRP ACI advisory committee.

The session commenced with an overview presentation by Dr Martin Stoddart (ARI, CH) summarizing the program goal to screen various macroporous materials, hydrogels, viral vectors and cell sources for cartilage repair, resulting in a final combination that can be investigated in a cartilage defect proof of concept study (PoC). The final PoC will investigate a woven macroporous polycaprolactone scaffold in various combinations with a hyaluronic acid based hydrogel (ARI) or a self-assembling peptide hydrogel (Barcelona, Spain). A further stimulus from an adeno-associated virus (AAV) overexpressing the cartilage transcription factor Sox9 will also be included.

Prof Farshid Guilak (Duke University, US) and Dr David Eglin (ARI, CH) then provided an update on the hard (woven macroporous polycaprolactone) and soft (hyaluronic acid based hydrogel) and self-assembling peptide hydrogel) materials chosen to be used within the final PoC. These materials were chosen from the large initial pool of combinations due to their promotion of chondrogenesis. Prof Henning Madry (University of Saarland, DE) presented the AAV vector that over expresses Sox9 and showed some of the improved chondrogenesis observed in Göttingen minipig studies focused on genetically modified implants. This was followed by an update on the Yucatan minipig PoC study and the post-mortem examination plans provided by Prof Rob Mauck and Dr George Dodge (University of Pennsylvania, US). The potential to confirm implant retention using arthroscopy was demonstrated. After a short coffee break, each of the methodologies to be implemented in the final PoC study were described in detail. Initially, Prof Henning Madry described the surgical approach, followed by a discussion on arthroscopy led by Dr George Dodge. A description of morphological assessment was then provided by Prof Henning Madry. The final post mortem assessments were explained by Prof Rob Mauck (indentation testing), Prof Farshid Guilak (MRI) and Dr George Dodge (histological evaluation). An active discussion was then moderated by Dr Martin Stoddart to obtain final comments from all present.

Breakout Sessions

The CRP breakout sessions took place in the morning of the second day. These sessions are crucial for the consortium partners and the program deliverables, as they provide the opportunity for face-to-face discussions of the partners with the program committee experts. Since the last phase of the program involves an *in vivo* PoC study with the developed device with both consortia, most of the discussions were related to this topic. Especially interactions among partners and the detailed research plan to meet the milestones for the following year were reviewed in discussion with the committee and finalized at this session.

In the afternoon the partners were invited by Prof Rob Mauck and Dr George Dodge on a tour and poster session at the Translational Research Center and the McKay Laboratory at the University of Pennsylvania. The day was concluded with a visit to the famous Barnes Foundation, which was a particular highlight. This was followed by a dinner with all meeting participants.

Visit Partner Site in New York

On the final day the CRP AFR team travelled to New York to the Mount Sinai Orthopedic Research Laboratories at the Icahn school of Medicine. Prof James Iatridis and his team took them on a fascinating tour through his laboratories and presented a comprehensive overview of their research activities.

Feedback from Participants & Outlook

The feedback on the Annual CRP Meeting 2015 was overwhelmingly positive. This is illustrated by emails received from the participants after the meeting: Prof Farshid Guilak: "Just wanted to thank AO/ARI as well as Rob and George for organizing such a great meeting. Not just for the usual excellent science and teamwork that is a hallmark of this group, but also for the wonderful hospitality and social events with an amazing group of friends." Prof Joost de Bruijn from the ARI Advisory Committee (University of Twente, NL): "As ARI advisor and somewhat of an outsider to your groups, I am impressed with the good scientific discussions, collegiality and friendship that exist within the AFR and ACI teams." Last but not least, Prof James Iatridis: "This is a wonderful, productive, and efficient scientific collaboration and the annual meeting is one of the highlights for my year".

Dr George Dodge updating the ACI consortium

AFR consortium during the breakout session

9.8 Extramural Projects

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:

Barriers and strategies for advanced bone regeneration, Stoddart M, 22.10.2015. DKOU, Germany

Pub:

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. 2015;21(1):115-23

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

Bioceramics for bone repair (BioBone) (Ongoing)
(M. Peroglio, M. Alini), FP7-PEOPLE-2011-ITN (nr. 289958), ARI Funding: EUR 275'000, Period: 01.03.2012 – 28.02.2016

The BIOBONE (Bioceramics for Bone Repair) European funded project aims at offering multidisciplinary training in the field of bioceramics, bioactive glasses and composites for bone repair in collaboration with industries and universities. The 12 PhD students and 3 post-docs are offered training at different 5 academic institutions and 4 industrial partners, all at the cutting-edge of their fields. The training program includes six months placings at partner institutions and the attendance of ten workshops organized by the consortium.

In 2014, ARI organized a three-day workshop on "Cell-material interactions" and hosted two PhD students from Imperial College London who evaluated the behavior of human stem cells on innovative biomaterial formulations for bone fillers. Based on this work, it was possible to select the materials with the highest *in vitro* mineralization potential. Collaborative studies performed with the University of Catalunya led to the identification of optimal roughness ranges for stem cell attachment on bioceramics with laser-patterning (Figure) and nano/microroughness gradients. These surface modifications have the potential to improve the integration of ceramic prosthesis to the host bone. ARI was also involved in the evaluation of the *in vitro* performance of three-dimensional printed bioceramics (Figure 9.8.1).

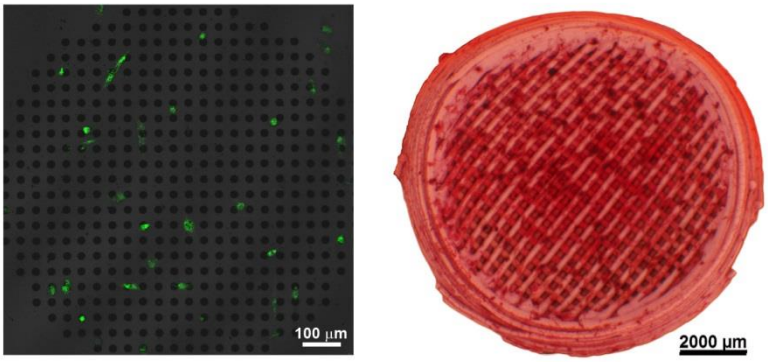

Figure 9.8.1: (left) human mesenchymal stem cell morphology on laser-pattered zirconia following 48 hours of in vitro culture and (right) mineralization of a three-dimensional printed alumina/zirconia scaffold following three weeks of in vitro culture assessed by alizarin red staining.

Pres:

Costa Machado G, García-Tuñón E, Eslava S, Peroglio M, Alini M, Saiz E. Composition and microporosity of calcium phosphate substrates influence the osteogenic differentiation of human mesenchymal stem cells. XXIV International Material Research Congress (MRS), Cancun, Mexico (oral).

Littmann E, Solanki AK, Alini M, Peroglio M, Autefage H, Stevens MM. Interactions of human mesenchymal stem cells with ion substituted bioactive glasses. XIV ECerS Conference, Toledo, Spain (oral).

Littmann E, Autefage H, Solanki AK, Jones JR, Alini M, Peroglio M, Stevens MM. Cobalt-doped bioactive glasses: using hypoxia to Influence mesenchymal stem cell behavior. TERMIS 2015, Boston, MA, USA (poster).

Littmann E, Autefage H, Solanki AK, Jones JR, Alini M, Peroglio M, Stevens MM. Bioactive glasses at the osteochondral interface: directing mesenchymal stem cell behavior for osteochondral tissue repair. TERMIS 2015, Boston, MA, USA (poster).

Stanciuc A, Flamant Q, Biotteau K, Stoddart M, Anglada M, Porporati AA, Kuntz M, Alini M, Peroglio M. Human primary osteoblast behavior on bioinert ceramics with nano- and micro-topography. TERMIS 2015, Boston, MA, USA (poster).

Stanciuc A, Flamant Q, Biotteau K, Stoddart M, Anglada M, Porporati AA, Kuntz M, Alini M, Peroglio M. Combined effect of nano- and microtopography of bioinert ceramics on human primary osteoblast behavior. Euromat 2015, Warsaw, Poland (oral).

Partners:

- Saiz E (PhD), Imperial College of Science, London, UK
- Anglada M (PhD), Universitat Politècnica de Catalunya, Spain
- Chevalier J (PhD),INSA-Lyon, France
- Boccaccini A (PhD), University of Erlangen-Nuremberg, Germany
- De Coninck J (PhD), University of Mons, Belgium
- Kunz M (PhD), CeramTec, Germany
- Fredholm Y (PhD), Noraker, France
- Zhang X (PhD), Ceram, UK
- Souto M (PhD), Keramat, Spain

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 signaling). 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.

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

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 was 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. Next, an alternative crosslinking method using visible light illumination was developed and allowed spatio-temporal control of HA-Tyr hydrogel formation (Figure 9.8.2). The influence of biophysical cues, such as stiffness and gelation mode of HA-Tyr substrates on cell behavior and proliferation was shown in 2D and 3D. Finally, the ability of hMSCs encapsulated in HA-Tyr hydrogels to form bone through hypertrophic cartilage was assessed *in vitro*.

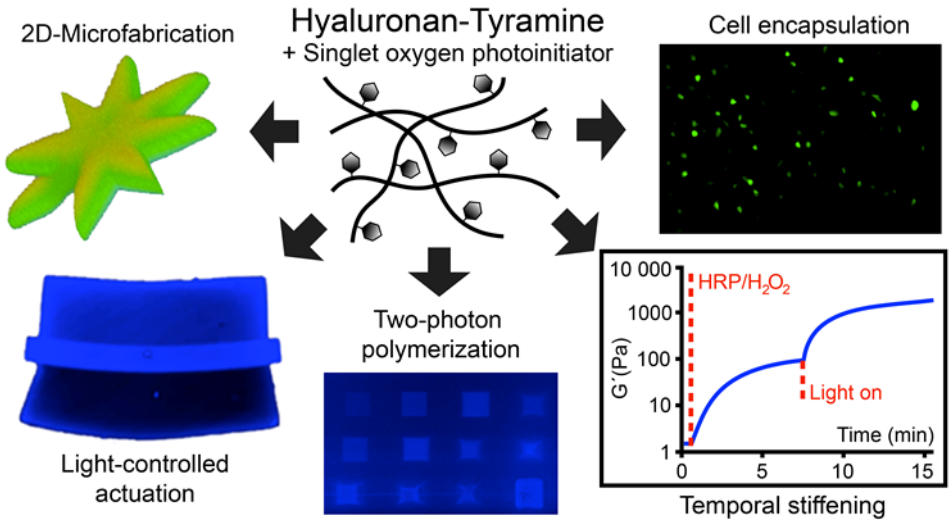

Figure 9.8.2: Microfabrication of photo-crosslinked hyaluronan hydrogels by single- and two-photon tyramine oxidation (from Loebel *et al.* Biomacromolecules 2015).

Pres:
Loebel C, Stauber T, D'Este M, Alini, M, Zenobi-Wong M, Eglin D. Tailoring of DMTMM Conjugated HA-Tyr Allows Precise Control of Cellular Environment. 2015 ESB.

Pub:
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.
Loebel C, Broguiere N, Alini M, Zenobi-Wong M, Eglin D. Microfabrication of Photo-Cross-Linked Hyaluronan Hydrogels by Single- and Two-Photon Tyramine Oxidation. Biomacromolecules 2015;16:2624-2630

Partners:
- Zenobi-Wong M (Prof), ETH, Zurich, Switzerland
- Mauck R (Prof), University of Pennsylvania, USA
- 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: 713'720 Euros, Period: 2013-2017
The goal of this European and Chinese consortium is to apply RP technologies to create custom-made tissue engineered biomaterial constructs 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. The main objective of this project is to apply precise and rapid prototyping technologies for custom-made bone tissue engineering with optimized macro-architecture, osteoinduction via the inclusion of calcium phosphate and a Chinese medicine phytomolecule (icaritin), and bactericidal properties. In this first period, the RAPIDOS project partners have developed a clinical CT imaging process technology workflow for development of anatomically relevant and precise custom-made macro-structured designed scaffolds. The goal of this workflow is to allow the surgeons to design and self-assess patient specific implants taking into account the constraints of the biomaterial and fabrication process.
The optimization of composite formulations; poly(trimethylcarbonate) (PTMC)/calcium phosphate for stereolithography has been performed and already implant scaffolds could be fabricated by stereolithography (Figure 9.8.3). Biodegradable polymeric nanofibers and microspheres loaded with icaritin, a Chinese medicine phytomolecule as potential drug delivery vehicle have been prepared for incorporation into the photo-polymerisable resin formulation for stereolithography. *In vitro* and *in vivo* studies have shown the osteopromotive effect of icaritin loaded into scaffolds.

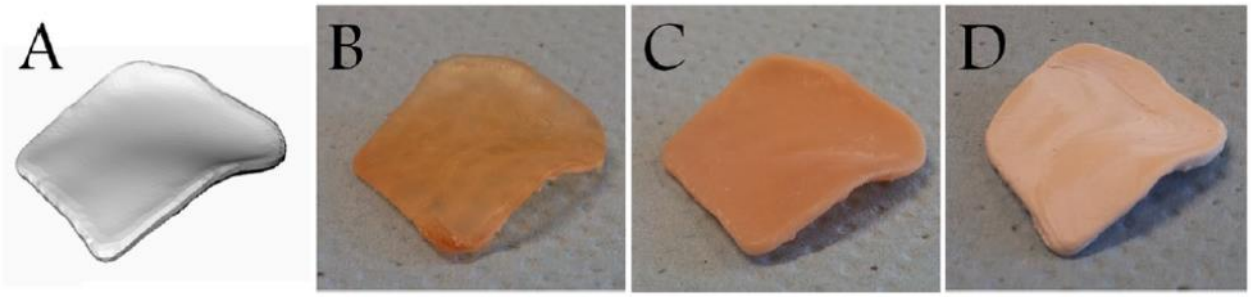

Figure 9.8.3: Patient specific implant model (A) and respective implant structures of PTMC (B), PTMC/Calcium phosphate composite with 10 wt% (C) and 40 wt% inorganic phase (D) (from Geven *et al.* Polym. Adv. Technol. 2015).

Pres:

Varjas V, Geven M, Grijpma DW, Wang X, Peng J, Eglin D, Kamer L. Designing patient specific implants fabricated by stereolithography for orbital wall reconstruction. Eur Cell Mater. 2015;30(Suppl 1):7.

Pub:

Eglin D, Alini M, de Bruijn J, Gautrot J, Grijpma DW, Kamer L, Lai Y, Lu S, Peijs T, Peng J, Tang TT, Wang X, Richards RG, Qin L. The RAPIDOS project—European and Chinese collaborative research on biomaterials. J Orthop Translation. 2015;3:78-84.

Geven MA, Varjas V, Kamer L, Wang X, Peng J, Eglin D, Grijpma DW. Fabrication of patient specific composite orbital floor implants by stereolithography. Polym Adv Technol 2015;26(12):1433-8.

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

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 orthopedics. The project NANOFOROSTEO consists of the development of a composite void filler for osteoporotic bone fractures consisting of:

- Multi-substituted nano-hydroxyapatite, including Si, Zn, Mg and Sr. During 2015 the preparation method of this nano-hydroxyapatite was developed. Compositions with 5% and 10% strontium were selected for further development.
- Hollow microcapsules for the delivery of strontium ranelate, a therapeutic agent used in osteoporosis able to both inhibit bone resorption and stimulate bone formation. In 2015 the delivery of strontium ranelate from the microparticles was studied. Different complex nano-hydroxyapatite content leads to different release profiles (Figure 9.8.4).
- A thermoresponsive hydrogel, for creating an injectable/moldable biomaterial delivering the nano-hydroxyapatite and strontium ranelate –containing particles. Owing to the gel characteristics the composite can fit a bone defect. In 2015 the cohesion of the formulation in physiological conditions and the injectability were assessed.
- Furthermore, high hydrostatic pressure is being used as an innovative method for sterilization. In 2015 a high hydrostatic pressure protocol was developed for the elimination of vegetative and more interestingly spore-forming bacteria.

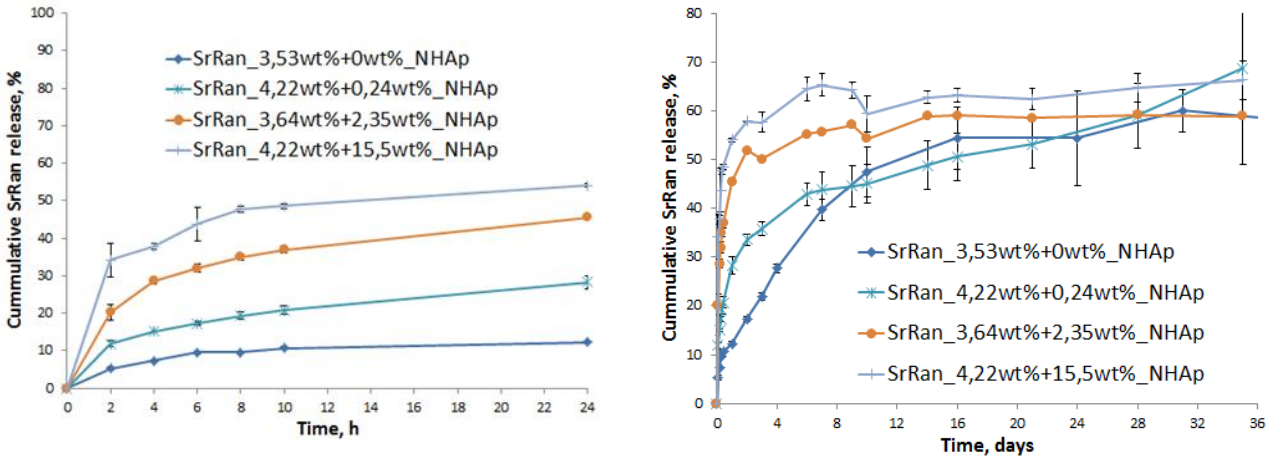

Figure 9.8.4: release of strontium ranelate from microparticles containing increasing amount of nano-hydroxyapatite. Left panel: first 24h of release. Right panel: long term release. It could be observed that for increasing nano-hydroxyapatite content there is a higher burst release.

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:
D' Este M, Eglin D, Alini M, Kyllönen L. Bone Regeneration with Biomaterials and Active Molecules Delivery. Curr Pharm Biotechnol. 2015;16(7):582-605.

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

An in vitro micro-vascular model mimicking the endothelial barrier (Microvasc) (ongoing) (M. Herrmann, S. Verrier), 3R # 139-14, 2 years, CHF 59'250
A functional micro-vasculature is critical for the homeostasis of vascularized tissues. In addition, the identification of mesenchymal stem cells at perivascular sites of the endothelial barrier, suggests that pericytes have a role as multipotent progenitors involved in tissue repair. Pericytes are an important component of the endothelial barrier in capillaries and other microvessels. During the past few years, it has been suggested that perivascular cells may also represent a physiological reservoir of adult mesenchymal stem cells (MSCs). Microfluidic technologies have shown the potential to closely mimic the vascular microenvironment and represent an alternative to animal models. In this project we developed a microfluidic system comprised of a 3D microvascular network embedded in a hydrogel enabling the investigation of perivascular cells in a physiologically relevant context. The microfluidic mold was fabricated out of polycarbonate by using a computerized numerical control machine and comprises 3 different layers creating an empty chamber upon assembly. A removable capillary with an outer diameter of 150 µm placed within the chamber enables creation of a microchannel within the gel upon retraction. Collagen type I (2 mg/ml) gel was injected into the chamber and polymerized at 37°C for 60 min. Microchannels were created by careful retraction of the capillary. Microchannels were successfully created within the collagen gel. Channels were regular with a diameter of 150 µm (Figure 9.8.5 A). GFP-tacked human umbilical vein endothelial cells (HUVECs) were injected into the microchannels and allowed to adhere for 2 hours. The chip can be connected to a reservoir of endothelial growth medium (EGM-2) and perfused using a piezo micro pump. Cell-seeded microchannels were perfused with EGM-2 and observed by time-lapse microscopy for 48 hours. Time lapse microscopy revealed

efficient cell attachment and complete coverage of the surface of the microchannel (Figure 9.8.5 B, C). Good viability of HUVECs was observed over the full duration of the experiment and vessel sprouting occurred 28 h after initiation of perfusion (Figure 9.8.5 D, E). Such a system will enable to further study (i) interactions between perivascular cells (seeded in the hydrogel) and endothelial cells as well as (ii) perivascular and transendothelial cell migration.

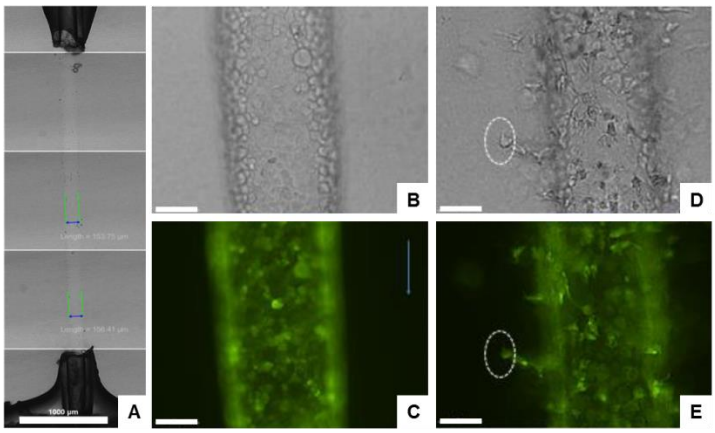

Figure 9.8.5: Microchannel within collagen gel. High magnification images of the microchannel seeded with GFP-HUVECs after 1 h (B, C) or 28 h (D, E) of perfusion. Circles indicate areas of sprouting. Scale bars 1000 µm (A); 100 µm (B-E).

Pub:

Barbe L, Alini M, Verrier S, Herrmann M. In vitro models to mimic the endothelial barrier. ATLA, 2015

Herrmann M, Verrier S, Alini M. Strategies to stimulate mobilization and homing of endogenous stem and progenitor cells for bone tissue engineering. Front Bioeng Biotechnol, 2015

Partner:

- Barbe L (Dr) CSEM, Landquart, Switzerland

Targeting cartilage regeneration in joint and intervertebral disc diseases (TargetCaRe) (started) (M. Alini, S. Grad), EU H2020-MSCA-ITN-2014 Marie Sklodowska-Curie Grant
ARI Funding CHF 530'000, Period: 2015-2019

Mobility, important for well-being, is seriously impaired by chronic low back pain and osteoarthritis in many people due to degeneration of cartilaginous tissue of the intervertebral disc and joint. The aim of the project TargetCaRe (Targeting cartilage regeneration in joint and intervertebral disc diseases) is to achieve regeneration of damaged and degenerated tissues by employing targeting strategies tailored to the pathology and the tissues involved. Towards this aim ARI scientists collaborate with other experts in advanced drug delivery carriers with dedicated targeting tools, state of the art imaging techniques, and joint or disc biology. Regeneration of diseased tissues will be achieved by loading biologically active agents in state-of-the-art nanocarriers. The biologically active agents will stimulate the body's own capacity to regenerate by attracting local stem cells or inhibit degeneration. Delivery and retention will be assessed by advanced in vivo and molecular imaging techniques to monitor distribution of the delivered compounds at the tissue level, as well as detect biological markers of regeneration.
TargetCaRe is a 4-year European Training Network (ETN) project run by a consortium of 12 partner institutions located in 5 different countries. One major objective of the Network is to train 15 young scientists who will complete their PhD thesis in the context of TargetCaRe. The role of the ARI is to provide advanced bioreactor systems for joint and disc in order to evaluate the newly developed nanocarriers with bioactive factors in relevant ex-vivo conditions.

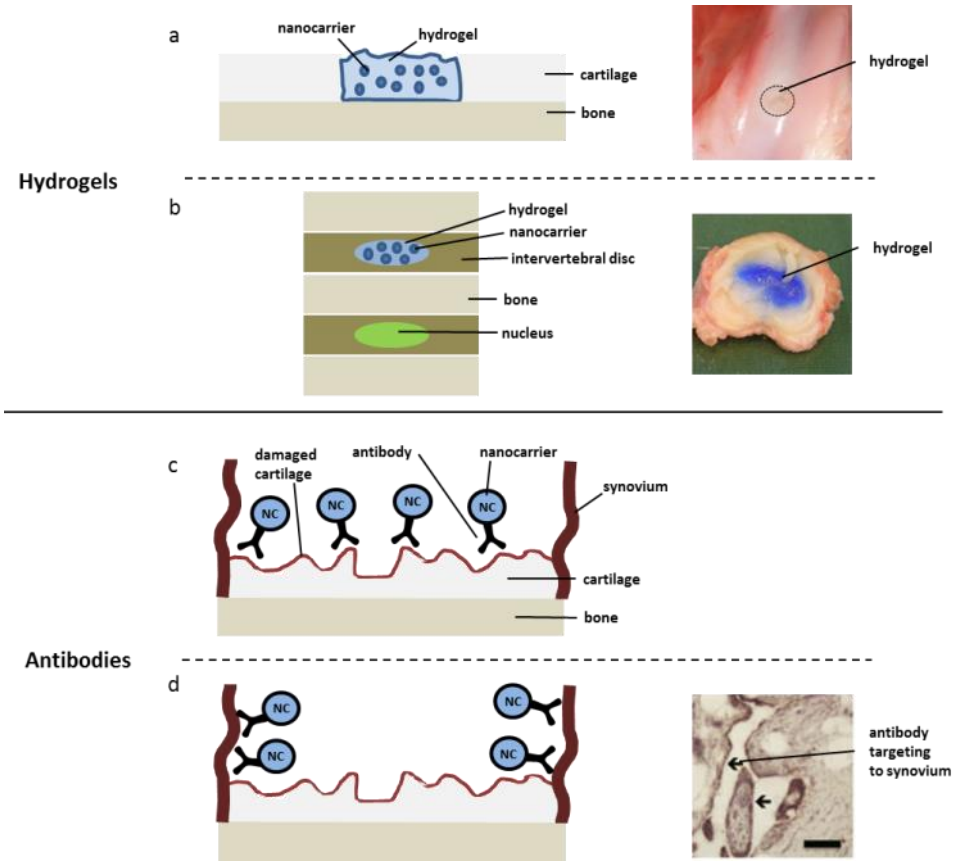

Figure 9.8.6: Targeting and Delivery. Immobilisation of the nanocarriers using hydrogels as local delivery to treat damaged cartilage (a) or damaged intervertebral discs (b). Targeting of the nanocarriers will also be achieved via specific binding to diseased cartilage (c) or synovium (d) using antibodies, hyaluronic acid or homing receptors.

Partners:

- van Osch G (Prof), Erasmus University Medical Centre, NL
- Creemers L (PhD), University Medical Centre Utrecht, NL
- Machluf M (Prof), Technion-Israel Institute of Technology, IL
- Stevens M (Prof), Imperial College London, UK
- de Bari C (Prof), University of Aberdeen, UK
- Howard K (Prof), University of Aarhus, DK
- Heeren R (Prof), Fundamenteel onderzoek der Materie, NL
- Chan A (PhD), Percuros BV, NL
- Caterson B (Prof), Cardiff University, UK
- Yayon A (PhD), ProCore, IL
- Savelsberg R, Omics2Image, NL
- Lether I (MSc), Dutch Arthritis Foundation, NL

Traditional Chinese Medicine compound delivery system for treatment of osteoarthritis (TCM-OA) (started) (M. Alini, S. Grad, M. Stoddart), Swiss-China Joint project (SNF), ARI funding: CHF 250'000, Period: 2015-2018

Owing to continuing demographic and life style changes, degenerative disorders have become an enormous medical and socio-economic challenge. Among them, osteoarthritis (OA) affects millions of patients worldwide; nonetheless, there is currently no effective and standardized treatment available, neither for repair nor for prevention of onset or progression of this disease. Three major problems need to be tackled for a comprehensive approach: defeating inflammation, regenerating damaged cartilage, and restoring the subchondral bone. The present proposal combines the anti-inflammatory and regenerative potential of Traditional Chinese Medicine (TCM) compounds with biomimetic delivery systems to address these challenges. Using a high throughput screening system, individual compounds will be tested for their ability to promote cartilage repair in an inflammatory environment. Concomitantly, compounds will be evaluated with respect to bone healing quality by the Chinese partner. A hyaluronan based release system (for cartilage) and PLGA/TCP-based scaffold (for bone) will be used to deliver the most promising compound(s) in a controlled manner in an established *ex vivo* bioreactor system and finally in an *in vivo* animal model of OA for osteochondral defect repair. The ultimate aim is to develop an effective TCM delivery system for regenerative therapy of early OA.

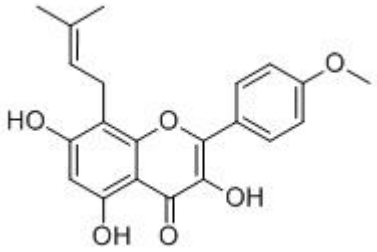

Figure 9.8.7, Left: Two stations of the 4-station *ex vivo* bioreactor system providing shear load by oscillation of the ceramic ball and compression along the cylindrical axis of the construct.
Right: Icaritin is a component of Epimedium flavonoid isolated from *Herba Epimedii*, which enhances osteoblastic differentiation of mesenchymal stem cells (MSCs) while it inhibits adipogenic differentiation of MSCs.

Partners:

- Xinluan Wang X (PhD), Shenzhen University, PR China
- Ling Qin (Prof), The Chinese University of Hong Kong, HK
- Yuxiao Lai (PhD), Shenzhen University, PR China
- Yan Huang (PhD), Shanghai Institute for Biological Sciences, PR China

Development of tools to control microbial biofilms with relevance to clinical drug resistance (BALI, Fintan 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 antimicrobial peptides developed within the BALI consortium. Murine studies have indicated the AMPs may have an effect in preventing infection in a subcutaneous model, which was supported with the results of rabbit studies performed in ARI.

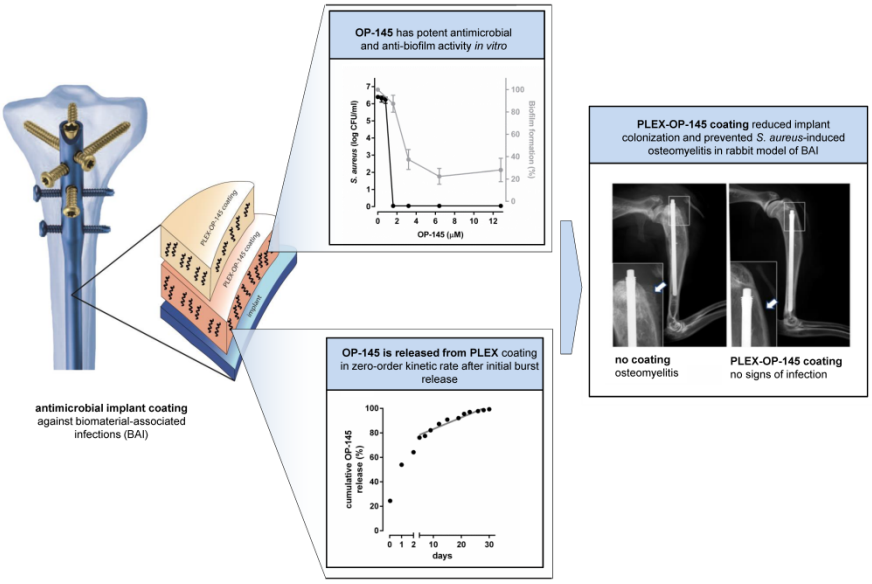

Figure 9.8.8: We incorporated the antimicrobial peptide OP-145 into a Polymer-Lipid Encapsulation MatriX (PLEX)-coating to obtain high peptide levels for prolonged periods at the implant-tissue interphase. We first confirmed that OP-145 was highly effective in killing S. aureus and inhibiting biofilm formation in vitro. OP-145 was released from the PLEX coating in a controlled zero-order kinetic rate after an initial 55%-burst release and displayed bactericidal activity in vitro. In a rabbit intramedullary nail-related infection model, the coated implants displayed an antibacterial effect.

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

Mets makers WJ, Emanuel N, Cohen O, Reichart M, Potapova I, Schmid T, Segal D, Riool M, Kwakman PH, de Boer L, de Breij A, Nibbering PH, Richards RG, Zaat SA, Moriarty TF. A doxycycline-loaded polymer-lipid encapsulation matrix coating for the prevention of implant-related osteomyelitis due to doxycycline-resistant methicillin-resistant Staphylococcus aureus. J Control Release. 2015 Jul 10;209:47-56.

Partners:

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

10 Operations standards and safety

Successful 2015 routine audit of AO Research Institute
On April 8th 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 with only 2 minor 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 SN EN ISO 13485:2012.

ARI is one of the very few academic research organizations to have achieved this certification.

AAALAC international certification of Preclinical facility:
The Preclinical Facility was first accredited by AAALAC International 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 only 2 accredited institutions in Switzerland, and the only accredited academic Research Institute in Switzerland. In November 2015 we had the second AAALAC international site visit and got some great comments on our facility. Therefore the full accreditation will continue for another 3 years.

GLP (Good Laboratory Practice)
ARI applied for GLP certification end of June 2015 and had a first pre discussion in September 2015 at Swissmedic in Berne. The inspection took place November 24-25 and the draft inspection report was received end of December 2015. We filed our statement regarding the proposed corrective actions on January 29th, 2016 and got the confirmation from the Federal Office of Public Health that we will get listed as GLP compliant test facility if we fulfil the 2 conditions of the final inspection report until April 29th. This is a major achievement for our institute after the AAALAC accreditation in 2013.
We are now able to offer contract research services to all interested customers under GLP, especially if they want to get their medical devices approved by the FDA. At the moment FDA has a new guideline in review (General considerations for animal studies for medical devices October 14, 2015) for preclinical studies, which will make GLP and AAALAC virtually mandatory for any submission to FDA. If a study would be done in a non GLP / AAALAC facility, the same standards would have to be proven.

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	Prof, PhD (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	Prof, PhD	01.07.05
Steiner Sandra	PhD	01.01.14
Wahl Sonia	Dipl DH Ökonomin HFP	01.12.95
Zeiter Stephan	Dr med vet, PhD, Dipl. ECLAM (01.02.00 – 12.05.02)	01.06.03

Scientific & Technical Staff

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
Berset Corina	Dr med vet	01.08.15 (AOF)
Bluvol Mauro	Chemielaborant (Eidg FA[1])	01.06.03
Buschbaum Jan	Dr rer med	01.08.15
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
Fahy Niamh	PhD	16.02.15
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
Goudsouzian Nora	BSc	01.02.02
Guillaume Olivier	PhD	01.03.15
Herrmann Marietta	Dr rer nat, PhD	01.11.12
Hofmann-Fliri Ladina	MSc ETH	01.10.09
Kamer Lukas	Dr med, Dr med dent (80%)	21.05.07
Keller-Stoddart Iris	MTL Technician (60%)	21.10.09
Kluge Katharina	Dr med vet (60%)	01.02.12
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
Linardi Flavio	Laborant Fachrichtung Chemie (Eidg FA[1])	01.08.15
Löbel Claudia	PhD Cand, Dr med	01.01.12
Menzel Ursula	PhD, Dipl Biol	01.07.11

[1] Eidg FA = Eidg Fähigkeitsausweis

Monaco Graziana	PhD Cand, MSc	02.11.15
Müller Gregor	Lic phil, Librarian (50%)	17.01.05
Müller Reto	Animal Care (Eidg FA[1])	13.11.01
Nehrbass Dirk	Dr med vet, FTA Pathol + Toxicopathol	01.10.10
Noser Hansrudi	PD Dr ès science EPFL	18.10.04
Peroglio Marianna	PhD	01.03.09
Perren Dominic	Animal Care	01.02.83
Peter Robert	Dipl Laborant HFP	15.09.84
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
Thompson Keith	PhD, BSc (Hons), MSc,	26.05.15
Urzi Federico	PhD Cand, MSc	01.09.15
Vainieri Letizia	PhD Cand, MSc	01.09.15
Varga Peter	PhD	04.08.14
Varjas Viktor	MSc, Software Engineer	01.01.14
Verrier Sophie	Dr *es* Sc, PhD	01.08.04
Vivalda Marisa	Administrative Assistant	01.05.03
Wahl Dieter	Dipl techn Werkzeugspezialist HFP	01.11.93
Windolf Markus	Dip Ing TU	01.11.04
Zderic Ivan	MSc ETH	01.02.11
Ziadlou Reihane	PhD Cand, MSc	01.11.15
Zweifel Erich	European Industrial Engineer EIE	30.11.92

Apprentice

Hassler Andri	Apprentice	04.08.14
Semere Yemane	Apprentice	01.06.15
Spiller Flurin	Apprentice	01.08.15

Internship

Douma Luzia	Internship ETH	01.11.15
Jenni Dominik	Internship ETH	15.06.15
Magnusson Wulcan Judit	Vet Internship	02.11.15
Moser Caroline	Internship ETH	01.08.15
Safari Fatemeh	Internship	15.06.15
Schneider Manuel	Internship	01.04.15

Medical Research Fellows

Acklin Yves	01.08.15
Arand Charlotte	01.10.15
Arruda André	24.02.15
Freitag Linda	12.04.15
Petkov Stoyan	01.09.15

Non Medical Research Fellows

Inzana Jason	08.01.15

Employees left 2015

Scientific & Technical Staff

Abegglen Nadine	Administrative Assistant (40%)	01.09.09 – 31.08.15
Camenisch Karin	MSc (80%)	07.04.08 – 30.09.15
Gardner Oliver	PhD Cand	27.10.11 – 31.12.15
Glarner Markus	Chem Messtechniker (Eidg FA[1])	01.11.97 – 30.04.15
Kyllönen Laura	PhD, MSc	13.02.13 – 28.02.15
Lanker Jann	Animal Care Taker	01.07.15
Vögtli Daniela	MSc	06.01.14 – 08.01.15

Apprentice

Adank Nando	Apprentice	01.08.11 – 31.07.15
Frey Kevin	Apprentice	01.08.11 – 21.02.15

Internship

Barchi Nicola	Internship	21.09.15 – 20.12.15
Canic Marko	Vet Internship	05.01.15 – 28.02.15
Fabian Gieling	Vet Internship	27.07.15 – 07.08.15
Hilbold Erika	Vet Internship	13.07.15 – 04.09.15
Hildebrand Maria	Internship	05.01.15 – 31.08.15
Pettinelli Silvia	Internship	01.02.15 – 31.08.15
Riehl Valentina	Vet Internship	09.03.15 – 01.05.15
Straumann Lukas	Internship	10.06.14 – 26.02.15
Vincek Anna	Vet Internship	18.05.15 – 12.07.15
Vissers Lore	Internship	01.08.15 – 28.08.15

Medical Research Fellows

Cosmelli Nicolo	Research Fellow	15.01.15 – 31.07.15
Dullaert Koen	Research Fellow	01.02.15 – 31.12.15
Fischer Julian	Dr med	04.08.14 – 31.03.15
Gehweiler Domninic	Dr med	01.01.15 – 31.12.15
Günther Christian	med vet	14.04.14 – 30.09.15
Hagen Jennifer	Dr med	01.09.14 – 28.02.15
Lang Gernot	Dr med	14.01.14 – 15.01.15
Russo Fabrizio	Dr med	05.01.14 – 31.01.15
Sommerer Theresia	Research Fellow	01.01.15 – 30.06.15
Voss Jan	Dr med	10.02.14 – 30.01.15
Zhang Ying	Dr med	12.02.15 – 07.07.15

Non Medical Research Fellows

Barcik Jan	07.07.15 – 07.10.15
McCarl Benjamin	01.02.15 – 31.07.15

Guests

Attinger Marc	Biomedical Services (D.Wahl), Inselspital Bern, 23.03.-02.04.2015
Armiento Angela	Musculoskeletal Regeneration (M. Stoddart), 18.5.-18.11.2015
Barandun Ariane	Biomedical Services (D.Wahl), Inselspital, Universität Bern, Switzerland, 12.01.-16.01.2015
Barcik Jan	Biomedical Services (B. Gueorguiev), University of Science and Technology, Krakow, 02.03.2015
Berset Corina Michaela	Preclinical Services Focus Area Surgery (D. Arens), CIBM EPFL, Lausanne, 25.3-02.04.2015
Braun Felix	Musculoskeletal Regeneration (M. Stoddart), Colorado College, Colorado Springs, US, 17.08.-31.12.2015
Bresina Stephen	Biomedical Services (D. Wahl), Scyon Orthopaedics, 23.02.-27.02.15
Buschbaum Jan	Biomedical Services (B. Gueorguiev), Hochschule Kaiserslautern, 09.-10.03.2015
Campana Laura	Musculoskeletal Regeneration (M. D'Este), 11.08.-28.08.2015
Chevalier Yan	Biomedical Services (P. Varga), University Hospital Munich, Dept of Orthopaedic Surgery, 15.07.2015
Coombs Dana	Biomedical Services (D. Wahl), DePuy Synthes, West Chester, 09.11.-11.11.2015
Duttenhöfer Fabian	Biomedical Services (P. Varga) MUG-Chirurgie Uniklinik Freiburg, 02.12.2015
D'Amora Ugo	Musculoskeletal Regeneration (M. D'Este), Institute of Polymers, Naples, Italy, 09.05.-06.11.2015
Emms Craig	Biomedical Services (D. Wahl) DePuy Synthes, Zuchwil, 16.03.2015
Fösel Andreas	Biomedical Services (D. Wahl), Inselspital Bern, 25.03.-02.04.2015
Gieling Fabian	Preclinical Services (D. Arens), Tilto Hannover, Internship, 27.07.-07.08.2015
Gross Christoph	Biomedical Services (I. Zderic), Mathys AG, Bettlach, 19.08.2015
Häberli Janosch	Biomedical Services (I. Zderic), Mathys Medical, Bettlach, 06.08.-21.08.2015
Harris Llinos	Musculoskeletal Infection (F. Moriarty), Swansea UK, 22.06.2015
Henle Philipp	Biomedical Services (I. Zderic), Sonnenhof Bern, 13.08.2015
Huan Yuan	Biomedical Services (B. Gueorguiev), Queensland University of Technology, Brisbane, Australia, 19.10.2015-08.01.2016
Kaczmarek Beata	Musculoskeletal Regeneration (M. Alini), Nicolaus Copernieus University, Tovun, Poland, 01.07.-31.07.2015
Kerstan Dirk	Biomedical Services (D. Wahl), DePuy Synthes, Zuchwil, 12.11.2015
Klammer Georg	Biomedical Services (D.Wahl), Inselspital Universität Bern, Switzerland, 13.01.-14.01.2015
Klos Kajetan	Biomedical Services (D. Wahl), Katholisches Klinikum Mainz, Germany, 05.01.-09.01.2015
Knell Sebastian	Biomedical Services (I. Zedric), Tierspital Zürich, 06.07.-07.07.2015, 27.07.-31.07.2015
Krall Caroline	Preclinical Services (S. Zeiter), Royal (Dick) School of Veterinary, Edinburgh, 17.08.-28.08.2015
Krause Fabian	Biomedical Services (D.Wahl), Inselspital Universität Bern, Switzerland, 12.01.-16.01.2015
Lang Gernot	Musculoskeletal Regeneration (Z. Li), Uniklinik Freiburg, 23.10.-25.10.2015
Ledermann Alex	Biomedical Services (D. Wahl), DePuy Synthes, 27.02.2015
Loca Dagnija	Musculoskeletal Regeneration (M. D'Este) "COST", 09.02.-22.02.2015
Long Rose	Musculoskeletal Regeneration (S. Grad) Collaboration CRP Annulus Fibrosus Repair with Icahn School of Medicine at Mount Sinai, New York, USA, 02.-08.07.2015 / 01.08.2015-31.07.2016
Marugg Fintan	Musculoskeletal Regeneration (S. Grad), SAMD Davos, 02.11.-13.11.2015
McLaren Jane	Musculoskeletal Infection (F. Moriarty), University of Nottingham, UK, 23.06.-26.06.2015
Metsemakers Willem-Jan	Musculoskeletal Infection (F. Moriarty), UZ Leuven, Belgium, 24.08.-28.08.2015 / 06.-09.01.2015 / 09.-13.02.2015

Mihaela Corina	Preclinical Services (D. Arens), 25.03.-27.03.2015
Montes Esther Tejeda	Preclinical Services (S. Zeiter), School of engineering and materials science, London 21.07.-24.07.2015
Nienhaus Michael	Biomedical Services (I. Zedric), University Mainz, 10.11.-11.11.2015
Nagels-Marcon Claire	Biomedical Services (D. Wahl), DePuy/Synthes, 27.02.2015
Neuroni Elia	Preclinical Services (S. Zeiter/U. Lanker), ETH Zürich, 04.05.-22.05.2015
O'Brien Etienne	Preclinical Services (T. Schmid), Royal Veterinary College, Hatfield UK, 27.07.2015
Perez Adrian	Guest Scientist (D. Eglin), Fundacion CIDETEC, Donostia San Sebastian, Spain, 05.05.-26.06.2015
Perminov Ekaterina	Preclinical Services (S. Zeiter) Exchange Student, Western University of Health Science, Ontario 18.05.-28.07.2015
Qin Shi	Musculoskeletal Regeneration (D. Eglin), Soochow University, Suzhou, China, 21.09.-20.12.2015
Reumann Marie	Biomedical Services (B. Gueorguiev), BG Klinik Tübingen, 01.06.-03.06.2015
Ripamonti Ugo	Musculoskeletal Regeneration (M. Alini), University of the Witwatersrand, Johannesburg, South Africa, 23.06.-24.06.2015
Sakai Daisuke	Musculoskeletal Regeneration (S. Grad), Tokai University, Japan, 17.08.2015
Salomon Sophie	Preclinical Services (S. Zeiter), Veterinärmedizinische Universität Wien, 13.07.-14.07.2015
Scherrer Simon	Biomedical Services (I. Zedric), DePuy Synthes, Zuchwil, 03.12.2015
Schmierer Philipp	Biomedical Services (D. Wahl), Tierspital Zürich, 06.07.-07.08.2015
Schmitz Paul	Biomedical Services (B. Gueorguiev), Universität Regensburg, Germany, 23.-24.02.2015 / 03.-04.08.2015
Siegenthaler Urs	Biomedical Services (D. Wahl), EMPA-Prüfung + Kalibrierung, 08.06.-12.06.2015
Szychlinkska Marta	Musculoskeletal Regeneration (M. Stoddart), Guest PhD Student, Collaboration, 16.04.-30.09.2015
Simons Paul	Biomedical Services (D. Wahl), Katholisches Klinikum Mainz, 05.01.-09.01.2015, 16.03.-18.03.2015
Stricker Andrej	Biomedical Services (P. Varga), 02.12.2015
Thöny Sandra	Musculoskeletal Infection (B. Stanic), BGU Murnau, 28.04.-30.04.2015
Torre Daniel	Biomedical Services (D. Wahl / U. Eberli), Scanco Medical AG, Brüttisellen, 16.07.2015
Violin Kalan	Musculoskeletal Regeneration / Tissue Morphology (N. Goudsouzian), Energy and Nuclear Research Institute Sao Paulo, Brazil, 16.02. – 27.02.2015
Von Känel Robin	Musculoskeletal Regeneration (S. Grad) Gymnasium Könzi-Lerbermatt, 20.07.-24.07.2015
Wagner Daniel	Biomedical Services (L. Kamer), Uni-Medizin Mainz, 06.07.-07.07.2015
Walter Pia	Div. Groups, Internship (S.Grad), 13.04.-17.04.2015
Wijayathunga Vithanage	Biomedical Services (D.Wahl/U. Eberli), University of Leeds, 16.07.2015
Wu Yabin	Musculoskeletal Regeneration (M. Stoddart), ETH Zürich, 02.03. – 30.04.15

Guest Presentations at AO Center

On January 7, 2015 Dr Xiao-Hua Qin from Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Austrian Cluster of Tissue Regeneration, Vienna, Austria gave a guest presentation with the title: Laser Processing of Cell-Laden Hydrogel Constructs for Complex Tissue Regeneration.

On February 13, 2015 Prof Giuseppe Calamita from University Aldo Moro, Bari, Italy gave a guest presentation with the title: Aquaporin water channels: Biological features and suggested roles in musculoskeletal fluid homeostasis.

On April 13, 2015 Elena Cambria from École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland gave a guest presentation with the title: Sortase-mediated ligation of epidermal growth factor to the pre-formed PEG hydrogels for *in vitro* tissue models.

On May 21, 2015 Dr Brennan Bailey from École Polytechnique Fédérale de Lausanne (EPFL), Institute of Materials, Lausanne, Switzerland gave a guest presentation with the title: Modification and testing of polymers towards enhanced regeneration of biological tissues and self-healing in composite coatings.

On May 28, 2015 Maria Letizia Vainieri from Imperial College London and Policlinico Umberto I, Rome, Italy gave a guest presentation with the title: New protocol of heterotopic transplant of mesenchymal stem cells.

On June 1, 2015 Dr Marie Reumann from Berufsgenossenschaftliche Unfallklinik, Tübingen, Germany gave a guest presentation with the title: Angiogenesis in bone healing models.

On June 1, 2015 Dr Thomas Freude from Berufsgenossenschaftliche Unfallklinik, Tübingen, Germany gave a guest presentation with the title: Impaired bone healing in patients with type 2 diabetes mellitus.

On June 22, 2015 Prof Ugo Ripamonti from Bone Research Laboratory, Department of Oral Medicine and Periodontology, School of Oral Health Sciences, University of the Witwatersrand, Johannesburg, South Africa gave a guest presentation with the title: Re-evaluating the induction of bone formation in primates: hTGF-B3 initiates bone induction by up-regulating endogenous BMP's and is blocked by hNoggin.

On July 1, 2015 Prof Ilse Jonkers from Human Movement Biomechanics Research Group, Department of Kinesiology, Katholieke Universiteit, Leuven, Belgium gave a guest presentation with the title: Understanding the role of local cartilage loading: Optimization of treatment methods for cartilage regeneration in the tibo-femoral joint.

On July 2, 2015 Dr Sooraj H. Nandyala from 3B's Lab, University of Minho, Portugal gave a guest presentation with the title: Lanthanide glass reinforced hydroxyapatite composite materials for antibacterial and bone applications.

On July 3, 2015 Junichi Taniguchi from Department of Chemistry, Graduate School of Science, Kyoto University Kitashirakawa-Oiwakecho, Sakyo-Ku, Kyoto, Japan gave a guest presentation with the title: Synthetic DNA-Binding Epigenetic Switches for Cell Fate Control.

On July 23, 2015 Dr Karin Wuertz-Kozak from Institute for Biomechanics, Department of Health Science & Technology (D-HEST), ETH Zurich, Switzerland gave a guest presentation with the title: From molecular pathophysiology to regenerative medicine: Is this possible for degenerative disc disease?

On July 24, 2015 Dr Sabrina Jahn from Soft Matter and Interfaces, Weizmann Institute of Science, Israel gave a guest presentation with the title: The effect of glucosamine sulfate on surface interactions and lubrication by hydrogenated soy phospatidylcholine (HSPC) liposomes.

On August 4, 2015 Prof Luigi Ambrosio from Institute of Polymers, Composites & Biomaterials and Department of Chemical Sciences & Materials Technology, National Research Council of Italy,

Rome, Italy gave a guest presentation with the title: Advanced biomaterials for skeletal tissue repair/regeneration.

On August 13, 2015 Tanja Hausherr from École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland gave a guest presentation with the title: In vivo loading combined with cell therapy affects the bone volume density in a tissue-engineering scaffold.

On September 29, 2015 Prof Philipp J. Thurner from Institute for Lightweight Design and Structural Biomechanics, Vienna University of Technology, Vienna, Austria gave a guest presentation with the title: Microstructural failure of bone tissue.

On October 20, 2015 Dr M. Hankanson from CSEM Landquart, Switzerland gave a guest presentation with the title: Inartis Network – Promoting interdisciplinary life science to go to innovation.

On October 20, 2015 Dr H. Chai-Gao from CSEM Landquart, Switzerland gave a guest presentation with the title: Optodex – linking value to surface.

On November 2, 2015 Prof Dr Hans-Joachim Wilke from University of Ulm, Germany gave a guest presentation with the title: Ideas and limitations for nucleus pulposus replacement and annulus fibrosus repair.

On December 2, 2015 Dr Andrea Vilardi from Eurac Institut für Angewandte Fernerkundung, Bolzano, Italy gave a guest presentation with the title: Extreme Environment Simulator.

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

Filed 2015

Kit for assembling a medical device provided with data acquisition means
- First Application: PCT/CH2015/000062 filed 2015-04-29
- Case:
- Developer / Inventors: M. Windolf

Bone plate
- First Application: PCT/ CH2015/000117 filed 2015-08-10
- Case:
- Developer / Inventors: M. Windolf, D. Epari, M. Schütz, T. Pohlemann, C. Nötzli

Surgical power drill including a measuring unit suitable for bone screw length determination
- First Application: PCT/CH2015/000168 filed 2015-11-17
- Case:
- Developer / Inventors: M. Windolf, M. Schütz

13 Publications & Presentations

13.1 Peer reviewed publications

published papers (epub & on paper)

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Ozonated saline shows activity against planktonic and biofilm growing Staphylococcus aureus in vitro: a potential irrigant for infected wounds.
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Arens D, Wilke M, Calabro L, Hackl S, Zeiter S, Zderic I, Richards RG, Moriarty TF.
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13.2 Paper published in conference proceedings

Arlt S, Noser H, Heinecke M, Marintschev I, Hofmann G, Mendel T.
Hat die kongenitale Hüftgelenksdysplasie Einfluss auf die Größe des infraazetabulären Korridors im Hinblick auf die Versorgung von Azetabulumfrakturen − eine 3d-radiomorphometrische Analyse.
2015 DKOU (oral)

Bara J, Nehrbass D, Eglin D, Anton M, Daculsi G, Alini M, Stoddart M.
Doxycycline inducible adenoviral delivery of Bmp-2 with mesenchymal stem cells and a calcium phosphate ceramic for the repair of critically-sized bone defects in a rat model.
2015 ORS (poster)

Bäumlein M, Hanke A, Gueorguiev B, Glaab R, Nerlich M, Ryf C, Rillmann P, Loibl M.
Posttraumatische Arthrose nach intraartikulären Tibiakopffrakturen bei Skifahrern.
2015 DKOU (oral)

Boudrieau RJ, Sprecher CM, Suter T, Milz S.
Corrosion of cast stainless steel plates and the possible association to with peri-implant osteosarcoma.
2015 oneAO (poster)

Cavalli E, Loebel C, Eglin D, Zenobi-Wong M.
Towards an extracellular matrix based, in-situ crosslinkable scaffold for cartilage repair.
2015 ORS (poster)

Cruz MA, Illien-Junger S, Eglin D, Hecht AC, Iatridis JC.
Structural, chemical and cellular enhancements fo improve adhesive and bulk properties of fibrin-genipin in sealing the annulus fibrosus.
2015 ORS (poster)

Eberli U, Widmer D, Varga P, Schwyn R, Brianza S, Gueorguiev B, Zeiter S, Fürst A.
Biomechanical and numerical investigation on the applicability of a pin-sleeve system for external fixation of equine distal limb fractures.
2015 ESB (BioMech) (oral)

Eglin D.
Hard and soft materials for articular cartilage repair.
2015 ORS (oral)

Erichsen C, Morgenstern M, Moriarty TF, Hungerer S, Militz M, Bühren V.
Implantat Infektionen mit Staphylokokken - Korrelation zwischen bakteriellen Eigenschaften und klinischem Outcome.
2015 VSOU (oral)

Erichsen C, Morgenstern M, Post V, Hackl S, Moriarty TF, Hungerer S, Bühren V, Richards RG, Kates SL.
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2015 DKOU (oral)

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.
2015 BOTA 2015 (oral)

Filipov O, Gueorguiev B.
Biplane double–supported screw fixation extremely reduces the risk of fixation failure in femoral neck fractures. Clinical outcomes in 207 patients.
2015 BOTA (oral)

Filipov O, Gueorguiev B.
Biplane double–supported screw fixation extremely reduces the risk of fixation failure in femoral neck fractures. Clinical outcomes in 207 patients.
2015 FFN (oral)

Filipov O, Gueorguiev B.
Biplane double–supported screw fixation extremely reduces the risk of fixation failure in femoral neck fractures. Clinical outcomes in 207 patients.
2015 SICOT / OWC (e-poster + oral)

Filipov O, Gueorguiev B.
Filipov's method of biplane double–supported screw fixation extremely reduces the risk of fixation failure in femoral neck fractures to 2.4%.
2015 WCORT (oral)

Freitag L, Herrmann M, Hildebrand M, Stadelmann VA, Zeiter S.
Comparison of blood sampled from the sublingual and the tail vein in F344 rats.
2015 AAALAC / ESLAV / ECLAM (poster)

Grechenig S, Nerlich A, Dreu M, Dolcet C, Gueorguiev B, Berner A, Loibl M, Lidder S.
Denervation of the posterior interosseous nerve through a volar approach: A new technique with anatomical considerations.
2015 DKOU (poster)

Grechenig S, Gänsslen A, Nerlich A, Gueorguiev B, Wahl D, Müller M, Schmitz P.
Pmma-augmented si screw: A biomechanical analysis of stiffness and pull-out force in a matched paired human cadaver model.
2015 DKOU (poster)

Grüneweller N, Raschke MJ, Widmer D, Zderic I, Wähnert D, Gueorguiev B, Richards RG, Fuchs T, Windolf M.
Biomechanical evaluation of augmented versus non-augmented sacroiliac screws in a newly developed hemi-pelvis model.
2015 EFORT (poster).

Gueorguiev B, Hagen JE, Richards RG, Lenz M, Simons P, Klos K.
Utilizing weightbearing CT to evaluate syndesmotic reconstructions.
2015 SICOT / OWC (oral)

Gueorguiev B, Hagen JE, Sands AK, Richards RG, Swords M, Rammelt S.
Hindfoot stability following medial talar facet excision.
2015 SICOT / OWC (oral)

Gueorguiev B, Triana M, Helfen T, Zderic I, Agarwal Y, Krause F, Richards RG.
The novel surgical LagLoc technique for locking plate systems. Biomechanical investigation and first clinical applications.
2015 SICOT / OWC (oral)

Gueorguiev B, Stoffel K, Zderic I, Sommer C, Eberli U, Mueller D, Oswald M.
The new femoral neck system for femoral neck fracture fixation. Biomechanical performance in comparison to diverse standard implants for osteosynthesis.
2015 SICOT / OWC (oral)

Hagen J, Gueorguiev B, Richards RG, Simons P, Klos K.
Direct comparison of syndesmotic reconstructive techniques using weightbearing CT.
2015 OTA (oral)

Hanke A, Gueorguiev B, Gehmert S, Glaab R, Frölich T, Kuttner H, Nerlich N, Ryf C, Rillmann P, Bäumlein M, Loibl M.
Klinisch-radiologischer Langzeitverlauf nach intraartikulärer Tibiakopffraktur bei Skifahrern. 2015 GOTS (poster & oral: 3rd prize Young Investigator Award)

Herrmann M, Bara JJ, Jalowiec JM, Menzel U, Sprecher C, Scherberich A, Alini M, Verrier S.
The role of pericytes in bone tissue engineering - an in vitro comparison of pericytes from different human tissues.
2015 ISBR (oral)

Herrmann M, Bara JJ, Menzel U, Jalowiec J, Osinga R, Scherberich A, Alini M, Verrier S.
Pericytes support bone regeneration by complementary mechanisms - an in vitro investigation into the angiogenic and osteogenic properties of pericytes derived from multiple tissue sources.
2015 ORS (poster)

Hofmann-Fliri L, Götzen M, Zeiter S, Arens D, Richards RG, Windolf M, Blauth M.
Influence of implant augmentation with bone cement on adjacent subchondral bone and cartilage.
2015 WCO-IOF-ESCEO (poster)

Inzana J, Münch C, Varga P, Hofmann-Fliri L, Südkamp N, Windolf M.
Variable biomechanical benefits of screw augmentation in proximal humerus fractures.
2015 EORS (oral)

Inzana J, Münch C, Hofmann-Fliri L, Varga P, Südkamp NP, Windolf M.
Enhancing fixation of osteoporotic proximal humerus fractures: insights from a systematic evaluation of PHILOS screw augmentation.
2015 Whitaker International Scholars workshop (poster)

Jalowiec J, Herrmann M, Menzel U, D'Este M, Bara JJ, Alini M, Verrier S.
Platelet rich plasma gel as an autologous delivery system of growth factors and cells.
2015 ORS (poster)

Jalowiec J, Menzel U, D'Este M, Bara JJ, Alini M, Verrier S, Herrmann M.
The influence of platelet concentration on mechanical and biological properties of platelet rich plasma hydrogels.
2015 DKOU (oral)

Kazezian Z, Gawri R, Haglund L, Ouellet J, Mwale F, O'Gaora P, Pandit A, Alini M, Grad S.
Gene expression profiling identifies interferon signaling and IGFBP3 as mediators in human intervertebral disc degeneration.
2015 ORS (poster)

Klos K, Lenz M, Gueorguiev B, Hagen J, Richards RG, Simons.
Untersuchung der Bewegung in der Syndesmose in Abhängigkeit von der Integrität der einzelnen Anteile. Eine Biomechanische Kadaverstudie.
2015 VSOU (oral)

Lang G, Li Z, Chen X, Sacks H, Weber F, Yayon A, Alini M, Grad S.
Biomimetischer Nucleus-pulposus-Ersatz zur Behandlung der degenerativen Bandscheibenerkrankung.
2015 DKOU (oral)

Lang S, Brockhoff G, Gueorguiev B, Huber M, Zellner J, Angele P, Prantl L, Nerlich M, Gehmert S, Loibl M.
Modifikation der Zentrifugation zur Reduktion der Leukozytenzahl in PRP und die Auswirkung auf die Proliferation von autologen mesenchymalen Stammzellen.
2015 GOTS (poster & oral) First prize Young Investigator Award

Lang S, Gueorguiev B, Zellner J, Huber G, Angele P, Nerlich M, Gehmert S, Loibl M.
Modifikation der Zentrifugation zur Reduktion der Leukozytenzahl in platelet-rich Plasma.
2015 DKOU (poster)

Lenz M, Stoffel K, Gueorguiev B, Kielstein H, Hofmann GO.
Anterolaterale Doppelplatte oder verriegelbarer Plattenaufsatz bei periprosthetischen Femurfrakturen Typ Vancouver B1? – eine biomechanische Studie.
2015 DKOU (oral)

Loebel C, Stauber T, D'Este M, Alini, M, Zenobi-Wong M, Eglin D.
Tailoring of DMTMM conjugated HA-Tyr allows precise control of cellular environment.
2015 ESB (BioMat) (oral)

Loibl M, Korsun M, Reiss J, Gueorguiev B, Grechenig S, Baumann F, Nerlich M, Neumann C.
Perkutane Stabilisierung von Frakturen der Brust- und Lendenwirbelsäule mit Hilfe eines minimal-invasiven Schanz-Schrauben-Systems: Klinische und radiologische Ergebnisse nach einem Jahr.
2015 DKOU (oral)

Loibl M, Lang S, Brockhoff G, Gueorguiev B, Herrmann M, Nerlich M, Prantl L, Gehmert S.
Platelet-rich-plasma-induced expression alteration of transcription factors in adipose-tissue derived mesenchymal stem cells.
2015 DKOU (oral)

Long RG, Litsas DC, Eglin D, Blanquer SB, Grijpma DW, Hecht AC, Iatridis JC.
Fibrin based annular sealant has low risk of herniation in bending in bovine IVD injury model.
2015 ORS (poster)

Metsemakers WJ, Emanuel N, Cohen O, Reichert M, Schmid T, Richards RG, Segal D, Moriarty TF.
Prevention of implant-related osteomyelitis using a doxycycline coating in a humeral non-fracture rabbit model.
2015 EFORT (poster)

Peroglio M, Caprez S, Benneker LM, Alini M, Grad S.
Stem cells contribution to the restoration of degenerated intervertebral discs depends on their degenerative state.
2015 ORS (oral)

Peroglio M, Caprez S, Benneker LM, Alini M, Grad S.
Stem cell effect is influenced by the degenerative state of intervertebral discs.
2015 DKOU (oral)

Post V, Morgenstern M, Richards RG, Moriarty TF.
Characterisation of nasal methicillin-resistant staphylococcus aureus from an international cohort of orthopaedic surgeons.
2015 EFORT (oral)

Poxleitner PJ, Iliev K, Nelson K, Ziebart T, Stoddart M, Schmelzeisen R, Voss P.
Palatinaler Defekt verursacht Sinusitis bei Zoledronatbehandelten Schafen.
2015 DGMKG (oral)

Riede G, Schmölz W, Gueorguiev B, Stigler RG, Rasse M.
Biomechanical in vitro evaluation after reconstruction of an ovine mandibular continuity defect with one vs. two plates.
2015 DGfB (oral)

Rosenzweig DH, Moir J, Gawri R, Eglin D, Weber M, Quellet J, Steffen T, Haglund L.
Dynamic loading, matrix maintenance and cell injection therapy of human intervertebral discs cultured in a bioreactor.
2015 ORS (poster)

Sabaté Bresco M, Kluge K, Ziegler M, Nowicki B, Richards RG, O'Mahoney L, Moriarty TF.
The role of biomechanical stability on Staphylococcus epidermidis osteomyelitis in a murine fracture model.
2015 EFORT (oral)

Sabaté Bresco M, Kluge K, Ziegler M, Richards RG, Moriarty TF, O'Mahoney L.
Immune response during bone healing in a murine fracture model with osteomyelitis: role of biomechanical stability.
2015 WIRM (oral & poster)

Sands A, White C, Blankstein M, Zderic I, Ernst M, Windolf M, Richards RG, Gueorguiev B.
Assessment of ankle and hindfoot stability and joint pressures using a human cadaveric model of a large lateral talar process excision. A biomechanical study.
2015 EFORT (oral)

Schmid T, Keller I, ter Boo GA, Zeiter S.
Elevated C reactive protein level – an indicator of infection in rabbits in a contaminated fracture model.
2015 ACVS (oral)

Schmidutz F, Müller PE, Agarwal Y, Richards RG, Gueorguiev B, Sprecher CM.
Sind Finite Elemente Analysen geeignet um Knochenumbauprozesse in der Endoprothetik vorherzusagen? Eine FEA und Explantate-Studie an zementfreien Oberflächenersatzprothesen.
2015 VSOU (oral)

Schmidutz F, Helfen T, Eberli U, Müller P, Richards RG, Gueorguiev B, Sprecher C.
Der osteoporotische Knochensubstanzverlust führen am proximalen Humerus zu einer deutlichen Abnahme der kortikalen Dicke und Zunahme der Porosität: Eine Analyse der mikrostrukturellen Umbauprozesse.
2015 DKOU (poster)

Schmitz P, Grechenig S, Gueorguiev B, Heiss P, Müller M, Nerlich M.
A new cementless hip stem to achieve immediate stability after THA in geriatric patients. A biomechanical comparison of a locking screw hip stem (Scyon Orthopaedics AG) and a cemented Müller-straight stem.
2015 DKOU (oral)

Schroeder G, Kepler C, Grad S, Alini M, Markova D, Koerner J, Rajasekaran S, Chapman J, Vaccaro A.
A cell based assay on the effect of Riluzole on bone formation.
2015 ORS PSRS (poster)

Schwinn J, Hofmann-Fliri L, Gueorguiev B, Schwyn R, Kielstein H, Hofmann GO, Lenz M.
Biomechanische Untersuchungen zur Insertionstiefe der Schenkelhalsklinge und deren Auswirkungen auf die Fixationsstabilität.
2015 DKOU (poster)

Seelbach R, Fransen P, Royo M, Albericio F, Alini M, Mata A, Eglin D.
Peptide binding dendrimer decorated injectable hyaluronan hydrogels modulate the controlled release of BMP-2 and TGF-ß1.
2015 ESB (BioMat) (oral)Simons P, Klos K, Gueorguiev B, Wahl D, Lenz M, Knobe M, Richards RG, Hagen JE.
Beurteilung des stabilisierenden Effekts der einzelnen Anteile der Syndesmose.
2015 DAF (oral)

Sprecher CM, Haasters F, Ockert B, Hertel RW, Südkamp N, Richards RG, Braunstein V.
Verbesserung der Inklinations- und Versionskorrektur bei Implantation einer Schulter-Endoprothese durch Verwendung eines patientenspezifischen Zielgerätes.
2015 DKOU (oral)

Sprecher C, Schmidutz F, Helfen T, Gueorguiev B, Richards RG, Milz S.
Korrelieren DXA Messungen am distalen Radius mit der Knochendichte im proximalen Humerus?
2015 DKOU (poster)

Sprecher C, Schmidutz F, Schiuma D, Windolf M, Richards RG, Popp AW.
Die hochauflösende, quantitative Computertomographie unterschätzt die kortikale Dicke und Porosität an der distalen Tibia gegenüber der Histomorphometrie.
2015 DKOU (poster)

Stoffel K, Zderic I, Sommer C, Eberli U, Müller D, Oswald M, Gueorguiev B.
Biomechanical evaluation of femoral neck fracture fixation with the new femoral neck system compared to diverse standard implants for osteosynthesis.
2015 ESB (BioMech) (poster)

Stoffel K, Zderic I, Sommer C, Eberli U, Mueller D, Oswald M, Gueorguiev B.
Biomechanische Beurteilung der Fixation von Schenkelhalsfrakturen mit dem neuen Femoral Neck System im Vergleich zu drei durchbohrten Schrauben, DHS-Klinge und DHS mit Antirotationsschraube.
2015 DKOU (poster)

ter Boo GA, Grijpma DW, Richards RG, Moriarty TF, Eglin D.
An antibiotic delivery system based upon poly(trimethylene carbonate) loaded with a hydrophobic gentamicin.
2015 EFORT (poster)

Triana M, Helfen T, Zderic I, Agarwal Y, Krause F, Richards RG, Gueorguiev B.
LagLoc: A new surgical technique for locking plate systems.
2015 SCCOT (poster)

Varga P, Schwiedrzik J, Zysset P, Gueorguiev B, Blauth M, Windolf M.
How to augment the osteoporotic proximal femur? – Ask the bone.
2015 ESB (BioMech) (oral)

Varga P, Schwiedrzik J, Zysset PK, Sprecher C, Gueorguiev B, Blauth M, Windolf M.
Optimierung der Knochencement-basierten prophylaktischen Augmentation des proximalen Femurs anhand von FEA.
2015 DKOU (poster)

Venkatesan JK, Rey-Rico A, Gardner O, Schmitt G, Eglin D, Alini M, Stoddart M, Cucchiarini .
Effects of rAAV Sox9 gene transfer upon the chondrogenic differentiation of Hmscs seeded in polyurethane scaffolds.
2015 ORS (poster)

Voss JO, Löbel C, Duttenhöfer F, Alini M, Stoddart M.
Effect of IL-1β short-term stimulation on human MSCs in co-culture with MG63-GFP cells.
2015 DGMKG (oral)

Wagner D, Sawaguchi T, Kamer L, Noser H, Rommens PM.
Virtuelle trans-sakrale Implantatpositionierung im Becken - kritische Verhältnisse in S1, hingegen immer möglich in S2.
2015 DKOU (oral)

Zeiter S.
The team approach to implementing the 3Rs.
2015 ORS (oral)

13.3 Books and bookchapters

Calabro L, Richards RG, Moriarty TF.
Preclinical Models of Infection in Bone and Joint Surgery.
in: Zimmerli W (Ed.)
Bone and Joint Infections: From Microbiology to Diagnostics and Treatment
Wiley Blackwell; 2015. p. 39-54.

Gardner OF, Alini M, Stoddart MJ.
Mesenchymal Stem Cells Derived from Human Bone Marrow.
in: Doran PM (Ed.)
Cartilage Tissue Engineering. Methods and Protocols.
Methods in Molecular Biology. Springer Protocols. 1340.
Springer / Humana Press; 2015. p. 41-52.

Stoddart MJ, Alini M.
Biocomposites used in Orthopedic Applications: Trends in Biocompatibility Assays
in: Antoniac IV (Ed.).
Handbook of Bioceramics and Biocomposites. Living Reference Work, Continously updated Edition.
Springer International Publishing; 2015. p. 1-27 (online).

13.4 Abstracts published in Journals

Bara JJ, Herrmann M, Menzel U, Benneker L, Alini M, Stoddart M.
Culture and characterisation of naive bone marrow-derived cells encapsulated in fibrin.
Tissue Eng Part A. 2015;21(S1):S338 (TERMIS / poster)

Cavalli E, Loebel C, Eglin D, Zenobi-Wong M.
In-situ crosslinkable, extracellular matrix based scaffold for cartilage repair.
Eur Cell Mater. 2015;30(Suppl 1):24 (SSB+RM / oral)

Emanuel N, Metsemakers WJ, Cohen O, Estrada RO, Reichert M, de Breij A, Potapova I, Schmid T, Segal D, Richards RG, Zaat SAJ, Moriarty TF.
Efficacy of a lipid-and-polymer-based drug delivery coating containing doxycycline for the prevention of implant-related osteomyelitis.
Eur Cell Mater. 2015;30(Suppl 2):34 (eCM / oral)

Grad S, Peroglio M, Li Z, Alini M.
Endogenous cell homing for intervertebral disc regeneration.
Eur Spine J. 2015;24(3):646 (BioSpine / oral)

Grüneweller N, Raschke MJ, Widmer D, Zderic I, Wähnert D, Gueorguiev B, Richards RG, Fuchs T, Windolf M.
Biomechanical evaluation of augmented versus non-augmented sacroiliac screws in a newly developed hemi-pelvis model.
Eur J Trauma Emerg Surg. 2015;41(Suppl 2):S62 (ECTES / oral)

Guillaume O, Park J, Monforte X, Redl H, Petter-Puchner A, Gruber-Blum S, Teuschl A.
Optimization of silk mesh for soft tissue reinforcements: preliminary in vitro investigations toward cell-based therapy.
Eur Cell Mater. 2015;30(Suppl 1):16 (SSB+RM / oral)

Herrmann M, Bara JJ, Hildebrand M, Menzel U, Sprecher C, Scherberich A, Alini, M, Verrier S.
The role of pericytes in bone tissue engineering – an in vitro investigation of the angiogenic and osteogenic potential of pericytes.
Osteologie. 2015;24(2):A53 (SVGO / oral)

Herrmann M, Bara JJ, Hildebrand M, Menzel U, Sprecher CM, Scherberich A, Alini M, Verrier S.
Plasticity - Investigation of the angiogenic and multilineage potential of pericytes.
Tissue Eng Part A. 2015;21(S1):S213 (TERMIS / poster)

Hildebrand M, Jalowiec J, Menzel U, Bara JJ, Alini M, Verrier S, Herrmann M.
Platelet rich plasma gel as a 3D culture system and its effect on the osteogenic potential of MSCs.
Osteologie. 2015;24(2):A53 (SVGO / oral)

Inzana JA, Trombetta RP, Schwarz EM, Kates SL, Awad HA.
3D printed bioceramics for dual antibiotic delivery to treat implant-associated bone infection.
Eur Cell Mater. 2015;30(Suppl 2):52 (eCM / poster)

Kazezian Z, Li Z, Alini M, Grad S, Pandit A.
Hyaluronic acid down-regulates interferon signalling in an injured bovine intervertebral disc.
Tissue Eng Part A. 2015;21(S1):S292 (TERMIS / poster)

Kyllönen L, Stadelmann V, Alini M, Eglin D.
Injectable hydrogel for the delivery of bone anabolic factors in osteoporotic bone.
Tissue Eng Part A. 2015;21(S1):S254 (TERMIS / poster)

Leite Pereira C, Goncalves RM, Eglin D, Alini M, Grad S, Barbosa MA.
Intervertebral disc regeneration: The role of mscs recruitment by hyaluronan-based delivery of stromal cell-derived factor-1 in matrix production improvement.
Eur Spine J. 2015;24(3):651-2 (BioSpine / oral)

Li Z, Lang G, Xu C, Sacks H, Alini M, Grad S.
Biomimetic polyurethane scaffold for nucleus pulposus replacement.
Eur Spine J. 2015;24(3):632 (BioSpine / oral)

Littmann E, Autefage H, Solanki AK, Jones JR, Alini M, Peroglio M, Stevens MM.
bioactive glasses at the osteochondral interface: Directing the mesenchymal stem cell response for osteochondral tissue repair.
Tissue Eng Part A. 2015;21(S1):S282 (TERMIS / poster)

Littmann E, Autefage H, Solanki AK, Jones JR, Alini M, Peroglio M, Stevens MM.
Cobalt-doped bioactive glasses: Using hypoxia to influence mesenchymal stem cell behaviour.
Tissue Eng Part A. 2015;21(S1):S315 (TERMIS / poster)

Metsemakers WJ, Emanuel N, Cohen O, Reichart M, Schmid T, Segal D, Richards RG, Zaat S, Moriarty TF.
Prevention of implant-related osteomyelitis due to doxycycline-resistant methicillin-resistant staphylococcus aureus using a doxycycline-loaded polymer-lipid encapsulation matrix coating.
Bone Joint J. 2015;97-B(Suppl 16 Orthopaedic Proceedings):105 (EBJIS / oral)

Morgenstern M, Erichsen C, Hackl S, Mily J, Militz M, Friederichs J, Hungerer S, Bühren V, Moriarty TF, Post V, Richards RG, Kates SL.
Antibiotic resistance of commensal staphylococcus aureus and coagulase negative staphylococci in an international cohort of surgeons.
Eur Cell Mater. 2015;30(Suppl 2):4 (eCM / oral)

Peroglio M, Caprez S, Benneker LM, Alini M, Grad S.
Influence of disc degeneration on the efficacy of stem cell treatment: an ex-vivo study.
Eur Spine J. 2015;24(3):647-8 (BioSpine / oral)

Peroglio M, Li Z, Lezuo P, Alini M, Grad S.
Why using bioreactors for whole organ cultures of intervertebral discs?
Eur Spine J. 2015;24(3):658-9 (BioSpine / oral)

Petta D, Eglin D, Grijpma DW, D'Este M.
Synthesis and characterization of hyaluronan amphiphilic derivatives for biomedical applications.
Eur Cell Mater. 2015;30(Suppl 1):74 (SSB+RM / poster)

Petta D, Fussell G, Hughes L, Buechter DD, Sprecher CM, Alini M, et al.
A new β-tricalcium phosphate / thermoresponsive hyaluronan hydrogel composite as injectable bone graft substitute delivering drugs.
Eur Cell Mater. 2015;29(Suppl 1):39 (ScSB / oral)

Post V, Morgenstern M, Richards RG, Moriarty TF.
Characterisation of nasal Methicillin-resistant staphylococcus aureus from orthopaedic surgeons.
Eur Cell Mater. 2015;30(Suppl 2):62 (eCM / poster)

Post V, Wahl P, Richards RG, Moriarty TF.
Eradication of bacterial biofilms from titanium implants by vancomycin: beyond the reach of common local delivery.
Eur Cell Mater. 2015;30(Suppl 2):63 (eCM / poster)

Sabaté Bresco M, Kluge K, Ziegler M, Richards RG, O'Mahoney L, Moriarty TF.
The role of biomechanical stability on Staphylococcus epidermidis osteomyelitis in a murine fracture model.
Eur Cell Mater. 2015;30(Suppl 2):30 (eCM / oral)

Schmid T, Keller I, ter Boo GA, Moriarty TF, Eglin D, Zeiter S.
Elevated C reactive protein level is an indicator of infection in rabbits in a contaminated fracture model.
Eur Cell Mater. 2015;30(Suppl 2) (eCM / poster)

Stadelmann VA, Camenisch K, Eberli U, Furlong P, Moriarty TF.
Patterns of bone evolution near infected implants.
Eur Cell Mater. 2015;30(Suppl 2):73 (eCM / poster)

Stadelmann VA, Guenther C, Eberli U, Camenisch K, Zeiter S.
The effects of age on implant integration
Osteologie. 2015;24(2):A53-4 (SVGO / oral)

Stadelmann VA, Guenther C, Eberli U, Camenisch K, Zeiter S.
The effects of age on bone implant integration: in vivo monitoring in a rat model.
Eur Cell Mater. 2015;30(Suppl 1):63 (SSB+RM / poster)

Stanciuc A, Flamant Q, Biotteau K, Stoddart M, Anglada M, Porporati MM, Kuntz M, Alini M, Peroglio M.
Human primary osteoblast behaviour on bioinert ceramics with nano- and micro-topography.
Tissue Eng Part A. 2015;21(S1):S329 (TERMIS / poster)

Tekari A, Chan SC, Frauchiger DA, Wuertz K, Sakai D, Benneker LM, et al.
Nucleus pulposus contain progenitor-like cells able to differentiate into osteogenic and adipogenic lineages in vitro.
Eur Cell Mater. 2015;30(Suppl 1):66 (SSB+RM / poster)

Tekari A, Chan SC, Wuertz K, Sakai D, Benneker LM, Grad S, et al.
Bovine coccygeal intervertebral discs contain multipotent tie2+ cells which can differentiate into osteogenic and adipogenic lineages.
Eur Spine J. 2015;24(3):650-1 (BioSpine / oral)

ter Boo GA, Arens D, Keller Stoddart I, Metsemakers WJ, Schmid T, Zeiter S, et al.
An injectable formulation of thermo-responsive hyaluronic acid-pNIPAm loaded with gentamicin for infection prophylaxis in an in vivo contaminated fracture model in rabbits.
Eur Cell Mater. 2015;30(Suppl 1):13 (SSB+RM / oral)

ter Boo GA, Arens D, Keller Stoddart I, Metsemakers WJ, Schmid T, Zeiter S, et al.
Release of gentamicin from a thermo-responsive hyaluronan hydrogel in an in vivo contaminated fracture model.
Eur Cell Mater. 2015;30(Suppl 2):76 (eCM / poster)

Vadala G, Russo F, Musumeci G, De Strobel F, Bernardini M, Eglin D, et al.
A reproducible disc degeneration scale in a large animal model.
Eur Spine J. 2015;24(3):642 (BioSpine / oral)

Varjas V, Geven M, Grijpma DW, Wang X, Peng J, Eglin D, et al.
Designing patient specific implants fabricated by stereolithography for orbital wall reconstruction.
Eur Cell Mater. 2015;30(Suppl 1):7 (SSB+RM / oral)

Zaat SAJ, Riool M, De Breij A, Kwakman PH, de Boer L, Hibbering PH, et al.
Synthetic antimicrobial and antibiofilm peptides from controlled release coatings to prevent implant-associated infection and derangement of immune responses.
Eur Cell Mater. 2015;30(Suppl 2):26 (eCM / oral)

13.5 Master theses, Dissertations & Habilitations

Aeberhard S.
Fluoroscopy based measurement of bone rotation.
2015 Albrecht-Ludwigs-Universität Freiburg (Windolf M) – MSc

Gardner O.
The regulation of human mesenchymal stem cell chondrogenesis through multiaxial load.
2015 Cardiff University (Stoddart M, Blain EJ) - PhD

Hristov M.
Development of a system for ultrasound telemetric monitoring of osseointegration during skeletal reconstruction .
2015 Technical University of Varna (Gueorguiev B, Marinov A) – MSc

Jalowiec J.
An in vitro investigation of PRP-gel as a cell and growth factor delivery vehicle for tissue engineering.
2015 Vetsuisse Universität Zürich (Verrier S, Auer JA) – DVM / fellow

Lenz MS.
Biomechanische Untersuchungen zur Osteosynthese periprothetischer Femurfrakturen.
2015 Friedrich Schiller Universität Jena
(Hofmann GO) - Habilitation / medical fellow

Metsemakers WJ.
Long bone fractures in (poly)trauma patients: risk analyses of musculoskeletal complications and strategies to prevent them.
2015 KU Leuven (Nijs S, Richards RG) – PhD

Seelbach R.
The molecular toolbox: Dendrimer decorated biomaterials for musculoskeletal regeneration.
2015 Universitat de Barcelona (Eglin D, Mata A) – PhD

Wähnert D.
Biomechanische Untersuchungen zur Versorgung osteoporotischer Femurfrakturen.
2015 Westfälische Wilhelms-Universität Münster
(Raschke MJ, Mückley T) – Habilitation / medical fellow

13.6 Presentations (not in conference proceedings)

05.02.2015	Richards Geoff: "Current State of Infection", AO North America OneAO "Common Problems and Common Solutions Across Disciplines", Las Vegas, Nevada, USA (Invited Speaker)
03.04.2015	Richards Geoff: "AO infection research: an overview", AOTrauma Belgium - Luxemburg, Meeting on Bone and Implant Infection, Brussels, Belgium (Keynote Lecture)
08.04.2015	Richards Geoff: "Preclinical Translation", Block Course: Skeletal Repair (ZHAW / ETHZ), AO Center Davos, Switzerland (Speaker)
14.06.2015	Richards Geoff: "From basic research to patient care", AO Asia Pacific Retreat, Bangkok, Thailand (Invited Speaker)
19.06.2015	Richards Geoff: "Data transparency in medicine", Board of Trustees Meeting, Chiang Mai, Thailand (Speaker)
19.06.2015	Richards Geoff: "Report from AO Research Institute", Board of Trustees Meeting, Chiang Mai, Thailand (Speaker)
01.09.2015	Richards Geoff: "Medical Translational Research: A different route to Fundamental Research", European Society for Biomaterials (ESB), Krakow, Poland (Plenary Lecture)
14.10.2015	Richards Geoff: "The role of biofilm in implant-associated infection", AOTrauma Symposium – Updates on Infection after Fracture Surgeries, Seoul, Korea (Invited Speaker)
14.10.2015	Richards Geoff: "Case session – My failure cases, what could have been done differently?", AOTrauma Symposium – Updates on Infection after Fracture Surgeries, Seoul, Korea (Session Moderator)
14.10.2015	Richards Geoff: "Local antibiotic delivery in the prevention and treatment of osteomyelitis", AOTrauma Symposium – Updates on Infection after Fracture Surgeries, Seoul, Korea (Invited Speaker)
23.10.2015	Richards Geoff: "Infection and Inflammation", Deutscher Kongress für Orthopädie und Unfallchirurgie (DKOU), in cooperation with EORS, Berlin, Germany (Session Moderator)
23.10.2015	Richards Geoff: "Towards clinically relevant bone infection research" Deutscher Kongress für Orthopädie und Unfallchirurgie (DKOU), in cooperation with EORS, Berlin, Germany (Keynote Lecture)
28.11.2015	Richards Geoff: "Healing monitoring: feedback by intelligent implants", 3rd Luxembourg Osteotomy Congress, Luxembourg (Invited Speaker)
28.11.2015	Richards Geoff: "Effect of implants surfaces on bony integration", 3rd Luxembourg Osteotomy Congress, Luxembourg (Invited Speaker)
10.12.2015	Richards Geoff: "The influence of implant surfaces", AOTrauma Course– Management of Fractures of the Hand and Wrist, Davos, Switzerland (Speaker)
30.03.2015	Alini Mauro: ORS 2015 Marshall Urist Award Lecture, Las Vegas, USA
09.04.2015	Alini Mauro: "Spine Research at the AO Research Institute Davos", The 5th International Congress on Biotechnologies for Spinal Surgery, Berlin, Germany (Invited Speaker)
29.04.2015	Alini Mauro: "The 11th Homing of disc cell for IVD regeneration strategies", International Turkish Spine Congress, Cesme – Ismir, Turkey (Invited Speaker)
18.06.2015	Alini Mauro: "Entering a new era at the AO: the regenerative one", Board of Trustees Meeting, Chiang Mai, Thailand (Invited Speaker)
17.-19.09.2015	Alini Mauro: "Endogenous cell homing for intervertebral disc regeneration", International Seminar on Biomaterials and Regenerative Medicine (BIOREMEDI), Orada, Romania (Invited Speaker)
14.10.2015	Alini Mauro: "Bone, cartilage and intervertebral disc TE/biological regeneration?", AOTrauma Symposium – Updates on Infection after Fracture Surgeries, Seoul, Korea (Invited Speaker)
15.10.2015	Alini Mauro: "Strategies to promote vascularization for bone healing", 3D Printing and Orthopaedic Translational Research Workshop, Shanghai, China (Invited Speaker)
27.10.2015	Alini Mauro: "New strategies in the regeneration of the intervertebral disc", NuvaAccademy, case-baded forum, Parma, Italy (Invited Speaker)

08.02.2015	Gueorguiev Boyko: "Theoretische und experimentelle Überlegungen zu Augmentationstechniken", AO Kurs "Zugangswege und Osteosynthesen", Graz, Austria (Invited Speaker)
15.09.2015	Gueorguiev Boyko: "Simulationsgestützte Entwicklung von Implantaten", Swiss Medtech Expo, Innovation Symposium AO – Fraunhofer Institute "Mobilität schaffen – innere und äussere Behandlungsstrategien am Bewegungsapparat", Lucerne, Switzerland (Invited Speaker)
21.10.2015	Gueorguiev Boyko: "Non unions – just a biomechanical problem?", DKOU, AOTrauma Europe Simposium "Non unions", Berlin, Germany (Invited Faculty)
21.10.2015	Gueorguiev Boyko: Session "Biomechanik", in cooperation with DGfB (Deutsche Gesellschaft für Biomechanik), DKOU, Berlin, Germany (Session Moderator)
16.03.2015	Grad Sibylle: "Cell Therapy for intervertebral disc regeneration". Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano, Milan, Italy (Invited Speaker)
10.04.2015	Grad Sibylle: "Endogenous cell homing for intervertebral disc regeneration". BioSpine 2015, Berlin, Germany (Invited Speaker)
14.04.2015	Grad Sibylle: "Inflammatory pathway and disc degeneration", SIAF – AO Exchange Meeting, Davos, Switzerland (Invited Speaker)
27.07.2015	Grad Sibylle: "Cell homing for intervertebral disc regeneration". University of Ulm, Germany (Invited Speaker)
10.11.2015	Grad Sibylle: "Translation of organ culture models into clinics and back". ORS Philadelphia Spine Research Symposium, Philadelphia, US (Invited Speaker)
03.04.2015	Moriarty Fintan: "The basic science of bone infection", AOTrauma Belgium – Luxemburg, Meeting on Bone and Implant Infection, Brussels, Belgium
08.&10.12.2015	Moriarty Fintan: "Local antibiotic delivery in the prevention and treatment of osteomyelitis", AOTrauma Masters Course–Current Concepts Infection, Davos, Switzerland (Invited Speaker)
22.01.2015	Stoddart Martin: "Towards intra-operative cell repair", University Medical Center of Johannes Gutenberg University, Mainz, Germany (Invited Speaker)
14.04.2015	Stoddart Martin: "Inflammation and MSC differentiation into osteoblast", SIAF – AO Exchange Meeting, Davos, Switzerland (Invited Speaker)
15.05.2015	Stoddart Martin: "Cells, genes and Mechanics-Drivers of repair in orthopaedics", Galway Symposium, Galway, Ireland (Invited Speaker)
27.07.2015	Stoddart Martin: "Mechanical Induction of Stem cells" University of Keele, UK (Invited Speaker)
19.08.2015	Stoddart Martin: "Effects of Mechanics on Steem cell behavior", Davos Knee Symposium, AO Center, Davos, Switzerland (Speaker)
22.10.2015	Stoddart Martin: "Barriers and strategies for advanced bone regeneration", Deutscher Kongress für Orthopädie und Unfallchirurgie (DKOU), in cooperation with EORS, Berlin, Germany (Invited Speaker)
09.11.2015	Stoddart Martin: "Stem cells in Orthopaedics", Davos Science City, Davos Exhibition, Public Forum, Davos, Switzerland
08.12.2015	Stoddart Martin: "Bone substitutes and advances for enhancing bone healing", AOTrauma Masters Course–Current Concepts Nonunion, Davos, Switzerland (Invited Speaker)
11.12.2015	Stoddart Martin: "Biological enhancement of bone healing: looking at potential options for use of growth factors and stem cells", AOTrauma Course–Advance Principles of Fracture Management, Davos, Switzerland (Invited Speaker)
13.12.2015	Stoddart Martin: "Biology of bone healing", AOTrauma Course–Basic Principles of Fracture Management for Swiss Surgeons, Davos, Switzerland (Invited Speaker)
21.10.2015	Verrier Sophie: "Frakturheilung, Osteologie", Deutscher Kongress für Orthopädie und Unfallchirurgie (DKOU), Berlin, Germany (Session Moderator)
23.10.2015	Windolf Markus: "Fracture monitor sensor", DKOU, EORS session "New technologies for clinical outcome assessment", Berlin, Germany (Invited Faculty)
15.09.2015	Ernst Manuela: "Sensorgesteuerte Überwachung des Frakturheilungsverlaufs", Swiss Medtech Expo, Innovation Symposium AO – Fraunhofer Institute

	"Mobilität schaffen – innere und äussere Behandlungsstrategien am Bewegungsapparat", Lucerne, Switzerland (Invited Faculty)
14.04.2015	Herrmann Marietta: "Vessel formation and inflammatory cytokines", SIAF – AO Exchange Meeting, Davos, Switzerland (Invited Speaker)
29.05.2015	Herrmann Marietta: "Tissue Engineering of Vascularized Bone Implants", Helmholtz Symposium, Aachen, Germany (Invited Speaker)
09.11.2015	Herrmann Marietta: "Stem cells in Orthopaedics", Davos Science City, Davos Exhibition, Public Forum, Davos, Switzerland
16.03.2015	Peroglio Marianna: "Molecular therapy for intervertebral disc repair", Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano, Milan, Italy (Invited Speaker)
09.04.2015	Peroglio Marianna: "Why using bioreactors for whole organ cultures of intervertebral discs?", BioSpine 2015, Berlin, Germany (Invited Speaker)
18.06.2015	Peroglio Marianna: "Biological responses of cells and tissues to biomaterials", European Ceramic Society Summer School, Ceramic & Glass Science & Technology, application to bioceramics & bioglasses, Madrid, Spain (Invited Speaker)
28.08.2015	Peroglio Marianna: "Homing of disc cells for IVD regeneration strategies", Swiss Society for Spinal Surgery 2015 Annual Meeting, Basel, Switzerland (Invited Speaker)

Speed Limit on Clavadeler Street

After several years, with different approaches to get the very dangerous situation on Clavadeler Street eased, we finally succeeded with stage one.

We have had a lot of serious accidents, and even one person died in the past at the entrance to the AO Centre, yet the responsible authorities from the Canton and the local Gemeinde were still not willing to enforce a speed limit on the road to the AO Center.

After the last accident (end of November 2014), Geoff Richards took the initiative to invite the Graubünden Regierungsrat and Gemeinde to visit the AO Research Institute Davos, and pulled all the available strings to put pressure on the Canton and the Gemeinde to impose a speed limit on the street.

On Friday, December 18th, 2015 the speed limit signs were mounted. We are happy to have the situation on this dangerous road improved.

For stage two, a possible sidewalk to the AO Centre is in discussion. This is making good progress, for possible implementation in autumn 2016.