

AO Research Institute Davos

Activity Report 2016



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1 Introduction

In 2016 new strategies have been set by the AO Foundation to strengthen Innovation for the future. These include governance and funding structures and the main new drive being the AO Foundation Development Incubator, which had its first meeting at the end of 2016. Until now innovation was mainly in the form of intellectual property with valorization of patents mainly from AO Research Institute Davos (ARI) often together with AO surgeons and until 2006 licensing of the patents for a revenue stream to Synthes (and previously Mathys and Stratec Medical). In 2006 the intellectual property rights to the patents, together with the tradename Synthes were sold to Synthes. This set up the AO Foundation's endowment, which funds areas such as the AO Research Institute Davos. New ideas have continued to be developed since that time but there was no route for valorization. With the Strategy Fund and now the AO Development Incubator, possibilities to take these ideas further may be opening. In 2016, a large amount of time and ARI's resources (through the various ARI internal funding mechanisms) have been dedicated to develop some of our more practical and likely realizable ideas through the difficult development stages. This was to demonstrate proof of concept and to bring the ideas to a level where they could be submitted to the new Development Incubator in 2017 for funding. Ensuing stages of licensing or setting up of a spin off company, are also supported in the new structure where the AO Foundation has created a group "AO Invest". This should help the transition from producing a patent and a "laboratory" model to proof of concept, and potentially even further. With these new developments, I believe the ARI will have the right conditions within the AO Foundation to promote success in the translation of scientific results into procedures and devices to help the patient, which is why we exist as a foundation.

On the academic side, the ARI remains stable at a very high level. I am proud to lead such a multidisciplinary team of dedicated, motivated hardworking knowledgeable scientists, engineers, clinicians and veterinarians. Together with the multifactorial pieces of being in one location, having project based R&D (and funding), always with the mission of helping patients in mind, with the AO Foundation's clinical network keeping us real are the extra ingredients of success. I wish to thank the ARI advisory committee for their advice and monitoring for all of the direct AO Foundation funded projects along with the clinical divisions R&D committees for their clinical advice and monitoring of the studies from the ARI retainer which are under their clinical supervision. Our academic Key Performance Indicators are in excellent shape. ARI published 74 peer reviewed publications (the equal highest number ever from ARI) with an average impact factor 3.44 (well above average in the field). Non-AO Foundation extramural grants amounted to 2.2 million which has increased from 2014 and 2015. The ARI's annual eCM scientific conference (In 2016 "Stem Cells, Bone Fixation, Repair & Regeneration") was again cost neutral (at full cost approach, meaning no subsidy from AO funds) and also rated well by attendees. Please check the Institutional and Professional Relations and Good News sections to see how the team is developing academically with international recognition along with the project Abstracts and Publications for details of the work.

On the accreditation side ARI was re-certified according to ISO 9001:2008 and the Biomedical Development Program was re-certified as Medical Device Manufacturer according to ISO 13485:2012. The Preclinical Facility was re-certified with AAALAC International accreditation for the humane treatment of animals (only two such institutes in Switzerland). The ARI are very proud that we received the official Statement of GLP Compliance from the Federal Office of Public Health, of the Swiss Confederation through Swissmedic (Swiss Agency for Therapeutic products) together representing the Swiss GLP monitoring authorities. The ARI is one of only two academic institutes certified for GLP in Switzerland. All these accreditations demonstrate ongoing ARI's commitment in fulfilling the highest standards in research.

Sincerely



Prof Dr R Geoff Richards FBSE, FIOR,
Director AO Research Institute Davos (ARI)

2 Mission / Goals / Outlook

Mission

Excellence in applied Preclinical R&D 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 R&D 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.
- Provide research environment / research mentorship / research support for AO clinicians.

2016 Outlook - Achievements

- Focusing resources on creating new surgical solutions such as for smart surgery **PARTIALLY ACHIEVED**, (*only partially since ARI's budget is not in our own control, but is in many separate commissions, which makes this focusing in this direction very difficult*)
- Bringing preclinical research to the highest accreditation, retaining ISO certification, AAALAC accreditation and finalizing GLP certification **ACHIEVED 2016**
- Maintaining academic excellence with the tissue engineering and regenerative medicine program **ACHIEVED 2016**

3-5 year goals - partial Achievements

- Develop productive potential of ARI innovation technology portfolio and create an ARI intellectual property strategy. **IP Strategy Achieved** (to be used by AO Foundation); ARI productive potential ongoing.
- Enabling the environment to foster competitive Innovation within the ARI collaborative research consortia. **(Ongoing)**
- Exploitation of diverse innovative ARI translational research bringing more economic sustainability to the AO Foundation. **(Ongoing)**

2017 Outlook

- Support AO Clinical Divisions with cutting edge research for their clinical problems.
- Initiate agreements to further develop and translate our ideas including Autogauge and X-in-One.
- Initiate new ARI multi-partner consortium on the theme Osteochondral defect repair.

Rolling Outlook ARI (3-5 years until 2021)

- Support AO Clinical Divisions with cutting edge research for their clinical problems.
- Development & translation of our unique smart surgery concepts: Implant Sensors & initiation towards BIG DATA, Autogauge and X-in-One.
- Maintain our world-class research level and nurture our in-house talents for long-term innovation for AO.

3 Funding Summary

Income Statement	2015 Actual		2016 Actual	
	abs	%	abs	%
in CHF '000				
AO Foundation Contribution	8'708	69%	8'418	67%
3rd party Income	2'193	17%	2'212	18%
AO Intercompany	1'651	13%	1'950	16%
Total Income	12'552	100%	12'579	100%
AOTrauma *	3'921	32%	3'602	29%
AOSpine*	440	4%	424	3%
AOCMF *	505	4%	645	5%
AOVET *	77	1%	102	1%
AOTK *	622	5%	699	6%
AOER	1'532	13%	1'953	16%
AO Foundation *	2'797	23%	2'686	22%
3rd party projects	2'193	18%	2'212	18%
Total Expenses	12'087	100%	12'321	100%
Net Result	464		258	

* incl. AO Intercompany

3rd Party Income' amounted to CHF 2,212 K and remained 7% (CHF 151 K) above budget and 1% (CHF 18 K) above previous year. The main reasons for the increase versus budget were a higher number of commercial studies that could be executed.

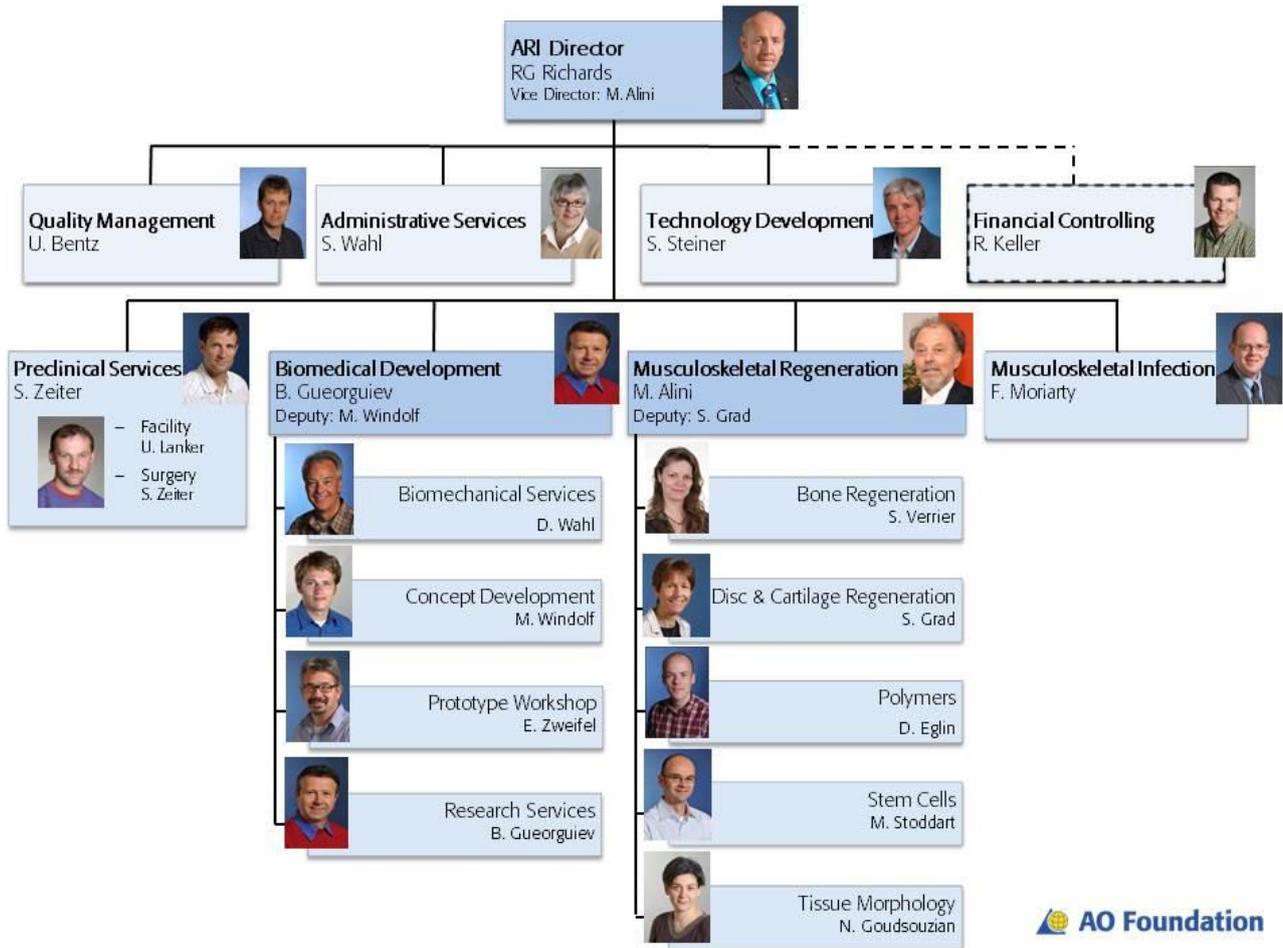
With regard to the split of the 'Total Expenses' by organizational unit, 'Musculoskeletal Regeneration' had the highest stake with 33% followed by 'Biomedical Development' with 17% and 'Preclinical Services' with 15%. The underspend versus budget of 'Preclinical Services' amounted to CHF 199 K (-10%) and was mainly caused by lower personnel expenses and less material costs. The increase in 'Fellowships' of CHF 179 (+40%) versus budget resulted mainly from additionally hired Internships and Fellows due to additional 3rd party / IC income. The variance versus budget in 'Musculoskeletal Regeneration' (+CHF 205 K / +5%) is driven by additional personnel expenses for PhD's due to extra grants, extra costs for guest researchers and therefore additional project expenses. The reason for an overspend in 'Management' of 11% versus budget is mainly due to losses on currencies in extramural projects and for the up-front fees for the 2017 TERMIS conference.

From a cost type point of view, the main categories were 'Personnel Expenses' with 67%, followed by 'Material Expenses' with 13% and 'Scientific & Regional Expenses' with 6%.

Overall, a positive 'Net Result' of CHF 258 K was achieved compared to a balanced budget.

4 Research Structure & Advisory Committees

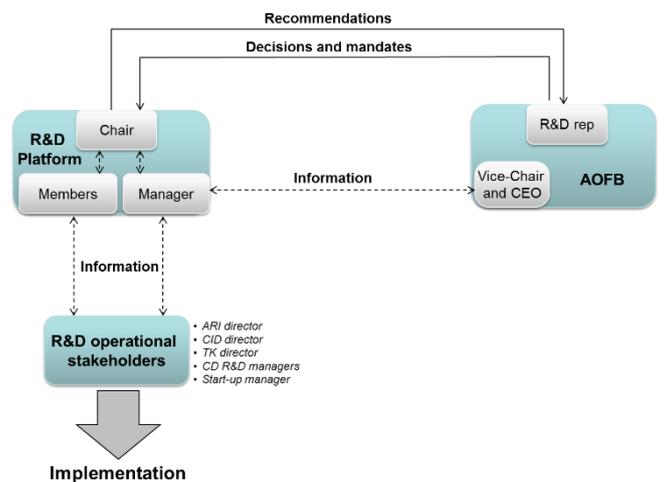
4.1 AO Research Institute Davos (ARI) Organigram



4.2 AO Foundation R&D Platform

The AO R&D Platform monitors, reviews and further develops the strategy defining clinical needs and implementation on behalf of the AO Foundation Board (AOFB) in an advisory capacity. The AOFB is responsible for setting the strategy, providing the funding and evaluating the outcomes for all AO research and development* initiatives. All research stakeholders are accountable to the AOFB. The AO R&D Platform coordinates among research stakeholders of the Institutes and clinical divisions to exchange information and develop best practice in operations and evaluation. It has no funding and decision authority.

*This includes any R&D funded by the AO Foundation, it does not include industrial funded R&D or extramural funded R&D carried out through AOTK, AOCID or ARI.



4.3 AO Research Institute Davos Advisory Committee

The ARI Advisory Committee (ARI AC) met in June and December at the AO Centre, Davos. The ARI AC gives operational and strategic scientific advice and guidance to the ARI. The ARI AC monitors the ARI output of direct funded projects on behalf of the AO Foundation Board (AOFB) and is a group with expertise relevant to the R&D objectives of the AO Foundation. It acts as both a sounding board and sparring partner for the ARI management team. Optionally (upon request from the ARI director) ARI AC can also advise (and often does) on science of indirect funding programs (e.g. extramural funding and funding from the clinical divisions through Clinical Priority programs (CPP's)).

The ARI AC is composed of three PhD or equivalent preclinical research scientists of high international standing and one clinician with several years' experience in preclinical research. One of the members should also have previous board experience for an institute or research driven industrial company with regards to technology transfer. The team should cover all general areas within which the ARI (including Biology, Bioengineering and Biomaterials). The chair represents the committee as a member of the R&D Platform and is also an ex-officio Trustee of the AO Foundation.

The ARI Advisory Committee (ARI AC) (December 2013 - December 2016) is

- Prof Dr Michael Schütz (Chair/ clinician), Queensland University of Technology, Australia (since 2016, Co-Director Musculoskeletal Surgery, Charité, Germany)
- 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



5 ARI Teams / Personnel

5.1 Biomedical Development Program

Program Leader: Boyko Gueorguiev-Rüegg, Deputy: Markus Windolf

Team Members: Jan Barcik, Jan Buschbaum, Jan Caspar, Benno Dicht, Ursula Eberli, Manuela Ernst, Billy Grill, Ladina Hofmann-Fliri, Dominic Gehweiler, Jason Inzana, Dominik Jenni, Lukas Kamer, Hansrudi Noser, Alexander Schiedeck, Manuel Schneider, Ronald Schwyn, Flurin Spiller, Vincent Stadelmann, Peter Varga, Viktor Varjas, Dieter Wahl, Ivan Zderic, Erich Zweifel

Fellows: Yves Acklin, Charlotte Arand, Leonard Grünwald, Eduardo Moran, Nina Schmitz, Dimitar Todorov

Guests: Sebastian Breden, Fabian Duttenhöfer, Mark Lenz, Mauro Maniglio, Michael Nienhaus, Irfan Shah, Andres Stricker, Daniel Wagner

The Biomedical Development Program performs research, development and service work in close collaboration with clinical, scientific and industrial partners to improve patient care. The activities are structured and organized in four focus areas: Concept Development, Biomechanical Services, Research Services and Prototype Workshop.



A variety of clinical problems is addressed by development of new concepts, methods, approaches, medical devices, tools and novel implant prototype systems for surgical applications and research in the field of trauma and orthopedics aiming at:

- ✓ Continuous assessment of the fracture healing progression via monitoring of interfragmentary movements with smart implant systems
- ✓ Investigation of the influence of temporal fracture mechanics modulation on bone healing speed and robustness via execution of arbitrary stimulation protocols at the fracture site with actuator-driven implants
- ✓ Enhancement of existing modalities for fracture treatment with a better control of the fracture mechanics by application of novel implant designs for more elastic fixation with predictable interfragmentary movements
- ✓ Implementation of simplified computer aided surgery systems utilizing conventional C-arms as imaging and navigation means for implant positioning and improvement of surgical routine interventions
- ✓ Systematic biomechanical screening and investigation of new implant design ideas, research questions and strategies for fixation of osteoporotic fragility fractures at the proximal humerus via computational simulations with the use of a robust validated software tool kit
- ✓ Automatic measurement of the actual drill depth during bone drilling and estimation of the required bicortical screw length for plate osteosynthesis of long bone fractures in real time

AO Fracture Monitor – a system for continuous assessment of the fracture healing progression with implementation of smart implants for monitoring of interfragmentary movements, data processing and wireless transfer to the surgeon for improved therapeutic decision making – an example with the use of a standard LCP.



The process of finding optimal solutions 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 such steps of operative fracture treatment as advanced surgical decision making and reinforcement techniques with the use of bone cements.

A variety of methods and procedures are developed to meet the demand of the increasingly sophisticated experimental designs for investigation of bone quality, fracture pattern and osseointegration by means of CT and medical image processing and analysis. Computer knowledge and expertise are used to develop fitting workflows and 3D virtual and statistical bone models in this regard. 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 to produce medical devices, it is involved in the prototype development processes from the very beginning.

5.2 Preclinical Services

Leader: Stephan Zeiter and Urban Lanker

Team Members: Daniel Arens, Corina Berset (AOF), Peter Erb, Loris Faoro, Pierina Faoro, Linda Freitag, Andrea Furter, Fabian Gieling, Christian Imfeld, Katharina Kluge, Jann Lanker, Reto Müller, Dominic Perren, Tanja Schmid, Patrizia Wagner

Fellows: Linda Freitag, Valentina Riehl

Student Externs: Judit Magnusson Wulcan, Charlotte Wittman, Fabian Gieling, Sinja Martens, Charlene Riberau, Giovanna Perossa, Karlijn Debusschere

Guests: Tim Buchholz, Johanna Freitag, Tahsin N Kahn, Mauro Maniglio, Mareike Sauer, Irfan Shah, Valentina Stenger, Cameron Wood, Andrew Worth

Currently, the reproducibility of preclinical studies is intensively debated. This is an important discussion and it will lead to improved study design, better conduction and analysis of experiments resulting in scientifically and ethically more valuable data. At the ARI, we conduct all our *in vivo* studies with great responsibility. Animal welfare and the quality of the data generated are important to us. Therefore, we became an AAALAC International accredited institution in 2013 and in 2016, we were awarded the official "Statement of GLP Compliance" from the Swiss GLP monitoring authorities. Together with the ISO 9001:2008 accreditation, there are now three quality assurance programs in place demonstrating our commitment in fulfilling the highest standards in preclinical research. Further, staff of Focus Area Surgery are highly qualified and specialized in laboratory

animal medicine (ECLAM) and surgery (ECVS) and our animal care givers have gained extensive experience with different preclinical models over the last decades.

Preclinical Services conduct all ARI (internal/external/commercial) *in vivo* studies – often in close collaboration with other Focus Areas. For example, together with the Focus Area Infection, CT Imaging and Focus Area Polymers and Surfaces we have employed our developed preclinical infection models in mice, rats, rabbits and sheep to investigate different aspects (diagnosis, treatment, applied research) of bone infections. Together with the Musculoskeletal Regeneration Program new bone regeneration therapies using different biomaterials and cells were investigated and the role of the immune system during bone healing was investigated. For these studies either standardized models have been used or new models tailored to the research questions have been developed. Last, but not least, projects aiming to refine the surgical and analgesic technique of existing preclinical models have been conducted.

5.3 Musculoskeletal Regeneration Program

Program Leader: Mauro Alini, Deputy: Sibylle Grad

Team Members: Angela Armiento, Jennifer Bara, Mauro Bluvol, Matteo D'Este, Luzia Douma, David Eglin, Niamh Fahy, Janna Geries, Nora Goudsouzian, Olivier Guillaume, Verena Hasselmann, Andri Hassler, Marietta Herrmann, Mario Inauen, Patrick Lezuo, Bojun Li, Zhen Li, Flavio Linardi, Claudia Löbel, Ursula Menzel, Graziana Monaco, Caroline Moser, Dirk Nehrbass, Alessio Nuzzio, Marianna Peroglio, Robert Peter, Dalila Petta, Stijn Rotman, Fatemeh Safari, Yemane Semere, Tiziano Serra, Christoph Sprecher, Ana-Maria Stanciuc, Martin Stoddart, Gert-Jan ter Boo, Federico Urzi, Letizia Vainieri, Sophie Verrier, Jessica Zahn, Reihane Ziadlou

Fellows: André Arruda, Peter Behrendt, Ming-Hsien Hu, René Rothweiler, Sebastian Wangler, Michael Wirth, Zhou Zhiyu

Guests: Lotta Bergfeld, Ugo D'Amora, Mike Geven, Aysun Guney, Lisbet Haglund, Patrick Hörnlmann, Ilse Jonkers, Byung-il Lee, Yishun Liu, Andrea Lolli, Rose Long, Mauro Maniglio, Robert Ossendorf, Sven Otto, Bernhard Rieder, Irfan Shah, Suzanne Tabboa, Johan van der Stok

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 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 graft when available) the blood supply is 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 (e.g., polyurethane) under autologous biological stimulation able to restore vascularization, bone integrity and biomechanical properties.

Stem Cell Focus Area

The Stem Cell Focus area is particularly interested in stem cell therapies for bone and cartilage that could be applied within a clinical setting. We aim to investigate the role of mechanical and soluble factors in the activation of mesenchymal stem cells, and the promotion of differentiation and tissue repair. Mechanical forces are one way stem cell fate could be manipulated by way of rehabilitation protocols. In addition, differentiation under load has led us to identify novel therapeutic targets that do not appear under standard static culture conditions. A greater understanding of the role of strain applied to cells would also improve fracture healing outcomes. Such studies are forming the basis of the emerging field of regenerative rehabilitation. 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 become the tissue of interest. Activating secretome production, 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, with exosomes and miRNA increasingly being used as a diagnostic and therapeutic tool. A serum based biomarker approach would dramatically improve patient specific clinical decisions.

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 carrier and drug delivery system. 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. These include stem cell applications and anti-inflammatory therapy. The disc/cartilage focus group is utilizing *in vivo* 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 3D structures for bone and cartilage tissue engineering, using tailored polymers and composites manufactured with additive manufacturing processes. Our experience lies in the design of biocompatible, biodegradable polymers and their processing with controlled architecture and embedded biologics. A second field of research investigates the preparation of hyaluronan, a natural occurring biopolymer, based biomaterials which can be used to deliver drugs and cells. These injectable biodegradable materials have considerable potential in infection prophylaxis and tissues repair.

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 stainings 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.

5.4 Musculoskeletal Infection Focus Area

Leader: Fintan Moriarty

Team Members: Pamela Furlong, Iris Keller, Virginia Post, Marina Sabaté Bescó, Barbara Stanic, Keith Thompson

Fellows: Willemijn Boot, Stoyan Petkov, Jan Puetzler, Aikaterini Stylianaki

Guests: Ricarda Eijer, Mauro Maniglio, Willem-Jan Metsemakers, Mario Morgenstern, Kasinath Raj, Irfan Shah, Thorsten Wichmann

The Musculoskeletal Infection team performs research focussed 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.

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. Additionally, we have introduced clinically relevant antibiotic prophylaxis and therapeutic regimens to these models, to more closely recapitulate the clinical condition modelled in our studies.

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.

5.5 ARI Technology Development

Technology Development Officer: Sandra Steiner

The ARI has reviewed, adapted and implemented a revised patent strategy. A review of the standard AO Foundation process applied over the past decades became necessary in order to prevent accumulation of underutilized patents. The new strategy allows scientists to protect their inventions at moderate costs at an early stage via a Swiss patent filing. The subsequent twelve months (priority period) can then be used by the inventors to generate solid proof-of-concept data. Towards the end of the priority period it is decided whether the invention shows potential and worldwide protection should be envisaged or whether to drop the application. If continued protection is chosen then the Swiss patent application can be converted and filed as an international application and the early Swiss filing date will become valid worldwide. Applying this process patent protection can be extended to up to 21 years.

A close collaboration with IGE in Bern ensures the best possible basis for a patent application. The Institute for Intellectual Property (IGE) in Bern is offering to Swiss research institutes expert assisted patent searches at a very competitive rate. While inventors are advised to travel to Bern for their first patent search since most recently it is likely possible that subsequent searches can be performed on-line with an IGE expert via internet.

Several IGE supported patent searches have been performed by ARI inventors in 2016. The inventors generally felt that the patent search was extremely valuable for obtaining an overview of the specific patent landscape and for the subsequent patent writing and claim formulation process. Towards the end of 2016 a first Swiss patent has been filed after approval of proof-of-concept studies to be carried out in the subsequent 12 months priority period.

5.6 eCM Journal Production

Editor-in-Chief: R Geoff Richards

Production Editor: Iolo ap Gwynn (*external*)

Junior Production Editor: Simona Ciriello

Webmaster, Web Editors: R Geoff Richards, Martin Stoddart, Simona Ciriello

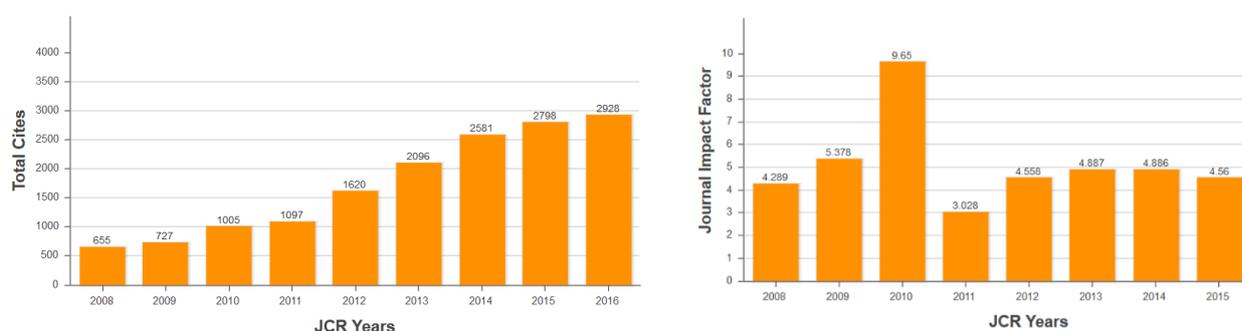
eCM Journal (Eur Cell Mater) was the first Not-for-Profit, open access scientific peer reviewed journal in the field (initiated in 1999). It was created by scientists for scientists and is still run fully by scientists. eCM Journal is published by AO Research Institute Davos, a Not-for-Profit foundation in Switzerland. eCM initiated the initial version of the transparent review process in 2000 (naming reviewers with the published manuscript). eCM initiated the first transparent route to becoming an official listed journal reviewer (member of the eCM International Review Panel). eCM Journal

provides an interdisciplinary forum for publication in the musculoskeletal field (Trauma, Maxillofacial (including dental), Spine and Orthopaedics) of preclinical research, including the field of tissue engineering & regenerative medicine.

eCM Journal is Open Access Compliant. All publications in eCM have been immediately freely available upon publication since eCM was conceived in 1999. Articles are freely accessible to the public without any embargo period, irrespective of who funded the research. This is equivalent to the new term "Gold Open Access" where articles are immediately available for others to read, download and share (e.g. can be uploaded on ResearchGate).

eCM Impact Factor (InCites, Journal Citation Reports, Thompson Reuters).

In June 2016 JCR announced eCM's Impact factor as 3.654 and our five-year impact factor as 5.202, which was later found to be wrongly calculated by them. JCR had counted individual conference abstract pages as manuscripts. Our findings were reported to them and they corrected the impact factor to 4.560 our five-year impact factor as 5.680, but unfortunately only on their help file. Adjusted metrics were only added to the reload of the Journal Citation Reports in September, which naturally hurt the submissions to the journal, as authors only look in June at the impact factor tables.



Since 2016, all of the eCM articles are also held within the CLOCKSS digital archive to ensure they remain available forever. (CLOCKSS (Controlled LOCKSS) is a not-for-profit joint venture between the world's leading academic publishers and research libraries whose mission is to build a sustainable, geographically distributed dark archive with which to ensure the long-term survival of Web-based scholarly publications for the benefit of the greater global research community).

In 2016 eCM became a member of CROSSREF. Crossref's general purpose is to promote the development and cooperative use of new and innovative technologies to speed and facilitate scholarly research. Crossref's specific mandate is to be the citation linking backbone for all scholarly information in electronic form. Crossref is a collaborative reference linking service that functions as a sort of digital switchboard. It holds no full text content, but rather effects linkages through Crossref Digital Object Identifiers (Crossref DOI), which are tagged to article metadata supplied by the participating publishers. The end result is an efficient, scalable linking system through which a researcher can click on a reference citation in a journal and access the cited article. The eCM Digital Object Identifier is DOI:10.22203/eCM

5.7 ARI Administrative Services

Manager: Sonia Wahl

Q-Manager & Purchasing: Ulrich Bentz

Team Members: Isabella Badrutt, Claudia Barblan, Simona Ciriello, 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, housing etc.)
- ARI Fellowship organization and support



2016 the ARI Administrative Service Group has organized for:

AO Research Institute (ARI)

18.-19.03.2016 Block course: Skeletal Repair for ETHZ and ZHAW students, Davos, Switzerland

08.04.2016 CMF Exchange visit with group of Prof. R. Schmelzeisen from Freiburg i. Breisgau, Davos, Switzerland

20.-23.06.2016 eCM XVII Stem Cells, Bone Fixation, Repair & Regeneration, Convention Center, Davos, Switzerland

23./24.06.2016 ARI Advisory Committee (ARI AC) Meeting, Davos, Switzerland

06.12.2016 ARI Advisory Committee (ARI AC) Meeting, Davos, Switzerland

09.12.2016 Meeting definition Fracture Related Infection (FRI), Davos, Switzerland

AOTrauma Research Commission (AOTRC)

19.02.2016 AOTRC Meeting, Dubai, United Arab Emirates

28./29.05.2016 AOTRC Meeting, Chengdu, China

28./29.10.2016 AOTRC Meeting, Barcelona, Spain

03.09.2016 AOT Annual CPP Meeting Bone Infection, Richmond, Virginia, USA

AOTrauma Middle East (AOTME)

13.10.2016 AOTME Education Committee Meeting, Dubai, United Arab Emirates

15.10.2016 AOTME Research Committee Meeting, Dubai, United Arab Emirates

17.10.2016 AOTME Community Development Committee Meeting, Dubai, United Arab Emirates

19.10.2016 AOTME Board Meeting 2016-II, Dubai, United Arab Emirates

20.10.2016 AOTME General Assembly 2016, Dubai, United Arab Emirates

6 Institutional and Professional Relations

Geoff Richards has appointment as honorary Professor at Cardiff School of Biosciences, Cardiff University, Wales, GB. He is Professor at the Medical Faculty of Albert-Ludwigs University, Freiburg, Germany. He is a Distinguished Professor at The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China. He is a Fellow of Biomaterials Science and Engineering (FBSE) and Fellow of International Orthopaedic Research (FIOR). He has Doctor Honoris Causa from the Technical University of Varna, Bulgaria. Geoff is cofounder and Editor-in-Chief of the Not-for-Profit open access eCM Journal. Geoff is an Associate Editor of the Journal of Orthopaedic Translation. He has Life Honorary Membership of the Swiss Society of Biomaterials (president in 2007-2009). Geoff 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 Steering Committee. He is a guest lecturer of the MSc Course Skeletal Repair at the Department Health Science and Technology of the ETH Zurich. He is representative to the AOTrauma R&D Commission from ARI.



Mauro Alini is an adjunct Professor at the Division of Orthopaedic Surgery of the McGill University, Montreal, Canada. He serves as a member of the Award Committee for The GRAMMER European Spine Journal Award. In 2016 he became Fellow of International Orthopaedic Research (FIOR). 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 of Orthopaedic Research and Associate Editor of Tissue Engineering and Regenerative Medicine (Frontiers in Bioengineering and Biotechnology). Mauro is a member of the ORS International Committee. He is representative to the AOSpine R&D Commission from ARI.



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 is representative to the AOTK System from ARI.



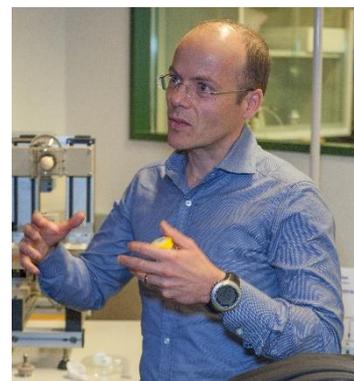
Stephan Zeiter is the chair elect of the Preclinical Models Section of the Orthopaedic Research Society. He is a member of the scientific committee of the Swiss Laboratory Animal Science Association and the vice president of the Davoser Society for Natural Sciences. For the European College of Laboratory Animal Medicine (ECLAM) he serves as a member of the education committee and as member of the council (treasurer-elect). Stephan is the representative to the AOVET R&D Commission from ARI.



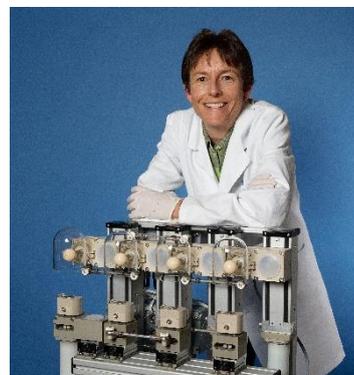
Fintan Moriarty is a scientific editor for the eCM Journal and a member of the board of associate editors of the journal of orthopaedic trauma. He is a guest lecturer at the Bern University of Applied Sciences, MSc programme in Medical Technology. He lectures on the Skeletal Repair MSc module at the ETH Zürich. He is a team leader in the AOTrauma Bone Infection Clinical Priority Program (CPP). Fintan is co-organizer of the eCM conferences Implant Infection meetings.



David Eglin is the secretary of the Executive Committee of the Swiss Society for Biomaterials and regenerative Medicine (SSB&RM), and Committee member of 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. He lectures on the Skeletal Repair MSc module at the ETH Zürich and in the Biomedical Engineering MSc Program at the University of Bern.



Sibylle Grad is organizer and lecturer of the MSc Course Skeletal Repair at the Department Health Science and Technology (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. Sibylle is co-organizer of the eCMconferences Cartilage & Disc: Repair and Regeneration meetings. She is also a member of the ORS Program Committee of the Annual ORS Meeting and a member of the ORS Spine section committee. Sibylle is also an ICRS Fellow member. She is an Associate Faculty Member of the Faculty of 1000 Medicine. Sibylle Grad is Vice president of the Graduate School Graubünden AG.



Martin Stoddart is an Honorary Professor at the Medical Faculty of Albert-Ludwigs University, Freiburg, Germany and at the Institute for Science and Technology in Medicine, University of Keele, United Kingdom. He lectures on the Skeletal Repair MSc module at the ETH Zürich. In 2016 he was elected as a Fellow of the Royal Society of Biology (FRSB). He is the Chair of the Orthopaedic Research Society (ORS) Basic Science Education Committee, and a member of the ORS Communications Council. He is Co-Deputy Chair of the the International Cartilage Repair Society (ICRS) Basic Science Committee and an ICRS Fellow member. He is Scientific Editor for eCM Journal, Journal Editor for Tissue Engineering Parts A, B, C, an editor of BioMed Research International Orthopedics, an editor of Journal of Functional Morphology and Kinesiology and a member of the Review Editorial Board of Frontiers in Craniofacial Biology. He is the Conference Chair of the yearly eCM conferences and a webeditor of eCM. He is also an Associate Faculty Member of Faculty of 1000 Medicine. He is the ARI representative to the AOCMF R&D commission.



Sophie Verrier is board member of the Swiss Bone and Mineral Society (SBMS). She is Co-chair of the Orthopaedic Research Society (ORS) Women's Leadership Forum committee and member of the ORS Annual Meeting committee. She is a member of the eCM International Review Panel. Sophie is co-organizer of the eCM conferences Bone Tissue Engineering meetings.



Other Professional Relations

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

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

Hansrudi Noser is an adjunct professor at the University of Zurich at the request of the Faculty of Economics. In addition, he acts as a member of the High School Graduation Committee of Liechtenstein.

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

7 Good News

New Extramural funding

The Stiftung für Innovation, Entwicklung und Forschung Graubünden funded the following project "Graubünden Healthcare Additive Manufacturing Hub, Aufbau Kompetenzzentrum" for a total of CHF 180'000 for the next 5 years. (D Eglin, PI).

The Kommission für Technologie und Innovation funded the following collaborative project "Personalized Ceramic Printable Ink for Patient Specific Implant Fabrication." for a total of CHF 292'700 for 3 years. (RG Richards and D Eglin PI, PI P Buechler, University of Bern, O Lieger, Inselspital Bern, M Thurner, RegenHU Ltd).

Deutsche Arthrose-Hilfe. Synoviale Stammzellen als alternative Zellquelle für das Knorpel Tissue Engineering - die Rolle der mechanischen Stimulation. 09/2016 - 09/2017 EUR 10'000 (M Stoddart Co-Applicant, PI J Kubosh, Albert-Ludwigs-Universität, Freiburg, Germany).

AOCMF Bone regeneration using tissue engineering and CAD-CAM technology – Their impact on facial bone reconstruction Open Call: Mandibular Condyle Regeneration. 01.06.2017-31.05.2020 CHF 373'433 (M Stoddart Co-Applicant, PI; D Gawlitta, University Medical Center Utrecht)
PEEK CAM Implant with Anti-bacterial Protection 01.04.2017-31.03.2019 CHF 120'000 (O Guillaume and D Eglin Co-Applicants, PI Benjamin Notellet, University of Montpellier, France)
3D printed osteogenic and hierarchical biomineralizing scaffold for bone regeneration 01.04.2017-31.03.2019 CHF 140'000 (M D'Este and D Eglin Co-Applicants, PI Alvaro Mata, Queen's Mary University College of London, UK).

RenoDisc project. "Renodisc: The impact of the tissue-Renin-Angiotensin-System towards degenerative disc disease" is a 2-year project funded by German Spine Foundation (DWG). The project partners include ARI scientists Prof Mauro Alini, Dr Sibylle Grad and Dr Zhen Li, in collaboration with Dr Gernot Lang, Prof Anke Bernstein, Prof Norbert Südkamp, Dr Hagen Schmal and Dr David-Christopher Kubosch from Albert-Ludwigs-Universität Freiburg, Germany. Funding is EUR 23'000 in total and includes a MD fellow visit from Freiburg to Davos.

SET project. "Inflamodisc: Biological and mechanical effect of selective proinflammatory cytokine inhibition in degenerative disc disease" is a 2-year project funded by Foundation for the Promotion of Alternate and Complementary Methods to Reduce Animal Testing (SET). The project partners include ARI scientists Prof Mauro Alini, Dr Sibylle Grad and Dr Zhen Li, in collaboration with Dr Gernot Lang, and Prof Norbert Südkamp from Albert-Ludwigs-Universität Freiburg, Germany. Funding is EUR 94'000 in total and includes 3 MD fellow visits from Freiburg to Davos (6 months each).

Sino-Swiss Exchange Grant. "Beta-catenin signaling in intervertebral disc degeneration disease" is a 2-year project funded by Sino Swiss Science and Technology Cooperation and China Scholarship Council. ARI scientists Dr Sibylle Grad and Dr Zhen Li, in collaboration with Dr Zhiyu Zhou, Sun-yat Sen University, Guangzhou and Prof Guangqian Zhou, Shenzhen University, Shenzhen. Funding is CHF 54'000 in total and supports Dr Zhiyu Zhou for a 2 years fellowship at ARI.

Finite element analysis of the alveolar ridge splitting technique, CAMLOG Foundation, Basel, Switzerland. EUR 25'000. (A Stricker, PI, University Hospital of Freiburg; B Gueorguiev-Rüegg, Co-Applicant; F Duttenhöfer, Co-Applicant, University Hospital of Freiburg).

Biomechanical testing of alternative sacrum fracture fixation techniques, Freiwillige Akademische Gesellschaft Basel, Switzerland. CHF 10'000. (Y Acklin, PI, Cantonal Hospital Baselland; B Gueorguiev-Rüegg, Co-Applicant).

AO Start-up grant application S-16-47R: Fluorescence guided bone resection – Comparison of auto-fluorescence and tetracycline-fluorescence for the treatment of Medication Related Osteonecrosis of the Jaw: A Large animal model CHF 120'000 for 24 months. PI: Ristow Oliver, Ruprecht-Karls-Universität Heidelberg Co PI: Zeiter Stephan.

External Positions / Awards

Dr med vet Stephan Zeiter was elected as Vice President of the Davoser Society for Natural Science at their general assembly in June 2016.

Prof Martin Stoddart has been appointed Co-Deputy Chair of the the International Cartilage Repair Society (ICRS) Basic Science Committee.

Dr Sibylle Grad was elected Vice President of Graduate School Graubünden AG, a daughter organization of Academia Raetica.

Dr Marietta Herrmann became a guest lecturer in the Master Program Biomedical Engineering at the RWTH Aachen University.

Dr Sophie Verrier was appointed Co-Chair of the ORS Women Leadership Forum committee (WLF).
Dr Sophie Verrier became a board member of Swiss Bone and Mineral Society.

Doctor Honoris Causa Award for Prof Geoff Richards from the Technical University of Varna

In the framework of the collaboration between the ARI and the Technical University of Varna (TUV), a delegation from the University, led by Prof. Rosen Vasilev, Rector, together with Prof Hristo Skulev, Vice-Rector of International Cooperation, and Dipl Eng Ivan Rusev, Vice-Rector of Management, visited ARI on May 11, 2016 to confer Prof Geoff Richards, Director ARI with the honorary degree Doctor Honoris Causa. This honorary award is the highest distinction the University can give in recognition of the notable academic and scientific contribution of an outstanding person with a special link with the institution. Within the 54-year history of the TUV, there have been a total of only 17 people from all over the world awarded with this honorary degree at the University. Following this, the University Scientific Academic Board decided to confer this honorary award.



Prof Rosen Vasilev (left) gives Prof Geoff Richards (right) the Certificate of Doctor Honoris Causa of the Technical University of Varna



From left to right: Dipl Eng Ivan Rusev, Prof Boyko Gueorguiev, Prof Rosen Vasilev, Prof Geoff Richards and Prof Hristo Skulev in front of the main entrance of the AO Center



Prof Geoff Richards holding a unique statuette, hand-crafted at the Technical University of Varna

The Certificate of Honorary Award with the degree Doctor Honoris Causa of the Technical University of Varna was given to Prof Geoff Richards by the Rector Prof Vasilev in a special academic ceremony in presence of the ARI management. A unique statuette, symbolizing the eternal human wish and aspiration to strive towards flying and excellence, hand-crafted by one of the TUV professors (Prof Plamen Bratanov, Department of Industrial Design), was also given to Geoff Richards.

Prof Martin Stoddart, awarded Honorary Professorship from Keele University, UK



Prof Martin Stoddart has been awarded another Honorary Professorship, this time from Keele University, UK. Ongoing research collaborations, including the EU FP7 Grant Biodesign, and joint PhD studentships between Prof Stoddart and Prof Alicia el Haj from the Institute of Science and Technology in Medicine at Keele University, continue to strengthen ties between the two institutes. His work in cell based therapies for bone and cartilage repair has led to this and highlights ARIs expertise in this area.

Additionally, on the April 1, 2016 Prof Stoddart was elected as a fellow of the Royal Society of Biology, in recognition of his outstanding contribution to the advancement of biological sciences. The Royal Society of Biology (RSB), previously called the Society of Biology, is a learned society, registered charity and professional association in the United Kingdom created to advocate biology within academia, industry, education, and research. The society has a Royal Charter and is a registered charity. Election as a fellow is merit based and fellows may use FRSB after their name.

Elected Fellows of International Orthopaedic Research (FIOR)



In September 2016 at the first International Combined Orthopaedic Research Societies (ICORS) meeting in Xian (China) Professor Mauro Alini (nominated by ORS) and Professor Geoff Richards (nominated by EORS) were elected Fellows of International Orthopaedic Research (FIOR). Fellows are expected, through word and deed, to foster the field of orthopaedics and to support its professional development as a practical and intellectual endeavour. This is a public recognition of individuals who have gained a status of excellent professional standing and high achievements in the field of orthopaedic research.

From left to right, holding their FIOR certificates: Prof Mauro Alini, Prof Ling Qin (The Chinese University of Hong Kong-former ARI fellow in 1992), Prof Geoff Richards, Prof Theodore Miclau (Orthopaedic Trauma Institute, San Francisco, USA; Chair elect, ARI Advisory Committee, former ARI fellow in 1991)

Distinguished Professorship, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

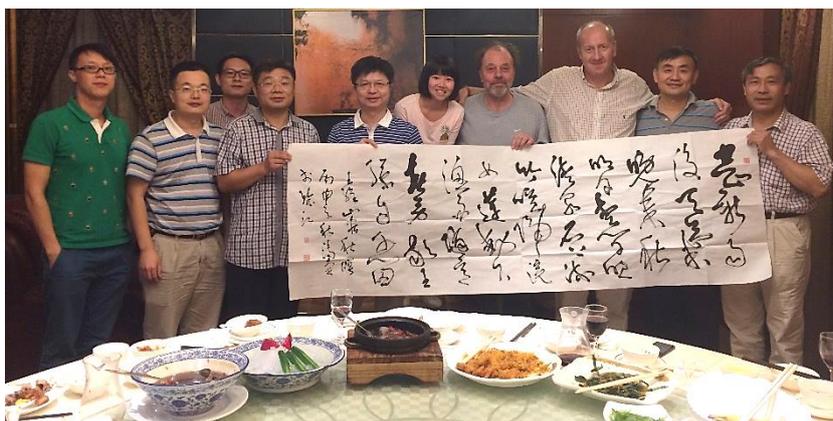
Prof Geoff Richards was appointed distinguished Professor, The First Affiliated Hospital, of Sun Yat-sen University Guangzhou, P.R. China in September 2016.



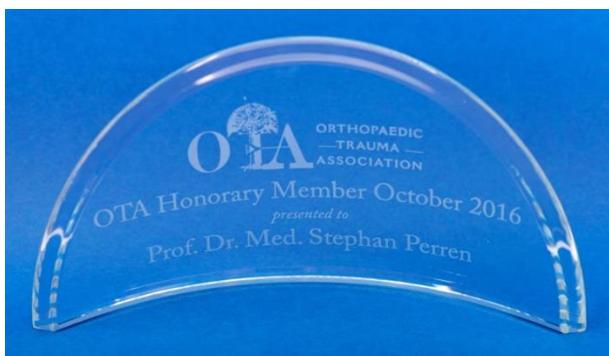
He presented to the Orthopaedic Research Institute at the Department of Orthopaedic Surgery, along with Prof Mauro Alini and Dr Zhen Li of ARI.

The ARI has had two fellows, so far from The First Affiliated Hospital, Zhou Zhiyu who has been instrumental in setting up this collaboration and initiated the Sino-Swiss Exchange Grant with ARI. Junxuan Ma was present at these lectures, decided to become a fellow with ARI, got his first year paid for by the hospital and will have the second year paid for by the ARI Fellowship scheme. The third fellowship is in the making.

From left to right, Geoff Richards, Prof Zou Xuenong (Spine Surgery Orthopaedic Research Institute, the First Affiliated Hospital of Sun Yat-sen University) and Prof Zeng Jinsheng (Vice President First Affiliated Hospital of Sun Yat-sen University)



Prof Dr med Stephan Perren – OTA Honorary Member



Prof Dr med Dr hc Stephan M Perren, former Director of the AO Research Institute Davos and a pillar of the AO Foundation, received honorary membership of the OTA (Orthopaedic Trauma Association) in October 2016. In addition to Prof Perren's role as an AO Founder, he chaired the AO Technical Commission and the AO Development Steering Committee for 16 years and for 28 years was the Director of the AO Research Institute Davos. Prof Perren's other professional duties also include his work as a medical doctor and an

Honorary Professor at the Universities of Bern, Montevideo and Aberysthwyth. In addition, he was also co-founder of the European Society of Biomechanics and International Society for Fracture Repair. This is only the third person to receive such an award.

Conference Awards

Olivier Guillaume was awarded best abstract presentation for his work entitled "3D printing of osteopromotive poly(trimethylene carbonate)-hydroxyapatite implants for bone regeneration." at the International Combined Orthopaedic Research Societies 2016 in September 2016 at X'ian, China.

Jessica Zahn won the best student poster prize at the EORS 2016 conference in Bologna, Italy.

Linda Freitag won the best student poster award at the eCM 2016 Conference in Davos, Switzerland.

Letizia Vainieri was awarded for best podium presentation in the category "Medical Sciences and Life Sciences" at the 5th Conference Graubünden Forscht - Young Scientists in Contest, Davos.

Abstract: Vainieri ML, Wahl D, van Osch GJ, Alini M, Grad S. Investigating the homing behaviour of endogenous stem cells in a joint bioreactor to regenerate articular cartilage.

Zhen Li has won the AOSpine EU Young Researcher Award 2016 (5th place) with the paper entitled "Development of an *ex vivo* cavity model to study repair strategies in loaded intervertebral discs".

Best Poster Presentation Award: H Yuan, Y Acklin, P Varga, B Gueorguiev, M Windolf, D Epari, M Schuetz, B Schmutz, Does bone-nail radius of curvature mismatch predict the ease of nail insertion? Australian Biomedical Engineering Conference, 30 Oct - 2 Nov 2016, Brisbane, Australia.

Virginia Post and Fintan Moriarty, alongside clinical collaborator Peter Wahl of Kantonsspital Winterthur, were awarded the 1st prize for the best scientific paper at the 35th meeting of the European Bone and Joint Infection Society, which was held in Oxford, UK in September 2016.

Marina Sabate Bresco of the Musculoskeletal Infection group received an academic award for her poster at the Graubünden Forscht Young Scientists in Contest 2016 meeting in Davos.

Organized Student Courses / Meetings / Workshops / Sessions at conferences

A Scientific Workshop on "Additive Manufacturing for Personalized Bone Grafts" was organized by the ARI with the partners of the European and Chinese funded project called RAPIDOS at the International Combined Orthopaedic Research Societies 2016 in September 2016 at X'ian, China.



At the DKOU 2016 in Berlin, Prof Mauro Alini and Prof Martin Stoddart organized a joint AO Foundation / ORS session on Acute Cartilage Injury to highlight work performed in the collaborative research program of the same name. Prof Alini chaired the session, along with clinical chairs Prof Brenner (Ulm) and Prof Südkamp (Freiburg). Dr David Eglin spoke on "Biomaterials for cartilage regeneration" followed by Prof Cucchiari (Homburg) presenting on "Gene therapy approaches for cartilage repair". The final two talks were Prof Martin Stoddart on the "Influence of mechanical environments on chondrogenesis" and Prof Dodge (Philadelphia) on "Translationally relevant animal models of cartilage repair". The incorporation of presentations on preclinical studies into the largest surgical conference in Germany is crucial to bridge the scientific and clinical communities.

At the DKOU 2016 in Berlin ARI's 'Smart Surgery' session was chaired by Prof Geoff Richards & Prof Norbert Südkamp (Freiburg). Talks Smart positioning: X-in-One – AO implant positioning

assistant, Windolf M; Smartfix – monitoring external fixation, Ernst M; Smart plates: AO fracture monitor, Windolf M; Smart drilling: AO auto-gauge, & Smart implant optimization Varga P.



ARI's Smart Drill demos at AO Lounge during DKOU 2016, 25-28 October 2016, Berlin, Germany.

Practical course "Skeletal Repair" for students from ETHZ / ZHAW



On Friday and Saturday, March 18-19, 2016, forty-five students from the Federal Institute of Technology Zürich (ETHZ) and the University of Applied Sciences Winterthur (ZHAW) met at the AO Center in Davos to join the practical course in "Skeletal Repair". This course, organized by ARI, is also part of a lecture series for ETH Master Students of the directions Health Science and Technology and Biomedical Engineering. The goals of the course are to gain insight into the basics of fracture treatment and into the translational research of the ARI.

In the initial lecture, Prof R Geoff Richards briefly explained the history of the AO Foundation and highlighted the objectives of the contemporary research at the ARI. With some recent examples, he impressively illustrated the close collaboration between the ARI and the clinics with the overall goal to improve patient care. Gian Bühler, an orthopedic surgeon then outlined the basics of fracture healing and the most important surgical techniques for proper fracture treatment.

During the subsequent osteosynthesis exercises the participants could practice the application of different surgical implants using artificial bones. The students recognized and experienced the challenges of appropriate placing of intramedullary nails, external fixators and osteosynthesis plates; so the support by the table instructors was highly appreciated. Dr Raphael



Jenni, a leading orthopedic surgeon at the Cantonal Hospital in Chur, and his team of clinician experts guided and instructed the students well, so that finally all the artificial fractures were treated properly. At the hands-on stations of the "skill training lab", the students were then introduced into the important relationships between biomechanics, physics and surgery. A qualified ARI team, led by Dieter Wahl, with Manuela Ernst, Ivan Zderic, Perter Varga and Dominik Jenni, demonstrated how to put theory into practice.

Hands-on Workshops on Skeletal Repair

On the second day, emphasis was put on nine different workshops led by scientists from the ARI, ZHAW and clinicians. Topics ranged from cell survival (Marietta Herrmann), adenoviral transduction (Martin Stoddart, Ursula Menzel), joint anatomy (Jennifer Bara), implant infection (Fintan Moriarty), biomaterial technology (David Eglin), bioreactors (Zhen Li), to pre-clinical models (Stephan Zeiter), endoprosthetics (Daniel Baumgartner and Bernd Heinlein) and clinical cases (Raphael Jenni). The workshops also provided excellent insight into the laboratories and in state-of-the-art methodologies at the ARI. The students were highly motivated and some of them showed great interest in a Master thesis project at an ARI lab. Such projects will further strengthen the long-standing collaboration between the ARI and the ETHZ/ZHAW. The practical course in Skeletal Repair was organized by Sibylle Grad, Christoph Sprecher and the ARI Administrative Service team.



Students from ETHZ and ZHAW during osteosynthesis exercises

Launch of new section on Preclinical Models of the Orthopaedic Research Society (ORS)

In July 2016 the new section on Preclinical Models of the Orthopaedic Research Society (ORS) was launched. This section will leverage the expertise within ORS to promote high quality preclinical research by multidisciplinary teams of scientists, surgeons, veterinarians, as well as specialists in laboratory animal medicine. Dr med vet Stephan Zeiter was actively involved in getting the sections started, since he has organized Research Interest Groups on preclinical model at the ORS congresses 2015 and 2016, bringing together veterinarians and non-veterinarians, all of whom use preclinical models in their research and who struggle with the issues that this work raises.

AO CMF Webinar

Prof Martin J Stoddart and Dr Stephan Zeiter from ARI together with Dr Sven Otto from Munich performed an AOCMF Webinar entitled ARONJ 'Anti-osteoclastic drugs and their impact on maxillofacial and orthopedic bone biology, surgery, disease, and treatment'. This webinar was targeted at surgeons, residents, and clinicians from all specialties who are interested in and deal with ARONJ.

Fracture-Related Infection discussed by international group of experts in Davos

The AO Foundation has consistently supported educational and research activities focused on the clinical problem of Fracture-Related Infection (FRI). As part of this ongoing effort AOTrauma, AOTK and ARI hosted a discussion group on FRI in Davos in December 2016. The quality of the clinical literature produced on fracture-related complications has suffered from the lack of a widely accepted or adopted definition for FRI. Past ARI medical research fellow Willem-Jan Metsemakers (Leuven, BE) described this issue in his PhD, which was partly performed at ARI. In a systematic review, he found that the majority of randomized controlled trials in fracture care do not mention any recognized definition of infection. The absence of a working definition of an infected fracture makes existing studies on infection incidence, costs of treatment, effectiveness of treatment strategies and outcomes for patients, difficult to evaluate or compare.



Willem-Jan Metsemakers addresses the members of the international expert group.

In response to this need, Willem-Jan, together with another past ARI medical research fellow Mario Morgenstern (Basel, CH) and ARI's Fintan Moriarty, prepared a survey for AO members on the need for a clear definition of FRI. The AO network clearly supported the proposal, with over 90% of the more than 2,000 responders suggesting a definition of FRI is required. With this mandate in place, ARI, AOTrauma and the AOTK Anti-Infection task force (AITF) hosted a dedicated meeting in Davos in December 2016. The group was composed of invited experts representing international organizations (eg AO Foundation, European Bone and Joint Infection Society, EBJIS) and prominent orthopedic trauma centers with a major interest in FRI. The group was asked to review and consider the published literature on definitions of infection developed for periprosthetic joint infection (PJI) and other orthopedic conditions, and brought their extensive clinical, diagnostic and scientific experience to the problem as it relates to fracture care.



Members of the group from China, Germany, Israel, The Netherlands, Switzerland, the UK, and the USA.

The group discussed the problem in four separate sessions focused upon classification, anatomical location, terminology and diagnostic criteria. A consensus was achieved on the fundamental features of FRI, and a proposal for defining the presence of FRI was reached. It is important to note that this is a definition and does not attempt to classify infection or to guide treatment, which remain tasks for the future. The establishment of a definition does, however, offer the opportunity to standardize clinical reports on the prevalence of FRI and to improve the reporting of clinical studies in FRI. The results are expected to be published in the coming months in *Injury*.

General

Doctoral Thesis (PhD) for ARI Medical Research Fellow, Dr Willem-Jan Metsemakers

ARI medical research fellow, Dr Willem-Jan Metsemakers, received his PhD in Biomedical Sciences in 2016 on the topic of "Long bone fractures in (poly)trauma patients: risk analyses of musculoskeletal complications and strategies to prevent them" from the Catholic University Leuven, Belgium. ARI Director, Professor R Geoff Richards, served as thesis co-promoter (pictured). Thesis promoter was Professor Dr. Stefaan Nijs, Chairman of the Department of Trauma Surgery, University Hospitals Leuven, Belgium.

Willem-Jan is currently a trauma surgeon at the Department of Trauma Surgery, University Hospitals Leuven, Belgium. He has a specific interest in implant-related infection and compromised fracture healing. In 2014, he was accepted into the medical research fellowship program at the ARI for six months. During his fellowship, Willem-Jan worked within the Musculoskeletal Infection Group on experimental models of implant-related infection and novel anti-infective implant coatings. This preclinical research was complimented by his clinical studies that focused on complications after intramedullary nailing performed in the Department of Trauma Surgery, University Hospitals Leuven. Following his period in the ARI, he became a surgical fellow at the Department of Septic and Reconstructive Surgery, Trauma Centre Murnau, Germany. With help of an additional AOTrauma grant, supported by AOTrauma CPP Bone Infection principal investigator Prof Dr Stephen Kates, Willem-Jan worked the septic surgery unit at the Trauma Centre Murnau. During this fellowship, he was exposed to the treatment of complications following musculoskeletal trauma surgery, including compromised fracture healing and implant-related infection, as is currently done at other specialist centers. This exposure offered a valuable clinical perspective to his time away from his home clinic, where he will now assume responsibility for the management of such cases.



*Dr Willem-Jan Metsemakers during the defence of his thesis.
Prof Dr Stefaan Nijs (left) and co-promoter Prof R Geoff Richards (right).*

Claudia Loebel successfully completed her PhD thesis at ETH ZURICH, Zurich, Switzerland. The supervisors were David Eglin (ARI) and Prof Marcy Zenobi-Wong (Zurich). Thesis title: Engineering Hyaluronan-Tyramine Hydrogels to Modulate Mesenchymal Stem Cell Behavior.

Gert-Jan Ter Boo successfully completed his PhD thesis at the University of Twente, Enschede, The Netherlands. The supervisors were David Eglin (ARI) and Prof Dirk W Grijpma (Enschede). Thesis title: Delivery of gentamicin from resorbable polymeric carriers as anti-infective strategy for implant-associated osteomyelitis

Christoph Sprecher successfully completed his PhD thesis at the Ludwig-Maximilians-Universität zu München, Germany. The supervisors were Prof Geoff R Richards (ARI) and Prof Stefan Milz (München). Thesis title: Funktionelle und altersbezogene Anpassung des Knochengewebes an Implantate aus künstlichen Werkstoffen - Analyse von verschiedenen Anwendungen an Tier und Mensch

Oliver Gardner's thesis "The regulation of human mesenchymal stem cell chondrogenesis through multiaxial load" was accepted for his PhD at the University of Cardiff, UK. The supervisors were Martin Stoddart (ARI) and Prof Charlie Archer (Cardiff).

Martina Glück successfully defended her medical thesis at the Albert-Ludwigs-Universität, Freiburg, Germany. The thesis entitled "Induction of Osteogenic Differentiation in Human Mesenchymal Stem

Cells by Crosstalk with Osteoblasts" was supervised by Martin Stoddart (ARI) with Prof Dr med Hagen Schmal and Prof Dr rer nat Anke Bernstein (Freiburg).

Caroline Moser successfully defended her MSc thesis at the D-HEST, ETHZ, with the maximum grade of 6. Title: Directing osteogenic differentiation of mesenchymal stromal cells *in vivo*
ARI Supervisors: Jennifer Bara, Martin Stoddart. Thesis Advisor: Prof Christian Wolfrum, Laboratory of Translational Nutritional Biology, ETHZ

Luzia Douma successfully defended her MSc thesis at the D-HEST, ETHZ, with the maximum grade of 6. Title: The effect of the degenerative state of the intervertebral disc on the efficacy of stem cell regeneration therapies. ARI Supervisors: Marianna Peroglio, Sibylle Grad. Thesis advisor: Prof Stephen J Ferguson, Laboratory for Orthopaedic Technology, ETHZ

New Facilities

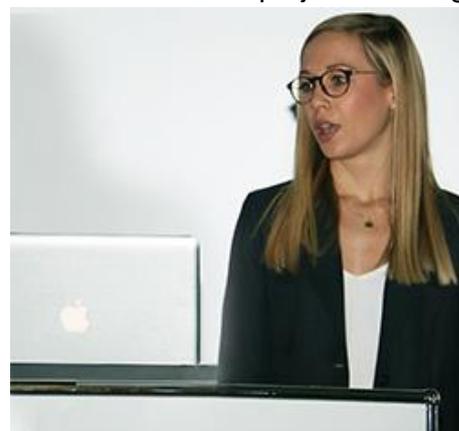
The ARI with the financial support of the Stiftung für Innovation, Entwicklung und Forschung Graubünden has set-up a new full biofabrication suite equipped with the state of the art research 3D discovery® bioprinter from RegenHU Ltd, fuse deposition modeling printer for prototyping and a large range of printable materials for development of innovative solutions for the care of trauma and orthopedic patients (Figure 7.1).



Figure 7.1: AO Research Institute Davos biofabrication unit equipped with state of the art 3D discovery® bioprinter from RegenHU Ltd.

Continuing the long-standing collaboration between the University of Freiburg and ARI, a joint research symposium was held in Davos on April 8, 2016

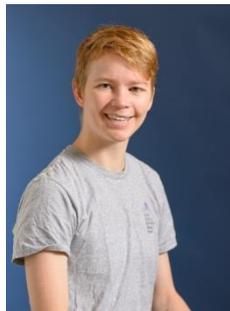
Organized by Prof Martin Stoddart (ARI) and Dr Dr Fabian Duttenehoefer (Freiburg) the Davos Freiburg Research Symposium was an excellent open exchange of current research projects running at both institutes. Both Prof Stoddart (Stem Cell Focus Area Leader) and Prof Geoff Richards (ARI Director) have Honorary Professorships at the University of Freiburg and this exchange aimed to explore further areas of cooperation and interaction for the future. Team members from Prof Dr Rainer Schmelzeisen, Prof Dr Südkamp and Prof Dr Bernstein presented their work followed by presentations from members of the ARI team. After an introduction by Prof Dr Schmelzeisen and Prof Stoddart a total of 15 lectures were given on multiple topics. This led to lively discussions and a plan of action was drawn up during the wrap up session. Since the meeting there has already been further interaction between the two institutes, further strengthening the connection.



Dr Laura Wanner describing morbidity after iliac crest harvest

Whitaker Fellowships in ARI

In conjunction with the Whitaker International Program, the ARI was pleased to host the Whitaker pre-doctoral research fellowship of Rose Long for the period August 2015-July 2016 and the Whitaker post-doctoral research fellowship Jason Inzana for the period January 2015–February 2016.



Rose Long joined the ARI during her doctoral studies at the Icahn School of Medicine at Mount Sinai under the leadership of Dr James Iatridis in New York, USA. In the words of Rose: “My fellowship at the ARI enabled me to participate in a large animal *in vivo* study with surgeons, veterinarians, scientists and engineers. I was able to pursue a separate project where I learned new techniques such as cell culture, gene expression analysis and histology. I was also able to apply my biomechanics experience in a new model in a cross-disciplinary and multi-cultural environment. My colleagues were brilliant and respectful, and the facilities were well-maintained. I felt freedom to explore scientifically with strong leadership and guidance as needed. This fellowship

added considerable value to my doctoral studies and I look forward to working with my new colleagues in the future.”



Jason Inzana joined ARI after his successful PhD defense as a member of Prof Hani Awad, Prof Stephen Kates and Prof Edward Schwarz teams at the University of Rochester Medical Center in Rochester, NY, USA. In the words of Jason: "I was very fortunate to have the opportunity to perform my post-doctoral fellowship at the ARI. It was an ideal setting to grow as an orthopedic scientist and engineer as well as to develop personally and broaden my perspectives in the highly multicultural and cross-disciplinary environment. All of the people at the ARI were wonderful to work with and the facilities were top notch. Overall, my experience was educational, challenging, and a great deal of fun!" During his stay in ARI

Jason was a member of the Biomedical Development Program and gained experience in finite element analysis, biomechanical testing and high-resolution imaging techniques. He especially developed computational tools for systematic investigation of proximal humerus fracture fixation and performed in-vitro biomechanical characterization to validate finite element models of implant biomechanics at this anatomical location.

Orthopedic resident Johan van der Stok visited the ARI from June 27- July 29, 2016

As part of a European Orthopedic Research Society (EORS) travel grant, orthopedic resident Johan van der Stok visited the ARI for five weeks in June. Johan came to ARI from the Department of Orthopedic Surgery, Reinier de Graaf Hospital, Delft and the Dept. of Orthopedic surgery, Erasmus Medical Center, Rotterdam where he obtained his PhD on bone regeneration. His PhD-thesis focused on the development of bone graft substitutes using cells and materials and translating these new bone graft substitutes towards clinical applications in orthopaedic surgery. This topic is relevant for every orthopedic surgeon, because bone grafts are still used in one out of every ten surgeries. Johan was attracted to the ARI as it is well recognized for its high-quality R&D aimed towards clinical applications in orthopedic surgery.

During his stay at ARI, Johan worked on an idea to regenerate the lunate bone using a stem cell-based approach. This stem cell-based approach aims to stimulate regeneration of the bone through endochondral ossification of stem cells incorporated in a patient-specific 3D-printed scaffold. The EORS travel grant provided a great opportunity for a clinician to immerse himself in a research environment and both parties hope to maintain this new-found link in the future.



8 eCM annual Conference

In 2016 the 17th annual eCM conference on the topic of "Stem Cells, Bone Fixation, Repair & Regeneration" was held at the Congress Center Davos, Switzerland from June 20 - 23, 2016. eCMXVII, was organized by the eCM conferences chair, Prof Martin Stoddart, together with help from Dr Sibylle Grad, Dr David Eglin and Dr Sophie Verrier from the ARI. The conference examined the multifunctional role of stem cells, with a focus on one of their common functions: Bone healing. Although bone has a remarkable propensity to repair, there are a number of situations where the repair process fails. This leads to many complications both social and economic. To meet these challenges, a complete understanding of bone biology, at the molecular, cellular and mechanical level is required. Furthermore the knowledge gained must be implemented into clinically relevant applications. This conference aims to address precisely these topics while exploring issues such as general stem cell behavior, biomaterials and clinical approaches.



Ex ARI Fellow Fabian Duettenhoefer being questioned after his Keynote presentation.

The conference had a number of internationally renowned keynotes that formed the basis of the sessions, with 44 oral presentations over 10 sessions. A new aspect to this year's conference was the addition of an Innovation session that aimed to highlight the challenges of translating science into a product. As is the case every year, the Robert Mathys student prizes were highly competitive. The prize for the best oral presentation was awarded to Albert Barba for his talk "Biomimetic nanostructured calcium phosphate scaffolds: osteoinduction and osteogenesis". First prize in the poster category was awarded to Linda Freitag for her poster describing work performed at ARI "The efficacy of local bisphosphonate and BMP-2 delivery in improving bone mass and mechanical implant stability".

9 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



Willemijn Boot, University Medical Centre Utrecht, Netherlands

ARI Project: Musculoskeletal Infection Group; StaphGel: Injectable formulation of HApNIPAm-gentamicin for infection treatment in a large animal model.

After finishing her studies in biomedical sciences, Willemijn started her PhD at the orthopedic department at the University Medical Centre Utrecht, with the topic "prosthetic joint infections". She is almost finished and hopes to defend her thesis in 2017. Willemijn starts as a research fellow in the Musculoskeletal Infection group and is excited to gain more experience in animal studies and implant-related infections.

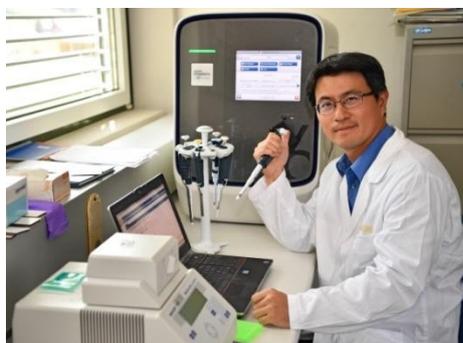


Leonard Grünwald, University of Tübingen, Germany

ARI Project: Biomedical Development Program; Radiographic navigation for distal femoral corrective osteotomies / Development of a computational test-kit for the proximal humerus.

Leonard is 29 years old and studied medicine at the University of Tübingen, where he earned his medical as well as his doctor's degree in 2015. Afterwards he started to work as a trauma resident at the Department of Trauma and Reconstructive Surgery at BG Trauma Hospital Tübingen, University of Tübingen. Leonard already got involved in surgical

and orthopedic research during his academic studies and continued this work after his degree at BG Trauma Hospital Tübingen. He appreciates the opportunity to focus on orthopedic trauma research, especially in the cooperation of an interdisciplinary team to do research and combine practical clinical issues with basic research.



Ming-Hsien Hu, Taipei Medical University, Taiwan

ARI Project: Musculoskeletal Regeneration Group; Transdisc: Stem cell based intervertebral disc regeneration – evaluation of cell carrier for pre-clinical application.

Ming Hsien was born in Kaohsiung, Taiwan and graduated from Taipei Medical University in 2004. From 2004-2010 he worked as an orthopedic resident in Taipei Veterans General Hospital. Since 2010 Ming Hsien became a spine surgeon at Show Chwan Memorial Hospital. He also started PhD at Department

of BioMedical Engineering, National Cheng Kung University. In 2016 Ming Hsien joined ARI's Musculoskeletal Regeneration Program for a period of six months, and is a member of Dr Sibylle Grad's group which is mainly focusing on disc regeneration. He hopes to gain experience in treating degenerated intervertebral disc.



Eduardo Moran, Universidad del Zulia, Maracaibo, Venezuela
ARI Project: Biomedical Development Program; Reconstruction of lateral tibia plateau fractures with a triangular support screw fixation.
Eduardo is an orthopaedic surgeon who graduated in Maracaibo, Venezuela. Since then he completed two fellowships in high energy trauma and reconstruction surgery in Barcelona, Spain. He has always been interested in alignment and trauma surgery as well as the best way of treatments. This particular chance in the AO Foundation gives him a great opportunity to be part of a great team of researchers and high level of scientists.



Jan Pützler, University of Heidelberg, Germany
ARI Project: Muskuloskeletal Infection Group; Infect-fx: Use of a rabbit humeral LCP model to provide evidence for treatment & prophylaxis concepts in open fracture care.
Jan is an AOTrauma medical research fellow from University Hospital Münster (Dept. of Trauma- Hand- and Reconstructive Surgery). He studied medicine and health economics at the University of Heidelberg and graduated in 2014. He is interested in implant associated infection and prolonged fracture healing in trauma patients. He appreciates the opportunity to gain experience in preclinical research and work with an interdisciplinary team of international scientists.



Valentina Riehl, Ludwig-Maximilian-University Munich, Germany
ARI Project: Preclinical Services Program; Fentaloc: Investigation of fentanyl plasma levels after application of a fentanyl patch in three different locations in order to refine postoperative pain management in rabbits.
Valentina finished her studies in veterinary medicine in 2016. In the last five and a half years she was studying at the Ludwig-Maximilian-University in Munich. During her studies she already spent two months at the ARI for a veterinarian externship in 2015. Now she is part of the Preclinical Services Team by doing a one-year Research Fellowship participating in several animal projects. Furthermore she would like to write her dissertation on one of these projects as well.



René Rothweiler, University of Freiburg, Germany
ARI Project: Muskuloskeletal Regeneration Program; Ostmonit: *In vivo* assessment of osteogenesis.
After finishing medical school in Freiburg in Breisgau, Germany, in the year 2012, René continued his academic studies in dentistry from 2012 to 2015. In 2012 he completed his first dissertation in medicine at the Department of Cardiology where he had investigated the effect of different stations on BMPER, a recently new identified BMP-modulator. In 2016 René finished his second dissertation in dentistry at the Department of Craniomaxillofacial Surgery where he had examined the influence on the outcome of severely injured people operated on their facial injuries. Before doing his specialization in Craniomaxillofacial Surgery René has joined ARI's Muskuloskeletal Regeneration Program in January 2016 for a period of one year. In his year in Davos, he is looking forward to gaining new experience and knowledge especially in different new molecular biological methods as well as maybe in 3D-printing, which has always been a great interest to him. René is also looking forward to meeting many scientists from all over the world.



Nina Schmitz, University of Mainz, Germany
ARI Project: Biomedical Development Program; Influence of RIA reaming diameter on stiffness and failure loads of human femora.

Nina studied medicine at the University of Mainz, Germany. She earned her medical degree in 2012 in Mainz and started her clinical training at the Department of Trauma, Hand and Reconstructive Surgery of the University Hospital Rostock. In 2014 she continued her clinical training at the Department of Trauma, Hand and Reconstructive Surgery of the University

Hospital Münster. She did her dissertation during her studies at the institute of biochemistry in neuroscience at the University of Mainz on the AAV-mediated overexpression of a protein of the endocannabinoid-system.



Aikaterini Stylianaki, Centre Hospitalier de Luxembourg
ARI Project: Musculoskeletal Infection Group; Trauser: Investigating the effect of the inflammatory response to trauma on local antibacterial defences.

Katerina is a resident in Trauma and Orthopedic surgery. During her residency programme she realized her great interest for musculoskeletal infections and applied for a fellowship in the AO in this field of research. The AO is one of the leading research foundations in this domain and she feels very happy to have the chance to work with very distinguished scientists.



Dimitar Todorov, Sofia Medical Univeristy, Bulgaria
ARI Project: Biomedical Development Program; Biomechanical investigation of augmented versus conventional LISS plating of distal femoral fractures.

After finishing medical school of Plovdiv in 2012, Dr. Todorov started working as a resident in the orthopaedics and traumatology department at the University hospital "N.I.Pirogov" in Sofia. In 2015 he became an assistant and started a PhD on analysis of the results after fixation of distal femur fractures with locking plates. In 2016 he earned a master degree in healthcare management at the Sofia Medical University. He is interested in gaining experience in preclinical

and clinical trauma research.



Sebastian Wangler, Medical School Bern, Switzerland
ARI Project: Musculoskeletal Regeneration Program; Discregen: Cell homing in the degenerative intervertebral disc: Characterization of migrating cells and their regenerative potential.

Sebastian graduated from medical school Bern in 2014. In the past year he acquired some initial experience as an intern in orthopedic surgery. Realizing that he wanted to learn more about basic science and particularly to better understand the potential of Regenerative Medicine he decided to suspend his clinical education. Therefore, he will join the Musculoskeletal Regeneration Program / Stem Cells Group. He is looking

forward to being part of an interdisciplinary and high-level team of scientists from all over the world. The insights gained this year will provide an excellent basis for his future carrier as an orthopedic surgeon.

10 Project Abstracts by Sponsors

10.1 AOCMF

Computerized workflow for CT-based planning of mandibular bone defect reconstruction and design of 3D printable layered scaffold constructs (V Varjas, L Kamer)

Surgical reconstruction of large mandibular defects might be performed following a trauma, tumor or malformation. Standard techniques include a bone graft harvested and transferred from the donor to the recipient site. However, this procedure remains a demanding task and also requires functional and aesthetical considerations to be taken into account.

Computerized approaches may be used to define new methods for improved and facilitated defect reconstruction. They may be used to virtually plan and reconstruct a mandibular defect, as well as to manufacture a new type of 3D printable scaffold therefore. 3D printing of large scaffolds to replace hard tissues offers great opportunities in regenerative medicine approaches for bone repair. Current approaches aim to produce a single-piece graft. Whereas this leads to ease of handling, it raises questions regarding the potential to seed the scaffold with cells or unprocessed cells such as bone marrow. Additionally, depending on the scaffold dimensions and composition, growth of vasculature may be reduced.

Computed tomography (CT) and computer-assisted planning represent techniques that could be adopted to generate a new, all-in-one computerized workflow supporting the surgeon and the technical expert to design and manufacture a new type of a 3D printable layered scaffold for reconstruction of large mandibular defects. This approach could be used as a basis for planning and performance of individualized mandibular reconstructions without the need of a bone harvesting procedure.

A software process is developed in the frame of this project for CT and computer-assisted planning to generate a new, all-in-one computerized workflow for designing and manufacturing of a 3D printable layered scaffold construct. The application of the workflow resulted in virtual reconstruction of a mandibular defect for the mandibular body and front. The defect site was virtually reconstructed via computer templates, i.e. via a computerized 3D printable layered scaffold construct, that matched the size and shape of the defect.

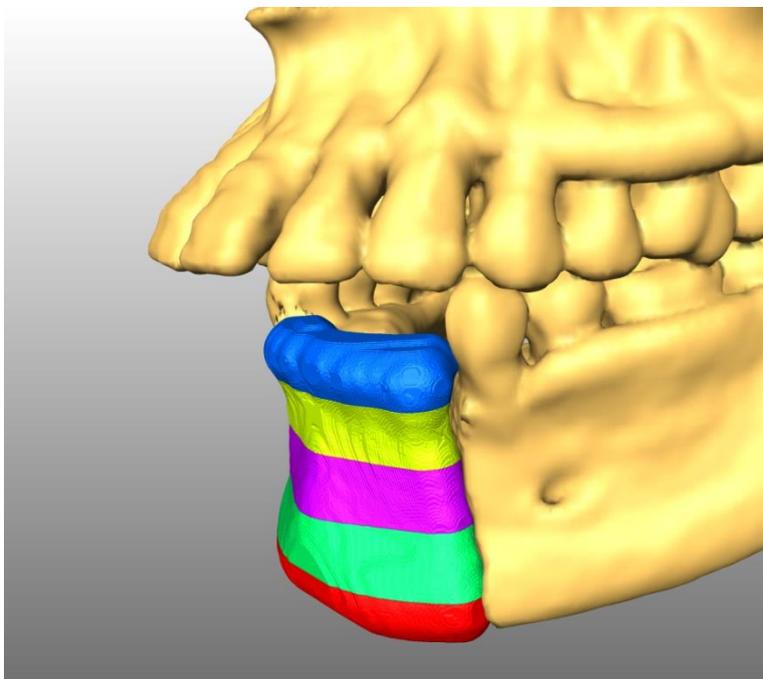


Figure 10.1.1: 3D CT visualization illustrating computerized reconstruction of a defect of the mandibular front. The defect has been virtually reconstructed by differently coloured computer templates which form the basis for a 3D printable layered scaffold construct.

Computer-assisted ranking to assist risk evaluation, diagnosis and treatment decision (ongoing) (L Kamer, H Noser)

This project is related to antiresorptive agent-induced osteonecrosis of the jaw. The term ARONJ refers to necrosis associated with administration of anti-osteoclastic drugs that may be indicated for treatment of bone diseases such as osteoporosis or cancer. Such a treatment includes different bisphosphonates or other antiresorptive drugs. Despite the clinical benefits, the agents may lead to osteonecrosis of the jaw, a complication observed in a subset of patients. Even though ARONJ can occur spontaneously, it is more often associated with specific medical and dental conditions and procedures that increase the risk of experiencing a bone trauma within the maxillofacial region.

The definition of ARONJ risk factors as well as the diagnosis and treatment modalities rely on the medical history and clinical examination as they are considered to be the most sensitive tools. Clinical signs and symptoms may be supported by radiographic assessment. Oral cancer must be considered in the differential diagnosis. Once a diagnosis is made, it is possible to refer the patient to treatment. Currently, different treatment modalities (conservative vs. surgical management) are used. However, the clinical standard procedure for risk assessment, diagnosis, and treatment decision still remains a demanding task leaving an open space for interpretations. There are cases where clinical signs of osteonecrosis may not be obvious or detectable. Additional radiographic assessment might demonstrate no or unspecific signs, exhibit a late stage or complex course, or even display signs of malignant conditions. The clinical condition might be aggravated by potential risk factors and comorbidities. An early and facilitated diagnosis might prevent or reduce the morbidity resulting from advanced destructive lesions of the jaw bone.

Artificial intelligence is being used increasingly as an aid to diagnosis in medicine. The aim of this project is to develop a computerized ARONJ ranking system and rank given ARONJ cases to improve and facilitate the risk assessment, diagnosis and treatment decision. It is planned to collect patient records and radiographs from a retrospective series of patients affected by ARONJ, by oral cancer with jaw bone involvement – along with a control group of patients – and elaborate a ranking system, based on the patient data and machine learning, that allows classification of a new case in a more objective and near to automated fashion.

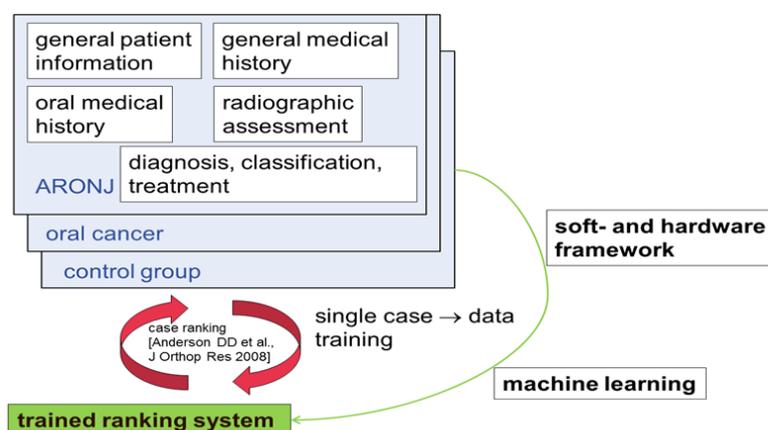


Figure 10.1.2: Development of a computerized ARONJ ranking system using data of patients affected by ARONJ, by oral cancer with jaw bone involvement, and patient data in a control group, according to Anderson DD et al., (J Orthop Res 2008).

Pres:

Lukas Kamer, Anti-osteoclastic drugs, impact on maxillofacial and bone, AOCMF ARONJ meeting, 12 Sept 2016, London, UK

Partners:

- Rana M (MD), Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie, Medizinische Hochschule Hannover, Germany
- Lutz I (MD), Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie, Medizinische Hochschule Hannover, Germany
- Gellrich NC (MD), Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie, Medizinische Hochschule Hannover, Germany

Bisphosphonate related osteonecrosis of the Jaw- Role of soft tissue healing (ARIBRONJ) (Completed) (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. Within the framework of the AOCMF BRONJ clinical priority program, ARI has been extensively collaborating with AOCMF surgeons to develop a robust BRONJ large animal model in the minipig. A yearly oncological dose of zoledronate is applied over 12 weekly infusions, followed by a tooth extraction. Using this model, potential preventative strategies were investigated as a primary step towards evidence based clinical recommendations. A clinically proposed preventative strategy after tooth removal is a combination of soft tissue flap and antibiotics. Within the minipig model this reduced the incidence of BRONJ from 100% to 50% and decreased severity.

The incidence of BRONJ could be further reduced if there was a pause between the last BP administration and tooth extraction. The additional application of a drug holiday reduced BRONJ incidence to ~10%. Due to the long-term binding of BPs to bone, the pause between last administration and tooth removal suggests an influence on soft tissue healing. Further studies into the use of platelet rich plasma did not demonstrate any additional benefits. Taken together, the data suggests that BP application potentially delays soft tissue healing after wounding, thus allowing a bacterial infection to take hold, creating an environment for BRONJ to develop. While a great deal of attention has been focussed on understanding the disease from a skeletal perspective, comparatively little has been done to investigate the influence of BPs on soft tissue healing.

Pres:

Bisphosphonate Related Osteonecrosis of the Jaw– Role of Soft Tissue Healing. 12.09.2016. AOCMF1st ARONJ Conference. London, UK.

Bisphosphonate Related Osteonecrosis of the Jaw– Prevention Options. 12.09.2016. AOCMF1st ARONJ Conference. London, UK.

Pub:

Von der Zellkultur über das Großtiermodell zur Optimierung der klinischen Prophylaxe und Therapie medikamenten-assoziiertes Kiefernekrosen S. Otto S, Probst F, Burian E, Ristow O, Arens D, Nehrbass D, Stoddart M, Pautke C, Ehrenfeld M. Der MKG-Chirurg. 2016, Volume 9, Issue 3, pp 191–195

Partners:

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

10.2 AOSpine

Stem cell based intervertebral disc regeneration – evaluation of cell carrier and delivery strategy for pre-clinical application (Transdisc) (Completed) (S Grad)

The aim of this study was to investigate intervertebral discs (IVD) response to human mesenchymal stem cell (hMSC) treatment based on disc degenerative state and hMSC carrier. A degenerative state was induced in bovine coccygeal IVDs by high frequency loading and low glucose conditions using a bioreactor system specifically designed for IVD whole organ cultures. Control discs were cultured under low frequency loading and high glucose conditions. Discs were partially nucleotomised and restored with hMSCs in either fibrin or saline. Administration of hMSCs with fibrin stimulated the anabolic response of degenerative discs, while saline solution proved to be an inefficient carrier, highlighting the importance of a careful selection of the cell carrier (Figure 10.2.1). Moreover, the degenerative state of the disc influenced hMSC differentiation. Specific discogenic markers were significantly increased in hMSCs implanted into physiological discs compared to degenerative discs (Figure x). In conclusion, host disc cells and hMSC response depend on IVD degenerative state and hMSC carrier. These two aspects need to be considered for successful translation of hMSC therapies for the treatment of IVD degeneration.

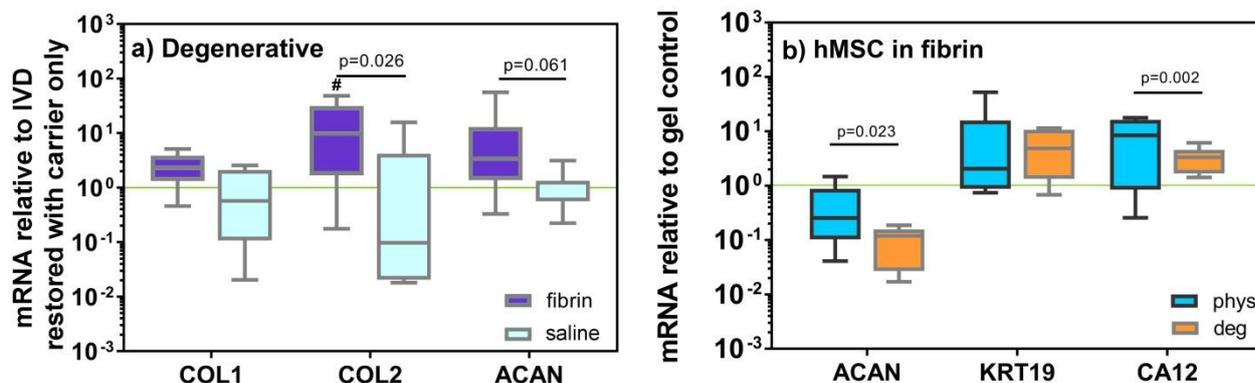


Figure 10.2.1: a) Anabolic gene expression of IVDs with a degenerative background treated with hMSCs in fibrin or saline. COL1: collagen type I, COL2: collagen type II, ACAN: aggrecan. Data are expressed relative to IVDs receiving the carrier alone (fibrin or PBS) (n=12); # p<0.05 relative to fibrin alone. b) Expression of nucleus pulposus cell markers in hMSCs cultured for 7 days in discs with a physiological or degenerative background. Data are expressed relative to hMSC-fibrin gel cultured in a well plate (n=12). KRT19: cytokeratin-19, CA12: carbonic anhydrase 12.

Pub:

Li Z, Lezuo P, Pattappa G, et al. Development of an *ex vivo* cavity model to study repair strategies in loaded intervertebral discs. *Eur Spine J.* 2016;25(9):2898-2908.

Antunes JC, Pereira CL, Teixeira GQ, Silva RV, Caldeira J, Grad S, Gonçalves RM, Barbosa MA. Poly(γ -glutamic acid) and poly(γ -glutamic acid)-based nanocomplexes enhance type II collagen production in intervertebral disc. *J Mater Sci Mater Med* 28(1):6, 2017.

Peroglio M, Li Z, Benneker LM, Alini M, Grad S. Chapter 8: Intervertebral disc whole organ cultures. In: *Biological approaches to spinal disc repair and regeneration for clinicians*. Editors: Haertl R and Bonnassar L. Thieme Publishers, New York 2017.

Pres:

Perez-San Vicente A, Peroglio M, Ernst M, Casuso P, Dupin D, Cabanero G, Grande HG, Eglin D, Alini M, Loinaz I. Injectable and self-healing dynamic hydrogel as efficient nucleus pulposus replacement for intervertebral disc repair. *WBC* 2016 (oral).

Partners:

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

10.3 AOTrauma

New stabilization concept to improve fracture healing – animal study (2Pinvivo) (Ongoing) (L Hofmann-Fliri, M Windolf)

Problem: Current clinical aftercare following bridged lower limb fracture fixation suggests restricted-to non-weight bearing for several weeks to prevent failure of the fixation. According to the current clinical practice, reduced load bearing is recommended until callus becomes apparent on X-rays. Recent animal experiments suggest that current aftercare of patients undergoing osteosynthesis treatment is fundamentally wrong. Day one weight bearing is believed to be of utmost importance to achieve fast and reliable fracture healing. Furthermore, despite the generally robust and forgiving nature of bone healing there is still a significant number of persisting complications (>10%), resulting in non- or delayed unions. Besides biological factors, the mechanical environment installed at the fracture plays an important role. Conventional fixation hardware for plating does not allow to control the mechanics in a sufficient manner, because patient loading and geometrical parameters such as working length of the plate render the resulting interfragmentary motion unpredictable. In extreme cases mechanical over- or understimulation of the fracture occurs.

A new plating concept was proposed by ARI in collaboration with QUT (Queensland University of Technology, Brisbane, Australia). It is aimed to enhance the existing treatment modalities of splinting and flexible fixation by redesigning of the conventional bone plate.

Goal: To test the feasibility of a new stabilization principle *in vivo* in a large animal experiment.

Results: Robustness of fracture healing with a novel plate design is investigated in a sheep tibia defect model under varying fracture conditions as well as under varying functional loading. Experiments are ongoing. This project is believed to deliver important information necessary to assess the potential of the new stabilization concept for human application.

Partners:

- Epari D (PhD), Queensland University of Technology, Brisbane, Australia
- Schütz M (Prof), Queensland University of Technology, Brisbane, Australia

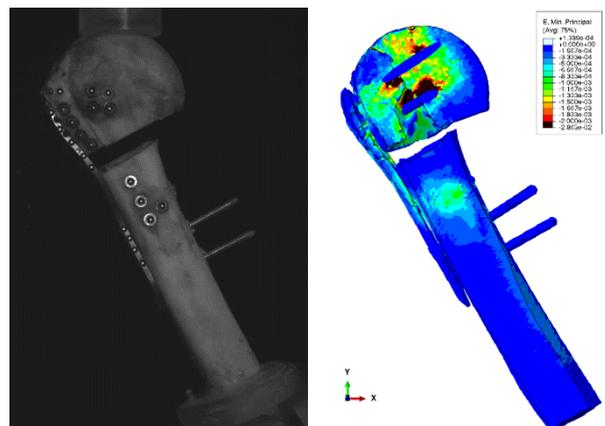
**Development of a computational test kit for proximal humerus (SystemFix) (Ongoing)
(P Varga, M Windolf)**

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 render the fixation particularly complex. These complications are difficult to model *in vivo* 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 result in considerable time and cost savings.

Goal: To develop and validate a robust set of computational tools, algorithms, and datasets that will enable systematic biomechanical simulations of osteoporotic fracture fixation at the proximal humerus.

Results: The previously developed computer modeling approach has been validated with biomechanical experiments. Unstable three-part fractures (AO 11-B3.2) were created in ten pairs of proximal humeri from elderly donors, fixed with the PHILOS plate and tested to failure in a previously established cyclic varus-bending setup. Case-specific, CT-based finite element (FE) models of the instrumented humeri were created and the experimental loading conditions were simulated. The FE-based strain around the screws was strongly correlated with the experimental number of cycles to failure ($R^2 = 0.90$), providing validity to the models.

Figure 10.3.1: Experimental (left) and numerical (right) testing of a PHILOS-plated proximal humerus fracture.



Pres:

Inzana J, Varga P, Windolf M. Implicit modeling of screw threads for bone-implant finite element analysis. 2016. ESBiomech

Varga P, Inzana J, Gruenwald L, Gueorguiev B, Richards RG, Blauth M, Südkamp N, Windolf M. SystemFix - Smart implant optimization. 2016. DKOU

Pub:

Inzana J, Varga P, Windolf M. Implicit modeling of screw threads for efficient finite element analysis of complex bone-implant systems. J Biomech. 2016. 49(9):1836-44.

Partners:

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

The influence of temporal fracture mechanics modulation on bone healing (ActiveFix) (Ongoing) (M Ernst, M Windolf)

Problem: Despite decades of research on mechanobiology of fracture repair, certain aspects in the field remain untouched. Especially the impacts of temporal variation of mechanical stimulus are only barely understood. However, there might be huge potential in the field to improve speed and robustness of healing. Recent animal experiments (ImpCon2 Project) suggest that fracture stimulation in an early post-operative phase could be of high importance for robust and timely healing. Within the current project, this important matter should be further investigated in a large animal setting.

Goal: A recently introduced experimental two-defect fracture model (QUT, Brisbane, Australia), comprising an actuator-driven external fixator, allows to execute arbitrary stimulation protocols to the fracture site completely independent from the functional loading of the animal. This implant system will be improved and adapted to the needs of the project and applied *in-vivo* to compare immediate to delayed fracture stimulation.

Results: A new control unit for the active external fixator was designed. The system is based on a single-board computer and allows programming and execution of stimulation protocols with regard to displacement amplitude, frequency and duration at specified times. Moreover, a load cell was integrated in the control loop in order to acquire stiffness properties of the repair tissue and perform force-controlled stimulation. The device is able to run autonomously during the course of the experiment. Following mechanical and electrical design, a fully functional prototype was built. Attached to a synthetic bone model, the prototype was subjected to a series of *in-vitro* tests. Stimulation protocols ranging from a displacement of 0.1 mm to 1.5 mm at frequencies from 0.1 Hz to 2 Hz were verified with and without simulated soft callus in the fracture gap. The system will be applied in a sheep osteotomy model in 2017.

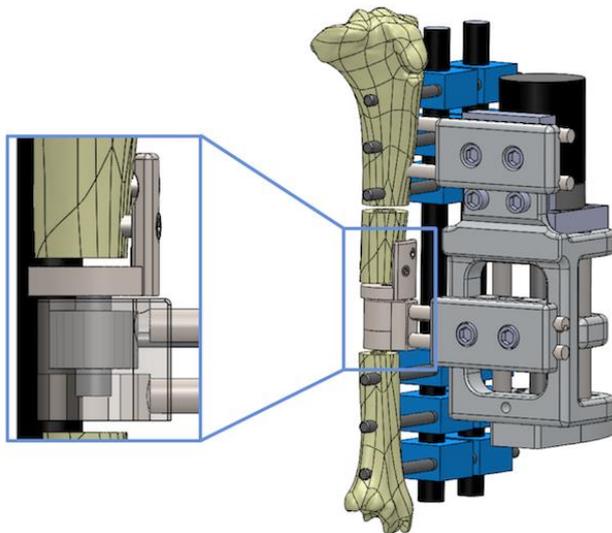


Figure 10.3.2: Illustration of the actuator-driven external fixator with incorporated load cell in the critical size defect (enlarged section).

Theses:

- Barcik JP: Actuator-sensor unit to investigate the influence of mechanical stimulation on bone healing, Master's Thesis, AGH University of science and technology, Krakow, Poland

Partner:

- Epari D (PhD), Queensland University of Technology (QUT), Brisbane, Australia

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 by means of surgical intervention may be able to help avoiding the fracture in case of a sideways 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 evaluation of the strengthening effect of metal implants was continued by investigating the prophylactic augmentation potential of the PFNA. The nail component of this implant provides a lateral support that was found to be missing in previously developed and investigated metal-based prophylactic strengthening strategies. Ten pairs of human proximal femora from elderly donors (70 ± 15 years) were instrumented with PFNA in another project. In the current project, the nail was removed from one randomly selected side of each pair and all bones were tested in a previously developed drop tower test mimicking the sideways fall. Fracture load was significantly higher in the PFNA-augmented group, but the pair-wise differences showed a large variance, including cases where the augmented side was weaker. These results and earlier findings of this project suggest that, despite encouraging results from finite element models, rigid metal implants are not able to provide a predictable and reproducible strengthening effect to the osteoporotic proximal femur.

The state of the art on the topic of prophylactic augmentation was summarized based on the existing literature and valuable experiences gained in this project in a review paper (Varga et al. BoneKEY Reports 2016). It is concluded that none of the previously presented approaches have been able to deliver the sufficient and reliable strengthening effect that would be required to protect a highly osteoporotic proximal femur from a fracture in sideways fall and therefore the clinical application of prophylactic augmentation is not yet justified.

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
- Varga P, Jenni D, Inzana J, Gueorguiev B, Blauth M, Windolf M. Strengthening effect of novel prophylactic augmentation approaches for the osteoporotic proximal femur as evaluated using computer simulations. 2016. EORS

Theses:

- Jenni D. Finite element modelling of an implant-based prophylactic augmentation approach in the proximal femur. MSc Thesis ETH Zürich D-HEST 2016

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 vivo* strength of human proximal femora assessed in a dynamic sideways fall setup. J Mech Behav Biomed Mater. 2016. 57:116-127.
- Varga P, Fliri-Hofmann L, Blauth M, Windolf M. Prophylactic augmentation of the osteoporotic proximal femur—mission impossible? BoneKEY Reports 5, Article number: 854 (2016).

Partners:

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

Guiding concept for fracture reduction and corrective osteotomies (SmartRep) (Ongoing) (J Buschbaum, M Windolf)

Problem: The aim of corrective osteotomies and fracture reduction is to restore normal bone, joint and limb anatomy. However, the target alignment is usually not known intraoperatively which can result in undesired anatomical malalignments.

Goal: To develop an X-ray based method for intraoperative determination of anatomical parameters derived from the intact contralateral femur to facilitate femoral osteosynthesis and osteotomy planning.

Results: A concept was developed enabling selection of anatomical landmarks from X-ray images and computing the length and anteversion of an intact femur. According to this concept, X-ray images of explicit anatomical regions are taken in different planes. Following, specific anatomical landmarks are selected manually. Finally, the three-dimensional position of the anatomy is defined by means of a designed marker bar allowing the computation of the required anatomical parameters bone length, axis and anteversion. These parameters may then be mirrored to determine the anatomical target alignment of the injured or misaligned limb.

A calibration dummy was used to test the precision of the method. X-rays images from different C-arm positions and orientations were taken and the deviation of lengths and angles was evaluated to be $0.67 \text{ mm} \pm 0.33 \text{ mm}$ (length) and $0.26^\circ \pm 0.26^\circ$ (angle). This precision is considered to be clinically acceptable.

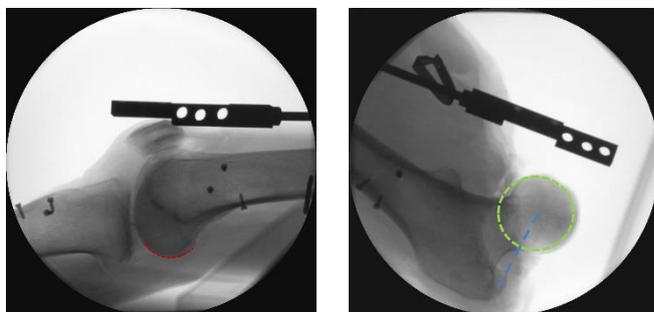


Figure 10.3.3: Visualization of the method for intraoperative determination of the intact femur anatomical parameters with the use of a designed marker bar (left) and selection of specific anatomical landmarks (middle and right).

Partner:

- Pohlemann T (Prof) Department of Trauma, Hand and Reconstructive Surgery, University Hospital of Saarland, Homburg, Germany

Biomechanical evaluation of a new gliding screw concept for proximal humerus fracture plating (HumSlide) (I Zderic)

Problem: Proximal humerus fractures are very frequently observed injuries. Their incidence in elderly patients with osteoporotic bone quality is increasing. In severely displaced fractures, intramedullary nailing and plating have become widely accepted methods of treatment and have proven to be biomechanically stable. Nevertheless, operative treatment is associated with a high complication and reoperation rate. One severe complication is secondary screw perforation that occurs in 8-11% of the cases with screw tips destroying the glenoid in up to 56%. Although different methods for dynamic plating of proximal femoral fractures or less-rigid plating of proximal humeral fractures exist, there are no existing solutions for dynamic plating of proximal humeral fractures, aiming at preventing cut-out in poor bone quality. For that purpose, a new prototype plate for dynamic proximal humerus fracture fixation was developed. Its design resembles the PHILOS plate, however, the proximal locking holes are replaced with four short barrels for fixation with 3.5 mm gliding shaft screws. Shaft screws allow anchorage in locations with high subchondral bone mineral density and their blunt tip might be beneficial to reduce screw perforation.

Goal: To evaluate biomechanically the new gliding screw concept for plating in three-part proximal humerus fractures - with and without screw tip augmentation using bone cement - under physiological loading and compare it to the well-established PHILOS plate.

Results: Based on initiation of screw telescoping, the new gliding screw concept may represent a valid alternative to conventional PHILOS plating, especially in terms of cut-out prevention.

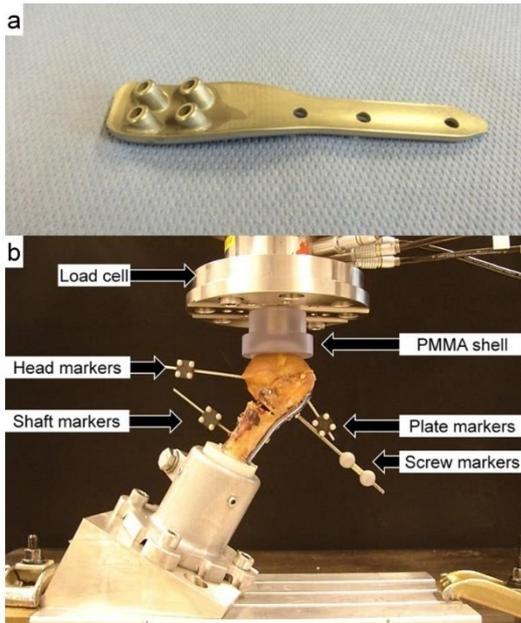


Figure 10.3.4: The new plate prototype for proximal humerus fracture fixation with four short barrels for gliding of its proximal screws (a, top); Test setup with a plated humerus specimen, equipped with retro-reflective markers for optical motion tracking and mounted for biomechanical testing (b, bottom).

Partner:

- Acklin Y (MD), University Hospital of Basel, Basel, Switzerland

Development of a novel flexible antimicrobial local delivery platform for infection prophylaxis (HYDROBAC) (Completed) (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 10.3.5). *In vivo* studies have shown the ability of a gentamicin loaded injectable formulation in preventing an infection.

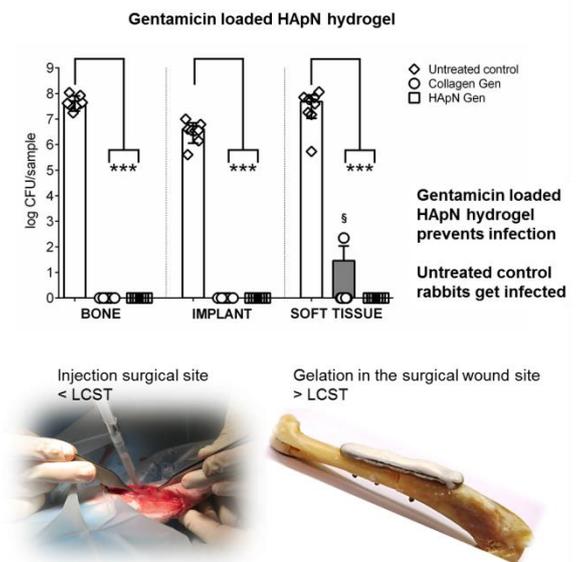


Figure 10.3.5: Injectable gentamicin-loaded thermo-responsive hyaluronic acid derivative prevents infection in a rabbit model (ter Boo et al. *Acta Biomater.* 2016;43:185-194)

Pres:

- [1] ter Boo GA, Arens D, Schmid T, Metsemakers WJ, Zeiter S, Nehrbass D, et al. A thermo-responsive hyaluronan based hydrogel loaded with gentamicin prevents infection in an *in vivo* fracture model with plating osteosynthesis. Thesinge Biofilm Meeting. Thesinge2016.
- [2] ter Boo GA, Arens D, Schmid T, Zeiter S, Metsemakers WJ, Nehrbass D, et al. A thermo-responsive hyaluronan based hydrogel loaded with gentamicin prevents infection in an *in vivo* fracture model with plating osteosynthesis. YSBMch. Zürich2016.
- [3] ter Boo GA, Schmid T, Nehrbass D, Zderic I, Grijpma DW, Richards RG, et al. Efficacy of a thermo-responsive hyaluronan based hydrogel containing gentamicin in an *in vivo* fracture model with plating osteosynthesis and *S. aureus* contamination. *Eur Cell Mater* 2016;32:25.

[4] ter Boo GA, Schmid T, Nehrbass D, Zderic I, Grijpma DW, Richards RG, et al. Efficacy of a thermo-responsive hyaluronan based hydrogel containing gentamicin in an *in vivo* fracture model with plating osteosynthesis and *S. aureus* contamination. AFPM Advanced Functional Polymers for Medicine. Enschede 2016.

Pub:

[5] ter Boo GA, Richards RG, Moriarty TF, Grijpma DW, Eglin D. Hyaluronic acid derivatives and its polyelectrolyte complexes with gentamicin as a delivery system for antibiotics. Polym Adv Technol 2016; epub Sep 23.

[6] ter Boo GA, Arens D, Metsemakers WJ, Zeiter S, Richards RG, Grijpma DW, et al. Injectable gentamicin-loaded thermo-responsive hyaluronic acid derivative prevents infection in a rabbit model. Acta Biomater 2016;43:185-94.

[7] ter Boo GA. Delivery of gentamicin from resorbable polymeric carriers as anti-infective strategy for implant-associated osteomyelitis: University of Twente, Enschede; 2016.

Partners:

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

Injectable hydrogel for releasing osteogenic factors in osteoporotic bone fracture (OSTEOGEL) (Completed) (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 vivo*. 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, enhanced local bone density to the level of non-osteoporotic animal.

Bone targeted delivery of antibiotics (TargetOS) (Started) (D Eglin)

In this project, we aim to address the clinical problem of failed treatment of bone infection. Recently, it has been identified that bacteria may reside deep within bone tissue and these bacteria may be a possible cause of treatment failure. We hypothesize that current antibiotic treatment modalities (local and systemic) do not deliver sufficient antibiotic concentration specifically within the bone region for sufficient time periods to eradicate all bacteria present in infected bone. This short come explains why the long-term recurrence rate on some groups of patients (for example with open fractures) remains at approximately 20% to 30%.

The aim of this project is to explore different methods to increase antibiotic retention in bone tissue and to enhance their efficacy to treat locally bone infection. This will be achieved by the incorporation of antibiotic agents with novel bone-targeting delivery carriers. We will prepare antibiotic-loaded nano/microsize vehicles, whose surface will be functionalized by molecules exhibiting strong affinity to the bone tissue (e.g bisphosphonates). These bone-seeking molecules have already been described and characterized in pre-clinical models for bone cancer, and we intend to further develop this concept and apply it to the field of bone infection. Then, we will characterize the affinity of these new delivery systems to bone-like materials and their efficacy to treat local infection, under *in vivo* and *in vivo* conditions.

We hypothesize that, if we can increase the retention of antibiotic agents within bone, and the penetration of antibiotics throughout the bone matrix, we expect improved antibacterial efficacy at the site of infection.

MiRNA analysis to discover fracture related biomarkers (MiDiag) (Started) (M Stoddart)

Biomarkers predictive of fracture healing outcomes would provide a useful tool that allows surgeons to proactively make patient based clinical decisions. Currently, even in high risk groups, there are no accurate ways to determine the potential of a particular patient to progress to delayed or non-union. Such a tool would enable more reliable patient stratification, thus allowing for earlier diagnosis and increasing the potential success of additional early interventions by the surgeon. The presence, or concentration, of serum proteins are increasingly being investigated for their potential to identify at risk patients. One disadvantage of proteins is their relatively short half-life and their propensity to adhere to local components of the extra-cellular matrix.

Small non-coding RNA sequences have been shown to be powerful regulators of cellular behaviour. These micro RNA sequences (miRNAs) have been demonstrated to be heavily involved in cell regulation, in both healthy and diseased environments. They function by interacting with messenger RNA sequences and thereby modifying protein expression. miRNAs normally act intracellularly, but due to the action of exosomes released by cells they are able to signal over large distances and thus exosomes are a critical signalling pathway between different cells. Exosomes and miRNA have the advantage of being extremely stable, detectable in complex body fluids such as serum, and provide information directly relating to cellular function. MicroRNA (miRNA) studies are already transitioning from basic research applications to clinical applications in areas such as cancer diagnosis.

Within this project we aim to identify fracture related miRNA sequences, present in exosomes, in the serum of patients. Then establish their function within primary human mesenchymal stem cells, and propose predictive markers that could be used to screen patients early after injury. In addition, functionally active miRNA species identified as lacking in non-healing patients can also be used as a potential off-the-shelf treatment to enhance fracture repair in patients shown to have a decreased level of expression.

Partner:

- Kubosch J (MD), University Hospital Freiburg, Freiburg, Germany

Use of a rabbit humeral LCP model to provide evidence for treatment & prophylaxis concepts in open fracture care (Opin-fect) (F Moriarty)

One of the most challenging complications in trauma surgery is fracture related infection (FRI). FRI may result in permanent functional loss or even amputation of the affected limb in patients who would otherwise be expected to achieve complete, uneventful healing. Much of the surgical and medical treatment concepts currently applied to FRI have been adopted from prosthetic joint infection (PJI) treatment algorithms. A majority of the preclinical studies investigating best practice in the prevention and treatment of bone infection have also been applied with a focus upon PJI. Specific data tailored towards the musculoskeletal trauma patient is comparatively scarce. There are important distinctions between the elective arthroplasty patient and the trauma patient, both in terms of the risk of infection at the primary surgery, and in the options for treatment. With this project, we wish to address the features of FRI that are specifically critical for trauma surgery and ensure these aspects are reflected in our preclinical research studies in ARI.

Antibiotic prophylaxis is critical for the prevention of FRI in trauma patients, particularly those with open wounds. Administration of prophylactic antibiotics prior to arrival at the hospital (e.g. by paramedics) may reduce intraoperative bacterial load and has been recommended; however scientific evidence for pre-hospital administration is scarce. The Opin-fect project has established a model of an open fracture that allows to procedures (an initial "fracture" followed by a later "surgical fixation"). The data indicates early antibiotic administration can significantly reduce bacterial burden during surgical debridement and revision, however, un unable to independently prevent infection in this model.

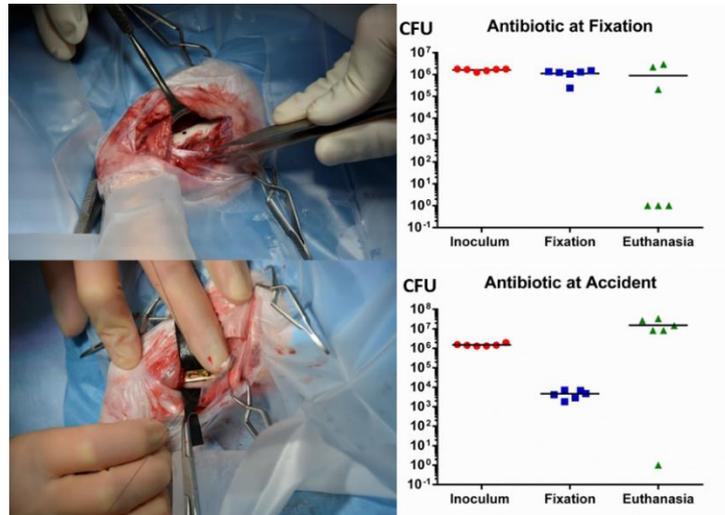


Figure 10.3.6: The surgical procedure developed in this project includes an initial surgical procedure to create bone damage and bacterial inoculation (upper left image). Delivering systemic antibiotic in a single shot at this time reduces bacterial load in the wound approximately 100-fold, although these remaining bacteria do go on to establish infection (upper right chart). The second surgical procedure involves debridement and irrigation (lower left image), and antibiotic administration at this time, for 24 hours, is unable to prevent infection (lower right chart).

Impact of risk factors on implant-related bone infections (BONSAI) (K Thompson, U Eberli, F Moriarty)

To date, the available literature concerning the impact of co-morbidities, for example, post-menopausal osteoporosis (PMO) on implant-related bacterial infection requires clarification. To investigate this we have developed an *in vivo* model system that allows us to use microCT scanning to monitor in real-time the bone changes resulting from the implantation of an inoculated screw in the rat proximal tibia.

Our work to date has demonstrated that microCT imaging can detect *S. epidermidis*-induced osteolysis as early as day 6, with peak osteolysis occurring around days 9-14. Antibiotic treatment (rifampin and cefazolin), administered on day 7, is particularly effective at clearing bacteria but did not reduce osteolysis. Interestingly, a low bone mass state resulting from ovariectomy (to mimic bone loss observed in PMO) does not affect the bacterial load but does markedly reduce antibiotic efficacy. Furthermore, bisphosphonate (BP) treatment (zoledronic acid, ZOL) did not prevent osteolysis in OVX rats but did increase total bacterial load, suggesting that inhibition of osteoclast activity is detrimental for an efficient host response to *S. epidermidis*.

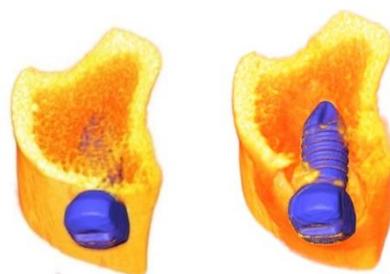
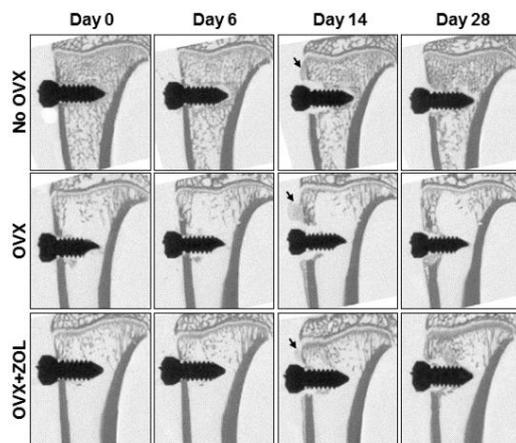


Figure 10.3.7: Left panel) Loss of bone over a 28-day period following implantation of a *S. epidermidis* inoculated screw into the proximal tibia of a rat under normal bone mass conditions (No OVX), low bone mass (OVX), or low bone mass plus BP treatment (OVX+ZOL). The areas indicated by arrows highlight a proliferative periosteal response as the infection proceeds. Right panel) A 3D reconstruction of a microCT scan from a sterile screw (left) or *S. epidermidis* inoculated screw in No OVX animal (right) 14 days after implantation.

Pub:

***In vivo* monitoring of Staphylococcus epidermidis implant infection using microCT imaging.**
K Thompson *et al.* Abstract eORS meeting (Sept 14-16, 2016), Bologna (oral presentation).

***S. epidermidis* bone infections associated with implanted medical devices in human patients (EpiLog) (B Stanic, F Moriarty)**

This project aims to provide improved understanding of the pathophysiological mechanisms specifically employed by *S. epidermidis* to limit/resist host protective immune responses. Upon completion of the recruitment phase in December 2016, 62 patients have had been recruited in the study based upon suspicion of bone infection (including 25 culture negative patients). Intraoperative bone marrow material as well as peripheral blood samples have been taken perioperatively. Since patient recruitment recently ceased, we have recently begun to analyse the cellular and molecular mechanisms underlying infection in a batch analysis manner.

The analysis of immunodominant proteins of *S. epidermidis* origin in the context of osteomyelitis has been continued by comparing the profiles of specific antibodies against *S. epidermidis* among a) control – non-infected patients, b) patients with *S. epidermidis* bone infection and c) patients with *S. aureus* bone infections (n=8 for all groups) in plasma samples, and culture supernatants of patient samples derived cells after restimulation with heat-killed *S. epidermidis in vivo*. Data analysis and selection of candidate proteins are in progress with the support of the functional genomics center at the University of Zurich.

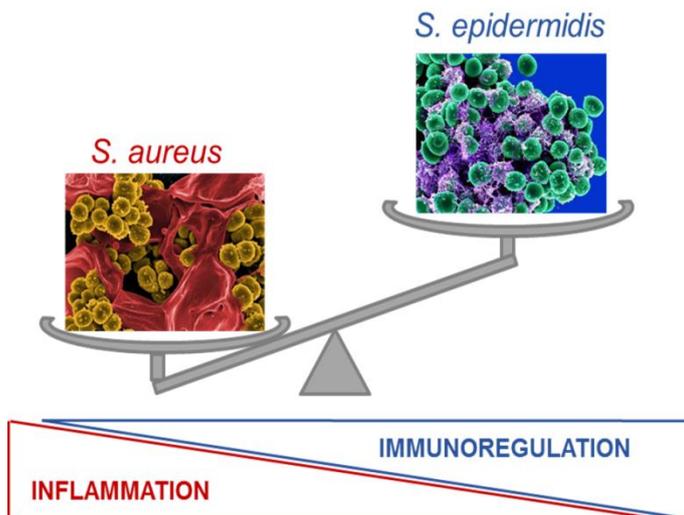


Figure 10.3.8: Overall profile of immune response toward *S. epidermidis* is likely to be dominated by immunoregulatory mechanisms when compared with *S. aureus* supporting different clinical presentations of infections.

Assessing the Role of stability on the Development of Infection (Immunobact) (M Sabaté Brescó, S Zeiter, F Moriarty)

Mechanical stability of the bone-implant construct has been described to impact infection risk. However, little is known about the mechanisms underlying this phenomenon. We have developed a murine femur osteotomy model, with rigid and flexible internal fixators, to study the influence of implant stability on the development of infection. A clinical *Staphylococcus epidermidis* isolate has been used to contaminate the operative field and the progression of the infection has been assessed after several days and weeks. The results showed that animals carrying a rigid implant could clear the infection in a higher percentage compared to animals with a flexible implant. From gene expression analysis, an increase in inflammation markers was observed in inoculated animals and in not-inoculated mice with a flexible device. Additionally, it was observed that IL-17A production was induced upon inoculation of bacteria and that this cytokine could be important for infection clearance. To understand the role of IL-17A in infection, our fracture-related infection model was tested in IL-17A knock-out mice. The source of IL-17A in bone has been identified and the project continues with the aim of understand if IL-17 type responses may be relevant for infection clearance.

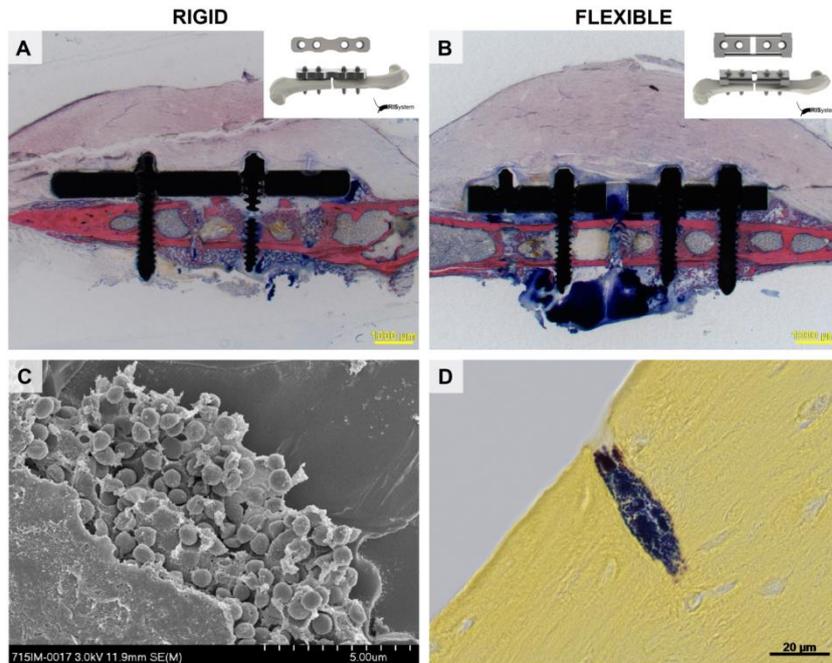


Figure 10.3.9: Giemsa-Eosin staining of murine femurs, with a rigid (A) or a flexible (B) device, 14 days after surgery. *S. epidermidis* observed over the implant in a scanning-electron microscope micrograph (C) or locating in bone canaliculae in a Brenn&Brown stained section (D).

Pub:

Rochford ET, Sabaté Bescó M, Zeiter S, Kluge K, Poulsson A, Ziegler M, Richards RG, O'Mahony L, Moriarty TF. *Monitoring immune responses in a mouse model of fracture fixation with and without staphylococcus aureus osteomyelitis.* **Bone** 2016 Feb;83:82-92

Pres:

Sabaté Bescó M, Berset C, Ziegler M, Richards RG, O' Mahony L, Moriarty TF. ***Staphylococcus epidermidis* infection progression and associated immune response in a murine fracture model (poster).** YSBM.ch Graduate Research Symposium 2016, 12th February, Zürich, Switzerland

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

World Immune Regulation Meeting X, 16th-19th March 2016, Davos, Switzerland

Sabaté Bescó M, Berset C, Kluge K, Richards RG, O'Mahony L, Moriarty TF. **Immune responses in a murine device-related infection model (poster).** Graubünden forscht 2016: Young Scientists in Contest, 14th-15th September, Davos, Switzerland

Sabaté Bescó M, Berset C, Kluge K, Richards RG, O'Mahony L, Moriarty TF. **Immune responses in a murine device-related infection model: role of IL-17A (oral).** X Catalan Society of Immunology Congress, 17th-18th November, Barcelona, Spain

Partners:

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

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

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. The optimal duration of perioperative antibiotic prophylaxis (PAP) for open fractures remains controversial due to heterogeneous or unclear guidelines and highly variable prophylactic regimens in clinical practice. We aimed at testing different durations under controlled experimental conditions in a contaminated fracture model. Postoperative duration of PAP had a significant impact on the success of antibiotic prophylaxis. Whereas the single shot regimen completely failed to prevent infection, the 24 hours regimen showed a reduced infection rate, but only the 72-hour course was able to prevent Fracture Related Infection (FRI) in all animals in our model.

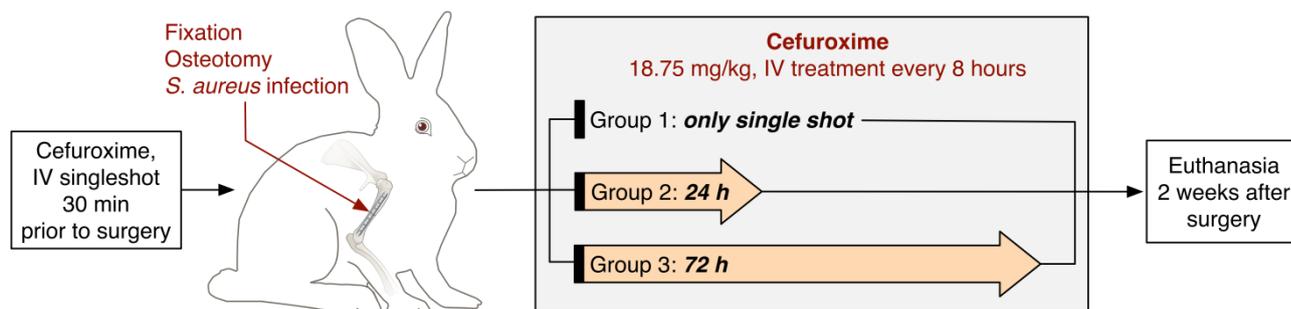


Figure 10.3.10: Outline of study design and rabbit fracture model. All rabbits received an intravenous single shot of cefuroxime 30 minutes prior to surgery. A 7-hole-LCP with six bicortical screws was placed on the right humerus. Then, a mid-diaphyseal osteotomy and standardized inoculation with *S. aureus* were performed. The antibiotic prophylaxis was discontinued, continued for 24 hours, or continued for 72 hours. Euthanasia was scheduled two weeks postoperatively.

Pub:

Titanium and steel fracture fixation plates with different surface topographies: Influence on infection rate in a rabbit fracture model. Metsemakers WJ, Schmid T, Zeiter S, Ernst M, Keller I, Cosmelli N, Arens D, Moriarty TF, Richards RG. *Injury*. 2016 Mar;47(3):633-9.

Influence of implant properties and local delivery systems on the outcome in operative fracture care. Metsemakers WJ, Moriarty TF, Nijs S, Pape HC, Richards RG. *Injury*. 2016 Mar;47(3):595-604. doi: 10.1016/j.injury.2016.01.019.

Infection after fracture fixation: Current surgical and microbiological concepts. Metsemakers WJ, Kuehl R, Moriarty TF, Richards RG, Verhofstad MH, Borens O, Kates S, Morgenstern M. *Injury*. 2016 Sep 11

Development of a large animal model to study the biology of two-stage hardware exchange due to implant related osteomyelitis (T Schmid, V Post, S Zeiter, F Moriarty)

The treatment of chronic orthopedic device-associated infection (ODRI) often requires multiple surgeries and prolonged antibiotic therapy. Despite this extensive treatment protocol, the procedure is associated with significant failure rates. Currently, no large animal model is available that recapitulates a failed revision. Our aim was therefore to establish a large animal model for failed treatment of an ODRI in order to serve as a testbed for future interventional strategies.

We have successfully established an implant related osteomyelitis model with a two-stage exchange in sheep using a methicillin-susceptible *S. aureus* and a methicillin resistant *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 was the MSSA infection completely eradicated and the MRSA infection was not treatable by the currently used antibiotic regimens. Novel interventions may be assessed using this model, including antibiotic and non-antibiotic interventions.

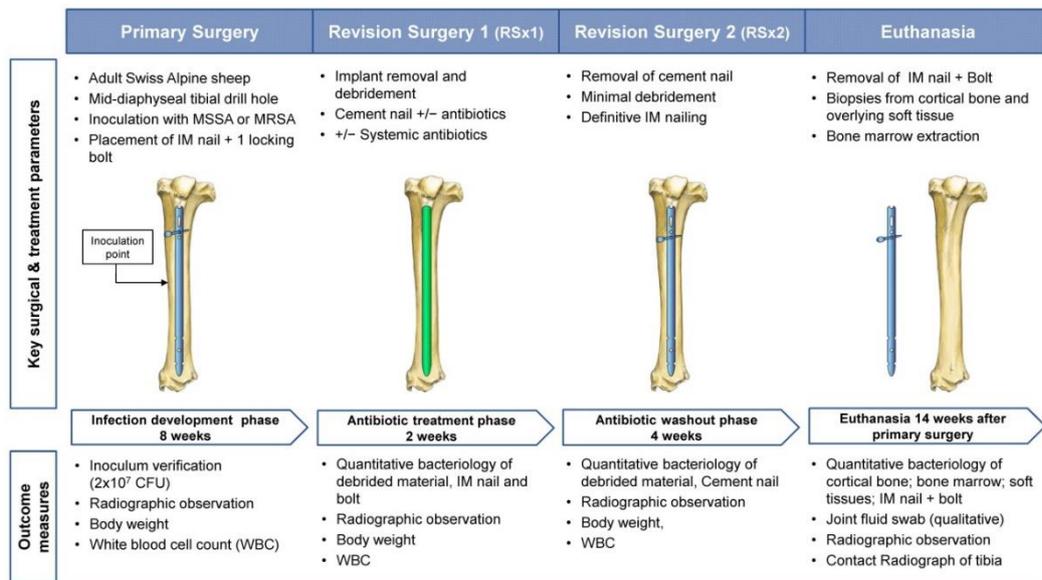


Figure 10.3.11: Schematic overview of the infection development phase and subsequent treatment steps in the staged re-nailing of the infected tibial IM nail in the sheep. Upper text describes key surgical parameters at each surgical intervention and biopsy sampling at euthanasia. The lower text describes key outcome measures including routine observations and quantitative bacteriological measures at each surgical intervention and at euthanasia.

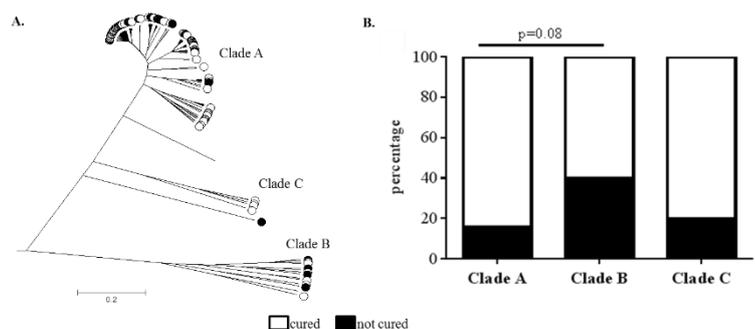
Partners:

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

Molecular epidemiology of staphylococcal isolates from musculoskeletal infections associated with orthopaedic devices (V Post, F Moriarty)

In the most recent activity of the StaphSeq project, we focussed on analysing the whole genome sequences of *S. epidermidis* isolated from patients with implant related bone infection in addition to conventional analyses such as biofilm forming ability. The patients have been categorized into "cured" or "not cured" clinical outcome according to definitions developed with clinical partners. Using the whole genome data, we observed that the clinical *S. epidermidis* isolates clustered in 3 clades (Figure 1). A trend was observed with more "not cured" isolates clustering in clade B vs clade A ($p=0.08$). A statistically significant correlation between strong biofilm formation and "not cured" outcome was seen ($p=0.031$) and the biofilm-associated *bhp* gene was also more prevalent in "not cured" outcome isolates ($p=0.023$). Furthermore, a plasmid-born antiseptic resistance *qacA* gene ($p=0.023$), genes *ccrB* and *ccrA* ($p=0.034$ and $p=0.042$, respectively) responsible for insertion of methicillin-resistance mediating mobile element *SCCmec* as well as IS256 mobile element ($p=0.085$) were present in a significant higher prevalence in "not cured" outcome isolates. Hence these elements could be used as molecular markers for identification of *S. epidermidis* leading to a poorer clinical outcome.

Figure 10.3.12: Population structure of *S. epidermidis* isolates constructed from 123 core genes and implemented in CLONALFRAME. In **A**, all 104 isolates of the complete cohort study and in **B**, all 70 isolates of the lower extremity are labelled according to the clinical follow-up (FUP) outcome: "not cured" (black circle) and "cured" (open circle). **C** and **D** shows the percentage distribution of "cured" and "not cured" outcome in the three clades A, B, C with **C** showing the complete cohort and **D** the lower extremity cohort



Pres:

Post V, Harris L, Morgenstern M, Richards RG, Moriarty TF. Prevalence and Characterization of Nasal Methicillin-Resistant *Staphylococcus aureus* from Human and Veterinary Surgeons. 2016 SSM SGM (poster)

Post V, **Wahl P**, Richards RG, Moriarty TF. Vancomycin displays time-dependent eradication of mature *S. aureus* biofilms. 2016 EBJIS (oral)

Pub:

Post V, Wahl P, Richards RG, Moriarty TF. Vancomycin displays time-dependent eradication of mature *Staphylococcus aureus* biofilms. J Orthop Res. 2017 Feb;35(2):381-388

Post V, Harris L, Morgenstern M, Richards RG, Sheppard SK, Moriarty F. Characterisation of nasal methicillin-resistant *Staphylococcus aureus* isolated from international human and veterinary surgeons. J Med Microbiol. 2016 Dec 21

Morgenstern M, **Post V**, Erichsen C, Hungerer S, Richards R, Militz M, Buehren V, Moriarty TF. Biofilm formation increases treatment failure in *Staphylococcus epidermidis* device-related osteomyelitis of the lower extremity in human patients. J Orthop Res. 2016 Nov;34(11):1905-1913

Collaborators:

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

Investigating the effect of the inflammatory response to trauma on local antibacterial defense (TrauSer-feasibility) (K Thompson, A Stylianaki, F Moriarty)

The majority of implant related bone infections are believed to be seeded during the perioperative period i.e. just prior to, or soon after placement of the implant. In cases where an infection develops, the bacteria that enter the wound in this time are inadequately killed by cells of the immune system. This is believed to be partly due to a localized deficiency in immune cell function (frustrated phagocytosis). Numerous studies have shown that severe trauma itself induces changes in immune cell function and the magnitude and duration of this immune dysfunction appears to be influenced by the severity of the traumatic episode. Our hypothesis is that the initial trauma will influence the risk of local implant related bacterial infection due to deficiencies in the antibacterial function of innate immune cells. As this early perioperative period is the critical time for seeding of the implant, we believe this may be a critical phase in the development of implant related infection.

The objectives of this study are to determine if serum from polytrauma patients negatively affects immune cell function and antibacterial efficacy, compared to serum from healthy donors, and to identify potential soluble mediators responsible for these inhibitory effects.

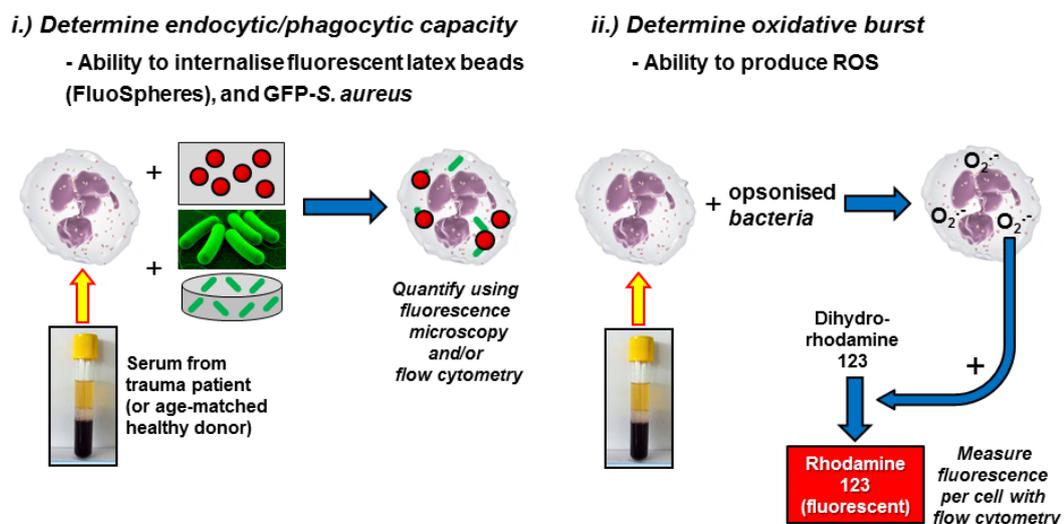


Figure 10.3.13: Schematic representation of *in vivo* assays used to determine the ability of polytrauma patient sera to induce functional changes in immune cell behaviour.

10.4 AOVET

Computational and experimental evaluation of hybrid non-locking and locking canine pancarpal arthrodesis plates (PancarFE) (Ongoing) (I Zderic)

Problem: Although numerous canine pancarpal arthrodesis (PCA) fixation techniques exist, the most common procedure relies on a dorsally applied plate, despite its biomechanical disadvantage. Dorsally applied plates are also related to some biological disadvantages inherent to soft tissue tension during wound closure. To address these limitations, a hybrid non-locking plate with a tapered profile, a round radio-carpal (RC) and dynamic-compression plate holes, is one of the most frequently used PCA implants to bridge the radius and the third metacarpal. Recently, new tapered hybrid LCP PCA plates were developed in two designs. While mechanical superiority of the hybrid non-locking plates over LC-DCPs was recently reported, comparisons between standard hybrid non-locking and LCP PCA plates are missing.

Goal: To investigate the mechanical behavior of the hybrid non-locking and LCP PCA plates. The project is conducted in two phases. In phase 1 (computational), construct compliance, maximum angular deformation and plate strains are compared by means of Finite Element Analysis applying a previously published protocol. In phase 2 (experimental), fixation strength and mechanical behavior of each plate design will be investigated under cyclic loading with the use of strain gauges. Should the hybrid LCP PCA plates offer a mechanical advantage, implant-related complications could be reduced and implant life-extended.

Results: Setup for mechanical testing is established. Results from the performed Finite Element Analysis will be used to determine the best possible location for strain gauge application in phase 2 of the project.

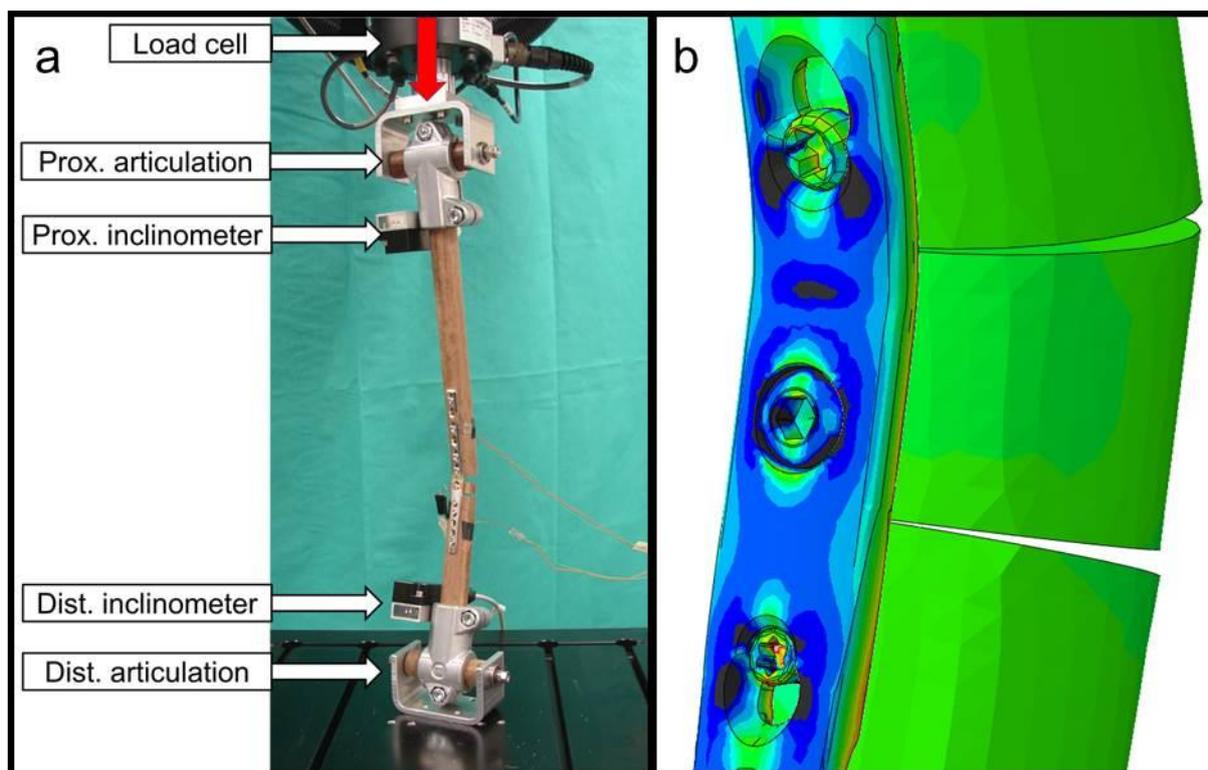


Figure 10.4.1: Test setup with a specimen mounted for mechanical testing (left, a). Principal strains at a hybrid LCP PCA plate as predicted by the Finite Element Analysis (right, b).

Partners:

- Déjardin LM (Prof), Michigan State University, East Lansing, MI, USA
- Marturello D (DVM), Michigan State University, East Lansing, MI, USA
- Asimus E (DVM), Ecole Nationale Vétérinaire de Toulouse, Toulouse, France
- Kowaleski M (Prof), Tufts University, Medford, MA, USA

10.5 AOTK System

AO Fracture Monitor (SmartFix/SmartPlate) (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 limitations 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 ARI within a related project (ImpCon 2). Based on this approach, a medical device – AO Fracture Monitor – shall be developed and validated in clinics.

Goal: The AO Fracture Monitor will be applied non-invasively within a clinical trial to assess the diagnostic value of the recorded parameters. In a parallel work-stream, the system is refined to meet the requirements for an internal application with bridging plates.

Results: Patients recruitment in the pilot clinical study testing the AO Fracture Monitor in fractures treated with external fixation started in 2015. Nine patients were followed up for six months post operation. By the end of 2016, data collection was completed. All patients had a history of bone infection. The data derived from the AO Fracture Monitor showed a moderate response of the healing curve in seven patients. In two obvious non-union cases, the healing curve remained unchanged throughout the monitoring period. Radiographic evaluation did not allow reliable diagnostics. In the light of this very demanding patient collective, it may be concluded, that the AO Fracture Monitor is capable of detecting healing progression where radiological assessment fails.

In parallel the AO Fracture Monitor is further developed and laid out for internal application with bridging plates. The device follows the same measurement principle as for external fixation but will be implantable and attachable to standard locking plates for continuous measurement and data processing with a wireless link to outside. A second-generation electronic module was finalized. Currently, the main development focus is on further miniaturization and improved power management. Pre-clinical *in vivo* testing will be conducted soon.

Pres:

Windolf M. Smart Plates: AO fracture monitor. 2016. DKOU

Ernst M. Smartfix – monitoring external fixation. 2016. DKOU

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

Anatomical evaluation for new fixation concepts in pelvic and acetabular fractures. CT based 3D statistical modeling and analysis of the pelvis in Asians and European Caucasians (PelMorph) (L Kamer, H Noser)

Problem: The growing number of osteoporotic pelvic and acetabular fractures requires consideration of the unique and variable pelvic anatomy and particularly of the bone stock distribution. Reconstruction of acetabular fractures remains a surgical challenge especially in elderly patients with osteoporosis. The fracture pattern typically involves the quadrilateral surface and leads to subchondral impaction of the acetabular dome due to forces applied by the femoral head. Both functional outcome and preservation of the femoral head depend on the congruency of the acetabular articular surface. Hence, meticulous reconstruction of these anatomical structures is of critical importance. Adapted operative strategies are required to improve the overall surgical outcome particularly in presence of low bone quality.

Goal: To perform a three-dimensional (3D) anatomical evaluation of the entire pelvis by means of computational modelling and analysis.

Results: A total of 150 computed tomography (CT) scans of the intact pelvis of adult Asians and European Caucasians were used to create a 3D statistical model of the pelvis and an averaged 3D model with the grey values given in Hounsfield Units.

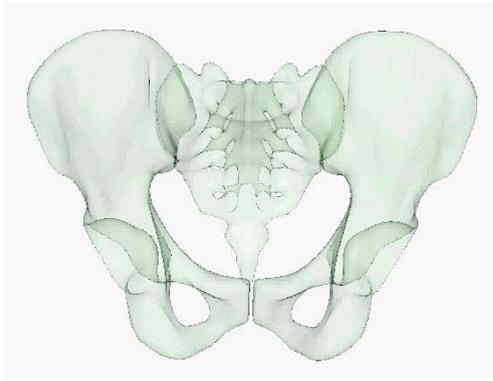


Figure 10.5.1: Frontal views illustrating pelvic mean shape (left) and average grey value distribution (right) as derived from the computational modelling.

Pres:

Arand C, Wagner D, Noser H, Kamer L, Sawaguchi T, Richards RG, Rommens PM. 3D statistisches Modell des knöchernen Beckens - Anatomische Variabilität und biomechanische Relevanz. DKOU 2016, October 25-28, 2016, Berlin, Germany.

Partners:

- Arand C (MD), Department of Trauma Surgery, Center for Musculoskeletal Surgery, University Medical Centre, Mainz, Germany
- Wagner D (MD), Department of Trauma Surgery, Center for Musculoskeletal Surgery, University Medical Centre, Mainz, Germany
- Rommens P (Prof), Department of Trauma Surgery, Center for Musculoskeletal Surgery, University Medical Centre, Mainz, Germany
- Sawaguchi T (Prof), Department of Orthopaedics & Joint Reconstructive Surgery, Toyama Municipal Hospital, Toyama, Japan

Biomechanical investigation on the influence of RIA reaming diameter on failure loads of human cadaveric femora (RIABiomech) (Ongoing) (D Gehweiler, B Gueorguiev-Rüegg)

Problem: Treatment of large bone defects is one of the unsolved problems in orthopedic and trauma surgery today. Autologous bone grafting is currently the gold standard to fill such defects. Cancellous bone is therefore usually harvested from the iliac crest. This procedure often allows only a small amount of bone to be collected from one side, and is associated with several complications and postoperative morbidity. The Reamer-Irrigator-Aspirator (RIA) was introduced as minimally invasive surgical device for bone graft harvesting from the medullary canal of the femur. With this promising procedure large amounts of bone graft can be extracted. However, postoperative femur fractures have been observed after this procedure. One critical aspect in the process is the choice of an appropriate reaming diameter.

Goal: To determine the influence of the reaming diameter and reaming geometry on the percentage reduction of bone strength in human cadaveric femora using a recently optimized RIA system.

Methods: Forty five pairs of human cadaveric femora were randomly assigned to one of the following three treatment groups, taking into consideration gender, age, bone mineral density and isthmus diameter: I – standard size reaming (+1.5 mm larger than femoral isthmus), II – oversized reaming (+2.5 mm), III – maximal reaming (+4.0 mm). One femur of each pair was randomly reamed, the other served as unreamed control. All specimens were loaded quasi-statically to 750N axial compression at a rate of 1 mm/min and then internally rotated until failure at a rate of 0.25 deg/sec. Reaming and fracture morphology of the reamed group was analyzed by means of CT scans.

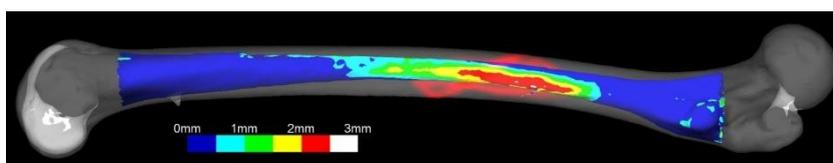


Figure 10.5.2: Medial view of a reamed femur specimen: outer surface – gray transparent, amount of reaming from the medullary canal – color coded, fracture lines – red transparent on outer surface.

Partners:

- Raschke MJ (Prof) Department of Trauma, Hand and Reconstructive Surgery, University Hospital Münster, Münster, Germany
- Wähnert D (PD) Department of Trauma, Hand and Reconstructive Surgery, University Hospital Münster, Münster, Germany

AO Implant Positioning Assistance (RotCor) (Ongoing) (J Buschbaum, 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: A clinical handling test of the X-in-One module for proximal humeral plating was initiated in collaboration with UZ Leuven, Belgium. The final approval by the Federal Agency for Medicines and Health Products is expected soon.

A novel X-in-One module for corrective osteotomies was developed in collaboration with the Joint Preservation Expert Group (JPEG). X-in-One tracking markers, attachable to the two Schanz's screws (distally and proximally to the osteotomy) were designed and produced. A software algorithm detects these markers in a single X-ray image and computes their spatial orientation. During surgery the prevailing values of the achieved correction are computed and displayed. The surgeon can thus easily monitor the performed correction and act accordingly. Feasibility of the system was proven in cadaveric experiments and accuracy was assessed in bench tests. The rotational error was $0.65^{\circ} \pm 0.55^{\circ}$ which fulfills the clinical requirements. To pursue the path to clinical application a clinical handling test in collaboration with BGU Tübingen, Germany has started.



Figure 10.5.3: Navigation tool for assisting rotational osteotomies in a laboratory setup, containing the software module implemented on a tablet computer (upper right) and the special designed markers (lower right).

Partners:

- Nijs S (Prof) UZ Leuven, Belgium
- Schröter S (PD), BG Unfallklinik Tübingen, Germany

Automated ranking of fracture severity in serial CT scans of pilon fractures (Ongoing) (H Noser, L Kamer)

Problem: There is an ongoing discussion whether the quality of reduction or the injury/fracture severity has the highest impact on the final outcome.

Goal: The aim of this CT-based project is related to identification of objective fracture severity criteria and the most important predictors of the functional outcomes following pilon fractures.

Results: Within a first project phase a software tool was developed and tested in collaboration with members of the Lower Extremity Expert Group (LEEG) in order to search for observer independent CT criteria to objectively assess severity of pilon fractures. The tool automatically extracted numerous fracture properties (e.g. number of fracture segments or degree of dislocation) from standard CT scans. Expert surgeons were asked to rank given clinical CT cases according to fracture severity in order to train the software tool learning system. The process exhibited a high concordance with the experts rankings. The concordance between the experts and the artificial intelligence system did not differ from the concordance obtained among the experts. The software tool was successfully applied to 71 previously unknown clinical CT cases.

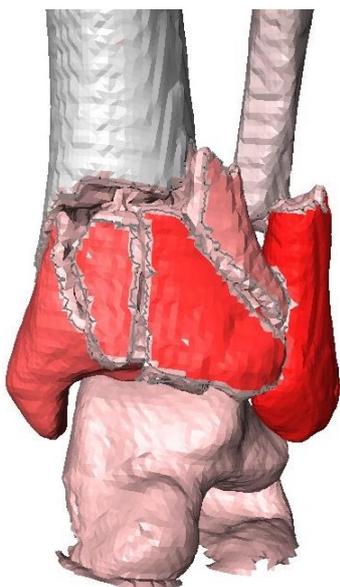


Figure 10.5.4: Example of a previously unknown clinical CT case that was ranked using the computerized fracture severity tool.

Partners:

- Nork SE (MD), Harborview Medical Center, Department of Orthopedic Surgery, Seattle, USA
- Graves M (MD), University of Mississippi Medical Center Jackson, Mississippi, USA
- Goldhahn S, Consultant, AOCID, Dübendorf, Switzerland
- Sommer C (MD), Kantonsspital Graubünden, Department of Surgery, Chur, Switzerland, Switzerland

10.6 ARI Exploratory Research

Smart Drill: Development of a laser-based device for automated screw length detection (AutoGauge) (Ongoing) (P Varga, M Windolf)

Background: Appropriate plate osteosynthesis of long bone fractures requires placement of screw with correct lengths in order to ensure fixation stability and avoid soft tissue irritation. The use of the current state-of-the-art manual depth gauge to measure screw length after drilling has been reported to often lead to selection of wrong screws, replacement of which increases surgery cost, time and radiation dose. These limitations could be overcome with a newly invented "smart drill" concept, which would allow measurement of the actual drill depth directly during drilling and detection of the required screw length on the fly.

Goal: Development and testing of a laser-based smart add-on device prototype to monitor the actual drill depth and provide an automated estimate of bi-cortical screw length for plate osteosynthesis of long bone fractures.

Results: A fully functional and sterilizable add-on device prototype (AutoGage) has been developed and manufactured, including an electronic unit containing a laser sensor, computer, battery, a screen for user feedback and a robust cortex detection software algorithm. Besides performing several technical safety tests, the accuracy of the prototype has been tested extensively in the laboratory on human cadaver femora, humeri and distal radii and found to be – compared to CT standard – better than 1.0 mm in 95% of the 166 drillings (standard deviation 0.52 mm). The prototype has been tested during sheep and rabbit surgeries in the ARI Preclinical Facility. Moreover, the prototype has been showcased to more than 170 surgeons. More than 70% of the participants rated the potential benefit of AutoGauge to be high.

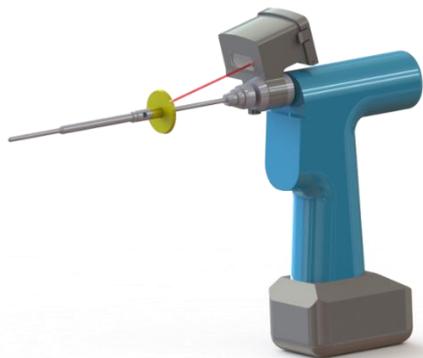


Figure 10.6.1: The AutoGauge prototype as a CAD drawing (left) and in action during a sheep surgery.

Pres:

Varga P, Varjas V, Gehweiler D, Gruenwald L, Richards RG, Schuetz M, Windolf M. AutoGauge – the Smart Drill. A device for automated screw length determination. 2016. DKOU (oral)

Partner:

- Schuetz M (Prof), Charité UM Berlin, Germany

A novel concept for guided growth regulation (GoForce) (Ongoing) (J Buschbaum, M Windolf)

Problem: Corrections of limb deformities are frequent interventions in pediatric orthopedic surgery. In most cases temporary epiphysiodesis is used whereby the growth is guided by temporarily blocking the physis. Currently utilized implants are not "passively" safe. They require timely surgical intervention (removal), because ongoing growth leads to a steady rise of the reaction force of the fixation, and thereby to plate and screw deformation and consequently to devastating events like implant breakage or growth arrest. To avoid these issues, a new implant concept for guided growth regulation was proposed.

Goal: To develop an implant prototype based on the proposed principle and test its functionality in a large animal experiment.

Results: A new epiphysiodesis implant for limb deformity correction was developed. The implant is designed to be "passively" safe, since it will not climax in a catastrophic failure and is hypothesized to allow for controlled regulation of the growth. Bench testing was carried out to verify the basic function and mechanical characteristics of the implant. The efficacy of the implant in terms of magnitude of varus-valgus correction is currently tested in lambs. All lambs were treated in a hemiepiphysiodesis setting to create varus deformity. Preliminary results look promising. This *in-vivo* project provides important and currently unknown information to enhance the knowledge on bone growth processes and improve the treatment of limb deformities.

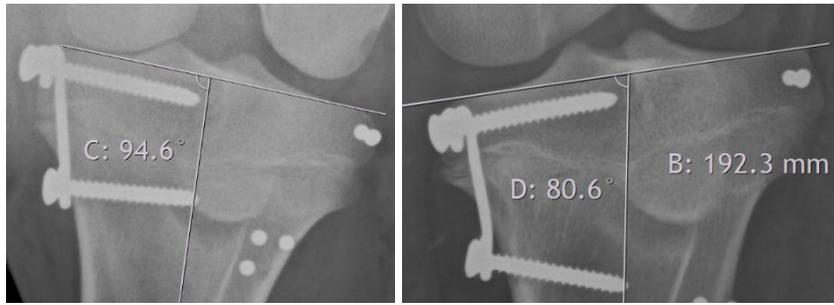


Figure 10.6.2: Varus deformity as obtained with the new implant concept, comparing the medial proximal tibial angle postoperatively (left image) and after 16 weeks (right image).

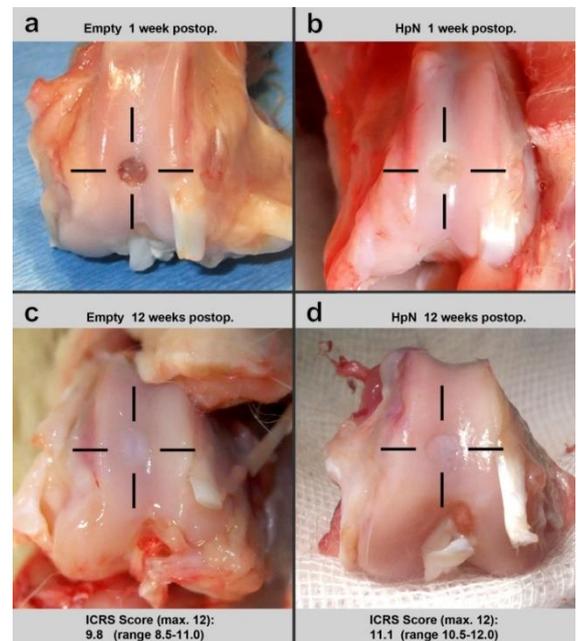
Thesis:

- Schiedeck A. Implant development for growth by steering Epiphysiodesis in childhood and adolescence, including quality management according to EN ISO 13485. 2016. University of Applied Sciences, Gelsenkirchen Bocholt Recklinghausen – Master Thesis

Thermoresponsive hydrogels based on natural polysaccharide (CARTHA) (Completed) (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 10.6.3).

Figure 10.6.3: Representative macroscopic images of cartilage defect site containign or not an injectable thermoresponsive hydrogel (HpN). (Reprinted from D'Este et al. JBMRA 2016, 104(6), 1469-78.)



Pres:

- [1] Russo F, Vadalà G, D'Este M, Alini M, Eglin D, Giordano R, et al. A hyaluronic acid / platelet rich plasma hydrogel for mesenchymal stem cells delivery to the intervertebral disc: rheological and biological characterization. EORS. Bologna2016.
- [2] Russo F, D'Este M, Vadalà G, Papalia R, Alini M, Denaro V. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: Rheological evaluation. ORS. Orlando2016.
- [3] D'Este M. Hyaluronic acid derivatives for in situ tissue engineering and additive manufacturing. AFPM. Enschede2016.

[4] D'Este M, Sprecher C, Milz S, Nehrbass D, Dresing I, Zeiter S, et al. Evaluation of an injectable thermoresponsive hyaluronan hydrogel in a rabbit osteochondral defect model. WBC. Montreal2016.

[5] D'Este M, Sprecher C, Kyllonen L, Milz S, Schmid T, Alini M, et al. SDF-1 and CCL5 delivered from thermoresponsive hyaluronan hydrogel induce cell homing in an osteochondral defect repair model in rabbit. WBC. Montreal2016.

Pub:

[1] Petta D, Eglin D, Grijpma DW, D'Este M. Enhancing hyaluronan pseudoplasticity via 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride-mediated conjugation with short alkyl moieties. *Carbohydr Polym* 2016;151:576-83.

[2] Russo F, D'Este M, Vadala G, Cattani C, Papalia R, Alini M, et al. Platelet Rich Plasma and Hyaluronic Acid Blend for the Treatment of Osteoarthritis: Rheological and Biological Evaluation. *PLoS One* 2016;11:e0157048.

[3] D'Este M, Sprecher CM, Milz S, Nehrbass D, Dresing I, Zeiter S, et al. Evaluation of an injectable thermoresponsive hyaluronan hydrogel in a rabbit osteochondral defect model. *J Biomed Mater Res A* 2016;104:1469-78.

Partners:

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

Fibrous polymeric patch for annulus fibrosus repair (AFEPATCH) (Completed) (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 and nucleus pulposus repair strategies were developed using sutured polyurethane membranes designed to prevent herniation, scaffolds and hydrogels, fibrin-genipin adhesive and their combination. These repair strategies were evaluated for biomechanical restoration, herniation risk and failure mode using a bovine injury model (Figure 10.6.4).

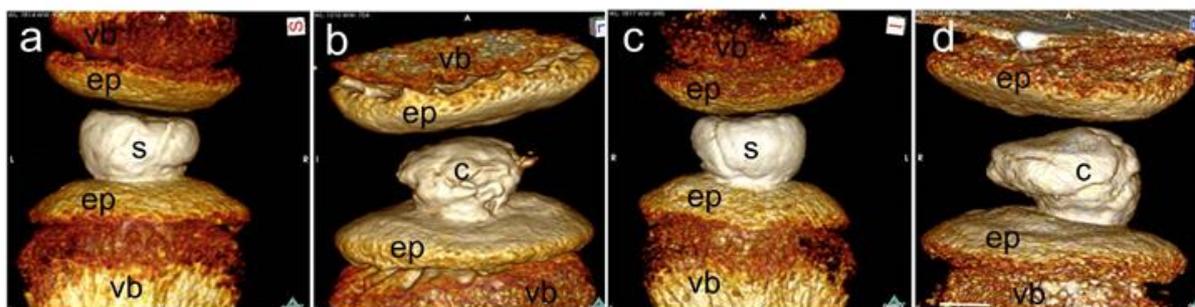


Figure 10.6.4: X-ray tomography reconstruction images of Injected Hydrogels in full IVD motion segments (s and C hydrogels, ep: endplate, vb: vertebral body) scale bar = 3 mm, from Peroglio et al. 2016 ORS abstract.

Pres:

[1] Peroglio M, Perez-San Vicente A, Ernst M, Casuso P, Dupin D, Alini M, et al. Self-healing dynamic hydrogel for nucleus pulposus restoration: Mechanical characterization of spine motion segments. ORS2016.

[2] Perez-San Vicente A, Peroglio M, Ernst M, Casuso P, Dupin D, Cabanero G, et al. Injectable and self-healing dynamic hydrogel as efficient nucleus pulposus replacement for intervertebral disc repair. WBC. Montreal2016.

[3] Leite Pereira C, Ferreira J, Eglin D, Grad S, Barbosa MA, Goncalves RM. Extracellular Matrix Remodeling in intervertebral Disc by Mesenchymal Stem/Stromal Cells Recruitment from the Cartilaginous Endplate: a new perspective for IVD regenerative strategies Eur Spine J 2016;25:S347.

[4] Long RG, Rotman SG, Hom WW, Assael DJ, Illien-Jünger S, Grijpma DW, et al. Polyethylene glycol and poly(trimethylene carbonate) block copolymers for annulus fibrosus repair have high cytocompatibility, restore axial range of motion and have some herniation risk. YSBMch. Zürich2016.

Partners:

- Annulus Fibrosus Ruptures Collaborative Research Programs Consortium
- Iraida Loinaz (Dr.) Materials Division, IK4-CIDETEC Research Centre, Donostia-San Sebastián, Spain

Bio-adhesive biopolymers for integration of cartilage injury regenerative therapy (GELHOME) (Ongoing) (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 10.6.5).

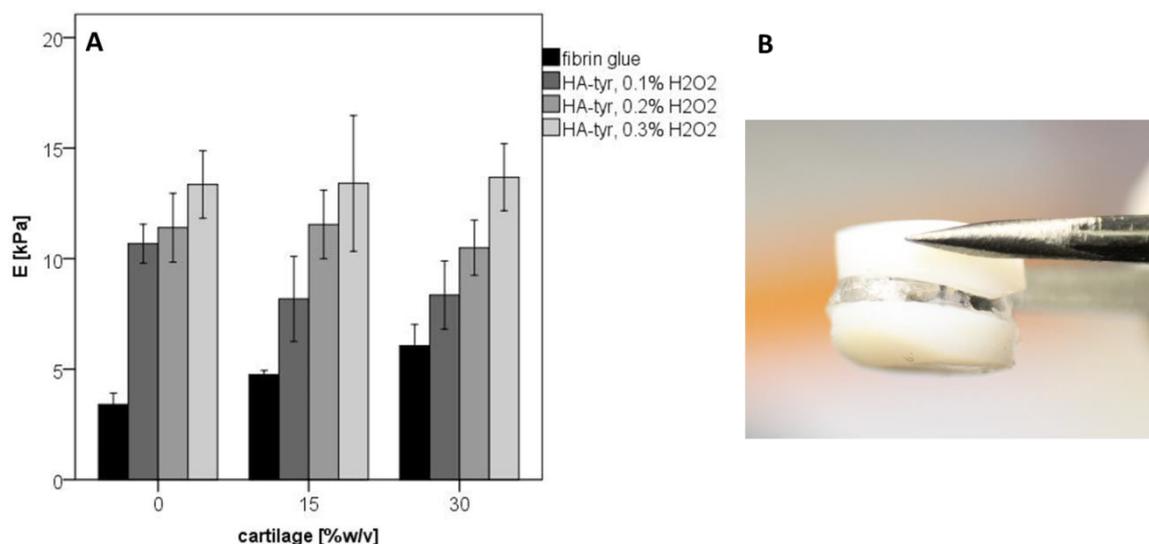


Figure 10.6.5: Compressive modulus of gels loaded with 0, 15 and 30% of cartilage particles. B: HA-tyr mediates the adhesion of two cartilage cylinders to each other from Cavali et al. 2015, ORS abstract.

Pres:

[1] Loebel C, Cosgrove B, Alini M, Zenobi-Wong M, Mauck RL, Eglin D. Crosslinking Chemistry of Tyramine-Modified Hyaluronan Hydrogels Alters Mesenchymal Stem Cell Attachment and Behavior WBC. Montreal2016.

[2] Loebel C, Alini M, Zenobi-Wong M, Eglin D. Cell-matrix interactions in hyaluronan-tyramine hydrogels matrix alter stem cell behaviour in 3D. Eur Cell Mater 2016;31:o118.

[3] Stauber T, Öztürk E, Loebel C, Eglin D, Zenobi-Wong M. Hydrogels made from cartilage-mimetic sulfated alginate polymers via di-tyramine bond formation show increased stability and adhesion to cartilage. Eur Cell Mater 2016;32:54.

[4] Loebel C, Cosgrove B, Alini M, Zenobi-Wong M, Mauck RL, Eglin D. Crosslinking strategy of hyaluronan-tyramine hydrogels alters mesenchymal stem cell attachment and behavior. Eur Cell Mater 2016;32:47.

Partner:

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

In vivo assessment of osteogenesis (Ostmonit) (Completed) (M Stoddart)

This project has developed online monitoring methodologies that can be used to reduce the experimentation required for the *in vivo* testing of osteogenic cells, materials and therapies. We have demonstrated that individual markers are often not sufficient to establish accurately cell behaviour. To provide a more accurate assessment of cell fate decisions, we have determined that ratios of mRNA messages for commonly investigated master transcription factors, such as Sox9 (chondrocyte) and Runx2 (Osteoblast) provide a more accurate assessment of cell behaviour. We have demonstrated that the ratio of Runx2:Sox9 mRNA message on day 7 can predict calcification potential of human bone marrow derived mesenchymal stem cells on day 28. The standard method to quantify mRNA expression on day 7 is destructive. Using dual SmartFlare probes, we successfully developed protocols for live cell sorting according to the mRNA expression of Runx2/ Sox9. The sorting strategy harvested new populations of cells that were not present under control conditions, but appeared after osteogenic induction (Figure 9.6.6). The sorted cells reproducibly show a different mRNA expression pattern depending on gate (Figure 9.6.6 C). The sorted cells were reseeded and analyzed for their proliferation rate and osteogenic differentiation. It was demonstrated that osteogenically induced hBMSCs are not homogeneous, and cells have different proliferation rates and osteogenic differentiation potentials. These heterogeneous cells can be sorted into relatively homogeneous populations based on mRNA expression of Runx2 and Sox9. At the mRNA level, Population 1 (P1) has undetectable Sox9, low Runx2, low Col 1, low ALP but high osteocalcin. This is suggestive of a more mature phenotype and this has been verified in multiple donors. Among these sorted cells, P1 has the highest osteogenic differentiation potential, as assessed by alizarin red staining, and lowest proliferation rate. This has resulted in a population of cells that has potential therapeutic use. Also, the enhanced sorting into more homogeneous groups allows for a more detailed understanding of osteoblast differentiation and biology.

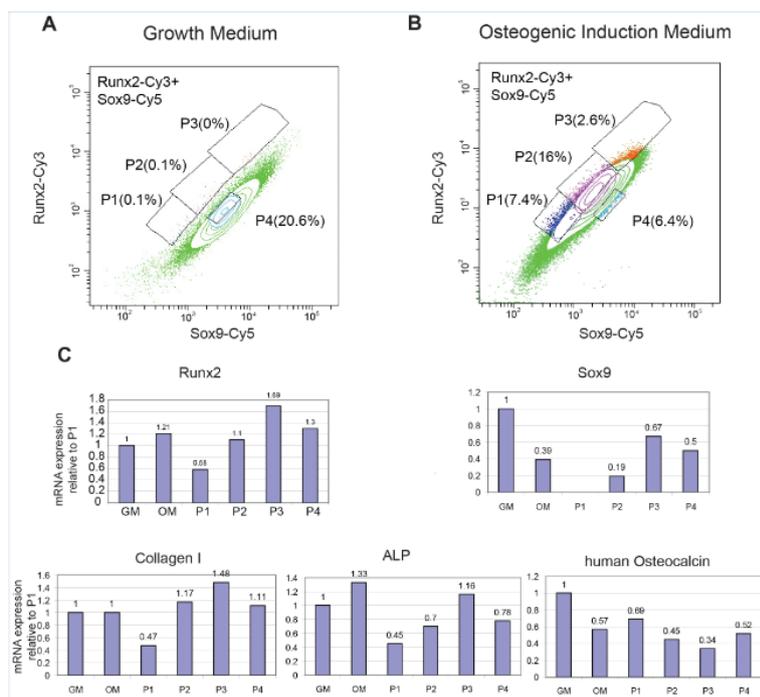


Figure 10.6.6: Dual SmartFlare probes can detect Runx2/Sox9 mRNA expression in individual live cells. (A, B) hBMSCs with dual SmartFlare probes Runx2-Cy3/Sox9-Cy5 in growth medium (A) or osteogenic induction medium (B) after cultured for 6 days. Cells in osteogenic induction medium were gated into 4 groups P1, P2, P3 and P4 based on the relative intracellular fluorescence of Sox9 in relation to Runx2. P1, P2 and P3 only appear after osteogenic differentiation. (C): Real time PCR results of Runx2, Sox9, Collagen I, ALP and human Osteocalcin expressions in sorted osteogenic induced hBMSCs.

Pub:

Bojun Li, Ursula Menzel, Claudia Loebel, Mauro Alini, Martin Stoddart (2016) Monitoring live human mesenchymal stem cell differentiation and subsequent selection using fluorescent RNA-based probes. *Nature Scientific Reports*. 6:26014. doi: 10.1038/srep26014.

Pres:

Outcome measures for bioreactors in orthopaedics. 08.11.2016. Bioreactors and Growth environments for Tissue Engineering, Keele University, United Kingdom.

Investigation of bone marrow stem cells in the bone marrow niche in an *in vivo* system (Stemcart) (Completed) (M Stoddart)

The aim of this project was to culture whole marrow mononuclear cells in a quiescent state. Most *in vivo* studies investigate monolayer expanded or selected cells, which would not be the cell type present during the natural repair process. We were 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. 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 vivo* 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. Within the final year we have been investigating the selectivity of the naïve cells from whole bone marrow to infection with standard gene therapy vectors. Therefore, we immuno-phenotyped bone marrow derived mononuclear cells (BM-MNCs) transduced with and adenoviral vector over-expressing green fluorescent protein (A-GFP).

Analysis of BM-MNCs revealed that Ad-GFP preferentially transduced non-granular CD45+CD3-CD14+ monocyte containing populations. Of the 7.7%GFP+ cells, 81% were CD45+CD3-CD14+ (monocyte/ macrophage) with 82% of this population small and non-granular when considering side-scatter profile (Fig x). When considering the entire cell population, 54.7% were CD45+ of which 10.5% were GFP+. The CD45+CD3-CD14+ fraction represented 10.7% of the total cell population, 75.3% of which were GFP+. The CD45+CD56+CD14- natural killer cell containing population represented 4.7% of total cells, none of which were GFP+. CD45+CD19+CD3- B cells represented 4.7% of the total cell population with 0.7% also GFP+. The HSC containing fraction was 1.8% (CD34+CD38-), 9.2% of which were also GFP+.

Of the un-transduced cell population, 7.8% were CD38+. This increased to 9.8% following transduction. 82% of all GFP+ cells were also CD38+ (Fig. x). Together this suggests that Ad-transduction induces CD38+ expression/antigen presentation. This is in accordance with literature describing CD38 expression on both activated lymphocytes and monocytes in response to viral infection. The results obtained demonstrate that viral vectors can be used to selectively target specific cell populations within whole bone marrow.

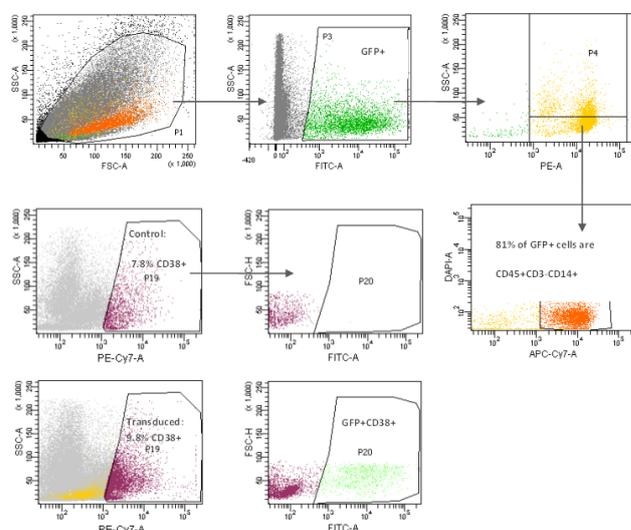


Figure 10.6.7: Flow cytometry analysis of BM-MNC subsets transduced with Ad-GFP.

Pub:

Bara JJ, Herrmann M, Menzel U, Benneker L, Alini M, Stoddart MJ. 3D culture and characterisation of mononuclear cells from human bone marrow. *Cytherapy*. 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 *ex vivo* system for mesenchymal stem cell differentiation and cartilage integration (Vivoload) (Started) (M Stoddart)

Current culture models to investigate cartilage repair therapies are often highly simplified. Even critical *in vivo* signals such as kinematic load are commonly lacking. This limits the efficacy of *in vivo* tests, placing a higher burden on *in vivo* models. This project aims to develop a novel *ex vivo* culture system, which is more representative of the *in vivo* articulating joint. Media composition, vis-à-vis synovial fluid, will be considered, as will osteochondral plug development that will allow interaction/signaling between cartilage, bone and implant. Finally, complex multiaxial load will be applied to produce a mechanical environment more associated with the articulating joint. Due to the time frames involved, the main outcome parameters will be based on the differentiation, maturation and integration of *de novo* chondral and osteochondral implants containing human mesenchymal stem cells. This offers the advantage of being able to compare outcomes to previous published studies.

We expect the incorporation of a more viscous physiological culture medium to modulate the chondrogenic induction of human mesenchymal stem cells induced by interfacial shear. Confining the implant within an osteochondral defect will also modify the response due to paracrine signaling from the viable cartilage and underlying bone. In addition, there is the potential for cell migration from the surrounding "host" tissue, which may also influence the response. Each of the conditions being modified is to bring the *in vivo* situation nearer to that found *in vivo*.

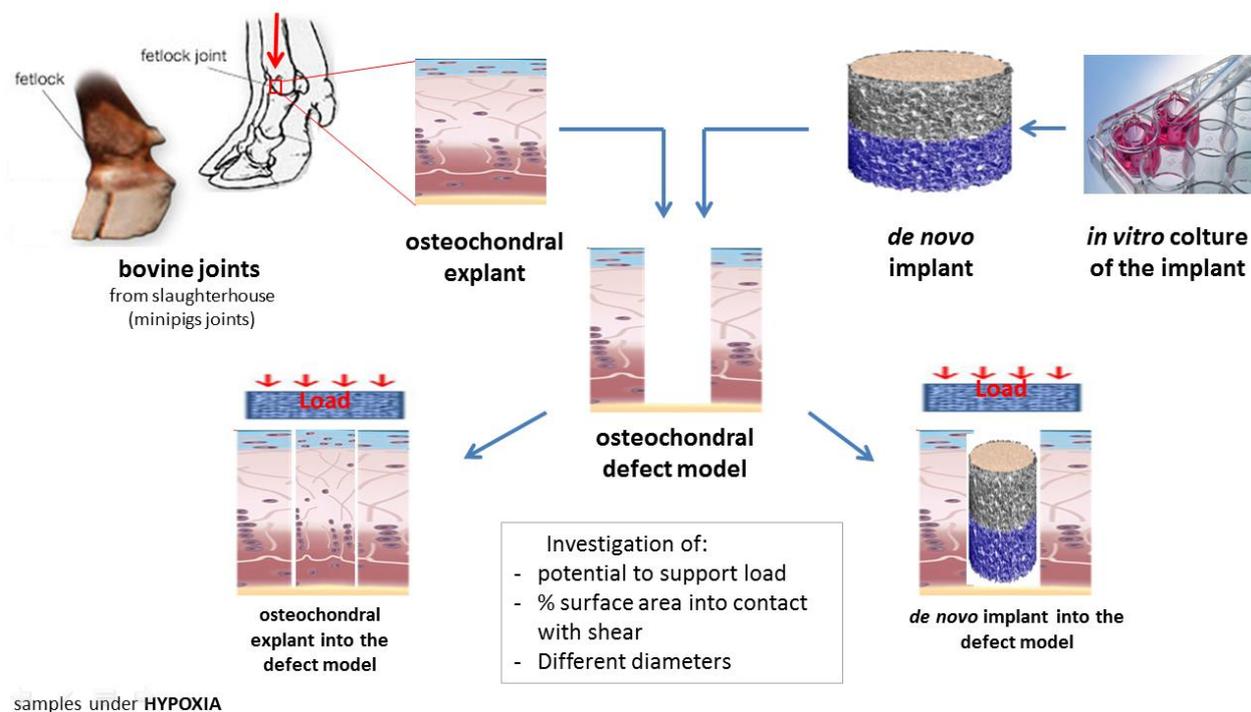


Figure 10.6.8: Schematic overview of experimental design.

Pres:

Development of *ex vivo* system for MSC differentiation and cartilage integration; Graziana Monaco, Mauro Alini, Martin J. Stoddart; YSBM.ch Graduate Research Symposium 2016, ETH Zürich, February 12, 2016

Development of *ex vivo* system for human mesenchymal stem cells differentiation and cartilage integration; Monaco Graziana, Fahy Niamh, Alini Mauro, Stoddart Martin J.; Conference Graubünden forscht 2016, Davos, September 14-15, 2016

Effect of exogenous hyaluronan on human Mesenchymal Stem Cell chondrogenesis; G. Monaco, N. Fahy, M. Alini, M. J. Stoddart; Biointerfaces International 2016, University of Zurich, August 23-25, 2016

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. Our recent work has shown that CD34-CD146+ pericytes can be efficiently isolated from bone marrow by magnetic-activated cell sorting (MACS®). We could further show that these cells have multilineage potential and the ability to support tube-like structures in angiogenesis assays. Next we investigated how these cells respond to the microenvironment associated with bone injury. The early events in bone healing are simulated by the factors released from activated blood platelets (platelet-rich plasma, PRP) and injured bone cells (Fig. 10.6.9 A). We here analyzed the response of pericytes to such environments with regards to their gene expression (genes associated with immunomodulation, angiogenesis and apoptosis), proliferation, migration and osteogenic differentiation ability. Platelet-released factors promoted proliferation of pericytes (Figure 10.6.9 B). Our results indicate that a microenvironment simulating bone injury elicits strong immunomodulatory and pro-angiogenic activity of pericytes (Figure 10.6.9 C). This suggests that in the early stage of bone healing the prime function of pericytes is in regulating the immune response and inducing neovascularization.

To confirm those results and further investigate the pericyte function in response to injury related signal, we are currently developing a microfluidic platform. This ex-vivo model enables the formation of perusable micro-vessels mimicking the endothelial barrier and perivascular niche (see project MicroVasc, page 71) in a more physiological context.

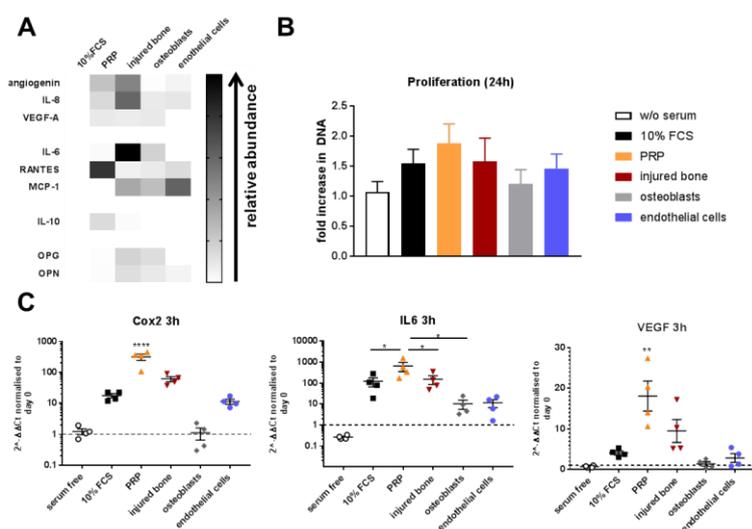


Figure 10.6.9: **A.** Characterization of conditioned medium simulating different microenvironments. Conditioned medium from osteoblasts and endothelial cells and growth medium containing 10% FCS served as control for a healthy microenvironment. Displayed is the relative abundance of selected proteins related to angiogenesis, inflammation and bone formation. **B.** Proliferation of pericytes incubated for 24h with the indicated conditioned medium. **C.** Gene expression of selected marker in perivascular stem cells incubated in different microenvironments. Shown is the fold change of Cox2, IL-6 and VEGF expression relative to day 0.

Pres:

Herrmann M, Hildebrand M, Menzel U, Fahy N, Alini M, Loibl M, Benthien J, Verrier S, Stoddart MJ, Bara JJ. Phenotypic characterisation of mononuclear cell and bone marrow stromal cell populations from different tissue sources of bone marrow. 2016 ICRS (oral)

Zahn J, Herrmann M, Loibl M, Alini M, Verrier S. Platelet Rich Plasma as autologous cell delivery and pro-angiogenic hydrogel for bone tissue engineering applications. 2016 EORS (poster - Young investigator poster award)

Pub:

Herrmann M, Bara JJ, Sprecher CM, Menzel U, Jalowiec JM, Osinga R, Scherberich A, Alini M, Verrier S. Pericyte plasticity - comparative investigation of the angiogenic and multilineage potential of pericytes from different human tissues. Eur Cell Mater. 2016;31:236-49

The role of immunosuppression in bone healing (ImmunoSup) (Ongoing) (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 constructs 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 mice and Fisher rats treated with immunosuppressive drugs. In the first year we evaluated the immune response during the course of bone healing (exemplary results for blood are shown in Figure 10.6.10).

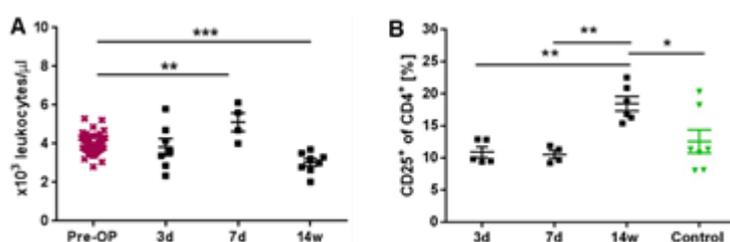


Figure 10.6.10: **The immune response caused by an osteotomy.** Blood samples were analyzed 3 days (3d), 7 days (7d) and 14 weeks (14w) after surgery. **A.** Leukocyte counts in full blood showing increased values after 7 days. Pre-OP animal served as control (in purple). **B.** Relative amount of CD25+ regulatory T cells (T_{REG}) as part of the CD4 positive lymphocyte population in blood. Control animal were no treated (in green). Note that an increased frequency of T_{REG} was detected at late stages of the healing process (14 weeks after surgery). Data is plotted as mean \pm standard error of the mean (SEM). * $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$; calculated by One-way Anova with Tukey's multiple comparisons test.

Pres:

Hildebrand M, Herrmann M, Alini M, Zeiter S, Verrier S. The involvement of immune cells in fracture healing and xenograft rejection in Fisher rats. 2016 YSBMch (poster)

Hildebrand M, Zeiter S, Alini M, Verrier S*, Herrmann M. The adaptive immune response in fracture healing and xenograft rejection in Fisher rats. 2016 Graubünden forscht / Young Scientists in Contest (oral)

Partner:

- Akdis C, (Prof), Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland

The role of innate lymphoid cells in bone healing (preImBone) (Ongoing) (M Herrmann)

Inflammation in the early phase after fracture as well as a timely resolution of inflammation is a prerequisite for healing. It has been recently suggested that the immune status of patients can critically influence the healing outcome of patients. Cellular sources and target cells of inflammatory mediators are however poorly understood.

Innate lymphoid cells (ILCs) are hematopoietic cells, which have the typical characteristics of lymphocytes but lack the expression of recombination activating gene-dependent (RAG) antigen receptors of T and B cells. It was shown that ILCs rapidly produce 10-100 times more cytokines than T cells. While ILCs have been studied in the context of allergic and autoimmune disease, microbial defense, obesity and many others, their role in bone healing and physiology is unknown. Our preliminary results suggest that certain ILC subtypes maybe critically involved in the early stage of bone healing, as demonstrated by accumulation of ILC2s and ILC3s in the repair tissue of a femoral osteotomy (Figure 10.6.11).

In this collaborative project with SIAF, we aim to investigate the function of distinct ILC subsets in bone.

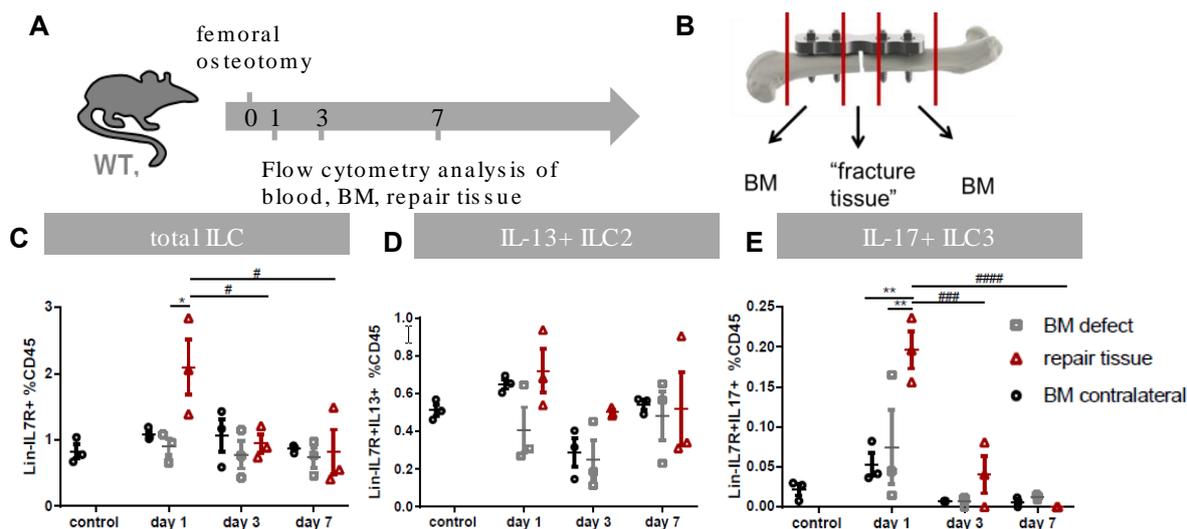


Figure 10.6.11: ILCs in early repair tissue after femoral osteotomy. **A.** A femoral osteotomy fixed with an internal titanium plate (MouseFix) was created in female skeletally mature C57BL/6 mice. Blood, bone marrow (BM) and repair tissue were harvested for flow cytometry analysis from control animals and operated animals 1 day, 3 days or 7 days after surgery. **B.** Sample preparation from defect site: Repair tissue was defined as bone tissue and hematoma harvested from the region between the two central screws of the plate. Distal and proximal parts of femora were used to harvest BM from the defect site. **C-E.** Frequency of ILCs in BM (defect and contralateral site) and repair tissue as assessed by flow cytometry, ILCs were identified as Lin-IL7R+ cells within the CD45+ cell population.

Partners:

- Akdis C, (Prof), Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland
- Morita H, (Prof) Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland / University of Tokyo, Japan

Cell homing in the degenerative intervertebral disc: Characterization of migrating cells and their regenerative potential (DISCREGEN) (Ongoing) (S Grad)

Recent research aiming at biological regeneration of the degenerative intervertebral disc (IVD) has focused on cell therapies using human mesenchymal stem cells (MSCs). It has been shown that MSCs are able to migrate through the tissue inside IVDs in response to tissue damage. MSC homing has been proposed as an alternative to MSC injection. It is hypothesized that, among the heterogeneous MSC pool, distinct MSC sub-populations demonstrate superior homing capacity. Cells expressing cluster of differentiation 146 (CD146, also known as melanoma cell adhesion molecule MCAM) have been described to be involved in cell homing in different musculoskeletal tissues. Therefore, we postulated that CD146+ MSCs may represent a sub-population of MSCs with superior homing capacity towards degenerative IVDs.

Using a trans-well assay, it was found that the proportion of migrating MSCs migrating towards degenerative disc conditioned medium was significantly higher for CD146+ compared to CD146-. These results were confirmed also in organ culture experiment, whereby CD146+ MSCs migrated in higher number of compared to the CD146- MSCs (Figure). In conclusion, CD146 is a marker for MSCs with superior migration capacity toward degenerative intervertebral discs.

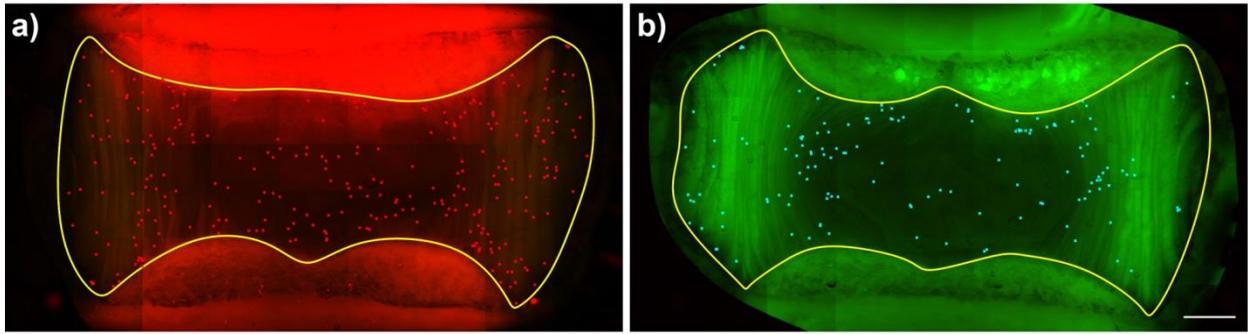


Figure 10.6.12: Combined red and green fluorescent image of migrated MSCs in a sagittal section of bovine intervertebral discs: a) CD146+ MSCs (red); right: CD146- MSCs (blue). The intervertebral disc region without endplates is marked with a yellow line. Scale bar = 2 mm.

Pub:

Pereira CL, Teixeira GQ, Ribeiro-Machado C, Caldeira J, Costa M, Figueiredo F, Fernandes R, Aguiar P, Grad S, Barbosa MA, Gonçalves RM. Mesenchymal Stem/stromal Cells seeded on cartilaginous endplates promote intervertebral disc regeneration through extracellular matrix remodeling. *Sci Rep* 6:33836, 2016.

Alini M, Grad S, Wilke HJ, Galbusera F, Colombini A. DiscOver – State of the art of biology, mechanics, genetics of the disc. In: *AOSpine Master Series Volume 8: Back pain*. Series Editor: Vialle LR; Volume Editors: Wang J and Lamartina C. Thieme Medical Publishers 2016

Partners:

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

10.7 Extramural Projects

***In vivo* investigation and finite element analysis of the alveolar ridge splitting technique (BoneSplit) (P Varga, B Gueorguiev-Rüegg), CAMLOG Foundation grant, ARI Funding: EUR 253'000, Period: 01.01.2016 – 31.06.2016**

Background: Alveolar ridge splitting and expansion is a surgical technique for dental implant fixation in the challenging edentulous intraoral situation. Following longitudinal splitting of the ridge and preparation of two vertical relief incisions, the cavity for the implant is created by distracting the buccal segment. However, in a long-standing edentulous situation, the success of the procedure is endangered by the high risk of fracturing the severely resorbed and thus fragile buccal lamella during the expansion. This risk may be alleviated by pre-operatively predicting the magnitude of allowed distraction.

Goal: To develop a relevant biomechanical model for the ridge splitting technique, apply it to human cadaveric specimens and simulate it with the finite element (FE) method.

Results: Sixteen splits were prepared on completely edentulous mandibulae and maxillae of three elderly female donors, scanned with different CT and DVT devices and tested to failure by controlled opening of the buccal lamella mimicking the real distraction procedure. A high resolution motion tracking system was used to measure the movements of the lamellae. Case-specific FE models of the split specimens were created from CT images and loaded according to the experimental conditions. The biomechanical tests resulted in clinically relevant fracture modes. The FE analyses predicted well the experimental fracture load and fracture displacement, and provided a good qualitative match of the fracture pattern in twelve cases. The ability of the FE models to predict fractures of the split lamellae suggests that this method could be used to virtually plan and potentially optimize the surgical technique in a patient-specific manner.

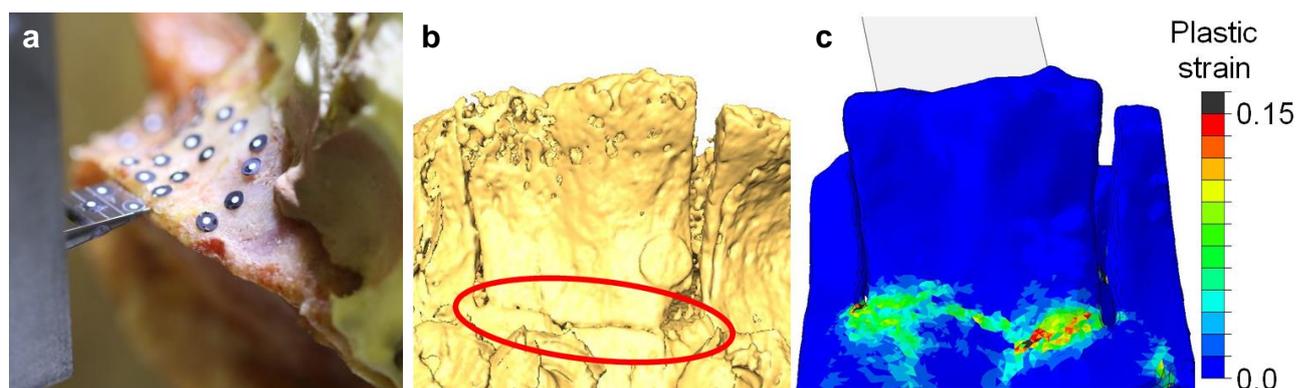


Figure 10.7.1: Experimental test setup (a), induced fracture line (b, red ellipse) and FE-based plastic strains (c).

Partners:

- Stricker A (PD), University Hospital of Freiburg, Freiburg, Germany
- Duttonhöfer F (MD), University Hospital of Freiburg, Freiburg, Germany

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

The goal of this European and Chinese consortium is to apply rapid prototyping (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 optimised 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 optimisation of composite formulations; poly(trimethylcarbonate) (PTMC)/calcium phosphate for stereolithography has been performed and already implant scaffolds could be fabricated by stereolithography (Figure 9.7.2). 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 vivo* and *in vivo* studies have shown the osteopromotive effect of icaritin loaded into scaffolds.

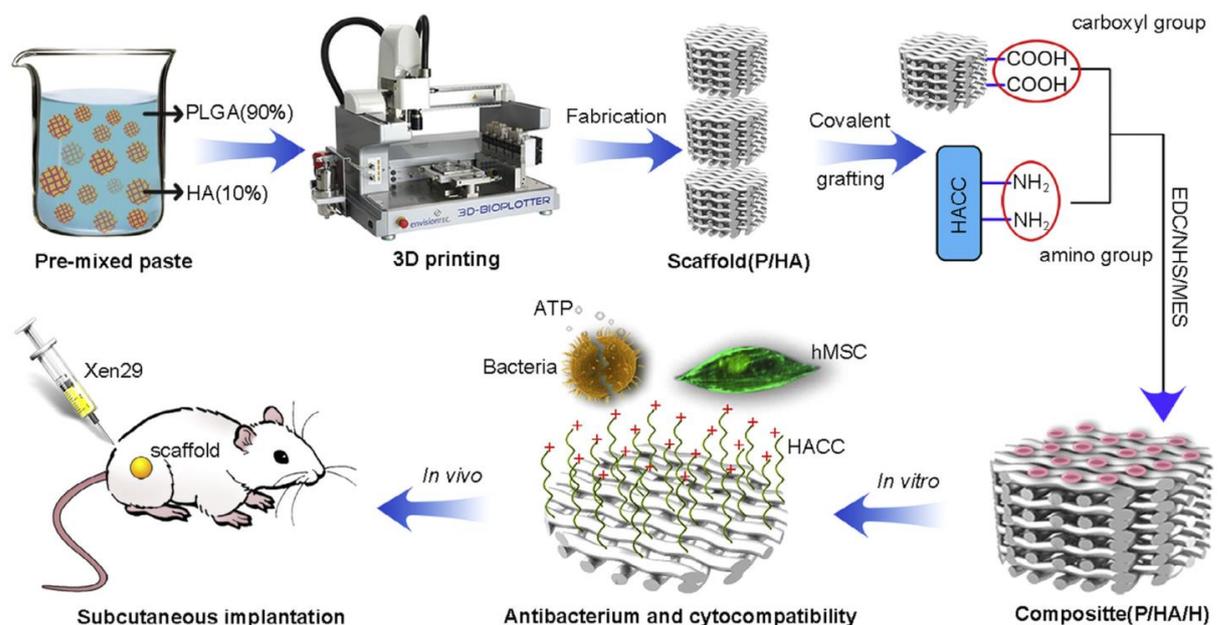


Figure 10.7.2: Schematic illustration for the synthesis and antibacterial mechanism of P/HA/H composite scaffolds (reproduced from Yang et al. Acta Biomater 2016;46:112-28).

Pres:

- [1] Guillaume O, Geven M, Eberli U, Zeiter S, Grijpma D, Alini M, et al. Composition of poly(trimethylene carbonate)-hydroxyapatite printed scaffold affects bone healing. Biofabrication Meeting. Winston-Salem2016.
- [2] Guillaume O, Kluge K, Stadelmann V, Schmid T, Eglin D, Zeiter S. Introduction of a new surgical drilling device to perform cranial defect: performance of conventional dental station compared to Anspach driller in cadaveric study. J Orthop Translation 2016;7:116-7.
- [3] Guillaume O, Geven M, Eberli U, Zeiter S, Grijpma D, Alini M, et al. Introduction of a new biodegradable composite implant for bone repair: poly(trimethylene carbonate)-hydroxyapatite made by stereolithography. Eur Cell Mater 2016;32:15.
- [4] Guillaume O, Geven M, Kluge K, Eberli U, Zeiter S, Grijpma D, et al. Poly(trimethylene carbonate)-hydroxyapatite printed scaffolds for bone healing: *in vivo* and *in vivo* characterization. AFPM Advanced Functional Polymers for Medicine. Enschede2016.

[5] Guillaume O, Geven M, Kluge K, Eberli U, Zeiter S, Grijpma DW, et al. 3D printing of osteopromotive poly(trimethylene carbonate)-hydroxyapatite implants for bone regeneration. *J Orthop Translation* 2016;7:80.

[6] Guillaume O, Geven M, Kluge K, Eberli U, Zeiter S, Grijpma D, et al. Poly(trimethylene carbonate)-hydroxyapatite printed scaffolds for bone healing: *in vivo* and *in vivo* characterization. *Eur Cell Mater* 2016;32:37.

[7] Guillaume O, Kluge K, Eberli U, Zeiter S, Geven M, Grijpma D, et al. *In vivo* and *in vivo* evaluation of osteoinductive composite scaffolds manufactured by stereolithography. WBC. Montreal2016.

Pub:

[1] Geven MA, Sprecher C, Guillaume O, Eglin D, Grijpma DW. Micro-porous composite scaffolds of photo-crosslinked poly(trimethylene carbonate) and nano-hydroxyapatite prepared by low-temperature extrusion-based additive manufacturing. *Polym Adv Technol* 2016;epub Aug 22.

[2] Guillaume O, Geven MA, Grijpma DW, Tang TT, Qin L, Lai YX, et al. Poly(trimethylene carbonate) and nano-hydroxyapatite porous scaffolds manufactured by stereolithography. *Polym Adv Technol* 2016;epub Aug 17.

[3] Yang Y, Yang S, Wang Y, Yu Z, Ao H, Zhang H, et al. Anti-infective efficacy, cytocompatibility and biocompatibility of a 3D-printed osteoconductive composite scaffold functionalized with quaternized chitosan. *Acta Biomater* 2016;46:112-28.

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 orthopaedics. 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 2016 the particles were thoroughly characterized via HR-TEM, XRD, FTIR. Compositions with 5% and 10% strontium were employed for the following steps.
- Hollow microcapsules for the delivery of strontium ranelate, a therapeutic agent used in osteoporosis able to both inhibit bone resorption and stimulate bone formation. During 2016 release studies were performed and biological characterization performed
- 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.
- Furthermore, high hydrostatic pressure was developed as an innovative method for the elimination of vegetative spore-forming bacteria. This method affects the material properties much less than steam sterilisation (see figure below).

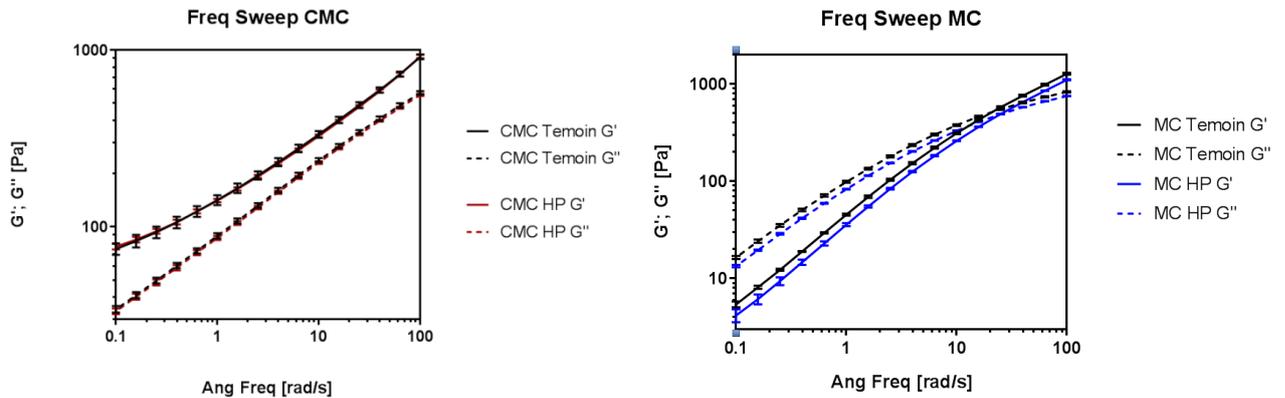


Figure 10.7.3: Viscoelastic spectrum before (black lines) and after (red or blue lines) high hydrostatic pressure treatment. Left panel: CarboxyMethyl Cellulose (CMC); Viscoelastic shear moduli were unchanged upon treatment. Right panel: Methyl Cellulose (MC); Viscoelastic shear moduli displayed a slight loss upon treatment. Steam sterilisation (not shown) would bring to a considerable decrease of viscoelastic moduli.

Partners

- Locs J (Prof) Riga Technical University, Rudolfs Cimdin's 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

Personalized Ceramic Printable Ink for Patient Specific Implant Fabrication (InCePt) (Started) (RG Richards, D Eglin), KTI (Nr. 18060.1), ARI Funding: CHF 292'700, Period: 2016-2019

RegenHU Ltd has teamed up with the AO Research Institute Davos and the Institute for Surgical Technology of the University of Bern to develop a novel chairside CAD/CAM manufacturing solution for patient specific bone substitutes dedicated to cranio-maxillofacial surgeries. This innovative approach combining novel osteoinductive calcium phosphate inks enables the manufacturing of personalised bone substitutes within a surgical intervention (Figure 10.7.4). This novel product generation addresses a \$3.3 billion market in which regenHU aims to become a leading market player.

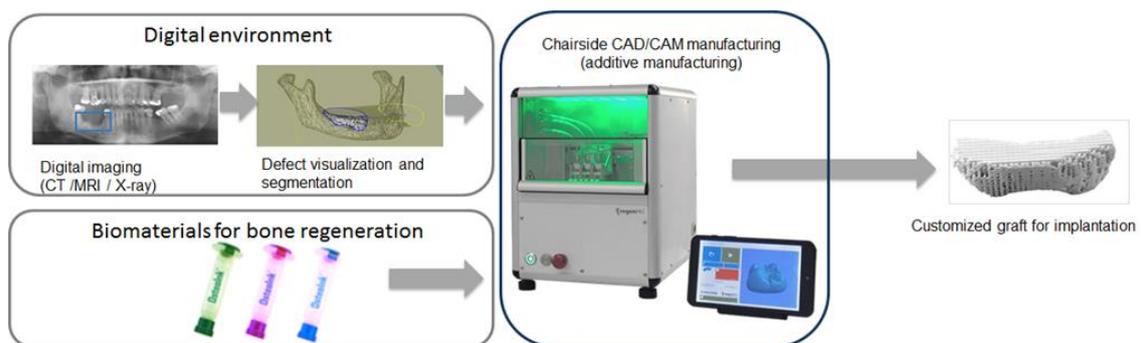


Figure 10.7.4: The InCePt project technology.

Partners:

- Thurner M, RegenHU Ltd, Villaz-Saint-Pierre, Switzerland
- Büchler P (Dr), Institute for Surgical Technology and Biomechanics, University of Bern, Switzerland
- Lieger O (Dr MD), Department of Cranio-Maxillofacial Surgery, Inselspital, University Hospital Bern, University of Bern, Switzerland

Rational Bioactive Materials Design for Tissue Regeneration (Biodesign) (Completed)
(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. Within BIODESIGN we performed 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. The correlation between *in vivo* studies and *in vivo* outcomes was directly compared and challenged. It was noted that many of the commonly used *in vivo* assays are extremely limited in their *in vivo* predictions. More predictive in-vitro methods allowing significant reduction in development time and use of preclinical models are needed if a 3Rs policy is to be implemented. BIODESIGN has stimulated technological innovation, utilization of research results, transfer of knowledge and technologies and creation of technology based business in Europe. ARIs part within this consortium was the analysis of materials for bone regeneration. ARI also developed novel *in vivo* testing algorithms to improve the predictive mature of the *in vivo* assays. In particular it was noted that for inert materials. The greatest predictor of outcome is often human donor variation.

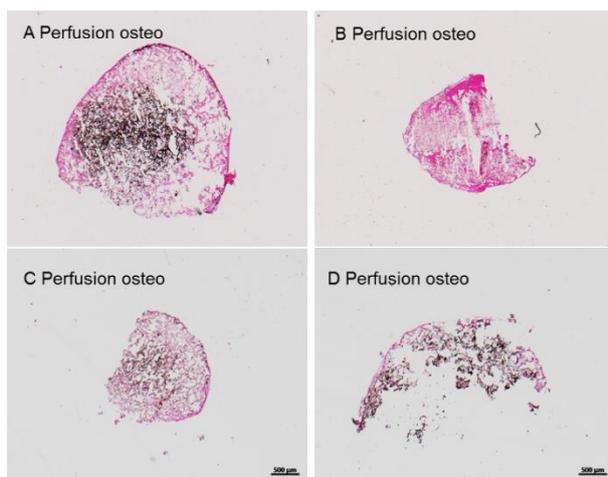


Figure 10.7.5: von Kossa staining hMSCs (four donors A – D) on PLGA scaffolds were cultured in perfusion conditions in osteogenic vs. control media as indicated. Samples were fixed at day 21 and paraffin embedded. Sections were stained with von Kossa and the donor variation could be clearly seen due to the variation in black staining (calcium deposition) observed.

Pub:

A doxycycline inducible, adenoviral BMP-2 gene delivery system to bone. Bara JJ, Dresing I, Zeiter S, Anton M, Daculsi G, Eglin D, Nehrass D, Stadelmann VA, Betts DC, Müller R, Alini M, Stoddart MJ. J Tissue Eng Regen Med. 2016 Dec 13. doi: 10.1002/term.2393.

Hulsart-Billström G, Dawson JI, Hofmann S, Müller R, Stoddart MJ, Alini M, Redl H, El Haj A, Brown R, Salih V, Hilborn J, Larsson S, Oreffo RO. A surprisingly poor correlation between *in vivo* and *in vivo* testing of biomaterials for bone regeneration: results of a multicentre analysis. Eur Cell Mater. 2016 May 24;31:312-22.

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.

The effect of spatial, temporal and mechanical cues on the modulation of human mesenchymal stem cell chondrogenesis and hypertrophy (Gradiff) (Completed)
(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. This project investigated how cartilage formation is affected by the way cells talk to each other (Paracrine signaling). 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. Constructs were created that produced gradients of cells, soluble factors or both and physiological load was applied to induce stem cells to become the cells of cartilage (chondrocytes). One advantage of gene therapy is that it can be used to 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 (Figure 10.7.6). Asymmetric seeding of scaffolds, whereby the upper surface has a higher concentration of cells, resulted in a more robust chondrogenesis and the formation of a superficial zone similar to that found in normal cartilage. Additionally, complex multiaxial load resulted in differential regulation of chondrogenesis compared to growth factor induced chondrogenesis. This has identified novel targets that are clinically relevant as they are only expressed during articulation. The data obtained within this project can be used to develop novel cartilage repair strategies and is forming the basis of the emerging field of regenerative rehabilitation.

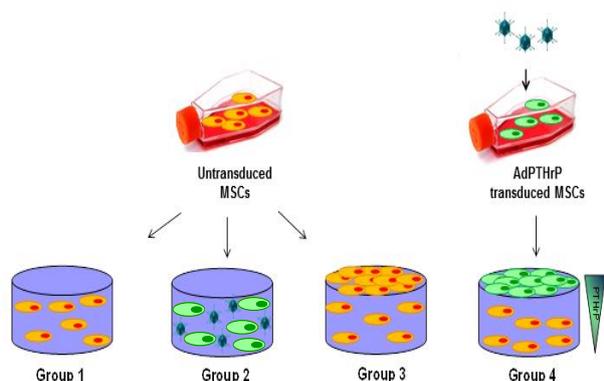


Figure 10.7.6: Schematic describing different seeding patterns that enable gradient formation to be established using gene therapy.

An *in vivo* micro-vascular model mimicking the endothelial barrier (Microvasc) (Completed)
(M Herrmann, S Verrier) 3R # 139-14, 2 years, CHF 59'250

A functional micro-vasculature is critical for the homeostasis of vascularised tissues. Beside endothelial cells, pericytes are an important component of the endothelial barrier in capillaries and other microvessels. In recent years, mesenchymal stem cells have been identified in the perivascular niche, and it has been proposed that perivascular cells may constitute a physiological reservoir of adult mesenchymal stem cells (MSC). Microfluidic technologies have shown the potential to closely mimic the vascular microenvironment and represent a powerful ex-vivo microvascular platform to study pericyte cell function in an environment close to physiological conditions. In this project we further developed a microfluidic platform comprised of a 3D microvascular network embedded in a hydrogel enabling the investigation of perivascular cells in a physiologically relevant context. The new designed microfluidic platform is made out of Poly (methyl metacrylate) (PMMA) and comprises two inlet and two outlet capillary (Figure 10.7.7 A). Those capillaries are also used as guide to insert thinner capillaries (outer diameter of 150 μm) through the collagen type I (2 mg/ml) gel filled compartment. The chamber is closed with a PDMS lid and placed at 37°C for 60min for gel polymerization. Upon full polymerization, the inner capillaries are removed leaving two parallel micro-channels separated by 400 μm .

The chip is placed in a 37°C 5%CO₂ humidified on stage incubator and connected to a reservoir of endothelial growth medium (EGM-2) for perfusion using a piezo micro pump. After proving their

stability over 24h of perfusion (Figure 10.7.7 B), the micro-channels are injected with fluorescent-tagged human umbilical vein endothelial cells (HUVECs) and allowed to adhere for 2 hours. Cell-seeded micro-channels were perfused with EGM-2 and observed by time-lapse microscopy for 48 hours (Figure 10.7.7 C). Time lapse microscopy revealed efficient cell attachment and complete coverage of the surface of the microchannel. Good viability of HUVECs was observed over the full duration of the experiment. 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 trans-endothelial cell migration.

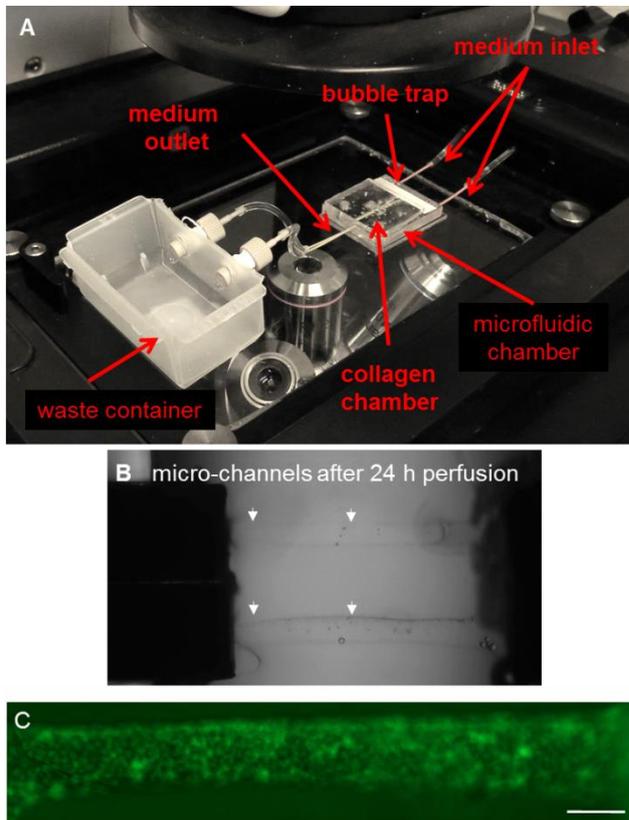


Figure 10.7.7: **Micro-fluidic platform.** **A.** Set-up of the new microfluidic chamber installed on EVOS® FL Auto Cell Imaging System. **B.** Stable channels embedded in a collagen gel generated in the new chamber. **C.** GFP-labeled HUVEC could be successfully injected in the chamber and were homogeneously distributed. Scale bar 100 μm .

Pres:

Herrmann M, Wang Z, Alini M, Barbe L, Verrier S. An organ-on-chip model of the endothelial barrier to study the role of perivascular cells in bone regeneration. *Osteologie*. 2016;25(2):A58 (SVGO/SBMS - oral)

Herrmann M, Wang Z, Alini M, Barbe L, Verrier S. The endothelial barrier on-chip. *Eur Cell Mater*. 2016;31(Suppl 1):p140 (TERMIS-EU / poster)

Partner:

- Barbe L, (Dr) CSEM

Bioceramics for bone repair (BioBone) (Completed) (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 main aim was to offer a multidisciplinary training in the field of bioceramics, bioactive glasses and composites for bone repair in collaboration with industries and universities. The training programme included six months secondments at partner institutions and the attendance of ten workshops organised by the consortium. In total, twelve PhD students and three post-docs were enrolled in the program and were offered training at different five academic institutions and four industrial partners, all at the cutting-edge of their fields.

In 2014, ARI organised a highly appreciated three-day workshop on "Cell-material interactions" and hosted two PhD students from Imperial College London for 9 months who evaluated the behaviour of human stem cells on innovative bioglass and calcium phosphate formulations for bone fillers. Collaborative projects were performed with the University of Catalunya on stem cell behaviour on laser-patterned and nano/microroughness gradient zirconia (Figure 10.7.8). These surface modifications have the potential to improve osseointegration of ceramic hip prosthesis. INSA Lyon and ARI have also developed and *in vivo* tested three-dimensional printed bioceramics, based on zirconia-toughened alumina.

The Journal of the European Ceramic Society will publish in 2017 a Special Issue comprising various papers produced as part of the Biobone project. ARI is actively involved in this Special Issue at both the editorial and authorship levels.

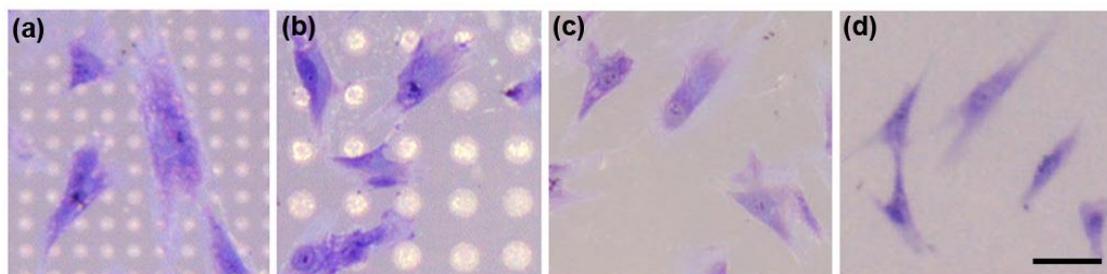


Figure 10.7.8: toluidine blue staining of human mesenchymal stem cells on (a, b) laser-patterned zirconia and (c, d) hydrofluoric-acid etched zirconia. Laser patterned features with diameter of (a) 10 and (b) 20 microns (depth = 3 microns); (c) polished, not etched zirconia and (d) hydrofluoric-acid etched zirconia (30 minutes in 40% HF). Scale bar = 50 micron. Note the changes in cell morphology depending as a result of surface roughness modifications.

Pub:

Flamant Q, Stanciuc AM, Pavailler H, Sprecher CM, Alini M, Peroglio M, Anglada M. Roughness gradients on zirconia for rapid screening of cell-surface interactions: Fabrication, characterization and application. *J Biomed Mater Res A*. 2016;104(10):2502-2514.

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

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

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 inflammation or degeneration. Delivery and retention will be assessed by advanced molecular imaging techniques to monitor distribution of the delivered compounds at the tissue level, as well as detect biological markers of regeneration.

The 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 ETN is to train 15 young scientists (PhD candidates, postdocs). The role of the ARI is to provide advanced bioreactor systems for cartilage and disc in order to evaluate the newly developed nanocarriers with bioactive factors in relevant ex-vivo conditions. Therefore a loaded osteochondral defect model has been developed for testing of hydrogels and drug releasing nanocarriers in collaboration with project partners (Figure 10.7.9).

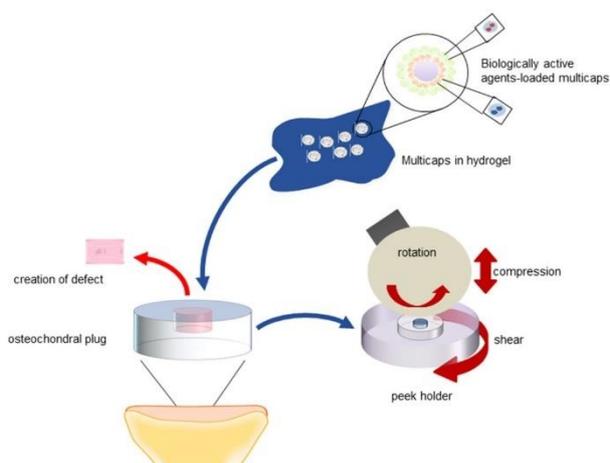


Figure 10.7.9: Experimental set-up for ex-vivo testing of nanocarrier systems.

Pres

Vainieri ML, van Osch GJVM, Grad S, Alini M. Targeting cartilage regeneration by acellular hydrogel containing nanocarriers on a joint bioreactor. YSBM Graduate Research Symposium 2016, ETH Zürich

Vainieri ML, Wahl D, van Osch GJ, Alini M, Grad S. Investigating the homing behaviour of endogenous stem cells in a joint bioreactor to regenerate articular cartilage. Congress Graubünden Forscht 2016, Davos.

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
- Yayan 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) (Ongoing) (M Alini, S Grad, M Stoddart), Swiss-China Joint project (SNF), ARI Funding: CHF 250'000, Period: 2015-2018

Osteoarthritis (OA) affects millions of patients worldwide; nonetheless, there is currently no effective and standardised 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, 40 individual TCM compounds are tested for their ability to promote cartilage repair in an inflammatory environment. Concomitantly, compounds are evaluated with respect to their bone healing capacity by the Chinese partner. It was found that distinct compounds improved the matrix synthesis of human osteoarthritic chondrocytes in a dose dependent manner. The ultimate goal is to develop an effective TCM release system for OA therapy.

Pres:

Ziadlou R, Grad S, Stoddart MJ, Martin I, Wang X, Qin L, Alini M. Traditional Chinese Medicine (TCM) compound delivery system for treatment of osteoarthritis. YSBM Graduate Research Symposium 2016, ETH Zürich

Ziadlou R, Grad S, Stoddart MJ, Martin I, Wang X, Qin L, Alini M. Traditional Chinese Medicine (TCM) compound delivery system for treatment of osteoarthritis. Congress Graubünden Forscht 2016, Davos.

Partners:

- Martin I (Prof), University of Basel, CH
- Wang X (PhD), Shenzhen University, PR China
- Qin L (Prof), The Chinese University of Hong Kong, HK
- Lai Y (PhD), Shenzhen University, PR China
- Huang Y (PhD), Shanghai Institute for Biological Sciences, PR China

Biological and mechanical effect of selective proinflammatory cytokine inhibition in degenerative disc disease (Inflamodisc) (Started) (Z Li, S Grad, M Alini), German 3R Grant, funded by Foundation for the Promotion of Alternate and Complementary Methods to Reduce Animal Testing (SET), EUR 94'000, Period: 2016-2018

Low back pain (LBP) is a major health issue and it is considered that degeneration of the intervertebral disc (IVD), which is initiated through an early inflammatory process, is one of the main causes for LBP. Anti-inflammatory treatment with Disease-Modifying Anti-rheumatic drugs (DMARDs) may offer a less invasive alternative for symptomatic degenerative disc disease (DDD). The aim of this study is to (1) develop an inflammation model for early stage degenerative disc disease with bovine IVDs and (2) evaluate the effect of different inhibitors of proinflammatory cytokines as possible alternative treatment strategy.

As the first step, a proinflammatory and degenerative IVD organ culture model was established by combining TNF- α intradiscal injection, detrimental loading and limited nutrition. Under combined TNF- α injection and degenerative culture condition, an upregulation of catabolic and inflammatory marker gene expression was observed, together with enhanced glycosaminoglycan and NO release, as well as cell death, which indicate an accelerated inflammatory and degenerative effect. This model will be used for screening of therapeutic agents in further pre-clinical studies.

Partner:

- Gernot Lang (MD), Norbert Südkamp (Prof), Albert-Ludwigs-Universität Freiburg, Freiburg, Germany

Gentamicin loading of Calcium Phosphate-coated implants prevents experimental *Staphylococcus aureus* device associated infection *in vivo* (CaPhScrew) (S Petkov / K Thompson, ARI; H. Eijer, Spital Emmental, 1 year)

Calcium phosphate (CaPh) coating of orthopedic implants such as hip and knee prostheses has been shown to improve osseointegration. However, despite advances in implant integration device associated infection (DAI) is an infrequent but potentially devastating complication associated with all orthopedic devices. Current strategies to prevent DAI include systemically applied antibiotics and/or local antibiotic delivery systems, such as antibiotic-loaded bone cement, but successful resolution of DAI requires effective strategies for preventing initial colonization of the implant or the clearance of established bacteria from implant surfaces. The aim of this study was to determine if gentamicin may be loaded into a CaPh coating and determine its efficacy as a strategy for preventing DAI *in vivo*.

Our previous results utilizing CaPh-coated TAN disks and screws established the optimum loading conditions for gentamicin *in vivo*, with maximal loading of gentamicin into the CaPh coating observed within 1 minute. The release of gentamicin was similarly rapid, with $\geq 95\%$ gentamicin released within 15 mins, as determined spectrophotometrically and by assessing antibacterial efficacy for a methicillin-sensitive *Staphylococcus aureus* strain NCTC 12973 (MSSA) in zone of inhibition assays. Furthermore, we also confirmed this antibacterial effect *in vivo*, with a gentamicin-loaded CaPh-coated TAN screw able to completely prevent *S. aureus* infection in 7/8 inoculated animals.

Despite this, there still exists an issue regarding this potential strategy in the clinical setting, since gentamicin may potentially interfere with osseointegration of the implant. We have therefore conducted further *in vivo* experiments with CaPh-coated TAN screws in the absence or presence of gentamicin to determine if the presence of gentamicin on such a CaPh coating inhibits osseointegration using histological analysis.

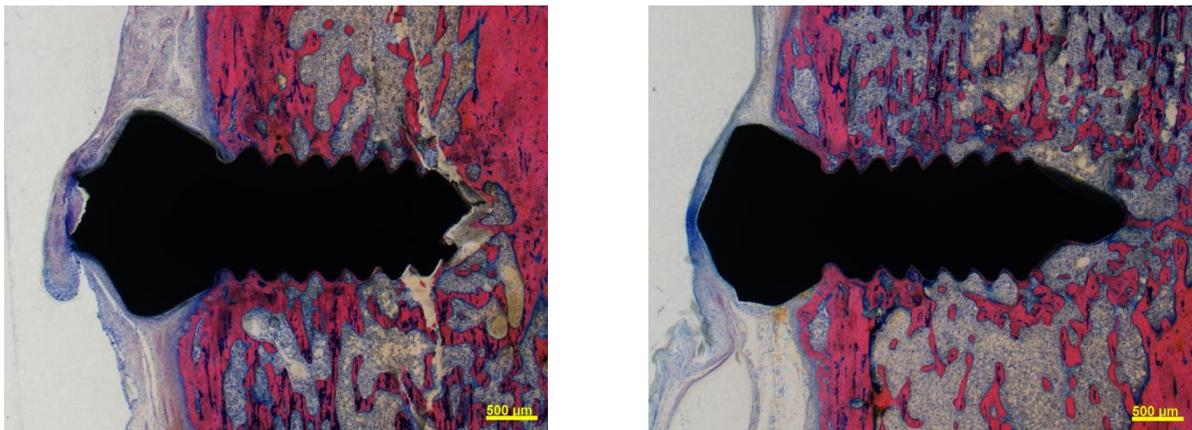


Figure 10.7.10: Representative images to demonstrate osseointegration of CaPh-coated TAN screws implanted into the tibia of female Wistar rats, in the absence (left panel) or presence (right panel) of gentamicin. CaPh-coated screws were dipped into 0.9% (w/v) saline or gentamicin for 1 min prior to implantation, and the integration of the screw was assessed after 28 days. Osseointegration of the screw into the surrounding bone tissue was assessed using Giemsa and Eosin staining to permit quantification of bone-implant contact by histomorphometry. Scale bar is 500 μ m.

11 Operations standards and safety

Successful 2016 renewal audit of AO Research Institute Davos



From March 14 to 15, 2016 two external auditors from the SQS (Swiss Association for Quality and Management Systems; www.sqs.ch) visited ARI two full days for the renewal audit of the institute. ARI has received the renewal of the certification until September 2018 without any non-conformities requiring immediate actions.

The entire AO Research Institute is certified according to the international standard ISO 9001:2008.

The Biomedical Services Program is additionally certified as a medical device manufacturer according to ISO 13485:2003.

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

AAALAC international accreditation 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. According to the final report accreditation shall continue for another 3 years.

GLP (Good Laboratory Practise)

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 29, 2016. ARI is now listed as GLP compliant test facility, after we fulfilled the 2 conditions of the final inspection. 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. The first commercial study started in summer 2016 and we have quoted for several other new customers to do GLP studies at our facility.

12 Team Members

Director

Richards R. Geoff 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, Prof, PhD, MPhil 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
 Armiento Angela PhD 01.01.2016
 Badrutt Isabella Administrative Assistant 16.07.12
 Barblan Claudia Administrative Assistant (70%) 15.11.10
 Berset Corina Dr med vet 01.08.15 (AOF)
 Bluvol Mauro Chemielaborant (Eidg FA¹) 01.06.03
 Buschbaum Jan Dr rer med 01.08.15
 Caspar Jan Poly mechanics 01.01.09
 Ciriello Simona Journal Production Editor 12.09.16
 D'Este Matteo PhD 01.04.11
 Dicht Benno Mechaniker (Eidg FA¹) 01.01.78
 Eberli Ursula MSc ETH 01.02.11
 Eglin David PhD 01.06.06
 Erb Peter Animal Care (Eidg FA¹) 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 Loris Animal Care Taker 01.11.16
 Faoro Pierina Arztgehilfin, Animal Care (Eidg FA¹) (70%) 01.12.07
 Freitag Linda Med vet 10.04.16
 Furlong-Jäggi Pamela Chemikerin FH, BSc (40%) 01.02.04
 Furter Andrea Animal Care (Eidg FA¹) 24.04.06
 Gehweiler Dominic Dr, med 01.03.16
 Geret Vreni Auxiliary Force (19.08.63 – 31.12.10) 01.03.15
 Gieling Fabian PhD Candidate 18.04.16
 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
 Lanker Urban Animal Care (Eidg FA¹) 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 FA¹) 01.08.15
 Menzel Ursula PhD, Dipl Biol 01.07.11

¹ Eidg FA = Eidg Fähigkeitsausweis

Menzel Ursula	PhD, Dipl Biol	01.07.11
Monaco Graziana	PhD Candidate, 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 (60%)	20.09.10
Rotman Stijn	PhD	26.08.16
Sabaté Brescó Marina	PhD Cand, MSc	17.01.13
Schmid Tanja	Dr med vet, Dipl ECVS (80%)	07.01.13
Schneider Monika	Administrative Assistant (60%)	06.02.06
Schwyn Ronald	Dipl Medizintechniker HF	01.11.92
Serra Tiziano	Research Scientist	01.10.16
Sprecher Christoph	Dipl Ing FH	01.02.00
Stanic Barbara	PhD	01.06.14
Thompson Keith	PhD, BSc (Hons), MSc,	26.05.15
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 sc nat	01.08.04
Vivalda Marisa	Administrative Assistant	01.05.03
Wagner Patrizia	Junior Project Leader	18.01.16
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	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

Behrendt Peter	Internship	01.11.16
Geries Janna	Internship	19.09.16
Hasselmann Verena	Internship	01.10.16
Inauen Mario	ETH Internship	01.10.16

Medical Research Fellows

Stylianaki Aikaterini	Med	01.11.16
Riehl Valentina	VET Research Fellow	18.04.16
Zhiyu Zhou	PhD	21.03.16

Non Medical Research Fellows

See under Employees left 2016

Employees left 2016

Scientific & Technical Staff

Bara Jennifer	PhD, BSc	01.02.13 – 31.12.16
Imfeld Christian	Animal Care Taker	04.04.16 – 29.05.16
Imfeld Christian	Animal Care Taker	01.08.16 – 31.10.16
Kluge Katharina	Dr med vet (60%)	01.02.12 – 31.03.16
Löbel Claudia	PhD Cand, Dr med	01.01.12 – 05.08.16
Schraner Daniela	Administrative Assistant (40%)	15.04.10 – 23.10.16
Stadelmann Vincent	PhD, Bioengineering EPFL	24.01.11 – 30.01.16
Stanciuc Ana-Maria	PhD Cand, MSc	20.01.13 – 31.12.16
ter Boo Gert-Jan	PhD Cand, MSc, Biomedical Engineering	15.01.12 – 31.07.16
Urzi Federico	PhD Cand, MSc	01.09.14 – 31.08.16

Internship

Barcik Jan	Masterthesis	16.06.16 – 15.12.16
Debusschere Karlijn	VET Externship	03.10.16 – 23.12.16
Douma Luzia	Internship ETH	01.11.15 – 30.06.16
Grill Billy	Internship	01.07.16 – 22.07.16
Jenni Dominik	Internship ETH	15.06.15 – 31.07.16
Magnusson Wulcan Judit	Vet Internship	02.11.15 – 29.01.16
Mertens Sinja	Vet Internship	13.06.16 – 05.08.16
Moser Caroline	Internship ETH	01.08.15 – 30.04.16
Nuzzo Alessio	ETH Fellowship	05.09.16 – 05.12.16
Perasso Guariglia Giovanna	VET Internship	01.08.16 – 31.12.16
Riberau Charlene	Vet Internship	08.08.16 – 30.09.16
Safari Fatemeh	Internship	15.06.15 – 22.03.16
Schiedeck Alexander	Internship	01.04.16 – 19.10.16
Schneider Manuel	Internship	01.04.15 – 29.02.16
Wirth Michael	Internship	01.07.16 – 18.09.16
Wittmann Charlotte	Vet Internship	15.02.16 – 10.04.16
Zahn Jessica	Internship	29.02.16 – 05.10.16

Medical Research Fellows

Acklin Yves	Dr, Dr, med, MD, DMedSc	01.08.15 – 29.02.16
Arand Charlotte	Med	01.10.15 – 30.06.16
Arruda André	Med	24.02.15 – 29.01.16
Freitag Linda	Med vet	12.04.15 – 09.04.16
Grünwald Leonard	Dr med	01.01.16 – 31.12.16
Hu Ming-Hsien	Dr med	01.07.16 – 31.12.16
Moran Eduardo	Dr med	30.06.16 – 30.06.16
Petkov Stoyan	Dr med	01.09.15 – 29.02.16
Pützler Jan	Dr med, MSc	01.06.16 – 31.12.16
Rothweiler René	Dr med	01.01.16 – 31.12.16
Schmitz Nina	Dr med	01.03.16 – 31.08.16
Todorov Dimitar	Med	01.07.16 – 31.12.16
Wangler Sebastian	Med	01.01.16 – 31.12.16

Non Medical Research Fellows

Boot Willemijn	MSc	01.03.16 – 31.12.16
Inzana Jason	PhD	08.01.15 – 27.02.16

Guests

Bergfeld Lotta	Musculoskeletal Regeneration (S Grad), Guest SAMD Davos, 31.10.-11.11.2016
Breden Sebastian	Biomedical Development (P Varga), Guest Scientist LMU München, 18. - 20.10.2016
Buchholz Tim	Preclinical Services (S Zeiter), Guest Tierärztliche Hochschule Hannover, 06.12.2016
D'Amora Ugo	Musculoskeletal Regeneration (M D'Este) Institute of Polymers, Naples, Italy, 04.04.-24.04.2016
Duttenhöfer Fabian	Biomedical Development (P Varga), Guest MUG-Chirurgie Uniklinik Freiburg, 12.02.2016
Eijer Ricarda	Musculoskeletal Infection (I Keller), Gymnasium Burgdorf Maturaarbeit 14+15.04 / 20-22.04.2016
Freitag Johanna	Preclinical Services (S Zeiter), JLU Giessen, 05.01.2016
Geven Mike	Musculoskeletal Regeneration (D Eglin) Guest Scientist, University of Twente, Enschede 06.03 – 02.04.2016
Guney Aysun	Musculoskeletal Regeneration (D Eglin), Guest University of Twente, Enschede, 14. - 26.11.2016
Haglund Lisbet	Musculoskeletal Regeneration (D Eglin) Montreal General Hospital, 17.04.-26.04.2016
Hörnlimann Patrick	Musculoskeletal Regeneration (S Grad) Guest Student ETH Zürich, 06.06 – 01.07.16
Jonkers Ilse	Muskuloskeletal Regeneration (M Stoddart), Visiting Professor, KU Leuven, Belgien, 04.10. – 23.12.2016
Kahn Tahsin N.	Preclinical Services (S Zeiter), Vet Practica Western University of Health Sciences, Pomona, 17.05 – 24.06.16
Lee Byung-il	Musculoskeletal Regeneration (S Verrier), Visiting Professor 29.02.16 – 31.08.2016
Lenz Mark	Biomedical Development (B Gueorguiev), University Hospital Jena, Germany, 15. – 20.02.16
Liu Yishun	Musculoskeletal Regeneration, 22.04.16 – 17.10.16

Lolli Andrea	Musculoskeletal Regeneration (D Eglin), Guest Scientist ERASMUS Medical Center, Rotterdam, 03.10. - 04.11.2016
Long Rose	Musculoskeletal Regeneration (S Grad) Collaboration CRP Annulus Fibrosus Repair with Icahn School of Medicine at Mount Sinai, New York, USA, 01.08.15 – 31.07.16
Maniglio Mauro	Visit all ARI Groups, AO CID Fellowship, 13.-14.06.2016
Metsemakers Willem	Musculoskeletal Infection (F Moriarty) University Hospital Leuven, Belgium, 19.-29.07.2016
Morgenstern Mario	Musculoskeletal Infection (F Moriarty), BG Unfallklinik Murnau, Germany, 22-26.02.2016
Nienhaus Michael	Biomedical Services (I Zderic) Universität Mainz, Germany, 15.02.2016
Ossendorf Robert	Musculoskeletal Regeneration (S Grad), Guest University of Freiburg, Germany, 02. - 09.11.2016
Otto Sven	Musculoskeletal Regeneration (M Stoddart) LMU Munich, 06.-12.6.2016
Raj Kasinath	Musculoskeletal Infection (F Moriarty) Guest from DPS, 25.04.-28.04.2016
Rieder Bernhard	Musculoskeletal Regeneration (M Stoddart), University of Applied Sciences Technikum, Vienna, 04.04.-14.05.2016
Sauer Mareike	Preclinical Services (S Zeiter) University Hospital Zurich, 6.-8.06.2016
Schmitz Nina	Biomedical Development (J Buschbaum), Guest University Hospital Münster, Germany, 04.01. - 05.01.2016
Shah Irfan	Visit all ARI Groups, AO CID Fellowship, 13.-14.06.2016
Stenger Valentina	Preclinical Services (S Zeiter), Guest Tierärztliche Hochschule Hannover, 06.12.2016
Stricker Andres	Biomedical Development (P Varga) University Medical Center Freiburg, Germany, 12.02.2016
Tabboa Suzanne	Musculoskeletal Regeneration (S Grad), Guest Presentation, Orthopaedic Research Center, Colorado State University, Fort Collins, 20.09.2016

van der Stok Johan	Musculoskeletal Regeneration (S Verrier), EORS Fellowship Erasmus University, Rotterdam, 27.6-29.7.2016
Wagner Daniel	Biomedical Development (L Kamer) University Mainz, Project HMS 08.03.2016 + 28.-29.11.2016
Wichmann Thorsten	Musculoskeletal Infection (F Moriarty), Kantonsspital Winterthur, 26.-30.09.2016
Wood Cameron	Preclinical Services (S Zeiter), Vet Practica Western University of Health Sciences, Pomona, 14.06.- 25.07.2016
Worth Andrew	Preclinical Services (S Zeiter), Massey University, Palmerston, NZ, 26.4.2016

Guest Presentations at AO Center

Jan 28, 2016 Prof Xavier Garric from Pharmacy-University of Montpellier IBMM – Max Mousseron Institute of Biomolecules, Artificial Biopolymers Department, Montpellier, France gave a guest presentation with the title: Applications of degradable polymers based on poly(lactic acid) in the fields of implantable medical devices, drug delivery and tissue engineering.

Jan 28, 2016 Dr Benjamin Nottelet from Pharmacy-University of Montpellier IBMM – Max Mousseron Institute of Biomolecules, Artificial Biopolymers Department, Montpellier, France gave a guest presentation with the title: Surface modifications of implantable biomaterials to provide anti-infectious effects and *in vivo* visualization.

Feb 10, 2016 Dr Sylvia Nürnberger from Ludwig Boltzmann Institute, Vienna, Austria gave a guest presentation with the title: Tissue engineering in cartilage regeneration – clinical and experimental aspects addressed in Vienna.

Feb10, 2016 Dr Andreas Teuschl from Fachhochschule Technikum, Vienna, Austria gave a guest presentation with the title: Silk – a versatile biomaterial for tissue engineering.

Feb 15, 2016 Prof Dr Reinhard Henschler, medical and managing director, blood donor service swiss red cross SRK Graubünden, Switzerland, gave a guest presentation with the title: Fate of MSCs after systemic delivery in mice.

Mar 21, 2016 Dr Patrik Christen from Laboratory for Bone Biomechanics, ETH Zurich, Switzerland gave a guest presentation with the title: Local mechanoregulation of bone remodelling in humans.

Mar 21, 2016 Duncan Betts from Laboratory for Bone Biomechanics, ETZ Zurich, Switzerland gave a guest presentation with the title: Quantification of mechanical stimuli provoking bone formation in fracture healing using *in vivo* time-lapsed imaging.

Mar 30, 2016 Prof Alicia El-Haj from Institute for Science & Technology in Medicine, Keele University, UK gave a guest presentation with the title: Bioengineering and nanomedicine in tissue regeneration.

Apr 20, 2016 Dr Lisbet Haglund from the Orthopaedic Research Laboratory, Montreal General Hospital, Canada gave a guest presentation with the title: Molecular mechanisms of IVD degeneration and pain.

Jun 10, 2016 Dr Xinluan Wang from the Center for Translational Medical R&D, Shenzhen Institutes of Advanced Technology, Shenzhen, China gave a guest presentation with the title: Phytoestrogens from Traditional Chinese Medicine (TCM) fufang for bone defect repair.

Sep 13, 2016 Dr Peter Behrendt from the Clinic of Orthopedic and Trauma Surgery, University Clinic Schleswig-Holstein, Campus Kiel, Germany gave a guest presentation with the title: New insights into chondro-regeneration by anti-inflammatory Interleukin-10.

Sep 20, 2016 Dr Suzanne Tabbaa, Postdoctoral Researcher at Colorado State University and University of California, San Diego, USA gave a guest presentation with the title: Removal of marrow to enhance osteochondral allograft repair.

Oct 5, 2016 Prof Enrico Lucarelli from Istituto Ortopedico Rizzoli, Bologna, Italy gave a guest presentation with the title: Open challenges in musculoskeletal reconstruction in oncological patients.

Nov24, 2016 Dr Valentina Basoli from Department of Biomedical Sciences, University of Sassari, Italy and LBI, Vienna, Austria gave a guest presentation with the title: Epigenetic and molecular behaviour of cells expose to biophysical stimuli.

Nov 24, 2016 Prof Margerita Maioli from Department of Biomedical Sciences, University of Sassari, Italy gave a guest presentation with the title: Biophysical energy applied to cellular models in regenerative medicine.

13 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

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 navigation 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

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

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 2015-01-13
- Case: 10.3180
- Developer / Inventors: L Kamer, D Eglin

Kit for assembling a medical device provided with data acquisition means

- First Application: PCT/CH2015/000062 filed 2015-04-29
- Case: 10.3211
- Developer / Inventors: M Windolf

Bone plate

- First Application: PCT/ CH2015/000117 filed 2015-08-10
- Case: 10.3302
- 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 2015-11-16
- Case: 10.3312
- Developer / Inventors: M Windolf, M Schütz

Bone Implant for Correcting Unbalanced Growth Plate Activity

- First Application: CH2016/01338 filed 2016-10-01
- Case: 10.3487
- Developer / Inventors: M Windolf, M Schütz

14 Publications & Presentations

14.1 Peer reviewed publications

published papers (epub & in print)

Acklin YP, Zderic I, Buschbaum J, Varga P, Inzana JA, Grechenig S, Richards RG, Gueorguiev B, Schmitz P. Biomechanical comparison of plate and screw fixation in anterior pelvic ring fractures with low bone mineral density. *Injury*. 2016;47(7):1456-1460

Antunes JC, Leite Pereira C, Teixeira GQ, Silva RV, Caldeira J, Grad S, Goncalves RM, Barbosa MA. Poly(γ -glutamic acid) and poly(γ -glutamic acid)-based nanocomplexes enhance type II collagen production in intervertebral disc. *J Mater Sci Mater Med*. 2016; epub Nov 24

Bara JJ, Dresing I, Zeiter S, Anton M, Daculsi G, Eglin D, Nehrass D, Stadelmann VA, Betts DC, Muller R, Alini M, Stoddart MJ. A doxycycline inducible, adenoviral BMP-2 gene delivery system to bone. *J Tissue Eng Regen Med*. 2016; epub Dec 13

Collin EC, Kilcoyne M, White SJ, Grad S, Alini M, Joshi L, Pandit AS. Unique glycosignature for intervertebral disc and articular cartilage cells and tissues in immaturity and maturity. *Sci Rep*. 2016;6:23062

D'Este M, Sprecher CM, Milz S, Nehrass D, Dresing I, Zeiter S, Alini M, Eglin D. Evaluation of an injectable thermoresponsive hyaluronan hydrogel in a rabbit osteochondral defect model. *J Biomed Mater Res A*. 2016;104(6):1469-78

de Breij A, Riool M, Kwakman PH, de Boer L, Cordfunke RA, Drijfhout JW, Cohen O, Emanuel N, Zaat SA, Nibbering PH, Moriarty TF. Prevention of *Staphylococcus aureus* biomaterial-associated infections using a polymer-lipid coating containing the antimicrobial peptide OP-145. *J Control Release*. 2016;222:1-8

Dullaert K, Hagen J, Klos K, Gueorguiev B, Lenz M, Richards RG, Simons P. The influence of the Peroneus Longus muscle on the foot under axial loading: A CT evaluated dynamic cadaveric model study. *Clin Biomech (Bristol, Avon)*. 2016;34:7-11

Dullaert K, Hagen JE, Simons P, Gras F, Gueorguiev B, Richards RG, Klos K. Influence of the tibialis posterior muscle actuation on the foot anatomy under axial loading; a CT human cadaveric model study. *Foot Ankle Surg*. 2016;av online Jul 20

Erhart J, Unger E, Schefzig P, Varga P, Trulsson I, Gormasz A, Trulsson A, Reschl M, Hagmann M, Vecsei V, Mayr W. Rotational Stability of Scaphoid Osteosyntheses: An *In vivo* Comparison of Small Fragment Cannulated Screws to Novel Bone Screw Sets. *PLoS One*. 2016;11(6):e0156080

Evans CH, Stoddart MJ. Editorial. Why does bone have TERM limits? *Injury*. 2016;47(6):1159-61

Flamant Q, Stanciuc AM, Pavailler H, Sprecher CM, Alini M, Peroglio M, Anglada M. Roughness gradients on zirconia for rapid screening of cell-surface interactions: Fabrication, characterization and application. *J Biomed Mater Res A*. 2016;104:2502-2514

Gardner OF, Fahy N, Alini M, Stoddart MJ. Differences in human mesenchymal stem cell secretomes during chondrogenic induction. *Eur Cell Mater*. 2016;31:221-35

Gardner OF, Musumeci G, Neumann AJ, Eglin D, Archer CW, Alini M, Stoddart MJ. Asymmetrical seeding of MSCs into fibrin-poly(ester-urethane) scaffolds and its effect on mechanically induced chondrogenesis. *J Tissue Eng Regen Med*. 2016, epub Jul 13

Gardner OF, Fahy N, Alini M, Stoddart MJ. Joint mimicking mechanical load activates TGFbeta1 in fibrin-poly(ester-urethane) scaffolds seeded with mesenchymal stem cells. *J Tissue Eng Regen Med*. 2016; epub Jul 22

Geven MA, Sprecher C, Guillaume O, Eglin D, Grijpma DW. Micro-porous composite scaffolds of photo-crosslinked poly(trimethylene carbonate) and nano-hydroxyapatite prepared by low-temperature extrusion-based additive manufacturing. *Polym Adv Technol.* 2016; epub Aug 22

Grad S, Bow C, Karppinen J, Luk KD, Cheung KM, Alini M, Samartzis D. Systemic blood plasma CCL5 and CXCL6: Potential biomarkers for human lumbar disc degeneration. *Eur Cell Mater.* 2016;30:1-10

Grässer C, Scheuer C, Parakenings J, Tschernig T, Eglin D, Menger MD, Laschke MW. Effects of macrophage-activating lipopeptide-2 (MALP-2) on the vascularisation of implanted polyurethane scaffolds seeded with microvascular fragments. *Eur Cell Mater.* 2016;32:74-86

Grüneweller N, Raschke MJ, Zderic I, Widmer D, Wähnert D, Gueorguiev B, Richards RG, Fuchs T, Windolf M. Biomechanical comparison of augmented versus non-augmented sacroiliac screws in a novel hemi-pelvis test model. *J Orthop Res.* 2016; epub Aug 26

Guillaume O, Geven MA, Grijpma DW, Tang TT, Qin L, Lai YX, Yuan H, Richards RG, Eglin D. Poly(trimethylene carbonate) and nano-hydroxyapatite porous scaffolds manufactured by stereolithography. *Polym Adv Technol.* 2016; epub Aug 17

Häberli J, Henle P, Acklin YP, Zderic I, Gueorguiev B. Knee joint kinematics with dynamic augmentation of primary anterior cruciate ligament repair - a biomechanical study. *J Exp Orthop.* 2016;3(1):29

Herrmann M, Bara JJ, Sprecher CM, Menzel U, Jalowiec JM, Osinga R, Scherberich A, Alini M, Verrier S. Pericyte plasticity - comparative investigation of the angiogenic and multilineage potential of pericytes from different human tissues. *Eur Cell Mater.* 2016;31:236-49

Hesse B, Salome M, Castillo-Michel HA, Cotte M, Fayard B, Sahle C, De Nolf W, Hradilova J, Masic A, Kanngiesser B, Bohner M, Varga P, Raum K, Schrof S. Full-field Calcium K-Edge X-ray Absorption Near-Edge Structure Spectroscopy on Cortical Bone at the Micron-Scale: Polarization Effects Reveal Mineral Orientation. *Anal Chem.* 2016;88(7):3826-35

Hesse B, Varga P, Schrof S, Männike N, Pacureanu A, Langer M, Suhonen H, Maurer P, Cloetens P, Peyrin F, Raum K. Synchrotron-Nano-Tomografie mit Phasenkontrast. Eine neue Dimension in der Analyse von Osteozytenlakunen, Kanalikuli und der extrazellulären Knochenmatrix.[Synchrotron radiation nanotomographie with phase contrast. A new dimension in the analysis of the osteocyte lacuno-canalicular network and the extracellular bone matrix]. *Osteologie.* 2016;25(2):83-91

Hulsart-Billstrom G, Dawson JI, Hofmann S, Muller R, Stoddart MJ, Alini M, Redl H, El Haj A, Brown R, Salih V, Hilborn J, Larsson S, Oreffo RO. A surprisingly poor correlation between *in vivo* and *in vivo* testing of biomaterials for bone regeneration: results of a multicentre analysis. *Eur Cell Mater.* 2016;31:312-22

Inzana JA, Varga P, Windolf M. Implicit modeling of screw threads for efficient finite element analysis of complex bone-implant systems. *J Biomech.* 2016;49(9):1836-1844

Kamer L, Noser H, Blauth M, Lenz M, Windolf M, Popp AW. Bone Mass Distribution of the Distal Tibia in Normal, Osteopenic, and Osteoporotic Conditions: An *Ex vivo* Assessment Using HR-pQCT, DXA, and Computational Modelling. *Calcif Tissue Int.* 2016;99:588-597

Kazezian Z, Li Z, Alini M, Grad S, Pandit A. Injectable Hyaluronic Acid Down-regulates Interferon Signaling Molecules, IGFBP3 and IFIT3 in the Bovine Intervertebral Disc. *Acta Biomater.* 2016; epub Dec 18

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Kubosch D, Kubosch EJ, Gueorguiev B, Zderic I, Windolf M, Izadpanah K, Südkamp NP, Strohm PC. Biomechanical investigation of a minimally invasive posterior spine stabilization system in comparison to the Universal Spinal System (USS). *BMC Musculoskelet Disord.* 2016;17(1):134

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- May C, Gueorguiev B, Heuberger R, Sague J, Gross C, Henle P, Delfosse D, Häberli J. Low metallic wear of dynamic intraligamentary stabilization. Tribology International. 2016; epub Dec 27
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- Metsemakers WJ, Schmid T, Zeiter S, Ernst M, Keller I, Cosmelli N, Arens D, Moriarty TF, Richards RG. Titanium and steel fracture fixation plates with different surface topographies: Influence on infection rate in a rabbit fracture model. Injury. 2016;47(3):633-9
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- Metsemakers WJ, Moriarty TF, Morgenstern M, Kuehl R, Borens O, Kates S, Richards RG, Verhofstad M. Letter to the Editor: New Definition for Periprosthetic Joint Infection: From the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res. 2016;474:2726-2727
- 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: A Prospective Point-Prevalence Study. PLoS One. 2016;11(2):e0148437
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Morgenstern M, Erichsen C, von Ruden C, Metsemakers WJ, Kates SL, Moriarty TF, Hungerer S. Staphylococcal orthopaedic device-related infections in older patients. *Injury*. 2016;47(7):1427-1434

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14.3 Abstracts published in journals

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14.4 Conference proceedings

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Arand C, Noser H, Kamer L, Sawaguchi T, Richards RG, Rommens P. 3D statistisches Modell des knöchernen Beckens - anatomische Variabilität und biomechanische Relevanz. 2016 DKOU (oral)

Armiento AR, Eglin D, Stoddart MJ. The stimulatory effect of retinoblastoma protein on alkaline phosphatase activity and mineralisation of human mesenchymal stromal cells. 2016 EORS (oral)

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Bäumlein M, Gueorguiev B, Rillmann P, Nerlich A, Hanke A, Loibl M. Klinisch-radiologischer Langzeitverlauf nach intraartikulärer Tibiakopffraktur bei Skifahrern. 2016 DGSP+DGRP (poster)

Bäumlein M, Hanke A, Gueorguiev B, Rillmann P, Loibl M. Clinical and radiological long term development of intraarticular tibia plateau fractures in skiers. 2016 DKG (poster)

D'Amora U, D'Este M, Eglin D, Gloria A, De Santis R, Alini M, Ambrosio L. Collagen density gradient on poly(epsilon-caprolactone) surface for the design of 3D printed osteochondral. 2016 WBC (poster)

D'Amora U, D'Este M, Eglin D, Safari F, Gloria A, De Santis R, Alini M, Ambrosio L. Collagen gradient on 3D printed scaffolds for interface tissue engineering. 2016 GNB (poster)

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D'Este M. Hyaluronic acid derivatives for in situ tissue engineering and additive manufacturing. 2016 AFPM (oral - invited lecture)

Douma L, Peroglio M, Ferguson SJ, Alini M, Grad S. The effect of the degenerative state of the intervertebral disc on the efficacy of stem cell regeneration therapies. 2016 YSBMch (poster)

Evers J, Fischer M, Zderic I, Wähnert D, Gueorguiev B, Raschke MJ, Ochman S. The role of a small PMF in trimalleolar ankle fractures. 2016 Foot International (oral)

Fahmy-Garcia S, Mumcuoglu D, de Miguel L, van der Eerden BCJ, Eglin D, Kluitman SGJM, van Osch GJVM, Farrell E. Injectable synthetic collagen beads hydrogel loaded with BMP2 promotes ectopic bone formation. 2016 TERMIS-EU (poster)

Fahmy-Garcia S, Mumcuoglu D, de Miguel L, van der Eerden BCJ, Eglin D, Kluitman SGJM, van Osch GJVM, Farrell E. Injectable synthetic collagen beads hydrogel loaded with BMP2 promotes ectopic bone formation. 2016 eCM (oral)

Fahy N, Gardner O, Alini M, Stoddart M. Investigation of the effect of spatial PTHrP signalling gradients on human mesenchymal stem cell chondrogenesis and hypertrophy. 2016 GRC Musculoskeletal Biology & Bioengineering (poster)

Filipov O, Stoffel K, Gueorguiev B, Sommer C. Filipov's method of biplane double-supported screw fixation extremely reduces the risk of fixation failure in femoral neck fractures. Clinical outcomes in 207 patients. 2016 ISFR (oral)

Freitag L, Günther C, Kyllönen L, Eberli U, Thompson K, Arens D, Zeiter S, Eglin D, Stadelmann V. The efficacy of local bisphosphonate and BMP-2 delivery in improving bone mass and mechanical implant stability. 2016 eCM (poster)

Freitag L, Günther C, Kyllönen L, Eberli U, Thompson K, Arens D, Zeiter S, Eglin D, Stadelmann V. The efficacy of local bisphosphonate and BMP-2 delivery in improving bone mass and mechanical implant stability. 2016 Graubünden forscht / Young Scientists in Contest (oral)

Freitag L, Günther C, Kyllönen L, Eberli U, Thompson K, Arens D, Zeiter S, Eglin D, Stadelmann V. The efficacy of local bisphosphonate and BMP-2 delivery in improving bone mass and mechanical implant stability. 2016 SBMS conference (oral)

Freitag L, Günther C, Kyllönen L, Eberli U, Thompson K, Arens D, Zeiter S, Eglin D, Stadelmann V. The efficacy of local bisphosphonate and BMP-2 delivery in improving bone mass and mechanical implant stability. 2016 eCM conference (poster)

Gardner OF, Fahy N, Alini M, Stoddart MJ. A secretomic comparison of the induction of chondrogenesis in human mesenchymal stem cells via TGF- β 1 and mechanical load. 2016 ORS (oral)

Gardner O, Archer C, Alini M, Stoddart MJ. Tribological tissue engineering of cartilage. 2016 GRC Musculoskeletal Biology & Bioengineering (poster)

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Grechenig S, Nerlich M, Gueorguiev B, Pfeifer C, Dreu M, Acklin Y, Loibl M, Schmitz P. Three competitive methods to achieve primary stability in THR: Biomechanical analysis. 2016 DKOU (poster)

Gueorguiev B, Lenz M, Sommerer T, Klos K, Zderic I, Richards RG, Simons P. Biomechanical evaluation of foot medial column fusion using two novel plating systems. 2016 ESB (BioMech) (oral)

Gueorguiev B, Hagen J, Richards RG, Lenz M, Simons P, Klos K. Investigation of syndesmotic reconstructions utilizing weightbearing computer tomography. 2016 ESB (BioMech) (oral)

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Gueorguiev B, Ernst M, Höntzsch D, Schwyn R, Döbele S, Richards RG, Windolf M. Non-unions – just a biomechanical problem? 2016 BOTA (oral)

Gueorguiev B, Lenz M, Perren SM, Richards RG, Fernandez Dell'Oca A, Höntzsch D, Windolf M. Benefit and harm of cerclages for osteosynthesis augmentation. 2016 BOTA (oral)

Gueorguiev B, Hofmann-Fliri L, Richards RG, Blauth M, Windolf M. Implant augmentation with bone cement in osteoporotic bone. 2016 BOTA (oral)

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Gueorguiev B, Ernst M, Höntzsch D, Schwyn R, Döbele S, Richards RG, Windolf M. Non-unions – just a biomechanical problem? 2016 UBK (oral)

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Gueorguiev B, Henle P, Zderic I, Acklin Y, Häberli J. Stability of the knee joint after dynamic intraligamentary stabilization. 2016 DKOU (oral)

Guillaume O, Geven M, Kluge K, Eberli U, Zeiter S, Grijpma D, Alini M, Eglin D. Poly(trimethylene carbonate)-hydroxyapatite printed scaffolds for bone healing: *in vivo* and *in vivo* characterization. 2016 SSB+RM (poster)

Guillaume O, Geven M, Eberli U, Zeiter S, Grijpma D, Alini M, Eglin D. Introduction of a new biodegradable composite implant for bone repair: poly(trimethylene carbonate)-hydroxyapatite made by stereolithography. 2016 eCM (oral)

Guillaume O, Kluge K, Eberli U, Zeiter S, Geven M, Grijpma D, Alini M, Eglin D. *In vivo* and *in vivo* evaluation of osteoinductive composite scaffolds manufactured by stereolithography. 2016 WBC (oral)

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Häberli J, Zderic I, Acklin Y, Henle P, Gueorguiev B. Knee joint stability after dynamic intraligamentary stabilization – a biomechanical study. 2016 ESB (BioMech) (oral)

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Herrmann M, Zeiter S, Eberli U, Hildebrand M, Camenisch K, Menzel U, Alini M, Verrier S, Stadelmann V. Improved fracture healing by short-term G-CSF treatment. 2016 eCM (oral)

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Krause F, Barandun A, Klammer G, Zderic I, Gueorguiev B, Schmid T. Ankle joint pressure changes in high tibial and distal femoral osteotomies. 2016 EFORT (oral)

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Krause F, Barandun A, Klammer G, Zderic I, Gueorguiev B, Schmid T. Ankle joint pressure changes in high tibial and distal femoral Osteotomies. 2016 AOFAS (oral)

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Lenz M, Stoffel K, Kielstein H, Mayo K, Hofmann GO, Gueorguiev B. Longer plate or bicortical locking?-A biomechanical comparison of two techniques for periprosthetic femur fracture fixation. 2016 EFORT (poster)

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Lenz M, Stoffel K, Kielstein H, Mayo K, Hofmann GO, Gueorguiev B. Fixation of periprosthetic fractures – trochanteric hook or subtrochanteric bicortical locking screws? 2016 ESB (BioMech) (oral)

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Li B, Menzel U, Loebel C, Alini M, Stoddart M. Monitoring and selection of live mesenchymal stem cells based on differentiation induced changes in mRNA expression. 2016 ORS (poster)

Li B, Menzel U, Loebel C, Alini M, Stoddart MJ. Monitoring and isolation of live mesenchymal stem cells based on differentiation induced changes in mRNA expression. 2016 flowcytometryUK (poster)

Li Z, Grad S, Zhang Y, Lezuo P, Peroglio M, Rozhnova O, Schelkunova E, Mikhailovsky M, Sadovoy M, Ouellet J, Haglund L, Alini M. Is the cell phenotype in idiopathic scoliotic intervertebral disc related to the asymmetric dynamic loading condition? 2016 GRC Musculoskeletal Biology & Bioengineering (poster)

Li Z, Grad S, Alini M. Endogenous versus exogenous strategies for repairing annulus fibrosus tissue. 2016 Matrix Biology Ireland (oral)

Li B, Menzel U, Loebel C, Alini M, Stoddart MJ. Identification and isolation of live mesenchymal stem cells based on differentiation induced changes in mRNA expression. 2016 eCM (oral)

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Loebel C, Alini M, Zenobi-Wong M, Eglin D. Cell-matrix interactions in hyaluronan-tyramine hydrogels matrix alter stem cell behaviour in 3D. 2016 TERMIS-EU (oral)

Loebel C, Cosgrove B, Alini M, Zenobi-Wong M, Mauck RL, Eglin D. Crosslinking strategy of hyaluronan-tyramine hydrogels alters mesenchymal stem cell attachment and behavior. 2016 SSB+RM (poster)

Loebel C, Cosgrove B, Alini M, Zenobi-Wong M, Mauck RL, Eglin D. Crosslinking Chemistry of Tyramine-Modified Hyaluronan Hydrogels Alters Mesenchymal Stem Cell Attachment and Behavior 2016 WBC (oral)

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Metsemakers WJ, Schmid T, Zeiter S, Ernst M, Keller I, Cosmelli N, Arens D, Moriarty TF, Richards RG. Role of implant material and surface topography on infection susceptibility in a rabbit fracture model. 2016 ORS (poster)

Monaco G, Alini M, Stoddart MJ. Development of *ex vivo* system for MSCs differentiation and cartilage integration. 2016 YSBMch (oral)

Monaco G, Fahy N, Alini M, Stoddart MJ. Development of *ex vivo* system for human mesenchymal stem cells differentiation and cartilage integration. 2016 Graubünden forscht / Young Scientists in Contest (oral)

Monaco G, Fahy N, Alini M, Stoddart MJ. Effect of exogenous hyaluronan on human Mesenchymal Stem Cell chondrogenesis. 2016 Biointerfaces Int (poster)

Moser C, Bardsley K, Wolfrum C, El Haj AJ, Alini M, Stoddart MJ, Bara JJ. Perfusion culture regulates the differentiation of mesenchymal stromal cells on polylactic-glycolic acid *in vivo*. 2016 eCM (poster)

Moser C, Wolfrum C, Bardsley K, Alini M, Stoddart MJ, Bara JJ. Directing osteogenic differentiation of mesenchymal stromal cells *in vivo*. 2016 YSBMch (poster)

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Petta D, Sprecher CM, Grijpma DW, Eglin D, D'Este M. Exploiting enzymatic-visible light dual-gelation for 3D printing of tyramine-modified hyaluronan. 2016 SSB+RM (oral)

Petta D, Eglin D, Grijpma DW, D'Este M. Remarkable rheological properties of short alkyl chain derivatives of hyaluronic acid. 2016 WBC (poster)

Petta D, Sprecher CM, Grijpma DW, Eglin D, D'Este M. Tyramine-modified hyaluronic acid bioink with a dual crosslinking mechanism. 2016 AFPM (poster)

Petta D, Eglin D, Grijpma DW, D'Este M. Remarkable rheological properties of hyaluronic acid short alkyl chain derivatives synthesized via DMTMM chemistry. 2016 YSBMch (rapid fire poster)

Petta D, Sprecher C, Grijpma D, Eglin D, D'Este M. Tyramine-modified hyaluronic acid as a bioink for 3D BioPrinting. 2016 Graubünden forscht / Young Scientists in Contest (oral)

Poirier G, Degryse AD, Hedenqvist P, Jacobson C, Kalman R, Klein H, Ritskes-Hoitinga M, Voipio HM, Weilenmann R, Zeiter S. European strategy for laboratory animal veterinary training 2016 FELASA (oral)

Post V, Harris LG, Morgenstern M, Richards RG, Moriarty TF. Prevalence and characterization of nasal methicillin-resistant *Staphylococcus aureus* from human and veterinary surgeons. 2016 SGM / SSM (poster)

Russo F, D'Este M, Vadala G, Papalia R, Alini M, Denaro V. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: Rheological evaluation. 2016 ORS (poster)

Russo F, D'Este M, Vadalà G, Cattani C, Papalia R, Alini M, Denaro V. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: rheological and biological evaluation. 2016 EORS (poster)

Russo F, Vadalà G, D'Este M, Alini M, Eglin D, Giordano R, Denaro V. A hyaluronic acid / platelet rich plasma hydrogel for mesenchymal stem cells delivery to the intervertebral disc: rheological and biological characterization. 2016 EORS (poster)

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. 2016 WIRM (poster)

Sabaté Bresco M, Berset C, Ziegler M, Richards RG, O'Mahoney L, Moriarty TF. Staphylococcus epidermidis infection progression and associated immune response in a murine fracture model. 2016 YSBMch (poster)

Sabaté Bresco M, Berset C, Kluge K, Richards RG, O'Mahoney L, Moriarty TF. Immune responses in a murine device-related infection model. 2016 Graubünden forscht / Young Scientists in Contest (poster)

Safari F, Eglin D, Alini M, Eslaminejad MB, Stoddart M. Evaluation of proliferation and cartilage differentiation of hBM-MSCs on human Wharton's jelly-derived microcarriers. 2016 YSBMch (poster)

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Schmid T, Nehrbass D, Zeiter S. A refined and clinically more relevant, preclinical osteochondral defect model in rabbits. 2016 TERMIS-EU (oral)

Schmidutz F, Schiuma D, Windolf M, Richards RG, Sprecher CM, Popp AW. Die kortikale Dicke und Porosität an der distalen Tibia werden durch die hochauflösende Computertomographie unterschätzt, korrelieren aber mit der lokalen Festigkeit 2016 VSOU (oral)

Schmierer P, Smolders L, Zderic I, Gueorguiev B, Pozzi A, Knell S. Biomechanical evaluation of different plating techniques for feline ilial fracture stabilization. 2016 ESB (BioMech) (oral)

Schmitz P, Müller M, Baumann F, Weber J, Gueorguiev B, Acklin Y, Nerlich M, Grechenig S. Der zementaugmentierte Transiliacale Fixateur interne (caTIFI) zur Osteosynthese osteoporotischer Beckenringfrakturen: Erste klinische Ergebnisse. 2016 DKOU (oral)

Schwinn J, Hofmann-Fliri L, Gueorguiev B, Schwyn R, Kielstein H, Hofmann GO, Lenz M. A biomechanical study of the insertion depth of the femoral neck blade and its effects on fixation stability. 2016 EFORT (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. 2016 NOUV (poster)

Siemens C, Reumann MK, Ehnert S, Mannheim J, Ernst M, Gueorguiev B, Freude T, Nussler AK. Veränderte knöchernen Integrität über den Verlauf der Alterung im Tiermodell. 2016 DKOU (oral)

Sprecher CM, S.F. S, Hensler S, Milz S. Osteointegration in a CapFlex-PIP© finger implant: a histological case report. 2016 eCM (poster)

Stanciu 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. 2016 YSBMch (poster)

Stanic B, O'Mahoney L, Richards RG, Moriarty TF. Differential immune reactivity to Staphylococcus aureus and Staphylococcus epidermidis. 2016 WIRM (poster)

Stauber T, Öztürk E, Loebel C, Eglin D, Zenobi-Wong M. Hydrogels made from cartilage-mimetic sulfated alginate polymers via di-tyramine bond formation show increased stability and adhesion to cartilage. 2016 SSB+RM (poster)

Stoddart MJ. Role of mechanics in chondrogenesis. 2016 TERMIS-EU (oral)

Stoddart MJ. Role of Biomechanics on the Stem Cell Fate - Relevance for the Hip. 2016 ICRS (oral)

Stoddart MJ. Role of Mechanics in Mesenchymal Stem Cell Chondrogenesis. 2016 TERMIS-AP (oral)

Stoddart MJ. Effect of Complex loading on stem cell chondrogenesis. 2016 MRN Symposium (oral)

Stoddart MJ. The role of load & cell distribution on mesenchymal stem cell chondrogenesis & matrix deposition. 2016 Matrix Biology Ireland (oral)

Stoffel K, Zderic I, Sommer C, Eberli U, Mueller D, Oswald M, Gueorguiev B. The new Femoral Neck System for femoral neck fracture fixation. Biomechanical performance versus diverse standard implants for osteosynthesis. 2016 EORS (poster)

Teixeira GQ, Antunes JC, Leite Pereira C, Castro F, Ferreira JR, Gomez-Lazaro, M, Aguiar P, Silva RV, Caldeira J, Neidlinger-Wilke C, Grad S, Barbosa MA, Goncalves RM. Local treatment of inflammation in degenerated intervertebral disc using poly(γ -glutamic acid)-based nanocomplexes promotes extracellular matrix remodelling. 2016 TERMIS-EU (oral)

Tekari A, Chan SC, Wuertz K, Sakai D, Benneker LM, Grad S, Gantenbein B. Tie2+ cells from the bovine coccygeal discs are multipotent cells capable of differentiating into osteogenic, adipogenic and chondrogenic lineages. 2016 ORS (poster)

ter Boo GA, Schmid T, Nehrbass D, Zderic I, Grijpma DW, Richards RG, Moriarty TF, Eglin D. Efficacy of a thermo-responsive hyaluronan based hydrogel containing gentamicin in an *in vivo* fracture model with plating osteosynthesis and *S. aureus* contamination. 2016 AFPM (poster)

ter Boo GA, Arens D, Schmid T, Zeiter S, Metsemakers WJ, Nehrbass D, Richards RG, Grijpma DW, Moriarty TF, Eglin D. A thermo-responsive hyaluronan based hydrogel loaded with gentamicin prevents infection in an *in vivo* fracture model with plating osteosynthesis. 2016 YSBMch (rapid fire poster)

ter Boo GA, Arens D, Schmid T, Metsemakers WJ, Zeiter S, Nehrbass D, Grijpma DW, Richards RG, Eglin D, Moriarty TF. A thermo-responsive hyaluronan based hydrogel loaded with gentamicin prevents infection in an *in vivo* fracture model with plating osteosynthesis. 2016 Thesinge Biofilm Meeting (oral)

ter Boo GA, Schmid T, Nehrbass D, Zderic I, Grijpma DW, Richards RG, Moriarty TF, Eglin D. Efficacy of a thermo-responsive hyaluronan based hydrogel containing gentamicin in an *in vivo* fracture model with plating osteosynthesis and *S. aureus* contamination. 2016 SSB+RM (poster)

Thompson K, Freitag L, Eberli U, Camenisch K, Arens D, Richards RG, Stadelmann V, Moriarty TF. *In vivo* monitoring of Staphylococcus epidermidis implant infection using microCT imaging. 2016 EORS (oral)

Urzi F, Peroglio M, Li Z, Creemers LB, Alini M, Grad S. Efficiency of loaded nanocarriers in a degenerative intervertebral disc bioreactor system. 2016 YSBMch (poster)

Urzi F, Peroglio M, Li Z, Creemers LB, Alini M, Grad S. An innovative model for intervertebral disc degeneration in a bioreactor system. 2016 Graubünden forscht / Young Scientists in Contest (oral)

Vadala G, D'Este M, Russo F, Alini M, Eglin D, Giordano R, Denaro V. A hyaluronic acid / platelet rich plasma hydrogel for mesenchymal stem cells delivery to the intervertebral disc: rheological and biological characterization. 2016 SSB+RM (oral)

Vainieri ML, van Osch G, Grad S, Alini M. Targeting cartilage regeneration by acellular hydrogel containing nanocarriers on a joint bioreactor. 2016 YSBMch (poster)

Vainieri L, Wahl D, van Osch GJ, Alini M, Grad S. Investigating the homing behaviour of endogenous stem cells in a joint bioreactor to regenerate articular cartilage. 2016 Graubünden forscht / Young Scientists in Contest (oral)

- Varga P, Jenni D, Inzana J, Gueorguiev B, Blauth M, Windolf M. Strengthening effect of novel prophylactic augmentation approaches for the osteoporotic proximal femur as evaluated using computer simulations. 2016 EORS (oral)
- Voss JO, Varjas V, Raguse JD, Thieme N, Richards RG, Kamer L. CT-basierte Frakturposition bei komplexen Frakturen des Unterkiefers. 2016 MKG Chirurgie (oral)
- Wu Y, Stoddart M, Wuertz-Kozak K, Grad S, Alini M, Ferguson SJ. Metabolic response of tissue engineered cartilage during articulation: influence of synovial fluid and its viscosity. 2016 ORS (poster)
- Yuan H, Acklin Y, Varga P, Gueorguiev B, Windolf M, Epari D, Schuetz M, Schmutz B. Does bone-nail radius of curvature mismatch predict the ease of nail insertion? 2016 AOTAP (poster)
- Yuan H, Acklin Y, Varga P, Gueorguiev B, Windolf M, Epari D, Schuetz M, Schmutz B. Does bone-nail radius of curvature mismatch predict the ease of nail insertion? 2016 ABEC (poster - best poster award)
- Zahn J, Herrmann M, Loibl M, Alini M, Verrier S. Platelet Rich Plasma as autologous cell delivery and pro-angiogenic hydrogel for bone tissue engineering applications. 2016 EORS (poster - Young investigator poster award)
- Zhou X, Chen L, Grad S, Alini M, Pan H, Lu W, Huang S, Peng S. MicroRNA-224 associates with the severity of LDH and regulates disc progenitor cell between chondrogenic and fibrogenic differentiation. 2016 ORS (poster)
- Ziادلou R, Grad S, Stoddart MJ, Martin I, Wang X, Qin L, Alini M. Traditional Chinese Medicine (TCM) compound delivery system for treatment of osteoarthritis. 2016 YSBMch (poster)
- Ziادلou R, Grad S, Stoddart MJ, Martin I, Wang X, Ling Q, Alini M. Traditional Chinese Medicine (TCM) compound delivery system for treatment of osteoarthritis. 2016 Graubünden forscht / Young Scientists in Contest (poster)

14.5 Dissertations

- Gardner OFW. The regulation of human mesenchymal stem cell chondrogenesis through multiaxial load. 2016 Cardiff University (MJ Stoddart, EJ Blain) - PhD
- Glück M. Induction of osteogenic differentiation in human mesenchymal stem cells by crosstalk with osteoblasts. 2016 Albert-Ludwigs-Universität Freiburg im Breisgau (Schmal H, Stoddart M) - Dr med / medical fellow
- Götzen M. Implant augmentation in osteoporotic fracture management and the effect on the overlying joint cartilage. 2016 Universität Innsbruck (Schmölz W, Blauth M, Zeiter S, Hofmann-Fliri L) – PhD
- Loebel C. Engineering hyaluronan-tyramine hydrogels to modulate mesenchymal stem cell behavior. 2016 ETH Zürich (Zenobi-Wong M, Eglin D) – PhD
- Schopper CO. Biomechanical evaluation of the femoral neck fracture fixation technique with the new implant FNS in comparison to DHS Blade, DHS Screw with antirotation screw and Three Cannulated Screws. 2016 Universität Ulm (Gebhard F, Gueorguiev B.) – Dr med
- Sprecher CM. Funktionelle und altersbezogene Anpassung des Knochengewebes an Implantate aus künstlichen Werkstoffen – Analyse von verschiedenen Anwendungen an Tier und Mensch. 2016 LMU München (Milz S, Richards RG) – PhD
- ter Boo GA. Delivery of gentamicin from resorbable polymeric carriers as anti-infective strategy for implant-associated osteomyelitis. 2016 University of Twente, Enschede (Grijpma DW, Eglin D) - PhD
- Douma LS. The effect of the degenerative state of the intervertebral disc on the efficacy of stem cell regeneration therapies. 2016 ETH Zürich (Ferguson SJ, Grad S, Peroglio M) – MSc

Moser C. Directing osteogenic differentiation of mesenchymal stromal cells *in vivo*. 2016 ETH Zürich (MJ Stoddart, C Wolfrum) – MSc

Schiedeck A. Implant development for growth by steering Epiphysiodesis in childhood and adolescence, including quality management according to EN ISO. 2016 Westfälische Hochschule (Lilienhof H, Windolf M, Buschbaum J) - MSc

Schneider M. Finite element modelling of arrested bone growth. 2016 Universität Stuttgart (Röhrlé O, Varga P, Gueorguiev B) – MSc

14.6 Presentations (not in conference proceedings)

- 18.03.2016 Richards Geoff: "Introduction AO Research Institute Davos and preclinical translation", Practical course "Skeletal Repair" for students from ETHZ and ZHAW, Davos, Switzerland
- 28.04.2016 Richards Geoff: "Infection", BSSH The British Society for Surgery of the Hand, Spring Scientific Meeting, London, GB (Guest Lecture)
- 16.06.2016 Richards Geoff: "Rapid Prototyping of Custom-Made Bone-Forming Tissue Engineering Constructs", MRN Musculoskeletal Regenerative Medicine Network Symposium "The Joint as an Organ", Utrecht, Netherlands (Invited Speaker)
- 10.07.2016 Richards Geoff: "Report from AO Research Institute Davos", Board of Trustees Meeting, Amsterdam, Netherlands (Invited Speaker)
- 15.09.2016 Richards Geoff: "Infection", EORS European Orthopaedic Research Society Annual Meeting 2016, Bologna, Italy (Session Moderator)
- 08.12.2016 Richards Geoff: "Smart Surgery – Implants that monitor patient activity and fracture healing", AOTrauma Course – Basic Principles of Fracture Management, Davos, Switzerland (Invited Speaker)
- 11.01.2016 Alini Mauro: "Hydrogel for intervertebral disc regeneration", Prof. Luigi Ambrosio, Institute of Polymers Composites and Biomaterials (IPCB), Napoli, Italy (Invited Speaker)
- 28.01.2016 Alini Mauro: "Endogenous vs exogenous repair of intervertebral disc", Prof. Alicia El Haj, Institute for Science & Technology in Medicine, Keele University, Keele, UK (Invited Speaker)
- 25.04.2016 Alini Mauro: "Complex hydrogel for osteoporosis treatment", European consortium: EuroNanoMed, Cluj-Napoca, Romania (Invited Speaker)
- 16.06.2016 Alini Mauro: "Bioreactor for IVD research: Better than animal studies?"
- 04.07.2016 Alini Mauro: "New trends in advanced therapies for intervertebral disc regeneration", University Campus Bio-Medico, Rome, Italy (Invited Speaker)
- 26.09.2016 Alini Mauro: "Chemoattractant for the homing of MSC into the IVD", Sun Yat-sen University, Guangzhou, P. R. China (Invited Speaker)
- 09.12.-10.12.2016 Alini Mauro: "Chemoattractant for the homing of MSC into the IVD", Italian Orthopaedic Research Society Congress, Rome, Italy
- 29.09-02.10.2016 Gueorguiev Boyko: Implant augmentation with bone cement in osteoporotic bone, in "Pelvis, polytrauma, osteoporosis session", 13th National Congress BOTA, Sofia, Bulgaria (Session Chair)
- 29.09-02.10.2016 Gueorguiev Boyko: Non-unions – just a biomechanical problem? in "Bone and soft tissue substitutes session", 13th National Congress BOTA, Sofia, Bulgaria (Session Chair)
- 29.09-02.10.2016 Gueorguiev Boyko: Benefit and harm of cerclages for osteosynthesis augmentation, in "Pelvis, polytrauma, osteoporosis session", 13th National Congress BOTA, Sofia, Bulgaria (Session Chair)
- 19.-23.10.2016 Gueorguiev Boyko: Development of orthopedic implants assisted by computer simulations, 8th National Biomechanics Congress, Ankara, Turkey (Invited Speaker)
- 19.-23.10.2016 Gueorguiev Boyko: Implant augmentation with bone cement in osteoporotic bone, 8th National Biomechanics Congress, Ankara, Turkey (Invited Speaker)
- 19.-23.10.2016 Gueorguiev Boyko: Non-unions – just a biomechanical problem? 8th National Biomechanics Congress, Ankara, Turkey (Invited Speaker)

- 03.-05.11.2016 Gueorguiev Boyko: Why and how do locking plates fail? OTC Foundation hot topic workshop on complications of plating–evolution of treatment, Boston, USA (Invited Speaker)
- 25.10.2016 Sibylle Grad: "Stem cells for intervertebral disc regeneration: success and hurdles", DKOU 2016 Annual Meeting, Berlin, Germany (ORS Keynote lecture)
- 01.-03.09.2016 Moriarty Fintan: Opening keynote "Experimental studies on infection after osteosynthesis", European Bone and Joint Infection Society Meeting, Oxford, UK (Invited Speaker)
- 23.-25.06.2016 Moriarty Fintan: "Biofilm and Implant related infection: How to win the battle" Malaysian Orthopaedic Association & ASEAN Arthroplasty Association Meeting Johor Bahru, Malaysia (Invited Speaker)
- 16.06.2016 Stoddart Martin: "Effect of Complex loading on stem cell chondrogenesis", Musculoskeletal Regeneration Network Symposium "The Joint as an Organ", University Medical Center Utrecht, The Netherlands (Invited Speaker)
- 08.11.2016 Stoddart Martin: "Outcome measures for bioreactors in orthopaedics", Bioreactors and Growth environments for Tissue Engineering, Keele University, UK (Invited Speaker)
- 17.11.2016 Stoddart Martin: "The role of load and cell distribution on mesenchymal stem cell chondrogenesis and matrix deposition", Matrix Biology Ireland, NUI Galway, Ireland (Invited Speaker)
- 25.11.2016 Stoddart Martin: "Comparing human MSC chondrogenesis under static and loading conditions", 10th Oswestry Cartilage Symposium, The Robert Jones & Agnes Hunt Orthopaedic Hospital, UK
- 01.-03.06.2016 Windolf Markus: "Biomechanical principles of augmentation", 17th EFORT Congress, Geneva, Switzerland (Invited Speaker)
- 25.-28.10.2016 Windolf Markus: "Smart plates: AO fracture monitor", DKOU 2016, Berlin, Germany (Invited Speaker)
- 25.-28.10.2016 Windolf Markus: "Smart positioning: X-in-One AO implant positioning assistant", DKOU 2016, Berlin, Germany (Invited Speaker)
- 25.-28.10.2016 Ernst Manuela: "SmartFix – monitoring external fixation", DKOU 2016, Berlin, Germany (Invited Speaker)
- 26.09.2016 Zhen Li: "Cartilage and intervertebral disc regeneration using mechanical loading bioreactor system", Department of Orthopaedic Surgery, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China (Invited Speaker)
- 12.10.2016 Zhen Li: "Intervertebral disc regeneration using mechanical loading bioreactor system", School of Medicine, Shenzhen University, Shenzhen, China (Invited Speaker)
- 25.-28.10.2016 Varga Peter: "AutoGauge – the Smart Drill. A device for automated screw length determination", DKOU 2016, Berlin, Germany (Invited Speaker)
- 25.-28.10.2016 Varga Peter: "SystemFix – smart implant optimization", DKOU 2016, Berlin, Germany (Invited Speaker)