AO Foundation

AO Research Institute Davos

Activity Report 2017

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1 Introduction

During 2017 the AO Research Institute Davos (ARI) has strengthened its international collaborations through collaborative research programs funded either externally from national and international grants and internally funded consortia. ARI collaborates in many fields with other top institutes and universities world wide. This is reflected strongly in the project reports and the good news sections within this activity report. In recent years we have made a strong push to share our academic knowledge with Chinese teams and have brought numerous fellows over to Davos mainly from the Guangdong province where we have several collaborations. It is a pleasure to work with these enthusiastic motivated hardworking groups. The collaborations have also resulted in three Chinese grants in 2017 for ARI.

The ARI medical research fellowships are again firmly rooted into our foundations and positions are highly competitive to acquire. Both scientists and medical research fellows apply for external funding mechanisms to join us (from scholarships etc.) from several months to a year and we have had a good number join ARI in recent years.

If I must choose one highlight of 2017, this would be TERMIS-EU chapter congress we organized as a team in ARI. Bringing in over 1 million CHF in participant fees, sponsorships etc., we ran this meeting hiring the whole congress centre for 1301 participants. We showed through efficient cost management and effective team work Davos can be a great conference and meeting venue. TERMIS-EU 2017 Davos presented more than 350 lectures, and over 800 poster presentations. The number of presentations on patient-specific tissues from 3D printers highlighted the increasing significance of this technology, which ARI has been developing in over the last few years (As a historical note 3D printing is not new, in 1991 LECD (ARI) had its own purpose built stereolithography machine (only 4 other, custom built machines were available at that time world wide), the resolution though was mm's and the epoxy resin was not suitable for human use, just models).

The reputation of ARI team members continues to grow internationally with many of our principal scientists on important scientific society boards and committees, many as editorial members of high level scientific journals in the field, several teachings at ETH Zurich and other top tier universities. ARI publications remain well above the average for the trauma field with 65 peer reviewed papers with an average impact factor of 3.45. The 3 million extramural funding (aided by organizing TERMIS 2017) was the highest extramural funding acquisition for research ever at the AO Foundation.

In 2017, the ARI Advisory Committee took over the handling of the "AO Foundation Berton Rahn Research Award". Originally for start up grants this is now for the best external research project financed by the AO Foundation. This was awarded to Prof Rob Mauck, University of Pennsylvania, for his work as part of ARI's Acute Cartilage Injury Collaborative Research Program.

The ARI Activity report has a wealth of information on ARI's output in this very productive year. Please take some time to see what ARI does for the AO Foundation, maintaining the foundation's academic credibility and putting the AO firmly on the orthopaedic map of the scientific world.

I thank the Clinical Division's R&D Committee members for their dedication to the clinical relevance of the projects they monitor and the ARI Advisory Committee members for their dedication to push the scientific level of all the ARI projects. Thank you AOFB for your support of many ARI initiatives and several for the AO Foundation as a whole.

Finally, I would like to thank the whole ARI team, which I am very proud to lead, for their motivation, dedication and great work in 2017.

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

2 ARI 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

2016/17 Outlook - Achievements

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

3-5 year goals - partial Achievements

- Develop productive potential of ARI innovation technology portfolio and create an ARI intellectual property strategy. **Ongoing** (Process used now as standard by AO Foundation)
- 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)**

Rolling Outlook ARI (3-5 years until 2018-2022)

- Nurture innovation and further develop ARI technology portfolio
- Support AO Clinical Divisions with cutting edge research for their clinical problems (e.g. Bone Infection models, patient specific implants)
- Complete Development and translation of Autogauge / Perfect Circle system
- Development & translation of our unique smart surgery concepts: e.g. Implant Sensors
- Initiate Europe's first Specific Pathogen Free Sheep flock for better reproducibility and reliability
- Maintain our world-class certifications (ISO, AAALAC, GLP)
- Continue to develop our 3D polymer printing & bioprinting technologies
- Nurture our scientific networks (e.g. ARI collaborative research consortium)
- Obtain Proof of concept for functional cellular biomarkers

3 Funding Summary

Income Statement	2016 Actual		2017 Actual	
in CHF '000	abs	%	abs	%
AO Foundation Contribution	8'418	67%	9'576	70%
3rd party Income	2'212	18%	3'590	26%
AO Intercompany	1'950	16%	529	4%
Total Income	**12'579**	**100%**	**13'695**	**100%**
AOTrauma *	3'602	29%	3'541	29%
AOSpine*	424	3%	419	3%
AOCMF *	645	5%	588	5%
AOVET *	102	1%	87	1%
AOTK *	699	6%	656	5%
AOER	1'953	16%	1'718	14%
AO Foundation *	2'686	22%	1'708	14%
3rd party projects	2'212	18%	3'590	29%
Total Expenses	**12'321**	**100%**	**12'308**	**100%**
Net Result	**258**		**1'387**	

* incl. AO Intercompany

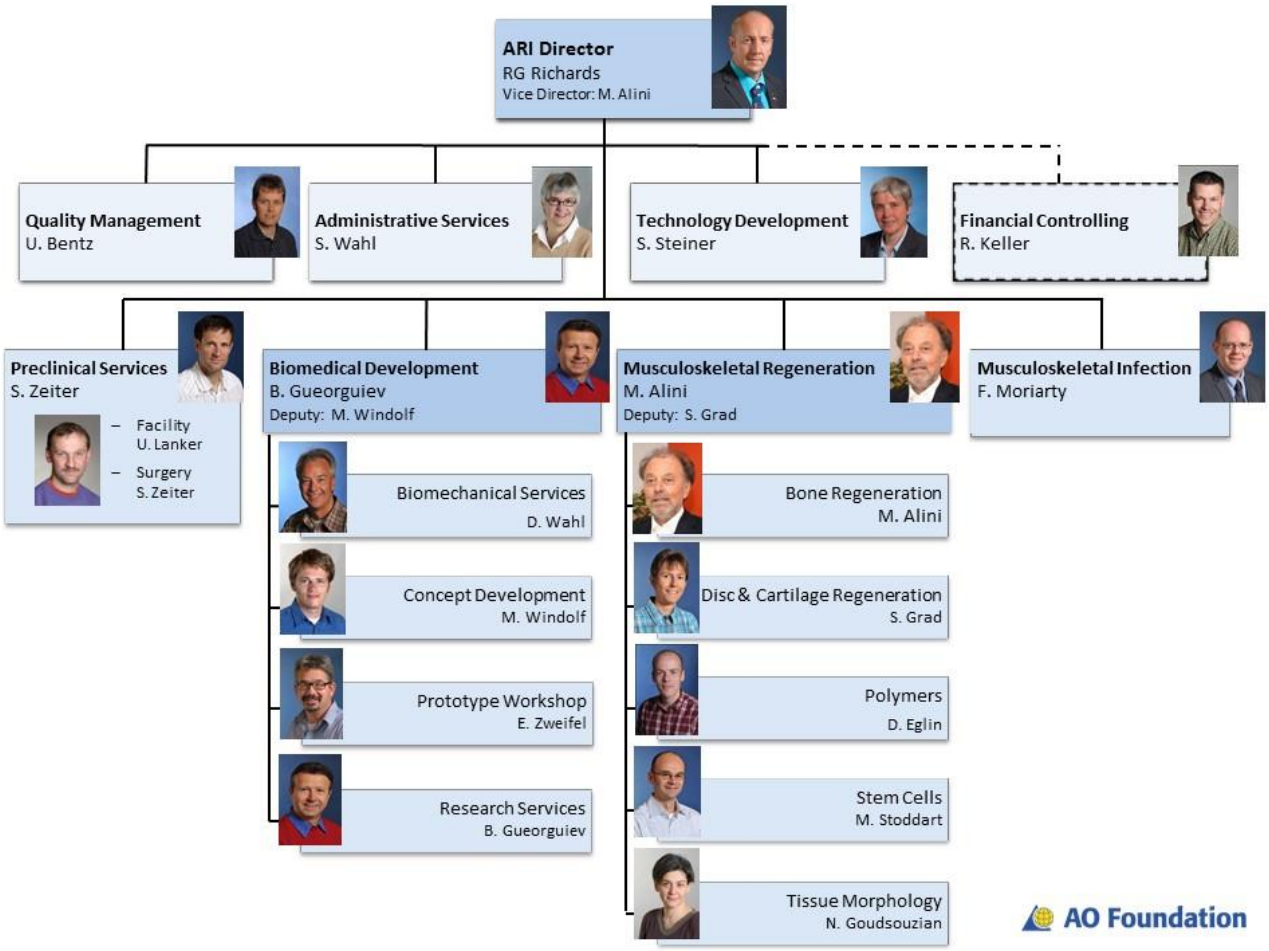
3rd Party Income' amounted to CHF 3,590 K and remained 83% (CHF 1,627 K) above budget and 62% (CHF 1,379 K) above previous year. The main reasons for the increase versus budget were the income from the successful one-time realization of the TERMIS-EU chapter meeting in June in Davos of CHF 935 K, the execution of a higher number of commercial studies of CHF 445 K and additional 3rd party funded grants amounting to CHF 180 K.

From a cost type point of view, the main categories were 'Personnel Expenses' with 68%, followed by 'Material Expenses' with 13% and 'Scientific & Regional Expenses' and 'Expenses and Fees Non-Employees' with 4% each.

Overall, a positive 'Net Result' of CHF 1,387 K was achieved compared to a balanced budget, which rolls over into 2018 and 2019 Mid Term Plan.

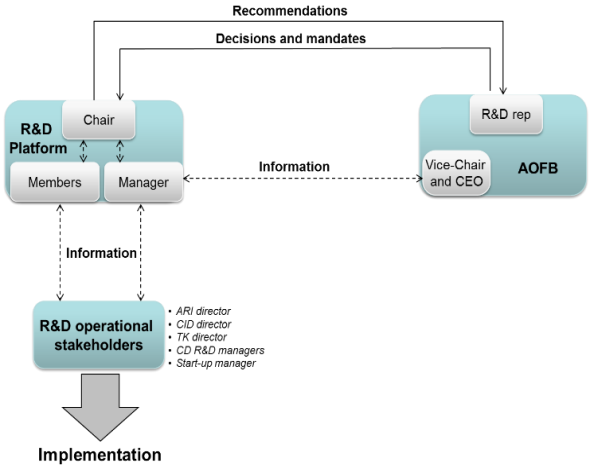
4 Research Structure & Advisory Committees

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 overall AO Foundation 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 initiatives including research and development*. All 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 or final decision authority. *This includes any R&D funded by the AO Foundation. It does not include extramural funded R&D (including industrial funded) carried out through AOTK (Technical Commission), AOCID (Clinical Investigation and Documentation) or ARI.



4.3 AO Research Institute Davos Advisory Committee

The ARI Advisory Committee (ARI AC) met in June and December 2017 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 scientific output of direct funded projects on behalf of the AO Foundation Board (AOFB) and is a distinguished 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 director and management team. Upon request from the ARI director, ARI AC also advises (and often does) on science and development potential of indirect funding programs or projects (e.g. extramural funding and ARI's earmarked 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 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 AC (December 2017):

- Prof Dr Theodore Miclau (Chair/ clinician), Orthopaedic Trauma Institute, San Francisco, USA
- Prof Brian Johnstone, Oregon Health & Science University, USA
- Prof Joost de Bruijn, University of Twente, NL & CEO Kuros Biosciences AG, CH.
- Prof Christopher Evans, Mayo Clinic, Rochester, USA

Left to right: Prof Geoff Richards, Prof Christopher Evans, Prof Dr Theodore Miclau, Prof Brian Johnstone, Prof Joost de Brujin

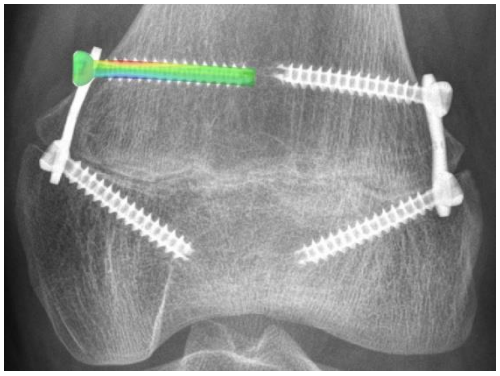
5 ARI Teams / Personnel

5.1 Biomedical Development Program

Program Leader: Boyko Gueorguiev-Rüegg, Deputy: Markus Windolf
Team Members: Pinaki Acharya, Jan Barcik, Jan Buschbaum, Jan Caspar, Daniel Ciric, Benno Dicht, Ursula Eberli, Manuela Ernst, Dominic Gehweiler, Ladina Hofmann-Fliri, Lukas Kamer, Dominic Mischler, Karen Mys, Hansrudi Noser, Ronald Schwyn, Flurin Spiller, Luisa Thiemann, Peter Varga, Viktor Varjas, Dieter Wahl, Ivan Zderic, Erich Zweifel

Fellows: Marc Daniel Ahrend, Mariya Hadzhinikolova, Lyubomir Rusimov
Visiting Professor: Marc Balligand
Guests: Lisa Actis, Charlotte Arand, Beatrice Böhme, Constantin Dlaska, Annabel Hayoz, Daniela Husarik, Roberto Khatchadourian, Cédric Laurent, Isabelle Lutz, Jean Philippe Ponthot, Majeed Rana, Thomas Rüedi, Ivan Rusev, Simon Scherrer, Timo Schmid, An Sermon, Hristo Skulev, Johanna Ueberberg, Daniel Wagner, Tobias Zschaler

By supporting the in-house processes for development and design of medical devices according to EN ISO 13485, as well as running advanced projects in close collaboration with clinical, scientific and industrial partners, the Biomedical Development Program offers extensive know-how, expertise and experience in the fields of biomechanical testing and computational analyses to improve patient care.



Radiograph of a distal femur with two plates for epiphysiodesis, superimposed with illustration of the resulting strains in one of the deformed plate screws during management of leg length discrepancy in children and adolescents, as calculated by means of Finite Element Analysis.

A variety of clinical problems are addressed by development of new concepts, approaches, tools and novel implant systems for surgical applications and research in traumatology and orthopedics. The process of finding optimal solutions to clinical questions is enhanced by capabilities ranging from in silico methods to very well-equipped anatomical labs for quick and effective hands-on work when an anatomical environment is required. Specifically, tailored test procedures with implementation of supplemental X-rays, video and motion tracking systems are applied in diverse experiments on fracture fixation and joint reconstruction. Advancing with state-of-the-art technologies, powerful numerical methods and comprehensive tools for virtual simulations are integrated to answer various questions with special reference to biomechanical behavior of bone-implant constructs.

Modalities for medical imaging, processing and analysis, including CT scanners with a wide range of resolutions and scanned volumes, are interlinked to account for increasingly sophisticated demands for morphological investigations, extract statistical and individual information from medical image data and extend the knowledge on variations of biomechanical bone characteristics and their role in persisting clinical problems.
The capabilities of the Program are completed by its Prototype Workshop offering rapid and high-quality manufacturing of devices, tools and implants.

Illustration of the main components of a virtual tool-kit for systematic investigation and analysis of fracture fixation at the proximal humerus.

5.2 Preclinical Services

Focus Area Leaders: Stephan Zeiter and Urban Lanker
Team Members: Daniel Arens, Corina Berset (AOF), Peter Erb, Loris Faoro, Pierina Faoro, Linda Freitag, Andrea Furter, Fabian Gieling, Jann Lanker, Reto Müller, Dominic Perren, Valentina Riehl, Tanja Schmid, Patrizia Wagner

Fellows: Valentina Riehl, Christian von Deimling
Student Externs: Nathalie Enk, Dana Carina Schubert, Sean Wyatt, Sophia Mayr

Guests: Silvia Feini Qu

The necessity of preclinical studies is under scrutiny, which should lead to improved study design, better conduction and analysis of experiments resulting in scientifically and ethically more valuable data in the field. At the ARI, we conduct all *in vivo* studies with the highest responsibility and reproducibility. Animal welfare, the quality of the data generated, and occupational health and safety are of high importance to us. Therefore, we became an AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care) International accredited institution in 2013 (AAALAC is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs). We are committed to serve the development and implementation of ethical, translationally relevant and validated animal models for musculoskeletal research. We intend to pursue best in class policies in the sensitive area of animal models.

In 2016, ARI was awarded 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 (in 2016/17) certified for GLP in Switzerland. GLP is an internationally recognized quality system concerned with the organizational process and conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. The ARI is the only Swiss Institute with both GLP and AAALAC accreditation. The FDA has a new guideline in review (General considerations for animal studies for medical devices) for preclinical studies, which will make GLP and AAALAC virtually mandatory for any submission to FDA. This demonstrates our commitment in fulfilling the highest standards in preclinical research. 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. The GLP accreditation lead to an increased demand of external studies. For example, we performed a risk assessment study investigating the safety and effectiveness of a laser prototype in a sheep model comparing the healing of bone after a laser cut and a cut made by an oscillating saw. Another study was conducted to investigate the safety of a new implant coating to prevent infection in our established rabbit model which was developed in the past together with the ARI Focus Area Infection. Both studies were performed in accordance with the GLP guidelines as a prerequisite demanded by the customers. We also continuously refine our models and methodology. Last year, a study in collaboration with Swiss Institute of Allergy and Asthma Research (SIAF) in Davos was conducted to improve the post-operative analgesic protocol in rabbits.

Preclinical Services was involved or organized both nationally and internationally preclinical workshops, scientific sessions and practical courses throughout the year.

5.3 Musculoskeletal Regeneration Program

Program Leader: Mauro Alini, Deputy: Sibylle Grad
Focus Area Leaders: David Eglin, Nora Goudsouzian, Martin Stoddart.
Team Members: Danielle Admiraal, Angela Armiento, Adriana Augurio, Valentina Basoli, Mauro Bluvol, Matteo D'Este, Nina Derron, Nunzia Di Luise, Jie Du, Niamh Fahy, Olivier Guillaume, Sonja Häckel, Verena Hasselmann, Andri Hassler, Marine Heriot, Mario Inauen, Yann Ladner, Patrick Lezuo, Bojun Li, Zhen Li, Flavio Linardi, Ursula Menzel, Graziana Monaco, Dirk Nehrbass, Ana Rita Pereira, Marianna Peroglio, Robert Peter, Dalila Petta, Stijn Rotman, Yemane Semere, Tiziano Serra, Christoph Sprecher, Keith Thompson, Ricardo Tognato, Letizia Vainieri, Sophie Verrier, Sebastian Wangler, Laura Wystrach, Reihane Ziadlou

Fellows: Peter Behrendt, Yannik Gehlen, Janna Geries, Fabian Heizmann, Junxun Ma, Andreas Naros, Kalan Violin, Zhou Zhiyu

Guests: Mike Geven, Ilse Jonkers, Louai Bensaid, Fabio Hehli, Valentina Bonfrate, Irene Citterio, Elena Della Bella, Niko Kovermann, Anna Lapomarda, Ganesh Pandian Namasivayam, Jan-Tobias Weitkamp, Antoine Frayssinet, Eva Gleissner, Anastasia Gigliotti, Serena Provveduto, Armin Picenoni, Fatemeh Safari, Taryn Saggese, Robert Ossendorff, Bernardo Antunes, Domenic D'Atri, Ana Caixado Ortiz

The Musculoskeletal Regeneration program develops biological approaches addressing pathologies of the musculoskeletal system, with a focus on bone, cartilage and intervertebral disc. The ultimate goals are to identify strategies for prevention or attenuation of degenerative processes and to re-establish tissue functionality.

Bone Regeneration Focus Area
Bone healing in response to fracture involves a complex sequence of dynamic events, including numerous different cell types and growth factors. A critical factor for bone repair is the maintenance, or effective restoration, of an adequate blood supply, which is necessary to provide the damaged tissue with oxygen, nutrients and growth factors, as well as immune cells and mesenchymal stem cells required to repair the damage and induce new bone formation. Although bone generally has a high regenerative capacity, in some cases this inherent bone healing is compromised, which results in delaying healing or non-union of the bone fracture with increased health care costs and reduced quality of life issues for affected patients. While a variety of risk factors have been identified that predispose to an increased risk of developing delayed bone healing or non-union, it is currently not possible to identify specific at-risk patients at an early stage. Using in vitro, in vivo and microfluidic technologies, the aim of the Bone Regeneration Focus Area is to gain a greater understanding of the cellular interactions and mediators underlying such impaired healing responses. By determining how cells such as immune cells, mesenchymal stem cells and endothelial cells normally interact during the repair process, and how this process is altered during impaired healing, we can then identify key mediators of the healing process. Our goal is to use tissue engineering and regenerative medicine approaches to promote bone healing, aimed at restoring bone integrity and its effective biomechanical properties.

Disc / Cartilage Regeneration Focus Area
The intervertebral disc is a complex structure that is composed of interrelated tissues with specific mechanical functions. Damage and degeneration lead to different pathologies that need specific therapies for repair and regeneration. Our focus area is utilizing in vitro cell, tissue and whole organ culture models to reproduce cell and tissue alterations occurring during degeneration. Triggers, such as mechanical injury, inflammatory and catabolic signals, and nutritional challenges are used to induce different types and degrees of cell and tissue damage. Novel therapies for intervertebral disc regeneration that are currently under investigation include the application of injectable hydrogels used for structural support, as cell carrier and as drug delivery system. Furthermore, we are studying underlying mechanisms of tissue failure and of the natural tissue repair to identify new approaches for preventing adverse reactions and activating regenerative responses. Migration or homing of stem cells towards the induced-degenerative disc and interactions between stem cells and disc cells are presently investigated.

We utilize custom-made cell and organ culture bioreactors for translational research aiming to reproduce the in vivo microenvironment as closely as possible. For predictive pre-clinical ex vivo testing of cartilage repair strategies, an osteochondral explant model was recently developed where compression and shear can be applied, mimicking joint articulation. The explant model with viable bone and cartilage is used to mimic (osteo)chondral defects and assess new scaffolds, hydrogels, drug and cell delivery systems and their interaction with the native tissue under simulated-physiological load. Efficacy of anabolic and anti-inflammatory proteins and small molecules are under investigation. Collaborations with clinicians provide us with human cells and patient samples for many studies, which facilitates the identification of diagnostic and eventually therapeutic targets in the laboratory.

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 biomedical material solutions for bone, disc and cartilage tissue engineering, using tailored polymers and composites manufactured notably using novel 3D printing technologies and biofabrication processes. Our experience lies in the design of biocompatible, biodegradable polymers and their processing with controlled architecture and embedded biologics. An important field of research investigates the preparation of chemical derivatives of natural occurring biopolymers, based stimuli responsive biomaterials which can be used to deliver drugs and cells and as bioinks. Injectable and printable biodegradable materials have considerable potential in the field of infection and tissue repair, but also for the guiding of cells behavior in *in vitro* mode

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 are increasingly investigating donor variation with the aim to predictively identify the potency of cells from individual donors. In the search for biomarkers to determine patient specific healing potential, exosomes and non-coding RNA sequences such as miRNA are increasingly being used as a diagnostic and therapeutic tool. The development of a serum-based biomarker approach would dramatically improve patient specific clinical decisions. We also 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 able to modify stem cell fate and can be applied by way of rehabilitation protocols. Such studies are forming the basis of the emerging field of regenerative rehabilitation. In addition to the effect of load on direct differentiation, it is known that biomechanical stimulation can modulate the cell secretome. Investigating these changes could lead to the identification of new targets, that may be present during articulation. This offers new avenues for potential clinical therapies.

Tissue Morphology Focus Area
The Tissue Morphology Focus area primarily supports the other Focus areas within the ARI, but also works with external collaborators and commercial contractors. Hard tissue, undecalcified bone with or without implants, is the majority of the tissue that is processed. With specialized hard tissue microtomes, sectioning and modified stainings of these tissues are considered routine. Conventional microtomes such as paraffin and cryostat are also used, especially by the investigators performing *in vitro*, *ex vivo*, and cell culture experiments. Immunohistochemical staining is also routinely performed. Fluorescence microscopy, scanning electron microscopy (SEM), equipped with an Energy-dispersive X-ray spectroscope (EDX) to identify chemical elements for surface evaluation and profilometry, and confocal microscopy complement the spectrum of available techniques.

5.4 Musculoskeletal Infection Focus Area

Focus Area Leader: Fintan Moriarty
Team Members: Pamela Furlong, Marloes Hofstee, Iris Keller, Virginia Post, Marina Sabaté Brescó, Barbara Stanic, Keith Thompson, Willemijn Boot

Fellows: Aikaterini Stylianaki, Alejandro Vallejo Diaz, Eamon Sheehy

Guests: Nadja Fuchs

The Musculoskeletal Infection team focusses their research activities on Fracture-Related Infection (FRI), with a focus on novel preventative and therapeutic interventions. The studies include preclinical *in vitro* and *in vivo* studies, as well as clinical observational studies of FRI progression in human patients.

The development of preclinical animal models of FRI has been a major focus due to the need for models that more accurately represent the clinical situation. In collaboration with ARI colleagues, we now have models that can mimic an open fracture, with a chronology and fixation that more accurately reflects clinical reality. Further advancements in our animal models in the past year include the use of antibiotic resistant pathogens such as methicillin resistant *Staphylococcus aureus* (MRSA), and monitoring tissue pharmacokinetics after local delivery of antibiotics. The preclinical evaluation of novel anti-infective interventions under Good Laboratory Practice (GLP) conditions has also expanded in recent years as candidate technologies come closer to clinical implementation.

On the *in vitro* side, our studies have begun to investigate the mechanisms for the failure of antibiotic therapy in a significant portion of patients. This includes the optimal means to eradicate bacterial biofilm from implanted devices and how locally applied antibiotics can offer crucial adjunctive support to systemic antibiotic therapy. Within this research theme, the ARI thermo-responsive antibiotic-loaded hydrogel has been proven to be superior to the conventional antibiotic-loaded bone cement in a single stage exchange of an intramedullary nail due to infection.

In patient samples, we have an interest in monitoring the impact of polytrauma on antibacterial efficacy of host defence mechanisms. These studies provide real clinical relevance in the risk of developing an FRI and may point towards future interventions aimed at the host response, rather than relying solely on antibiotic-driven interventions.

5.5 ARI Technology Development

Technology Development Officer: Sandra Steiner

Technology Development at ARI is aiming at providing orthopedic surgeons with tailored solutions addressing their unmet needs in the operation room (OR). This is one important avenue by which ARI is contributing to the overall mission of the AO Foundation to improve patient care.

To learn first-hand about the unmet needs of surgeons, the presence of ARI engineers and scientists in the OR during operations has turned out to be a most successful approach.
This has recently been demonstrated by the team of Dr Markus Windolf from ARI and the surgeon Prof Michael Schütz. Markus Windolf has spent a twelve months fellowship with Michael Schütz at the Institute of Health and Biomedical Innovation in Brisbane, Australia. During his time at Brisbane Markus Windolf has spent many days together with Michael Schütz in the OR and observed the handling and processes during the operations. Afterwards the two discussed the steps and tools that could be improved or developed to allow for more accurate and more efficient handling.

Since the return of Markus Windolf to ARI he has evaluated and tested an impressive list of the new ideas and concepts born during his stay in Brisbane.
Up to now three of these ideas have been translated into new patent applications.

The ownership rights of these co-invented patents were transferred by the Institute and the inventors to AO Technology AG (AOTAG) after a profit sharing ruling for profits resulting from patent exploitation was signed by the parties.

In the meantime, an international MedTech company showed strong interest in one of the co-invented devices termed Autogauge. This device allows the surgeon to measure the depth of a drilling hole during the drilling process. The company intends to combine this drill depth measurement device with its own orthopedic drill. In summer 2017 a twelve months licensing agreement was signed between the company and ARI / AOTAG. The company is currently in the process of building prototypes with the Autogauge device integrated to their drill. These will be used to obtain a first feedback from a selected group of clinicians. Following the evaluations, the company will decide whether to take a license for the use of Autogauge.

5.6 ARI Administrative Services

Manager: Sonia Wahl
Q-Manager & Purchasing: Ulrich Bentz
Team Members: Isabella Badrutt, Claudia Barblan, Simona Ciriello, Carla Escher, Gregor Müller, Monika Schneider, 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 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

2017 the ARI Administrative Service Group has organized for:

AO Research Institute (ARI)

21./22.04.2017	Block course: Skeletal Repair for ETHZ and ZHAW students, Davos, Switzerland
23.06.2017	ARI Advisory Committee (ARI AC) Meeting, Davos, Switzerland
25.06.2017	MRN Meeting (incl. Rapidos Symposium), AO Center, Davos, Switzerland
25./26.06.2017	Practical Course RISystem, AO PCF, Davos, Switzerland
26.-30.06.2017	TERMIS-EU 2017, Personalized Therapies for Regenerative Medicine, Convention Center, Davos, Switzerland
30.06./01.07.2017	TargetCaRE Consortium Meeting (EU-Project), AO Center Davos, Switzerland
05./06.12.2017	ARI Advisory Committee (ARI AC) Meeting, Davos, Switzerland

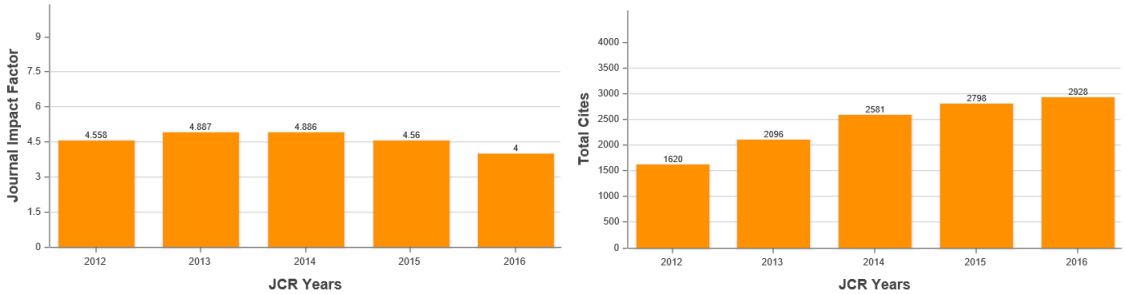
6 eCM Journal & eCM periodical

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 musculoskeletal field (initiated in 1999, implemented with the launch of the first volume in January 2001 - http://www.ecmjournal.org/history.html). It was created by scientists for scientists and is still run fully by scientists. eCM Journal is published by the AO Research Institute Davos, a Not-for-Profit foundation in Switzerland.

eCM is an Open Access journal: all publications have been immediately freely available upon publication since the journal start. 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. In 2000 reviewing the first papers before launch of published papers in 2001, eCM initiated a transparent review process, naming reviewers within all published manuscripts. Reviewers have a transparent route for becoming an official listed eCM reviewer (member of the eCM International Review Panel).

In June 2017, Journal Citation Reports (JCR) announced eCM's Impact factor (IF), which was unfortunately wrong for the second consecutive year (calculated IF 3.343). JCR counted individual conference abstracts as manuscripts. Upon appeal from eCM, the corrected 2016 IF (4.000) and the five-year IF (5.182) were published on JCR "Help File". Unfortunately, adjusted metrics were added to the reload of the JCR /Clarivate Analytics data only in September 2017, which affected submissions to eCM. Randomly, since 2013, eCM supplements were being used in the JCR calculation of eCM IF. For this reason, in June 2017, the eCM journal council decided to discontinue and remove all old supplements published in eCM journal. eCM supplements were pure conference abstracts, which should have not been included in the IF calculation ("non-citable item"). eCM and many other journals do not even allow manuscripts to cite conference abstracts. Indeed, from the 17 supplements published in 2014 and 2015, and used for the calculation of the 2016 JCR Impact Factor, there were zero citations. eCM supplements did not have a DOI, are/were not searchable on PubMed, are/were not deposited in CLOCKSS and are/were not allowed to be cited by eCM, as they are not peer reviewed. Despite this, JCR/Clarivate Analytics have used these non-citable supplements in the calculation of 2016 Impact Factor. This has wrongly caused a drop of eCM's 2016 Impact Factor to 4.000 from a value of 4.633 (without abstracts).



All old supplements are now hosted in a new format, on a separate new web site eCM Online Periodical (ecmconferences.org), which is not part of the eCM journal publication, but is owned as a separate part of eCM. A separate ISSN (2522-235X) was assigned to eCM conferences Open Access online periodical. eCM Conferences Open Access online periodical hosts all eCM official society meeting abstracts along with other collections of abstracts for various congresses.

In December 2017, eCM joined iThenticate, a provider of plagiarism detection technology to ensure the originality of written work before publication. iThenticate compares manuscripts against its

database of over 60 billion web pages and 155 million content items, including 49 million works from 800 scholarly publisher participants of Crossref Similarity Check powered by iThenticate software.

In September 2017, eCM Journal and eCM Online Periodical decided to highlight published papers and eCM Conferences updates through social media platforms: LinkedIn, Facebook and Twitter.

Ten good reasons for publishing a paper in eCM

1. World-wide open access, Not-for-profit Publisher, authors retain copyright to their articles (CC-BY-SA).
2. Rigorous open peer reviewing (reviewers have to request their name to be withheld).
3. Speed of publication: ~3 weeks after acceptance, paper is online.
4. Discussion with reviewers feature, as an integral section of the paper, allows sensible arguments to be included.
5. Five-year Impact Factor 2016: 5.18, Impact Factor 2016: 4.00.
6. Scopus CiteScore* 2017: 4.50.
7. Indexed in the Science Citation Index Expanded (under the "Materials Science" 11th, "Engineering Biomedical" 8th and "Cell and Tissue Engineering" 5th citation index categories) BIOSIS Previews, DOAJ, Scopus, SJR, Journal Citation Reports/Science Edition, Google Scholar, National Center for Biotechnology Information (NCBI databases) NLM catalog (U.S. National Library of Medicine), PubsHub and SHERPA/RoMEO databases. eCM articles can be searched directly from PubMed and Biomedsearch.
8. Digital archive of manuscripts through CLOCKSS and Europe PMC. eCM is a member of CROSSREF (Crossref Digital Object Identifiers (DOI:10.22203/eCM), tagged to article metadata).
9. Transparent route to becoming a member of the International Review Panel.
10. Created (and run) by scientists for the benefit of Science rather than profit.

*(The Scopus CiteScore 2017 measures the average number of citations received in 2017 to documents published in 2014, 2015 and 2016. CiteScore™ metrics are a comprehensive, transparent, current and free set of metrics that measure your journal‘s citation impact.)

7 Institutional and Professional Relations

Geoff Richards has appointment as full Professor at the Medical Faculty of Albert-Ludwigs University, Freiburg, Germany. He has an honorary Professorship at Cardiff School of Biosciences, Cardiff University, Wales, GB. 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 Global Member-At-Large of the TERMIS Governing Board (Tissue Engineering & Regenerative Medicine International Society). He is a member of International Combined Orthopaedic Research Societies Steering Committee and Chair of the International College of Fellows for Orthopaedic Research. He is a guest lecturer of the MSc Course Skeletal Repair at the Department Health Science and Technology (D-HEST) of the ETH Zurich. He is a member of European Society for Biomaterials (ESB) International Advisory Committee for annual meetings. Geoff is Vice President of Science City Davos. 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. He is a Fellow of International Orthopaedic Research (FIOR). He is co-Editor in Chief of the newly launched Journal Orthopaedic Research Spine. He is on the Assistant Editorial Board of the European Spine Journal. He is a member of the Scientific Editorial Board of the eCM Journal. He is also in the international Editorial Board of the Journal of Orthopaedic Translation and Journal Orthopaedic Research. 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 an Honorary Member of the Serbian Trauma Association. He is appointed as Associate Editor and Editorial Board Member of the Journal of Orthopaedic Trauma, 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. For the European College of Laboratory Animal Medicine (ECLAM) he serves as a member of the council (treasurer). Stephan is a member of the eCM International Review Panel. He is the vice president of the Davoser Society for Natural Sciences. He is the representative to the AOVET R&D Commission from ARI.

Fintan Moriarty is a guest lecturer at the Bern University of Applied Sciences, MSc program in Medical Technology.
Fintan Moriarty is a lecturer in the MSc Course Skeletal Repair at the Department Health Science and Technology (D-HEST) of the ETH Zurich. He is a scientific editor for the eCM Journal.
Fintan Moriarty is also a thesis examiner at the Academic Medical Center (AMC, Amsterdam, The Netherlands).

David Eglin is the President of the Swiss Society for Biomaterials and regenerative Medicine (SSB&RM). He is a Committee member of the Tissue Engineering and Regenerative Medicine International Society (TERMIS) EU Chapter. He is 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 of the Department Health Science and Technology (D-HEST) at the ETH Zürich and also 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 is a member of the eCM Journal International Review Panel and a co-organizer of the eCM conference on cartilage and disc. She is a member of the Local Organization Committee and Women-in-Term committee of the TERMIS-EU 2017. She is also an officer of the ORS Spine Section, where she is serving as the Section Research Chair. Sibylle Grad is 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. He is also Honorary Professor at the Institute for Science and Technology in Medicine, University of Keele, United Kingdom. He is an elected Fellow of the Royal Society of Biology (FRSB). He lectures on the Skeletal Repair MSc module at the at the Department Health Science and Technology (D-HEST) of ETH Zürich. He is the Chair of the Orthopeadic Research Society (ORS) Basic Science Education Committee, and a member of the ORS Communications Council. He is Co-Deputy Chair of 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 Co-ordinator and organizer of the yearly eCM conference and a web editor of eCM Journal. He is 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 Orthopedic 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 Verrier is co-organizer of the annual eCM conferences on Bone. She is a member of the Local Organization Committee and Women-in-Term committee of the TERMIS-EU 2017.
Sophie has been appointed Chair of the ORS Women Leadership Forum Committee (WLF).

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 Guest Professor at the Medical School of Shenzhen University, Shenzhen, China. She is lecturing on the advanced research in intervertebral disc at Shenzhen University. She is the European Development Committee Member of International Chinese Musculoskeletal Research Society. Zhen is a member of the eCM Journal 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 certified Project Management Associate SGO. She is also a member of the eCM Journal International Review Panel.

8 Good News

New Extramural funding

The "Kommission für Technologie und Innovation" (now called Innosuisse – Swiss Innovation Agency) funded the following collaborative project "Cartilage Friendly Hemiprosthesis" for a total of CHF 224'800 for 3 years. (D Baumgartner, ZFH Zürcher Fachhochschule; S Zeiter, ARI; R Lerf, Mathys Ltd Bettlach)

AOCMF Bone regeneration using tissue engineering and CAD-CAM technology – Their impact on facial bone reconstruction Open Call: "Periosteal CAD-CAM Prefabricated Vascularized Bone Grafts" CHF 140'400 (F Duttenhoefer, University Hospital Freiburg; G Giessler, Klinikum Kassel; S Zeiter, ARI)

AOCMF grant application: Anti-osteoclastic drugs and their impact on maxillofacial and orthopedic bone biology, disease, diagnosis, surgery, and treatment modalities (ARONJ). Open Call: "Large animal model for periodontitis related antiresorptive drug induced osteonecrosis of the jaw" CHF 222'527 (M Tröltzsch, University of Munich; D Arens, ARI; F Probst, University of Munich; O Ristow, University of Heidelberg; S Otto, University of Munich)

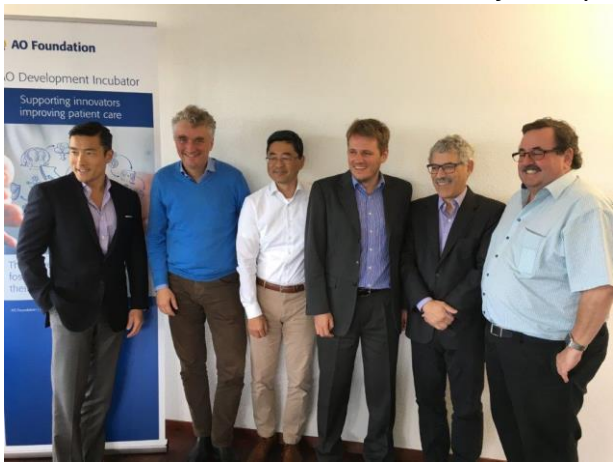
Guangdong Province Orthopedic Key Research Lab Open Grant
"DiscLncRNA: The role of LncRNAs in degenerative disc disease and Translational Research" is a 2-year project funded by Guangdong Province Orthopedic Key Research Lab Open Grant. The project partners include ARI scientist Prof Zhen Li, in collaboration with Prof Zhiyu Zhou from Sun Yat-sen University, Shenzhen, China. Funding is CNY 50'000 in total and includes an MD fellow visit (12 months) from Sun Yat-sen University at ARI Davos.

Grant from National Natural Science Foundation of China
"AF Repair: Annulus Fibrosus Regeneration with Endogenous Stem Cell Activation and Function Inducing Cell Transplantation" is a 2-year project funded by National Natural Science Foundation of China. The project partners include ARI scientist Prof Zhen Li, in collaboration with Prof Guangqian Zhou from Shenzhen University, Shenzhen, China. Funding is CNY 250'000 in total and includes a post-doctoral researcher's visit (24 months) from Shenzhen University at ARI Davos.

Chinese Research Council Scholarship
Junxuan Ma received a one-year Chinese Research Council Scholarship to perform research at ARI in the field of intervertebral disc degeneration.

The Supporting Program for Interaction-Based Initiative Team Studies, Japan (PR)
Synergistic integrated technologies to mimic transcription factors and reconstruct articular cartilage components 01-04.2017-31.03.2019. Yen 4'950'000 (CHF 43'400) (M Stoddart)

The AO Development Incubator (AODI), a new innovation driver at the AO Foundation, during an open call funded the project "AO Fracture Monitor" for a total of CHF 1'900'000 for 3.5 years (M Windolf and his team ARI). The AO Fracture monitor which was created within the ARI and we believe will be a major change to internal fracture fixation for the future. (The AODI received 80 applications from 30 countries across all specialist fields in this, its first call for proposals of 2018, with two being accepted to move forwards).



AO Development Incubator Board (l-r): Han Jo Kim, Michael Schütz, Keita Ito, (Markus Windolf as awardee), D. Todd Dollinger and Robert Frigg.

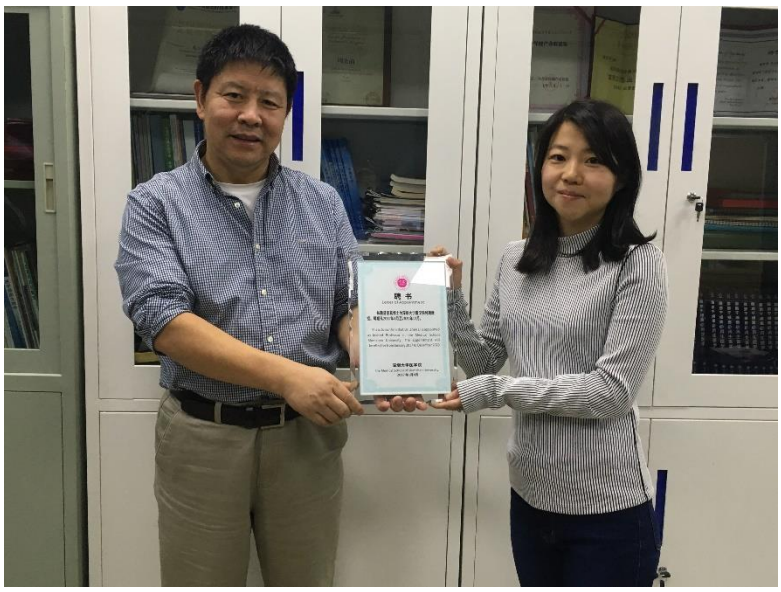
External Positions / Awards
ARI scientists strengthen their reputations and research network connections with southern Chinese universities of the Guangdong region

Prof Xuenong Zou (the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China) visited ARI Davos. Pictured, from left to right, are Prof Zhen Li, Prof Boyko Gueorguiev, Prof Geoff Richards, Prof Xuenong Zou, Prof Mauro Alini, Dr Zhiyu Zhou, Dr Junxuan Ma, Dr Marianna Peroglio.

In the recent years, ARI and high-ranking universities in China have built long-lasting and close collaborations on orthopaedic research and training of young clinician scientists. In 2016, Dr Zhiyu Zhou of the First Affiliated Hospital of Sun Yat-Sen University received a two-year scholarship from the Sino-Swiss Science and Technology Cooperation and, under the scientific supervision of ARI's Zhen Li, conducted degenerative disc disease research at ARI. The fruitful training program, with support from the AO Research Fellowship, China Scholarship Council and European ITN project, has provided the opportunity for several additional fellows to come to ARI, including, respectively, Dr Junxuan Ma and Dr Wei Guo of the First Affiliated Hospital of Sun Yat-Sen University; and Jie Du of Shenzhen University. More fellows from the region will be coming to Davos.

In autumn 2017, Prof Geoff Richards and Prof Martin Stoddart, attended the 12th International Congress of Chinese Orthopaedic Association COA2017 in Zhuhai, China, where they spoke to the Chinese Medical Association. Geoff Richards, who was invited by Manyi Wang (Ji Shui Tan Hospital, Beijing) and spoke on smart surgery. Martin Stoddart spoke at an International Combined Orthopaedic Research Societies (ICORS) workshop titled, Cartilage Biology and Regeneration on the Physical Modulation of Chondrogenic Cell Fate. During the visit, they joined Dr Zhiyu Zhou (the First Affiliated Hospital of Sun Yat-Sen University) on a visit to Zhuhai hospital (the fifth Affiliated Hospital of Sun Yat-Sen University) with Huading Lu, the orthopaedic department's director. The visit included lectures from Xuenong Zou, Martin Stoddart and Geoff Richards. The meeting was attended by scientists from Guangzhou, Shenzhen and Chongching and resulted in three fellows to attend ARI. Dr Shaoming Chen and Dr Yan Chen, who will come in early 2018 and Shangbin Cui who will come in 2018 or 2019.

Following COA2017, ARI's Dr Zhen Li was acknowledged for her excellent contribution to science and her continuing successful collaboration with Shenzhen University. An enthusiastic young researcher, Dr Zhen Li was appointed as a guest professor at the Medical School of Shenzhen University on November 25, 2017. On the same day, she gave a guest lecture about the advanced research on intervertebral disc regeneration on the symposium of bone and joint research at Shenzhen University, Shenzhen, China.



Prof Guangqian Zhou (left, Assistant Dean Medical School of Shenzhen University) presents Dr Zhen Li (right) with an appointment of guest professorship at the Medical School of Shenzhen University

China is a fast-developing country in terms of economics and orthopedic research and ARI is proud to have a strong role in aiding this development. The collaboration is beneficial to both the AO Foundation and the Chinese universities.

Honorary Membership for Boyko Gueorguiev from the Serbian Trauma Association

Prof Dr Milorad Mitkovic (right) gives Prof Dr Boyko Gueorguiev (left) the Diploma of Honorary Membership of the Serbian Trauma Association.

Prof Dr Boyko Gueorguiev was elected as an Honorary Member at the year's Serbian Trauma Association (STA) congress held in Nis, Serbia, from September 27-30, 2017. Following his several keynote lectures, the nomination was approved at the General Assembly of the Association. The Diploma of Honorary Award was given to him at a special ceremony by the STA President, Prof Dr Milorad Mitkovic, who is a founder of the Society and a Corresponding Member of the Serbian Academy of Science and Art. During the award ceremony, Prof Dr Mitkovic expressed the intention of the STA, founded in 2008, for a further implementation of European achievements of trauma and emergency surgery in Serbia. The STA helps young surgeons to interact with European colleagues, as well as improving the continual development of trauma care. Prof Dr Milorad Mitkovic is a long-term colleague and friend of Prof Dr Stephan Perren, who is a founder of the AO Foundation, instrumental in establishing its success and directed the Labor für experimentelle Chirurgie Davos (LECD - Laboratory for Experimental Surgery Davos), now ARI for nearly 30 years.

ARI strengthens ties with national and international societies

Prof Mauro Alini has been announced as one of the chief editors of the new ORS international, multidisciplinary, open access journal JOR Spine. The Orthopaedic Research Society (ORS) aims to advance musculoskeletal research worldwide. JOR Spine will be edited by Profs Mauro Alini (AO Foundation, CH), Robert L Mauck (University of Pennsylvania, US) who won the AO Foundation Berton Rahn Research award for 2017 and who is also a long-term collaborator of the ARI in the Collaborative Research program on acute cartilage injury, and Daisuke Sakai (Tokai University School of Medicine, JP) who is a long-term collaborator of the ARI in the Collaborative Research program on Annulus fibrosis. The new journal will service the spine community by publishing peer-reviewed articles focused on basic and translational orthopedic research. The inclusion of Prof Alini amongst the chief editors demonstrates his international standing in the field.

David Eglin elected President of the Swiss Society for Biomaterials & Regenerative Medicine

During the 23rd Annual Meeting of the Swiss Society for Biomaterials and Regenerative Medicine (SSB+RM) at Empa in St. Gallen, CH Dr David Eglin was elected to President of the Swiss Society for Biomaterials and Regenerative Medicine. This prestigious position is for an initial one-year term and highlights the quality of research being performed in this area within ARI and the Biomaterials Focus Area that Dr Eglin leads. This is the second time an ARI member has been president, as Geoff Richards was president from 2007-2009 when the society was the Swiss Society for Biomaterials (SSB), and he is a lifetime honorary member for his services to the society.

Dr David Eglin with Katharina Maniura, PhD former president SSB+RM.

Furthermore, Claudia Löbel, supervised by Dr David Eglin, won the 2017 Research Award of the SSB+RM for her outstanding PhD thesis on 'Engineering hyaluronan-tyramine hydrogels to modulate mesenchymal stem cell behavior'.

Claudia Löbel won the 2017 Research Award of the SSB+RM.

Conference Awards

Research award for best experimental study: A Stricker, P Varga, D Jenni, L Grünwald, B Gueorguiev, F Duttenhöfer, Finite Element Analysis of the Alveolar Ridge Splitting Technique, 31 German Society of Implantology (DGI) Congress, 30 November – 2 December 2017, Düsseldorf, Germany

Yishan Liu, an MD fellow from Freiburg University who performed her MD thesis study at ARI Davos supervised by Prof Zhen Li, obtained a Research fellowship grant for students from the German Society of Orthopedics and Orthopedic Surgery (DGOOC), and the best abstract and oral presentation award from the German Spine Congress (DWG) 2017.

Sebastian Wangler, supervised by Dr Marianna Peroglio, was awarded the best oral presentation at the 2017 AO Spine Masters Symposium in Bern. Title of the presentation: "Mesenchymal Stem Cells Expressing the Cell Adhesion Molecule CD146 Present Increased Homing Potential Towards Degenerative Intervertebral Discs - an Organ Culture Study".

Dalila Petta, supervised by Dr David Eglin, won best Oral presentation award at the Italian Society of Biomaterials (SIB) annual meeting 2017.

Organized Student Courses / Meetings / Workshops / Sessions at conferences

In January, Preclinical Services hosted a training course for cardiologist how to implant wireless pacemaker for heart failure patients.

Preclinical Services and Romano Matthys from RISystem (www.risystem.com) organized a 2-day practical course on bone healing models in rodents in June.

A workshop on good practice in preclinical studies has been organized by Stephan Zeiter and Corina Berset at the Preclinical Services on 15 September 2017.

Preclinical Services hosted the AO Spine course on Minimally invasive surgery (MIS) on Vertebroplasty during the AO courses in December.

Session 'Hard Tissue Biomechanics', European Society of Biomechanics, 2 – 5 July 2017, Seville, Spain

Session 'Implants and Orthotics', European Society of Biomechanics, 2 – 5 July 2017, Seville, Spain Symposium 'Smart Surgery–AO Research Institute Davos', European Orthopaedic Research Society, 13 – 15 September 2017, Munich, Germany

Dr Sophie Verrier organized and chaired a workshop on "Driving Vascularization: The Key to Bone Repair" at the ORS 2017 annual meeting in San Diego, CA, USA.

Dr Sibylle Grad and Dr Sophie Verrier co-organized and chaired the Women-in-TERM symposium on "Personalized medicine– Ethical considerations for clinical translation" at the TERMIS-EU 2017, in Davos, Switzerland.

Dr Sophie Verrier organized a SBMS symposium on "Stem cells for Bone Regeneration" at the TERMIS-EU 2017, Davos Switzerland.

AO joins the first International Symposium on Bone Infection Defects in Chongqing, China

Southwest Hospital in Chongqing is a leading center for the treatment of bone infection and defects in China. The head of the Southwest hospital bone infection unit, Prof Xie Zhao hosted an "International Symposium on Bone Infection and Bone Defects" in an effort to promote best practice in the management of these difficult cases in the region. In this first ever meeting, there was a large attendance of approximately 1,000 orthopedic and trauma surgeons, which is a clear indication of the interest within the Chinese clinical community.

The large audience in attendance for the first ever Bone Infection meeting in Chongqing (China) highlights the clinical interest in educational events on this topic in China.

The symposium included an invited international faculty, many of whom were involved in the initiative to provide a definition of fracture related infection (FRI) hosted by the ARI in December 2016. Musculoskeletal trauma surgeon and past ARI medical research fellow Willem-Jan Metsemakers (Leuven, BE, and is a member of the AOTK anti infective Task Force), who was instrumental in the FRI definition initiative, delivered the opening address, summarizing the clinical need for a definition of FRI. Furthermore, he presented the definition agreed to by the international experts only a few months previously, in what was the first international statement on this new definition.

International faculty in attendance at the first Bone Infection and Bone Defect meeting in Chongqing included (L-R) Geoff Richards, Peter Ochsner, Willem-Jan Metsemakers and Fintan Moriarty.

Further invited addresses were provided by ARI director Geoff Richards, who outlined the many interactions between ARI and Chinese institutions, including medical research fellowships, collaborative scientific projects and professorships. He continued with a presentation on ARI's antibiotic-loaded thermo-responsive hydrogel as a prophylaxis against FRI. ARI's Fintan Moriarty then presented an outline of current scientific thinking on the problem of antibiotic resistance and biofilm formation; issues that significantly complicate the treatment of implant related bone infection. Further keynote addresses were provided by Alain Masqulelet (Paris, FR) on the induced membrane technique, Martin McNally (Oxford, UK) on clinical findings with the use of an antibiotic loaded resorbable bone void filler. Peter Ochsner (Liestal, CH), who has been working on bone infection with the AO for over 30 years with the AO, also provided an overview of his view of bone infection including the histological documentation of a selection of clinical cases. Finally, the executive

chairman from Southwest hospital, Prof Jianzhong Xu also shared his experience of defect reconstruction with tissue engineered bone, and the host, Prof Zhao Xie (member of the AOTK anti infective Task Force), presented his data on a large series of bone infection patients treated with induced membrane technique.

Clearly, there is an enormous clinical interest in bone infection in China, as evidenced by the large attendance. The AO has taken the opportunity with this meeting to join with local committed surgeons in an effort to share common interests in this important clinical problem.
On behalf of the invited foreign faculty, ARI would like to thank Prof Jianzhong Xu and Prof Zhao Xie for their generous hospitality.

Invited international faculty and local organizing committee. L-R: Huang Ke, Yu Shengpeng, Sun Dong, Jean Luis Briard, Qiu Yongzheng, Alain Masquelet, Peter Ochsner, Charisse Sparks, Xie Zhao, Willem-Jan Metsemakers, Xu Jianzhong, Fintan Moriarty, Chen Yuting, Geoff Richards, Huang Qiang, Sheng Jie

2017 Musculoskeletal Regeneration Network Symposium

On June 25th, ARI hosted the third official Musculoskeletal Regeneration Network symposium. The main organizers were David Eglin, Mauro Alini and Geoff Richards.

The MRN was founded in 2013 at The Chinese University of Hong Kong (CUHK) International Symposium on Stem Cell Biology & Regenerative Medicine organized by Prof Gang Li. The main driver was Prof Kai Ming Chan, Emeritus Professor of Orthopaedics and Traumatology, Prince of Wales Hospital, CUHK.

The founding members were CUHK, Karolinska Institute, Utrecht University Medical Centre, Stanford University, University of Pittsburgh, ARI, Shanghai Jiao Tong University and Zhejiang University. The MRN was created to be a global network to enhance mutual advancement in the field of regenerative technology. The first MRN meeting was then held at the Karolinska Institute in Stockholm, Sweden and 2016 MRN in Utrecht, Netherlands both maintaining this momentum of this network, continuing person-to-person and institution-to-institution collaborations. The establishment of the MRN has encouraged joint research programs in musculoskeletal research and regenerative medicine between many of the member groups and for ARI has built on the great long-term relationships with ex ARI fellows: Professor QIN Ling (Professor and Director of Musculoskeletal Research Laboratory, Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong) was a fellow at ARI in 1992 and 1993 and has remained a good friend and collaborator of Geoff and later Mauro ever since. Tingting Tang (Professor and Director, Shanghai Key Laboratory of Orthopaedic Implant, Associate Chairman, Department of Orthopaedic Surgery, Shanghai Ninth People's Hospital, China.) was a fellow in Mauro's program in 2004 and has been in close collaboration and friends with Mauro and Geoff since.

The 2018 MRN will be in Hangzhou, China, hosted by Prof HongWei OuYang at Zhejiang University and the 2019 MRN in Odense, Denmark, to be hosted by Prof Ming Ding and Prof Soren Overgaard at University of Southern Denmark.

Since the inaugural meeting of the MRN, the group has grown rapidly and has many participants to the network. It is a developing network and has great future potential

Biannual consortium meeting TargetCaRe

TargetCaRe consortium partners meeting at the ARI in Davos.

From June 30 to July 1, 2017, the biannual consortium meeting of the European Horizon2020 project TargetCaRe took place at the ARI. Twenty-five scientists and Early Stage Researchers (ESRs) from 12 partner institutions attended the meeting that was organized by Prof Mauro Alini, Head of the ARI Musculoskeletal Regeneration Program, and Sibylle Grad, Focus Area Leader Disc and Cartilage Research. Chronic low back pain and osteoarthritis, caused by degeneration of intervertebral disc and articular cartilage, severely impair the mobility and the quality of life of many people worldwide. The project TargetCaRe aims to develop innovative therapies by combining expertise in highly advanced drug delivery carriers, dedicated targeting tools, state-of-the-art imaging techniques, stem cell and joint biology. Regeneration of damaged and degenerated tissues will be achieved by employing targeting strategies tailored to both the pathology and the tissues involved. An important feature of this ITN (Innovative Training Network) project is the dedicated training of 15 young scientists, by 15 partner institutions located in five different countries.
ARI scientists contribute extensively to the ex vivo studies of TargetCaRe through their extended research experience with specific bioreactor systems for cartilage and disc. The ESRs are studying the regenerative and anti-inflammatory effects of nanocarriers containing therapeutic molecules in whole organ culture models. Osteochondral explants are used by Letizia Vainieri, PhD cand. in a cartilage bioreactor that simulates the load and motion of an articulating joint. For intervertebral disc studies, supported by Zhen Li, an organ culture bioreactor is employed where whole bovine discs are cultured under relevant loading conditions. The consortium meeting at the ARI included scientific presentations of the young scientists and breakout sessions on specific drug delivery systems. Prof Johan Engbersen, attending advisory board member from the Technical University of Twente (NL), greatly appreciated the intense interaction between the partners, the creditable progress and the top quality of the presented work.

TargetCaRe Partner organizations, and PIs

Erasmus MC, Rotterdam, NL: Gerjo van Osch
UMC Utrecht, NL: Laura Creemers
Technion, Israel: Marcelle Machluf
AO Research Institute, CH: Mauro Alini, Sibylle Grad
Cardiff University, UK: Bruce Caterson, Clare Hughes
University of Aberdeen, UK: Cosimo de Bari
Maastricht University, NL: Ron Heeren, Berta Cillero Pastor
Imperial College London, UK: Molly Stevens, Ben Pierce
iNANO, Aarhus, DK: Ken Howard
ProCore, Israel: Avner Yayon
Hebrew University, Israel: Efrat Monsonego Ornan;
Percuros, NL: Alan Chan
Omics2Image, NL: Hans R. Poolman
Dutch Arthritis Foundation, NL: Nienke Klomp

University of Freiburg Faculty of Medicine strengthens collaborations with ARI

On October 20, 2017, the University of Freiburg Faculty of Medicine visited the ARI for its 3rd ARI Freiburg Symposium. Organized by Prof Martin Stoddart from ARI and Prof Rainer Schmelzeisen from the University of Freiburg, the symposium was held alongside an ongoing AOTK CMF meeting in Davos. It brought together CMF and trauma surgeons, with ARI researchers and ARI Clinical Fellows, offering the opportunity to share updates on current projects and exchange ideas.
Commenting on the new presentations, Prof Schmelzeisen said: "For the 19 projects presented, I proposed a format that included a five-minute talk followed by 10 minutes of discussion. This format proved extremely successful and led to multiple new areas of collaboration and mutual benefit."
The ARI-Freiburg collaborations led to Prof Geoff Richards and Prof Martin Stoddart being awarded lifetime honorary Professorships at the University of Freiburg Faculty of Medicine in 2015. This event has been a great success in the past and together with the longstanding relationship has led to many successful collaborative projects.
The wide-ranging work being performed at both institutes was highlighted:

- cartilage and disc regeneration
- infection studies
- imaging and preoperative planning
- 3D printing
- additive manufacturing

"It was particularly satisfying to see how many of the current presentations had authors from both institutions," said Prof Geoff Richards, ARI Director. He continued, "There were also many referenced presentations from authors who have either been ARI Medical Fellows, such as Dr Dr René Rothweiler, Dr Dr Marc Anton Füssinger and Dr Dr Philipp Poxleitner, or collaborate in consortia with ARI. It's wonderful to connect the knowledge of the past with today's researchers."
Prof Richards also congratulated Prof Stoddart for having organized the meeting and networking so well.
The event built upon the success of the previous symposium two years ago that led to collaborative grants. Additional grants are now planned as the collaboration goes from strength to strength. The clinical input from Freiburg combined with the research expertise of ARI offers a type of interdisciplinary format that's needed for successful translation of novel therapeutics in the future.

ARI Davos hosts practical course for students from ETHZ and ZHAW

Group photo with participants and faculty

On April 21–22, 2017, 60 students in Biomedical Engineering in the Department Health Science and Technology (D-HEST) the Federal Institute of Technology Zürich (ETHZ) and the University of Applied Sciences Winterthur (ZHAW) participated in a practical training at the ARI Davos. The aim of this block course, that is part of the ETHZ Masters course "Skeletal Repair" taught by ARI, is to provide hands-on insight into osteosynthesis principles and current research methods.

The course started with an educational lecture on "preclinical translation" given by the ARI Director Prof R Geoff Richards who illustrated present surgical tools and techniques that have been designed by the AO over the years and the most recent developments that may be translated to clinical application in the near of further future. Afterwards, Dr Gian Bühler, Senior Surgeon at the Hospital Davos, introduced the participants to the basic principles of bone healing and fracture treatment.

The afternoon program included osteosynthesis and skill training exercises. Dr Raphael Jenni, Leading Surgeon at the Cantonal Hospital Chur, excellently guided the students step-by-step through the methods of surgical fracture treatment. Using artificial bones, all participants could practice the application of intramedullary nails, "fixateur externe" and compression plates, doubtlessly a highlight of the course. Students were instructed and supported by the surgeons Drs Raphael Jenni, Veit Schoenborn, Sabrina Weber and Berit Binken from the Hospital Chur and Dr Alejandro Vallejo from Colombia, a current ARI MD Research Fellow. The skills training exercises were organized by Dieter Wahl from the ARI Biomedical Development team. In four stations that were explained and demonstrated by ARI employees Manuela Ernst, Ivan Zderic, Peter Varga and Jan Buschmann, the attendees could personally experience the challenges and perils of proper handling of surgical tools.

Workshops about clinical imaging, basic and translational research were the focus of the second day. Raphael Jenni and Veit Schoenborn addressed cases of joint fractures and ligament rupture, whereas Bernd Heinlein and Daniel Baumgartner from the ZHAW focused on clinical problems in endoprosthetics. ARI scientists organized workshops on intervertebral disc organ culture bioreactors (Zhen Li and Patrick Lezuo), adenoviral gene transfer (Martin Stoddart and Ursula Menzel), 3D printing (David Eglin and Tiziano Serra), infection and antibiotics (Fintan Moriarty and Iris Keller-Stoddart), cell viability in hydrogels (Olivier Guillaume and Angela Armiento), joint anatomy and microscopy (Dirk Nehrbass and Letizia Vainieri), preclinical models and surgery (Stephan Zeiter). The final workshop presentations by the participants confirmed their high motivation and the overall excellent teaching and learning effects.

The experience gained at this practical training has encouraged several students to undertake their internship or Master Thesis at the ARI in Davos. Thereby the long-standing collaboration between the ARI and the hospitals of Davos and Chur, ZHAW and ETHZ is further strengthened and extended. The block course was organized and run by Sibylle Grad, Christoph Sprecher, Sonia Wahl, Laura Hartmann, Mauro Bluvol and Isabella Badrutt from the ARI. We acknowledge DePuy Synthes and RISystems for providing training material.

Faculty group picture, from left: Geoff Richards, Sabrina Weber, Alejandro Vallejo, Bernd Heinlein, Raphael Jenni, Berit Brinken, Sibylle Grad, Daniel Baumgartner, Veit Schoenborn

Collaborations
Strengthened collaboration with Rush University Medical Center Chicago

A symposium on Osteoarthritis of the knee and hip joint was held at the ARI, on July 28, 2017, organized by the Musculoskeletal Regeneration Program of the ARI in collaboration with Prof Markus Wimmer from the Department of Orthopaedics of the Rush University Medical Center in Chicago, US. Prof Mauro Alini, Head of the Musculoskeletal Regeneration Program, and Prof Wimmer welcomed the audience by explaining the origins of their collaboration. The cooperation between Mauro Alini and Markus Wimmer started in 1999 at the ARI with the development of a novel pin-on-ball bioreactor system for cartilage tissue engineering and related research. Since then these cartilage bioreactors have been further developed both in Davos and in Chicago and have resulted in numerous publications about mechanical effects on cartilage repair and chondrogenesis of mesenchymal stem cells.

During the morning sessions of the symposium, scientists from Markus Wimmer's team presented their projects related to knee/hip replacement and to recent bioreactor studies. Jade He introduced a "smart" pressure insole for gait retraining, Jacqueline Simon presented functional analysis of contact forces in total knee replacement, and Spencer Fullam showed patient-derived multi-activity inputs for wear testing. Markus Wimmer presented his bioreactor for testing of mechanical and biological responses of articular cartilage, Catherine Yuh showed cartilage stiffness changes following cartilage-on-cartilage articulation, and Simona Radice introduced her work on combining wear and cell culture. In the afternoon, ARI researchers demonstrated their projects related to cartilage repair and osteoarthritis. Prof Martin Stoddart summarized his in-depth studies, using the cartilage bioreactor, on the physical regulation of mesenchymal stem cell differentiation. Patrick Lezuo presented a finite element modeling method for scaffolds under multiaxial load; Graziana Monaco explained how to better mimic the in-vivo environment in cartilage research; Letizia Vainieri introduced a new bioreactor-loaded osteochondral defect model, and Reihane Ziadlou presented a Traditional Chinese Medicine approach for biological treatment of osteoarthritis.

In conclusion, this symposium clearly demonstrated the common interests and complementary expertise of the research teams from ARI and Rush University. This research visit strengthened the long-lasting cooperation and opened the door for new collaborative projects.

ARI strengthens its research network with Varna Medical University

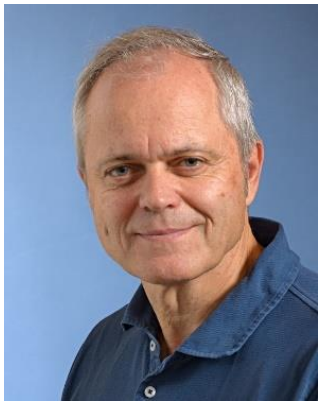
26-27 September 2017, Prof Dr Geoff Richards visited with Prof Dr Boyko Gueorguiev three sites in Varna – the Medical University 'Prof Paraskev Stoyanov', the University Hospital 'St Marina' and the Technical University. Prof Dr Hristo Skulev, Director of International Cooperation and Foreign Students at the Technical University facilitated the visits to foster collaborations between the three institutions. The meetings allowed for information exchange and good discussions on innovative ideas for cooperation. A trilateral letter of intent (LOI) was signed between ARI and both universities with the intention to:

- initiate fellowships (research and medical) from both institutions in ARI
- introduce and incorporate, with AOTrauma, clinical training modules (CTMs) for ORP in Bulgaria in the teaching curricula for students and postgraduates practicing nurses, the CTM's are currently being translated by volunteers from Varna Medical University into Bulgarian
- foster, together with AOCMF, collaborations through seminars and courses in the field of craniomaxillofacial surgery, with a symposium in 2018 and courses afterwards
- conduct joint research and implement innovative projects

All the three institutes committed to further developing their partnership for successful outcomes and future achievements.

From left to right: Dr Preslav Penev, Prof Dr Boyko Gueorguiev, Prof Dr Hristo Skulev, Prof Dr Tsvetan Tonchev, Dr Aneta Dokova, Prof Dr Geoff Richards and Prof Dr Metodi Abadzhiev in front of the main entrance of Medical University Varna

Prof Dr Marc Balligand – Visiting Professor in ARI



Prof Dr Marc Balligand, who is a full professor in small animal surgery at the University of Liege, Belgium, Faculty of veterinary medicine, as well as Past-president of European College of Veterinary Surgery (ECVS) and Vice-president of European Society of Veterinary Orthopedics and Traumatology (ESVOT), has commenced his sabbatical stay in ARI in October 2017. His present main focus of interest is related to fracture treatment. He has been developing a new concept of elastic external fixation in small animals. In addition, he has investigated bones and implants strains and stresses in a reverse-engineering approach for improving implants design.

General
Best masters thesis award: Jan Barcik, under the supervision of Prof Dr Boyko Gueorguiev. Actuator-sensor unit to investigate the influence of mechanical stimulation on bone healing, AGH University of Science and Technology, November 2017, Krakow, Poland.

Corina Berset (Residency in Laboratory Animal Medicine, AO Foundation) has been appointed convenor of the FELASA (Federation of European Laboratory Animal Science Associations) Working Group (WG) for Farm Animals – Health and Welfare of Ruminants and Pigs. This WG aims to write new FELASA recommendations in order to define criteria of animals' acquisition, including the control of the animals' health status before purchase, which is in line with the goal of the AO strategy project. Further, they will organize a session on farm animals in research at the FELASA Congress in June 2019.

Fabian Gieling successfully completed his Dr med vet thesis at the Vetsuisse Faculty of the University of Zürich, Switzerland. The supervisors were Stephan Zeiter und Prof Martin Stoddart (ARI) and Prof Anton Fuerst (Zürich). Thesis title: Does the sorting of mesenchymal stem cells based on their Runx2/Sox9 expression ratio improve bone healing incalvarial defects in rats?

Ana-Maria Stanciuc successfully completed her PhD thesis at INSA Lyon, France. The supervisors were Dr Marianna Peroglio (ARI) and Dr Laurent Gremillard (INSA Lyon). Thesis title: In vitro evaluation of cell-material interactions on bioinert ceramics with novel surface modifications for enhanced osseointegration.

02.10.2017
Gert-Jan ter Boo successfully defended his PhD thesis at the University of Twente, The Netherlands
Title: Delivery of gentamicin from resorbable polymeric carriers as anti-infective strategy for implant-associated osteomyelitis. ARI Supervisors: David Eglin
Thesis Advisor: Prof Dirk W Grijpma, University of Twente, Enschede, The Netherlands

31.03.2017
Mario Inauen successfully defended his MSc thesis at the D-HEST, ETHZ
Title: Development of gentamicin sulfate loaded hydrogel formulation for in-situ gelling in trauma surgery to prevent infections after fracture fixation. ARI Supervisors: Matteo D'Este, David Eglin
Thesis Advisor: Prof Stephen J Ferguson, Laboratory for Orthopaedic Technology, ETHZ

01.09.2017
Marine Heriot successfully defended her MSc thesis at the University of Monpellier, France
Title: Development of a gentamicin sulfate-loaded injectable hydrogel for local antibiotic delivery in trauma and orthopedic surgery. ARI Supervisors: Matteo D'Este, Olivier Guillaume, David Eglin
Thesis Advisor: Dr Benjamin Notellet, IBMM, University of Montpellier, France

Maria Hildebrand successfully defended her MSc thesis in Biology, UZH, with the grade of 5.6. Title: Characterization of the Immune Response Following a Large Bone Defect in the Presence and Absence of a Human Xenograft in a Rat Model.
ARI Supervisors: Marietta Herrmann, Mauro Alini. Thesis Advisor: Cezmi Akdis, Swiss Institute of Allergy and Asthma Research, UZH.

Claudia Loebel was awarded ETH-Zürich Outstanding Doctoral thesis 2017 for her thesis on entitled: Engineering Hyaluronan-Tyramine Hydrogels to Modulate Mesenchymal Stem Cell Behavior.
ARI Supervisor: David Eglin
ETH Thesis Advisor: Marcy Zenobi

Caroline Moser was awarded the highly prestigious ETH Gold medal for her Masters thesis "Directing osteogenic differentiation of mesenchymal stromal cells in vitro".
ARI Supervisors: Jennifer Bara, Martin Stoddart

Visit from local politicians to the AO Research Institute Davos

On May 16, 2017, the members of the Upper Council Davos, Tarzisius Caviezel, Simi Valär, Stefan Walser, Herbert Mani and Valérie Favre Accola, as well as Klosters-Serneus, Kurt Steck, Stefan Darnuzer and Josias Jenny, and two community writers Michael Straub, Davos and Michael Fischer, Klosters, visited ARI to get a personal impression of the current activities.

Following the introductory presentation by Prof Geoff Richards, the team of Dr Markus Windolf, group leader concept development, gave an insight into two ongoing projects. After a demonstration of the AO fracture monitor - an implantable device for the tracking of fracture healing - the politicians were able to prove their surgical skill while drilling the artificial bone. They tested a tool for medical drilling machines, which allows the correct screw length to be determined directly during the drilling process, thus avoiding the partial cumbersome and inaccurate manual measurement.

During the subsequent visit of the respective premises, there was a good discussion about the livestock management of Urban Lanker and Dr med vet Stephan Zeiter answered. In particular, the peculiarities compared to an agricultural use were discussed.

Finally, Dr Sibylle Grad and Dr Christoph Sprecher explained to the visitors about ongoing research on simulators and implants for the patient. The activities with the new 3D printer in the area of degradable bone substitutes for applications on the jaw and the face have been of particular interest, as evidenced by detailed questions. The 3D bio printer was procured about a year ago with the support of the Innovation Foundation Graubünden, as well as the Commission for Technology and Innovation.

From an ARI apprenticeship in Davos to the Swiss Guard in the Vatican

Nando Adank, who recently completed a four-year apprenticeship as a "Polymechaniker" in the ARI prototype workshop attended his public swearing in as a member of the Swiss Guard at the Vatican on May 6, 2017.

Formed in 1506 and often called the "smallest army in the world" or the "Pope's army", the Swiss Guard have had a rich history. On May 6 in 1527, during a military coup called the Sack of Rome, 147 of the 189 Swiss Guards gave their lives to protect the Pope as he escaped. After surrender, twelve of the remaining Swiss Guards nonetheless chose to join the Papal Guard along with their former enemies, the German and Spanish mercenaries. But it was not until 300 years later when the Papal State and its Papal Guard was abolished that only the Pontifical Swiss Guards remained.

From that day onwards, the Swiss Guards have been solely responsible for protecting the Pope and his residence in the Vatican and his summer residence in Castel Gandolfo. Besides that, they also perform various ceremonial responsibilities: guarding the Apostolic Palace, keeping vigil at various Vatican checkpoints, and taking part in celebratory masses and events. To commemorate the sacrifice of the Swiss Guards on that fated day in 1527, the swearing-in ceremony of 30-some new Swiss Guards is held on May 6 each year.

Not everyone can aspire to become a Swiss Guard. Each applicant must meet a litany of rigorous requirements:

1. Must be male.
2. Must be Roman Catholic.
3. Must be a citizen of Switzerland.
4. Must be at least 1.74 meters tall.
5. Must be between 19 and 30 years of age. However, a retired guard, who is over 30, may be able to return in exceptional cases.
6. Must be single. However, a guard may be permitted to marry if he is over 25 years of age, has already completed at least 3 years in service, is at least of a Corporal rank, and commits to serve for an additional 3 years.
7. Must have a high school degree or a professional diploma.
8. Must have completed service with the Swiss army. After getting enlisted, they undergo further training, especially in unarmed combat techniques and in countering terrorist attacks.
9. Must commit a minimum of 2 years.
10. Must be of great moral and ethical upstanding.

When asked about his reasons for spending at least two years as a Swiss Guard, Nando explained that, "I think you should use the possibility as a Swiss citizen. In addition, it is a very good life experience. Also my Roman Catholic faith was an important factor in my registration and I am very honored to be chosen".

2017 Berton Rahn Research Award

The Berton Rahn Research Award was established in recognition of Berton Rahn's immense contribution to the AO Foundation. The prize honors the best completed AO Foundation's external research each year (including consortia and clinical division mini grants and regional grants) from the AO Foundation's Clinical Divisions and Institutes and is decided within the AO Research Institute Davos's Advisory Committee (ARI AC). The award is based upon final reports and the publications resulting from all completed studies. The award consists of a keynote award presentation (in 2017 at TERMIS-EU chapter meeting in Davos and future meetings at eCM Conference in Davos), a certificate, and a financial prize.

The 2017 winner was Robert L Mauck, PhD, the Mary Black Ralston Professor of Education and Research in Orthopaedic Surgery and Professor of Bioengineering at the University of Pennsylvania. His work for this award was within the AO Research Institute Davos's Acute Cartilage Injury (ACI) Consortium which was inaugurated in the summer of 2011

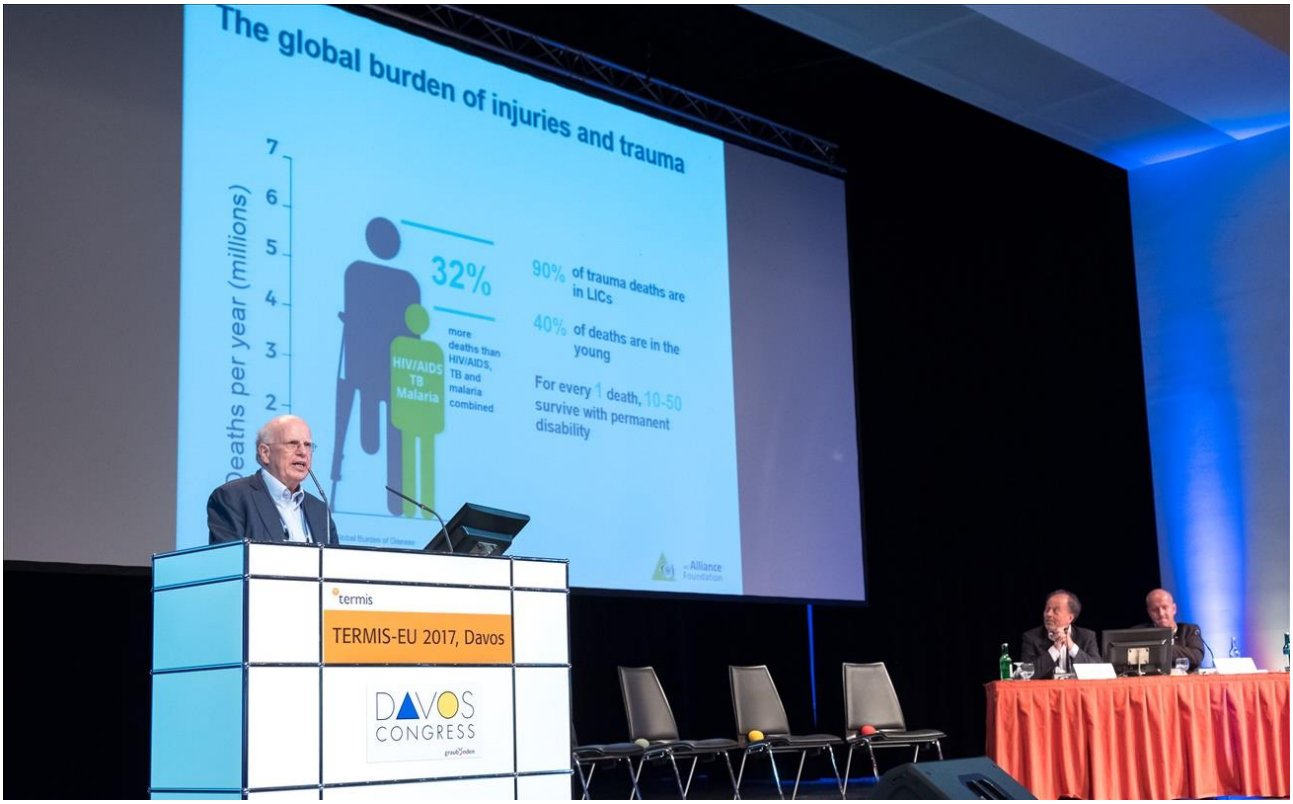
9 TERMIS Conference

Tissue Engineering and Regenerative Medicine European Chapter annual meeting successfully organized by ARI in Davos

Opening Ceremony TERMIS-EU Davos

1301 scientists including clinicians and industrial attendees from various research institutes, universities, hospitals and industry worldwide met from 26th – 30th June 2017 in Davos for the annual meeting of the international society for "Tissue Engineering and Regenerative Medicine" (TERMIS-EU). The renowned congress was organized and implemented by the ARI under the guidance of Prof R Geoff Richards and Prof Mauro Alini. Co-organizers were the scientists David Eglin, Sibylle Grad, Claudia Loebel, Martin Stoddart and Sophie Verrier, as well as the administration team of the ARI for organisational aspects. Under the lead theme "personalized therapies for regenerative medicine" more than 350 lectures were held and more than 800 studies presented as posters at TERMIS-EU 2017 Davos.

Opening Ceremony TERMIS-EU Davos



AO Foundation CEO, Rolf Jeker introduces the AO Alliance Foundation to the audience.

The latest findings from scientific and clinical research demonstrated the potential of stem cells, as well as natural and synthetic materials or remedies, for the regeneration of injured or worn tissue. In regenerative medicine, methods are also increasingly being developed to stimulate or speed up the body's endogenous healing potential. The production of patient-specific tissues from 3D printers was also presented several times. Besides bone the topics discussed were, joint and tendon regeneration, cartilage, the healing of eye, nerve, heart and skin diseases. A special symposium focused on the ethical aspects of personalized medicine, which met with great interest. The section of the young scientists also offered an attractive program for students and young researchers. TERMIS-EU prizes were awarded for outstanding achievements of emerging researchers and for outstanding contributions to scientific literature. The acknowledged "AO Foundation Berton Rahn Research Award" for the best external research project financed by the AO Foundation was awarded to Prof Rob Mauck, University of Pennsylvania, for his work as part of the AO Research Institute Davos's Acute Cartilage Injury Collaborative Research Program.


AO Foundation booth with Ladina Lanker

Plenary Lecture from Jeff Karp

Professor Molly Stevens presenting at the Davos Debate chaired by Prof David Williams, Past Global President of TERMIS (to her left), followed by Professor Giuseppe Remuzzi, Professor Rocky Tuan, Professor Milica Radisic.

Within the framework of the TERMIS congress, scientists from the AO Research Institute Davos organized a symposium for 60 students of two local Davos schools, the SAMD and the sports gymnasium, focusing on biology. Prof. Martin Stoddart and Dr. Sibylle Grad clearly explained the founding of the AO Foundation almost 60 years ago as well as the worldwide importance of the AO principles for fracture treatment. While in the 1940s still 60% of all thigh fractures led to permanent disability, this rate is now 2-3% thanks to the achievements of the AO. The treatment of bone fractures by means of a wide range of implants is still being further developed and given to the surgeons in more than 700 practical courses worldwide.

Professor Martin Stoddart presenting to Davos School pupils.

In the field of tissue engineering and regenerative medicine, AO is investigating new methods for treating bone, cartilage and disc injuries. The researchers explained the biological basis of the different tissues and the possibilities of the patient's own stem cells for their regeneration. The cells react strongly to mechanical stress and may vary depending on the stress mode into different cell types, e.g. cartilage or bone cells. This provides the biological basis of the well-established Perren strain principle. Special bioreactors for cartilage and intervertebral disc tests allow ARI researchers to simulate normal stress and overload on cells and tissues within the laboratory. The findings, which were also presented at the TERMIS congress, contribute to the improvement of cell therapy and the optimization of physiotherapy. This insight into orthopedic research and development was very instructive for the middle school pupils and the teachers present, especially as the local professional opportunities for biologists, chemists, engineers and doctors were shown.

With the help of the Davos Trackclub, the TERMIS organization team organized a run / walk around the Davos lake (4 KM) for the conference participants. More than 270 delegates and students from all over the world partook in this unique event.

Participants of the Davos Lake TERMIS run / walk

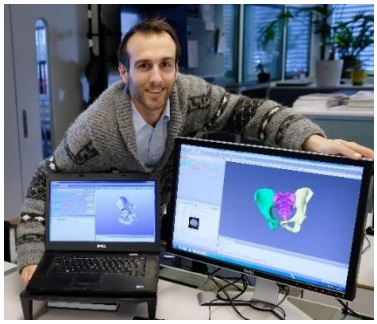
TERMIS-EU 2017 Davos was run at a true full cost model (including all personnel, overhead and material costs), made a profit which is being used for collaborative purposes within the ARI.

Participants of the Davos Publishing Debate chaired by Mauro Alini

10 ARI Fellows

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

- Creation of tangible results in research
- Possibility of 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

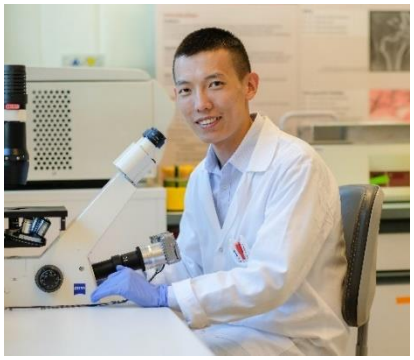


Marc-Daniel Ahrend: BG Unfallklinik, Tübingen, Germany
ARI Project: **Strategy Fund "For Asia specific artificial bone models"**
After finishing medical school, I took the amazing opportunity to work in the ARI as a medical research fellow for one year - an experience I will never forget. Working in the Biomedical Development Program under the supervision of Boyko Gueorguiev revealed several interesting insights in highly quality research in orthopedic and traumatology. During my time in Davos, I worked on projects regarding the 3D bone morphology of the pelvic region as well as the scaphoid bone with support of Lukas Kamer and Hansrudi Noser. Moreover, I was encouraged by the staff of the ARI to concept and develop own research ideas and projects which will be very useful for my further scientific career in the future. Besides the opportunity of meeting and learning from great scientists, I made good friends and collected amazing memories in the beautiful landscape of Davos. I already miss the time and people in the AO. I want to thank the whole staff of the institute - especially Geoff Richards, Boyko Gueorguiev, Lukas Kamer, Hansrudi Noser and Dieter Wahl.

Sonja Häckel: Charité – Medicine Berlin, Germany
ARI Project: **TargetCaRE "Targeting Cartilage Regeneration in joint and intervertebral disc diseases"**
At the beginning of my fellowship I had a solid knowledge of working in the lab but with the help of my colleagues here at the ARI, my work as well my scientific mind improved a lot. I really enjoyed the last months here in Davos. The ARI gives you a nice work environment with a lot of flexibility and there are regularly group activities organized by the AO. This is something that you are usually not used to have as a MD working in a hospital. Since I am working for an international project, I have recently been in Israel for a 2-week secondment, where I gained a lot of new impressions and ideas. I am not at all regretting my decision to leave clinics for this 1-year fellowship.

Mariya Hadzhinikolova: University Hospital of Emergency Medicine and Active Treatment "N.I. Pirogov", Sofia, Bulgaria
ARI Project: **DistRadPlate "biomechanical investigation of double-plated distal radius fractures in comparison to volar locking fixation"**
I Joined the Biomedical Development team in the beginning of October 2017. As a resident in the Orthopedic and Trauma department in my hospital I find this topic very intriguing and clinically important. The clinical experience that I gained during my training was very helpful for the specimen preparation. On the other hand, I had the great opportunity to work with amazing people, who are highly competent and skillful colleagues. They helped me to apply physics, mathematics and engineering to answer medical questions. At ARI I met wonderful, easy-going and helpful people and made a lot of friends from all over the world. I definitely miss living in Davos, a small and cozy city with interesting history, breathtaking views and amazing places for hiking. Davos will always stay in my heart as a place I can call home and I will always feel the people in ARI as a family.

Niko Kovermann: Freie Universität Berlin, Germany
ARI Project: **Synovial stem cells (hSDSC) as alternative cell source for the cartilage tissue engineering – the role of mechanical stimulation**
I joined the Musculoskeletal Regeneration Group at the ARI in September 2017 for my doctoral thesis. I work in the stem cell group of Prof Martin Stoddart. I want to see if these stem cells can be an alternative cell source for the cartilage tissue engineering. I studied veterinary medicine and completed the final examination in April 2017. It is an honor for me to work in such a great institute. The team spirit is amazing, my working colleagues are from all over the world. At the ARI, I profit a lot from research and lab work. I really enjoy the time in Davos, the countryside with all the mountains is very beautiful. Furthermore, I enjoy skiing in Davos besides working in the lab.



Junxuan Ma: The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
ARI Project: **Neurodisc "innervated organ culture model of discogenic pain"**
I enjoyed every moment here in Davos. My work focuses on very meaningful subject of clinical low back pain. Thanks to the previous foundation of organ culture in our group, creating the challenging model of low back pain now seems to be attainable. The procedure got widely support from the whole ARI and was performed in a well-organized way. I'm so happy for what I learnt here including not only lab techniques but also the training of project management. The experience of living and working with international colleagues is amazing and the beautiful sightseeing in Davos during four different seasons is unforgettable.

Andreas Naros: University Hospital, Tübingen, Germany
ARI Project: **MiDiag "miRNA biomarker analysis for predicting patient outcomes after fracture**
Eight months of my fellowship have already passed, full of experiences and impressions. The friendly and familiar atmosphere at the ARI makes it very easy to settle in and feel as part of the AO family. This enables fellows to easily focus on their scientific work. Various group activities strengthen the sense of belonging and motivates everybody to work even harder. The most impressive is the constant exchange with experienced scientists of different groups which turns your own project into an AO project.

Lyubomir Rusimov: Pirogov Hospital for Active Treatment and Emergency Medicine, Sofia, Bulgaria
ARI Project: **Biomechanical investigation of conventional versus augmented PHILOS plating using intramedullary grafting**
As part of the ARI Fellowship program I have gained a unique experience in the research field by finishing a personal project and taking part in two more. What I have learned in the Biomechanical department has showed me a new and different perspective of the fracture fixation which I can now apply in my clinical practice every day. Working in ARI was a great experience for me not only because of the stimulating working environment but for all the great professionals working there ready to help you in every moment. During these three months in line with the tough days of experimenting and writing I have met many different people from all over the world. ARI for me is a special place where you can not only improve your professional skills but also make great friendships. It is one big family spread not only on a couple of floors in a remarkable building but all over the world. Thank you, ARI for letting me be part of it!

Eamon Sheehy: Royal College of Surgeons, Ireland
ARI Project: **C-RCSIm 114074 "Evaluation of a collagen-based antibiotic loaded scaffold system for the treatment of osteomyelitis in a rabbit model**
I joined the Infection Group in the ARI in October 2017 to work on a collaborative infection project. My background is in Tissue Engineering, so my time here has allowed me to gain key experience in the field of Microbiology and has greatly enhanced my understanding of infectious microorganisms. I have found the ARI to be a fantastically welcoming place to work, and one which puts an emphasis on developing a community spirit. It seemed that after only a few days here, everyone in the Institute knew my name and vice versa. It has also been wonderful to live in such a beautiful town as Davos, where the sight of the Alps every morning on the way to work is sure to put you in a good mood. The skiing's not half bad either.

Alejandro Vallejo: Universidad Pontificia Bolivariana, Medellin, Antioquia, Colombia
ARI Project: **OpInFect "use of a rabbit humeral LCP model to provide evidence for treatment & prophylaxis concepts in open fracture care" ARI Project: Infect-fx "influence of material and microtopography on the development of local infection experimental investigations"**
AO Foundation has been present during my entire formation as an orthopedic surgeon, from residency, where I had my first contact with an excellent group of professionals, that shared and taught me techniques and use of devices for fracture treatment, and afterwards, during clinical practice, applying those techniques and allowing me, since a while, to join the group of regional faculties, with the possibility to continue with the line of knowledge to other colleagues and the new generation of traumatologists. In January 2017, I had the opportunity to join the ARI for one year to work as a research fellow with the infection group. The ARI became more than a work and research place, became my home and my colleagues became wonderful friends and my family in Davos. Working at the ARI gave me an amazing experience increasing my networking, expertise, knowledge, framed in a great landscape and together with wonderful people.
(This year's front cover photo was taken by Alejo - Thanks)

Kalan Violin: IPEN, Sao Paulo, Brazil
ARI Project: Discform **"role of the intervertebral disc in the development and progression of spinal deformities"**
ARI Project: Januscaf II "Biphasic Elastomeric Scaffold"
I joined the ARI in February 2017 as a fellow to work on several projects, mainly related to immunohistochemistry and IVD. We were able to confirm the presence of various proteins using related antibodies inside NP cells from scoliotic patient's IVDs. The time I spent at ARI was very educational in a wide sense, scientifically and socially. While in Davos, I had a very good time meeting new people and making friends, which I will carry with me for life, as well as establishing a working partnership with the group.

Christian von Deimling: University of Bern, Switzerland
ARI Project: **"C-RCSim" and "OpinMRSA", Fracture-related Infection**
During my Medical Research Fellowship, I worked for 12 months at the Preclinical Services at the ARI. During that year I was involved in several projects which were mostly dealing with treating infections in fracture-related infection and improving local or systemic antibiotic treatment. I especially enjoyed the AO Spirit within the ARI and working together with renowned scientists. Besides working at the ARI, I enjoyed all the advantages that living in Davos offers.

11 Project Abstracts by Sponsors

11.1 AOCMF

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

Background: Antiresorptive drug-related osteonecrosis of the jaw (ARONJ) is a severe clinical condition that may be related to management of bone diseases such as osteoporosis or cancer. Its early diagnosis and treatment may prevent or reduce the morbidity resulting from advanced destructive lesions of the jaws. Currently, the diagnosis and treatment decisions are related to clinical tasks that usually rely on the medical history, clinical examination and radiographic assessment, as they are considered to be the most sensitive tools. However, these tasks still remain difficult to be accomplished and leave a wide open space for subjective interpretation.

Goal: To develop a computerized ARONJ ranking tool with implementation of Artificial Intelligence and to rank given ARONJ cases in order to improve and facilitate the risk assessment, diagnosis and treatment decision in the clinics.

Results: More than 200 patient records and image data (panoramic radiographs, computed tomography and cone beam computed tomography scans) were collected from a retrospective series of patients affected by ARONJ and oral cancer with jaw bone involvement, as well as patients with dental implant cases considered of a control group. Labeling of the panoramic radiographs was performed.

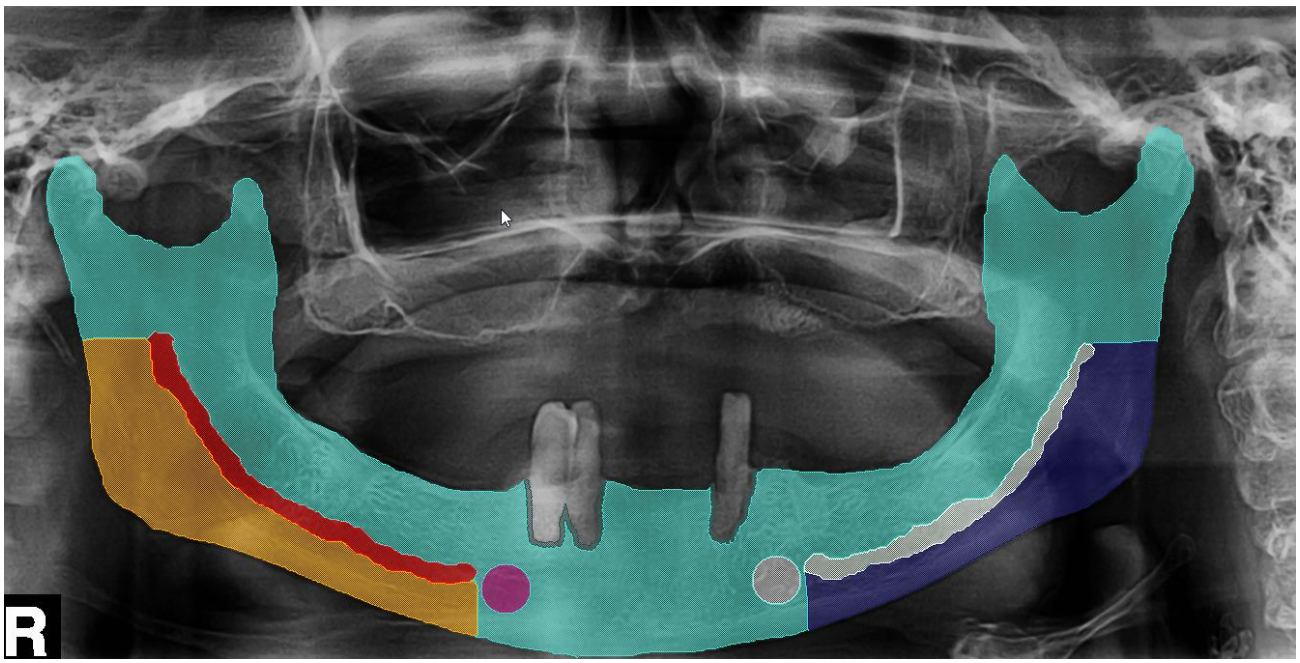


Figure 11.1.1: Exemplified panoramic radiograph demonstrating labeling of the mandible with defined specific regions of interests (colored).

Partners:

- Rana M, Department for Oral and Maxillofacial Surgery, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany
- Lutz I, Center of Dental, Oral and Maxillofacial Science, Medical School Hannover, Hannover Medical School, Hannover, Germany
- Gellrich NC, Department of Cranio-Maxillofacial Surgery, Hannover Medical School, Hannover, Germany

Printable Ceramic Ink for Patient Specific Implant Fabrication (CeramInk) (D Eglin, M Stoddart)

It is estimated that more than 500,000 bone-grafting procedures are performed annually in the US alone. Worldwide, the bone graft substitute market is expected to growth over 6 % in the next 10 years reaching over 5 billion dollars by the end of 2027. Among the different acute bone fractures leading to a high burden for our societies and unbearable affliction for the patient, the region of the head and the face is a major target for development of patient specific implants. Reconstruction of large bone fractures and defects in cranio-maxillofacial surgery requires restitution of the pre-injury bone anatomy to re-establish form, function and aesthetics. To further improve the clinical outcome and to meet the criteria for a true-to-original reconstruction individual bone implant, new personalized printable materials are required. The goal of this project is to optimize an osteoconductive calcium phosphate cement product for printing patient specific implant, focusing on the development of a fast printing and cement setting process for adequate handling, mechanical and structural stabilities and rapid implantation (Figure 11.1.2).

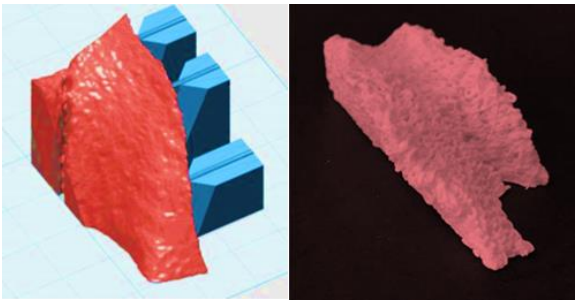


Figure 11.1.2: Planned mandibular defect implant shape with support & representative ceramic 3D printed structure.
Pub: Stadelmann, Geven et al. 2017

3D printing of cellularized tissue engineered constructs. Bioinks & Methods toward clinical translation) (Bioink) (Started (M Stoddart, D Eglin)

Patient specific implants based on additive manufacturing principles hold great promise in CMF applications, where anatomical fidelity is paramount. As the imaging to printing workflows improve, one major hurdle is the development of bioinks that are osteoinductive, while at the same time having a realistic path through regulatory approval. By avoiding complex material developments and following a "less is more" approach, we believe a novel material with clinical approval can be obtained faster. This project aims to investigate the printability of three clinically approved natural materials and further improve their function with minor modifications. The potential to improve their osteoinductive properties will be investigated by the addition of simple osteoinductive molecules that are already clinically approved or would have a less challenging approval process. The goal of this project is to develop the 3D printing of clinically relevant biopolymer hydrogel products, namely collagen type I, fibrin glue and hyaluronan for the manufacturing of cellular 3D tissue engineered constructs (Figure 11.1.3).

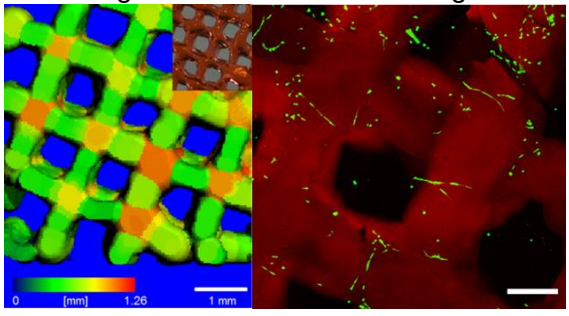


Figure 11.1.3: Reconstruction of microCT scan of 3D printed hyaluronan ink (image of the printed structure in insert) & confocal image of cells seeded printed hyaluronan hydrogel.

Pres: Petta, Grijpma et al. 2017, Petta, Grijpma et al. 2017

Prospective isolation and characterization of stem cells from human adult tissues (Truestem) (Started) (M Stoddart)

Cell based therapies have long been proposed as a solution for larger orthopedic defects, with stem cells often highlighted as having particular potential. However, current stem cell isolation strategies are quite crude and do not result in a homogeneous cell population. Due to the variable nature of the cells obtained it has been impossible to conclusively show the benefit of adding exogenous cells, nor elaborate their mode of action. Without a method to prospectively isolated a pure population of cells, their utility and function may never be fully clarified. This gap in the knowledge needs to be filled if their potential for clinical use will ever be fully realized. Within this project we aim to prospectively isolate live stem cells using nondestructive fluorescence based labeling of intracellular stem cell markers. The cells will be characterized for purity and function. The long-term aim is to use the purified population to answer the question regarding their clinical utility.

11.2 AOSpine

Functional cell therapy for annulus fibrosus repair (ongoing) (Z Li, S Grad)

Functional annulus fibrosus (AF) repair is critical to reduce disc re-herniation risk. To reconstruct functional AF tissue, an effective cell population with functional repair ability is demanded. CD146 is a cell adhesion molecule that is associated with improved wound healing. Thus CD146+ AF cells may be an appropriate cell source for functional AF repair. The current study aims to investigate: 1) the CD146 expression in AF cells, and their associated characteristics and functions; and 2) if encapsulation in hydrogel/scaffold carriers can maintain a CD146+ phenotype.
The CD146 protein expression of AF cells was up-regulated from 33% to 85% by exogenous TGFβ supplementation. The cells cultured with TGFβ also showed greater cell contractility than cells cultured with basal medium. AF cells encapsulated in collagen gel maintained marker gene expression level comparable to the cells cultured with TGFβ (Figure 11.2.1). Collagen gel is thus a valuable candidate carrier to maintain the functional phenotype of AF cells, as indicated by gene expression of CD146 and multiple AF markers. Delivery or induction of CD146+ AF cells may enhance the regenerative capacity of the IVD by promoting AF healing.

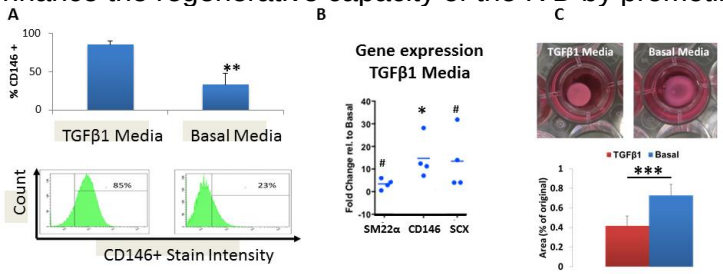


*Figure 11.2.1. (A) FACS data indicating the induction of CD146 in AF cells by addition of TGFβ1 to the culture medium, n=3, **p<0.01. (B) TGFβ1 media resulted in higher CD146, SM22a and SCX gene expression, n=4, #p<0.1, *p<0.05. (C) Collagen gel contraction of human AF cells, n=4, ***p<0.001.*

Pres:
Long RG, Nakai T, Sakai D, Benneker LM, Iatridis JC, Alini M, Grad S, Li Z. TGFβ1 induces a contractile CD146+ phenotype of human annulus fibrosus cells showing affinity to collagen scaffold aimed for annulus fibrosus repair. 2017 ORS (poster)

Zhou Z, Alini M, Grad S, Li Z. Effect of the CCL5 releasing fibrin gel for intervertebral disc regeneration. 2017 TERMIS-EU (poster)

Pub:
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. 2017;52:118-29

Partners:
- Sakai D (Prof), Tokai University School of Medicine, Isehara, Japan
- Benneker LM (Prof), Inselspital, University of Bern, Bern, Switzerland
- Iatridis JC (Prof), Icahn School of Medicine at Mount Sinai, New York, NY
- Pandit A (Prof), CURAM, National University of Ireland, Galway, IRL

Evaluation of hyaluronan-based hydrogels for nucleus pulposus repair (ongoing) (M Peroglio, S Grad)

The ability of intervertebral discs (IVDs) to withstand cyclic mechanical loads is strongly linked to the confinement of nucleus pulposus (NP), a highly hydrated tissue with strong swelling potential. With degeneration, the confinement and/or swelling potential of the NP is diminished. Therefore, there is the need for hydrogels which (i) have high swelling potential, (ii) are capable of withstanding cyclic loads and (iii) support IVD regeneration. Herein, we evaluate the potential of chemically crosslinked hyaluronic acid hydrogels to address these goals.
Hyaluronic acid crosslinked with 1,4-butanediol diglycidyl ether hydrogels (BDDE-HA) (degree of crosslinking, DS= 7.5-100%, 2.5% w/v) were prepared and lyophilised. Swelling analyses were performed in DMEM-10% foetal calf serum. For in vitro studies, bovine nucleus pulposus cells (NPCs) were seeded on the lyophilised gels and cultured free swelling or in an agarose mold. Cell viability and matrix deposition were evaluated by lactate dehydrogenase/ethidium homodimer and safranin-O/fast green staining, respectively. Gene expression was quantified by RT-PCR. For whole organ cultures, bovine nucleotomized IVDs filled with NPC-seeded hydrogels were cultured under loading for 3 weeks.
BDDE-HA swelling ratio was proportional to the extent of crosslinking and ranged from 40 to 120, which is comparable to young bovine NP tissue. NPC viability was maintained in BDDE-HA, while phenotype marker expression was maintained depending on the degree of crosslinking. In organ culture, all hydrogels fully occupied the nucleotomized space following cyclic loading, attesting their ability to recover height following dynamic compression. Hence, these hydrogels have a strong potential for NP repair.

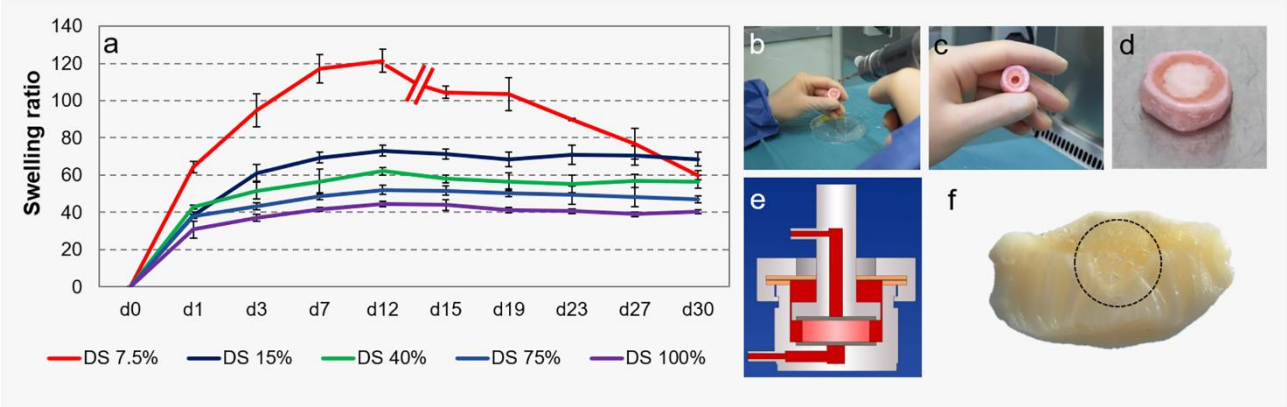


Figure 11.2.2 a) swelling ratio of hyaluronic acid hydrogels with different degrees of cross-linking; b) drilling of intervertebral disc (IVD) through the endplate; c) IVD following drilling and partial nucleotomy; d) IVD following restoration with the hydrogel and sealing with bone cement; e) IVD bioreactor; f) cross-section of restored IVD following physiological loading in the bioreactor (dotted circle indicates the restored area).

Pres:
Hu M, Nuzzo A, D'Este M, Richards RG, Lee P, Alini M, Grad S, Peroglio M. In vitro and organ culture evaluation of chemically crosslinked hyaluronic acid hydrogels for nucleus pulposus repair. 2017 TERMIS-EU (oral)

Pub:
Peroglio M, Douma LS, Caprez TS, Janki M, Benneker LM, Alini M, Grad S. Intervertebral disc response to stem cell treatment is conditioned by disc state and cell carrier: An ex vivo study. J Orthop Translation. 2017;9:43-51.

11.3 AOTrauma

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

Background: Treatment of fragility fractures at the proximal humerus remains a major challenge in orthopedic 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 vitro and to accommodate with traditional implant design strategies, thus leading to limitations in each surgical solution. In contrast to laboratory experiments, computational simulations can enable a more versatile, efficient and systematic screening process for new design ideas or research questions and can provide dramatic 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 in the proximal humerus.
Results: The previously developed and validated simulation framework has been utilized to investigate aspects of proximal humerus fracture fixations with direct relevance to the clinical practice. The effect of screw length, screw configuration, screw augmentation with bone cement, plate position and plate type were analyzed in sub-projects using 20-26 low-density subjects, an instable three-part fracture model and three physiological loading modes. Additionally, the influence of the screw orientations was investigated to predict whether a variable-angle fixation could be superior to the fixed-angle implant.
Screw length was found to have a significant effect with a smaller tip-to-joint distance providing significantly higher stability. Out of four different screw configurations, the one utilizing the calcar screws of the PHILOS plate performed the best. The benefit of cement augmentation was higher for the posterior screws than the anterior ones and increased from proximal to distal. Plate position had no significant effect when using four head fragment screws, however, even a 2-mm proximal shift significantly improved and a 2 mm distal shift significantly reduced the predicted implant stability for a six-screw fixation. Comparison of the PHILOS plate with the periarticular proximal humerus LCP using five proximal screws showed no clear preference between the two implants. The parametric analysis of the screw orientations among 20 subjects with PHILOS plate fixation identified an optimized screw angle configuration that provided 18 ± 9% strain reduction compared to the fixed-angle configuration.
The developed test-kit can be a powerful tool to improve clinical outcomes through implant design or procedure enhancements.

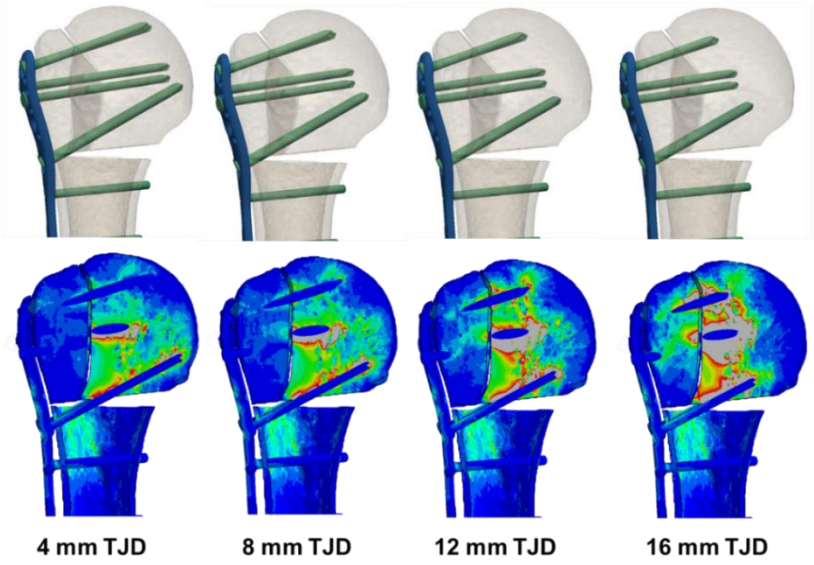


Figure 11.3.1 Increasing tip-to-joint (TJD) distance, i.e. decreasing length of the proximal screws in proximal humerus plating results in higher strains within the peri-implant bone region and therefore a higher risk of fixation failure.

Pub:
Varga P, Grünwald L, Inzana JA, Windolf M. Fatigue failure of plated osteoporotic proximal humerus fractures is predicted by the strain around the proximal screws. J Mech Behav Biomed Mater. 2017. 75:68-74.

Pres:
Varga P, Grünwald L, Inzana J, Windolf M. Fatigue failure of plated osteoporotic proximal humerus fractures is predicted by the strain around the screws. ESBiomech. 2017 (oral).
Varga P, Inzana J, Grünwald L, Gueorguiev B, Richards RG, Blauth M, Südkamp N, Windolf M. A virtual toolkit for systematic implant development and optimization. Smart Surgery Symposium. EORS. 2017 (oral).

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

AO Implant Positioning Assistance (SimpCAS, Xin1) (Ongoing) (J Buschbaum, M Windolf)

Problem: The task of placing implants plays a key role in orthopedic trauma surgery. Current solutions for computer aided surgery lack of wider acceptance due to considerable disadvantages regarding complexity, costs and effectiveness.
Goal: To develop a simplified computer aided surgery system 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: Two Xin1 modules are currently under clinical investigation to pursue the path to clinical application. A handling test of the Xin1 system for proximal humeral plating was initiated in collaboration with UZ Leuven, Belgium. Nine out of ten patients were treated. Results reveal promising system performance in terms of a surgical handling and validity of the system in the clinical context. Concise data evaluation will follow.
Secondly, the Xin1 module for corrective osteotomies which has been developed with the clinical eyes of the AOTK Joint Preservation and Osteotomy Expert Group (JPEG) watching, is currently clinically tested at BGU Tübingen, Germany. The project is almost complete and preliminary results show that the Xin1 system is able to deliver a relevant intraoperative benefit to facilitate and improve corrective osteotomy treatment.

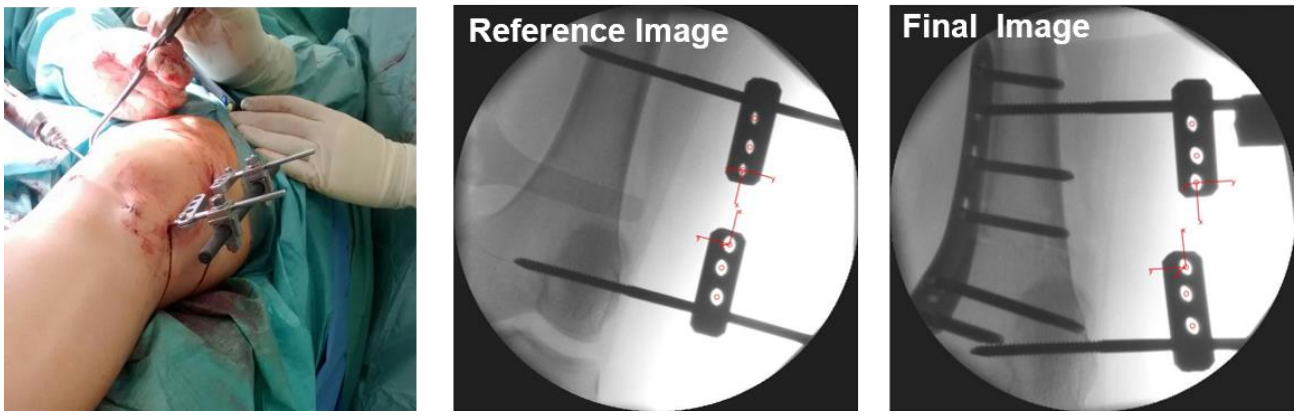


Figure 11.3.2 Xin1 module for corrective osteotomies in clinical trial (left). X-ray with Xin1 markers before correction (middle) and after correction (right).

Pres:
Grünwald L, Buschbaum J, Lobenhoffer P, Windolf M, Schröter S. X-Ray based navigation system for torsional correction - first clinical data. DKG. 2017 (oral).

Knierzinger D, Buschbaum J, Konschake M, Richards R G, Blauth M, Windolf M. Ex-vivo evaluation of a novel system for implant positioning assistance at the proximal humerus using angular stable plates. DGfB. 2017 (poster).

Buschbaum J. AO implant positioning assistant - placing implants safe and sound. Smart Surgery Symposium. EORS. 2017 (oral).

Partners:

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

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

Problem: The aim of fracture reduction and corrective osteotomies is to restore normal bone, joint and limb anatomy. However, the target alignment is usually unknown intraoperatively and thus 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 and facilitate femoral osteosynthesis and osteotomy planning.
Results: A concept was developed to enable selection of anatomical landmarks from X-ray images and calculate the length and anteversion of an intact femur. X-ray images of explicit anatomical regions were taken in different planes and specific anatomical landmarks were selected manually. Three-dimensional position of the anatomy was computed by means of a custom-designed marker bar enabling calculation of the bone length, bone axis and anteversion. These parameters may then be mirrored to determine the anatomical target alignment of the injured or misaligned limb.
The precision of the method was tested using a phantom model. X-ray images from different C-arm positions and orientations were taken. The deviations of length and angle were evaluated to be 0.67 ± 0.33 mm (mean ± SD) and 0.26 ± 0.26°. Following, feasibility of the system was proven using 16 human cadaveric femora. Length and anteversion were determined and compared to results from CT measurements, with deviations of lengths and angles 2.5 ± 1.39 mm and 1.98 ± 1.07°. These residuals are considered as clinically acceptable.

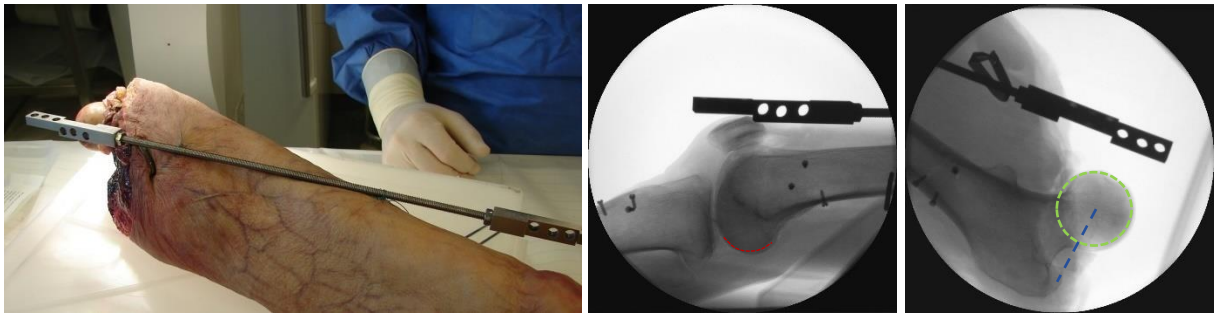


Figure 11.3.3: Method for intraoperative determination of anatomical parameters. Prototype of the marker bar (left) and selection of anatomical landmarks (middle and right).

Partner:

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

Influence of temporal fracture mechanics modulation on bone healing (ActiveFix) (Ongoing) (J Barcik, 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 suggest that fracture stimulation in an early post-operative phase could be of high importance for robust and timely healing.
Goal: To apply in an in vivo large animal setting an implant system for investigation of immediate versus delayed mechanical fracture stimulation. For this purpose, a recently introduced experimental two-defect fracture model (QUT, Brisbane, Australia), implementing an actuator driven external fixator for execution of arbitrary stimulation protocols to the fracture site which are completely independent from the functional loading of the animal, will be improved and adapted.
Results: A design refinement loop was conducted to improve the mechanical and electrical performance of the active external fixator. In vitro tests were performed to verify robustness and validity of the control algorithm and data acquisition system. After successful in vitro testing, the active fixator was implanted in two pilot sheep. Two different postoperative stimulation protocols were applied to the animals to mimic early and delayed weight bearing. Both sheep tolerated the fixation well and the system kept functioning over the whole course of the experiments. Preliminary test data is currently evaluated.

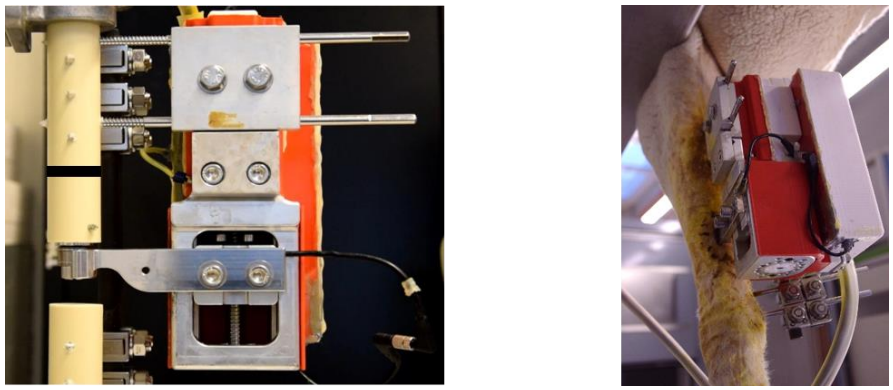


Figure 11.3.2: Setup with the active external fixator on an artificial bone (left) and in on an in vivo sheep tibia (right). Axial interfragmentary motion is applied to the mobile fragment through a lever arm with force sensor.

Partners:

- Epari D, Queensland University of Technology (QUT), Brisbane, Australia
- Dlaska C, Charitè UM Berlin, Germany
- Lubieniecki M, AGH University of Science and Technology, Krakow, Poland

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

Problem: Most of bone fractures heal following plate fixation. However, healing complications may still occur in approximately 10% of the cases whereof a significant portion can be attributed to unfavorable mechanical conditions at the fracture site. Furthermore, prolonged recovery times with limited limb function impact ability to work and contribute to lost productivity. Current fracture fixation plates have principally not changed for decades. Their design permits substantial variance in construct stiffness. Moreover, state of the art plates are prone to catastrophic failure either in the early post-operative phase from excessive loading or in the late phase due to fatigue in combination with inadequate healing and load sharing.
A new plating concept, biphasic plating, was proposed by ARI in collaboration with QUT (Brisbane, Australia) to enhance the existing treatment modalities of splinting and flexible fixation by redesigning of the conventional bone plate.
Goal: To test the feasibility of the biphasic stabilization principle in vivo in a large animal model.
Results: Ongoing pre-clinical experiments in a sheep tibia defect model under varying fracture conditions as well as under varying functional loading demonstrate robust callus formation with a specially designed biphasic plate compared to a control plate. Moreover, no biphasic plate deformation or failure were observed under full weight bearing for 12 weeks in 30 animals. This project is believed to deliver important information to estimate the potential of the new stabilization concept for human application.

Pres:

Hofmann-Fliri L. Biphasic Plating – a novel fixation concept to enhance mechanobiological fracture healing. Smart Surgery Symposium. EORS. 2017 (oral).

Partners:

- Epari D, Queensland University of Technology, Brisbane, Australia
- Schütz M (Prof), Charité UM Berlin, Germany and Queensland University of Technology, Brisbane, Australia

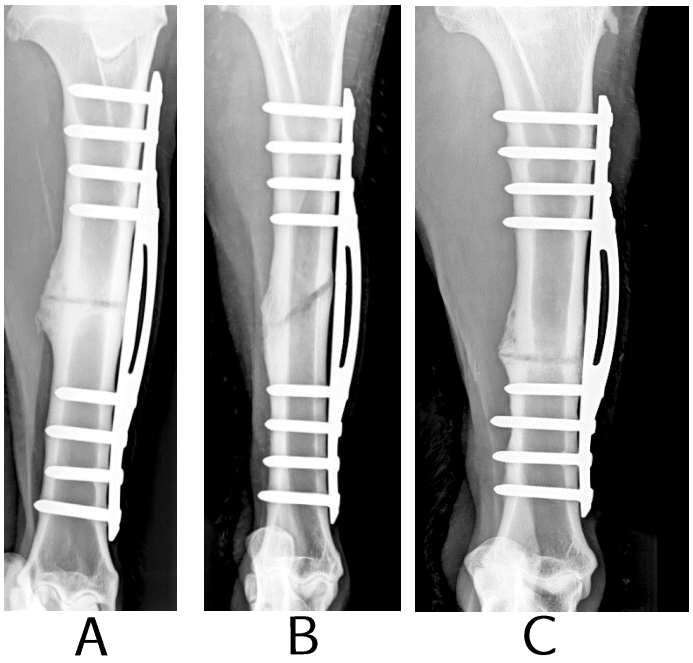


Figure 11.3.3: Biphasic plating shows robust callus formation under varying fracture conditions: A – 2mm transverse centered osteotomy; B – 2mm oblique osteotomy; C – 2mm transverse offset osteotomy)

A novel concept for guided bone 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 where the growth is guided by temporarily blocked physis. Currently utilized implants have their disadvantages. They are not 'passively' safe and require timely surgical intervention (removal), because ongoing growth leads to steady rise of the reaction force of the fixation, and thereby to plate and screw deformation with consequent devastating events such as implant breakage or growth arrest. To avoid these issues, a new implant concept for guided bone growth regulation was developed in ARI. The implant is designed to be 'passively' safe, capable of applying constant force to the physis, and hypothesized to allow a controlled regulation of the growth.
Goal: To test the functionality and efficacy of the new implant concept in an in vivo large animal experiment.
Results: Eighteen lambs were treated with the proposed implant prototypes in a hemi-epiphysiodesis setting to create varus deformity. The animals were assigned into three force level groups (60 N, 120 N and 200 N implant force). The achieved deformity was assessed by the change of the medial proximal tibial angle measured on two-week radiographs. Significant differences were detected between all three groups, whereby the highest deformity was achieved with the 200 N implant, followed by the 120 N one. Almost no effect was observed with the 60 N implant. The results show that a regulation of the growth is feasible when applying the new implant concept. Moreover, no implant related issues, such as screw bending or breakage were observed. This project provides important and currently missing information to expand the knowledge on bone growth processes and improve the treatment of limb deformities.

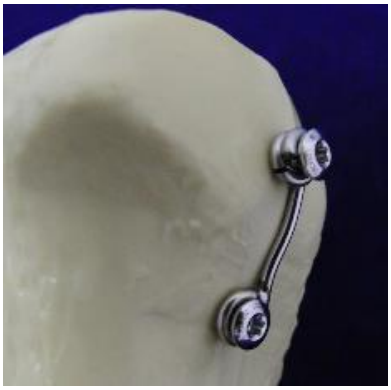


Figure 11.3.4: Implant prototype, capable of applying constant force to the physis, mounted on a plastic bone.

Partner: Slongo T, Children's University Hospital, Bern, Switzerland

Bone targeted delivery of antibiotics (TargetOS) (D Eglin, TF Moriarty)

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 shortcome 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 (Figure 11.3.5). 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.

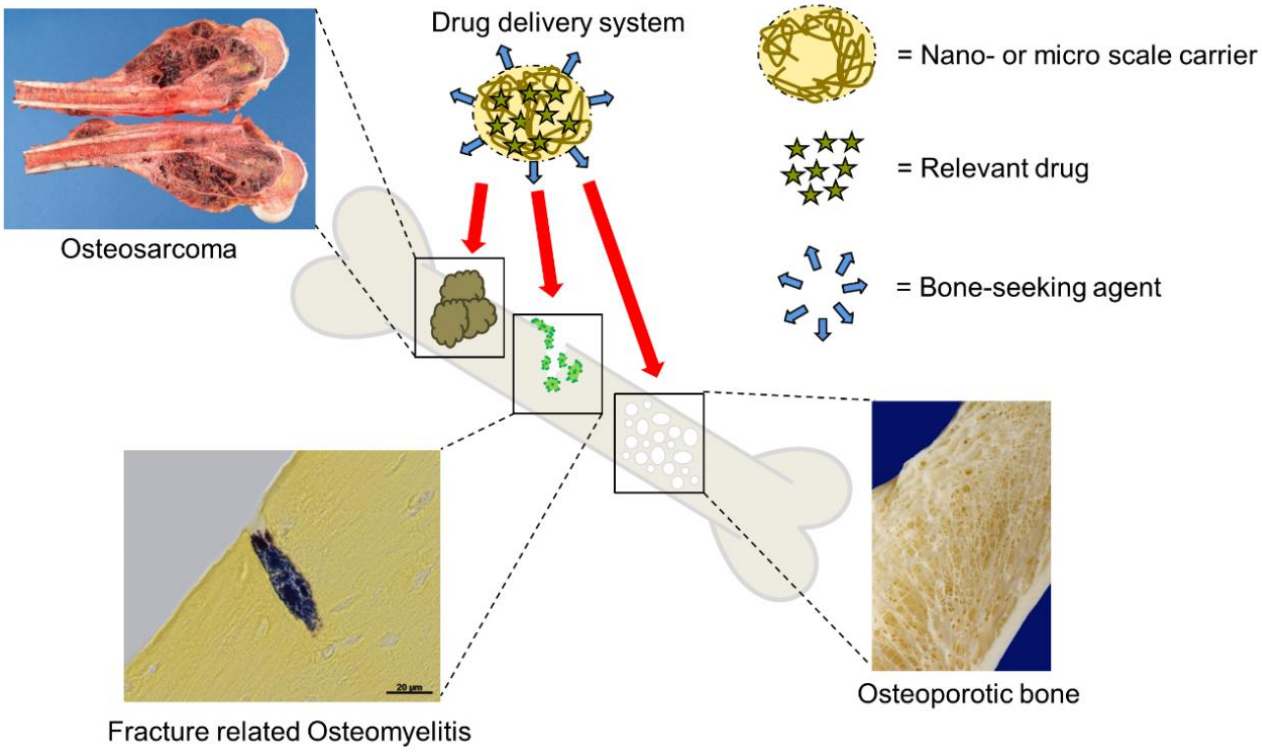


Figure 11.3.5: Drug delivery systems functionalized with bone mineral seeking agents for bone targeted therapeutics (from Rotman et al. 2017).

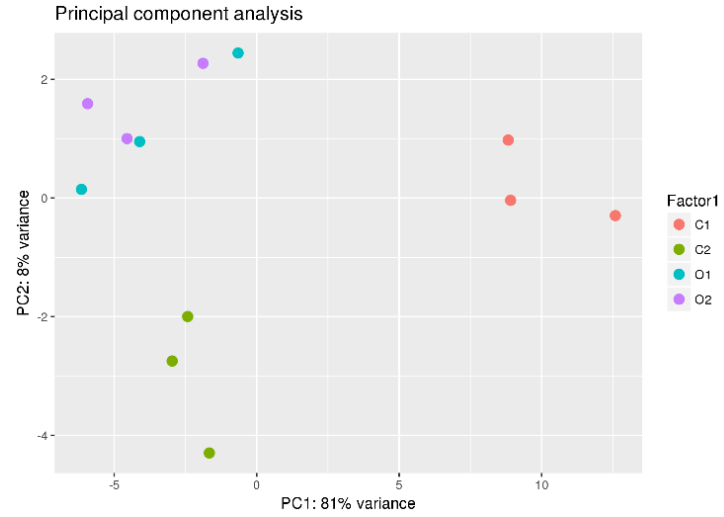
Pres:
Rotman, Grijpma et al. 2017, Rotman, Grijpma et al. 2017, Rotman, Grijpma et al. 2017

Pub:
Rotman, Grijpma et al. 2017

Partner:
- Grijpma D (Prof), University of Twente, NL

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

Biomarkers predictive of fracture healing outcomes would provide a useful tool to allow 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 behavior. 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 signaling 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. We have identified a number of miRNA targets that are regulated during early osteogenesis.



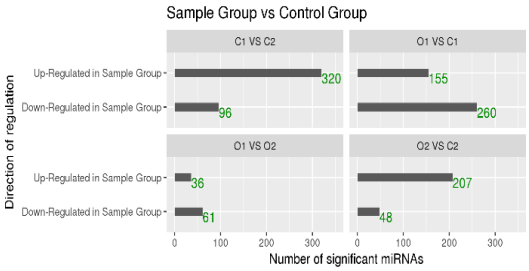


Figure 11.3.6: Principal component analysis showing miRNA expression patterns based on time of osteogenic induction (Left). On Day 7 415 miRNAs are differentially regulated (right)

Partner:

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

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

Currently it is unknown how various co-morbidities, such as the presence of implant-related wear particles, or long-term drug treatments such as non-steroidal anti-inflammatory medications (NSAIDs), impact on implant-related bacterial infection. 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 a *S. epidermidis*-inoculated screw in the rat proximal tibia. Our recent work has demonstrated that the presence of titanium wear particles in the local vicinity of the screw appears to worsen the osteolytic damage resulting from *S. epidermidis* infection, potentially by interfering with host immune responses and/or by serving as an additional surface upon which the invading bacteria may form a biofilm.

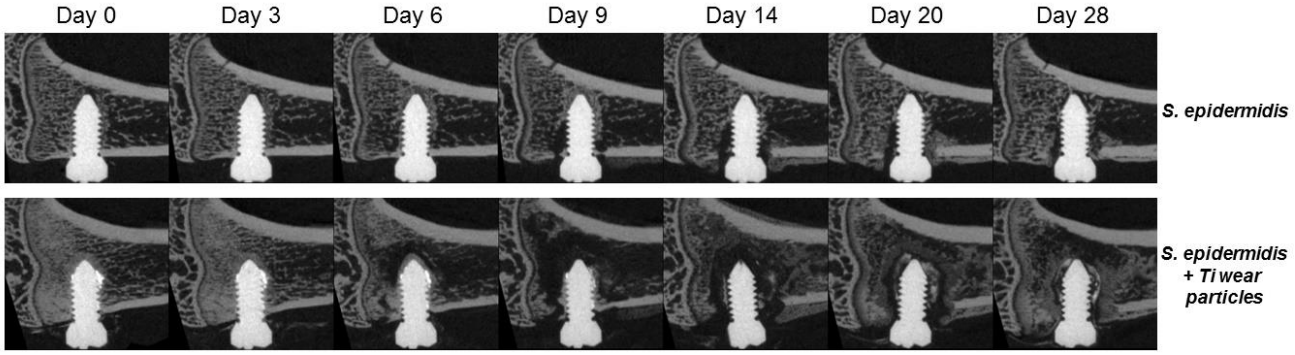


Figure 11.3.7: Time-course demonstrating bone changes resulting from the implantation of a S. epidermidis inoculated screw into the proximal tibia of a rat over a 28-day period. Typically, osteolytic changes can be observed around the screw within 6-9 days following implantation of the screw inoculated with S. epidermidis alone (top row). The addition of titanium wear particles to the screw hole (which can be easily observed as bright white regions around the screw threads at early timepoints, e.g. days 0-6) appears to exacerbate the osteolytic response to S. epidermidis (middle row).

Pres:
Stadelmann VA, Camenisch K, Thompson K, Eberli U, Zeiter S, Moriarty TF. A standardized rat model for monitoring bone changes in implant-related osteomyelitis with fully automated in vivo microCT image processing workflow. 2017 SSB+RM (oral)

Thompson K, Freitag L, Arens D, Eberli U, Camenisch K, Zeiter S, Richards RG, Stadelmann VA, Moriarty TF. Impact of low bone mass and anti-resorptive therapy on Staphylococcus epidermidis implant-related infection and response to antibiotic treatment. 2017 SSB+RM (poster)

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

The EpiLog project seeks to identify *S. epidermidis* immunogenic proteins in patients with *S. epidermidis* infection. This information will support the development of diagnostic assays for these patients, who often present with subclinical infection that may be a challenge to differentiate from aseptic complications. Seventy immunogenic *S. epidermidis* proteins were identified using plasma samples of *S. epidermidis* infected patients and/or experimentally infected mice. Seventeen of these were selected for recombinant production and applied in a 17-plex bead-based Luminex assay to quantify relative titers of specific antibodies in patients. The immunogenicity of all selected proteins was confirmed by the higher relative IgG titers than that of respective IgM subclass. Interestingly, we have identified a significantly elevated *isaA* specific antibody response in eight patients with single *S. aureus* bone infection relative to eight non-infected controls.

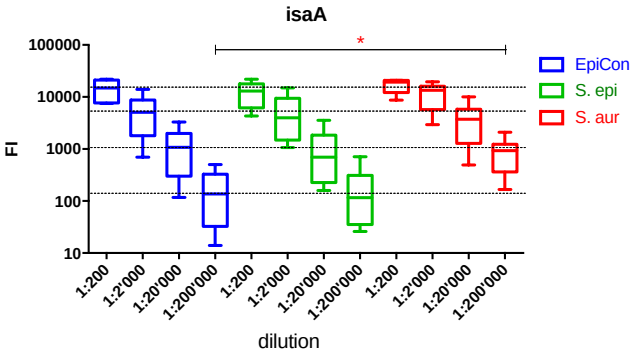


Figure 11.3.8: Relative isaA specific IgG response in plasma samples from S. epidermidis and S. aureus bone infected patients relative to non-infected (EpiCon) patient controls

Pres:
Stanic B, Konta M, Sabate Bresco M, Ladouce R, Mercep M, Richards RG, Moriarty TF. Identification of immunodominant peptides of *Staphylococcus epidermidis* origin in the bone infection of human patients and experimental mice. 11th World Immune Regulation Meeting, March 2017, Davos, Switzerland

Stanic B, Richards RG, O'Mahony L, Moriarty TF. Immunoregulatory mechanisms tailored by *Staphylococcus epidermidis in vitro*. 11th World Immune Regulation Meeting, March 2017, Davos, Switzerland

Stanic B, Morgenstern M, Thöny S, Konta M, Sabate Bresco M, Mercep M, Daiss J, Schwarz E, Richards RG, Moriarty TF. Identification of immunogenic peptides of *Staphylococcus epidermidis* origin in the context of bone infection using combined systematic immunoproteomics approach. Gordon Research Seminar - Staphylococcal Diseases: Staphylococci at the Host-Pathogen Interface, Aug 2017, Waterville Valley, NH, USA

Stanic B, Richards RG, O'Mahony L, Moriarty TF. Immunoregulatory mechanisms tailored by *Staphylococcus epidermidis in vitro*. Gordon Research Conference – Staphylococcal Diseases: Staphylococcal Biology, Pathogenesis, Infection and Treatment, Aug 2017, Waterville Valley, NH, USA

Assessing the Role of the Implant material and stability on the Development of Infection (Immunobact) (M Sabaté Brescó, TF Moriarty)

Instability of the bone after fracture is considered a risk factor for infection; however, little experimental data is available confirming this belief. In this study, a femur osteotomy murine model was used to investigate infection progression when fractures were fixed with rigid (stable) or flexible (unstable) implants. Implant-associated infection was caused inoculating *Staphylococcus epidermidis*, one of the leading etiologic agents for such infections. From day 7, mice with a rigid implant (stable) cleared the infection in a higher percentage compared to animals carrying a flexible implant (unstable). Inoculation of bacteria was associated with an increase of inflammatory markers (such as TNF-α or IL-6), which peaked at day 7. An increase of IL-17A+ cells was detected in local lymph nodes, especially in animals where bacteria were cleared. When using IL-17A KO mouse strain, it was observed that 100% of the animals remained infected at day 14 compared to 75% in WT. However, the differences were not significant, suggesting that IL-17A partially contributes to infection clearance but other factors are also involved.

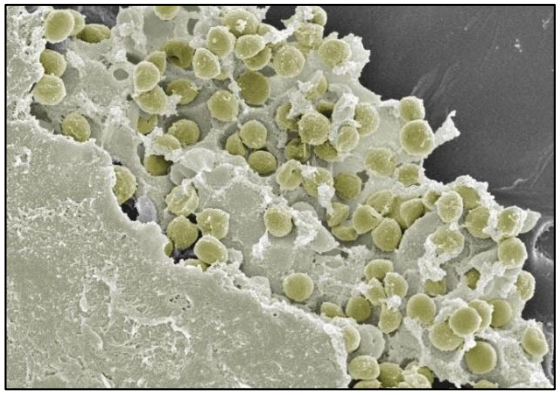


Figure 11.3.9: Staphylococcus epidermidis observed in a biofilm on the surface of an explanted fracture fixation device.

Pub:
Influence of fracture stability on *Staphylococcus epidermidis* and *Staphylococcus aureus* infection in a murine femoral fracture model. Sabaté Brescó M, O'Mahony L, Zeiter S, Kluge K, Ziegler M, Berset C, Nehrbass D, Richards RG, Moriarty TF. Eur Cell Mater. 2017 Nov 21;34:321-340.

Pathogenic Mechanisms and Host Interactions in *Staphylococcus epidermidis* Device-Related Infection. Sabaté Brescó M, Harris LG, Thompson K, Stanic B, Morgenstern M, O'Mahony L, Richards RG, Moriarty TF. Front Microbiol. 2017 Aug 2;8:1401.

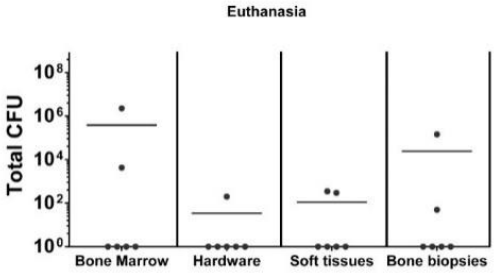
Partners:

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

MRSA infection in a large animal model: prophylaxis and treatment with local and systemic antibiotics (T Schmid, S Zeiter, W Boot, TF Moriarty)

Both one and two stage replacement of fracture fixations have a high reinfection rate, especially for infections caused by bacteria resistant to antibiotics. We have developed a two-stage exchange model with MRSA infection in sheep, which has recently been adapted to antibiotic treatment that is currently used in the clinics. In a pharmacokinetic and safety study (Figure 11.3.10), we measured local (ultrafiltration of intramedullary extracellular fluid) and systemic (serum) antibiotic concentrations after administration of vancomycin, rifampicin and cotrimoxazole. Local and systemic concentrations were reassured, and for vancomycin, the only antibiotic with a known serum target, we found the dose to be both well tolerated by the sheep and to fit within the therapeutic window. When treating the infection with this regimen in an additional series of sheep, a vancomycin and gentamicin-containing spacer was placed, and the sheep received IV infusions of vancomycin for two weeks followed by 4 weeks of rifampicin and cotrimoxazole infusions. After 2 weeks of an antibiotic free flush out period, the therapy was successful in 50% of sheep. Next steps will be to test the ARI hydrogel in this model.

Figure 11.3.10: Bacteriological results of the main study at euthanasia showed that three out of six sheep were culture negative.



Presentations/Posters

The European Bone and Joint Infection Society, Nantes, France, 07-09/09/2017. Local gentamicin delivery from a thermoresponsive hyaluronan hydrogel successfully treats a chronic implant-related infection in a single stage revision in sheep. Boot W, D'Este M, Schmid T, Zeiter S, Richards RG, Eglin D, Moriarty TF.

Treatment of chronic implant-related infection in sheep in a single stage revision by local gentamicin delivery with a thermoresponsive hyaluronan hydrogel. Swiss society for biomaterials and regenerative medicine 17-18/05/2017 St. Gallen, Switzerland. D'Este M, Boot W, Moriarty TF, Schmid T, Zeiter S, Richards RG, Eglin D.

Local antibiotic delivery with thermos-responsive hyaluronan hydrogel successfully treats chronic intramedullary nail-related infection in a single stage revision. TERMIS 2017, Davos, Switzerland. 26 – 30/06/2017. Boot W, D'Este M, Schmid T, Zeiter S, Richards RG, Eglin D, Moriarty TF.

Local Antibiotic Delivery With Hydrogels: Pre-Clinical Results Malaysian Orthopedic Association, Kuala Lumpur, Malaysia, 19-21/05/2017. Moriarty TF, Eglin D, Richards RG.

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

Antibiotic prophylaxis is critical for the prevention of fracture related infection (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 may be a particularly suitable means to apply the ARI gentamicin loaded thermoresponsive hydrogel. The ARI contaminated rabbit humeral osteotomy was modified to include two procedures, one to replicate the "accident" and contamination and a second to debride and irrigate the wound, and to fix a complete osteotomy. The results revealed that pre-hospital administration of systemic antibiotics significantly reduced the bacterial load in the operative field at the time of debridement compared to regular prophylaxis administered immediately prior to surgery. However, continuation of systemic antibiotics is necessary in order to prevent infection in this model.

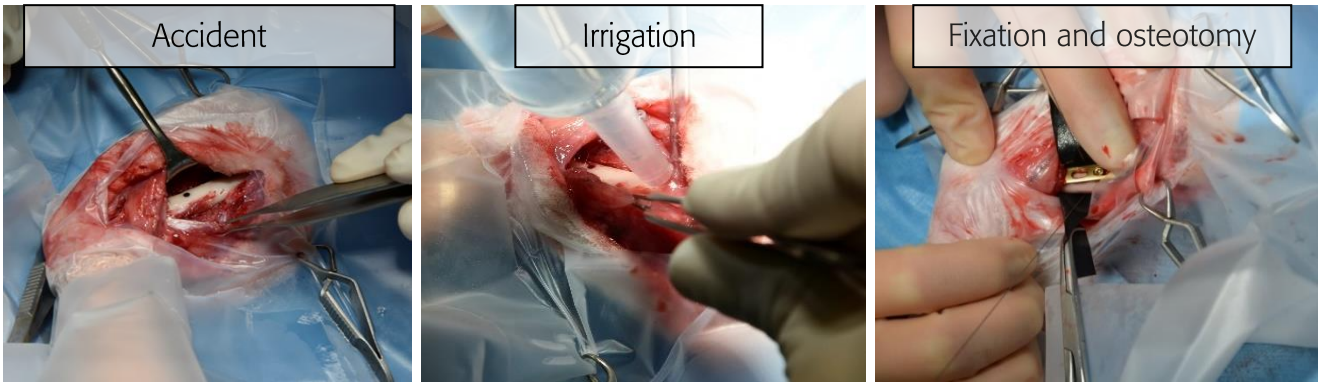


Figure 11.3.11: Intraoperative images of the rabbit model showing the "Accident" surgery. a. Drill hole acting as an open fracture. b Irrigation and cleaning of the wound and c, fixation and osteotomy.

Pres:
The European Bone and Joint Infection Society, Nantes, France, 07-09/09/2017. Pre-Hospital antibiotic prophylaxis reduces bacterial burden at time of debridement in a rabbit open fracture model. Vallejo A, Morgenstern M, Puetzler J, Arens D, Moriarty TF, Richards RG.

Investigating antibiotic efficacy and release patterns for treating implant-related bone infection (TF Moriarty, W Boot)

In treating an established infection, the amount and duration of antibiotic required to eradicate an infection remains somewhat poorly defined, with short (2 weeks) and long (many months) interval systemic delivery options commonly applied. Supportive local antibiotic delivery may influence the treatment outcome in conjunction with systemic antibiotic delivery, but the local concentration-time profile that most effectively eradicates the infection remains unknown. In this study we have begun to identify antibiotic release targets based on an *in vitro* biofilm model using human plasma to stimulate biofilm formation. Using this model, we have seen that burst release profiles, as may be achieved by conventional local delivery vehicles have little to no impact on biofilm viability. More refined exposure protocols will be required and are currently under investigation.

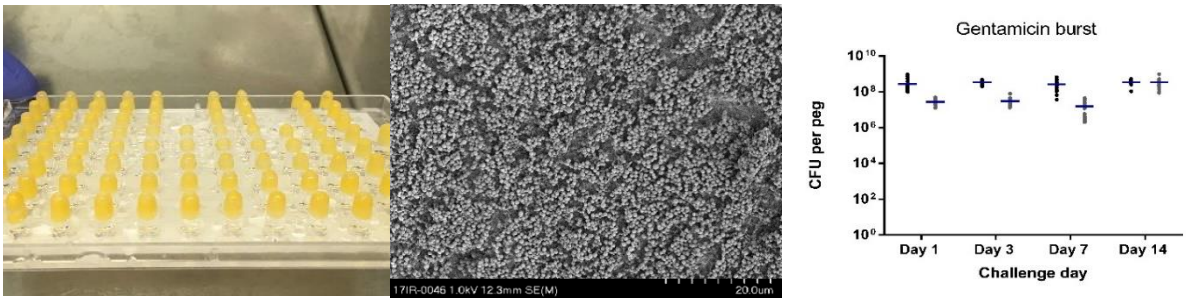


Figure 11.3.12: A 5-day old biofilm, grown in TSB + 1% human plasma was used for the challenge experiments. Left: 5-day old biofilm on an MBEC lid. Middle: SEM of a 5-day old biofilm of S. aureus. Right: Results of a challenge with gentamicin with a burst release pattern (black dots = negative control, grey dots = challenged biofilms).

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

In the StaphSeq project we have prospectively collected 104 *S. epidermidis* and 94 *S. aureus* strains from patients with implant related bone infection. 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 identified a number of factors associated with a poor clinical outcome. These were strong biofilm forming ability, the presence of the biofilm-associated *bhp* gene, the antiseptic resistance *qacA* gene (p=0.023), and *ccrB* and *ccrA* genes (p=0.034 and p=0.042, respectively)) The analysis of the *S. aureus* isolates is currently ongoing, with early data shown in the figure below. An increased prevalence of bacteriophage associated genes in the "not cured" outcome isolates is striking and will now be further analysed using PHASTER (PHAge Search Tool-Enhanced Release) in collaboration with external collaborators.

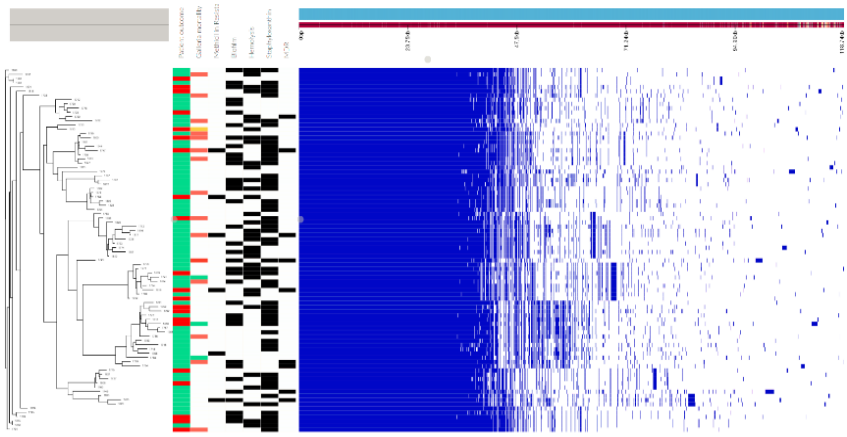


Figure 11.3.13: ROARY analysis of S. aureus genome in relation to selected outcome and analysis metrics. Images visualizes gene presence / absence in core & accessory genome linked to meta-data.

Pres:
Post V, Morgenstern M, Harris L, Mageiros L, Hitchings MD, Meric G, Pascoe B, Sheppard SK, Richards RG, Moriarty TF. Phenotypic and genotypic characterization of *Staphylococcus epidermidis* from orthopaedic device-related infections correlated with patient outcome. 2017 EBJIS (oral)

Pub:
Post V, Harris L, Morgenstern M, Mageiros L, Hitchings MD, Meric G, Pascoe B, Sheppard SK, Richards RG, Moriarty TF. A comparative genomics study of *Staphylococcus epidermidis* from orthopedic device-related infections correlated with patient outcome. J Clin Microbiol. 2017; 55:3089-3103

Partners:
- Morgenstern M (MD), Kantonsspital Basel, Basel, Switzerland
- Erichsen C (MD), BGU Murnau, 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 - AOTrauma feasibility) (A Stylianaki, B Stanic, K Thompson, TF Moriarty)

Severe trauma has been shown to activate the immune system, which can result in an increased risk of multi-organ failure and sepsis. Our research question was whether trauma can also influence the risk of local implant-related bacterial infection in patients receiving implants for bone fracture fixation through effects on immune cell function. Nine polytrauma patients with an Injury Severity Score (ISS) >15 admitted to Thriassio General Hospital (Athens, Greece) provided serum samples at regular intervals post-admission (from days 0-7). Control sera was provided by 10 healthy human donors. No changes in phagocytic capacity were observed when human THP-1 monocytic cells were pretreated for 4h with either polytrauma (from days 0-7) or healthy sera following incubation with a 10:1 ratio of 1 micrometre fluorescently-labelled latex beads for 16h. Similarly, there was no difference in the internalization of fluorescently-labelled (pHrodo Green) *Staphylococcus aureus*

bacteria between the neutrophil-like differentiated PLB-985 (dPLB) cell line after treatment with either healthy donor sera or with polytrauma sera (days 0-7). However, despite having little effect on phagocytic capacity, treatment with polytrauma sera markedly decreased the ability of dPLB neutrophil-like cells to undergo an fMLP (N-formyl-met-leu-phe)-induced oxidative burst at all time points tested, although this was only significant at day 3 and day 5 ($P<0.05$). This reduction in neutrophil antibacterial function was also associated with profound decreases in a range of neutrophil-related markers in polytrauma sera, such as IL-8, IL-1alpha, MMP-8, Elastase-2 and myeloperoxidase, compared to levels observed in healthy donors. This study demonstrates that polytrauma patient sera contains factors impairing host neutrophil antibacterial efficacy through effects on production of reactive oxygen species as well as potential effects on neutrophil recruitment and activity. These inhibitory effects of neutrophil function may predispose polytrauma patients to an increased risk of implant-related infection.

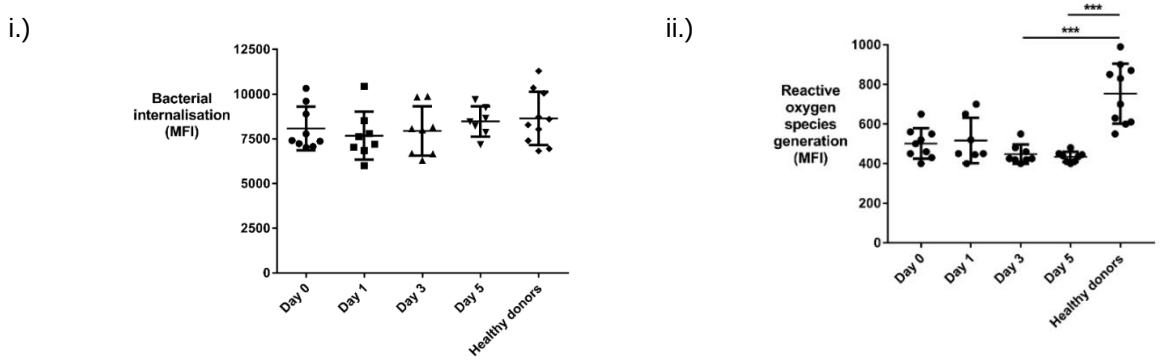


Figure 11.3.14: Effect of polytrauma serum on antibacterial properties of neutrophil-like differentiated PLB-985 cells (dPLB cells). dPLB cells were treated for 4 hours with either normal healthy donor serum or polytrauma serum (from days 0 – 5) before co-culture with either fluorescently-labelled S. aureus (left panel) or activation with the stimulatory peptide fMLP to induce an oxidative burst (right panel). Flow cytometric analysis of the dPLB cells was then used to quantify the extent of phagocytosed bacteria (left panel), or production of reactive oxygen species using CellROX reagent (right panel). Results show no effect on bacterial internalization (i), but a significant decrease in RS generation at all time points relative to healthy controls (ii).

Partner:

- Morgenstern, M (MD), Universitätsspital Basel, Basel, Switzerland

11.4 AOVET

Computational and experimental evaluation of hybrid non-locking and locking canine pancarpal arthrodesis plates (PancarFE) (I Zderic, H Noser, P Varga)

Problem: The most common procedure for canine pancarpal arthrodesis (PCA) relies on dorsal plating. However, it is related to some biological disadvantages inherent to soft tissue tension during wound closure. To address these limitations, a hybrid non-locking plate with tapered profile is one of the most frequently used implants to bridge the radius and the third metacarpal. Recently, two new tapered hybrid locking PCA plates were developed.
Goal: To compare the biomechanical competence of the hybrid non-locking and locking PCA plates in an artificial bone model.
Results: Eighteen artificial specimens, simulating radius, carpus and metacarpal bone, were instrumented with the three different plates and investigated mechanically under cyclic loading with the use of strain gauges. In addition, finite element analysis (FEA) was performed, mimicking the setup and loading conditions from the mechanical tests.
Peak plate strains were detected around the radiocarpal screw holes. Their magnitudes calculated by means of the FEA were in line with the experimental results. The measured differences in construct stiffness and peak plate strains between the plates were reflected in the FEA.
Partners:

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

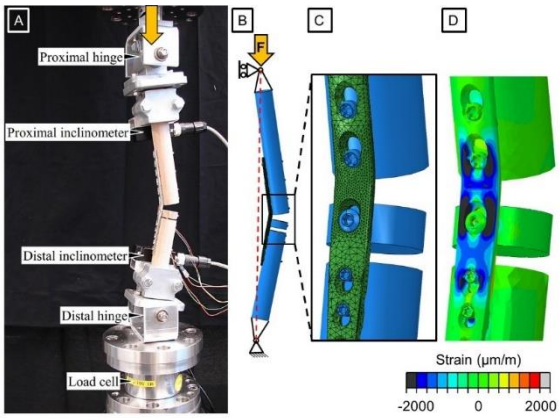


Figure 11.4.1: Setup with a specimen mounted for mechanical testing and a vertical arrow denoting the loading direction (A); computational model mimicking the test setup (B); magnified view of the finite element model (C); representative FEA results showing peak strains in the radiocarpal region of the PCA plate (D).

11.5 AOTK System

Influence of RIA reaming diameter on failure loads of human cadaveric femora (RIABiomech) (B Gueorguiev-Ruegg, D Gehweiler)

Problem: Treatment of large bone defects is still one unsolved problem in today's orthopedic and trauma surgery. Autologous bone grafting from the iliac crest is the current gold standard to manage such defects. The Reamer Irrigator Aspirator (RIA) technique is applied for minimally invasive bone graft harvesting by reaming of the medullary femoral canal. In contrast to bone graft harvesting from the iliac crest this procedure allows, besides other advantages, extraction of large bone graft amounts. However, some postoperative femoral fractures have been observed after RIA and the reaming diameter is one of the most discussed reasons for them.
Goal: To determine the influence of the reaming diameter on the decrease of bone strength and analyze the 3D morphology of the reaming and fracture pattern in human cadaveric femora using a recently developed RIA system.
Results: Forty-five human cadaveric femoral pairs were randomized to three groups with 15 pairs each. Within each pair, one of the specimens was randomly reamed with either 1.5 mm (group 1), 2.5 mm (group 2) or 4.0 mm (group 3) larger diameter than the isthmus, while its contralateral part was left intact without reaming. Following, all specimens were quasi-statically tested to failure in internal rotation under 750N axial load. Reaming and fracture morphology was analyzed by means of CT scanning.
Results: Torsional stiffness decreased significantly after reaming in group 3, but not in groups 1 and 2. Torque at failure revealed decrease after reaming in all 3 groups. Regardless of the reaming diameter, the biggest relative decrease in femoral shaft wall thickness occurred medially between the second and fourth eighths of the femoral shaft. As the diameter of reaming increases, an overlap of the fracture line with the region of maximal wall thickness decrease becomes more frequent. Reaming with 4mm should be considered as critical.

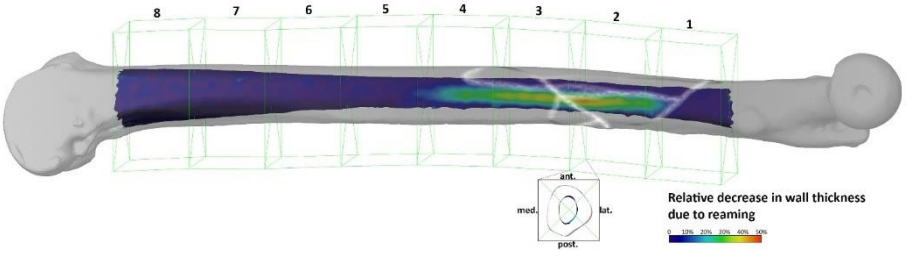


Figure 11.5.1: Medial view of a reamed femur with gray transparent outer surface, color coded amount of reaming from the medullary canal, and white lines on outer surface representing the fracture pattern.

Partners:

- Raschke MJ (Prof), University Hospital Münster, Münster, Germany
- Wähnert D (PD), University Hospital Münster, Münster, Germany

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 limited value of radiographic methods. A novel approach to continuously measure both fracture healing and patient activity has been recently developed in ARI. First clinical data collection was completed using a prototype device designed for healing assessment in patients treated with external fixation.
Goal: To extend clinical data collection and strengthen the clinical value proposition of the AO Fracture Monitor. Development of an implantable version to be pursued.
Results: The AO Fracture Monitor was further refined in terms of performance, size and energy consumption. Now it incorporates smartphone connectivity. The system was extensively tested and showed reliable performance in combination with standard locking plates and external fixators. An Android smartphone application was developed for communicating with the implant, as well as for automatic data download which could be performed by the patient from home. Two pilot animals were operated with instrumented locking plates. For the next clinical trial phase on external fixation, patient recruitment will start in spring 2018 at BGU Tübingen, Germany. The trial will include ten patients to be monitored for a follow-up period of up to twelve months. During the first 4 months, patients will additionally be equipped with sensor insoles. An AO Development Incubator project was recently initiated to pave the path for translation of the concept into clinical routine.

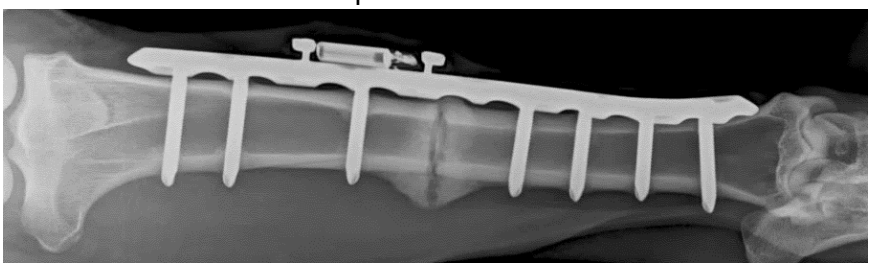


Figure 11.5.2: Sheep tibia with instrumented plate.

Pres:
Ernst M. AO fracture monitor – objectively assessment of bone healing, Smart Surgery Symposium. EORS. 2017 (oral).

Partners:

- Döbele S, BG Unfallklinik Tübingen, Germany
- Höntzsch D (Prof), BG Unfallklinik Tübingen, Germany
- Pohlemann T (Prof), UK Homburg, Germany

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

Problem: It's still unclear whether the quality of fracture reduction or the injury/fracture severity has the highest impact on the clinical outcomes. Goal: To develop a workflow in order to identify objective fracture severity criteria and the most important predictors of the functional outcomes following pilon fractures. Results: A computer tool, developed in a previous project phase, was used to assess 71 CT scans obtained from a multicenter study of the AOTK Lower Extremity Expert Group. Fracture severity of the clinical cases was assessed by three different expert surgeons and subjected to the computer tool for analysis by means of Artificial Intelligence techniques. A series of 37 different CT features were extracted and considered for evaluation. A prediction model was developed generating results comparable to the experts' assessment. All CT data were successfully processed and analyzed with identified severity features. The number of fracture segments was identified as one of the most important features contributing to fracture severity.

Partners:

- Rüedi T (Prof), AO Foundation, Davos, Switzerland
- Stoffel K (Prof), Kantonsspital Baselland, Liestal, and University Basel, Basel, Switzerland
- Nork SE (Prof), Harborview Medical Center, Seattle, USA
- Graves M, University of Mississippi Medical Center Jackson, Mississippi, USA
- Sommer C, Kantonsspital Graubünden, Chur, Switzerland

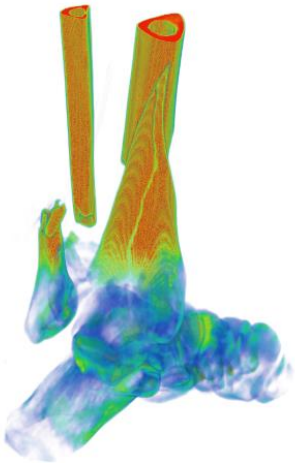
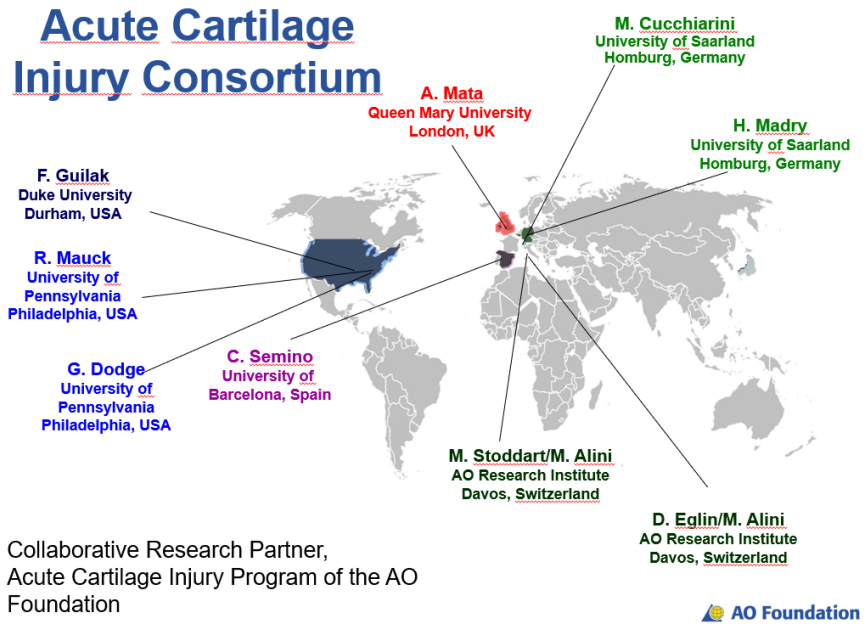


Figure 11.5.3: Volume rendering visualization of a given CT pilon fracture case.

11.6 ARI Exploratory Research

ARI Collaborative Research Program (CRP) Acute Cartilage Injury (ACI) (2011-2018)
A multicomponent repair device for the treatment of acute cartilage injuries

Acute cartilage injuries often result in cartilage degeneration and osteoarthritis, which are leading causes of disability. The avascular nature of cartilage coupled with the limited proliferative activity of mature chondrocytes severely impairs cartilage lesion healing.
The ARI sponsored ACI CRP aims to address this clinical need and to develop an off-the-shelf device that stimulates repair of acute cartilage injuries. A consortium of scientists and clinicians with complementary expertise embarked in 2011 on a repair strategy that combines state-of-the art material science, biomechanics, gene therapy, bioactive molecules and cells.
In the following years the consortium developed novel chondrogenic hydrogel biomaterials that can encapsulate cells and viral vectors. When combined with a newly developed 3D woven scaffold the device stays within the defect, supports joint loading, and through its biologically active components aimed to induce a repair. Pilot studies investigating various combinations of biomaterials, viral vectors and cells were carried out to select the most promising candidate devices and reduce the initial number of potential combinations.
In the final two years of the program (2016-2018) the consortium has been testing the most promising multicomponent repair devices, with or without an adeno-associated virus vector carrying the Sox9 gene, in a pre-clinical proof-of-concept minipig chondral defect model. Full thickness chondral defects were created in minipig femoral condyles to compare the experimental repair to the “gold standard” of microfracture. One group of animals compares the woven scaffold alone or in conjunction with a peptide-based or a hyaluronan-based hydrogel to facilitate chondrogenesis. A second group of animals additionally include gene therapy enhanced repair, where cells in bone marrow aspirates were virally transduced prior to implantation. Repaired defects will be evaluated after 12 months both histologically and biomechanically to compare their properties with those of authentic articular cartilage and with microfracture repair tissue. The final data set will be available in the summer of 2018.



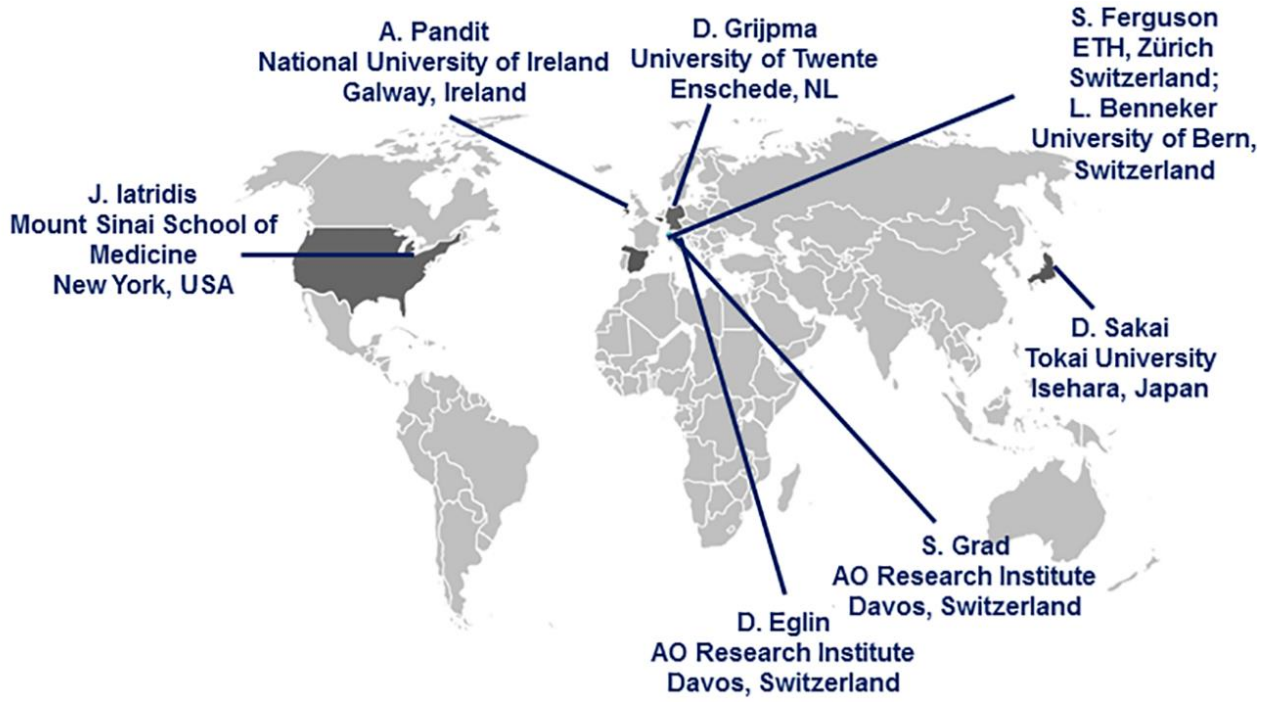
Collaborative Research Partner,
Acute Cartilage Injury Program of the AO Foundation

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

The program is coordinated by Sandra Steiner and guided and monitored by Mats Brittberg (clinician), Brian Johnstone and Peter Roughley (scientists) who report to the ARI AC.

ARI Collaborative Research Program (CRP) Annulus Fibrosus Repair (AFR) (2011-2018)

Intervertebral disc herniation is the most frequent pathological condition requiring spinal surgery, and its incidence is increasing in the Western world. Sustainable repair of disc lesions and of annulus fibrosus (AF) ruptures remain a substantial challenge in daily clinical practice. The goal of the CRP AFR is to develop implants that will enable the repair of the ruptured AF. Within the first years, consortium partners worked together to develop effective biomaterial and bioactive solutions for AF repair. Furthermore, pilot studies in ovine lumbar and cervical discs demonstrated the general feasibility of the implantation of combined consortium materials, including structured scaffolds, adhesive glues and closure membranes, into AF defects created with a biopsy punch. During the final period of the AFR Program, a pre-clinical proof-of-concept study was performed using the ovine full thickness cervical AF defect model. Two repair concepts, namely an "inert" and a "bioactive" treatment, were considered in individual groups of animals. For the inert concept, defects were treated with a Fibrin-Genipin glue according to the outcome of the pilot studies. Treated and untreated control levels were analyzed by computed tomography, magnetic resonance imaging, histology and biomechanically after termination of the study 12 months post-surgery.
Regarding the bioactive concept, in vitro and organ culture experiments were performed to identify the most suitable treatment group for the proof-of-concept study. The delivery of chemoattractant releasing hydrogels or autologous mesenchymal stem cells were tested in a pilot study on ovine cervical AF defects. All consortium partners are involved in the implant production, testing, the surgical procedure of the proof-of-concept study, and the final histological, biomechanical and imaging analysis. Valuable pre-clinical data on the safety and feasibility of inert and bioactive approaches to AF repair will be the primary consortium deliverable. The final data sets will be available in the summer of 2018.



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

The program is coordinated by Sandra Steiner and professionally guided and monitored by the CRP committee members Gunnar Anderson (clinician) and Peter Roughley (scientist) who report to the ARI AC.

ARI Collaborative Research Program (CRP) Osteochondral Defect (OCD) (2017-2020)

Osteochondral defects are still a major clinical challenge. They represent a large societal burden as they limit employment and impede daily life activities of millions of Europeans. Moreover, these injuries often lead to further degeneration of the joint, into a disabling disease known as osteoarthritis (OA). The defect bridges two major tissue types (cartilage and bone) that also have zonal structures within and specific healing capacities. Additionally, the cartilaginous surface must follow the patient specific contour of the surrounding tissue to avoid arthritic changes. To address these specific challenges, multilayered materials combined with cell-therapy have been proposed; however, the effectiveness of such approaches has not been validated due to lack of systemic and rational studies. Within this consortium (started in June 2017), we bring together multidisciplinary international expertise in materials, bioprinting, bioreactors, biomechanics, macrophages and animal models. These are combined using an additive manufacturing approach to produce constructs with precisely controlled internal architecture and the potential for patient specific implants. The consortium aims to systematically evaluate the influence of physical and chemical parameters on cartilage repair. In addition, as the immune response and inflammatory environment is known to directly influence the repair tissue produced, the effect of the material combination on macrophage behavior will be investigated. Rational scaffold design will be further enhanced by incorporation of bioactive molecules to modulate inflammation. Furthermore, through the use of common methodologies aiming to predict chondrogenic outcomes, in vitro and with the use of multiaxial bioreactor developed at the ARI, we aim to improve the implant design process. The bioreactor and the culture models that include multiple tissues of the joint complete with immune cells can be used to reduce in vivo experimentation along 3R Principles.

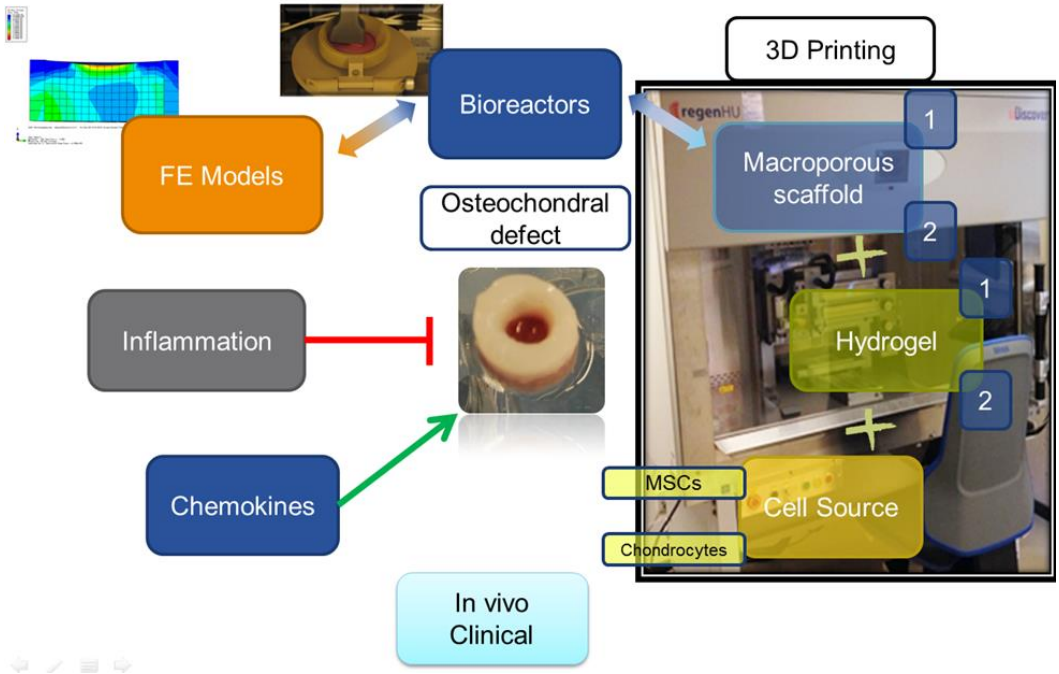
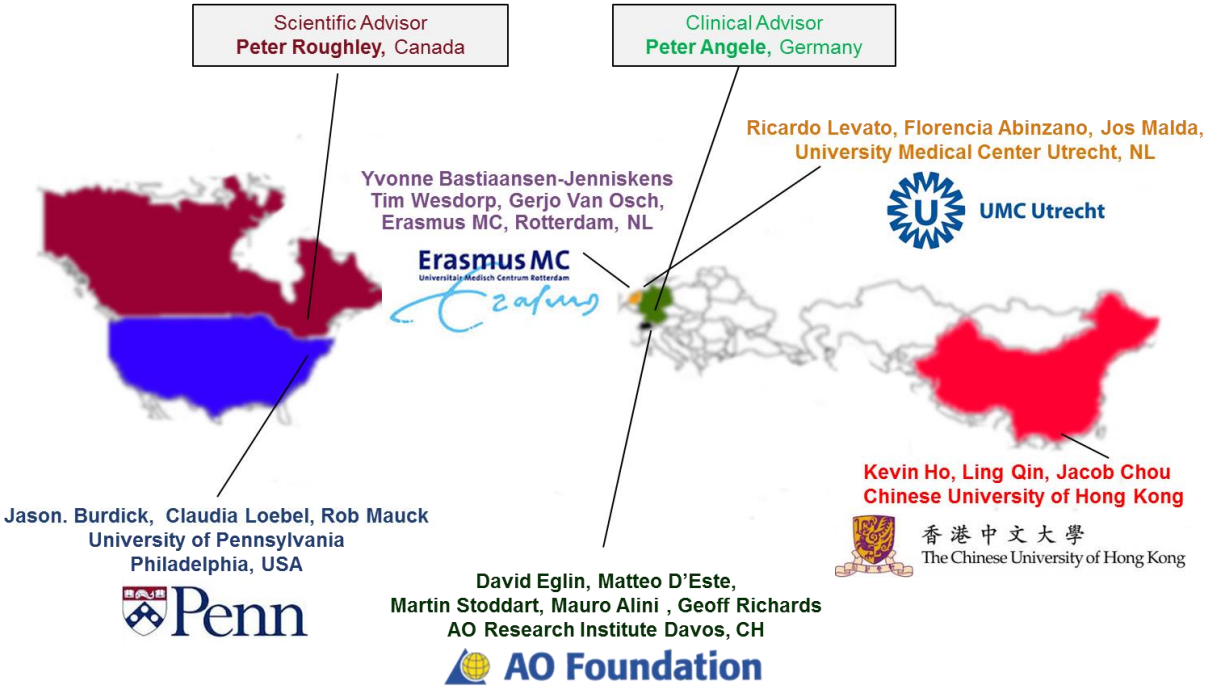


Figure 11.6.1: ***Overview of consortium plan,*** *which encompasses expertise in hydrogels and elastomers, fiber reinforcement of hydrogels, macroporous scaffolds, understanding the chemokine/inflammatory environment, and bioreactors. The Partners will work together towards the common goal of an osteochondral defect, using cells, materials and bioreactors for construct optimization.*

To promote youth and develop their careers, the team is composed of young PI's supported by experienced Co-PI's as well as several PhD students and postdocs.
Prof. Jason A. Burdick, PhD is a Professor of Bioengineering at the **University of Pennsylvania**, US; Co-PI: **Prof. Robert L. Mauck**. Dr. Burdick's research involves the development of hydrogels for various biological applications and his laboratory is specifically interested in understanding and controlling polymers on a molecular level to control overall macroscopic properties. Dr. Burdick uses his expertise in hydrogel design to construct improved hydrogel bioinks for printing of the cartilage constructs.

Dr. Riccardo Levato is associate professor at **Utrecht University**, NL; with strong expertise in bioprinting, biomaterials, stem cell culture and hydrogels for bone and cartilage regeneration, Co-PI: **Prof. Jos Malda**. His current research focus in on the generation of mature and functional cartilage grafts via biofabrication and progenitor cell-supporting bioinks. Dr. Levato brings his expertise of biomaterials, bioprinting and chondroprogenitors to the project.
Prof. Dr. Kevin Ho MBChB, MSc, FRCS (Tr&Orth) is an Assistant Professor at the Department of Orthopaedics and Traumatology at the Prince of Wales Hospital and **The Chinese University of Hong Kong**; Co-PI: **Prof. Ling Qin**. His major research interests lie in Arthroplasty, Traumatology, Lower Extremity Surgery and Degenerate Joint Condition. Dr Ho has been working on advanced treatment of osteoarthritis in both basic science in-vitro and in-vivo research. He has also pioneer a clinical trial using mesenchymal stem cells therapy on osteoarthritis in Hong Kong. He brings is clinical and translational expertise to the consortium in addition to the 3D print of construct for bone repair.
Dr. Yvonne Bastiaansen-Jenniskens, Assistant Professor, **Erasmus MC**, NL; Co-PI: **Prof. Dr. Gerjo van Osch**. Her interest is in examining the involvement of macrophages in orthopaedic (related) subjects. Dr. Bastiaansen will bring her expertise on macrophage cultures, the response of macrophages to biomaterials and co-culture between macrophages and other cell types in this consortium as well as expertise on cartilage tissue engineering and specifically MSC chondrogenesis in hydrogels, integrative cartilage repair and inflammatory cytokines and cartilage generation.



The ARI is coordinating and contributing to this joint effort under the guidance of Prof Mauro Alini and Prof Geoff Richards. The whole consortium is managed by Dr David Eglin, with scientific support from Prof Martin Stoddart, Principal Investigator responsible for the Stem Cell Focus Area. In 2017, the consortium was monitored by Prof Peter Roughley from the McGill University, CN and Prof James Richardson from the Robert Jones & Agnes Hunt Orthopaedic Hospital, NHS Foundation Trust, Oswestry, UK.

Generic Asian pelvic bone model – AO Strategy Fund project (PelBone) (Ongoing) (B Gueorguiev-Rüegg, H Noser, L Kamer)

Background: Human bones exhibit complex variations in size and shape across individuals and demographic populations. Due to the growing surgery demands in the Asian region the education of orthopedic trauma surgeons has to be more specific to their needs. Currently, the available bone models for training and education do not properly represent the Asian population and the majority of anatomical aids are based on European and Caucasian morphology. However, they are often disproportionate and difficult to apply to Asian patients. Moreover, the same limitations are directly applicable to osteosynthesis constructs that require both implant and bony morphology to be considered. Therefore, specific Asian bone models are needed for training with implants and surgery technics. This is particularly true for the complex anatomy of the pelvis.
Goal: To develop a generic hardware Asian pelvic bone model as a base for training, education and further development of more anatomically correct Asian implants.
Results: Based on 100 CT scans of an Asian population collective, consisting of the three major ethnic groups in this area, namely from Indian, Chinese and Malay descent, acquired by the University of Malaya, a statistical pelvic bone model was developed and designed in ARI, followed by evaluation and creation of an average computer Asian pelvic bone model considering both genders. The corresponding data files are sent to SYNBONE for development of an anatomically correct generic hardware Asian pelvic bone model.

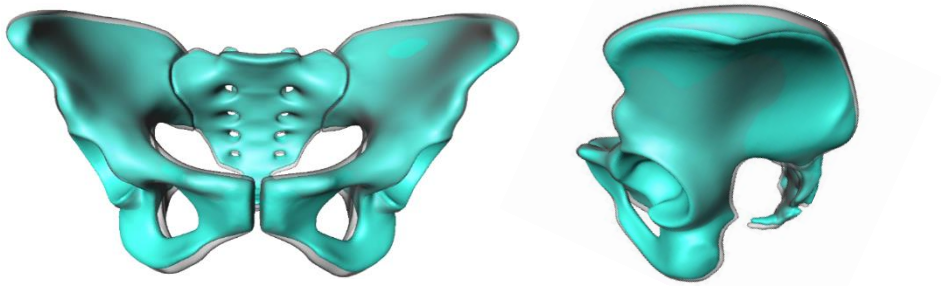


Figure 11.6.2: Anteroposterior (left) and lateral (right) views of the overall (female plus male) Asian pelvic mean model (semi-transparent grey) with its female mean submodel (green) superimposed.

Partners:

- Sri T (Prof), University of Malaya, Kuala Lumpur, Malaysia
- Kamarul T (Prof), University Malaya Medical Center, Kuala Lumpur, Malaysia
- Shanmugam R, Department of Orthopedic Surgery, University of Malaya, Kuala Lumpur, Malaysia
- Burr F, SYNBONE AG, Malans, Switzerland

SmartDrill: 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 screws 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 for screw length measurement after drilling has been reported to often lead to selection of wrong screws, whose replacement increases surgery cost, time and radiation dose. These limitations could be overcome with a newly invented Smart Drill concept, which allows measurement of the actual drill depth directly during drilling and detection of the required screw length on the fly.
Goal: To develop and test a laser-based smart add-on device prototype monitoring the actual drill depth and providing an automated estimate of bicortical screw length for plate osteosynthesis of long bone fractures.
Results: A novel detection algorithm was developed and implemented. Given the encouraging results and acceptance of the previous prototype, a new version of the device was developed with significantly reduced size and component costs. Its performance was tested on artificial and human cadaveric bones. Transfer of the concept into clinical practice is underway.

Figure 11.6.3: The previous (left) and new (right) SmartDrill prototypes mounted on a surgical drill.

Pres:
Windolf M, Varga P, Varjas V, Gehweiler D, Grünwald L, Richards RG, Schuetz M. AutoGauge - screw length estimation from bone drilling characteristics. EORS. 2017 (oral).

Partners:
- Schütz M (Prof), Charité UM Berlin, Germany

Investigation of fentanyl plasma levels after application of a fentanyl patch in three different locations in order to refine postoperative pain management in rabbits (Fentaloc) (V Riehl, D Arens, S Zeiter)

With this study we sought to investigate three different localizations (neck, inner and outer ear) for fentanyl patch application to provide adequate and reliable pain control. Apart from practical aspects, the absolute concentration of fentanyl was measured in the rabbits' blood plasma via a commercially available ELISA. Based on data from human patients, a Fentanyl plasma level of more than 0.5ng/ml was considered to be analgesic.
18 animals (New Zealand White Rabbits) were equally allocated to the three groups. Preparation was done with a strict protocol to avoid deviations due to differing preparation. Blood samples were taken at different time points for determination of plasma fentanyl concentration. During the study, rabbits were assessed for their general conditions and practical aspects were rated.
In rabbits with the patch in the neck, levels of more than 0.5ng/ml were measured in all rabbits between 6 and 72h. On the outside of the ear pinna a level comparable to this was reached from 9 to 48h in all animals after patch attachment. The threshold of 0.5ng/ml was not reached by all animals of the inside-ear group which portended an insufficient plasma level. Evaluation of the practical aspects indicated the best results in this group, whereas attachment in the neck caused the most effort and problems by clipping thin and dense fur.
In conclusion, the neck and outside of the ear are appropriate locations for fentanyl patch application in rabbits. For longer application the neck is recommended, whereas for shorter application the outside of the ear pinna might be more practical.

Thesis:
Riehl V: Investigation of fentanyl plasma levels after application of a fentanyl patch in three different locations in order to refine postoperative pain management in rabbits - Dr med vet Vetsuisse Faculty University of Bern (in preparation)
Pub:
Riehl V, C Deimling, H Rohrbach, C Spadavecchia, S Zeiter. Investigation of fentanyl plasma levels after application of a fentanyl patch in three different locations in order to refine postoperative pain management in rabbits (in preparation)

Partner:
- Rohrbach H (Dr med vet) and Prof C Spadavecchia, Vetsuisse Faculty, University of Bern, Switzerland
- Spadavecchia C (Prof), Vetsuisse Faculty, University of Bern, Switzerland

Accuracy of healing outcome prediction is influenced by plate fixation stiffness and defect size in a rat femoral osteotomy model (Immunosup) (Ongoing) (M Hildebrand, K Thompson, S Zeiter)

Although a variety of risk factors have been identified that predispose to an increased risk of developing delayed bone healing or non-union, it is currently not possible to identify specific at-risk patients at an early stage. We therefore sought to establish a pre-clinical model with predictable healing outcome, to allow the early identification of delayed healing animals using microCT imaging. Our previous work using a rat femoral osteotomy model identified poor healing responses when a 2mm osteotomy was internally fixated using a 2 mm PEEK plate. The aim of this study was to compare the impact of different plate stiffnesses (2 mm vs 1.25 mm PEEK plate), and the influence of gap size (2 mm vs 1 mm) on healing outcome in this model. Healing outcome was determined using longitudinal in vivo microCT scanning.
Our findings demonstrate that, while healing outcome for the 2-mm defect was consistently poor (1/7 animals healed within 14 weeks), reducing the plate stiffness improved rates of bridging and the kinetics of bone formation in the defect site. Interestingly, the ultimate healing response of the 2mm defect could be accurately predicted as early as 4 weeks, which was independent of the plate fixation stiffness. Regarding the smaller 1mm gap, the 1.25 mm plate had improved healing outcomes compared to the 2-mm plate, although it was not possible to accurately predict healing outcome at 4 weeks. Further studies involving histological analysis to confirm the healing status of individual animals is currently ongoing.

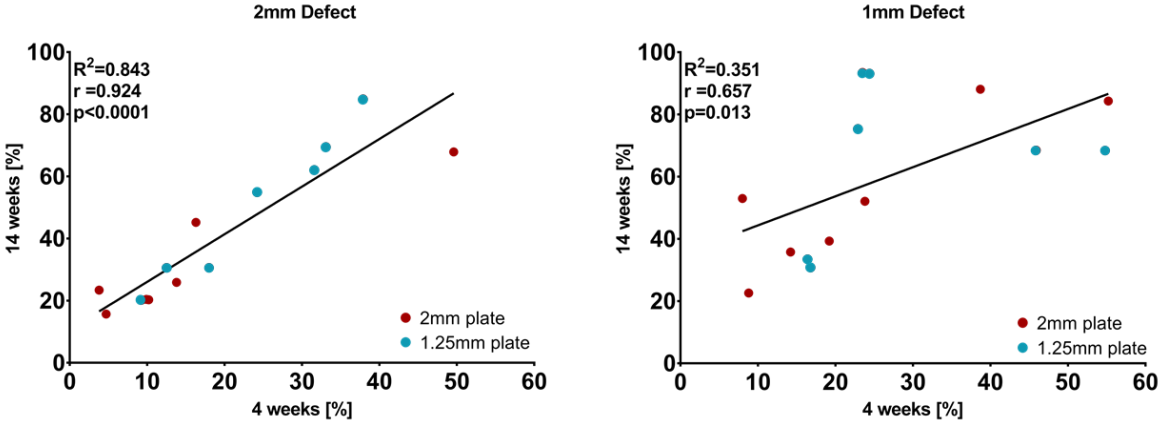


Figure 11.6.4: Correlation of bone formation as the percentage of the osteotomy gap filled at 4 weeks (x axis) with overall bone formation after 14 weeks (y axis), for all animals with the 2mm defect (left panel) or 1mm defect (right panel). The red dots indicate data from animals which received the 2mm plate, blue dots indicate the 1.25mm plate.

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

Stem cells have shown regenerative effects in degenerative intervertebral discs (IVDs). Homing of human mesenchymal stem cells (MSCs) has been described as a potential alternative to stem cell injection, whereby the annulus structure is not further damaged by injection. Our group has previously shown that MSCs are able to migrate through the endplate and this migration is stronger in degenerative discs compared to healthy discs. IVDs contain a progenitor cell population with multipotent differentiation potential, which is characterized by the expression of the marker Tie2 (also known as CD202b or angiopoietin-1 receptor TEK tyrosine kinase). However, the fraction if Tie2+ cells decreases with IVD degeneration and ageing.
Using an IVD whole organ culture model, it was found that MSC migration consistently leads to an increase of Tie2 positive IVD cells compared to control IVDs that did not receive MSCs. Interestingly, this effect was not observed when MSCs were in contact with IVDs but migration was hindered through a physical barrier, indicating that MSC migration into the IVD is required to trigger an enhancement in the proportion of Tie2 positive IVD cells (Figure 11.6.5). Moreover, MSC migration induced a proliferative response in IVD cells, as attested by a higher proportion of Ki-67 positive IVD cells in IVD receiving MSCs compared to control IVDs that did not receive MSCs. In conclusion, our

results suggest that MSC homing may represent a powerful strategy to enhance IVD endogenous regenerative capacity. Following fusion of a spinal segment, stem cell homing could be used as prophylactic treatment to prevent degeneration of the adjacent discs.

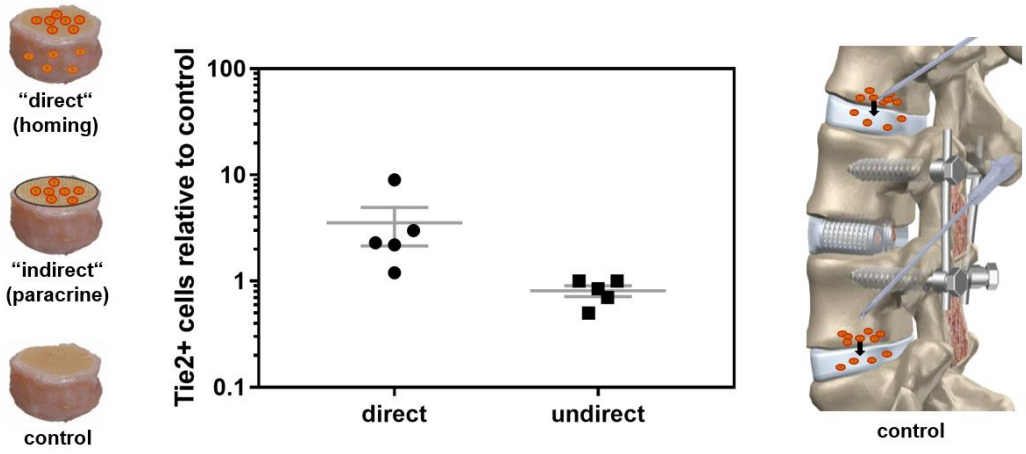


Figure 11.6.5: ***The response of disc cells to homing of stem cells****: (left) scheme representing setup where stem cell migration inside the intervertebral disc is permitted ("direct"), stem cell migration is hindered by a physical barrier ("undirect"), and control disc without stem cell treatment ("control"); (mid) comparison of Tie2 expression in direct and undirect groups versus control; (right) potential clinical application.*

Pres:

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. Mesenchymal Stem Cells Expressing the Cell Adhesion Molecule CD146 Present Increased Homing Towards Degenerative Intervertebral Discs - an Organ Culture Study. ORS 2017, San Diego (US) (oral)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. CD146 positive mesenchymal stem cell possess a superior migration potential both in vitro and in whole organ culture. BioSpine 2017, Berlin (Germany) (oral)

Grad S. Cell homing and intervertebral disc regeneration – lessons from organ culture studies. TERMIS 2017, Davos (Switzerland) (oral)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. Role of CD146 in mesenchymal stem cell homing and regeneration of the intervertebral disc: an in vitro and whole organ culture study. TERMIS 2017, Davos (Switzerland) (poster)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. CD146 positive mesenchymal stem cells possess a superior migration potential towards induced degenerative intervertebral discs. AOSpine Masters Symposium 2017, Bern (Switzerland) (oral)

Pub:

Peroglio M, Gaspar D, Zeugolis DI, Alini M. Relevance of bioreactors and whole tissue cultures for the translation of new therapies to humans. DOI: 10.1002/jor.23655

Wangler S, Li Z, Grad S, Peroglio M. Intervertebral disc whole organ cultures: How to choose the appropriate model. Taylor & Francis 2017

Collin EC, Carroll O, Kilcoyne M, Peroglio M, See E, Hendig D, Alini M, Grad S, Pandit A. Ageing affects chondroitin sulfates and their synthetic enzymes in the intervertebral disc. Signal Transduct Target Ther. 2017;2(publ online Sept 22)

Partners:

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

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

Pericytes (PCs) are constitutive components of microvessels and are present in all vascularized tissues. Recently it was suggested that PCs represent common ancestor cells providing an *in vivo* source of mesenchymal stem cells (MSCs). The aim of this project was to identify the potential role of PCs in bone regeneration. In a first phase, we isolated pericytes from different human tissues and investigated their angiogenic and osteogenic potential *in vitro*. PCs ($CD34^{neg}/CD146^{pos}$) were enriched from human adipose tissue (AT) and human bone marrow (BM) using MACS® and Flow Cytometry technologies. After characterization using surface marker profiles (MSC markers: CD44, CD73, CD90, CD105; pericyte markers: CD146, NG2, PDGFRb), we showed that only PCs derived from BM exhibited trilineage (osteogenic, adipogenic and chondrogenic) differentiation potential. Interestingly the osteogenic differentiation potential was more efficient in AT-PCs and BM-PCs compared to their respective full mesenchymal stem cells (MSCs) populations. We also showed the ability of $CD34^{neg}/CD146^{pos}$ PCs to integrate and support the formation of microcapillary-like structures in angiogenesis assays. To investigate the potential role of PCs in bone healing, we studied the PCs response to different physiological and pathological micro-environments. PCs were exposed to different conditioned media mimicking healthy bone (primary human endothelial cells and osteoblasts secretome), injured bone (bone fragments), and early injury response (activated platelets, PRP). Cells showed a specific response to different micro-environment (Figure 11.6.6). Cell proliferation was observed in all media with highest values in presence of injury related environments (bone fragments, PRP). Injury simulating conditions also induced the up-regulation of pro-inflammatory genes (such as IL6 and IL8), chemokines (CXCL6, CCL20), pro-angiogenic genes (VEGF) and genes involved in immunomodulatory signaling (Cox2, PTGES) in cells stimulated with PRP-CM and injured bone-CM suggesting a strong paracrine activity of cells.
The perivascular location of PCs together with their multilineage differentiation potential, their role in neo-vessel formation and their potential immunoregulatory effect suggest a possible role of PCs during in the early stage of bone healing.
The study of specific injury related factors will be conducted next using our in-house developed on-chip 3D perfusable microvascular network.

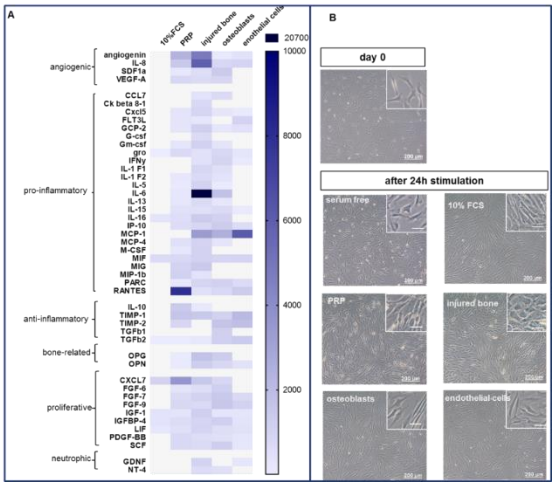


Figure 11.6.6: ***(A) Conditioned media cytokines content analysis.*** *A membrane-based antibody array, detecting 80 cytokines, was used for semi-quantitative analysis of cytokine content in the different CM. Abundance of proteins is shown in arbitrary numbers, where darkest colors depict the highest protein concentrations.* ***(B) Conditioned media induces changes in cell morphology and proliferation. A.*** *Cell morphology and density was observed before and after 24h of incubation in the different media.*

Pres:

Herrmann M, Hildebrand M, Alini M, Verrier S. Mimicking the early regenerative response of perivascular stem cells in vitro. 2017 DKOU (oral)

Zahn J, Loibl M, Sprecher C, Nerlich A, Alini M, Verrier S, Herrmann M. Platelet-rich plasma as an autologous and pro-angiogenic cell delivery system. 2017 DKOU (oral)

Herrmann M, Hildebrand M, Alini M, Verrier S. Mimicking the early regenerative response of perivascular stem cells in vitro. 2017 TERMIS-EU (poster)

Pub:

Zahn J, Loibl M, Sprecher C, Nerlich M, Alini M, Verrier S, Herrmann M.
Platelet-Rich Plasma as an Autologous and Proangiogenic Cell Delivery System.
Mediators Inflamm. 2017;2017:1075975

A perfused in-vitro-micro-vascular system for the study of Pericytes mobilization and migration (ongoing) (S Verrier)

Bone regeneration relies on adequate vascularization. Pericytes (PCs) are located on the outside of capillaries, play a pivotal role in blood vessel formation, show multilineage plasticity and are suggested to contribute to regenerative processes. Little is known about their response to paracrine signal in vivo. Microfluidic technologies have shown the potential to closely mimic the vascular microenvironment and represent an alternative to animal models. Here we developed a microfluidic microvascular network comprising PCs and human umbilical vein endothelial cells (HUVECs) in a hydrogel for the study of perivascular cells in a physiologically relevant context.
The microfluidic platform comprises three different parts: a glass slide stage, a polycarbonate chamber including two capillary guides and a PDMS lid. After polymerization of type I Collagen gel, two parallel microvascular channels are generated by retraction of micro-capillaries. Each channel is connected to a reservoir of endothelial growth medium perfused using a micro-pump, injected with GFP-HUVECs and PKH-pre-stained PCs, and perfused under physiological conditions (≤10 µl/min) (Figure 11.6.7). Observations are performed using a time-lapse microscope.
The created channels showed regular and stable shape (2 mm length, 150 µm diameter) in static and perfusion conditions. The seeding procedure and perfusion conditions allowed for good cell viability and efficient endothelialization of the channel. In parallel, we identified potent mobilization factors (injury, inflammation, see project Perivasc) and optimized concentration for PCs mobilization in a 2D co-culture system.
We successfully produced an on-chip perfusable microvascular network. Next, pericyte behavior and mobilization will be monitored in response to bone injury related factors.

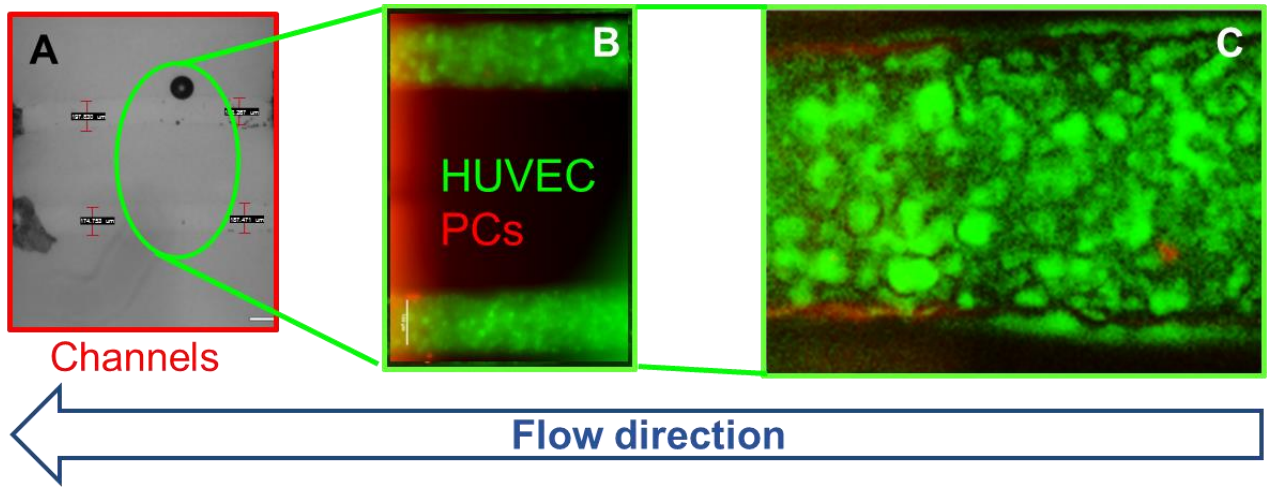


Figure 11.6.7: ***Perfusable on-chip micro-capillaries.*** *(A) Microscopal view of parallel channels embedded in collagen. (B) Channels were successfully cellularized with GFP-HUVECs and red PKH-pre-stained PCs. (C) Higher magnification Z-stack imaging showing the integration of PCs in the perivascular environment of the channels.*

Pres:
Pereira AR, Barbe L, Herrmann M, Alini M, Verrier S. Cellularized Perfusable Microvessels for the Study of Human Pericytes Response to Paracrine Signals. 2017 SBMS, Bern, Switzerland (oral)

Pereira AR, Barbe L, Herrmann M, Alini M, Verrier S. Development of a Perfusable On-Chip Microvascular Network for the Study of Pericytes Migration and Plasticity in Response to Bone Healing Related Signals. 2017 Bone-Tec, Munich, Switzerland (oral)

Multiple crosslinked bio-inks for 3D microextrusion of tissue-like constructs and biodegradable thermoplastic elastomer for fuse deposition manufacturing (MultibioInk) (Started) (D Eglin, M D'Este, M Alini)

Osteochondral injuries are increasing in numbers and yet still pose a major challenge in orthopedics. An active, aging population is leading to increased number of traumatic injuries that later progress to debilitating osteoarthritis (OA). While there is a significant amount of research into cartilage regeneration, little progress has been made in the treatment of patients. The most frequently used technique is still marrow stimulation, such as microfracture. Cell based therapies, such as autologous chondrocyte implantation, are increasing but only slowly due to costs and remaining doubts regarding efficacy. In addition, chondral defects frequently involve the underlying bone and both tissues must be repaired to allow long term patient mobility. For this reason, a number of groups are looking for materials that promote osteochondral repair. These materials could then enhance the repair tissue formed, while providing structural support for the de novo tissue. Additionally, the required cues for cartilage, 3D combined with lower stiffness, are different to that required for osteogenesis, stiff microrough 2D. This suggests that the most suitable solution may require a composite approach that combines the various required stimuli into a single implant.
This project is part of a joint consortium effort aiming at developing a patient specific osteochondral implant using additive manufacturing technologies. This project is focusing on the development of suitable matrices for cartilage repair.

Bio-adhesive biopolymers for integration of cartilage injury therapy GELHOME (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 biologics and fill articular cartilage defect (Figure 11.6.8). We showed that the embedding of cells affects the storage modulus of the hyaluronan tyramine derivative hydrogel, but not its adhesion to native articular cartilage since the bond strength of the hydrogel to articular cartilage compared favorably to clinically used fibrin gel. The bioadhesive hydrogel could be mechanically loaded to induce the activation of the endogenous TGF-β1 produced by the embedded cells. Therefore, the bio-adhesive hydrogel is a suitable cell carrier candidate to improve stability and integration into mechanically loaded articular cartilage.

Pres:
Behrendt, Lippross et al. 2017, Behrendt, Lippross et al. 2017, Behrendt, Lippross et al. 2017

Pub:
Behrendt, Feldheim et al. 2017

Partner:
- Lipross S (Prof), University Medical Center Schleswig-Holstein, Kiel, Germany

Behrendt P (MD), University Medical Center Schleswig-Holstein, Kiel, Germany

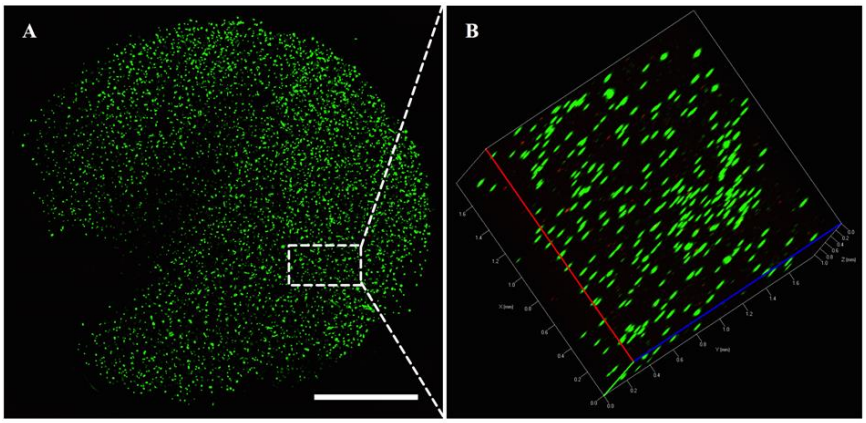
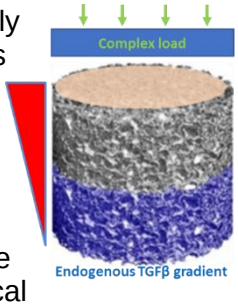


Figure 11.6.8. Representative confocal images of distribution and viability of embedded cells in HA-Tyr hydrogel.

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 lacking. This limits the efficacy of in vitro 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, interaction/signaling between cartilage, bone and implant. Finally, complex multiaxial load will also be applied to produce a mechanical environment more associated with the articulating joint. We have previously shown that a mechanical environment is able to generate signaling gradients that lead to anisotropic tissue formation. The additional signals produced by surrounding cartilage and underlying bone will allow for a 3D spatial patterning that will influence MSC differentiation.

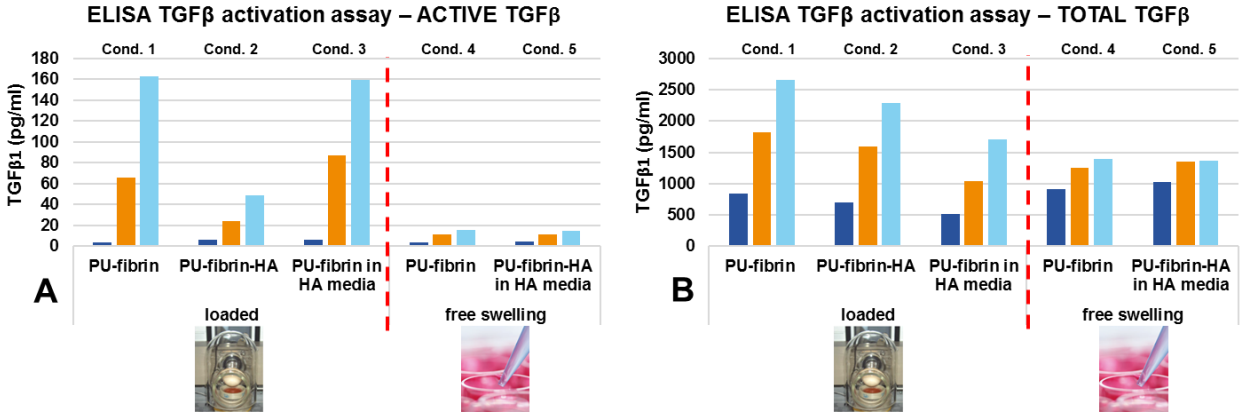


Figure 11.6.9: ELISA TGFβ activation assay on media collected from PU-fibrin cell seeded scaffolds. Cumulative data represent the active TGFβ1 present into the culture media produced by the hMSCs and activated by the loading in non-activated plate (A) and total TGFβ1 produced by the hMSCs in activated plate (B) that include the active and latent form of the TGFβ1 after 0 hours (DAY3) , 2 hours (DAY5) , and 4 hours (DAY7) of loading. Values represent the mean of one hMSCs donor (n=2).

We have also shown that the chondrogenic signal is in part generated by the mechanical induction and activation of TGF-β growth factor. This can be used as a new outcome measure to assess novel biomaterials for cartilage regeneration (Figure 11.6.9). 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 vitro situation nearer to that found in vivo.

Pres:

Physical modulation of chondrogenic cell fate. 15.11.2017. The 2nd Orthopedics Salon of Guangdong Provincial Key Laboratory of Orthopedics and Traumatology, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China.

Physical modulation of chondrogenic cell fate. Chinese Orthopaedics Research Society ICORS session, 14.11.2017. Zhuhai, China.

Comparing human MSC chondrogenesis under static and loading conditions. 7th CUHK International Symposium on Stem cell biology and Regenerative medicine, 13 November 2017, Hong Kong.

Multiaxial Load as a Driver of Human MSC Chondrogenesis. 6th Annual Symposium on Regenerative Rehabilitation, November 1-3, 2017, Pittsburgh, USA

Mechanically induced chondrogenesis ex vivo- Towards Regenerative Rehabilitation. EMPA, St. Gallen, 25.09.2017

Mechanobiology: Converting load to cellular signals, EORS, Munich, Germany, 14.09.2017
Regulating chondroprogenitor cell fate using mechanical stimulation. TERMIS-EU 2017, 27.06.2017. Davos, Switzerland

Regulation of chondrogenesis by growth factors and mechanical stimulation. Orthopaedic Research Society Annual Meeting 2017. Growth Factors Research Interest Group. 20.03.2017 San Diego, US

Pub:
Yabin Wu, Martin J. Stoddart, Karin Wuertz-Kozak, Sibylle Grad, Mauro Alini, Stephen J. Ferguson Hyaluronan supplementation as a mechanical regulator of cartilage tissue development under joint-kinematic-mimicking loading. Published 2 August 2017. DOI: 10.1098/rsif.2017.0255

Fahy N, Alini M, Stoddart MJ. Mechanical Stimulation of Mesenchymal Stem Cells: Implications for Cartilage Tissue Engineering. J Orthop Res. 2017 Aug 1. doi: 10.1002/jor.23670

Cochis A, Grad S, Stoddart MJ, Fare S, Altomare L, Azzimonti B, Alini M, Rimondini L. Bioreactor mechanically guided 3D mesenchymal stem cell chondrogenesis using a biocompatible novel thermo-reversible methylcellulose-based hydrogel. Sci Rep. 2017;7:45018

Partner:
- El Haj A (Prof, PhD) University of Keele, UK

Rational design of scaffolds for cartilage regeneration using finite element modelling (FEScaf) (Started) (M Stoddart)

The repair of traumatic injuries to articular cartilage is one of the major challenges in orthopedics. While there is agreement that new biomaterials to enhance repair are required, the development cycle of novel materials is laborious and frequently done on a trial and error basis. A more rationale design, based on clearly defined validated principles, would greatly enhance the development of new materials for cartilage repair. Within the clinical environment, the regular application of growth factors post-surgery is challenging and not currently approved. Thus, one of the main drivers of chondrogenesis is likely to be the mechanical environment sensed by the implanted/invading cells. Therefore, the transmission of load through any scaffold material will play a major role in determining the eventual outcome. In previous studies we have shown using primary human bone marrow derived stromal cells that chondrogenesis can be induced using mechanics alone. We have also shown that redistributing cells within the scaffold can dramatically enhance matrix deposition, while the cell number is kept constant. To investigate further the underlying mechanism, we developed a finite element (FE) model to characterize the various stimulation components that develop within the scaffold under dynamic load and using this model we established that the component strain distribution best matched the observed histological outcome. Using this as a base, we aim to investigate how scaffold geometries and material properties leads to changes in the distribution of component strain. The scaffolds proposed by the FE model will then be synthesized, either by salt leaching or 3D additive manufacturing, and the effect on chondrogenesis determined under complex load. The data obtained can be implemented into the FE model, further refining the data obtained, and expanding the functionality of the model. This iterative approach should lead to design of new scaffolds based on clearly defined design elements, and can be used to assist with scaffold design using novel biomaterials

Pres:
Bioreactors for Musculoskeletal Research. Orthopaedic Research Society Annual Meeting 2017. 20.03.2017 San Diego, US

Assessing and rectifying donor variation for musculoskeletal applications (Varidon) (Started) (M Stoddart)

In the development of cell based therapies for osteochondral defects and diseases there is still considerable debate regarding which is the most suitable source of cells. Chondrocytes lose phenotype during monolayer expansion, while bone marrow derived MSCs have a wide ranging chondrogenic efficiency and a propensity to undergo terminal hypertrophy. Articular cartilage derived chondroprogenitors (ACPCs) have features that are particularly interesting but have been largely unexplored. However, studies, including our own, suggest they are resistant to hypertrophy and are mechanoresponsive. While differences in chondrogenic potential from cells derived from different sources are well known, the underlying mechanisms for these differences have remained elusive. Studies involving primary human MSCs suffer from the wide variation observed. For in vitro studies this leads to challenges involving statistical significance and the requirement for repeats from multiple donors. For clinical translation of autologous therapies, the lack of an underlying mechanism causing the variation would result in the population of poor responders being unsuitable for autologous cellular based therapies. However, the prediction of which patients are likely to respond well is currently not possible and the spread of responses obtained is loosely dismissed as donor variation. If the underlying functional mechanism for the failure to respond was determined, not only would the suitability of a particular donor for cell therapy be able to be predicted, but also a corrective measure may be realized. Within this study we aim to identify a prospective chondroprogenitor marker that will allow for better patient stratification. The ability to then reverse the functional deficit will open new avenues for further cartilage repair therapies.

Pres:
Can we rely on stem cells to be introduced to the clinics? - A scientific perspective. ICRS Osteoarthritis in Athletes. Zürich, Switzerland. 28.09.2017

Partner:
- Johnstone B (Prof, PhD), Oregon Health & Science University, USA

11.7 Extramural Projects

Effect of cement augmentation of TFNA and PFNA head elements in osteoporotic bone (TFNAugCad) (I Zderic)

Problem: Fractures around the hip represent the most debilitating effect of osteoporosis with a steadily increasing incidence in an aging population. Intramedullary nailing of osteoporotic proximal femoral fractures can be challenging due to poor implant anchorage in the femoral head.
Goal: To assess biomechanically the increase in fixation strength and cut-out resistance provided by augmentation of TFNA and PFNA head elements (HE) with PMMA-based bone cement in osteoporotic cadaveric femoral heads.
Results: A setup for biomechanical testing under progressively increasing cyclic loading was adopted from a previous project. Fifteen pairs of human cadaveric femoral heads were instrumented with either TFNA Blade, TFNA Screw or PFNA Blade (5 pairs per HE type). Within each pair – implanted with the same HE type – one of the specimens was randomly augmented with Traumacem V+, while its contralateral part was left without cement augmentation. Load at failure of each HE type was significantly higher in its augmented versus non-augmented state. The increase in failure load was 40.0% for TFNA Blade, 29.6% for TFNA Screw, and 32.2% for PFNA Blade. From biomechanical perspective, implant augmentation with Traumacem V+ is a valid supplementary treatment option in osteoporotic bone.

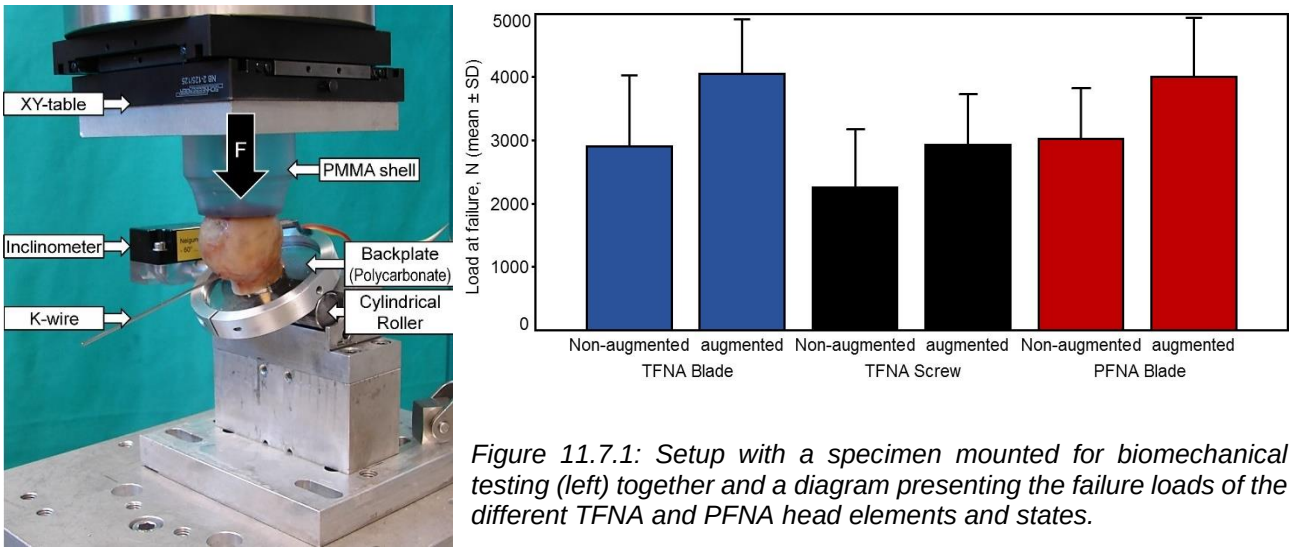


Figure 11.7.1: Setup with a specimen mounted for biomechanical testing (left) together and a diagram presenting the failure loads of the different TFNA and PFNA head elements and states.

Partner:

- Sermon A (Prof), University Hospitals Leuven, Leuven, Belgium

Biological and mechanical effect of selective proinflammatory cytokine inhibition in degenerative disc disease (Inflamodisc) (ongoing) (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: 2016.04-2018.03

Low back pain (LBP) is a major health issue; 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). Currently most of DMARDs are used in other fields like Rheumatoid arthritis or Crohn's Disease, though recent research suggests several cytokine inhibitors may have a significant therapeutic potential in 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 of this project, a proinflammatory and degenerative IVD organ culture model was established by combining TNF-α intradiscal injection, detrimental loading and limited nutrition. TNF-α combined with detrimental loading and low glucose medium up-regulated interleukin 1β (IL-1β),

IL-6, and IL-8 gene expression in disc tissue, nitric oxide and IL-8 release from IVD, which indicate a proinflammatory effect. The combined initiators up-regulated matrix metalloproteinase 1 gene expression, down-regulated gene expression of type I collagen in annulus fibrosus and type II collagen in nucleus pulposus and reduced the cell viability. Furthermore, the combined initiators induced a degradative effect, as indicated by markedly higher glycosaminoglycan release into conditioned medium. This model will be used for screening of therapeutic agents in further studies.

Pres:
Lang G, Liu Y, Zhou Z, Kubosch D, Suedkamp N, Alini M, Grad S, Li Z. A Proinflammatory and Degenerative Intervertebral Disc Organ Culture Model to Investigate Novel Anti-inflammatory Treatment Approaches for Degenerative Disc Disease. Global Spine Journal. 2017;7(2 Suppl):68S (GSC / oral)
Liu Y, Lang GM, Heizmann F, Geries J, Zhou Z, Kubosch DC, Südkamp N, Alini M, Grad S, Li Z. Establishment of a proinflammatory and degenerative intervertebral disc ex vivo system to simulate the early phase of degenerative disc disease. Eur Spine J. 2017;26(11):2978. https://doi.org/10.1007/s00586-017-5336-8 (DWK / oral)

Lang G, Liu Y, Zhou Z, Kubosch D, Südkamp N, Alini M, Grad S, Li Z. A proinflammatory and degenerative intervertebral disc organ culture model by combining TNF-α intradiscal injection and detrimental dynamic loading. 2017 ORS (poster)

Lang G, Liu Y, Zhou Z, Kubosch D, Südkamp N, Richards RG, Alini M, Grad S, Li Z. Establishment of a proinflammatory and degenerative intervertebral disc organ culture model. 2017 BioSpine (oral)

Lang G, Liu Y, Zhou Z, Kubosch D, Südkamp N, Richards RG, Alini M, Grad S, Li Z. An intervertebral disc organ culture model mimicking proinflammatory and degenerative disease condition. 2017 TERMIS-EU (oral)

Lang G, Liu Y, Geries J, Kubosch D, Südkamp NP, Alini M, Grad S, Li Z. Establishment of a proinflammatory and degenerative intervertebral disc ex vivo system to investigate anti-inflammatory therapies for degenerative disc disease. 2017 DKOU (oral)

Li Z, Lang G, Liu Y, Geries J, Zhou Z, Kubosch D, Südkamp N, Alini M, Grad S. Short- and mid-term effect of TNF-α intradiscal injection and detrimental dynamic loading in intervertebral disc organ culture. 2017 AOSpine Masters (oral)

Li Z, Lang G, Heizmann F, Liu Y, Geries J, Kubosch D, Südkamp N, Alini M, Grad S. Anti-inflammatory and regenerative drug therapy for the treatment of degenerative disc disease: Validation in organ culture model. 2017 ORS PSRS (poster)

Pub:
Lang G, Liu Y, Geries J, Zhou Z, Kubosch D, Südkamp N, Richards RG, Alini M, Grad S, and Li Z. An intervertebral disc whole organ culture system to investigate proinflammatory and degenerative disc disease condition, J Tis Eng Reg Med, 2018 DOI:10.1002/term.2636

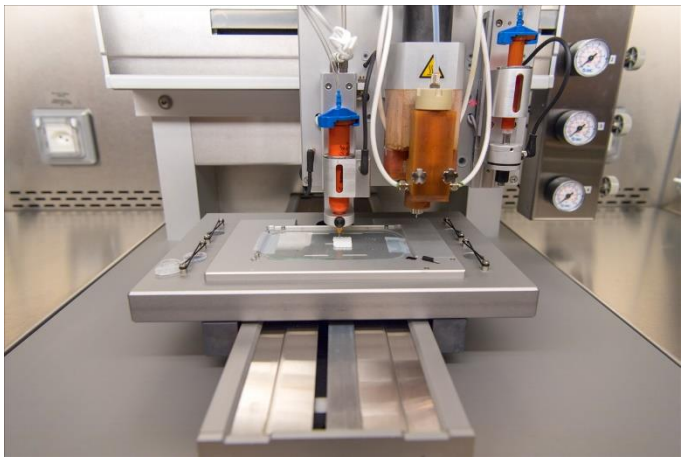
Partners:
- Lang G (MD), Albert-Ludwigs-Universität Freiburg, Freiburg, Germany
- Südkamp N (Prof), Altert-Ludwigs-Universität Freiburg, Freiburg, Germany

Personalized Ceramic Printable Ink for Patient Specific Implant Fabrication (InCePt) (Started) (D Eglin, G Richards), CTI/KTI (Nr 18060.2), ARI Funding: CHF 292‘700, Period: 2017-2019

The aim of this project is to develop and commercialize a chairside CAD/CAM solution for use in CMF indications. This innovative solution rests on the freeform fabrication process (bioprinting) developed by regenHU Ltd and a proprietary hydraulic calcium phosphate ink. In collaboration with ARI and University of Berne, the technology which is currently in a pre-prototype phase will be physically and clinically assessed in order to gain market approval. regenHU envision to market launch a first product generation by 2018.
One of the crucial goals is to develop a formulation ink product for chairside manufacturing solution. Currently, the materials used for the reconstruction of bone replacement implants in the maxillofacial area are mainly materials lacking osteoinductivity like titanium, polytetrafluoroethylene, polyethylene and silicone rubbers and sometime augmented with particulate calcium phosphate. These materials can be easily shaped by free-hand bending; however, due to the complex anatomy and the limited intra-operative access, precise reconstruction of the bones, such as for example, the orbit, is extremely difficult. Recent advances in imaging techniques and navigation systems enable the surgeon to perform pre-operative planning and more accurate intra-operative placement of the implants. Nevertheless, even with the help of these modern tools, free hand-bent synthetic implants are not the optimal implants in precise anatomical reconstructions of the orbit and lack osteoinduction. Autologous bone is not an option due to its limited availability and poor shaping ability. Thus, no product exists with the ability to accurately reconstruct the anatomy of large bony defects (e.g. orbital fractures), notably products that allow for a limited thickness profile and possess osteoinductive property.
Chairside manufacturing enables intra-operative enhancement of implants with autologous material during the manufacturing process. Therefore, the proposed chairside concept is a unique approach to manufacture osteoinductive PSI which would fall under medical device regulation processes far less stringent, time consuming and costly than bioactive products going through advanced therapeutic products legislation (ATP).

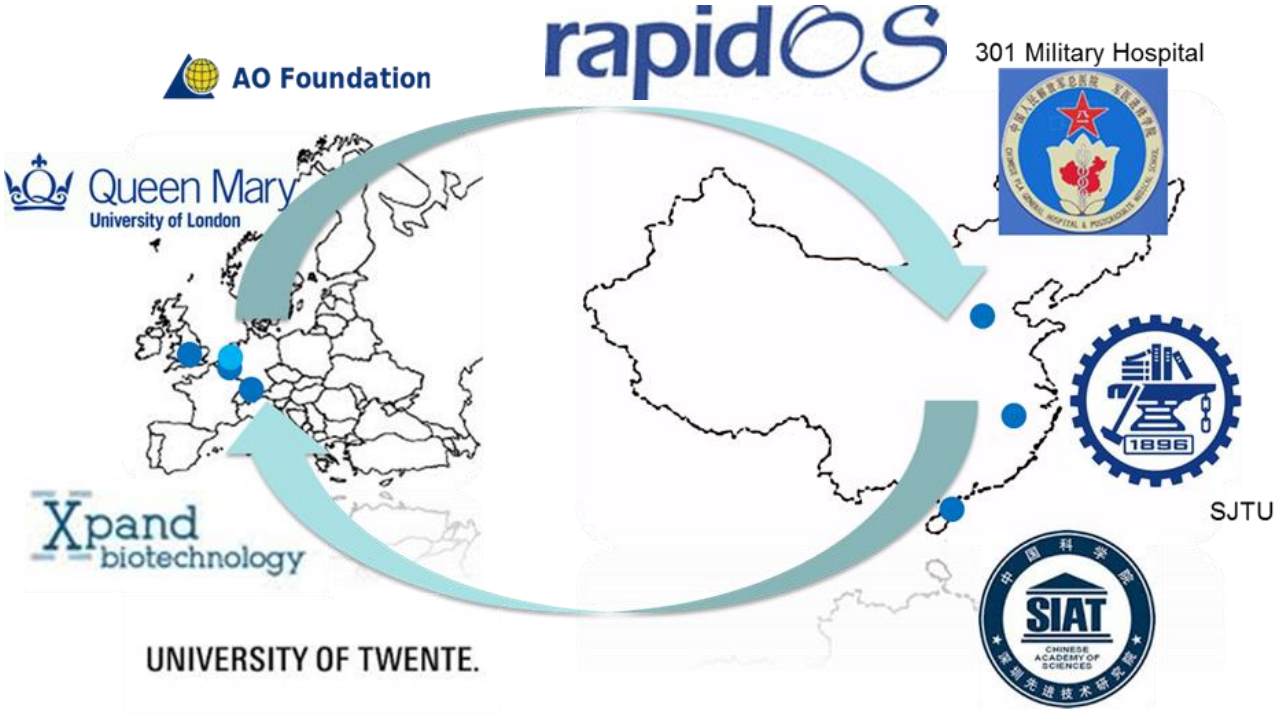
Partners:

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



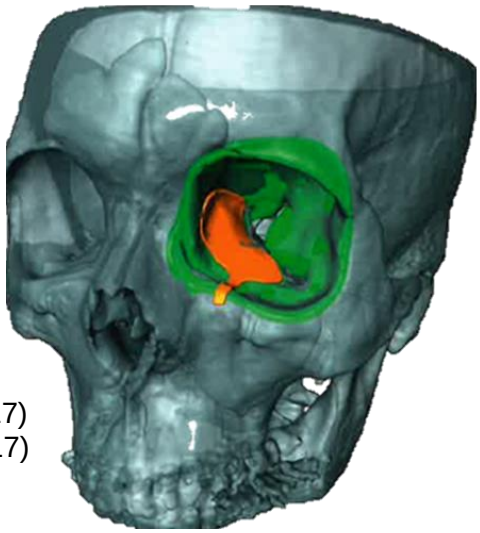
Rapid Prototyping of Custom-Made Bone-Forming Tissue Engineering Constructs (RAPIDOS) (Completed) (D Eglin, M Alini, G Richards), FP7-NMP-2013-EU-China (Nr. 604517), ARI Funding: EUR 713'720, Period: 2013-2017

In this RAPIDOS European and Chinese consortium, RP technologies were applied to create custom-made 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 was to apply precise and rapid prototyping technologies for custom-made bone implants with optimized macro-architecture, osteoinduction via the inclusion of calcium phosphate and a Chinese medicine phytomolecule (icaritin), and bactericidal properties.



The 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 patented 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. Next, biodegradable composite materials were developed and their printability by low-temperature rapid prototyping and stereolithography established. Functionalization with bactericidal macromolecules and loading with icaritin were performed. The optimization of composite formulations; poly(trimethylcarbonate) (PTMC)/calcium phosphate and poly(lactic-co-glycolic)/tricalcium phosphate/magnesium (PLGA/TCP/Mg) respectively, for stereolithography and low temperature rapid manufacturing has been performed and already implant scaffolds were fabricated by both stereolithography and low temperature rapid prototyping. Biodegradable polymeric nanofibers and microspheres loaded with icaritin, a Chinese medicine phytomolecule as potential drug delivery vehicle have been prepared and incorporated into the photo-polymerizable resin formulation for stereolithography and assessed in vitro. In vitro studies have also shown the osteopromotive effect of the hydroxyapatite nanoparticles loaded into PTMC scaffolds. *In vivo* studies in rabbit calvarial defects showed the enhance bone ingrowth in Calcium phosphate nanoparticles loaded PTMC Stereolithography scaffolds in comparison to PTMC scaffolds (Figure 11.7.2). The osteopromotive effect of icaritin in PLGA/TCP/Mg and hydroxyapatite/PTMC scaffolds was assessed too *in vivo* and *in vitro*. Quaternised chitosan and magnesium were shown to decrease biofilm formation onto the surface of PLGA/TCP/Mg scaffolds *in vitro* and *in vivo* without being detrimental to mesenchymal stem cells osteogenic differentiation. Finally, a preclinical proof of concept showed the robustness of the process and the patient specific osteoinductive orbital floor implant produced by stereolithography.

The European and Chinese RAPIDOS project activities have already led to 25 peer-review manuscripts and the filing of 2 EU and 9 Chinese patents. Four workshops were organized and attended by European and Chinese partners with several exchange missions between partners. Finally, the RAPIDOS results have contributed to the creation of one Chinese Spin-off company for production of new biomaterials and facilitated the merging of European industry partner.



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(Guillaume, Geven et al. 2017) (Guillaume, Geven et al. 2017) (Stadelmann, Geven et al. 2017) (Guillaume, Geven et al. 2017) (Guillaume, Zhang et al. 2017) (Guillaume, Geven et al. 2017)

Pub:

(Guillaume, Geven et al. 2017) (Guillaume, Geven et al. 2017) (Geven, Sprecher et al. 2017)

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

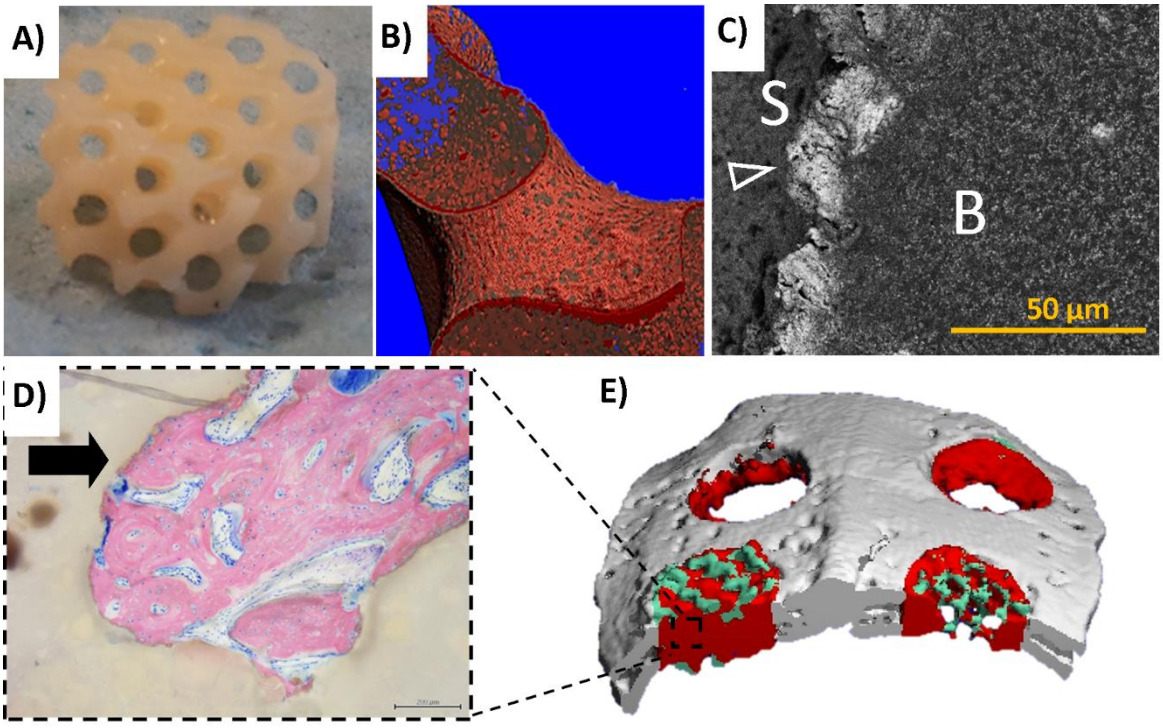

Figure 11.7.2: SLA-fabricated macroporous PTMC 20 (A) and nHA surface-enrichment characterized by microCT (CaP appeared in red, B) and BSE-SEM (nanoHA appears white, "S" surface and "B" bulk, C). Histological observation of the interface bone-PTMC 40 (D) and of the new bone formed after 6 weeks (new bone in red and scaffolds in green, E).

Targeting cartilage regeneration in joint and intervertebral disc diseases (TargetCaRe) (ongoing) (M Alini, S Grad), EU H2020-MSCA-ITN-2014 Marie Sklodowska-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.
The aim of ARI's project was 1) to generate osteochondral explants in a reproducible manner, 2) to create accurate and reproducible defects and 3) to adapt and validate our bioreactor system that recapitulates articulating motion for osteochondral explants. Osteochondral plugs were harvested from bovine stifle joint and full thickness chondral or osteochondral defects were reproducibly generated (Figure 11.7.3). Cells within both cartilage and bone regions remained viable throughout the culture period, as assessed by LDH staining. Compression and shear loading did not wear the cartilage in comparison to the free swelling controls, as assessed by safranin-O/fast green staining. These results provided confidence that this new testing system will be adequate to screen new biomaterials and regenerative therapies and study the cell responses under relevant mechanical stimuli for cartilage repair.

Figure 11.7.3: Bovine osteochondral explants, intact and with full-thickness defect.

Pres

Vainieri ML, Wahl D, Lezuo P, Van Osch GJVM, Alini M, Grad S. Novel ex-vivo osteochondral defect model in a joint bioreactor system for articular cartilage repair studies. 2017 GRC Cartilage Biology & Pathology (poster)
Vainieri ML, Wahl D, Lezuo P, van Osch G, Alini M, Grad S. Novel ex-vivo osteochondral defect model in a joint bioreactor system for articular cartilage repair studies. 2017 TERMIS-EU (poster)

Partners:

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

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

Osteoarthritis (OA) is the most prevalent degenerative joint disorder that affects millions of patients worldwide. Due to the poor self-healing capacity of articular cartilage, there is currently no effective and standardized treatment available, neither for repair nor for prevention of onset or progression of this disease. In this study we tested 40 small molecules with biological structure which are extracted from herbal Chinese medicine. Using a high-throughput screening method, the chondrogenic effects of a selection of 40 TCM (traditional Chinese medicine) compounds were assessed on human osteoarthritic chondrocytes in pellet cultures. Specifically, the DNA content and glycosaminoglycan (GAG) synthesis of the cells in response to different doses of TCM compounds were evaluated.
In the next step the anti-inflammatory effects of the compounds were investigated using an inflammatory model. Interestingly, the GAG synthesis was re-established after treatment with 4-Hydroxybenzoic acid, whereas no significant recovery was observed in the inflammatory control group. In further experiments, a hyaluronan based release system for the delivery of the bioactive compound will be optimized and the bioactivity of released compound in terms of cartilage repair will be tested.

Pres
Ziadlou R, Grad S, Stoddart MJ, Xinluan W, Ling Q, Barbero A, Martin I, Alini M. The anabolic and anti-inflammatory effects of biological small molecules for treatment of osteoarthritis.
2017 GRC Cartilage Biology & Pathology (poster)

Ziadlou R, Grad S, Stoddart M, Wang X, Ling Q, Barbero A, Martin I, Alini M. The anabolic and anti-inflammatory effects of biological small molecules for treatment of osteoarthritis.
2017 SSB+RM (poster)

Ziadlou R, Grad S, Stoddart MJ, Barbero A, Martin I, Alini M. Screening of anabolic and anti-inflammatory effect of biological small molecules for treatment of osteoarthritis.
2017 TERMIS-EU (poster)

Ziadlou R, Grad S, Stoddart M, Wang X, Qin L, Barbero A, Martin I, Alini M. High throughput screening towards a herbal drug delivery system for treatment of osteoarthritis.
2017 FIRM (poster)

Ziadlou R, Grad S, Stoddart M, Barbero A, Martin I, Eglin D, Alini M. Screening of herbal small molecules towards drug delivery system for treatment of osteoarthritis.
2017 SSB+RM YS (poster)

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

12 Operations standards and safety

Successful 2017 renewal audit of AO Research Institute Davos

From April 3 to 4 2017, an external auditor 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 Davos is certified (in 2017) according to the international standard ISO 9001:2008.

The Biomedical Services Program (in 2017) is additionally certified as a medical device manufacturer according to EN ISO 13485:2012.

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 Practice):
ARI is listed as GLP compliant test facility since February 2016.
(https://www.anmeldestelle.admin.ch/chem/en/home/themen/gute-laborpraxis/pruefeinrichtungen.html)
This is a major achievement for our institute.
We are 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.
Since the achievement of the GLP certification all major commercial studies have been conducted under GLP (without pilot studies).

13 Team Members

Director

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

ARI Management

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

Scientific & Technical Staff

Arens Daniel	Dr med vet	01.11.07
Armiento Angela	PhD	01.01.16
Badrutt Isabella	Administrative Assistant	16.07.12
Barblan Claudia	Administrative Assistant (70%)	15.11.10
Barcik Jan	PhD Candidate	01.04.17
Basoli Valentina	Post Doc	01.04.17
Berset Corina	Dr med vet	01.08.15 (AOF)
Bluvol Mauro	Chemielaborant (Eidg FA[1])	01.06.03
Boot Willemijn	Post Doc	01.03.17
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 FA[1])	01.01.78
Di Luise Nunzia	Post Doc	15.06.17
Du Jie	PhD Candidate	24.07.17
Eberli Ursula	MSc ETH	01.02.11
Eglin David	PhD	01.06.06
Erb Peter	Animal Care (Eidg FA[1])	03.05.93
Ernst Manuela	MSc, Human Movement Science	01.10.11
Escher Carla	Administrative Assistant (40%)	01.01.95
Faoro Loris	Animal Care	01.11.16
Faoro Pierina	Arztgehilfin, Animal Care (Eidg FA[1]) (70%)	01.12.07
Furlong-Jäggi Pamela	Chemikerin FH, BSc (40%)	01.02.04
Furter Andrea	Animal Care (Eidg FA[1])	24.04.06
Gehweiler Dominic	Dr, med	01.03.16
Gieling Fabian	PhD Candidate	18.04.16
Goudsouzian Nora	BSc	01.02.02
Guillaume Olivier	PhD	01.03.15
Hofmann-Fliri Ladina	MSc ETH	01.10.09
Hofstee Marloes	PhD Candidate	20.11.17
Kamer Lukas	Dr med, Dr med dent (80%)	21.05.07
Keller-Stoddart Iris	MTL Technician (60%)	21.10.09
Lanker Jann	Animal Care	temporary
Lanker Urban	Animal Care (Eidg FA[1])	16.06.86
Lezuo Patrick	Dipl Eng	01.08.03
Li Zhen	PhD	01.08.11
Linardi Flavio	Laborant Fachrichtung Chemie (Eidg FA[1])	01.08.15
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 Candidate, MSc, Biotechnology	01.01.14
Post Virginia	PhD (60%)	20.09.10
Rotman Stijn	PhD Candidate	26.08.16
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 Tizziano	PhD	01.10.16
Sprecher Christoph	PhD, Dipl Ing FH	01.02.00
Stanic Barbara	PhD	01.06.14
Thompson Keith	PhD, BSc (Hons), MSc,	26.05.15
Vainieri Letitzia	PhD Candidate, 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
Wahl Dieter	Dipl techn Werkzeugspezialist HFP	01.11.93
Wangler Sebastian	PhD Can	01.02.17
Windolf Markus	Dr biol hum Dipl Ing	01.11.04
Zderic Ivan	MSc ETH	01.02.11
Zhiyu Zhou	PhD	21.03.16
Ziadlou Reihane	PhD Candidate	01.11.15
Zweifel Erich	European Industrial Engineer EIE	30.11.92

Apprentice

Semere Yemane	Apprentice	01.06.15
Spiller Flurin	Apprentice	01.08.15
Hassler Andri	Apprentice	04.08.14 – 31.07.17

Medical Research Fellows

Häckel Sonja	Research Fellow (Germany)	27.09.17
Ma Junxuan	Research Fellow Guest (China)	02.03.17
Naros Andreas	Research Fellow (Germany)	01.07.17
Ahrend Marc-Daniel	Research Fellow (Germany)	01.02.17 – 31.12.17
Hadzhinikolova Mariya	Research Fellow (Bulgaria)	01.10.17 – 31.12.17
Riehl Valentina	Research Fellow VET (Germany)	18.04.16 – 16.07.17
Rusimov Lyubomir	Research Fellow (Bulgaria)	10.10.17 – 31.12.17
Stylianaki Aikaterini	Research Fellow (Greek)	01.11.16 – 30.06.17
Vallejo Alejandro	Research Fellow (Colombia)	04.01.17 – 31.12.17
Violin Kalan	Research Fellow (Brazil)	01.02.17 – 31.08.17
Von Deimling Christian	Research Fellow (Germany)	04.01.17 – 31.12.17

Internship

Admiraal Daniëlle	Internship (The Netherlands)	06.09.17
Ciric Daniel	Internship Guest (Australia)	01.09.17
Gehlen Yannik	Internship Guest (Germany)	14.08.17
Kovermann Niko	Internship Guest (Germany)	25.09.17
Ladner Yann	Internship ETH (Switzerland)	04.09.17
Mischler Dominic	Internship ETH (Switzerland)	06.09.17
Thiemann Luisa	Internship (Germany)	16.10.17
Augurio Adriana	Internship (Italy)	10.04.17 – 10.09.17
Behrendt Peter	Internship Guest (Germany)	01.11.16 – 15.09.17

Bensaid Louai	Internship Guest (France)	10.07.17 – 08.09.17
Derron Nina	Internship ETH (Switzerland)	15.09.17 – 31.12.17
Enk Nathalie	Internship VET (Switzerland)	09.01.17 – 03.03.17
Geries Janna	Internship (Germany)	19.09.16 – 16.04.17
Hasselmann Verena	Internship (Germany)	01.10.16 – 30.06.17
Heizmann Fabian	Internship Guest (Germany)	20.02.17 – 30.09.17
Heriot Marine	Internship (France)	01.04.17 – 31.08.17
Inauen Mario	Internship ETH (Switzerland)	01.10.16 – 07.04.17
Mayr Sophia	Internship VET (Germany)	01.10.17 – 24.11.17
Mys Karen	Internship (Belgium)	15.08.17 – 15.12.17
Oliveira Pereira Ana Rita	Internship (Portugal)	05.01.17 – 30.06.17
Pinaki Acharya	Internship (India)	01.06.17 – 31.07.17
Sheehy Eamon	Internship (Ireland)	16.10.17 – 21.12.17
Schubert Dana	Internship VET (Germany)	15.05.17 – 15.07.17
Tognato Riccardo	Internship (Italy)	10.04.17 – 10.09.17
Wyatt Sean	Internship VET (USA)	29.05.17 – 29.07.17
Wystrach Laura	Internship Guest (Germany)	13.02.17 – 15.04.17

Employees left 2017

Scientific & Technical Staff

Fahy Niamh	PhD	16.02.15 – 15.02.17
Freitag Linda	Med vet	10.04.16 – 31.12.17
Herrmann Marietta	Dr rer nat, PhD	01.11.12 – 31.03.17
Li Bojun	PhD	06.01.14 – 31.03.17
Sabate Bresco Marina	PhD Candidate, MSc	17.01.13 – 30.04.17
Wagner Patrizia	Junior Project Leader	18.01.16 – 27.11.17

[1] Eidg FA = Eidg Fähigkeitsausweis

Visiting Professors

Balligand Marc	Biomedical Development (B Gueorguiev), 02.10.2017 – 30.09.2018, Université de Liège, (Guest self funded Sabbatical)
Jonkers Ilse	Musculoskeletal Regeneration, (S Grad), 04. – 05.12.2017 KU Leuven, (Guest self funded Sabbatical)

Visitors

Actis Lisa	Biomedical Development (B Gueorguiev), 02. – 04.10.2017 BME, San Antonio, USA, Guest
Arand Charlotte	Biomedical Services (L Kamer), 23. – 25.10.2017 Universitätsmedizin Mainz, Germany, Guest Scientist
Berner Tanja	Visit all ARI Departments, 27.03.2017 University Zürich
Böhme Beatrice	Biomedical Development (B Gueorguiev), 27.11.2017 University of Liège, Guest Presentation
Citterio Irene	Muskuloskeletal Regeneration (M Alini), 03. – 11.07.2017 High School Project, Savosa, Guest Student

Gleissner Eva	Musculoskeletal Regeneration (D Eglin), 14.08. – 18.8.2017 ETH Zürich, Guest Scientist
Heitz Dominique	Preclinical Services (S Zeiter), 15.09.2017 Novartis Pharma AG, Basel, Workshop
Husarik Daniela	Biomedical Development (L Kamer), 28.03.2017 Gzo Hospital, Wetzikon
Khatchadourian Roberto	Biomedical Development (D Wahl), 11. – 13.01.2017 DePuy Synthes, Schweiz, Guest
Khoroska Dmitriy	Musculoskeletal Regeneration (F Linardi), 12.04.2017 SAMD, Davos, Guest
Laurent Cédric	Biomedical Development (B Gueorguiev), 27.11.2017 Universiteé de Lorraine, Guest Presentation
Lutz Isabelle	Biomedical Development (L Kamer), 08.03.2017 Kieferchirurgie, Medical School, Hannover, Guest
Ossendorff Robert	Musculoskeletal Regeneration (S Grad), 15. – 18.05.2017 Universität Freiburg, Guest
Ponthot Jean Philippe	Biomedical Development (B Gueorguiev), 27.11.2017 University of Liège, Guest Presentation
Rana Majeed	Biomedical Development (L Kamer), 08.03.2017 Kieferchirurgie, Medical School, Hannover, Guest
Rrahmani Blerim	Preclinical Services (S Zeiter), 15.09.2017 Novartis Pharma AG, Basel, Workshop
Rüedi Thomas	Biomedical Development (L Kamer), 16.08.2017 Mithilfe TK-Projekt
Rusev Ivan	Biomedical Development (B Gueorguiev), 21. – 24.11.2017 Technical University Varna
Safari Fatemeh	Musculoskeletal Regeneration (M Stoddart), 03. – 04 07.2017, Royan Institute, Teheran, Iran, Guest Scientist
Saggese Taryn	Musculoskeletal Regeneration (Z Li), 08. – 12.05.2017 University of Ulm, Guest Scientist
Scherrer Simon	Biomedical Development (D Wahl), 11. – 13.01.2017 & 10. – 11.05.2017, DePuy Synthes, Schweiz, Guest
Schmid Timo	Biomedical Development (I Zderic), 04. – 08.09.21017 Inselspital Bern, Guest Scientist
Sermon An	Biomedical Development, (I Zderic), 12.01.2017 University Hospital, Leuven
Sheehy Eamon	Musculoskeletal Infection (F Moriarty), 23.08.2017 RCSI Scaffold Project

Skulev Hristo	Biomedical Development (B Gueorguiev), 21. – 24.11.2017 Technical University Varna
Ueberberg Johanna	Biomedical Development (D Gehweiler), 09. – 12.11.2017 UKM Münster, Germany
Wagner Daniel	Biomedical Development (L Kamer), 18. – 19.12.2017 University of Mainz, Guest Scientist
Weiss Tilla	Preclinical Services (S Zeiter), 15.09.2017 Novartis Pharma AG, Basel, Workshop
Zschaler Tobias	Biomedical Development, (D Gehweiler), 10. – 13.04.2017 University Münster, Germany

Guests

Bonfrate Valentina	Musculoskeletal Regeneration (T Serra), 01.04. – 07.05.2017 University of Salento, Guest Scientist
D'Atri Domenico	Musculoskeletal Regeneration (S Grad), 22.09. – 13.10.2017 Israel Institute of Technology, Haifa, Guest Scientist
Dlaska Constantin	Biomedical Development (P Varga), 09. – 12.10.2017 CMSC Berlin Charité, Guest Scientist
Della Bella Elena	Musculoskeletal Regeneration (M Stoddart), 01.02. - 30.04.2017 and 13. – 27.09.2017, University of Bologna, Guest Scientist
Destremps Ashley	Preclinical Services (C Berset), 13.03. – 01.04.2017 New England Ovis, Rollinsford
Frayssinet Antoine	Musculoskeletal Regeneration (M D'Este), 01. – 23.04.2017 École normale supérieure (ENS), Montpellier, Guest Scientist
Fuchs Nadja	Musculosceletal Infection (F Moriarty), 11.07. – 19.08.2017 Maturaarbeit, SAMD Davos, Guest Student
Geven Mike	Musculoskeletal Regeneration (O Guillaume), 13.03. – 28.04.2017, University of Twente, Enschede, Guest Scientist
Gigliotti Anastasia	Musculoskeletal Regeneration (M D'Este), 14. – 25.8.2017 Savosa, TI, Maturaarbeit
Hayoz Annabel	Biomedical Development (I Zderic), 04. – 08.09.21017 Inselspital Bern, Guest Scientist
Hehli Fabio	Musculoskeletal Regeneration (S Grad), 22.05.2017 SAMD Davos, Maturaarbeit
Hurley Julie	Preclinical Services (C Berset), 13.03. – 21.03.2017 New England Ovis, Rollinsford
Lapomarda Anna	Musculoskeletal Regeneration (O. Guillaume), 13.03. – 28.04.2017, University of Twente, Enschede, Guest Scientist

Namasivayam Ganesh	Musculoskeletal Regeneration (M Stoddart), Exchange Visit University Kyoto, Japan, 02. – 18.8.2017
Picenoni Armin	Musculoskeletal Regeneration (D Eglin), 10. – 31.12.2017 SIAF, Davos, SIAF Student (using our lab)
Provveduto Serena	Musculoskeletal Regeneration (M D'Este), 14. – 25.8.2017 Savosa, TI, Maturaarbeit
Qu Feini	Preclinical Services (S Zeiter), 19.06. – 09.07.2017 University of Pennsylvania, Guest
Weitkamp Jan-Tobias	Musculoskeletal Regeneration (D Eglin), 21.08 – 08.09.2017 Anatomisches Institut, Kiel, Germany, Guest Scientist

Guest Presentations at AO Center

Jan 11, 2017 Prof Lucie Germain from Department of Surgery, Faculty of Medicine of Université Laval, Canada gave a guest presentation with the title: Challenges in translating the bench to the patient: Skin and cornea as examples.

Jan 16, 2017 Andrea Aloia from ETH Zurich, Institute of Molecular Health Sciences, Zurich, Switzerland gave a guest presentation with the title: The sialyl-glycolipid stage-specific embryonic antigen 4 marks a subpopulation of chemotherapy-resistant breast cancer cells with mesenchymal features.

Feb 03, 2017 Dr Cornelia Neidlinger-Wilke from University of Ulm, Germany, gave a guest presentation with the title: Multiscale levels for the study of disc degeneration and regeneration: the challenges and benefits of cell- and organ culture approaches.

Feb 03, 2017 Dr Taryn Saggese from University of Auckland, New Zealand gave a guest presentation with the title: From Auckland to Ulm: Studies on IVD cell mechanobiology.
Feb 03, 2017 Dr Kelly Rusel Wade from University of Auckland, New Zealand gave a guest presentation with the title: From Auckland to Ulm: How disc microstructure influences the herniation process.

Feb 20, 2017 Dr Denis Bron from Forschung Flugärztlicher Dienst, Dübendorf, Switzerland gave a guest presentation with the title: What we are interested about our flight pilots.

April 10, 2017 Dr Massimiliano Cerletti from University College, London, UK gave a guest presentation with the title: Small molecules reverse age-related dysfunction in muscle stem cells and enhance muscle repair.

May 24, 2017 Prof Xuenong Zou, Head of Guangdong Provincial Key Laboratory of Orthopedics and Traumatology/Orthopedic Research Institute, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, P. R. China gave a guest presentation with the title: Introduction of Sun Yat-Sen University, The Epigenetic Mechanisms of Cellular Stress and Homeostasis on the Process of Bone Forming Induced by Bone Repair Materials.

May 31, 2017 Prof Gerald J Atkins from University of Adelaide, Australia gave a guest presentation with the title: Is there a role for the osteocyte in bone infection?

July 26, 2017 Prof Alex Dommann, Head of Department "Materials meet Life", Empa St. Gallen, Switzerland gave a guest presentation with the title: Materials meet Life.

Aug 10, 2017 Dr Ganishi Namashibayamu from University of Kyoto, Japan gave a guest presentation with the title: Cellular Reprogramming using Smart Transcription Factors.

Aug 25, 2017 Dr Melanie Tempel and Dr Marco Nardi from Università degli Studi di Trento, Department of Industrial Engineering, Trento, Italy gave a guest presentation with the title: Functionalization of SiC/SiOx core/shell nanowires: oxidative stress-generating nanomaterials for anti-cancer therapy.

Nov 27, 2017 Prof Marc Balligand and Dr Beatrice Boehme from University of Liege, Belgium gave a guest presentation with the title: State of the art in veterinary orthopedics.

Nov 27, 2017 Prof Jean-Philippe Ponthot from University of Liege, Belgium and Prof Cedric Laurent from University of Lorraine, Belgium gave a guest presentation with the title: Finite Element Analysis at the Universities of Liege and Lorraine.

14 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: ARI, 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: ARI, M Windolf

Cannula and Kit for Bone Cement Injection
- First Application: PCT/CH2011/000007 filed 2011-04-19
- Case: 10.2567
- Developer / Inventors: ARI, 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: ARI, 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

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

Surface Acoustic Wave (SAW) 3D Printing Method
- First Application: CH01058/17 filed 2017-08-25
- Case: 10.F5004
- Developer / Inventors: T. Serra, D. Eglin, M. Alini

15 Publications & Presentations

15.1 Published peer reviewed papers (epub & in print)

Acklin YP, Zderic I, Grechenig S, Richards RG, Schmitz P, Gueorguiev B. Are two retrograde 3.5 mm screws superior to one 7.3 mm screw for anterior pelvic ring fixation in bones with low bone mineral density? Bone Joint Res. 2017;6(1):8-13

Acklin YP, Zderic I, Richards RG, Schmitz P, Gueorguiev B, Grechenig S. Biomechanical investigation of four different fixation techniques in sacrum Denis type II fracture with low bone mineral density. J Orthop Res. 2017;epub Nov 6

Armiento AR, Stoddart MJ, Alini M, Eglin D. Biomaterials for Articular Cartilage Tissue Engineering: Learning from Biology. Acta Biomater. 2017;epub Nov 8

Behrendt P, Feldheim M, Preusse-Prange A, Weitkamp JT, Haake M, Eglin D, Rolauffs B, Fay J, Seekamp A, Grodzinsky AJ, Kurz B. Chondrogenic potential of IL-10 in mechanically injured cartilage and cellularized collagen ACI grafts. Osteoarthritis Cartilage. 2017;epub Nov 21

Bonfrate V, Manno D, Serra A, Salvatore L, Sannino A, Buccolieri A, Serra T, Giancane G. Enhanced electrical conductivity of collagen films through long-range aligned iron oxide nanoparticles. J Colloid Interface Sci. 2017;501:185-91

Cochis A, Grad S, Stoddart MJ, Fare S, Altomare L, Azzimonti B, Alini M, Rimondini L. Bioreactor mechanically guided 3D mesenchymal stem cell chondrogenesis using a biocompatible novel thermo-reversible methylcellulose-based hydrogel. Sci Rep. 2017;7:45018

Collin EC, Carroll O, Kilcoyne M, Peroglio M, See E, Hendig D, Alini M, Grad S, Pandit A. Ageing affects chondroitin sulfates and their synthetic enzymes in the intervertebral disc. Signal Transduct Target Ther. 2017;2(publ online Sept 22)

Cruz MA, McAnany S, Gupta N, Long RG, Nasser P, Eglin D, Hecht AC, Illien-Junger S, Iatridis JC. Structural and Chemical Modification to Improve Adhesive and Material Properties of Fibrin-Genipin for Repair of Annulus Fibrosus Defects in Intervertebral Disks. J Biomech Eng. 2017;139(8)

D'Amora U, D'Este M, Eglin D, Safari F, Sprecher CM, Gloria A, De Santis R, Alini M, Ambrosio L. Collagen density gradient on three-dimensional printed poly(epsilon-caprolactone) scaffolds for interface tissue engineering. J Tissue Eng Regen Med. 2017;epub Aug 17

Donnelly H, Smith CA, Sweeten PE, Gadegaard N, Meek RD, D'Este M, Mata A, Eglin D, Dalby MJ. Bone and cartilage differentiation of a single stem cell population driven by material interface. J Tissue Eng. 2017;8:2041731417705615

Fahy N, Alini M, Stoddart MJ. Mechanical stimulation of mesenchymal stem cells: Implications for cartilage tissue engineering. J Orthop Res. 2017;epub Aug 11

Ferstl R, Frei R, Barcik W, Schiavi E, Wanke K, Ziegler M, Rodriguez-Perez N, Groeger D, Konieczna P, Zeiter S, Nehrbass D, Lauener R, Akdis CA, O'Mahony L. Histamine receptor 2 modifies iNKT cell activity within the inflamed lung. Allergy. 2017;72:1925-1935

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15.5 Theses / Dissertations

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2017 Universität Zürich (Moriarty TF, O'Mahony L) – PhD

Gieling F. Does the sorting of mesenchymal stem cells based on their Runx2/Sox9 expression ratio improve bone healing in calvarial defects in rats?
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Barcik JP. Actuator - Sensor unit to investigate the influence of mechanical stimulation on bone healing. 2017 AGH University of Science and Technology Kraków (M. Lubieniecki, M. Ernst, M. Windolf) – MSc

15.6 Abstracts published in Journals

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Wagner D, Hofmann A, Kamer L, Sawaguchi T, Noser H, Rommens PM. Alarmingly Low Sacral Bone Mass in Sacra with a Fragility Fracture of the Sacrum. Global Spine Journal. 2017;7(2 Suppl):346S (GSC / poster)

Wichmann T, Moriarty TF, Keller I, Pfister S, Deggim-Messmer V, Gautier E, Kalberer F, Koch PP, Wahl P.

Perioperative contamination of knitted cotton outer gloves in hip and knee arthroplasty surgery. Swiss Med Wkly 2017;147(Suppl 223):5 S (SwissOrthop /oral)

Wystrach L, Kubosch DC, Südkamp N, Bernstein A, Alini M, Grad S, Li Z, Lang GM.
The Tissue-Renin-Angiotensin-System of the Human Intervertebral Disc.
Eur Spine J. 2017;26(11):2978 (DWK / poster)

15.7 Abstracts of Conference Presentations

Acklin YP, Zderic I, Richards RG, Schmitz P, Gueorguiev B, Grechenig S. Biomechanical comparison of different fixation techniques in sacrum Denis type II fracture with low bone mineral density. 2017 EFORT (oral)

Acklin YP, Zderic I, Grechenig S, Richards RG, Schmitz P, Gueorguiev B. Are two retrograde 3.5mm screws superior to one 7.3mm screw for anterior pelvic ring fixation in low bone mineral density? A biomechanical study. 2017 EFORT (oral)

Armiento A, Alini M, Stoddart M. Modulation of Runx2 and pRb during in vitro chondrogenesis and osteogenesis of human mesenchymal stromal cells. 2017 TERMIS-EU (oral)

Armiento AR, Basoli V, Alini M, Stoddart MJ. Role of Runx2 and pRb during chondrogenic and osteogenic commitment of mesenchymal stromal cells. 2017 FIRM (oral)

Augurio A, Cortelletti P, Alini M, Eglin D, Serra T, Speghini A. 3D printed upconverting nanoparticles loaded gelatin methacrylate for non-invasive tracking and manipulation.
2017 SSB+RM YS (poster)

Behrendt P, Lippross S, Richards RG, Alini M, Eglin D, Armiento A. Tyramine-modified hyaluronan hydrogel for human chondrocyte encapsulation: cell viability, rheological and bioadhesive properties. 2017 SSB+RM (poster)

Behrendt P, Lippross S, Richards RG, Eglin D, Armiento A. Tyramine-modified hyaluronan hydrogel for mesenchymal stromal cell encapsulation: cell viability and rheological properties. 2017 TERMIS-EU (oral)

Behrendt P, Lippross S, Richards RG, Alini M, Eglin D, Armiento AR. Characterisation of tyramine-modified hyaluronic acid hydrogels in tissue engineering and regenerative medicine applications for articular cartilage repair. 2017 FIRM (oral)

Berset CM, Lanker U, Zeiter S. Sheep Usage in Biomedical Research: an ESLAV, ECLAM, SGV, AFSTAL, Swiss AWO and VOLE survey. 2017 LAVA-ESLAV-ECLAM (poster)

Berset C. FELASA Working Group on Farm Animals: Health and Welfare of Ruminants and Pigs. 2017 SGV (abstract published as a communication in the proceedings)

Boot W, D'Este M, Moriarty F, Schmid T, Zeiter S, Richards RG, Eglin D. Local antibiotic delivery with thermoresponsive hyaluronan hydrogel successfully treats chronic intramedullary nail-related infection in a single stage revision. 2017 TERMIS-EU (poster)

Cochis A, Grad S, Stoddart MJ, Faré S, Altomare L, Azzimonti B, Sorrentino R, Alini M,
Rimondini L. Bioreactor Mechanically Guided 3D Mesenchymal Stem Cell Chondrogenesis in a Novel Thermo-Reversible Methylcellulose-Based Hydrogel. 2017 ESB (poster)

Cunha C, Teixeira GQ, Leite Pereira C, Eglin D, Grad S, Goncalves RM, Barbosa MA. Rat Intervertebral Disc Degeneration and Herniation Model for Local Biomaterial Delivery. 2017 ESB (poster)

Czekanska EM, Rothweiler R, Bara JJ, Richards RG, Alini M, Stoddart MJ.
Differentiating mesenchymal stromal cells towards an early osteocyte-like phenotype in vitro. 2017 ORS (poster)

D'Amora U, D'Este M, Eglin D, Gloria A, De Santis R, Alini M, Ambrosio L.
Design of additive manufactured structures with functional gradients for interface tissue engineering. 2017 TERMIS-EU (poster)

D'Este M, Plumecoq A, Alini M, Demazeau G. High hydrostatic pressure for decontamination of soft biomaterials. 2017 SSB+RM (oral)

D'Este M, Boot W, Moriarty TF, Schmid T, Zeiter S, Richards RG, Eglin D. Treatment of chronic implant-related infection in sheep in a single stage revision by local gentamicin delivery with a thermoresponsive hyaluronan hydrogel. 2017 SSB+RM (poster)

Dlaska CE, Dufekci P, Tavakoli A, Shanker M, Saifzadeh S, Windolf M, Schütz M, Epari D. Full control of the fracture: A novel in-vivo method that allows studying the mechanobiology of a fracture. 2017 DKOU (poster)

Duttenhoefer F, Jenni D, Varga P, Gruenwald L, Schmelzeisen R, Stricker A. Distraktionskapazität und Frakturverhalten der Bone-Split Technik: Biomechanische Validierung von Finite-Elemente Modellen. 2017 MKG Chirurgie (oral)

Fahmy-Garcia S, Mumcuoglu D, de Miguel L, Dieleman V, van der Eerden B, Eglin D, Kluijtman S, van Osch G, Farrell E. Alginate and hyaluronic acid as injectable hydrogels to apply BMP2-loaded microspheres induced differences in macrophage infiltration, vascularisation and bone formation. 2017 TERMIS-EU (poster)

Fahy N, Gardner O, Alini M, Stoddart M. Effect of spatial PTHrP signalling gradients on human mesenchymal stem cell chondrogenesis and hypertrophy. 2017 TERMIS-EU (poster)

Frauchiger D, Tekari A, Benneker LM, Sakai D, Grad S, Stoyanov J, Bertolo A, Gantenbein B. Protocols for isolation of nucleus pulposus progenitor cells from bovine intervertebral disc. 2017 BioSpine (oral)

Frauchiger D, Tekari A, Benneker LM, Sakai D, Grad S, Stoyanov J, Bertolo A, Gantenbein B. Fishing nucleus pulposus progenitor cells from bovine intervertebral discs using three different sorting methods. 2017 TERMIS-EU (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. 2017 ORS (ICORS best poster)

Gardner OF, Fahy N, Alini M, Stoddart MJ. Mechanically induced chondrogenesis ex vivo - Towards regenerative rehabilitation. 2017 GRC Cartilage Biology & Pathology (oral)

Grad S, Li Z, Peroglio M, Alini M. Cell homing and intervertebral disc regeneration - lessons from organ culture studies. 2017 TERMIS-EU (oral)

Grüneweller N, Raschke MJ, Widmer D, Zderic I, Wähnert D, Gueorguiev B, Fuchs T, Windolf M. Biomechanische Implantattestung von augmentierten und nicht-augmentierten iliosakralen Schrauben in einem neuen Hemi-Pelvis-Modell. 2017 DGfB, Hannover (poster)

Grüneweller N, Raschke MJ, Widmer D, Zderic I, Wähnert D, Gueorguiev B, Fuchs T, Windolf M. Biomechanische Untersuchung von augmentierten und nicht-augmentierten SI-Schrauben in einem neuartigen Hemi-Pelvis-Modell. 2017 DGCH, München (oral)

Grünwald L, Buschbaum J, Lobenhoffer P, Windolf M, Schröter S. X-Ray based navigation system for torsional correction - first clinical data. 2017 DKG (oral)

Gueorguiev B, Todorov D, Zderic I, Stoffel K, Lenz M, Richards RG, Enchev D. Augmented LISS plating is biomechanically advantageous over conventional LISS plating. 2017 DKOU (oral)

Gueorguiev B, Nienhaus M, Stoffel K, Zderic I, Wahl D, Sommer C, Rommens PM. Locked intraosseous nailing in transverse patella fractures – a biomechanical comparison to tension band wiring through cannulated screws. 2017 DKOU (oral)

Guillaume O, Zhang X, Richards RG, Peijs T, Eglin D, Gautrot J. Hybrid polymeric structure for drug delivery purpose adaptable to photo-crosslinkable resin. 2017 SSB+RM (poster)

Guillaume O, Geven M, Zeiter S, Grijpma D, Alini M, Richards RG, Eglin D.
Patient-specific implant made of degradable poly(trimethylene carbonate) – hydroxyapatite implant for bone repair: in vitro and in vivo evaluation. 2017 TERMIS-EU (oral)

Guillaume O, Geven M, Sprecher C, Zeiter S, Grijpma D, Alini M, Richards RG, Eglin D. Surface-enriched PTMC scaffolds with hydroxyapatite for bone tissue regeneration. 2017 BioMAT (oral)

Guillaume O, Geven M, Stadelmann V, Zeiter S, Grijpma D, Alini M, Richards RG, Eglin D. 3D-Printed Disparate Scaffold with Spatially Controlled Repartition of Hydroxyapatite: New Generation of Implants for Bone Repair and Beyond? 2017 ESB

Guillaume O, Geven M, Schmid T, Grijpma D, Bos R, Richards RG, Alini M, Eglin D. Patient-Specific Implant Made by Stereolithography for Orbital Floor Regeneration. 2017 bone-tec (oral)

He X, Milz S, Michalke B, Sprecher CM, Gahlert M, Röhling S, Kniha H, Hoegg C, Reich F. The release of titanium and zirconium in mini pig maxillae from titanium-implants and zirconia implants. 2017 TERMIS-EU (poster)

He X, Milz S, Michalke B, Sprecher CM, Gahlert M, Röhling S, Kniha H, Högg C, Reichl FX. Comparison of titanium and zirconium release from titanium- and zirconia implants in mini pig maxillae. 2017 EORS (oral)

Herrmann M, Hildebrand M, Alini M, Verrier S. Mimicking the early regenerative response of perivascular stem cells in vitro. 2017 TERMIS-EU (poster)

Herrmann M, Hildebrand M, Alini M, Verrier S. Mimicking the early regenerative response of perivascular stem cells in vitro. 2017 DKOU (oral)

Hu M, Nuzzo A, D'Este M, Richards RG, Lee P, Alini M, Grad S, Peroglio M. In vitro and organ culture evaluation of chemically crosslinked hyaluronic acid hydrogels for nucleus pulposus repair. 2017 TERMIS-EU (oral)

Knierzinger D, Buschbaum J, Konschake M, Richards RG, Blauth M, Windolf M. *Ex-vivo* evaluation of a novel system for implant positioning assistance at the proximal humerus using angular stable plates. 2017 DGfB (poster)

Lang G, Liu Y, Zhou Z, Kubosch D, Südkamp N, Alini M, Grad S, Li Z. A proinflammatory and degenerative intervertebral disc organ culture model by combining TNF-α intradiscal injection and detrimental dynamic loading. 2017 ORS (poster)

Lang G, Liu Y, Zhou Z, Kubosch D, Südkamp N, Richards RG, Alini M, Grad S, Li Z. Establishment of a proinflammatory and degenerative intervertebral disc organ culture model. 2017 BioSpine (oral)

Lang G, Liu Y, Zhou Z, Kubosch D, Südkamp N, Richards RG, Alini M, Grad S, Li Z. An intervertebral disc organ culture model mimicking proinflammatory and degenerative disease condition. 2017 TERMIS-EU (oral)

Lang G, Liu Y, Geries J, Kubosch D, Südkamp NP, Alini M, Grad S, Li Z. Establishment of a proinflammatory and degenerative intervertebral disc ex vivo system to investigate anti-inflammatory therapies for degenerative disc disease. 2017 DKOU (oral)

Leite Pereira C, Teixeira GQ, Caldeira J, D'Este M, Eglin D, Alini M, Grad S, Barbosa MA, Goncalves RM. Mesenchymal stem/stromal cells recruitment from the cartilaginous endplate: a new perspective for IVD regenerative strategies through ECM remodeling.
2017 TERMIS-EU (oral)

Leite Pereira C, Teixeira G, Caldeira J, D'Este M, Eglin D, Grad S, Barbosa MA, Goncalves RM. Hyaluronan-based Hydrogel for SDF-1 Delivery in the Intervertebral Disc: Insights from an Ex Vivo Model. 2017 ESB

Li Z, Lang G, Liu Y, Geries J, Zhou Z, Kubosch D, Südkamp N, Alini M, Grad S. Short- and mid-term effect of TNF-α intradiscal injection and detrimental dynamic loading in intervertebral disc organ culture. 2017 AOSpine Masters (oral)

Li Z, Lang G, Heizmann F, Liu Y, Geries J, Kubosch D, Südkamp N, Alini M, Grad S. Anti-inflammatory and regenerative drug therapy for the treatment of degenerative disc disease: Validation in organ culture model. 2017 ORS PSRS (poster)

Loebel C, Szczesny SE, Cosgrove BD, Zenobi-Wong M, Mauck RL, Alini M, Eglin D. Dual Crosslinked Hydrogels for Tailoring Cells Spatial and Temporal Microenvironment. 2017 ESB

Long RG, Nakai T, Sakai D, Benneker LM, Iatridis JC, Alini M, Grad S, Li Z. TGFβ1 induces a contractile CD146+ phenotype of human annulus fibrosus cells showing affinity to collagen scaffold aimed for annulus fibrosus repair. 2017 ORS (poster)

Long R, Ferguson S, Zeiter S, Benneker L, Alini M, Iatridis J, Grad S. Genipin cross-linked fibrinogen repairs annular defects with restoration of biomechanics in vitro and in vivo.
2017 TERMIS-EU (poster)

Matsuura M, Schmidutz F, Sprecher C, Müller P, Chevalier Y. Micro finite element analysis of periprosthetic bone tissue and stemless humeral implants. 2017 EORS (oral)

Milz S, Sprecher CM, Suter T, Keating JH, McCarthy RJ, Gueorguiev B, Richards RG, Boudrieau RJ. Association of peri-implant osteosarcoma and corroding cast stainless steel implants in dogs. 2017 EORS (poster)

Monaco G, Fahy N, Alini M, Stoddart MJ. Hyaluronan supplemented culture media positively influences human mesenchymal stem cell chondrogenesis. 2017 Gordon Res Conf (poster)

Monaco G, Fahy N, Alini M, Stoddart MJ. Hyaluronan supplemented culture media positively influences human mesenchymal stem cell chondrogenesis. 2017 SBMS (oral)

Monaco G, Fahy N, Alini M, Stoddart M. Effect of hyaluronan supplemented culture media on human mesenchymal stem cell chondrogenesis. 2017 TERMIS-EU (poster)

Monaco G, Alini M, El Haj AJ, Stoddart MJ. Effect of hyaluronan supplemented culture media on human mesenchymal stem cell chondrogenesis. 2017 SSB+RM YS (poster)

Moran E, Zderic I, Klos K, Simons P, Triana M, Richards RG, Gueorguiev B, Lenz M. Reconstruction of the lateral tibia plateau fracture with a third triangular support screw. A biomechanical study. 2017 EFORT (oral)

Pereira AR, Barbe L, Herrmann M, Alini M, Verrier S. Cellularized Perfusable Microvessels for the Study of Human Pericytes Response to Paracrine Signals. 2017 SBMS (oral)

Pereira AR, Barbe L, Herrmann M, Alini M, Verrier S. Development of a Perfuseable On-Chip Microvascular Network for the Study of Pericytes Migration and Plasticity in Response to Bone Healing Related Signals. 2017 bone-tec (oral)

Perez-San Vicente A, Peroglio M, Ernst M, Casuso P, Loinaz I, Grande HJ, Alini M, Eglin D, Dupin D. Injectable and self-healing dynamic hydrogel as potential artificial nucleus pulposus for intervertebral disc repair. 2017 TERMIS-EU (poster)

Petta D, Grijpma DW, Armiento A, Eglin D, D'Este M. Tyramine modified hyaluronic acid ink for 3D-printed cellularized construct. 2017 SSB+RM (oral)

Puetzler J, Zeiter S, Vallejo A, Gehweiler D, Richards RG, Moriarty TF. Influence of early versus delayed antibiotic intervention on treatment of Staphylococcus aureus fracture-related infection in rabbits. 2017 SSB+RM (oral)

Pützler J, Arens D, Metsemakers WJ, Zeiter S, Kuehl R, Richards RG, Raschke M, Moriarty TF. Antibiotic prophylaxis with cefuroxime: influence of duration on infection rate with staphylococcus aureus in an open fracture model.2017 DKOU (oral)

Rotman SG, Grijpma DW, Moriarty TF, Richards RG, Eglin D, Guillaume O. Poly(ε-caprolactone) particulate carrier systems for antibiotic drug delivery applications. 2017 SSB+RM (poster)

Rotman SG, Grijpma DW, Moriarty TF, Guillaume O, Eglin D. Surface modified polyester microparticles for bone targeted drug delivery. 2017 FIRM (oral & poster)

Rotman SG, Grijpma DW, Moriarty TF, Guillaume O, Eglin D. Surface modified polyester microparticles for bone targeted drug delivery. 2017 SSB+RM YS (poster)

Sabaté Bresco M, Berset C, Richards RG, Moriarty TF, O'Mahony L. Immune responses in a murine device-related infection model: role of IL-17A. 2017 EAACI Immunology (poster)

Sabaté Bresco M, Berset C, Zeiter S, Schmid T, Richards RG, Moriarty TF, O'Mahony L. Role of IL-17A in a murine device-associated infection model. 2017 WIRM (poster)

Safari F, Eglin D, Alini M, Stoddart MJ, Eslaminejad MB. Cartilage differentiation of hBM-MSCs on human wharton's jelly-derived scaffolds. 2017 TERMIS-EU (poster)

Serra T, Bonfante V, Manno D, Serra A, Salvatore L, Buccolieri A, Giancane G. Electrically conductive collagen films by long range aligned iron oxide nanoparticles. 2017 ESB

Sprecher CM, Schmidutz F, Milz S, Schiuma D, Windolf M, Richards RG, Popp AW. Increasing porosity correlates with decreasing T-scores in the distal tibia of postmenopausal women. 2017 SSB+RM (poster)

Stadelmann V, Acevedo C, Freitag L, Eberli U, Inzana J, Zeiter S. Mice tibia do not weaken mechanically under long-term intense in vivo fatigue loading. 2017 SBMS (oral)

Stadelmann VA, Camenisch K, Thompson K, Eberli U, Zeiter S, Moriarty TF. A standardized rat model for monitoring bone changes in implant-related osteomyelitis with fully automated in vivo microCT image processing workflow. 2017 SSB+RM (oral)

Stadelmann VA, Geven M, Grijpma D, Richards RG, Eglin D, Guillaume O. A novel micro-computed tomography procedure for the quality control of personalized 3D-printed implants: an illustration using stereolithography-printed scaffolds. 2017 TERMIS-EU (poster)

Stanic B, Richards RG, O'Mahony L, Moriarty TF. Immunoregulatory mechanisms tailored by *Staphylococcus epidermidis in vitro*. World Immune 2017 WIRM (poster)

Stanic B, Konta M, Sabaté Bresco M, Ladouce R, Mercep M, Richards RG, Moriarty TF. Identification of immunodominant peptides of *Staphylococus epidermidis* origin in the bone infection of human patients and experimental mice. 2017 WIRM (poster)

Stanic B, Richards RG, O'Mahony L, Moriarty TF. Immunoregulatory mechanisms tailored by *Staphylococcus epidermidis in vitro*. 2017 GRS Staph Dis (poster)

Stanic B, Morgenstern M, Thöny S, Konta M, Sabaté Bresco M, Mercep M, Daiss JL, Schwarz EM, Richards RG, Moriarty TF. Identification of immunogenic peptides of *Staphylococus epidermidis* origin in the context of bone infection using combined systematic immunoproteomics approach. 2017 GRC Staph Dis (poster)

Stanciuc A, Alini M, Peroglio M, Gremillard L. Robocast zirconia toughened alumina scaffolds: processing and human primary osteoblast response. 2017 TERMIS-EU (poster)

Stoddart MJ. Bioreactors for musculoskeletal research. 2017 ORS (oral)

Stoddart M. Gene transfer for musculoskeletal regeneration. 2017 TERMIS-EU (oral)

Stoddart M. Regulating chondroprogenitor cell fate using mechanical stimulation. 2017 TERMIS-EU (oral)

ter Boo GA, Schmid T, Grijpma DW, Richards RG, Moriarty TF, Eglin D. Preventing Infection in a Fracture Model In Rabbits Using a Gentamicin-Loaded ThermoResponsive Hyaluronic Acid. 2017 ESB (poster)

Thompson K, Petkov S, Zeiter S, Sprecher CM, Baumann A, Richards RG, Moriarty TF, Eijer H. Gentamicin loading of calcium phosphate-coated implants prevents experimental Staphylococcus aureus device-associated infection. 2017 SSB+RM (oral)

Thompson K, Bara JJ, Dresing I, Zeiter S, Anton M, Daculsi G, Eglin D, Nehrbass D, Betts DC, Müller R, Stadelmann VA, Alini M, Stoddart MJ. Efficacy of Doxycycline-Inducible, Adenoviral BMP-2 Delivery for Repair of Large Bone Defects. 2017 bone-tec (poster)

Todorov D, Zderic I, Stoffel K, Richards RG, Lenz M, Enchev D, Gueorguiev B. Is augmented LISS plating biomechanically advantageous in comparison to conventional LISS plating? 2017 EFORT (oral)

Todorov D, Zderic I, Stoffel K, Richards RG, Lenz M, Enchev D, Gueorguiev B. Biomechanical investigaton of augmented versus conventional LISS plating of distal femoral fractures. 2017 ESBioMech (poster)

Todorov D, Gueorguiev B, Zderic I, Stoffel K, Richards RG, Lenz M, Enchev D, Baltov A. Are there biomechanical benefits in augmentation of LISS plating compared to conventional LISS plating? 2017 Osteosynthese International (oral)

Todorov D, Gueorguiev B, Zderic I, Stoffel K, Richards RG, Lenz M, Enchev D, Baltov A. Biomechanical comparison of augmented locking plate fixation versus conventional locking plating. 2017 EORS (oral)

Tognato R, Giancane G, Alini M, Eglin D, Serra T. 3D electrically conductive gelatin hydrogel for cell alignment. 2017 SSB+RM YS (poster)

Triana M, Zderic I, Klos K, Simons P, Richards RG, Gueorguiev B, Lenz M, Munoz A, Moran E. Manejo quirúrgico de las fracturas del platillo tibial lateral con técnica novedosa. [Surgical management of lateral tibial plateau fractures with a novel technique.] 2017 Cardioinfantil (poster)

Vainieri ML, Wahl D, Lezuo P, Van Osch GJVM, Alini M, Grad S. Novel ex-vivo osteochondral defect model in a joint bioreactor system for articular cartilage repair studies. 2017 GRC Cartilage Biology & Pathology (poster)

Vainieri ML, Wahl D, Lezuo P, van Osch G, Alini M, Grad S. Novel ex-vivo osteochondral defect model in a joint bioreactor system for articular cartilage repair studies. 2017 TERMIS-EU (poster)

Varga P, Grünwald L, Inzana J, Windolf M. Fatigue failure of plated osteoporotic proximal humerus fractures is predicted by the strain around the screws. 2017 ESBioMech (oral)

Varga P, Jenni D, Grünwald L, Gueorguiev B, Duttenhöfer F, Stricker A. Experimental and numerical investigation of the alveolar ridge splitting technique. 2017 ESBioMech (oral)

Wagner D, Sawaguchi T, Kamer L, Noser H, Rommens PM. Dramatische Abnahme der Knochenmasse bei Fragilitätsfrakturen des Sakrums, dargestellt in einem statistischen Modell. 2017 VSOU (oral)

Wahl P, Sprecher CM, Brüning C, Meier C, Gautier E, Moriarty TF. Bony integration of porous tantalum despite ongoing infection: histologic workup of an explanted shoulder prosthesis. 2017 SSB+RM (poster)

Wahl P, Sprecher CM, Brüning C, Meier C, Gautier E, Moriarty TF. Bony integration of porous tantalum despite ongoing infection: histologic workup of an explanted shoulder prosthesis. 2017 EBJIS (poster)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. Mesenchymal Stem Cells Expressing the Cell Adhesion Molecule CD146 Present Increased Homing Potential Towards Degenerative Intervertebral Discs - an Organ Culture Study.
2017 ORS (oral)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. CD146 positive mesenchymal stem cell possess a superior migration potential both in vitro and in whole organ culture. 2017 BioSpine (oral)

Wangler S, Menzel U, Li Z, Benneker LM, Richards RG, Alini M, Peroglio M, Grad S. Role of CD146 in mesenchymal stem cell homing and regeneration of the intervertebral disc: an in vitro and whole organ culture study. 2017 TERMIS-EU (poster)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. CD146 positive mesenchymal stem cells possess a superior migration potential towards induced degenerative intervertebral discs. 2017 SSB+RM YS (oral)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. CD146 positive mesenchymal stem cell possess a superior migration potential both in vitro and in whole organ culture. 2017 AOSpine Masters (oral)

Wichmann T, Moriarty TF, Keller I, Pfister S, Deggim-Messmer V, Gautier E, Kalberer F, Koch PP, Wahl PP. Contamination of knitted cotton outer gloves during hip and knee arthroplasty surgery might be an infection risk. 2017 EBJIS (poster)

Wu Y, Stoddart M, Wuertz-Kozak K, Grad S, Alini M, Ferguson S. The Influence of Synovial Fluid Properties on Tissue Engineering Cartilage Development. 2017 ORS (poster)

Zahn J, Loibl M, Sprecher C, Nerlich A, Alini M, Verrier S, Herrmann M. Platelet-rich plasma as an autologous and pro-angiogenic cell delivery system. 2017 DKOU (oral)

Zderic I, Oh JK, Stoffel K, Helfen T, Camino Willhuber G, Nork SE, Sommer C, Gueorguiev B. Do quality of reduction and screw orientation affect the performance of the proximal femoral locking plate? 2017 ESBioMech (oral)

Zderic I, Nienhaus M, Wahl D, Gueorguiev B, Rommens PM. Biomechanical investigation of locked intraosseous nailing for transverse patella fracture fixation. 2017 ESBioMech (oral)

Zderic I, Acklin Y, Richards RG, Schmitz P, Gueorguiev B, Grechenig S. Biomechanical comparison of four different fixation techniques in sacrum Denis type II fractures. 2017 ESBioMech (oral)

Zeiter S. Design of an animal study - a stepwise approach. 2017 TERMIS-EU (oral)

Zeiter S. Rodents have a right for asepsis. 2017 SGV (oral)

Zhou Z, Alini M, Grad S, Li Z. Effect of the CCL5 releasing fibrin gel for intervertebral disc regeneration. 2017 TERMIS-EU (poster)

Zhou Z, Alini M, Grad S, Li Z. An organ culture model mimicking early onset of degenerative disc disease induced by one strike. 2017 ORS PSRS (poster)

Ziadlou R, Grad S, Stoddart MJ, Xinluan W, Ling Q, Barbero A, Martin I, Alini M. The anabolic and anti-inflammatory effects of biological small molecules for treatment of osteoarthritis. 2017 GRC Cartilage Biology & Pathology (poster)

Ziadlou R, Grad S, Stoddart M, Wang X, Ling Q, Barbero A, Martin I, Alini M. The anabolic and anti-inflammatory effects of biological small molecules for treatment of osteoarthritis. 2017 SSB+RM (poster)

Ziadlou R, Grad S, Stoddart MJ, Barbero A, Martin I, Alini M. Screening of anabolic and anti-inflammatory effect of biological small molecules for treatment of osteoarthritis.
2017 TERMIS-EU (poster)

Ziadlou R, Grad S, Stoddart M, Wang X, Qin L, Barbero A, Martin I, Alini M. High throughput screening towards a herbal drug delivery system for treatment of osteoarthritis.
2017 FIRM (poster)

Ziadlou R, Grad S, Stoddart M, Barbero A, Martin I, Eglin D, Alini M. Screening of herbal small molecules towards drug delivery system for treatment of osteoarthritis.
2017 SSB+RM YS (poster)

15.8 Presentations (not in conference proceedings)

25.02.2017	Richards Geoff: "Experimental studies of Infection after osteosynthesis", Southwest Orthopedic Forum, Chongqing, China (Invited Speaker)
13.03.2017	Richards Geoff: "Research & Innovation at the AO Foundation", csemviva! Von der Technologie zum Markt – Innovation in Zeiten des Wandels, Hamilton Bonaduz AG, Switzerland (Invited Speaker)
28.03.2017	Richards Geoff: "Research Developments in Trauma Care, Imaging and Beyond", International Diagnostic Course, Davos, Switzerland (Invited Speaker)
31.03.2017	Richards Geoff: "AO Research Institute Davos", Information Day WSL-Institute for Snow and Avalanche Research SLF, Davos (Invited Speaker)
11.04.2018	Richards Geoff: "Infected fractures and plates: help from the future", AOTrauma Advanced Symposium, Noordwijk, Netherlands (Invited Speaker)
21.04.2017	Richards Geoff: "Introduction AO Research Institute Davos and preclinical translation", Practical course "Skeletal Repair" for students from ETHZ and ZHAW, Davos, Switzerland
19.-21.05.2017	Richards Geoff: "Influence of the implant surface on tissue reactions during fracture fixation", Malaysian Orthopaedic Association, 47th Annual Scientific Meeting, Kuala Lumpur, Malaysia (Invited Speaker)
08.07.2017	Richards Geoff: "Report from AO Research Institute Davos", Board of Trustees Meeting, Miami, FL, USA (Invited Speaker)
05.-07.09.2017	Richards Geoff: "Multi disciplinary translation research to solve clinical problems to help the patient: The AO success since 1959", 28th Annual Conference of the European Society for Biomaterials ESB, Athens, Greece (Invited Speaker)
14.09.2017	Richards Geoff: Session "Smart Surgery by AO Research Institute Davos", EORS (European Orthopaedic Research Society) 25th Annual Meeting, Munich, Germany (Session Chair)
14.09.2017	Richards Geoff: Plenary Lecture Chris Evans "Progress in the clinical translation of orthopaedic gene therapy", EORS (European Orthopaedic Research Society) 25th Annual Meeting, Munich, Germany (Chair)
16.11.2017	Richards Geoff: "Smart Surgery", The 12th International Congress of Chinese Orthopaedic Association COA2017, Zhuhai, China (Invited Speaker)
08.12.2017	Richards Geoff: "Latest developments from the AO Research Institute that will help the surgeon and patient", AOTrauma Course – Basic Principles of Fracture Management, Davos, Switzerland (Invited Speaker)
17.02.2017	Alini Mauro: "Endogenous repair for IVD", Rizzoli Hospital, Bologna, Italy (Invited Speaker)
10.05.2017	Alini Mauro: "Bone: structure and properties, cell biology and physiology. Training school: Non living materials meet living biology", COST MP 1301, NEWGEN, Patras, Greece (Invited Speaker)
13.05.2017	Alini Mauro: "Chemoattractant and Stem Cells in the Regeneration of Intervertebral Discs", BIOMED 2017, 22nd Biomedical Science & Technology Symposium, Ankara, Turkey (Invited Speaker)
07.07.2017	Alini Mauro: "Mechanical Loading and Cell Differentiation", Workshop to honour Prof Yannis Missirlis, Thessaloniki, Greece (Invited Speaker)
13.07.2017	Alini Mauro: "Endogenous vs. exogenous repair for IVD", 2nd International Conference on Stem Cells (ICS2017), Teheran, Iran (Invited Speaker)
14.07.2017	Alini Mauro: "MSC and Complex Loading Pattern for Cartilage Repair", 2nd International Conference on Stem Cells (ICS2017), Teheran, Iran (Invited Speaker)
31.05.-02.06.2017	Gueorguiev Boyko: "Are two retrograde 3.5mm screws superior to one 7.3mm screw for anterior pelvic ring fixation in low bone mineral density? A Biomechanical Study", 18th EFFORT Congress (European Federation of National Association of Orthopaedics and Traumatology), Vienna, Austria

02.-05.07.2017	Gueorguiev Boyko: "Biomechanical comparison of four different fixation techniques in sacrum Denis type II fractures", ESB (European Society of Biomechanics), Seville, Spain (Invited Speaker)
11.07.2017	Gueorguiev Boyko: "Implant augmentation with bone cement in osteoporotic bone", Universitätsklinikum Regensburg, Germany (Invited Speaker)
12.07.2017	Gueorguiev Boyko: "AO Translational Research", University Stuttgart, Stuttgart, Germany (Invited Speaker)
29.09.2017	Gueorguiev Boyko: "Why and how do locking plates fail?", 5th Serbian Trauma Association Congress, Nis, Serbia (Invited Speaker)
29.09.2017	Gueorguiev Boyko: "AO Translational Research", 5th Serbian Trauma Association Congress, Nis, Serbia (Invited Speaker)
24.-27.10.2017	Gueorguiev Boyko: "Augmented LISS plating is biomechanically advantageous over conventional LISS plating", DKOU (Deutscher Kongress für Orthopädie und Unfallchirurgie), Berlin, Germany (Invited Speaker)
25.09.2017	Eglin David: "Keynote lecture", FIRM symposium, Gerona, Spain (Invited Speaker)
08.12.2017	Eglin David: "Keynote lecture AO Research Institute – The cutting edge on scaffolds", AOTrauma Course – Advanced Principles of Fracture Management, Davos, Switzerland (Invited Speaker)
27.04.2017	Grad Sibylle: "Debate session: Where disc regeneration research should go – Annulus fibrosus", BioSpine 6th International congress on biotechnologies for spinal surgery, Berlin, Germany (Invited Speaker)
28.04.2017	Grad Sibylle: Working group lecture "Annulus fibrosus repair", BioSpine 6th International congress on biotechnologies for spinal surgery, Berlin, Germany (Invited Speaker)
21.06.2017	Grad Sibylle: "Cell delivery and cell recruitment – the role of supporting hydrogel for repair and regeneration", Advanced Summer School: The Research/Clinic Interface at the Spine, Porto, Portugal (Invited Speaker)
27.06.2017	Grad Sibylle: "Cell delivery, homing and regeneration – lessons from organ culture studies", TERMIS-EU Chapter meeting, Davos, Switzerland (Invited Speaker)
25.10.2017	Grad Sibylle: "Cell migration into degenerative intervertebral disc: The good and the bad", ORS Philadelphia Spine Research Symposium, Lake Harmony, USA (Invited Speaker)
25.02.2017	Moriarty Fintan: "Biofilm formation and antibiotic resistance", Southwest Orthopedic Forum, Chongqing, China (Invited Speaker)
16.03.2017	Moriarty Fintan: "Local antibiotic delivery with polymeric carriers: pre-clinical results", Pro-Implant Foundation workshop on periprosthetic joint infection, Berlin, Germany (Invited Speaker)
19.-21.05.2017	Moriarty Fintan: "Local antibiotic delivery with hydrogels: Pre-clinical results", Malaysian Orthopaedic Association, 47th Annual Scientific Meeting, Kuala Lumpur, Malaysia (Invited Speaker)
28.09.2017	Moriarty Fintan: "Preclinical *in vivo* models of implant related bone infection", Academic medical center (AMC), symposium on device associated infections, AMC, Amsterda, Netherlands (Invited Speaker)
17.05.2017	Stoddart Martin: "Training for scientific writing: Tips and Tricks", SSBRM 2017 Young Scientist Pre-Conference Workshop, St. Gallen, Switzerland (Invited Speaker)
25.09.2017	Stoddart Martin: "Mechanically induced chondrogenesis ex vivo – Towards Regenerative Rehabilitation", EMPA, St. Gallen, Switzerland (Invited Speaker)
13.11.2017	Stoddart Martin: "Comparing human MSC chondrogenesis under static and loading conditions", 7th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine, Hong Kong (Invited Speaker)
14.11.2017	Stoddart Martin: "Physical modulation of chondrogenic cell fate", Chinese Orthopaedics Research Society ICORS session, Zhuhai, China (Invited Speaker)

15.11.2017	Stoddart Martin: "Physical modulation of chondrogenic cell fate", The 2nd Orthopedics Salon of Guangdong Provincial Key Laboratory of Orthopedics and Traumatology, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China
05.12.2017	Stoddart Martin: "Bone substitutes and advances for enhancing bone healing", AOTrauma Masters Kurs – SDL-Nonunion/Malunion, Davos, Switzerland (Invited Speaker)
10.12.2017	Stoddart Martin: "Biology of bone healing", AOTrauma Course – Basic Principles of Fracture Management for Swiss Surgeons, Davos, Switzerland (Invited Speaker)
24.05.2017	Berset Corina: "Challenges and opportunities to use sheep in biomedical research", 3rd meeting Large Animals in Research Network (LARN) "Opening the doors to large animal research in high containment", Pirbright Institute, UK
23.03.2017	Ernst Manuela: "New developments and future directions in MIO", 134. Jahreskongress der deutschen Gesellschaft für Chirurgie (DGCH), Munich, Germany (Invited Speaker)
25.11.2017	Li Zhen: "An intervertebral disc whole organ culture system to investigate biological and biomaterial treatments for degenerative disc disease", School of Medicine, Shenzhen University, Shenzhen, China (Invited Speaker)
24.10.2017	Peroglio Marianna: "Biobone – bioceramics for bone regeneration", DKOU (Deutscher Kongress für Orthopädie und Unfallchirurgie), Berlin, Germany (Keynote Speaker)
05.05.2017	Verrier Sophie: "Stem cells and Progenitor cells in Bone formation", SBMS summer school, Interlaken, Switzerland (Invited Speaker)
24.08.2017	Verrier Sophie: "Bone healing in Mammals", Cost Action Training School, Universität Bern, Zollikofen, Switzerland (Invited Speaker)


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