AO Foundation

AO Research Institute Davos

Activity Report 2018

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1 Introduction

2018 was again an excellent year for the AO Research Institute Davos (ARI).

In this report, what is very pleasing is to read all the comments from the scientific and medical fellows, visiting professors and interns who have really made use of their time here in ARI. Some mentioned they had life changing experiences and others, more senior that their fellowship here was the most exciting parts of their careers. This can be attributed to the highly motivated team of the ARI, the friendliness of our staff and students and the great atmosphere to which they arrive into, being involved at the cutting edge of science. We have a huge diversity of fellows from all over the world, of diverse religions and cultures, but here we are all focused together on one thing, advancing patient care through our innovative research and development. Being a team of multidisciplinary scientists, engineers and clinicians sets us apart from nearly all other academic institutions in the field and focusses our minds to solving the clinical issues at hand.

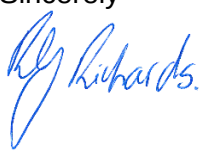
ARI continually collaborates in all fields with other top institutes and universities worldwide and has pushed in recent years in opening up in many areas of China, which has resulted in numerous fellows from this region (many self paying and from Chinese grants) coming to Davos to learn at ARI. These international collaborations are reflected strongly in the project reports and the good news sections within this activity report. This year we also hosted two self paying visiting Professors from Belgium and USA, both having really enjoyed their research here with the ARI and one staying on beyond the visit.

I thank the Clinical Division's R&D Committee members for their continued 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 and helping with translation ideas. Thank you AOFB for your support and trust in ARI, which has brought and continues to bring the academic credibility to the whole of the AO Foundation. This can be seen in our Institutional and Professional Relations listed within the report, our publications, memorandums of understanding and institutional collaborations, presentations at international society conferences and awards at these meetings along with our high level within European and Swiss grant acquisitions.

Yet again the ARI has by far the lowest turnover rate of permanent employees of the AO Foundation, some having worked here for decades. I would particularly note Benni Dicht who retired this year after 41 years' service to ARI and the AO Foundation.

Most importantly, I would like to thank the whole ARI team, which I am honored and very proud to lead, for their continued motivation, dedication and great work in 2018.

Sincerely



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

2 ARI Purpose / Goals / Outlook

Purpose

In its work to further the AO Foundation's mission (promoting excellence in patient care and outcomes in trauma and musculoskeletal disorders), ARI's purpose is to advance patient care through innovative orthopedic research and development.

Goals

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

2016/17 Outlook - Achievements

- Support AO Clinical Divisions with cutting edge research for their clinical problems: **ACHIEVED** and **Ongoing.**
- Initiate agreements to further develop and translate our ideas including Autogauge and X-in-One: **Ongoing,** with translation and contract with DPS near completion.
- Initiate new ARI multi-partner consortium on the theme Osteochondral defect repair: **ACHIEVED.**

3-5-year goals - Achievements

- Develop productive potential of ARI innovation technology portfolio and create an ARI intellectual property strategy: **Ongoing** (ARI Processes used now as standard by AO Foundation, ARI projects evaluated with Canvas model for possible valorization and translation).
- 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 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 (2019)
- Development & translation of our unique smart surgery concepts: e.g. Implant Sensors
- Initiate Europe's first Specific Pathogen Free Sheep flock for 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	**2017 Actual**		**2018 Actual**	
in CHF '000	abs	%	abs	%
AO Foundation Contribution	9'576	70%	9'745	77%
3rd party Income	3'590	26%	2'278	18%
AO Intercompany	529	4%	560	4%
Total Income	**13'695**	**100%**	**12'584**	**100%**
AOTrauma *	3'541	29%	3'821	30%
AOSpine*	419	3%	506	4%
AOCMF *	588	5%	526	4%
AOVET *	87	1%	53	0%
AOTK *	656	5%	561	4%
AOER	1'718	14%	2'066	16%
AO Foundation *	1'708	14%	2'863	23%
3rd party projects	3'590	29%	2'278	18%
Total Expenses	**12'308**	**100%**	**12'674**	**100%**
Net Result	**1'387**		**-90**	

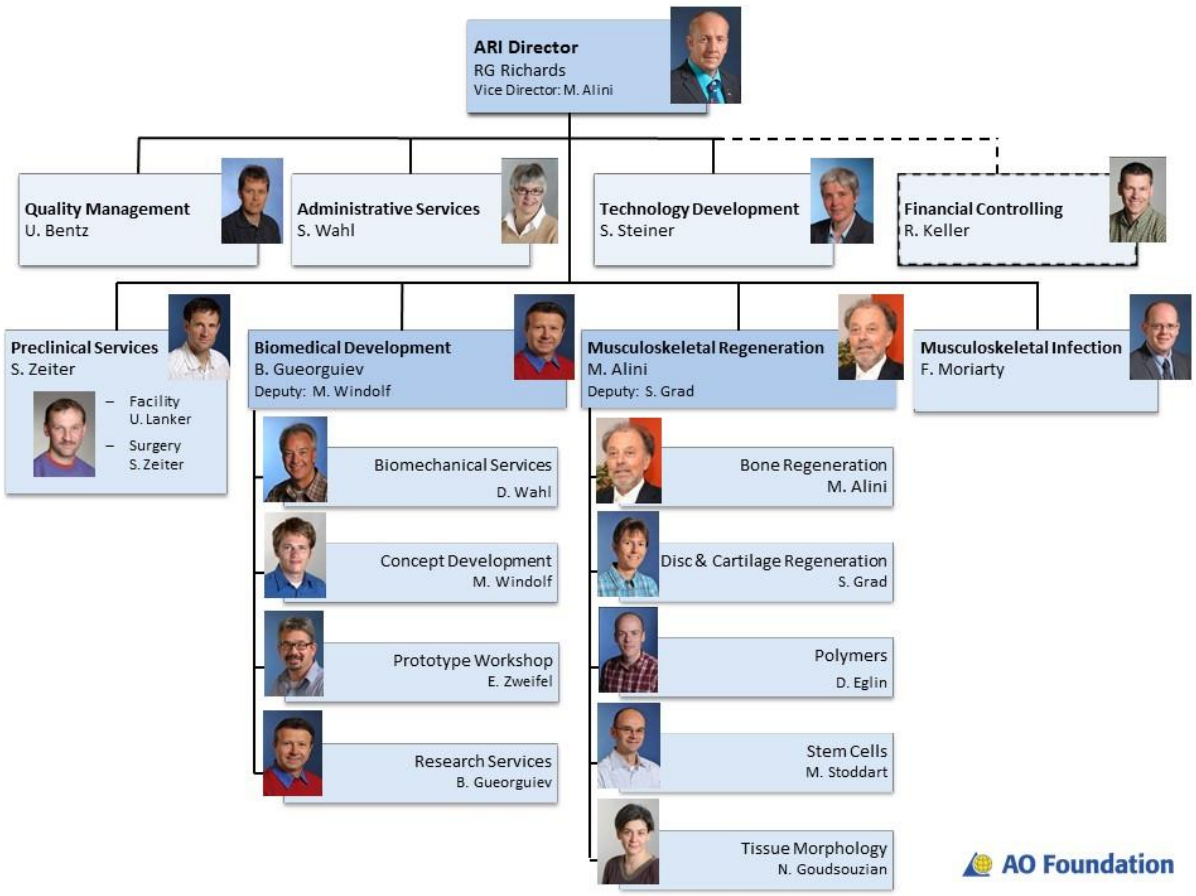
* incl. AO Intercompany

Overall, a negative 'Net Result' of CHF -90 K was achieved compared to a balanced budget.

From a funding perspective, 41% (2017: 47%) of the ARI internal funding was spent on 'Trauma' projects, followed by 'Foundation' with 28% (2017: 20%) and 'Exploratory Research' with 20% (2017: 20%).

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 2018 at the AO Centre, Davos. The ARI AC gives operational and strategic scientific advice 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 a Trustee of the AO Foundation.

The ARI AC (December 2018):
Chair

- Prof Dr Theodore Miclau, Orthopaedic Trauma Institute, San Francisco, USA

Members

- 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: Jan Barcik, Benjamin Burkhard, Jan Buschbaum, Jan Caspar, Daniel Ciric, Benno Dicht, Ursula Eberli, Manuela Ernst, Dominic Gehweiler, Maximilian Heumann, Ladina Hofmann-Fliri, Lukas Kamer, Dominic Mischler, Karen Mys, Bharath Narayanan, Hansrudi Noser, Ronald Schwyn, Flurin Spiller, Peter Varga, Viktor Varjas, Dieter Wahl, Ivan Zderic, Erich Zweifel

Fellows: Igor Escalante, James Fletcher, Vasiliki Panagiotopoulou, Preslav Penev, Yavor Pukalski, Juan Silva, Parvan Yanev, Liza Wenzel

Visiting Professor: Marc Balligand

Guests: Charlotte Arand, Okan Avci, Adam Breceda, Dominik Matschi, Johanna Menze, Verena Neumann, Iacopo Portiaclio, Marco Rossini, Oliver Röhrle, Giuseppe Rupica, Fabrizio Russo, Sergio De Salvatore, Thomas Schaber, Martin Schulze, Luisa Thiemann, Zubin Trivedi, Gianluca Vadalà, Arndt Wagner, Jan-Tobias Weitkamp

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

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 performance 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 the Prototype Workshop offering rapid and high-quality manufacturing of devices, tools and implants.

Biphasic Plate principle demonstration by team member Ladina Hofmann-Fliri for surgeon feedbacks at DKOU 2018.

5.2 Preclinical Services

Program Manager: Stephan Zeiter, Deputy: Urban Lanker

Team Members: Daniel Arens, Corina Berset, Carmen Brazerol, Peter Erb, Loris Faoro, Pierina Faoro, Andrea Furter, Fabian Gieling, Reto Müller, Dominic Perren, Tanja Schmid, Christian von Deimling

Fellows: Tim Buchholz, Valentina Stenger

Student Externs: Anika Biercher, Lena Cieciora, Lena Gens, Hubertus Kähn, Stefania Vogdanou, Josephine Ziebart

Guests: Darleen Tu

Animal welfare, the quality of the data generated, and occupational health and safety are of high importance to us and we conduct all our *in vivo* studies with great responsibility and reproducibility. Our commitment in fulfilling the highest standards in preclinical research was confirmed in 2018 by the external inspections of our three quality assurance programs (AAALAC (since 2013), GLP (since 2016) and ISO 9001:2015), which we passed successfully.

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. Nevertheless, development and implementation of ethical, translationally relevant and validated animal models for musculoskeletal research is an ongoing task. Being active in different societies i.e. the Preclinical Model Section at the Orthopaedic Research Society (ORS), the European College of Laboratory Animal Medicine (ECLAM), the Federation for Laboratory Animal Science Associations (FELASA) and the Swiss Laboratory Animal Science Association (SGV), ensures that we pursue best in class policies in the sensitive area of animal models. 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

Team Members: Luca Ambrosio, Angela Armiento, Cecilia Bärtschi, Roman Bagnol, Valentina Basoli, Mauro Bluvol, Clamba Ioan-Catalin, Eshwari Dathathri, Elena Della Bella, Matteo D'Este, Nunzia Di Luise, Jie Du, David Eglin, Nora Goudsouzian, Olivier Guillaume, Phelipe Hatt, Shahrbanoo Jahangir, Philippa Jörger, Tino Jucker, Hermann Kasper, William Lackington, Yann Ladner, Zhen Li, Flavio Linardi, Junxuan Ma, Ursula Menzel, Graziana Monaco, Dirk Nehrbass, Daniele Pellicciotta, Marianna Peroglio, Robert Peter, Dalila Petta, Stijn Rotman, Andrea Schwab, Yemane Semere, Tiziano Serra, Christoph Sprecher, Despina Stefanoska, Martin Stoddart, Keith Thompson, Riccardo Tognato, Letizia Vainieri, Sophie Verrier, Sebastian Wangler, Christina Wapp, Jessica Zahn, Reihane Ziadlou, Mona Zolfaghar

Fellows: Peter Behrendt, Yannik Gehlen, Sonja Häckel, Judith Pfannkuche, Naomi Pötter, Feras Qawasmi, Frederik Westbrock, Yichi Xu, Zhou Zhiyu

Guests: Daniëlle Admiraal, Ivan Al Saify, Bernardo Antunes, Zohreh Arabpour, Sima Bordbar, Lino Casty, Gabriele Fortunato, Chris Gabbot, Wei Guo, Jessica Keller, Niko Kovermann, Adrian Perez, Alexander Sieberath, Janis Stoffel, Andrea Vernengo, Elham Vojoudi

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, directed by 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, including immunoregulation, 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 Focus Area
We aim at investigating the potential mechanisms leading to intervertebral disc (IVD) damage and evaluating novel biological treatment methods for IVD repair and regeneration. Acute and chronic damage to the IVD are major causes of low back pain. However, the factors that contribute to the loss of function of the IVD and the underlying pathophysiology are still poorly understood. We have established a whole IVD organ culture system with the ability to maintain entire discs with the endplates for several weeks under controlled nutrient and mechanical loading conditions. Within this bioreactor, the beneficial or detrimental effects of nutrition, mechanical forces, and/or biochemical factors on disc cell viability and metabolic activity can be investigated. We have developed various defect and degeneration models, allowing us to design and evaluate appropriate biological treatment strategies. These include implantation of cells, delivery of anabolic, anti-catabolic or anti-inflammatory molecules, biomaterials or a combination thereof. Data from *ex vivo* models are also correlated to *in vivo* observations to identify molecular markers of IVD damage or degeneration.

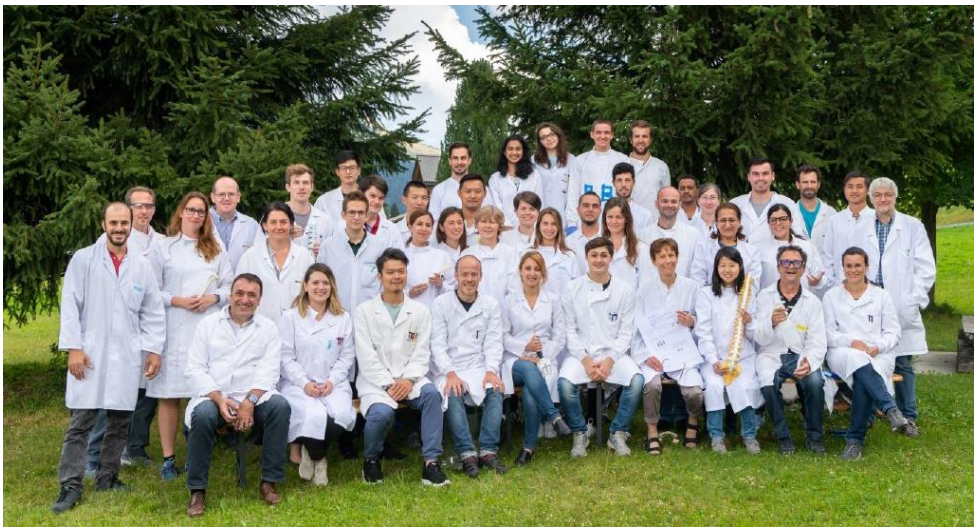
To study the potential of new therapies for articular cartilage repair and regeneration, a bioreactor system applying multiaxial load to tissue-engineered constructs or osteo-chondral explants has been established. The bioreactor mimics the load and motion characteristics of an articulating joint. Chondral and osteochondral defect and disease models enable us to test tailored treatments under physiologically relevant mechanically loaded ex-vivo conditions. Cell- and material-based therapies as well as chondrogenic or anti-inflammatory factors are under investigation for cartilage repair and regeneration.

Polymers and Surfaces Focus Area

Biomaterials for skeletal repair can provide structural and mechanical features for the filling of defects, but also be carrier for drugs, cells and biological factors. One of our goals is the development of 3D structures for bone and cartilage tissue engineering, using tailored polymers and composites manufactured with additive manufacturing processes. Our experience lies in the design of biocompatible, biodegradable polymers and their processing with controlled architecture and embedded biologics. A second field of research investigates the preparation of hyaluronan, a natural occurring biopolymer, based biomaterials which can be used to deliver drugs and cells. These injectable biodegradable materials have considerable potential in infection prophylaxis and tissues repair. We are also developing innovative technologies for the structuration and assembly of tissue-like matrices aiming to mimic for example, biological matrix mechanical and structural anisotropy.

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 can be applied by way of rehabilitation protocols and are able to modify stem cell and macrophage function. 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.



5.4 Musculoskeletal Infection Focus Area

Leader: Fintan Moriarty

Team Members: Pamela Furlong, Iris Keller, Virginia Post, Barbara Stanic, Willemijn Boot, Marloes Hofstee, Alexandra Wallimann

Fellows: Yan Chen, Alexander Milstrey, Eamon Sheehy

Guests: Carina Guntli, Jan Puetzler

The Musculoskeletal Infection team focusses their research activities on Fracture-Related Infection (FRI), with goals to optimize antibiotic prophylaxis, reduce the burden of therapeutic interventions, and study the impact of co-administered medication on infection. Our studies include preclinical *in vitro* and *in vivo* studies, as well as an increasing focus on observational studies in human patients.

In collaboration with ARI colleagues in the preclinical testing facility, 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 controlled delivery of antimicrobials via the use of programmable, implantable pumps to more precisely control antibiotic dosing. In addition, we have investigated in more detail the use of anti-inflammatory medication in our animal studies and found it can have a major impact on treatment outcome, and so will be a focus for future studies with clear relevance for trauma patients. The preclinical evaluation of novel anti-infective interventions under Good Laboratory Practice (GLP) conditions has also continued in the past year, with two novel antimicrobial intervention studies performed in this space in the past year.

On the *in vitro* side, we have begun to develop an *in vitro* model for *Staphylococcus aureus* infection that has the potential to include human immune system cell-lines. This can not only reduce future animal studies but will also allow us to test interventions in a human-specific system. The antibiotic loaded hydrogel that has been in testing in ARI for several years, has now also been tested against MRSA biofilms and continues to be superior to aqueous solutions of antibiotics.
In patient samples, we have made our first preparations for a study on the impact of antibiotic therapy on the human gut and skin microbiome. This is an under explored area of immense potential for bone health and will be a multi-year investigation with expert collaborations internationally.

Virginia Post at work in the infection laboratory.

5.5 ARI Administrative Services

Manager: Sonia Wahl
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.

5.6 Operations standards and safety

Q-Manager: Ulrich Bentz

Successful 2018 renewal audit of AO Research Institute

An audit conducted by the Swiss Association for Quality and Management Systems (SQS) has led to the successful recertification of ARI. In April, two external auditors from the SQS visited ARI for the recertification audit of the institute according to the revised standards ISO 9001:2015 and EN ISO 13485:2016. Following this, ARI has achieved certification for the next three years. After having several open discussions with numerous staff members and management, the auditors were impressed by the levels of commitment and knowledge of staff. The entire ARI is now certified according to the new completely revised version of the international standard ISO 9001:2015. The Focus Areas Biomechanical Services and Concept Development of the Biomedical Development Program are additionally certified to develop and test medical devices according to the completely revised EN ISO 13485:2016 standard. "Obtaining recertification according to the revised ISO standards shows our commitment to continuous improvement and the highest levels of performance," stated Ulrich Bentz, Quality Manager. "Obtaining this certification was a challenge as the expectations of the certification body are constantly rising as new EU regulations in the medical device field became effective in May 2017," added Bentz.

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, no-profit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. ARI is one of only 2 accredited institutions in Switzerland and the only accredited academic research institute in Switzerland. In November 2018, we received the third AAALAC international site visit, resulting in another 3-year accreditation.

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).

The second inspection took place in June 2018 and, on the 12 of October 2018, the Swiss Federal Office of Public Health renewed the statement of GLP compliance for the next 3 years. This is a major achievement for our institute after the AAALAC accreditation in 2013.
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. Indeed, since the achievement of the GLP certification, all major commercial studies have been conducted under GLP (excluding pilot studies).

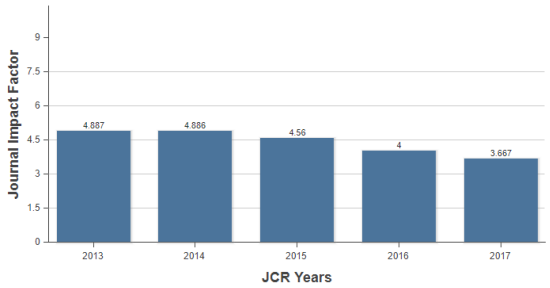
6 eCM Journal & eCM periodical

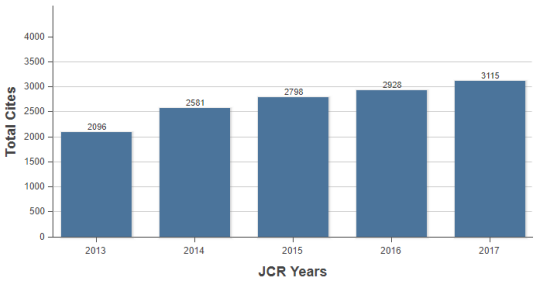
Editor-in-Chief: R Geoff Richards
Production Editor: Iolo ap Gwynn (external)
Junior Production Editor: Simona Ciriello
Webmaster, Web Editors: R Geoff Richards, Martin Stoddart, Simona Ciriello

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). It was created by scientists for scientists and is still run fully by scientists. eCM Journal is published by the ARI, 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 also have a transparent route for becoming an official listed eCM reviewer (member of the eCM International Review Panel).

In June 2018, Journal Citation Reports (JCR) announced eCM's 2017 Impact factor (IF) to be 3.667.
JCR 5-year Impact Factor: 4.842.
Scopus CiteScore2017 was calculated at 4.50. 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 a journal's citation impact.





Since July 2018, eCM introduced the payment of an Article Publishing Charge (APC) of $1000. The APC goes towards the costs of eCM staffing, web costs and general publishing costs.

From August 2018, after invitation, eCM is indexed on the China Knowledge Resource Integrated Database, where full eCM published articles are available directly after publication.

eCM publishes preclinical research that has clinical relevance in the musculoskeletal field (Orthopaedics, Trauma, Maxillofacial (including dental) and Spine). eCM's definition of the musculoskeletal field includes bone, teeth, cartilage, intervertebral discs, skeletal muscle (not smooth or cardiac muscle), tendons and ligaments (it does not include the spinal cord or neural tissues).
Within the musculoskeletal field areas include:
Assessment of materials for biomedical use
Tissue Engineering and Regenerative Medicine (TERM)
Structure, function, biology and biomechanics of connective and mineralized tissues
Stem and Progenitor Cells
Infection

Ten good reasons for publishing a paper in eCM

1. World-wide Gold Open Access, authors retain copyright to their articles (CC-BY-SA).
2. eCM is a Not-for-profit journal published by a Not-for-Profit foundation in Switzerland.
3. Rigorous open peer reviewing (reviewers have to request their name to be withheld).
4. Speed of publication: ~3 weeks after acceptance, paper is online.
5. Unique discussion with reviewers, as an integral section of the paper, allows sensible arguments to be included.
6. Scopus CiteScore*2017: 4.50. JCR Impact Factor 2017: 3.667. JCR 5-year Impact Factor: 4.842.
7. Indexed in the Science Citation Index Expanded and Web of Science (under the "Cell and Tissue Engineering", "Engineering Biomedical", "Materials Science" and " Orthopedics" 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 China Knowledge Resource Integrated Database.
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.

eCM Open Access Not-for-Profit online periodical
eCM Periodical was initiated in 2017, previously run within eCM journal as eCM supplements. eCM Conference Online Periodical is not part of the eCM journal publication but is owned as a separate part of eCM. It hosts all eCM official society meeting abstracts along with other abstracts for various congresses as collections of combined individual meeting abstracts in PDF format. The individual abstracts within the abstract collections have been peer reviewed by the respective conference organizers. eCM Periodical has been recorded permanently in the ISSN Register, ISSN: 2522-235X from the ISSN International Centre. The abstract collections do not have a DOI, and the abstracts are not searchable on PubMed. eCM Conference Online Periodical was established to solve the long-standing problem of eCM supplements being used in the JCR/Clarivate Analytics calculation of eCM impact factor and, unfortunately, accounting for approximately 15% of eCM citable items.

eCM journal council / eCM Editorial Board

6.1 eCM annual conference

The eighteenth eCM Conference, the third of which dedicated to "Cartilage & Disc: Repair and Regeneration", was held at the Congress Center Davos, Switzerland, June 25-28, 2018. eCMXVIII, was organized by Prof Martin Stoddart, Dr Sibylle Grad and Dr David Eglin.

Articular cartilage and intervertebral disc have many structural and functional similarities although they are different tissues. Despite their well-defined structure, repair remains a clinical challenge. While notorious for their limited repair capacity, recent developments are showing real promise in clinics, particularly in cartilage repair. Molecular characterization, to enable a more accurate assessment of phenotype, is improving and there is more active pursuit of predictive chondrogenic markers. The theme of eCMXVIII was to highlight the progress being made in the field of cartilage and disc repair and regeneration to renew optimism that novel clinical approaches are closer to reality than ever before.

Awards were assigned as follow:

- S Dreher, T Walker, W Richter
  Hypertrophy-associated regulation of RUNX3 and MEF2C during chondrogenesis of human mesenchymal progenitor cells
  Best Student Oral Presentation Award

- N Hecht, T Walker, W Richter
  Mechanosensitive miR clusters regulated after loading of human engineered cartilage
  Best Student Oral Presentation Award

- W Herod, SP Veres
  Establishing a target for annular repair: variations in molecular-level collagen structure of the annulus with circumferential location, radial depth, & disc level
  Best Student Poster Presentation Award

- Voskamp, J van de Peppel, S Gasparini, P Giannoni, JPTM van Leeuwen, GJVM van Osch, R Narcisi
  Selecting living human mesenchymal stem cells with an increased proliferation using a TWIST1 RNA-based probe
  Best Student Poster Presentation Award

- FC Bach, AR Tellegen, M Beukers, A Miranda-Bedate, M Teunissen, WAM de Jong, SAH de Vries, LB Creemers, K Benz, BP Meij, K Ito, MA Tryfonidou
  Biologic canine and human intervertebral disc repair by notochordal cell-derived matrix: from bench towards bedside
  Best Spine Oral Presentation Award

- D Lin, D Docheva
  Uncovering novel roles of Tenomodulin in intervertebral disk tissue
  Best Spine Poster Presentation Award

- DH Rosenzweig, R Fairag, AP Mathieu, L Li, D Eglin, M D'Este, T Steffen, MH Weber, JA Ouellet, L Haglund
  Hyaluronan-hydrogel seeded with autologous nucleus pulposus cell regenerates human intervertebral discs in an *ex vivo*, physiological culture model
  Best Spine Poster Presentation Award

All abstracts from this conference can be found at
http://www.ecmconferences.org/abstracts/2018/Collection3/ecm18.html

7 Institutional and Professional Relations

Geoff Richards is Director of the AO Research Institute Davos since 2009. He has an 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), being elected in the inaugural ICORS College of Fellows class. He has Doctor Honoris Causa from the Technical University of Varna, Bulgaria. In 2018, Geoff was appointed for a five-year term as member of High-end Foreign Experts Program, Sun Yat-sen University, State Administration of Foreign Experts Affairs, China. In 2017 Geoff founded of the International College of Fellows for Orthopaedic Research at the International Combined Orthopaedic Research Societies (ICORS), Steering Committee where he represents AO Foundation as a committee member. Geoff is chair of the International College of Fellows for Orthopaedic Research. Geoff is cofounder and Editor-in-Chief of the Not-for-Profit open access eCM Journal and eCM periodical. He is an Associate Editor of the Journal of Orthopaedic Translation. He has Life Honorary Membership of the Swiss Society of Biomaterials. He is Global president elect and Global Member-At-Large of the TERMIS Governing Board (Tissue Engineering & Regenerative Medicine International Society). He is a guest lecturer of the MSc Course Skeletal Repair at the Department Health Science and Technology (D-HEST) of the ETH Zurich. Geoff is Vice President of Science City Davos. He is representative to the AOTrauma R&D Commission from ARI.

Mauro Alini is Vice Director of the AO Research Institute Davos since 2009. He 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) and a Fellow of the Tissue Engineering Regenerative Medicine Society (FTERM). He is co-Editor in Chief of the Journal Orthopeadic 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. He is representative to the AOSpine R&D Commission from ARI.

Boyko Gueorguiev–Rüegg is program leader of Biomedical Development at the AO Research Institute Davos. He is an honorary professor at the Technical University of Varna, Bulgaria in the fields of biomedical engineering and biotechnology. He is General Secretary of the European Orthopaedic Research Society (EORS), Honorary Member of the Serbian Trauma Association, and Member of the Academic Council at the University Multiprofile Hospital for Active Treatment and Emergency Medicine 'N I Pirogov', Bulgaria. He is appointed as Associate Editor and Editorial Board Member of the Journal of Orthopaedic Trauma, Section Editor for Orthopaedic Biomechanics at the Indian Journal of Orthopaedics, 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 a program manager of the Preclinical Services at the AO Research Institute Davos. He is the chair of the Preclinical Models Section of the Orthopaedic Research Society (ORS). 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) and he is the vice president of the Davoser Society for Natural Sciences (NGD). Stephan is a member of the eCM International Review Panel and a guest lecturer in the MSc Course Skeletal Repair at the Department Health Science and Technology (D-HEST) of the ETH Zurich. He is the representative to the AOVET R&D Commission from ARI.

Fintan Moriarty is a Principal Scientist and Focus Area Leader for Infection at the AO Research Institute Davos. He 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 and a co-organizer of the annual eCM conference on the topic infection.

David Eglin is a Principal Scientist and Focus Area Leader for Polymers and Surfaces at the AO Research Institute Davos. He is the President of the Swiss Society for Biomaterials and Regenerative Medicine (SSB&RM), and Committee member of the Tissue Engineering and Regenerative Medicine International Society (TERMIS) EU Chapter. He is also a member of the International Editorial Board of Journal of Orthopaedic Translation (JOT). He is a member of the eCM Journal International Review Panel and a co-organizer of the annual eCM conference on the topic biofabrication. He lectures on the Skeletal Repair MSc module at the ETH Zürich and in the Biomedical Engineering MSc Program at the University of Bern.

Sibylle Grad is a Principal Scientist and Focus Area Leader for Disc and Cartilage at the AO Research Institute Davos. She 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 eCM Journal International Review Panel and a co-organizer of the annual eCM conference on the topic disc and cartilage. She is a member of the International Review Board of JOR Spine. She is also an officer of the ORS Spine Section, where she is serving as the Section Research Chair. Furthermore, she is the topic chair for Intervertebral Disc sessions of the ORS Annual Meeting. Sibylle Grad is an ICRS Fellow member. Sibylle Grad is Vice president of the Graduate School Graubünden AG.

Martin Stoddart is a Principal Scientist and Focus Area Leader for Stem Cells at the AO Research Institute Davos. He is an Honorary Professor at the Medical Faculty of Albert-Ludwigs University of Freiburg, Germany. He is also Honorary Professor at the Institute for Science and Technology in Medicine, University of Keele, UK. 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 a member of the TERMIS EU Meeting and Sponsorship Committee. 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 conferences and a web editor of eCM Journal and eCM periodical. He is a member of the International Consortium for Regenerative Rehabilitation Leadership Council. He is the ARI representative to the AOCMF R&D commission.

Sophie Verrier is a Principal Scientist at the AO Research Institute Davos. She is board member and upcoming president of the Swiss Bone and Mineral Society (SBMS). She is also active member of the Orthopaedic Research Society (ORS) where she chaired the Women's Leadership Forum Committee and is member of the ORS Annual Meeting Committee. She is a member of tissue engineering and regenerative medicine society (TERMIS) and of the eCM International Review Panel (eCM Journal). She is also co-organizer of topic specific annual eCM conferences.

Other Professional Relations

Daniel Arens is a member of the board of directors of the Swiss Association of Veterinarians in Industry and Research and member of the credential committee of Swiss Veterinary Laboratory Animal Science (SVLAS).

Angela Armiento was elected member of the ORS International Committee for a 3-year term (2018-2021).

Valentina Basoli is lecturing at the University of Sassari Medical School, Italy on molecular biology, gene regulation and epigenetic within the course of biology.

Zhen Li is a Visiting 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 Li 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

8.1 New Extramural funding

German Research Foundation (DFG), Special Research Area (Sonderforschungsbereich, SFB): 'Collaborative Research Centre 1313 – Interface-Driven Multi-Field Processes in Porous Media'. The project partners include Prof Boyko Gueorguiev (ARI), in collaboration with Prof Oliver Röhrle (University of Stuttgart). Overall 4-year project funding is 8.5 million Euro, ARI funding for project area 'Fluid-solid phase change' is 100'000 Euro.

Mereo BioPharma, UK: 'Multicentre placebo-controlled double-blind study in adult patients with type I, II or IV osteogenesis imperfecta treated with BPS804'. The aim of the project is to investigate the effect of a new anabolic drug on individuals with osteogenesis imperfecta including pre-clinical studies and a multicentre human clinical trial. The project partners include Dr Peter Varga (ARI), McGill University, Canada, and University of Berne, Switzerland. ARI funding is 63'800 CAD.

EU (Joint programming initiative on antimicrobial resistance, JPIAMR). ARI is coordinator. Project name: Antibio-LAB. Approved for ARI 250 K EUR (total Budget 810 K EUR). Awarded to Fintan Moriarty, David Eglin, Stephan Zeiter.

BGU (German workman's compensation hospitals fund). Non-union project, 60'000 Euro awarded to Fintan Moriarty, Barbara Stanic.

BRIDGE (offered by the Swiss National Science Foundation (SNSF) and Innosuisse). "3D Sound Induced Morphogenesis (3D-SIM)" proposal submitted by Dr T. Serra from the ARI was successful was successful and started in March 2018, it aims to develop a new assembling biotechnology.

Sino-Swiss Science & Technology Cooperation (SSTC) "Biofabrication of cartilage particulate microtissues laden hyaluronan tissue engineered constructs" this is a 1-year scientific exchange collaboration of the ARI and Prof Jiang Peng at the Institute of Orthopedics, Peking Key Lab of Regenerative Medicine in Orthopaedics, Key Lab of Chinese PLA, Chinese PLA General Hospital. The funding from Switzerland (30kCHF) and China is supporting PhD/MD candidate Yichi Xiu during staying of 12 months at the ARI.

SNF Grant "Identifying novel therapeutic targets for articular cartilage repair" for a four-year project totaling 417,720k. Applicant Martin Stoddart, Project Partners Mauro Alini and Sophie Verrier.

Sino-Swiss Science and Technology Cooperation (SSSTC) grant "Intervertebral Disc 3D Printing with Decellularized Extracellular Matrix Bioink" and China Scholarship Council (CSC). The project partners include ARI scientist Prof Zhen Li, in collaboration with Prof Songsong ZHU from West China Hospital of Stomatology, Sichuan University, Chengdu. Funding is CHF 30k in total and includes an MD fellow visit (12 months) at ARI.

H2020 Project "iPSpine: Induced pluripotent stem cell-based therapy for spinal regeneration" was approved for funding by the European Commission as a “European-led research effort to identify a future advanced therapeutic strategy that results into a radical new treatment of intervertebral disc degeneration-induced low back pain”. The project is coordinated by Prof Marianna Tryfonidou from the University of Utrecht, The Netherlands, whereby ARI is one of 20 partners. The total budget is EUR 15 Million; the ARI budget is EUR 491k, and ARI scientists involved are Sibylle Grad, Marianna Peroglio and Mauro Alini. The 5-year project starts in January 2019.

8.2 New AO Foundation Intramural funding (grants beyond ARI retainer)

AO Development Incubator (AODI): 'Biphasic Plating – Next Generation Locked Plating'. Project partners are Dr Markus Windolf (ARI) and Dr Devakar Epari (Queensland University of Technology). Overall project funding is 1.7 million CHF for 4 years.

AO Development Incubator (AODI): 'AO Fracture Monitor – Development Phase'. Main applicant and coordinator of the project is Dr Markus Windolf (ARI). Overall funding is 1.9 million CHF for 3.5 years. The AO Fracture Monitor was created in ARI and is believed to be a major change to internal fracture fixation in the future.

AOCMF Start-up Grant "Investigating effects of BMPER on osteogenic and chondrogenic differentiation. AOCMFS-18-25R was accepted for 24 months. 2018-2020, CHF 50'000, main applicant Dr René Rothweiler, University of Freiburg, Germany with Prof Martin Stoddart as co-applicant.

8.3 Awards

AO Foundation Berton Rahn Research Award

The 2018 winner of the Berton Rahn Research Award is Daisuke Sakai, MD, PhD, Associate Professor at the Department of Orthopaedic Surgery, Tokai University School of Medicine in Kanagawa, Japan. Sakai's clinical interest focuses on the pathology of degenerative spine disease and the management of spinal deformity including adolescent idiopathic scoliosis, adult spinal deformity, and functional rehabilitation. The work this award recognizes took place under the ARI Collaborative Research Project (ARI CRP) consortium Annulus Fibrosus Repair.
The Berton Rahn Research Award was established in recognition of Berton Rahn's immense contribution to the AO Foundation. Initially designed to honor the best completed AO start up project in any one year (based on final reports and publications from all completed studies), since 2017 any AO funded preclinical research project has been eligible for the award.
The award comprises a keynote presentation at ARI's eCM conference, certificate, registration, travel and accommodation for the meeting. The ARI Advisory Committee (ARI AC) reviews submissions from the various AO Foundation and Clinical Division's research committees and selects one as the winner. ARI employees cannot be nominated.

Sakai gave a presentation titled Exploration of cells and their niche in the intervertebral disc: studies from AO CRP Annulus Fibrosus Repair at the 2018 eCM Conference: Cartilage & Disc: Repair and Regeneration (June 2018, Congress Centre Davos, Switzerland).
On behalf of the AO Foundation, we congratulate Sakai on winning this prestigious award.

R Geoff Richards, ARI Director, presents Daisuke Sakai with the Berton Rahn Research Award, the most prestigious research award from the AO Foundation, given annually. eCM Congress, Davos, Switzerland, June 2018.

International Fellows of Tissue Engineering and Regenerative Medicine (FTERM)

FTERM awardees, Gerjo van Osch, Anthony Weiss, TERMIS President Rui Reis (presenting the awards), Milica Radisic, Mauro Alini (ARI).

The ARI is proud to announce that Prof Mauro Alini, Vice director of the institute and Musculoskeletal Regeneration program leader was awarded the FTERM at the world TERMIS conference in Kyoto in September 2018. Alini has spent 20 years at ARI working in the field of tissue engineering and regenerative medicine, following his previous research on developmental biology of the growth plate in McGill University in Montreal, Canada. The Tissue Engineering and Regenerative Medicine International Society (TERMIS) brings together the international community of people engaged or interested in the field of tissue engineering and regenerative medicine, promoting International Education and Collaboration for the Advancement of Tissue Engineering & Regenerative Medicine.
The International Fellows of Tissue Engineering and Regenerative Medicine (FTERM) was created to recognize a distinguished leader within the tissue engineering and regenerative medicine field. FTERM was established to recognize an individual's role in shaping the tissue engineering and regenerative medicine field and TERMIS.
Prof Geoff Richards, ARI's director, and president elect of TERMIS in 2018 noted "It is extremely prestigious for a member of ARI to become FTERM, as only five individuals in the world became FTERM in 2018 and the next intake of fellows will not be until 2021, when Europe hosts the world conference. We are extremely proud of Mauro and his achievements."
We are also proud that Prof Geoff Richards was nominated to be one of the six world candidates for Global president of TERMIS, which he won during the election. He was previously a global member at large of the TERMIS governing board.

International Society for Biofabrication (ISBF) Young Investigator Award

Tiziano Serra won the International Society for Biofabrication (ISBF) Young Investigator Award 2018. The purpose of the ISBF's Young Investigator award is to recognize outstanding achievements by members of the International Society for Biofabrication (ISBF) who are in the early stages of a career in the field of Biofabrication. The abstract entitled "Homing of Mesenchymal Stem Cells Enhances Tie2^{+} Progenitor Cells and Induces a Proliferative Response in Intervertebral Disc Organ Culture" was awarded an ORS Spine Section Poster Award 2018. Authors: Sebastian Wangler, Marianna Peroglio, Ursula Menzel, Lorin M Benneker, Daisuke Sakai, Mauro Alini, Sibylle Grad.

Tiziano Serra received the ISBF Young Investigator Award 2018 at the society annual meeting.

Gernot Lang was granted an ORS 2019 Travel Award from the DKOU for the project "Renodisc": "The Tissue-Renin-Angiotensin-system of the human intervertebral disc", in collaboration with ARI scientists Zhen Li, Sibylle Grad, and Mauro Alini.

A total of seven prizes were awarded at Graubünden Forscht which took place from September 19-20, 2018 in Davos, including one to Sebastian Wangler from the ARI in the medical sciences category. Title: Migration of mesenchymal stem cells into degenerative intervertebral discs.

Medical sciences winner Sebastian Wangler, ARI.

MD student Yannik Gehlen, under the supervision of Dr Zhen Li (ARI) and Dr Gernot Lang (Freiburg University), obtained a student scholarship from the German Society of Orthopedic and Orthopedic Surgery (DGOOC), with his doctoral thesis "the effect of the selective JAK3-Inhibitor Tofacitinib in degenerative disc disease".

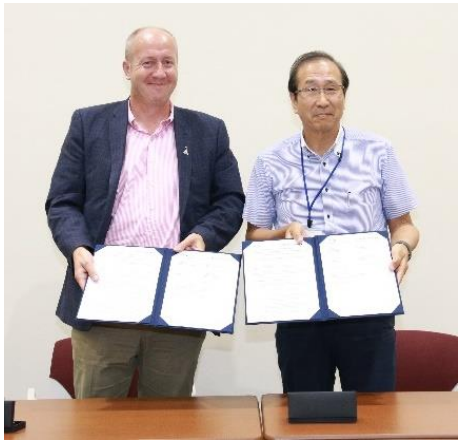
8.4 ARI New MOU's (Memorandums of Understanding)

MoU: ARI & Kyoto University's Institute for Integrated Cell Material Sciences (iCeMS).

ARI members left to right: Prof Mauro Alini; Dr David Eglin; Prof Zhen Li; Dr Sibylle Grad; Dr Sophie Verrier; Prof Geoff Richards; iCeMS Director Prof Susumu Kitagawa; iCeMS PI Dr Ganesh Namasivayam Pandian, and Prof Martin Stoddart.

On September 3, 2018, ARI established a memorandum of understanding (MoU) with Kyoto University's Institute for Integrated Cell Material Sciences (iCeMS). iCeMs seeks to develop materials to comprehend cellular functions (materials for understanding cells), produce materials to control processes in cells (materials for controlling cells), and eventually to create functional materials inspired by cellular processes (cell-inspired materials). Combining Kyoto University's established strengths in cell biology, chemistry, physics, and mathematics to delve deeply into this field at the boundary of materials and life, they make concerted efforts through interdisciplinary research to pioneer the new research domain of integrated cell-material sciences. The exchange between the two institutes began in 2014, when Dr Ganesh Namasivayam Pandian of iCeMS met Professor Martin Stoddart from ARI. Pandian, later joined by members of iCeMS PI Hiroshi Sugiyama's Laboratory, and Stoddart had exchange visits on several occasions to foster their scientific collaborations. Which led to Pandian being made the first ARI Honorary Visiting Scientist

in February 2018. To date, two collaborative grants have been obtained by Stoddart and Pandian with the aim to expand the collaboration to members of both institutes.



iCeMS Director Professor Susumu Kitagawa, Pandian, the ARI Director Professor Geoff Richards, Vice-Director Professor Mauro Alini, and Prof Martin Stoddart attended the signing ceremony, where fifty researchers from both institutes celebrated the agreement at Kyoto University. iCeMS is the latest institution to partner with ARI. This agreement will open doors for future collaboration that will compliment both the institutes. ARI is expected to advance the materials developed in iCeMS for high quality applied Preclinical Research and Development focused towards clinical applications/solutions.

ARI Director Professor Geoff Richards (left) and iCeMS Director Professor Susumu Kitagawa.

MoU: University of Freiburg, Medical Center, G.E.R.N. Tissue Replacement, Regeneration & Neogenesis, Germany

ARI has a long-standing collaboration with the University of Freiburg, Germany that goes back decades. Both Prof Geoff Richards and Prof Martin Stoddart have Honorary professorships within the University of Freiburg Medical Faculty. On the 26th November 2018 this long-time collaboration was formalized with the signing of a memorandum of understanding (MoU). ARI Director Prof R Geoff Richards, Prof Mauro Alini, Prof Martin Stoddart, Dr Sibylle Grad, Dr David Eglin, Dr Andrea Schwab, Dr Keith Thompson and Dr Angela Armiento went to the University of Freiburg for a joint symposium in the beautiful Uni-Haus Schauinsland. The groups of Prof Norbert Südkamp (Director, Dept. of Orthopedics and Trauma Surgery), Prof Rainer Schmelzeisen (Director, Dept. of Oral, Maxillofacial, & Regional Plastic Surgery), Prof Bernd Rolauffs (Director GERN) and Prof Anke Bernstein (Principal Scientist GERN) also presented their work, with the intention to identify new areas of potential collaboration. The symposium was followed by a dinner with a presentation on the art of wine making, followed by the MOU signing ceremony. This will strengthen ties and encourage joint grant applications and the hosting of Freiburg medical fellows and students within ARI.

MoU: ARI & Bulgarian Academy of Sciences, Institute of Metal Science (IMS).

On November 23, 2018, ARI established a memorandum of understanding (MoU) with Bulgarian Academy of Sciences, Institute of Metal Science 'Acad A Balevski' (IMS). The subject of the collaboration is integration of research, educational and innovation activities between both institutes with the aim of conducting joint research and implementing innovative projects. The MoU was signed by Professor Geoff Richards, ARI Director, Professor Boyko Gueorguiev, Program Leader Biomedical Development at ARI, and Professor Ljudmil Drenchev, IMS Director.

In a currently running project, and in the frame of a joint PhD studentship between the institutes, an automated electromechanical system is being developed for comprehensive in-depth investigation of the effect of local mechanical stimulation on fracture healing progression. This is achieved by ensuring a well-controlled mechanical environment at the fracture site, in combination with continuous monitoring.

IMS has an established reputation in basic and applied research in metal science, crystallization, structure and properties of metals, alloys and composites under dynamic loading. In combination with ARI's expertise in bone fracture biomechanics and biomedical engineering, this MoU will open doors for future collaboration maximizing the strengths of both partners.

IMS Director Professor Ljudmil Drenchev (left) and Professor Boyko Gueorguiev, ARI (right).

8.5 New Board Positions

European Orthopaedic Research Society (EORS)

EORS executive Committee Gianluca Vadala, spine surgeon Rome, Italy (Vice President), Prof Denitsa Docheva, Regensburg, Germany (President), Prof Boyko Gueorguiev, ARI, Switzerland (General Secretary), Jeannette Penny, Foot and Ankle surgeon, Denmark (Treasurer)

It is with great pleasure that we announce that Prof Boyko Gueorguiev, Biomedical Development program leader at ARI was elected to be General Secretary in the executive committee (EC) of the European Orthopaedic Research Society (EORS). He was elected at the society's general assembly held at EORS 2018 in Galway, Ireland. This position keeps a strong connection of the AO Foundation with the EORS. Previously Prof Geoff Richards was a member at large of EORS from 2011 until 2016, after organizing the EORS 2010 in Davos.

Prof Richards mentioned that "We are very proud that Boyko is in the EC of EORS, continuing a long collaboration with the ARI. As a senior member, he will be able to give good advice to the new young board." EORS is a member of the International Combined Orthopaedic Research Societies (ICORS), which will hold the global summit of orthopedic research, hosted by another constituent member – the Canadian Orthopaedic Research Society (COA) in Montreal in June 2019. The ICORS 2019 meeting will highlight advances in orthopedic research with an emphasis on how new discoveries translate into improved clinical care – from the bench to the bedside. ICORS has met consistently every three years since 1992. In 2013 Prof Richards founded the International College of Fellows and Honorary status of Fellow of International Orthopaedic Research (FIOR) within ICORS which inducted its first fellows in Xian, China in 2016. Prof Richards is the chair of the college (2016-2019) and both he and Mauro Alini are inaugural fellows from Xian.

8.5 Collaborations

International Consensus Meeting on the Diagnosis and Treatment of Fracture-Related Infection (FRI), Zürich, February 2018

Members of the international consensus group in Zürich to discuss the diagnosis and treatment of FRI.

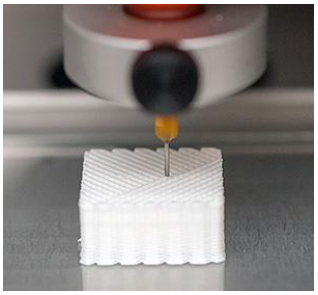
A Fracture-Related Infection (FRI) consensus meeting in Davos in December 2016 achieved consensus on the fundamental features of FRI, and a proposal for defining the presence of FRI was reached. The establishment of this definition offers the opportunity to standardize preclinical research, improves the reporting of clinical studies and finally of course also aids in the decision-making during daily clinical practice. In the following 18 months, the expert group shifted attention to the next phase, validating the diagnostic criteria and develop treatment principles for FRI and a consensus on diagnosis and treatment principles for FRI. In reflecting the greater complexity of this question, and to engage with other professional organizations, the group has grown to include external partners. Joining the ARI, AOTrauma and the AOTK Anti-Infection task force (AITF), is the EBJIS, the Orthopaedic Trauma Association (OTA), and the Pro-Implant Foundation, as well as a broadened panel of experts with extensive clinical experience in FRI. A first meeting of the expert group took place in Zürich in February. Prior to the meeting, the group was asked to review and consider the published literature on FRI, within nine specific concepts that were then presented for discussion in dedicated sessions during the meeting. The meeting engaged 35 experts and key opinion leaders in the field of FRI. Recommendations were developed on diagnosis and treatment of FRI. These guiding principles will be made available through scientific publications and an AO Bone Infection App. The whole project is a milestone achievement, where multiple international organizations have come together for the first time to try and improve the care for patients with FRI.

Medical additive manufacturing collaboration with University Hospital Basel

Medical additive manufacturing (MAM) technology is poised to revolutionize patient care, from improved medical education by using 3-D printed models for teaching to additively manufactured, patient-specific implants. As part of AOCMF's project, ARI is collaborating with two leading institutions to more effectively bring patient needs into its MAM research and development: the 3D Print Lab at the University Hospital Basel (USB) and the University of Basel Department of Biomedical Engineering Medical Additive Manufacturing Group.

3-D Discovery Printer in a biosafety cabinet from regenHU Ltd. in the ARI.

The collaboration was initiated on March 29, 2018 with a joint scientific workshop at ARI. Bringing invaluable expertise to the meeting were experts from both sides of the joint effort, including Dr Florian Thieringer, USB Assistant Medical Director and Lecturer for Cranio- and Maxillofacial Surgery, Head of the MAM research group at the University of Basel's Department of Biomedical Engineering, and co-founder and co-director of the USB 3D Print Lab; Thieringer's team; ARI scientists; and representatives of AOCMF and the AOTK system.



3-D Discovery Printer in the ARI produces personalized implants.

The meeting began with introductions by Florian Thieringer, David Eglin, and Geoff Richards.

- Biofabrication and Additive Manufacturing at ARI (Dr David Eglin)
- Medical 3-D Printing at University Hospital Basel (Dr Florian Thieringer)
- Personalized Ceramic Printable Ink for Patient-Specific Implant Fabrication CTI/KTI project (Dr Christoph Sprecher, project leader, Musculoskeletal Regeneration, ARI)
- Reconstruction of a Large Maxillary Defect by an Engineered Vascular Bone Graft (Dr Alexander Haumer, University Hospital Basel)
- A Tissue-Adhesive Hyaluronan Bioink That Can Be Cross-Linked Enzymatically and by Visible Light (Dr Matteo D'Este, Research Scientist, Musculoskeletal Regeneration, ARI)
- Patient-Specific Surgical Implants Made of 3-D-Printed PEEK (Dr Neha Sharma, University Hospital Basel)
- Experimental Study on Prefabrication Customized, Vascularized Tissue-Engineered Bone Based on 3D-Printing for Mandibular Reconstruction in Rhesus Monkey (Mr Shuaishuai Cao, University Hospital Basel)
- 3-D Sound Induced Morphogenesis: a BRIDGE Project (Dr Tiziano Serra, Research Scientist, Musculoskeletal Regeneration, ARI)

ARI strengthens partnership with University of Malaya, University of Malaya Medical Centre, and SYNBONE

In the framework of the AO Strategy Fund Project Generic Asian Pelvic Bone Model, Professor Boyko Gueorguiev, Program Leader Biomedical Development at the ARI, visited three sites in Malaysia on 7-9 May 2018: The University of Malaya, the University of Malaya Medical Centre in Kuala Lumpur, and the SYNBONE Asia Pacific subsidiary in Johor (SYNBONE SDN BHD). The University of Malaya, and the University of Malaya Medical Centre in Kuala Lumpur. The organizations are international collaboration partners with ARI in the development and production of the first evidence-based anatomical model of the Asian pelvic bone for surgical training, education, and implant development. With its state-of-the-art production facility in the newly built industrial park in Johor, in the year of its 30th anniversary, SYNBONE is expanding its activities by enhancing the development and production of models for surgical training and education with 65 employees located in the Asia Pacific area, and views this as a key development vector.

The visit to the University of Malaya and the University of Malaya Medical Centre was followed by participation in the 48th Malaysian Orthopaedic Association Annual Scientific Meeting, 10-12 May 2018 in Penang. B Gueorguiev was warmly welcomed by Prof Dr Tunku Kamarul Zaman, Director of the University of Malaya Medical Centre and orthopedic surgeon, Prof Dr Saw Aik, Director of Silent Mentor Program and orthopedic surgeon, and Dr Rukmanikanthan Shanmugam, a recent AO Medical Research Fellow at ARI in Davos (CH), and current Senior Lecturer and orthopedic surgeon at the University of Malaya. ARI then held further discussions with its partners on the procedure for processing, evaluating, and implementing clinical CT data to enable modelling of the Asian pelvic bone, comprising the three major ethnic groups – Indian, Chinese, and Malay descent. The parties committed to further fostering ARI research fellowships for surgeons from the University of Malaya whilst continuing to deliver outstanding collaborative research.

L-R: Dr Sureshan Sivananthan, Dr Howe Tet Sen, Prof Dr Lee Eng Hin, Prof Dr Tunku Kamarul Zaman, Dr Rukmanikanthan Shanmugam, and Prof Dr Boyko Gueorguiev during the Orthopaedic Research Session, at the 48th Malaysian Orthopaedic Association Annual Scientific Meeting.

Symposium between the ARI and CMF Surgery, University of Tübingen

Dr Andreas Naros

On October 22, 2018 a joint symposium between the ARI and the Department of CMF Surgery, University of Tübingen explored the options available to ARI medical fellows after they complete their fellowships in Davos. Dr Andreas Naros, a CMF surgeon, was an ARI fellow from July 1, 2017 to June 30, 2018. He was investigating *in vitro* changes in RNA expression in primary human bone marrow derived stem cells during osteogenesis in order to identify predictive functional markers that would identify good and bad donors. After his successful 12-month fellowship with ARI's Musculoskeletal Regeneration Program came to a close, Dr Andreas Naros and his ARI supervisor Professor Martin Stoddart arranged a visit to ARI for Dr Naros' host clinical department at the University of Tübingen, to discuss potential avenues for continuing this collaboration.

ARI has significant experience in the culture and differentiation of human bone marrow MSCs, while the laboratory at the University of Tübingen has many years' experience with the harvest and isolation of stem cells from jaw periost (the soft tissue covering the outside of bones). This offers an ideal opportunity to exchange cell expertise and techniques to identify the optimal combinations for cell therapies. The scientific symposium opened with a welcome address from ARI Director Professor R Geoff Richards and an introduction to Tübingen from Professor Siegmar Reinert. Six presentations were given by participants from the University of Tübingen and four presentations were given by people representing ARI, offering an overview of the scientific direction in each of the institutes. This was followed by discussions on areas of mutual interest and planning from a future joint grant application perspective.

This is an excellent example of how a medical fellowship can be just the beginning of a long-standing collaboration. Everyone at ARI wishes Dr Naros well in his future research and clinical career, and we look forward to future opportunities to work together with him on his area of focus.

ARI members with the visiting group from the department of CMF Surgery, University Tübingen.

ARI joins the International Consortium for Regenerative Rehabilitation (ICRR)

Leaders in the field discuss the future direction of Regenerative Rehabilitation, at the Sixth Annual International Symposium on Regenerative Rehabilitation, Pittsburgh (US), November 2017.

The ARI is proud to partner with the International Consortium for Regenerative Rehabilitation (ICRR) in its valuable work to improve patient care. Professor Martin Stoddart of the Musculoskeletal Regeneration Program joined the ICRR Leadership Council on July 1, and in this new role is ideally placed to promote the clinical implications of orthopedic rehabilitation and mechanobiology. The Seventh Annual International Regenerative Rehabilitation Symposium was held in Seattle, United States, October 11-13, 2018 where Stoddart was an invited speaker. The ICRR comprises 16 partners from all over the world who have a shared mission 'to bring together leading scientists and clinicians across the domains of regenerative medicine and rehabilitation science to drive the creation and transfer of knowledge associated with the development and translation of technologies that restore function and enhance the quality of life of patients.'
This mission complements the purpose statement of the ARI which is 'to advance patient care through innovative orthopedic research and development' and the Mission of the AO Foundation, which is 'promoting excellence in patient care and outcomes in trauma and musculoskeletal disorders.' The mechanical environment is known to drive the bone healing process, with rigidity leading to direct bone healing, while limited motion leads to indirect bone healing via a cartilage template (callus).

Regenerative rehabilitation is the convergence and integration of regenerative medicine and physical rehabilitation sciences. Physical therapy (PT) is essential to support the return to function of a damaged or repaired tissue, but the specific effects of PT at a cellular level during regeneration remain largely unexplored. Conversely, when thinking of regenerative approaches, the mechanical environment that cells and scaffolds must withstand in orthopedic repair is often regarded as a challenge that needs to be endured or overcome rather than as an opportunity that can be leveraged. Regenerative rehabilitation can be used as an approach to translational mechanobiology, where the mechanical cues driving cell differentiation and function are directed by rehabilitation routines to promote repair and regeneration.

ARI fosters collaboration with Shenzhen Institutes of Advanced Technology (SIAT)

ARI scientist's Dr Sibylle Grad, Prof Zhen Li, and Reihane Ziadlou visited the Shenzhen Institutes of Advanced Technology (SIAT) of the Chinese Academy of Sciences. The purposes of the visit were to present recent advances in cartilage and intervertebral disc research achieved at the Musculoskeletal Regeneration Program of the ARI, and to discuss the progress of the running collaborative research project: Traditional Chinese Medicine (TCM) compound delivery system for treatment of osteoarthritis. The project is funded by the Swiss National Science Foundation (SNSF) under the Sino-Swiss Science and Technology Cooperation (SSSTC).

ARI scientists visiting SIAT Chinese Academy of Sciences.

During a seminar held at SIAT, S Grad gave a presentation entitled 'mechanically stimulated organ culture for evaluation of biological osteochondral repair methods'; and Z Li presented her work on cell-based annulus fibrosus repair. Thereby, the presentation of the organ specific bioreactors for articular cartilage and intervertebral disc research, developed within the ARI labs, attracted great attention. The aim of the joint project between Switzerland and China is to develop a TCM compound delivery system for the treatment of osteoarthritis. Reihane Ziadlou, PhD candidate at the ARI and the University of Basel, presented recent findings on the anabolic and anti-inflammatory effects of specific TCM molecules on human osteoarthritic chondrocytes. While Dr Xinluan Wang from SIAT outlined their progress on the benefits of TCM compounds for the bone regeneration. Appropriate biomaterial-based drug delivery systems for cartilage and bone are being developed for administration of the compounds to osteochondral defects. To get more insight in the advanced 3-D material printing techniques developed at SIAT, Ziadlou stayed at the Shenzhen laboratories as an exchange student for two more weeks. Dr Yuxiao Lai, Executive director, Center for Translational Medicine Research and Development at SIAT was recently awarded Honorary Visiting Scientist at the ARI for a three-year period beginning July 1, 2018. The award (the second that ARI has given) was in recognition of her collaboration with Eglin, Alini, and Richards through a European Chinese FP7 project on Rapid Prototyping of Custom-Made Bone-Forming Tissue Engineering RAPIDOS, FP7-NMP-2013-EU-China.

The team also visited Prof Ling Qin at the Chinese University of Hong Kong (CUHK). Ideas were discussed for continued collaboration of the ARI with SIAT and the CUHK in the field of biologics and biomaterials application for bone and cartilage repair and regeneration. Prof Geoff Richards, ARI's director, noted "It is great that these visits and collaborations happen with SIAT and CUHK, which are important institutes in the pearl river area. Prof Ling Qin was a fellow in ARI in 1992 and has continued to be actively involved in research collaborations with all of us at ARI ever since."

ARI scientists visiting Prof Ling Qin at The Chinese University of Hong Kong.

8.6 Congress news

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

On April 6-7, 2018, around 50 students from ETH Zürich and the University of Applied Sciences (ZHAW) in Winterthur met at the ARI, to participate in hands-on training. The course was part of the lecture series on 'Skeletal Repair' at ETH Zürich organized by Sibylle Grad, Martin Stoddart, David Eglin, Fintan Moriarty, and Stephan Zeiter, scientists from the ARI. The students' studies are focused on Health Sciences, Health Technologies, and Biomedical Engineering. The goal of this two-day course was to provide basic insight in osteosynthesis principles and in current research activities within the ARI, thereby highlighting the interfaces between medicine, biology, and engineering.
Prof R Geoff Richards, ARI Director, opened the course with an introduction into the AO Foundation, its worldwide importance, and its continuing research towards improved patient care. Richards stressed ARI's role in translational pre-clinical research and illustrated some recent examples of new technologies, such as the fracture monitoring device or new developments for the prevention of infection. In the second lecture, Dr Veit Schoenborn, orthopaedic and trauma surgeon at the Cantonal Hospital in Chur, comprehensively explained the principles of bone fractures, bone healing, and surgical fracture management.

Osteosynthesis and skill training
The hands-on part started with the first osteosynthesis exercise. Under the guidance of Dr Raphael Jenni, leading surgeon at the Cantonal Hospital in Chur, the participants practiced the placement of an intramedullary nail using the provided surgical instruments and artificial bones. An expert team of surgeons from the Cantonal Hospital in Chur instructed and supported the students in their first attempts of bone fracture treatment. Further exercises included the placement of external fixators and compression plates, complementing the most important surgical techniques. The students were delighted with the practical experience, which was described as a valuable addition to the theoretical lectures. To further challenge the hands-on competence of the participants, four skill training stations were built and supervised by ARI's biomedical development team under the guidance of Dieter Wahl. The four instructors Ivan Zderic, Peter Varga, Dominic Gehweiler, and Dieter Wahl explained the direct relationships between biomechanical and biophysical phenomena, the correctness of surgical instrument handling and the success criteria of implant fixation. All students were able to experience with their own hands, the potential pitfalls and consequences of treatment success.

On the second day, the students participated in two of ten different workshops organized by the surgeons from the Cantonal Hospital in Chur, instructors from ZHAW, and ARI scientists. ARI workshops implemented hands-on protocols for gene transfer (Ursula Menzel, Yann Ladner), 3-D printing (David Eglin, Tiziano Serra), joint dissection, anatomy, microscopy (Dirk Nehrbass, Elena Della Bella), and bioreactor applications for cartilage (Angela Armiento, Matteo D'Este), and intervertebral disc research (Zhen Li, Sebastian Wangler). Bacterial infection and prevention as well as pre-clinical *in vivo* models for fracture studies were also addressed (Fintan Moriarty, Iris Keller). The application of specially designed implants (kindly provided by RISystems) for rat models, by Stephan Zeiter, was one of the highlights. Daniel Baumgartner, ZHAW, organized an interesting workshop about endoprosthetics, different materials, and potential complications. During the workshops led by Veit Schoenborn and Raphael Jenni, clinical trauma cases were discussed, and different diagnostic tools including imaging techniques demonstrated. Finally, short presentations of

all workshops given by the students were very well-performed, confirming that the leaders successfully explained the topics, and the participants captured the take-home messages.
These student courses strongly contribute to the strengthening of ARI's collaborations with ZHAW and ETH Zürich. Indeed, most of the Masters theses at the ETH Department of Health Sciences and Technology (D-HEST) carried out at the ARI in recent years, were based on the initial experiences during this course. The block course was organized and run by Sibylle Grad, Christoph Sprecher, Sonia Wahl, Mauro Bluvol, and Isabella Badrutt from the ARI. We acknowledge DePuy Synthes and RISystems for providing training material.

At one of the skill training stations, a student learns how to use a drill without injuring the soft tissue with ARI's Peter Varga.

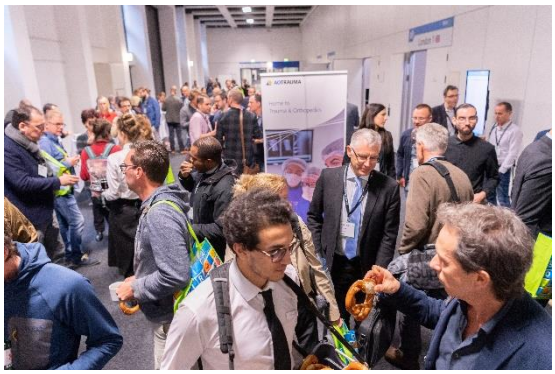
Students work on sample preparation for the bioreactor workshop.

Graubünden Forscht

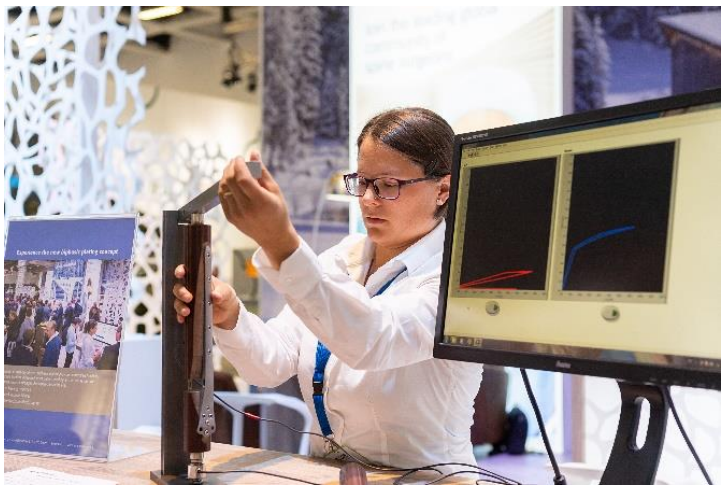
The topics on which research is conducted in the Canton of Graubünden are often very complex. At Graubünden Forscht - The Young Researchers Convention in Davos - which took place from September 19-20, 2018 at the Congress Center in Davos, the young scientists set themselves the goal of presenting their research in a clear and understandable way to an audience that was not familiar with the subject. The Graduate School Graubünden, which organized the event, offered a special course in advance to help the participants with their communication skills.
On the first day of the conference, the Graduate School Graubünden honored the researchers who successfully completed their doctoral thesis at one of the research institutions in the Canton from 2016-2018.

Graubünden research 2018' winners with the President of the Graduate School Graubünden, Walter Reinhart (from left to right): Stephanie Mayer, Karin Fieten, Vincent Simonin, Urszula Radzikowska (representing Kirstin Jansen), and Sebastian Wangler. Not shown: Hannes Merbold, Oliver Wirz.

Over 2'000 specialists attend AO Foundation symposia at DKOU 2018



The AO Foundation had a strong presence at Europe's leading conference for orthopedic trauma surgery in Berlin from October 23-26, 2018. Twenty-five AO speakers and faculty members delivered 11 symposia which attracted over 2,000 specialists. The ARI invited DKOU participants to experience the new biphasic plating concept at the AO lounge. The concept was co-developed by Markus Windolf from ARI and Devakar Epari from Queensland University of Technology, Australia, and was initially funded by AO Trauma Research Commission and AOTK System and is now funded by the AO Development Incubator for delivering the proof of concept. The biphasic principle allows you to control mechanical stimuli in a fracture to promote bone healing, while also significantly increasing implant strength to prevent pate failures.



ARI showcases the biphasic plating concept at DKOU 2018.

8.7 Visits of ARI

Switzerland Global Enterprise visits ARI

On August 28, 2018 the ARI welcomed a delegation from Switzerland Global Enterprise (SGE, formerly OSEC) as part of its 2018 Summer Academy, hosted by the Canton of Grisons. This is an annual event focusing on the latest developments and current best practice in investment promotion. This year Grisons was the host Canton and ARI was chosen by the Canton along with Hamilton company by Chur to represent the Canton. The strategy of the Cantonal government is to strengthen the Grisons as a location for research and innovation and to improve the visibility of the 'Innovation Canton of Grisons.' This includes the creation of areas for the settlement of spin-offs and start-ups (as part of the business incubator Grisons) which Richards mentioned fits very well with the development strategy of the AO Foundation to translate research to reality for patients.

The delegation from Switzerland Global Enterprise watch a demonstration by an ARI employee Peter Varga during their visit to the AO Center in Davos.

Swiss Business Hubs delegations from Brazil, China, France, Germany, India, Italy, Japan, South Korea, Russia, the UK, and the US were given tours of the AO Foundation's Davos headquarters.
The AO also welcomed visitors from several Swiss Cantons and Cantonal Economic Development Agencies, national and international corporations (SIX Swiss Exchange, Investiere/Verve Capital Partners, Innosuisse, fDi Intelligence, PwC, Invest in Estonia, and the World Economic Forum), Switzerland Global Enterprise, and the Swiss State Secretariat for Economic Affairs. The tour highlighted current research and development again towards personalized medicine and Richards highlighted the world-wide impact of AO specifically addressing work in China and the ARI's fellowship program attracting future leaders to ARI to understand preclinical research.
The AO Foundation sets the gold standard in research and education on the treatment of trauma and musculoskeletal disorders and takes pride in being a good partner to local and international agencies, corporations, and organizations.

ARI opens its doors to employees' children

As part of Switzerland's National Future Day, ARI opened the doors to employees' children. This initiative aims to help school children consider their career options, and girls and boys from the 5th to 7th class were invited to accompany a relative to work for the day. Inviting children into the workplace provides them with insight into the profession chosen by their parents or relatives and allows them to experience the numerous career paths and experiences available to them in the future. This helped them learn about the impact the AO has on patient care and outcomes in fracture treatment around the world.

Regional politicians from the Canton of Graubünden visit ARI

On September 12, 2018 a delegation of high-profile local and regional politicians from the Canton of Grisons visited the AO Center (Geschäftsprüfungskommission Kanton Graubünden, with Commission President Simi Valär). They were welcomed by Professor R Geoff Richards who gave an animated insight into the AO Foundation's history, recent achievements, and future plans. Richards highlighted both the valuable role that the AO Foundation plays in the Canton and the importance it places on having positive relations with the Cantonal authorities. He described the AO Foundation's origins, and the global reach of the impact that AO innovations have today.

From left to right: Prof R Geoff Richards, Simi Valär, Dr Christian Rathgeb, and Jon Domenic Parolini, watch a demonstration by ARI employee Manuela Ernst during their visit to the AO Center in Davos.

The delegation, which included Regierungsräte members Jon Domenic Parolini and Dr Christian Rathgeb, and Davos Kleine Landrat member Simi Valär toured the ARI, where scientists gave an overview of four key developing areas: from smart digital sensors (for continual measurement of bone healing), bioreactors (to prescreen and improve hypotheses before *in vivo* work), 3-D printing (for patient specific implants and personalized medicine) to our AAALAC accredited preclinical research sections. The visitors showed particular interest in ARI's work to develop digital monitors that track fracture healing in real-time and are able to communicate the data directly to the patients' digital files. Richards stressed that this has great potential to improve patient treatment times and outcomes, with cost reductions in on site checks – especially in hard-to-reach or remote areas.
At the end of the tour, several of the members explicitly mentioned how interesting and exciting the research being carried out at the ARI was. Many were not aware of this 'hidden gem' in the Canton of Grisons.

The Delegation with AO employees gathers outside the AO Center in Davos.

Students of Schweizerische Alpine Mittelschule Davos (SAMD) visit ARI Laboratories

In November 2018, ten students from SAMD with focus on biology and chemistry and their teacher Dimitriy Khoroshev took the opportunity to get insight into activities within the Musculoskeletal Regeneration Program, including polymer synthesis, 3D printing, cell culture, biological / biochemical analyses and microscopy. Possibilities for Matura projects were discussed.

International University Professors select ARI for sabbatical

Andrea Vernengo demonstrates 3-D printing in the ARI.

Andrea Vernengo joined ARI from July 2018 and will remain as a Research Fellow until July 2019. She is an Associate Professor of Chemical and Biomedical Engineering (joint appointment) and director of the Tissue Engineering and Biomaterials Laboratory at the Henry M. Rowan College of Engineering in Glassboro, New Jersey, United States. Sponsored by Rowan University, Vernengo will spend her sabbatical with ARI's team to further current tissue engineering approaches for the intervertebral disc (IVD). Specifically, Andrea will focus on the design of a new 3-D printed scaffold with biomimetic, region-specific architecture, and mechanical properties to repair the annulus fibrosus (AF).
Andrea received her PhD from Drexel University in 2007. She has 15 years of research experience in the development of novel biomaterials for repair and regeneration of the intervertebral disc. Recently, she has been active in the development of degradable, injectable biomaterials, including as principal investigator on a project funded by the National Institutes of Health, entitled “Development of Self-Assembling Biomimetic Hydrogels with Adhesive Properties for Nucleus Pulposus Regeneration.” Vernengo says: “I chose to spend my sabbatical at ARI because I saw a great opportunity to pursue mutually beneficial research in a supportive environment with colleagues who have both supplementary and complementary expertise to my own. I look forward to a year of high productivity and learning.”

An AOVET member for many years, Prof Marc Balligand joined ARI as a visiting professor, having been granted sabbatical leave for ten months, from October 2017 to July 2018, by the University of Liège, Belgium, where he became full professor of small animal surgery in 2004. His strong interest in biomechanics started in the early 1980`s during a 13-month Research Fellowship at the University of Pennsylvania where professors David Nunamaker (Veterinary School) and Jonathan Black (Medical School) taught him the basic principles. After more than three decades of teaching, clinical duties as chief of the Small Animal surgery service, clinical research, and a variety of community and society services – including positions as president and chair of the European College of Veterinary Surgeons, president of University of Liège veterinary clinical sciences department, president elect of the European Society of Veterinary Orthopaedics and Traumatology – not to mention raising four children with his wife Magda who is also a veterinary surgeon – Marc Balligand eventually fulfilled his dream of dedicating a full academic year to advanced research activities in a very strong biomedical engineering environment. During his sabbatical at ARI he split his time between the Biomedical Development Program (Prof Dr Boyko Gueorguiev), and to a lesser degree in the Preclinical Services Group (Dr Stephan Zeiter) where his surgical competencies were very useful for his veterinary colleagues. As Marc Balligand said: “Those ten months at ARI and in Davos were among the most inspiring of my whole career. The scientific environment was exceptional, the working atmosphere was very stimulating, colleagues from various specialties and with diverse cultural backgrounds were always ready to help and share their knowledge. All that in a magnificent mountain environment!”

During his stay in Davos, Marc Balligand had the opportunity to deepen his knowledge on various aspects of biomechanical tests with biological specimens. He received two grants allowing him to work on external fixation of feline fractures (in cats) and on smart implants (locking plates) to be used in dogs with a special focus on monitoring of interfragmentary strain, a key factor in callus formation.

Last but not least, there are excellent opportunities for future collaboration between ARI and University of Liège, in particular with a project to develop in silico models of specific fracture scenarios as well as new biomaterials from animal origin.

As a passionate cross-country skier and runner, Marc Balligand took the opportunity to participate in both the extremely popular Engadin Skimarathon (42 km in length), and the Swiss Alpine mountain marathon K43 (42.9 km length and 1425 m altitude difference).

We are very grateful to both Vernengo and Balligand for choosing ARI for their sabbaticals.

Marc Balligand demonstrates the importance of plate positioning at the AOVET Davos Courses 2017.

9 AO Research Institute Davos Fellows

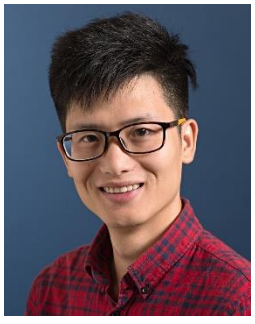
The ARI's Research Fellowship program again attracted resident and senior surgeons from around the world. Some of the many benefits to a surgeon of undertaking an ARI Fellowship are:

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

Research Fellows

Tim Buchholz: University of Veterinary Medicine, Hannover, Germany
ARI project: **Investigation of the pharmacokinetics of fentanyl patches at different locations on sheep.**
In April 2018 I became a part of the Preclinical Services team. After 8 months in this beautiful place surrounded by mountains, I got a very good insight into *in vivo* research. To do the daily work with such a nice team was really a pleasure. But I did not "just" gain experience in research during my fellowship, also, as a veterinarian, I learned much in the fields of anesthesia and surgery. To work with people from many different disciplines is also a big benefit at the ARI. It widens your horizon exceedingly. A special highlight of my fellowship was to get in touch with the experts in small animal surgery during the AO Vet Courses. The combination between so many different sports to do, especially in the winter, and such a high-quality research, is unique.

Yan Chen: First Affiliated Hospital, Sun Yat-sen University, Guangdong Sheng, China. ARI Project: A**ntibioiflim synergism between TCM compounds and antibiotics.**
I am an orthopedic PhD candidate in China since I finished my master and resident training. Before I joined the ARI, my major interests were osteogenic and antibacterial biomaterials. It was a wonderful experience to spend eight months learning the research approach of microbiology and investigating the interaction between osteogenic, chondrogenic or anti-inflammatory traditional Chinese Medicine (TCM) compounds and antibiotics within the Musculoskeletal Infection group. The people from different countries with different cultures, each group meeting presentation, each scientific event with various topics, the famous AO Courses Davos, and of course, those funny parties and majestic mountains in Switzerland are unforgettable. Thanks to my supervisors Fintan Moriarty and Willemijn Boot, thanks to everyone in ARI who gave me the opportunity to learn from them. I will continue and further improve the project I started at ARI and hopefully someday I will have another opportunity to come back, share with them what I achieve and learn from the people in ARI again as well.



Jie Du: Shenzhen University, Shenzhen, China. ARI Project: **CD146+ annulus fibrosus cells for functional repair of annulus defect.**
I am very honored that I used it to be a member of the AO family. I will miss this unforgettable experience. Everyone is very nice and friendly, but serious when it comes to science. People are always willing to communicate and solve problems together. The laboratory must be the most organized laboratory in the world, so that you can easily complete the experiment. Besides, Davos is such a beautiful town, summer is cool and calm, winter is warm and passionate.

Igor A. Escalante Elguezabal: Hospital Universitario de Caracas, UCV, Caracas, Venezuela. ARI Project: **Complex patellar fractures. Fixation methods. Experimental patellar osteotomy.**
From being in touch with AO for a long time I always felt it as something very much like home and family. Working at ARI for ten months allowed me to get in touch with great talents from all the working teams. The friendly environment makes it very easy to blend in: I felt welcomed from day one. The multiculturality makes the experience even better. If you put all that together along with a very interesting project related with my passion, "The Knee and Vicinity", you will obtain an unforgettable experience that I will surely share with my fellow faculties and residents back at home.

Alexander Milstrey: University Hospital Münster, Münster, Germany
ARI Project: **High-energy focused extracorporeal shockwave as an adjunct to antibiotic treatment in fracture related infection in rabbits.**
I really enjoyed my fellowship in the Musculoskeletal Infection group. I arrived in Davos during the hot summer days, I directly jumped into the project`s work, where we tested the effect of ESWT combined with antibiotics in a fracture-related infection model in the humeri of rabbits. Also, I had the opportunity to get to know the amazing outdoor summer activities and still am very happy to have survived my first mountain-bike experiences. As time passed by, I extended my project to an *in vitro* part, where we tested the ESWT as well on bacterial biofilms on metal discs with different antibiotics. And, last but not least, I am also still very happy to have had the opportunity of participating in the AO Courses during the first two weeks of December.

Vasiliki Panagiotopoulou: University College London, London, UK
ARI Project: **Analysis of perforation of locking screws in proximal humerus fractures.**
Being interested in bone-implant interface, I joined ARI and the Biomedical Development program in September 2018. I really enjoyed working here, in an innovative environment, surrounded and supported by world-leading engineers and researchers in the field of orthopedics, having access to well-equipped laboratories that enabled my project to be shaped and take off. I also had the chance to go to the AO courses, to meet with orthopedic surgeons and past fellows, learn about the clinical relevance of my project and exchange ideas. Last but not least, Davos is surrounded by amazing nature, and my morning walk to work, constantly changing due to different weather conditions (warm / sunny to chilly and snowy), is one of the highlights of my day.

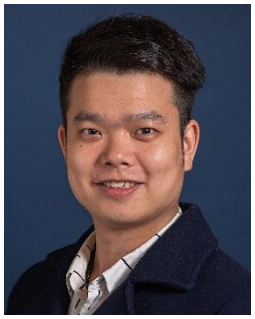
Yavor Pukalski: UMHATEM “N. I. Pirogov”, Sofia, Bulgaria
ARI Project: **Coronoid Pro - Development of a novel coronoid prosthesis for the treatment of complex elbow injuries.**
I joined the AO team as part of the Biomedical Development team under Prof Boyko Gueorguiev. My practice revolves around pediatric trauma and I have significant interests in upper extremity fracture care. My four-months fellowship has allowed me to acquire skills in research and opened-up many new opportunities for the future. I can confidently say that the ARI is truly a Mecca for research with ground-breaking innovations being made behind its walls. And the people are always friendly and helpful, ready to give you a hand or advice whenever you need it. The friendships I made during my stay are ones I am sure are going to last for a lifetime. If I can give one advice to other people? Should you ever get to opportunity to be part of the AO research family, DO NOT HESITATE even for a moment, it is going to be the best decision you have ever made.

Feras Qawasmi: Hadassah Medical Center, Jerusalem, Israel
ARI project: **VIVOLOAD - Development of *ex vivo* system for mesenchymal stem cell differentiation and cartilage integration.**
Spending one year working in basic research as an orthopedic surgeon within the Stem Cell and Biomedical groups was a life changing event that widened my innovative thinking and my understanding of how to perform quality research and of the importance of research for improving our comprehension of the problem and solution. This year changed my plans for the upcoming years, bringing research and clinical application closer to each other. It is a first step for everyone who would like to open the door of research. The year spent at ARI will be the beginning for future collaborations that will reshape my future. ARI structure and the collaboration between different groups enforces team work and helps improving personal skills and building interpersonal relationships. ARI is a multicultural environment, and this gave me the chance to explore and improve my understanding and acceptance of other cultures. Spending this time at ARI widened my network, improved many of my personal skills and my research knowledge.

Juan Diego Silva: Universidad de Los Andes, Bogotá, Colombia
ARI project: **Computational investigation of diverse fixation techniques for osteoporotic bone fractures.**
I joined the Biomedical Development group at the ARI from July to November 2018. During my time, I got the opportunity to work in applied projects in collaboration with surgeons as well as other projects more oriented towards academia following my own personal interests. Being formed as a mechanical engineer, working with the Biomedical Development group gave me a unique chance to know the biomedical development industry and find spaces where I could use my skills obtaining positive results and producing significant and tangible impact. ARI is an extremely welcoming place where people are always warm and friendly. Throughout my time, I established great friendships and scientific partnerships that will remain active for several years.

Valentina Stenger: University of Veterinary Medicine, Hannover, Germany
ARI Project: **USBlock. Ultrasound guided block of sciatic and femoral nerves in experimental sheep.**
After my studies and a short time in a small animal clinic, the veterinary research fellowship opened my mind to a complete other direction of veterinary work. The friendly and familiar atmosphere at the Preclinical facility makes it very easy to settle in and feel as part of the AO research family. Even though I have never thought about it before, I know now that I see my professional future as a veterinarian in research. I also very much enjoy the Davos landscape and outdoor activities. For all these reasons, I have decided to stay with the AO for longer and I am very happy that my contract has been extended. In the future I will continue to work on my project on ultrasound-guided nerve block in sheep. This study will serve as my doctoral thesis.

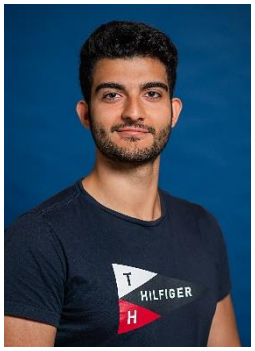
Lisa Wenzel: Berufsgenossenschaftliche Unfallklinik, Murnau, Germany
ARI Project: **Biomechanical testing of two different stabilisation methods of acetabular fractures in elderly patients with hip arthrosis.**
I love to be reminded of my time at ARI as I met a lot of lovely people from all over the world and I could join and experience different biomechanical projects to broaden especially in the field of biomechanic research. But also, the opportunity to interact with researchers with different qualifications was very inspiring. After staying six months in summer in Davos I can also tell that not only the winter is a great time to experience the great nature of Switzerland's mountains.



Yichi Xu: Chinese P.L.A. General Hospital, Beijing, China
ARI Project: **Biofabrication of cartilage particulate microtissues laden hyaluronan tissue engineered constructs** (provided by the China Scholarship Council, CSC and Sino Swiss Science and Technology Cooperation, SSSTC).
During my time at ARI as a research fellow in the Musculoskeletal Regeneration Program, I focused on hydrogel-based biomaterials, biofabrication of cell-laden microspheres, 3D printing, cell culture, confocal microscopy, RT-PCR, histology and biomechanics. Full of experiences and impressions, not only the research work at AO, but also living in Davos. I have expanded my international vision, touched the academic front, worked within a multidisciplinary team of renowned scientists and provided myself with a new lifestyle. The group activity, the parties as well as the travels made me enjoy my life in Davos and strengthened the sense of belonging and motivation to work even harder. This is, for sure, the most unforgettable experience in my life!

Parvan Yanev: UMHATEM `N.I. Pirogov, Sofia, Bulgaria
ARI Project: **Clavicle plate – comparing three type of plate fixation for midshaft clavicle fractures in case of delayed union.**
During the 4 months at the AO, I had the chance to get familiar with the scientific and research work. The people in the team were very kind and responsive, the work atmosphere is pleasant and predisposing. I have learned many new things that I intend to apply in my clinical practice.

Guest Students



Ivan Al Saify: University of Applied Sciences, Eindhoven, the Netherlands
ARI Project: **GENSWITCH – Investigation of enhancing expression with small active epigenetic molecules *versus* over-expression with GFP-adenovirus of SOX9, the key regulator for chondrogenesis.**
I have made amazing experiences, everyone in ARI is welcoming and passioned about sharing their knowledge, making the learning experiences more enjoyable. Without doubt, this internship has turned into one of the most memorable moments in my life. Davos is a great place to live if you like mountains, snow and sports. A lot of small events are organized at the ARI, so your colleges become your friends in no time!

Zohreh Arabpour: Tehran University of Medical Sciences, Tehran, Iran
ARI Project: **Autologous 3D printed scaffolds.**
I have spent 6 months at the ARI as a guest researcher of the bone regeneration group. During this period, I have gained some experience in the preparation and characterization of bone scaffolds and I have learned how to use 3D printers for tissue regeneration. Also, I have found the ARI family very intimate and scientific. The experience of living in Davos was so wonderful for me. I felt like I was living in a beautiful painted panel.

Yannik Gehlen: University Medical Center, Freiburg, Germany
ARI Project: **InflamoDisc - Anti-inflammatory and anti-degenerative effects of anti-rheumatic drugs in an intervertebral disc organ culture model.**
During the eight months of my stay at the ARI I joined the spine research team for a collaborative project. The ARI offers a professional working environment which encourages your project and your scientific development. One of the biggest advantages of the familiar atmosphere at ARI is that there is always someone you may ask for advice. Each project profits from this support and the opportunity of a steady exchange with experienced scientists. From the first day on I felt as part of the team due to that great community spirit. Furthermore, Davos is the perfect place for sport enthusiasts, either for skiing in winter or for hiking and mountain biking in summer.

Wei Guo: The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
ARI Project: **A hyaluronic-acid-based interpenetrating network for repairing degenerated intervertebral disc.**
The one-year fellowship at ARI allowed me to gain scientific knowledges and research techniques which are hardly acquired from clinical work. Now I know better how to design, conduct and review research focusing on biomaterials. Moreover, people from different groups and programs are very easy-going and willing to offer help for both scientific and personal issues. This excellent experience made my life and training unforgettable and gave me a direction for my future research work.

Dominic Mischler: ETH, Zurich, Switzerland
ARI Project: **SystemFix – Computational Osteosynthesis Test Kit for the Proximal Humerus.**
During the six months of my master thesis, I was focusing on the finite element analysis of medical implants in the biomedical development department. I really appreciated being granted the opportunity and privilege to work in an interdisciplinary group of highly motivated scientists and surgeons from all over the globe. The provided opportunity to work in such a team allowed me to exchange with medical fellows which helped me to broaden my horizon, gain insight into clinically relevant problems and deepen my understanding of the needs that the medical industry has. But despite the professional benefits I acquired during this time, I was able to establish long-lasting friendships. Eventually, I was so amazed by this institute that I decided to continue working here after finishing my studies.

Internships

Luca Ambrosio: Campus Bio-Medico University of Rome, Italy
ARI Project: **MultiBio-ink – Multiple crosslinked bio-inks for 3D microextrusion of tissue-like constructs.**
I have spent two wonderful months at the ARI focusing my efforts on the development of a scaffold consisting of a tyramine-functionalized hyaluronic acid and collagen blend for cartilage regeneration. As a medical doctor with some basic research background, I have struggled with the fundamentals of tissue engineering at the beginning, but the strong guidance provided by the Polymer Group helped me get the most out of this experience. Moreover, the warm and multicultural environment, as well as Davos breathtaking landscapes, tremendously contributed to make these two months unforgettable.

Benjamin Burkhard: Swiss Federal Institute of Technology, Zurich, Switzerland. ARI Project: **SmartPlate – Prediction of interfragmentary motion based on implant strain.**
As the primary component of my master studies at ETH, I joined ARI in October 2018 for a 2-month internship followed by a 6-month master thesis. During my initial 6 six weeks, I conducted biomechanical tests with the "AO Fracture Monitor" to assess the relationship between the monitor's output signal and interfragmentary motion of long bone fractures. I am enthused by working in a highly motivated and dedicated interdisciplinary team in the Biomedical Development Group. Furthermore, I appreciated being immediately integrated into the social activities among the other members at ARI, such as the AO soccer team and the weekend skiing trips. Highly motivated, I continue to pursue my research endeavors undertaken in Davos and I am grateful for the opportunity to do my master thesis at the ARI.

Daniel Ciric: Flinders University, Adelaide, Australia
ARI Project: **Development of finite element model for predicting screw perforation in osteoporotic proximal humerus fractures.**
From an internship to a Master Thesis, the time as a member of ARI team has been a fantastic experience. During the time at ARI, I have been exposed to many aspects of pioneering research, from experimental biomechanics to computational studies with the group in the Biomedical Development Program. I am currently conducting research for my master thesis, which requires me to investigate the effect current surgical implant decisions have on the failure mechanisms in osteoporotic proximal humeral fractures. The nature of such a project has required me to work alongside with surgeons, engineers and scientists who all share the same vision. Through this exposure, I have acquired experience and skills only possible at such an institute all the while making many close friends along the way. Working amongst an interdisciplinary group of individuals from all different countries has been beneficial both professionally and personally.

Gabriele Maria Fortunato: University of Pisa, Pisa, Italy. ARI Project: **Design, functionalization and characterization of a bioactive sensing platform to evaluate cell behavior.**
I spent three months at the ARI from April to June 2018. I joined the Polymer group to work on my master thesis about a conductive polymer to be used for tissue engineering applications. Thanks to the collaboration between the Research Center “E. Piaggio” of the University of Pisa and ARI I was able to develop a device for the electrical stimulation of muscle cells cultured on a conductive substrate. In these very productive months I increased my engineering knowledge, especially in the field of cell cultures. All this has been helped by a fantastic working environment and colleagues always willing to help and give advice. In addition to an organized and avant-garde center, what contributed a lot to a pleasant time in Davos was the wonderful scenery in which the center is located, with breathtaking natural landscapes.

Maximilian Heumann: University of Applied Sciences, Ansbach, Germany
ARI Project: **A Smart Implant for Continuous Monitoring of Spinal Bone Consolidation.**
I started at ARI on the 1st of March 2018. For the following six months I worked in the Biomedical Development Department (Focus area: Concept Development) on my Bachelor Thesis. I gained so many new insights and met so many different scientists from around the world. It was a pleasure for me as a young Bachelor`s student to be part of such an innovative, multidisciplinary R&D team. The friendly and family-like interaction of all members contributes to a great working atmosphere. All in all, it was an amazing time at the ARI.

Shahrbanoo Jahangir: Iran University of Medical Sciences, Tehran, Iran
ARI Project: **Guest Project: Chondrocyte differentiation of bone marrow derived – mesenchymal stem cells seeded on hydrogel with MMP-13 inhibitor.**
I started my internship at the ARI in April 2018, where I stayed for six months for a part of my PhD project. The ARI is a friendly place where to carry a scientific project. It felt like a big family, where everybody transmits positive energies and made me feel like at home. I was also very happy to have the chance to live in such a wonderful city as Davos.

Philippa Jörger: ETH, Zürich, Switzerland. ARI Project: **Immunospine – Hyaluronan-based interpenetrating network (IPN) for nucleus pulposus repair.**
I have learned so much in the 2 months I have been at AO. I had just finished my master in Health Science and Technology when I began. For this reason, I was really keen to get some work experience and learn how to manage a small research project. I was happy to do so in a very international environment. What I valued most about working at AO was the truly warm and friendly dealing with one another, which made it very easy for me to dedicate myself to the project.

Tino Jucker: ETH, Zürich, Switzerland. ARI Project: **GelHome2 – Synthesis and characterization of double network tough hydrogels based on natural extracellular matrix components.**
I joined the ARI in August 2018 and I am currently performing my master thesis in the polymer group, where we are working on a new technology for tough hydrogels suitable for tissue regeneration. The ARI is a condensed place of great scientists and the most modern technology. This pushes the scientific exchange to an amazing level and leads to a strong increase in knowledge, which reflects in the quick improvement of skills and outcomes. Besides this work-friendly environment, Davos has a lot to offer located in the beautiful alps.

Hubertus Kähn: University of Veterinary Medicine Hannover, Germany
ARI Project: **Silcoat – Comparison of bone healing between antimicrobial silver-coated locking plates vs. uncoated locking plates – An experimental study in a rabbit humerus midshaft osteotomy model.**
During the compulsory year of the practical training necessary for my veterinary degree, I joined ARI for 7 weeks. A special thanks goes to the team of the preclinical services under the leadership of Stephan Zeiter and in particular my supervisor Daniel Arens, they all made me feel very welcome. I took home experiences that will help me tremendously during my future career as a veterinarian and the memories of all the (cross-country) skiing and sledging we enjoyed together. I will always recommend ARI as fabulous place to work and meet wonderful people.

Jessica Keller: Zürcher Hochschule für angewandte Wissenschaften, Biotechnologie. ARI Project: **Development and Cellularization of Microfluidic Channels in Collagen gels.**
I had the opportunity to spend my early stage internship at ARI and it was one of the most life changing experiences I have had so far. The AO has a unique familiar atmosphere and every opinion on a project matters – the different groups and members meet as equals and work together interdisciplinary. I have learned a lot about the scientific way of working and got a great insight into working with experienced scientists from all over the world. The strong group cohesion makes it easy to stay motivated and focused and gain new skills. I want to thank AO and especially Dr Sophie Verrier for this opportunity.

Yann Ladner: ETH Zürich, Switzerland. ARI project: **Towards a mechano-resilient cell-laden hydrogel for *in vitro* chondrogenesis.**
After my first internship in industry, I wanted to see what working in research entails. Therefore, I decided to spend some time at the ARI to broaden and deepen my knowledge in the field of tissue engineering. Here, I immediately had the opportunity to work on different projects with various experienced people. My expectations were certainly exceeded when I started working with viruses and different biomaterials. Furthermore, meeting new people from all over the world that share the same enthusiasm for the musculoskeletal field make this institute a great place to be.

Daniele Pellicciotta, University Ca' Foscari, Venice, Italy
ARI project: **3D-SIM: 3D Sound Induced Morphogenesis.**
I started my internship at ARI in April 2018 in the Polymer group and it was a very formative experience as it was my first experience outside my university and Italy. I felt immediately accepted and everyone was willing to help when I had questions, so I could fit in very fast. This is a perfect environment to focus on research and collaborate with different groups, learning many things on the way. In addition, many group activities make it possible to create even stronger bonds with the fellow researchers. Davos is a beautiful place and I liked the skiing in winter.

Naomi Pötter: University Hospital Freiburg, Germany
ARI Project: **PRP-Load – Chondrocyte maturation under the influence of platelet-rich plasma and mechanical stimulation.**
The time at the ARI flew by far too quickly – it has been wonderful to live and work with the big AO family. The interdisciplinary mode of operation gives the opportunity to learn from all kinds of disciplines and helps you to broaden your horizon.

Stefania Vogdanou: Veterinary Medicine, Warsaw University of Life Sciences, Poland. ARI Project: **Infectwave – High-energy focused extracorporeal shockwave as an adjunct to antibiotic treatment in fracture related infection in rabbits.**
I joined the Preclinical facilities of AO Foundation in August 2018. During my three-month externship, I was involved in many different projects and I was responsible for the pre- and post-operatively care of animals. The time spent in AO was a valuable one since I got to know how the life of a vet is, gained knowledge on anesthesia and surgical protocols and learnt to collaborate with a team. The work place environment is very supportive and pleasant, and I would definitely recommend it to someone wishing to proceed on an externship or a fellowship.

Christina Wapp: ETH Zürich, Switzerland. ARI Project: **DiscRegen2 – Cross talk between mesenchymal stem cells and intervertebral disc cells.**
Three months ago, I arrived in Davos and started working on my thesis in the Musculoskeletal Regeneration group. During this short period, I learned a lot and could benefit from the close collaborations between the people working here. Independently whether you are a student, PhD or postdoc, everyone is willing to help each other if you ask for it. The atmosphere at ARI is very supportive and familial, which makes it a great place to focus on scientific work. The group activities and all the open-minded people make it easy to find friends here and finally to feel at home in Davos.

10 Project Abstracts by Sponsors

10.1 AOCMF

Antiresorptive-related osteonecrosis of the jaw (ARONJ): Computer-assisted ranking to facilitate risk evaluation, diagnosis and treatment decision (ongoing) (L Kamer, H Noser)

Background: Antiresorptive drug-related osteonecrosis of the jaw (ARONJ) is a disease observed in a subset of patients treated with anti-osteoclastic drugs indicated for metabolic bone diseases, osteoporosis and cancer. Early diagnosis and treatment may prevent or reduce the morbidity resulting from advanced destructive lesions of the jaw. Currently, the clinical procedure relies on the medical history, clinical and radiographic assessment, as they are thought to be the most sensitive tools. However, in early clinical stages ARONJ may not be obvious or even clinically detectable when applying an existing treatment workflow. Artificial Intelligence (AI) is increasingly used as an aid to diagnosis in medicine. AI might be adopted and used to rank given ARONJ cases, thus facilitating clinical assessment.
Goal: To develop a computerized ARONJ ranking tool to improve and facilitate risk assessment, diagnosis and treatment decision in the clinics. The tool should be developed with the use of retrospective series of patient records, panoramic radiographs, computed tomography and cone beam computed tomography scans.
Results: A total of 175 ARONJ cases were collected. The developed computerized AI tool for ranking of ARONJ cases allowed analysis of the data within less than one minute. It implemented data acquisition, data pre-processing, features extraction, models training, best model identification and predictor model creation.

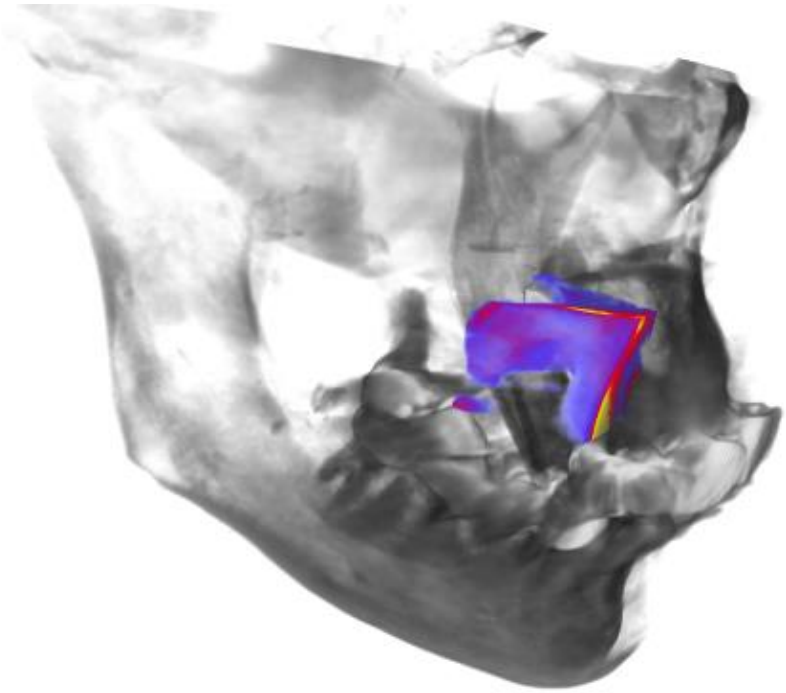


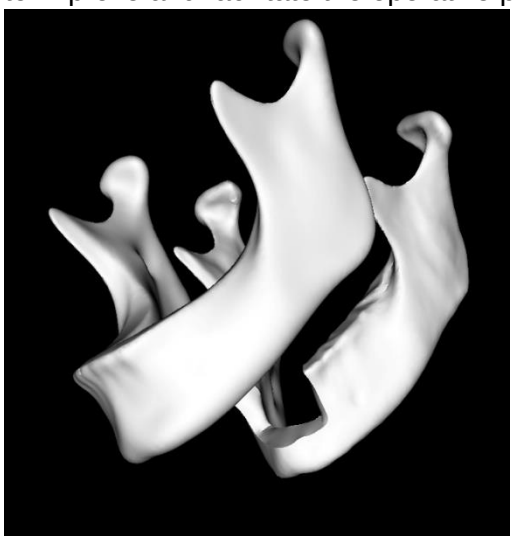
Figure 10.1.1: Exemplified cone beam computed tomography (CBCT) scan with a colored region of interest (ROI) corresponding to an alveolar defect at the right upper jaw affected by ARONJ. The ROI was extracted and analyzed via Artificial Intelligence workflow.

Partners:

- Rana M, Heinrich Heine University of Düsseldorf, Germany
- Lutz I, Medical School, Germany
- Zimmerer R, Hannover Medical School, Germany
- Gellrich NC, Hannover Medical School, Germany

Virtual reconstruction of mandibular defects using a 3D statistical model of the mandible and Gaussian regression (CMF morphology and navigation) (L Kamer, B Gueorguiev-Rüegg, H Noser)

Background: Mandibular defect reconstruction can be long-lasting and demanding and might be indicated in patients suffering from different pathologies including benign or malignant lesions, trauma, deformities or infection. 3D imaging and computerized preoperative planning represent techniques that may be adopted to virtually reconstruct mandibular defects, thus helping the surgeon to improve and facilitate the operative procedure.

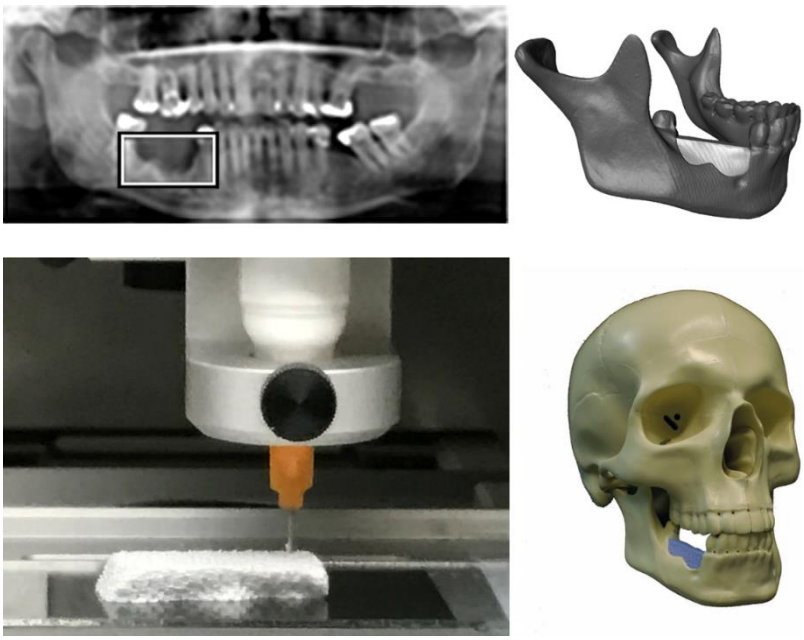


Goal: To virtually reconstruct mandibular defects using a priori knowledge (anatomical reference data) and advanced computational techniques. Specifically, 3D statistical size and shape modeling of the mandible should be applied with the use of Gaussian regression.
Results: A computerized workflow was developed in "Scalismo-Lab", an open source software for statistical shape modeling and model-based image analysis using Scala programming language. Additional processing and analysis were performed using other software applications. The developed computerized approach was successfully tested using a virtually created mandibular defect.

Figure 10.1.2: Virtual reconstruction of an anterior mandibular defect using Gaussian regression and 3D statistical modeling techniques.

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

Background: Worldwide, the number of bone grafts used in surgical procedures has been estimated at over 24 million in 2010. The overall bone graft sales are forecasted to reach a total of $3.3 billion worldwide in 2017. In 2003, the synthetic bone graft substitutes made only 8% of the bone grafts market, while it now makes more than 20% of the market and continuously develop. The global increase of needs for bone graft substitutes and emergence of large healthcare providers in Asia support the necessities for better bone repair solutions based on innovative biomaterials.
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.
Goal: This project aims 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 10.1.3).
Results: A novel coaxial extrusion-based 3D-printing process was developed leading to the rapid initial setting of a commercial calcium phosphate cement past allowing for high-fidelity and rapid manufacturing of patient specific implant.



10.1.3: Representative workflow from clinical CT, mandibular defect reconstruction, printing of calcium phosphate cement and implant fit in defect.

Pres:
Eglin D. Status and future of 3D printing in cranio-maxillofacial surgeries. An AOCMF symposium. 2018 EORS (oral).
Sprecher CM, Thurner M, Büchler P, Richards RG, Eglin D. Improved post-processing stability of a 3D printed cement paste via co-axial extrusion of organic solvents. 2018 SSB+RM (poster).

Partner:
- Thurner M, regenHU Ltd, Villaz-Saint-Pierre, Switzerland

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

Background: 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 of the major remaining hurdles 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 more rapidly. 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 with be investigated by the addition of simple osteoinductive molecules that are already clinically approved or would have a less challenging approval process.
Goal: 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.
Results: We have investigated several materials, with or without biological enhancers, for their bone forming capabilities both *in vitro* and *in vivo.* Surprisingly, the results of these assays often do not correlate, suggesting that current material testing algorithms are sub-optimal.

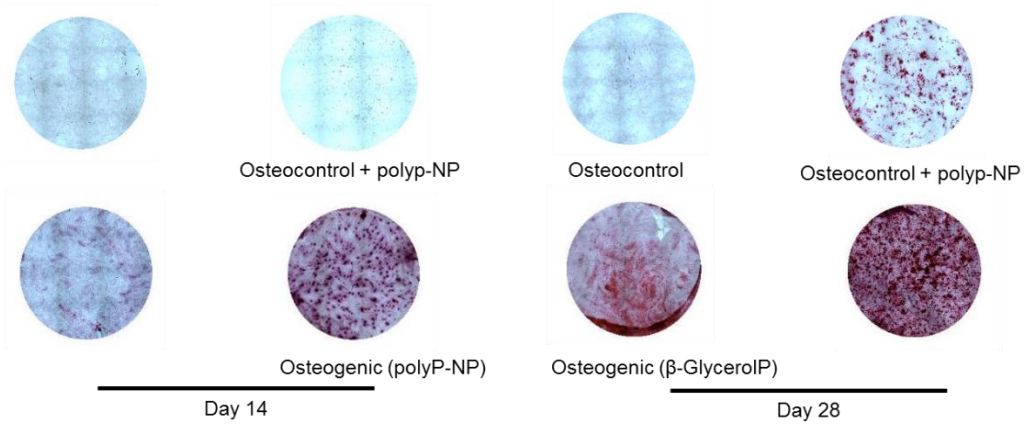


Figure 10.1.4: Osteogenic potential of various material composites containing human mesenchymal stem cells.

Pres:
Behrendt P, Ladner Y, Stoddart MJ, Lippross S, Alini M, Eglin D, Armiento AR. Highly tunable di-tyramine hyaluronan hydrogel enables mechanical stimulation of encapsulated mesenchymal stromal cells towards chondrogenesis. 2018 eCM (poster).

10.2 AOSpine

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

Background: Low back pain is the leading cause of disability worldwide and often associated with intervertebral disc (IVD) degeneration. Current treatments of low back pain symptoms range from conservative management to surgical intervention. However, none of these treatments are capable to restore a degenerative disc. Therefore, research has focused on regenerative approaches based on biomaterials, cells or combination of both. The latter approach is very promising, but one of the major challenges is to provide a biomaterial that can restore mechanical functionality while at the same time providing a relatively soft matrix for adequate cell encapsulation.
Goal: To develop an interpenetrating network (IPN) hydrogel system to address these contrasting requirements of biomechanical and cellular compatibility.
Results: A first hydrogel network (based on chemically crosslinked hyaluronan, HA-BDDE) was infiltrated with a cell suspension in a thermoreversible hyaluronan hydrogel (HA-pNIPAM) and gellified in situ, leading to an interpenetrating network (Figure 10.2.1). The optimal concentrations of HA-BDDE and HA-pNIPAM required to obtain a homogeneous IPN were determined. Hydrogels were stable in culture medium for two months in the absence of cells. When intervertebral disc cells were seeded in the IPN, applied to nucleotomized discs and mechanically loaded for one week (3 hours/day at 0.2 Hz, 0-0.1 MPa; 7 days), both IPN and HA-BDDE allowed for an adequate cell retention, while this was not the case of HA-pNIPAM hydrogels.
In conclusion, an innovative IPN hydrogel system combining good cell retention and ability to withstand cyclic load was developed and tested. This IPN hydrogel holds a strong potential for regenerative approaches in the treatment of degenerated IVDs following discectomy.

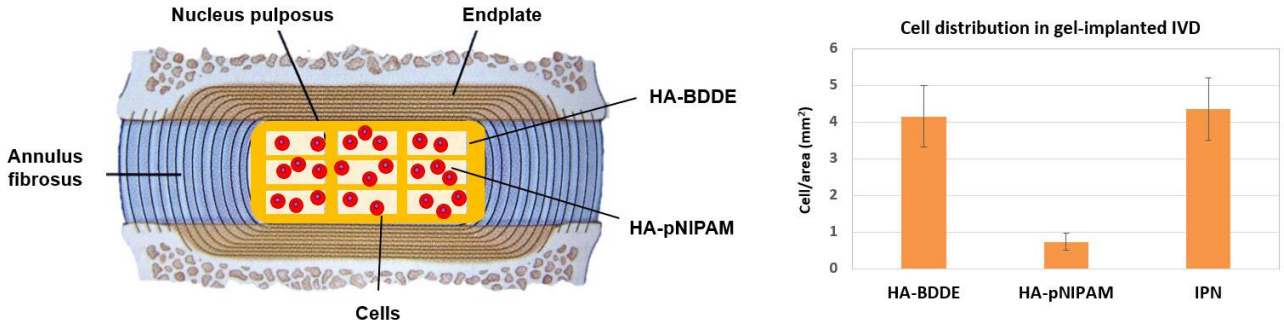


*Figure 10.2.1**: Interpenetrating network (IPN) hydrogel based on hyaluronic acid (HA) as a mechanically-competent cell delivery system for nucleus pulposus repair**. Left side: scheme representing the IPN made by infiltrating the lyophilized chemically crosslinked HA network (HA-BDDE) with a thermoreversible HA hydrogel (HA-pNIPAM). Right side: cell retention in the different hydrogels following application into nucleotomized intervertebral discs and mechanical loading (mean and standard error, n=15).*

Pub:

Caprez S, Menzel U, Li Z, Grad S, Alini M, Peroglio M. Isolation of High-Quality RNA from Intervertebral Disc Tissue via Pre-Digestion. J Orthop Res Spine 2018;1(2): https://doi.org/10.1002/jsp2.1017.

Annulus fibrosus repair (ongoing) (Z Li, S Grad)

Background: Both endogenous cell homing and exogenous cell transplantation have been proposed for annulus fibrosus (AF) regeneration and AF rupture healing, although further pre-clinical data are needed before clinical translation. We previously found that CD146+ AF cells deposited collagen type I rich extracellular matrix (ECM) more intensely compared to CD146- AF cells.
Goal 1: To evaluate the potential of chemokine CCL5 delivery to recruit endogenous AF cells to the injury sites and facilitate the repair of ruptured AF.
Results 1: A trans-well *in vitro* study revealed a chemotactic effect of CCL5 on AF cells with a dose dependent manner. However, in organ culture and in a pilot sheep animal study, CCL5 did not stimulate homing of AF cells towards the defect sites. These results demonstrated a good predictive potential of the AF puncture organ culture model for pretesting of therapies before conducting an animal study.
Goal 2: To induce a functional CD146+ cell population from AF cells for enhanced AF ECM synthesis and repair.
Results 2: By stimulating human AF cells with TGF-β1, we were able to enrich the CD146+ cell population. TGF-β1 also increased the expression of AF markers SM22α, Scleraxis, and cell contractility, which is pivotal for tissue remodeling.
The induced AF cell population was further tested for its repair effect in an *ex vivo* IVD annulotomy organ culture system. Implanted AF cells were maintained and started matrix production in polyurethane-collagen scaffolds after 14 days organ culture with physiological loading. Supplementation with TGF-β1 enhanced the cell number, collagen matrix production (Figure 10.2.2), collagen I and CD146 gene expression. Ongoing studies are focusing on the underlying mechanism of TGF-β1 signaling in human AF cells.

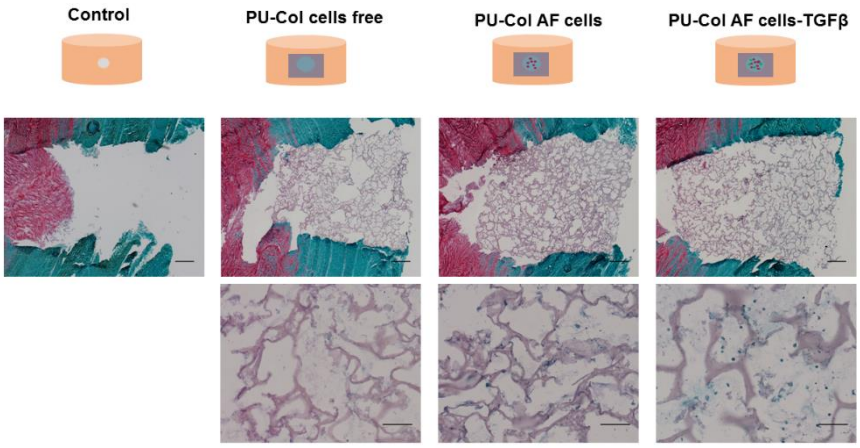


Figure 10.2.2: Representative Safranin O/Fast Green stained sections of annulotomized IVD without repair (control), with polyurethane scaffold-collagen I hydrogel (PU-Col cells free), polyurethane scaffold-collagen I hydrogel with AF cells (PU-Col AF cells), and polyurethane scaffold-collagen I hydrogel with AF cells and TGF-β1, after 14 days culture with physiological loading. Scale bar: top row – 500 µm, bottom row – 100 µm.

Pres:
Günay B, Isa ILM, Conrad C, Scarcelli G, Grad S, Li Z, Pandit A. A hyaluronan-based hydrogel system for annulus fibrosus repair. 2018 EORS (oral)
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 a collagen gel. 2018 ISL&T (oral)

Pub:
Zhou Z, Zeiter S, Schmid T, Sakai D, Iatridis JC, Zhou G, Richards RG, Alini M, Grad S, Li Z. Effect of the CCL5 releasing fibrin gel for intervertebral disc regeneration. Cartilage, 2018 DOI: 10.1177/1947603518764263
Long RG, Zderic I, Gueorguiev B, Ferguson SJ, Alini M, Grad S, Iatridis JC. Effects of Level, Loading Rate, Injury and Repair on Biomechanical Response of Ovine Cervical Intervertebral Discs. Ann Biomed Eng 46(11):1911-1920, 2018.
Huang Yong-Can, Hu Yong, Li Zhen, Luk Keith D.K. Biomaterials for intervertebral disc regeneration: current status and looming challenges. J Tis Eng Reg Med 2018 DOI: 10.1002/term.2750

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

10.3 AOTrauma

Predicting patient-specific mechanical failure of proximal humerus fracture plating with computer simulations (SystemFixII) (ongoing) (P Varga, M Windolf)

Background: The high failure rate of osteoporotic proximal humerus fracture fixations and the expected increase of their incidence indicate the need for improved fixation strategies and careful planning. Validated computer models have a high potential to complement or partially replace conventional biomechanical testing, expedite implant optimization and design, refine surgical guidelines, support decision making and allow patient-specific pre-operative planning. Ultimately, simulations are expected to help improving patient outcomes of osteoporotic proximal humerus fracture treatment.
In the first project phase (SystemFixI), a virtual osteosynthesis test kit was developed to simulate proximal fracture plating and predict mechanical fixation failure. This tool was validated experimentally and utilized in a series of virtual pilot studies to indicate ways of improving the usage of plates, to compare different implants and to optimize the implant design towards improved stability. However, the models have not yet been demonstrated to predict mechanical fixation failure in real clinical cases.
Goal: To extend the simulation tool from virtual to real clinical scenario and to validate it clinically by predicting patient-specific risk of mechanical fixation failure.
Results: The second project phase was successfully initiated and consequently follows-up on the completed first project phase (SystemFixI). A two-center clinical study has been designed and initiated with our clinical partners in Leuven and Innsbruck, recruiting PHILOS-plated osteoporotic proximal humerus fracture patients. Besides the standard-of-care investigations, a post-OP CT scan of each patient will be collected, and shoulder activity will be measured with sensors. Applications for ethical approval have been submitted. Biomechanical validity of the simulations is extended from the previously investigated cut-through failure to secondary screw perforation in currently running sub-projects, combining experimental testing and computer modeling.

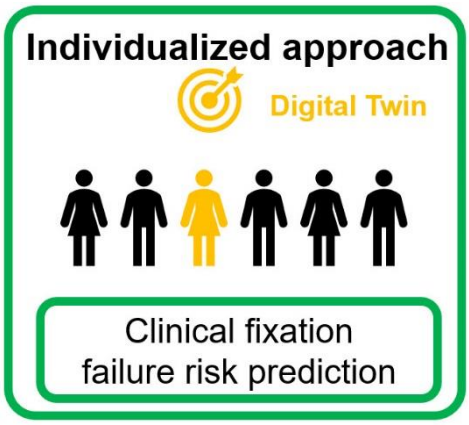


Figure 10.3.1: Approach for prediction of clinical fixation failure risk by means of patient-specific computer simulations.

Pres: (from SystemFixI)
Varga P, Inzana JA, Hofmann-Fliri L, Südkamp N, Windolf M. Finite element analysis of the optimal cement augmentation strategy for plate fixation of osteoporotic proximal humerus fractures. 2018. WCBiomech (poster)
Varga P, Windolf M. Application of validated computational models of proximal humerus fracture fixation to guide clinical practice. 2018. ECCM 6 (invited oral)

Theses:
Mischler D. Optimization of a proximal humerus implant by means of Finite Element Analysis. Master Thesis, ETH Zürich, 2018

Pub: (from SystemFixI)
Varga P, Grünwald L, Inzana JA, Windolf M. The prediction of cyclic proximal humerus fracture fixation failure by various bone density measures. J Orthop Res. 2018. Epub
Varga P, Inzana J, Gueorguiev B, Südkamp N, Windolf M. Validated computational framework for efficient systematic evaluation of osteoporotic fracture fixation in the proximal humerus. Med Eng Phys. 2018. 57:29-39.

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

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

Background: Corrections of limb deformities, in particular varus-valgus deformities and leg length discrepancies, are frequent interventions in paediatric orthopedic surgery. In most cases temporary epiphysiodesis is used, whereby the growth is guided by temporarily blocking the 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 leads to plate and screw deformation and consequently to devastating events such as implant breakage or growth arrest. To avoid such issues, a new implant concept for guided growth regulation was developed. The implant is designed to be 'passively' safe and capable to apply constant forces to the physis, which is hypothesized to allow controlled regulation of the growth.
Goal: To test the functionality and efficacy of the proposed implant concept in a large animal experiment.
Results: In a first preclinical trial, 18 lambs were treated with the proposed implant in a hemi-epiphysiodesis setting to create varus deformity. The animals were divided into three groups depending on the implants force level (60 N, 120 N and 200 N). The achieved deformity was assessed by measuring the change of the medial proximal tibial angle from biweekly radiographs. Statistically significant differences were revealed between all three groups, with highest deformity achieved in the 200 N group, followed by the 120 N group. Almost no effect was observed with the use of the 60 N implant.
To prove the implant efficacy for treatment of leg length discrepancies, a second trial is currently running. 18 lambs were treated with two implants in a bilateral setting and were randomly assigned to three groups (60 N, 120 N and 200 N). Leg lengths are measured on biweekly radiographs. Preliminary trends suggest similar tendencies as in the previous trial.
The results from the experiments are promising and show that a regulation of the growth is feasible applying the proposed implant concept. Moreover, no implant related issues, such as implant or screw breakage were observed during the tests. Apart from medical device development aspects, this in-vivo study provides important and currently unknown scientific information to enhance the knowledge on bone growth processes and to improve the treatment of limb deformities.

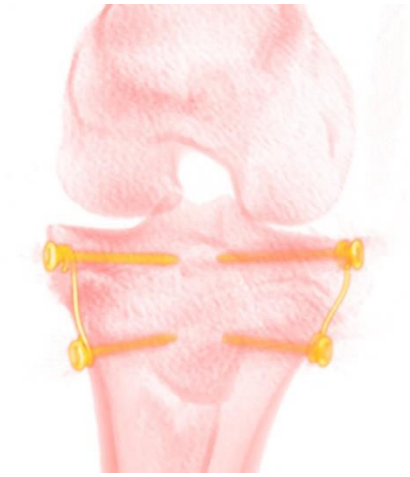


Figure 10.3.2: Implant for constant force application to the tibia physis in an epiphysiodesis setting.

Partner:

- Slongo T (Prof), Children’s University Hospital, Berne, Switzerland

Influence of temporal fracture mechanics modulation on bone healing (ActiveFix) (ongoing) (J Barcik, M Ernst, M Windolf)

Background: The impact of temporal variation of mechanical stimulus on bone healing are only barely understood. There might be potential to improve speed and robustness of fracture healing. Recent animal experiments (project ImpCon2) suggest that fracture stimulation in an early post-operative phase could be of high importance for robust and timely healing. A recently introduced experimental two-defect fracture model (QUT, Brisbane, Australia), including an actuator driven external fixator, allows executing arbitrary stimulation protocols to the fracture site completely independent from functional loading of the animal.
Goal: To improve the implant system for execution of arbitrary stimulation protocols to the fracture site completely independent from the large animal functional loading, and to apply it *in vivo* for comparison between immediate and delayed fracture stimulation.
Results: Following the results of a pilot study conducted in 2017, the mechanical design of the active external fixator was refined to increase its inherent stiffness. *In vitro* tests were conducted to verify the reliability of the improved design and to characterize the mechanical properties of the fixator. The refined fixator was implanted in 8 sheep assigned to 2 groups. Different postoperative protocols were applied to the study groups, mimicking early or delayed weight bearing. Daily stimulation of the experimental defect, conducted in the group with early weight bearing, provided data to detect healing onset and to measure *in vivo* callus stiffness in the early stage of bone healing. Data evaluation is currently ongoing.

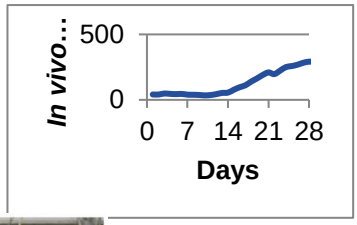


Figure 10.3.3: Mean in vivo stiffness of the tissue in the fracture gap of an exemplary animal at an early stage of bone healing.

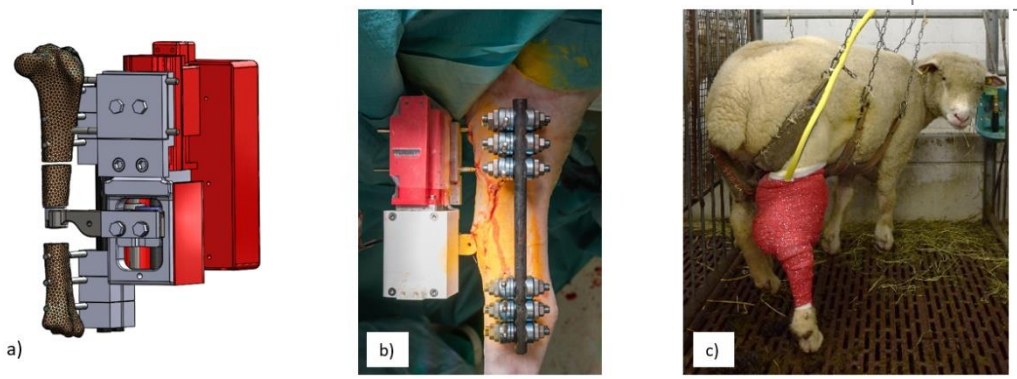


Figure 10.3.4: a) CAD model of the active external fixator; b) active fixator as implanted in a sheep tibia; c) postoperative care–sheep with implanted system.

Pres:

Barcik J, Ernst M, Freitag L, Dlaska CE, Gueorguiev B, Epari D, Windolf M. Promoting bone regeneration by optimization of rehabilitation protocols.2018 Regenerative Rehabilitation Symp, Seattle, USA. 11.-13.10.2018 (oral)
Barcik J, Ernst M, Freitag L, Dlaska CE, Gueorguiev B, Epari D, Windolf M. An active fixation system to investigate the influence of rehabilitation protocols on fracture healing – *in vivo* preclinical application. 2018 Regenerative Rehabilitation Symp, Seattle, USA. 11.-13.10.2018 (poster)
Barcik J, Ernst M, Freitag L, Dlaska CE, Gueorguiev B, Epari D, Windolf M. *In vivo* preclinical application of an active external fixator to investigate the influence of local mechanical conditions on the fracture healing. 2018 DGBMT Annual Conference, Aachen, Germany, 26.-28.09.2018 (oral), Biomed Tech. 2018;63:(s1) S161
Barcik J, Ernst M, Freitag L, Dlaska CE, Gueorguiev B, Epari D, Windolf M. An active fixation system to investigate the influence of local mechanical conditions on fracture healing. 2018 Graubünden forscht, Davos, Switzerland, 19.-20.09.2018 (poster)

Partners:

- Epari D, Queensland University of Technology (QUT), Brisbane, Australia
- Dlaska CE, Orthopaedic Research Institute of Queensland, Townsville, Australia
- Balligand M (Prof), University of Liège, Belgium
- Lubieniecki M, AGH University of Science and Technology, Krakow, Poland

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

Background: The task of placing implants plays a key role in trauma and orthopedics surgery. Current solutions for computer aided surgery lack of wider acceptance due to considerable disadvantages regarding complexity, costs and effectiveness.
Goal: 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 under clinical investigation. The proximal humeral plating system is tested in University Hospital Leuven, Belgium. Results reveal promising system performance in terms of a surgical handling and validity of the system in the clinical context. Concise data evaluation is in progress.
The Xin1 module for rotational corrective osteotomies, developed in collaboration with the Joint Preservation and Osteotomy Expert Group (JPEG), has been successfully tested at BGU Tübingen, Germany. Twelve patients, undergoing a torsional correction, were included in the study. Based on the intraoperative captured radiographs, the performed torsional correction was determined with the Xin1 software and compared against CT measures. The mean torsional deviation is less than two degrees (1.86°± 0.78°, mean ± SD) which fulfills the clinical requirements. Hence, the Xin1 system can deliver a relevant intraoperative benefit to facilitate and improve corrective osteotomy treatment.
Furthermore, a prototype module to obtain perfect circle alignment during freehand nail interlocking was developed. This task is considered as technically demanding and often results in high x-ray exposure and increased surgery time. The Xin1 system computes the required orientational adjustment of the c-arm based on a single x-ray image and guides the user through this step without changing standard surgical routine. This considerably enhances the process of freehand interlocking and reduces time, x-ray and costs.

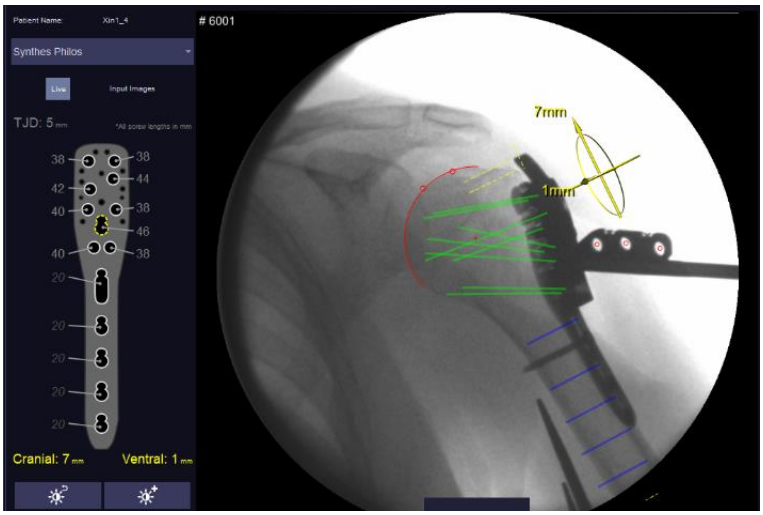


Figure 10.3.5: Xin1 software module for proximal humeral plating – developed in cooperation with MeVis Medical Solutions AG and currently in clinical testing.

Partners:

- Nijs S (Prof), University Hospital Leuven, Belgium
- Schröter S (MD), BG Unfallklinik Tübingen, Germany
- Mevis BreatCare (Mevis Medical Solutions AG), Bremen, Germany

A method for creating Statistical Form Model of the geometry of cortical bone of the distal Radius (corticalSMF) (ongoing) (B Gueorguiev-Rüegg, H Noser, L Kamer)

Background: Knowing in detail the cortical geometry of human bones and some related cortical thickness statistics is useful in many fields such as education, pre-operative planning, or implant optimization. The creation of virtual bones based on image data is an important aspect of this project. A virtual bone is a three-dimensional (3D) computer model reconstructed from a given Computed Tomography (CT) scan or a high resolution peripheral quantitative CT (pQCT) scan. For creation of a virtual bone the image data are used to model the outer cortical bone surface as a triangulated surface model.
Goal: To develop a method for creating cortical statistical form models (cSFMs) of the cortical shell of human bones and to apply it to distal radii. It is planned to:

- use existing pQCT scans and results from the former AOTrauma project SynPorOpti
- create automatically thickness statistics at given locations and correlate them with the osteoporosis status
- validate the cSFM by showing that the training set and newly created bone sets produce the same thickness statistics
- create a predictor for prediction of osteoporosis status based on thickness data and available meta information (age, gender) by applying machine learning

The focus of the project is on development of method and workflow to create a cSFM of a human bone by modelling the outer and inner form of the cortical shell with two surfaces. The proposed applications and validation should demonstrate aspects of potential future clinical applications.
Results: Currently, a method to create a cSFM of the distal radius is developed. Each vertex on the outer shell of the virtual bone surface has a homologous vertex on the inner shell.

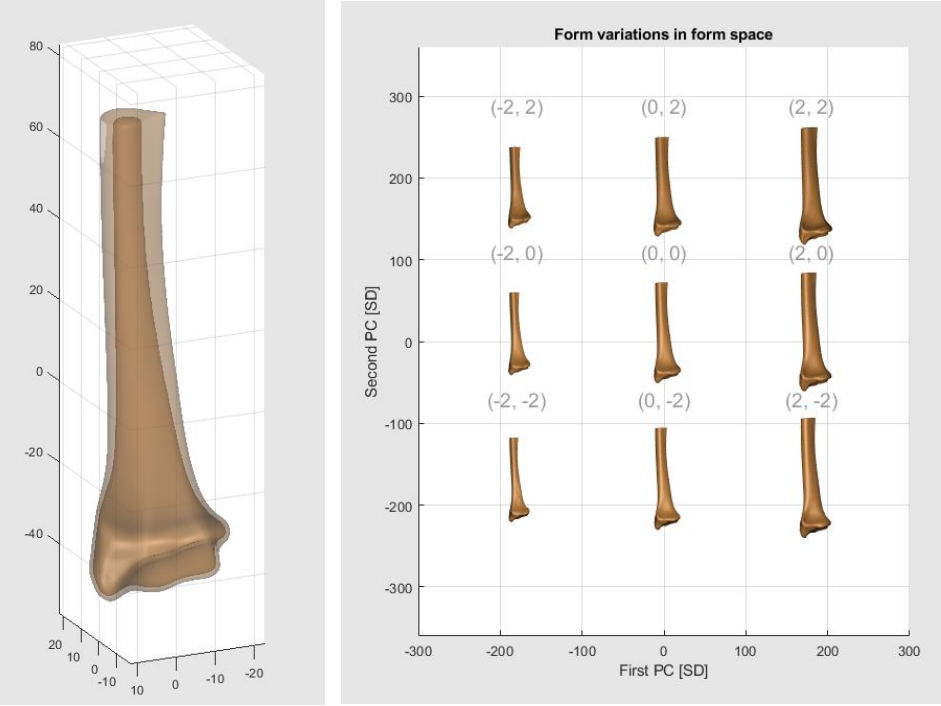


Figure 10.3.6: Left – transparent mean distal radius shape including both outer and inner cortical shells; right – the most important form variations of the cortical distal radius model modeled by the first two Principal Components within a range of ± 2 standard deviations.

Symmetry analysis of the pelvic ring (SymPel) (L Kamer, H Noser)

Background: The human pelvis is a complex bone and exhibits a highly variable anatomy. Innominate bones, sacrum and coccyx form a ring-building structure, also termed as the pelvic ring. In general, it displays a symmetric configuration with the mid-sagittal plane separating the pelvic ring into a homolateral and contralateral side. Each of the two sides is thought to be a mirror image of each other. In orthopaedic surgery and trauma care analysis of the symmetry of the pelvic ring is an important task and can be used to study symmetry patterns in healthy cases but can also be applied to malformations, degenerative changes or fractures. Likewise, the research subject might be transferred to other bones or tissues of the human body or even to other species. However, there is currently only limited information on pelvic ring symmetry and how to apply symmetry analysis on this ring-building structure.
Goal: To assess the symmetry of the pelvic ring and to define a method thereof to be used for research, development, and clinical applications.
Results: Within the first project phase, a computerized workflow has been developed to evaluate the symmetry plane and symmetry configurations of the pelvic ring.

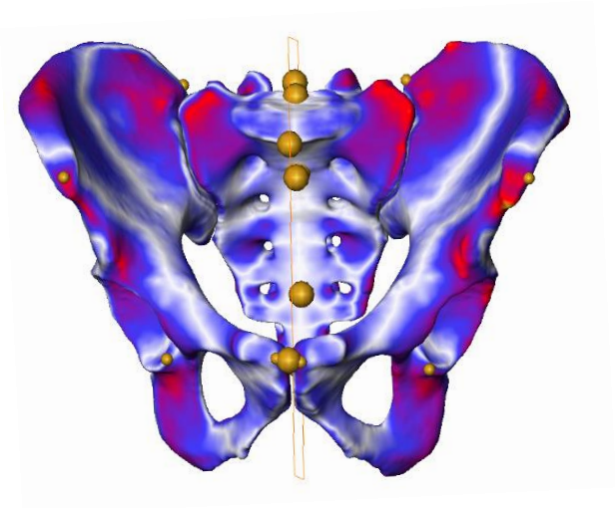


Figure 10.3.7: Pelvic model with landmarking of its pelvic ring (small yellow dots) used to define the plane of symmetry (big yellow dots and plane outlined by orange line) by means of 3D distance mapping technique comparing the ipsilateral and contralateral side of the pelvic ring.

Partners:
- Rommens PM (Prof), University Medical Center, Mainz, Germany
- Mayo K (Prof), University of Washington School of Medicine, Seattle, USA
- Sawaguchi T (Prof), Toyama Municipal Hospital, Toyama, Japan
- Arand C (MD), University Medical Center, Mainz, Germany
- Wagner D (MD), University Medical Center, Mainz, Germany

3D statistical model of the scaphoid to assess osseous and cartilaginous anatomy (HMSC) (H Noser, B Gueorguiev-Rüegg, L Kamer)

Background: Scaphoid fractures are the most common carpal fractures. They are often misdiagnosed and challenging to treat. Surgical fixation requires implant positioning at anatomical sites with only limited space and under consideration of cartilaginous anatomy for good implant positioning.
Goal: To improve anatomical knowledge of the scaphoid and to understand its relevance to fracture treatment, focusing on:
- Identification of particular anatomical regions with high and low bone density
- Description of possible implant pathways with regard to bony and cartilaginous surfaces, implant entry points, screw lengths and bone mass distribution

Method: Forty-three unpaired fresh-frozen human cadaveric hand specimens were subjected to high-resolution peripheral quantitative computed tomography (HR-pQCT) scanning. Following, they were dissected to identify the cartilaginous and osseous boundaries of the scaphoid. All image data were post-processed to generate a 3D statistical model of the scaphoid with its cartilaginous and osseous surfaces, and spatial bone density distribution.

Results: The computed model offered possibility for detailed analysis of the osseous and cartilaginous anatomy of the scaphoid. Regions with different volumetric bone mineral density were identified. Screw length of intraosseous pathways, bone mass profile along these pathways, and neighboring osseous and cartilaginous surfaces were identified.

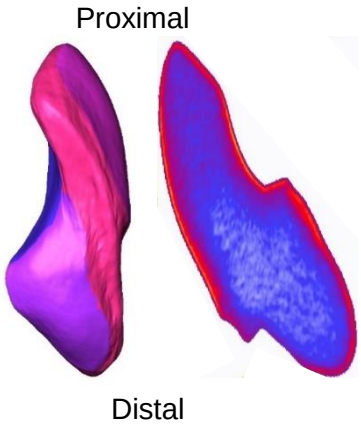


Figure 10.3.8: Left: 3D scaphoid model with cartilaginous surfaces (blue and purple colors) and osseous surface (pink); right: orthogonal slice with semi-quantitative visualization of averaged volumetric bone mineral density – regions with high bone mineral density (red and orange), intermediate bone mineral density (blue) and low bone mineral density (white).

Partners:

- Teunis T (MD, PhD), University Medical Center Utrecht, The Netherlands
- Ahrend MD (MD), BG Trauma Center Tübingen, Germany

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

Background: Recently, it has been identified that bacteria may reside deep within bone tissue and these bacteria may be a possible cause of treatment failure of infected bone. Thus, it is likely tha 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 could be a factor for the long-term recurrence rate on some groups of patients (for example with open fractures) remains at approximately 20% to 30%.
Goal: This project aims to explore different methods to increase antibiotic retention in bone tissue and to enhance their efficacy to treat locally bone infection by the incorporation of antibiotic agents with novel bone-targeting delivery carriers (Figure 10.3.9).
Results: We prepared antibiotic-loaded nano/microsize vehicles, whose surface has been functionalized by molecules exhibiting strong affinity to the bone tissue (e.g. bisphosphonates, polyaspartic acid). Then, we are characterizing 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.

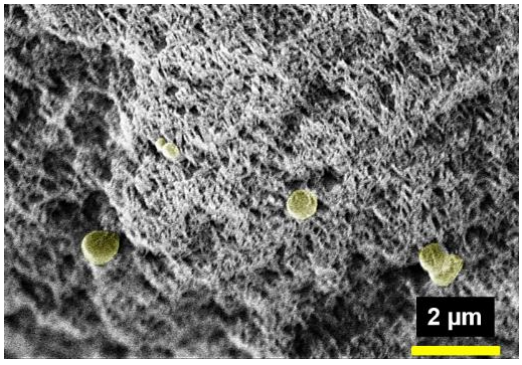


Figure 10.3.9: Electron microscopy image of bone targeting microparticles delivery vehicle.

Pres:
Rotman SG, Grijpma DW, Richards RG, Moriarty TF, Eglin D, Guillaume O. Biodegradable and bone targeting drug delivery system for antibiotics. 2018 SSB+RM (poster).
Rotman S, Grijpma D, Richards RG, Moriarty TF, Eglin D, Guillaume O. Development of a poly(ε-caprolactone) bone targeting antibiotic drug delivery system by implementation of alendronate bone seekers. 2018 GR forscht (oral).
Rotman SG, Grijpma DW, Richards RG, Moriarty TF, Eglin D, Guillaume O. Bone seeker functionalized microparticles as a targeted local antibiotic drug delivery for bone related infections. 2018 Thesinge Biofilm (oral).

Pub:
Guillaume O, Perez-Tanoira R, Fortelny R, Redl H, Moriarty TF, Richards RG, Eglin D, Petter Puchner A. Infections associated with mesh repairs of abdominal wall hernias: Are antimicrobial biomaterials the longed-for solution? Biomaterials. 2018;167:15-31.
Guillaume O, Perez Kohler B, Fortelny R, Redl H, Moriarty TF, Richards RG, Eglin D, Petter Puchner A. A critical review of the *in vitro* and *in vivo* models for the evaluation of anti-infective meshes. Hernia. 2018;22:961-974.
Heriot M, Nottelet B, Garric X, D'Este M, Richards RG, Moriarty TF, Eglin D, Guillaume O. Interaction of gentamicin sulfate with alginate and consequences on the physico-chemical properties of alginate-containing biofilms. Int J Biol Macromol. 2018;121:390-397

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

Principal Design Components for Patient Specific 3D Bone Models. Vascular structures (3D-VASC) (S Verrier, D Eglin, T Serra) Feasibility

Background: Bone has a very high self-healing capacity, but in some cases related to patient status and health, poor healing and non-union will occur. It is difficult to predict bone healing in relation to the biological status (e.g. age, disease, others) of the patient. Despite classical 2D *in vitro* cell models are relatively easy to set-up, they do not fully recapitulate the complexity of the native tissue, limiting the ability to use them as predictive tools or models for screening biological therapies. Bone is a complex 3D microenvironment, consisting of different tissues, cell types producing extracellular matrix (ECM) and signaling molecules. All together, these components determine important aspects of physiology and healing response. 3D models for studying bone physiology in normal and diseased conditions, could become powerful tool for screening patient's bone healing potential or bone disease status and thus to provide personalized treatments. Therefore, we hypothesis that 3D additive manufacturing (AM) technologies will enable the *in vitro* recreation of the bone complexity that can be use has predictive tool for bone healing capacity. Significant technical hurdles still exist toward the development of such models. A first challenge is the formation of long-lasting vascular networks for oxygen and nutrient supply as well as metabolic by-products removal.
Goal: Therefore, the aim of this feasibility study project is to develop the technological tools to produce vascular like structures in a 3D model as a basic structural element toward 3D bone *in vitro* model.
Results: An AM technology allowed the development of a vasculature network embedded in an ECM-like hydrogel, all included in a silicone cage for perfusion (Figure 10.3.10). Optimization of 3D printing parameters for the generation of branched tubular structures was carried out. After ECM casting and sacrificial vasculature dissolution, endothelial cells (HUVECs) were perfused. The pump vessel/connections and the external hydrogel matrix stability were main critical issue in the generation of stable and functional vessels. However, HUVECs adhesion within the vessels was achieved by using GelMA hydrogel as casted bulk hydrogel.

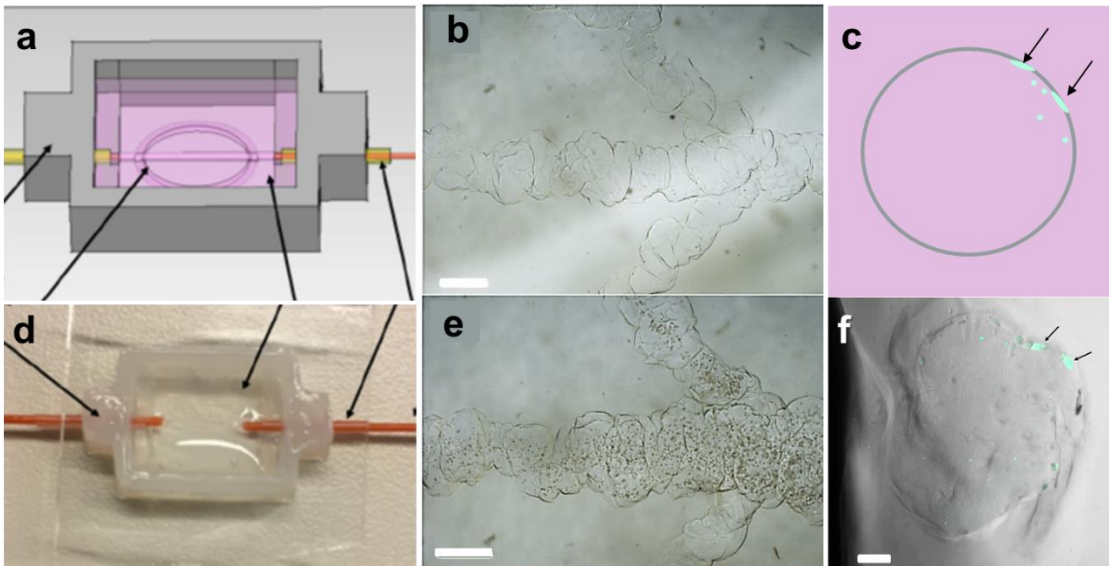


Figure 10.3.10: a) Schematic illustration of the 3D printed vascularized tissue-on-chip and d) image of the 3D printed perfusable model. b) Triple branched vascular channel within GelMA hydrogel before perfusion and e) after perfusion of endothelial cells (HUVECs), reference bar: 500 µm. c) schematic and f) fluorescence image of cross-sectioned vessel seeded with HUVECs cells after 35 hrs; Black arrows indicate cells started to adhere on the vessel surface, reference bar: 50 µm

Pres:
Hatt P, Serra T, Eglin D. Optimisation of sacrificial gelatin ink for production of perfusable tubular network in cellularized hydrogel matrix. (poster) 6-7 June 2018, Fribourg, Swiss Society for Biomaterials and Regenerative Medicine (SSB+RM).

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

Background: 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.
Goal: 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. Serum was obtained from patients at various times 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.
Results: We have identified a number of miRNA targets that are regulated during early osteogenesis. We also identified the presence of some of these markers in serum taken from fracture patients within days after fracture.

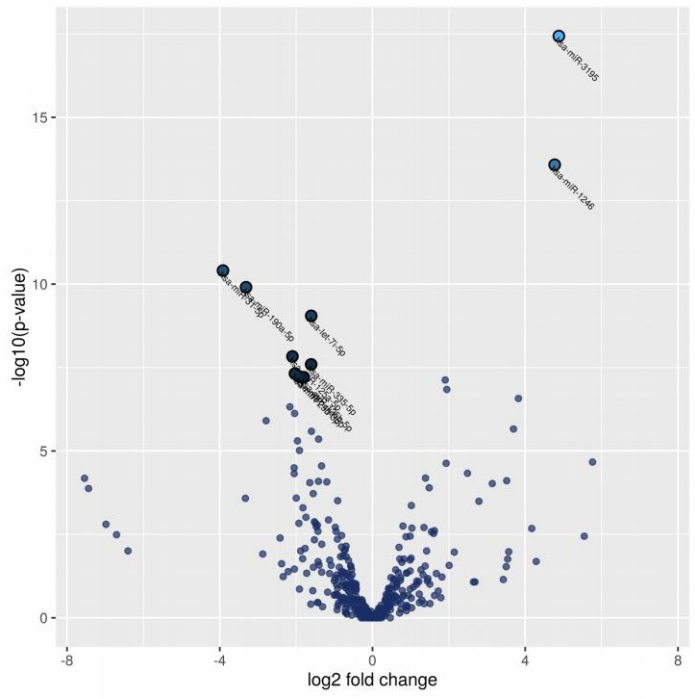


Figure 10.3.11: Volcano plot showing the relationship between the p-values and the fold change in normalized expression between the experimental groups "O1" and "C1". The 10 miRNAs with the lowest p-values are marked with names on the plot.

Pres:
Advances in Biological Markers for Patient Outcomes. ICORS session, Chinese Orthopaedic Association, Xiamen, China. 22.11.2018

Partner:
- Kubosch J (MD), Albert-Ludwigs University Medical Center Freiburg, Germany

Development of 3 dimensional *in vitro* models of bone infection (Immunobact 2) (M Hofstee, K Thompson, M Stoddart, S Zeiter, TF Moriarty)

Background: Advanced *in vitro* cell culture models have been developed in numerous basic science fields to reduce our reliance on the use of laboratory animals. These advanced *in vitro* cell culture models can incorporate human cells, more closely resemble *in vivo* tissue than conventional cell culture models and allow for higher throughput experimentation.
Goal: The application of these models to the study of Fracture related infection (FRI) has not been performed to date and is the goal of this project.
Results: We have shown that *Staphylococcus aureus,* the most prominent pathogen in FRI, forms 3-dimensional (3D) structures called microcolonies in a mouse model of FRI, which are surrounded by infiltrating immune cells (Figure 10.3.12, left). We have been able to develop an *in vitro* model displaying similar features with both bacteria and immune cells (Figure 10.3.12, Right). Furthermore, these *in vitro* grown *S. aureus* microcolonies are more resistant against high concentrations of antibiotics, reflecting a key characteristic of these infections, and further indicating the model will be a useful tool in the study of *S. aureus* FRI.

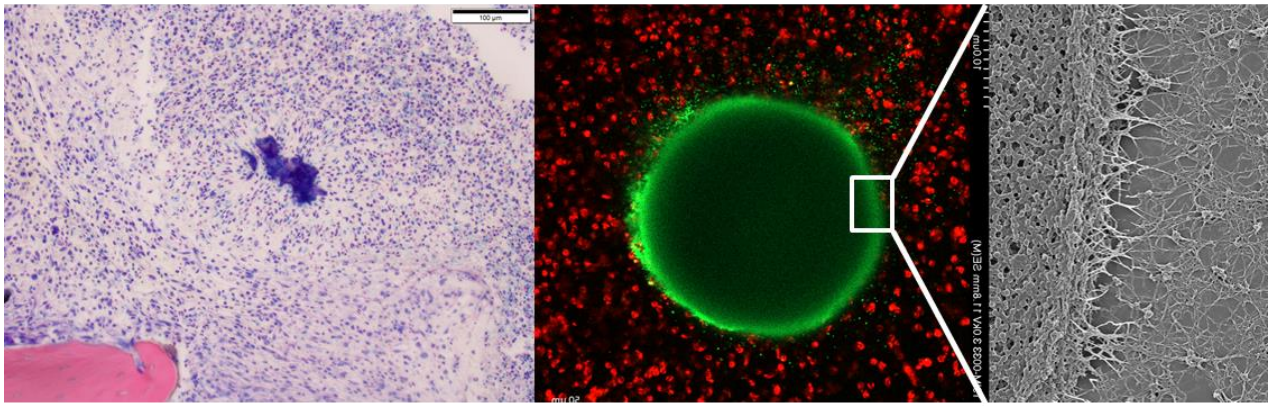


Figure 10.3.12: On left, a Staphylococcus aureus microcolony surrounded by infiltrating immune cells observed within the intramedullary canal of a mouse with FRI. Center, an in vitro grown S. aureus micro-colony (green) surrounded by neutrophil-like cells (red). On right, scanning electron microscope image of the edge of the microcolony displaying bacterial aggregates and protruding fibers, assumed to be a fibrin mesh.

Partner:

- Zaat S.A.J. (MD), Amsterdam UMC, Amsterdam, The Netherlands

High-energy focused extracorporeal shockwave as supplement treatment in fracture related infection in rabbits (Infect-Wave) (J Pützler, A Milstrey, S Zeiter, TF Moriarty)

Background: Focused high-energy extracorporeal shockwave therapy (fhESWT) stimulates bone healing and was shown to have anti-bacterial effects. Both the bone healing and the antibacterial effects of fhESWT could be beneficial as a supplemental treatment to the conventional treatment of FRI.
Goal: Evaluate fhESWT as an adjunct to conventional treatment in a clinically relevant rabbit model of fracture related infection.
Results: A complete humeral osteotomy in 31 rabbits was fixed with a 7-hole-LCP and an infection with *S. aureus* was established. After two weeks to allow the infection to establish, a revision surgery (debridement, irrigation and implant retention) was performed. Rabbits then received either no further treatment (controls), shock waves (4000 Impulses with 23kV at day 2 and 6 after revision, (Figure 10.3.13), daily antibiotics (rifampin and nafcillin) or the combination of antibiotics and shock waves over a period of one week.
Our results showed that fhESWT in combination with antibiotic treatment lowered the bacterial burden at euthanasia by a factor of 100 compared to antibiotic treatment alone (p=0.47). This effect was most prevalent for the implant sample (p=0.08). There was no sign of *S. aureus* growth in the dissected organs and blood cultures. According to these results, fhESWT could be a helpful adjunct to conventional treatment in certain difficult-to-treat infections and warrants further investigation.

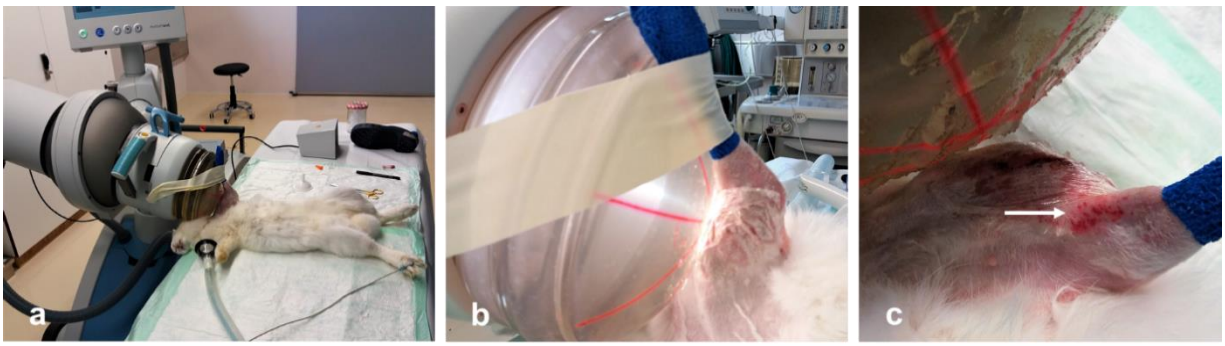


Figure 10.3.13: Experimental setup during ESWT: a) rabbit is under sedation and is placed in supine position. ESWT machine (LithoSpace® Ortho, Jena Medtech) stands next to the operation table with therapy head aiming at the osteotomy, b) application of 4000 Impulses at 4Hz with 23kV, c) petechia at the target area after ESWT application (arrow).

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

Background: The impact of long-term treatment with non-steroidal anti-inflammatory medications (NSAIDs) has been associated with bone healing complications in patients but it is currently unknown how NSAID treatment affects implant-related bacterial infection, or its response to antibiotic therapy.
Goal: To investigate how NSAID treatment affects implant-related bacterial infection.
Results: We developed and extensively characterized an *in vivo* model system that allows us to use microCT scanning to investigate the bone changes resulting from the implantation of a *S. epidermidis*-inoculated screw in the rat proximal tibia. Our recent work has revealed that NSAID treatment has dramatic effects on the bone changes resulting from *S. epidermidis* infection, with decreased osteolysis as well as additional inhibitory effects on the reparative responses to infection. Furthermore, NSAID treatment dramatically affects the efficacy of a combination antibiotic treatment that reliably clears the infection in healthy animals.

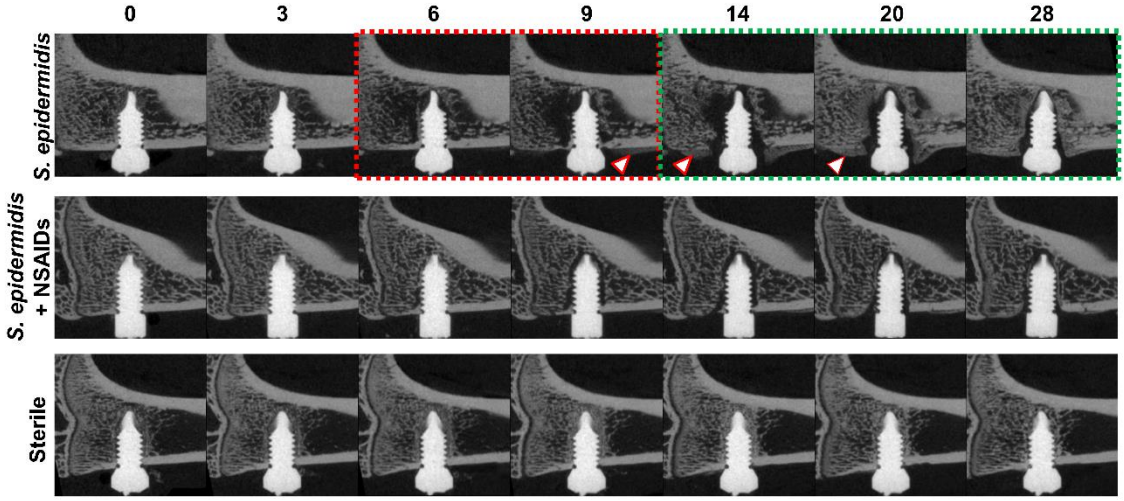


Figure 10.3.14: Time-course demonstrating bone changes resulting from the implantation of a S. epidermidis inoculated screw into the proximal tibia of a rat over a 28-day period. Osteolytic changes can typically be observed in the local vicinity of the screw within 6-9 days (as indicated by the red dashed rectangle) following implantation of the S. epidermidis-inoculated screw and reparative responses (as indicated by the green dashed rectangle) occurring from days 14-28 (top row). Periosteal proliferation (observed at days 9-20) is indicated by red/white triangles. NSAID treatment dramatically reduces infection-induced osteolysis and also prevents the periosteal/reparative response observed in healthy animals (middle row). Non-infected controls are also shown for comparison (bottom row).

The influence of the gut microbiota on bone (BacBone) (A Wallimann, K Thompson, S Zeiter, TF Moriarty)

Background: It has become evident that the gut microbiota plays a crucial role in many diseases, including bone-associated morbidities such as osteoporosis, and possibly also fracture healing.
Goal: In this project, we are investigating the impact of the gut microbiota on bone, based on *in vitro, in vivo* and clinical sources.
Results: One mechanism of interaction of gut microbiota with bone is through production of metabolites, especially short-chain fatty acids (SCFAs), derived from metabolism of dietary fibers. Butyrate is one class of SCFAs and we found that the SCFA butyrate inhibits murine, as well as human osteoclast formation *in vitro* (Figure 10.3.15). This result suggests the microbiome may have important role in modulating bone health and will be further investigated *in vivo* in the coming year.
In a separate phase of the study, exopolysaccharide (EPS) of the probiotic Bifidobacterium longum 35624 has also been shown to inhibit osteoclast formation *in vitro*. To further validate this result *in vivo*, B. longum 35624 wildtype and a *B. longum* 35624 EPS -/- strain has administered to a murine post-menopausal osteoporosis model, with data available early 2019.

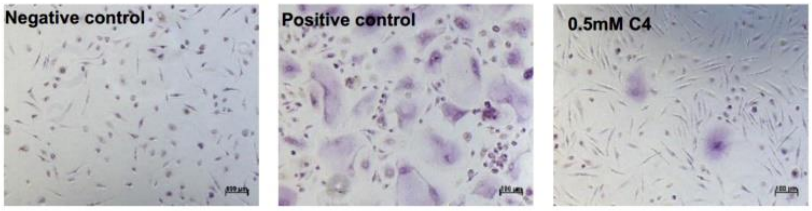


Figure 10.3.15: Butyrate (C4, right hand image) inhibits the formation of human osteoclasts in vitro.

Poster Presentations:
"The influence of microbial-derived metabolites on bone health" at Graubünden forscht Kongress (19th and 20th of September 2018, Davos)
"The influence of microbial-derived metabolites on bone health" at the Bone Healing Conference (16th and 17th of November 2018, Zurich)

Partners:
- Akdis C (Prof), Swiss Institute for Asthma and Allergy Research, Davos, Switzerland
- O'Mahony L (Prof), University College Cork, Ireland

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

Background: Both one and two stage revision in cases of fracture related infection (FRI) have a high reinfection rate, especially for infections caused by bacteria resistant to antibiotics.
Goal: Developed a two-stage exchange model with MRSA infection in sheep.
Results: When treating the MRSA infection with this regimen, 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 has been shown to fully treat 50% of sheep.
In addition, we included a group that did not receive the antibiotic-laden spacer in between revision surgeries, but instead received a vancomycin and gentamicin-containing hydrogel during both revision surgeries in the intramedullary canal. After the flush out period, this therapy was shown to be very successful and treat all sheep of their MRSA infection. The follow-up study will be to test the locally applied antibiotics in a one-stage procedure to treat MRSA infection.

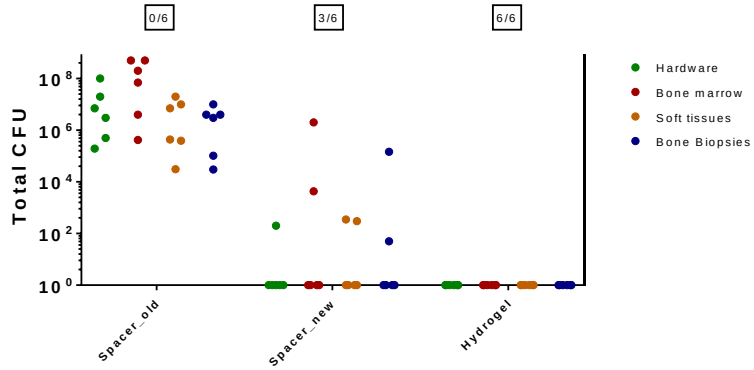


Figure 10.3.16: Bacteriological results of three different sheep models: spacer with experimental antibiotics; spacer with standard-of-care antibiotics; local antibiotics in hydrogel. The experimental antibiotics fail to treat the animals, the standard-of-care antibiotics reflect clinical practice and are successful in 50% of cases, and the local antibiotics treat all animals.

Pres:
European Orthopedic Research Society (EORS) 2018, Galway Ireland, September 25-28. The design and preclinical evaluation of antibiotic releasing biomaterials. F Moriarty
The 10th Clare Valley Bone Meeting, Mar 23 - 26, 2018. Large animal models of bone infection T Fintan Moriarty, T Schmid, S Zeiter
The 10th Clare Valley Bone Meeting, Mar 23 - 26, 2018. Novel antimicrobial approaches to preventing orthopaedic device related infection T Fintan Moriarty, RG Richards, D Eglin

Investigating antibiotic efficacy and release patterns for treating implant-related bone infection (ARI Rabscrew) (W Boot, Y Chen, T Schmid, S Zeiter, TF Moriarty)

Background: 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.
Goal: Determine key parameters for successful antibiotic eradication of biofilm.
Results: In this study we grew biofilm *in vitro* in the presence of human plasma (Figure 10.3.17) to test various antibiotic challenge patterns. We have seen that burst release profiles, as may be achieved from implant coatings have little impact on biofilm viability. Clinically, antibiotics such as gentamicin are given once or twice daily to maximize killing efficacy and minimizing toxicity risks. By reducing antibiotic exposure to two short periods per day, we could see bacterial killing was approaching levels achieved by constant exposure. In an additional series of experiments, the Traditional Chinese Compounds Curcumin, Neobavaisoflavone, Isobavachalcone, and Bavachin were tested and found to act synergistically with gentamicin against these biofilms. These compounds have the potential therefore to reduce the dosage of antibiotics required and enhance anti-biofilm efficacy.

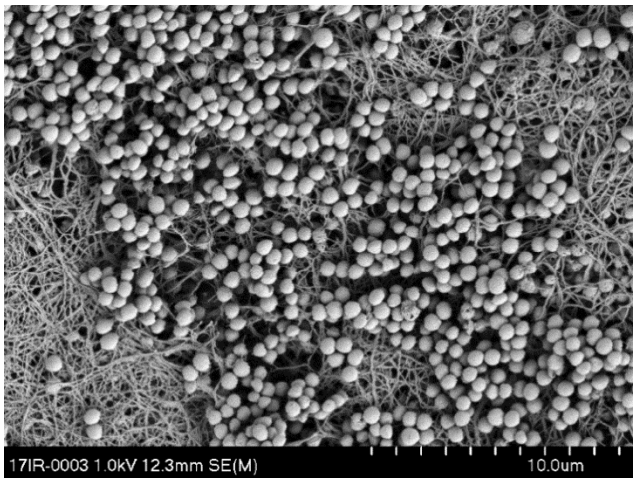


Figure 10.3.17: A 5-day old biofilm, grown in standard bacteriological culture medium supplemented with 1% human plasma. Inoculated microorganism was Staphylococcus aureus. Note strands of fibrin formed as part of the biofilm matrix that serves to protect the biofilm from host defense mechanisms.

Pres:
8th ASM conference on Biofilms, October 7-11, 2018, Washington DC, US. Challenging Staphylococcus aureus biofilms with different dosing patterns of gentamicin in combination with rifampicin. W Boot, RG Richards, TF Moriarty
The Antimicrobial Resistance on Biomaterials Workshop, October 25th, 2018, St. Gallen, Switzerland. Challenging *Staphylococcus aureus* biofilms with different dosing patterns of gentamicin in combination with rifampicin. W Boot, RG Richards, TF Moriarty
The Antimicrobial Resistance on Biomaterials Workshop, October 25th, 2018, St. Gallen, Switzerland. Synergism between Traditional Chinese Medicine compounds and antibiotics against *Staphylococcus aureus*. Y Chen, V Post, TF Moriarty, RG Richards, R Ziadlou, S Grad, W Boot

Staphylococcus epidermidis bone infections associated with implanted medical devices in human patients (EpiLog) (B Stanic, TF Moriarty)

Background: *Staphylococcus epidermidis* is a permanent member of normal human microbiota, populating skin and mucosal surfaces from early infancy. However, it has more recently emerged as an opportunistic pathogen in nosocomial (hospital acquired) infections associated with the use of indwelling medical devices.
Goal: Develop improved diagnosis of *S. epidermidis* infections.
Results: We employed a systematic immunoproteomics approach that included both 2D SDS-PAGE and immunoprecipitation followed by mass spectrometry to identify antigens that were present in patients with confirmed infection and absent or reduced in healthy, non-infected controls. Seventeen of the identified S. epidermidis antigens were selected, and full-length recombinant proteins were generated and applied in a 17-plex bead-based assay to measure relative titers of specific antibodies (IgG and IgM) in patients and age-matched controls.
Specific IgG responses against four *S. epidermidis* antigens were found to be significantly higher in infected patients compared to controls ($p<0.05$). Significantly lower titers of specific IgM were observed for 14 of the 17 antigens in patients relative to controls. AUC values of individual ROC curves ranged from 0.76-0.83, $p<0.05$, while multivariate analysis revealed discrete panel of 6 antigens reached AUC=0.880. This discrete panel of S. epidermidis antigens shows potential for a novel, serology-based test for the diagnosis of *S. epidermidis* infection. A simple serology based diagnostic assay could increase diagnosis rates allowing earlier medical and surgical intervention for affected patients.

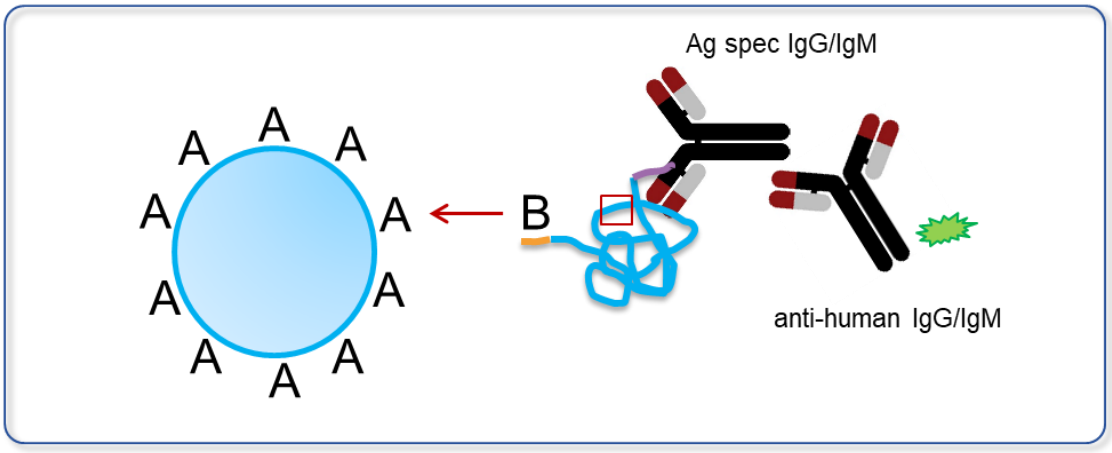


Figure 10.3.18: Schematic of the antigen labelling and detection approach used to measure Staphylococcus epidermidis antigen specific antibodies in patients with orthopaedic device related infection.

Pres:
18th International Symposium on Staphylococci and Staphylococcal Infections, 23 - 26 August 2018, Copenhagen, Denmark. Identification and validation of a discrete panel of *S. epidermidis* antigens for the diagnosis of *S. epidermidis* bone infections. B Stanic, J Puetzler, M Morgenstern, M Mercep, JL Daiss, EM Schwarz, RG Richards, TF Moriarty
Swiss symposium in point of care diagnostics, Chur, Switzerland, October 18, 2018. Identification and validation of a discrete panel of *S. epidermidis* antigens for the diagnosis of *S. epidermidis* bone infections. B Stanic, J Puetzler, M Morgenstern, M Mercep, JL Daiss, EM Schwarz, RG Richards, TF Moriarty

Use of a rabbit humeral LCP model to provide evidence for treatment & prophylaxis concepts in open fracture care (Opin-Fect) (F Moriarty, D Arens, C von Deimling, A Vallejo Diaz, S Zeiter)

Background: Open fractures are immediately colonized by bacterial contaminants and are at significant risk of developing a fracture related infection (FRI), despite the routine administration of perioperative antibiotic prophylaxis. Early application of antibiotic prophylaxis is known to reduce infection rates; however, most international guidelines focus on post-operative duration rather than pre-hospital administration.
Goal: Compared conventional perioperative prophylaxis against early pre-hospital prophylaxis either as a systemic single shot of cefuroxime or a locally applied gentamicin-loaded hydrogel.
Results: Our results showed that early systemic antibiotic administration can significantly reduce bacterial burden in the operative field, however, is insufficient in preventing infection on its own. The local application of an antibiotic loaded hydrogel displayed superior efficacy than both early systemic therapy and conventional gold standard 24-hour systemic therapy and should be considered for the management of open fracture cases in future.

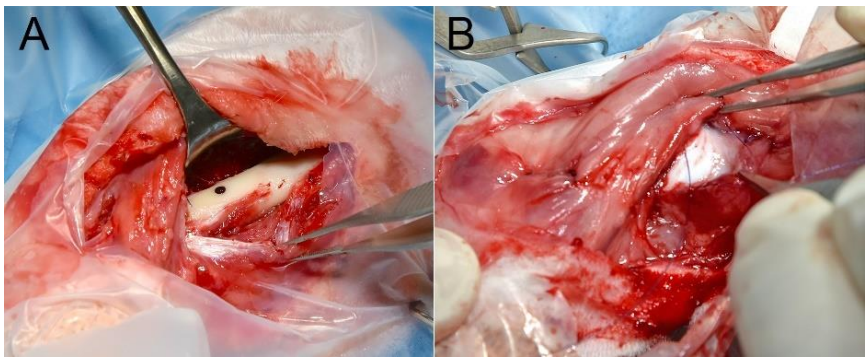


Figure 10.3.19: Intraoperative images showing a), the initial soft tissue opening, exposure of the bone and creation of a drill hole.; b), the application of the thermo-responsive antibiotic loaded hydrogel after jellification within the wound prior to closure. The gel was found to outperform systemic antibiotic therapy, which is the current clinical standard of care.

Pub:
Preclinical *in vivo* models of fracture-related infection: a systematic review and critical appraisal. Vanvelk N, Morgenstern M, Moriarty TF, Richards RG, Nijs S, Metsemakers WJ. Eur Cell Mater. 2018 Oct 17;36:184-199
Antibiotic Prophylaxis With Cefuroxime: Influence of Duration on Infection Rate With Staphylococcus aureus in a Contaminated Open Fracture Model. Puetzler J, Metsemakers WJ, Arens D, Zeiter S, Kuehl R, Raschke MJ, Richards RG, Moriarty TF. J Orthop Trauma. 2018 Apr;32(4):190-195

Pres:
European Bone and Joint Infection Society (EBJIS), Helsinki, Finland, 6-8th September 2018. The Effect of Local Antibiotic Prophylaxis in Open Limb Fractures. M Morgenstern, A Vallejo, M McNally, F Moriarty, J Ferguson, S Nijs, WJ Metsemakers.
European Bone and Joint Infection Society (EBJIS), Helsinki, Finland, 6-8th September 2018. Current Practices in the Management of Open Fractures: A Worldwide Survey Among Orthopaedic Trauma Surgeons. J Pützler, C Zalavras, F Moriarty, MHJ Verhofstad, S Kates, M Raschke, S Rosslenbroich, WJ Metsemakers.
European Bone and Joint Infection Society (EBJIS), Helsinki, Finland, 6-8th September 2018. A Systematic Review of Preclinical Models of Fracture-Related Infection. N Vanvelk, M Morgenstern, F Moriarty, S Nijs, WJ Metsemakers.

10.4 AOVET

Autonomous long term interfragmentary strain data collection in dogs (SmartDog) (ongoing) (M Ernst, M Windolf)

Background: The optimal mechanical environment at the fracture site is still speculative and much debated. Different concepts have been proposed in the past, from the minimum effective strain (MES) theory to the concept of inverse dynamization. In order to choose or design the right implant, the relationship between implant strain, interfragmentary motion and healing outcome needs to be examined.
Goal:

1. To scale down the existing implantable 'AO Fracture Monitor' sensors/monitors (providing *in vivo* access to continuously measured implant strain and patient activity data) to fit to 3.5-mm Vet-LCPs
2. To determine the relationship between implant strain and interfragmentary motion from *in vitro* bench tests
3. To apply the new implantable monitors in a clinical pilot study on 5 mid-size to large breed dogs at the University Veterinary Clinic in Liège, Belgium

Results: The design of the implantable monitor and accessories was fitted to the 3.5-mm Vet LCPs. Currently, the hardware is in production and will be delivered to Liège after assembly and calibration.

Figure 10.4.1: Implantable telemetric system with a sensor affixed to bone plate for continuous monitoring of healing progression in canine comminuted long bone fractures.

Partner:

- Balligand M (Prof), University of Liège, Belgium

10.5 AOTK System

AO Fracture Monitor – clinical data collection on external fixator patients (SmartFix II) (ongoing) (M Ernst, M Windolf)

Background: The AO Fracture Monitor is a system developed for continuous *in vivo* monitoring of fracture healing in order to overcome the shortcomings of radiographic methods and deliver a reliable, quantitative and timely feedback on fracture healing progression. While the system already delivered preclinical proof of concept, further evidence on the performance and usability of the system in a clinical setting is needed.
Goal: To apply AO Fracture Monitor prototypes in 10 clinical cases with externally fixated tibia fractures until removal of the fixation hardware at BGU Tübingen, Germany. The healing parameters generated by the device shall reflect the course of healing as observed from clinical and radiological evaluation and thereby strengthen the evidence of the system in a challenging clinical setting.
Results: AO Fracture Monitor prototypes were applied in clinical cases with patients having received bone segment transport to bridge large bone defects and recruited between July 2018 and January 2019. Healing data was acquired autonomously, continuously and automatically downloaded and forwarded to the server using patients' smartphones. Based on the preliminary results, the AO Fracture Monitor appears capable of resolving healing progression even in difficult cases (segment transport, bone infection, complex implant configuration). So far, good performance and reliability of the data logger is confirmed, providing valuable inputs regarding usability of the system in clinics.

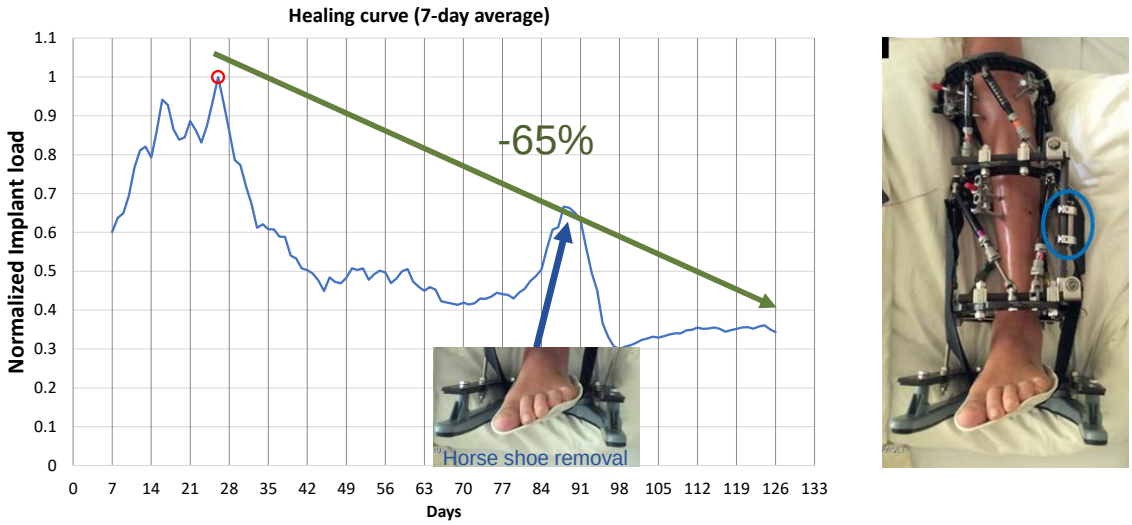


Figure 10.5.1: Left: normalized implant load on the external fixator of one exemplified patient over time. Despite modifications to the fixation hardware (partial removal of the 'horse shoe' around day 91), a decline of the curve is evident during the first 100 days, indicating progressive bone healing. Right: complex Taylor-Spatial-Frame construction of the patient, where the AO Fracture Monitor is marked with a blue circle.

Partners:

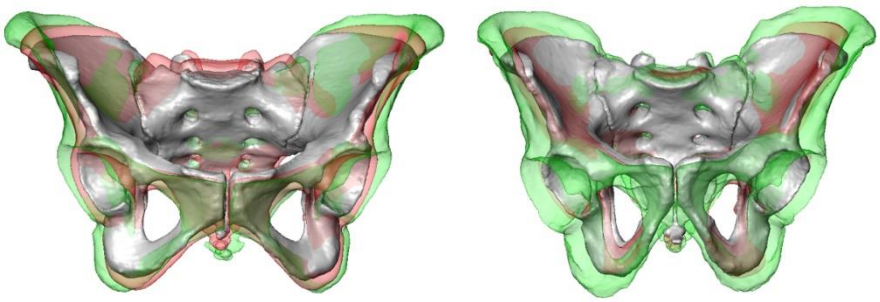
- Döbele S (MD), BG Unfallklinik Tübingen, Germany
- Höntzsch D (Prof), BG Unfallklinik Tübingen, Germany
- Pohlemann T (Prof), UK Homburg, Germany

Pelvic 3D models (EurAsiaPel) (ongoing) (L Kamer, H Noser, B Gueorguiev-Rüegg)
Background: Evaluation of pelvic anatomy is important for plates designing.

Background: Human bones exhibit complex variations in size and shape across individuals and demographic populations. With its quadrilateral surface, the pelvic prim represents an interesting anatomical site for development of anatomically pre-contured implants for fracture fixation.
Goal: To process and analyze pelvic CT scans by means of virtual 3D pelvic models and 3D printed pelvic models generated thereof.
Results: The following 4 pelvic CT data sets were used:

1. Asian women, mean age 51.7 years
2. Asian men, mean age 57.9 years
3. Caucasian women, mean age 58.6 years
4. Caucasian men, mean age 60.7 years

Twelve pelvic models (mean, small and a large pelvic model from each data set) were generated and 3D printed. In addition, 3D maps of the quadrilateral surface and the pelvic brim were computed.



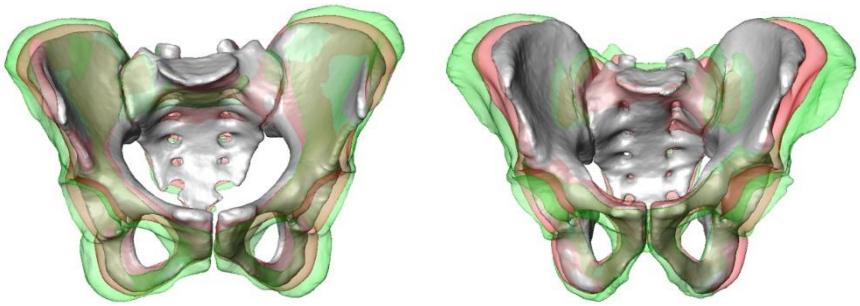


Figure 10.5.2: Mean (red), small (grey) and large (green) pelvic models of Asian women (upper left), Asian men (upper right), Caucasian women (lower left) and Caucasian men (lower right).

Partners:

- Barrall B, DePuy Synthes, USA
- van Citters P, DePuy Synthes, USA

Testing of two different implant concepts for growth plate modulation in sheep (Nitinvivo) (ongoing) (B Gueorguiev-Rüegg, D Gehweiler)

Background: Leg length discrepancy (LLD) in children is a relevant problem in today's orthopedic surgery. If left untreated, LLD can lead to serious damage in adulthood. The standard treatment is the use of Eight Plates in the longer leg bridging the growth plate to slow down bone growth. However, this plate is not approved for LLD corrections and complications such as screw deformations and breakage can occur. In addition, it is difficult to determine the correct time for implant removal, not least because overshooting growth (rebound effect) may occur after removal.
Goal: To compare a new implant prototype to the existing Eight Plate in their ability to slow down bone growth in a sheep model.
Results: In the first pilot phase of the project, metatarsal bones were operated, the implants were removed after 24 weeks, and the growth was monitored for another 12 weeks. It was found that the new implant prototype has a more homogeneous effect on the complete growth plate, whereas the Eight Plate seems to slow down the bone growth only close to the implant.

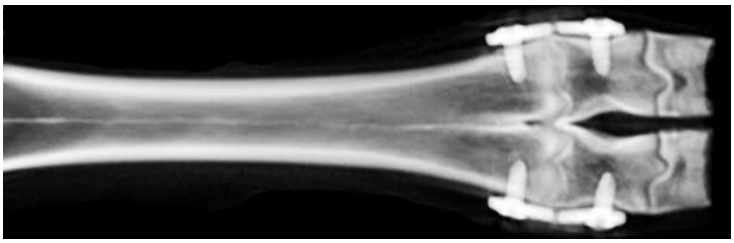


Figure 10.5.3: X-ray of sheep metatarsal bone instrumented with 2 Eight Plates for LLD correction via temporary epiphysiodesis slowing down the bone growth at the physis.

Partners:

- Dwyer J, University Hospital of North Staffordshire, Stoke-on-Trent, United Kingdom
- Slongo T (Prof), University Children's, Hospital, Berne, Switzerland
- Narayanan U (Prof), University of Toronto, Toronto, Canada
- Mukhopadhaya J, Paras Hospital, Patna, India
- Sepulveda M, Universidad Austral de Chile, Valdivia, Chile

Patella Statistical Form Model (PatellaSamplingFromSFM) (B Gueorguiev-Rüegg, H Noser, L Kamer)

Background: Virtual patella models are needed to determine size and shape of patella implants. Two statistical form models (SFM), generated in a previous project, were used to produce new sampled sets of patella models for further analysis.
Goal: To create gender specific sampled patella sets for further analysis, reflecting the patella form variability.
Results: Virtual patella models were sampled from the two existing SFMs in STL and IGS formats. Validation and specification documents of both SFM and sampled patella models were issued.

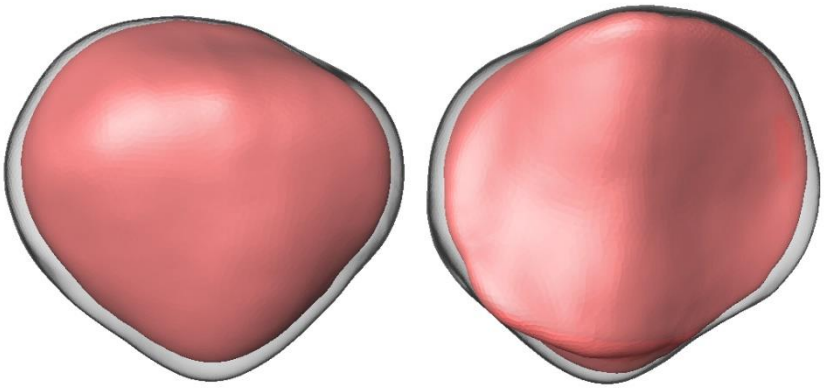


Figure 10.5.4: Virtual sampling using 3D statistical form modeling of the patella to generate specific patella models. Patella mean model (grey transparent) and sampled patella (red) in anterior (left) and posterior (right) view.

10.6 ARI Exploratory Research

Development of *ex vivo* system for mesenchymal stem cell differentiation and cartilage integration (Vivoload) (Started) (M Stoddart)

Background: 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.
Goal: 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.
Results: 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.

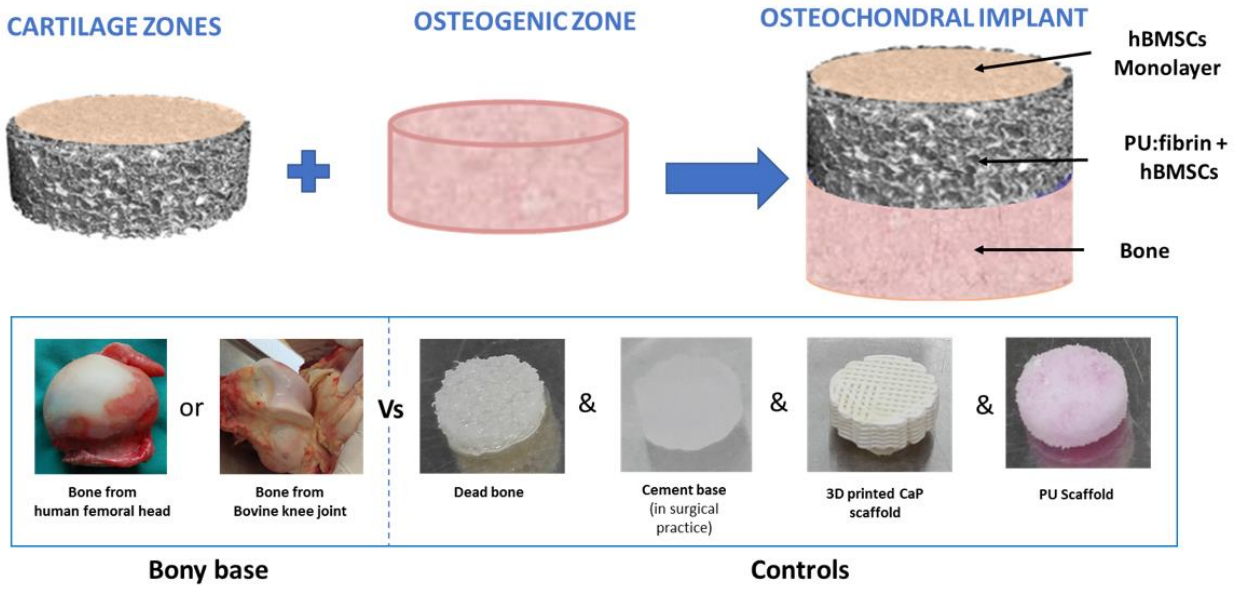


Figure 10.6.1: Multilayered de novo osteochondral implants mimicking the structure of native tissue

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. 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. New 3 layer de novo implants have been produced and subjected to complex load, allowing for the development of signaling gradients to be developed under defined conditions. 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:

Biomechanical regulation of musculoskeletal cell fate: From strain to secretome. Zentrum für Rheuma- und Knockenerkrankungen. Zürich, Switzerland. 19.11.2018

Biomechanical regulation of musculoskeletal cell fate: From strain to secretome. 7th Annual Symposium on Regenerative Rehabilitation. Kirkland, Seattle, USA. 12.10.2018

Modulating Mesenchymal Stem Cell chondrogenesis by mechanics: Implications for materials design. ARI-TCBE-TERG Research Symposium. Dublin, Ireland. 28.09.2018

Investigating chondrogenesis under multiaxial load. EORS Galway, Ireland. 26.09.2018

Mechanical influences on cells of the musculoskeletal system. The Joint Seminar Series, Rush University Medical Center, Chicago, USA. 22.07.2018

Mechanical regulation of chondroprogenitor fate. 8th World Congress of Biomaterials. 10.07.2018.

Inducing chondrogenesis by multiaxial load: Cell differentiation and biomarker discovery. 2018 eCM XVIII: Cartilage & Disc: Repair and Regeneration, 25th - 28th June 2018, Congress Center, Davos, Switzerland

Regulating Mesenchymal Stem Cell chondrogenesis: Modulating cell behaviour by mechanics. 21.04.2018. Kyon Symposium, Zürich, Switzerland

Bioreactors & Bioactive Cartilage Repair Constructs. 11.04.2018. ICRS2018, Macau, China

Mechanically Induced Chondrogenesis - Differentiation & Biomarker Discovery. 09.04.2018. ICRS2018, Macau, China

Chondrogenesis in response to mechanical load for cartilage repair. 11.03.2018. ORS Annual Meeting, New Orleans, USA

Pub:

Fahy N, Gardner O, Alini M PhD, Stoddart MJ. PTHrP gradients affect the progression of mesenchymal stem cell chondrogenesis and hypertrophy. Tissue Eng Part A. 2018 May;24(9-10):849-859. doi: 10.1089/ten.TEA.2017.0337

Salzmann GM, Niemeyer P, Hochrein A, Stoddart MJ, Angele P. Articular Cartilage Repair of the Knee in Children and Adolescents. Orthop J Sports Med. 2018 Mar 13;6(3):2325967118760190. doi: 10.1177/2325967118760190

Gottardi R, Stoddart MJ. Regenerative Rehabilitation of the Musculoskeletal System. J Am Acad Orthop Surg. 2018 Jul 2. doi: 10.5435/JAAOS-D-18-00220. [Epub ahead of print] PubMed PMID: 29985246.

Graceffa V, Vinatier C, Guicheux J, Evans CH, Stoddart M, Alini M, Zeugolis DI. State of art and limitations in genetic engineering to induce stable chondrogenic phenotype. Biotechnol Adv. 2018 Jul 13.

Taghiyar L, Hosseini S, Safari F, Bagheri F, Fani N, Stoddart MJ, Alini M, Eslaminejad MB. New Insight into Functional Limb Regeneration: A to Z Approaches. J Tissue Eng Regen Med. 2018 Jul 16. doi: 10.1002/term.2727.

Graceffa V, Vinatier C, Guicheux J, Stoddart M, Alini M, Zeugolis DI. Chasing Chimeras - The elusive stable chondrogenic phenotype. Biomaterials. 2018 Nov 9;192:199-225. doi: 10.1016/j.biomaterials.2018.11.014.

Venkatesan JK, Gardner O, Rey-Rico A, Eglin D, Alini M, Stoddart MJ, Cucchiarini M, Madry H. Improved Chondrogenic Differentiation of rAAV SOX9-Modified Human MSCs Seeded in Fibrin-Polyurethane Scaffolds in a Hydrodynamic Environment. Int J Mol Sci. 2018 Sep 5;19(9). pii: E2635. doi: 10.3390/ijms19092635.

Armiento AR, Alini M, Stoddart MJ. Articular fibrocartilage - Why does hyaline cartilage fail to repair? Adv Drug Deliv Rev. 2018 Dec 31. pii: S0169-409X(18)30319-3. doi: 10.1016/j.addr.2018.12.015.

Partner:

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

Bio-adhesive biopolymers for integration of cartilage injury regenerative therapy (GELHOME) (Completed) (D Eglin)

Background: 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.

Goal: 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.

Results: 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 (Figure 10.6.2). 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.

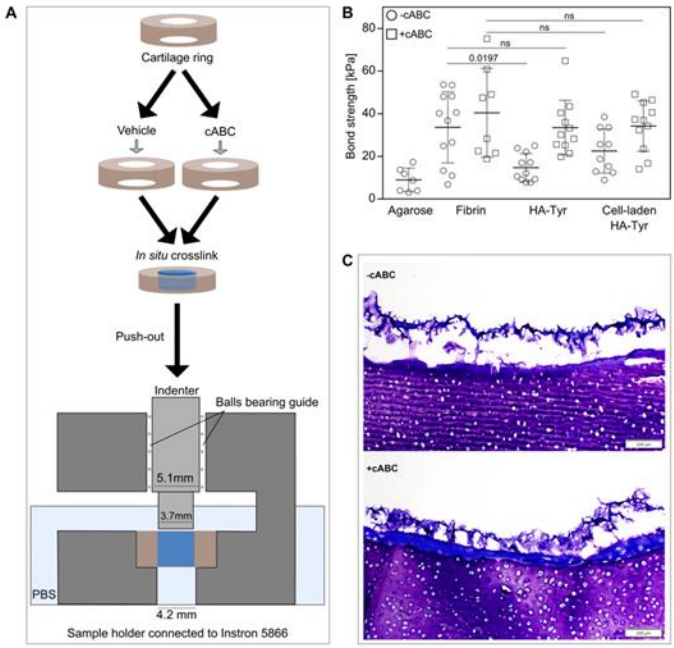


Figure 10.6.2. (A) Workflow of push-out test; (B) Quantification of bond strength as in agarose (negative control), fibrin glue (positive control), HA-Tyr (experimental group); (C) Toluidine blue staining following push-out test shows residual of HA-Tyr. The effect of cABC on chondroitin sulphate GAG is visible as blue area. Scale bar: 200um.

Pub:

De Pieri A, Ribeiro S, Tsiapalis D, Eglin D, Bohner M, Dubruel P, Procter P, Zeugolis DI, Bayon Y. Joint academic and industrial efforts towards innovative and efficient solutions for clinical needs. J Mater Sci Mater Med. 2018;29:129.

Fahmy-Garcia S, Mumcuoglu D, de Miguel L, Dieleman V, Witte-Bouma J, van der Eerden BCJ, van Driel M, Eglin D, Verhaar JAN, Kluijtmans S, van Osch G, Farrell E. Novel in Situ Gelling Hydrogels Loaded with Recombinant Collagen Peptide Microspheres as a Slow-Release System Induce Ectopic Bone Formation. Adv Healthc Mater. 2018;7:e1800507.

Partners:

- Lipross S (Prof), University Medical Center Schleswig-Holstein, Kiel, Germany
- Behrend P (MD), University Medical Center Schleswig-Holstein, Kiel, Germany

Enhancing cartilage self-repair using cell-free IPN biopolymer hydrogels (GELHOME 2) (Started) (M D'Este, D Eglin)

Background: Acute cartilage defects are a significant source of suffering and disability, leading to productivity loss and significant healthcare costs. Aging population and increase in physical activity at all ages are amplifying the societal impact of cartilage defects, which in the long-term contribute to osteoarthritis onset. Materials trying to match cartilage resilience are usually unsuitable for cell invasion, new tissue formation and adhesion to native tissue, which is the first requirement for lateral integration. Double-network hydrogels are specialized interpenetrated polymeric networks with outstanding strength and toughness. Double networks were initially developed from non-biodegradable materials unsuitable for long-term implantation. Recent advances have demonstrated how the same design paradigm can be employed to fabricate biopolymer-based tough double network hydrogels. Preliminary data from our group demonstrate how tyramine-enriched gelatin and hyaluronic acid display adhesion to wet bovine cartilage yet ability to be invaded with cells migrating from adjacent cartilage.

Goal: With the present project, we intend to further develop these materials using double-network approach to develop a biomaterial responding to these requirements: i) high resilience approaching values of articular cartilage; ii) high strength to withstand repeated mechanical load; iii) adhesion to cartilage under physiological conditions; iv) cytocompatibility and capability of being invaded by cells from underlying bone marrow and/or adjacent cartilage; v) patentability and overall design prone to clinical translation and development into a product.

Results: In situ formation of dual hydrogel networks made of gelatin and hyaluronan derivatives do not systematically create tougher hydrogels than the single networks (Figure 10.6.3). Interferences between the crosslinking mechanisms play a significant role in the reduce mechanical properties of the double network. Experiments are on-going to address this short-coming.

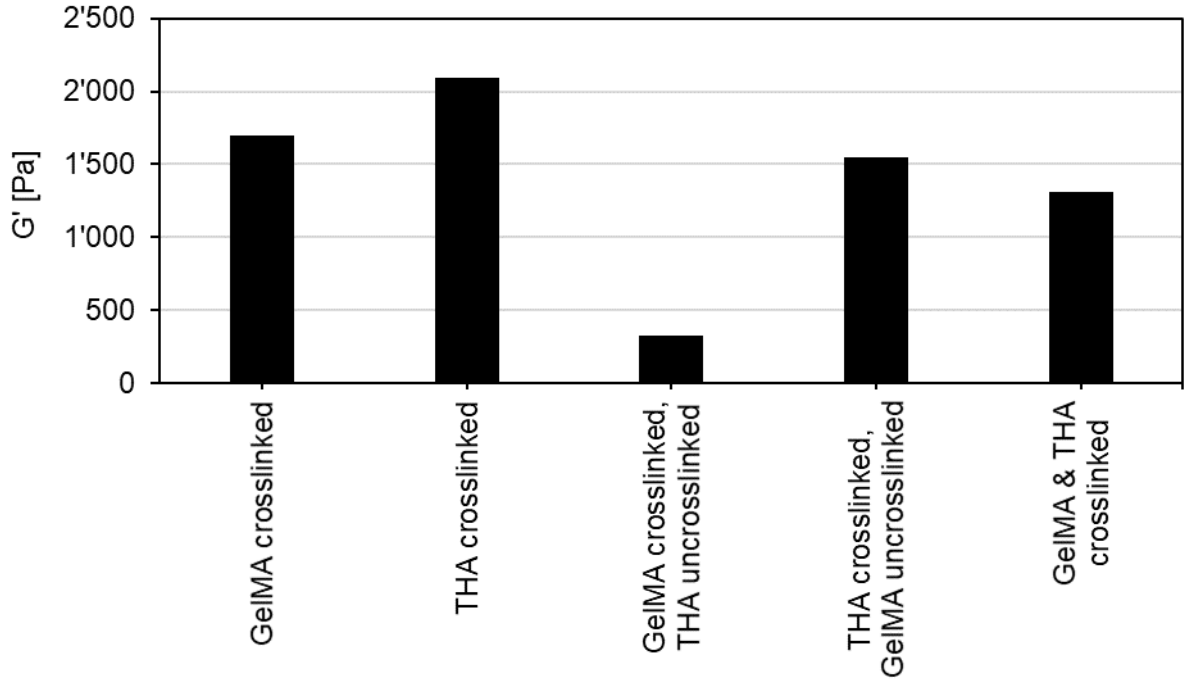


Figure 10.6.3: Comparison of elastic moduli (G') at 0.1% strain in an amplitude sweep measurement for 5 % (w/v) Gelatin Methacryloyl (GelMA) and 3 % (w/v) Tyramine derivative of Hyaluronan (THA).

Partner:

- Ferguson S (Prof), ETH Zurich, Zurich, Switzerland

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

Background: 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.
Goal: 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.
Results: 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.

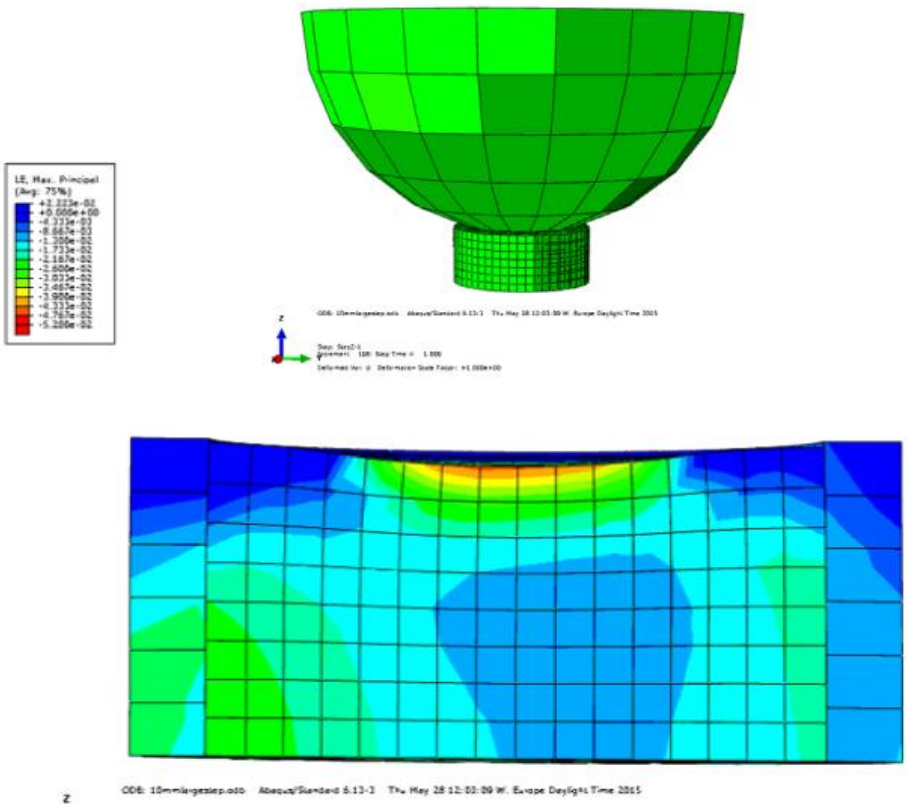


Figure 10.6.4: Finite element model representing the application of load to a fibrin polyurethane scaffold by way of a ceramic hip ball-based bioreactor system. Changes in strain due to compression, shear, or a combination of both can be compared.

Pub:

Glatt V, Evans CH, Stoddart MJ. Regenerative Rehabilitation: The role of mechanotransduction in orthopaedic regenerative medicine. J Orthop Res. 2018 Dec 17. doi: 10.1002/jor.24205. [Epub ahead of print]

Maioli M, Redl H, Stoddart MJ. Environmental Influences on Stem Cell Behavior. Stem Cells International 2018:1-2. doi: 10.1155/2018/7415460

Armiento AR, Stoddart MJ, Alini M, Eglin D. Biomaterials for Articular Cartilage Tissue Engineering: Learning from Biology. Acta Biomater. 2018 Jan;65:1-20. doi: 10.1016/j.actbio.2017.11.021

Generic Asian pelvic bone model – AO Strategy Fund (PelBone) (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 needs to be more specific to their needs. Currently, the available bone models for training and education do not properly represent the Asian population and most 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. Additionally, female models with missing bony S1 corridor were sampled from the statistical pelvic bone model. The corresponding data files were sent to SYNBONE for development of

anatomically correct generic hardware Asian pelvic bone models. Finally, two gender-specific Asian models were manufactured by SYNBONE.

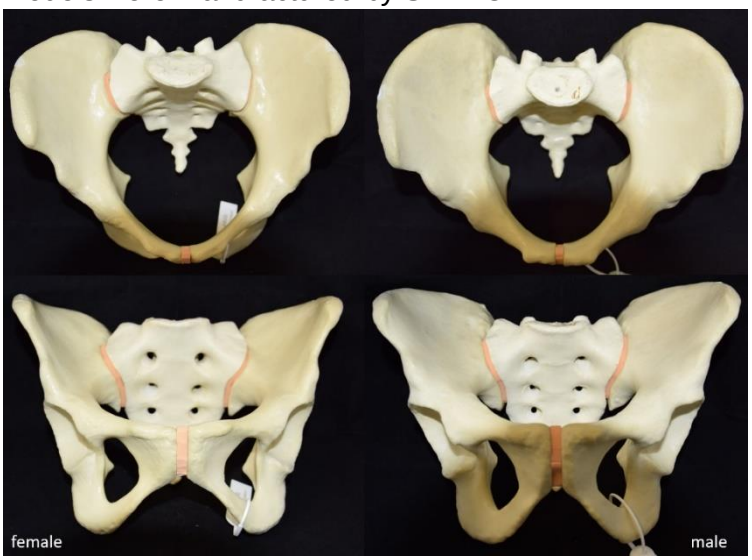


Figure 10.6.5: Gender-specific Asian mean models manufactured by SYNBONE AG (Zizers, Switzerland) using specially formulated polyurethane foam; left – female model with missing bony S1 corridor, right – male mean model.

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
- Hügli H, SYNBONE AG, Zizers, Switzerland
- Burr F, SYNBONE AG, Zizers, Switzerland

Xin1 functional extensions for photo-based X-ray transmission and real-time feedback (Xin1-Go) (ongoing) (J Buschbaum, M Windolf)

Background: The task of placing implants plays a key role in trauma and orthopedics surgery. To improve a variety of surgical routine interventions, a simplified computer aided surgery system (Xin1) has been developed at ARI, utilizing a conventional C-arm as imaging and navigation means. The system demonstrates simple integration into standard clinical routine and strong potential for improving clinical practice. However, the system still faces two drawbacks. Due to non-standardized interfaces, the image transfer between C-arm and processing unit is difficult to realize, which compromises universal usage of the system. Further, the concept relies on static X-ray shots where movements in-between remain undetectable. Real-time feedback of the surgeon's actions would be beneficial for many applications.
Goal: To overcome the current system issues by providing: (a) photo-based X-ray transfer, and (b) photo-based real-time feedback to the surgeon.
Results: A software prototype for photo-based X-ray transmission was developed and implemented on a mobile device (tablet). By using the device's photo camera and image processing algorithms, the radiograph on the C-arm screen is automatically detected, captured and subsequently transferred to already existing Xin1 Humerus Plating software. All required tasks can be done by using a single mobile device without any wired connection, which enhances the universal usage of the system. Feasibility and accuracy tests are currently running.
Additionally, an Xin1-Go prototype for real-time feedback during corrective osteotomies was realized. The software is running on a mobile device and captures two specially designed reference flags attached to routinely used Schanz pins. By processing a continuous video stream, the spatial relation between both flags for measurement of the achieved corrections is computed and displayed intraoperatively. The accuracy was assessed in bench tests. The rotational error was 0.63°±0.42° (mean ± SD) thus fulfilling the clinical requirements.
Photo-based x-ray transfer possibility and real-time capability of the Xin1 system could considerably enlarge the scope of its application.

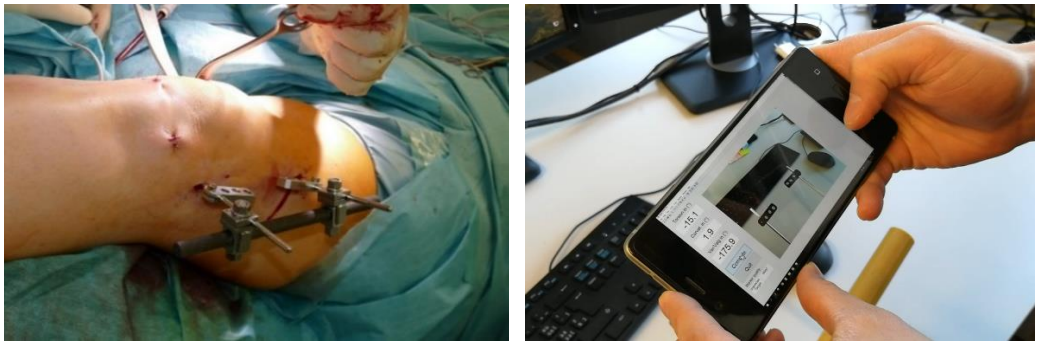


Figure 10.6.6: Xin1-Go concept for assisting corrective rotational osteotomies. Left: a potential clinical case application with the use of two metallic flags; right: the new mobile app displaying the performed correction based on the captured reference flags (not in clinical use yet).

Patent:

- J Buschbaum, M Windolf. Reference device for real-time tracking of bone and/or surgical objects in computer-assisted surgery (Swiss patent application 00145/18)

Virtual Bone Factory (VBF) (B Gueorguiev-Rüegg, H Noser, L Kamer)

Background: Form variability of human bones plays an important role in research, development and education. Therefore, it is necessary to acquire and analyze large representative sets of bone forms. However, the acquisition of such bone sets is time consuming and expensive because typical workflows demand contracts with partners, project grant approval, ethical approval, patient consents (or specimen acquisition), CT scans, and segmentation of CT image data to create virtual bone sets. Typically, such a workflow lasts longer than one year and costs some thousands of CHF. Sampling from statistical form models (SFMs) represents an alternative to create sets of virtual human bones decreasing dramatically time and costs by factors of 5 to 50. However, it needs to be demonstrated, that such sampled bone sets (from SFMs) are equivalent to the training set of virtual human bones used to create the corresponding SFMs.
Goal: To plan and realize an environment for a non-profit Virtual Bone Factory (VBF) where interested users can order 3D virtual bone models of the human skeleton covering the most important form variations of human bones. The virtual bones will be sampled from SFMs based on Principal Components Analysis and bone surface models produced from CT scans.
Results: A framework of the VBF was established addressing commercial, legal and ethical aspects. The first catalog of the VBF contains 4 SFMs of the patella, pelvis, tibia, and femur, including sampling options, specifications, and 'Terms and Conditions'. The integration of the VBF into ARI's quality management system (ISO 9001:2008) is nearly terminated. It was shown, that some size and length measurement statistics obtained from the training set and sampled virtual bone sets nearly identical.

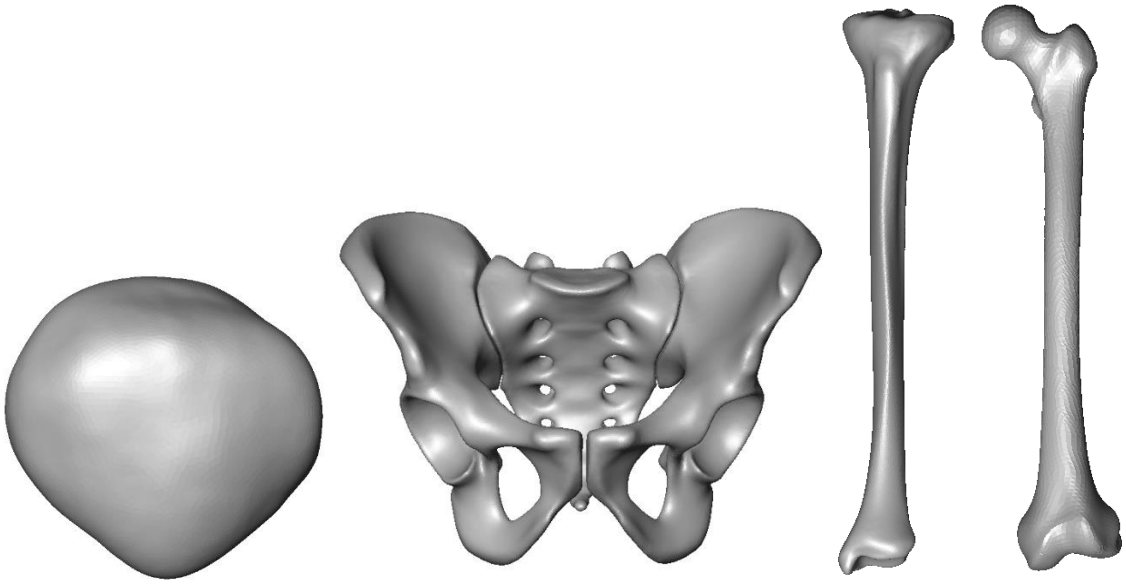


Figure 10.6.7: Mean forms of patella, pelvis, tibia, and femur statistical form models, featuring the first four products of the virtual bone factory.

Biomechanical evaluation of three different plating techniques for fixation of displaced midshaft clavicle fractures (P Yanev, I Zderic)

Background: Displaced midshaft fractures are the most common surgically treated clavicle fractures. However, they are still associated with high complication rates after plating due to fixation failure in terms of plate breakage, screw breakage or screw loosening.
Goal: To compare the biomechanical competence of three different plating techniques for fixation of displaced midshaft clavicle fractures.
Method: Displaced midshaft fractures type 2B according to Robinson classification were simulated by standardized osteotomies in 18 artificial clavicles. The specimens were assigned to three groups for plating with either superiorly placed Dynamic Compression Plate, locked Superior Anterior Clavicle Locking Compression Plate, or two non-locked Reconstruction Plates placed superiorly and anteriorly. Each specimen was mounted horizontally for mechanical testing under craniocaudal cantilever bending, combined with torsion around the shaft axis. The acromial clavicle end was cyclically loaded over 720000 cycles or until failure occurred.
Results: From biomechanical perspective, double plating of unstable midshaft clavicle fractures with reconstruction plates seems to provide the highest stability under dynamic loading, when compared to single compression or locked plating, whereas the latter is associated with considerably inferior performance.

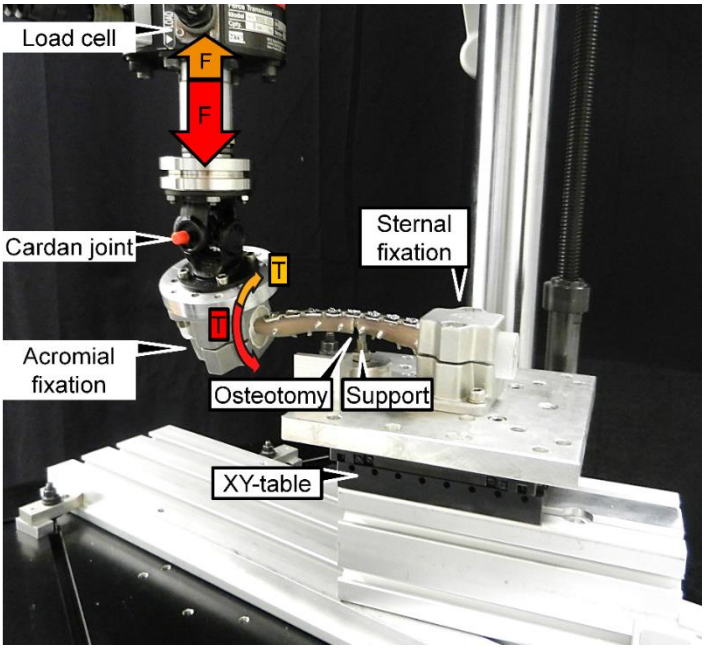


Figure 10.6.8: Test setup with a specimen mounted for mechanical testing.

Partners:

- Baltov A (Prof), University Hospital for Emergency Medicine 'NI Pirogov', Bulgaria
- Enchev D (Prof), University Hospital for Emergency Medicine 'NI Pirogov', Bulgaria
- Rashkov M, University Hospital for Emergency Medicine 'NI Pirogov', Bulgaria

Biomechanical testing of two techniques for locked mesh plating versus tension band wiring of complex patella fractures (I Escalante, I Zderic)

Background: Fixation of complex patella fractures remains challenging. As treatment option, locked mesh plating has the potential for multiplanar fragment stabilization with reduced risk of postoperative loss of reduction.
Goal: To investigate the biomechanical performance of two different techniques for locked mesh plating versus tension band wiring of complex patella fractures.
Method: Six-part complex AO/OTA 34-C3 patella fractures were simulated in 18 human cadaveric knees by means of osteotomies. The specimens were assigned to 3 groups for: (1) anterior locked mesh plating with orthogonally bent proximal and distal hole rows; (2) anterolateral locked mesh plating with a long arm reaching the inferior patella pole; (3) tension band wiring using K-wires. Each specimen was biomechanically tested over 5000 cycles by pulling on the quadriceps tendon to simulate active knee extension and passive flexion.
Results: From biomechanical perspective, anterior locked mesh plating of complex patella fractures provides superior stability than both anterolateral locked mesh plating and tension band wiring. Moreover, the latter is associated with considerably inferior performance.

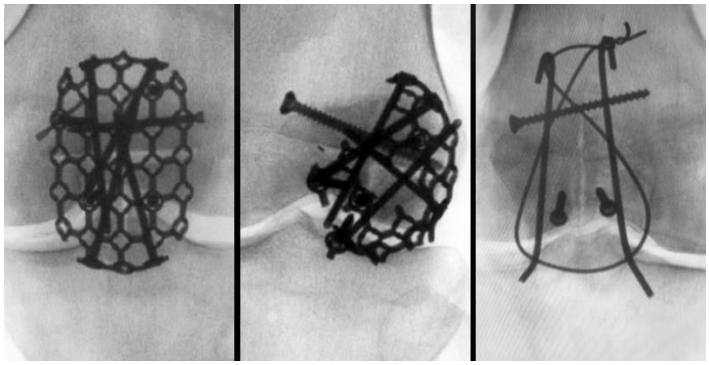


Figure 10.6.9: X-rays representing anterior locked mesh plating (left), anterolateral locked mesh plating (middle) and tension band wiring with an additional screw (right).

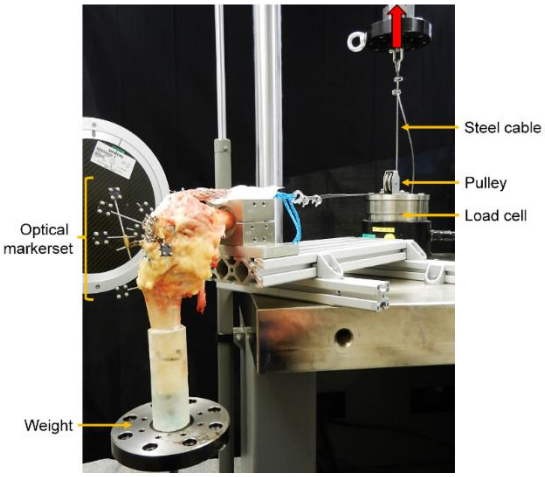


Figure 10.6.10: Setup with a specimen mounted for biomechanical testing.

Partner:

- Kfuri M (Prof), University of Missouri, USA

Influence of titanium elastic nail pre-contouring on the fixation of paediatric diaphyseal forearm fractures (Y Pukalski, B Gueorguiev-Rüegg)

Background: Paediatric diaphyseal forearm fractures occur at a rate of 560 per 100000 in the age of 5 to 14 years. Growing incidence of this pathology, as well as an increasing number of cases treated with elastic stable intramedullary nailing have been reported.
Goal: To evaluate the influence of titanium elastic nail (TEN) pre-contouring on the postoperative radiographic outcome in AO PCCF 22-D/4.1 fractures of the forearm.
Method: Human cadaveric forearms with simulated AO PCCF 22-D/4.1 fracture were assigned for TEN fixation with the use of either two straight nails, 1 curved radial and 1 straight ulnar nail, and two curved nails. Radiographic assessment of each specimen was performed on anteroposterior x-rays in intact and instrumented state.
Results: Use of TENs of identical size and curvature ensures superior reduction of AO PCCF 22-D/4.1 fractures. In contrast, fixation with 1 curved radial and 1 straight ulnar implant leads to overcorrection of the radial bow, whereas utilization of 2 straight TENs leads to inferior outcomes, including straightening of the maximal radial bow and anticipated loss of range of motion in the clinical scenario.

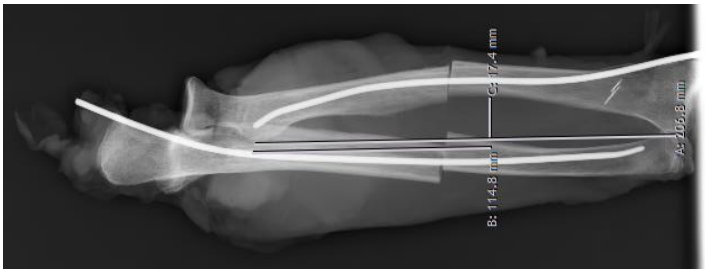


Figure 10.6.11: Anteroposterior radiograph of human cadaveric forearm with simulated AO PCCF 22-D/4.1 fracture, instrumented with 2 curved titanium elastic nails. Both implants left longer for easier explantation.

Partners:

- Enchev D (Prof), University Hospital for Emergency Medicine 'NI Pirogov', Bulgaria
- Baltov A (Prof), University Hospital for Emergency Medicine 'NI Pirogov', Bulgaria
- Rashkov M, University Hospital for Emergency Medicine 'NI Pirogov', Bulgaria

Impact of different Lisfranc ligament injuries on CT findings under axial loading (P Penev, B Gueorguiev-Rüegg)

Background: Being commonly missed in the clinical practice, Lisfranc injuries can lead to arthritis and long-term complications. There are controversial opinions about the contribution of the main stabilizers of the joint – the dorsal, interosseous and plantar Lisfranc ligaments. Moreover, the role of the ligament that connects the medial cuneiform (MC) and the third metatarsal (MT3) is not well investigated. Despite the broad use of CT scans, there is no established correlation between the CT findings and the severity of this injury.
Goal: To investigate the influence of different Lisfranc ligament injuries on CT findings under axial loading.
Method: Sixteen fresh-frozen human cadaveric lower limbs were embedded in PMMA at mid-shaft of the tibia and placed in a weight-bearing radiolucent frame for CT scanning. All intact specimens were initially scanned under 7.5 kg and 70 kg loads in neutral foot position. A dorsal approach was then used for sequential ligaments cutting: first–the dorsal and the interosseous ligaments; second–the plantar ligament between the MC and MT3; third–the plantar Lisfranc ligament between the MC and the MT2. All feet were rescanned after each cutting step under the two loads. Based on the CT scans, the distances between MT1 and MT2, as well as between MC and MT2 were measured. In addition, the alignment and the dorsal displacement of MT2 were assessed.
Results: A slight increase in the distances MT1-MT2 and MC-MT2 was observed after the first disruption of the dorsal and the interosseous ligaments under both loads. A further increase in those distances was registered after the second disruption of the ligament between MC and MT3. The largest distances MT1-MT2 and MC-MT2 were measured after the final plantar Lisfranc ligament cut under the two loads. In contrast to the previous two cuts, misalignment and dorsal displacement of MT2 were seen at this final disrupted stage.

Figure 10.6.12: Custom-made, radiolucent, air pressure-controlled frame with a lower leg model mounted for CT scanning under axial loading.

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

Background: 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 mesenchymal stromal cells (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.
Goal: Within this study we aim to identify predictive markers of human MSC chondrogenesis that can be used to stratify patient populations.
Results: We have identified a prospective chondroprogenitor marker profile that will allow for better patient stratification. Using this profile, we are also able to reverse the deficit, thus converting poor responders to more chondrogenic cells by way of a simple treatment with siRNA silencing. We are further exploring alternative strategies to manipulate cell function, using the profile as an outcome parameter. The ability to reverse this functional deficit will open new avenues for further cartilage repair therapies.

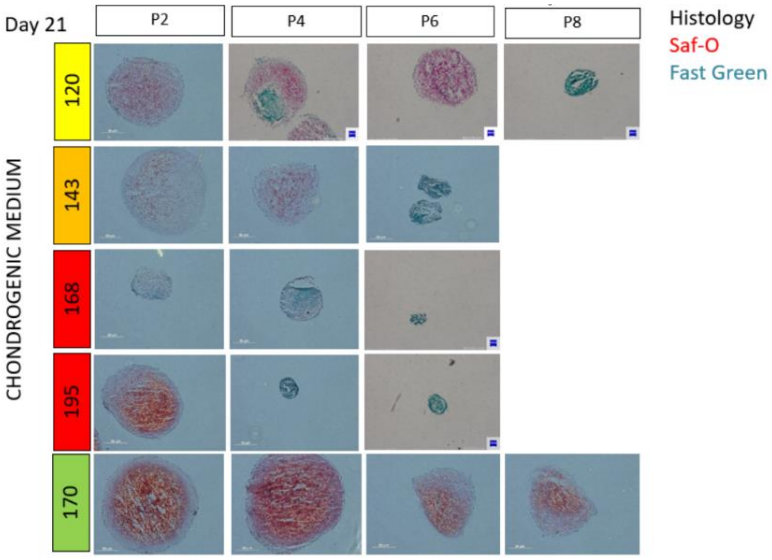


Figure 10.6.13: Human MSC chondrogenesis assessed over passages with 5 human donors. The donor variation, and the inconsistency over time can be seen by the variation in staining for glycosaminoglycan (orange).

Partner:

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

Dorsal root ganglion response to intervertebral disc degenerative environment (NEURODISC2) (Ongoing) (M Peroglio, M Alini)

Background: Lower back and neck pain have been reported by the Global Burden of Disease Study group as leading cause of disability worldwide considering the incidence, prevalence and years lived with disability. Back pain can result from many different origins and is therefore difficult to treat, especially in the case of chronic back pain. Nonetheless, there is a consensus that intervertebral disc (IVD) degeneration is a major cause, with a correlation between degeneration and pain.
Goal: To investigate how the intervertebral disc degenerative environment influences the response of the adjacent neural structure.
Results: Using an IVD organ culture model where degeneration was induced by high-frequency mechanical loading, we have found that the degenerative IVD induces activation, proliferation and migration of microglial cells (Figure 10.6.14). These results evidence the important role of microglia in maintaining the neuro-inflammatory microenvironment of the degenerative IVD and their implication in the development of chronic back pain. The effect of the degenerative disc microenvironment (characterized by low pH, low glucose, and low oxygen) on the dorsal root ganglion (DRG) neurons that innervate the outer portion of the intervertebral disc was also investigated. *In vitro* and ex-vivo studies evidenced that hypoxia (2% versus 20% O_2) promoted DRG neuronal outgrowth elongation and branching. The longer outgrowth under hypoxia could possibly explain the deeper innervation observed in human painful IVD tissues. Our current work is focused on better understanding the link between neoinnervation and pain, which will set the ground for the evaluation of treatments targeting back pain.

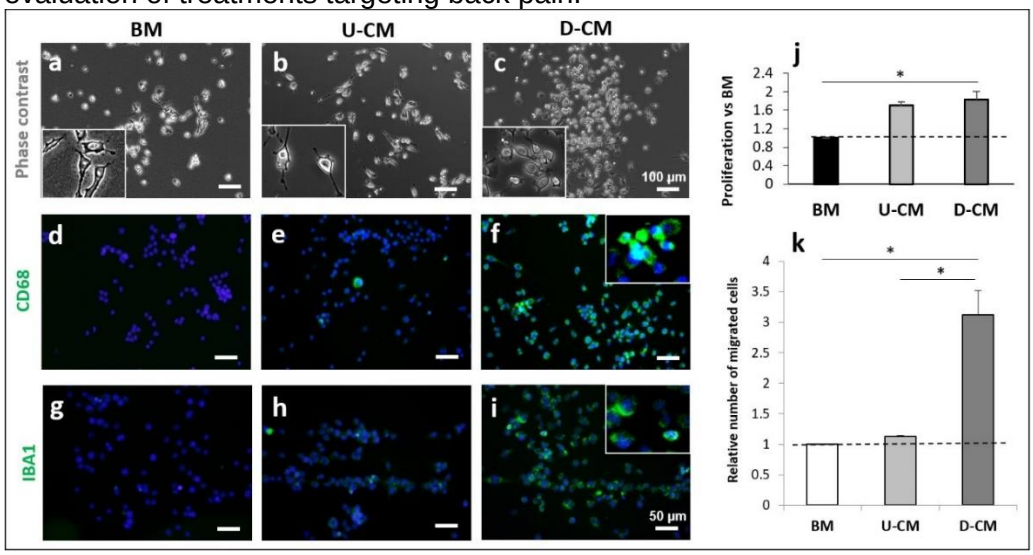


*Figure 10.6.14: Degenerative intervertebral disc conditioned medium (IVD-CM) induces activation, proliferation and migration of microglial cells. N9 microglial cell line morphological changes from ramified in basal medium (BM) and unloaded IVD conditioned medium (U-CM) to amoeboid in D-CM (degenerative IVD conditioned medium) (a-c); exposure to D-CM induced a higher expression of CD68 and IBA1 markers (d-i), a stronger proliferation (j) and migration (k) compared to N9 cells cultured in BM. * indicates p<0.05 (from Navone, Peroglio et al., 2018).*

Pres:

Ma J, Stefanoska D, van Donkelaar CC, Grad S, Alini M, Peroglio M. Hypoxia in degenerative intervertebral disc promotes neurite outgrowth. 28th eCM Conference, Davos (Switzerland), 25-28 June 2018 (oral).
Ma J, Stefanoska D, van Donkelaar CC, Grad S, Alini M, Peroglio M. Hypoxia in degenerative intervertebral disc promotes neurite outgrowth. 6th Graubünden Forscht, Davos (Switzerland), 19-20 September 2018 (oral).

Pub:

Navone SE, Peroglio M, Guarnaccia L, Beretta M, Grad S, Paroni M, Cordiglieri C, Locatelli M, Pluderi M, Rampini P, Campanella R, Alini M, Marfia G. Mechanical loading of intervertebral disc modulates microglia proliferation, activation, and chemotaxis. Osteoarthritis & Cartilage 2018; 26(7): 978-87.

Cell homing in the degenerative intervertebral disc: Characterization of migrating cells and their regenerative potential (DISCREGEN2) (Ongoing) (S Grad, M Peroglio)

Background: Homing of mesenchymal stem cells (MSCs) has been described as potential alternative to MSC injection into the degenerative disc, aiming to enhance the regenerative capacity of the intervertebral disc (IVD). We have previously shown that MSC homing into the IVD could increase the activity of the IVD cells.
Goal: To investigate the effect of MSC homing on the Tie2 (Angiopoietin-1 receptor) positive IVD progenitor cell population, the IVD cell survival and their proliferative response.
Caudal IVDs with the endplates were isolated from bovine tails. Fluorescent labeled human MSCs were placed onto the endplates and let migrate into the IVD. Human non-degenerated, traumatic and degenerative IVD tissues were obtained with ethical approval. IVD tissue was separated in two equal portions, and MSCs were added onto one tissue portion using the second portion as untreated control. After 5 days of culture with MSC migration, IVD cells were isolated by tissue digestion and percentages of Tie2 positive IVD progenitor cells, dead IVD cells, and proliferating IVD cells were evaluated by flow cytometry.
Results: MSC homing into the IVD significantly increased the proportion of Tie2 positive IVD progenitor cells in all bovine IVDs and in 7 out of 10 human IVDs; MSC homing also decreased the fraction of dead IVD cells in bovine IVDs and in 7 out of 10 human IVDs; furthermore, MSC homing induced a proliferative response in bovine IVDs and human IVDs. Taken together, our findings suggest a prominent role for paracrine stimulation by homed MSCs. This indicates that homed MSCs may represent "biological factor delivery systems", secreting growth and survival factors to help resident cells to reverse or slow down a potential ongoing degenerative process.

Pres:
Sebastian Wangler, Marianna Peroglio, Ursula Menzel, Lorin M. Benneker, Daisuke Sakai, Mauro Alini, Sibylle Grad. Homing of Mesenchymal Stem Cells Enhances Tie2^{+} Progenitor Cells and Induces a Proliferative Response in Intervertebral Disc Organ Culture. ORS New Orelans 2018
Sebastian Wangler, Marianna Peroglio, Zhen Li, Ursula Menzel, Lorin M. Benneker, R. Geoff Richards, Mauro Alini, Sibylle Grad. CD146 is a marker for stem cells with increased migration potential towards degenerative intervertebral discs. eCM Davos 2018
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Pub:
Leite Pereira C, Q Teixeira G, R Ferreira J, D'Este M, Eglin D, Alini M PhD, Grad S, Barbosa M, Goncalves R. SDF-1-mediated migration of MSCs enhances collagen type II expression in intervertebral disc. Tissue Eng Part A. 2018 Jun 19. doi: 10.1089/ten.TEA.2018.0131.
Sakai D, Schol J, Bach FC, Tekari A, Sagawa N, Nakamura Y, Chan SCW, Nakai T, Creemers LB, Frauchiger DA, May RD, Grad S, Watanabe M, Tryfonidou MA, Gantenbein B. Successful fishing for nucleus pulposus progenitor cells of the intervertebral disc across species. JOR Spine 1(2), e1018, 2018.
Buckley CT, Hoyland JA, Fujii K, Pandit A, Iatridis JC, Grad S. Critical Aspects and Challenges for Intervertebral Disc Repair and Regeneration - Harnessing Advances in Tissue Engineering. JOR Spine e1029, 2018
Wangler S, Li Z, Grad S, Peroglio M. Chapter 5: Intervertebral disc whole organ cultures: How to choose the appropriate model. In: Gene and cell delivery for Intervertebral disc degeneration. Editors: Goncalves RM and Barbosa MA. CRC Press Taylor and Francis Group 2018.
Leite Pereira C, Grad S, Barbosa MA, Goncalves RM. Chapter 9: Cell Recruitment for Intervertebral Disc. In: Gene and cell delivery for Intervertebral disc degeneration. Editors: Goncalves RM and Barbosa MA. CRC Press Taylor and Francis Group 2018.

Partners:
- Benneker L (Prof), Inselspital Bern, Switzerland
- Sakai D (Prof), Tokai University School of Medicine, Japan
- Haglund L (Prof), Montreal General Hospital, Montreal, Canada

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

Background: 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.
Goal: We aim to develop 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.
Results: 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 10.6.15 A). 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. When perfusing platelet lysate in one the of channels, we could observe a paracrine effect of this injury signal model on the capillary integrity (Figure 10.6.15 B). We successfully produced a perfused on-chip microvascular network. Our preliminary results suggest the possible local and paracrine response of microvascular cells to injury related factors.

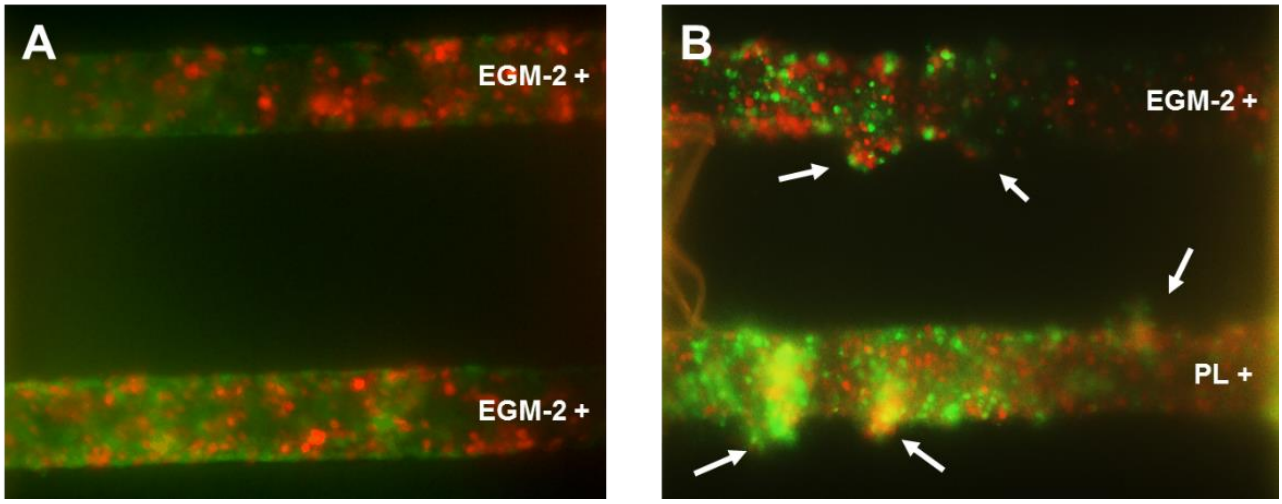


Figure 10.6.15: (A, B). Fluorescence microscopy images (time lapse) of cellularized microchannels. (A) Two parallel microchannels were seeded with both GFP-HUVECs (green) and RFP- MSC (red, PCs-like) and perfused with EGM-2 for at least 4 hours. (B) The top channel was perfused with EGM-2, while the bottom channel was perfused with EGM-2 containing PL. Observation was performed during 24h. A disruption of the cell organization can be observed in both channels (arrows). We can note that in the channel perfused with EGM-2 only this disruption (sprouting) seems to be unidirectional towards the channel containing PL.

Pres:
Verrier S, Pereira AR, Barbe L, Alini M. Study of Pericytes potential for bone repair in a perfusable 3D microvascularized model. 2018 TERMIS World Congress

Autologous 3D printed scaffolds (AutoInk) (started) (S Verrier)

Background: Biofabrication using additive manufacturing technologies and autologous cells is being considered for the creation of autologous biological tissues with personalized shape and architecture. However, the inks which provides the extracellular matrix environment of the cellular components, protecting them during the extrusion printing and after formation of the customized tissue, are of synthetic or allogenic origin.
Naturally rich in fibrinogen and platelets and originally liquid, Platelet Rich Plasma (PRP) can be prepared out of patient's own blood. PRP jellifies upon thrombin and calcium-chloride activation and has shown beneficial outcome in many human and veterinary medical applications including tendon and craniomaxillofacial/dentistry repair. The production and use of PRP in form of spray or injectable gel is widely accepted in the clinic.
Goal: Our aim is to develop a bioink based on patient's autologous PRP for the printing shape specific 3D structure that can be tailored regarding its biological and mechanical properties.
Results: Different additives have been tested to increase PRP properties regarding its viscosity, injectability and mechanical properties. Gelatin methacrylate (GelMa) and Hyaluronane Methacrylate (MeHA) have been added to PRP preparations in different combinations and concentrations. The addition of both GelMa and meHA conferred adequate properties to PRP solution compatible with 3D printing. The properties (stiffness, viscosity, injectability, degradation rate) of the selected gel combination in presence of cells are currently being investigated.

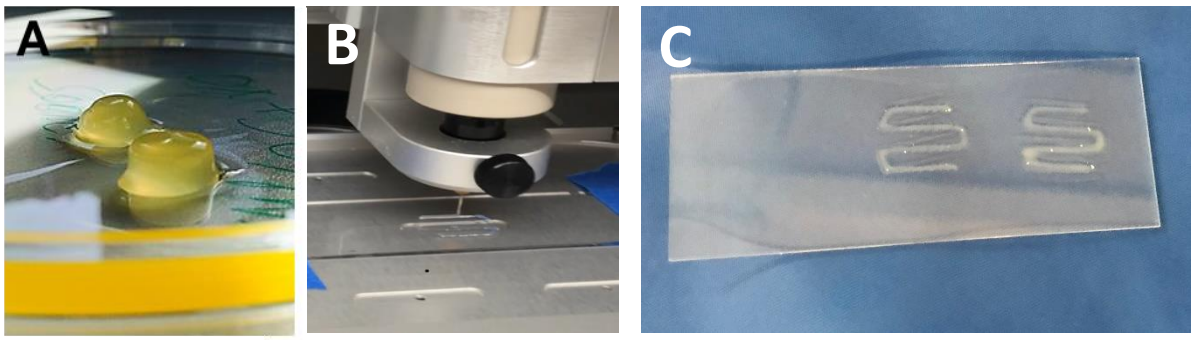


Figure 10.6.16: (A, B, C). (A) PRP gel. (B) modified PRP gel compatible for 3D printing. (C) 3D printed PRP threads.

Pres:
Arabpour Z, Keller J, Serra T, Alini M, Eglin D, Verrier S. Influence of polymeric adjuvants on the properties of Platelet Rich Plasma gel. Osteologie. 2018;27(2):A55-(SVGO+SBMS/oral)

Local delivery of IL-1Ra as a strategy to enhance long bone healing (HealBone) (ongoing) (W Lackington, K Thompson)

Background: Patients with long bone fractures, particularly those that suffer from delayed healing or non-union, typically display prolonged activity of pro-inflammatory cytokines, including IL-1β. These patients might benefit by a treatment strategy that modulates their immune response during bone healing. This project focuses on investigating the therapeutic efficacy of IL-1Ra, the receptor antagonist to IL-1β, for promoting bone repair.
Goal: To develop an innovative treatment to enhance the healing of long bone defects, based on attenuating the negative effects of prolonged inflammation by local delivery of IL-1Ra.
Results: We have identified and characterized a suitable pre-clinical model with which to test the efficacy of IL-1Ra administration *in vivo*. This model utilizes a 2 mm femoral osteotomy in skeletally mature female Fischer 344 rats, with internal fixation provided by a 1.25 mm-thick PEEK plate. Mechanical properties, pro-inflammatory cytokine and chemokine levels in the systemic circulation and in the local microenvironment, and callus formation at 10 days post-surgery were characterized and compared to a 2 mm-thick PEEK plate or an external fixator. Additionally, *in vitro* osteogenic assays have demonstrated the potential of IL-1Ra to mitigate the negative impact of IL-1β treatment on osteogenesis of rat mesenchymal stromal cells (Figure 10.6.17). Using this information, we have developed a thermoresponsive hyaluronic acid-based biomaterial to serve as a platform for the delayed delivery of IL-1Ra *in vivo*, in addition to it serving as a template for bone repair. The release of IL-1Ra from this hyaluronic acid-based biomaterial is characterized by an initial diffusion-mediated burst release, followed by a later degradation-dependent phase. Ongoing studies are aimed at identifying novel factors to improve the osteogenic potential of the hyaluronic acid-based biomaterial and to use this biomaterial as a delivery vehicle to facilitate local IL-1Ra administration aimed at promoting bone healing *in vivo*.

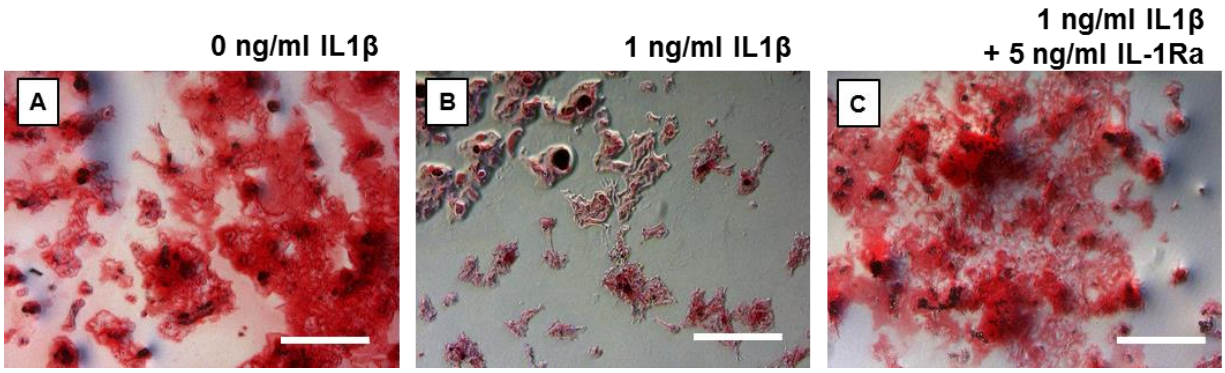
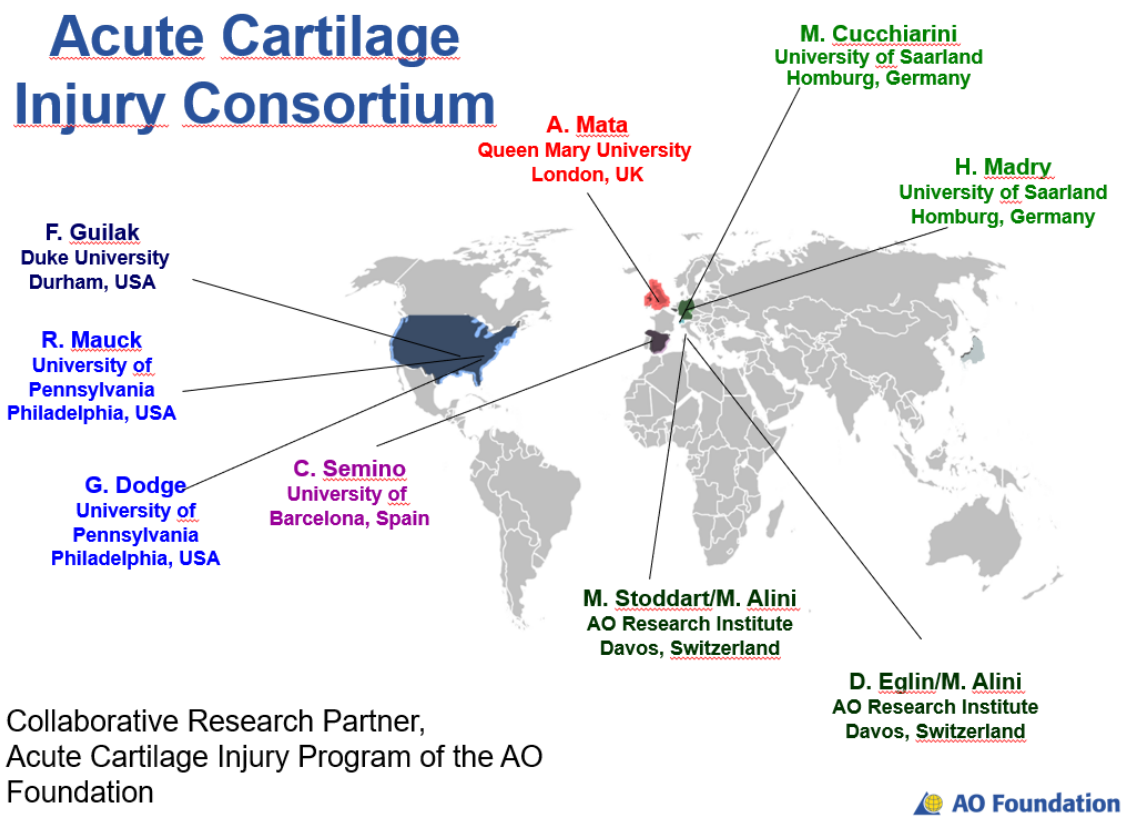


Figure 10.6.17: ***Impact of IL-1β administration, and antagonism of IL-1β bioactivity by IL-1Ra, on the osteogenic differentiation of rat mesenchymal stromal cells in vitro.*** *Alizarin red staining of calcium deposition by rat mesenchymal stromal cells cultured under osteogenic conditions for 21 days. (A) Normal osteogenic culture conditions. (B) Cells receiving 1 ng/ml IL-1β, which inhibits osteogenesis. (C) Cells receiving 5 ng/ml IL-1Ra in addition to 1 ng/ml IL-1β, which mitigates the negative effects of IL-1β on osteogenesis. Scale bar, 500 μm.*

10.7 ARI Collaborative Research Programs (CRPs)

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 with the final results being presented in the summer of 2018. 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 tested the most promising multicomponent repair devices, with or without an adeno-associated virus vector carrying the Sox9 gene, in two pre-clinical proof-of-concept minipig chondral defect studies. 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 compared 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. Together the data demonstrated the critical role played by the subchondral bone in chondral defects. The advantages of complimentary teams, working together towards a common goal are clear when considering the output generated. With over 90 publications, 6 PhD Thesis, 1 MD Thesis, 1 Vet Thesis and 2 workshops the data was presented in many different formats. Furthermore, over 5 million Swiss Francs in additional research funds were raised from other funding sources based on data obtained in this consortium.



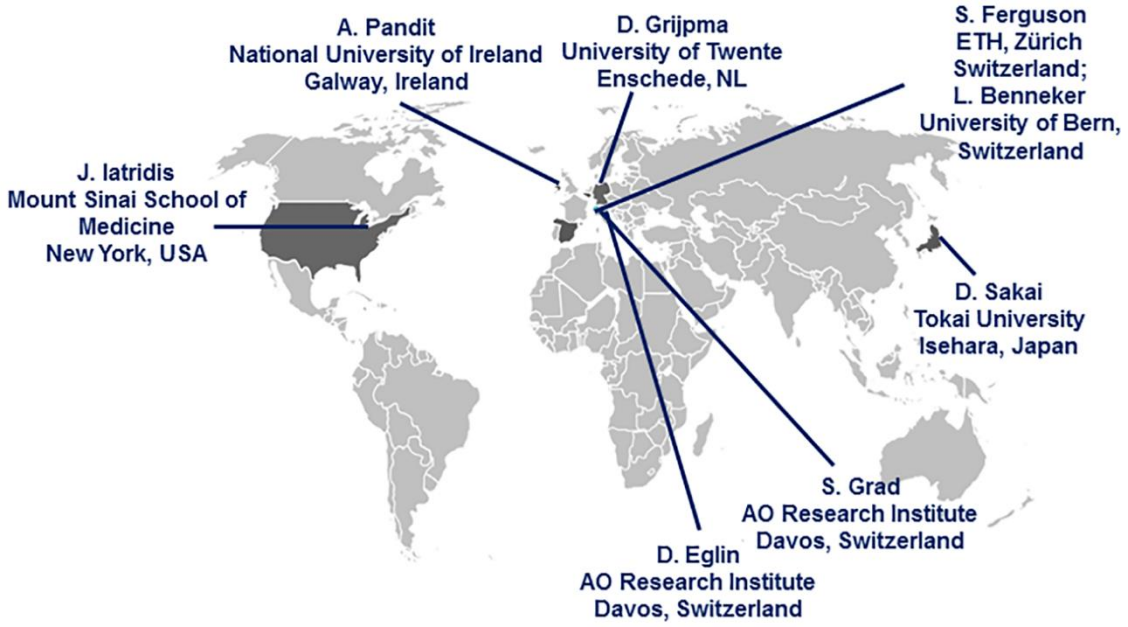
The partners of the CRP ACI consortium include:
- Alvaro Mata, Queen Mary University of London, GB, Carlos Semino, Parc Cientific Barcelona, ES
- Robert Mauck, George Dodge, University of Pennsylvania, Philadelphia, US
- Henning Madry, Magali Cucchiarini, The Saarland University, Homburg, D
- Farshid 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.

ACI final meeting in Davos, June 2018.

Annulus Fibrosus Repair (AFR) (2011-2018)
Development of implants to repair or regenerate ruptured annulus fibrosus

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 Collaborative Research Program (CRP) Annulus Fibrosus Repair (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, which had previously been extensively tested in organ culture and biomechanical experiments. 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 were 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 were generated as primary consortium deliverable.



The partners of the CRP AFR consortium:
• 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 was coordinated by Sandra Steiner and professionally guided and monitored by the CRP committee members Gunnar Anderson (clinician) and Peter Roughley (scientist).

AFR final meeting in Davos, June 2018.

Annulus Fibrosus Rupture Repair Proof of Concept Study (Discpatch; finished) (S Zeiter, S Grad, AFR Consortium Partners)

The overall aim of the Collaborative Research Project Annulus Fibrosus Repair was to develop an implant for closure of annulus fibrosus (AF) defects based on biomaterials with or without the implementation of cells or bioactive factors. As last step, large animal proof-of-concept studies were carried out to test the safety and effect of the developed biomaterials alone ("inert repair") and of delivered cells and factors ("bioactive repair"). In the first pilot study, full thickness AF defects (2 mm diameter) were created in the lumbar intervertebral discs (IVDs) and were filled with different biomaterials: polytrimethylene carbonate scaffolds, Fibrin-Genipin (FibGen) glue, with or without a polyurethane membrane sutured onto the AF. Outcomes after 3 months revealed remarkable iatrogenic endplate defects due to the small disc height and challenging access to the sheep lumbar spine. In the second pilot study cervical discs were used, while the same defects and treatments were applied; the use of cervical discs facilitated the access and reduced the iatrogenic damage.

The main study for inert repair used cervical discs of 10 sheep; 3 levels were injured with 2 mm biopsy punch, of which 2 levels were repaired with FibGen glue. The 12-months outcome measurements included biomechanical response to cyclic torsion and axial loading, histology, and vertebral body changes with computed tomography. There were no differences in torque range, stiffness, axial range of motion or axial compliance between injured and FibGen treated discs. Both groups showed similar rates of AF fiber disruption, while blood vessels were slightly reduced in FibGen treated group (Figure 10.7.1). The similarity in biomechanical response and AF disruption in both Injured and FibGen groups suggested similar repair responses. The high prevalence of ossifications in both groups indicated that the large injury created with biopsy punch requires further refinement.

For the bioactive repair, a 3 months pilot study was performed comparing the injection of autologous bone marrow derived mesenchymal stem cells and the chemotactic factor CCL5, whereby the histological outcomes were similar. CCL5 had previously been demonstrated chemo-attractive activity on AF cells in vitro. However, CCL5 delivery did not show any effect on cell recruitment or AF repair, neither in vivo nor in a whole organ culture AF defect model. Further studies are required to identify an efficient bioactive treatment for large AF defect repair.

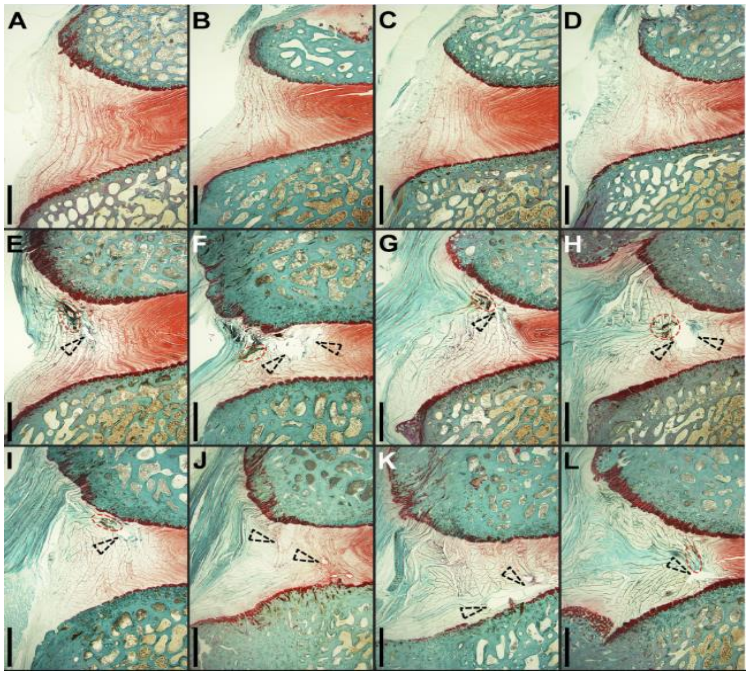


*Figure 10.7.1**:** Histological findings of the 12-month study.* ***A–D. Intact*** *samples showed highly aligned AF lamellae.* ***E–H. Injured*** *unrepaired specimens had discontinuous AF tissue (arrow), blood vessels (red circle) and endplate disruption.* ***I–L. FibGen*** *repaired specimens showed discontinuous AF tissue (arrow), blood vessels and endplate disruption. Overview microphotographs of thick-sections of sheep cervical IVDs (non-decalcified, resin-embedded, Safranin O-Fast Green-stained material; scale bar: 2 mm; image orientation: left = ventral, bottom = caudal).*

Pres:
B. Günay, I.L. M. Isa, C. Conrad, G. Scarcelli, S. Grad, Z. Li, A. Pandit. A hyaluronan-based hydrogel system for annulus fibrosus repair. 2018 EORS (oral)
Long R.G, Nakai T, Sakai D, Benneker L.M, Iatridis J.C, Alini M, Grad S, Li Z. TGFβ1 induces a contractile CD146+ phenotype of human annulus fibrosus cells showing affinity to a collagen gel. 2018 ISL&T (oral)

Pub:
Zhou Z, Zeiter S, Schmid T, Sakai D, Iatridis JC, Zhou G, Richards RG, Alini M, Grad S, Li Z. Effect of the CCL5 releasing fibrin gel for intervertebral disc regeneration. Cartilage, 2018 DOI: 10.1177/1947603518764263
Long RG, Zderic I, Gueorguiev B, Ferguson SJ, Alini M, Grad S, Iatridis JC. Effects of Level, Loading Rate, Injury and Repair on Biomechanical Response of Ovine Cervical Intervertebral Discs. Ann Biomed Eng 46(11):1911-1920, 2018.

Partners: CRP AFR consortium:
- Lorin M Benneker, Prof, Inselspital, University of Bern, Bern, Switzerland
- 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

10.8 OCD Consortium

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. The ARI collaborative research program (CRP) OsteoChondral Defect (OCD), bring together multidisciplinary expertise in materials, bioprinting, bioreactors, biomechanics, macrophages and animal models. Additive manufacturing and biofabrication approaches are used to produce constructs systematically evaluated to assess the influence of physical and chemical parameters on cartilage and bone 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 is being investigated. Rational scaffold design may be further enhanced by incorporation of bioactive molecules to modulate inflammation. Bioreactor and culture models that include multiple tissues of the joint completed with immune cells are used to reduce *in vivo* experimentation along 3R Principles. Clinical insights drive the research of the OCD to ensure that a route to translation is always a consideration. Therefore, as an underlying principle, increases in implant complexity will be justified by significant increases in implant function, thus ensuring sufficient biological benefit of additional regulatory requirements.

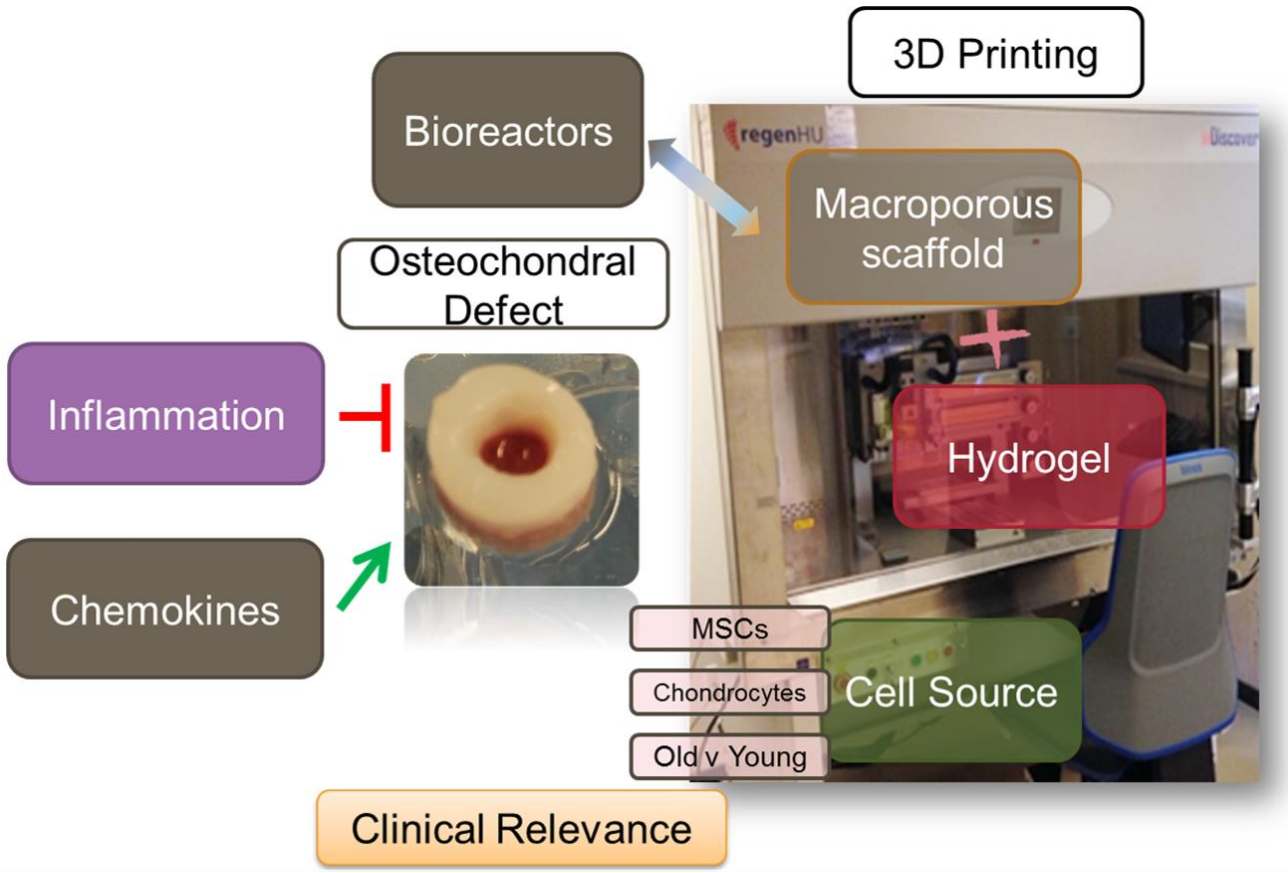


Figure10.8.1: OCD collaborative research program tools toward osteochondral defect regeneration.

The project started in June 2017 and will be funded for 4 years. This strong consortium is composed of five teams respectively from the University of Pennsylvania, United State, with Dr Jason Burdick, Dr Claudia Loebel and Dr Robert Mauck; The University Medical Center Utrecht, the Netherlands, with Florencia Abinzano, Dr Riccardo Levato and Prof Jos Malda; The University Medical Center Rotterdam, the Netherlands, with Tim Wesdorp, Dr Yvonne M. Bastiaansen-Jenniskens and Prof

Gerjo JVM van Osch; the Chinese University of Hong-Kong, Hong-Kong, with Dr Kevin Ho and Prof Ling Qin, and the ARI, Switzerland, with Dr Andrea Schwab, Dr Matteo D'Este, Dr David Eglin, Prof Martin Stoddart, Prof Mauro Alini and Prof Geoff Richards with multidisciplinary expertise in materials, bioprinting, bioreactors, biomechanics, cell biology and immunology. The team was supported by Prof Peter Roughley and Prof James Richardson acting as advisory experts for the first year, and now by Prof Peter Angele and Prof Peter van der Kraan.

This first annual meeting of the OCD collaborative research program was held at the Erasmus University Medical Center Rotterdam, the second largest hospital of the Netherlands, on May 25th, 2018.

The OCD Consortium partners at their 1st annual meeting in Rotterdam, NL.

This annual meeting was the first one bringing all the partners together with one of the monitoring expert members, the late, Prof Peter Roughley from the Shriners Hospital for Children, Canada. The meeting was dedicated to bringing together the research partners and discuss together the progress and future directions of the consortium.
The meetings began with a welcome address by the host, Dr Bastiaansen-Jenniskens and a short introduction on the goals of the consortium from Dr Eglin (ARI, CH). This was followed by progress reports from the research partners and post-presentation discussions. The consortium reported already 6 publications in peer-reviewed scientific journals and several conference abstracts. Four scientific exchange visits took place in this first year and many more are planned to strength-up and integrate the activities of the respective team. The overall feedback on this first Annual OCD CRP Meeting 2018 was very positive and motivating. The ample discussion time that was extremely valuable for open discussion and planning the future step of the collaborative activities of the consortium, while keeping in sight the clinical goal which should be driving the development of the innovative solutions of the consortium to ensure a route to translation.

Multiple crosslinked bio-inks for 3D microextrusion of tissue-like constructs and biodegradable thermoplastic elastomer for fuse deposition manufacturing (Started) (Multibio-Ink, CRP-OCD project) (D Eglin, M D'Este, M Stoddart, 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.

Pres:
Petta D, Armiento A, Grijpma DW, Alini M, Eglin D, D'Este M. A tissue adhesive hyaluronan bioink with double gelation mechanism for direct printing into a cartilage defect. 2018 SSB+RM (poster).
Petta D, Grijpma DW, Alini M, Eglin D, D'Este M. A Tyramine-Modified Hyaluronan Bioink With Double Gelation Mechanism for Independent Tuning of Shear-Thinning and Post-Printing Curing. 2018 Biofabrication (oral).
Frayssinet A, Petta D, Eglin D, D'Este M, Mosser G, Helary C. Development of collagen/hyaluronic acid-tyramine (COLL/THA) composite hydrogels with tunable gelling kinetic and THA content for the treatment of nucleus pulposus. Bone Joint J. 2018; 100-B(Suppl 14, Orthopaedic Proceedings):96 (EORS/oral).

Pub:
Petta D, Grijpma DW, Alini M, Eglin D, D'Este M. 3D printing of a tyramine hyaluronan derivative with double gelation mechanism for independent tuning of shear thinning and post-printing curing. ACS Biomater Sci Eng. 2018;4:3088-98.
Petta D, Armiento AR, Grijpma D, Alini M, Eglin D, D'Este M. 3D bioprinting of a hyaluronan bioink through enzymatic-and visible light-crosslinking. Biofabrication. 2018;10:044104.

Partners:
- Malda J (Prof) and Levato R (PhD), The University Medical Center Utrecht, the Netherlands
- Bastiaansen-Jenniskens YM (PhD) and van Osch G (Prof), The University Medical Center Rotterdam, the Netherlands
- Ho K (MD, PhD), Qin L (Prof, MD), Chinese University of Hong-Kong, Hong-Kong
- Burdick J (PhD), Mauck R (Prof), the University of Pennsylvania, USA

10.9 AO Development Incubator

AO Fracture Monitor (ongoing) (M Ernst, M Windolf)

Background: Information on healing progression and load-bearing characteristics in fracture patients is only barely tapped due to inaccessibility of a confined biological region and limited value of radiographic methods. A novel approach to continuously measure both fracture healing and patient activity has been recently developed in ARI. The system comprises an implantable data logger which autonomously collects relevant parameters to access fracture healing. Wireless synchronization of the assessed healing data via patient's mobile phone allows for remote monitoring by the treating physician. Proof of concept is obtained from preclinical experiments and from first clinical data collection with prototype devices on external fixation (project SmartFix).

Figure 10.9.1: Illustration of the AO Fracture Monitor concept built around an implantable data logger allowing for remote assessment of fracture healing progression.

Goal: To further develop AO Fracture Monitor into a commercially applicable system for femoral bridging plating. Both implantable device and accompanying software shall be tested according to the regulatory requirements and undergo clinical evaluation thereafter.

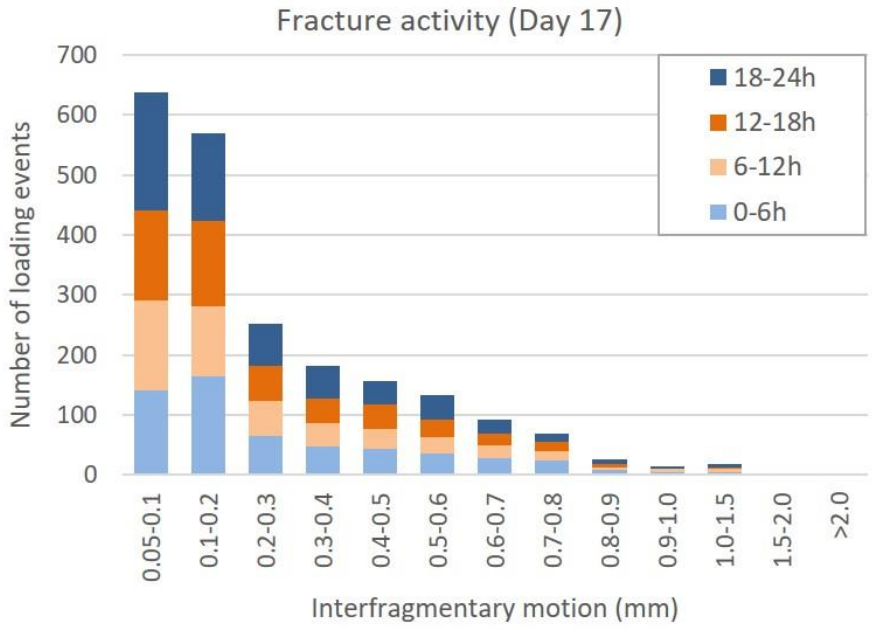


Figure 10.9.2: Preclinical fracture activity data at an arbitrary day during the consolidation period. The histogram shows a total of 2154 loading events detected at the fracture site over 24 hours. The events are distributed to 13 intensity ranges in terms of interfragmentary motion. The colors indicate breakdown into four 6-hour intervals during the day.

Results: A first prototype, attachable to standard locking plates and with wireless connectivity to commercial smartphones, was evaluated in a sheep experiment. The progression of bone healing was clearly trackable from the monitor data over time. From this proof-of-principle experiment, the path towards certified medical device was followed. Adhering to the fundamental measurement principle and data collection concept, the Fracture Monitor underwent a major revision. Most important aspects to the refinement loop were miniaturization to reduce the risk for potential soft tissue irritation, long-term implantability through hermetic encapsulation, and compliance with the stringent regulatory requirements.

Pres:
Windolf M. AO Fracture Monitor – towards clinical translation. 2018. WCBiomech.

Partner:
- Pohlemann T (Prof), UK Homburg, Germany

Biphasic Plating – new stabilization concept to improve fracture healing (Biphasic Plate) (ongoing) (L Hofmann-Fliri, M Windolf)

Background: Most of bone fractures heal following plate fixation. However, healing complications may still occur in approximately 10% of cases whereof a significant portion of these can be attributed to unfavorable mechanical conditions at the fracture site. Moreover, state-of-the-art plates are prone to catastrophic failure either in the early post-operative phase from excessive loading or at a later stage due to fatigue as a consequence of impaired healing. A new plating concept, biphasic plating, was proposed by ARI in collaboration with QUT (Brisbane, Australia) to enhance the existing treatment modalities of locked plating by redesigning the conventional bone plate. So far, the biphasic plating concept was proven by mechanical testing and preclinical experiments. In a sheep tibia defect model robust callus formation was demonstrated under varying fracture conditions and varying functional loading, using a biphasic implant specifically designed for the animal's anatomy (project 2Pinvivo).
Goal: To design an anatomical distal femur plate as a pilot implant ready for clinical use. As the consequent next step involves translation of the biphasic plating concept into clinics, clinical evidence will be collected to demonstrate clinical feasibility of the concept.
Results: Following the project kick-off, users' needs and requirements have been compiled and translated into design inputs. With the help of surgeon surveys, radiographic case evaluations, computer modelling, mechanical and wet lab testing, design details are currently being determined and finalized. At the same time technical documentation is build up according to regulatory requirements. Manufacturing processes are under definition.

Figure 10.9.3: Rapid prototype of a biphasic distal femur plate produced with Selective Laser Sintering.

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

10.10 Extramural Projects

Cone-beam computed tomography as a fast alternative for high-resolution peripheral computed tomography (K Mys, P Varga)

Background: High-resolution peripheral computed tomography (HR-pQCT) is considered as the best technique to measure human bone microarchitecture *in vivo*. However, a breakthrough for medical applications is inhibited, due to the restricted field of view (FOV) and a relatively long acquisition time, which inhibits scanning of large FOV *in vivo*. High-resolution cone-beam computed tomography (CBCT) is a relatively new alternative in the orthopedic field. It is already used in daily clinical practice for dental application because of the large FOV (approx. 12x12x8 ccm), fast scanning time (approx. 18–31s), high resolution (voxel size up to 75 µm) and low radiation dosage.

Goal: To evaluate the accuracy of a CBCT on trapezia and radii relative to micro-computed tomography (microCT) as the gold standard and to compare to the accuracy of HR-pQCT when quantifying trabecular bone microstructural parameters and bone mechanical parameters.

Method: Nineteen trapezium bones of arthritic patients and nineteen distal radii were scanned four times *ex vivo*: (1) microCT (SkyScan1172, @19.84 µm for trapezia or VivaCT40, @19 µm for radii), (2) HR-pQCT (XTremeCT-I, @82 µm), (3) HR-pQCT (XTremeCT-II, @60.7 µm), and (4) CBCT (NewTom 5G, @75 µm). HR-pQCT and microCT were reconstructed and segmented following the manufacturer guidelines. CBCT was reconstructed with in-house developed software and segmented using an adaptive segmentation technique. Bone morphometric parameters were calculated including bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp) and trabecular number (Tb.N). Bone stiffness was calculated using micro-finite element analyses with loading of the joint proximally.

Results: CBCT had a slightly higher accuracy than XTremeCT-I and a slightly lower accuracy than XTremeCT-II regarding the bone microstructural parameters and mechanical parameters. The enhanced CBCT images had accuracy comparable to HR-pQCT for quantification of bone structural and mechanical parameters. The broader range of application, larger field of view and shorter acquisition time make CBCT a valuable alternative to HR-pQCT where high resolution is desired in clinical practice.

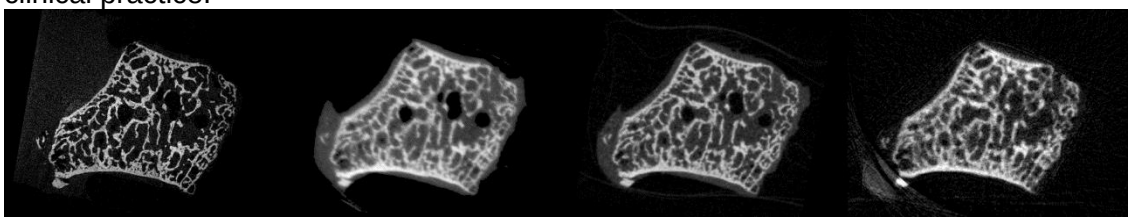


Figure 10.10.1: One representative reconstructed slice of a trapezium as obtained with (from left to right) microCT, Xtreme CT-I, XTremeCT-II, and CBCT.

Fund: Research Foundation Flanders CHF 6'000, Period: 2018**;** European Society of Biomechanics CHF 4'000, Period: 2017**;** KU Leuven CHF 6'000, Period: 2017.

Awards:

Fonds Wetenschappelijk Onderzoek (FWO) mobility award

Young Investigator Award of the Quantitative Musculoskeletal Imaging (QMSKI) conference

Pres:

Mys K, Varga P, Gueorguiev B, Stockmans F, Van Lenthe GH. Cone-beam computed tomography can quantify trapezium bone microstructure and stiffness as good as high-resolution peripheral quantitative computed tomography. 2018 WCB, Dublin, Ireland (poster)

Pub:

Mys K, Varga P, Gueorguiev B, Hemmatian H, Stockmans F, van Lenthe GH. Correlation between cone-beam computed tomography and high-resolution peripheral computed tomography for assessment of wrist bone microstructure, J Bone Miner Res (accepted)

Partners:

- Van Lenthe GH (Prof), KU Leuven, Leuven, Belgium
- Stockmans F (Prof), KU Leuven, Kortrijk, Belgium

Effect of subtalar motion on calcaneal osteotomies (Pescavus) (I Zderic, B Gueorguiev)

Background: There is evidence that the subtalar joint may compensate supramalleolar deformities and thereby slower or halt progression of ankle arthritis. The mobile subtalar joint may also compensate the effect of realigning osteotomies of the calcaneus and the tibia. The compensation is influenced by joint orientation and range of motion (ROM).
Goal: To investigate whether:

1. posterior facet curvature influences subtalar ROM
2. subtalar ROM influences subtalar compensatory capacity
3. there is a compensation of realigning osteotomies through a mobile subtalar joint
4. calcaneus osteotomy (COT) is more affected by the compensation than the supramalleolar tibia osteotomy (SMOT)

Method: Eleven fresh-frozen human cadaveric lower legs were mounted into a radiolucent loading frame. High resolution pressure sensors were fixed in the ankle joint via anterior arthrotomy. Axial load of 300 N was applied according to half body weight and Achilles tendon pull was simulated. Center of force (COF) migration, maximum pressure (Pmax), and loaded area were measured in the ankle with 10 mm varus/valgus sliding COT and 10° varus/valgus SMOT. Computed tomography evaluation of subtalar anatomy (posterior facet curvature) was conducted and correlation between posterior facet curvature and subtalar motion, as well as between SMOT/COT effect and subtalar motion were calculated.
Results: Compensatory capacity of the mobile subtalar joint limits the effect of COT more than SMOT, likely because the subtalar joint is closer to COT than to SMOT. Biomechanically, COT is therefore less effective in influencing ankle joint pressure than SMOT. COT effect is more reliable in stiff subtalar joints. Posterior facet curvature correlates with subtalar ROM.

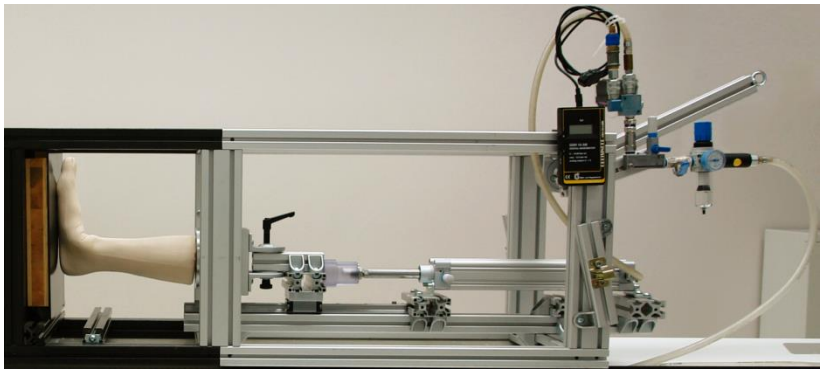


Figure 10.10.2: Cadaveric lower leg mounted on the loading frame for CT scanning.

Fund: University Hospital Berne, CHF 20'000, Period: 2017.

Partners:

- Schmid T (MD), Valais Hospital, Sion, Switzerland
- Krause F (MD), University Hospital Berne, Switzerland

Antibiotic-eluting scaffolds eliminate infection and facilitate bone tissue regeneration in a rabbit model of osteomyelitis (RCSI) (E Sheehy, C von Deimling, S Zeiter, F Moriarty)

The standard treatment for chronic Osteomyelitis (OM) is surgical debridement of the infected bone followed by the administration of systemic antibiotics for a period of four to six weeks. In this study, we sought to compare the capacity of two antibiotic-eluting scaffolds (containing vancomycin or gentamicin) to eliminate infection and facilitate bone healing in a rabbit model of chronic OM.
Antibiotic-eluting collagen-hydroxyapatite scaffolds containing either vancomycin (Vanc-scaff) or gentamicin (Gent-scaff) were fabricated. The radii of New Zealand White rabbits were inoculated with *S. aureus* and after a four-week observation period, the infected area was debrided and either left empty, or treated with a commercially available gentamicin fleece, a Vanc-scaff or a Gent-scaff. The treatment period lasted eight weeks, during which all animals received systemic antibiotics for the first four weeks. At the end of the treatment period, 6/6 animals treated with the Gent-scaff were found to be infection-free, compared to 4/6 animals that were treated with the Vanc-scaff or Septocoll E, and 1/6 animals where defects were left empty. CT evaluations demonstrated a significantly higher bone volume in the Vanc- and Gent-scaff groups at week eight compared to week, highlighting the capacity of antibiotic-eluting scaffolds to facilitate bone healing in this model. These antibiotic-eluting scaffolds may prove to be a powerful tool in the fight against chronic OM, as they can be implanted into an infected bone defect left void following debridement to aid in bacterial clearance. Furthermore, since the scaffolds are biodegradable and facilitate bone healing, they do not require a second procedure for removal, thereby reducing hospital times and costs.

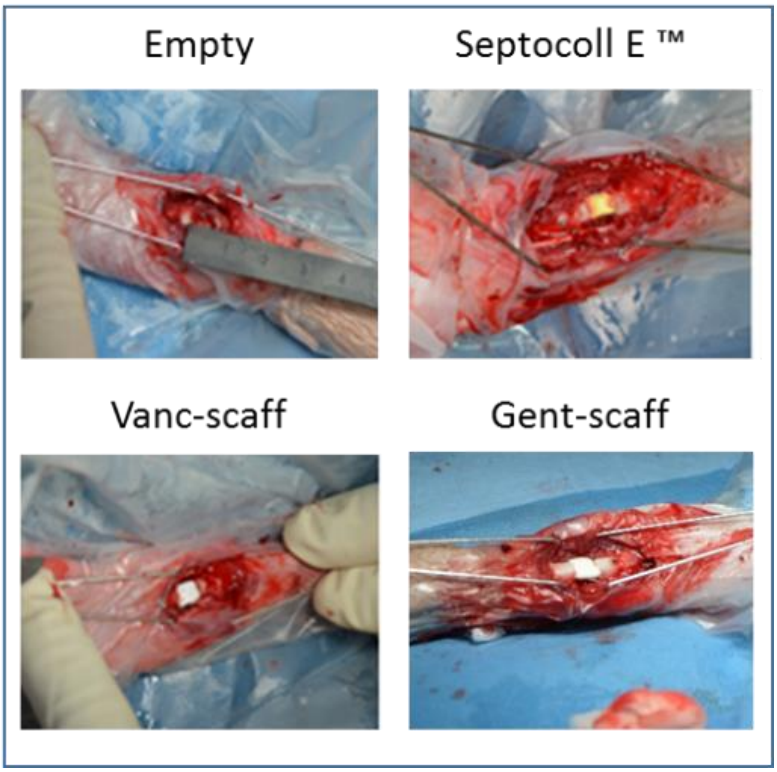


Figure 10.10.3: Intraoperative images showing placement of each test group, and empty controls. Materials were placed in the defect after debridement and confirmation of infection. In the absence of local antibiotics, the infection was not treated by debridement alone.

Fund: Science Foundation Ireland; CHF 165'000, 2017-2018.

Pres:
EORS 2018, Galway Ireland, September 25-28. Evaluation of the capacity of an antibiotic-eluting scaffold to treat infection in a rabbit model of chronic osteomyelitis. Eamon Sheehy (IE)

Collaborators:
O'Brien F (Prof), Royal College of Surgeons in Ireland, Dublin, Ireland

Targeting cartilage regeneration in joint and intervertebral disc diseases (TargetCaRe) (ongoing) (M Alini, S Grad),

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 is aimed to be achieved by loading biologically active agents in state-of-the-art nanocarriers. The biologically active agents should stimulate the body's own capacity to regenerate by attracting local stem cells or inhibit inflammation or degeneration. The ability of Fibrin-Hyaluronan (HA) and HA-Tyramine hydrogels to support mesenchymal stem cell migration, ingrowth and differentiation was investigated *in vitro* and *in vivo*. Labelled bone marrow hMSCs were seeded to form spheroids of 500 cells, embedded in HA-Fibrin or different HA-Tyramine cross-linked hydrogels and cultured with/without the chemotactic factor, platelet derived growth factor with two B subunits (PDGF-BB). Migratory area of the cells from the core was measured by microscopy. Bovine osteochondral defect biopsies were filled with HA-Fibrin and HA-Tyramine hydrogels with/without PDGF-BB and subcutaneously implanted in nude mice for 4 weeks. PDGF-BB induced a progressive increase of cell migration from the spheroids in HA hydrogels over three days culture. HA-Fibrin supported the widest cells migration area (5-fold increase compared to HA-Tyramine hydrogels (Figure 10.10.4). However, no significant differences of cell ingrowth were detectable in presence of PDGF-BB. After 4 weeks *in vivo* HA hydrogels with/without PDGF-BB showed cell infiltration and an amenable microenvironment for cartilage production. These processes were better supported in HA-Fibrin compared to HA-Tyramine hydrogels.
To conclude, HA-Fibrin hydrogel enabled abundant MSCs recruitment *in vivo*, resulting in hyaline cartilage production; even in the absence of chemotactic stimulus, such as PDGF-BB.

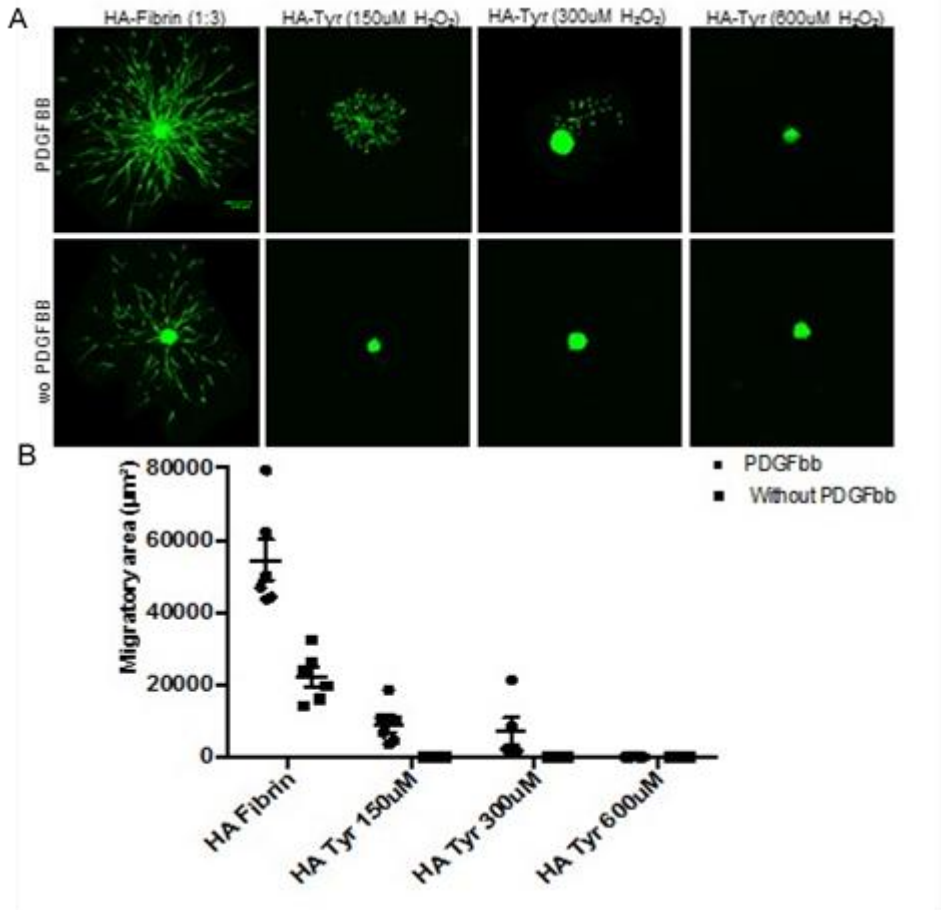


Figure 10.10.4: Spheroid-based migration assay. MSC spheroids 3D migration into HA-Fibrin and HA-Tyramine (HA-Tyr) hydrogels was monitored and quantified at 72h in presence or absence of PDGF-BB. A) Representative images; B) quantification of hMSCs migration.

Fund: EU H2020-MSCA-ITN-2014 Marie Sklodowska-Curie Grant ARI Funding CHF 530'000, Period: 2015-2019.

Pub:
Vainieri ML, Wahl D, Alini M, van Osch G, Grad S. Mechanically stimulated osteochondral organ culture for evaluation of biomaterials in cartilage repair studies. Acta Biomater 81:256-266, 2018.

Pres
Vainieri ML, Sivasubramaniyan K, Lolli A, Eglin D, Wexselblatt E, Yayon A, Alini M, Grad S and van Osch G. Hyaluronic acid-based hydrogels promote mesenchymal stem cell ingrowth and cartilage production *in vitro* and *in vivo*. ICRS April 2018
Vainieri ML, Sivasubramaniyan K, Lolli A, Eglin D, Yayon A, WexselblattE, Alini M, Grad S, van Osch G. Novel hyaluronan-based hydrogels to support endogenous cartilage repair. SBB+RM, May 2018
Vainieri ML, Wahl D, van Osch G, Alini M, Grad S. Novel ex-vivo osteochondral model for cartilage repair in mechanical stimulated joint bioreactor. ECM June 2018

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)

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. From the 40 compounds tested, several showed significant anabolic effects. After induction of inflammation, the pro-inflammatory and catabolic marker genes were up-regulated, and GAG/DNA ratio was significantly decreased; while several compounds had anti-catabolic effects, by down-regulating pro-inflammatory markers including. After 2 weeks of treatment with the compounds following inflammation, the GAG/DNA ratio was restored by Psoralidin, (Ps), Vanilic acid (VA), Protocatechuicaldehyde (PCA), Epimedin C (Epi C), 4-Hydroxybenzoicacid (4-HBA) treatment. Immunohistochemistry and Safranin-O staining confirmed the accumulation of cartilaginous matrix in compound treated pellets. A local drug delivery system for the bioactive compound is envisioned and their efficacy for cartilage repair will be tested.

Fund: Swiss-China Joint project (SNF) ARI funding: CHF 250'000, Period: 2015-2018.

Pres:

Xiangbo Meng, Long Li, Yuxiao Lai, Sibylle Grad, Mauro Alini, Ling Qin, Xinluan Wang. "Biphasic Bioabsorbable Osteochondral Scaffold". eCM XVIII Conference, Davos, Switzerland, June 2018.

Xinluan Wang, Xiangbo Meng, Long Li, Yuxiao Lai, Sibylle Grad, Mauro Alini, Ling Qin. "Biphasic Biodegradable Osteochondral Scaffold". 5th TERMIS World Congress, Kyoto, Japan, September 2018.

Xinluan Wang, Ling Li, Cuishan Huang, Huijuan Cao, Jiani Wang, Long Li, Yuxiao Lai, Sibylle Grad, Mauro Alini, Ling Qin. "A novel 3D printing composite scaffold with phytoestrogenic osteopromotive puerarin for potential bone regeneration". 5th TERMIS World Congress, Kyoto, Japan, September 2018.

Reihane Ziadlou, Sibylle Grad, Martin Stoddart, Xinluan Wang, Ling Qin, Andrea Barbero, Ivan Martin, Mauro Alini. Anabolic and anti-catabolic effects of small molecules applied in traditional Chinese medicine for treatment of osteoarthritis. eCM XVIII Conference, Davos, Switzerland, June 2018.

Reihane Ziadlou, Sibylle Grad, Martin Stoddart, Xinluan Wang, Ling Qin, Andrea Barbero, Ivan Martin, Mauro Alini. Screening of small molecules applied in traditional Chinese medicine: towards biological treatment of osteoarthritis. 5th TERMIS World Congress, Kyoto, Japan, September 2018

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

Personalised Ceramic Printable Ink for Patient Specific Implant Fabrication (InCePt) (D Eglin, G Richards)

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).

Fund: CTI/KTI (nr 18060.2), ARI Funding: CHF 292‘700, Period: 2017-2019.

Pres:
Sprecher CM, Thurner M, Büchler P, Richards RG, Eglin D. Improved post-processing stability of a 3D printed cement paste via co-axial extrusion of organic solvents. 2018 SSB+RM (poster).

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

3D Sound Induced Morphogenesis (3D-SIM) (T Serra)

3D cell technologies are revolutionizing drug discovery and personalized medicine. They can better recapitulate native physiological milieu in comparison to standard cell cultures and animal models. Also, animal testing shows lack of reproducibility, poor correlation with humans and raises important ethical and political issues. Thus, 3D cell technologies are fundamental to improve drug screening efficacy and minimize animal testing, in accordance with the 3Rs principle. Within this context, the development of fast and affordable 3D cell technologies represents one of the main challenges for pharmaceuticals, biotechnology firms and research institutions. Here, a novel 3D cell technology, named 3D Sound Induced Morphogenesis (3D-SIM), is proposed. 3D-SIM is based on an acoustic wave 3D printing method. Acoustic waves can move cells dispersed in a fluid. Depending on the amplitude and frequency of the waves, cell patterns are produced and then stabilized through gelation. 3D cell models, in a wide range of off-the-shelf gelling biomaterial matrices, can be very rapidly created in a controlled fashion by staking different layers of patterned cells. This project aims to create a 3D-SIM prototype that is: 1/ easily implemented into laboratory environment (small, portable, suitable for sterile setting), 2/ affordable and user friendly, 3/ able to create 3D cell models in a time-effective manner, with sufficient spatial complexity, retaining cell viability. Furthermore, in order to prove the suitability of 3D-SIM technology to build highly hierarchical tissue-like constructs with heterogeneous organization of cells and extracellular matrices, a proof of concept of a 3D vascularized bone model will be developed in collaboration with expert partner (Dr Moretti, SIRM). In particular, functionality of the achieved proof of concept will be assessed against 3D models already used and published. The guidance of industrial partners (Kuros Biosciences, CellSpring) will be instrumental in focusing the project toward customers' needs. We will demonstrate the added value of 3D-SIM over the state-of-the-art technologies and deliver the technological foundation for the creation of a start-up company.

Fund: BRIDGE (nr 20B1-1_178259) CHF 130'000, Period: 2018-2019.

Pres:
Serra T, Tognato R, Giancane G, Alini M, Eglin D. Magnetically responsive gelatin-based nanocomposite ink for remote control of 3D printed bio-inspired structures. 2018 ESB (oral).
Serra T, Tognato R, Armiento AR, Richards RG, Alini M, Eglin D. Using sound to pattern cells: 3D sound induced morphogenesis (3D-SIM). 2018 ESB (oral).
Serra T, Augurio A, Cortelletti P, Alini M, Eglin D, Speghini A. Non-invasive tracking and manipulation of 3D printed nanoparticles gelatin methacrylate hydrogel. 2018 ESB (poster).
Tognato R, Armiento AR, Richards RG, Eglin D, Alini M, Serra T. Using sound for cell assembling: 3D Sound Induced Morphogenesis, 3D-SIM. 2018 Biofabrication (oral).
Tognato R, Armiento AR, Bonfrate V, Levato R, Malda J, Alini M, Eglin D, Giancane G, Serra T. 3D-printing of magnetically-responsive soft-robotics for biomedical applications. 2018 Biofabrication (poster).
Pellicciotta D, Richards RG, Alini M, Eglin D, Serra T. A Molecular Dynamics Simulation for 3D-SIM, a Sound-Induced Biofabrication Technology. 2018 Biofabrication (poster).
Serra T. Sound-induced fabrication of complex organoids network. 2018 BioMAH (oral).

Pub:

Fortunato GM, De Maria C, Eglin D, Serra T, Vozzi G. An ink-jet printed electrical stimulation platform for muscle tissue regeneration. Bioprinting. Vol11, Sept 2018, e00035.
Tognato R, Armiento AR, Bonfrate V, Levato R, Malda J, Alini M, Eglin D, Giancane G, Serra T. A Stimuli-Responsive Nanocomposite for 3D Anisotropic Cell-Guidance and Magnetic Soft Robotics. Adv. Funct. Mater. 2018, 1804647.

Partners:

- Moretti M (PhD), Swiss Institute for Regenerative Medicine, Switzerland
- de Bruijn J (Prof), Kuros Biosciences, Switzerland
- Millan C (PhD), CellSpring, Switzerland

Biofabrication of cartilage particulate microtissues laden hyaluronan tissue engineered constructs (**D Eglin)**

Patient specific Tissue Engineering based on additive manufacturing principles holds great promise in articular cartilage repair, where anatomical fidelity and recapitulation of the tissue architecture is paramount. Recent development of a functional cartilage microtissue aggregates strategy for one-step surgery has shown original prospects for fast repair of cartilage. Thus, this project will address the hypothesis that improvement and broadening of their clinical applications could be achieved by combining cartilage particulate microtissues into a chondro-permissive bioink and produce structured and shape specific 3D printed cartilage constructs. Under rotary cell culture system, bone marrow stromal cells (BMSCs) have shown to proliferate rapidly and differentiate into mature chondrocytes after 21 days of culture on the surface of particulate decellularized extracellular matrix. Functional cartilage microtissue aggregates were formed. Further, the microtissue aggregates directly implanted into trochlear cartilage defects in a rat model indicated better and more rapid joint function recovery and superior cartilage repair compared to the control groups. In addition, tyramine derivatives of hyaluronan enzymatically crosslinked could be used to embed viable BMSCs and be extruded to create 3D structures. The bioprinting of microparticulate cellularized tissue have been reported to allow for the fabrication of constructs with high cell concentration and viability. However, hyaluronan chondropermissive environment has not been exploited in combination with microtissues in a biofabrication set-up. In addition, the ability to control size and polydispersity of microparticles via electrospray technique and potentially print cartilage microtissues containing bioink formulations not yet explored fully.

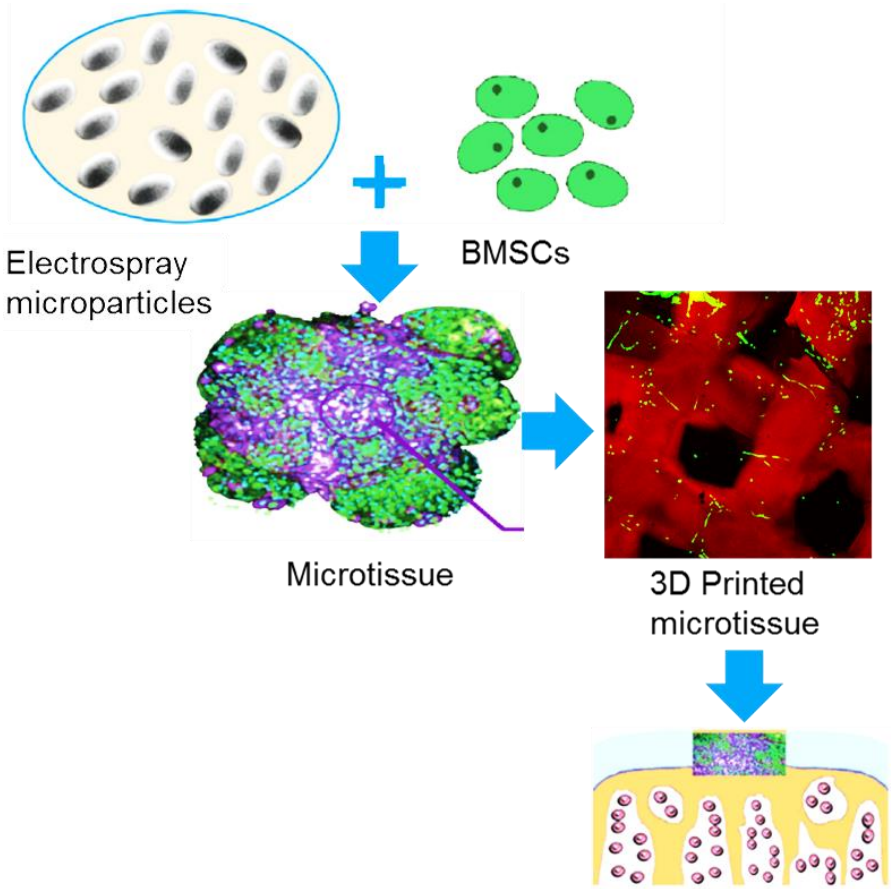


Figure 10.10.5: Scheme of the Project Proposal approach. Electrospray particles containing of not BMSCs will be produced from biopolymers. BMSCs embedded or seeded microparticles will be cultured for chondrogenic differentiation before dispersion into extrusion based printed construct.

Fund: SSSTC exchange (nr EG 08-122016), Funding: CHF 30'000 Period: 2018-2019.

Partners:

- Peng J (Prof, MD), the Institute of Orthopedics, Peking Key Lab of Regenerative Medicine in Orthopaedics, Key Lab of Chinese PLA, Chinese PLA General Hospital, People's Republic of China

Identifying novel therapeutic targets for articular cartilage repair (M Stoddart)

Novel therapies for cartilage regeneration have had limited success. Chondrogenic differentiation of mesenchymal stem cells (MSCs) under load is different to that observed during classical static culture conditions. This is highly clinically relevant, considering that patients receive weight-bearing rehabilitation therapy following cartilage repair. Additionally, as most *in vitro* cartilage repair studies are performed under static conditions, the lack of mechanical stimulation may explain why it has been challenging to reproduce promising *in vitro* results *in vivo*. Marrow stimulation techniques, such as microfracture, are the most commonly used clinical approach for cartilage repair with unpredictable results. Using a unique *in vivo* kinematic join simulating bioreactor, we have previously shown that while complex multiaxial load induces hMSC chondrogenesis, it also induces the expression of a number of soluble molecules not typically found under static culture conditions. This identified novel mechanically induced targets, such as nitric oxide (NO), that are potentially clinically relevant. Within this project we aim to better understand the role of mechanical load on the molecules induced during human MSC chondrogenesis vs standard conditions (static and with TGF-beta). We will identify new potential treatment targets, while investigating the biological function of nitric oxide.

Rationale: The joint contains multiple tissue types, and dysregulation of the surrounding tissues is a key factor in joint degeneration. The functional modulation of the non-cartilage cell types by MSC secretome will provide valuable further insight into the pathology of joint destruction.
Impact: Cartilage injury and subsequent degeneration is a leading cause of pain, lost mobility and increasing financial costs. Identification of novel targets that only present during chondrogenic differentiation under mechanical stimulation would offer the opportunity to identify potential clinical targets, while providing a greater understanding of the underlying biology.

Fund: Swiss National Funds (nr 31003A_179438 / 1), Funding: CHF 417'720, Period: 08/2018-07/2022.

Biological and mechanical effect of selective proinflammatory cytokine inhibition in degenerative disc disease (Inflamodisc) (ongoing) (Z Li, S Grad, M Alini)

Disease modifying anti-rheumatic drugs (DMARDs) have shown pain relieving effects in the treatment of degenerative disc disease. However, their underlying anti-inflammatory and regenerative activity is poorly explored. The present project aimed to investigate the effects of the TNF-α inhibitor Etanercept and the selective JAK3-inhibitor Tofacitinib in a degenerative, inflammatory intervertebral disc (IVD) organ culture model.
Whole bovine caudal IVDs were cultured within a bioreactor. The control group (PHY) was cultured under physiological loading and high glucose medium. In the degenerative group (DEG+TNF-α), detrimental loading and low glucose medium was applied together with TNF-α intradiscal injection (100 ng/IVD). Etanercept (3.5 mg/70 µL/IVD) or Tofacitinib (2.5 µg/mL) was applied under DEG+TNF-α conditions by intradiscal injection or medium supplement respectively. After 4 days, the effect on cellular gene expression and molecule release from IVDs was analyzed.
DEG+TNF-α treatment upregulated the expression of catabolic enzymes MMP-1, MMP-3, and proinflammatory cytokines IL-1β, IL-6, IL-8; whereas Etanercept and Tofacitinib partially reduced these effects (Figure 10.10.6). DEG+TNF-α conditions induced ECM degradation, as indicated by markedly elevated GAG release; and was partially attenuated by both drugs. NO and IL-8 release from IVD were increased under DEG+TNF-α conditions. Etanercept partially attenuated the release of NO and IL-8 protein, whereas Tofacitinib had no effect on it.
The combination of detrimental dynamic loading, nutrient deficiency, and intradiscal TNF-α injection synergistically triggered a proinflammatory and degenerative situation within the IVD. Etanercept and Tofacitinib showed the ability to slow down the degenerative response and reduce inflammation in the organ culture model.

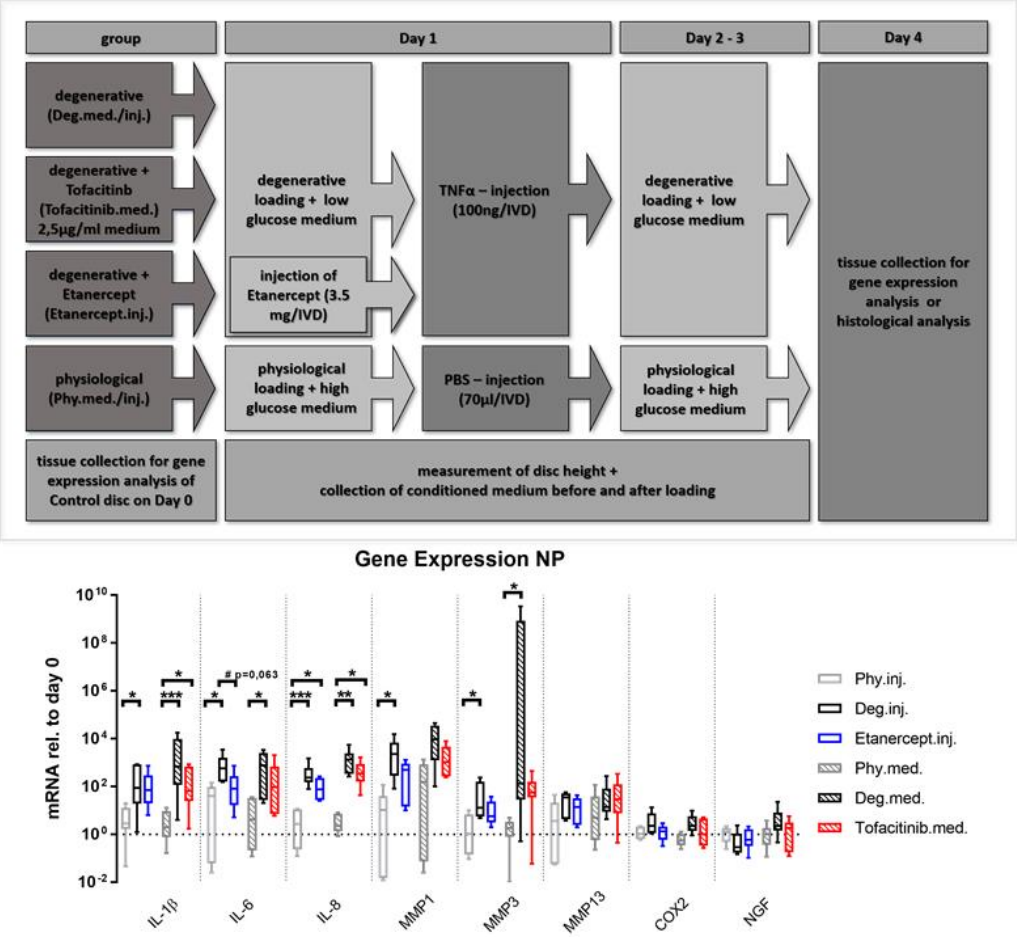


*Figure 10.10.6: (top) experiment design; (bottom) relative gene expression of disc cells in NP tissue. *p<0.05, **p<0.01, ***p<0.001.*

Fund: German 3R Grant, funded by Foundation for the Promotion of Alternate and Complementary Methods to Reduce Animal Testing (SET), EUR 94'000, Period: 2016.04-2019.05.

Pres:

Grad S, Li Z, Heizmann F, Liu Y, Geries J, Kubosch DC, Südkamp N, Alini M, Lang GM. Validation of anti-inflammatory and regenerative drug therapy in a bioreactor-guided intervertebral disc organ culture model. 2018 ISSLS (poster)

Lang G, Gehlen Y, Heizmann F, Kubosch D, Südkamp NP, Alini M, Grad S, Li Z. Validation of anti-inflammatory and regenerative drug therapy in an intervertebral disc organ culture model. 2018 eCM (poster)

Lang G, Wystrach L, Bernstein A, Kubosch D, Südkamp N, Grad S, Alini M, Li Z. The tissue-Renin-Angiotensin-System of the human intervertebral disc. 2018 DKOU (oral)

Gehlen Y, Heizmann F, Kubosch D, Südkamp N, Alini M, Grad S, Lang G, Li Z. Antiinflammatory and anti-degenerative drug therapy as biological treatment for degenerative disc disease. 2018 DKOU (oral)

Heizmann F, Lang G, Liu Y, Geries J, Kubosch D, Südkamp N, Alini M, Grad S, Li Z. Validation of anti-inflammatory and anti-degenerative drug therapy using a bioreactor-guided intervertebral disc organ culture model. 2018 EuroSpine (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 12(4):e2051-e2061, 2018.

Partner:

- Lang G (MD) and Südkamp N (Prof), Albert-Ludwigs-Universität Freiburg, Freiburg, Germany

11 Team Members

Director

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

Vice Director

Alini Mauro	Prof, PhD	01.07.99

ARI Management

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, MPhil	(01.08.95 – 30.09.96)	01.07.05
Steiner Sandra	PhD		01.01.14
Wahl Sonia	Dipl DH Ökonomin HFP		01.12.95
Zeiter Stephan	Dr med vet, PhD	(01.02.00 – 12.05.02)	01.06.03

Scientific & Technical Staff

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, MSc	01.04.17
Basoli Valentina	PhD	01.04.17
Bluvol Mauro	Chemielaborant (Eidg FA[1])	01.06.03
Boot Willemijn	PhD	01.03.17
Brazerol Carmen	Animal Care (Eidg FA[1])	01.03.18
Buschbaum Jan	Dr rer med	01.08.15
Caspar Jan	Poly mechanics	01.01.09
Ciriello Simona	Journal Production Editor	12.09.16
Della Bella Elena	PhD	
D'Este Matteo	PhD	01.04.11
Di Luise Nunzia	PhD	15.06.17
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
Goudsouzian Nora	BSc	01.02.02
Hofmann-Fliri Ladina	MSc ETH	01.10.09
Hofstee Marloes	PhD Candidate, MSc	20.11.17
Kamer Lukas	Dr med, Dr med dent (80%)	21.05.07
Kasper Hermann	Dipl Technician HF Systemtechnik	01.10.18
Keller-Stoddart Iris	MTL Technician (60%)	21.10.09
Lackington William	PhD	02.07.18
Ladner Yann	PhD Candidate, MSc	01.08.18
Lanker Urban	Animal Care (Eidg FA[1])	16.06.86
Li Zhen	Assistant Prof, PhD	01.08.11
Linardi Flavio	Laborant Fachrichtung Chemie (Eidg FA[1])	01.08.15
Ma Junxuan	Dr med, PhD	02.03.17
Menzel Ursula	PhD, Dipl Biol	01.07.11

Mischler Dominic	MSc Medical Technology (06.09.17 - 28.02.18)	01.10.18
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
Post Virginia	PhD (60%)	20.09.10
Rotman Stijn	PhD Candidate, MSc	26.08.16
Schwab Andrea	PhD	01.04.18
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
Wallimann Alexandra	PhD Candidate, MSc	01.02.18
Windolf Markus	Dr biol hum Dipl Ing	01.11.04
Zderic Ivan	MSc ETH	01.02.11
Ziadlou Reihane	PhD Candidate, MSc	01.11.15
Zweifel Erich	European Industrial Engineer EIE	30.11.92

Apprentice

Bärtschi Cecilia	Apprentice	01.08.18
Semere Yemane	Apprentice	01.06.15
Spiller Flurin	Apprentice	01.08.15

Medical Research Fellows

Buchholz Tim	VET Fellow (Germany)	16.04.18
Chen Yan	Research Fellow (China)	01.05.18 – 20.12.18
Du Jie	Research Fellow (China)	24.07.17 – 31.12.18
Escalante Igor	Research Fellow (Venezuela)	01.01.18 – 05.10.18
Fletcher James	Research Fellow (Great Britain)	30.04.18 – 31.10.18
Häckel Sonja	Research Fellow (Germany)	27.09.17 – 17.09.18
Ma Junxuan	Research Fellow Guest (China)	02.03.17 – 28.02.18
Milstrey Alexander	Research Fellow (Germany)	23.07.18
Neumann Verena	Research Fellow Guest (Germany)	17.03.18 – 30.10.18
Panagiotopoulou Vasiliki	Research Fellow (Greece)	03.09.18
Parvan Yanev	Research Fellow (Bulgaria)	01.09.18 – 24.12.18
Penev Preslav	Research Fellow (Bulgaria)	02.07.18 – 31.08.18
Pfannkuche Judith-Johanna	Research Fellow Guest (Germany)	01.11.18
Pötter Naomi	Research Fellow Guest (Germany)	01.05.18 – 31.12.18
Pukalski Yavor	Research Fellow (Bulgaria)	01.09.18 – 24.12.18
Qawasmi Feras	Research Fellow (USA)	01.01.18 – 31.12.18
Sheehy Eamon	Research Fellow Guest (Ireland)	15.01.18 – 13.04.18
Silva Juan Diego	Research Fellow (Colombia)	12.07.18 – 09.11.18
Stenger Valentina	VET Research Fellow (Germany)	01.01.18 – 31.12.18
Wenzel Lisa	Research Fellow (Germany)	01.04.18 – 28.09.18
Westbrock Frederik	Research Fellow Guest (Germany)	15.10.18
Xu Yichi	Research Fellow (China)	29.03.18

Internship

Admiraal Daniëlle	Internship (The Netherlands)	06.09.17 – 28.02.18
Ambrosio Luca	Internship (Italy)	01.09.18 – 02.11.18
Bagnol Romain	Internship (France)	01.06.18 – 31.08.18
Biercher Anika	VET Practica (Germany)	05.03.18 – 29.04.18
Burkhard Benjamin	Internship ETH (Switzerland)	22.10.18
Casty Lino	Internship Guest (Switzerland)	02.07.18 – 10.08.18
Cieciora Lena	VET Practica (Germany)	11.06.18 – 20.07.18
Ciric Daniel	Internship Guest (Australia)	01.09.18
Clamba Ioan-Catalin	Internship (Rumania)	03.04.18 – 31.08.18
Dathathri Eshwari	Internship (India)	16.07.18 – 15.11.18
Fortunato Gabriele Maria	Internship Guest (Italy)	09.04.18 – 30.06.18
Gens Lena	VET Practica (Germany)	29.10.18 – 21.12.18
Hatt Phelipe	Internship ETH (Switzerland)	01.04.18 – 21.12.18
Heumann Maximilian	Internship (Germany)	01.03.18 – 31.08.18
Jahangir Shahrbanoo	Internship Guest (Iran)	18.04.18 – 28.09.18
Jörger Philippa	Internship ETH (Switzerland)	01.10.18
Jucker Tino	Internship ETH (Switzerland)	01.08.18
Kähn Hubertus	VET Practica (Germany)	08.01.18 – 23.02.18
Keller Jessica	Internship (Switzerland)	08.01.18 – 31.08.18
Narayanan Bharath	Internship (India)	18.06.18 – 15.09.18
Pellicciotta Daniele	Internship (Italy)	23.04.18
Stefanovska Despina	Internship (The Netherlands)	12.04.18
Thiemann Luisa	Internship Guest (Germany)	16.10.17 – 28.02.18
Tognato Riccardo	Internship (Italy)	05.02.18 – 31.05.18
Tu Darleen	VET Practica Guest (USA)	01.06.18 – 27.07.18
Vogdanou Stefania	VET Practica (Poland)	02.08.18 – 26.10.18
Wapp Christina	Internship ETH (Switzerland)	01.10.18
Zolfaghar Mona	Internship (Iran)	01.04.18 – 28.09.18
Ziebarth Josephine	VET Practica (Germany)	01.05.18 – 25.05.18

Visiting Professors

Balligand Marc	Biomedical Development (B Gueorguiev), Université de Liège, Belgium (Guest self-funded Sabbatical)	02.10.17 – 31.07.18
Vernengo Andrea	Musculoskeletal Regeneration (D Eglin) Rowan University, Glassboro, NJ, USA (Guest self-funded Sabbatical)	01.07.18

Guest Scientists / Students

Al Saify Ivan	Guest Student (The Netherlands) University of Applied Sciences, The Netherlands	01.09.18
Antunes Bernardo	Guest Student (Portugal) Hebeen University of Jerusalem, Rehovot	04.06.18 – 31.08.18
Arabpour Zohreh	Guest Student (Iran) Tehran University of Medical Science (TUMS)	11.01.18 – 11.07.18
Bordbar Sima	Guest Student (Iran) Tehran University of Medical Science (TUMS)	06.02.18 – 27.07.18
Gehlen Yannik	Guest Student (Germany) Albert-Ludwigs-Universität, Freiburg, Germany	15.08.17 – 16.03.18
Guo Wei	Guest Student (China) Hospital of Sun Yat-sen University Zhongshan, China	01.01.18
Kovermann Niko	Guest Student (Germany) University of Berlin, Germany	25.09.17 – 25.07.18
Mys Karen	Guest Student KU Leuven	12.03.18
Sieberath Alexander	Guest Scientist (Germany) Newcastle University, United Kingdom	18.06.18 – 27.07.18
Vojoudi Elham	Guest Student (Iran) Tehran University of Medical Science (TUMS)	11.01.18 – 11.07.18

Employees left 2018

Scientific & Technical Staff

Berset Corina	Dr med vet	03.08.15 – 31.10.18
Dicht Benno (retired)	Mechaniker (Eidg FA[1])	01.01.78 – 30.09.18
Gieling Fabian	PhD Candidate, med vet	18.04.16 – 28.02.18
Guillaume Olivier	PhD	01.03.15 – 31.05.18
Lezuo Patrick	Dipl Eng	01.08.03 – 15.01.18
Petta Dalila	PhD Candidate, MSc, Biotechnology	01.01.14 – 30.04.18
Schmid Tanja	Dr med vet, Dipl ECVS (80%)	07.01.13 – 31.12.18
von Deimling Christian	med vet	26.02.18 – 26.04.18
Wangler Sebastian	PhD Candidate, Dr med	01.02.17 – 31.12.18
Zhiyu Zhou	PhD	21.03.16 – 28.02.18

[1] Eidg FA = Eidg Fähigkeitsausweis

Guests

Arand Charlotte	Biomedical Development, 05. - 09.03.2018 University Mainz, Collaboration Project
Avci Okan	Biomedical Development (B Gueorguiev), 13.08.2018 Fraunhofer IPA, Project Meeting
Behrendt Peter	Musculoskeletal Regeneration (D Eglin), 01.02. - 31.03.2018 Guest Scientist
Breceda Adam	Biomedical Development, 26.03. - 06.04.2018 New York, USA, Traveling Research Fellow
Brüsch Inga	Preclinical Services (D Arens), 04.06. - 08.06.2018 Medizinische Hochschule Hannover, Practica Large Animal
Cesarovic Nikola	Preclinical Services (S Zeiter), 08.02.2018 Guest
Del Fabbro Lea	Musculoskeletal Regeneration (S Grad), 02.08. - 09.08.2018 Master Thesis
De Salvatore Sergio	Biomedical Development (B Gueorguiev), 24.05. - 25.05.2018 Campus Bio-Medico, University of Roma, Anatomy Lab Spine
Drenka Trivanovic	Musculoskeletal Regeneration/Preclinical (S Verrier, S Zeiter) University Würzburg, Collaboration, Guest, 25.09. - 28.09.2018
Fleischmann Thea	Preclinical Services (S Zeiter), 08.02.2018 Guest
Gabbott Chris	Musculoskeletal Regeneration (D Eglin), 12.02. - 16.02.2018 Guest Scientist
Gaillard Claire	Musculoskeletal Regeneration (M Peroglio), 12.02. - 6.02.2018 INSA Lyon, Collaboration, Guest
Guntli Carina	Musculoskeletal Infection (F Moriarty), 09.-20.07.2018 Student from High School Sargans, Matura work

Herrmann Marietta	Musculoskeletal Regeneration/Preclinical (S Verrier, S Zeiter) University Würzburg, Collaboration, Guest, 24.09. - 28.09.2018
Kellenberger Cedric	Preclinical Services (A Furter), 16.04. - 04.05.2018 Apprentice exchange, Animal care
Keltz Eran	Biomedical Development (B Gueorguiev), 27.10. - 09.11.2018 Rambam Health Care Campus, Haifa, Israel Stephan Perren Fellowship
Matschi Dominik	Biomedical Development (P Varga), 29.08.2018 GOM GmbH, Braunschweig, Germany, Demo measuring technology
Menze Johanna	Biomedical Development, (I. Zderic), 07.12.2018 DePuy Synthes, Zuchwil, Biomechanical Testing
Mora Alberto Jorge	Biomedical Development (B Gueorguiev), 27.10. - 10.11.2018 Hospital Clinico Universitario de Santiago de Compostela, Stephan Perren Fellowship
Moraru Constantin	Musculoskeletal Regeneration (S Grad), 12.02. - 23.02.2018 INSERM, Nantes, Guest Student
Panyasantisuk Jarunan	Biomedical Development (P Varga), 16.02.2018 ETH Zurich, Enhance Project Meeting
Perez Adrian	Musculoskeletal Regeneration (D Eglin), 05.11. - 17.11.2018 CIDETEC, San Sebastian, Collaboration
Perez Barbara	Musculoskeletal Regeneration (D Eglin), 16.04. - 04.05.2018 University of Alcalá, Madrid
Portiaclio Iacopo	Biomedical Development (B Gueorguiev), 24.05. - 25.05.2018 Campus Bio-Medico, University of Roma, Anatomy Lab Spine
Pützler Jan	Musculoskeletal Infection (F Moriarty), 07.05. - 10.05.2018 Guest
Röhrle Oliver	Biomedical Development (B Gueorguiev), 13.08.2018 University Stuttgart, Project Meeting
Rossini Marco	Biomedical Development (B Gueorguiev), 24.05. - 25.05.2018 Campus Bio-Medico, University of Roma, Anatomy Lab Spine
Rupica Giuseppe	Biomedical Development (B Gueorguiev), 24.05. - 25.05.2018 Campus Bio-Medico, University of Roma, Anatomy Lab Spine
Russo Fabrizio	Biomedical Development (B Gueorguiev), 24.05. - 25.05.2018 Campus Bio-Medico, University of Roma, Anatomy Lab Spine
Schaber Thomas	Biomedical Development (P Varga), 29.08.2018 Metiris GmbH, Gebenstorf, Schweiz, Demo measuring technology
Schulze Martin	Biomedical Development (D Gehweiler), 01.03.2018 Project Meeting

Stoffel Janis	Musculoskeletal Regeneration (F Linardi), 23.07. - 12.08.2018 Matura work
Tatti Roberta	Musculoskeletal Regeneration (D Eglin), 12.01 - 31.01.2018 IMEM-CNR, Povo, Guest Student
Trivedi Zubin	Biomedical Development (B Gueorguiev), 13.08.2018 University Stuttgart, Project Meeting
Vadalà Gianluca	Biomedical Development (B Gueorguiev), 24.05. - 25.05.2018 Campus Bio-Medico, University of Roma, Anatomy Lab Spine
Wagner Arndt	Biomedical Development (B Gueorguiev), 13.08.2018 University Stuttgart, Project Meeting
Weitkamp Jan-Tobias	Biomedical Development (I Zderic), 05.02. - 31.03.2018 / 25. - 26.06.2018, Klinik für Mund-Kiefer und Gesichtschirurgie Hamburg, Guest Scientist
Whitaker Weston	Biomedical Development (B Gueorguiev), 21.03.2018, Project Meeting
Zhou Xiaojing	Preclinical Services (D Arens), 22.01. - 29.01.2018 Harbin University, Rongcheng, Vet Practica, Guest Internship

Guest Presentations at AO Center

Feb 05, 2018 Andrea Schwab from University of Würzburg, Germany gave a guest presentation with the title: *Ex vivo* cartilage test system.

Feb 16, 2018 Dr Claire Gaillard from ISPB Faculté de Pharmacy, Université Lyon 1, UMR CNRS 5510/MATEIS Equipe I2B-"Interactions Biologiques et Biomatériaux", Lyon, France gave a guest presentation with the title: 50 shades of biocompatibility: from nanodrug to prosthesis.

April 16, 2018 Dr Barbara Perez Köhler from CIBER-BBN (Department of Surgery, Medical and Social Sciences Faculty of Medicine and Health Sciences University of Alcala, Madrid, Spain gave a guest presentation with the title: Use of biomaterials for abdominal wall repair and strategies for preventing postoperative infections.

July 18, 2018 Herrmann Brugger from EURAC Research, Bolzano, Italy gave a guest presentation with the title: Climatic Chamber Performance.

Aug 13, 2018 Arndt Wagner from University of Stuttgart, Germany gave a guest presentation with the title: Multi-component modelling of biological tissues based on the Theory of Porous Media.
Aug 13, 2018 Oliver Röhrle from University of Stuttgart, Germany gave a guest presentation with the title: Multi-scale continuum-mechanical modelling of the musculoskeletal system.

Aug 24, 2018 Giuseppe Filardo from Rizzoli Research Institute, Bologna, Italy gave a guest presentation with the title: Joint preservation strategies: potential, limitations, and perspectives.

12 ARI Patents

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

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 / Inventor: 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 / Inventor: ARI, M Windolf

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

Device and Method for Real-Time Tracking, Navigation and Manipulation of Bone Fragment, Surgical Instruments, Tools or Implants in Computer-Assisted Surgery ("X-in-1 GO")

- First Application: CH00145/18 filed 2018-07-02
- Case: 10.3567
- Developer / Inventor: J Buschbaum

Surgical power drill including a measuring unit suitable for bone screw length determination ("Autogauge II")

- First Application: CH00945/18 filed 2018-07-31
- Case: 10.3604
- Developer / Inventors: M Windolf, V Varjas, P Varga

13 Publications & Presentations

13.1 2014-2018 Five-year ARI Key Performance Indicators

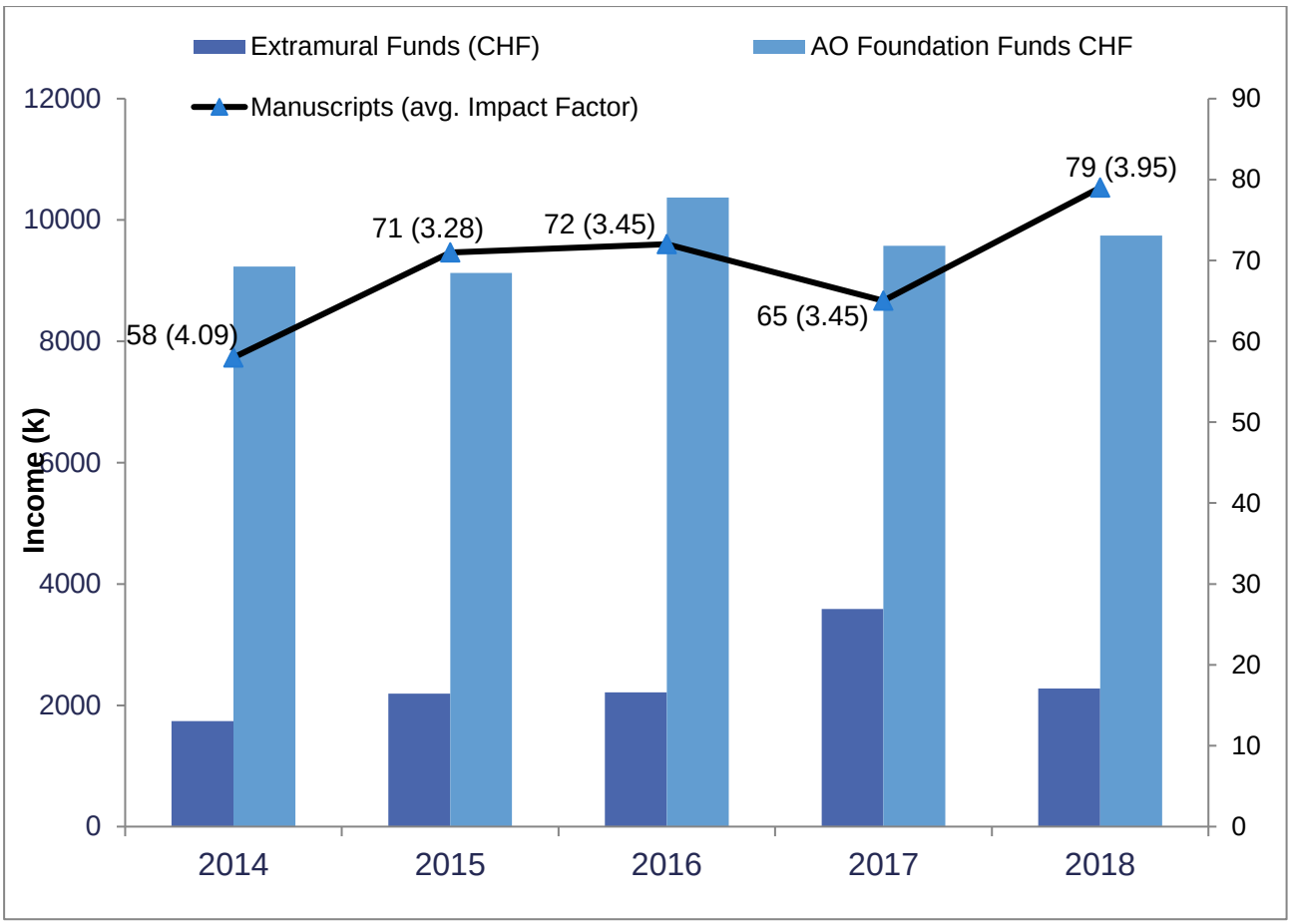


*Figure 13.1.1: ARI five-year KPI's. AO Foundation funds acquired from grants from the Clinical Divisions, AOTK, Strategy Fund and AO Development Incubator (AOPDI) (light blue); Extramural funds (Dark Blue) * 2017 included the costs of hosting TERMIS 2017; Number of manuscripts with impact factor (line) and the average of the whole year's publications impact factor for the ARI (which should be above 2.4).*

13.2 2018 Published peer reviewed papers (epub & in print)

Acevedo C, Stadelmann VA, Pioletti DP, Alliston T, Ritchie RO. Fatigue as the missing link between bone fragility and fracture. Nat Biomed Eng. 2018;2:62-71

Acklin YP, Bircher A, Morgenstern M, Richards RG, Sommer C. Benefits of hardware removal after plating. Injury. 2018;49 Suppl 1:S91-S5.

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13.4 Books

Stoddart MJ, Craft AM, Pattappa G, Gardner OFW (Eds.). Developmental Biology and Musculoskeletal Tissue Engineering. Principles and Applications. Boston: Academic Press / Elsevier; 2018, 1st Edition Paperback ISBN: 9780128114674

13.5 Bookchapters

Gueorguiev B, Moriarty TF, Stoddart M, Acklin YP, Richards RG, Whitehouse MR. Trauma: Principles of fractures. In: Blom A, Warwick D, Whitehouse M (Eds.) 2018. Apley & Solomon's System of Orthopaedics and Trauma 10th Edition. Boca Raton: CRC Press

Gueorguiev-Rüegg B, Stoddart M. Biology and biomechanics in bone healing. In: Buckley R, Moran C, Apivatthakakul T (Eds.) 2018. AO Principles of Fracture Management. Third Edition. Davos, Stuttgart: AOTrauma / Thieme, p. 9-26

Richards RG. Implants and biotechnoloy. In: Buckley R, Moran C, Apivatthakakul T (Eds.) 2018. AO Principles of Fracture Management. Third Edition. Davos, Stuttgart: AOTrauma / Thieme, p. 27-38

Wangler S, Li Z, Grad S, Peroglio M. Intervertebral Disc Whole Organ Cultures: How to Choose the Appropriate Model. In: R. Goncalves, M. Barbosa (Eds.) 2018. Gene and Cell Delivery for Intervertebral Disc Degeneration. Boca Raton: CRC Press.

13.6 Theses / Dissertations

Binder A. Mesenchymale Stammzellen entwickeln durch direkten Zell-Zell-Kontakt mit Endothelialen Vorläuferzellen einen perizytenähnlichen Phänotyp. 2018 Universität Regensburg (Nerlich M, Verrier S) - MD

Clamba I-C. Development of antibiotics loaded injectable carboxymethyl cellulose formulations for treatment of difficult infections in trauma surgery. 2018 University of Montpellier (Nottelet B, Eglin D, D'Este M) – BSc / Master-1

Fortunato G. Design, functionalization and characterization of a bioactive sensing platform to evaluate cell behavior. 2018 University of Pisa (Vozzi G, De Maria C, Serra T, Eglin D) – MSc

Freitag L. The relative effects of age on implant integration in a rat model: a longitudinal *in vivo* microCT study. 2018 Universität Zürich (Fürst T, Stadelmann V, Zeiter S) – DVM

Grad S. Intervertebral disc degeneration: Developments in phenotype markers, biological therapies and organ culture models. 2018 ETH Zürich – Habilitation / PD

Hatt P. Development of 3D perfusable interconnected tubular structures within a biomaterial towards a vascularised *in vitro* bone model. 2018 ETHZ (Ferguson SJ, Serra T, Eglin D) – MSc D-HEST

Heumann M. A Smart Implant for Continuous Monitoring of Spinal Bone Consolidation - Feasibility Study. 2018 University of Applied Sciences Ansbach (Boger A, Hofmann-Fliri L) – BSc

Mischler D. Optimization of a Proximal Humerus Implant by Means of Finite Element Analysis. 2018 ETH Zürich (Ferguson SJ, Varga P) – MSc ETH HST

Ossendorff R. Autologous Chondrocyte Implantation in Osteoarthritic Surroundings - TNFα and its Inhibition by Adalimumab in a Knee-Specific Bioreactor. 2018 Albert-Ludwigs-Universität Freiburg (Salzmann G, Grad S) - MD

Petta D. Development of hyaluronic acid derivatives for applications in biomedical engineering. 2018 University of Twente (Grijpma DW, Eglin D, D'Este M) – PhD

Schmitz P. Fragility fractures of the pelvis - clinical and biomechanical aspects.2018 Universität Regensburg (Nerlich M, Gueorguiev) – Habilitation / PD

13.7 Abstracts published in journals

Arabpour Z, Keller J, Serra T, Alini M, Eglin D, Verrier S. Influence of polymeric adjuvants on the properties of Platelet Rich Plasma gel. Osteologie. 2018;27(2):A55- (SVGO+SBMS/oral)

Arand C, Gehweiler D, Wagner D, Noser H, Kamer L, Richards RG, Sawaguchi T, Rommens PM. Percutaneous retrograde transpubic screw fixation – a statistical analysis of availability, length of the screw corridor and local bone stock based on a 3D statistical model of the pelvic ring. Eur J Trauma Emerg Surg. 2018;44(2 Suppl):S315 (ECTES/oral)

Barcik J, Ernst M, Freitag L, Dlaska CE, Gueorguiev B, Epari D, Windolf M. *In vivo* preclinical application of an active external fixator to investigate the influence of local mechanical conditions on the fracture healing. Biomed Tech. 2018;63:(s1)S161 (BMT/oral)

Eglin D, Geven M, Schmid T, Grijpma D, Bos RRM, Richards RG, Alini M, Guillaume O. Personalised bioactive implant made by stereolithography for orbital floor fracture repair. Bone Joint J. 2018;100-B(Suppl 14, Orthop Proc):132 (EORS/oral)

Frauchiger DA, Tekari A, Benneker LM, Sakai D, Grad S, Stoyanov J, Bertolo A, Gantenbein B. Nucleus pulposus progenitor cells: Isolation and injection into degenerative disc. Global Spine J. 2018;8(3 Suppl):7S-8S (AOSpine Masters Symp 2017)

Frayssinet A, Petta D, Eglin D, D'Este M, Mosser G, Helary C. Development of collagen/hyaluronic acid-tyramine (COLL/THA) composite hydrogels with tunable gelling kinetic and THA content for the treatment of nucleus pulposus. Bone Joint J. 2018; 100-B(Suppl 14, Orthop Proc):96 (EORS/oral)

Gehweiler D, Schulze M, Schultz M, Wähnert D, Müller M, Hartensuer R, Raschke MJ. Prediction of the material properties of vertebral body spongiosa using quantitative computer tomography. Eur Spine J. 2018;27(11):2938 (DWK/poster)

Grad S. Pre-clinical testing of biological therapies for the intervertebral disc using whole organ bioreactors. Bone Joint J. 2018;100-B(Suppl 16, Orthop Proc):113 (EORS/oral)

Gueorguiev B. Why and how do locking plates fail? Bone Joint J. 2018;100-B(Suppl 16, Orthop Proc):81 (EORS/oral)

Günay B, Isa ILM, Conrad C, Scarcelli G, Grad S, Li Z, Pandit A. A hyaluronan-based hydrogel system for annulus fibrosus repair. Bone Joint J. 2018;100-B(Suppl 16, Orthop Proc):119 (EORS/oral)

Haeckel S, Li Z, Yayon A, Hoppe S, Benneker L, Alini M, Grad S. Investigation of hydrogel and growth factors for intervertebral disc regeneration. Osteologie. 2018;27(2):A55 (SVGO+SBMS/oral)

Heizmann F, Lang G, Liu Y, Geries J, Kubosch D, Südkamp N, Alini M, Grad S, Li Z. Validation of anti-inflammatory and anti-degenerative drug therapy using a bioreactor-guided intervertebral disc organ culture model. Eur Spine J. 2018;27(Suppl 5):S679 (EuroSpine/poster)

Hildebrand M, Herrmann M, Gieling F, Gehweiler D, Verrier S, Alini M, Zeiter S, Thompson K. Early prediction of healing outcome in a large bone defect rodent model via microCT. Osteologie. 2018;27(2):A55- (SVGO+SBMS/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 inter-vertebral disc organ culture. Global Spine J. 2018;8(3 Suppl):27S-8S (AOSpine Masters Symp 2017)

Lolli A, Sivasubramaniyan K, Vainieri ML, Eglin D, Wexselblatt E, Yayon A, Grad S, Alini M, van Osch GJ. Hyaluronan-based hydrogel delivering antimiR-221 for the guidance of endogenous cartilage repair. Osteoarthritis Cartilage. 2018;26 (Suppl 1):S163 (OARSI/poster)

Monaco G, Alini M, El Haj AJ, Stoddart MJ. Chondrogenic culture media supplemented with high molecular weight hyaluronan to mimic healthy synovial fluid of the human knee joint. Osteologie. 2018;27(2):A55- (SVGO+SBMS/oral)

Morgenstern M, Vallejo A, McNally D, Moriarty TF, Ferguson J, Nijs S, Metsemakers W. The effect of local antibiotic prophylaxis in open limb fractures: A systematic review and meta-analysis. Bone Joint J. 2018;100-B(Suppl 17, Orthop Proc):89- (EBJIS / oral)

Moriarty TF. The design and preclinical evaluation of antibiotic releasing biomaterials. Bone Joint J. 2018;100-B(Suppl 16, Orthop Proc):33 (EORS/oral)

Pützler J, Zalavras C, Moriarty TF, Verhofstad MHJ, Kates S. Current practices in the managment of open fractures: A worldwide survey among orthopaedic trauma surgeons. Bone Joint J. 2018;100-B(Suppl 17, Orthop Proc):24- (EBJIS / oral)

Schmid T, Nehrbass D, Zeiter S. A refined and clinically more relevant, preclinical osteo-chondral defect model in rabbits. Vet Comp Orthop Traumatol. 2018;31(S 02): A13 (VOS/oral)

Schulze M, Wähnert D, Riesenbeck O, Evers J, Raschke MJ, Vordemvenne T, Hartensuer R, Gehweiler D. The complex loosening mechanisms of pedicle screws in human vertebrae of reduced bone density under physiological gait simulation: an *in vitro* study. Eur Spine J. 2018;27(11):2918-9 (DWK/oral)

Stoddart M. Investigating chondrogenesis under multiaxial load. Bone Joint J. 2018;100-B (Suppl 15, Orthop Proc):53 (EORS/oral)

Wagner D, Kamer L, Sawaguchi T, Noser H, Rommens P.M. Bone mass and length depending on screw pathway in pedicle screw fixation in S1. Eur J Trauma Emerg Surg. 2018;44(2 Suppl):S285-S286 (ECTES/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. Global Spine J. 2018;8(3 Suppl):26S-7S (AOSpine Masters Symp 2017)

13.8 Abstracts (conference presentations)

Acklin Y, Zderic I, Inzana J, Grechenig S, Schwyn R, Windolf M, Richards RG, Gueorguiev B. A new gliding screw concept for plating of proximal humerus fractures. 2018 EFORT (poster)

Acklin Y, Zderic I, Inzana J, Grechenig S, Schwyn R, Windolf M, Richards RG, Gueorguiev B. A new gliding screw concept for plating of proximal humerus fractures. 2018 WCB (oral)

Ahrend M, Noser H, Kanthan S, Kamarul T, Burr F, Richards RG, Kamer L, Gueorguiev B. Evidenz-basiertes Beckenmodell für Forschung, Lehre und Entwicklung auf Grundlage asiatischer CTs und 3D statistischer Modellierung. 2018 DKOU (oral)

Antunes BP, Vainieri ML, Monsonego-Ornan E, Alini M, Grad S, Yayon A. Effects of mechanical stimulation combined with FGF18 on bovine chondrocytes embedded in a novel Fibrin: HA hydrogel. 2018 eCM (poster)

Armiento A, Alini M, Stoddart MJ. New insights into the interplay between Runx2 and protein Rb during fate commitment of mesenchymal stromal cells. 2018 ORS (poster)

Ateschrang A, Stöckle U, Schröter S, Ahrend M. Einfluss der Rupturmorphologie bei primärer VKB Naht mit dynamischer intraligamentärer Stabilisierung (Ligamys). 2018 DKOU (oral)

Barcik J, Ernst M, Freitag L, Dlaska CE, Gueorguiev B, Epari D, Windolf M. An active fixation system to investigate the influence of local mechanical conditions on fracture healing. 2018 GR forscht (poster)

Barcik J, Ernst M, Freitag L, Dlaska CE, Gueorguiev B, Epari D, Windolf M. An active fixation system to investigate the influence of rehabilitation protocols on fracture healing – *in vivo* preclinical application. 2018 Regenerative Rehabilitation Symp (oral+poster)

Basoli V, Della Bella E, Alini M, Stoddart MJ. Role of glucocorticoids during Chondro-genic commitment in mesenchymal stromal stem cells. 2018 TERMIS WC (poster)

Basoli V, Kovermann N, Della Bella E, Alini M, Lischer C, Schmal H, Stoddart MJ, Kubosch EJ. BMP2 and TGFβ differently cooperate to induce chondrogenesis in SDSC under Dexamethasone influence. 2018 GR forscht (oral)

Behrendt P, Ladner Y, Stoddart MJ, Lippross S, Alini M, Eglin D, Armiento AR. Highly tunable di-tyramine hyaluronan hydrogel enables mechanical stimulation of encapsulated mesenchymal stromal cells towards chondrogenesis. 2018 eCM (poster)

Berset CM, Lanker U, Richards RG, Zeiter S. The AO Sheep project: the healthiest European sheep. 2018 GR forscht (oral)

Boot W, Richards RG, Moriarty TF. Challenging Staphylococcus aureus biofilms with different dosing patterns of gentamicin in combination with rifampicin. 2018 ASM on Biofilms (poster)

Boot W, Richards RG, Moriarty TF. Challenging Staphylococcus aureus biofilms with different dosing patterns of gentamicin in combination with rifampicin. 2018 ARB WS (poster)

Ciric D, Rusimov L, Zderic I, Enchev D, Rashkov M, Hadzhinikolova M, Richards RG, Gueorguiev B, Baltov A. Does supplemental intramedullary grafting increase stability of plated proximal humerus fractures? 2018 GR forscht (poster)

Ciric D, Hadzhinikolova M, Zderic I, Enchev D, Baltov A, Rusimov L, Richards RG, Gueorguiev B, Rashkov M. Supplemental dorsal locked plating enhances stability of unstable distal radius fractures. 2018 GR forscht (poster)

Della Bella E, Armiento AR, Menzel U, Stoddart MJ. Identification and selection of MSCs based on early functional markers. 2018 GRC MBB (poster)

Eglin D. Stimuli Responsive Hydrogels for Cellular Microenvironment Engineering. 2018 AFPM (oral)

Eglin D, Tognato R, Giancane G, Alini M, Serra T. Magnetically responsive gelatin methacrylate bioink. 2018 TERMIS WC (poster)

Eglin D, Geven M, Schmid T, Grijpma D, Bos RRM, Richards RG, Alini M, Guillaume O. Osteoinductive composite implant made by stereolithography for orbital floor fracture repair. 2018 TERMIS WC (poster)

Eglin D. Status and future of 3D printing in cranio-maxillofacial surgeries. An AOCMF symposium. 2018 EORS (oral)

Fiole D, Yu B, Pacureanu A, Varga P, Olivier C, Gouttenoire P-J, Langer M, Cloetens P, Peyrin F. Evaluation of bone collagen fibril three-dimensional orientation in nano-CT images using a refined autocorrelation-based method. 2018 WCB (oral)

Fortunato G, De Maria C, Eglin D, Serra T, Vozzi G. Design, functionalization and characterization of a bioactive sensing platform to evaluate cell behaviour. 2018 SSB+RM (poster)

Frauchiger DA, May RD, Zhang X, Stoyanov J, Bertolo A, Benneker LM, Sakai D, Grad S, Tryfonidou MA, Gantenbein B. Comparing three cell isolation techniques for “fishing” angiopoetin-1 (Tie 2) positive progenitor cells from the nucleus pulposus. 2018 eCM (poster)

Gehlen Y, Heizmann F, Kubosch D, Südkamp N, Alini M, Grad S, Lang G, Li Z. Antiinflammatory and anti-degenerative drug therapy as biological treatment for degenerative disc disease. 2018 DKOU (oral)

Gehweiler D, Sermon A, Zderic I, Wahl D, Khatchadourian R, Scherrer S, Gueorguiev B. Fixation strength and cut-out resistance of TFNA helical blades and screws can be increased by bone cement augmentation. 2018 EORS (poster)

Gehweiler D, Schmitz N, Wähnert D, Zderic I, Grünwald L, Richards RG, Raschke M, Gueorguiev B. 3D geometry of femoral reaming. 2018 EORS (poster)

Gomes G, Zderic I, Kojima K, Ahrend M, Lambert S, Belangero W, Richards RG, Gueorguiev B. Biomechanical evaluation of bridged compression plating in humeral shaft fractures using two versus three screws per segment. 2018 WCB (poster)

Gottardi R, Stoddart M. Regenerative rehabilitation: the possibility of leveraging mechanotherapies to optimize regenerative medicine outcomes. 2018 EORS (oral)

Grad S, Li Z, Heizmann F, Liu Y, Geries J, Kubosch DC, Südkamp N, Alini M, Lang GM. Validation of anti-inflammatory and regenerative drug therapy in a bioreactor-guided intervertebral disc organ culture model. 2018 ISSLS (poster)

Grad S, Pandit A. Intervertebral disc biology: from basic science to translation. 2018 EORS (oral)

Gueorguiev B, Noser H, Nilsson J, Voss J, Varjas V, Eglin D, Stoddart M, Kamer L. Virtual modelling and planning workflows for CMF surgery. 2018 BG SOMS (oral)

Gueorguiev B, Ernst M, Schwyn R, Richards RG, Windolf M. Non-Unions: Just a biomechanical problem? 2018 MOA (oral)

Gueorguiev B, Lenz M. Why and how do locking plates fail? 2018 MOA (oral)

Gueorguiev B, Schmitz N, Gehweiler D, Wähnert D, Zderic I, Grünwald L, Richards RG, Raschke M. RIA diameter influences femoral bone strength, fracture geometry and amount of harvested bone graft. 2018 SICOT (oral)

Gueorguiev B, Zderic I, Gehweiler D, Wahl D, Khatchadourian R, Scherrer S, Sermon A. Bone cement augmentation increases fixation strength & cut–out resistance of TFNA helical blades and screws. 2018 SICOT (e-poster)

Gueorguiev B, Zderic I, Inzana J, Grechenig S, Schwyn R, Windolf M, Richards RG, Acklin Y. Development & testing of new gliding screw concept for plating of proximal humerus fractures. 2018 SICOT (e-poster)

Gueorguiev B, Hadzhinikolova M, Zderic I, Ciric D, Enchev D, Baltov A, Rusimov L, Richards RG, Rashkov M. Increased stability of unstable distal radius fractures after supplemental dorsal locked plating. 2018 SICOT (e-poster)

Gueorguiev B, Makelov B, Apivatthakakul T. Supercutaneous LISS Plating of the proximal tibia in a polytrauma patient with 'Floating Knee' injury. 2018 SICOT (e-poster)

Gueorguiev B, Rusimov L, Zderic I, Ciric D, Enchev D, Rashkov M, Hadzhinikolova M, Richards RG, Baltov A. Supplemental intramedullary grafting increases stability of plated proximal humerus fractures. 2018 SICOT (e-poster)

Gueorguiev B, Zderic I, Inzana J, Grechenig S, Schwyn R, Windolf M, Richards RG, Acklin Y. A new gliding screw concept for plating of proximal humerus fractures. 2018 DKOU (oral)

Gueorguiev B, Zderic I, Gehweiler D, Wahl D, Khatchadourian R, Scherrer S, Sermon A. Does bone cement augmentation increase the fixation strength and cut-out resistance of TFNA helical blades and screws? 2018 DKOU (oral)

Gueorguiev B, Rusimov L, Zderic I, Enchev D, Rashkov M, Hadzhinikolova M, Richards RG, Baltov A. Does intramedullary grafting increase stability of plated proximal humerus fractures? 2018 DKOU (oral)

Guillaume O, Geven M, Schmid T, Grijpma D, Bos RRM, Richards RG, Alini M, Eglin D. Novel patient specific implant for orbital floor repair using osteoinductive biomaterials. 2018 SSB+RM (oral)

Guillaume O, Geven M, Schmid T, Grijpma D, Bos R, Richards RG, Alini M, Eglin D. Preclinical evaluation of a composite implant made by stereolithography for orbital floor fracture repair. 2018 ESB (oral)

Guo W, Hu M, D'Este M, Richards RG, Lee P-Y, Alini M, Grad S, Peroglio M. Dualhydrogel network based on hyaluronic acid for intervertebral disc repair: an *in vitro* study. 2018 GR forscht (poster)

Hadzhinikolova M, Zderic I, Ciric D, Enchev D, Baltov A, Rusimov L, Richards RG, Gueorguiev B, Rashkov M. Does supplemental dorsal plating increase stability of distal radius fractures after volar plating? 2018 EFORT (poster)

Hadzhinikolova M, Zderic I, Ciric D, Enchev D, Baltov A, Rusimov L, Richards RG, Gueorguiev B, Rashkov M. Supplemental dorsal locked plating enhances stability of unstable distal radius fractures. 2018 WCB (oral)

Hadzhinikolova M, Zderic I, Ciric D, Enchev D, Baltov A, Rusimov L, Richards RG, Gueorguiev B, Rashkov M. Does supplemental dorsal plating increase stability of distal radius fractures after volar plating? 2018 EORS (poster)

Haeckel S, Li Z, Yayon A, Hoppe S, Benneker L, Alini M, Grad S. Investigation of hydrogel and growth factors for intervertebral disc regeneration. 2018 GR forscht (poster)

Hatt P, Serra T, Eglin D. Optimisation of sacrificial gelatin ink for production of perfusable tubular network in cellularized hydrogel matrix. 2018 SSB+RM (poster)

Helfen T, Siebenbürger G, Fleischhacker E, Biermann N, Sprecher C, Böcker W, Ockert B. CT-gestützte Evaluation des trabekulären Knochens am proximalen Humerus - Eine Methode zur Prädiktion des Komplikationsrisikos nach winkelstabiler Plattenosteosynthese? 2018 DVSE (oral)

Helfen T, Siebenbürger G, Biermann N, Fleischhacker E, Sprecher C, Böcker W, Ockert B. Die CT-gestützte Quantifizierung der Knochenqualität des proximalen Humerus. 2018 DKOU (oral)

Heriot M, Nottelet B, Garric X, D'Este M, Richards RG, Moriarty TF, Eglin D, Guillaume O. Physico-chemical evolution of EPS during antibiotherapy and its potential consequence in Cystic Fibrosis biofilm persistence. 2018 Thesinge Biofilm (poster)

Hildebrand M, Herrmann M, Thompson K, Gieling F, Gehweiler D, Verrier S, Alini M, Zeiter S. Early prediction of healing outcome in a large bone defect rodent model via microCT. 2018 ORS (poster)

Hildebrand M, Herrmann M, Thompson K, Gieling F, Gehweiler D, Verrier S, Alini M, Zeiter S. Early prediction of healing outcome in a large bone defect rodent model via microCT. 2018 GR forscht (poster)

Karppinen J, Koivisto K, Ketola J, Haapea M, Paananen M, Herzig K-H, Alini M, Lotz J, Dudli S, Samartzis D, Risteli J, Majuri M-L, Alenius H, Kyllönen E, Järvinen J, Niinimäki J, Grad S. Serum biomarkers for Modic changes among chronic low back pain patients. 2018 ISSLS (oral)

Korch V, Armiento A, Stoddart M, Schmal H, Südkamp NP, Kubosch EJ. Synovium-derived stem cells as a potential cell source for cartilage repair – the role of mechanical stimulation. 2018 eCM (poster)

Kovermann N, Basoli V, Della Bella E, Alini M, Lischer C, Schmal H, Stoddart MJ, Kubosch EJ. BMP2 and TGF-β differently cooperate during synovial derived stem cell chondrogenesis in a dexamethasone dependant manner. 2018 eCM (poster)

Ladner Y, Behrendt P, Stoddart MJ, Lippross S, Alini M, Eglin D, Armiento AR. Hyaluronan-based hydrogel enables mechanical stimulation of encapsulated mesenchymal stem cells towards chondrogenesis. 2018 GR forscht (oral)

Lang G, Gehlen Y, Heizmann F, Kubosch D, Südkamp NP, Alini M, Grad S, Li Z. Validation of anti-inflammatory and regenerative drug therapy in an intervertebral disc organ culture model. 2018 eCM (poster)

Lang G, Wystrach L, Bernstein A, Kubosch D, Südkamp N, Grad S, Alini M, Li Z. The tissue-Renin-Angiotensin-System of the human intervertebral disc. 2018 DKOU (oral)

Li Z, Zhou Z, Alini M, Grad S. One strike loading organ culture model to investigate the early stage degenerative disc disease condition. 2018 TERMIS WC (poster)

Leite Pereira C, Cunha C, Teixeira GQ, D'Este M, Eglin D, Alini M, Grad S, Barbosa MA, Goncalves RM. SDF-1 mediated-mesenchymal stem cells recruitment: a new perspective for intervertebral disc degeneration treatment. 2018 eCM (poster)

Long R, 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 a collagen gel. 2018 ISL&T (oral)

Ma J, Stefanoska D, van Donkelaar CC, Grad S, Alini M, Peroglio M. Hypoxia in degenerative intervertebral disc promotes neurite outgrowth. 2018 eCM (oral)

Ma J, Stefanoska D, van Donkelaar R, Grad S, Alini M, Peroglio M. Hypoxia in degenerative intervertebral discs promotes neurite outgrowth. 2018 GR forscht (oral)

Meng X, Li L, Lai Y, Grad S, Alini M, Qin L, Wang X. Biphasic bioabsorbale osteochondral scaffold. 2018 eCM (poster)

Monaco G, Alini M, El Haj AJ, Stoddart MJ. Hyaluronan supplemented chondrogenic culture media to mimic synovial fluid behavior of the human knee joint. 2018 ORS (poster)

Monaco G, Alini M, Stoddart MJ. Stem cell-based implant fed with hyaluronan chondrogenic media to mimic synovial fluid behaviour of the human knee joint microenvironment. 2018 eCM (poster)

Mys K, Varga P, Gueorguiev B, Stockmans F, van Lenthe GH. Cone-beam computed tomography can quantify trapezium bone microstructure and stiffness as good as high-resolution peripheral quantitative computed tomography. 2018 WCB (poster)

Pellicciotta D, Richards RG, Alini M, Eglin D, Serra T. A Molecular Dynamics Simulation for 3D-SIM, a Sound-Induced Biofabrication Technology. 2018 Biofabrication (poster)

Petta D, Armiento A, Grijpma DW, Alini M, Eglin D, D'Este M. A tissue adhesive hyaluronan bioink with double gelation mechanism for direct printing into a cartilage defect. 2018 SSB+RM (poster)

Petta D, Grijpma DW, Alini M, Eglin D, D'Este M. A Tyramine-Modified Hyaluronan Bioink With Double Gelation Mechanism for Independent Tuning of Shear-Thinning and Post-Printing Curing. 2018 Biofabrication (oral)

Pützler J, Zalavras C, Verhofstad M, Moriarty TF, Roßlenbroich S, Raschke M, Kates SL, Metsemakers W-J. Strategien der Infektprävention nach offenen Frakturen: Befragung von 1197 Unfallchirurgen weltweit. 2018 DKOU (oral)

Richards RG, Morgenstern M. Orthopaedic device-related infection. 2018 EORS (oral)

Rosenzweig D, Fairag R, Eglin D, Mathieu A, Weber M, Quellet J, Steffen T, Haglund L. Autologous nucleus pulposus cell-seeded hydrogel implantation to isolated human intervertebral discs promotes tissue repair during physiological culture. 2018 ISSLS (oral)

Rosenzweig DH, Fairag R, Mathieu AP, Li L, Eglin D, D'Este M, Steffen T, Weber MH, Quellet JA, Haglund L. Hyaluronan-hydrogel seeded with autologous nucleus pulposus cell regenerates human intervertebral discs in an *ex vivo*, physiological culture model. 2018 eCM (poster)

Rotman SG, Grijpma DW, Richards RG, Moriarty TF, Eglin D, Guillaume O. Biodegradable and bone targeting drug delivery system for antibiotics. 2018 SSB+RM (poster)

Rotman S, Grijpma D, Richards RG, Moriarty TF, Eglin D, Guillaume O. Development of a poly(-caprolactone) bone targeting antibiotic drug delivery system by implementation of alendronate bone seekers. 2018 GR forscht (oral)

Rotman SG, Grijpma DW, Richards RG, Moriarty TF, Eglin D, Guillaume O. Bone seeker-functionalized microparticles as a targeted local antibiotic drug delivery for bone related infections. 2018 Thesinge Biofilm (oral)

Rusimov L, Zderic I, Ciric D, Barcik J, Enchev D, Rashkov M, Hadzhinikolova M, Richards RG, Gueorguiev B, Baltov A. Does supplemental intramedullary grafting increase stability of plated proximal humerus fractures? 2018 EFORT (poster)

Rusimov L, Zderic I, Ciric D, Enchev D, Rashkov M, Hadzhinikolova M, Richards RG, Gueorguiev B, Baltov A. Biomechanical evaluation of conventional versus augmented philos plating using intramedullary grafting. 2018 WCB (poster)

Rusimov L, Zderic I, Ciric D, Enchev D, Rashkov M, Hadzhinikolova M, Richards RG, Gueorguiev B, Baltov A. Does intramedullary grafting increase stability of plated proximal humerus fractures? 2018 EORS (poster)

Sabaté Brescó M, Berset C, Zeiter S, Richards RG, Moriarty F, O'Mahony L. *Staphylococcus epidermidis* infection progression and associated immune response in a murine fracture model: role of IL-17A. 2018 WIRM (poster)

Sabaté Bresco M, Berset C, Zeiter S, Richards RG, O'Mahony L, Moriarty TF. *Staphylococcus epidermidis* infection progression and associated immune response in a murine fracture model: role of biomechanical stability. 2018 asm microbe (poster)

Sermon A, Zderic I, Gehweiler D, Wahl D, Khatchadourian R, Scherrer S, Gueorguiev B. Does bone cement augmentation increase the fixation strength and cut-out resistance of TFNA helical blades and screws? 2018 EFORT (oral)

Schmitz N, Gehweiler D, Wähnert D, Zderic I, Grünwald L, Richards RG, Raschke M, Gueorguiev B. Does RIA diameter influence femoral bone strength, fracture geometry and amount of harvested bone graft? 2018 EFORT (oral)

Schmitz N, Gehweiler D, Wähnert D, Zderic I, Grünwald L, Richards RG, Raschke M, Gueorguiev B. Biomechanical investigation of femoral bone strength after intramedullary bone graft harvesting. 2018 WCB (oral)

Schmitz N, Gehweiler D, Wähnert D, Zderic I, Grünwald L, Richards RG, Gueorguiev B, Raschke M. Influence of the reaming diameter on failure loads of human femora 2018 DKOU (oral)

Schmoelz W, Keiler A, Mayr R, Gueorguiev B, Goetzen M. Improvement of screw anchorage by augmentation, from macroscopic to nanoscopic level. 2018 WCB (oral)

Serra T, Tognato R, Giancane G, Alini M, Eglin D. Magnetically responsive gelatin-based nanocomposite ink for remote control of 3D printed bio-inspired structures. 2018 ESB (oral)

Serra T, Tognato R, Armiento AR, Richards RG, Alini M, Eglin D. Using sound to pattern cells: 3D sound induced morphogenesis (3D-SIM). 2018 ESB (oral)

Serra T, Augurio A, Cortelletti P, Alini M, Eglin D, Speghini A. Non-invasive tracking and manipulation of 3D printed nanoparticles gelatin methacrylate hydrogel. 2018 ESB (poster)

Sprecher CM, Thurner M, Büchler P, Richards RG, Eglin D. Improved post-processing stability of a 3D printed cement paste via co-axial extrusion of organic solvents. 2018 SSB+RM (poster)

Stanic B, Morgenstern M, Thöny S, Konta M, Mercep M, Daiss JL, Schwarz EM, Richards RG, Moriarty TF. Identification and validation of immunogenic peptides of Staphylococcus epidermidis in the patients with bone infection. 2018 WIRM (poster)

Stanic B, Hofstee M, Stylianaki A, Morgenstern M, Richards RG, Moriarty TF, Thompson K. Severe musculoskeletal polytrauma induces reduced anti-bacterial responses in neutrophils. 2018 WIRM (poster)

Stanic B, Pützler J, Morgenstern M, Mercep M, Daiss JL, Schwarz EM, Richards RG, Moriarty TF. Identification and validation of a discrete panel of *S. epidermidis* antigens for the diagnosis of bone infections. 2018 ISSSI (poster)

Stanic B, Puetzler J, Morgenstern M, Mercep M, Daiss JL, Schwarz EM, Richards RG, Moriarty TF. Identification and validation of a discrete panel of S. epidermidis antigens for the diagnosis of *S. epidermidis* bone infections. 2018 PoCDx Symposium (poster)

Stockmans F, Mys K, Varga P, Gueorguiev B, van Lenthe GH. Cone-beam computed tomography can adequately visualize and quantify bone microstructure of the wrist. 2018 ASSH IWIW (oral)

Stoddart M. Bioreactors & bioactive cartilage repair constructs. 2018 ICRS (oral)

Stoddart M. Mechanically induced chondrogenesis differentiation & biomarker discovery. 2018 ICRS (oral)

Stoddart MJ, Monaco G, Alini M. Effect of hyaluronan supplemented culture media on human mesenchymal stem cell chondrogenesis. 2018 ICRS (poster)

Stoddart MJ. Inducing chondrogenesis by multiaxial load: Cell differentiation and biomarker discovery. 2018 eCM (oral)

Stoddart MJ. Mechanical regulation of chondroprogenitor fate. 2018 WCB (oral)

Thompson K, Hildebrand M, Zeiter S, Gieling F, Gehweiler D, Verrier S, Alini M, Herrmann M. Immunological and tomographic characterization of a large bone defect model in rats. 2018 ORS (poster)

Tognato R, Armiento AR, Richards RG, Eglin D, Alini M, Serra T. Using sound for cell assembling: 3D Sound Induced Morphogenesis, 3D-SIM. 2018 Biofabrication (oral)

Tognato R, Armiento AR, Bonfrate V, Levato R, Malda J, Alini M, Eglin D, Giancane G, Serra T. 3D-printing of magnetically-responsive soft-robotics for biomedical applications. 2018 Biofabrication (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. 2018 Endoprothetik (poster)

Vainieri ML, Sivasubramaniyan K, Lolli A, Eglin D, Yayon A, Wexselblatt E, Alini M, Grad S, van Osch G. Hyaluronic acid-based hydrogels promote mesenchymal stem cell ingrowth and cartilage production *in vitro* and *in vivo*. 2018 ICRS (poster)

Vainieri L, Sivasubramaniyan K, Lolli A, Eglin D, Yayon A, Wexselblatt E, Alini M, Grad S, Van Osch G. Novel hyaluronan-based hydrogels to support endogenous cartilage repair. 2018 SSB+RM (oral)

Vainieri ML, Wahl D, van Osch G, Alini M, Grad S. Novel ex-vivo osteochondral model for cartilage repair in mechanical stimulated joint bioreactor. 2018 eCM (poster)

Vainieri ML, Sivasubramaniyan K, Lolli A, Eglin D, Yayon A, Wexselblatt E, Alini M, Grad S, van Osch GJVM. Hyaluronic acid-based hydrogel for cartilage tissue engineering. 2018 GR forscht (oral)

Varga P, Windolf M. Application of validated computational models of proximal humerus fracture fixation to guide clinical practice. 2018 ECCM (oral)

Varga P, Schneider M, Buschbaum J, Joeris A, Röhrle O, Dwyer J, Slongo T, Gueorguiev B. Biomechanical analysis of paediatric long bone growth modulation treatment by patient-specific finite element modelling. 2018 WCB (oral)

Varga P, Inzana J, Hofmann-Fliri L, Südkamp N, Windolf M. Finite element analysis of the optimal cement augmentation strategy for plate fixation of osteoporotic proximal humerus fractures. 2018 WCB (poster)

Varga P. Effect of sclerostin inhibition on bone mechanical properties in a murine model of osteogenesis imperfecta as revealed by micro finite element analysis. 2018 WCCM (oral)

Verrier S, Pereira AR, Barbe L, Alini M. Study of Pericytes potential for bone repair in a perfusable 3D microvascularized model. 2018 TERMIS WC (poster)

Wahl P, Meier C, Dommann A, Neels A, Sprecher CM. Delamination of the hydroxyapatite coating from the stem 14 months after total hip arthroplasty – A case report. 2018 SSB+RM (poster)

Wallimann A, Thompson K, O'Mahony L, Moriarty TF. The influence of microbial-derived metabolites on bone health. 2018 GR forscht (poster)

Wang X, Li L, Huang C, Cao H, Wang J, Li L, Lai Y, Grad S, Alini M, Qin L. A novel 3D printing composite scaffold with phytoestrogenic osteopomotive puerarin for potential bone regeneration. 2018 TERMIS WC (poster)

Wang X, Meng X, Li L, Lai Y, Grad S, Alini M, Qin L. Biphasic biodegradeble osteochondral scaffold. 2018 TERMIS WC (poster)

Wangler S, Peroglio M, Menzel U, Benneker LM, Sakai D, Alini M, Grad S. Homing of mesenchymal stem cells enhances Tie2+ progenitor cells and induces a proliferative response in intervertebral disc organ culture. 2018 ORS (poster)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. CD146 is a marker for stem cells with increased migration potential towards degenerative intervertebral discs. 2018 eCM (poster)

Wangler S, Peroglio M, Li Z, Menzel U, Benneker LM, Richards RG, Alini M, Grad S. Migration of mesenchymal stem cells into degenerative intervertebral discs. 2018 GR forscht (poster)

Weitkamp JT, Benz K, Lippross S, Eglin D, Armiento A, Seekamp A, Kurz B, Behrendt P. Injectable hydrogel versus collagen scaffold: *In vitro* comparison of two clinically applied biomaterials for autologous chondrocyte implantation (ACI). 2018 eCM (poster)

Windolf M, Ernst M, Gehweiler D, Varjas V, Schwyn R, Richards RG, Gueorguiev B. The AO Fracture monitor. 2018 WCB (oral)

Xu Y, Meng H, Eglin D, Peng J, Lu S. Degradation of magnesium alloy and bone formation *in vivo*: micro-CT. 2018 SSB+RM (poster)

Ziadlou R, Grad S, Stoddart MJ, Wang X, Qin L, Barbero A, Martin I, Alini M. Anabolic and anti-catabolic effects of small molecules applied in traditional Chinese medicine for treatment of osteoarthritis. 2018 eCM (poster)

Ziadlou R, Grad S, Stoddart M, Wang X, Qin L, Barbero A, Martin I, Alini M. Screening of small molecules applied in traditional Chinese medicine: towards biological treatment of osteoarthritis. 2018 TERMIS WC (poster)

13.9 Presentations (not in conference proceedings)

19.02.2018 Richards Geoff: "Latest work at the AO Research Institute Davos – with a little history and some of the new projects", Academic Day at Fundacion Santa Fe de Bogota, Colombia (Invited Speaker)

22.-23.04.2018 Richards Geoff: "AO Development Incubator", Musculoskeletal Regeneration Research Network (MRN) Symposium, Hangzhou, China (Invited Speaker)

10.03.2018 Richards Geoff: "Fracture Related Infection", Orthopaedic Research Society (ORS) Annual Meeting, New Orleans, LA, USA (Spotlight Speaker)

24.04.2018 Richards Geoff: "Smart Surgery", 3rd Academic Salon of Guangdong Provincial Key Laboratory of Orthopedics & Traumatology, Shenzhen, China (Invited Speaker)

24.04.2018 Richards Geoff: "Fracture Related Infection", Center for Translational Medicine Research and Development, Shenzhen Institutes of Advanced Technology, CAS, China (Invited Speaker)

28.09.2018 Richards Geoff: "AO Foundation and the latest research developments in smart surgery", ARI-TCBE-TERG Research Symposium, Trinity Centre for Bioengineering, Dublin, Ireland (Invited Speaker)

22.11.2018 Richards Geoff: "Latest Developments at AO in Smart Surgery – the digitization revolution", ICORS session, Chinese Orthopaedic Association, Xiamen, China (Invited Speaker)

07.12.2018 Richards Geoff: "Latest innovative research from AO Research Institute to advance patient care", AOTrauma Course – Advanced Principles of Fracture Management, Davos, Switzerland

16.-18.04.2018 Alini Mauro: "MSC and Complex Loading Pattern for Cartilage Repair", 9th International Workshop on Interfaces: New Frontiers in Biomaterials", Santiago de Compostela, Spain (Invited Speaker)

24.04.2018 Alini Mauro: "Hyaluronan hydrogel platform for musculoskeletal regeneration", Shenzhen, China (Invited Speaker)

26.-28.04.2018 Alini Mauro: "Cell migration into degenerative intervertebral disc: The good and the bad", BioSpine Asia Pacific 2018, Seoul, Korea (Invited Speaker)

13.-16.06.2018 Alini Mauro: "Hyaluronan hydrogel platform for musculoskeletal regeneration", Chemistry for Beauty and Health, Torun, Poland (Invited Speaker)

07.-12.07.2018 Alini Mauro: "ECM for regenerative medicine: hyaluronan hydrogel platform for musculoskeletal regeneration", 43rd FEBS congress, Prague, Czech Republic (Invited Speaker)

16.-18.08.2018 Alini Mauro: "Present and Future Biological Approaches to Human Disc Degeneration", Pittsburgh Spine Summit – Allegheny Health Network, Pittsburgh, USA (Invited Speaker)

23.-26.10.2018 Alini Mauro: "Cell migration into degenerative intervertebral disc: The good and the bad", DKOU, Berlin, Germany (Invited Speaker)

28.11.-01.12.2018 Alini Mauro: "Chemoattractant and stem cells in the regeneration of intervertebral discs", The 3rd National Festival and International Congress on Stem Cell and Regenerative Medicine, Tehran, Iran (Invited Speaker)

26.-28.04.2018 Gueorguiev Boyko: "3D planning in CMF: virtual modelling and planning workflows for CMF surgery", AOCMF Seminar – Trauma Reconstruction, 3rd National Congress of Oral and Maxillofacial Surgery with International Participation, Varna, Bulgaria (Invited Speaker)

09.05.2018 Gueorguiev Boyko: "Biomechanics of bone fracture fixation – metallic implants and techniques", University of Malaya and University Malaya Medical Centre, Kuala Lumpur, Malaysia (Invited Speaker)

10.-12.05.2018 Gueorguiev Boyko: "Metals, ceramics and polymers as biomaterials in medicine – focus on traumatology and orthopedics?", 48th Malaysian Orthopaedic Association (MOA) Annual Meeting, Penang, Malaysia (Invited Speaker)

10.-12.05.2018 Gueorguiev Boyko: "Non-unions: just a biomechanical problem?", 48th Malaysian Orthopaedic Association (MOA) Annual Meeting, Penang, Malaysia (Invited Speaker)

13.05.2018 Gueorguiev Boyko: "Biomechanics of cerclage wiring in periprosthetic fracture treatment", 12th Asia Pacific AOTK Experts' Symposium, Hong Kong (Invited Speaker)

25.-28.09.2018 Gueorguiev Boyko: "Why and how do locking plates fail?", EORS, Galway, Ireland (Invited Speaker)

28.09.2018 Eglin David: "Additive manufacturing for musculoskeletal tissue repair", ARI-TCBE-TERG Research Symposium, Trinity Centre for Bioengineering, Dublin, Ireland (Invited Speaker)

18.06.2018 Grad Sibylle: EUROSPINE EduWeek MODULE 1. SESSION 2: Fundamental Research: Biology of the Lumbar Intervertebral Disc (Education program, Invited Speaker)

18.06.2018 Grad Sibylle: EUROSPINE EduWeek MODULE 1. SESSION 2: Fundamental Research: Cellular and Molecular Research (Education program, Invited Speaker)

11.09.2018 Grad Sibylle: "2Mechanically stimulated tissue culture for evaluation of biologics for cartilage repair", Symposium Shenzhen Institutes of Advanced Technology, Chinese Academy of Science, Shenzhen, China (Invited Speaker)

13.09.2018 Grad Sibylle: "The relevance of organ culture bioreactors for pre-clinical orthopaedic research", Hong Kong University Scientific Seminar, Hong Kong (invited speaker)

28.09.2018 Grad Sibylle: "Pre-clinical testing of biological therapies for the intervertebral disc using whole organ bioreactors, 26th European Orthopaedic Research Society (EORS) Annual Meeting, Galway, Ireland (Invited Speaker)

24.03.2018 Moriarty Fintan: "Large animal models of bone infection", The 10th Clare Valley Bone Meeting in conjunction with Australia New Zealand Bone and Mineral Society (ANZBMS), (Invited Speaker)

24.03.2018 Moriarty Fintan: "Novel antimicrobial approaches to preventing orthopedic device related infection", The 10th Clare Valley Bone Meeting in conjunction with Australia New Zealand Bone and Mineral Society (ANZBMS), (Invited Speaker)

18.09.2018 Moriarty Fintan: "Local antibiotic delivery systems designed for traumatic open wounds", Antimicrobial biomaterials and Biofilm injection symposium, supported by the Sino Swiss Science and Technology Cooperation (SSSTC), Tianjin, China (Invited Speaker)

25.-28.09.2018 Moriarty Fintan: "The design and preclinical evaluation of antibiotic releasing biomaterials", 26th European Orthopaedic Research Society (EORS)Annual Meeting, Galway, Ireland (Invited Speaker)

28.09.2018 Moriarty Fintan: "Local antimicrobial delivery in the prevention and treatment of fracture-related infection", ARI-TCBE-TERG Research Symposium, Trinity Centre for Bioengineering, Dublin, Ireland (Invited Speaker)

25.10.2018 Moriarty Fintan: "The preclinical evaluation of an antibiotic-releasing hydrogel targeting MRSA infection", The Antimicrobial Resistance on Biomaterials Workshop, Empa, St. Gallen, Switzerland (Invited Speaker)

11.03.2018 Stoddart Martin: "Chondrogenesis in response to mechanical load for cartilage repair", Orthopaedic Research Society (ORS) Annual Meeting, New Orleans, USA (Invited Speaker)

09.04.2018 Stoddart Martin: "Mechanically Induced Chondrogenesis – Differentiation & Biomarker Discovery", International Cartilage Regeneration & Joint Preservation Society (ICRS) 2018, Macau, China (Invited Speaker)

11.04.2018 Stoddart Martin: "Bioreactors & Bioactive Cartilage Repair Constructs", International Cartilage Regeneration & Joint Preservation Society (ICRS) 2018, Macau, China (Invited Speaker)

21.04.2018 Stoddart Martin: "Regulating Mesenchymal Stem Cell chondrogenesis: Modulating cell behavior by mechanics", Kyon Symposium, Zurich, Switzerland (Invited Speaker)

25.-28.06.2018 Stoddart Martin: "Inducing chondrogenesis by multiaxial load: Cell differentiation and biomarker discovery", 2018 eCM XVIII: Cartilage & Disc: Repair and Regeneration, Davos, Switzerland (Congress Organizer)

10.07.2018 Stoddart Martin: "Mechanical regulation of chondroprogenitor fate", 8th World Congress of Biomaterials, Dublin, Ireland (Invited Speaker)

22.07.2018 Stoddart Martin: "Mechanical influences on cells of the musculoskeletal system", The Joint Seminar Series, Rush University Medical Center, Chicago, USA (Invited Speaker)

17.09.2018 Stoddart Martin: "Bisphosphonate Related Osteonecrosis of the Jaw – Role of Soft Tissue Healing and Prevention Options", AOCMF 2nd ARONJ Conference, Munich, Germany (Invited Speaker)

26.09.2018 Stoddart Martin: "Investigating chondrogenesis under multiaxial load", 26th European Orthopaedic Research Society (EORS) Annual Meeting, Galway, Ireland (Invited Speaker)

28.09.2018 Stoddart Martin: "Modulating Mesenchymal Stem Cell chondrogenesis by mechanics: Implications for materials design", ARI-TCBE-TERG Research Symposium, Trinity Centre for Bioengineering, Dublin, Ireland (Invited Speaker)

12.10.2018 Stoddart Martin: "Biomechanical regulation of musculoskeletal cell fate: From strain to secretome", 7th Annual Symposium on Regenerative Rehabilitation, Kirkland, Seattle, USA (Invited Speaker)

19.11.2018 Stoddart Martin: "Biomechanical regulation of musculoskeletal cell fate: From strain to secretome", Zentrum für Rheuma- und Knochenerkrankungen, Zürich, Switzerland (Invited Speaker)

22.11.2018 Stoddart Martin: "Advances in Biological Markers for Patient Outcomes", ICORS session, Chinese Orthopaedic Association, Xiamen, China (Invited Speaker)

30.11.2018 Stoddart Martin: "Stress and strain concept in bone healing", 4th Luxembourg Osteotomy Congress, Luxembourg (Invited Speaker)

04.12.2018 Stoddart Martin: "Bone substitutes and advances for enhancing bone healing", AOTrauma Masters Course, Davos, Switzerland (Invited Speaker)

09.12.2018 Stoddart Martin: "Biology of bone healing", AOTrauma Course – Basic Principles of Fracture Management for Swiss Surgeons, Davos, Switzerland (Invited Speaker)

22.06.2018 Zhen Li: "Whole Organ Culture System for Preclinical Investigation of Degenerative Disc Disease Treatments", Musculoskeletal Regeneration Network Meeting, Hangzhou, China (Invited Speaker)

24.06.2018 Zhen Li: "Whole Organ Culture System for Preclinical Investigation of Degenerative Disc Disease Treatments", the 5th Affiliated Hospital of Sun Yat-sen University, Shenzhen, China (Invited Speaker)

24.06.2018 Zhen Li: "Whole Organ Culture System for Preclinical Investigation of Degenerative Disc Disease Treatments", Shenzhen Institutes of Advanced Technology, Chinese Academy of Science, Shenzhen, China (Invited Speaker)

11.09.2018 Zhen Li: "Annulus Fibrosus Repair", Shenzhen Institutes of Advanced Technology, Chinese Academy of Science, Shenzhen, China (invited speaker)

26.11.2018 Zhen Li: "Whole Organ Culture System for Preclinical Investigation of Degenerative Disc Disease Treatments", University of Freiburg, Freiburg, Germany (Invited Speaker)

10.03.2018 Verrier Sophie: "Why I am a Research Scientist", Perry Initiative course "Inspiring young women to be leaders in the field of Orthopedic surgery, Engineering and Research" (within the frame of ORS 2018, New Orleans, USA, Invited Speaker)

04.09.2018 Verrier Sophie: "Development of a perfused on-chip 3D microvascular network", Joint iCEMS ARI Symposium, Kyoto, Japan (Invited Speaker)

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