Research Institute Davos

ARI Activity Report 2021

Education and research. graubünden

Contents

AO Research Institute Davos August 2021 (majority of the team, as some were at external meetings)

1 Introduction

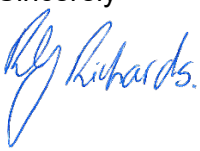
2021 unfortunately like 2020 continued with the onslaught of the COVID 19 pandemic which affected everyone in the world. Within "our" research world, this reduced our face to face meetings of scientists and surgeons to nearly zero, this crushed the chance for youngsters to build their networks, since virtual meetings could never replace real human contact. For the longer term members of ARI, we are lucky that we have made so many real connections in the last decades that we could manage to override this situation, but this must have been extremely difficult for our young researchers. Face to face human contact is so important for our wellbeing, not only in our normal day to day lives but also in our work and our futures.

Our team worked extremely hard on acquiring extramural grants, writing scientific publications, connecting virtually through webinars and regular meetings to the inside and outside world and of course pursuing the research and development within the restrictions of people per lab space etc. This ended up with our largest amount of extramural funding ever (despite the very unfortunate situation that Switzerland stopped negotiations with the EU, causing Switzerland to being removed from applying to many EU networks). We achieved our highest number of publications ever and also our highest average impact factor ever. We are extremely proud of these achievements.

The ARI and newly integrated AO Network Preclinical Research (AO NPR) are a very strong team together, full of experience and huge knowledge. I continue to be extremely proud to lead this team. I am so proud of our mentoring skills keeping the flow of youngsters into this special spirit we have in Davos. Thank you all in the ARI team from the mentors to the mentees.

Thank you also to our partners in the AO Foundation Institutes, clinical divisions, and service groups for your contributions to these great achievements. I also strongly thank the AO network for their clinical advice to our projects, enthusiasm, motivation, and time (especially to our advisors at ARI AC, AO Trauma, AO CMF; AO Spine, AO Vet, AO Development Incubator, AO Strategy Fund and beyond). Without you it would be very difficult to keep the patient's issues at the center of all our thinking working always towards the mission of the AO.

Sincerely



Prof Dr R Geoff Richards FLSW, FBSE, FIOR, FORS, FTERM
Executive Director AO Research & Development
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 has the purpose to advance orthopedic patient care through innovative orthopedic R&D.

Orthopedics concerns musculoskeletal, spine and cranio-maxillo-facial trauma, degenerative musculoskeletal diseases, infections, and congenital disorders.

Goals

- Contribute to 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.

Goal Achievements

- Development & translation of our unique smart surgery concepts: AO Fracture Monitor **In Progress** - in 2021 this continued with the preparatory work for regulatory approval)
- **CE mark achieved** Development and translation of the ARI biphasic plate.
- Establishment of the first European SPF sheep facility (AO Specific Pathogen Free Sheep) **Completed** in 2021. The Biogas facility to produce green energy was built.
- Strengthen and advance our research activities in patient diagnostics and stratification **In Progress**
- Support Mimix Biotherapeutics in valorization of ARI-based biofabrication technology **Achieved** – Bioprinter is now commercially available- Cymatix by Mimics.

Rolling Outlook ARI goals (3 years 2022-2024):

- Translation of the AO Fracture Monitor
- Build up of the SPF sheep flock and use in studies
- Clinical handling of the ARI biphasic plate in collaboration with AO Innovation Translation Centre (AO ITC).
- Strengthen and advance our research activities in patient diagnostics and stratification
- Continue support of Mimix Biotherapeutics in R&D for valorization of ARI-based Sound Induced Morphogenesis (SIM) biofabrication technology.

Rolling Outlook ARI (next 5 years >2026)

- Maintain world-class research level and nurture in-house talents for long-term innovation
- Support AO with cutting edge R&D for clinical problems
- Continue developing ARI technology portfolio. Translate / valorize ARI innovations together with AO technology Transfer office (AO TTO) of the AO ITC.
- Maintain our world-class certifications (ISO, AAALAC, GLP).
- Continue to develop our 3D polymer printing & SIM bioprinting technologies.
- Strengthen project-based research within the ARI
- Strengthen our ARI Focus Areas
- Nurture our scientific networks, global societies (*e.g.,* ORS, TERMIS, ICORS) and European societies we work with (ESB-Biomaterials, ESB-Biomechanics, EORS, TERMIS-EU).

3 Funding Summary

Income Statement	2020 Actual		2021 Actual	
in CHF '000	abs	%	abs	%
AO Foundation Contribution	9'318	73%	10'180	66%
3rd party Income	2'540	20%	3'588	23%
AO Intercompany °	944	7%	1'732	11%
Total Income	**12'803**	**100%**	**15'500**	**100%**
AOTrauma * °°	3'528	28%	2'788	17%
AOSpine*	456	4%	337	2%
AOCMF	648	5%	675	4%
AOVET	20	0%	79	0%
AOTK *	306	2%	389	2%
AO Fundamental Research	1'960	16%	1'332	8%
AO Foundation * °°	3'125	25%	7'430	45%
3rd party projects	2'540	20%	3'588	22%
Total Expenses	**12'583**	**100%**	**16'617**	**100%**
Net Result	**219**		**-1'117**	
* incl. AO Intercompany				
° incl. Internal Revenue				
°° incl. Internal Expenses				

The variance of the net result compared with the budget for ARI of CHF -1,117 K and 11% is mainly caused by the integration of 'Network Preclinical Research (NPR)' with CHF -1,029 K. Excluding this integration, the net result for ARI ends in an overspend of only CHF 88 K or less than 1%.

Income:
Deducting CHF 563 K ARI internal revenue, the income amounted to CHF 4,757 K, which is CHF 377 K higher than budgeted. The good result was achieved due to a higher number of successfully applied 3rd party funded projects (public funding bodies EU and Switzerland) and a big commercial study that was realized.

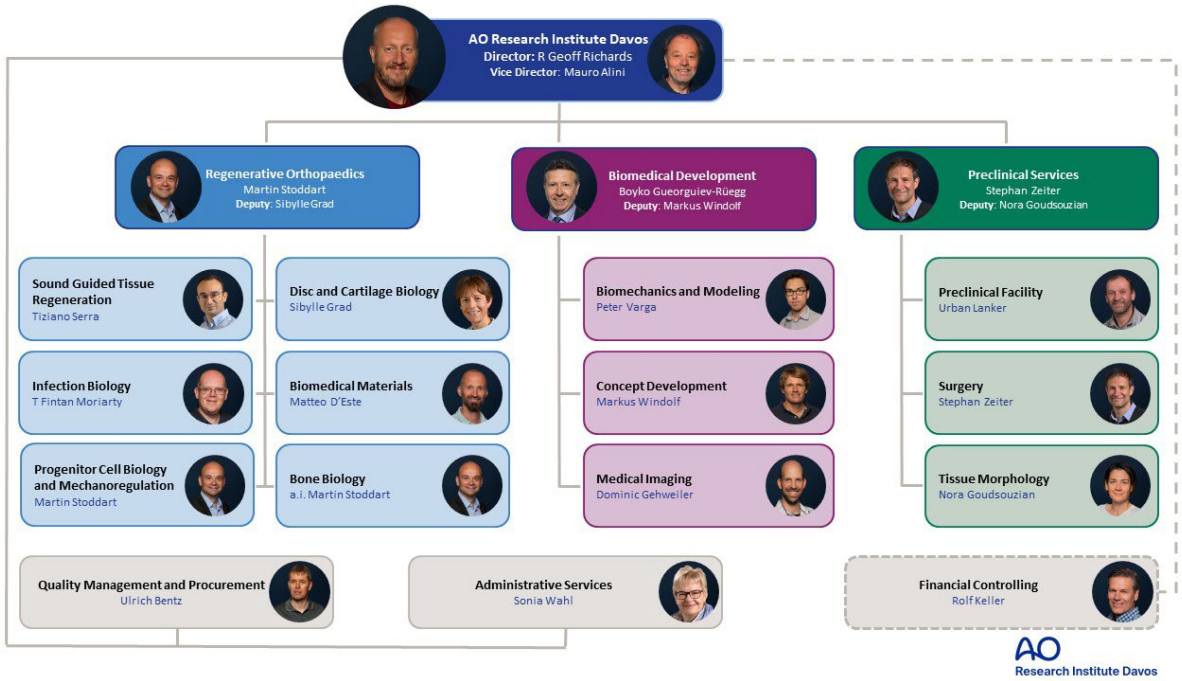
Expenses:
The overspend of CHF 2,057 K on the expenses is driven by the integration of 'Network Preclinical Research (NPR)' with an actual unplanned amount of CHF 1,029 K into the ARI. In addition, 3rd party funded projects generated additionally expenses which were compensated by higher income. Therefore, also the overspend in 'Regenerative Orthopaedics' and 'Preclinical Services' can be explained with additional expenses for mainly material and 3rd party services triggered by the higher number of projects. Due to COVID-19 restrictions savings for travel in all areas occurred but were balanced by higher expenses for maintenance of the aging machinery and rental for the high number of guest researchers who were hosted by ARI during 2021.

The biggest program is 'Regenerative Orthopaedics' with 38% of the total expenses and twice as much staff as the program 'Biomedical Development'. 'Biomedical Development' concluded with 18% and 'Preclinical Services' with 18% of total expenses. The portion of the new integrated NPR is 6% of total expenses.

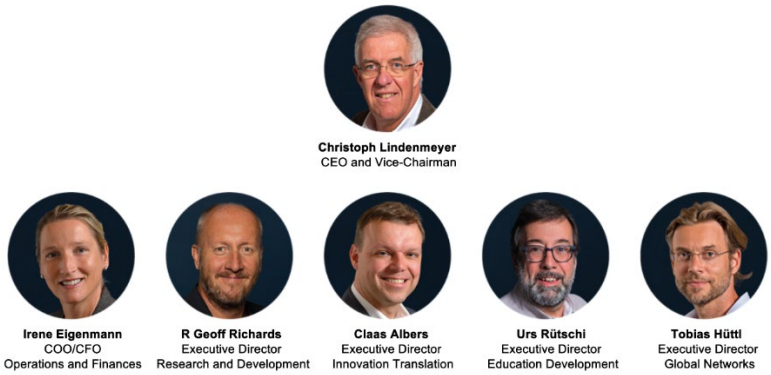
Cost category:
The main cost categories, except NPR, are 'Personnel Expenses' with 62%, followed by 'Material Expenses' with 13% and 'Scientific & Regional Expenses' with 7% of total cost. In NPR the main categories are 'Scientific & Regional Expenses' (external grants) with 61% followed by 'Personnel Expenses' with 27% and 'IT Expenses' (specific software for the R&D Platform) with 10% of total cost.

4 Research Structure & Advisory Committees

4.1 AO Research Institute Davos (ARI) Organigram



4.2 AO Foundation Executive Committee (AOEC)



4.3 AO Foundation R&D Platform

The AO R&D Platform supports the active exchange and mutual discussion about strategies of the AO units with respect to their related goals in R&D. It supports the AO Foundation Board (AOFB) in defining general strategic areas and their implementation in an advisory function. It ensures that relevant activities are in line with the AO Mission and strategies as defined by the AOFB. All research stakeholders are finally accountable to the AOFB. The AO R&D Platform will further develop the strategies and their implementation on behalf of the AOFB in an advisory capacity. It has no funding and decision authority. The R&D Platform is represented on the AOEC by the AO Executive Director of Research and Development. The R&D expert of the AOFB is the Chair of the R&D Platform, currently Prof Anita Ignatius, Director and Chair of the Trauma Research Center Ulm (ZTF), University Hospital Ulm, Germany. A virtual R&D Platform meeting was held in December 2021.

4.4 AO Research Institute Davos Advisory Committee

The AO Research Institute Davos Advisory Committee (ARI AC) provides operational and strategic scientific advice to the ARI on behalf of the AO Foundation Board (AOFB). ARI AC acts as both a sounding board and sparring partner for the Director and scientists of the ARI. The ARI AC 's tasks and responsibilities include advising ARI on:
Portfolio of competences (skills of personnel and type of equipment)
Strategy and priority setting for direct funds of AO Research Institute Davos
Exploratory collaborative research program(s)
Business development and initial advice on technology transfer
Regulatory issues
Use of ARI funds
Advancement of the ARI capabilities, to assure the efficient use of the infrastructure

The AO Research Institute Davos Advisory Committee comprises the following members:
Prof Theodore Miclau (Chair, represents the AO Research Institute Davos Advisory Committee on the AO R&D Platform), Orthopedic Trauma Institute, USA
Prof Chris Evans, Mayo Clinic, USA
Prof Brian Johnstone, Oregon Health and Science University, USA
Prof Joost de Bruijn, University of Twente, the Netherlands

4.5 AO CMF Research Commission

The AO CMF R&D is the international coordination body for all activities of the AO CMF clinical division for research and development of the AO Foundation (AOF). Its mission is to promoting excellence in patient care and treatment outcomes in trauma and musculoskeletal disorders. The AOCMF R&D Commission works closely with the regional craniomaxillofacial-related AO organizations and surgeon network to establish a cohesive global vision and strategy for AOCMF R&D. It supports the coordination between the surgeon network and the central AO functions and services.

AO CMF R&D has focused in building an interdisciplinary team, AO CMF Consortium, to tackle the clinical problem of large bone defect healing, and in parallel also offers funding opportunities for young researchers. This consortium is coordinated by ARI Program Leader and Principal Scientist Prof Martin Stoddart.
The AO CMF Research and Development Commission comprises the following members:
Prof. Eppo Wolvius, AO CMF Research Commission Chair, Rotterdam, The Netherlands
Prof. Andreas Thor, AO CMF Research Commission, Uppsala, Sweden
Dr. Thomas B. Dodson, AO CMF Research Commission member, Seattle, WA, USA
Dr. Lamont Jones, AO CMF NA Research Committee chair, Detroit, MI, USA
Prof. Daniel Buchbinder, AO CMF Technical Commission chair, New York, NY, USA
Dr. Chelsea Bahney, AO CMF Research Commission Guest, Vail, CO, USA
Dr. Catherine Chaussain, AO CMF Research Commission, Paris, France
Prof Martin Stoddart, ARI Program Leader Regenerative Orthopaedics, Davos, Switzerland
Mr. Joffrey Baczkowski, AO Senior Project Manager CMF & Trauma, Dübendorf, Switzerland

4.6 AO Spine Research Commission

AO Spine performs preclinical research in collaboration with the AO Research Institute Davos (ARI). The focus of AO Spine's preclinical research activities is on intervertebral disc (IVD) regeneration and degeneration and postoperative spine infection, led by ARI Vice Director, Prof Mauro Alini, and coordinated by Principal Scientist, Dr Sibylle Grad. The preclinical outcomes are brought to the AO Spine Knowledge Forums, which are international expert-driven clinical study groups, for clinical evaluation. In 2021, there were four preclinical projects being performed:

1. Bioreactor: the establishment of the first-ever bioreactor which houses the culture of a whole IVD with long term physiological loading.
2. Theranostic: the evaluation of biological therapies and diagnostic targets for the degenerative IVD.
3. Printdisc: a translational approach integrating developmental biology and tissue engineering towards regeneration of the annulus fibrosus.
4. Immunospine: an evaluation of the impact of the immune status on the susceptibility to postoperative spine infection.
The AO Spine Research Commission comprises the following members:
Dr. Charles Fisher, Chair, The University of British Columbia, Vancouver, Canada
Dr. Dino Samartzis, Past Chair, Rush University Medical Center, Chicago, IL, USA
Dr. Brian Kwon, AO Spine Knowledge Forum SCI Representative, The University of British Columbia, Vancouver, Canada
Dr. Stephen Lewis, AO Spine Knowledge Forum Deformity Representative, Toronto Western Hospital, Toronto, Canada
Dr. S. Tim Yoon, AO Spine Knowledge Forum Degenerative Representative, Emory University, Atlanta, GA, USA
Dr. Laurence Rhines, AO Spine Knowledge Forum Tumor Representative, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA
Dr. Klaus Schnake, AO Spine Knowledge Forum Trauma Representative, Malteser Waldkrankenhaus St. Marien, Erlangen, Germany
Dr. Nelson Astur, AO Spine Latin America Regional Research Officer, Santa Casa de São Paulo, São Paulo, Brazil
Dr. Daniel Sciubba, AO Spine North America Regional Research Officer, Northwell Health, New York, NY, USA
Dr. Jason Cheung, AO Spine Asia Pacific Regional Research Officer, The University of Hong Kong, Hong Kong, China
Dr. Waleed Awwad, AO Spine Middle East and Northern Africa Regional Research Officer, King Saud University, Riyadh, Saudi Arabia
Dr. Marko Neva, AO Spine Europe and Southern Africa Regional Research Officer, Tampere University Hospital, Tampere, Finland
Prof. Mauro Alini, ARI Representative, ARI Davos, Davos, Switzerland

4.7 AO Trauma Research Commission (AO TRC)

AO Trauma focuses on two main research areas: bone Infection and patient outcomes. AO Trauma research also offers funding opportunities for research that supports clinical issues. AOTRC has also resources for surgeons who are interested in or are already conducting research.

The AO TRC is the international coordination body for all activities of the AO Trauma clinical division for research and development of the AO Foundation. The AO TRC partners with external institutes and funds research projects and clinical studies in collaboration with external institutes as part of consortia within clinical priority programs (CPP).

AO Trauma Research strategy focuses on two fields:

1) To be a knowledge leader, performing large research projects (CPPs) as a consortia with external opinion leaders, experienced clinicians and researchers in collaboration with ARI and AO ITC that help AO Trauma gain scientific knowledge and enhance academic recognition and credibility. Gaining state-of-the-art knowledge serves to promote AO Trauma to maintain its leadership position. To this aim, AO Trauma conducts two CPPs that focus on clinically highly relevant topics. AO Trauma CPP Bone Infection, led by Prof. Stephen Kates (VCU, Richmond, VI, USA) and Prof. Edward Schwarz (Rochester University, NY, USA), and AO

Trauma CPP Patient Outcome lead by Dr. Marylin Heng (MGH, Boston, MA, USA). The approval process for these projects includes the AO RRC (Research Review Commission) process without exception.

2) AO TRC provides individual support to young clinicians to increase awareness of research and provide training in the fundamentals of research processes. Within this framework, the AO TRC offers funding programs for smaller projects. These grants follow the AO Foundation Board guidelines in terms of target group (young clinicians < 40 years), access (open to all Clinical Divisions) and adding a review of the application by the AO VET in case animal tests are planned. Out of this pool of young clinicians, new talents are identified. AO TRC also coordinates research symposiums and offers research fellowships programs.

AOTRC comprises the following members:
Prof. Pol Rommens, AO TRC Chair, Mainz, Germany
Prof. Mandeep Dhillon, AO TAP R&D Committee chair, Chandigarh, India
Prof. Ahmed Kholeif, AO TMENA R&D Committee chair, Cairo, Egypt
Prof. Peter Giannoudis, AO TESA R&D Committee chair, Leeds, UK
Dr. Joshua Gary, AO TNA R&D Committee chair, Los Angeles, CA, USA
Dr. Vincenzo Giordano, AO TLA R&D Committee chair, Rio de Janeiro, Brazil
Prof Geoff Richards, AO Executive Director Research & Development, Davos, Switzerland
Dr. Alex Joeris, AO ITC Head of Clinical Science, Dübendorf, Switzerland

4.8 AO Vet Research Commission

AO VET R&D pursues two main goals with its research activities. First one is to perform research activities that help to gain scientific knowledge and enhance academic recognition and credibility. Gaining state-of-the-art knowledge serves to promote the AO to maintain its leadership position. AO VET R&D also provides individual support to young clinicians to increase awareness of research and provide training in the fundamentals of research processes as well as identifying new talents. The preclinical research activities of AO VET are coordinated at ARI by Dr med vet Stephan Zeiter, Program manager Preclinical Services.

AO VET R&D also supports the other AO Clinical Divisions as an advisory body (Animal Welfare Advisory Committee (AWAC) and AAALAC)

The AO VET Research and Development Commission comprises the following members:
Prof. Kenneth Johnson, AO VET R&D Commission chair, Sidney, Australia
Ass. Prof. Kyla Ortved, AO VET R&D Commission member, Pennsylvania, MI, USA
Dr. Diego Quinteros, AO VET R&D Commission member, Buenos Aires, Argentina
Dr. Junya Ogawa, AO VET R&D Commission member, Kamakura, Japan
Dr. Kevin Parsons, AO VET R&D Commission member, Bristol, UK
Dr. Caroline Constant, ARI Preclinical Services Project Leader, Davos, Switzerland

4.9 AO Research Review Commission (AO RRC)

The AO RRC is an independent peer review body valid for all AO decision-making bodies for grants to all external applicants for AO research funding. The AORRC is assigned jurisdiction over many external AO peer review process, while other internal AO Peer Review Policies and expectations govern specific AO Institute research programs, partnering, internal research contracting, and some limited external research funding processes.

Decision-making bodies are defined as bodies that have funding allocation roles within the AO Foundation, including AO Trauma, AO Spine, AO CMF, AO VET, and their respective Research Commissions (RCs). For ARI Collaborative Research Programs, the decision-

making body is ARI together with the ARI Advisory Committee (ARI AC). For each Clinical Division (CD) research grant, the decision-making body is that respective CD RC.

The chairperson of the AO RRC is David Grainger.

4.10 AO Network Preclinical Research (AO NPR)

The AO Network Preclinical Research (AO NPR) was created in 2021 out of the clinical division's individual research divisions to gain in efficiency and effectiveness with one central team for all external preclinical research. AO NPR is the international coordination group for all external preclinical research activities of the AO. AO NPR manages and supports the global research commissions of the AO Trauma, AO CMF, and AO VET to establish a cohesive global research vision and strategy for AOF worldwide. AO NPR supports coordination between external partner institutes and AO Institutes and works closely with ARI, AO Innovation Translation Center (AO ITC), and AO Global Networks (AO GN).

AO NPR partners with external research institutes and research clinicians to gain additional expertise to strengthen the position of AO as knowledge leader. It has centralization of created knowledge which should enable easy overview of AO research throughout specialties and regions and help prevent redundancy. AO NPR is the entry point for all external research partners for preclinical research. AO NPR promotes excellent research of all AO partners, which are directly or indirectly related with clinical needs in patient care. It helps to strengthen networking among AO clinicians and researchers worldwide, making clinically relevant research attractive for the young generation of AO surgeons.

AO NPR Manages the Clinical Priority Programs (CPP's) of Clinical Divisions and the Research activities of Clinical Divisions AO Trauma, AO CMF, and AO VET together with the AO GN regions. AO NPR manages the research governance of the Research Commissions of the Clinical Divisions AO Trauma, AO CMF and AO VET, the AO R&D Platform, and the AO Research Review Commission (AORRC)

The manager of the team is Philipp Buescher, who was formerly managing the AO Trauma clinical division research.

Team Members: Tania Bosque, Anna Doenz, Anita Anton.

5 ARI Teams / Personnel

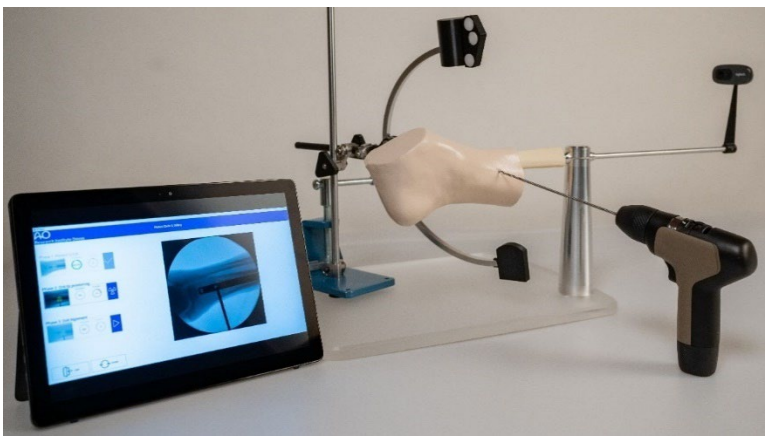
5.1 Biomedical Development

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

Team Members: David Ambühl, Paolo Antonacci, Jan Barcik, Amirsiavosh Bashardoust, Jan Buschbaum, Jan Caspar, Daniel Ciric, Manuela Ernst, Dominic Gehweiler, Maximilian Heumann, Ladina Hofmann-Fliri, Oliver Hüsser, Manuel Knecht, Anna Knill, Elisa Marani, Dominic Mischler, Karen Mys, Simone Poncioni, Magdalena Remppis, Peter Schwarzenberg, Ronald Schwyn, Flurin Spiller, Linda Steiger, Lara Tenisch, Peter Varga, Viktor Varjas, Antoine Vautrin, Celina Wolfisberg, Ivan Zderic Erich Zweifel

Fellows: Philipp Kastner, Torsten Pastor, Firas Souleiman, Kenneth van Knegsel, Luke Visscher
Guests: Emir Benca, Rositza Dimitrova, Cornelius Fritzsche

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 AO Innovation Translation Center, 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. Moreover, digital, and hands-on technologies for surgical training and education are developed.
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.



Digitally enhanced hands on training module for distal nail interlocking to improve surgical skills.

5.2 Preclinical Services

Program Leader: Stephan Zeiter, Deputy: Nora Goudsouzian

Team Members: Daniel Arens, Mauro Bluvol, Carmen Brazerol, Tim Buchholz, Caroline Constant, Peter Erb, Loris Faoro, Pierina Faoro, Andrea Furter, Lena Gens, Nilo Hämmerl, Maria Hildebrand, Urban Lanker, Reto Müller, Dirk Nehrbass, Dominic Perren, Monika Schneider

Fellows: Hella Schwegler, Mai Thanh Vo, James Tapia-Dean
Student Externs: Marie Elisabeth Nehring

The opening of the new facility for specific pathogen free (SPF) sheep was one of our highlights in 2021. After several years of planning, the first AO SPF sheep moved into their new living quarters in September. Over the next years the flock will be enlarged to about 250 sheep. These AO SPF sheep will further reduce and refine ARI`s animal studies demonstrating our commitment to the 3R principle (Replace, Reduce and Refine). This commitment is important as animal studies are a sensitive topic with great responsibility. We also ensure that the generated data of our studies is of high quality. In 2021 we successfully passed all inspections for re-accreditation of our quality management systems (GLP, AAALAC and ISO 9001:2015).
Last year, we worked on over 20 studies in the field of regenerative orthopedics, implant associated infections and implant development involving different models in mice, rats, rabbits, and sheep. Studies under GLP regulations as a part of the legal approval process continue to be an integral part of our work.
Another important aspect is the training of students, fellows, and scientists: Throughout the year, persons were trained in histological techniques and preclinical research with a special emphasis on hands-on experience. We also started a collaboration with the Zurich Integrative Rodent Physiology (ZIRP) at the University of Zurich to exchange surgical expertise in rodent models.
Being active in different societies *i.e.,* the European College of Laboratory Animal Medicine (ECLAM), the Preclinical Model Section at the Orthopaedic Research Society (ORS), the Specialized Veterinarians in Laboratory Animal Science (SVLAS) and the Swiss Laboratory Animal Science Association (SGV), ensures that we pursue best in class policies in the sensitive area of animal models. Further, continued membership to pathology societies such as the European Society of Toxicologic Pathology (ESTP) and the Society of Toxicology Pathology (STP) keeps knowledge in the field of analysis up to date.

5.3 Regenerative Orthopaedics

Program Leader: Martin Stoddart, Deputy: Sibylle Grad

Team Members: Gion Alig, Mauro Alini (Vice Director), Angela Armiento, Romain Bagnol, Cecilia Bärtschi, Valentina Basoli, Ezgi Irem Bektas Tas, Marco Chitto, Elena Della Bella, Matteo D'Este, Nicolas Devantay, Nicola Di Marzio, Sarah Egger, Janick Eglauf, Sina Enzmann, Lara Ettinger, Ciara Ferris, Priscilla Füllemann, Pamela Furlong-Jäggi, Géraldine Guex, Phelipe Hatt, Manuel Herzog, Joseph Hintermann, Marloes Hofstee, Shahrbanoo Jahangir, Thomas Jörimann, Hermann Kasper, Iris Keller-Stoddart, Jessica Keller, Nadine Kluser, Yann Ladner, Zhen Li, Junxuan Ma, Laura Mecchi, Ursula Menzel, Alessia Meyer, Gregor Miklosic, Carina Mini, Fintan Moriarty, Andrea Nüesch, Robert Peter, Simone Poncioni, Virginia Post, Roots Randriantsilefisoa, Aapo Ristaniemi, Andrea Rossoni, Kathrin Schärer, Andrea Schwab, Amra Sercovic, Tiziano Serra, Claudia Siverino, Astrid Soubrier, Christoph Sprecher, Flurina Staubli, Eric Sumrall, Keith Thompson, Win-Hon Trinh, Daphne van der Heide, Andrea Vernengo, Sophie Verrier, Nadja Vonlanthen, Alexandra Wallimann, Leya Weber, Liru Wen, Sylvie Wirth, Jacek Wychowaniec, Taiyo Yamamoto, Donya Ziadlou, Daniele Zuncheddu

Fellows: Samson Arveladze, Susanne Bärtl, Franziska Breulmann, Helen Bumann, Wei Hao, Ensi Zhao

Guests: Teresa Brose, Elena Canciani, Zhenhao Chen, Baixing Chen, Jingzhi Fan, Yanan Fu, Matthias Gruber, Peng Guo, Chen Guoliang, Maria Rosa Iaquinta, Marie Isenmann, Carmen Lanzillotti, Giovanni Lauretta, Kaihu Li, Marika Mosina, Sara Palladino, Babak Saravi, Artemijs Sceglovs, Alexander Sieberath, Jana Vecstaudza

Biomedical Materials Focus Area

The Biomedical Materials focus area is committed to the design of advanced biomaterials and the development of manufacturing technologies to achieve improved patient care and outcome in musculoskeletal disorders. Biomaterials for skeletal repair can provide structural and mechanical features for the filling of defects, be carrier for drugs, cells, and biological factors. One of our goals is to develop 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 macromolecular networks and their processing with controlled architecture and embedded biologics. A second field of research investigates the preparation of hyaluronan-based biomaterials which can be used to deliver drugs and cells. These injectable biodegradable materials have considerable potential in tissue repair and drug delivery. One further area of research is the implementation of structural anisotropy and macromolecular architecture in biofabrication, to increase our capacity to reproduce tissue complexity.

Bone Biology 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 delayed 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* and *in vivo* techniques, the aim of the Bone Regeneration Focus Area is to gain a greater understanding of the immunoregulation, cellular interactions and mediators and underlying mechanoregulation. 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 events in 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 and Cartilage Biology Focus Area

We aim to investigate mechanisms that lead to intervertebral disc (IVD) damage and evaluate novel biological treatments for IVD repair and regeneration. Acute and chronic damage to the IVD are major causes of low back pain. However, factors that contribute to loss of IVD function 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 are 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.

Infection Biology Focus Area

Fracture-related infection (FRI) remains one of the most challenging complications in orthopedic and musculoskeletal trauma surgery. FRI has been convincingly shown to delay healing, worsen functional outcome, and incur significant socio-economic costs. Antibiotic prophylaxis, wound debridement, and postsurgical care can reduce, but not prevent, the incidence of these infections and so novel interventional strategies are required. The musculoskeletal infection team work on *in vitro*, *in vivo* and *ex vivo* studies to better understand, diagnose, prevent, and treat FRI.

A significant portion of the work performed by the Infection Biology team involves collaboration with the preclinical services team in ARI to model FRI in a complex living system and provide robust evaluation of the new interventional technologies under development such as antibiotic loaded hydrogels. This expertise also extends to extramural studies performed with industrial partners to evaluate external innovations in the prevention and treatment of FRI prior to clinical implementation. In parallel to the preclinical *in vivo* evaluations, greater focus has been applied to the opportunities of working with human materials, either *in vitro* through basic cell culture studies and also in clinical studies with patients experiencing FRI. Through partnerships with clinician scientists in the AO network, we have gained access to biological materials from patients with FRI in an effort to more accurately study host pathogen interactions and microbiome studies, as two recent examples.

Progenitor Cell Biology and Mechanoregulation Focus Area

The Progenitor Cell biology and Focus area is particularly interested in stem cell therapies for bone and cartilage that could be applied within a clinical setting. We have been identifying predictive markers of 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, extracellular vesicles, 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.

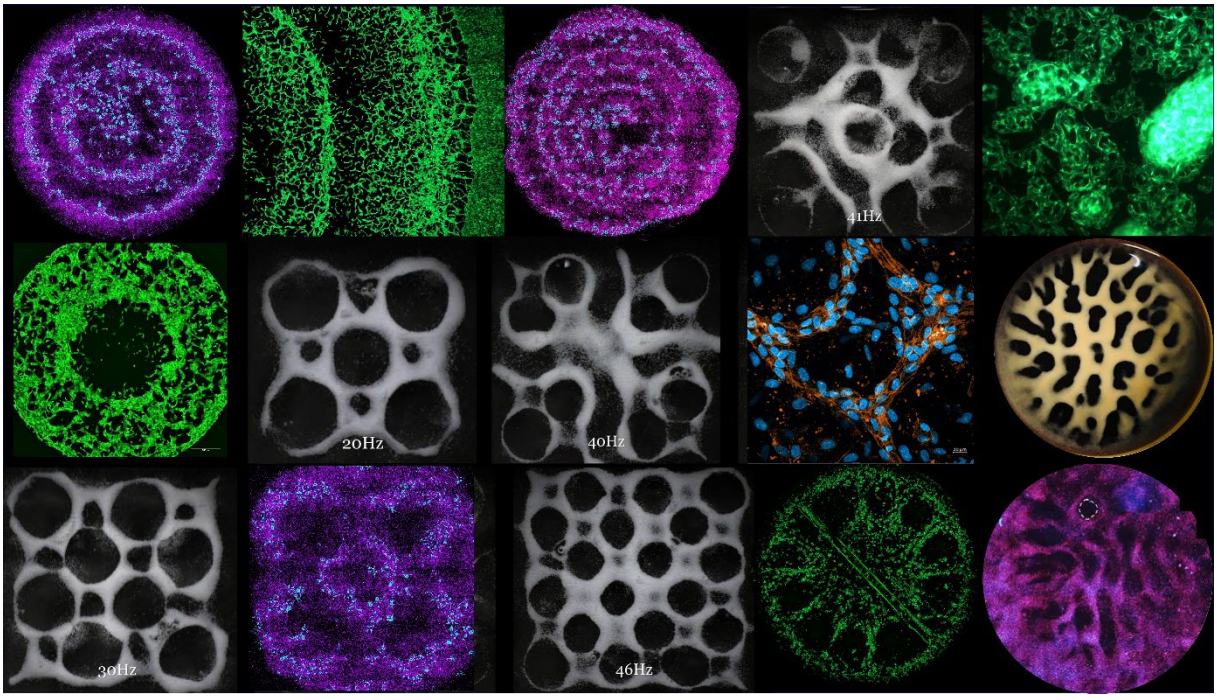
Sound Guided Tissue Regeneration Focus Area

The Sound Guided Tissue Regeneration focus area uses sound waves for repair, regeneration, and diagnostics.

Spatial patterns of cells, organoids, or inorganic particles can be forced on demand using acoustic surface standing waves, such as Faraday waves. This technology allows tuning of parameters (such as sound frequency, amplitude, chamber shape) under contactless, fast and mild culture conditions, for morphologically relevant tissue generation. We call this method Sound Induced Morphogenesis (SIM). We use SIM for morphogenesis induction and further explorations in the regenerative medicine and cell therapy fields.

Our activities are articulated around the translation of innovative biofabrication technologies for the repair of musculoskeletal disorders and development of cutting-edge 3-D *in vitro* disease models for drug screening and personalized medicine. To do that, we use our sound wave-based approach and other extrinsic fields (***e.g.,*** light, magnetic, electric) for contactless cell assembly and stimulation.

Based on this technology, ARI and AODI supported the start-up company Mimix Biotherapeutics which launched the world's first acoustic bioprinter in 2021.



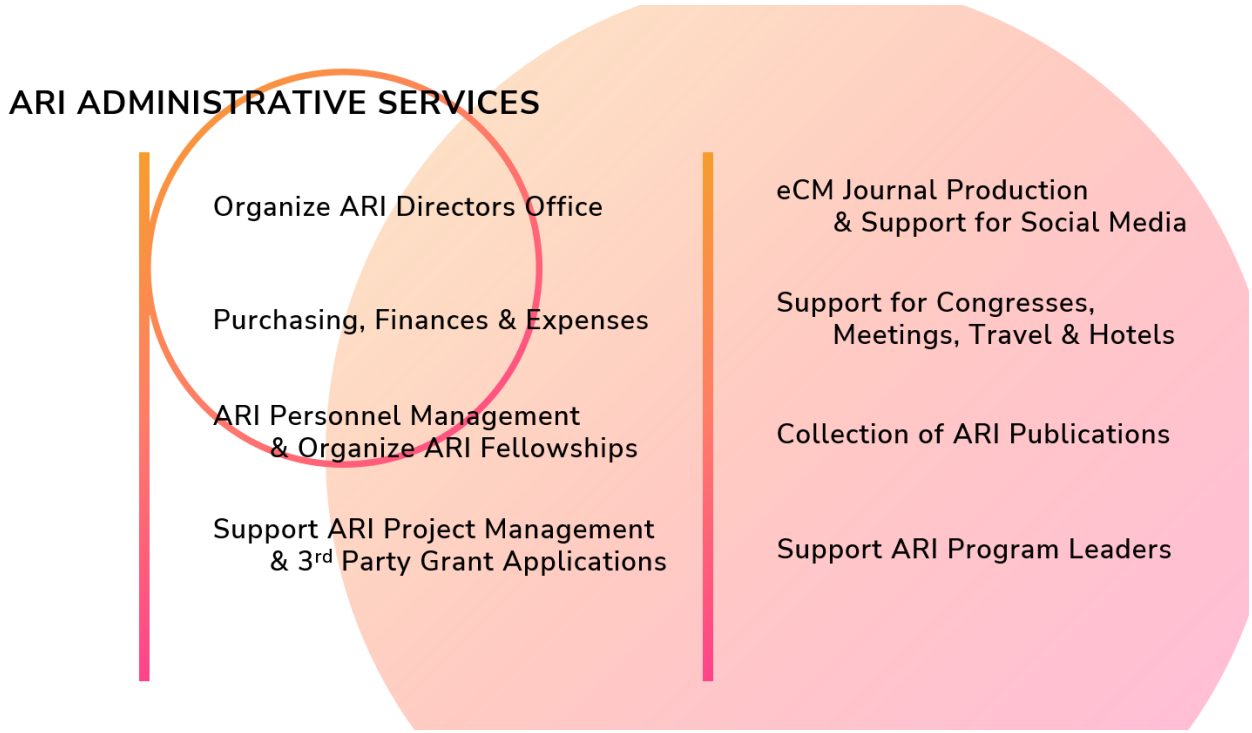
5.4 ARI Administrative Services

Manager Admin Services: Sonia Wahl
Manager Purchasing: Ulrich Bentz

Team Members: Isabella Badrutt, Claudia Barblan, Simona Ciriello, Nunzia Di Luise, Carla Escher, Gregor Müller, Marisa Vivalda

Administrative support services are essential to the operation of any organization. It includes the tasks performed on a day-to-day basis that keep the institute running smoothly and efficiently.

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.



5.5 Operations standard and safety

Quality Manager: Ulrich Bentz

Successful 2021 renewal audit of AO Research Institute Davos

From March 15 to 16 2021, an external auditor from the SQS (Swiss Association for Quality and Management Systems; www.sqs.ch) inspected ARI two days for the recertification audit of the institute. ARI has received the recertification until April 2024 without any non-conformities requiring immediate actions.

The entire AO Research Institute Davos is certified according to the international standard ISO 9001:2015.

Parts of the Biomedical Services Program are additionally certified to develop medical devices according to EN ISO 13485:2016.

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

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 third inspection by Swissmedic took place in May 2021 and ARI has received the renewed statement of GLP compliance on September 30th, 2021, from the Swiss Federal Office of Public Health for the next 3 years.
This is another major achievement for our institute and confirms our commitment to the highest quality standards.
We can offer contract research services to all interested customers under GLP, especially if they want to get their medical devices approved by the FDA.
Since the achievement of the GLP certification all major commercial studies have been conducted under GLP (without pilot studies).

AAALAC international accreditation of Preclinical facility

The Preclinical Facility was first accredited by AAALAC International in early 2013. The Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. AO Research Institute Davos is one of only 4 accredited institutions in Switzerland, and the only accredited academic Research Institute in Switzerland. In November 2021 we had the fourth AAALAC international site visit and got some great comments on our facility. The final confirmation for the renewal of the full accreditation by the AAAALAC International Council on Accreditation arrived February 28th.

6 eCM Journal & eCM periodical

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

eCM Journal (https://www.ecmjournal.org) was arguably the first Not-for-Profit, open access online scientific peer-reviewed journal in the world (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 (and partially subsidized) by the ARI, a Not-for-Profit foundation in Switzerland.
All publications are immediately freely available upon publication. Articles are freely accessible to the public without any embargo period, irrespective of who funded the research. This is equivalent to the 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 (which is also common among journals nowadays), 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), which is visible on the journal's website.

In June 2021, Journal Citation Reports (JCR) announced eCM's 2020 **Impact factor** (IF) to be 3.942. JCR 5-year Impact Factor: 4.784.

eCM is listed in the following JCR categories:

JCR Category	Category Rank	Category Quartile
CELL & TISSUE ENGINEERING *in SCIE edition*	18/29	Q3
ENGINEERING, BIOMEDICAL *in SCIE edition*	30/89	Q2
MATERIALS SCIENCE, BIOMATERIALS *in SCIE edition*	21/41	Q3
ORTHOPEDICS *in SCIE edition*	16/82	Q1

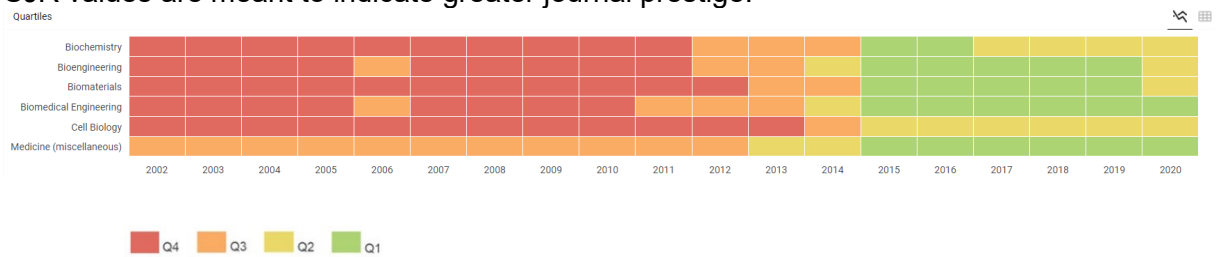
Category	Rank	Percentile
Engineering └ Biomedical Engineering	#50/229	78th
Biochemistry, Genetics and Molecular Biology └ Biochemistry	#92/415	77th

Scopus CiteScore 2020: 6.8. The Scopus CiteScore 2020 measures the average number of citations received in 2017-2020 to documents published in the same time frame.

Materials Science └ Biomaterials	#28/106	74th
Chemical Engineering └ Bioengineering	#39/148	73rd
Biochemistry, Genetics and Molecular Biology └ Cell Biology	#87/279	68th

CiteScore rank 2020

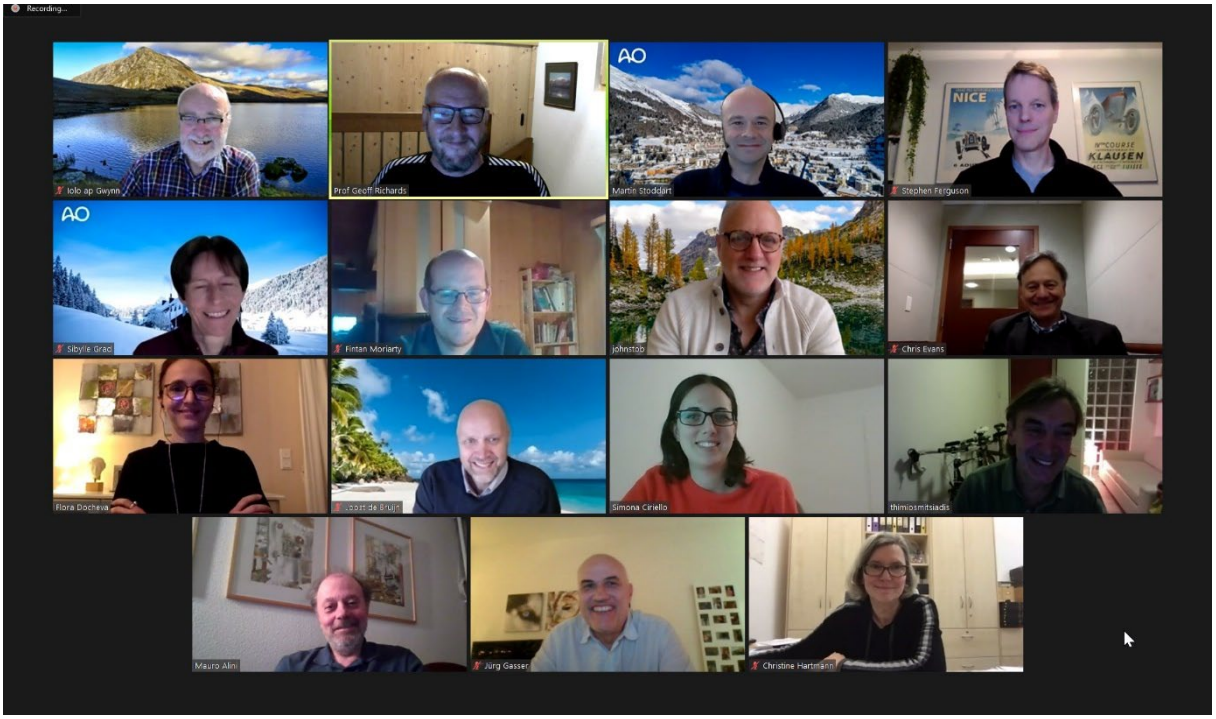
SJR H index: 83. The SCImago Journal Rank (SJR) indicator is a measure of the scientific influence of scholarly journals that accounts for both the number of citations received by a journal and the importance or prestige of the journals where the citations come from. A journal's SJR is a numeric value indicating the average number of weighted citations received during a selected year per document published in that journal during the previous three years. Higher SJR values are meant to indicate greater journal prestige.



eCM publishes preclinical research that has clinical relevance in the musculoskeletal field (Orthopedics, Trauma, Maxillofacial (including dental) and Spine).

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

Special Issues launched in 2021
Tendons and Ligaments Special Issue: This Special Issue provided an up-to-date synopsis on tendon stem/progenitor cell biology under degenerative and regenerative conditions, cell-to-matrix/material interactions controlling cell behavior, 3D niches/models, tendon engineering and biofabrication strategies as well as repair/regeneration models.
Bone Mechanics and Mechanobiology Special Issue: This Special Issue provided a current overview of the complex interplay between the mechanics and biology of bone health, highlighting novel insights across all scales from the protein through the cell to the tissue and organ, afforded by advances in imaging, experimental mechanics, simulation, *in vitro* and *in vivo* model systems.



eCM council meeting in January 2021

eCM Open Access Not-for-Profit online periodical
eCM Periodical (https://www.ecmconferences.org) 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.

6.1 eCM annual conference
Due to the spread of the omicron variant a few days before the start of the conference and consequent governmental travelling restrictions, the eCM XX: Biofabrication for Orthopaedics was cancelled. The abstracts though, having been reviewed, were published.

7 Institutional and Professional Relations

R.Geoff Richards has been Director of the ARI since 2009 (having been at ARI since 1991). He has an appointment as full Professor at the Medical Faculty of Albert-Ludwigs University, Freiburg, Germany (since 2015). He has an honorary Professorship at Cardiff School of Biosciences, Cardiff University, Wales, GB (since 2007). He is a Distinguished Professor at The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China (since 2016). He is a Fellow of: Biomaterials Science and Engineering (FBSE), International Orthopaedic Research Societies (FIOR), Orthopaedic Research Society (FORS), Tissue Engineering and Regenerative Medicine International (FTERM). He was awarded honorary Fellow in 2019 of his alma mater at Aberystwyth University in Wales. In 2020 Geoff was elected Fellow of the Learned Society of Wales (FLSW) (the national academy for arts and sciences of Wales). He has Doctor Honoris Causa from the Technical University of Varna, Bulgaria. In 2017 Geoff co-founded of the International College of Fellows for Orthopaedic Research at the International Combined Orthopaedic Research Societies (ICORS), where he represents AO Foundation as a executive committee member. 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 past president (2022-2024) of TERMIS Global (Tissue Engineering & Regenerative Medicine International Society). He is Chair of International Fellows of Tissue Engineering and Regenerative Medicine (2022-2024). He is Past Chair of the International College of Fellows for Orthopaedic Research (2022-2025) and is a member of the ICORS executive committee. 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 President of Science City Davos. He is the ARI representative to the AOTrauma R&D Commission.

Mauro Alini is Vice Director of the AO Research Institute Davos since 2009 (having been at ARI since 1998). 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), Orthopaedic Research Society (FORS), Tissue Engineering and Regenerative Medicine International (FTERM). He is co-Editor in Chief of the Journal Orthopaedic Research, Spine. He is on the Assistant Editorial Board of the European Spine Journal. He is a member of the Scientific Editorial Board of the eCM Journal. He is also in the international Editorial Board of the Journal of Orthopaedic Translation and Journal Orthopaedic Research. He is the ARI representative to the AOSpine R&D Commission.

Boyko Gueorguiev–Rüegg is program leader of Biomedical Development at the ARI since 2010 (having been at ARI originally in 2003). He is an Honorary Professor at the Technical University of Varna, Bulgaria in the fields of biomedical engineering and biotechnology. He is Vice President of the European Orthopaedic Research Society (EORS). He is honorary Member of the Bulgarian Orthopedic and Traumatology Association and of the Serbian Trauma Association. He is a 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, BMC Musculoskeletal Disorders, and Medicina, 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 the ARI representative to the AOTC System.

Martin Stoddart is a Principal Scientist and Program Leader for Regenerative Orthopaedics at the ARI since 2020 (having been at ARI since 2005). He is a full Professor at the Medical Faculty of Albert-Ludwigs University of Freiburg, Germany. He is 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 Department Health Science and Technology (D-HEST) of ETH Zurich. He is the Chair of the Orthopaedic Research Society (ORS) LearnORS Committee, a member of the ORS Communications Council and a member of the ICORS steering Committee. 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, an editor of BioMed Research International Orthopedics, an editor of Journal of Functional Morphology and Kinesiology, an Associate editor for Frontiers in Bioengineering and Biotechnology, and a member of the Review Editorial Board of Frontiers in Craniofacial Biology. He is the Co-coordinator 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.

Stephan Zeiter is a program manager of the Preclinical Services at the ARI since 2014 (having been at ARI since 2003). He is the president of the European College of Laboratory Animal Medicine (ECLAM). He is a member of the scientific committee of the Swiss Laboratory Animal Science Association. In Davos, he is the co-president of the 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 ARI`s radiation safety officer. He is the ARI representative to the AO Vet Research Commission.

Matteo D'Este is a Principal Scientist and Focus Area Leader for Biomedical Materials at the ARI. He is Adjunct Professor at the Département de génie des mines, de la métallurgie et des matériaux of the Laval University, Québec City, Canada. He is a member of the European Society for Biomaterials Council and of the Executive Committee of the Swiss Society for Biomaterials and Regenerative Medicine (SSB+RM). He is lecturer at the Department Health Science and Technology (D-HEST) of ETH Zurich, teaching Biomaterials for the Skeletal Repair and Advanced Hydrogels for the Practical methods in tissue engineering course. Matteo is member of the eCM Journal International Review Panel.

Sibylle Grad is a Principal Scientist and Focus Area Leader for Disc and Cartilage Biology at the ARI. She is adjunct professor in biomedical engineering at the Department Health Sciences and Technology (D-HEST) of the ETH Zurich, organizer and lecturer of the ETH MSc Course Skeletal Repair and co-organizer of the course Practical Methods in Tissue Engineering. She is a scientific editor for the eCM Journal 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 and associate editor for Frontiers in Bioengineering and Biotechnology. Sibylle Grad is an EUROSPINE EduWeek Faculty member, ICRS Fellow member, and she is Board member of Academia Raetica.

Fintan Moriarty is a Principal Scientist and Focus Area Leader for Infection Biology at the ARI. 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. He is also a member of the Editorial Board of Journal of Orthopaedic Trauma (JOT).

Peter Varga is a Focus Area Leader for Biomechanics and Modeling at the ARI. He is a lecturer of the virtual Tissue Biomechanics Laboratory course within the Master in Biomedical Engineering program at the University of Bern. The University of Bern granted Peter his habilitation in 2021, enabling him to independently teach as Privatdozent for Biomedical Engineering at its Medical Faculty. He is a guest lecturer in the MSc Course Skeletal Repair at the Department Health Science and Technology (D-HEST) of the ETH Zurich. He is an academic editor of the BioMed Research International journal.

Other Professional Relations of ARI team

Daniel Arens is member of the credential committee of Specialized Veterinarians in Laboratory Animal Science (SVLAS).

Angela Armiento was elected member of the ORS International Committee for a 3-year term (2018-2021). She is the ARI representative in the Program Committee of the Graduate School Graubünden AG. Since October 2020 she is the Project Manager for Italian in Zurich within the Native Scientist, a not-for-profit organization with the mission promote and exploit cultural and linguistic diversity in STEM through science outreach for children.

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

Caroline Constant is a member of the Diversity Equity and Inclusion Committee of the American College of Veterinary Surgery (ACVS). She is the co-representative to the AOVET R&D Commission from ARI.

Elena Della Bella is a member of the Teaching Board of the PhD course in Biomedical Sciences and Biotechnology, University of Ferrara (Italy) for the academic year 2021-2022. Elena is Deputy Editor in Basic Science & Molecular Biology for Craniomaxillofacial Trauma & Reconstruction Open Journal (AO CMF journal) and member of the eCM Journal International

Review Panel. She is a member of Tissue Engineering and Regenerative Medicine Society (TERMIS), Orthopaedic Research Society (ORS), and of the ORS International Section of Fracture Repair.
Yann Ladner is a member of the Young Scientists organizing committee of the Swiss Society for Biomaterials and Regenerative Medicine (SSBM+RM). He is also assistant for the Practical Methods in Tissue Engineering MSc course at the ETH in Zurich.

Zhen Li is a Visiting Professor at the Medical School of Shenzhen University, Shenzhen, China. She was elected as Member-at-large of ORS Spine Section Board for a 2-year term (2020-2021). She is the European Development Committee Member of International Chinese Musculoskeletal Research Society (ICMRS). Zhen Li is a member of the JOR Spine Advisory Review Board and eCM Journal International Review Panel.

Junxuan Ma was visiting scientist at the Science Foundation Ireland funded Centre for Research in Medical Devices (CÚRAM) at the National University of Ireland, Galway for 3 months.

Christoph Sprecher is lecturer at the Fachhochschule Graubünden in Chur, at the block course for ETH/ZHAW students at ARI and for Tecday in Zuoz.

Daphne Van der Heide is a member of the Young Scientists of the Swiss Society for Biomaterials and Regenerative Medicine (SSBM+RM). She contributed organizing the 4th Young Scientist Symposium – From Micro To Macro In Biomedicine which replaced the annual SSB+RM meeting in 2021. The event took place at the ETH Zurich, AudiMax.

Sophie Verrier is a board member and the president of the Swiss Bone and Mineral Society (SBMS). She is also a member of the eCM International Review Panel (eCM Journal). She is also co-organizer of topic specific annual eCM conferences.

8 Good News

8.1 New non commercial 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 Professor Oliver Röhrle (University of Stuttgart). Overall 4-year project funding is EUR 8.5 million, ARI funding for project area 'Fluid-solid phase change' is EUR 100'000.

FLAMIN-GO, H2020-NMBP-TR-IND, "From pathobiology to synovia on chip: driving rheumatoid arthritis to the precision medicine goal". Rheumatoid arthritis (RA) is an autoimmune disorder associated with inflammation in the synovial fluid that lines the joints. Response to current drugs is far from optimal. The EU-funded project proposes to overcome conventional clinical trials for testing the efficacy of novel treatment modalities through the development of an organ-on-chip platform. The approach uses patient biopsies to construct 3D models which mimic the complexity of the RA joint and can be tailored for each individual patient. The models should be used for optimal drug identification in less than two months, offering a faster, more cost-effective and ethically sound approach for drug screening. Project partners include Tiziano Serra, Mauro Alini. ARI funding CHF 500’000.

Eurostars project OA-BIO: Life changing therapy for Osteo-Arthritis patients: a biomarker lead approach. The project partners include Zhen Li, Mauro Alini (ARI), in collaboration with Francis Berenbaum (4Moving Biotech, France), Felix Eckstein (Chondrometrics GmbH, Germany), and Marianna Tryfonidou (Utrecht University, the Netherland). Overall 3-year project funding is EUR 2.1 million, ARI funding is EUR 250'000.

OSTASKILLS EU H2020 H2020-MSCA-COFUND-2020. "Holistic training of next generation Osteoarthritis researchers". This EU PhD training mechanism consists of 13 Partners and will run from 2021-2026. ARI funding is EUR 441’000, with Martin Stoddart being involved as WP leader.

NSF Spark: The aim of this work is to develop a 3D printing method for the fabrication of three-dimensional tissue engineering scaffolds with immunomodulatory surface textures to promote healing in chronically inflamed musculoskeletal tissues. The project PI is Andrea Vernengo. Project funding is CHF 100'000.

Innosuisse: NIOXIS aims to develop a compact, proof-of-concept device for real-time monitoring of nitric oxide concentration in joint after orthopedic surgeries. Using an optical nano-sensor technology, this medical device enables continuous monitoring of nitric oxide in a joint related to Osteoarthritis. The project partners are Dr Valentina Basoli (ARI), Dr Vitaijs Zubkov (CSEM) and Prof Ardemis Boghossian (EPFL). Overall, 18 months project funding CHF 489’500, ARI funding is CHF 165'000.

Valentina Basoli was awarded a Scholarship MAS in Translational Medicine and Biomedical Entrepreneurship at Sitem-Insel School, Universität Bern.

Valentina Basoli was awarded the FY2021 JSPS Postdoctoral Fellowship for Research in Japan (short-Term) for the "Study of Epigenetic methylation in health and osteoarthritic cell population into the joints" at University of Kyoto.

BioInspire Sensing: The BioInspireSensing project is a trans-national training network inaugurated to train PhD students, in investigating, building, and producing a new generation of bioinspired implantable sensors of infection through pressure, temperature and acidity. ARI (Fintan Moriarty) will host a visiting PhD student for this project.

C3-Coating: The C3 project is a collaborative and knowledge exchange grant awarded by the KULeuven to Fintan Moriarty, ARI and Prof Hans Steenackers of KULeuven to further test an anti-biofilm technology using the ARI's preclinical testing facility and to transfer the knowledge to the veterinary facility in Leuven, total value CHF 120'000.

HiLo: The HiLo project is a collaborative project with ARI, Fintan Moriarty, funded by the University Hospital Regensburg (Partner, Volker Alt) to investigate the role of virulence factors in *Staphylococcus aureus* fracture-related infection, CHF 45'000.

IsmarD "Smart, Multifunctional Dental Implants: A Solution for Peri-Implantitis and Bone Loss" (NMBP-TR-IND-2018-2020): To address the clinical problem of bacterial biofilm formation and peri-implantitis, the I-SMarD project proposes to develop multi-functional dental implants that can respond to environmental threats such as bacteria by releasing nanoparticles and antibiotics, will match the anatomical characteristics of dental tissues and offer the potential to monitor the healing process after surgery. The project partners include Peter Varga (ARI). Total budget EUR 5.1 million over a project duration of 4 years (2020-2024), the ARI budget is EUR 618'000.

BoneFix: "A Paradigm Shift in Fracture Fixations via On-Site Fabrica-tion of Bone Restoration Patches" (H2020-EICFETPROACT-2019): BoneFix is a new adhesive based bone fixation and restoration technology which aims to supplant metal fixators and transplants as the gold standard in fracture fixation and reconstruction. Total budget EUR 4.0 million over a project duration of 4 years (2020-2024), the ARI budget is EUR 400'000, with Peter Varga involved as WP leader.

8.2 New AO Foundation intramural funding (grants beyond ARI retainer & Clinical Division Research Commission grants)

AO Development Incubator (AODI): 'AO Fracture Monitor – Development Phase'. Main applicant and coordinator of the project is Markus Windolf (ARI). Overall funding is CHF 4.0 million for 4 years. The AO Fracture Monitor was created in ARI and is believed to be a major change to internal fracture fixation in the future.

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

AO Development Incubator (AODI): 'Growth modulation implant'. Main applicant and project coordinator is Markus Windolf (ARI). Overall funding is CHF 1.6 million for 4 years. Novel implant approach to significantly improve treatment of growth deformities in children.

AO Strategy Fund (AOSF): 'OSApp: Virtual osteosynthesis tool for surgical education'. Main applicant and coordinator of the project is Peter Varga (ARI). Project funding is CHF 522'000 for 2.5 years.

AO Strategy Fund (AOSF): 'Digitally enhanced hands-on surgical training'. Main applicant and coordinator of the project is Jan Buschbaum (ARI). Project funding is CHF 482'000 for 3 years.

AO Development Incubator (AODI): Antibiotic loaded hydrogel for infection prophylaxis in open fractures. Investigators: Fintan Moriarty, Matteo D'Este and Andrea Montali. Overall project funding is CHF 400'000 for 2 years.

8.3 New SPF Facility

Opening the doors to Europe's first specific pathogen free (SPF) sheep flock at the ARI. The sheep facility opened in August 2021 with the first 24 sheep free of specific pathogens, into their new safe, spacious, and highly protected living quarters in Davos which will be enlarged to a flock of over 200.

The pre-inauguration gave invitees a one-time chance to tour the facility, before all areas get disinfected, and it then officially closes to all but the sheep and their caregivers. All were impressed with the state-of-the-art, 6,575-square-meter zone expansion that is due to house the world's first SPF flock of sheep outside of North America this September. Beyond the impressive facilities, this expansion fulfils the community's clear commitment to be global research leaders and continues to put Davos on the map within Science City Davos. This facility and indeed the flock themselves will fulfill an unmet need in Europe and beyond while maintaining the highest principles of animal welfare. It will achieve this, according to Richards, through the use of SPF sheep, and careful breeding, that in turn will reduce and refine animal experiments. "The AO, whenever possible, uses other means to develop new treatments that do not involve animals (in silico, in vitro and ex vivo) and strongly follows 3R principles to reduce, refine and replace animal experiments where possible. Despite this, there is a need to use animals in preclinical research before treatments can be applied to help both human and animal patients. We do this with care, caution, and respect, minimizing the burden on the animals," Richards said.

When preclinical research into bone fractures and therapies involving animals is needed to ensure that new treatments are effective and safe, sheep are often selected because the healing of a fracture is very similar in sheep and humans.

SPF animals are better than non-SPF animals for such research, as they are free of certain pathogens that the animal could carry without showing clinical symptoms. Once sheep are part of a study, a disease could break out and either, in the worst case, result in losing the animals, or affecting the outcome of the study, as the sheep would have to fight the disease. Further, certain pathogens can also infect humans. Hence the desire to use SPF sheep in studies. Animal welfare has always been, and remains, central to the AO and ARI, therefore SPF animals used in research also follows this, as Zeiter explains "Sheep without underlying diseases not only increase the reproducibility and safety for the sheep and humans, but we will use fewer sheep in research because there is less variability involved".

Breeding SPF sheep comes with many challenges. Lambs must initially be delivered by caesarean section and thoroughly examined to ensure that they do not have diseases transmitted in the womb or acquired at birth through the birth canal. They then need to be carefully separated from other animals that could carry the pathogens. A biosecurity barrier, quarantine zone, easy-to-clean walls and installations will help keep the necessary hygiene.

During the tour, Lanker, Manager Preclinical Facility at ARI, explained how important both the breeding process as well as designing the unique facilities are, and how they broke new ground in ensuring the highest quality and standards to ensure lambs delivered by C-section are healthy and beyond as they grow. The facility has ventilation systems that adapt to the temperature conditions outside, while the lighting is also programmed to give natural light cycles, rendering the whole facility as open air and natural as possible including a spacious open-air plan. During the tour, Lanker demonstrated how the facility is set up to ensure the highest levels of hygiene. Instruments and machines are disinfected beforehand and only used in the hygiene zone, caregivers must also take special precautions for example changing clothes and taking either traditional water or an air shower.

Biogas facility adjacent to the new SPF facility

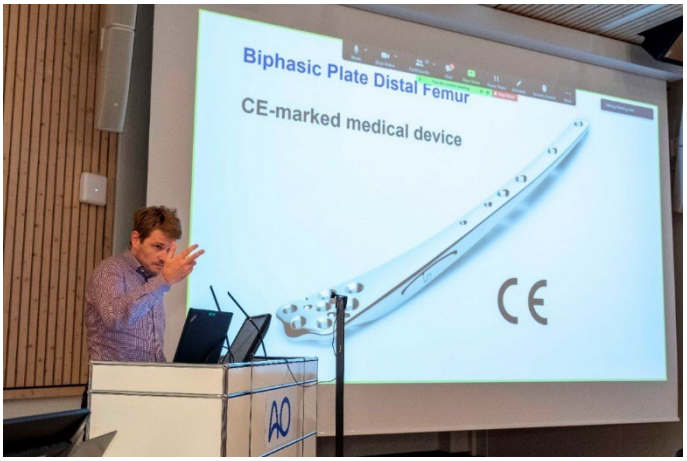
Built into this facility is a biogas project that will reduce methane output to the atmosphere and churn out renewable green energy and heat. The unit will utilize the sheep dung as well as grass cutting from non-agriculture areas. Further, solar panels were installed on the biogas unit producing even more green energy. Richards sees this adjacent biogas facility as an exciting future motivator for the next generation “We will invite local schools on a yearly basis to visit our biogas unit to help motivate the young generations to the power of renewable energy and to encourage local farmers to consider this process for their farms."

Once open, the facility will house over 200 sheep, the biogas unit including solar panels will produce energy and heat not only for the SPF facility but also for the adjacent preclinical facility. There will be power stations to charge the machines used within the facility, as well as electrical cars. Finally, the remaining product can still be used as a high-quality (methane-free) fertilizer.

During the excavation of an old Davos town dump from the 60's and 70's interesting articles were found that would be recycled nowadays. The color of the newspaper was almost immaculate from the day it was printed, but the fashion has certainly changed.

8.4 Biphasic Plate receives CE Mark

As brainchild of ARI Focus Area Leader Markus Windolf and QUT Associate Professor Devakar Epari (Brisbane, Australia), the biphasic plating principle finally matured into a fully fledged medical device. In close collaboration with the AO Innovation Translation Center and 41medical AG as legal manufacturer, the Biphasic Plate Distal Femur received CE certification for clinical use in Europe in April 2021. An unprecedented success for the project team and for the AO. Case collection is now the consequent next step for proving the clinical value of the concept.



Markus Windolf elaborating on the CE marking of the Biphasic Plate Distal Femur during AO Davos Courses 2021.

Core project team from ARI, QUT and 41medical AG in Bettlach, Switzerland.

8.5 Awards

Profs R Geoff Richards and Mauro Alini named as 2021 Fellows of the Orthopaedic Research Society (FORS)

Profs R Geoff Richards and Mauro Alini were honored as 2021 fellows of the Orthopaedic Research Society (ORS) during its virtual annual meeting on February 15.
ORS Fellows, selected by the ORS Board of Directors, are longstanding ORS members who have demonstrated exemplary service and leadership, substantial achievement, expert knowledge, and significant contributions to the ORS, its governance, and the field of musculoskeletal research.

Fellows are thought leaders and experts in their respective disciplines and serve as role models in the ORS community and in the field of musculoskeletal research exemplifying the core values of the Society. Longtime ORS members Richards and Alini have had numerous roles within the society, including various committee memberships.

JOR Spine Early Career Award

Prof Zhen Li has been awarded the JOR Spine Early Career Award. With support from the ORS Spine Section, the JOR Spine Early Career Award is designed to recognize the "rising stars" in the field of Spine research and highlight their outstanding work published in the JOR Spine journal.

Racquel LeGeros Award

Gregor Miklosic and Daphne Van der Heide both from ARI have been awarded the Racquel LeGeros Award of the European Society for Biomaterials (ESB). This award is given to two graduate students per year who would like to pursue their research in International or European academic laboratories or companies dedicated to biomaterials and regenerative medicine, with the aim to increase their knowledge in a specific topic and /or a technology. The award is assigned by a committee in the ESB Council.

Free Paper Award Trauma

Torsten Pastor, Ivan Zderic, Dominic Gehweiler, Matthias Knobe, Boyko Gueorguiev, Biomechanical analysis of recently released cephalomedullary nails for trochanteric femoral fracture fixation in a human cadaveric model, Virtual EFORT Congress, Vienna, Austria, 30 June-2 July (2021).

Best Poster presentation

Nicola Di Marzio and Nadine Kluser have been awarded the best poster presentation at the 4th Young Scientist Symposium (SSB+RM) - From Micro to Macro in Biomedicine. Zurich. 07.10.2021

8.6 ARI new MOU's (Memorandums of Understanding)

Due to the COVID Pandemic and lack of travel no new MOU's were undertaken in 2021.

8.7 New Board Positions

Prof R Geoff Richards appointed president of Science City Davos

ARI Director R Geoff Richards has taken over the role as president of Science City Davos at the start of 2021. Richards has been actively involved with Science City Davos for a number of years, serving as vice president from 2015 to 2021 and as a member of Science City Davos and Executive Committee of Science City Davos since 2013.

Science City Davos is a small society striving to promote and expand the global reputation of Davos as a pioneering center of excellence and innovation in research and education. The society fosters a close connection between the various high-level institutes, schools, societies, hospitals, and rehabilitation centers in Davos, raising public awareness and foregrounding their role as central economic pillars in the Canton of Grisons. The society collaborates with sister societies such as Academia Raetica and Natural sciences Davos (Naturforschende Gesellschaft Davos, NGD) and other interested parties, including the University of Applied Sciences of the Grisons, which is a member. As president, Richards has already set several goals for diversity, inclusion, and public awareness, launched a LinkedIn site, initiated a collaboration with empowerment lab and focused the duties within the governing board.

Dr Matteo D'Este, Principal Scientist and Focus Area Leader Biomedical Materials was elected to the council of the European Society for Biomaterials (ESB)

This election indicates how ARI's reputation in the Biomaterials field is well recognized at international level and consolidates ARI's connection with the ESB. The late Prof Berton Rahn was one of the founders of this society in the 70's and this new appointment helps keep the strong connection.

8.8 Habilitation

Dr Peter Varga, leader of the Biomechanics and Modeling Focus Area at the ARI, has received his habilitation from the University of Bern's Faculty of Medicine. The qualification is a recognition of Peter's contributions to teaching and research in the field of biomedical engineering. It also allows him to teach at the university independently as a private lecturer. Peter was granted his habilitation on the basis of his academic achievements as well as his research activity. Proof of previous collaboration with the University of Bern was also a prerequisite. Apart from having acted as responsible lecturer for the Tissue Biomechanics Lab course since 2018 within the university's Biomedical Engineering master's program, Peter also engaged in several joint projects with Prof Philippe Zysset's research group at the ARTORG Center for Biomedical Engineering Research in recent years.

8.9 Collaborations

AO Research Institute – Sun Yat-sen University Webinar Series
The quarterly ARI – Sun Yat-sen University (SYSU) webinars were organized by Prof Zhen Li (ARI) and Prof Zhiyu Zhou (SYSU) on 12.03.2021, 10.06.2021, 02.09.2021, and 09.12.2021. The goal of this webinar series was to share the most recent research from both institutes and other scientific partners of ARI in China. High quality presentations and active discussions within these webinars facilitate the continuation of current collaborations and build new collaboration initiatives between the institutes. The topics covered by these webinars include intervertebral disc degeneration treatment with hyaluronic acid and mesenchymal stem cells secretome, postnatal limb development of mice based on single-cell RNA-Seq, multifunctional magnesium incorporated scaffolds by 3D-Printing for comprehensive bone defect repair, mechanical stimulation-based biomimetic biomaterials for bone regeneration, role of multiaxial load on cartilage differentiation, multifunctional nanodrugs and biomaterials for osteosarcoma treatment and related bone defect repair, delivery of anti-infective agents with microparticles, and single-cell transcriptional atlas of immune cells in spinal cord injury and its application in spinal cord repair.

ARI Chinese Fellows and team members, 2021.

ARI-SYSU webinar, held on June 10th, 2021.

AO Research Institute Davos scientists awarded synchrotron Diamond Light Source (DLS) experimental time
Diamond Light Source (DLS) is the synchrotron placed in the United Kingdom. It effectively harnesses the power of electrons travelling near the speed of light to produce bright X-ray light that can be used to study structure and dynamics of all sorts of materials, spanning atomic, molecular, and biological matter, in real time. This machine is 10,000 times more powerful than a traditional microscope. As part of several ongoing projects (ImmunoBioInks, INDEED and BBCE), Jacek Wychowaniec (from Biomedical Materials Focus Area) and the interdisciplinary team were awarded a beamtime (SM29767) to perform a series of measurements to reveal the role of molecular interactions between hyaluronic acid (HA) and biopolymers for the design of next generation functional hydrogels for musculoskeletal repair. The measurements take place at Diamond Light Source beamline B21, a small-angle X-ray scattering (SAXS) instrument. One remaining issue when tackling musculoskeletal tissue regeneration is the design of proper functioning matrix that not only supports regeneration but also modulates immune system or provides antibacterial moieties keeping homeostasis. HA is an anionic, non-sulphated glycosaminoglycan widely distributed throughout connective, epithelial, and neural tissues. Recent reports indicate that HA can be chemically modified with amino acids to increase cross-linking densities and achieve better control over physicochemical properties of formed hydrogels or to obtain increased bioactivity with additional short peptide sequences (*e.g.,* RGD, a cell binding specific motif). Understanding structure-function relationships of HA-based functional materials combining biocompatibility and stable long-term bioactivity is therefore of high interest in multiple tissue engineering (TE) applications and in biomedical 3D

printing. This project is heavily supported by the local beamline contact and Jacek's collaborator, Dr Charlotte Edwards-Gayle - an enthusiastic early career stage researcher working in the antimicrobial peptides area. Together, by bringing the capabilities of DLS and expertise of Dr Edwards-Gayle we expect to advance our understanding of the importance of molecular interactions between HA and its modifications with self-assembling peptides and collagen to allow better designs of hydrogels for future musculoskeletal tissue engineering applications, including immunomodulation, antimicrobial resistance and generating printed models.

Participants/Team
Dr Jacek Wychowaniec, AO Research Institute Davos; Dr Charlotte Edwards-Gayle, Diamond Light Source; Dr Matteo D'Este, ARI; Mr Gregor Miklosic, ARI; Mr Artemijs Sceglovs, Riga Technical University; Dr sc ing Kristine Salma-Ancane, Riga Technical University

ARI participates in a new international consortium for the development of research in musculoskeletal biomanufacturing with Chilean scientists
Francisco Verdugo, a dental surgeon, and a PhD student at Jorge's Roberto Toledo Alonso group at the University of Concepción in Chile (UdeC), has recently initiated and contributed to building on new Tissue Engineering Unit in the faculty of Biological Sciences. Concepción in a coastal city located in south Chile in the Biobío Region, which is focused on promoting innovation and research in line with the national vision of the "Regional Development Strategy 2015-2030", which includes the intention that the region "is inserted in the world, prioritizing the generation of knowledge, research, technology, talent attraction, innovation and entrepreneurship." In this spirit, Francisco Verdugo reached out to Jacek Wychowaniec from the Biomedical Materials Focus Area at ARI to start a new international consortium in this area and continue on some mutual ideas to develop "Active Bone-Gels, a next generation osteogenic cell-free scaffolds for critical size bone tissue repair. In December 2021 this project has been successfully funded by the National Agency for Research and Development in Chile (Agencia Nacional de Investigación y Desarrollo de Chile). This project has special relevance for the healthcare area, specifically musculoskeletal, due to the accelerated ageing of local population, mainly in the Metropolitan, Valparaíso, and Biobío regions in Chile. This is causing an increase in bone pathologies (*e.g.,* osteoporosis) and an increase in derived surgeries. This project will support the development of an innovation cluster in tissue engineering and strengthen the production of new innovative products in favor of new therapeutic measures for bone regeneration with a high impact potential, both in the Region of Biobío, nationally and internationally. ARI scientists will contribute their knowledge in a form of bilateral series of seminars and virtual teaching, on the interdisciplinary topics of bone regeneration and biomaterials designs. Furthermore, ARI scientists will support preliminary design and testing (rheology, 3D printing) of an Active Bone-Gel, deriving sufficient preliminary data to yield future larger-scale collaborative grants.

Participants/Team
Jorge Roberto Toledo Alonso (University of Concepción); Francisco Javier Verdugo Avello (University of Concepción); Juan Pablo Acevedo Cox (University of Los Andes)
Dr Matteo D'Este, ARI; Dr Jacek Wychowaniec, ARI

Grants details:

Grant: Competition to promote international links for regional research institutions. call 2021.
Agency: National Agency for Research and Development (ANID)
Title: Creation of an international consortium for the development of research in musculoskeletal biomanufacturing in the new UdeC Tissue Engineering Unit.
Grant code: FOVI210016 J

8.10 Congress news

AO joins forces with Davos Digital Forum: streaming live on January 28, 2021

The Davos Digital Forum Partners Health Edition was streaming live from the AO headquarters in Davos on January 28, for a special edition that focused on health. Thought leaders and major business figures from around the world came together at the event to address the most important challenges the sector faces today. More than 1000 participants registered for the Davos Digital Forum – Health Edition.

AO President Elect Florian Gebhard's keynote speech titled 'The Future of Surgery' outlined the major recent advances seen in digital technology: surgeons, medical professionals, hospitals, and patients. Florian Gebhard asked how surgery has changed in the past 170 years since anesthesia was developed, and how much about it has stayed the same. His talk covered the partnership between patients and clinicians on the threshold of digital revolution: looking at robot-assisted surgery, genome testing, 3D bioprinting, AI, AR, and VR.

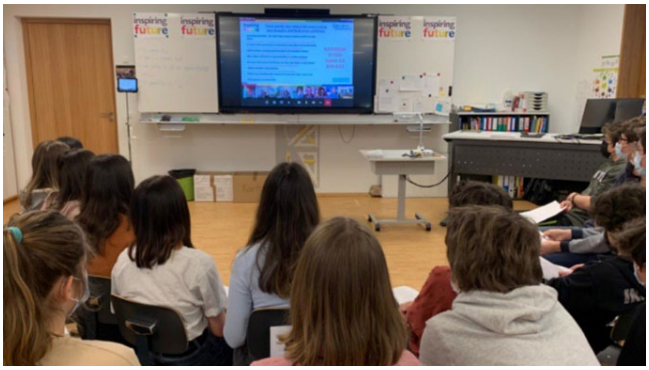
Prof R Geoff Richards, Executive Director Research and Development at the AO, and Manuela Ernst, Project Leader at the ARI gave a talk titled Digitized Aftercare in Orthopedics, assessing the potential ways of integrating technological developments into surgical aftercare. Their main example of this was the novel implant system developed by ARI to provide continuous, objective, data on healing status.

AO's Richards and Topalovic support charity's effort to keep students inspired

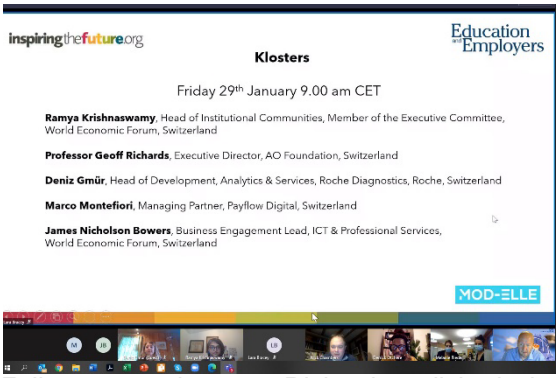
Each January for the past two years, the charity UK Education and Employers has organized an event for WEF annual meeting participants to visit Davos-area schools and raise students' awareness about the many career paths available to them. With the postponement of the 2021 WEF meeting, the charity didn't want young people to miss a chance to be inspired so – in partnership with the Geneva based Swiss charity MOD-ELLE and with support from Organisation for Economic Co-operation and Development (OECD) – it organized four virtual "Inspiring the Future" sessions over three days. The online events brought students together with inspiring professionals, including ARI Director Prof Geoff Richards and AO Senior Program Manager Diversity, Inclusion and Mentorship Tatjana Topalovic.

In a January 27 session, students met and talked with Snapchat CEO and cofounder Evan Spiegel, and during the January 28 event, primary school students in three different Davos classrooms joined an interactive, virtual "Primary Futures" session in German, featuring multilingual volunteers answering questions and discussing their careers.

On January 29, students in Klosters interacted with a panel that included Richards and representatives of the WEF, Roche Diagnostics, and Payflow Digital. The same day, students in Davos heard from a diverse international panel that included Topalovic, the town's mayor, representatives of the OECD, business, industry, and education.



Students in Klosters



Follow your dreams: Richards relished the opportunity to encourage the young participants.

8.11 Termis Presidency

In November 2021 at the World TERMIS Conference, Geoff Richards completed his three year presidency of TERMIS (Tissue Engineering & Regenerative Medicine International Society).

Achievements
Renewed TERMIS Mission with guide on how we try to achieve it
Updated Core Values for TERMIS
Initiated & Implemented Code of Ethics for TERMIS
Created a TERMIS Diversity Statement
Created detailed TERMIS Officer Roles & Responsibilities
Developed and had the membership approve new best practice TERMIS By-Laws
Brought in new officers Treasurer, Secretary, and the new single role as Legal Counsel (no longer combined with Secretary)
New transparent finance processes from budgeting to actuals to tax submissions.
New Membership model and platform for society sustainability (with reduced registration fee to attend TERMIS conferences)
New updated Emerging Country group (with a reduced membership fee)
New affiliations (ISBF and AST with webinar series')
"Student and Young Investigator Sections" (SYIS) chairs brought to the Governing Board, as non-voting members
New contract with Mary Ann Liebert Inc publishers

TERMIS Governing Board meeting

Working with past presidents on TERMIS Mission at TERMIS EU Rhodes.

Meeting with TERMIS EU 2019 organisers

Geoff particularly enjoyed working together with Sarah Wilburn, the TERMIS Executive Administrator through these difficult times and appreciated the dedicated help of the new officers he brought on (Chelsea Bahney, Eric Farrell and MacKenna Roberts).

9 AO Research Institute Davos Medical Research 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 are:

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

ARI Fellows, Guest Students, Internships 2021

Research Fellows

Samson Arveladze: Emek Medical Center, Afula, Israel
ARI Project: **1. The role of human-specific virulence factors in *S. aureus* implant-related osteomyelitis in a humanized mouse model (HuMouse). 2. Fracture-related infection model featuring main components of the clinical condition (FrenchFri).**
During my time in ARI as a medical fellow in the Infection Biology Focus Area, I spent first my time studying lab work processes and techniques. After that, I was involved in HuMouse and FrenchFRI projects. We collaborated with ARI's Preclinical Facility to design and implement our mouse model and worked with other programs *in vitro* experiments and microbiological assays. During my fellowship, I did the systematic review together with Fintan Moriarty and other colleagues outside of the institute. Having the chance to work at ARI immediately after my orthopedic program gave me the unique opportunity to meet basic science scientists worldwide and underscored the value of clinically inspired translational research. I believe that integrating clinical work and basic science research is necessary for further research projects and a better

understanding of the field of research. It was my first time living in Switzerland. It was an exciting opportunity to meet new, wonderful people, learn the history of this beautiful country, and try myself in different Swiss sport activities.

Franziska Breulmann: Trauma-, Hand- and Reconstructive Surgery, University Hospital Münster, Germany
ARI Project: **Differential expressed microRNAs during chondrogenic differentiation of human bone marrow derived mesenchymal stromal cells to identify possible biomarkers for non-union fractures.**
During my time at the ARI Davos as a medical research fellow, I was part of the Progenitor Cells and Biology group working on the regeneration of bone while studying the chondrogenic differentiation. We did *in vitro* experiments to define microRNAs during chondrogenic differentiation as a part of fracture healing processes. Further on we collaborated with different Hospitals in Austria and Italy to validate these miRNAs in fracture patients to further use them as biomarkers *in vivo*. It was a great chance to work at the ARI and to get to know good research practices, as well as getting to know a lot of inspiring scientists from all over the world. Especially during such an early part of my clinical career, it was really inspiring and motivating to see such huge potential of science and to learn being part of this.

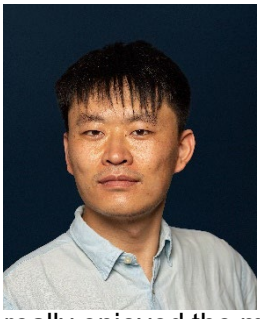
Helene Bumann: University of Basel, Switzerland
ARI Project: **Porcine notochordal cells embedded into a hydrogel transplantation into an enzymatic degeneration model of bovine caudal intervertebral discs.**
During my time in Davos as a medical research fellow in Disc and Cartilage Biology, I spent most of my time researching the effect of porcine notochordal cells embedded into a hydrogel on the nucleus pulposus of bovine discs, which have been treated with an enzymatic degeneration reagent beforehand. My work was part of a huge project called iPSpine with collaborations all over major research facilities all over Europe to develop an injection therapy for disc degeneration. Having the chance to work at ARI gave me the unique opportunity to meet scientists and clinicians from all over the world. Apart from work, there is no place in the world I think where you combine mountain sports so easily with your daily work life, such as going to work by cross-country skiing!

Firas Souleiman: University Hospital, Leipzig, Germany
ARI Projects: **1. Biomechanical and imaging investigation of shoulder instability. 2. 3D imaging evaluation of the distal tibiofibular joint. 3. Biomechanical evaluation of different types of syndesmotic stabilizations. 4. Differences of 3D segmentation between conebeam CT and clinical CT. 5. AI based 3D segmentation.**
During my time in Davos as a medical research fellow in the Biomedical Development Program, I focused on the biomechanical assessment of joint injuries (specialized in shoulder and distal tibiofibular joint). I had the opportunity to understand the details of the anatomical-morphological interaction of different joint partners. Therefore, the latest imaging techniques and biomechanical evaluation systems were available. An international team of different scientists and the great infrastructure had a very motivating effect. In Davos, I met wonderful people and was able to work together with excellent surgeons/scientists from all over the world. Davos is and remains for me a unique place as a top address for research, embedded in stunning surroundings. By the way: ‘Children of winter never grow old. The mountain is calling, and I must go!’

James Tapia-Dean: University of Bern, Vetsuisse Faculty, Bern, Switzerland
ARI Project: **Development of a robust humanized mouse model for evaluating the role of human specific Leukocidins in bone infection.**
Being welcomed back at the ARI in Davos as a Veterinary Fellow was a great pleasure. Taking on the diverse challenges faced during the daily work at the Preclinical Facility (PCF) was always enriching in many ways. Getting to know in depth the meaning of conducting planning and organizing preclinical studies proved to be an eye-opening experience. I was grateful to have the opportunity to work with and learn from an amazing team of specialists in the field of orthopedic research, anesthesia, surgery, and biomedical imaging enrolled in the preclinical work. Besides enjoying my time at the AO, I found exploring the surrounding of Davos just as fascinating. Diving into the year-round magnificent natural world on foot by bike or skis will be something I will never forget.

Kenneth van Knegsel: Cantonal Hospital Lucerne, Switzerland
ARI Projects: **1. A reliable predictor of post-operative lateral wall fracture in trochanteric fractures - an update.**
2. Effect of lateral wall thickness in trochanteric femur fractures on fracture stability - a biomechanical analysis in human cadavers.
3. Influence of knot number on holding capacity of two high strength sutures in different media - a biomechanical analysis.
In 2021, I got the unique opportunity to boost my career as a researcher and medical doctor during an AO Fellowship at ARI Davos. During that time, I focussed on the biomechanical testing of medical material on human cadavers. Working in a highly motivated, competent, and open-minded team resulted in great work and lasting friendships. Despite of the intense time with corona, home office, lock down and reduced contact we managed to get together, drink some beer, and did some skiing and mountain biking in the beautiful mountains of Switzerland. I'm lucky to have regularly planned comebacks to enjoy Davos and continue work on further projects.

Luke Visscher: Redcliffe Hospital, Queensland, Australia
ARI Project: **1. HumFx – image processing and virtual fracture reduction for understanding complex proximal humerus fractures.**
2. Clinical article on filling metaphyseal voids in elderly proximal humerus fractures.
I was privileged to continue an ongoing tradition of international collaboration and exchange between Brisbane and Davos and attend ARI on a medical research Fellowship in 2021. I worked in the Biomedical Development team under Professor Boyko Gueorguiev-Rüegg and Dr Peter Varga on image processing for computer assisted surgery – a topic that I am passionate about. My work focused on analysis of complex proximal humerus fractures, for understanding morphology and classification. I also worked on intraoperative assisted reality visual aids, to help surgeons achieve improved reduction in trauma. It was great to work in a well-resourced department, with a diverse team of talented and driven scientists, engineers, and surgeons. I enjoyed having a great group of likeminded fellows, with whom I could relax, ski and travel with – and have made friends that I will keep for life.



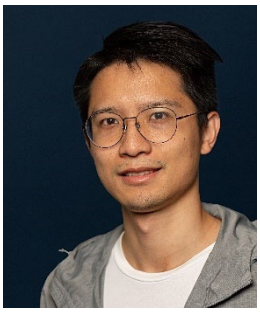
Ensi Zhao: The seventh affiliated hospital of Sun Yet-sen University, Guangzhou, China
ARI Project: **Effect of BMP-2 induced IL-1b secretion by macrophages on bone healing.**
I worked in the Regenerative Orthopeadics program. I spent most of my time in studying effect of BMP-2 on bone healing and how does that happen. We worked with both THP-1 cells and monocytes from Buffy coat. It was very good training for scientific research. Besides that, I learnt swimming, skiing, and snowboarding. It was my first time in Europe. I really enjoyed the mountains there. People seem nice and always cheering. It is good you can enjoy both science and the mountains. I am already looking forward to coming back again.

Guest Students

Emir Benca: Department of Orthopedics and Trauma Surgery, Medical University of Vienna, Austria
ARI Projects: **1. Fixation of the odontoid type II fracture using an allograft osteosynthesis system.**
2. Fixation of the ACL using an allograft osteosynthesis system.
(Jan-Jun 2021), I worked with the Biomedical Development team. Under the supervision of Peter Varga and Boyko Gueorguiev, in two separate projects, we biomechanically evaluated an allograft system for graft fixation in anterior cruciate ligament reconstruction and for treatment of odontoid fractures. It was a pleasure to work in such a dedicated and inspiring team. Scenic Davos was the perfect place to be during the time of lockdowns, imposed across Europe.

Elena Canciani: University of Eastern Piedmont, UPO-CAAD, Novara, Italy
ARI Project: **Flamin-Go – From pathobiology to synovia on-chip: driving rheumatoid arthritis to the precision medicine goal.**
I am a Research Technologist specialized in the morphological evaluation of regenerated bone tissues with biomaterials and osseointegrated implants. I was a guest visiting member in the Sound Guided Tissue Regeneration Focus Area under Dr Tiziano Serra, I improved my skills by learning the principles of 3D bioprinting. From 10 Oct to 5 Dec 2021, I had the precious opportunity to follow all stages of bioprinting, from hydrogel preparation to formulating a cellularized bio-ink for bone and cartilage tissue printing. ARI group is a very friendly and professional advanced workplace located in a beautiful city immersed in lush nature, an extraordinary place for hiking and country skiing where you can have fun.

Baixing Chen: Catholic University Leuven (KU Leuven), Belgium
ARI Project: **Antibiofilm therapy using local application of bacteriophages in a mouse model of MRSA and P. aeruginosa.**
I am a doctoral candidate at the Catholic University Leuven (KU Leuven). I worked as a general orthopedic surgeon at the First Affiliated Hospital of Guangzhou University of Chinese Medicine and finished training for residency. Meanwhile, I have been involved in both pre-clinical and clinical research during my master's. Due to my interest in orthopedic trauma surgery, I started a PhD project focusing on 'safety and efficacy of bacteriophages in the treatment of musculoskeletal infection'. During my time at the ARI Davos under the supervision of Fintan Moriarty in the Infection Biology Focus Area, I studied the impact of the bacteriophage in hydrogels on orthopedic device-related infection in a murine model. I had the precious opportunity to learn a lot about bacteriophage preparation and phage testing protocol. I greatly appreciated the opportunity to gain experience in preclinical research and was excited to work together with an interdisciplinary team of international scientists.



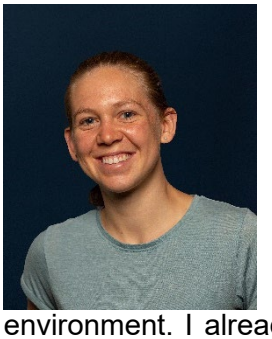
Zhenhao Chen: Huashan Hospital, Fudan University, Shanghai, China
ARI Project: **Evaluation of biological therapies and diagnostic targets for the degenerative intervertebral disc.**
I am a PhD candidate majoring in Orthopedics at Fudan University. I worked as a visiting student member in the Regenerative Orthopaedics program from Jun to Dec 2021 where I had the precious opportunity to study the effect of secretome of MSCs on the regeneration of IVD. I had a great time hiking in Davos, and I am really honored to work in this interdisciplinary and internationally renowned research environment.

Rositza Dimitrova: Institute of Metal Science, Equipment and Technologies with Hydro and Aerodynamics Centre "Acad. A. BALEVSKI" at Bulgarian Academy of Sciences, Sofia, Bulgaria
ARI Project: **Structural investigations of metals and alloys used as materials in diverse currently running projects at the AO Research Institute Davos.**
At the Institute of Metal Science, Equipment and Technologies with Hydro and Aerodynamics Centre "Acad. A. BALEVSKI", where I am a senior assistant professor, I do research at the metallographic and CT laboratory. During my stay at the ARI Davos from 31 May to 09 July 2021, I gained new skills as a guest scientist in the Biomedical Development Program, where I performed measurements and analyses using Drop Shape Analysis System (DSA) Kruss and imaging software Amira. In addition, I discussed results from structural investigations of orthopaedic plates with the colleagues from Biomedical Development. I am impressed by the state-of-the-art laboratories and other facilities at the Institute, as well as by all the nice colleagues I have met and the work atmosphere there. Davos is a picturesque city, and it has been a pleasure for me to do sightseeing walks and hiking tours in the amazing Alps.

Sina Enzmann: Swiss Federal Institute of Technology, Zurich, Switzerland
ARI Project: **MechEndro – Effect of resting period in mechanically driven mesenchymal stem cell differentiation.**
I am studying Health Sciences and Technology with a major in Medical Technology at the ETH Zurich and performed a 3-month internship as well as my master thesis in the Regenerative Orthopaedics program at ARI Davos. My project concerned the differentiation of human mesenchymal stem cells upon different mechanical deformation. I got the opportunity to deepen my knowledge in musculoskeletal regeneration and to gain practical experience in cell culture as well as working in an interdisciplinary and international team. I explored Davos with its beautiful mountains with skiing, snowboarding, cross-country skiing, and hiking.

Jingzhi Fan: Riga Technical University, Riga, Latvia
ARI Project: **BBCE long term training, macrophages, and biomaterials interaction.**
I am a PhD candidate studying biomaterials under BBCE project. Because of the long-term strategic cooperation between ARI and RTU RBIDC, I went for the training on *in vitro,* especially macrophage, related knowledge, from 20 Sept to 20 Dec 2021. I improved a lot from this wonderful academic experience. The knowledge such as assay kits, instrumentation, academic concept helps me to advance my research progress and academic career. I will memorize all the kind friends from AO and will miss this lovely town for my life.

Maria Rosa Iaquinta: University of Ferrara, Ferrara, Italy
ARI Project: **Mechanisms of dexamethasone-induced osteogenesis of human bone marrow derived mesenchymal stromal cells.**
I am a PhD candidate in Molecular Medicine majoring in Regenerative Medicine at University of Ferrara, Ferrara, Italy. I joined the Progenitor Cell Biology and Mechanoregulation Focus Area of the Regenerative Orthopaedics Program from Aug to Nov 2021. I had the opportunity to conduct experiments on a project focused on the mechanisms of dexamethasone-induced osteogenesis of human bone marrow derived mesenchymal stromal cells. I am very pleased to have worked in the ARI Davos. I gained a lot of new knowledge working with a team of international scientists. Davos is a beautiful place ideal for hiking, and it has given me the precious possibility to meet many interesting people from all over the world.



Marie Isenmann: Albert-Ludwigs-University, Freiburg, Germany
ARI Project: **Investigating effects of BMPER on osteogenic and chondrogenic differentiation.**
I am a medical student at the University of Freiburg. From March 2021 to March 2022, I interrupted my studies to spend 13 months at the ARI Davos. As part of the Regenerative Orthopaedics program, I investigated the effects of BMPER expression on osteogenic differentiation as part of my medical doctoral thesis. It was a remarkable opportunity for me to learn a lot about molecular biology in this supportive and friendly environment. I already knew that I love the mountains in summer but living in the beautiful winter environment of Davos and doing winter sports was just fantastic. The combination of learning and working and doing outdoor sports made my time at ARI just perfect for me.

Carmen Lanzillotti: University of Ferrara, Ferrara, Italy
ARI Project: **The role of dexamethasone in osteogenic differentiation of the human bone marrow mesenchymal stem cells.**
I am a PhD candidate in Molecular Medicine majoring in Regenerative Medicine at the University of Ferrara. At the ARI Davos, I studied as a visiting PhD student member in the Regenerative Orthopaedics program from May to August 2021 where I had the precious opportunity to learn a lot on the role of dexamethasone during the osteogenic differentiation of human bone marrow mesenchymal stem cells. Davos is a natural paradise that gives you the possibility to learn a lot of exciting sports. There, you can meet people from all over the world and learn about different cultures. Davos was an extraordinary experience in my whole life.

Giovanni Lauretta: University of Catania, Italy
ARI Project**: Effect of TGFβ1 priming and mechanical loading on hBM-MSCs whitin GelMA/HA hydrogels.**
I am a PhD candidate in Translational Biomedicine at University of Catania. At the ARI Davos, I studied as a visiting PhD student member in the Regenerative Orthopaedics program from March to Nov 2021 where I focused my research on biological activity of human BM-MSCs during chondrogenic differentiation, particularly the influence of mechanical stimuli and the role of different molecules and growth factors. For me it was a very important and stimulating experience since I had the opportunity to improve my skills, and it was a great experience of professional and personal growth.

Kaihu Li: Department of Orthopaedics, Xiangya Hospital, Central South University, Changsha, China
ARI Project: **Anti-inflammatory therapy for cartilage preservation.**
I got my bachelor's degree of clinical medicine and master's degree of orthopedics at Central South University in Changsha, China. Afterwards, I worked as an orthopedic surgeon at the First Affiliated Hospital of University of South China for 3 years. I then became a PhD candidate student in Xiangya Hospital of Central South University. As part of my doctoral study, I came to ARI Davos as a joint PhD student in February 2021. During my first year here, he successfully established a preclinical inflammatory osteoarthritic model, and the study was recently published. In the following year, I will work on screening potential drugs for osteoarthritis treatment. I am very honored to learn the cutting-edge technology in cartilage regeneration and enjoy the healthy lifestyle in Davos.

Carina Mini: Swiss Federal Institute of Technology, Zurich, Switzerland
ARI Project: **3D Bioprinting of intervertebral disc tissue analogues.**
I am a master's student from ETH majoring in Medical Technology. With my interest in Tissue Engineering and Regenerative Medicine, I got the chance to join the Regenerative Orthopaedics program at the ARI Davos. The project I worked on at ARI aims to create a natural biomimetic biomaterial for cartilage regeneration. During my stay from Oct 2021 to March 2022 I could gain valuable laboratory experience and extend my knowledge. The student dinners, game nights, skiing days, and many good talks made the experience in Davos and at ARI extraordinary.

Marika Mosina: Riga Technical University, Riga, Latvia
BBCE Project: ***In vitro* investigation of biomaterials/biomaterials for tissue regeneration.**
I am a second year PhD student in materials science at Riga Technical University (RTU). I am doing scientific activity within Baltic Biomaterials Centre of Excellence (BBCE) project in Rudolfs Cimdins Riga Biomaterials Innovations and Development Centre of RTU. Within the BBCE project I visited the ARI Davos as a guest researcher in the Biomedical Materials and Infection Biology Focus Areas of the Regenerative Orthopaedics Program from Sept 2021 to Jan 2022. I gained new knowledge in *in vitro* investigation of biomaterials and had the opportunity to work with friendly and professional colleagues.

Sara Palladino: Université Laval, Canada and Politecnico di Milano, Italy
ARI Project: **Bioink from collagen and hyaluronic acid for cardiovascular 3D bioprinting.**
I am a PhD student in Laboratory for Biomaterials and Bioengineering, Canada and at GenT Laboratory, Italy. I joined the Biomedical Materials Focus Area at ARI Davos as a guest PhD from March to Dec 2021, under the supervision of Dr Matteo D'Este. It was an incredible opportunity to learn more about hyaluronic acid, bioinks, and bioprinting. I deeply appreciated the supportive environment, the mutual exchange of experience, and the investment in the growth of all students. Life in Davos is full immersion in nature, and I really enjoyed discovering mountains and all the outdoor activities.

Artemijs Sceglovs: Riga Technical University, Riga, Latvia
BBCE Project: ***In vitro* investigation of biomaterials/biomaterials for tissue regeneration.**
I am a first year PhD student in materials science in Riga Technical University (RTU). Currently I am doing scientific activity within Baltic Biomaterials Centre of Excellence (BBCE) project in Rudolfs Cimdins Riga Biomaterials Innovations and Development Centre of RTU. Within the BBCE project I visited the ARI Davos as guest researcher in the Biomedical Materials and Infection Biology Focus Areas of the Regenerative Orthopaedics Program from Sept 2021 to Jan 2022. I had an amazing and sufficient opportunity to learn and to use in practice a lot of techniques connected with *in vitro* investigation of biomaterials, basic theoretical knowledges in microbiology section and principles of rheological studies.

Alexander Sieberath: Newcastle University, Newcastle upon Tyne, UK
ARI Project: **Development of an osteoporosis disease model.**
I am a PhD candidate at the University of Newcastle and my research project has been run in cooperation with the ARI Davos. During my research project I had twice the opportunity to visit and conduct research at the ARI in the Regenerative Orthopaedics program (06.-07.2018 and 03.-07.2021). During these visits I learned a lot about 3D cell culture and bone cell biology and through the support of various ARI members I was able to collect essential data for my thesis. Next to the excellent scientific support, Davos is a great place to stay for ski and mountain enthusiast.

Eliza Tracuma: Riga Technical University, Riga, Latvia
ARI Project: **Design of soft hydrogels and their composites with mineralized components for musculoskeletal regeneration.**
I am a 1st year PhD student at Riga Technical University. During the short-term visit at the ARI Davos from Nov to Dec 2021 I had the opportunity to join the Polymer laboratory team. My research focus is on soft hydrogels for musculoskeletal regeneration. I am very thankful and excited for the opportunity to work in such an interdisciplinary team.

Jana Vecstaudza: Riga Technical University, Riga, Latvia
BBCE Project: **Baltic Biomaterials Centre of Excellence.**
I am a PostDoc researcher at Riga Technical University with background in Materials Science and Chemical Engineering. I was a guest researcher within the SGTR Focus Area within the Regenerative Orthopaedics program at the ARI Davos from Sept to Dec 2021. During my training visit I learned a lot about 3D printing and characterization of soft biomaterials for organ on a chip development. This was new and valuable experience as well as acquiring of practical skills.

Celina Wolfisberg: Swiss Federal Institute of Technology, Zurich, Switzerland
ARI Project: **Interpretability of implant load regarding fracture healing progression based on finite element modelling and fracture monitor measurements.**
I recently completed the Master in Health Sciences and Technology at the ETH Zurich with a Major in Medical Technology. In my Master's Thesis project at ARI Davos, I validated a finite element fracture model and participated in the product development of a biofeedback sensor system, giving me the opportunity to gather valuable insight into a fascinating research field. In Davos, I also had the chance to combine my scientific work with my passion for mountain biking and cross-country skiing.

Internships

Sarah Egger: Swiss Federal Institute of Technology, Zurich, Switzerland
ARI Project: **Engineered hydrogel matrices to support freeform anisotropic patterning of cells in three dimensions for annulus fibrosus tissue engineering.**
I am a Master student from ETH studying Biomedical Engineering with specialization in Molecular Bioengineering, and I completed a research internship followed by my Master thesis in the Regenerative Orthopaedics group at the ARI Davos. In my project, I focused on biomaterial optimization and hydrogel fabrication for cell culture studies, as well as freeform 3D bioprinting of the annulus fibrosus tissue of the intervertebral disc. I appreciated to have been given the opportunity to work on a clinically relevant topic together with an interdisciplinary and internationally renowned team of scientists, and I enjoyed gaining hands-on experience in the field of tissue engineering. Besides my work at the ARI, I loved spending time skiing, cross-country skiing, riding, and cooking with my friends. Further, I was happy to meet locals by joining the volleyball team of Davos.

Lara Ettinger: Biomedicine study, Switzerland
After having graduated the Swiss Matura in September 2020 I wanted to invest some time to find out the right direction for my future. As my interest in natural science and research increased, I applied for a short internship at ARI Davos. During this time, I was able to get an extensive insight in laboratory work and, despite my little background knowledge, I had the possibility to gain research experience in many projects. I also had helpful conversations with some students working at the ARI, which were of great importance for my further decisions regarding the choice of study. I really enjoyed the friendly atmosphere and the supportive nature of the team. But I also loved the moments in the beautiful mountains or spending time with new friends.

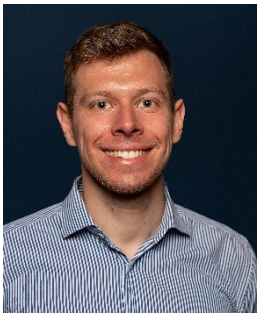
Oliver Hüsser: Swiss Federal Institute of Technology, Zurich, Switzerland
After completing my bachelor's degree in electrical engineering, I decided to do an internship at the ARI in Davos. I worked on two main projects. One was the development of the OSapp absolute stability module where I programmed animations showing the concept of fracture fixation with absolute stability. The other project aimed at exploring machine learning applications for medical image analysis. To that end, I had to learn about computer vision with deep learning. Then I set up and tested the nnUNet, a recently published software that does exactly what we were looking for. I was happy to share my excitement about the results of this new technology with brilliant and supportive colleagues. I enjoyed skiing, hiking, playing football and many more things. I met amazing people that I will never forget.

Anna Knill: Swiss Federal Institute of Technology, Zurich, Switzerland
ARI Project: **Medical imaging processing and programming.**
During my masters studies of Biomedical Engineering at ETH I got the chance to do an internship at the ARI Davos. I worked on various projects including HumFix where I performed segmentation of clinical CT images and evaluated fracture morphology in the proximal humerus. As an intern I had the opportunity to support other projects as needed and therefore got a deeper insight into ongoing research at the ARI. In addition, I got to meet many new people from all over the globe. Thank you for this unique time I was able to spend in Davos.

Elisa Marani: Swiss Federal Institute of Technology, Zurich, Switzerland
ARI Project: **Development of an interactive osteosynthesis learning platform.**
I joined the ARI Davos after having finished my bachelor's degree in Mechanical Engineering at the ETH Zurich. I worked in the Biomechanics and Modelling Group on the OSapp project and focused on the validation of the simulation results and helped to develop and program the learning platform. This internship at ARI gave me the possibility to get to know the field of biomechanics and biomedical development and to make use of my engineering knowledge on an interesting and fascinating subject. I enjoyed working in a friendly and supportive environment and contributing to an innovative research project. I loved the cold, white winter in Davos, making new friends and spending time out in the nature to go hiking or skiing.

Laura Mecchi: Politecnico di Milano, Milan, Italy
ARI Project: **Acoustic stimulation for chondro-differentiation.**
I joined ARI as an intern for 11 months in 2021 just after graduating from my Master in Biomedical Engineering at Politecnico di Milano. I worked in the field of tissue engineering, using sound waves to stimulate cells, with the ultimate aim of cartilage regeneration. I learned a lot about biomaterial science and tissue engineering, but most of all I enjoyed the teamwork and the proactive attitude of the workplace at ARI. I also enjoyed the closer outlook on nature that's possible in Davos, with its snowy winter and cool summer.

Simone Poncioni: University of Bern, Switzerland
ARI Project: **Biomechanical testing of novel thread design.**
I joined the Biomechanics and Modeling Focus Area for a 9-months internship. During this period, I mainly focused on the development and implementation of biomechanical tests on bovine bone samples. These were used to evaluate the primary stability of new thread designs used in orthopaedic screws. This internship has allowed me to learn more about the world of research, to apply my knowledge as an engineer and to meet numerous people who have helped me in my personal and professional growth. As a great lover of the mountains, I did not waste a free second to enjoy the breathtaking views Davos had to offer.

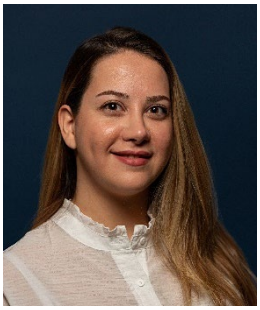


Andrea Rossoni: University College Dublin, Ireland
ARI Project: **Sound induced sculpturing of the extracellular matrix.**
After having completed my master’s degree in Biomedical Engineering at Politecnico di Milano, I joined ARI Davos as an intern. I worked in the Sound Guided Tissue Regeneration Focus Area from Feb to Nov 2021. My internship project was focused on the obtainment of a method to locally condense the extracellular matrix by using an acoustic bioprinting platform. During my time in Davos, I had the opportunity to work in the field of regenerative medicine using cutting-edge technologies and I learned key skills that will be extremely useful during my PhD. I am grateful to have worked in such a supportive environment and I will never forget the good times I spent inside and outside the lab.

Linda Steiger: Kantonsschule Küsnacht, Zurich, Switzerland
I joined ARI after having finished high school to complete a three-month internship. During my stay at the ARI, I had the chance to get an insight in all three different departments. I could help in several small projects like the SNMouse. I had the possibility to develop new skills like working with computer programs (Amira) and learned a lot about surgeries. I really enjoyed my stay, especially because of the nice and openminded people and the friendly working environment. I loved the beautiful scenery with the mountains and having various possibilities to do sports like hiking, skiing, and biking.

Lara Tenisch: Swiss Federal Institute of Technology, Zurich, Switzerland
ARI Project: **Prediction of mechanical failure in proximal humerus fracture fixations using patient-specific FE analyses.**
I joined ARI for an internship and to write my master's thesis as part of my master's degree studies in Biomedical Engineering at ETH Zurich. In Davos, I was working in the Biomechanics and Modelling group, which is part of the Biomedical Development program. During my internship, as well as during my master's thesis, I was working on projects which both focus on proximal humerus fracture fixation and the applicability of Finite Element modelling to such fracture fixation cases. At ARI, I was given the opportunity to independently tackle real world clinical problems in close contact with an interdisciplinary and international team. I highly enjoyed working in such an encouraging and motivating environment and getting the chance to gain insight into various fields of biomedical development. Not only did I enjoy working at ARI, but I also appreciate the time I got to spend in Davos' beautiful nature while making new friends from all around the world.

Leya Weber: Swiss Federal Institute of Technology, Zurich, Switzerland
ARI Project: **Testing HA-based bioink provided by Fidia Farmaceutici SpA.**
I joined ARI as an intern for my master's degree in Health Science and Technology with a major in Medical Technology. My project was a collaboration with the company Fidia Farmaceutici SpA in which I tested their HA-based bioink. To evaluate and compare different formulations of the bioink my experiments were very diverse: printing assays, mechanical testing, and cytocompatibility tests. As it was my first lab work experience, I could benefit a lot from the broad spectrum of experiments. Working with such supportive and experienced scientists and contributing to this research project is something I am very grateful for. Of course, I also appreciated the time outside of ARI with the team. We had a great time doing all kinds of sports or having dinner together. I enjoyed every minute in Davos.



Donya Ziadlou: University of Geneva, Switzerland
ARI Project: **Patterning dorsal root ganglion cells in gelatine methacryloyl with sound induced morphogenesis.**
I joined ARI Davos after graduating my master's degree from University of Geneva. I have worked in the Sound Guided Tissue Regeneration Focus Area on the effect of sound on dorsal root ganglions (DRG) condensation and viability with the use of GelMA hydrogel as a scaffold. This internship at ARI provided me the opportunity to get to know the field of biomedical and to make use of my knowledge on neuroscience field on this innovative project. I had a great time working in a supportive team and contribute to their cutting-edge research. I enjoyed the amazing nature of Davos both in winter and summer with fascinating activities and spending time with great friends.

10 Project Abstracts by Sponsors

10.1 AOCMF

Biofunctional membrane for treatment of mandibular defect (Masticate) (ongoing) (T Serra, D Eglin)

Background: In clinical practice the development of guided tissue regeneration has considerably influenced the possibility of implant use in the jaw regions with bone defects and those with a bone anatomy that is unfavorable for implant anchorage. Membranes used for guided tissue regeneration are used in combination with bone grafts or bone graft substitutes to support vertical bone augmentation, growth, and closure of periodontal soft tissue. Still, dehiscence- and fenestration-type defects persist in a significant percent of patients. This may be due to difficulty in achieving primary wound closure and suboptimal speed of soft and hard tissue healing as a result of the large volume to be revascularized, covered and repaired.
Goal: The overall aim of this study is to develop a dual layer membrane using a surface acoustic wave additive manufacturing technology with 1) a bone layer made of assembled osteoconductive CaP microparticles into parallel lines in a collagen matrix and 2) a soft tissue layer made of pre-assembled adipose tissue-derived microvascular fragments within a collagen matrix, for fast vascularization and bone healing.
Results: A method for generating membranes based on CaP particles in collagen-based hydrogels was established (Figure 10.1.1 a). A method for generating tissue engineered membranes with spatially organized microvasculature was established (Figure 10.1.1 b) and published.

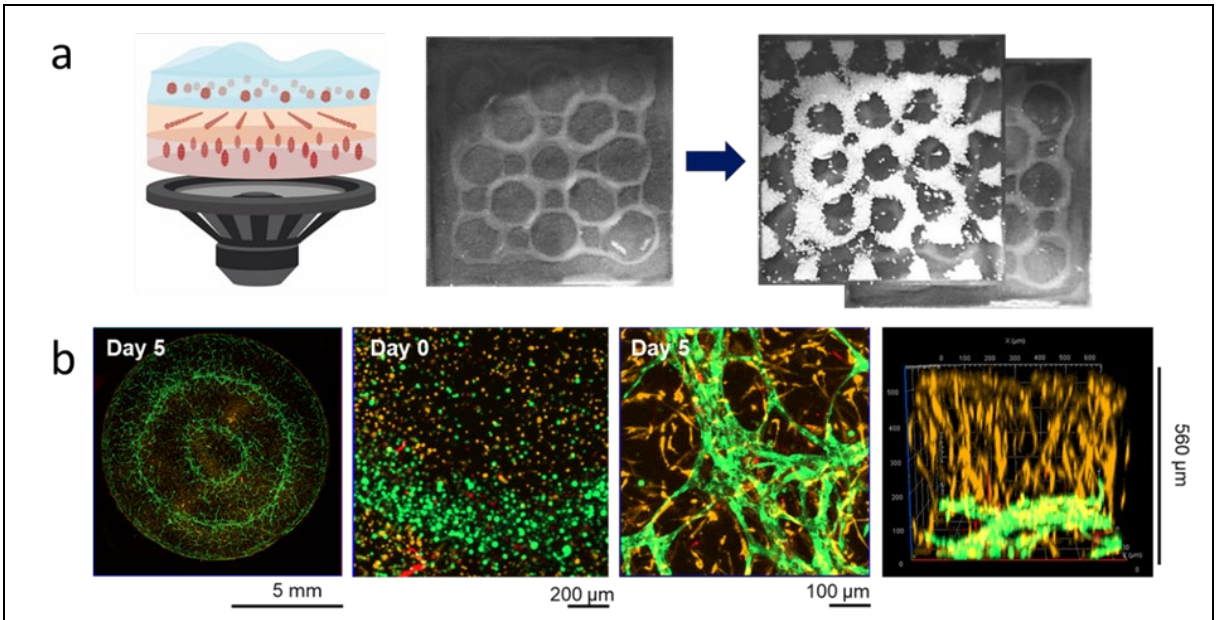


Figure 10.1.1 a) multi-layered membranes based on CaP particles and cell patterns in in collagen-based hydrogels. Figure 10.1.1 b) Tissue engineered multi-layered constructs with spatially organized microvasculature. GFP-endothelial cells in green, hMSCs in organge.

Pres:
29.-31.07.2021 Serra Tiziano: "3D printing for orthopaedics: biofabrication repair solutions", Asia Pacific Orthopaedic Association (APOA) Conference, Kuala Lumpur, Malaysia (Online) (Invited Speaker)

Pub:
Guex AG, Di Marzio N, Eglin D, Alini M, Serra T. The waves that make the pattern: a review on acoustic manipulation in biomedical research. Mater Today Bio. 2021 Mar 24;10:100110.

Bottom up printing approach (BUPA2) (ongoing) (A Armiento, M Stoddart)

Background: 3D-printed personalized scaffolds are an attractive approach for mandibular bone repair. The challenging loading environment of this site requires biomaterials with suitable mechanical resilience, which may be provided via the addition of flexible materials such as thermoplastic polyurethane (TPU).
Goal: This work aims to create a 3D printable personalized scaffold with a configurable layered composition, enhanced mechanical properties and improved cell adhesion.
Results: Varying material combinations are mixed to obtain a printable ink (RegenHu Discovery®). After printing, surface microporosity and cytotoxicity is assessed using scanning electron microscopy (SEM) and CellTiter-Blue®, respectively. A 3D model of a mandibular defect is derived from CT scans, then sliced and modified with CAD to obtain LEGO®-like structures. The personalized scaffolds are printed as a series of layers incorporating an interlocking mechanism. Scaffolds with precise and interconnected filaments can be printed and SEM images show surface microporosity, while no cytotoxicity is reported in 3T3 cells. Large scale personalized mandibular implants can be successfully printed and assembled.

Partner:
- Zenobi-Wong M (Prof), Institute for Biomechanics, ETH Zurich, Switzerland

Inducing bone regeneration through immuno-modulation of biomaterials (RAIMBO) (ongoing) (M D'Este, D Eglin)

Background: Bone repair in the craniomaxillofacial region is still a clinical challenge with a major impact on patients. For large defects after trauma or tumor resection, bone autografts are generally adopted as the clinical standard. However, this solution is far from ideal, as donor site morbidity and the limited amount of material available impose limitations. Bone graft substitutes from natural or synthetic biomaterials would be a valid alternative, although their efficacy is limited since they do not have the intrinsic healing properties of viable autologous bone. Additionally, they may still trigger deleterious immune responses, such as fibrous encapsulation, resulting in impaired new bone formation and possibly even leading to implant rejection. Adaptive and innate immune cells such as T cells, macrophages and neutrophils play a central role in modulating the immune responses to biomaterials used in the fabrication of implantable devices. While some general principles governing the immune response to implanted biomaterials topography and chemistry have been investigated, the consequences of interactions of 3D printed constructs with the host immune system remains mostly unknown. The systematic knowledge of how variations in shape, topochemistry and composition of 3D printed constructs interacts with the host immune system opens the possibility of modulating the immune response to biomaterials, and ultimately to improve bone healing.
Goal: The overall goal of this project is to investigate the effect of specific material properties on immune cells such as neutrophils or macrophages. This will contribute to the design of biomaterials targeting clinical problems such as osteointegration; infection; fibrous encapsulation; osteolysis; implant rejection; new bone formation.
Results: We isolated human primary neutrophils from peripheral blood and exposed them to a broad panel of hard, soft, naturally- and synthetically derived materials. The overall trend showed increased neutrophil survival on naturally derived constructs, together with higher oxidative burst, decreased neutrophil extracellular trap (NET) formation and cytokine secretion compared to neutrophils on synthetic materials. The culture model is a first step to better understand the immune modulation elicited by biomaterials. Further studies are needed to correlate the neutrophil response to tissue healing and to elucidate the mechanism triggering the cell response and their consequences in determining inflammation onset and resolution. The results of the RAIMBO project, closed in 2021, are being followed up in the ARI AC funded BEAN project.

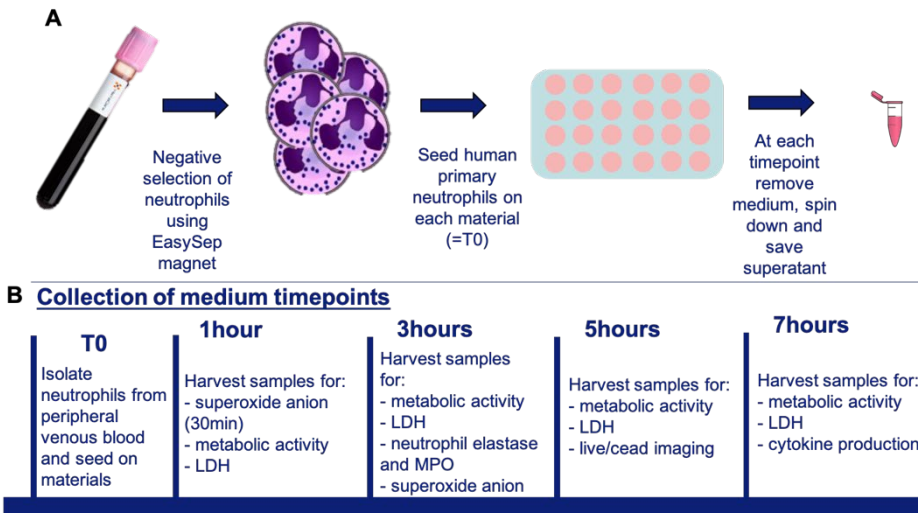


Figure 10.1.2: Summary of the assays performed. A) Schematic experimental outline from drawing peripheral blood to collection of media from each material. B) Timeline of the assays that were carried out at each time points.

Pres:
Wesdorp MA, Schwab A, Eglin D, Narcisi R, van Osch G, D'Este M; A culture model to analyze the acute biomaterial-dependent reaction of human primary neutrophils. Oral presentation at the 2021 eCM: Biofabrication for Orthopaedics. Conference cancelled but abstract published.

Pub:
Wesdorp MA, Schwab A, Narcisi R, Eglin D, Stoddart MJ, van Osch G, D'Este M; A culture model to analyze the acute biomaterial-dependent reaction of human primary neutrophils *in vitro*. Submitted.

Partners:
- Wesdorp T, The University Medical Center Rotterdam, Netherlands
- Narcisi R (PhD), The University Medical Center, Rotterdam, Netherlands
- van Osch G (Prof), The University Medical Center, Rotterdam, Netherlands

10.2 AOSpine

A translational approach integrating developmental biology and tissue engineering towards regeneration of the annulus fibrosus of the intervertebral disc (Printdisc) (ongoing) (A Vernengo, Z Li, M Alini, S Grad)

Background: Intervertebral disc (IVD) degeneration can lead to chronic low back pain, which is a leading cause of disability worldwide. IVD degeneration can be characterized by the dehydration of the central nucleus pulposus (NP) and subsequent structural breakdown of the peripheral annulus fibrosus (AF). Currently, there are no clinically acceptable solutions for sealing the ruptured AF, so biologic based therapies, such as tissue engineering, are being investigated. We posit that the current state of AF tissue engineering can be advanced with a strategy that captures the essential building blocks of AF tissue morphogenesis: Biomimetic cell patterning and mechanical stimulation to induce circumferential cell elongation.
Goal: Herein we propose two important milestones never explored before in IVD tissue engineering: 1) The development of a free-form reversible embedding technique that supports the bioprinting of cells and cell-laden bioinks into biomimetic patterns within three-dimensional hydrogel matrices, and 2) The exploration of cell-scale and macro-scale mechanical stimulations on cytoskeletal organization and AF collagen assembly by the patterned MSCs (Figure 10.2.1).
Results: We have developed a cell-friendly hydrogel support bath comprised of temperature-sensitive poly(N-isopropylacrylamide) hydrogels and embedded Carbopol® microparticles. The hydrogel support baths possess flow points and self-healing rheological behaviors that enable the patterning of extruded bioinks in three-dimensional space. The support baths also present controllable mechanical cues for tuning the cytoskeletal properties of the patterned cells.

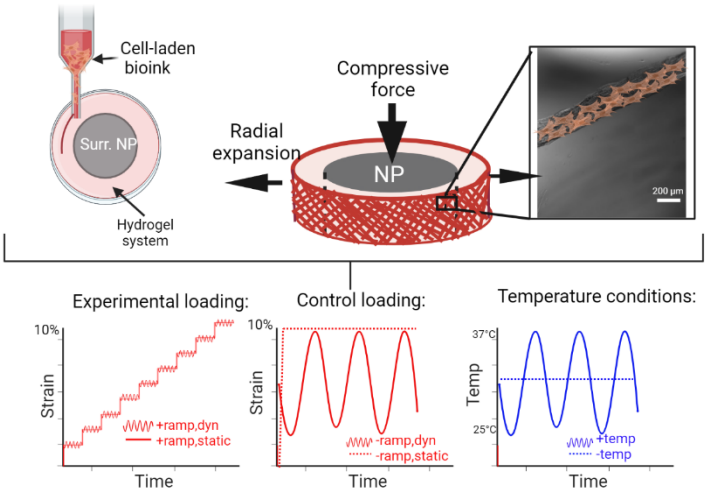


Figure 10.2.1: Summary of the 3D bioprinting system for annulus fibrosus (AF) tissue engineering.

Significance: The outcome of this work will be a novel biofabrication strategy that enables anisotropic patterning of cells or cell-laden bioinks spatially within a 3D hydrogel. The project will also produce a novel approach to the multiscale mechanical stimulation of cells embedded within the hydrogels, with potential to improve the organization and biomechanical properties of engineered aligned musculoskeletal tissues. In future work, the technique may be adapted to tissue engineering of the central NP, paving the way towards the goal of regenerating a whole IVD tissue.

Pres:
Egger S, Alig G, D'Este M, Grad S, Alini M, Vernengo A. 2021. 'Temperature-responsive engineered matrices for spatial positioning and long-term culture of bioprinted cells'. eCM XX: Biofabrication for Orthopaedics, Davos, Switzerland, (poster).
Alig G, D'Este M, Grad S, Alini M, Vernengo A. 2021. Temperature-responsive engineered hydrogel support baths for spatial positioning and long-term culture of bioprinted cells. International Conference on Biofabrication: Biofabrication 2021, virtual meeting, (paper and poster).

Pub:
Russo F, Ambrosio L, Peroglio M, Guo W, Wangler S, Gewiess J, Grad S, Alini M, Papalia R, Vadalà G, Denaro V. A hyaluronan and platelet-rich plasma hydrogel for mesenchymal stem cell delivery in the intervertebral disc: an organ culture study. Int. J. Mol. Sci. 2021, 22, 2963.
Guo W, Douma L, Hu MH, Eglin D, Alini M, Šećerović A, Grad S, Peng X, Zou X, D'Este M, Peroglio M. Hyaluronic acid-based interpenetrating network hydrogel as a cell carrier for nucleus pulposus repair. Carbohydr Polym. 2022 Feb 1;277:118828. DOI: 10.1016/j.carbpol.2021.118828.

Evaluation of biological therapies and diagnostic targets for the degenerative intervertebral disc (Theranostic) (ongoing) (S Grad, Z Li, M Alini)

Background: Intervertebral disc (IVD) degeneration is a major factor contributing to the development of back and neck pain, which represents a global burden for patients, clinicians, and the society. For patients with early signs and symptoms who are not responsive to conservative treatment but do not yet qualify for spine surgery, therapeutic options are scarce. Intradiscal injection of mesenchymal stromal cells (MSCs) derived from bone marrow has shown promising outcome in patients suffering from discogenic low back pain. The therapeutic effect of locally delivered MSCs has been attributed to their secretion of immune-modulatory, anti-inflammatory, and regenerative mediators. Direct application of MSC secretome is therefore an attractive therapeutic approach, avoiding some of the hurdles and risks of cell injection.
Goal: The aim of this project is to evaluate the potential of MSC secretome for IVD regeneration using cell and organ culture models. First, the secretome of human MSCs stimulated with different human IVD conditioned media will be characterized to assess the MSCs response to the IVD environment. Secondly, the therapeutic effect of stimulated MSCs' secretome on IVD cells and tissues will be investigated. Composition of the secretome will be correlated to its regenerative effect to identify potent secretomes for further pre-clinical study.
Results: Stimulation of MSCs with IVD conditioned media induced a more complex MSC secretome, involving more diverse sets of upregulated biological processes, compared to stimulation with IL-1β as proinflammatory control. Furthermore, the MSCs' response to stimulation with IVD conditioned medium was dependent on the IVD's pathological status. The MSC secretome seemed to match the primary need of the IVD: homeostasis maintenance in the case of healthy IVDs, *versus* immunomodulation, adjustment of extracellular matrix synthesis, degradation, and (re)organization in the case of traumatic and degenerative IVDs.

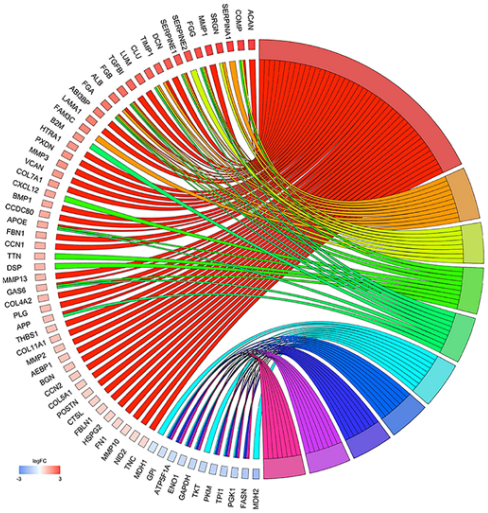


Figure 10.2.2: Analysis of proteomics data of released proteins following stimulation of MSCs with degenerative IVD conditioned medium. Top 5 upregulated (upper part) and downregulated (lower part) gene ontology terms (functional database: biological processes) are displayed. From: DOI: 10.1186/s13287-020-02062-2.

Pres:

Wangler S, Kamali A, Wapp C, Wuertz-Kozak K, Häckel S, Fortes C, Benneker LM, Haglund L, Richards RG, Alini M, Peroglio M, Grad S. Mesenchymal stem cell secretome: a potential anabolic and immunomodulatory therapy for modulation of early intervertebral disc degeneration. ORS Annual Meeting 2021 (oral).

Wangler S, Kamali A, Wapp C, Wuertz-Kozak K, Häckel S, Fortes C, Benneker LM, Haglund L, Richards RG, Alini M, Peroglio M, Grad S. Mesenchymal stem cell secretome: a potential anabolic and immunomodulatory therapy for early intervertebral disc degeneration. Global Spine Congress 2021 (oral).

Nüesch A, Zhen Z, Wangler S, Li Z, Grad S. The influence of mesenchymal stromal cells secretome on nucleus pulposus cells exposed to a proinflammatory environment. SSBRM Young Scientists conference 2021.

Pub:

Wangler S, Kamali A, Wapp C, Wuertz-Kozak K, Häckel S, Fortes C, Benneker LM, Haglund L, Richards RG, Alini M, Peroglio M, Grad S. Uncovering the secretome of mesenchymal stromal cells exposed to healthy, traumatic, and degenerative intervertebral discs: a proteomic analysis. Stem Cell Res Ther. 2021 Jan 7;12(1):11. DOI: 10.1186/s13287-020-02062-2.

Karppinen J, Koivisto K, Ketola J, Haapea M, Paananen M, Herzig KH, Alini M, Lotz J, Dudli S, Samartzis D, Risteli J, Majuri ML, Alenius H, Kyllönen E, Järvinen J, Niinimäki J, Grad S. Serum biomarkers for Modic changes in patients with chronic low back pain. Eur Spine J. 2021 Jan 9. DOI: 10.1007/s00586-020-06713-z.

Cui S, Zhou Z, Chen X, Wei F, Richards RG, Alini M, Grad S, Li Z. Transcriptional profiling of intervertebral disc in a post-traumatic early degeneration organ culture model. JOR Spine. 2021 Apr 8;4(3):e1146. DOI: 10.1002/jsp2.1146. eCollection 2021 Sep.

Ren W, Cui S, Alini M, Grad S, Zhou Q, Li Z, Razansky D. Noninvasive multimodal fluorescence and magnetic resonance imaging of whole-organ intervertebral discs. Biomed Opt Express. 2021 May 7;12(6):3214-3227. DOI: 10.1364/BOE.421205.

Du J, Guo W, Häckel S, Hoppe S, Garcia JP, Alini M, Tryfonidou MA, Creemers LB, Grad S, Li Z. The function of CD146 in human annulus fibrosus cells and mechanism of the regulation by TGF-β. J Orthop Res. 2021 Oct 18. DOI: 10.1002/jor.25190. Online ahead of print.

Kamali A, Ziadlou R, Lang G, Pfannkuche J, Cui S, Li Z, Richards RG, Alin M, Grad S. Small molecule-based treatment approaches for intervertebral disc degeneration: Current options and future directions. Theranostics. 2021 Jan 1;11(1):27-47. DOI: 10.7150/thno.48987. eCollection 2021.

Croft AS, Illien-Jünger S, Grad S, Guerrero J, Wangler S, Gantenbein B. The application of mesenchymal stromal cells and their homing capabilities to regenerate the intervertebral disc. Int. J. Mol. Sci. 2021, 22, 3519.

Thesis

The influence of mesenchymal stromal cells secretome on nucleus pulposus cells exposed to a proinflammatory environment. Andrea Nüesch MSc ETHZ.

10.3 AOTrauma

Predicting patient-specific mechanical failure of proximal humerus fracture plating with computer simulations (SystemFixII) (ongoing) (P Varga, D Mischler, B Burkhard, D Ciric, VC Panagiotopoulou, C Schopper, M Remppis, L Tenisch, 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 high potential to complement or partially replace experimental biomechanical testing, expedite implant optimization and design, refine surgical guidelines, support decision making and allow patient-specific preoperative planning. Ultimately, simulations are expected to help improve patient outcomes of osteoporotic proximal humerus fracture treatment. In the first project phase (SystemFixI), a virtual osteosynthesis test kit was developed and used to simulate proximal fracture plating and predict mechanical fixation failure. The tool was validated experimentally and utilized in a series of *in silico* studies to indicate ways of improving the application of plates, to compare different implants and to optimize the implant design towards improved stability. However, the models have not yet demonstrated prediction of mechanical fixation failure in real clinical cases.
Goal: To expand the simulation tool application from virtual to real clinical scenarios and validate it clinically by predicting the patient-specific risk of mechanical fixation failure.
Results: Clinical data including postoperative CT scans and shoulder motion data is being collected in a prospective clinical study in Leuven and Innsbruck, with 26 of the planned 40 patients recruited so far. In an ongoing analysis, several measures such as bone mineral density, fracture reduction quality, instrumentation configuration and accuracy, as well as range in frequency of shoulder motions are assessed and predictive power of these parameters is evaluated. All these aspects are incorporated in subject-specific finite element models generated from combined preoperative and postoperative CT images and sensor data, and used to predict an individualized failure risk that is then compared with the clinical fixation failure / no-failure outcomes at 6-months postoperatively. To complement these analyses, a biomechanical sub-study demonstrated significant effect of pilot hole overdrilling on the risk of screw perforation during cyclic loading. The occurrence of overdrilling events is recorded in the clinical study and the potential influence of this frequently overlooked aspects on the clinical failure risk is also considered in the analyses.

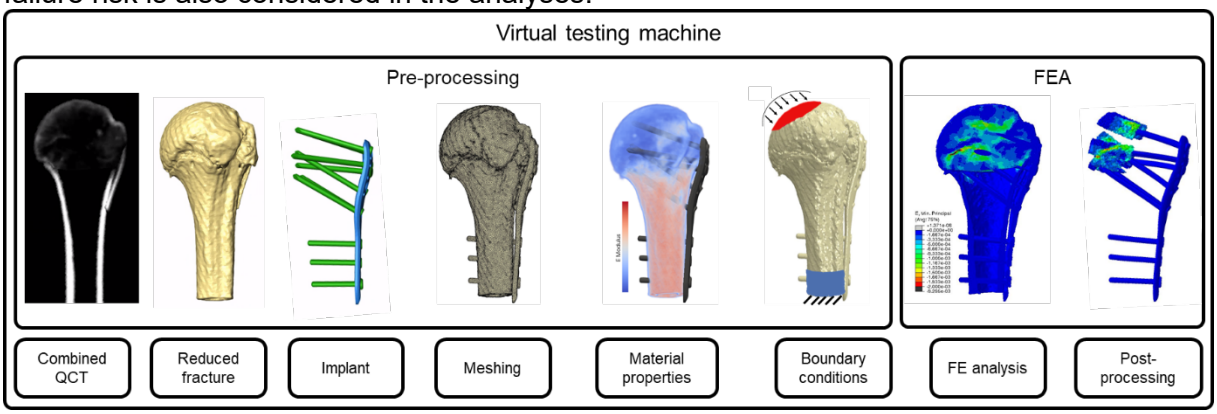


Figure 10.3.1: Subject-specific finite element (FE) simulation workflow.

Pres:
Panagiotopoulou VC, Ovesy M, Gueorguiev B, Richards RG, Zysset P, Varga P. Prediction of screw perforation in the proximal humerus using micro finite element analyses. 2021 ESBiomech (oral).
Burkhard B, Schopper C, Ciric D, Mischler D, Gueorguiev B, Varga P. Pilot hole overdrilling increases screw perforation risk in locked plating of complex proximal humerus fractures. 2021 ESBiomech (poster).

Theses:
Remppis M. Postoperative shoulder activity tracking of patients with proximal humerus fractures treated with locking plates. MSc Thesis, University of Stuttgart, 2021.
Tenisch L. Prediction of mechanical failure in proximal humerus fracture fixations using patient-specific FE analyses. MSc Thesis, ETH Zurich, 2021.

Pub:
Panagiotopoulou VC, Ovesy M, Gueorguiev B, Richards RG, Zysset P, Varga P. Experimental and numerical investigation of secondary screw perforation in the human proximal humerus. J Mech Behav Biomed Mater. 2021. 116:104344.
Burkhard B, Schopper C, Ciric D, Mischler D, Gueorguiev B, Varga P. Overdrilling increases the risk of screw perforation in locked plating of complex proximal humeral fractures – a biomechanical cadaveric study. J Biomech. 2021. 117:110268.

Partners:
- Nijs S (Prof), University Hospital Leuven, Belgium
- Hengg C (MD), Medical University Innsbruck, Austria

Temporal sequence of callus stiffening and mechanical callus induction limit (ActiveFix) (ongoing) (J Barcik, M Windolf)

Background: Despite decades of research on the mechanobiology of fracture repair, certain aspects in the field remain unaddressed. It is widely accepted that strain stimulus (mechanical stimulation) is required to promote callus formation during secondary bone healing. However, previous preclinical studies have provided conflicting results when attempting to quantify the impact of the temporal distribution of mechanical stimulation on fracture healing. Moreover, the lower strain threshold that fosters callus formation remains unknown.
Goal: To investigate (1) the short-term effect of mechanical stimulation on fracture healing, (2) the role of stimulation timing along the healing period (early *versus* delayed stimulation), and (3) the callus induction strain threshold (callus induction limit), using a controlled active fixation instrumented on a sheep tibia.
Results: The experimental results from the previous study group demonstrated the importance of resting periods in-between stimulation cycles. The continuous monitoring of the fracture repair tissue in response to mechanical stimulation revealed that the stiffness of the repair tissue did not steadily increase throughout the stimulation and resting periods. A decrease in stiffness was often observed during stimulation periods. Consequently, the stiffness of the repair tissue predominantly increased during resting periods. To further investigate the role of mechanical stimulation on callus formation, a previously established tilting wedge active fixator is applied that enables combined investigation of (1) callus response to different strain levels and (2) the impact of stimulation timing on callus formation (early *versus* delayed stimulation). To identify the callus induction strain threshold, the fixator was modified to apply a strain gradient in the range from 0% to 20%. So far, the modified tilting wedge fixator has been implanted in four sheep split in two groups. The experimental groups will be completed in 2022 to allow for statistical analysis of the callus induction limit and comparison of early *versus* delayed stimulation treatment.

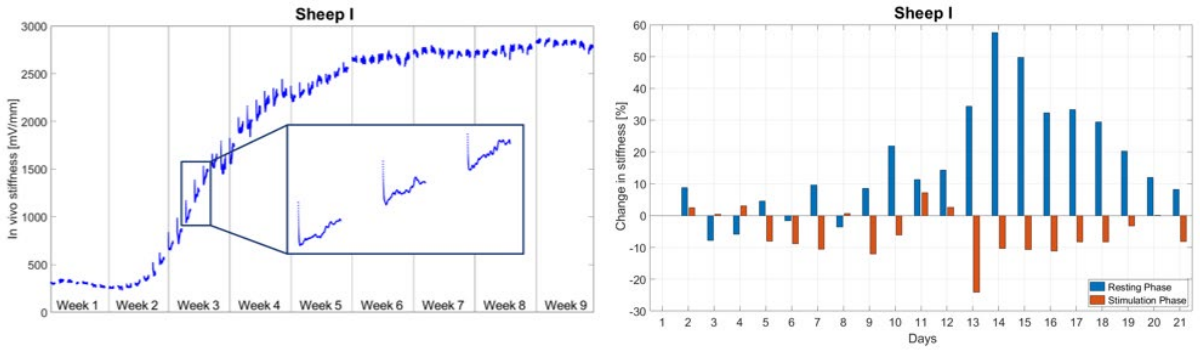


Figure 10.3.2: Experimental data from an exemplary animal visualizing continuous measurements of the tissue stiffness (left) and daily changes in stiffness during the resting and stimulation phases for the first three weeks post operation (right, Barcik et al. Biomedicines, 2021).

Pres:
Barcik J, Ernst M, Buchholz T, Constant C, Zeiter S, Gueorguiev B, Windolf M. *In vivo* preclinical application of an active fixator system for the systematic investigation of the influence of the mechanical environment on fracture healing. 2021 EORS (oral).

Theses:
Barcik JP. Modulation of fracture mechanical conditions and feedback approach to determine the optimal healing environment. PhD thesis, Bulgarian Academy of Sciences, 2021.

Pub:
Barcik J, Ernst M, Balligand M, Dlaska CE, Drenchev L, Zeiter S, Epari DR, Windolf M. Short-term bone healing response to mechanical stimulation – a case series conducted on sheep. Biomedicines. 2021 Aug 10;9(8):988.
Barcik J and DR Epari. Can optimizing the mechanical environment deliver a clinically significant reduction in fracture healing time? Biomedicines 2021; 9(6):691.

Partner:
- Epari D (Prof), Queensland University of Technology (QUT), Brisbane, Australia

RehabFE: improving rehabilitation protocols of plated long bone fractures (ongoing) (P Varga, D Mischler, B Gueorguiev, M Windolf)

Background: Fixation failures and bone healing complications still have high incidence rates. Besides preoperative planning and intraoperative execution, postoperative rehabilitation protocols influence the outcome of osteosynthesis. However, to successfully guide a rehabilitation protocol, a clear understanding of potential pitfalls, such as plate failure and healing disturbances must be present. Ideally, these failures could be predicted based on patient parameters and surgical outcome, which could in turn be used to determine the appropriate subject-specific loading protocol to avoid those issues.
Goal: To develop and validate a finite element simulation methodology to predict fixation failures based on an *in vivo* preclinical model and AO Fracture Monitor data.
Results: Ovine tibiae osteotomized and fixed with a locking plate were biomechanically tested until plastic deformation of the implant. Deformations were recorded by means of an AO Fracture Monitor sensor and via optical stereographical 3D motion analysis on the plate surface strains. Interfragmentary motions were evaluated. Based on postoperative CT scans, subject-specific finite element models were created, and the experimental loading conditions were replicated. Bone displacements and plate deformations were accurately replicated by the simulations suggesting a valid modelling approach. The validated models will be used for further analysis of *in vivo* conditions.

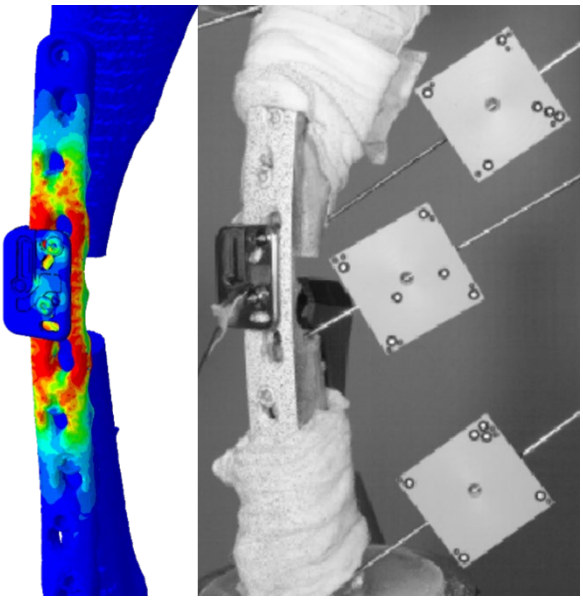
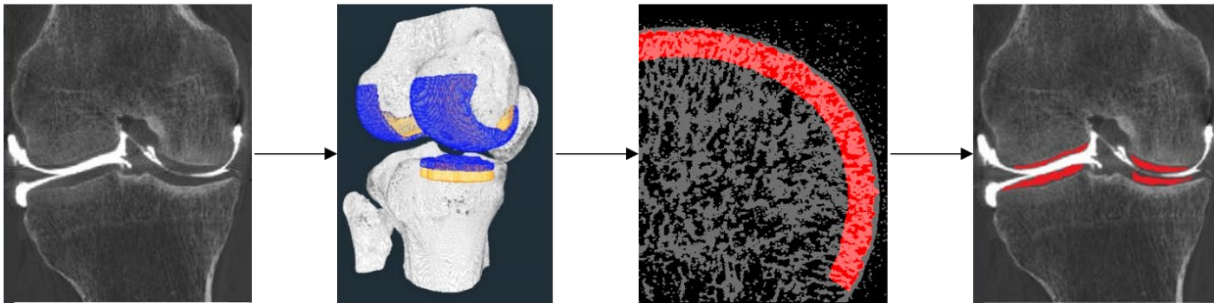


Figure 10.3.3: Finite element analysis results (left) and corresponding experimental setup (right) of a sheep tibia osteotomy fixed with a locking plate and attached AO Fracture Monitor.

Cartilage and subchondral bone changes in osteoarthritis can be detected quantitatively using *in vivo* imaging (CarCT) (K Mys, D Gehweiler, P Antonacci, B Gueorguiev)

Background: Cartilage diseases, such as osteoarthritis, rheumatoid arthritis and posttraumatic arthritis after intra-articular fractures and osteochondral defects have an important impact on the patient's quality of life and are a heavy burden for the healthcare system. Better understanding, early detection and proper follow-up could improve quality of life and reduce healthcare related costs. Imaging is a valuable tool to detect and monitor these cartilage-related diseases and investigate how they progress.
Goal: (1) to evaluate the accuracy of subchondral bone and cartilage quantification with advanced clinically available imaging techniques; (2) to assess whether difference between osteoarthritic (OA) and non-osteoarthritic (non-OA) knees can be detected quantitatively on cartilage and subchondral bone level with advanced clinically available imaging techniques.
Results: Two OA and three non-OA human cadaveric knees were scanned three times. A high-resolution peripheral quantitative computed tomography (HR-pQCT) scan (XtremeCT, Scanco Medical AG, Switzerland) was performed to visualize the bone microstructure. A contrast-enhanced clinical CT scan (GE Revolution Evo, GE Medical Systems AG, Switzerland) was made to measure cartilage thickness. A microCT scan (VivaCT40, Scanco Medical AG, Switzerland) served for validation. Bases on those scans, bone microstructural parameters and cartilage thickness were quantified. The microCT results highly correlated with the XtremeCT and clinical CT ones. The overall cartilage thickness was reduced in the OA and *versus* non-OA knees and the subchondral bone quality decreased accordingly within the femoral medial condyle. The largest differences were observed at the medial part of the femoral medial condyle for both cartilage and bone parameters, corresponding to clinical observations. Subchondral bone microstructural parameters and cartilage thickness were quantified with high accuracy using *in vivo* available imaging and apparent differences between the OA and non-OA knees were detected. Those results may improve OA follow-up and diagnosis and could lead to a better understanding of OA. However, further *in vivo* studies are needed to validate these methods in clinical practice.



1. Scanning *2. ROI selection* *3. Quantification trabecular parameters* *4. Quantification cartilage parameters*

Figure 10.3.4: Overview of the technique: (1) the bones were scanned with the three scanners, (2) Regions of interest (ROIs) were defined semi-automatically, (3) bones were segmented, and trabecular bone quantified, (4) cartilage was defined and quantified.

Partners:

- Dauwe J (MD), UZ Leuven, Belgium
- Eglin D (Prof), Ecoles des Mines Saint Etienne, France

Evaluation of the biomechanical benefit of optimized patient-specific fixations for complex proximal humerus fractures (PSPH) (D Mischler, L Tenisch, J Schader, J Dauwe, B Gueorguiev, M Windolf, P Varga)

Background: Despite past advances of implant technologies, complication rates of fixations remain high at challenging sites such as the proximal humerus. Computational approaches allow for systematic analyses with high throughput which is ideal for implant optimization tasks. Using parametric finite element (FE) simulations, a previous study demonstrated that improving screw angles of a locking plate could significantly reduce the predicted risk of cut-out failure.
Goal: To evaluate whether a computationally enhanced (EH) screw trajectory design of a locking plate can provide superior fixation stability compared to the original (OG) design via biomechanical testing, and to assess the instrumentation accuracy and its potential influence on the predictive ability of FE predictions.
Results: The EH implant configuration resulted in significantly more biomechanically assessed cycles to cut-out failure compared with the OG design (EH: 14080 ± 1414, OG: 11368 ± 1313, $p < 0.01$) in eight pairs of proximal humeri, confirming the significantly lower peri-implant bone strain, *i.e.,* failure risk, predicted by FE for EH (367 ± 52 µmm/mm) *versus* OG (460 ± 44 µmm/mm, $p < 0.001$). The magnitude of instrumentation inaccuracies was small but had a significant effect on the FE-predicted failure risk ($p < 0.01$). The sample-specific FE predictions strongly correlated with the experimental results ($R^2 = 0.70$) when incorporating instrumentation inaccuracies.

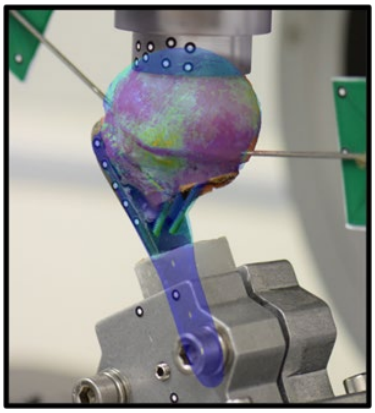


Figure 10.3.5: Finite element analysis result overlayed on the cadaveric bone during experimental testing.

Pres:
Schader JF, Mischler D, Dauwe J, Gueorguiev B, Varga P. Could patient-specific locking plates improve primary stability of proximal humerus fracture fixation? 2021 ESBiomech (oral).
Mischler D, Schader JF, Dauwe J, Gueorguiev B, Varga P. Computationally optimized implants improve biomechanical fixation stability of complex proximal humerus. 2021 ESBiomech (oral).
Mischler D, Schader JF, Dauwe J, Windolf M, Gueorguiev B, Varga P. Evaluation of the biomechanical benefit of computationally optimized fixations for complex proximal humerus. 2021 EORS (oral).

Pub:
Schader JF, Mischler D, Dauwe J, Richards RG, Gueorguiev B, Varga P. One size may not fit all: patient-specific computational optimization of locking plates for improved proximal humerus fracture fixation. J Shoulder Elbow Surg. 2022. 31:192–200.

miRNA analysis to discover fracture related biomarkers (MiDiag2) (ongoing) (M Stoddart, M Alini, H Schmal)

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 way 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. In a previous AOTrauma project (MiDiag) we investigated changes in small non-coding RNA in fracture patients and during osteogenic differentiation.
Goal: A panel of prospective microRNA (miRNA) markers were identified, and this now requires further validation. In addition, we aim to use the methods developed, and the database of patient serum non-coding RNA created, to further investigate markers that are mechanically regulated and would be associated with secondary bone healing.
Results: Mechanically induced chondrogenesis is exploited to identify which miRNAs are involved into callus formation, the first step to endochondral ossification and fracture healing. A multiaxial loading bioreactor was used to investigate early mechanically induced chondrogenesis (3 days) and identify differentially expressed miRNA. RNAseq was performed to screen for potential candidates to be validated *in vitro* and in clinical samples from fracture patients (Figure 10.3.6). Investigations are ongoing to validate the correlation between early miRNA expression with the differentiation outcome.

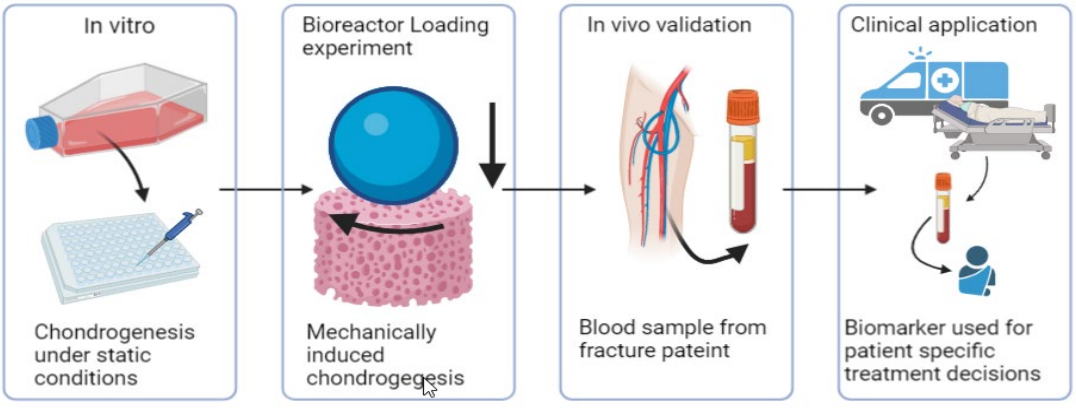


Figure 10.3.6: schematical overview of the experimental design and workflow

Pres:
Della Bella E, Menzel U, Basoli V, Tourbier C, Alini M, Stoddart MJ. Dexamethasone regulates circRNA expression during human bone marrow MSC differentiation. Poster. 6th World TERMIS Congress 2021.

Pub:
Guo P, Liu X, Zhang P, He Z, Li Z, Alini M, Richards RG, Grad S, Stoddart MJ, Zhou G, Zou X, Chan D, Tian W, Chen D, Gao M, Zhou Z, Liu S. A single-cell transcriptome of mesenchymal stromal cells to fabricate bioactive hydroxyapatite materials for bone regeneration. Bioact Mater. 2021 Aug 11;9:281-298. DOI: 10.1016/j.bioactmat.2021.08.009.
Della Bella E, Koch J, Baerenfaller K. Translation and emerging functions of non- coding RNAs in inflammation and immunity. Allergy 2022. DOI: 10.1111/all.15234.
Della Bella E, Buetti-Dinh A, Licandro G, Ahmad P, Basoli V, Alini M, Stoddart MJ. Dexamethasone induces changes in osteogenic differentiation of human mesenchymal stromal cells via SOX9 and PPARG, but not RUNX2. Int J Mol Sci. 2021 Apr 30;22(9):4785. DOI: 10.3390/ijms22094785.
Ahmad P, Stoddart MJ, Della Bella E. The role of noncoding RNAs in osteogenic differentiation of human periodontal ligament stem cells. Craniomaxillofacial Trauma & Reconstruction Open. January 2021. DOI:10.1177/2472751221999229.

Thesis:
Manuel Herzog. Identification of microRNAs involved in mechanically driven differentiation of human mesenchymal stromal cells. Master of Science ETH in Health Sciences and Technology (MSc ETH HST). March 2021. Supervisors: Prof Dr Marcy Zenobi-Wong, ETH Zurich; Prof Dr Martin Stoddart, AO Research Institute Davos.

Partners:
- Kubosh EJ (Dr), Department of Orthopedics and Traumatology, University Medical Center Freiburg, Germany
- Zaffagnini S (Prof), Istituto Ortopedico Rizzoli, Bologna, Italy
- Mattiassich G (Priv Doz Dr), Klinik Diakonissen, Schladming, Austria
- Bischofreiter M (Dr), Klinik Diakonissen, Schladming, Austria

Local delivery system for improving efficacy of bacteriophages combined with antibiotics (Gelphage) (ongoing) (M D`Este, F Moriarty)

Background: Bacteriophages, viruses that kill bacteria, are emerging as attractive interventions against antibiotic resistant infections, including fracture-related infection. In clinical settings, bacteriophage therapy is always an adjunct to antibiotic therapy.
Goal: The goal of this project is to assess the effect of combining antibiotics with bacteriophages to determine the effect of any interaction on bacterial killing efficacy. Furthermore, the effect of combining antibiotic and bacteriophages in a hydrogel delivery system shall be evaluated.
Results: Synergistic or antagonistic effects of antibiotic with bacteriophages were evaluated in checkerboard settings. To date, we have tested the interaction of daptomycin, gentamicin, and vancomycin with *S. aureus* phage ISP and 44AHJD against planktonic *S. aureus* (including methicillin/gentamicin resistant strains). Data indicates that certain combinations can display both synergistic and antagonistic interactions, which is a significant concern, and suggesting such testing would be critical for each infecting pathogen before commencing phage therapy.

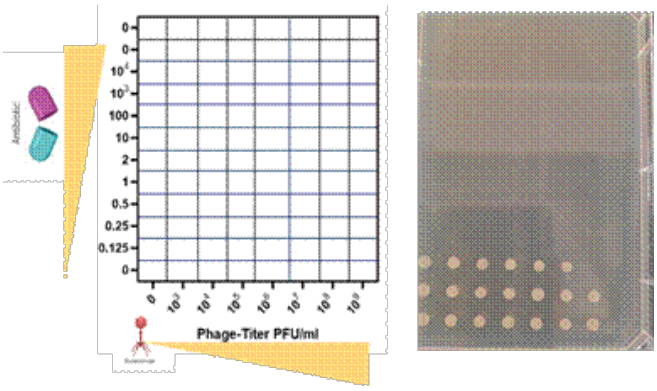


Figure 10.3.7: Left: Schematic illustration of the checkerboard setting, with antibiotic concentration and phage titer arranged in a matrix of combinations. Right: Agar plate showing result, with colonies present where the combination failed to kill all bacteria.

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

Background: Within bone marrow, *S. aureus* pathophysiology involves abscess formation, which consist of central staphylococcal abscess communities (SACs), surrounded by a fibrin pseudocapsule and infiltrating immune cells. Previous data from this project suggested that SACs might directly cause myeloid-derived suppressor cell (MDSC) expansion from bone marrow cells.
Goal: Recent investigations aimed to further explore this by co-culturing the *in vitro* SAC with murine bone marrow cells.
Results: Compared to negative control cultures, the positive control culture (MDSC expansion due to IL-6 and GM-CSF supplementation) and SAC – bone marrow co-culture had more monocytes and less neutrophils (Figure 10.3.8). SAC-exposed bone marrow cultures differed in neutrophil percentages alone or both neutrophil and monocyte percentages in comparison with dispersed, planktonic *S. aureus* or *S. epidermidis* aggregates cultures, respectively (Figure 10.3.8). No T cell suppression was observed for cultures with the negative control cells, but positive control monocytes and neutrophils suppressed T cells proliferation and absolute numbers and, thus, were indeed MDSCs. With a protein biomarker assay, potential factors that mediate SAC-induced MDSC expansion and activation, such as GM-CSF, IL-1β, IL-6, and TNFα, were identified.

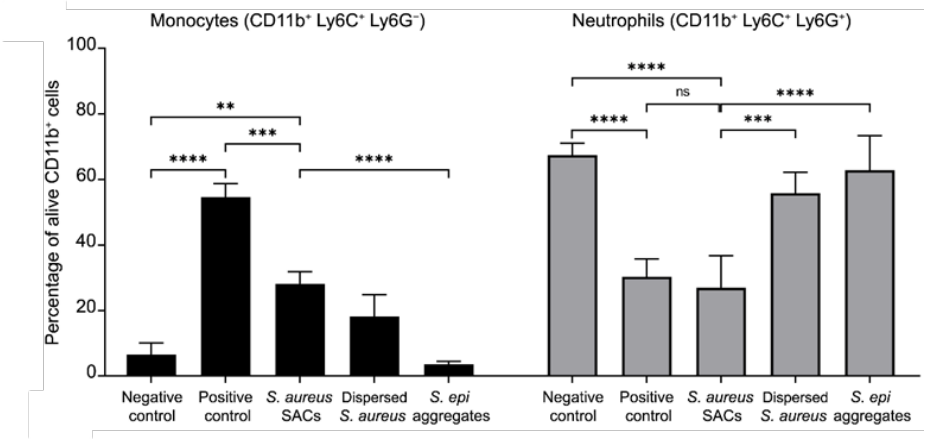


*Figure 10.3.8: Murine bone marrow cells were co-cultured with in vitro S. aureus SACs. As comparison to this co-culture, murine bone marrow cells were kept untreated (negative control), were treated with GM-CSF and IL-6 (positive control) or were co-cultured with dispersed S. aureus in a collagen gel or S. epidermidis aggregates. The percentage of monocytes (Ly6C⁺) and neutrophils (Ly6G⁺) from alive CD11b⁺ cells was determined with flow analysis. ns = non-significant, **p < 0.01, ***p < 0.001, and ****p < 0.0001.*

Pres:
A 3-dimensional *in vitro Staphylococcus aureus* abscess community model. KNVM & NVMM 2021, 30&31 March 2021, (virtual).
Staphylococcus aureus abscess communities and myeloid-derived suppressor cells: *in vivo* and *in vitro* studies. 15th World Immune Regulation Meeting, 30 June-3 July 2021, virtual.

Pub:
Hofstee MI, Riool M, Gieling F, Stenger V, Constant C, Nehrbass D, Zeiter S, Richards RG, Zaat SAJ, Moriarty TF. ~~A~~ murine *Staphylococcus aureus* fracture-related infection model characterized by fracture non-union, staphylococcal abscess communities, and myeloid-derived suppressor cells. *eCells & Materials*, 44, 774-792 (2021).
Hofstee MI, Heider A, Häckel S, Constant C, Riool M, Richards RG, Moriarty TF, Zaat SAJ. *In vitro* 3D *Staphylococcus aureus* abscess communities induce bone marrow cells to expand into myeloid-derived suppressor cells. *Pathogens*, 10, 1446 (2021).

Partner:
- Zaat SAJ, Amsterdam UMC location AMC, The Netherlands

A combination enzybiotic and anti-virulence approach for the treatment of *S. aureus* fracture-related infections infection (Enzybiotic2) (ongoing) (M Chitto, F Moriarty)

Background: Despite the extensive treatment protocols, outcomes after fracture-related infection remain relatively poor. Enzybiotics are a novel class of antimicrobial enzymes, naturally derived from bacteria and bacteriophages, which have been demonstrated *in vitro* and in animal models to be highly effective in killing bacteria.
Goal: The identification and testing of an enzyme-based treatment protocol that may degrade biofilm components and penetrate fibrin barriers and rapidly lyse bacterial cells.
Results: The tested enzybiotic combination showed significant anti-biofilm effects in several *in vitro* models (Figure 10.3.9). Subsequent steps will look to couple this functionality with greater matrix and fibrin degrading activity.

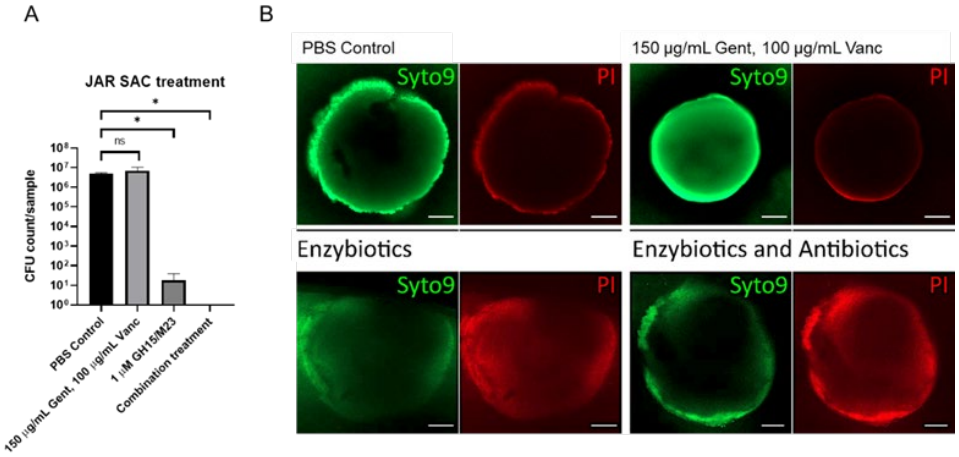


*Figure 10.3.9: Enzybiotics are effective at treating an in vitro staphylococcal abscess communities (SAC) model. (**A**) Resulting CFU counts per sample of 24-hour SACs treated with enzybiotics and antibiotics. Combination treatment indicates a full treatment with antibiotic (gentamicin and vancomycin) and enzymes (n = 3). (**B**) Representative fluorescence microscopy images of treated SACs as in (**A**) stained with nucleic acid dyes Syto9 (green, membrane-permeable) and propidium iodide (red, non-membrane-permeable). Scale bars are 100 µm*

Pub:
Sumrall ET, Hofstee MI, Arens D, Röhrig C, Baertl S, Gehweiler D, Schmelcher M, Loessner M. An enzybiotic regimen for the treatment of methicillin-resistant *Staphylococcus aureus* orthopaedic device-related infection. Antibiotics (Basel).Oct; 10(10): 1186 (2021).

The influence of the gut microbiota on bone (BacBone2) (ongoing) (A Wallimann, K Thompson, F Moriarty)

Background: The gut microbiota was shown to play a crucial role in human health, whereby perturbations of the gut microbiota, such as through antibiotic intervention, is involved in many diseases.
Goal: In this project we investigate the potential of gut microbial-derived compounds and metabolites in benefit for bone health.
Results: In the latest series of experiments, we investigated if long-term antibiotic therapy, which is applied to patients with an orthopedic-device related infection, alters the gut microbiome composition and function. We observed a marked drop in gut microbial diversity during the course of antibiotic therapy with only slow recovery to baseline (Figure 10.3.10). In addition, at the timepoint with lowest gut-microbial diversity, many pro-inflammatory cytokines were upregulated compared to baseline. Together, this indicates that the antibiotic-induced perturbations are not limited to the intestine, but influence systemic inflammation levels, which further potentially affects bone health in these patients.

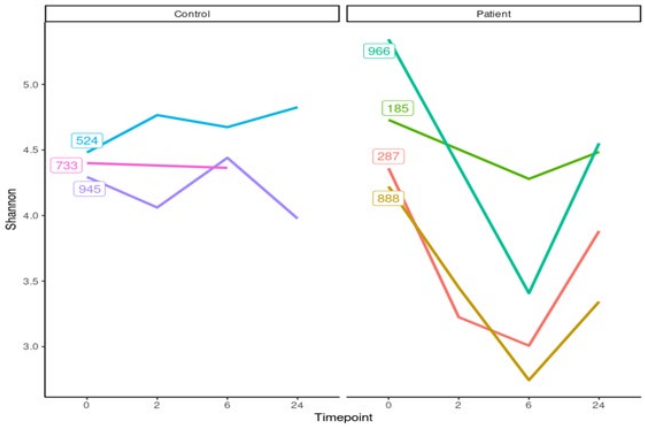


Figure 10.3.10: Impact of long-term antibiotic therapy on the gut microbiota composition of ODRI patients. Healthy controls without any antibiotic intervention are shown left.

Pres:
Short-chain fatty acids and antibiotics affect local and systemic processes relevant for bone healing. Gut-Bone-Axis Meeting, 21-23 June 2021. (online meeting) *Award for best oral student presentation at this meeting.*
Short-chain fatty acids and antibiotics affect local and systemic processes relevant for bone healing. World Microbe Forum, 20-24 June 2021. (online meeting).
Short-chain fatty acids and antibiotics affect local and systemic processes relevant for bone healing. WIRM, 30 June – 4 July 2021. (online meeting).
Impact of rifampicin and levofloxacin on gut microbiome and short-chain fatty acid production in mice with bone fracture: consequences for bone health. ECCMID, 9-12 July 2021. (online meeting).

Pub:

Wallimann A, Magrath W, Thompson K, Moriarty TF, Richards RG, Akdis CA, O`Mahony L, Hernandes CJ. Gut microbial-derived short-chain fatty acids and bone: a potential role in fracture healing. *eCells &Materials*, Apr21;41:454-470 (2021).
Wallimann A, Magrath W, Pugliese B, Stocker N, Westermann P, Heider A, Gehweiler D, Zeiter S, Claesson MJ, Richards RG, Akdis CA, Hernandez CJ, O`Mahony L, Thompson K, Moriarty TF. Butyrate inhibits osteoclast activity *in vitro* and regulates systemic inflammation and bone healing in a murine osteotomy model compared to antibiotic-treated mice. Mediators Inflamm., Dec 10;2021:8817421 (2021).

Partners:
- Akdis C (Prof), SIAF, Davos, Switzerland
- O´Mahony L, University College Cork, Ireland

Implant retention in a sheep fracture related infection model: evaluating fracture healing and an antibiotic loaded hydrogel (DAIR) (ongoing) (C Siverino, S Zeiter, L Gens, F Moriarty)

Background: Management of fracture related infection (FRI) often involves further surgical procedures with poor long-term outcomes. Debridement, Antibiotics, Irrigation, and implant Retention (DAIR) is a surgical treatment protocol often applied to acute/early FRI. Clinically relevant pre-clinical models of DAIR in FRI are scarce and none have been developed in large animals.
Goal: This project aims to develop a large animal model for FRI including a DAIR approach.
Results: The first outcomes prove that it is possible to establish a model of FRI with plating osteosynthesis. Evaluation of the metal plate by scanning electron microscopy (SEM) at revision show the presence of biofilm over the implant (Figure 10.3.11 A). After 3 weeks of infection period, all the animals show a high bacterial burden at revision and at euthanasia with a high bacterial colonization of the bone marrow and bone (Figure 10.3.11 B). The presence of bacteria within the bone was also confirmed by histology (Figure 10.3.11 C).
Now that the model is established, novel interventional strategies including debridement/lavage of the intramedullary (IM) canal may be tested. The development of this large animal model represents a significant addition to the portfolio of animal models available at ARI.

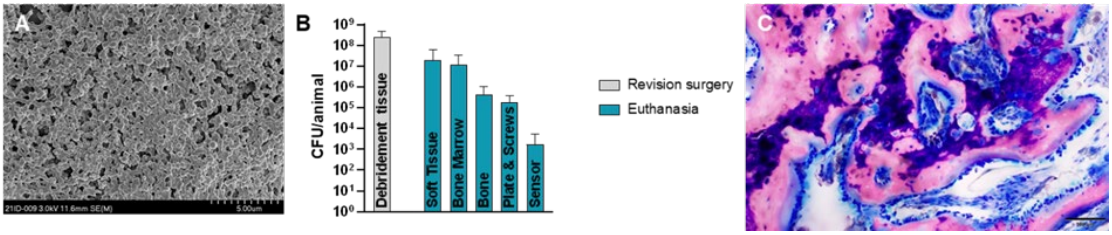


Figure 10.3.11: ***A:*** *SEM of biofilm on the metal plate 3 weeks from initial surgery;* ***B:*** *Bacterial quantification at revision surgery and euthanasia;* ***C:*** *G&E staining of bone isolated from the infected area at euthanasia.*

Exopolysaccharide coated material surfaces modulating foreign body reactions (EPSIm) (ongoing) (F Moriarty, R Bagnol)

Background: The gut microbiota and its assortment of surface associated polymers and secreted metabolites have been shown to impact nearly all organs of the human body including bone.
Goal: In this study we look to investigate the extracellular polysaccharide (EPS) produced by *Bifidobacterium longum* and evaluate its potential as an implant surface coating.
Results: The EPS has been successfully used in conjunction with chitosan to produce polyelectrolyte coatings with varying number of layers. The coatings have been tested on human peripheral blood mononuclear cells and have shown a dose dependent stimulation of interleukin 10, which persists for at least 7 days.
Future steps will include coating on other support materials, further characterization of the coatings effects on other types of cells, and eventually coating the surface of orthopedic devices to determine its effect on host cellular responses *in vitro* and *in vivo.*

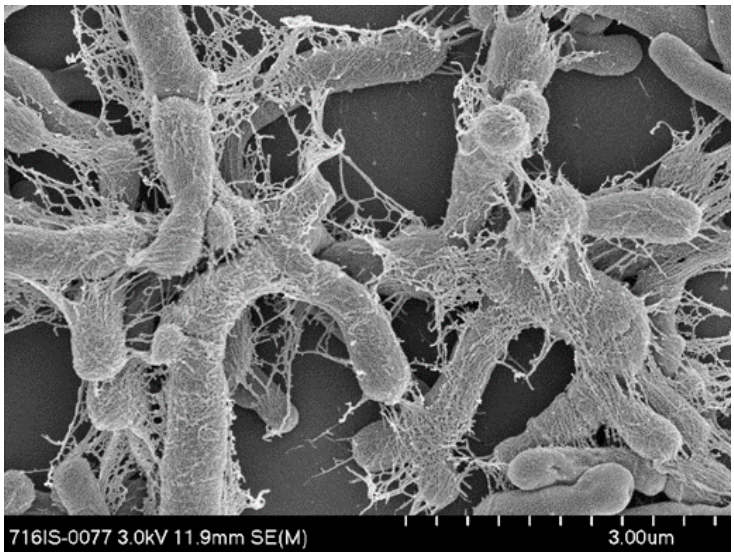


Figure 10.3.12: Scanning electron micrograph of Bifidobacterium longum with extracellular polymeric substances forming a meshwork around the bacteria.

Partners:

- Eglin D (Prof), Ecoles des Mines Saint Etienne, France
- O'Mahony L, University College Cork, Ireland

Bone defect healing after chronically infected non-union (Mascot) (ongoing) (C Siverino, S Zeiter, F Moriarty)

Background: In chronically infected non-unions, surgical intervention involves extensive debridement to remove necrotic and infected bone, often resulting in large defects requiring elaborate and prolonged bone reconstruction techniques. However, reconstruction techniques may yield poorer results in patients with a chronically infected non-union compared to non-infected equivalents.

Goal: To establish a rabbit humerus model with plating osteosynthesis that includes the induced membrane technique (IMT) and bone grafting.

Results: The animal model (Figure 10.3.13) was successfully established. The development of this preclinical *in vivo* model would be a valuable resource to explore treatment concepts of infected non-union and facilitate studies into the many clinically driven questions behind current treatment concepts.

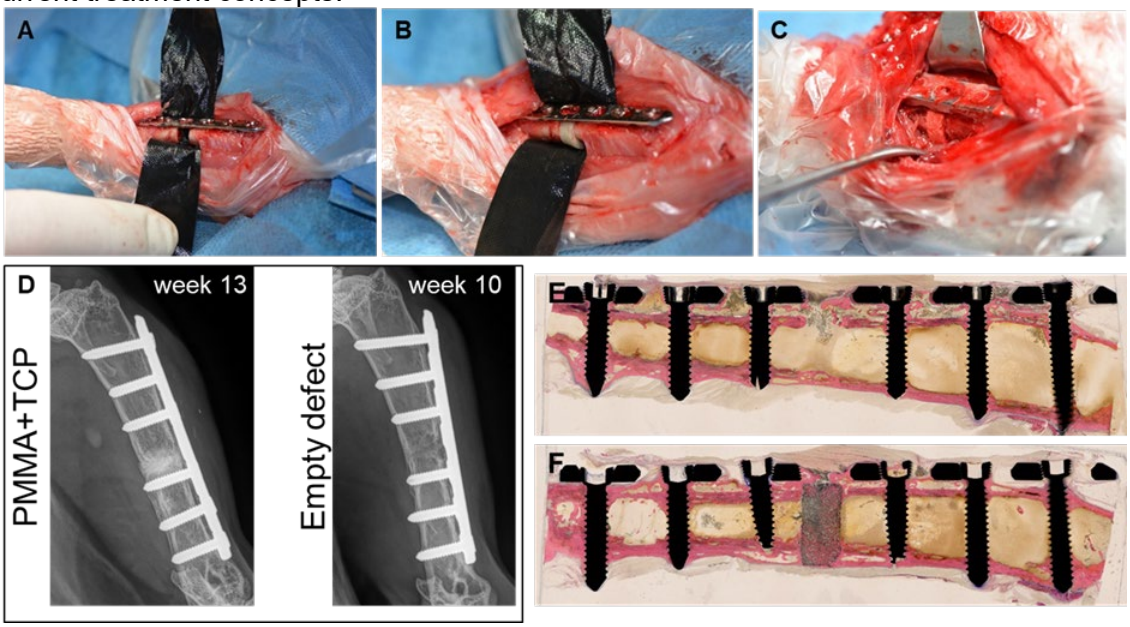


*Figure 10.3.13: Rabbit humerus model. **A:** 5 mm empty humerus defect after surgery stabilized with the 2.4 mm plate; **B:** PMMA spacer filling the 5 mm osteotomy; **C:** chronOs inserted at the osteotomy site; **D:** X-ray of the bone filled with chronOs (TCP) or empty; **E** and **F:** G&E staining of bone formation after 12 weeks from revision **E** with an empty defect compared to **F** ChronOs.*

Partner:

- Morgenstern M (MD), University Hospital Basel, Switzerland

Immunoprofiling of fracture patients to determine predictive biomarkers of healing (NUPredict) (ongoing) (K Thompson, MJ Stoddart, M Alini)

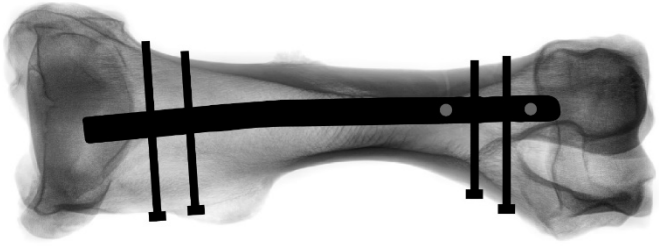
Background: In the context of fracture repair, a significant number of patients (<10%) continue to display healing deficiencies, despite marked advances in the understanding of fracture healing. Although specific co-morbidities such as diabetics and smokers may increase risk of delayed healing and potential progression to non-union, currently it is not possible to identify specific patients at elevated risk of delayed healing. A number of recent studies have indicated that specific populations of blood-resident immune cells are altered in patients with diminished fracture healing. These immune cell changes act to inappropriately maintain a pro-inflammatory environment that negatively affects bone regeneration. In addition, certain non-coding microRNA signatures have also been identified in the blood of non-union patients, suggesting that profiling of such markers may be a means to identify patients at risk of non-union and allow earlier therapeutic interventions when healing capacity may be recovered. However, the majority of these reported studies are hampered by small sample numbers, meaning that the applicability of such assays to identify non-union patients currently requires further investigation.
Goal: To conduct in-depth immunophenotyping of blood-resident immune cells in delayed healing patients compared to normal healing patients. In addition, we seek to identify whether specific profiles of blood-resident miRNAs can be used to identify delayed healing patients.
Results: To date we have identified a number of changes in both circulating levels of specific T cell subsets and miRNA signatures in 12 non-union patients compared to 8 normal healing patients. The functional consequences of such changes in immune cell proportions and their correlated surface marker expression, such as immune cell-mediated production of pro- and anti-inflammatory cytokines, are now being further investigated and assessed *versus* clinical parameters. In addition, a panel of miRNA biomarkers are now the subject of a further validation in a wider patient cohort to determine whether such changes correlate with healing outcome.

10.4 AOVET

An In Vitro Biomechanical Investigation of an Interlocking Nail System and Locking Compression Plate Fixation of Osteotomized Equine Humerus (C Constant, S. Zeiter)

Background: Complete humeral fractures in mature horses (>300 kg body weight) are common, but surgical treatments have a guarded prognosis due to unsuitable surgical implants that do not have sufficient strength to achieve adequate stability.
Goal: The aim of this in-vitro study is to examine the biomechanical properties of intramedullary interlocking nail (IIN) combined with a cranial locking compression plate (LCP) to stabilize osteotomized humerus from mature horses. Construct pairs will be tested in compression to determine stiffness and failure properties, as well as torsional stiffness and yield load. This study will determine if commercially available IIN human system could be used to successfully repair humeral fractures of mature horses and become a surgical alternative to euthanasia or conservative treatment.

Results: Currently no results.



Schematic representation of the IIN for equine humerus

Partner: E. Marchionatti, Vetsuisse Faculty, University of Bern, Switzerland

10.5 AOTC System

Investigation of screw-suture *versus* suture-button dynamic stabilization systems for syndesmotic repair (F Souleiman, T Pastor, B Gueorguiev)

Background: The quest for optimal treatment of acute distal tibiofibular syndesmotic disruptions is still in progress. Using suture-button repair devices is one of the dynamic stabilization options, however, they may not be always appropriate for stabilization of length-unstable syndesmotic injuries. Recently, a novel screw-suture repair system was developed to address such issues.
Goal: To investigate the performance of the novel screw-suture repair system in comparison to a suture-button stabilization of unstable syndesmotic injuries.
Results: Eight pairs of human cadaveric lower legs were CT scanned under 700 N single-leg axial loading in five foot positions – neutral, 15° external/internal rotation and 20° dorsi-/plantarflexion – in 3 different states: (1) pre-injured (intact); (2) injured, characterized by complete syndesmosis and deltoid ligaments cuts simulating pronation-eversion injury types III and IV as well as supination-eversion injury type IV according to Lauge-Hansen; (3) reconstructed, using a screw-suture (FIBULINK, Group 1) or a suture-button (TightRope, Group 2) implants for syndesmotic stabilization, placed 20 mm proximal to the tibia plafond/joint surface. All specimens were: (1) biomechanically tested over 5000 cycles under combined 1400 N axial and ±15° torsional loading; (2) rescanned with CT. Clear space (diastasis), anterior tibiofibular distance, talar dome angle and fibular shortening were measured radiologically from the CT scans. Anteroposterior (AP), axial, mediolateral and torsional movements at the distal tibiofibular joint level were evaluated biomechanically via motion tracking. In each group clear space increased significantly after injury ($p \leq 0.004$) and became significantly smaller in reconstructed compared with both pre-injured and injured states ($p \leq 0.041$). In addition, after reconstruction it was significantly smaller in Group 1 compared to Group 2 ($p < 0.001$). AP and axial movements were significantly smaller in Group 1 compared with Group 2 ($p < 0.001$). No further significant differences were detected between the groups ($p \geq 0.113$). Although both implant systems demonstrate ability for stabilization of unstable syndesmotic injuries, the novel screw-suture reconstruction provides better anteroposterior translation and axial stability of the tibiofibular joint and maintains it over time under dynamic loading. Therefore, it could be considered as a promising option for improved treatment of syndesmotic disruptions.

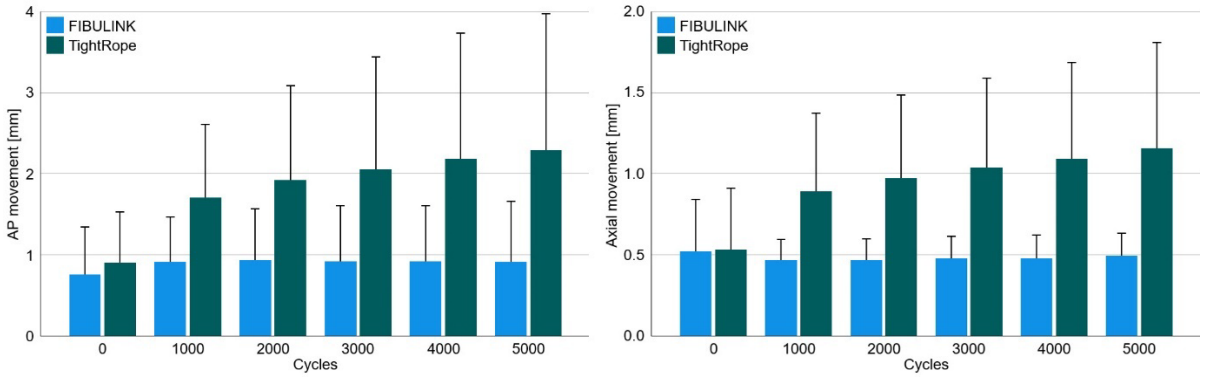


Figure 10.5.1: Anteroposterior (AP, left) and axial (right) movements at distal tibiofibular joint level in Group 1 (FIBULINK) and Group 2 (TightRope) during biomechanical testing.

Partners:

- Swords M (MD), Michigan Orthpaedic Center, Lansing, MI, USA
- Schepers T (Prof), Amsterdam Academic Medical Center, Amsterdam, The Netherlands
- Tomlinson M (MD), The Orthopaedic Clinic, Auckland, New Zealand

Statistical analysis of complex proximal humerus fractures (HumFx) (ongoing) (P Varga, K Mys, T Pastor, K van Knegsel, L Visscher, J Dauwe, A Bashardoust, A Knill, D Gehweiler, B Gueorguiev, M Windolf)

Background: Fixation of complex proximal humerus fractures has remained challenging with failure rates ranging up to 35%. This is partially due to large variations in the number, shape and displacement of fragments, rendering the understanding and classification of fractures difficult, and the treatment decision prone to errors.
Goal: To perform statistical description of the pattern and spatial distribution of complex fractures in the proximal humerus.
Results: Anonymized preoperative CT datasets of 100 patients with three- or four-part proximal humerus fractures were collected retrospectively. All fracture fragments were segmented semi-automatically on the CT images and the fracture lines were identified using advanced custom-developed image processing tools. The fractures were virtually reduced by solving the 3D puzzle utilizing the intact contralateral side as template. A statistical shape model of the proximal humerus was built based on the contralateral humeri and the fracture lines of the ipsilateral side were projected on the mean shape model to describe the variability of fracture patterns and evaluate their spatial distribution. The fracture lines predominantly passed through the surgical neck and between the tuberosities and tendon insertions. In contrast to previous reports, fracture lines passed through the bicipital groove. In a comprehensive and systematic approach, the zones of the proximal humerus with highest fracture probability were identified, demonstrating a considerable variability of fracture patterns in complex cases. Detailed analysis of these results is expected to contribute to improved understanding of fracture pattern variability, enhance surgical training and education, and aid development of advanced implant designs.

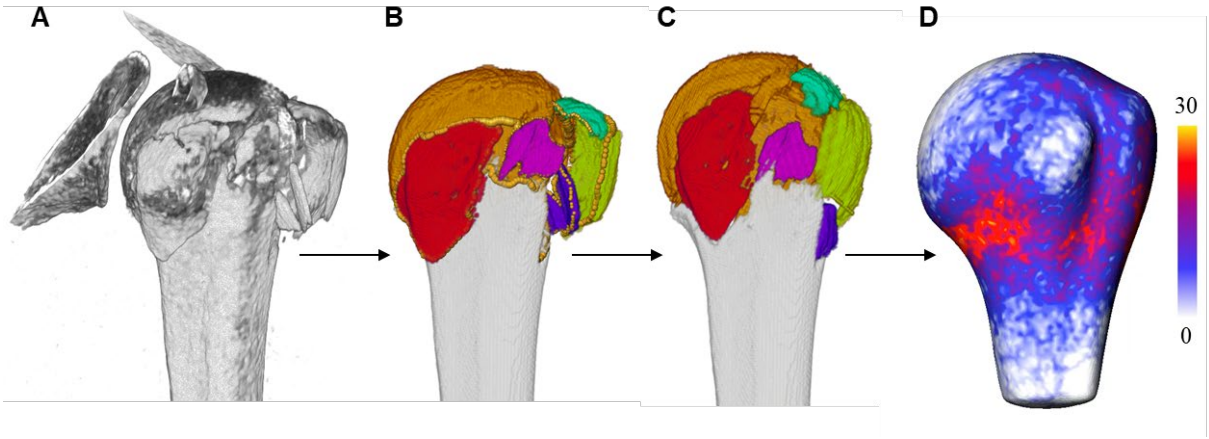


Figure 10.5.2: CT image (A) segmented to identify fragments and fracture lines (B) and perform virtual fracture reduction (C); fracture lines of 100 clinical cases mapped on statistical mean shape model, resulting in fracture probability map (D).

Pres:
Mys K, van Knegsel K, Pastor T, Gehweiler D, Bashardoust A, Windolf M, Gueorguiev B, Nijs S, Lambert S, Varga P. Digital mapping of bone fracture patterns: statistical analysis of complex proximal humerus fractures. 2021 DKOU (oral).

Partners:
- Knobe M (Prof), Lucerne Cantonal Hospital, Lucerne, Switzerland
- Lambert S (MD), University College of London Hospital, UK
- Nijs S (Prof), UZ Leuven, Belgium

Biomechanical testing of anterior variable-angle locked plating for simple and complex patella fractures (I Zderic, B Gueorguiev)

Background: Treatment of both simple and complex patella fractures represents a challenging clinical problem. It aims to restore the integrity of the extensor mechanism and the congruity of patellofemoral joint. Controversy exists regarding the most appropriate fixation method. Tension band wiring, aiming to convert the pulling forces on the anterior aspect of the patella into compression forces across the fracture site, is the standard of care; however, it is associated with high complication rates. Recently, anterior variable angle locking plates have been developed for treatment of both simple and comminuted patella fractures.
Goal: To investigate the biomechanical performance of the recently developed anterior variable angle locking plates *versus* tension band wiring used for fixation of simple and complex patella fractures.
Results: Sixteen pairs of human anatomical knee specimens were used to simulate either two-part transverse simple AO/OTA 34-C1 or five-part complex AO/OTA 34-C3 patella fractures by means of osteotomies, with each fracture model being created in eight pairs. The complex fracture pattern was characterized with a medial and a lateral proximal fragment, together with an inferomedial, an inferolateral, and an inferior fragment mimicking comminution around the distal patellar pole. The specimens with simple fractures were pairwise assigned for fixation with either tension band wiring through two parallel cannulated screws, or an anterior variable angle locking core plate. The knees with complex fractures were pairwise treated with either tension band wiring through two parallel cannulated screws plus circumferential cerclage wiring, or an anterior variable angle locking three-hole plate. Each specimen was tested over 5000 cycles by pulling on the quadriceps tendon, simulating active knee extension and passive knee flexion within the range from 90° flexion to full knee extension. Interfragmentary movements were captured by means of motion tracking. For both fracture types, the articular displacements, measured between the proximal and distal fragments at the central aspect of the patella between 1000 and 5000 cycles, together with the relative rotations of these fragments around the mediolateral axis were all significantly smaller following the anterior variable angle locked plating compared with the tension band wiring ($p < 0.01$). From a biomechanical perspective, anterior locked plating of both simple and complex patella fractures provides superior construct stability *versus* tension band wiring.

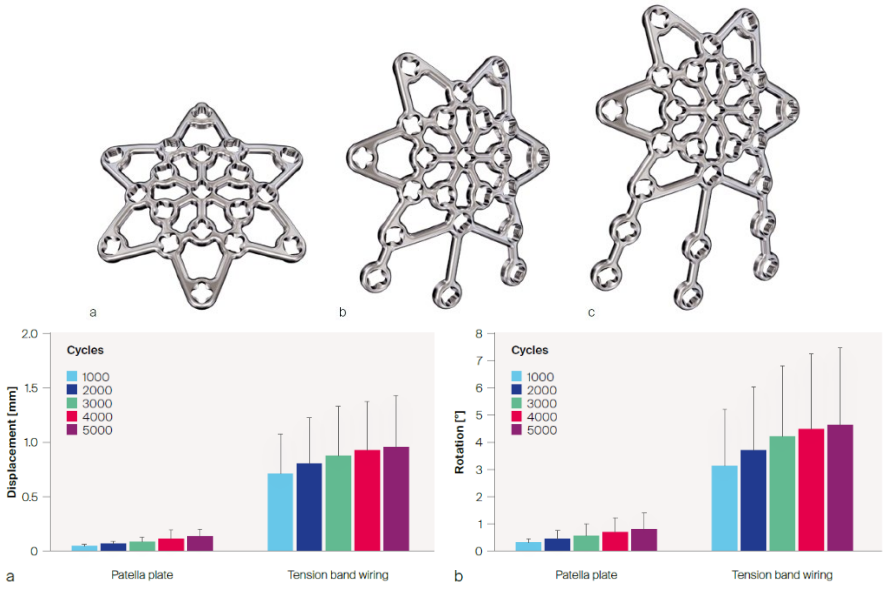


Figure 10.5.3: Top: core (a), three-hole (b), and six-hole (c) standard Variable Angle Locking Anterior Patella Plates 2.7 for treatment of simple and complex patella fractures; bottom: articular displacement at the central aspect of the patella (a) and rotation (b), both measured between the proximal and distal fragments after 1000, 2000, 3000, 4000, and 5000 cycles and featuring complex fractures fixed by either anterior variable angle locked plating or tension band wiring in terms of mean and standard deviation.

Partners:

- Sommer C (MD), Cantonal Hospital Graubünden, Chur, Switzerland
- Stoffel K (Prof), University Hospital Basel, Basel, Switzerland
- Saura-Sanchez E (MD), University Hospital of Elche, Elche, Spain
- Woodburn W, DePuy Synthes, West Chester, USA
- Castle R, DePuy Synthes, West Chester, USA
- Penman J, DePuy Synthes, West Chester, USA

Bacteriophage therapy for fracture-related infection due to *Staphylococcus aureus* (PhageS) (ongoing) (F Moriarty, S Zeiter, V Post)

Background: Bacteriophage therapy has received increasing interest as an alternative to antibiotic therapy for treating musculoskeletal infection.
Goal: This project aims to provide proof of concept data for phage therapy of difficult to treat, antibiotic resistant orthopaedic device-associated infections, when applied prophylactically or therapeutically.
Results: In the prevention study, all animals received a single shot of antibiotic prophylaxis preoperatively. Infection was not prevented in the control group. Phage loaded hydrogel reduced the average bacterial burden by up to one hundred-fold, however, it did not prevent infection from occurring. In the phage in buffer group, the majority of rabbits were infection free at euthanasia (Figure 10.5.4).

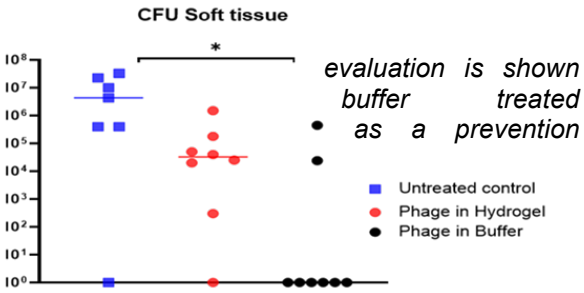


Figure 10.5.4: Quantitative bacteriological evaluation is shown for control, phage-loaded hydrogel and phage in buffer treated animals receiving treatment soon after inoculation as a prevention measure. Note phage in buffer (black dots) are the best performing intervention in this study.

Partners:

- Lavigne R, KU Leuven, Belgium
- Trampuz A, Charite Berlin, Germany

10.6 ARI Exploratory Research

A novel implant concept to amplify interfragmentary strain in large bone defects (StrainAmp) (J Buschbaum, M Windolf)

Background: Bone defects from trauma, infection and non-unions often require demanding treatment. Today, the defect can either be bridged with autologous bone graft generating secondary trauma, or it may be treated by bone lengthening or segmental transport methods. In both cases the disturbing impact on quality of life represents a significant burden to the patient. A novel implant concept may offer a quick and one step solution for critical sized bone defect healing. The concept intents to mechanically amplify the interfragmentary strain in a defect situation to optimize the biomechanical conditions. The underlying principle refers to Stephan Perren's strain theory which implies that optimal interfragmentary strain triggers a chain of mechanobiological events inducing and enabling bone repair.
Goal: To develop a strain amplifying implant prototype for first *in vivo* application and to investigate the concept in a pilot animal experiment.
Results: Based on the strain amplification principle, a first implant prototype suitable for *in vivo* use was designed and attached to ARI's Quarterpipe dynamic fixator system for controlled axial stimulation. The device was implanted in a 30 mm transverse tibial defect of two pilot sheep to assess its ability to trigger and improve healing in large bone defects. Healing

progression was monitored with biweekly radiographs and monthly CT scans until euthanasia at 32 weeks post operation. Biomechanical tests and histopathological analysis were conducted to assess final healing status. No significant callus and bone formation was overserved.

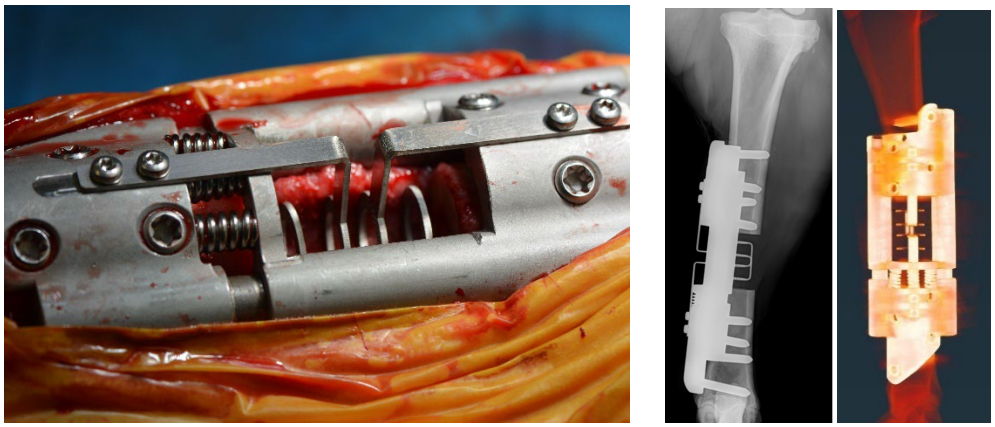


Figure 10.6.1: Left: Strain amplifying implant with dynamic fixator implanted in a sheep critical size defect. Right: Radiograph and CT scan used for monitor healing progression.

Partner:

- Perren N, Perrens 101 GmbH, Davos, Switzerland

Biomechanical assessment of implant fixation stability in ACL reconstruction (E Benca, J Caspar, K van Knegsel, B Gueorguiev, P Varga)

Background: Numerous methods and devices are available for implant fixation in anterior cruciate ligament (ACL) reconstruction. Their stability has been mostly assessed in terms of fixation stiffness – calculated from machine actuator displacement – and ultimate load.
Goal: To provide a better insight into measuring structural characteristics and biomechanical behavior of ACL implant fixations in a clinical context.
Results: The ACL was reconstructed in 14 human cadaveric tibial specimens. A quadrupled semitendinosus and gracilis tendon graft was pulled through a drilled 8 mm bone tunnel and secured with an 8 x 28 mm BioComposite Interference Screw (Arthrex Inc.) or an 8.0 mm Shark Screw ACL (surgebright GmbH). All specimens were tested to failure under progressively increasing cyclic loading with monitoring by motion tracking to accurately assess the screw migration in the tunnel. Significant differences were detected between the displacement of the proximal and distal graft ends, and the machine actuator displacement. The latter – commonly used to assess fixation stiffness – was up to 400% higher than the graft displacements and thus caused a significant underestimation of the fixation stiffness while still allowing qualitative comparison between different fixation methods and devices for ACL reconstruction. The ultimate load – usually indicating a high degree of graft slippage after the actual onset of clinical failure – can be used as a standardized variable for comparison between different fixation methods, however, it alone is not a sufficient measure to qualitatively describe fixation stability.

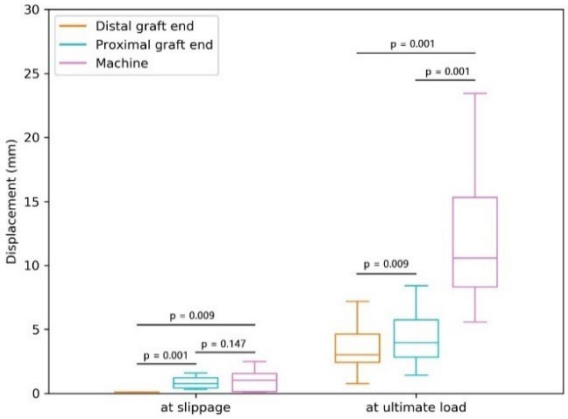


Figure 10.6.2: Displacements of the proximal and distal graft ends, and machine actuator displacement assessed at slippage initiation and ultimate load.

Pub:
Benca E, Zderic I, Caspar J, van Knegsel K, Hirtler L, Gueorguiev B, Widhalm H, Windhager R, Varga P. On measuring implant fixation stability in ACL Reconstruction. Sensors. 2021. 21(19):6632.

Partners:
- Hirtler L (MD), Medical University of Vienna, Austria
- Widhalm H (Prof), Medical University of Vienna, Austria
- Windhager R (Prof), Medical University of Vienna, Austria

Feasibility of the AO Fracture Monitor for measuring spinal fusion (SmartFusion) (ongoing) (M Heumann, M Windolf)

Background: CT based monitoring of spinal fusion cases has multiple limitations. Beside the radiation exposure to the patient, the interpretation of CT images is highly subjective. Furthermore, CT only provides a coarse visual overview (snapshots) of the fusion process as no continuous data is available. The AO Fracture Monitor is an implantable sensor system allowing for continuous and wireless implant load monitoring which may also provide an objective means to monitor the progress of spinal fusion to rapidly react to complications such as implant loosening.
Goal: To investigate feasibility of applying the AO Fracture Monitor measurement principle for spinal fusion assessment.
Results: Two sheep underwent posterolateral fusion surgery with posterior instrumentation using an asymmetric 3-level pedicle screw and rod system. Three modified AO Fracture Monitor sensors were attached between each screw pair as a first prototype device for proving the principle. After euthanasia – 23 weeks post operation – biomechanical testing of the spine was conducted to validate the sensor data. The spine was loaded unconstrained in flexion-extension, lateral bending, and axial rotation using a customized test setup. Furthermore, an *in vitro* model of a fused and a non-fused segment was tested for comparison, based on range of motion, sensor measurements and strain gauge signals measured directly on the instrumentation. All three parameters demonstrated differences between fused and a non-fused segments. Preliminary *in vivo* and *ex vivo* data supports the hypothesis that continuous rod load sensoring can provide a reliable and objective means to monitor the progress of fusion and rapidly react to complications. Further testing is required to obtain proof of the measuring principle.

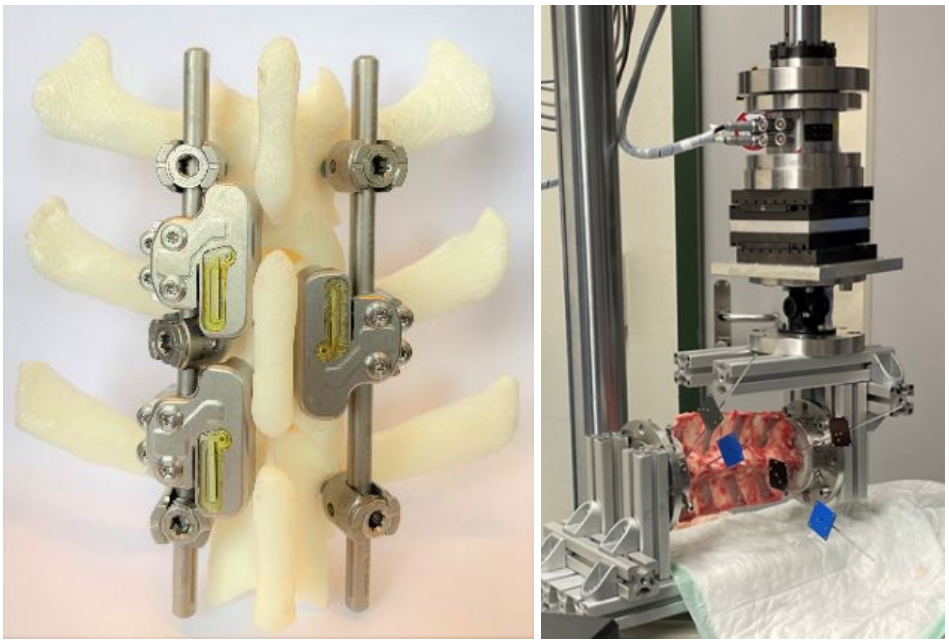


Figure 10.6.3: Instrumented rod-screw construct (left) and test setup for unconstraint loading of an ovine spine (right).

Pres:
Heumann M, Varjas V, Constant C, Benneker L, Schwyn R, Ernst M, Windolf M. Spinal fusion monitoring – transfer of measuring principles to the spine. 2021 EORS (oral).

Partners:
- Benneker L (Prof), Inselspital Bern, Switzerland
- Davies E, University Hospital Southampton, UK
- Wilke HJ (Prof), University Ulm, Ulm, Germany

Biomechanical determination of fracture loads and patterns of the odontoid process (E Benca, I Zderic, K van Knegsel, J Caspar, B Gueorguiev, P Varga)

Background: Odontoid fracture of the second cervical vertebra (C2) is the most common spinal fracture type in elderly patients. However, very little is known about the biomechanical fracture mechanisms that could be relevant for fracture prevention and treatment.
Goal: To assess the biomechanical competence and fracture characteristics of the odontoid process under consideration of bone mineral density, and to determine whether the load direction and the fusion state of the ossification centers have an effect on the mechanical strength and fracture patterns.
Results: A total of 42 human cadaveric C2 specimens were CT scanned, assigned to 6 groups ($n = 7$) and subjected to quasi-static loading until fracturing at inclinations of -15°, 0° and 15° in sagittal plane, and -50° and 0° in transverse plane. Bone mineral density (BMD), specimen height, fusion state of the ossification centers, stiffness, yield load, ultimate load, and fracture type according to Anderson and d'Alonzo were assessed. While the lowest values for stiffness, yield, and ultimate load were observed at load inclination of 15° in sagittal plane, no significant differences were observed among the six groups ($p \geq 0.235$). Specimens with only clearly distinguishable fusion of the ossification centers demonstrated even less differences among the groups for all mechanical parameters. BMD was positively correlated with yield load ($p < 0.001$), and ultimate load ($p < 0.001$), but not with stiffness ($p = 0.070$). Type III was the most common fracture type. No association between fracture type and sustained ultimate load or BMD was identified. Load direction plays a subordinate role in traumatic fractures of the odontoid process in contrast to BMD, the latter being a strong determinant of stiffness and

strength. Thus, odontoid fractures appear to result from an interaction between load magnitude and bone quality.

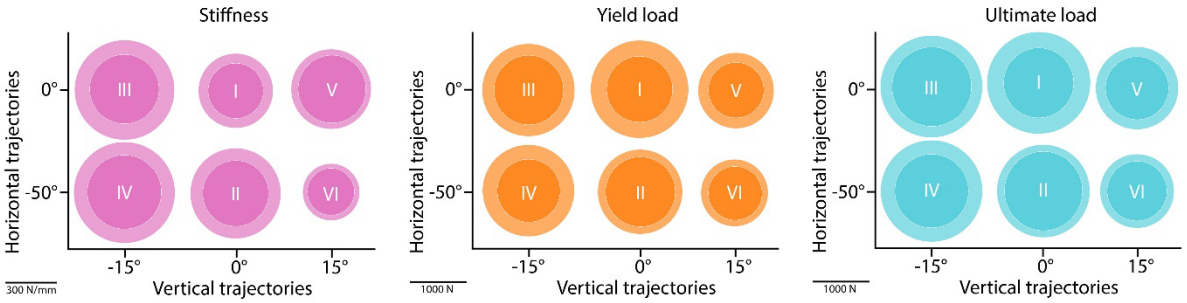


Figure 10.6.4: Graphical presentation of stiffness, yield-, and ultimate load for the single groups (I - VI) with inner circles representing mean value and outer rings – standard deviation.

Partners:

- Hirtler L (MD), Medical University of Vienna, Austria
- Fuchssteiner C (MD), Medical University of Vienna, Austria
- Strassl A, Medical University of Vienna, Austria
- Windhager R (Prof), Medical University of Vienna, Austria
- Widhalm H (Prof) Medical University of Vienna, Austria

Biomechanical analysis of osteochondral glenoid loss measures used for prediction of shoulder instability (F Souleiman, I Zderic, B Gueorguiev)

Background: Osteochondral glenoid loss is associated with recurrent shoulder instability. The critical threshold for surgical stabilization is multifactorial and conclusively unknown. Whereas the concavity gradient has been demonstrated to correlate significantly with the shoulder stability ratio (SSR), its measurement in the clinical setting is difficult and time-consuming.
Goal: To provide a well-measurable and reliable surrogate parameter of an unstable shoulder joint for the frequently observed anterior-inferior dislocation direction.
Results: SSR of 10 paired human cadaveric glenoids was determined in anterior-inferior dislocation direction. Osteochondral defects were simulated by gradually removing the corresponding structures in 5% stages up to 20% of the intact diameter. Glenoid depth, concavity gradient and defect radius were measured at each stage by motion tracking. The loss of SSR, concavity gradient and depth increased significantly with increasing defect size. The loss of SSR correlated strongly with the losses of concavity gradient and depth. In contrast, the percentage defect size – based on intact diameter measurements – correlated weaker with SSR. Small osteochondral defects led to significantly higher SSR decrease in small (diameter < 25mm) *versus* large (diameter ≥ 25 mm) glenoids ($p \leq 0.009$). From a biomechanical perspective, the losses of concavity gradient and glenoid depth correlate strong with the loss of SSR. Therefore, especially the loss of glenoidal depth may be considered as a valid and reliable alternative parameter to describe shoulder instability. Smaller glenoids are more vulnerable to become unstable in case of small osteochondral loosening. On the other hand, the standardly used percentage defect size – based on intact diameter measurements – correlates weaker with the magnitude of instability and may therefore not be a valid parameter for shoulder instability assessment.

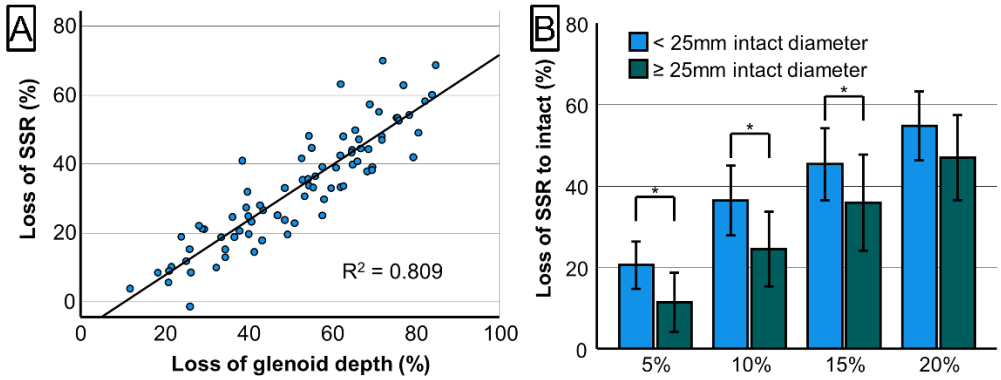


Figure 10.6.5: Effect of glenoid depth and concavity on shoulder instability in osteochondral glenoid loss. A) Loss of glenoid depth plotted versus loss of SSR for each separate specimen; B) Loss of SSR relative to intact state for small (< 25 mm) and large (≥ 25 mm) glenoids, presented for each stage of osteochondral loss separately, with stars indicating significant differences.

Partners:

- Osterhoff G (Prof), University Hospital Leipzig, Leipzig, Germany
- Hepp P (MD), University Hospital Leipzig, Leipzig, Germany

Biomechanical analysis of glenoid cartilage loss influence on shoulder stability (F Souleiman, I Zderic, B Gueorguiev)

Background: Glenohumeral bone and cartilage lesions are common injuries associated with recurrent shoulder instabilities. The effect of labrum and bone defects on shoulder stability has been well studied. However, the contribution of cartilage to the concavity gradient and the corresponding biomechanical influence of a cartilage defect or cartilage loss on shoulder stability ratio (SSR) in relation to the dislocation direction remain unclear. In absence of such association, it is unclear which cartilage lesions require surgical treatment.
Goal: To investigate the biomechanical effect of two states of cartilage loss on shoulder stability in different dislocation directions.
Results: Joint dislocation was provoked for 11 human cadaveric glenoids in seven different directions between 3 o'clock (anterior) and 9 o'clock (posterior). SSR and concavity gradient were assessed in intact state, and after 3 mm and 6 mm simulated cartilage loss. The influence of cartilage loss on SSR and concavity gradient was assessed. Between intact and 6 mm cutting states, both SSR and concavity gradient decreased significantly in every dislocation direction ($p \leq 0.038$), except concavity gradient decrease in 4 o'clock direction. Anterior-inferior dislocation directions were associated with biggest SSR and concavity gradient decrease, being significantly bigger for SSR *versus* all other dislocation directions ($p \leq 0.040$). The correlations between concavity gradient and SSR for pooled dislocation directions were significant for all three specimen's states ($p < 0.001$). From a biomechanical perspective, articular cartilage of the glenoid contributes significantly to the concavity gradient, strongly correlating with the associated loss in glenohumeral joint stability. The biggest effect of cartilage loss is observed in anterior-inferior dislocation directions, suggesting that surgical intervention should be considered for recurrent shoulder dislocations in presence of cartilage loss.

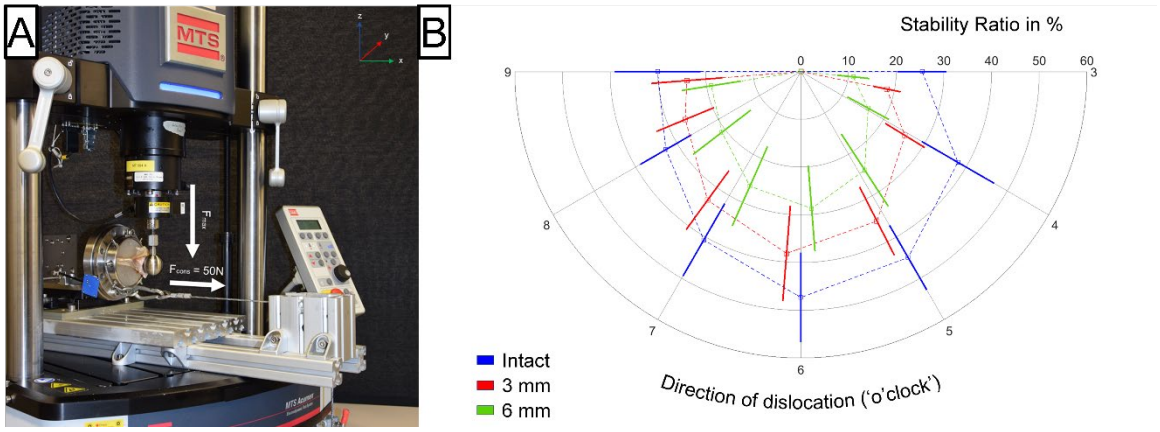


Figure 10.6.6: Influence of cartilage loss on shoulder instability. A) Test setup with a specimen mounted for biomechanical testing; B) Radial plot presenting SSR (%) for each dislocation direction at the different stages of cartilage loss separately in terms of mean and standard deviation.

Partners:

- Osterhoff G (Prof), University Hospital Leipzig, Germany
- Hepp P (MD), University Hospital Leipzig, Germany

Biomechanical investigation of low-profile dual mini-fragment plating of diaphyseal clavicle fractures (T Pastor, I Zderic, B Gueorguiev)

Background: Implant removal rates after clavicle plating are high. Recently, low-profile dual mini-fragment plate constructs have proven to be safe for fixation of diaphyseal clavicle fractures.
Goal: To investigate (1) the biomechanical competence of different low-profile dual mini-fragment plate designs and (2) to compare them *versus* 3.5 mm single superoanterior locked plate fixation.
Results: Twelve artificial clavicles were osteotomized to simulate an unstable AO/OTA 15.2C clavicle shaft fracture, assigned to 2 groups and instrumented with titanium matrix mandible plates as follows: Group 1 (dual 2.5 mm anterior plus 2.0 mm superior plating) and Group 2 (dual 2.0 mm anterior plus 2.0 mm superior plating). All specimens were cyclically tested to failure under craniocaudal cantilever bending, superimposed with torsion around the shaft axis. Results were compared to previous published data on 3.5 mm superoanterior locked plating tested under the same conditions (Group 3). Low-profile dual 2.0/2.0 plates (Group 2) demonstrated similar initial stiffness compared with 3.5 mm single locked plates (Group 3), however, the former revealed significantly lower endurance to failure. In contrast, low-profile dual 2.5/2.0 plates (Group 1) demonstrated significantly higher initial stiffness and similar resistance to failure compared with 3.5 mm single locked plates (Group 3) and can therefore be considered as a useful alternative for diaphyseal clavicle fracture fixation. These results complement the promising outcomes of several clinical studies.

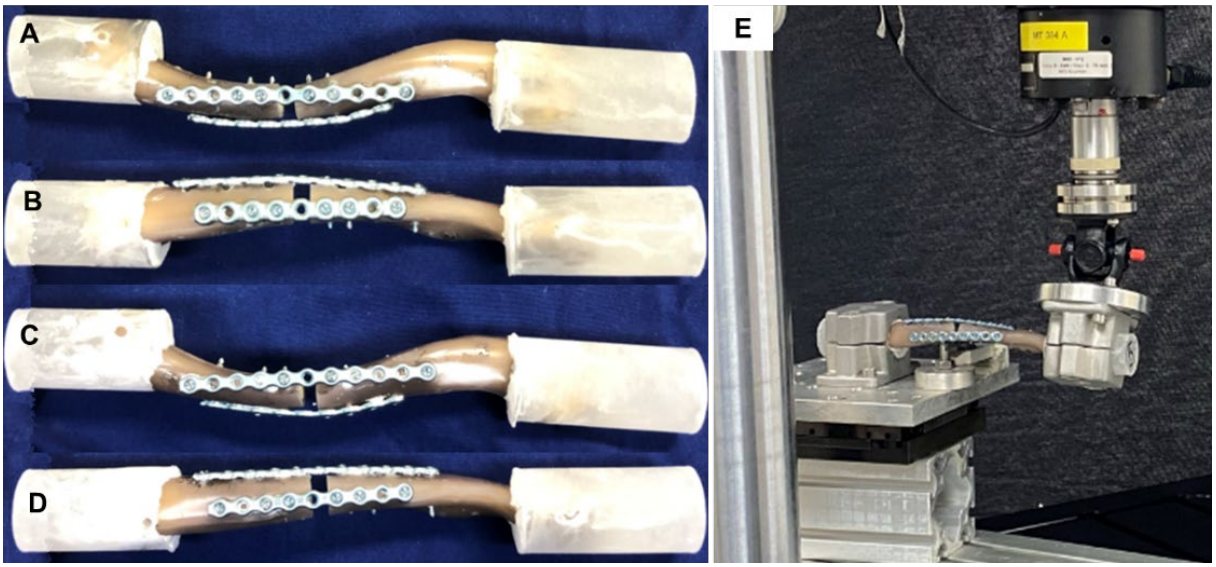


Figure 10.6.7: Biomechanical testing of low-profile dual mini-fragment plating in diaphyseal clavicle fractures. A–D) Exemplified photographs of two left artificial claviculae in superior (A,C) and anterior (B,D) views, double plated in 2.5/2.0 (A,B) and 2.0/2.0 (C,D) configurations; E) Setup with a specimen mounted for biomechanical testing.

Partners:

- Knobe M (Prof), Lucerne Cantonal Hospital, Switzerland
- Beeres F (MD), Lucerne Cantonal Hospital, Switzerland

Biomechanical analysis of helical *versus* straight plating of proximal third humeral shaft fractures (T Pastor, I Zderic, K van Knegsel, B Gueorguiev)

Background: Proximal humeral shaft fractures are commonly treated with long straight locking plates endangering the radial nerve distally.
Goal: To investigate the biomechanical competence of 90° helical plates *versus* conventional straight lateral plates in a human cadaveric model of proximal third comminuted humeral shaft fractures.
Results: Eight pairs of humeral cadaveric humeri were osteotomized to simulate an unstable proximal humeral shaft fracture with 5 cm gap and instrumented using either a long 90° helically bent PHILOS plate (Group 1) or a straight long PHILOS plate (Group 2). All specimens were tested under quasi-static loading in axial compression, internal and external rotation, and bending in four directions. Subsequently, progressively increasing loading to failure was applied in internal rotation and interfragmentary movements were monitored by motion tracking. Flexion/extension deformation was significantly higher in Group 1, $p < 0.01$. Varus/valgus deformation, shear and torsional displacements were not significantly different between the groups, $p \geq 0.39$. During cyclic testing shear and torsional displacements were significantly higher in Group 1, $p \leq 0.04$. Cycles to catastrophic failure were not significantly different between the groups, $p = 0.24$. Although 90° helical plating was associated with comparable resistance against varus/valgus deformation, it demonstrated bigger flexion/extension, shear and torsional movements compared with straight plating. From a biomechanical perspective, 90° helical plates performed inferior compared with straight plates and alternative helical plate designs with lower twist should be investigated in future studies.

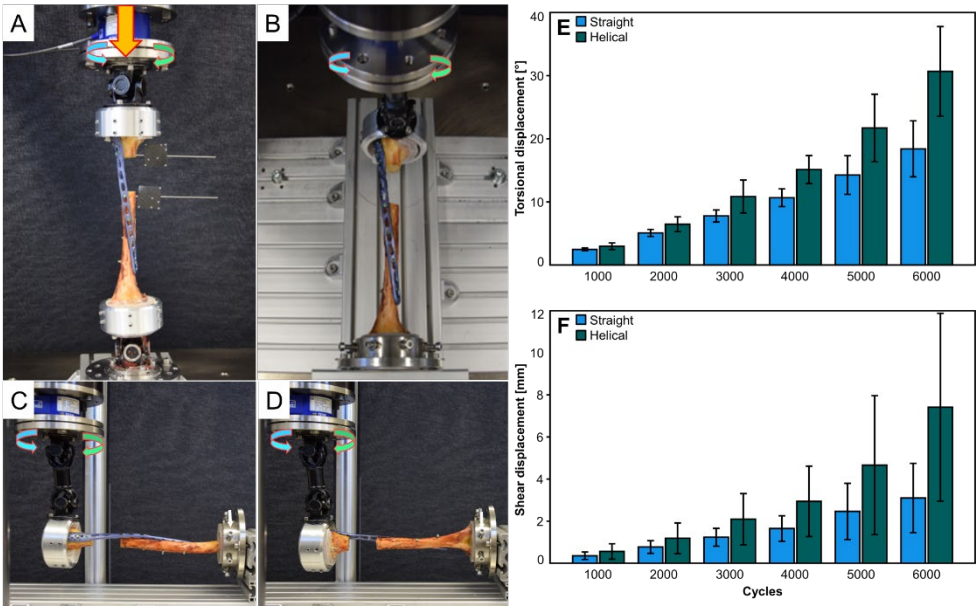


Figure 10.6.8: Biomechanical analysis of helical versus straight plating of proximal third humeral shaft fractures. A-D) setup with a right humerus instrumented with 90° helical plate and mounted for biomechanical testing; A) axial compression or internal/external rotation; B, C) bending loading in varus/valgus in two different views; D) bending loading in flexion/extension; E) torsional and F) shear displacement over the course of selected cycles presented for Group 1 (Helical) and Group 2 (Straight) in terms of mean and standard deviation.

Pres:
Pastor T, Zderic I, Richards RG, Gueorguiev B, Knobe M. Medial helical *versus* lateral straight plating of distal femoral fractures – a biomechanical comparative study. 2021 EORS (oral).

Partner:
- Knobe M (Prof), Lucerne Cantonal Hospital, Switzerland

Accurate screw pull-out force prediction using non-linear explicit microFE simulations (M Ovesy, J Silva-Henao, J Fletcher, B Gueorguiev, P Varga)

Background: Screws are the most frequently used implants for treatment of bone fractures. Their anchorage to bone is an essential component of stability. Screw fixation failure via cut-out or pull-out still have relatively high prevalence that could be reduced via improved designs. Virtual simulations could be used for implant optimization to develop fixation strategies, ultimately reducing failure rates, and improving outcomes of fracture treatments. However, reliable, and robust simulations are required to predict the bone-screw interface failure.
Goal: To evaluate the accuracy of micro-finite element (microFE) simulations in predicting pull-out force of cortical screws in human tibial bone.
Results: Axial pull-out experiments using 3.5 mm screws were performed in human cadaveric tibial cortical bone and ultimate force was measured. Micro CT scans of each specimen were acquired before and after screw insertion and bone volume around the screw was measured. MicroFE models were created, and screw pull-out was simulated via linear and non-linear microFE analyses to predict ultimate force. The explicit non-linear microFE simulation provided quantitatively correct prediction of the experimental screw pull-out force with higher accuracy (R^2 = 0.913) compared to both linear microFE (R^2 = 0.861) and bone volume around the screw evaluation (R^2 = 0.866). These results indicate that validated non-linear explicit microFE simulations would have strong potential for design optimization of screws via *in silico* studies.

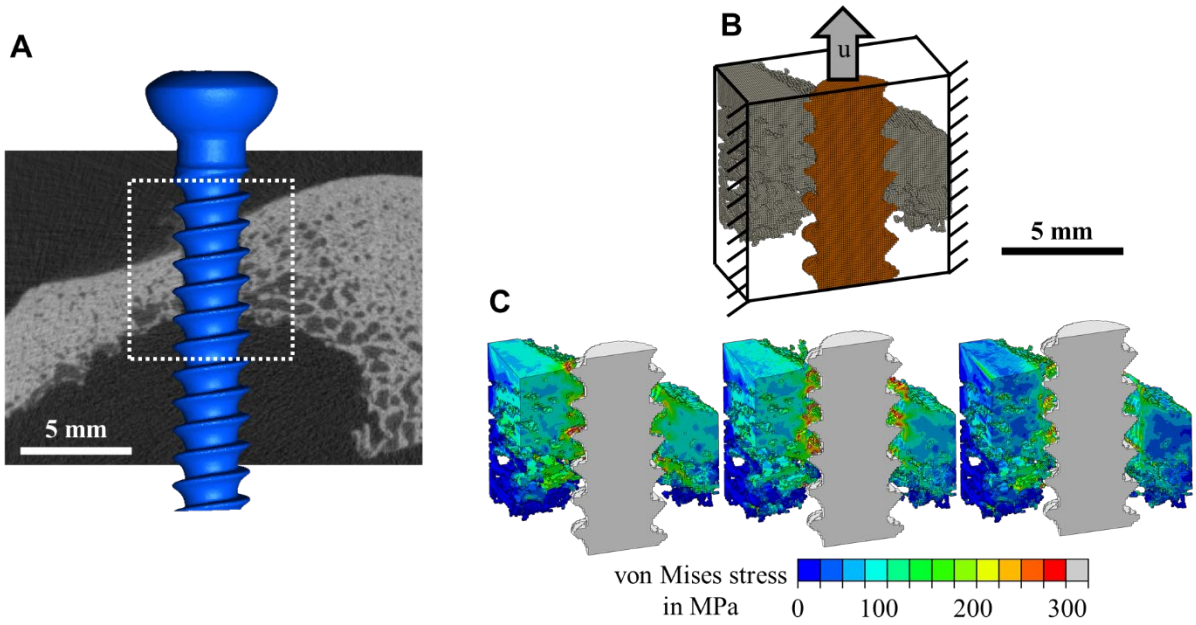


Figure 10.6.9: MicroCT image with overlayed screw model (A) used to create microFE model and simulate screw pull-out (B, arrow with "u" indicates applied displacement) and predict bone failure around the implant, illustrated at the contour plots of von Mises stresses at three different stages (C), with the second stage corresponding to the pull-out failure, i.e., maximum force.

Pub:
Ovesy M, Silva-Henao JD, Fletcher JWA, Gueorguiev B, Zysset PK, Varga P. Non-linear explicit micro-FE models accurately predict axial pull-out force of cortical screws in human tibial cortical bone. Mech Behav Biomed Mater. 2022. 126:105002.

Partner:
- Zysset P (Prof), University of Bern, Switzerland

Biomechanical investigation of minimally invasive surgical techniques for stabilization of osteoporotic posterior pelvic ring fractures (C Fritzsche, I Zderic, B Gueorguiev)

Background: Minimally invasive surgical techniques have advanced to become the gold standard for treatment of pelvic insufficiency fractures, however, clinical studies demonstrate limitations with screw loosening and dislocations in osteoporotic bone. Validated biomechanical studies to test the stability of the procedures are insufficient to date.
Goal: To investigate biomechanically two surgical techniques for stabilization of an anterior and posterior osteoporotic pelvic ring fracture in a human cadaveric model.
Results: Ten human cadaveric pelvises were randomized to 2 groups according to age, gender, and bone density. An anterior and posterior pelvic ring FFP-IIc fracture was created in a standardized manner and surgically treated using either a transiliac transsacral screw or a sacroiliac screw. A pelvic one-leg stance model was used to test the pelvises under progressively increasing cyclic loading to failure. Interfragmentary movements were monitored by motion tracking. No significant differences for axial stiffness and cycles to failure were detected between the groups ($p \geq 0.44$). However, significantly higher stability was demonstrated with the transiliac transsacral screw fixation in terms of flexion, vertical shear movement and overall mobility ($p < 0.01$). The results from this biomechanical study suggest adequate fracture treatment with both surgical techniques, however, a clear trend towards better fracture stability with use of the transiliac transsacral screw is demonstrated. In view of this, the application of a transiliac transsacral screw for treatment of osteoporotic posterior pelvic ring fractures may be prioritized to ensure the best possible patient care.

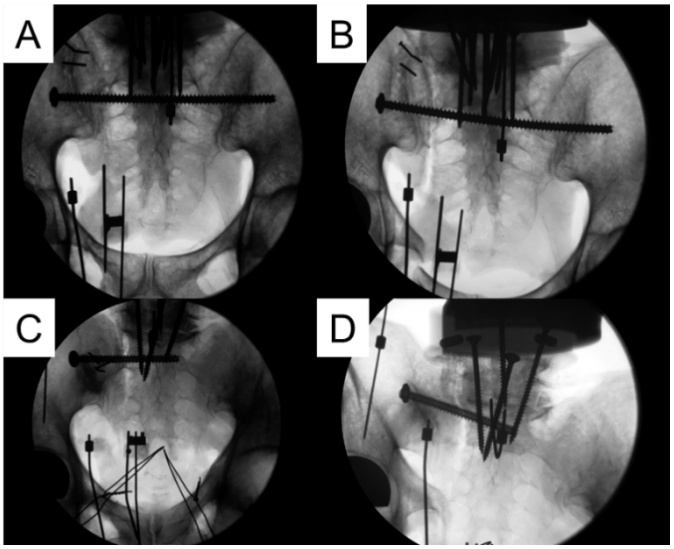


Figure 10.6.10: Anteroposterior X-rays of pelvises treated with transiliac transsacral (A,B) and sacroiliac (C,D) screws before (A,C) and after (B,D) cyclic testing.

Partners:

- Gebhard F (Prof), University Hospital Ulm, Germany
- Schütze K (MD), University Hospital Ulm, Germany

Development of a novel reliable patient-specific predictor of secondary lateral wall fracture following trochanteric fractures (K van Knegsel, E Benca, T Pastor, B Gueorguiev, P Varga)

Background: The lateral wall thickness (LWT) in trochanteric femoral fractures is a known predictive factor for postoperative fracture stability. Currently, the AO/OTA classification uses the absolute LWT (aLWT) to distinguish stable A1.3 from unstable A2.1 fractures based on a threshold of 20.5 mm. However, aLWT is a patient non-specific measure and its use potentially results in interpatient deviations due to different bone morphologies and consequent variations in fracture stability.
Goal: To develop a novel patient-specific measure of relative LWT (rLWT) and explore whether it results in a more accurate prediction of postoperative fracture stability compared to the conventional aLWT measure.
Results: Part 1 of the study evaluated pelvic radiographs of 146 non-fractured patients to assess left-right symmetry regarding the caput-collum-angle (CCD) and total trochanteric thickness (TTT) and used the results to establish the novel rLWT measurement technique. High bilateral symmetry of the femur was demonstrated regarding both CCD and TTT ($p > 0.827$), allowing to mirror morphology and geometry from the contralateral intact to the fractured femur. Part 2 reevaluated radiographs of 202 trochanteric femoral fracture patients from a previous study cohort to analyze their rLWT *versus* aLWT and evaluate the accuracy of distinguishing postoperative stable and non-stable fractures. The analysis revealed an increased classification accuracy for the new determined rLWT measure using a threshold of 50.5% *versus* the standard 20.5 mm aLWT threshold, providing improved sensitivity and specificity. The novel patient-specific rLWT measure was proven as assessable – based on the intact contralateral femur anatomy – and demonstrated to be a more accurate predictor of a secondary lateral wall fracture in comparison with the conventional aLWT measure. This study established the threshold of 50.5% rLWT as a reference value for prediction of fracture stability and selection of an appropriate implant for fixation of trochanteric femoral fractures.

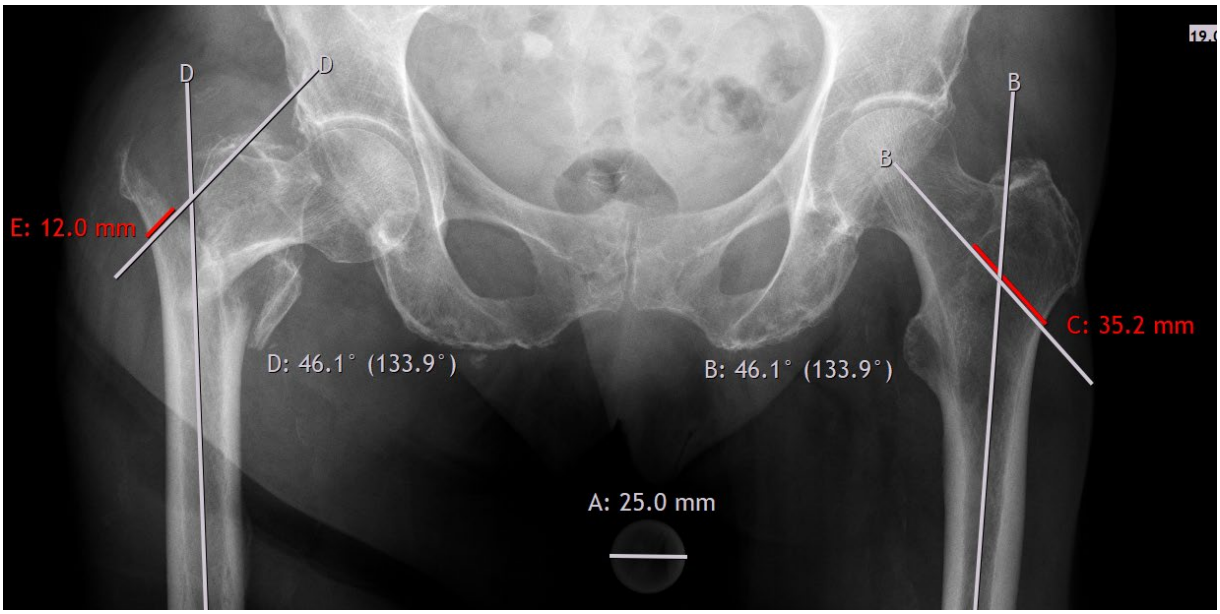


*Figure 10.6.11: Illustration of the new measurement technique for assessment of rLWT. A: calibration; B: Measuring CCD angle on the healthy contralateral side; C: Measuring TTT as the distance from the lateral cortex to the intertrochanteric line along the caput-collum axis line; D: Mirroring of the CCD angle from the contralateral to the fractured side; E: Measuring the LTW as the distance from the lateral cortex to the fracture line along the caput-collum axis line; rLWT (%) = LWT/TTT*100.*

Partners:

- Knobe M (Prof), Lucerne Cantonal Hospital, Switzerland
- Hsu C (MD), Taichung Veterans General Hospital, Taiwan
- Huang K (MD), Taichung Veterans General Hospital, Taiwan
- Ganse B (Prof), Saarland University, Homburg, Germany

Anti-inflammatory therapy for cartilage preservation (CartRegen) (ongoing) (Z Li, S Grad)

Background: Osteoarthritis (OA) is affecting a large proportion of the population and is associated with significant burden on patients and health care systems. Traumatic joint injury is a major risk factor for the development of OA. Early intervention after an acute injury may therefore prevent progressive joint deterioration. It is believed that the acute inflammatory response plays a major role in the progression towards the chronic painful condition. Early anti-inflammatory and chondroprotective treatment may halt or even reverse the deteriorating process.
Goal: The aim of this project is to evaluate the chondroprotective and anti-inflammatory activity of small molecule compounds in an inflammatory 3D pellet culture system and inflammatory osteochondral explant model. The overall goal is to generate pre-clinical data and identify small molecules with disease modifying effect for OA treatment.
Results: An *ex vivo* inflammatory OA model was induced using different concentrations of interleukin one beta (IL-1β) and tumor necrosis factor α (TNF-α) on explants from the human femoral head. In the inflammatory OA groups, the gene expression levels of cartilage catabolism (MMP1, MMP3), and inflammation (IL-6, IL-8) markers were significantly upregulated, while the anabolic genes (COL2, ACAN, and PRG4) were downregulated compared to the control group. The release of cytokines (IL-6, IL-8) and nitric oxide (NO) in the conditioned medium was also upregulated in inflammatory OA groups. The Safranin O/Fast Green staining showed loss of proteoglycan in the superficial zone cartilage after cytokine treatment (Figure 10.6.12). The results indicated that an *ex vivo* inflammation and degeneration model was successfully established using osteochondral explants from the

human femoral head. This model can be used to elucidate the in-depth mechanism of inflammatory OA and to screen new drugs for OA treatment.

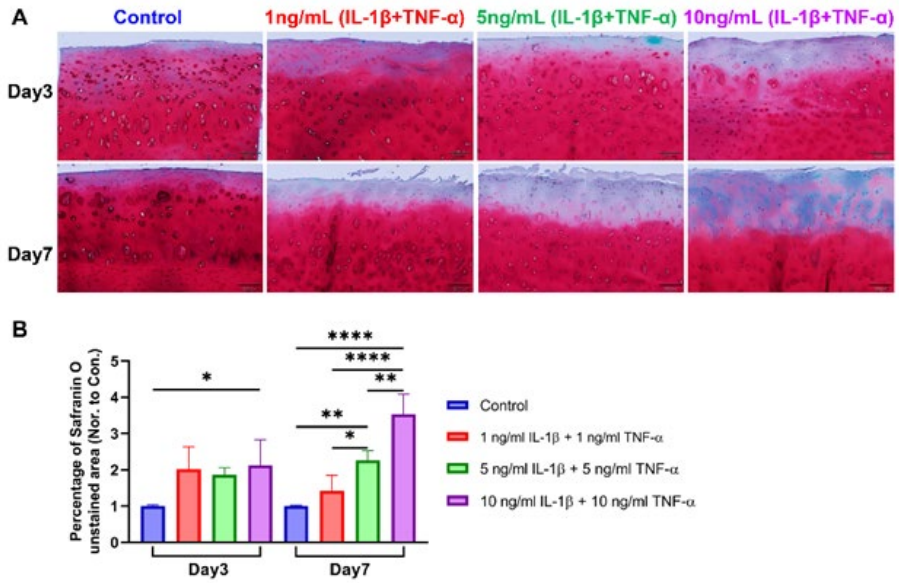


*Figure 10.6.12: Safranin O/Fast Green staining on sections of unstimulated and IL-1β- and TNF-α-stimulated osteochondral explants from human femoral heads. (A) Representative staining images of explants. Scale bars, 200 µm. (B) Safranin O-unstained area normalized to the control group of each donor as 1 (n=3). Means +SD. *p < 0.05, **p < 0.01, ****p < 0.0001.*

Pres:
Zhang P, Basoli V, Wang X, Alini M, Grad S, Li Z. Anti-inflammatory and regenerative effects of small molecules for osteoarthritis – *in vitro* and *ex vivo* evaluation. ORS, Feb 12-15, 2021 (poster).
Zhang P, Li K, Basoli V, Alini M, Grad S, Li Z. *In vitro* and *ex vivo* screening of small molecule therapeutics for osteoarthritis. TERMIS, Maastricht, Nov 15-19, 2021 (poster).

Pub:
Li K, Zhang P, Zhu Y, Alini M, Grad S, Li Z, Establishment of an *ex vivo* inflammatory osteoarthritis model with human osteochondral explants. Frontiers in Bioengineering and Biotechnology 9 (2021) 787020.
Ziadlou R, Rotman S, Teuschl A, Salzer E, Barbero A, Martin I, Alini M, Eglin D, Grad S. Optimization of hyaluronic acid-tyramine/silk-fibroin composite hydrogels for cartilage tissue engineering and delivery of anti-inflammatory and anabolic drugs. Mater Sci Eng C Mater Biol Appl. 2021 Jan;120:111701. DOI: 10.1016/j.msec.2020.111701.

Partner:
- Wang X (Prof), Shenzhen Institute of Advanced Technology, Shenzhen, China

Biomaterials Taming Neutrophils for Healthy Inflammation (BEAN Project) (ongoing) (M D'Este, K Thompson, F Moriarty, M Stoddart)

Background: Bone related diseases and injuries are generally caused by trauma, genetic malformations, bone loss/overgrow, infections and tumors. While simple fractures are easy to treat, complex fractures and pathological disorders entail arduous treatments. Current orthopaedic solutions encompass invasive surgical procedures and bone grafting (autografts, allografts, and xenografts). Even though they are approved and commonly used methods, they have some disadvantages such as donor site morbidity and insufficiency of materials for grafting. Natural or synthetic biomaterials would be an alternative solution to the clinical

standards. However, implants might lead undesired immune responses, such as chronic inflammation, fibrous tissue formation or pathogen associated infection, which in turn cause interruption in repair and regeneration, and impaired bone formation.

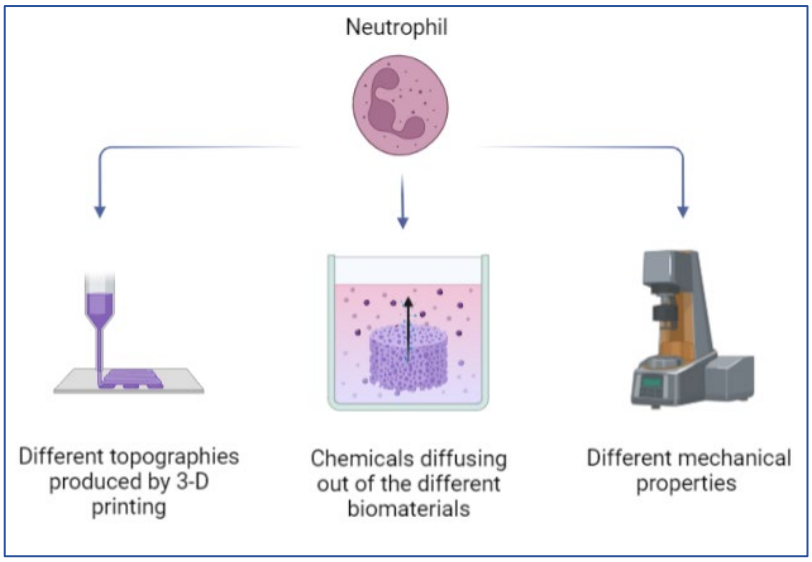


Figure 10.6.13: Schematic overview of the investigation on neutrophil and biomaterial interactions to establish design principles for the appropriate immune response inducing healthy tissue repair and regeneration.

Neutrophils play a pivotal role in orchestrating the immune response to biomaterials, the onset and resolution of chronic inflammation and macrophage polarization. However, their response to biomaterials and consequent impact on tissue regeneration has been mostly overlooked. Results from the AOCMF RAIMBO project showed that neutrophils have stronger response to hard surfaces compared to soft ones. However, the implications in tissue regeneration and the design principles to design materials driving an inflammatory response bringing to tissue healing are still unclear. Therefore, evaluating and understanding the interactions between neutrophils and biomaterials are the essence of overcoming the clinical drawbacks.
Goal: The purpose of this project is to establish how biomaterial composition, mechanical properties, and topographical features influence neutrophils inflammatory profile and phagocytic activity. Additionally, it is intended to verify whether different biomaterial-induced inflammatory profile has an impact on macrophage polarization. In a broader context, with this project we are aiming to contribute towards establishing principles on how to design biomaterials priming a neutrophil response avoiding chronic inflammation, inducing later M2 polarization of macrophages, and preserving phagocytic activity towards bacteria.

Partner:
- Swiss Institute of Asthma and Allergy (SIAF), Davos, Switzerland

Optimized chondrogenesis in an osteochondral defect model (VariDon2) (ongoing) (M Stoddart, E Della Bella)

Background: Bone marrow derived stem (or stromal) cells (BMSCs) have been proposed a source of cells for autologous cell therapy. While showing promise *in vitro*, translation into the clinics has proven challenging. One reason for this is the inability to accurately predict cell function and hence, whether cells from a patient will behave in a predictable manner. In a previous AO funded study (Varidon), we defined a TGF-β receptor ratio that was predictive of chondrogenesis. Furthermore, by relatively simple manipulation of the receptor ratio we could convert non-responsive donors and make them responsive to chondrogenic signals.
Goal: Within this study, we aim to develop this technology further to improve chondrogenic differentiation within biomaterials with implant design in mind. Furthermore, we will activate chondrogenesis by way of multiaxial load, in an *ex vivo* endochondral defect model that more faithfully resembles a cartilage defect.
Results: We have recently demonstrated that expansion of hBMSCs in presence of TGF-β1 can improve their chondrogenic potential in pellet culture and reverse the phenotype of cells poorly responding to TGF-β1 during chondrogenesis. Here, we investigated more in details

how TGF-β1-expanded cells respond to mechanically-induced chondrogenesis using a multiaxial load bioreactor (Figure 10.6.14). Basal gene expression levels of chondrogenic markers and of TGF- β receptors are altered after expansion of cells with TGF-β1. While chondrogenesis in pellet culture seem to benefit from cell priming, results obtained from constructs subjected to mechanically induced chondrogenesis seem to indicate that priming increases the progression to hypertrophy.

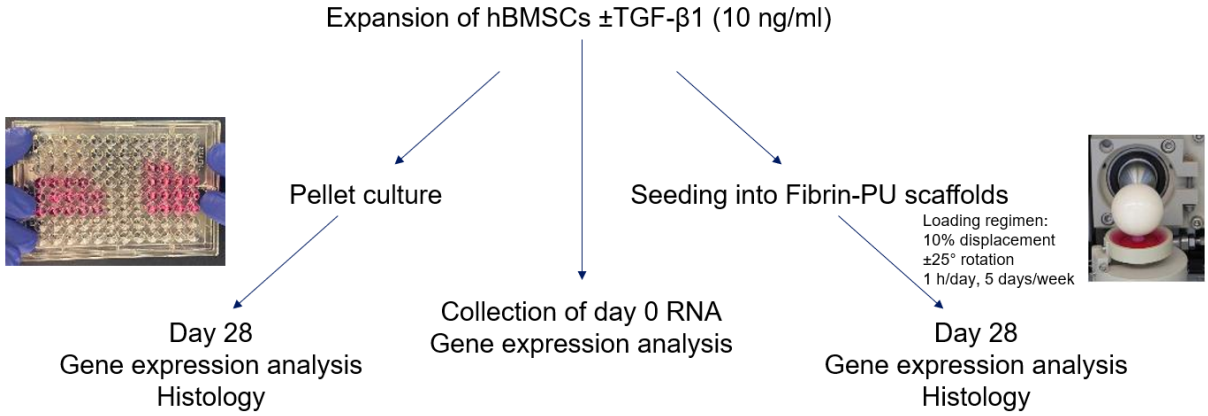


Figure 10.6.14: Schematic overview of the investigation on hBMSC chondrogenic potential after expansion in presence of TGF-β1.

Pres:

Regenerative rehabilitation: from proteins to patients. TERMIS 6th World Congress. Online. 18.11.2021.

Challenges and trends in MSK regenerative medicine. Mayo Regenerative Medicine & Surgery Symposium. Online Keynote. 6.11.2021.

Mechanoregulation of chondrogenesis: can we repurpose rehabilitation? 57th ÖGU & 2nd ÖGOuT Annual Meeting. 07.10.2021.

Increasing the complexity of *in vitro* cartilage models. EORS Annual Meeting 2021. 16.09.2021.

The effect of multiaxial load on cartilaginous constructs. 5th International Conference on BioTribology. Online. 27.04.2021. (plenary).

Mechanically induced MSC chondrogenesis: using movement to drive biological responses. EU Project OActive conference. Online. 23.04.2021.

Cartilage biomechanics. EU ITN project CARTHAGO. Online. 12.04.2021.

Regulating human MSC chondrogenic differentiation by mechanics. Lindbergh lecture series, University of Wisconsin-Madison. Online. 25.02.2021.

Mechanoregulation of human mesenchymal stem cell chondrogenesis. Stanford lecture series. Online. 11.02.2021.

Pub:

Basoli V, Della Bella E, Kubosch EJ, Alini M, Stoddart MJ. Effect of expansion media and fibronectin coating on growth and chondrogenic differentiation of human bone marrow-derived mesenchymal stromal cells. Sci Rep. 2021 Jun 22;11(1):13089. DOI: 10.1038/s41598-021-92270-4. PMID: 34158528; PMCID: PMC8219706.

Jahangir S, Eglin D, Pötter N, Khozaei Ravari M, Stoddart MJ, Samadikuchaksaraei A, Alini M, Baghaban Eslaminejad M, Safa M. Inhibition of hypertrophy and improving chondrocyte differentiation by MMP-13 inhibitor small molecule encapsulated in alginate-chondroitin sulfate-platelet lysate hydrogel. Stem Cell Res Ther. 2020 Oct 9;11(1):436. DOI: 10.1186/s13287-020-01930-1. PMID: 33036643.

Pötter N, Westbrock F, Grad S, Alini M, Stoddart MJ, Schmal H, Kubosch D, Salzmann G, Kubosch EJ. Evaluation of the influence of platelet-rich plasma (PRP), platelet lysate (PL) and mechanical loading on chondrogenesis *in vitro*. Sci Rep. 2021 Oct 12;11(1):20188. DOI: 10.1038/s41598-021-99614-0.

Establishing the interplay of soluble and physical signals on endochondral development (MechSignal) (ongoing) (A Armiento, M Stoddart)

Background: Endochondral and intramembranous ossification describe the two natural healing mechanisms of long bone fractures, during which the locally applied strain is known to affect the final healing outcome. Locally derived progenitors from bone marrow and periosteum are major cellular contributors to the fracture callus, being able to undergo endochondral and intramembranous differentiation to differing degrees. While controlling the mechanical environment across a fracture gap is a well-accepted, classical AO principle, there is little understanding of the underlying biological changes. A greater understanding of the underlying biological responses to the soluble and physical factors present during early healing, coupled with potential markers related to mechanical stimulation, may help in assessing at early time points whether a fixation is suitably stable for the desired healing outcome.
Goal: This project aims to create an *in vitro* model to study the interplay between signaling molecules such as TGF-β, BMPs and nerve growth factor (NGF), cell types including mesenchymal cells and macrophages, and mechanical load (Figure 10.6.15). This model will uncover cellular/molecular aspects of endochondral differentiation during fracture healing.
Results: Cell-laden fibrin gels are cultured in serum-free chondro-permissive medium (CpM) for 24h. The samples are then divided in sixteen different groups based on the growth factor supplementation and cultured for nine days. Medium supplemented with growth factors is refreshed every third day and samples are collected at day 0 and day 9 73.
Within the first 24h the fibrin gels remodel into 3D pellets with an average diameter of 1 mm and 1.5 mm when in absence or presence of TGF-β1, respectively. The pellet size positively correlates with the DNA content. sGAG production is sustained by TGF-β1 supplementation and enhanced when in combination with NGF and BMP-2. The secretion of alkaline phosphatase is driven by the combined effect of TGF-β1 and BMP-2. Gene expression analysis shows an overall trend for cartilage matrix protein upregulation while the enzymes associated with matrix degradation are downregulated.

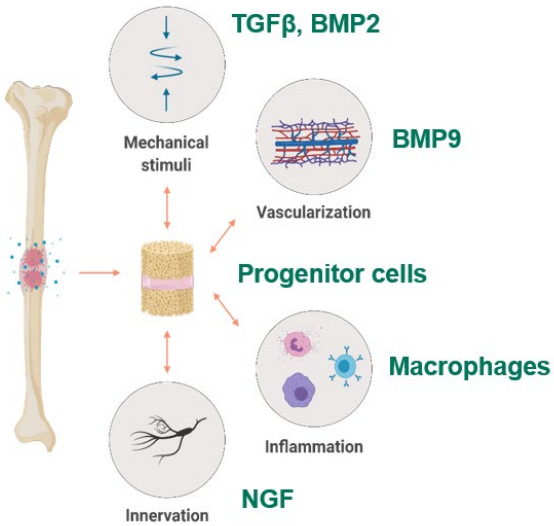


Figure 10.6.15. Interplay of multiple signals during early fracture repair.

Identification of mechanical conditions promoting hypertrophic endochondral differentiation *in vitro* (MechEndro) (ongoing) (S Verrier, M Stoddart)

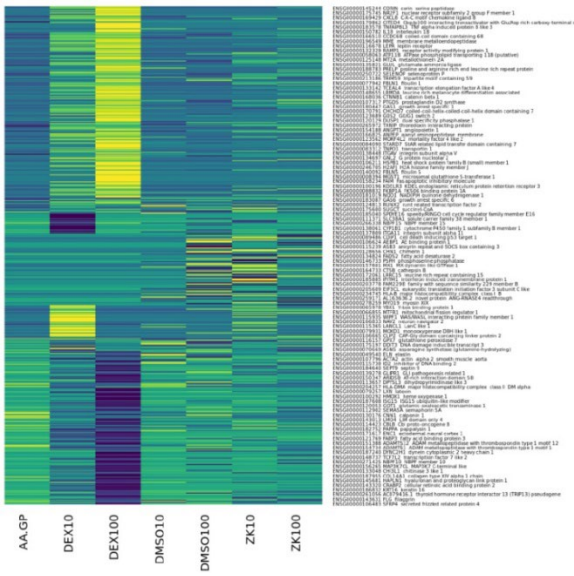
Background: It is widely accepted that secondary fracture healing requires a certain level of mechanical stimulation to initiate and promote callus formation. By means of *in vivo* experimental setups, several groups have shown that cyclic compressive strain applied to a diaphyseal fracture fosters healing via the formation of a stronger cartilaginous callus leading to earlier bone bridging. Though, optimal loading parameters have not yet been entirely

defined. There are still uncertainties concerning the magnitude of strain, its frequency, optimal temporal distribution, and duration. More importantly, the influence of those parameters on the cellular process of hypertrophic cartilage formation and remodeling - critical for bone healing - is still not fully understood.
Goal: To better understand the biological effect of strain at the cellular level. We specifically aim to define *in vitro* the lower strain induction limit for the hypertrophic endochondral differentiation of MSC and callus-like matrix formation.
Results: For this project, a StrainBOT multi-well bioreactor system was used (RISystem AG). The device enables uni-axial defined deformation of 24 tissue engineered constructs in parallel and offers large flexibility in the choice of both strain level to be applied, and application of multi-segmental deformation protocols. In preliminary studies aiming to validate the function and reliability of the bioreactor, mesenchymal stem cells (MSCs) were seeded in 2% agarose gels as well-defined model material. Samples were cultured under different mechanical loading conditions (0, 10 and 30% strain) either in presence of classical chondrogenic medium (containing 10 ng/mL transforming growth factor β1 (TGFβ1)), or chondro-permissive medium, in which TGFβ1 was omitted. Over three weeks of continuous cyclic deformation, no adverse events were experienced. Cell viability remained comparable between all conditions, and agarose constructs remained intact even when deformed by 30% of their height. Real time PCR analysis also showed regulation of specific genes, such as Cartilage oligomeric matrix protein (COMP) or Matrix metalloproteinase (MMP)-13 in response to the strain magnitude, indicating an effective transmission of the deformation to the model agarose constructs, and a response of the cells to strain.

Partners:
- RISystem AG, Landquart, Switzerland
- Perren N, Perrens 101 GmbH, Davos, Switzerland

Transcriptomic and molecular dynamics analysis of early osteogenic differentiation: role of dexamethasone (OsteoSeq - Feasibility) (started) (E Della Bella, M Stoddart, G Licandro, A Buetti-Dinh, G Grasso)

Background: Poor translational potential of *in vitro* results for biomaterials testing is now recognised as a limiting factor in the field of bone regenerative medicine. Standard protocols for osteogenic differentiation of human mesenchymal stromal cells include dexamethasone (DEX), a synthetic glucocorticoid that is widely prescribed for treating various inflammatory conditions. The clinical, long-term use of DEX may negatively affect bone health, resulting frequently in an impairment of bone homeostasis leading to osteoporosis and osteonecrosis. *In vitro*, DEX is usually regarded as having a promoting effect on cell differentiation towards osteoblastic lineage, but it is also known to inhibit terminal osteoblast maturation and osteocalcin production. Preliminary results from our group showed that DEX induces osteogenic commitment of human bone marrow-derived mesenchymal stromal cells (BMSCs) by SOX9 downregulation, rather than promoting RUNX2 expression. However, DEX-dependent osteogenesis is accompanied by a dose-dependent upregulation of PPARG, which leads to pre-adipocyte-like cells within mineralizing cultures. New insights in terms of both DEX-mediated bone healing and molecular reasons behind the undesirable effect of DEX were therefore highlighted.
Goal: The OsteoSeq project aims to further clarify DEX's mechanism of action by exploiting the adequacy and strength of genome-wide transcriptomic analyses on samples derived from the early osteogenic differentiation of patient derived BMSCs. OsteoSeq will elucidate (novel) key signalling actors/pathways controlled by DEX, which guides the dual differentiation outcome, thus favouring the rational selection of suitable candidates to be targeted for a specific and selective control over osteogenic cell fate, avoiding the off target adipogenic differentiation. Furthermore, the effect of dexamethasone on the dynamics/function of the identified main actors will be assessed.



Results: RNAseq was performed using a Nanopore-based technology, which allowed to gather information not only on differential gene expression, but also on the differential transcript usage of the same gene. Bioinformatic analysis is undergoing to identify DEX unique targets involved in the transactivation of gene expression which is the likely pathway for DEX-induced osteogenesis (Figure 10.6.16). Furthermore, Molecular Dynamics simulations are exploring the possible interactions between the glucocorticoid receptor and SOX9 at the protein level.

Figure 10.6.16: Heatmap of differentially expressed genes ordered by DEX trend.

Pres:

Della Bella E, Ahmad P, Buetti-Dinh A, Licandro G, Basoli V, Alini M, Stoddart M. Dexamethasone: a friend or a foe in osteogenic differentiation of human BMSCs? 6th World TERMIS Congress 2021 (poster).

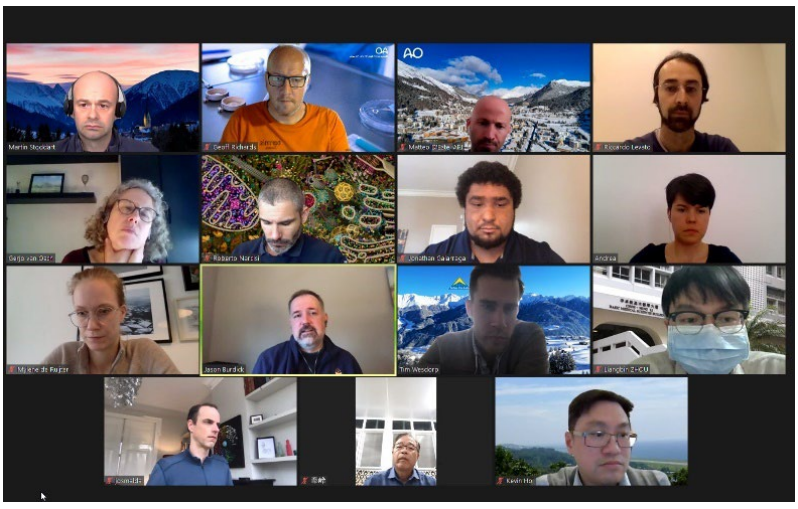
Partners:

- Licandro G (MSc), Dalle Molle Institute for Artificial Intelligence, USI/SUPSI, Lugano, Switzerland
- Buetti-Dinh A (PhD), SUPSI, Bellinzona, Switzerland
- Grasso G (PhD), Dalle Molle Institute for Artificial Intelligence, USI/SUPSI, Lugano, Switzerland

10.7 OCD Consortium

3D printed constructs for osteochondral defect repair (OCD Consortium) (Finished)

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.



The ARI collaborative research program (CRP) OsteoChondral Defect (OCD) brings together multidisciplinary expertise in materials, bioprinting, bioreactors, biomechanics, macrophages, and animal models. Additive manufacturing and biofabrication approaches are

used to produce constructs that were 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. Bioreactor and culture models that include multiple tissues of the joint, combined 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.
The project started in June 2017 and was funded for 5 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 Roberto Narcisi 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 is supported by Prof Peter Angele and Prof Peter Van der Kraan acting as advisory experts.

Multiple, crosslinkable bio-inks for 3D microextrusion of tissue-like constructs and biodegradable thermoplastic elastomer for fuse deposition manufacturing (Multibio-Ink) (ongoing) (A Schwab, D Eglin, M D'Este, M Stoddart)

Background: ARI input into the OCD Consortium was within the Multi-bioink project. With the overall project aim to develop a cell free implant, a cartilage ring model was used to compare THA and THA-col with col and empty defect as controls. Endogenous chondrocyte migration after implantation of acellular hydrogels in 4 mm cartilage defects was demonstrated by live-dead staining and MTT staining. Further, a quantitative migration score with three independent observers scored two slides of n=3 replicates on the presence of cells in the periphery and the defect center as well as the material-cartilage integration. Col performed best, followed by THA-col. Only few cells migrated into THA, thus confirming the MSC migration results (Wesdorp *et al*, in preparation). A second prerequisite is the capacity of embedded cells to deposit cartilaginous matrix.
Goal: Therefore, we investigated the effect of the polymer concentrations of col and THA on hMSC chondrogenesis. To address these research questions, hMSC spheroids (250 hMSCs per spheroid), also referred as aggregates, were embedded in THA and THA-col at different ratios (Table 1) at a final concentration of 5 Mil cell per ml hydrogel volume, corresponding to 1000 spheroids per ml hydrogel.

Results:

Table 10.7.1: Composition of tyramine modified hyaluronan (THA) and collagen (col) biomaterials.

Material			**THA [mg/ml]**	**Col [mg/ml]**
T12.5-C2.5	THA-col 1:1	THA low	12.5	2.5
T12.5-C1.7	-		12.5	1.7
T16.7-C2.5	-	THA high	16.7	2.5
T16.7-C1.7	THA-col 2:1		16.7	1.7

Storage shear moduli of the composites at 1% strain were in the same order of magnitude for all materials, ranging from 360 – 910 Pa. Samples were additionally light crosslinked to reduce biomaterial shrinking during culture. hMSC spheroids underwent chondrogenic differentiation

in all four composites marked by deposition of proteoglycans and positive staining of collagen type II and aggrecan immuno-histological stainings (Figure 10.7.1 A/B). hMSC spheroids embedded in the lower THA content hydrogels (12.5 mg/ml) showed a more pronounced chondrogenic gene expression marked by higher Col2A1/Col10A1 and Col2/Col1A1 ratios (Figure 10.7.1 C).

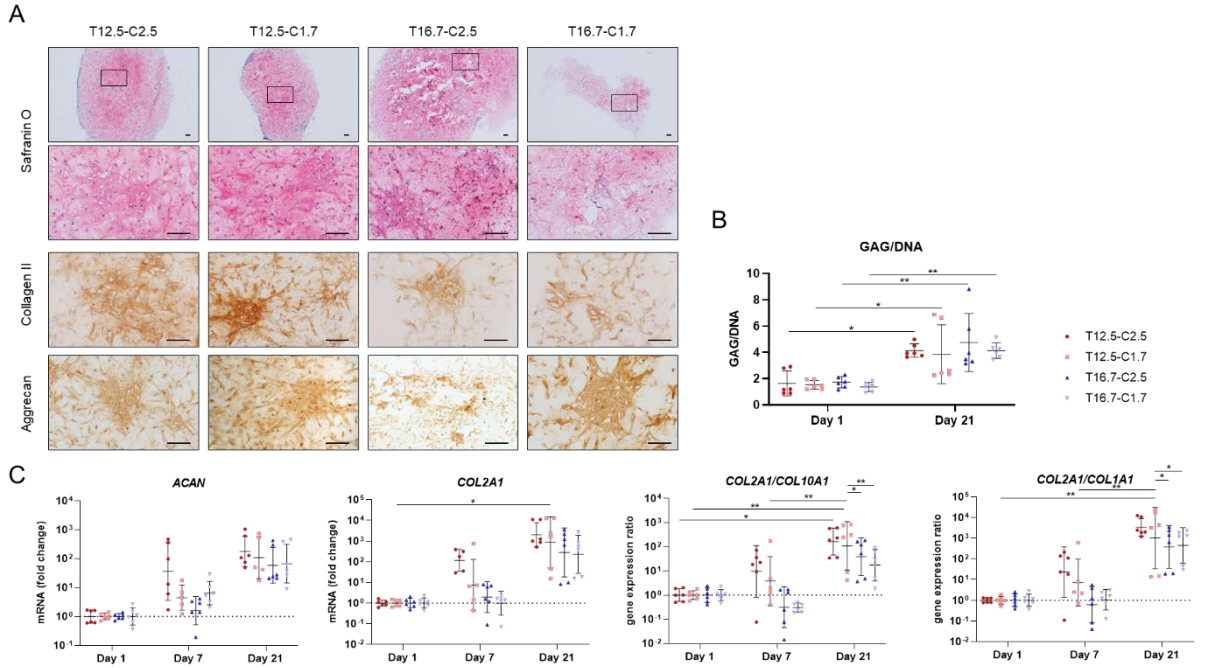


*Figure 10.7.1: A) (immuno-)histological stainings of samples after 3 weeks of differentiation showing deposition of proteoglycans (Safranin O and aggrecan positive staining) and collagen type 2 in al hydrogel formulations. B) Quantification of GAGs retained in sample and after normalization to DNA content showing no differences after 3 weeks of culture. C) Gene expression analysis of cartilaginous (ACAN, COL2A1) and gene expression ratios (COL2A1/ COL10A1, COL2A1/ COL10A1) of hMSC spheroids embedded in hyaluronan-collagen (THA-Col) hydrogels with higher (16.7 mg/ml, blue) and lower THA (12.5 mg/ml, red) content and two Col concentrations (2.5 mg/ml and 1.7 mg/ml). Samples with lower biopolymer content showed more pronounced upregulation of cartilage associated genes. N = 3 donors with 2 technical replicates each. 2 way anova, p<0.05 = *, p<0.01 = #, p<0.001 = $.*

To conclude, THA-col biomaterial- and bio-ink are promising for cartilage repair allowing for chondrocyte invasion, hMSC migration and hMSC chondrogenesis. We observed a tendency that lower THA (12.5 mg/ml) content is more favorable for these cell instructive properties compared to high THA (16.7 mg/ml) materials, but no clear trend was observed regarding col content. A research paper was submitted (Staubli *et al*, 2021).

Pres:

D'Este M, Schwab A, Eglin D, Staubli F. Micro-extrusion induced orientation of collagen fibrils embedded in hyaluronan and bioinks chondrogenic property. ESB 2021 (oral presentation).

Schwab A, Staubli F, Eglin D, D'Este M. 3D Bioprinting of a tissue mimetic hyaluronan bioink containing collagen fibers with controlled orientation. Euromat 2021 (oral).

Staubli F, Stoddart M, D'Este M, Schwab A. hMSC spheroids – effect of cell packing and biomaterial composition on chondrogenic differentiation *in vitro*. EORS 2021 (oral).

Schwab A, Alini M, Eglin D, D'Este M. Chondrogenic hyaluronan bio-ink containing collagen fibers with controlled orientation modulating cell orientation and morphology; ISBF Biofabrication 2021 (oral).

Schwab A, Staubli F, Wesdorp T, van Osch G, Stoddart M, D'Este M. Einfluss der Biomaterialzusammensetzung auf die Migration von Chondrozyten und hMSC Chondrogenese *in vitro* – Kollagen als stimulierender Faktor. DKOU 2021.

Schwab A, Meyer A, van Osch G, Grad S. Chondrozyten aus der Deep Zone – eine Subpopulation der Knorpelzellen mit Migrations- und Proliferationspotential und der Fähigkeit proteoglykanreiche Matrix *in vitro* zu produzieren. DKOU 2021.
Schwab A, Wesdorp MA, Loebel C, Levato R, Burdick JA, Malda J, Stoddart M, van Osch G, Eglin D, D'Este M. *Ex vivo* migration of chondrocytes – cell invasion into acellular biomaterials filled in a cartilage ring model is dependent on biomaterial composition. TERMIS 2021 (oral).
Schwab A, Staubli F, Eglin D, D'Este M. Effect of biomaterial composition on MSC chondrogenesis embedded in a hyaluronan composite containing collagen fibrils. TERMIS 2021.
Palladino S, Schwab A, D'Este M, Copes F, Candiani G, Mantovani D. Innovative bioink from collagen and hyaluronic acid with tunable rheological and biological properties for cardiovascular 3D bioprinting. TERMIS 2021 (oral).

Pub:
Xu Y, Yin H, Chu J, Eglin D, Serra T, Docheva D. An anisotropic nanocomposite hydrogel guides aligned orientation and enhances tenogenesis of human tendon stem/progenitor cells, Biomater Sci 9(4) (2021) 1237-1245.

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

10.8 AO Development Incubator

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

Background: The current generation of fracture fixation plates focuses on minimizing the impact of surgery and preserving biological healing potential. However, their design poorly controls a second critical aspect – the mechanical environment of the fracture. Furthermore, these plates fail frequently, which limits function and delays return to work. 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 plate. By means of a slot in its undersurface, the Biphasic Plate provides a beneficial mechanical environment at the fracture site for robust fracture healing. Furthermore, its increased implant strength carries potential to permit early full weight bearing and prevent implant fatigue-related failure. Finally, biphasic plating standardizes and, therefore, simplifies the surgical procedure.
Goal: To develop and obtain CE Mark of a biphasic anatomical plate for distal femur fracture treatment as a pilot implant and to collect clinical evidence demonstrating the concept feasibility.
Results: On April 21, 2021, the Biphasic Plate DF (Distal Femur) obtained CE certification as a class IIb medical device. A first series of Biphasic Plates was produced and is now available in selected clinics in Switzerland with first clinical application imminent.

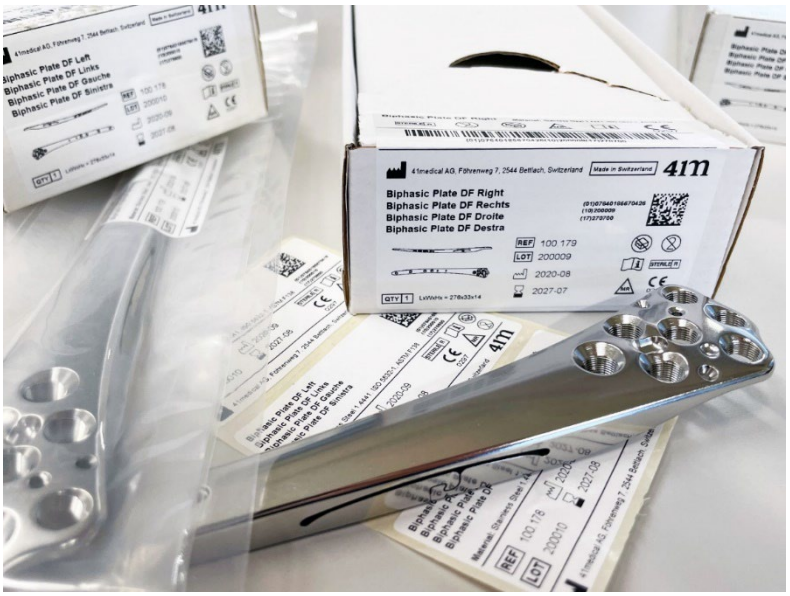


Figure 10.8.1: Packaged and CE-marked Biphasic Plate DF ready for clinical use.

Partners:

- Epari D (Prof), Queensland University of Technology, Brisbane, Australia
- Schütz M (Prof), Jamieson Trauma Institute, Brisbane, Australia
- 41medical AG, Bettlach, Switzerland

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

Background: Information on healing progression and load-bearing characteristics in fracture patients is only barely tapped due to the inaccessibility of a confined biological region and the limited value of radiographic methods. A novel approach to continuously measure both implant load and patient activity has recently been developed in ARI. The system comprises an implantable data logger autonomously collecting relevant parameters to support surgical decision-making during fracture healing. Wireless synchronization of the assessed implant load data via the patient's mobile phone allows for remote monitoring by the treating physician. Proof of concept is obtained from both preclinical experiments and the first clinical data collection with prototype devices on external fixation.
Goal: To further develop the AO Fracture Monitor into a commercially applicable system for long bone bridge plating. Implantable device and accompanying software shall be developed and tested according to the regulatory requirements and undergo clinical evaluation thereafter.
Results: The design of the implantable system components was frozen. Production processes were finalized with manufacturing partners. Production equivalent samples were manufactured, and verification/validation (V&V) activities have commenced according to ISO13485. These include mechanical testing, testing for active implantable devices according to EN45502, electromagnetic compatibility testing (IEC60601) and long-term reliability testing. Further validation activities have been setup including biocompatibility (ISO10993), cleaning, sterilization, packaging/transport, and software validation (IEC62304). Additional 9 sheep was equipped with AO Fracture Monitor devices within the DAIR project to strengthen the preclinical evidence. Over the study duration of 11 weeks, seamless data acquisition was achieved. Clinical trial preparation is ongoing for submission to the respective authorities upon completion of the required V&V testing.

Figure 10.8.2: Fracture Monitor T1 system with packaging and labeling.

Pres:
Windolf M. The AO Fracture Monitor – current status and capabilities of a novel technology to objectivize rehabilitation. 2021 EORS (oral).
Ernst M, Richards RG. Digitalized aftercare in orthopedics. 2021 Davos Digital Forum 2021 (oral online).
Richards RG, Ernst M. Smart Implants: the AO Fracture Monitor. 2021 AO Trauma Symposium – Advances in Trauma (oral online).
Richards RG, Ernst M. Smart surgery with the AO Fracture Monitor. 2021 Asia Pacific Orthopaedic Association – APOA (oral online).

Theses:
Wolfisberg C. Interpretability of implant load regarding fracture healing progression based on finite element modelling and fracture monitor measurements. MSc Thesis, ETH Zurich, 2021.

Partners:
- Braun B (MD), BG Unfallklinik Tübingen, Germany
- Pohlemann T (Prof), UK Homburg, Germany

Constant force growth modulation implant (ongoing) (J Buschbaum, M Windolf)

Background: Lower limb deformities in children and adolescents are often corrected with temporary (hemi-) epiphysiodesis technique, where the physis is bridged by an implant to inhibit growth and balance deformity. Currently utilized implants have their disadvantages. They are not passively safe and require timely surgical removal – as the implant load steadily increases with ongoing growth, potentially leading to devastating complications such as implant-related failures, over-corrections, unwanted secondary deformities, or permanent physeal closure of the growth plate. A novel passively safe implant concept was developed that exerts a predefined, growth-independent constant compression force to the physis to avoid the complications observed when using standard implants. Preclinical experiments have confirmed safe, effective, and controlled treatment with this new implant concept.
Goal: To translate the concept into a clinically usable medical device.
Results: A new implant design following the constant force principle was developed featuring all necessary aspects for human application. Dimensions and force level were tailored to human treatment as determined by mechanical testing, finite element simulations and *in vivo* collected data. Prototype implants were manufactured, and their basic functionality was verified via mechanical testing. A surgical handling and usability test was performed together with the AO TC Pediatric Expert Group (PAEG). Important findings were incorporated into the design. Final testing is underway for next *in vivo* application in a preclinical *in vivo* model.

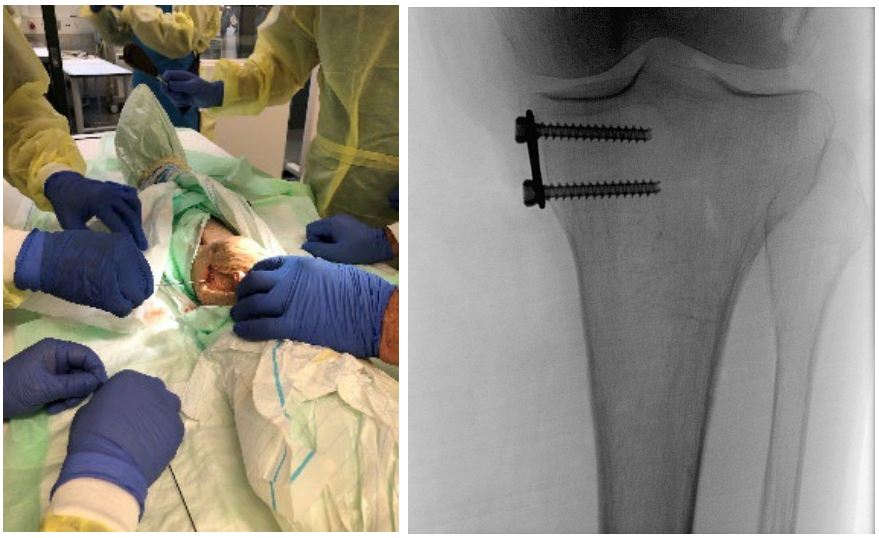


Figure 10.8.3: First surgical handling and usability test with the novel human applicable implant.

Pub:
Buschbaum J, Freitag L, Slongo TF, Zeiter S, Schütz M, Windolf M. Growth modulation of angular deformities with a novel constant force implant concept – preclinical results. J Child Orthop. 2021 Apr 19;15(2):137-148.

Partner:
- AO TC Pediatric Expert Group (PAEG)

3D-SIM
Background: Vascular tissue engineering – the generation of tissue that includes vessels – has the potential to significantly impact the treatment of a wide variety of medical conditions. It could provide *in vitro*-generated vascularized tissue and be useful for *in vitro* models for diagnostic and drug discovery indications. However, developing a large-scale, functional, vascularized construct is still a major challenge and an unsolved clinical problem.
3D Sound Induced Morphogenesis (3D SIM), uses sound waves to generate a network of cells in a matter of seconds, providing a self-assembled substrate for vascularization. This has potential to make vascularized tissue-engineered constructs based on autologous materials that are widely available in a laboratory environment. It has excellent potential for use in operation rooms in the future due to its speed, and as no needles are involved in the printing process, there is no fluid stress on the cells printed and consequently no cell damage or death.
Goal: the main goals are: 1) development of an acoustic patterning device (3D-SIM bioprinter), 2) optimization of hydrogels for patterning and definition of biomaterials and labware portfolio for mimix; 3) first *in vivo* anastomosis assessment of spatially organized vascular network.
Results: Mimix officially launched the first acoustic bioprinter, named CymatiX, on the market during WORLD TERMIS Conference 2021 (Figure 10.8.4). Labware and biomaterials portfolio were established. User manuals to provide user guidance for a successful patterning experience (Figure 10.8.5) and white papers for several applications were published.

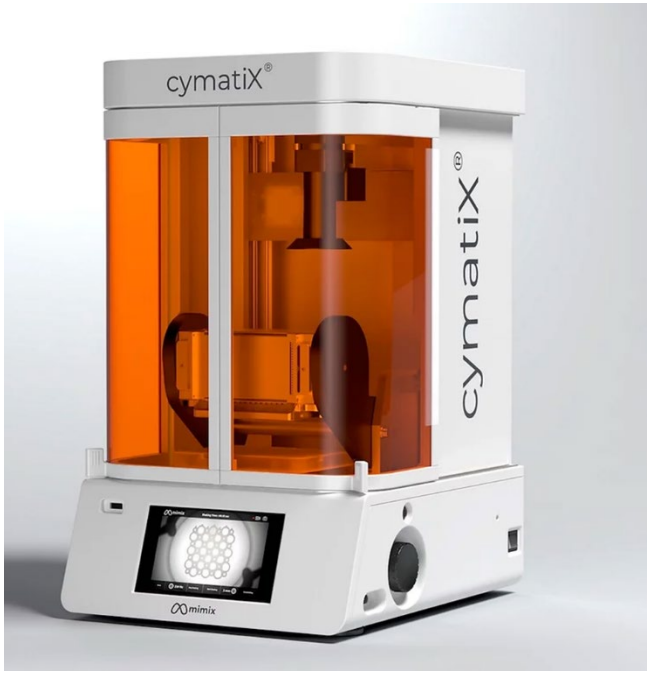


Figure 10.8.4. CymatiX, the acoustic bioprinter.

Partners:

- AO Research Institute Davos, Switzerland
- mimix Biotherapeutics, Switzerland
- Ehrbar M (Prof), Universitätsspital Zürich, Switzerland

Pres:

Guex AG, Di Marzio N, Alini M, Serra T. Sound waves and biomaterials to re-create the extracellular matrix. 6th World TERMIS Congress, Maastricht, The Netherlands, 2021.

Serra T. Sound patterns as a novel biofabrication platform. 6th World TERMIS Congress, Maastricht, 2021.

Pub:

Guex AG, Di Marzio N, Eglin D, Alini M, Serra T. The waves that make the pattern: a review on acoustic manipulation in biomedical research. Mater Today Bio. 2021 Mar 24;10:100110.

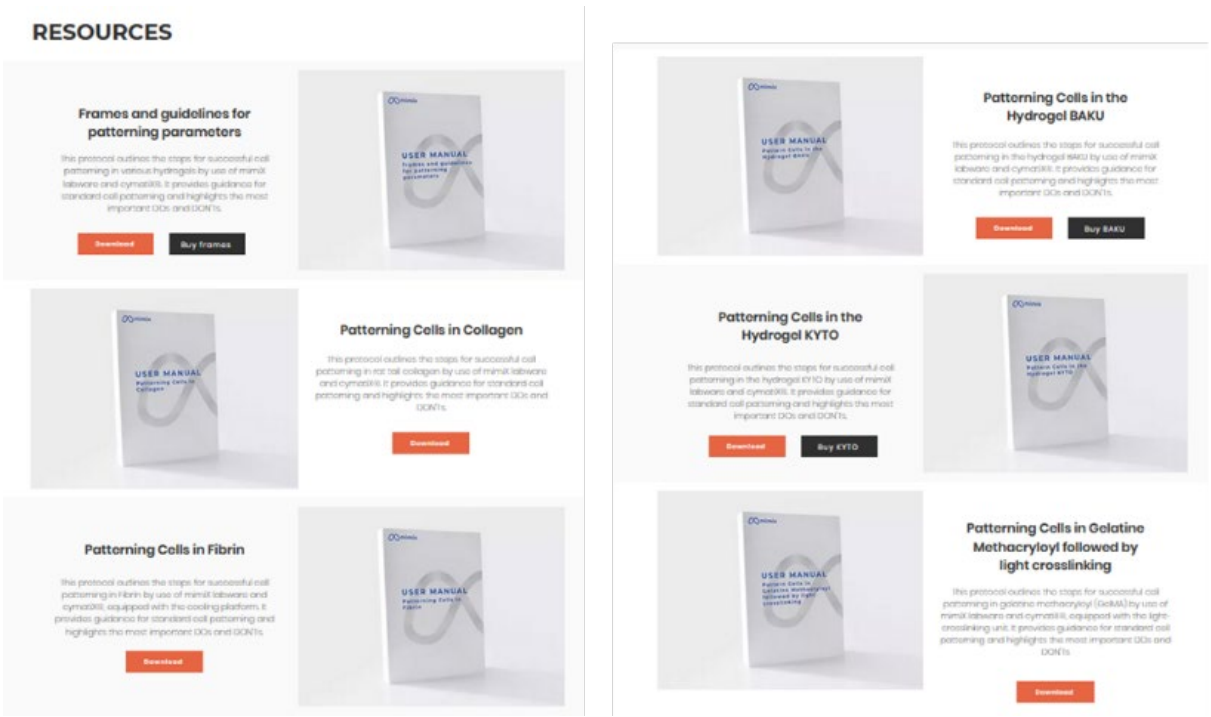


Figure 10.8.5: User manuals for sound patterning published on mimixbio.com

White papers for mimixbio.com:

Bridging from bench to bedside. *In vivo* evaluation of sound-patterned endothelial cells. Link: https://www.mimixbio.com/post/bridging-from-bench-to-bedside

In Vitro Vascularization Controlled by Local Cell Density Enhancement

Link: https://www.mimixbio.com/post/local-cell-density-enhancement-ii-in-vitro-vascularisation

Sculpturing the extracellular matrix by use of sound. Local densification and fibrillogenesis of collagen. Link: https://www.mimixbio.com/post/sculpturing-the-extracellular-matrix-by-use-of-sound

Engineering musculoskeletal tissue by sound. Micro-Pellet patterning within specific hydrogels to control cell sprouting. Link: https://www.mimixbio.com/post/engineering-musculoskeletal-tissue-by-sound

Tumor Model to Evaluate Drugs. Engineering the vascular tumor micro environment by patterning endothelial cells with sound. Link: https://www.mimixbio.com/post/disease-model-ii-a-saturn-like-tumor-model-to-evaluate-drugs

In Vitro Model to Study Pain. A multicellular system of dorsal root ganglions created by sound. Link: https://www.mimixbio.com/post/disease-model-i-an-in-vitro-model-to-study-pain

10.9 AO Strategy Fund

Digitally enhanced hands-on surgical training (DEHST) (ongoing) (J Buschbaum, M Windolf)

Background: Outcomes of orthopedic trauma surgery are highly determined by the skills and training level of the operating surgeon. Hands-on and tactile exercises are an essential pillar of a comprehensive training concept. Conventional hands-on training is typically offered only in course events – limited to basic skill training – and lacks data collection to measure training success. Current digital technologies offer strong opportunities to augment known predominantly mechanical training models with enhanced training scope, user experience and comprehensive training data assessment. They allow to decentralize the training – if desired – from course events to home-based training at any time.
Goal: To develop a skill station product line consisting of cost-effective, transportable, and digitally augmented modules for hands-on surgical training targeting the most relevant operational skills in trauma and orthopedics.
Results: The first DEHST module for practicing the technically demanding task of freehand distal interlocking of intramedullary nails was further refined and developed into a usable device ready for field testing. The system features an artificial X-ray imaging engine that generates radiation-free simulated X-rays for realistic training experience, and a proprietary optical tracking system utilizing a conventional video camera to monitor the training. Users can practice all relevant steps of perfect circle alignment, drill tip positioning and drilling. Training success is assessed by performance metrics, fed back to the user, and collected for holistic skills training improvements. The participant can access the data via a webapp for comprehensive training assessment and analytics. Opposed to classical hands-on training solutions, the system measures training outcome and progress, which is fundamental to future skills certification processes, and offers potential for integration into other AO skills training and education programs. The prototype was exhibited during the DKOU 2021 and the AO Davos Courses. Collected feedback was encouraging, confirming the clinical need and usefulness of the training concept, and demonstrating the demand for further DEHST training modules.

Figure 10.9.1: DEHST prototype for training of free hand distal interlocking, exhibited at AO Davos Courses.

Pres:
Buschbaum J. DEHST – Digitally enhanced hands-on surgical training. 2021 EORS (oral).

Partners:
- Höntzsch D, (Prof), BG Unfallklinik Tübingen, Germany
- SYNBONE AG, Zizers, Switzerland

OSapp: Virtual osteosynthesis tool for surgical education (OSAppSF) (ongoing) (P Varga, D Mischler, M Knecht, B Gueorguiev, M Windolf)

Background: Fracture fixation complications not only occur due to existence of suboptimal implants and instruments but are often caused by incorrect surgical techniques. Despite the well taught principles of fracture fixation treatment, less experienced surgeons sometimes fail to understand the underlying biomechanical concepts and thus select the incorrect fixation approach. Especially in trauma surgery, standardized procedures are rare, and the treatment is highly dependent on the clinical case, which requires a mechanical sense and awareness to correctly interpret the situation and chose the appropriate fixation strategy. To reduce complication rates, it is therefore of utmost importance to not only know the guidelines but also understand the underlying biomechanical principles.
Goal: To foster the understanding of the biomechanical principles of facture fixation and bone healing via a virtual and interactive osteosynthesis learning platform, and to augment and complement existing AO offerings with its unique possibilities of animating and displaying biomechanical simulations.
Results: The open online OSapp platform (https://osapp.ch/) has received traction and several collaborations have been established. The range of models, applications and virtual case discussions has been and is being continuously extended with the support of AO expert surgeons. The platform is being integrated into the Fundamentals module of AO Milestones to interactively illustrate biomechanical principles and used for learning assessment. OSapp was interlinked with AO Surgery Reference within a first pilot module related to cortical lag screws. During the Basic Principles Course at the AO Davos Courses 2021, the AO Skills Lab station on plate mechanics was supplemented with a custom-made OSapp module, allowing course participants to repeat core lessons at a later stage with the goal to manifest the learnings. OSapp has received internal AO and external attention through various channels and was showcased during the AO Davos Courses 2021 and the DKOU 2021 congress.

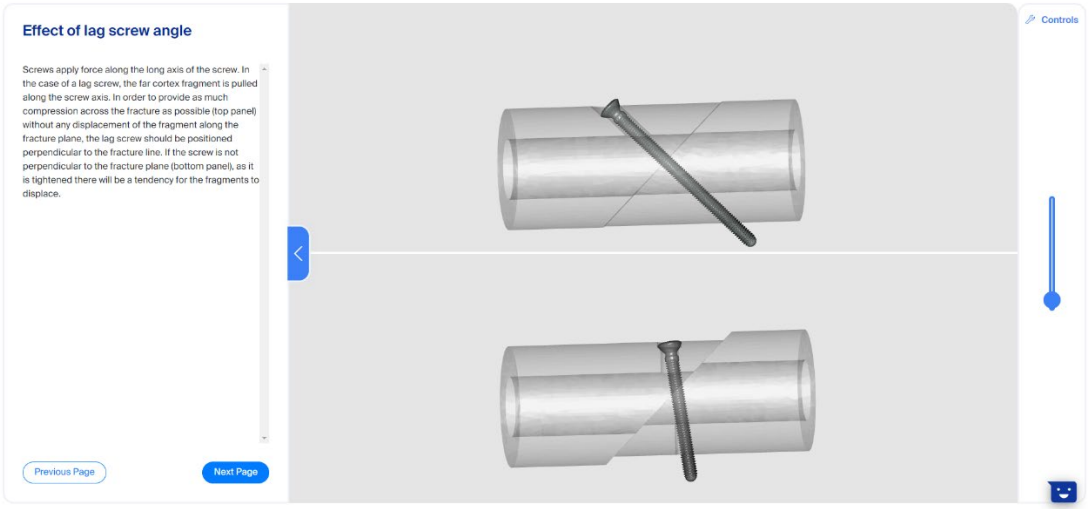


Figure 10.9.2: OSapp module on cortical lag screws, recently interlinked with AO Surgery Reference (https://osapp.ch/).

Pub:
Lambert S, Mischler D, Windolf M, Regazzoni P, Dell'Oca AF, Gueorguiev B, Varga P. From creative thinking to scientific principles in clinical practice. Injury. 2021. 52(1):32-36.

Partners:
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- Gebhard F (Prof), Universitätsklinikum Ulm, Germany
- Jäger M (MD), Universitätsklinikum Freiburg, Germany
- Schuetz M (Prof), Royal Brisbane Hospital, Brisbane, Australia

10.10 Extramural Projects

Smart multifunctional dental implants (I-SmarD) (ongoing) (A Vautrin, P Varga)

Background: Over 40% of dental implant cases will lead to peri-implantitis – an inflammatory condition caused by bacterial colonization that affects the tissue and bone around the implant. To address this problem, this EU-funded project proposes to develop multi-functional dental implants able to respond to environmental threats such as bacteria by releasing nanoparticles and antibiotics. Moreover, they should match the anatomical characteristics of dental tissues and offer potential to monitor the healing process after surgery. Collectively, the multi-functional dental implants should offer a personalized approach to prevent bacterial biofilm formation and peri-implantitis. The deposition of the biomaterials requires presence of porosities in the implant design. The implants have to be made of 3D printed titanium as conventional manufacturing techniques are not able to produce the desired porous geometries. The presence of porosities decreases the mechanical resistance of an implant. Therefore, investigating and optimizing the mechanical behavior of porous titanium structures via design features is needed to preserve structural integrity throughout its life cycle.
Goal: To optimize the design of porous 3D printed dental implants with regard to their fatigue lifetime via a combined experimental testing and validated finite element (FE) simulation approach.
Results: A pilot study was carried out to establish a validated simulation methodology to characterize fatigue behavior of porous 3D printed structures. Porous cylinder designs were generated with two different cell unit geometries – Schwarz Primitive (SP) and the Schwarz W (SW). 3D printed titanium samples were tested until failure under bending-compression fatigue loading according to the ISO 14801 standard. The results allowed an initial validation of an FE model simulating both designs at different load levels. The results demonstrate that the SP

unit cell has a longer fatigue life than the SW design and indicate the potential of this method to compare different porous geometries for design optimization.

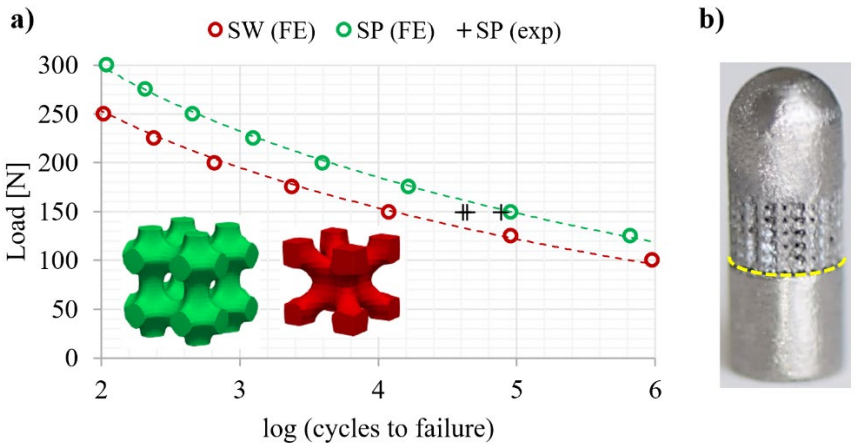

Figure 10.10.1: a) Number of cycles to failure versus fatigue load level predicted by FE simulations of both SP (green circles) and SW (red circles) cells geometry designs, together with experimental results for SP design (black crosses). b) Failed 3D printed porous titanium sample with fracture line indicated in yellow.

Partners:

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- Anastasiou A, University of Manchester, UK
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A novel highly customizable bone fixation solution (BoneFix) (ongoing) (P Schwarzenberg, P Varga)

Background: Traditional metal osteosynthesis hardware cannot be easily customized for a fracture in the operating theatre. Furthermore, metal solutions can lead to debilitating soft tissue adhesions that can impair joint mobility, especially in complex areas such as the hand, and require secondary surgery to remove the implant. A new osteosynthesis method, BoneFix, has been developed using light-curable polymer composites for highly customizable fixation solutions that have been demonstrated to induce no soft tissue adhesions. This biocompatible platform can be shaped *in situ* and be cured with a handheld high energy visible light through thiol-ene coupling chemistry in just 10 seconds. The platform is designed to use a self-etching primer to adhere directly to the bone surface and planned to be completely bioresorbable, leaving no hardware behind in the body.
Goal: To investigate and validate the biomechanical properties of the current BoneFix platform prototype in multiple loading modes and compare it to traditional metal solutions in *ex vivo* ovine models, *in vivo* ovine models, and human cadaveric models.
Results: Twenty-one ovine phalanges were assigned to three groups: narrow BoneFix patch, wide BoneFix patch, and traditional metal hardware. The BoneFix patches in both groups were fixed to the bone with traditional metal screws to isolate the biomechanics of the composite osteosynthesis method. Specimen-specific 3D printed guides were used to standardize the osteotomies and BoneFix application, and all samples were tested in torsion until failure. These initial biomechanical results were promising, showing that the BoneFix osteosynthesis patches had superior torsional stiffness than the traditional metal hardware and could sustain similar torques to failure. This indicates that BoneFix is not inferior to traditional metal orthopedic plates in torsion in this ovine phalanx model.

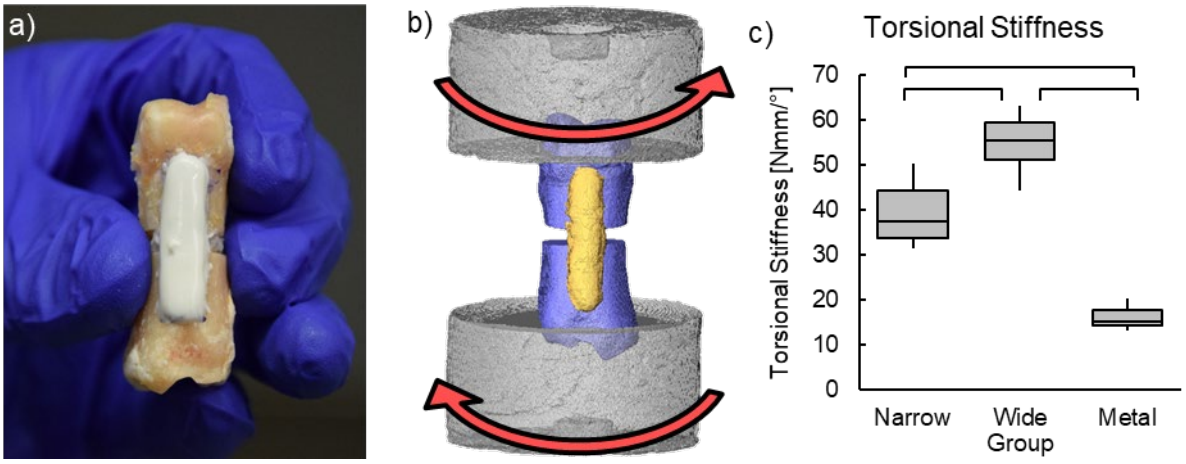

Figure 10.10.2: a) BoneFix osteosynthesis patch applied to ovine proximal phalange with transverse osteotomy. b) CT derived geometric models with torsional loading arrows illustrated. c) Box plot of the torsional stiffness comparing narrow and wide BoneFix patches to traditional metal hardware. In torsion, both BoneFix groups were stiffer than the metal group.

Partners:

- Malkoch M (Prof), KTH Royal Institute of Technology, Sweden
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- Wong C (MD), Region Hovedstaden, Denmark
- Svensson C (Prof), Karolinska Institute, Sweden
- Eglin D (Prof), Institut Mines-Telecom, France
- Granskog V, Biomedical Bonding AB, Sweden

Modeling of material injection processes into porous structures applied to vertebroplasty (CemFlow) (J Wychowaniec, M D'Este, D Gehweiler, E Zweifel, B Gueorguiev)

Background: Vertebroplasty has become an important technique for stabilization of osteoporotic vertebral fractures and other weakening lesions such as angioma or metastatic tumors. However, this procedure presents a significant risk through cement leakage that can result in serious complications such as pulmonary embolism or compressions of nerve roots or the spinal cord. Simulations of the bone cement injection processes could predict injection rates, injection pressures, bone cement distribution within the vertebra and the probability of cement leakage, thus providing a valuable risk assessment tool. However, risk assessment can only be performed if realistic simulations of the entire vertebra are performed.
Goal: To collect experimental data by quasi-continuous CT scanning during injection and rheological measurements of bone cement for modeling of material injection processes in vertebroplasty to describe bone cement flow behavior and distribution, biomechanical behavior at the interface between bone cement and trabecular structure, and bone cement curing.
Results: Bone cement flow behavior was measured using rotational rheology in two geometries: parallel plate-plate and cone-plate. Reproducible flow curves were obtained showing shear-thinning behavior during initial times and rapid recovery upon cycling shearing. Time-dependent rheology indicated critical curing time of approximately 700 seconds, upon which rapid increase of viscosity was observed, indicative of bone-cement curing. Obtained flow curves data was modelled according to the Power and Carreau laws to extract the shear-thinning exponents and relaxation times, which were subsequent used in analytical modelling to re-simulate injection pressure of the real experiment. The new developed model provides hitherto control over future use of non-Newtonian bone cements for vertebroplasty applications.

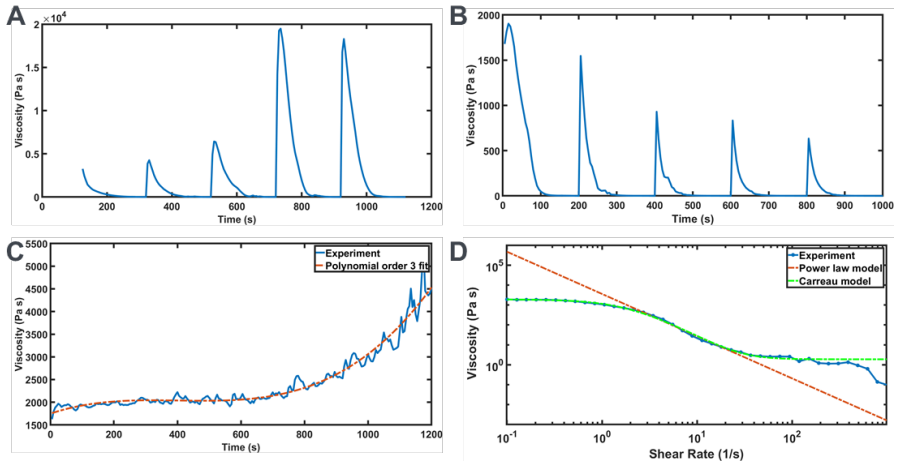

Figure 10.10.3: Cycling rotational rheology of bone cements in (A) cone plate and (B) plate-plate arrangement. Time-dependent curing of bone cement (C). Exemplary fitting of Power and Carreau models of first cyclic flow curve (D).

Pres:
Trivedi Z, Gehweiler D, Bleier C, Wagner A, Ricken T, Gueorguiev-Rüegg B, Röhrle O. Biophysics of living porous media: theory, experiment, modeling, and characterization. 2021 InterPore (oral).

Partners:
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- Wagner A (Prof), University of Stuttgart, Germany
- Trivedi Z, University of Stuttgart, Germany

Biomechanical analysis of cephalomedullary nails for trochanteric femoral fracture fixation (T Pastor, I Zderic, D Gehweiler, B Gueorguiev)

Background: Trochanteric femoral fractures are associated with increasing incidence due to the aging population and represent a serious adverse effect of osteoporosis. Their cephalomedullary nailing in poor bone stock can be a challenging endeavor associated with insufficient implant fixation in the femoral head. Despite the ongoing implant improvements, the rate of mechanical complications in the treatment of unstable trochanteric femoral fractures is still high. Recently, two novel concepts for nailing with the use of a helical blade – with or without bone cement augmentation – or an interlocking screw have demonstrated advantages as compared with single-screw systems with regard to rotational stability and cut-out resistance. However, these two concepts have not been subjected to a direct biomechanical comparison so far.
Goal: To investigate in a human cadaveric model with low bone density (1) the biomechanical competence of cephalomedullary nailing with the use of a helical blade *versus* an interlocking screw, and (2) the effect of bone cement augmentation on the fixation strength of the helical blade.
Results: Twelve osteoporotic and osteopenic human cadaveric femoral pairs were assigned for pairwise implantation using either a short TFN-ADVANCED Proximal Femoral Nailing System (TFNA) with a helical blade head element, offering the option for cement augmentation, or a short TRIGEN INTERTAN Intertrochanteric Antegrade Nail (InterTAN) with interlocking screws. Six osteoporotic femora, classified within the lower DEXA T-score range among the pairs and implanted with TFNA, were augmented with 3 ml TRAUMACEM V+ bone cement. Four study groups were created and combined in two clusters comprising specimens of the same donors each – Group 1 (TFNA) paired with Group 2 (InterTAN), both consisting of osteopenic specimens, and Group 3 (TFNA augmented) paired with Group 4 (InterTAN), both consisting of osteoporotic specimens. An unstable trochanteric AO/OTA 31-A2.2 fracture was

simulated by means of osteotomies. All specimens were biomechanically tested until failure under progressively increasing cyclic loading featuring a physiologic load trajectory. Interfragmentary movements were monitored by motion tracking. Stiffness in Group 3 was significantly higher *versus* Group 4, p = 0.03. Varus and femoral head rotation around the femoral neck axis after 10000 cycles were significantly lower in Group 3 *versus* Group 4, p = 0.04. Cycles to failure and failure load at 5° varus or 10° femoral head rotation around the neck axis were significantly higher in Group 3 *versus* Group 4, p = 0.04. From a biomechanical perspective, cephalomedullary nailing of trochanteric femoral fractures with the use of helical blades is comparable to interlocking dual screws fixation in femoral head fragments with low bone quality. Bone cement augmentation of helical blades provides significantly greater fixation strength in poor bone quality compared with interlocking screws constructs.

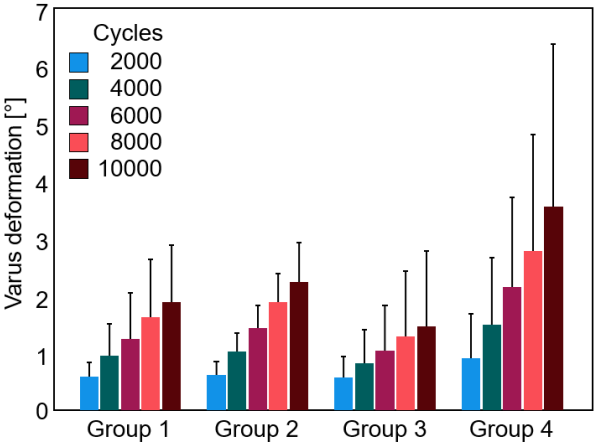

Figure 10.10.4: Varus deformation of the specimens in the four groups between 2000 and 10000 cycles in terms of mean value and standard deviation.

Pres:

Pastor T, Zderic I, Gehweiler D, Richards G, Gueorguiev B, Knobe M. Biomechanical analysis of recently released cephalomedullary nails for trochanteric femoral fracture fixation in a human cadaveric model. 2021 EORS (oral).

Pastor T, Zderic I, Gehweiler D, Knobe M, Gueorguiev B. Biomechanical analysis of recently released cephalomedullary nails for trochanteric femoral fracture fixation in a human cadaveric model. 2021 EFORT (online oral).

Pastor T, Zderic I, Gehweiler D, Knobe M, Gueorguiev B. Biomechanical analysis of cephalomedullary nails for trochanteric femoral fracture fixation. 2021 ESBiomech (online oral).

Pastor T, Zderic I, Gehweiler D, Richards G, Gueorguiev-Rüegg B, Knobe M. Biomechanische Analyse von Marknägeln zur Fixierung von Pertrochantären Femurfrakturen. 2021 DKOU (e-poster).

Partners:

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- Michael Gardner (MD), Stanford Hospitals and Clinics, Stanford, USA
- Karl Stoffel (Prof), University Hospital Basel, Basel, Switzerland
- Glen Pierson, DePuy Synthes, West Chester, USA
- Randy Mays, DePuy Synthes, West Chester, USA

Biomechanical investigation of a novel concept for angular stable nailing of unstable distal tibia fractures *versus* other nail designs (I Zderic, J Caspar, B Gueorguiev)

Background: Intramedullary nails are frequently used for treatment of unstable distal tibia fractures. However, insufficient fixation of the distal fragment could result in delayed healing, malunion or nonunion. Recently, a novel concept for angular stable nailing has been developed that maintains the principle of relative stability and introduces improvements expected to reduce nail toggling, screw migration and secondary loss of reduction. It incorporates polyether ether ketone (PEEK) inlays integrated in the distal and proximal canal portions of the nail for angular stable screw locking. The nail can be used with new standard locking screws and low-profile retaining locking screws, both designed to enhance cortical fixation.

Goal: To investigate the biomechanical competence of the novel angular stable intramedullary nail concept for treatment of unstable distal tibia fractures, compared with other nail designs in an artificial bone model under dynamic loading.
Results: The distal 70 mm of thirty artificial tibiae (SYNBONE) were assigned to 5 groups for distal locking using either four different commercially available nails – Group 1: Expert Tibia Nail (DePuy Synthes); Group 2: TRIGEN META-NAIL with Internal Hex Captured Screws (Smith & Nephew); Group 3: T2 Alpha with Advanced Locking Screws (Stryker); Group 4: Natural Nail System featuring StabiliZe Technology (Zimmer) – or the novel angular stable TN-Advanced nail with low-profile screws (Group 5, DePuy Synthes). All specimens were biomechanically tested under quasi-static and progressively increasing combined cyclic axial and torsional loading in internal rotation until failure, with monitoring by motion tracking. From a biomechanical perspective, the novel angular stable intramedullary nail concept with integrated PEEK inlays and low-profile screws provides ameliorated resistance against nail toggling and loss of reduction under static and dynamic loading compared with other commercially available intramedullary nails used for fixation of unstable distal tibia fractures.

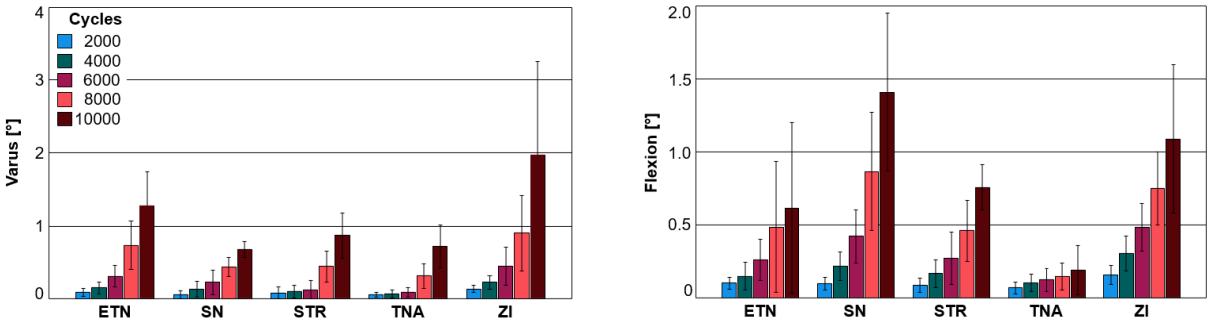

Figure 10.10.5: Varus (left) and flexion (right) of the specimens in the five groups (Group 1 = ETN, Group 2 = SN, Group 3 = STR, Group 4 = ZI, Group 5 = TNA) between 2000 and 10000 cycles in terms of mean value and standard deviation.

Pres:
Zderic I, Caspar J, Blauth M, Weber A, Koch R, Stoffel K, Finkemeier C, Hessmann M, Gueorguiev B. Angular stable intramedullary nailing improves construct stability in a distal tibia fracture model – a biomechanical study. 2021 EORS (oral).
Zderic I, Caspar J, Blauth M, Weber A, Koch R, Stoffel K, Finkemeier C, Hessmann M, Gueorguiev B. Improved stability of distal tibia fractures after angular stable intramedullary nailing – a biomechanical study. 2021 ESBiomech (online oral).
Zderic I, Caspar J, Blauth M, Weber A, Koch R, Stoffel K, Finkemeier C, Hessmann M, Gueorguiev B. Improved construct stability after angular stable intramedullary nailing of distal tibia fractures. A biomechanical study. 2021 EFORT (online oral).

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- Weber A, DePuy Synthes, Zuchwil, Switzerland
- Koch R, DePuy Synthes, Zuchwil, Switzerland

Biomechanical analysis of the Influence of knot number on holding capacity of two high strength sutures in different media (T Pastor, K van Knegsel, B Gueorguiev)

Background: High strength sutures are commonly used in arthroscopic procedures for refixation of tendons or ligaments. However, knot slippage can occur when these sutures are

heavily loaded, leading to a laxity of the fixation with gap formation between the repaired structures. Recently, a new suture was designed to minimize repair laxity to preserve consistent tissue approximation while improving footprint compression.
Goal: To compare the biomechanical competence two different high strength sutures and evaluate the influence of knot number and testing conditions on holding capacity.
Results: Alternating surgical knots of two different high strength sutures – Group 1: FibreWire and Group 2: DynaCord – were tied with 25 N force using a custom-made device. Biomechanical testing was performed in dry, wet, and fatty-wet conditions applying a monotonically increasing tension load until failure, the latter resulting from either knot slippage or suture rupture. Different numbers of knots ranging from 3 to 7 were investigated. Seven specimens were tested per group, test condition and knot number. The minimum number of knots preventing slippage failure and thus resulting in suture rupture was determined and used as criterium for superior performance when comparing the two groups in each condition. For each group and condition, failure occurred via suture rupture of all seven specimens for the following minimum knot numbers: Group 1: dry: 7, wet: 7, fatty-wet: 7; Group 2: dry: 6, wet: 4, fatty-wet: 5. The direct comparison between the groups when using 7 knots demonstrated significantly larger slippage in Group 1 *versus* Group 2 in wet condition, $p < 0.01$. Ultimate load was comparable between the two groups for all three conditions. The lower number of required knots providing sufficient repair stability, smaller slippage levels and identical suture strength, combined with the known laxity alleviation effect demonstrates clear advantages of DynaCord *versus* FibreWire.

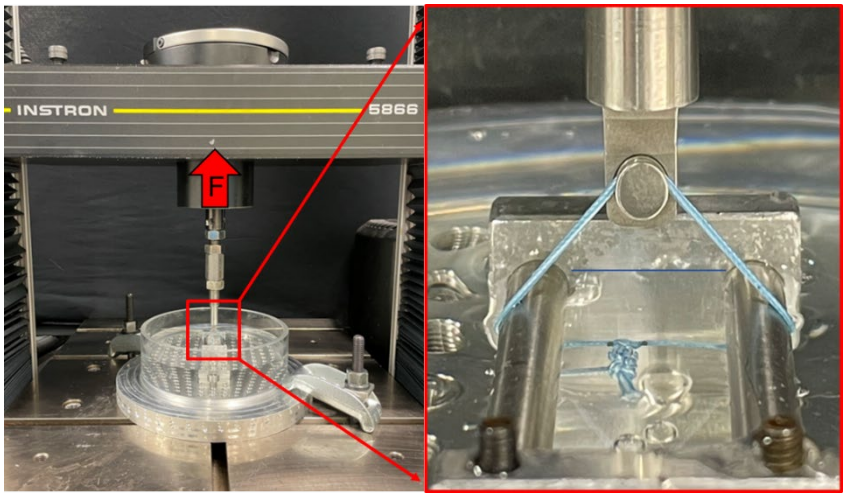

Figure 10.10.6: Setup with a specimen mounted for testing in saline (wet condition) and red arrow indicating loading direction.

Partners:
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- Beeres F (MD), Lucerne Cantonal Hospital, Switzerland

Biomechanical investigation of cementless femoral stem implantation in total hip arthroplasty with periprosthetic clamshell fracture (P Kastner, B Gueorguiev)

Background: One of the most serious complications in hip arthroplasty is the periprosthetic femoral fracture as it is economically costly and can pose great obstacles for the surgeon. The medial femoral wall plays an important role in primary arthroplasty, providing stability of cementless fixed stems. However, the role of a non-addressed, medial wall fragment for stem stability has not been elaborated yet.
Goal: To evaluate biomechanically the stability of a diaphyseal-anchored cementless stem in presence of a proximal periprosthetic femoral medial wall defect compared to the stability of the stem without such a defect.
Results: Twenty-two paired human cadaveric femora were assigned pairwise either to a defect group – featuring a non-addressed proximal medial wall fragment involving 40% of the medial anchoring distance – or to a control group without such a defect. A diaphyseal anchoring stem was implanted in each group and all specimens underwent progressively increasing cyclic loading to failure. Implant axial displacement of 1 mm was defined as criterion for stem loosening. Load, cycles, and respective body weight percentage at stem loosening were measured. Initial stiffness was not significantly different between the groups, $p = 0.86$. Load (control: 3210.5 ± 1073.2 N, defect: 2543.6 ± 576.4 N), cycles (control: 27105 ± 10732,

defect: 20432 ± 5764) and body weight percentage (control: 548.3 ± 158.5%, defect: 441.4 ±104%) at stem loosening were significantly higher in the control group, $p \leq 0.03$. However, from a biomechanical perspective, even a rather severe fracture scenario involving 40% of the medial anchoring distance of a primary implanted diaphyseal anchored press fit stem can be left unfixed without harming stem stability within physiologic load boundaries. Thus, intraoperative effort might be considerably reduced leading to decreased operation time, blood loss and overall complication rate.

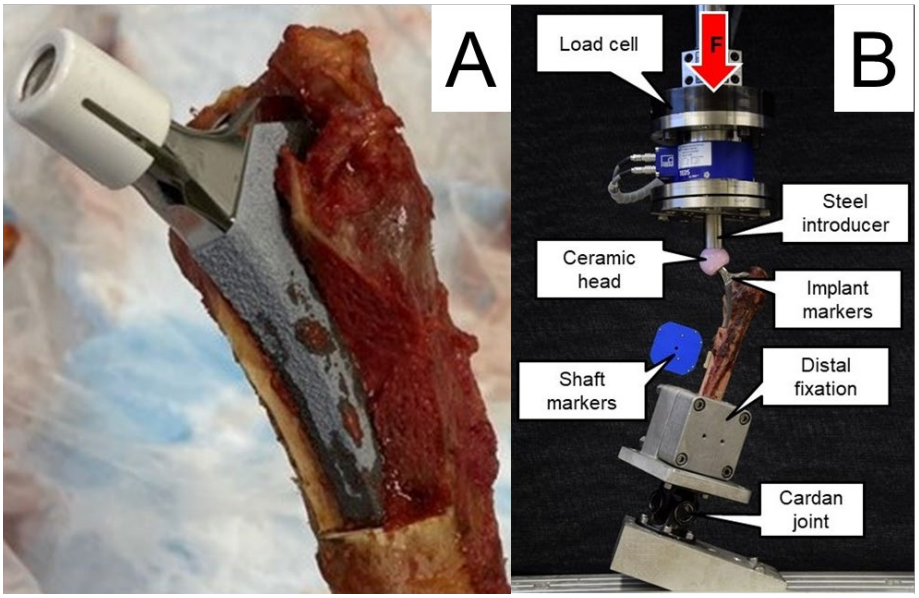

Figure 10.10.7: A) Photograph of a specimen with simulated Clamshell fracture, characterized by a proximal medial wall defect around a press fit stem; B) Test setup with a specimen mounted for biomechanical testing.

Partner:

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Precision medicine for musculoskeletal regeneration, prosthetics, and active ageing (PREMUROSA) (ongoing) (T Serra, M Alini)

Background: Musculoskeletal diseases are reported to affect roughly half of the world's population over 60, strongly impacting the quality of life. They are a major burden on individuals, healthcare, and welfare systems, with huge direct and indirect costs. Currently treatment of musculoskeletal disorders is often based either on prosthetic rehabilitation or on regenerative surgical procedures, including scaffold implantation. In both cases, individual tissue healing and regeneration response, and the appropriateness of the implanted device, markedly affect the outcome. Personalized medicine has evolved as a model aiming to transform translational research into a patient-specific ("precise") concept, which incorporates tailored diagnostic measures and customized targeted therapies, improving the clinical success rate. This approach is currently applied in some medical fields such as Oncology, but it has received poor attention in orthopedics where the concept of "personalization" is still mostly limited to a mere adaptation of the device geometry to the patient anatomy without taking into account any patient-specific capability in tissue regeneration. In addition, despite the great improvement in developing multi-functional smart biomaterials and medical devices for tissue regeneration by classical "design and engineering" approaches, the pre-clinical models for the biological assessment of their efficacy have not followed the same evolution and because of that no more than one third of innovations are translated to clinical practice. The complexity of the regenerative process and the difficulty in predicting and controlling the interaction between tissue and biomaterial, as well as the lack of reliable and rapid execution

preclinical models addressed to predict the clinical performances are certainly responsible for these gaps.
Goal: The aim of PREMUROSA (Precision medicine for musculoskeletal regeneration, prosthetics, and active ageing) is thus to help precise patient centered application of regenerative treatments by developing new *in vitro* tests and decision support systems (DSS), while training 13 young scientists (ESRs) with a multidisciplinary approach and interaction.

Results: 3D advanced cell models were developed to study the cell/stress responses, the role of extracellular matrix including and vascularization, by using a contactless sound wave based biofabricaton process.

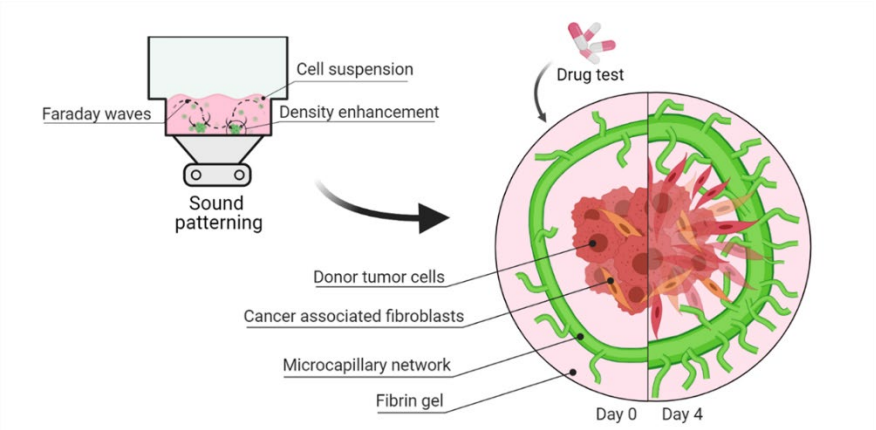

Figure 10.10.8: The tumor microenvironment is simulated in the Saturn-like 3D tumor model (STM). Firstly, (A) Sound patterning is used for shaping reproducible rings of GFP-HUVEC and human pericytes in fibrin within a commercially available multi-well plate. The cells self-assemble in a microcapillary network while retaining the ring architecture. Secondly, (B) a tumor heterotypic spheroid is embedded in fibrin gel and added onto the microcapillary network bed. The basal bed recapitulates the hierarchically organized microcapillary network stimulated by an establishing tumor in its proximity. (C) The model's microvascular morphology can be monitored, and the readouts could serve in drug testing applications to predict patient tailored treatments.

Significance: The method here exposed can be easily translate for studying personalized therapies in musculoskeletal regeneration by biofabricating reproducible *in vitro* vascularized models in a HTS setup. This will be the further explored in 2022.

Pres:
Di Marzio N. Acoustic waves driven assembly of capillary networks. Poster presentation. International Society for Biofabrication (ISBF) Twitter Poster Conference. 17.02.2021 (online).
Di Marzio N. Saturn-like vascularized tumor model: combining spheroid with a ring-shaped microvasculature by using sound. Biofabrication Australia 2021. Online. 27-29.09.2021 (oral).
Di Marzio N. Saturn-like vascularized tumor model: combining spheroid with a ring-shaped microvasculature by using sound. 4th Young Scientist Symposium (SSB+RM) - From micro to macro in biomedicine, Zurich. 07.10.2021 (poster)
Di Marzio N. Development of a 3-dimensional vascularized cancer model via sound induced morphogenesis (SIM). TERMIS 2021 World Congress. 15-19.11.2021 (online poster).

Funding: H2020-MSCA-ITN, ARI Funding EUR 281'276; Period: 2020-2023.

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- Obradovic B (Prof), University of Belgrade, Belgrade, Serbia
- Rimondini L (Prof), Università del Piemonte Orientale, Novara, Italy
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- Chiocchetti A (Prof), Università del Piemonte Orientale, Novara, Italy
- Corazzari M (Prof), Università del Piemonte Orientale, Novara, Italy
- Venturin M (Dr), Enginsoft SpA, Padova, Italy
- Pandit A (Prof), National University of Ireland, Galway, Ireland

Eurostar project: E - RegenMed2.0, EU: Re-define regenerative medicine with a point-of-care tissue production technology

Background: ARI previously invented and patented a new 3D bioprinting solution that offers the opportunity for bedside printing of patient specific material.
Goal: The scope of the project is to validate a novel Point-Of-Care (POC) tissue production solution that will be at the core of a disruption in the field of personalized regenerative medicine. The solution aims to deliver a patient specific graft manufactured bed-side, starting with a small healthy biopsy of patient's own tissue, first converted into micrografts to be, in a second step, valorised as a transplant graft within a "Sound Induced Morphogenesis" biofabrication process.
Results: A process and protocol for patterning autologous micrograft within gelling biological components has been developed and tested on large animal model.

Significance: the use of a fast and mild approach for generating large and spatially organized autologous components which can be directly implanted bed side could open novel strategies for cost-effective intraoperative procedures and faster healing processes.

Funding: Eurostar; ARI Funding EUR 150'000; Period: 2020-2022.

Partners:
- mimiX Biotherapeutics, Switzerland
- Rigenera HBW, Italy

Induced pluripotent stem cells, biomaterials, intraventricular disc degeneration, regenerative medicine (IPSpine) (Ongoing) (A Vernengo, Z Li, M Alini, S Grad)

Background: Notochordal cells (NCs) are a promising candidate for cell-based therapies for intervertebral disc (IVD) degeneration. A multitude of *in vitro* studies in 2D monolayers and 3D hydrogels indicate beneficial molecular effects of NCs on resident IVD cells, like increased protection from apoptosis and stimulation of GAG production. In this work, we evaluated the therapeutic effects of NC-based therapy in an *ex vivo* bovine organ culture model of IVD degeneration. In this model, degeneration was induced enzymatically with injection of the enzyme collagenase. In previous studies, we showed that collagenase II induces significant losses in disc height, formation of a void at the site of injection, and degenerative shifts in gene expression by 7 days of dynamically loaded culture. Here, it was hypothesized that the injection of porcine-derived notochordal cells after 7 days of collagenase digestion would have regenerative effects on the bovine tissue by enhancing GAG content, upregulating anabolic gene expression, and mitigating IVD height loss.
Results: Gross observations of collagenase-digested specimens at day 21 of culture revealed greater structural integrity for the collagenase-digested IVDs which received notochordal cells (+NC) compared to the untreated group (-NC, Figure 10.10.9 A). The glycosaminoglycan (GAG) content in the inner annulus fibrosus (iAF) at day 21 was higher for the +NC group compared to the –NC group ($p=0.04$, Figure 10.10.9 B). Mean loss of viability in the iAF and nucleus pulposus (NP region) was significantly greater at day 21 for the -NC group (67.6 ± 31.1%) *versus* +NC group (34.19 ± 19.9%, $p=0.009$, Figure 10.10.9 C).

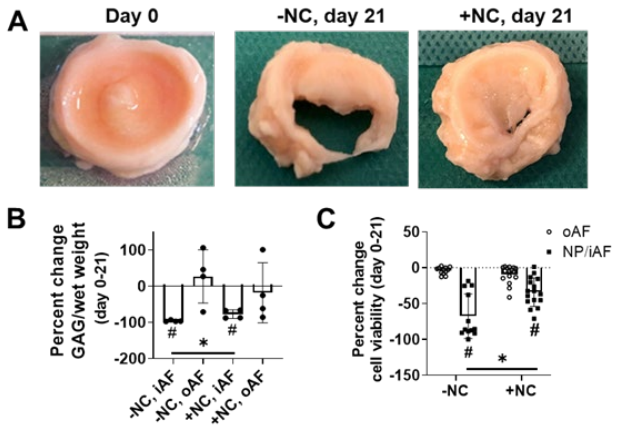


Figure 10.10.9: A) Macromorphological properties of collagenase-degenerated bovine IVDs with or without notochordal cell treatment (+NC or -NC, respectively) compared to day 0 intact specimen. B) Mean GAG content of collagenase-digested bovine IVDs with or without notochordal cell treatment. C) Average percent change in cell viability over 21 days with or without notochordal cell treatment.

Significance: Recent research in the field of IVD repair focuses on the generation of NC-like cells from human induced pluripotent cells (iPSCs), a promising approach that can potentially transform the clinical treatment of low back pain. Results from this study point towards the regenerative benefits of NCs, and we propose this *ex vivo* IVD degeneration model as a translational, cost-effective screening tool for such therapies.

Funding: EU H2020-SC1-BHC-2018-2020 RIA- Grant; ARI Funding EUR 491'250; Period: 2019-2023.

Pub:

Lee NN, Salzer E, Bach FC, Bonilla AF, Cook JL, Gazit Z, Grad S, Ito K, Smith LJ, Vernengo A, Wilke HJ, Engiles JB, Tryfonidou MA. A comprehensive tool box for large animal studies of intervertebral disc degeneration. JOR Spine. 2021 Jun 14;4(2):e1162. DOI: 10.1002/jsp2.1162. eCollection 2021 Jun.

Partners:

- Tryfonidou M (Prof), University of Utrecht, Netherlands
- Creemers L (PhD), University Medical Centre Utrecht, Netherlands
- Ito K (Prof), Technical University of Eindhoven, Netherlands
- Guicheux J (Prof), University of Nantes, France
- Pandit A (Prof), National University of Galway, Ireland
- Wilke H-J (Prof), University of Ulm, Germany
- Gantenbein B (Prof), University of Bern, Switzerland
- Jorgensen C (Prof), Institute National de la Sante, France
- Templin M, Naturwissenschaftliches und Medizinisches Institut, Germany
- Le Maitre C (Prof), Sheffield Hallam University, United Kingdom
- Vadala G, University Campus Biomedico, Rom, Italy
- De Boer M, Ntrans Technologies, Netherlands
- Noel D, University of Montpellier, France
- Isasi R, University of Miami, US
- Kienle A, Spineserv Gmbh, Germany
- Chan D, The University of Hong Kong, Hong Kong
- Buljovcic Z, Pharmalex Gmbh, Germany
- Lether I, National Reumafonds, Netherlands

Topographical immunomodulation: a new 3D printing strategy for annulus fibrosus (AF) tissue engineering (ongoing) (A Vernengo)

Background: Intervertebral disc (IVD) degeneration is a chronic inflammatory condition predominantly regulated by macrophages, characterized by elevated levels of cytokines, matrix degrading activities, and neurovascular ingrowth. These degenerative changes lead to altered biomechanics and the formation of ruptures in the peripheral annulus fibrosus (AF) of the IVD. There is a growing body of evidence that mitigating the inflammation present in the degenerated IVD is critical for establishing a permissive environment for regeneration. However, the current scaffold-based tissue engineering approaches largely ignore inflammation-modulating function.
Goal: Our group developed an innovative melt-extrusion-based 3D printing method for the fabrication of scaffolds, mimicking the 3D macroarchitecture of the native AF, with defined surface topographies that guide cellular morphology and behavior. In the current study, we sought to understand the effects of such surface topography on the polarization signature of M0, M1 and M2-stimulated THP-1 derived macrophages.
Results: Polycaprolactone scaffolds were 3D printed in this study via extrusion through two types of custom-made nozzles: a round control nozzle and patterned nozzle possessing circumferential sinusoidal peaks. The smaller size features of the topography produced by the round nozzle induced significantly lower cell circularity and cell area compared to the patterned nozzle (Figure 10.10.10), factors known to produce anti-inflammatory shifts in macrophages. Compared to monolayer controls, M2 polarization on the scaffolds resulted in higher expression of anti-inflammatory markers IL-10 and CCL18. Additionally, the M2 marker CD206 trended towards greater upregulation on the 3D printed scaffolds compared to monolayers.

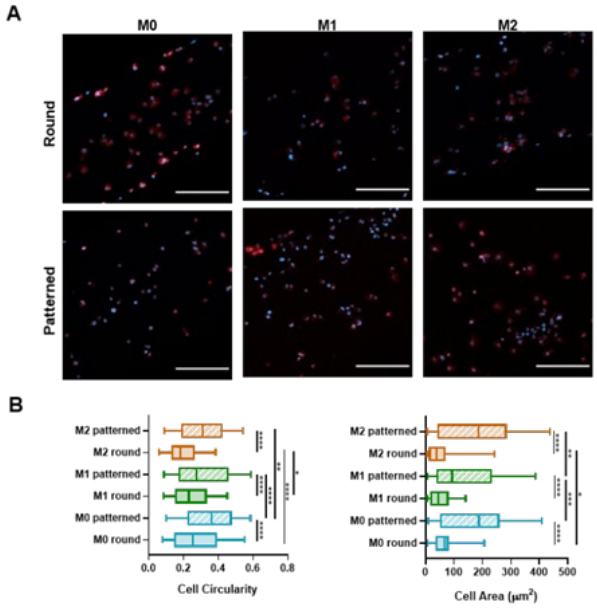


Figure 10.10.10: A) Representative of DAPI and phalloidin stained M0, M1 and M2-like THP-1 derived macrophages is shown in (scalebars 200 μm). B) Cell nuclear circularity and cell area with significant shifts towards more elongated nuclei and smaller area for cells on round compared to patterned scaffolds.

Significance: The results point towards the immunomodulatory capacity of the 3D printed scaffolds, which may be useful in the regeneration of multiple types of musculoskeletal tissues where chronic inflammation hampers healing cascades.

Funding: SNF Spark project number CRSK-3_195938; ARI Funding 100'000 CHF; Period 2021-2022.

Life changing therapy for osteo-arthritis patients: a biomarker lead approach (OA_BIO) (started) (Z Li, M Alini)

Background: Osteoarthritis (OA) is the most common chronic joint disease and a leading cause of disability worldwide, affecting more than 300 million people. Current treatments only relieve OA symptoms but have no impact on the progression of the disease. The pressing need to bring novel disease-modifying OA drugs (DMOAD) to patients is made even more challenging by the lack of clinical specific disease biomarkers. OA-BIO represents the breakthrough development of two components that address an unmet need in advancing OA treatment (therapy and biomarkers). The consortium, composed of both industrial and academic partners, will join in their expertise to advance to phase II clinical trial 4P004, a novel first-in-class disease-modifying drug for OA, and to validate new OA imaging and liquid biopsy biomarkers needed for 4P004 efficacy determination and patient selection in phase II/III clinical trials.
Goal: The aim of ARI within the OA_BIO project is to validate existing and identify novel liquid biopsy biomarkers from synovial fluid, blood, and urine samples for patient stratification and treatment response monitoring of 4P004, and to develop and validate novel cartilage regeneration biomarkers related with the efficacy of 4P004 for OA treatment (Figure 10.10.11).

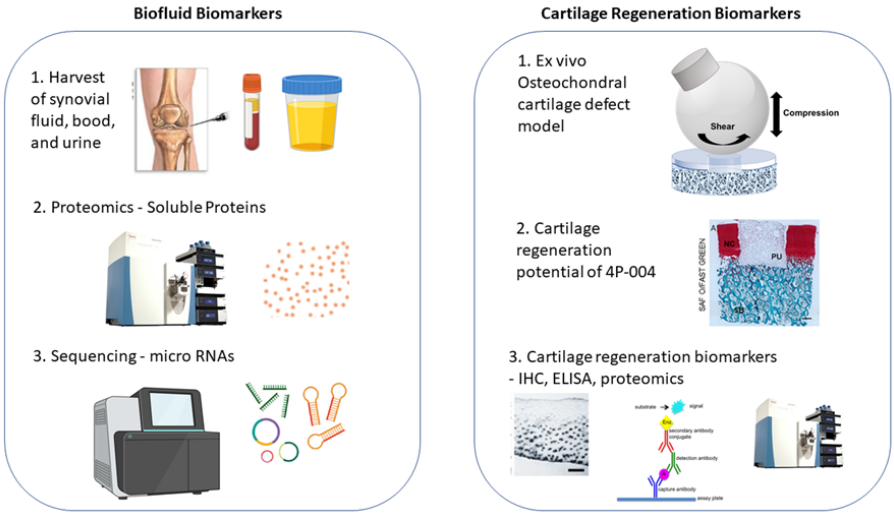


Figure 10.10.11: In the OA_BIO project new OA liquid biopsy biomarkers (synovial fluid, blood, and urine) will be validated, and used for patient stratification and selection. Moreover, they will allow for the first time to effectively monitor treatment response in OA by detecting of cartilage degradation and/or regeneration at early stages, before irreversible tissue damage.

Funding: Eurostars Grant**,** ARI Funding EUR 250'000; Period: 2021-2024.

Partners:
- Berenbaum F (Prof), 4Moving Biotech, Saint-Antoine Hospital, Sorbonne University, Paris, France
- Tryfonidou M (Prof), Utrecht University, Utrecht, Netherlands
- Eckstein F (Prof), Chondrometrics GmbH, Ainring, Germany

Advanced *in vitro* organ degeneration models for musculoskeletal research (Multireact) (ongoing) (S Grad, M Alini, A Secerovic, A Ristaniemi)

Background: Currently, the translation of research from the lab to the clinic is not reliable due to an oversimplification of the *in vitro* models and limitations of animal testing. The musculoskeletal system incorporates bones, cartilage, skeletal muscles, tendons, and ligaments to provide mechanical support and permit movement. Most *in vitro* models provide

static or oversimplified dynamic (*e.g.*, only compression) environments over short-term tissue culture periods.
Goal: The overall objective is to develop a multi-axis dynamic *in vitro* system to mimic movement (with a focus on intervertebral discs) for long-term musculoskeletal tissue culture. This interdisciplinary project is a collaboration between CSEM (6-DOF bioreactor), ETH Zurich (biomechanics) and ARI (*in vitro* organ models). The first phase concentrates on the validation of a new generation of bioreactor with uniaxial mechanical loading. The second phase will deliver a universal and versatile six degrees-of-freedom bioreactor for long-term musculoskeletal tissue culture. The third phase will generate a new set of degeneration models that are clinically relevant. Intervertebral disc (IVD) organ culture is pursued as a showcase.
Results: In a biological and mechanical study a new sample holder for bovine IVDs with adjacent bone was validated according to bioreactor requirements for multiaxial loading and long-term IVD culture. During three weeks of culture under axial compression loading, the new model maintained the cell viability comparable to the standard model. When differently directed motions were applied, the holder-IVD interface with side screws resisted compression and torsion above reference values, and the combination of side and top screws resisted tension and bending at high values.

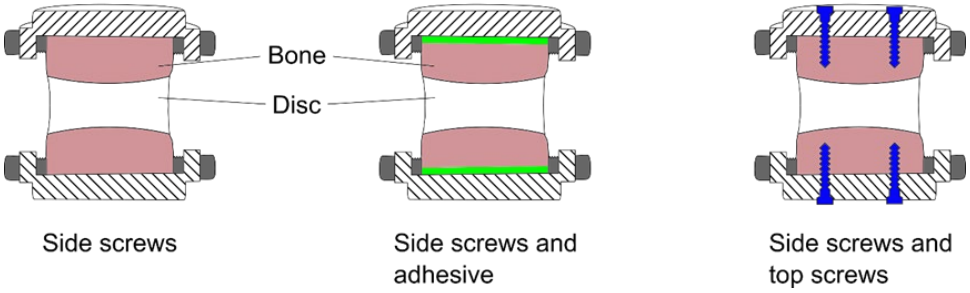


Figure 10.10.12: New holding system for whole bovine intervertebral disc with vertebral bone, allowing multiaxial loading.

Funding: SNF Sinergia; ARI Funding CHF 670,410; 2020-2023.

Partners:
- Ferguson SJ (Prof), ETH Zürich, Switzerland
- Weder G (Dr), CSEM Neuchâtel, Switzerland
- Heub S (Dr), CSEM Neuchâtel, Switzerland

Cartilaginous tissue regeneration by non-viral gene therapy; taking the hurdles towards efficient delivery (Carthago) (started) (S Grad, M Stoddart)

Background: Chronic low back pain due to intervertebral disc (IVD) degeneration and osteoarthritis (OA) worldwide impact human health and well-being due to pain and impaired mobility. Non-viral gene therapy has great promise as safe and precision treatment to restore IVD and joint tissue health. However, the lack of accessibility of the affected cartilaginous tissues to drugs has inhibited progress in this field. "Carthago" will finally fulfil the promise of non-viral gene therapy in these diseases. We will do this through educating 15 young researchers in 10 different countries in physics, quality by design, nucleic acid chemistry, nanomedicine, cartilage and IVD biology, ethics, entrepreneurship, and academic transferable skills.
Goal: This highly multidisciplinary team will exploit the potential of gene therapy in IVD and joint disease by taking a multi-faceted approach towards the delivery and activity of oligonucleotides and encoding nucleic acids (NA). The role of the ARI team is to test the newly developed NA delivery systems in our cell and organ culture models using bioreactor systems for cartilage and IVD. Two PhD candidates (Early-Stage Researchers) are performing the *in vitro / ex vivo* studies, while being trained in interdisciplinary fields.

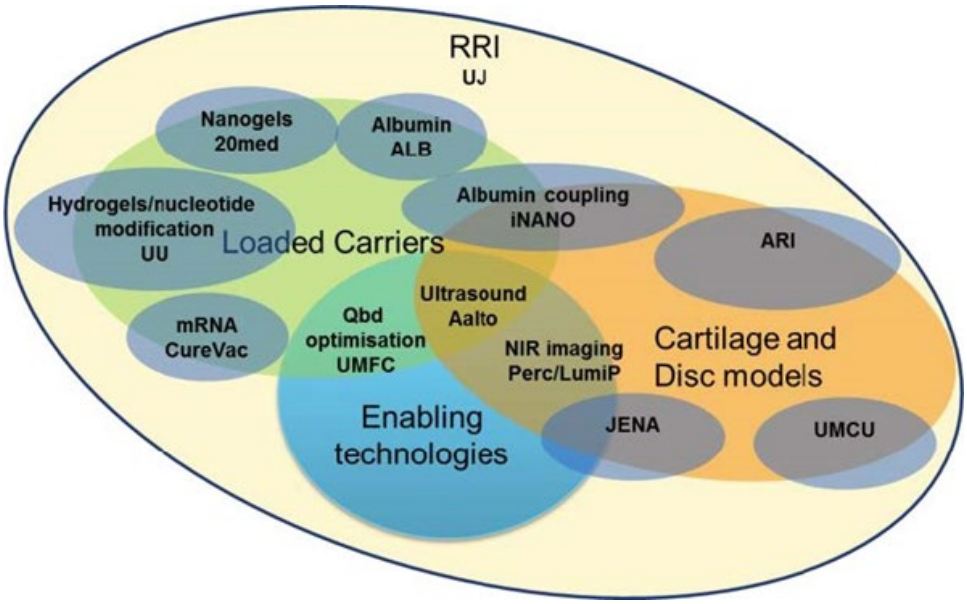


Figure 10.10.13: Multidisciplinary approach to advance nucleic acid therapy for cartilage and intervertebral disc regeneration; while educating 15 young researchers.

Funding: EU H2020-MSCA-ITN-2020; ARI Funding EUR 562'553; Period: 2020-2024.

Partners:

- Creemers L (Prof), University Medical Center Utrecht, Netherlands
- Oommen V (Prof), University of Uppsala, Sweden
- Tomuta I (Prof), Medical and Pharmaceutical University Cluj-Napoca, Romania
- Howard K (Prof), Aarhus University, Denmark
- Nieminen H (Prof), Aalto University, Finland
- Pego A (Dr), INEB, Porto, Portugal
- Waligora M (Dr), University Krakow, Poland
- Chan A (Dr), Percuros BV, Leiden, Netherlands
- Cameron J (Dr), Albumedix, Nottingham, United Kingdom
- Engbersen J (Prof), 20Med Therapeutics BV, Hengelo, Netherlands
- Kralisch D (Dr), Jenacell, Jena, Germany

Rising competitiveness of early-stage researchers and research management in Latvia (RISEus2) (ongoing) M D'Este, M Alini

Background: The aim of the RISEus2 project is to increase the research profile of early-stage researchers and strengthen the research management capacity of leading staff at RTU Rudolfs Cimdins Riga Biomaterials Innovation and Development Centre in the area of biomaterials development for bone tissue replacement and regeneration. The project is a close cooperation between the ARI, Institut National Polytechnique de Toulouse CIRIMAT (INPT-CIRIMAT) and FORM-Lab Frankfurt Orofacial Regenerative Medicine, Goethe University Frankfurt (GUF).
Early-stage researchers' mobility visits are foreseen to expand and strengthen their knowledge and professional experience and therefore gain positive impact on the international networking skills, overall research, and innovation potential of the RTU RBIDC and society of Latvia. These visits are focused on the development of skills and knowledge on new scientific models, facilities, optimization of methods, new directions, multidisciplinary approaches *etc*. The ARI hosted Ms. Eliza Tracuma, first year PhD Student at RTU, for a visit focusing on the design of soft hydrogels and their composites with mineralized components for musculoskeletal regeneration, which was implemented from 21.11.2021 to 17.12.2021.

Figure 10.10.14: Left: Jacek Wychowaniec, Rotsiniaina Randriantsilefisoa, Eliza Tracuma and Matteo D'Este in the Biomedical Materials laboratory. Right: Jacek Wychowaniec and Eliza Tracuma while measuring rheological properties of hyaluronan- ε-polylysine composites.

Results: The obtained results demonstrated the potential of Hap/HA/ε-PL composites to be used as bone regeneration materials as well as to act as ε-PL delivery systems, thus combining the promising features for more effective bone infection treatment. This investigation will be continued with the development of various CaP/HA/ε-PL compositions with different solid to liquid phase ratios, in order to discover the composition which could satisfy all the requirements for an ideal bioink.
One further activity to increase earlystage researcher capacity is the organization of schools and workshops. ARI participated to the RISEus2 1st Winter School "Calcium Phosphates and Composites" held in Riga from September 27th-29th, 2021 with Dr Andrea Vernengo and Nadine Kluser giving a practical training on hydrogels as tissue adhesives.

Funding: RISEus2 supported by European Union's Horizon 2020 research and innovation programme (GA No 952347), has a duration of 3 years and a total budget of EUR 900'000; ARI's budget is CHF 143'000.

Partners:
- Loca D (Prof), Riga Technical University Rudolfs Cimdins Riga Biomaterials Innovation and Development Centre, Riga, Latvia
- Locs J (Prof), Riga Technical University Rudolfs Cimdins Riga Biomaterials Innovation and Development Centre, Riga, Latvia
- Ghanaati S (Prof), Johann Wolfgang Goethe University, Frankfurt, Germany
- Combes C (Prof), INTP-CIRIMAT, Toulouse, France

Baltic Biomaterials Centre of Excellence (BBCE) (ongoing) (M D'Este, N Goudsouzian, M Alini)

Background: According to recent studies, Latvia is the 4th from the bottom in Research excellence performance compared to the other EU countries. Scores of the Research excellence indicators show that currently Latvia is significantly below the EU27 average performance in Science and Technology (S&T) Excellence. The total R&D expenditure in percentage of Gross Domestic Product (GDP) in Latvia, both public and private combined, has been one of the lowest in Europe rating almost 4 times lower than the EU average. In addition, given geopolitical instability, residual funds of public financing will be devoted mostly for defense issues, whereas R&D funding will not be increased significantly.
Goal: The Baltic Biomaterials Centre of Excellence (BBCE) overall objective is to develop a joint BBCE for advanced biomaterials development based on the long-term strategic cooperation between Riga Technical University, Latvian Institute of Organic Synthesis, Rīga Stradiņš University and Rīga Stradiņš University Institute of Stomatology on the one hand, and the ARI plus Friedrich-Alexander University of Erlangen-Nuremberg, Germany, on the other.
Results: Like in 2020, a rich series of online trainings was organized for topics including quality management systems, standard operating procedures, quality manual, biomaterials for skeletal repair, bioreactors and mechanoregulation. A series of lectures was delivered also by colleagues from the AO Development Incubator, covering lean business canvas model, intellectual property protection, and drafting of development projects highlighting the differences from pure research.
Besides trainings implemented in a virtual format, in 2021 we could finally hold visits face to face. In August, the ARI team was glad to welcome the Latvian delegation for "Bio-go-Higher", a nation-wide scientific contest where high school students get engaged in scientific activities and need to interpret scientific experiments. The winning team was rewarded with a visit to ARI. Five high school students along with 2 chaperones could get a glimpse of the ongoing research activities and participate in hands-on exercises, including the fracture course by Dr Sprecher and Dr Breulmann illustrated in the picture below.
Two other separate delegations spent eight and ten days in Davos, respectively. Visitors included Project Coordinator Prof Janis Locs from the Riga Technical University (RTU), together with work package leaders Prof Dagnija Loca (RTU) and Prof Arita Dubņika (RTU). Also visiting ARI were scientific group leaders Prof Kristaps Kļaviņš (RTU), Dr Antons Sizovs from the Latvian Institute of Organic Synthesis (LIOS), Prof Agnese Brangule from the Riga Stradins University (RSU), and Prof Laura Neimane from the Riga Stradins University Institute of Stomatology (RSU IS). Besides these short-term visits, a total of 5 PhD students and postdocs spent between 1 and 4 months at ARI premises, working side by side with ARI researchers on specific research projects in infection prevention, immunomodulatory biomaterials, and viscoelastic properties of injectable biomaterials.

Figure 10.10.15: The 5 Latvian students, winners of the Bio-go-Higher contest while taking the hands-on fracture course delivered by Dr Sprecher and Dr Breulmann.

The BBCE's primary objective is to build research capacity in the Baltic area. Apart from a wide variety of technical topics including soft biomaterials research, drug delivery, and 3D biomaterials printing, the project covers more general subjects such as lab management, leadership gender equality and research ethics.

Funding: EU H2020 grant agreement No 857287; ARI Funding CHF 1.4 M; period: 2020 – 2026.

Partners:

- Riga Technical University Rudolfs Cimdins Riga Biomaterials innovations and development centre, Riga, Latvia
- Latvian Institute of Organic Synthesis, Riga, Latvia
- Riga Stradins University, Riga, Latvia
- Riga Stradins University Institute of Stomatology, Riga, Latvia
- The Institute of Biomaterials at the Department of Materials Science and Engineering of the University of Erlangen-Nuremberg, Germany

3D printed-matrix assisted chemically modified RNAs bone regenerative therapy for trauma and osteoporotic patients (cmRNAbone) (ongoing) (D van der Heide, M D'Este, M Stoddart)

Background: Mostly bone injuries heal successfully, however, there is an increasing number of cases where bone defects result in delayed healing or non-union. Current treatments such as autografting and bone graft substitutes containing growth factors have limitations, due to donor site morbidity and dose-related safety concerns, respectively. Additionally, current clinically available therapies lack control over spatial architecture to anatomically match defect sites. The cmRNAbone project aims to create a novel bone regenerative therapeutic approach,

where biofabrication offers a great potential in producing patient-specific scaffolds that exihibit control over shape, architecture, and composition.
Goal: In this project a 3D-printable bone mimetic composite biomaterial-ink for bone regeneration is developed. This ink combines osteoinductive calcium phosphate particles (CaP) with tyramine modified hyaluronic acid (HA-Tyr) for the delivery of chemically modified RNAs (cmRNAs), to induce nerve, vessel, and bone formation (Figure 10.10.16). To achieve this aim, Semaphorin 3A (SEMA3a), Vascular endothelial growth factor (VEGF), Platelet-derived growth factor (PDGF-BB) and Bone Morphogenetic Protein-7 (BMP-7) cmRNAs targeting neurogenesis, vasculogenesis and osteogenesis will be synthesized, and delivered using vectors based on lipids and polysaccharide nanocapsules. A 3D printed HA-Tyr-CaP biomaterial-ink, that is customized to patient specific defect sites, will be loaded with the cmRNAs-vectors to release them and induce intrinsic osteoinductivity and guide sensory neurons and endothelial cells ingrowth for bone regeneration.

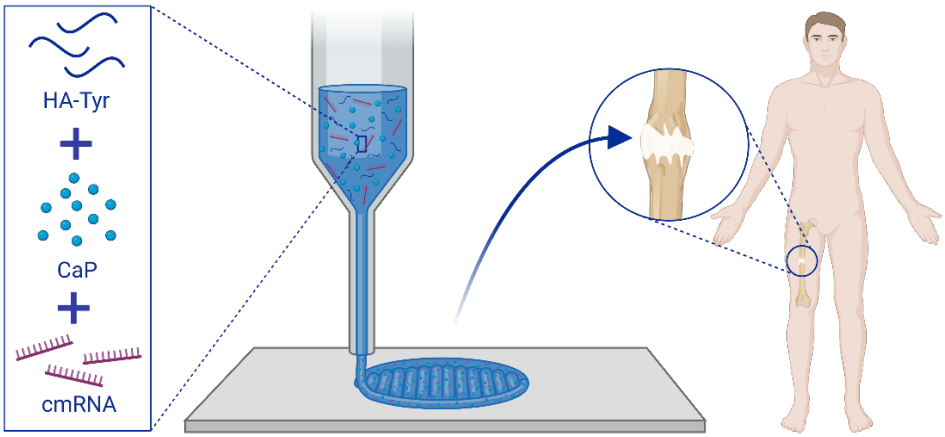


Figure 10.10.16: Graphical abstract cmRNAbone project. Composite biomaterial-ink consisting of tyramine modified hyaluronic acid (HA-Tyr), calcium phosphate particles (CaP), and chemically modified RNA (cmRNA) for bone regneration.

Funding: H2020-SC1-BHC-2018-2020. Total Budget EUR 6.26 million, ARI Budget EUR 710'000, Period 2020-2023 97.

Partners:
- Stoddart M (Prof), AO Research Institute Davos, Switzerland (Coordinator)
- Banfi A (Prof, PhD), University of Basel, Switzerland
- Plank C (Prof, PhD), ETHRIS GmbH, Germany
- Schepp N, EURICE - European Research and Project Office GmbH, Germany
- Damien D (PhD), CIDETEC, Spain
- De Groot F (PhD), Kuros Biosciences BV, Netherlands
- Zelphati O, OZ Biosciences SAS, France
- Fernández A (PhD), Idonial Technological Center, Spain
- Van Griensven M (Prof, PhD), Maastricht University, Netherlands
- Amédée J (Prof, PhD), University of Bordeaux, France

Instructing immune system to regenerate musculoskeletal tissues via structurally programmable bio-inks (ImmunoBioInks) (ongoing) (J Wychowaniec, M D'Este)

Background: The musculoskeletal tissue is the framework of our lives. It holds shapes and supports freedom of movement of our body and protects the crucial internal organs (brain, heart and lungs). It is responsible for our body's immunity by providing source of stem cells (bone marrow) that readily transform to immune system cells fighting pathogens, so any damage it poses significant threat to the individual's quality of life. The patient's immune system does not only play crucial role in fighting various pathogens but is also vital in inducing

normal healing of damaged tissues. Patients, especially with prolonged diseases, ranging from diabetes to HIV tend to have decreasing capacity for healing after injuries due to their compromised immune system.

Goal: The scope of the EU-funded ImmunoBioInks project is to develop 3D-printed materials to treat musculoskeletal defects in patients with an immune system imbalance. The idea is to combine self-assembling peptides, hyaluronic acid and nanomaterials into printable scaffolds of defined architecture and with carefully designed mechanical properties that can reprogram the patient's own immune cells. The interaction of immune cells with this innovative 3D scaffold is expected to trigger the necessary healing response.

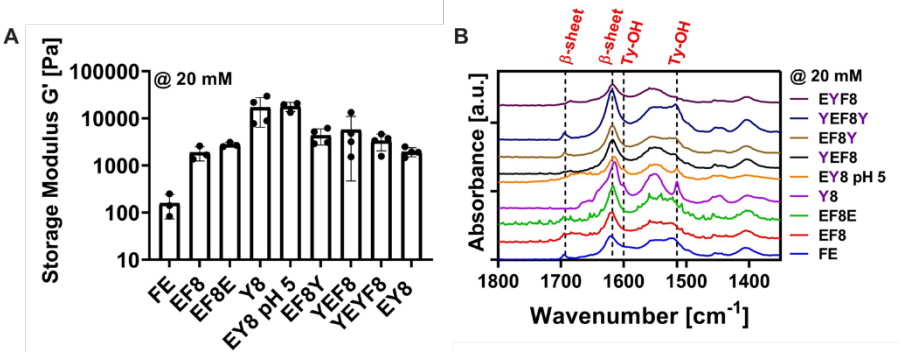


Figure 10.10.17: ***(A)*** *Storage modulus (reflecting stiffness) of a family of a new family of peptide-based hydrogels.* ***(B)*** *Fourier transform infrared spectroscopy results showing all peptides adopt β-sheet conformations. Distinct signals were also observed for peptides incorporating Tyrosine.*

Results: A selection of peptide sequences based on the alternation of hydrophobic and hydrophilic amino acids: **ABACABAC** (**A**: hydrophobic residue: **F** phenylalanine or **Y** tyrosine, **B**/**C**: hydrophilic residue *e.g.*: **K** lysine or **E** glutamic acid) were designed. A parametric study was then carried out to verify the effect of rational peptide sequence modification on final physicochemical properties of composite hydrogels. All parental peptides self-assemble into semi-flexible networks and hydrogels above critical gelation concentration in the region of 2.5-5 mM and contain high β-sheet content (Figure 10.10.17). Tyramine-modified Hyualuronic acid was also synthesized at two different molecular weights (280 kDa and 1640 kDa) and used to form composite hydrogels with self-assembling peptides. Self-assembly, and rheological properties of both peptide and peptide-THA hydrogels can be controlled by the choice of primary peptide sequence, fabrication technique and final crosslinking mechanisms including enzymatic (HRP, H_2O_2) and visible green light crosslinking using Eosin. These hydrogels are characterised by shear-thinning behaviour and rapid recovery allowing extrusion-based fabrication of scaffolds for immunomodulatory tissue engineering.

Pres:

Invited speaker at the RSC Biomaterials Chemistry Group 16th Annual Meeting. Responsive hydrogels: towards spatiotemporally controllable biomaterials. London, UK, 10-12.01.2022.

Fund: H2020- MSCA-IF 893099; 01/07/2021–30/6/2023; Budget: EUR 191'149,44: https://cordis.europa.eu/project/id/893099.

Partner:

- Eglin D (Prof), Mines Saint-Étienne, Univ Lyon, Univ Jean Monnet, INSERM, U1059 Sainbiose, Saint-Étienne, France

Engineered full-organ 3D intervertebral disc as standardized model for studying disc degeneration and disease (INDEED) (ongoing) (M D'Este)

Background: Degeneration of the intervertebral disc (IVD) is still insufficiently understood and treated, despite its high prevalence, debilitating effect on patient quality of life, and significant financial burden on the healthcare system. Addressing this requires better models of the IVD, recapitulating its intrinsic properties such as the heterogeneous composition and mechanical function under challenging loading conditions. Conventional *in vitro* models, such as 2D and 3D cell cultures, are oversimplifications, failing to reproduce its composition and organization, and unable to capture its mechanical properties. The use of explanted human IVDs is rarely an option, owing to their scarcity, comorbidities, and significant donor variability. Animal discs are traditionally employed as more accessible alternatives; however, they too display wide variability and important biological, compositional, and biochemical interspecies differences, limiting their usefulness. Bioprinting, with its precise control over the cell microenvironment, offers a promising avenue for the fabrication of models with better reproducibility and likeness, which could further our understanding of disc degeneration and its treatments.
Goal: The overall aim of the project is the use of biofabrication to create a tissue-engineered, reproducible, and adaptable three-dimensional (3D) IVD model, outperforming state of the art options for the study of IVD disorders. The know-how generated will furthermore be a step towards the biofabrication of IVD tissue replacements.
Results: We prepared and investigated biomaterial ink composites from a tyramine-derivative of hyaluronan (THA) and unmodified type I collagen. The composites undergo gelation via collagen self-assembly, enzymatic oxidation, or visible-light triggered crosslinking, with preservation of collagen fibrillogenesis. In oscillatory and rotational shear characterizations, the biomaterial inks demonstrated shear-thinning and good recovery of elasticity. We demonstrated a composition with 3% THA and 2% collagen, and a combination of gelation methods which result in shear and compressive mechanics in the range of values previously reported for the nucleus pulposus of healthy human IVD (Figure 10.10.18). The printability of our composites was further verified with preliminary fabrication of simple lattice-based structures (Figure 10.10.19). To characterize the material interactions with living cells, we embedded bovine nucleus pulposus cells in cast composites and demonstrated good cell viability and proliferation up to at least day 5 (Figure 10.10.20). Work is now continuing with the next phase of experiments, including an assessment of long-term cell-material interactions and printing of cell-laden constructs.

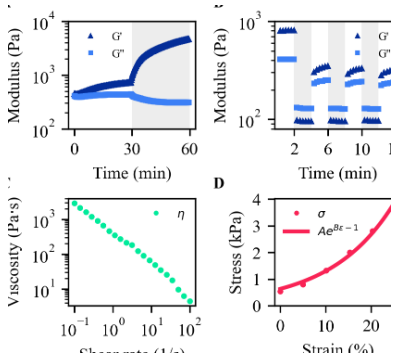


Figure 10.10.18: Shear and compressive properties of the biomaterial ink after enzymatic (B, C) and light (D) gelation. A) Oscillatory time sweep in shear, showing material gelation with light exposure period shaded. B) Cyclic intervals of 0.1% and 300% (shaded) oscillatory shear strains. C) Rotational shear rate sweep. D) Equilibrium compressive stress under progressively increasing strains, fit to an exponential model.

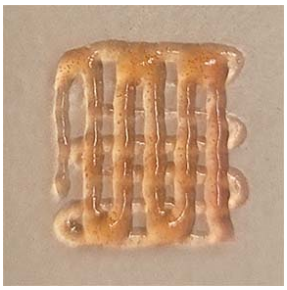


Figure 10.10.19: A 2-layer lattice printed through a 25G (I.D. = 0.26 mm) needle. Light crosslinking was performed after deposition of each layer, to strengthen the structure.

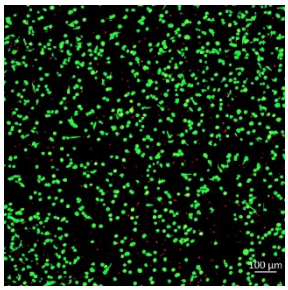


Figure 10.10.20: Bovine nucleus pulposus cells embedded in cast composites at 5 million cells/ml, demonstrating good viability at day 5 of culture. Live cells stained with calcein AM (green), dead with ethidium homodimer-1 (red).

Funding: SNF 310030E_189310; ARI funding CHF 377'000; Period: 2020 – 2024.

Pres:
Miklosic G, Hélary C, Ferguson SJ, D'Este M. Dense extracellular matrix derivatives for the bioprinting of nucleus pulposus-like structures. 31st Conference of the European Society for Biomaterials. Virtual, 2021 (poster).
Miklosic G, Hélary C, Ferguson SJ, D'Este M. Extracellular matrix-based bioink for the printing of nucleus pulposus analogues. International Conference on Biofabrication. Virtual, 2021 (poster).
Miklosic G, Hélary C, Ferguson SJ, D'Este M. Extracellular matrix-based biomaterial ink for the printing of nucleus pulposus-like structures. 4th SSB+RM Young Scientists Symposium. Zürich, 2021 (poster).
Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Extracellular matrix-based biomaterial ink for the printing of nucleus pulposus-like structures. eCM XX: Biofabrication for Orthopaedics. Davos, 2021 (oral).

Real time quality monitoring of engineered tissue for regenerative medicine (RT-Monet) (finished) (V Basoli)

Background and aims: Despite the growing demand and interest in biofabrication in the field of tissue engineering and regenerative medicine for the generation of customized tissues/biological constructs, currently there are no efficient methods for monitoring construct function and behaviour over time. This gap in the field is a big disadvantage that is strongly influencing further applications. For that reason, in this project we aim to create an innovative method based on insertable micro-biosensors that can screen in real time and non-invasively cellular behaviour including the encapsulation into the scaffold, during (bio)fabrication process, *in vitro* maturation till the *in vivo* application. We will develop a device with miniaturized sensors that can measure parameters and send the information to a remote controller. The monitoring will aim at quality control (viability, differentiation capacity during the manufacturing process), to increase the success rate for therapeutic transplantation in animals or patients. Nowadays the most common analysis techniques include the sampling of medium and measurement of analytes by spectrophotometric assays, HPLC or gene expression analysis, which requires the user constantly controlling the measurement. Other methods measure viability using confocal imaging but the use of chemicals like fluorescence labels and the high energy produced by the laser can damage the samples. Recently, sensors for the measurement of biochemical parameters in culture media have been proposed. However, due to their large size (diameter of 1-7mm) it is impossible to perform any measurement inside the construct. Miniaturized biosensors have been used in a simple and reproducible way, with a limited cost and in a non-destructive way for animals/vegetal tissues and organic/inorganic materials. With this ambition, we aim to create an innovative and non-invasive way to study the behavior of cells with ad hoc insertable specific miniaturized micro-biosensors that allow *in situ* and real-time quality control of tissue engineering constructs. The monitoring is done on a cellular environment level on a large scale on multiple samples (inside tissue culture plates) over culture time by an easy, cost-effective, analytic, and reproducible method using specific markers based on the desired type of observation.

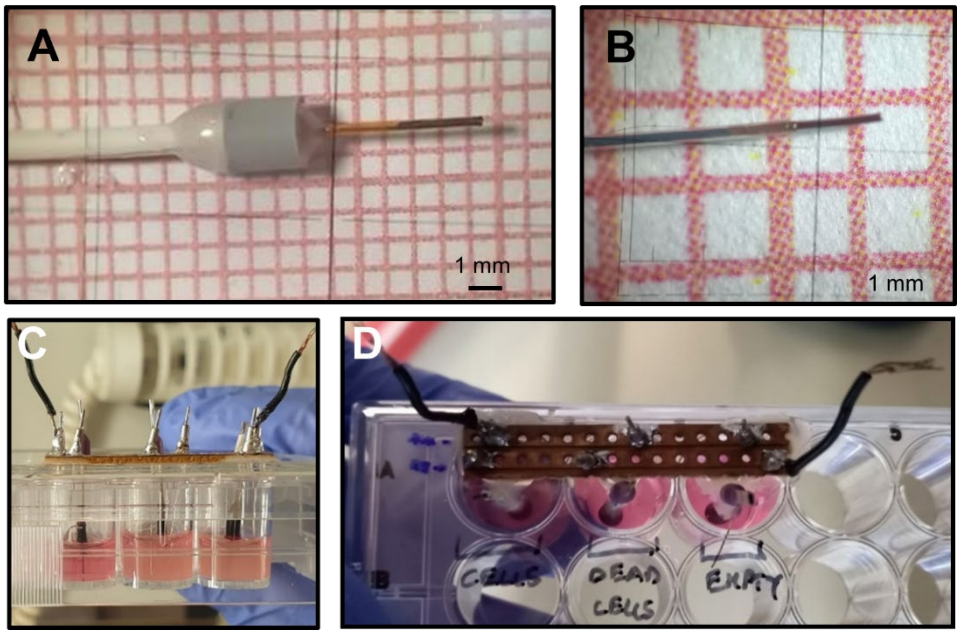


Figure 10.10.21: Prototype µSensor Unit based on plate modification to allow the insertion of the sensors Oxygen (A) and Glucose (B). Top view of µSensor Unit during measurement in Hydrogel with cells (C) Details of the electrical bridge design (D)

Funding: SNF- Spark; ARI Funding CHF 100'000; Period: 2020-2021.

Pres:
Siverino C, Zuncheddu D, Rocchitta G, Generelli S, Kurth F, Serra PA, Moriarty F, Grad S, Basoli V. Impact of UV, ethylene oxide and x-ray sterilization on glucose implantable biosensors stability: a step further to sterile biomedical application. World Biosensor 2021.
Zuncheddu D, Schwab A, Della Bella E, Generelli S, Kurth F, Serra Pier A, Rocchitta G, Kasper H, Grad S, Basoli V. Development and characterization of a microsensor device for real time oxygen monitoring in 3D tissue engineered constructs. TERMIS World 2021.

Pub:
Zuncheddu D, Della Bella E, Schwab A, Petta D, Rocchitta G, Generelli S, Kurth F, Parrilli A, Verrier S, Rau J, Fosca M, Maioli M, Serra PA, Alini M, Redl H, Grad S, Basoli V. Quality control methods in musculoskeletal tissue engineering: from imaging to biosensors. Bone Res 9, 46 (2021). https://doi.org/10.1038/s41413-021-00167-9.
Fosca M, Basoli V, Della Bella E, Russo F, Vadalà G, Alini M, Rau JV, Verrier S. Raman spectroscopy in musculoskeletal disorders and tissue engineering, status and prospective. Tissue Eng Part B Rev. 2021 Sep 28. DOI: 10.1089/ten.TEB.2021.0139. Epub ahead of print. PMID: 34579558.

Partner:
- Generelli S (Dr), CSEM, Centre suisse d'électronique et de microtechnique, Neuchâtel, Switzerland

In-JOINT APPlication of non-viral mRNA therapy for OsteoArthritis (Joint-Approach) (ongoing) (S Grad, V Basoli, M Alini)

Background and aim: OA is the most common chronic joint condition, affecting >40 million Europeans. With increasing life expectancy and rising levels of obesity, OA is predicted to become the 4th leading cause of disability worldwide. In 2017, the first OA gene therapy was approved and several more are in clinical development. All, however, use unsatisfactory (viral)

delivery approaches, which result in suboptimal transfection and potential risks in joint tissues. JOINT-APPROACH will provide a non-viral and targeted alternative.
Intra-articular (in-joint) gene therapy-like mRNA therapy offers a promising highly innovative solution for the treatment of osteoarthritis (OA). In gene therapy, genes encoding therapeutic products are introduced into target cells. Upon transfection, the therapeutic product is synthesized endogenously over extended periods of time to have a therapeutic effect. The aim of the project is the development of a novel safe (non-viral) and effective gene therapy-like mRNA therapy for osteoarthritis (OA). Using unique in-joint injectable polymer-based nanoparticle carriers, intracellular delivery of mRNA into joint-related tissues can be ensured. This therapy will suppress inflammation by delivery of IL-1Ra or IL-10 mRNA, and support cartilage and tendon tissue regeneration by delivery of PRG4 or PDGF mRNA. The project will perform the preclinical development to generate proof-of-concept, required for subsequent regulatory pre- and clinical validation.

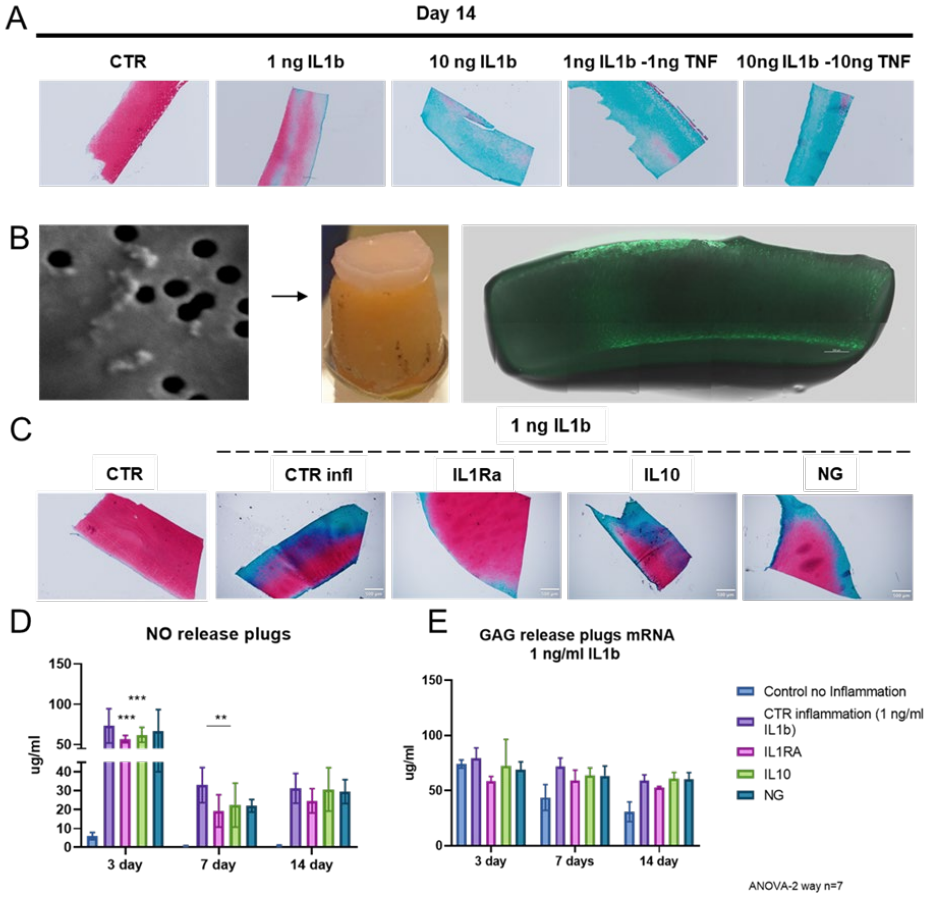


Figure 10.10.22: Osteochondral plug OA model (A), SEM picture of NG and transfection of cartilage with GFP-mRNA (B) Effect of IL1RA and IL10 on inflamed plugs over 14 days (C) Nitric oxide release (D) and GAG release into medium (E)

Funding: Eurostars; ARI Funding EUR 200'000; Period 2019-2022.

Pres:

Basoli V, Li Z, Andreas T, Sanchez J, Plank C, Rip J, Alini M, Grad S. Effect of nanoparticle-based mRNA delivery on modulation of inflammation in an osteochondral inflammation model. OARSI 2021 (online).
Sturm L, Schwemberger B, Geiger J, Aneja M, Hujaya SD, Engbersen J, Rip J, Alini M, Traweger A, Grad S, Basoli V. Comparison of different transfection methods for mRNA delivery in articular joint cells. TERMIS Maastricht 2021.

Pub:
Sturm L, Schwemberger B, Geiger J, Aneja M, Hujaya SD, Engbersen J, Alini M, Traweger A, Grad S, Basoli V. Comparison of different transfection methods for mRNA delivery in articular joint cells. Biomedicines 2021, *9*(7), 794; https://doi.org/10.3390/biomedicines9070794.

Partners:
- Engbersen J (Prof), 20Med Therapeutics, Netherlands
- Planck C (Prof), Ethris Gmbh, Germany
- Traweger A (Prof), Paracelsus Medical University, Austria

Nitric oxide optical sensors for inflammation monitoring (NIOXIS) (started) (V Basoli, S Grad)

Background: Joint injuries, such as cartilage defects or ligament ruptures, can lead to the development of chronic pathologies such as osteoarthritis (OA). The pathology that causes enormous motor disabilities can lead to the development of subsequent secondary pathologies that exacerbate the injury. The extent of the resulting damage can be minimized through effective injury monitoring and treatment at the early stages. Unfortunately, chronic inflammatory diseases of the skeletal system usually are not diagnosed in the early stages, and the diagnosis often comes only when the damage becomes irreversible.
During inflammation, the damaged tissues produce large quantities of nitric oxide (NO), which is also produced in patients with OA. Therefore, using NO as a biomarker for developing OA, it may be possible to detect the progression of the inflammation through continuous NO monitoring. Real-time NO monitoring offers a promising means of mitigating inflammation and disease progression through early diagnosis and treatment.
Aim: The proposed monitoring method is based on optical sensors that can be implanted under the skin at the joint. The miniaturization and the absence of wires in the sensor would allow a non-invasive means of monitoring NO at the joint. The optical NO sensor may be read by a portable reader, so inflammation measurement could be used to administer any preventative action or treatment when necessary.

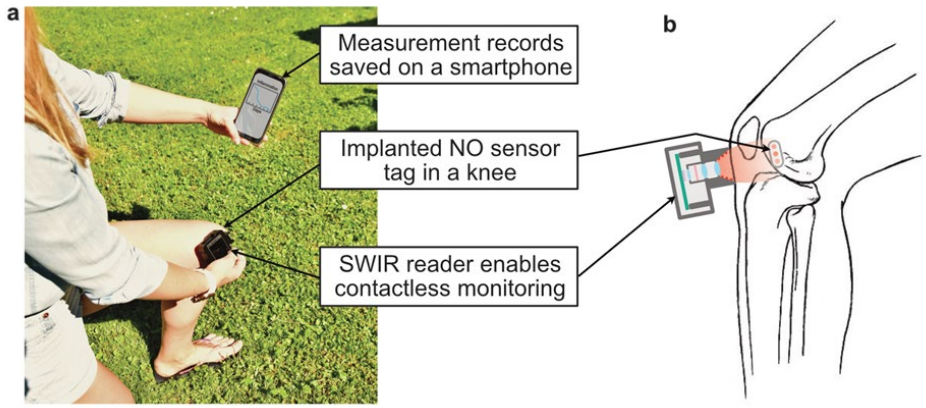


Figure 10.10.23: Concept of optical sensor for real time NO detection.

Funding: Innosuisse; ARI Funding CHF 164'966; Period: 2021-2023.

Partners:
- Zubkovs V (Dr), CSEM, Centre suisse d'électronique et de microtechnique, Neuchâtel, Switzerland
- Boghossian A (Prof), EPFL, École Polytechnique Fédérale de Lausanne, Switzerland

Antibiofilm therapy using local application of bacteriophages (AntiBioLab) (ongoing), (F Moriarty, M Chitto, V Post, M D'Este)

Background: Antimicrobial chemotherapy of difficult to treat, antibiotic resistant orthopaedic device-associated infections are highly likely to fail, and new alternatives are required. One promising approach is bacteriophage therapy, however, the ideal therapy regime is not yet established.
Goal: The goals of the project are to test efficacy of *in vitro*-evolved *P. aeruginosa* phages when loaded in an injectable degradable hydrogel in combination with antibiotics (Figure 10.10.24 A) to treat multi-drug resistant infection.
Results: Our results to date have included the production of two evolved *P. aeruginosa* phages, which display increased anti-biofilm activity. The phages were loaded within a hydrogel (phageA) or in alginate beads (phageB) in order to better control temporal release of the phage (Figure 10.10.24).

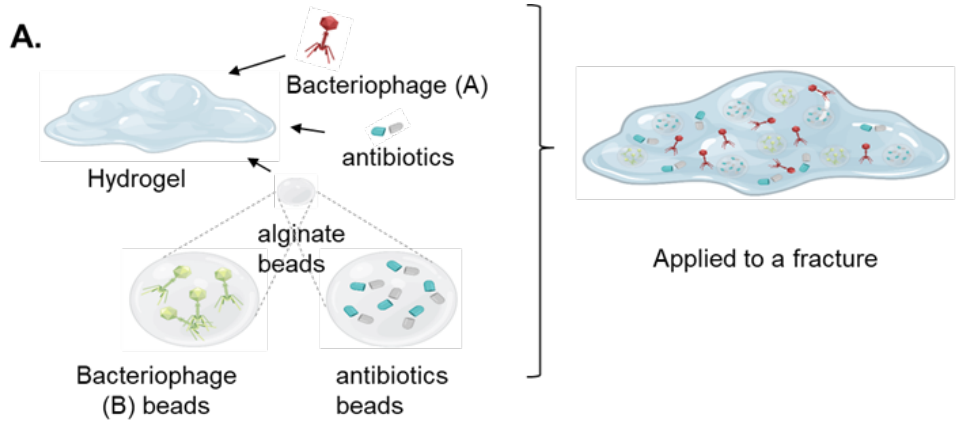


Figure 10.10.24: Schematic diagram of 2 P. aeruginosa phages loaded within an injectable hydrogel and alginate microbeads.

Pub:
Onsea J, Post V, Buchholz T, Schwegler H, Zeiter S, Wagemans J, Pirnay JP, Merabishili M, D`Este M, Rotman SG, Trampuz A, Verhofstad MHJ, Obremskey WT, Lavigne R, Richards RG, Moriarty TF, Metsemakers WJ. Bacteriophage therapy for the prevention and treatment of fracture-related infection caused by *Staphylococcus aureus*: a preclinical study, Microbiol Spect. Dec22;9(3)e0173621 (2021).

Comparison of high-virulent *versus* low-virulent *Staphylococcus aureus* in a murine bone infection model (HiLo) (ongoing) (S Baertl, S Zeiter, F Moriarty)

Background: *Staphylococcus aureus* is the leading pathogen in fracture-related infection (FRI). Virulence factors vary significantly between different strains, which may have a decisive influence on the course of infection, although this is poorly understood.
Goal: This study aimed to compare a supposed high- and low-virulent *S. aureus* isolate (based on course of infection in original human hosts) in a murine FRI model.
Results: Quantitative bacteriological results 4 days after surgery revealed a higher bacterial load in soft tissue samples in mice inoculated with the high virulence strain, as well as higher rates of organ dissemination (Figure 10.10.25). By day 14, a more pronounced proinflammatory response, indicated by increased serum cytokine levels of IFN-γ, IL-1β, and IL-6, was observed in mice infected with the supposed high virulence strain.

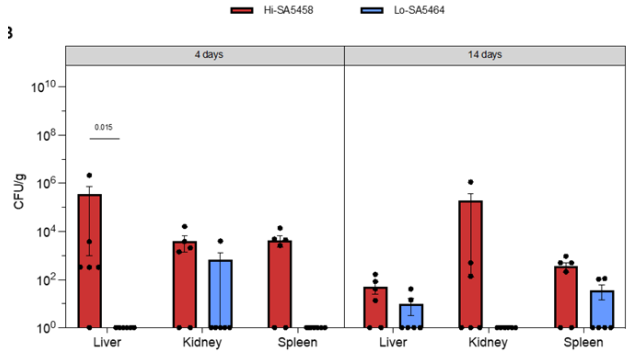


Figure 10.10.25: Quantitative bacteriology of Hi-SA5458 and Lo-SA5464 infected animals organ samples (liver, kidney, and spleen) at euthanasia on day 4 and day 14 after surgery. Results are presented as means ± SEM (n = 6 per group) and were compared by Mann-Whitney-U-test.

The present study demonstrated distinct bacteriological and histopathological differences between two different virulent *S. aureus* strains previously shown to have different courses in human patients. While host physiology is often considered to have a major impact on the course of FRI, this study highlights the critical influence of the invading pathogen and its virulence characteristics.

Pres:
Comparison of a high-virulent *versus* a low virulent *Staphylococcus aureus* strain in a murine fracture-related infection model. European Bone and Joint Infection Society, 2021 Annual meeting, Slovenia, October 7-9, 2021. Winner, best basic science presentation.

Partner:
- Alt V (MD), University Hospital Regensburg, Germany

The role of *Staphylococcus aureus* leukotoxin panton-valentine leukocidin in humanized or BALB/c mice (SN-Mouse) (ongoing) (M Hofstee, S Zeiter, F Moriarty)

Background: *Staphylococcus aureus* has many known virulence mechanisms including the secretion of leukotoxins such as Panton-Valentine leukocidin (PVL). PVL is a pore-forming toxin that targets the C5aR1 and C5aR2 receptor of human neutrophils, monocytes, and macrophages, which are not present, or only weakly targeted, in mouse models.
Goal: develop a humanized mouse model of implant related bone infection and compare virulence in the presence and absence of PVL.
Results: In the absence of PVL, humanized mice had a less severe infection as revealed by lower bacterial counts in the operated limb, less culture positive organs and fewer dead myeloid cells (Figure 10.10.26) suggesting that PVL does play a pivotal role in the pathogenesis of an implant-associated osteomyelitis in humanized mice.

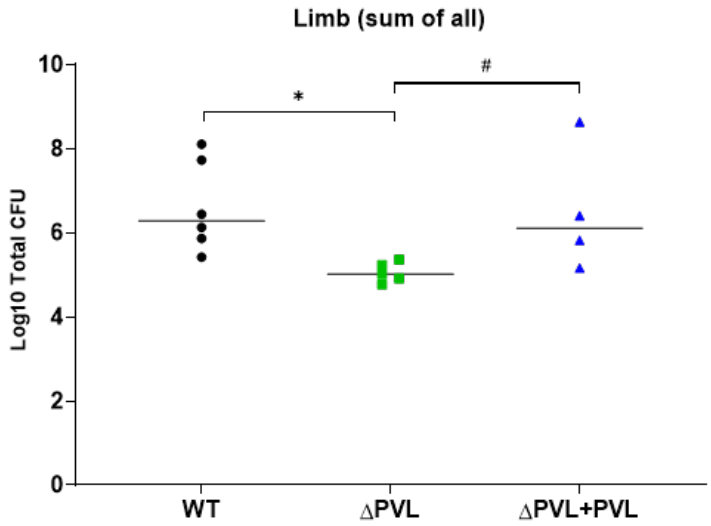


Figure 10.10.26: Bacterial culture of the operated limb of humanized mice after infection with wild-type S. aureus (WT), or a PVL knockout mutant (ΔPVL) or the complemented strain.

Partners:

- Muthukrishnan G, University of Rochester Medical Center, Rochester, USA
- Zaat SAJ, Amsterdam UMC location AMC, Amsterdam, Netherlands

11 Team Members

Director		
Richards R Geoff	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
Gueorguiev Boyko	Prof, PhD, MSc (01.03.03 – 30.09.09)	01.07.10
Keller Rolf	Technischer Kaufmann	17.06.96
Stoddart Martin	Prof, Prof, PhD (01.08.95– 30.09.96)	01.07.05
Wahl Sonia	Dipl DH Ökonomin HFP	01.12.95
Zeiter Stephan	Dr med vet, PhD (01.02.00 – 12.05.02)	01.06.03
ARI Management Plus (Focus Area Leaders)		
D'Este Matteo	PhD	01.04.11
Gehweiler Dominic	Dr med	01.03.16
Goudsouzian Nora	BSc	01.02.02
Grad Sibylle	PD, Dr sc nat, PhD	03.08.00
Lanker Urban	Animal Care (Eidg FA[1])	16.06.86
Moriarty Fintan	PhD, BSc	19.03.07
Serra Tiziano	PhD	01.10.16
Varga Peter	PhD	04.08.14
Windolf Markus	PhD (Dr biol hum) Dipl Ing	01.11.04
Scientific & Technical Staff		
Arens Daniel	Dr med vet	01.11.07
Badrutt Isabella	Sn. Executive Assistant	16.07.12
Bagnol Romain	PhD Student, MSc	01.10.19
Barblan Claudia	Sn. Administrative Assistant (70%)	15.11.10
Barcik Jan	PhD	01.04.17
Basoli Valentina	PhD	01.04.17
Bektas Tas Ezgi Irem	PhD	01.08.21
Bluvol Mauro	Chemielaborant (Eidg FA[1])	01.06.03
Brazerol Carmen	Animal Care (Eidg FA[1])	01.03.18
Buchholz Tim	Dr med vet	01.04.19
Buschbaum Jan	Dr rer med	01.08.15
Caspar Jan	Poly mechanics	01.01.09
Chittò Marco	Dr rer Nat, PhD	01.08.21
Ciric Daniel	MSc (Engineering)	01.07.20
Ciriello Simona	PhD, Journal Production Editor	12.09.16
Constant Caroline	Dr med vet, MENG	01.08.19
Della Bella Elena	PhD	01.01.18
Devantay Nicolas	MSc (Nanosciences)	02.12.19
Di Luise Nunzia	PhD	15.06.17
Di Marzio Nicola	PhD Student, MSc	01.01.20
Erb Peter	Animal Care (Eidg FA[1])	03.05.93
Ernst Manuela	MSc, Human Movement Science	01.10.11
Escher Carla	Sn. 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
Füllemann Priscilla	BSc (01.11.19 – 31.12.20)	01.01.21
Furlong-Jäggi Pamela	Chemikerin FH, BSc (40%)	01.02.04

Furter Andrea	Animal Care (Eidg FA[1])	24.04.06
Gens Lena	med vet	01.06.21
Guex Geraldine	PhD	01.03.20
Hatt Phelipe	PhD Student, MSc	01.01.20
Heumann Maximillian	PhD Student, MSc	01.06.21
Hildebrand Maria	MSc (Immunology)	01.01.18
Hofmann-Fliri Ladina	MSc ETH	01.10.09
Hofstee Marloes	PhD Student, MSc	20.11.17
Jahangir Shahrbanoo	PhD (18.04.18 – 28.09.18)	01.04.21
Kasper Hermann	Dipl Technician HF Systemtechnik	01.10.18
Keller-Stoddart Iris	MTL Technician (60%)	21.10.09
Ladner Yann	PhD Student, MSc	01.08.18
Li Zhen	Assistant Prof, PhD	01.08.11
Ma Junxuan	Dr med, PhD	02.03.17
Menzel Ursula	PhD, Dipl Biol	01.07.11
Miklosic Gregor	PhD Student, MSc	01.02.20
Mischler Dominic	Junior Project Leader (06.09.17 - 28.02.18)	01.10.18
Müller Gregor	Lic phil, Librarian (50%)	17.01.05
Müller Reto	Animal Care (Eidg FA[1])	13.11.01
Mys Karen	PhD	01.06.19
Nehrbass Dirk	Dr med vet, FTA Pathol + Toxicopathol	01.10.10
Perren Dominic	Animal Care	01.02.83
Peter Robert	Dipl Laborant HFP	15.09.84
Post Virginia	PhD (60%)	20.09.10
Randriantsilefisoa Roots	PhD	01.07.21
Ristaniemi Aapo	PhD	16.11.20
Schneider Monika	Administrative Assistant (60%)	06.02.06
Schwarzenberg Peter	PhD	01.09.21
Sercovic Amra	PhD	01.09.20
Siverino Claudia	PhD	01.11.19
Soubrier Astrid	PhD Student, MSc	05.08.19
Spiller Flurin	Polymechaniker EFZ (Eidg FA[1])	01.08.15
Sprecher Christoph	PhD, Dipl Ing FH	01.02.00
van der Heide Daphne	PhD Student, MSc	01.09.20
Vautrin Antoine	PhD	15.04.21
Vernengo Andrea	PhD	01.09.19
Verrier Sophie	Dr sces sc nat	01.08.04
Vivalda Marisa	Administrative Assistant	01.05.03
Wallimann Alexandra	PhD Student, MSc	01.02.18
Wen Liru	PhD Student	06.07.21
Wychowaniec Jacek	PhD	01.07.21
Zderic Ivan	MSc ETH	01.02.11
Zuncheddu Daniele	PhD Student	01.02.20
Zweifel Erich	European Industrial Engineer EIE	30.11.92

Apprentice

Ambühl David	Apprentice	01.08.20
Bärtschi Cecilia	Apprentice	01.08.18 – 31.07.21
Hämmerl Nilo	Apprentice	01.04.19
Vonlanthen Nadja	Apprentice	01.08.21

[1] Eidg FA = Eidg Fähigkeitsausweis

Medical Research Fellows

Arveladze Samson	Research Fellow (Israel)	18.01.21 – 23.12.21
Bärtl Susanne	Research Fellow (Germany)	01.10.20 – 31.03.21
Breulmann Franziska	Research Fellow (Germany)	01.07.21
Bumann Helen	Research Fellow (Switzerland)	01.07.21
Gens Lena	VET Research Fellow (Germany)	01.06.20 – 31.05.21
Hao Wei	Research Fellow (China)	01.10.20 – 31.03.21
Kastner Philipp	Research Fellow (Austria)	01.07.21
Pastor Torsten	Research Fellow (Germany)	01.11.20 – 31.10.21
Schwegler Hella	VET Research Fellow (Germany)	28.09.20 – 30.04.21
Souleiman Firas	Research Fellow (Germany)	01.04.21 – 31.10.21
	Guest Research Fellow	01.11.21 – 24.12.21
Tapia-Dean James	VET Research Fellow (GB, Spain)	15.02.21
Van Knegsel Kenneth	Research Fellow (Netherlands)	04.01.21 – 30.06.21
Visscher Luke	Research Fellow (Australia)	16.07.21 – 24.12.21
Vo Mai Thanh	VET Research Fellow (Germany)	28.09.20 – 30.04.21
Zhao Ensi	Research Fellow (China)	02.03.21

Non Medical Research Fellows

Kluser Nadine	MSc (Switzerland)	01.02.21

Internships

Alig Gion	Internship (Switzerland)	01.10.20 – 31.07.21
Antonacci Paolo	Internship (Italy)	16.11.20
Bashardoust Amirsiavosh	Internship (Iran)	19.08.20 – 18.02.21
Egger Sarah	Internship (Switzerland)	01.07.21 – 31.10.21
	Guest Internship	01.11.21
Eglauf Janick	Internship (Switzerland)	01.06.20 – 15.11.20
	Guest Internship (Switzerland)	16.11.20 – 31.05.21
Enzmann Sina	Guest Internship (Switzerland)	01.09.21 – 28.02.22
	Internship	01.03.22
Ettinger Lara	Internship (Switzerland)	12.04.21 – 30.06.21
Ferris Ciara	Internship (Italy)	01.09.21 – 30.11.21
Herzog Manuel	Guest Internship (Switzerland)	01.09.20 – 28.02.21
	Internship	01.03.21 – 31.05.21
Hintermann Joseph	Internship (Switzerland)	01.09.20 – 31.12.20
	Guest Internship	01.01.21 – 30.06.21
Hüsser Oliver	Internship (Switzerland)	01.03.21 – 31.08.21
Jörimann Thomas	Internship (Switzerland)	01.12.20 – 28.02.21
	Guest Internship	01.03.21 – 15.09.21
Keller Jessica	Internship (Switzerland)	01.09.21
Knecht Manuel	Internship (Switzerland)	01.09.20 – 09.04.21
Knill Anna	Internship (Switzerland)	20.09.21 – 19.12.21
Marani Elisa	Internship (Switzerland)	01.08.21
Mecchi Laura	Internship (Italy)	01.02.21 – 24.12.21
Meyer Alessia	Internship (Switzerland)	01.03.21 – 31.05.21
	Guest Internship	01.06.21 –20.12.21
Mini Carina	Guest Internship (Switzerland)	04.10.21
Nüesch Andrea	Internship (Switzerland)	01.06.21 – 01.12.21
Poncioni Simone	Internship (Switzerland)	01.04.21 – 18.12.21
Remppis Magdalena	Internship (Germany)	01.09.20 – 31.03.21
Rossoni Andrea	Internship (Italy)	01.02.21 – 30.11.21
Schärer Kathrin	Internship (Switzerland)	01.08.21
Staubli Flurina	Guest Internship (Switzerland)	01.06.20 – 30.11.20
	Internship	01.12.20 – 31.05.21

Steiger Linda	Internship (Switzerland)	01.09.21 – 30.11.21
Tenisch Lara	Internship (Switzerland)	01.02.21 – 30.04.21
	Guest Internship	01.05.21 – 31.10.21
Trinh Win-Hon	Internship (Switzerland)	01.10.20 – 31.12.20
	Guest Internship	01.01.21 – 16.07.21
Weber Leya	Internship (Switzerland)	01.07.21 – 24.12.21
Wirth Sylvie	Internship (Switzerland)	01.10.20 – 31.12.20
	Guest Internship	01.01.21 – 30.06.21
	Internship	01.07.21 – 24.12.21
Wolfisberg Celina	Guest Internship (Switzerland)	01.03.21 – 30.09.21
Yamamoto Taiyo	Internship (Switzerland)	01.04.21 – 31.08.21
Ziadlou Donya	Internship (Iran)	15.09.21

VET Student

Nehring Marie	VET Student University of Veterinary Medicine, Hanover, DE	01.02.21 – 31.03.21

Guest Scientists / Students

Benca Emir	Guest Scientist University Vienna, AUT	04.01.21 – 30.06.21
Brose Teresa	Guest Internship Albert-Ludwigs-Universität, Freiburg, GER	01.03.20 – 28.02.21
Canciani Elena	Guest Scientist University of Eastern Piedmont, IT	10.10.21 – 05.12.21
Chen Zhenhao	Guest PhD Student Fudan University, CN	03.06.21 – 07.11.21
Chen Baixing	Guest Student KU Leuven, BEL	09.11.21
Dimitrova Rositza	Guest PostDoc Bulgarian Academy of Sciences, Sofia, BGR	01.06.21 – 09.07.21
Fan Jingzhi	Guest PhD Student Riga Technical University, LVA	20.09.21 – 20.12.21
Fu Yanan	Guest Internship University Bejing, CN	10.11.20 – 18.04.21
Gruber Matthias	Guest Student Albert-Ludwigs-University, Freiburg, GER	01.10.21
Guo Peng	Guest PhD Student The 7th Affiliated Hospital, Sun Yat-Sen University, Shenzhen, CN	10.11.20 – 13.11.21
Guoliang Chen	Guest PhD Student Sun Yat-sen University, Guangzhou, CN	10.11.20 – 13.11.21
Iaquinta Maria Rosa	Guest PhD Student University of Ferrara, IT	15.08.21 – 15.11.21
Isenmann Marie	Guest medical Fellow Albert-Ludwigs-Universität, Freiburg, GER	01.03.21
Lanzillotti Carmen	Guest PhD Student University of Ferrara, IT	15.05.21 – 15.08.21
Lauretta Giovanni	Guest PhD Student University of Catania, IT	01.03.21 – 30.11.21
Li Kaihu	Guest PhD Student Central South University, Changsha, CN	02.02.21
Mosina Marika	Guest PhD Rudolfs Cimdins Riga, LVA	14.09.21
Palladino Sara	Guest PhD Student Politecnico di Milano, IT	06.03.21 – 24.12.21
Saravi Babak	Guest Researcher University of Freiburg, GER	01.08.20 – 31.08.21
Sceglovs Artemijs	Guest PhD Rudolfs Cimdins Riga, LVA	14.09.21

Sieberath Alexander	Guest PhD Student Newcastle University, UK	01.03.21 – 30.06.21
Vecstaudza Jana	Guest Scientist Riga Technical University, LVA	20.09.21 – 20.12.21

Employees left 2021

Armiento Angela	PhD	01.01.16 – 31.10.21
Schwab Andrea	PhD	01.04.18 – 31.10.21
Schwyn Ronald	Dipl Medizintechniker HF	01.11.92 – 31.01.21
Steiner Sandra	PhD	01.01.14 – 30.04.21
Sumrall Eric	PhD	01.10.19 – 31.03.21
Thompson Keith	PhD, BSc (Hons), MSc,	26.05.15 – 29.10.21
Varjas Viktor	MSc, Software Engineer	01.01.14 – 31.05.21

Guest Presentations at AO Center

August 17, 2021 Dr Kristaps Klavins from Riga Technical University, Riga, Latvia gave a guest presentation with the title: How and why use metabolomics in biomaterials research.

November 29, 2021 Prof Fabiana Arduini from Department of Chemical Science and Technologies, University of Rome Tor Vergata, Italy gave a guest presentation with the title: Miniaturized electrochemical (bio)sensors for smart detection of biomarkers.

December 10, 2021 Utkan Demirci from Department of Radiology, Stanford University, School of Medicine, Stanford, USA gave a guest presentation with the title: Microfluidic label free technologies for applications in biofabrication and medicine.

December 10, 2021 Dr Esther Wehrle from Department of Health Sciences and Technology, ETH Zurich, Switzerland gave a guest presentation with the title: Towards *in vivo* mechanomics of fracture healing.

12 ARI Patents

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

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 2010-12-24
- Case: 10.2676
- Developer / Inventors: AOR&D, S Brianza, R Schwyn

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

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 2015-08-07
- Case: 10.3302
- Developer / Inventors: M Windolf, D Epari, M Schütz, T Pohlemann, C Nötzli

Bone Implant for Correcting Unbalanced Growth Plate Activity
- First Application: CH2016/01338 filed 2016-10-06
- 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 2018-02-07
- Case: 10.3567
- Developer / Inventor: J Buschbaum, M Windolf

Identification and isolation of osteoprogenitor cells (TGFb Receptor)
- First Application: EP19184241.8 filed 2019-07-03
- Case: F5969
- Developer / Inventors: M Stoddart

Patterning device for the preparation of three-dimensional structures (3D SIM Device)
- First Application: EP20190203370 filed 2019-10-15
- Case: BFHTI-4-EP
- Developer / Inventors: T Serra, M Thurner

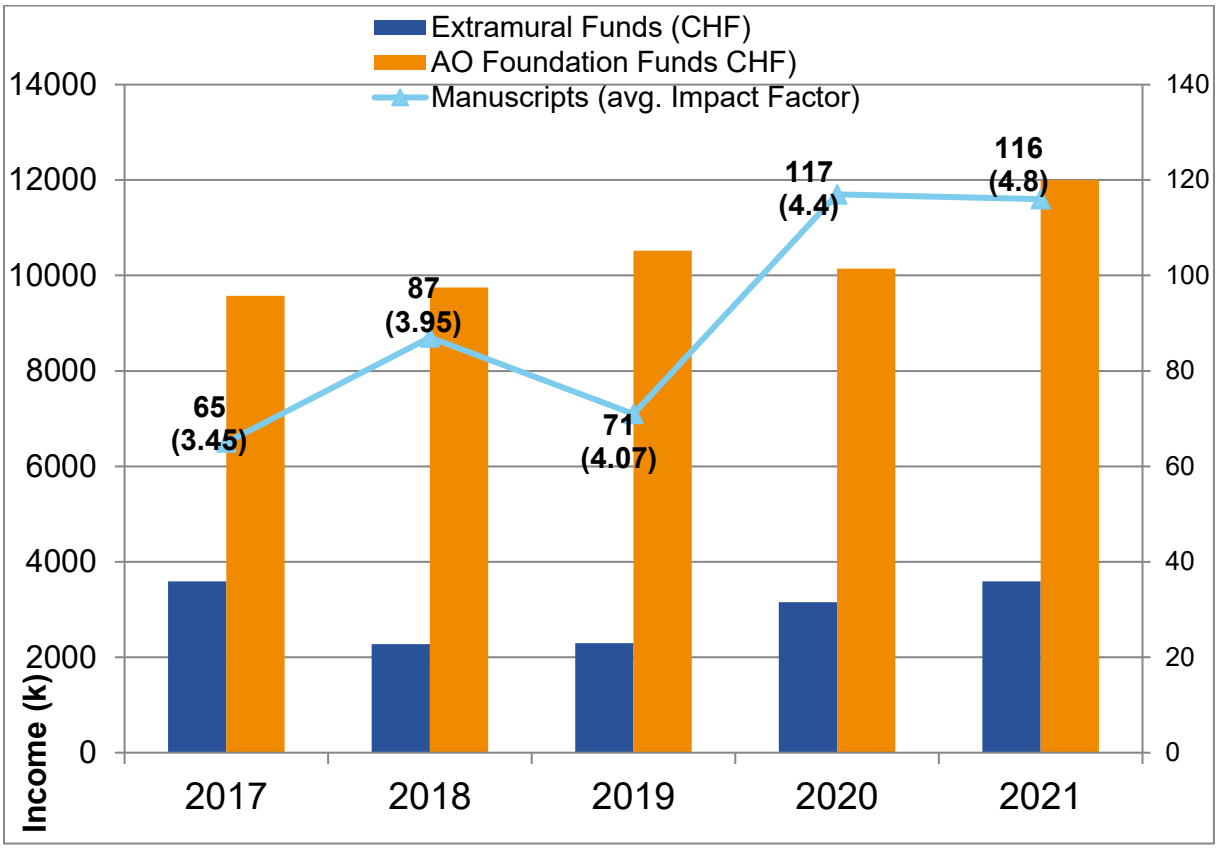
Device for measuring, processing and transmitting implant parameters (Fracture Monitor III)
- First Application: CH01335/19 filed 2019-10-22
- Case: 10.3988
- Developer / Inventors: M Windolf

Biphasic Plate (Biphasic Plate II)
- First Application: CH 01515/19 filed 2019-11-29
- Case: 10.4024
- Developer / Inventors: M Windolf, D Epari

None-stick antibiotics gels (GEDAI gel)
- First Application: CH 01628/19 filed 2019-12-16
- Case: F6183
- Developer / Inventors: M D'Este

13 Publications & Presentations

13.1 2015-2021 Six-year ARI Key Performance Indicators



Note AO Funds in 2021 include 2 million of grants for development projects from AO Development Incubator and AO Strategy fund (sections 10.8 and 10.9).
All AO funds are monitored by external clinical R&D Committees (AOCMF, AOSpine, AOTrauma, AO Vet, ARI AC, AO DI, and AO strategy fund).

13.2 2021 Published peer reviewed papers (epub & in print)

Ahmad P, Stoddart MJ, Della Bella E. The role of noncoding RNAs in osteogenic differentiation of human periodontal ligament stem cells. CMTRO. 2021;6:2472751221999229

Ahmad P, Alam MK, Aldajani A, Alahmari A, Alanazi A, Stoddart M, Sghaireen MG. Dental robotics: a disruptive technology. Sensors. 2021;21(10):3308

Ahrend M-D, Rühle M, Springer F, Baumgartner H. Distance from the magnification device contributes to differences in lower leg length measured in patients with TSF correction. Arch Orthop Trauma Surg. 2021;epub Mar 6

Ahrend M-D, Teunis T, Noser H, Schmidutz F, Richards RG, Gueorguiev B, Kamer L. 3D computational anatomy of the scaphoid and its waist for use in fracture treatment. J Orthop Surg Res. 2021;16(1):216

Ahrend M-D, Kühle L, Riedmann S, Bahrs SD, Bahrs C, Ziegler P. Radiographic parameter(s) influencing functional outcomes following angular stable plate fixation of proximal humeral fractures. Int Orthop. 2021;45:1845-1852

Ahrend MD, Eisenmann T, Herbst M, Gueorguiev B, Keller G, Schmidutz F, Döbele S, Schröter S, Ihle C. Increased tibial tubercle-trochlear groove and patellar height indicate a higher risk of recurrent patellar dislocation following medial reefing. Knee Surg Sports Traumatol Arthrosc. 2021;epub May 25

Ahrend MD, Baumgartner H, Ihle C, Histing T, Schröter S, Finger F. Influence of axial limb rotation on radiographic lower limb alignment: a systematic review. Arch Orthop Trauma Surg. 2021;epub Oct 1

Arand C, Wagner D, Richards RG, Noser H, Kamer L, Gehweiler D, Hopf J, Rommens PM. Anatomical evaluation of the transpubic screw corridor based on a 3D statistical model of the pelvic ring. Sci Rep. 2021;11(1):16677

Baertl S, Metsemakers WJ, Morgenstern M, Alt V, Richards RG, Moriarty TF, Young K. Fracture-related infection. Bone Joint Res. 2021;10(6):351-3

Bagnol R, Sprecher C, Peroglio M, Chevalier J, Mahou R, Büchler P, Richards RG, Eglin D. Coaxial micro-extrusion of a calcium phosphate ink with aqueous solvents improves printing stability, structure fidelity and mechanical properties. Acta Biomater. 2021;125:322-32

Barcik J, Ernst M, Dlaska CE, Drenchev L, Zeiter S, Epari DR, Windolf M. Programable active fixator system for systematic *in vivo* investigation of bone healing processes. Sensors. 2021;21(1):17

Barcik J, Epari DR. Can optimizing the mechanical environment deliver a clinically significant reduction in fracture healing time? Biomedicines. 2021;9(6):691

Barcik J, Ernst M, Balligand M, Dlaska CE, Drenchev L, Zeiter S, Epari DR, Windolf M. Short-term bone healing response to mechanical stimulation – a case series conducted on sheep. Biomedicines. 2021;9(8):988

Basoli V, Della Bella E, Kubosch EJ, Alini M, Stoddart MJ. Effect of expansion media and fibronectin coating on growth and chondrogenic differentiation of human bone marrow-derived mesenchymal stromal cells. Sci Rep. 2021;11(1):1308

Benca E, Zderic I, Caspar J, van Knegsel K, Hirtler L, Gueorguiev B, Widhalm H, Windhager R, Varga P. On measuring implant fixation stability in ACL reconstruction. Sensors. 2021;21(19):6632

Boot W, Schmid T, D'Este M, Guillaume O, Foster A, Decosterd L, Richards RG, Eglin D, Zeiter S, Moriarty TF. A gentamicin and vancomycin loaded hyaluronic-acid hydrogel successfully eradicates chronic MRSA orthopedic infection in a sheep model. Antimicrob Agents Chemother. 2021;65:e01840-20

Brose TZ, Kubosch EJ, Schmal H, Stoddart MJ, Armiento AR. Crosstalk between mesenchymal stromal cells and chondrocytes: The hidden therapeutic potential for cartilage regeneration. Stem Cell Rev Rep. 2021;epub May 05

Burch MA, Keshishian A, Wittmann C, Nehrbass D, Styger U, Muthukrishnan G, Arens D, Stadelmann VA, Richards RG, Moriarty TF, Thompson K. The non-steroidal anti-inflammatory drug carprofen negatively impacts new bone formation and antibiotic efficacy in a rat model of orthopaedic-device-related infection. Eur Cell Mater. 2021;41:739-55

Burkhard B, Schopper C, Ciric D, Mischler D, Gueorguiev B, Varga P. Overdrilling increases the risk of screw perforation in locked plating of complex proximal humeral fractures – a biomechanical cadaveric study. J Biomech. 2021;117:110268

Buschbaum J, Freitag L, Slongo TF, Zeiter S, Schütz M, Windolf M. Growth modulation of angular deformities with a novel constant force implant concept-preclinical results. J Child Orthop. 2021;15:137-148

Chen J-X, Li Y-H, Wen J, Li Z, Yu B-S, Huang Y-C. Annular defects impair the mechanical stability of the intervertebral disc. Global Spine J. 2021;epub Mar 30

Coppola GA, Onsea J, Moriarty TF, Nehrbass D, Constant C, Zeiter S, Aktan MK, Braem A, Van der Eycken EV, Steenackers HP, Metsemakers W-J. An improved 2-aminoimidazole based anti-biofilm coating for orthopedic implants: activity, stability, and *in vivo* biocompatibility. Front Microbiol. 2021;12(806)

Croft AS, Illien-Jünger S, Grad S, Guerrero J, Wangler S, Gantenbein B. The application of mesenchymal stromal cells and their homing capabilities to regenerate the intervertebral disc. Int J Mol Sci. 2021;22(7):3519

Cui S, Zhou Z, Chen X, Wei F, Richards RG, Alini M, Grad S, Li Z. Transcriptional profiling of intervertebral disc in a post-traumatic early degeneration organ culture model. JOR Spine. 2021 Apr 8;4(3):e1146

Della Bella E, Buetti-Dinh A, Licandro G, Ahmad P, Basoli V, Alini M, Stoddart MJ. Dexamethasone induces changes in osteogenic differentiation of human mesenchymal stromal cells via SOX9 and PPARG, but not RUNX2. Int J Mol Sci. 2021;22(9):4785

de Mesy Bentley KL, Galloway CA, Muthukrishnan G, Echternacht SR, Masters EA, Zeiter S, Schwarz EM, Leckenby JI. Emerging electron microscopy and 3D methodologies to interrogate *Staphylococcus aureus* osteomyelitis in murine models. J Orthop Res. 2021;39:376-388

Du J, Guo W, Hackel S, Hoppe S, Garcia JP, Alini M, Tryfonidou MA, Creemers LB, Grad S, Li Z. The function of CD146 in human annulus fibrosus cells and mechanism of the regulation by TGF-beta. J Orthop Res. 2021;epub Oct 18

Epari DR, Gurung R, Hofmann-Fliri L, Schwyn R, Schuetz M, Windolf M. Biphasic plating improves the mechanical performance of locked plating for distal femur fractures. J Biomech. 2021;115:110192

Ernst M, Baumgartner H, Döbele S, Höntzsch D, Pohlemann T, Windolf M. Clinical feasibility of fracture healing assessment through continuous monitoring of implant load. J Biomech. 2021:110188

Evers J, Fischer M, Raschke M, Riesenbeck O, Milstrey A, Gehweiler D, Gueorguiev B, Ochman S. Leave it or fix it? How fixation of a small posterior malleolar fragment neutralizes rotational forces in trimalleolar fractures. Arch Orthop Trauma Surg. 2021;epub Jan 28

Fletcher JWA, Sommer C, Eckardt H, Knobe M, Gueorguiev B, Stoffel K. Intracapsular femoral neck fractures — A surgical management algorithm. Medicina. 2021;57(8):791

Fletcher JWA, Neumann V, Wenzel L, Gueorguiev B, Richards RG, Gill HS, Whitehouse MR, Preatoni E. Screw tightness and stripping rates vary between biomechanical researchers and practicing orthopaedic surgeons. J Orthop Surg Res. 2021;16(1):642

Fosca M, Basoli V, Della Bella E, Russo F, Vadala G, Alini M, Rau JV, Verrier S. Raman spectroscopy in skeletal tissue disorders and tissue engineering: present and prospective. Tissue Eng Part B Rev. 2021;epub Sep 28

Gehweiler D, Styger U, Gueorguiev B, Colcuc C, Vordemvenne T, Wähnert D. Local bone quality measure and construct failure prediction: a biomechanical study on distal femur fractures. Arch Orthop Trauma Surg. 2021;epub Feb 15

Gehweiler D, Schultz M, Schulze M, Riesenbeck O, Wähnert D, Raschke MJ. Material properties of human vertebral trabecular bone under compression can be predicted based on quantitative computed tomography. BMC Musculoskelet Disord. 2021;22(1):709

Gehweiler D, Schmitz N, Gueorguiev B, Zderic I, Grünwald L, Richards RG, Wähnert D, Raschke MJ. 3D geometry of femoral reaming for bone graft harvesting. Sci Rep. 2021;11(1):17153

Germscheid N, Cheung JPY, Neva MH, Oner FC, Kwon BK, Valacco M, Awwad W, Sciubba DM, Lewis SJ, Rhines LD, Yoon ST, Alini M, Grad S, Fisher CG, Samartzis D. Research practices and needs among spine surgeons worldwide. Global Spine J. 2021;epub Dec 6

Geven MA, Lapomarda A, Guillaume O, Sprecher CM, Eglin D, Vozzi G, Grijpma DW. steogenic differentiation of hBMSCs on porous photo-crosslinked poly(trimethylene carbonate) and nano-hydroxyapatite composites. Eur Polym J. 2021;147:110335

Giannoudis PV, Richards RG. A tribute to Professor Stephan M Perren: a pioneer and visionary man of the AO Foundation. Injury. 2021;52(1):1-2

Giannoudis PV, Richards RG. Publishing research that could be further developed and translated should continue to be a priority. Injury. 2021;52(1):9-10

Gomes GS, Zderic I, Ahrend M-D, Kojima KE, Varga P, Belangero WD, Richards RG, Lambert SM, Gueorguiev B. Is bridge plating of comminuted humeral shaft fractures advantageous when using compression plates with three *versus* two screws per fragment? A biomechanical cadaveric study. Biomed Res Int. 2021;2021:6649712

Groetsch A, Zysset PK, Varga P, Pacureanu A, Peyrin F, Wolfram U. An experimentally informed statistical elasto-plastic mineralised collagen fibre model at the micrometre and nanometre lengthscale. Sci Rep. 2021;11(1):15539

Guo P, Liu X, Zhang P, He Z, Li Z, Alini M, Richards RG, Grad S, Stoddart MJ, Zhou G, Zou X, Chan D, Tian W, Chen D, Gao M, Zhou Z, Liu S. A single-cell transcriptome of mesenchymal stromal cells to fabricate bioactive hydroxyapatite materials for bone regeneration. Bioact Mater. 2021;9:281-298

Guo W, Douma L, Hu MH, Eglin D, Alini M, Secerovic A, Grad S, Peng X, Zou X, D'Este M, Peroglio M. Hyaluronic acid-based interpenetrating network hydrogel as a cell carrier for nucleus pulposus repair. Carbohydr Polym. 2021;epub Oct 29

Hente RW, Perren SM. Tissue deformation controlling fracture healing. J Biomech. 2021;125:110576

Herbst M, Ahrend MD, Grünwald L, Fischer C, Schröter S, Ihle C. Overweight patients benefit from high tibial osteotomy to the same extent as patients with normal weights but show inferior mid-term results. Knee Surg Sports Traumatol Arthrosc. 2021;epub Feb 11

Hofstee MI, Riool M, Gieling F, Stenger V, Constant C, Nehrbass D, Zeiter S, Richards RG, Zaat SA, Moriarty TF. A murine *Staphylococcus aureus* fracture-related infection model characterised by fracture non-union, staphylococcal abscess communities and myeloid-derived suppressor cells. Eur Cell Mater. 2021;41:774-92

Hofstee MI, Heider A, Häckel S, Constant C, Riool M, Richards RG, Moriarty TF, Zaat SAJ. *In vitro* 3D *staphylococcus aureus* abscess communities induce bone marrow cells to expand into myeloid-derived suppressor cells. Pathogens. 2021;10(11):1446

Kamali A, Ziadlou R, Lang G, Pfannkuche J, Cui S, Li Z, Richards RG, Alini M, Grad S. Small molecule-based treatment approaches for intervertebral disc degeneration: Current options and future directions. Theranostics. 2021;11(1):27-47

Kamer L, Noser H, Arand C, Handrich K, Rommens PM, Wagner D. Artificial intelligence and CT-based 3D statistical modeling to assess trans-sacral corridors and plan implant positioning. J Orthop Res. 2021;39:2681-2692

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 in patients with chronic low back pain. Eur Spine J. 2021;30:1018-1027

Keltz E, Fletcher J, Mora AJ, Yavnai N, Gueorguiev-Rüegg B, Keren Y. Orthopedic screws insertion simulation with immediate feedback enhances surgical skill. Clin Biomech. 2021;epub April 27:105367

Kfuri M, Escalante I, Schopper C, Zderic I, Stoffel K, Sommer C, Qawasmi F, Knobe M, Richards RG, Gueorguiev B. Comminuted patellar fractures: the role of biplanar fixed angle plate constructs. J Orthop Translat. 2021;27:17-24

Knobe M, Iselin LD, van de Wall BJM, Lichte P, Hildebrand F, Beeres FJP, Link BC, Gueorguiev B, Nebelung S, Ganse B, Migliorini F, Klos K, Babst R, Haefeli PC. Reduced pre-operative skin oxygen saturation predicts revision after open reduction and internal fixation in calcaneal fractures. Int Orthop. 2021;45:2355-2363

Krause F, Zderic I, Gueorguiev B, Vellasamy A, Schmid T. The effect of the mobile subtalar joint on calcaneal and supramalleolar osteotomies. Foot Ankle Int. 2021;42:1606-1612

Lackington WA, Gehweiler D, Zderic I, Nehrbass D, Zeiter S, González-Vázquez A, O'Brien FJ, Stoddart MJ, Thompson K. Incorporation of hydroxyapatite into collagen scaffolds enhances the therapeutic efficacy of rhBMP-2 in a weight-bearing femoral defect model. Mater Today Commun. 2021;29:102933

Lenz M, Varga P, Mischler D, Gueorguiev B, Klos K, Fernandez dell'Oca A, Regazzoni P, Richards RG, Perren SM. Helical plating - a novel technique to increase stiffness in defect fractures. Eur Cell Mater. 2021;42:110-21

Lewis GS, Mischler D, Wee H, Reid JS, Varga P. Finite element analysis of fracture fixation. Curr Osteoporos Rep. 2021;19:403-4016

Li K, Zhang P, Zhu Y, Alini M, Grad S, Li Z. Establishment of an *ex vivo* inflammatory osteoarthritis model with human osteochondral explants. Front Bioeng Biotechnol. 2021;9:787020

Link BC, van Veelen N, Knobe M, Gueorguiev B. Letter to the editor regarding: does the helical blade lead to higher rates of fixation failure as compared to lag screw in the cephalomedullary nailing treatment of hip fractures? A systematic review and meta-analysis. J Orthop Trauma. 2021;35:e355

Lodde MF, Katthagen JC, Schopper CO, Zderic I, Richards RG, Gueorguiev B, Raschke MJ, Hartensuer R. Biomechanical comparison of five fixation techniques for unstable fragility fractures of the pelvic ring. J Clin Med. 2021;10(11):2326

Lodde MF, Katthagen JC, Schopper CO, Zderic I, Richards RG, Gueorguiev B, Raschke MJ, Hartensuer R. Is anterior plating superior to the bilateral use of retrograde transpubic screws for treatment of straddle pelvic ring fractures? A biomechanical investigation. J Clin Med. 2021;10(21):5049

Lodde MF, Katthagen JC, Schopper CO, Zderic I, Richards RG, Gueorguiev B, Raschke MJ, Hartensuer R. Does cement augmentation of the sacroiliac screw lead to superior biomechanical results for fixation of the posterior pelvic ring? A biomechanical study. Medicina. 2021;57(12):1368

Ma J, Patil V, Pandit A, Quinlan LR, Finn DP, Grad S, Alini M, Peroglio M. *In vitro* model to investigate communication between dorsal root ganglion and spinal cord glia. Int J Mol Sci. 2021;22(18):9725

Milstrey A, Rosslenbroich S, Everding J, Raschke MJ, Richards RG, Moriarty TF, Puetzler J. Antibiofilm efficacy of focused high-energy extracorporeal shockwaves and antibiotics *in vitro*. Bone Joint Res. 2021;10(1):77-84

Mischler D, Schopper C, Gasparri M, Schulz-Drost S, Brace M, Gueorguiev B. Is intrathoracic rib plate fixation advantageous over extrathoracic plating? A biomechanical cadaver study. J Trauma Acute Care Surg. 2021;epub Oct 22

Monaco G, El Haj AJ, Alini M, Stoddart MJ. *Ex vivo* systems to study chondrogenic differentiation and cartilage Integration. J Funct Morphol Kinesiol. 2021;6(1):6

Monaco G, El Haj AJ, Alini M, Stoddart MJ. Sodium hyaluronate supplemented culture medium combined with joint-simulating mechanical loading improves chondrogenic differentiation of human mesenchymal stem cells. Eur Cell Mater. 2021;41:616-32

Monaco G, Ladner YD, El Haj AJ, Forsyth NR, Alini M, Stoddart MJ. Mesenchymal stromal cell differentiation for generating cartilage and bone-like tissues *in vitro*. Cells. 2021;10(8):2165

Moriarty TF, Muthukrishnan G, Daiss JL, Xie C, Nishitani K, Morita Y, Awad H, de Mesy Bentley KL, Masters E, Bui T, Yan M, Owen J, Mooney B, Gill S, Puetzler J, Wenke JC, Morgenstern M, Metsemakers WJ, Noll C, Joeris A, Richards RG, Schwarz EM, Kates SL. Bone infection: a clinical priority for clinicians, scientists and educators. Eur Cell Mater. 2021;42:312-33

Muthukrishnan G, Wallimann A, Rangel-Moreno J, de Mesy Bentley KL, Hildebrand M, Mys K, Kenney HM, Sumrall ET, Daiss JL, Zeiter S, Richards RG, Schwarz EM, Moriarty TF. Humanized mice exhibit exacerbated abscess formation and osteolysis during the establishment of implant-associated *Staphylococcus aureus* osteomyelitis. Front Immunol. 2021;12(809)

Mys K, Varga P, Stockmans F, Gueorguiev B, Neumann V, Vanovermeire O, Wyers CE, van den Bergh JPW, van Lenthe GH. High-resolution cone-beam computed tomography is a fast and promising technique to quantify bone microstructure and mechanics of the distal radius. Calcif Tissue Int. 2021;108:314-323

Mys K, Stockmans F, Gueorguiev B, Wyers CE, van den Bergh JPW, van Lenthe GH, Varga P. Adaptive local thresholding can enhance the accuracy of HR-pQCT-based trabecular bone morphology assessment. Bone. 2021;epub Oct 9:116225

Onsea J, Post V, Buchholz T, Schwegler H, Zeiter S, Wagemans J, Pirnay JP, Merabishvili M, D'Este M, Rotman SG, Trampuz A, Verhofstad MHJ, Obremskey WT, Lavigne R, Richards RG, Moriarty TF, Metsemakers WJ. Bacteriophage therapy for the prevention and treatment of fracture-related infection caused by *staphylococcus aureus*: a preclinical study. Microbiol Spectr. 2021;9:e0173621

Panagiotopoulou VC, Ovesy M, Gueorguiev B, Richards RG, Zysset P, Varga P. Experimental and numerical investigation of secondary screw perforation in the human proximal humerus. J Mech Behav Biomed Mater. 2021;116:104344

Pastor T, Zderic I, Gehweiler D, Gardner MJ, Stoffel K, Richards RG, Knobe M, Gueorguiev B. Biomechanical analysis of recently released cephalomedullary nails for trochanteric femoral fracture fixation in a human cadaveric model. Arch Orthop Trauma Surg. 2021;epub Nov 8

Pereira AR, Lipphaus A, Ergin M, Salehi S, Gehweiler D, Rudert M, Hansmann J, Herrmann M. Modeling of the human bone environment: Mechanical stimuli guide mesenchymal stem cell–extracellular matrix interactions. Materials. 2021;14(16):4431

Pötter N, Westbrock F, Grad S, Alini M, Stoddart MJ, Schmal H, Kubosch D, Salzmann G, Kubosch EJ. Evaluation of the influence of platelet-rich plasma (PRP), platelet lysate (PL) and mechanical loading on chondrogenesis *in vitro*. Sci Rep. 2021;11(1):20188

Ren W, Cui S, Alini M, Grad S, Zhou Q, Li Z, Razansky D. Noninvasive multimodal fluorescence and magnetic resonance imaging of whole-organ intervertebral discs. Biomed Opt Express. 2021;12(6):3214-27

Russo F, Ambrosio L, Peroglio M, Guo W, Wangler S, Gewiess J, Grad S, Alini M, Papalia R, Vadalà G, Denaro V. A hyaluronan and platelet-rich plasma hydrogel for mesenchymal stem cell delivery in the intervertebral disc: an organ culture study. Int J Mol Sci. 2021;22(6):2963

Sabaté Brescó M, Berset CM, Zeiter S, Stanic B, Thompson K, Ziegler M, Richards RG, O'Mahony L, Moriarty TF. Fracture biomechanics influence local and systemic immune responses in a murine fracture-related infection model. Biology Open. 2021;10(9):bio057315

Saravi B, Li Z, Pfannkuche J, Wystrach L, Häckel S, Albers CE, Grad S, Alini M, Richards RG, Lang C, Südkamp N, Schmal H, Lang G. Angiotensin II type 1 receptor antagonist losartan inhibits TNF-α-induced inflammation and degeneration processes in human nucleus pulposus cells. Applied Sciences. 2021;11(1):417

Saravi B, Lang G, Grad S, Alini M, Richards RG, Schmal H, Südkamp N, Li Z. A proinflammatory, degenerative organ culture model to simulate early-stage intervertebral disc disease. JoVE. 2021(168):e62100

Saravi B, Li Z, Lang CN, Schmid B, Lang FK, Grad S, Alini M, Richards RG, Schmal H, Südkamp N, Lang GM. The tissue renin-angiotensin system and its role in the pathogenesis of major human diseases: quo vadis? Cells. 2021;10(3):650

Saravi B, Vollmer A, Lang G, Adolphs N, Li Z, Giers V, Stoll P. Impact of renin-angiotensin system inhibitors and beta-blockers on dental implant stability. Int J Implant Dent. 2021;7(1):31

Schader JF, Zderic I, Gehweiler D, Dauwe J, Mys K, Danker C, Acklin YP, Sommer C, Gueorguiev B, Stoffel K. Standardized artificially created stable pertrochanteric femur fractures present more homogenous results compared to osteotomies for orthopaedic implant testing. BMC Musculoskelet Disord. 2021;22(1):371

Schader JF, Mischler D, Dauwe J, Richards RG, Gueorguiev B, Varga P. One size may not fit all: patient-specific computational optimization of locking plates for improved proximal humerus fracture fixation. J Shoulder Elbow Surg. 2021;epub Jul 20

Schmidutz F, Yan SG, Schopf C, Ihle C, Ahrend M-D, Sprecher CM. Cortical bone thickness predicts the quantitative bone mineral density of the proximal humerus. Arch Osteoporos. 2021;16(1):33

Schmidutz F, Schopf C, Yan SG, Ahrend MD, Ihle C, Sprecher C. Cortical bone thickness of the distal radius predicts the local bone mineral density. Bone Joint Res. 2021;10(12):820-9

Schopper C, Keck K, Zderic I, Migliorini F, Link B-C, Beeres FJP, Babst R, Nebelung S, Eschbach D, Knauf T, Ganse B, Schoeneberg C, Hildebrand F, Gueorguiev B, Knobe M. Screw-blade fixation systems for implant anchorage in the femoral head: horizontal blade orientation provides superior stability. Injury. 2021;52:1861-1867

Sennett ML, Friedman JM, Ashley BS, Stoeckl BD, Patel JM, Alini M, Cucchiarini M, Eglin D, Madry H, Mata A, Semino C, Stoddart MJ, Johnstone B, Moutos FT, Estes BT, Guilak F, Mauck RL, Dodge GR. Long term outcomes of biomaterial-mediated repair of focal cartilage defects in a large animal model. Eur Cell Mater. 2021;41:40-51

Sermon A, Zderic I, Khatchadourian R, Scherrer S, Knobe M, Stoffel K, Gueorguiev B. Bone cement augmentation of femoral nail head elements increases their cut-out resistance in poor bone quality – a biomechanical study. J Biomech. 2021;118:110301

Sermon A, Hofmann-Fliri L, Zderic I, Agarwal Y, Scherrer S, Weber A, Altmann M, Knobe M, Windolf M, Gueorguiev B. Impact of bone cement augmentation on the fixation strength of TFNA blades and screws. Medicina. 2021;57(9):899

Siverino C, Freitag L, Arens D, Styger U, Richards RG, Moriarty TF, Stadelmann VA, Thompson K. Titanium wear particles exacerbate *S. epidermidis*-induced implant-related osteolysis and decrease efficacy of antibiotic therapy. Microorganisms. 2021;9(9):1945

Stenger V, Zeiter S, Buchholz T, Arens D, Spadavecchia C, Schüpbach-Regula G, Rohrbach H. Is a block of the femoral and sciatic nerves an alternative to epidural analgesia in sheep undergoing orthopaedic hind limb surgery? A prospective, randomized, double blinded experimental trial. Animals. 2021;11(9):2567

Sturm L, Schwemberger B, Menzel U, Häckel S, Albers CE, Plank C, Rip J, Alini M, Traweger A, Grad S, Basoli V. *In vitro* evaluation of a nanoparticle-based mRNA delivery system for cells in the joint. Biomedicines. 2021;9(7):794

Sumrall ET, Hofstee MI, Arens D, Röhrig C, Baertl S, Gehweiler D, Schmelcher M, Loessner MJ, Zeiter S, Richards RG, Moriarty TF. An enzybiotic regimen for the treatment of methicillin-resistant *staphylococcus aureus* orthopaedic device-related infection. Antibiotics. 2021;10(10):1186

van de Wall BJM, Beeres FJP, Rompen IF, Link BC, Babst R, Schoeneberg C, Michelitsch C, Nebelung S, Pape HC, Gueorguiev B, Knobe M. RIA *versus* iliac crest bone graft harvesting: A meta-analysis and systematic review. Injury. 2021;epub Oct 15

van Knegsel KP, Ganse B, Haefeli PC, Migliorini F, Scaglioni MF, van de Wall BJM, Kim BS, Link BC, Beeres FJP, Nebelung S, Schoeneberg C, Hildebrand F, Gueorguiev B, Knobe M. Trochanteric femur fractures: application of skeletal traction during surgery does not alter soft-tissue microcirculation. Medicina (Kaunas). 2021;57(9):884

Wähnert D, Frank A, Ueberberg J, Heilmann LF, Sauzet O, Raschke MJ, Gehweiler D. Development and first biomechanical validation of a score to predict bone implant interface stability based on clinical qCT scans. Scientific Reports. 2021;11(1):3273

Wähnert D, Grüneweller N, Gueorguiev B, Vordemvenne T, Gehweiler D. Removal of cement-augmented screws in distal femoral fractures and the effect of retained screws and cement on total knee arthroplasty: a biomechanical investigation. J Orthop Traumatol. 2021;22(1):5

Wallimann A, Hildebrand M, Groeger D, Stanic B, Akdis CA, Zeiter S, Richards RG, Moriarty TF, O'Mahony L, Thompson K. An exopolysaccharide produced by *Bifidobacterium longum 35624(R)* inhibits osteoclast formation via a TLR2-dependent mechanism. Calcif Tissue Int. 2021;108(5):654-66

Wallimann A, Magrath W, Thompson K, Moriarty T, Richards RG, Akdis CA, O'Mahony L, Hernandez CJ. Gut microbial-derived short-chain fatty acids and bone: a potential role in fracture healing. Eur Cell Mater. 2021;41:454-70

Wallimann A, Magrath W, Pugliese B, Stocker N, Westermann P, Heider A, Gehweiler D, Zeiter S, Claesson MJ, Richards RG, Akdis CA, Hernandez CJ, O'Mahony L, Thompson K, Moriarty TF. Butyrate inhibits osteoclast activity *in vitro* and regulates systemic inflammation and bone healing in a murine osteotomy model compared to antibiotic-treated mice. Mediators Inflamm. 2021;2021:8817421

Wangler S, Kamali A, Wapp C, Wuertz-Kozak K, Häckel S, Fortes C, Benneker LM, Haglund L, Richards RG, Alini M, Peroglio M, Grad S. Uncovering the secretome of mesenchymal stromal cells exposed to healthy, traumatic, and degenerative intervertebral discs: a proteomic analysis. Stem Cell Res Ther. 2021;12(1):11

Weitkamp J-T, Wöltje M, Nußpickel B, Schmidt FN, Aibibu D, Bayer A, Eglin D, Armiento AR, Arnold P, Cherif C, Lucius R, Smeets R, Kurz B, Behrendt P. Silk fiber-reinforced hyaluronic acid-based hydrogel for cartilage tissue engineering. Int J Mol Sci. 2021;22(7):3635

Wildemann B, Ignatius A, Leung F, Taitsman LA, Smith RM, Pesantez R, Stoddart MJ, Richards RG, Jupiter JB. Non-union bone fractures. Nat Rev Dis Primers. 2021;7(1):57

Windolf M, Richards RG. Generic implant positioning technology based on hole projections in X-ray images. J Med Device. 2021;15(2): 025002

Xu Y, Yin H, Chu J, Eglin D, Serra T, Docheva D. An anisotropic nanocomposite hydrogel guides aligned orientation and enhances tenogenesis of human tendon stem/progenitor cells. Biomater Sci. 2021;9:1237-1245

Zderic I, Varga P, Styger U, Drenchev L, Gueorguiev B, Asimus E, Saunders WB, Kowaleski M, Boudrieau RJ, Dejardin LM. Mechanical evaluation of two hybrid locking plate designs for canine pancarpal arthrodesis. Biomed Res Int. 2021;2021:2526879

Zderic I, Gueorguiev B, Blauth M, Weber A, Koch R, Dauwe J, Schader JF, Stoffel K, Finkemeier C, Hessmann M. Angular stable locking in a novel intramedullary nail improves construct stability in a distal tibia fracture model. Injury. 2021;epub Nov 6

Zhang F, Liu X, Li B, Li Z, Grad S, Chen D, Gao M, Liu S. The effect of hyaluronic acid on nucleus pulposus extracellular matrix production through hypoxia-inducible factor-1alpha transcriptional activation of CD44 under hypoxia. Eur Cell Mater. 2021;41:142-52

Zhang P, Liu X, Guo P, Li X, He Z, Li Z, Stoddart MJ, Grad S, Tian W, Chen D, Zou X, Zhou Z, Liu S. Effect of cyclic mechanical loading on immunoinflammatory microenvironment in biofabricating hydroxyapatite scaffold for bone regeneration. Bioact Mater. 2021;6(10):3097-108

Zuncheddu D, Della Bella E, Schwab A, Petta D, Rocchitta G, Generelli S, Kurth F, Parrilli A, Verrier S, Rau JV, Fosca M, Maioli M, Serra PA, Alini M, Redl H, Grad S, Basoli V. Quality control methods in musculoskeletal tissue engineering: from imaging to biosensors. Bone Res. 2021;9(1):46

13.3 2021 Conference papers

Trivedi Z, Bleiler C, Gehweiler D, Gueorguiev-Rüegg B, Ricken T, Wagner A, Röhrle O. Simulating vertebroplasty: A biomechanical challenge. Proc Appl Math Mech. 2020;20(1):e202000313 (conference paper GAMM 2020 virtual / oral)

13.4 2020 epub, 2021 in print

Ahrend M-D, Finger F, Grünwald L, Keller G, Baumgartner H. Improving the accuracy of patient positioning for long-leg radiographs using a taylor spatial frame mounted rotation rod. Arch Orthop Trauma Surg. 2021;141(1):55-61 (epub 2020; May 6)

Breceda A, Sands A, Zderic I, Schopper C, Schader J, Gehweiler D, Mischler D, Richards RG, Gueorguiev B. Biomechanical analysis of peri-implant fractures in short *versus* long cephalomedullary implants following pertrochanteric fracture consolidation. Injury. 2021;51(1):60-5 (epub 2020; Sep 18)

Ernst M, Richards RG, Windolf M. Smart implants in fracture care - only buzzword or real opportunity? Injury. 2021;52(Suppl 2):S101-S5 (epub 2020; Sep 17)

Foster AL, Moriarty TF, Zalavras C, Morgenstern M, Jaiprakash A, Crawford R, Burch MA, Boot W, Tetsworth K, Miclau T, Ochsner P, Schuetz MA, Richards RG, Metsemakers WJ. The influence of biomechanical stability on bone healing and fracture-related infection: the legacy of Stephan Perren. Injury. 2021;51(1):43-52 (epub 2020; Jun 26)

Foster AL, Boot W, Stenger V, D'Este M, Jaiprakash A, Eglin D, Zeiter S, Richards RG, Moriarty TF. Single-stage revision of MRSA orthopedic device-related infection in sheep with an antibiotic-loaded hydrogel. J Orthop Res. 2021;39(2):438-48 (epub 2020; Dec 11)

Grünwald L, Schröter S, Windolf M, Gueorguiev B, Richards RG, Buschbaum J. *In vivo* test of a radiography-based navigation system for control of derotational osteotomies. J Orthop Res. 2021;39(1):130-5 (epub 2020; Jun 21)

Handrich K, Kamer L, Mayo K, Sawaguchi T, Noser H, Arand C, Wagner D, Rommens PM. Asymmetry of the pelvic ring evaluated by CT-based 3D statistical modeling. J Anat. 2021;238(5):1225-32

Herbst M, Kuwashima U, Ahrend MD, Gueorguiev BG, Schröter S, Ihle C. Health-related quality of life - an underestimated factor to evaluate the treatment success after open wedge HTO surgery: prospective 6-years follow-up. Gesundheitsbezogene Lebensqualität - ein unterschätztes Kriterium zur Bewertung des Behandlungserfolgs und der Indikationsstellung bei HTO: prospektive 6-Jahres-Ergebnisse. Z Orthop Unfall. 2021;159(3):288-97 (epub 2020; Feb 27)

Holweg P, Dauwe J, Grechenig P, Holter M, Staresinic M, Feigl G, Bakota B. Screw placement in two different implants for proximal humeral fractures regarding regional differences in bone mineral density: An anatomical study. Injury. 2021;52(Suppl 5):S17-S21 (epub 2020; Oct 10)

Kadekar S, Barbe L, Stoddart M, Varghese OP, Tenje M, Mestres G. Effect of the addition frequency of 5-azacytidine in both micro- and macroscale cultures. Cell Mol Bioeng. 2021:14:121-130 (epub 2020; Oct 6)

Lambert S, Mischler D, Windolf M, Regazzoni P, Dell'Oca AF, Gueorguiev B, Varga P. From creative thinking to scientific principles in clinical practice. Injury. 2020;52(1):32-6 (epub 2020; Sep 29)

Lenz M, Hofmann-Fliri L, Kasper LA, Varga P, Zderic I, Gehweiler D, Klos K, Hofmann GO, Stoffel K, Gueorguiev B. Biomechanical evaluation of retrograde docking nailing to a total hip arthroplasty stem in a periprosthetic femur fracture model. Injury. 2020;52:53-59 (epub 2020; Oct 19)

Lenz M, Acklin YP, Kasper LA, Mischler D, Varga P, Zderic I, Gehweiler D, Klos K, Gueorguiev B, Stoffel K. Biomechanical evaluation of the docking nail concept in periprosthetic fracture fixation around a stemmed total knee arthroplasty. J Biomech. 2021;115:110109 (epub 2020; Nov 18)

Meng X, Grad S, Wen C, Lai Y, Alini M, Qin L, Wang X. An impaired healing model of osteochondral defect in papain-induced arthritis. J Orthop Translat. 2021;26:101-10 (epub 2020; Sep 22)

Metsemakers WJ, Zalavras C, Schwarz EM, Chen AF, Trampuz A, Moriarty TF. Antimicrobial resistance, the COVID-19 pandemic, and lessons for the orthopaedic community. J Bone Joint Surg Am. 2021;103(1):4-9 (epub 2020; Dec 2)

Mys K, Varga P, Stockmans F, Gueorguiev B, Wyers CE, van den Bergh JPW, van Lenthe GH. Quantification of 3D microstructural parameters of trabecular bone is affected by the analysis software. Bone. 2021;142:115653 (epub 2020; Oct 12)

Penev P, Qawasmi F, Mosheiff R, Knobe M, Lehnert M, Krause F, Raykov D, Richards G, Gueorguiev B, Klos K. Ligamentous lisfranc injuries: analysis of CT findings under weightbearing. Eur J Trauma Emerg Surg. 2021;47(4):1243-8 (epub 2020; Jan 16)

Schmidutz F, Milz S, Schiuma D, Richards RG, Windolf M, Sprecher CM. Cortical parameters predict bone strength at the tibial diaphysis, but are underestimated by HR-pQCT and muCT compared to histomorphometry. J Anat. 2021;238(3):669-78 (epub 2020; Oct 20)

Thompson K, Freitag L, Styger U, Camenisch K, Zeiter S, Arens D, Richards RG, Moriarty TF, Stadelmann VA. Impact of low bone mass and antiresorptive therapy on antibiotic efficacy in a rat model of orthopedic device-related infection. J Orthop Res. 2021;39(2):415-25 (epub 2020; Dec 15)

Wilson CJ, Epari DR, Ernst M, Arens D, Zeiter S, Windolf M. Morphology of bony callus growth in healing of a sheep tibial osteotomy. Injury. 2020:52:66-70 (epub 2020; Oct 19)

Windolf M, Ernst M, Schwyn R, Arens D, Zeiter S. The relation between fracture activity and bone healing with special reference to the early healing phase - a preclinical study. Injury. 2020;52:71-77 (epub 2020; Oct 10)

Zderic I, Wagner D, Schopper C, Lodde M, Richards RG, Gueorguiev B, Rommens P, Acklin YP. Screw-in-screw fixation of fragility sacrum fractures provides high stability without loosening-biomechanical evaluation of a new concept. J Orthop Res. 2021;39(4):761-70 (epub 2020; Oct 24)

Zheng Z, Eglin D, Alini M, Richards RG, Qin L, Lai Y. Visible light-induced 3D bioprinting technologies and corresponding bioink materials for tissue engineering: a review. Engineering, 2021; 7: 966-978 (epub 2020; Sep 20)

Zhou Z, Cui S, Du J, Richards RG, Alini M, Grad S, Li Z. One strike loading organ culture model to investigate the post-traumatic disc degenerative condition. J Orthop Translat. 2021;26:141-50 (epub 2020; Oct 20)

Ziadlou R, Rotman S, Teuschl A, Salzer E, Barbero A, Martin I, Alini M, Eglin D, Grad S. Optimization of hyaluronic acid-tyramine/silk-fibroin composite hydrogels for cartilage tissue engineering and delivery of anti-inflammatory and anabolic drugs. Mater Sci Eng C Mater Biol Appl. 2021;120:111701 (epub 2020; Nov 5)

13.5 Book chapters / Theses

Constant C, Calabro L, Metsemakers W-J, Richards RG, Moriarty TF. Preclinical models of infection in bone and joint surgery. in: Zimmerli W, editor. Bone and joint infections: from microbiology to diagnostics and treatment. Second Edition. Wiley; 2021. p. 99-115

Barcik JP. Modulation of fracture mechanical conditions and feedback approach to determine the optimal healing environment. 2021 Bulgarian Academy of Sciences Sofia (L Drenchev, S Todorov, B Gueorguiev) – PhD

Schader JF. Standardized artificially created stable pertrochanteric femur fractures present more homogenous results compared to osteotomies for orthopaedic implant testing. 2021 Universität Basel (K Stoffel, B Gueorguiev) – MD

Stenger VH. Is a block of the femoral and sciatic nerves an alternative to epidural analgesia in sheep undergoing orthopaedic hind limb surgery? A prospective, randomized, double blinded, experimental trial. 2021 University of Bern / Vetsuisse (H Rohrbach) – DVM

Vainieri ML. Towards cartilage regeneration: biomaterial-assisted cell-free approach in a physiological joint-like environment. 2021 Erasmus University Rotterdam (G van Osch, S Grad) – PhD

Antonacci P. Cartilage and subchondral bone visualization and quantification with contrast enhanced computed tomography. 2021 Politecnico di Torino (K Mys, B Gueorguiev) – MSc

Eglauf J. 3D *in vitro* model to investigate the role of annulus fibrosus tissue in intervertebral disc nerve ingrowth. 2021 ETH Zürich (T Serra, J Ma, M Zenobi-Wong) – MSc ETH HAST

Jörimann T. Effect of strain on mesenchymal stem cell differentiation: A bioreactor *in vitro* study 2021 ETH Zürich (S Verrier, K Maniura) – MSc ETH HST

Nüesch A. The influence of mesenchymal stromal cells secretome on nucleus pulposus cells exposed to a proinflammatory environment. 2021 ETH Zürich (Z Li, S Grad, S Ferguson) – MSc ETH HAST

Remppis M. Postoperative shoulder activity tracking of patients with proximal humerus fractures treated with locking plates 2021 University of Stuttgart (P Varga, O Röhrle, B Gueorguiev) – MSc

Tenisch L. Prediction of mechanical failure in proximal humerus fracture fixations using patient-specific FE analyses 2021 ETH Zürich (P Varga, SJ Ferguson) – MSc ETH BME

Wolfisberg C. Interpretability of implant load regarding fracture healing progression based on finite element modelling and fracture monitor measurements 2021 ETH Zürich (M Ernst, J Snedeker) – MSc ETH HST

13.6 Abstracts published in journals

Ahrend MD, Noser H, Shanmugam R, Kamer L, Burr F, Hügli H, Zaman TK, Richards RG, Gueorguiev B. Evidence-based generic asian pelvic bone models for research, development, and teaching using CT-based 3D statistical modelling. Orthopaedic Proceedings. 2021;103-B(Suppl 4):12 (EORS 2019 / oral)

Barcik J, Ernst M, Freitag L, Dlaska CE, Drenchev L, Todorov S, Gueorguiev B, Skulev H, Zeiter S, Epari D, Windolf M. Automated electromechanical system designed to investigate the effect of local mechanical conditions on fracture healing progression. Orthopaedic Proceedings. 2021;103-B(Suppl 4):7 (EORS 2019 / oral)

Barcik J, Ernst M, Balligand M, Dlaska CE, Drenchev L, Todorov S, Gueorguiev B, Skulev H, Zeiter S, Epari D, Windolf M. Continuous monitoring of fracture healing to analyze short-term response of bone repair tissue to mechanical stimulation. Orthopaedic Proceedings. 2021;103-B(Suppl 4):11 (EORS 2019 / oral)

Gallazzi E, Sanchez Rosenberg G, Galbusera F, Varga P, Gueorguiev B, Alini M, Schirò GR, Giorgi PD, Cina A. Artificial intelligence can accurately and reliably detect traumatic thoracolumbar fractures on sagittal radiographs. Brain and Spine. 2021;1(Suppl 1):100046 (2021 EuroSpine / oral)

Gomez-Sierra MA, Lackington WA, Alini M, Thompson K. Local non-viral gene delivery to immunomodulate and enhance fracture healing. Orthopaedic Proceedings. 2021;103-B(Suppl 4):13 (EORS 2019 / oral)

Hofmann-Fliri L, Epari D, Schwyn R, Zeiter S, Windolf M. Biphasic plating: *In vivo* study on a novel fixation concept to enhance mechanobiological fracture healing. Orthopaedic Proceedings. 2021;103-B(Suppl 4):14 (EORS 2019 / oral)

Hofstee MI, Riool M, Thompson K, Stoddart MJ, Zaat SAJ, Moriarty TF. A novel 3D *in vitro* model for osteomyelitis-associated staphylococcal abscess communities. Orthopaedic Proceedings. 2021;103-B(Suppl 4):20 (EORS 2019 / oral)

Jansen JU, Teixeira GQ, Vernengo A, Grad S, Neidlinger-Wilke C, Wilke H-J. Chondroitinase *versus* papain digestion leads to different outcome for *in vitro* simulation of degenerated discs. Brain and Spine. 2021;1(Suppl 1):100008 (2021 EuroSpine / oral)

Lodde M, Katthagen C, Schopper C, Zderic I, Richards RG, Gueorguiev B, Riesenbeck O, Raschke M, Hartensuer R. Biomechanical comparison of two fixation techniques for B2 fractures of the sacrum according to the AO Spine sacral classification system. Global Spine J. 2021;11(2 Suppl):145S (Global Spine Congress / oral)

Makelov B, Silva JD, Apivatthakakul T, Gueorguiev B, Varga P. Externalized locked plating of unstable proximal tibial fractures can provide sufficient stability under partial weightbearing: A finite element study. Orthopaedic Proceedings. 2021;103-B(Suppl 4):22 (EORS 2019 / oral)

Mischler D, Schader JF, Windolf M, Varga P. Improving fixation techniques of proximal humerus fractures by means of finite element analysis. Orthopaedic Proceedings. 2021;103-B(Suppl 4):19 (EORS 2019 / oral)

Penev P, Zderic I, Qawasmi F, Mosheiff R, Knobe M, Krause F, Richards RG, Raykov D, Gueorguiev B, Klos K. Influence of different lisfranc ligament injuries on CT findings. Orthopaedic Proceedings. 2021;103-B(Suppl 4):6 (EORS 2019 / oral)

Schopper C, Zderic I, Menze J, Muller D, Rocci M, Knobe M, Shoda E, Richards RG, Gueorguiev B, Stoffel K. Better stability and more predictive fixation of the femoral neck system *versus* two Hansson pins in Pauwels II femoral neck fractures: a biomechanical study. Orthopaedic Proceedings. 2021;103-B(Suppl 4):23 (EORS 2019 / oral)

Wangler S, Kamali A, Wapp C, Wuertz-Kozak K, Häckel S, Fortes C, Benneker LM, Haglund L, Richards RG, Alini M, Peroglio M, Grad S. Mesenchymal stem cell secretome: a potential anabolic and immunomodulatory therapy for early intervertebral disc degeneration. Global Spine J. 2021;11(2 Suppl):102S-3S (Global Spine Congress / oral)

13.7 Abstracts (conference presentations)

Alig G, D'Este M, Grad S, Alini M, Vernengo A. Temperature-responsive engineered matrices for the spatial positioning and long-term culture of bioprinted cells. 2021 BIOFAB online (poster)

Arand C, Wagner D, Kamer L, Gehweiler D, Noser H, Handrich K, Rommens P. Pelvic incidence und acetabuläre Orientierung - eine Subgruppenanalyse basierend auf einem 3D statistischen Modell des Beckenrings. 2021 DKOU (oral)

Bagnol R, Sprecher C, Peroglio M, Chevalier J, Ligier O, Mahou R, Büchler P, Richards RG, Eglin D. Coaxial micro-extrusion of a calcium phosphate ink with aqueous solvents improves printing stability, structure fidelity and mechanical properties. 2021 ESBiomat virtual (poster)

Barcik J, Ernst M, Buchholz T, Constant C, Zeiter S, Gueorguiev B, Windolf M. *In vivo* preclinical application of an active fixator system for the systematic investigation of the influence of the mechanical environment on fracture healing. 2021 EORS (oral)

Basoli V, Li Z, Traweger A, Sanchez J, Plank C, Rip J, Alini M, Grad S. Effect of nanoparticle-based mRNA delivery on modulation of inflammation in an osteochondral inflammation model. 2021 OARSI Connect virtual (poster)

Burkhard B, Schopper C, Ciric D, Mischler D, Gueorguiev B, Varga P. Pilot hole overdrilling increases screw perforation risk in locked plating of complex proximal humerus fractures. 2021 ES Biomech online (poster)

Constant C, Zderic I, Arens D, Pugliese B, Gehweiler D, Gueorguiev-Rüegg B, Zeiter S. Improved biomechanical properties of modified 5.5mm cortex screw with larger head size in an equine lateral condylar fracture model. 2021 ACVS surgery summit virtual (oral)

Coppola GA, Onsea J, Moriarty TF, Nehrbass D, Constant C, Zeiter S, Aktan MK, Braem A, Van der Eycken EV, Steenackers HP, Metsemakers W-J. An improved 2-aminoimidazole based anti-biofilm coating for orthopedic implants: activity, stability, and *in vivo* biocompatibility. 2021 ES B virtual (poster)

Cui S, Li W, Teixeira G, Neidlinger-Wilke C, Wilke H-J, Richards RG, Alini M, Grad S, Li Z. Neoepitope peptides biomarker for different types of intervertebral disc degeneration. 2021 ORS virtual (oral)

Della Bella E, Ahmad P, Buetti-Dinh A, Licandro G, Basoli V, Alini M, Stoddart M. Dexamethasone: a friend or a foe in osteogenic differentiation of human BMSCS? 2021 TERMIS world congress digital (poster)

Della Bella E, Menzel U, Basoli V, Tourbier C, Alini M, Stoddart MJ. Dexamethasone regulates circular RNA expression during human bone marrow mesenchymal stromal cells differentiation. 2021 TERMIS world congress digital (poster)

de Mesy Bentley KL, Galloway CA, Muthukrishnan G, Echternacht SR, Masters EA, Zeiter S, Leckenby JI, Schwarz EM. Emerging methods for 3-dimensional volume interrogation of *Staphylococcus aureus* pathogenesis in the osteocyte canalicular network. 2021 ORS virtual (oral)

De Oliveira S, Miklosic G, D'Este M, Hélary C. Collagen/hyaluronan polyionic complexes as a new building block to develop a bioink for muskulo-skeletal applications. 2021 eCM cancelled (poster) / abstract published

D'Este M, Schwab A, Eglin DO, Staubli F. Micro-extrusion induced orientation of collagen fibrils embedded in hyaluronan and bioinks chondrogenic property. 2021 ES Biomat virtual (oral)

D'Este M, Beninatto R, Di Lucia A, Staubli F, Schwab A, Galesso D, Pavan M. Printability and cytocompatibility of a photo-initiator-free bioink based on coumarin-modified hyaluronic acid and gelatin. 2021 TERMIS world congress digital (poster)

Di Marzio N, Ananthanarayanan P, Guex AG, Alini M, Riganti C, Serra T. Saturn-like vascularized tumor model: combining spheroid with a ring-shaped microvasculature by using sound. 2021 BIOFAB online (oral)

Di Marzio N, Ananthanarayanan P, Guex AG, Alini M, Riganti C, Serra T. Saturn-like vascularized tumor model: combining spheroid with a ring-shaped microvasculature by using sound 2021 SSB+RM YSS (poster)

Egger S, Alig G, D'Este M, Grad S, Alini M, Vernengo A. Temperature-responsive engineered matrices for spatial positioning and long-term culture of bioprinted cells. 2021 eCM cancelled (poster) / abstract published

Eglin D, Sprecher C, Marquette C, Courtial EJ. Toward core-shell 3D printed photonic strain sensing medical device. 2021 ES Biomat virtual (poster)

Eglin D, Sprecher C, Marquette C, Courtial EJ. Liquid crystal hydroxylpropyl cellulose-silicon 3D printed photonic strain sensing structure. 2021 eCM cancelled (poster) / abstract published

Di Marzio N, Ananthanarayanan P, Guex AG, Alini M, Riganti C, Serra T. Development of a 3-dimensional vascularized cancer model via sound induced morphogenesis (SIM). 2021 TERMIS world congress digital (poster)

Fleischhacker E, Milz S, Sprecher C, Gleich J, Siebenbürger G, Helfen T, Böcker W, Ockert B. Posttraumatische Schultersteife nach winkelstabiler Plattenosteosynthese proximaler Humerusfrakturen. Hat das Implantatmaterial einen Einfluss? 2021 DKOU (oral)

Gueorguiev B, Zderic I, Blauth M, Weber A, Koch R, Dauwe J, Schader J, Stoffel K, Finkemeier C, Hessmann M. Angular stable locking in a novel intramedullary nail improves construct stability in a distal tibia fracture model. 2021 GOMTS virtual (poster)

Gueorguiev B. Nonunions - just a biomechanical problem? 2021 EORS (oral)

Gueorguiev B, Zderic I, Pastor T, Gehweiler D, Richards RG, Knobe M. Double plating of unstable distal femoral fractures: Is augmented lateral plating with a helically shaped medial plate biomechanically advantageous over a straight medial plate? 2021 EORS (oral)

Guex AG, Di Marzio N, Alini M, Serra T. Sound waves and biomaterials to re-create the extracellular matrix. 2021 TERMIS world congress digital (poster)

Guex AG, Mecchi L, Alini M, Serra T. Spatial control over cell assembly by sound: towards a vascularized *in vitro* engineered osteochondral tissue. 2021 eCM cancelled (poster) / abstract published

Guillaume O, Geven MA, Varjas V, Varga P, Grijpma DW, Eglin D. 3D printing of osteoinductive and patient specific implant for CMF repair. 2021 eCM cancelled (poster) / abstract published

Guo P, Vernengo A, Miklosic G, D'Este M, Grad S, Alini M, Li Z. A natural biomimetic hydrogel for cartilage regeneration. 2021 SSB+RM YSS (oral)

Guo P, Mini C, Miklosic G, Vernengo A, D'Este M, Grad S, Alini M, Li Z. A hydrogel based on decellularized extracellular matrix particles for cartilage regeneration. 2021 eCM cancelled (oral) / abstract published

Häckel S, Häne S, Eglauf J, Ma J, Li Z, Pfannkuche JJ, Peroglio M, Hoppe S, Benneker LM, Lang GM, Alini M, Grad S. Can the COX-2 inhibitor Celecoxib influence discogenic pain signals? An *in vitro* study with inflamed annulus fibrosus cells. 2021 ORS virtual (oral)

Häckel S, Häne S, Eglauf J, Ma J, Li Z, Pfannkuche JJ, Peroglio M, Hoppe S, Benneker LM, Lang GM, Alini M, Grad S. Can the COX-2 inhibitor Celecoxib influence discogenic pain signals? An *in vitro* study with inflamed annulus fibrosus cells. 2021 ISSLS virtual (poster)

Häckel S, Häne S, Eglauf J, Ma J, Pfannkuche J, Hoppe S, Albers C, Grad S. Die modulierende Wirkung des Cyclooxygenase-2 Inhibitors Celecoxib auf diskogenen Schmerz - eine *in vitro* Studie mit humanen Annulus fibrosus Zellen. 2021 DKOU (oral)

Hadzhinikolova M, Zderic I, Ciric D, Barcik J, Enchev D, Rusimov L, Richards RG, Gueorguiev B, Baltov A, Rashkov M. How many screws are necessary for plate fixation of the dorsoulnar fragment? 2021 BOTA (poster)

Hatt LP, Wirth S, Thompson K, Mys K, Gehweiler D, Eglin D, Stoddart MJ, Armiento AR. LEGO®-inspired microporous scaffolds for personalized mandibular bone repair. 2021 TERMIS world congress digital (oral)

Hatt LP, Wirth S, Ristaniemi A, Thompson K, Eglin D, Stoddart MJ, Armiento AR. LEGO®-inspired microporous scaffolds for personalized mandibular bone repair. 2021 eCM cancelled (oral) / abstract published

Hofstee MI, Riool M, Terjajevs I, Thompson K, Stoddart MJ, Zaat SAJ, Moriarty T.F. A 3-dimensional *in vitro Staphylococcus aureus* abscess community model. 2021 KNVM & NVMM virtual (oral)

Kluser N, Sprecher C, Häckel S, Albers C, Li Z, Alini M, Grad S, Eglin D, Vernengo A. 3D printed annulus fibrosus tissue engineering scaffolds with multiscale, uniaxial surface topographies that promote the spatial control of cell density and alignment. 2021 ORS virtual (oral)

Hofstee MI, Riool M, Gieling F, Stenger V, Constant C, Nehrbass D, Heider A, Zeiter S, Richards RG, Zaat SAJ, Moriarty TF. *Staphylococcus aureus* abscess communities and myeloid-derived suppressor cells: *in vivo* and *in vitro* studies. 2021 WIRM digital (oral)

Kluser N, Sprecher C, Häckel S, Alini M, Grad S, Eglin D, Vernengo A. 3D printed scaffolds with multiscale surface topography inducing three-dimensional cell patterning. 2021 eCM cancelled (poster) / abstract published

Lackington WA, Gehweiler D, Zderic I, Nehrbass D, Zeiter S, González-Vázquez A, O'Brien F, Stoddart M, Thompson K. IL-1 receptor antagonist enhances rhBMP-2-induced new bone formation during femoral fracture healing in rats. 2021 ES Biomat virtual (oral)

Lackington WA, Gehweiler D, Zderic I, Nehrbass D, Zeiter S, González-Vázquez A, O'Brien FJ, Stoddart MJ, Thompson K. IL-1Ra enhances rhBMP-2-induced new bone formation during femoral fracture healing. 2021 eCM cancelled (poster) / abstract published

Li Z, Zhang P, Basoli V, Alini M, Grad S. *In vitro* and *ex vivo* screening of small molecule therapeutics for osteoarthritis. 2021 TERMIS world congress digital (poster)

Lodde MF, Raschke MJ, Hartensuer R, Katthagen C, Schopper C, Zderic I, Richards RG, Gueorguiev B. Führt die Augmentation der perkutanen Iliosakralschraube zu besseren biomechanischen Ergebnissen für die Fixierung des hinteren Beckenrings? Does cement augmentation of the sacroiliac screw lead to superior biomechanical results for fixation of the posterior pelvic ring? 2021 DWK (oral)

Ma J, Eglauf J, Alini M, Serra T. Spatial orchestration of large animal DRG multicellular system using sound. 2021 BIOFAB online (oral)

Marani E, Ma J, Alini M, Serra T. Sound induced multicellular system of dorsal root ganglion cells. 2021 eCM cancelled (poster) / abstract published

Miklosic G, Hélary C, Ferguson SJ, D'Este M. Dense extracellular matrix derivatives for the bioprinting of nucleus pulposuslike structures. 2021 ES Biomat virtual (poster)

Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Extracellular matrix-based biomaterial ink for the printing of nucleus pulposus-like structures. 2021 eCM cancelled (oral) / abstract published

Makelov B, Dimitrov N, Raykov D, Gueorguiev B. Initial clinical results following one-stage externalized locked plating of multifragmentary proximal tibia fractures 2021 BOTA (oral)

Mecchi L, Guex AG, Alini M, Serra T. Sound induced morphogenesis: chondrogenic differentiation of hMSC driven by acoustic stimulation. 2021 SSB+RM YSS (poster)

Miklosic G, Hélary C, Ferguson SJ, D'Este M. Extracellular matrix-based bioink for the printing of nucleus pulposus analogues. 2021 BIOFAB online (poster)

Mischler D, Schopper C, Gasparri M, Schulz-Drost S, Brace M, Gueorguiev B. Biomechanical human cadaveric investigation of intrathoracic *versus* extrathoracic rib fracture plating. 2021 GOMTS virtual (poster)

Mischler D, Schader J, Dauwe J, Gueorguiev B, Varga P. Computationally optimized implants improve biomechanical fixation stability of complex proximal humerus fractures. 2021 ES Biomech online (oral)

Muller Q, Josseline R, van der Heide D, Le-Meins J-F, Garbay B, Stoddart MJ, D'Este M, Amédée J, Oliveira H. Fabrication of hyaluronan-based matrices functionalized with laminin derived peptides, to sustain cellular adherence and axonal growth in bone regeneration applications. 2021 ES Biomat virtual (poster)

Mys K, Stockmans F, Gueorguiev B, Neumann V, Wyers CE, van den Bergh JPW, van Lenthe GH, Varga P. Trabecular microstructure can be quantified with Xtremect more accurately using adaptive thresholding. 2021 ES Biomech online (oral)

Nüesch A, Chen Z, Wangler S, Li Z, Grad S. The influence of mesenchymal stromal cells secretome on nucleus pulposus cells exposed to a proinflammatory environment. 2021 SSB+RM YSS (poster)

Palladino S, Schwab A, Copes F, D'Este M, Candiani G, Mantovani D. Bioink from collagen and hyaluronic acid: design and characterization of a cardiovascular-specific formulation for 3D bioprinting. 2021 SSB+RM YSS (poster)

Palladino S, Schwab A, D'Este M, Copes F, Candiani G, Mantovani D. Innovative bioink from collagen and hyaluronic acid with tunable rheological and biological properties for cardiovascular 3D bioprinting. 2021 TERMIS world congress digital (oral)

Palladino S, Schwab A, Copes F, D'Este M, Candiani G, Mantovani D. Composite collagen/hyaluronic acid bioink guiding anisotropic *in vitro* vascular network formation. 2021 eCM cancelled (poster) / abstract published

Panagiotopoulou V, Ovesy M, Gueorguiev B, Richards RG, Zysset P, Varga P. Prediction of screw perforation in the proximal humerus using micro finite element analyses. 2021 ES Biomech online (oral)

Pastor T, Zderic I, Gehweiler D, Knobe M, Gueorguiev B. Biomechanical analysis of recently released cephalomedullary nails for trochanteric femoral fracture fixation in a human cadaveric model. 2021 GOMTS virtual (poster)

Pastor T, Zderic I, Gehweiler D, Knobe M, Gueorguiev B. Biomechanical analysis of recently released cephalomedullary nails for trochanteric femoral fracture fixation in a human cadaveric model. 2021 EFORT virtual (poster)

Pastor T, Zderic I, Gehweiler D, Knobe M, Gueorguiev B. Biomechanical analysis of cephalomedullary nails for trochanteric femoral fracture fixation. 2021 ES Biomech online (oral)

Pastor T, Zderic I, Gehweiler D, Richards RG, Knobe M, Gueorguiev B. Biomechanical analysis of recently released cephalomedullary nails for trochanteric femoral fracture fixation in a human cadaveric model. 2021 EORS (oral)

Pastor T, Zderic I, Richards RG, Gueorguiev B, Knobe M. Medial helical *versus* lateral straight plating of distal femoral fractures. A biomechanical comparative study. 2021 EORS (oral)

Pastor T, Zderic I, Gehweiler D, Richards RG, Gueorguiev B, Knobe M. Biomechanische Analyse von Marknägeln zur Fixierung von pertrochantären Femurfrakturen. 2021 DKOU (poster)

Richards RG, Ernst M. Digitalized aftercare in orthopaedics. 2021 DDF virtual (oral)

Richards RG, Moriarty TF, D'Este M. Novel antimicrobial approaches to prevent orthopedic devicerelated infection. 2021 EORS (oral)

Sanchez Rosenberg G, Cina A, Giorgi P, Schiro G, Gueorguiev B, Alini M, Varga P, Galbusera F, Gallazzi E. Artificial intelligence accurately detects traumatic thoracolumbar fractures on sagittal radiographs. 2021 EORS (oral)

Saravi B, Basoli V, Alini M, Grad S, Südkamp N, Schmal H, Li Z, Lang G. Angiotensin II type 1, type 2, and MAS receptors are present in human nucleus pulposus cells and associated with inflammatory processes. 2021 DKOU (oral)

Saravi B, Pfannkuche J, Häckel S, Alini M, Grad S, Südkamp N, Schmal H, Kubosch D, Li Z, Lang G. Losartan suppresses TNF-alpha induced inflammatory response and degeneration of human nucleus pulposus cells. 2021 TERMIS world congress digital (oral)

Schader JF, Mischler D, Dauwe J, Gueorguiev B, Varga P. Could patient-specific locking plates improve primary stability of proximal humerus fracture fixation? 2021 ES Biomech online (oral)

Schader JF, Zderic I, Dauwe J, Sommer C, Gueorguiev B, Stoffel K. Old battle with new implant systems – biomechanical comparison of intramedullary *versus* extramedullary fixation concepts of stable pertrochanteric fractures. 2021 DKOU (poster)

Schwab A, Staubli F, Eglin D, D'Este M. 3D Bioprinting of a tissue mimetic hyaluronan bioink containing collagen fibers with controlled orientation. 2021 EuroMat virtual (oral)

Schwab A, Eglin D, Helary C, Alini M, D'Este M. Chondrogenic hyaluronan bio-ink containing collagen fibers with controlled orientation modulating cell orientation and morphology. 2021 BIOFAB online (oral)

Schwab A, Staubli F, Eglin D, D'Este M, editors. Effect of biomaterial composition on MSC chondrogenesis embedded in a hyaluronan composite containing collagen fibrils. 2021 TERMIS world congress digital (oral)

Schwab A, Wesdorp MA, Loebel C, Levato R, Burdick JA, Malda J, Stoddart M, van Osch GJVM, Eglin D, D'Este M. *Ex vivo* migration of chondrocytes - cell invasion into acellular biomaterials filled in a cartilage ring model is dependent on biomaterial composition. 2021 TERMIS world congress digital (oral)

Serra T. Sound waves for the assembly and control of tissues organization. 2021 eCM cancelled (oral) / abstract published

Siverino C, Freitag L, Arens D, Eberli U, Stadelmann V, Richards RG, Stoddart MJ, Moriarty TF, Thompson K. Titanium wear particles exacerbate implant-related osteolysis and decrease efficacy of antibiotic therapy. 2021 WIRM digital (poster)

Soubrier A, Kasper H, Alini M, Jonkers I, Grad S. Traction to optimize intervertebral disc mechanobiology: A bovine organ model feasibility study. 2021 EORS (oral)

Staubli F, Stoddart M, D'Este M, Schwab A. Mesenchymal stromal cell spheroids – effect of cell packing and biomaterial composition on chondrogenic differentiation *in vitro*. 2021 EORS (oral)

Stoddart M. Mechanisms of bone regeneration. 2021 WIRM digital (oral)

Stoddart M. Regenerative rehabilitation: from proteins to patients. 2021 TERMIS world congress digital (oral)

Sturm L, Schwemberger B, Geiger J, Manish A, Dewi HS, Engbersen J, Rip J, Alini M, Traweger A, Grad S, Basoli V. Comparison of different transfection methods for mRNA delivery in articular joint cells. 2021 TERMIS world congress digital (poster)

Triana M, Gueorguiev B, Sommer C, Stoffel K, Agarwal Y, Zderic I, Helfen T, Krieg JC, Krause F, Knobe M, Richards RG, Lenz M. LagLoc - a new surgical technique for locking plate systems. 2021 OTA (poster)

van der Heide D, Della Bella E, Yuan H, De Groot-Barrère F, Stoddart MJ, D'Este M. Composite biomaterial-ink based on hyaluronan and nano hydroxyapatite for biofabrication of bone graft substitutes delivering chemically modified RNAs. 2021 ES Biomat virtual (oral)

van der Heide D, Della Bella E, Yuan H, De Groot-Barrère F, Stoddart MJ, D'Este M. Biofabrication of bone graft substitutes using a composite biomaterialink based on hyaluronan and nano hydroxyapatite for delivering chemically modified RNAs. 2021 BIOFAB online (oral)

van der Heide D, De Groot-Barrère F, Stoddart MJ, D'Este M. A composite biomaterial-ink based on hyaluronan and nano hydroxyapatite delivering chemically modified RNA for bone regeneration. 2021 TERMIS world congress digital (poster)

van der Heide D, Della Bella E, Yuan H, De Groot-Barrère F, Stoddart MJ, D'Este M. Composite hyaluronic acid and calcium phosphate biomaterial ink for the delivery of chemically modified RNAs for bone regeneration. 2021 eCM cancelled (poster) / abstract published

Vernengo A, Kluser N, Soubrier A, Gewiess J, Jansen JU, Neidlinger-Wilke C, Wilke H-J, Li Z, Alini M, Grad S. The influence of dynamic physiological loading on an enzyme-induced *ex vivo* model of intervertebral disc degeneration. 2021 TERMIS world congress digital (poster)

Wallimann A, Magrath W, Thompson K, Pugliese B, Akdis CA, Richards RG, Hernandez CJ, O'Mahony L, Moriarty TF. Butyrate and antibiotics affect local and systemic processes relevant for bone healing. 2021 WIRM digital (poster)

Wallimann A, Magrath W, Thompson K, Pugliese B, Akdis CA, Richards RG, Hernandez CJ, O'Mahony L, Moriarty TF. Short-chain fatty acids and antibiotics affect local and systemic processes relevant for bone healing. 2021 World Microbe Forum online (poster)

Wallimann A, Magrath W, Thompson K, Pugliese B, Akdis CA, Richards RG, Hernandez CJ, O'Mahony L, Moriarty TF. Short-chain fatty acids and antibiotics affect local and systemic processes relevant for bone healing. 2021 Gut-Bone Axis Meeting virtual (oral)

Wallimann A, Magrath W, Thompson K, Pugliese B, Akdis CA, Richards RG, Hernandez CJ, O'Mahony L, Moriarty TF. Impact of tifampicin levofloxacin on gut microbiome and short-chain fatty acid production in mice with bone fracture: consequences for bone health. 2021 ECCMID online (poster)

Wangler S, Kamali A, Wapp C, Wuertz-Kozak K, Häckel S, Fortes C, Benneker LM, Haglund L, Richards RG, Alini M, Peroglio M, Grad S. Mesenchymal stem cell secretome: a potential anabolic and immunomodulatory therapy for modulation of early intervertebral disc degeneration. 2021 ORS virtual (oral)

Weber L, Beninatto R, Di Lucia A, Staubli F, Schwab A, Galesso D, Pavan M, D'Este M. A photoinitiator-free hyaluronan bioink with high modularity and printability. 2021 eCM cancelled (poster) / abstract published

Wenzel L, Sandriesser S, Glowalla C, Gueorguiev-Rüegg B, Perl M, Stuby F, Augat P, Hungerer S. Kranial verankerte Pfanne oder Platte und Pfanne bei Azetabulumfrakturen des vorderen Pfeilers? Ein biomechanischer Vergleich. 2021 DKOU (oral)

Wesdorp MA, Schwab A, Eglin D, Narcisi R, van Osch GJVM, D'Este M. A culture model to analyze the acute biomaterial-dependent reaction of human primary neutrophils. 2021 eCM cancelled (oral) / abstract published

Zderic I, Caspar J, Blauth M, Weber A, Koch R, Stoffel K, Finkemeier C, Hessmann M, Gueorguiev B. Improved construct stability after angular stable intramedullary nailing of distal tibia fractures – a biomechanical study. 2021 GOMTS virtual (poster)

Zderic I, Caspar J, Blauth M, Weber A, Koch R, Stoffel K, Finkemeier C, Hessmann M, Gueorguiev B, editors. Improved construct stability after angular stable intramedullary nailing of distal tibia fractures. A biomechanical study. 2021 EFORT virtual (oral)

Zderic I, Varga P, Styger U, Drenchev L, Gueorguiev B, Asimus E, Saunders B, Kowaleski M, Boudrieau RJ, Dejardin L. Mechanical evaluation of two hybrid locking plate designs for canine pancarpal arthrodesis. 2021 ECVS online (oral)

Zderic I, Varga P, Styger U, Drenchev L, Gueorguiev B, Asimus E, Saunders B, Kowaleski M, Boudrieau RJ, Dejardin L. Mechanical evaluation of two hybrid locking plate designs for canine pancarpal arthrodesis under fatigue loading. 2021 ECVS online (oral)

Zderic I, Caspar J, Blauth M, Weber A, Koch R, Stoffel K, Finkemeier C, Hessmann M, Gueorguiev B. Improved stability of distal tibia fractures after angular stable intramedullary nailing – a biomechanical study. 2021 ES Biomech online (oral)

Zderic I, Varga P, Styger U, Gueorguiev B, Drenchev L, Asimus E, Saunders B, Kowaleski M, Boudrieau RJ, Déjardin L. In-silico and experimental deformation analysis of two hybrid plate designs for canine pancarpal arthrodesis. 2021 ES Biomech online (oral)

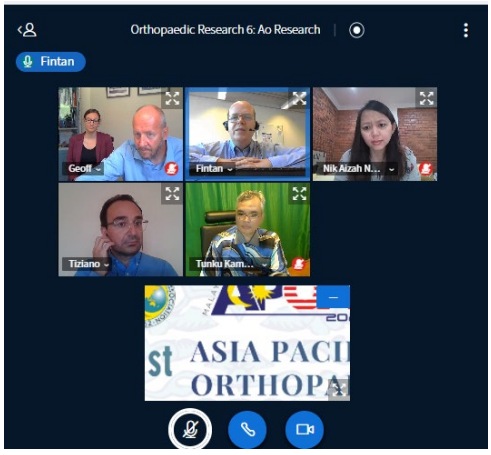
Zderic I, Varga P, Styger U, Gueorguiev B, Drenchev L, Asimus E, Saunders B, Kowaleski M, Boudrieau RJ, Déjardin L. Fatigue life assessment of two hybrid plate designs for canine pancarpal arthrodesis. 2021 ES Biomech online (poster)

Zderic I, Caspar J, Blauth M, Weber A, Koch R, Stoffel K, Finkemeier C, Hessmann M, Gueorguiev B. Angular stable intramedullary nailing improves construct stability in a distal tibia fracture model - a biomechanical study. 2021 EORS (oral)

Zhang P, Basoli V, Wang X, Alini M, Grad S, Li Z. Anti-inflammatory and regenerative effects of small molecules for osteoarthritis – *in vitro* and *ex vivo* evaluation. 2021 ORS virtual (oral)

Zuncheddu D, Siverino C, Rocchitta G, Generelli S, Kurth F, Serra PA, Moriarty TF, Alini M, Grad S, Basoli V. Impact of UV, ethylene oxide and x-ray sterilization on implantable glucose biosensors. 2021 Biosensors online (poster)

Zuncheddu D, Schwab A, Della Bella E, Generelli S, Kurth F, Serra PA, Rocchitta G, Kasper H, Grad S, Basoli V. Development and characterization of a microsensor device for real time oxygen monitoring in 3D tissue engineered constructs. 2021 TERMIS world congress digital (poster)



13.8 Presentations (not in conference proceedings)

28.01.2021	Richards Geoff: Digitalized aftercare in orthopaedics. Davos Digital Forum (Online) (Invited Speaker)
15.-16.04.2021	Richards Geoff: Smart Implants: the AO Fracture Monitor. AOTrauma Online Symposium-Advances in Trauma, Virtual, The Netherlands (Invited Speaker)
30.07.2021	Richards Geoff: Smart surgery with the AO Fracture Monitor. Asia Pacific Orthopaedic Association (APOA) Conference, Kuala Lumpur, Malaysia (Online) (Invited Speaker)
09.11.2021	Richards Geoff: AO Trauma Latin America webinar – Translating basic science into clinical care (Online) (Invited Speaker)
25.03.2021	Alini Mauro: 3D printing technologies for patient specific applications. Riga Stradins University Research Week 2021, Latvia (Online) (Plenary Speaker)
14.06.2021	Alini Mauro: Design and biological response of patient scientific implant for orbital floor bone repair. Scandinavia Society of Biomaterials, Riga, Latvia (Online) (Keynote Speaker)
30.07.2021	Alini Mauro: Preclinical research: Mesenchymal stem cell homing capacity: Implications for intervertebral disc regeneration. Asia Pacific Orthopaedic Association (APOA) Conference, Kuala Lumpur, Malaysia (Online) (Invited Speaker)
15.09.2021	Alini Mauro: 30 years of spine basic research: nothing new on the clinical horizon? European Orthopaedic Research Society (EORS) 29th Annual Meeting, Rome, Italy (Plenary Lecture)
19.11.2021	Alini Mauro: Organ culture and bioreactors for assessing biomaterials (and more) for tissue regeneration. World TERMIS 2021, Maastricht, The Netherlands (Online) (Keynote Lecture)
25.-26.06.2021	Gueorguiev Boyko: Digital trends in the field of traumatology & orthopedics. Eurasian Orthopedic Forum, Moscow, Russia (online) (Invited Speaker)
01.07.2021	Gueorguiev Boyko: Femoral fracture fixation: getting it right first time. Biomechanics and design of intramedullary nails, SICOT-AO Trauma Webinar, Program of Innovative Orthopaedic Networking, e-learning, Education & Research (PIONEER) (Invited Speaker)
15.-17.09.2021	Gueorguiev Boyko: Nonunions – just a biomechanical problem? European Orthopaedic Research Society (EORS), Rome, Italy (Keynote Lecture)
22.09.2021	Gueorguiev Boyko: Digitally-enhanced implant research and development. Seminar "Medical and technical aspects of implant research and development", Golden Sands, Varna, Bulgaria (Invited Speaker)
01.-03.10.2021	Gueorguiev Boyko: Digital trends in the field of traumatology and orthopaedics. 25th Conference of the Bulgarian Orthopaedic and Traumatology Association, Borovets, Bulgaria (Keynote Lecture)
08.10.2021	Gueorguiev Boyko: Digital trends in the field of traumatology and orthopaedics. 6th International Partnerships Forum "60 years of building synergies: education, innovation and partnerships", Medical University Varna, Bulgaria (online) (Invited Speaker)
11.02.2021	Stoddart Martin: Mechanoregulation of human mesenchymal stem cell chondrogenesis. Stanford lecture series (online)

25.02.2021	Stoddart Martin: Regulating human MSC chondrogenic differentiation by mechanics. Lindbergh lecture series, University of Wisconsin-Madison (Online)
12.04.2021	Stoddart Martin: Cartilage Biomechanics. EU ITN project CARTHAGO (Online)
23.04.2021	Stoddart Martin: Mechanically induced MSC chondrogenesis: using movement to drive biological responses. EU Project OActive conference (Online)
27.04.2021	Stoddart Martin: The effect of multiaxial load on cartilaginous constructs. 5th International Conference on BioTribology (Online) (Plenary Lecture)
29.04.2021	Stoddart Martin: Impact and management of the Covid-19 pandemic in research. European Orthopaedic Research Society (EORS) Online webinar series
03.07.2021	Stoddart Martin: Mechanisms of bone regeneration. World Immune Regulation Meeting XV (Online) (Keynote Lecture)
30.07.2021	Stoddart Martin: Current Status of Biological Enhancement of Bone Healing. Asia Pacific Orthopaedic Association (APOA) Conference, Kuala Lumpur, Malaysia (Online) (Invited Speaker)
02.11.2021	Stoddart Martin: History of ARI bioreactors and mechanoregulation research. Online Baltic Biomaterials Centre of Excellence training.
06.11.2021	Stoddart Martin: Challenges and Trends in MSK Regenerative Medicine. Mayo Regenerative Medicine & Surgery Symposium (Online) (Keynote Lecture)
18.11.2021	Stoddart Martin: Regenerative Rehabilitation: from proteins to patients. TERMIS 6th World Congress, Maastricht, The Netherlands (Online) (Invited Speaker)
23.11.2021	Bektas Ezgi: Delivery of small molecules via natural hydrogels for cartilage tissue engineering. Oral presentation. Baltic Biomaterials Centre of Excellence teaming visit. Davos
04.-05.09.2021	Della Bella Elena: Controversial role of dexamethasone on mesenchymal stem cells differentiation toward osteogenesis and chondrogenesis. 17th Royan International Virtual Congress on Stem Cell Biology and Technology, Teheran, Iran (Online) (Invited Speaker)
26.10.2021	D'Este Matteo: Journal Club: why and how to run it. Online Baltic Biomaterials Centre of Excellence training
01.11.2021	D'Este Matteo: Biomaterials for skeletal repair: general principles. Online Baltic Biomaterials Centre of Excellence training
03.11.2021	D'Este Matteo: Hydrogels for skeletal repair and drug delivery. Online Baltic Biomaterials Centre of Excellence training
17.12.2021	D'Este Matteo: Biomaterials for skeletal repair, polymeric biomaterials. Online Autumn School Advance Fibrous Materials Amirkabir University of Technology, Tehran, Iran
28.01.2021	Ernst Manuela: Digitalized aftercare in orthopaedics. Davos Digital Forum (Online) (Invited Speaker)
30.07.2021	Ernst Manuela: Smart surgery with the AO Fracture Monitor. Asia Pacific Orthopaedic Association (APOA) Conference, Kuala Lumpur, Malaysia (Online) (Invited Speaker)

12.-16.02.2021	Grad Sibylle: Clinical relevance of organ culture models: recent advancements and future perspectives. ORS Spine Section Scientific Meeting, ORS Annual Meeting (Online) (Invited Speaker)
14.-18.06.2021	Grad Sibylle: Mechanical regulation of cartilage repair: relevance for tissue engineering and rehabilitation. RME/WSCS Regenerative Rehabilitation Symposium, Wake Forest School of Medicine, Winston-Salem, NC, USA (Online) (Invited Speaker)
29.-31.07.2021	Grad Sibylle: Multi-disciplinary approaches for cell-based cartilage regeneration. 21st Congress of the Asia Pacific Orthopaedic Association, 2021, Kuala Lumpur, Malaysia (Online) (Invited Speaker)
04.-05.09.2021	Grad Sibylle: Chondrocyte- and stem cell-based cartilage regeneration: effect of biomaterial and biomechanics. 17th Royan Congress, Teheran, Iran (Online) (Invited Speaker)
15.-17.09.2021	Grad Sibylle: Clinical relevance of whole intervertebral disc organ models. Symposium lecture, EORS 29th Annual Meeting, Rome, Italy
07.-09.10.2021	Grad Sibylle: Mesenchymal stromal cells for regeneration of the intervertebral disc. 6th ISIAT Congress, Krakow, Poland (hybrid)
15.-17.12.2021	Grad Sibylle: Bioreactor controlled cell and tissue models for cartilage regeneration. Société Francophone d' Arthroscopie SFA Meeting, Geneva, Switzerland
08.06.2021	Li Zhen: Osteochondral explant *ex vivo* models for the investigation of joint pathology and therapy. Swiss Bone and Mineral Society Annual Meeting (Online) (Invited Speaker)
04.12.2021	Miklosic Gregor: Extracellular matrix-based biomaterial ink for the printing of nucleus pulposus-like structures. Oral presentation. Baltic Biomaterials Centre of Excellence teaming visit. Davos
01.04.2021	Moriarty Fintan: Preclinical models of implant related bone infection suitable for testing antimicrobial interventions. Presented to Faculty of Medicine, Dentistry and Health, The University of Sheffield
30.07.2021	Moriarty Fintan: Fracture related infection latest research results at ARI. Asia Pacific Orthopaedic Association (APOA) Conference, Kuala Lumpur, Malaysia (Online) (Invited Speaker)
29.10.2021	Moriarty Fintan: Local antibiotic therapy for the treatment of chronic MRSA osteomyelitis. Presented to the joint working party (Arbeitsgruppe) Infection of the Swiss Society of Orthopedic Surgery (swissorthopaedics) and the Swiss Society of Infectious Diseases
29.10.2021	Moriarty Fintan: Systemic antibiotic therapy for the treatment of osteomyelitis and impact on bone health. Presented to the joint working party (Arbeitsgruppe) Infection of the Swiss Society of Orthopedic Surgery (swissorthopaedics) and the Swiss Society of Infectious Diseases
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11.11.2021	Moriarty Fintan: Fracture-related infection - role of implant material and biomechanical stability. Presented at symposium “Advancing the interface: biomaterials & regenerative cells", for the MATEGRA: Enhanced porous biomaterials functionalized with stem cells for improved osteointegration of implants consortium.
29.11.2021	Moriarty Fintan: Bacteriophage and phage-based interventions to address musculoskeletal infection. Webinar for the Department of Research, Innovation & Technology (RIT) Rizzoli Institute Bolgna, Italy
29.-31.07.2021	Serra Tiziano: 3D printing for orthopaedics: biofabrication repair solutions. Asia Pacific Orthopaedic Association (APOA) Conference, Kuala Lumpur, Malaysia (Online) (Invited Speaker)
25.08.2021	Serra Tiziano: mimiX Biotherapeutics. Presentation of the sound wave biofabrication technology, ZHAW, Wädenswil, Switzerland
04.-05.09.2021	Serra Tiziano: Sound-induced morphogenesis of multicellular systems for rapid orchestration of vascular networks. 17th International Congress on Stem Cell Biology & Technology, Teheran, Iran (Online) (Invited Speaker)
15.-19.11.2021	Serra Tiziano: Sound patterns as a novel biofabrication platform. TERMIS 6th World Congress, Maastricht, The Netherlands (Online) (Keynote Speaker)
24.11.2021	Serra Tiziano: A sound waves-based platform for 3D cancer model development. 33rd AICC Annual Conference: International Meeting on Cancer Metabolism, Torino, Italy (Invited Speaker)
03.-05.12.2021	Serra Tiziano: Sound waves for the assembly and control of tissues organization. eCM XX Conference: Biofabrication for Orthopaedics, Davos, Switzerland (Keynote Speaker)
28.01.2021	van der Heide Daphne: 3D-Printed Matrix with Calcium Phosphate and Chemically Modified RNAs for Bone Regeneration of Trauma and Osteoporotic Patients. SYRN Swiss Young Researchers Network, Webinar
12.07.2021	Varga Peter: Pilot hole overdrilling increases screw perforation risk in locked plating of complex proximal humerus fractures. 26th Congress of the European Society of Biomechanics (ESB) (Online) (Invited Speaker)
14.07.2021	Varga Peter: Could patient-specific locking plates improve primary stability of proximal humerus fracture fixation? 26th Congress of the European Society of Biomechanics (ESB) (Online) (Invited Speaker)
09.2021	Vernengo Andrea: Hydrogels and bioadhesives: Tools for tissue repair. RiseUs2 Winter School, Riga, Latvia
11.2021	Vernengo Andrea: Essentials of biofabrication for musculoskeletal repair. Biomaterials course, The Cooper Union, New York, NY, USA
25.11.2021	Wychowaniec Jacek: Importance of molecular interactions in controlled molecules delivery. Oral presentation. Baltic Biomaterials Centre of Excellence teaming visit. Davos

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