# Research Institute Davos

## ARI Activity Report 2022

Education and research. graubünden

# Contents

# 1 Introduction

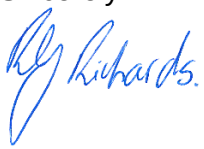
In February, the ARI operations returned to regular pre-COVID pandemic levels. The pandemic still influenced our daily work and collaboration (internal and external), but most conferences and collaboration meetings were again held face to face including our own eCM20 Cartilage and Disc Repair and Regeneration conference in June, Davos. Again, the opportunity during this time to focus on writing scientific publications was taken and resulted in a high number of papers and even a very exceptional average impact factor for 2022 of 7.8. I am also very happy with the public outreach through Swiss Broadcasting Corporation (TV program Einstein and Swissinfo news and videos on AO Courses and ARI).

2021 marked the start of the new HORIZON EUROPE program. Switzerland's status was reverted from 'To Be Associated' to 'a non-associated third country in the Horizon Europe research program' in June. This happened after Switzerland's Federal Council (bypassing the Swiss electorate by triggering an emergency law to enact quick decrees) suddenly unilaterally broke off negotiations on a Swiss-EU framework agreement. Two years after the start of Horizon Europe, the situation is still under discussion. Fortunately, as partial improvement until this situation is resolved, the Swiss State Secretariat for Education, Research, and Innovation (SERI) guaranteed to directly fund our researchers where they are eligible to participate and has introduced transitional measures to cover schemes where our participation is currently excluded. As a non-associated third country, ARI can still participate in the majority of collaborative projects. The Swiss project partner will not be funded by the EC but by SERI. Researchers in Switzerland (including ARI) are no longer eligible for European Research Council, Marie Skłodowska-Curie (MCSA) or European Innovation Council funding. Funding is only part of the picture. The greater loss for Swiss researchers (including ARI) is not being able to work seamlessly in research projects freely with peers across Europe. From this perspective, there is also a loss for researchers in the EU. This could long-term damage our third-party funding at ARI and we would be happier if the Swiss government resumed negotiations with the EU as soon as possible.

Our integrated AO Network Preclinical Research (AO NPR) settled in nicely in the last year and collaborations and streamlining are going extremely well. The continual clinical advice on our research projects from the clinical division research commissions (AO Trauma, AO CMF, AO Spine, AO Vet) is very important to us and interactions with them are so important to keep us in the right direction clinically for improving patient care. We have received translational grants from the AO Development Incubator (Technology Transfer Board) and our collaborations with their team to valorize our R&D projects are so important for AO. Finally, the advice from the ARI AC for all our direct funded projects is invaluable to the direction of our research and knowing when to fail fast rather than flog a dead horse.

I thank the whole ARI team for unwavering dedication to the AO mission, keeping ARI at the cutting edge of science and bringing this knowledge to AO surgeons and operational room personnel all over the world to improve patient care. Our team also trains numerous interns, students, and medical fellows, which is so important for the future. The fellows' reports show how they have loved their time here, which can be attributed to the highly motivated team of the ARI, and the great atmosphere within ARI. We are also proud to have the least turnover of permanent employees, showing not only AO is a good employer, but stability in our leadership throughout ARI. Our employees are important to us.

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

To further the AO's mission, ARI advances innovation in orthopedics through translational research and development.

*Orthopedics concerns musculoskeletal, spine, and craniomaxillofacial trauma, degenerative musculoskeletal diseases, infections, and congenital disorders.*

## Overall goals

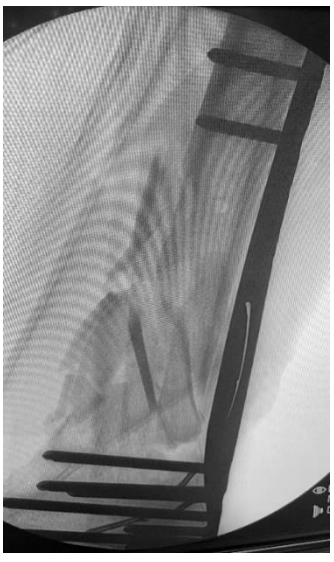
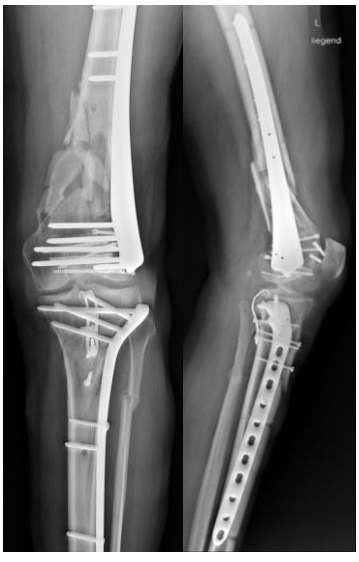
- Contribute high-quality applied preclinical research and development (exploratory and translational) focused on clinical solutions and applications.
- Investigate and improve the performance of materials, biologics, and devices for surgical procedures and treatments.
- Foster a close relationship with the AO network, academic societies, and universities.
- Provide a supportive and inclusive research environment and mentorship for our employees, scientists, and the AO network.

## ARI goals, 2023-2025

- Valorize AO Fracture Monitor together with AO ITC's (AO Innovation Translation Center) Technology Transfer (TT) team.
- Implement the specific-pathogen-free sheep flock in studies.
- Valorize the biphasic plate together with AO ITC's TT team.
- Strengthen and advance research activities in diagnostics and personalized medicine.
- Develop training technologies to support AO Education and the AO network.

## ARI principles

- Maintain world-class research and nurture in-house talents for long-term innovation.
- Support the AO network with cutting-edge research and development for clinical problems.
- Continue developing ARI technology portfolio. Translate and valorize ARI innovations together with the AO ITC's Technology Transfer team.
- Maintain our world-class certificates (ISO, AAALAC, GLP).
- Continue developing 3D (bio)printing and SIM technologies.
- Engage with scientific networks and consortia: global (eg, ORS, TERMIS, ICORS) and European societies (eg, DKOU, ECLAM, ESB-Biomaterials, ESB-Biomechanics, EORS, TERMIS-EU).

# 3 Funding Summary

| CHF in '000 | | | | | |
|---|---|---|---|---|---|
| | 2021 Dec YTD Actual | 2022 Dec YTD Actual | 2022 Dec YTD Budget | Var. CY/Bud YTD abs | Var. CY/Bud YTD % |
| 1100 Management & Overhead ARI | 660 | 705 | 724 | -18 | -3% |
| 1101 Regenerative Orthopeadics | 1,921 | 2,358 | 2,012 | 345 | 17% |
| 1102 Biomedical Development | 1,658 | 1,717 | 2,078 | -361 | -17% |
| 1103 Preclinical Services | 1,082 | 775 | 601 | 174 | 29% |
| 1104 Fellowships | | 0 | | 0 | |
| 1106 Network Preclinical Research | | 10 | | 10 | |
| **Total Income** | **5,320** | **5,566** | **5,415** | **150** | **3%** |
| 1100 Management & Overhead ARI | -2,435 | -2,157 | -2,288 | 131 | -6% |
| 1101 Regenerative Orthopeadics | -6,312 | -6,499 | -6,307 | -192 | 3% |
| 1102 Biomedical Development | -2,952 | -3,071 | -3,407 | 336 | -10% |
| 1103 Preclinical Services | -3,073 | -2,849 | -2,603 | -246 | 9% |
| 1104 Fellowships | -817 | -754 | -705 | -48 | 7% |
| 1106 Network Preclinical Research | -1,029 | -2,055 | -2,977 | 922 | -31% |
| **Total Expenses** | **-16,617** | **-17,385** | **-18,287** | **902** | **-5%** |
| **Total Net Result** | **-11,297** | **-11,819** | **-12,872** | **1,052** | **-8%** |

Comments: The variance of the net result compared with the ARI budget of CHF 1,052 K and 8% is mainly caused by the underspending of 'Network Preclinical Research (NPR)' with CHF 931 K. Excluding NPR, the net result for ARI ends in an underspend of CHF 121 K which is less than 1% and can be fully explained by the contractual research grants that were not renewed to be in line with the ongoing financial sustainability program of the AO Foundation (AOF) for 2023 and onwards (visible under Management & Overhead).

Income: The extramural income amounted to CHF 5,566 K, which is CHF 150 K or 3% higher than budgeted. The good result was achieved due to additional commercial studies realized and a constant high number of public grants which is not self-evident in the current phase of Switzerland no longer being a full member in the EU Horizon program.

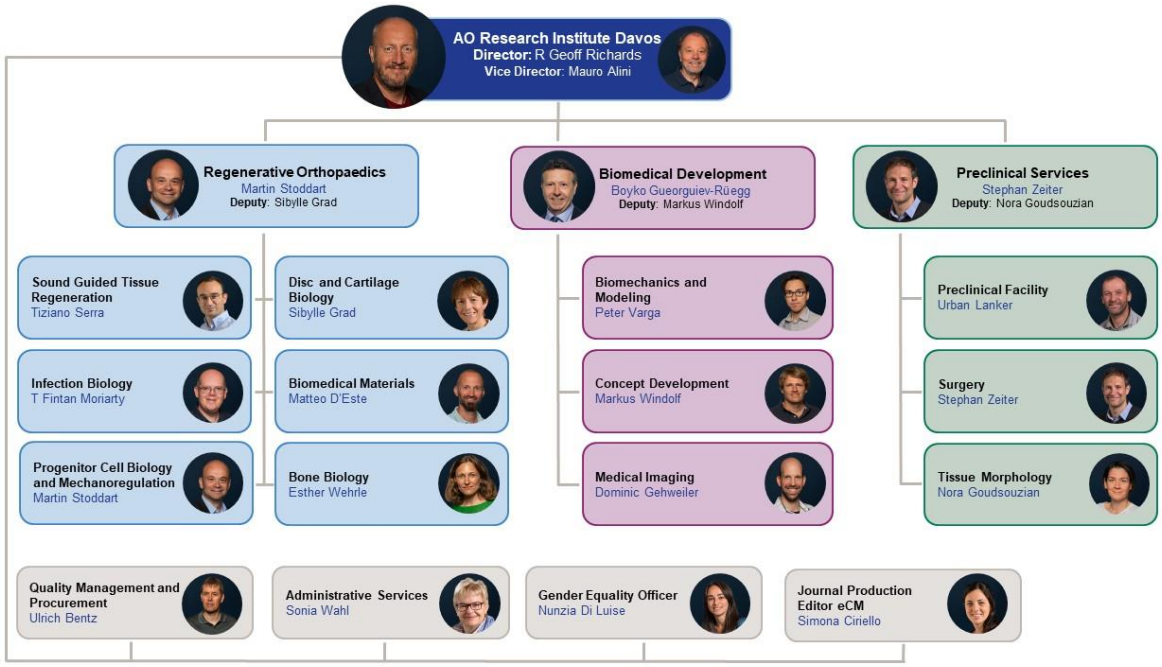
Expenses: The underspend of CHF 902 K on the expenses side is a mix of higher expenses in the Regenerative Orthopaedics and the Preclinical Services Program with additional expenses for mostly material and third-party services triggered by the higher number of 3rd party funded projects. On the other hand less expenses were incurred in the Biomedical Development Program due to delays in projects funded by the Development Incubator, which consequently resulted in lower intercompany income. The underspending in NPR is driven by two Clinical Priority Program studies that had to be stopped and the delay in another material project.

The biggest program within ARI is 'Regenerative Orthopaedics' with 37% followed by 'Biomedical Development' with 18% and 'Preclinical Services' with 16% of total expenses. The portion of NPR is 12% of total expenses.

Cost category: The main cost categories are 'Personnel Expenses' with 57%, followed by 'Material Expenses' with 11% and 'Scientific & Regional Expenses' with 10% of the total.

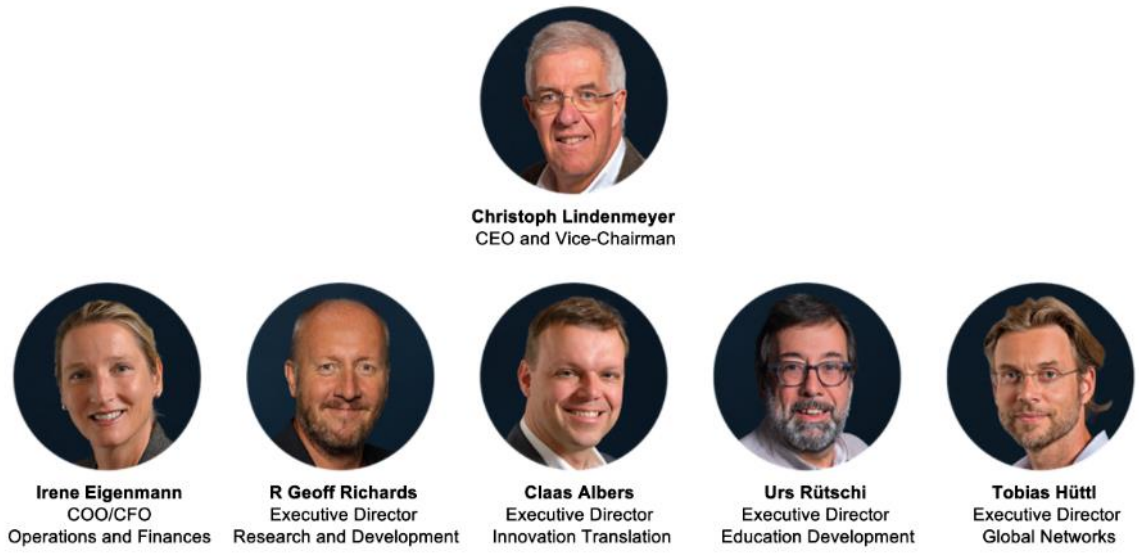
# 4 Research Structure & Advisory Committees

## 4.1 AO Research Institute Davos (ARI) Organigram




## 4.2 AO Foundation Executive Committee (AOEC)

The AO's Executive Committee reports directly to the AO Foundation Board, and includes the CEO, CFO/COO and executive directors representing key areas of AO activity.



## 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 (AO FB) 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 AO FB. All research stakeholders are finally accountable to the AO FB. The AO R&D Platform will further develop the strategies and their implementation on behalf of the AO FB in an advisory capacity. It has no funding or decision authority. The R&D Platform is represented on the AO EC by the AO Executive Director of Research and Development.

The R&D expert of the AO FB 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.

*AO R&D Platform members and guests, Vancouver June 2022 (not all were present).*

## 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 FB. ARI AC acts as both a sounding board and sparring partner for the Director and mentor group to the Program Leaders, Focus Area Leaders and ARI scientists. 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 ARI
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 ARI AC comprises the following external members:
Prof Theodore Miclau Orthopedic Trauma Institute, USA (Chair). Represents ARI AC on the AO R&D Platform and Innovation Platform),
Prof Joost de Bruijn, University of Twente, the Netherlands
Prof Chris Evans, Mayo Clinic, USA
Prof Brian Johnstone, Oregon Health and Science University, USA
Prof Gerjo Van Osch, Vice dean of Research Erasmus, Rotterdam, NL

*AO Research Institute Davos Advisory Committee (ARI AC) members from left to right: RG Richards (ARI Director), Joost de Bruijn, Gerjo Van Osch, Brian Johnstone, Ted Miclau (chair), Chris Evans.*

## 4.5 AO CMF Research Commission (AO CRC)

The AO CRC is the international coordination body for all activities of the AO CMF clinical division for research and development of the AOF. Its mission is to promote excellence in patient care and treatment outcomes in trauma and musculoskeletal disorders of the craniomaxillofacial specialty. The AO CRC Commission works closely with the regional craniomaxillofacial-related AO organizations and surgeon network to establish a cohesive global vision and strategy for AO CRC. It supports the coordination between the surgeon network and the ARI and AO ITC and central AO functions and services.
AO CRC has focused in building an interdisciplinary team, AO CMF Consortium - Translational approaches for bone constructs: their impact on facial bone reconstruction.
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 CRC comprises the following members, permanent guests, and AO representatives:
Prof Eppo Wolvius, Rotterdam, The Netherlands (Chair)
Prof Daniel Buchbinder, New York, NY, USA (AO CMF Technical Commission chair)
Dr Thomas B. Dodson, Seattle, WA, USA (member)
Dr Lamont Jones, Detroit, MI, USA (AO CMF NA Research Committee chair)
Prof Andreas Thor, Uppsala, Sweden (member)
Dr Chelsea Bahney, Vail, CO, USA (Permanent guest, Scientist)
Dr Catherine Chaussain, Paris, France (Permanent guest, Scientist)
Philipp Buescher, Head AO Network Preclinical Research (NPR)
Prof Martin Stoddart, ARI Program Leader Regenerative Orthopaedics, Davos, Switzerland
Joffrey Baczkowski, AO Senior Project Manager, AO ITC, Dübendorf, Switzerland

## 4.6 AO Spine Research Commission (AO SRC)

AO Spine Research Commission clinically guides some of the spine preclinical research in at the ARI. The focus of AO Spine's preclinical research activities are led by Principal Scientist, Dr Sibylle Grad. This research is on intervertebral disc (IVD) degeneration, postoperative spine infection, and organ models. The preclinical outcomes are brought to the AO Spine Knowledge Forums, which are international expert driven clinical study groups, for clinical evaluation where the AO SRC works with AO ITC Clinical Sciences division. The Commission and Knowledge Forums are managed by AO NCR (Network Clinical Research).

In 2022, 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 SRC comprises the following members:
Dr Charles Fisher, Vancouver, Canada (Chair)
Dr Brian Kwon, Vancouver, Canada (AO Spine Knowledge Forum SCI Representative)
Dr Stephen Lewis, Toronto, Canada (AO Spine Knowledge Forum Deformity Representative)
Dr S. Tim Yoon, Atlanta, USA (AO Spine Knowledge Forum Degenerative Representative)
Dr Laurence Rhines, Houston, USA (AO Spine Knowledge Forum Tumor Representative)
Dr Klaus Schnake, Erlangen, Germany (AO Spine Knowledge Forum Trauma Representative)
Dr Nelson Astur, São Paulo, Brazil (AO Spine Latin America Regional Research Officer)
Dr Shekar N. Kurpad, Milwaukee, USA (AO Spine North America Regional Research Officer)
Dr Daisuke Sakai, Tokyo, Japan (AO Spine Asia Pacific Regional Research Officer)
Dr Waleed Awwad, Riyadh, Saudi Arabia (AO Spine Middle East and Northern Africa Regional Research Officer)
Dr Aron Lazary, Budapest, Hungary (AO Spine Europe and Southern Africa Regional Research Officer)
PD Dr Sibylle Grad, ARI Representative, Davos, Switzerland

## 4.7 AO Trauma Research Commission (AO TRC)

The AO TRC is the international coordination body for all activities of the AO Trauma clinical division for research and development of the AOF. 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 TRC offers funding opportunities for surgeons and scientists in preclinical and clinical research on important clinical issues.

AO TRC strategy focuses on two fields:
1) To be a knowledge leader, performing large research CPP consortia with external experienced clinicians and researchers in collaboration with ARI and AO ITC Clinical Sciences 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 Fracture Related Infections (FRI), 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 (Miami, 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 provides training in the fundamentals of research processes. Within this framework, the AO TRC offers funding programs for smaller projects. These grants follow the AO FB 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 fellowship programs.

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

## 4.8 AO Vet Research Commission (AO VRC)

AO VRC pursues two main goals with its research activities. The 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 VRC also provides individual support to young clinicians to increase awareness of research and provides 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 VRC also supports the other AO Clinical Divisions as an advisory body (Animal Welfare Advisory Committee (AWAC) and AAALAC).

The AO VRC Commission comprises the following members and AO representatives:
Prof Kenneth Johnson, Sidney, Australia (Chair)
Dr Junya Ogawa, Kamakura, Japan (Member)
Ass Prof Kyla Ortved, Pennsylvania, MI, USA (Member)
Dr Kevin Parsons, Bristol, UK (Member)
Dr Diego Quinteros, Buenos Aires, Argentina (Member)
Philipp Buescher, Head AO Network Preclinical Research (NPR)
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 AOF, including AO Trauma, AO Spine, AO CMF, AO VET, and their respective Research Commissions (RCs). For each Clinical Division (CD) research grant, the decision-making body is that respective CD RC.

The chairperson of the AO RRC is Prof David Grainger, University of Utah, USA.

## 4.10 AO Network Preclinical Research (AO NPR)

The goal of the AO Network Preclinical Research (AO NPR) is to gain 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 AOF.
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 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 (AO RRC).
AO NPR is headed by Philipp Buescher. Team members are Tania Bosque, Anna Doenz and Anita Anton.

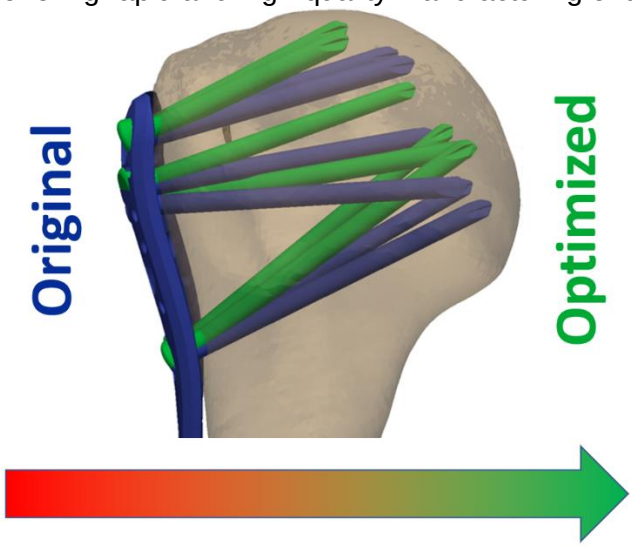
# 5 ARI Teams / Personnel

## 5.1 Biomedical Development

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

Team Members: David Ambühl, Paolo Antonacci, Jan Barcik, Till Berk, Jan Buschbaum, Jan Caspar, Daniel Ciric, Manuela Ernst, Alicia Feist, Dominic Gehweiler, Carla Hetreau, Maximilian Heumann, Ladina Hofmann-Fliri, Philipp Kastner, Florian Kessler, Sara Lindenmann, Elisa Marani, Rayna Mechkarska, Dominic Mischler, Karen Mys, Tatjana Pastor, Georgi Raykov, Jérôme Schlatter, Peter Schwarzenberg, Flurin Spiller, Alessia Valenti, Peter Varga, Antoine Vautrin, Ivan Zderic, Daniel Zhelev, Erich Zweifel

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 the 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.

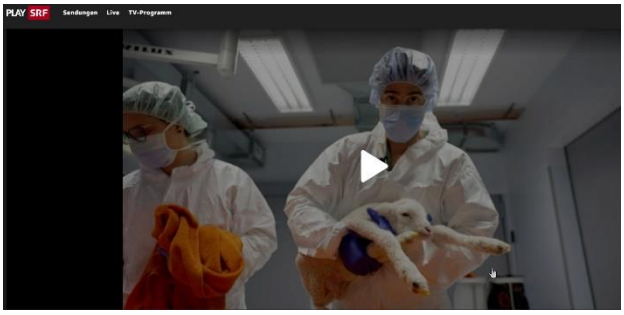



*Proximal humerus fracture plating: optimization of screw trajectories.*

## 5.2 Preclinical Services

Program Leader: Stephan Zeiter, Deputy: Nora Goudsouzian

Team Members: Daniel Arens, Mauro Bluvol, Carmen Brazerol, Jonas Brückner, Tim Buchholz, Caroline Constant, Peter Erb, Loris Faoro, Pierina Faoro, Andrea Furter, Lena Gens, Nilo Hämmerl, Maria Hildebrand, Tabea Hutabarat, Urban Lanker, Alexandra Lopez, Leonie Mollet, Reto Müller, Dirk Nehrbass, Dominic Perren, André Salvatore, Götz Schlipf, Monika Schneider, James Tapia-Dean




In February 2022 the Swiss public clearly rejected the initiative to ban animal studies. This sign of trust is taken seriously and comes with the responsibility of conducting these studies with great care. Further, it is also important to be transparent and to inform the public why and how these studies are undertaken. In July Swiss TV broadcasted a report on preclinical studies at the ARI within their knowledge and science format program "Einstein" showing our commitment to have open doors and to following the 3R principle (Replace, Reduce and Refine).

In 2022, 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. Our quality management systems (GLP, AAALAC and ISO 9001:2015). ensure that the generated data of our studies is of high quality.

The team is active in different societies i.e., the European College of Laboratory Animal Medicine (ECLAM), European Academy of Laboratory Animal Surgery (EALAS), 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) as well as continued membership to pathology societies such as the European Society of Toxicologic Pathology (ESTP) and the Society of Toxicology Pathology (STP). This ensures that we pursue best in class policies in the sensitive area of animal models.
Last but not least, we spread our expertise and experience by offering training in histological techniques and preclinical research with a special emphasis on hands-on experience. In 2022, together with the Zurich Integrative Rodent Physiology (ZIRP) and the support of the Swiss 3R Competence Center (3RCC) we started to give courses on best practices in rodent surgery aiming to raise standards.

## 5.3 Regenerative Orthopaedics

Program Leader: Martin Stoddart, Deputy: Sibylle Grad

Team Members: Katsuhiko Abe, Mauro Alini (Vice Director), Jhaleh Amirian, Adriana Augurio, Romain Bagnol, Valentina Basoli, Ezgi Irem Bektas Tas, Laura Belcastro, Franziska Breulmann, Helen Bumann, Oscar Chan, Baixing Chen, Marco Chittò, Eda Ciftci-Dede, Carolina Maria Cordeiro, Elena Della Bella, Matteo D'Este, Nicolas Devantay, Nicola Di Marzio, Sarah Egger, Karina Egle, Sina Enzmann, Pia Fehrenbach, Wenli Feng, Priscilla Füllemann, Pamela Furlong-Jäggi, Wei Gao, Matthias Gruber, Géraldine Guex, Phelipe Hatt, Marloes Hofstee, Marie Isenmann, Shahrbanoo Jahangir, Hermann Kasper, Iris Keller-Stoddart, Jessica Keller, Olivia Kim, Aline Klaus, Nadine Kluser, Thomas Krüger, Eliane Kuhn, Yann Ladner, Carina Lanker, Kaihu Li, Zhen Li, Junxuan Ma, Joos Mathieu, Vuyisa Siphelele Mdingi, Laura Mecchi, Huan Meng, Ursula Menzel, Lana Micko, Gregor Miklosic, Carina Mini, Fintan Moriarty, Marcia Mürner, Pamela Nylund, Reza Ojaghi, Louise Ortet, Romedi Parolini, Robert Peter, Athanasia Pylostomou, Maria Eugenia Pirera, Virginia Post, Roots Randriantsilefisoa, Aapo Ristaniemi, Kathrin Schärer, Amra Sercovic, Tiziano Serra, Claudia Siverino, Antons Sizovs, Astrid Soubrier, Christoph Sprecher, Baiba Svalbe, Riccardo Tognato, Clemens Unterguggenberger, Daphne van der Heide, Nils Vanvelk, Jana Vecstaudza, Andrea Vernengo, Sophie Verrier, Reinis Vilskersts, Nadja Vonlanthen, Alexandra Wallimann, Davina Walser, Esther Wehrle, Ferdinand Weisemann, Liru Wen, Jacek Wychowaniec, Jiangyao Xu, Ensi Zhao, Donya Ziadlou, Daniele Zuncheddu

**Biomedical Materials Focus Area**

The Biomedical Materials Focus Area is committed to the design of advanced biomaterials and the development of (bio)manufacturing technologies to achieve improved patient care and outcomes in musculoskeletal disorders. Using a variety of chemical approaches, we create responsive biomaterials that react to environmental stimuli and actively interact with cells and tissues. We design biomaterial surfaces and antibacterial delivery systems for prevention and treatment of infections, and we are investigating how materials "talk" to the body at the cellular level by harnessing the inflammatory processes to trigger a healing response and prevent chronic inflammation. We also develop bio-processing technologies for translating tissue engineering approaches to regenerative, patient-tailored precision medicine.
By deepening our understanding on how materials dynamically interact with/in the body, and how additive manufacturing and bioprocessing modulate these interactions, we aim to advance orthopaedic patient care.

**Bone Biology Focus Area**

Bone healing depends on biological factors and the mechanical conditions in the defect region. Despite the advances in fracture fixation, there remains a subset of patients that suffer from healing complications, resulting in delayed healing and non-unions. Currently it is not possible to reliably identify healing complications at an early stage when treatments may be more effective. Within the Bone Biology Focus Area, we study biological factors involved in the different phases of bone healing with a major focus on early immunological, angiogenic and mechano-molecular components. The immune system is involved in guiding and directing the healing response. We are investigating how modulation of inflammation may be used to enhance the bone healing process, as well as assessing the potential of immune cell characterization to be used as a predictive biomarker of the individual healing potential.
Mechano-molecular mechanisms are important for successful bone healing. Via our novel technology we aim to precisely study how mechanics influence molecular mechanism during bone healing in vivo (femur defect loading model in mice) and in vitro (bone bioreactor). In combination with emerging molecular omics techniques, we want to comprehensively characterize the local and systemic mechano-molecular regulation of bone healing. Via this combined in vivo and in vitro approach, we aim for identification of novel therapeutic targets, systemic biomarkers, and mechanical intervention therapies relevant towards translation of personalized medicine approaches for impaired healing conditions.

**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 different whole IVD organ culture systems with the ability to maintain entire discs with the endplates for several weeks under controlled nutrient and mechanical loading conditions. Within our bioreactors, the beneficial or detrimental effects of nutrition, mechanical forces, and/or biochemical factors on disc cell viability and phenotype are investigated. The novel 6-degrees-of-freedom bioreactor allows us to recapitulate the complex mechanical environment of the IVD. 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 therapeutics, biomaterials, or a combination thereof. Data from *ex vivo* models are also correlated to *in vivo* observations to identify molecular markers of IVD health and disorder. To study the potential of new therapies for articular cartilage repair and regeneration, a bioreactor system applying multiaxial load to tissue-engineered constructs or osteochondral 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.

**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 Mechanoregulation 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 prospectively 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

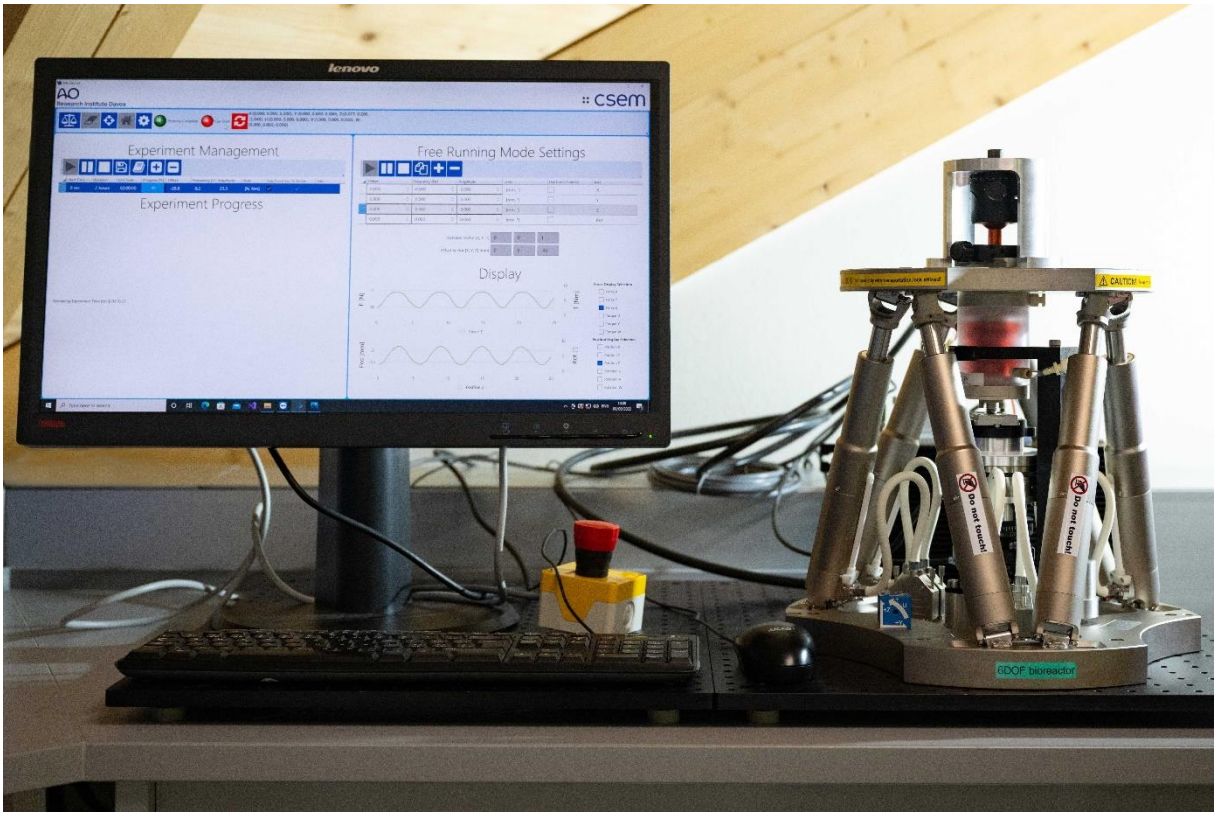
could lead to the identification of new targets that may be present during articulation. This offers new avenues for potential clinical therapies.

**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.




*ARI's novel 6-degrees-of-freedom bioreactor to recapitulate the complex mechanical environment of the intervertebral disc applying multiaxial load to tissue-engineered constructs or osteochondral explants within, the organs being cultured for several weeks under controlled nutrient and mechanical loading conditions.*

## 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, Melanie Rösch, 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 standards and safety

Quality Manager: Ulrich Bentz

**Successful 2022 routine audit of AO Research Institute Davos:**

From May 30 to 31 2022, a new external auditor from the SQS (Swiss Association for Quality and Management Systems) inspected ARI two days for the routine audit of the institute. ARI has passed the routine audit without any non-conformities requiring immediate actions.

The entire ARI 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. ARI is a GLP (Good Laboratory Practice) compliant test facility since February 2016.

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. There was no inspection in 2022.
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 accreditation was received February 28, 2022.

# 6 Gender Equality Initiative

Gender Equality (GE) is a fundamental value of the European Union (EU). In 2021, Switzerland adopted the first National strategy for Gender Equality 2030. GE benefits Research and Innovation (R&I) by improving the quality and relevance of R&I, attracting, and retaining more talents, and ensuring that everyone can maximize their potential.
In January 2022, ARI appointed an internal Gender Equality Working Group (GEWG) with the aim of establishing a set of commitments and actions. The GEWG has been composed in line with the recommendations of the Horizon Europe Guidance on Gender Equality Plans and includes representatives of all major position groups, hierarchy levels, educational backgrounds, and genders from the Institute.
An initial assessment of the gender equality status quo of ARI has been conducted in 2022. The specific methodological approaches used to carry out the assessment were: 1) identification and review of existing measures promoting gender equality at ARI; 2) collection of sex-disaggregated data about ARI employees; 3) ARI employee survey. The results of the initial assessment allowed to identify the strengths and weaknesses concerning gender equality at ARI and were used as baseline to set up clear objectives and prioritized set of measures.

*Gender equality working group composition.*

A summary of the Gender Equality Plan 2023-2025 is showed below:

Area 1: Work life balance and organizational culture
- Objective 1.1: Promoting reconciliation of career and family life
- Objective 1.2: Continuing promoting alternative and flexible working arrangements
- Objective 1.3: Promoting use of inclusive language around the organization

Area 2: Gender balance in leadership and decision making
- Objective 2.1 Supporting and promoting women in leadership positions

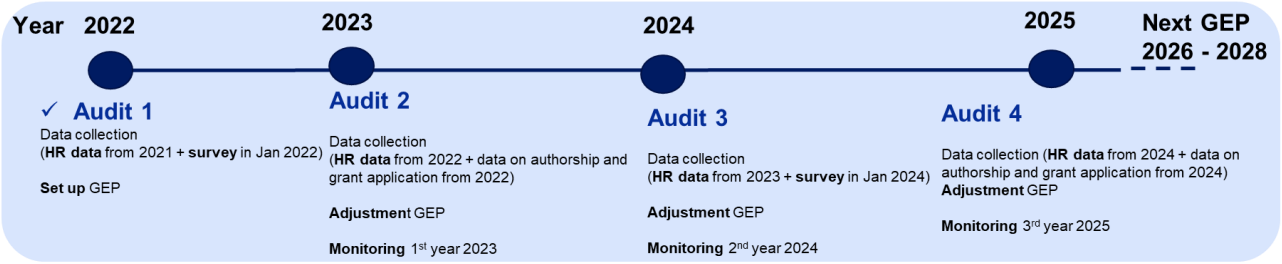
Area 3: Gender equality in recruitment and career progression
- Objective 3.1: Raising awareness on gender issues at different levels
- Objective 3.2: Updating the ARI career path

Area 4: Measures against gender-based violence, including sexual harassment
- Objective 4.1. Preventing chance of gender-based violence, incl. sexual harassment

Area 5: Integrating sex dimension into research content

- Objective 5.1: Raising awareness of including sex aspect in research content
- Objective 5.2: Setting up standard procedures integrating sex aspect into research content

Regular meetings are organized: 3-4 meetings per year with the whole GEWG and task forces meetings in between to discuss specific objectives and measures. There is data collection, followed by analysis, reviewing, and reporting.




Dedicated resources allocated by ARI for the GEP include:

1. A dedicated ARI gender equality function composed by one gender equality officer, a team with different expertise, including one human resource representative, and an executive leadership member (director of the Institute), publicly supporting the whole function (see section 2.1 for more details).
2. Earmarked staff time for the whole ARI gender equality function to work throughout the whole GEP cycle.

Earmarked budget to supporting specific measures and areas of the GEP, such as work-life balance and parental leave, as well as staff training, and development will be evaluated and potentially allocated in the next few years.

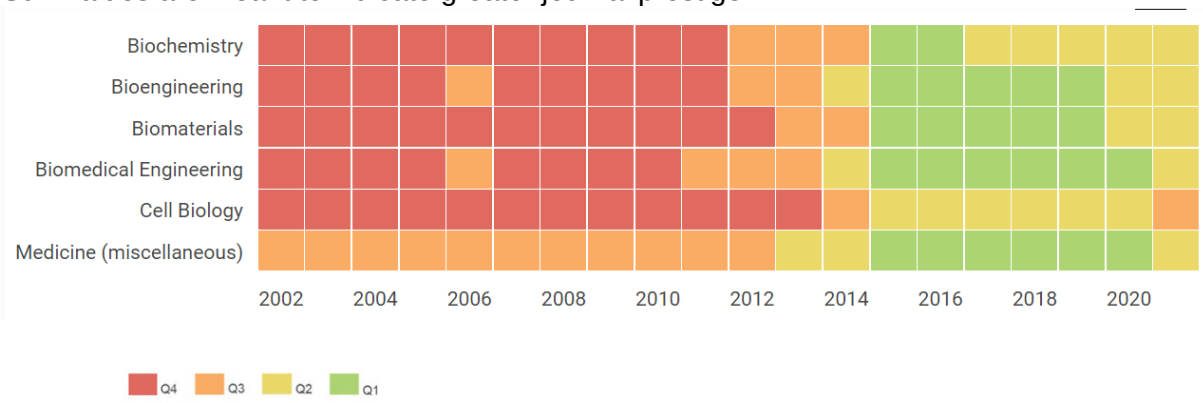
# 7 eCM Journal & eCM periodical

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 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 2022, Journal Citation Reports (JCR) announced eCM's 2021 **Impact factor** (IF) to be 4.325. JCR 5-year Impact Factor: 5.126.

**SJR H index**: 87. 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 Issue launched in 2022**
Temporo-mandibular joint Special Issue: The temporomandibular joints (TMJs) connect the jaw to the skull and are the most used joints of the human body. TMJ disorders (TMD) are severely debilitating and a significant public health issue. Therapies for TMD have mixed success so there is a great need for new research into the TMJ to prompt therapies that are more effective. The eCM journal is facilitating this by producing a special issue focused on the TMJ, which serves as a platform for the publication of manuscripts describing novel basic science on TMJ development, growth, homeostasis, pathologies, and therapies.

**eCM Open Access** Not-for-Profit online periodical
eCM Periodical was initiated in 2017, previously run within eCM journal as eCM supplements. eCM Conference Online Periodical is not part of the eCM journal publication but is owned as a separate part of eCM. It hosts all eCM official society meeting abstracts along with other abstracts for various congresses as collections of combined individual meeting abstracts in PDF format. The individual abstracts within the abstract collections have been peer reviewed by the respective conference organizers. eCM Periodical has been recorded permanently in the ISSN Register, ISSN: 2522-235X from the ISSN International Centre. The abstract collections do not have a DOI, and the abstracts are not searchable on PubMed.

## 7.1 eCM annual conference

The 20th edition of the European Cells and Materials (eCM) Conference took place at the Davos Congress Center from June 15 to 18, 2022, with a record number of scientists in attendance from universities, research institutes, clinics, and industry. 181 international participants joined this high-level conference to meet and discuss the latest results of applied research and clinical studies related to the subject of this year's meeting: cartilage and disc repair and regeneration. ARI hosts the annual conference under ARI Director Geoff Richard's leadership, and in 2022 it was organized by Martin Stoddart, Sibylle Grad, and Zhen Li of ARI's Regenerative Orthopaedics Program.

Injuries as well as wear and tear of the joints and spine are ubiquitous, yet their treatment is extremely difficult. In particular, damaged cartilage and intervertebral disc tissues present significant challenges to patients and physicians. The potential for self-healing is low and the available treatments are often unsatisfactory. However, new developments in cellular and molecular biology, biomechanics, and biomaterials research offer hope for the future. For example, therapies using stem cells, gene therapies, and the administration of new biological materials have already proven their effectiveness in preclinical studies. In addition, mathematical models and artificial intelligence can improve diagnosis and enable individualized treatment. Twenty renowned experts presented their latest findings on these subjects at this year's eCM Conference, with topics including an investigation into the causes of joint and back pain; supporting the body's capacity for regeneration; and targeted administration of novel drugs and materials. Forty-four student presentations were delivered during the conference.


The 2020, 2021, and 2022 recipients of the AO Foundation's esteemed Berton Rahn Research Award were honored at the conference since no meeting could be held in 2020 and 2021. The winners - Prof Stephen Ferguson (2022), Prof Jos Malda (2021), and Prof Ling Qin (2020) - presented their work to those in attendance.

Throughout the four-day conference, scientists engaged in a lively multi-disciplinary exchange. The conference's focused format – a single session (no parallel meetings) featuring auditorium presentations, poster sessions, and group hikes – is designed to encourage in-depth discourse between established experts and young researchers alike related to basic, translational, and clinical research. These exchanges promise approaches that will one day prevent or alleviate the discomfort of patients suffering from joint or intervertebral disc diseases.

## 7.2 eCM conference- Swiss Young Researchers prize

The AOF also supports the Swiss Young Researchers (Schweizer Jugend Forscht, SJf) through a partnership agreement.

SJf is a federally recognized non-profit foundation. It is committed to the sustainable promotion of talented young people with scientific curiosity, creativity and problem-solving skills. In addition to school education, it offers various support programs where young people can gain initial experience in scientific work and are encouraged to conduct independent research. It also promotes the development of skills for later career or study choices. SJf operates on a national level and networks with like-minded organizations, educational institutions, science and business.
SJf's promotion offer includes three activities: study weeks, the National Competition and the International Swiss Talent Forum (ISTF). In connection with the National Competition, young people with outstanding work also have the opportunity to win a special prize. The AO Foundation supports SJf with a special prize within our partnership. Our target group is the talented high school and vocational school students (16 - 21 years old) whose work at the National Competition has received the rating "very good" or "excellent" from the SJf expert jury.
The special price includes a five-day stay in Davos incl. travel, accommodation and the visit of the AO Foundation as well as the visit of the eCM conference. This conference is a platform where scientists (biologists, engineers, material scientists, etc.), clinicians and industry meet. Together, they bring clinical problems to the table, consider industry requirements for potential solutions, and often initiate joint projects to solve these clinical problems. For the special award participants, this platform results in an opportunity to think about what the science and technology landscape might look like in the future and how it can be influenced. This provides students with new knowledge and skills, connections, and a broader perspective. By endowing the special award, AOF specifically recognizes and supports the young generation's commitment to science.

The 2022 winners were Leo Koch from Seengen and Tamara Papararo from Bassersdorf.

# 8 Institutional and Professional Relations

**Director, Program Leaders & Managers and Focus Area Leaders**

R. Geoff Richards has been Director of the ARI since 2009 (having been at ARI since 1991). He is a 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) and an Honorary Professor, Aberystwyth School of Veterinary Science, Aberystwyth University, Wales, UK since 2022. He has Doctor Honoris Causa from the Technical University of Varna, Bulgaria. In 2020 Geoff was elected Fellow of the Learned Society of Wales (FLSW) (the national academy for arts and sciences of Wales). He is also a Fellow of: Biomaterials Science and Engineering (FBSE) since 2012, International Orthopaedic Research Societies (FIOR) since 2016, Orthopaedic Research Society (FORS) since 2021, Tissue Engineering and Regenerative Medicine International (FTERM) since 2021. He was awarded honorary Fellow in 2019 of his alma mater at Aberystwyth University in Wales. 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 of Health Sciences and Technology (D-HEST) of the ETH Zurich. He is the ARI representative to the AO Trauma R&D Commission. Locally, Geoff is President of Science City Davos (since 2021, member since 2013). He was elected to the "Stiftungsrat" (Board of Trustees), Stiftung Sport Gymnasium Davos (Sport Foundation, Gymnasium high School Davos), Swiss Olympic Sport School, Davos in 2022. He is a member of numerous Davos and Graubünden committees including Davos Regional Development Digital advisory Council.

Mauro Alini is Vice Director of the ARI 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 is a Fellow of: International Orthopaedic Research (FIOR) since 2016, Orthopaedic Research Society (FORS) since 2021, Tissue Engineering and Regenerative Medicine International (FTERM) since 2018. 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 ARI co-representative to the AO Spine Research Commission (AO SRC).

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 (since 2016). He is Vice President of the European Orthopaedic Research Society (EORS) and in the board since 2018. He is Honorary Member of the Bulgarian Orthopedic and Traumatology Association and of the Serbian Trauma Association (2019). He is a Member of the Academic Council at the University Multiprofile Hospital for Active Treatment and Emergency Medicine 'N I Pirogov', Bulgaria (2017). He is Honorable Research Fellow of the Institute of Metal Science, Equipment and Technologies with Hydro- and Aerodynamics Centre "Acad A Balevski" at the Bulgarian Academy of Sciences (2022). 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 AO TC 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 (since 2015). He is honorary Professor at the Institute for Science and Technology in Medicine, University of Keele, UK (Since 2016). In 2016 he was elected Fellow of the Royal Society of Biology (FRSB) and an ICRS Fellow member. Since 2022 he is a Fellow of the International Combined Orthopaedic Research Societies (FIOR). He lectures on the Skeletal Repair MSc module at the Department of Health Sciences 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 a Member at large on the TERMIS EU Council, Global Membership Committee and Global Governing Board. He is a member of the International Consortium for Regenerative Rehabilitation Leadership Council. 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 the ARI representative to the AO CMF Research Commission (AO CRC).

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 guest lecturer in the MSc Course Skeletal Repair at the Department of Health Sciences and Technology (D-HEST) of the ETH Zurich. He is ARI`s radiation safety and animal welfare officer. He has been co-founder of the Preclinical Model Section of ORS and the European Academy of Laboratory Animal Surgery (EALAS).

Matteo D'Este is 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 of Health Sciences 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 Scientific Chair and main organizer of the European Society for Biomaterials Annual Conference 2023, Scientific Editor of the eCM Journal and co-organizer of the annual eCM conference on the topics of biomaterials and biofabrication.

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 of 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 topics 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. She is ARI co-representative to the AO Spine Research Commission (AO SRC). Locally she is a 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 of Health Sciences 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). He is lecturer in infection biology at the Center for Muskuloskeletal Infections (ZMSI), University Hospital Basel, Basel, Switzerland (since 2022).

Tiziano Serra is a Research Scientist and Focus Area Leader of Sound Guided Tissue Regeneration at ARI. He is Assistant Professor at the Complex Tissue Regeneration Department, MERLN Institute for Technology-Inspired Regenerative Medicine (Maastricht University, NL) and Adjunct Professor at the University of Eastern Piedmont "Amedeo Avogadro", UPO (Novara, Italy) where he held a course of Bioengineering within the Master Degree in Medical Biotechnology. He is co-organizer of the annual eCM conference on the topics of biomaterials and biofabrication.

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 of Health Sciences and Technology (D-HEST) of the ETH Zurich. He is an academic editor of the BioMed Research International journal.

Esther Wehrle is the Focus Area Leader for Bone Biology at the ARI. She also holds a position as senior research associate at the Laboratory for Biomechanics (LBB) at ETH Zurich. Esther Wehrle is a lecturer at the Department of Health Sciences and Technology (D-HEST) of ETH Zurich where she lectures on the MSc Courses “Skeletal Repair” and “Bone Biology and Consequences for Human Health”. She is a scientific editor for Scientific Reports and a co-organizer of the annual eCM conference on the topic Bone and Fracture Repair.

**Other Professional Relations of ARI team**

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

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 AO VET research 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) (academic year 2021-2022). She is a member of the Scientific Communications Committee of ORS (2022-2025). 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.

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), National University of Ireland, Galway for 3 months.

Peter Schwarzenberg is Member of the Orthopaedic Research Society International Section of Fracture Repair (ORS ISFR) Membership Committee (2-year term). The aim of the Committee is to promote the section worldwide.

Christoph Sprecher is lecturer at the block course for ETH/ZHAW students at ARI; additionally, he contributed to teaching activities for high school students from the Schweizerische Alpine Mittelschule Davos and for the Future Days.

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 numerous symposia and networking events for this section of the society.

Sophie Verrier is Principal Investigator in the Regenerative Orthopaedics Program, Bone Biology Focus Area. She a board member and the president of the Swiss Bone and Mineral Society (SBMS) in 2022. She is part of the eCM International Review Panel (eCM Journal) and also co-organizer of topic specific annual eCM conferences.

# 9 Good News

## 9.1 New noncommercial extramural funding

German Research Foundation (DFG), Special Research Area: Collaborative Research Centre 1313 – Interface-Driven Multi-Field Processes in Porous Media – Flow, Transport and Deformation. Overall budget EUR 9.5 Mio, ARI budget EUR 60k (project area: fluid-solid phase change), 2022-2025. ARI personnel Boyko Gueorguiev, Dominic Gehweiler.

NMBP-TR-IND-2018-2020: Smart, multifunctional dental implants – a solution for peri-implantitis and bone loss (I-SMarD). Overall budget EUR 5.1 Mio, ARI budget EUR 618k, 2020-2024. ARI personnel Peter Varga.

H2020-EICFETPROACT-2019: A paradigm shift in fracture fixations via on-site fabrication of bone restoration patches (BoneFix). Overall budget EUR 4.0 Mio, ARI budget EUR 400k, 2020-2024. Peter Varga (David Eglin).

Alfred und Anneliese Sutter-Stöttner Stifftung: Cement augmentation at the posterior pelvis ring for treatment of geriatric osteoporotic fragility fractures – in collaboration with University Hospital Berne – Inselspital. ARI budget CHF 50k, 2022. ARI personnel Boyko Gueorguiev, Ivan Zderic.

SINPAIN: “A game changer for the treatment of osteoarthritis: a cost effective combined advanced therapy to treat knee osteoarthritis” (HORIZON-HLTH-2021-TOOL-06-02). ARI personnel Zhen Li, Huan Meng, Sibylle Grad, and Sophie Verrier. Total budget EUR 5.3 million over a project duration of 4.5 years (2022.05-2026.10), the ARI budget is CHF 640’000.

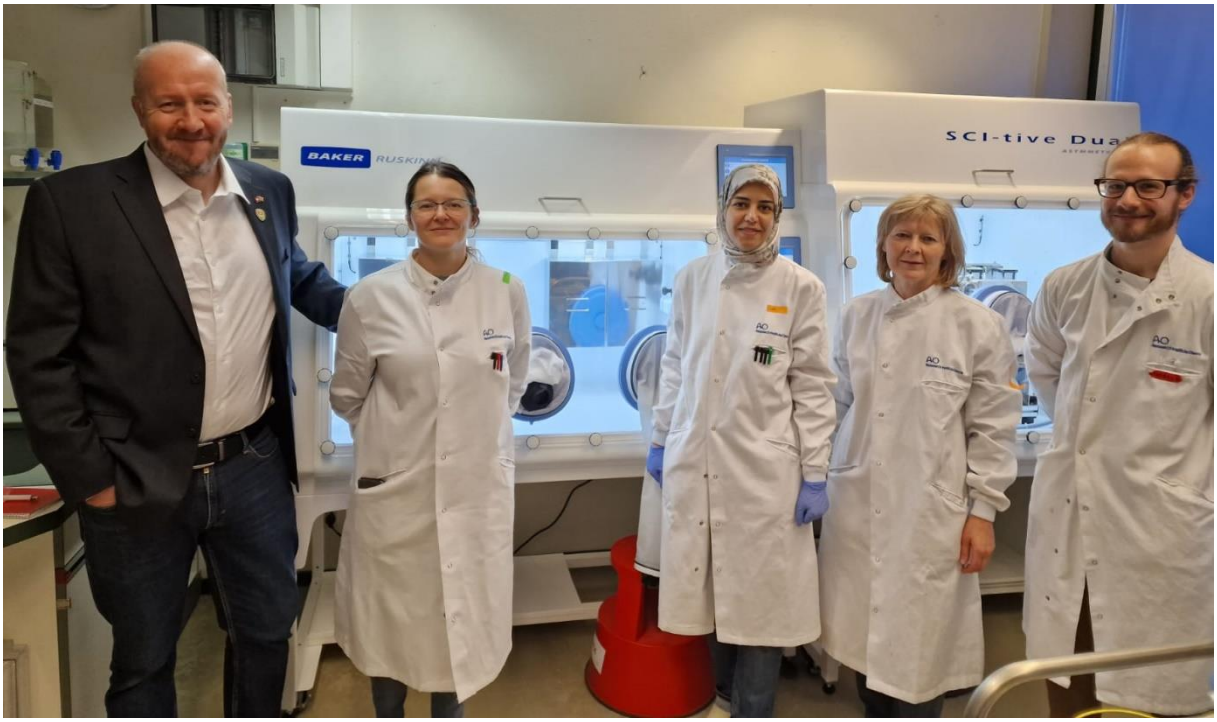
"Research Partnership Grant 2022" of the Leading House MENA (15,000 CHF) was awarded to Jacek Wychowaniec in collaboration with Prof Jeremy Teo from New York University Abu Dhabi in the United Arab Emirates for the project entitled: Space ImmunoBioInks. The project will run for 1 year (01.2023-12.2023) and will focus on studying behavior of self-assembling peptide-based bioinks, used for modulation of immune system cells, under microgravity, with an ultimate future goal of providing basis for novel biofabrication tools for studies in space.

PANDORA: “Pan-European Educational Platform on Multidrug Resistant Tumors and Personalized Cancer Treatment” CIG Cost Innovation Grant from CA17104. ARI will organize a training School on 3D Models for personalized diagnosis, drug screening in patients with MDR tumors and evaluation of toxicological aspects of new drugs. The ARI budget is EUR 25k. ARI personnel Tiziano Serra, Mauro Alini.

**ARI achieves US charitable organizations equivalency status**

ARI is proud to announce it has received a new recognition with the acquisition of a US status known as Equivalency Determination (ED) that validates that non-US-based organizations are on par with US-based 501(c)(3) charities. After a rigorous approval process by NGOsource, it is now possible for US donors to make tax-deductible donations to ARI. New individual and institutional donors need only approach NGOsource to initiate the process. The new status allowed ARI to receive a very large donation from a US-based benefactor. These funds will be used to significantly enhance ex vivo model systems for cartilage regeneration by further augmenting ARI's world-leading cartilage bioreactor system. The modified system will combine physiological oxygen levels, allowing a mechanical load to be applied under conditions that recapitulate the articulating joint. This state-of-the-art system will be used to screen new clinical therapies while dramatically reducing the use of large animal models.

Hightide Foundation donation (via a 501(c)(3) organization equivalency mechanism). Establishment of physioxic mechanical load bioreactor environment. $1,200,000. The project partners at ARI are Martin Stoddart and Geoff Richards, Sibylle Grad, Zhen Li.




*Arrival of our new physioxic incubator, with our unique cartilage bioreactor installed within it.*

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

AO Development Incubator (AODI): AO Fracture Monitor – development phase. Overall Budget CHF 4.0 Mio, 2019-2023. ARI personnel Manuela Ernst, Markus Windolf.

AO Development Incubator (AODI): Growth modulation implant. Overall budget CHF 1.6 Mio, 2021-2024. ARI personnel Jan Buschbaum, Daniel Ciric.

AO Strategy Fund (AOSF): OSApp – virtual osteosynthesis tool for surgical education. ARI budget CHF 522 K, 2020-2023. ARI personnel Peter Varga, Dominic Mischler.

AO Strategy Fund (AOSF): Digitally enhanced hands-on surgical training. ARI budget CHF 482 K, 2020-2023. ARI personnel Jan Buschbaum, Daniel Ciric.

AO Milestones: Digitally enhanced hands-on surgical training – productization phase. Overall budget CHF 303 K, 2022-2023. ARI personnel Jan Buschbaum, Daniel Ciric.

## 9.3 New ARI biogas reactor

Using manure from the flock of specific-pathogen-free (SPF) sheep at the ARI, the plant will drive down the institute's electricity and heating costs and help decrease its carbon footprint and improve the quality of the dung for fertilizer.
A new biogas plant has started operation at the specific-pathogen-free (SPF) sheep stable at ARI's preclinical research facility.

The reactor uses manure from the institute's flock of SPF sheep and local neighbor's cows and employees bio waste from gardens and cooking to generate biomethane to create renewable electrical and thermal energy. The investment in the actual facility is a lighthouse to the local community and will take some years to recuperate financially, but will reduce methane lost to the atmosphere, reducing environmental air pollution.
"The biogas plant is a very interesting option for us," explains Urban Lanker, the manager of ARI's preclinical facility and the idea and initiator of the project. "We're a bulk consumer and we require electricity around the clock. With all of its machinery, including ventilation systems and large-scale washing stations, the preclinical facility clocks up around 125,000 kilowatt hours every year." In comparison, an average four-person household requires around 5,000 kilowatt hours annually.
The biogas plant will also generate enough excess warmth to supply heat. In the case of the preclinical facility alone, this means that 40,000 liters of fuel oil can be saved per year. The heat will also be used to generate hot water for the regular disinfection of the sheep stables, eliminating the need to utilize chemical disinfectants. During the warmer summer months, excess warmth from the plant can be routed to the haystacks to ventilate and dry the animal feed - which in turn will itself one day end up in the reactor. Furthermore, the plant is housed by a photovoltaic-paneled roof that generates additional renewable electricity for ARI.

## 9.4 Top scientists

**ARI researchers among the world's top two per cent of scientists**

Seven scientists from the ARI rank among the most-cited researchers in the world across all scientific fields according to researchers at Stanford University.


Professor Geoff Richards, Professor Mauro Alini, Professor Martin Stoddart, have been ranked among the most-cited scientists in the world regardless of scientific discipline. They were included in a list compiled by a group of researchers at Stanford University, which measures the impact of scientists' research publications over the duration of their active careers.

*Geoff Richards, Martin Stoddart, Mauro Alini, Sibylle Grad, Fintan Moriarty (from left to right).*

The three also appear in a separate list of most-cited authors in the year 2022, along with four other current and former ARI scientists: Dr Sibylle Grad, Dr Fintan Moriarty, Prof Stephan M Perren, Dr Markus Windolf as well as Prof David Eglin, (formerly a principal investigator and Focus Area Leader Polymers and Surfaces. Dr Eglin has since left the ARI for the École Mines de Saint-Étienne in France, where he oversees the Biomaterials Engineering department). Led by Prof John P.A. Ioannidis, the research group at Stanford University first published its database of over 100,000 most-cited authors from around the world across all scientific fields in 2020. Their rankings are based on a composite indicator drawing on six citation metrics from Scopus, an abstract and citation database maintained by the Dutch science publisher Elsevier. Apart from the composite indicator, the database provides standardized information on citations, h-index, co-authorship-adjusted hm-index, and citations to papers in different authorship positions. The Stanford researchers maintain two versions of their list: in order to measure the impact of scientists over the course of their entire careers, one ranking is compiled using citation data beginning in 1996. The other list focuses on a single calendar year.
The seven ARI representatives appear in the list's latest iteration, which was published in Autumn 2022.

**ARI researchers publish paper in 'Nature Reviews Disease Primers'**

The prestigious peer-reviewed medical journal Nature Reviews Disease Primers has published a benchmark paper on fracture-related infection (FRI) that was led and co-authored by researchers at the ARI together with colleagues from the AO's extended networks. "This publication partially arises from the highly successful research produced by ARI and partners in AO Trauma's Clinical Priority Program (CPP) Bone Infection with several former ARI fellows and PhDs invited to co-author the paper, and it also benefited from the AO Innovation Translation Center's Anti-Infection Global Expert Committee," said ARI Director Prof Geoff Richards. Richards is the paper's corresponding and senior author.

This comprehensive FRI overview – written by scientists, trauma surgeons, and infectious disease physicians – is sure to reach a global audience with this high-impact publication. Richards said: "This publication is a testament to the AO's highly collaborative approach in which research, education, and innovation are cross-pollinated, leading to new discoveries and solutions that promote excellence in patient care and outcomes in trauma and musculoskeletal disorders."

## 9.5 Swiss Ambassadors visit to Graubünden

The 2022 Canton Conference Day of the Swiss Ambassadors of the Federal Department of Foreign Affairs (FDFA) was held in August. In glorious weather, the Government of the canton Graubünden welcomed the President of the Confederation (Ignazio Cassis) and over 180 Ambassadors to Switzerland in the Upper Engadin. Prof Richards was invited to present the AO Foundation and ARI research innovations (under the title Alpine Innovation Lab – The AO Foundation) to around 60 of the ambassadors including the Swiss President. Marcus Caduff (Canton President) and Daniel Spadin (The Head of Canton Chancellery) noted in their thank you letter afterwards "You made a significant contribution to Graubünden's being perceived as an attractive location tor companies and tor research and development beyond the borders of the Canton. In particular, you succeeded in conveying the innovative power of AO Foundation to the participants and in presenting Graubünden as a place to live with exciting employment opportunities".

*(Botschafterkonferenz) Geoff Richards as participant representing Science City Davos and the AO/ARI, Kanton Graubünden/Grisons, Diavolezza, Engiadina, Switzerland, 2022 (with our ARI "Bone Jovi" skeleton displaying many ARI innovations, beside President Cassis and regional president Marcus Caduff on the cable car down from Diavolezza).*

*Geoff Richards, Ignazio Cassis (President of the Swiss Confederation), Jon Domenic Parolini (Regional Department of Education, Culture and the Environment), Marcus Caduff (Regional Department of Economics and Social Affairs).*

## 9.6 Awards

When Prof Geoff Richards (director of the ARI) and Dr Theodore Miclau (director of orthopedic trauma at the University of California San Francisco (UCSF) and Chair of the Advisory Committee for ARI, and AO Trustee) first met at the AO over 30 years ago, little did they know that they would one day both be recognized for their impact on the global orthopedic community through their sustained strategic and visionary activities. Richards and Miclau were each presented with an inaugural International Combined Orthopaedic Research Societies' (ICORS) Transformative Contribution Award at the ICORS World Orthopaedic Research Congress that took place September 7-10, 2022, in Edinburgh, Scotland. This new award pays tribute to Richard's and Miclau's international impact on orthopedics through their networking, scientific collaboration and exchange, the promotion of young investigators, and major contributions to basic and clinical orthopedic research. Each received the award individually for their contributions to the establishment and governance of ICORS and the college of Fellows of International Orthopaedic Research (FIOR), collaboratively leading to a substantial transformation of ICORS. Geoff was the founder of Fellows of International Orthopaedic Research (FIOR) and is past FIOR Chair.

*ICORS President Gun-Il Im, MD (left), presenting Prof Geoff Richards (middle) and Dr Theodore Miclau (right) with ICORS Transformative Contribution Awards.*


*Prof Geoff Richards (left) and Prof Dr Theodore Miclau (right) after receiving the ICORS Transformative Contribution Awards at the ICORS World Orthopaedic Research Congress, September 8, 2022 in Edinburgh (at exactly the time that Queen Elizabeth's death was announced on news channels- 18:30 UK).*

In September 2022 Prof Martin Stoddart was inducted by the International Combined Orthopaedic Research Societies (ICORS) as a Fellow of International Orthopaedic Research (FIOR). The ICORS FIOR nomination recognizes an individual's exceptional professional standing and achievements in the field of orthopedic research and their status as accomplished role models for their peers.

Dr Marco Chittò was awarded the Best Overall Presentation award at ICORS 2022 in Edinburgh, Scotland. The title of his presentation was "Dual application of bacteriophages and meropenem using microbead-loaded hydrogel for treatment of multidrug-resistant Pseudomonas aeruginosa in a mouse model of bone infection".

*Marco Chittò (far left) beside the other winners.*

First Best Research Paper Award for Firas Souleiman AGA Kongress, Vienna, Austria, 15-17 September 2022. Souleiman F, Heilemann M, Hennings R, Hepp P, Gueorguiev B, Richards G, Gehweiler D, Osterhoff G. Die aussagekräftigste Fussposition zur nichtinvasiven Detektion einer Verletzung der Syndesmose: Eine 3D-Analyse.

Daphne van der Heide and Gregor Miklosic were awarded the best oral presentation awards at the 8th Graubünden Forscht conference which took place from 21-22 October 2022 in Davos.


*Left to right: Barbara Haller Rupf, Director Academia Raetica; Britta Allgöwer, President Academia Raetica; Selina Steiner, Fachhochschule Graubünden; Danielle Fehr, CK-CARE; Conrad Schwanitz, PMOD/WRC; Marion Caduff, SLF; Francesca Suter, Pädagogische Hochschule Graubünden; Gregor Miklosic, AO Research Institute Davos; Daphne van der Heide, AO Research Institute Davos; Gion Lechmann, Head of Amt für Höhere Bildung / Kanton Graubünden.*

## 9.7 ARI new MOU's (Memorandums of Understanding)

The AOF and Balgrist University Hospital in Zurich – two pioneers with the complementary goal of improving patient care and outcomes in trauma and musculoskeletal disorders are initiating strategic collaborations in several areas. AO and Balgrist University Hospital officials met September 23, 2022, at the ARI to sign a memorandum of understanding outlining their potential collaborative synergies in research, innovation, and education. The collaboration includes two jointly supervised PhD projects focused on shared research at ARI and Balgrist University Hospital. The collaboration has its roots in the AO Davos Courses 2021 where Balgrist University Hospital Medical Director Mazda Farshad, MD, participated in the AO Spine Course, Endoscopy. After the course, he and Richards brainstormed about possible opportunities for the AO and his hospital to collaborate and exchanges have taken place in both Zurich and Davos to refine and make the collaboration concrete during 2022.

*AO Executive Director Research and Development Prof Geoff Richards and Balgrist University Hospital Medical Director Prof Mazda Farshad after signing the memorandum of understanding, September 23, 2022.*

A Memorandum of Understanding for academic cooperation was signed between the University 'Prof Dr Assen Zlatarov', Bulgaria, and the ARI. The Parties agreed to collaborate within the rules and regulations applicable in each of the institutions and subject to the availability of funds and resources, aiming at conducting joint research, implementing innovative projects, and improving specialists' training. The collaboration foresees conducting of scientific research on agreed themes including preparation of joint projects for obtaining of grant funding, exchange of scientific and technical information, and joint scientific supervision of post graduate students on the basis of cooperation and direct connections including possible exchange visits.

*From left to right: Prof Valentin Vasilev – Dean Faculty of Public Health, Prof Boyko Gueorguiev, Prof Sotir Sotirov – Vice Rector International Cooperations, and Prof Hristo Bozov, Dean Faculty of Medicine.*

## 9.8 New Board Positions

Prof  was elected by the TERMIS EU membership as Member at large on the TERMIS EU Council (and thereby also a Member TERMIS Global Membership Committee and member of the TERMIS Global Governing board).

Prof Boyko Gueorguiev, Biomedical Development program leader at ARI was awarded Honorable Research Fellow of the Institute of Metal Science, Equipment and Technologies with Hydro- and Aerodynamics Centre "Acad. A. Balevski" at the Bulgarian Academy of Sciences (IMS–BAS). The Institute has an established reputation in basic and applied research in metal science, crystallization, structure and properties of metals, alloys, and composites under dynamic loading. This award is a recognition of the extensive scientific collaboration between the two institutions within the subject of their MoU for integration of research, educational and innovation activities.

*IMS–BAS Director Prof Ljudmil Drenchev (left) handing over the award to Prof Boyko Gueorguiev.*

With great pleasure we announce that Peter Varga, PD, PhD, Biomechanics and Modelling Focus Area Leader at the ARI, was elected as Chair of the Meeting WebPortal Committee for the Council of The European Society of Biomechanics. This position builds upon the strong connection between the ARI and the Society, initiated by Professor Stephan Perren who was one of the Society's founders and was recognized for his tremendous contribution by creation of the ESB SM Perren Award.

## 9.9 Collaborations

**2022 Meeting of the AOTrauma Clinical Priority Program on Bone Infection**

The AO Trauma (AO T) Clinical Priority Program (CPP) Bone Infection meeting took place in Edinburgh, Scotland on September 11th, 2022, following the AO Trauma Research Commission Meeting. The principal investigator of the AO T CPP Bone Infection, Prof Steven Kates MD (Richmond, USA), and his co-Principal Investigator Prof Edward Schwarz PhD (Rochester, USA) assembled the CPP project leaders, affiliates and the members of the AO TRC, and the latest updates were presented. A total of 28 people attended the meeting.

**Prof Hamish Simpson**, Professor of Orthopaedics and Trauma at the University of Edinburgh presented the invited talk for the CPP meeting. The content of Prof Simpson's talk covered a range of clinically relevant areas related to fracture related infection (FRI). His highly interesting talk covered the relative resources available in different regions of the world and how to match trauma care to local resources.

**Prof Schwarz** from the University of Rochester opened the scientific talks with two reports on research related to the CPP's breakthrough discovery of S. aureus invasion and colonization of the osteocyte lacuna-canaliculi network (OLCN) of cortical bone during the establishment of chronic osteomyelitis.  Prof Schwarz's second talk described how the CPP has developed the first bone-targeted antibiotic via conjugating bisphosphonate to sitafloxacin.  Data demonstrating the efficacy of this new drug in vitro and in a murine model of implant-associated osteomyelitis was shown. **Prof Awad** from the University of Rochester presented on the fabrication of 3D printed PCL scaffolds containing calcium phosphate (CaP) microparticles or amorphous CaP (ACP) nanoparticles (NPs). **Prof Steven Kates** then presented an overview of the POSSI study, which was run with the hypothesis that a comprehensive "bundle" of infection prevention measures can be employed to substantially reduce the incidence of

surgical site infections from 5% to 3.75% for closed fractures and 10% to 7.5% for open fractures in those hospitals that adopt the bundle.
**Tina Bui-Bullock** from Prof Steven Gill's lab at the University of Rochester presented on the crosstalk between gut microbiota and host immunity that regulates *S. aureus* osteomyelitis severity in obesity-related type 2 diabetes. **Dr Bader and Dr Noll** from the University of Göttingen presented several novel approaches in the diagnostics of periprostethic joint infections. Next to the possibility to detect alpha defensins in synovial aspirates by mass spectrometry and the development of carbon nanotube sensors detecting bacterial growth, they showed a series of experiments focussing on the direct preparation of live bacteria from various joint-infection related sample types in order to identify the microorganisms using MALDI-TOF mass spectrometry, generally reducing time-to-result by 24h.
**Dr Muthukrishnan** from the University of Rochester presented on elucidating T cell immunity against *Staphylococcus aureus* osteomyelitis in humanized mice. This novel humanized CD34+ HSC mice model of transtibial implant-associated osteomyelitis was originally developed in collaboration with ARI. **Dr Chao Xie** from the University of Rochester presented on the *In vivo* multiphoton imaging of the race for the surface in mice. The established paradigm to explain the initiation of implant-associated infections caused by *Staphylococcus aureus* posits a competition between host cells and contaminating bacteria immediately following implantation, broadly known as "the race for the surface".
**Claudia Siverino** from the AO Research Institute Davos presented the project: "Implant retention in a sheep fracture related infection model: Evaluating fracture healing and an antibiotic loaded hydrogel". The sheep model with plating osteosynthesis and infection was successfully developed and different infection periods were tested. In all the cases, the results indicate that systemic antibiotic treatment does not clear the infection and mainly the infection burden in the intramedullary channel is still high at euthanasia.
**Fintan Moriarty** from ARI, wrapped up the meeting with a talk covering the recent research performed in ARI on bacteriophages and phage-derived enzymes. Bacteriophage therapy is re-emerging as a potential treatment of difficult to treat FRI, although the underlying scientific evidence for best practice is absent.

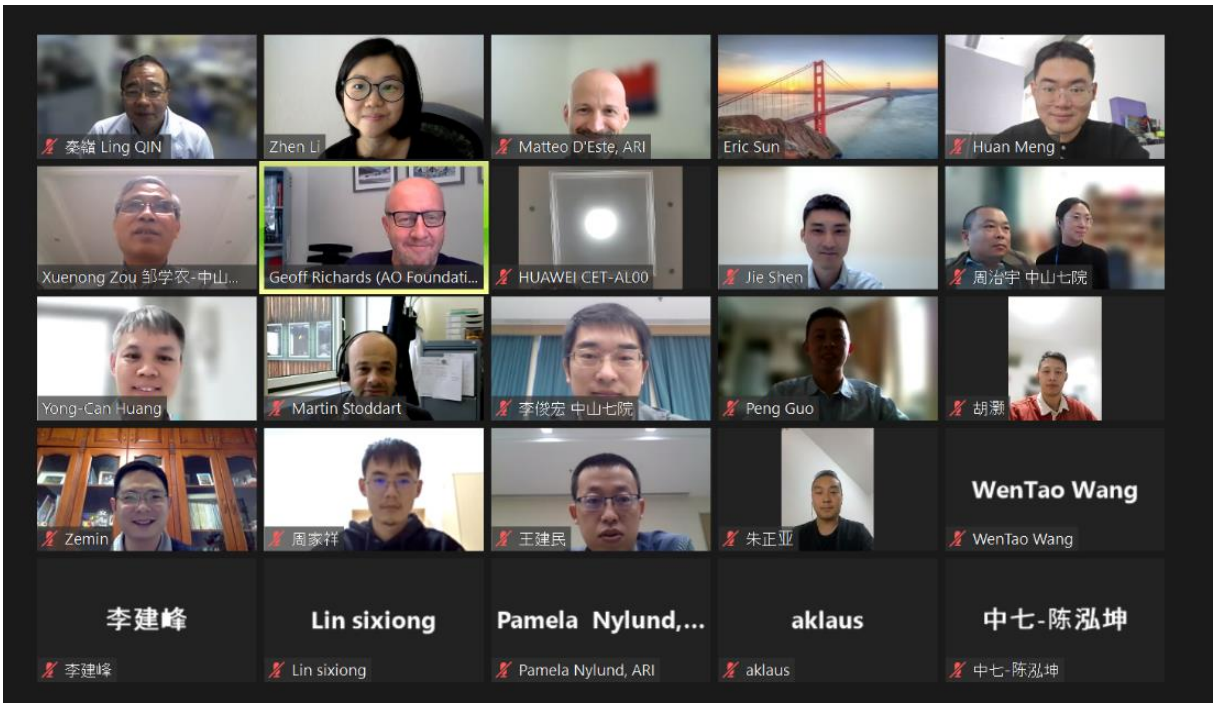
The meeting was held at an exceptional time in history. Queen Elizabeth's coffin arrived in Edinburgh from her summer home in the Scottish Highlands, past tens of thousands of mourners lining the route, ending up at the royal Palace of Holyroodhouse in the Scottish capital along the Royal mile which the team managed to join during a break.

*The AO Trauma clinical priority program on bone infection annual meeting in Edinburgh in September 2022.*

**Building research excellence through strategic collaboration**
Baltic Biomaterials Centre of Excellence delegations visit the ARI


As part of the Baltic Biomaterials Centre of Excellence (BBCE), ARI is supporting the establishment of a joint center for advanced biomaterials development in Latvia.
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. This collaboration started in 2020 and is ongoing with face-to-face trainings and visits of team members in both directions. EU H2020 grant agreement No 857287; ARI Funding CHF 1.4 M; period: 2020 – 2026.

**ARI – Sun Yat-sen University Webinar Series**
The ARI – Sun Yat-sen University (SYSU) (1$^{st}$ (Guangzhou) and 7th (Shenzhen) Affiliated Hospitals) webinars were organized by Prof Zhen Li (ARI) and Prof Zhiyu Zhou (SYSU) on 10.03.2022, 02.06.2022, and 01.12.2022. The goal of this webinar series is to share the most recent research from both institutes and other scientific partners of ARI in China and Hong Kong. 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 included 3D printing and tissue engineering for challenging musculoskeletal regeneration, Sound Guided Tissue Regeneration Focus Area activities and mimiX Biotherapeutics, magnetic resonance imaging R2* sequences can better detect microstructural cartilage changes than T2 mapping in cynomolgus monkeys with limited knee range of motion, anti-inflammatory therapy for cartilage preservation, nanomaterial-modified fibrous scaffolds for regulation of stem cell growth and differentiation, molecular mechanism of tensile mechanical stimulation in the progression of ossification of posterior longitudinal ligament, bioprinting and bioinks for musculoskeletal research at ARI, influence of particle aggregate state on magnesium ion microenvironmental establishment and biological performances of bio-nanocomposite, and the role and mechanism of Ly6a/Ly6e positive cells in the development and degeneration of articular cartilage.




*ARI-SYSU webinar, held on December 01, 2022.*

**PREMUROSA hands-on workshop at AO Research Institute Davos**

As partner organization of PREMUROSA MSCA ITN project, ARI organized a hands-on workshop for all ESRs in Davos. The goal of the workshop was to introduce and educate the ESRs (early-stage researchers) to the possibilities that 3D printing offers in biomedical research, as well as their in-house developed sound patterning technique. The two-day course started with a broad introduction on 3D printing strategies and sound patterning. The 3D printing technique allows researchers to create 3D structures by extruding a bioink, which is a mixture of cells, hydrogels, and other biocompatible materials through a syringe equipped with a nozzle. Sound patterning allows the creation of patterns formed by various types of particles or cells within a hydrogel upon application of soundwaves to the suspension. The theory and physics behind these platforms were presented and discussed with the ESRs. The program then continued with a tour to the research labs where the technologies were demonstrated by AO experts. Both hard and soft material 3D printing techniques were showcased. Afterwards, the ESRs were divided into groups of two to familiarize themselves with the biofabrication platforms. The experts at AO challenged the ESRs with technical problems to which the ESRs had to apply their newfound knowledge to provide solutions.


*PREMUROSA ESRs welcomed by PREMUROSA partner organisation AO Research Institute. From left to right: Ksenia Menshikh (ESR5), Hugo Abreu (ESR9), Virginia Alessandra Gobbo (ESR3), Ivana Banićević (ESR4), Nina Hofmaenner, Mari Lallukka (ESR1), Ilijana Kovrlija (ESR2), Nicola di Marzio (ESR6), Elzbieta Panczyszyn (ESR10) and Aert Scheper (ESR13).*

**Training event for the PIANO MSCA ITN project**
ARI, EU partners seek holistic solution to the problem of pain


*Researchers attending training for the PIANO project at the AO Research Institute Davos, Switzerland, April 2022.*

Fifteen young researchers specializing in a wide range of different areas came together at the ARI under the auspices of PIANO, a project addressing musculoskeletal pain, the leading global cause of disability, through the development of tools that identify and visualize mechanisms of nociception in the dorsal root ganglia outside of the central nervous system. PIANO is a Marie Skłodowska-Curie Actions-Innovative Training Networks (MSCA-ITN) project funded by the EU's Horizon 2020 research and innovation program.
The project's first training event, targeting young students and researchers all over the world, was held from April 4 to April 6, 2022. ARI carries out research into orthopaedic regeneration, hence connecting with pain researchers is an important part of this work. Back pain is, for example, the most common type of pain in the world, but there is little understanding of its mechanism.

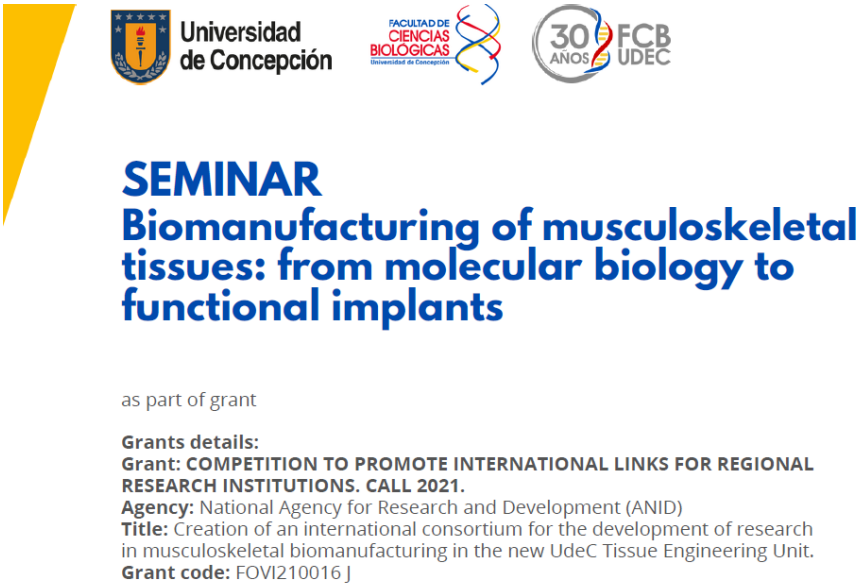
**iPSpine Consortium Meeting**
From June 14-15, 2022, the ARI hosted a consortium meeting of the EU Horizon 2020 project iPSpine (Induced pluripotent stem cell-based therapy for spinal regeneration). The iPSpine consortium is a collaboration of 20 participant organizations from Europe, Hong Kong, and USA, including universities, companies, and research institutes. Around 60 participants joined the consortium event in Davos, discussing recent progress and future studies towards the consortium goals. The iPSpine consortium was formed to initiate a European-led research effort to identify a future advanced therapeutic strategy that results into a radical new treatment of intervertebral disc degeneration-induced low back pain. With their multi-disciplinary expertise in the development of advanced therapies and their translation from bench to bedside, the aim of the iPSpine team is to investigate and develop a new advanced therapy medicinal product (ATMP) of the future, based on a novel developmental biology-based therapeutic strategy employing pluripotent stem cells (iPSC) and smart biomaterials. The iPSpine consortium will develop and demonstrate Proof-of-concept with the aid of novel and extended knowledge, tools, and technology platforms.

**Carthago Consortium Meeting**

The consortium meeting of the EU Horizon 2020 ITN project Carthago (Cartilaginous tissue regeneration by non-viral gene therapy; taking the hurdles towards efficient delivery) was organized by the ARI from June 18-20, 2022. The Carthago consortium combines 12 European participant organizations and 6 partner institutions. Around 30 participants attended the consortium event in Davos. The Early-Stage Researchers presented their progress reports and an outlook towards the individual and consortium aims. The Carthago consortium addresses the unmet problems of chronic low back pain due to intervertebral disc (IVD) degeneration and osteoarthritis (OA) that worldwide impact human health and well-being. Non-viral gene therapy has great promise as a 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. The consortium aims to fulfil the promise of non-viral gene therapy in these diseases. This aim is approached 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.

**ARI participates in a new international consortium for the development of research in musculoskeletal biomanufacturing with Chilean scientists**

In 2022, ARI participated in a newly formed international consortium for the development of research in musculoskeletal biomanufacturing with Chilean scientists Francisco Verdugo, dental surgeon, and PhD student at Jorge's Roberto Toledo Alonso group at the University of Concepción in Chile (UdeC). As part of the grant, Jacek Wychowaniec and Matteo D'Este hosted an online two-day webinar series entitled: "Biomanufacturing of musculoskeletal tissues: from molecular biology to functional implants" on the 11th and 12th of October 2022. Together with the Chilean partners, Francisco Javier Verdugo Avello and Jorge Roberto Toledo Alonso from UdeC and Juan Pablo Acevedo Cox from Universidad de los Andes, the event brought together a two-days of knowledge exchange and encouraged scientists from two continents to establish new collaborations. This exchange is being followed up by experimental work to get preliminary data for potential future collaborations.




*Advertisement of the seminar series that took place on the 11th and 12th of October, hosted by ARI.*

**Funding**: 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.

**ARI scientists awarded 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 various matter in real time, being 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 took place at DLS beamline B21, a small-angle X-ray scattering (SAXS) instrument. This project was 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 advanced our understanding of the importance of molecular interactions for generating structure-function relationships in generated biomaterials. For example, SAXS helped us unravel:

1) the changes in structure of chemically and physically crosslinked composite hyaluronic acid (HA) and ε-polylysine hydrogels as a function of the feeding components' ratio.
2) the type of fibrillar networks formed from self-assembling peptides (fibrillar versus lamellar), and their network types upon compositing with chemically functionalized HA.
3) changes in structure of HA-collagen composites indicating the effects NaCl salts have on the formation of homogenous networks.
4) thermoresponsive behavior of novel support baths composed of thermoresponsive block-co-polymers combined with gelatin and Carbopol.

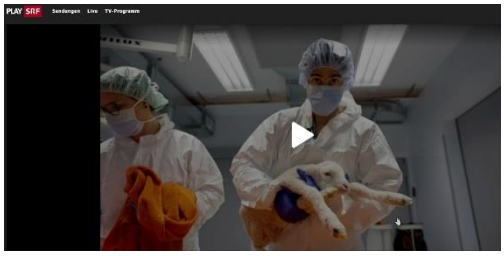
The obtained results will allow better designs of hydrogels for future musculoskeletal tissue engineering applications and in biomedical 3D printing.

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

## 9.10 Swiss News

ARI was several times on Swiss news in 2022 both at SWI swissinfo.ch - a branch of Swiss Broadcasting Corporation SRG SSR and on SRG television science program Einstein.

The first television program was in June on Animal experiments: what surgery can learn from laboratory sheep (Video in German). "Einstein" looks at the tension between animal experiments, animal welfare and cutting-edge research. In the AO Center Davos, bone fractures are researched with a special flock of sheep. What can surgery learn from these laboratory animals?



The first article and broadcast from Swiss info was on How Davos's storied past is shaping the future of medicine with a video on the gathering of the Bone Doctors. Davos, host to the World Economic Forum (WEF), also attracts surgeons and doctors from all over the world to its cutting-edge research and training institutes. It's part of a long history of scientific innovation in the small Alpine ski town.


The second article and broadcast from Swiss info was on studying Bones in the lab. Before 1960, broken bones were treated by using plaster casts or traction. Thirteen Swiss surgeons began rethinking fracture treatment: they standardized instruments, screws and nails, scientifically evaluated every operation, and started training surgeons and nurses. Swissinfo go behind the scenes to see what new technologies are currently being developed in ARI.

# 10 ARI 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
- Knowledge about how to approach research challenges
- Inspiration from being part of a world-renowned international multidisciplinary team
- Inside knowledge of the AOF
- 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, Interns 2022*

**Research Fellows**

**Till Berk**: University Hospital Zurich, Department of Trauma, Zurich, Switzerland
ARI Project: **Evaluation of Cannulated Compression Headless Screw (CCHS) as an alternative implant in comparison to standard S1/S2 screw fixation of the posterior pelvis ring: a biomechanical study.**
During my time in the Biomedical Development program under my mentor Boyko Gueorguiev, I was given the opportunity to work with many outstanding scientists and to research clinically relevant topics on artificial bone models. The main focus was on a special double-threaded screw (CCHS) and its broader applicability for improved stability in various pelvic injuries. During my time, the creativity of the team and the excellent collaboration with many other groups at the ARI, allowed us to produce and test our own medical product with clinically relevant results. Coming from the big city of Zurich, my family and I have enjoyed the particularly beautiful nature and mountains in Davos and Graubünden has become our favorite canton. I am very grateful to have been part of such a professional and brilliant team and to go back to my clinical work with many important and clinically relevant detections. The crowning glory of the fellowship was the participation in the AO courses, where I was able to learn many new aspects for my clinical work and discuss the new findings of my research with colleagues from all over the world.

**André de Souza Salvatore**: São Paulo State University (UNESP – Botucatu Campus) São Paulo, Brazil
ARI Project: **Mouse osteotomy models pain scoring and weight loss analysis. Refining and evaluating correlation between evidence base data of different surgical research models.**
Being welcomed as the first Brazilian Veterinarian at the ARI in Davos as a Veterinary Fellow was a great honor. During my stay I supported the team in all running animal studies and gained an insight and experience in the field of preclinical surgery and research, laboratory animal medicine, RX and CT imaging and I started working on my doctoral thesis. I was grateful to have the opportunity to work with and learn a lot from an amazing team of specialists in the field of orthopedic research, anesthesia, surgery, and biomedical imaging enrolled in the preclinical work. And I was also very happy to work with other groups such Histology, Biomedical Development, and Infection Biology. And of course, for a Brazilian, the Davos nature and snow was a show by itself. Special thanks to Stephan Zeiter and Daniel Arens for the opportunity and the amazing encouragement and support they offered me for my still growing professional career. It was and still is, a great adventure.

**Vuyisa Mdingi**: Orthopaedic Trauma, Sepsis and Limb Reconstruction, Dr Pixley Ka Isaka Seme Memorial Hospital, Durban, South Africa
ARI Project: **The interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics in staphylococcal infections.**
During my time as a medical research fellow at the ARI Davos, I was part of the Infection Biology Focus Area. I spent my time doing both *in vitro* and *in vivo* experiments investigating whether certain classes of NSAIDs negatively affected the efficacy of antibiotics. We also performed micro-CT analysis within the different classes of NSAIDs. I also had the opportunity to test the combination of bacteriophages and NSAIDs *in vitro* on different strains of *Staphylococcus aureus*. Joining the ARI after having recently completed my orthopaedic surgery residency allowed me the opportunity to delve deeper into basic science research under the guidance of world-class scientists and researchers. It was the perfect foundation for my future research projects.

**Rayna Mechkarska**: University Hospital for Active Treatment and Emergency Medicine "N.I. Pirogov", Sofia, Bulgaria
Projects related to: **Distal ulnar fractures, subtalar arthrodesis, total talus replacement, and more.**
I was able to travel to many destinations across the country, from small villages to big cities and magnificent mountain peaks. I collected wonderful memories of the places I went and even more wonderful moments with the people I met. Thanks to this opportunity to work at ARI Biomedical Development, I gained a lot of knowledge of joint kinematics and biomechanical research and how to do this through different setups, thanks to all the engineers in the department. I am leaving Davos with many new ideas and a new pair of freeride skies. I can say that I approached a higher level in my profession and almost an expert level in cheese.

**Tatjana Pastor**: Inselspital Bern, Clinic for Hand and Plastic Surgery, Berne, Switzerland
ARI Projects: **1. Biomechanical analysis of recently released new suture material for tendon transfer in radial nerve palsy 2. Biomechanical effect of plate working length 3. Low – profile dual mini-fragment plating of diaphyseal clavicle fractures.**
During my research fellowship at ARI my focus was mostly on research regarding biomechanical analysis of various implants and suture material. Working with an international team with people of different specialization backgrounds represented an enrichment not only for my research at ARI but has also affected my translational research in the future. I have met fantastic new people and I am looking forward to spending more time with them not only at ARI but also in this beautiful landscape.

**Maria Eugenia Pirera**: Pontifica Universidad Católica Argentina, Buenos Aires, Argentina
ARI Project: **Combination of the collagen membranes within the LEGO® inspired interlocking system, a new therapeutic alternative for bone regeneration in maxillary defects.**
During my time in Davos as a medical research fellow in regenerative orthopedics, my goal was to find a suitable collagen membrane capable of retaining cells within the pre-engineered scaffold structure with a configurable layer composition based on the LEGO principle® to achieve the promotion of cell viability and response.
LEGO®-like structures are virtually designed with CAD software (Autodesk Fusion 360®) and printed on polycaprolactone (PCL) composite layer scaffolds with the RegenHu 3D Discovery® bioprinter. The collagen membranes we used were: 1. Lyostypt (B. Braun) and 2. Collagen Cell Carrier (CCC) (Viscofan Bio Engineering). These membranes are placed between layers of 3D printed scaffolding that interlock with each other through the LEGO® system.
Without a doubt, it was not only a great professional experience, but also a personal one. The change was huge and for the better. I came to Davos with totally different expectations and life gave me a great reward. Spending hours operating on patients while working with cells was a great challenge! Having the opportunity to work at ARI gave me a unique opportunity to expand my knowledge and underscored the value of clinically inspired translational research. I enjoyed mountain activities, enjoyed skiing with friends and traveled all over Europe. I met many wonderful people in Davos, ready to welcome me. For me AO is not a company, it's like a family, that's how I felt this year.

**Georgi Raykov**: Medical University Varna, Bulgaria
ARI Project: **1. Biomechanical stability of delta screw configuration in subtalar arthrodesis. 2. CT findings on ankle stability after 3D printed total talar replacement.**
In the autumn of 2022, I had the amazing opportunity to do a 4-month research fellowship in the Biomedical Development program under Professor Boyko Gueorguiev. Under the guidance of Dr Dominic Gehweiler and Dr Ivan Zderic, we managed to conduct various cadaveric experiments in the field of foot and ankle surgery. We combined CT scanning and 3D software to gain an insight of the change of stability in the foot, following bone replacement surgery. Alongside that we conducted biomechanical testing on various screw fixations in the subtalar joint on cadaveric paired feet. I got to enjoy working in the field I am passionate about and explored the beauty of the Davos region - biking, running, and climbing. Most importantly the people at ARI, thanks to whom my stay is so memorable, were amazing. For me it has certainly been a once in a lifetime experience.

**Clemens Unterguggenberger**: University of Freiburg, Germany
ARI Project: **Effect of irrigation fluid compositions on articular chondrocytes.**
I joined the ARI as a medical research fellow in September 2022. During my time in Davos, I investigated the effect of irrigation fluid compositions on articular cartilage. My project was based on a collaboration with the orthopedics department of the university hospital in Freiburg. I highly appreciated the opportunity to gain experience and knowledge in experimental research. It was an exciting - and personally very valuable - time working in the field of cartilage biology with an interdisciplinary group of scientists from all over the world. In my free time I enjoyed doing mountain sports in the stunning surroundings of Davos. There are only a few places in the world that can offer a living in the middle of the mountains while still working in such a renowned facility. In the upcoming year I will complete my medical studies at my home university in Freiburg. I look forward to stay in touch (and visit again!).

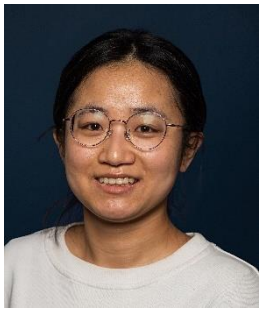
**Niels Vanvelk**: Erasmus MC, Rotterdam, the Netherlands
ARI Project: **1. Establishment of an *ex vivo* model for *S. aureus* invasion of the osteocyte lacuna-canalicular network.**
**2. Development and characterization of a subcutaneous implant-related infection model in mice to test novel antimicrobial treatment strategies.**
**3. Development of a fracture-related infection model featuring the main components of the clinical condition.**
During my time at ARI, I worked as a medical research fellow in Infection Biology. I was welcomed by a group of smart scientists and clinicians, who taught me a lot and have become good friends. I participated in the development of multiple preclinical models, which allowed me to work together with other ARI departments, such as the Preclinical Facility and the Histology group. By working in the lab and using the microscope I learned several skills that will help me for the rest of my scientific career. Outside of work, I learned skiing, went for hikes in the beautiful mountains, and enjoyed après-skiing. I have lots of fond memories from my time in Davos and look forward to collaborating with ARI on future projects.

**Guest Students**

**Jhaleh Amirian**: Riga Stradins University, Riga, Latvia (BBCE)
ARI Project: **Development of natural protein based bioinks as dual drug delivery systems for bone regeneration.**
I joined the ARI as a member of the BBCE project on July 1st, 2022, for a five-months period. My research at Davos focused on the formulation of bioinks using SFMA and HAMA, the evaluation of their physical, chemical, and rheological properties, and 3D printing. My goal in the future is to evaluate their *in vitro* biocompatibility and differentiation in the presence of anti-inflammatory and osteoinductive drugs. Working with an interdisciplinary team of highly motivated and dedicated biomedical materials researchers enthuses me. Furthermore, I enjoyed being integrated into social activities at ARI with other members. Working at AO is such a pleasant experience with so much friendly interaction between all the members that it contributes to the great working atmosphere. Spending time in nature and making new friends in Davos was wonderful, especially in the cold, white winter. I look forward to gaining new experiences and collaborating with the AO family on an international scale.

**Oscar Chan**: Medres – medical research GmbH, Köln, Germany
ARI Project: **Characterization of a novel bovine *in vitro* neurite sensitization model.**
I joined ARI for a 5-month secondment after having completed my degree in Biomedical Science at the University of York (UK) and having been 6-months into an EU ('PIANO') ITN project. I worked in the Regenerative Orthopedics program under 'Disc and Cartilage Biology', where I focused on characterizing a novel pain model to monitor nociceptive-derived pain. This stint at ARI gave me the opportunity to apply my knowledge in cell biology and neurophysiology to validate an *in vitro* sensitization model that could be used to observe pain, and to investigate its viability for future 19F delivery using MRI. I thoroughly enjoyed being in a friendly and productive, yet fun and relaxed working environment. My colleagues were extremely kind, helpful, and cooperative and helped me get the most out of my time in Davos, both in and out of the lab. Of course, the beautiful nature and serene landscape of Davos, the ability to do so many outdoor activities and meeting new friends from all different kinds of backgrounds contributed immensely to the whole experience.

**Karina Egle**: Riga Technical University, Riga, Latvia (BBCE)
Project: **BBCE long term outgoing visit No.10 "*in vivo/vitro* imaging".**
As part of my doctoral studies, I had the opportunity to join ARI for 3 months. Under the supervision of Matteo D'Este and Géraldine Guex, I worked in the Regenerative Orthopedics program, where I studied the cytotoxicity of biomaterials and drugs *in vitro*. This long-term visit to ARI gave me the opportunity to get to know the cell environment, learn to work independently with cells and conduct research. There was also an opportunity to learn how to work with a confocal microscope, getting the opportunity to look at the morphology of cells. I really liked working in a friendly and supportive team, trying to help other researchers in their projects. I enjoyed my time in Davos, the opportunity to make new friends and go hiking.



**Wen-Li Feng**: Beijing University of Chemical Technology, Beijing, China
ARI Project: **Targeted poly(D-amino acids) nanoparticles loaded with antibiotics for staphylococcal biofilm eradication.**
I am a PhD student from Beijing University of Chemical Technology majoring in Chemical Engineering and Technology. I mainly focused on the synthesis and application of biomedical materials. In 2022, I had the incredible opportunity to join the ARI's Focus Area on Infection Biology for a one-year internship in the field of implant-related infections. This internship at ARI gave me the possibility to evaluate the application of our biomedical materials in implant-related biofilm infection. Aside from that, I gained valuable laboratory experience and broadened my knowledge. I enjoyed working with lots of cute people in this welcoming and encouraging environment.

**Wei Gao**: Lanzhou University of Technology, Lanzhou, China
ARI Project: **Sound-induced robots with magnetic responsiveness.**
My main interests in ARI were the acoustic induction of magnetic microstructures and the implementation of diverse magnetic field-driven motions. The Acoustic Induction Morphology Group is the leader in this branch of biological tissue molding technology, and the associated preparation equipment has been developed. I've mastered the fundamental concepts, theoretical underpinnings, and testing principles of this technology throughout my time, and finally I was able to conduct relevant experiments on my own. Not only the equipment was perfect, but there was also frequent academic debate and a relaxed scientific research atmosphere. I enjoyed every moment of my time, it was full of natural beauty and endless outdoor activities.

**Florian Kessler**: University of Bern, Switzerland
ARI Project: **Biomechanical stability of bone screws in the proximal humerus.**
I was given the opportunity to conduct my master's thesis in a joined program with ARI and the University of Bern. With the aim of better understanding implant fixation failure, I tested screws in bone samples under cyclic loading and investigated their migration at different load levels. Further, scans of these specimens allowed me to conduct finite element analyses. Thanks to my time at ARI, I got to know several different research methods that would be a great help for my future. Additionally, I was able to have a look at other people's projects and learn about their research. Staying in Davos for a couple of months was a great pleasure for me. I enjoyed the countless outdoor activities and made many new friends from all over the world.

**Olivia Kim**: The Cooper Union for the Advancement of Science and Art, New York, USA
ARI Project: **A translational approach integrating developmental biology and tissue engineering towards regeneration of the annulus fibrosus of the intervertebral disc.**
I had the wonderful opportunity to partake in an internship at ARI over the summer before the completion of my bachelor's degree in Chemical Engineering at The Cooper Union for the Advancement of Science and Art based in New York City. I was part of the Biomedical Materials Group and worked on the testing of patternable hydrogels for long-term cell culture. This project allowed me to gain valuable laboratory experience with advanced technologies that aren't readily accessible to me at my institution. By being able to incorporate my knowledge and skills from my engineering background, I was able to apply my newfound skills in the research I did. It was during this time that I was able to explore the beautiful landscape of Switzerland and share my time with the friends I made. I am so thankful that I was able to meet and collaborate with the amazing people at AO Davos.

**Alexandra López de Victoria**: Western University of Health Sciences in Pomona, California, USA
ARI Project: **Antibiofilm therapy using local application of bacteriophages in a mouse model of MRSA and *P. aeruginosa* ODRI.**
During my time in Davos as a Veterinary Research Fellow in the Preclinical Facility (PCF) I collaborated and worked on many ongoing research projects. My focus during my time there was the use of bacteriophage therapy for the treatment of orthopedic device related infections with MRSA and *P. aeruginosa* on mice. My experience at AO helped me gain confidence in my clinical skills and solidified my interest in Orthopedic Surgery within veterinary medicine. I had the opportunity to work with amazing veterinarians whose teachings and lessons I will take with me in my career. Besides the wonderful time I had at AO, I also enjoyed the cultural aspect of this opportunity. I was able to explore Davos' beautiful surroundings and take in nature by going on hikes and mountain bike rides. Suffice it to say, I will never forget my summer in Davos.

**Lana Micko**: Riga Stradins University, Institute of Stomatology, Riga, Latvia (BBCE)
Project: **Platelet Rich Fibrin (PRF) characterization with biochemical assay ELISA and immune profile characterization.**
During residency studies of Oral and Maxillofacial surgery at Riga Stradins University I started doctoral studies focusing on Platelet-Rich fibrin in orthognathic surgery and had a great possibility to be a guest PhD student for 3 months in ARI due to the BBCE project. Joining the Biomedical Materials Regenerative Orthopaedics group, I was able to improve my knowledge in the bioengineering field and to develop my skills in science working in the lab. It was a pleasure to be a part of the community of professional and creative scientists as well as pleasant, friendly, and supportive people. It was a great place to work and also to recreate forces enjoying nature in Davos. I got great experiences working in science.

**Athanasia Pylostomou**: Riga Technical University, Riga, Latvia (BBCE)
Project: **Polymer application as biomaterials for bone regeneration**
I am a PhD candidate in Chemical Engineering at Riga Technical University within the BBCE project. I came as a guest student from October till December 2022 and joined the Biomedical Biomaterials group of the Regenerative Orthopedics program. There, I worked on 3D bioprinting using thermoresponsive hydrogels and human mesenchymal stem cells derived from bone marrow to develop a system for preliminary endochondral ossification. The training at ARI gave me the opportunity to gain knowledge on the fascinating subject of 3D bioprinting and of thermoresponsive hydrogels, while simultaneously becoming even more familiar with cell cultures. I enjoyed working in a supportive and friendly environment, meeting new people from all over the world and making new friends, having fun in the snow, and travelling around Switzerland and nearby countries.

**Antons Sizovs**: Latvian Institute of Organic Synthesis, Riga, Latvia
ARI Project: **Baltic Biomaterials Centre of Excellence (BBCE)**
I joined the ARI Preclinical Services Program as part of the BBCE project. During my 1-month stay, I learned about ARI's organizational and experiment planning aspects, how to obtain ethical permits, and the onboarding process for new personnel and students. I also learned about the creation and use of standard operating procedures, as well as data collection and management. I observed sheep surgeries and recovery monitoring, gained knowledge about 3D modeling for orthopedic implant development, and histological evaluation of tissues. I also had the opportunity to meet with many talented scientists to discuss scientific ideas. I enjoyed the beautiful nature around Davos and swimming in the cold waters of Lake Davos.

**Baiba Svalbe**: Latvian Institute of Organic Synthesis, Riga, Latvia
ARI Project: **Baltic Biomaterials Centre of Excellence (BBCE)**
I am a post-doc researcher at the Latvian Institute of Organic Synthesis with a background in life sciences and pharmacology. I attended and got practical experience with a surgical procedure for a mouse femoral defect model with plating and the rat calvarial defect model. After surgeries, I got trained on the scoring rules for evaluating animal well-being (mice, rats, and rabbits). I enjoyed working in a friendly and supportive environment. This was a great experience and I got new knowledge, which I brought back to my home laboratory and started to use. I enjoyed Davos' downhill skiing, hiking, and art museum.

**Reinis Vilskerts**: Latvian Institute of Organic Synthesis, Riga, Latvia
ARI Project: **Baltic Biomaterials Centre of Excellence (BBCE)**
I am a leading researcher at Latvian Institute of Organic Synthesis. At the ARI Davos I was able to take part in some training regarding the topic of Quality Management and to attend the ISO 9001 and ISO 13485 audits of the ARI. Many discussions took place with the Quality Manager regarding ARI's implemented SOPs. In addition, I had a chance to take part in the day-to-day activities of the histology laboratory: preparing sections of soft and hard tissues and performing their analysis together with the ARI pathologist. Finally, I was able to spend time at the Preclinical Facility observing surgeries and learning about the surgical methods and sterile techniques employed at the ARI. On weekends I enjoyed hiking in the mountains and cowbell concerts in the countryside.

**Internships**

**Laura Belcastro**: Tor Vergata University of Rome, Italy
ARI Project: **Developme.nt of sensors for inflammation monitoring - MoNOSens, NIOXIS.**
I joined ARI after finishing my bachelor's degree in Chemistry at University of Rome Tor Vergata for a 7-months internship. Here I worked in the Disc and Cartilage Biology Focus Area on the MoNOSens and NIOXIS projects, focusing on the development of an electrochemical and optical sensor for nitric oxide monitoring during inflammation. This gave me the opportunity to learn how to work in a biology lab and deepen my knowledge in sensors and biosensors applied in biomedical studies. I enjoyed working with my group, staying in the beautiful mountains of Davos, and spending time with great friends.

**Alicia Feist**: University of Bern, Switzerland
ARI Project: **Support and content expansion of theosteosynthesis learning platform (OSapp).**
I joined the Biomechanics and Modelling Group at ARI during my Masters in Biomedical Engineering at the University of Bern. Here I mainly worked on the content extension of the OSapp, focusing on external fixation. This internship gave me the possibility to gain some specific work experience, especially since I did my bachelor's degree in a different area (Industrial Engineering). I really enjoyed working on the OSapp since it combines technical, medical, and educational aspects. I really appreciated the great atmosphere at work and the supportive team members. I enjoyed staying in Davos while spending a lot of the time in the mountains and developing an unexpected passion for road biking.

**Alisa Hangartner**: Swiss Federal Institute of Technology (ETH), Zurich, Switzerland
ARI Project: **Investigation of multicomponent photoinitiator-free hyaluronan bioinks.**
I am a Master student in Biomedical Engineering at the ETH Zurich, and I conducted an internship and my Master thesis in the Regenerative Orthopedics program at the ARI. I was part of the Biomedical Materials team, where I investigated a radical-free photopolymerizable hyaluronan bioink for articular cartilage tissue engineering in collaboration with the company Fidia Farmaceutici SpA. I had the opportunity to dive into the field of extrusion-based 3D printed hydrogels, gained hands-on experiences with cell cultures and expanded my knowledge in rheological characterization or *in vitro* assessments. I made great memories with my team members while cross country skiing, touring, climbing, or cooking and playing games together. I am grateful that I had the opportunity to work in such an inspiring and fun place – thank you very much.

**Carla Hetreau**: Swiss Federal Institute of Technology (ETH), Zurich, Switzerland
ARI Project: **1. Development of an interactive osteosynthesis learning platform. 2. Validation of finite element predictions of fracture healing with the fracture monitor.**
I am a Master student in Biomedical Engineering at ETH Zürich with a specialization in Biomechanics. During my 6-month internship, I developed new modules for OSapp, an online educational platform using interactive finite element simulations to illustrate biomechanical principles of fracture fixation. The goal of my Master's Thesis was to validate finite element predictions of fracture healing based on data obtained from the *in vivo* implanted Fracture Monitor. I sincerely enjoyed my time at ARI, and I am very grateful for having had the chance to spend one year here. I loved living in Davos, especially because the cross-country ski slopes and the mountain bike trails are right next door.

**Aline Klaus**: Swiss Federal Institute of Technology (ETH), Zurich, Switzerland
ARI Project: **Effect of resting period and number of deformations in mechanically driven mesenchymal stromal cell differentiation.**
I came to ARI as part of my master's degree in Biomedical Engineering. I performed a 6-month internship in the bone biology group, where I worked on a project investigating the cellular response to different deformation protocols. I analyzed the cellular response with different methods like histology, mechanical tests, and PCR. This allowed me to deepen my skills in cell culture and molecular analyses while putting the knowledge I gained during my studies to practical use. I appreciated working in such a supportive and friendly environment, and I am grateful to all who enriched my time at the ARI, whether it was with fun lunchtime conversations or with advice and support both for my work at ARI and for my future in science.

**Sara Lindenmann**: Swiss Federal Institute of Technology (ETH), Zurich, Switzerland
ARI Project: **Validation of a shape-matching-based fracture reduction navigation approach.**
I recently completed my Master's degree in Biomedical Engineering at the ETH Zurich. For my Master's Thesis Project I was grateful to be able to join the Biomechanics and Modeling Group under Peter Varga. I spent most of my time improving and validating a software for shape-matching-based fracture reduction navigation tool. While it was a very theoretic and computer-based project, I really appreciated the opportunities to help out in the lab with other projects and gather many valuable experiences. I quickly made memorable friendships through the very inviting and friendly atmosphere at ARI. I of course also enjoyed the amazing location in Davos where I was able to go on frequent skiing and biking trips or just generally enjoyed the beautiful nature.

**Marcia Mürner**: Swiss Federal Institute of Technology (ETH), Zurich, Switzerland

ARI Project: **Rational design of a hybrid bioink to instruct immune cells towards better healing of musculoskeletal tissue.**

As part of my Master's studies at ETH Zürich in Biomedical Engineering, I had the pleasure to be part of the Biomedical materials group. Under the supervision of Dr Jacek Wychowaniec, I worked on the development of a novel bioink consisting of hyaluronic acid and β-sheet forming, self-assembling peptides. This internship gave me the great opportunity to dive deep into theory and practical aspects of hydrogels. I gained a lot of lab experience in physical chemistry and am now able to work more independently. Being surrounded by smart, innovative, and enthusiastic people who are so deeply involved in musculoskeletal research truly inspired me. I also spent many hours outdoors: starting in fall with running on small trails lined by yellow-brown larches, I switched to cross-country and alpine skiing as the winter arrived. I am very thankful for this whole experience, in and outside of the lab.

**Louise Ortet**: Institut Supérieur d'Ingénieurs de Franche-Comté, Université de Franche-Comté, Besançon, France

ARI Project: **MechEndro - Effect of short time vs long time stimulation on human mesenchymal stem cells differentiation fate.**

I was studying Biomedical engineering at the University of Besançon in France, with a particular taste for the field of tissue regeneration in research. At ARI I had the opportunity to perform a 6-month internship in the Regenerative Orthopaedics program from May to October 2022 to obtain my engineering degree. The project I worked on aims to understand better the differentiation of human mesenchymal stem cells upon different mechanical deformation. During this time, I've been able to make use of my knowledge from past experience while gaining skills about lab work/techniques (PCR, 3D cultures, etc.) and about musculoskeletal regeneration. Working in an interdisciplinary and international institute was a very stimulating experience, with great opportunities to meet and exchange with so many fantastic people. I enjoyed spending time with my AO friends by playing volleyball, going to the Davos Lake, doing some (not so easy...but wonderful) hikes to discover the mountains, and, of course, eating a few Swiss culinary specialties. I look forward to being back at Davos and/or AO Research Institute if I have the opportunity again.

**Romedi Parolini**: Scuol, Switzerland

ARI Project: **IVD with neurovascular network: an *in vitro* discogenic pain model**

After having graduated the Matura in Chur, I joined the Swiss army for my mandatory service. After having finished my days in service, I joined the ARI at the end of 2022 for a 6-month internship. Not having studied yet, I didn’t have much background knowledge. Nonetheless I had the chance to gain a lot of research experience. This insight into the work-life of a scientist in combination with conversations I had with students helped me to decide which course of studies is best suited for me. Therefore, I am very grateful for the opportunity AO gave me. Working in the mountains of Davos I felt just like at home, being from the neighbor valley Engadin.

**Jérôme Schlatter**: Swiss Federal Institute of Technology (ETH), Zurich, Switzerland

ARI Project: **Predicting patient-specific mechanical failure of proximal humerus fracture plating with computer simulations (SystemFixII).**

As part of my studies for the Master of Science in Mechanical Engineering with specialization in Biomedical Engineering at ETH Zurich, I joined ARI for a 9-month internship. I mainly worked with clinical data of patients that had experienced proximal humerus fractures and had been treated with PHILOS plates. While analyzing sensor data obtained from postoperative shoulder activity tracking and creating patient-specific finite element models based on pre- and postoperative CT scans to predict mechanical failure of the fracture fixations, I learned a lot about the aspects of biomechanical research and biomedical development. Nevertheless, it was the inspiring workplace culture and the supportive character of the team that made my stay in Davos a memorable experience. I also very much enjoyed hiking through the snowy landscape and taking up the beauty of the surrounding nature.

**Götz Schlipf**: Ludwig-Maximilians-University, Munich, Germany

During my clinical rotations as a veterinary student, I was gladly given the chance in 2022 to do an internship at the Preclinical Facility at the ARI. As I have always been interested in research as well as clinical surgery it included a perfect combination of both. I was able to get a glance at multiple projects that even increased my fascination for clinical research and helped me to choose a science-based career path after my graduation. The whole team was very eager to integrate students and supported me throughout the whole internship. Not only did I enjoy the atmosphere at the institute, but also the wonderful winter in Davos, being able to ski and hike in the surrounding beautiful mountains.

**Alessia Valenti**: University of Bern, Switzerland

ARI Project: **Investigate patient-specific healing status and failure risk of long bone fractures.**

During my master's studies of Biomedical Engineering with a major in Biomechanical Systems, I had the opportunity to discover a research-based working environment by joining ARI for a period of 9 months. This great experience started with a 3-month internship followed by my Master's thesis project. I had the pleasure of working on two ongoing research projects focusing on patient-specific healing status and failure risk of long bone fractures fixed with locking plates using CT image-based FE models. This provided me with valuable knowledge and personal growth. I really enjoyed my time and work at ARI in such a pleasant and motivating environment.

**Davina Walser**: Swiss Federal Institute of Technology (ETH), Zurich, Switzerland

ARI Project: **Advanced *in vitro* organ degeneration models for musculoskeletal research.**

Through my bachelor's degree in human medicine at the ETH in Zurich, I got the chance to do a 3-month internship combined with my master thesis in the Regenerative Orthopaedics program at ARI Davos. This internship allowed me to gain valuable insight into this unique multidisciplinary project. I could learn a lot about *in vitro* organ models of IVD degeneration as well as bioreactors for IVD organ culture. I am grateful for this experience and thankful to get to know many interesting people.

# 11 Project Abstracts by Sponsors

## 11.1 AO CMF

**AO CMF Clinical Priority Program (CPP) Consortium:** Instructive bone regenerating hydrogel for translational bone repair **(AO CMF BOOST) (started) (**ARI consortium personnel: M Stoddart, E Della Bella, T Serra, M D'Este, E Bektas)

**Background:** As part of a strategy to better utilize funding streams, AO CMF made an open call for collaborative clinical priority program (CPP), with the instruction to ideally to include both ARI with external partners. After an open call eligible consortia were independently evaluated by the AO RRC and the highest ranked consortia was selected.
**Goal:** Due to the lack of sufficient autograft volume, large bone defects commonly require additional material, both as a void filler and as a source of osteogenic material. This project aims to develop a novel bone forming substitute comprising of a self-assembling peptide system, combined with a bone allograft. The unique aspect of the material is that it can be used to regulate exposure to endogenously produced growth factors, thus improving osteogenesis while at the same time controlling the immune response and inflammation. This is achieved by the incorporation of peptides that can selectively bind, organize, and present specific growth factors (Interleukin-1, vascular endothelial growth factor, bone morphogenetic protein 2). The binding efficiency can be fine-tuned, thus regulating the presentation to cells and subsequent downstream signaling. The graft will be prepared intraoperatively and in addition can also be 3D printed intraoperatively using soundwaves to produce defined patterned sheets that can be sutured into calvarial defects. Furthermore, the artificial bone graft is mixed with bone marrow aspirate concentrate (BMAC) to form a rich intraoperative cell-based implant material that is precellularized. A further challenge in the development of novel bone biomaterials are the methodologies commonly used to test their functionality in vitro. A significant number of materials, if not most, have been tested in vitro with promising results, yet they commonly go on to fail in vivo. This suggests there is a fundamental flaw in the process used to test materials in vitro. With this in mind, a second arm of this study will specifically address how materials are tested in vitro and ex vivo, with in vivo data being reverse correlated to in vitro results in order to establish more predictive early outcome measures. This will be achieved by requiring a detailed analysis of immune regulation, inflammation, and osteogenic differentiation.

**Partners:**

- Mata Alavro (D.Eng), University of Nottingham, United Kingdom
- Akdis Cezmi (MD) & Akdis, Mübeccel (MD, PhD), Swiss Institute of Allergy & Asthma Research, University Zurich, Davos, China
- Zhiyu Zhou (MD, PhD) & Yingying Lu (MD, PhD),, The Seventh Affiliated Hospital / Orthopaedics Dept., Scientific Research Center Sun Yat-sen University, China

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

**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 were 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.

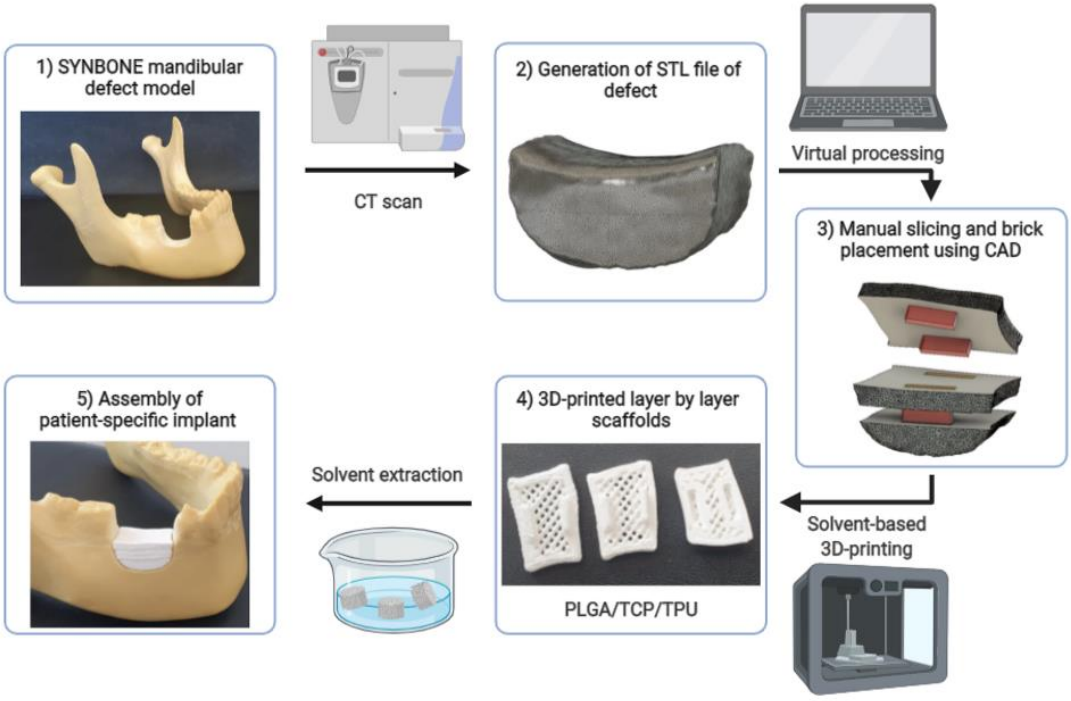



*Figure 11.1.1: Overview schematic of approach.*

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

**Pub:**
Hatt LP, Armiento AR, Mys K, Thompson K, Hildebrand M, Nehrbass D, Müller WEG, Zeiter S, Eglin D, Stoddart MJ. Standard in vitro evaluations of engineered bone substitutes are not sufficient to predict in vivo preclinical model outcomes. Acta Biomater. 2022 Aug 18:S1742-7061(22)00497-4. DOI: 10.1016/j.actbio.2022.08.021.
Hatt LP, Thompson K, Helms JA, Stoddart MJ, Armiento AR. Clinically relevant preclinical animal models for testing novel cranio-maxillofacial bone 3D-printed biomaterials. Clin Transl Med. 2022 Feb;12(2):e690. DOI: 10.1002/ctm2.690.

## 11.2 AO Spine

**A translational approach integrating developmental biology and tissue engineering towards regeneration of the annulus fibrosus of the intervertebral disc (Printdisc) (finished) (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). The current state of AF tissue engineering could 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.
**Goals:** 1) 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) Exploration of cell-scale and macro-scale mechanical stimulations on cytoskeletal organization and AF collagen assembly by the patterned cells.
**Results:** We have developed a cell-friendly hydrogel support bath comprised of temperature-sensitive poly(N-isopropylacrylamide) hydrogels and embedded Carbopol® microparticles *(Figure 11.2.1)*. 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.

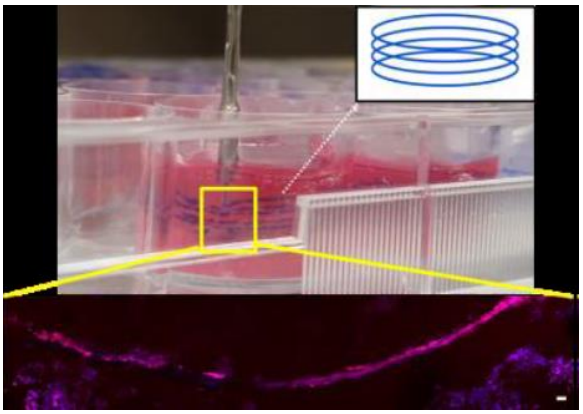


*Figure 11.2.1: Freeform printing of unsupported rings within the patternable hydrogels at 25°C. Scale bar = 100 µm.*

**Pres:**
Egger S, Alig G, D'Este M, Wychowaniec JK, Weiser JR, Grad S, Vernengo AJ. Microextrusion-based anisotropic cell patterning within temperature-sensitive hydrogel matrices for annulus fibrosus regeneration. eCells & Materials Conference 2022.

**Pub:**
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) (finished) (S Grad, Z Li, M Alini)**

**Background:** Diagnostic markers for early intervertebral disc (IVD) degeneration still need to be identified. During the degeneration process, initial degenerative events occur at the extracellular matrix level. Thereby neoepitope peptides appear that are formed by the cleavage of aggrecan and collagen. These peptides could be explored as targets for early diagnosis of IVD degeneration.
**Goal:** This project aimed to elucidate the spatial and temporal alterations of aggrecan and collagen neoepitope levels during IVD degeneration. Bovine caudal IVDs were cultured under different conditions to mimic different degenerative situations. Human IVD samples were obtained from patients diagnosed with lumbar disc herniation (LDH) or adolescent idiopathic scoliosis (AIS).

**Results:** In bovine IVD sections *(Figure 11.2.2.)*, the aggrecan neoepitope was accumulated in nucleus pulposus (NP) and cartilage endplate (EP) regions following mechanical overload in the one strike model. As for the inflammatory cytokine induced degeneration, the collagen neoepitope was significantly increased in the annulus fibrosus (AF) region. LDH patients showed higher neoepitope expression in NP and AF regions compared with AIS patients. In summary, aggrecan and collagen neoepitope profiles showed degeneration induction and region-specific differences in the IVD organ culture models. Different IVD degeneration types are correlated with specific neoepitope expression profiles. These neoepitopes may be helpful as biomarkers of extracellular matrix degradation in early IVD degeneration and indicators of different degeneration phenotypes.

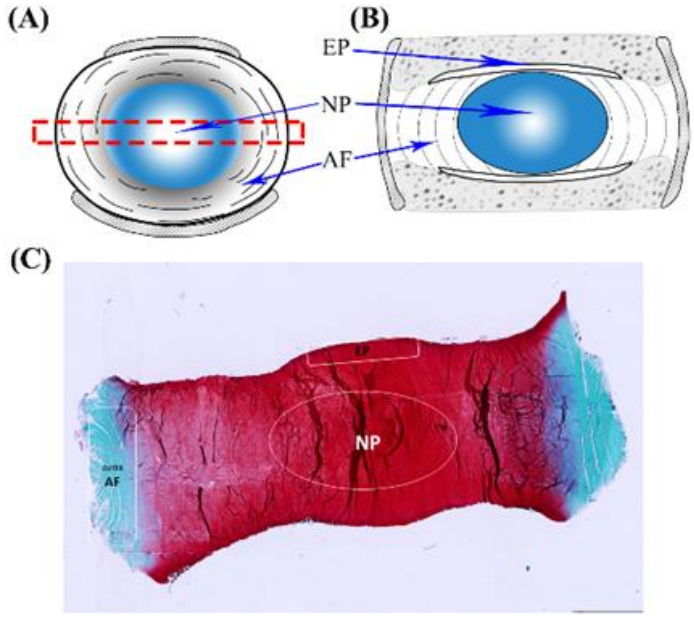



*Figure 11.2.2: (A) Schematic drawing of IVD cross section. The red box represents the medial region of the IVD that was used to make the sagittal sections. (B) Schematic drawing of IVD sagittal section. (C) Representative Safranin-O Fast Green stained image of IVD sagittal section labeled with regions of interest (ROI). The ROI include nucleus pulposus (NP), outer annulus fibrosus (AF) and the middle of cartilage endplate (EP). Scale bar 5 mm.*

**Pres:**

Wangler S, Nüesch A, Chen Z, Häckel S, Albers CE, Bigdon S, Li Z, Alini M, Grad S. MSC secretome as potential immunomodulatory and regenerative treatment strategy for IVD degeneration. Orthopaedic Research Society Annual Meeting 2022.

Soubrier A, Kasper H, Alini M, Jonkers I, Grad S. Cyclic traction loading facilitates water uptake in a healthy bovine disc culture: preliminary study. ORS 6th International Spine Research Symposium 2022.

Soubrier A, Kasper H, Alini M, Jonkers I, Grad S. Influence of traction on intervertebral disc mechanobiology: preliminary results in a bovine organ culture. eCells & Materials Conference 2022.

**Pub:**

Tang SN, Bonilla AF, Chahine NO, Colbath AC, Easley JT, Grad S, Haglund L, Le Maitre CL, Leung V, McCoy AM, Purmessur D, Tang SY, Zeiter S, Smith LJ. Controversies in spine research: Organ culture versus in vivo models for studies of the intervertebral disc. JOR Spine. 2022 Dec;5(4):e1235. DOI: 10.1002/jsp2.1235. eCollection 2022 Dec. Review. PubMed PMID: 36601369; PubMed Central PMCID: PMC9799089.

Cui S, Li W, Teixeira GQ, Neidlinger-Wilke C, Wilke HJ, Haglund L, Ouyang H, Richards RG, Grad S, Alini M, Li Z. Neoepitope fragments as biomarkers for different phenotypes of intervertebral disc degeneration. JOR Spine. 2022 Sep;5(3):e1215. DOI: 10.1002/jsp2.1215. eCollection 2022 Sep. PubMed PMID: 36203866; PubMed Central PMCID: PMC9520770.

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. 2022 Jul;40(7):1661-1671. DOI: 10.1002/jor.25190. Epub 2021 Oct 18. PubMed PMID: 34662464.

## 11.3 AO Trauma

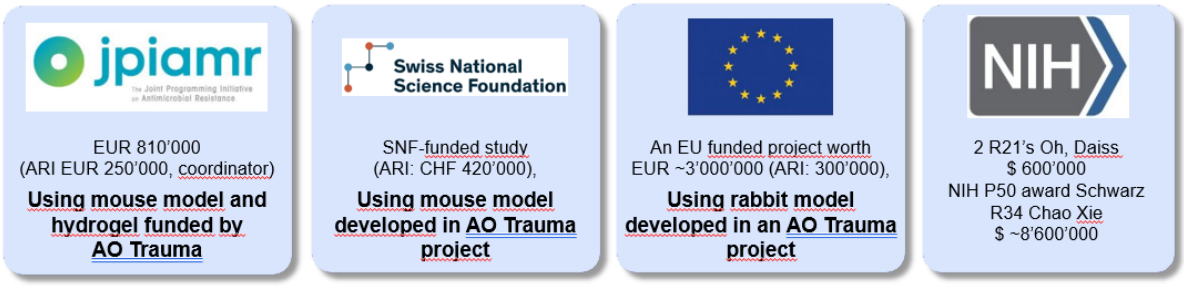
### The AO Trauma Clinical Priority Program Bone Infection

The Clinical Priority Program (CPP) of AO Trauma (AO T) is an initiative to focus internal and external research funding on issues of high clinical relevance. The 5-year cycle of the CPP is aimed at providing sufficient time to make a significant contribution to both clinical and scientific aspects of the problem as well as building research networks of both surgeons and scientists.

AO Trauma has long acknowledged the challenge posed by bone infection and defined it as the focus of a CPP, with the aim to achieve better understanding of bone infection, provide solutions for the most pressing clinical problems, and have a positive impact on patient care.

Led by Prof Steven Kates MD (Richmond, USA), and his co-Principal Investigator Prof Edward Schwarz PhD (Rochester, USA,) the AO T CPP Bone Infection under the supervision of the AO Trauma Research Commission (AO TRC) has made numerous remarkable achievements throughout its cycle. During the CPP, the term of "Fracture-related infection, (FRI)" was coined, and numerous consensus papers have been published on clinical aspects of the definition, management, and diagnosis of FRI. This was also done in collaboration with the support of the anti-infective global expert committee of AO ITC. From the basic science perspective, new diagnostic and treatment concepts have been developed, as well as more in-depth understanding of the basic pathophysiology of FRI.

The AO T CPP Bone Infection leaves a legacy of both clinical and scientific advances and serves as an example of the AO Trauma research funds can be used to foster clinical and scientific collaboration and make advances in areas of relevance to the core interests of the AO Foundation. It has also helped leverage grants.




*A few examples of grants leveraged from the CPP.*

*Bone Infection CPP meeting of collaborating partners, guests and the governing AO TRC.*

**Predicting patient-specific mechanical failure of proximal humerus fracture plating with computer simulations (SystemFixII) (ongoing) (P Varga, D Mischler, D Ciric, J Schlatter, 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 osteosynthesis strategies and careful planning. Validated computer models have a high potential to complement or partially replace conventional biomechanical testing, expedite implant optimization and design, refine surgical guidelines, support decision making and allow patient-specific pre-operative planning. Ultimately, simulations are expected to help 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. This tool was validated experimentally and utilized in a series of in silico studies to indicate ways of improving the use of plates, to compare different implants and to optimize the implant design towards improved stability. However, the models have not yet been demonstrated to predict mechanical fixation failure in real clinical cases.
**Goal:** To extend the simulation tool from the virtual to the real clinical scenario and validating it clinically by predicting the patient-specific risk of mechanical fixation failure.
**Results:** A multicentric prospective clinical study has been concluded in Leuven and Innsbruck, providing detailed postoperative CT scans and continuous sensor-based shoulder motion data for 29 patients, five of whom had mechanical failure of the locking plate fixation until the 6-months follow-up visit. Analysis of the entire cohort is currently underway to investigate whether the individualized fixation failure risk can be predicted with either (1) a statistical approach combining various parameters or (2) a combination of the fixation's load bearing capacity predicted via subject-specific FE models and the loading intensity assessed with the surrogate of sensor-based postoperative shoulder activity. Additionally, to better understand the phenomenon of secondary screw perforation, an experimental sub-study has been performed to simulate and describe the axial propagation behavior of a cyclically loaded screws in the proximal humerus.

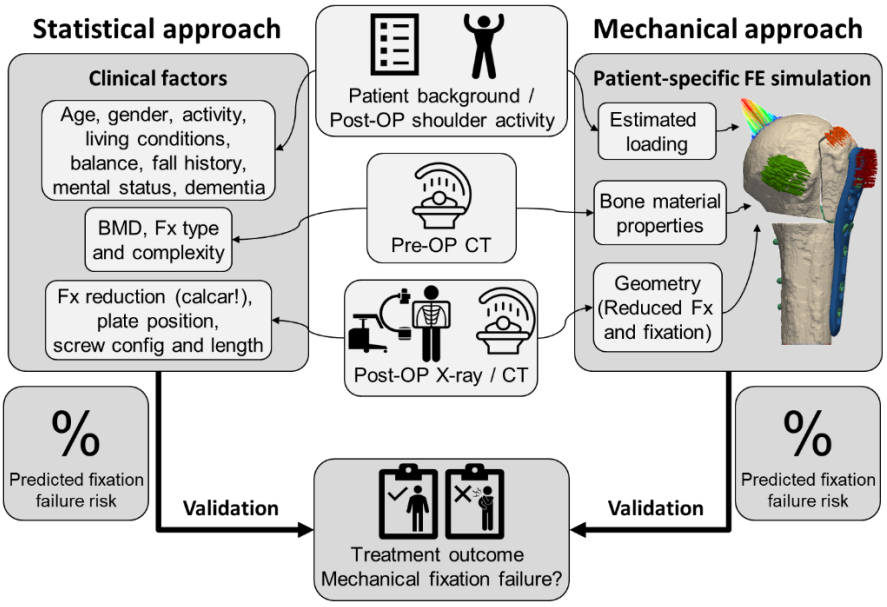



*Figure 11.3.1: Illustration of the strategy to predict subject-specific fixation failure risk using a statistical model combining various parameters and individualized finite element simulations.*

**Theses:**
Kessler F. Biomechanical stability of bone screws in the proximal humerus. Master Thesis, University of Bern, 2022.

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

**Improving rehabilitation protocols of plated long bone fractures (RehabFE) (ongoing) (P Varga, D Mischler, A Valenti, B Gueorguiev, M Windolf)**

**Background:** Despite advances in medical technology, the relatively high incidence of bone healing complications and fixation failures remains a concern. The success of osteosynthesis depends on multiple factors, including preoperative planning, intraoperative execution, and postoperative rehabilitation. To ensure optimal outcomes, it is crucial to have comprehensive understanding of potential pitfalls that may arise, such as plate failure due to excessive loading or disturbances in the healing process due to inappropriate fracture gap motion. Ideally, these failures could be anticipated based on various patient parameters and the surgical outcome. This information could then be used to design a subject-specific rehabilitation protocol based on finite element (FE) simulations that addresses the individual needs of each patient and reduces the risk of complications. This tailored approach could minimize the likelihood of plate failure and ensure a smooth healing process, resulting in improved outcomes for patients undergoing osteosynthesis.
**Goal:** To develop and validate an FE simulation methodology to predict fixation failures based on an in vivo sheep model and AO Fracture Monitor data.
**Results:** In vivo CT image data of a previous preclinical study using ovine tibia osteotomy model fixed with a locking plate was evaluated. Images of various postoperative and follow-up timepoints were co-registered and analyzed to quantify the amount of plastic deformation. Plate bending was observed in eight out of twelve ovine tibiae. Moderate correlation between fracture gap size and plate bending angle was observed. Subject-specific FE models were developed to quantify the loading required to induce the quantified plate bending. Towards this end, it was crucial to evaluate the mechanical behavior of the implant materials. Tensile testing was performed to quantify the elastic properties of titanium and stainless steel, respectively. The plastic construct behavior observed in the in vitro tests could be well predicted using the FE models considering the experimentally assessed material properties.

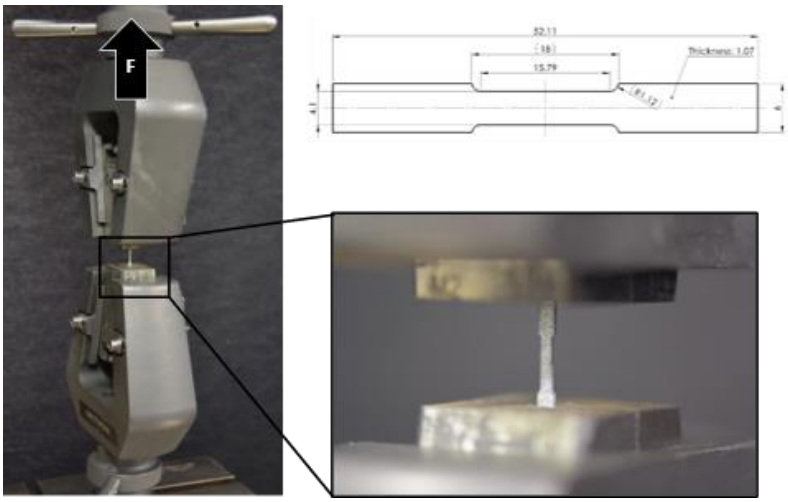



*Figure 11.3.2: Tensile testing of implant raw material to quantify elastic and plastic material properties.*

**Theses:**
Valenti A. Failure risk prediction of fracture fixations using subject-specific finite element analysis. Master Thesis, University of Bern, 2022.

**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 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 an established tilting wedge model.
**Results:** Following the first animal experiments in 2020 and 2021, eight additional sheep underwent operation to complete the study groups with either immediate stimulation (from first day post-op) or delayed stimulation (from 22 day post-op). The daily stimulation protocol consisted of 1000 loading cycles evenly distributed from 9 am to 9 pm and was executed until euthanasia at five weeks post-op. The evaluation of weekly X-rays and post-mortem pQCT data revealed significantly larger callus response in the immediate group. These results clearly indicate the beneficial effect of immediate versus delayed stimulation.

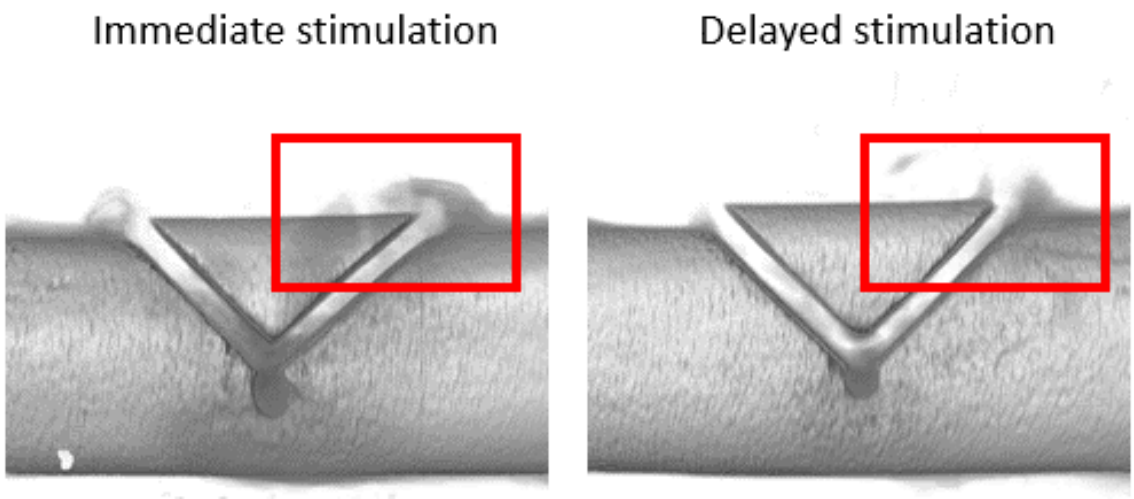



*Figure 11.3.3: 3D volume rendering of pQCT scans of two exemplary animals from the study groups. The callus volume was significantly bigger for the immediate group. The red frame indicates the region of interest where callus volume was evaluated.*

**Partner:**

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

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

**Background:** The priority in the management of fracture related infection (FRI) is fracture stability and eradication of the infection. One surgical approach is Debridement, Antibiotics, and implant Retention (DAIR) and it is 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**: Develop a large animal model for FRI, with treatment using the DAIR approach.
**Results:** The initial results showed that conventional DAIR fails to eradicate the infection, with a large number of bacteria particularly found in the bone marrow at euthanasia (Figure 11.3.4A). Histopathology of the bone marrow revealed many active osteoclasts and bacteria (Figure 11.3.4B).

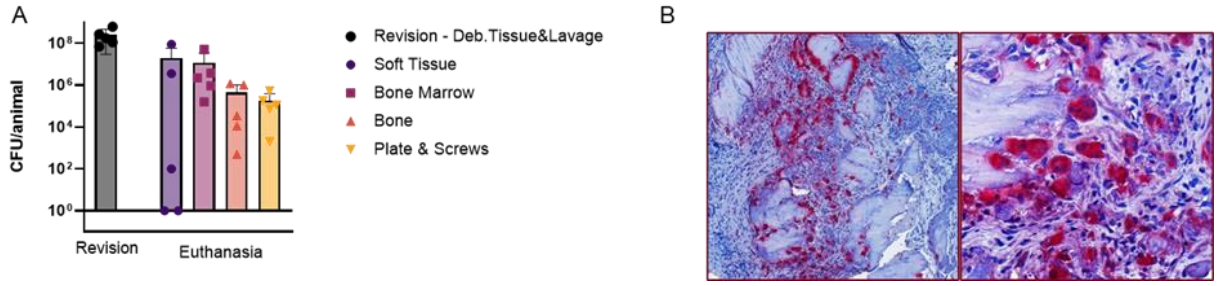



*Figure 11.3.4: (A) Bacterial quantification at revision surgery and euthanasia showing failure of DAIR to eradicate infection in the IM canal; (B) Tartrate phosphatase staining of content of the IM canal.*

**Pres:**
Siverino C. Implant retention in a sheep fracture related infection model: Evaluating fracture healing and an antibiotic loaded hydrogel. CPP Meeting Edinburgh, 11 September 2022.

**A combination enzybiotic and anti-virulence approach for the treatment of S. aureus fracture-related infections (Enzybiotic2) (ongoing) (TF Moriarty,** M Chittò, S Zeiter, C Constant, L Gens**)**

**Background:** *Staphylococcus aureus* is a pathogen commonly found in FRI and possess several key virulence factors that support its ability to cause acute and chronic infection. In the presence of human plasma, *S. aureus* possess virulence factors that enable it to subvert host coagulation pathways to its advantage by encapsulating itself into a pseudocapsule, which protect the bacteria from host defense cells and antimicrobial therapy.
**Goal:** In this study we tested the activity of a phage-derived enzyme targeting the pseudocapsule with / without support of antibiotic treatment on *S. aureus*.
**Results:** Breaking down the protective pseudocapsule increased the activity of antimicrobials against infecting bacteria and increased access of host defense cells to phagocytose the bacteria.

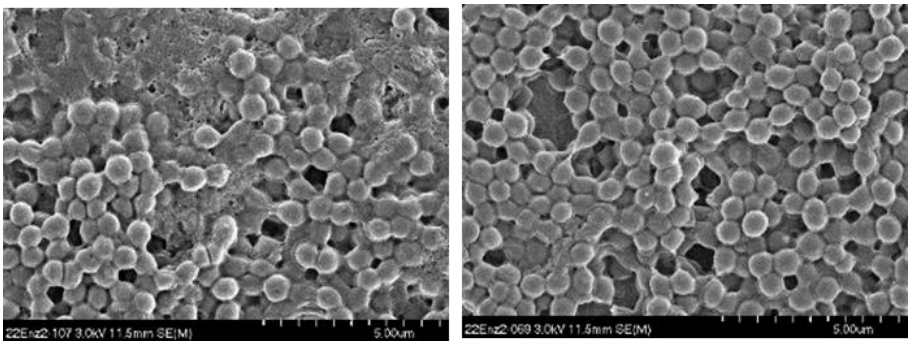


*Figure 11.3.5: Representative SEM images of S. aureus JAR biofilm without (left) and with (right) enzyme treatment. Yellow arrows indicate the fibrin matrix which is almost not present after treatment.*

**Partner:**
- Rob Lavigne, KU Leuven, Belgium

**Bone defect healing after chronically infected non-union (Mascot) (ongoing) (C Siverino, TF Moriarty**, D Arens, S Zeiter, D Nehrbass, N Vanvelk**)**

**Background:** In chronically infected non-unions, treatment always includes extensive debridement to remove necrotic and infected bone, often resulting in large defects requiring elaborate and prolonged bone reconstruction techniques. One of those reconstruction approaches includes the induced membrane technique (IMT). **Goal:** Therefore, we developed a novel rabbit humerus defect model including plating osteosynthesis and infection. We compared the outcomes in terms of bone healing between IMT approach and empty defect in aseptic and septic scenario.
**Results:** We successfully developed a preclinical *in vivo* model to investigate the treatment of long bone defects with the IMT approach. In the infected setting, extensive debridement and systemic antibiotic treatment allow for healing of the defect. The IMT achieves better healing after infection with higher RUST values compared to the empty defect group. The rabbit humerus model including infection and plating osteosynthesis offers a highly relevant model to further investigate the IMT.

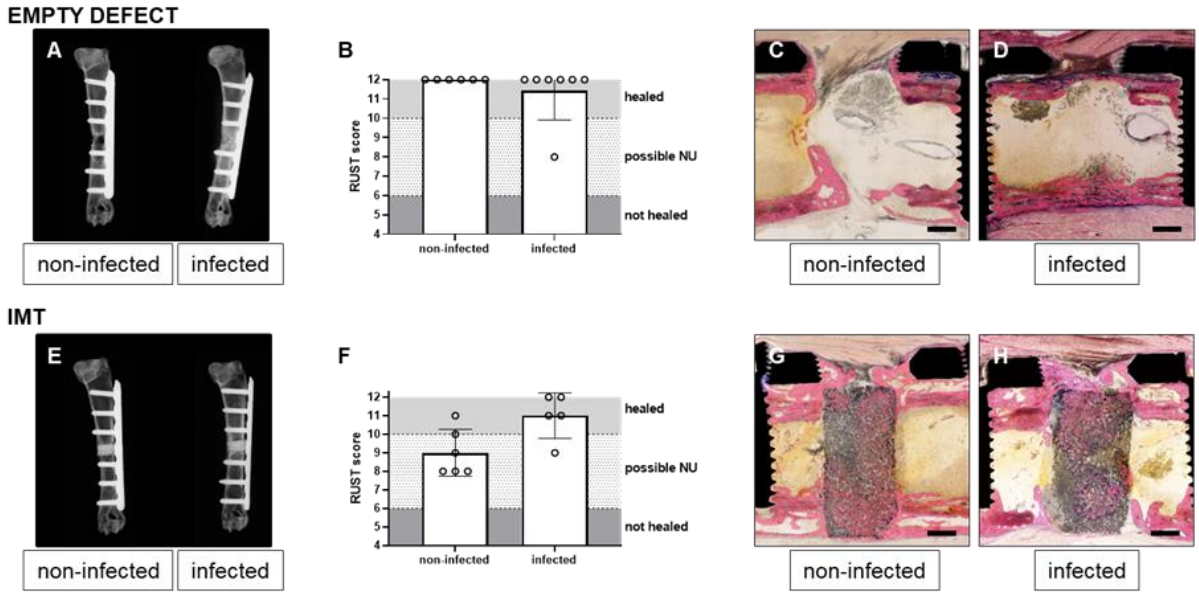



*Figure 11.3.6: (A) and (E) Radiographs of the humerus in the empty defect or in the IMT group, non-infected and infected animals; (B) and (F) Radiographic union score for tibial fractures (RUST) of empty defect and IMT at the end of the study; (C), (D), (G), and (H). G&E staining of bone formation in the different groups. Scale bar 2 mm.*

**Pres:**
Siverino C. Bone defect healing using the induced-membrane technique after chronically infected non-union in a novel rabbit model. ICORS Edinburgh, 7 September 2022.

**Partner:**
- Mario Morgenstern (PD Dr), University Hospital Basel, Switzerland

**Establishment of an *ex vivo* model for *Staphylococcus aureus* invasion of the osteocyte lacuno-canalicular network (Invibo) (ongoing) (C Siverino, TF Moriarty,** N Vanvelk**)**

**Background:** *S.aureus* is one of the primary pathogens responsible for fracture-related infection (FRI). It has developed multiple mechanisms to evade the host immune system and increase its resistance to current treatment strategies. Recently, it has been shown to invade the osteocyte lacuno-canalicular network (OLCN). **Goal:** This study aimed to develop an *ex vivo* model to investigate this phenomenon. **Results:** The tibiae and femora of freshly euthanized mice were "infected" with a pin containing either wild-type *S. aureus* or a mutated version that is unable to invade the OLCN (ΔPBP4). The presence of bacteria in the OLCN was confirmed by SEM (Figure 11.3.7A) and by BB staining (Figure 11.3.7B). The mean percentage of occupied lacunae was 2.36% in wild-type *S. aureus*, compared to 0.22% in the mutated version ($p$=0.057) (Figure 11.3.7C). These preliminary results demonstrate the reliability of the model to study this phenomenon and evaluate the efficacy of future treatment strategies.

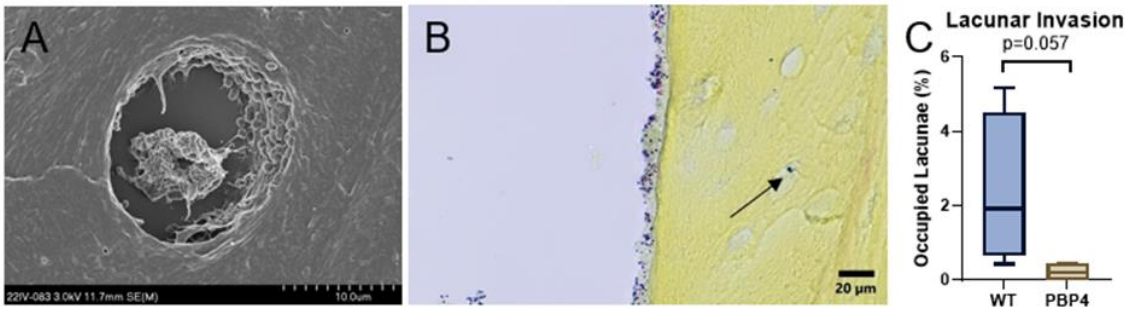



*Figure 11.3.7: (A) S. aureus invasion of an osteocyte lacuna of a murine tibia shown on SEM and (B) by BB staining (arrow). (C) Comparison of lacunar invasion by wild-type S. aureus and a ΔPBP4 mutated version.*

**Investigating the impact of nonsteroidal anti-inflammatory drugs (NSAIDs) treatments on fracture-related infection (NSAID) (ongoing) (TF Moriarty, S Zeiter,** M Chittò, VS Mdingi, L Gens**)**

**Background:** Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in trauma therapy due to their anti-inflammatory and analgesic effects and as an alternative to the use of opioids. NSAIDs reduce systemic inflammation and pain by decreasing prostaglandin synthesis (COX inhibitors). Since inflammation and prostaglandins play an important role in bone healing, NSAIDs can have a negative impact, especially when taken in the early inflammation-related phase of fracture healing. The role of COX selectivity remains controversial and poorly investigated. **Goal:** With our study we wanted to investigate whether COX selectivity differentially affects antibiotic activity in a rat model. **Results:** Our results demonstrated that celecoxib (COX2 inhibitor) in combination with antibiotics fails in clearing the infection. However, despite this negative effect, celecoxib treatment showed a higher bone formation and a lower bone resorption in the early stage of the infection. Further investigations are ongoing to evaluate whether a short celecoxib treatment shows better outcome compared to a long treatment.

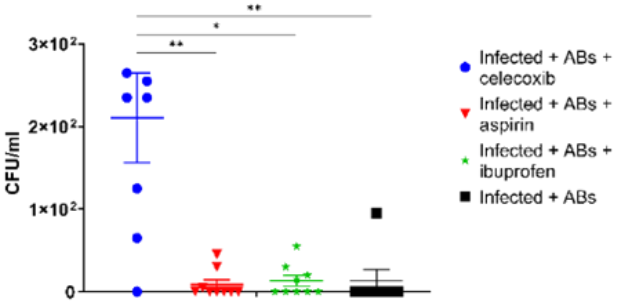



*Figure 11.3.8: Quantitative bacteriological evaluation of animals treated with antibiotics and different NSAIDs for an S. epidermidis infection. Data shown are the mean ±SEM. Two-way ANOVA with a Tukey's post-hoc test for multiple comparison was performed in n=12 animals/group. *p<0.05;**p<0.01;***p<0.001*

**Fracture-related infection: testing an antimicrobial and osteoinductive functionalized scaffold in a rabbit model (SugarFRI) (ongoing) (C Siverino, S Zeiter, TF Moriarty)**

**Background:** Surgical management of Fracture-related infection (FRI) includes debridement of affected tissues, dead space management, and systemic antimicrobial therapy. The use of scaffolds incorporating local antimicrobials and bone enhancers like the Bone Morphogenetic Protein 2 (BMP2) would enhance bone healing while treating the infection in a FRI setting.
**Goal:** Develop and assess the ability of a dual antibiotic-BMP2 loaded scaffold to manage infection and support bone healing.
**Results:** First, the collagen scaffold is absorbed with BMP2 and tobramycin (Figure11.3.9A). The *in vitro* activity, BMP2 release and antimicrobial activity are measured overtime showing a burst release effect of either BMP2 or tobramycin from the scaffold (Figure 11.3.9B,C).

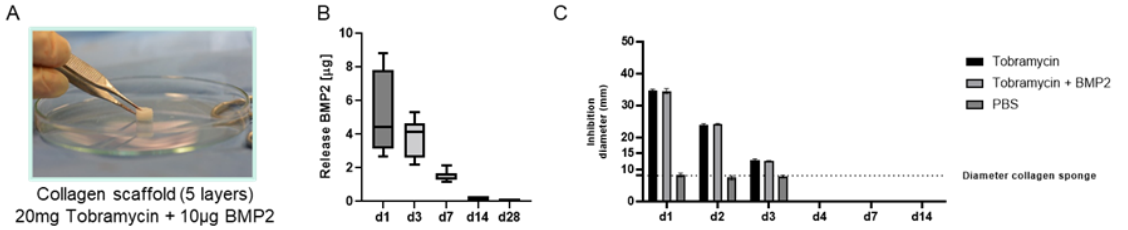



*Figure 11.3.9: (A) Collagen scaffold (8mm diameter) absorbed with BMP2 and tobramycin; (B) BMP2 release over 28 days from the collagen scaffold (5 layers); (C) antimicrobial activity measured by the inhibition zone formed from tobramycin released from collagen scaffold on S. aureus agar plate.*

**Host pathogen interaction in *Staphylococcus aureus* bone infection (SACTAK), (ongoing) (TF Moriarty,** P Fehrenbach, C Siverino**)**

**Background:** Under normal circumstances, healthy bone has a balanced activity of bone-forming osteoblasts and bone-resorbing osteoclasts. However, during infection, microbial and host factors shift the balance of bone homeostasis in favor of bone destruction. Within bone marrow, *S.aureus* can form so-called staphylococcal abscess communities (SACs) that lie at the center of abscesses and support survival of the bacteria despite local infiltration of immune cells. **Goal:** Develop 3-dimensional model to study the interaction of SACs with bone cells. **Results:** SAC supernatants, generated using the 3-dimensional in vitro model, have shown cytotoxic activity against osteoclasts. Furthermore, proteomic analysis of SAC supernatant has revealed a high concentration of secreted toxins, which may be responsible for this activity.

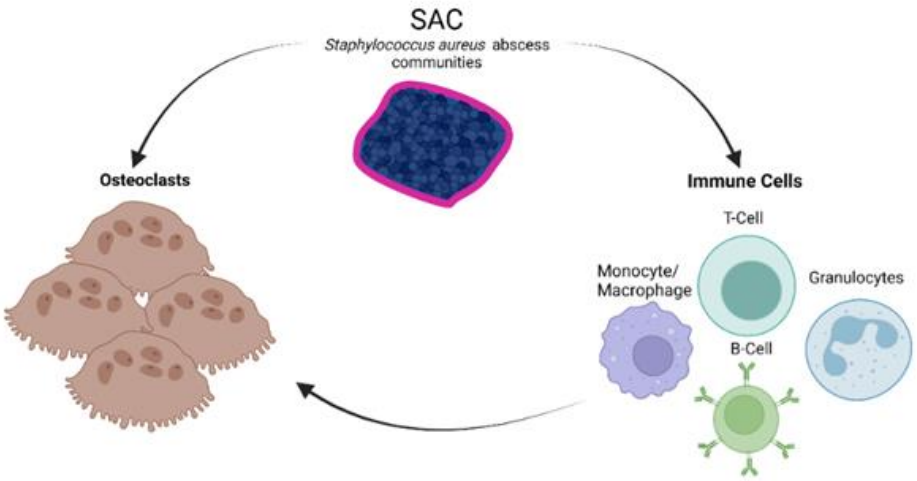



*Figure 11.3.10: Schematic of the interactions between Staphylococcal abscess communities, osteoclasts, and immune cells that are being investigated in this project.*

**Partners:**
- Sebastian AJ Zaat, University of Amsterdam, The Netherlands
- Esther DeJong, University of Amsterdam, The Netherlands

**Fracture-Related Infection Model Featuring Main Components of the Clinical Condition**

**Background**: Fracture-related infection (FRI) represents a significant challenge in orthopedic trauma surgery with poor outcomes despite extensive treatment protocols. Even with a growing research interest in FRI prevention and treatment, only 6% of preclinical models currently in use have combined all the main clinical features of FRI (fracture creation, soft tissue damage, and delay in treatment), and none of those provide a stable fixation. Thus, most investigations in prevention and treatment strategies for FRIs currently use preclinical models missing some clinical features that may limit clinical relevance and/or clinical translation. Crucially, the importance of the type of bone injury and soft tissue trauma has not yet been proven regarding infection severity in animal models. This question should first be answered before we can justify using models with increased severity and burden, such as traumatic fractures, on animal welfare grounds.
**Goal**: This study aims to evaluate the combined effect of etiology and severity of bone discontinuity and traumatic soft tissue injury on the animal welfare, inflammatory response, and bacterial burden of clinically relevant FRI preclinical model in rats.
**Results**: This study successfully created a reproducible traumatic fracture model in rats using a weight being dropped in a controlled apparatus that could be repaired using a plate and locking screws (Figure 11.3.11). The result from the first pilot animals operated for this study showed that the creation of a bone discontinuity resulting from a surgical bone cut (osteotomy) or from an external trauma (fracture) followed by inoculation with S. epidermidis were both able to establish a reliable FRI. In addition, the preliminary bacteriology results obtained from these pilot animals suggest that the severity of the fracture-related infection is increased in rats undergoing traumatic fracture creation compared to an osteotomy. This result is illustrated in Figure 11.3.12 by the colony-forming unit (CFU) counts from the affected tissues obtained following euthanasia

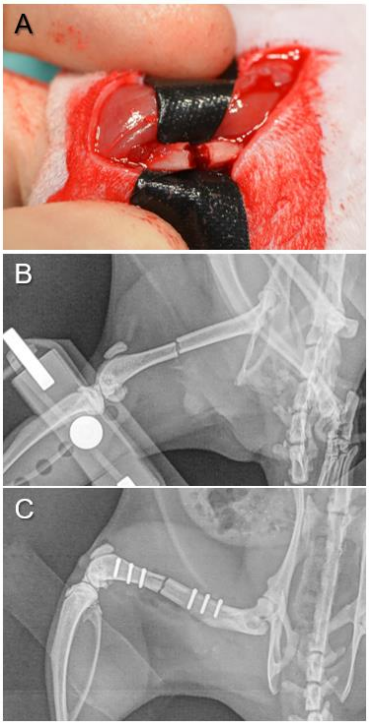



*Figure 11.3.11: Intraoperative (A) and radiographic (B, C) images of traumatic fracture creation and repair.*

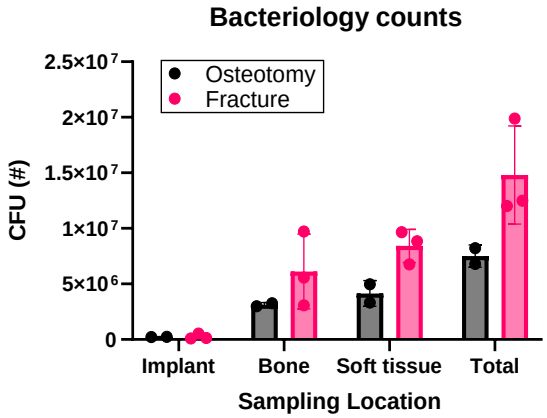



*Figure 11.3.12: CFU counts differences between the fracture and osteotomy groups for each sampling locations*

**Targeted poly(D-amino acids) nanoparticles loaded with antibiotics for staphylococcal biofilm eradication (Nanolysin) (ongoing) (TF Moriarty**, W Feng, M Chittò**)**

**Background:** Biofilm formation on the implant is one of the key features of fracture-related infection (FRI). The biofilm includes a self-produced extracellular matrix wherein bacteria are embedded. **Goal:** we aim to develop a targeted poly(D-amino acid) nanoparticle to deliver antibiotics to the biofilm. **Results:** Live/Dead staining results (Figure 11.3.13A) showed that antibiotic-loaded nanoparticles significantly changed the integrity of the biofilm and caused more dead bacteria (red stain) compared to untreated biofilm. Meanwhile, the scanning electron microscope (SEM) images (Figure 11.3.13B) also show the antibiotic-loaded nanoparticles may weaken the strength of biofilm, leading to loss of biofilm during fixation for SEM.

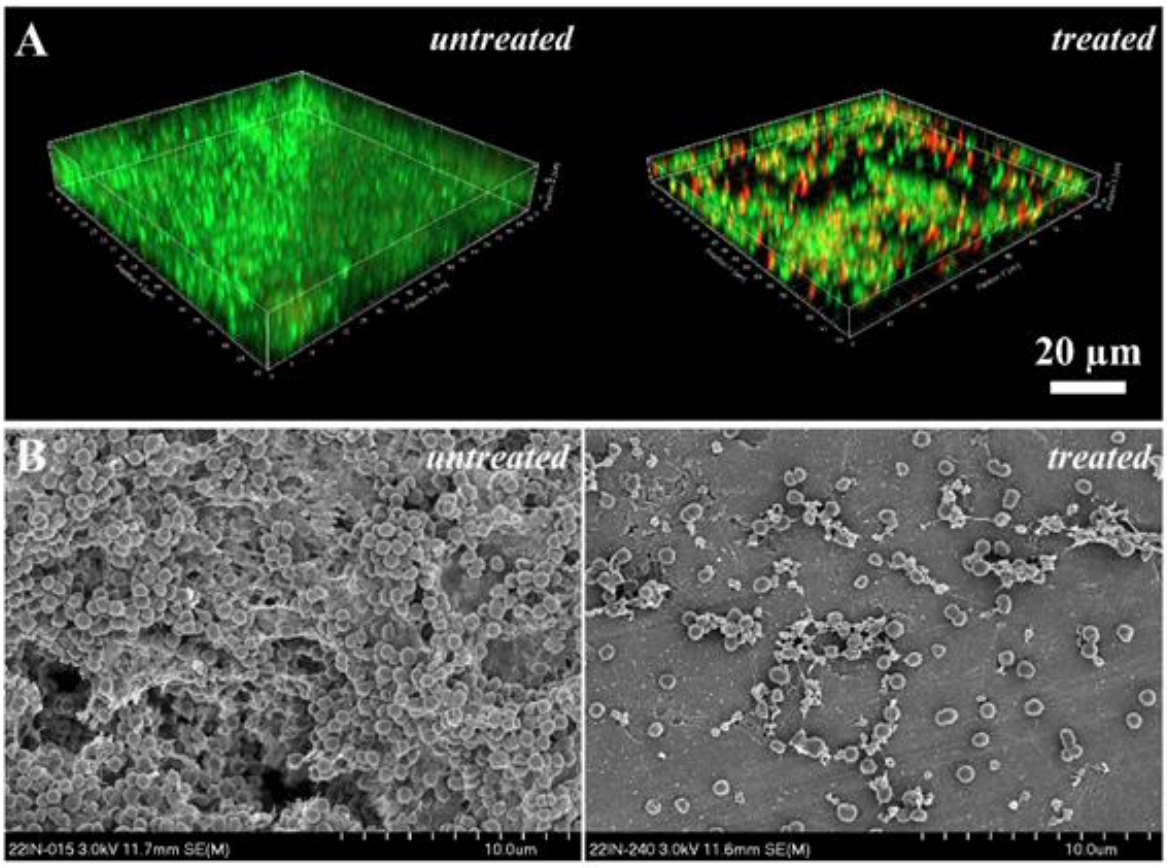



*Figure 11.3.13: The morphology of S.epidermidis biofilms before and after treatment with nanoparticles. (A) Confocal laser scanning microscope images of untreated and antibiotic-loaded nanoparticles treated biofilms stained using LIVE/DEAD BacLight Kit with live bacteria in green, and dead bacteria in red. scale bar: 20 µm. (B) SEM images of untreated and antibiotic-loaded nanoparticles treated biofilm biofilms.*

**Partners:**

- Xing Wang (Prof), Beijing University of Chemical Technology, China
- Qun Ren (Dr), Empa St. Gallen, Switzerland

**miRNA analysis to discover fracture related biomarkers (MiDiag2) (ongoing)**
**(M Stoddart, M Alini, H Schmal,** E Della Bella**,** F Breulmann, U Menzel**)**

**Background:** Biomarkers predictive of fracture healing outcomes would provide a useful tool to allow surgeons to proactively make patient based clinical decisions. Currently, even in high-risk groups, there are no accurate ways to determine the potential of a particular patient to progress to delayed or non-union. Such a tool would enable more reliable patient stratification, thus allowing for earlier diagnosis and increasing the potential success of additional early interventions by the surgeon. In a previous AO Trauma 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. Investigations are ongoing to validate the correlation between early miRNA expression with the differentiation outcome.

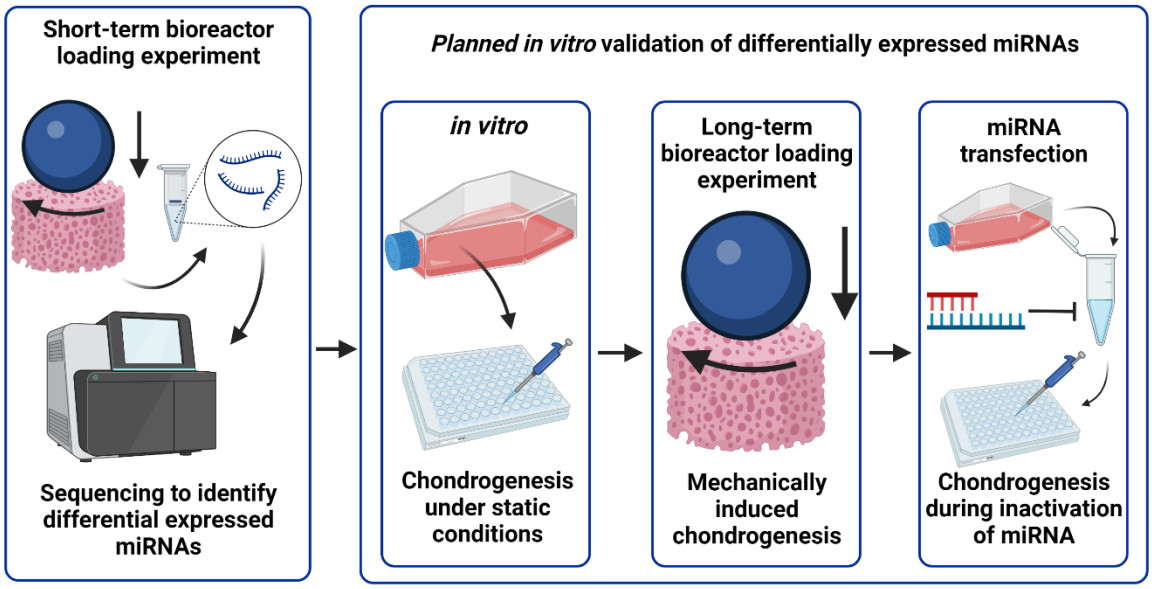



*Figure 11.3.14: MiDiag2 Study overview*

**Pres:**
Breulmann FL, Ramasamy S, Herzog M, Pandian GN, Della Bella E, Stoddart MJ. Differentially expressed microRNAs during early endochondral differentiation of human mesenchymal stromal cells as biomarkers for non-union fractures. 2022 SSB+RM (poster).
Breulmann F, Herzog M, Stoddart M, Della Bella E. Differentially expressed microRNAs during endochondral differentiation of human bone marrow derived mesenchymal stromal cells to identify possible biomarkers for non-union fractures. 2022 TERMIS EU (oral).
Stojceski F, Grasso G, Buetti-Dinh A, Stoddart M, Della Bella E. Influence of dexamethasone on the interaction between glucocorticoid receptor and SOX9: A molecular dynamics study. 2022 TERMIS EU (oral).

**Pub:**
Miclau K, Hambright WS, Huard J, Stoddart MJ, Bahney CS. Cellular expansion of MSCs: Shifting the regenerative potential. Aging Cell. 2022 Dec 19:e13759. DOI: 10.1111/acel.13759.
Breulmann FL, Hatt LP, Schmitz B, Wehrle E, Richards RG, Della Bella E, Stoddart MJ. Prognostic and therapeutic potential of microRNAs for fracture healing processes and non-union fractures: A systematic review. Clin Transl Med. 2023 Jan;13(1):e1161. DOI: 10.1002/ctm2.1161.
Della Bella E, Koch J, Baerenfaller K. Translation and emerging functions of non-coding RNAs in inflammation and immunity. Allergy. 2022;77:2025-2037.

**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

**Linking mechanics and omics to improve early bone healing (MechOmics) (ongoing) (E Wehrle, M Stoddart, S Zeiter, S Verrier,** M Schröder, J Barcik, D Arens**)**

**Background**: Mechanical loading is a key factor for normal progression of the fracture healing process. Despite the advances in fracture fixation, there remains a subset of patients that suffer from healing complications, resulting in delayed healing and non-unions. Currently it is not possible to reliably identify healing complications at an early stage when treatments, e.g. mechanical intervention therapies may be more effective. Understanding of the underlying mechanically induced molecular mechanisms on an individual basis could enable wider-scale harnessing of the mechano-sensitivity of the regenerative process in clinical applications. Novel multimodal approaches in small animals have the potential to precisely capture and understand these mechanical-induced biological changes during fracture healing on an individual basis. Within this project we will use and adapt well-established equipment for precisely controllable local application of cyclic mechanical loading in mouse femur defect models.
**Goal**: To identify systemic biomarkers indicating early deviations from normal healing progression also allowing for initiation and targeted adjustments of individualized mechanical intervention therapies.
**Results**: Preliminary tests have shown that the force-controlled loading system can be extended via a displacement-controlled loading mode. This will allow for early application of mechanical loading during the fracture healing process in mouse femur defect models.

**Partner**:
- Neashan Mathavan, Institute for Biomechanics, ETH Zurich

## 11.4 AO VET

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

**Background**: The humerus is the most commonly fractured proximal bone in thoroughbred racehorses, with a prevalence of 50% of all proximal limb and pelvic fractures occurring on race-day and during training. Complete humeral fractures in mature horses (>300 kg body weight) are difficult to treat by internal fixation and the principal decision has to be between euthanasia or extended stall rest. The guarded prognosis is a consequence of unsuitable surgical implants that do not have sufficient strength to achieve adequate stability. Intramedullary interlocking nail (IIN) fixation has been used successfully in veterinary orthopedics and has resulted in successful outcomes in foals with diaphyseal humeral fractures. However, the IIN veterinary systems are designed for small animals and are too weak to be used in mature horses with the size of the largest nail available (8-mm diameter) limiting its usage to neonatal or young foals. A larger custom INN prototype with a 12.7-mm diameter) has been described for humeral and femoral fracture fixation and showed encouraging results in horses up 377 kg in combination with a cranial bone plate. Although IIN fixation seems a promising surgical option, IIN systems for use in large animal fracture fixation are not yet commercially available for veterinary purposes.
**Goal**: To examine the biomechanical properties of humerus from mature horses and to compare them to osteotomized bone repaired with human IIN combined with a cranial locking compression plate (I/LCP).
**Results**: Long oblique osteotomy created to mimic the most common humeral fracture pattern was successfully repaired using a human IIN commercially available (16-mm diameter, 240-mm length) locked with 2 proximal and 4 distal bolts (4.5-mm and 5.0-mm diameter) combined with a 5.5 broad LCP cranially (10 holes, 5.5-mm narrow). Axial and torsional stiffness for intact specimens were greater than following repair (8.8 vs 4.1N/mm and 58.4 vs 12.6Nm/deg; p=0.05 and 0.02). While none of the intact specimens failed (remained intact at 25kN and 250 Nm; end of test), all repaired specimens failed during testing, but this difference was only significant for axial failure load (17kN, p=0.0007). Nevertheless, repaired specimens failed at a load equivalent to more than 3.5 times the weight of an average mature thoroughbred horse (450 kg).

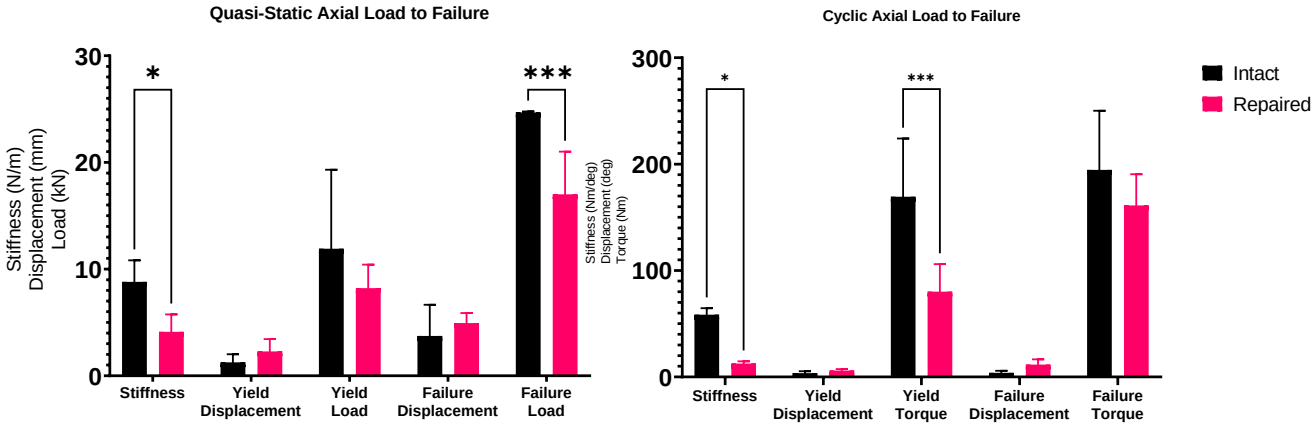



*Figure 11.4.1: Effect of fracture repair (16-mm INN with 5.5 broad LCP) on biomechanical stability (stiffness, yield, failure load and torque) of equine complete humeral fracture compared to intact bones. Values are mean ± SD. * means that the values are significantly different between the groups (p<0.05)'*

**Partner:**

- Emma Marchionatti, University of Bern, Switzerland

## 11.5 AOTC System

**Lateral rim variable angle locked plating versus tension band wiring of simple and complex patella fractures (I Zderic, B Gueorguiev)**

**Background**: Treatment of both simple and complex patella fractures represents a challenging clinical problem. Recently, lateral rim variable angle locking titanium and steel plates have been developed for treatment of both simple and comminuted patella fractures.
**Goal**: To investigate the biomechanical performance of the lateral rim variable angle locking plates versus tension band wiring used for fixation of simple and complex patella fractures.
**Results**: Sixteen pairs of human cadaveric knees 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 six pairs. The specimens with simple fractures were pairwise assigned for fixation with either tension band wiring through two parallel cannulated screws, or a lateral rim variable angle locking plate. The knees with complex fractures were pairwise treated with either tension band wiring through two parallel cannulated screws plus circumferential cerclage wiring, or a lateral rim variable angle locking 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 via motion tracking. From a biomechanical perspective, lateral rim locked plating of both simple and complex patella fractures provides superior construct stability versus tension band wiring.

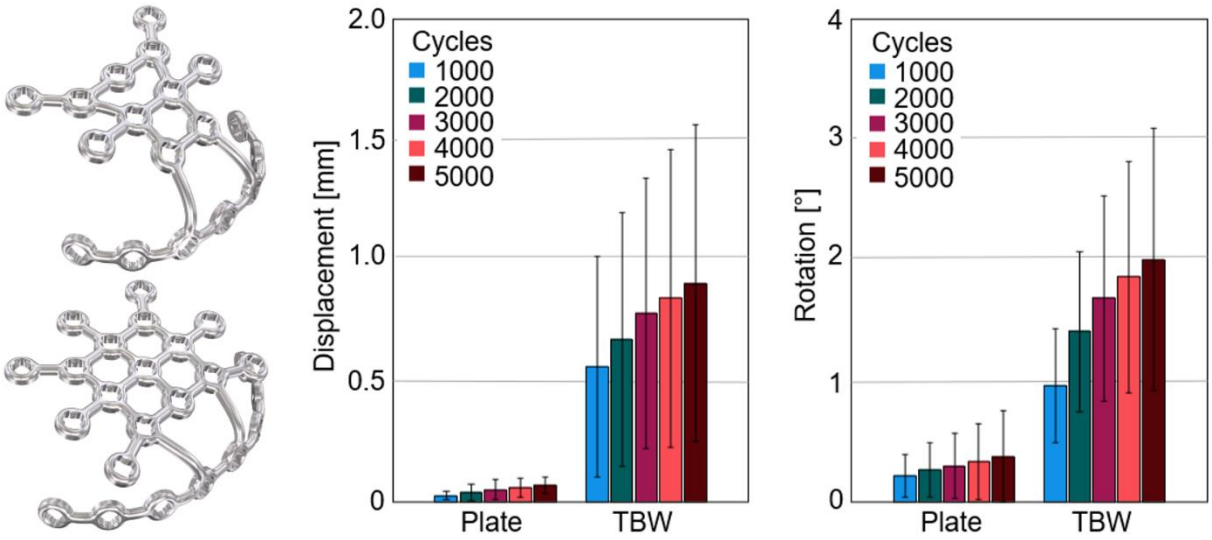



*Figure 11.5.1. Left: Variable angle locking lateral rim patella plates 2.4/2.7 designed for treatment of simple and complex patella fractures. Right: Articular displacement at the central aspect of the patella and rotation around the mediolateral axis, both measured between the proximal and distal fragments after 1000, 2000, 3000, 4000 and 5000 cycles and featuring complex fractures fixed by either lateral rim variable angle locked plating (plate) or tension band wiring (TBW) in terms of mean and SD.*

**Partners:**

- Stephen Warner (Prof), University of Texas Health Science Center, Houston, USA
- Christoph Sommer (MD), Cantonal Hospital Graubünden, Chur, Switzerland
- Karl Stoffel (Prof), University Hospital Basel, Basel, Switzerland
- Eladio Saura-Sanchez (MD), University Hospital of Elche, Elche, Spain
- William Woodburn, DePuy Synthes, West Chester, USA
- Richard Castle, DePuy Synthes, West Chester, USA
- Jessica Penman, DePuy Synthes, West Chester, USA

**Fractographic analysis of two different plate designs used for orthopaedic trauma surgery (I Zderic, B Gueorguiev)**

**Background**: Under normal conditions, orthopaedic plates need to bridge the load transmission only for a limited time until bone healing settles. However, if the latter is disturbed, the plate is condemned to continued periodic stresses leading to its failure.
**Goal**: To perform fractographic analysis of two biomechanically tested plate designs associated with clinically negative results in terms of plate fracturing.
**Results**: Stainless-steel 8-hole 3.5 mm straight reconstruction plates for midshaft clavicle fracture fixation and 12-hole 2.7/3.5 mm hybrid canine pancarpal arthrodesis plates featuring an oval radiocarpal hole were investigated. Stress analysis was conducted via finite element simulations to identify the locations with highest strains and stresses. Fractographic analysis was performed by means of digital photography, stereomicroscopy, and scanning electron microscopy. Clinically, fractures of the two plate designs can be attributed most likely to fracture healing disturbances, leading to prolonged cyclic loading of the plates, and ultimately resulting in their fatigue failure.

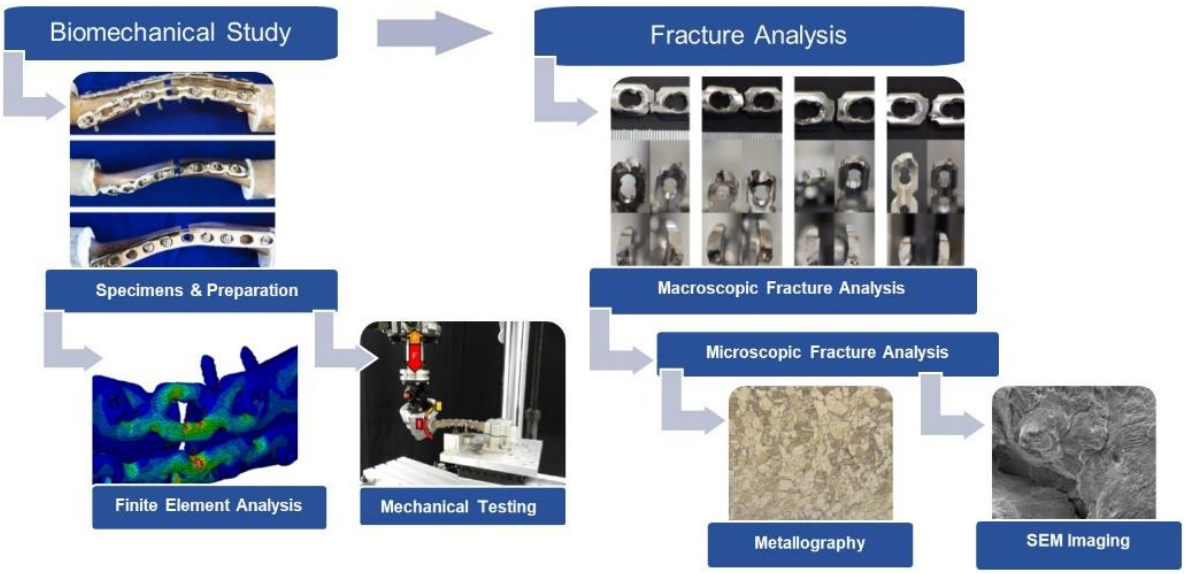



*Figure 11.5.2: Flowchart visualizing single steps undertaken to complete the biomechanical study and fracture analysis.*

**Pres:**
Zderic I, Dimitrova R, Petkov V, Sprecher CM, Mischler D, Richards G, Gueorguiev B, Drenchev L. Fractographic analysis of two different plate designs used for orthopaedic trauma surgery. 2022. International Conference of Metals, Ceramics and Composites (ICMCC) (oral).

**Pub:**
Zderic I, Dimitrova R, Petkov V, Sprecher CM, Mischler D, Richards G, Gueorguiev B, Drenchev L. Fractographic analysis of two different plate designs used for orthopaedic trauma surgery. Engineering Failure Analysis. 2022.139:106440.

**Partners:**
- Drenchev L (Prof), Institute of Metal Science, Bulgarian Academy of Sciences, Sofia, Bulgaria
- Dimitrova R, Institute of Metal Science, Bulgarian Academy of Sciences, Sofia, Bulgaria

## 11.6 ARI AC (AOF Direct Funds)

**Bone healing status assessment with implant load sensors – validation by CT image-based computer simulations (HealFE) (ongoing) (P Schwarzenberg, P Varga)**

**Background**: An accurate measurement of the healing progress in fractured bones is important for timely diagnosis of complications and recommendations on weight bearing protocols. Fracture status is characterized by the mechanical competence of the healing callus. Clinically available methods use surrogate measures of callus stability, mainly via visual X-ray based evaluations that are subjective and cannot provide reliable and quantitative assessments of healing status. Two quantitative approaches have been recently developed for mechanical characterization of the healing status of fractured bones and both technologies are available at the ARI: (1) AO Fracture Monitor, providing continuous data on implant loading, and (2) subject-specific CT-based finite element (FE) analysis at given time points for virtual mechano-structural analysis of the healing callus.
**Goal**: To evaluate whether the reduction of implant load measured via the AO Fracture Monitor correlates with the increase of torsional rigidity of the healing callus predicted by subject-specific CT-based FE modeling.
**Results**: Sensor data from previous preclinical studies of an ovine tibial osteotomy healing model have been evaluated and aligned with in vivo CT scans taken through the healing process. From these CT scans, subject-specific FE models have been constructed to simulate the in vivo situation at specific time points. Due to the specimen-specific nature of both sensor data and CT data, the data at each specific time point can be readily correlated. Preliminary results show that the FE models are able to predict the healing trends seen in the AO Fracture Monitor data and can even identify the same delayed healing response seen in a larger gap fracture model. These results highlight the potential of such a technology and the need for further refinement.

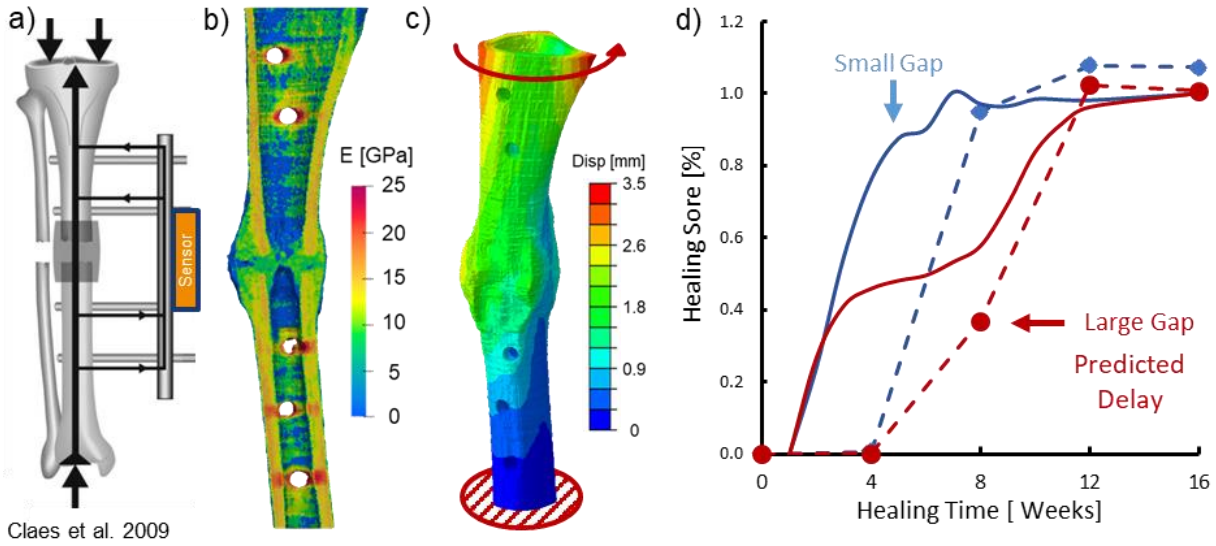



*Figure 11.6.1: (a) Diagram of load sharing scenario between the healing fracture and the implant where the sensor is located. (b) Contour plot of material properties of an ovine fractured bone 12 weeks post operation. (c) FE simulation showing deformation under a torsional load. (d) Healing curves of both AO Fracture Monitor (solid line) and FE predictions (dotted line) for a small and large fracture gap model.*

**Impact of anterior malposition and bone cement augmentation on the fixation strength of cephalic intramedullary nail head elements (I Zderic, B Gueorguiev)**

**Background**: Intramedullary nailing of trochanteric fractures can be challenging and sometimes the clinical situation does not allow perfect implant positioning.
**Goal**: To compare in human cadaveric femoral heads the biomechanical competence of two recently launched cephalic implants – TFNA helical blade and TFNA screw – inserted in either an ideal (centre-centre) or less-ideal anterior off-centre position, and to investigate the effect of bone cement augmentation on their fixation strength in the less-ideal position.
**Results**: Proper centre-centre implant positioning in the femoral head is of utmost importance. In cases when this is not achievable in a clinical setting, the helical blade is more forgiving in the less ideal (anterior) malposition when compared to the screw, the latter revealing unacceptable low resistance to femoral head rotation and early failure. Cement augmentation of both off-centre implanted helical blade and screw increases their resistance against failure; however, this effect might be redundant for helical blades and is highly unpredictable for screws.

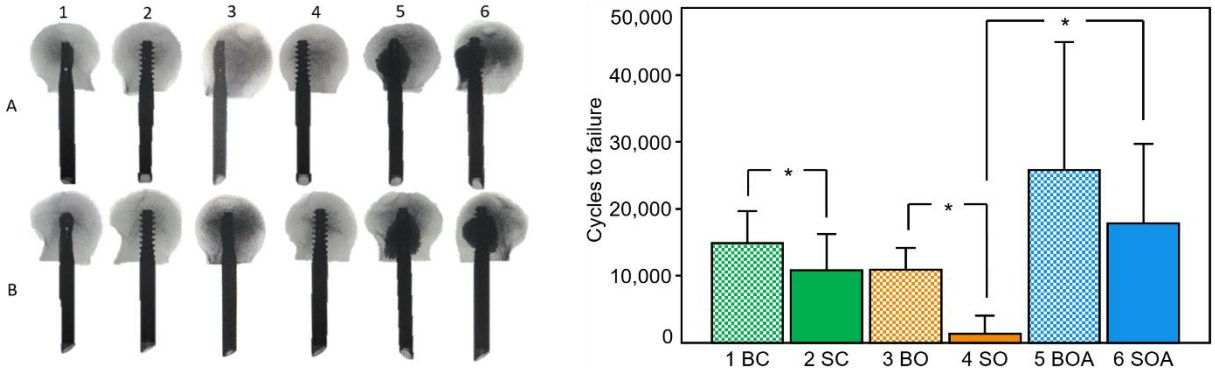



*Figure 11.6.2. Left: implanted human cadaveric heads in superoinferior (A) and anteroposterior (B) views; 1 and 2: helical blade and screw in centre-centre position; 3 and 4: helical blade and screw in anterior off-centre position; 5 and 6: helical blade and screw in anterior off-centre position augmented with bone cement. Right: cycles to failure in each separate group (n = 6) in terms of mean value and SD. 1 BC: helical blade centre-centre; 2 SC: screw centre-centre; 3 BO: helical blade off-centre; 4 SO: screw off-centre; 5 BOA: helical blade off-centre augmented; 6 SOA: screw off-centre augmented. Stars indicate significant differences.*

**Pub:**
Pastor T, Zderic I, Schopper C, Haefeli PC, Kastner P, Souleiman F, Gueorguiev B, Knobe M. Impact of anterior malposition and bone cement augmentation on the fixation strength of cephalic intramedullary nail head elements. Medicina. 2022.58(11):1636.

**Partners:**
- Knobe M (Prof), University of Zurich, Zurich, Switzerland
- Pastor T (MD), Cantonal Hospital Lucerne, Lucerne, Switzerland

**Biomechanical evaluation of Cannulated Compression Headless Screw as an alternative implant in comparison to standard S1/S2 screw fixation of the posterior pelvis ring (T Berk, I Zderic, B Gueorguiev)**

**Background**: Posterior pelvic ring injuries represent typical high-energy trauma injuries in young adults. Joint stabilization with two cannulated sacroiliac (SI) screws at the level of sacral vertebrae S1 and S2 is a well-established procedure. However, high failure and implant removal (IR) rates have been described. Washer recovery can pose the most difficult part of the IR surgery, often associated with complications.
**Goal**: To evaluate the biomechanical stability of S1/S2 stabilization of the SI joint using three different screw designs.
**Results**: Artificial hemi-pelvises were assigned to three groups for SI joint stabilization through S1 and S2 corridors via either two 7.5 mm cannulated compression headless screws (CCH), two 7.3 mm partially threaded SI screws (PT), or two 7.3 mm fully threaded SI screws (FT). An SI joint dislocation injury type III APC according to the Young and Burgess classification was simulated before implantation. All specimens were biomechanically tested to failure under progressively increasing cyclic axial loading. Interfragmentary and bone-implant movements were captured via motion tracking. From a biomechanical perspective, S1/S2 SI joint stabilization using either two cannulated compression headless screws or two partially threaded SI screws exhibited higher interfragmentary stability compared to two fully threaded SI screws. The former can therefore be considered as a valid alternative to standard SI screw fixation in posterior pelvic ring injuries.

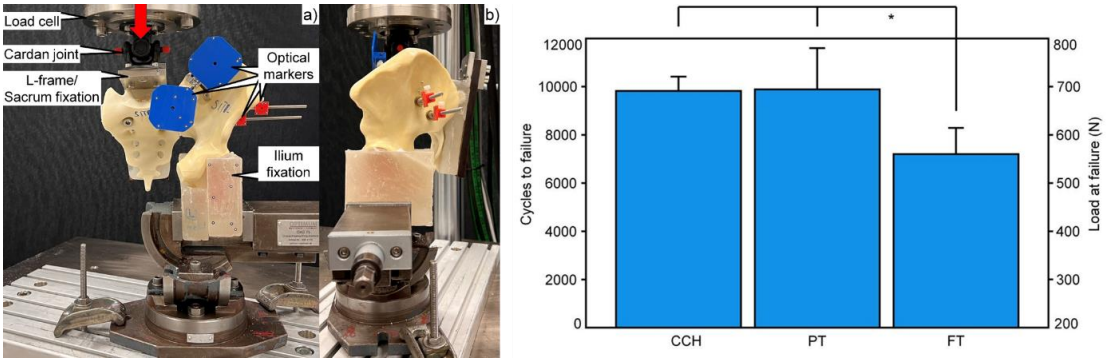



*Figure 11.6.3. Left: Setup in frontal (a) and lateral (b) view, with a specimen mounted for biomechanical testing. Right: Cycles to failure and corresponding load at failure presented in terms of mean value and SD for each group separately. Star indicates significant differences among the groups.*

**Partner:**

- Pape HC (Prof), University Hospital Zurich, Zurich, Switzerland

**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 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 in plate osteosynthesis, 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 to spinal fusion assessment.
**Results**: Three additional sheep underwent posterolateral fusion surgery with posterior instrumentation at two separate motion segments. A sensing device was attached to the rod between each pedicle screw pair, resulting in four implanted sensors per animal. Loading of

the construct was continuously monitored over 16 weeks. A validated test setup was used to assess the range of motion of the segments after euthanasia. An additional test series on an in vitro fusion model confirmed the results from the animal study, and furthermore, the transfer of the measurement principle to interbody fusion cases was biomechanically demonstrated.
The outcomes from in vivo and in vitro studies underline the previous preliminary results and support the hypothesis that continuous implant load monitoring can help determine objectively the progress of spinal fusion.

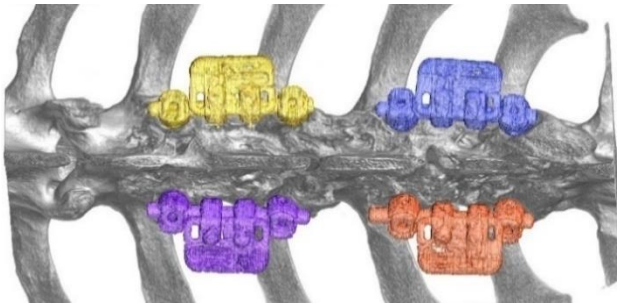


*Figure 11.6.4: Instrumented ovine spine with sensors attached between each pedicle screw pair.*

**Pres:**
Heumann M, Gueorguiev B, Wilke HJ, Windolf M. Rod loading differences on posterior spinal instrumentation after simulated spinal fusion – A biomechanical study. 2022. ICORS (poster).

**Pub:**
Windolf M, Heumann M, Varjas V, Constant C, Ernst M, Richards RG, Wilke H-J, Benneker LM. Continuous Rod Load Monitoring to Assess Spinal Fusion Status – Pilot In Vivo Data in Sheep, Medicina. 2022.58(7):899.

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

**Biomaterials Taming Neutrophils for Healthy Inflammation (BEAN) (ongoing) (M D'Este, M Stoddart, F Moriarty, E I Bektas)**

**Background:** Neutrophils are the first immune cells recruited to the sites of injury, inflammation, or infection, and play a major role in the innate immune response upon implantation of biomaterials. They are very sensitive to environmental changes; therefore, the physical and chemical properties of biomaterials could have an influence on the activation of neutrophils. Investigating and understanding the interactions between biomaterials and neutrophils is crucial to establish design principles for biomaterials to provide an immune response fostering tissue repair and regeneration.
**Goal:** The purpose of this project is to establish how biomaterial composition, mechanical properties, and topographical features influence neutrophils inflammatory profile and phagocytic activity. 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.
**Results:** A method was established to investigate neutrophil functions describing their interaction with biomaterials; a research paper was published (Wesdorp *et al*). Preliminary studies were carried out to investigate the role of topography and the presence of serum for culturing neutrophils. Our results indicate that the presence of serum leeds to neutrophil activation *in vitro*. Although serum is obviously present *in vivo*, isolated neutrophils are particularly prone to activation, and serum proteins act as an activator trigger. Further investigations are ongoing to understand the regulatory effects of neutrophils on tissue repair and regeneration.

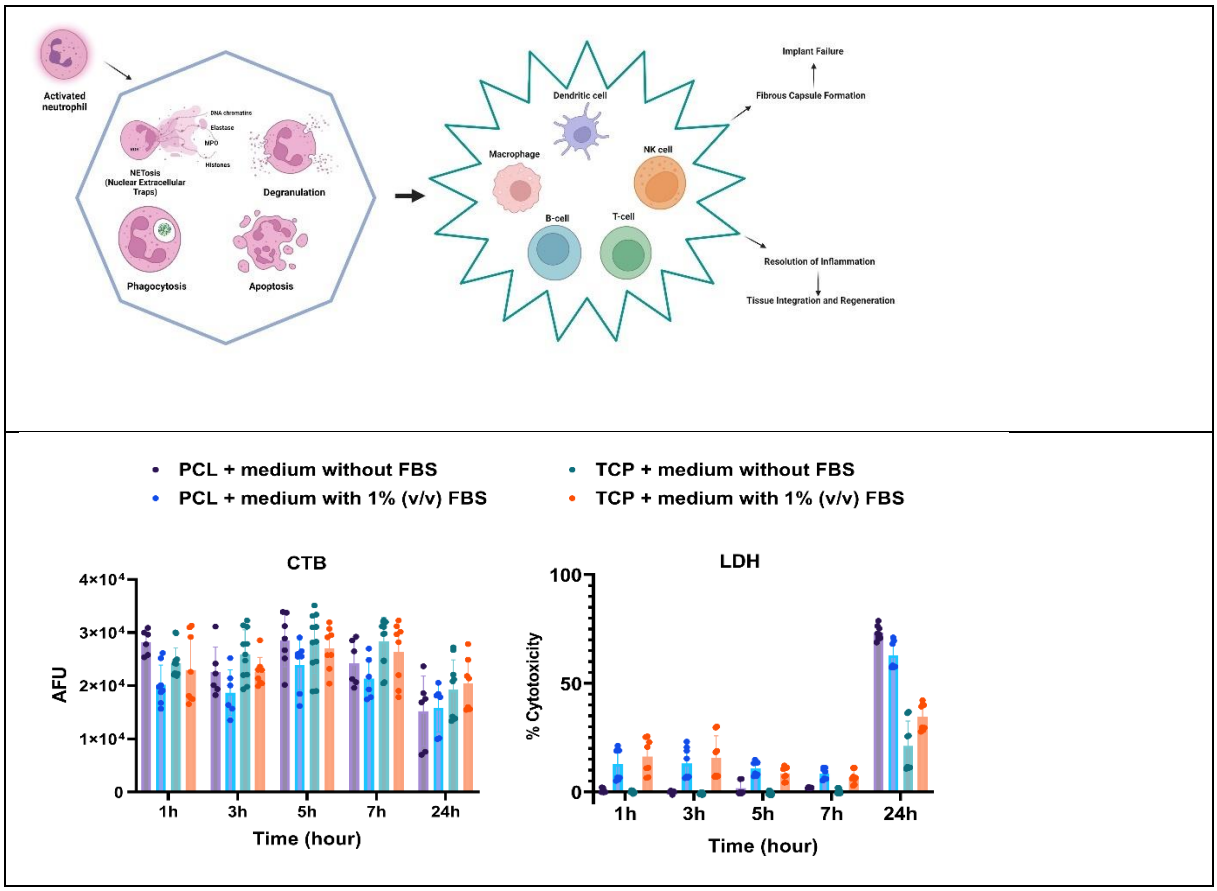



*Figure 11.6.5: Top: Schematic overview of neutrophil activation and its downstream effects. Bottom left: metabolic activity of neutrophils represented as arbitrary fluorescence units over time on polycaprolactone (PCL) and tissue culture plastic (TCP) in present or not of Fetal Bovine Serum (FBS). Bottom right Lactate Dehydrogenase (LDH) release by neutrophils cultured on different material surfaces represented as percent.*

**Pres:**

M D'Este, Towards deciphering neutrophils role in the immune response to biomaterials, Biomaterials and novel technologies for Healthcare-BioMaH, Rome, Italy, 18-21 October 2022 (oral).

Bektas EI, Wesdorp MA, Wychowaniec JK, Miklosic G, D'Este M. Influence of biomaterials surface composition and topography on the activation of neutrophils. Bordeaux, France, European Society for Biomaterials 32nd annual conference, 4-8 September 2022 (poster).

Bektas EI, Wychowaniec JK, Miklosic G, Wesdorp MA, D'Este M. The influence of stiffness and protein coating on the neutrophil activation. SSB+RM Zürich Swiss Society for Biomaterials + Regenerative Medicine 26th Annual Meeting Biomaterials: From Innovation to Translation, 7-9 June 2022 (poster).

**Pub:**

Wesdorp MA, Schwab A, Bektas EI, Narcisi R, Eglin D, Stoddart MJ, et al. A culture model to analyze the acute biomaterial-dependent reaction of human primary neutrophils in vitro. Bioact Mater. 2023;20:627-37.

**Partner:**

- Swiss Institute for Asthma and Allergy Research, SIAF, Davos, Switzerland

**Anti-inflammatory therapy for cartilage preservation (CartRegen) (completed) (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 establish explant coculture models and evaluate the chondroprotective and anti-inflammatory activity of small molecule compounds on different joint tissues using the coculture model.
**Results:** An inflammatory ex vivo coculture system with bovine osteochondral explants (OCEs) and synovial explants (SEs) was induced using 1 ng/mL IL-1β and TNF-α. Meanwhile, OCE and SE monoculture groups served as controls to test the effects of coculture on cartilage and synovium tissues (Figure 11.6.6). 5-aminosalicylic acid (5-ASA), a promising OA drug reported previously, was assessed in the coculture system to evaluate the effects of 5-ASA and the potential of the system to be applied in OA-drug screening.
Under inflammatory stimulation, cartilage and synovium tissues displayed a strong inflammatory response transcriptionally, biochemically, and histologically. Coculture markedly upregulated the gene expression of IL-6 in synovium, compared with SE monoculture under inflammatory conditions. At protein level, the amount of IL-8 in the coculture medium was significantly higher than the additive amount in OCE and SE monoculture media under inflammatory microenvironment. In the coculture system, 5-ASA could inhibit the IL-6 release into the medium. This preclinical coculture system could be used to evaluate the effects of novel OA drugs on both cartilage and synovium and explore the crosstalk mechanisms between intra-articular tissues.

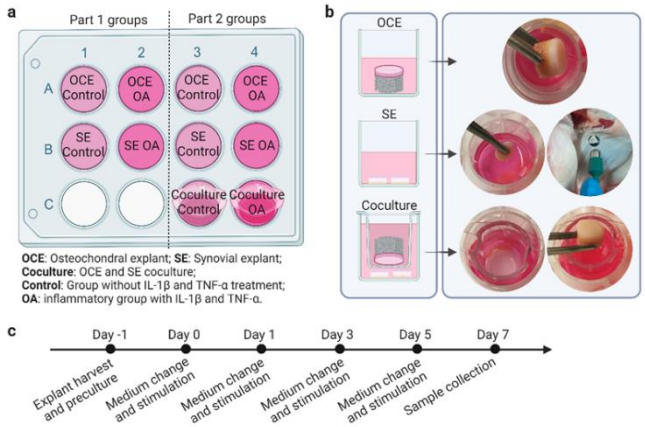



*Figure 11.6.6: Experimental groups and design. (a) Schematic diagram of grouping in experiment part 1 and part 2. (b) Representative images of osteochondral explant culture, synovial explant culture and harvest, and their coculture. (c) Timeline and workflow of the study. Figure made with Biorender.*

**Pres:**
Li K, Zhu Y, Zhang P, Alini M, Grad S, Li Z. Anti-inflammatory and pro-anabolic effects of 5-aminosalicylic acid on inflammatory human osteoarthritic chondrocytes in vitro. eCM, Davos, Switzerland, June 15-18, 2022 (oral).
**Pub:**
Li K, Zhu Y, Zhang P, Alini M, Grad S, Li Z, Osteochondral explants for diarthrodial joint diseases: bridging the gap between bench and bedside, Eur Cell Mater 44 (2022) 74-98.
Zhou L, Guo P, D'Este M, Tong W, Xu J, Yao H, Stoddart MJ, van Osch GJVM, K. Ho K, Li Z, Qin L, Functionalized hydrogels for articular cartilage tissue engineering, Engineering 13 (2022) 71-90.
**Partner:**
- Xinluan Wang (Prof), Shenzhen Institute of Advanced Technology, Shenzhen, China

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

**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 how TGF-β1-expanded cells respond to mechanically induced chondrogenesis using a multiaxial load bioreactor. 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 indicate that priming increases progression to hypertrophy. In situ modification of the receptor profile in 3D gels shows a beneficial change in receptor expression profile.
**Pres:**
Chen G, Basoli V, Guex AG, Stoddart M, Della Bella E. Improving chondrogenic potential of mesenchymal stromal cells by siRNA delivery in hydrogels. 2022 TERMU (oral).

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

**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. 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 into 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.

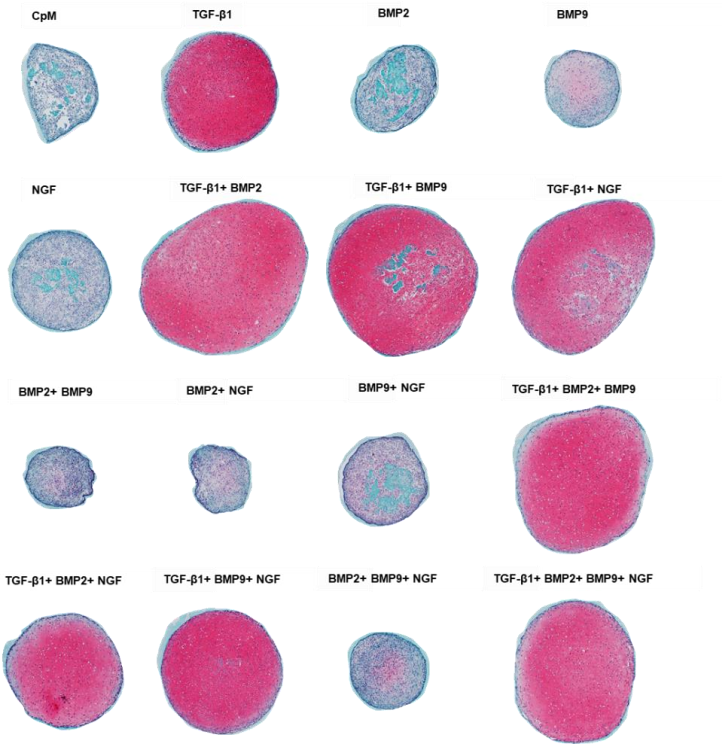



*Figure 11.6.7: Paraffin sections, day 9, Safranin O/Fast Green staining. Scale bar: 500µm. Chondrogenic differentiation is growth factor dependent.*

**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 degree of mechanical stimulation to initiate and promote callus formation. Several groups have shown that cyclic compressive strain applied in vivo to a diaphyseal fracture fosters healing via the formation of a stronger cartilaginous callus leading to earlier bone bridging. However, 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 remodelling - 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.
**Methods:** Using a custom made uni-axial multi-well bioreactor system (StrainBot, RISystem AG), 0, 10 of 30% deformation were applied to naïve human bone marrow derived mesenchymal stem cells (MSCs) in 8% GelMa hydrogels. hMSCs were subjected to deformation cycles (5 sec / 2 hours break) 24 hours per day, for 14 days. The effect of Strain on MSCs was studied in the presence of Chondro-permissive medium (CP, no TGFβ1), chondro-permissive plus medium (CP+, CP with 2ng/mL TGFβ1), or chondrogenic medium (C+, CP with 10ng/mL TGFβ1).
**Results**: Gene expression analysis results suggested that strain alone (10%, 30% CP medium) can influence naïve MSC differentiation toward a hypertrophic-like phenotype. Hypertrophic-chondrocyte associated genes MMP13, COMP and Type 10 collagen were significantly upregulated in response to deformation and in absence of exogenous TGFβ1, suggesting a possible hypertrophic-chondrocyte differentiation of MSCs in response to strain. The addition of a low dose (2ng/mL) TGFβ1 in the medium showed the tendency to mask the effect of strain on above cited MSC gene expression. Those results were confirmed by histology staining (Fig 11.6.8), where 10% strain alone led to cells larger than in chondrogenic medium. Likewise, Safranin O Fast green staining indicated less/absence of proteoglycans

production in 10% strain CP when compared to chondrogenic TGFβ1 medium, results compatible with a hypertrophic-chondrocyte-like differentiation.
**Conclusion:** Cyclic uni-axial deformation induces naïve MSCs differentiation towards a hypertrophic-chondrocyte-like phenotype. In our model, strain and TGFβ1 do not seem to act in synergy but to define different cell differentiation routes. Further work will investigate the influence of the pause between cycles on the cell differentiation, and intra-cellular signaling.

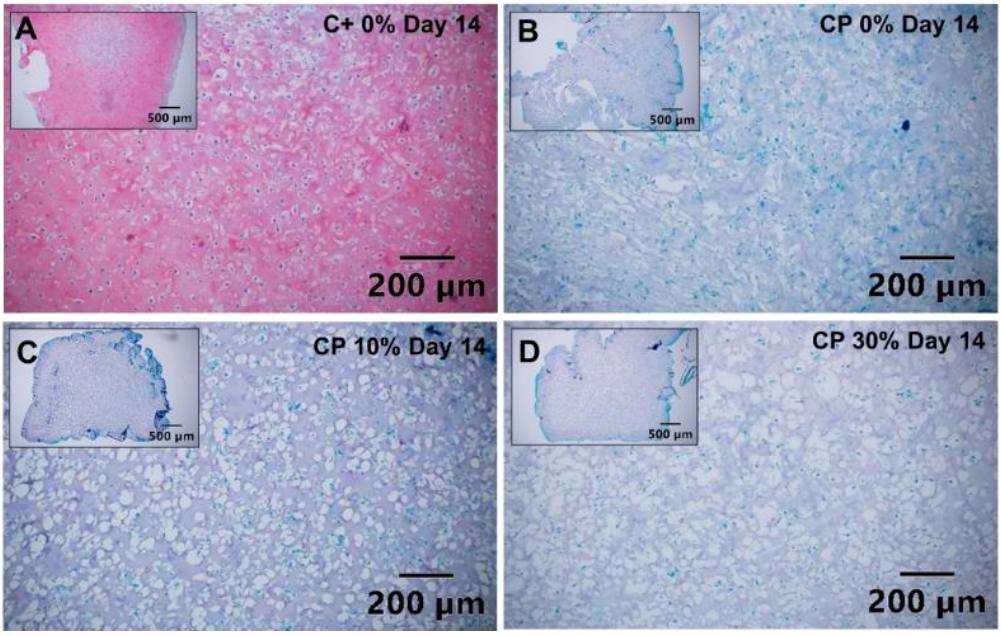



*Figure 11.6.8. Safranin O Green Histology staining performed on paraffin thin sections after 14 days in C+ medium no strain (A), or in CP medium with 0%, 10% or 30% strain (B, C, D). Higher proteoglycan deposition was observed in the presence of C+ medium when compared to samples in CP medium at the same strain (B), or higher (C, D). When subjected to 10% strain (C) cells showed a rounder and larger appearance when compared to samples cultured without strain in chondrogenic medium (A) or chondro-permissive medium (B).*

**Presentations:**
"Strain induces hypertrophic differentiation of naïve human MSCs in a 3D in vitro model", Thomas Jörimann, Priscilla Füllemann, Romano Matthys, Martin Stoddart, Sophie Verrier. ORS 2022 Poster
"Effect of strain on naïve human MSC differentiation, an in vitro bioreactor study", Thomas Jörimann, Priscilla Füllemann, Romano Matthys, Martin Stoddart, Sophie Verrier. SVGO-SBMS 2022 Podium
"Shorter resting period between cycles induces stronger MSC response to mechanical stimuli". Sina Enzmann, Romano Matthys, Martin Stoddart, Sophie Verrier, SVGO-SBMS 2022 Podium

**Thesis:**
Effect of strain on Mesenchymal stem cells differentiation: a bioreactor study. Thomas Jörimann, MSc ETH.
Effect of resting period and number of deformations in mechanically driven mesenchymal progenitor cell differentiation. Sina Enzmann, MSc ETH.
Effect of short time of stimulation on endochondral MSC differentiation. Jessica Keller, MSc, ZHAW.

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

**Systemic administration of anti-IL-1β to enhance bone healing (HealBone2) (ongoing) (M Stoddart, E Wehrle,** M Schröder, L Gens, S Zeiter**)**

**Background:** Although 90% of fractures typically heal without complications, there remains a small proportion (≤ 10%) of fractures that experience delayed healing or non-union. In patients with such healing complications, there appears to be an important contribution of an inappropriately maintained pro-inflammatory environment to the defective fracture healing process. Interestingly, growth factors e.g. BMP-2, used in bone regenerative approaches have recently been shown to induce pro-inflammatory cytokine release. Thus, immunomodulation of the local fracture microenvironment could be an effective way to enhance fracture healing in troublesome healing environments. The preceding project, HealBone, showed that local administration of IL-1Ra, the receptor antagonist of the pro-inflammatory cytokine IL-1β, can improve BMP-2 induced bone healing in a rat segmental femoral defect. However, the rapid degradation of IL-1Ra in vivo suggests that improved bone healing efficacy may be observed with more effective strategies to inhibit IL-1β activity, such as anti-IL-1β monoclonal antibody therapy. Therefore, the current project focuses on investigating the therapeutic efficacy of systemic anti-IL-1β administration to improve BMP-2 induced bone healing in challenging healing environments.
**Goal:** To characterize BMP-induced cytokine and proteomic profiles during bone healing, and to test the efficacy of systemic anti-IL-1β administration to improve BMP-2 induced bone healing in challenging healing environments.
**Results:** A first in vivo study showed pronounced differences in early callus formation and mineralization dependent on treatment (empty, collagen, collagen + BMP-2) of the segmental defect. The study will be supplemented with the assessment of local and systemic cytokine expression profiles.

## 11.7 AO Development Incubator

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

**Background**: The current generation of bone 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 and collaborators at with QUT (Brisbane, Australia) to enhance the existing treatment modalities of locked plating by redesigning the conventional 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, it increases implant strength, carries potential to permit full, early 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 fractures as a pilot implant and to collect clinical evidence demonstrating the concept feasibility.
**Results**: Having obtained CE marking in April 2021, a soft launch of the Biphasic Plate DF was accomplished in 2022 with selected clinics in the DACH region. By the end of the year, the Biphasic Plate DF has been successfully implanted in 19 patients with encouraging first outcomes. Furthermore, the Biphasic Plate DF received AO TC approval. In the course of this year, the project has been transferred completely from ARI to AO ITC's Technology Transfer group and QUT Brisbane, where the group of a co-inventor D. Epari investigates the transferability of the biphasic feature to other anatomical regions and implants.

*Figure 11.7.1: Clinical case discussions during a user's meeting at the AO Davos Courses 2022.*

**Pres:**
Sommer C. Biphasic Plating: first clinical case results. AO Innovation Symposium - AO's innovation strategies. 2022. DKOU (oral online).

**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 the ARI. The system comprises an implantable data logger which autonomously collects relevant parameters to support surgical decision-making during fracture healing. Wireless synchronization of the assessed implant load data via patient's mobile phone allows for remote monitoring by the treating physician. Proof of concept is obtained from preclinical experiments and from first clinical data collection with prototype devices on external fixation.
**Goal**: To 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 project is already in an advanced stage and the design of the implantable device was frozen in 2021. This year was marked by the completion of the verification and validation activities of the Fracture Monitor T1 with the endpoint of releasing the system for clinical investigation. This included, amongst others, standard testing for active implantable medical devices (ISO 14708-1) and biocompatibility (ISO 10993 series) as well as device specific performance and safety testing such as firmware validation, long term reliability testing, mechanical testing and battery safety evaluation. In December, the application for the clinical investigation was submitted to the competent authorities and is currently under review.

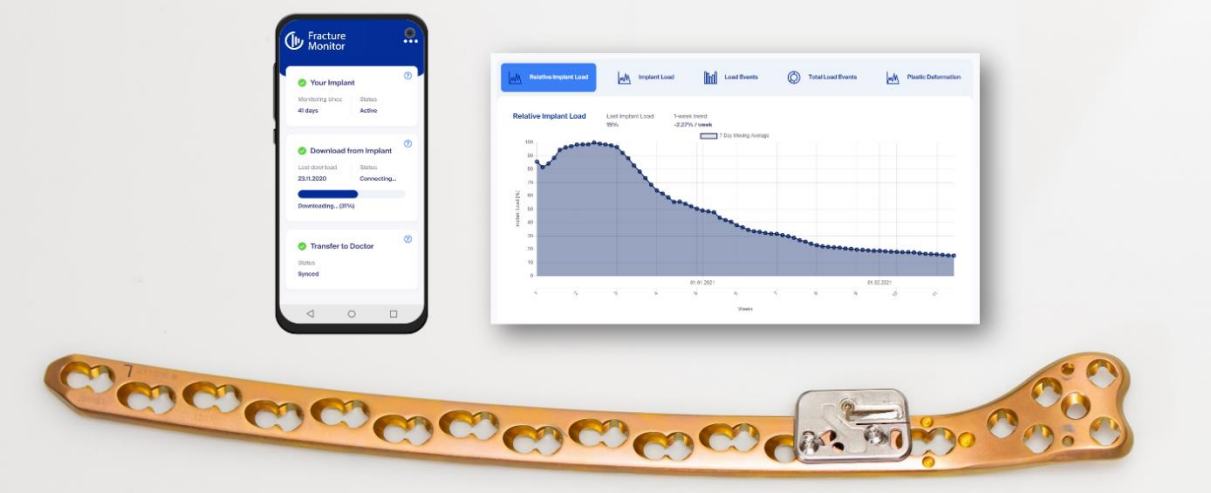



*Figure 11.7.2: AO Fracture Monitor T1 system with the implantable data logger mounted to a locking plate; smartphone app and exemplary data output as visualized in the webapp.*

**Pres:**
Windolf M. Continuous implant load monitoring. 2022. ICORS (oral).
Windolf M. AO Fracture Monitor: Sensor zur individualisierten Nachbehandlung – Momentaner Stand. 2022. AO Trauma Dreiländertagung (oral).
Ernst M. AO Fracture Monitor: Bringing orthopaedic aftercare to the 21st century. 2022. Orthopaedica Belgica (oral).

**Pub:**
Windolf M, Varjas V, Gehweiler D, Schwyn R, Arens D, Constant C, Zeiter S, Richards RG, Ernst M. "Continuous implant load monitoring to assess bone healing status – evidence from animal testing" Medicina (2022).58(7):858.

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

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

**Background**: Lower limb deformities in children and adolescents are often corrected with temporary (hemi-) epiphysiodesis technique. Currently utilized implants have their disadvantages by being not "passively" safe and requiring 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 of 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**: The previously developed implant prototype went through several design iterations resulting in a new design optimized for human treatment. On top of incorporating features to improve surgical handling, the focus was on adapting the implant contour to human anatomical conditions. Findings from computer simulations, mechanical tests and a surgical usability test were incorporated into the development process. Comprehensive mechanical tests have been carried out to confirm functionality. AOTC Pediatric Expert Group members have tested and approved the new implant design in a wet lab. Full-construct tests are in preparation to verify safety-relevant aspects and thus complete the design phase.

*Figure 11.7.3: AOTC Pediatric Expert Group during a usability lab testing the optimized implant design.*

**Partner:**

- AOTC Pediatric Expert Group (PAEG)

**GEDI – Antibiotic Eluting Gel (ongoing) (F Moriarty, M D'Este, A Montali, P Nylund)**

**Background:** Fracture related infections (FRI) can be a serious outcome for orthopedic trauma patients, they lead to longer treatment times, and sometimes permanent disability or loss of limbs. The FRI are directly translated into increased health care costs. Main treatment options for FRI include debridement and implant retention (DAIR) in combination with systemic antibiotics, or debridement, antimicrobial therapy and implant exchange or removal if the fracture has healed. In many instances the delivery of the antibiotics can be compromised due to damage in the vascular system, or the antibiotics do not reach a therapeutically effective concentration in the affected area. To circumvent the aforementioned problems an injectable hydrogel has been developed with the intention to control the release of the antibiotic, keeping the local concentration high while avoiding side effects due to high systemic concentrations. The gel was designed to stick to metal more than to surgical gloves for optimal surgical handling.

**Goal:** The main goal of this project is to produce all the technical data and documentation necessary for regulatory approval and for future clinical studies and attract the attention of industrial partners capable of bringing this idea to the market. As part of the project, we will show efficacy and safety of the gel in treatment of fracture related infection. This will, among other things, be done by performing three separate in-vivo studies on a large animal model without infection and with a large bone defect with and without an infection.

**Results:** The manufacturing process of the hydrogel has been further developed and adapted by using all ingredients of pharmaceutical grade. Specimens of the materials were received and tested. Specifications were established and stability studies have been started, and this has evolved into a better understanding of the manufacturing and storage conditions, critical to stability of the product. The gel in combination with Gentamicin sulphate and Vancomycin has shown efficacy in treatment of methicillin resistant *S. aureus*-orthopedic device-related infection (manuscript in preparation). The gel mixed with only Gentamicin sulphate is currently being tested in a large animal model for FRI treatment. Active contacts were established with industrial contractors for manufacturing the product under Good Manufacturing Practices.

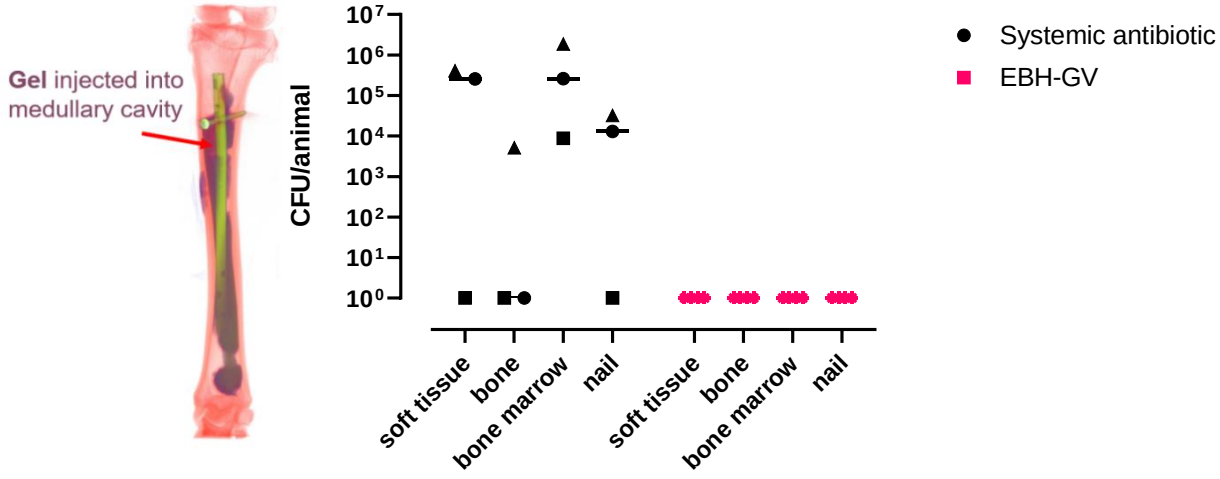



*Figure 11.7.4: Left: Radiograph of a cadaveric test where GEDI gel made radiopaque with potassium iodide was implanted in sheep tibia with distal tibia nail. Right: Quantitative bacteriology analyses of soft tissue, bone, bone marrow and nail after systemic antibiotic treatment or GEDI gel with Gentamycin and Vancomycin at revision. Culture-negative samples were arbitrarily assigned a value of 1 for the purposes of displaying on a log10 axis.*

## 11.8 AO Strategy Fund

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

**Background**: Fracture fixation complications not only occur due to 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 case, which requires a mechanical sense and awareness to correctly interpret the situation and choose 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 fracture fixation and bone healing via a virtual and interactive osteosynthesis learning platform. Augment and complement existing AO offerings with their unique possibilities of animating and displaying biomechanical simulations.
**Results**: A new version of OSapp has been developed and successfully released in 2022. The content has been extended with more than 100 new units in 32 lessons and restructured towards a knowledge hub of interactive biomechanical principles for all major fracture fixation concepts, also represented with a novel website layout and user interface. The new version was integrated into the AO Trauma Course "Basic Principles of Fracture Management for Swiss Surgeons" during the AO Davos Courses. Six faculty lectures were augmented with OSapp animations presented on 38 slides. A novel "Biomechanics Challenge" lecture was introduced and presented by Prof Reto Babst and Dr Simon Lambert supported by the ARI team to illustrate principles based on an educational clinical case and including a task to be solved by the participants using OSapp. Four stations of AO Skills Lab (developed at ARI) were augmented with QR codes redirecting participants to the corresponding digital replica in OSapp. Feedback was positive and encouraging from both participants and faculty members. During the first six weeks after its release, the new OSapp version attracted over 100'000 page views from more than 7'000 unique users and more than 90% positive feedback from over 250 responders. The collaboration with AO Milestones, AO Surgery Reference and other AO offerings have been continued to integrate and interlink OSapp content.

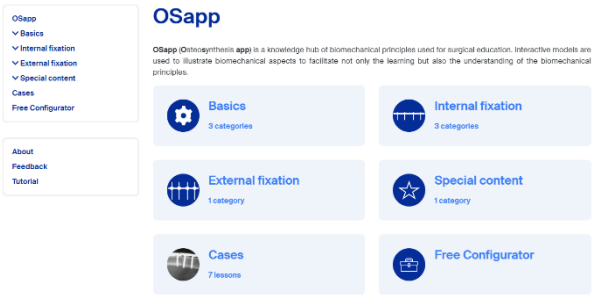



*Figure 11.8.1: The new OSapp version released in 2022, representing a systematic collection of biomechanical principles of fracture fixation in a knowledge hub concept.*

**Pres:**
Mischler M, Knecht M, Varga P. Experimentally validated computer simulations of locking plate fixations for surgical education. 2022. ICORS (oral).
Mischler M, Knecht M, Varga P. Systematic validation of finite element simulations of locking plate fixations. 2022. ESBiomech (oral).

**Partners:**
- Lambert S (MD), University College of London Hospital, UK
- Babst R (Prof), Luzerner Kantonsspital, Switzerland
- Gebhard F (Prof), Universitätsklinikum Ulm, Germany
- Jäger M (MD), Universitätsklinikum Freiburg, Germany
- Schütz M (Prof), Royal Brisbane Hospital, Brisbane, Australia

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

**Background**: Outcomes of orthopedic and trauma surgery are 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 lack data collection to measure training success. Current digital technologies offer opportunities to augment known predominantly mechanical training models with enhanced training scope, user experience and comprehensive training data assessment. They allow for decentralization of the training 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**: Surgeon feedback from the freehand distal locking training module confirmed the usefulness of the DEHST training concept. A follow-up prototype module was developed, which trains the crucial steps for the proximal femoral nailing system's cephalic component insertion. Following the DEHST concept, the user can practice the surgical steps of nail positioning, guide wire insertion and placing the cephalic component in a synthetic bone model under simulated fluoroscopic guidance. Performance metrics are captured and made available to the user for a comprehensive training assessment in a web app. At the DKOU congress in Berlin and during the AO Davos Courses, the module was extensively tested and exceedingly positively appraised. Complemented by the existing distal interlocking module and a future module for nail entry point determination, this module will be part of a larger package covering the training of the most relevant skills for proximal femoral nailing. In close collaboration with the AO Milestones program, this package's productization is the 2023 aim. Further modules will be implemented in the coming year.

*Figure 11.8.2: Demonstration of the second DEHST module for practicing the insertion of the cephalic component of the proximal femoral nailing system at DKOU Berlin (left) and during the AO Davos Courses (right).*

**Pres:**
Pastor T, Knobe M, Kastner P, Souleiman F, Pastor T, Gueorguiev B, Windolf M, Buschbaum J. Validation of a novel device for digitally enhanced hands-on surgical training of intramedullary nail distal interlocking. 2022. Swiss Congress of Surgery (poster).
Ernst M , Buschbaum J, Windolf M. DEHST – Digitally enhanced hands-on surgical training. 2022. Orthopaedica Belgica (oral).
Pastor T, Knobe M, Kastner P, Souleiman F, Pastor T, Gueorguiev B, Windolf M, Buschbaum J. Validation of a novel device for digitally enhanced hands-on surgical training of intramedullary nail distal interlocking. 2022. ICORS (oral).
Pastor T, Knobe M, Kastner P, Souleiman F, Pastor T, Gueorguiev B, Windolf M, Buschbaum J. Validation of a novel device for digitally enhanced hands-on surgical training of intramedullary nail distal interlocking. 2022. DKOU (oral).
**Pub:**
Pastor T, Pastor T, Kastner P, Souleiman F, Knobe M, Gueorguiev B, Windolf M, Buschbaum J. Validity of a Novel Digitally Enhanced Skills Training Station for Freehand Distal Interlocking. Medicina. 2022.58(6):773.
**Partners:**
- Höntzsch D (Prof), BG Unfallklinik Tübingen, Germany
- SYNBONE AG, Zizers, Switzerland
- AO Milestones, Davos, Switzerland

## 11.9 Extramural Projects

**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 and can lead to issues in complex areas such as the hand, leading to require secondary surgery to remove the implant. A new osteosynthesis method, BoneFix, has been developed by the consortium partners at KTH using light-curable polymer composites for highly customizable fixation solutions that have been shown to induce no soft tissue adhesions. This biocompatible platform can be shaped in situ and is designed to use a self-etching primer to adhere directly to the bone surface 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**: An ovine phalanx model was used to test BoneFix patches and metal plates in both torsion and bending. These initial biomechanical results showed that the BoneFix osteosynthesis patches had superior stiffness in torsion and for well reduced fractures in bending. Additionally, the BoneFix patches would sustain similar torques to failure in torsion. This indicates that BoneFix is not inferior to traditional metal plates in bending and torsion in this ovine phalanx model. To further this inquiry, a cadaver study was conducted to measure the internal forces acting on the osteosyntheses in the hand during rehabilitation exercises to determine the loading they must sustain. Results from this cadaver study will allow BoneFix to be optimized for a clinical environment.

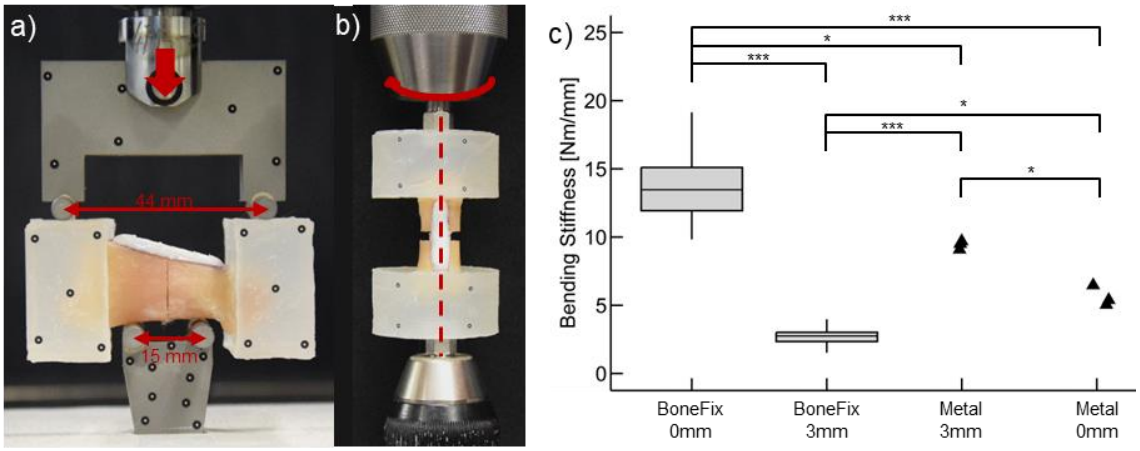



*Figure 11.9.1: Setup with a specimen mounted for 4-point bending (a) and torsion (b) testing. Box plot of the bending stiffness comparing well- and poorly reduced fractures to traditional metal hardware (c).*

**Pres:**

Schwarzenberg P, Colding-Rasmussen T, Hutchinson DJ, Mischler D, Horstmann P, Petersen MM, Malkoch M, Wong C, Varga P. Light-curable fracture fixation solution comparable with metal plates in torsion. 2022. ICORS (oral).

Schwarzenberg P, Colding-Rasmussen T, Hutchinson DJ, Mischler D, Horstmann P, Petersen MM, Malkoch M, Wong C, Varga P. Light-curable fixation comparable with plates in torsion. 2022. ESBiomech (oral).

**Partners:**

- Malkoch M (Prof), KTH Royal Institute of Technology, Sweden
- Mustafa K (Prof), University of Bergen, Norway
- 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) (ongoing) (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**: Collection of experimental data by quasi-continuous CT scanning during injection and rheological measurements of bone cement for modelling of material injection processes in vertebroplasty, describing bone cement flow behavior and distribution, biomechanical behavior at the interface between bone cement and trabecular structure, and bone cement curing.
**Results**: The bone cement was first characterized to quantify its time and shear rate dependence. The time dependence was determined by measurements with a rheometer over a period of time, while the shear rate dependence was modeled by a rheological power law model whose parameters were determined by injecting the bone cement through a syringe and a cannula of known dimensions and using analytical solutions for the flow of non-Newtonian fluids through a tube. To validate the computational model, a benchmark problem was developed in which the bone cement was injected into an aluminum foam with dimensions and structure similar to that of a vertebra at controlled flow rates. The force required for the injection was measured and the injection process was recorded with CT images. The results were then compared with simulations to validate the computational model.

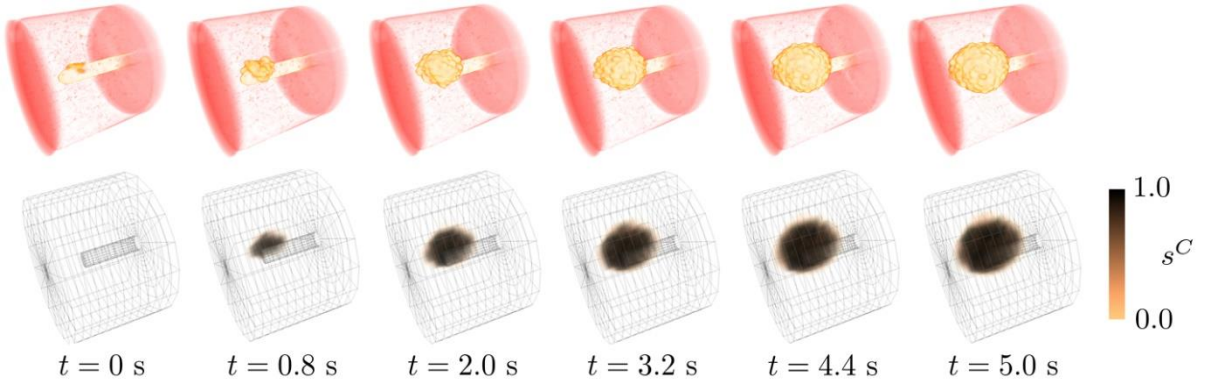



*Figure 11.9.2: CT images of bone cement injection through aluminum foam (top row) and comparison with results from simulation using the computational model (bottom row).*

**Pub:**
Trivedi Z, Bleiler C, Gehweiler D, Gueorguiev-Rüegg B, Ricken T, Wagner A, et al. Simulating vertebroplasty: A biomechanical challenge. PAMM. 2021.20(1):e202000313.
Trivedi Z, Gehweiler D, Wychowaniec JK, Ricken T, Gueorguiev-Rüegg B, Wagner A, et al. A continuum mechanical porous media model for vertebroplasty: Numerical simulations and experimental validation. 2022. http://arxiv.org/abs/2209.14654.

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

**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, the EU-funded I-SMarD project proposes to develop multi-functional dental implants that can respond to environmental threats such as bacteria by releasing nanoparticles and antibiotics. Moreover, these implants will match the anatomical characteristics of dental tissues and offer the potential to monitor the healing process after surgery. Collectively, the I-SMarD dental implants should offer a personalized approach for preventing bacterial biofilm formation and peri-implantitis. The deposition of these biomaterials requires presence of porosities in the implant design. The implants will 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**: Design optimization of porous 3D-printed dental implants for fatigue lifetime via a combined experimental testing and validated finite element (FE) simulation approach.
**Results**: FE simulation methodology has been established and validated to characterize fatigue behavior of porous 3D-printed structures. Six porous sample geometries were generated with two-unit cell types at three porosity levels. Monotonic (N = 4) and fatigue (N = 24) bending-compression tests were performed according to the ISO 14801 standard to determine the ultimate monotonic load and endurance limit, i.e., infinite fatigue life, of each design. The FE models provided a good correlation ($R^2$=0.93) between the simulated stiffness and the experimental endurance limit. Thus, this calibrated FE model is able to predict quantitatively the fatigue performance of porous configurations. These models are currently being utilized to assist the development of the I-SMarD implant design.

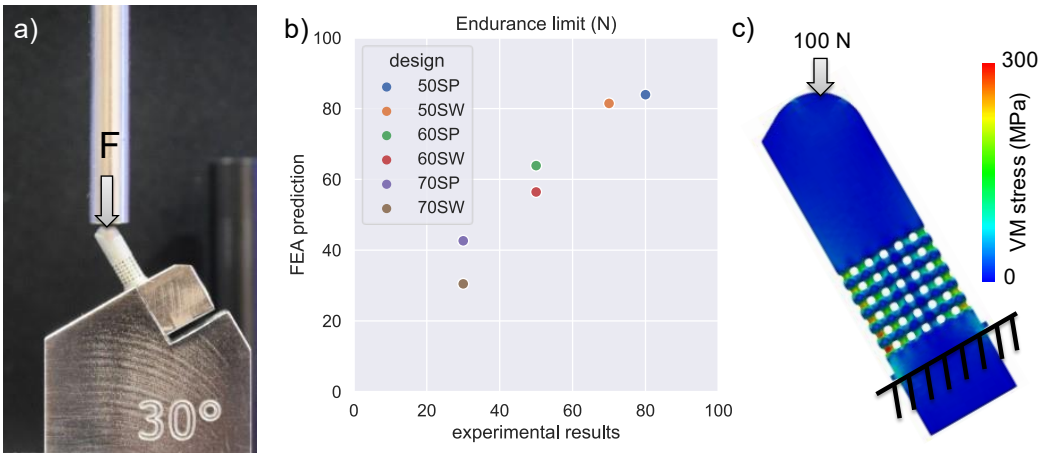



*Figure 11.9.3: (a) bending-compression testing setup according to ISO 14801; (b) comparison of experimental and simulated force values corresponding to infinite fatigue life values of each design; (c) boundary conditions and stress distribution for the 60SP design's FE model under a 100 N load.*

**Pres:**
Vautrin A, Aw J, Attenborough E, Varga P. Validated finite element simulation of porous titanium samples under fatigue loading for design optimization. 2022. ESBiomech (oral).

**Partners:**
- Attenborough E, Attenborough Dental, UK
- Ja A, University of Leeds, UK
- Anastasiou A, University of Manchester, UK
- Kontonasaki E, Aristotle University of Thessaloniki, Greece
- Amorese C, ICMEA, Italy

**Advances in fixation strength of reorienting rectangular triple pelvic innominate osteotomies – a biomechanical investigation of two screw fixation techniques (D Ciric, B Gueorguiev)**

**Background**: Reorientating pelvic osteotomies are performed to improve femoral head coverage and prevent femoroacetabular impingement or degenerative arthritis, particularly in young population. A Toennis-Kalchschmidt triple pelvis innominate osteotomy (3PIO) is used in symptomatic patients. Bone healing complications and rehabilitation programs rely on fixation stability.
**Goal**: To investigate biomechanical behavior of two acetabular screw configurations for 3PIO.
**Results**: A bidirectional screw alignment does not lead to significant advantages compared to a pure monoaxial fixation technique if all three axial screws are evenly distributed over the osteotomy geometry. An optimal long-range screw path in the medullary canal with high contact pressure between the two cortices of the iliac bone is more critical. Therefore, using screws with a larger diameter may be advantageous in the dorsal os ilium. The 3PIO is susceptible to changes in anteversion and inclination under partial weight bearing. A cautious rehabilitation protocol is still recommended.

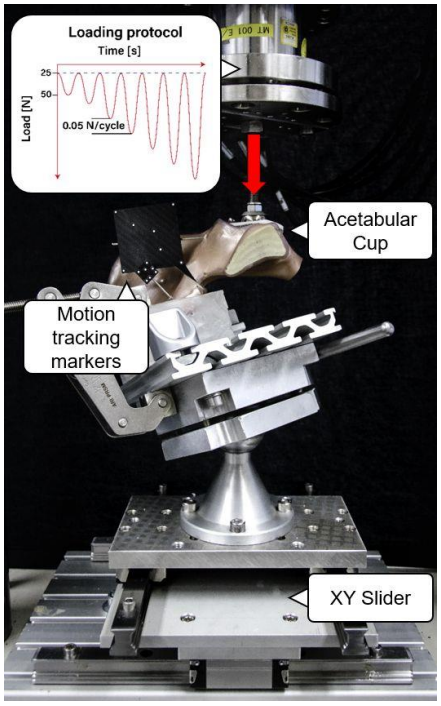



*Figure 11.9.4: Setup with a specimen equipped with two marker sets for motion tracking and mounted for biomechanical testing.*

**Pres:**
Richter J, Kalchschmidt K, D'Aurelio C-S, Ciric D, Gueorguiev B. Stabilität von Schraubenosteosynthesen nach 3fach Beckenosteotomie. 2022. DKOU (oral)

**Partner:**
- Richter J (MD), Helios University Clinic Wuppertal, Germany

**Ideal site of cement application for augmented sacroiliac screw fixation – biomechanical perspective (I Zderic, B Gueorguiev)**

**Background**: Diminished purchase of sacroiliac (SI) screws in fixation of osteoporotic pelvic fractures is a concern.
**Goal**: To compare construct stability of cement augmented SI screws using two different cementation sites in a biomechanical model of a fragility fracture of the pelvis (FFP).
**Results**: An FFP Type IIB was created in human cadaveric pelvises. Sacral fracture stabilization was achieved with bilateral 7.3 mm fully threaded SI screws. Cement augmentation was performed at the tip of the screw (group A) on one side and at the midshaft of the screw (group B) on the contralateral side. Biomechanical testing was conducted under physiologic cyclic loading separately on both sides. The results demonstrated less fragment and screw displacement in the FFP IIB fracture model by cement augmentation of sacroiliac screws at the level of the lateral mass (group B) compared to the center of vertebral body of S1 (group A).

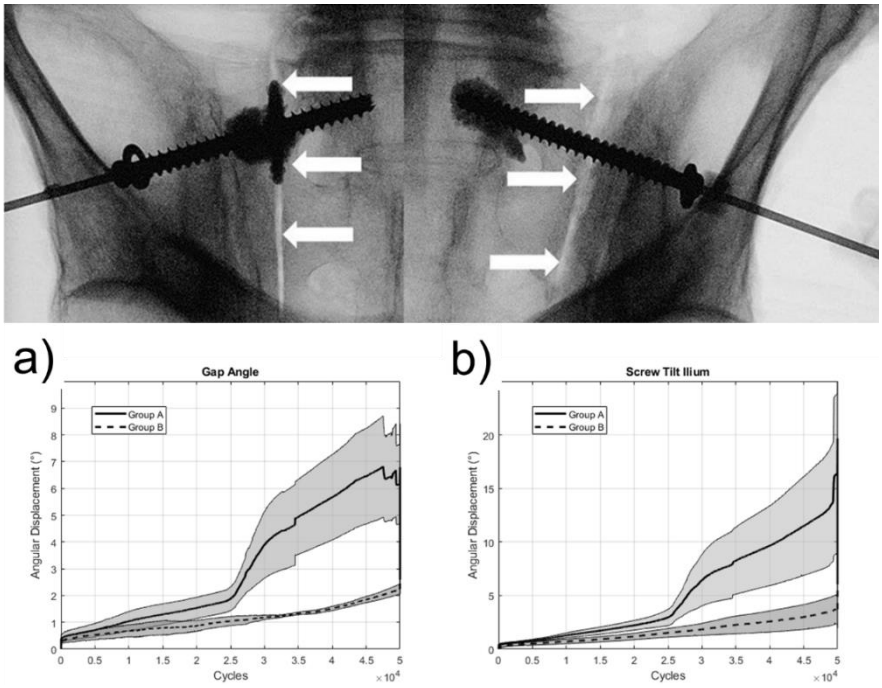



*Figure 11.9.5. Top: Fluoroscan visualizing instrumented specimen following screw tip augmentation (left) and screw midshaft augmentation (right). Arrows indicate simulated fracture. Bottom: Outcome measures for a) gap angle and b) screw tilt ilium, presented over the course of the first 50,000 cycles for each group separately in terms of mean value and SEM.*

**Pub:**
Albers CE, Zderic I, Kastner P, Gueorguiev B, Tosounidis TH, Keel MJ, Bastian JD. The ideal site of cement application in cement augmented sacroiliac screw fixation: the biomechanical perspective. European journal of trauma and emergency surgery. 2022.

**Partners:**
- Bastian JD (Prof), Inselspital, Berne, Switzerland
- Albers CE (MD), Inselspital, Berne, Switzerland

**3D Printed-Matrix Assisted Chemically Modified RNAs Bone Regenerative Therapy for Trauma and Osteoporotic Patients (cmRNAbone) (ongoing) (M Stoddart, M D'Este, D van der Heide, E Della Bella)**

**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.
**Goal:** The cmRNAbone project aims to create a 3D-printable bone mimetic composite biomaterial-ink for bone regeneration. This ink combines osteoinductive calcium phosphate particles (CaP) with tyramine modified hyaluronic acid (THA) and collagen type I (Col) for the delivery of chemically modified RNAs (cmRNAs), to induce nerve, vessel, and bone formation to together promote bone regeneration, Figure 11.9.6.
**Results:** A composite biomaterial-ink was created that showed viscoelastic properties suitable for 3D printing. Scaffolds produced by this ink were characterized and showed reduced swelling when including Col and CaP, while compressive moduli increased when incorporating Col and CaP. *In vitro* indirect cytotoxicity according to ISO guidelines did not show any toxicity from any of the components alone or when combined with different concentrations of CaP up to 30% w/v. *In vitro* direct cytocompatibility showed higher cell metabolic activity, viability and cell attachment when including Col and CaP compared to the THA alone. Further, preliminary *in vitro* investigation suggests that the lowest concentration of CaP included into the biomaterial-ink, 10% w/v, shows the most osteogenic potential *in vitro*.

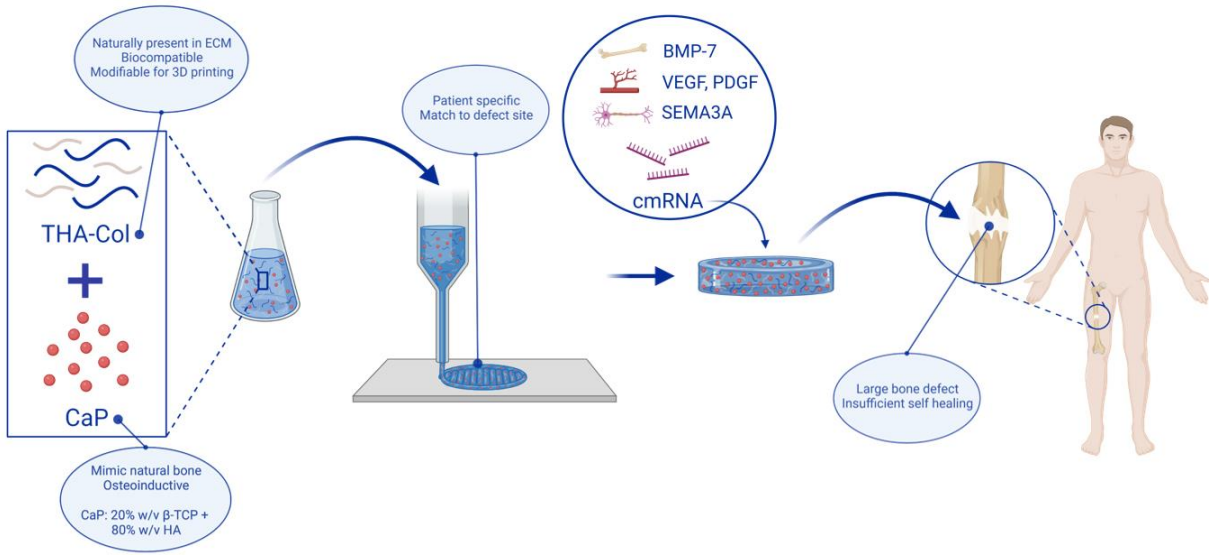



*Figure 11.9.6: Graphical abstract cmRNAbone project. Composite biomaterial-ink consisting of tyramine modified hyaluronic acid (THA), collagen type I (Col), calcium phosphate particles (CaP), and chemically modified RNA (cmRNA) for bone regeneration.*

**Fund:** H2020-SC1-BHC-2018-2020. Total Budget €6.26 million, ARI Budget €710k, Period 2020-2023 97.

**Pres:**
van der Heide D, Della Bella E, Yuan H, de Groot-Barrère F, Stoddart MJ, D'Este M. Bone resembling composite biomaterial-ink consisting of hyaluronan, collagen and calcium phosphate particles for bone regeneration. 2022 SSB+RM (poster).
van der Heide D, Della Bella E, Yuan H, De Groot-Barrère F, Stoddart MJ, D'Este M. Composite biomaterial-ink with hyaluronan, collagen and calcium phosphate particles for delivery of chemically modified RNA to promote bone regeneration. 2022 TERMIS EU (oral).

van der Heide D, Della Bella E, Huipin Y, de Groot-Barrère F, Stoddart M, D'Este M. Natural bone inspired 3D printed composite biomaterial-ink composed of hyaluronan, collagen and calcium phosphate particles to promote bone regeneration. 2022 GR forscht (oral).
D'Este M, van der Heide D, Amédée J, Stoddart MJ. cmRNAbone project: 3D printed-matrix assisted chemically modified RNAs bone regenerative therapy for trauma and osteoporotic patients. ESB 2022, Bordeaux (oral).
van der Heide D, Della Bella E, Huipin Y, de Groot-Barrère F, Stoddart M, D'Este M. Bone Mimetic Composite Biomaterial-Ink combining Hyaluronan, Collagen and Calcium Phosphate Particles for the Delivery of Chemically Modified RNA for Treatment of Bone Defects. ESB 2022, Bordeaux (oral).

**Pub:**
van der Heide D, Cidonio G, Stoddart M, D'Este M. 3D printing of inorganic-biopolymer composites for bone regeneration. Biofabrication. 2022;14:042003.

**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, The Netherlands
- Zelphati O, OZ Biosciences SAS, France
- Fernández A (PhD), Idonial Technological Center, Spain
- Van Griensven M (Prof, PhD), Maastricht University, The 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, E I Bektas, R Randriantsilefisoa, A Vernengo)**

**Background:** The musculoskeletal tissue is the framework of our lives. It holds shapes and supports movement of our body, protects the crucial internal organs and it contributes to the body's immunity via haematopoiesis. 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.

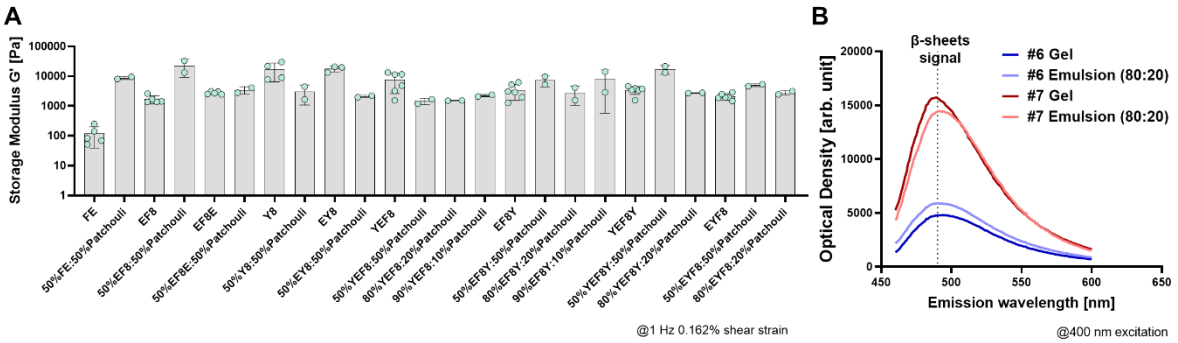



*Figure 11.9.7: (A) Storage modulus (reflecting stiffness) of a family of peptide-based hydrogels and emulgels. (B) Fluorescent emission of hydrogels and emulgels upon excitation at 400 nm. Dashed line shows expected emission of ThT bound to β-sheets.*

**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) was designed. A parametric study was carried out to verify the effect of rational peptide sequence modification on final physicochemical properties of composite hydrogels and emulsion-based gels (emulgels). Tyramine-modified hyaluronic 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 peptide hydrogels, emulgels and peptide-THA composites can be controlled by the choice of primary peptide sequence and feeding ratios of oil to water for emulgels (Figure 11.9.7A), whereas for peptide-THA composites their viscoelasticity depends on the fabrication technique and final crosslinking mechanism. These hydrogels and emulgels are characterised by shear-thinning behaviour, proven for all nine peptide hydrogels, and quantified by calculating the power law index ($n$), with extracted $n$ values in all cases being $n<1$. We also demonstrated the primary constituent β-sheet structure persists in emulgels (Figure 11.9.7B). Finally, we established multiple protocols for successful harvesting and manipulation of monocytes from human peripheral blood mononuclear cells (PBMCs) towards peptide and HA-based immunomodulation. Using ELISAs we uncovered the upregulation of the inflammatory cytokine TNFα for tyrosine-containing peptide, as compared to the sequence without terminal tyrosine. This indicated the importance of the amino acid sequence on the resulting inflammatory state of macrophages cultured in the presence of the peptide. Finally, all hydrogels displayed rapid frequency and rotational recovery allowing extrusion-based fabrication of scaffolds for immunomodulatory tissue engineering.

**Funding:** Horizon 2020, Marie Skłodowska-Curie Individual Fellowship (MSCA-IF); budget**:** €191’149,44; period: 01/07/2021–30/6/2023; Grant agreement ID: 893099; Project website: https://cordis.europa.eu/project/id/893099.

**Pres:**

Wychowaniec JK. Aim high: from proper review structure to making impact in your field. 2022 RISEus2 School (invited lecture).

Wychowaniec JK. Materials for controlled release. 2022 ARI-Chile webinar series (oral).

Wychowaniec JK, Bektas EI, Devantay N, Eglin D, D'Este M. Design of 3D printable supramolecular self-assembling β-sheet peptide-hyaluronic acid hydrogels with immunomodulatory properties. 2022 TERMIS EU (oral).

Wychowaniec JK. Rheology – a powerful tool in probing properties of soft biomaterials and Probing nano- and macro-scopic ordering in nanomaterial and biopolymer solutions using small angle X-ray scattering. 2022 Baltic Biomaterials Centre of Excellence (BBCE) project (H2020-EU.4.a., 857287 (invited lectures).

Wychowaniec JK, D'Este M, Elsawy M, Saiani A, Miller A, Crean J, Brougham DF. From tuneable peptide self-assembly to biologically instructive materials. 2022 MRS spring meeting (oral).

Wychowaniec JK. Probing nano- and macro-scopic ordering in nanomaterial solutions using small angle X-ray scattering. 2022 Technical University Dresden (invited lecture).

Wychowaniec JK, Brougham DF. Responsive Hydrogels: Towards Spatiotemporally Controllable Biomaterials. 2022 RSC Biomaterials Chemistry Group 16th Annual Meeting (online).

Mürner M, Edwards-Gayle CJC, Bektas EI, Eglin D, D'Este M, Wychowaniec JK. Effect of tyrosine-including sequence on the physicochemical properties of β-sheet peptide hydrogels. 2023 5th SSB+RM Young Scientists Symposium (poster).

Wychowaniec JK, Edwards-Gayle CJC, Bektas EI, Eglin D, D'Este M. 3D printable supramolecular self-assembling β-sheet peptide and tyramine-modified hyaluronan hydrogels with immunomodulatory properties. 2022 ESB (Biomaterials) (poster).

Wychowaniec JK, Edwards-Gayle CJC, Bektas EI, Eglin D, D'Este M. Tyramine position dictates properties of 3D printable supramolecular self-assembling β-sheet peptide and tyramine-modified hyaluronan hydrogels. 2022 SSB+RM (poster).

**Pub:**

Wychowaniec JK, Saini H, Scheibe B, Dubal DP, Schneemann A, Jayaramulu K. Hierarchical porous metal-organic gels and derived materials: from fundamentals to potential applications. Chem Soc Rev. 2022;51:9068-9126; https://doi.org/10.1039/D2CS00585A.

Wychowaniec JK, Brougham DF. Emerging magnetic fabrication technologies provide controllable hierarchically-structured biomaterials and stimulus response for biomedical applications. Adv Sci (Weinh). 2022;9:e2202278; https://doi.org/10.1002/advs.202202278.

Salma-Ancane K, Sceglovs A, Tracuma E, Wychowaniec JK, Auniņa K, Ramata-Stunda A, Nikolajeva V, Loca D. Effect of crosslinking strategy on the biological, antibacterial and physicochemical performance of hyaluronic acid and ε-polylysine based hydrogels. Int J Biol Macromol. 2022;208:995-1008; https://doi.org/10.1016/j.ijbiomac.2022.03.207.

Walsh CM, Wychowaniec JK, Brougham DF, Dooley D. Functional hydrogels as therapeutic tools for spinal cord injury: New perspectives on immunopharmacological interventions. Pharmacol Ther. 2022;243:108043; https://doi.org/10.1016/j.pharmthera.2021.108043.

**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, G Miklosic)**

**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 for this work. 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 that with a composition of 3% THA and 2% collagen, we can obtain shear properties in the range of values ranging from healthy to degenerated human IVD (Figure 11.9.8). Furthermore, we verified the extrudability and printability of our composites (Figure 11.9.9). To characterize the material interactions with living cells, we embedded bovine nucleus pulposus cells in cast composites and demonstrated good cell viability up to at least 7 days (Figure 11.9.10). 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.

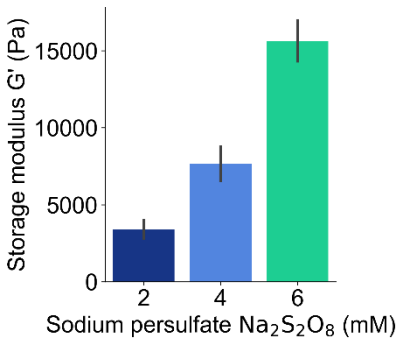



*Figure 11.9.8: Shear storage modulus tunability of composite bioink with variation in light crosslinking intensity. Achieved by varying sodium persulfate concentration.*

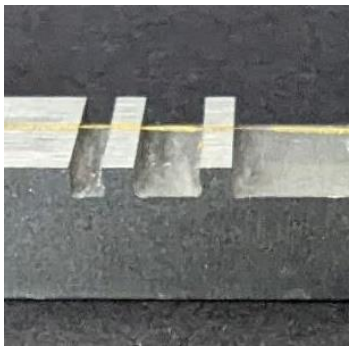


*Figure11.9.9: Bioink strand extruded over a series of pillars with a 22G needle, demonstrating good bridging capabilities and strand uniformity.*

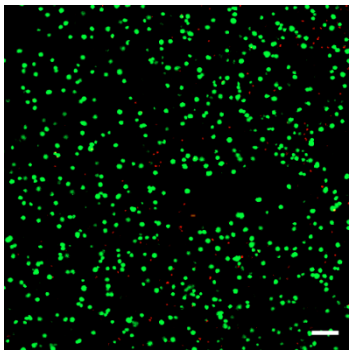


*Figure 11.9.10: Live (green) and dead (red) bovine chondrocytes embedded in cast gel, demonstrating good viability after 7 days of culture.*

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

**Pres:**
De Oliveira S, Miklosic G, D'Este M, Hélary C. Optimized collagen/hyaluronan formulations to develop a novel biomimetic ink to synthesize composite hydrogels for tissue engineering. 2022 PNG (poster).
De Oliveira S, Miklosic G, D'Este M, Grastilleur S, Véziers J, Hélary C. Collagen/hyaluronan polyionic complexes as a new building block to develop a novel bioink to model the intervertebral disc. 2022 ESB (Biomaterials) (poster).
Grastilleur S, Humbert P, Miklosic G, de Oliveira S, Halgand B, Loll F, Delplace V, D'Este M, Hélary C, Clouet J, Fusellier M, Guicheux J, Le Visage C. In vitro evaluation of ovine IVD cells interactions with a collagen/hyaluronic acid biomaterial ink: On the way to a bio-printed IVD model. 2022 eCM (poster).
Le Visage C, Grastilleur S, Humbert P, Miklosic G, Halgand B, Loll F, D'Este M, Hélary C, Fusellier M, Guicheux J. On the way to a bio-printed intervertebral disc (IVD) model: In vitro evaluation of the interactions of ovine IVD cells with a collagen/hyaluronic acid bio-ink. 2022 TERMIS AP (poster).
Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen composite bioink for the printing of nucleus pulposus-like structures. 2022 SSB+RM (poster).
Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen composite bioink for the printing of nucleus pulposus-like structures. 2022 eCM (poster).
Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen composite bioink for the printing of nucleus pulposus-like structures. 2022 ESB (Biomaterials) (poster).
Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen bioink for the printing of intervertebral disc models. 2022 GR forscht (oral).
Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen composite bioink for the printing of nucleus pulposus-like structures. 2022 Biofabrication (oral).

**Partners:**
- Laboratory for Orthopaedic Technology (Prof Stephen J. Ferguson), ETH Zürich, Zürich, Switzerland
- Le laboratoire de Chimie de la Matière Condensée de Paris (Dr Christophe Hélary), UMR 7574, Sorbonne Université, Paris, France
- Regenerative Medicine and Skeleton (Prof Jerome Guicheux, Dr Catherine Le Visage), INSERM UMRS 1229

**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. We show the use of sound patterning as a fast and cell-friendly approach to spatially organize and condense cells, to generate a 3D *in vitro* platform from which simple readouts of drug tests can be extracted by image analysis, with the potential to provide a model system for tailored tumor therapy.

**Significance**: The method here exposed can be easily translated for studying personalized therapies in musculoskeletal regeneration by biofabricating reproducible *in vitro* vascularized models in a HTS setup. This will be further explored in 2023.

**Pub:**
Di Marzio N, Ananthanarayanan P, Guex AG, Alini M, Riganti C, Serra T. "Sound-based assembly of a microcapillary network in a saturn-like tumor model for drug testing". Materials Today Bio 16, 100357 https://doi.org/10.1016/j.mtbio.2022.100357

**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.

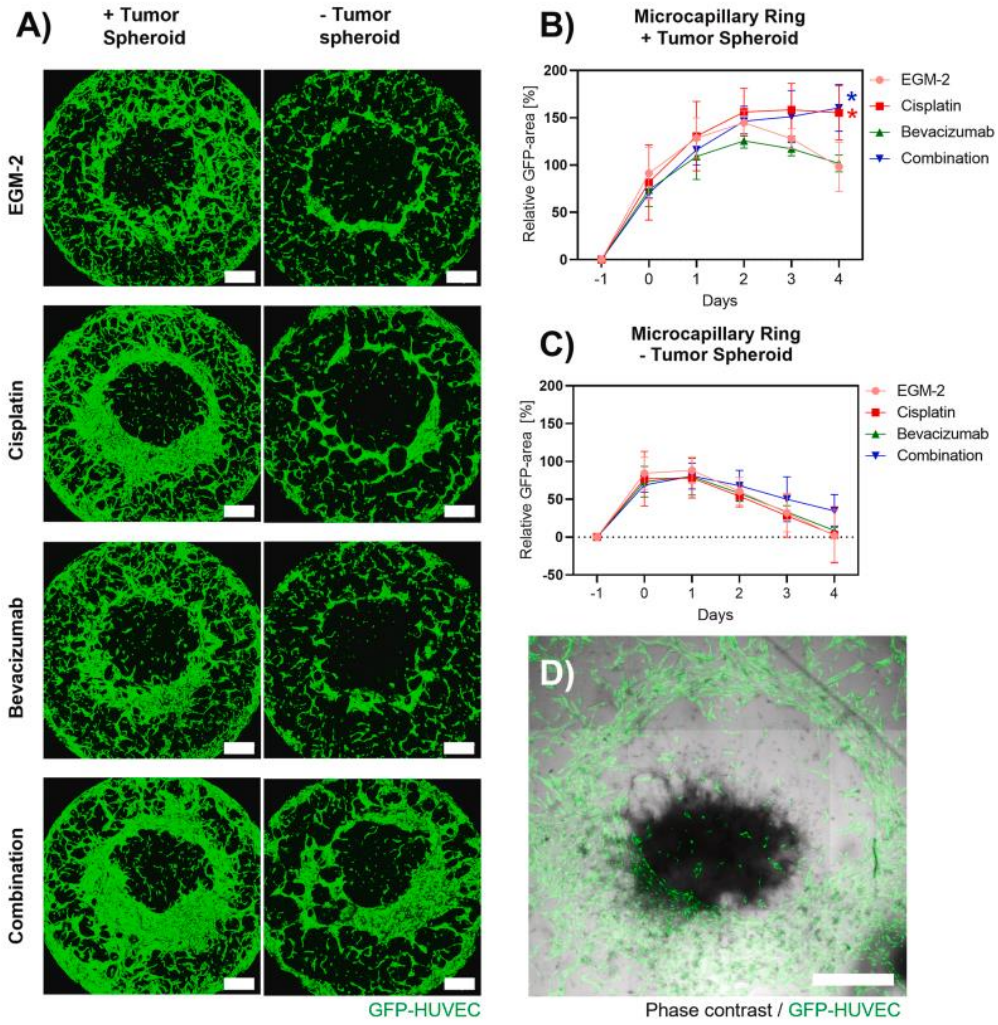



*Figure 11.9.11: Changes in the microcapillary network growth over time. (A) At the study end point day 4, the difference in the ring microcapillary maturation with/without the spheroid in presence of different treatments is clearly visible. (B) The growth trend of GFP-HUVEC network's area over time indicates that the presence of the tumor spheroid is able to stimulate the microcapillary network growth. Additionally, when the STM is treated with the anticancer drug, Cispatin (50 μM) and Bevacizumab (10 μg·mL−1), alone or in combination, it induces the ring microcapillary network to cover 50% more area compared to the EGM-2 treated condition. While (C), the growth trend of the GFP-HUVEC network's area over time is inverted if the tumor spheroid is not added onto the microcapillary network and the drug treatments do not reveal a macroscopic change. (D) At day 4 in culture the established microcapillary network coexists with the tumor spheroid which is sprouting and invading fibrin (composite of GFP- and phase contrast-channel). N = 3 and n = 3. Scale bars 500 μm.*

**Partners:**

- Vernè E (Prof), Politecnico di Torino, Torino, Italy
- Locs J (Prof), Riga Technical University, Riga, Latvia
- Loca D (Prof), Riga Technical University, Riga, Latvia
- Massera J (Prof) Tampereen Korkeakoulusaatio SR, Tampere, Finland
- Obradovic B (Prof), University of Belgrade, Belgrade, Serbia
- Rimondini L (Prof), Università del Piemonte Orientale, Novara, Italy
- Lamghari M (Prof), Instituto Nacional de Engenharia Biomedica, Porto, Portugal
- 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 (complete) (T Serra, M Alini)**

**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

**FLAMIN-GO, H2020-NMBP-TR-IND, "From pathobiology to synovia on chip: driving rheumatoid arthritis to the precision medicine goal" (running) (T Serra, M Alini)**

**Background:** Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder, primarily characterized by synovial joint inflammation, affecting ~0.5 to 1% of the overall population (~2900000 patients in the EU) and is more common in women than men (3:1). RA is a huge public health problem as it leads over time to permanent disability. There is no cure for RA but remission of symptoms is more likely when treatment begins early. However, approximately 40% of RA patients fail to achieve even 20% improvement in disease activity, with significant disability remaining in about a third of patients, and major work-related and social costs for patients and society. In addition, 10-20% of patients do not respond to any current medication, pointing to considerable disease heterogeneity and the need for testing and developing new drugs. A further point related to RA heterogeneity, is that there are no biomarkers of treatment response to individual drugs. Thus, a number of unmet needs still persist particularly related to response/non-response to powerful but expensive drugs. Conventional randomized clinical trials (RCT) may address some of these challenges, but they are time-consuming, expensive and are ethically doubtful, since many patients (currently ~40% regardless of the modality of action) fail to achieve disease benefit, while being exposed to potentially toxic drugs. Thus, the rheumatology community has a need for developing an alternative strategy to deliver innovative trials.

**Goal:** FLAMIN-GO's goal is to develop a personalized next-generation synovia-on-chip (SoC), that by effectively mimicking the complexity of a rheumatoid arthritic joint, will permit patient-specific clinical trials-on-chip (CToC). This includes i) selecting the best on-market drug for each patient's treatment, to obtain maximum benefits, reducing risk of side effects, and ii) enable rapid discovery and testing of new therapeutic targets, contributing to determine a new drug development path.

**Results:** A process and protocol for generation of a 3D printed personalized RA osteochondral unit on a chip (OC-U) tissue has been produced.

**Pres:**
Jahangir S, Vecstaudža J, Canciani E, Ločs J, Alini M, Serra T. Development of bioprinted osteochondral tissue: an in-vitro model for drug discovery. TERMIS EU Conference 2022, Krakow, Poland 28.06-01.07, 2022.

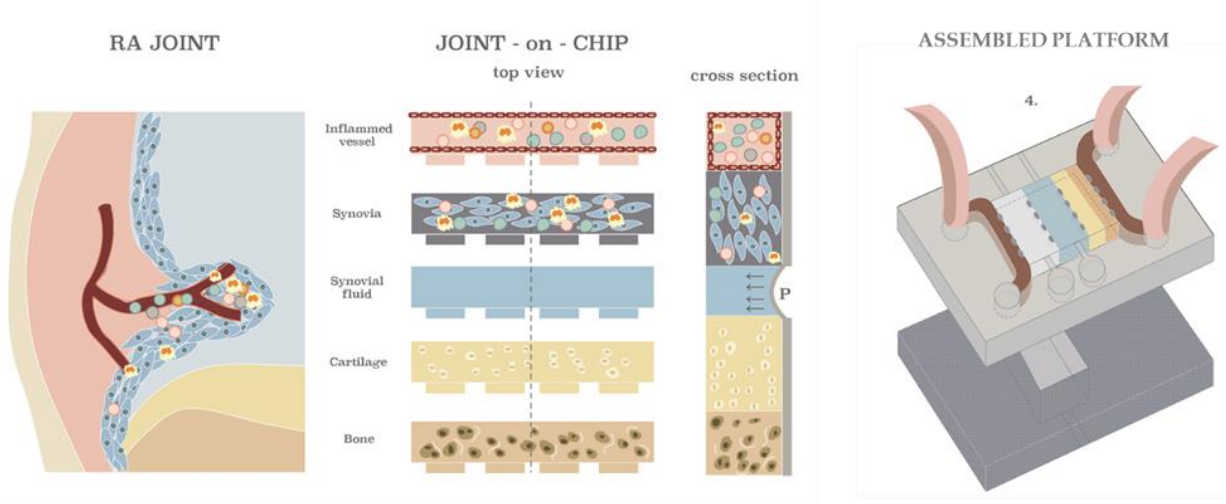



*Figure 11.9.12: Sketch of the FLAMIN-GO RA synovia-on-chip (SoC), a multi-tissue platform including "vascularized" engineered microtissues and a mechanical actuator.*

**Significance:** The idea is to use these models for optimal drug identification in less than two months, offering a faster, more cost-effective and ethically sound approach for drug screening.

**Funding: H2020**; ARI Funding EUR 500'000; Period: 2021-2024.

**Partners:**

- Ineb-Instituto Nacional de Engenharia Biomedica, Portugal
- Consiglio Nazionale delle Ricerche, Italy
- Queen Mary University of London, United Kingdom
- Associazione per la Ricerca che Cura Organizzazione non Lucrativa di Utilita Sociale, Italy
- Rigas Tehniska Universitate, Latvia
- Enginsoft Turkey Muhendislik Yazilim Ticaret Limited Sirketi, Türkiye
- Standard Biotools France SARL, France
- Trustech SRL, Italy
- Max-Planck-Gesellschaft zur Förderung der Wissenschaften EV, Germany
- Znanost Na Cesti, Zavod Za Promocijo Znanosti, Ljubljana, Slovenia
- Regenhu SA, Switzerland Development of bioprinted osteochondral tissue: an in-vitro model for drug discovery
- EU Core Consulting SRL, Italy

**Life-changing therapy for Osteo-Arthritis patients: a biomarker lead approach (OA_BIO) (ongoing) (Z Li, S Grad, M Alini,** E Ciftci**)**

**Background:** Osteoarthritis (OA) is the most common degenerative joint disease and a leading cause of disability worldwide, affecting >40 million people in Europe. With the aging population, OA is predicted to affect 170 million people globally by 2030. Current treatments only relieve OA symptoms. Liraglutide is well known as an anti-diabetic medication that is used to treat type 2 diabetes, and obesity, and to support chronic overweight management. Liraglutide has shown a unique triple effect (anti-inflammation, pain relief, and cartilage regeneration) in inflammatory and post-traumatic OA animal models.
**Goal:** The aim of this study is to determine and validate the anti-inflammatory and regenerative effect of liraglutide on human OA chondrocytes.
**Results:** The experiment was performed with two non-toxic doses (0.5 and 10 µM) selected after cytotoxicity analysis on human OA chondrocytes. Pellets formed with human OA chondrocytes were cultured with IL-1β to mimic an inflammatory OA condition. The Nitric Oxide concentrations of the OA+0.5µM Liraglutide and OA+10µM Liraglutide groups were lower than the OA group. The DNA content of the OA+0.5µM Liraglutide and OA+10µM Liraglutide groups were higher than the OA group on day 14. The qRT-PCR results showed that the anabolism (ACAN, COMP, and COL2) markers were higher expressed in the OA+0.5µM Liraglutide and OA+10µM Liraglutide groups when compared with the OA group. The inflammation (CCL-2 and IL-8) markers and catabolism markers (MMP-1, MMP-3, ADAMTS4, and ADAMTS5) had lower expression levels in the OA+ Liraglutide groups compared to the OA group. The histomorphometric analysis (Figure 11.9.13) supported the qRT-PCR results. The results indicate that Liraglutide has anabolic and anti-inflammatory effects on human OA chondrocyte pellets.

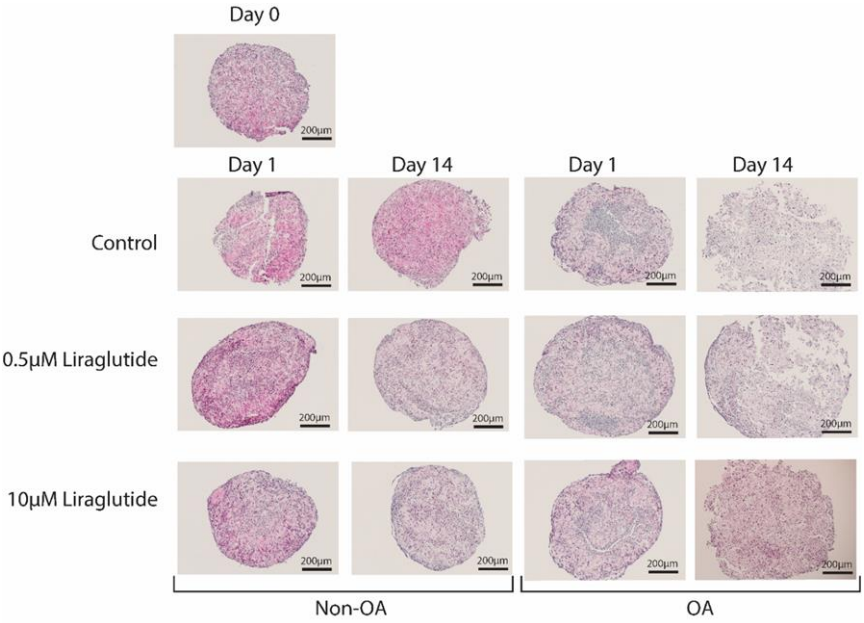



*Figure 11.9.13:* Representative *Safranin O/Fast Green staining of paraffin sections from liraglutide-treated and untreated human chondrocyte pellets. Scale bars, 200 µm.*

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

**Partners:**
- Francis Berenbaum (Prof), 4Moving Biotech, Saint-Antoine Hospital, Sorbonne University, Paris, France
- Marianna Tryfonidou (Prof), Utrecht University, Utrecht, the Netherlands
- Felix Eckstein (Prof), Chondrometrics GmbH, Ainring, Germany

**Pres:**
Ciftci Dede E, Li K, Grad S, Alini M, Li Z. Anti-inflammatory and regenerative effects of liraglutide on inflammatory human osteoarthritic chondrocytes in vitro. Graubünden Forscht, September 21-22, 2022 (oral).

**A game changer for the treatment of osteoarthritis: a cost effective combined advanced therapy to treat knee osteoarthritis (SINPAIN) (started) (Z Li, S Grad, S Verrier,** H Meng**)**

**Background:** According to the WHO Osteoarthritis (OA) is one major cause of years lived with disability in the elderly and considered a high burden disease, which makes it a research priority in Europe. There is no cure for OA and anti-OA treatments need to be reconsidered. Current pharmacological interventions consist of analgesic, anti-inflammatory drugs as well as intraarticular steroids and hyaluronic acid (IA-HA) with moderate efficacy and associated long-term side effects. New medications are thus needed both to alleviate pain and slow down disease progression.
**Goal:** Taking advantage of the explosion of RNA technologies in the last years, SINPAIN aims to develop a pipeline of siRNA-based therapy built on the combination of current technologies (dynamic IA-HA and nanocarriers) that will be designed step-by-step in order to reach a successful management of inflammation and innervation therapy for the treatment of early (grade 0-1) and later stages (grade 3-4) of knee OA.
**ARI role:** The aim of ARI in this project is to develop ex vivo OA models by co-culturing of human pericytes - chondrocytes, and sensory neurons - chondrocytes in 3D scaffolds with the application of pro-inflammatory conditions (Figure 11.9.14). Then the efficacy of nanotherapeutics developed by our partners will be tested in these OA models in unique bioreactors mimicking joint environment and biomechanics. The efficacy of anti-fibrosis, anti-inflammatory and anti-neural growth, and sensitization of selected nanotherapeutics will be measured.

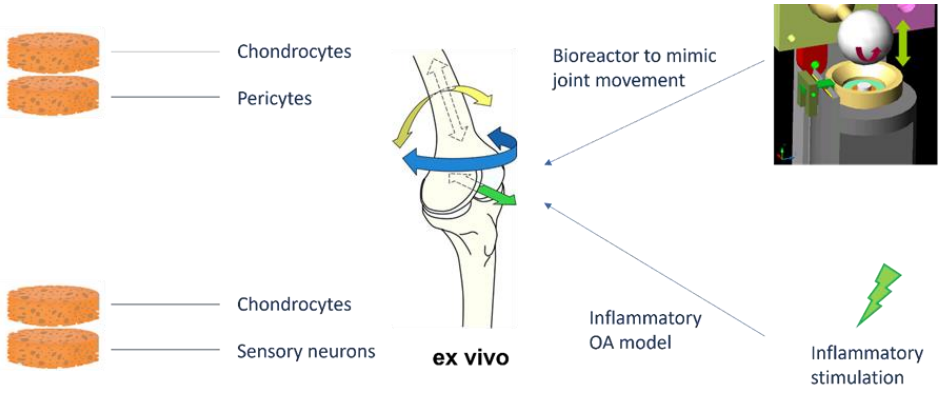



*Figure 11.9.14: Schematic of ex vivo OA models. The chondral-subchondral bone OA models consisted of chondrocytes - pericytes and chondrocytes-sensory neurons will be established. Multiaxial loading and inflammatory cytokines will be applied to mimic the OA joints.*

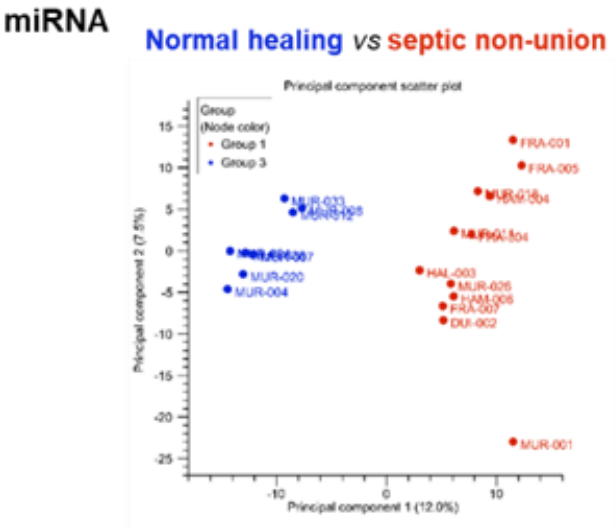
**Funding:** Horizon EU Grant, ARI Funding CHF 640’000, Period: 2022-2026.

**Partners:**
- Fundacion Cidetec, Spain
- OZ Biosciences SAS, France
- Universität des Saarlandes, Germany
- Asphalion SL, Spain
- Instituto de Investigacao e Inovacao em Saude da Universidade do Porto, Portugal
- Universita degli Studi del Piemonte Orientale Amedeo Avogadro, Italy
- The University of Liverpool, UK
- Eurice European Research and Project Office GmbH, Germany
- Haskolinn i Reykjavik Ehf, Island
- The Regents of the University of California, US
- Institut National de la Santé et de la Recherche Médicale, France

**Proteomics and miRNA analysis to discover biomarkers of non-union and fracture related infection (Pseudarthrosis) (ongoing) (TF Moriarty,** F Weisemann, C Siverino)

**Background:** Non-union is a failure of bone healing at least 6 months after fracture fixation. One of the underlying causes for nonunion is infection, and this requires specific intra- and post-operative treatment that differs substantially from the treatment of aseptic non-union. The pre-operative diagnosis of infected non-union is therefore critical. A pre-operative blood test would be of great value to diagnose infection. Standard blood markers such as white blood cell count or C-reactive protein do not show robust and reproducible results. **Goal:** Therefore, the aim of this study is to search for a biomarker in a preoperative blood sample to differentiate infected from aseptic non-union in human patients. **Results:** In total, 138 patients were recruited for this study. From the analyses of the miRNA, hsa-miR-16-5p and hsa-miR-486-5p showed differential expression in septic non-union patients. Further examinations with quantitative measurement of proteins and miRNA might help to define a cutoff for sufficient preoperative diagnosis of infected nonunion.


*Figure 11.9.15: (A) Overview of the prospective study enrolling adult patients in eight level 1 trauma centers in Germany; (miRNA)*




*Principal component scatter plot of differential expressed miRNA in healed vs septic non-union patients.*

**Funding:** German workman's compensation fund; ARI Funding 100'000 CHF; 2019-2024.

**Partner:**

- Simon Hackl (MD), BGU-Murnau, Murnau Germany

**Antibiofilm therapy using Local Application of Bacteriophages (Antibio-LAB) (finished) (TF Moriarty**, B Chen, M Chitto, V Post**)**

**Background:** The project aims to develop and assess a local application for bacteriophage therapy of difficult to treat, antibiotic resistant orthopaedic device-associated infections. The goals of the project are to test stability of evolved *P. aeruginosa* phages provided by consortium member in Berlin, a) when loaded in an injectable degradable hydrogel Gedai and also b) when loaded in Gedai together with antibiotics (Figure 11.9.16A). Furthermore, 1 of the evolved phages should be loaded within the Gedai in alginate beads and also antibiotic should be loaded into alginate beads to maintain a high level of antibiotic and a constant release of phages and antibiotic.
**Results:** Our achievements to date have included to evolve two *P. aeruginosa* phages R9 and R3.6. Testing phage R9 individually or in combination with antibiotic (meropenem) for its stability in hydrogel Gedai, showed that phage R9 is stable in the hydrogel for at least 8 days (Figure11.9.16C). Whereas antibiotic meropenem in hydrogel was less stable and activity decreased rapidly within 5 days (Figure 11.9.16B). Stability of phage R3.6 in alginate beads is also stable for up to 5 days (data not shown).

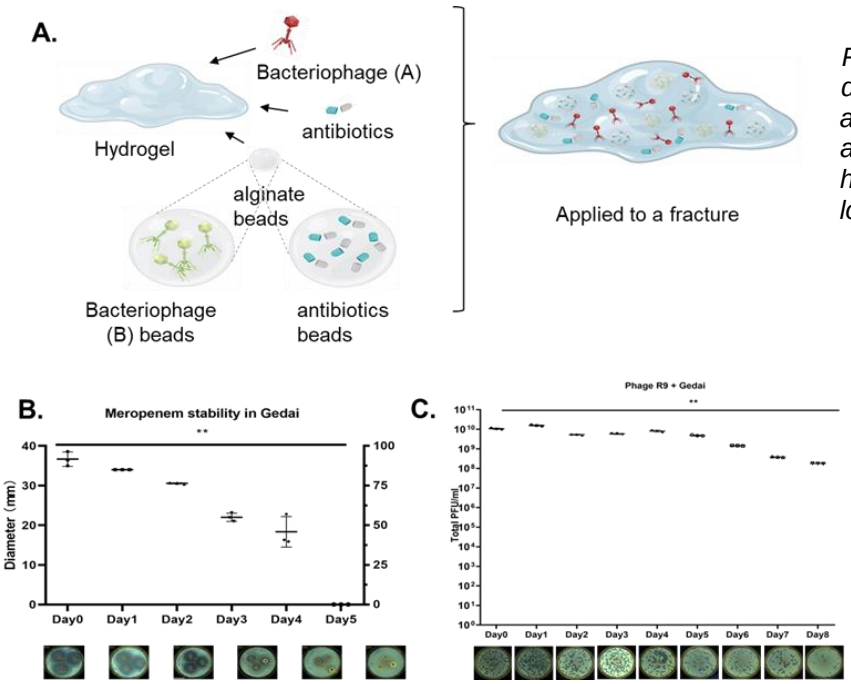



*Figure 11.9.16: Schematic diagram of loading P. aeruginosa phages and antibiotic into injectable hydrogel Gedai and also loading of alginate beads.*

**Funding:** Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), ARI funding 287'000 CHF: period:2019-2022.

**Pub:**
Clinical microbiology and infection. Bacteriophage therapy for human musculoskeletal and skin/soft tissue infections. Willem-Jan Metsemakers, Jolien Onsea, Thomas Fintan Moriarty, Lia Nadareishvili, Mariam Dadiani, Mzia Kutateladze (epub ahead of print).

**Pres:**
Chitto M. Dual application of bacteriophages and meropenem using microbead-loaded hydrogel for treatment of multidrug-resistant *Pseudomonas aeruginosa* in a mouse model of bone infection. World Congress of Orthopaedic Research ICORS 2022 Edinburgh, September 2022.

**Partners:**
- Andrej Trampuz (PD Dr med), Charité University Hospital Berlin, Germany
- Willem-Jan Metsemakers (Prof), University Hospitals Leuven, Belgium
- Rob Lavigne (Prof), KU Leuven, Belgium

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

**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**: 2022 has been a year of resurgence under many aspects, and the almost full return to travel has had a significantly positive impact in the implementation of this project. In 2022, the ARI Team organized a series of short-term visits a total of about 55 person/day visits for the topics of "Soft tissue management after implantation of bone replacement biomaterials", "Patient specific implants", reinforcing of connection with Dr Florian Thieringer and establishing new connections with the companies AdMirabiles, MediCoat. In addition to the visits in person to ARI, additional preparatory and complimentary training were delivered online.


*BBCE delegation visiting the companies AdMirabiles, MediCoat, the group and research facilities of Dr Florian Thieringer from the University Hospital Basel and ARI.*

ARI personnel were also involved in visiting the project core partners in Riga for a total of 25 person/days sharing and exchanging technical aspects of research and soft skills for topics including "Project Writing and Partner Search", "Soft Biomaterials Synthesis, Characterization and Properties", Sample Preparation and Confocal Microscopy", "Good Cell Culture Practice and in vitro Assessment of Toxicity" and "Quality Systems according to ISO and GLP". ARI is also grateful to the AO Innovation Translation, namely Development Incubator and Clinical Science, and to IP Manager for support and collaboration with some of the trainings. A visit to the core partners in Riga took place for training in "Planning and Organizing Clinical Studies" and "Implementation of Patient Data Safety Regulations and Digital Medical Records" by Ivo Schauwecker and Alexander Joeris, and "Business Plan and Business Canvas for the Tech Transfer Journey with Regulatory Considerations" and "IP Strategy Development at Early-Stage Biomaterials Research" by Andrea Montali and Ulf Schaberg.
ARI also hosted 7 different researchers for a total of 17 person/months of long-term exchange visits for research training.
Another significant milestone for the project was the acquisition of equipment and research infrastructure by the core partners, which gives BBCE the technical tools to carry out research at high level and to reinforce collaboration with ARI.

**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

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

**Background:** Rising the research performance to level out differences among European countries is of the outmost importance for the European Commission. Due to its recent past and geopolitical economic situation, Latvia has been underperforming in research compared to other countries, and it could increase its research performance by training Early-Stage Researchers and leading staff to give them opportunities to work with top groups in the EU area.
**Goal**: 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.
**Results:** In 2022, ARI was involved in 5 training and networking events, including two workshops organized by the partner institutions GUF and INPT-CIRMAT covering the topics of histology and drug delivery systems; one RTU leading staff visit to ARI on the topic of quality management systems; meeting enterprises that bring ideas from the lab to a commercial product, and a "Winter" School teaching event organized by RTU on therapeutics and drug

and cell delivery systems where Dr Sibylle Grad from ARI was involved with teaching a day session. The main event organized by ARI in 2022 for this project was the "Summer" School on "How to Write Scientific Reviews". Chaired by Matteo D'Este with excellent support from Nora Goudsouzian and Nunzia di Luise, this week-long training gave participants the opportunity to refine their skills in writing scientific reviews, and to appreciate their importance and significance. Many ARI Team members contributed to this by sharing their knowledge and giving personal advice to participants.
Another important event organized by ARI was the visit to the group of Florian Thieringer, at the University Hospital Basel, and to the companies AdMirabiles and MediCoat. This visit was a combined event involving also the BBCE project, and it has been extremely fruitful creating new connections and reinforcing existing ones.

*Group picture with participants and instructors for the RISEus2 School on "How to write scientific reviews".*

**Funding**: RISEus2 supported by European Union's Horizon 2020 research and innovation program (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

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

**Background:** Osteoarthritis (OA) is characterized by chronic joint pain and functional impairment and imposes a huge burden on the individual patient and health care systems. Current treatments relieve symptoms, but do not counteract disease progression. Intra-articular (in-joint) gene therapy-like mRNA therapy offers a promising highly innovative solution for the treatment of OA.

**Aim:** This project proposes a novel approach, using polymer nanoparticle-based delivery of stabilized mRNA candidates. The patented nanotechnology of 20MED is combined with the proprietary stabilized non-immunogenic mRNA technology of ETHRIS, to deliver a non-viral mRNA-based 'transcript therapy' for injection into the joint. The preclinical efficacy will be tested in ex-vivo joint bioreactors and rat disease models by ARI and Paracelsus Medical University.

**Results:** Suitable cartilage inflammation models were developed, and therapeutic mRNA transfection was studied and optimized. First, an in vitro inflammation model for chondrocytes (2D) was evaluated, and subsequently, the development of the ex vivo osteochondral explant organ culture model was started. The efficacy of optimized therapeutic mRNA formulations was demonstrated in 2D with a candidate molecule approach (IL1Ra mRNA), and this approach was then applied to the bioreactor loaded osteochondral explant model *(Figure 11.9.17).*

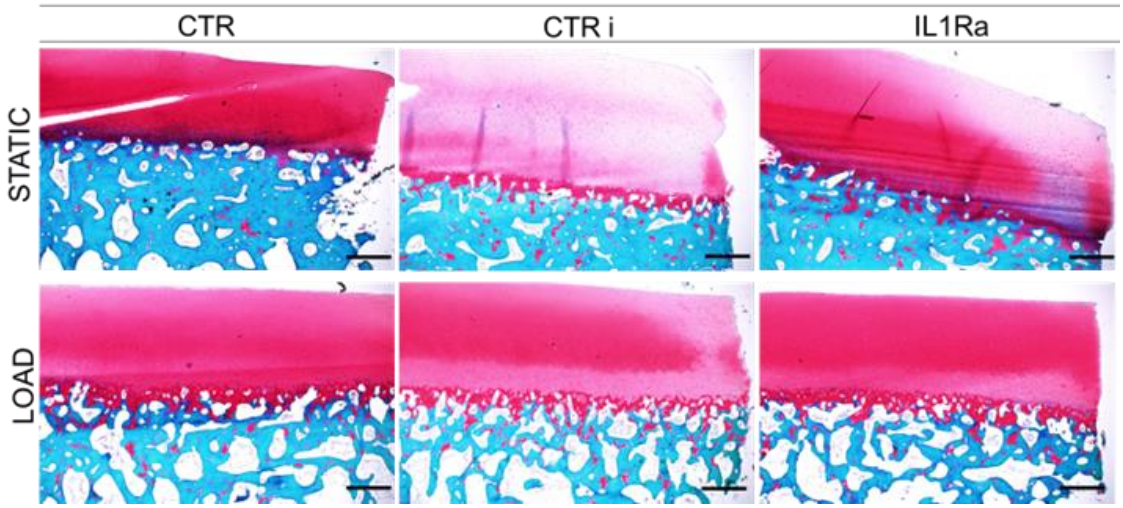



*Figure 11.9.17: Safranin-O staining showed that use of 1 ng/ml IL1b induced a high loss of matrix compared to non-inflamed control; the loading limited the loss of quality mainly in the group treated with IL1RA mRNA.*

**Fund:** Eurostars; ARI Funding EUR 200,000; Period 2019-2022.

**Pres:**

Basoli V, Traweger A, Plank C, Rip J, Alini M, Grad S. Effect of therapeutic IL1Ra and IL10 mRNA vehiculated by polymeric nanoparticles in osteochondral ex-vivo model: a new approach for osteoarthritis treatment. eCells & Materials Conference 2022.

Basoli V, Traweger A, Plank C, Rip J, Alini M, Grad S. Effect of therapeutic IL1Ra and IL10 mRNA vehiculated by polymeric nanoparticles in osteochondral ex-vivo model: a new approach for osteoarthritis treatment. Orthopaedic Research Society Annual Meeting 2022.

**Partners:**

- Engbersen J (Prof), 20Med Therapeutics, NL
- Planck C (Prof), Ethris Gmbh, DE
- Traweger A (Prof), Paracelsus Medical University, AT

**Induced pluripotent stem cell-based therapy for spinal regeneration (iPSpine) (ongoing) (S Grad,** A Vernengo**)**

**Background:** This multicentre project aims to develop and demonstrate the Proof-of-Concept for a novel induced pluripotent stem cell (iPSC)-based therapeutic strategy as a regenerative therapy. iPSpine is targeting a societal challenge affecting millions of people, *i.e.,* low back pain caused by intervertebral disc degeneration. The *iPSpine* team will: 1) differentiate iPSCs towards notochordal-like cells which are specialised tissue specific progenitor cells with a critical role in rejuvenating the intervertebral disc; 2) develop smart biomaterials as a conductive microenvironment to prime iPSCs towards notochordal-like cells and instruct intervertebral disc regeneration, and 3) demonstrate the safety and efficacy of the *iPSpine* advanced therapy in clinically relevant pre-clinical models.
**Aims:** The aims of the ARI investigators are (i) to create a suitable organ culture model using bovine intervertebral discs (IVDs) and (ii) to test biomaterial and notochordal cell-based therapies in this preclinical ex-vivo setting.
**Results:** Enzymatic matrix digestion with collagenase induced macroscopic voids in bovine IVDs. Treatment with a thermoresponsive hydrogel (NPgel) with or without encapsulated porcine notochordal cells served as a filler of the void. Possible tissue integration into the hydrogel could be seen in the NPgel group (Figure 11.9.18). During the treatment period of IVD culture, the hydrogel injected groups trended toward lower disc height loss than the control group.

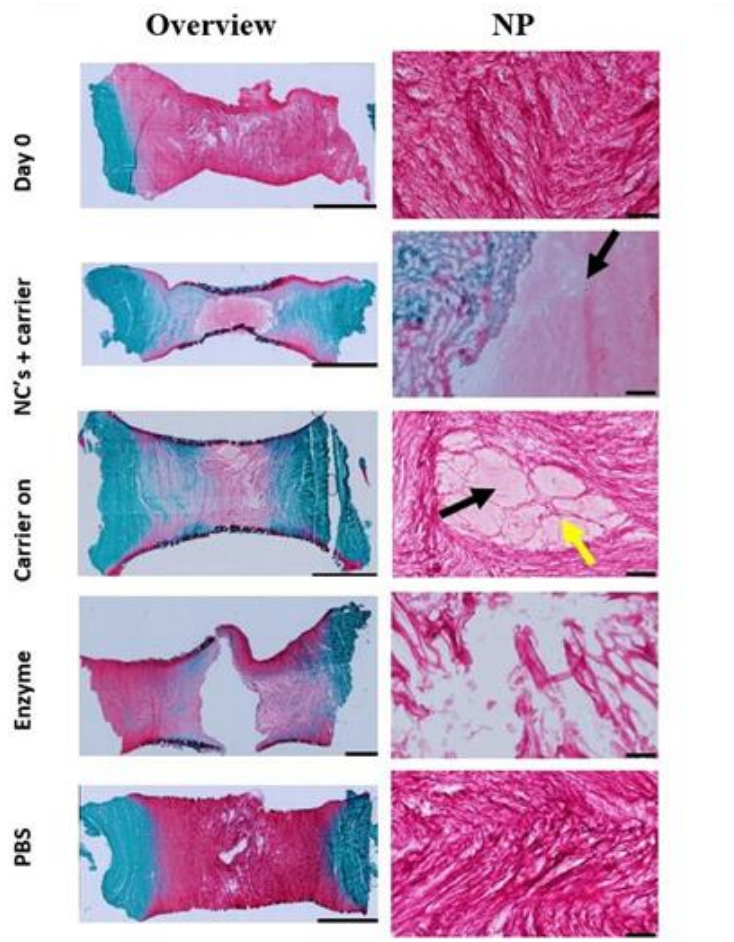



*Figure 11.9.18: IVDs treated with notochordal cells with/without NPgel. Representative Safranin O/ Fast Green results. Black arrows highlight NPgel, yellow arrow possible tissue integration.*

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

**Pres:**
Vernengo A, Bumann H, Kluser N, Soubrier A, Gewiess J, Jansen JU, Neidlinger-Wilke C, Wilke HJ, Grad S. Enzyme-induced bovine explant models of intervertebral disc degeneration. eCells & Materials Conference 2022.
Bumann H, Kluser N, Soubrier A, Secerovic A, Zuncheddu D, Williams R, Snuggs J, Janani R, Sammon C, Jansen JU, Neidlinger-Wilke C, Wilke HJ, Le Maitre C, Vernengo A, Grad S. Notochordal cells encapsulated within hydrogel in an enzymatic bovine IVD degeneration model. eCells & Materials Conference 2022.
Jansen JU, Teixeira GQ, Vernengo A, Grad S, Benz K, Neidlinger-Wilke C, Wilke HJ. How to create artificial disc degeneration by enzyme digestion for biomechanical testing of biomaterials. eCells & Materials Conference 2022.
Vernengo A, Bumann H, Kluser N, Jansen JA, Neidlinger-Wilke C, Wilke HJ, Alini M, Li Z, Grad S. Porcine notochordal cell injected into a bovine organ culture model of intervertebral disc degeneration. Orthopaedic Research Society Annual Meeting 2022.

**Partners:**
- Tryfonidou M (Prof), University of Utrecht, NL
- Creemers L (PhD), University Medical Centre Utrecht, NL
- Ito K (Prof), Technical University of Eindhoven, NL
- Guicheux J (Prof), University of Nantes, FR
- Pandit A (Prof), National University of Galway, IE
- Wilke H-J (Prof), University of Ulm, DE
- Gantenbein B (Prof), University of Bern, CH
- Jorgensen C (Prof), Institute National de la Sante, FR
- Templin M, Naturwissenschaftliches und medizinisches Institut, DE
- Le Maitre C (Prof), Sheffield Hallam University, UK
- Vadala G, University Campus Biomedico, Rom, IT
- De Boer M, Ntrans Technologies, NL
- Noel D, University of Montpellier, FR
- Isasi R, University of Miami, US
- Kienle A, Spineserv Gmbh, DE
- Chan D, The University of Hong Kong, HK
- Buljovcic Z, Pharmalex Gmbh, DE
- Lether I, National Reumafonds, NL

**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. 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 (IVD), 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).
**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 11.9.19*).

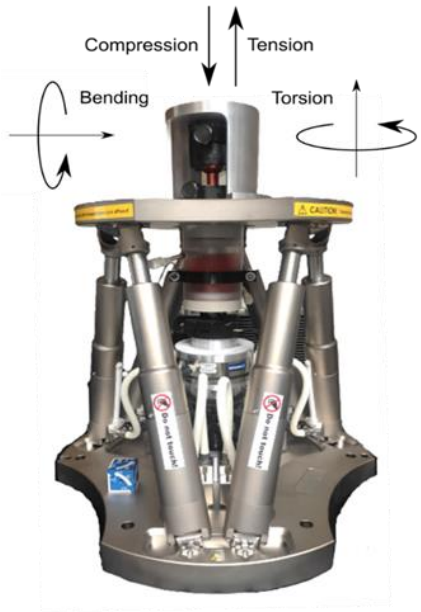



*Figure 11.9.19: A new generation of bioreactor for multiaxial loading of IVDs.*

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

**Pres:**
Šećerović A, Ristaniemi A, Cui S, Li Z, Alini M, Weder G, Heub S, Ledroit D, Grad S. Ex vivo organ model and sample holder for intervertebral disc studies in a new generation of multiaxial bioreactors. World Congress of Orthopaedic Research ICORS 2022.
Ristaniemi A, Secerovic A, Ferguson SJ, Grad S. Viscoelastic characterization of bovine annulus fibrosus lamellae. World Congress of Biomechanics 2022.
Secerovic A, Ristaniemi A, Cui S, Li Z, Alini M, Weder G, Heub S, Ledroit D, Grad S. Towards the development of multiaxial loading bioreactor for intervertebral disc studies: validation of an ex vivo organ model and customized sample holder. TERMIS EU 2022.
Šećerović A, Ristaniemi A, Li Z, Crivelli F, Heub S, Ledroit D, Alini M, Weder G, Ferguson S, Grad S. A new generation of multiaxial spine bioreactor for advanced studies of intervertebral disc degeneration and repair. eCells & Materials Conference 2022.
Ristaniemi A, Šećerović A, Grad S, Ferguson S. J. A novel viscoelastic bovine intervertebral disc finite element model. eCells & Materials Conference 2022

**Pub:**
Šećerović A, Ristaniemi A, Cui S, Li Z, Soubrier A, Alini M, Ferguson SJ, Weder G, Heub S, Ledroit D, Grad S. Toward the Next Generation of Spine Bioreactors: Validation of an Ex Vivo Intervertebral Disc Organ Model and Customized Specimen Holder for Multiaxial Loading. ACS Biomater Sci Eng. 2022 Sep 12;8(9):3969-3976. DOI: 10.1021/acsbiomaterials.2c00330. Epub 2022 Aug 17. PubMed PMID: 35977717; PubMed Central PMCID: PMC9472220.

**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) (ongoing) (S Grad, M Stoddart,** L Wen, D Zuncheddu)

**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. "Carthago" will 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 (Figure 11.9.20).
**Goal:** This 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.

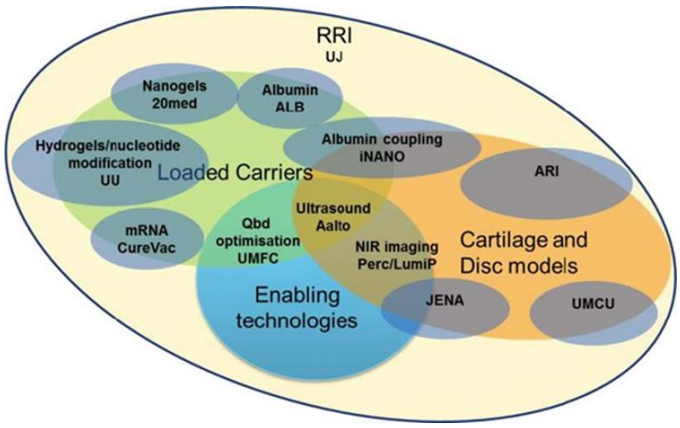



*Figure 11.9.20: Multidisciplinary approach to advance nucleic acid therapy for cartilage and intervertebral disc regeneration, while educating 15 young researchers.*

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

**Pres:**
Zuncheddu D, Kluser N, Bumann H, Creemers LB, Grad S. Effects of different glucose supplementation on bovine intervertebral disc organ cultures under physiological loading. eCells & Materials Conference 2022.
Wen L, Armiento A, Creemers L, Stoddart MJ. The role of Noggin in TGF-β1 or TGF-β3 driven chondrogenesis of BMMSCs. eCells & Materials Conference 2022.

**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

**Nitric oxide optical sensors for inflammation monitoring (NIOXIS) (ongoing) (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). 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. Real-time nitric oxide (NO) monitoring offers a promising means of mitigating inflammation and disease progression through early diagnosis and treatment.
**Goal:** 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 11.9.21).

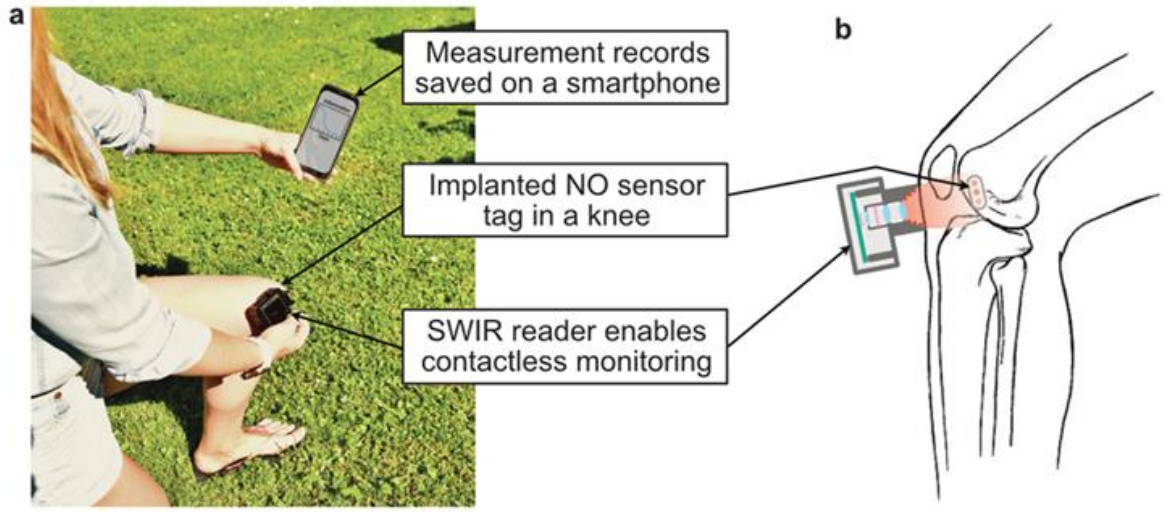



*Figure 11.9.21: Concept of optical sensor for real time NO detection.*

**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

**Holistic training of next generation Osteoarthritis researchers (OSTASKILLS) (started) (M Stoddart,** L Mecchi, C Cordeiro, G Guex**)**

**Background**: Osteoarthritis (OA) is the single most common cause of disability in older adults. The 2010 Global Burden Disease Study reports that the burden of musculoskeletal disorders is much larger than estimated in previous assessments and accounts for 6.8% of DALYs (Disability Adjusted Life Years) worldwide. The prevalence of OA is increasing due to population ageing and an increase in related factors such as obesity. Dutch Arthritis Society (ReumaNL), as leading Dutch charity foundation on rheumatic diseases, invests approximately €15Mio yearly in research via an extensive national and international research network. In a recent evaluation of the research projects financed by ReumaNL, it was noted that many promising scientific achievements with potential impact for patients die at the lab bench and never make it to clinical translation. Obviously, the reason for this observation is multifactorial with an important factor being that current training programs for doctoral candidates are mainly aimed at training the next generation of basic scientists or clinicians but not at training the next generation of entrepreneurial scientists capable of translating basic research in clinical applications and products for the health care market.
**Goal**: To implement the next step in OA treatments there is a strong need to engage this worldwide epidemic disease in a holistic and multidisciplinary way, and hence train the next generation of entrepreneurial scientist & MD's on translational research in an innovative approach. The OSTASKILLS doctoral programme provides this unique training experience for Early Stage Researchers (ESR's) to engage in a holistic approach bringing innovations in medical devices, ATMPs and pharmaceutical products aimed at treating OA, to patients and the health care markets.

**Pres:**
Mecchi L, Guex AG, Stoddart M. Developing materials for cartilage regeneration under mechanical load. 2022 GR forscht (oral).

**Funding:** EU H2020 H2020-MSCA-COFUND-2020 ARI Funding €441,000; Period: 2021-2026.

**Partners:**
- Stichting Nationaal Reumafonds, The Netherlands
- Maastricht University UNIMAAS, The Netherlands
- University Hospital Basel UNIBAS, Switzerland
- Twente University UT, The Netherlands
- University Hospital of Regensburg UHREG, Germany
- Lund University LU, Sweden
- Orthros Medical OTR, The Netherlands
- Artialis ART, Belgium
- Hy2Care Hy2, The Netherlands
- CO.DON AG CDON, Germany
- Tetec Tissue Engineering Technologies AG Tetec, Germany
- Chondropeptix

**Identifying novel therapeutic targets for articular cartilage repair (STEMSEC) (finished) (M Stoddart,** Y Ladner**)**

**Background:** Novel therapies for cartilage regeneration have had limited success. Chondrogenic differentiation of mesenchymal stem cells (MSCs) under load is different to that observed during classical static culture conditions. This is highly clinically relevant, considering that patients receive weight-bearing rehabilitation therapy following cartilage repair. Additionally, as most *in vitro* cartilage repair studies are performed under static conditions, the lack of mechanical stimulation may explain why it has been challenging to reproduce promising *in vitro* results *in vivo*. Marrow stimulation techniques, such as microfracture, are the most commonly used clinical approach for cartilage repair with unpredictable results. Using a unique *in vivo* kinematic joint simulating bioreactor, we have previously shown that while complex multiaxial load induces hMSC chondrogenesis, it also induces the expression of a number of soluble molecules not typically found under static culture conditions. This identified novel mechanically induced targets, such as nitric oxide (NO), that are potentially clinically relevant. Within this project we aim to better understand the role of mechanical load on the molecules induced during human MSC chondrogenesis vs standard conditions (static and with transforming growth factor β (TGF-β)). We will identify new potential treatment targets, while investigating the biological function of nitric oxide.
**Goal:** This project aims to establish the functional modulation of non-cartilage cell types by mechanically stimulated MSC secretome, thus providing valuable further insight into the pathology of joint destruction.
**Results:** Using a design of experiments (DoE) approach, we have established optimal loading conditions to a) increase TGFβ production and b) increase the mechanical activation of latent TGFβ protein. Interestingly the protocol optimal for expression is not the same as that optimal for activation. This suggests that rehabilitation protocols may need to increase in complexity to improve cellular differentiation.

**Funding:** Swiss National Funds (nr 31003A_179438 / 1), Funding: CHF 417'720, Period: 08/2018-12/2022.

**Pres:**
Ladner YD, Armiento AR, Stoddart MJ. A multi-well bioreactor for cartilage tissue engineering. 2022 SSB+RM (poster).
Ladner Y, Armiento A, Stoddart M. A multi-well bioreactor for cartilage tissue engineering. 2022 TERMIS EU (poster).
Ladner Y, Armiento A, Stoddart M. Mechano-induced chondrogenesis of human MSCs in a biomaterial: A factorial design of experiment approach. 2022 TERMIS EU (poster).

**Pub:**
Ladner YD, Armiento AR, Kubosch EJ, Snedeker JG, Stoddart MJ. Optimization of loading protocols for tissue engineering experiments. Sci Rep. 2022 Mar 24;12(1):5094.
DOI: 10.1038/s41598-022-08849-y.

**Partner:**
- Snedeker Jess G (Prof, PhD), ETH Zurich, Switzerland

# 12 Team Members

**Director**

| | | |
|---|---|---|
| Richards R Geoff | Prof, Prof, PhD | 01.10.91 |

**Vice Director**

| | | |
|---|---|---|
| Alini Mauro | Prof, PhD | 01.07.99 |

**ARI Management**

| | | | |
|---|---|---|---|
| Bentz Ulrich | Dipl Ing HTL Mikrotechnik | | 01.08.07 |
| Büscher Philipp | Dipl Ing | (01.03.1996 at AO) | 01.06.21 |
| Gueorguiev Boyko | Prof, PhD | (01.03.03 - 30.09.09) | 01.07.10 |
| Stoddart Martin | 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 | 19.03.07 |
| Serra Tiziano | Assistant Prof, PhD | 01.10.16 |
| Varga Peter | PD, PhD | 04.08.14 |
| Windolf Markus | PhD (Dr biol hum) Dipl Ing | 01.11.04 |
| Wehrle Esther | Dr med vet, Dr rer nat | 14.04.22 |

**Scientific & Technical Staff**

| | | |
|---|---|---|
| Arens Daniel | Dr med vet | 01.11.07 |
| Augurio Adriana | PhD | 01.05.22 |
| Badrutt Isabella | Senior Executive Assistant (16.03.1998 at AO) | 16.07.12 |
| Bagnol Romain | PhD Student, MSc | 01.10.19 |
| Barblan Claudia | Senior 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 |
| Bosque Tanja | Senior Assistant AO Network (19.08.2019 at AO) | 01.06.21 |
| Buschbaum Jan | Dr rer med | 01.08.15 |
| Brazerol Carmen | Animal Care (Eidg FA[1]) | 01.03.18 |
| Caspar Jan | Poly mechanics | 01.01.09 |
| Chittò Marco | Dr rer, PhD nat | 01.08.21 |
| Ciftci-Dede Eda | PhD | 01.04.22 |
| Ciric Daniel | MSc (Engineering) | 01.07.20 |
| Ciriello Simona | PhD, Journal Production Editor | 12.09.16 |
| Constant Caroline | Dr med vet, MSc (Engineering) | 01.08.19 |
| Cordeiro Carolina Maria | PhD Student, MSc | 08.08.22 |
| 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 |
| Dönz Anna | Administrative Assistant (80%) (15.08.2003 at AO) | 23.08.21 |
| Erb Peter | Animal Care (Eidg FA[1]) | 03.05.93 |
| Ernst Manuela | MSc, Human Movement Science | 01.10.11 |

| | | |
|---|---|---|
| Escher Carla | Senior Administrative Assistant (40%) | 01.01.95 |
| Faoro Loris | Animal Care (Eidg FA[1]) | 01.11.16 |
| Faoro Pierina | Arztgehilfin, Animal Care (Eidg FA[1]) (70%) | 01.12.07 |
| Fehrenbach Pia | PhD Student, MSc | 01.04.22 |
| Furlong-Jäggi Pamela | Chemikerin FH, BSc (40%) | 01.02.04 |
| Furter Andrea | Animal Care (Eidg FA[1]) (05.01.1988 at AO) | 24.04.06 |
| Gens Lena | Dr 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 |
| Jahangir Shahrbanoo | PhD (18.04.18 - 28.09.18) | 01.04.21 |
| Keller-Stoddart Iris | MTL Technician (60%) | 21.10.09 |
| Krüger Thomas | BSc | 01.06.22 |
| Kuhn Eliane | PhD Student, MSc | 01.05.22 |
| Li Zhen | Assistant Prof, PhD | 01.08.11 |
| Ma Junxuan | Dr med, PhD | 02.03.17 |
| Mecchi Laura | PhD Student, MSc | 01.03.22 |
| Meng Huan | PhD | 01.11.22 |
| Menzel Ursula | PhD, Dipl Biol | 01.07.11 |
| Miklosic Gregor | PhD Student, MSc | 01.02.20 |
| Mischler Dominic | MSc, Medical Technology (06.09.17 - 28.02.18) | 01.10.18 |
| Mollet Leonie | Animal Care | 01.09.22 |
| Müller Gregor | Lic phil, Librarian (50%) | 17.01.05 |
| Müller Reto | Animal Care (Eidg FA[1]) | 13.11.01 |
| Nehrbass Dirk | Dr med vet, FTA Pathol/Toxicopathology | 01.10.10 |
| Nylund Pamela | PhD | 01.03.22 |
| 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 |
| Rösch Melanie | Administrative Assistant | 01.11.22 |
| Schneider Monika | Senior 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 |
| Tapia-Dean James | Med vet | 01.07.22 |
| Tognato Riccardo | PhD | 01.04.22 |
| van der Heide Daphne | PhD Student, MSc | 01.09.20 |
| Vautrin Antoine | PhD Student, MSc | 15.04.21 |
| Vernengo Andrea | PhD | 01.09.19 |
| Verrier Sophie | Dr sces sc nat | 01.08.04 |
| Vivalda Marisa | Senior Administrative Assistant | 01.05.03 |
| Wen Liru | PhD Student, MSc | 06.07.21 |
| Wychowaniec Jacek | PhD | 01.07.21 |
| Xu Jiangyao | Guest PhD Student, MSc | 20.12.22 |
| Zderic Ivan | PhD | 01.02.11 |
| Zuncheddu Daniele | PhD Student, MSc | 01.02.20 |
| Zweifel Erich | European Industrial Engineer EIE | 30.11.92 |

[1] Eidg FA = Eidg Fähigkeitsausweis

**Apprentices**

| | | |
|---|---|---|
| Ambühl David | Apprentice | 01.08.20 |
| Hämmerl Nilo | Apprentice | 01.04.19 |
| Vonlanthen Nadja | Apprentice | 01.08.21 |

**Medical Research Fellows**

| | | |
|---|---|---|
| Berk Till | Research Fellow (Germany) | 13.07.22 - 23.12.22 |
| Breulmann Franziska | Research Fellow (Germany) | 01.07.21 - 30.06.22 |
| Bumann Helen | Research Fellow (Switzerland) | 01.07.21 - 30.06.22 |
| Gruber Matthias | Guest Research Fellow (Germany) | 01.10.21 - 30.09.22 |
| Isenmann Marie | Guest Research Fellow (Germany) | 01.03.21 - 31.03.22 |
| Kastner Philipp | Research Fellow (Austria) | 01.07.21 - 30.06.22 |
| Mechkarska Rayna | Research Fellow (Bulgaria) | 01.09.22 |
| Pastor Tatjana | Research Fellow (Germany) | 01.11.22 |
| Pirera Maria Eugenia | Research Fellow (Argentina) | 03.01.22 - 15.02.22 |
| Raykov Georgi | Research Fellow (Bulgaria) | 01.09.22 - 22.12.22 |
| Salvatore André | VET Research Fellow (Brazil) | 18.02.22 |
| Siphelele Mdingi Vuyisa | Research Fellow (South Africa) | 18.01.22 - 23.12.22 |
| Tapia-Dean James | VET Research Fellow (GB, Spain) | 15.02.21 - 30.06.22 |
| Unterguggenberger Clemens | Guest Research Fellow (Germany) | 01.09.22 |
| Vanvelk Nils | Research Fellow (Belgium) | 01.04.22 |
| Weisemann Ferdinand | Guest Research Fellow (Germany) | 03.01.22 - 30.06.22 |
| Zhao Ensi | Research Fellow (China) | 02.03.21 - 28.02.22 |
| Zhelev Daniel | Research Fellow (Bulgaria) | 01.04.22 - 30.06.22 |

**Non-Medical Research Fellow**

| | | |
|---|---|---|
| Kluser Nadine | Internship (Switzerland) | 01.02.21 - 31.01.22 |

**Internships**

| | | |
|---|---|---|
| Antonacci Paolo | Internship (Italy) | 16.11.20 - 31.10.21 |
| | Guest Internship | 01.11.21 - 31.07.22 |
| Belcastro Laura | Internship (Italy) | 01.04.22 - 30.10.22 |
| Egger Sarah | Internship/Master Student (Switzerland) | 01.07.21 - 30.06.22 |
| Enzmann Sina | Guest Internship (Switzerland) | 01.09.21 - 28.02.22 |
| | Internship | 01.03.22 - 30.06.22 |
| Feist Alicia | Internship (Germany) | 01.05.22 - 31.08.22 |
| Hangartner Alisa | Internship/Master Student (Switzerland) | 01.10.22 |
| Hetreau Carla | Internship/Master Student (France, Germany) | 01.07.22 |
| Keller Jessica | Internship (Switzerland) | 01.09.21 - 28.02.22 |
| Kessler Florian | Guest Internship (Switzerland) | 01.03.22 - 31.08.22 |
| Kim Olivia | Guest Internship (USA) | 01.06.22 - 31.07.22 |
| Klaus Aline | Internship (Switzerland) | 01.10.22 |
| Lanker Carina | Guest Internship/Master Student (Switzerland) | 09.05.22 - 29.07.22 |
| Lopez Andrea | Guest Internship (USA) | 10.06.22 - 22.07.22 |
| Marani Elisa | Internship (Switzerland) | 01.08.21 - 31.01.22 |
| Mini Carina | Guest Internship (Switzerland) | 04.10.21 - 31.03.22 |
| Mürner Marcia | Internship/Master Student (Switzerland) | 01.10.22 |
| Ortet Louise | Internship (France) | 01.05.22 - 31.10.22 |
| Parolini Romedi | Internship (Switzerland) | 01.12.22 |
| Schärer Kathrin | Internship (Switzerland) | 01.08.21 - 31.03.22 |
| Schlatter Jérôme | Internship/Master Student (Switzerland) | 01.10.22 |
| Valenti Alessia | Internship /Master Student (Switzerland) | 01.03.22 - 30.11.22 |
| Walser Davina | Guest Internship/Master Student (Switzerland) | 09.05.22 - 29.07.22 |
| Ziadlou Donya | Internship (Iran) | 15.09.21 - 31.07.22 |

**VET Students**

| | | |
|---|---|---|
| Brückner Jonas | Vet Student (Germany) | 23.05.22 - 15.07.22 |
| Hutabarat Tabea | Vet Student (Germany) | 01.03.21 - 30.04.22 |
| Schlipf Götz | Vet Student (Austria) | 03.01.22 - 28.02.22 |

**Guest Scientists / Students**

| | | |
|---|---|---|
| Abe Katsuhiko | Guest PhD Student (Japan) | 20.12.22 |
| Amirian Jhaleh | Guest Researcher (Iran) | 01.07.22 - 30.11.22 |
| Chan Oscar | Guest PhD Student (GB) | 01.04.22 - 01.09.22 |
| Chen Baixing | Guest PhD Student (China) | 09.11.21 - 30.09.22 |
| Egle Karina | Guest Researcher (Latvia) | 12.09.22 - 10.12.22 |
| Feng Wenli | Guest Student (China) | 01.03.22 |
| Gao Wei | Guest Scientist (China) | 18.04.22 |
| Li Kaihu | Guest PhD Student (China) | 02.02.21 - 05.11.22 |
| Lindenmann Sara | Guest Student (Switzerland) | 01.02.22 - 31.07.22 |
| Mathieu Joos | Guest Researcher (Belgium) | 23.01.22 - 03.03.22 |
| Micko Lana | Guest Researcher (Latvia) | 12.09.22 - 14.12.22 |
| Ojaghi Reza | Guest Researcher (Iran) | 01.02.22 - 12.02.22 |
| Pylostomou Athanasia | Guest PhD Student (Latvia) | 01.10.22 - 30.11.22 |
| Sizovs Antons | Guest Researcher (Latvia) | 29.05.22 - 24.06.22 |
| Svalbe Baiba | Guest Scientist (Latvia) | 04.04.22 - 06.05.22 |
| Vecstaudza Jana | Guest Scientist (Latvia) | 01.04.22 - 30.06.22 |
| Vilskersts Reinis | Guest Researcher (Latvia) | 29.05.22 - 04.07.22 |

**Employees left 2022**

| | | |
|---|---|---|
| Buchholz Tim | Dr med vet | 01.04.19 - 31.12.22 |
| Füllemann Priscilla | BSc | 01.01.21 - 21.12.22 |
| Hofmann-Fliri Ladina | MSc, Human Movement Science | 01.10.09 - 30.04.22 |
| Hofstee Marloes | PhD Student, MSc | 20.11.17 - 16.03.22 |
| Kasper Hermann | Dipl Technician HF Systemtechnik | 01.10.18 - 31.01.22 |
| Ladner Yann | PhD Student, MSc | 01.08.18 - 22.12.22 |
| Mys Karen | PhD | 01.06.19 - 01.12.22 |
| Ristaniemi Aapo | PhD | 16.11.20 - 15.11.22 |
| Wallimann Alexandra | PhD Student, MSc | 01.02.18 - 31.07.22 |
| Windolf Markus | Dr biol hum Dipl Ing | 01.11.04 - 23.12.22 |

**Guest Presentations at AO Center**

February 18, 2022 PD Dr Martin Clauss from University Hospital Basel, Switzerland gave a guest presentation with the title: A clinical perspective on periprosthetic joint infection.

February 18, 2022 PD Dr Mario Morgenstern from University Hospital Basel, Switzerland gave a guest presentation with the title: A clinical perspective on fracture related infection & introduction to The National Center of Competence in Research.

July 4, 2022 Prof Darrell Abernethy from Aberystwyth School of Veterinary Science gave a guest presentation with the title: What's in a P? People, Penguins and Programs.

# 13 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

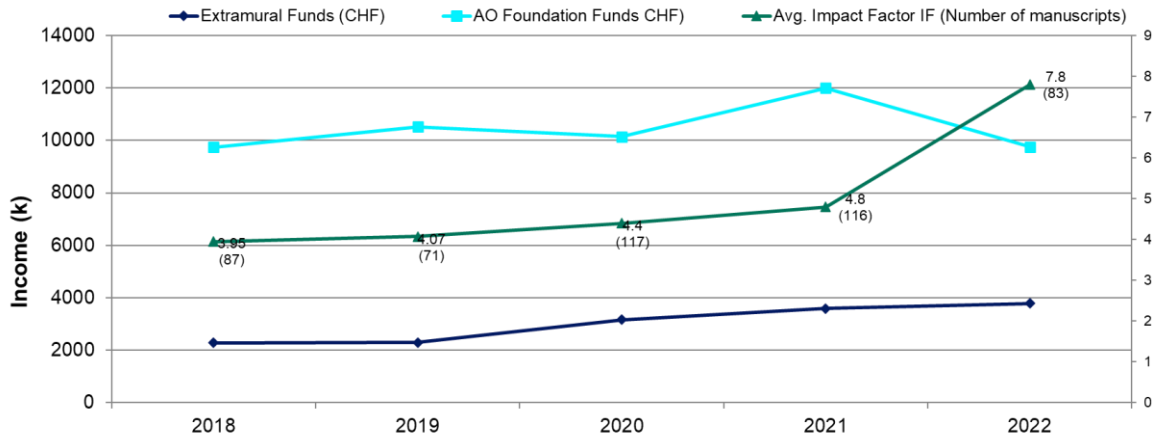
*Device for measuring, processing and transmitting implant parameters (Fracture Monitor III)*
- First Application: CH01335/19 filed 2019-10-22
- Case: 10.3988
- Developer / Inventors: M Windolf

*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

# 14 Publications & Presentations

## 14.1 2018-2022 Five-year ARI Key Performance Indicators




The five year key performance indicators of extramural funds and average publication Impact Factor show steady growth.

The extramural funds have risen since 2007 from 1.16 million CHF to 3.78 million CHF in 2022 (with strong growth since 2019 2.29 million) which the ARI team members can be very proud of. The fact that Switzerland became a non-associated third country in the Horizon Europe research program in June 2022 may affect the future numbers.

The number of publications have steadily grown, which were 53 in 2007, over 60 since 2015 and over 70 since 2018 with an extreme blip during covid times of over 100, setling to above 80 2022.

The average Impact Factor has been steadily increasing which was 1.85 in 2007 and has been above 3 since 2014 and above 4 since 2019, which we aim to keep.

The AO funding has remained steady since 2008 after having merged with AO Development Institute at that time. The extra AO funds in 2021 were due to 2 million of AO Development Incubator grants for specific valorization projects.

## 14.2 2022 Published peer reviewed papers (epub & in print)


Albers CE, Zderic I, Kastner P, Gueorguiev B, Tosounidis TH, Keel MJB, Bastian JD. The ideal site of cement application in cement augmented sacroiliac screw fixation: the biomechanical perspective. Eur J Trauma Emerg Surg. 2022;epub Dec 12

Arand C, Noser H, Kamer L, Gehweiler D, Handrich K, Rommens PM, Wagner D. Is there a correlation between pelvic incidence and orientation of the acetabulum? An analysis based on a three-dimensional statistical model of the pelvic ring. J Anat. 2022;241:756-764

Bagnol R, Grijpma D, Eglin D, Moriarty TF. The production and application of bacterial exopolysaccharides as biomaterials for bone regeneration. Carbohydr Polym. 2022;291:119550

Benca E, Zderic I, van Knegsel KP, Caspar J, Hirtler L, Fuchssteiner C, Strassl A, Gueorguiev B, Widhalm H, Windhager R, Varga P. Biomechanical determination of fracture loads and patterns of the odontoid process. Spine (Phila Pa 1976). 2022;47:1212-1220

Benca E, van Knegsel KP, Zderic I, Caspar J, Strassl A, Hirtler L, Fuchssteiner C, Gueorguiev B, Windhager R, Widhalm H, Varga P. Biomechanical evaluation of an allograft fixation system for ACL reconstruction. Front Bioeng Biotechnol. 2022;10:epub Nov 03

Boot W, Foster AL, Guillaume O, Eglin D, Schmid T, D'Este M, Zeiter S, Richards RG, Moriarty TF. An antibiotic-loaded hydrogel demonstrates efficacy as prophylaxis and treatment in a large animal model of orthopaedic device-related infection. Front Cell Infect Microbiol. 2022;12

Chen X, Myers CA, Clary CW, Varga P, Coombs D, DeWall RJ, Fritz B, Rullkoetter PJ. Impact of bone health on the mechanics of plate fixation for Vancouver B1 periprosthetic femoral fractures. Clin Biomech (Bristol, Avon). 2022;100:105801

Constant C, Zderic I, Arens D, Pugliese B, Gehweiler D, Gueorguiev-Rüegg B, Zeiter S. Influence of screw head diameter on ex vivo fixation of equine lateral condylar fractures with 5.5 mm cortical screws. Vet Surg. 2022;51:576-591

Constant C, Hom WW, Nehrbass D, Carmel E-N, Albers CE, Deml MC, Gehweiler D, Lee Y, Hecht A, Grad S, Iatridis JC, Zeiter S. Comparison and optimization of sheep in vivo intervertebral disc injury model. JOR SPINE. 2022;5:e1198

Constant C, Moriarty TF, Arens D, Pugliese B, Zeiter S. Peri-anesthetic hypothermia in rodents: A factor to consider for accurate and reproducible outcomes in orthopedic device-related infection studies. J Orthop Res. 2022;epub Jun 18

Constant C, Stroncek JD, Zeiter S, Arens D, Nehrbass D, Gehweiler D, Menzel U, Benneker LM, Hill RS, Albers CE. Venous injection of a triphasic calcium-based implant in a sheep model of pulmonary embolism demonstrates minimal acute systemic effects. Eur Spine J. 2022;31:2812-2821

Constant C, Desrochers A, Gagnon CA, Provost C, Nichols S, Marchionatti E, Gara-Boivin C. Single-step production of autologous bovine platelet concentrate for clinical applications in cattle. J Dairy Sci. 2022;epub Nov 21

Constant C, Marchionatti E, Desrochers A, Babkine M, Nichols S. Admission lactate concentration has predictive value for death or severe complications within 30 days after admission in cattle with long-bone fractures. J Am Vet Med Assoc. 2022;epub Nov 24

Cui S, Li W, Teixeira GQ, Neidlinger-Wilke C, Wilke H-J, Haglund L, Ouyang H, Richards RG, Grad S, Alini M, Li Z. Neoepitope fragments as biomarkers for different phenotypes of intervertebral disc degeneration. JOR Spine. 2022;5:e1215

Della Bella E, Koch J, Baerenfaller K. Translation and emerging functions of non-coding RNAs in inflammation and immunity. Allergy. 2022;77:2025-2037

Diaz-Payno PJ, Kalogeropoulou M, Muntz I, Kingma E, Kops N, D'Este M, Koenderink GH, Fratila-Apachitei LE, van Osch GJVM, Zadpoor AA. Swelling-dependent shape-based transformation of a human mesenchymal stromal cells-laden 4D bioprinted construct for cartilage tissue engineering. Adv Healthc Mater. 2022;epub Oct 29:e2201891

Di Marzio N, Ananthanarayanan P, Guex AG, Alini M, Riganti C, Serra T. Sound-based assembly of a microcapillary network in a saturn-like tumor model for drug testing. Mater Today Bio. 2022;16:100357

Du J, Garcia JP, Bach FC, Tellegen AR, Grad S, Li Z, Castelein RM, Meij BP, Tryfonidou MA, Creemers LB. Intradiscal injection of human recombinant BMP-4 does not reverse intervertebral disc degeneration induced by nuclectomy in sheep. J Orthop Translat. 2022;37:23-36

Esmaeili A, Alini M, Eslaminejad MB, Hosseini S. Engineering strategies for customizing extracellular vesicle uptake in a therapeutic context. Stem Cell Res Ther. 2022;13(1):129

Feng W, Chittò M, Moriarty TF, Li G, Wang X. Targeted drug delivery systems for eliminating intracellular bacteria. Macromol Biosci. 2022;epub Oct 3:e2200311

Fleischhacker E, Sprecher CM, Milz S, Saller MM, Gleich J, Siebenbürger G, Helfen T, Böcker W, Ockert B. Functional outcomes before and after implant removal in patients with posttraumatic shoulder stiffness and healed proximal humerus fractures: does implant material (PEEK vs. titanium) have an impact? - a pilot study. BMC Musculoskelet Disord. 2022;23(1):95

Fletcher JWA, Neumann V, Silva J, Burdon A, Mys K, Panagiotopoulou VC, Gueorguiev B, Richards RG, Whitehouse MR, Preatoni E, Gill HS. Augmented screwdrivers can increase the performance of orthopaedic surgeons compared with use of normal screwdrivers. Sci Rep. 2022;12(1):20076

Gantenbein F, Buchholz T, Wever KE, Ritskes Hoitinga M, Zeiter S, Seebeck P. Protocol for a systematic review of good surgical practice guidelines for experimental rodent surgery. BMJ Open Science. 2022;6(1):e100280

Gens L, Marchionatti E, Steiner A, Stoddart MJ, Thompson K, Mys K, Zeiter S, Constant C. Surgical technique and comparison of autologous cancellous bone grafts from various donor sites in rats. J Orthop Res. 2022;epub Aug 11

Gueorguiev B, Lenz M. Zementaugmentation und Knochenersatz - Materialien und Biomechanik [Cement augmentation and bone graft substitutes-Materials and biomechanics]. Unfallchirurgie. 2022;125:430-435

Hadzhinikolova M, Zderic I, Ciric D, Barcik JP, Enchev D, Baltov A, Rusimov L, Varga P, Stoffel K, Richards RG, Gueorguiev B, Rashkov M. Volar versus combined dorsal and volar plate fixation of complex intraarticular distal radius fractures with small dorsoulnar fragment - a biomechanical study. BMC Musculoskelet Disord. 2022;23(1):35

Hagen JE, Sands AK, Swords M, Rammelt S, Schmitz N, Richards RG, Gueorguiev B, Souleiman F. Medial talar resection: how much remains stable? Eur J Trauma Emerg Surg. 2022;48:3961-3967

Hasan A, Bagnol R, Owen R, Latif A, Rostam HM, Elsharkawy S, Rose FRAJ, Rodríguez-Cabello JC, Ghaemmaghami AM, Eglin D, Mata A. Mineralizing coating on 3D printed scaffolds for the promotion of osseointegration. Front Bioeng Biotechnol. 2022;10

Hatt LP, Armiento AR, Mys K, Thompson K, Hildebrand M, Nehrbass D, Müller WEG, Zeiter S, Eglin D, Stoddart MJ. Standard in vitro evaluations of engineered bone substitutes are not sufficient to predict in vivo preclinical model outcomes. Acta Biomater. 2022;epub Aug 18

Hristov S, Visscher L, Winkler J, Zhelev D, Ivanov S, Veselinov D, Baltov A, Varga P, Berk T, Stoffel K, Kralinger F, Gueorguiev B. A novel technique for treatment of metaphyseal voids in proximal humerus fractures in elderly patients. Medicina (Kaunas). 2022;58(10):1424

Ihle C, Dorn J, Ateschrang A, Baumgartner H, Herbst M, Döbele S, Histing T, Schröter S, Ahrend MD. Work intensity and quality of life can be restored following double-level osteotomy in varus knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2022;epub Mar 10

Isik M, Okesola BO, Eylem CC, Kocak E, Nemutlu E, Emregul E, D'Este M, Derkus B. Tuning the cell-adhesive properties of two-component hybrid hydrogels to modulate cancer cell behavior, metastasis, and death pathways. Biomacromolecules. 2022;23(10):4254-67

Ivanov S, Stefanov A, Zderic I, Rodemund C, Schepers T, Gehweiler D, Dauwe J, Pastor T, Makelov B, Raykov D, Richards RG, Gueorguiev B. Percutaneous fixation of intraarticular joint-depression calcaneal fractures with different screw configurations - a biomechanical human cadaveric analysis. Eur J Trauma Emerg Surg. 2022;48:3305-3315

Ivanov S, Valchanov P, Hristov S, Veselinov D, Gueorguiev B. Management of Complex Acetabular Fractures by Using 3D Printed Models. Medicina (Kaunas). 2022;58(12):1854

Kastner P, Zderic I, Gueorguiev B, Richards G, Schauer B, Hipmair G, Gotterbarm T, Schopper C. Cementless femoral stem revision in total hip arthroplasty: The periprosthetic clamshell fracture. A biomechanical investigation. J Orthop Res. 2022;epub Jun 23

Lackington WA, Gehweiler D, Zhao E, Zderic I, Nehrbass D, Zeiter S, Gonzalez-Vazquez A, O'Brien FJ, Stoddart MJ, Thompson K. Interleukin-1 receptor antagonist enhances the therapeutic efficacy of a low dose of rhBMP-2 in a weight-bearing rat femoral defect model. Acta Biomater. 2022;149:189-197

Ladner YD, Armiento AR, Kubosch EJ, Snedeker JG, Stoddart MJ. Optimization of loading protocols for tissue engineering experiments. Sci Rep. 2022;12(1):5094

Li KH, Zhu Y, Zhang PH, Alini M, Grad S, Li Z. Osteochondral explants for diarthrodial joint diseases: bridging the gap between bench and bedside. Eur Cell Mater. 2022;44:74-98

Li Y-H, Wu H-L, Li Z, Li B-B, Zhu M, Chen D, Ye F-H, Yu B-S, Huang Y-C. Species variation in the cartilaginous endplate of the lumbar intervertebral disc. JOR Spine. 2022;5:e1218

Marchionatti E, Constant C, Steiner A. Preoperative skin asepsis protocols using chlorhexidine versus povidone-iodine in veterinary surgery: A systematic review and meta-analysis. Vet Surg. 2022; 51(5):744-752

Masters EA, Ricciardi BF, de Mesy Bentley KL, Moriarty TF, Schwarz EM, Muthukrishnan G. Skeletal infections: microbial pathogenesis, immunity and clinical management. Nat Rev Microbiol. 2022;20:385-400

Mischler D, Schader JF, Dauwe J, Tenisch L, Gueorguiev B, Windolf M, Varga P. Locking plates with computationally enhanced screw trajectories provide superior biomechanical fixation stability of complex proximal humerus fractures. Front Bioeng Biotechnol. 2022;10: 919721

Monaco G, Qawasmi F, El Haj AJ, Forsyth NR, Stoddart MJ. Chondrogenic differentiation of human bone marrow MSCs in osteochondral implants under kinematic mechanical load is dependent on the underlying osteo component. Front Bioeng Biotechnol. 2022;10:998774

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. J Mech Behav Biomed Mater. 2022;126:105002

Pastor T, Beeres FJP, Kastner P, Gehweiler D, Migliorini F, Nebelung S, Scaglioni MF, Souleiman F, Link B-C, Babst R, Gueorguiev B, Knobe M. Anatomical analysis of different helical plate designs for distal femoral fracture fixation. Injury. 2022;53:2636-2641

Pastor T, Knobe M, van de Wall BJM, Rompen IF, Zderic I, Visscher L, Link B-J, Babst R, Gueorguiev B, Beeres FJP. Low-profile dual mini-fragment plating of diaphyseal clavicle fractures. A biomechanical comparative testing. Clin Biomech. 2022;94:105634

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## 14.4 Books, Book chapters, Theses

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## 14.5 Abstracts published in journals

Bless N, Sailer J, Dalcanale F, De Wild M, Gueorguiev B, Zderic I, Knecht M, Müller A. Biomechanical properties of a novel AC and CC stabilization technique using a novel cadaveric system with integration of the deltoideotrapezoideal fascia. Swiss Med Wkly. 2022;152(Suppl 259):10 S (swiss orthopaedics / oral)

Gantenbein F, Hartnack S, Buchholz T, Wever K, Ritskes-Hoitinga M, Zeiter S, Seebeck P. Training of rodent surgeons – current practice and available guideline. 2022;56(1 Suppl):105 (FELASA / oral)

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van Knegsel KP, Hsu C-E, Huang K-C, Benca E, Ganse B, Pastor T, Gueorguiev B, Varga P, Knobe M. A reliable predictor of secondary lateral wall fracture following tro-chanteric fractures – an update. Swiss Med Wkly. 2022;152(Suppl 259):33 S (swiss orthopaedics / oral)

## 14.6 Abstracts (conference presentations)

Antonacci P, Belcastro L, Rocchitta G, Arduini F, Serra PA, Alini M, Grad S, Basoli V. Development of electrochemical nitric oxide microsensors for the real time monitoring of inflammation in chondrocytes. 2022 eCM (poster)

Antonacci P, Dauwe J, Varga P, Ciric D, Gehweiler D, Gueorguiev B, Mys K. Osteoarthritic knees can be quantified with in vivo scanners. 2022 ESB (Biomechanics) (oral)

Antonacci P, Dauwe J, Varga P, Ciric D, Gehweiler D, Gueorguiev B, Mys K. Cartilage and subchondral bone changes in osteoarthritis can be detected quantitatively using in vivo imaging. 2022 ICORS (poster)

Bagnol R, O'Mahony L, Moriarty TF, Eglin D. Physico-chemical and immunoregulatory characterization of polyelectrolytes coatings from a bacterial exopolysaccharide. 2022 ESB (Biomaterials) (poster)

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Bärtl S, Gens L, Zeiter S, Rupp M, Moriarty F, Alt V. Vergleichende Untersuchung von hoch- und niedrigvirulenten Staphylococcus aureus Isolaten bei frakturassoziierten Infektionen im Mausmodell. 2022 DKOU (oral)

Basoli V, Traweger A, Plank C, Rip J, Alini M, Grad S. Effect of therapeutic IL1Ra and IL10 mRNA vehiculated by polymeric nanoparticles in osteochondral ex-vivo model: a new approach for osteoarthritis treatment. 2022 ORS (poster)

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Bektas EI, Wychowaniec JK, Miklosic G, Wesdorp MA, D'Este M. The influence of stiffness and protein coating on the neutrophil activation. 2022 SSB+RM (poster)

Bektas EI, Wesdorp MA, Wychowaniec JK, Miklosic G, D'Este M. Influence of biomaterials surface composition and topography on the activation of neutrophils. 2022 ESB (Biomaterials) (poster)

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Benca E, Zderic I, Caspar J, van Knegsel K, Hirtler L, Gueorguiev B, Windhager R, Widhalm H, Varga P. On measuring implant fixation stability in ACL reconstruction. 2022 ESB (Biomechanics) (poster)

Benca E, van Knegsel K, Zderic I, Caspar J, Strassl A, Hirtler L, Fuchssteiner C, Gueorguiev B, Windhager R, Widhalm H, Varga P. Biomechanical evaluation of an allograft fixation system for ACL reconstruction in comparison to the interference screw. 2022 ICORS (poster)

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Benca E, Zderic I, van Knegsel K, Caspar J, Hirtler L, Fuchssteiner C, Strassl A, Gueorguiev B, Widhalm H, Windhager R, Varga P. Biomechanische Bestimmung von Frakturlasten und Typen des Dens axis unter Berücksichtigung der Lastrichtung. 2022 ÖKOT (oral)

Benca E, Zderic I, Caspar J, van Knegsel K, Hirtler L, Gueorguiev B, Windhager R, Widhalm H, Varga P. Biomechanischer Vergleich des Allograft-Fixationssystems Shark Screw ACL für die Rekonstruktion des vorderen Kreuzbandes mit der Interferenzschraube. 2022 ÖKOT (oral)

Breulmann FL, Ramasamy S, Herzog M, Pandian GN, Della Bella E, Stoddart MJ. Differentially expressed microRNAs during early endochondral differentiation of human mesenchymal stromal cells as biomarkers for non-union fractures. 2022 SSB+RM (poster)

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Bryk E, Sands A, Zderic I, Swords M, Rammelt S, Grujic L, Gehweiler D, Ciric D, Roth C, Nötzli C, Gueorguiev B. First tarsometatarsal (TMT-1) joint fusion in the foot – A biomechanical human anatomical specimen analysis with use of continuous compression implants. 2022 SICOT (oral)

Bumann H, Kluser N, Soubrier A, Secerovic A, Zuncheddu D, Williams R, Snuggs J, Janani R, Sammon C, Jansen JU, Neidlinger-Wilke C, Wilke H-J, Le Maitre c, Vernengo A, Grad S. Notochordal cells encapsulated within hydrogel in an enzymatic bovine IVD degeneration model. 2022 eCM (poster)

Chen G, Basoli V, Guex AG, Stoddart M, Della Bella E. Improving chondrogenic potential of mesenchymal stromal cells by siRNA delivery in hydrogels. 2022 TERMU (oral)

Chittò M, Chen B, Kunisch F, Wychowaniec J, Post V, Zeiter S, Wagemans J, Trampuz A, Gonzales Moreno M, Lavigne R, Moriarty TF. Controlled release of bacteriophages for the treatment of multidrug-resistant Pseudomonas aeruginosa bone infection in vitro and in vivo. 2022 VoM (poster)

Chittò M, Chen B, Kunisch F, Wychowaniec J, Onsea J, Post V, Richards RG, Zeiter S, Wagemans J, Trampuz A, D'Este M, Gonzales Moreno M, Lavigne R, Moriarty TF. Dual application of bacteriophages and meropenem using microbead-loaded hydrogel for treatment of multidrug-resistant Pseudomonas aeruginosa in a mouse model of bone infection. 2022 ICORS (oral)

Chittò M, De Maesschalck V, Wagemans J, Lavigne R, Moriarty TF. A new strategy for the treatment of staphylococcus aureus fracture-related infections using bacteriophage-derived enzymes and antibiotics. 2022 GR forscht (oral)

Ciftci Dede E, Li K, Grad S, Alini M, Li Z. Anti-inflammatory and regenerative effects of liraglutide on inflammatory human osteoarthritic chondrocytes in vitro. 2022 GR forscht (oral)

Constant C, Hom W, Nehrbass D, Carmel E-N, Albers C, Deml MC, Gehweiler D, Lee Y, Hecht A, Grad S, Iatridis JC, Zeiter S. Comparison and optimization of sheep in vivo intervertebral disc injury model. 2022 ORS (poster)

Constant C, Moriarty TF, Arens D, Pugliese B, Zeiter S. Peri anesthetic hypothermia in rodents: a factor to consider for accurate and reproducible outcomes in orthopedic device-related infection studies. 2022 ICORS (poster)

Constant C. Cutting edge advancements in septic arthritis in ruminants. 2022 ACVS Surgery Summit (oral)

Constant C, Marchionatti E, Desrochers A, Babkine M, Nichols S. Lactate measurement in long bone fractures in cattle. Capillary lactate concentration predicts 30-day post-admission mortality and complications in cattle with long bone fractures. 2022 ACVS Surgery Summit (oral)

Dauwe J, Mys K, Putzeys G, Schader JF, Richards RG, Gueorguiev B, Varga P, Nijs S. Advanced CT visualization improves the accuracy of orthopaedic trauma surgeons and residents in classifying proximal humeral fractures: a feasibility study. 2022 Orthopaedica Belgica (poster)

D'Este M, van der Heide D, Amédée J, Stoddart MJ. cmRNAbone project: 3D printed-matrix assisted chemically modified RNAs bone regenerative therapy for trauma and osteoporotic patients. 2022 ESB (Biomaterials) (oral)

De Oliveira S, Miklosic G, D'Este M, Hélary C. Optimized collagen/hyaluronan formulations to develop a novel biomimetic ink to synthesize composite hydrogels for tissue engineering. 2022 PNG (poster)

De Oliveira S, Miklosic G, D'Este M, Grastilleur S, Véziers J, Hélary C. Collagen/hyaluronan polyionic complexes as a new building block to develop a novel bioink to model the intervertebral disc. 2022 ESB (Biomaterials) (poster)

Di Marzio N, Alini M, Serra T. Programming vasculature morphogenesis by using sound. 2022 ISBF Twitter poster conference

Di Marzio N, Guex AG, Alini M, Serra T. Controlling the shape of microcapillary networks in 3D in vitro models through sound patterning. 2022 TERMIS EU (oral)

Egger S, Alig G, D'Este M, Wychowaniec JK, Weiser JR, Grad S, Vernengo AJ. Microextrusion-based anisotropic cell patterning within temperature-sensitive hydrogel matrices for annulus fibrosus regeneration. 2022 eCM (oral)

Enzmann S, Matthys R, Stoddart M, Verrier S. Shorter resting period between cycles induces stronger MSC response to mechanical stimuli. 2022 SVGO / SBMS (oral)

Fleischhacker E, Helfen T, Milz S, Saller M, Sprecher C, Siebenbürger G, Gleich J, Böcker W, Ockert B. Outcome und inflammatorische Gewebereaktion nach Entfernung winkelstabiler Platten aus PEEK und Titan am proximalen Humerus. 2022 DVSE (oral)

Fleischhacker E, Sprecher CM, Milz S, Wirz R, Zobray R, Parrilli A, Saller MM, Helfen T, Ockert B. Comparative study of particle loads in peri-implant soft tissue over osteosynthesis plates made of CFR-PEEK and titanium. 2022 MTE Implants (poster)

Gehweiler D, Mys K, van Knegsel K, Pastor T, Visscher L, Dauwe J, Bashardoust A, Knill A, Gueorguiev B, Windolf M, Nijs S, Lambert S, Varga P. Statistical analysis of complex proximal humeral fractures. 2022 QMSKI & ISUCB

Gehweiler D, Pastor T, Gueorguiev B, Jaeger M, Lambert S. In vitro methodology for systematic CT investigation of the periclavicular space. 2022 EFORT (poster)

Gehweiler D, Pastor T, Beeres FJP, Kastner P, Migliorini F, Nebelung S, Scaglioni MF, Souleiman F, Link B-C, Babst R, Gueorguiev B, Knobe M. Anatomical analysis of different helical plate designs for distal femoral fracture fixation. 2022 ICORS (oral)

Gehweiler D, Pastor T, Gueorguiev B, Jaeger M, Lambert S. In vitro methodology for systematic CT investigation of the periclavicular space. 2022 ICORS (oral)

Gewieß J, Sprecher CM, Milz S, Gleich J, Helfen T. Cortical microarchitecture impacts distal clavicle fracture morphology. 2022 eCM (poster)

Gewiess J, Eglauf J, Soubrier A, Grad S, Alini M, Peroglio M, Ma J. Influence of mechanical loading regimes on spontaneous response of dorsal root ganglion neurons. 2022 eCM (poster)

Gewiess J, Sprecher C, Milz S, Gleich J, Helfen T. Einfluss der Knochenmatrix auf die Frakturmorphologie der lateralen Klavikula. 2022 DVSE (oral)

Grad S, Gewiess J, Eglauf J, Soubrier A, Alini M, Peroglio M, Ma J. Intensively loaded intervertebral disc enhances the spontaneous calcium oscillation in CGRP-negative dorsal root ganglion neurons. 2022 ISSLS (oral)

Grastilleur S, Humbert P, Miklosic G, de Oliveira S, Halgand B, Loll F, Delplace V, D'Este M, Hélary C, Clouet J, Fusellier M, Guicheux J, Le Visage C. In vitro evaluation of ovine IVD cells interactions with a collagen/hyaluronic acid biomaterial ink: On the way to a bio-printed IVD model. 2022 eCM (poster)

Gueorguiev B, Pastor T, Beeres FJP, Kastner P, Gehweiler D, Migliorini F, Nebelung S, Scaglioni MF, Souleiman F, Link B-C, Babst R, Knobe M. Anatomical analysis of different helical plate designs for distal femoral fracture fixation. 2022 EFORT (oral)

Gueorguiev B, Pastor T, Kastner P, Souleiman F, Gehweiler D, Link B-C, Peeres FJP, Babst R, Nebelung S, Ganse B, Richards G, Knobe M. Anatomical analysis of different helical plate designs for proximal third humeral shaft fracture fixation. 2022 EFORT (oral)

Gueorguiev B, Stoffel K, Zderic I, Sanchez E, Woodburn W, Castle R, Penman J, Sommer C. Is anterior variable angle locked plating of simple and complex patella fractures advantageous over tension band wiring? A biomechanical cadaveric study. 2022 EFORT (oral)

Gueorguiev B, Souleiman F, Heilemann M, Hennings R, Hepp P, Richards G, Osterhoff G, Gehweiler D. Effect of weightbearing and foot position on 3D distal tibiofibular joint parameters. 2022 EFORT (poster)

Guex AG, Krattiger LA, Carrara BM, Alini M, Ehrbar M, Serra T. Sound-based cell assembly to recreate complex tissue architectures for regenerative medicine. 2022 SSB+RM (oral)

Guex AG, Krattiger LA, Carrara BM, Alini M, Ehrbar M, Serra T. Cell density matters: Local cell density enhancement by sound to increase the therapeutic efficacy in regenerative medicine 2022 TERMIS EU (oral)

Guex AG, Krattiger LA, Carrara BM, Alini M, Ehrbar M, Serra T. Increasing local cell density by sound to engineer vascularized bone constructs. 2022 ICORS (oral)

Häckel S, Ma J, Häne S, Eglauf J, Soubrier A, Peroglio M, Li Z, Hoppe S, Benneker L, Wangler S, Alini M, Grad S. An in vitro large animal model to investigate the effect of celecoxib on discogenic pain-associated sensory neuronal sensitization. 2022 Global Spine Congress (oral)

Hadzhinikolova M, Enchev D, Baltov A, Gueorguiev B, Rusimov L, Rashkov M. Instability after reverse shoulder prosthesis treatment. 2022 BOTA (oral)

Hadzhinikolova M, Enchev D, Baltov A, Gueorguiev B, Rusimov L, Rashkov M. Shear wave elastography for assessment of m.deltoideus in patients after reverse shoulder prosthesis treatment. 2022 BOTA (oral)

Hatt LP, Wirth S, Armiento AR, Ristaniemi A, Thompson K, Gehweiler D, Eglin D, Stoddart MJ. Delivery of mesenchymal stromal cells using collagen membranes embedded in LEGO®-inspired multicomponent scaffolds for personalised mandibular defect repair. 2022 SSB+RM (oral)

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Hatt LP, Wirth S, Armiento AR, Pirera ME, Ristaniemi A, Thompson K, Gehweiler D, Eglin D, Stoddart MJ. LEGO®-inspired multicomponent 3D-printed bone substitute for personalised facial bone repair. Wie wir das LEGO®-Prinzip in die Herstellung eines Knochen-Ersatzes eingefügt haben. 2022 GR forscht (oral)

Heilemann M, Souleiman F, Hennings R, Hepp P, Gueorguiev B, Richards G, Osterhoff G, Gehweiler D. Einfluss von Fußposition und Gewichtsbelastung auf die Stellung des distalen Tibiofibulargelenks. 2022 DGfB (oral)

Jahangir S, Vecstaudza J, Canciani E, Locs J, Alini M, Serra T. Development of bioprinted osteochondral tissue: an in-vitro model for drug discovery. 2022 TERMIS EU (oral)

Jahangir S, Vecstaudža J, Canciani E, Locs J, Alini M, Serra T. Development of bioprinted osteochondral tissue: an in-vitro model for drug discovery. 2022 GR forscht (oral)

Jansen JU, Teixeira GQ, Vernengo A, Grad S, Benz K, Neidlinger-Wilke C, Wilke H-J. How to create artificial disc degeneration by enzyme digestion for biomechanical testing of biomaterials. 2022 eCM (oral)

Jörimann T, Füllemann P, Matthys R, Stoddart M, Verrier S. Strain induces hypertrophic differentiation of naïve human MSCs in a 3D in vitro model. 2022 ORS (poster)

Jörimann T, Füllemann P, Matthys R, Stoddart M, Verrier S. Effect of strain on naïve human MSC differentiation, an in vitro bioreactor study. 2022 SVGO / SBMS (oral)

Kastner P, Zderic I, Gueorguiev B, Richards G, Schauer B, Hipmaier G, Gotterbarm T, Schopper C. Cementless femoral stem revision in total hip arthroplasty- the periprosthetic clamshell fracture. A biomechanical investigation. 2022 DKOU (oral)

Ladner YD, Armiento AR, Stoddart MJ. A multi-well bioreactor for cartilage tissue engineering. 2022 SSB+RM (poster)

Ladner Y, Armiento A, Stoddart M. A multi-well bioreactor for cartilage tissue engineering. 2022 TERMIS EU (poster)

Ladner Y, Armiento A, Stoddart M. Mechano-induced chondrogenesis of human MSCs in a biomaterial: A factorial design of experiment approach. 2022 TERMIS EU (poster)

Le Visage C, Grastilleur S, Humbert P, Miklosic G, Halgand B, Loll F, D'Este M, Hélary C, Fusellier M, Guicheux J. On the way to a bio-printed intervertebral disc (IVD) model: In vitro evaluation of the interactions of ovine IVD cells with a collagen/hyaluronic acid bio-ink. 2022 TERMIS AP (poster)

Li KH, Zhu Y, Zhang P, Alini M, Grad S, Li Z. Anti-inflammatory and pro-anabolic effects of 5-aminosalicylic acid on inflammatory human osteoarthritic chondrocytes in vitro. 2022 eCM (oral)

Lodde MF, Katthagen JC, Schopper C, Zderic I, Richards RG, Gueorguiev B, Raschke MJ, Hartensuer R. Is cement augmentation of the sacroiliac screw biomechanically superior for fixation of B2 fractures of the sacrum? 2022 Global Spine Congress (oral)

Ma J, Marani E, Alini M, Serra T. Engineering dorsal root ganglion multicellular system towards in vivo cross excitation function. 2022 TERMIS EU (oral)

Marani E, Ma J, Alini M, Serra T. Sound assembly of dorsal root ganglion multicellular system. 2022 ScSB (oral)

Mecchi L, Guex AG, Stoddart M. Developing materials for cartilage regeneration under mechanical load. 2022 GR forscht (oral)

Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen composite bioink for the printing of nucleus pulposus-like structures. 2022 SSB+RM (poster)

Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen composite bioink for the printing of nucleus pulposus-like structures. 2022 eCM (poster)

Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen composite bioink for the printing of nucleus pulposus-like structures. 2022 ESB (Biomaterials) (poster)

Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen bioink for the printing of intervertebral disc models. 2022 GR forscht (oral)

Miklosic G, De Oliveira S, Grastilleur S, Hélary C, Ferguson SJ, D'Este M. Hyaluronan-collagen composite bioink for the printing of nucleus pulposus-like structures. 2022 Biofabrication (oral)

Mischler D, Tenisch L, Schader JF, Dauwe J, Gueorguiev B, Windolf M, Varga P. Effect of instrumentation inaccuracies on biomechancial and computational failure risk of fracture fixations. 2022 ESB (Biomechanics) (oral)

Mischler D, Knecht M, Varga P. Systematic validation of finite element simulations of locking plate fixations. 2022 ESB (Biomechanics) (oral)

Mischler D, Tenisch L, Schader JF, Dauwe J, Gueorguiev B, Windolf M, Varga P. Instrumentation inaccuracies strongly influence the biomechanical and computational failure risk of fracture fixations. 2022 ICORS (poster)

Mosina M, Siverino C, Stipniece L, Moriarty F, Locs J. Biocompatible Gallium doped hydroxyapatite. 2022 ScSB (oral)

Ossendorff R, Börger V, Wirtz DC, Grad S, Giebel B, Schildberg FA. Extracellular Vesicles (MSC-EV) - influence on cartilage regeneration in osteoarthritic surroundings. 2022 eCM (oral)

Pastor T, Knobe M, Kastner P, Souleiman F, Pastor T, Gueorguiev B, Windolf M, Buschbaum J. Validation of a novel device for digitally enhanced hands-on surgical training of intramedullary nail distal interlocking. 2022 Swiss Congress of Surgery (poster)

Pastor T, Knobe M, Ciric D, Zderic I, van de Wall B, Rompen I, Visscher L, Link B-C, Babst R, Richards G, Gueorguiev B, Beeres F. Low-profile dual mini-fragment plating of diaphyseal clavicle fractures. A biomechanical study. 2022 ICORS (oral)

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Pastor T, Kastner P, Souleiman F, Gehweiler D, Link B-C, Beeres F, Babst R, Gueorguiev B, Knobe M. Anatomical analysis of different helical plate designs for proximal humeral shaft fracture fixation. 2022 ICORS (poster)

Pastor T, Knobe M, van de Wall B, Zderic I, Rompen I, Link B, Babst R, Gueorguiev B, Beeres F. Low-profile dual mini-fragment plating of diaphyseal clavicle fractures. A biomechanical comparative analysis. 2022 DKOU (oral)

Pastor T, Kastner P, Souleiman F, Gehweiler D, Link B, Beeres F, Babst R, Gueorguiev B, Knobe M. Anatomical analysis of different helical plate designs for proximal humeral shaft fracture fixation. 2022 DKOU (poster)

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Pirera ME, Hatt LP, Wirth S, Stoddart MJ. Combination of the collagen membranes within the LEGO® inspired interlocking system, a new therapeutic alternative for bone regeneration in maxillary defects. 2022 GR forscht (oral)

Richter J, Ciric D, Kalchschmidt K, D'Aurelio C, Pommer A, Dauwe J, Gueorguiev B. Advances in fixation strength of reorienting rectangular triple pelvic innominate osteotomy. 2022 ESB (Biomechanics) (oral)

Richter J, Ciric D, Kalchschmidt K, D'Aurelio C, Pommer A, Dauwe J, Gueorguiev B. Advances in fixation strength of reorientating rectangular triple pelvic innominate osteotomy. 2022 ICORS (oral)

Richter J, Kalchschmidt K, D'Aurelio C-S, Ciric D, Gueorguiev B. Stabilität von Schraubenosteosynthesekonzepten nach 3fach Beckenosteotomie. 2022 DKOU (oral)

Ristaniemi A, Šećerović A, Grad S, Ferguson SJ. A novel viscoelastic bovine intervertebral disc finite element model. 2022 eCM (oral)

Ristaniemi A, Secerovic A, Ferguson SJ, Grad S. Viscoelastic characterization of bovine annulus fibrosus lamellae. 2022 WCB (oral)

Schol J, Warita T, Sako K, Grad S, Alini M, Sakai D, Watanabe M. Vertebral transplantation of mesenchymal stromal cells for intervertebral disc repair outperforms intradiscal injection in a rat tail disc degeneration model: A preliminary study. 2022 ORS (oral)

Schol J, Warita T, Sako K, Grad S, Alini M, Sakai D, Watanabe M. Vertebral mesenchymal stromal cell transplantation for intervertebral disc repair; a preliminary rat tail disc degeneration study. 2022 ISSLS (poster)

Schwab A, Staubli F, Stoddart MJ, D'Este M. Cell micro-pellets: An alternative to single cell embedding in biomaterials to evaluate the effect of material properties on chondrogenic differentiation. 2022 OARSI (hybrid / poster)

Schwab A, Staubli F, Alini M, D'Este M. Bioinks with controlled fiber architecture modulating cell behavior. 2022 ICRS (oral)

Schwab A, Wesdorp TM, Xu J, Abinzano F, Levato R, Loebel C, Narcisi R, Burdick J, Malda J, Eglin D, Stoddart MJ, D'Este M, van Osch GJVM. Effect of biomaterial composition on cell migration and tissue formation for cell-free osteochondral defect repair. 2022 NBTE (oral)

Schwarzenberg P, Colding-Rasmussen T, Hutchison DJ, Mischler D, Horstmann P, Petersen MM, Malkoch M, Wong C, Varga P. Light-curable fixation comparable with plates in torsion. 2022 ESB (Biomechanics) (oral)

Schwarzenberg P, Colding-Rasmussen T, Hutchison DJ, Mischler D, Horstmann P, Petersen MM, Malkoch M, Wong C, Varga P. Light-curable fracture fixation solution comparable with metal plates in torsion. 2022 ICORS (oral)

Šećerović A, Ristaniemi A, Li Z, Crivelli F, Heub S, Ledroit D, Alini M, Weder G, Ferguson S, Grad S. A new generation of multiaxial spine bioreactor for advanced studies of intervertebral disc degeneration and repair. 2022 eCM (poster)

Šećerović A, Ristaniemi A, Cui S, Li Z, Alini M, Weder G, Heub S, Ledroit D, Grad S. Towards the development of multiaxial loading bioreactor for intervertebral disc studies: validation of an ex vivo organ model and customized sample holder. 2022 TERMIS EU (oral)

Šećerović A, Ristaniemi A, Cui S, Li Z, Alini M, Weder G, Heub S, Ledroit D, Grad S. Ex vivo organ model and sample holder for intervertebral disc studies in a new generation of multiaxial bioreactors. 2022 ICORS (oral)

Serra T, Alini M, Di Marzio N. Sound programmable vasculature morphogenesis. 2022 TERMIS AP (oral)

Serra T. A sound assembly platform to control tissue organization. 2022 BioMaH (oral)

Sieberath A, Eglin D, Della Bella E, Sprecher C, Ferreira AM, Gentile P, Dalgarno K. Development of a bone remodelling in vitro model. 2022 eCM (poster)

Siverino C, Arens D, Zeiter S, Richards RG, Moriarty TF. Bone defect healing using the induced-membrane technique after chronically infected non-union in a novel rabbit model. 2022 ICORS (oral)

Soubrier A, Kasper H, Alini M, Jonkers I, Grad S. Influence of traction on intervertebral disc mechanobiology: preliminary results in a bovine organ culture. 2022 eCM (poster)

Soubrier A, Kasper H, Alini M, Jonkers I, Grad S. Cyclic traction loading facilitates water uptake in a healthy bovine disc culture: preliminary study. 2022 ORS PSRS (poster)

Souleiman F, Zderic I, Pastor T, Gehweiler D, Gueorguiev B, Galie J, Kent T, Tomlinson M, Schepers T, Swords M. Better anteroposterior translation and axial tibiofibular joint stability provided by novel dynamic screw-suture stabilization system for syndesmotic repair. 2022 ICORS (oral)

Souleiman F, Heilemann M, Gueorguiev B, Hennings R, Hepp P, Richards G, Gehweiler D, Osterhoff G. Effect of weightbearing and foot position on 3D distal tibiofibular joint parameters. 2022 ICORS (oral)

Souleiman F, Zderic I, Pastor T, Varga P, Helfen T, Richards G, Gueorguiev B, Theopold J, Osterhoff G, Hepp P. Influence of cartilage loss on shoulder instability. A biomechanical study. 2022 ICORS (oral)

Souleiman F, Zderic I, Pastor T, Varga P, Gueorguiev B, Hepp P, Theopold J, Osterhoff G. Osteochondral glenoid loss: Remaining glenoid depth and concavity are stronger predictive parameters for shoulder instability than defect size. 2022 ICORS (oral)

Souleiman F, Zderic I, Pastor T, Varga P, Richards G, Gueorguiev B, Osterhoff G, Hepp P, Theopold J. Glenoidaler Knorpel-Knochenverlust bei Schulterinstabilitäten: Der Verlust der glenoidalen Tiefe und der Konkavität sind relevantere Vorhersagewerte als die Defektgröße. 2022 DVSE (oral)

Souleiman F, Zderic I, Pastor T, Varga P, Richards G, Gueorguiev B, Osterhoff G, Hepp P, Theopold J. Rekurrente Schulterinstabilität: Einfluss glenoidalen Knorpelverlusts auf Konkavität und biomechanische Stabilität. 2022 DVSE (oral)

Souleiman F, Heilemann M, Hennings R, Hepp P, Gueorguiev B, Richards G, Gehweiler D, Osterhoff G. Die aussagekräftigste Fußposition zur nichtinvasiven Detektion einer Verletzung der Syndesmose: Eine 3D-Analyse. 2022 AGA (oral)

Souleiman F, Hennings R, Zderic I, Pastor T, Gehweiler D, Gueorguiev B, Galie J, Kent T, Tomlinson M, Schepers T, Swords M. Die dynamische Stabilisation des distalen Tibiofibulargelenkes – Ein Vergleich zwischen Suture-button und Screw-Suture System. 2022 AGA (oral)

Souleiman F, Heilemann M, Gueorguiev B, Hennings R, Hepp P, Richards G, Gehweiler D, Osterhoff G. Einfluss der belasteten und unbelasteten Fußstellung auf die Stellung des distalen Tibiofibulargelenks – eine dreidimensionale Analyse 2022 AGA (oral)

Souleiman F, Zderic I, Pastor T, Varga P, Richards G, Gueorguiev B, Osterhoff G, Hepp P, Theopold J. Glenoidaler Knorpel-Knochenverlust bei Schulterinstabilitäten: Der Verlust der glenoidalen Tiefe und der Konkavität sind relevantere Vorhersagewerte als die Defektgröße. 2022 AGA (oral)

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Souleiman F, Zderic I, Pastor T, Gehweiler D, Gueorguiev B, Galie J, Kent T, Tomlinson M, Schepers T, Swords M. Ein neues dynamisches Implantatsystem zur Stabilisation des distalen Tibiofibulargelenkes: verbesserte anteroposteriore und axiale Translation bei der längeninstabilen Verletzung der Syndesmose. 2022 DKOU (oral)

Souleiman F, Heilemann M, Hennings R, Hepp P, Richards G, Gueorguiev B, Gehweiler D, Osterhoff G. Einfluss der belasteten und unbelasteten Fußstellung auf die Stellung des distalen Tibiofibulargelenks - eine dreidimensionale Analyse. 2022 DKOU (oral)

Souleiman F, Zderic I, Pastor T, Varga P, Richards G, Gueorguiev B, Osterhoff G, Hepp P, Theopold J. Glenoidaler Knorpel-Knochenverlust bei Schulterinstabilitäten: Der Verlust der glenoidalen Tiefe und der Konkavität sind relevantere Vorhersagewerte als die Defektgröße. 2022 DKOU (poster)

Stoddart M. Cell therapy for cartilage repair-modelling - Increasing complexity of cartilage models. 2022 ICRS (oral)

Stoddart MJ. In vitro testing of bone biomaterials - opportunities and challenges. 2022 TERMIS EU (oral / invited Keynote)

Stoddart M. Reproducing kinematic load in vitro for chondrogenesis studies. 2022 TERMIS AP (oral)

Stoffel K, Zderic I, Pastor T, Woodburn W, Castle R, Penman J, Sanchez ES, Gueorguiev B, Sommer C. Anterior variable-angle locked plating versus tension band wiring of simple and complex patella fractures – a biomechanical study. 2022 ICORS (poster)

Stojceski F, Grasso G, Buetti-Dinh A, Stoddart M, Della Bella E. Influence of dexamethasone on the interaction between glucocorticoid receptor and SOX9: A molecular dynamics study. 2022 TERMIS EU (oral)

Trivedi Z, Gehweiler D, Wagner A, Gueorguiev B, Ricken T, Röhrle O. A porous media flow model for simulating flow of non-Newtoninan bone cement inside a deformable vertebra in the context of vertebroplasty. 2022 InterPore (oral)

Trivedi Z, Gehweiler D, Wychowaniec J, Wagner A, Gueorguiev B, Ricken T, Röhrle O. Simulating vertebroplasty using a continuum model based on the Theory of Porous Media and its validation. 2022 GAMM (oral)

van der Heide D, Della Bella E, Yuan H, de Groot-Barrère F, Stoddart MJ, D'Este M. Bone resembling composite biomaterial-ink consisting of hyaluronan, collagen and calcium phosphate particles for bone regeneration. 2022 SSB+RM (poster)

van der Heide D, Della Bella E, Yuan H, De Groot-Barrère F, Stoddart MJ, D'Este M. Composite biomaterial-ink with hyaluronan, collagen and calcium phosphate particles for delivery of chemically modified RNA to promote bone regeneration. 2022 TERMIS EU (oral)

van der Heide D, Della Bella E, Huipin Y, de Groot-Barrère F, Stoddart M, D'Este M. Natural bone inspired 3D printed composite biomaterial-ink composed of hyaluronan, collagen and calcium phosphate particles to promote bone regeneration. 2022 GR forscht (oral)

van Knegsel K, Hsu C-E, Huang K-C, Benca E, Pastor T, Gueorguiev B, Varga P, Knobe M. Influence of knot number on holding capacity of two high strength sutures in different media - a biomechanical analysis. 2022 ICORS (poster)

van Knegsel K, Hsu C-E, Huang K-C, Benca E, Ganse B, Pastor T, Gueorguiev B, Varga P, Knobe M. A reliable predictor of secondary lateral wall fracture following trochanteric fractures - an update. 2022 DKOU (poster)

van Knegsel K, Zderic I, Kastner P, Varga P, Gueorguiev B, Knobe M, Pastor T. Influence of knot number on holding capacity of two high strength sutures in different media - a biomechanical analysis. 2022 AGA (poster)

Vautrin A, Aw J, Attenborough E, Varga P. Validated finite element simulation of porous titanium samples under fatigue loading for design optimization. 2022 ESB (Biomechanics) (oral)

Vernengo A, Bumann H, Kluser N, Jansen JA, Neidlinger-Wilke C, Wilke H-J, Alini M, Li Z, Grad S. Porcine notochordal cell injected into a bovine organ culture model of intervertebral disc degeneration. 2022 ORS (poster)

Vernengo A, Bumann H, Kluser N, Soubrier A, Gewiess J, Jansen JU, Neidlinger-Wilke C, Wilke H-J, Grad S. Enzyme-induced bovine explant models of intervertebral disc degeneration. 2022 eCM (poster)

Wangler S, Nüesch A, Chen Z, Häckel S, Albers CE, Bigdon S, Li Z, Alini M, Grad S. MSC secretome as potential immunomodulatory and regenerative treatment strategy for IVD degeneration. 2022 ORS (poster)

Wen L, Armiento A, Creemers L, Stoddart MJ. The role of Noggin in TGF-β1 or TGF-β3 driven chondrogenesis of BMMSCs. 2022 eCM (poster)

Wesdorp MA, Bektas EI, Schwab A, Narcisi R, Eglin D, Stoddart MJ, van Osch GJVM, D'Este M. Towards deciphering neutrophils role in the immune response to biomaterials. 2022 BioMaH (oral)

Wolf S, Sprecher CM, Milz S, Woelfler H, Gahlert M, Janner S, Meng B, Cochran DL, Roehling S. Artificially induced peri-implant inflammation around mechanically loaded Zirconia and Titanium implants. 2022 MTE Implants (oral)

Wychowaniec JK, D'Este M, Elsawy M, Saiani A, Miller A, Crean J, Brougham DF. From tuneable peptide self-assembly to biologically instructive materials. 2022 MRS spring meeting (oral)

Wychowaniec JK, Edwards-Gayle CJC, Bektas EI, Eglin D, D'Este M. Tyramine position dictates properties of 3D printable supramolecular self-assembling β-sheet peptide and tyramine-modified hyaluronan hydrogels. 2022 SSB+RM (poster)

Wychowaniec JK, Bektas EI, Devantay N, Eglin D, D'Este M. Design of 3D printable supramolecular selfassembling β-sheet peptide-hyaluronic acid hydrogels with immunomodulatory properties. 2022 TERMIS EU (oral)

Wychowaniec JK, Edwards-Gayle CJC, Bektas EI, Eglin D, D'Este M. 3D printable supramolecular self-assembling β-sheet peptide and tyramine-modified hyaluronan hydrogels with immunomodulatory properties. 2022 ESB (Biomaterials) (poster)

Yamamoto T, Randriantsilefisoa R, Sprecher CM, D'Este M. Extracellular matrix polymer-based cryogels mimicking the arcade-like structure of articular cartilage fabricated by directional freezing. 2022 SSB+RM (poster)

Yan S, Constant C, Ramazanian T, Kremers HM, Larson N. Automated Cobb angle measurement in adolescent idiopathic scoliosis: Validation of a previously-published deep learning method. 2022 IEEE ICHI (poster)

Yan S, Sagheb E, Constant C, Ramazanian T, Aubin C-E, Sohn S, Kremers HM, Larson AN. Transforming electronic health records (EHR) of scoliosis patients into clinical registries using natural language processing (NLP) and computer vision methods. 2022 SRS (poster)

Zderic I, Pastor T, Beeres F, van de Wall B, Rompen I, Visscher L, Link B-C, Babst R, Gueorguiev B, Knobe M. Low-profile dual mini-fragment plating of diaphyseal clavicle fractures. A biomechanical comparative analysis. 2022 EFORT (oral)

Zderic I, Pastor T, van Knegsel K, Richards G, Gueorguiev B, Knobe M. Biomechanical analysis of helical versus straight plating of proximal third humeral shaft fractures. 2022 EFORT (poster)

Zderic I, Pastor T, van Knegsel K, Richards G, Gueorguiev B, Knobe M. Helical plating of proximal third humeral shaft fractures. A biomechanical comparative study. 2022 EFORT (poster)

Zderic I, Souleiman F, Pastor T, Varga P, Helfen T, Richards G, Gueorguiev B, Theopold J, Osterhoff G, Hepp P. Influence of cartilage loss on shoulder instability - a biomechanical study. 2022 EFORT (poster)

Zderic I, Pastor T, van Knegsel K, Link BC, Beeres FJP, Migliorini F, Babst R, Nebelung S, Ganse B, Schoeneberg C, Gueorguiev B, Knobe M. Biomechanical analysis of helical versus straight plating of proximal third humeral shaft fractures. 2022 ESB (Biomechanics) (oral)

Zderic I, Dimitrova R, Petkov V, Sprecher CM, Mischler D, Richards G, Gueorguiev B, Drenchev L. Fractographic analysis of two different plate designs used for orthopaedic trauma surgery. 2022 ICMCC (oral)

Zderic I, Pastor T, van Knegsel K, Richards RG, Gueorguiev B, Knobe M. Helical plating of proximal third humeral shaft fractures - a biomechanical comparative study. 2022 DKOU (oral)

Zderic I, Pastor T, van Knegsel K, Link B, Beeres F, Babst R, Gueorguiev B, Knobe M. Biomechanical analysis of helical versus straight plating of proximal third humeral shaft fractures. 2022 DKOU (poster)

Zhelev D, Hristov S, Zderic I, Ivanov S, Baltov A, Gueorguiev B. Benefit of PMMA augmentation of locked plating of unstable proximal humerus fractures – a biomechanical investigation. 2022 BOTA (oral)

Zhelev D, Hristov S, Zderic I, Ivanov S, Baltov A, Gueorguiev B. Biomechanical investigation of two configurations for screw fixation of capitellum humeri. 2022 BOTA (poster)

Zuncheddu D, Kluser N, Bumann H, Creemers LB, Grad S. Effects of different glucose supplementation on bovine intervertebral disc organ cultures under physiological loading. 2022 eCM (poster)

## 14.7 Presentations (not in conference proceedings)

17.02.2022 Richards Geoff: "AO and translational orthopedic research", Webinar: Opportunities and challenges of translational medicine and the role of Journal of Orthopaedic Translation" (JOT Webinar Series, Online)

30.03.2022 Richards Geoff: "AO Webinar: Osteoporosis – The Silent Killer" (Moderator)

22.04.2022 Richards Geoff: "Introduction AO Research Institute Davos (ARI) and translational research", Block course: Skeletal Repair for ETHZ and ZHAW Students, Davos, Switzerland (Speaker)

08.06.2022 Richards Geoff: Besuch Rektoren Mittelschulen Kanton Graubünden (Amt für Höhere Bildung) – Begrüssung und Präsentation AO Forschungsinstitut Davos

09.06.2022 Richards Geoff: "AO PEER Webinar: Bone infection – a priority for clinical and translational researchers" (Moderator)

15.06.2022 Richards Geoff: "Opening Session and Berton Rahn Research Award", eCM Conference 2022, Cartilage and Disc Repair and Regeneration, Davos, Switzerland (Session Chair)

29.06.2022 Richards Geoff: Plenary Session "Cartilage regeneration: the challenges of regenerating a “simple” non-vascularised tissue", TERMIS EU Conference 2022, Krakow, Poland (Moderator)

20.07.2022 Richards Geoff: "AO: A model for translation of science to the clinics – AO Fracture monitor, Biphasic Plate and beyond", BiomMedD 2022 Conference, Bucharest, Romania (Invited Plenary Speaker)

27.07.2022 Richards Geoff: " The future of fracture care – Smart Implants, the AO Fracture Monitor", Sino-Swiss Innotech Forum 2022 (Online)

23.08.2022 Richards Geoff: "Forschungsplatz Graubünden / Vernetzung der Forschungsinstitutionen", Vorstellung AO Foundation, Botschafterkonferenz 2022, Pontresina, Switzerland (Invited Speaker)

04.07.2022 Richards Geoff: "Bone Infection, latest research at AO Research Institute Davos", Hospital Symposium, Department of Orthopaedic Surgery, Korea University Guro Hospital, Seoul, South Korea (Invited Speaker)

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| 04.07.2022 | Richards Geoff: "Bone Infection, latest research at AO Research Institute Davos", Kyungpook National University Hospital, Daegu, South Korea (Invited Speaker) |
| 07.10.2022 | Richards Geoff: Fellows of Tissue Engineering and Regenerative Medicine (FTERM) Session, "How can TERMIS make a real impact on regenerative medicine within the next 10 years?" Tissue Engineering and Regenerative Medicine, International Society Asia-Pacific Chapter Conference 2022, Jeju, Korea (Speaker, Moderator) |
| 05.12.2022 | Richards Geoff: " From the present to the future of fracture treatment", AO Trauma Course–Basic Principles of Fracture Management for Swiss Surgeons, Davos, Switzerland (Invited Speaker) |
| 07.04.2022 | Alini Mauro: "Sound waves in orthopaedics", Achilles Dublin EU Meeting, Dublin, Ireland (Keynote Lecture) |
| 12.06.2022 | Alini Mauro: "Choosing the right partner for a successful consortium", Scandinavia Society of Biomaterials annual meeting, Riga, Latvia (Invited Speaker) |
| 22.06.2022 | Alini Mauro: "Bioreactors for cartilage and intervertebral disc tissue engineering", Third PREMUROSA Network School, Belgrade, Serbia (Invited Speaker) |
| 21.07.2022 | Alini Mauro: "Sound induced morphogenesis: a new contactless bioprinting's technology", BiomMedD 2022 Conference, Bucharest, Romania (Invited Speaker) |
| 08.09.2022 | Alini Mauro: "How is the pre-clinical scientist looking at biologics?", AOGO Symposium at ICORS, Edinburgh, Scotland (Invited Speaker) |
| 20.09.2022 | Alini Mauro: "Osteochondral regeneration", Plenary Relay Session at Bioceramics 32 Conference, Venice, Italy (Invited Speaker) |
| 04.10.2022 | Alini Mauro: "SIM in orthopaedics", International Conference on Recent Advances in Musculoskeletal Tissue Regeneration, Kyungpook National University Hospital, Daegu, South Korea (Invited Speaker) |
| 10.10.2022 | Alini Mauro: "Sound Induced Morphogenesis: A possible breakthrough in TERM", TERMIS-AP, Jeju, South Korea (Invited Speaker) |
| 18.10.2022 | Alini Mauro: "Fracture-related infection: Hydrogel-Antibiotics for treating bone infection", Biomaterials and Novels Technologies for Healthcare (BioMaH), Rome, Italy (Invited Speaker) |
| 30.11.2022 | Alini Mauro: "Sound waves for the assembly, control and stimulation of tissues organization", Rencontres annuelles des Groups de Recherche (GDR) Mecabio Santé et Réparer l'Humain Conférence, Paris, France (Invited Speaker) |
| 30.03.2022 | Gueorguiev Boyko: "Can anything be done to minimize the risk of fractures in the elderly?", AO Webinar: Osteoporosis – The Silent Killer (Online) |

22.06.-24.06.2022 Gueorguiev Boyko: "Current trends in research and the clinical setting on bone regeneration", 23rd EFFORT Congress, Lisbon, Portugal (Invited Speaker)

29.09.-02.10.2022 Gueorguiev Boyko: "Biomechanics and design of intramedullary nails", 15th Congress of the Bulgarian Orthopedic and Traumatology Association (BOTA), Burgas, Bulgaria (Invited Speaker)

29.09.-02.10.2022 Gueorguiev Boyko: "Why and how do locking plates fail?", 15th Congress of the Bulgarian Orthopedic and Traumatology Association (BOTA), Burgas, Bulgaria (Invited Speaker)

07.03.2022 Stoddart Martin: "Mechanical regulation of MSC chondrogenesis: Can we repurpose rehabilitation?", DBMR Research Conference, Bern Switzerland (Invited Speaker)

16.03.2022 Stoddart Martin: "Cells, Bioreactors and a Spacecraft: A Journey in Musculoskeletal Research", Institute for Biology ETHZ Seminar (Online)

22.03.2022 Stoddart Martin: "Outcome measures for bioreactors", University of Keele Bioreactor Course (Online)

14.04.2022 Stoddart Martin: "Cell Therapy for Cartilage Repair – Increasing Complexity of Cartilage Models", ICRS 2022 Berlin (Online)

29.06.2022 Stoddart Martin: "In vitro testing of bone biomaterials – opportunities and challenges", TERMIS EU 2022, Krakow, Poland (Invited Speaker)

20.09.2022 Stoddart Martin: "Regulating MSC differentiation using mechanics", International Trauma Symposium Ulm, Germany (Invited Speaker)

04.10.2022 Stoddart Martin: "Bone regeneration – Latest research at the AO Research Institute Davos", International Conference on Recent Advances in Musculoskeletal Tissue Regeneration, Kyungpook National University Hospital, Daegu, South Korea (Invited Speaker)

10.10.2022 Stoddart Martin: "Reproducing kinematic load in vitro for chondrogenesis studies", TERMIS AP 2022, Jeju, South Korea (Invited Speaker)

05.12.2022 Stoddart Martin: "Biology of bone healing", AO Trauma Course–Basic Principles of Fracture Management for Swiss Surgeons, Davos, Switzerland (Invited Speaker)

12.04.-15.04.2022 D'Este Matteo: "Bioinks with controlled fiber architecture modulating cell behaviour", World Congress ICRS International Cartilage Regeneration & Joint Preservation Society, Berlin, Germany (Invited Speaker)

04.09.-08.09.2022 D'Este Matteo: "cmRNAbone project: 3D printed-matrix assisted chemically modified RNAs bone regenerative therapy for trauma and osteoporotic patients", European Society for Biomaterials Conference 2022, Bordeaux, France (Invited Speaker)

11.10.&12.10.2022 D'Este Matteo: "Bioprinting and bioinks for musculoskeletal research @ARI", Webinar with Universidad de Conception Chile, title of the event: "Biomanufacturing of musculoskeletal tissues: from molecular biology to functional implants" (Online)

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| 18.10.-21.10.2022 | D'Este Matteo: "Towards deciphering neutrophils role in the immune response to biomaterials", Biomaterials and novel technologies for Healthcare BioMaH, Rome, Italy (Invited Speaker) |
| 07.11.2022 | D'Este Matteo: "Behind the scene scientific conferences", Webinar of the young scientists of the Scandinavian Society for Biomaterials (Online) |
| 20.05.2022 | Ernst Manuela: "AO Fracture Monitor: Bringing orthopaedic aftercare to the 21st century", Orthopaedica Belgica 2022, Bruges, Belgium (Invited Speaker) |
| 20.05.2022 | Ernst Manuela: "DEHST – Digitally Enhanced Hands-on Surgical Training Prototype" Orthopaedica Belgica 2022, Bruges, Belgium (Invited Speaker) |
| 13.06.2022 | Gehweiler Dominic: "Statistical Analysis of Complex Proximal Humeral Fractures", 23rd International Workshop on Quantitative Musculoskeletal Imaging (QMSKI), Noordwijk, Netherlands (Invited Speaker) |
| 07.09.2022 | Gehweiler Dominic: "In Vitro Methodology for Systematic CT Investigation of the Periclavicular Space", International Combined Orthopaedic Research Societies (ICORS), Edinburgh, UK (Invited Speaker) |
| 25.02.2022 | Grad Sibylle: "Chondrocyte and Stem Cell-Based Carilage Regeneration: Effect of Biomaterial and Biomechanics", McGill Seminar Series, Montreal, Canada (online) |
| 18.04.2022 | Grad Sibylle: "Translational spine research at ARI: Where preclinical studies address clinical questions", AO Spine KF Degenerative Webinar (online) |
| 22.06.2022 | Grad Sibylle: "Development of a 6-degrees-of-freedom bioreactor – The potential and challenges, ExcellMater / Premurosa Cluster Event Seminar, Belgrade, Serbia (Invited Speaker) |
| 27.06.2022 | Grad Sibylle: Biology of the Lumbar Intervertebral Disc" and "Cellular and Molecular Research", Eurospine EduWeek, Strasbourg, France (Invited Speaker) |
| 25.08.2022 | Grad Sibylle: "Delivery of therapeutics for intervertebral disc regeneration", RiseUs2 Winter School Riga, Latvia (Invited Speaker) |
| 30.09.2022 | Grad Sibylle: "The role of bioreactors in orthopaedic research – in compliance with the 3R guidelines", ExcellMater Biomaterials Workshop, Belgrade, Serbia (Invited Speaker) |
| 02.11.2022 | Grad Sibylle: "Hydrogels and scaffold for intervertebral disc repair", ExcellMater Topic School, Belgrade, Serbia (Invited Speaker) |
| 03.11.2022 | Grad Sibylle: "The role of bioreactors and the 3R rule", ExcellMater Topic School, Belgrade, Serbia (Invited Speaker) |
| 09.11.2022 | Grad Sibylle: "Next Generation Treatment", ORS PSRS Lightening Talk, Skytop, PA, USA (Invited Speaker) |
| 05.10.2022 | Serra Tiziano: "Sound programmable vasculature morphogenesis". TERMIS-AP 2022. Tissue Engineering and Regenerative Medicine International Society, Asia-Pacific Chapter Conference, ICC Jeju, South Korea (Invited Speaker) |

14.09.2022 Serra Tiziano: "Controlling morphogenesis by sound". Biointerfaces International Conference 2022, ETH Zurich, Zurich, Switzerland (Invited Speaker)

07.09.2022 Serra Tiziano: "Sound-based biofabrication strategies". International Combined Orthopaedic Research Societies (ICORS), Edinburgh, UK (Invited Speaker)

04.09.2022 Serra Tiziano: "Contactless and dynamic tuning of living materials". European Society of Biomaterials Conference. Bordeaux, France (Invited Speaker)

22.06.2022 Serra Tiziano: "A sound-based biofabrication platform for rapid orchestration of multicellular living systems". 23rd EFORT Congress, Lisbon, Portugal (Invited Speaker)

26.06.-29.06.2022 Varga Peter: "Systematic validation of finite element simulations of locking plate fixations", 27th Congress of the European Society of Biomechanics, Porto, Portugal (Invited Speaker)

26.06.-29.06.2022 Varga Peter: "On measuring implant fixation stability in ACL reconstruction", 27th Congress of the European Society of Biomechanics, Porto, Portugal (Invited Speaker)

07.09.-09.09.2022 Varga Peter: "Experimentally validated computer simulations of locking plate fixations for surgical education", International Combined Orthopaedic Research Societies (ICORS), Edinburgh, UK (Invited Speaker)

07.09.-09.09.2022 Varga Peter: "Relative Lateral Wall Thickness: An improved predictor for post-OP lateral wall fracture after trochanteric femoral fracture osteosynthesis", International Combined Orthopaedic Research Societies (ICORS), Edinburgh, UK (Invited Speaker)

06.12.2022 Varga Peter: "Biomechanical challenge", AO Trauma Course–Basic Principles of Fracture Management for Swiss Surgeons, Davos, Switzerland (Invited Speaker)

06.05.2022 Windolf Markus: "AO Fracture Monitor: Sensor zur individualisierten Nachbehandlung – Momentaner Stand", AO Trauma Dreiländertagung, Wien, Österreich (Invited Speaker)

07.09.-09.09.2022 Windolf Markus: "Continuous implant load monitoring", ICORS 2022, Edinburgh, UK (Invited Speaker)

*AO Research Institute Davos Preclinical Facility in Foreground with SPF Facility and Biogas Facility (covered in Solar power photovoltaic panels), with the AO Center in middle and Davos in the background.*

*Ariel view of AO Center in middle and ARI Preclinical Facility on the left with SPF Facility and Biogas Facility.*


*AO Research Institute Davos team, October 2022.*

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