Bone & Joint Program of the Department for BioMedical Research (DBMR)

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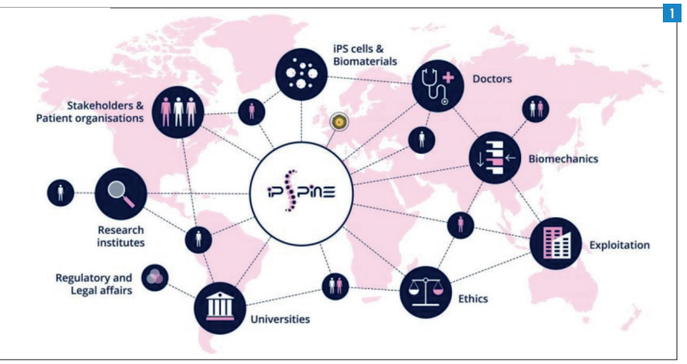

Schematic view of research partners in the ongoing project iPspine.

Research Profile

The skeletal system is subject to traumatic conditions (fractures, large bone defects) and pathology due to degeneration (osteoporosis, osteoarthritis, intervertebral disc degeneration). The demand for improved and efficient treatments are increasing as the population of the elderly grows and wants to stay physically active. Surgical procedures for the repair of large bone defects or degenerated spinal discs, however, still need tremendous improvements. The regeneration of skeletal tissues is the focus of the Bone & Joint Research Program. To this aim, strategies based on cells, materials, and growth factors are currently employed ex vivo (2D/3D cell cultures, bioreactors) and in vivo. Pioneering orthopedic surgery, which has been a long tradition in Bern, requires interactions between surgeons and scientists. The Bone & Joint Research Program will continue and extend this tradition and provide the clinicians with tools to improve the treatment of patients.

Intervertebral Disc Regeneration in Orthopedic Research

There are currently four competitive funded research projects active in the field of intervertebral disc regeneration or in the field of improved spinal fusion. Two of these research projects are funded by the horizon H2020 framework, one in the field, one by the Swiss National Science Foundation, and one by the center of Applied science and Molecular Medicine (CABMM). The first topic is on progenitor cell research and financed by iPspine, a 16 M € research project, which was funded to the consortiums

leader Prof. Marianna Tryfonidou, a leading veterinarian from the University Medical Center (UMC) Utrecht & Universiteit Utrecht (https://cordis.europa.eu/project/id/825925) 1. The iPSpine partners, which include both universities and companies, joined together in January 2019 to begin researching a new, advanced therapy for the treatment of LBP caused by disc deterioration. The ultimate aim of this project is to investigate and develop a new advanced biological therapy using a type of cell called induced pluripotent stem cells (iPSCs) (https://ipspine.eu). These cells are created by re-programming fully mature cells, such as cells from blood or skin, into spine-specific cells. Over the next five years, the iPSpine partners want to show that iPSCs can work as a therapeutic strategy. By the end of the project, the therapy should be ready for advancement to the first clinical trial in people. Within this highly cross-disciplinary consortium, our group was able to isolate primary cells isolated from human trauma IVDs with written consent from patients. These cells were then delivered to consortium partners at the INSERM in Montpellier and Nantes, France. These partners were able to derive novel iPS cell lines. These cell lines can be used for future cell therapy to possibly cure degenerated IVDs.

A second highlight is the investigation into engineered silk scaffolds for IVD repair. Here, a new project funded by the Swiss National Science has been started that targets regeneration of the IVD by using "cross-linked growth-factors and engineered" silk fibres and using knitting techniques developed by Dr. Michael Wöltje at the "Technische Universität Dresden, Institut für Textilmaschinen, und Textile Hochleistungswerktofftechnik", Dresden, Germany. 2

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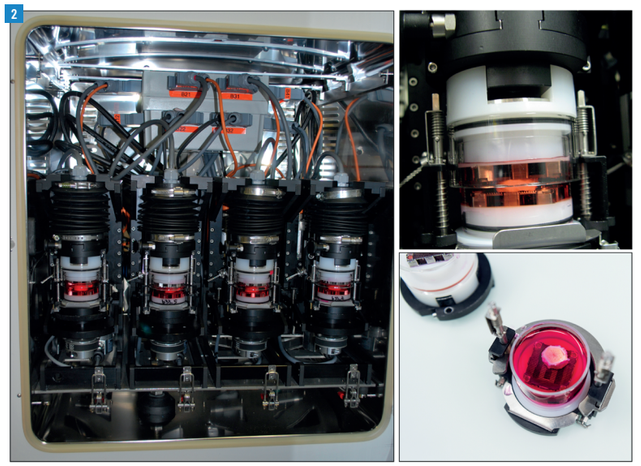

Specialized Bioreactor to apply compression and torsion for culturing entire units of bovine-derived intervertebral disc explants in organ culture under compression and torsion. Left inside incubator, upper right: close-up view of culture chamber, lower right: Inside view of culture chamber with positioned bovine coccygeal intervertebral disc. This device is worldwide unique.

A third key topic was started in Nov 2020, which involves artificial intelligence, statistical shape modelling and finite element modelling, and organ culture models for IVD regeneration 3: The 4M € funded "Disc4All" project aims to tackle this issue through collaborative expertise of clinicians; computational physicists and biologists; geneticists; computer scientists; cell and molecular biologists; microbiologists; bioinformaticians; and industrial partners (https://cordis.europa.eu/project/id/955735). It provides interdisciplinary training in data curation and integration; experimental and theoretical/computational modelling; computer algorithm development; tool generation; and model and simulation platforms to transparently integrate primary data for enhanced clinical interpretations through models and simulations. The consortium is led by the biomedical engineer Prof. Jérôme Noailly from the Universitat Pompeu Fabra (UPF) in Barcelona, Spain (https://www.upf.edu/web/disc4all). The Disc4All early-stage researchers will provide a new generation of internationally mobile professionals with unique skill sets for the development of thriving careers in translational research applied to multifactorial disorders.

Finally, the fourth topic is the development of a coccygeal rat non-fusion model for the intervertebral disc. Here, in collaborative efforts with the RMS foundation (Bettlach, SO), porous ceramics implants are currently being tested in an in-vivo rat animal model for spinal fusion. This project has been awarded in Dec 2021 with the best-poster award at the German Spine Society Conference. 4

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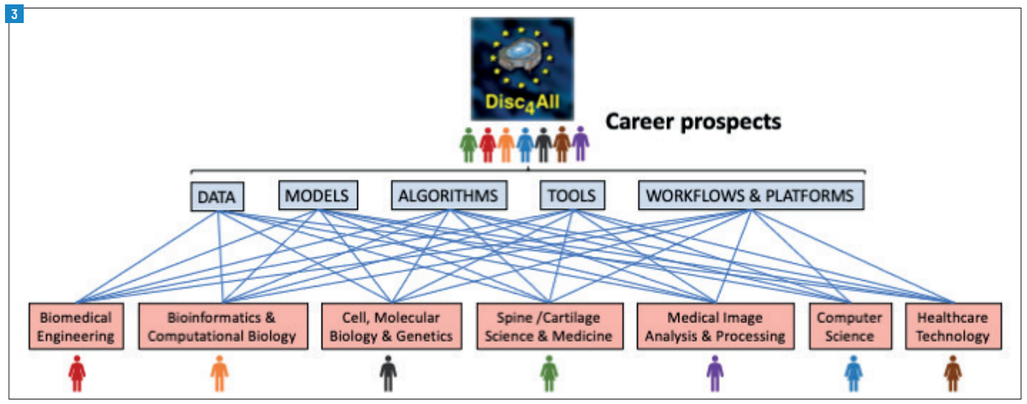
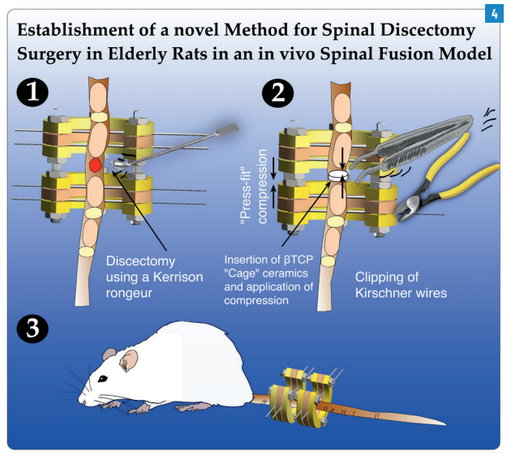


Illustration of the translational research ITN project "disc4all". It is a complex interaction of computer sciences, biologists and engineers to achieve major insights into the prevention of low back pain caused by intervertebral disc degeneration.



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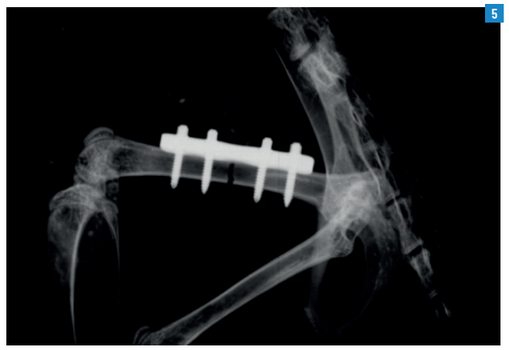
An overview of procedures of a newly established non-spinal fusion model. Spinal fusion in vivo animal model illustrating the concept of the procedure 1) discectomy of coccygeal intervertebral disc 2) placement of a ceramic of βTCP that was coated with cytokines 3) Schematic view of operated Wistar rat with fixator extern that applies compression to induce spinal fusion.



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X-ray of a fixed bone fracture in a large bone defect model in black six mice 12-week post-operation.

Bone Biology and Orthopedic Research

A further topic of interest in orthopedics is the healing of osteoporotic bone treated with bisphosphonates (BP), a class of drugs inhibiting osteoclastic bone resorption. In the past year, a mouse model of OVX and βTCP-filled femoral critical size defects was applied to investigate whether treatments with BP affect defect healing and biomaterial turnover were impaired. After harvesting all the tissue samples and preparation of the RNA, presently the outcomes are assessed by histomorphometry and 2nd Generation Sequencing. This work is performed by Franziska Strunz, Ph.D. student, and supported by a grant from the Alfred & Anneliese Sutter-Stöttner Foundation.

Gadolinium (Gd) is a component of contrast agents frequently used in clinical practice. Despite the frequent application, it is not clear, whether incorporation of Gd in tissues may cause negative long-term effects. In this project, the effects of ionized Gd and of complexed Gd on the development and activation of bone cell lineages are investigated. This work is performed by Franziska Strunz, Ph.D. student, in collaboration with Dr. Rainer Egli (Clinic of Diagnostic and Interventional Radiology) and supported by a grant from the Inselspital. In collaboration with Dr. Philippe Krebs (Department for Pathology, University of Bern) the effects of a deficiency in the Inositol-Polyphosphat-5-Phosphatase (SHIP1) on osteoclast development and activity is being assessed. SHIP1-deficient Styx mice are characterized by a low bone mass phenotype, and within this project, the cellular base for this phenotype is analysed in vitro and in vivo.

Cranio Maxillo Facial (CMF) Research

The interest of the Saulacic Research Group is focused on translational research. Key topics within the field of bone regeneration are the development of new biomaterials, assessment of the biocompatibility, and the influence of the biodegradation on guided bone regeneration.

The indication for a specific bone substitute material is related to the type and the stage of alveolar-ridge resorption. Vertical bone defects are considered the most demanding for reconstruction. The feasibility of simultaneous vertical bone augmentation using block grafts (bone ring) and implant placement was established in collaboration with Advance Research Center, The Nippon Dental University School of Life Dentistry at Niigata, Japan. In terms of osseointegration, single-stage implant placement with autogenous bone has been demonstrated as useful to shorten an overall treatment period. Different biomaterials in block form have been developed to avoid the use of the autogenous block bone grafts.

Selected Publications

[1] Croft AS, Roth Y, Oswald KAC, Ćorluka S, Bermudez-Lekerika P, Gantenbein B (2021). In Situ Cell Signalling of the Hippo-YAP/TAZ Pathway in Reaction to Complex Dynamic Loading in an Intervertebral Disc Organ Culture. International Journal of Molecular Sciences, 22, 13641.

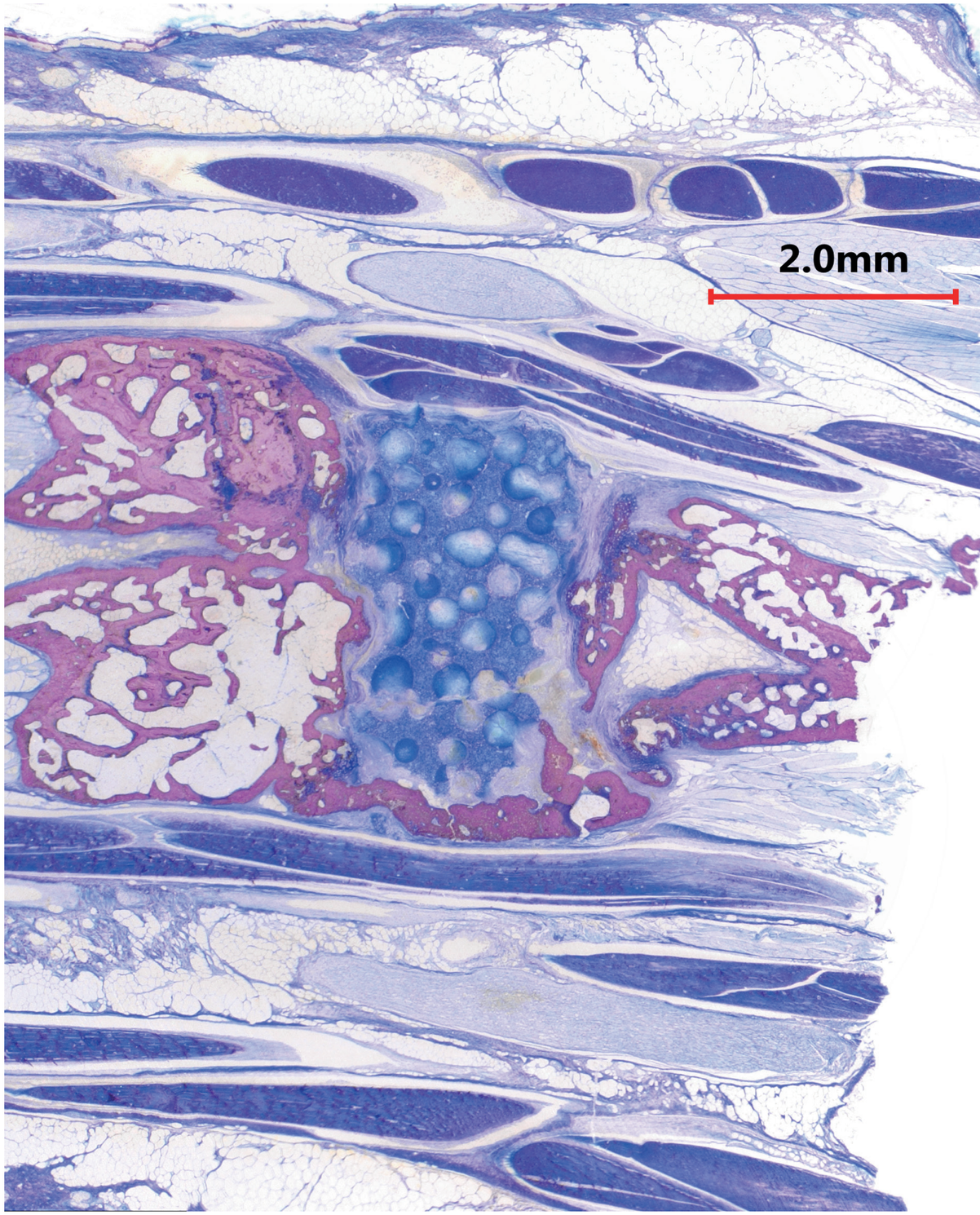
[2] Gantenbein B, May RD, Bermudez-Lekerika P, Oswald KAC, Benneker LM, Albers CE (2021). EGR2, IGF1 and IL6 Expression Are Elevated in the Intervertebral Disc of Patients Suffering from Diffuse Idiopathic Skeletal Hyperostosis (DISH) Compared to Degenerative or Trauma Discs Applied Sciences, 11, 4072.

[3] Guerrero J, Häckel S, Croft AS, Hoppe S, Albers CE, Gantenbein B (2021). The nucleus pulposus microenvironment in the intervertebral disc: the fountain of youth? European cells & materials, 41, 707-738, 3568.

[4] Lazarus E, Bermudez-Lekerika P, Farchione D, Schofield T, Howard S, Mambetkadyrov I, Lamoca M, Rivero IV, Gantenbein B, Lewis CL, Wuertz-Kozak K (2021). Sulfated Hydrogels in Intervertebral Disc and Cartilage Research Cells, 10.

[5] Saulacic N, Muñoz F, Kobayashi E, Chappuis V, Gonzáles-Cantalapiedra A, Hofstetter W (2019). Effects of local application of alendronate on early healing of extraction socket in dogs. Clin Oral Investig, 24, 1579-1589.

[6] Schnyder D, Albano G, Kucharczyk P, Dolder S, Siegrist M, Anderegg M, Pathare G, Hofstetter W, Baron R, Fuster DG (2021). Deletion of the sodium/hydrogen exchanger 6 causes low bone volume in adult mice Bone, 153, 116178.



Histology of Toluidin blue/Fuchsin Red staining of Tri calcium Phosphate (TCP) carrier implanted in a rat tail animal spinal fusion model of the elderly 12 weeks post-op. The carrier was only partially resorbed by addition of 1 µg/ carrier Bone Morphogenic Protein 2 (BMP2).