Tissue and Organ Mechanobiology

Benjamin Gantenbein, Head of Research Group
Email: benjamin.gantenbein@istb.unibe.ch
Phone: +41 31 631 59 51

Benjamin Gantenbein | Sufian Ahmad | Daniela Frauchiger | Shuping Gao | Silvan Heeb | Anna Krismer | Rahel May | Alessandro Marazza | Eva Roth | Adel Tekari | Simon Wuest

Research Partners

Dr med Sandro Kohl, Department of Orthopedics, Knee Team, Insel Hospital, University of Bern
PD Dr med Lorin Benneker, Department of Orthopedic Surgery & Traumatology, Spine, Insel Hospital, University of Bern
Prof Dr Klaus Siebenrock, Department of Orthopedics, Insel Hospital, University of Bern
Prof Dr Paul Heini, Spine Surgeon, Orthopedics, Sonnenhof Clinic
Prof Dr Stefan Eggli, Knee Surgeon, Orthopedics, Sonnenhof Clinic

Research Profile

The Tissue & Organ Mechanobiology (TOM) Group of the Institute for Surgical Technology and Biomechanics (ISTB), University of Bern, conducts translational research in the intersection of tissue engineering, biology and applied clinical research. The group's primary aim is to understand the cellular response onto biomechanical stimuli and how cellular communities are affected *in situ* using 3D tissue and organ culture models. Their research can be divided into two main foci: On the one hand the group investigates causes of low back pain due to intervertebral disc (IVD) degeneration and on the other hand the group focuses on the human knee. Where they aim to identify cell-based solutions for the delayed or the non-healing of ACL following injury (or rupture). The common focus of the TOM group is to advance *in vitro* organ culture models, which mimics as closely as possible the human situation and where regenerative therapeutic strategies, such as novel biomaterials and cells, can be tested in a most authentic *in vitro* set-up.

Intervertebral Disc Degeneration, Regeneration and Low Back Pain

The TOM group conducted research in the field of IVD research in the area of regeneration but also in the area of non-successful spinal fusion to understand the development of pseudo-arthrosis.
The group presented new research in two main directions (i.e. improve fusion or rescue/improve the disc cell phenotype) using *ex vivo* bioreactor research at the Biospine 5 Meeting, which took place in Berlin in April 2015. The main research foci of the group are understanding the balance between BMP agony and antagony and how IVD can be regenerated using BMP signaling. For this we use a combination of 3D tissue/organ culture approaches.
Furthermore, the TOM group received the best poster award at the International Society of the Study of the Lumbar Spine (ISSLS) meeting in San Francisco (8-12 June) on BMP signaling and possible involvement of BMP antagonists in the secretome of IVD cells. Current research is ongoing to identify the main proteins involved in the secretome and in this important signaling pathway.
In a Gebert Rüf financed project, a novel type of silk material is currently being investigated for IVD repair (Figures 1 and 2).
Here, the TOM group started to investigate into new growth-factor-enriched silk, which is produced from genetically transducted silk worms (*Bombyx mori*), which covalently link the growth factor of interest directly into the silk. The new biomaterial has been tested *in vitro* on disc cells and mesenchymal stem cells but also in our 3D bovine organ culture model and the complex loading bioreactor together with a fibrin hydrogel (Figure 3 is NPPC). Here, D. Frauchiger won the best poster award at the annual meeting of the Swiss Society for Biomaterials and Regenerative Medicine in Lausanne. The TOM group advanced further into the understanding of complex forces such as compression and torsion onto IVD cells in situ in organ culture. In a Swiss National Science Foundation project, we investigated towards the understanding of duration of mechanical loading for IVD cells. We investigated the effect of compressive loading (8h per day) on the IVD cells apoptosis. The group developed a strong *ex vivo* model using bovine IVD organ culture. This model has been used to explore fast and reliable models for disc degeneration using non-clinical relevant enzymes such as papain.

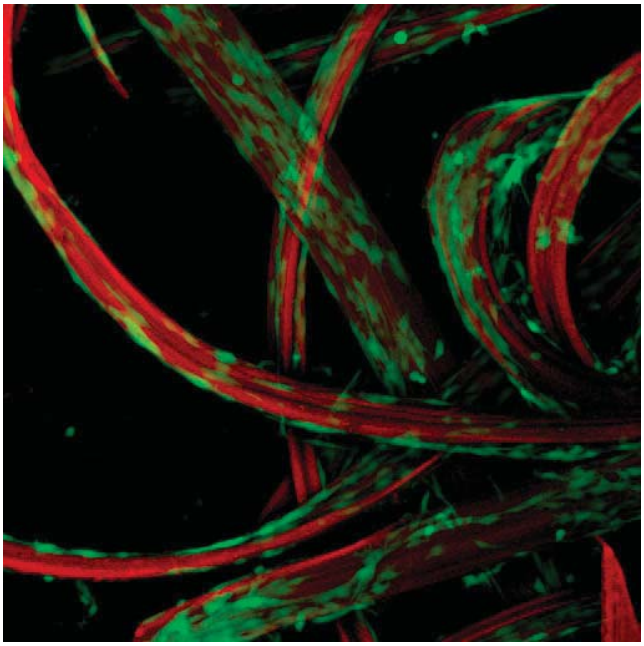

Figure 1. Z-projections of ~500 µm thick confocal laser scanning microscopy scans into GMP-compliant silk fleece with bovine intervertebral cells (annulus fibrosus cells). Cells were seeded onto 5x5mm² scaffold area and kept in culture for 4 days. Annulus fibrosus cells were stained with calcein-AM (green) and silk auto-fluorescences in the red wavelength range.

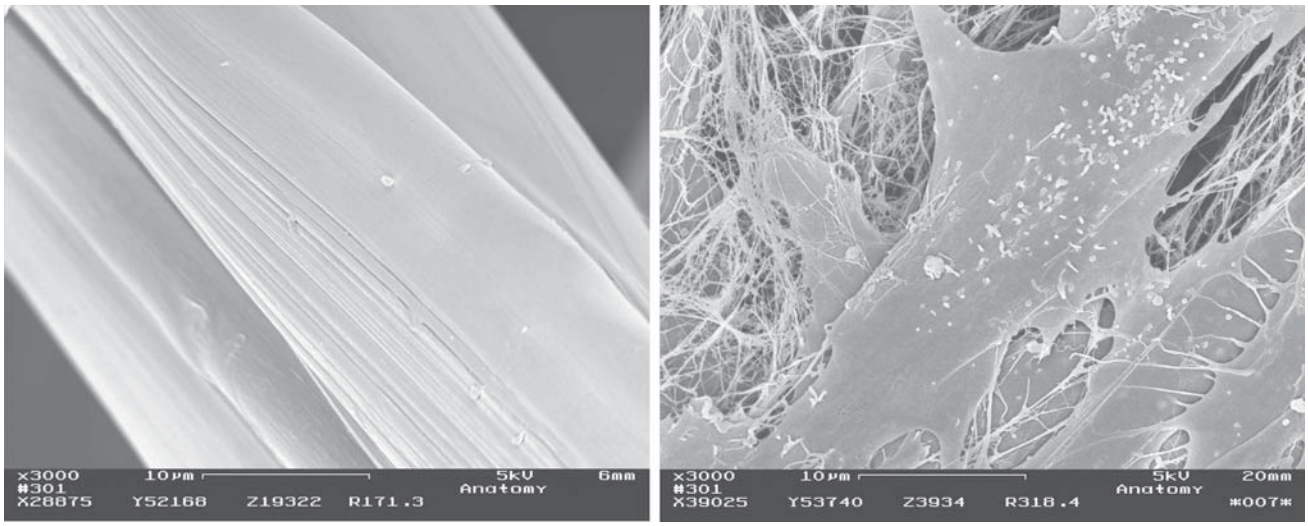

Figure 2. Scanning electron microscopy images of genetically engineered silk fibers (left) and seeded with human mesenchymal stem cells (hMSC) for 7 days (right) at 3000x magnification. The silk is obtained from ***Bombyx mori*** and is designed such that a growth factor known to drive hMSC towards a disc like phenotype is incorporated into the silk. Currently the silk is tested in our lab in cell culture and on bovine IVDs in organ culture to assess its suitability for disc regeneration and repair.

Finally, our group investigated in the nature of nucleus pulpous progenitor cells (NPPC). We concentrated on the presence of NPPC in bovine tail disc, their differential capacity (Figure 3) and their application potential for IVD regeneration..

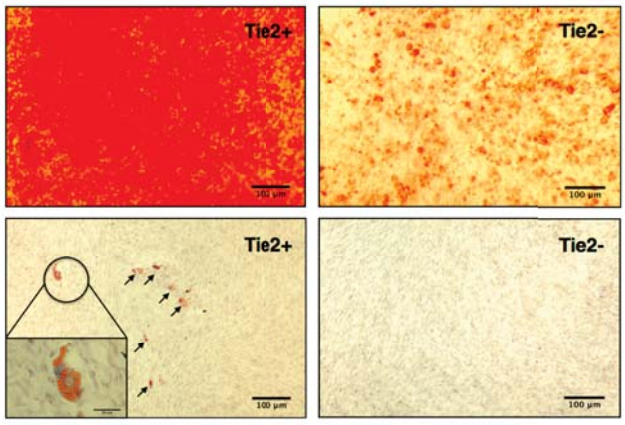

Figure 3. Bovine coccygeal-derived nucleus pulposus cells were isolated and sorted for the angiopoietin-1 receptor (Tie2). The obtained Tie2- and Tie2+ subpopulation of cells were subjected to differentiation assays ***in vitro*** to address their multipotency potential. After 3 weeks of culture, Tie2+ cells deposited an extensive mineralized matrix suggesting their osteogenesis, in contrast to Tie2- cells (top row). Similarly, only Tie2+ were able to differentiate into adipocytes and form lipid droplets as highlighted by arrows (bottom row).

Biological Repair of the ruptured Anterior Cruciate Ligament

ACL injuries are very common; in Switzerland the incidence of ruptures is estimated at 32 per 100,000 in the general population and in the sports community this rate more than doubles. Current gold standard for ACL repair is reconstruction using an autograft. However, this approach has shown some limitations. A new method has been heralded by the Knee Team at the Bern University Hospital (Inselspital) and the Sonnenhof clinic called Dynamic Intraligamentary Stabilization (DIS) which keeps ACL remnants in place in order to promote biological healing and makes use of a dynamic screw system. Here, cell-based approaches using collagen patches or application of platelet derived plasma (PRP) are of interest. The aim of this study was to investigate the use of collagen patches, the application of platelet rich plasma (PRP) and platelet rich fibrin (PRF) in combination with DIS to support regeneration of the ACL and to quantify the biological response. Furthermore, a novel bioreactor has been designed and realized to culture full human ACL.

Selected Publications

1. Chan SC, Tekari A, Benneker LM, Heini PF, Gantenbein B (2015) Osteogenic differentiation of bone marrow stromal cells is hindered by the presence of intervertebral disc cells. Arthritis Res Ther 18(1):29. doi: 10.1186/s13075-015-0900-2
2. Chan SC, Walser J, Ferguson SJ, Gantenbein B (2015) Duration-dependent influence of dynamic torsion on the intervertebral disc: an intact disc organ culture study. Eur Spine J : doi: 10.1007/s00586-015-4140-6
3. Gantenbein B, Gadhari N, Chan SCW, Kohl S, Ahmad S (2015) Mesenchymal stem cells and collagen patches for anterior cruciate ligament repair. World J Stem Cells 7(2):537-550 doi: 10.4252/wjsc.v7.i2.537
4. Gantenbein B, Illien-Jünger S, Chan SC, Walser J, Haglund L, Ferguson SJ, Iatridis JC, Grad S (2015) Organ Culture Bioreactors - Platforms to Study Human Intervertebral Disc Degeneration and Regenerative Therapy. Curr Stem Cell Res Ther 10(4):339-352
5. Frauchiger DA, Chan SCW, Benneker LM, Gantenbein B (2015) Repair of annulus fibrosus with genipin enhanced fibrin hydrogel and silk membrane fleece. European Spine Journal 24(3):624-660 doi: 10.1007/s00586-015-3794-4
6. Gao S, Tekari A, Gantenbein B. (2015) Assessment of bovine adipose-derived stem cells osteogenic and adipogenic differentiation in Normoxic and hypoxic conditions. 11th Swiss Stem Cell Network Annual Meeting, 29 June. Basel.
7. May R, Frauchiger DA, Gazdhar A, Geiser T, Benneker LM, Gantenbein B (2015) Non-Viral Gene Delivery of Growth and Differentiation Factor 6 (GDF6) to whole bovine Intervertebral Disc. European Spine Journal 24(3):624-660 doi: 10.1007/s00586-015-3794-4
8. Tekari A, Chan SCW, Wuertz K, Saikai D, Benneker LM, Grad S, Gantenbein B (2015) Tie2+ cells of the bovine Nucleus Pulposus are Progenitor Cells capable of differentiating into Osteocytes and Adipocytes. Global Spine J 05(A127): doi: 10.1055/s-0035-1554231
9. Evangelopoulos DS, Kohl S, Schwienbacher S, Gantenbein B, Exadaktylos A, Ahmad SS (2015) Collagen application reduces complication rates of mid-substance ACL tears treated with dynamic intraligamentary stabilization. Knee Surg Sports Traumatol Arthrosc doi: 10.1007/s00167-015-3838-7