Tissue & Organ Mechanobiology

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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 tissues 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 non-healing or delayed ruptures of the anterior cruciate ligament (ACL). The common focus of the TOM group is to develop *in vitro* organ culture models, which match closely the human situation and where regenerative therapy strategies, such as novel biomaterials and cells, can be tested in a most authentic *in vitro* set-up.

Intervertebral Disc Degeneration and Low Back Pain

The year 2014 has been a year of exploration of the new two degree of freedom bioreactor to test the importance of complex loading. The TOM group investigated further into the understanding of complex forces such as compression and torsion onto IVD cells *in situ in organ* culture. Here, we investigated towards the understanding of duration of mechanical loading for IVD cells. The team explored the effect of increased cell death by application of a duration of 8h of dynamic compressive loading. 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.

Furthermore, the group explored non-viral gene therapy as an option for IVD regeneration using growth and differentiation factor 6 (GDF6 = BMP13) as a primary target for differentiating human mesenchymal stem cells towards IVD-like precursor cells. Here, new approaches to deliver plasmid to target cells are under investigation.

In a Gebert Rüf financed project a novel type of silk material is currently being investigated for IVD repair. This futuristic sounding project attracted the attention of media, such as 20min.ch.

Silk is a very old and interesting biomaterial with high elastic properties and low allergenic potential once the amino acid sericin has been removed. 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 will be tested *in vitro* on disc cells and mesenchymal stem cells but also in their 3D organ culture model using the bioreactor for applying complex loading protocols.

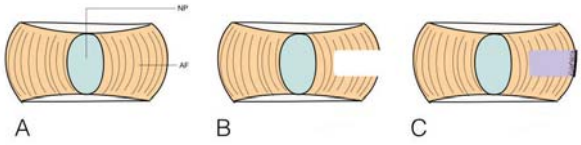

Fig. 1 Overview of disc repair approach using a hydrogel and silk fleece membrane composite. A. Intact disc with annulus fibrosus (AF) forming the outer fibrous ring and nucleus pulposus (NP) as gelatinous core. B. Round circular AF defect introduced by a biopsy punch. C. Defect filled with a fibrin based hydrogel and sealed with a silk fleece membrane composite.

Biological Repair of the Ruptured Anterior Cruciate Ligament (ACL)

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 increases more than double. 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 high interest. The aim of this study was to investigate the use of collagen patches, in combination with the application of platelet rich plasma (PRP) and platelet rich fibrin (PRF) together 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.

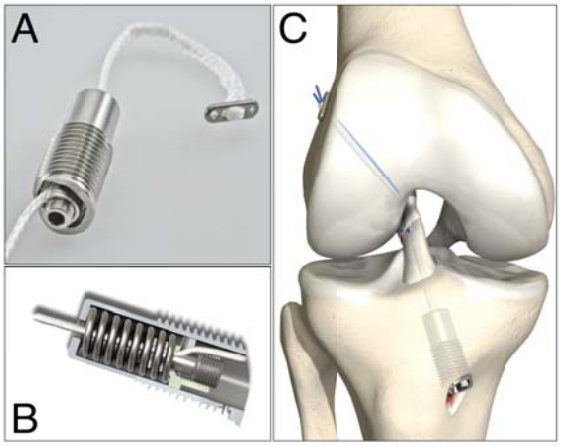

Fig. 2 Dynamic Intraligamentary Stabilization (DIS) screw called Ligamys© (Mathys, inc. Bettlach, Switzerland). A: Close-up of the outside of the screw made of titanium and illustrating with a mounted lace which mimics the polyethylene string that is mounted in the real surgery to stabilize the knee joint in case of an anterior cruciate ligament (ACL) rupture. B: Inside of the dynamic fixation screw with the spring that takes the dynamic load of the ACL and stabilizes the joint, C: Illustration of the exact position of the DIS *in situ* in the knee joint.

Fig. 3 Regenerative approaches for anterior cruciate ligament repair using patient's own blood. In order to accelerate ACL rupture healing, patient's autologous growth factors isolated and enriched from their blood are wrapped in a porcine-derived collagen 1/3 scaffold. Here is an overview of the preparation techniques. PRP isolation using commercial kit, B. PRP centrifuge, C. Specialized PRF centrifuge D. PRF box. E. PRF cut in pieces before application.

Exploring Ion Channel Communication under Microgravity[1]

Disuse or prolonged mechanical unloading of cartilage leads to enhanced degeneration. This is especially of concern for bed-ridden patients and astronauts while in space. Because cartilage has limited capacity for self-repair, restoration of damaged or degenerated cartilage remains a major clinical issue. Data from space experiments and experiments under simulated microgravity by using a so called Random Positioning Machine (RPM) suggest that mechanical unloading enhances the signs for degeneration and accelerates the phenotype dedifferentiation at the same time. Because the conversion of mechanical force into intracellular signal has not been fully elucidated yet, it is still not clear what mechanisms are responsible for the modifications of cartilage and chondrocytes to either real or simulated microgravity. Among other proteins, mechano-sensitive ion channels could play a crucial role in allowing the cell to detect external forces.

For future work a oocyte patch clamp device is further optimized to allow an electrophysiological examination of mechanosensitive ion channels, particularly under various gravitational loads as well as hypergravity. Furthermore the RPM shall be tested for its feasibility to modulate chondrocyte dedifferentiation. Thereby they also examine potential changes in the expression pattern of selected mechanosensitive ion channel genes that might occur under simulated microgravity conditions. This project is a collaboration with the CC Aerospace Biomedical Science & Technology, Space Biology Group, Lucerne, which also finances the PhD student.

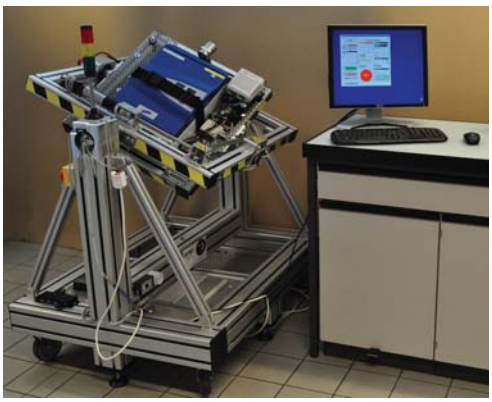

Fig. 4 Random Positioning Machine to simulate microgravity, which harbors an incubator for cell culture. (Picture courtesy of S. Wüest, CC Aerospace Biomedical Science and Technology, Space Biology Group, Lucerne University of Applied Sciences and Arts).

Selected Publications

1. Bertolo A., Gemperli A., Gruber M., Gantenbein B., Baur M., Pötzel T. and Stoyanov J., "*In Vitro* Cell Motility as a Potential Mesenchymal Stem Cell Marker for Multipotency", Stem Cells Transl Med. doi: 10.5966/sctm.2014-0156, 2014.
2. Gantenbein B., Calandriello E., Wuertz-Kozak K., Benneker LM, Keel MJ and Chan SC, "Activation of intervertebral disc cells by co-culture with notochordal cells, conditioned medium and hypoxia", BMC Musculoskelet Disord 15(1):422. doi: 10.1186/1471-2474-15-422, 2014.
3. Wuest SL, Richard S., Kopp S., Grimm D. and Egli M., "Simulated Microgravity: Critical Review on the Use of Random Positioning Machines for Mammalian Cell Culture", Biomed Res Int 2015. doi: 10.1155/2015/971474, 2015
4. Chan S., Calandriello E., Wuertz K., Keel M., Benneker LM and Gantenbein-Ritter B., "Coculture of Notochordal Cells with Nucleus Pulposus and Annulus Fibrosus Cells under Normoxia and Hypoxia", Global Spine J 04(S 01):st6.05 doi: 10.1055/s-0034-1376563, 2014.
5. Chooi WH, Chan SCW, Gantenbein-Ritter B. and Chan BP, "Cellular Stress Response of Intervertebral Cells to Compressive Loading. Proceedings of TERMIS-EU Meeting", 10-13 June. Genova, Italy, 2014.
6. Horovitz R., Ahmad S., Chan SCW, Kohl S. and Gantenbein-Ritter B. "Suitability of Common Collagen Scaffolds for Anterior Cruciate Ligament Repair", J Tissue Eng Regen Med 8(suppl 1):207-518 doi: 10.1002/term.1932, 2014.
7. Studer T., Fortunato G., Gadhari N., Frauchiger D., Rossi R. and Gantenbein-Ritter B., "Engineering niches for intervertebral disc cells using random and aligned silk nano-fibres", Proceedings of the Swiss Society of Biomaterials and Regenerative Medicine, 7-8 May. Basel, 2014.

[1]This project is an external collaboration and funded by the CC Aerospace Biomedical Science and Technology, Space Biology Group, Lucerne University of Applied Sciences and Arts.