Clinical problem

• Rupture of the anterior cruciate ligament (ACL) results in direct instability of the knee joint. The ACL is poorly vascularized and does not self-heal upon rupture. Therefore, it is often reconstructed with a patient’s own tendon.

• Post-operatively, the tendon undergoes a remodeling process, i.e. a transition from tendon to ligament tissue that often results in mechanical dysfunction. Consequently, many patients suffer from post-operative complications: 1) rupture of the graft, 2) knee instability caused by graft laxity and 3) meniscus and cartilage degeneration.

The key challenge

• At surgery, graft properties correspond with the native ACL. During the remodeling process post-op, mechanical properties deteriorate, tissue composition changes and the tissue transforms from highly anisotropic to isotropic. These features are characteristic of a fibrotic scarring process, and can explain the high prevalence of mentioned complications.

• The fundamental challenge is to deduce the cause and prevent declining mechanical properties during ligamentization by elucidating dysfunctional remodeling and to redirect it towards functional remodeling.

Hypotheses

To prevent adverse graft remodeling, the underlying causes for suboptimal remodeling need to be exposed. This project is based on two fundamental features that contribute to adverse remodeling events

- Stress deprivation contributes to the onset and progression of adverse graft remodeling

  During the first post-operative weeks, the knee is hardly loaded to prevent bone tunnel pull-out. Stress deprivation very likely contributes to the onset of fibrotic scarring and decreased graft mechanical properties.

- Cell polarity state drives remodeling of the reconstructed ACL

  Healthy tendon and ligament contain parallel collagen fibers that polarize cells by providing strong topographical cues. However, matrix disorganization destroys this topographical cue, transforming cell morphology from ‘spindle-shaped’ to ‘stellate’, which is known to progress fibrotic scarring.

Goal

• Graft remodeling is associated with stress deprivation and a loss of cell polarity and directionality, factors know to drive fibrotic scarring.

• Tools are thus required to 1) mechanically stimulate cells locally in stress deprived 3D tissue, 2) force a spindle-shaped cell morphology in 3D.

• The goal is thus to exploit magnetic microbeads, a direction-tunable strong topographical cue to polarize, orient and mechanically stimulate cells in 3D tissue.

• Upon binding of beads to cells, they will be embedded in tendon organoids (using an established platform) and magnetic actuation will train (cyclic movement) and orient the cells by forming beads-on-a-string (Fig 1).