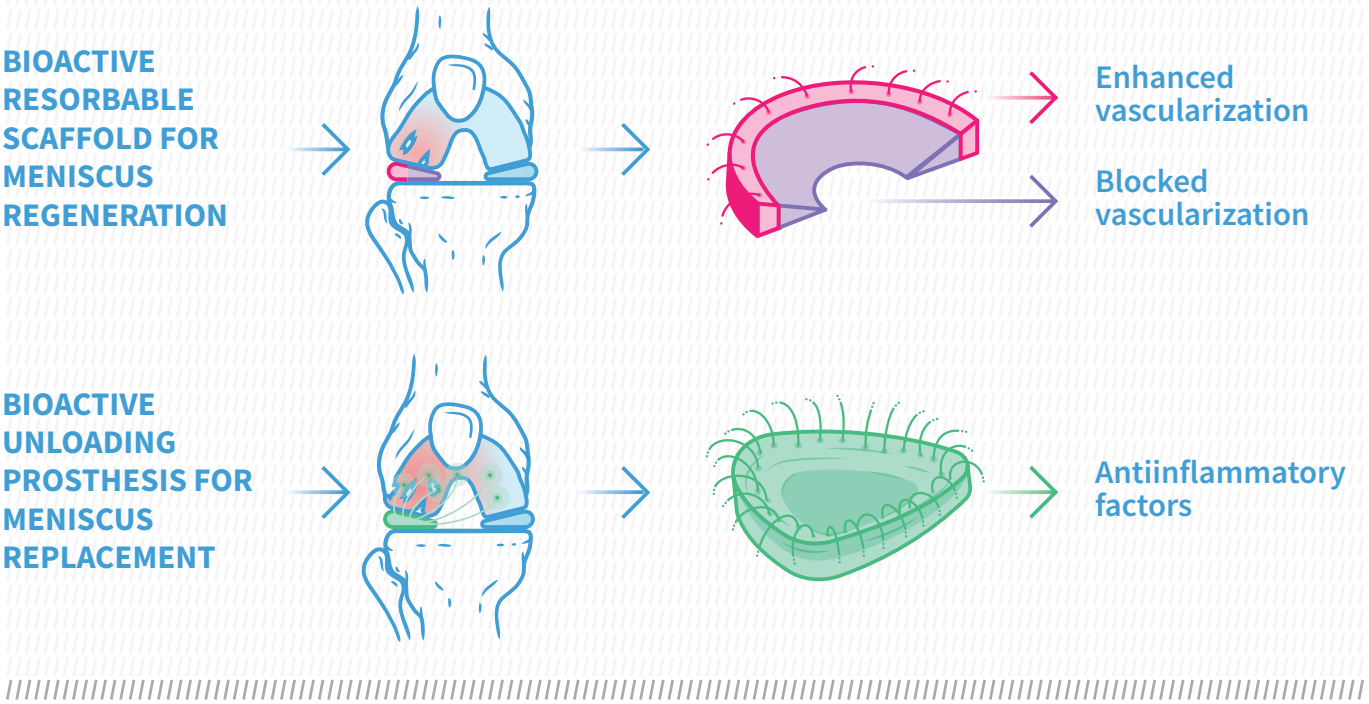
MEFISTO

Meniscal functionalised scaffold to prevent knee Osteoarthritis onset after meniscectomy

Final publishable summary



Summary of the context and overall objectives

Meniscal injuries are one of the most common orthopaedic disorders due to active lifestyles across all age groups. Current treatments like meniscal repair and replacement have limited indications, and meniscectomy (removal of the damaged meniscus), which is often the preferred approach, leads to poor clinical outcomes and progression to osteoarthritis (OA), especially in younger, active patients.

MEFISTO aims to prevent post-meniscectomy OA with innovative bioactive materials. Specific objectives include developing two treatment solutions: a bioactive degradable scaffold for younger patients and a non-degradable implant with drug delivery for older patients with advanced knee OA. In addition, a predictive treatment algorithm based on morphological profiling of meniscectomy patients is created and the socio-economic impact of the meniscus solutions analysed.

Work performed and main results achieved

For the morphological profiling of meniscectomy patients, clinical and MRI data were collected from 120 asymptomatic and 120 symptomatic patients. 240 accurate 3D post-meniscectomy knee models were created from manually segmented MRI scans. Neural networks were trained to automatically segment bone and cartilage from MRI scans. Landmark identification on the distal femur and proximal tibia was automated and validated. Statistical shape models were used to describe patient-specific bone morphology. The morphology-based predictive algorithm could accurately predict medial post-meniscectomy syndrome two years after partial meniscectomy.

Several approaches were taken to design and fabricate a bioactive, degradable, meniscal scaffold. A collagen bio-ink was used for 3D printing of dual-zone human-sized medial meniscal implants. Post-processing of the printed scaffolds was established, and printability was optimized for porosity and mechanical stability. Functionalization of the 3D printed collagen scaffold was achieved with peptide complexes and drugs that modulate angiogenesis and stem cell response. The active compounds were incorporated into the 3D-printed scaffolds in a zone-dependent manner, mimicking the anisotropic meniscus structure.

The 3D printed collagen meniscus implant required reinforcement for suturing, initially attempted with polymer structures within the scaffolds or wrapping with a collagen membrane. However, polymer reinforcement proved to be insufficient, leading to the adoption of collagen membrane wrapping. After post-processing and X-ray sterilization, the 3D printed and reinforced collagen menisci were subjected to physicochemical and mechanical characterization. In vitro tests evaluated cell infiltration, survival and the efficacy of the functionalizing compounds. Handling tests in a human cadaver knee showed that the size and shape of the meniscus prototypes could be adapted to a partially and a fully meniscectomized knee, but delamination of the collagen membrane occurred.

This led to a change in manufacturing from 3D printing to casting the collagen slurry. The casted scaffold was reinforced with a collagen membrane and re-characterized. Mechanical test results were similar to the 3D printed collagen samples, but with larger pore sizes and no delamination. Functionalized and neat collagen scaffolds were produced and sterilized. To test the functionalised and neat collagen scaffolds in vivo, the scaffolds were implanted into the medial menisci of 6 rabbits in a pars intermedia model (6-week endpoint). Medial menisci with collagen scaffolds and medial menisci from unoperated contralateral controls were harvested for histological evaluation. In addition, femurs and tibias were harvested from the legs to evaluate the cartilage surfaces of the operated and contralateral knees.

The results from the pars intermedia defect model indicate that pro-angiogenic functionalised scaffolds accelerate meniscal tissue regeneration compared to neat collagen scaffolds and are therefore able to better protect the underlying cartilage. Thus, functionalisation of the collagen scaffold with pro-angiogenic dendrimers has a beneficial effect on both meniscal regeneration and cartilage preservation potentially delaying the early onset of OA.

For the non-biodegradable meniscus implant, medical grade PCU implants were functionalized with an anti-inflammatory drug releasing polymer coating or with a combination of a dendrimer anti-inflammatory coating on the concave side and one promoting tissue growth at the convex side of the implant. In-vitro testing was used to assess the adequate drug loading, immunotoxicology, biocompatibility and efficacy of the PCU implants with

and without functionalization. The initial delamination of the polymer coating from the PCU substrate observed in vitro was improved by plasma treatment of the PCU surface.

Two in vivo pilot studies in sheep optimized implant fixation and coating stability. The surgical procedure was standardised for the final sheep study and specific packaging was developed for the dendrimer-coated implants to protect the functionalization. Sterile implants were provided for surgical implantation in four groups of 3 sheep each: meniscectomy, uncoated implant, anti-inflammatory polymer coating, and a dendrimer coating. The 3 sheep with the drug-releasing polymer coating had to be sacrificed prematurely, while the other groups reached the planned 3-month endpoint without any adverse events.

At sacrifice, tissue samples were collected from the sheep's knees for imaging and semi-quantitative histopathological analysis, which was performed on different areas of all knees. In addition, PCU implants were retrieved for scanning electron microscopy (SEM) analysis. Macroscopic and histomorphometric evaluation of the joint tissues analyzed showed that the dendrimer-coated implants resulted in better histologic scores compared to the uncoated implants and the meniscectomy group. While uncoated implants did not show a distinct protective effect compared to meniscectomy within the 3-month timeframe, longer-term studies may be necessary to fully elucidate their potential benefits given the demonstrated association between meniscectomy and cartilage degeneration. SEM analysis of the retrieved implants strongly suggests that the applied dendrimer coating led to a stabilization of the implant by promoting new tissue formation at the suture and convex areas thus minimizing wear of both tissues and implant.

A cost-effectiveness model was developed to evaluate the socio-economic impact of the two MEFISTO solutions in specific countries, using key performance indicators from stakeholder engagement.

Progress beyond the state of the art, results and potential impacts

Many patients experience severe symptoms after meniscectomy, and their knee is at risk of early degeneration, requiring joint replacement at a relatively young age. The morphology-based predictive algorithm developed in MEFISTO paves the way for a clinical decision support tool to help clinicians further optimise patient selection in a data-driven manner.

MEFISTO developed breakthrough coating technologies easily applicable to both non-degradable implants for total meniscectomy and biodegradable scaffolds for the regeneration of meniscus tears. The industrial feasibility of these coatings was demonstrated by scale-up production and compliant packaging and sterilisation procedures.

For the non-degradable implants, MEFISTO provides surgeons with key parameters required to stabilise implants during the surgery (suture fixation) and in the early phase after implantation.

www.mefisto-project.eu
info@mefisto-project.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 814444 (MEFISTO).