

# Meniscus Extracellular Matrix Formation Retained in Co-cultures of Meniscons and MSCs

Jasmijn Korpershoek<sup>1,2</sup>, Katherine Lydon<sup>1</sup>, Lucienne Vonk<sup>2,3</sup>, Caroline Struijk<sup>1</sup>, Aaron Krych<sup>1</sup>, Roel Custers<sup>2</sup>, Daniel Saris<sup>1,2</sup>  
<sup>1</sup>Mayo Clinic, Rochester, MN, USA; <sup>2</sup>University Medical Center Utrecht, Utrecht, The Netherlands; <sup>3</sup>Xintela AB, Lund, Sweden  
[Korpershoek.jasmijn@mayo.edu](mailto:Korpershoek.jasmijn@mayo.edu)

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**ABSTRACT INTRODUCTION:** The meniscus has a poor ability for endogenous repair, and meniscus injury is strongly correlated to the development of osteoarthritis in the knee. Therefore, cell therapies are emerging. Like articular cartilage, the meniscus contains cells surrounded by a pericellular matrix (meniscons) and these cells can be isolated intra-operatively using a rapid isolation protocol. Supplementing these autologous meniscons with allogeneic Mesenchymal Stromal Cells (MSCs) would enable one-stage applications for meniscus regeneration. Here, we aim to assess meniscus extracellular matrix formation in different ratios of meniscus-MSC co-cultures.

**METHODS:** Font is Times New Roman 8 point Font. Meniscons were isolated from redundant tissue that was obtained during total knee arthroplasty, that was digested using 0.75 units/mL dispase and 125 U/mL collagenase type 2 overnight at 37°C. Adipose-derived MSCs were provided by the GMP cell facility at Mayo Clinic and used at passage 4-6. 250 000 cells were mixed in various ratios, embedded in 100 µL fibrin glue, and cultured for 4 weeks in absence of growth factors. After this, constructs were digested using papain and DNA content (Pico Green assay) and proteoglycan content (DMMB assay) were quantified. Other constructs were embedded in paraffin and stained with Safranin-O and immunohistochemistry for type I collagen. All constructs were compared to 100% meniscus constructs.

**RESULTS:** After 4 weeks culture, constructs containing 100% meniscons had higher DNA content than 100% MSCs. Furthermore, proteoglycan content normalized for DNA was comparable between most constructs. Constructs consisting of 25% meniscus and 75% MSCs had significantly higher proteoglycan content, although there was a large donor variation. None of the constructs showed positive staining for safranin-O, similar to a healthy meniscus tissue control. All the constructs were positive for type I collagen.

**DISCUSSION:** MSCs can be used to partially replace meniscons without compromising meniscus extracellular matrix formation, and with even a higher normalized proteoglycan production in case 25% meniscons and 75% MSCs are used. Since cell yield of autologous meniscons intra-operatively would be insufficient for use in without expansion, supplementing with off-the-shelf available MSCs will allow translation of a single-stage procedure.

**SIGNIFICANCE/CLINICAL RELEVANCE:** This study demonstrates the initial feasibility of one-stage meniscus regenerative treatments using a combination of meniscons and allogeneic MSCs.

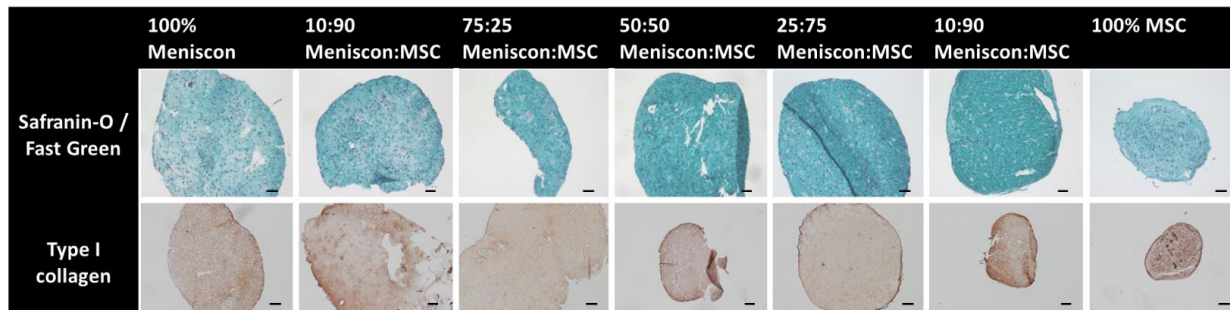


Figure 2. Safranin-O staining and immunohistochemistry to type I collagen of cultured meniscus constructs. Scale bar is 100 µm.

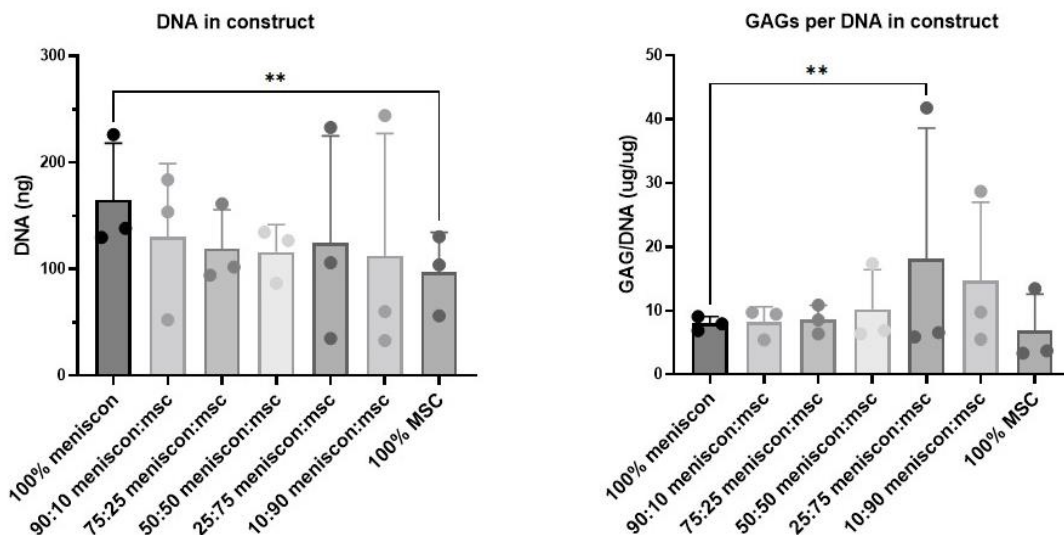


Figure 1. Proteoglycans and DNA in cultured meniscus constructs