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# Cell Therapy of Tendinopathy: Cell Tracking and Follow-Up Using MRI in an Equine Model

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**Summary**:
With MRI, it is possible to follow SPIO-labelled mesenchymal progenitor cells applied to tendons in vivo for up to 12 weeks.

**Abstract**:
INTRODUCTION
The treatment of tendinopathy is one of the biggest challenges in orthopedic surgery. The horse as the athlete among the animals suffers from degenerative tendinopathy and ruptures just like human athletes. The application of multipotent mesenchymal progenitor cells is among the most promising treatment options. Studies in equine patiens suggest that these cells promote tendon regeneration and reduce re-injury rates. However, the fate of the applied cells and their mechanism of action are not yet fully understood.

MRI is a standard modality for monitoring tendon healing and can be used for non-invasive cell tracking when cells are labelled with superparamagnetic iron (SPIO) particles. Visualization of SPIO-labelled cells in tendons is complicated by the hypointense MRI signal of healthy tendon tissue. We aimed to overcome this difficulty by applying an imaging technique using the “magic angle effect” and to perform cell tracking and parallel monitoring of tendon healing by MRI in the equine model for the first time.

METHODS
Tendon explants were seeded with different numbers of SPIO-labelled cells in vitro and subjected to MRI and histology (n=3). MRI was performed using low- and high-field magnets (0.27 T, 3 T and 7 T). Images were obtained in different sequences and with the tendons positioned at 90° and 54° angles to the magnetic field. Cell traceability was assessed and validated.

Thereafter, labelled progenitor cells were applied locally for treatment of tendon disease in 3 horses with induced tendinopathy and f3 horses with natural tendinopathy. Control tendons were injected with non-labelled cells or serum. Clinical, ultrasonographical and low-field MRI assessment was performed regularly. MRI was performed directly before and after cell application and at 2, 4, 8 and 12 weeks using T1-, T2*- and T2-weighted (w) as well as STIR sequences.

RESULTS
The in vitro study demonstrated that cells are traceable in tendon tissue by low- and high-field MRI. The magic angle effect lead to hyperintense signal from the tendon tissue, allowing to distinguish hypointense artefacts generated by

the labelled cells from the surrounding tendon. Quantitative image analysis showed good correlations between seeded cell numbers, the extent of hypointense artefacts in MRI and the extent of iron staining in histology. Sensitivity of cell detection strongly depended on the sequences and the field strength of the magnet used. In 0.27 T low-field MRI, T2*-w sequences obtained at 54° were most sensitive.
The in vivo study confirmed that the established MRI technique is feasible for cell tracking in the living animal. Hypointense artefacts related to the applied cells could be detected at the injection site directly after injection and remained visible during the follow-up in T2*-weighted images. Migration of cells to more distant locations was not evident. Good progress in tendon regeneration could be observed in T2-w and STIR images, matching the clinical and ultrasonographical findings.

CONCLUSIONS
Both the in vitro and in vivo study confirmed that MRI cell tracking is possible after injection of labelled cells. The results of this study are fundamental for the future treatment of human tendinopathy with cell therapy.