

HLA-independent use of mesenchymal stem cells for regeneration of bone: Preliminary results of a critical size defect study in the sheep tibia

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INTRODUCTION: Mesenchymal stem cells (MSC) from bone marrow represent an attractive cell source for tissue engineering purposes such as the regeneration of bone. With regard to a lack of expression of immunological relevant surface antigens, this cell type might even be available for HLA-independent (i.e. allogenic) transplantation¹. Although immunosuppressive properties have been demonstrated *in vitro*² and xenogenic MSC show an engraftment after transplantation in immune-competent mice, it remains unclear if HLA-mismatched MSC contain a re-generation potential equal to autologous MSC.

METHODS: After isolation, *in vitro* expansion and cultivation on mineralized collagen as described earlier³, xenogenic human and autologous ovine MSC were transplanted in a 3.0 cm metaphyseal tibia defect of Swiss mountain sheep. Animals were sacrificed after 3 (2 animals per group) and 6 months (5 animals per group). Unloaded mineralized collagen served as control. Radiography was performed every 2 weeks, after euthanasia histological evaluation was performed (including *in-situ* hybridization for detection of human MSC).

Bone regeneration was measured as percentage of the defect size filled with mineralized bone using the digital image software analysis program *GIMP*. For histological analysis areas presence of bone tissue was determined semi-quantitatively.

RESULTS: At the time of data evaluation, radiographic results up to 12 weeks *p.o.* were available of all sheep included in the present study (and 5 sheep up to 24 weeks), while histology was available for the short running group of animals (3 months) and for 4 sheep of the long running group (6 months).

Radiographies revealed a significant increase of bone formation in the autologous group after 8 weeks *in vivo* with a further increase up to week 12, while in the xenogenic group a increase could not be detected before week 12. Nevertheless, the amount of bone detected in radiographies was

higher in the xenogenic group compared to unloaded scaffolds.

Only scaffolds loaded with MSC showed islands of mature bone tissue in the center of the defect (Fig.1B-D). No comparable bone formation was found in controls without MSCs.

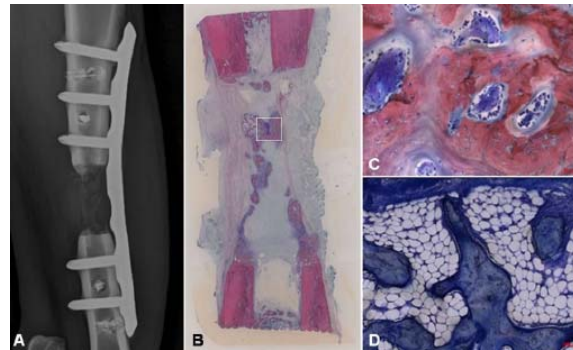


Figure 1: x-ray 12 weeks after surgery (A) and histology (B-D) of sheep treated with autologous MSC

DISCUSSION & CONCLUSIONS: Although no severe adverse effects of xenogenic MSC have been observed, the use of HLA-mismatched MSC seems to lead to reduced amounts of regenerated bone compared to autologous MSC. Nevertheless engraftment of these cells could also be demonstrated. However, these findings need to be seen in context with the preliminary character of the present study and further investigation will have to elucidate the issue.

REFERENCES:

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