

Mesoangioblast Stem Cells in Regenerative Therapies

T.Q. Kajhøj^{1,2}, EM. Füchtbauer¹, H. Løvschall²

¹*Department of Molecular Biology, Faculty of Science, Aarhus University, Aarhus, DK,*

²*School of Dentistry, Faculty of Health Sciences, Aarhus University, Aarhus, DK*

INTRODUCTION: Mesoangioblasts are stem cells with mesodermal differentiation potential. They were originally isolated from dorsal aorta of mouse embryos but can also be isolated from postnatal blood vessels. *In vitro* and *in vivo* studies show that mesoangioblasts can differentiate into a wide variety of mesodermal cell types even after clonal selection and many passages in cell culture.

The ease of mesoangioblast cultivation and expansion, their differentiation potential and their low ectopic differentiation make these stem cells obvious targets for therapeutic gene modification.

This PhD project is divided into two parts and explores the skeletal myogenic and the osteogenic potentials of mesoangioblasts and aims to use these cells in regenerative treatment of Duchenne Muscular Dystrophy and for reconstruction of oro-facial defects.

METHODS: Mesoangioblast differentiation is evaluated both in culture and *in vivo*. All *in vivo* work is done on mice. For oro-facial reconstruction mesoangioblasts are currently evaluated for attachment, proliferation and differentiation on hydroxypaptite/tricalciumphosphate (HA/TCP) in culture. Mesoangioblasts expressing BMP2 attached to such granules will be inserted in dorsal subcutaneous pockets, in gingival pockets and in subperiosteal bone defects to assess *in vivo* osteogenic differentiation.

For the therapeutic use in Duchenne Muscular Dystrophy mesoangioblasts are engineered into retroviral packaging cells for a micro dystrophin. Such mesoangioblast packaging cells will be administered systemically to dystrophic mice and muscle fibers will be analyzed histologically and immunochemically. Methods for systemic delivery of cells are being analyzed with the aim to efficiently deliver cells to all affected sites of the body.

RESULTS: In culture we observe a better spreading and attachment of mesoangioblasts to

HA/TCP pre-conditioned with serum or serum containing medium. Additionally, the granula size and composition of HA/TCP makes a remarkable difference in the amount of cells attaching and adhering after 24 hours. Mesoangioblasts expressing BMP2 are under development and are to be compared to original mesoangioblasts in culture and *in vivo*.

Mesoangioblast packaging cells have been shown to work in culture in a transient protocol in which they were able to transduce receiver 3T3 NIH cells. In order to test mesoangioblast packaging cells *in vivo* on dystrophic model mice cells must be engineered into stable packaging cells.

Intra cardial injection of mesoangioblast for systemic distribution of cells has been tested and found inefficient for the distribution of cells to skeletal muscle.

DISCUSSION & CONCLUSIONS: An important perspective for the therapeutic use is the specific delivery of cells to sites of damage. In the case of Duchenne Muscular Dystrophy damage sites are widely distributed throughout the body whereas in the case of oro-facial defects damage sites are localized in one region of the body. It is our hope that implementing an intra arterial cell injection will result in a more efficient regional cell delivery and improved regenerative treatment.

REFERENCES: Minasi, M. et al., Development (2002); (129): 2773-83 ; Sampaolesi, M. et al., Science (2003); (301): 487-92 ; Sampaolesi M, et al., Nature (2006); 444(7119); 574-9 ; Vohra, S. et al., J Mater Sci: Mater Med 2008; (19):3567-74

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