Stem Cells and the Treatment of Spinal Cord Injury: a Preclinical and Clinical Study
Eva Syková, Pavla Jendelová, Aleš Homola
Corresponding Author: sykova@biomed.cas.cz
Institute of Experimental Medicine ASCR and Center for Cell Therapy and Tissue Repair, Charles University, Prague, Czech Republic

Introduction
In the last decade, both embryonic and adult stem cells have been the subject of widespread investigation due to their therapeutic potential in brain and spinal cord injury (SCI). Mesenchymal stem cells (MSC), olfactory ensheathing glia (OEG) and neural progenitor cells (PNC) from embryonic or fetal tissue have the capacity to migrate towards lesions and induce better regeneration. Our preclinical studies revealed their capacity to improve regeneration and function after SCI, leading us to initiate a non-randomized phase I/II clinical study in 2003 (1).

Materials and Methods
We used a balloon-induced compression lesion (SCI) in adult Wistar rats, followed by the transplantation of mononuclear cells (BMC), MSC, OEG or PNC labeled in culture with iron-oxide nanoparticles; in vivo MRI was used to track their migration and fate. After acute (7 days post-injury) or chronic (5 weeks post-injury) transplantation, the animals were tested using the BBB (motor) and plantar (sensory) tests once a week for up to 6 months. Human patients with subacute SCI (up to 30 days post-injury) or with chronic complete cervical or thoracic SCI received a transplant 10 to 467 days post-injury. Patients received cells within 5h of harvesting either intravenously or intra-arterially by catheterization of a. vertebralis. BMC were separated via sedimentation and about 150 x 10^6 cells were adjusted to a final volume of 20-30ml (i.a.) or 500ml (i.v.). Follow up examinations were done at 3, 6, and 12 months after implantation by 2 independent neurologists using the ASIA score, MRI, MEPs and SEPs.

Results
In rats, the implantation of all cell types resulted in significantly smaller lesions and higher BBB scores. The transplantation of BMC, MSC, OEG or PNC labeled in culture with nanoparticles and tracked by in vivo MRI proved that all cell types migrated into the lesion and survived there for several months. Comparing the effects of implanted BMC, PNC, OEG and MSC showed that there were no significant differences among the cell types. All the implanted rats significantly improved motor and sensory function and had significantly smaller lesion cavities. Autologous BMC implantation was therefore used in a Phase I/II clinical trial in patients with acute or chronic SCI (n=34). The results show that implantation is safe and has a beneficial effect if administered in the first 4 weeks after injury, although mild improvement of the ASIA score was found in patients even 467 days post-injury. However improvement was found only after intra-arterial application close to the injury site in patients with cervical lesions (80% of patients improved their ASIA score and evoked potentials).

Discussion and Conclusions
Our clinical trial showed that implantation was safe, the therapeutic window extended up to 3-4 weeks post-injury, intra-arterial administration led to better results than did intravenous injection, and significant improvement was observed in 80% of acute patients with cervical lesions implanted by i.a. administration. Final conclusions about the functional outcome of this therapy, however, cannot be drawn from this small and heterogeneous group of patients. Future therapy will include a combination of cell therapy and lesion bridging.

References

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Disclosures
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