Research Profile

Kirsten Haastert

1994	Intermediate diploma in Biology Heinrich-Heine-University, Düsseldorf, Germany
1999	State examination in Veterinary medicine University of Veterinary Medicine, Hannover, Germany
2002	Doctorate, Dr. med. vet., Clinic for Neurosurgery, Hannover Medical School and Institute for Pharmacology, Toxicology and Pharmacy, University of Veterinary medicine Hannover, Germany
since 2002	Research Associate at the Institute of Neuroanatomy, Hannover Medical School, Hannover, Germany
2005	Research stay (07-10 2005) at the University of California, Los Angeles, USA, Department of Physiological Science & Department of Neurosurgery, David Geffen School of Medicine (Prof. Fernando Gomez-Pinilla)
2009	State doctorate with Specialism Anatomy (Habilitation, Venia legendi in Anatomie), Hannover Medical School, Germany

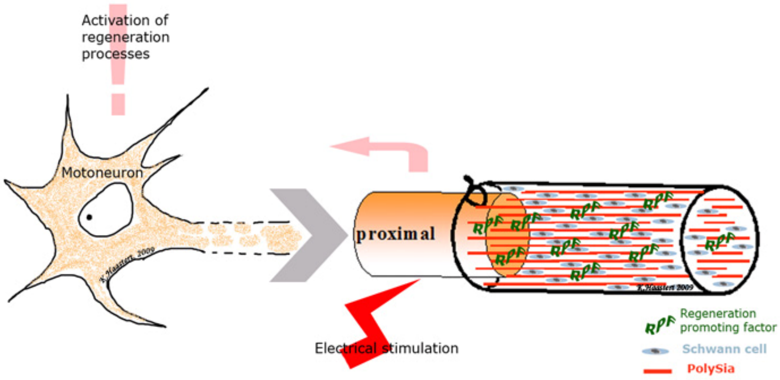
Research Topic

Development of alternative tissue-engineered nerve grafts and therapies for the reconstruction of extended peripheral nerve gaps.

The concepts aim to (1) improve peripheral nerve regeneration after the standard therapy of nerve autotransplantation and (2) to replace autologous nerve transplants which are only available in limited amounts. The term "tissue-engineering" describes the combination of biomedical materials with the transplantation of cells to replace lost tissue. For the reconstruction of peripheral nerves, tubular transplants are needed which could be sutured between the separated nerve stumps and would guide the regenerating axons towards the distal nerve stump and the denervated target tissue. The enrichment of the graft with regeneration-promoting factors provides further possibilities to increase the outcome of regeneration. To lines of investigations will be explained in more detail below.

Figure 1: Current research concepts.

Electrical stimulation of the proximal nerve stump directly prior to reconstruction of long nerve gaps is investigated for its potential to activate regeneration of motoraxons. PolySialic acid (PolySia) from bacterial origin in its soluble form as well as PolySia-nanofibres or PolySia-nanoparticles is evaluated with regard to the development of new biomaterials for nerve grafts (project embedded into two working packages of DFG-FOR 548 (grants to Prof. Grothe), speaker Prof. Gerardy-Schahn). Regeneration promoting factors may either be covalently bound to or released from the graft material or delivered via genetically modified transplanted Schwann cells.



1. Impact of electrical stimulation of the proximal nerve stump on motor recovery after reconstruction of long nerve gaps

During the last years we investigated several ways to increase peripheral nerve regeneration across long gaps. We demonstrated before that regeneration promoting growth factors like fibroblast growth factor-2 can be increased at the site of nerve reconstruction by ex vivo gene therapy. Electrical stimulation of the proximal peripheral nerve stump prior to end-to-end coaptation or tubular bridging of small nerve gaps has been reported to increase preferential motor reinnervation and functional motor recovery. My group investigates the effects of electrical stimulation on regeneration across long, 13 mm peripheral nerve gaps in rats. We combine electrical stimulation to the standard therapy, nerve autotransplantation, as well as to nerve reconstruction with Schwann cell filled synthetic nerve grafts. The outcome of regeneration is studied on a functional (electrodiagnostic measurements) as well as on a histomorphometrical level (number of regenerated myelinated axons, nerve fibre density and g-ratio of regenerated myelinated axons).

Electrical stimulation is a clinically easy achievable treatment and will be combined with other experimental strategies (see Fig.1) in the future, if its positive effects prove also to be relevant in long gap peripheral nerve regeneration.

2. Impact of a truncated C3bot-Peptide on peripheral nerve regeneration

The Clostridium botulinum C3 exoenzyme (C3bot) causes inactivation of the cellular functions of Rho. Truncated C3bot-fragments of 29 aminoacid fragments demonstrate a Rho-independent effect on axonal growth and axonal branching in vitro which seems to be restricted to specific neuronal subtypes. In cooperation with the Institute of Toxicology (Prof. Dr. Ingo Just) at the Hannover Medical School my group investigates the effects of single C3bot-Peptide application at the lesion site on peripheral nerve regeneration. In a pilot study, 10 mm nerve gaps in adult rats were bridged with autologous nerve tissue and in the proximal as well as in the distal suture site 20 µl of C3bot-Peptide solution were applied. First results indicate an increase in motor recovery in the C3bot-Peptide treated animals in comparison to the vehicle treated control animals. Currently additional animals are under investigation. Future studies will be done in a nerve crush model to systematically compare C3bot-Peptide application in different dosages to C3bot-wildtype application, the application of nerve growth factor as a positive control as well as vehicle-controls. Functional as well as histomorphological evaluation will be done.

C3bot-Peptides are supposed to cause much less adverse effects as a cell-permeable form of C3bot-wildtype (Cethrin®) which is currently under clinical phase II investigation for the treatment of spinal cord injuries. Therefore, incorporation of C3bot-Peptides may prove to be a candidate regeneration promoting factor for incorporation into peripheral nerve grafts.

Selected publications:

Haastert, K., Lipokatic, E., Fischer, M., Timmer, M., Grothe, C. (2006) Differentially promoted peripheral nerve regeneration by grafted Schwann cells over-expressing different FGF-2 isoforms. Neurobiol of Dis *21(1), 138-153.*

Haile, Y., Haastert, K., Cesnulevicius, K., Stummeyer, K., Timmer, M., Berski, S., Drager, G., Gerardy-Schahn, R., Grothe, C. (2007) Culturing of glial and neuronal cells on polysialic acid. Biomaterials *28 (6), 1163-1173.*

Haastert, K., Mauritz, C., Chaturvedi, S., Grothe, C. (2007) Adult human and rat Schwann cell cultures - fast and efficient enrichment and highly effective non-viral transfection protocol. Nature Protocols *2 (1), 99-104.*

Haastert,K., Ying,Z.., Grothe,C., Gómez-Pinilla,F. (2008) The effects of FGF-2 gene therapy combined with voluntary exercise on axonal regeneration across peripheral nerve gaps. Neurosci Lett 443(3):179-83.

Haastert, K., Grosheva, M., Angelova, S., Guntinas-Lichius, O., Skouras, E., Joern, M., Grothe, C., Dunlop, S., Angelov, D.N. (2009) Schwann cells over-expressing FGF-2 alone or combined with manual stimulation do not promote functional recovery after facial nerve injury.J Biomed Biotechnol 2009: 408794

Schmitte, R., Stein,V.M., Schenk, H., Flieshardt, C., Tipold,A., Grothe, C. Haastert, K., Genetically modified canine Schwann cells – in vitro and in vivo evaluation of their suitability for peripheral nerve tissue engineering. J Neurosci Meth *2009 Dec 3. [Epub ahead of print]*

Haastert, K., Joswig, H., Jäschke, K.-A., Samii, M., Grothe, C. Nerve repair by end-to-side nerve coaptation - histological and morphometrical evaluation of axonal origin and functionality in a sciatic nerve model in rats. Neurosurgery *in press.*

Group structure:

Group leader: PD Dr. Kirsten Haastert

Doctoral fellows: Dipl. Biol. Janett Schaper-Rinkel (ZSN-PhD-student), Nele Korte, DVM

Bachelor students: Annelie Handreck, Irene Bauer, Eghlima Kiaei

Technicians: Gesa Hellmich, Silvana Taubler-Gerling

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