5 ZUSAMMENFASSUNG

Die Entwicklung und Regeneration des zentralen Nervensystems wird durch sogenannte Leitmoleküle gesteuert. Diese wirken in vielfältiger Weise entweder anziehend oder abweisend auf auswachsende Neurone, deren umgebendes Zellmilieu und sich vermehrende Zellen und führen so zu einem Wachstumsstop, bzw. Zelltod oder zu Zellwachstum und –vermehrung.

In dieser Arbeit wurde das kürzlich gefundene repulsive guidance molecule (RGMa) charakterisiert. Dieses ist zuvor im retino-tectalen System von Hühnern studiert worden, wo es selektiv das Auswachsen temporaler, nicht aber nasaler Fasern hemmt und im Auswachs- und Streifenassay zu einem Kollaps der Wachstumskolben führte. Die Zielsetzung dieser Arbeit beinhaltete den generalisierbaren Nachweis von RGMa und einer gleichartigen Wirkung auch im ZNS von Nagetieren als einen weiteren Schritt zur vollständigeren Charakterisierung dieses Leitmoleküls. Es wurden mittels Immunhistochemie und in-situ-Hybridisierung Studien zur Distribution im Hirn durchgeführt und darauffolgend in vitro assays, die die Rolle und Funktion von RGMa im entorhino-hippocampalen System während der Entwicklung und nach entorhinaler Cortexläsion untersuchten.

Das RGMa-Protein wird auf Neuronen des Cortex, hier insbesondere in den Schichten 3 und 5 des entorhinalen Cortex, sowie auf Hilusneuronen des Hippocampus exprimiert. Die aufgrund der zusätzlichen Distribution des Moleküls im Gyrus dentatus auf Fasern der inneren Molekularschicht angenommene Funktion als repulsiver Faktor auf einwachsende Fasern aus dem entorhinalen Cortex bestätigte sich. Der repulsive Effekt wurde durch in vitro Experimente wie Streifen- und Auswachsassays sowie durch entorhino-hippocampale Co-Kulturen nachgewiesen. Der selektive, inhibitorische Effekt von RGMa auf auswachsende Fasern von Neuronen aus dem entorhinalen Cortex konnte in den Auswachsassays demonstriert werden. In den Streifenassays konnte gezeigt werden, dass RGMa die Faszikelbildung induziert und die Richtung des Wachstums der Neuriten beeinflusst, indem es auf Fasern aus dem entorhinalen Cortex repulsiv wirkt. RGMa retiniert die entorhinalen Fasern in ihrer Terminierungszone - der äußeren Molekularschicht des Gyrus dentatus. Dieser Effekt konnte durch gezielte Unterbrechung der RGMa-Wirkung in den Co-

Kulturen aufgehoben werden, was in vitro zu einem überschiessenden Auswachsen der Neuriten und damit zu einer gestörten Entwicklung der entorhino-hippocampalen Formation führte.

Nach entorhinaler Cortexläsion, die zu einer selektiven Durchtrennung und nachfolgendem Absterben der Fasern führt, die in der äusseren Molekulärschicht terminieren, kommt es zu einer verstärkten Expression von RGMa auch im adulten Hippocampus. RGMa-Protein wird nach entorhinaler Cortexläsion im Hilus des Hippocampus und in der inneren Molekularschicht wieder vermehrt exprimiert, nachdem die Expression nach Abschluss der embryonalen Entwicklung im adulten Tier auf ein Basisniveau zurückgewichen ist. Hieraus kann für RGMa eine Wiederaufnahme der repulsiven Funktion, die es während der embronalen Entwicklung hatte, in der Phase posttraumatischer Regeneration abgeleitet werden.

Insgesamt konnte am Beispiel der entorhinalen Projektion gezeigt werden, dass RGMa ein potenter Hemmer von neuronalem Auswachsen ist und eine spezifische Wirkung auf die laminäre Anordnung im Hippocampus hat. Dadurch, dass das entorhino-hippocampale Modell allgemein als beispielhaft für die Entwicklung des ZNS anerkannt wird, lassen sich aus dieser Arbeit Rückschlüsse auf die Wirkung von RGMa im menschlichen ZNS ziehen, wo eine Distribution des Proteins bereits nachgewiesen wurde.

In experimentellen Studien zur medikamentösen Therapie traumatischer Verletzungen des Rückenmarks wird inzwischen auf eine neue Generation von Medikamenten, die durch Blockade der hemmenden Einflüsse von Leitmolekülen zu einem vermehrten Aussprossen der regenerativen Fasern führt, gesetzt. In diesem Sinn könnte man das Wissen über die Hemmung der RGMa-Wirkung in Zukunft therapeutisch nutzen, da in neuen Studien auch für RGMa belegt werden konnte, dass es im Tierversuch zu einer verbesserten Regeneration und Rekonnektion von zerstörten Nervenbahnen kommt.

6 LITERATURVERZEICHNIS

Amaral, D.G. and Witter, M.P.: The three-dimensional organization of the hippocampal formation: a review of anatomical data (1989) Neuroscience 31(3), S. 571-91.

Arber, S., Barbayannis, F.A., Hanser, H., Schneider, C. and Stanyon, C.A.: Regulation of dynamics through phosphorylation of Cofilin by LIM-kinase (1998) Nature *393,* S.805-809.

Aubert, I., Ridet, J.L., Schachner, M., Rougon, G. and Gage, F.H.: Expression of L1 and PSA during sproutin and regeneration in the adult hippocampal formation (1998) J Comp Neurol *399*, S. 1-19.

Bagri, A., Marin, O., Plump, A.S., Mak, J., Pleasure, S.J., Rubenstein, J.L. and Tessier-Lavigne, M.: Slit proteins prevent midline crossing and determine the dorsoventral position of major axonal pathways in the mammalian forebrain (2002) Neuron *33(2)*, S. 233-48.

Baier, H. and Bonhoeffer, F.: Attractive axon guidance molecules (1994) Science *265*, S.1541-1542.

Bandtlow, C.E. and Schwab, M.E.: NI-35/250/Nogo-A: a neurite growth inhibitor restricting structural plasticity and regeneration of nerve fibers in the adult vertebrate CNS (2000) Glia *29*, S.175-181.

Bear, J.E., Svitkana, T.M., Krause, M., Schafer, D.A. and Loureiro, J.J.: Antagonism between Ena/VASP proteins and actin filament capping regulates fibroblast motility (2002) Cell *109*, S.509-521.

Becker, T., Anliker, B., Becker, C.G., Taylor, J., Schachner, M., Meyer, R.L. and Bartsch, U.: Tenascin-R inhibits regrowth of optic fibers in vitro and persists in the optic nerve of mice after injury (2000) Glia *29*, S.330-346.

Bixby, J.L. and Harris, A.W.: Molecular mechanisms of axon growth and guidance (1991) Annu Rev Cell Biol *7*, S.117-159.

Blasi, E., Barluzzi, R., Bocchini, V., Mazzolla, R. und Bistoni, F.: Immortalization of murine microglial cells by a v-raf/v-myc carrying retrovirus (1990) J Neuroimmunol *27*, S.229-237.

Bocchini, V., Mazzolla, R., Barluzzi, R., Blasi, E., Sick, P. und Kettenmann, H.: An immortalized cell line expresses properties of activated microglial cells (1992) J Neurosci Res. *31*, S.616-621.

Borrell, V., Del Rio, JA., Alcantara, S., Derer, M., Martinez, A., D´Arcangelo, G., Nakajima, K., Mikoshiba, K., Derer, P., Durran, T. and Soriano, E.: Reelin regulates the development and synaptogenesis of the layer-specific entorhino-hippocampal connections (1999) J Neurosci *19*, S.1345-1358.

Bräuer, A.U., Savaskan, N.E., Kuhn, H., Prehn, S., Ninnemann, O. and Nitsch, R.: A new phospholipid phosphatase, PRG-1, is involved in axon growth and regenerative sprouting (2003) Nat Neurosci *6(6),* S. 572-578.

Brenner, S.: The genetics of Caenorhabditis elegans (1974) Genetics *77*, S.71-94.

Brinks, H., Conrad, S., Vogt, J., Oldekamp, J., Sierra, A., Deitinghoff, L., Bechmann, I., Alvarez-Bolado, G., Heimrich, B., Monnier, P.P., Mueller, B.K. and Skutella, T.: The Repulsive Guidance Molecule RGMa Is Involved in the Formation of Afferent Connections in the Dentate Gyrus (2004) J Neurosci *24(15)*, S.3862-3869.

Brummendorf, T. and Rathjen, F.G.: Cell adhesion molecules 1: immunoglobin superfamily (1995) Protein Profile *2*, S.963-1108.

Burden-Gulley, S.M., Ensslen, S.E. and Brady-Kalnay, S.M.: Protein tyronsine phosphatase-mu differentially regulates neurite outgrowth of nasal and temporal neurons in the retina (2002) J Neurosci *22*, S.615-627.

Cai, D., Qiu, J., Cao, Z., McAtee, M., Bregman, B.S. and Filbin, M.T.: Neuronal cyclic AMP controls the developmental loss in ability of axons to regenerate (2001) J Neurosci *21*, S.4731-4739.

Cai, D., Shen, Y., DeBellard, M., Tang, S. and Filbin, M.T.: Prior exposure to neurotrophins blocks inhibition of axonal regeneration by MAG and myelin via a cAMP-dependent mechanism (1999) Neuron *22*, S.89-101.

Cai, H. and Reed, R.R.: Cloning and characterisation of neuropilin-1-interacting protein: a PSD-95/Dlg/ZO-1 domain-containing protein that interacts with the cytoplasmic domain of neuropilin-1 (1999) J Neurosci *19*, S.6519-6527.

Callahan, C.A., Muralidhar, M.G., Lundgren, S.E., Scully, A.L. and Thomas, J.B.: Control of neuronal pathway selection by a Drosophila receptor protein-tyrosine kinase family member (1995) Nature *376,* S.171-174.

Castellani, V., Chedotal, A., Schachner, M., Faivre-Sarrailh, C., Rougnon, G.: TI - Analysis of the L1-deficient mouse phenotype reveals cross-talk between SemaIIIA und L1 signaling pathways in axonal guidance (2000) Neuron *27*, 237-249

Catalano, S.M., Messersmith, E.K., Goodman, C.S., Shatz, C.J. and Chédotal, A.: Many major CNS axon projections develop normally in absence of semaphorin III (1998) Mol Cell Neurosci *11*, S.173-182.

Ceranik, K., Deng, J., Heimrich, B., Lubke, J., Zhao, S., Forster, E. and Frotscher, M.: Hippocampal Cajal-Retzius cells project to the entorhinal cortex: retrograde tracing and intracellular labelling studies (1999) Eur J Neurosci *11(12)*, S. 4278-90.

Chang, C., Yu, T.W., Bargmann, C.I. and Tessier-Lavigne, M.: Inhibition of netrin-mediated axon attraction by a receptor protein tyronsine phosphatase (2004) Science *305(5680)*, S. 103-6.

Chedotal, A., Del Rio, J.A., Ruiz, M., He, Z., Borrell, V., de Castro, F., Ezan, F., Goodman, C.S., Tessier-Lavigne, M., Sotelo, C. and Soriano,E.: Semaphorins III and IV repel hippocampal axons via two distinct receptors (1998) Development *125(21)*, S. 4313-23.

Chen, H., Chedotal, A., He, Z., Goodman, C.S., Tessier-Lavigne, M.: Neuropilin-2, a novel member of the Neuropilin familiy, is a high affinity receptor for the semaphorins SemaE and SemaIV but not SemaIII (1997) Neuron *19*, S.547-559.

Cheng, H.-J., Bagri, A., Yaron, A., Stein, E., Pleasure, S.J., Tessier-Lavigne, M.: Plexin-A3 mediates semaphorin signaling and regulates the development of hippocampal axonal projections (2001) Neuron *32*, S.249-263.

Colamarino, S.A. and Tessier-Lavigne, M.: The axonal chemoattractant netrin-1 is also a chemorepellent for trochlear motor axons (1995) Cell *81*, S.621-629.

Cramer, S.C. and Chopp, M.: Recovery recapitulates ontogeny (2000) Trend

Neurosci *23(6)*, S.265-271.

Cremer, H. Chazal, G., Goridis, C. and Represa, A.: NCAM is essential for axonal growth and fasciculation in the hippocampus (1997) Mol Cell Neurosci *8(5)*, S. 1117-35.

Cuthford, T. and Harrison, C.J.: Ephs and ephrins close ranks (1999) Trends Neurosci *25*, S.332-334.

D'Arcangelo, G., Miao, C.G., Chen, S.C., Soares, H.D., Morgan, J.I. and Curran, T. : A protein related to extracellular matrix proteins deleted in the mouse mutant reeler (1995) Nature *374(6524)*, S. 719-23.

D'Arcangelo, G., Nakajima,K., Miyata, T., Ogawa, M., Mikoshiba, K. and Curran.T. : Reelin is a secreted glycoprotein recognized by the CR-50 monoclonal antibody (1997) J Neurosci *17(1)*, S. 23-31.

DeBellard, M.E., Tang, S., Mukhopadhyay, G, Shen, Y.J. and Filbin, M.T.: Myelin-associated glycoprotein inhibits axonal regeneration from a variety of neurons via interactionwith a sialoglycoprotein (1996) Mol Cell Neurosci *7*, S.89-101.

Del Rio, J.A., Heimrich, B., Borrell, V., Förster, E., Drakew, A., Alcantara, S., Nakajima, K, Miyata, T., Ogawa, M. and Mikoshiba, K.: A role for Cajal-Retzius cells and reelin in the development of hippocampal connections (1997) Nature *385*, 70-74.

Del Rio, J.A., Solé, M., Borrell, V., Martinez, A. and Soriano, E.: Involvment of Cajal-Retzius cells in robust and layer-specific regeneration of the entorhino-hippocampal pathways (2002) Eur J Neurosci *15*, S.1881-1890.

Deller, T., Frotscher, M. and Nitsch, R.: Morphological evidence for the sprouting of inhibitory commissural fibers in response to the lesion of the excitatory entorhinal input to the rat dentate gyrus (1995) J Neurosci *15(10)*, S. 6868-78.

Deller, T., Drakew, A. and Frotscher, M.: Different primary target cells are important for fiber lamination in the fascia dentata: A lesson from reeler mutant mice (1999) Exp Neurol *156*, S.239-253.

Deller, T. und Frotscher, M.: Lesion-induced plasticity of central neurons: sprouting of single fibres in the rat hippocampus after unilateral entorhinal cortex lesion (1997) Prog Neurobiol *53(6)*, S. 687-727.

Deller, T., Haas, C.A. and Frotscher, M.: Reorganization of the rat fascia dentata after unilateral entorhinal cortex lesion. The role of the extracellular matrix (2000) Ann N Y Acac Sci *911*, S. 207-20.

De Winter, F., Oudega, M., Lankhorst, A.J., harners, F.P., Blits, B., Ruitenberg, M.J., Pasterkamp, R.J., Gispen, W.H. and Verhaagen, J.: Injury-induced class 3 semaphorin expression in the rat spinal cord (2002) Exp Neurol *175(1)*, S. 61-75.

Dickson, B.J.: Rho GTPAses in growth cone guidance (2001) Curr Opin Neurobiol *11*, S.103-110.

Dityatev, A and Schachner, M.: Extracellular matrix molecules and synaptic plasticity (2003) Nat Rev Neurosci *4*, S.456-468.

Domeniconi, M., Cao, Z. Spender, T., Sivasankaran, R. and Wang, K.: Myelin-associated glycoprotein interacts with the Nogo66 receptor to inhibit neurite outgrowth (2002) Neuron *35*, S.283-290.

Dontchev, V.D. and Letouneau, P.C.: Nerve growth factor and semaphorin3A signaling pathways interact in regulating sensory neuronal growth cone motility (2002) J Neurosci *22*, S.6659-6669.

Drejer, J., Larsson, O.M. und Schousboe, A.: Characterization of L-glutamate uptake into and release from astrocytes and neurons cultured from different brain regions (1982) Exp. Brain Res. *47(2),* S.239-269.

Drosopoulos, N.E., Walsh, F.S. and Doherty, P.: A soluble version of the receptor-like protein tyronsine phosphatase kappa stimulates neurite outgrowth via a Grb2/MEK1-dependent signaling cascade (1999) Mol Cell Neurosci *13*, S.441-449.

Elowe, S., Holland, S.J., Kulkami, S. and Pawson, T.: Downregulation of the Ras-mitogen-activated protein kinase pathway by the EphB2 receptor tyrosine kinase is required for ephrin-induced neurite retraction (2001) Mol Cell Biol *21*, S.7429-7441.

Fagan, A.M., Suhr, S.T., Lucidi-Phillipi, C.A., Peterson, D.A., Holtzman, D.M. and Gage, F.H.: Endogenous FGF-2 is important for cholinergic sprouting in the denervated hippocampus (1997) J Neurosci 17(7), S. 2499-511.

Fan, J. and Raper, J.A.: Localized collapsing cues can steer growth cones without inducing their full collapse (1995) Neuron *14*, S.263-274.

Fawcett, J.W. and Asher, R.A.: The glial scar and central nervous system repair (1999) Brain Res Bull *6*, S.377-391.

Fazeli, A., Dickinson, S.L., Hermiston, M.L., Tighe, R.V., Steen, R.G., Small, C.G., Stoeckli, E.T., Keino, M.K., Masu, M., Rayburn, H., Simons, J., Bronson, R.T., Gordon, J.I., Tessier-Lavigne, M. and Weinberg, R.A.: Phenotype of mice lacking functional Deleted in colorectal cancer (Dcc) gene (1997) Nature *386*, S.796-804.

Feiner, L., Koppel, A.M., Kobayashi, H., Raper, J.A.: Secreted chick semaphorins bind recombinant neuropilin with similar affinities but bind different subsets of neurons in situ (1997) Neuron *19*, S.539-545.

Förster, E., Kaltschmidt, C., Deng, J., Cremer, H., Deller, T. and Frotscher, M.: Lamina-specific cell adhesion on living slices of hippocampus (1998) Deveopment *125(17)*, S. 3399-410.

Förster, E., Zhao, S. and Frotscher, M.: Hyaluronan-associated adhesive cues control fiber segregation in the hippocampus (2001) Development *128*, S.3029-3039.

Freund, T.F. und Antal, M.: GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus (1988) Nature *336*, S.170-173.

Fricke, C., Lee, J.S., Geiger-Rudolph, S., Bonhoeffer, F. and Chien, C.B.: Astray, a zebrafishroundabout homolog required for retinal axon guidance (2001) Science *292*, S.507-510.

Frotscher, M. und Leranth, C.: The cholineric innervation of the rat fascia dentata: identification of target structures on granule cells by combining choline acetyltransferase immunocytochemistry and Golgi impregnation (1986) J Comp Neurol *243*, S.58-70.

Frotscher, M., Haas, C.A. and Förster, E.: Reelin controls granule cell migration in the dentate gyrus by acting on the radial glial scaffold (2003) Cerebral Cortex *13*, S.634-640.

Frotscher, M., Heimrich, B and Deller, T.: Sprouting in the hippocampus is layer-specific (1997) Trends Neurosci *20/5*, S.218-223.

Fujisawa, H., Kitsukawa, T, Kawakami, A., Takagi, S, Shimizu, M and Hirata, T. : Roles of a neuronal cell.surface molecule, neuropilin, in nerve fiber fasciculation and guidance (1997) Cell Tissue Res *290(2)*, S. 465-70.

Galko, M.J. and Tessier-Lavigne, M.: Function of a chemoattractant modulated by metalloprotease activity (2000) Science *289*, S.1365-1367.

Gallo, G., Lefcort, F.B. and Letourneau, P.C.: The trkA receptor mediates growth cone turning toward a localized source of nerve growth factor (1997) J Neurosci *17*, S.5445-5454.

Gao, P.P., Yue, Y., Cerretti, D.P., Dreyfus, C. and Zhou, R.: Ephrin-dependent growth and pruning of hippocampal axons (1999) Proc Natl Acad Sci USA *96*, S.4073-4077.

Gavazzi, I.: Semaphorin-neuropilin-1 interactions in plasticity and regeneration of adult neurons (2001) Cell Tissue Res *305*, S.275-284.

Giger, R.J., Pasterkamp, R.J., Heijnen, S., Holtmaat, A.J. und Verhaagen, J.: Anatomical distribution of the chemorepellent semaphrorin III/collapsin-1 in the adult rat and human brain: predominant expression in structures of the olfactory-hippocampal pathway and the motor system (1998) J Neurosci. Res. *51(2),* S. 27-42.

Goodman, C.S., Bastiani, M.J., Doe, C.Q., du Lac, S., Helfand, S.L., Kuwada, J.Y. and Thomas, J.B.: Cell recognition during neuronal development (1984) Science *225*, S.1271.

GrandPre, T., Li, S. and Strittmatter, S.M.: Nogo-66 receptor antagonist peptide promotes axonal regeneration (2002) Nature *417(6888)*, S. 547-51.

Grenningloh, G., Rehm, E.J. and Goodman, C.S.: Genetic analysis of growth cone guidance in Drosophila: fasciclin II functions as a neuronal recognition

molecule (1991) Cell *76(1),* S.45-57.

Grumet, M., Friedlander, D.R. and Edelman, G.M.: Evidence for the binding of Ng-CAM to laminin (1993) Cell Adhes Commun *1*, S.177-190.

Gulyás, A.I., Tóth, K., Danos, P. und Freund, T.F.: Innervation of different peptide-containing neurons in the hippocampus by GABAergic septal afferents (1990) Neuroscience *37*, S.31-44.

Gumbiner, B.M.: Regulation of cadherin adhesive activity (2000) J Cell Biol *148*, S.399-404.

Haas, C.A., Rauch, U., Thon, N., Merten, T. and Deller, T.: Entorhinal cortex lesion in adult rats induces the expression of the neuronal chondroitin sulfate proteoglycan neurocan in reactive astrocytes (1999) J Neurosci *19*, S.9953-9963.

Hall, A.: Rho GTPases and the actin cytoskeleton (1998) Science *279*, S.509-514.

Harrelson, A.L. und Goodman, C.S.: Growth cone guidance in insects: fasciclin II is a member of the immunoglobulin superfamily (1988) Science *242(4879),* S. 700-708.

Hedgecock, E.M., Culotti, J.G., Hall, D.H.: The unc-5, unc-6 and unc-40 genes guide circumferential migrations of pioneer axons and mesodermal cells on the epidermis in C. elegans (1990) Neuron *4*, S.61-85.

Hedgecock, E.M., Norris, C.R.: Netrins evoke mices reactions in motile cells (1997) Trends Genet *13*, S.251-253.

Heimrich, B. und Frotscher, M.: Formation of the septohippocampal projection in vitro: an electron microscopic immunocytochemical study of cholinergic synapses (1993) J Neurosci *52(4)*, S. 815-827.

Heimrich, B. und Frotscher, M.: Slice cultures as a model to study entorhinal-hippocampal interaction (1993) Hippocampus 3Spec No: 7-11.

Hiramoto, M., Hiromi, Y., Giniger, E., and Hotta, Y.: The Drosophila Netrin receptor Frazzled guides axons by controlling Netrin distribution (2000) Nature *406*, S.886-889.

Hirata, T., Takagi, S., Fujisawa, H.: The membrane protein A5, a putative neuronal recognition molecule, promotes neurite outgrowth (1993) Neurosci Res *17*, S.159-169.

Horner, P.J. and Gage, F.H.: Regenerating the damaged central nervous system (2000) Nature *407*, S.963-970.

Hu, H.: Chemorepulsion of neuronal migration by Slit2 in the developing mammalian forebrain (1999) Neuron *23*, S.703-711.

Huang, E.J. und Reichardt, L.F.: Neurotrophins: roles in neuronal develpment and function (2001) Annu Rev Neurosci *24*, S.677-736.

Huber, A.B., Kolodkin, A.L., Ginty, D.D. und Cloutier, J.F.: Signaling at the growth cone: ligand-receptor complexes and the control of axon growth and guidance (2003) Annu Rev Neurosci *26*, S. 509-526.

Hynes, R.O. and Lander, A.D.: Contact and adhesive specificities in the associations, migrations and targeting of cells and axons (1992) Cell *68*, S.303-322.

Inagaki, S., Furuyama, T., Iwahashi, W.: Identification of a member of the mouse semaphrin family (1995) FEBS Lett *370*, S.269-272.

Ishii, N., Wadsworth, W.G., Stern, B.D., Culotti, J.G., Hedgecock, E.M.: Unc-6, a laminin-related protein, guides cell and pioneer axon migrations in C.elegans (1992) Neuron *9*, S.873-881.

Jin, Z. & Strittmatter, S.M.: Rac1 mediates collapsin1-induced growth cone collapse (1997) J Neurosci *17*, S.6256-6263.

Jossin, Y., Ignatova, N., Hiesberger, T., Herz, J., Lambert de Rouvroit, C. and Goffinet, A.M.: The central fragment of Reelin, generated by proteolytic processing in vivo, is critical to its function during cortical plate development (2004) J Neurosci *24*, S.514-521.

Kamiguchi, H. und Lemmon, V.: Recycling of the cell adhesion molecule L1 in axonal growth cones (2000) J Neurosci. *20*, S.3676-3686.

Kelley, M.S. and Steward, O.: Injury-induced physiological events that may modulate gene expression in neurons and glia (1997) Rev Neurosci *8(3-4)*,

S-147-77.

Kennedy, T.E., Serafini, T., de la Torre, Jr. and Tessier-Lavigne, M.: Netrins are diffusible chemotrophic factors for commissural axons in the embryonic spinal cord (1994) Cell *78*, S.425-435.

Kidd, T., Bland, K.S. and Goodman, C.S.: Slit is the midline repelllent for the robo receptor in Drosophila (1999) Cell *96*, S.785-794.

Kimura, K., Ito, M., Amano, M., Chihara, K. und Fukata, Y.: Regulation of myosin phosphatase by Rho and Rho-associated kinase (Rho-kinase) (1996) Science *273*, S.245-248.

Kitsukawa, T., Shimono, A., Kawakami, A., Kondoh, H., Fujisawa, H.: Overexpression of a membrane protein, neuropilin, in chimeric mice causes anomalies in the cardiovascular system, nervous system and limbs (1995) Development *121*, S.4309-4318.

Knoll, B und Drescher, U.: Ephrin-As as receptors in topographic projections (2002) Trends Neurosci. *25*, S.145-149.

Kolodkin, A.L.: Semaphorins: mediators of repulsive growth cone guidance (1996) Trends Cell Biol *6*, S.15-22.

Kolodkin., A.L., Matthes, D.J., O'Connor, T.P., Patel, N.H., Admon, A., Bentley, D. and Goodman, C.S.: Fasciclin IV: sequence, expression, and function during growth cone guidance in the grasshopper embryo (1992) Neuron *9(5)*, S. 831-45.

Kovac, A.D., Kwidzinski, E., Heimrich, B., Bittigau, P., Deller, T., Nitsch, R. and Bechmann, I.: Entorhinal cortex lesion in the mouse induces transsynaptic death of perforant path target neurons (2003) Brain Pathol. *14(3)*, S.113-118.

Kramer, S.G., Kidd, T., Simpson, J.H. und Goodman, C.S.: Switching repulsion to attraction: changing responses to slit during transition in mesoderm migration (2001) Science *292*, S.737-740.

Kullander, K. und Klein R.: Mechanisms and functions of Eph and ephrin signalling (2002) Nat Rev Mol Cell Biol *3*, S.475-486.

Kullmann, D.M., Min, M.Y., Asztely, F. and Rusakov, D.A.: Extracellular glutamate diffusion determines the occupancy of glutamate receptors at CA1 synapses in the hippocampus (1999) Philos Trans R Soc Lond B Biol Sci *354*, S.395-402.

Kwidzinski, E., Mutlu, L.K., Kovac, A.D., Bunse, J., Goldmann, J., Mahlo, J., Aktas, O., Zipp, F., Kamradt, T., Nitsch, R. and Bechmann, I.: Self-tolerance in the immune priviledged CNS: lessons from the entorhinal cortex lesion model (2003) J Neural Transm *65 (Suppl)*, S.29-49.

Lander, A.D.: Molecules that make axons grow (1987) Moll Cell Neurosci. *1(3)*, S.213-245.

Lee, S., Williamson, J., Lothman, E.W., Szele, F.G., Chesselet, M.F., Von Hagen, S., Sapolsky, R.M., Mattson, M.P. and Christakos, S.: Early induction of mRNA for calbindin-D28k and BDNF but not NT-3 in rat hippocampus after kainic acid treatment (1997) Brain Res Mol Brain Res *47(1-2)*, S. 183-94.

Lehmann, M., Fournier, A., Selles-Navarro, I., Dergham, P und Sebok, A.: Inactivation of Rho signalling pathway promotes CNS axon regeneration (1999) J Neurosci *19*, S.7573-7547.

Liu, B.P., Fournier, A., GrandPre, T und Strittmatter, S.M.: Myelin-associated glycoprotein as a functional ligand for the Nogo66 receptor (2002) Science *297*, S.1190-1193.

Long, H., Sabatier, C., Ma, L., Plump, A., Yuan, W., Ornitz, S., Tmada, A., Murakami, F., Goodman, C.S. and Tessier-Lavigne, M.: Conserved roles for Slit and Robo Proteins in Midline Commissural Axon Guidance (2004) Neuron *42*, S.213-223.

Luo, L.: Rho GTPases in neuronal morphogenesis (2000) Nat Rev Neurosci *1*, S.173-180.

Luo, L.: Actin cytoskeleton regulation in neuronal morphogenesis and structural plasticity (2002) Annu Rev Cell Dev Biol *18*, S.601-635.

Lynch, G, Matthews, D.A., Mosko, S., Parks, T. and Cotman, C.: Induces acetylcholinesterase-rich layer in rat dentate gyrus following entorhinal lesions (1972) Brain Res *42(2)*, S.311-318.

Mackay, D.J.G., Nobes, C.D., Hall, A.: The Rho´s Progress: a potential role during neuritogenesis for the Rho family of GTPases (1995) Trends Neurosci *18*, S.496-501.

Maeda, N. und Noda, M.: Involvment of receptor-like protein tyrosine phosphatase zeta/RPTPbeta and its ligand pleiotrophin/heparin-binding growth-associated molecule (HB-GAM) in neuronal migration (1998) J Cell Biol *142*, S.203-216.

Maeda, N., Ichihara-Tanaka, K., Kimura, T., Kadomatsu, K., Muramatsu, T und Noda, M.: A receptor-like protein-tyrosine phosphatase PTPzeta/RTPTbeta binds a heparin-binding growth gactor midkine. Involvement of arginine 78 of midkine in the high affinity binding to PTPzeta (1999) J Biol Chem. *274:12*, S.474-479.

Mark, M.D., Lohrum, M. and Püschel, A.W.: Patterning neuronal connections by chemorepulsion: the Semaphorins (1997) Cell Tissue Res *290*, S.299-306.

Mark, M.D., Lohrum, M., Püschel, A.W.: Pattering neuronal connections by chemorepulsion: the semaphorins (1997) Cell Tissue Res *290*, S.299-306.

Masliah, E., Fagan, A.M., Terry, R.D., DeTeresa, R., Mallory, M. and Gage, F.H.: Reactive synaptogenesis assessed by synaptophysin immunireactivity is associated with GAP-43 in the dentate gyrus of the adult rat (1991) Exp Neurol 113(2), S. 131-42.

Matsunaga, E., Tauszig-Delamasure, S., Monnier, P.P., Müller, B.K., Strittmatter, S.M., Mehlen, P. and Chedotal, A.: RGM and its receptor neogenin regulate neuronal survival (2004) Nature Cell Biology *6(8)*, S.749-755.

McKenna, M.P. and Raper, J.A.: Growth cone behavior on gradients of substratum bound laminin (1988) Dev Biol *130*, S.232.

McKeon, R.J., Jurynec, M.J. and Buck, C.R.: The chondroitin sulfate proteoglycans neurocan and phosphacan are expressed by reactive astrocytes in the chronic CNS glial scar (1999) J Neurosci *19*, 10778-10788

McKerracher, L., David, S., Kackson, D.L., Kottia, V., Dunn, R.J. und Braun, P.E.: Identification of myelin-associated glycoprotein as a magor myelin-derived inhibitor of neurite growth (1994) Neuron *13*, S.805-811.

Meima, L., Klijavin, I.J., Moran, P., Shih, A., Winslow, J.W. and Caras, I.W.: AL-1 – induced growth cone collapse of rat cortical neurons is correlated with REK7 expression and rearrangement of the actin cytoskeleton (1996) Eur J Neurosci *9*, 177-190.

Messersmith, E.K., Leonardo, E.D., Shatz, C.J., Tessier-Lavigne, M., Goodman, C.S., Kolodkin, A.L.: SemaphorinIII can function as a selective chemorepellent to pattern sensory projections in the spinal cord (1995) Neuron *14*, S.949-959.

Miao, H., Wei, B.R., Peehl, D.M., Li, Q. und Alexandrou, T.: Activation of EphA receptor tyrosine kinase inhibits the Ras/MAPK pathway (2001) Nat Cell Biol *3*, S.527-530.

Min, M.Y., Rusakov, D.A. and Kullmann, D.M.: Activation of AMPA, kainate, and metabotropic receptors at hippocampal mossy fiber synapses: a role of glutamate diffusion (1998) Neuron *21*, S.561-570.

Ming, G., Henley, J., Tessier-Lavigne, M. Song, H. und Poo, M.: Electrical activity modulates growth cone guidance by diffusible factors (2001) Neuron *29*, S.441-452.

Ming, G., Song, H., Berninger, B., Inagaki, N., Tessier-Lavigne, M., Poo, M.: Phospholipase C-gamma and phosphoinositide 3-kinase mediate cytoplasmic signaling in nerve growth cone guidance (1999) Neuron *23*, S.139-148.

Monnier, P.P., Sierra, A., Macchi, P., Deitinghoff, L., Andersen, J.A., Mann, M., Flad, M., Hornberger, M.R., Stahl, B., Bonhoeffer, F. and Müller, B.K.: RGM is a repulsive guidance molecule for retinal axons (2002) Nature *419*, S.392-395.

Monnier, P.P., Sierra, A., Schwab, J.M., Henke-Fahle, S. and Mueller, B.K.: The Rho/ROCK pathway mediates neurite growth-inhibitory activity associated with the chondroitin sulfate proteoglycans of the CNS glial scar (2003) Moll Cell Neurosci *22*, S.319-330.

Moreau-Fauvarque, C., Kumanogoh, A., Camand, E., Jaillard, C., Barbin, G., Boquet, I., Love, C., Jones, E.Y., Kikutani, H., Lubetzki, C., Dusart, I. and

Chedotal, A.: The transmembrane semaphoring Sema4D/CD100, an inhibitor of axonal growth, is expressed on oligodendrocytes and upregulated after CNS lesion (2003) J Neurosci *23(27),* S. 9229-99239.

Morgenstern, D.A., Asher, R.A. and Fawcett, J.W.: Chondroitin sulphate proteoglycans in the CNS injury response (2002) Progn Brain Res *137*, S.313-332.

Mori, T.: Differential expressions of the wph family of receptor tyrosine kinase genes (sek, elk, eck) in the developing nervous system of the mouse (1995) Brain Res Mol Brain Res *29*, S.325-335.

Müller, B.K.: Growth Cone Guidance: First Steps Towards a Deeper Understanding (1999) Annu Rev Neurosci *22*, S.351-388.

Müller, B.K., Jay, D.G. and Bonhoeffer, F.: Chromophore-assisted laser inactivation of a repulsive guidance molecule (1996) Current Biology *6, No. 11*, S.1497-1502.

Mukhopadhyay, G., Doherty, P., Walsh, F.S., Crocker, P.R. and Filbin, M.T.: A novel role for myelin-associated glycoprotein as an inhibitor of axonal regeneration (1994) Neuron *13(3)*, S. 757-67.

Neumann, S., Bradke, F., Tessier-Lavigne, M. and Basbaum, A.I.: Regeneration of sensory axons within the injured spinal cord induced by intraganglionic cAMP elevation (2002) Neuron *34(6)*, S.885-93.

Nguyen-Ba-Charvet: Slit2-mediated chemorepulsion and collapse of developing forebrain axons (1999) Neuron *22*, S.463-473.

Nguyen-Ba-Charvet, K.T., Plump, A.S., Tessier-Lavigne, M. und Chedotal, A.: Slit1 and Slit2 proteins control the development of the lateral olfactory tract (2002) J Neurosci *22*, S.5473-5480.

Nichols, N.R., Laping, N.J., Day, J.R. and Finch, C.E.: Increases in transforming growth factor-beta mRNA in hippocampus during response to entorhinal cortex lesions in intact and adrenalectomized rats (1991) J Neurosci Res *28(1),* S. 134-9.

Nicholson, C. and Sykova, E.: Extracellular space structure reveales by diffusion

analysis (1998) Trends Neurosci *21(5),* S. 207-15.

Niederkofler, V., Salie, R., Sigrist, M. and Arber, S.: Repulsive Guidance Molecule (RGM) Gene Functions is Required for Neural Tube Closure But Not Retinal Topography in the Mouse Visual System (2004) J Neurosci *24(4)*, S.808-818.

Nobes C.D., Hall, A.: Rho, Rac and Cdc42 GTPases regulate the assembly of multimolecular focal complexes associated with actin stress fibers, lamellipodia and filopodia (1995) Cell *81*, S.53-62.

Nusser, N., Gosmanove, E., Zheng Y. und Tigyi, G.: Nerve growth factor signals through TrkA, phophatidylinositol 3-kinase, and Pac1 to inactivate RhoAduring the initiation of neuronal differentiation of PC12 cells (2002) J Biol Chem *277*, S.840-846.

Oakley, R.A. and Tosney, K.W.: Contact-mediated mechanisms of motor axon segmentation (1993) J Neurosci *13*, S.3773.

Oldekamp, J., Krämer, N., Alvarez-Bolado, G. and Skutella, T.: Expression pattern of the repulsive guidance molecules RGM-A, -B and -C during mouse development (2004) Gene Expression Patterns *4*, S.283-288.

Parise, L.V., Lee, J. and Juliano, R.L.: New aspects of integrin signaling in cancer (2000) Semin Cancer Biol *10(6)*, S. 407-14.

Pascual, M., Pozas, E. and Soriano, E.: Role of Class 3 Semaphorines in the Development and Maturation of the Septohippocampal Pathway (2005) Hippocampus *15(2)*, S.185-202.

Pasterkamp, R.J. und Verhaagen, J.: Emerging roles for semaphorins in neural regeneration (2001) Brain Res. Brain Res. Rev. *35*, S. 36-54.

Pavlov, I., Lauri, S., Taira, T and Rauvala, H.: The role of ECM molecules in activity-dependent synaptic development and plasticity (2004) Birth Defects Research *72*, S.12-24.

Peles, E., Schlessinger, J. und Grumet, M.: Multiligand interactions with receptor-like protein tyrosine phosphatase beta: implications for intercellular signaling (1998) Trends Biochem Sci *23*, S.121-124.

Pesheva, P., Gennarini, G., Goridis, C. Schachner, M.: The F3/11 cell adhesion molecule mediates the repulsion of neuron by the extracellular matrix glycoprotein J1-160/180 (1993) Neuron *10*, S.69-83.

Plump, A. S., Erskine, L., Sabatier, C., Brose, K. und Epstein, C.J.: Slit1 and Slit2 cooperate to prevent premature midline crossing of retinal axons in the mouse visual system (2002) Neuron *33*, S.219-232.

Pozas, E., Pascual, M., Nguyen Ba-Charvet, K.T., Guijarro, P., Sotelo, C., Chedotal, A., Del Rio, J.A., Soriano, E.: Age-dependent effects of secreted Semaphorins 3A, 3F and 3E on developing hippocampal axons: in vitro effects and phenotype of Semahorin 3 (-/-) mice (2001) Mol Cell Neurosci *18(1),* S. 26-43.

Properzi, F., Asher, R.A. and Fawcett, J.W.: Chondroitin sulphate proteoglycans in the central nervous system: changes and synthesis after injury (2003) Biochem Soc Trans *31*, S.335-336.

Püschel, A.W., Adams, R.H., Betz, H.: Murine semaphorinD/collapsin is a member of a diverse gene family and creates domains inhibitory for axonal extension (1995) Neuron *14*, S.941-948.

Rajagopalan, S., Vivancos, V., Nicolas, E. und Dickson, B.J.: Selecting a longitudinal pathway: Robo receptors specify the lateral position of axons in the Drosophila CNS (2000) Cell *103*, S.1033-1045.

Rajagopalan, S., Deitinghoff, L., Davis, D., Conrad, S., Skutella, T., Chedotal, A., Müller, B.K. and Strittmatter, S.M.: Neogenin mediates the action of repulsive guidance molecule (2004) Nature Cell Biology *6(8),* 756-62.

Ranscht, B.: Cadherins: the molecular codes for axon guidance and synapse formation (2000) Int J Dev Neurosci *18*, S.643-651.

Raper, J.A., Bastiani, M.J. and Goodman, C.S.: Guidance of neuronal growth cones: selective fasciculation in the grasshopper embryo (1984) J Neurosci *4*, S.2329.

Reeves, T.M., Prins, M.L., Zhu, J., Povlishock, J.T. and Phillips, L.L.: Matrix Metalloprotease Inhibition alters the functional and structural correlates of deafferentiation-induced sprouting in the Dentate Gyrus (2003) J Neurosci

23, S.10182-10189.

Reichardt, L.F. and Tomaselli, K.J.: Extracellular matrix molecules and their receptors: Functions in neural development (1991) Annu Rev Neurosci *14*, S.531-570.

Ridley, A.J., Hall, A.: The small GTP-binding protein Rho regulates the assembly of focal adhesions and actin stress fibers in response th growth factors (1992) Cell *70*, S.389-399.

Rohatgi, R., Ma, L., Miki, H., Lopez, M. and Kirchhausen, T.: The interaction betwenn N-WASP and the Arp2/3 complex links Cdc42-dependent signals to actin assembly (1999) Cell *97*, S.221-231.

Sanders, L.C., Matsumura, F., Bokoch, G.M. and de Lanerolle, P.: Inhibition of myosin light chain kinase by p21-activated kinase (1999) Science *283*, S. 2083-85.

Savaskan, N.E., Skutella, T., Bräuer, A.U., Plaschke, M., Ninnemann, O. and Nitsch, R.: Outgrowth-promoting molecules in the adult hippocampus after perforant path lesion (2000) Eur J Neurosci *12*, S.1024-1032.

Schmidtmer, J. and Engelkamp, D.: Isolation and expression pattern of three mouse homologues of chick Rgm (2004) Gene Expression Patterns *4*, S.105-110.

Schubert, D., Heinemann, S., Carlisle, W., Tarikas, H., Kimes, B., Steinbach, J.H., Culp, W. und Brandt, B.L.: Clonal cell lines from the rat central nervous system (1974) Nature *249*, S.224-227.

Schwab, J.M., Brechtel, K., Mueller, C.-A., Kaps, H.-P., Meyermann, R. and Schluesener, H.: Akute Rückenmarksverletzung: Experimentelle Strategien als Basis zukünftiger Behandlungen (2004) Deutsches Ärzteblatt *20*, S. 1422-1434.

Schwab, J.M., Conrad, S., Monnier, P.P., Julien, S., Mueller, B.K. and Schluesener, H.J.: Spinal cord injury-induced lesional expression of the repulsive guidance molecule (RGM) (2005) Eur J Neurosci *21*, S. 1569-1576.

Schwegler, H. and Crusio, W.E.: Correlations between radial-maze learning and structural variations of septum and hippocampus in rodents (1995) Behav Brain Res *67*, S.29-41.

Serafini, T.: Netrin-1 is required for commissural axon guidance in the developing vertebrate nervous system (1996) Cell *87*, S.1001-1014.

Serafini, T., Kennedy, T.E., Galko, M.J., Jessell, T.M. and Tessier-Lavigne, M.: The netrin define a family of axon outgrowth promoting proteins homologous to C.elegans unc-6 (1994) Cell *78*, S.409-424.

Shapiro, S.D.: Matrix metalloproteinase degradation of extracellular matrix: biological consequences (1998) Curr Opin Cell Biol *10(5)*, S. 602-8.

Shepherd, I., Luo, Y., Lefcort, F., Reichardt, L.F., Raper, J.A.: A sensory axon repellent secreted from ventral spinal cord explants is neutralized by antibodies raised against collapsin-1 (1997) Development *124*, S.1377-1385.

Shirasaki, R., Tamada, A., Katsumata, R., Murakami, F.: Guidance of cerebellofugal axons in the rat embryo: directed growth toward the floor plate and subsequent elongation along the longitudinal axis (1995) Neuron *14*, S.961-972.

Simpson, J.H., Bland, K.S., Fetter, R.D. und Goodman, C.S.: Short-range and long-range guidance by Slit and its Robo receptors: a combinatorial code of Robo receptors controls lateral position (2000) Cell *103*, S.1019-1032.

Skaliora, I., Singer, W., Betz, H. and Püschel, A.W.: Differential patterns of Semaphorin expression in the developing rat brain (1998) Eur J Neurosci *10*, S.1215-1229.

Skutella, T. and Nitsch, R.: New molecules in hippocampal development (2001) Trends Neurosci *24*, S.107-113.

Skutella, T., Savaskan, N.E., Ninnemann, O. and Nitsch, R.: Target-and Maturation-Specific Membrane-Associated Molecules Determine the Ingrowth of Entorhinal Fibers into the Hippocampus (1999) Dev Biol *211*, S.277-292.

Sofroniew, M.V., Howe, C.L. und Mobley, W.C.: Nerve growth factor signaling, neuroprotection, and neuronal repair (2001) Annu Rev Neurosci *24*, S.1217-1281.

Song, H.J. and Poo, M.M.: Signal transduction underlying growth cone guidance by diffusible factors (1999) Curr Opin Neurobiol *9*, S.355-363.

Song, H.J., Ming, G.-L. and Poo, M.M.: cAMP induced switching in turining direction of nerve growth cones (1997) Nature *388*, S.275-279.

Song, H.J., Ming, G., He, Z., Lehmann, M., McKerracher, L., Tessier-Lavigne, M., Poo, M.: Conversion of neuronal growth cone response from repulsion to attraction by cyclic nucleotides (1998) Science *281(5382)*, S.1515-8.

Squire, L.R.: Memory and hippocampus: a synthesis from findings with rats, monkeys, and humans (1992) Psychol Rev *99*, S.195-231.

Stein, E. und Tessier-Lavigne, M.: Hierarchical organization of guidance receptors: silencing of netrin attraction by slit through a Robo/DCC receptor complex (2001) Science *291*, S.1928-1938.

Stein, E., Savaskan, N.E., Ninnemann, O., Nitsch, R., Zhou, R. and Skutella, T.: A role of the Eph ligand ephrin-A3 in entorhinal-hippocampal axon targeting (1999) J Neurosci 19(20), S. 8885-93.

Steup, A., Lohrum, M., Hamscho, N., Savaskan, N.E., Ninnemann, O., Nitsch, R., Fijisawa, H., Püschel, A.W., Skutella, T.: Sema3C and netrin-1 differentially affect axon growth in the hippocampal formation (2000) Mol Cell Neurosci *15*, S.141-155.

Stevens, A. und Jacobs, J.R.: Integrins regulate responsiveness to slit repellent signals (2002) J Neurosci *22*, S.4448-4455.

Sun, Q.L., Wang, J, Bookman, R.J. und Bixby, J.L.: Growth cone steering by receptor tyrosine phosphatase delta defines a distinct class of guidance cues (2000) Mol Cell Neurosci *16*, 686-695

Sykova, E., Mazel, T., Vargova, L., Vorisek, I., Prokopova-Kubinova, S.: Extracellular space diffusion and pathological states (2000) Prog Brain Res *125*, S. 155-78.

Szeidemann, Z., Jakab, R.L., Shanabrough, M. and Leranth, C.: Extrinsic and intrinsic substance P innervation of the rat lateral septal area calbindin cells (1995) Neuroscience *69(4)*, S. 1205-21.

Takahashi, T., Fournier A., Nakamura, F., Wang, L.H., Murakami, Y., Kalb, R.G., Fijisawa, H. und Strittmatter, S.: Plexin-Neuropilin-1complexes form functional semaphorin-3A receptors (1999) Cell *99*, S.59-69.

Tamagnone, L., Artigiani, S, Chen H., He, Z., Ming, G.-L., Song, H.J., Chedotal, A., Winberg, M.L., Goodman, C.S., Poo, M.M., Tessier-Lavigne, M. und Comoglio, P.M.: Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates (1999) Cell *99*, S.71-80.

Tayler, T.D., Robichaux, M.B. and Garrity, P.A.: Compartmentalization of visual centers in the Drosophila brain requires Slit and Robo proteins (2004) Development *131*, S.5935-5945.

Tessier-Lavigne, M. und Goodman, C.S.: The Molecular Biology of Axon Guidance (1996) Science *274*, S.1123-1133.

Tuttle, R. und O´Leary, D.D.M.: Neurotrophins rapidly modulate growth cone response to the axon guidance molecule, collapsin-1 (1998) Mol Cell Neusosci *11*, S.1-8.

Varela-Echavarria, A., Tucker, A., Püschel, A.W., Guthrie, S.: Motor axon subpopulations respond differentially to the chemorepellents netrin-1 and semaphorinD (1997) Neuron *18*, S.193-207.

Vielmetter, J., Stolze, B., Bonhoeffer, F. and Stuermer, C.A.: In vitro assay to test differential substrate affinities of growing axons and migratory cells (1990) Exp Brain Res *81(2),* S. 283-287.

Wadsworth, W.G., Bhatt, H., and Hedgecock, E.M.: Neuroglia and pioneer neurons express unc-6 to provide global and local netrin cues for guiding migrations in C.elegans (1996) Neuron *16*, S.35-46.

Wahl, S., Barth, H., Ciossek, T., Aktories, K. und Mueller, B.K.: Ephrin-A5 induces collapse of growth cones by activating Rho and Rho kinase (2000) J Cell Biol *149*, S.263-270.

Wang, B., Zhou, J.X., Ek-Rylander, B. und Ruoslahti, E.: R-Rhas contains a proline-rich site that binds to SH3 domains and is required for guidance in Drosophila: genes necessary for guidance toward or away from the midline (2000) Neuron *10*, S.409-426.

Wang, J. und Bixby, J.L.: Receptor tyrosine phosphatase-delta is a homophilic, neurite-promoting cell ahesion molecule for CNS neurons (1999) Mol Cell Neurosci *14*, 370-384

Wang, K.C., Kim, J.A., Sivansakaran, R., Segal, R. und He, Z.: p75 interacts with the Nogo receptor as a co-receptor for Nogo, Mag, and OMgp (2002) Nature *420*, 74-78

Wang, K.C., Koprivica, V., Kim, J.A., Sivansakaran, R. und Guo, Y.: Oligodendrocyte-myelin glycoprotein is a Nogo receptor ligand that inhibits neurite outgrowth (2002) Nature *417*, S.941-944.

Weiss, K.H., Johanssen, C., Tielsch, A., Herz, J., Deller, T., Frotscher, M. and Förster, E.: Malformation of the radial glial scaffold in the dentate gyrus of reeler mice, scrambler mice, and ApoER2/VLDLR-deficient mice (2003) J Comp Neurol *460*, S.56-65.

Whitford, K.L., Marillat, V., Stein, E., Goodman, C.s., Tessier-Lavigne, M., Chedotal, A. and Ghosh, A.: Regulation of cortical dendrite development by Slit-Robo interactions (2002) Neuron *3(33)*, S. 47-61.

Wizenman, A., Thanos, S., von Boxberg, Y. and Bonhoeffer, F.: Appearance of target-specific guidance information for regenerating axons after CNS-lesions (1993) Development *117*, S.725.

Wong, J.T.W., Yu, W.T.C., O´Connor, T.P.: Transmembrane grashopper semaphorinI promotes axon outgrowth in vivo (1997) Development *124*, S.3597-3607.

Wu, J.Y., Feng, L., Park H.T., Havlioglu, N., Wen, L., Tang, H., Bacon, K.E., Jiang, Z., Zhang, X and Rao, Y.: The neuronal repellent Slit inhibits leukocyte chemotaxis induced by chemotactic factors (2001) Nature *410(6831)*, S. 948-52.

Xiao, Z.-C., David, S., Braun, P.E. and McKerracher, L.: Characterisation of a new

myelin-derived growth inhibitory activity (1997) Soc. Neurosci Abstr *23*,

Yang, N., Higuchi, O., Ohashi, K., Nagata, K. and Wada, A.: Cofilin phosphorylation by LIM-kinase 1 and its role in Rac-mediated actin reorganization (1998) Nature *393*, S.809-812.

Yu, T.W., Hao, J.C., Lim W., Tessier-Lavigne, M. and Bargmann, C.I.: Shared receptors in axon guidance: SAX-3/Robo signals via UNC-34/Enabled and a Netrin-independent UNC-40/DCC function (2002) Nat Neurosci *5*, S.1147-1154.

Zeng, L., D´Alessandri, L., Kaloussek, M.B., Vaughan, L. und Pallen, C.J.: Protein tyrosine phosphatase alpha (PTPalpha) and contactin form a novel neuronal receptor complex linked to the intracellular tyrosine kinase fyn (1999) J Cell Biol *147*, S.707-714.

Zhang, J.H.: Dynamic expression suggests multiple reoles of the eph family receptor brain-specific kinase (Bsk) during mouse neurogenesis (1997) Brain Res Mol Brain Res. *47*, S.202-214.

Zhao, S., Chai, X., Förster, E. and Frotscher, M.: Reelin is a positional signal for the lamination of dentate granule cells (2004) Development *131*, S.5117-5125.

Zhao, S., Förster, E., Chai, X. and Frotscher, M.: Different signals control laminar specificity of commissural and entorhinal fibers to the dentate gyrus (2003) J Neurosci *23*, S.7351-7357.

Zhao, S., Förster, E., Chai, X. and Frotscher, M.: Different Signals Control Laminar Specificity of Commissural and Entorhinal Fibers to the Dentate Gyrus (2003) J Neurosci *23*, S.7351-7357.

Zuo, J., Hernandez, Y.J. and Muir, D.: Chondroitin sulfate proteoglycan with neurite-inhibiting activity is up-regulated follwing peripheral nerve injury (1998) J Neurobiol *34*, S.41-54.

7 ANHANG

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7.3 Veröffentlichungen

Poster Presentation: Brinks, H., Sierra, A., Vogt, J., Oldekamp, J., Bechmann, I., Monnier, P.P., Heimrich, B., Mueller, B.K. and Skutella, T.: The repulsive guidance molecule RGM is involved in the formation of hippocampal connections (2003) Versammlung der deutschen Gesellschaft für Anatomie, Dresden.

Brinks, H., Conrad, S., Vogt, J., Oldekamp, J., Sierra, A., Deitinghoff, L., Bechmann, I., Alvarez-Bolado, G., Heimrich, B., Monnier, P.P., Mueller, B.K. and Skutella, T.: The Repulsive Guidance Molecule RGMa Is Involved in the Formation of Afferent Connections in the Dentate Gyrus (2004) J Neurosci *24(15)*, S.3862-3869.

7.4 Eidesstattliche Erklärung

Ich erkläre an Eides Statt, dass ich die vorliegende Dissertation “Das repulsive guidance molecule RGMa in der Entwicklung und Regeneration des entorhino-hippocampalen Systems“ selbst und ohne unzulässige Hilfe Dritter verfasst habe, sie auch in Teilen keine Kopie anderer Arbeiten darstellt und die benutzten Hilfsmittel sowie die Literatur vollständig angegeben sind.

Bern, den 15. März 2006

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Henriette Brinks