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Research Interests

1. Regulation of synaptic vesicle transport and molecular motor motility in *C. elegans*

Neuronal cells are composed of a cell body and long cytoplasmic processes termed dendrites and axons. In the neuronal cell body proteins are synthesized, packed in vesicles and transported long ranges thru the axon and dendrites to the synapses. The neuronal processes are, however, overloaded with vesicles, synaptic precursors, molecular motors and cytoskeletal elements. Thus, it is not surprising that defects in the motor-cargo transport system can lead to abnormal aggregation of disease proteins and concomitant neuronal cell death. It is remarkable that many of these disease-related proteins have been identified as motor-interacting proteins or proteins present in cargo. For example **Alzheimer's disease** occurs due to the accumulation of amyloid precursor proteins which is a cargo for the molecular motor KIF5A. A mutation in the motor dynein rescues axonal transport defects and extends the life span of **ALS (Amyotrophic lateral sclerosis)** mice. LIS1 is associated with dynein while a mutation in LIS causes **lissencephaly** (severe mental retardation and poor control of movement). A mutation in the molecular motor KIF1Bbeta causes the human peripheral neuropathy **Charcot-Marie-Tooth disease type 2A** (leading to severe muscle weakness, inability to perceive touch, pain and temperature changes). A single base-pair change in the p150 Glued subunit of the motor adaptor protein dynactin causes **LMN (lower motor neuron disease)**. Finally, **senile dementia** is based on neuronal cell death caused by defects in the transport of synaptic vesicle precursors by the molecular motor KIF1A.

These examples show that proper regulation of the motor-cargo transport system is critical and that many neurodegenerative diseases display accumulation of cargo based on defects in molecular motors. However, the mechanisms of cargo transport and the regulation of motors on the molecular level is only partial known. One of the basic questions is how to explain the frequent observed bidirectional movement of molecular motors and vesicles. One common hypothesis is that one vesicle binds multiple types of motors and they either act in a cooperative manner or they compete with each other in a tug-of-war. In contrast to bidirectional movement of vesicles (on which surfaces can bind multiple cargos), the frequent observed bidirectional movement of single GFP-tagged motors might be explained by direct interaction of an opposing motor. One of our hypothesis is that bidirectional movement of anterograde (from the cell body to the synapses) moving kinesins can be explained by a direct and regulating interaction with retrograde moving dynein (from the synapses to the cell body)

and that this regulating interaction may be mediated by the dynein-cargo adaptor protein dynactin.

We are also interested in how molecular motors are targeted to synaptic sites. Based on this interest we are currently studying the interaction between the molecular motors KIF1A(UNC-104) and KIF17(OSM-3) and the presynaptic density/active zone proteins RIM(UNC-10), MALS/Veli(LIN-7) and CASK/MAGUK(LIN-2).

2. Bio-Chip and AFM-based nano-mechanics system: mechanical properties of neurons isolated from *C. elegans* with neuropathological phenotypes grown on a Bio-Chip investigated by atomic force microscopy (AFM)

In the past decades tremendous scientific effort has been made on curing neurodegenerative diseases as Alzheimer's, ALS, Huntington and lissencephaly. Surprisingly, most recent progress on neurodegenerative diseases shows that in many cases cytoskeletal proteins are involved in these serious diseases not only affecting aged but also young people. However, recent focus on biomedical research is based on classic biochemical, molecular biological and genetic techniques only. Due to fact that the cytoskeleton affects the mechanical properties of the cells, we believe that it is of importance to focus on developing a disease model which includes proposed changes in mechanical properties of pathological neurons. We propose a mechanism by which the cytoskeletal damage (due to neurodegenerative disorders) may largely reduce the stiffness of axons which may result in loosening the connection to a neighboring neuron, thus, affecting synaptic signaling. To prove the above hypothesis is correct, neurons isolated from model organism *C. elegans* will be employed to study the elasticity variation in different inherit neurodegenerative disease phenotypes. Two basic tools will be employed, a **Bio-Chip for neuron growth** (and localized stimulation) and a **AFM (atomic force microscopy) based nano-mechanics system** for the investigation of the elasticity of the neuron.

3. Bio-Chip system to identify neural stem cells from a mixture of human tissue containing neural precursor cells: In collaboration with Prof. Tseng Fan-Gang from the Dept. of Engineering and System Science (Nano/Micro Biotechnology and Fluidics lab) and Prof. Chen Linyi and Prof. Yeh Shih-Rung from our Department of Life Sciences we are currently designing and testing a bio-chip that allows for identifying neural precursor cells from a mixture of cells isolated from human tissue extracts. The process allows for on-chip preselecting of neural precursor cells and *on the same chip* for identifying differentiated neurons based on axonal outgrows and verifying of action potentials after electrical stimulation. The chip will help to identify the amount of stem cells able to differentiate into neurons from human tissue extracts not only as a fully-automated quality control system but also for further growing and maintaining of identified and isolated differentiated neurons.

4. Mapping the brain of C. elegans ("the mind of the worm ver. 2"): In collaboration with Prof. Chiang Ann-Shyn, Prof. Lo Szecheng (Chang Gung University) and and Prof. Wu Yi-Chun (NTU) we are using high resolution confocal microscopy to build-up a complete map of C. elegans head-neurons. We will determine changes in neuronal connectivity and circuits upon aging and in mutants with neuropathological phenotypes

Recent SCI Publications

1. **Wagner, O. I.**, Esposito, A., Köhler, B., Wenzel, D., Shen, C. P., Wu, G..H., Mandalapu, S., Shen K., Wouters F. S., and Klopfenstein D. R. (2008). Active zone protein SYD-2/liprin-alpha regulates kinesin-3 motor UNC-104/KIF1A motility and clustering along axons. *in submission*.
2. **Wagner, O. I**., Rammensee, S., Korde, N., Wen, Q., Leterrier, J. F., and Janmey, P. A. (2007). Softness, strength and self-repair in intermediate filament networks. Exp. Cell Res. 313, 2228-2235.
3. Dalhaimer, P., **Wagner, O. I.**, Leterrier, J. F., Janmey, P. A., Aranda-Espinoza, H., and Discher, D. E. (2005). Flexibility transitions and looped adsorption of wormlike chains. J. Polym. Sci. B 43, 280-286.
4. **Wagner, O. I.**, Ascano, J., Tokito, M., Leterrier, J. F., Janmey, P. A., and Holzbaur, E. L. F. (2004). The interaction of neurofilaments with the microtubule motor cytoplasmic dynein. Mol. Biol. Cell 15, 5092-5100.
5. **Wagner, O. I**., Lifshitz, J., Janmey, P. A., Linden, M., McIntosh, T. K., and Leterrier, J. F. (2003). Mechanisms of mitochondria-neurofilament interactions. J. Neurosci. 23, 9046-9058.

SCI-indexed Conference Proceedings and Bookchapters

1. **Wagner, O. I.**, Esposito, A., Shen, K., Wenzel, D., Köhler, B., Wouters, F., and Klopfenstein, D. R. (2006). How the LAR-interacting protein SYD-2 both clusters and regulates motor activity of KIF1A/UNC-104 in C. elegans. Eur. J. Cell. Biol. 85, 23S.
2. Janmey, P. A., **Wagner, O. I.**, Mullin, C., and Leterrier, J. F. (2004). Charge effects in neurofilament networks. J. Am. Chem. Soc. 228, 37 U485-U485 217-COLL Part 1.
3. Georges, P., **Wagner, O.**, Yeung, T., and Janmey, P. A. (2004). Biopolymer Networks and Cellular Mechanosensing. Gravitational and Space Biology Bulletin 17(2):45-50.
4. Bereiter-Hahn, J., Schindler, R., and **Wagner, O.** (2003). Modulation of actin polymerisation and mechanics with conventional and unconventional binding proteins. Comp. Biochem. Phys. *A* 134, 109S .
5. Dalhaimer, P., **Wagner, O.**, Janmey, P., Discher, D., and Aranda-Espinoza, H. (2003). Simulations of polymer adsorption: conversions for persistence length based on confinement dimensionality and lasso formation. Biophys. J. 84(2), 473A.

Invited Talks and Poster Presentations

1. Tu W-T, Yeh S-R, **Wagner O. I.**, and Tseng F-G. "Design of a bio-chip for identification and selection of neural stem cells from mixtures of various cell types". 2008 Nanotechnology Conference at Tsing-Hua University, Beijing, China. Oct 2008. *Oral presentation*.
2. Wu G-H, Shen C-P, Tien N-W, Chen C-W, Klopfenstein D. R., and **Wagner O. I.** "Regulation of molecular motors in the nervous system of C. elegans". 24th Biology Summer Camp in Chi-Tou, Taiwan. August 2008. *Oral presentation*.
3. Tien N-W and **Wagner O. I.** "Obstacles on the highway: tau, MAP1A and neurofilaments in Kinesin-3 regulation". 2008 NTHU Neuroscience Colloquium, Hsinchu, Taiwan. July 2008. *Oral presentation* (by Tien N-W).
4. Shen C-P and **Wagner O. I.** "The role of RIM(UNC-10) and CASK(LIN-2) in the KIF1A (UNC-104)/Liprin-alpha(SYD-2) complex". 2008 NTHU Neuroscience Colloquium, Hsinchu, Taiwan. July 2008. *Oral presentation* (by Shen C-P).
5. Shen C-P, Wu G-H, Chen C-W, Chien L-S, Klopfenstein D. R., and **Wagner O. I.** "Regulation of molecular motors in the nervous system of C. elegans". 1st Bilateral Meeting of National University Singapore and National Tsing-Hua University, Hsinchu, Taiwan. May 2008. *Oral presentation*.
6. Wu G-H, Shen C-P, Chen C-W, Chien L-S, Klopfenstein D.R., and **Wagner O. I.** "Regulation of molecular motors in the nervous system of C. elegans". 2007 NHRI-NTHU Joint Research Conference, Zhunan, Taiwan. Nov 2007. *Oral presentation*.
7. **Wagner, O. I.**, Esposito, A., Köhler, B., Wenzel, D., Shen K., Wouters F. S., and Klopfenstein D. R. "LAR-interacting protein SYD-2 both clusters and regulates motor activity of KIF1A/UNC-104 in *C. elegans*." Department of Life Science, National Tsing-Hua University, Hsinchu, Taiwan. April 2006. *Oral presentation*.
8. **Wagner, O. I.**, Esposito, A., Köhler, B., Wenzel, D., Shen K., Wouters F. S., and Klopfenstein D. R. "How the LAR-interacting protein SYD-2 both clusters and regulates motor motility of UNC-104." International symposia of the German Society for Cellbiology (DGZ), Braunschweig, Germany. March 2006. *Poster Presentation*.
9. **Wagner, O. I.**, Köhler, B., and Klopfenstein D. R. "LAR-interacting protein SYD-2 may affect directionality of the kinesin motor UNC-104 in *C. elegans*." 3rd Internat. Meeting on Protein and Membrane Transport, Max-Planck-Institute for Biophys. Chem., Göttingen, Germany. July 2004. *Poster Presentation*.
10. Janmey, P. A., **Wagner, O. I.**, Mullin, C., and Leterrier, J. F. "Charge effects in neurofilament networks." 228th ACS National Meeting, Philadelphia, USA. Aug 2004. *Poster and oral presentation* (by Janmey, P. A.).
11. Janmey, P. A., Georges, P., **Wagner, O. I.**, and T. Yeung. "Biopolymer Networks and Cellular Mechanosensing." 19th Annual Meeting of the American Society for

Gravitational and Space Biology, Huntsville, USA. Nov. 2003. *Oral presentation* (by Janmey, P. A.)

12. Bereiter-Hahn, J., Schindler, R., and **Wagner, O.** "Modulation of actin polymerisation and mechanics with conventional and unconventional binding proteins." Annual Main Meeting of the Society for Experimental Biology, Southampton, UK. April 2003. *Poster and oral presentation* (by Bereiter-Hahn, J.)
13. Dalhaimer P, **Wagner O.**, Janmey P., Discher D., and Aranda-Espinoza H. "Simulations of polymer adsorption: conversions for persistence length based on confinement dimensionality and lasso formation." 47th Annual Meeting of the Biophysical Society, San Antonio, Texas, USA. March 2003. *Poster Presentation.*