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6<sup>th</sup> **IWCAD** – International Winter Conference on Alzheimer's Disease!

**(December 05 – 08, 2009)**

This year they ask the provocative question:

*WHY DO WE HAVE SO FEW DRUGS FOR TREATMENT OF ALZHEIMER'S DISEASE – WRONG PATIENTS, WRONG TARGETS, WRONG DRUGS?*

More information on the meeting website:

[www.ad-zuers.com](http://www.ad-zuers.com)

We are looking forward welcoming you in Zuers!

Do not miss to visit the JSW Life Sciences booth #643 at this year's **Neurosciences Conference (October 17 – 21, 2009)** in **Chicago**. The floor plan, available on our website (<http://www.jsw-lifesciences.com/images/bilder/UserFloorplan-1.jpg>) will make it easy for you to find us.

**To get your special gift on our booth at the Neurosciences Conference in Chicago follow this link** [http://www.jswresearch.com/preclinic/en/metanav/contact\\_popup.php](http://www.jswresearch.com/preclinic/en/metanav/contact_popup.php)

See you in Chicago!

Las Vegas  
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Clinical Trials on Alzheimer's Disease

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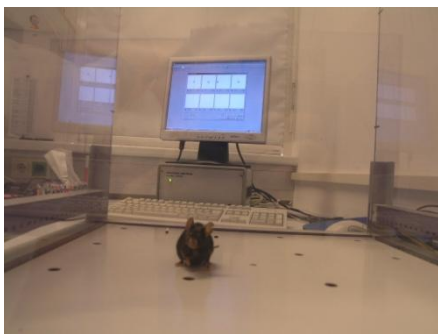
Hannover,  
Nov. 21-25, 2009

European Society of Gene & Cell Therapy

<http://www.esgct.eu/>

## Behavioral tests assessing motor function and spontaneous activity in mice

Behavioral paradigms to test motor function and spontaneous activity are of a manifold use in the evaluation of the efficacy of compounds in animal models of motor dysfunction, neurodegeneration and neuromuscular diseases as, Parkinson's and Huntington's disease or stroke models, but also to detect possible side effects of drugs on motor function. JSW Life Sciences provides several customized test setups evaluating motor coordination, balance and neuromuscular abilities in mice and rats, as well as animal models of motor dysfunction e.g. MPTP and 6-OHDA lesion.



Locomotor and exploratory behavior can be determined using the Open Field Test. Animals are placed in a square arena and length of the path, speed as well as number of rearing are evaluated as parameters for spontaneous activity. These parameters are influenced by impaired motor abilities by anxiety as well as

by arousal and respond therefore to drug treatment influencing those factors as well (e.g. sedative or stimulant drugs).

Mice naturally turn over when they are placed on the back, which is referred to as righting reflex and which can be used to assess, if basic motor reflexes are present.

The wire hanging and the grip strength test measure muscle strength and neuromuscular integration, referred to as grasping reflex and are therefore useful tools to evaluate models of neuromuscular diseases. In the wire hanging test animals are suspended from a wire which is placed in a certain distance above the surface. Hanging time is determined to conclude on forelimb strength and grasping abilities.

To assess the grip strength mice are allowed to grasp a triangular pull bar and are then pulled back in horizontal plane. The force applied to the bar before releasing the grip is recorded. Since the grip strength can be evaluated for each limb separately, especially effects of unilateral deterioration of motor centers in the brain can



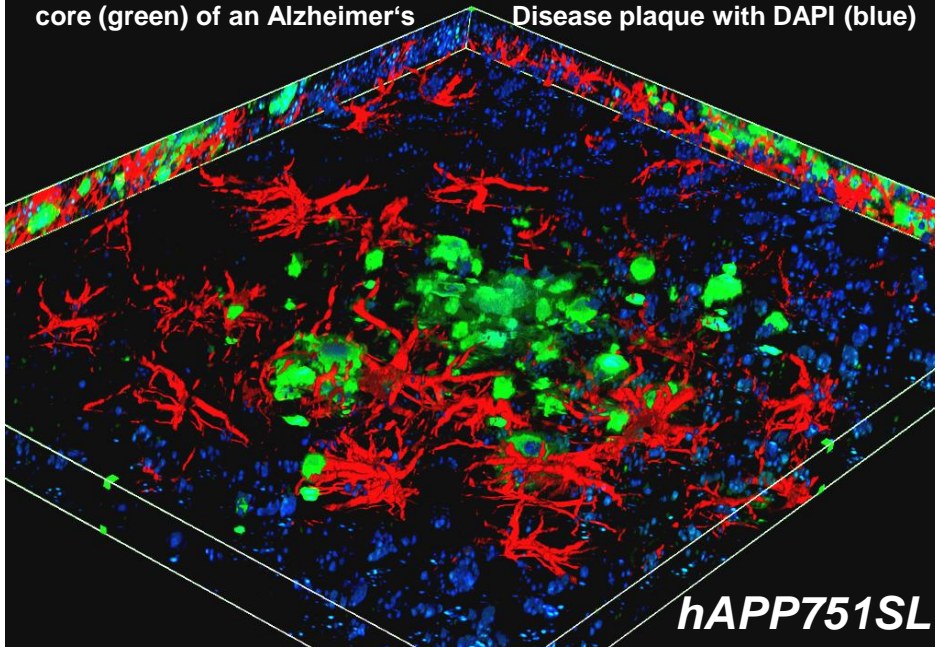
be quantified.

Gross deficits in motor coordination, balance and equilibrium can be determined using the Rotarod apparatus. The mouse is placed on a rod, which accelerates gradually.



Short latency to fall from the rod and low speed at falling off are indicators for disturbed motor coordination and balance. To evaluate deficits in the fine motor coordination, the beam walking and challenging beam walking tests are useful tools. The beam walking test examines the ability of the animal to remain upright and to walk on an elevated and relatively narrow beam without falling off or slipping to one side of the beam. Again, unilateral brain injury models tend to induce a hemiparesis, which can

3D reconstruction of reactive astrocytes (red) around a ThioS positive core (green) of an Alzheimer's Disease plaque with DAPI (blue)



cause the rodent to slip to one side. In the challenging beam walk setup, animals are trained to traverse a narrowing beam. On the test day the Plexiglas beam is replaced by a mesh grid. A high number of slips is reflecting motor coordination deficits.

A typical symptom of Parkinson's disease is bradykinesia, which can be evaluated in animal models using e.g. the pole test. The mouse is placed on top of a vertical pole and the time to turn around and get back to the target cage is determined. An increase in time is considered as bradykinesia.

1. Crawley JN (2000). What's Wrong with My Mouse?: Behavioral Phenotyping of Transgenic and Knockout Mice. Wiley-Liss: New York. xiii, 329pp.
2. Fleming SM, Salcedo J, Fernagut PO, Rockenstein E, Masliah E, Levine MS, Chesselet MF (2004) *J Neurosci* 24:9434-9440.
3. Ogawa N, Hirose Y, Ohara S, Ono T, Watanabe Y. (1985) *Res Commun Chem Pathol Pharmacol*. 50(3):435-41.

### Inflammation: Astrocytosis and Microgliosis – the Escort of Neurodegenerative Diseases

Reactive astrocytosis and activation of microglia accompany many brain diseases, such as AD, PD or HD as a sign of manifest inflammatory processes.

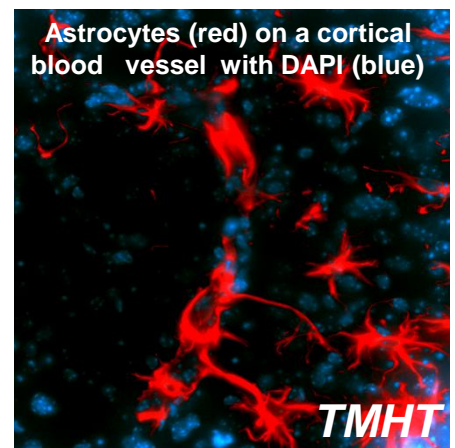
Both are closely related to abnormal accumulation and deposition of proteins, respectively. In this context modulation of inflammation that chaperones and/or triggers deposition comes more and more into the focus of interest becoming a drug target for the amelioration of clinical symptoms in a row of neurodegenerative disorders.

Astrocytes are essential for a vast lot of functions in the brain. Most of them are only marginally investigated today and it can be undoubtedly said that it is just scratching the surface of understanding.

They build the protection line of the brain tissue to the surrounding and represent a dominant part of the connective brain tissue delineating the different brain regions. Astroglia nurture neurons, are keepers of the homeostasis and play the major role in scarring after injuries. Furthermore they are even in the position to potentiate transmitter release at single synapses.

Recently Köhler et al. stated a pivotal role of astrocytes in dynamic signalling within the neurovascular unit. The regulation of local brain blood flow can be of importance when dealing with e.g. cerebral angiopathies, since GFAP reactive astrocytes are often directly associated with the vessel walls (see image) where they play a determining role in the control of blood brain barrier function.

As described by Kuchibhotla, one key question will be how increased astrocyte signaling impacts neuronal function, and another will be whether astrocyte activity limits or intensifies plaque deposition. This applies not only for plaques but also for other pathologies.



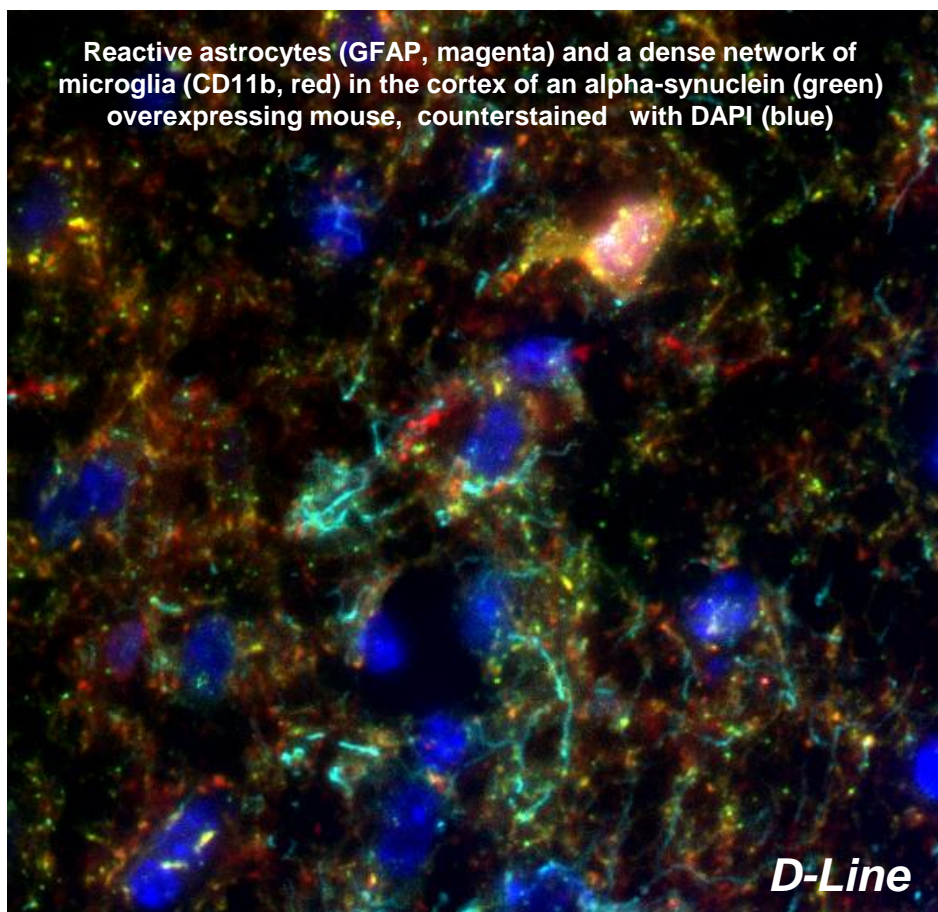
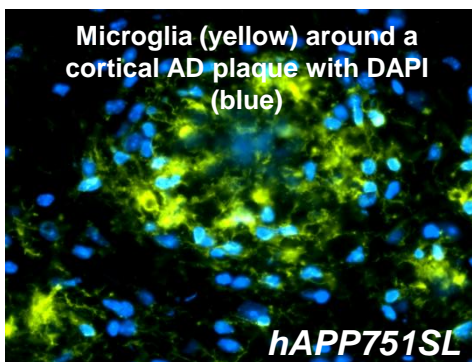
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Microglia is the cleaner of the brain digesting any rubbish the brain will produce. However, this macrophage activity is only one of their manifold functions. The cross-talk between neurons and microglia orchestrates the balance between synaptogenesis and neuronal death. As recently reported and imaged, microglia spreads its ultra-fine filaments to synapses and “ask” them via electric pulse if they are alive and working. (Wake et al. 2009).

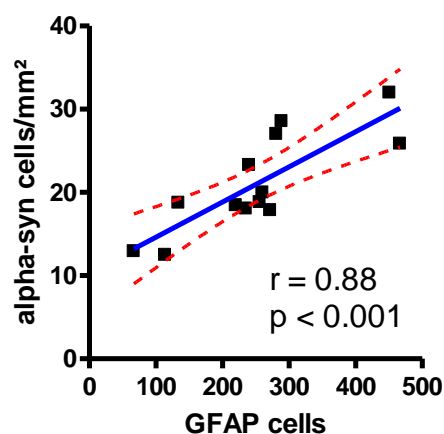
In amyloid plaques activated microglia spreads its fine filaments into the depositions and try to digest debris (see image lower left corner), while astroglia in concert tries to encapsulate it.

In human alpha-synuclein overexpressing mice (D-Line) microglia build a dense reactive network attached to the overloaded neuropil (see image right upper corner).

JSW routinely provides the service to investigate astro- and microgliosis in animal models. This reaches from antibody testing, protocol development and staining interpretation to quantification of astro- and microglia associated to pathological hallmarks such as amyloid depositions, Lewy-body like inclusions or Huntingtin positive neurons.



Quantification of hallmark and inflammation immunoreactivity in 10µm thick cryo sections (20x) allows correlation of pathology and inflammation in large subfields of the brain.



This figure exemplarily shows the correlation of astrocytosis and pathology investigated in the hippocampus of human alpha-synuclein overexpressing mice.

No doubt that the results of effectively pathology modifying compounds should be rounded off with the investigation of inflammation to clarify how the brain immune system reacts on the intervention, no matter for which disease and target, respectively.

1. Perea & Araque. Astrocytes potentiate transmitter release at single hippocampal synapses. *Science* 2007, 317: 1083-6
2. Köhler RC, Roman RJ, Harder DR. Astrocytes and the regulation of cerebral blood flow. *Trends Neurosci.* 2009 Mar32(3):160-9
3. Kuchibhotla KV, Lattarulo CR, Hyman BT, Bacskai BJ. Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. *Science.* 2009 Feb 27;323(5918):1211-5
4. Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J, Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. *J Neurosci.* 2009 Apr 1;29(13):3974-80

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