



G. Bicker

**Gerd Bicker**

- 1979** Ph.D., University of Freiburg, Germany  
  
Postdoctoral work at the Weizmann Institute of Science/Israel, University of California, Santa Cruz/USA, University of Alberta, Edmonton/Canada, and the Free University of Berlin/Germany
- 1993** Heisenberg Fellow at Free University of Berlin and University of California, Berkeley
- since 1997** Professor of Cell Biology at the School of Veterinary Medicine, Hannover

**Current Research**

During the development of the brain, neurons establish thousands of synaptic connections with other nerve or muscle cells. The signalling mechanisms that mediate the formation and maturation of neuronal connectivity are therefore central for an understanding of the computational power of the brain. Our group is interested in the cellular mechanisms underlying growth, adult plasticity and regeneration of synaptic connectivity. We are favouring a model system approach, focussing mainly on the development of individually identifiable neurons in insects such as the grasshopper and the fruit fly *Drosophila*. One advantage of the grasshopper is the almost complete understanding of the motor circuitry for flight, leg movements and escape behavior, facilitating studies of functional repair after neural injury. Moreover, the grasshopper nervous system offers the possibility for pharmacological manipulation in whole embryo culture whereas the accessibility of *Drosophila* to genetic analysis is unrivalled.

1. Nitric oxide / cyclic GMP signalling during function and formation of neural circuits

The gaseous messenger nitric oxide (NO) is one of the intercellular signals that regulates synaptic plasticity in developing and mature neurons. In target cells, NO stimulates its main effector enzyme guanylyl cyclase to produce cGMP, which in turn mediates many of the cell biological functions of the NO signal transduction pathway. In the area of synaptic plasticity we have shown that NO is a retrograde synaptic messenger in the postembryonic visual system of the grasshopper and at the neuromuscular junction of *Drosophila*.

The dynamic regulation of nitric oxide synthase activity and cyclic GMP levels during development suggests additional functional roles in the formation of nervous systems. Signalling by intracellular second messengers such as cyclic nucleotides and Ca<sup>2+</sup> regulates attractive and repulsive guidance of axons by extracellular factors. Our studies on pioneer neuron outgrowth implicate NO/cGMP signalling as a positive regulator in axonal elongation. The NO/cGMP signalling cascade is also permissive for the migration of postmitotic neurons in the enteric nervous system of the embryonic grasshopper. Since several signal transduction pathways that regulate axon guidance mechanisms in invertebrate and vertebrate animals are strikingly conserved in function, it is conceivable that nitric oxide signalling may also play an important role during neuronal migration in the vertebrate brain.

2. General features of brain development and repair

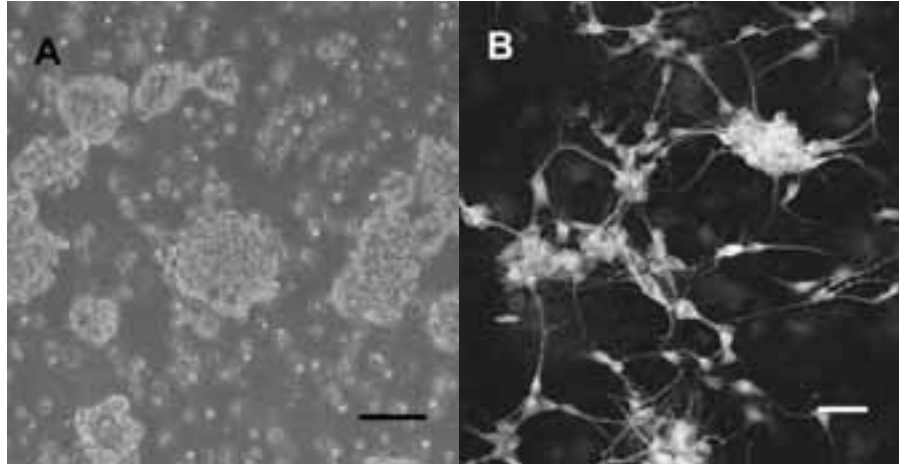
Another field of our interest is aiming at understanding the general features of brain design across animals. In collaboration with other groups, we have shown that in the *Drosophila* embryo the first interconnection of the cephalic hemispheres is made by axons that are guided across the midline by a bridge of neuronal cell bodies. This resembles the formation of the corpus callosum in the mouse, where axonal projections cross to the other brain hemisphere dorsal to the 'sling' – a transient bridge-like structure composed of immature neurons. Some neurochemical features are also common to both invertebrate and vertebrate nervous systems. For example, acetylcholinesterase (AChE) does not only catalyze the hydrolytic cleavage of ACh, but functions as cell surface molecule to mediate neurite outgrowth. Similar to the mammalian nervous system, regeneration of crushed axons is hardly possible in the adult insect CNS whereas peripheral axons have the capability to regenerate. We are currently exploring the possibility to improve the repair of central circuits by using AChE as cell surface substrate and by pharmacological manipulations of cyclic nucleotide levels.

3. Pathophysiological studies on human model neurons

To overcome the complexity of the mammalian nervous system, we are employing a human teratocarcinoma cell line (NTera-2) that can be induced to terminally differentiate into postmitotic neurons. However, the differentiation process described in the literature is rather time consuming. We introduced a cell proliferation step in free floating sphere cultures which shortened the total time of terminal differentiation to about a month. Differentiated cells show neuronal morphology, express neuronal markers,

Differentiation of NT-2 cells into neurons.

A Expansion of NT-2 precursors in free floating cell spheres. This technique resembles the sphere culture method used in embryonic stem cell differentiation. Scale 100  $\mu$ m



B Differentiated NT-2 neurons stained with immunofluorescence. Spindle shaped cell bodies send out neural processes. Scale 50  $\mu$ m

and are immunoreactive to members of an evolutionary conserved protein family (Elav-HuC/D) which is essential for the development of neuronal phenotype. The neurons are used to establish an in vitro assay system that allows to investigate mechanisms of hypoxic-ischaemic cell damage.

## Future Projects and Goals

There is a huge demand in current biomedical research for growing human nerve cells in culture systems. The generation of Ntera-2 neurons on a large scale allows for high-throughput screening of neuroprotective compounds effective in the human brain. Our improved production of neurons using the cell sphere culture method opens up new opportunities to study mechanisms of nerve cell differentiation. At the systems level, optical imaging techniques sensitive to cellular activity will allow to analyze the formation of synaptic connectivity in human neuronal circuits. To enhance chances for the regeneration of injured axonal connections in experimental animals, Ntera-2 neurons can be utilized as a source for cell transplantation. These transplantation studies will serve as model for the repair of damaged nerves in human patients.

## Selected Publications

- [1] Bicker G (1998) NO news from insect brains. **Trends Neurosci** 21: 349-355
- [2] Wildemann B and G Bicker (1999) Nitric oxide and cyclic GMP induce vesicle release at *Drosophila* neuromuscular junction. **J Neurobiol** 39: 337-346
- [3] Seidel C and G Bicker (2000) Nitric oxide and cGMP influence axonogenesis of antennal pioneer neurons. **Development** 127: 4541-4549

[4] Haase A and G Bicker (2003) Nitric oxide and cyclic nucleotides are regulators of neuronal migration in an insect embryo. **Development** 130: 3977-3987

[5] Paquet-Durand F, Tan S, and G Bicker (2003) Turning teratocarcinomas into nerve cells: Rapid differentiation of NT-2 cells in floating spheres. **Dev Brain Res** 142: 161-167

## Group Structure

Group leader:	Gerd Bicker
Senior scientist:	Michael Stern
Postdoctoral fellow:	François Paquet-Durand
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