

# Function and Dysfunction of the Nervous System

Funktion und Dysfunktion des Nervensystems

Coordinator: Carmen Birchmeier

Signalling Pathways and Mechanisms  
in the Nervous System

Coordinator: Carmen Birchmeier

Imaging of the Living Brain

Coordinator: Frauke Zipp

Pathophysiological Mechanisms of  
Neurological and Psychiatric Disorders

Coordinator: Helmut Kettenmann



Carmen Birchmeier-Kohler

## Structure of the Group

### Group Leader

Prof. Dr. Carmen  
Birchmeier-Kohler

### Scientific Manager

Dr. Michael Strehle

### Senior Scientists

Dr. Thomas Müller  
Dr. Alistair Garratt

### Scientists

Dr. Dominique Brühl  
Dr. Cyril Cheret

## Developmental Biology/ Signal Transduction

We analyze the functions of signaling molecules and of transcription factors in development of the nervous system and muscle. For this work, we use mice as a model organism. The molecular genetics of mice is well developed, and homologous recombination combined with embryonic stem cell technology can be used to introduce deletions or insertions into the genome. A further development of the technique, the Cre/LoxP technology, allows us now to introduce conditional mutations that are restricted to a particular cell lineage. We have used these technologies to analyze signals that maintain muscle progenitor cells and allow the formation of satellite cells, the stem cells of the adult muscle. In addition, we identified the function of several transcription factors in development of the nervous system. Among these is a novel factor, *Insm1*, that we found unexpectedly to perform also important functions in development of pancreatic beta-cells, the insulin-producing endocrine cells.

### The role of *Insm1* in neuronal development

Robert Storm, Jochen Welcker, Kira Balueva and Shiqi Jia (in collaboration with John Jacob and James Briscoe, MRC, London).

*Insm1* (insulinoma associated antigen) encodes a Zn-finger factor that is transiently expressed in differentiating neurons throughout the developing nervous system, as well as in endocrine cells of the pancreas and intestine. We generated mice with a targeted mutation to analyze the function of the *Insm1* gene. In an initial analysis, we identified *Insm1* as a factor crucial for the differentiation of beta-cells in the pancreas. Impaired function or loss of pancreatic beta-cells causes diabetes, a prevalent humane disease throughout the world. In the absence of *Insm1*, the expression program for hormones and a plethora of genes coding for proteins involved in secretion and vesicle transport was downregulated in beta-cells.

However, *Insm1* is not only required in endocrine cell development, but is also a crucial component of the transcriptional network that controls neuronal development. In *Insm1* mutant mice, differentiation of sympatho-adrenal precursors was strongly delayed, which was accompanied by reduced proliferation of the precursors. Whereas sympathetic neurons differentiated late and in reduced numbers, resulting in small sympathetic ganglia, terminal differentiation of adrenal chromaffin cells, the major source of noradrenaline, did not occur. The catecholamine noradrenaline is essential for fetal heart function and survival. Due to a pronounced noradrenaline deficiency, *Insm1* homozygous mutant mice died during mid-gestation, but we could rescue them by administration of catecholamine intermediates. Analysis of the transcriptional network governing sympatho-adrenal precursor differentiation indicated that *Insm1* acts downstream of *Mash1* (*Ascl1*) and *Phox2b*.