

## A NEW MOUSE MODEL OF AMYOTROPHIC LATERAL SCLEROSIS WITH FUS GENE MUTATION: MECHANISMS OF NEUROPATHOLOGY AND EFFECTS OF STANDARD AND NEW TREATMENTS

Tatyana Strekalova

Graduate College University Würzburg, Germany

A novel transgenic mouse line, which is based on the mutation of the DNA/RNA-binding factor Fused in sarcoma protein (FUS), DNA/RNA-binding factor, was used as a paradigm for amyotrophic lateral sclerosis (ALS).

**Aims:** We investigated the motor, behavioral, and molecular parameters of FUS-transgenic (FUS-tg) male and female mice and their wild-type littermates during the pre-symptomatic and symptomatic phases of pathology. Several new treatments have been applied, from standard therapy, riluzole, to new pharmaca, herbal antioxidants, and transplantation therapy, to study their potential efficacy. In addition, we address a role of systemic inflammation in the development of ALS-like syndrome in these mice.

**Methods.** Motor parameters were studied in the cat walk, Pole and Wire and rotarod tests. Emotionality was tested using the forced swim, tail suspension, sucrose preference, and dark-light O-maze tests. Cognitive functions were investigated using the new object recognition and food pellet displacement paradigms. Muscle weight, motor neuron scores, water and food intake, body weight, and onset of paralysis were assessed. A histological investigation of motor neuron degeneration was performed in the lumbar parts of the spinal cord. Bio-

chemical changes were studied by metabolome and ELISA assays. Changes in gene expression of several markers of cellular distress and inflammation were examined using PCR. Markers of oxidative stress have been studied in the brain and the spinal cord.

**Results.** We found multiple emotional and cognitive aberrations and altered behavioral responses to systemic inflammation in FUS-tg mice at the pre-symptomatic stage. At the symptomatic stage, FUS-tg mice displayed profound changes in the markers of oxidative stress, inflammation, and advanced motor neuron degeneration. Positive effects of several applied treatments were found on these measures, as well as on motor and basic physiological functions accompanying a prolongation of the life span. Remarkably, some of these treatments, such as for example, stem cell therapy and thiamine (B1) derivatives, were shown to be more pronounced than the effects of the standard drug riluzole.

**Conclusions.** First, the proposed FUS-tg model of ALS serves as a reliable tool for investigating new therapies for ALS. Second, our study suggests that there is still room for substantial improvement in the therapy of this fatal disease in the clinic.