

## Characterization of motor neuron loss in animal models featuring prolonged disease duration

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Motor neuron loss is a feature of amyotrophic lateral sclerosis (ALS), spinal muscle atrophy (SMA) and it is recently described in other neurodegenerative disorders. In humans these disorders vary from dramatically short up to long disease duration. A short disease duration in humans ranges from some months up to 1 or 2 years. In contrast animal models commonly used to evaluate motor neuron disorders are extremely short lasting, where motor impairment lasts about a few weeks. This is the case of the G93A mouse model which is expected to reproduce ALS in humans. Despite commonalities, this condensed time interval is likely to produce different pathological correlates. Therefore, it is not surprising that experimental morphology and therapeutics fail to detect some hallmarks of human disorders in these animal models. This temporal discrepancy is often missed out and genetic background as well as evolution-based structural differences in motor systems are considered as critical determinants instead. The present communication wish to introduce the benefits of a long-lasting animal model of motor neuron disorders. In detail, we had been able to characterize the motor failure, the biochemical abnormalities and the morphological alterations which develop only at prolonged time interval (18 months) using a single knock out double transgenic mouse model of human SMAIII.

In these mice we had been able to dissect for the first time morphological alterations typical of human disorders such as motor neuron heterotopy as well as motor neuron loss. This is correlated with a profound loss of the survival motor neuron (SMN) protein. There was a remarkable somatotopic correlation between the specific motor deficit (proximal vs distal limb muscles) and the severity of motor neuron loss in the corresponding pool (medial vs lateral) of motor neurons in the spinal cord. This ideal experimental context provides the chance to evaluate the therapeutic effects of specific drugs administered in the long run ruling out bias due to experimental variability when the drugs are administered only for a few weeks. In this way it is also easy to discern symptomatic vs disease modifying effects.

In line with this, we compared the effects of GSK3 beta inhibitors and/or autophagy activators and we found a remarkable induction in the SMN protein which was in line with protection from motor neuron loss and a steady effect counteracting the long term progressive motor deterioration.

Keywords: Motor neuron disorders, animal models, survival motor neuron protein, autophagy.