Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease with four to five years of average survival time after the diagnosis. ALS is relatively frequent: more than 220.000 people across the globe were diagnosed in 2015 and this number is unfortunately expected to reach over 370.000 in 2040. Over the last decades many famous people were diagnosed with ALS including: Lou Gehrig – a US baseball player, Stephen Hawking – internationally renowned physicist or Donald George Revie – a UK professional football player. Despite years of intensive study, there is still no cure for ALS, and the only EU approved drug "Riluzole" increases the patient's lifespan by approximately 2 – 3 months. The main feature of ALS is the degeneration of specific nerve cells called motoneurons. These cells create a signal that is transferred by the nerve fiber to the muscle, eliciting muscle contractions. If motoneurons are damaged, contractions are not possible any longer and upon disease endstage, patients die due to paralysis of the respiratory muscles. However, the degeneration of motoneurons is not uniform. Within the motoneurons cell group, some cells will be affected very early in the disease, whereas some others will be resistant and survive up to the very disease endstage. What is the cause of this difference, and how do the resistant cells protect themselves from the disease? In sharp contrast with the dominant excitotoxicity theory that suggests that motoneuron activity is increased up to a harmful level, our recent studies indicate that motoneurons display fundamentally different pathophysiology in ALS. Their functioning is inhibited, not exaggerated.- Indeed, both intrinsic excitability and synaptic excitation level are reduced in motoneurons. This general reduction indicates that the normal regulation, called homeostasis, between excitability and synaptic excitation, is breakdown and emerges as a key factor contributing to motoneuron degeneration. However, we still do not know what causes this homeostatic breakdown.

In our project, we aim to determine what causes this breakdown and whether rescuing it may have a positive impact on disease progression. To this aim we will investigate which activity-dependent intracellular pathways are dysregulated in motoneurons. Following pathway-identification, we will rescue it with an appropriate gene delivery using virus and we will test the impact of our manipulation on motoneuron physiological properties, and disease progression. The study will be conducted on mice harboring a human mutated SOD1 gene because these mice display an ALS phenotype similar to humans. Thereby our investigations have the potential to be further translated to human studies. In order to achieve the goals of the project we will use a cutting edge in vivo electrophysiological techniques enabling intracellular recordings of individual mouse motoneurons and innovative viruses which will enable us to modify selected intracellular pathways. All experiments will be performed in keeping to the 3R principles. As a result of this project, we expect to significantly improve our knowledge about ALS pathophysiology and pave the way for innovative therapeutic approaches which will focus on the intracellular pathways identified by this project.