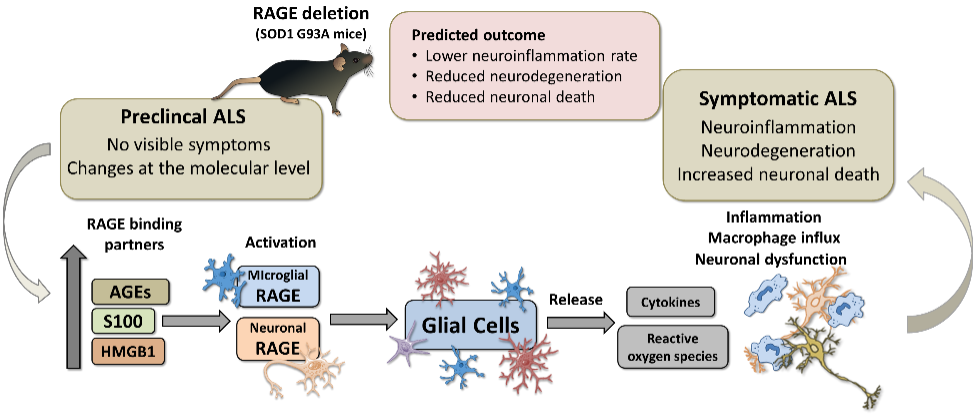
The role of RAGE, receptor for advanced glycation end-products, in the progressive spinal motor neuron degeneration in familial Amyotrophic Lateral Sclerosis in the mouse model of the disease

RAGE (the receptor for advanced glycation end-products) is a powerful immunoglobulin receptor present primarily on the surface of immune, nervous and epithelial cells. RAGE was discovered in the early 90s as a receptor of Advanced Glycation End-Products (AGEs). AGEs are chemical compound molecules occurring naturally during the physiological process of aging. Outside the body, AGEs can be found in a number of food products following food processing (frying, roasting, smoking). Increased AGE production is also observed in many disorders such as - diabetes, atherosclerosis, renal failure, and in many neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease or Amyotrophic Lateral Sclerosis (ALS). AGEs modify the chemical structure of many key proteins essential for the proper functioning of the cell, impairing their function and, in extreme cases, leading to cellular death. Studies have shown that in nervous tissue, bonds between RAGE and AGE increase inflammation in affected tissues, slowing down regenerative processes and exacerbating inflammation thus leading to cellular malfunction.

In our project, we plan to determine the role of RAGE in ALS – a rapidly progressive, incurable disease of motor cells of the spinal cord. The accompanying impairment of peripheral nerve leads to weakness, slow atrophy and paralysis of skeletal muscles, resulting in death after three to five years post diagnosis. Every year in Europe, fifteen thousand new cases of the disease are diagnosed. So far, despite intensive studies, efforts have failed to establish a coherent image of the causes of this disease. It is currently believed that the neurodegenerative changes that occur in the ALS spinal cord arise from a number of overlapping processes such as cellular stress, mitochondrial defects, neuroinflammation, axonal transport deficiencies and the formation of protein aggregates. One of the proposed factors, considered to be a possible link between the various processes occurring in ALS is the RAGE protein.

In this project, based on the results of our previous studies and existing knowledge, we hypothesize that the pathological processes occurring in ALS-affected neurons trigger the production of RAGE binding molecules (AGEs, S100, HMGB1) and incite RAGE activation. Once activated, RAGE stimulates production of pro-inflammatory factors from glial cells, amplifying oxidative and neuronal stress and exacerbated neuroinflammation, leading to neurodegeneration and neuronal cell death. We predict that the deletion of the RAGE gene will decrease oxidative stress and neuronal degeneration, reducing ALS symptoms and offering neuronal protection in mice affected with ALS (Figure 1).



We aim to uncover general mechanisms governing RAGE-triggered neuroinflammation in ALS and believe that by doing so, the results of our studies might be translated into the clinic – replacing genetic deletion with RAGE-pharmacological-blockade, supplemented with anti-inflammatory therapy, thus alleviating symptoms of the disease and improving the quality of life in ALS patients.