FONDATION THIERRY LATRAN
Under the aegis of Fondation de France

# Role of the major histocompatibility complex I (MHCI) in ALS

**Principal Investigator:** Dr. Giovanni Nardo

**Other Investigator:** Dr. Caterina Bendotti

**Grant: 120,000€**

**Project duration: two years**


## Summary of the research project

Motoneuron loss is the primary cause of ALS but there are increasing evidences suggesting that immune cells have an important influence on the disease course in ALS patients and mouse models. In fact, although the central nervous system is considered immunoprivileged due to the blood brain barrier (BBB), immune cells infiltrates are found in brain and spinal cord of post-mortem ALS patients. In addition, the axons of spinal motoneurons which are not protected by BBB can communicate with the immune system during the entire course of the disease.
We recently found that spinal motoneurons of a mouse model of familial ALS activate a series of key molecules involved in such communication like the immunoproteasome and the molecules of major histocompatibility complex I(MHCI). In particular we observed that these molecules accumulate preferentially in motor axons and neuromuscular junction of SOD1G93A mice at the disease onset.

With the present project we intend to investigate if this phenomenon represents an attempt of the motoneurons to protect themselves from the progressive degeneration, or if it takes part to the pathogenic mechanism that leads the motoneurons to death.
Addressing this issue is of fundamental importance to understand the mechanisms responsible for the rapid progression of the disease and to identify useful approaches that may stop or at least slow down considerably its course. For this we will study how and through which mechanism, the lack of β2-microgoblulin, an essential component of MHCI, will affect the development and course of disease in a mouse model of ALS.
Determining the extent to which the neuronal and immune system share similar mechanisms is a *sine qua non* condition before we can think of developing a targeted pharmacological treatment. With the present project, we propose to study the activity of MHC-I in ALS. Once we have clarified its specific role in the pathogenesis it will be possible to develop innovative immunotherapies at the early stages of the disease through a positive regulation of the inflammatory response. The outcome of the proposed project will elucidate poorly understood biological mechanisms related to CNS / immune system cross-talk, and may provide new avenues for the diagnosis, treatment and prevention of ALS

**Giovanni Nardo**: In 2009, he earned PhD in Biochemistry and Molecular Biology at the Mario Negri Institute. Since 2010 he is a post doctoral research fellow at the Mario Negri Institute (Italy) in the Molecular Neurobiology lab (Dept. Neuroscience), directed by Dr. Caterina Bendotti.