



## **Translational modulation of synaptic inputs to MN through PKA-coupled receptors: bringing excitation to the clinics**

**Acronym: TriALS**

**Principal Investigator:** Francesco ROSELLI

**Co PI:** Daniel ZYTNICKI

**Grant: 100 000€**

**Duration: three years**

### **Summary of the research project**

In projects previously funded by the Thierry Latran Foundation (Prof. D. Zytnicki), we have found that motoneurons vulnerable to ALS display reduced firing early in disease, and this hypoexcitability is associated with the reduced efficiency and loss of GluR4 receptors in Ia excitatory synapses.

Restoring motoneuron excitation is neuroprotective, and we have demonstrated that synaptic efficiency can be improved by activating the PKA signaling pathway.

We propose to use this information to investigate drugs that could be used to improve motoneuron excitation in human patients. In experiments performed in Ulm and in Paris, we will investigate if PKA activation in motoneurons via dopaminergic, histaminergic or adrenergic agonists can enhance receptor trafficking to synapses, restore Ia synaptic physiology and motoneuron excitation and affect clinical progression and survival in two distinct models of ALS (mutant SOD1 and mutant FUS). We will focus on repurposing drugs already approved for human use in order to proceed quickly to human trials.

Our approach not only opens up an innovative way to intervene in ALS but may also drive clinical trials in shorter time, since we focus on repurposing existing drugs rather than developing them from scratch.

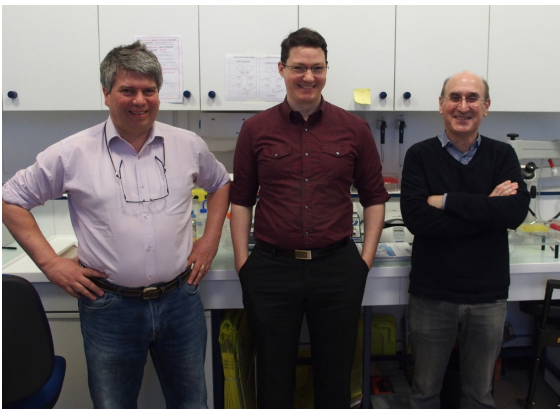
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The study will be conducted by Francesco Roselli, Dept. of Neurology, Ulm University School of Medicine.



From left to right: Najuwa Ouali-Alami, Sarah Holl, Alberto Catanese, Qian Li, Thomas Lenk, Florian olde Heuvel, Francesco Roselli (the one above), Akila Chandrasekar, David Bayer, Barbara Commisso, Rida Rehman.

And Daniel Zytnicki, Centre de Neurophysique, Physiologie et Pathologie; CNRS UMR 8119 Université Paris Descartes



The group of permanent researchers in the lab:  
B. Lamotte d'Incamps, left  
Marin Manuel, in the middle, and  
Daniel Zytnicki will be the main researchers on the Paris side  
involved in this project.