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## RESEARCH PROJECT:

**Clinical, neuroradiological and molecular investigation of Adult-onset Autosomal Dominant LeukoDystrophy (ADLD): dissection of Lamin B1-mediated pathophysiological mechanisms in cellular and mouse models.**

### **The aim of the research:**

Lamin B1 (LMNB1) is a component of the nuclear lamina.

It has been recently discovered that the presence of an extra copy of the gene encoding this protein causes autosomal dominant leukodystrophy (ADLD). ADLD is an invariably fatal neurodegenerative disease characterized by white matter loss, movement disorders and dysfunction of the cardiovascular, genito-urinary, gastrointestinal systems and thermoregulation. The pathogenic mechanisms by which LMNB1 overexpression leads to disease are unknown. This project aims at clarifying such mechanisms. To this end, we will perform genetic studies to elucidate ADLD genetic defects; we will study autonomic functions and magnetic resonance (MR) features of affected individuals to identify presymptomatic markers of disease useful for early therapeutic intervention. The effects of LMNB1 overexpression on cellular function will be studied in cultures of cells derived from ADLD patients. In addition, we will generate a transgenic mouse model of LMNB1 overexpression. Such model will be instrumental to investigate cerebral neurodegenerative mechanisms associated with altered levels of LMNB1. Results from this study will clarify LMNB1-mediated pathogenic mechanisms and will potentially identify novel molecular targets for ADLD therapy.

INVESTIGATOR OF RESEARCH PROJECT: GASPARINI Laura

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