# 12th Call for Research – Lay summaries of selected projects

Full information can be found here: SMA Europe | Our Call for Research Projects | SMA Innovation

**Dr. Gabriella Viero** (National Research Council, Trento, Italy)

**"Leveraging SMN role in translation to develop the next-gen of biomarkers for SMA."**

While the development of treatments increasing SMN levels marks significant progress in managing SMA, challenges persist and new symptoms are emerging in treated individuals that affect various bodily functions beyond muscles and nerves. This underscores the need for a broader understanding of SMA as a systemic condition. As existing biomarkers for SMA are limited and focus only on neuromuscular indicators, Dr. Viero and her team aim to develop advanced biomarkers, using molecular data to track disease progression and treatment responses accurately. Dr. Viero's previous work has showed how SMN loss affects protein translation in SMA models. Using advanced technologies, the team will now test samples from SMA patients treated with approved drugs. Their goals include confirming the role of SMN in protein production, identifying specific translational changes indicative of SMA subtypes, and validating these biomarkers in real-world patient samples.

**Prof. Dr. Simon Parson** (University of Aberdeen, UK)

**"Are microvascular defects relevant in Spinal Muscular Atrophy?: Characterisation of the mouse model."**

While the pathology in nerve and muscle is most significant in people living with SMA, Prof. Parson and his team have shown wide ranging changes in the cardiovascular, gastrointestinal and renal systems, and observed an underlying defect in the blood vessels which supply these systems. Importantly, defects in blood vessels are associated with nerve cell loss. In this project, the team will characterize a new transgenic mouse model to determine if these defects in blood vessels may cause or make worse patient symptoms. The findings will help guide the future development of therapies to target these aspects of the pathology.

**Dr. Morgan Gazzola** (I-Stem - Institute for Stem cell Therapy and Exploration of Monogenic diseases, Corbeil-Essonnes, France)

**"Deciphering the Molecular Landscape of Neuromuscular Development in Spinal Muscular Atrophy."**

Although new treatments for SMA have been approved, many challenges remain in terms of cost, side effects and timing of use. To develop new combinatorial therapies, further efforts are needed to better understand the pathophysiology of SMA and identify new molecular mechanisms driving this pathology. Dr. Gazzola's project will use advanced cellular and molecular techniques to investigate how the loss of SMN affects the development of the neuromuscular junction, the region where nerves and muscles connect. By differentiating human stem cells into complex mini neuromuscular organs (called neuromuscular organoids), the team aims to enhance understanding of SMA at the neuromuscular junction and explore changes in gene expression and DNA structure. Ultimately, this

project could identify novel molecular targets for the development of combined therapies, and improve outcomes for SMA patients.

**Dr. Nathalie Didier** (INSERM - Institut national de la santé et de la recherche médicale, France)

**"Skeletal Muscle Stem Cells as untapped therapeutic targets for SMA long-term treatment (SATSMA)."**

While the approved disease-modifying therapies for SMA have provided significant benefits for people living with this condition, the long-term effects of these treatments remain unknown, and results are more variable for late-treated patients and those with milder forms. Therefore, it is crucial to better define SMN protein requirements and the effects of the treatments in all tissues, especially muscle, which is particularly affected by the disease. Dr. Didier and her team, including Dr. Smeriglio, discovered that muscle stem cells (MuSCs) have a high requirement for SMN, and that a lack of SMN in these cells is sufficient to induce motor neuron death. Given the key role of MuSC in maintaining muscle tissue and its ability to repair itself, it is essential to determine whether the approved therapies are able to preserve these cells. Accordingly, Dr. Didier, in collaboration with Dr. Smeriglio, will focus on better understanding the link between MuSC and motor neurons, and exploring whether and how oral risdiplam treatment acts on these cells.

**Dr. Sorana Ciura** (Institut Imagine, Paris, France)

**"Investigating Calcium-induced mitochondrial dysfunction in zebrafish and iPSC models of SMA."**

While breakthrough therapies have emerged for SMA, several patients still experience severe symptoms, highlighting the need for complementary treatments. To address this, Dr. Ciura and her team have developed a new zebrafish model mimicking SMA, which show versatility for both mechanistic investigations and screening platforms to test new drugs. By studying this model, the team has found links between calcium levels, mitochondria (the cell's energy factories), and SMA symptoms. Using both zebrafish and patient-derived cells, the team will now explore whether targeting calcium pathways could be a new strategy to treat SMA.