Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
Università degli Studi di Napoli Federico II

**PNRR Missione 4, Componente 2, Investimento 1.4 "Potenziamento strutture di ricerca e creazione di "campioni nazionali di R&S" su alcune Key Enabling Technologies"**
*Iniziativa finanziata dall'Unione europea –- NextGenerationEU.*

**National Center for Gene Therapy and Drugs based on RNA Technology**
**Sviluppo di terapia genica e farmaci con tecnologia a RNA**

Codice progetto MUR: **CN00000041** – CUP UNINA: **E63C22000940007**

**Doctorate of National Interest**
**RNA THERAPEUTICS AND GENE THERAPY**

**TITLE OF THE RESEARCH PROJECT**
**Targeting the inflammatory response via mitochondrial ion homeostasis modulation**

**SELECT ONE OF THE FOLLOWING RESEARCH AREA:**
☒ **Mechanisms of Diseases and Drug Target Identification**
☐ **Design and Delivery of New Gene Therapy and RNA-Based Medicines**
☐ **Validation and Safety In Preclinical and Clinical Studies**

**LOCATION OF THE RESEARCH ACTIVITY (INSTITUTION/DEPARTMENT):**

Department Biomedical Sciences

**TUTOR:**
Rosario Rizzuto

**PROPOSED RESEARCH ACTIVITIES (max 300 words):**
Inflammation is a fundamental immune response to infection or injury, characterized by redness, heat, swelling, and pain. Chronic inflammation can lead to various diseases, including autoimmune disorders and chronic inflammatory conditions. The inflammasome is a critical player in the inflammatory response: activation of this multiprotein complex leads to the production of pro-inflammatory cytokines such as IL-1β and IL-18, which are crucial for orchestrating the immune response.

Mitochondria, known primarily for their role in energy production, are also key regulators of inflammation. They house calcium and potassium channels that are essential for maintaining mitochondrial and cellular homeostasis. The mitochondrial calcium uniporter (MCU) and potassium channels (like mitoKATP) regulate the influx of calcium and potassium ions, respectively, which are vital for mitochondrial function and health.

Calcium signaling within mitochondria is crucial for various cellular processes, including ATP production, metabolism, and apoptosis. The MCU allows the entry of calcium into the mitochondrial matrix, which is necessary for activating several enzymes involved in the Krebs cycle, thereby boosting ATP production. However, excessive mitochondrial calcium uptake can lead to mitochondrial dysfunction, increased production of reactive oxygen species (ROS), and initiation of cell death pathways. Elevated ROS levels are known to activate the NLRP3 inflammasome, thereby linking mitochondrial dysfunction to inflammation. Similarly, potassium channels in mitochondria help maintain mitochondrial membrane potential and protect against cellular stress. Disruption of potassium homeostasis can trigger inflammasome activation. Specifically, a decrease in intracellular potassium levels is a well-known trigger for NLRP3 inflammasome activation, leading to the maturation and release of IL-1β and IL-18. Thus, the proper function of mitochondrial calcium and potassium channels is critical in regulating inflammasome activation and, consequently, the inflammatory response. Targeting these channels via RNA based modulation of these fundamental channels may offer new therapeutic strategies for controlling excessive inflammation and treating chronic inflammatory diseases.