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
Understanding the complex interplay between gut microbiota, calcium and potassium signaling

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 of Biomedical Sciences – University of Padova
Sanofi – (Italia)

TUTOR:

Rosario Rizzuto (University of Padova)
Mariangela Amoroso (Sanofi-italia)

PROPOSED RESEARCH ACTIVITIES (max 300 words):

The human gut microbiota plays a crucial role in maintaining intestinal health, but its dysregulation is linked to inflammatory bowel disease (IBD), a chronic condition characterized by persistent inflammation of the gastrointestinal tract. Emerging research highlights the intricate connections between microbiota, inflammation, calcium and potassium signaling, mitochondrial function, and inflammasome activation in the pathogenesis of IBD. In IBD, the balance of gut microbiota is disrupted, leading to dysbiosis, which triggers an inappropriate immune response. This abnormal response is partly mediated by changes in intracellular calcium and potassium levels. Calcium signaling is essential for various cellular processes, including the regulation of immune responses. Inflammatory conditions often lead to altered calcium flux, which can exacerbate inflammation by promoting the activation of immune cells and the production of

pro-inflammatory cytokines. Potassium, another vital ion, also plays a significant role in maintaining cellular homeostasis and modulating immune responses. Altered potassium levels can activate the NLRP3 inflammasome, a multiprotein complex that detects pathogenic microorganisms and stress signals. Upon activation, the NLRP3 inflammasome triggers the cleavage of pro-caspase-1 into active caspase-1, leading to the production and secretion of the pro-inflammatory cytokines IL-1β and IL-18. This process amplifies the inflammatory response, contributing to the chronic inflammation observed in IBD. Mitochondria are crucial for cellular energy production and regulation of apoptosis, in IBD mitochondrial dysfunction is common, characterized by reduced ATP production, increased reactive oxygen species (ROS) generation, and impaired mitochondrial membrane potential. Mitochondrial damage can further activate the NLRP3 inflammasome, creating a vicious cycle of inflammation and cellular damage. Manipulation of the calcium and potassium channels of the mitochondria might thus be therapeutically relevant in the activation of the inflammatory response and will be tested in vitro and in vivo. Understanding the complex interplay between gut microbiota, calcium and potassium signaling, mitochondrial function, and inflammasome activation could open new therapeutic strategies for IBD. Targeting these pathways may help restore intestinal homeostasis, reduce inflammation, and improve the quality of life for patients suffering from this debilitating condition.