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

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):

Università Federico II Napoli, Dipartimento di Medicina Molecolare e Biotecnologie Mediche

TUTOR:

Francesca Carlomagno

PROPOSED RESEARCH ACTIVITIES (max 300 words):

Role of NCOA4 in Ferroptosis

Iron is necessary to sustain cell metabolism and DNA replication and its dysregulation is associated to several diseases such as anaemia, hemochromatosis, and cancer. Iron is also involved in a novel form of programmed cell death, ferroptosis, promoted by phospholipids peroxidation. Ferroptosis is involved in pathologic processes such as reperfusion damage and neurodegeneration. NCOA4 is an iron-sensing protein that, in iron deficiency, mediates autophagic degradation of ferritin (ferritinophagy) to restore intracellular iron concentration and inhibits DNA replication origin activation to avoid replication stress. NCOA4 has been shown to be involved also in ferroptosis, even if the relevance of such involvement in vivo has not been described yet. Since ferroptosis relies on an increase of intracellular iron concentration to allow lipid peroxidation, NCOA4-mediated ferritinophagy is expected to be essential to fuel iron for peroxidation spreading.

The project aims at understanding: i) whether NCOA4-mediated release of iron storage from ferritin is essential to activate ferroptosis in vivo; ii) which are the signaling pathways that promote ferroptosis, especially those that insist on NCOA4 activation. These aims will be developed by exploring ferroptosis susceptibility of NCOA4 $^{-/-}$ mice treated with ferroptosis inducers or crossed to ferroptosis prone mouse models (CreER^{T2}/GPX4$^{fl/fl}$). Moreover, a knock-in NCOA4 I489-W497 mouse selectively deficient of ferritinophagy will be developed and subjected to treatment with ferroptosis inducers or crossed with CreER^{T2}/GPX4$^{fl/fl}$ mice. Finally, a proteomic screening will be performed to identify possible phosphorylation sites of NCOA4 upon ferroptosis induction. With this project we expect to understand whether NCOA4 represents a positive regulator of ferroptosis and a possible target for RNA-based therapies of diseases promoted by ferroptosis.

Selected articles of the PI

1. Bellelli R, et al. Mol Cell 2014; 55:123-37.
2. Bellelli R, et al. Cell Rep 2016; 14:411-2.
3. Federico G, et al. Cell Rep 2022; 40:111207.