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):

DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA, UNIVERSITA' MAGNA GRAECIA CATANZARO

TUTOR:

GIUSEPPE VIGLIETTO

PROPOSED RESEARCH ACTIVITIES (max 300 words):

Background

Cancer cells rewire their metabolism to satisfy the bioenergetic, biosynthetic, and redox demands of tumors, which is necessary for the maintenance of highly proliferating cancer cells. However, the metabolic reprogramming of cancer cells creates metabolic vulnerabilities that can be therapeutically targeted [1]. A recent work performed on a panel of 689 cancer cell lines, represented the first characterization of the landscape of metabolic pathway vulnerabilities in cancer cell lines [1]. In this seminal work, the activity of metabolic pathways was inferred by gene expression data from 689 cancer cell lines overlapping between the Cancer Cell Line Encyclopedia (CCLE) [2,3] and the Cancer Dependency Map [4] using single-sample gene set enrichment analysis

(ssGSEA) of the RNAseq data from each cell line normalized to all other cell lines (normalized enrichment scores, ssNESs).

Proposed research

The general objective of the project is to perform a characterization of the miRNAs involved in metabolic pathways in tumors of patients affected by ovarian cancer (OC) and identify the corresponding metabolic vulnerabilities.

This objective will be pursued by applying a bio-informatic pipeline recently implemented for analysis of cell lines [1] and adapted for analysis of tumor data (Metabolic Pathway and Dependency Algorithm, MeDPA) (our preliminary unpublished results). The algorithm will be applied to OC patients that will be characterized for the activities of metabolic pathways both by analysis of miRNA expression and by measurement of metabolites' concentration in fluids and/or samples. The activity of metabolic pathways will be subsequently validated in organoids established by the same patients and metabolic dependencies of tumors will be inferred by the MeDPA algorithm. Finally, metabolic dependencies of tumors will be validated in selected cultures of organoids on the basis of the metabolic dependencies identified, by investigating the effects of specific metabolic-targeting drugs on cell proliferation and/or survival in organoids.

References

1. Joly JH, Chew BTL, Graham NA (2021) PLoS Comput Biol 17(4): e1008942.
2. Ghandi M, et al. Nature. 2019;569: 503–508. pmid:31068700
3. Barretina J, et al. Nature. 2012;483: 603–607.
4.Tsherniak A, et al. Cell. 2017;170: 564–576.e16.