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
Investigating and targeting the DNA damage response to generate new cancer therapies

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 Molecular Medicine and Medical Biotechnology, University of Naples "Federico II", Naples, Italy.

TUTOR:
Dr. Luca Palazzo

PROPOSED RESEARCH ACTIVITIES (max 300 words):
Poly(ADP-ribose) polymerases (PARPs) are the major family of enzymes that synthesize an abundant posttranslational protein modification called ADP-ribosylation. Through their ability to modify different target proteins and to respond to variety of stimuli, PARPs control genome stability, cell differentiation, metabolism and immune responses. Inherited defects in the protein components of the pathways regulated by PARPs often cause disease in humans such as cancer, immunodeficiencies, neurodegeneration and developmental syndromes.

In recent years it has become apparent that using specific drugs to inhibit or modulate protein ADP-ribosylation can be very effective in disease treatment (e.g., breast, ovarian, pancreatic and prostate

cancer). Thus, furthering our knowledge of the protein factors and pathways regulated by PARPs provides a basis for the development of new therapies.

PARP1 is the most active PARP enzyme in human cells and it is critical for the regulation of nuclear processes such as DNA damage repair, transcription, maintenance of chromatin structure and replication. We recently identified a PARP1 interactor, HPF1 (histone PARylation factor 1), and showed that HPF1 allows PARP1 to specifically ADP-ribosylate serine residues in histones and many other proteins important for the maintenance of genome stability. Additionally, we uncovered that ARH3 enzyme act as a specific hydrolase that reverses serine ADP-ribosylation in cells. The aim of the PhD project will be to elucidate the exact molecular and pathophysiological functions of HPF1, ARH3 and their target proteins in regulation of genome stability. Furthermore, the PhD candidate will address the implications of targeting/modulating serine-ADP-ribosylation pathways as a novel therapeutic approach for killing cancer cells, thus providing new options for chemo-resistant tumors.

Our laboratory covers a large variety of techniques that will enable us to efficiently study such molecular pathways on different levels (protein biochemistry, cell biology and bioinformatics). The doctoral student will spend six months in a collaborative laboratory abroad.