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 THERAPUETICS 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):

University of Bologna, Department of Medical and Surgical Sciences

TUTOR: Prof.Caterina Garone

PROPOSED RESEARCH ACTIVITIES (max 300 words):

The PhD program will focus on the development and characterization of 2D and 3D (organoids) models for studying the disease mechanisms and identify novel targets for therapy in mitochondrial DNA (mtDNA) maintenance disorders. mtDNA maintenance disorders are caused by Mendelian inherited defects in nuclear-encoded proteins playing a role in the mtDNA machinery or *de novo*/salvage pathway of mitochondrial nucleotides pool causing quantitative (depletion) or qualitative (point mutations and multiple deletions) mtDNA defect. Clinically, they present as a spectrum ranging from severe infantile multi-systemic disease, rapidly progressing to exitus, to childhood myopathy slowly progressing to severe motor dysfunction in adult age or infantile, childhood or adult-onset tissue-specific disorders, with brain and muscle being the most affected tissues. The mechanisms responsible for clinical variability and tissue specificity are unknown. No definitive cure has been found for this severely debilitating and life-threatening disorders.

The PhD student will **generate and characterize patient-derived? 2D pluripotent and differentiated stem cell lineages** under the supervision of an expert team. Fibroblast cell lines will be reprogrammed to human pluripotent stem cells and differentiated into neuronal, muscle, heart, and liver lineages. Confocal microscopy studies, biochemical and molecular genetics analyses will be performed to characterize these models. By combining **multiple omics advanced technologies** such 3D genomics (HiC) and epigenomics (ATAC-seq), proteomics and metabolomics, we will aim to identify key players in the disease pathogenesis, prognostic factors and potential target for therapy. The 2D models will be used to generate organoids for further corroborating the results from the 2D-derived multiomics studies in a more complex, tissue-like system, which allows studying the cytoarchitecture organization in health and disease. A library of **CRISPR/Cas9 prime editing strategies** will be designed to address the single gene defects in patients' derived models. This will represent a proof-of-concept for a gene therapy approach.