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 Padova

Department of Biomedical Sciences

TUTOR: Prof. Carlo Viscomi

PROPOSED RESEARCH ACTIVITIES (max 300 words):

Mitochondrial diseases are rare, genetically determined conditions due to faulty oxidative phosphorylation and caused by mutations in either mitochondrial or nuclear genes. Although singly extremely rare, they are overall the most common cause of genetically determined neurological impairment. No cure is currently available for these conditions. Thus, there is a clear and unmet medical need for more effective therapies for these conditions. Adeno-associated viral vectors (AAVs) are particularly promising tools to deliver therapeutic genes to affected tissues *in vivo*. Previous work by our and other labs has shown that they can be very effective in preventing and/or correcting the phenotype of mouse models of mitochondrial diseases. However, there are still huge

challenges to ensure full correction of the defect in brain and skeletal muscle, two exquisite targets of mitochondrial dysfunction.

The research activities will focus on developing new and more effective AAV-based gene therapies for primary mitochondrial diseases under the supervision of Prof Carlo Viscomi.

A number of mouse models for mitochondrial disorders have been developed and several of them are available to the lab, offering a unique tool to develop AAV-based gene therapies. In particular, we will exploit (i) the *Ndufs4*$^{-/-}$ mice, characterized by complex I deficiency and severe Leigh-like encephalopathy, (ii) the *Surf1*$^{-/-}$ mice, associated with complex IV deficiency in all tissues, and (iii) muscle-specific *Cox15*$^{-/-}$ mice, characterized by severe complex IV deficiency in skeletal muscle leading to severe myopathy. We will test single-stranded and self-complementary AAV9-derived serotypes to re-express the missing gene in brain and/or skeletal muscle of the different mouse models in order to assess the most suitable platform to treat mitochondrial encephalomyopathies.

Deep in vivo and ex vivo phenotypization will contribute to the understanding of the pathogenetic mechanisms of mitochondrial diseases. In addition, the experimental work will develop a robust AAV-based platform that will be translated into the clinics.