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 degli studi di Milano

Dipartimento di Scienze Farmacologiche e Biomolecolari "Rodolfo Paoletti",

TUTOR:

Angelo Poletti

Co-Tutor: Riccardo Cristofani

PROPOSED RESEARCH ACTIVITIES (max 300 words):

Title: Inhibition of protein neurotoxicity by modulating translation in motoneuron diseases.

Proposed Research: The project has two aims: i) one is to block the aberrant repeat associated AUG-independent (RAN) translation of the (G4C2)n sequence in the C9ORF72 transcript, though to be responsible for the production of neurotoxic dipeptides in C9ORF27 associated familial forms of amyotrophic lateral sclerosis (fALS) and frontolateral temporal dementia (FLTD); ii) the second one is to redirect translation start from a leader AUG driving the production of an androgen receptor (AR) containing a neurotoxic polyglutamine tract (polyQ) causative of spinal and bulbar muscular

atrophy (SBMA), to a second AUG located downstream to the CAG repeat encoding the polyQ, thus giving rise to the translation of a shorter AR-A isoform lacking devoid of the polyQ and non-toxic, but maintaining full androgenic properties.

Both Aims are based on the use of ASOs, morpholinos, shRNAs capable (i) to modulate specific kinases we found specifically involved in RAN translation of the (G4C2)n stretch in the C9ORF72 transcript in the case of fALS, or (ii) ASO and SINEUPs interfering with regions surrounding the first AUG of the AR mRNA transcript.

Experience in the use of iPSCs and their differentiation to motoneurons. Experience in cell cultures of motoneuronal cells. Experience in the analysis of biochemical properties of misfolded protein impacting on the protein quality control system.