Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
Università degli Studi di Napoli Federico II

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:
Modeling and treating alpha-synuclein aggregation in Parkinson's disease patient iPSC-derived neuronal circuits and organoids.

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):
CNR-Instituto di Neuroscienze - Via Follereau 3, 20854 Vedano al Lambro (MB).

TUTOR:
Dr. Vania Broccoli

PROPOSED RESEARCH ACTIVITIES (max 300 words):
Patient-derived induced pluripotent stem cells (iPSCs) can yield unlimited number of affected cells providing a superior in vitro system for deciphering the pathological mechanisms underlying human diseases. Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by selective loss of nigrostriatal dopaminergic neurons, and the presence of Lewy bodies (LB) and Lewy neurites constituted by alpha-Synuclein protein aggregates. In collaboration with the CNR-IGB Institute, we have identified PD patients carrying combinations of rare genetic variants that can synergize together to promote and accelerate the disease progression and degeneration. This combination of genetic variants is intriguing since combines multiple risk variants that alone are not sufficient to directly cause PD. Intriguingly, in some cases these variants can control different aspects of alpha-Synuclein homeostasis and, thus, it might be postulated that these gene alterations contribute to alpha-Synuclein aggregation in an additive fashion. In this project, iPSCs will be generated by these patients and differentiated into dopaminergic neurons monoculture and nigral organoids. alpha-Synuclein aggregation, autophagy and mitophagy alterations and electrophysiological, amperometric and inflammatory properties will be assessed. Next, each single gene alteration will be corrected by

CRISPR/Cas9 gene editing and their impact on the pathological traits will be assessed. Thus, progressive correction of the gene alterations will enable to determine their relative impact and their synergy in promoting pathological alpha-Synuclein aggregation. This study will enable to identify novel disease targets and understand the molecular logics which controls synergic polygenic inheritance and disease probability in PD.