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
Understanding and targeting myocarditis in patients with desmosomal gene mutations

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):**

Unit of Inherited Cardiomyopathies, Centro Cardiologico Monzino IRCCS, Milan

TUTOR:

Prof. Giulio Pompilio

PROPOSED RESEARCH ACTIVITIES (max 300 words):

Myocarditis is mainly caused by viral infections, toxic agents, and autoimmune mechanisms. Over the last decade, however, a strict connection between pathogenic variants in cardiomyopathic genes (mainly desmosomal) and familial myocarditis has been identified. On the other hand, myocardial inflammation has recently been implicated not only in the phenotypes of traditionally desmosomal-genes cardiomyopathies, but also as an active player in disease pathogenesis.
The aim of this project is to identify novel mechanisms and druggable targets for molecular treatment of the inflammatory process, with the ultimate goal of lowering disease morbidity and mortality. Cardiomyocytes derived from iPSC will be used as cell models to understand the crosstalk between genetics and myocardial inflammation in the evolution of desmosomal-gens cardiomyopathies. In

particular, a iPSC line from a patient with recurrent myocarditis and a mutation in *DSP* is already available. An isogenic pair will be produced in which the mutation is corrected. The comparison of electrical, contractile, transcripts and secretory phenotypes of the cardiomyocytes from the two lines will reveal if the myocarditis phenotype is directly dependent on the mutation and if it can be targeted by gene therapy. Other control lines are represented by cardiomyocytes from an acquired myocarditis (COVID) patient, and those from a typical desmosomal-gene mutated patient, carrier of a *PKP2* mutation and without signs of myocarditis.
Antiarrhythmic and anti-inflammatory drugs, as well as advanced therapeutics against the identified targets will constitute the proof of principle of curative interventions.