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:
Synthesis of steroidal analogues in LNP formulations to improve the RNA transfection efficiency

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): Department of Phamracy

Tutors: Carmen Festa/ Angela Zampella CHIM-06 (CHEM-05/A)

PROPOSED RESEARCH ACTIVITIES:
The ascent of RNA drugs give rise to need to develop of potential treatments for hundreds of diseases and disorders. Lipid nanoparticles (LNPs) are self-assembled nanostructures with the ability to encapsulate, protect, and deliver nucleic acids. LNPs are multicomponent lipid systems, containing in addition to cationic or ionizable lipids also phospholipids (for example, phosphatidylcholine and phosphatidylethanolamine), cholesterol or polyethylene glycol (PEG)-functionalized lipids (PEG-lipids). LNP structure and morphology influence drastically cellular uptake, endosomal escape and are essential for efficient packaging and release of its cargo.
Cholesterol is typically one of the four major components, representing between 35-45% of lipid composition. The incorporation of cholesterol in the LNPs enhances their stability and gene transfection and is crucial for intracellular delivery and biodistribution. Recent studies highlight the importance of cholesterol in LNP formulations and reveal that incorporation of cholesterol variants or naturally occurring analogues, such as phytosterols, affects LNP morphology and nucleic acids encapsulation, internalization, cell transfection and biodistribution.
The aim of this project is the identification and structural characterization of new synthetic functionalized version of these natural molecules in LNP formulation, able to improve the RNA transfection efficiency by LNP.

The proposed project will be achieved with a multidisciplinary approach combining chemical synthesis of a large library of steroid derivatives and the assembly and validation of LNP aimed at the delivery of nucleic acids.
Structure-activity analysis of cholesterol analogues will be functional on the understanding of characteristics within the LNP structure and will reveal the structural features necessary to enhance gene transfection, driving the selection of next generation of cholesterol analogues and their rational design.