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**

SPOKE 4 - Metabolic and cardiovascular diseases

Design of Modulators of miRNAs Involved in Cardiovascular and Metabolic Disorders through Machine/Deep Learning Techniques and Biosimulations

MicroRNAs (miRNAs) are single-stranded RNA molecules of approximately 22 nucleotides, non-coding for proteins, that act through the recognition of specific mRNA targets to degrade or repress their translation [1]. Alterations in miRNA functions are involved in the progression of various diseases, including cancer, metabolic disorders, and cardiovascular diseases. Inhibition of miRNAs using antisense oligonucleotides (ASOs) represents a promising therapeutic approach, with nine ASOs already approved [2].
Stiffening of the central arteries, particularly the aorta, plays a significant role in the development of hypertension and associated organ damage [3]. Under various conditions such as aging, diabetes, obesity, hypertension, and cigarette smoking, the aorta becomes stiffened, and this stiffening is associated with the deposition of collagen and fibronectin in the perivascular tissues, particularly in the adventitia. T cells and the cytokines derived from them appear to play an important role in this process through mechanisms that are not yet fully understood.
MiRNA-214 plays a crucial role in the regulation of cardiac and renal fibrosis and is expressed by immune cells. In a recent study, miRNA-214 was identified as the only significantly overexpressed miRNA in the vessels of animal models of hypertension, with a predominant site of overexpression being the perivascular tissues [4]. Furthermore, this study highlighted that miR-214$^{-/-}$ mice did not develop perivascular fibrosis after angiotensin II infusion.
In this doctoral project, the focus will be on designing miRNA modulators for metabolic and cardiovascular diseases. The main objectives include: i) designing ASOs as specific miRNA inhibitors, such as miRNA-214; ii) studying the functional mechanisms governing the recognition of ASOs by the target; iii) predicting the tertiary structure of native and chemically modified oligonucleotides and their target, integrating computational chemistry, bioinformatics, molecular dynamics simulations, and machine/deep learning approaches [5,6]. The designed ASOs will be synthesized and subsequently tested in vitro and in vivo using appropriate cellular and animal models to evaluate their effects on perivascular fibrosis.

References

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