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 7: Bio-Computing-

Application of computational methods to investigate and optimize the structural stability and the pharmacokinetic properties of lipid-based RNA nanocarriers

RNA-based gene therapy requires therapeutic RNA referred as small interfering RNAs (siRNAs), microRNAs (miRNAs) or messenger RNA (mRNA) [1]. The most relevant example of this last case is represented by mRNA vaccines used to fight the COVID-19 outbreak [2-3], and also its use in the field of anticancer drug development, due to their role in encoding tumour antigens, tumour suppressors and cytokines [4]. In order to increase the effectiveness of such therapeutic RNAs, delivery systems were designed such as lipid nanofibers (LNF) [5-6] and lipid-based nanoparticles (LNPs) [1], which nowadays represent the most common nanocarriers for nucleic acid delivery. Key factors required to improve the efficacy and the stability of such delivery systems are linked not only to the chemical modification of the RNAs structure topology [7], but especially to the lipid ratio and composition [8], as well as their size and morphology. Such features, in fact, affect some crucial pharmacokinetic properties such as the biodistribution within specific organs and tumor permeability [9]. Given such evidences, in order to rationally design and optimize LNF- and LNP-based nanocarriers, molecular-level understanding is required to rationalize how the lipid composition can affect the stability and the efficacy of such nanocarriers. With this aim, the proposed project theme concerns the employment of computational methods (e.g. Molecular Dynamics, Coarse-Grained) to simulate the LNFs and LNPs with specific formulation or compositions, to establish relationships between the structural and the functional/pharmacokinetic properties of such delivery systems and optimize their lipid formulation by predicting their structural properties and how they can be related to their functional performance. Integrating molecular simulations with experimental approaches will be crucial to fill such critical gap. For this reason, a collaboration with the Spoke 8 activities is planned.

Riferimenti bibliografici

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