Dipartimento di
Farmacia
Dipartimento di Eccellenza
2018-2022 2023-2027
UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

PROPOSTA PROGETTUALE
DOTTORATO IN RNA therapeutics and gene therapy
CICLO XLI*

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PROJECT TITLE: New Phosphoramidite Building Blocks and Their Application for the Synthesis of Modified Aptamers

Project description

The present research project aims to synthesize new small molecules as phosphoramidite building blocks to be used as nucleoside analogues in the automated solid-phase synthesis of modified nucleic acids, including therapeutic RNA, DNA aptamers, or DNA/RNA chimeras. At least one of the aptamers will be selected to target functional proteins of the extracellular matrix or membrane[1,2] involved in the development and/or etiology of oncological[3,4], viral[5], neurodegenerative[6], or inflammatory[7] diseases (as an example, the aptamer recognizing extracellular domain of c-Met; the binding of this aptamer to c-Met triggers a cascade of events leading to c-Met degradation via the proteasome machinery[4,8,9]). The modified aptamers will incorporate strategically positioned nucleoside analogues to: i) modulate the innate immune response associated with the administration of therapeutic nucleic acids[10,11], through an analysis of correlations between cellular immune response and the introduced modifications; ii) enhance the bioactive conformation[10] in recognizing the target protein. To achieve these goals, the experimental plan, structured in different stages, includes: i) synthesis of rationally designed molecules with specific properties (e.g., photosensitivity to radiation at specific wavelength) and ii) their conversion into phosphoramidite building blocks, to be used in automated solid-phase synthesis of nucleic acids; iii) synthesis of multiple aptamer variants, obtained replacing residues at specific positions with the new building block(s). All synthesized species will undergo spectroscopic (UV, CD, 1D and 2D NMR) and spectrometric (MS, HRMS) characterization to define their three-dimensional structure and will be tested in *vitro* for their biological properties. The aptamer variants exhibiting the best pharmacological profile within the same series will be selected for DNA/RNA chimera preparation. The use of appropriate spacers will ensure proper spacing between the two nucleic acid sections, while different chemical strategies, including click chemistry, will facilitate their conjugation.

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***Per il dottorato *in RNA Therapeutics and gene therapy* selezionare anche una delle seguenti aree tematiche):**

- ☐ **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**