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***

**Tutor: Francesco Saverio Di Leva (PA, CHEM-07/A)**

**Co-tutor: Greta Donati (RTD-B, CHEM-02/A)**

**PROJECT TITLE**

Integrated Artificial Intelligence and Advanced Computational Approaches for the Development of RNA-Based and RNA-Targeting Therapeutics in Cancer and Neurodegeneration.

**Project description (**max 300 words**)**

RNA-based therapeutics are emerging as transformative agents in the treatment of many diseases including cancer and neurodegeneration, offering novel strategies to modulate gene expression and protein interactions at the post-transcriptional level [1,2]. Among these are RNA aptamers, short, structured oligonucleotides capable of binding protein targets with high affinity and specificity, representing a promising class of targeted biologics [3]. In parallel, small molecules that selectively bind disease-associated RNA structures have shown therapeutic potential by interfering with RNA-mediated pathogenic mechanisms [4,5].
This PhD project aims to integrate state-of-the-art computational methodologies for the discovery and development of both RNA-based and RNA-targeting therapeutics. The project will leverage a multidisciplinary toolkit encompassing bioinformatics, chemoinformatics, molecular and quantum mechanics, and machine learning/artificial intelligence (ML/AI) to model RNA structures, predict binding interactions, and optimize ligand design. These methodologies will guide the in silico discovery and optimization of RNA aptamers for extracellular targets, as well as small molecules targeting structured RNA elements such as G-quadruplexes, repeat expansions, or regulatory motifs.
Our research group has established expertise in both RNA-based and RNA-targeting strategies, as demonstrated by recent publications reporting the structural characterization of aptamers against glioblastoma and breast cancer [6,7], and the rational design of small molecule modulators of pathogenic RNA extended repeats in SLA-related genes [8-10].
This PhD position offers a unique opportunity to train in cutting-edge computational techniques and apply them to the discovery of next-generation RNA therapeutics within the framework of gene therapy. The selected candidate will contribute to advancing precision medicine at the interface of RNA biology, structural chemistry, and therapeutic innovation.

## REFERENCES

1. Zhu, Y., et al. RNA-based therapeutics: an overview and prospectus. Cell Death Dis., 2022, 13, 644
2. Rupaimoole, R.; Slack, F.J. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. *Nat. Rev. Drug. Discov.* 2017, 16, 203–222.
3. Keefe, A.D. et al. Aptamers as therapeutics. *Nat. Rev. Drug. Discov.* 2010, 9, 537–550.
4. Warner, K.D. et al. Principles for targeting RNA with drug-like small molecules. *Nat. Rev. Drug Discov.* 2018, 17, 547–558.
5. Childs-Disney, J. L. et al. Targeting RNA structures with small molecules. *Nat. Rev. Drug Discov.* 2022, 21 736–762.
6. Diakogiannaki, I. et al. Targeting Glioblastoma Stem Cells via EphA2: Structural Insights into the RNA Aptamer A40s for Precision Therapy. *J. Chem. Inf. Model.* 2025, in press.
7. Quintavalle, C. et al. Ex.50.T aptamer impairs tumor-stroma cross-talk in breast cancer by targeting gremlin-1. *Cell Death Discov.* 2025, 11, 94.
8. Maiocchi, A. et al. Design, Synthesis and Characterization of Aryl bis-Guanyl Hydrazones as RNA Binders of C9orf72 $G_4C_2$ extended repeats. *Eur. J. Med. Chem.* 2025, 293, 117736.
9. Bonomo, I. et al. HuR modulation counteracts lipopolysaccharide response in murine macrophages. *Dis. Model Mech.* 2023, 16, dmm050120.
10. Facen, E. et al. Novel, soluble 3-heteroaryl-substituted tanshinone mimics attenuate the inflammatory response in murine macrophages. *Sci Rep.* 2024, 14, 24501.

## FUNDS

- PRIN 2022 – Title: "*Interrogating Artificial Intelligence for the discovery of Formyl Peptide Receptor 2 Modulators in the Resolution of (Neuro)Inflammation*". Role: **PI**. Expiration date: 28/02/2026.
- PNRR 2022 – Title: "*National Center for Gene Therapy and Drugs based on RNA Technology*" (CN3, Spoke7: Biocomputing). Role: participant. Expiration date: 31/10/2025.
- FISM Multi-Centre 2023 – Title: "*Targeting Smoothened/AMPK pathway to boost central nervous system remyelination*". Role: participant. Expiration date: 28/02/2027.

***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**

**Dipartimento di Farmacia**
Via Domenico Montesano, 49 • 80131 Napoli, Italia
angelo.izzo@unina.it • + 39 081678658
www.farmacia.unina.it