University of Naples Federico II
Department of Pharmacy
Doctoral Course in Pharmaceutical Sciences XL Cycle

PEPTIDES TO TARGET NONCANONICAL NUCLEIC ACID STRUCTURES IN CANCER CELLS AND PATHOGENS

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DNA and RNA can form several noncanonical secondary structures besides the classic double helix. A structure that has received great attention in recent years is the G-quadruplex (G4). This is a four-stranded structure formed by the stacking of guanine tetrads. G4s can form both in vivo and in vitro, influencing DNA replication and transcription, which makes them attractive targets for anticancer therapies. Exciting recent reports have revealed roles for G4 structures in several important human microbial pathogens. Interestingly, G4s are present in pathogens that come from a range of kingdoms – bacteria, protozoa, and viruses – and all facilitate immune evasion in different ways. In particular, G4s have been implicated in the antigenic variation systems of bacteria and protozoa, as well as in the silencing of at least two major human viruses: human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV). Thus, highly disparate pathogens can use G4 motifs to control DNA/RNA dynamics in ways that are relevant to common virulence phenotypes.

Peptides offer the versatility needed for a successful drug discovery approach. Besides being biologically active, some peptides are also excellent carriers for the delivery of drugs to their targets. Their use as DNA/RNA-targeted therapeutics is an exciting research area with great promise for the future, particularly in anticancer and antimicrobial therapies.

Therefore, the research topic of this PhD proposal concerns the design, synthesis, and characterization of novel peptides (both natural and chemically-modified) that can bind G4s with high affinity and selectivity, and the evaluation of their biological activity. The project can fits into the themes of the TRAVEL Excellence Project, as it involves the identification and validation of new pharmacological targets, as well as the development of peptide-based drugs. This activity is in line with the main objective of the TRAVEL project, which is to promote innovation and excellence in the research and the development of new therapies.

The expertise of the tutors in the chemical synthesis and characterization of putative therapeutic agents, as well as in the study of their interaction with targets, will provide the PhD student with a comprehensive and high-level training path. The tutors' long-established and fruitful scientific collaboration in the field (Nucleic Acids Res. 2024 doi: 10.1093/nar/gkae471; Int. J. Biol. Macromol. 2023 doi: 10.1016/j.ijbiomac.2023.126749), further strengthens this opportunity. Access to research funds (PRIN PNRR 2022 id. P20223RKJ7 to J.A., PRIN 2022 id. 202242MEP7 and PRIN PNRR id. P20225ZAMB to F.M.) will ensure adequate financial support for carrying out the research and training activities.